ENANTIOSPECIFIC STEREOSPECIFIC STRATEGY FOR THE TOTAL SYNTHESIS OF SARPAGINE AND MACROLINE RELATED OXINDOLE ALKALOIDS: FIRST TOTAL SYNTHESIS OF AFFINISINE OXINDOLE, ISOALSTONISINE, ALSTOFOLINE, MACROGENTINE, *N*(1)-DEMETHYLALSTONISINE, ALSTONOXINE A AND SECOND GENERATION SYNTHESIS OF ALSTONISINE

by

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ABSTRACT

ENANTIOSPECIFIC STEREOSPECIFIC STRATEGY FOR THE TOTAL SYNTHESIS OF SARPAGINE AND MACROLINE RELATED OXINDOLE ALKALOIDS: FIRST TOTAL SYNTHESIS OF AFFINISINE OXINDOLE, ISOALSTONISINE, ALSTOFOLINE, MACROGENTINE, *N*(1)-DEMETHYLALSTONISINE, ALSTONOXINE A AND SECOND GENERATION SYNTHESIS OF ALSTONISINE

by

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University of Wisconsin-Milwaukee, 2015
Under the Supervision of Professor James M Cook

The (**7*R***)-sarpagine/macroline related oxindole alkaloids (–)-isoalstonisine (**27**) and (–)-macrogentine (**31**) together with the (**7*S***)-sarpagine/macroline related oxindole alkaloids (–)-affinisine oxindole (**24**), (–)-alstonoxine A (**19**), (+)-alstonisine (**8**, second generation total synthesis), (+)-N_a-demethylalstonisine (**17**) and (+)-alstofoline (**18**) were concisely synthesized during these studies.

These oxindole alkaloids were isolated from plants of the genus *Alstonia* which is characterized by the preponderance of sarpagine/macroline-type indole and oxindole alkaloids. Plants that belong to this genus are mainly distributed over tropical regions of Central America, Africa, and Asia where they are used locally in traditional medicine, for example, in the treatment of malaria and dysentery. The main *Alstonia* species that have been studied in detailed to date are *A. muelleriana*, *A. angustifolia*, and *A. macrophylla*.

A highly enantio- and diastereoselective general strategy to access the members of the sarpagine/macroline family of oxindole alkaloids was developed from cheap, commercially-available and optically active **D-(+)-tryptophan**. The built-in chirality in D-(+)-tryptophan was used and expanded, *via intramolecular asymmetric induction*, to form

new enantio rich compounds. Although the routes were usually stereospecific any diastereomeric byproducts enabled their facile separation by methods such as column chromatography or crystallization. This only occurred in a few instances but was the reason the chirality was built in from the beginning. At the heart of this approach was the diastereospacific generation of the spiro[pyrrolidine-3,3′-oxindole] moiety at an early stage of the route *via* a *tert*-butyl hypochlorite-promoted oxidative rearrangement of chiral tetrahydro-β-carbolines derivatives. This key transformation determined the spatial configuration at the C-7 spiro center to be either *R* or ***S***. Other key enantiospecific initial reactions were the asymmetric Pictet–Spengler and Dieckmann cyclization which were scalable 300-600 gram levels. This early construction of the spiro oxindole moiety had the important advantage that there was no need to perfom complex studies for every single target molecule at the end of the route which involved the optimization of reaction conditions to the particular system under study, *e.g.* finding the suitable oxindole-generating reaction or screening of chiral catalysts to obtain the desired stereochemistry at C-7. On the other hand, it was well-known that oxindoles at C-7 could equilibrate between 7*R* and 7*S* through a retro-Mannich process. Consequently, confirmation of the diastereomeric outcome of oxindole reactions had to be executed. As a consecuance of our studies on this topic, we were able to find a set of two reaction conditions that enabled the 7*R* to 7*S*-interconversion (and *vice versa*) validated by X-ray crystallography in many cases as well as 1D NOE-NMR studies.

The utility of a mild Pd-promoted enolate-driven cross-coupling at room temperature, that generated the chiral center at C-14 and the Wacker–Cook oxidation process for the generation of the E-ring in the oxindole systems was demostrated.

Finally, the complete structural elucidation of the final products corroborated the studies by Kam et al. who isolated these oxindole alkaloids from plants and performed their initial structure determination in many cases by X-ray crystallography.

To

My parents Juan & Sonia

My grandmother Josefina and my brother Gabriel

My lovely wife Veronica Maria Marco Alvarez

and her parents Oldemar & Zelmira

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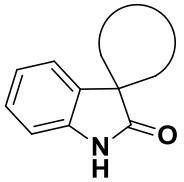
1) Introduction

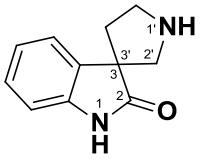
1.1) Chemical Structure and Classification of Sarpagine-Macroline Oxindole Alkaloids and Related Structures

The spirooxindole general structure (**1**) is found in many complex natural products, many of which have been reported to possess important biological properties, Figure 1.[1] The first oxindole alkaloids were found in the roots of *Gelsemium sempervirens* (wild yellow jasmine). In particular, the oxindole alkaloids containing the 3,3′-pyrrolidinyl-spirooxindole moiety (**2**) belong to a family of natural products that were mainly isolated from plants of the *Apocynaceae* and *Rubiacae* families and in particular from the *Aspidosperma, Mitragyna, Rauwolfia*, *Uncaria, Alstonia,* and *Vinca* genera.[2] Other oxindoles of this type have been isolated from fungi like *Aspergillus fumigatus*.[3] The key structural characteristic of these compounds is the spiro ring fusion at the 3-position of the oxindole core with varying degrees of substitution around the pyrrolidine and oxindole rings.

Figure 1. 3,3′-Pyrrolidinyl-spirooxindole structure



(**1**)

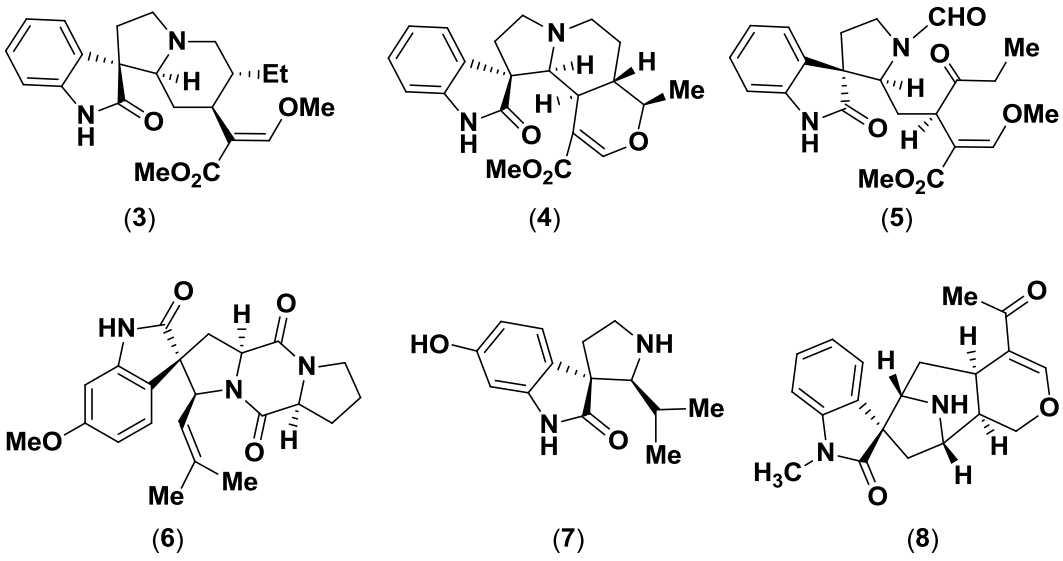


(**2**)

The 3,3′-pyrrolidinyl-spirooxindole alkaloids can be classified into six distinct groups according to their chemical architecture; some examples of representative alkaloidal structures are depicted in Figure 2:

1. The tetracyclic secoyohimbane group [*e.g*. rhyncophylline[4] (**3**)]
2. The pentacyclic heteroyohimbane group [*e.g*. formosanine[4] (**4**)]
3. The D-*seco* corynanthe group [*e.g*. alkaloid Us-8[5] (**5**)]
4. The 2,5-diketopiperazine group [*e.g*. spirotryprostatin A[3] (**6**)]
5. The tricyclic group [*e.g*. elacomine[6] (**7**)]
6. The sarpagine-ajmaline-akuammiline group [*e.g*. alstonisine[7] (**8**)]

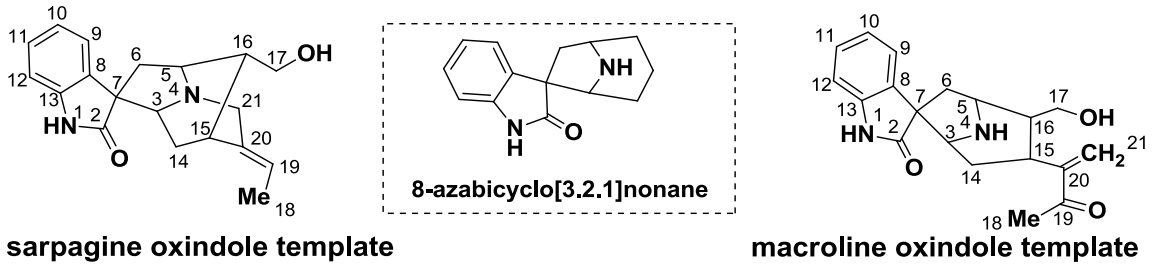
Figure 2. Representative oxindole alkaloids



The present study focuses on the development of a general, stereoselective synthetic approach towards a class of oxindole alkaloids included in the sarpagine-ajmaline-

akuammiline group: the sarpagine-macroline related oxindole alkaloids. The common structural feature of these alkaloids is the presence of an 8-azabicyclo[3.2.1]nonane moiety, which is shown in Figure 3 along with the basic chemical framework shared by these oxindoles and its systematic numbering used in the literature. At the time of writing this work, 46 natural oxindole alkaloids had been reported in the literature from *Alstonia*, *Voacanga*, and *Gardneria* species (Figures 4, 5 and 6). It is worth noting that these oxindoles can be further divided according to the configuration around the C-7 spiro-center (*R*-series or *S*-series). In view of a systematic error involving the labeling of the configuration at the spirocyclic carbon C-7 in some previously isolated *Alstonia* oxindole alkaloids, Kam et al. reported the corrected *R/S* labeling in a recent communication.[18]

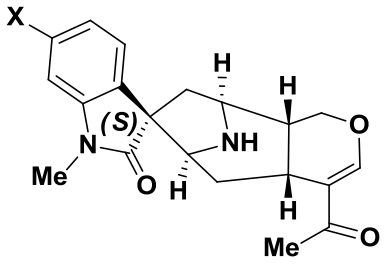
Figure 3. 8-Azabicyclo[3.2.1]nonane moiety and numbering



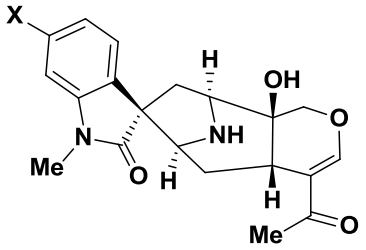
1.1.1) Natural Oxindole Alkaloids from *Alstonia* Species

Figure 4. Classification (part 1)

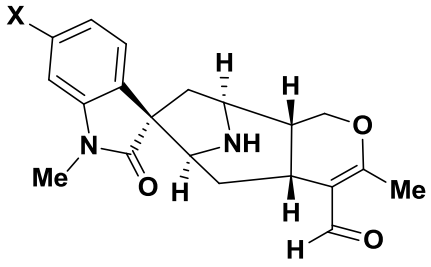
C7-(*S*) Subgroup



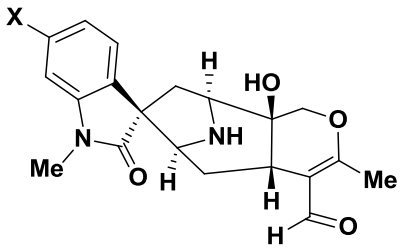
X = H, (+)-alstonisine (**8**)[7]
X = OMe, (+)-*N*(2)-demethylalstophylline oxindole (**9**)[8]



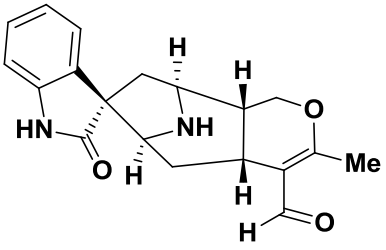
X = H, (+)-16-hydroxyalstonisine (**10**)[9]
X = OMe, (+)-16-hydroxy-*N*(2)-demethylalstophylline oxindole (**11**)[10]



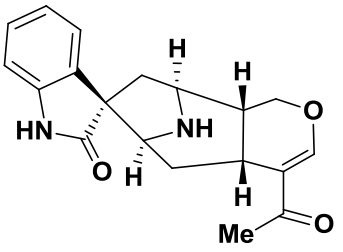
X = H, (+)-alstonal (**12**)[11]
X = OMe, (+)-*N*(2)-demethylalstophyllal oxindole (**13**)[11]



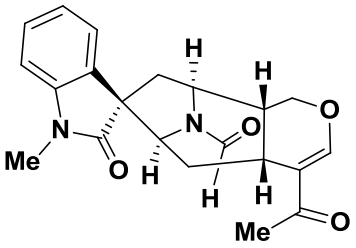
X = H, (+)-16-hydroxyalstonal (**14**)[9]
X = OMe, (+)-16-hydroxy-*N*(2)-demethylalstophyllal oxindole (**15**)[9]



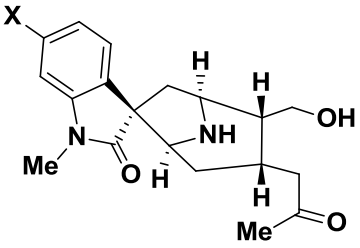
(+)-*N*(1)-demethylalstonal (**16**)[12]



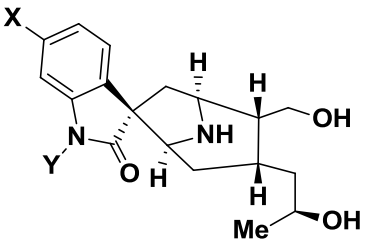
(+)-*N*(1)-demethylalstonisine (**17**)[12]



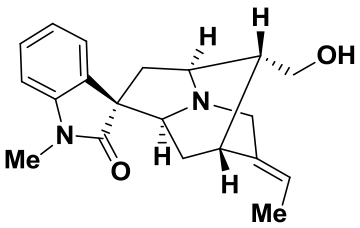
(+)-alstofoline (**18**)[12]



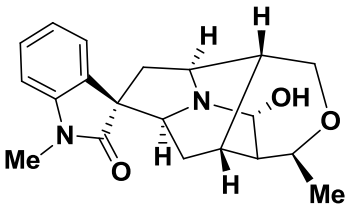
X = H, (–)-alstonoxine A (**19**)[12]
X = OMe, (–)-alstonoxine C (**20**)[18]



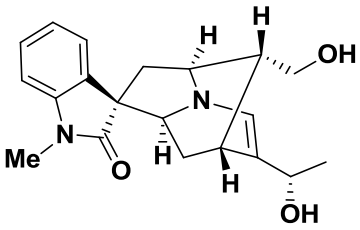
X = H, Y = Me, (–)-alstonoxine B (**21**)[12,18]
X = OMe, Y = Me, (–)-alstonoxine D (**22**)[18]
X = H, Y = H, (–)-alstonoxine E (**23**)[19]



(–)-affinisine oxindole (**24**)[14]

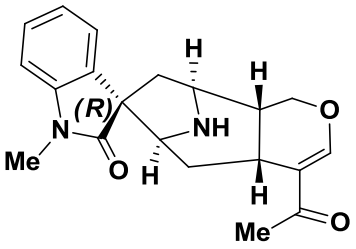


(–)-talpinine oxindole (**25**)[19]

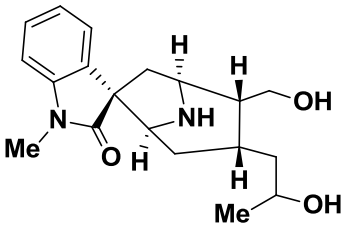


(–)-alstoumerine oxindole (**26**)[19]

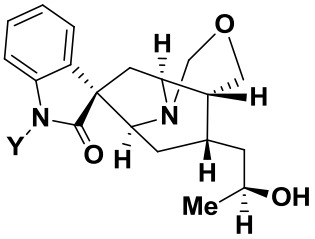
C7-(*R*) Subgroup



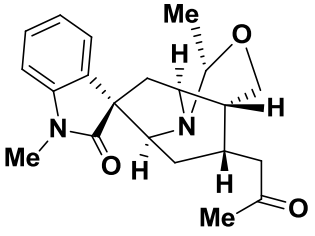
(+)-isoalstonisine (**27**)[12]



(+)-isoalstonoxine B (**28**)[19]



Y = Me, (+)-macroxine (**29**)[13,19]
Y = H, (–)-macrogentine A (**30**)[19]

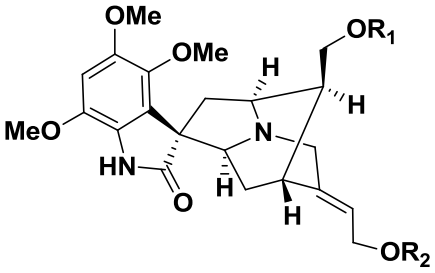


(–)-macrogentine (**31**)[12]

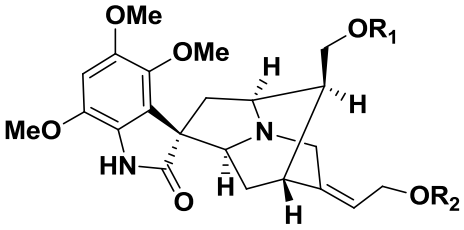
1.1.2) Natural Oxindole Alkaloids from *Gardneria* Species

Figure 5. Classification (part 2)

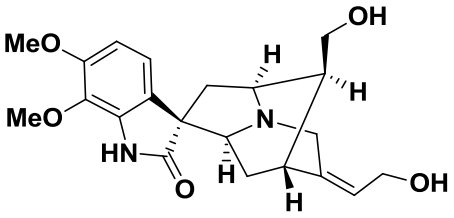
C7-(*S*) Subgroup



R_1 = R_2 = H, (–)-gardmultine A (**32**)[20]
R_1 = H, R_2 = OH, (–)-gardmultine B (**33**)[20]
R_1 = Glc, R_2 = OCH_3, (–)-gardmultine C (**34**)[20]

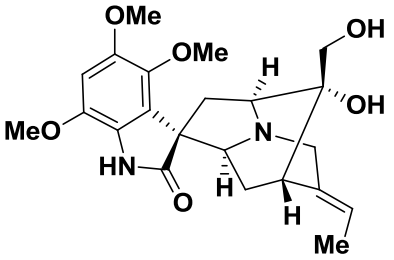


R_1 = H, R_2 = OH, (–)-gardmultine D (**35**)[20]
R_1 = H, R_2 = OCH_3, (–)-gardmultine E (**36**)[20]

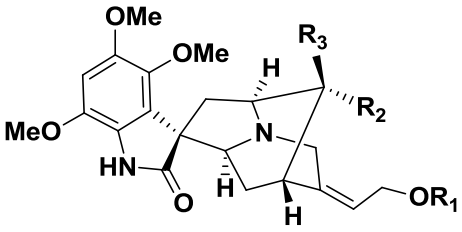


(–)-gardmultine F (**37**)[20]

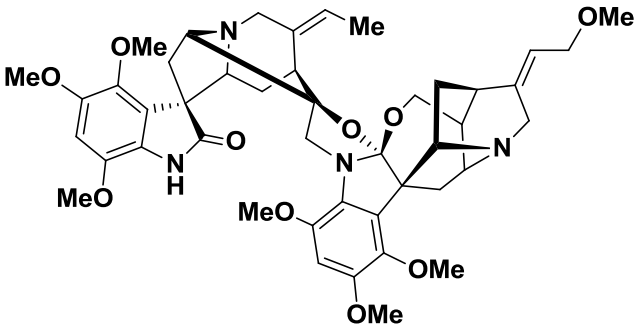
C(7)-(*R*) Subgroup



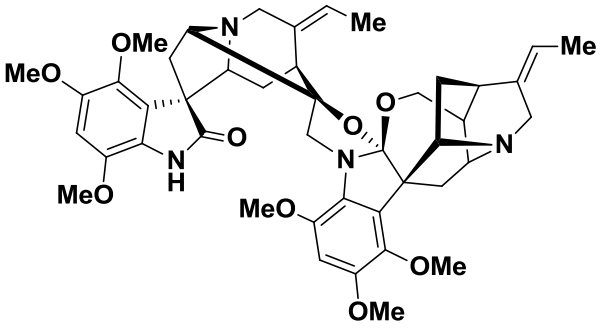
(–)-chitosenine (**38**)[15]



R_1 = CH_3, R_2 = H, R_3 = CH_2OH alkaloid I (**39**)[21]
R_1 = CH_3, R_2 = CH_2OH, R_3 = H alkaloid J (**40**)[21]
R_1 = CH_3, R_2 = OH, R_3 = CH_2OH alkaloid N (**41**)[20,21]
R_1 = H, R_2 = H, R_3 = CH_2OH alkaloid M (**42**)[21]
R_1 = H, R_2 = CH_2OH, R_3 = H alkaloid L (**43**)[21]



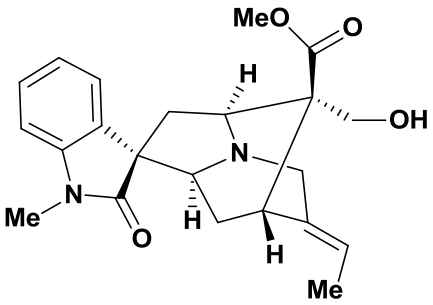
(–)-gardmultine (**44**)[16]



(–)-demethoxygardmultine (**45**)[16]

1.1.3) Natural Oxindole Alkaloids from *Voacanga* Species

Figure 6. Classification (part 3)



(–)-voachalotine oxindole (**46**)[17]

1.1.4) Natural Imino-Ether Alkaloids from *Gardneria* Species

In terms of chemical structure, a closely related group of alkaloids found in *Gardneria* species that contain an imino-ether moiety instead of the oxindole moiety deserves to be mentioned. An acid/base-catalyzed, reversible interconversion between these forms is depicted in Figure 7. A total of 14 natural imino-ether alkaloids have been reported in the literature, to date, and their known structures are shown in Figure 8.

Figure 7. Imino-ether/oxindole structural relationship

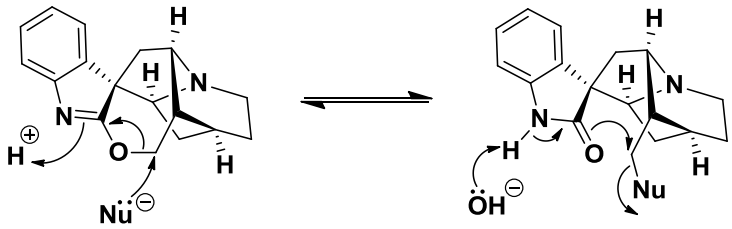
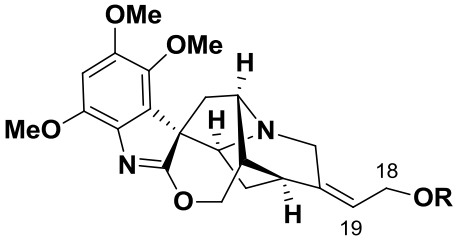
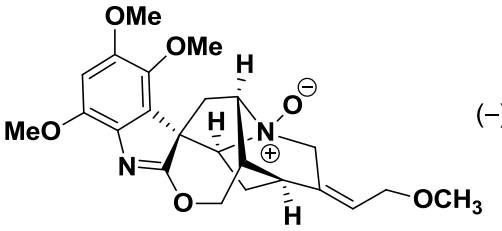


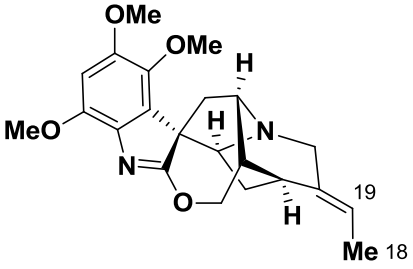
Figure 8. Classification (part 4)



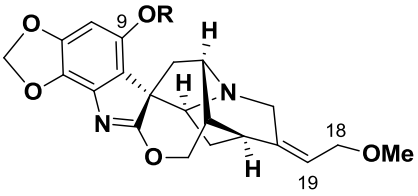
R = CH_3, (–)-gardneramine (**47**)[15,24,30,31]
R = H, (–)-18-demethylgardneramine (**48**)[24,30]



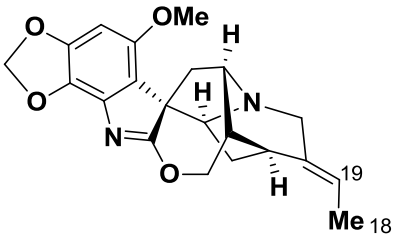
(–)-gardneramine-*N*(4)-oxide (**49**)[32]



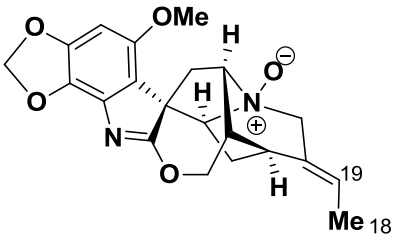
(–)-19-(*E*)-18-demethoxygardneramine (**50**)[15]



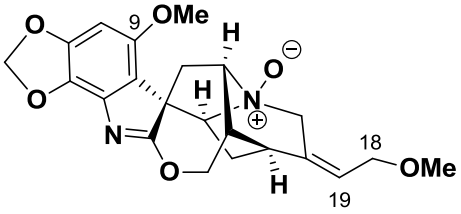
R = Me, (–)-gardfloramine (**51**)[28,29]
R = *O*-β-D-glc, (–)-gardfloramine-9-*O*-β-D-glucopyranoside (**52**)[33]



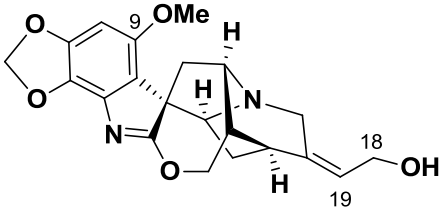
(–)-19-(*E)*-18-demethoxygardfloramine (**53**)[28,29]



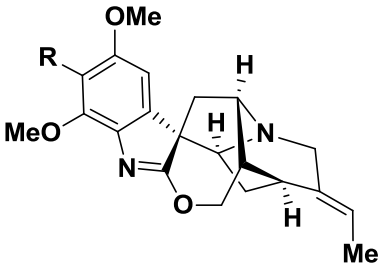
(–)-19-(*E)*-18-demethoxygardfloramine-*N*(4)-oxide (**54**)[33]



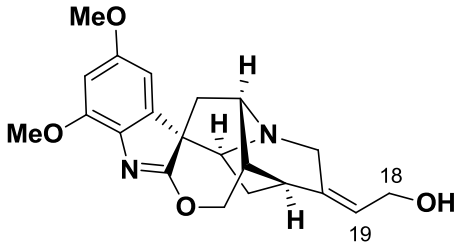
(–)-gardfloramine-*N*(4)-oxide (**55**)[33]



(–)-18-demethylgardfloramine (**56**)[33]



R = H, (–)-19-(*E)*-9,18-didemethoxygardneramine (**57**)[33]
R = OMe, (–)-19-(*E)*-11-methoxy-
-9,18-didemethoxygardneramine (**58**)[33]



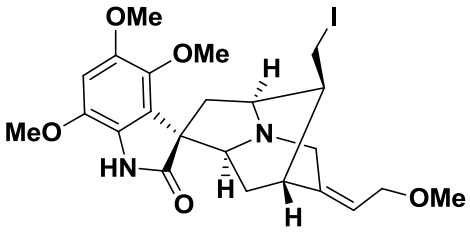
(–)-9-demethoxy-
-18-demethylgardnernamine (**59**)[33]

1.2) Aspects of Biological Activity

1.2.1) Biological Activity of Sarpagine-Macroline Oxindole Alkaloids

Ozaki and Harada[22] studied the effect of *Gardneria* alkaloids on ganglionic transmission in rabbit and rat superior cervical ganglia. One of the most potent ganglion blocking effects was found with alkaloid I (**39**). Sakai developed ulcer-inhibiting formulations utilizing a mixture of indole alkaloids, one of those components was a non-natural iodine-containing oxindole alkaloid (**60**) (Figure 9) which was generated when gardneramine was treated with MeI in benzene.[23,24]

Figure 9. Non-natural oxindole (**60**)



non-natural oxindole (**60**)[23]

Alstonisine (**8**) showed moderate *in vitro* antiplasmodial activity against *Plasmodium falciparum*, with an IC_{50} value of 7.6 μM.[25] Also, alstonisine (**8**) was used for structure-based design of non-peptide MDM2 inhibitors for anticancer drugs.[26] Morita reported the potent vasorelaxant activity of alstonisine (**8**) and alstonal (**12**) on rat aortic arteries. This effect was attributed to the inhibition of the Ca^{2+} influx through a voltage-dependent Ca^{2+} channel (VDC) and/or receptor-operated Ca^{2+} channel (ROC).[27]

Lately in 2014, Peng et al. reported that oxindole alkaloids gardmutine D (**35**) and gardmutine E (**36**) exhibited inhibitory effects against three human cancer cell lines: breast cancer (MCF-7), colon cancer (SW480), and HeLa cells (derived from cervical cancer).[20]

1.2.2) Biological Activity of Sarpagine-Macroline Imino-Ether Alkaloids

Gardneramine (**47**) produced a hypotensive effect in rabbits. This effect seems to be derived from its peripheral vasodilation action, direct depressive action on the myocardium, and central depressive action. It produced vasodilation in the hind limb preparation from dogs and a depressive effect on atria isolated from guinea pigs. Gardneramine (**47**) inhibited the movement of smooth muscle organs such as stomach and intestine. It seem to have a papaverine-like action in peripheral organs.[34] Gardneramine (**47**) exhibited central nervous system depressant activity in mice. It has a slight analgesic effect and antagonized convulsions induced by nicotine. Depression of spontaneous motor activity, a weak antagonistic effect on hypermotility induced by methamphetamine, motor incoordination, prolongation of hexobarbital sleep time, and a hypothermic effect were seen following the administration of gardneramine.[35] Gardneramine inhibited the gastroc-

nemius contractions elicited by electrical stimulation of the sciatic nerve, but exerted little or no inhibition on the contractions elicited by direct stimulation of the muscle. This inhibitory effect of gardneramine was a little stronger than that of hexamethonium and was very weak when compared with that of *d*-tubocurarine.[36] Gardneramine showed short acting, potent ganglion blocking effect in the rabbit and rat superior cervical ganglionic *in situ* preparations. The activity of gardneramine was about a half (rabbit) and about a quarter (rat) as potent as that of hexamethonium. On the other hand, the effect of 18-demethylgardneramine (**48**) was very weak.[22] Gardneramine inhibited the contraction of the urinary bladder induced by electrical stimulation of the pelvic nerves. Its potency was about a half of that of hexamethonium. The effect was of short duration. It depressed the contraction induced by intraarterial dimethylphenylpiperazinium, with no antagonizing action to the acetylcholine-induced contraction. Gardneramine (**47**) and 18-demethoxy-gardneramine (**50**) showed a medium grade of acute toxicity.[37]

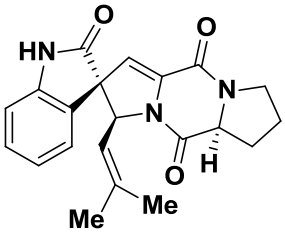
1.2.3) Selected Examples of Biological Activity of other Spirooxindole Alkaloids Containing the 3,3′-Pyrrolidinyl-Spirooxindole Moiety

Other types of oxindole alkaloids containing the spiro[pyrrolidine-3,3′-oxindole]ring system are also known to possess a variety of bioactivity profiles, that further demostrates the biological relevance of alkaloids containing such a moiety, and selected examples found in the literature will be presented in this section.

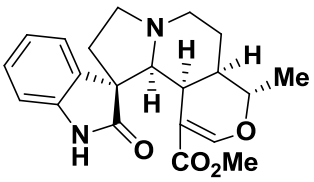
Two diketopiperazine alkaloids, spirotryprostatin A (**6**) and B (**61**) (Figure 10), are fungal secondary metabolites from *Aspergillus fumigatus*. They are of pharmaceutical impor-

tance owing to their cell cycle-arresting properties, which are useful in treatment of cancer. For instance, spirotryprostatin B completely inhibited the cell cycle progression of tsFT210 cells in the G2/M phase at final concentrations over 12.5 μg/mL. In addition, it also showed cytotoxic activity on the growth of human chronic myelogenous leukemia K562 cells and and human promyelocytic leukemia HL-60 cells with MIC values of 35 and 10 μg/mL.[38] Zhou reviewed the pharmacological studies of rhynchophylline (**3**, a main oxindole alkaloid in *Uncaria* species) with emphasis on cardiovascular and central nervous system diseases linked to the ethnopharmacological uses of *Uncaria* species. The cardiovascular effects of rhynchophylline are antihypertension (in rats, dogs, and rabbits), vasodilation (in rats), negative chronotropic and inotropic action (in guinea pigs), anti-arrhythmia (in rats, dogs, guinea pigs), calcium antogonist (in guinea pigs and rabbits), modulation of K^+ channels (in rats and humans), and depression of nerve potentials (in toads). Rhynchophylline also showed action on the central nervous system, anti-coagulation effects, inhibition of vascular smooth muscle cell proliferation, reducing mortality of endotoxemic mice, improving therapy for listeriosis, and antispamodic activity.[39] Pteropodine (**62**, Figure 10) is an oxindole alkaloid isolated from cat's claw, it is an immunologically active compound, showing a pronounced enhancement of phago-cytosis, as well as a modulatory effect on the muscarinic M1 and 5-hydroxytryptamine receptors in mouse.[40] Elacomine (**7**) derivative SOID-8 (**63**, Figure 10), inhibits growth and induces apoptosis of melanoma cells. The anticancer effects of this compound are associated with suppression of phosphorylated JAK2 and STAT3. Importantly, SOID-8 inhibits melanoma tumor growth in a mouse xenograft model.[41]

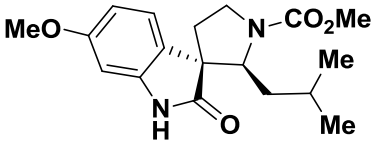
Figure 10. Biological aspects, examples



(**61**)



(**62**)



(**63**)

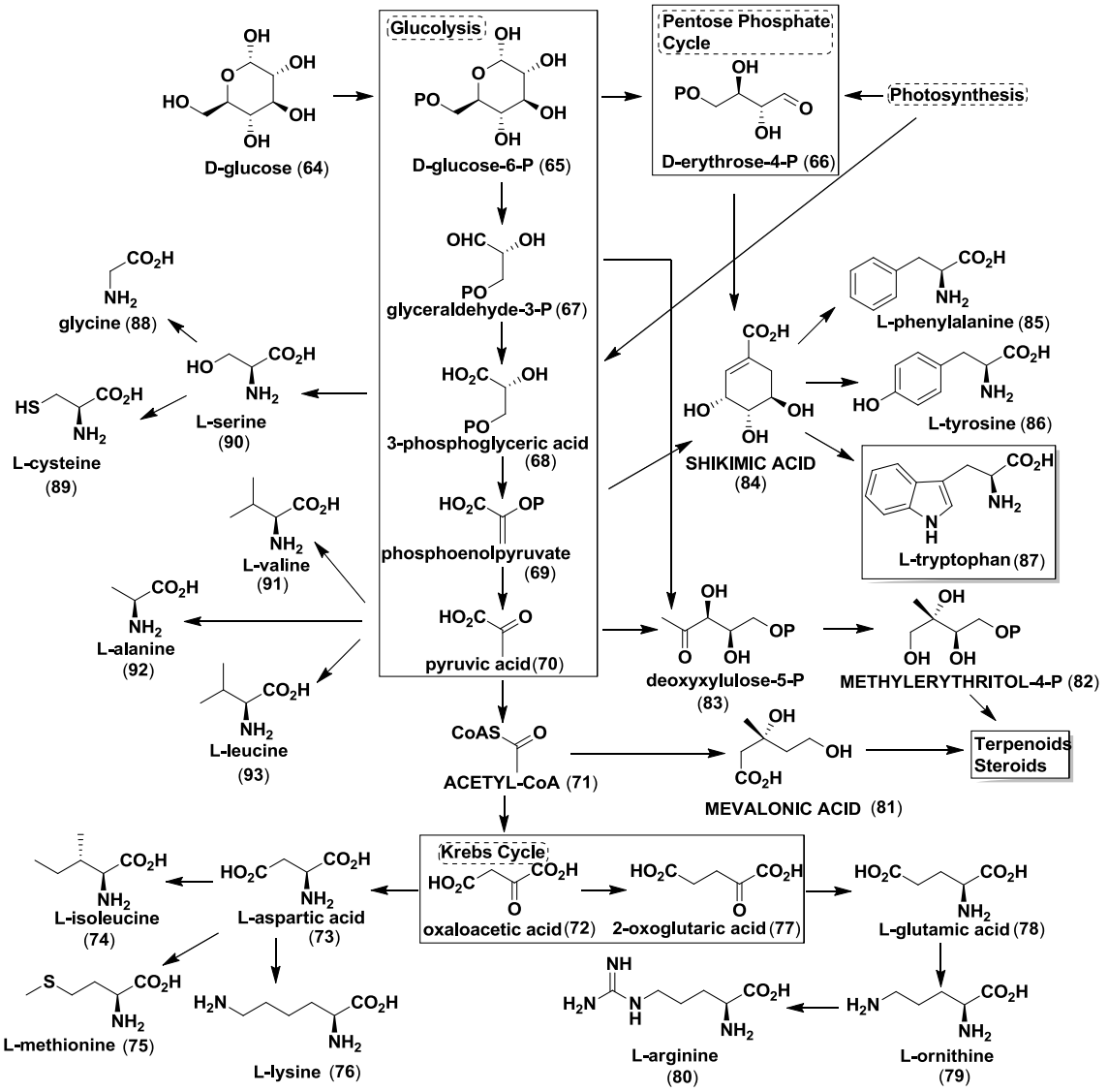
1.3) Biosynthetic Considerations

1.3.1) General Aspects

The building blocks for secondary metabolites in plants are derived from the primary metabolism, as indicated in Scheme 1.[42] It can be seen how metabolites are taken from the fundamental energy-generating processes of photosynthesis, glycolysis, and the Krebs cycle to provide biosynthetic intermediates. The number of building blocks is actually low, but a vast array of chemical structures can be built from a limited number of these simple precursors. The most important in the biosynthesis of secondary metabolites are derived from the intermediates acetyl coenzyme A (**71**, acetyl-CoA), shikimic acid (**84**), mevalonic acid (**81**), and methylerythritol phosphate (**82**). In addition to these building blocks, others based on amino acids are frequently employed in natural product synthesis. Peptides, proteins, alkaloids, and many antibiotics are derived from amino acids, and the origins of some of the more important amino acids are indicated in Scheme 1. Intermediates from the glycolytic pathway and the Krebs cycle are used in constructing many of

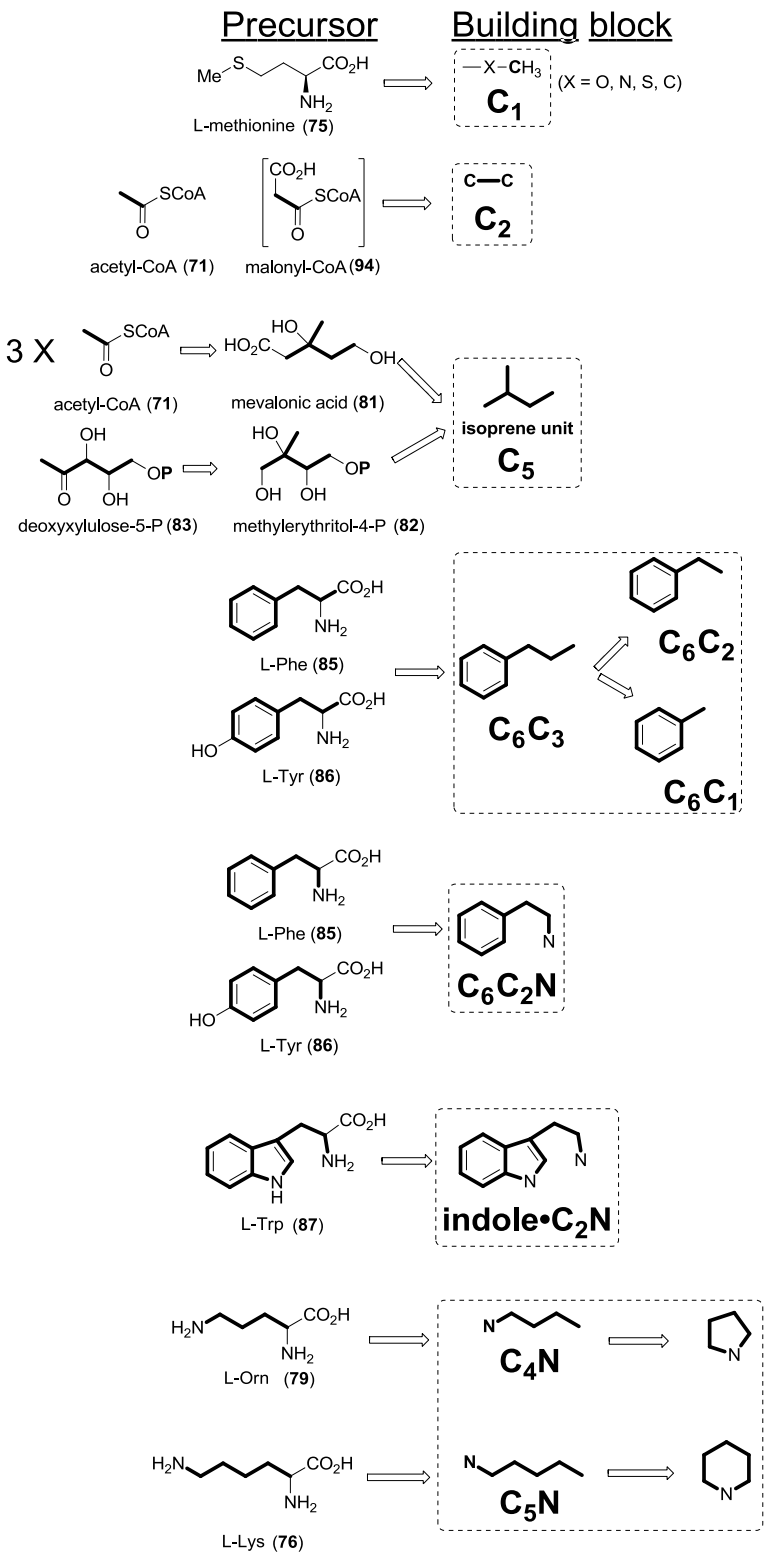
them, but the aromatic amino acids, phenylalanine (**85**), tyrosine (**86**), and tryptophan (**87**) are themselves products from the shikimate pathway. Ornithine (**79**), an amino acid not found in proteins, and its homologue lysine (**76**), are important alkaloid precursors and have their origins in the Krebs cycle intermediates. Importantly, secondary metabolites can be synthesized by combining several building blocks of the same type, or by using a mixture of different building blocks. A typical natural product might be produced by combining elements from the acetate, shikimate, and methylerythritol phosphate pathways, for example. Many secondary metabolites also contain one or more sugar units in their structure, either simple primary metabolites, such as glucose (**64**) or ribose, or alternatively substantially modified and unusual sugars. In order to appreciate how a natural product is elaborated, it is of value to dissect its structure into the basic building blocks from which it is constructed and to use fundamental chemical mechamisms to propose how these are joined together.[42]

Scheme 1[42d]



Only few building blocks are routinely employed, and a list including those most frequently encountered in producing the carbon and nitrogen skeleton of a natural product, together with their respective precursos, is given in Scheme 2. It is also important to notice that some natural products have been produced in processes by which a fundamental rearrangement of the carbon skeleton has occurred.

Scheme 2[42d]


Precursor
Building block
L-methionine (75)
(X = O, N, S, C)
C1
acetyl-CoA (71)
malonyl-CoA (94)
C2
3 X
acetyl-CoA (71)
mevalonic acid (81)
isoprene unit
C5
deoxyxylulose-5-P (83)
methylerythritol-4-P (82)
L-Phe (85)
L-Tyr (86)
C6C2
C6C3
C6C1
L-Phe (85)
L-Tyr (86)
C6C2N
L-Trp (87)
indole•C2N
L-Orn (79)
C4N
L-Lys (76)
C5N

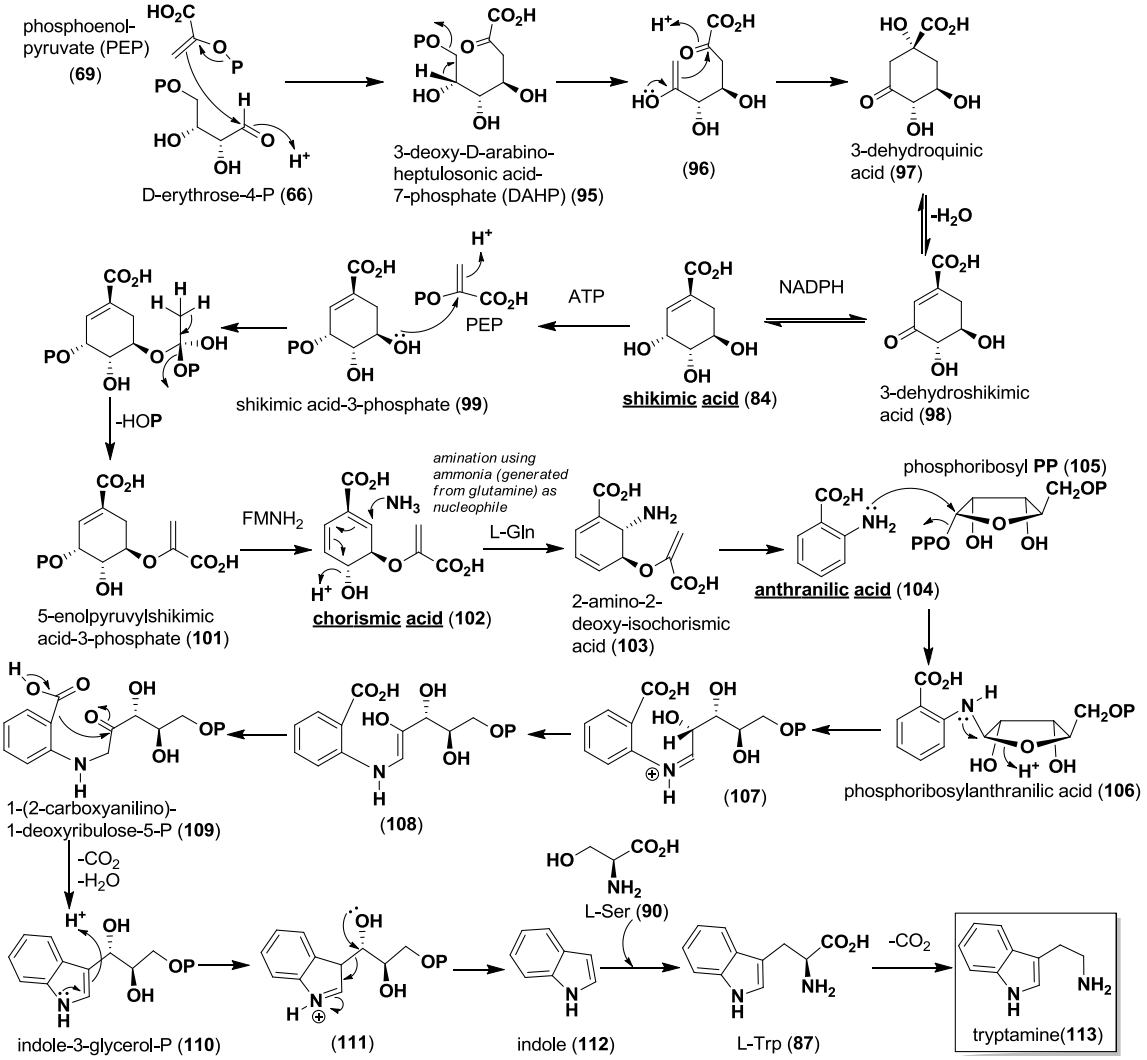
This is especially common with structures derived from isoprene units, and it disguises some of the original building blocks from immediate recognition. The same is true if one or more carbon atoms are removed by oxidation reactions.[42]

1.3.2) Monoterpene Indole Alkaloids

More than 3000 terpenoid indole alkaloids have been recognized, making this one of the major groups of alkaloids in plants. They are found mainly in eight plant families, of which the *Apocynaceae*, the *Loganiaceae*, and the *Rubiaceae* provide the best sources.

In virtually all structures, a ***tryptamine*** portion can be recognized. L-tryptophan (**87**), the natural precursor of tryptamine (**113**), is the amino acid containing an indole ring system. It has its origins in the shikimate pathway *via* the important intermediates shikimic acid (**84**), chorismic acid (**102**), and anthranilic acid (**104**, Scheme 3). The shikimate pathway is employed by microorganisms and plants, but not by animals who need to obtain these aromatic amino acids from their diet. The remaining fragment is usually a C_9 or C_{10} residue and three main structural types are discernible according to the arrangement of atoms in this fragment.

Scheme 3[42d]

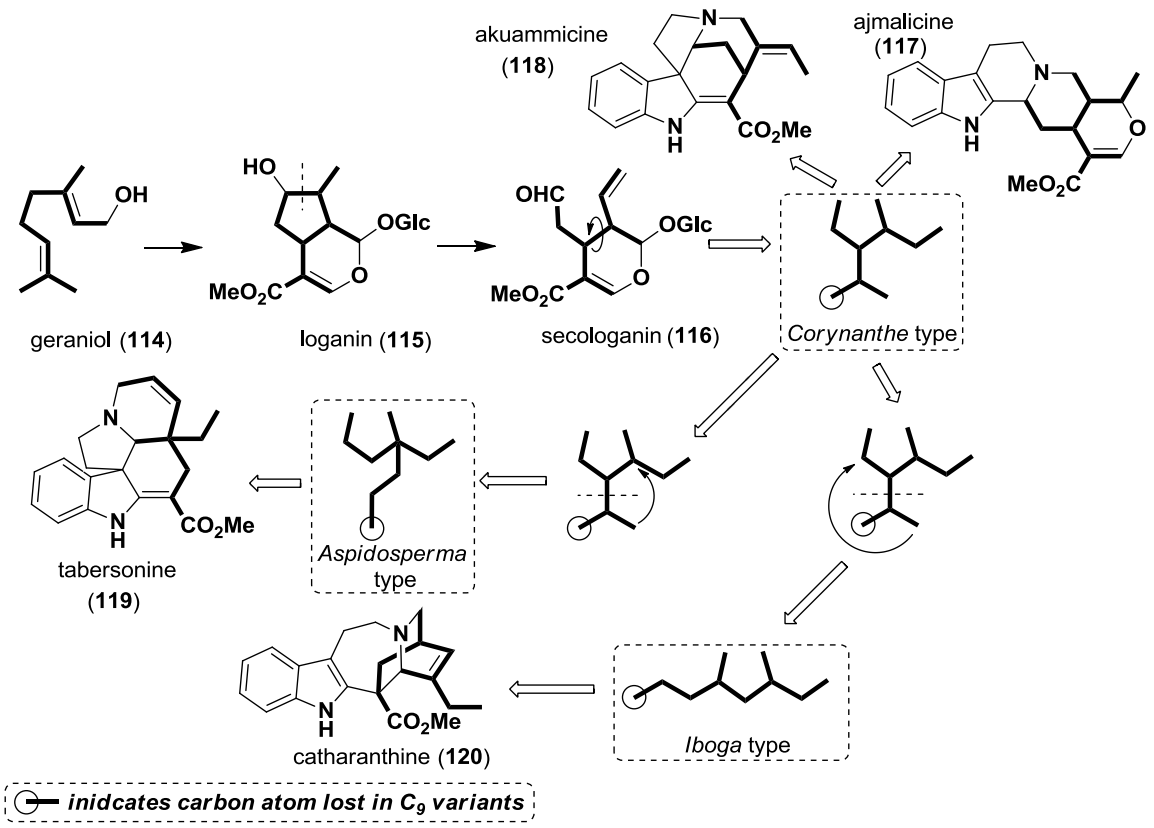


These are termed the *Corynanthe* type, as in ajmalicine (**117**) and akuammicine (**118**), the *Aspidosperma* type, as in tabersonine (**119**), and the *Iboga* type, exemplified by catharanthine (**120**, Scheme 4).

The C_9 or C_{10} fragment was shown to be of terpenoid origin, and the secoiridoid ***secologanin*** (**116**) was identified as the terpenoid derivative which initially combined with the tryptamine portion of the molecule. Furthermore, the *Corynanthe*, *Aspidosperma* and

Iboga groups of alkaloids could then be rationalized in terms of rearrangements occurring in the terpenoid part of the structures. Secologanin (**116**) itself contains the 10-carbon framework that is typical of the *Corynanthe* group. The *Aspidosperma* and *Iboga* groups could then arise by rearrangement of the *Corynanthe* skeleton, as shown in Scheme 4.

Scheme 4[42d]



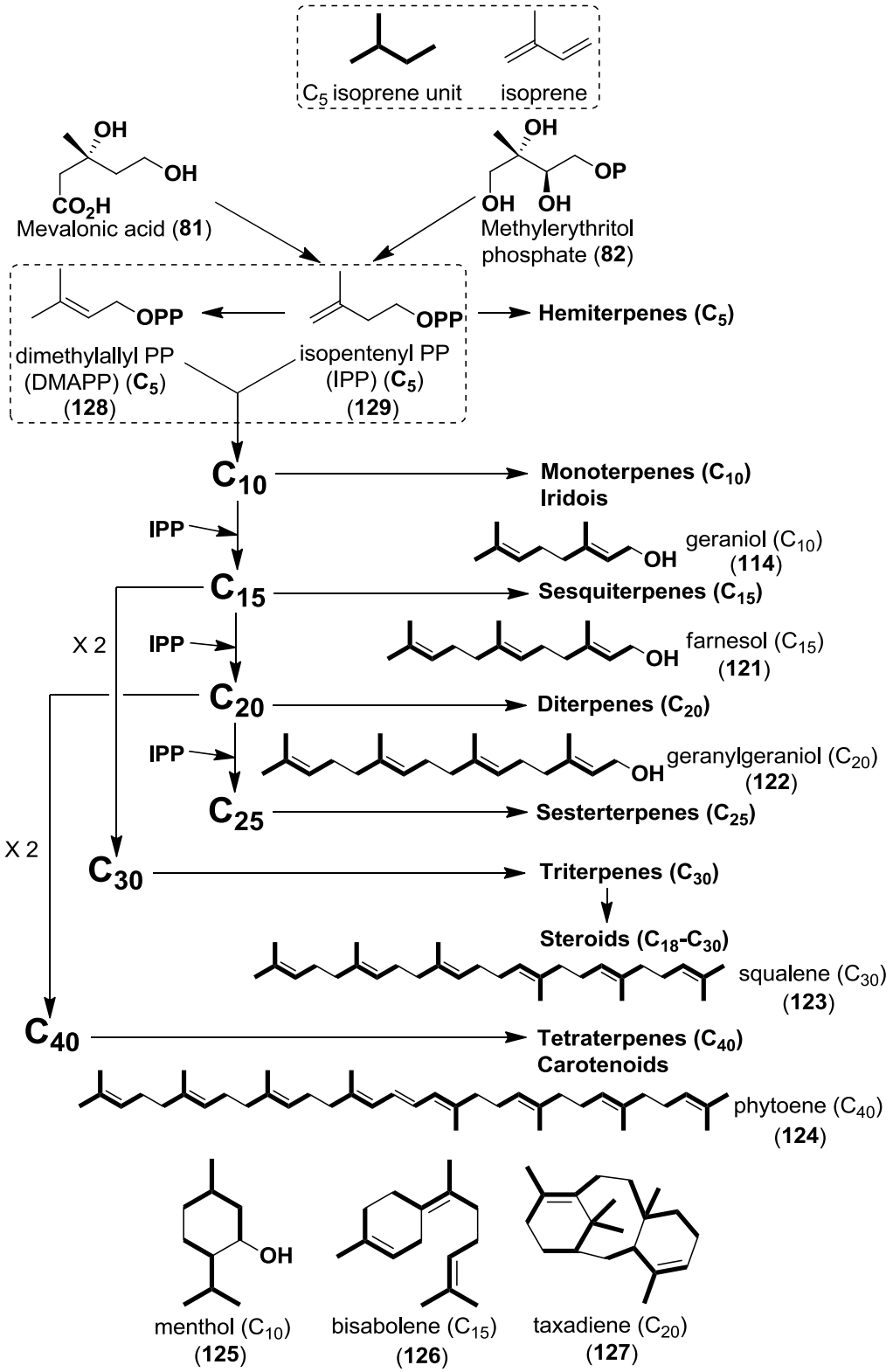
This is represented by detachment of the three-carbon unit which is then rejoined to the remaining C_7 fragment in one of two different ways. Where C_9 terpenoid units are observed, the alkaloids normally appear to have lost the carbon indicated in the circle. This

corresponds to the carboxylate function of secologanin (**116**) and its loss by hydrolysis-decarboxylation.[42]

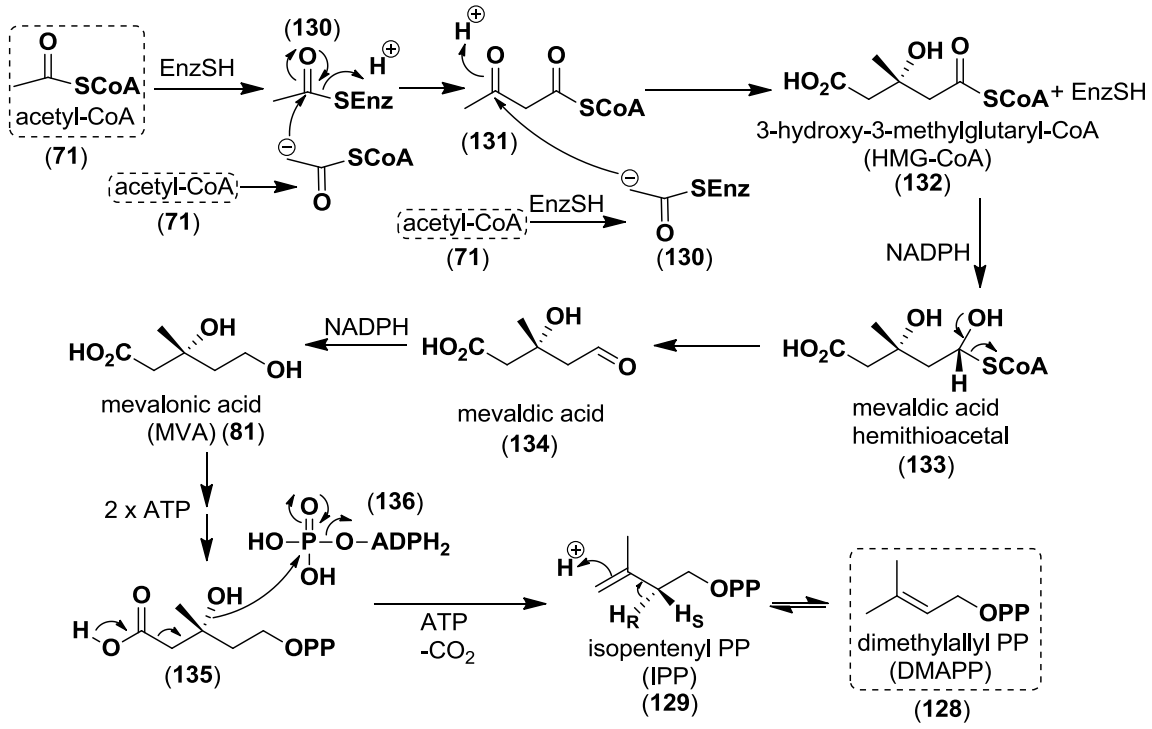
Terpenoids (also known as 'isoprenoids') form a large and structurally diverse family of natural products derived from C_5 isoprene units joined in a head-to-tail fashion. They comprise the largest group of natural products with over 35,000 known members. Typical structures contain carbon skeletons represented by $(C_5)_n$, and are classified as hemi-terpenes C_5, monoterpenes C_{10}, sesquiterpenes C_{15}, diterpenes C_{20}, sesterterpenes C_{25}, triterpenes C_{30}, and tetraterpenes C_{40} (Scheme 5). Relatively few of the natural terpenoids conform exactly to the simple concept of a linear head-to-tail combination of isoprene units as seen with geraniol (**114**), farnesol (**121**), and geranylgeraniol (**122**). Squalene (**123**) and phytoene (**124**), although formed entirely of isoprene units, display a tail-to-tail linkage at the center of the molecules. Most terpenoids are modified further by cyclization reactions, though the head-to-tail arrangement of the units can usually, still be recognized, for example menthol (**125**), bisabolene (**126**), and taxadiene (**127**). The linear arrangement of isoprene units can be much more difficult to appreciate in many other structures when rearrangement reactions have taken place, and in addition, where several carbon atoms have been lost.[42]

The biochemical isoprene units may be derived by two pathways: by way of intermediates mevalonic acid (**MVA**, **81**, Scheme 6) or 2-*C*-methyl-D-erythritol-4-phosphate (methylerythritol phosphate; **MEP**, **82**, Scheme 7). The MEP pathway is probably more utilized in nature than is the MVA pathway.[42]

Scheme 5[42d]


C5 isoprene unit
isoprene
OH
OH
CO2H
Mevalonic acid (81)
OH
OP
OH OH
Methylerythritol phosphate (82)
OPP
OPP
Hemiterpenes (C5)
dimethylallyl PP (DMAPP) (C5) (128)
isopentenyl PP (IPP) (C5) (129)
C10
Monoterpenes (C10)
Iridois
IPP
OH
geraniol (C10) (114)
C15
Sesquiterpenes (C15)
X 2
IPP
OH
farnesol (C15) (121)
C20
Diterpenes (C20)
IPP
OH
geranylgeraniol (C20) (122)
C25
Sesterterpenes (C25)
X 2
C30
Triterpenes (C30)
Steroids (C18-C30)
squalene (C30) (123)
C40
Tetraterpenes (C40)
Carotenoids
phytoene (C40) (124)
OH
menthol (C10) (125)
bisabolene (C15) (126)
taxadiene (C20) (127)

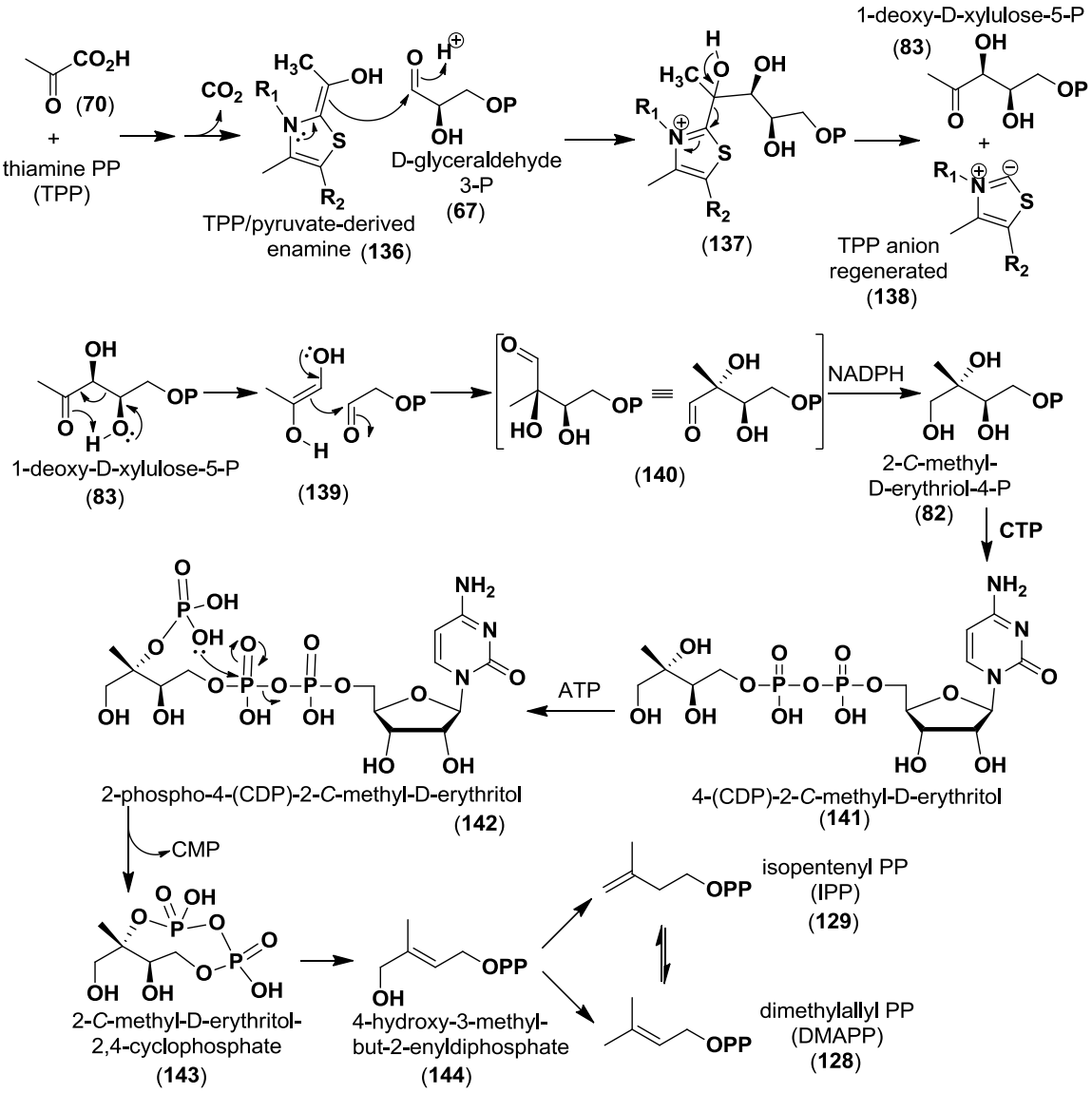
Scheme 6[42d]



Whether the mevalonate pathway or the MEP pathway supplies isoprene units for the biosynthesis of a particular terpenoid must be established experimentally. This can be determined from the results of feeding [1-^{13}C]-D-glucose as a precursor; this leads to different labelling patterns in the isoprene unit according to the pathway operating. Animals and fungi appear to lack the MEP pathway, so they utilize the mevalonate pathway exclusively. The MEP pathway is present in plants, algae, and most bacteria. Plants and some bacteria are equipped with and employ both pathways, often concurrently. In plants, the two pathways appear to be compartimentalized, so that the mevalonate pathway enzymes are localized in the cytosol, whereas the MEP pathway enzymes are found in chloroplasts. The cytosolic pool of IPP (**129**) serves as a precursor of C_{15}

derivatives and sesquiterpenes, and in due course triterpenoids and steroids. Accordingly, triterpenoids and steroids, and some sesquiterpenoids (cytosolic products) are formed by the mevalonate pathway, whilst most other terpenoids (C_{10}, C_{20}, C_{40}) are formed in the chloroplasts and are MEP derived. Of course there are exceptions.

Scheme 7[42d]



There are also examples where the two pathways can supply different portions of a molecule, or where there is exchange of last-stage common intermediates between the two pathways (cross-talk), resulting in a contribution of isoprene units from each pathway.[42]

Enzyme-catalyzed combination of DMAPP (**128**) and IPP (**129**) yields geranyl diphosphate (GPP, **146**, Scheme 8). The **iridane** skeleton found in iridoids is monoterpenoid in origin and contains a cyclopentane ring which is usually fused to a six-membered oxygen heterocycle (Figure 11). The iridoid system arises from geraniol (**114**) by a type of folding which is different from that already encountered with monoterpenoids; also markedly different is the lack of phosphorylated intermediates and subsequent carbocation mechanism in its formation (Scheme 9).[42]

Scheme 8[42d]

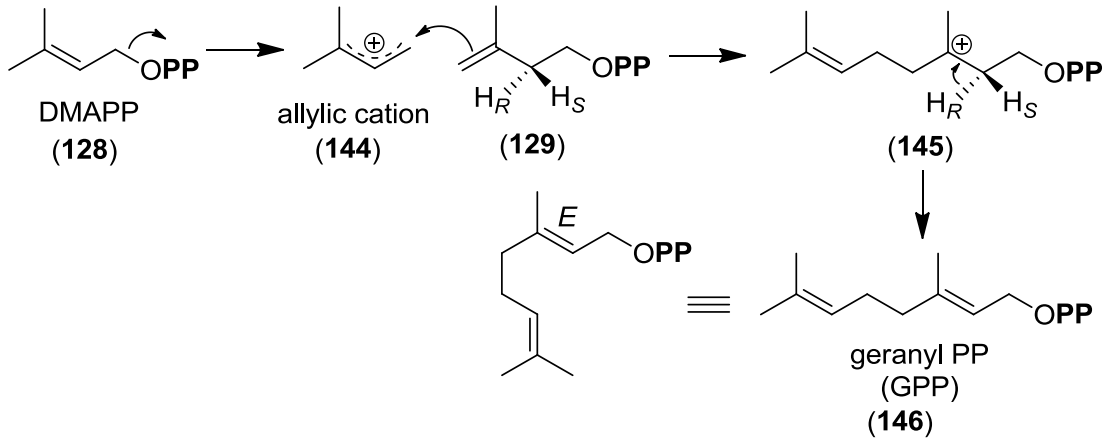
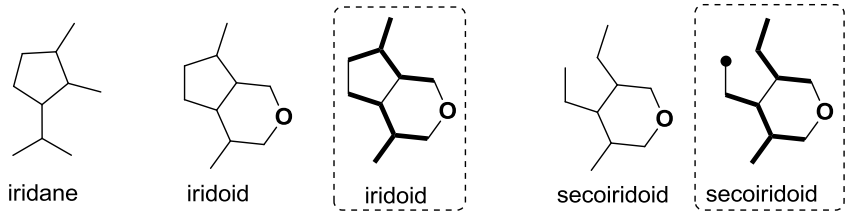
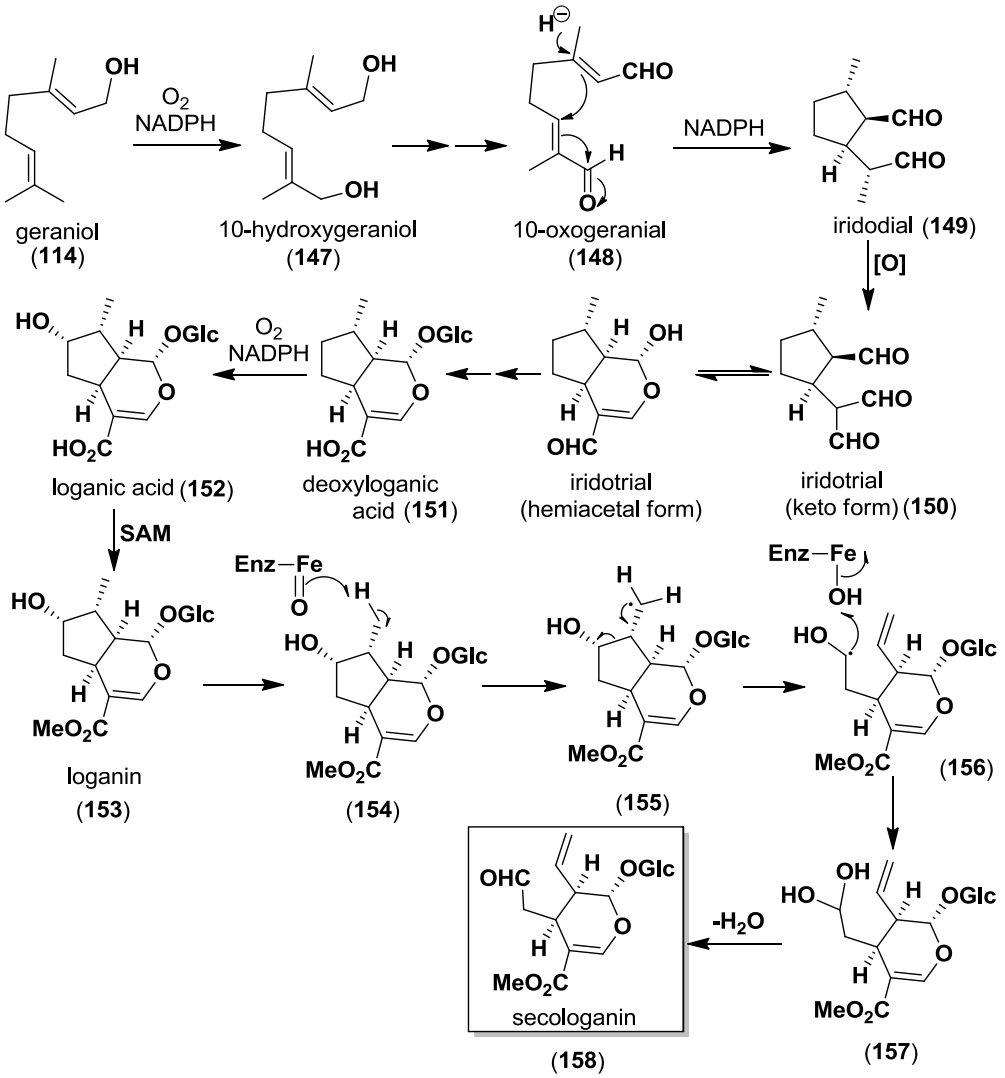


Figure 11.[42] Iridane skeleton and related structures

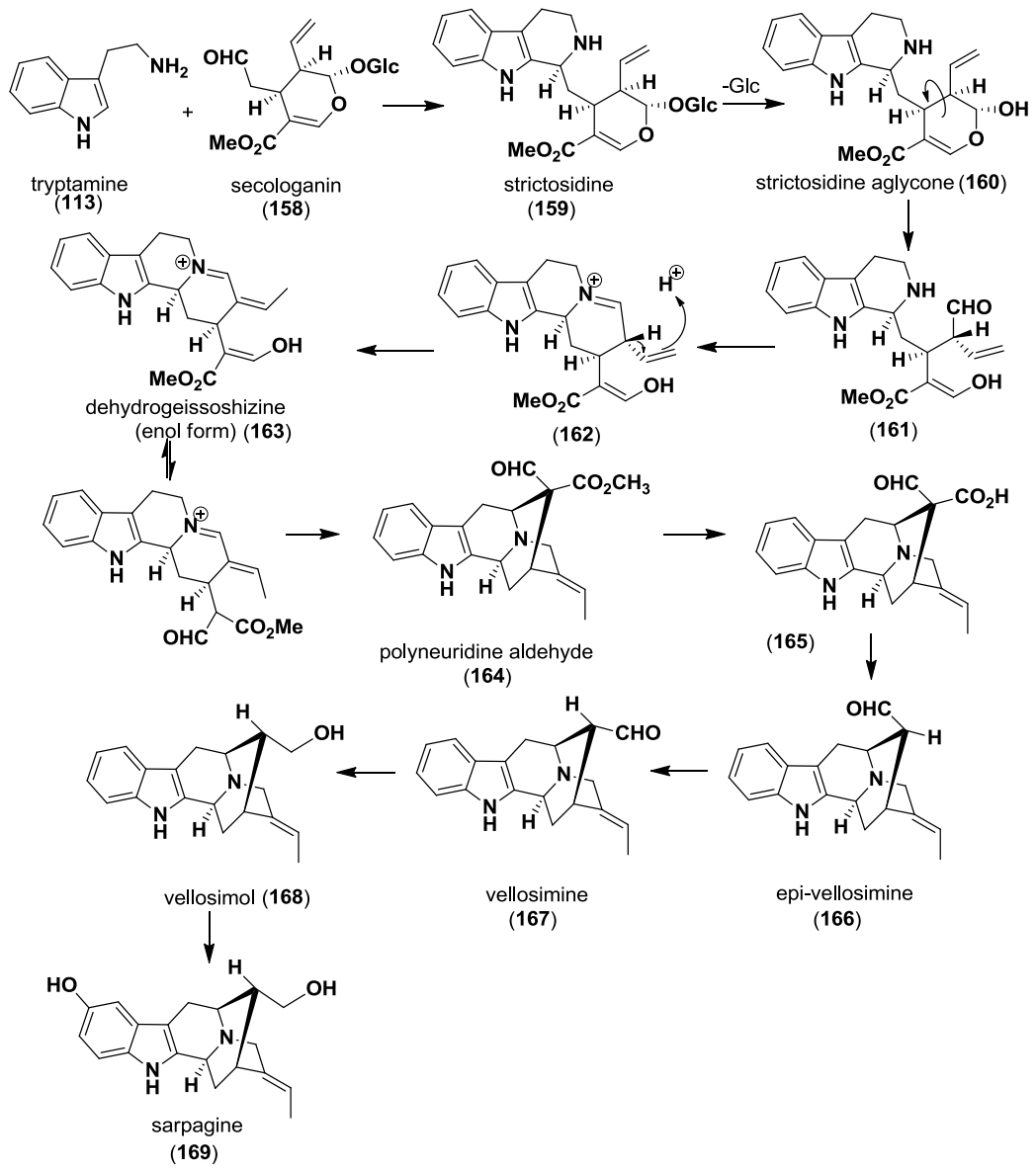


Scheme 9[42d]



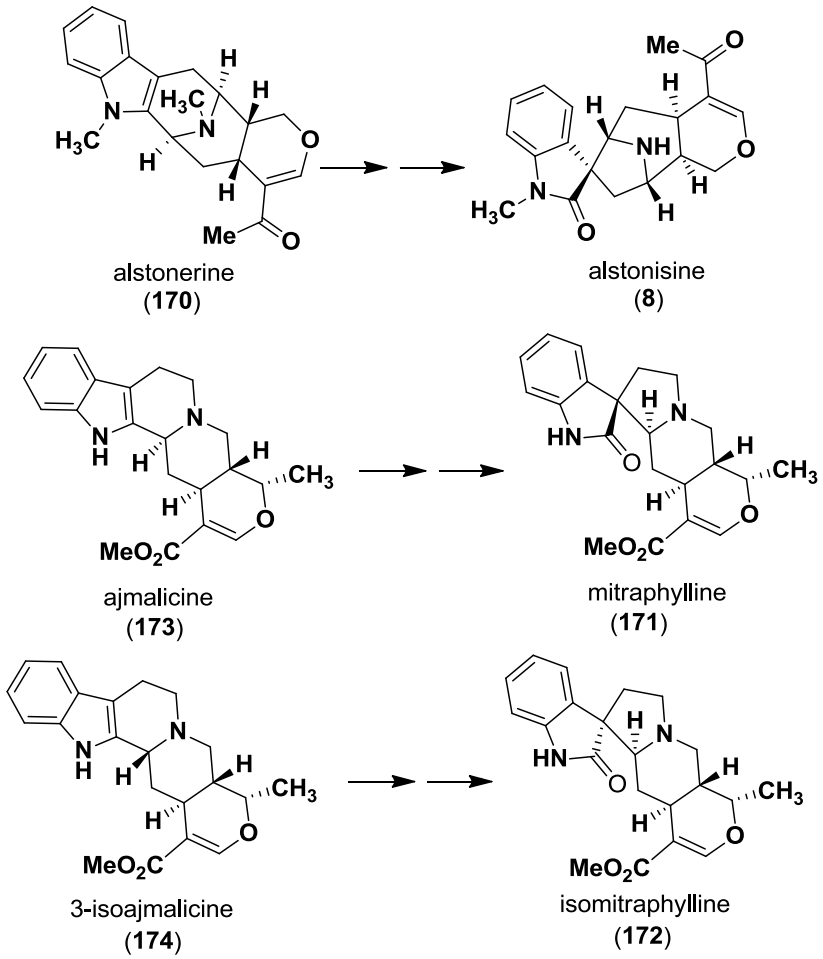
The condensation of secologanin (**158**) with tryptamine (**113**) in a Mannich-like reaction generates the tetrahydro-*β*-carboline system and produces strictosidine (**159**, Scheme 10).[43] Strictosidine is *the key intermediate* and branching point of nearly all monoterpene indole alkaloids. Hydrolysis of the glycoside function allows opening of the hemiacetal

Scheme 10[42]



and exposure of an aldehyde group which can react with the secondary amine function to give a quaternary iminium cation, alkaloid (**162**). Allylic isomerization, moving the vinyl double bond into conjugation with the iminium, generates dehydrogeissoschizine (**163**). The enzymatic transformation of dehydrogeissoschizine (**163**) to sarpagan-type compounds, according to Stöckigt et al, is shown in Scheme 10. His group has published evidence to support this pathway, where they used enzymes in ajmaline biosynthesis that had sarpagine-type intermediates.[44]

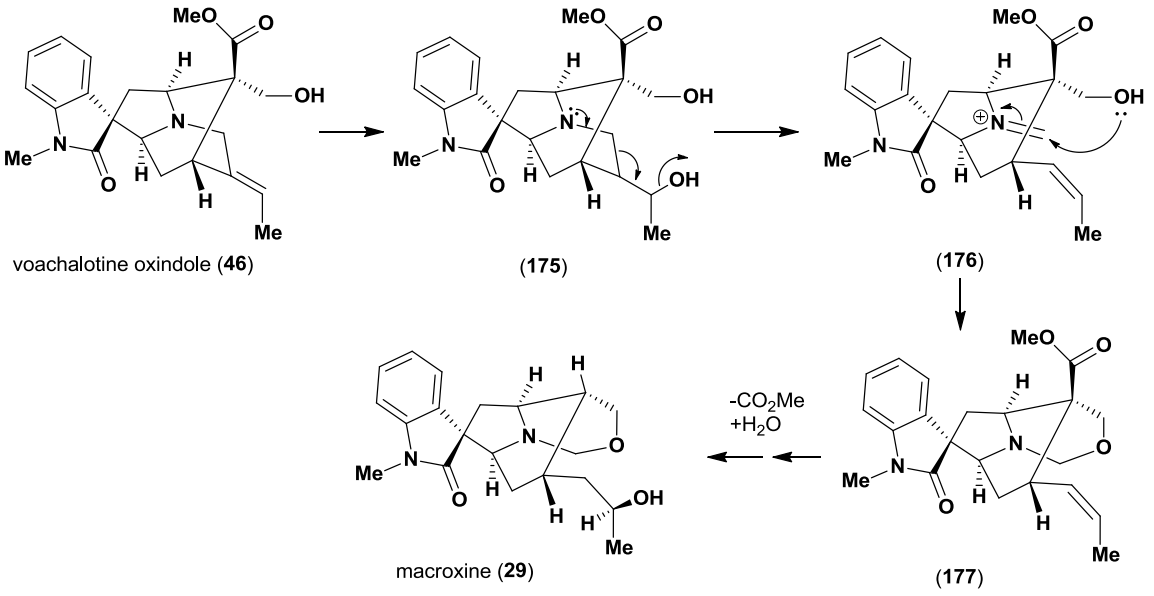
Scheme 11



There have not been any comprehensive studies reported in the literature on the biosynthesis of sarpagine-macroline type oxindole alkaloids; however, biogenetic considerations suggest that the indole alkaloid alstonerine (**170**) may serve as a precursor to alstonisine (**8**, Scheme 11).[45] Similarly, derivation of the oxindole alkaloids mitraphylline (**171**) and isomitraphylline (**172**) from the corresponding indole derivatives has been indicated by the apparent transformation of ajmalicine (**173**) and 3-isoajmalicine (**174**) into these alkaloids in *Mitragyna parvifolia* Korth. Some conclusions have also been reached about interrelationships of oxindole alkaloids in *Mitragyna* species.[46]

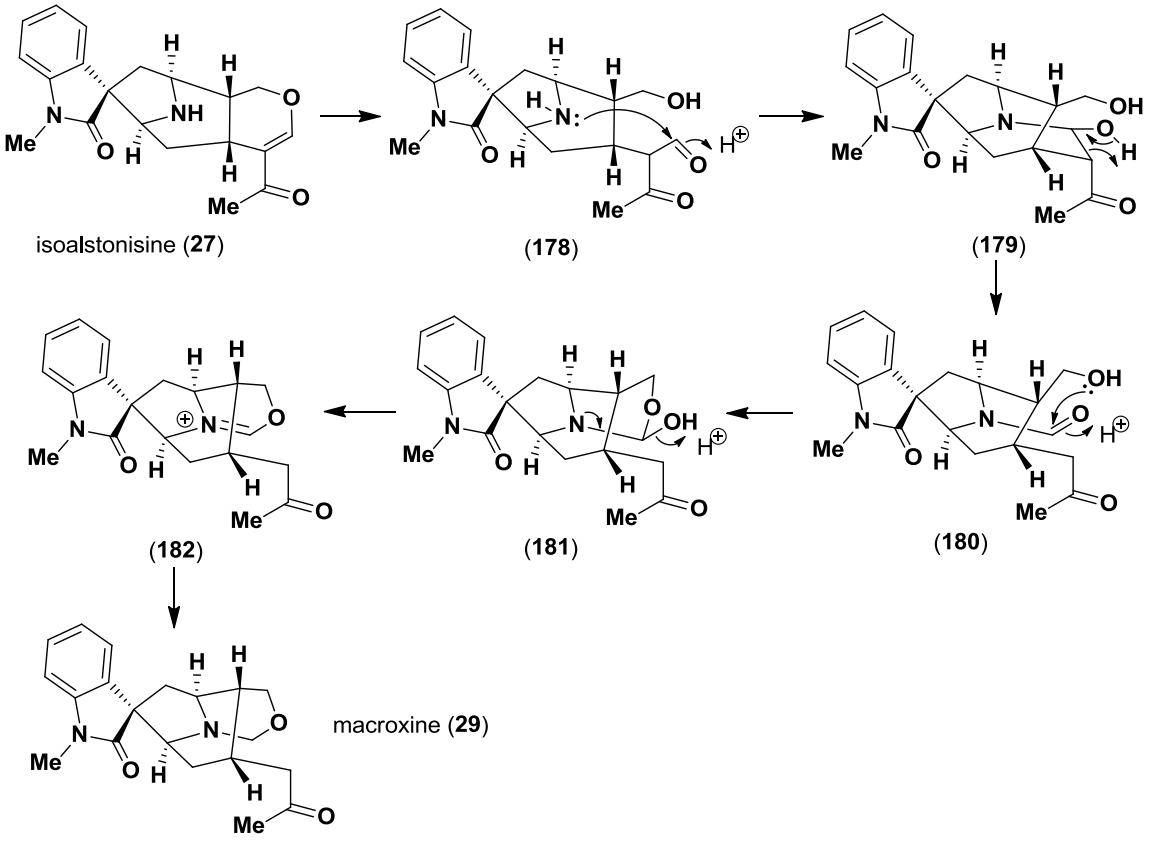
Atta-ur-Rahman and collaborators suggested that macroxine (**29**) may arise from voachalotine oxindole (**46**) or a closely related compound by fragmentation of the intermediate oxindole (**175**), trapping of the iminium ion species (**176**) by ether formation and hydration of the olefin (**177**, Scheme 12).[13]

Scheme 12



A different putative biosynthetic pathway to the macroxine (**29**) and macroxine-type alkaloids was suggested by Kam from isoalstonisine (**27**), which on hydrolysis led to the keto aldehyde (**178**, Scheme 13).[19] Intramolecular nucleophilic addition by *N*-4 gave the carbinol amine (**179**), which in turn furnished the formamide (**180**), *via* a retro-aldol-like reaction. Subsequent hemiacetal formation (**181**), followed by generation of the *N*-4 iminium ion (**182**) and reduction, resulted in macroxine (**29**).[19]

Scheme 13



2) Synthetic Approaches to The Construction of Spiro[pyrrolidine-3,3′-oxindoles]

The 3,3′-pyrrolidinyl-spirooxindole unit is a privileged heterocyclic motif that forms the core of a large family of alkaloid natural products with strong bioactivity profiles and interesting structural properties as discussed earlier. Significant, recent advances in the synthesis of this fused heterocyclic system have led to strong interest in the development of related compounds as potential medicinal agents or biological probes.

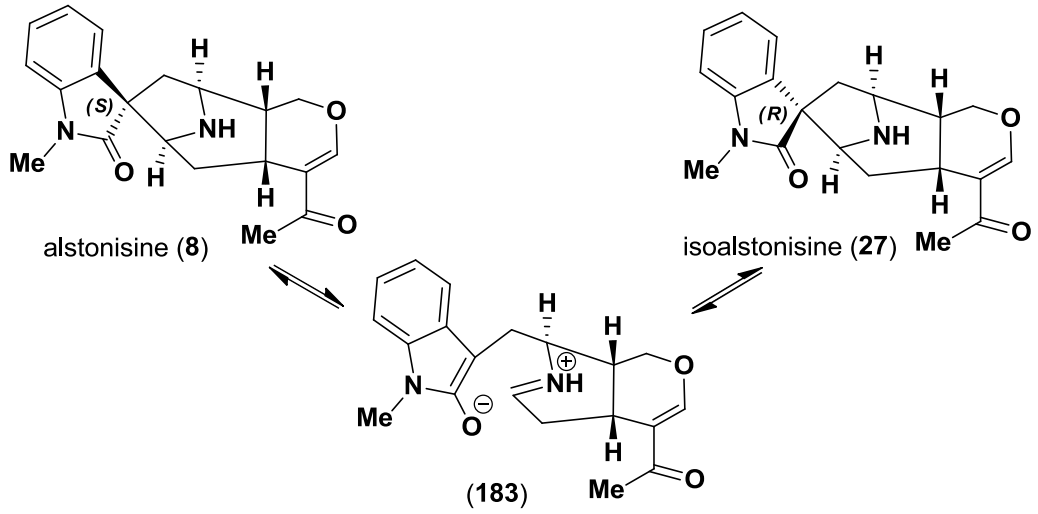
This section will focus on the various methods used in the formation of the quaternary spirocenter of mainly spiro[pyrrolidine-3,3′-oxindoles]. The importance of the topic in the context of the synthetic organic chemistry is given by the increasing number of reports in the recent literature. It is the intention of the author, at this point, to mention the outstanding contribution of Carreira et al. (2003);[47a] Danishefsky et al. (2003);[47b] Scheidt et al. (2007);[47e] Overman et al. (2003 & 2007);[47c,47f] Trost et al. (2009);[47h] Wang et al. (2011);[47m] Franz et al. (2010 & 2012);[47l,47p] Singh et al. (2012);[47q] Barbas et al (2014)[47t] and others[47] that helped rationalize the growing data for the synthesis of the spirooxindole moiety from different perspectives.

2.1) Intramolecular Mannich Reactions

Oxindole alkaloids often occur in nature as pairs of interconvertible isomers [e.g. alstonisine (**8**) and isoalstonisine (**27**), the (3*R*) epimer of alstonisine]. This observation can be explained by an isomerization mechanism, wherein both forms can be equilibrated

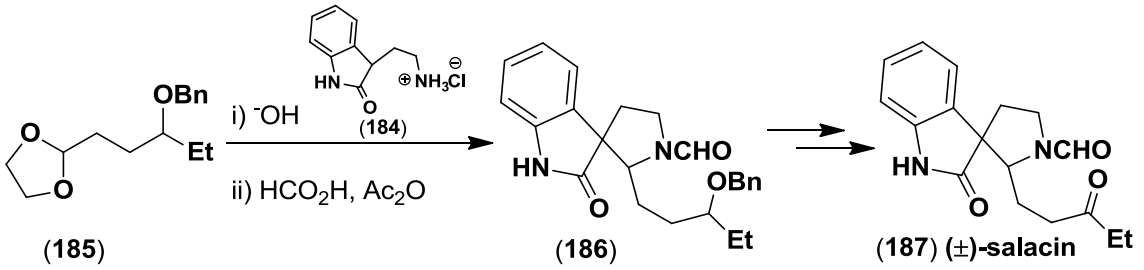
through the ring-opened form (**183**) that is accessed by a retro-Mannich reaction, as shown in Scheme 14.[48a]

Scheme 14



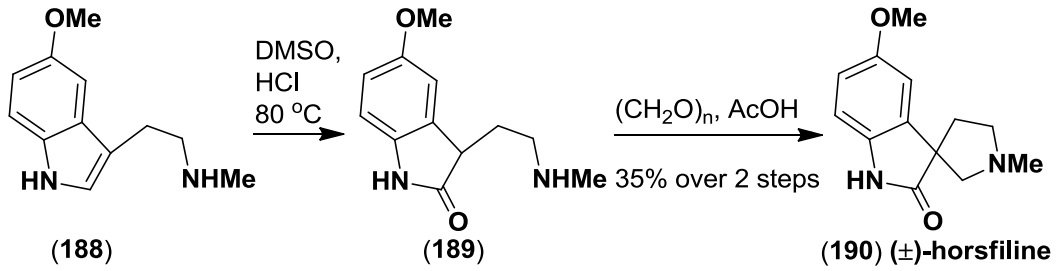
Synthetically, the spiro[pyrrolidine-3,3′-oxindole] core can be assembled by an intramolecular Mannich reaction. The precursors are available from tryptamine or a tryptophane derived oxindole and an aldehyde. For example, (±)-salacin (**187**) was isolated from *Uncaria salaccensis*, a Thai medicinal plant, by Sakai's group (Scheme 15). The research team performed the synthesis of salacin from oxytryptamine hydrochloride (**184**). Condensation of this amine with acetal (**185**), followed by intramolecular Mannich reaction afforded the spiro[pyrrolidine-3,3′-oxindole] intermediate (**186**). From oxindole (**186**), (±)-salacin was obtained in 3 steps.[48b]

Scheme 15



Laronze achieved the synthesis of horsfiline (**190)** through an intramolecular Mannich reaction by a spiro cyclization of tryptamine-oxindole (**189**) with formaldehyde (Scheme 16).[49]

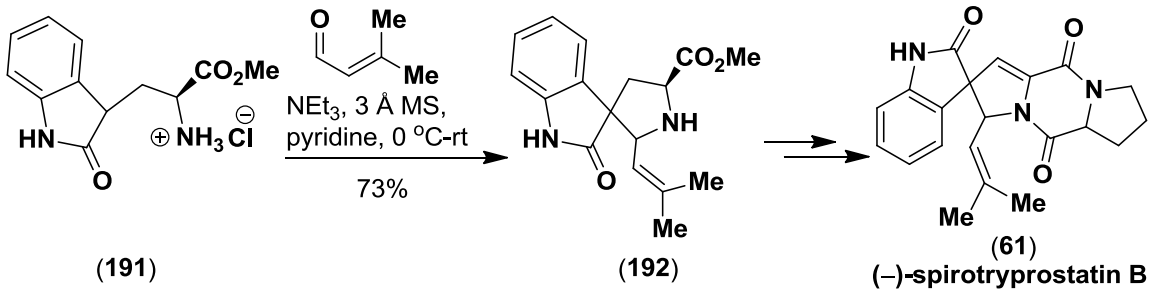
Scheme 16



Another interesting example of the application of this chemistry was reported by Danishefsky in his approach to spirotryprostatin B (**61**) (Scheme 17).[50] The reaction of oxindole (**191**) with 3-methylbut-2-enal afforded a mixture of diastereoisomeric (**192**) spiro-[pyrrolidine-3,3′-oxindoles]. These compounds were separable at a later stage in the ster-

eoselective synthesis and afforded (–)-spirotryprostatin B (**61**) in a very efficient sequence of reactions.

Scheme 17

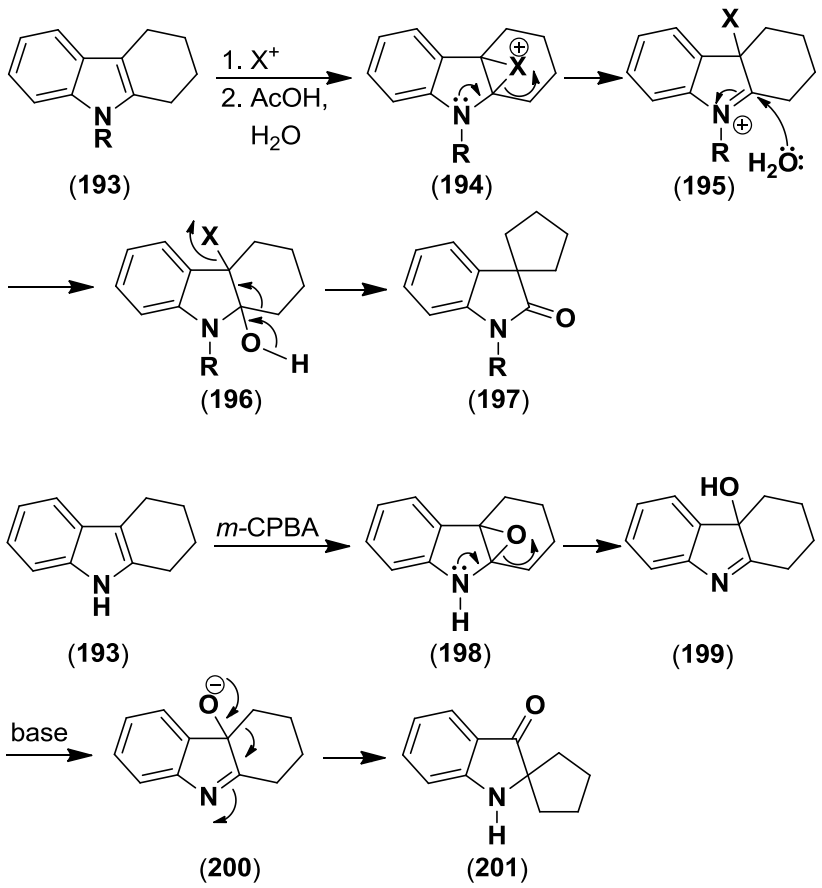


(**191**) (**192**) (**61**)
(–)-spirotryprostatin B

2.2) Oxidative Rearrangement Sequences

One of the most popular methods to form spiro[pyrrolidine-3,3′-oxindoles] is a sequence of oxidative rearrangements of tetrahydro-*β*-carbolines.[51] A variety of oxidants can be employed, including osmium tetroxide, lead(IV) acetate, *tert*-butyl hypochlorite, and *N*-bromosuccinimide. However, the indole could also be oxidized to form the indoxyl isomer. This regiochemical divergence of oxidation can be controlled through the use of appropiate oxidation conditions. Typically, *m*-chloroperbenzoic acid or other epoxidation reagents are used, followed by treatment with base to promote the rearrangement, as shown in Scheme 18.[52]

Scheme 18

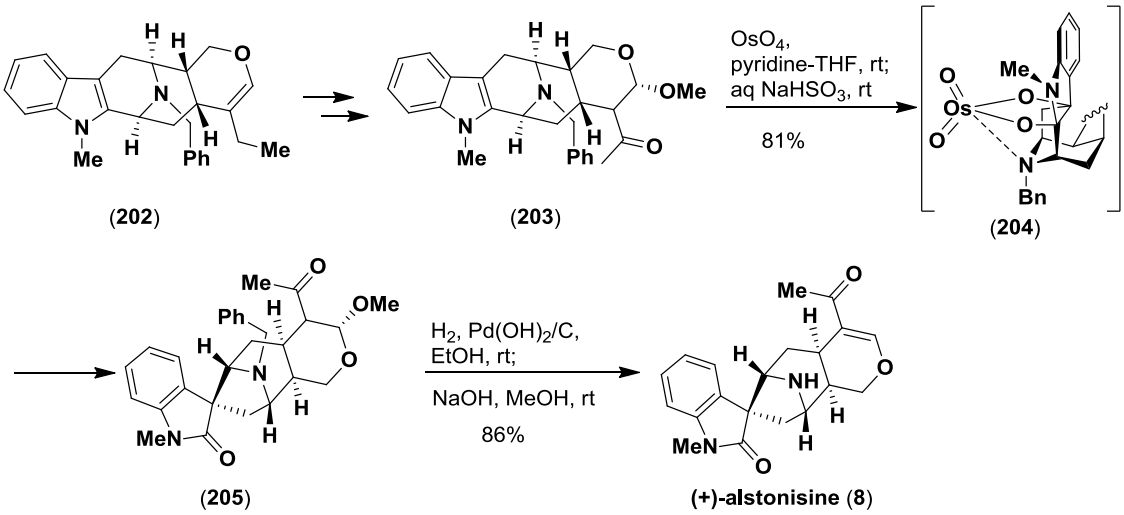


2.2.1) Osmium Tetroxide as The Oxidant

In 1989, Sakai introduced osmium tetroxide as reagent for the spiro rearrangement of tetrahydro-*β*-carbolines according to mechanistic considerations for the selective formation of the humantenirine skeleton.[53] Cook et al. demonstrated that osmium tetroxide reacted with tetrahydro-*β*-carbolines selectively to afford a single diastereomer.[45a,54] The osmium atom was presumably first complexed to the piperidine nitrogen atom and then dihydroxylation occurred intramolecularly from one face of the substrate. The opposite

face of the tetrahydro-β-carboline undergoes dihydroxylation by the use of bulky ligands such as Cinchona alkaloid derivatives DHQ-CLB and $(DHQ)_2PHAL$ ultimately leading to the spiro epimers. The key step in the stereoselective total synthesis of (+)-alstonisine by Wearing et al. used an oxidative rearrangement of keto acetal (**203**) obtained from olefin (**202**, Scheme 19).[55] The spiro[pyrrolidine-3,3′-oxindole] was obtained as the sole diastereomer (**205**) in 81% yield. The rationale for this selective transformation is the complexation of osmium tetroxide to the piperidine nitrogen atom. The synthesis of (+)-alstonisine (**8**) was completed from oxindole (**205**) by deprotection of the N_b-atom followed by base-induced elimination of methanol.[56]

Scheme 19

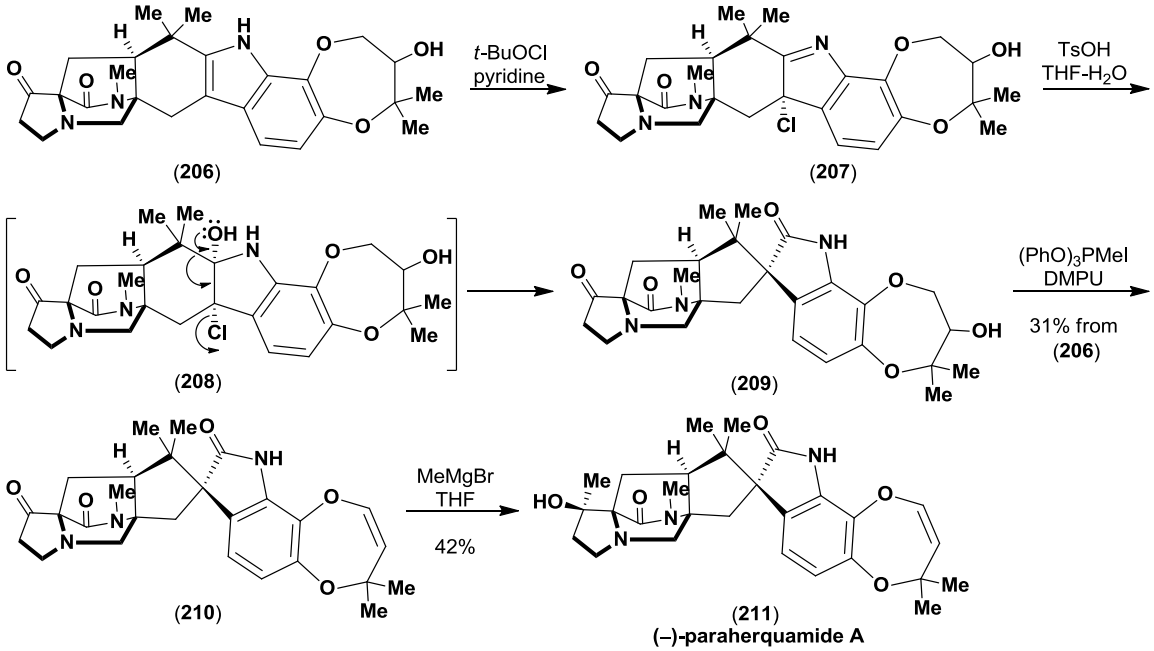


2.2.2) Halogenating Agents as Oxidants

2.2.2.1) *tert*-Butyl hypochlorite

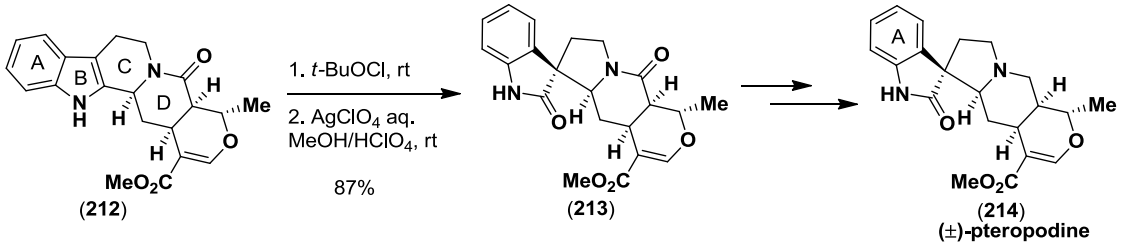
Other syntheses also utilized oxidative rearrangements to install the oxindole and spiro-cycle in a single chemical step. In Williams' asymmetric, stereocontrolled synthesis of paraherquamide A (**211**), the critical oxidative rearrangement was left until late in the synthesis (Scheme 20).[57] Rather than using osmium tetroxide to dihydroxylate the indole double bond, *tert*-butyl hypochlorite was added to form the 3-chloroindolinine (**207**), which formed the oxindole moiety (**209**) in 54% yield when treated with *p*-toluene-sulfonic acid in aqueous THF. The product was obtained as a mixture of diastereomers (unreported ratio), with (**209**) formed as the major isomer. Presumably, both the chlorination and the subsequent hydration of the imine occurred from the least hindered face of the indole to furnish the *syn*-configured chlorohydrin intermediate (**208**). Instal-lation of the enol ether follow by addition of methylmagnesium bromide to the ketone then formed paraherquamide A (**211**). The related alkaloid paraherquamide B was syn-thesized in a similar manner.[58] This chloroindolinine approach was employed by Taylor, Wenkert; Kutney, Cook and co-workers and others in the 1960's and 1970's.

Scheme 20



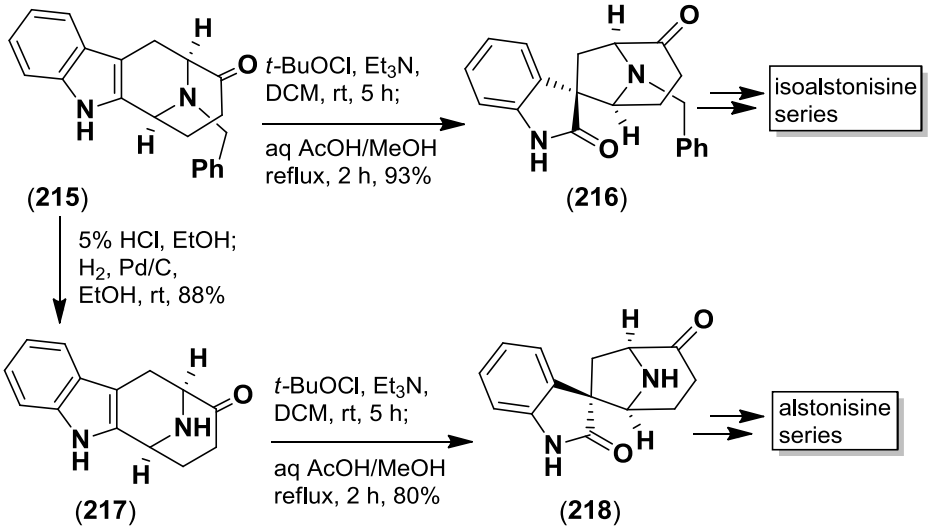
Taylor and collaborators revealed in a 1962 study that rhyncophylline (**3**) can be obtained from dihydrocorynantheine in a three-step procedure by oxidative rearrangement using *tert*-butyl hydrochlorite, *via* a chloroindolenine intermediate.[59] As a consequence, a general relationship between indole alkaloids and their oxindole analogues has been postulated by Shavel and Zinnes.[60] Martin et al. used this method for the oxidation of indoles, where the N_b-nitrogen atom was incorporated in a D-ring lactam (Scheme 21). The critical rearrangement of pentacycle (**212**) to oxindole (**213**) was achieved by addition of silver perchlorate to initiate rearrangement of the chloroindolenine and led ultimately to (±)-pteropodine (**214**).[61]

Scheme 21



Yu, Cook et al. reported a convenient method to convert N_a-H tetracyclic ketones of the type (**215**), Scheme 22, into either corresponding oxindoles (epimers at C-7), diastereo-specifically. Treatment of the N_a-H, N_b-benzyl tetracyclic ketone (**215**) with *tert*-BuOCl provided diastereomer (**216**, related to isoalstonisine), whereas the same process with N_a-H, N_b-H (or N_b-benzoyl, **217**) substituted analogs furnished the diastereomeric oxindole (**218**, related to alstonisine).[62,63]

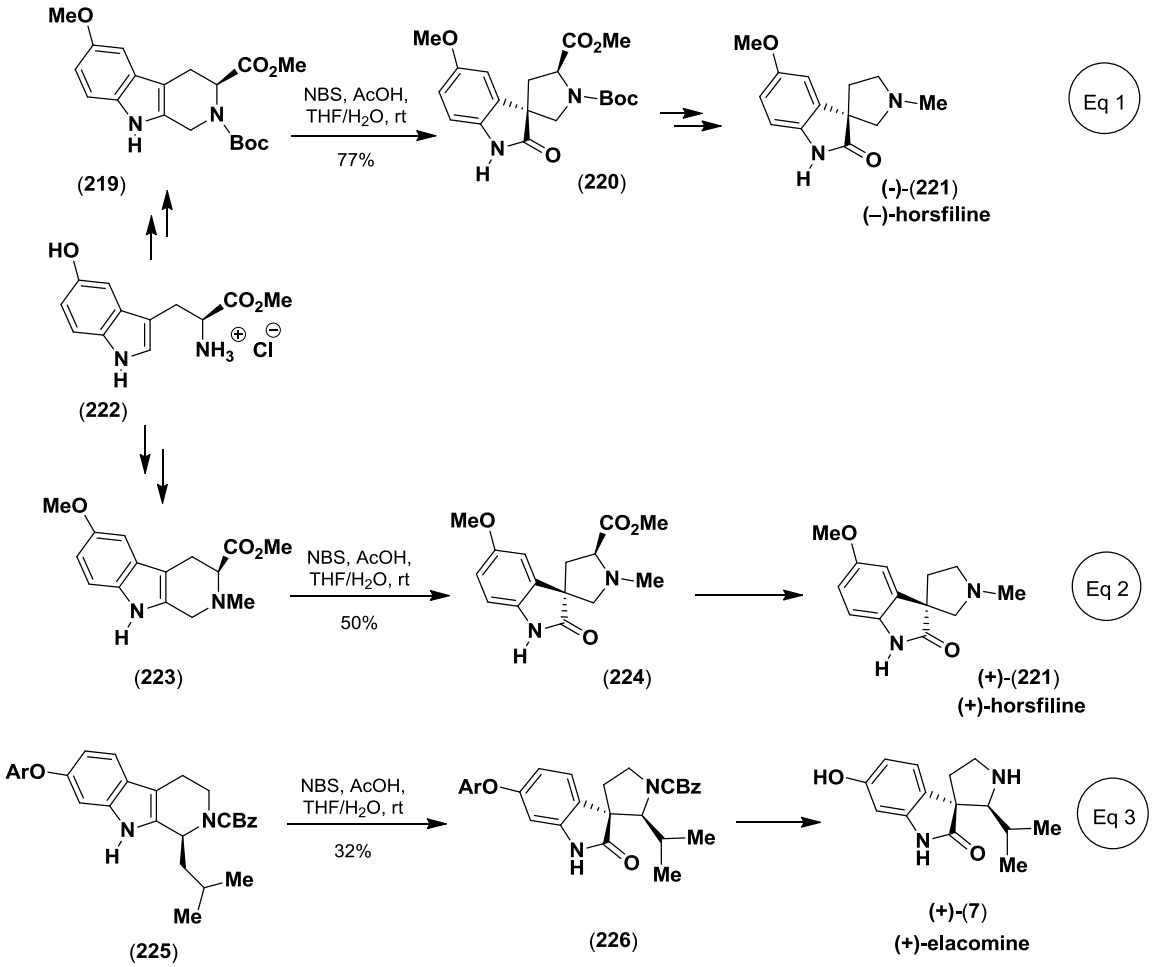
Scheme 22



2.2.2.2) *N*-Bromosuccinimide

N-Bromosuccinimide (NBS) as an oxidant is frequently used instead of *tert*-BuOCl. It was employed in early investigations toward the elucidation of the absolute configuration of horsfiline (**221**) through the synthesis of both enantiomers of horsfiline by Borschberg

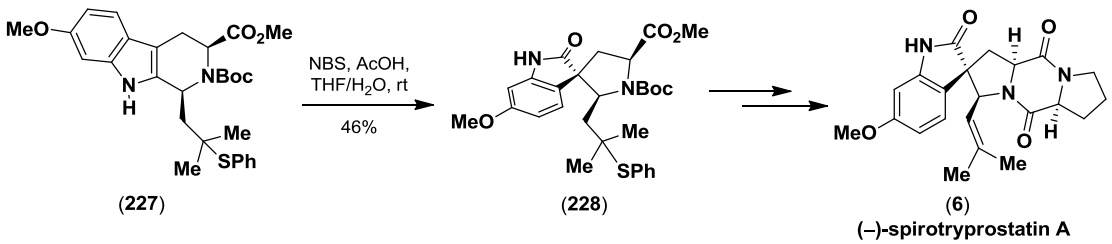
Scheme 23



(Scheme 23). In this context, it was observed that different substituents at the piperidine nitrogen atom led to a significant preference for the formation of one diastereomer over the other in the rearrangement step. It was therefore preferable to access spiro-[pyrrolidine-3,3′-oxindole] (**220**) from N_b-Boc derivative (**219**), and (**224**) from the N_b-methyl derivative (**223**). NOE-NMR experiments permitted for the structural assigments of the relative stereochemistry of diastereomeric oxindoles (**220**) and (**224**) and thus of the absolute configuration of their reduced counterparts (–)-(**221**) and (+)-(**221**) [equations 1 and 2 as shown in Scheme 23].[64] Borschberg was also able to synthesize (+)-elacomine (**7**), according to the same strategy [equation 3, Scheme 23].[65]

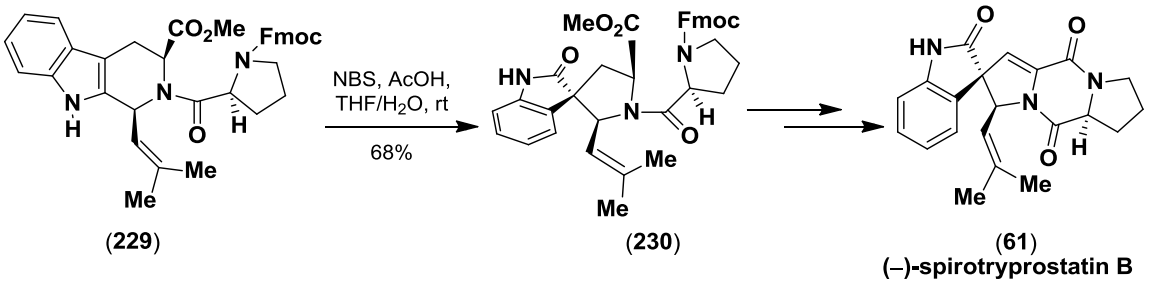
In Danishefsky's synthesis of (–)-spirotryprostatin A (**6**), N_b-Boc-protected tetrahydro-*β*-carboline (**227**) was used in the oxidative spiro rearrangement to oxindole (**228**, Scheme 24). Spirotryprostatin A (**6**) was stereoselectively obtained by deprotection of the carbamate, installation of the dioxopiperazine by coupling with *N*-Troc-L-proline and conversion of the tertiary sulfide to the unsaturated prenyl substituent.[66,67]

Scheme 24



In Ganesan's biomimetic route to (–)-spirotryprostatin B (**61**), rearrangement precursor (**229**) was obtained by an *N*-acyliminium mediated Pictet–Spengler reaction. The use of alkaloid (**229**), a tetrahydro-*β*-carboline already bearing the *N*-Fmoc-L-proline moiety, allowed for the crucial oxidative rearrangement without using unnecessary protection and deprotection sequences. Chemoselectivity issues related to the presence of the prenyl olefin were controlled by careful monitoring of the reaction and by avoiding large excesses of NBS. This route permitted for the very efficient assembly of (**230**), made possible by direct implementation of the prenal group in the Pictet–Spengler reaction and the introduction of the L-proline moiety prior to oxidative rearrangement. Although the route suffered from a lack of regioselectivity and poor yield in the final step, it has served to unambiguously confirm the original structural elucidation and supply material for biological screening (Scheme 25).[68]

Scheme 25

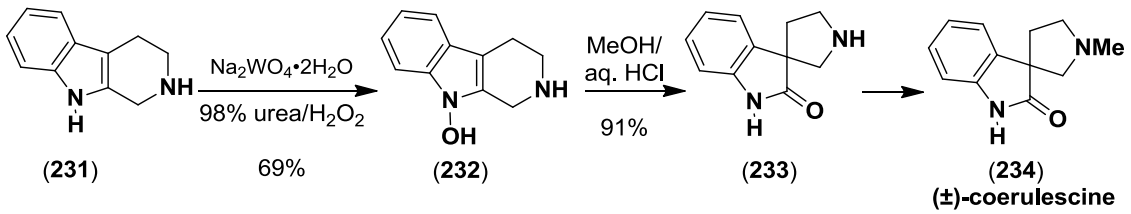


(**229**) (**230**) (**61**)
(–)-spirotryprostatin B

2.2.2.3) Sodium Tungstate as The Oxidant

Somei and collaborators introduced a new method for the synthesis of chloroindolenines that can be rearranged to spiro[pyrrolidine-3,3′-oxindoles]. This protocol has been applied to the synthesis of (±)-coerulescine (**234**).[69] The N_a-hydroxy-tetrahydro-β-carboline (**232**) was obtained from the corresponding hexahydro-β-carboline (**231**) by oxidation with sodium tungstate (catalytic amount, using urea/hydrogen peroxide as the reoxidant). Treatment with concentrated, aqueous HCl in methanol yielded the chloroindolenine, which undergoes rearrangement to oxindole (**233**). N_b-Methylation completed the synthesis of (±)-coerulescine (**234**), as shown in Scheme 26.

Scheme 26

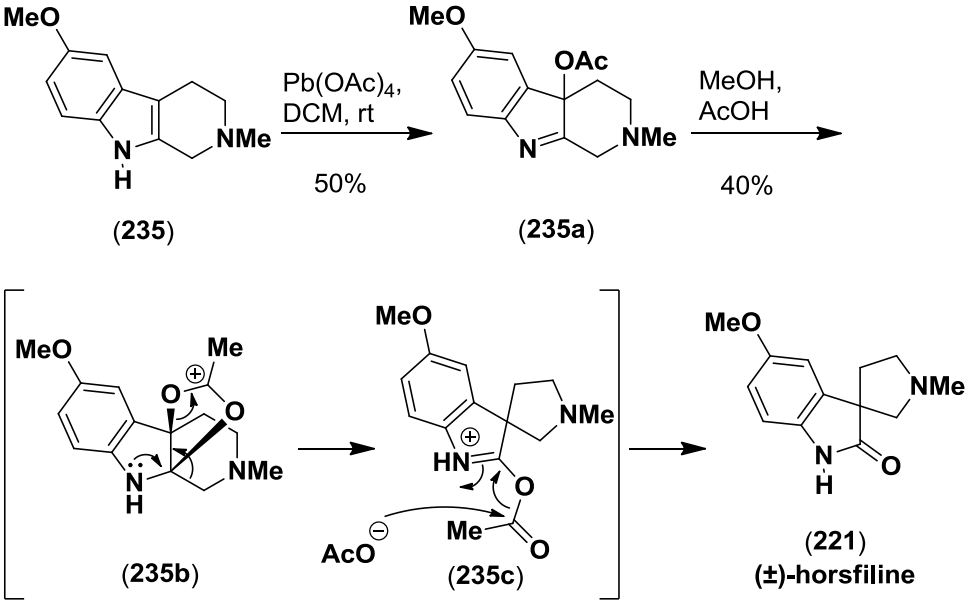


2.2.3) Lead Tretraacetate as The Oxidant

For the oxidative rearrangement of tetrahydro-β-carbolines to spiro[pyrrolidine-3,3′-oxindoles], lead tetraacetate was first investigated by Taylor in 1963.[70] Bodo employed this procedure to confirm the structure of (±)-horsfiline (**221**) by oxidation of the N_b-methyl-

tetrahydro-*β*-carboline (**235**, Scheme 27) with this reagent.[71] Lead tetraacetate was also used by Borschberg in a model study for the synthesis of (+)-elacomine (**7**).[65]

Scheme 27

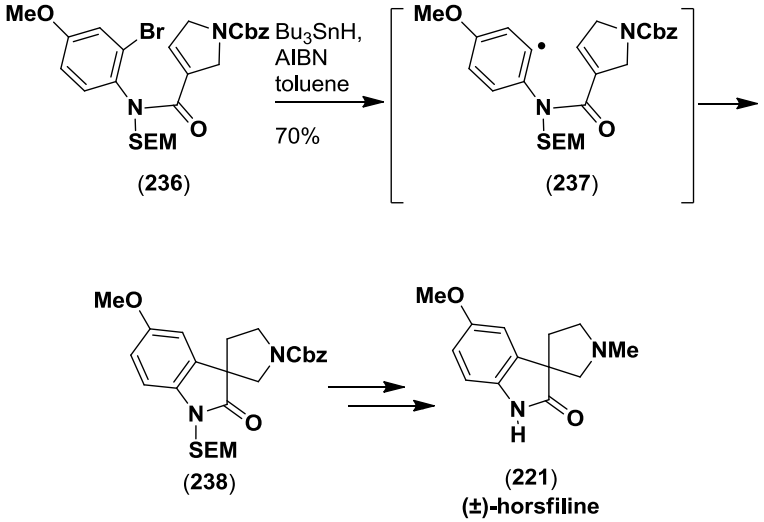


2.3) Radical Cyclization Reactions

Another successful way to construct the spiro[pyrrolidine-3,3′-oxindole] moiety is by radical cyclization. Jones and Wilkinson used this radical approach in their route to (±)-horsfiline (**221**) Scheme 28). The precursor (**236**) for the cyclization reaction was synthesized from 2-bromo-4-methoxyaniline and Cbz-protected glycine ethyl ester in a series of steps. The indole nitrogen had to be protected because radical cyclization of the unprotected derivative of (**236**) led only to reduction; transient TMS-protection led to considerable amounts of the undesired product from a 6-*endo* cyclization. Racemic horsfiline

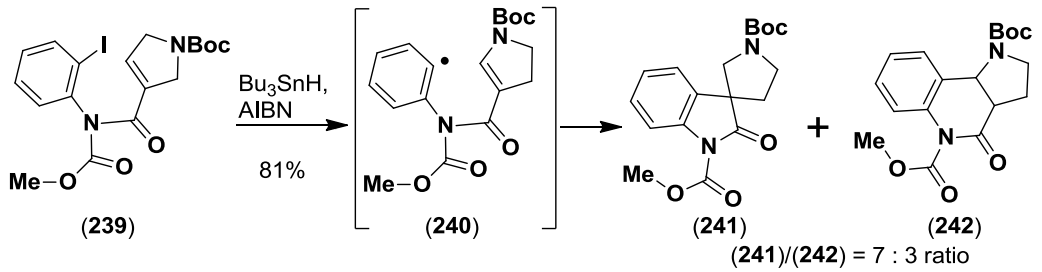
(**221**) was obtained after deprotection of (**238**) followed by methylation under the conditions by Eschweiler and Clarke.[72]

Scheme 28



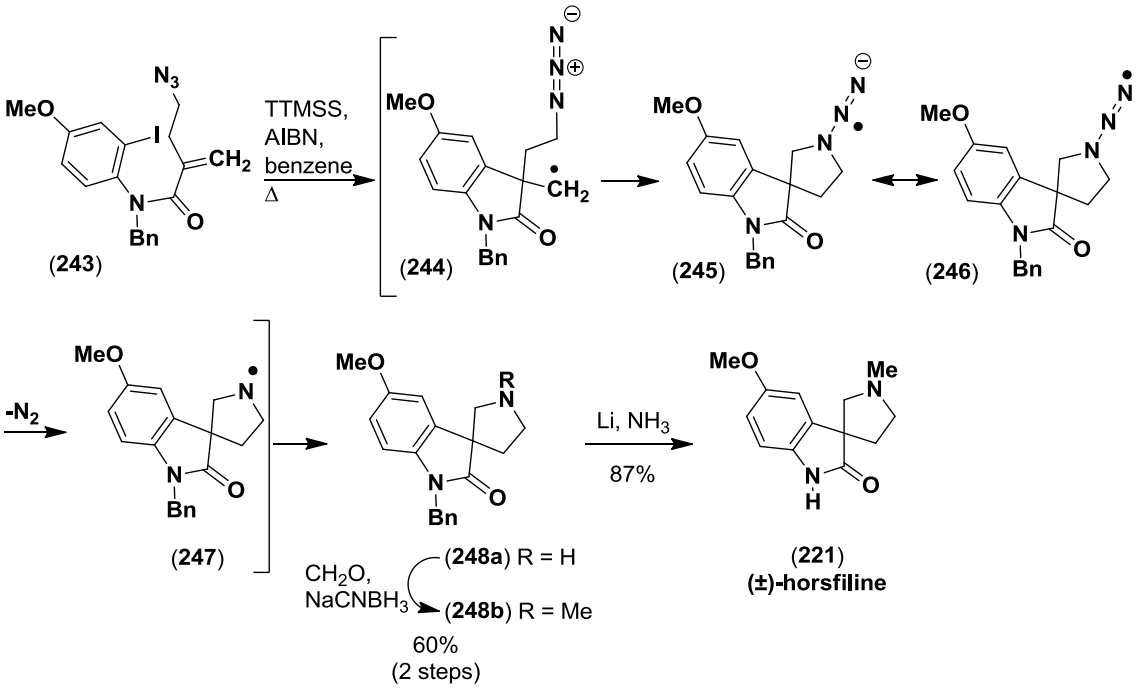
In a similar fashion, Cossy et al. reported a short access to spiropyrrolidinyl-oxindole alkaloids *via* a substituted ene-pyrrolidine carbamate (**239**), which was synthesized from the commercially available *tert*-butyl 1-pyrrolidine carboxylate (Scheme 29).[73]

Scheme 29



Murphy et al. used an aryl iodoazide tandem radical cyclization sequence for the synthesis of (±)-horsfiline (**221**). Cyclization of azide enone (**243**) with tris(trimethylsilyl)silane (TTMSS) afforded spiro-[pyrrolidine-3,3′-oxindole] (**248**), which was methylated *in situ* (Scheme 30). Racemic horsfiline (**221**) was obtained after deprotection of the indole nitrogen atom. The 6-*endo* product was not observed in the reaction.[74]

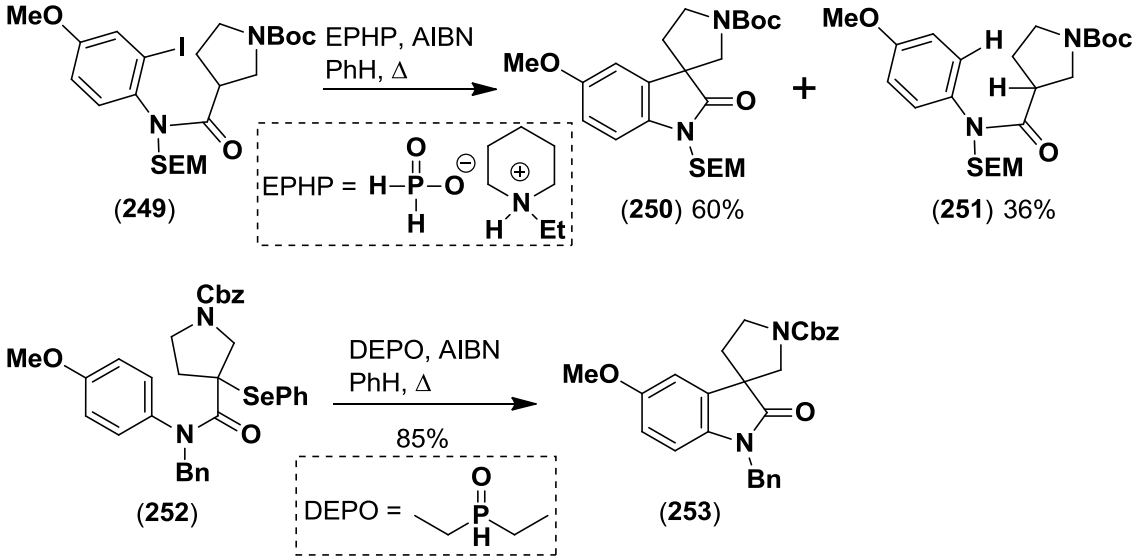
Scheme 30



In 2005, Murphy reported the use of radicals derived from phosphorus reagents, ethylpiperidine hypophosphite (EPHP) and diethylphosphine oxide (DEPO), in two related approaches to the synthesis of the alkaloid horsifiline (**221**). Particularly, he found that DEPO (which is significantly slower to quench carbon radicals than EPHP) proved

beneficial for effecting cyclizations at 80 °C that are difficult or impossible with Bu_3SnH (Scheme 31).[75]

Scheme 31

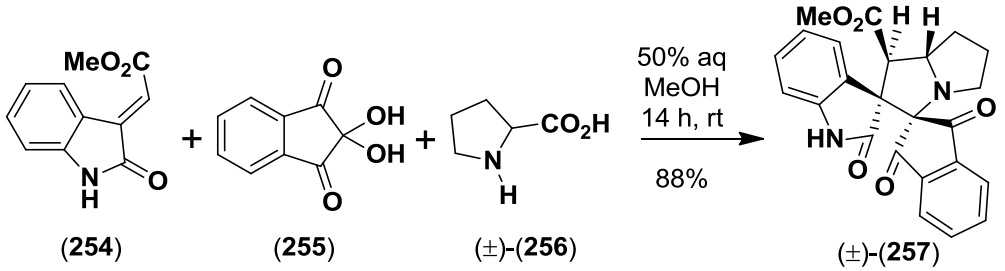


2.4) Dipolar Cycloaddition Reactions

Griggs and collaborators reported the first successful use of 1,3-dipolar cycloadditions in the synthesis of the spiro[pyrrolidine-3,3′-oxindole] skeleton. The *N*-substituted and *α,α*-disubstituted amino acids reacted with carbonyl compounds to generate 1,3-dipolar species under mild conditions (azomethine ylides by decarboxylative transamination). The 1,3-dipoles can be trapped both inter- and intra-molecularly to give bridgehead-nitrogen and spirocyclic products in good yield, an example is shown in Scheme 32.[76] In the example shown below, proline (**256**) reacted stereospecifically with ninhydrin (**255**, these

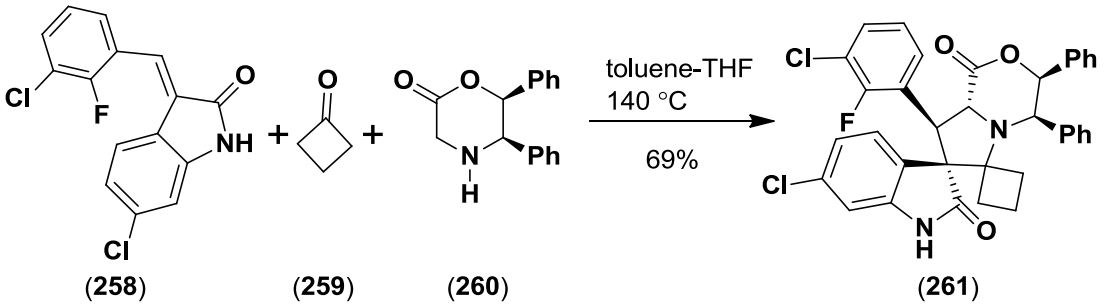
two forming the dipole) and the oxoindolin-3-ylidene acetate (**254**) (which is the dipolarophile) in 50% aqueous methanol (14 h, 25 °C) to give oxindole (**257**) in 88% yield.

Scheme 32



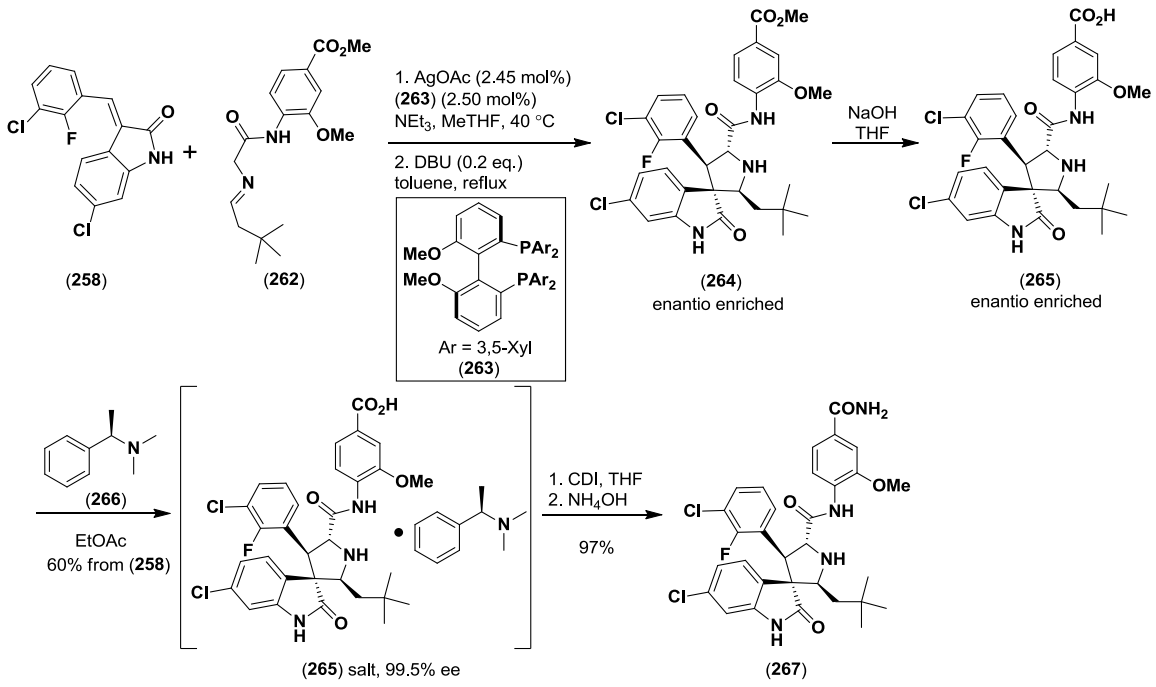
In 2014, Wang and collaborators have designed and synthesized a series of spirooxindoles as efficacious inhibitors of the MDM2-p53 interaction (MDM2 inhibitor). Inhibition of the MDM2-p53 protein-protein interaction is being actively pursued as a new anticancer therapeutic strategy. The key step in building the spirooxindole scaffold (**261**) was the asymmetric 1,3-dipolar cycloaddition reaction shown in Scheme 33.[77]

Scheme 33



A practical synthesis of a spiroindolinone pyrrolidinecarboxamide MDM2 antagonist (**267**) was reported by Shu et al. in 2013. The stereoselective cycloaddition of dipolarophile (**258**) with imine (**262**), in the presence of a silver chiral complex formed *in situ*, afforded a complex mixture of diastereomers that were isomerized to the desired stereoisomer (**264**) by heating the mixture in the presence of DBU (Scheme 34). After regioselective hydrolysis of the ester function in (**264**), the resulting product was resolved with a chiral amine to give an enantiopure acid (**265**) which was converted to the target oxindole product (**267**). The process by Shu et al. was scaled up to multigram scale.[78]

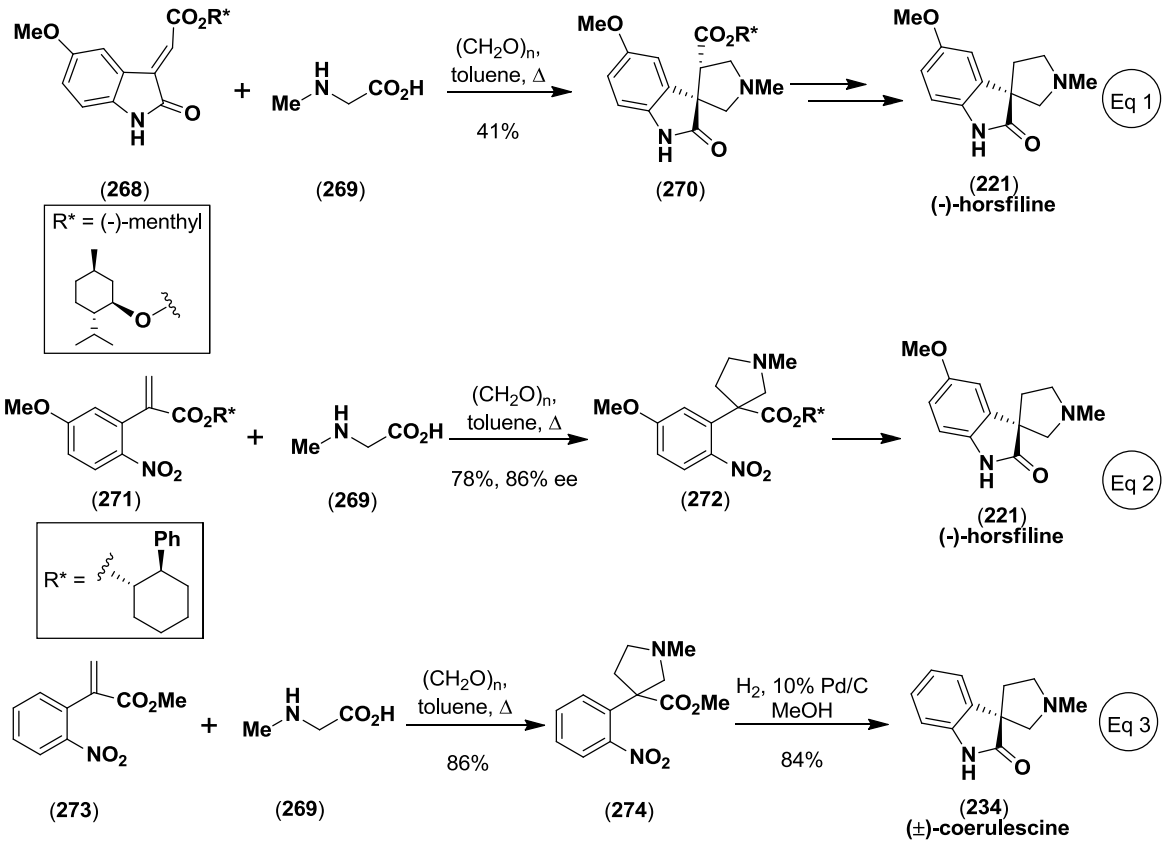
Scheme 34



Palmisano used a 1,3-dipolar cycloaddition as method for the construction of the spiro-[pyrrolidine-3,3′-oxindole] system in the context of natural product synthesis. It was

possible to access (–)-horsfiline (**221**) in five steps from dipolarophile (**268**), bearing a chiral auxiliary [R* = (–)-menthyl, Scheme 35]. Dipolarophile (**268**) was obtained by a Wittig olefination of 5-methoxyisatin. Dipolar cycloaddition with *N*-methyl-azomethine ylide, prepared *in situ* from formaldehyde and sarcosine (**269**), yielded oxindole (**270**).

Scheme 35



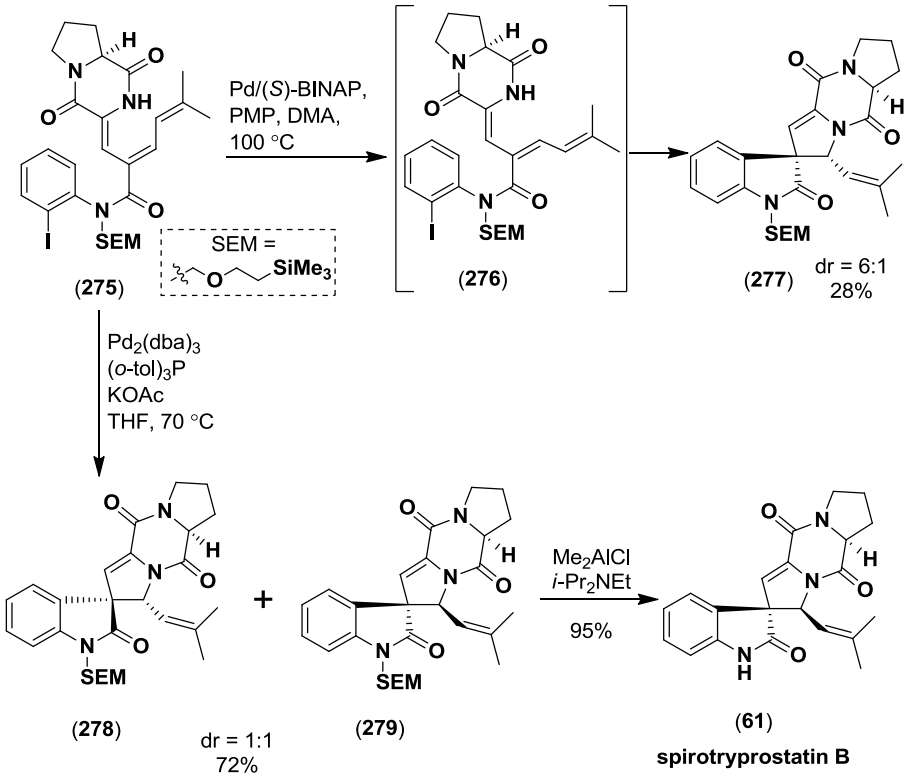
Hydrolysis of the ester and formal decarboxylation afforded (–)-horsfiline (**221**) (equation 1, Scheme 35).[79] In a subsequent work, Palmisano employed the [2 + 3]-cycloaddition with chiral auxiliaries in a more straightforward process on aromatic acrylate (**271**); the ester functionality of the resulting amine (**272**) was ultimately incorporated

into the indole core of (–)-horsfiline (**221**, equation 2, Scheme 35).[80] Selvakumar prepared (±)-coerulescine (**234**) and (±)-horsfiline (**221**) using the same key step as in the second-generation synthesis by Palmisano (equation 3, Scheme 35).[81]

2.5) Palladium-Catalyzed Heck Reactions

In 2000, Overman and Rosen reported the use of the Heck reaction in the total synthesis of (–)-spirotryprostatine B (**61**). In this synthesis, the spirocenter was formed using a diastereoselective Heck reaction followed by a nucleophilic capture of the resulting π-allylpalladium complex with a tethered amide (Scheme 36). The Heck reaction proved to be difficult to optimize: when a Pd/BINAP system was employed, isomerization of the triene occurred to form the more stable all-*trans* isomer (**276**) which, in turn, led to the formation of two diatereomers (**277**) of which the minor was spirotryprostatine B. On the other hand, using a Pd/(*o*-tol)$_3$P catalyst system, a 72% yield of a 1:1 diastereomeric mixture was obtained, one of which corresponded to the desired target. While the key step did not provide the desired (–)-spirotryprostatin B (**61**) with good selectivity, the desired product was still made in 10 steps and 9% overall yield from methyl acrylate and 3-methylbut-2-enal.[82a]

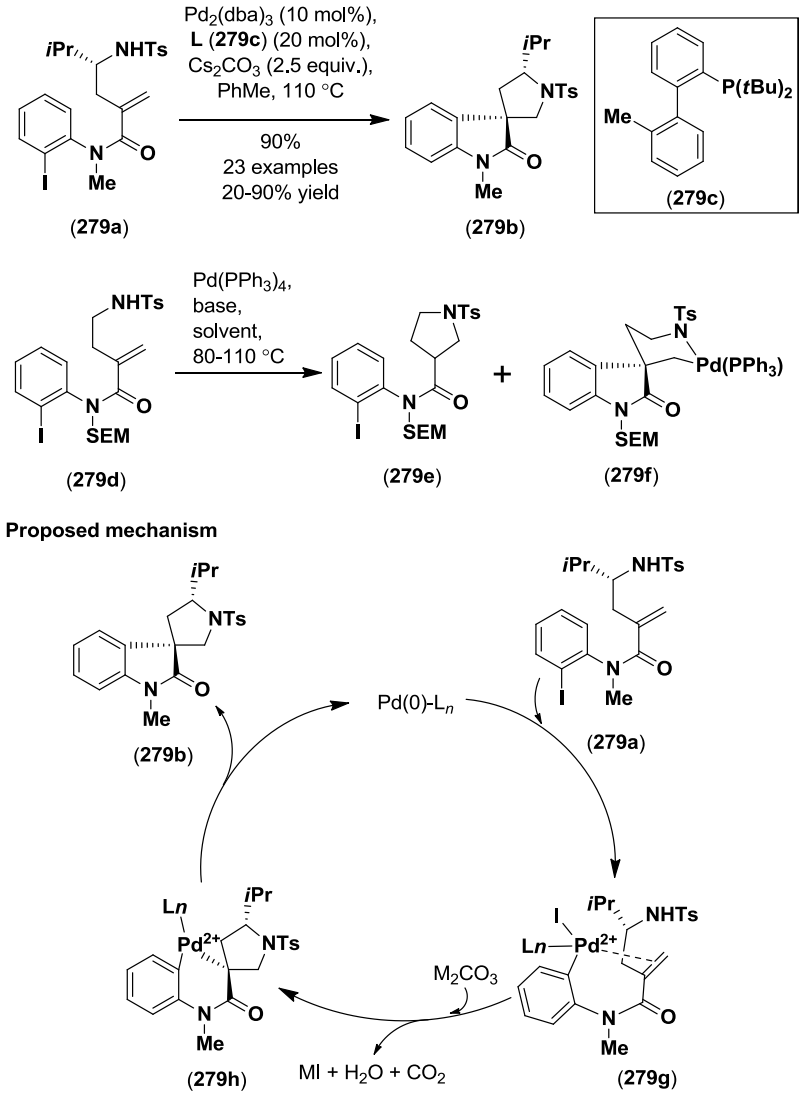
Scheme 36



Zhu and co-workers reported a procedure that employs a similar strategy for the rapid construction of spirooxindoles in Scheme 37.[82b] This reaction would appear to proceed through a 5-*exo*-*trig* cyclisation, followed by capture of the carbopalladated intermediate by the tosylamide moiety. This pathway, however, was ruled out on the basis of experimental observations. As one example, the pyrrolidine (**279e**) was formed as the major product through a disfavoured 5-*endo*-*trig* cyclisation (a process that occurred in the absence of catalytic amounts of palladium) under a variety of conditions. In addition, the use of $Pd(PPh_3)_4$ as a catalyst resulted in the formation of the palladacycle (**279f**), which was isolated in 78% yield. However, both (**279e**) and (**279f**) were unable to undergo

either enolate arylation or C(sp^3)–N reductive elimination, respectively. Then, the authors suggested that the initial oxidative addition formed the intermediate (**279g**) which was followed by intramolecular *trans*-carboamination to give the pyrrolidine palladacycle (**279h**). Subsequent C(sp^2)–C(sp^3) carbon–carbon bond formation via reductive elimination, then afforded the spirocyclic oxindole (**279b**).

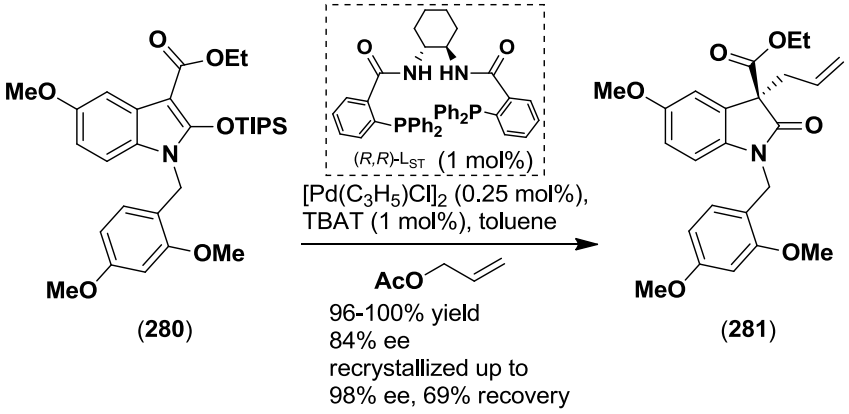
Scheme 37



2.6) Palladium-Catalyzed Allylic Alkylation Reactions

Trost et al. utilized another asymmetric reaction involving palladium catalysis in the synthesis of the oxindole alkaloid horsfiline (**221**).[83] The desired stereocenter that would later become the spirooxindole was set using a stabilized oxindole nucleophile and allyl acetate as the electrophile, in the presence of 0.25 mol% $[Pd(C_3H_5)Cl]_2$, 1 mol% of the standard Trost ligand [(*R,R*)-L_{ST}] and 15 mol% TBAT (tetrabutylammonium triphenyl-silylfluorosilicate) as shown in Scheme 38. The desired product was formed in 96-100% yield and in 84% ee. This enantioselectivity was further enhanced through recrystallization to 98% ee.

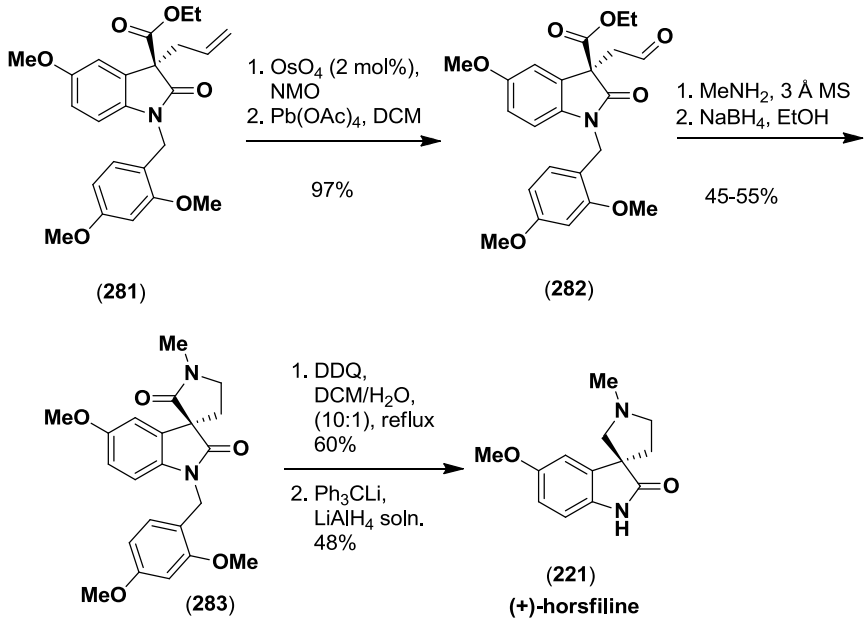
Scheme 38



The pyrrolidine ring was then formed by oxidative cleavage of the allyl group followed by reductive amination with methylamine and *in situ* cyclization to form lactam (**283**). The removal of the 2,4-dimethoxybenzyl group, followed by chemoselective reduction of

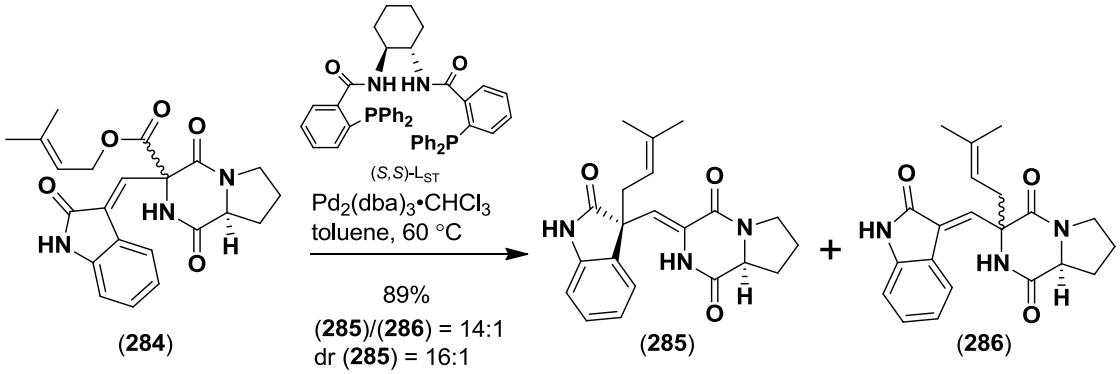
the tertiary amine over the oxindole amide then furnished (+)-horsfiline (**221**), as shown in Scheme 39.

Scheme 39



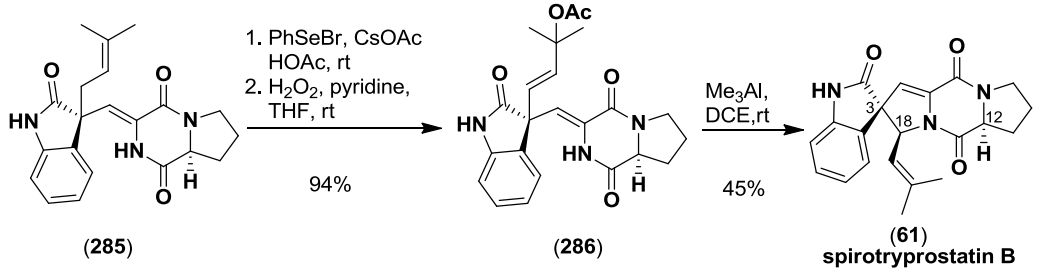
In Trost et al. synthesis of spirotryprostatin B (**61**) in 2007, a diastereoselective prenylation was used to form the chiral quaternary center that would later become the spirocenter (Scheme 40).[84] The palladium-catalyzed decarboxylative prenylation had both regio- and diastereoseletivity issues to address. Ultimately, when the *S,S*-enantiomer of the standard Trost ligand [(*S,S*)-L_{ST}] was used with 10 mol% $Pd_2(dba)_3$•$CHCl_3$ in toluene at 60 °C, the desired product was obtained in 16:1 diastereoselectivity and 14:1 regioselectivity.

Scheme 40



With the stereogenic quaternary center in place, only formation of the pyrrolidine unit remained. Installation of the allylic acetate group on the prenyl side chain was accomplished using PhSeOAc (prepared *in situ* using conditions developed by Sharpless and Lauer),[85] followed by oxidation of the resulting selenide and elimination (Scheme 41). The final cyclization to form the five-membered ring was successful when trimethylaluminum was employed as a promoter to give spirotryprostatin B (**61**) in 45% yield.

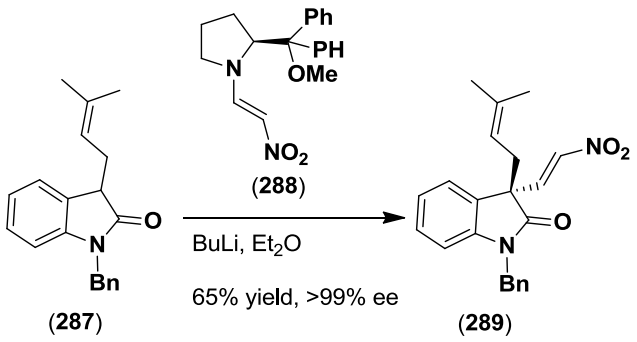
Scheme 41



2.7) Asymmetric Addition-Elimination Reactions

Fuji et al. developed an asymmetric nitroolefination protocol using a chiral auxiliary that was applied to the enantioselective synthesis of oxindoles (Scheme 42).[86] The reaction involved an oxindole enolate attack on the chiral nitroenamine auxiliary (**288**) through an addition-elimination mechanism.[87] Fuji and co-workers prepared several oxindole alkaloids using this methodology, including (–)-horsfiline (**221**)[88] and (–)-spirotryptrostatin B (**61**).[89] In Fuji et al. synthesis of (–)-horsfiline (**221**), the chiral quaternary center that would later be transformed into the spiro pyrrolidine was made using a proline-derived nitroolefination chiral auxiliary to give the desired product in 65% yield and >99% ee (Scheme 42).

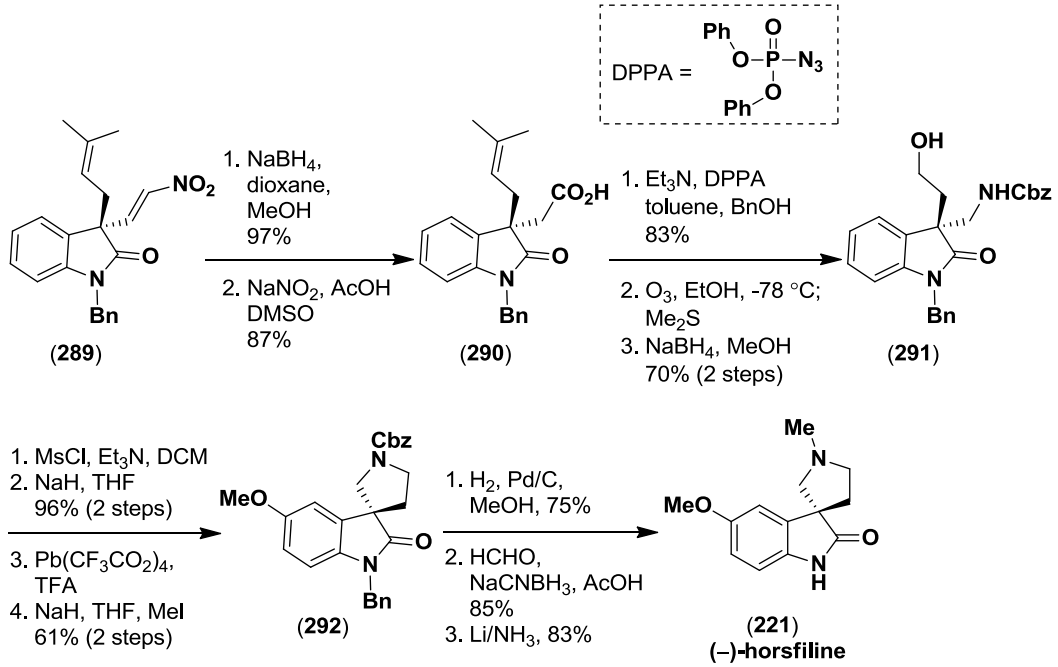
Scheme 42



When Fuji et al. performed the entire synthesis of horsfiline starting from 5-methoxyindole, it took several steps to prepare this starting material, thus, they revised the synthesis to start with the commercially available and less expensive isatin, and then later instal-

led the methoxy group towards the end of the synthesis. Conjugate reduction of the vinyl nitro group using sodium borohydride, followed by conversion of the nitroalkane into the carboxylic acid using sodium nitrite and acetic acid in DMSO furnished oxindole alkaloid (**290**, Scheme 43). Th thermal Curtius rearrangement followed by ozonolysis of the olefin and reductive workup formed the desired alcohol (**291**). Mesylation followed by treatment with NaH finished the construction of the pyrrolidine ring through an intermolecular substitution reaction. The regioselective oxidation at the 5-position using lead(IV) trifluoroacetate in trifluoroacetic acid and subsequent methylation resulted in spirooxindole (**292**). Removal of the Cbz group, followed by methylation of the pyrrolidine nitrogen and removal of the benzyl group provided (–)-horsfiline (**221**).

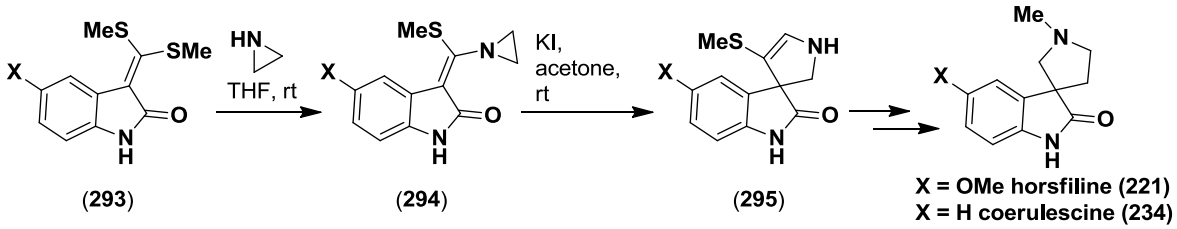
Scheme 43



2.8) Rearrangement of 3-[(Aziridin-1-yl)(methylthio)-methylene]-2-oxindoles

A new approach to obtain the spiro[pyrrolidine-3,3′-oxindole] ring system was introduced by Ila and Junjappa et al. in 2001, who applied it to the synthesis of (±)-coerulescine (**234**) and (±)-horsfiline (**221**, Scheme 44). *N*-Vinylaziridine (**294**), obtained from oxindole (**293**) upon treatment with an equimolar amount of aziridine, was shown to undergo easy iodide-induced rearrangement to oxindole (**295**). From oxindole (**295**), the natural products can be obtained by treatment with Raney nickel (W2) in refluxing methanol.[90]

Scheme 44

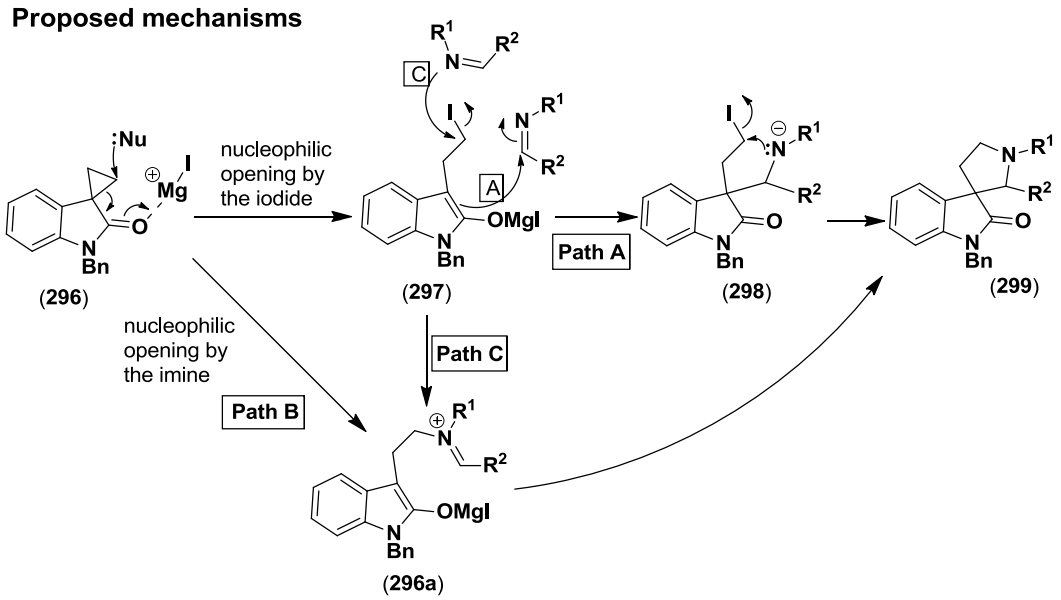


2.9) Ring Expansion

Carreira and co-workers developed another method for generating the spirooxindole moiety. It involves the ring expansion of a spirocyclicpropane using a magnesium salt.[91] This methodology was used in the synthesis of (±)-horsfiline (**221**),[92] (±)-strychnofoline (**310**),[93] and (–)-spirotryprostatin B (**61**).[94] While the transformation itself has been found to be compatible with a variety of imines and proceeds with high diastereoselectivity in

some cases,[91] there is currently no method for rendering it enantioselective. One of the proposed mechanisms of the ring expansion invokes the use of magnesium iodide as a bifunctional reagent, wherein the magnesium acts as a Lewis acid and the iodide as the nucleophile, acting in synergy to open the cyclopropane ring, resulting in intermediate (**297**). Two alternative routes have also been described (Scheme 45).

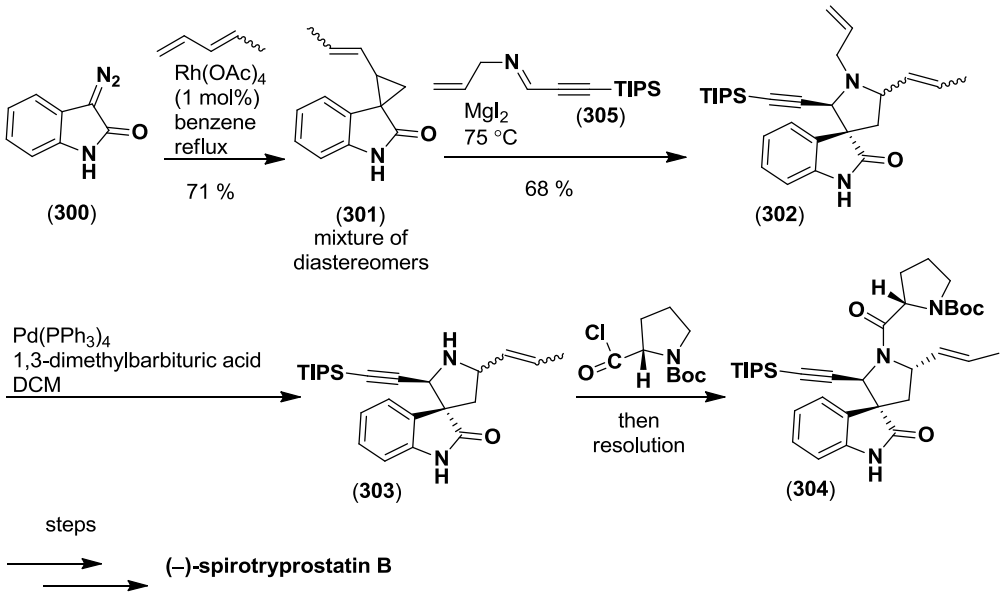
Scheme 45



Regarding the synthesis of (–)-spirotryprostatin B (**61**), the spirocyclopropane was prepared as a mixture of diastereomers using the diazo ketone (**300**), rhodium acetate and piperylene, as shown in Scheme 46. The resulting cyclopropane was heated in THF with the TIPS-imine (**305**) at 75 °C with one equivalent of magnesium iodide, which resulted in a mixture of diastereomers that favored the desired relative stereochemistry (6:1). This synthesis of (–)-spirotryprostatin B (**61**) was rendered asymmetric only by virtue of a

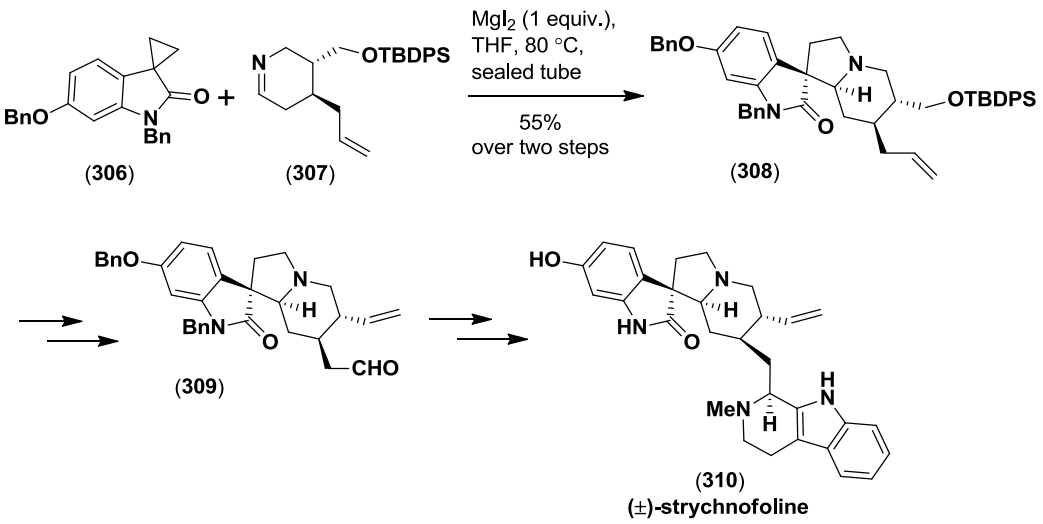
resolution, which was accomplished using the *N*-Boc-L-proline acid chloride to form separable diastereomers. Although the methodology used is very interesting, its utility would be vastly improved if the addition to the imine in the ring-expansion step were asymmetric.

Scheme 46



In the first total synthesis of (±)-strychnofoline (**310**),[95a] the magnesium iodide catalyzed coupling of spiro[cyclopropane-1,3′-oxindole] (**306**) with cyclic imine (**307**) yielded oxindole (**308**) as a single diastereoisomer (Scheme 47). The ring expansion enabled the efficient assembly of the key intermediate (**308**), which was converted into the aldehyde (**309**) by functional group interconversion. From oxindole (**309**), (±)-strychnofoline (**310**) was obtained in two steps through Pictet–Spengler reaction with *N*-methyl-tryptamine, followed by deprotection of the benzyl protecting groups.[93]

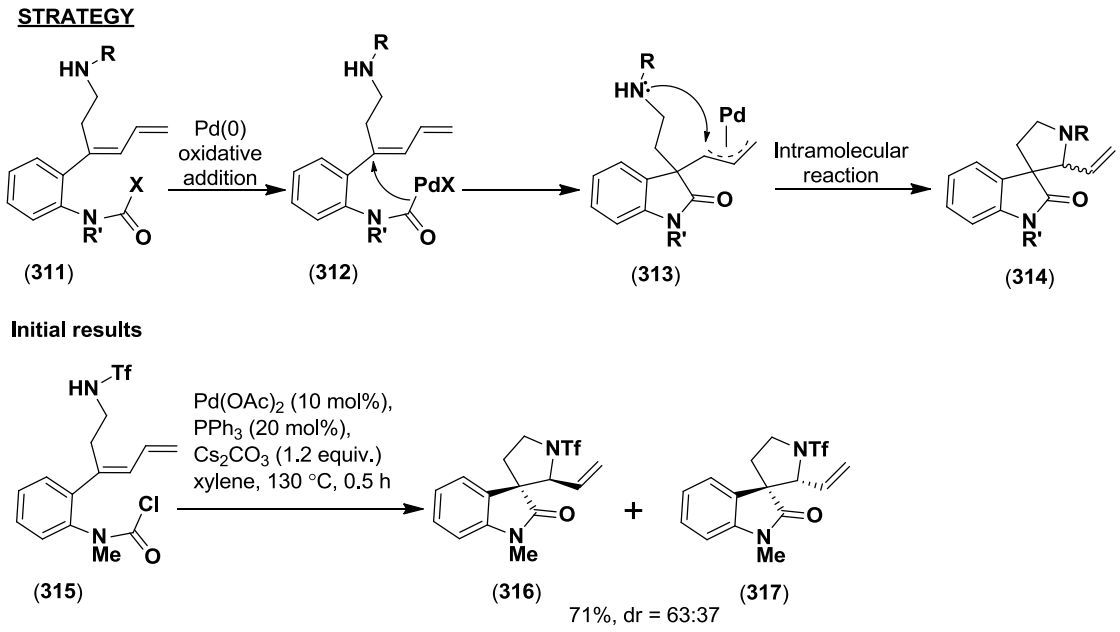
Scheme 47



2.10) Domino Palladium Catalyzed Reactions

Takemoto et al. developed a novel strategy based on palladium-catalyzed domino reaction capable of accessing the spiro[pyrrolidine-3,3′-oxindole] ring system.[51] This approach involved the sequential, palladium(0)-catalyzed amidation and intramolecular nucleophilic addition reactions of carbamoyl chlorides bearing a diene moiety (Scheme 48). These reactions were conducted in a single pot. Initially, the domino cyclization of carbamoyl (**315**) was performed in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Cs_2CO_3 (1.2 equivalents) at 130 °C, and gave the desired spirocyclic products (**316**) and (**317**) in a combined yield of 71% as a 63:37 mixture of two diastereomers. Although the selectivity of the spiro-ring formation was poor, they proceeded to investigate the application of this palladium-catalyzed spirooxindole formation for the synthesis of natural products.[51]

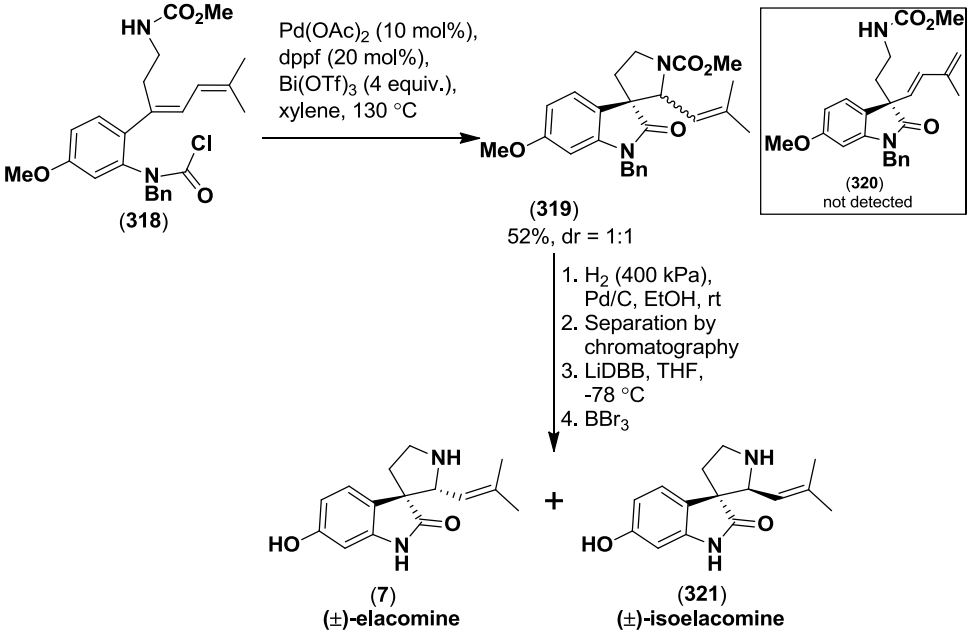
Scheme 48



It was envisioned that the application of the domino reaction to an carbamoyl compound bearing an internal 1,3-diene moiety would allow for the efficient construction of the spirooxindole skeleton of elacomine (**7**) and isoelacomine (**321**), as shown in Scheme 49. After screening a number of different ligands and additives, it was found out that by using 1,1'-bis(diphenylphosphino)-ferrocene (dppf) as the ligand and $Bi(OTf)_3$ as Lewis acid additives, the reaction would proceed smoothly to give the desired spirooxindole (**319**). The acidic conditions were critical in suppressing the formation of oxindole (**320**) as a major *β*-elimination biproduct. Hydrogenation of (**319**) under high pressure conditions provided diastereomers which were separated by column chromatography. Finally, the formal synthesis of elacomine (**7**) and isoelacomine (**321**) was achieved by the removal of the benzyl group from the nitrogen atom of the isoxazole ring with lithium di-*t*-

butyl biphenyl (LiDBB) and subsequent removal of carboxymethyl and methoxy groups by treatment with BBr_3.[51]

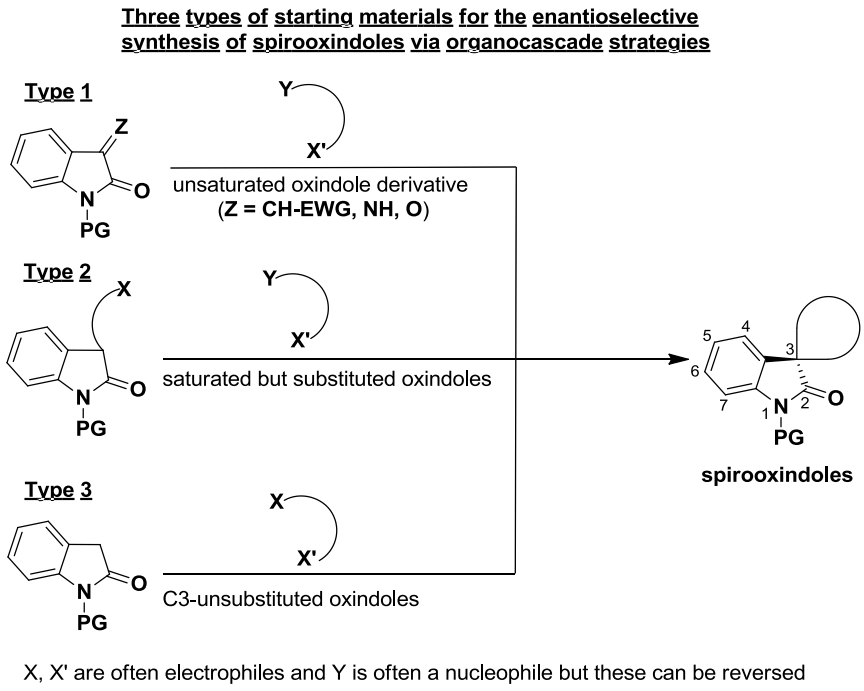
Scheme 49



2.11) Recent Advances in Organocatalytic Methods

The enantioselective synthesis of spirooxindoles via organocascade strategies can be organized according to three different types of starting materials, as shown below, Figure 12.[95b-f]

Figure 12. Spirooxindoles via cascade strategies



One can start from unsaturated oxindole derivatives, such as methyleneoxindole, isatin, or isatinimine. These unsaturated derivatives react with designed reaction partners that have both electrophilic and nucleophilic sites through an addition-cyclization sequence to produce spirooxindole motifs. Then in a different way, one can couple 3-substituted oxindoles with reaction partners *via* an addition-annulation process to provide the spirooxindole skeleton. Finally, oxindoles with a formal bis-nucleophilic center at the 3-position may be coupled with two other reaction components or with a single reaction partner with two electrophilic sites. The three reaction patterns depicted in Figure 12 can then be further subdivided according to the type of catalysis employed, including enamine and iminium catalysis, nucleophilic catalysis, *N*-heterocyclic carbene (NHC) catalysis, and hydrogen bonding catalysis. Representative examples, found in the recent literature,

which described the synthesis of spiro[pyrrolidine-3,3′-oxindole] systems utilizing these approaches are presented next.

2.11.1) Unsaturated Substrates

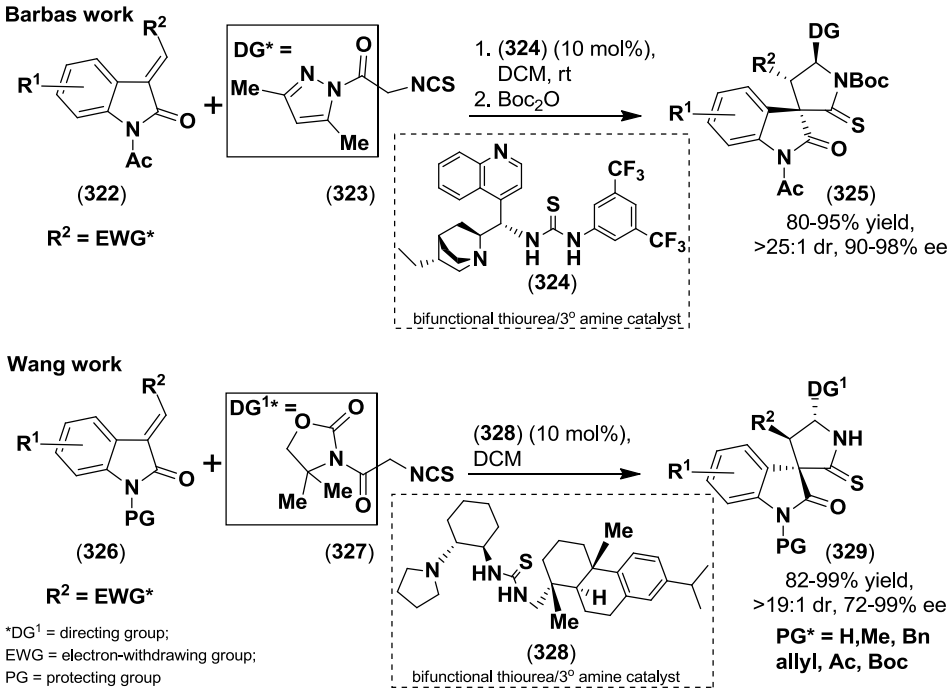
2.11.1.1) Hydrogen Bonding Catalysis

Hydrogen bonding catalysts are designed with the idea that small organic molecules are capable of increasing the electrophilic character of a substrate *via* H-bonding interactions with either oxygen or nitrogen lone pair of electrons in the reagent, making the reaction more likely to take place and with a high degree of stereocontrol.[96]

Very recently, H-bond donors, such as ureas and thioureas, have been recognized as efficient organocatalysts. McMillan and Jacobsen pioneered these approaches. Novel urea and thiourea derivatives act as general Brønsted acids in various transformations that yield chiral spirooxindoles.[97] The most common bifunctional catalysts contain a urea or a thiourea and a tertiary amine group, which also serves as an H-bonding catalyst. Barbas and Wang, independently, developed a highly enantioselective synthesis of thiopyrrolidonyl spirooxindole derivatives [(**325**), (**329**)] from methyleneoxindoles [(**322**), (**326**)] and α-isothiocyanato-imides [(**323**), (**327**)] respectively (Scheme 50).[98,99] The [3 + 2] cycloaddition reaction of rationally designed dimethylpyrazole isothiocyanato amides with methyleneoxindoles led to the formation of 3,3′-thiopyrrolidonyl spirooxindoles.[98] Initial studies of this reaction using oxazolidinone as the directing group gave poor diastereoselectivities. Then, Barbas et al. utilized a dimethylpyrazole directing group,

expecting that such substrates would have an extra H-bond acceptor site for the thiourea catalyst.[100] Experimental results showed that, in the presence of catalyst (**324**), this new methodology provided access to multisubstituted spirooxindole derivatives in excellent enantioselectivities (up to 98% ee) and almost complete diastereoselectivities (>25:1 dr in all cases), regardless of the stereoelectronic nature of the substituents. One important feature of this strategy is that the pyrazole moiety can be easily converted into other functional groups, such as alcohols.

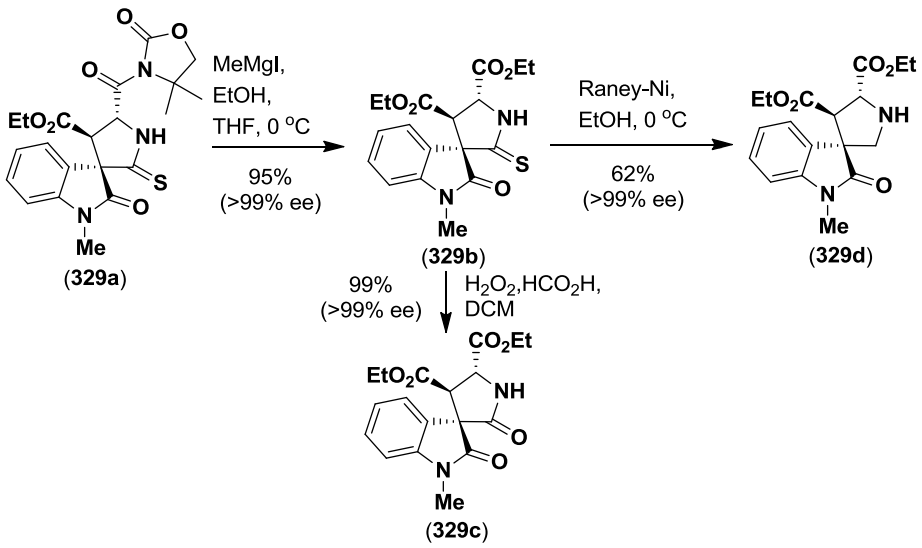
Scheme 50



Incontrast, Wang and co-workers employed rosin-derived bifunctional catalyst (**328**) with oxazolidinone isothiocyanato imides (**327**) to access thiopyrrolidonyl spirooxindoles

(**329**), which bear three contiguous stereocenters (Scheme 50, *Note*: rosin is a solid form of resin obtained from plants, mostly conifers, its main component is abietic acid).[99] In this procedure, both substrates are activated by the bifunctional catalyst. Barbas and co-workers proposed a [3 + 2] cycloaddition process for the reaction in which the methyl-eneoxindole is activated by the tertiary amine, and the α-isothiocyanato imide is enolized by deprotonation at its *α*-carbon atom by double H-bonding. Wang et al. proposed that the methyleneoxindole is activated by double H-bonding and that the *α*-isothiocyanato imide is enolized by the tertiary amine of the catalyst.

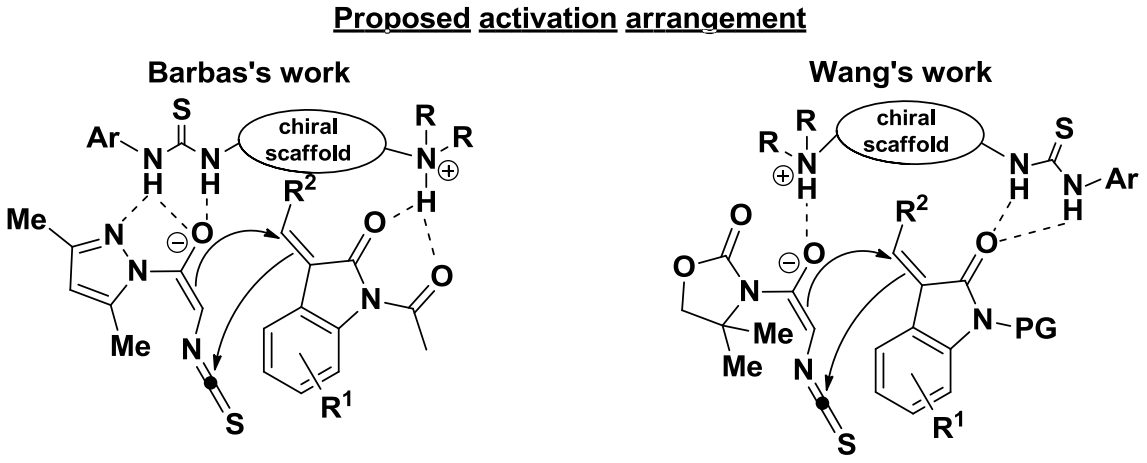
Scheme 51



As an example of this chemistry, one of the oxindoles (**329a**) was further transformed, first by conversion of the imide to ester by treatment with MeMgI which gave the ox-indole ester (**329b**), followed by oxidation of this product with H_2O_2 or catalytic reduc-tion to afford the spiro-products (**329c**) and (**329d**, Scheme 51), respectively, without any

loss of diastereoselectivity or enantioselectivity.[99] The proposed activation arrangement is presented in Figure 13.

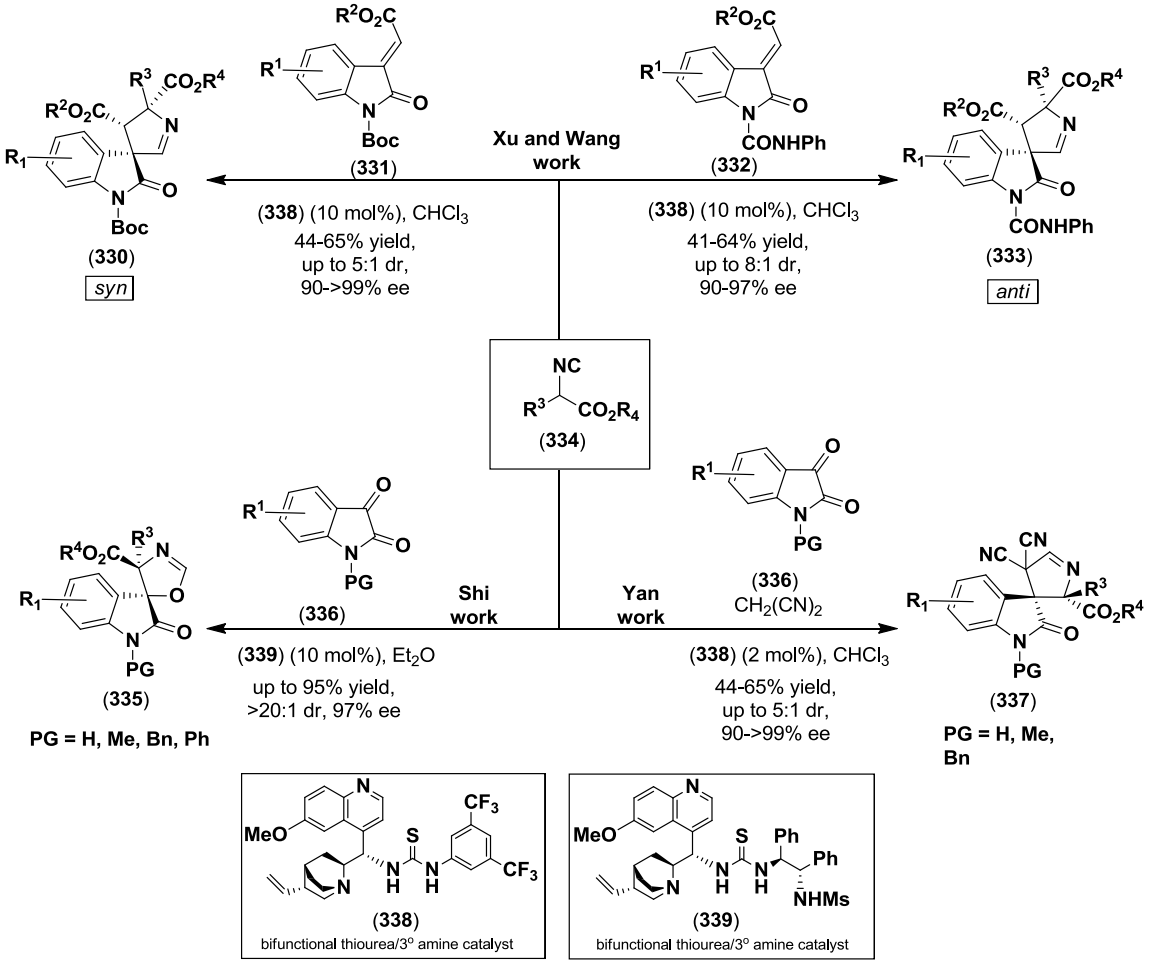
Figure 13. Hydrogen bonding catalysis: mechanism



Another way to access chiral spirooxindoles via cascade strategies is by utilizing isocyanoacetates (**334**), Scheme 52, which possess several potential reaction centers (an isocyano group, an acidic C-H, and a protected carboxylic acid) and show exceptional reaction diversity.

A novel [3 + 2] cycloaddition of isocyanoesters (**334**) and methyleneoxindoles [(**331**), (**332**)] in the presence of quinine-based thiourea tertiary amine catalyst (**338**) was employed by Wang et al., in 2012, to access optically active 3,3′-pyrrolidinyl spirooxindoles (**333**) with multiple contiguous stereocenters (Scheme 52).[101]

Scheme 52

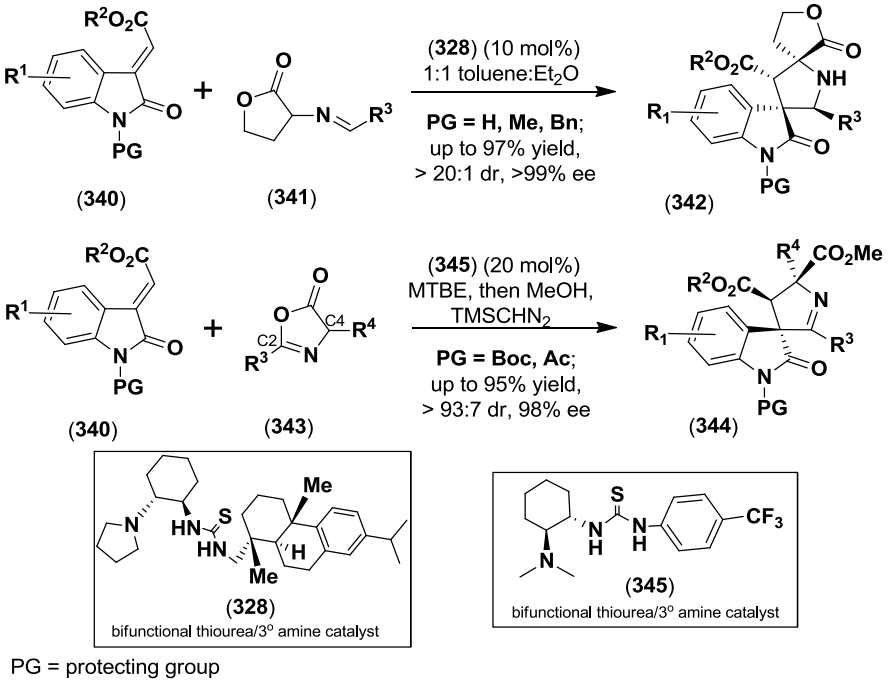


It is noteworthy that the *N*-protecting groups of the methyleneoxindoles had a significant effect on diastereoselectivity. *Syn* products (**330**) were obtained when the *N*-protecting group was *N*-*tert*-butoxycarbonyl, and *anti* products (**333**) when it was *N*-(phenylamido) carbonyl. Yan et al. reported a three-component reaction of isatins (**336**), malononitrile, and isocyanoacetates (**334**) catalyzed by a tertiary amine-thiourea catalyst (**338**, Scheme 52).[102] A number of 3,3′-dihydropyrrylspirooxindoles (**337**) were prepared in excellent yields and enantioselectivities. The products were transformed into valuable 3,3′-pyr-

rolidinyl-spirooxindoles simply by selective reduction of the imine group. For a further application of isocyanides, Shi et al. successfully executed a [3 + 2] cycloaddition strategy for the construction of optically active spirooxindole oxazolines (**335**, Scheme 52).[103] The reaction between α-aryl isocyanoacetates (**334**) and isatins (**336**) was accomplished using a quinine-derived bifunctional amine-thiourea catalyst (**339**) which contained a sulfonamide unit as an H-bonding donor. The desired products were obtained in good yields, high diastereoselectivities, and good to excellent enantioselectivities.

Wang et al. reported two additional examples of the 1,3-dipolar cycloaddition strategy for the preparation of chiral spirooxindoles in 2013 (Scheme 53).[104,105] For the first, a 1,3-dipolar cycloaddition reaction of homoserine lactone-derived cyclic imino esters (**341**) with methyleneoxindoles (**340**) was used to construct spiro[γ-butyrolactone-pyrrolidin-3,3′-oxindole] tricyclic skeletons (**342**).[104] Using bifunctional organocatalyst (**328**), the desired products were obtained with excellent levels of stereocontrol over four contiguous stereocenters. In the second example, the group took advantage of the nucleophilic C-4 and electrophilic C-2 atoms of azlactone (**343**) in an organocatalytic enantioselective 1,3-dipolar cycloaddition reaction between (**343**) and (**340**) to construct spirooxindole derivatives (**344**).[105] The bifunctional thiourea catalyst (**346**) deprotonated the azlactone to generate a cyclic mesoionic azomethine ylide and provide products with excellent enantioselectivity.

Scheme 53



2.11.1.2) Chiral Phosphoric Acid Catalysis

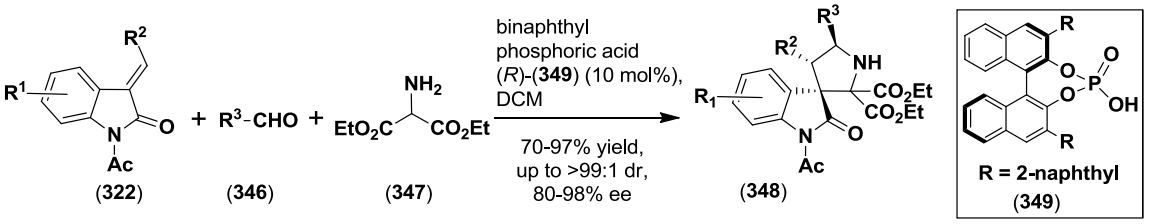
Chiral phosphoric acids and derivatives have been shown to be powerful Brønsted acid catalysts and bifunctional catalysts in numerous highly enantioselective transformations. Initially, the activation was restricted to reactive imine substrates, but recent reports have established the versatility of phosphoric acid catalysts in the activation of other functional groups in a stereocontrolled fashion.[106] The first enantioselective organocatalytic approach to the synthesis of spiro-[pyrrolidin-3,3′-oxindole] derivatives with high enantiopurity and structural diversity was reporteded by Gong et al. in 2009, as shown in Scheme 54.[106,107,108] The asymmetric catalytic three-component 1,3-dipolar cycloaddition of methyleneoxindoles (**322**) with aldehydes (**346**) and amino esters (**347**) in the presence

of chiral phosphoric acid catalyst (**349**) provided spirooxindole derivatives (**348**) in high yields with unusual regiochemistry and excellent stereoselectivities (up to 98% ee). Theoretical calculations revealed that both the azomethine ylide and the methyleneoxindole are H-bonded with the phosphoric acid, accounting for the high enantio- and regioselectivity, and that the unusual regioselectivity results from π-π stacking interactions between the oxindole and the conjugated esters. The authors hypothesized, on the basis of density functional theory calculations, that the unique regioselectivity arises from the energetically favored transition state (**353**) rather than (**352**). This chiral phosphoric acid strategy was pioneered by List during research in an enantiospecific Pictet–Spengler reaction.

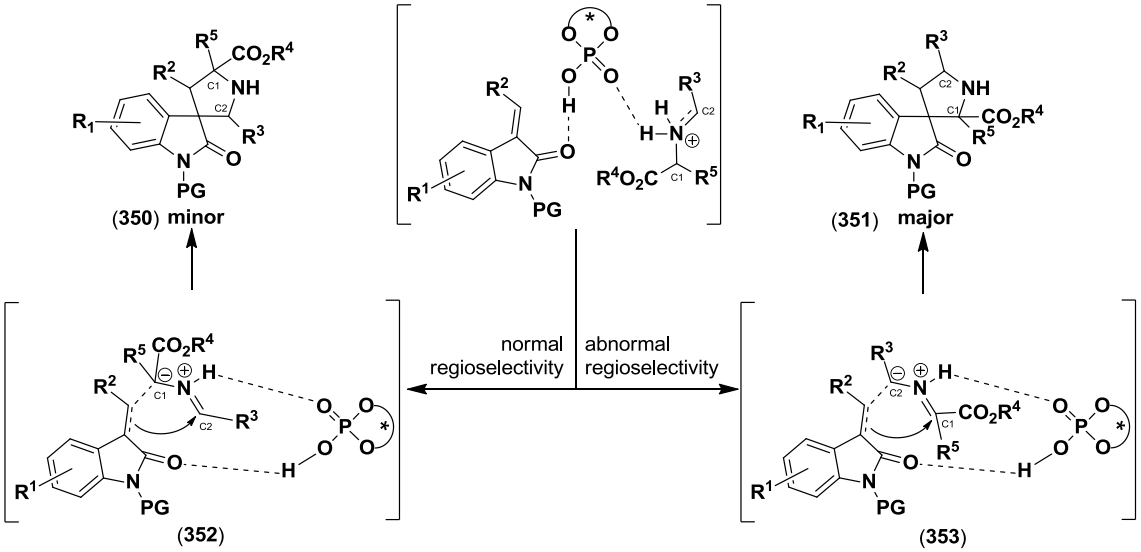
Gong et al. extended this catalytic asymmetric 1,3-dipolar cycloaddition reaction and established a strategy for the synthesis of spiro[pyrrolidin-3,2′-oxindole] scaffolds (**356**) from azomethine ylides generated *in situ* from isatins (**336**) and various electron-deficient olefins (Scheme 55).[109] Biphosphoric acid (**357**) was the most efficient catalyst of those evaluated. Theoretical calculations performed on the transition state was employed to rationalize the observed stereochemistry.

Inspired by a biomimetic transamination, Gong et al. reported the asymmetric, three-component 1,3-dipolar cycloaddition of *α*-keto esters (**360**) and benzylamine (**359**) with electron-deficient olefins (Scheme 56).[110] The most important feature of this study was the strategic use of phosphoric acid derivative (**349**) to catalyze the transamination of ketimines (**362**) formed from *α*-keto esters and amines to generate azomethine ylides (**363**) *in situ*. These ylides readily participate in a 1,3-dipolar cycloaddition with a structurally diverse range of dipolarophiles.

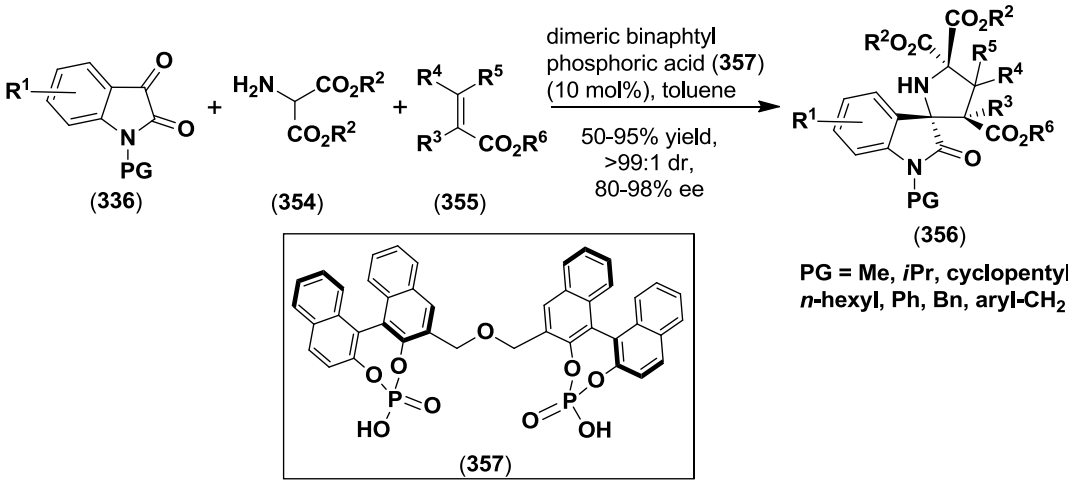
Scheme 54



Transition state models

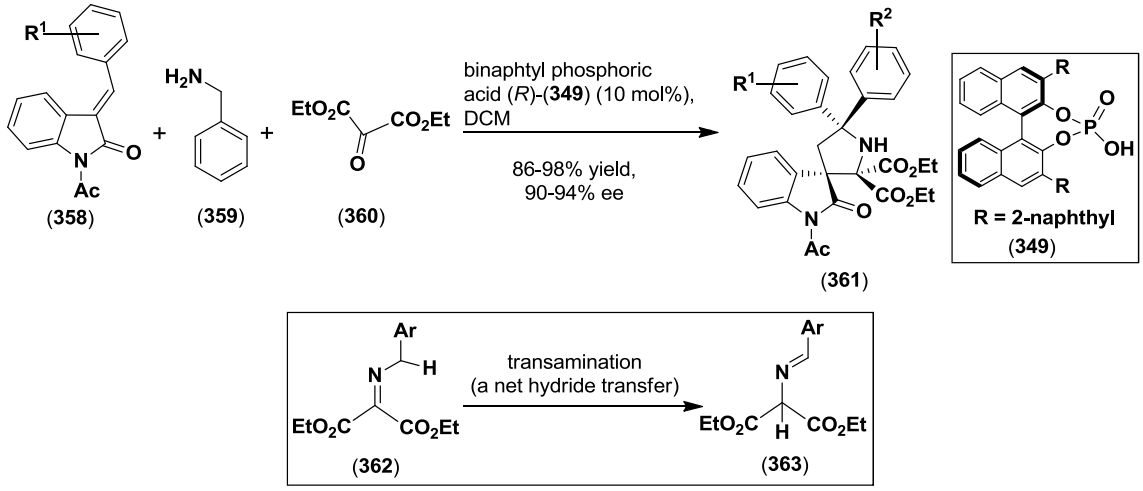


Scheme 55



The authors also showed that methyleneoxindoles (**358**) served as suitable substrates and generated a collection of spiro-[pyrrolidin-3,3′-oxindole] derivatives (**361**) with excellent results in the presence of phosphoric acid catalyst (**349**).

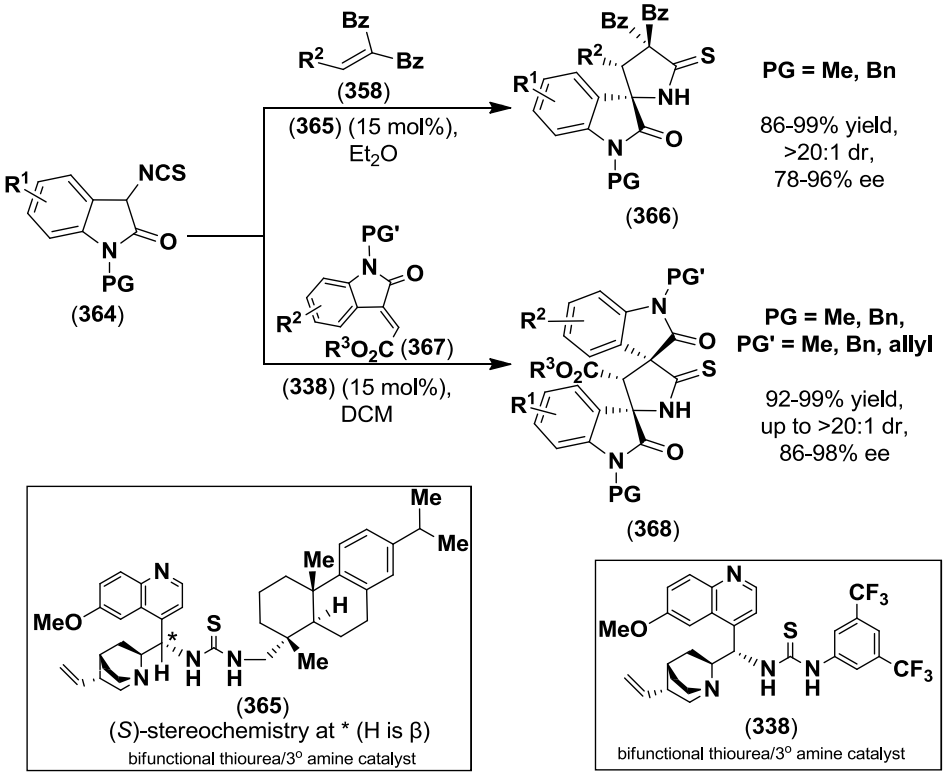
Scheme 56



2.11.2) Saturated Substrates: Michael Addition/Cyclization Reactions

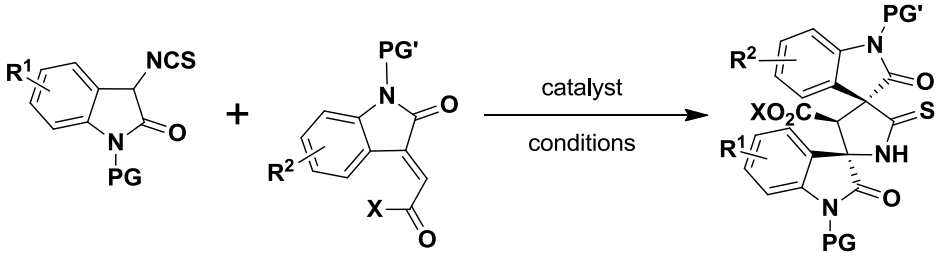
In 2013, Wang et al. reported that asymmetric Michael addition/cyclization reactions between isothiocyanato oxindoles (**364**) and electron-poor alkenes such as (**358**) and methyleneoxindoles (**367**) resulted in an efficient synthesis of enantioenriched spiro-oxindoles (**366**) and bispirooxindoles (**368**), respectively (Scheme 57).[111]

Scheme 57



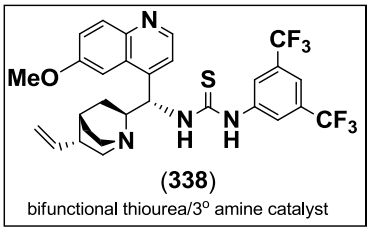
In 2013 Huang and Wang reported a cascade Michael/cyclization reaction between isothiocyanato oxindoles (**364**) and methyleneoxindoles (**369**) to access bispirooxindole derivatives (**370**), as shown in Scheme 58.[112] Bifunctional organocatalyst (**338**) developed by the Barbas group worked the best in catalyzing the reactions of methyleneoxindoles bearing different ester substituents, whereas for methyleneoxindoles bearing ketone moieties, catalyst (**371**) was better. All of the reactions were completed very fast under mild conditions and afforded bispirooxindole derivatives (**370**) in almost quantitative yield with excellent enantiomeric and diastereomeric purities. The authors demonstrated that the reaction occurs through dual activation. Chen et al. also reported this type of formal

Scheme 58

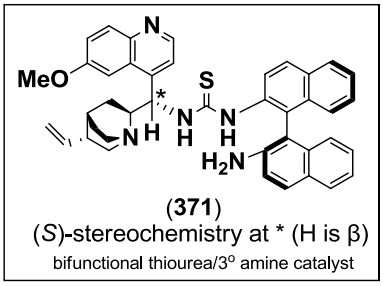


(**364**) (**369**) (**370**)

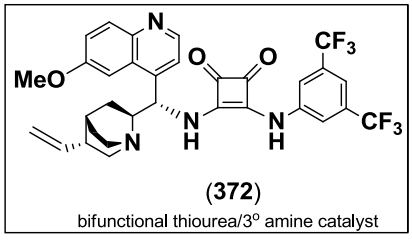
Huang and Wang
For X = OEt: (**338**) (15 mol%); PG = Me, Bn; PG' = Me, Bn, Ac;
98% yield, >20:1 dr, 92% ee
For X = (hetero)aryl: (**371**) (15 mol%); PG = Me, Bn; PG' = Me, Ac;
up to 99% yield, >20:1 dr, 99% ee
Chen and Xiao
For X = O-alkyl: (**372**) (1 mol%); PG = Me, Bn; PG' = H, Me, Bn, PMB, allyl, Ac;
up to 99% yield, >95:5 dr, 99% ee
Yuan
For X = O-Et: (**373**) (1 mol%); PG = Me, Et, Bn; PG' = Boc;
98% yield, >99:1 dr, 98% ee
(the -COX group can be replaced by aryl or heteroaryl as well)



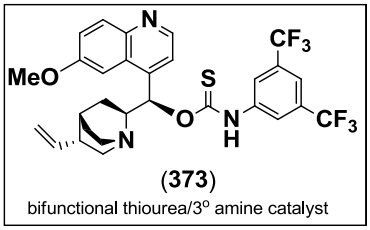
(**338**)
bifunctional thiourea/3° amine catalyst



(**371**)
(*S*)-stereochemistry at * (H is β)
bifunctional thiourea/3° amine catalyst



(**372**)
bifunctional thiourea/3° amine catalyst



(**373**)
bifunctional thiourea/3° amine catalyst

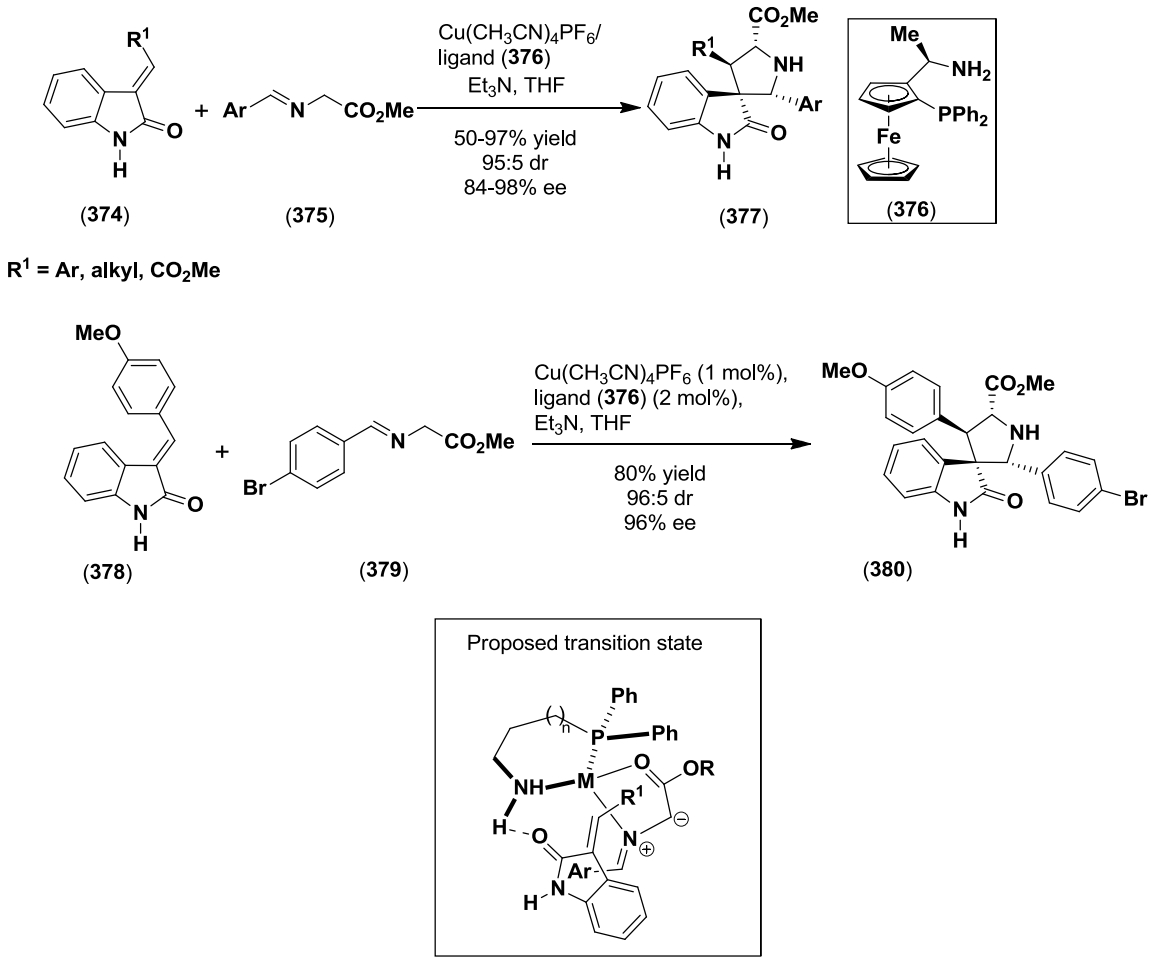
[3 + 2] cycloaddition utilizing a Cinchona-derived squaramide (**372**) as the catalyst, producing the desired bispirooxindole products (**370**) in almost quantitative yields with extremely high enantio and diastereoselectivities.[113] Furthermore, quinine-derived thiocarbamate (**373**) efficiently catalyzed the asymmetric cascade Michael/cyclization reac-

tion between (**364**) and (**369**).[114] Under optimal reaction conditions, a spectrum of densely functionalized thiopyrrolidineoxindoles (**370**) were synthesized with excellent diastereo- and enantioselectivity as well as good functional group compatibility.

2.12) Copper-Catalyzed Cycloaddition Reactions

Waldmann et al. reported the enantioselective synthesis of isomeric spiropyrrolidine oxindoles illustrated by (**374**) using a copper-catalyzed 1,3-dipolar cycloaddition reaction (Scheme 59).[115] This synthesis took place by means of an asymmetric Lewis acid-catalysed cycloaddition of an azomethine ylide (**375**) to a substituted 3-methylene-2-oxindole (**374**) using 1-3 mol% of a chiral catalyst formed from a *N,P*-ferrocenyl ligand (**376**) and $CuPF_6(CH_3CN)_4$. This was also highly enantioselective with up to 98% ee. A slight excess of ligand in a 1.1:1 ratio of ligand:Cu afforded a 91:9 diastereomeric ratio with only 72% ee, while a 2:1 ratio afforded a 95:5 diastereomeric ratio with 98% ee. Waldmann et al. proposed a stereochemical rationale in which the origin of the enantioselectivity is based on hydrogen-bonding interactions of the ligand complex with oxindole (**374**) while chelating of copper to imine (**375**). The authors also speculated that stabilizing π-π stacking interactions contribute to the selectivity (Scheme 59).

Scheme 59

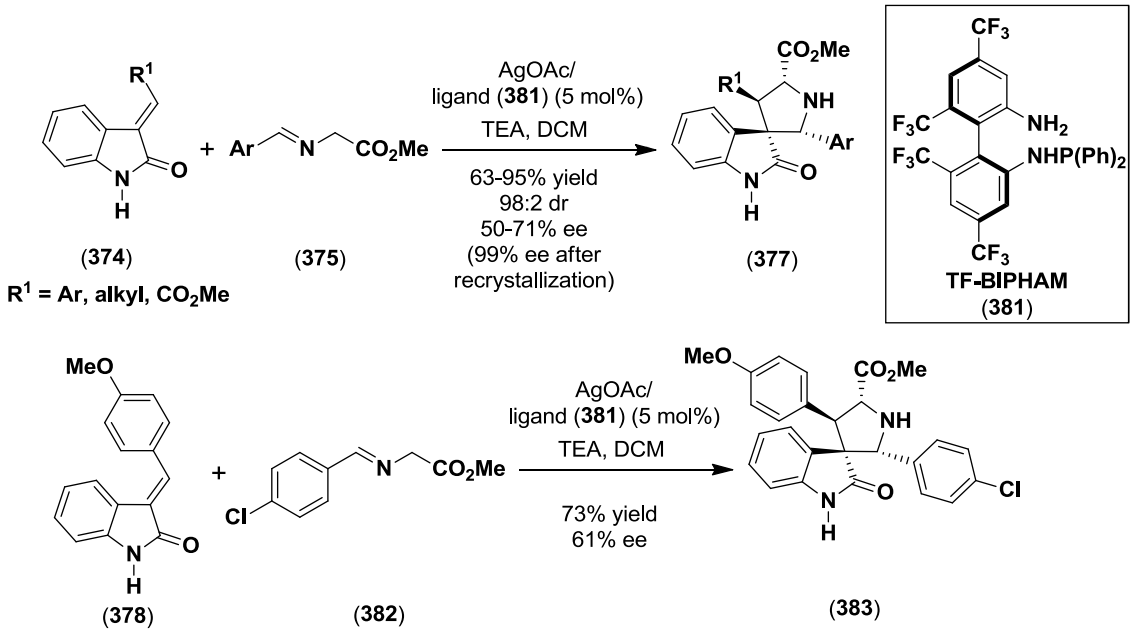


2.13) Silver-Catalyzed Cycloaddition Reactions

Wang et al. reported a related Ag(I)-catalyzed synthesis of spiropyrrolidine oxindole (**377**) using TF-BiphamPhos (TF-BIPHAM) (**381**) as the ligand (Scheme 60).[116,117] Using silver salts afforded high diastereoselectivity (98:2 dr) and higher enantioselectivity compared to copper salts with this same ligand. While the enantioselectivities were

generally modest (50-71% ee) relative to Waldmann's copper-catalyzed method, recrystallization afforded products with 99% ee.

Scheme 60

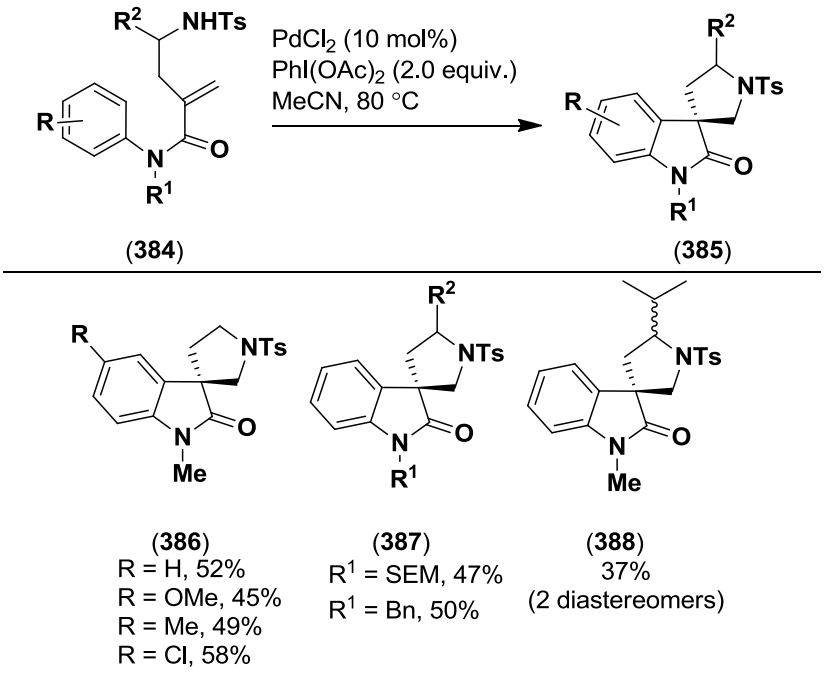


2.14) Fujiwara–Moritani (Oxidative Heck) Related Reactions: Pd-Catalyzed Carbo-Heterofunctionalization of Alkenes

The Fujiwara–Moritani variant of the Heck reaction permits for direct C-C coupling between an unactivated Ar-H bond and an olefin (Scheme 61).[118] The surprising finding of a small amount of the spirooxindole (**385**) after the cyclisation of (**384**) prompted the development of reaction conditions that would selectively enable access to these scaffolds. Use of $PdCl_2$ and $PhI(OAc)_2$ in acetonitrile at 80 °C boosted the yield of the

desired spirooxindole (**386**) up to 52% (Scheme 61). A range of similar spirocycles could also be prepared in comparable yields.

Scheme 61

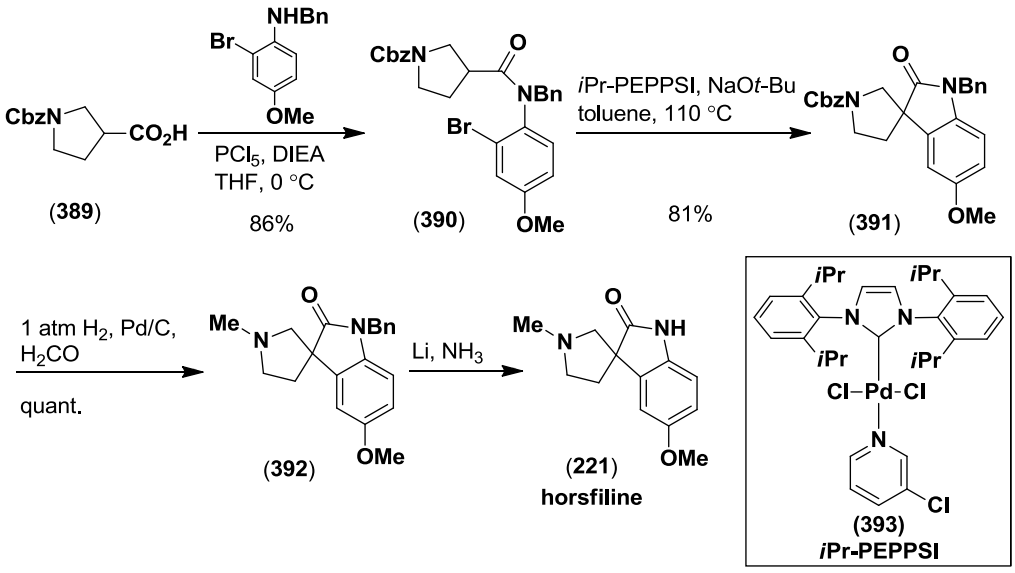


2.15) Enolate Arylation Reactions

Cross-coupling reactions provide an indispensable tool for the formation of carbon-carbon bonds, but substrates often require prefunctionalisation of both carbon atoms involved in the reaction. An elegant way to circumvent this is the α-arylation of metal enolates, which are usually easily generated *in situ* by deprotonation.[119] In 1998, Hartwig et al. reported the first example of intramolecular enolate arylation for the preparation of oxindoles.[120] More recently, in the course of a study devoted to the preparation of spiro-

cyclic oxindoles through enolate arylations, the natural product (±)-horsfiline (**221**) was prepared by Maison et al. (Scheme 62).[121] In this synthesis the preformed air- and moisture-stable *i*Pr-PEPPSI (**393**) was used as the catalyst.

Scheme 62



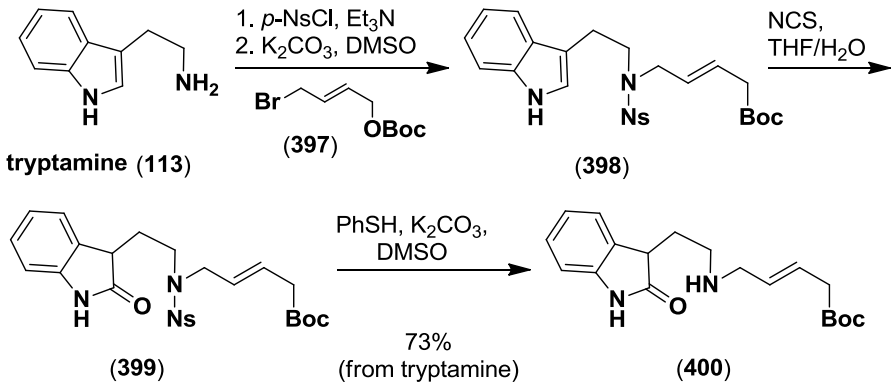
3) Recent Total Synthesis of Spirooxindole Alkaloids

3.1) Hiemstra et al.'s Total Synthesis of Corynoxine, Corynoxine B, Corynoxeine, and Rhynchophylline

A racemic total synthesis of spirocyclic oxindole alkaloids corynoxine (**394**), corynoxine B (**395**), corynoxeine (**396**), and rhynchophylline (**3**) was recently reported by Hiemstra and collaborators.[122] The Fukuyama procedure[123] (Scheme 63), was chosen for the selec-

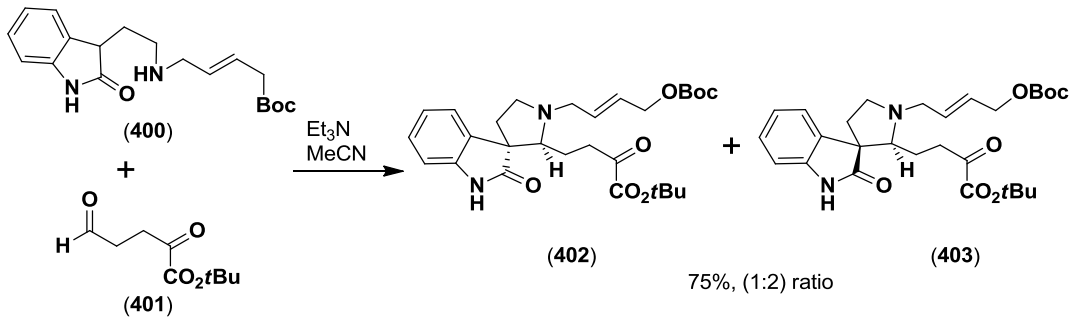
tive synthesis of secondary amine (**400**). In this way, tryptamine was first converted into its *p*-nitrosulfonyl derivative, which was then alkylated with allylic bromide (**397**) to furnish sulfonamide (**398**). Oxindole (**399**) was generated by treatment of (**398**) with *N*-chlorosuccinimide in aqueous THF under carefully controlled conditions and in excellent yield. The sulfonyl group was removed from the nitrogen atom to give the secondary allylic amine (**400**) in four steps from tryptamine and 73% overall yield.

Scheme 63



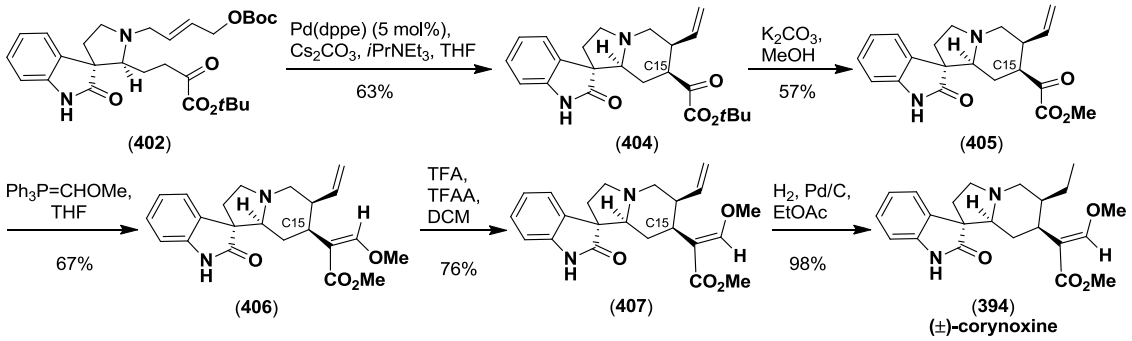
The key Mannich condensation reaction between equimolar amounts of amine (**400**) and aldehyde (**401**) proceeded in an anhydrous mixture of acetonitrile and triethylamine at room temperature to give a 1:2 mixture of spiro diastereomers (**402**) and (**403**) respectively in 75% yield (Scheme 64).

Scheme 64



When minor diastereomer (**402**) was subjected to reaction with 3 equivalents of a 1:1 molar mixture of cesium carbonate and diethylisopropylamine in the presence of 5 mol% of a palladium catalyst (allylpalladium chloride dimer as the Pd source with 1,2-bis-(diphenylphosphanyl)ethane (dppe) as ligand), a Tsuji–Trost cyclisation[124] reaction occurred to give the *cis* product (**404**) in 63% yield (Scheme 65). The *trans* product could not be isolated in a detectable amount. The mixture of the two bases was important for a good yield to be achieved, according to the authors, the soluble amine base picked up the proton from the substrate, and it was then irreversibly trapped by the carbonate. Next, they transformed the *tert*-butyl ester into its methyl ester (**405**), principally because the *tert*-butylester was fully unreactive towards the Wittig reagent for introduction of the methoxymethylene group. The transesterification reaction proceeded with only 57% yield because of some epimerization at C-15. The methyl ester (**405**) reacted to produce only the *Z*-alkene (**406**), which isomerized cleanly to give the more stable *E*-isomer (**407**) under acidic, anhydrous conditions. Finally, hydrogenation gave racemic corynoxine (**394**).[125]

Scheme 65



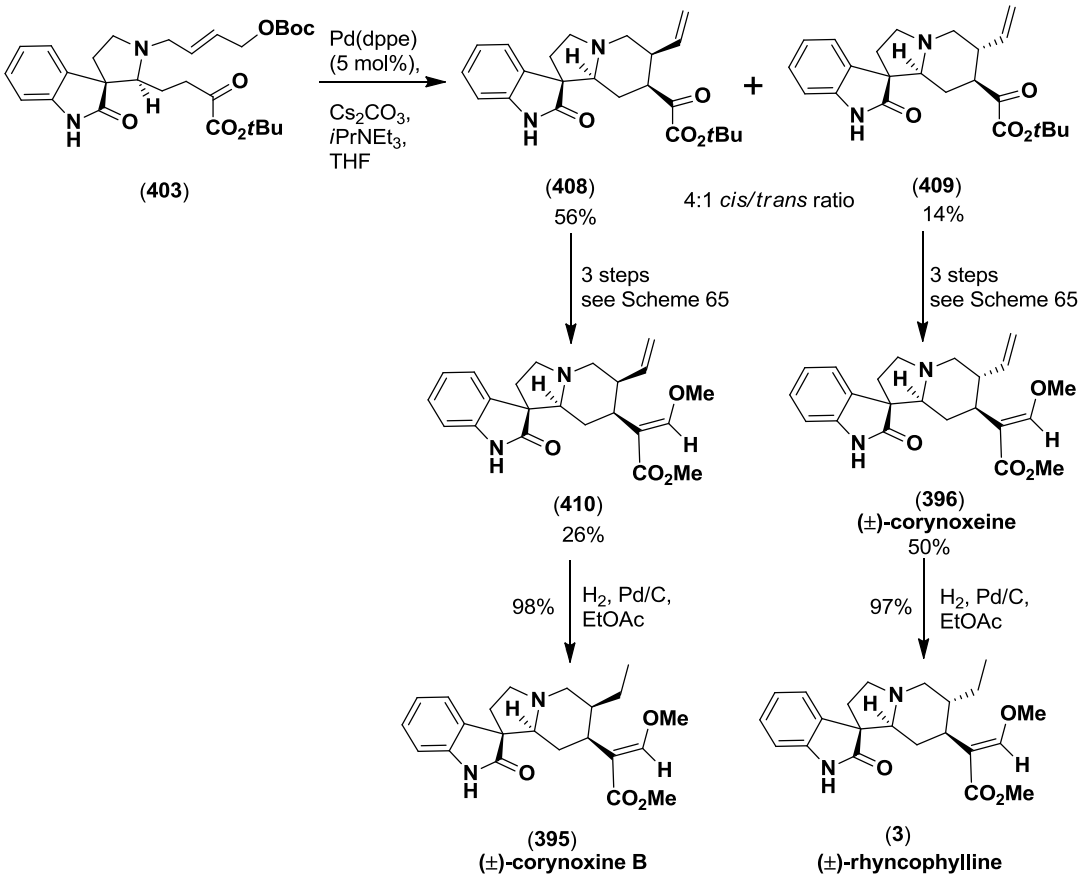
The same series of reactions was applied to the major spirocyclization product (**403**), as shown in Scheme 66. Palladium-catalysed Tsuji–Trost allylic alkylation led to a 4:1 *cis/trans* mixture of cyclisation products (**408**) and (**409**) in 56% and 14% isolated yields, respectively. In a similar way to that shown in Scheme 65, these tetracycles were converted into the target racemic natural products corynoxine B (**395**),[125] corynoxeine (**396**),[126] and rhynchophylline (**3**).[126]

3.2) Wang et al.'s Enantioselective Formal Synthesis of Rhynchophylline and Isorhyncophylline

The protection of the primary alcohol moiety of aldehyde (**411**), which was synthesized through the cross-metathesis of acrolein and 3-butenol with Grubbs second generation catalyst afforded the *α,β*-unsaturated aldehyde (**412**), as illustrated in Scheme 67.[127] After an organocatalytic asymmetric Michael addition of methylmalonate to unsaturated aldehyde (**412**), diester (**414**) was afforded as a crude product, which was used directly in the

subsequent cascade reaction. Condensation of 2-chlorotryptamine with (**414**) produced Schiff base (**415**), which upon treatment with trifluoroacetic acid afforded the key spiral tetracyclic core [(**416a**)/(**416b**) = 3:1) in 78% combined yield, with excellent enantio-selectivity [(**416**), 95% ee] from 2-chlorotryptamine.

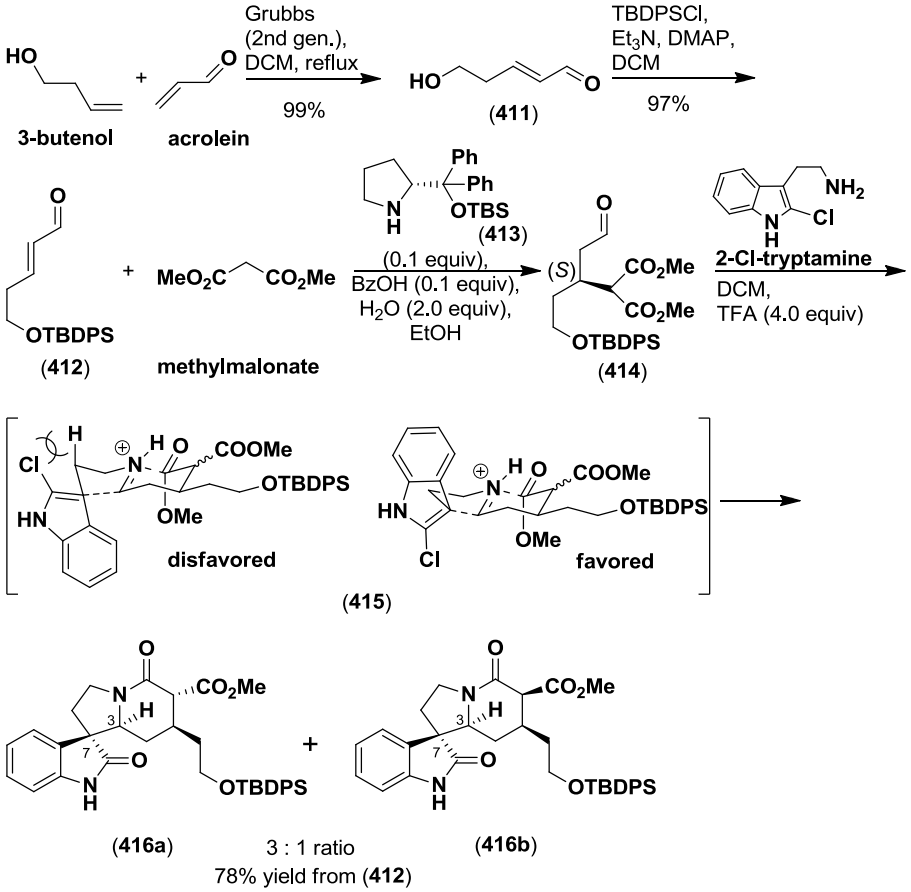
Scheme 66



It is important to note that (**412**) could be converted to the desired configuration through the subsequent steps, and no other stereoisomers were observed. In this regard, the observed stereochemistry during the formation of (**416**) could be rationalized through two

chair like transition states, as shown in Scheme 67. The destabilizing axial interactions would preclude the diastereomers epimeric at C-3, and the strong repulsion between the chlorine and hydrogen resulted in the exclusive formation of the C-7 epimer.

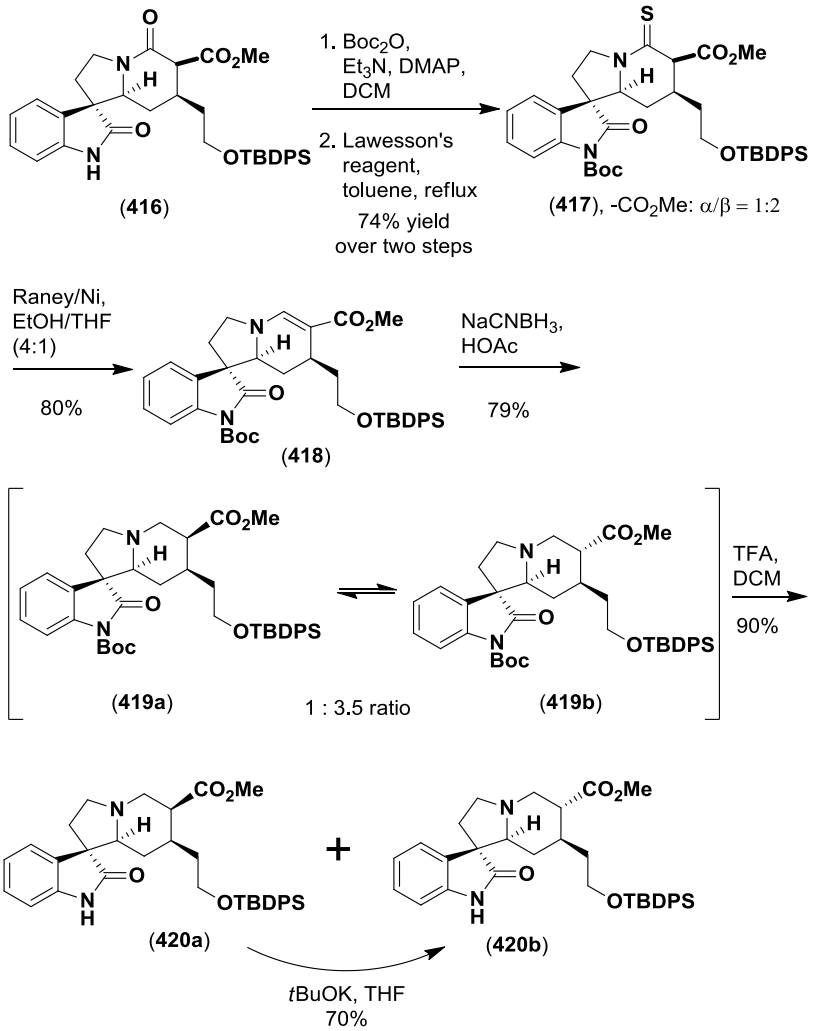
Scheme 67



Next, protection of (**416**) with $(Boc)_2O$ and a subsequent conversion of the lactam ester to the thiolactam (**417**) with Lawesson's reagent proceeded in 74% yield over two steps (Scheme 68). Oxindole (**417**) was then treated with Raney nickel to furnish *α,β*-unsaturated ester (**418**) in 80% yield. The C-C double bond was reduced by means of

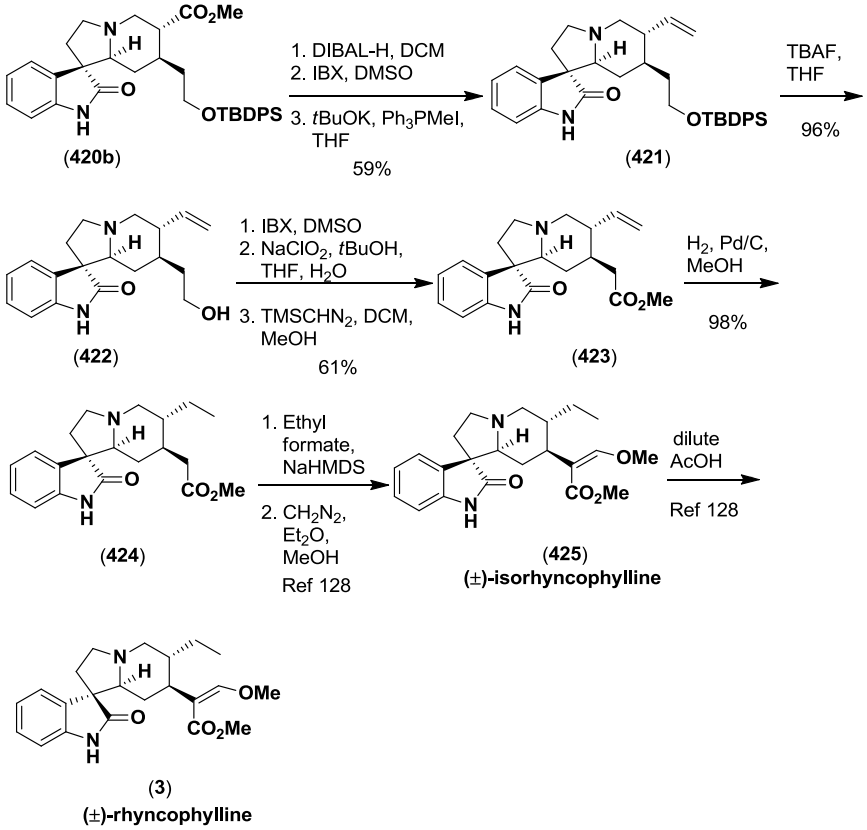
cyanoborohydride in acetic acid to afford the stereoisomeric (**419a**) and (**419b**) (1:3.5 ratio, respectively) in 79% combined yield. The Boc-protected oxindoles (**419**) were successfully deprotected with TFA in DCM, to give diastereomeric oxindoles (**420a**) and (**420b**) in 90% overall yield. The stereoisomer (**420a**) was epimerized to the desired configuration by treatment with potassium *tert*-butoxide in THF in 70% yield (Scheme 68).

Scheme 68



The chemoselective reduction of the ester (**420b**) with DIBAL-H, followed by an oxidation with IBX in DMSO and Wittig olefination, provided olefin (**421**) in 59% yield over three steps (Scheme 69). Desilylation with TBAF in tetrahydrofuran afforded the primary alcohol (**422**) in 96% yield. Accordingly, oxidation of the primary alcohol with IBX produced an aldehyde, which was subjected to Pinnick oxidation and esterification to afford ester (**423**) in 61% overall yield. Reduction of the double bond in oxindole (**423**) by Pd/C-catalyzed hydrogenation in methanol afforded tetracyclic oxindole (**424**) in 98% yield, which had been converted into both isorhynchophylline (**425**) and rhynchophylline (**3**) in two and three steps, respectively, according to reported procedures (Scheme 69).[128]

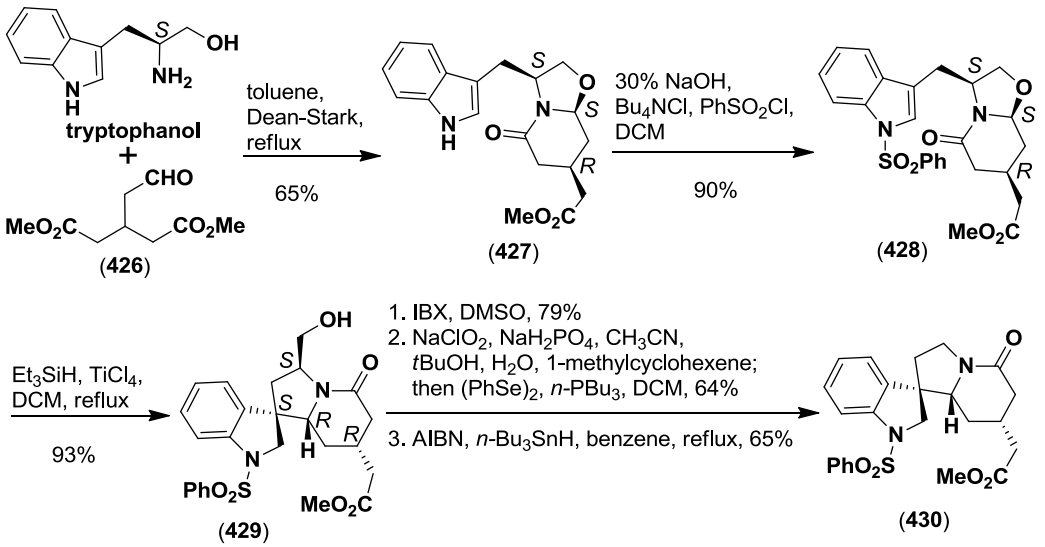
Scheme 69



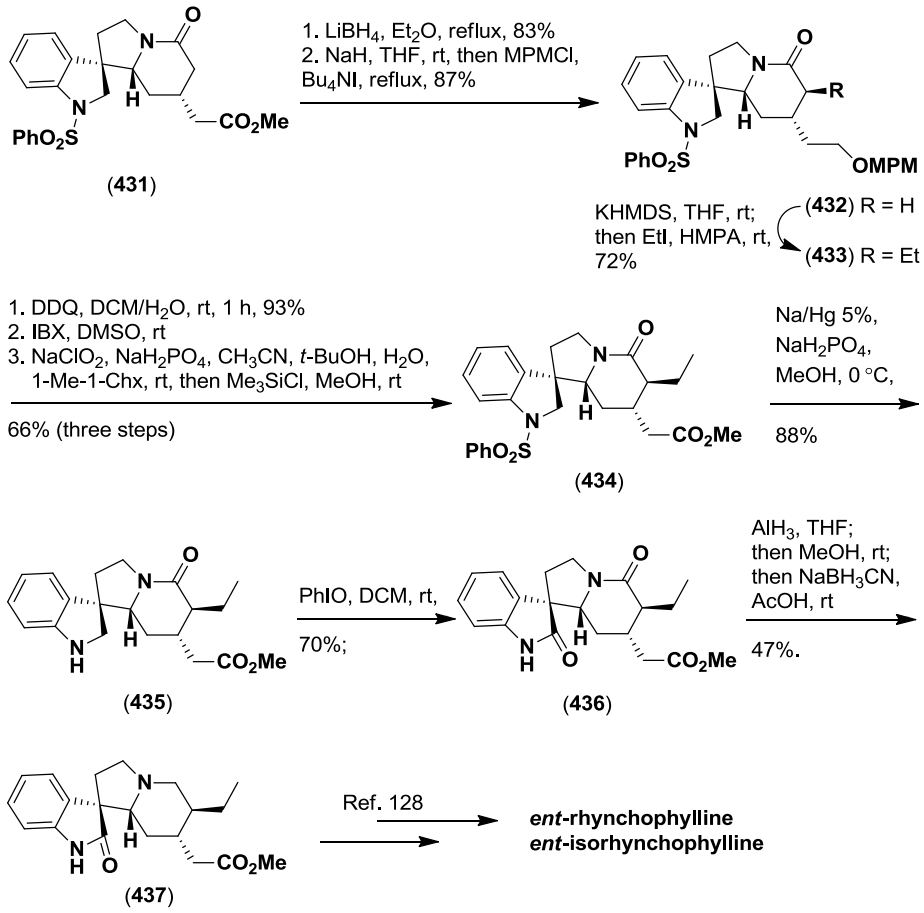
3.3) Amat et al.'s Enantioselective Formal Synthesis of *ent*-Rhynchophylline and *ent*-Isorhynchophylline

An enantioselective formal synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline was accomplished starting from (*S*)-tryptophanol (Scheme 70).[129] (*S*)-Tryptophanol had the advantage that it not only acted as the source of chirality but it also incorporated the tryptamine moiety present in several natural products. The synthesis featured as key steps a stereoselective cyclocondensation and a spirocyclization of an *N*-tosyl tryptophanol-derived oxazolopiperidone lactam (**428**), as shown in Scheme 70. Cyclocondensation of (*S*)-tryptophanol with the prochiral aldehyde-diester (**426**) led to the required bicyclic lactam (**427**), in a process that involved the enantioselective desymmetrization of two enantiotopic chains. To direct the key cyclization at the indole 3-position, the *N*-indole was protected with the deactivating group benzenesulfonyl. Treatment of lactam (**428**) with $TiCl_4$ in the presence of Et_3SiH resulted in a regio- and stereocontrolled cyclization, with concomitant reduction of the initially formed spiroindoleninium intermediate, leading to the tetracyclic spiroindoline (**429**) as a single stereoisomer in 93% yield (Scheme 70). For the enantioselective formal synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline, it was necessary to (Scheme 71): (1) remove the hydroxymethyl group, (2) introduce stereoselectively the C-20 ethyl substituent, (3) oxidize the indoline moiety to the oxindole functionality, and finally, (4) reduce chemoselectively the lactamcarbonyl.[128]

Scheme 70



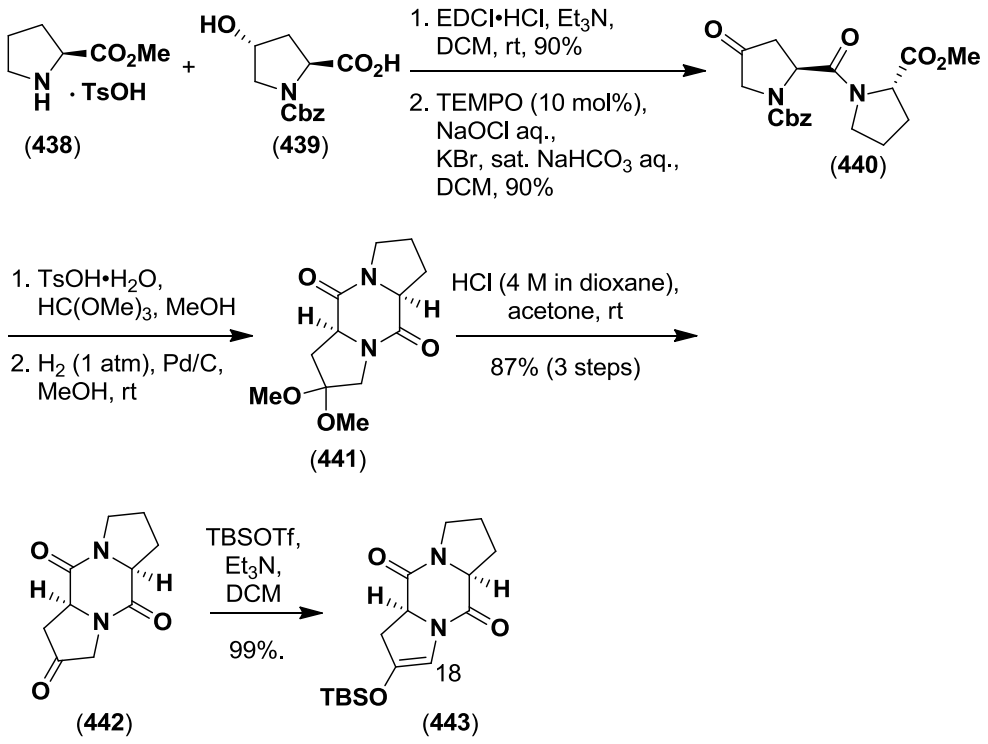
Scheme 71



3.4) Fukuyama et al.'s Stereoselective Synthesis of Spirotryprostatin A

Fukuyama et al. reported the stereoselective synthesis of spirotryprostatin A (**6**) by employing an intramolecular Heck reaction to introduce the quaternary spirocenter.[130] The synthesis started from proline derivatives (**438**) and (**439**) which reacted to form intermediate (**442**) *via* aldol condensation followed by dehydration and then diastereoselective hydrogenation from the presumed convex face of the diketopiperazine. Treatment of ketone (**442**) with TBSOTf and Et_3N furnished silyl enol ether (**443**) in 99% yield (Scheme 72).

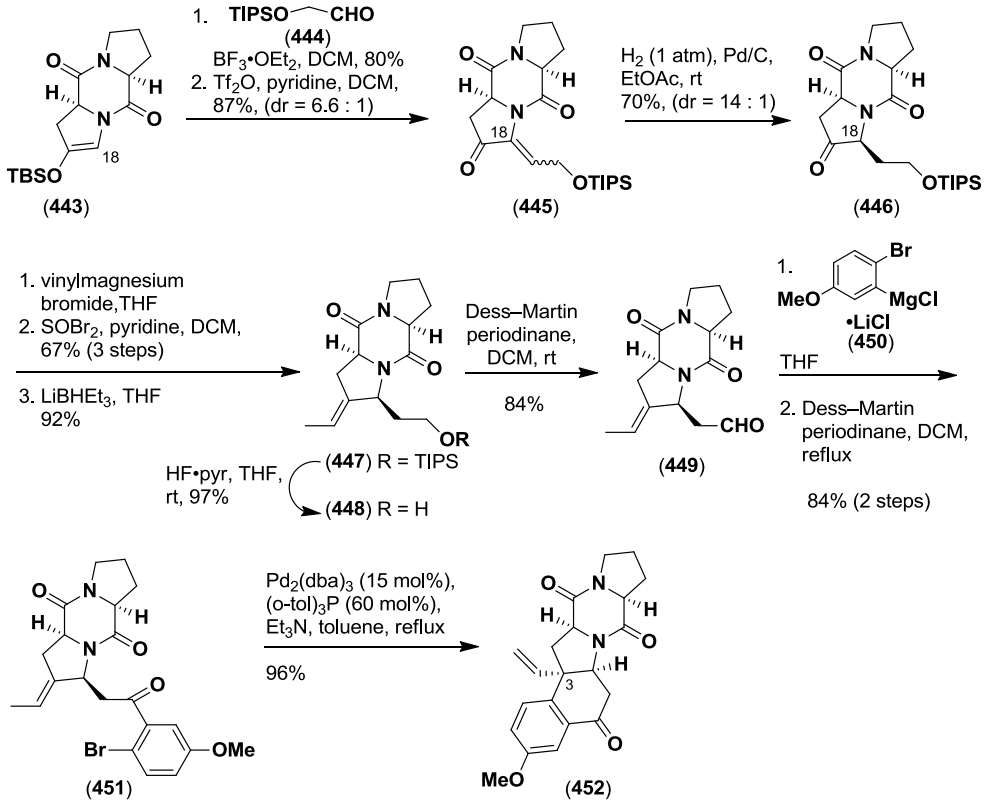
Scheme 72



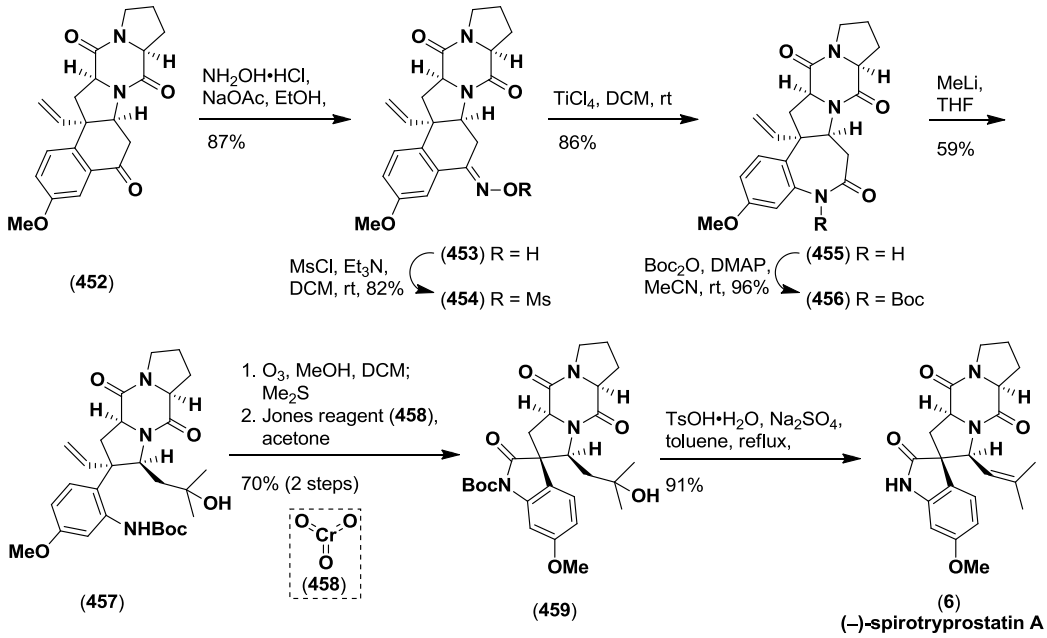
The alkyl group at C-18 was introduced by a Mukaiyama aldol reaction (Scheme 73) with silyloxy acetaldehyde (**444**). The resulting mixture of aldols was dehydrated by treatment with Tf_2O and pyridine which led to the unsaturated ketone (**445**) in 87% yield as a 6.6:1 mixture of the *E/Z* isomers. Diketopiperazine (**446**), with the desired C-18 (*S*) stereochemistry, was obtained after hydrogenation of the double bond. Then, the TIPS protected alcohol (**447**) was obtained after a three-step sequence which involved the addition of vinylmagnesium bromide to (**446**), treatment with thionyl bromide, and reduction of the rearranged allyl bromide with $LiEt_3BH$. It was known that a tethering unit containing an arylketone moiety has proven to work well for the Heck reaction. Thus, removal of TIPS group, followed by oxidation of the primary alcohol gave the aldehyde (**449**), to which was added the aryl Grignard reagent. The desired tethering ketone (**451**) required for the intramolecular Heck reaction was obtained after Dess–Martin oxidation. As a consequence of this tether, the aryl moiety approaches selectively from the desired face, leading to the ketone (**452**) in 96% yield.

For the construction of the spiroindolinone moiety, Scheme 74, ketone (**452**) was converted to oxime mesylate (**454**). Treatment of pentacyclic oxime mesylate (**454**) with $TiCl_4$ triggered a Beckmann rearrangement to afford lactam (**456**), after introduction of a Boc group. Addition of MeLi led to opening of the lactam to afford the tertiary alcohol (**457**). Ozonolysis of the vinyl group, followed by reaction with aniline gave a five membered hemiaminal, which after oxidation gave spiroindolinone (**459**). Spirotryprostatin A (**6**) was obtained in 91% yield after dehydration of the tertiary hydroxyl group and removal of the Boc group under acidic conditions (Scheme 74).

Scheme 73



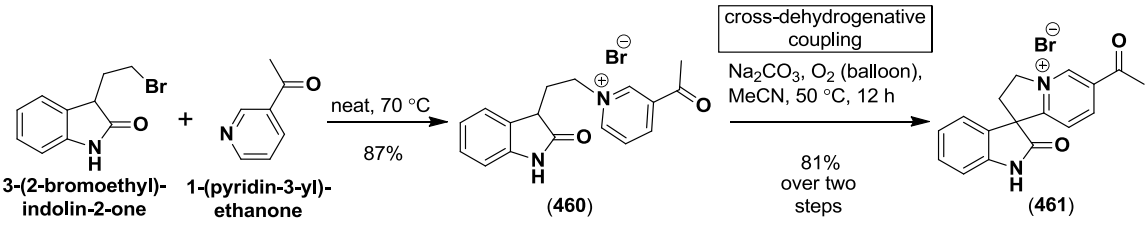
Scheme 74



3.5) Zhao et al.'s Synthesis of Racemic Corynoxine and Corynoxine B

Zhao et al. developed a straightforward method for the construction of the fused tetracyclic 3-spirooxindole skeleton, which exists widely in natural products.[131] To highlight the utility of the direct cross-dehydrogenative coupling, two natural products, (±)-corynoxine (**394**) and (±)-corynoxine B (**395**), were synthesized from the coupling product (**461**), as shown in Scheme 75. The pyridinium salt (**460**) was obtained by the treatment of 3-(2-bromoethyl)indolin-2-one with 1-(pyridin-3-yl)ethanone. Subsequently, the transition-metal-free cross-dehydrogenative coupling was performed using optimized conditions: Na_2CO_3 as the base, acetonitrile (polar solvent worked best), molecular oxygen as oxidant, and the temperature was set at 50 °C (otherwise the reaction would proceed slowly).

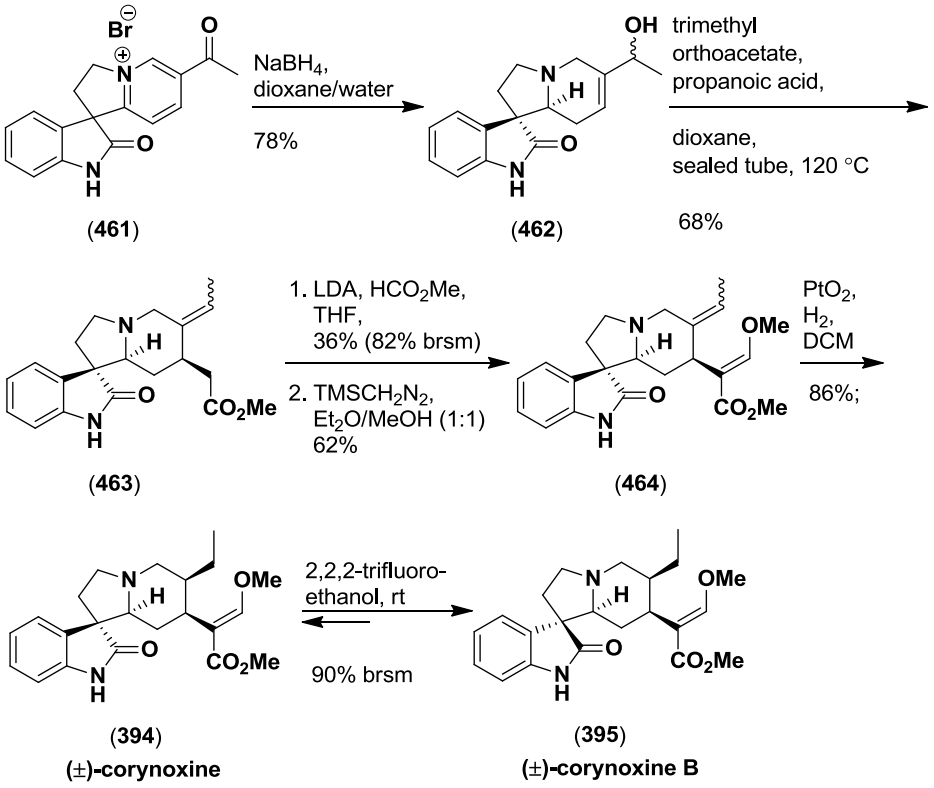
Scheme 75



Next, the coupling product, oxindole (**461**), was treated with $NaBH_4$ in a mixture of dioxane and water (20:1), subsequently the pyridinium and the ketone groups were reduced to afford the oxindole alcohol (**462**), as illustrated in Scheme 76. Although no selectivity

was observed at the newly formed hydroxyl group, it did not affect the efficiency of the total synthesis because both of the isomers afforded the same final product. The alcohol (**462**) was then subjected to Johnson−Claisen rearrangement by heating in trimethyl orthoacetate with a catalytic amount of propanoic acid to afford the ester (**463**).

Scheme 76



Treatment of the ester with LDA, followed by the addition of excess methyl formate, resulted in the desired enol ester intermediate in 36% yield (82% based on recovered starting material [brsm]). The crude enol ester was later methylated with trimethylsilyl diazomethane to give (**464**) in 62% yield. Finally, the catalytic hydrogenation of (**464**)

utilizing PtO_2 under a hydrogen atmosphere afforded the target compound, (±)-corynoxine (**394**), in 86% yield. Dissolution of (±)-corynoxine in 2,2,2-trifluoroenthanol led to formation of the epimeric (±)-corynoxine B (**395**) in six hours. Chromatographic separation of the mixture afforded a 90% yield of (±)-corynoxine B along with recovered (±)-corynoxine (31%). Clear evidence for this equilibrium ratio was found when (±)-corynoxine B was subject to the identical conditions and the same ratio was reached between (±)-corynoxine and (±)-corynoxine B within 6 hours.

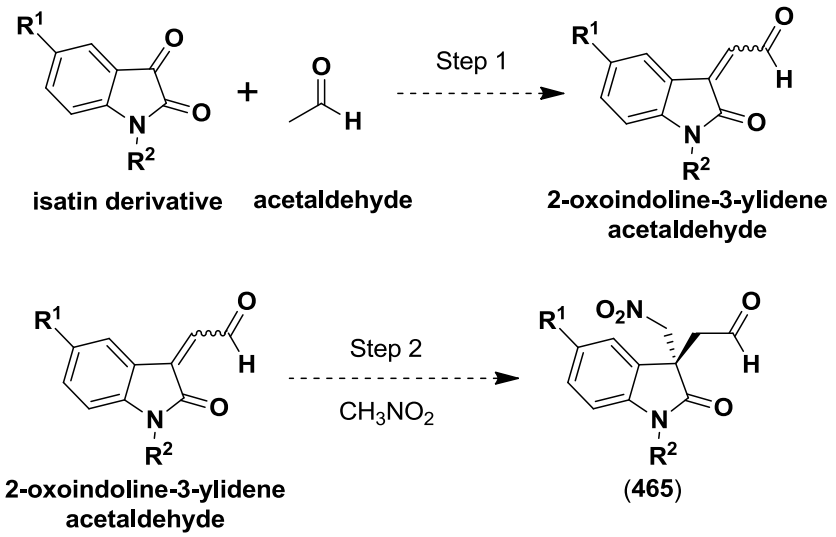
3.6) Hayashi et al.'s Synthesis of (–)-Horsfiline and (–)-Coerulescine by Asymmetric Organocatalyzed Michael Addition of Nitromethane to a 2-Oxoindoline-3-ylidene Acetaldehyde

Hayashi et al. recently reported the three one-pot sequential synthesis of both (–)-horsfiline (**221**) and (–)-coerulescine (**234**) by employing two key reactions, namely (1) the synthesis of a 2-oxoindoline-3-ylidene acetaldehyde from acetaldehyde and an isatin derivative and (2) the organocatalyzed Michael addition of nitromethane to the 2-oxoindoline-3-ylidene acetaldehyde to construct the all-carbon quaternary stereogenic centers with excellent enantioselectivity (Scheme 77).[132]

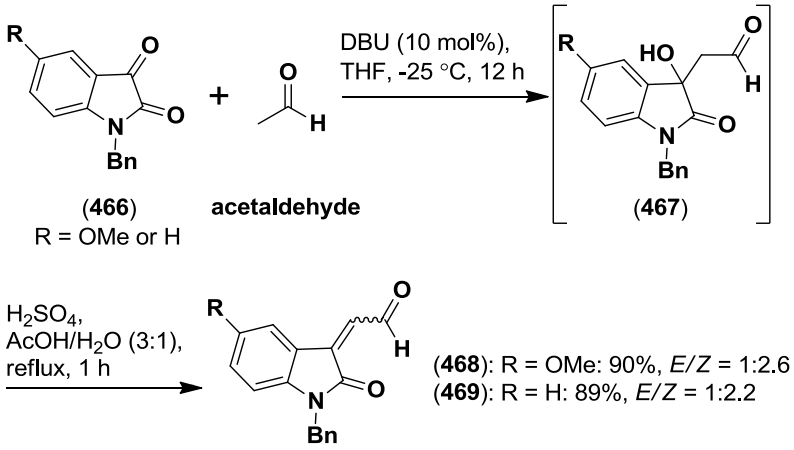
The synthesis started with the aldol addition of isatin derivatives (**466**) with acetaldehyde which generated the *β*-hydroxyaldehyde (**467**) and subsequent dehydration under acidic conditions provided the 2-oxoindoline-3-ylidene acetaldehyde (**468** or **469**) directly as a mixture of *E/Z* isomers (Scheme 78). The enals were both obtained in a one-pot operation

from the corresponding isatins in excellent yield. This method was found to be higher yielding and more convenient than reported methods.[132]

Scheme 77



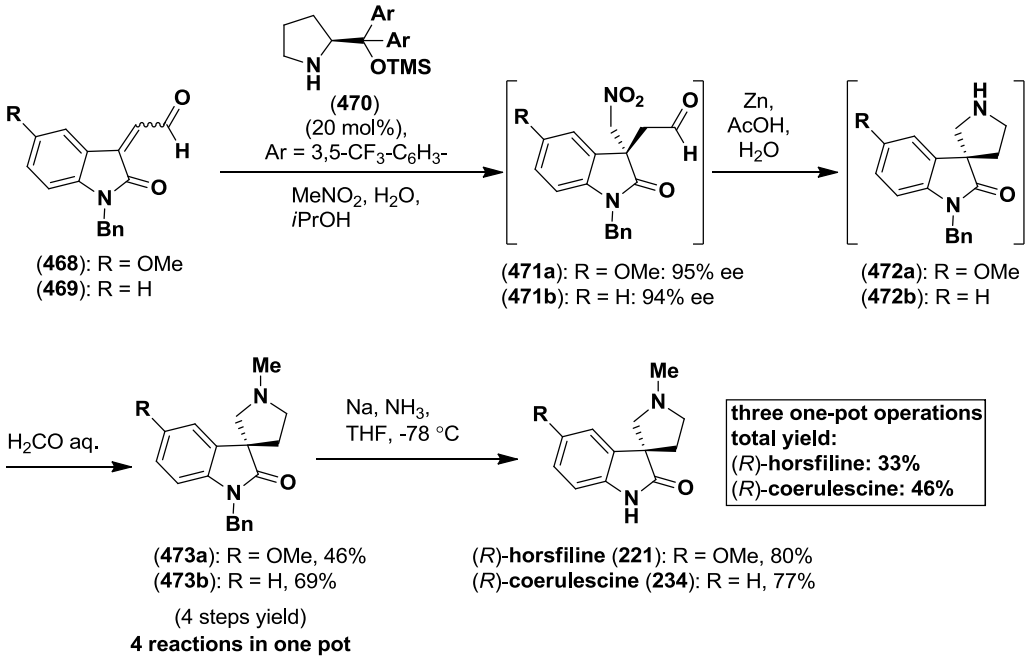
Scheme 78



The enantioselective conjugate addition of nitromethane to (**468** or **469**) generated aldehydes (**471**) with excellent enantioselectivity in the construction of the all-carbon quater-

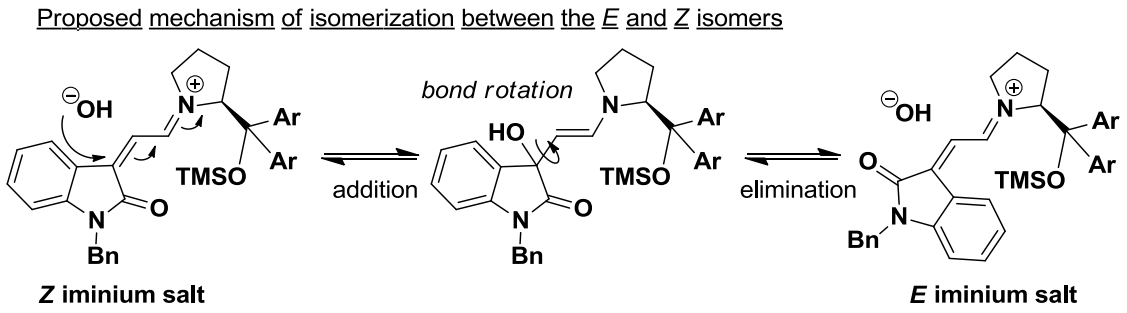
nary stereogenic centers (Scheme 79). Zn, AcOH, and water were added to the same reaction vessel to reduce the nitro group into an amine. At the same time, an intramolecular reductive amination proceeded to form the pyrrolidino spirocycle (**472**). Formaldehyde was then added to the reaction mixture sequentially to install the *N*-methyl group by an intermolecular reductive amination. This afforded (**473a**) and (**473b**) in 46% and 69% yield over 4 steps from their corresponding aldehydes. The four reactions from aldehydes (**468** or **469**) were performed in the same reaction vessel. The removal of the benzyl group under Birch conditions furnished (*R*)-horsfiline (**221**) and (*R*)-coerulescine (**234**) in good yields. The spirooxindole group tends to racemize under acidic conditions; therefore, the optical purity was checked by HPLC analysis over a chiral phase. This showed the ee values of (**221**) and (**234**) to be 95% and 94 %, respectively, which indicated that racemization did not occur during the synthesis (Scheme 79).

Scheme 79



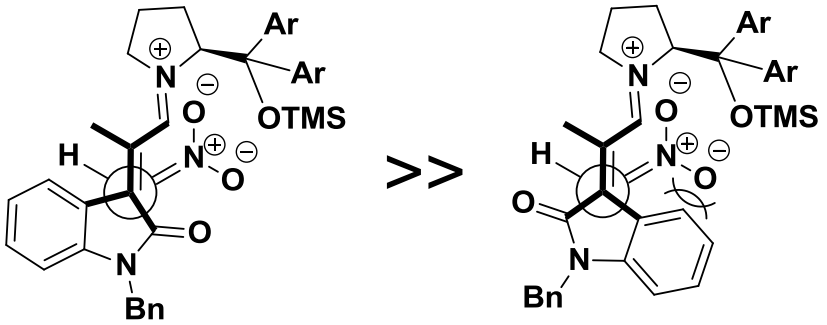
It should be noted that excellent enantioselectivity was observed even though a mixture of *E/Z* isomers of ylidene aldehydes (**468** or **469**) was used. It is assumed that isomerization between the *E*- and *Z*-isomers would occur through the addition and elimination of a hydroxy ion, as illustrated in Scheme 80.

Scheme 80



The proposed transition state models for Michael addition of a nitronate anion into the iminium salts are shown in Figure 14. The nitronate ion approaches the iminium salts *via* the acyclic synclinal transition state proposed by Seebach and Golinski, which maximizes the electrostatic interaction between the nitro group and iminium ion. **TS-1**, in which the *Z*-isomer reacts to provide the major enantiomer. On the other hand, there is a steric repulsion between the phenyl group and the nitro group at the synclinal position in **TS-2**. As a result, it is believed the addition of nitromethane proceeds preferentially *via* **TS-1** to form the major enantiomer.

Figure 14. Michael addition of a nitronate anion into the iminium salts



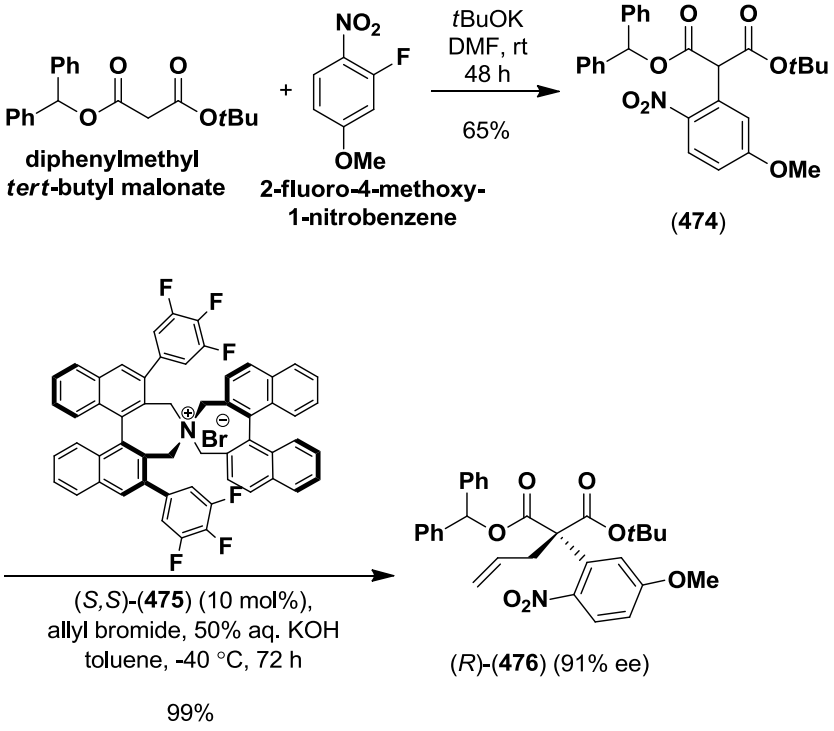
***Z* isomer**
TS-1

***E* isomer**
TS-2

3.7) Park et al.'s Enantioselective Phase-Transfer Catalytic Total Synthesis of (–)-Horsfiline

Park et al. reported an efficient synthetic method for the preparation of (–)-horsfiline (**221**) through the enantioselective phase-transfer catalytic α-allylation of malonate.[133] First, substrate (**474**) for the enantioselective phase-transfer catalytic (PTC) α-allylation was prepared from diphenylmethyl *tert*-butyl malonate (Scheme 81). Nucleophilic aromatic substitution with 2-fluoro-4-methoxy-1-nitro-benzene, under basic conditions (*tert*-BuOK) in dimethylformamide (DMF) at room temperature afforded α-arylmalonate (**474**, 65% yield). Next, the PTC mediated allylation of malonate (**474**) in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**476**), along with allyl bromide (5 equivalents) and 50% KOH (aq, 5 equivalents) at –40 °C in toluene (Scheme 81), gave the allylated compound (*R*)-(**476**) with excellent yield and enantiomeric excess (99%, 91% ee).

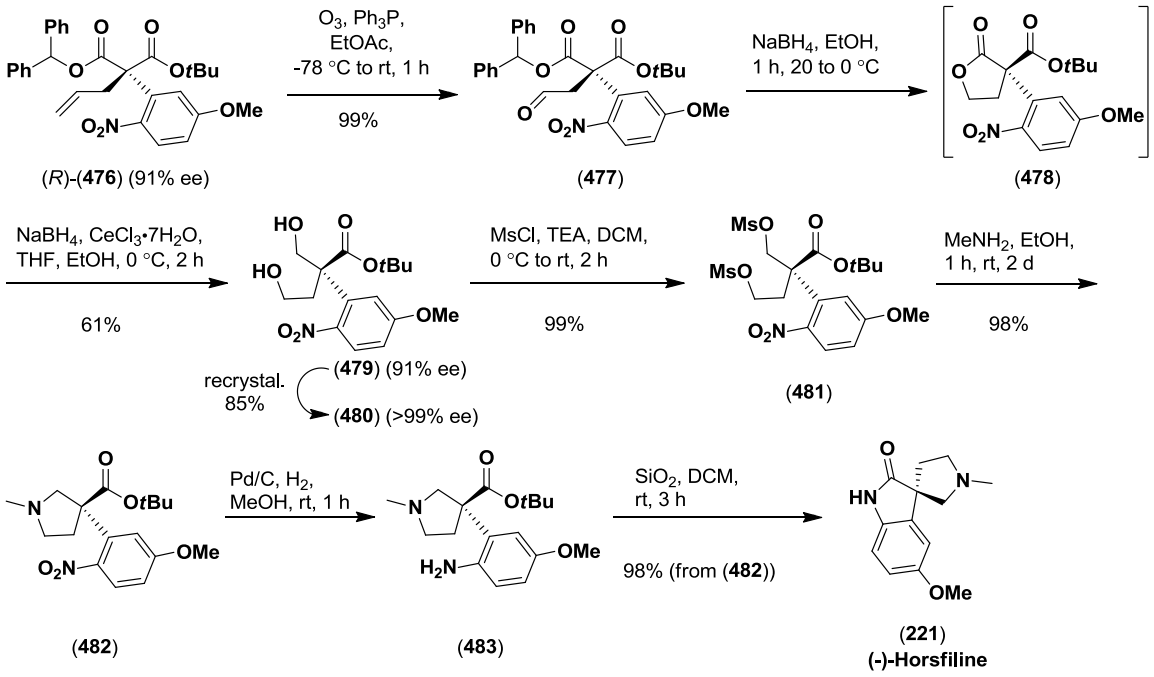
Scheme 81



Ozonolysis of (**476**), followed by reductive work up in the presence of triphenylphosphine afforded the corresponding aldehyde (**477**, 99%; Scheme 82). Aldehyde (**477**) was reduced by sodium borohydride in ethanol to provide lactone (**478**). Without purification, the lactone moiety of (**478**) could be selectively reduced again to the corresponding diol (**479**) *in situ* by additional treatment of sodium borohydride with cerium(III) trichloride and tetrahydrofuran as a co-solvent [61% from (**477**)]. As a side reaction, removal of the α-hydroxymethyl group was partially observed by deformylation *via* a retro aldol reaction, caused by the α-nitrophenyl group. The major enantiomer of diol (**479**) could be easily purified as a single stereoisomer (>99% ee) in 85% yield by recrystallization using hexane and ethyl acetate (5:1). Dimesylation of diol (**480**) (99% yield),

followed by double *N*-alkylation using excess methylamine successfully afforded *N*-methylpyrrolidine (**482**) in 98% yield. Finally, (–)-horsfiline (**221**) was successfully obtained by stirring methylpyrrolidine (**482**) with silica gel (SiO_2) in CH_2Cl_2 without racemization (98%, >99% ee).[133]

Scheme 82



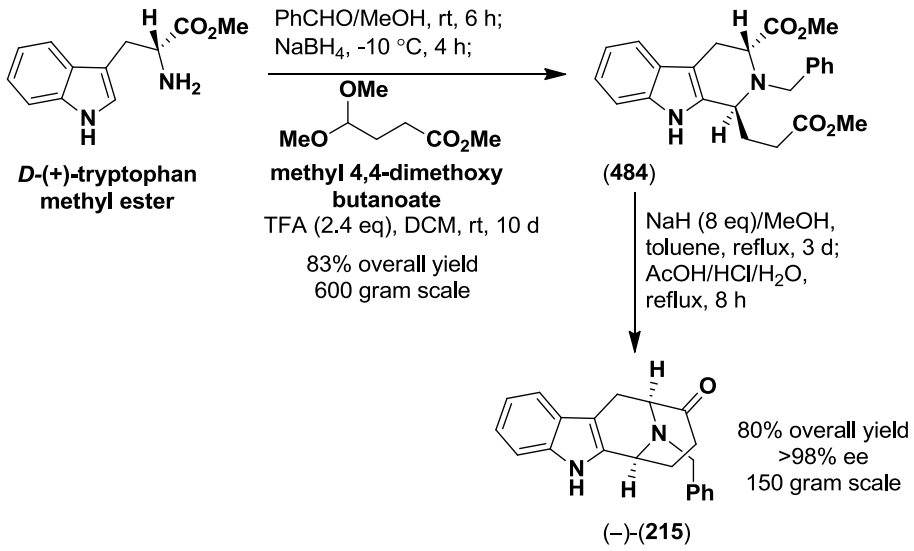
4) Wearing et al.'s Enantiospecific Synthesis of (+)-Alstonisine *via* a Stereospecific Osmylation Process and Proof of The Absolute Configuration of This Natural Product

Wearing et al. reported in 2002 an enantiospecific, stereospecific total synthesis of (+)-alstonisine (**8**).[56a,56b] The work established the correct absolute configuration of this nat-

ural oxindole alkaloid. It also confirmed its correct structure in agreement with that proposed by Le Quesne based on biogenetic grounds.[134,135,136] This corrected the structure reported in a *J. Am. Chem. Soc*. communication, incorrectly drawn from an X-ray crystal structure by Nordman et al. A method that provided entry into either spirocyclic oxindole, diastereomeric at C-7, was developed in the course of this work as well.

The synthesis of alstonisine (**8**) began with the preparation of the (–)-N_a-H, N_b-benzyl tetracyclic ketone (**215**) as the key building block on large scale (Scheme 83). D-(+)-Tryptophan methyl ester was diastereospecifically converted into azabicyclononone (**215**) in greater than 98% ee in a two-pot process on multihundred gram scale via tetrahydro-β-carboline (**484**). After N_b-benzylation of the tryptophan methyl ester with benzaldehyde and sodium borohydride in methanol was completed, at 0 °C, trifluoroacetic acid was added to the reaction vessel at 0 °C to neutralize the alkaline mixture. Removal of the solvent under reduced pressure was followed by the addition of CH_2Cl_2, TFA and methyl 4,4-dimethoxybutanoate to the vessel at 0 °C and the modified Pictet–Spengler reaction (600 g scale) was carried out to provide the *trans* diester (**484**) in 83% overall yield. In the second sequence of reactions (150 g scale), the Dieckmann cyclization was completed and the reaction solution was then cooled to 0 °C after which it was carefully quenched with glacial acetic acid. Concentrated glacial AcOH, aqueous HCl and H_2O were added to the residue, after removal of the solvent under reduced pressure, in the same vessel at 0 °C. The acidic hydrolysis and decarboxylation was then executed at reflux to provide (–)-(**215**) in 80% yield in greater than 98% ee.

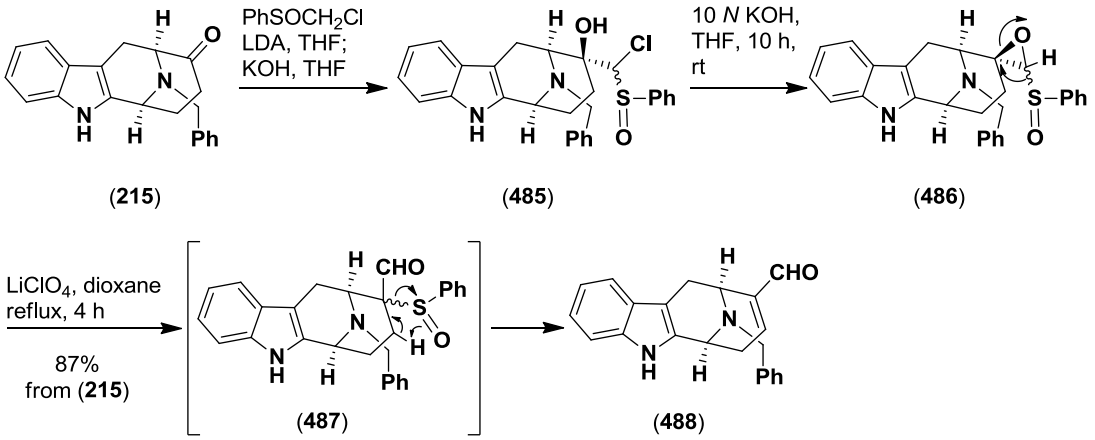
Scheme 83



With the tetracyclic ketone (**215**) constructed enantiospecifically, attention then turned to the preparation of the α,β-unsaturated aldehyde (**488**, Scheme 84). The conversion was achieved in good yield *via* the spirooxirane phenylsulfoxide (**486**) by the published methods of Satoh.[137] The N_a-H tetracyclic ketone (**215**) was treated with the anion of α-chloromethylphenyl sulfoxide generated *in situ* to furnish a chlorohydrin intermediate (**485**). Treatment of (**485**) with aq 10 *N* KOH/THF (3:7) converted the crude chlorohydrin into spirooxirane phenylsulfoxide (**486**). The spirooxirane phenylsulfoxides were then dissolved in a solution of dry dioxane which contained lithium perchlorate. The slurry which resulted was heated under nitrogen to provide the desired α,β-unsaturated aldehyde (**488**, 87% overall yield, >98% ee). Dioxane was employed to dissolve the catalytic amount of lithium perchlorate which permitted replacement of the original procedure (toluene) to avoid the use of tri-*n*-butylphosphine oxide. The phosphine oxide was difficult to remove

after the reaction was complete, consequently, the use of dioxane/$LiClO_4$ was an important impovement in a practical sense.

Scheme 84

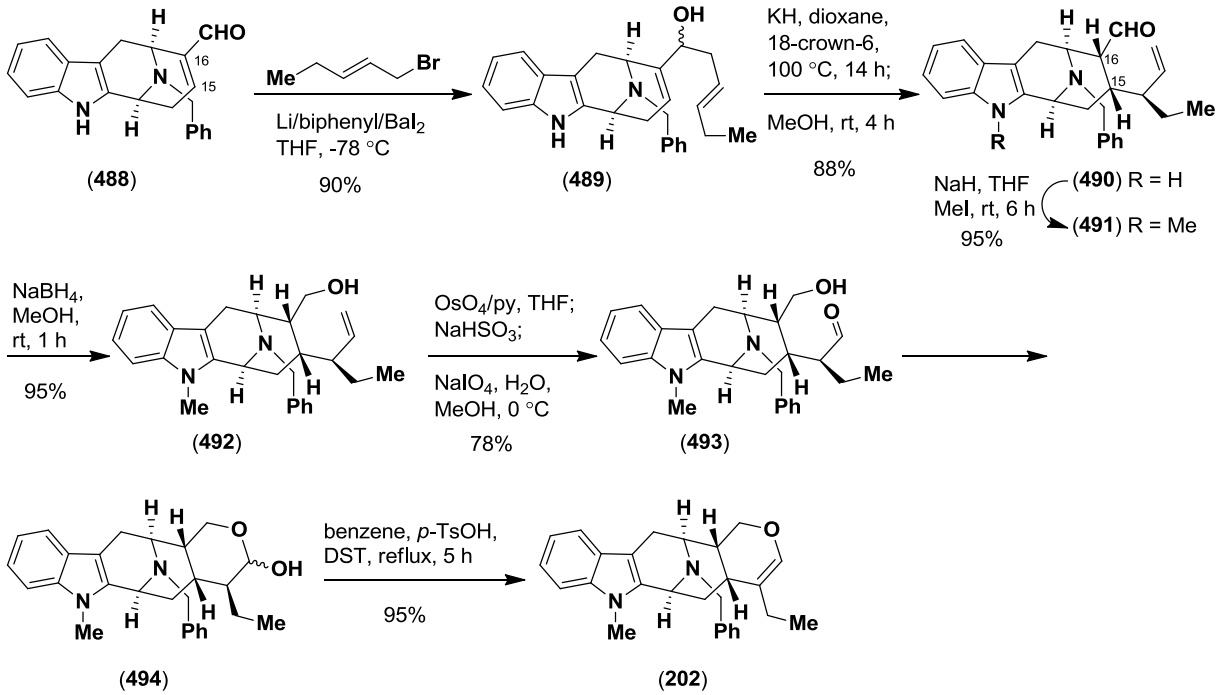


In the mechanism for the formation of the α,β-unsaturated aldehyde (Scheme 84), the Lewis acid catalyzed oxirane rearrangement was followed by a sulfoxide mediated *syn* elimination to generate (**488**).[56]

In order to functionalize the C-15 position of the α,β-unsaturated aldehyde (**488**), and to avoid allylic rearrangement of the allyl Grignard reagent which was prepared from 1-bromo-2-pentene, a barium-mediated 1,2-addition protocol was chosen (Scheme 85). The execution of a modified Yamamoto procedure[138] of the original report[139] in a fashion similar to a Barbier–Grignard process, with 1-bromo-2-pentene and Rieke barium, provided the desired allylic alcohol (**489**) in high yield. The reason for the high regioselectivity of the addition of the barium reagent through the α-carbon atom in this Barbier–Grignard process was believed due to the unusually long barium-carbon bond.[140]

The anionic oxy–Cope rearrangement took place in the N_a-H azabicyclononene system (**489**) almost exclusively from the desired bottom face of the C-15/C-16 olefinic bond, as expected, to afford olefin (**490**) in 88% overall yield. The diastereoselectivity at C-15 was greater than 30:1 in this system to provide the correct chirality at C-15. The purpose of adding methanol to the reaction mixture was to epimerize the newly formed aldehydic function at C-16 of the minor isomer into the more stable (desired) configuration. Then, when the olefinic aldehyde (**490**) was treated with sodium hydride and methyl iodide, an almost quantitative yield of the N_a-methyl olefinic aldehyde (**491**) was obtained. The aldehyde (**491**) obtained above was reduced with sodium borohydride in 95% yield to furnish monol (**492**, Scheme 85).

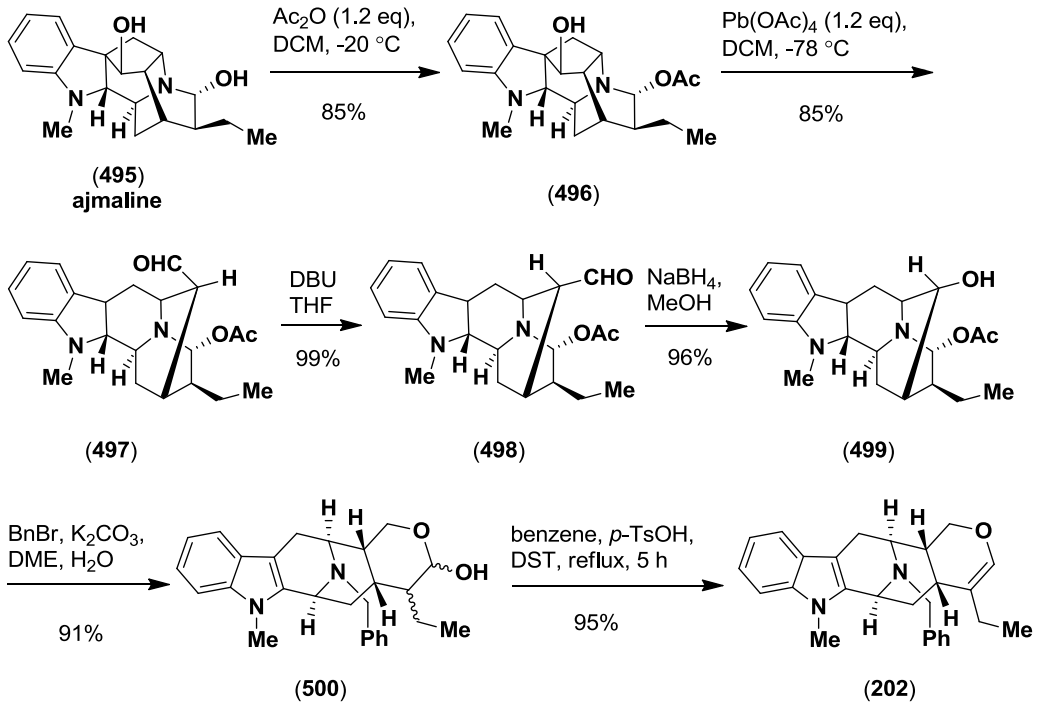
Scheme 85



Olefin (**492**) was next stirred with a premixed solution of OsO_4-pyridine in THF, oxidative cleavage of the olefinic unit occurred to give hemiacetal (**494**) in 78% yield. The intermediate aldehyde (**493**) which formed underwent cyclization simultaneously to form the desired E-ring without affecting the chirality at C-15 and C-16. The hemiacetal (**494**) was converted into a single pure enol ether (**202**) on dehydration with *p*-TSA in refluxing benzene (95% yield).

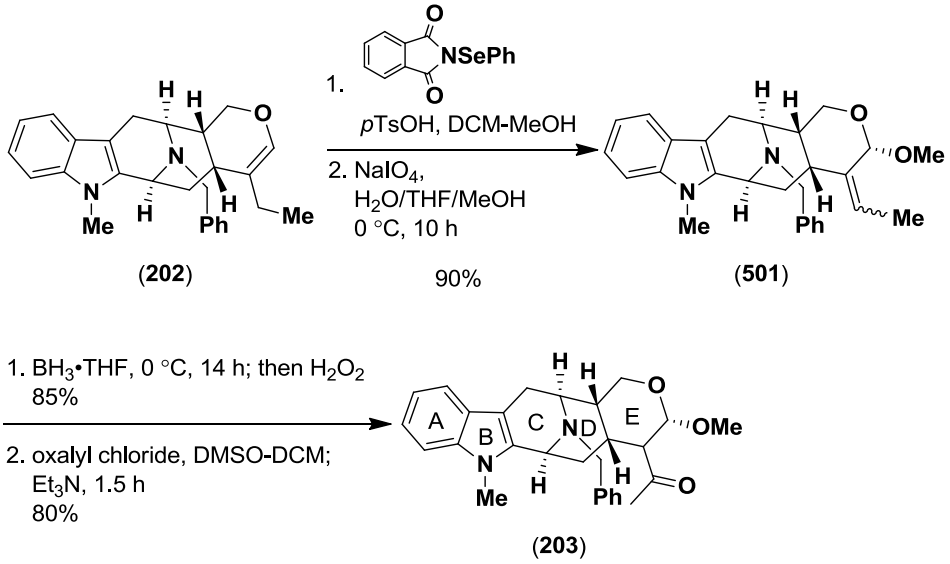
This macroline-related enol ether (**202**) was also obtained from the degradation of ajmaline (**495**) by a much improved modification of the procedures of Sakai[141] and Gan.[142] As illustrated in Scheme 86, the hydroxyl group at C-21 in ajmaline (**495**) was selectively protected in 85% yield with acetic anhydride to form the acetyl ester (**496**). Oxidation of the indoline moiety with lead(IV) acetate generated the aldehyde (**497**) in 85% yield. Epimerization of the stereogenic center at C-16 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry THF provided the thermodynamically more stable aldehyde (**498**) in almost quantitative yield. Reduction of the aldehyde function in (**498**) with sodium borohydride afforded the primary alcohol (**499**) in high yield. Next, the macroline-related hemiacetal (**500**) was formed in 91% yield by treatment of the aminoacetate (**499**) with benzyl bromide in the presence of K_2CO_3. Finally, dehydration of hemiacetal (**500**) in dry benzene at reflux in the presence of 1.1 equivalents of dry *p*-toluenesulfonic acid gave the N_b-benzyl enol ether (**202**) in very high yield (Scheme 86). The enol ether (**202**) obtained from the degradation of ajmaline (**496**) was identical to (**202**) that from olefinic aldehyde (**488**, Scheme 85).

Scheme 86



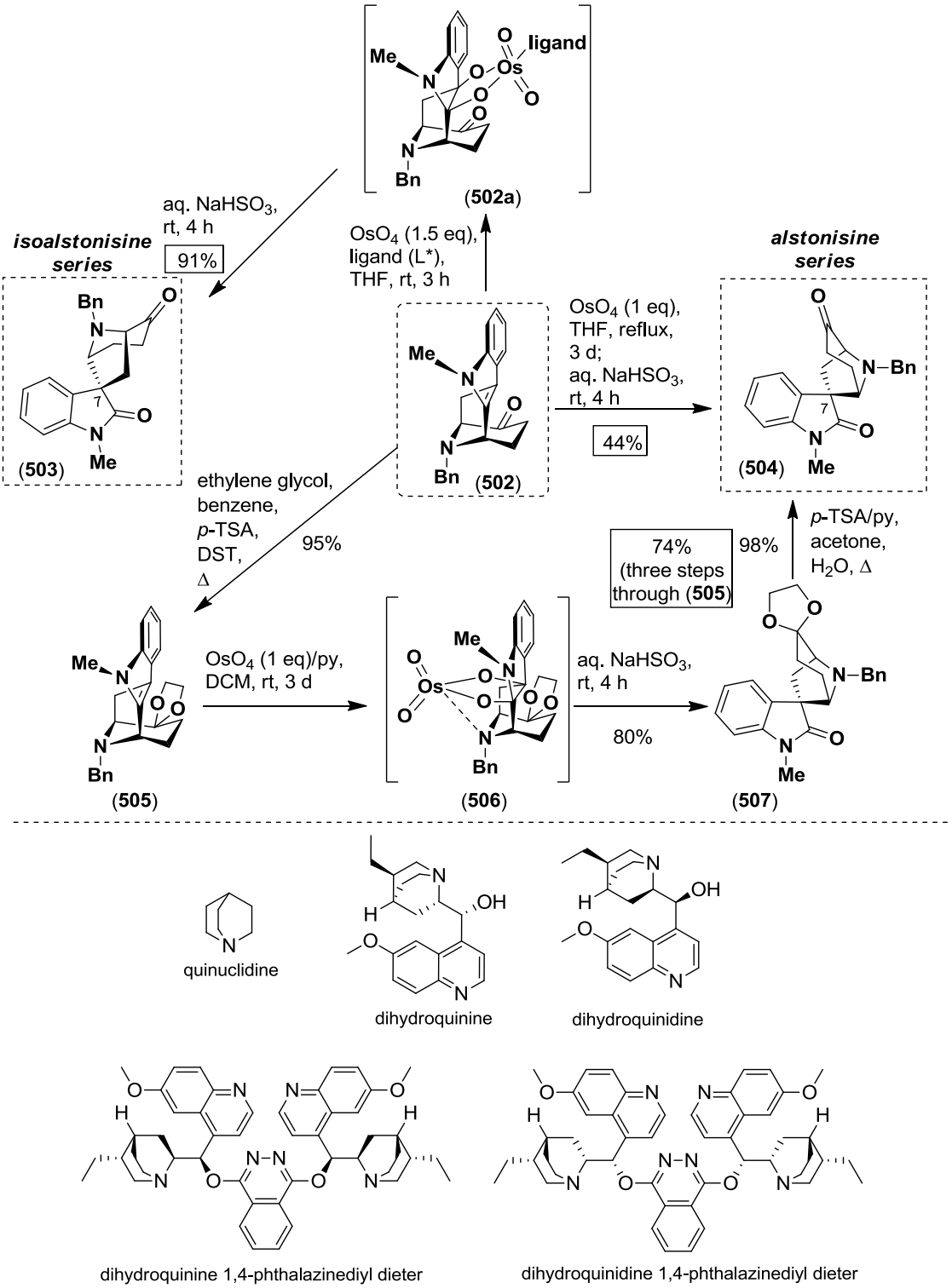
The regiospecific oxyselenation of the olefin (**202**) was carried out with *N*-phenylseleno phthalimide in CH_2Cl_2-MeOH in the presence of *p*-TSA to provide a mixture of seleno-acetals in high yield (Scheme 87). This mixture was directly treated with $NaIO_4$ in THF-MeOH-H_2O solution (without separation) to afford olefins (**501**) in 90% yield as a 4:1 mixture of *Z/E*-isomers. Treatment of the mixture of olefins (**501**) with the BH_3•THF complex and H_2O_2 oxidation, followed by the modified Swern oxidation conditions gave the ketoacetal (**203**) in 80% yield.

Scheme 87



With the availability of intermediate (**203**), Wearing et al. decided to approach the synthesis of alstonisine (**8**) in a stereocontrolled manner to establish the correct chirality at C-7. Initially, the conversion of tetracyclic ketone (**502**) into either diastereomeric N_b-benzyltetracyclic oxindole (**504**, proposed alstonisine stereochemistry) or (**503**, Scheme 88) with stoichiometric amounts of osmium tetraoxide in the presence or absence of Sharpless ligands was executed by Peterson et al.[143] Excellent diastereoselectivity was obtained in this process. In the presence of OsO_4, (**504**) was the major diastereomer (91:9), but in the presence of OsO_4 with a Sharpless ligand the opposite diastereomer (**503**) was obtained (97:3). In the case of ketal (**505**), only one diastereomer was formed in 80% yield (Scheme 88).

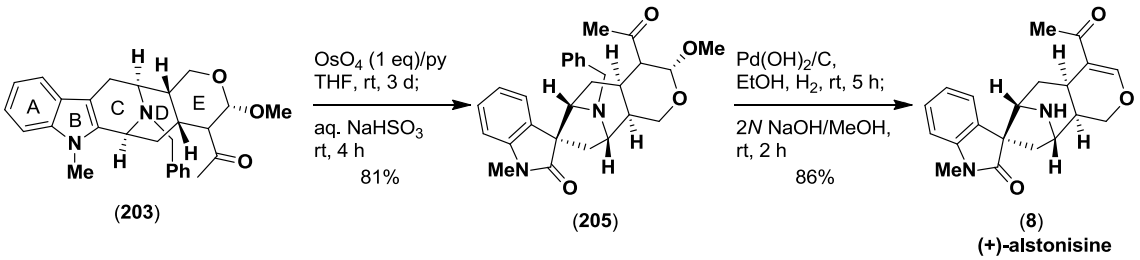
Scheme 88


ligand
(502a)
aq. NaHSO3, rt, 4 h
91%
isoalstonisine series
OsO4 (1.5 eq), ligand (L*), THF, rt, 3 h
alstonisine series
OsO4 (1 eq), THF, reflux, 3 d; aq. NaHSO3, rt, 4 h
44%
(503)
(502)
(504)
ethylene glycol, benzene, p-TSA, DST, Δ
95%
74% (three steps through (505))
98%
p-TSA/py, acetone, H2O, Δ
OsO4 (1 eq)/py, DCM, rt, 3 d
aq. NaHSO3, rt, 4 h
80%
(505)
(506)
(507)
quinuclidine
dihydroquinine
dihydroquinidine
dihydroquinine 1,4-phthalazinediyl dieter
dihydroquinidine 1,4-phthalazinediyl dieter

With this information in hand, a solution of ketoacetal (**203**) in THF-pyridine (5:1) was stirred with a premixed solution of osmium tetraoxide (1 equivalent) in THF-pyridine (5:1) at room temperature (Scheme 89). This was followed by reductive workup with aqueous $NaHSO_3$. From this process the ketoacetal oxindole (**205**) was obtained as the sole diastereomer in 81% yield. It was believed that the osmium tetraoxide coordinated to the piperidine nitrogen atom, delivering the reagent from the convex face of the substrate intramolecularly (as shown in the model reactions in Scheme 88). This complexation was presumably favored because of the axial preference (with respect to ring D) of the benzyl group [as seen in (**506**), Scheme 88 and also Scheme 19]. The concomitant complexation of osmium at the equatorial position (with respect to ring D) facilitated intramolecular attack of the osmium reagent to furnish osmate ester. The osmate ester was then reduced by sodium bisulfite, and the *cis*-diol that resulted underwent a pinacol rearrangement to furnish the desired oxindole (**205**, Scheme 89) diastereospecifically.

In the final stage of the synthesis, the benzyl group was successfully removed by hydrogenolysis when 2 equivalents of Pearlman's catalyst $[Pd(OH)_2/C]/H_2$ were used (Scheme 89). Base-mediated elimination of the elements of methanol was then carried out to furnish (+)-alstonisine (**8**) in 86% yield (two steps).

Scheme 89



The first total synthesis of alstonisine was accomplished, by Wearing and collaborators, in enantiospecific fashion in an overall yield of 12% (from tryptophan methyl ester) and in 17 reaction vessels. The structure and absolute configuration of (+)-alstonisine (**8**) at C-7 were determined by NOE-NMR spectroscopic experiments and was further confirmed by single-crystal X-ray analysis and comparison of the properties to natural alstonisine kindly provided by Professor LeQuesne. This corrected the structure earlier reported by Nordman which had been incorrectly drawn because the absolute configuration had been incorrectly correlated with that of ajmaline.

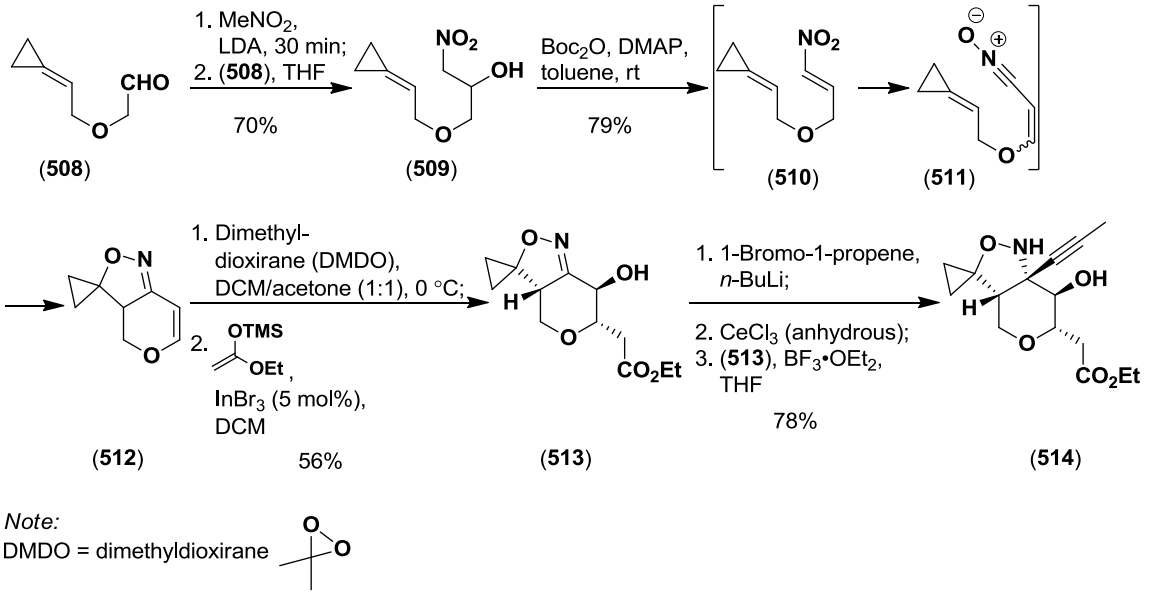
5) Recent Advances in The Total Synthesis of Related Natural Oxindole Alkaloids

5.1) Carreira et al.'s Total Synthesis of (±)-Gelsemoxonine

Carreira et al. reported a racemic total synthesis of gelsemoxonine (**524**) that utilized as the key step the ring contraction of a spirocyclopropane isoxazolidine to provide access to the azetidine moiety. An additional salient feature of the synthesis was the introduction of the congested quaternary oxindole stereocenter at C-7 by a diastereoselective reductive Heck cyclization. The route began with the construction of the pyran precursor (**514**) for the key ring contraction as depicted in Scheme 90.[144]

Aldehyde (**508**) was subjected to a Henry reaction with lithiated nitromethane, which furnished secondary alcohol (**509**) in 70% yield. This intermediate was then treated with Boc_2O in the presence of DMAP to deliver isoxazoline (**512**) *via* a sequence consisting of alcohol activation, elimination, dehydrative formation of a nitrile oxide, and intramolec-

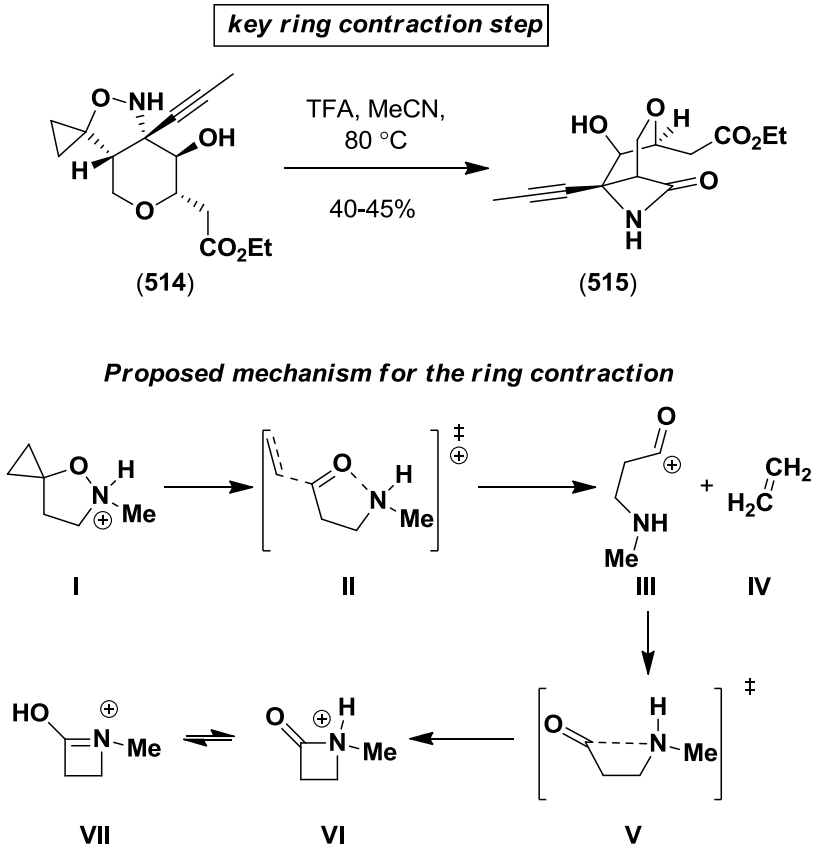
Scheme 90



ular dipolar cycloaddition. Epoxidation of the enol ether (**512**) using DMDO produced an unstable epoxide intermediate, which was immediately subjected to nucleophilic opening by ((1-ethoxyvinyl)oxy)trimethylsilane, under Lewis acid catalysis to furnish alcohol (**513**) in 56% yield. Although the epoxidation proceeded to give a 2:1 mixture of epoxide diastereomers in favor of the desired epoxide isomer, careful tuning of the reaction conditions permitted differential opening of only the major epoxide, with the minor diastereomer remaining unreactive. With isoxazoline (**513**) in hand, introduction of an alkyne moiety was subsequently addressed. Accordingly, addition of 1-propynyllithium to (**513**) in the presence of anhydrous $CeCl_3$ and BF_3•OEt_2 furnished diastereomerically pure oxazolidine (**514**) in 78% yield. Interestingly, the free secondary alcohol in (**513**) proved essential for the addition to proceed. The authors speculated that the hydroxyl group was involved as a directing group for the incoming organometallic species.

With a route to spirocyclopropane isoxazolidine (**514**) secured, the key ring contraction to the projected *β*-lactam was then addressed by Carreira et al., as shown in Scheme 91. Therefore, when (**514**) was treated with TFA at 80 °C, the system underwent ring contraction to yield the highly substituted *β*-lactam (**515**) in 40-45% after complete consumption of isoxazolidine (**514**). The structure of *β*-lactam (**515**) was unambiguously confirmed by X-ray crystallographic analysis. Carreira et al. recently proposed a mechanism for the ring contraction of spirocyclopropane isoxazolidines to form *β*-lactams based on experimental and computational studies (Scheme 91).[145]

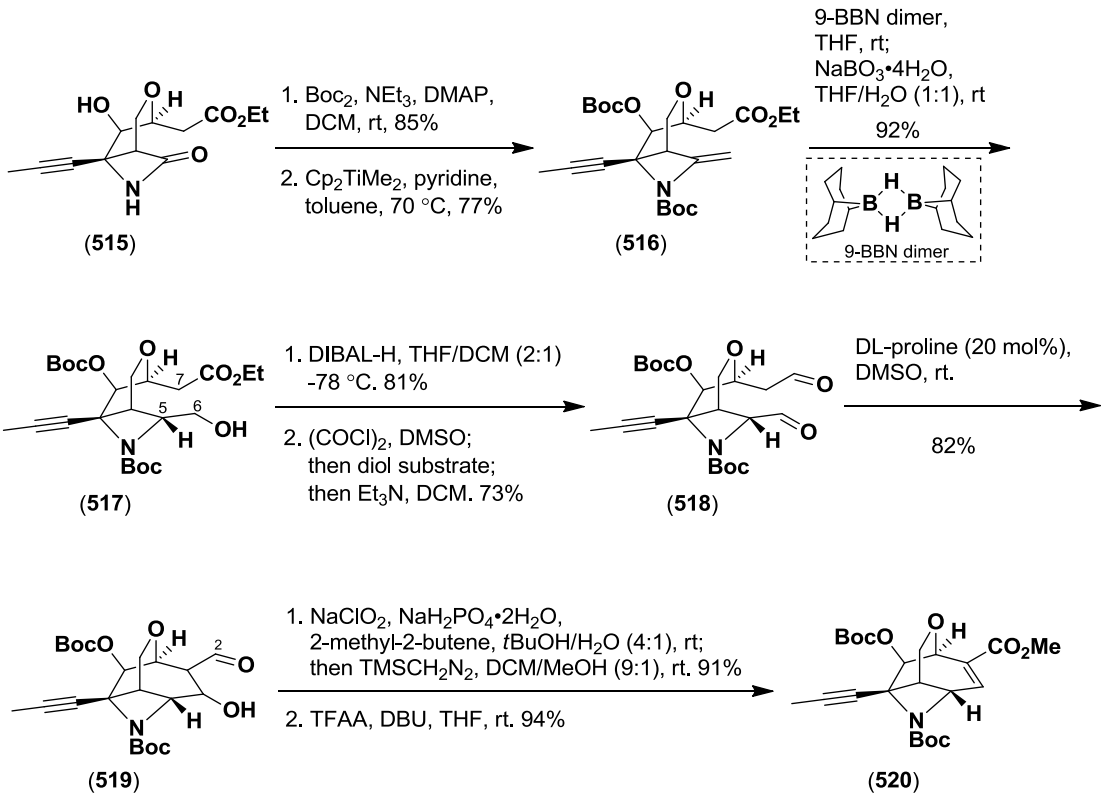
Scheme 91



The next hurdle in their synthetic effort was the methenylation of *β*-lactam (**515**, Scheme 92). To this end, amide (**515**) was first protected using Boc_2O to furnish the corresponding imide in 85% yield. Exposure of this substrate to Petasis' olefination conditions[146] led to clean conversion to strained enecarbamate (**516**), obtained in 77% yield. The stereocenter at C-5 was then installed by a hydroboration reaction. In this transformation it was observed that the strained olefin in (**516**) reacted exclusively from the *exo*-face. Thus, following oxidative workup ($NaBO_3$) primary alcohol (**517**) is obtained in 92% yield as a single diastereomer. With the full carbon backbone of the gelsemoxonine core in place, closure of the seven-membered carbocycle was pursued. It was decided to explore an aldol condensation approach to achieve the requisite ring closure. To this end, dialdehyde (**518**) was prepared by DIBAL reduction of (**517**) followed by oxidation of the intermediate diol under Swern conditions. When dialdehyde (**518**) was treated with 20 mol% of proline, aldol product (**519**) was isolated as a single diastereomer in 82% yield. Notably, no elimination of the secondary alcohol was observed under these conditions. Next, a sequence consisting of Pinnick oxidation/esterification in the presence of a free secondary alcohol delivered the corresponding methyl ester in 91% yield. Finally, elimination of the alcohol using TFAA furnished unsaturated ester (**520**) in 94% yield (Scheme 92).

With the tricyclic core scaffold of gelsemoxonine in hand by Carreira et al. focused on the introduction of the spiro-fused oxindole at C-7 (Scheme 93). Attention turned to the intramolecular addition of arylnucleophiles to the *α,β*-unsaturated carbonyl in (**520**). Consequently, an intramolecular reductive Heck reaction offered an attractive approach to achieve such a transformation. Although the Heck reaction had been commonly used

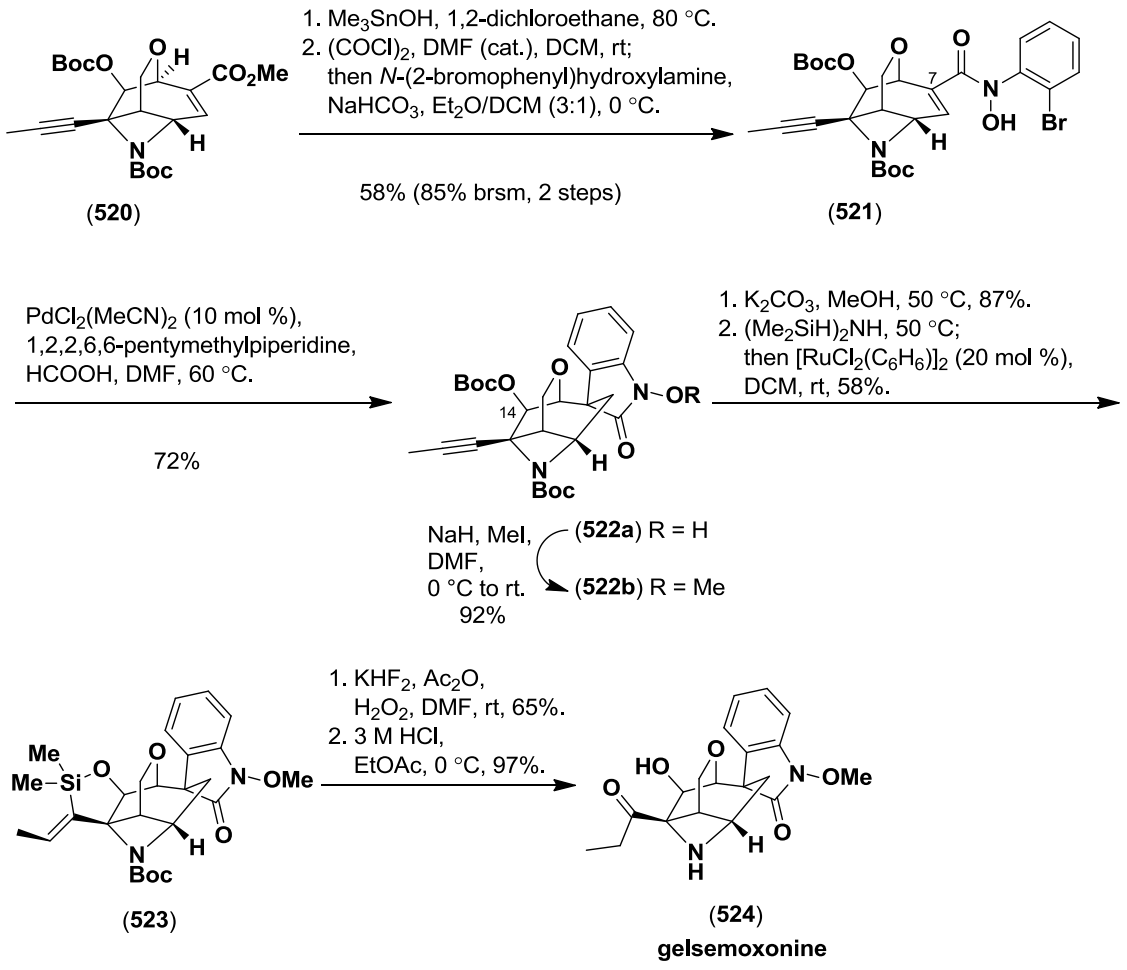
Scheme 92



for the construction of quaternary stereocenters, including oxindole ring systems, the desired reductive variant of this transformation posed a few challenges when applied to projected enone substrate (**521**). Given that a putative aryl-palladium intermediate would be regiospecifically required to add to the congested C-7 carbon atom, the stereochemical outcome could not be predicted on steric grounds. Additionally, reductive quenching of the resulting alkyl-palladium species could be complicated by a variety of undesired competing side reactions. These included reopening of the oxindole ring, *β*-hydride elimination, side reactions involving the adjacent azetidine ring, and a potential cleavage of the N-O bond in (**521**). In order to test the strategy, hydroxamic acid (**521**) was prepared

following hydrolysis of ester (**520**) using Me_3SnOH. The carboxylic acid which resulted was then converted into the acid chloride and coupled to *N*-(2-bromophenyl)hydroxylamine. Upon exposure of the aryl bromide (**521**) to reductive Heck conditions employed by Trost and collaborators,[147] which used formic acid as the reductant, the formation of oxindole (**522a**) was observed in 72% yield and as a single diastereoisomer. The *N*-hydroxyoxindole (**522a**) was then methylated to deliver *N*-methoxy oxindole (**522b**) in 92% yield. With the introduction of the oxindole secured, installation of the ethyl ketone remained as the final task in the synthetic route.

Scheme 93



To this end, a protocol, which involved involving hydroxyl directed hydrosilylation of the triple bond was employed. Following this strategy, the C-14 Boc-carbonate was selectively cleaved using K_2CO_3 in MeOH in 87% yield. The secondary alcohol, which resulted, was subjected to hydrosilylation conditions employing $[RuCl_2(C_6H_6)]_2$ as a catalyst to furnish the vinylsilane (**523**) in 58% yield as an inconsequential mixture of olefinic isomers. Oxidation of this mixture under Tamao−Fleming conditions[148] delivered ethyl ketone in 65% yield. The removal of the *N*-Boc carbamate using 3 M HCl delivered the natural product (±)-gelsemoxonine (**524**) in 97% yield.

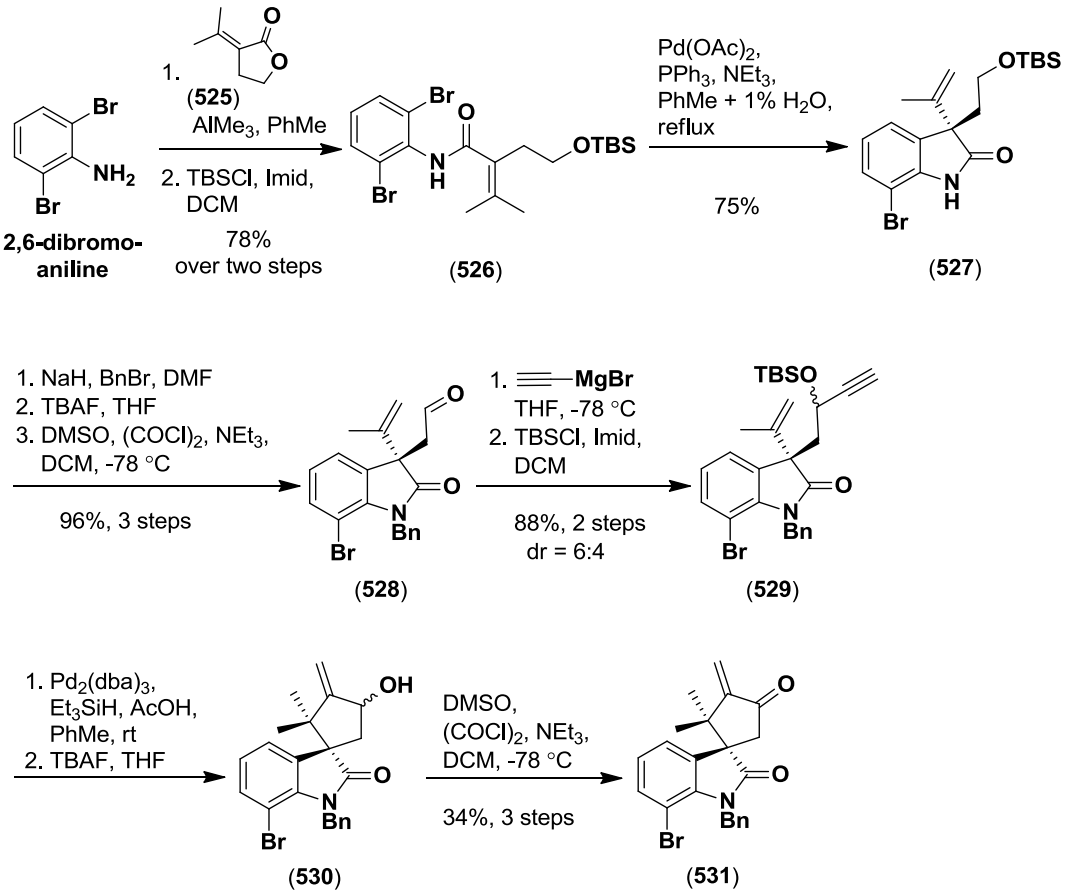
5.2) Wood et al.'s Enantioselective Total Synthesis of (+)-Citrinadin B

In 2013, Wood et al. reported an enantioselective synthesis of the naturally occurring alkaloid (+)-citrinadin B (**543**). The synthetic effort revealed an anomaly in the original structural assignment that has led to a stereochemical revision. The reported synthesis was convergent and employed a stereoselective intermolecular nitrone cyloaddition reaction as the key step.[149]

The synthesis began with exposure of 2,6-dibromoaniline to trimethylaluminum followed by lactone (**525**) which furnished an intermediate alcohol that was protected as the corresponding silyl ether (**526**, Scheme 94). Cyclization of the amide (**526**) to oxindole (±)-(**527**) under Heck conditions was followed by benzyl protection, silyl group cleavage, and alcohol oxidation to furnish aldehyde (±)-(**528**). At this point the stage was begun to be set for an eventual reductive ene-yne cyclization by treating oxindole (±)-(**528**) with ethynyl Grignard. Addition of the Grignard was immediately followed by protection of

the resulting diastereomeric alcohols as their corresponding silyl ethers (±)-(**529**). Cyclization of (±)-(**529**) was then accomplished under conditions developed by Trost,[150] which was then followed by a TBAF mediated deprotection process to afford a diastereomeric mixture of alcohols (±)-(**530**). Oxidation of the latter under Swern conditions provided the dipolar cycloaddition substrate, enone (±)-(**531**, Scheme 94).

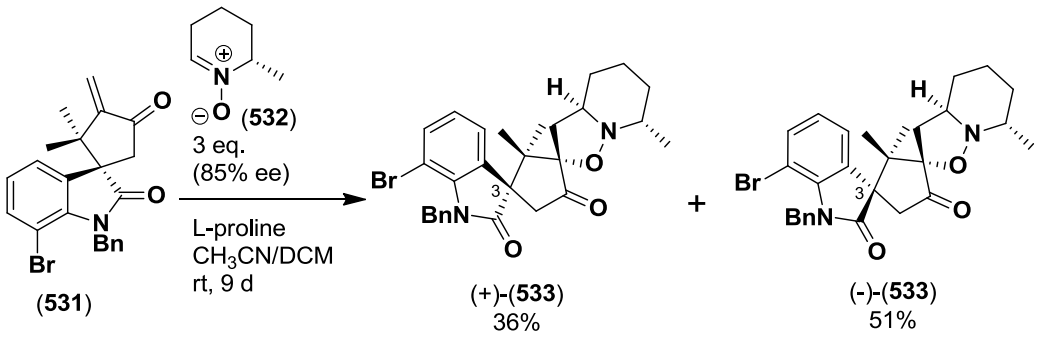
Scheme 94



With both enone (±)-(**531**) and nitrone (–)-(**532**)[151] in hand Wood et al. began exploring the critical [3 + 2] cycloaddition (Scheme 95). It was found under a variety of conditions

only two diastereomeric cycloaddition products, (+)-(**533**) and (–)-(**533**), were observed. After considerable experimentation, the addition of L-proline to this reaction had a beneficial effect on both the rate and the observed diastereomeric ratio. Extensive studies into the resultant stereochemistry revealed that cycloadducts (+)-(**533**) and (–)-(**533**) differed only by their configuration at the spirooxindole center at C-3. Moreover, the relative stereochemistry resident in the minor product (+)-(**533**) was that required for the conversion to the natural product.

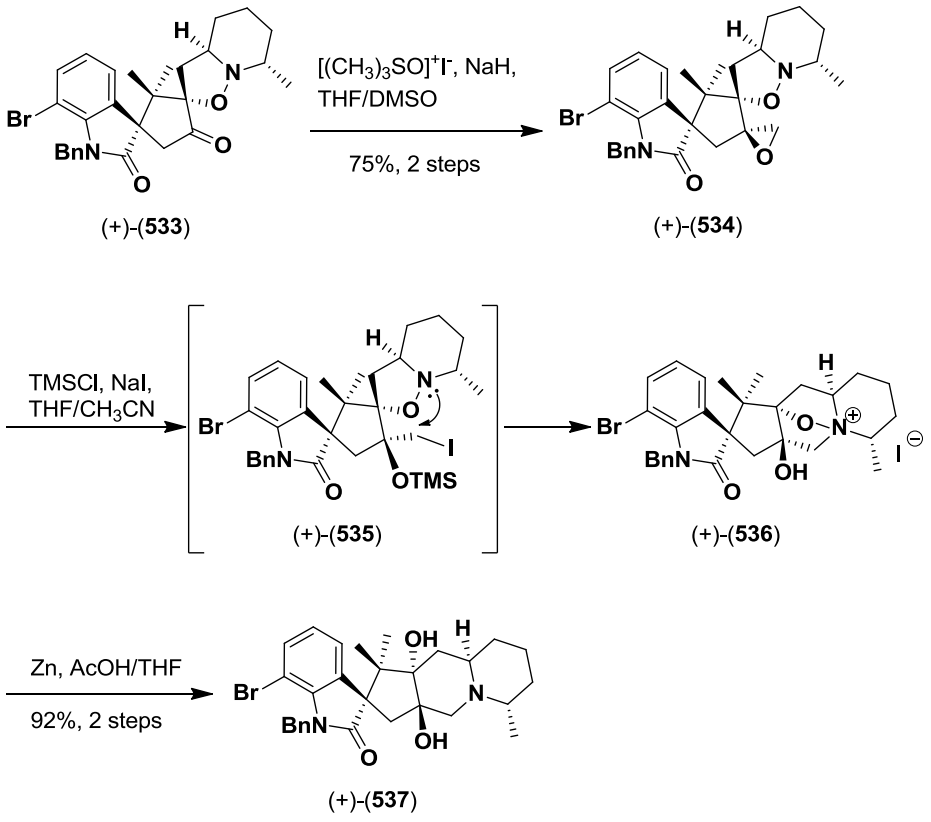
Scheme 95



Completion of the natural product by this approach required the addition of a carbon atom, as well as closure of the central fused ring-D of the citrinadin core. In order to address both of these concerns, it was reasoned that a Corey−Chaykovsky epoxidation would permit introduction of a single carbon atom and set the stage for subsequent ring closure *via* an intramolecular nucleophilic attack of the proximal nitrogen atom onto the derived epoxide. In any event, exposure of oxindole (+)-(**533**) to dimethylsulfoxonium methylide furnished the corresponding spiroepoxide (+)-(**534**) as a single diastereomer

(Scheme 96). While initial attempts to promote intramolecular opening of the epoxide were unsuccessful, eventually it was found that exposure of epoxide (+)-(**534**) to TMSI generated *in situ* furnished ammonium salt (+)-(**536**) in good yield, presumably, *via* the intermediacy of iodide (**535**). The ammonium salt (+)-(**536**) proved to be an excellent substrate for a Zn mediated N-O bond cleavage reaction that delivered diol (+)-(**537**).

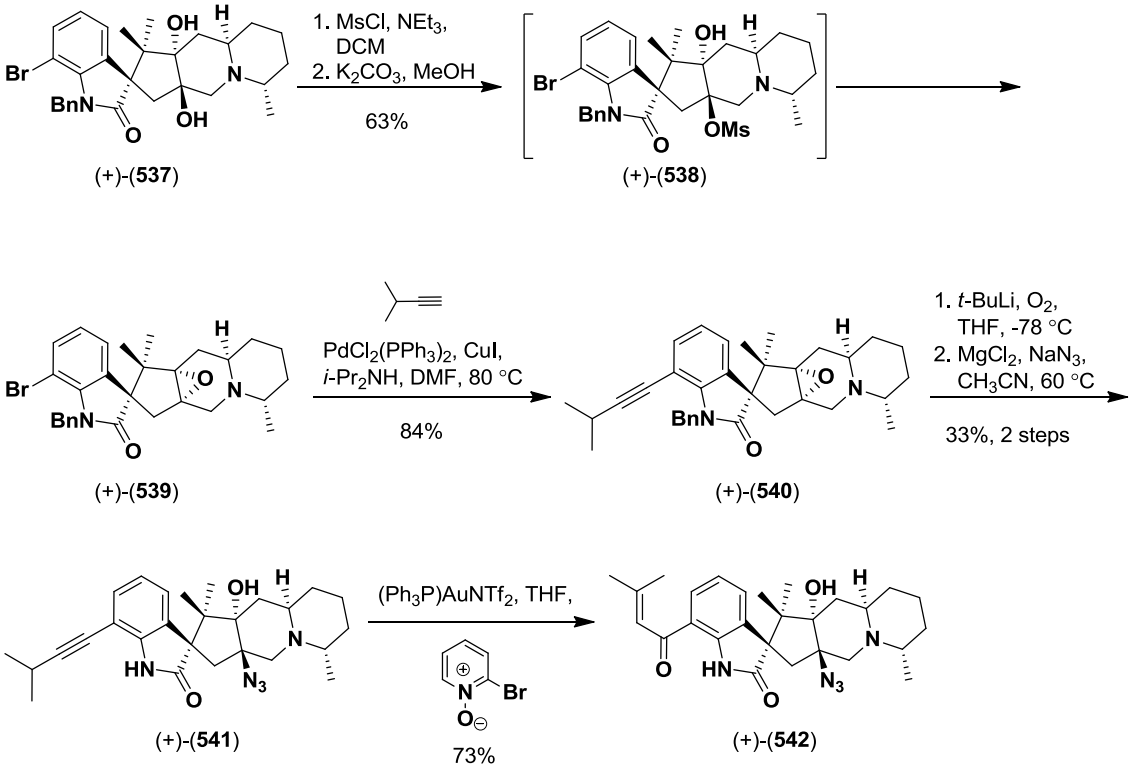
Scheme 96



Then, diol (+)-(**537**) was converted into the corresponding epoxide (+)-(**539**), which was subsequently coupled with 3-methyl-1-butyne under Sonogashira conditions to give alkyne [(+)-**540**, Scheme 97]. Importantly, the alkyne moiety in the derived product (+)-

(**540**) proved very resistant to the harsh benzyl deprotection conditions but tolerated a subsequent epoxide opening reaction with $MgCl_2/NaN_3$ to furnish azide (+)-(**541**). Thereafter, exposure of azide (+)-(**541**) to the gold mediated oxidation conditions reported by Zhang et al.[151] permitted conversion of the alkyne moiety to an enone, thereby delivering azido alcohol [(+)-**542**, Scheme 97).

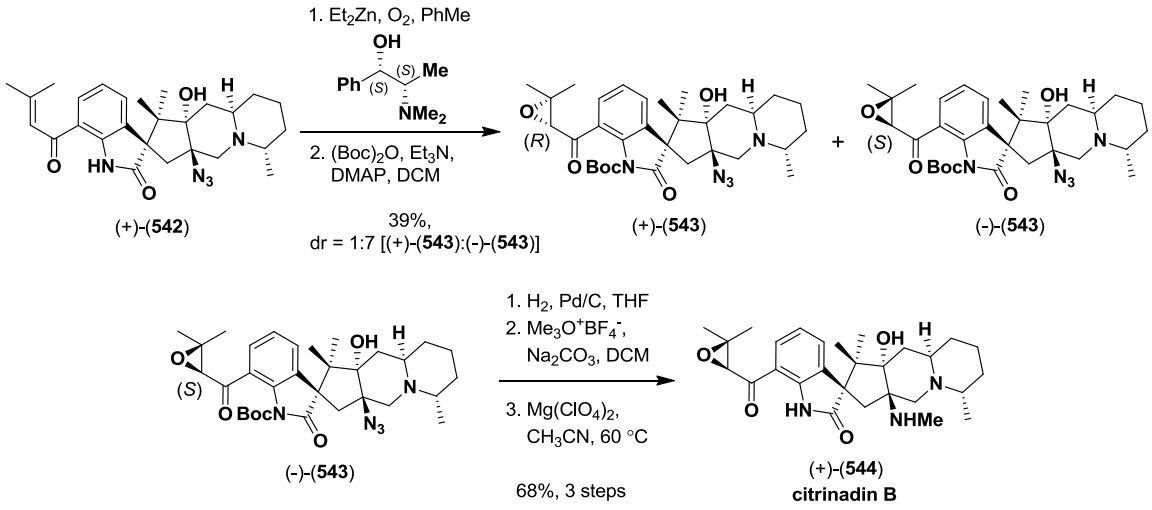
Scheme 97



Next, a diastereoselective enone epoxidation was selected to complete citrinadin B, and a protocol developed by Enders[152] proved most effective (the ratio of epoxide diastereomers could be increased in favor of (−)-(**543**) when (*S*,*S*)-*N*-methylpseudoephedrine was

used as an additive), as shown in Scheme 98. Pentacyclic epoxide (–)-(**543**) was advanced through the sequence of azide reduction, monomethylation, and deprotection, to furnish the target (+)-citrinadin B (**544**) in 68% over the last three steps.

Scheme 98



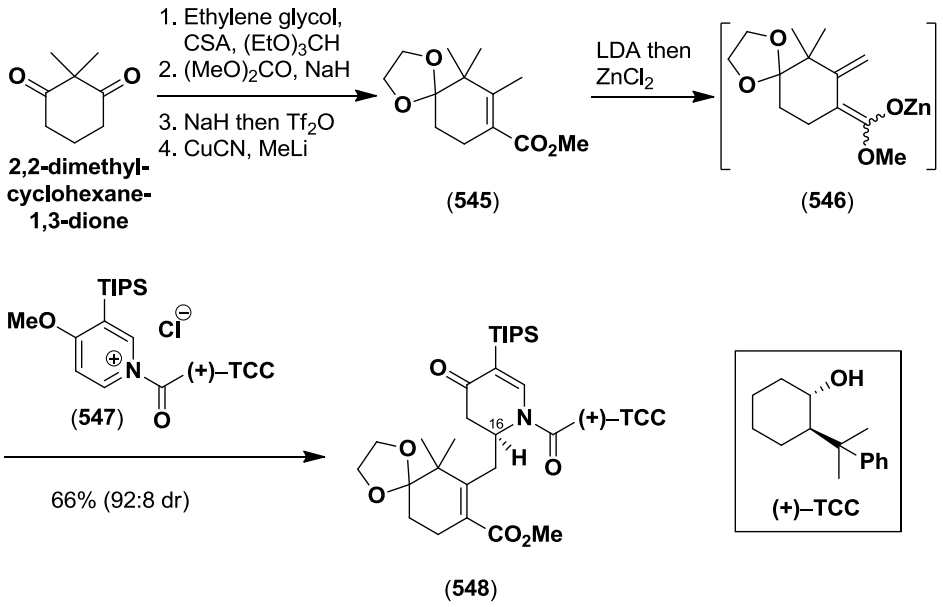
5.3) Martin et al.'s Enantioselective Total Synthesis of Citrinadins A and B.

Total Synthesis of (–)-Citrinadin A

Simultaneous with the report of Wood and co-workers, Martin et al. disclosed the first total synthesis of (–)-citrinadin A (**563**) by a linear approach in which the first chiral center was created by an enantioselective vinylogous Mannich addition, and the remaining stereocenters on the pentacyclic core were set by substrate based control.[154] The synthetic route began from commercially available 2,2-dimethylcyclohexane-1,3-dione,

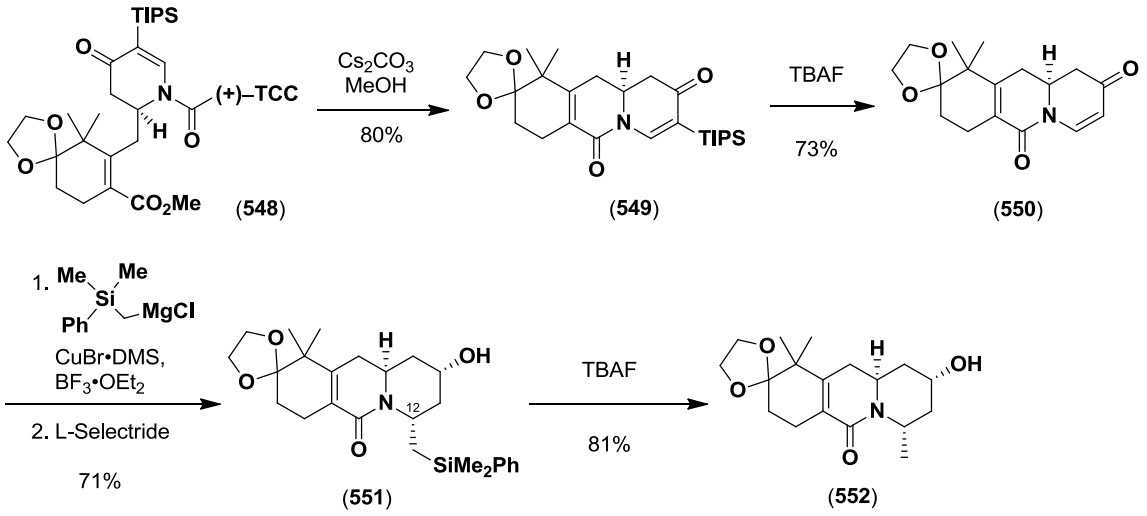
which was transformed into the *α,β*-unsaturated ester (**545**) in four straightforward steps that involved protection, crossed Claisen condensation, enol triflate formation, and methylation (Scheme 99). Deprotonation of ester (**545**) with lithium diisopropylamide (LDA), followed by transmetalation with $ZnCl_2$ gave the vinyloxy zinc adduct (**546**). After this success, the stereoselectivity of the addition of the zinc dienolate (**546**) to the chiral pyridinium salt (**547**) was examined. The salt (**547**) was generated *in situ* by the reaction of 3-TIPS-4-methoxypyridine and the chloroformate derivative of (+)-trans-2-(*α*-cumyl)-cyclohexanol [(+)-TCC], as shown in Scheme 99. This reaction proceeded successfully to give (**548**) with high diastereoselectivity (dr = 92:8), and the required absolute stereochemistry at the newly created stereocenter at C-16 was verified by X-ray crystallography of a derived intermediate.

Scheme 99



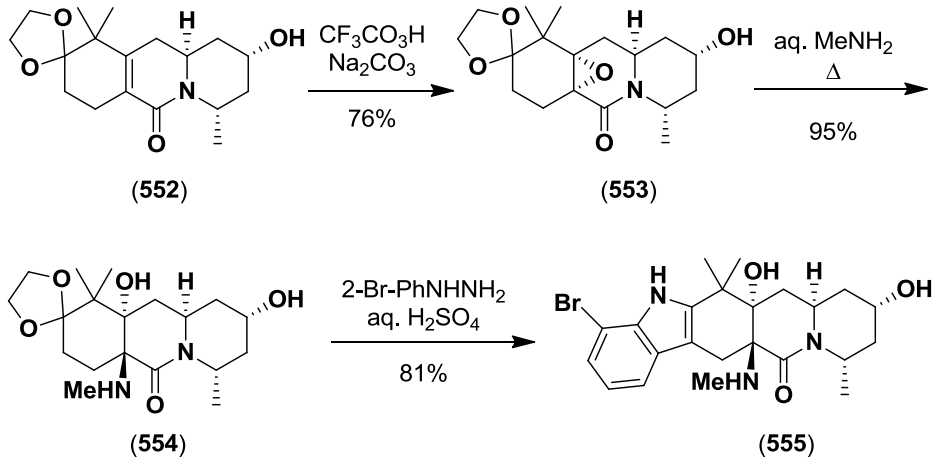
Exposure of (**548**) to Cs_2CO_3 in methanol induced removal of the (+)-TCC chiral auxiliary, and spontaneous cyclization ensued to provide the lactam (**549**) in 84% ee (improved to 99% ee after crystallization) together with about 70% recovered (+)-TCC. The desilylation of the lactam (**549**) was most efficiently effected employing excess TBAF and microwave-mediated heating to afford enone (**550**). Martin et al. discovered that the organocopper reagent generated from (dimethylphenylsilyl)-methylmagnesium chloride and CuBr•DMS added smoothly to enone (**550**) in the presence of BF_3•OEt_2 to give a mixture of ketones that were directly reduced using L-Selectride with high stereoselectivity to give (**551**) in 71% yield over two steps; 19% of the C-12 epimer of (**551**) was also isolated. They then proceeded to heat (**551**) with TBAF in a microwave oven to obtain the unsaturated lactam (**552**, Scheme 100).

Scheme 100



The transformation of enantiomerically pure (**552**) into (**555**) was straightforward. Epoxidation of (**552**) with peroxytrifluoroacetic acid in the presence of sodium carbonate was highly diastereoselective, proceeding from the more accessible, slightly convex face to furnish a single epoxide (**553**, Scheme 101). The reaction of epoxide (**553**) with aqueous methylamine in a sealed tube also occurred with high diastereoselectivity to deliver the requisite amino alcohol (**554**) in 95% yield. The heating of ketal (**554**) with *o*-bromophenylhydrazine hydrochloride in aqueous sulfuric acid provided the indole (**555**) in 81% yield (Scheme 101). The Fisher indole reaction could only occur regiospecifically to provide the 7-bromoindole (**555**).

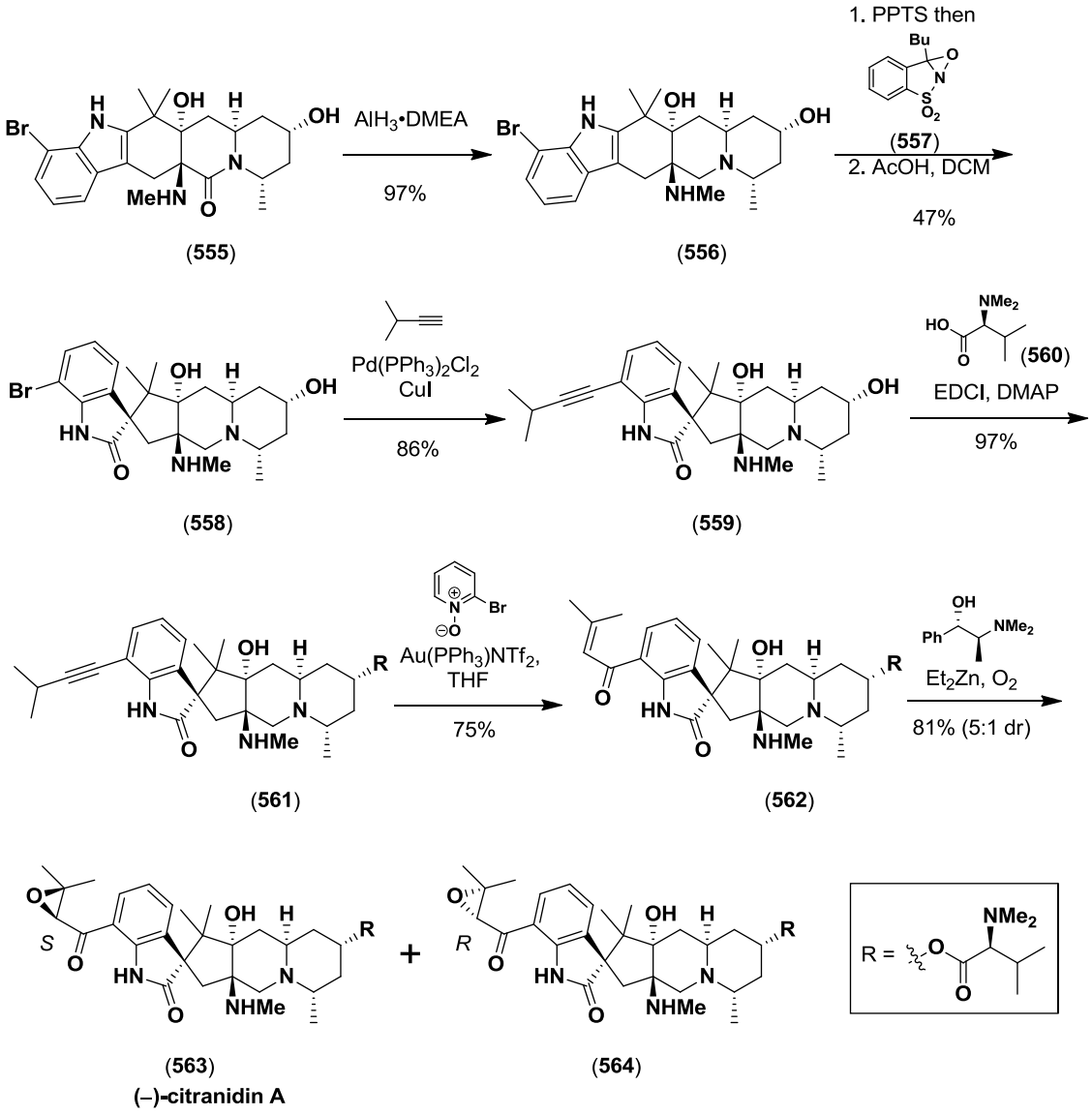
Scheme 101



In the last stages of the synthetic route, enantiomerically pure pentacyclic indole (**555**) was readily transformed into enantiomerically pure oxindole (**558**, Scheme 102). The reduction of the lactam (**555**) with the complex of alane and dimethylethylamine (DMEA) delivered reduced indole (**556**) in excellent yield. Subsequent treatment of

indole (**556**) sequentially with pyridinium *p*-toluenesulfonate (PPTS), excess of Davis's oxaziridine (**557**), and then acetic acid provided the spirooxindole (**558**) as a single stereoisomer (the unique role that PPTS played in controlling the stereochemical outcome of this reaction was not yet understood by the authors).

Scheme 102



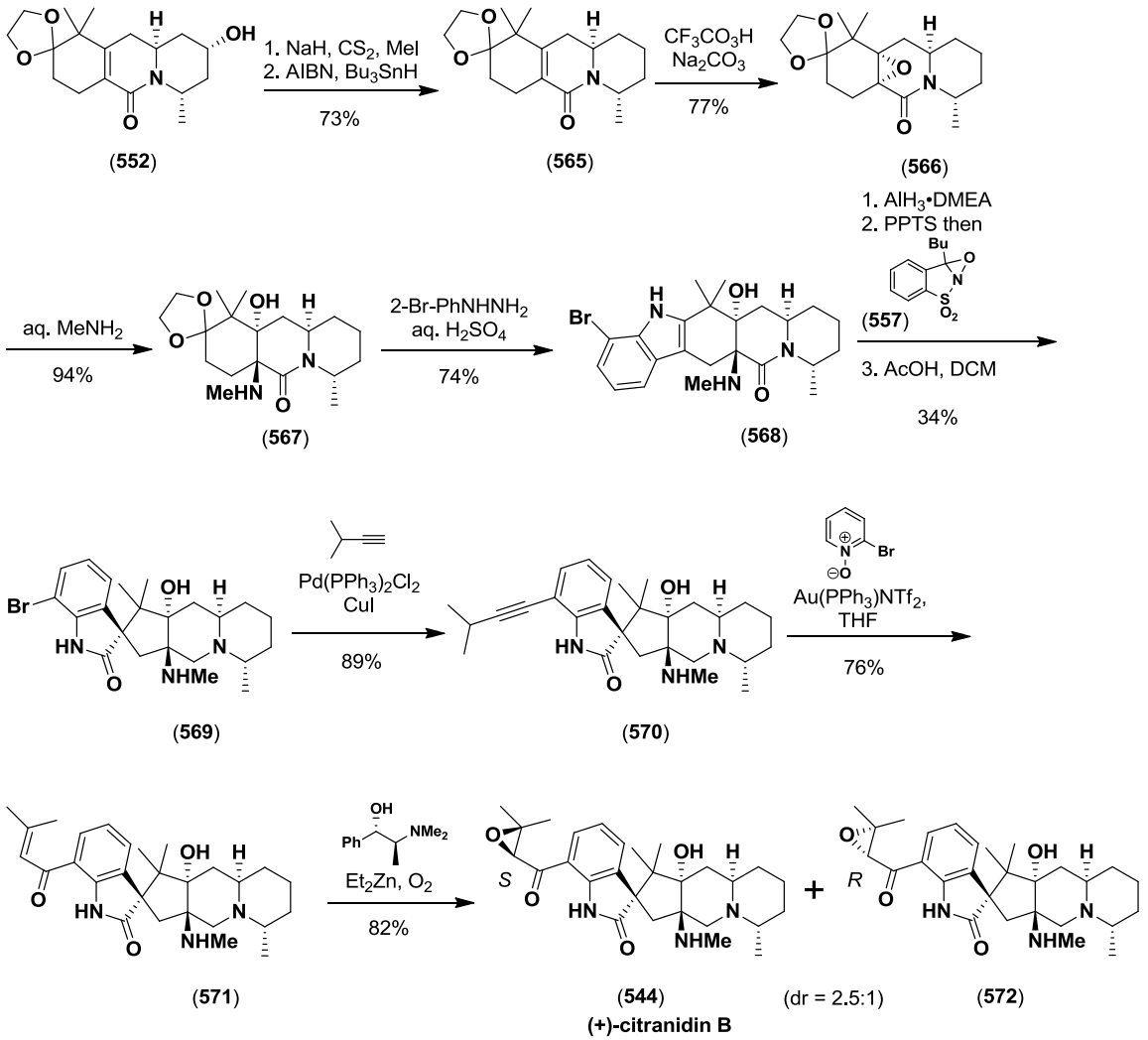
Then, Martin et al.[154] turned to a stepwise procedure that began with the Sonogashira coupling between oxindole (**558**) and 3-methylbut-1-yne to furnish the alkyne (**559**). Regiospecific acylation of the secondary hydroxyl group at C-14 with *N*,*N*-dimethyl-L-valine in the presence of 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDCI) and 4-*N*,*N*-dimethylaminopyridine (DMAP) provided oxindole ester (**561**) in excellent yield. The gold-promoted oxidation of alkyne (**561**) using 2-bromopyridine *N*-oxide according to a method reported by Zhang et al.[152] gave the enone (**562**). Finally, diastereoselective epoxidation of enone (**562**) to deliver a mixture (5:1) of epoxides (**563**) and (**564**), respectively, was achieved by applying an Enders protocol for the enantioselective synthesis of (*S*)-epoxides from *α,β*-unsaturated ketones using (*S,S*)-*N*-methylpseudoephedrine as the chiral ligand.

Total Synthesis of (+)-Citrinadin B

The difference between citrinadin A (**563**) and citrinadin B (**544**) is the presence of a dimethyl valine ester at C-14. Accordingly, it could be envisaged that deoxygenation at C-14 of a late stage intermediate in the synthesis of citrinadin A would give a precursor of citrinadin B. Thus, Barton's deoxygenation of alcohol (**552**) afforded lactam (**565**) in 73% yield (Scheme 103). Epoxidation of the *α,β*-unsaturated lactam (**565**) using buffered peroxytrifluoroacetic acid gave epoxide (**566**, 77% yield) as a single stereoisomer when (**566**) was heated with aqueous methylamine, the desired amino alcohol (**567**) was isolated in 94% yield. The Fisher indole reaction of acetal (**567**) with *o*-bromophenylhydrazine hydrochloride furnished the pentacyclic indole (**568**), which was then con-

verted into the spirooxindole (**569**) in 34% overall yield by sequential hydride reduction of the tertiary lactam, indole oxidation with Davis' oxaziridine (**557**), and acid-catalyzed rearrangement of the intermediate epoxide. The aryl bromide moiety of (**569**)

Scheme 103



was then elaborated via a Sonogashira coupling with 3-methylbut-1-yne to furnish the alkyne (**570**) that was processed to the enone (**571**) in 68% overall yield from (**569**) by

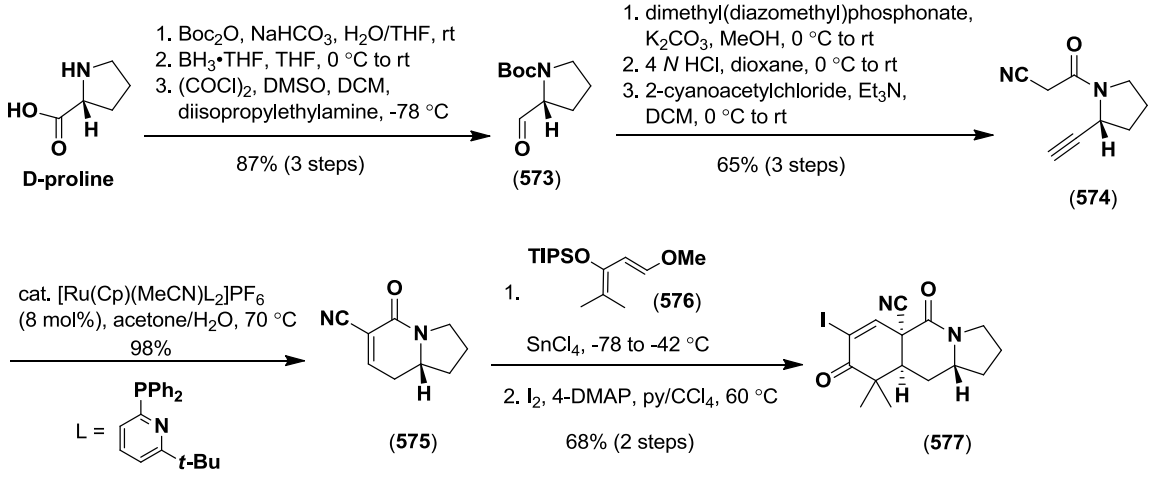
reaction with 2-bromopyridine *N*-oxide in the presence of gold. Finally, epoxidation of enone (**571**) using the Enders procedure[153] afforded a separable mixture of (+)-citrinadin (B) (**544**) and the (*R*)-diastereomer (**572**) (**544**/**572** dr = 2.5:1).

5.4) Sarpong et al.'s Enantioselective Total Synthesis of The *ent*-Citrinalin B and Cyclopiamine B

Sarpong et al. initiated their synthetic studies towards the total synthesis of *ent*-citrinalin B and cyclopiamine B with the protection of D-proline by a Boc group (Scheme 104), which was followed by the reduction of the carboxylic acid group and Swern oxidation of the resulting hydroxyl moiety to afford the aldehyde (**573**).[156] Alkynylative homologation of the aldehyde group of (**573**) using the Ohira–Bestmann method,[157] followed by removal of the *tert*-butoxycarbonyl group and acylation with 2-cyanoacetyl chloride gave alkyne (**574**). This served as a substrate for an unprecedented formal cycloisomerization that probably proceeds *via* a metal vinylidene intermediate[158], anti-Markovnikov hydration and Knoevenagel condensation to give tetrahydroindolizinone (**575**). At this stage, a $SnCl_4$-catalysed Diels–Alder reaction[159] between (**575**) and diene (**576**), and a subsequent basic work-up, afforded an enone (not shown),which was iodinated to yield iodoenone (**577**, Scheme 104). [160]

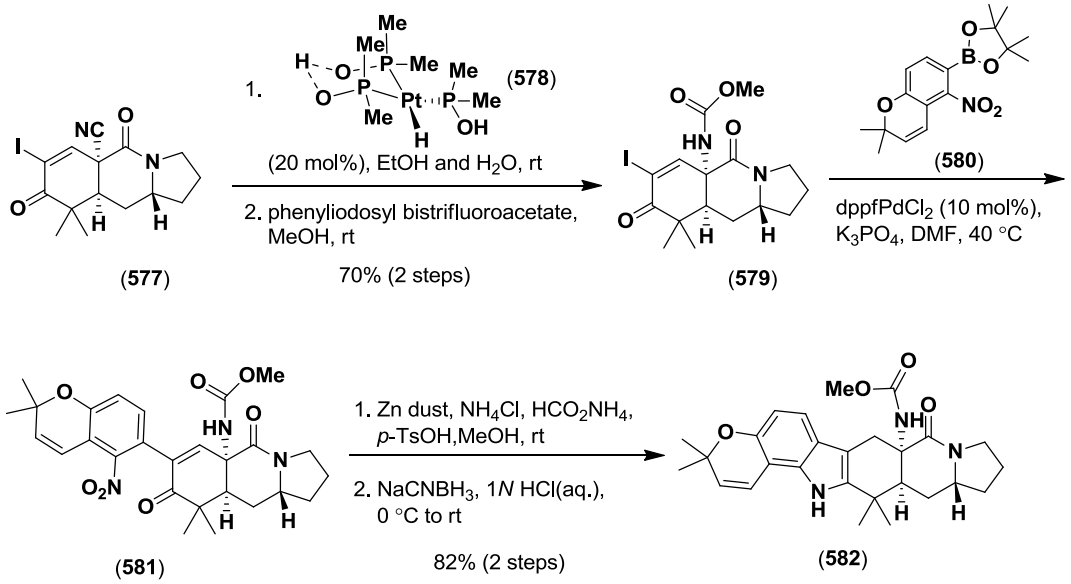
The hydrolysis of the nitrile group of (**577**) was achieved using a Pt-complex (**578**)[161] to afford the corresponding carboxamide,which served as a substrate for a Hofmann rearrangement that was effected with phenyliodosyl bistrifluoroacetate to yield carbamate (**579**).[162] The Suzuki cross-coupling of (**579**) with the known boronic ester (**580**)[163] gave

Scheme 104



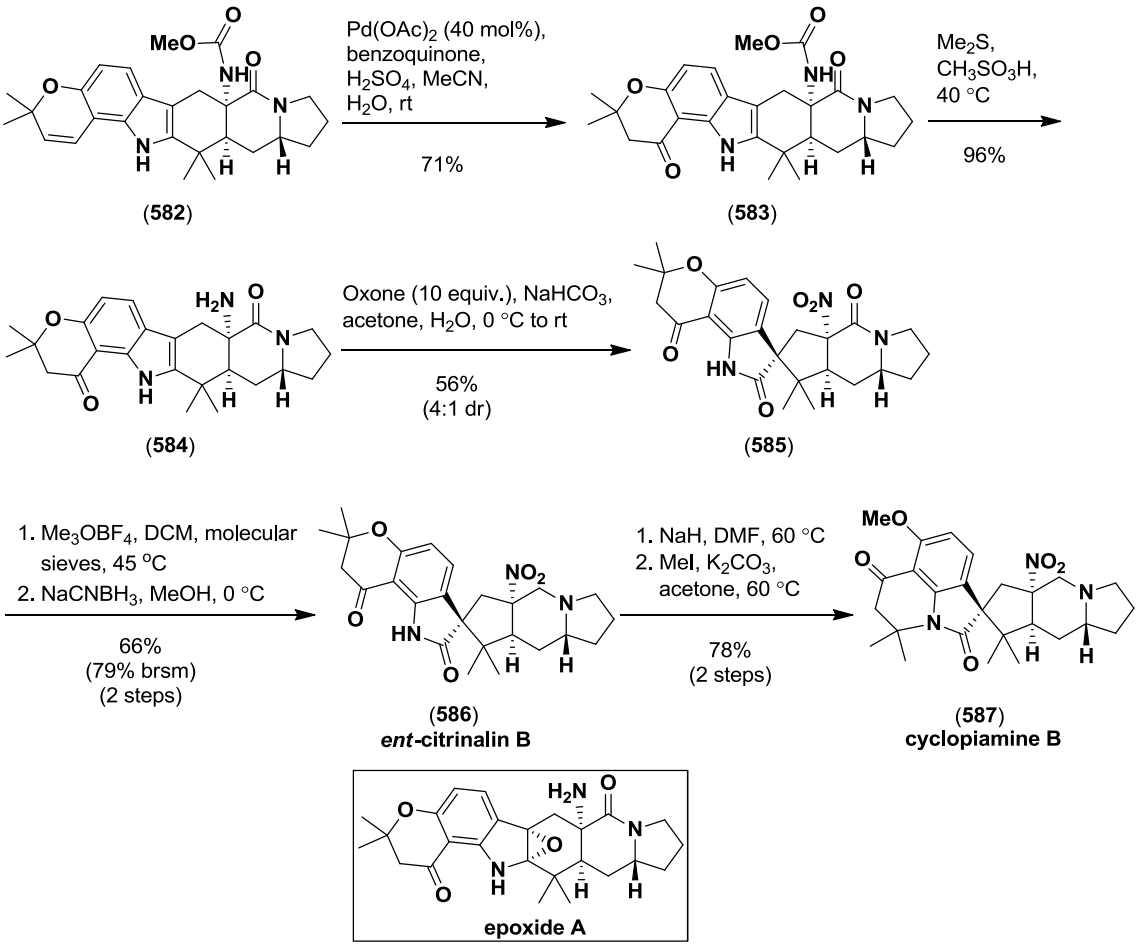
adduct (**581**), which was efficiently converted into the fused indole (**582**) using two sequential reductions, all in accord with the effective protocols established in the literature (Scheme 105).[164]

Scheme 105



Sarpong et al. opted, at this stage, to effect a Wacker oxidation of the chromene ring of (**582**) to afford chromanone (**583**, Scheme 106), which was advantageous because the chromanone unit is found in the citrinalins and cyclopiamines. Importantly, treatment of (**584**) [following removal of the methoxycarbonyl group in (**583**)] with an excess of dimethyldioxirane (formed *in situ* from acetone and Oxone) afforded spirooxindole (**585**) as the major product (diastereomeric ratio, 4:1) wherein the spiro centre was as desired and the nitro group was installed in one pot. Studies of dimethyldioxirane oxidations of indoles to spirooxindoles[165] suggested that spirooxindole (**585**) might arise from epoxide A (Scheme 106, inset). Therefore, it was possible that the introduction of the chromanone diminished the participatory role of the indole nitrogen lone pair leading, after rearrangement to (**585**). With spirooxindole (**585**) in hand, what remained was a selective removal of the tertiary amide carbonyl group by reduction, which had to be accomplished in the presence of the chromanone and secondary amide carbonyl groups as well as the newly introduced nitro group. After extensive investigation by Sarpong et al., this task was effectively accomplished using a modification of a known procedure[166] by treating oxindole (**585**) with a variant of Meerwein's salt ($Me_3O•BF_4$),which probably leads to a methylated amidinium intermediate that is cleanly reduced with sodium cyanoborohydride to give *ent*-citrinalin B (**586**) in 66% yield (79% based on recovered starting material). *Ent*-citrinalin B (**586**) was easily converted into cyclopiamine B (**587**) on treatment of oxindole (**586**) with sodium hydride followed by heating (to effect the conversion of chromanone to tetrahydroquinolone) and subsequent methylation of the phenol which resulted to give the target oxindole (**587**, Scheme 106).[156]

Scheme 106



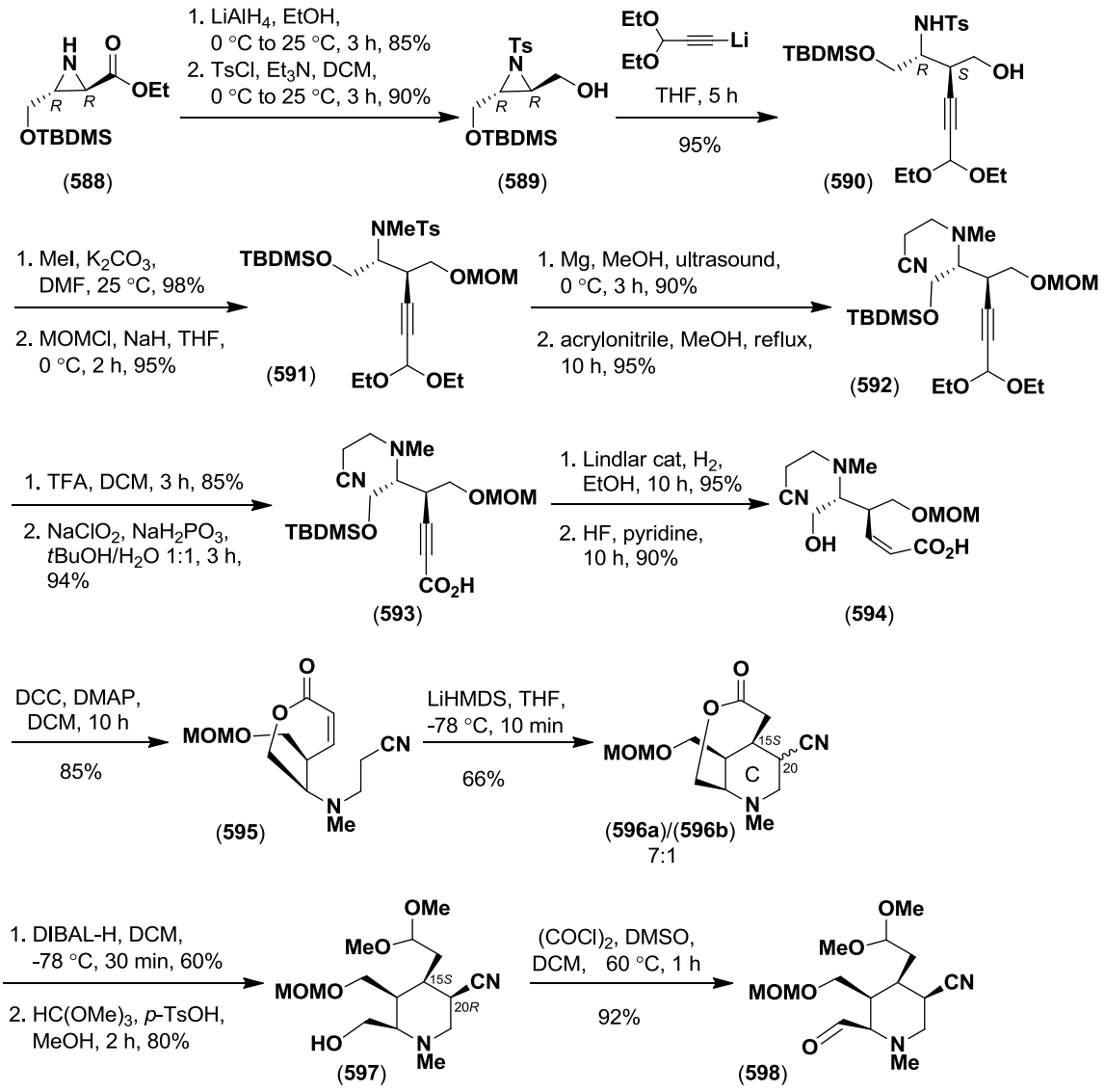
5.5) Qin et al.'s Biomimetic Total Synthesis of (+)-Gelsemine

Qin et al. reported a biomimetic total synthesis of (+)-gelsemine (**607**), in which the key reaction involved an intramolecular enol-oxonium cyclization that assembled the required cage structure in a highly efficient manner. In addition, a new biosynthetic pathway for the later stages of the biosynthesis of gelsemine was proposed based on the enol-oxonium cyclization procedure executed during these studies.[167]

Qin et al. began to ward gelsemine (**607**) by converting disubstituted aziridine (**588**) into the chiral *cis* tetra-substituted piperidinoaldehyde (**598**, Scheme 107).[167] Two steps of reduction and tosylation of (**588**) provided the alcohol (*R,R*)-(**589**) in moderate yield. The attack by (3,3-diethoxyprop-1-yn-1-yl)lithium on aziridine (**589**) occurred from the top face of the aziridine ring to afford alkyne diethylacetal (**590**) as a single stereoisomer in 95% yield. The excellent regio- and stereo-selectivity was presumebly due to coordination of the lithium reagent with the hydroxy group and efficient blockage of the bottom face of the aziridine ring by the bulky OTBDMS group in (**589**). Subsequent *N*-methylation with MeI and protection of the hydroxy group in alkyne (**590**) provided acetal (**591**) in excellent yield. After removal of the tosyl group with Mg dust using ultrasound, the amine, which resulted, reacted with acrylonitrile in MeOH at reflux to provide alkyne-nitrile (**592**) in excellent yield. Subsequent treatment of nitrile (**592**) with TFA, and oxidation of the resulting aldehydic group with sodium chlorite yielded acid (**593**) in 85% yield in two steps. The partial hydrogenation of the alkynyl group to an olefin with Lindlar catalyst and removal of the TBDMS group with HF/pyridine in (**593**) provided *cis* olefin (**594**) in excellent yield. To prepare the piperidine ring with an (*S*)-configuration at C-15 as in the structure of (+)-gelsemine, an oxepinone ring was first generated by condensation of the acid group with the hydroxy group in (**594**) to give lactone (**595**) in 85% yield. Intramolecular Michael addition at low temperature yielded two inseparable diastereomers (15*S*,20*R*)-(**596a**) and (15*S*,20*S*)-(**596b**) in 66% yield in a 7:1 ratio. The latter mixture of diastereomers became separable after the lactone group was reduced to an aldehyde with DIBAL-H at low temperature, and the aldehydic group, which resulted, was protected with a dimethoxy acetal group, affording the major isomer

of methylpiperidine (15*S*,20*R*)-(**597**) in 48% yield over two steps. The subsequent oxidation of the hydroxy group provided the *cis* tetra-substituted piperidinoaldehyde (**598**) in 92% yield (Scheme 107).

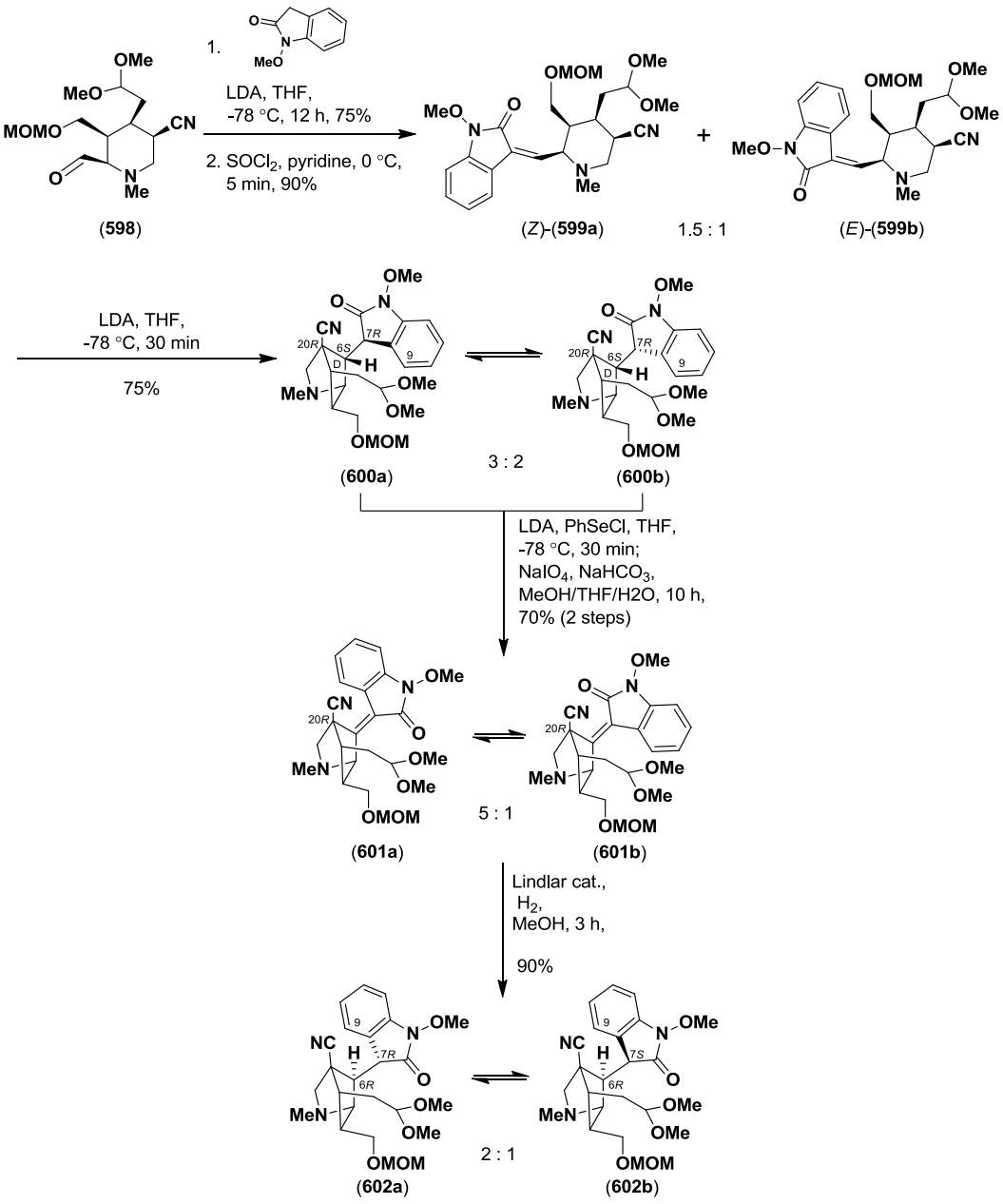
Scheme 107



With the piperidine (**598**) bearing the required stereochemistry in hand, Qin et al. began to prepare oxindole (**602**, Scheme 108). The condensation of piperidine (**598**) with *N*-methoxyoxindole in the presence of LDA, followed by dehydration of the resulting hydroxy group with $SOCl_2$/pyridine provided two separable geometric isomers (*Z*)-(**599a**) and (*E*)-(**599b**) in a 1.5:1 ratio. As expected by the authors, the isomeric mixture (**599**) easily underwent Michael addition in the presence of LDA in THF to yield two inseparable oxindole diastereomers (**600**, epimeric at C-7 in 75% yield). The Michael addition of (**599**) not only formed the D-ring, but also created the correct C-20 quaternary carbon center with an (*R*)-configuration. However, the addition led to an (*S*)-configuration at C-6 rather than the desired (*R*)-configuration. The (*S*)-configuration at C-6 prevented the oxindole moiety from gaining access to the oxonium cation that was formed *in situ* when the MOM group and the two methoxy groups in (**600**) were removed under acidic conditions. To invert the C-6 (*S*)-configuration in (**600**) to an (*R*)-configuration and thereby allow construction of the E- and F-rings by enol-oxonium cyclization, a double bond between C-6 and C-7 was generated to yield two separable geometric isomers (**601a**) and (**601b**) in 70% yield in a 5:1 ratio by using the standard protocol of olefination with PhSeCl/LDA/$NaIO_4$ (Scheme 108). Hydrogenation of the double bond in the isomeric mixture (**601**) with Lindlar catalyst and hydrogen in MeOH resulted in two inseparable diastereomers (**602a**) and (**602b**) in 90% yield in a 2:1 ratio. The hydrogenation proceeded such that the nucleophilic attack occurred from the less hindered bottom face of the double bond, thereby yielding (**602a**) and (**602b**) with C-6 exclusively in the (*R*)-configuration.

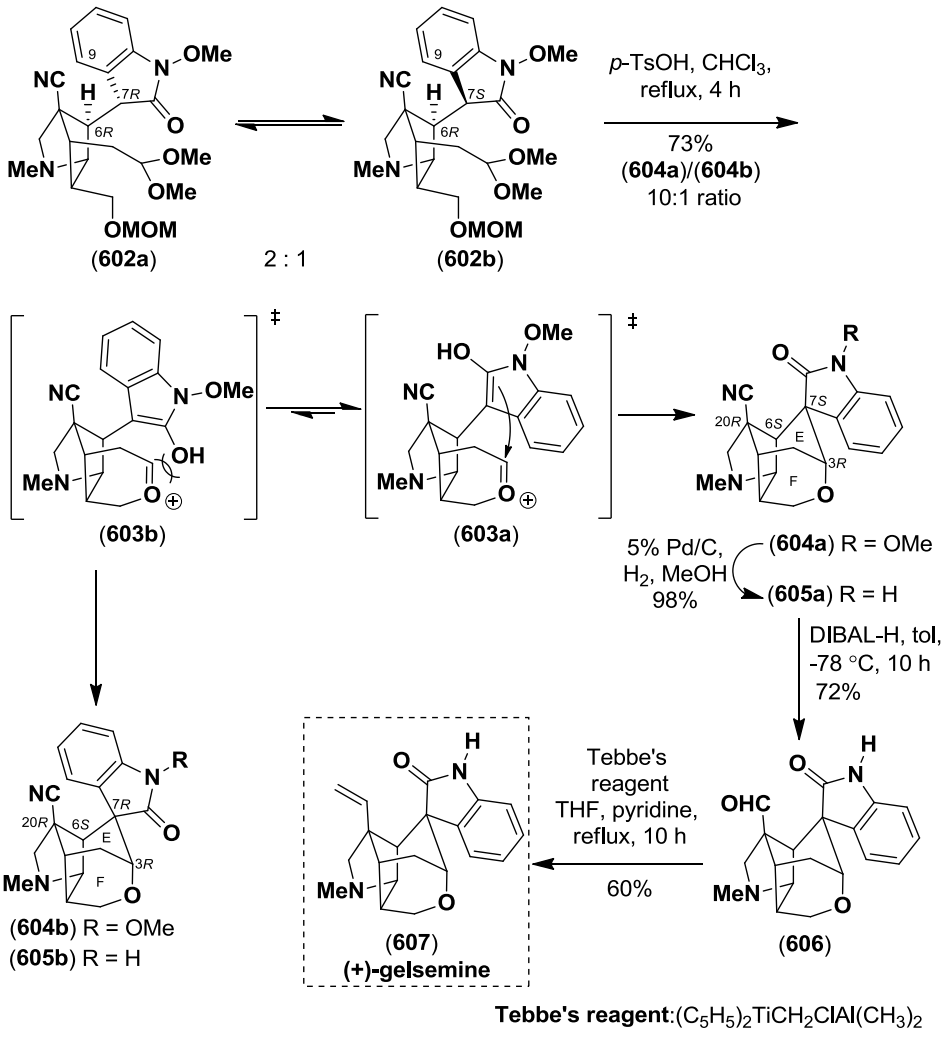
Qin et al. next carried out the planned one-pot, multi-step enol-oxonium cyclization reaction cascade to efficiently assemble both the E- and F-rings, and simultaneously establish the C-3 and C-7 stereocenters (Scheme 109). When the mixture of oxindole isomers (**602**) was treated with stoichiometric TsOH in $CHCl_3$ at reflux, two separable

Scheme 108



diastereomers (**604a**) and (**604b**) were obtained in 73% yield in a 10:1 ratio. Apparently, the reaction proceeded *via* two transition states (**603a**) and (**603b**).

Scheme 109



The natural major isomer (**604a**) with the desired (7*S*)-configuration was produced from the favored transition state (**603a**), in which an electronic repulsion between the oxonium cation and the hydroxy group of the enol functionality is avoided. In contrast, the dis-

favored transition state (**603b**), in which both electron repulsion and a steric effect are present, led to the unnatural minor isomer (**604b**) with the inverse (7*R*)-configuration. After having successfully synthesized (**604a**), which possessed all the ring systems and correct stereochemistry of the carbon stereocenters of the target (+)-gelsemine, attention turned to the final task of converting the nitrile substituent at C-20 in (**604a**) to an ethylene substituent. After removal of the methoxy group in (**604a**) by hydrogenation with 5% Pd/C, the nitrile group in (**605a**) was reduced to an aldehyde group to provide oxindole (**607**) in 71% yield in two steps. The olefination of aldehyde (**606**) with the Tebbe reagent[168] yielded (+)-gelsemine (**607**) in 60% yield (Scheme 109).

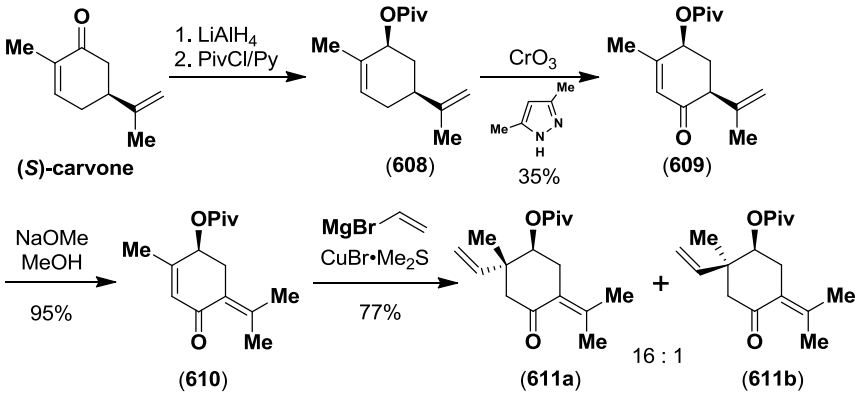
5.6) Garg et al.'s Total Synthesis of (−)-*N*-Methylwelwitindolinone C Isothiocyanate, (+)-*N*-Methylwelwitindolinone D Isonitrile, and (−)-*N*-Methylwelwitindolinone B Isothiocyanate

Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate:[169]

Garg et al.'s synthesis began with the concise preparation of enone (**612a**, Schemes 110 and 111). The (*S*)-carvone was elaborated to enone (**612a**) using a robust five-step procedure reported by Natsume in the enantiomeric series.[170]

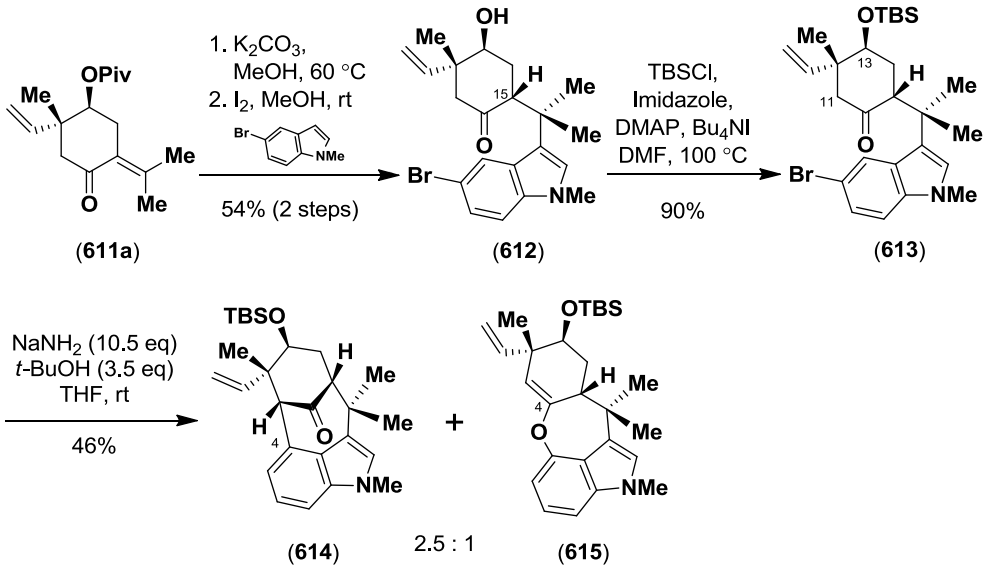
With easy access to enone (**611a**), the cleavage of the pivalate group was followed by I_2-promoted addition of 5-bromoindole to furnish indole adduct (**612**) in 54% yield over two steps.[171] The TBS protection of (**612**) provided silyl ether (**613**), which in turn was employed in the critical indolyne cyclization process.

Scheme 110



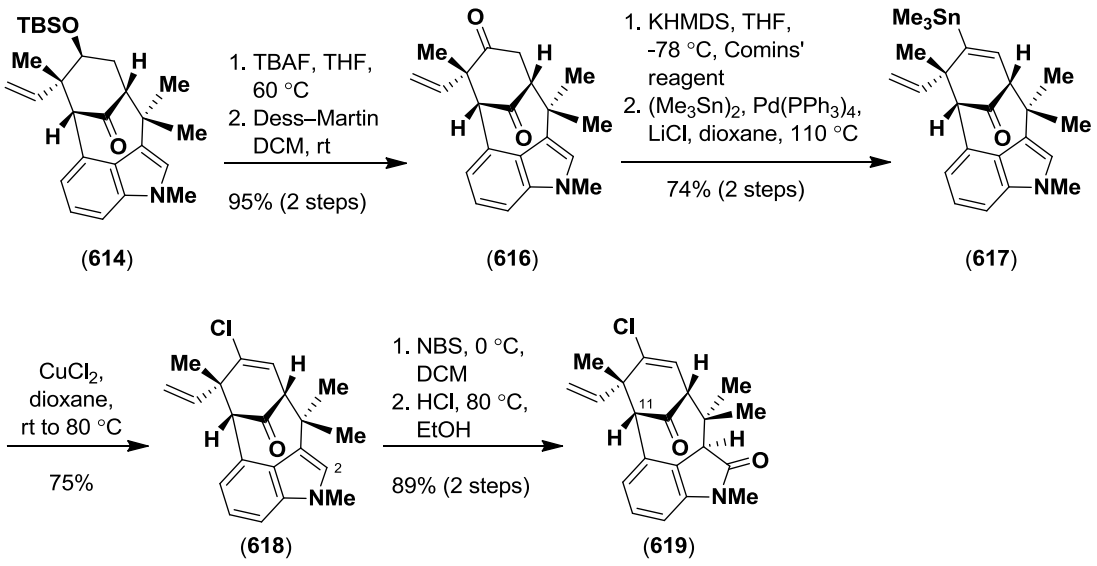
Treatment of (**613**) with $NaNH_2$ and *tert*-BuOH in THF at ambient temperature, led to indolyne adducts (**614**) and (**615**) in a combined 46% yield (2.5:1 ratio).[172] Although *O*-arylated product (**615**) was observed, the major product (**614**) possessed the desired [4.3.1]-bicyclic framework of the natural product and was available in gram quantities (Scheme 111).

Scheme 111



Since the bicyclic framework of the natural product was assembled, Garg et al. turned their efforts toward the introduction of the vinyl chloride and oxindole moieties (Scheme 112) into (**614**). Desilylation of (**614**), followed by Dess–Martin oxidation, smoothly furnished diketone (**616**). Subsequently, a sequence involving triflation and Pd-catalyzed stannylation[173] provided vinyl stannane (**617**). Exposure of the latter to $CuCl_2$ in dioxane afforded vinyl chloride (**618**).[174] To arrive at the necessary oxindole, a two-step procedure, which involved sequential C-2 bromination and hydrolysis, was employed to deliver late-stage intermediate vinyl chloride (**619**, Scheme 112).

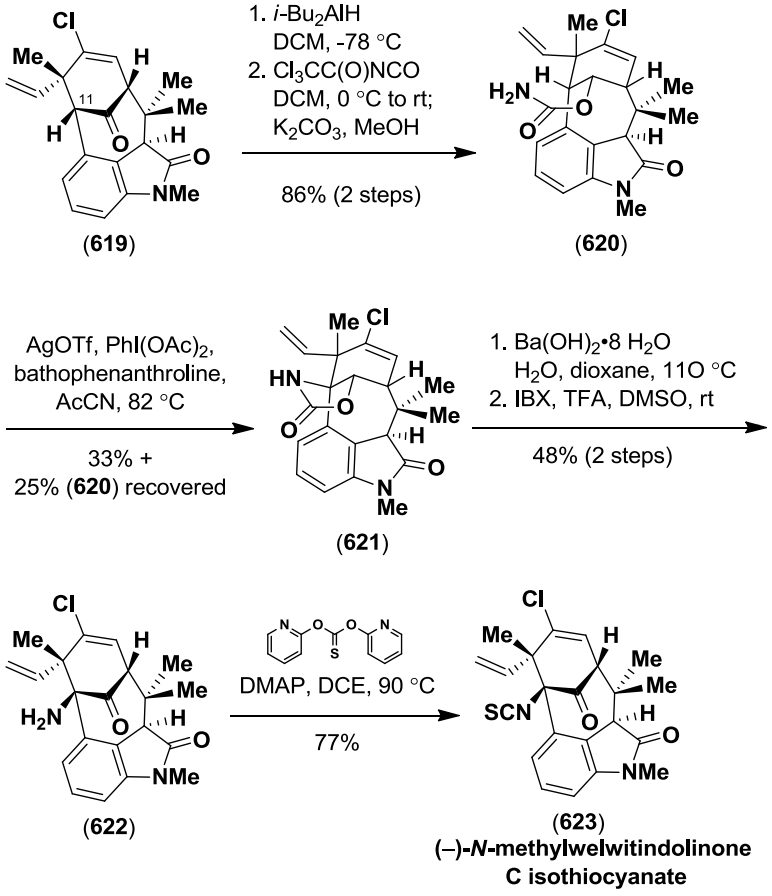
Scheme 112



With intermediate (**619**) lacking only the isothiocyanate substituent, attention turned to functionalization of the sterically congested C-11 bridgehead position (Scheme 113). It was postulated an intramolecular nitrene C-H insertion was a way to achieve the total

synthesis. Consequently, ketone reduction of (**619**) proceeded efficiently using *i*-Bu_2AlH to furnish a secondary alcohol intermediate as a single diastereomer (Scheme 113).

Scheme 113



Subsequent carbamoylation furnished tetracycle (**620**), which was the key substrate for the critical C-H insertion reaction. Upon treatment of oxindole (**620**) with AgOTf, batho-phenanthroline, and $PhI(OAc)_2$ in CH_3CN at elevated temperatures,[175] the desired nitrene insertion took place to deliver oxazolidinone (**621**) as the major product. Some starting material (**620**) was also recovered and could be recycled through the synthetic route. Nonetheless, hydrolysis of (**621**) followed by IBX oxidation generated the penultimate

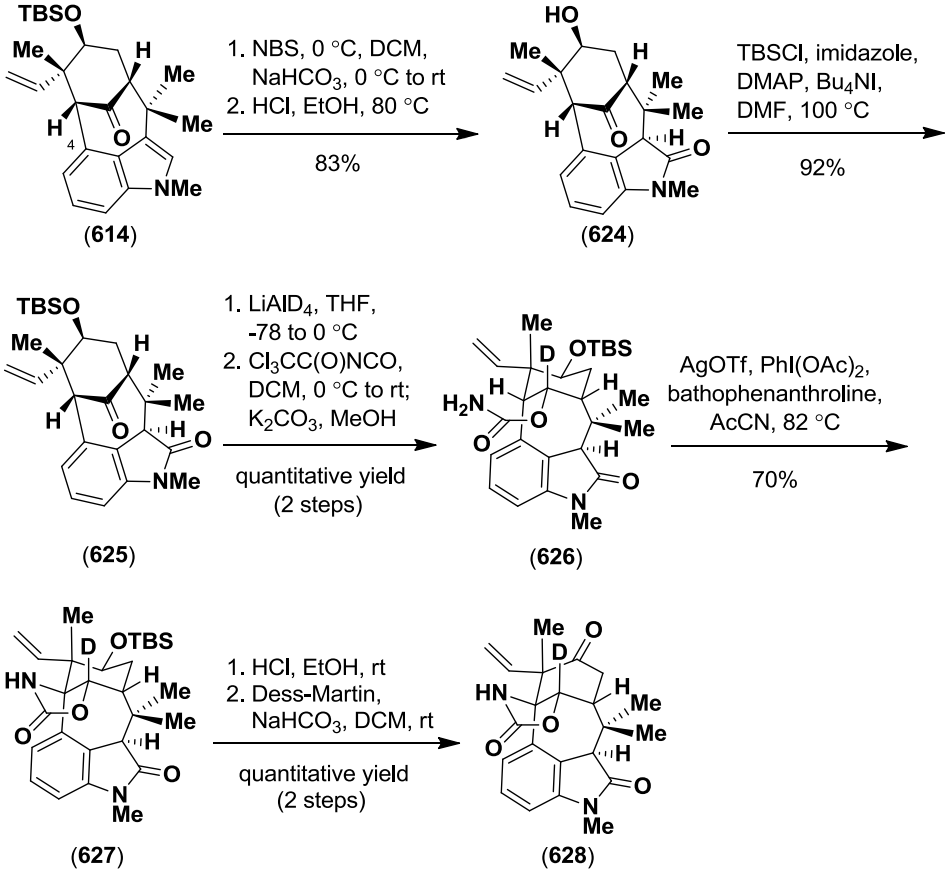
intermediate aminoketone (**622**). Final introduction of the isothiocyanate function (according to a known procedure by Baran et al.)[176] furnished (–)-*N*-methylwelwitindolinone C isothiocyanate (**623**).

Synthesis of (+)-*N*-Methylwelwitindolinone D Isonitrile:[177]

An extension of the chemistry developed by Garg et al.[170] (see above), made possible the synthesis of (+)-*N*-methylwelwitindolinone D isonitrile (**634**). The important intermediate indole (**614**, see Scheme 111) was at this point converted to oxindole (**624**) using a one-pot oxidation/hydrolysis sequence (Scheme 114). Since the acidic conditions led to desilylation, reprotection of the alcohol was necessary to provide TBS-protected indole (**625**). Deuteride reduction and carbamoylation proceeded without event to furnish deuterated-carbamate (**626**) in quantitative yield. Exposure of the latter to the conditions of an Ag-promoted nitrene insertion process, seen above, furnished oxindole (**627**) in 70% yield. The strategic use of deuterium minimized an undesirable competitive reaction, thus giving synthetically useful yields of the desired insertion product (**627**).[178] From oxindole (**627**), a standard deprotection/oxidation sequence delivered key intermediate (**628**, Scheme 114).

Next, Garg et al. found that simple exposure of (**628**) to tetrabutylammonium fluoride (TBAF) in acetonitrile in the presence of air efficiently delivered furan (**630**, Scheme 115).[179] In previous studies, it was found that TBAF/air can facilitate C-3 oxidation of oxindoles containing the welwitindolinone scaffold, but the use of TBAF/air to build an ethereal linkage through double C-H functionalization was unknown.[180]

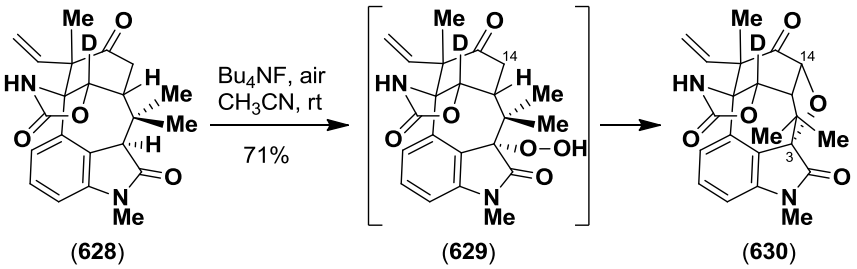
Scheme 114



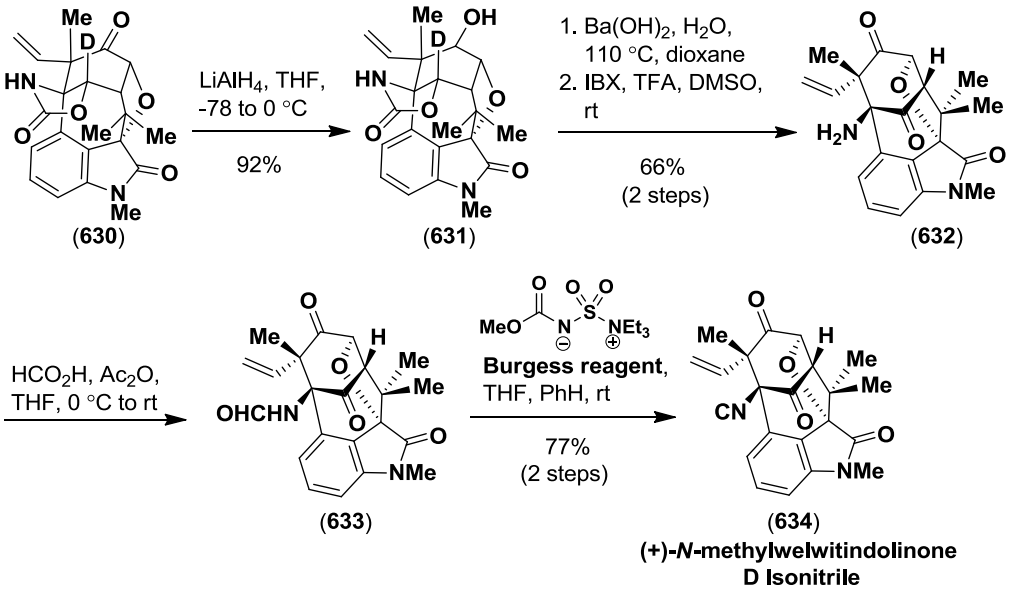
Notably, the use of other bases in place of TBAF, such as K_2CO_3 and Cs_2CO_3, also promoted the formation of (**630**), albeit in lower yields. It is likely that this method for introducing the tetrahydrofuran ring proceeded by initial diastereoselective C-3 oxidation, followed by cyclization. Related (C-3)-peroxy compounds were observed in previous studies by the Garg and Wood research groups.[177]

In order to complete the total synthesis it remained to elaborate the cyclic carbamate to the ketone and isonitrile functional groups present in the target molecule (**634**, Scheme 116).

Scheme 115



Scheme 116

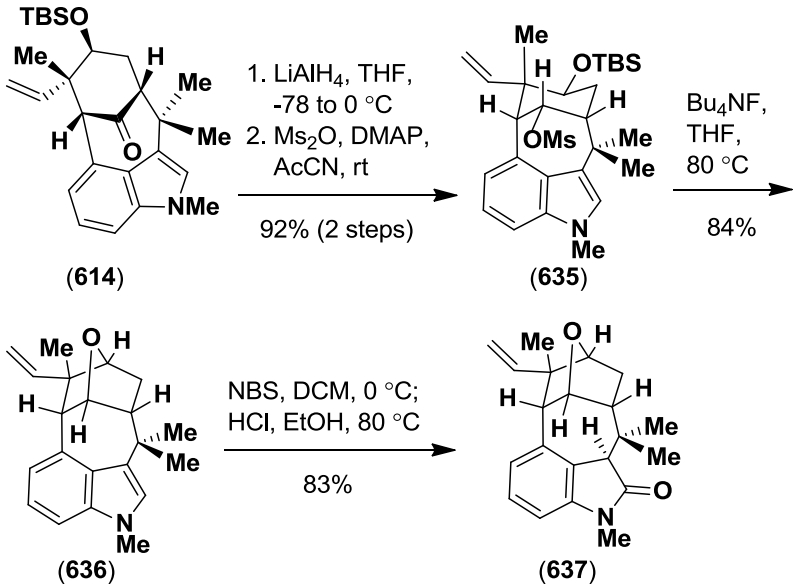


To this end, ketone (**630**) was reduced to the corresponding alcohol (**631**) with $LiAlH_4$. Upon exposure of alcohol (**631**) to the conditions of hydrolysis, cyclohexyl ring fragmentation was not observed, and hydrolysis gave the desired diol intermediate, which was oxidized with IBX to provide diketone (**632**). Finally, formylation of the latter amine provided *N*-formyl oxindole (**633**), which was directly exposed to standard dehydration conditions to deliver (+)-*N*-methylwelwitindolinone D isonitrile (**634**, Scheme 116).

Synthesis of (–)-*N*-Methylwelwitindolinone B Isothiocyanate:[181]

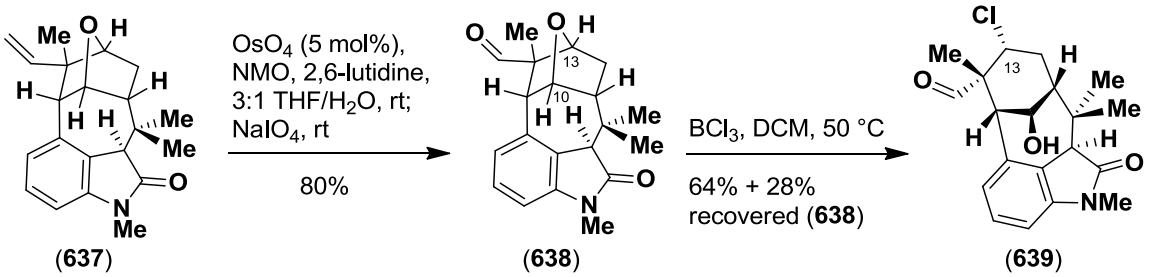
Garg et al. also took advantage of tetracyclic ketone (**614**) for the synthesis of (–)-*N*-methylwelwitindolinone B isothiocyanate (**644**). To this end, ketone (**614**) was elaborated to mesylate (**635**) in two steps, which involved reduction with $LiAlH_4$ followed by sulfonylation. Upon treatment of the mesyl indole (**635**) with Bu_4NF in THF at 80 °C, desilylation readily occurred with concomitant cyclization to afford oxabicycle (**636**) in 84% yield. Subsequently, a one-pot oxidation/hydrolysis protocol was used to elaborate (**636**) to the corresponding oxindole (**637**), which was formed as a single diastereomer (Scheme 117).

Scheme 117



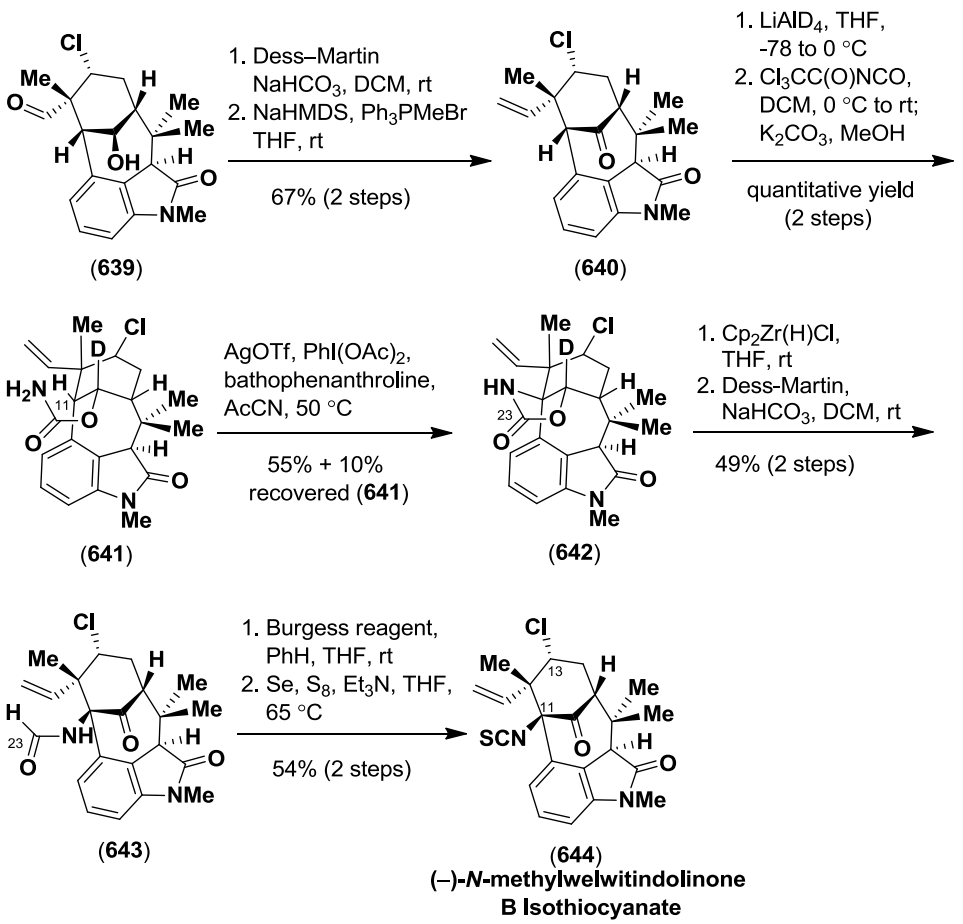
With rapid access to oxabicycle (**637**), Garg et al. were poised to attempt the key chlorinative ring-opening reaction (Scheme 118). Alkene (**637**) was exposed to modified oxidative cleavage conditions,[182] which furnished aldehyde (**638**). Treatment of (**638**) with BCl_3 in CH_2Cl_2 at 50 °C delivered the desired chlorinated product (**639**) in 64% yield as a single diastereomer.

Scheme 118



In order to finish the synthesis of the target molecule, oxidation of alcohol (**639**, Scheme 119), followed by Wittig olefination, afforded ketone (**640**). Subsequent reduction of (**640**) with $LiAlD_4$ occurred with complete diastereoselectivity to furnish an alcohol intermediate, which was carbamoylated to provide carbamate (**641**). Carbamate (**641**) proved to be a viable substrate for the desired nitrene insertion reaction; upon treatment of (**641**) with AgOTf, $PhI(OAc)_2$, and bathophenanthroline in CH_3CN at 50 °C, the C-11 functionalized product (**642**) was obtained in 55% yield (with 10% recovered starting material). With the latter insertion product (**642**) in hand, all that remained to complete the total synthesis of the target molecule was cleavage of the carbamate, followed by oxidation and *N*-functionalization.

Scheme 119



Despite previous success involving carbamate hydrolysis on related compounds, Garg et al. found that treatment of (**642**) with $Ba(OH)_2$ led to decomposition of the alkyl chloride. This led them to develop a milder means for cleavage of the carbamate. Prompted by the report of Snieckus, cleavage of *N*,*N*-dialkylcarbamate derivatives of phenols,[184] cyclic carbamate (**642**, Scheme 119) was exposed to the Schwartz's reagent $[(C_5H_5)_2Zr(H)Cl]$ in THF. In this way, the carbamate was cleaved selectively to give an amidoalcohol intermediate, where C-23 of (**642**) had conveniently been retained as a formyl group on the bridgehead nitrogen. Oxidation of the alcohol intermediate delivered formyl amide (**643**).

With the chloride still intact, dehydration with Burgess's reagent (see Scheme 116) and sulfurization[185] afforded (–)-*N*-methylwelwitindolinone B isothiocyanate (**644**).

5.7) Rawal et al.'s Synthesis of *N*-Methylwelwitindolinone D Isonitrile, (–)-*N*-Methyl-welwitindolinone C Isothiocyanate, (–)-*N*-Methylwelwitindolinone C Isonitrile, and (–)-3-Hydroxy-*N*-Methylwelwitindolinone C Isothiocyanate

Synthesis of *N*-Methylwelwitindolinone D Isonitrile:[185]

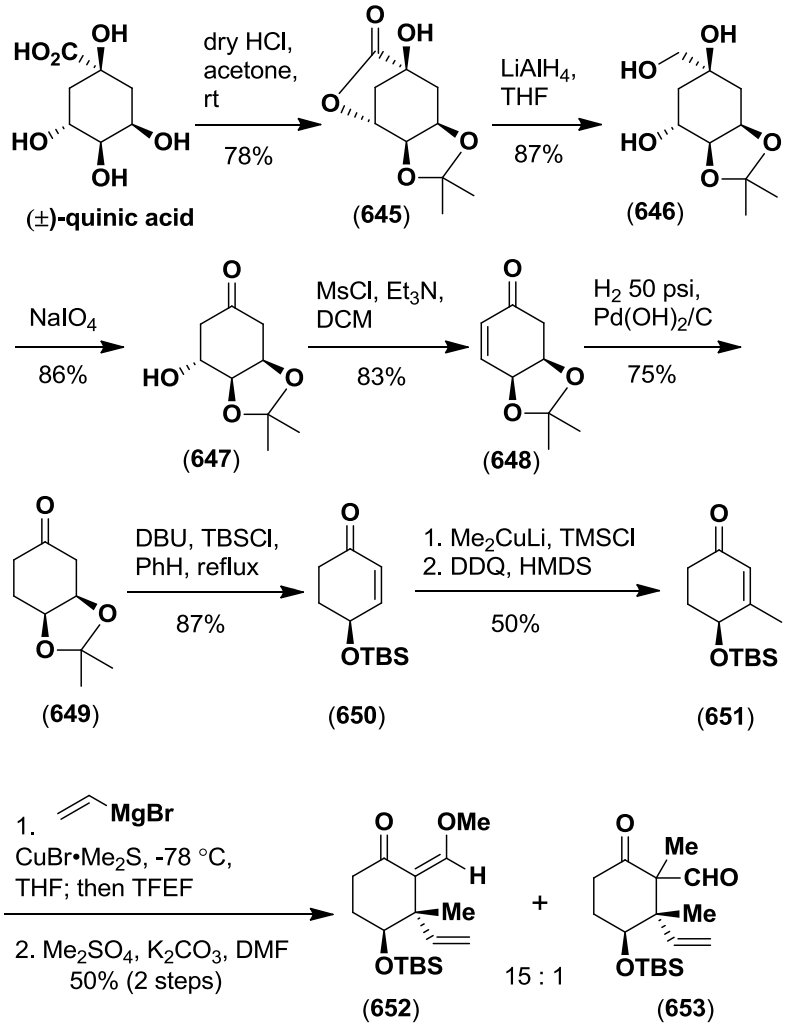
Rawal et al. reported a concise total synthesis of (±)-*N*-methylwelwitindolinone D isonitrile (**634**), the first in a family of complex bicyclo[4.3.1]decane-containing indole alkaloids to yield to synthesis. The complete carbon core of the natural product was assembled rapidly through a Lewis acid-mediated alkylative coupling process and this was followed directly by a palladium-catalyzed enolate arylation reaction. The final ring of the pentacycle was introduced by an indole oxidation/cyclization, and the isonitrile was installed through the rearrangement of an aldehyde to an isothiocyanate followed by desulfurization.

In preparation for the alkylative coupling, Rawal et al.[185] sought to quickly assemble the two partners, (**655**) and (**656**), from readily available materials (Scheme 121). Vinylogous ester (**652**) was prepared by addition of vinyl cuprate to the known enone (**651**, which was prepared as described in the literature from quinic acid, Scheme 120),[186] followed by quenching the intermediate enolate with Zayia's reagent, 2,2,2-trifluoroethyl formate (TFEF)[187]. Methylation of the resultant vinylogous acid then provided ester (**652**) in 47%

overall yield, together with trace quantities of the C-methylation product, ketoaldehyde (**653**). Indole coupling partner (**655**) was prepared from 3-acetyl-4-bromo indole (**654**) upon addition of methylmagnesium bromide to it (Scheme 121).

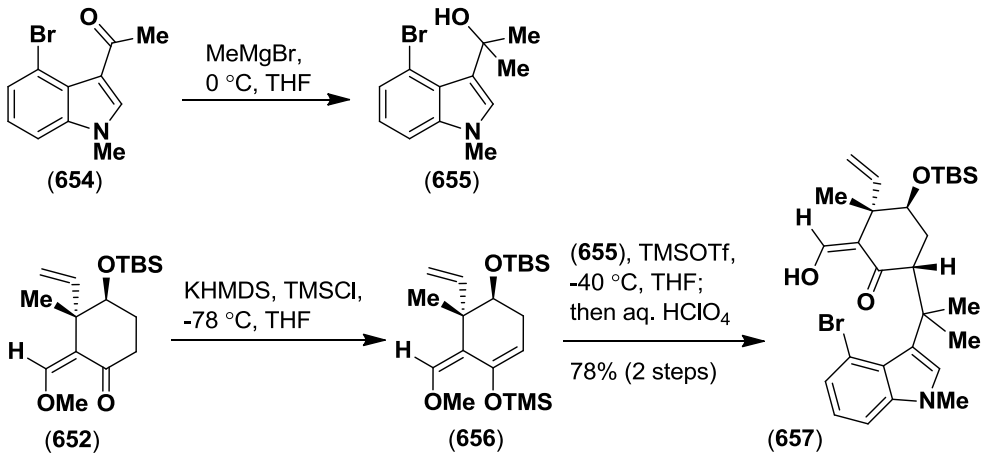
With the two required fragments in hand, they set forth on the crucial alkylative coupling. Vinylogous ester (**652**) was converted to silyl enol ether (**656**, Scheme 121). The reaction of silyl enol ether (**656**) and *N*-methyl indole alcohol (**655**) promoted with TMSOTf

Scheme 120



offered the best results. The rationale behind this approach was that an electron-rich *N*-methyl indole and the weakly basic triflate counterion would better stabilize the transient benzylic cation. Aqueous acidic workup of the reaction mixture afforded vinylogous acid (**657**) as a single diastereomer in 78% overall yield (Scheme 121).

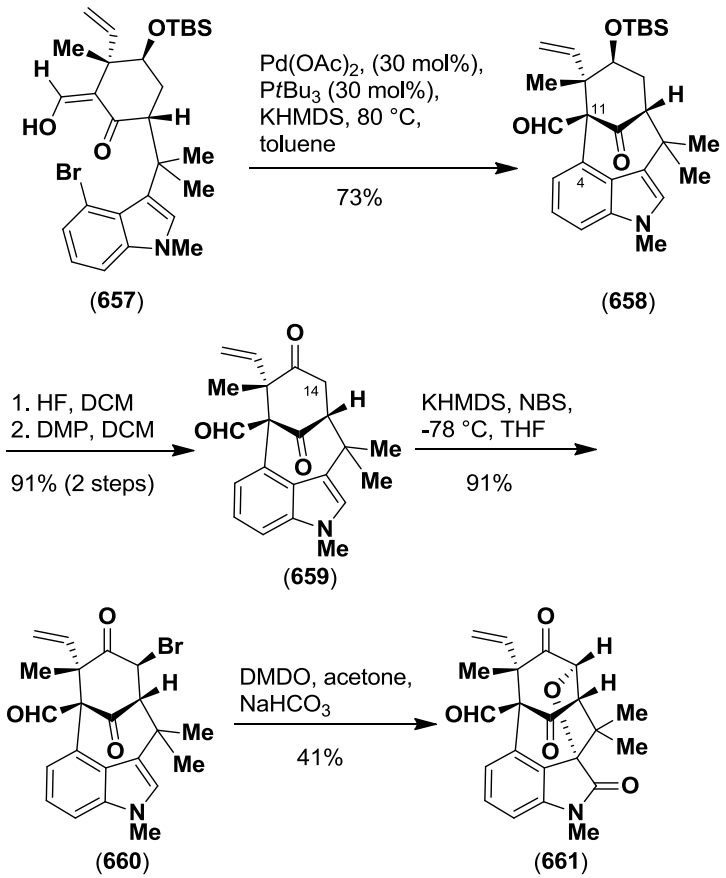
Scheme 121



Completion of the bicyclo[4.3.1]decane framework was expected to be accomplished using a palladium-catalyzed intramolecular enolate arylation to form the key C-4/C-11 bond (Scheme 122). This transformation presented a notable challenge in that it would set in place vicinal quaternary stereocenters. Moreover, the transition metal-catalyzed α-arylation of a β-ketoaldehyde was without precedent. An evaluation of palladium sources, ligands, bases, and solvents ultimately identified $Pd(OAc)_2$ and tri-*tert*-butylphosphine (1:1) as the optimum catalyst system. The use of this catalyst complex in combination with KHMDS in toluene afforded the desired tetracycle (**658**) in 73% yield. Next, atten-

tion turned to the installation of the spirocyclic tetrahydrofuran, the final ring in the pentacyclic structure of the natural product.

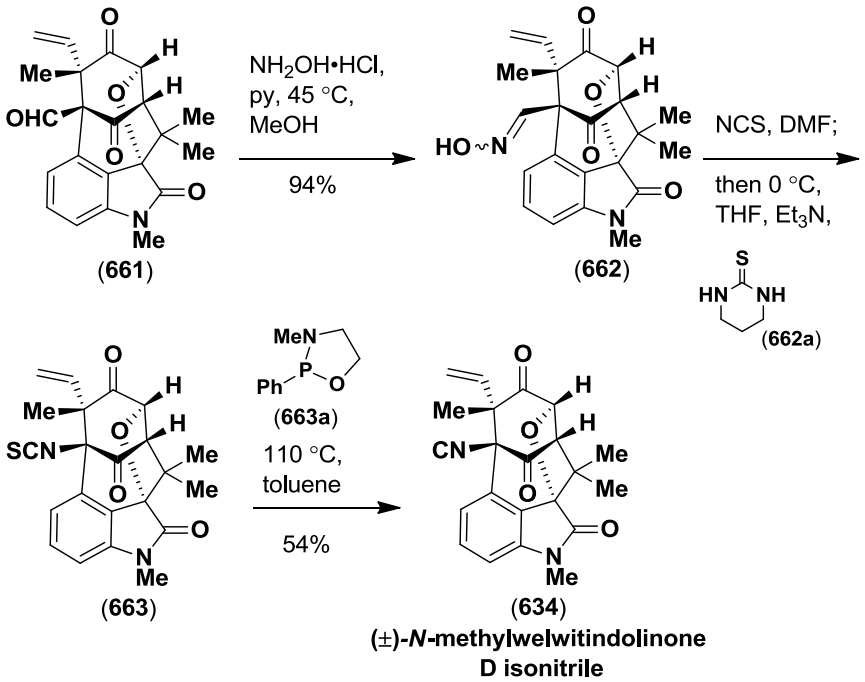
Scheme 122



To this end the TBS group in (**658**) was removed with HF, and the alcohol, which resulted, was oxidized using the Dess–Martin reagent to give diketone (**659**, Scheme 122). In view of the caged architecture of this tetracycle, *α*-bromination to the ketone at C-14 was expected to occur selectively from the convex face. In any event, deprotonation of (**659**) with KHMDS and treatment of the resulting enolate with *N*-bromosuccinimide gave rise to bromodione (**660**) as a single diastereomer, with the halide ideally oriented

for subsequent intramolecular displacement from the opposite face. Critical for the displacement reaction was selective introduction of the hydroxyl group at C-3 through oxidation of the indole moiety. Importantly, when (**660**) was subjected to reaction with a freshly prepared solution of dimethyldioxirane (DMDO), this process not only resulted in the desired diastereoselective oxidation of the indole to the 3-hydroxyoxindole but also in spontaneous cyclization of this intermediate to furnish the desired pentacycle (**661**, Scheme 122).

Scheme 123



In order to finish the synthesis, aldehyde (**661**) was converted to the corresponding oxime (**662**, Scheme 123). By following Kim's one-pot protocol,[188] oxime (**662**) was treated with *N*-chlorosuccinimide followed by propylenethiourea (**662a**) and triethylamine to

give isothiocyanate (**663**) in 65% yield. This transformation was postulated to proceed through a nitrile oxide, which then reacted with the thiourea to give an oxathiazoline through a formal [3 + 2] cycloaddition reaction. Rearrangement of the putative oxathiazoline then affords the isothiocyanate. Finally, desulfurization of the isothiocyanate was realized using oxazaphospholidine (**663a**)[189] to provide *N*-methylwelwitindolinone D isonitrile (**634**) in 54% yield (Scheme 123).

Synthesis of (–)-*N*-Methyl-welwitindolinone C Isothiocyanate, (–)-*N*-Methylwelwitindolinone C Isonitrile, and (–)-3-Hydroxy-*N*-Methylwelwitindolinone C Isothiocyanate:[190]

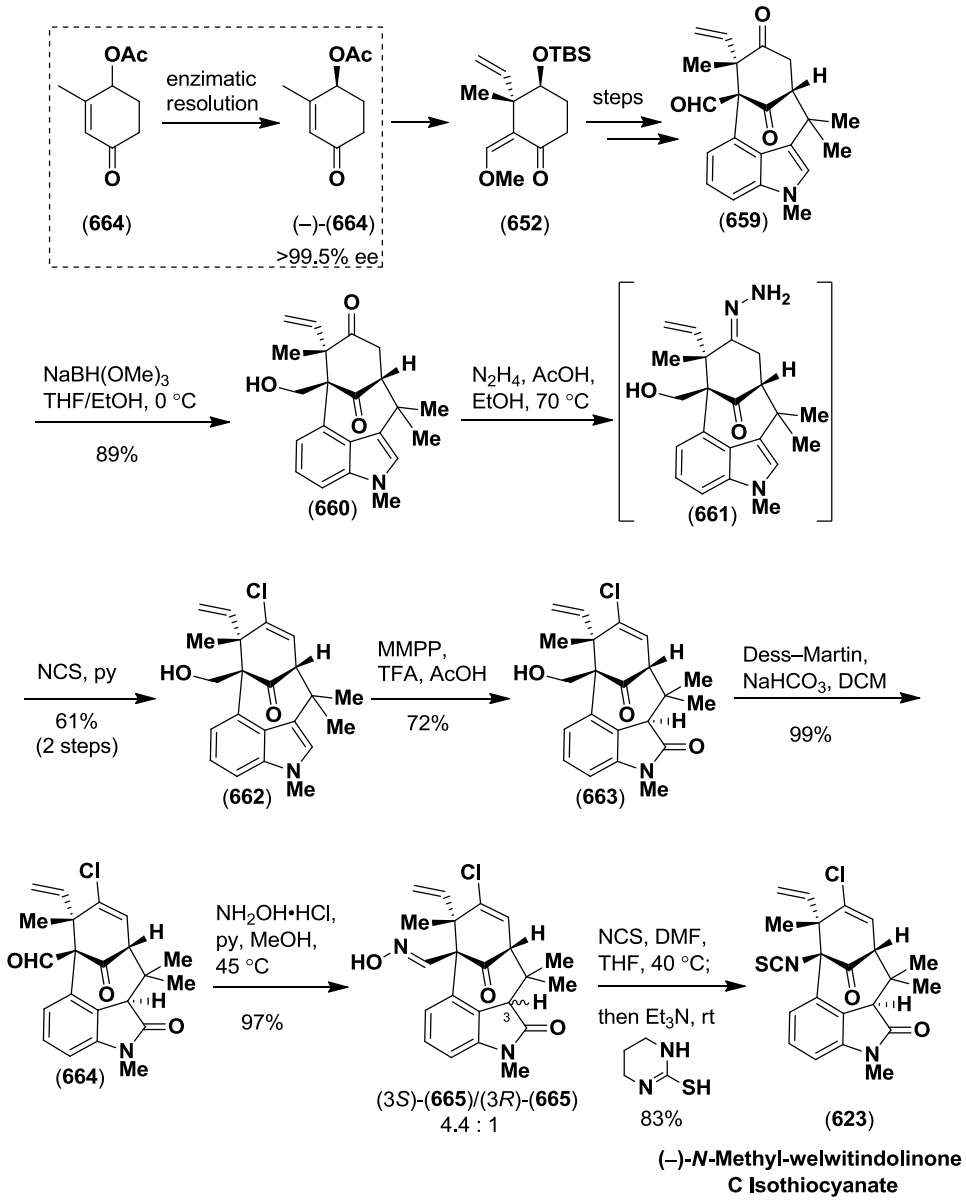
As part of a comprehensive strategy to the welwitindolinone alkaloids possessing a bicyclo[4.3.1]-decane core, Rawal et al. reported the concise asymmetric total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**623**), (–)-*N*-methylwelwitindolinone C isonitrile (**666**), and (–)-3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**667**) from a common tetracyclic intermediate (**659**). His approach toward *N*-methylwelwitindolinone C isothiocyanate (**623**) was based on late-stage introduction of the vinylic chloride functional group through electrophilic chlorination of hydrazone (**661**, Scheme 124), which would be available from ketone (**659**). It was envisioned the use of this compound (**659**), whose racemic synthesis was established en route to *N*-methylwelwitindolinone D isonitrile [(**634**), discussed before], would provide a strategic branching point from which to target several members of this alkaloid family.

In order to realize an asymmetric synthesis of (–)-(**623**), key intermediate (**659**) was prepared from enantioenriched acetate (–)-(**664**) (>99.5% ee), which was obtained through pig liver esterase-catalyzed resolution of racemic 4-acetoxy-3-methylcyclohexenone (Scheme 124).

A key challenge in the route was the installation of the vinyl chloride moiety at C-13. Rawal et al.'s plan was to introduce the chloride through electrophilic chlorination of the C-13 hydrazone.[192] Of the three different carbonyl groups in the starting tetracycle (**659**), the least likely to condense with hydrazine was the bridging ketone at C-10, due to its congested steric environment. In order to avoid formation of the hydrazone with the remaining aldehyde carbonyl, the idea was to protect this functionality as the corresponding alcohol (**660**). Thus, treatment of tricarbonyl (**659**) with $NaBH(OMe)_3$, chemoselectively reduced the aldehyde (Scheme 124), which was then condensed with hydrazine at high temperatures in the presence of acetic acid to give the desired hydrazone (**661**) selectively. Subsequent exposure of the crude hydrazone (**661**) to *N*-chlorosuccinimide in pyridine afforded vinyl chloride (**662**) in 61% yield. The next task was the oxidation of the indole, which proceeded cleanly when mild oxidant, magnesium monoperoxyphthalate (MMPP) was used, to afford oxindole (**663**) in 72% yield. Since the primary alcohol had served its purpose it was returned to the aldehyde state [compound (**664**)] in nearly quantitative yield using Dess–Martin periodinane. The condensation of aldehyde (**664**) with hydroxylamine provided a variable mixture of separable oximes [(3*S*)-(**665**) and (3*R*)-(**665**), 1.6:1 to 4.4:1], epimeric at C-3. The ready formation of the (3*S*)-diastereomer was noteworthy, as this stereochemistry was found in at least one member of the welwitindolinone family. Interestingly, the mixture of oxime diastereo-

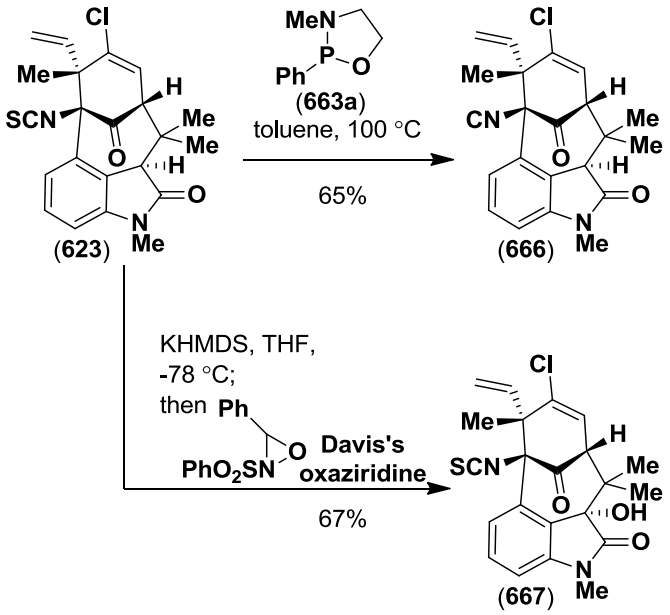
mers ultimately proved inconsequential, since both diastereomers, when subjected to the modified protocol for the Kim oxime rearrangement,[188] were converted smoothly to (–)-*N*-methylwelwitindolinone C isothiocyanate (**623**).

Scheme 124



With an efficient route to *N*-methylwelwitindolinone C isothiocyanate (**623**) at hand, the next goal was to uncover pathways by which this product could be directly converted to its related alkaloids, *N*-methylwelwitindolinone C isonitrile (**666**) and 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**667**, Scheme 125). Desulfurization of isothiocyanate (**623**) with Mukaiyama's oxazaphospholidine[189] (**663a**) gave rise to the first of these targets, isonitrile (**666**), in 65% yield. Conversion of (**623**) to hydroxyoxindole (**667**) posed a greater challenge given the susceptibility of sulfur to oxidants and the need for diastereoselective oxidation. Based on prior work, the conformation of the natural product was expected to provide some measure of diastereocontrol during oxidation. Indeed, it was found that treatment of (**623**) with KHMDS followed by the Davis oxaziridine reagent afforded a single compound (**667**) in 67% yield.

Scheme 125



5.8) Trost et al.'s Synthesis of Marcfortine B and (–)-Marcfortine C

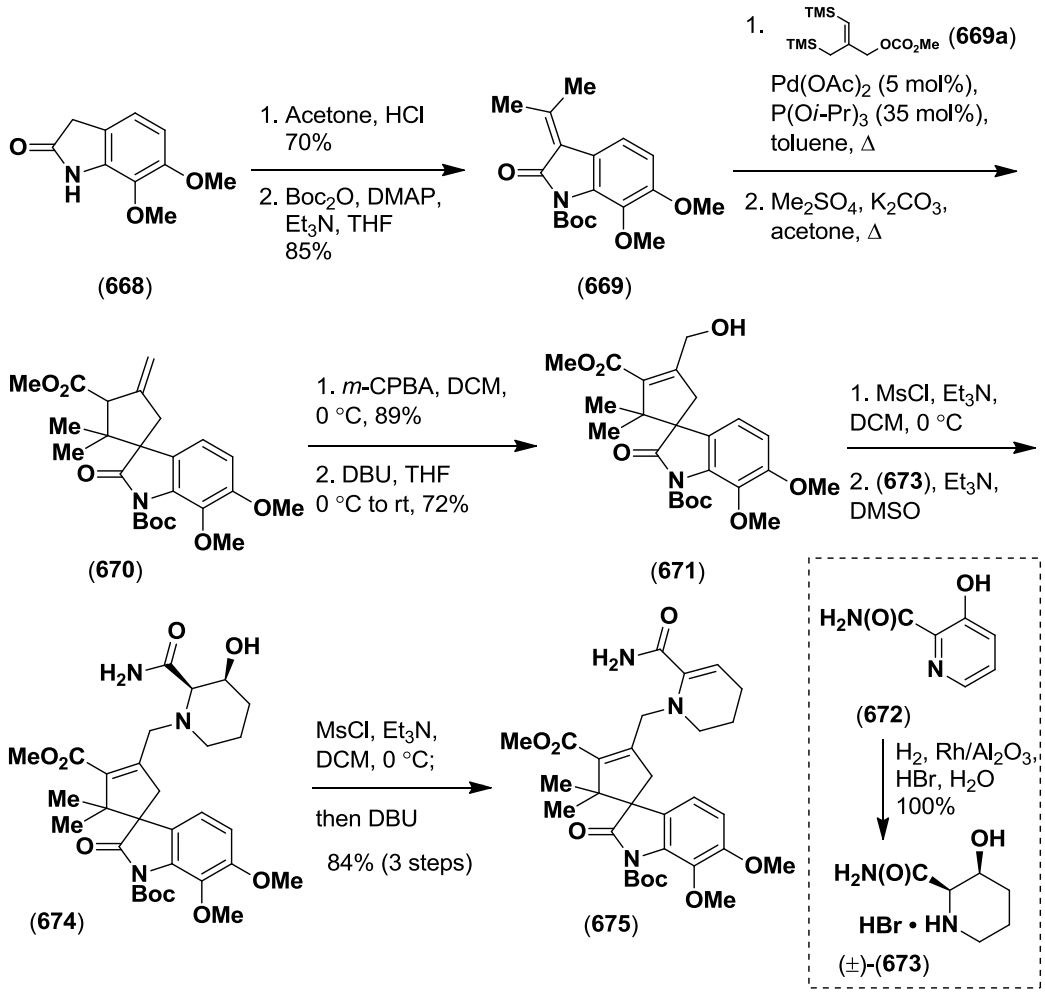
The marcfortines are complex secondary metabolites that show potent anthelmintic activity and are characterized by the presence of a bicyclo[2.2.2]diazaoctane fused to a spirooxindole. Trost et al. recently reported the synthesis of two members of this family.

Synthesis of (±)-Marcfortine B:

The synthesis of (±)-marcfortine B[194] (**687**) began with the preparation of isopropylidene oxindole (**669**) from the known oxindole (**668**)[195] in two steps (Scheme 126) and it subsequently underwent a highly efficient cycloaddition with silyl donor (**669a**) in the presence of 5 mol% palladium(II) acetate and 35 mol% triisopropyl phosphite. After hydrolytic workup and alkylation, methyl ester (**670**) was isolated in excellent yield as a 1:1 mixture of diastereomers. The use of dimethyl sulfate/potassium carbonate was chosen over the alternative conditions for methylation (*e.g.*, DCC/methanol or DBU/ CH_3I) and this minimized any isomerization of the double bond. Moreover, this process provided higher yields than in the case of the optimized conditions utilizing either CH_2N_2 or $TMSCHN_2$. The mixture of diastereomeric oxindoles (**670**) was used as is since the allylic stereocenter was subsequently destroyed and, therefore, of no consequence. The *exo*-methylene group was converted by an epoxidation-elimination to allylic alcohol (**671**), and the pipecolic acid derivative was introduced by way of mesylation and S_N2 coupling with amine (**673**), to provide an unstable secondary alcohol (**674**), which was

immediately subjected to the conditions for elimination to generate olefin (**675**) in good overall yield (Scheme 126).

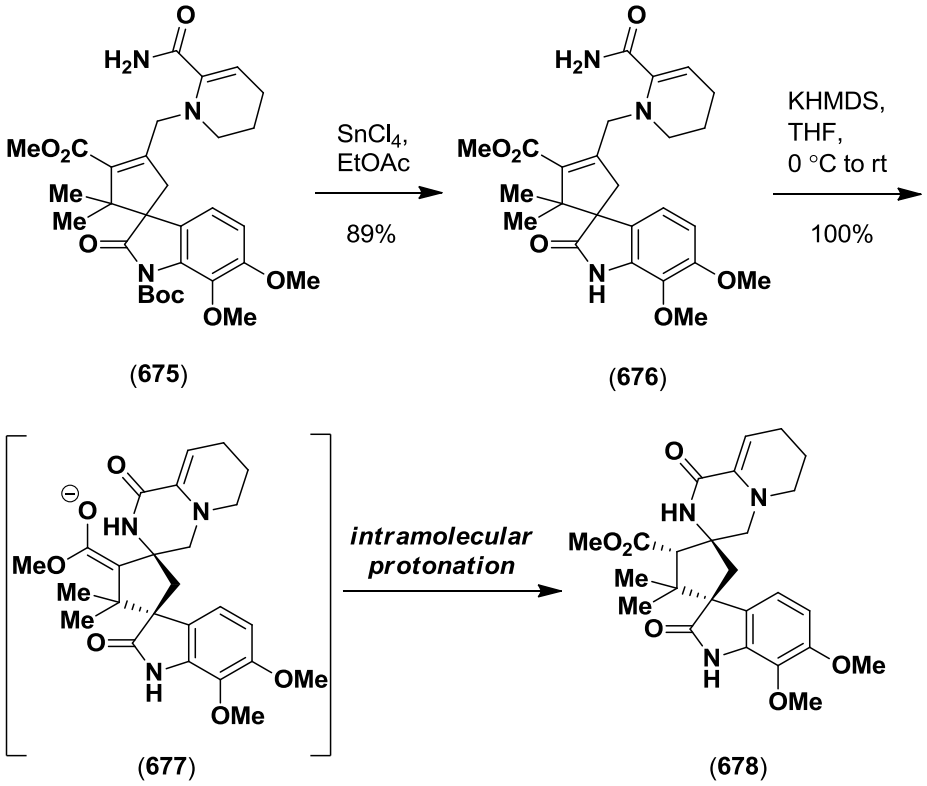
Scheme 126



The removal of the *tert*-butyl carbamate (Boc) protecting group for the Michael cyclization proved to be necessary to avoid decomposition. The deprotection was achieved with tin tetrachloride in ethyl acetate (Scheme 127).[196] Intramolecular Michael

addition was induced by treatment of the amide (**676**) with either 2-3 equivalents of sodium hydride or potassium hexamethyldisilazide in THF. The unsubstituted amide (**676**) gave exclusively the desired diastereomer (**678**) in excellent yield. This can be rationalized by an internal protonation of the ester enolate in the case of the derivative with a free amide proton (**676**, Scheme 127).

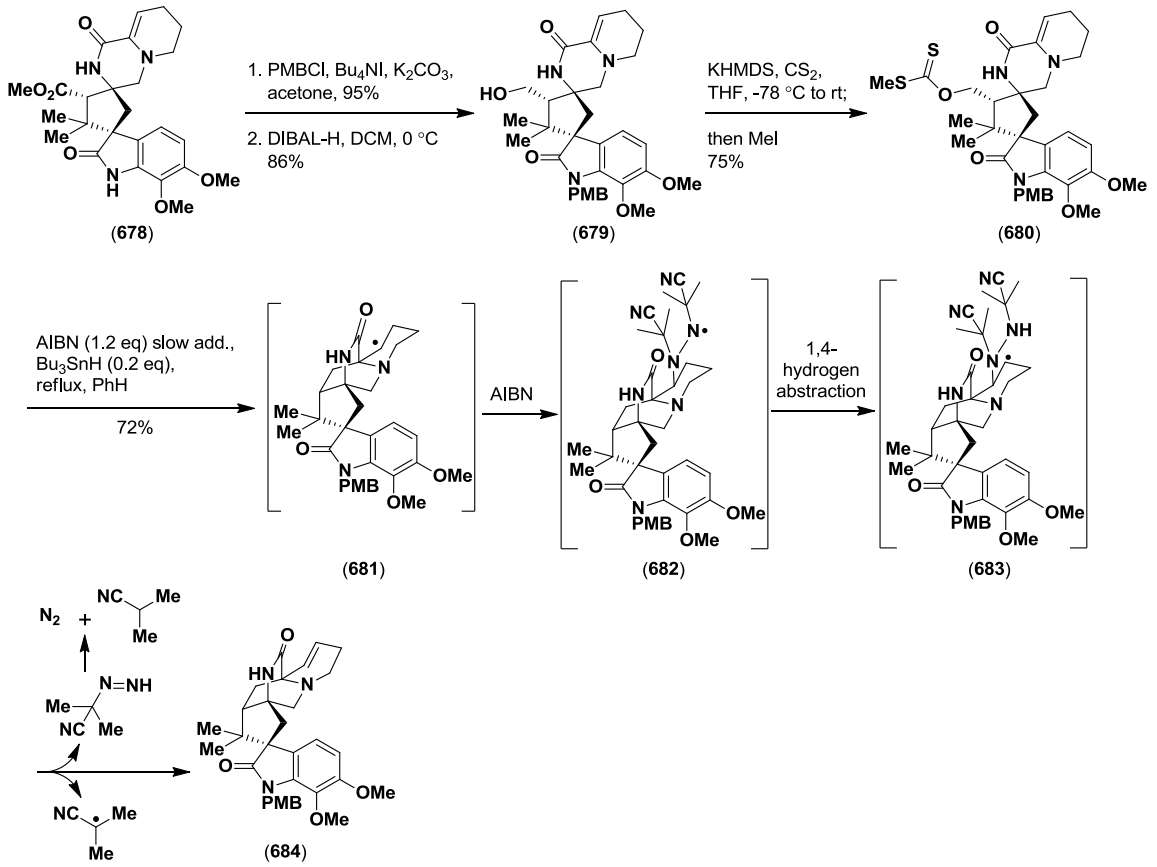
Scheme 127



Due to the poor solubility of the pentacycle (**678**), reprotection of the free amide nitrogen of the oxindole was necessary, wherein the best results were obtained using *p*-

methoxybenzyl (PMB) chloride in acetone with potassium carbonate as the base (Scheme 128).

Scheme 128

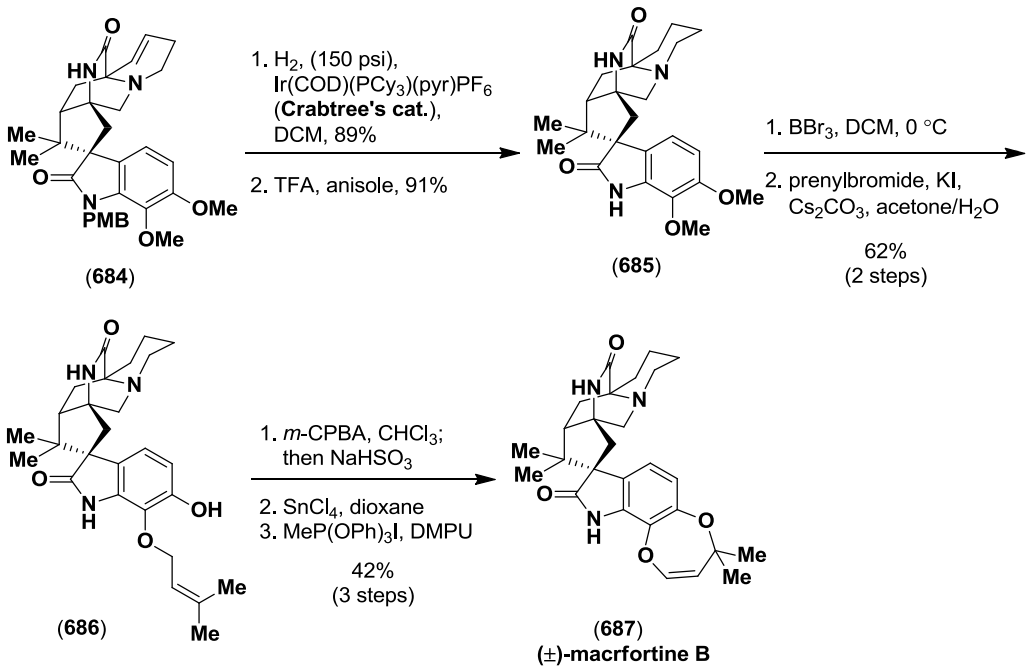


Subsequent reduction of the methyl ester with DIBAL-H proceeded smoothly in 86% yield and gave the primary alcohol (**679**), which was converted into the required xanthate ester (**680**), this gave the precursor for the proposed radical cyclization. Trost et al. found that superstoichiometric amounts of AIBN and catalytic amounts of tributylstannane were necessary for optimum yields. The resulting nitrogen-centered radical (**682**) can then participate in a 1,4-hydrogen abstraction to generate alkyl radical (**683**), which underwent

fragmentation to the observed unsaturated product (**684**), accompanied by an isobutyronitrile radical, and a monoalkyl diazene. This "oxidative" type of process under "reductive" conditions was unprecedented and resulted in the synthesis of a very useful alkene capable of further modification. For the purposes of the current synthesis, that modification was reduction, but useful analogs available by oxidation are also available and resemble other members of the family (Scheme 128).

The double bond of (**684**) proved to be very resistant toward attempted hydrogenation. The starting material was further purified by stirring over Raney nickel to remove any sulfur catalyst poisons from the previous step. Subsequently, the reduction was possible with Crabtree's catalyst[197] and worked best with a hydrogen pressure of 150 psi to obtain a fast and clean reaction (Scheme 129). Removal of the PMB protecting group in the next

Scheme 129

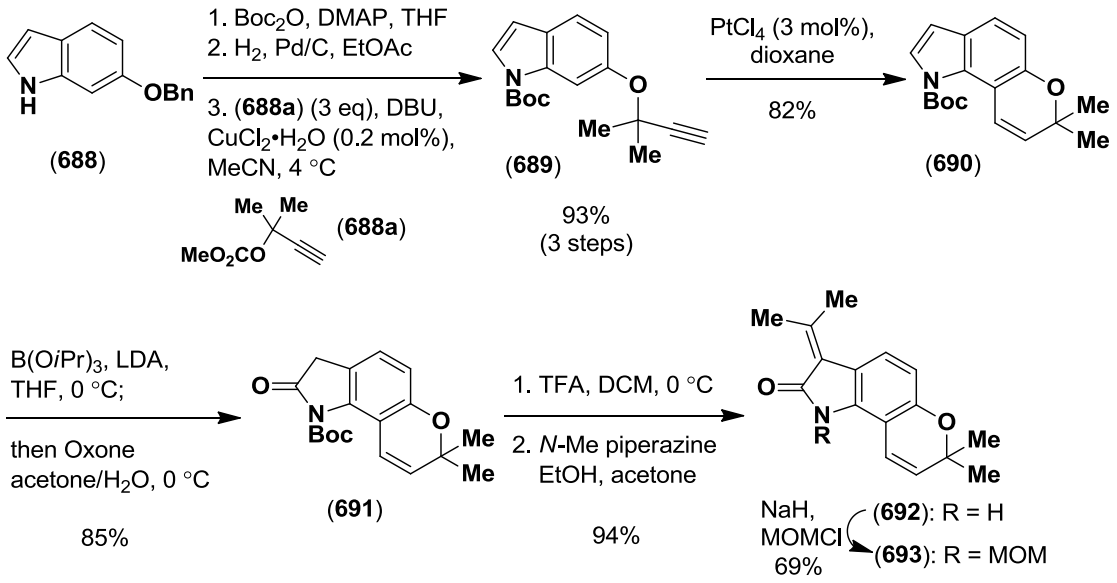


step was realized using protolytic conditions, which involved stirring in trifluoroacetic acid at reflux with anisole as the scavenger, to give oxindole (**685**). With all but the remaining dioxepin ring in place, the synthesis was completed using a known four-step protocol reported by Williams et al.[198] The aryl methyl ethers were deprotected with boron tribromide, and selective monoprenylation provided intermediate (**686**). After epoxidation with *m*-chloroperoxybenzoic acid, a tin tetrachloride-mediated *endo* cyclization took place, and the subsequent dehydration afforded (±)-marcfortine B (**687**, Scheme 129).

Synthesis of (–)-Marcfortine C:

The Trost group also reported the synthesis of (–)-marcfortine C[194] (**702**), which started from commercially available 6-benzyloxyindole (**688**) using a known procedure,[199] which involved Boc protection, benzyl ether hydrogenolysis, and copper-catalyzed propargylation to generate indole (**689**) in excellent overall yield (Scheme 130). The thermal Claisen rearrangement of (**689**) was known to proceed with the loss of the Boc group. On the other hand, the platinum-catalyzed methodology originally developed by Sames[200] permitted smooth formation of (**690**) in 82% yield. Treatment of this compound with LDA in the presence of triisopropyl borate led to the 2-indolylboronate, which was oxidized to yield oxindole (**691**) in 85% yield. At this stage, the Boc group was removed with trifluoroacetic acid, and the acetone adduct (**692**) was prepared by treatment with *N*-methyl piperazine. Preparation of *N*-methoxymethyl (MOM) derivative (**693**) was performed in good yield under standard conditions of alkylation (Scheme 130).

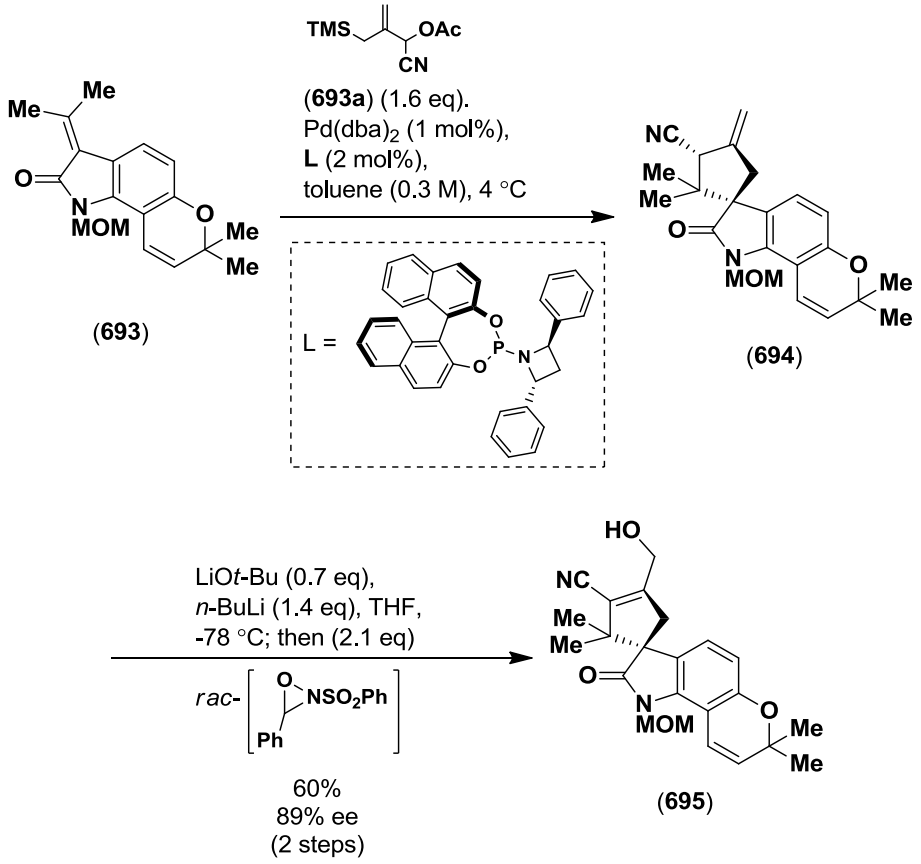
Scheme 130



Combination of the application of both the TMM reaction (a palladium-catalyzed [3 + 2] cycloaddition of trimethylenemethane (TMM) with an isopropylidene oxindole) and subsequent oxidation based on isopropylidene oxindole (**693**, Scheme 131) gave a 60% overall yield (on gram scale) of allylic alcohol (**694**) in 89% ee. Accordingly, this two-step sequence effectively set the stereochemistry at the spirocenter, which Trost et al. anticipated would allow them to establish all the remaining stereocenters in (–)-marcfortine C (**702**) by analogy to previous work in their group.

The piperidine functionality could now be readily introduced by an S_N2 alkylation, followed by elimination of the secondary alcohol to furnish (**696**) in 84% yield over 3 steps. Then, primary carboxamide (**696**) underwent intramolecular Michael addition in the presence of 1 equivalent of *tert*-BuOLi to provide (**697**) in 71% yield.

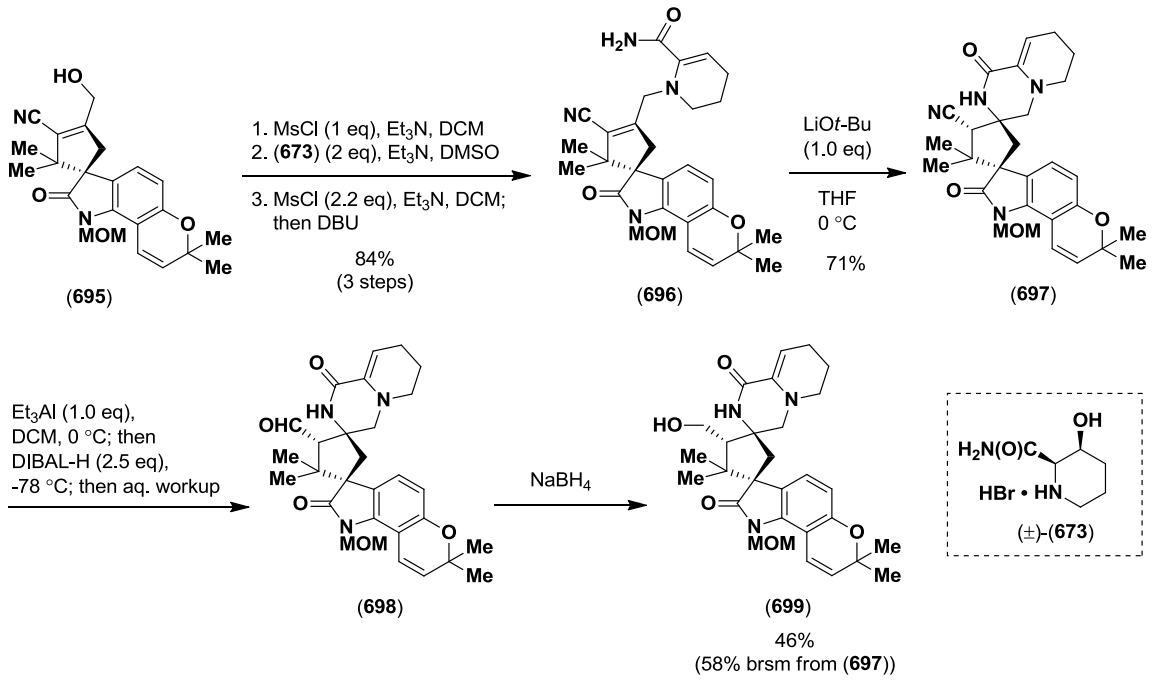
Scheme 131



With oxindole (**697**) in hand, Trost et al. sought to effect the crucial nitrile reduction (Scheme 132). After extensive experimentation positive results were obtained by employing triethylaluminum (as an *in situ* protecting group for the secondary amide) in DCM, and then DIBAL-H was added to provide the aldehyde (**698**). It was formed cleanly with a small amount of unreacted starting material. In practice, these two components were difficult to separate from each other; however, treatment of the mixture with an excess of sodium borohydride effectively reduced the aldehyde and allowed

recovery of any unreacted starting material. Under these conditions, the primary alcohol (**699**) was obtained in 58% yield based on recovered starting material.

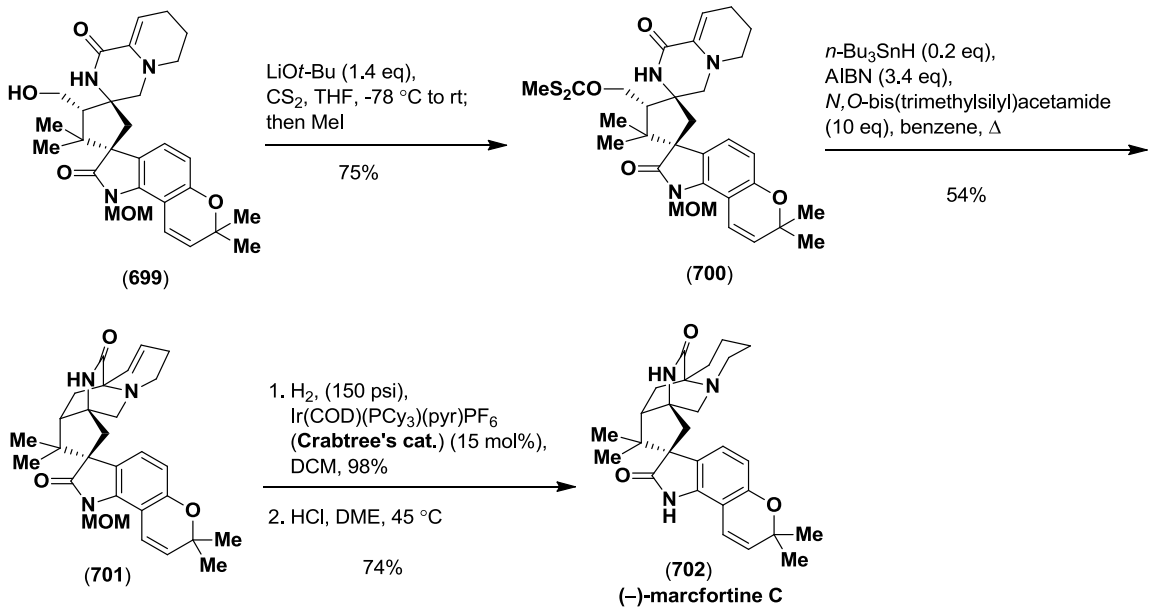
Scheme 132



With primary alcohol (**699**) in hand, Trost et al. was able to complete the synthesis of marcfortine C (Scheme 133). The xanthate ester formation proceeded in 75% yield using *tert*-BuOLi as the base to give compound (**700**). Importantly at this stage, when Trost et al. used an excess of *N*,*O*-bis(trimethylsilyl)acetamide (BSA), *n*-Bu_3SnH (0.2 equivalents), and AIBN (3.4 equivalents) with oxindole (**700**), then the bicyclo[2.2.2]diazaoctane (**701**) was generated in around 40% yield. It was also realized that doubling the equivalents of AIBN improved the yield to 54% (the use of BSA in such radical cyclizations was unprecedented). In a number of reactions wherein the substrates and/or

products may be subject to decomposition due to the adventitious presence of acid or moisture, addition of BSA has proven to be an innocuous acid and moisture trap. The authors suspected that it played a similar role here. On the other hand, a direct role in the radical process such as by turning over the tin catalyst by silylating the methylthio fragment could not be ruled out. As was observed earlier the cyclization reaction proceeded in an oxidative fashion to provide the unsaturated product. Thus, it was now necessary to effect a chemoselective reduction of this newly formed olefin (**701**) in the presence of the chromene moiety. Notably, both olefins were part of a fused six-membered heterocycle and possessed a vicinal tertiary carbon. Initial tests using either Wilkinson's or Crabtree's catalysts were highly chemoselective and the latter proceeded in nearly quantitative yield. Finally, deprotection was achieved with aqueous HCl in DME to provide (–)-marcfortine C (**702**) in 74% yield.

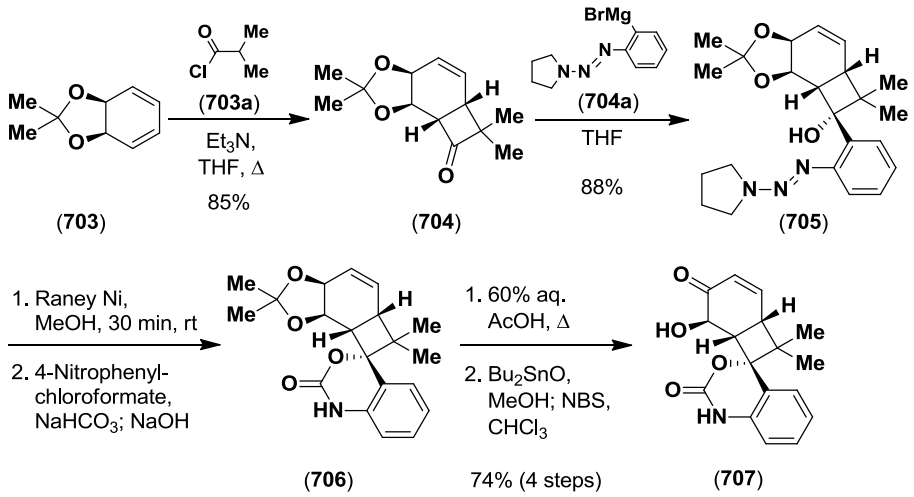
Scheme 133



5.9) Wood et al.'s Total Synthesis of (±)-Welwitindolinone A Isonitrile

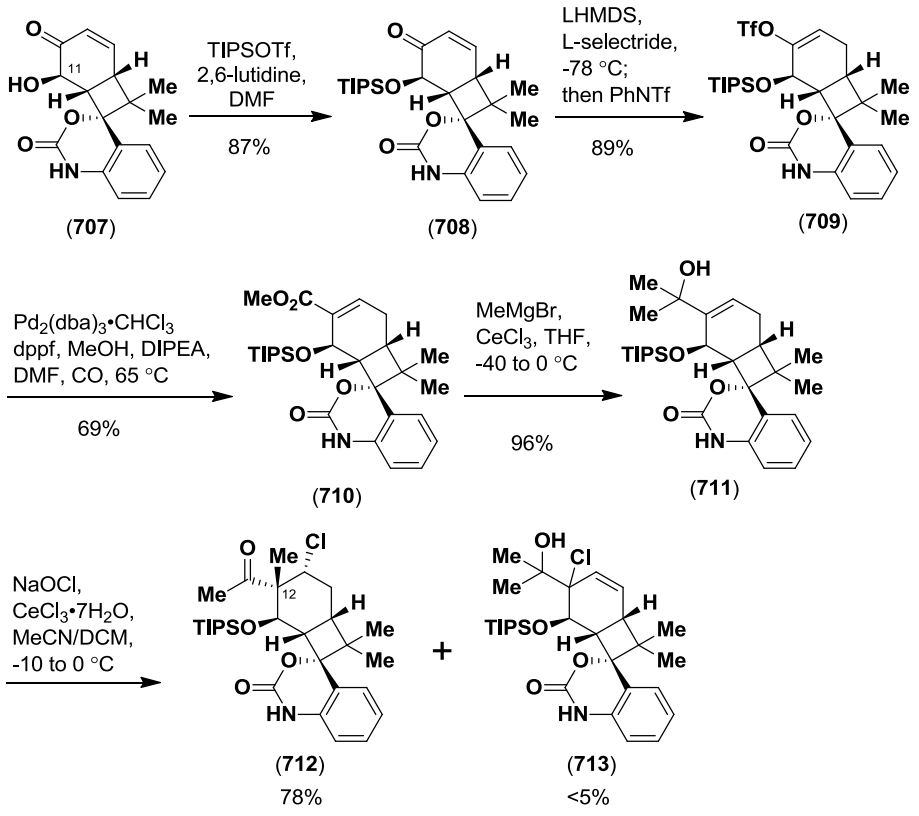
An efficient and highly stereoselective total synthesis of the natural product (±)-welwitindolinone A isonitrile (**724**) was described by Wood et al. in 2008.[201] The synthesis started with the [2 + 2] ketene cycloaddition of racemic acetonide (**703**) with excess isobutyryl chloride (**703a**) and triethylamine (to form dimethylketene *in situ*) in refluxing THF to give ketone (**704**) in 85% yield as a single regio- and diastereo-isomer (Scheme 134). Cyclobutanone (**704**) was treated with triazene-protected aryl Grignard reagent (**704a**) to give tertiary alcohol (**705**) in excellent yield as a single diastereomer. Reductive deprotection of the triazene was followed by urethane formation to furnish (**706**), which upon acidic hydrolysis of the acetonide and regioselective oxidation of the allylic alcohol provided hydroxy enone (**707**). By use of this efficient four step sequence, Wood et al. was able to obtain multigram quantities of enone (**707**) from acetonide (**705**) with only a single chromatographic purification.

Scheme 134



It was postulated that protection of the C-11 hydroxyl of enone (**707**) with a suitably large protecting group could over-ride the inherent facial bias of the bicyclic skeleton and promote chlorination from the concave face of the molecule. Consequently, *α*-hydroxy enone (**707**) was converted into the triisopropyl silyl ether (**708**, Scheme 135). Next, tertiary allylic alcohol (**713**) was prepared by a sequence which began by treatment of *α*-siloxy ketone (**708**) with LHMDS (to deprotonate the urethane) and this was followed by

Scheme 135



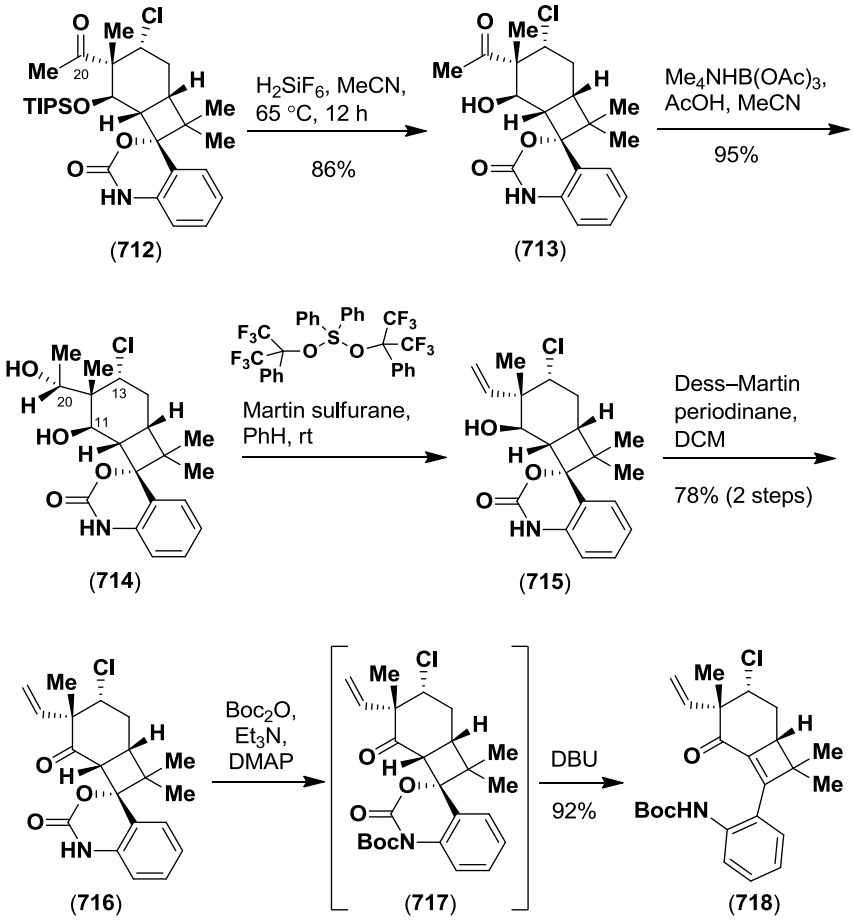
L-selectride then *N*-phenyltriflimide to give enol triflate (**709**) in 89% yield. The subsequent exposure of triflate (**709**) to $Pd_2(dba)_3$ and 1,1′-bis-(diphenylphosphino)-ferro-

cene (dppf) in the presence of methanol, DIPEA and carbon monoxide furnished enoate (**710**) in 69% yield. When the enoate (**710**) was subjected to reaction with excess methyl magnesium bromide and anhydrous cerium trichloride, this process provided tertiary allylic alcohol (**711**); the required semipinacol rearrangement substrate. To this end, Wood et al. found that using NaOCl/AcOH as the chlorine source with $CeCl_3$ in DCM/ MeCN and maintenance of the reaction temperature between −10 and 0 °C provided chloroketone (**712**) in 78% isolated yield as a single diastereomer (Scheme 135).

With chloroketone (**712**) in hand, attention turned to accessing the fully functionalized tetracyclicketone (**716**, see Scheme 136) by conversion of the C-20 ketone to the requisite vinyl functionality. After removal of the TIPS-protecting group with H_2SiF_6, hydroxy ketone (**713**) was reduced with $Me_4NHB(OAc)_3$ to give diol (**714**) in 82% overall yield (Scheme 136). Exposure of diol (**714**) to Martin's sulfurane[202] resulted in regioselective dehydration of the C-20 alcohol, to furnish the required vinyl moiety of the final target molecule. The subsequent oxidation of alcohol (**715**) using Dess–Martin periodinane furnished ketone (**716**) in 78% yield over two steps. The conversion of the carbamate (**716**) to the *N*-Boc-imide (**717**), followed by *in situ* treatment with DBU at room temperature delivered *N*-Bocaniline (**718**) in 92% yield (Scheme 136).

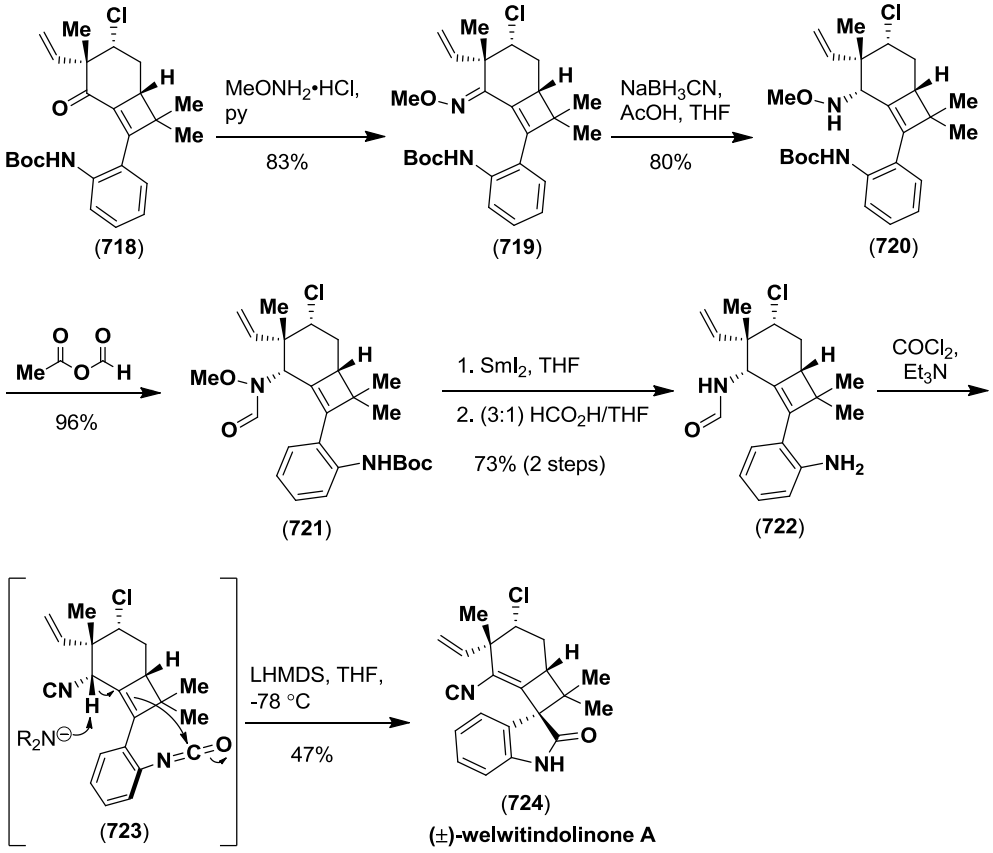
In the last stages of the synthesis, advancement of enone (**718**) to the corresponding methyl oxime (**719**) followed by exposure to reducing conditions, $NaBH_3CN$/AcOH, resulted in the formation of methoxylamine (**720**, Scheme 137). Subsequent formylation of the latter with acetic formic anhydride (AFA) provided a near quantitative yield of methoxyamide (**721**) which, upon sequential exposure to SmI_2[203] followed by formic acid, underwent N-O bond cleavage and Boc-deprotection to furnish aniline (**722**).

Scheme 136



In the final-ring closing event, treatment of formamide (**722**) with excess phosgene and triethylamine promoted simultaneous dehydration of the formamide to the isocyanide and conversion of the aniline to the isocyanate to deliver isocyano-isocyanate (**723**, Scheme 137). Upon removal of the triethylamine salts by filtration and drying in vacuo, it was found that treatment of (**723**) with excess LHMDS at −78 °C provided the final target alkaloid (**724**) in 47% yield.[204] However, attempts to further optimize the reaction by changing the base or rigorously drying the intermediate isocyano/isocyanate (**723**) did not significantly improve the yield of (**724**, Scheme 137).

Scheme 137



5.10) Baran et al.'s Enantiospecific Total Synthesis of Welwitindolinone A Isonitrile

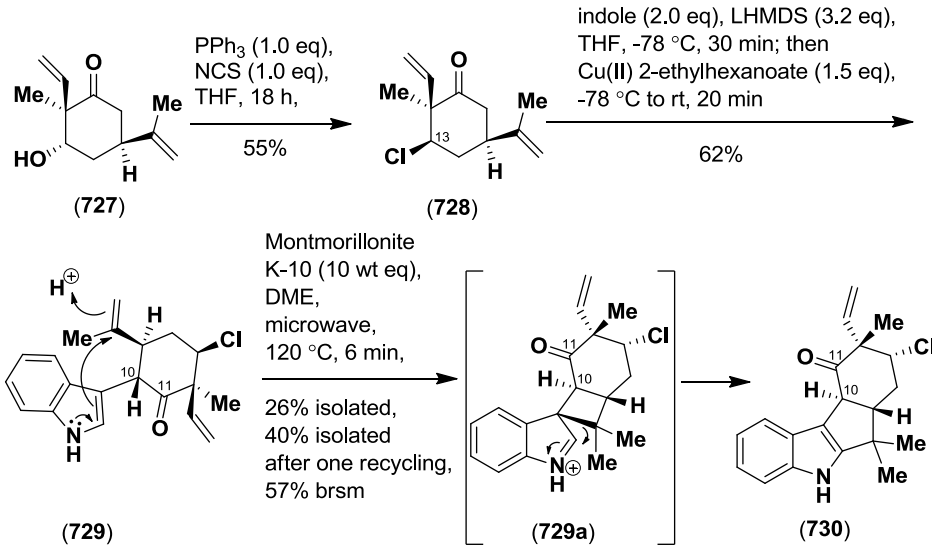
In 2008, Baran et al. published the enantiospecific total synthesis (+)-welwitindolinone A isonitrile (**724**) via a redox economic approach.[205] Initially, carvone oxide (**725**) (obtained from (*S*)-carvone, Scheme 138) was examined as a starting point for the production of chloroketone (**728**). After several failed attempts to generate the desired chloroketone (**728**), a successful route was finally developed by Baran's group inspired by a reaction developed in the Wender laboratory.[206] In Wender et al.'s study, α-epoxyketones were

first treated with strong base to form the corresponding enolate. Nucleophilic addition of an organometallic reagent (usually a Grignard reagent) to this epoxyenolate at the α-carbon (as opposed to the usual β-attack) formed the corresponding α-alkyl-β-hydroxy-ketone. However, a quaternary carbon installation during the course of this reaction was unprecedented. Despite this potential limitation, the reaction was attempted on carvone oxide to provide ketone (**727**) in about 30% yield (Scheme 138). Extensive optimization efforts (solvent, nucleophile, base, additives, temperature, addition rates) did not result in significant improvement in the overall efficiency of the reaction. Nevertheless, with alcohol (**727**) available, the chlorination was accomplished (NCS/PPh_3) in acceptable yield to provide the key chloroketone (**728**). Despite the modest overall yield of this two-step sequence, it was used to rapidly prepare multigram quantities of (**728**) and was therefore deemed as an acceptable solution to this problem by Baran et al., especially given the difficulties in preparing (**728**) via other routes.[205] With chloroketone (**728**) in hand, the stage was set to invoke the key direct indole coupling reaction which proceeded smoothly to provide the coupled product (**729**) in 62% yield as a single diastereomer. Several aspects of this particular coupling are noteworthy. First, it was remarkable that chloride elimination was not observed during the course of this coupling. Second, it was discovered that, as the reaction concentration was increased, the yield improved. Third, any C-13 diastereomer of (**728**) present in the reaction mixture did not participate in the coupling reaction and rather suffered elimination, presumably due to the axial disposition of the chlorine atom. Finally, this effective method for direct C-C bond formation enabled all the necessary carbon atoms of these complex natural products to be secured in only three steps and was routinely carried out on multigram scale (Scheme 138).

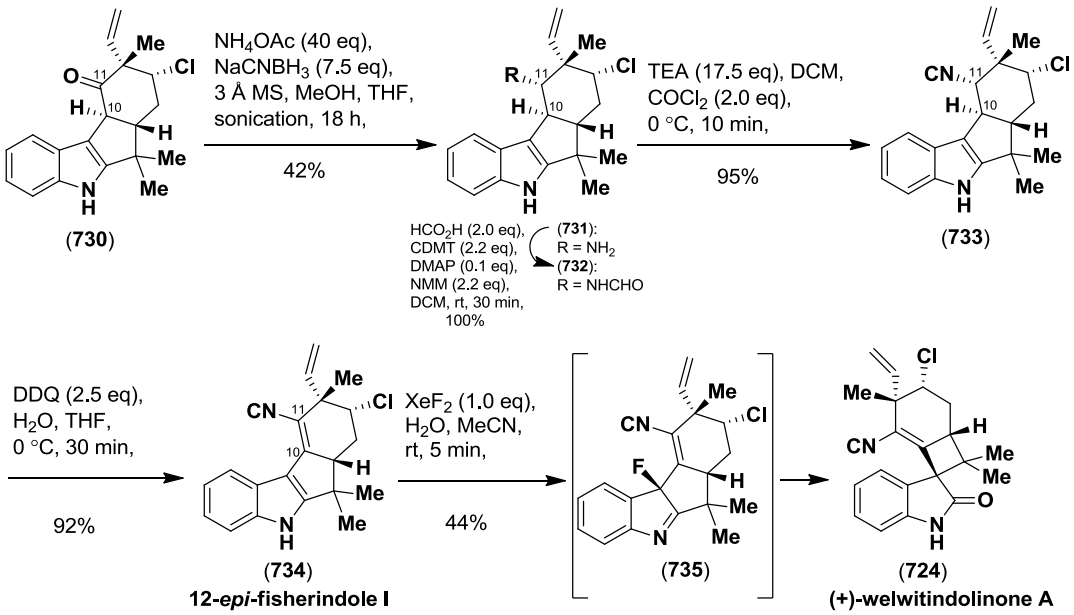
Functional group manipulations were all that remained to complete the synthesis of (+)-(**724**). In the next particular cyclization reaction, the olefin moiety at C-9 in (**729**) could be protonated to give a tertiary carbocation, which was intercepted by the indole ring to give intermediate (**729a**) which in turn led to the desired product (**730**). It was found by Baran's group that Montmorillonite K-10 acidic clay, with microwave irradiation, provided the desired product (**730**) without formation of several undesired byproducts,[205] although recycling of unreacted starting material was required (Scheme 138).

Amine (**731**) was obtained after performing a reductive amination protocol on ketone (**730**), as shown in Scheme 139. Next, amine (**731**) was formylated in quantitative yield to give (**732**). It was subsequently discovered by Baran et al. that initial dehydration of formamide provided isonitrile (**733**) in 95% yield. Treatment of this compound with DDQ,[207] provided 12-*epi*-fischerindole I (**734**) in 92% yield, which permitted access to large quantities of this natural product.[208] A mild method to accomplish the transformation of indole (**734**) into its corresponding oxindole was developed by Baran et al. in which (**734**) was treated with a solution of XeF_2 in wet acetonitrile to provide (**724**) in 44% yield, *via* the intermediacy of fluoroindoline (**735**).[208] The chemoselectivity of this reagent was noteworthy given the presence of an olefin in (**734**), which is known to react with XeF_2,[209] and the reactive isonitrile moiety (Scheme 139). This reaction was routinely performed on more than 50 mg of (**734**), and more than 580 mg of the natural product has been prepared to date.

Scheme 138



Scheme 139

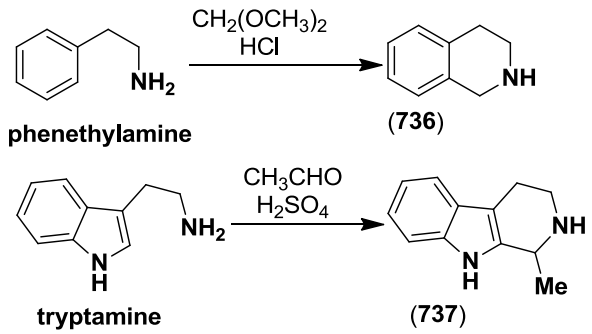


6) Latest Advances in the Asymmetric Pictet–Spengler Reaction

Alkaloids are an important class of natural products that are widely distributed in nature and produced by a large variety of organisms. They have a wide spectrum of biological activity and for many years were used in folk medicine. These days, alkaloids also have numerous applications in medicine as therapeutic agents. The importance of these natural products in inspiring drug discovery programs is proven and, therefore, their continued synthesis is of significant interest. The condensation discovered by Pictet and Spengler is the most important method for the synthesis of alkaloid scaffolds. The power of this synthetic method has been convincingly proven in the construction of stereochemically and structurally complex alkaloids.

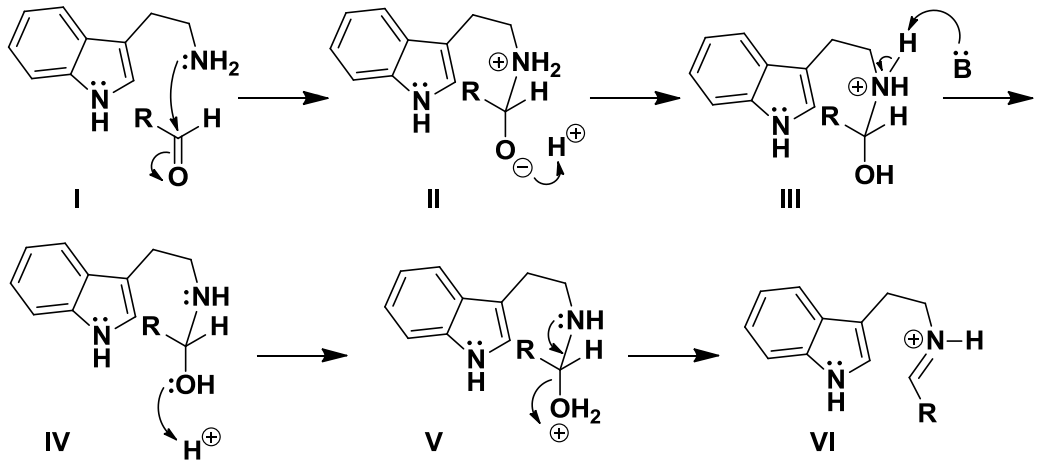
The purpose of this section is to take a look at the latest advances in the stereoselective Pictet–Spengler reaction. It is believed by the author that by doing so, it will help to put this work in a general synthetic perspective given the critical role that this reaction plays in the correct construction of the initial stereocenters. To that end, it was found that the excellent contributions by Lorenz and Van Linn (Lorenz, M.; Van Linn, M. L.; Cook, J. M. *Current Organic Synthesis* **2010**, *7*, 189-223) in Milwaukee and that by Stöckigt and Waldmann (Stockigt, J.; Antonchick, A. P.; Wu, F-R.; Waldmann, H. *Angew Chem. Int. Ed*. **2011**, *50*, 8538-8564) as key in order to quickly get access to some of the advances in the stereoselective applications of the Pictet–Spengler reaction up to 2011 and part of their work is worth mentioning here. The Pictet–Spengler reaction had been extensively reviewed by many before.[210]

Scheme 140



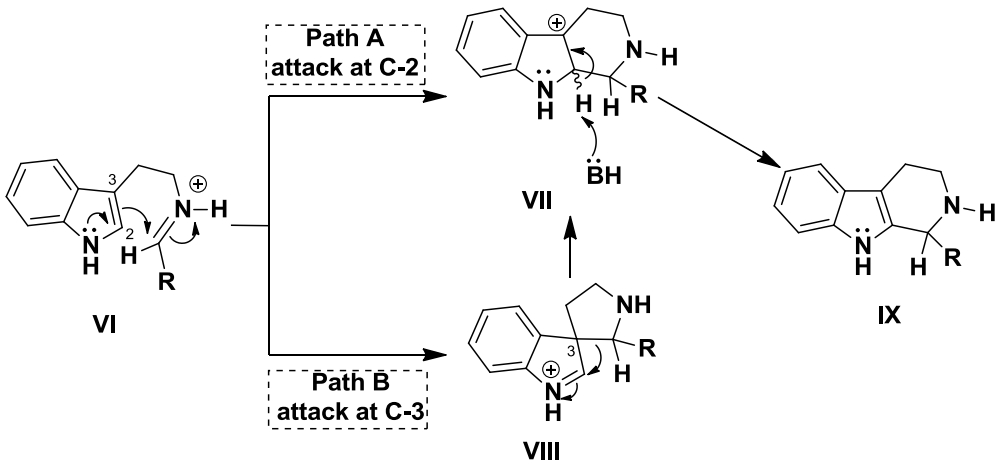
The reaction was first discovered in 1911 when phenethylamine with methylal were condensed to produce the tetrahydroisoquinoline (**736**).[211a] Tatsui in 1928, executed the first examples with indoles, when he utilized this reaction with indole bases to form 1-methyl-1,2,3,4-tetrahydro-*β*-carboline (**737**) from tryptamine and acetaldehyde (Scheme 140).[211b]

Scheme 141



The Pictet–Spengler reaction involves the cyclization of electron-rich aryl or heteroaryl groups onto imine or iminium ion electrophiles and has long been a standard method for the construction of both tetrahydro-*β*-carboline and tetrahydroisoquinoline systems. The proposed mechanism of Jackson et al. is illustrated in Schemes (141, 142).[212,213]

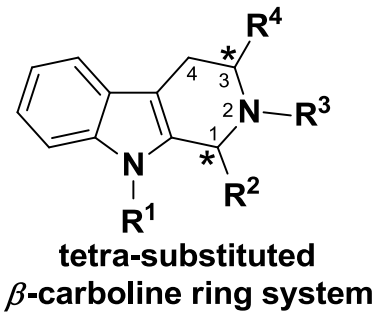
Scheme 142



6.1) Diastereospecific Pictet–Spengler Reactions via Internal Asymmetric Induction

Advances in the asymmetric Pictet–Spengler reaction originated from the need to form the 1,2,3,4-tetrahydro-*β*-carboline system in stereospecific fashion. The stereochemical direction of the reaction can be understood through the steric influence that substituents at the 1, 2, and 3 positions, as well as the functionality on the indole nitrogen, have on the course of the reaction (Figure 15).

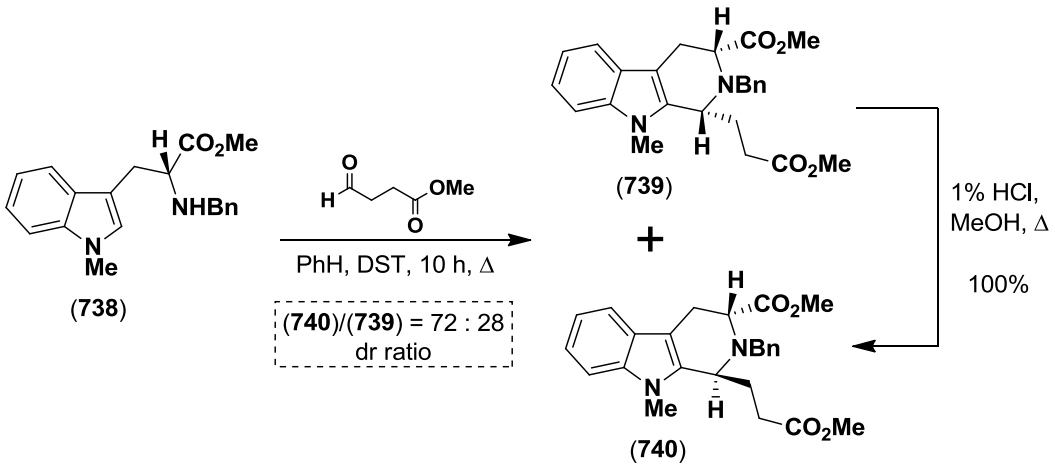
Figure 15. Tetra-substituted carboline system



In an effort to synthesize biologically important indole alkaloids in a diastereospecific fashion, the asymmetric Pictet–Spengler reaction was developed.[214] The Pictet–Spengler cyclization in nonacidic aprotic media was first reported by Sandrin et al.[215] The *cis* and *trans* isomers of the Pictet–Spengler cyclization were isolated from the condensation of tryptophan methyl ester with benzaldehyde using a Dean–Stark trap to remove the water formed in the process. Ungemach demonstrated later that N_b-benzyl tryptophan methyl ester could cyclize in a stereospecific fashion by making use of this modified Pictet–Spengler reaction in the total synthesis of indole alkaloids.[216] When the aldehyde substrate carried a bulky substituent, 100% *trans* diastereoselectivity was observed. A breakthrough in the enantiospecific preparation of the key azabicyclo[3.3.1]nonane (tetracyclic ketone) template was realized by Zhang (Scheme 143) when the optically pure D-N_a-methyl-N_b-benzyl tryptophan methyl ester (**738**) was employed as the substrate.[217] Under the nonacidic aprotic conditions (refluxing benzene/Dean–Stark trap), the D-N_a-methyl-N_b-benzyl tryptophan methyl ester reacted with methyl 3-formyl-

propionate to provide a diastereomeric mixture of *trans* and *cis* tetrahydro-*β*-carbolines in a ratio of 72:28, respectively.

Scheme 143



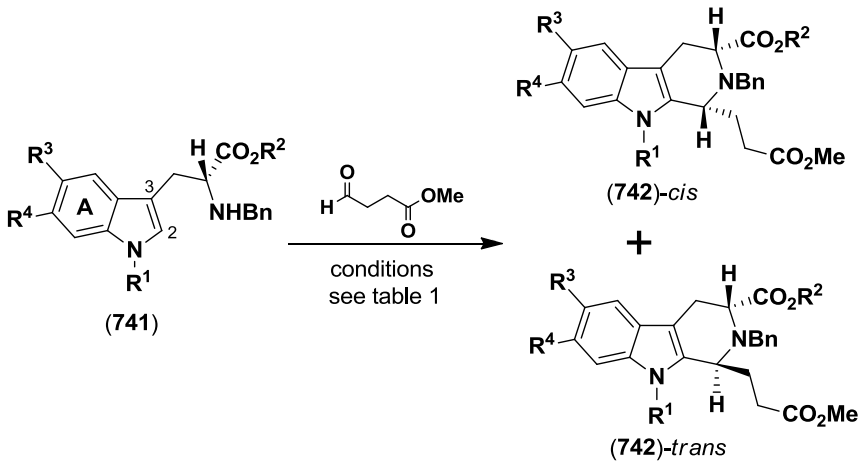
Zhang also showed that when the *cis* isomer was heated in 1% HCl in methanol, complete conversion into the *trans* isomer was observed (Scheme 143), while the *trans* isomer remained intact under the same conditions. The *trans* diastereomer was then elaborated further and eventually it was converted into the indole alkaloid alstonerine.[218] This represented the first enantiospecific synthesis of an indole alkaloid employing the asymmetric Pictet–Spengler reaction. The reaction conditions of this Pictet–Spengler cyclization were later modified to gain better entry into the desired *trans* diastereomer.[138,55b,219]

In order to evaluate the effects of kinetic or thermodynamic control on the Pictet–Spengler reaction, a series of experiments have been carried out. In regard to the

mechanism of the condensation itself, two possible pathways were proposed earlier by Jackson et al. (Schemes 141, 142). Attack at C-3 to form the spiroindolenine intermediate (**VIII**, Scheme 142) was demonstrated by Nakagawa et al., when a tetracyclic product was observed from the cyclization of tryptamines functionalized with nitrone moieties with cysteinals under conditions of a Pictet–Spengler condensation.[220] Jackson et al., Cook et al., Williams et al., and many others have also presented evidence in support of attack at the C-3 position; however, direct attack at the C-2 position could not be completely ruled out.[212,213,221] This was especially important when the C-2 position of the indole double bond was activated by a ring-A substituent(s) such as a 6-methoxy function. Under nonacidic aprotic conditions, various tryptophan derivatives were condensed with methyl 3-formyl-propionate to give a mixture of the *trans* and *cis* tetrahydro-β-carbolines in an approximate ratio of 72:28 in favor of the *trans* diastereomer (Table 1). The only exception arose from the cyclization of 6-methoxy N_a-H tryptophan ethyl ester (**741c**) and methyl 3-formyl-propionate (Table 1, entry 3). This process provided 95% *trans* diastereoselectivity from analysis of the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture.[222]

It is believed that the product distribution of this condensation under nonacidic aprotic conditions was obtained under kinetic control.[214,223] The attack from the face opposite of the ester function (*anti* spiroindolenine, Scheme 144) would be kinetically more favorable than the attack on the iminium ion from the same side of the ester function (*syn* spiroindolenine). In addition, calculation of the energy difference between the two different spiroindolenine intermediates indicated the *anti* spiroindolenine (**746a**) was energetically more favorable than the *syn* counterpart (**746b**) by about 2.1 kcal/mol.[223]

Table 1. Asymmetric Pictet–Spengler reaction

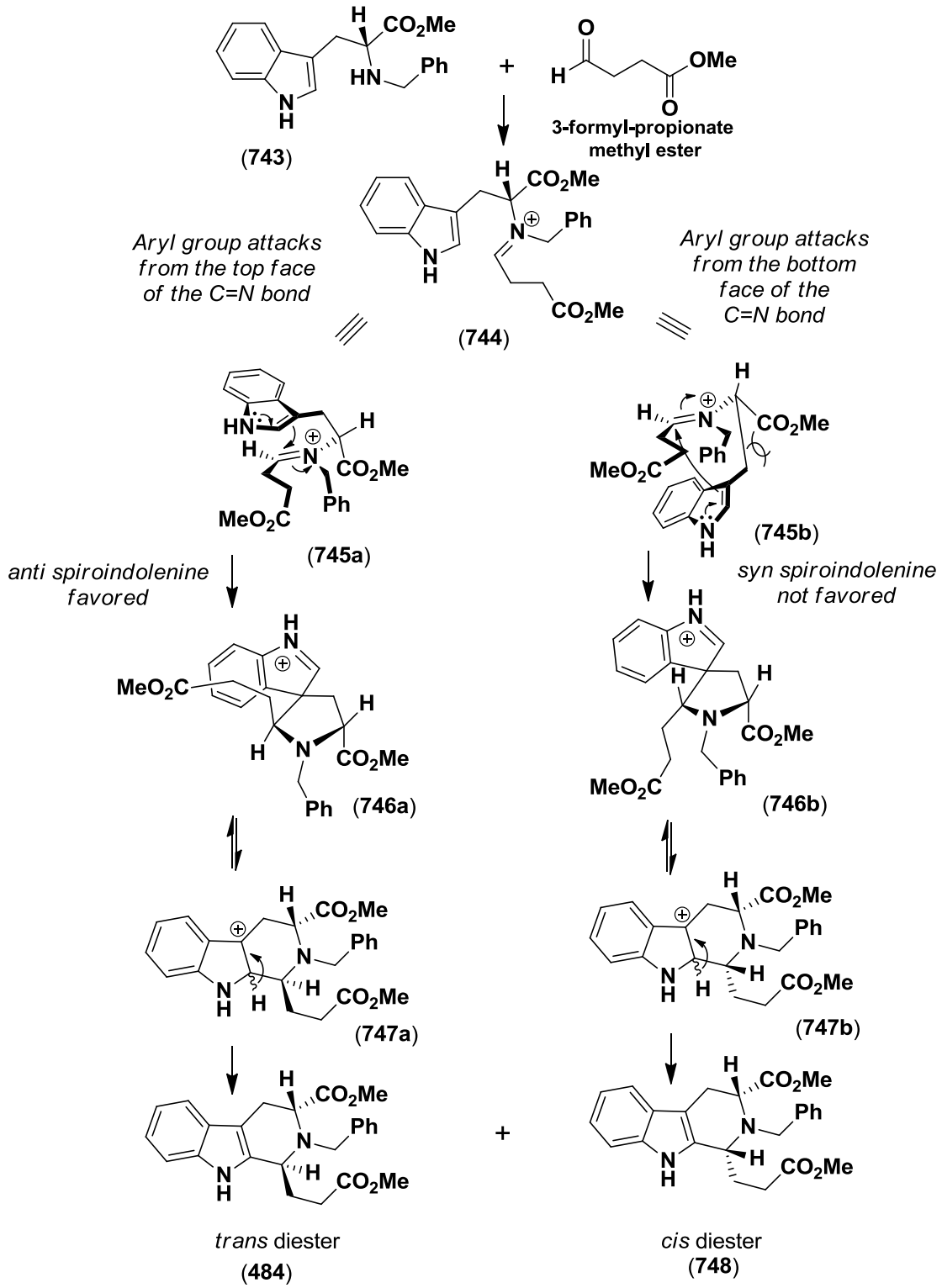


Entry	Substrate	R^1	R^2	R^3	R^4	***trans*/*cis* Ratio** **Nonacidic Conditions (PhH, DST, Δ)**	***trans*/*cis* Ratio** **Strongly Acidic Conditions (HCl, MeOH)**
1	**741a**	H	Me	H	H	80:20	100:0
2	**741b**	H	Et	OMe	H	85:15	100:0
3	**741c**	H	Et	H	OMe	> 95:5	100:0
4	**741d**	Me	Me	H	H	72:28	100:0
5	**741e**	Me	Et	H	OMe	71:29	100:0
6	**741f**	Me	Et	OMe	H	75:25	100:0

The *anti* spiroindolenine could then rearrange from C-3 to C-2 to provide the *trans* diastereomer. When the above Pictet–Spengler condensation was carried out with methyl 3-formyl propionate in the presence of acid (TFA or HCl), the *trans* diastereomers were obtained as the only detectable products (Table 1).[214,223] Any *cis* isomer that formed epimerized at C-1 to provide the *trans* isomer.

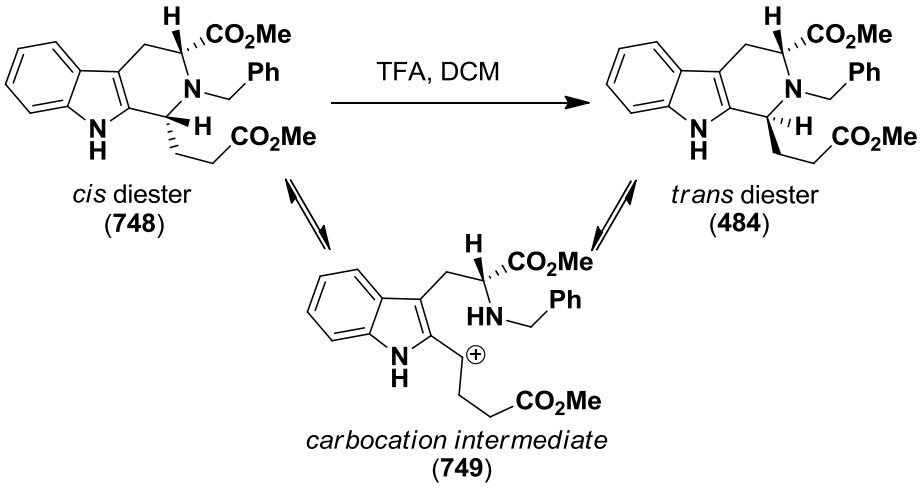
Several different mechanisms for the epimerization process have been proposed.[223] After a number of experiments have been executed, the mechanism of C-1/N-2 bond cleavage still remains the most consistent with all the data.[223]

Scheme 144


(743)
3-formyl-propionate methyl ester
(744)
Aryl group attacks from the top face of the C=N bond
Aryl group attacks from the bottom face of the C=N bond
(745a)
(745b)
anti spiroindolenine favored
syn spiroindolenine not favored
(746a)
(746b)
(747a)
(747b)
trans diester
(484)
cis diester
(748)

As illustrated in Scheme 145, it was felt the *cis* isomer (**748**) underwent C-1/N-2 bond scission to furnish the carbocationic intermediate (**749**). This was followed by bond rotation and ring closure to provide the thermodynamically more stable *trans* isomer (**484**). The isomerization of the *cis* isomer to the *trans* isomer (100% conversion) has been observed in TFA/CH_2Cl_2 on numerous occasions;[214,224] however, the *trans* to *cis* epimerization in this series under acidic conditions has not been observed. Thus, the complete *trans* diastereoselectivity in this process can be employed in the enantiospecific synthesis of indole alkaloids, the cyclization can simply be carried out in TFA/CH_2Cl_2.

Scheme 145



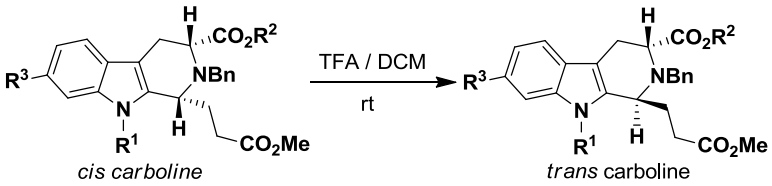
Recent work on the study of the carbocationic mechanism has been reported by Han and collaborators,[225] in which a conformational analysis of the C-ring of the 1,2,3,4-tetrahydro-*β*-carboline was carried out in order to study the potential structural basis for the carbocationic mechanism. The change in rate of the epimerization was observed by

varying the R^1, R^2 and R^3 substituents between molecules. A change in the degree of steric interaction with a group at R^1 affected the rate substantially. Moreover, a change in the electronic character of the indole ring at R^3 also altered the rate significantly (Table 2).[223,225] The rate of epimerization increased when a methoxy group was installed at R^3, presumably due to resonance stabilization with the proposed carbocationic intermediate. This observation alone, however, could not be employed to distinguish between the proposed mechanism and that of the retro Pictet–Spengler route since the intermediate iminium ion of the retro Pictet–Spengler pathway can also be stabilized through resonance.

Analysis of rate differences due to steric interactions can help to differentiate between these two mechanisms, although in an indirect way. In the N_a-methyl case, the rate was notably retarded. Here, the conformation of the C-ring played an important role in the epimerization process. In the *cis* N_a-methyl series, the ring took on a chair-like conformation wherein a boat-like structure was observed in the *cis* N_a-H series, as determined by nuclear Overhauser effects (NOE-NMR) and analysis of X-ray crystal structures.[225] After epimerization to the *trans* adducts, a chair-like conformation was observed.[225]

A careful analysis of the NMR data and X-ray crystal structures of both the *cis* and *trans* 1,2,3-trisubstituted tetrahydro-*β*-carbolines revealed that in most of the diastereoisomers [(**750**)**c**, (**750**)**t**, (**751**)**c**], the half-chair C-ring was found in the preferred conformer except in the important N_a-H *cis* diesters (**751**)**t** and (**742c**)**t**, which adopted a boat-like C-ring (see **I** and **II**, Figure 16). The N_a-H *cis* diastereoisomers (**751**)**t** and (**742e**)**t**, which existed in a boat-like conformation in which the σ*-orbital of the C-1/N-2 bond was

Table 2. Cis/trans epimerization



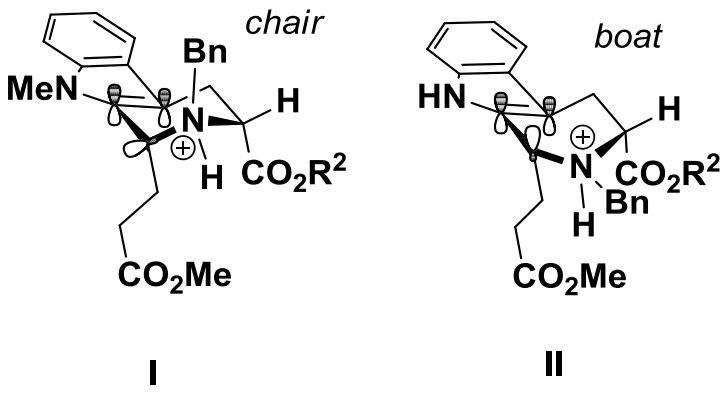
Substituent	*cis* carboline	*trans* carboline
$R^1 = CH_3$, R^2 = Et, R^3 = H	(**750**)**c**	(**750**)**t**
$R^1 = R^3$ = H, R^2 = Et	(**751**)**c**	(**751**)**t**
$R^1 = CH_3$, R^2 = Et, $R^3 = OCH_3$	(**742e**)**c**	(**742e**)**t**
R^1 = H, R^2 = Et, $R^3 = OCH_3$	(**742c**)**c**	(**742c**)**t**

Epimerization Reactions	Approximate Ratio of *cis*:*trans* Observed by ^{1}H NMR; 1.5 eq TFA Used									
	Initial		30 min		7 hr		3 days		10 days	
(750)c→(750)t	100	0					90	10	80	20
(751)c→(751)t	100	0					45	55	<3%	100
(742e)c→(742e)t	100	0	86	14	<3%	100				
(742c)c→(742c)t	100	0	<3%	100						

approximately parallel with the π-system of the indole ring, epimerized at a much faster rate than in the case of the half-chair N_a-methyl *cis* isomer, which would have to flip into a boat-like conformation to facilitate the C-1/N-2 bond scission via overlap with this σ*-orbital.[225,226]

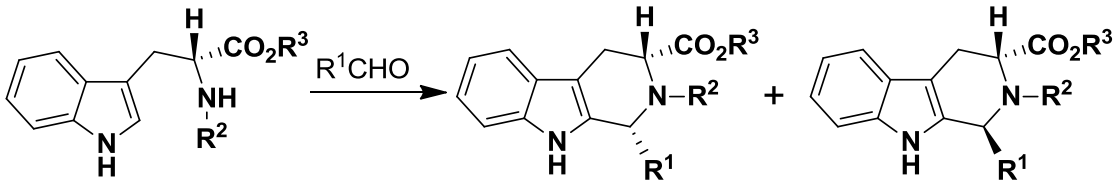
Still the actual mechanism by which the *trans* stereoisomer was formed, stereo-specifically, has not been elucidated to date, as mentioned above. Ungemach et al.[227] reported on the diastereospecific Pictet–Spengler reaction from condensation of N_b-benzyl tryptophan methyl ester with aldehydes which resulted in the 100% stereoselective formation of *trans* 1,3-disubstituted diastereomers.

Figure 16. Chair/boat conformations



Brown et al. had reported a similar phenomenon in approaches to the corynanthe-like skeleton.[228] Alternatively, several groups have extended the scope to examine the ratio of *cis*/*trans* isomers of the Pictet–Spengler reaction employing tryptophan derivatives with aldehydes and this has been reviewed.[214,223] Examination of a report by Czerwinski indicated that a mixture of *cis* and *trans* isomers of 1,2,3-trisubstituted-1,2,3,4-tetrahydro-*β*-carbolines was formed when N_b-benzyl alkyl esters were reacted with small aliphatic aldehydes under acidic and nonacidic, aprotic conditions for 36 hours. The steric bulk of both reactants, aldehyde and tryptophan alkyl ester, proved to be important in the stereochemical outcome of the process. When a large degree of steric bulk was present between reactants, such as when N_b-benzyl tryptophan methyl ester and cyclohexyl-carboxaldehyde were reacted under acidic or nonacidic aprotic conditions, 100% *trans* diastereoselectivity was realized (Table 3). When a smaller amount of steric interaction (*via* $H_{1,2}$ strain) was present, a mixture of both *cis* and *trans* isomers was observed.[223]

Table 3. Asymmetric Pictet–Spengler example



I **II-*cis*** **II-*trans***

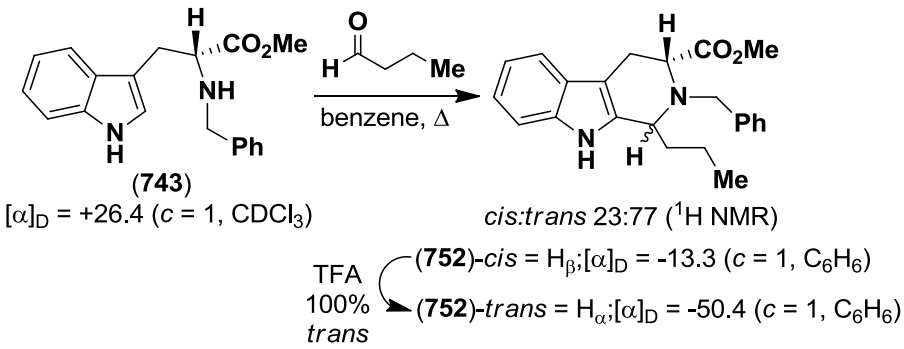
Entry	R_1	R_2	R_3	Nonacidic Aprotic[a]		Acidic[a]	
				cis	*trans*	*cis*	*trans*
1	CH_3	H	CH_3	not determined		75	25
2	CH_2CH_3	H	CH_3	not determined		43	57
3	C_6H_{11}	H	CH_3	40	60	41	59
4	CH_3	Bn	CH_3	26	74	12	88
5	$CH_2CH_2CH_3$	Bn	CH_3	23	77	11	89
6	C_6H_{11}	Bn	CH_3	<3%	100	<3%	100
7	CH_3	Bn	$CH(CH_3)_2$	23	77	13	87
8	$CH_2CH_2CH_3$	Bn	$CH(CH_3)_2$	13	87	12	88
9	C_6H_{11}	Bn	$CH(CH_3)_2$	<3%	100	<3%	100
10	CH_3	$CH(Ph)_2$	CH_3	10	90	<3%	100
11	$CH_2CH_2CH_3$	$CH(Ph)_2$	CH_3	<3%	100	<3%	100
12	C_6H_{11}	$CH(Ph)_2$	CH_3	<3%	<3% [b]	<3%	100
13	CH_3	$CH(Ph)_2$	$CH(CH_3)_2$	<3%	100	<3%	100
14	$CH_2CH_2CH_3$	$CH(Ph)_2$	$CH(CH_3)_2$	<3%	<3% [b]	<3%	100
15	C_6H_{11}	$CH(Ph)_2$	$CH(CH_3)_2$	<3%	<3% [b]	<3%	100

These studies conclusively indicated that the steric bulk of the incoming carbonyl compound, the substituents at the N_b-nitrogen atom and the size of the ester function played major roles in the diastereoselective formation of the *trans* isomer. However, when the *cis* isomer, or a mixture of *cis* and *trans* isomers was reacted with TFA, the *trans* isomer was obtained exclusively.[229] This observation had shown also that epimerization took place at the C-1 position of the tetrahydro-*β*-carboline nucleus. This was confirmed by a study of the optical rotation of the 1,2,3-trisubstituted-1,2,3,4-

tetrahydro-*β*-carbolines synthesized by the Pictet–Spengler reaction. In the case reported by Czerwinski (Scheme 146), the optical rotation of (**752**)-*cis* was found to be $[\alpha]^{25}_{D}$ = –13.3 (*c* = 1, benzene) and (**752**)-*trans* $[\alpha]^{25}_{D}$ = –50.4 (*c* = 1, benzene).[229] After complete epimerization of the *cis* isomer (CH_2Cl_2 with 2 equivalents of TFA over 12 hours), into the *trans* isomer, the optical rotation of the *trans* product was found to be $[\alpha]^{25}_{D}$ = –50.4 (*c* = 1.6, benzene).[230] If epimerization had taken place at C-3 rather than at C-1, the enantiomer of (**752**)-*trans* would have been formed and the optical rotation would have been equal and opposite, namely $[\alpha]^{25}_{D}$ = +50.4. Since the rotation of the *trans* isomer from the epimerization experiment and that of the *trans* ester synthesized independently matched, it was concluded that the epimerization process took place at the C-1 stereo-center.

Although progress has been made in regard to synthesis, interestingly, the mechanism of the *cis* to *trans* isomerization in the presence of Brønsted acids has not been fully defined as mentioned above. In efforts aimed at the investigation of the mechanism of the isomerization at C-1, a set of readily accessible electron-donating and electron-with-drawing aromatic aldehydes have been reacted with tryptophan ethyl ester to provide 1-(substituted)-phenyl-tetrahydro-*β*-carbolines.

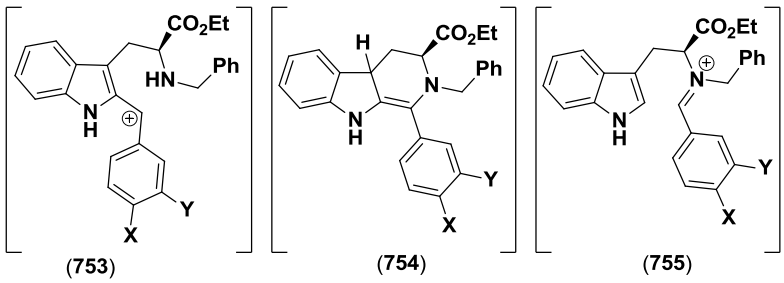
Scheme 146



It was well documented that N_a-methyl, N_b-benzyl tryptophan alkyl esters undergo the Pictet–Spengler reaction in nonacidic aprotic media with aldehydes of varied steric bulk to furnish the *trans* and *cis* diastereomers in an approximate ratio of 4:1, with the *trans* isomer predominating.[223] Furthermore, the diastereomeric ratio changes to approximately 3:2 for N_a-H, N_b-H tryptophan alkyl esters in both nonacidic and acidic media. Aldehydes as small as acetaldehyde provided the *cis* diastereomer in excess.[223] These diastereomers are usually separated via silica gel chromatography; however, this separation remained difficult in many cases due to the close retention times of the two diastereomers. On the other hand, the thermodynamically more stable *trans* isomer, an important chiral intermediate in the total synthesis of macroline/sarpagine/ajmaline indole alkaloids, could be exclusively obtained by epimerization of the *cis* stereoisomer or a mixture of the *cis* and *trans* isomers of the N_b-benzylated moieties under acidic conditions.[214,231,232] Upon reaction of the *cis* N_b-substituted isomers or a mixture of *cis* and *trans* isomers with TFA, the *trans* isomer was obtained exclusively.[233] Based on the elegant work of Joule et al.

and Hamaker et al. on reserpine,[234] three potential intermediates (Figure 17) were considered for this epimerization process at C-1.

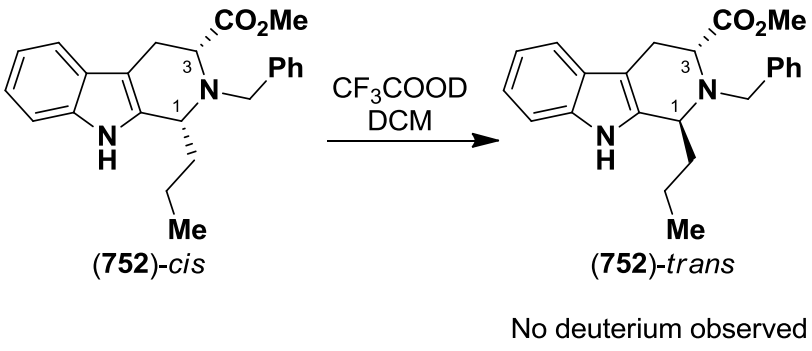
Figure 17. Epimerization mechanisms



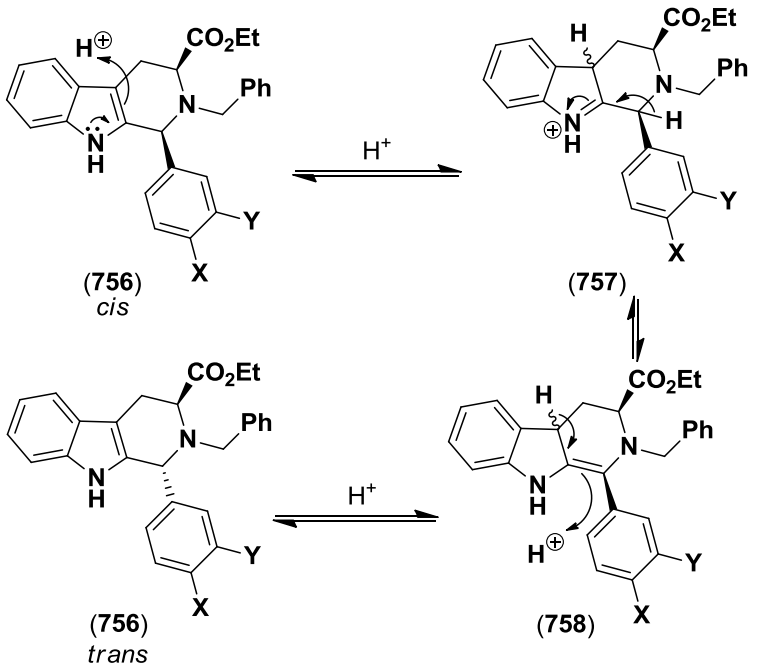
Among the three potential intermediates shown in Figure 17 in the *cis* to *trans* epimerization process, cation (**753**), which proceeded by protonation of the N_b-nitrogen atom with concomitant cleavage of the C-1/N-2 bond followed by reclosure to the *trans* isomer, was the most consistent with recent evidence.[223,225,235,236] The carbocation (**753**), so generated, after rotation of the C-1/C-9 carbon-carbon bond, could recyclize to provide the thermodynamically more stable *trans* diastereomer.[235,236] Recent results during the synthesis of alkoxy substituted indole alkaloids indicated that such an intermediate might be involved especially in the case of indoles substituted at C-4 or C-6 with methoxyl groups.[233,237] This epimerization afforded 100% stereoselective formation of the *trans* diastereomer, specifically at C-1, under standard acidic conditions of TFA/CH_2Cl_2.[223] Importantly, intermediate (**754**) was excluded based on epimerization experiments carried out in CF_3CO_2D (Scheme 147).[223] The 1-propyl analog (**752**)-*cis* was reacted in the presence of CF_3CO_2D in CH_2Cl_2. After complete epimerization at C-1, the ^1H NMR

spectrum was taken to determine if, in fact, deuterium was incorporated into the molecule, specifically at C-1. This would arise from protonation at the indole-3 position [see compound (**756**)-*cis*, Scheme 148], followed by subsequent deprotonation at C-1 to provide the intermediate (**754**). Deprotonation at the indole-3 position would permit re-aromatization of the indole ring system (Scheme 148), accompanied by protonation at C-1 to provide the *trans* product (**756**). Careful integration of the ^{1}H NMR spectrum of the crude material indicated that no deuterium had been introduced into the molecule [(**752**), Scheme 147]. This was verified by mass spectrometry as well. Therefore, intermediate (**754**) could not have been present over the course of epimerization, excluding the olefinic mechanism as a pathway for this process.[229]

Scheme 147



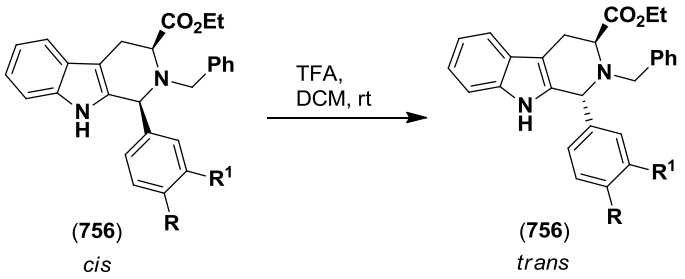
Scheme 148



As mentioned above, Han described the mechanism of epimerization of *cis* and *trans* N_a-methyl and N_a-H substituted N_b-benzyl diesters on a conformational basis. Here, the thermodynamically more stable *trans* isomer was formed from the corresponding *cis* isomer at different rates, depending upon the steric interactions between the substituent at the indole nitrogen and the substituent at the C-1 position.

Based on earlier data, epimerization had been shown to take place at the C-1 carbon atom. It was thought that direct electronic stabilization at this position would shed light on which of the two probable mechanisms which remained was involved. Molecules of interest could be prepared from substituted benzaldehydes and tryptophan ethyl ester to provide the desired 1-phenyl substituted tetrahydro-*β*-carbolines to be studied (Table 4).

Table 4. Epimerization experiments



(**756**)
cis

(**756**)
trans

Compound ***(cis or trans)***	**R**	**R_1**
a	NO_2	H
b	H	NO_2
c	Cl	H
d	CH_3	H
e	OCH_3	H

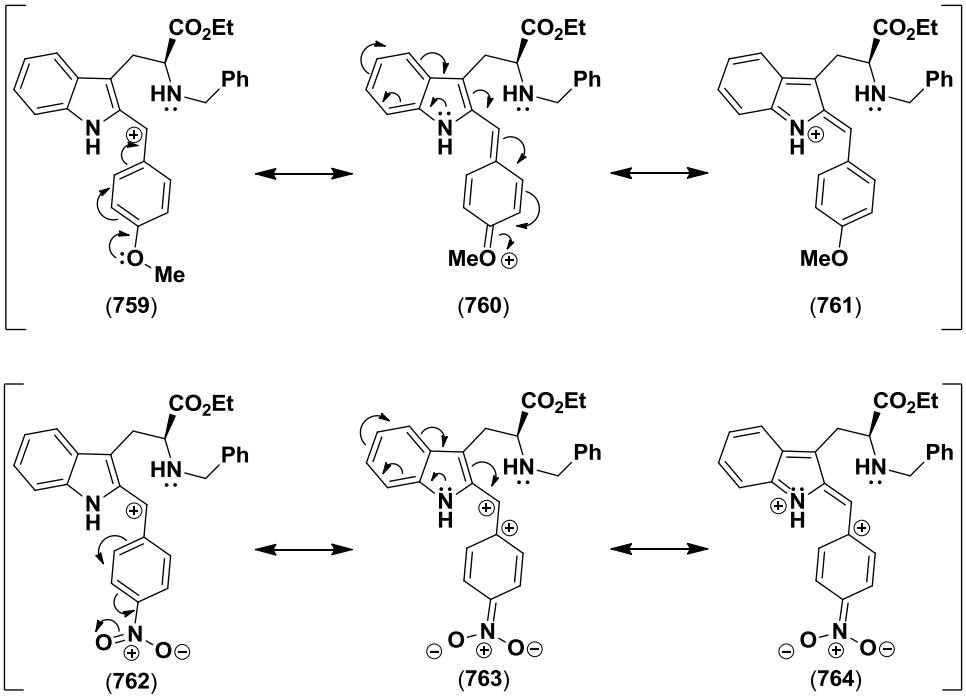
Epimerization Reaction	**Approximate Ratio of *cis*:*trans*[a]**				
cis to trans	**Initial**	**0.5 h**	**1 h**	**1.5 h**	**3 h**
a	100:0	78:22	45:55	14:86	6:94
b	100:0	70:30	40:60	25:75	0:100
c	100:0	58:42	19:81	0:100	
d	100:0[b]	2:98	0:100		
e	100:0[b]	0:100			
trans to cis	**Initial**	**0.5 h**	**1 h**	**1.5 h**	**3 h**
a	0:100[c]				0:100
e	0:100[c]				0:100

[a]Ratio determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture; [b]The epimerization of **d** and **e** went to completion in 0.5 h; [c] The *trans* to *cis* conversion was not observed in the last two reactions; TFA employed in these experiments was 1.5 equivalents.

Here, direct electronic effects on the proposed carbocationic intermediate could be observed (Figure 18). It was clear the *cis* *p*-methoxy substituted substrate (**756e**)-*cis* isomerized to the corresponding *trans* isomer much faster than in the *p*-nitro case illustrated in Table 4 and Figure 18. Examination of the results described herein *via*

kinetic data are in agreement with the generation of the carbocationic intermediate (**753**) as a key intermediate in this *cis* to *trans* epimerization process.[214,231] This is, presumably, important with regard to Pictet–Spengler reactions carried out under acidic conditions in both the tetrahydro-*β*-carboline and tetrahydroisoquinoline series.

Figure 18. Proposed mechanisms

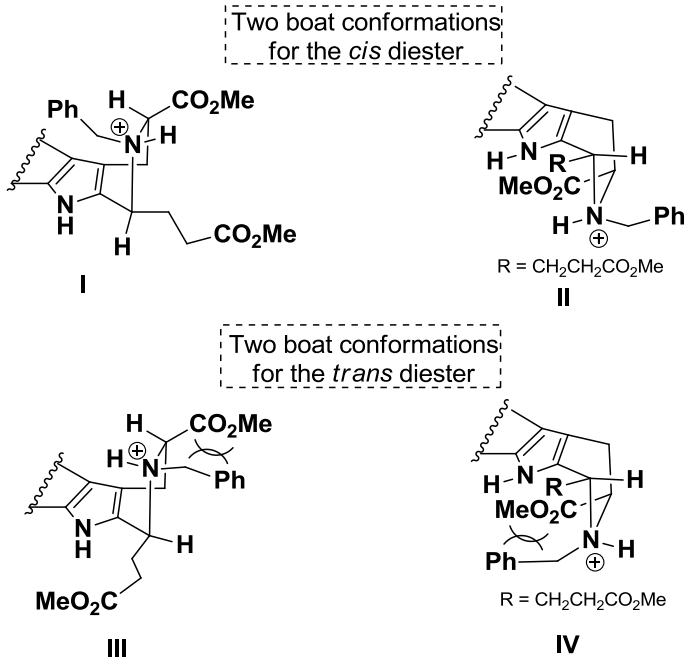


In summary, in order to readily break the C-1/N-2 bond, the σ* orbital of this bond should overlap well with the π bond of the 2,3-indole system, as mentioned. Ideally, when this C-1/N-2 bond was parallel to the π electrons of the indole ring, maximum overlap with the developing carbocationic intermediate would be realized. Examination of the conformations of these diesters via models also indicated that the transition states

for the bond breaking process were best achieved from the boat conformations of the diesters. Based on analysis of MM2 calculations, on the X-ray crystal data and on NMR studies, it was believed (under the conditions of isomerization) the protonated form of the *trans* diester would exist with the N_b-proton located in the β-position (up). In contrast, it would appear the *cis* diastereomers would exist in a conformation wherein the proton located at N-2 would be α (down). As can be seen from the calculations in the ground state, the stable chair conformation of the *trans* diester was much lower in energy than the *cis* diester. Illustrated in (Figure 19) are four possible boat conformations for the *trans*/*cis* diesters in the N_a-H, N_b-benzyl series. In fact, the energy difference between the boat conformation and the corresponding chair conformation (ground state) in the *cis* isomer was much less than the corresponding energy difference between boat and chair in the *trans* isomer. If the boat conformation (which permits better overlap with the developing carbocationic center) does more closely resemble the transition state, then it is easy to see why the *cis* isomer more readily undergoes C-1/N-2 scission. Moreover, in both boat conformations of the *cis* isomer, there are no eclipsed interactions between the N_b-benzyl group and the methyl ester group; while in the *trans* case, both isomers will be expected to experience severe eclipsing interactions between the N_b-benzyl group at N-2 and the ester moiety at C-3. This would increase the energy difference between the boat conformation and the chair conformation in the *trans* diastereomer, consequently, the activated boat was not achieved. Based on this analysis, it was felt during the isomerization process, the difference in the activation energies (for the C-1/N-2 bond breakage) of the *cis* and *trans* diesters (boat form similar to activated state) was larger than the energy difference of the *cis* and *trans* diesters in their (chair) ground states. This

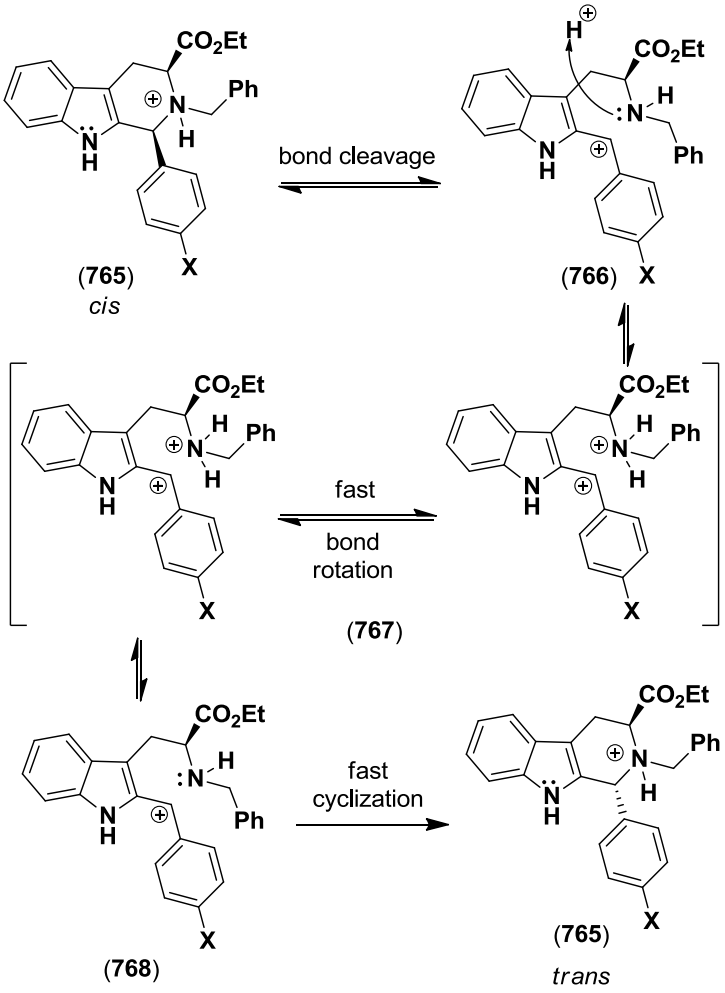
was in agreement with the facile bond breaking at C-1/N-2 for the *cis* isomer, while the *trans* isomer would be unlikely to achieve this boat conformation and undergo such a bond scission. Moreover, analysis of experimental results[214,223] demonstrated that the larger the group at the N_b-position, the higher the *trans* diastereoselectivity. This was in agreement with this boat-like transition state for high energy unfavorable interactions would occur in the boat conformations of the *trans* isomer (C-3, N_b-alkyl eclipsing) more so than in the corresponding *cis* diastereomer. Consequently, the *trans* isomer does not readily flip to the boat, does not readily provide the π electron overlap with the developing carbocation and therefore, does not readily undergo the C-1/N-2 ring scission and isomerization.[222,238,239,240]

Figure 19. Diester conformations



As mentioned above the olefinic pathway was ruled out, first by Czerwinski,[229] and also by Van Linn et al.[241] based on deuterium-labeling experiments. Results from epimerizations carried out in TFA-*d* indicated that no deuterium was incorporated at the C-1 position, which would be necessary if the olefinic pathway was to take place. In the same study, Van Linn et al. compared the remaining two mechanisms of epimerization, namely the carbocationic pathway and the retro-Pictet–Spengler pathway, on the basis of kinetic theory.[241] A series of 1-(4′-substituted)-phenyltetrahydro-*β*-carbolines were synthesized by the Pictet–Spengler cyclization in order to study the *cis* to *trans* epimerization mechanism followed by ^{1}H NMR spectroscopy. Analysis of the data, from the observed rate constants and construction of Hammet plots, supported the presence of a positively charged intermediate, although the existence of an iminium ion intermediate or a carbocationic intermediate could not be determined from this data alone. The rate of epimerization data demonstrated first-order kinetics with respect to TFA following the initial protonation of the substrate. This observation was consistent with the formation of a doubly protonated intermediate as the rate-determining step in the carbocation-mediated *cis* to *trans* epimerization process (Scheme 149). In addition, the observed first-order rate dependence was inconsistent with the retro-Pictet–Spengler mechanism since protonation at the indole-2 position was not rate determining as demonstrated by kinetic isotope effects. Based on this kinetic data, the retro-Pictet–Spengler pathway was ruled out for the *cis* to *trans* epimerization of 1,2,3-trisubstituted 1,2,3,4-tetrahydro-*β*-carbolines.

Scheme 149



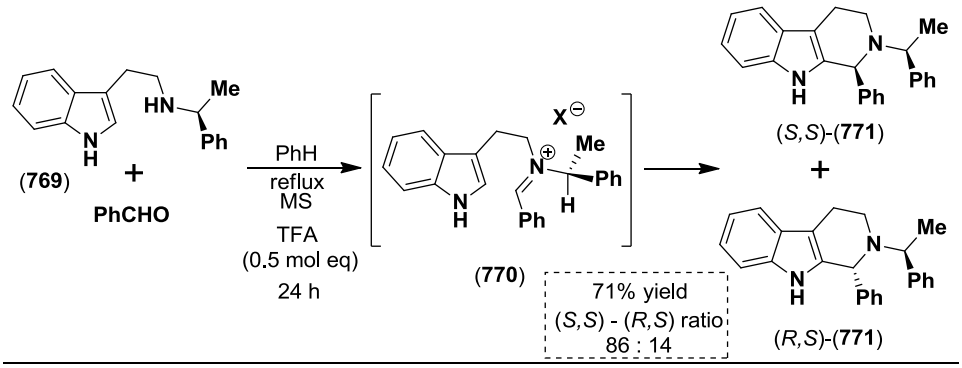
6.2) Recent Advances In The Asymmetric Pictet–Spengler Reaction

A recent challenge in synthetic chemistry has involved the formation of tetrahydro-*β*-carbolines and tetrahydroisoquinolines via a Pictet–Spengler reaction under catalytic conditions. Not only are catalytic conditions desired, product formation with a high degree of stereoselectivity is preferred. Initially, chiral auxiliaries were utilized to

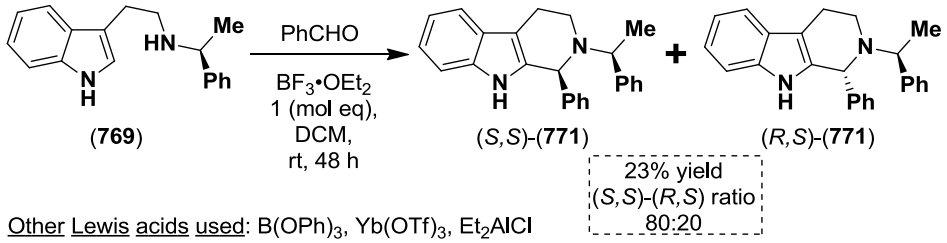
influence the stereochemical outcome of the Pictet–Spengler reaction. The first attempt was reported by Reddy et al.[242] in the total synthesis of 1,2,3,4-tetrahydroroeharmine. The α-methyl-benzylamine chiral auxiliary was installed on the N_b-nitrogen atom of 5,6-dimethoxytryptamine which provided asymmetric induction (3:2) in the Pictet–Spengler process. Nakagawa et al.[226b] expanded the utility of the α-methylbenzylamine chiral auxiliary in the asymmetric Pictet–Spengler reaction (Scheme 150). In the study, the chiral starting material (**769**) reacted with benzaldehyde under acidic conditions in different solvents. The best result in terms of diastereoselectivity was found when 0.5 equivalents of TFA was employed in benzene. Elevated yields were observed when less TFA was employed, however the diastereoselectivity decreased slightly. The diastereo-selectivity observed in this process may stem from cleavage of the C-1/N-2 bond followed by recyclization to provide more of the thermodynamically more stable (*S*,*S*)-diastereomer (**771**). Since an intermediate iminium ion (**770**) was believed to be present, chiral Brønsted acids were used in the Pictet–Spengler reaction (**I**-**V**, Scheme 150). It was anticipated that the chiral counter ion would interact ionically with the iminium ion intermediate (**770**) which would increase the stereoselectivity of the reaction; however, diastereoselectivity did not improve.

In addition to the Brønsted acids shown above, various Lewis acids were also employed in the Pictet–Spengler reaction with the chiral tryptamine derivative and benzaldehyde (Scheme 151).[226b] The solvent and reaction temperature were altered throughout the series of Lewis acids tested; however, none of the conditions improved the diastereo-selectivity. The best reult in terms of selectivity was when 1 eq. of BF_3•OEt_2 was used in DCM at room temperature, but the yield was very low, 23%.

Scheme 150



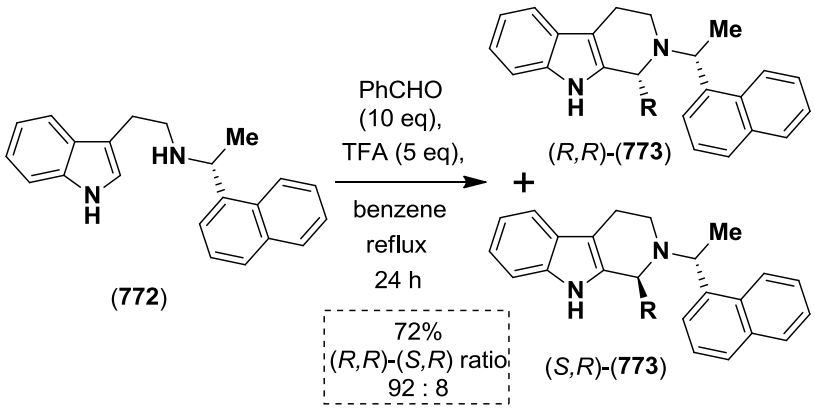
Scheme 151



Since the diasteromeric excess of the Pictet–Spengler reaction was only 72% de when the α-methylbenzyl amine chiral auxiliary was employed, it was thought that a larger chiral auxiliary would increase the diastereomeric excess. In that regard, a chiral α-naphthyl-ethyl group was installed on the N_b-nitrogen atom.[226b] With the starting tryptamine derivative in hand, various conditions were examined in the asymmetric Pictet–Spengler

reaction by Nakagawa. Optimal conditions were realized when a large excess of benzaldehyde (10 equivalents) and TFA (5 equivalents) were employed at reflux (Scheme 152). The scope of the reaction was also studied. Decreased yields, however, with high diastereoselectivity were observed with electron rich aldehydes. On the other hand, electron poor aldehydes provided better results than those of electron rich aldehydes and were similar to the results when benzaldehyde was employed in the asymmetric Pictet–Spengler reaction.

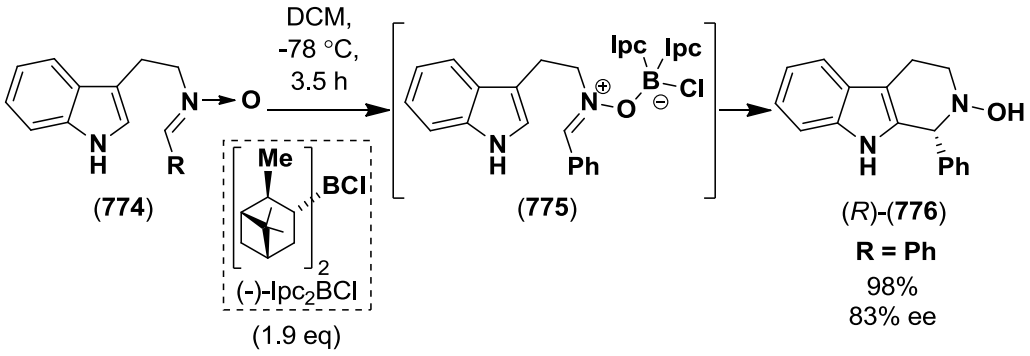
Scheme 152



In an effort to increase the stereoselectivity of these Pictet–Spengler reactions and provide a chiral auxiliary that is easier to remove, Nakagawa et al. turned to the use of chiral Lewis acid diisopinocampheylchloroborane (Ipc_2BCl) which was employed as a stoichiometric reagent and was reacted with the nitrones (Scheme 153).[243] An advantage of this method was the intial formation of the imine, because previous processes had undergone the Pictet–Spengler reaction with an imine or (iminium ion) generated *in situ*.

Dichloromethane was found to be the optimal solvent for these cyclizations.[226a] High yields were observed at room temperature, however, the enantioselectivity was poor. At lower temperatures the yields decreased to only 31%, however, the enantiomeric excess increased to 87% at –98 °C. The optimal temperature was found to be –78 °C, which provided 94% yield and 83% ee. In addition, the Lewis acidity of the chiral reagent was varied. Both the bromide and triflate anions were utilized (as opposed to chloride), however, no improvement in terms of yield nor enantiomeric excess was observed (Schme 153).

Scheme 153



Nakagawa also reported in the same study the use of Brønsted acid-assisted Lewis acids (BLAs) introduced by Yamamoto[244a] in the Pictet–Spengler cyclization.[226a] The results of these experiments are illustrated in Scheme 154. The stereochemical outcome of the BLA catalyzed Pictet–Spengler reactions could be explained by an intermediate in which the nitrone oxygen was coordinated to the boron of the BLA (Figure 20). In this case,

transition state **I** was preferred by the authors over transition state **II** due to the potential steric interactions between the indole ring and the BLA catalyst. The series of studies by Nakagawa et al. provided the foundation for some of the important breakthroughs in the asymmetric Pictet–Spengler reaction carried out under acidic conditions by others.

Scheme 154

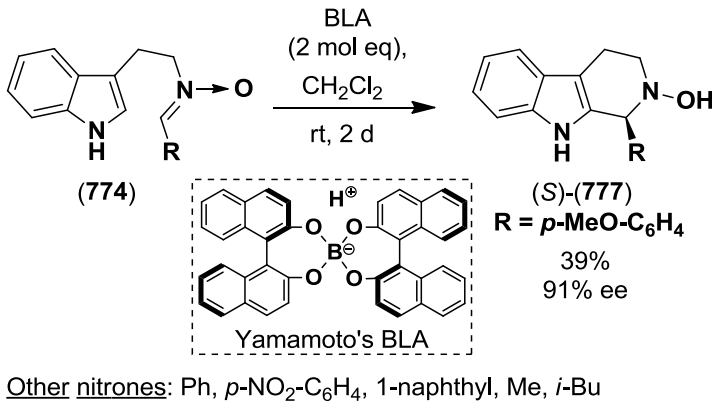
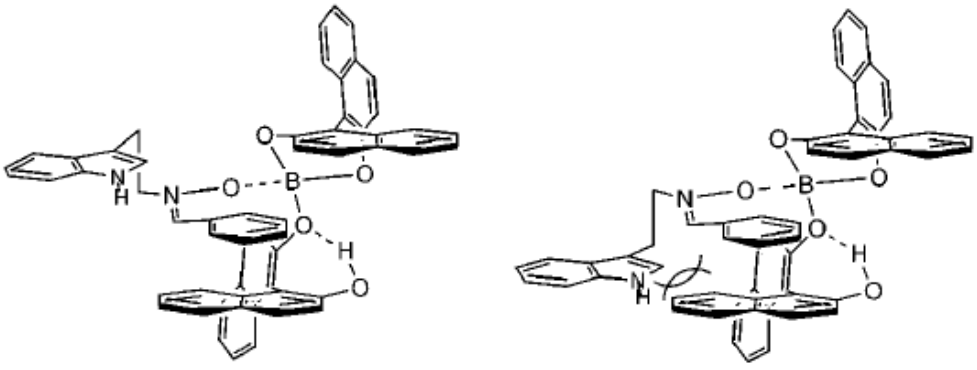
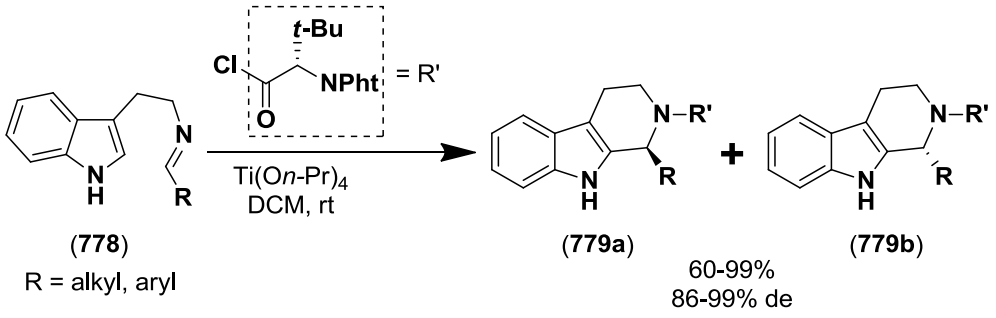


Figure 20. Proposed transition states



Waldmann et al. achieved high levels of diastereoselectivity in Pictet‑Spengler reactions using *N*,*N*-phthaloylamino acids as the chiral auxiliary (Scheme 155).[244b] Preformed imines were treated with amino acid chlorides in the presence of titanium alkoxides at room temperature. The desired products were obtained in good yields and with a diastereoselectivity of up to >98% de. The reaction conditions are general for the Pictet–Spengler reaction and suitable for a variety of aliphatic aldehydes as well as for electron-rich and electron-poor aromatic aldehydes.

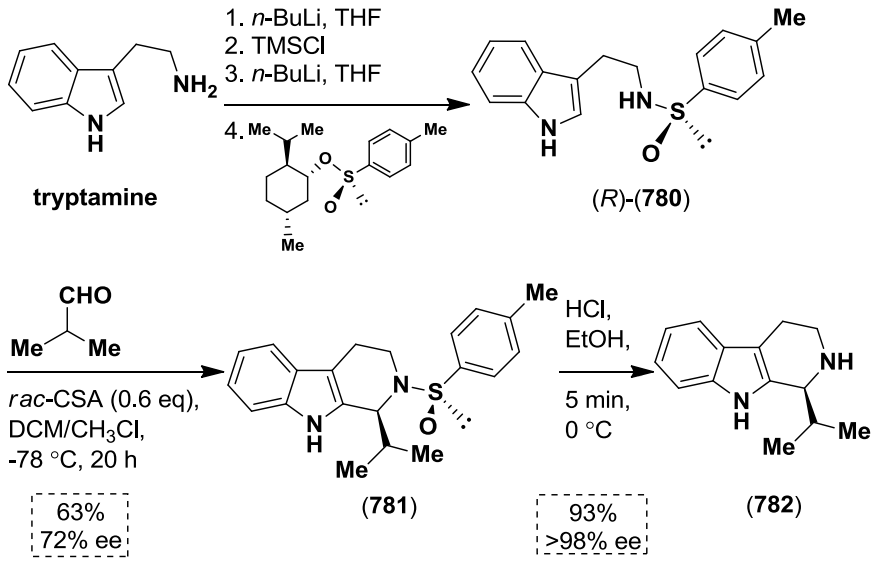
Scheme 155



The use of chiral *α*-methylbenzyl groups showed diastereoslectivity only with specific aldehydes.[226b] Chiral Lewis acids were used in the enantioselective Pictet–Spengler reactions of *N*-hydroxytryptamines but gave only satisfactory results with aromatic aldehydes.[226a] Acylation of imines from tryptamine with *N*,*N*-phthaloyl amino acid chlorides gave good diastereoselectivity in Lewis acid-catalyzed Pictet–Spengler reactions. A general drawback of these procedures is the fact that removal of the chiral

auxiliaries is often difficult and causes racemization due to the harsh conditions required for cleavage. In an effort to improve the selective formation of 1-alkyltetrahydro-*β*-carbolines, chiral sulfoxides (**780**) were used by Koomen et al., van Maarseveen et al. (Scheme 156).[244c] The application of *N*-sulfinyliminium ions in the Pictet–Spengler reaction of tryptamine provided the desired products with moderate ee's of up to 76% and good yields. A key feature of this method was the easy removal of the *N*-sulfinyl chiral auxiliary under acidic conditions with no loss of enantioselectivity.[244c]

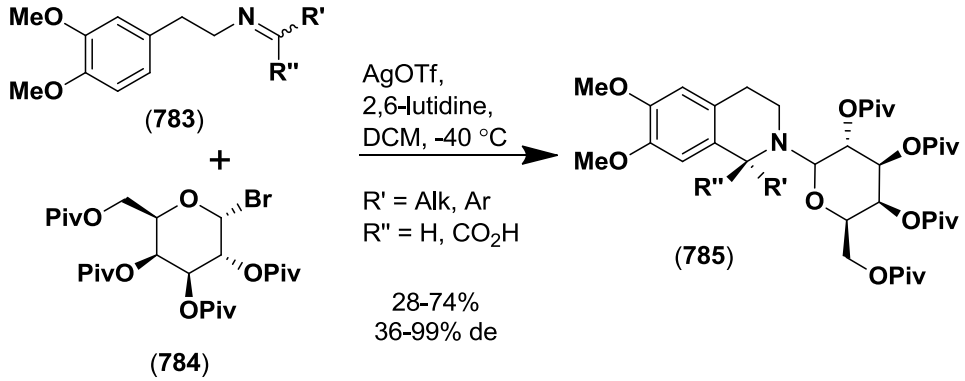
Scheme 156



Allef and Kunz demonstrated a diastereoselective Pictet–Spengler reaction for the synthesis of 1-substituted tetrahydroisoquinolines (Scheme 157).[244d] By using galactosyl bromide (**784**) as the chiral auxiliary and imines derived from 2-(3,4-dimethoxy-phenyl)ethylamine (**783**), the corresponding products were obtained with a diastereo-

selectivity up to >98% de. The chiral auxiliary can be removed in the presence of hydrochloric acid at room temptrerature without racemization.

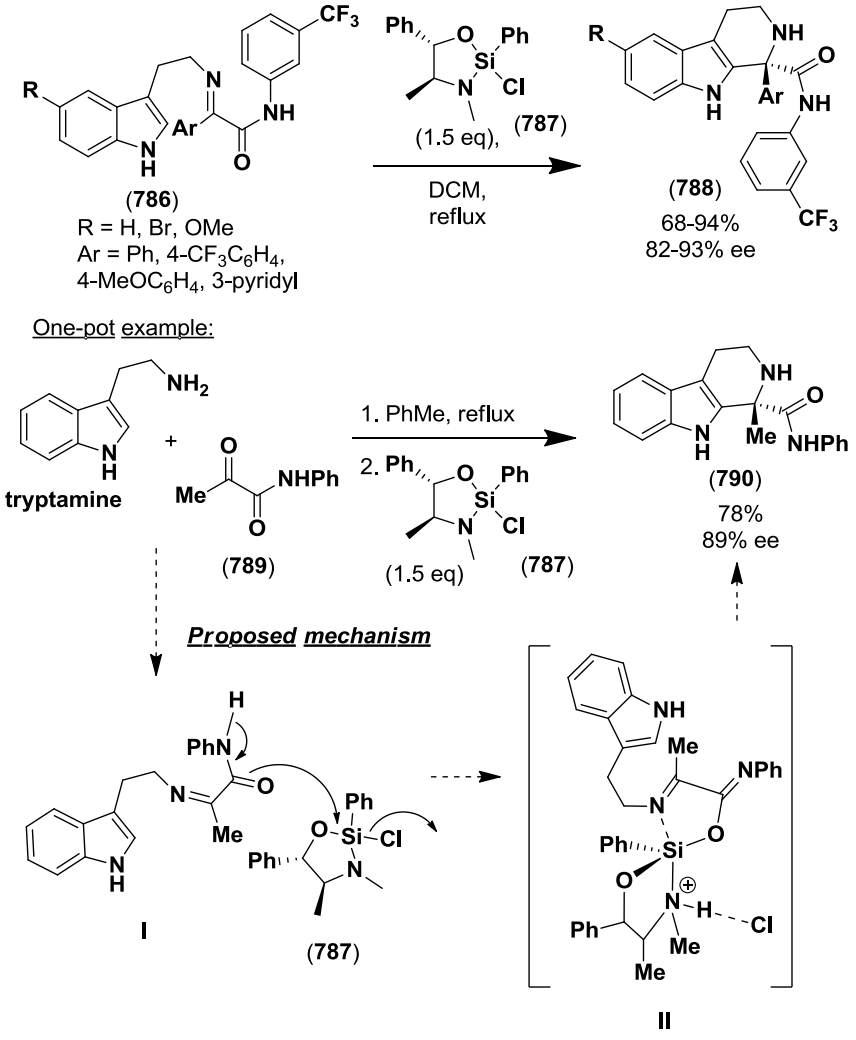
Scheme 157



Bou-Hamdan and Leighton recently developed a Pictet–Spengler reaction with α-ketoamide-derived ketimines to access a class of quaternary α-amino amides (Scheme 158).[244e] It was found that electron-withdrawing groups in the aniline moiety dramatically enhanced the reaction rate. Of the aryl amides screened, *N*-3-(trifluoromethyl)-phenylamide gave the best results. A one-pot procedure was developed wherein tryptamine and ketones were condensed and 1.5 equivalents of a chiral chorosilane were added upon completion of the imine formation. A variety of tryptamines and ketones were investigated under these conditions. The corresponding products were obtained in 67-86% yield and with 81-94% ee. Importantly, the reaction was readily scalable to the 5 mmol scale and the pseudoephedrine can be quantitatively recovered. Mechanistically, it was envisioned that *O*-silylation of compounds of the structure **I** with silane (*S,S*)-(**787**)

would give, by way of the illustrated complex **II**, the expected products (**790**, Scheme 158).

Scheme 158

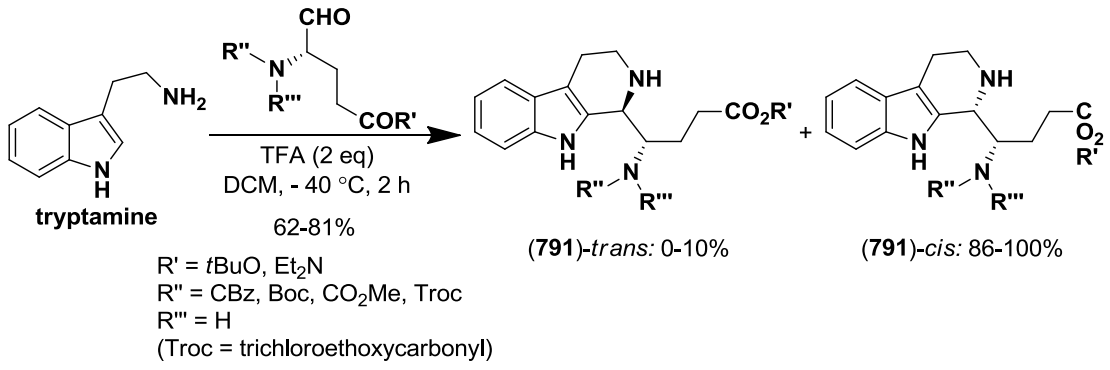


The critical step in the development of an asymmetric Pictet–Spengler reaction is the generation of a chiral iminium intermediate. Besides using chiral derivatives of tryptamine, such as tryptophan and different auxiliary groups, various chiral carbonyl

compounds have found application in asymmetric transformations. Different strategies were followed for the use of chiral carbonyl components in intermolecular Pictet–Spengler reactions and for the transfer of chirality to the newly generated center of tetrahydro-β-carbolines. Selected examples from the literature are described next.

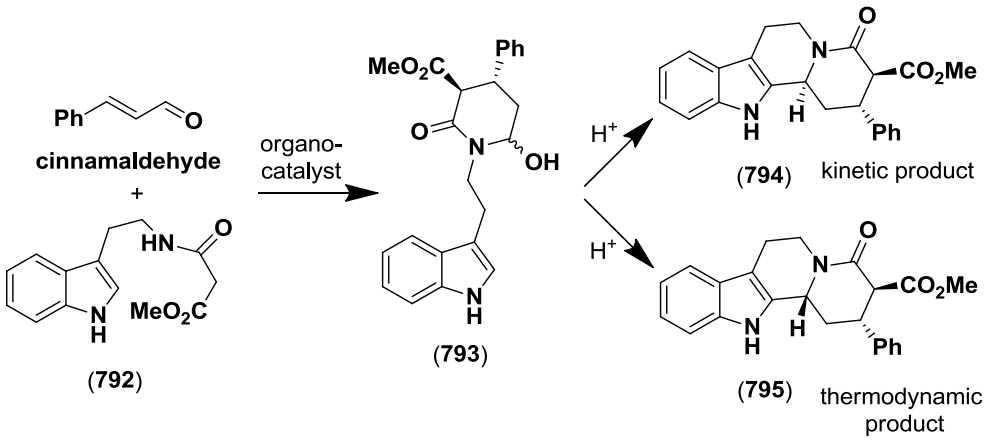
Tetrahydro-β-carbolines from tryptamine and protected α-aminoaldehydes derived from L-glutamic acid were studied.[245] The aldehydes were condensed with tryptamine under different conditions to form the products diastereoselectively. A series of carbamate-protected aldehydes led to the preferred formation of the *cis* diastereomer. This is because the sequence is in the N_b-H series shown by many including Ungemach et al. to provide more of the *cis* diastereomer. The size of the protecting group has only a minor influence on the stereoselective course of the reaction. Selective formation of the *cis* diastereomer was observed with benzyl carbamate (Cbz). Exchange of the protecting group with pyrrole or phthalimide led to the reversal of the diastereoselectivity. The *trans* diastereomer was obtained exclusively from pyrrole-protected aminoaldehydes (Scheme 159).

Scheme 159



A variety of new methods for the synthesis of chiral carbonyl compounds, especially aldehydes, by using organocatalysis has been developed during the last decade. These approaches also found application in the efficient construction of complex scaffolds by using iminium catalysis. Jacobsen has been the pioneer in this area followed by van Maarseveen and others. Franzen et al. performed the organocatalytic conjugate addition of a nucleophile derived from tryptamine amide and cinnamic aldehyde to yield a hemiaminal (**793**) with two stereogenic centers (Scheme 160).[246] An acyliminium cyclization was subsequently initiated under acidic conditions. A Pictet–Spengler cyclization was performed under kinetic or thermodynamic control, to yield two different tetracyclic products, epimers at C-1 [(**794**) and (**795**) respectively]. This epimeric switch provided an efficient protocol for the diastereo- and enantioselective synthesis of an alkaloid scaffold (Scheme 160).

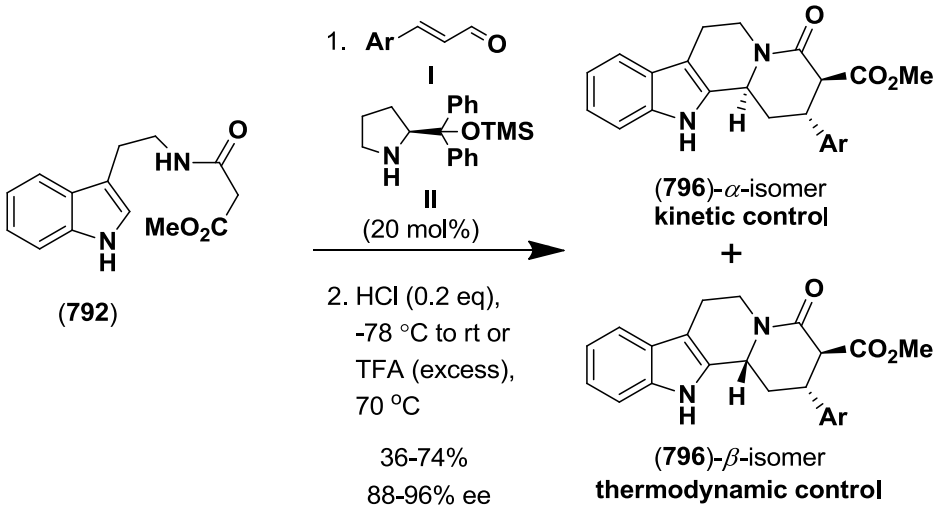
Scheme 160



The enantioselective addition of tryptamine amides (**792**) to α,β-unsaturated aldehydes, like **I**, was catalyzed by a chiral pyrrolidine of the type **II** (Scheme 161). In the second step of the one-pot sequence, the addition of a catalytic amount of hydrochloric acid at -78 °C led to the formation of the kinetically favored diastereomer (**796**). Alternatively, trifluoroacetic acid at 70 °C gave the thermodynamic product (Scheme 161). A variety of β-aryl-substituted acroleins with electron-withdrawing or -donating groups were well tolerated, as was a heteroaromatic (2-furyl) group. In contrast, the use of β-alkyl-substituted acrolein did not result in the corresponding product. By using kinetic or thermodynamic reaction conditions, both epimers were selectively obtained in 38-74% yield and 89-96% ee. The epimer ratio ranged from 90:10 to 17:83. Different 2-aryl ethylamines such as phenyl-, 3-benzofuryl-, and 2-furylethylamine were successfully employed. Variation of the reaction time and temperature led to different diastereomer ratios in the formation of the β-epimer under thermodynamic control. This observation led to the assumption that the α-epimer is formed initially, and this is epimerized to the thermodynamically more-stable β-epimer.[246] Presumably by C-1/N-2 cleavage studied by Van Linn.

An enantioselective one-pot Michael addition and Pictet–Spengler sequence was developed recently by Zhao et al.[247] This method was based on the synthesis of a hemiaminal from α,β-unsaturated aldehydes and β-ketoesters, which was followed by treatment with tryptamine in the presence of acid (Scheme 162). The initial organocatalytic conjugate addition of β-ketoesters to cinnamic aldehyde in the presence of a chiral pyrrolidine and benzoic acid in toluene was followed by addition of tryptamine and a stoichometric amount of benzoic acid. Incubation at 50 °C for 1 day led to the

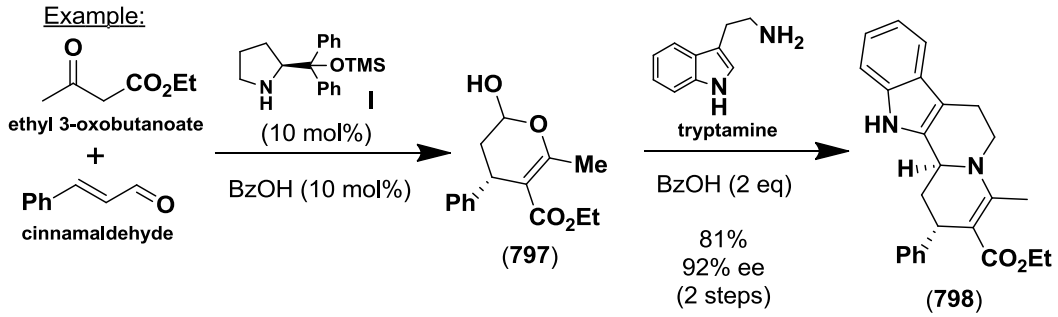
Scheme 161



selective formation of one indoloquinolizidine diastereomer in moderate yield and with good enantioselectivity. Investigation of the scope of the cascade one-pot reaction revealed that β-aryl- and β-alkyl-substituted α,β-unsaturated aldehydes can be employed. Aldehydes with aromatic or heteroaromatic substituents provided the products in 76-93% yield and with 88-95% ee. Notably, indoloquinolizidines were obtained from bulkyl acroleins in moderate yield and with 81-85% ee. The stereochemistry of the products was defined in the Michael addition step and the diastereoselectivity of the Pictet–Spengler reaction was controlled by the kinetically controlled reaction conditions (Scheme 162).

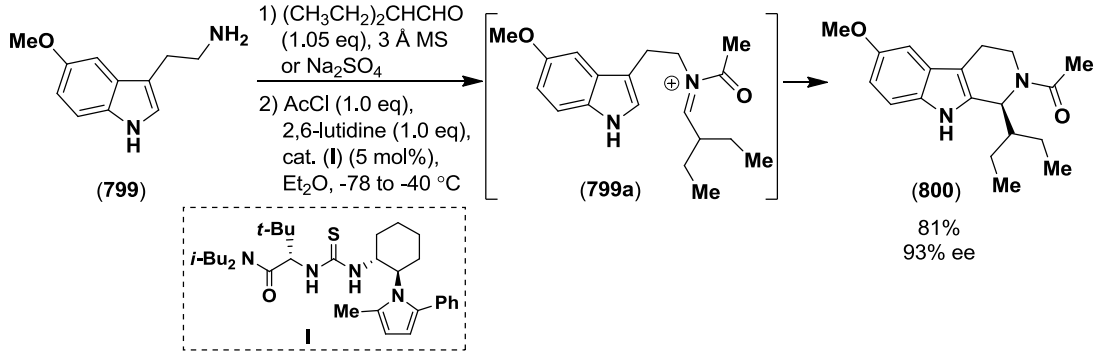
Recently, Jacobsen et al. reported the first asymmetric, catalytic Pictet–Spengler cyclization of *N*-acyliminium ions.[248] These important transformations were catalyzed by a thiourea catalyst of the type **I** as a chiral hydrogen bond donor (Scheme 163). Several thiourea catalysts were screened in the reaction of an imine with an acyl chloride in the presence of 2,6-lutidine in diethyl ether at reduced temperatures. A one-pot preparation of

Scheme 162



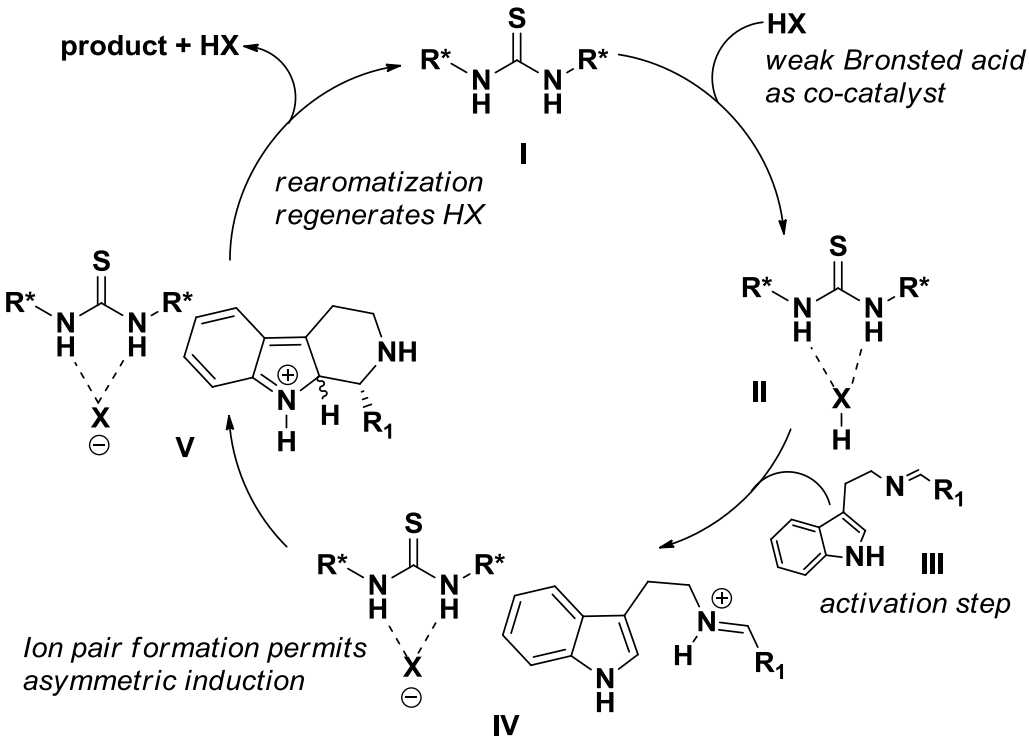
the corresponding *N*-acyliminium ion and subsequent cyclization was carried out (Scheme 163). Use of a thiourea catalyst provided reasonable yields of 1-alkyl-tetrahydro-*β*-carbolines with excellent enantiomeric excess (85-93% ee). The addition of a methoxy group on ring-A (at the 5 or 6 position) of the indole nucleus did not affect the yield nor the stereochemical outcome of the cyclization which is very important for the synthesis of ring-A alkoxy substituted indole alkaloids.

Scheme 163



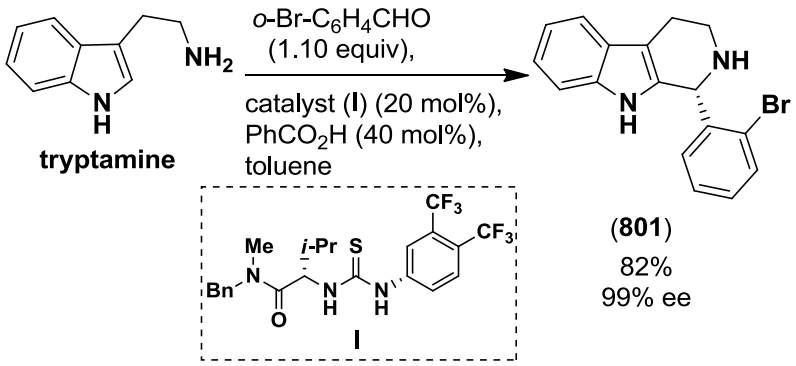
The involvement of thiourea-mediated catalysis in the Pictet–Spengler reaction was further investigated by Jacobsen et al.[249] Since the previous reactions in this series required the addition and subsequent removal of the acyl group, it was of importance to eliminate this requirement. It was proposed the addition of a weak Brønsted acid would form an iminium ion which would be more prone to cyclization since it would be much more electrophilic. The conjugate base of the weak acid could then coordinate to the thiourea catalyst through hydrogen bonding interactions. Enantioselectivity could then be induced by the chiral catalyst through the interaction of charged species. The co-catalyst (Brønsted acid) would then be regenerated from rearomatization of the indole ring system (Scheme 164).

Scheme 164



As shown in Scheme 165, a broad range of aryl aldehydes were tolerated in the Pictet–Spengler reaction catalyzed by thioureas; the yields were good to excellent and the degree of stereoselectivity realized was very high. It appeared that the tryptamine derivative must be activated toward cyclization in order for the process to take place, as shown in Scheme 164. This ion pair formation, presumably, permits the asymmetric induction.

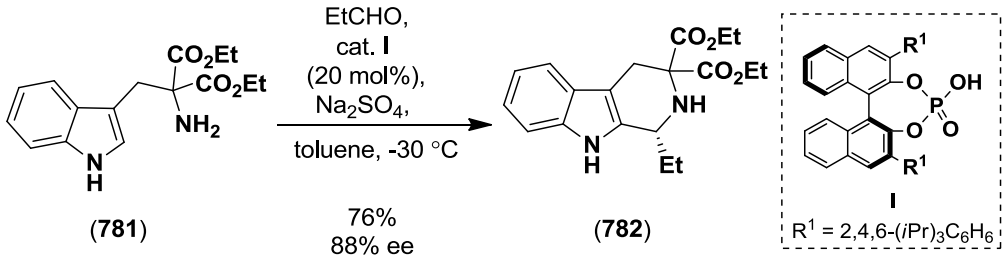
Scheme 165



List and collaborators utilized a *gem*-disubstituted tryptamine (**802**) in the catalytic asymmetric Pictet–Spengler reaction.[250] It was thought that the *gem*-substitution enhanced the likelihood of cyclization by virtue of the Thorpe–Ingold effect[251] and also electronic effects (the iminium ion is also much more electrophilic in the case of the diester as compared to a simple tryptamine, Scheme 166). After screening several substituted chiral phosphoric acids, catalyst **I** (Scheme 166) proved to be the most effective in terms of diastereoselectivity.[250] This catalyst was used to determine the scope of the Pictet–Spengler reaction with respect to both the substituted tryptamine and the aldehyde (both

aromatic and aliphatic), under the optimized reaction conditions: catalyst **I** (20 mol%), Na_2SO_4, toluene, −30 °C. They found that high yields (94-98%) and good ee's (86-90%) were obtained, although the yield suffered slightly when an unactivated disubstituted tryptamine was employed. Since *gem*-disubstituted tryptamine diesters were required for the cyclization to take place, synthetic uses of this approach are limited.

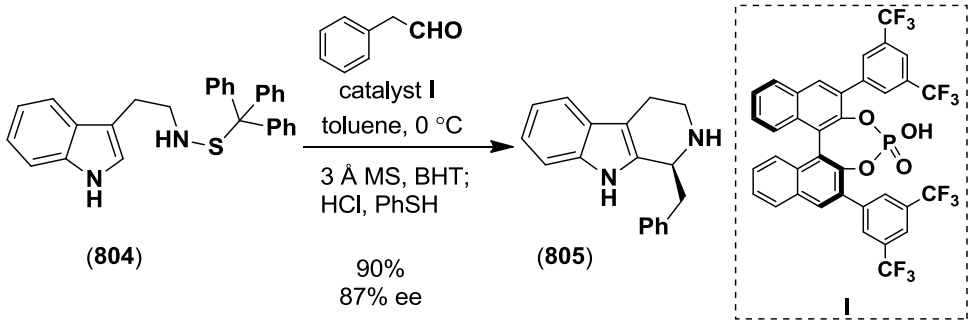
Scheme 166



Van Maarseveen and Hiemstra have employed chiral binaphthol-derived phosphoric acid catalysts similar to those of List (discussed above), in addition to the presence of an *N*-sulfenyl group which was installed to increase the reactivity of the process (Scheme 167).[252] The *N*-tritylsulfenyltetrahydro-*β*-carboline intermediate appeared to be rather unstable, possibly as a result of homolytic cleavage of the trityl-sulfur bond. The addition of 3,5-di(tert-butyl)-4-hydroxytoluene (BHT) to the reaction mixture as a radical scavenger prevented the problems associated with the decomposition of the product. Further improvements included a solvent change from chloroform to toluene and a decrease in the reaction temperature to 0 °C. Importantly, the addition of powdered 3 Å molecular sieves to remove the water released during the formation of the iminium salt

led to an improvement in both the yield and the enantioselectivity, as expected. The best result was obtained with catalyst **I**, in the presence of benzylaldehyde in a satisfactory 87% ee (Scheme 167). Next, the scope of the reaction with respect to the aldehyde substrate was investigated. Fast reactions with fair enantioselectivities occurred with *α*-unbranched aldehydes, except in the case of acetaldehyde. The best result was obtained with phenylacetaldehyde, the reaction of which led to the *β*-carboline product in 90% yield and with 87% ee. The aromatic aldehydes tested reacted more slowly; nevertheless, the corresponding products were furnished in satisfactory yields and with satisfactory ee values.

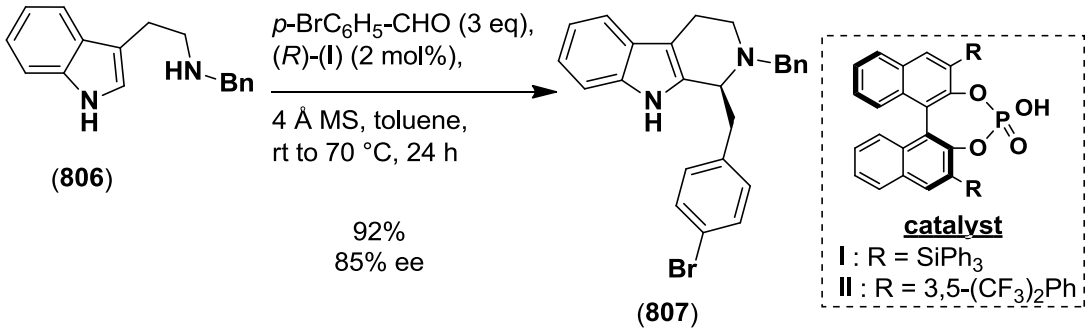
Scheme 167



Later, Van Maarseveen and Hiemstra[253] synthesized optically active tetrahydro-*β*-carbolines via an (*R*)-BINOL-phosphoric acid-catalyzed asymmetric Pictet–Spengler reaction of *N*-benzyltryptamine with a series of aromatic and aliphatic aldehydes. The tetrahydro-*β*-carbolines were obtained in yields ranging from 77 to 97% and with ee values up to 87%. The triphenylsilyl-substituted BINOLphosphoric acid proved to be the

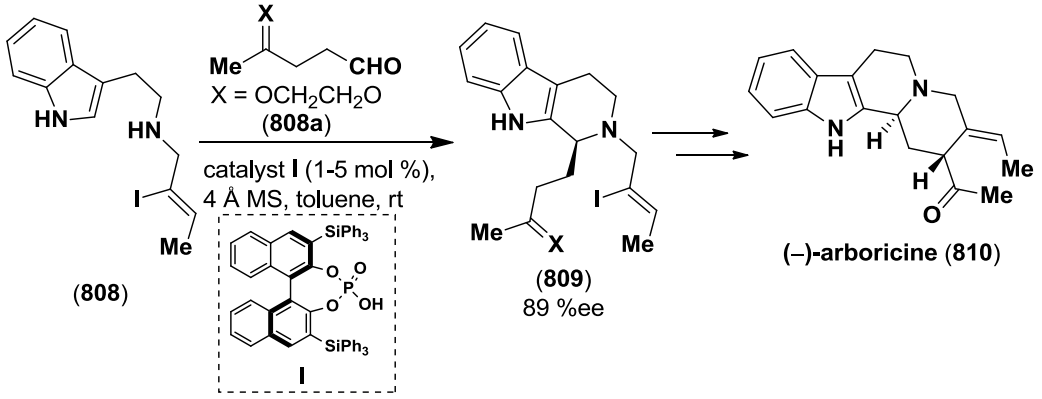
catalyst of choice for the reaction with aromatic aldehydes. For the aliphatic aldehydes, 3,5-bistrifluoromethylphenyl-substituted BINOL-phosphoric acid was identified as the best catalyst (Scheme 168).

Scheme 168



This asymmetric Pictet–Spengler reaction catalyzed by a chiral phosphoric acid has been employed recently in the elegant total synthesis of (–)-arboricine (**810**, Scheme 169).[254] The tryptamine derivative (**808**) was condensed with dioxolane aldehyde (**808a**) in the presence of (*R*)-3-3'-triphenylsilyl-binol phosphoric acid **I** (5 mol%) in toluene and 4 Å molecular sieves. The installation of the acetal protecting group improved the rate, as well as the % ee of the Pictet–Spengler reaction. With the desired tetrahydro-*β*-carboline in hand, the total synthesis of (–)-arboricine (**810**) was completed following a palladium-mediated enolate-involved cyclization. This is an excellent example of a facile synthesis of an indole alkaloid via the asymmetric Pictet–Spengler cyclization and was based on the earlier work reported from Milwaukee by Yu, Ma and others.[254]

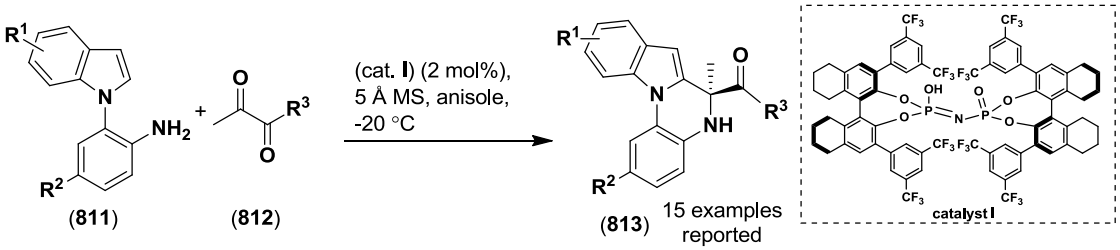
Scheme 162



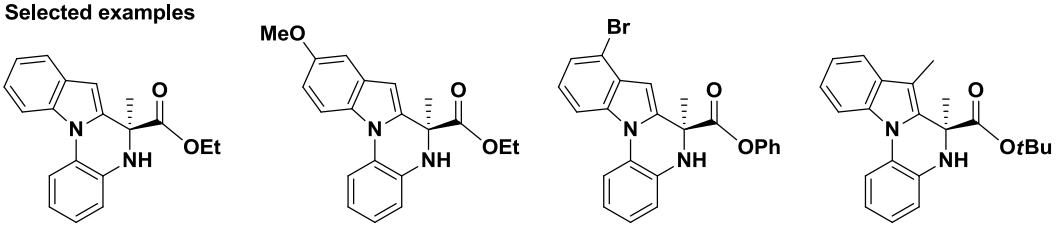
In 2014, Zhang and collaborators developed a H_8-BINOL-type chiral imidodiphosphoric acid catalyst **I** which they used for the the highly enantioselective synthesis of quaternary carbon-centered 5,6-dihydroindolo[1,2-*a*]quinoxalines (DHIQs) (**813**) and phenyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalines (PDHPQs) (**816**) via a Pictet−Spengler-type reaction (Schemes 170 and 171 respectively).[255] The methodogy shows excellent catalytic activity (up to 98% ee, 98% yield) and high efficiency (as low as 2 mol%) in this capacity. The synthesis of DHIQs (**813**), using the optimized reaction conditions, from indolyl anilines and activated ketones was shown to tolerate a variety of different substitution patterns (Scheme 170).

The successful enantioselective synthesis of chiral DHIQs, encouraged the authors to approach the enantioselective synthesis of chiral PDHPQs (**816**). In their work, construction of two kinds of PDHPQ frameworks containing a crowded quaternary chiral carbon center was realized by the newly developed H_8-BINOL imidodiphosphoric acid catalyst **I** with low catalyst loading (2 mol%) (Scheme 171). The reaction conditions were re-optimized, and the best result was obtained in 1,4-dioxane at 15 °C.

Scheme 170



Selected examples



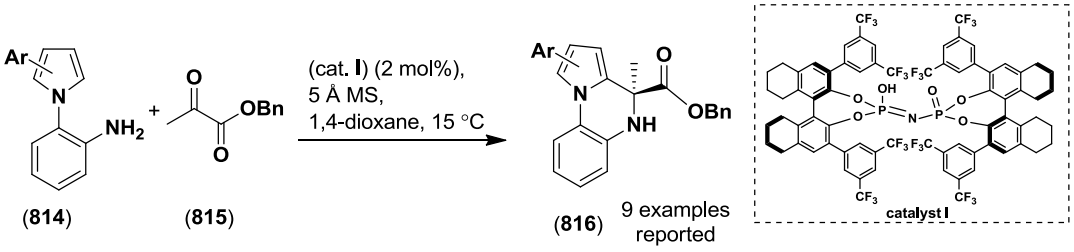
(**813a**)
97% yield, 93% ee

(**813b**)
90% yield, 93% ee

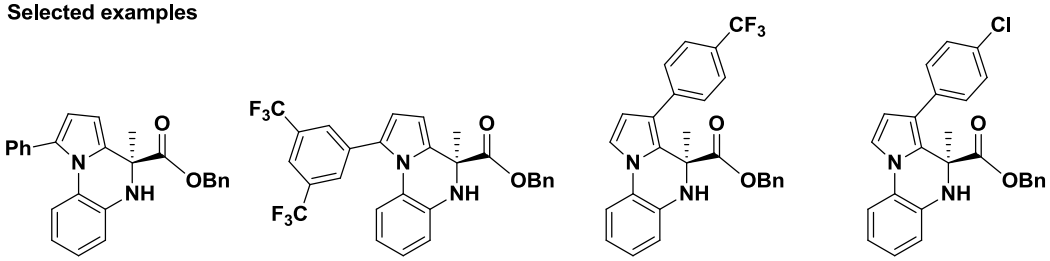
(**813c**)
96% yield, 94% ee

(**813d**)
91% yield, 92% ee

Scheme 171



Selected examples



(**816a**)
97% yield, 93% ee

(**816b**)
94% yield, 97% ee

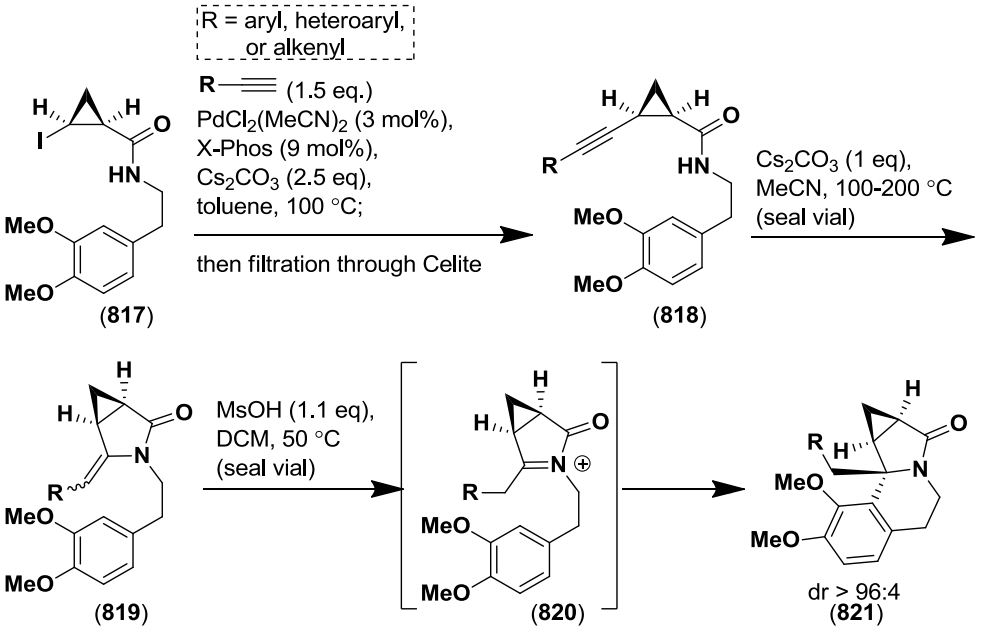
(**816c**)
94% yield, 98% ee

(**816d**)
94% yield, 98% ee

In 2015, Meyer and Cossy reported a diastereodivergent Pictet–Spengler cyclization of bicyclic *N*-acyliminium ions (Scheme 172).[256,257] The authors were able to get access to bicyclic enamides (**819**), which contained a 4-methylene-3-azabicyclo[3.1.0]-hexan-2-one core, by employing a two-step procedure that started from *cis*-2-iodocyclopropane-carboxamides (**817**), derived from homoveratrylamine. The sequence relied on a copper-free Sonogashira cross-coupling reaction between iodocyclopropane (**817**) and terminal aryl alkynes, heteroaryl alkynes, or conjugated enynes to lead to *cis*-2-alkynylcyclo-propanecarboxamide (**818**), which was not purified but directly subjected to a 5-*exo*-*dig* cyclization to yield bicycle (**819**). The *N*-acyliminium ion (**820**), which was generated by protonation of enamide (**819**), underwent a highly diastereoselective Pictet–Spengler cyclization to afford the tetracyclic nitrogen heterocycle (**821**). The diastereoselectivity that was observed in the Pictet–Spengler cyclization corresponded to the kinetically controlled addition of the 3,4-dimethoxyphenyl group to the less hindered face (opposite to the cyclopropane) of the bicyclic *N*-acyliminium ion (**820**). It is worth noting that tetracyclic compound (**821**) is configurationally stable even upon prolonged heating in the presence of MsOH in toluene at reflux (Scheme 172). In contrast, it was observed that enamide (**822**) exhibited a different behavior (Scheme 173). Indeed, under the previously developed conditions (MsOH, DCM, 50 °C, 4 h), the Pictet–Spengler cyclization of (**822**) proceeded through *N*-acyliminum ion intermediate (**823**) to generate a mixture of epimeric nitrogen heterocycles (**824a**) and (**824b**) in a 40:60 ratio (84% yield). Because of the higher nucleophilic character of indole compared to the 3,4-dimethoxyphenyl group, the Pictet–Spengler cyclization of (**822**) could be carried out at room temperature. Under these milder conditions, the reaction produced tetracyclic compound (**824a**) (84%

yield) as a single diastereomer [(**824a**)/(**824b**) >96:4] as a result of the kinetically controlled nucleophilic attack of the C-2 indole atom on the less-hindered face of *N*-acyliminium ion (**823**).

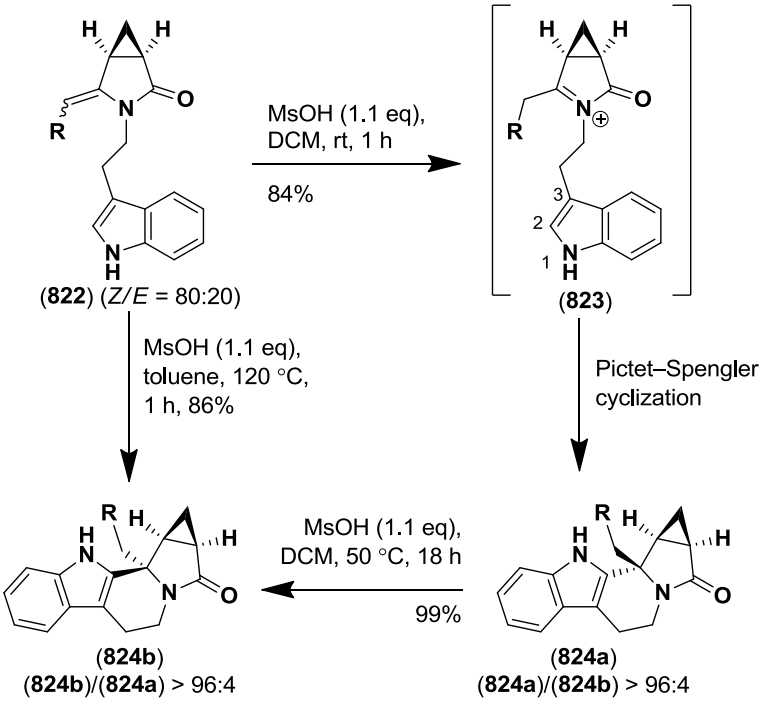
Scheme 172



In contrast, harsher conditions (MsOH, toluene, 120 °C, 1 h) resulted in the highly diastereoselective formation of tetracyclic compound (**824b**, 86% yield), which is an epimer of (**824a**) at the newly formed quaternary stereocenter at the ring junction [(**824b**)/(**824a**) >96:4]. In this latter case, the observed diastereoselectivity was explained by a thermodynamically controlled epimerization of the initially formed kinetic product, diastereomer (**824a**). Indeed, this result was confirmed by subjecting nitrogen heterocycle (**824a**) to prolonged heating in the presence of MsOH (DCM, 50 °C, 18 h). Under these

conditions, the thermodynamic product, epimer (**824b**) was obtained in nearly quantitative yield (Scheme 173). The authors provided evidence that a retro-Pictet–Spengler mechanism was involved in the equilibration process.[256,257]

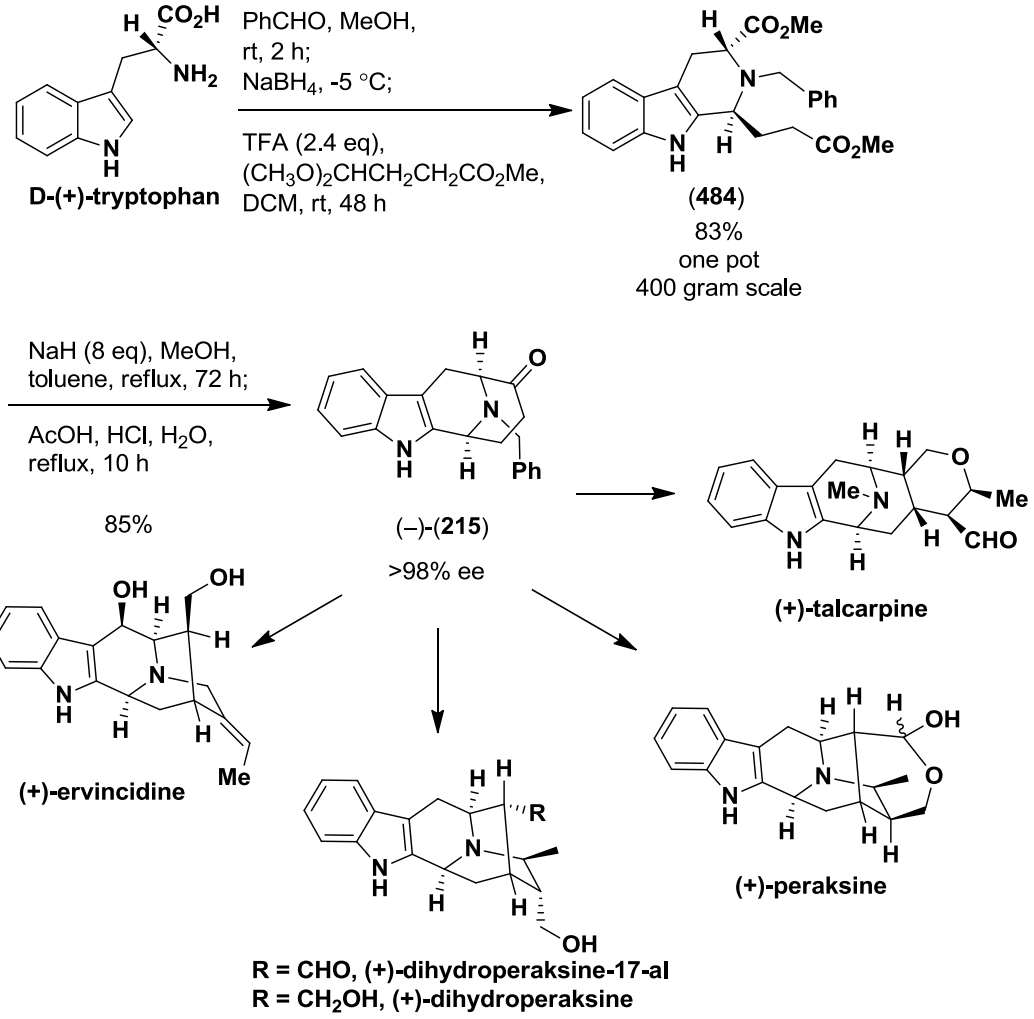
Scheme 173



Finally at this point, it is worth mentioning the recent stereoselective total syntheses of complex natural products accomplished in Milwaukee, in which the asymmetric Pictet–Spengler reaction was a key step, in recent years. In 2014, Edwankar R. V. et al. reported a detailed account of the development of a general strategy for the synthesis of the C-19 methyl-substituted alkaloids, including the total synthesis of 19(*S*),20(*R*)-dihydroperaksine-17-al, 19(*S*),20(*R*)-dihydroperaksine, and peraksine (Scheme 174).[258]

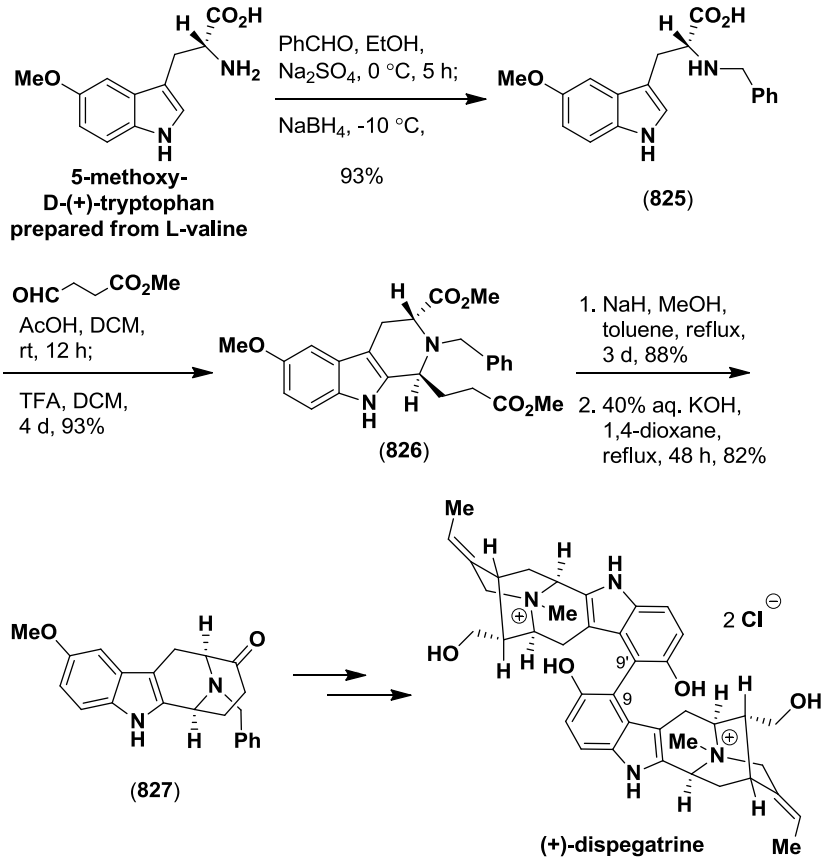
Also, Rallapalli et al. reported the stereospecific total synthesis of the indole alkaloid ervincidine, this study also served as structure proof and corrected the misassigned structure reported in the literature.[259] All the above mentioned natural indole alkaloids were prepared enantiospecifically and stereospecifically from D-(+)-tryptophan via the asymmetric Pictet–Spengler/Dieckmann protocol following a procedure developed in Milwaukee.

Scheme 174



In 2013, Edwankar C. R. et al. reported the first regio- and stereocontrolled total synthesis of the bisphenolic, bisquaternary alkaloid (+)-dispegatrine in an overall yield of 8.3% (12 reaction vessels) from 5-methoxy-D-tryptophan ethyl ester (**825**). In this synthesis, a crucial late-stage thallium(III) mediated intermolecular oxidative dehydro-dimerization was employed in the formation of the C-9/C-9′ biaryl axis in (+)-dispegatrine (Scheme 175). Additionally, the first total synthesis of the monomeric indole alkaloids (+)-spegatrine, (+)-10-methoxyvellosimine, (+)-lochnerine, lochvinerine, (+)-sarpagine, and (+)-lochneram were also achieved during these studies.[260]

Scheme 175



7) Main Objectives and Enantioselective Synthetic Strategy

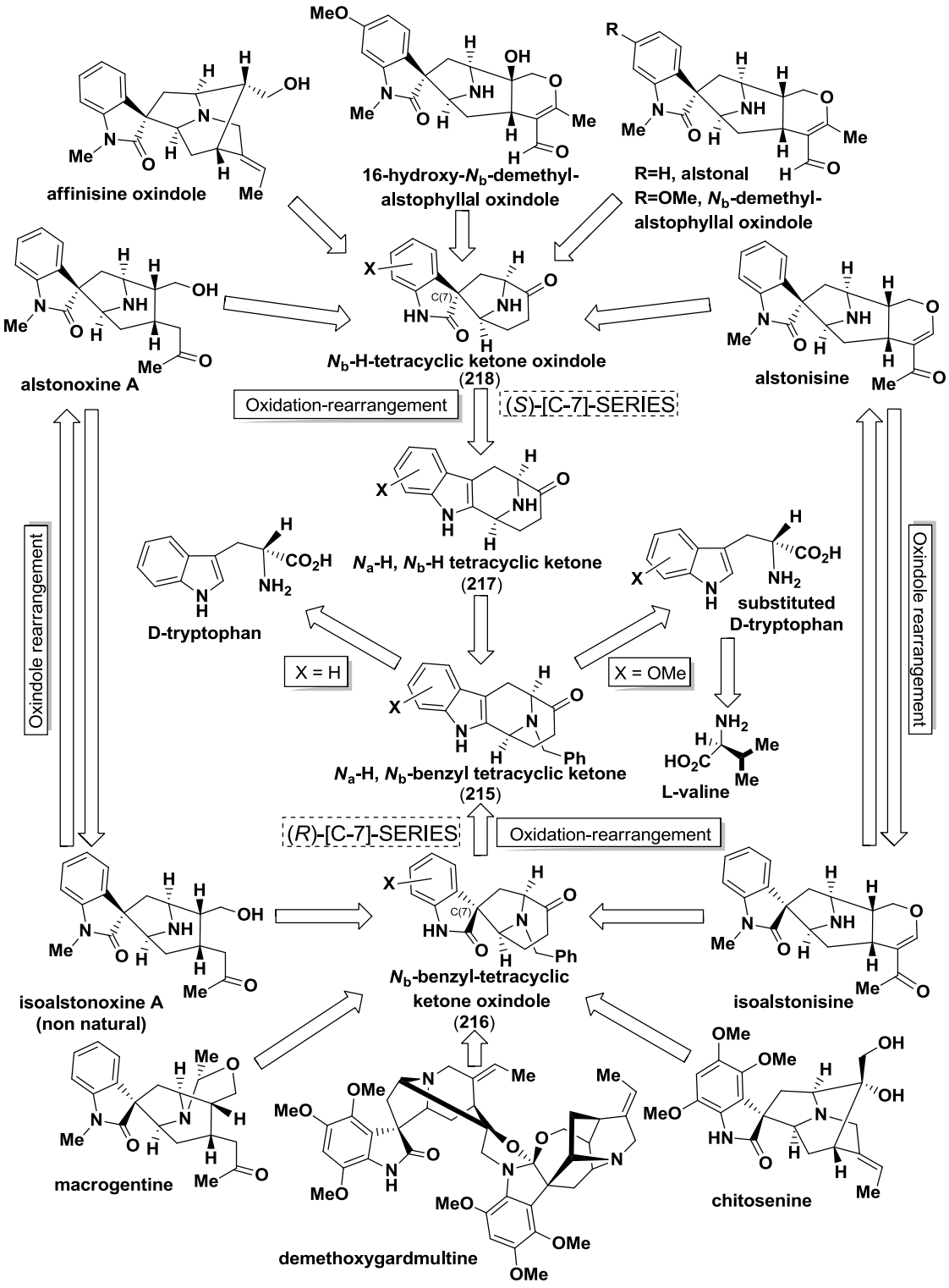
The main objectives of this research study were, *firstly*, to develop a highly enantio- and diastereoselective general strategy to gain easy entry to sarpagine and macroline bioactive oxindole alkaloids of either chirality at the C-7 spiro center from cheap, commercially-available, and enantiopure D-(+)-tryptophan (Scheme 176 hightlights the key characteristics of the route). *Secondly*, the study sought to demonstrate the utility in total synthesis of a diastereospecific *tert*-butyl hypochlorite-promoted oxidative rearrangement of chiral tetrahydro-β-carboline derivatives developed in Milwaukee by Yu et al.,[62] which would install the oxindole and spiro cycle in a single chemical step early in the synthetic route. The latter attribute renders the strategy very versatile by permitting the interconversion between oxindole diastereomers at the spirojuncture C-7 through careful selection of oxindole rearrangement conditions [see for example the isomerization of alstonoxine A to its (*R*)-[C-7]-series counterpart isoalstonoxine A (not isolated from natural sources yet), and also, the isomerization of alstonisine to generate isoalstonisine, or *vice versa*, as shown in Scheme 176]. This is a well documented characteristic of oxindoles;[261] however, unexplored in depth in the particular case of the sarpagine and macroline oxindole group. In addition, the applicability of the asymmetric Pictet–Spengler reaction; Dieckmann cyclization; stereospecific enolate-mediated palladium-catalyzed cross-coupling cyclization; modified Wacker–Cook oxidation-cyclization and other reactions would be tested during the synthetic sequence. *Thirdly*, although numerous alkaloids of the groups mentioned above were reported to possess very interesting bioactive properties, most members have not been biologically evaluated

in detail, due to paucity of isolable material. Therefore, having easy synthetic access to multigram quantities of these natural products was of great importance for their study as potential drug candidates. *Fourthly*, to provide supporting evidence of the correct structural elucidation of a number of natural oxindoles which had not been synthesized before.

The synthetic approach to sarpagine/macroline oxindole alkaloids under study here is depicted in a general retrosynthetic sense in Scheme 176. The common intermediate for those oxindole alkaloids in the (*S*)-[C-7]-series (top of Scheme 176) would be the N_b-H-tetracyclic ketone oxindole (**218**). The latter would arise from the *tert*-butyl hypochlorite-promoted oxidation-rearrangement sequence on the important N_b-H-tetracyclic ketone (**217**). The asymmetry of this tetrahydro-β-carboline would be constructed by means of the modified Pictet–Spengler reaction followed by a Dieckmann cyclization in a two-pot process from D-tryptophan as reported earlier.[262,55b] An analogous reasoning applies to those natural oxindole alkaloids in the (*R*)-[C-7]-series (bottom of Scheme 176). In this case, the N_b-benzyl-tetracyclic ketone oxindole (**216**) would be the common oxindole precursor. The presence of a bulky protecting group on the N_b-nitrogen atom in the N_b-benzyl-tetracyclic ketone (**215**) is a key structural feature that determines the diastereoselective generation of the (*R*)-configuration at the C-7 spiro center after the oxidation-rearrengement reaction.

Finally, although it was not part of the present study, it is important to mention two features in regard to the generality of the approach proposed here: (1) the sarpagine/macroline imino-ether alkaloids could also be accessed by the use of this strategy given their closely-related chemical structure with the oxindole group; and (2)

Scheme 176


affinisine oxindole
16-hydroxy-N_b-demethyl-alstophyllal oxindole
R=H, alstonal
R=OMe, N_b-demethyl-alstophyllal oxindole
alstonoxine A
N_b-H-tetracyclic ketone oxindole (218)
alstonisine
Oxidation-rearrangement
(S)-[C-7]-SERIES
N_a-H, N_b-H tetracyclic ketone (217)
D-tryptophan
substituted D-tryptophan
Oxindole rearrangement
X = H
X = OMe
N_a-H, N_b-benzyl tetracyclic ketone (215)
L-valine
(R)-[C-7]-SERIES
Oxidation-rearrangement
isoalstonoxine A (non natural)
N_b-benzyl-tetracyclic ketone oxindole (216)
isoalstonisine
macrogentine
demethoxygardmultine
chitosenine

those natural spirooxindole alkaloids bearing a substituted-benzene A-ring oxindole moiety (the methoxy group is the only type of substituent that has been found other than hydrogen atoms to date in this series) could be prepared through the proposed strategy in a similar fashion as those of the parent system from the corresponding enantiopure methoxy-substituted tryptophan. Since these methoxy-substituted tryptophans are not commercially available, a large scale synthesis is required. The palladium catalyzed heteroannulation strategy of Larock et al.,[263] could be employed to this end. This would originate from the palladium-mediated coupling reaction of a substituted iodoaniline and a chiral internal-alkyne, followed by hydrolysis of the Schöllkopf chiral auxiliary present in the indole molecule. The internal alkyne could be obtained from the alkylation of the Schöllkopf chiral auxiliary with a suitable activated derivative of propargyl alcohol. In turn, the Schöllkopf chiral auxiliary could be synthesized on kilogram scale from cheap, enantiopure L-valine following reported protocols by Cook et al.[231]

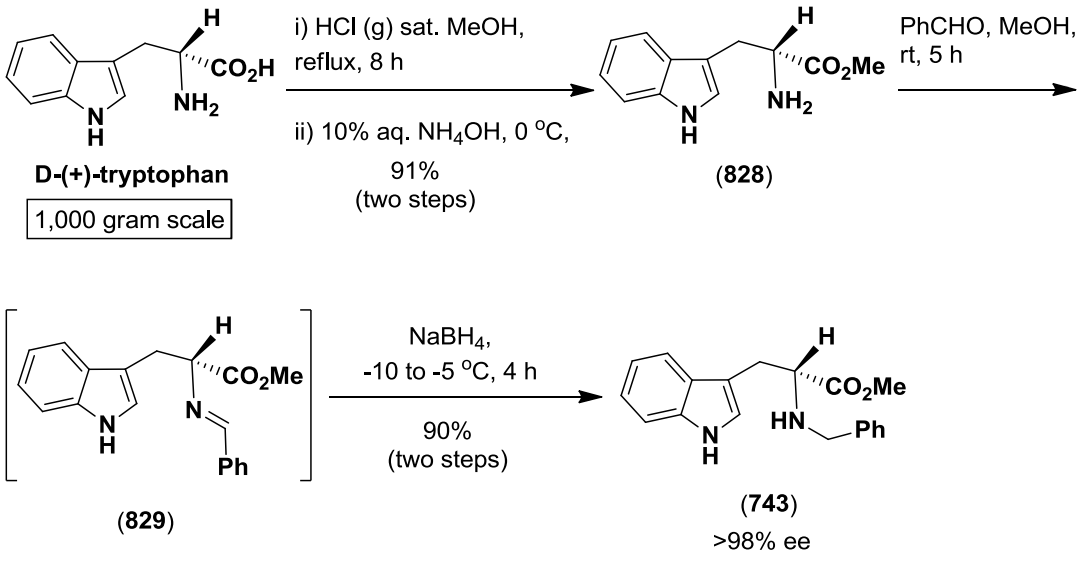
8) Results and Discussion

8.1) Synthesis of the key intermediates (–)-N_a-H, N_b-benzyl tetracyclic ketone (215) and (–)-N_a-H, N_b-H tetracyclic ketone (217) on large scale

According to the general synthetic strategy discussed in the previous section, the initial steps towards the synthesis of sarpagine/macroline oxindole alkaloids required the enantiospecific preparation of the important intermediates (–)-N_a-H, N_b-benzyl tetracyclic ketone (**215**) and (–)-N_a-H, N_b-H tetracyclic ketone (**217**) on large scale from commer-

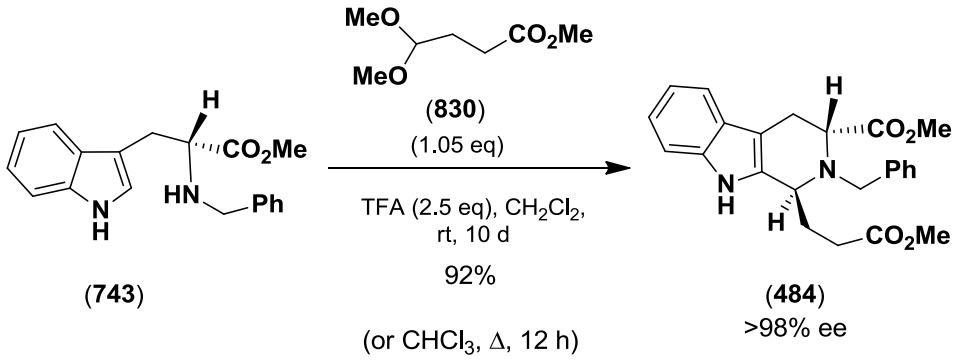
cially available D-(+)-tryptophan (Scheme 176), following the procedure developed in Milwaukee by Li et al.[264] The synthesis began with the Fischer esterification of D-(+)-tryptophan which was carried out in a hydrogen chloride saturated methanolic solution at reflux for 8 hours (Scheme 177). This reaction was scaled up to 1 kilogram scale. The hydrochloride salt, which precipitated after cooling was filtered and neutralized in methylene chloride with an ice cold (10%) aqueous NH_4OH solution to provide D-(–)-trytophan methyl ester (**828**) in 91% yield (over two steps). The N_b-H tryptophan methyl ester (**828**) was then converted into the N_b-benzyl tryptophan methyl ester (**743**) by means of a reductive amination procedure (Scheme 177). The reaction of amine (**828**) with 1.1 equivalents of benzaldehyde at room temperature (23 °C) over 5 hours in MeOH, generated the corresponding imine (**829**) which was reduced *in situ* with

Scheme 177

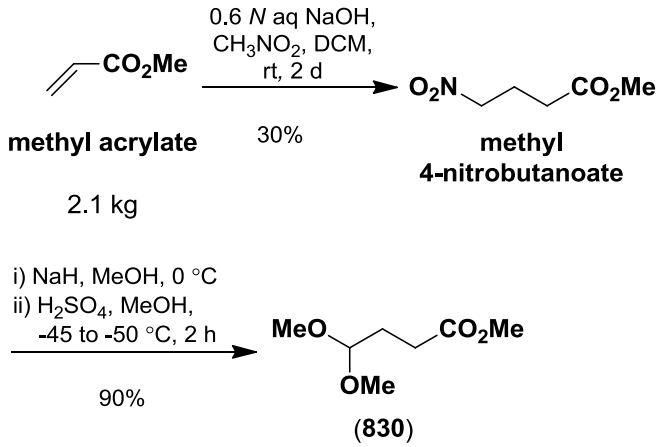


sodium borohydride over approximately 4 hours until disappearance of the intermediate imine (90% yield, two steps). Importantly, the temperature during the reduction was kept between −10 °C to −5 °C to avoid racemization of the chiral center. The enantio purity of the N_b-benzyl tryptophan methyl ester (**743**) prepared in this manner was found to be greater than 99% (>98% ee) as determined by comparison of the optical rotation [α] to that of an authentic sample.[55b,219]

Scheme 178



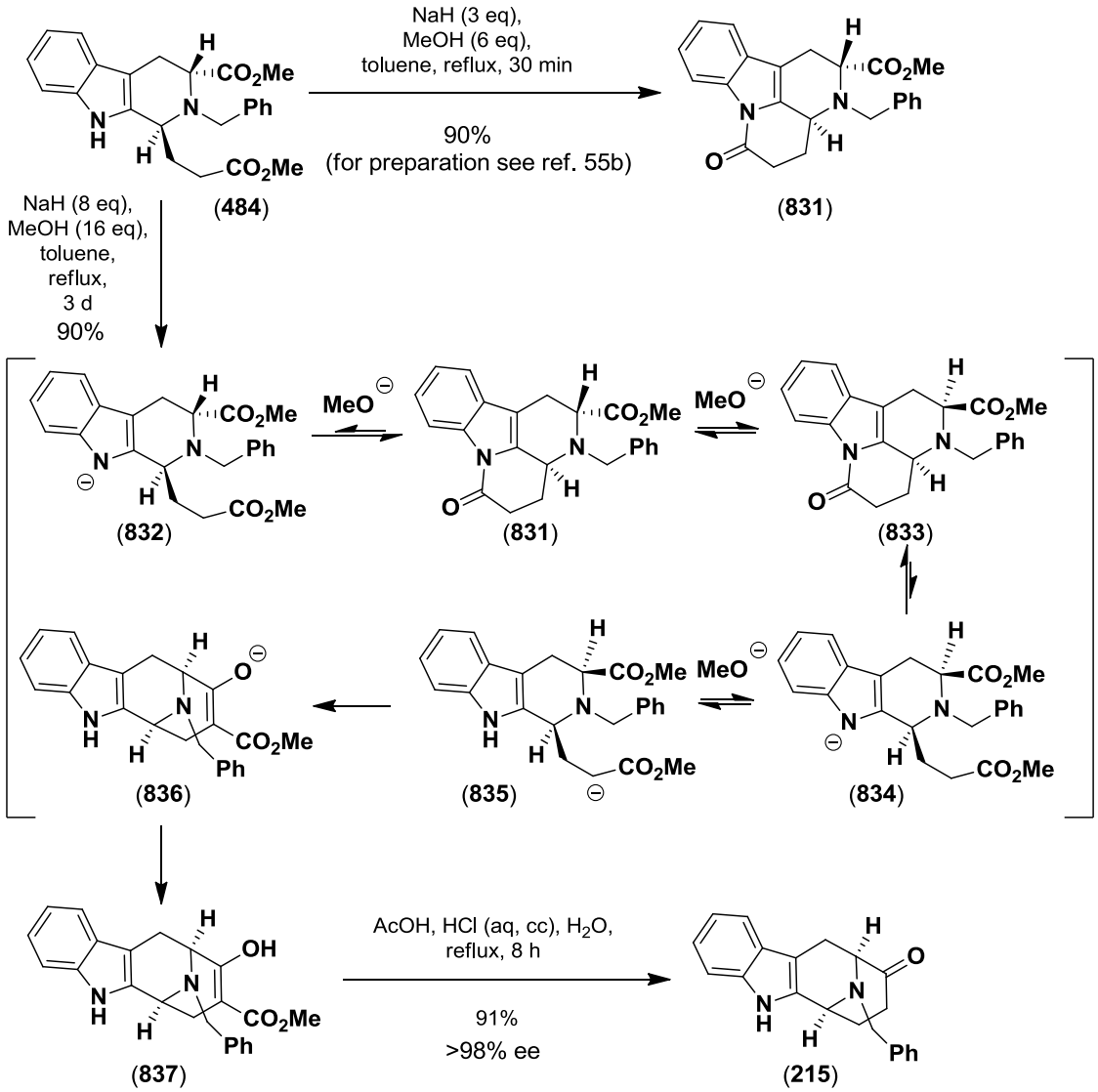
Synthesis of methyl 4,4-dimethoxybutanoate (830) on large scale[265]



To introduce the desired stereocenter at C-1 of the tetrahydro-β-carboline system, the asymmetric Pictet–Spengler reaction[214,223,225,241] (see Section 6 for a discussion on the asymmetric Pictet–Spengler and references therein) was employed with methyl 4,4-dimethoxybutyrate (**830**) (which can be prepared on a kilogram scale)[265] and N_b-benzyl tryptophan (**743**), in the presence of trifluoroacetic acid (2.5 equivalents), to provide the *trans* diester (**484**) as a single diastereomer in 92% yield (Scheme 178). This process was scaled up to the 400 gram level and purification was achieved by recrystallization from ethanol. Consequently, during the process of this Pictet–Spengler reaction the *cis* diester (**748**) was detected by TLC but was converted entirely into the *trans* diester (**484**), presumably *via* the carbocationic intermediate (see also Section 6, and Schemes 144 and 145).[225,241] After work up, the *trans* diester (**484**) was obtained as the only diastereomer in greater than 98% ee (Scheme 178). When the *trans* diester (**484**) was treated with 3 equivalents of sodium hydride in the presence of excess methanol in refluxing toluene (for 30 minutes),[217] the *trans* diester (**484**) was converted entirely into *trans* δ-lactam (**831**, Scheme 179). No further change was observed on prolonged heating. However, when diester (**484**) was treated with 8 equivalents of sodium hydride in the presence of excess methanol in refluxing toluene under these same reaction conditions for an extended period of time (72 hours), the desired Dieckmann β-enolester (**837**) was obtained in 90% yield. Presumably, the *trans* δ-lactam (**831**) formed and then underwent an epimerization at C-3 (of the β-carboline system) followed by a ring-opening process to provide the *cis* diester (**834**) under these conditions.[55b,266,267] This *cis* diester was in equilibrium with the *cis* intermediate (**835**) and the latter material was eventually converted into β-enolester (**837**) via the Dieckmann reaction. It was felt the δ-lactams

(**831** and **833**) were favored in the equilibrium over the diester intermediates (**832** and **834**); however, the irreversible formation of the enolate (**837**) in the Dieckmann cyclization gradually promoted completion of the process to provide the β-enolester (**837**), exclusively (Scheme 179).

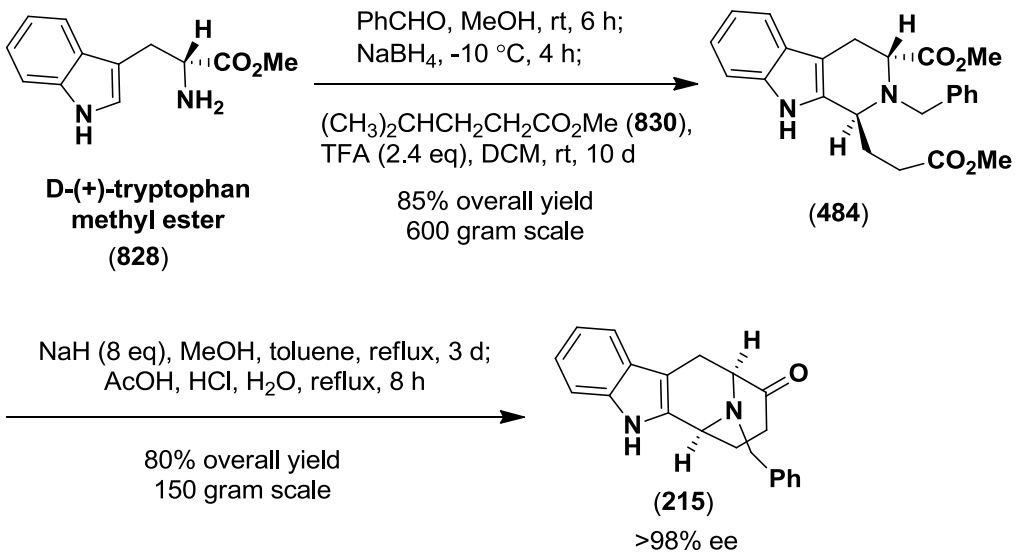
Scheme 179



The hydrolysis and subsequent decarboxylation of the *β*-enolester (**837**) under acidic conditions was achieved in one step to provide the template (–)-N_a-H, N_b-benzyl tetracyclic ketone (**215**) in 91% yield. The enantiomeric purity of ketone (**215**) was determined to be greater than 98% ee by comparison of its optical rotation to that reported before by Wearing et al. and Wang et al.[55b,267,268]

Recently, a much improved route to the key tetracyclic intermediate (**215**) was developed. The starting material D-(+)-tryptophan methyl ester was diastereospecifically converted [*via* (**484**)] into the benzyl tetracycle (**215**) in greater than 98% ee in a two pot process on multihundred gram scale, as depicted in Scheme 180. More specifically, after N_b-benzylation of D-tryptophan with benzaldehyde and sodium borohydride (1.1 equivalent) in methanol was completed, trifluoroacetic acid was added to the reaction vessel at 0 °C to neutralize the alkaline mixture. After removal of the solvent under reduced pressure, CH_2Cl_2, TFA and acetal (**830**) were added to the vessel at 0 °C and the modified Pictet–Spengler reaction (600 gram scale) was carried out to provide the *trans* diester (**484**) in 85% yield as a crystalline material. In the second sequence (150 gram scale), the Dieckmann cyclization was completed and the reaction solution was then cooled to 0 °C after which it was carefully quenched with glacial acetic acid. After removal of the solvent under reduced pressure, glacial acetic acid, concentrated aqueous hydrochloric acid and water were added to the residue in the same vessel at 0 °C. The acidic hydrolysis and decarboxylation of the *β*-enolester (**837**) was then executed at reflux to provide (–)-(**215**) in 80% crystalline yield in greater than 98% ee.[267,268]

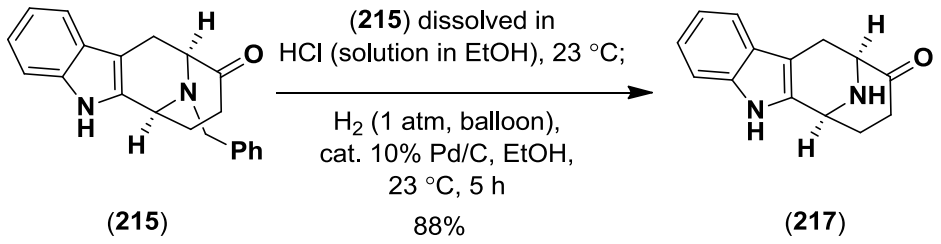
Scheme 180



With the N_a-H, N_b-benzyl tetracyclic ketone (**215**) in hand, the next step (following the general approach shown in Scheme 176) was to gain access to the corresponding N_a-H, N_b-H tetracyclic ketone (**217**) by effectively removing the bulky benzyl group on the N_b-nitrogen atom. To that end, a catalytic-debenzylation method, developed in Milwaukee by Yu and Wang et al., was utilized.[55b] Accordingly, when the starting N_a-H, N_b-benzyl tetracyclic ketone (**215**) was stirred with palladium on carbon under 1 atm of hydrogen under acidic conditions, the benzyl group was successfully removed (Scheme 181). After the formation of the N_a-H, N_b-benzyl tetracyclic ketone hydrochloride salt, the solvent was removed under reduced pressure. The residue was dissolved again in dry EtOH, and the solvent was removed. This process was repeated three more times, in order to remove the excess HCl (g). The reductive debenzylation process (H_2, in the presence of 10% Pd

on C, for 5 hours) in EtOH afforded only the expected product, N_a-H, N_b-H tetracyclic ketone (**217**) in 95% yield (10 g scale, Scheme 181).[55b]

Scheme 181

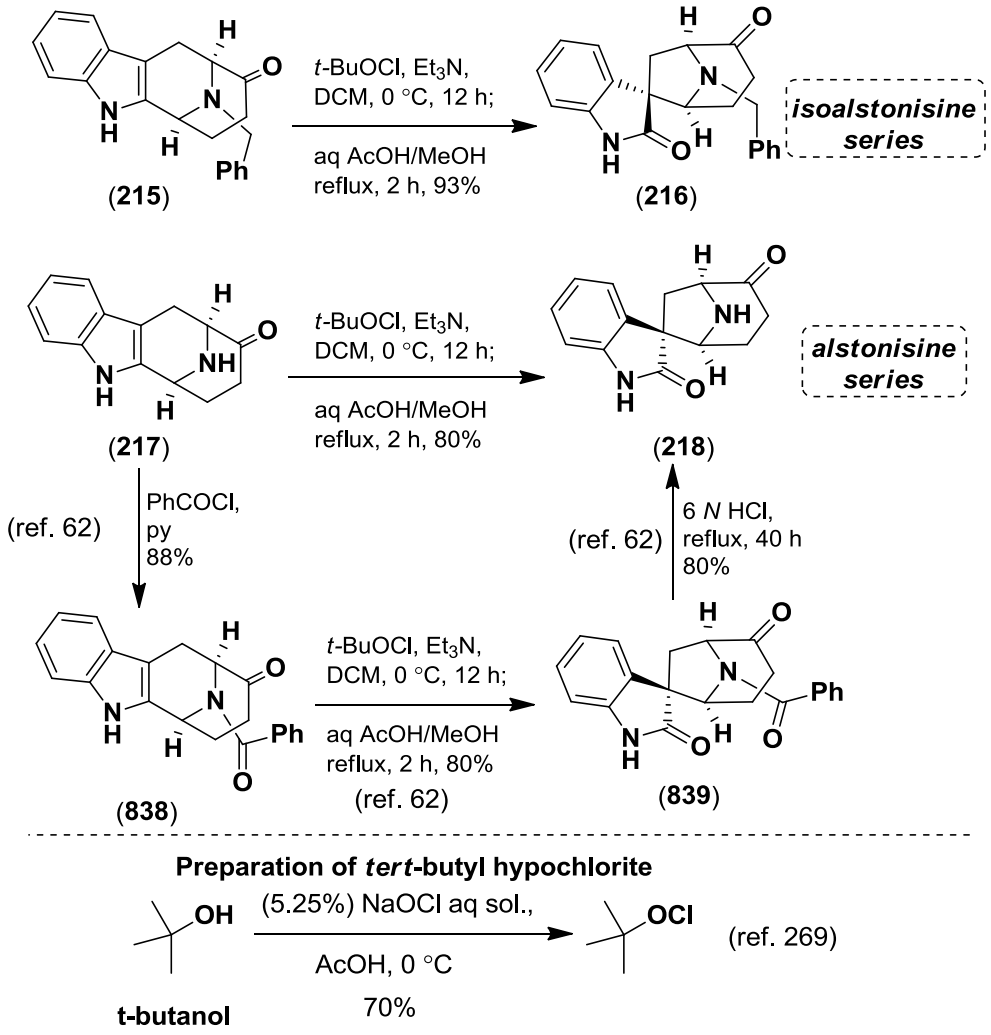


8.2) Diastereospecific conversion of (–)-N_a-H, N_b-benzyl tetracyclic ketone (215) and (–)-N_a-H, N_b-H tetracyclic ketone (217) into the respective (+)-N_a-H, N_b-benzyl tetracyclic ketooxindole (216) and (–)-N_a-H, N_b-H tetracyclic ketooxindole (218)

It is important to mention here the study by Peterson et al., in which a highly diastereo-selective route for the conversion of N_a-methylated tetracyclic ketones into either spirooxindole diastereomer at C-7 by employing the Sharpless osmylation process for asymmetric dihydroxylation was developed (see Section 4 for a detailed discussion of this approach and Scheme 88).[143] However, some drawbacks of this approach were (1) the fact that **N_a-methylated** tetracyclic ketones had to be used, rendering the synthetic route chemically less flexible; (2) the yields in the alstonisine series were modest; and (3) a stoichiometric amount of expensive, highly-toxic osmium tetroxide was required.[62] The possibility of an alternative, more efficient entry into these ketooxindoles (in a

diastereospecific fashion) was of synthetic interest. Consequently, Yu et al. reported a convenient, distereospecific method that solved the disadvantages mentioned above by replacing osmium tetroxide with *tert*-butyl hypochlorite (*tert*-BuOCl) as the oxidazing agent [Scheme 182 (and also mentioned briefly in Section 2.2, see Schemes 18 and 22)].[62]

Scheme 182



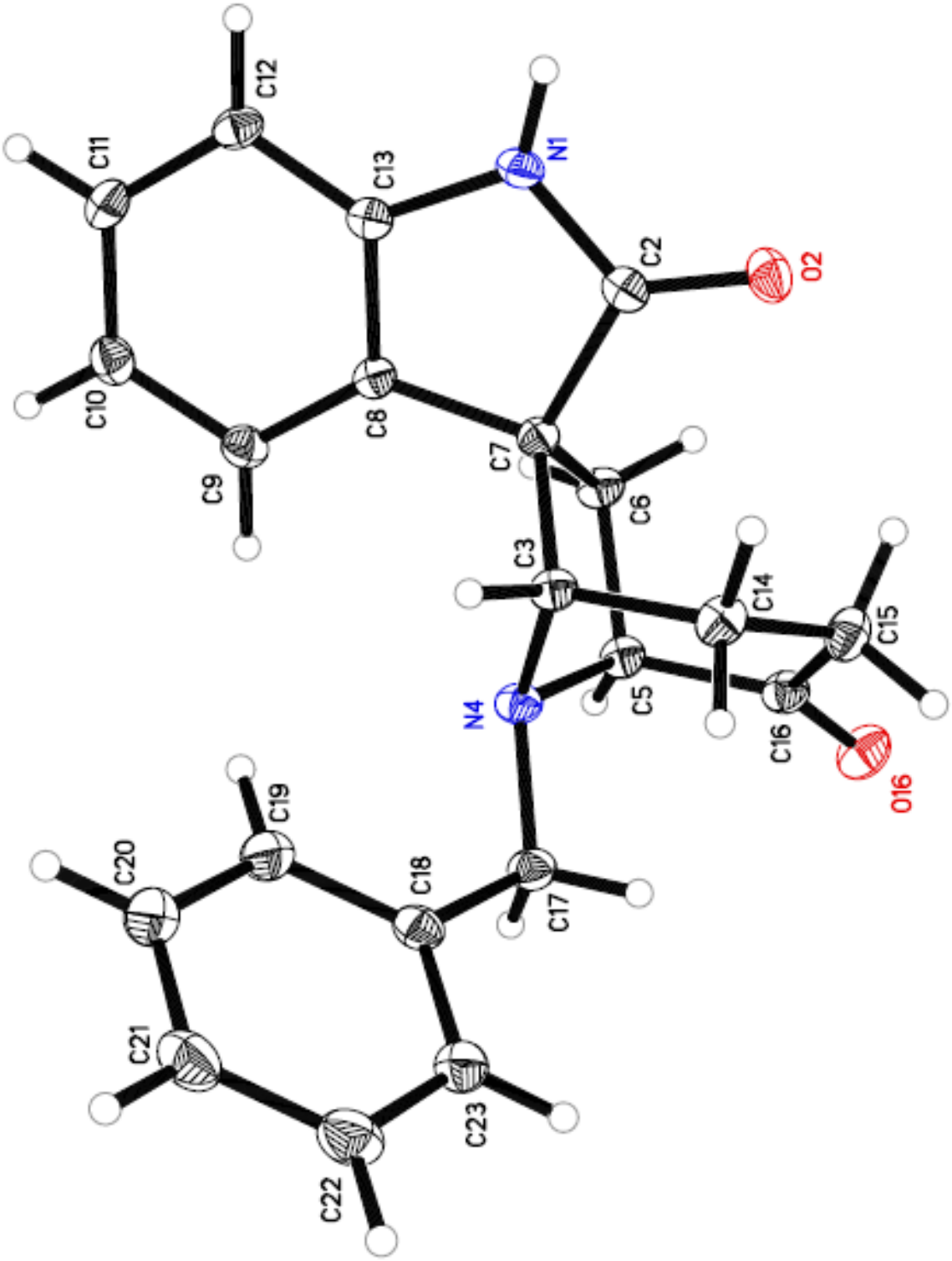
Following Yu et al. studies, the spiro[pyrrolidine-3,3′-oxindole] system (**218**, Scheme 182), with the alstonisine stereochemistry, was obtained stereospecifically (in 80% yield) upon reaction of the N_a-H, N_b-H tetracyclic ketone (**217**) with *tert*-BuOCl/Et_3N at 0°C in DCM, followed by treatment with acetic acid in methanol at reflux. In this same approach, when N_a-H, N_b-benzyl tetracyclic ketone (**215**) was reacted directly with *tert*-BuOCl/Et_3N, the isoalstonisine-series oxindole [**216**, ORTEP drawing of (**216**) is shown in Figure 21] was obtained in 93% yield in diastereospecific fashion, the stereochemical outcome of this reaction was confirmed by X-ray crystallography. The hypochlorite oxidazing agent was readily prepared in 10 minutes from *tert*-butanol (Scheme 182), commercial bleach (5.25% aq NaOCl solution) at 0 °C and acetic acid according to a literature procedure by Mintz et al. (Scheme 182). Due to its chemical instability, *tert*-butyl hypochlorite had to be prepared right before it was used. Once the compound is made, it had to be kept cold (below 5 °C), managed in dim light, and also, had to avoid contact with rubber.[269]

Interestingly, Yu et al. also showed that when the N_a-H, N_b-benzoyl tetracyclic ketone (**838**) was employed, N_a-benzoyl oxindole (**839**), which was structurally related to alstonisine, was diastereospecifically formed in 88% yield (Scheme 182). This result was of importance for potential future synthesis of other members of sarpagine/macroline oxindole alkaloids. Removal of the benzoyl group could be achieved in high yield under acidic conditions (6 *N* aq. HCl/reflux/40 hours, 80% yield).[62]

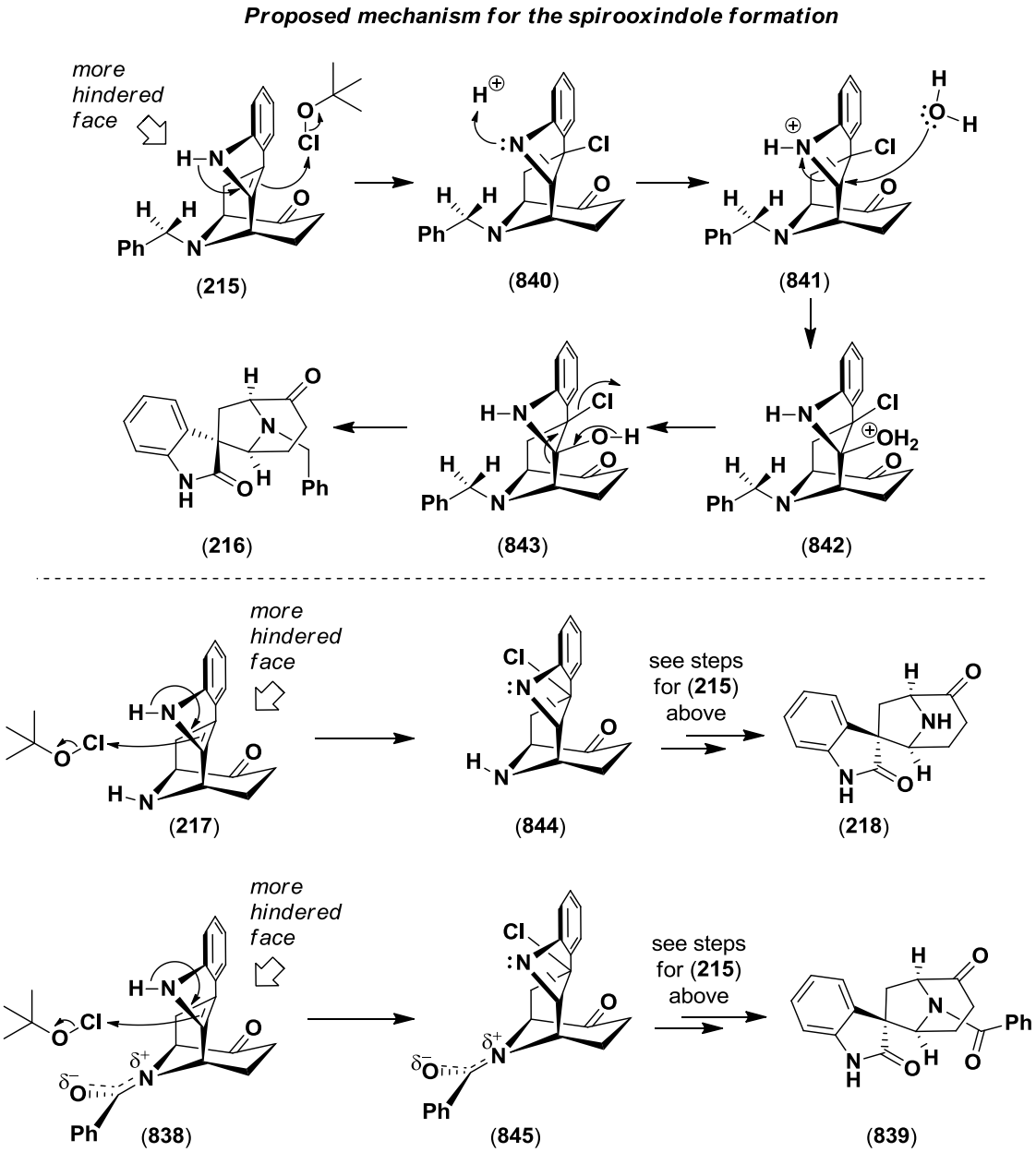
The 100% diastereoselectivity obtained during these transformations was a result of the difference in stereochemical reactivity of *tert*-butyl hypochlorite with the N_b-benzyl versus N_b-H tetracyclic ketone. The N_b-benzyl group in the N_a-H, N_b-benzyl tetracyclic

ketone (**215**), presumably, occupied the equatorial position (Scheme 183) and, therefore, blocked one face of the 2,3-indole double bond. This promoted attack by the "Cl^{+}" species from the concave face of the molecule. In the subsequent pinacol-type rearrangement the migrating group must attack from the face opposite the C-Cl bond in (**843**) to provide oxindole (**216**). Meanwhile, in the case of the N_a-H, N_b-H ketone (**217**), the concave face was more hindered when compared to the N_b-benzyl ketone (**215**, Scheme 183). In the tetrahydro-β-carboline (**217**), the 2,3-indole double bond was presumably attacked from the convex face to form oxindole (**218**), with the alstonisine stereochemistry. In the case of the N_b-benzoyl oxindole (**839**), it was believed that the O=C-N bond had planar amide character due to the porperties of the benzoyl carbonyl group which would establish the position of the benzoyl moiety in a more planar conformation away from the double bond of the carboline system. Again, as in the N_b-H ketone (**217**) case, the concave face of the molecule would be the more hindered to attack by *tert*-butyl hypoclorite (Scheme 183).[62,63]

Figure 21. ORTEP drawing of N_a-H, N_b-benzyl tetracyclic ketone oxindole (**216**)



Scheme 183



Finally, Yu et al. attempted to perform the *tert*-BuOCl oxidation with the corresponding N_a-methyl tetracyclic ketones analogues of ketones (**215**) and (**217**) but these failed, because these N_a-methyl analogues would not as readily undergo oxidation of the indole

2,3-double bond. Presumably, formation of the indolenine intermediate iminium ion at the N_a-methyl position, similar to (**841**) in Scheme 183, was too high in energy in this series.[270]

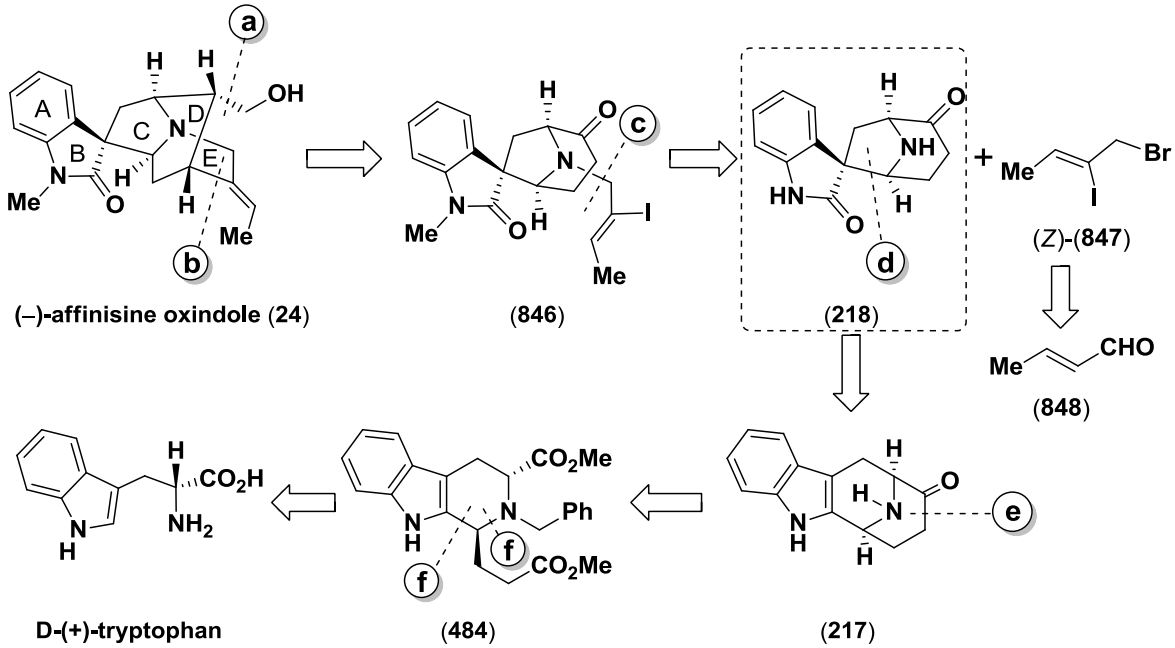
8.3) Enantiospecific total synthesis of the C7-(*S*) series oxindole alkaloid (–)-affinisine oxindole (24)[281]

The sarpagine-related C7-(*S*) series (–)-affinisine oxindole (**24**) was first isolated from the leaf extract of *Alstonia angustifolia* var. *latifolia* by Kam et al. and its structure was assigned in 2004.[14] The original structure and relative configuration of this alkaloid were established *via* analysis by IR, UV/VIS, NMR, and mass spectroscopy.[14] The configuration of the spirocyclic center C-7 was, initially, incorrectly determined to be (*R*) from the NOE interaction observed between H-9 and H-16 [the initial assignation (7*R*) was presumably an incorrect application of the Cahn–Ingold–Prelog priority rules]. Later, in a 2014 publication, Kam et al. changed the C-7 configuration to (*S*).[18] Also, the geometry of the (C-19, C-20) double bond was determined to be (*E*) from the NOE interaction observed between H-18 protons (methyl group) and H-15.[14]

As shown in the retrosynthetic analysis (Scheme 184), it was envisaged that the disconnection between C-16 and C-17 of (–)-affinisine oxindole (**24**, *disconnection a*) would provide the α-methylalcohol from the N_a-methyl, N_b-alkyl tetracyclic ketone oxindole (**846**) *via* a simple homologation sequence involving a series of 4 transformations: (1) a Wittig reaction followed by (2) hydrolysis of the enol ether and subsequent (3) epimerization and (4) reduction of the corresponding aldehyde. The E-ring

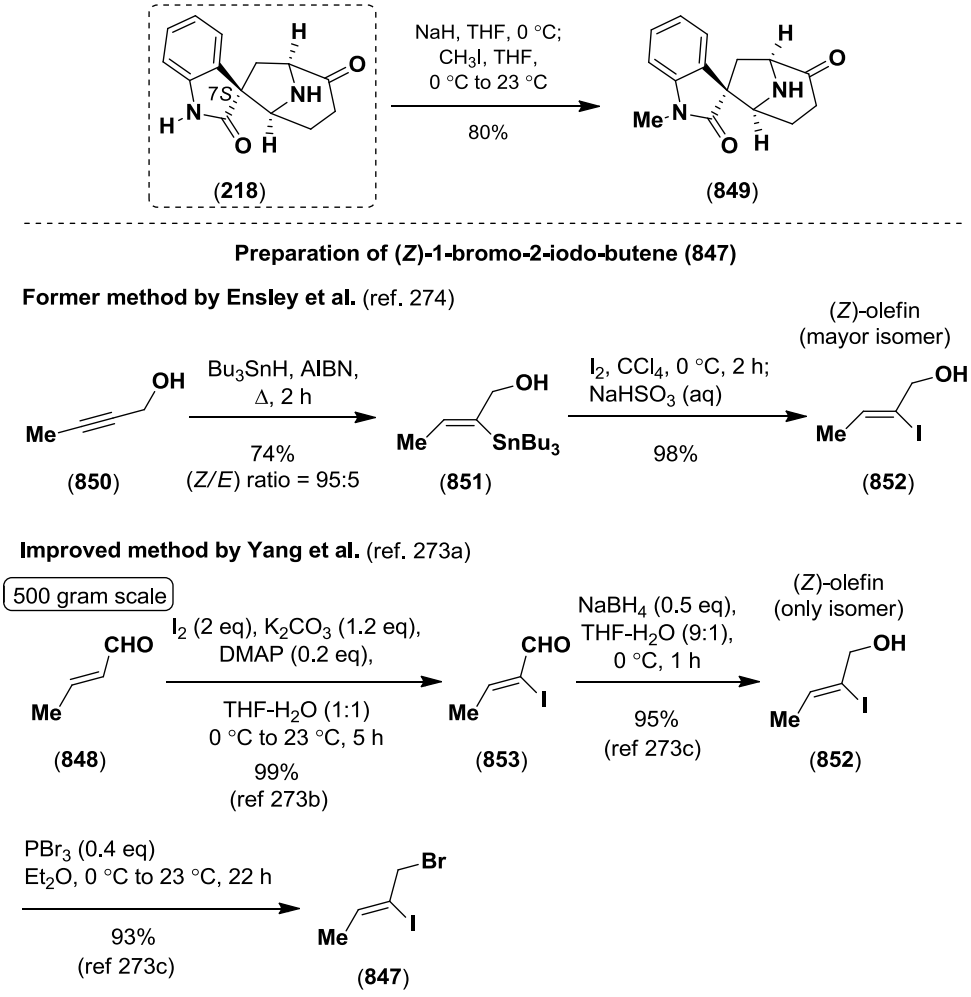
could be formed by an intramolecular enolate-driven palladium-cross coupling process with the corresponding (*Z*)-vinyl-iodide (**847**, *disconnection b*, this iodide could be made from (*E*)-2-butenal in two reaction vessels) which would be introduced through N_b-alkylation of the pyrrolidine-N_b nitrogen atom in the N_a-H, N_b-H tetracyclic ketone oxindole (**218**) with an 2-iodo-allylic bromide (*disconnection c*). The spiro junction and oxindole system would be constructed via a stereospecific one-pot oxidation/rearrangement of the N_a-H, N_b-H tetrahydro-β-carboline precursor (**217**) (*disconnection d*). Finally, tetracyclic ketone (**217**) would be made in large scale from commercially available D-(+)-tryptophan by an asymmetric Pictet–Spengler reaction (*disconnection f*) and Dieckmann-condensation (*disconnection e*) sequence, as discussed in the previous sections in this study (see Sections 8.1 and 8.2 for details).

Scheme 184



According to the retrosynthetic analysis depicted above (Scheme 184), the N_a-H, N_b-H substituted oxindole (**218**) was regiospecifically methylated at the indole N_a-pyrrolidine position [pK_a (DMSO): N_a-H ~ 18[271]; for N_b-H ~ 44[272]] with NaH in THF at 0 °C to effect complete conversion of the N_a-unsubstituted oxindole into the corresponding oxindolyl-sodium which was then treated with MeI in THF at 0 °C to provide the N_a-methylated oxindole (**849**) in 80% yield (Scheme 185).[270]

Scheme 185

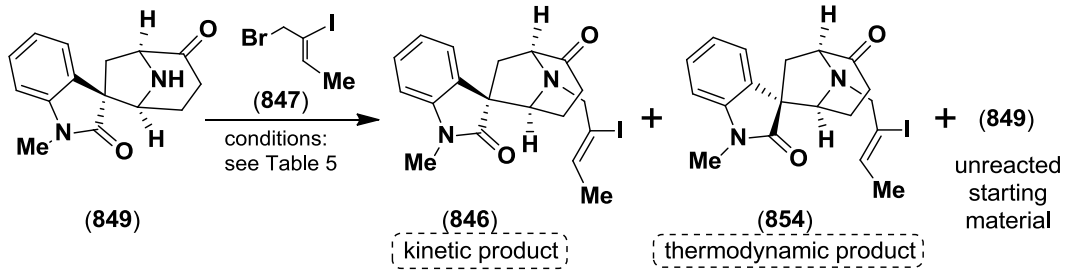


Next, the synthesis of the required (*Z*)-1-bromo-2-iodo-butene (**847**) was realized according to a reported 3-step sequence (in 2 pots) by Yang et al (Scheme 185).[273] This olefin (**847**) had been used many times in the synthesis of other natural products and in spite of the existing procedure (Ensley et al.)[274], the stereoselectivity and yield of this process were deemed unsatisfactory on a large scale (Scheme 185). About 5% of the (*E*)-isomeric olefin was obtained in this reaction and the (*Z*)-olefin had to be purified for a final yield of 74%. In 2005 Kraft et al.[273b] reported the α-iodination of α,β-unsaturated carbonyl compound (**848**) to offer the α-iodinated aldehyde (**853**) in almost quantitative yield (99%). This was an important advance for the large scale synthesis of olefin (**853**). Subsequent chemoselective reduction of aldehyde (**853**) with $NaBH_4$ in a THF-H_2O (9:1) solution gave the corresponding alcohol (**852**)[273c] in excellent yield (95%) and this was followed by bromination of the alcohol (**852**) with (0.4 equivalents) PBr_3 in diethyl ether to provide the desired (*Z*)-1-bromo-2-iodo-butene (**847**) [273d] in very high yield on up to 500 gram scale (Scheme 185). This procedure had many advantages over the one by Ensley et al., it was stereospecific, scalable, easier to handle, and cheaper.

With the key intermediates N_a-methyl, N_b-H tetracyclic ketone oxindole (**849**) and bromo butene (**847**) in hand, initial attempts to N_b-alkylate oxindole (**849**) under the conditions successfully employed for the parent system (indole system) with bromo butene [(**847**, 1.1 equivalents), K_2CO_3 (1.1 equivalents) as base, in dry THF at 23 °C for 24 hours[262b]] failed to provide the desired iodide (**846**). The starting material (**849**) was recovered intact even after treating the system at reflux for 24 hours (Table 5, entries 1 and 2). Replacement of the potassium carbonate base by diisoprpylethylamine [DIEA (Hünig's

base), 1.1 equivalents, under the same set of conditions as those shown in Table 5, entry 2] did not produce any improvements in the outcome of the reaction (Table 5, entry 3).

Table 5. Allylation at N_b reation



Entry	Solvent	Base (equiv.)	**847** (equiv.)	Temp. (°C)	Time (h)	**846**(%)	**854**(%)	**849**(%) (recovered)
1	THF	K_2CO_3(1.1)	1.1	23	24	0	0	100
2	THF	K_2CO_3(1.1)	1.1	66	24	0	0	100
3	THF	DIEA(1.1)	1.1	66	24	0	0	100
4	1,4-dioxane	DIEA(1.1)	1.1	60	24	0	0	100
5	DMF	DIEA(1.1)	1.1	60	4	complex mixture		
6	CH_3CN	DIEA(1.1)	1.1	82	12	40	40	15
7	**CH_3CN**	**DIEA(1.1)**	**1.1**	**82**	**48**	**5**	**90**	**5**
8	CH_3CN-CH_2Cl_2(9:1)	DIEA(1.1)	3	70	8	60	5	20
9	CH_3CN-CH_2Cl_2(1:1)	DIEA(1.1)	3	70	24	5	0	95
10	CH_2Cl_2	DIEA(1.1)	3	40	24	0	0	100
11	**neat**	**DIEA(2.5)**	**8**	**50**	**10**	**90**	**0**	**<5**

The use of 1,4-dioxane (Table 5, entry 4) as the reaction solvent, still showed no sign of allylation products after 24 hours at 60 °C. In contrast, the use of dimethylformamide (DMF) generated a complex mixture of very-high-polarity products when the reaction system was heated at 60 °C for 4 hours (Table 5, entry 5). It is well known that the N_b-nitrogen function of oxindoles in the alstonisine series is severely hindered to attack.[56] Interestingly, when oxindole (**849**) was treated with bromobutene (**847**, 1.1 equivalents), *N*,*N*-diisopropylethylamine (1.1 equivalents) in CH_3CN at reflux for 12 hours,[275] a

mixture of diastereomeric oxindoles at C-7 (**846**) and (**854**) in a 1:1 ratio (80% conversion) was obtained (Table 5, entry 6). When the time of heating was extended, this generated diastereomeric oxindole (**854**) in 90% yield and the desired product (**846**) in 5% yield (Table 5, entry 7). It was clear from the experimental data that oxindole (**854**) was the thermodinamically more stable oxindole under these conditions.

The polarity of the solvent system (acetonitrile and CH_2Cl_2) was then altered in order to study the diastereomeric ratio of (**846**) and (**854**) in the process (Table 5, entries 8 to 10). Tetracyclic oxindole (**846**) was first obtained as the major diastereomer with iodide (**847**, 3 equivalents) in a CH_3CN-CH_2Cl_2 (9:1) mixture at reflux (Table 5, entry 8) over 8 hours in moderate yield and 85% de. However, very little N_b-alkylation of N_b-H oxindole (**849**) occurred when the percentage of CH_2Cl_2 was elevated further to 50% in the solvent mixture (Table 5, entrie 9) and no alkylation products were isolated when pure CH_2Cl_2 was employed (Table 5, entrie 10).

Finally, the required N_a-methyl, N_b-allyl oxindole (**846**) was obtained as the sole diastereomer in high yield (90%) when N_a-methyl, N_b-H oxindole (**849**) was heated at 50 °C in a homogenous mixture, under solvent-free conditions, with 8 equivalents of bromo butene (**847**) and 2.5 equivalents of Hünig's base (Table 5, entry 11).

Careful selection of the experimental conditions permitted control of the diatereomeric outcome of the N_b-allylation as regards the configuration of the oxindole at C-7. This significant result provided an alternative route to access the (*R*)-(C-7)-isoalstonisine series or (*S*)-(C-7)-alstonisine series through an N_b-alkylation/oxindole-rearrangement reaction sequence. According to experimental observations during the progress of the N_b-allylation (analysis by TLC and NMR techniques), the oxindole (**854**) formed only after

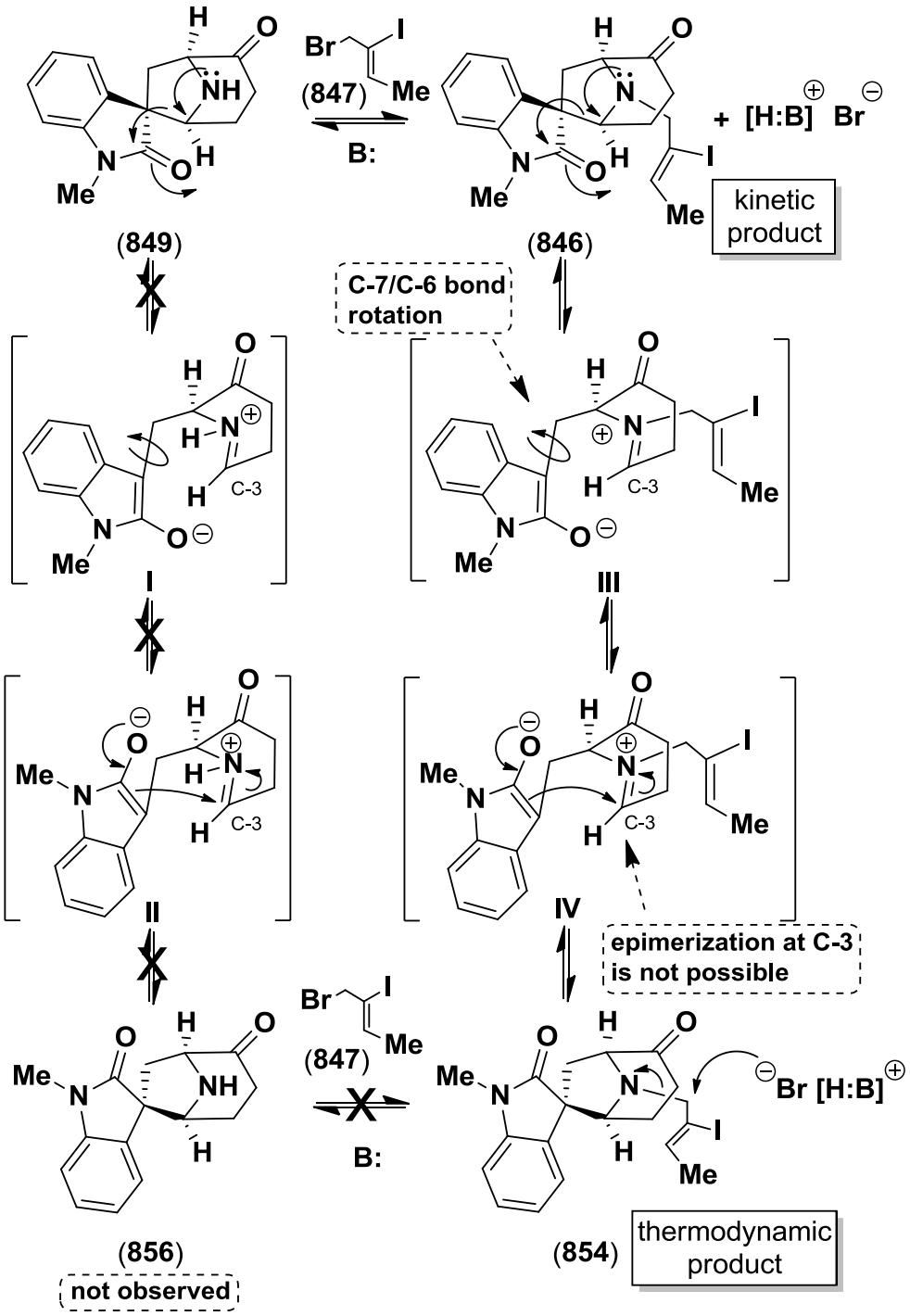
oxindole (**846**) had been observed in the reaction (Scheme 186); importantly, diastereomer (**856**) was not observed at any time under these conditions. Oxindole (**854**), therefore, was presumably generated only *via* an isomerization of oxindole (**846**). It was believed that, first, N_a-allylation of oxindole (**846**) took place and later the oxindole epimerization at C-7 occured. This proposed sequence of events (Scheme 186) was consistent with the fact that oxindole (**856**) was not detected in the reaction mixture, and also, oxindole (**854**) was always found after the allylation of oxindole (**849**) occurred.

Epimerization at C-3 had been observed in related oxindole systems; however, since the C/D ring fusion in (**846**) was *cis*, in the azabicyclo[3.2.1] system, isomerization was not favorable and the epimer at C-3 was not observed. Isomerization of related spirooxindole alkaloids was first reported by Wenkert et al. in 1959[261c] and has been employed generally to provide structural proof of diastereomeric oxindoles (at C-7) isolated as natural products. Recently, rigorous kinetic studies on this process were reported by Laus et al.[261a,261b]

As part of the structural proof of oxindoles (**846**) and (**854**), and also as part of later efforts to synthesize (*R*)-(C-7)-isoalstonisine-related oxindole alkaloids, N_b-allyl diastereomer (**854**) was synthesized through a different route from oxindole (**216**, Scheme 187). In this vein, oxindole (**216**) was first successfully methylated at the indole N_a-position with NaH and MeI in THF at 0 °C to provide diastereomeric oxindole (**855**) in 87% yield. Next, removal of the benzyl group at the N_b-nitrogen atom of (**855**) under catalytic reductive conditions used for the parent system was attempted.

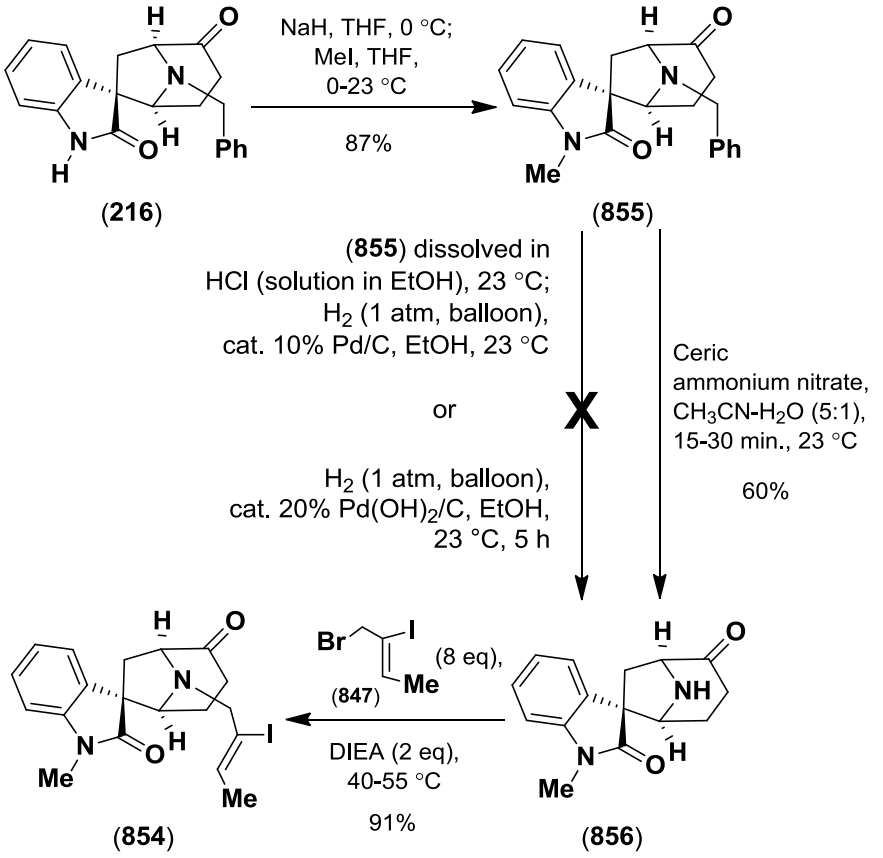
Scheme 186

Proposed reaction mechanism



The use of H_2 (1 atmosphere, balloon) in the presence of (10%) Pd/C catalyst on the previously formed hydrochloride salt of oxindole (**855**) did not have the intended effect and the starting oxindole was recovered intact (these reductive conditions were used for the N_b-debenzylation in the indole system,[55b] Scheme 187).

Scheme 187



The same outcome was observed when hydrogenolysis conditions with 2 equivalents of Pearlman's catalysist [$Pd(OH)_2/C$] and H_2 (1 atmosphere) were used (these were conditions used by Wearing et al.[56a,56b] in the final stage of the alstonisine synthesis).

However, rapid debenzylation of (**855**) (less than 30 minutes) under oxidative conditions with ceric ammoniun nitrate (CAN) in a CH_3CN-H_2O (5:1) solvent mixture at 23 °C afforded N_b-H oxindole (**856**) in 60% yield (Scheme 187).[276] Prolonged reaction times led to decomposition of the product, therefore careful monitoring of the process was required. Subsequent alkylation of the N_b-H pyrrolidine nitrogen function with allylic bromide (**847**) under solvent-free conditions (depicted in Table 5, entry 11), provided oxindole (**854**) in 91% yield.

The absolute configuration of diastereomeric oxindoles (**846**) and (**854**) was further confirmed by X-ray analysis (ORTEP drawings of (**846**) and (**854**) are shown in Figures 22 and 23, respectively). The structures of both oxindoles were now unequivocally confirmed and were diastereomeric at C-7 as expected.[62,261]

To complete the synthesis of (–)-affinisine oxindole (**24**), ketone (**846**) was converted into the desired pentacyclic ketone (**857**) in 65% yield (Scheme 188) *via* an intramolecular palladium-catalyzed enolate-mediated cross-coupling reaction, with conditions developed by Solé and Bonjoch et al., (10 mol%) $Pd(PPh_3)_4$/$PhONa•3H_2O$ (2.5 equivalents) in THF (previously freeze-pump-thaw degassed, 3-5 cycles, to remove all the oxygen from the solution) at reflux for 2 hours.[277] The use of a weak base was thought to be of critical importance to get access to the desired pentacyclic oxindole (**857**). The steric outcome of this reaction was again confirmed by X-ray analysis (Figure 24), especially important was the fact that no oxindole isomerization occurred during this process. However, during our studies on the total synthesis of isoalstonisine described in later sections, it was found that the use of (40 mol%) of Pd_2dba_3 as a palladium source, sodium bis(trimethylsilyl)amide (NaHMDS, 2 equivalents) in freeze-pump-thaw

degassed THF at room temperature (23 °C) significally improved the yield of the reaction to a 80% of pentacyclic ketone (**857**) after purification by chromatography. To the best of our knowledge, this was the first reported observation of this type of transformation occurring at room temperature on these type of macroline/sarpagine systems (Scheme 188).

The first examples of such important palladium-catalyzed coupling reactions involving vinyl halides were reported by Piers et al. at the beginning of the 1990s, when he described the intramolecular alkenylation of ketone enolates and then applied the reaction to the synthesis of the diterpenoid crinipellin B.[278] Some years later, another example of this coupling process was reported by Cook et al. in the context of the total synthesis of the alkaloid (+)-vellosimine,[262c] after which Bonjoch, Solé et al. reported their studies on the synthesis of nitrogen heterocycles by the Pd(0)-catalyzed intramolecular coupling of amino-tethered vinyl halides and ketone enolates.[277] Later on Buchwald described the intermolecular vinylation of ketone enolates.[279]

Scheme 188

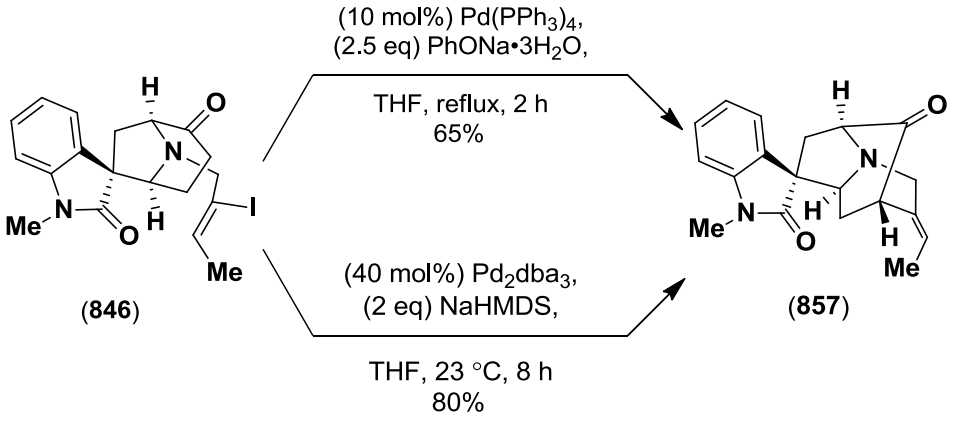


Figure 22. ORTEP drawing of N_b-allyl tetracyclicketone oxindole (**846**)

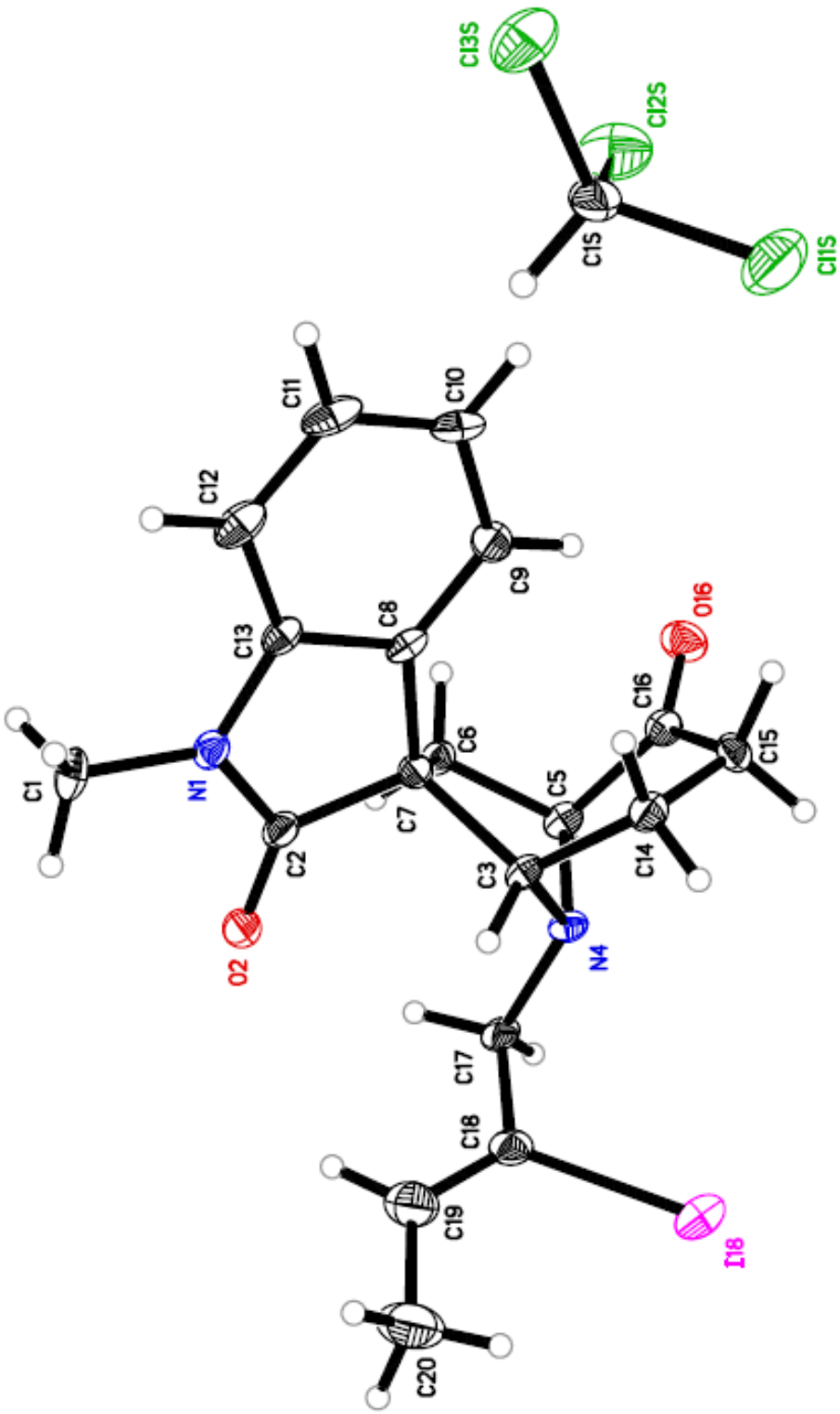
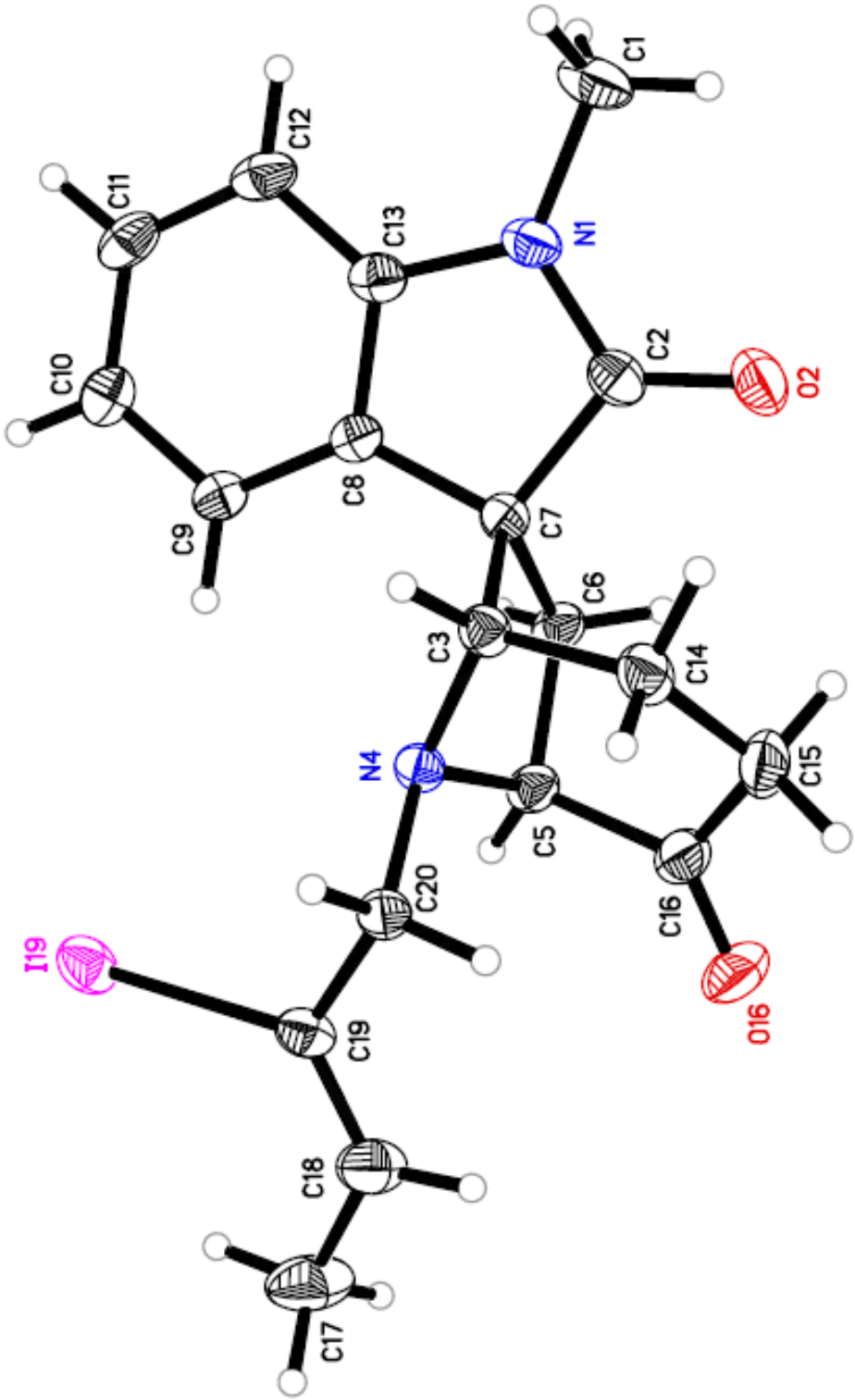


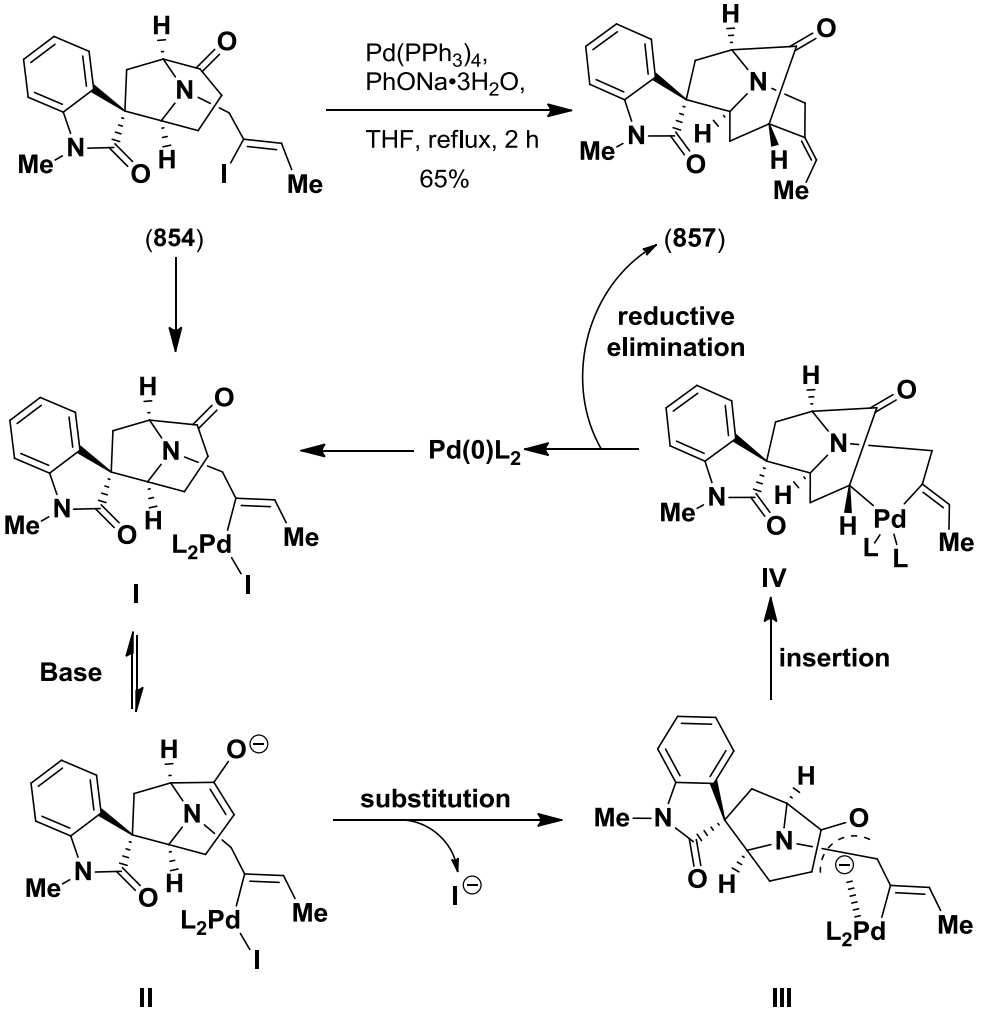
Figure 23. ORTEP drawing of N_b-allyl tetracyclicketone oxindole (**854**)



Initially, the application of reaction conditions developed in Milwaukee by Yu et al., (10 mol%) $Pd(OAc)_2/PPh_3$ (0.2 equivalents)/Bu_4NBr/K_2CO_3 in DMF-H_2O (9:1), at 70 °C for 5 hours and the ones developed later by Yin et al., (5 mol%) $Pd_2(dba)_3$/(7 mol%) DPEPhos/NaO*t*Bu (1.5 equivalents) in THF at reflux for 5 hours,[280] did not provide the expected coupling product in the oxindole series.[262c] The use of Piers et al. coupling conditions with (20 mol%) $Pd(PPh_3)_4$/KO*t*Bu in *t*BuOH-THF at room temperature or 60 °C also failed to generate the desired pentacyclic ketone oxindole.[278] It was believed that side reactions such as the elimination of HI led to alkynes which may have undergone subsequent coupling with the starting vinyl halides to afford dimeric compounds, and dealkylation at the N_b-nitrogen atom which resulted in very complex mixture of products. These side reactions were mainly attributed to the use of a strong base.[277] Nakada et al. reported a different set of conditions[281] for the palladium catalyzed intramolecular α-alkenylation during their synthetic studies on the taxane skeleton: (30 mol%) $Pd(PPh_3)_4$/PhOK (3 equivalents) in toluene at 100 °C for 2 hours. Under these, the expected oxindole coupling product was obtained in low yield (20%).

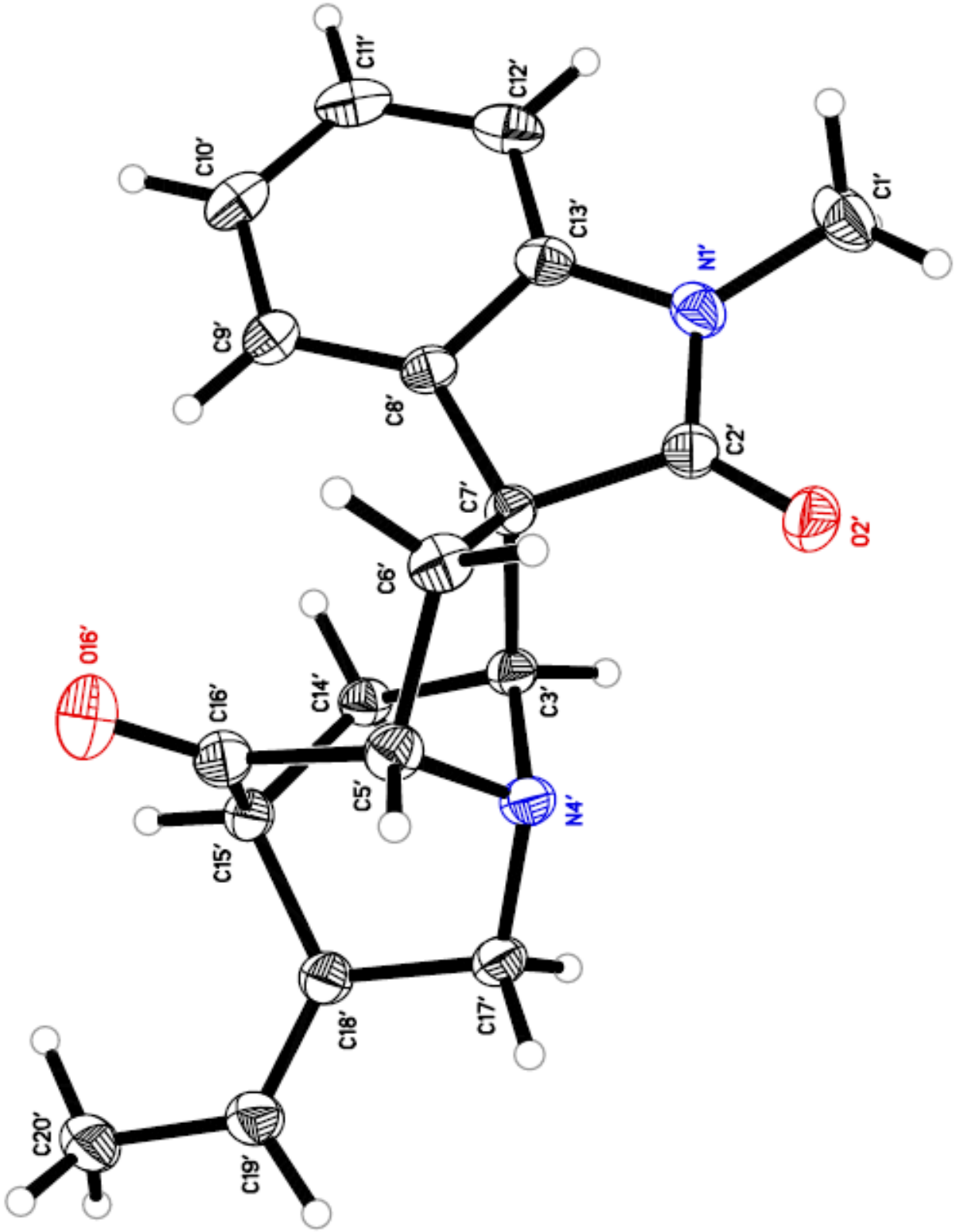
A plausible catalytic cycle for this enolate-driven palladium catalyzed α-vinylation reaction was proposed, which is illustrated in Scheme 189. The active $Pd(0)L_2$ species could undergo oxidative addition with the vinyl iodide (**846**) to form a vinyl palladium (II) iodide complex **I**. The enolate of the ketone **II** could then displace the coordinated iodide from the Pd to afford a Pd(II)-π complex **III** which then proceeded to the insertion phase to form a Pd-C bond complex **IV** (Scheme 189). Finally, reductive elimination of the carbon-bound Pd(II) intermediate would furnish the desired olefin (**857**), accompanied by regeneration of the active $Pd(0)L_2$ species.

Scheme 189



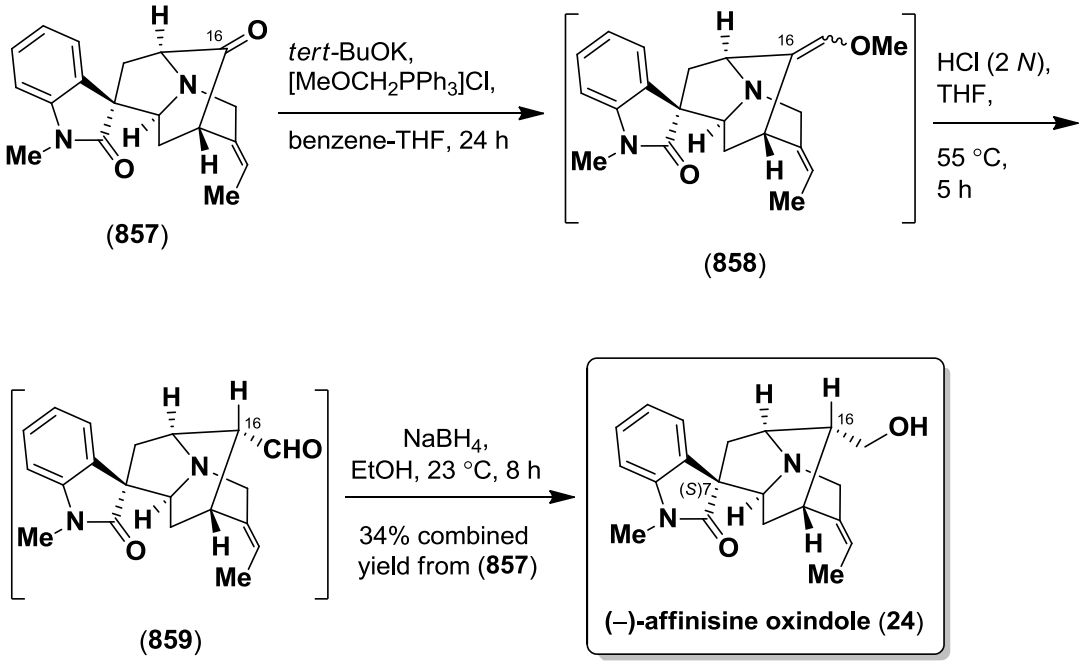
With easy access to the C-7-(*S*) pentacyclic ketone oxindole (**857**); consequently, it was subjected to a one carbon homologation process. The homologation of the carbonyl group at C-16 to give the C-17 functionalized aldehyde was realized by a simple Wittig-olefination reaction with (methoxymethyl) triphenyl-phosphonium chloride and anhydrous *tert*-BuOK in dry benzene with oxindole (**857**).

Figure 24. ORTEP drawing of pentacyclic ketone oxindole (**857**)



The mixture of stereoisomeric enol ethers (**858**) which formed was hydrolyzed under acidic conditions to afford the thermodynamically more stable α-epimeric aldehyde (**859**) as the sole diastereomer (Scheme 190).[268] Several attemps to purify aldehyde (**859**) by chromatography (using silica gel, as well as basic or neutral alumina) were unsuccesful. In the last stage of the total synthesis, the crude aldehyde was converted into its corresponding primary alcohol by hydride reduction with $NaBH_4$ in EtOH at room temperature to obtain the desired synthetic (–)-affinisine oxindole (**24**) in 34% overall yield and in a **1 pot** process from ketone (**857**, Scheme 190).[281]

Scheme 190



In conclusion, the first stereospecific total synthesis of the sarpagine-related (–)-affinisne oxindole (**24**) was successfully accomplished in 8 reaction vessels in a 10% overall yield from commercially available D-(+)-tryptophan.[281]

The spectral ^{1}H NMR (see Table 6 below) and ^{13}C NMR (see Table 7 below) data as well as the IR spectrum (dry film on KBr) 3375, 1711 cm^{-1} [literature[14] IR (dry film) 3384, 1712 cm^{-1}, and also the physical properties including the specific optical rotation $[\alpha]^{23}_{D}$ = –66° (*c* 0.3, $CHCl_3$) [literature[14] $[\alpha]^{23}_{D}$ = –70° (*c* 0.06, $CHCl_3$)]; and HRMS were in excellent agreement with those published in the literature by Kam et al.[14,281]

Table 6. Comparison of the ^{1}H NMR spectral data for synthetic (–)-affinisine oxindole (**24**)[281] to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[14]

	Proton NMR	
Position	Natural sample[14]	Synthetic sample (**24**)[281]
*N*1-CH_3	3.21 s	3.21 s
2	-	-
3	3.36 dd (10,2)	3.37 dd (10,2)
4	-	-
5	3.31 dd (6,3)	3.31 dd (6,3)
6	1.81 d (13) 2.79 dd (13,6)	1.82 d (13) 2.77 dd (13,6)
7	-	-
8	-	-
9	7.37 br d (8)	7.37 br d (8)
10	7.10 td (8,1)	7.09 td (8,1)

11	7.32 td (8,1)	7.31 td (8,1)
12	6.84 br d (8)	6.83 br d (8)
14	1.57 ddd (14,10,2) 2.18 ddd (14,4,2)	1.56 ddd (14,10,2) 2.18 ddd (14,4,2)
15	2.89 br s	2.88 br s
16	2.05 m	2.05 m
17	3.63 m (2H)	3.62 m (2H)
18	1.61 dt (7,2)	1.61 dt (7,2)
19	5.32 br q (7)	5.32 qt (7,2)
21	3.78 m (2H)	3.78 m (2H)

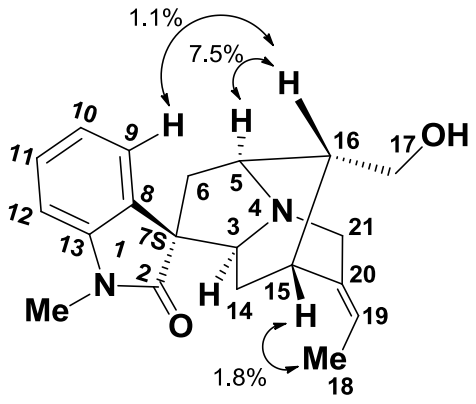
Table 7. Comparison of the ^{13}C NMR spectral data for synthetic (–)-affinisine oxindole (**24**)[281] to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[14]

	Carbon NMR	
Position	Natural sample[14]	Synthetic sample (**24**)[281]
*N*1-CH_3	26.6	26.5
2	181.4	181.8
3	63.0	62.8
4	-	-
5	59.3	59.1
6	44.4	44.6
7	56.4	56.7
8	129.9	130.4
9	126.7	126.6

10	121.8	121.5
11	128.4	128.1
12	108.0	107.8
14	28.7	28.8
15	26.3	26.1
16	48.0	47.9
17	65.5	65.7
18	12.5	12.4
19	115.2	114.8
21	48.9	48.8

Finally, selected NOE NMR experiments were then carried out on the synthetic (–)-affinisine oxindole (**24**), as shown in Figure 25.

Figure 25. NOE NMR, affinisine oxindole



C7-(*S*) series (–)-affinisine oxindole (24)

Irradiation of H-16 effected enhancement of H-6 by 7.5% and H-9 by 1.1% and *vice versa*. which would not have been observed in the other diastereomer at C-7, thus confirming the proposed configuration of the spiro center in (7*S*)-(–)-affinisine oxindole (**24**) as the same in the one proposed earlier by Kam et al.[14] Also, the geometry of the double bond was confirmed to be (*E*) by irradiating the CH_3 protons in the ^{1}H NMR signal and observing enhancement of the H-15 ^{1}H NMR signal.

As further structural proof, the oxindole epimeric at C-7 [*i.e.*, (*R*)-C-7] of (–)-affinisine oxindole (**24**) was also synthesized in a enantiospecific fashion during these studies, and its structure was fully characterized and confirmed by X-ray crystallography (see later sections in this work) which permitted the correlation of same signals to affinisine oxindole (**24**) here.[281]

8.4) Enantionspecific total synthesis of the C7-(*R*) series oxindole alkaloid (+)-isoalstonisine (27)

The successful first enantiospecific, diastereospecific total synthesis of the sarpagine related **C7-(*S*) series** (–)-affinisine oxindole (**24**) from D-(+)-tryptophan, *via* the designed synthetic approach discussed in Section 7 and Scheme 176, prompted us to demostrate the generality of its application by attempting to synthesize a **C7-(*R*) series** oxindole alkaloid–(+)-isoalstonisine (**27**) also from commercially available D-(+)-tryptophan.

The macroline related oxindole alkaloid isoalstonisine (**27**) was first obtained from the ground leaves of the Malayan tree *Alstonia angustifolia* var. *latifolia* in 2000 by Kam et

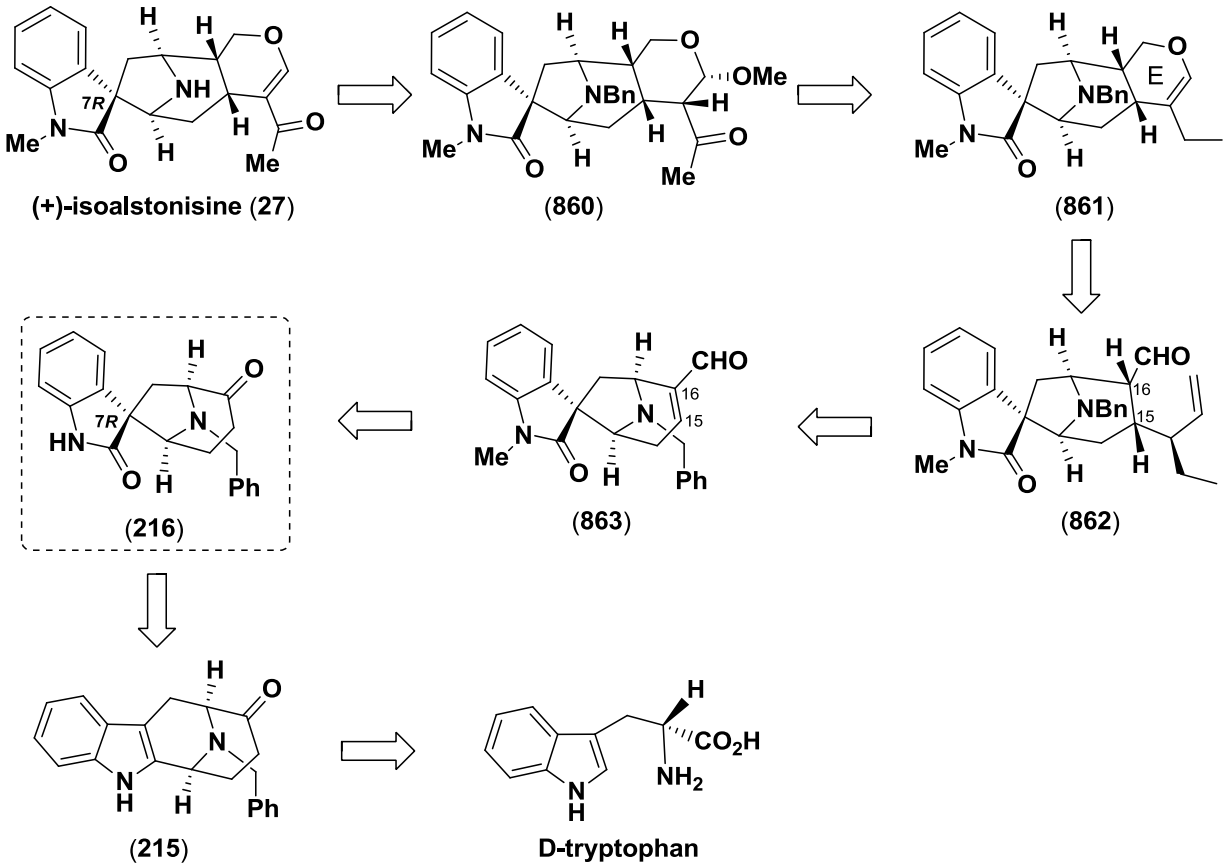
al.[12,14] It represented the first time that a C7-(*R*) series sarpagine/macroline oxindole alkaloid was isolated from plants [C7-(*R*) (–)-macrogentine (**31**) was also isolated during this work]. The strucutral elucidation, by Kam et al., was performed on the basis of mass spectrometry; IR and UV spectroscopic studies; and also ^{1}H, ^{13}C, and NOE NMR techniques. In order to confirm the assigned relative spatial arrangement of atoms in the structure of isoalstonisine (**27**), computational studies were carried out by Kam et al. (MM2, CS Chem3D Pro) in which the major and diagnostic differences in the observed NOE's of alstonisine (**8**, used for comparison) and isoalstonisine (**27**) were consistent with the predicted distances in the energy minimized strucutres.[12] The configuration of the spirocyclic center C-7 was, initially, incorrectly determined to be (*S*). The initial assignation (7*R*) was presumably an incorrect application of the Cahn–Ingold–Prelog priority rules. Later, Kam et al. corrected the C-7 configuration and labeled it (*R*).[18]

8.4.1) First enantiospecific approach to the total synthesis of (+)-isoalstonisine (27)

According to the general synthetic strategy depicted in Section 7 (Scheme176), the (*R*)-[C-7] series of oxindole alkaloids would be generated from a common intermediate, N_a-H, N_b-benzyl tetracyclic oxindole (**216**), which in turn would be formed from commercially available D-(+)-tryptophan in a highly enantiomeric and diastereomeric fashion *via* a *tert*-butyl hypochlorite promoted oxidation-rerrangement sequence of an N_a-H, **N_b-benzyl** tetrahydro-*β*-carboline intermediate (**215**, Scheme 191). The latter important carboline (**215**) would be synthesized from D-(+)-tryptophan through an improved, 1-pot procedure involving the (1) monobenzylation at the N_b-nitrogen atom (by reductive

amination); (2) asymmetric Pictet–Spengler reaction and (3) Dieckmann cyclization followed by decarboxylation in high yield. More specifically, isoalstonisine (**27**) could arise from the concomitant removal of the N_b-benzyl protecting group and reduction of the mixed acetal in pentacyclic oxindole (**860**) by catalytic hydrogenation (Scheme 191).

Scheme 191



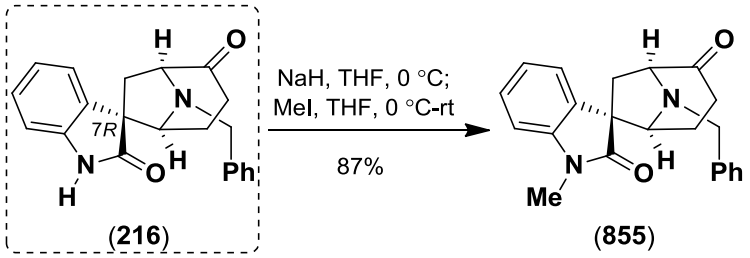
The key intermediate enol ether (**861**) may be obtained by a process which would involve regioselective oxyselenation. In addition, the synthesis of the E-ring enol-ether in oxindole (**861**) could be approached from the olefinic aldehyde (**862**) by oxidative

cleavage of the olefinic unit (latent aldehyde). In order to functionalize the C-15 position in (**863**) and generate tetracyclic aldehyde (**862**), a barium-mediated 1,2-addition followed by an diastereoselective anionic oxy–Cope rearrangement could be used. The C-15/C-16 α,β-unsaturated aldehyde (**863**) would be prepared from N_a-H, N_b-benzyl tetracyclic oxindole (**216**) via a spirooxirane phenylsulfoxide process by a modified method of Satoh et al. (Scheme 191).[137]

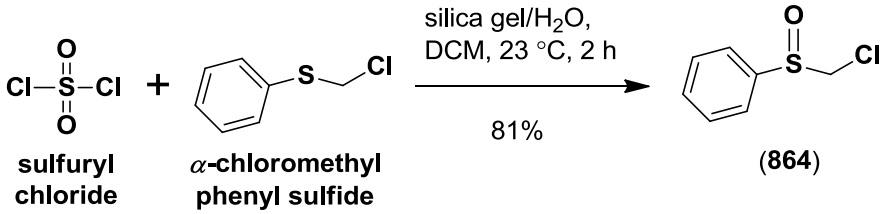
This first approach to isoalstonisine (**27**) was based on the excellent work by Wearing et al. in the first stereospecific total synthesis of the macroline related oxindole (7*S*)-(+)-alstonisine (**8**, see Section 4 for complete description of Wearing's synthesis).[56,267] The key difference between these two studies was that the oxindole and spiro center were generated in a much earlier stage in the route than that in the case of Wearing et al.

To this end the synthesis began with the regiospecific preparation of N_a-methyl, N_b-benzyl tetracyclic ketone (**855**) from the key (7*S*)-oxindole (**216**) in high yield by treating it with NaH in THF, followed by the addition of MeI as discussed before (Scheme 192 and also Section 8.3, Scheme 187). Then, the required α-chloromethyl phenyl sulfoxide (**864**) was prepared according to a reported procedure by Masuda et al. in 2 hours and high yield by oxidation of the corresponding sulfide with SO_2Cl_2 in the presence of SiO_2-H_2O in DCM (Scheme 192).[283] It was known that sulfuryl chloride reacted easily with methyl phenyl sulfide to give chloromethyl phenyl sulfide in high yields. Masuda et al. had found that, if this reaction was carried out in the presence of a small amount of wet silica gel, methyl phenyl sulfoxide was produced in an almost quantitative yield, without any formation of chloromethyl phenyl sulfide or the corresponding sulfone, due to overoxidation, which were difficult to remove from the reaction mixture.[283,282,267]

Scheme 192



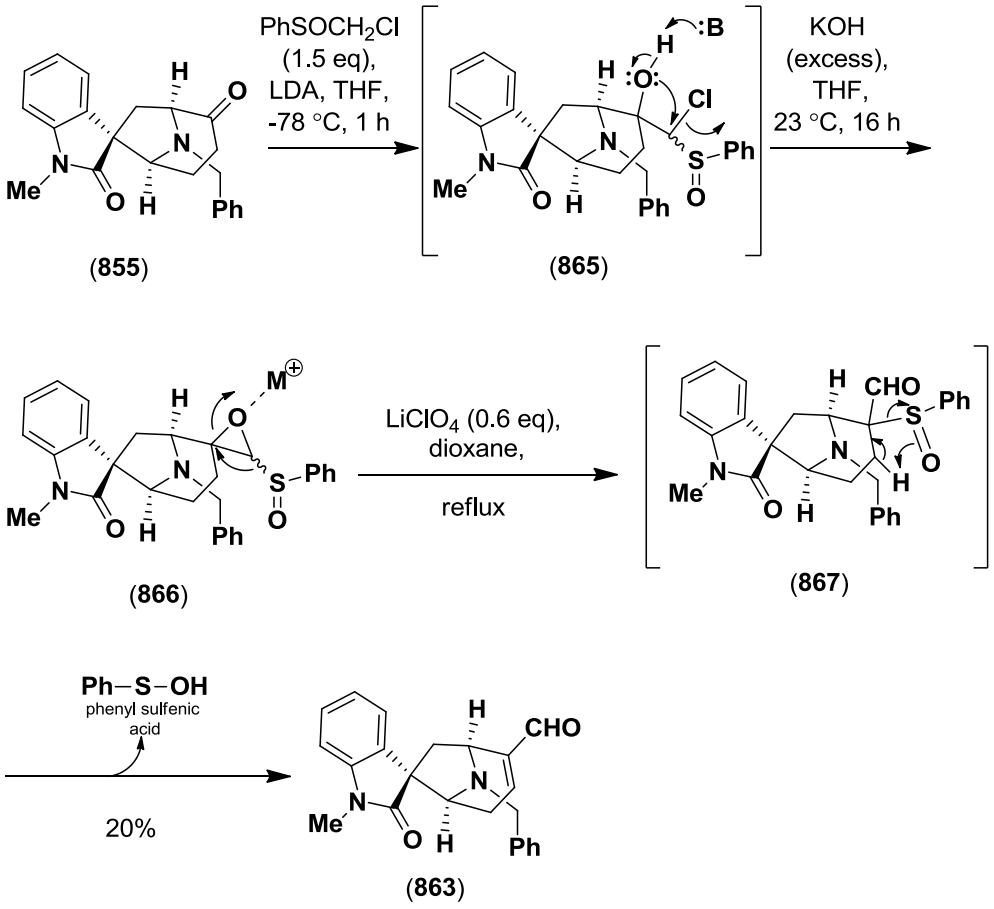
Preparation of α-chloromethyl phenyl sulfoxide (864)



Initially, the application of exactly the same experimental conditions used by Wearing et al. in the parent system (indole) were tested with (7*R*)-N_a-methyl, N_b-benzyl tetracyclic ketone oxindole (**855**).[267] Accordingly, in the first step of the ketone to enone homologation, formation of α-chloromethlyphenyl sulfoxide anion (1.5 equivalents) was realized with the use of a strong base, lithium diisopropylamide (LDA, formed *in situ* with diisopropylamine and *n*-butyl lithium), in THF at –78 °C (Scheme 193). After 20 minutes, a solution of oxindole (**855**, 1 equivalent) in THF was added dropwise to the reaction vessel (stirring was continued for 1 hour at –78 °C) to permit the regioselective 1,2-attack on the carbonyl group of the ketone to furnish chlorohydrin (**865**). In the second stage, the system was allowed to reach room temperature and an aqueous solution of KOH (excess) was added to the mixture to give the spiro oxirane (**866**). Finally, an aqueous workup was executed after 16 hours, and to the residue which resulted, was

added dry dioxane and catalytic lithium perchlorate ($LiClO_4$, 0.6 equivalents). The latter slurry was heated at 100 °C for 8 hours. The described protocol provided a complex mixture of products containing the expected α,β-unsaturated aldehyde (**863**) in very low yield (10%) after column chromatography (Scheme 193).

Scheme 193

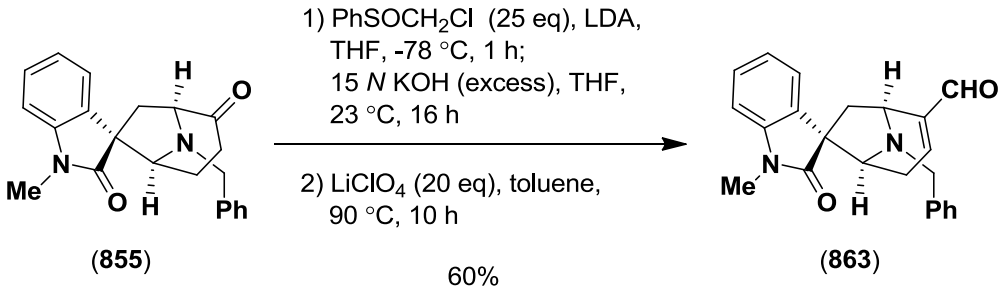


The mechanism for the formation of the α,β-unsaturated aldehyde is illustrated in Scheme 193. The Lewis acid catalyzed oxirane rearrangement was followed by a

sulfoxide mediated *syn* elimination to generate (**867**), according to the procedures of Taber et al.[285] and Satoh et al.[284] The α,β-unsaturated aldehyde (**863**, greater than 99% ee) contained the desired absolute configuration at C-7 to serve as key intermediate for the total synthesis of isoalstonisine (**27**) and related alkaloids.

A modification of the existing procedure for the parent system was required in order to improve the yield of the α,β-unsaturated aldehyde (**863**). In this vein it was found that the use of a large excess of $PhSOCH_2Cl$ anion (25 equivalents) allowed better access to the spiro oxirane oxindole (**866**). Interestingly, it was also realized that the reaction of the spiro oxirane (**866**) with 10 equivalents of $LiClO_4$, in toluene as the solvent on heating at 90 °C were necessary changes in the protocol. The use of excess reagents was believed to be due to a more sterically hindered access to the reaction site in the oxindole system *versus* its corresponding indole. In this way, the yield was improved to 60%, in a 2-pot sequence after purification of α,β-unsaturated aldehyde (**863**, Scheme 194). It is well known from previous work in Milwaukee that the oxindole intermediates are more sterically conjested than the parent indoles.

Scheme 194

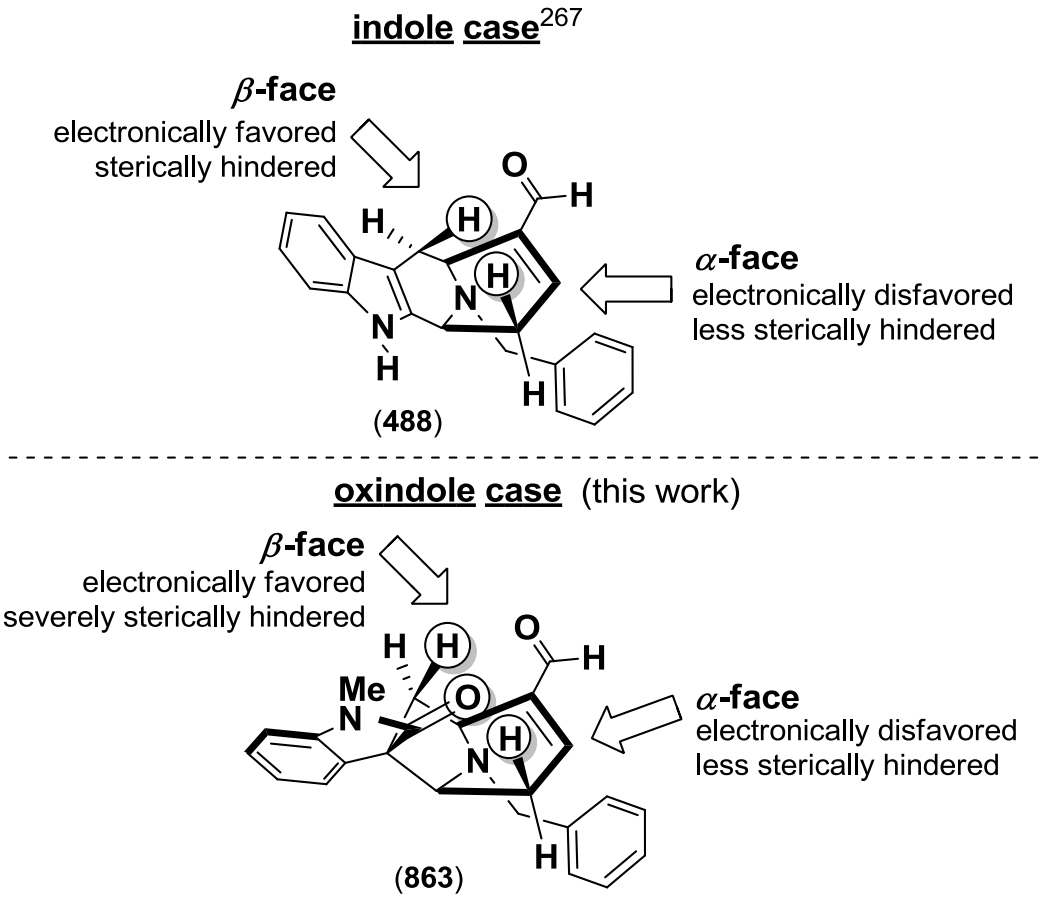


(**855**) (**863**)

With the α,β-unsaturated tetracyclic aldehyde (**863**) in hand, the next stage, according to the retrosynthetic analysis described in Scheme 191, was the functionalization of the C-15 position in a stereocontrolled fashion by an 1,4-addition of a substituted allylic moiety.

It was of importance at this point to mention the earlier precedents with regards to similar reactions in the parent indole systems. In the case of the parent (indole) system, several attempts had been made previously to effect the 1,4-addition (Michael addition) to enone (**488**, Figure 26) but unfortunately all met with failure[286,287,288] or low yield and diastereoselectivity.[282] The inability to intermolecularly functionalize C-15 of this tetracyclic system (**488**) was believed to be due to steric constraints (at C-15) inherent in the tetracyclic skeleton as well as stereoelectronic effects (Figure 26).[267] As shown in Figure 26, the spatial approximation of a nucleophilic agent to the C-15 carbon atom from the β-face (top face, axial attack) was electronically favored, but severely hindered by the H-H diaxial interactions with the indolomethylene bridge, while approach from the less hindered α-face (bottom face) of the tetracycle was electronically disfavored. The oxindole case was added in Figure 26, for comparison, and from a careful study of molecular models it was easy to see that the β-face in oxindole (**863**) was even more hindered than that of the parent system due to the presence of the oxindole carbonyl group effectivelly blocking the approaching path of a potential nucleophile towards C-15.

Figure 26. Orientation for the attack



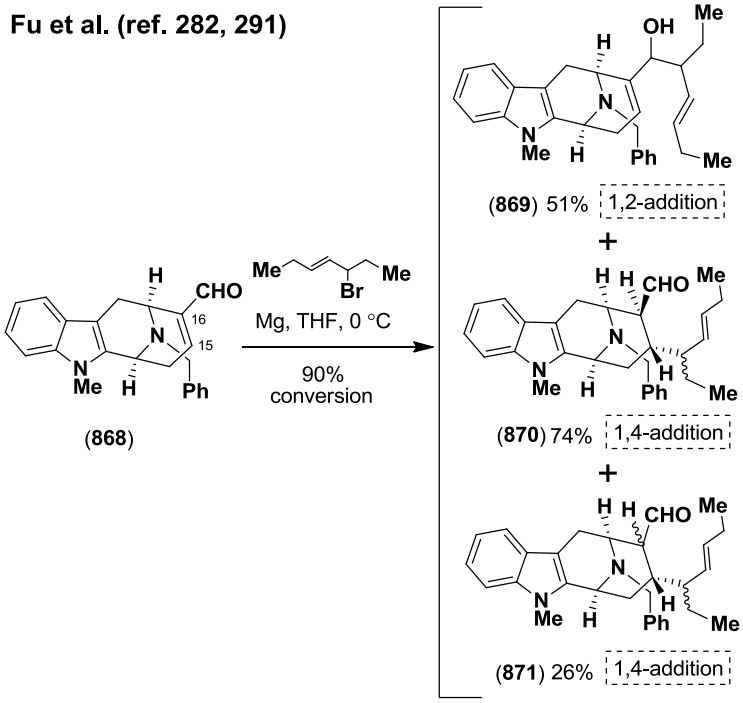
Therefore, in order to overcome the steric and electronic constraints mentioned above, the execution of an intramolecular approach to functionalize the parent tetracyclic system at C-15 was envisaged. In fact, an intramolecular [3,3]-sigmatropic rearrangement had been employed to introduce the four-carbon side chain at C-15 and generate the basic carbon skeleton for the synthesis of alstonerine, macroline and anhydromacrosalhine-methine while the diastereo selective anionic oxy–Cope rearrangement had been utilized for the total synthesis of ajmaline,[138,289] talpinine, talcarpine[55b] and suaveoline.[282,291]

In 1992, Fu et al. established the addition of a primary Grignard reagent, pent-2-enyl magnesium bromide, which was available from 1-bromo-2-pentene, to the α,β-unsaturated aldehyde (**868**) provided, the expected, but undesired alcohol (Scheme 195).[282,291] This resulted from allylic rearrangement of the allyl Grignard reagent (attack at the γ-position).[290] Later, Wearing et al. successfully accomplished the C-15 functionalization of tetracyclic ketone (**488**) in high yield as discussed in Section 4 (Scheme 85 and also Scheme 196).

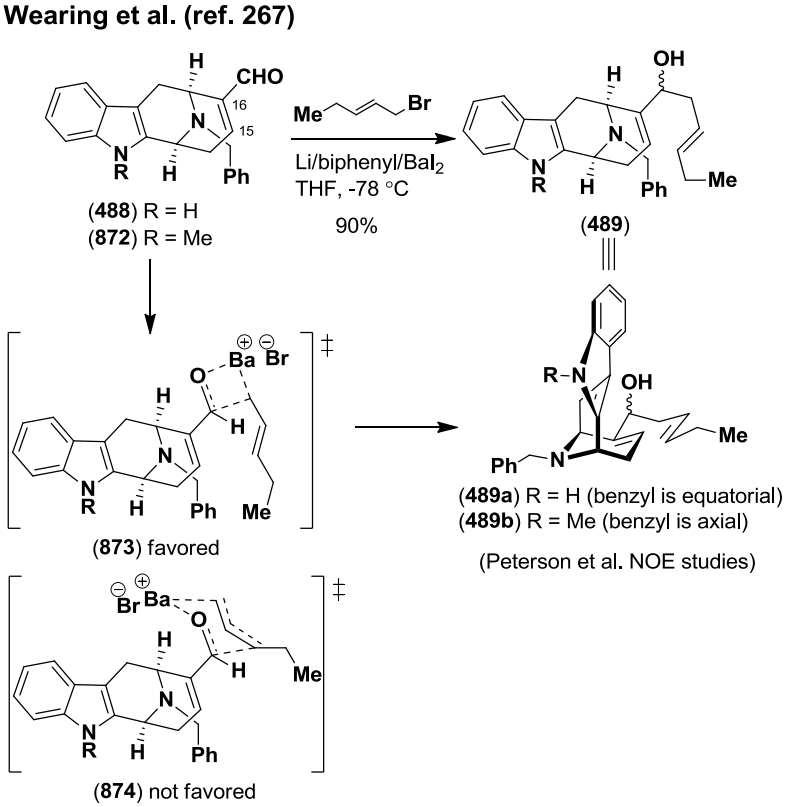
In order to avoid allylic rearrangement of the allyl Grignard reagent prepared from 1-bromo-2-pentene, a barium-mediated 1,2-addition was chosen as an approach to functionalize the C-15 position of the α,β-unsaturated aldehydes (**488** and **872**), as shown in Scheme 196. Since allylic substituted barium reagents had been reported by Yamamoto et al. to react with the carbonyl group to yield highly regioselective α-addition of the carbanion without allylic rearrangement,[139] this approach was examined with the α,β-unsaturated aldehydes (**488** and **872**). When pure *trans*-1-bromo-2-pentene was stirred with Rieke barium under the normal reaction conditions (–78 °C) of Yamamoto,[139] none of the desired olefinic alcohol (**489**) was observed. However, execution of a modified procedure[138,268] of the original report[139] in a fashion similar to a

Barbier–Grignard process provided the individual allylic alcohols (**489a** and **489b**) in high yield in both the N_a-methyl and N_a-H series (Scheme 196).

Scheme 195



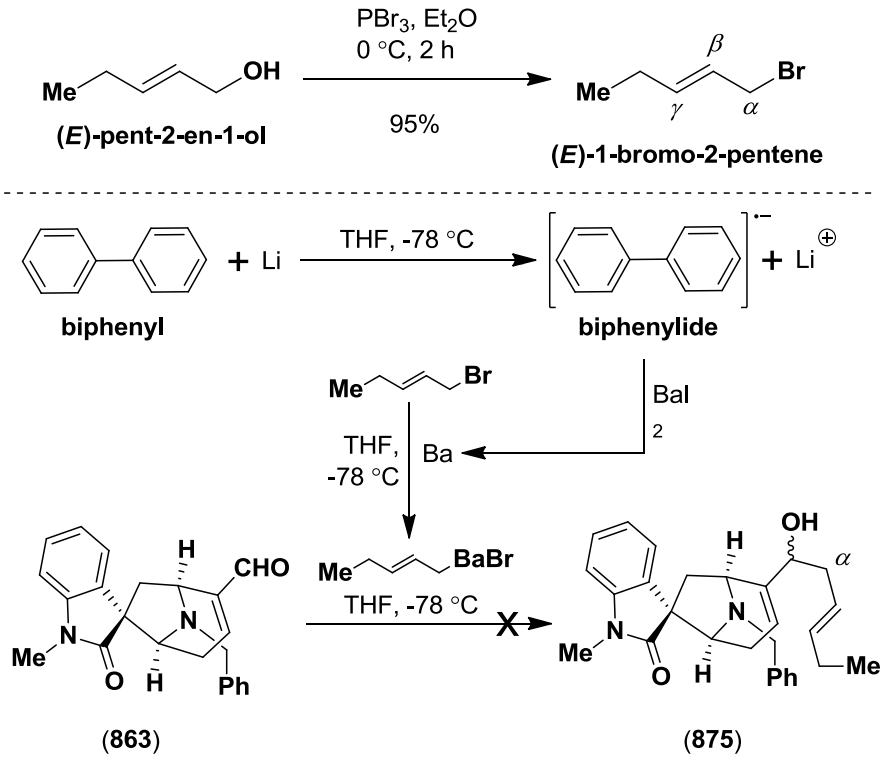
Scheme 196



This modified procedure of the barium-mediated 1,2-addition of the *cis*-1-bromo-2-pentene to N_a-methyl, α,β-unsaturated aldehyde (**872**) was first successfully executed by Li et al. (Scheme 196).[138] It was later found by Wang et al.[268] that addition of a mixture of *trans*-1-bromo-2-pentene and aldehyde (**488**, premixed at −78 °C) to freshly prepared barium metal at −78 °C, analogous to a Barbier–Grignard process, provided a 90% yield of the desired homoallylic alcohol (**489a**). This occurred without allylic rearrangement to provide the allylic alcohol (**489a**) as a mixture of two isomers in a ratio of 4:1. The reason for the high regioselectivity of the addition of the barium reagent *via* the α-carbon atom in this Barbier–Grignard process was believed to be due to the "unusually long barium-carbon bond (2.76-2.88 Å).[292,293] For the allylic magnesium stabilized carbanion (or zinc, and calcium), the formation of a six-membered cyclic transition state would lead to the γ-substituted product. This was the product of allylic rearrangement of the Grignard reagent. Presumably, for the barium stabilized allylic carbanion the unusually long barium-carbon bond retarded the formation of the six-membered cyclic transition state (**874**), in favor of a four-membered cyclic transition state (**873**), the one necessary for the α-selective allylation (Scheme 196). Yamamoto had previously described this model as one possible explanation for the unique regioselectivity of the barium reagent.[293]

In order to test Wearing's conditions for the 1,2-addition to the aldehyde (Scheme 196) in the oxindole system, first, the required *trans*-1-bromo-2-pentene was easily prepared (in 95% yield) by reacting *trans*-1-hydroxy-2-pentene with phosphorus tribromide (PBr_3) in dry diethyl ether at 0 °C for 2 hours (Scheme 197).

Scheme 197



The barium-mediated α-selective 1,2-addition protocol was then executed with N_a-methyl, N_b-benzyl tetracyclic oxindole (**863**). Reaction of 4 equivalents of highly reactive barium (Rieke et al.[294] method for reducing barium iodide with lithium biphenylide) formed *in situ* in THF with a solution containing oxindole (**863**, 1 equivalent) and the allyl bromide (4.3 equivalents) in THF at −78 °C for 2 hours provided a complex mixture in which the expected α-selective 1,2-addition product (**875**) could not be detected (Scheme 197, see experimental section for details about the procedure). The use of 1.1 equivalents of activated barium and 1.2 equivalents of the allyl bromide at −78 °C for 1 hour underwent a similar outcome.

It was believed that the integrity of the oxindole carbonyl was being compromised which in turn could lead to further decomposition of the starting material.

Given the low yield observed in the preparation of tetracyclic ketone oxindole (**863**) and the difficulties encountered during the attempted synthesis of the 1,2-addition-product alcohol (**875**), the work on this route was suspended and our synthetic efforts were focused on a different route to synthesize the E-ring of isoalstonisine (**27**) which is described in the following Section 8.4.2.

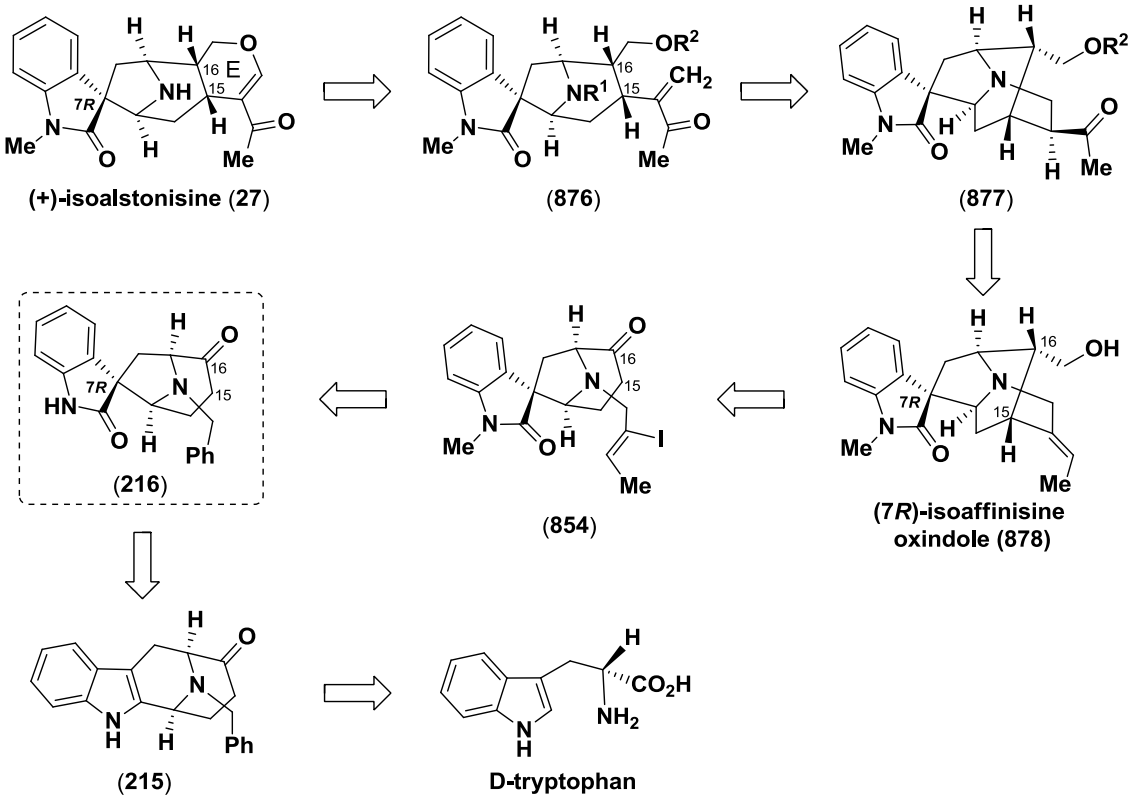
8.4.2) Enantiospecific total synthesis of (+)-isoalstonisine (27)

The alternative route, which was envisaged in order to diastereospecifically functionalize the C-15 position of the key oxindole intermediate (**216**, retrosynthetic analysis in Scheme 198), was based on the successful stereospecific synthesis of affinisine oxindole (**24**) during the course of these studies.[281]

Consequently, the chemistry described before for the preparation of affinisine oxindole (**24**)[281] could be employed starting with the N_a-H, N_b-benzyl tetracyclic ketone oxindole (**216**) instead of the ketone oxindole (**218**, compare Scheme 184 *versus* Scheme 198). Thus, the E-ring in isoalstonisine (**27**) would be generated from tetracyclic oxindole (**876**) through a modified Wacker-oxidation sequence which would be followed by regioselective removal of the N_b-protecting group (R^1).[298] In turn, oxindole (**876**) could be prepared with the execution of a base-promoted retro-Michael process on an N_b-alkyl quaternary ammonium salt of pentacyclic oxindole (**877**).[298,237a] The construction of the β-methyl ketone moiety in (**877**) would be feasible from oxindole (**878**) by a highly

regiospecific (*anti-Markovnikov*), stereospecific (*syn*) hydroboration-oxidation sequence to provide an alcohol which then could be oxidized by different methods. [298,237a]

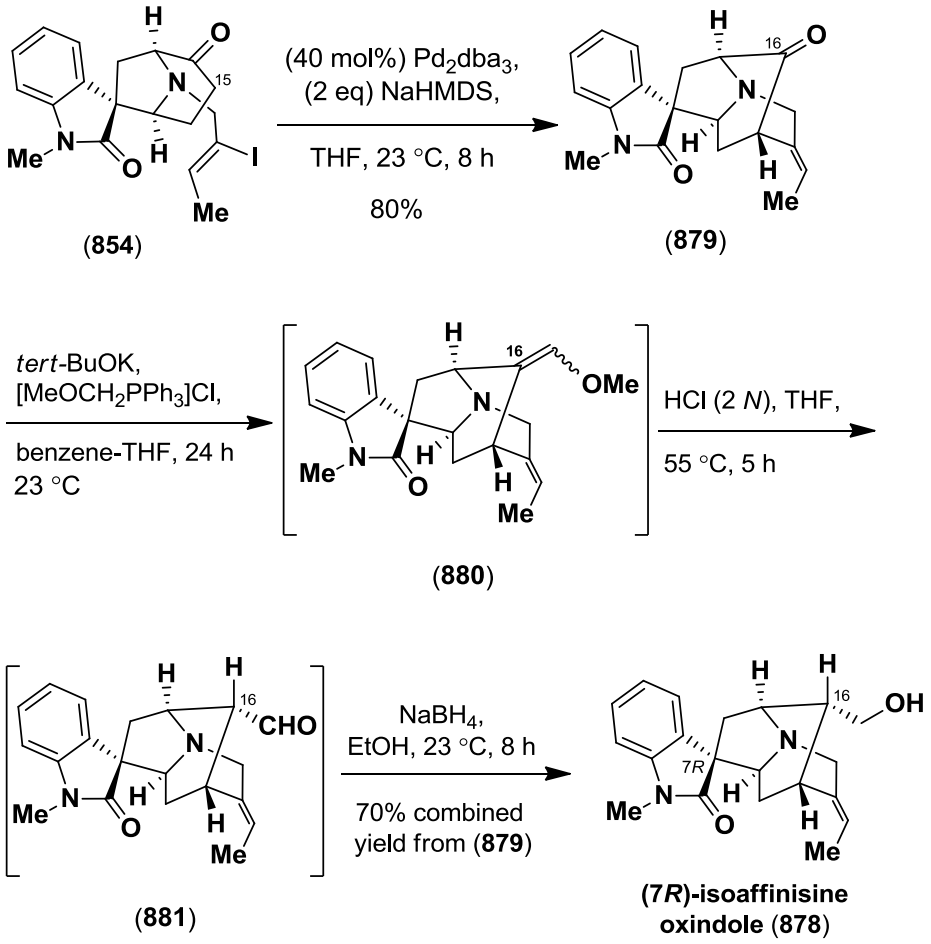
Scheme 198



It is important to note here that oxindole (**878**) is the [(*R*)-C-7] epimeric isomer of the natural affinisine oxindole (**24**). Therefore, the synthesis of oxindole (**878**) would also contribute to the structural proof of affinisine oxindole (**24**). Finally, the primary-hydroxy oxindole (**878**) would be prepared from tetracyclic ketone (**216**), and D-(+)-tryptophan as the initial starting material, by an analogous application of the chemistry discussed here in earlier sections.

According to the retrosynthetic analysis depicted in Scheme 198, N_a-methyl, N_b-allyl tetracyclic ketone oxindole (**854**, its synthesis from D-(+)-tryptophan was discussed in earlier sections of this work) was finally functionalized at the C-15 position in a stereospecific fashion through a modified palladium-catalyzed enolate-driven cross-coupling reaction[277,281] developed during the course of these studies (Scheme 199 and also Section 8.3, Scheme 188).

Scheme 199

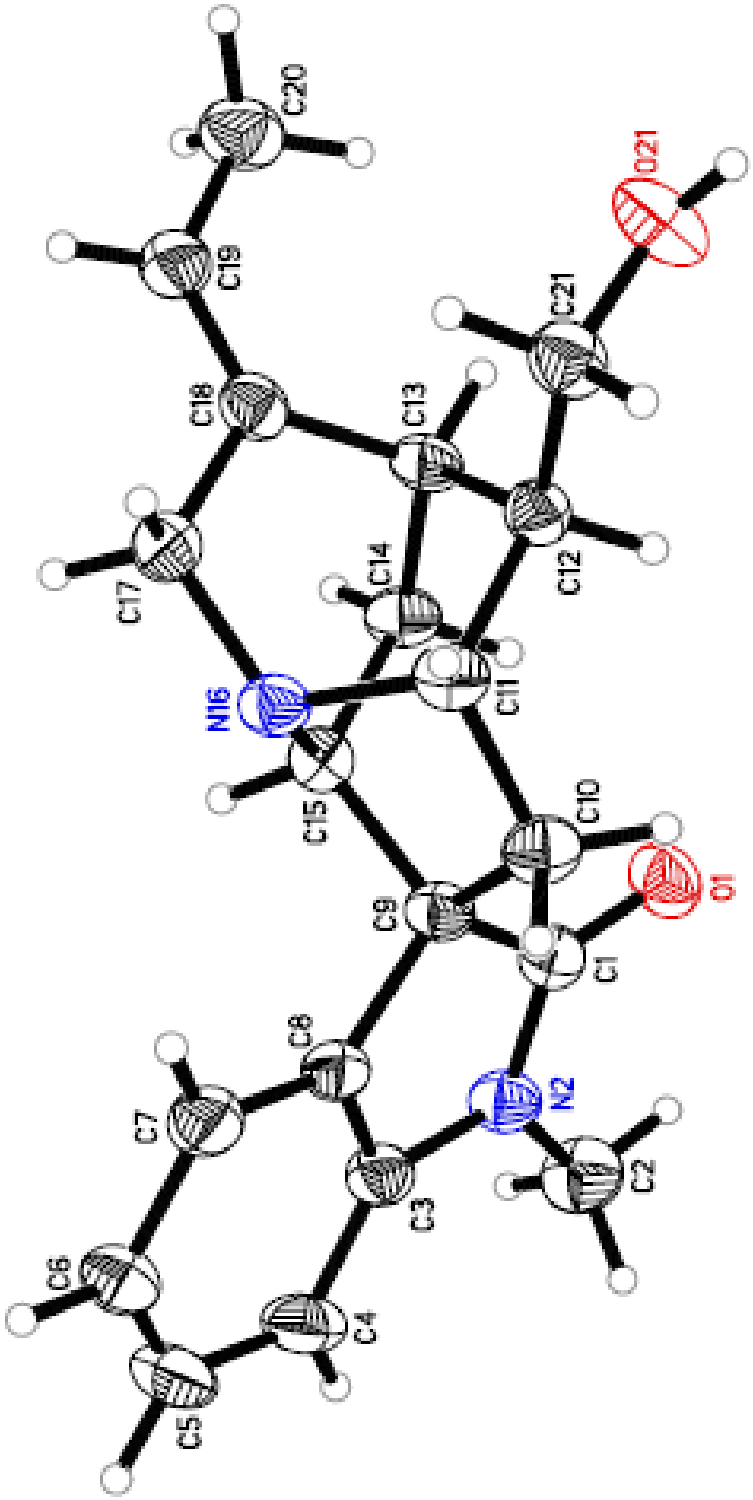


Treatment of oxindole (**854**) with 40 mol% of Pd_2dba_3, NaHMDS (2 equivalents) in THF (previously freeze-pump-thaw degassed, 3-5 cycles, to remove all the oxygen from the solution) at ambient temperature (23 °C) for 8 hours provided the desired pentacyclic ketone oxindole (**879**), diastereospecifically and in high yield (80%). In a similar manner as the preparation of [(*S*)-C-7] affinisine oxindole (**24**, Scheme 190) from oxindole (**857**),[281] the N_a-methyl pentacyclic ketone (**879**) was also treated through a 1-reaction-vessel (3 steps) homologation process of the carbonyl group at C-16 to give the C-17 functionalized aldehyde which was subsequently reduced to the corresponding hydroxy methyl moiety. This was easily executed by a successive Wittig-olefination reaction with (methoxymethyl) triphenyl-phosphonium chloride and anhydrous *tert*-BuOK in dry benzene. Then the mixture of stereoisomeric enol ethers (**880**) was hydrolyzed under acidic conditions to afford the thermodynamically more stable α-epimeric aldehyde (**881**) as a single diastereomer. Finally, the crude aldehyde product (no purification was required) was converted into its corresponding primary alcohol by reduction with $NaBH_4$ in EtOH at room temperature to provide the [(*R*)-C-7] isoaffinisine oxindole (**878**) in 70% overall yield from ketone (**879**, Scheme 199).[281]

The synthesis of oxindole (**878**) was of great importance since it was possible to perform X-ray crytallography on its crystals that served as additional proof of the correct stereochemical assignment of isoaffinisine oxindole as the epimer with the [(*R*)-C-7] spirocenter (Figure 27).

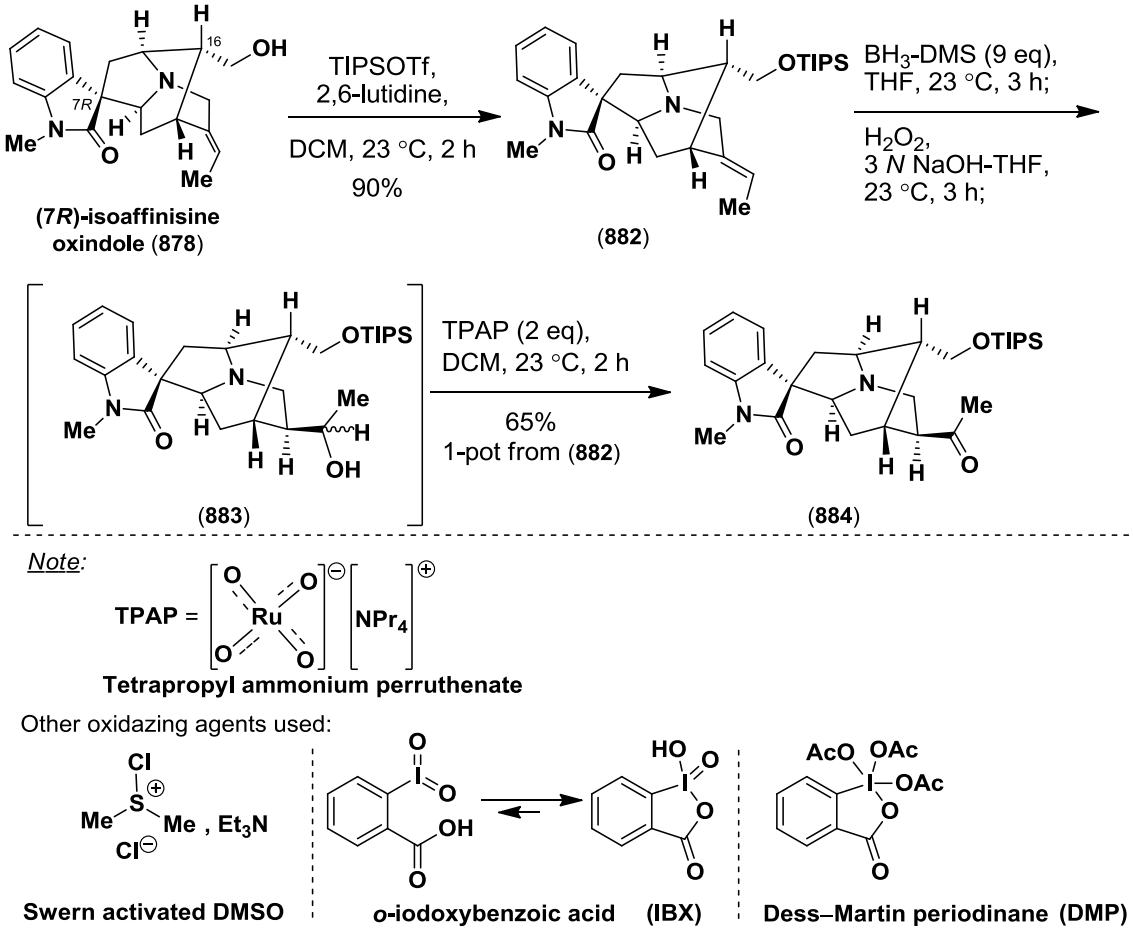
In the next stage of the synthesis, according to the retrosynthetic analysis depicted in Scheme 198, the primary hydroxy group of isoaffinisine oxindole (**878**) was chemo-specifically protected with the bulky triisopropylsilyl moiety in 90% yield by reaction of

Figure 27. ORTEP drawing of isoaffinisine oxindole (**878**)



oxindole (**878**) with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf, 1.6 equivalents) and 2,6-lutidine (2 equivalents) in DCM at room temperature for 2 hours. The TIPS protecting group was used successfully in the parent system for a similar transformation and showed better stability than smaller silyl groups like TBDMS.[231,298] The above result set the stage for the following hydroboration-oxidation sequence. Therefore, the hydroboration process was executed in THF at ambient temperature using a 9-fold excess of BH_3-DMS complex over 3 hours (Scheme 200).

Scheme 200



After carefully quenching the reaction mixture with water at 0 °C, an aqueous solution of NaOH (3 *N*) was added with stirring followed by addition of hydrogen peroxide (H_2O_2, 35% in water). The solution which resulted was allowed to stir for 3 hours at 23 °C to provide a mixture of secondary alcohols (**883**) which were easily purified through a very short column (wash column) to remove highly polar material (also <5% tertiary alcohol). Interestingly, the N_b-BH_3 complex of oxindole (**883**) was never detected after the hydroboration-oxidation protocol. This observation was not surprising and was actually consistent with the reactivity of the N_b-nitrogen atom in the oxindole system is significantly lower than that of the N_b-nitrogen atom in the parent system due to steric hindrance, as was also observed before in the N_b-allylation of oxindoles.

The diastereomeric mixture of secondary alcohols (**883**) was then subjected to oxidation conditions to generate the corresponding methyl ketone. Initially, the execution of very low temperature and mild Swern-oxidation conditions used in the parent system [DMSO (6 equivalents), $(COCl)_2$ (3 equivalents)] at –60 °C for 30 minutes; then alcohols (**883**) were added at –60 °C and let to react for 15 minutes. After this Et_3N (15 equivalents) in DCM was added to the solution which was stirred at –60 °C for 15 minutes and then the system was allowed to warm to room temperature to provide the expected product in very low yield (<10%).[55b,237a,295] Also, the conditions reported by Dess and Martin[296] with hypervalent iodine (Dess–Martin periodidane, DMP) and, also used by Liao et al. in our group for the mild oxidation of similar secondary alcohols in the parent system,[297] were employed. Therefore, when the mixture of diastereomeric alcohols (**883**) was treated in dry DCM with DMP (2-10 equivalents) at room temperature for 24 hours, the starting material (**883**) was recovered in all instances. The addition of different accelerants to the

mixture: water (1-1.2 equivalents); *tert*-butyl alcohol (1-2 equivalents); or trifluoroacetic acid (1-3 equivalents) did not change the outcome of the above process. The replacement of DMP for (3-10 equivalents) of *o*-iodoxybenzoic acid (IBX) in DMSO (or a mixture of DMSO-EtOAc, 1:1) for the oxidation of (**883**) either a room temperature or heated to 80 °C in a sealed tube (Liao et al.)[298] did not show any improvement. The starting mixture of alcohols was recovered intact. Gratifyingly, the use of 2 equivalents of organic-media stable tetra-*n*-propylperruthenate (TPAP, $[RuO_4]^{-1}$, Ru-oxidation state: +7) [299] in dry DCM afforded the desired methyl ketone in a very clean, mild process at 23 °C in 1.5 hours. The combined yield of the 1-reaction-vessel transformation from alkene oxindole (**882**) to the corresponding β-methyl ketone (**884**) was an acceptable 65% (Scheme 200). Normally, TPAP is employed in catalytic quantities in dry DCM with addition of *N*-methylmorpholine *N*-oxide (NMO) as the secondary oxidant.[300] However, a procedure in which 0.1 equivalents of TPAP, 1.2 equivalents of NMO were used in presence of 4 Å molecular sieves in DCM at room temperature for 2-5 hours provided the expected ketone in lower yield, 35%. Interestingly, it was found that the blocking effect of the bulky TIPS protecting group on the C-16 hydroxyl was greater on the oxindole system than that in the parent (indole) case since only the β-diastereomer was observed, the α-epimer was not detected. The high diastereospecificity occurred because the β-face (top face) of the tertiary olefin was sterically more hindered than the α-face (bottom face) towards the borane addition to the double bond.

With access to pentacyclic ketone (**884**), the next step, according to the retrosynthetic analysis described in Scheme 198, was the ring-opening of [**884** (or **877** in Scheme 198)] through a base-promoted retro-Michael reaction of an N_b-alkylated quaternary

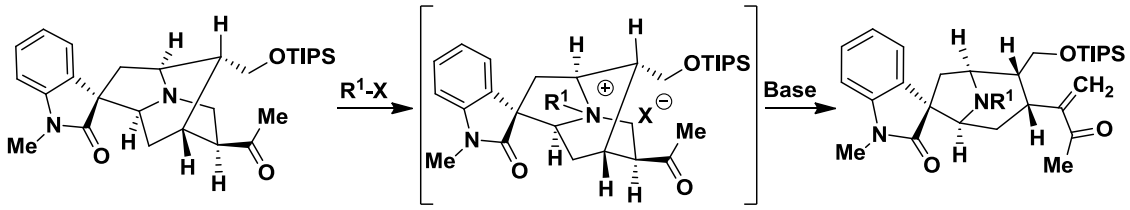
ammonium salt of oxindole (**884**). Since natural isoalstonisine (**27**) possessed an N_b-H functionalized nitrogen atom, it was advantageous to install an alkylating agent that could be removed easily from the secondary N_b-nitrogen at a later stage. It was known, however, that the steric access to the N_b-nitrogen position in these types of sarpagine/ macroline oxindole systems is highly hindered. Thus, initially, it was decided to use benzyl bromide (b.p. = 201°C) to achieve the N_b-alkylation that would in turn leave a N_b-benzyl functional group after the retro-Michael reaction.[301,302,303,304] The benzyl group would be later remove by known deprotection protocols (e.g. reductive hydrogenation or radical debenzylation as seen before in related systems). As shown in entries 1-6 of Table 8, oxindole (**844**) was first treated with 1.5-10 equivalents of BnBr in the presence of a weak base, $NaHCO_3$ (to help neutralize traces of HBr acid in the mixture), alone or with AgOTf (as a Lewis acid additive to help make the BnBr more electrophilic) in hot MeOH, AcCN, or DMF. Then, after the solvent was removed under vacuum, the crude mixture was reacted with K_2CO_3 (2 equivalents) in THF at 66 °C for 30 minutes. In all these cases a complex mixture of very polar biproducts was observed in which the TIPS protecting group was not present.

The substitution of the alkylating agent, BnBr, for the smaller allyl bromide[305,306] (b.p. = 71 °C, which could be removed by isomerization to the enamine under basic conditions, followed by hydrolysis)[307] failed to provide the expected α,β-unsaturated methyl ketone (**886**, Table 8) even when used neat (Table 8, entry 10).

At this point it was decided to treat oxindole (**884**) with methyl iodide (b.p. = 42.4 °C) which was successfully used for similar transformations in the parent system (indole).[298,237a] In this vein, MeI was heated at 70 °C, neat, in the presence of oxindole (**884**, in a

sealed tube) for 1 day. After removal of the excess MeI under reduced pressure, the crude solid, which resulted, was dissolved in dry THF in the presence of 2 equivalents of potassium *tert*-butoxide for 30 minutes at room temperature.

Table 8. Retro-Michael reaction



(**884**) (**885**) (**886**)

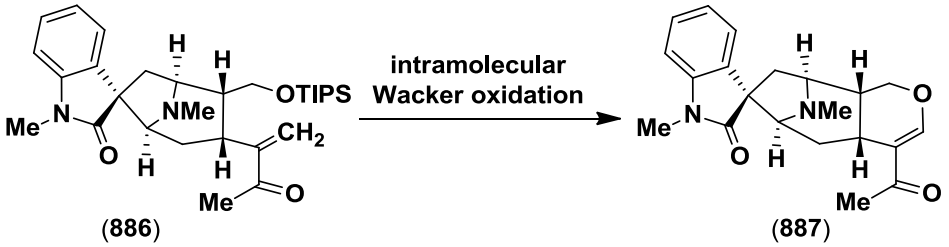
entry	Alkylation step			retro-Michael step		Result
	R^1-X (eq.)	**additive (eq.)**	**solvent/temp. (°C)/ 24 h**	**base (eq.)**	**solvent/temp (°C)/30 min**	
1	Bn-Br (1.5)	$NaHCO_3$ (1.6)	MeOH/64	K_2CO_3 (2)	THF/66	decomposition
2	Bn-Br (10)	$NaHCO_3$ (10)	MeOH/64	K_2CO_3 (2)	THF/66	decomposition
3	Bn-Br (10)	$NaHCO_3$ (10)	MeOH/64	K_2CO_3 (20)	THF/66	decomposition
4	Bn-Br (10)	$NaHCO_3$ (10)/AgOTf (5)	MeOH/64	K_2CO_3 (2)	THF/66	decomposition
5	Bn-Br (10)	$NaHCO_3$ (10)/AgOTf (5)	AcCN/82	K_2CO_3 (2)	THF/66	decomposition
6	Bn-Br (10)	$NaHCO_3$ (10)/AgOTf (5)	DMF/100	K_2CO_3 (2)	THF/66	decomposition
7	Allyl-bromide (10)	$NaHCO_3$ (10)/AgOTf (5)	THF/66	K_2CO_3 (2)	THF/66	decomposition
8	Allyl-bromide (10)	$NaHCO_3$ (10)/AgOTf (5)	DMF/100	K_2CO_3 (2)	THF/66	decomposition
9	Allyl-bromide (10)	$NaHCO_3$ (10)/AgOTf (5)	neat/70	K_2CO_3 (2)	THF/66	decomposition
10	Allyl-bromide		neat/70	K_2CO_3 (2)	THF/66	decomposition, 20% (**884**) recoverred
11	Me-I		neat/70	*t*-BuOK (2)	THF/23	(**886**) 30%
12	**Me-I**		**neat/70**	**NaHMDS (2)**	**THF/23**	**(886) 80%**

The desired α,β-unsaturated methyl ketone (**886**, Table 8, entry 11) was detected albeit in low yield (30%). The use of NaHMDS [sodium bis(trimethylsilyl)amide, 2 equivalents] under similar conditions improved the product yield to 80% (Table 8, entry 12).

The next stage in the synthesis of isoalstonisine (**27**) by the route depicted in Scheme 198 required the formation of a carbon-oxygen bond that would close the E-ring of the molecule. To this end, a modified Wacker-related process, used in the parent system by Liao et al., seemed promising. [298] The indutrial process of ethylene oxidation to acetal-dehyde using an aqueous solution of $PdCl_2$-$CuCl_2$ as the catalyst system is well-known as the Wacker process (also known as a Wacker-Tsuji process on laboratory scale modifications).[308] Application of this oxidation method to simple terminal olefins in organic media is a useful synthetic method for methyl ketones.[310,311] Tsuji et al. reported optimized Wacker-oxidation conditions for related internal α,β-unsaturated ketones using Na_2PdCl_4 as a catalyst because of its high solubility and *tert*-BuOOH as the best reoxidant of the reduced palladium.[309]

The execution of the intramolecular Wacker oxidation which worked in Liao et al. synthesis of (–)-alstonerine (Table 9, entry 1) failed to provide the expected product (complex mixtures of byproducts were recovered each time). Modification of these reac-tion conditions: shorter reaction time (entry 2); removal of the NaOAc additive (entry 3); and using *tert*-butanol instead of dioxane did not improve the outcome of the reaction.

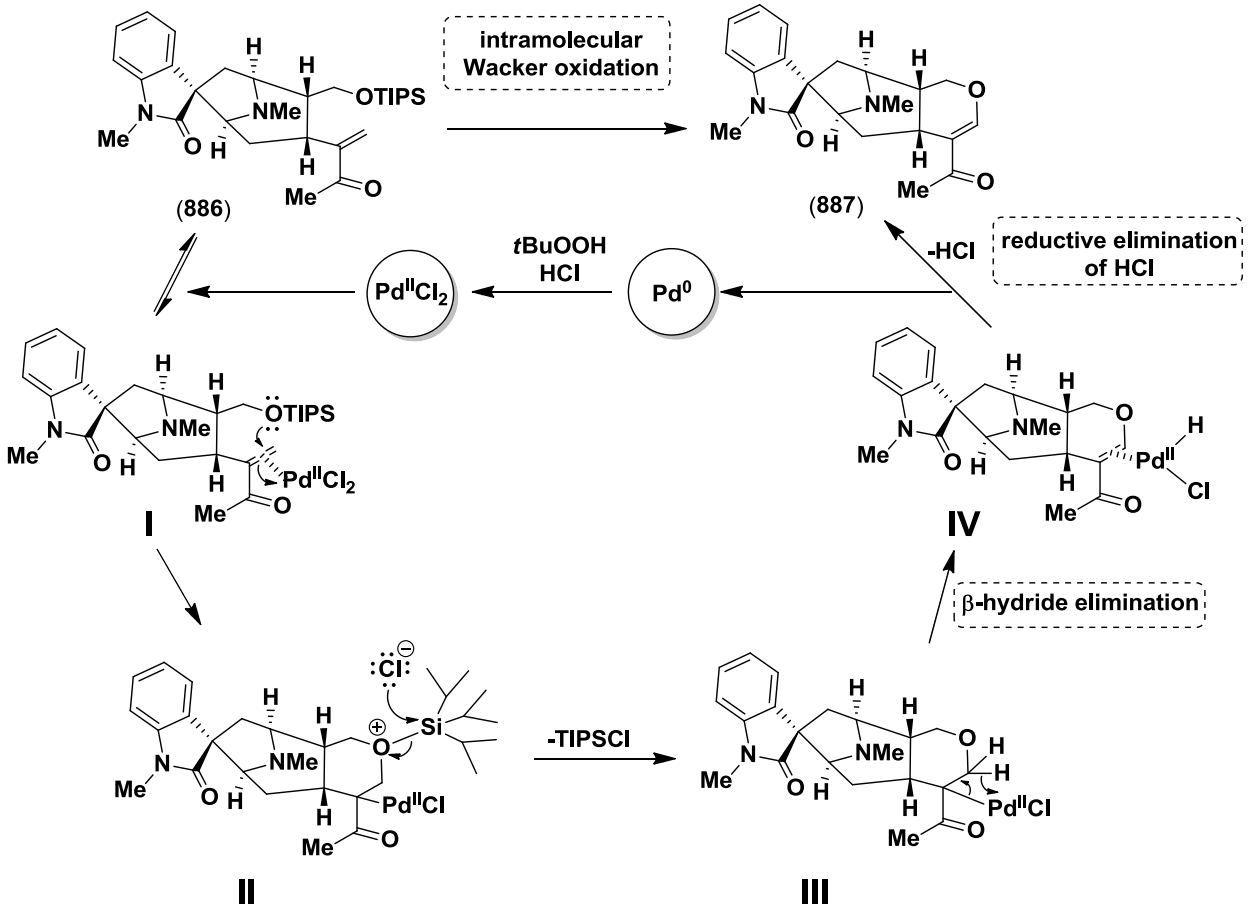
Table 9. Wacker-Cook oxidation



Entry	Catalyst (mol%)	Reoxidant/additive	Solvent system	Temp (°C)/ time (h)	Result
1	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)/ NaOAc (1 eq)	AcOH/dioxane/H_2O (1:3:3)	80/6	decomposition
2	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)/ NaOAc (1 eq)	AcOH/dioxane/H_2O (1:3:3)	80/2	decomposition
3	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)	AcOH/dioxane/H_2O (1:3:3)	80/6	decomposition
4	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)	AcOH/*t*-BuOH/H_2O (1:3:3)	80/6	decomposition
5	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)	dioxane/H_2O (6:1)	40/3	(**887**) 20%
6	**Na_2PdCl_4 (40)**	***t*-BuOOH (1.5 eq)**	**dioxane/H_2O (6:1)**	**85/6**	**(887) 65%**

It was hypothesized that the acidic media was the cause of the problem, presumably by promoting the equilibration of epimeric oxindoles at C-7, through a retro-Mannich type of process, that was operational under these acidic reaction conditions. Thus, since the acidic media was not required for the transformation, it was decided to remove the acetic acid and execute the protocol under neutral conditions. Gratifyingly, the pentacyclic ketone oxindole (**887**) was found in the reaction mixture, after heating at 40 °C for 3 hours, in 20% yield. The yield was later improved to 65% by exposing the starting materials to a higher temperature (85 °C) and longer time period (6 hours).

Scheme 201



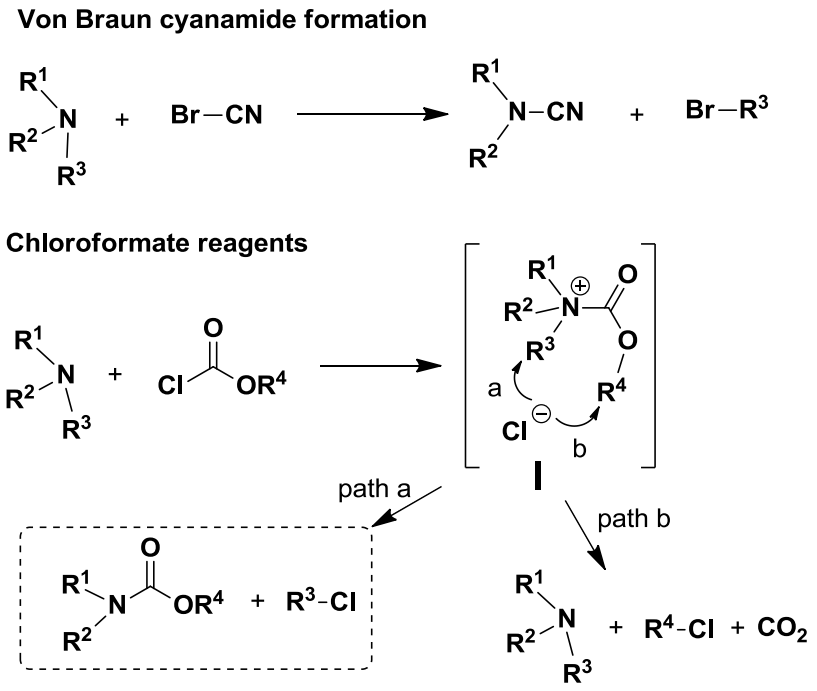
Although the mechanism has not been studied in detail, a proposed one is shown in Scheme 201.[298] It was believed that the process originally involved the fast and reversible coordination of the Pd(II) species to the alkene. Under neutral conditions, the nucleophilic oxygen atom of the silyloxy functional group would attack the Pd(II) olefin complex. This event would be followed by cleavage of the silyl moiety in the presence of chloride ions; then *β*-hydride elimination; and finally by reductive elimination to provided the desired product (**887**), while the Pd(0) was reoxidized to Pd(II) by *tert*-BuOOH (Scheme 201).

At this point, in order to complete the total synthesis of natural isoalstonisine (**27**), the N_b-methyl group had to be regioselectively removed. The methyl group, albeit inert to many chemical transformations, is not usually considered a good protective group because of the perceived difficulty in its removal, but fortunately, there are a number of methods described in the literature that can be used to cleave an *N*-methyl group in highly functionalized substrates.[312] It was found that one of the best methods of choice for the *N*-dealkylation of tertiary amines involved the use of carbonochloridate (chloroformate) reagents (Scheme 202),[313] which had proven to be more selective and produce cleaner reaction products than the prior cyanogen bromide (Von Braun reaction).[314]

As shown in Scheme 202, the 1:1 complex **I** which is formed has two fates: nucleophilic attack of the chloride ion on the *O*-alkyl portion, which has no net effect on the amine (path b), or nucleophilic attack by a chlorine anion on one of the substituents on nitrogen (path a) leading to carbamate ester formation, which can then be hydrolyzed to give a secondary amine. There are many different carbonochloridates reported in the literature, each new one claimed to be an improvement over the last. These advantages were either better yields, lower expense, increased availability of the reagent, or easier conversion of the carbamate esters into the desired secondary amines.[313]

It was believed that to date, the best method found in the literature for the *N*-dealkylation of tertiary amines was the one introduced by Olofson et al. which involved the use of the inexpensive reagent α-chloroethyl chloroformate (ACE-Cl).[315] The cleavage of the α-chloroethyl carbamate ester was done by simply heating it in methanol (addition of H^+ was not needed).

Scheme 202

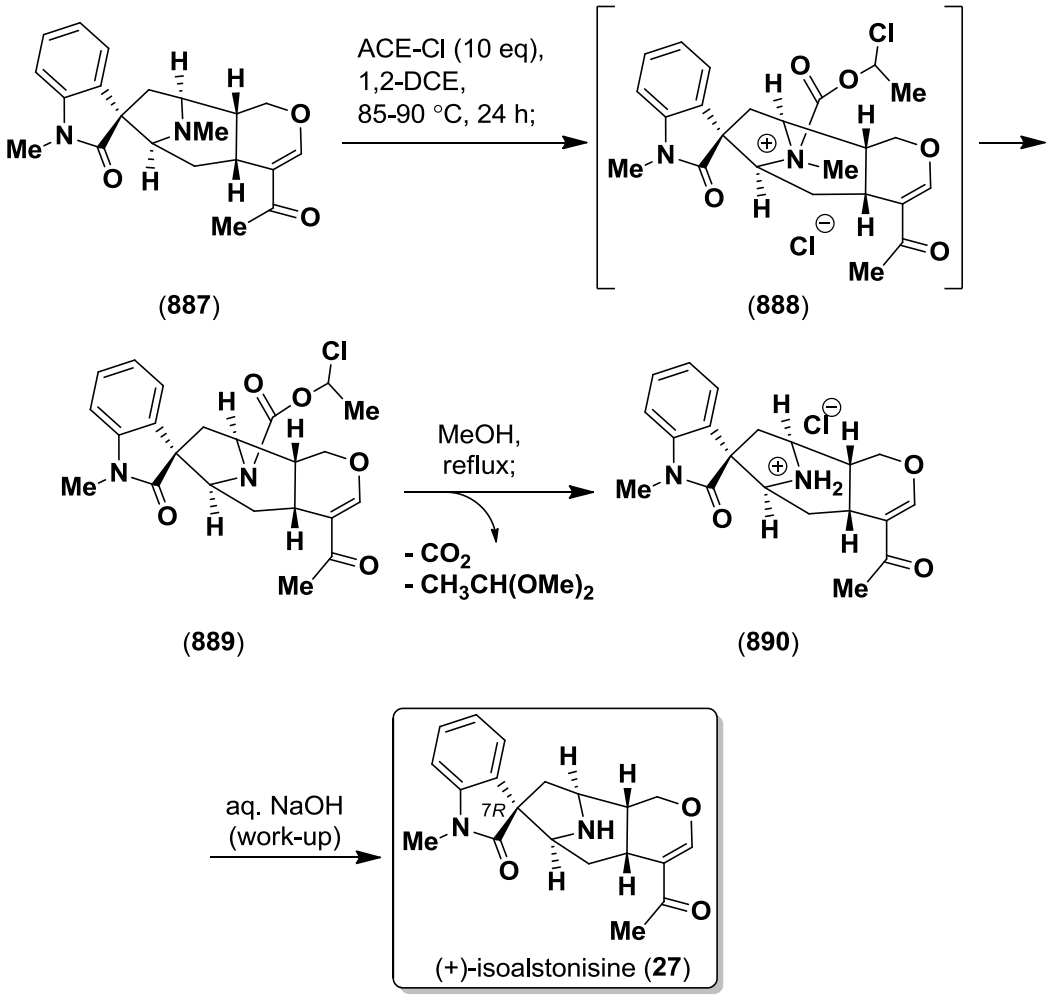


Olofson et al. argued that the high-yield of dealkylation (compare to other chloroformate reagents) was due to the fact that the α-chloroethyl moiety was sterically hindered to S_N2 attack by chloride anion and also that the related cation was too unstable to permit S_N1 substitution.[315] Many examples of the application of the Olofson et al. protocol could be found in the very recent literature, especially for debenzylation, deallylation and demethylation reactions.[316]

Accordingly, N_b-methyl pentacyclic oxindole (**887**) was exposed to the conditions by Olofson et al. with 10 equivalents of ACE-Cl in 1,2-dichloroethane [4.6 mmol (**887**)/mL] at 85 °C for 24 hours. The ammonium salt which formed was then treated with dried methanol at reflux for 5 hours. After basic work-up to neutralize the N_b-hydrochloride salt the expected isoalstonisine (**27**) was obtained in 80% yield (three steps in a 1-pot

process, Scheme 203). Reduction in the 24-hour time frame in the first step of the process drastically reduced the yield of the product. Increasing the number of equivalents of ACE-Cl did not have any effect in the final yield observed. The detailed proposed mechanism of the trasformation is shown in Scheme 204.

Scheme 203



The spectral ^{1}H NMR (see Table 10 below) and ^{13}C NMR (see Table 11 below) data as well as the IR spectrum [dry film on KBr: 1701 cm^{-1}, literature[12] IR (dry film) 1704 cm^{-1}], and the physical properties including the specific optical rotation {[α]$^{23}_{D}$ = +201° (*c* 0.15, $CHCl_3$), literature[12] [α]$^{23}_{D}$ = +207° (*c* 0.07, $CHCl_3$)]}, and HRMS were in excellent agreement with those published in the literature by Kam et al.[12]

Scheme 204

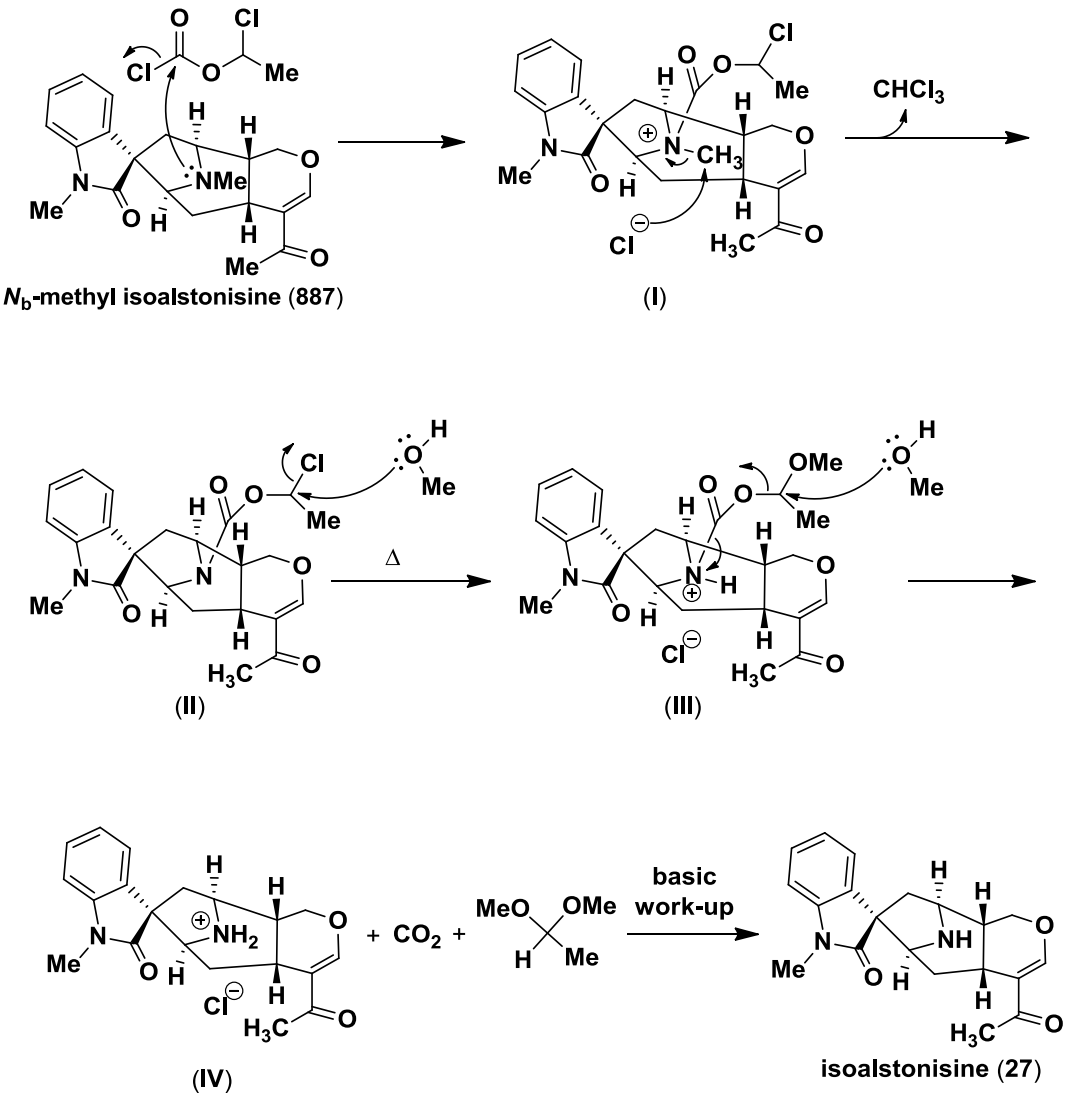


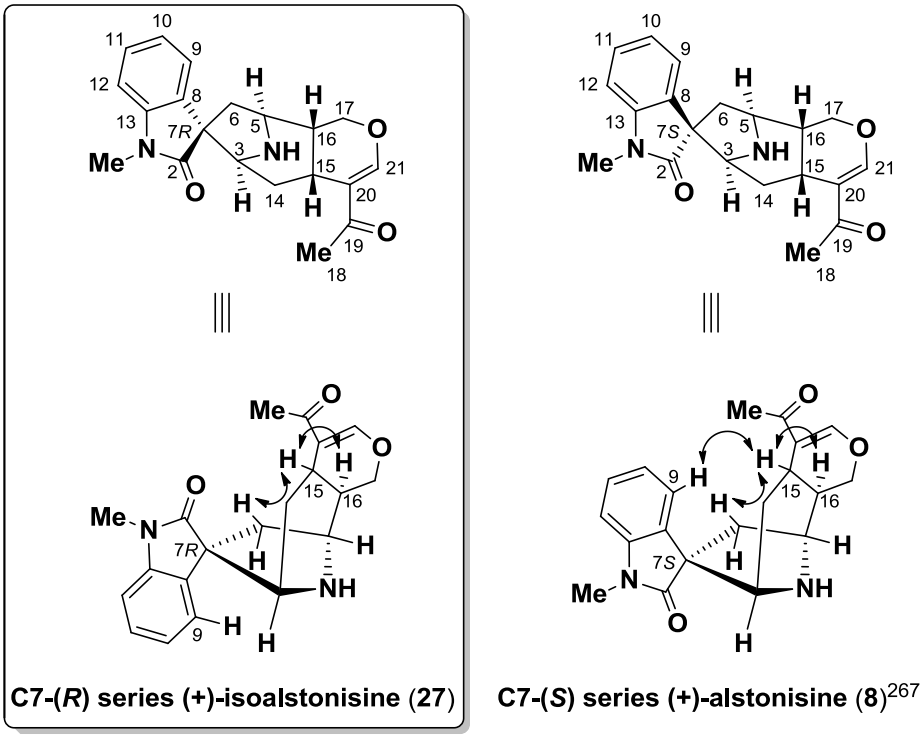
Table 10. Comparison of the ^{1}H NMR spectral data for synthetic (−)-isoalstonisine (**27**) to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

	Proton NMR	
Position	Natural sample[12]	Synthetic sample (**27**)
N_a-CH_3	3.26 s	3.22 s
3	3.15 t (3)	3.11 brt (3)
5	3.76 brd (7)	3.73 brd (7)
6	2.61 dd (14,2) 2.35 dd (14,8)	2.58 dd (14,2) 2.34 m
9	7.15 dd (8,1)	7.13 dd (8,1)
10	7.00 td (8,1)	6.98 td (8,1)
11	7.27 td (8,1)	7.25 td (8,1)
12	6.82 dd (8,1)	6.80 dd (8,1)
14	1.49 ddd (14,12,3) 2.33 ddd (14,6,3)	1.47 brdt (12,4) 2.34 m
15	4.03 dt (12,6)	3.99 m
16	2.01 m	1.96 brm
17	4.17 ddd (11,4,2) 4.26 t (11)	4.14 ddd (11,4,1) 4.24 t (11)
18	2.25 s	2.22 s
21	7.54 s	7.52 s

Table 11. Comparison of the ^{13}C NMR spectral data for synthetic (−)-isoalstonisine (**27**) to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

	Carbon NMR	
Position	Natural sample[12]	Synthetic sample (**27**)
N_a-CH_3	26.5	26.3
2	177.5	177.4
3	66.9	66.8
5	57.0	57.1
6	42.3	42.2
7	57.3	56.8
8	137.6	137.4
9	120.9	120.6
10	122.3	122.2
11	127.8	127.7
12	107.7	107.6
13	142.4	142.3
14	32.7	32.5
15	23.9	23.7
16	37.8	37.5
17	67.8	67.6
18	25.8	25.6
19	197.1	197.0
20	121.9	121.8
21	155.9	155.8

Figure 28. NOE NMR, Isoalstonisine

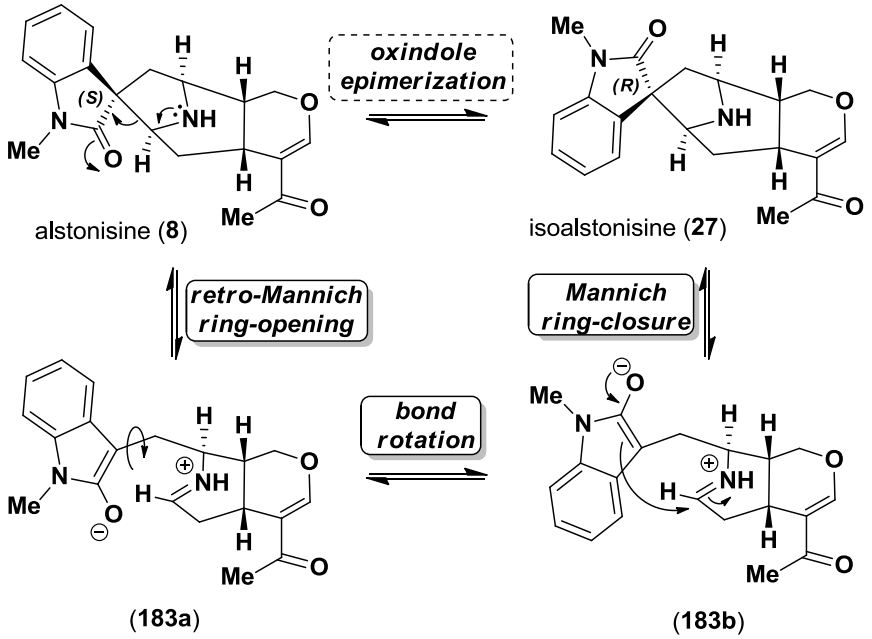


Selected NOE-NMR experiments were then carried out on synthetic (−)-isoalstonisine (**27**, Figure 28) and compared to those of Kam et al.[12] on natural isoalstonisine and Wearing et al. on alstonisine.[267] Irradiation of the diagnostic H-9 hydrogen-atom effected enhancement of H-15 by 20% and *vice versa*, in synthetic alstonisine according to Wearing et al.[267] Irradiation of H-9 in synthetic isoalstonisine (**27**) did not effect enhancement of H-15, thus confirming the correct assignation and also that there was no epimerization at C-7 during the last step.

8.5) Studies on the epimerization of sarpagine/macroline related oxindoles at C-7

The intramolecular retro-Mannich/bond-rotation/Mannich cascade reaction is a well-known method to access the spirooxindole functional groups with the desired stereo-chemistry.[261] In fact, this isomerization process has been utilized, as mentioned, for the identification and assignment of the stereochemistry of other natural alkaloids.[319,320,321] The epimerization of oxindole alkaloids was noticed as early as 1959 by Wenkert et al. and a concept of the underlying mechanism was put forward independently by the research groups of Wenkert et al. and Marion et al. A modification of which appears in Scheme 205 in the alstonisine case.[261c,318]

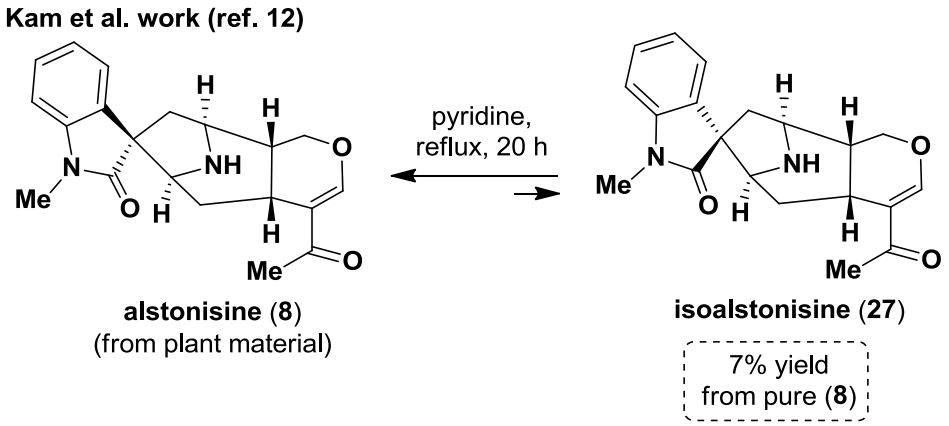
Scheme 205



The first encounter with the oxindole isomerization process during these studies occurred during the alkylation of ketooxindoles (**849**) and (**856**, Section 8.3). Initial efforts to introduce an allyl iodide moiety at the N_b-nitrogen atom of these two compounds (independent experiments) gave mixtures of the expected product (**846**, **854** respectively) and the corresponding diastereomer at C-7. At this point, it was realized that a study of sarpagine/macroline oxindoles toward isomerization, which had been exposed to a certain set of reaction conditions, would be of synthetic and mechanistic interest.

In this vein Kam et al. reported the isomerization of alstonisine (**8**) to isoalstonisine (**27**) by refluxing pure oxindole (**8**, 24 mg) in pyridine for 20 hours (for additional structural proof of alstonisine, Scheme 206). This process provided, after purification by column chromatography, a mixture of oxindole (**27**, 2 mg, in 7% yield) and recovered oxindole (**8**, 20 mg, 83%).

Scheme 206



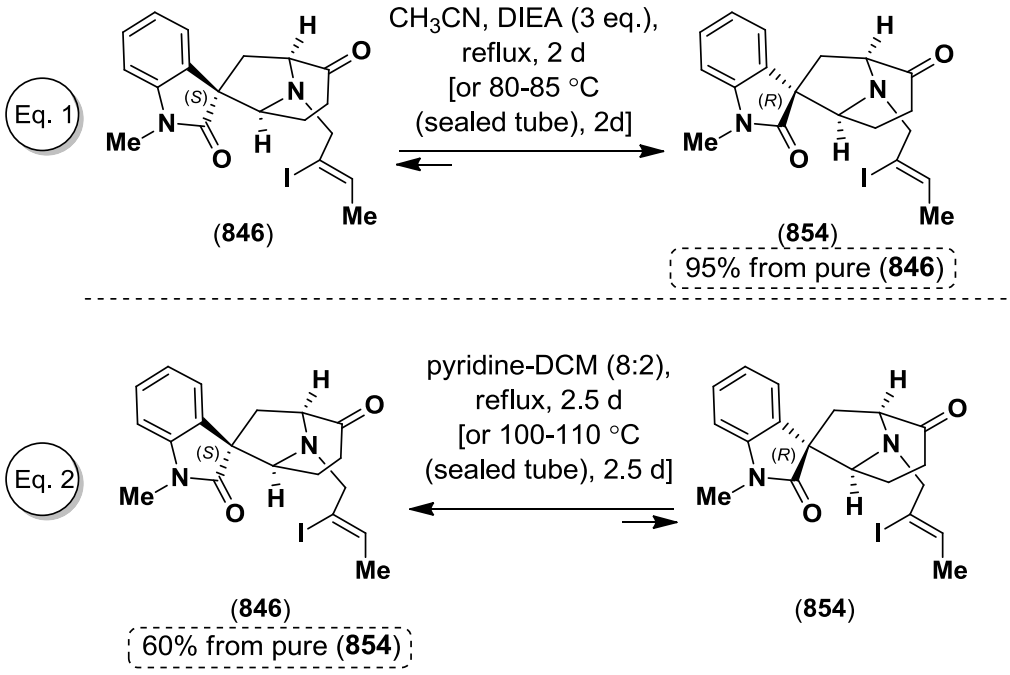
With the key precedents by Kam et al.,[12] the studies realized by Laus et al.[261] (on the effect of temperature, *p*H, solvent polarity on the isomerization of oxindoles) and our studies on the allylation of tetracyclic oxindoles during the synthesis of (–)-affinisine oxindole (**24**) and (+)-isoalstonisine (**27**) in mind, it was decided to find experimental conditions that would allow entry into the opposite stereochemistry at C-7 from the pure oxindoles (**846**) and (**854**) independently (Scheme 207). It was observed that when pure **7*S***-N_a-methyl, N_b-allyl oxindole (**846**) was heated at reflux in AcCN (or at 80-85 °C in sealed tube) for approximately 2 days in the presence of base [(3 equivalents) diiso-propylethylamine (or sodium carbonate)] an equilibrium was reached in which 95% of the starting oxindole (**846**) epimerized at C-7 to form **7*R***-oxindole (**854**, Scheme 207). On the other hand, when pure **7*R***-N_a-methyl, N_b-allyl oxindole (**854**) was treated at reflux in a (8:2) mixture of pyridine-DCM as the solvent (or at 100-110 °C in sealed tube) for 2.5 days, the final equilibrium showed that 60% of the starting material epimerized at C-7, as shown in Scheme 207. The latter conditons where based on Kam et al. studies but it was seen that the starting material was not completely soluble in pyridine, and therefore, a small amount of DCM was added to the mixture to make the system homogeneous. The above results were very interesting since it was possible to find a set of two reaction conditions that allowed the interconversion from the C-7-*R* stereochemistry to the epimeric C-7-*S* and *vice versa* in two simple transformations. Accordingly, the next step was to use these conditions to get access to other natural sarpagine/macroline oxindole alkaloids, which will be discussed later in this work.

Laus et al. reported on the effects of temperature, *p*H, and solvent polarity on the rate of isomerization and the equilibrium composition of the related tetracyclic spiro oxindole

alkaloids rhynchophylline and isorhynchophylline; corynoxeine and isocorynoxeine; mitraphylline and iso mitraphylline; pteropodine and isopteropodine; speciophylline and uncarine F.[261a,261b]

Importantly, Laus et al. performed the equilibration of rhynchophylline in water (*p*H = 7) and in methanol at different temperatures. At 25 °C after 4 hours, the equilibrium data showed that in

Scheme 207

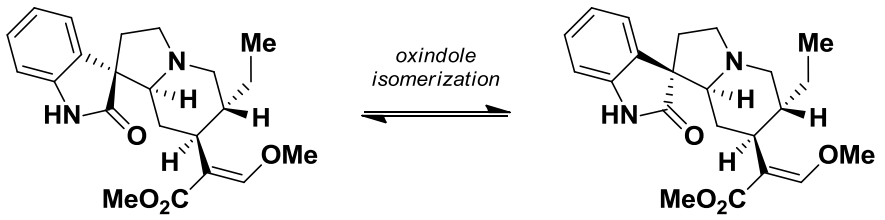


water the mol-ratio obtained was [rhynchophylline (**3**)/isorhynchophylline (**891**)] = 64.1:35.9. In **methanol**, on the other hand, the isomerization was considerably *slower* and the effect of the tamperature on the equilibrium was *reversed* [(**3**/**891**) mol-ratio = 22.3:77.7] which was reflected by the negative entropy of activation due to charge separation in a solvent with a small *relative permittivity* (dielectric constant).[261] The same

effect was observed by Laus et al. with other oxindole alkloids. This precedent study was of much significant since a change of the solvent polarity (*p*H of both experiments was the same), had a critical impact on the position of the equilibration equilibrium. Laus and collaborators extended this study to other solvents and observed that the isorhyncho-phylline (**891**) content of an equilibrated solution increased with diminishing polarity, *e.g*. 81% in ethanol, 96% in dimethyl sulfoxide, and 99% in dioxane (Table 12). In conclusion, the polar solvents reduced $\Delta G^{\ddagger}$ of the zwitterionic intermediate, while on the other hand apolar solvents stabilized the more lipophilic isomer in the equilibrium.[261]

Table 12. Laus et al. example

Laus et al. work (ref. 261a)



rhynchophylline (**3**) **isorhynchophylline** (**891**)

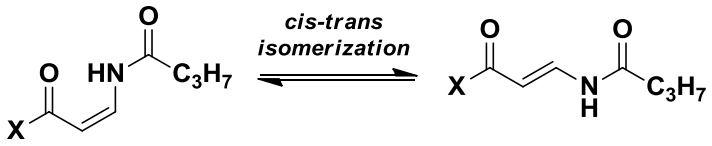
Solvent (at 50°C)	**Polarity E^{N}_{T} (323 K)[322]**	**<u>Isorhynchophylline</u> content in equilibrium (mol%)**
Water	1.00	36
Methanol	0.76	78
Ethanol	0.64	81
DMSO	0.42	96
Dioxane	0.17	99

Changing the position of an isomerization equilibrium with different solvent systems is a well-documented phenomenon and used for synthetic purposes. Many examples could be found in the literature, two interesting ones were introduced here: Kishi et al. (*J. Am. Chem. Soc* **1994**, *116*, 11205) reported the *cis-trans* isomerization of *N*-acyl vinylogous

ureas in the presence of acid catalysts (Table 13).[323] Mäder et al. (*Angew. Chem. Int. Ed.* **1969**, *8*, 602) studied the *cis-trans* isomerization of aziridinedicarboxylic esters *via* azomethine ylides (Table 14). The content of the *cis*-1 isomer in the equilibrium increased with increasing polarity of the solvent.[324]

Table 13. Kishi et al. example

Kishi et al. work (ref. 323)



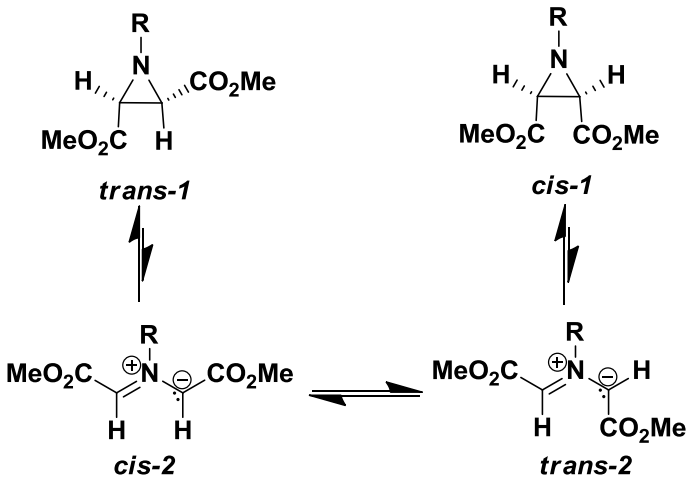
cis-isomer *trans-isomer*

X = NH-$(CH_2)_3$-OTBDPS

Solvent (at 23 °C)	Acid catalyst	Isomer (%)
toluene	CSA	*cis* (100%)
chloroform	CSA	*cis*(100%)
MeOH	CSA	no isomerization
MeCN	CSA	no isomerization
MeOH	HCl (gas)	*trans* (100%)
DMF	HCl (gas)	*trans* (100%)
MeCN	HCl (gas)	*trans* (100%)
DMSO	HCl (gas)	*trans* (75%)

Table 14. Mäder et al. example

Mäder et al. (ref. 324)



R = *p*-CH_3O-C_6H_4

Solvent (at 120 °C)	*cis*-1 (%)	E_T[322]
CCl_4	22	32.5
Ether	26	34.6
Dioxane	29	36.0
Ethyl acetate	30	38.1
Deuteriochloroform	32	39.1
Methylene chloride	32	41.1
Acetone	36	42.2
1,3-Dioxolan-2-one	47	46.6

8.6) Enantiospecific synthesis of (+)-alstonisine (8), (+)-N_a-demethylalstonisine (17) and (+)-alstofonile (18)

The first reported sarpagine/macroline-related oxindole alkaloid, alstonisine (**8**), was isolated in 1972 by Gilman et al. from *Alstonia muelleriama* Domin.[7] After this initial report, alstonisine (**8**) was also found in *Alstonia angustifolia* and *Alstonia macrophylla*.[9,11,12,14,317] The original structure and relative configuration of alstonisine were

determined by Nordman et al. through single-crystal X-ray analysis.[134] However, the absolute configuration reported for this molecule was assigned according to that deduced for ajmalicine and resulted in an incorrect determination of the structure of alstonisine (**8**).[134] The absolute configuration of alstonisine (**8**) was later determined by a biomimetic transformation of alstonisine (**8**) into talpinine;[136] however, direct confirmation of the configuration at the spirocenter had not been reported. The structure of alstonisine (**8**), especially the configuration at the spirocenter at C-7, was unambiguously established by Wearing et al., who achieved the first enantiospecific total synthesis of this alkaloid (see Section 4 for a summary of this work), followed by an X-ray crystal structure at low temperature to establish the absolute configuration as well.

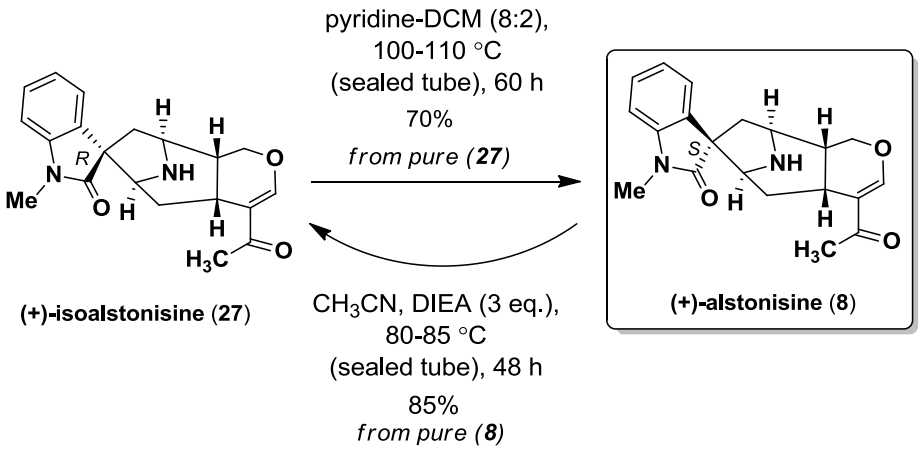
The oxindole alkaloids (+)-N_a-demethylalstonisine (**17**) and (+)-alstofonile (**18**) were first isolated by Kam and Choo et al. in 2000 from the Malayan *Alstonia angustifolia* var. *latifolia* K. and G.[12] The initial report incorrectly named the source plant as *Alstonia macrophylla* Wall but the authors then changed it in a later communication.[14] The alkaloidal content of *Alstonia macrophylla* Wall was studied by Kam and Choo et al. and published in a 2004 report.[9] The structures of these two oxindoles were determined using NMR techniques, UV, IR, optical-rotation and MS analysis. The corrected configuration at C-7, labeled (*S*), for both alkaloids was reported in by Kam et al. in a recent article.[18]

8.6.1) Generation of (+)-alstonisine by epimerization of isoalstonisine (27) at C-7

With isoalstonisine (**27**, Section 8.4) and the C-7-epimerization conditions developed for the the tetracyclic oxindole system (Section 8.5) in hand, it became of interest to explore

the isomerization of 7*R*-isoalstonisine (**27**) into 7*S*-alstonisine (**8**). The successful execution of the epimerization protocol in good yield would represent an improved route to this important oxindole alkaloid. Accordingly, our synthetic pure sample of iso-alstonisine (**27**) was treated at 100-110 °C (in a sealed tube) in a dry pyridine-DCM (8:2) mixture for 3 days to reach the equilibrium. After separation and analysis of the mixture of diastereomers, it was found that alstonisine (**8**) was present in a gratifying 70% yield (Scheme 208). The C-7 epimeric isoalstonisine (**27**) was detected in 18% yield and the rest (12%) of the material was an highly-polar unidentified mixture (baseline material on TLC analysis). If the decomposition material was taken into account, the final equilibration mol ratio would be (**27**)/(**8**) = 78/22, approximately. On the other hand, heating alstonisine (**8**) in acetonitrile at 80-85°C (in a sealed tube) in the presence of 3 equivalents of Hünig's base (sodium carbonate can also be used in pleace of Hünig's base) for 2 days, isoalstonisine (**27**) was generated in 85% yield, and alstonisine (**8**) was recovered in 9% yield with 6% of decomposition, the mol% of the mixture at the equilibrium would be approximately (**8**)/(**27**) = 1/9.

Scheme 208



The spectral ^{1}H NMR (see Table 15 below) and ^{13}C NMR (see Table 16 below) data as well as the IR spectrum [dry film on KBr: 1701 cm^{-1}, literature[12] IR (dry film) 1704 cm^{-1}], the physical properties including the specific optical rotation {$[\alpha]^{23}_{D}$ = +195° (*c* 0.2, EtOH), literature: $[\alpha]^{23}_{D}$ = +197° (*c* 1.0, EtOH)[267] and $[\alpha]^{23}_{D}$ = +200° (*c* 1.0, EtOH)[7]}, and HRMS were in excellent agreement with those published in the literature by Elderfield et al and Wearing et al.[7,267]

Table 15. Comparison of the ^{1}H NMR spectral data for synthetic (+)-alstonisine (**8**) to that obtained from *Alstonia* by Elderfield et al.,[7] and also the synthetic alstonisine by Wearing et al.[267]

	Proton NMR		
Position	Natural sample[7,12]	Synthetic sample (Wearing et al.)[267]	Synthetic sample (**8**)
N_a-CH_3	3.20 s	3.21 s	3.22 s
3	3.18 brs	3.20 m	3.20 m
5	3.68 brd (7)	3.68 d (6.9)	3.77 brd (7)
6	2.19 brd (13) 2.52 dd (13,7)	2.20 d (13.4) 2.53 dd (13.5,7.5)	2.20 d (13) 2.56 dd (13,7)
9	6.86 dd (7,1.5)	6.86 d (7.8)	6.89 dd (7,1)
10	7.30 td (8,1)	7.30 td (7.6,1.2)	7.32 td (7,1)
11	7.33 td (8,1)	7.34 td (7.6,1.2)	7.36 td (7,1)
12	6.88 brd (8)	8.26 d (7.7)	8.27 dd (7,1)
14	1.55 ddd (14,12,3) 2.25 ddd (14,6,3)	1.53-1.58 m 2.24-2.26 m	1.67 m 2.28 m
15	3.40 dt (12,6)	3.39 dt (11.8,6.0)	3.41 m
16	1.96 m	1.96 m	2.06 brm

17	4.26 ddd (11,4,2) 4.45 t (11)	4.25 ddd (11.0,4.0,1.5) 4.45 t (11.0)	4.29 ddd (11,4,1) 4.56 t (11)
18	2.24 s	2.25 s	2.26 s
21	7.62 s	7.63 s	7.64 s

Table 16. Comparison of the ^{13}C NMR spectral data for synthetic (+)-alstonisine (**8**) to that from *Alstonia* by Elderfield et al.,[7] and the synthetic alstonisine by Wearing et al.[267]

	Carbon NMR		
Position	Natural sample[7,12]	Synthetic sample (Wearing et al.)[267]	Synthetic sample (**8**)
N_a-CH_3	25.8	26.4	26.6
2	181.9	182.6	182.8
3	63.4	64.0	64.2
5	55.9	56.5	56.7
6	41.5	42.1	42.3
7	56.5	57.1	57.2
8	128.7	129.2	129.5
9	125.1	125.8	125.9
10	122.8	123.6	123.7
11	127.5	128.2	128.3
12	107.5	108.2	108.3
13	143.6	144.2	144.4
14	30.6	31.2	31.4
15	23.8	24.4	24.6
16	36.5	37.2	37.4
17	68.2	68.5	68.7
18	24.5	25.2	25.3

19	196.0	196.8	196.9
20	121.3	121.9	122.2
21	157.2	157.8	158.0

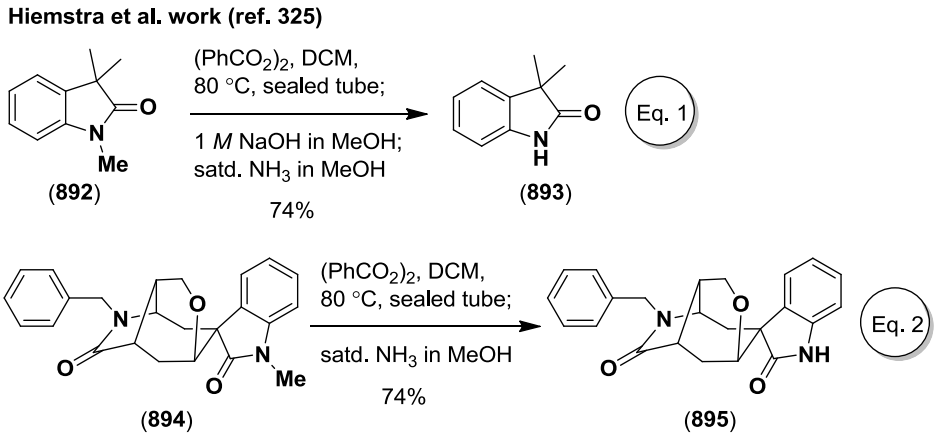
8.6.2) Transformation of (+)-alstonisine (8) into (+)-N_a-demethylalstonisine (17)

The 7S-series oxindole alkaloid (+)-N_a-demethylalstonisine (**17**) could be obtained from the corresponding (+)-N_a-H alstonisine (**8**), presumably, through a chemical transformation that chemoselectively removed the methyl functional group. While searching the literature, attention was drawn to a communication by Hiemstra et al. on the total synthesis of (+)-gelsedine,[325] in which the removal of a methyl group from an oxindole was readily accomplished by using a procedure which was known for removal of an *N*-methyl group from an indole system (by Nakatsuka et al.).[326] In this process treatment of an *N*-methyl oxindole (**892**) with dibenzoyl peroxide, followed by saturated NH_3 in methanol gave the expected oxindole *N*-H (**893**) in a remarkably high yield (>70%, model system, Eq 1, Scheme 209).[326] Similar results were obtained by Hiemstra et al. when the same conditions were applied to the gelsedine alkaloid system (Eq 2, Scheme 209). Interestingly, the methylene hydrogens of the benzyl group (in oxindole **894**, Scheme 209) did not react at all, although the benzyl radical might be even better stabilized, according to the authors.[325b] These conditions were also successfully used during the synthetic studies on vincorine by Takemoto et al.[327]

It was decided to make use of the conditions by Hiemstra et al. for the demethylation of alstonisine (**8**). A major souce of concern, however, was the presence of a secondary

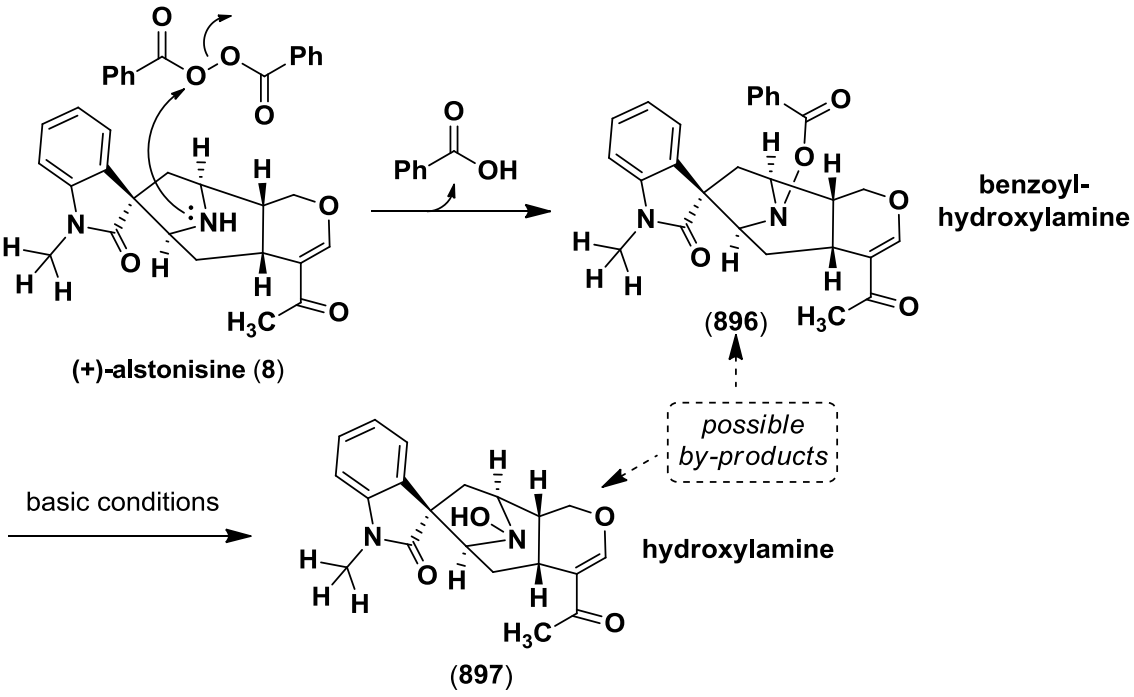
nitrogen atom (N_b-H) in the molecule. The reaction of dibenzoyl peroxide with secondary amines to provide *O*-benzoylhydroxylamines is well documented.

Scheme 209



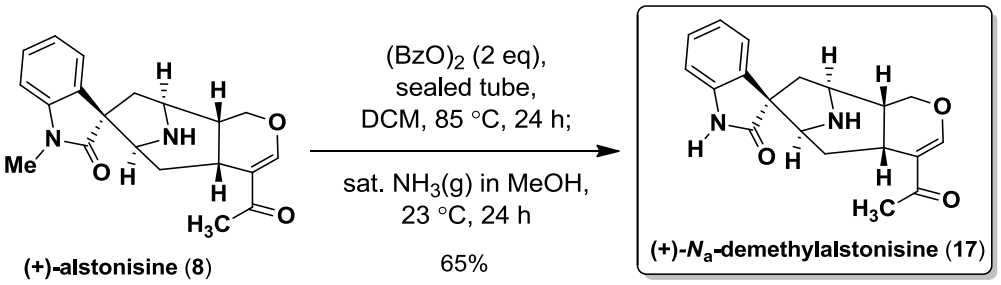
This process involved the nucleophilic displacement along the peroxide *O*-*O* linkage (Scheme 210). Since one equivalent of benzoic acid was generated, an excess of starting amine was used to trap the benzoic acid. It was expected to overcome this possible hurdle by using the minimum number of peroxide equivalents, considering the fact that the N_b-position is sterically much more hindered than the exposed N_a-methyl group in the sarpagine/macroline oxindoles (given our previous experience at trying different nucleophilic transformations at N_b-nitrogen position). It was reasonable to hypothesize that a large excess of peroxide would be required for the N_b-oxidation process to occur to a significant extent.[328]

Scheme 210

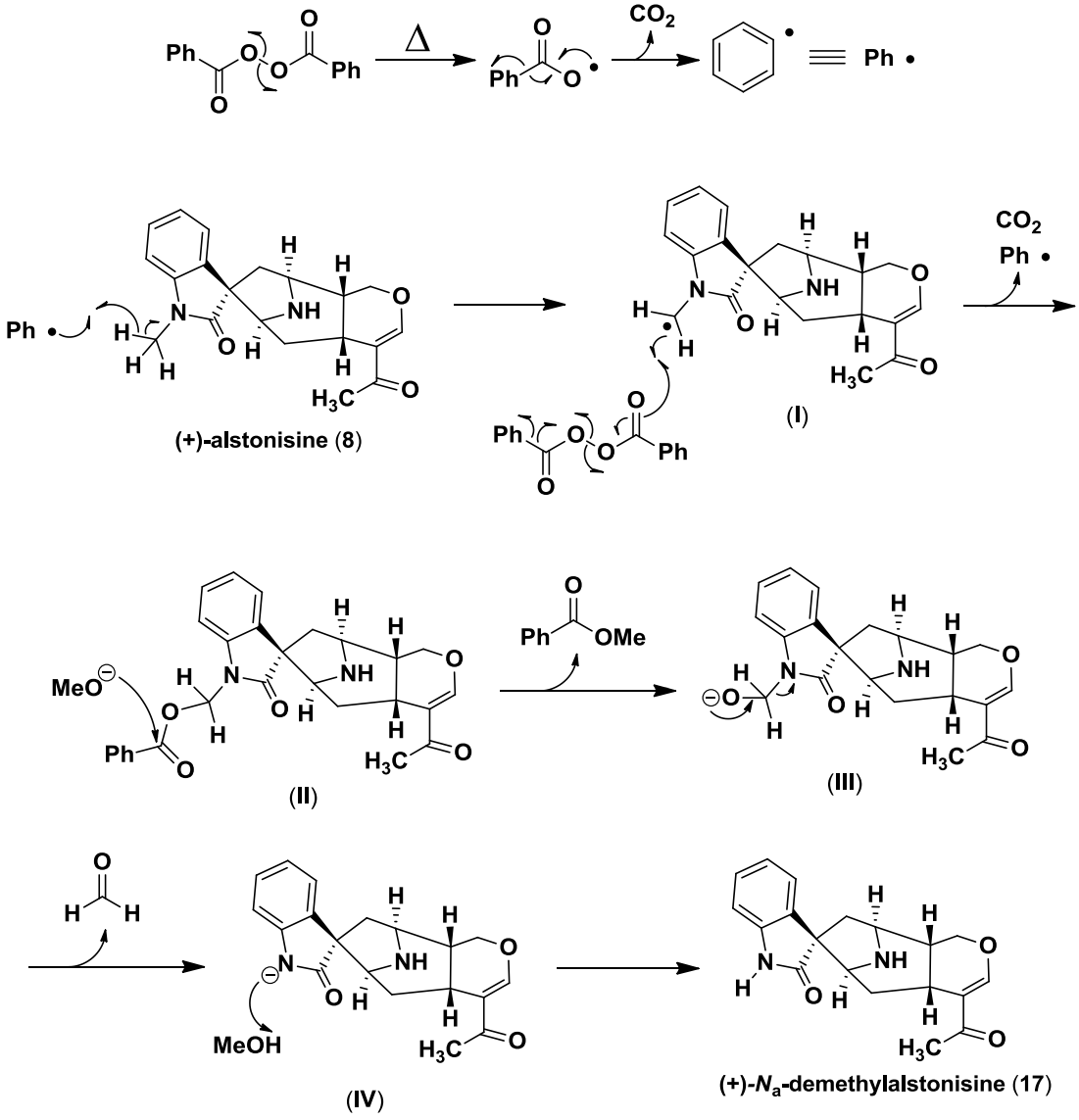


Accordingly, a solution of alstonisine (**8**) and 2 equivalents of dibenzoyl peroxide in DCM was heated in a sealed tube for 24 hours at 85 °C (Scheme 211). After concentrating the reaction mixture, a solution of saturated NH_3 in methanol was added, and the mixture was stirred for another 24 hours at ambient temperature to afford the expected (+)-N_a-demethylalstonisine (**27**) in moderate yield (65%). Attempts to increase the final yield by increasing the number of peroxide equivalents had the opposite effect, presumably for the reasons explained above, even though it could not be confirmed. A proposed mechanism for the demethylation of oxindoles is shown in Scheme 212.[325b]

Scheme 211



Scheme 212



The ^{1}H NMR (see Table 17 below) and ^{13}C NMR (see Table 18 below) spectral data and HRMS were in excellent agreement with those published in the literature by Kam et al.[12]

Table 17. Comparison of the ^{1}H NMR spectral data for synthetic (+)-N_a-demethylalstonisine (**17**) to that from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

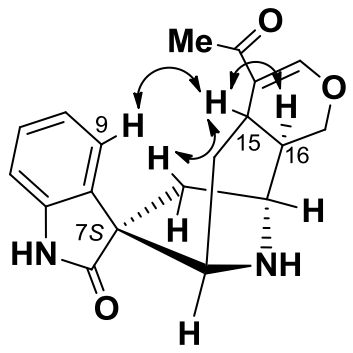
	Proton NMR	
Position	Natural sample[12]	Synthetic sample (**17**)
N_b-H	8.54 s	8.62 s
3	3.27 brs	3.27 brs
5	3.69 brd (7)	3.74 brd (6)
6	2.20 brd (13) 2.57 dd (13,7)	2.23 d (12) 2.63 dd (13,7)
9	8.22 brd (8)	8.28 dd (7,3)
10	7.25 m	7.31 td (6,1)
11	7.20 m	7.24 td (6,1)
12	6.91 brd (8)	6.92 dd (7,3)
14	1.57 ddd (14,12,2) 2.26 ddd (14,6,2)	1.65 m 2.32 ddd (14,6,2)
15	3.39 dt (12,6)	3.40 m
16	1.98 m	2.01 brm
17	4.26 ddd (11,4,2) 4.46 t (11)	4.25 ddd (10,4,2) 4.51 t (11)
18	2.24 s	2.30 s
21	7.63 s	7.68 s

Table 18. Comparison of the ^{13}C NMR spectral data for synthetic (+)-N_a-demethylalstonisine (**17**) to that from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

	Carbon NMR	
Position	Natural sample[12]	Synthetic sample (**17**)
2	184.2	184.5
3	64.0	64.3
5	56.4	56.6
6	41.9	42.3
7	57.3	57.7
8	129.6	129.9
9	126.1	126.4
10	123.4	123.7
11	128.0	128.5
12	109.4	109.8
13	140.8	141.3
14	31.0	31.3
15	24.2	24.6
16	37.1	37.5
17	68.6	69.0
18	24.9	25.3
19	196.6	197.1
20	121.8	122.3
21	157.6	158.0

Selected NOE-NMR experiments were then carried out on synthetic (+)-N_a-demethyl-alstonisine (**17**, Figure 29). Again, irradiation of the diagnostic H-9 hydrogen-atom effected enhancement of H-15 by 8% and *vice versa*, thus, confirming the 7***S*** configuration of the spirocenter.

Figure 29. NOE NMR, N_a-demethylalstonisine



***N*$_a$-demethylalstonisine (17)**

8.6.3) Transformation of (+)-alstonisine (8) into (+)-alstofoline (18)

Several different methods for formylation of amines could be found in the literature. General formylation methodologies typically utilized *mixed anhydrides* including acetic/formic acid anhydride,[330] formic acid/ethyl dimethylaminopropylcarbodiimide (EDAC),[331] formic acid/DCC[332] and formylpivaloyl anhydride.[333] Formylation with *formates* such as 2,2,2-trifluoroethyl formate,[334] pentafluorophenylformate,[335] cyano-methylformate,[336] and ammonium formate[337] have also been reported. In addition,

chloral,[338] formic acid/Lewis acids,[339] PEG-400,[340] KF-alumina,[341] and solid-supported reagents[342] have also been employed in *N*-formylation reactions.

With all these precedents in mind, it was decided to employ conditions developed by Hill et al., that used a simple alkyl formate as the source of the formyl group.[334] The reagent 2,2,2-trifluoroethyl formate (TFEF) can be used in a variety of reaction manifolds depending on the presence of other additives. It was reasonable to think, at the beginning, that the 2,2,2-trifluoroethanol produced in the reaction might act as a nucleophile and recycle the *O*-formyl adduct. However, it was reported that 2,2,2-trifluorethanol was too poor a nucleophile to deformylate this side product.[334] Consequently, when applied to oxindole (**8**, Scheme 213), it was found that the reaction of alstonisine (**8**) with 2,2,2-trifluoroethyl formate (used as the solvent; either prepared or from commercial sources) at 65 °C for 24 hours generated the expected N_b-formyl oxindole alstofoline (**18**) as a mixture of rotamers (in a 3:1 ratio, determined by ^{1}H NMR spectroscopy) in very high yield, 90%. In order to reduce the amount of formate, a number of solvents were screened. Using a concentrated solution of 1,2-dichloroethane and as low as 5 equivalents of the trifluoro formate for 24 hours provided the same final yield of the product (Scheme 213). Other solvents employed by Hill et al., *e.g.* MTBE (20% yield), IPAc (<5% yield) and THF (35% yield) failed to afford the formyl oxindole in high yield under the same reaction conditions.

The reagent TFEF was simple to prepare from heating formic acid and 2,2,2-trifluoro-ethanol at reflux for 24 hours and purified by fractional distillation (b.p. = <70 °C) using a straightforward literature procedure.[343,334]

The ^{1}H NMR (see Table 19 below) and ^{13}C NMR (see Table 20 below) spectral data, as well as the IR spectrum [dry film on KBr: 1713 cm^{-1}, literature[12] IR (dry film) 1706 cm^{-1}], the physical properties including the specific optical rotation {[α]$^{23}_{D}$ = +32° (*c* 0.10, $CHCl_3$), literature[12] [α]$^{23}_{D}$ = +39° (*c* 0.21, $CHCl_3$)]}, and HRMS were in excellent agreement with those published in the literature by Kam et al.[12] The irradiation of the diagnostic H-9 hydrogen-atom effected enhancement of H-15 by 10% and *vice versa*, thus, confirming the 7***S*** configuration of the spiro center (NOE-NMR).

Scheme 213

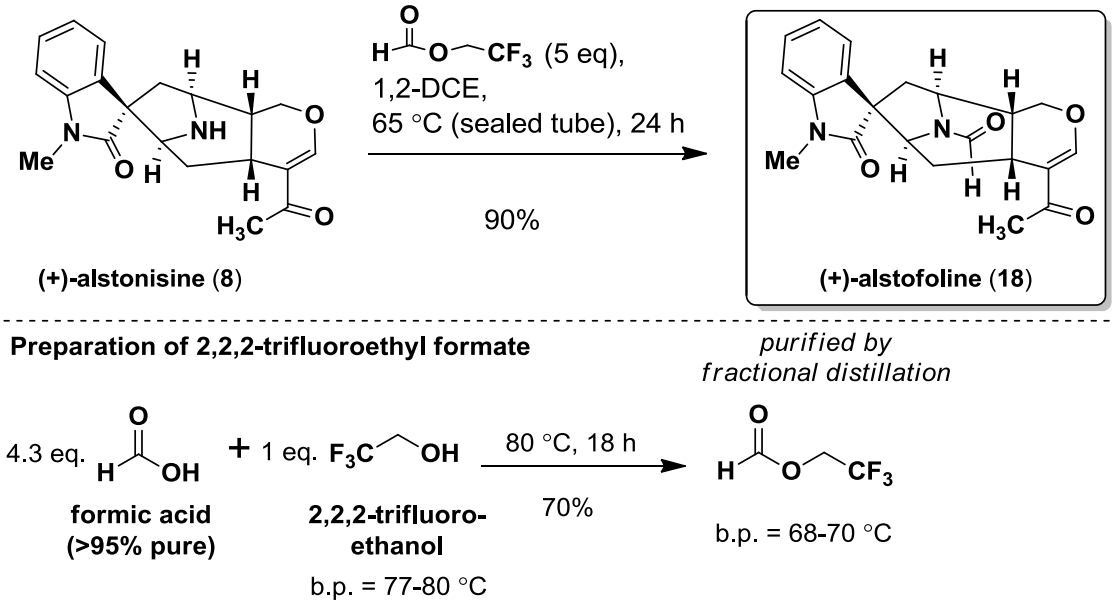


Table 19. Comparison of the ^{1}H NMR spectral data for synthetic (+)-alstofoline (**18**) to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

	Proton NMR			
Position	Natural sample, major rotamer[12]	Natural sample, minor rotamer[12]	Synthetic sample (**18**), major rotamer	Synthetic sample (**18**), minor rotamer
N_a-CH_3	3.18 s	3.17 s	3.19 s	3.17 s
N_b-CHO	8.10 s	8.10 s	8.11 s	8.11 s
3	3.82 brs	4.49 brs	3.84 brs	4.53 s
5	4.91 brd (7)	4.31 brd (7)	4.97 brd (6)	4.33 brd (6)
6	2.22 m 2.68 dd (13,7)	2.22 m 2.77 (13,7)	2.23 m 2.72 dd (13,7)	2.23 m 2.81 dd (13,7)
9	8.28 dd (8,1)	8.25 dd (8,1)	8.31 dd (7,1)	8.28 dd (7,1)
10	7.39 td (8,1)	7.39 td (8,1)	7.44 td (8,1)	7.44 td (8,1)
11	7.32 td (8,1)	7.32 td (8,1)	7.35 td (8,1)	7.35 td (8,1)
12	6.88 dd (8,1)	6.87 dd (8,1)	6.91 dd (7,1)	6.89 dd (7,1)
14	1.57 ddd (14,12,2) 2.53 ddd (14,6,3)	1.56 m 2.42 ddd (14,6,2)	1.61 m 2.56 ddd (13,6,2)	1.51 m 2.46 ddd (13,6,2
15	3.59 dt (12,6)	3.59 dt (12,6)	3.63 dt (12,6)	3.63 dt (12,6)
16	2.22 m	2.22 m	2.23 m	2.23 m
17	4.42 ddd (11,4,2) 3.90 t (11)	4.27 ddd (11,4,2) 3.96 t (11)	4.50 ddd (10,4,1) 3.93 t (10)	4.27 ddd (10,4,1) 4.01 t (10)
18	2.26 s	2.26 s	2.28 s	2.28 s
21	7.63 s	7.61 s	7.66 s	7.63 s

Table 20. Comparison of the ^{13}C NMR spectral data for synthetic (+)-alstofoline (**18**) to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

	Carbon NMR			
Position	Natural sample, major rotamer[12]	Natural sample, minor rotamer[12]	Synthetic sample (**18**), major rotamer	Synthetic sample (**18**), minor rotamer
N_a-CH_3	26.2	26.4	25.4	25.8
N_b-CHO	160.1	158.8	159.7	159.4
2	179.7	179.5	179.3	179.1
3	60.9	56.3	60.5	55.9
5	50.3	55.1	49.8	54.8
6	39.4	38.6	39.1	38.5
7	53.2	53.0	53.0	52.7
8	129.0	129.0	128.4	128.4
9	125.8	125.8	125.1	125.1
10	123.5	123.2	123.1	122.8
11	127.0	126.8	126.4	126.1
12	108.1	108.1	107.8	107.8
13	144.1	144.3	143.7	143.3
14	32.3	31.9	32.3	31.6
15	24.5	24.4	24.3	24.0
16	37.1	37.0	36.5	36.4
17	66.5	66.1	66.0	65.6

18	24.9	25.0	23.7	23.8
19	196.3	196.3	196.0	196.0
20	120.6	120.9	120.0	120.3
21	157.5	157.1	157.3	156.9

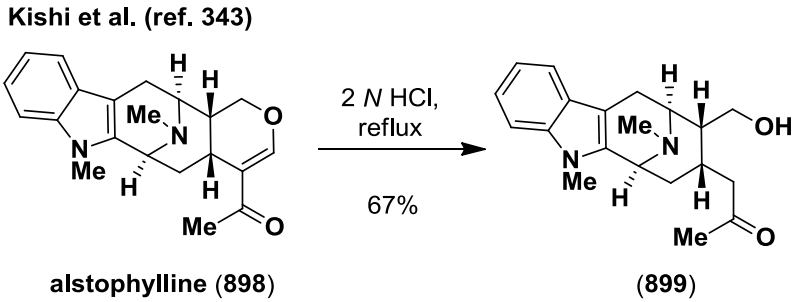
8.7) Enantiospecific synthesis of (–)-alstonoxine A (19) and (–)-macrogentine (31)

The oxindole alkaloids (–)-macrogentine (**31**) and (–)-alstonoxine A (**19**) were both isolated (by Kam et al.) from the stem-bark and leaf extract of a Malayan *Alstonia* species: *Alstonia angustifolia* var. *latifolia* K. G, but they were not found in the related Malayan *Alstonia macrophylla*.[9,12,14] The corrected C-7 assignation of configuration, which is 7*R* for macrogentine (**31**) and 7*S* for alstonoxine A (**19**), was recently published in a 2014 report.[18] The natural oxindole (–)-macrogentine (**31**) was the second sarpagine/ macroline oxindole isolated, after isoalstonisine (**27**), to possess the 7*R* configuration at the spirocenter.

The structural characterization of both alkaloids was done by Kam et al. by ^{1}H, ^{13}C, two-dimensional, and NOE NMR spectral techniques in conjunction with optical rotation measurements; UV and IR spectroscopy; and mass spectrometry.[9,12,14]

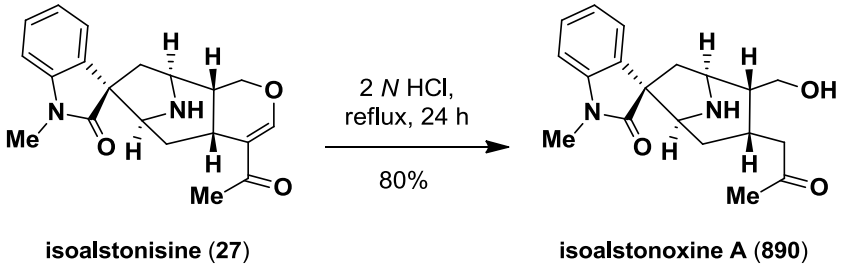
Natural (–)-alstonoxine A (**19**) is an oxindole in which cleavage of the E-ring has occurred. In a study on the alkaloid alstophylline, Kishi et al. reported experimental conditions for the acidic hydrolysis of the E-ring in the indole system (which Kam et al. also used for structural confirmation, Scheme 214).[343,12]

Scheme 214



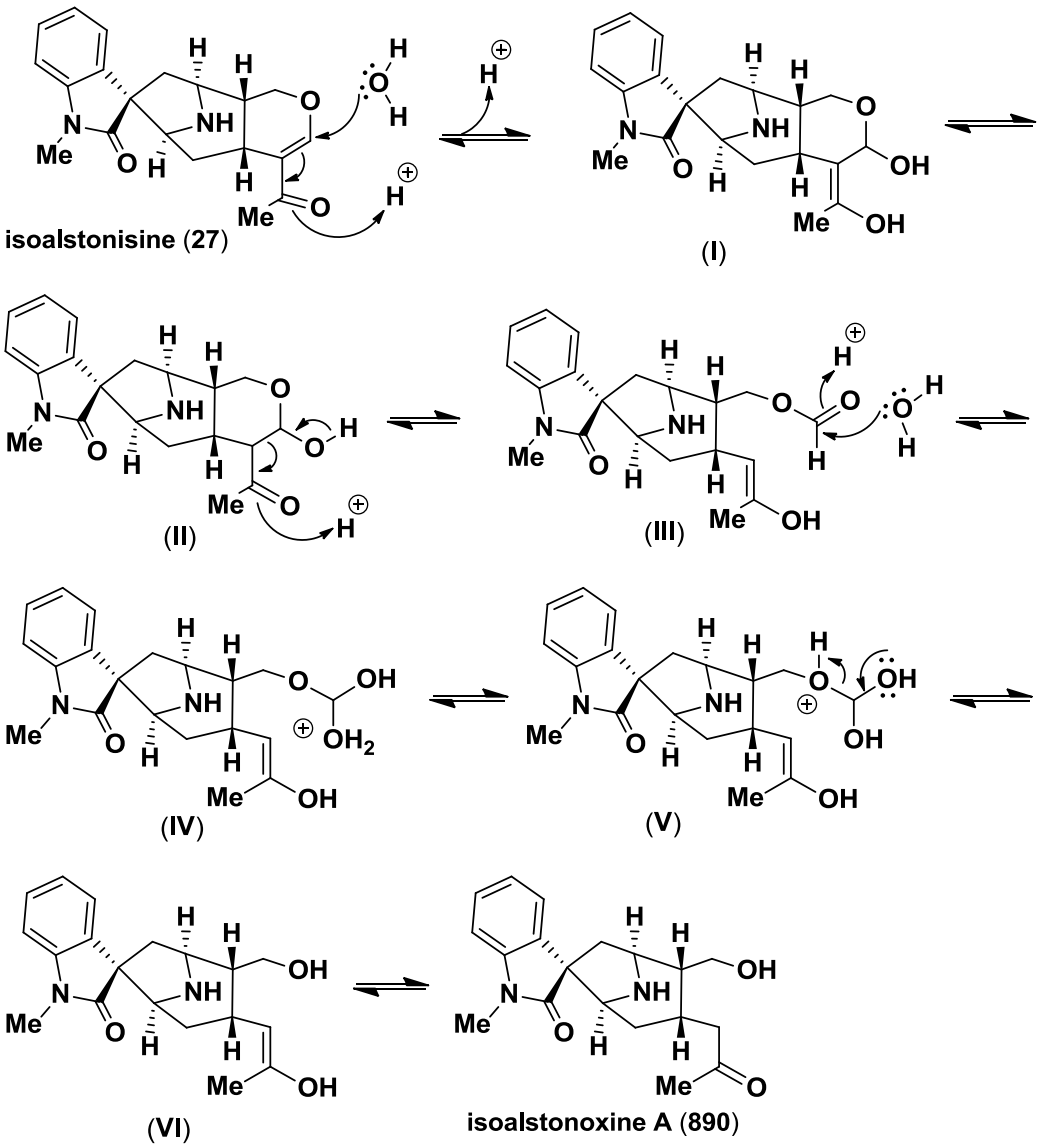
Thus, when isoalstonisine (**27**) was heated at reflux in 2 *N* HCl for 24 hours, cleavage of the E-ring was accomplished in 80% yield to provide isoalstonoxine A [**890**, C-7 epimer of alstonoxine A (**19**), Scheme 215].

Scheme 215



It is important to add that isomerization at the C-7 spiro center was not detected. Laus et al. observed that in acidic media the epimerization of oxindoles is remarkably slower due to protonation at the N_b-nitrogen atom.[261a,261b] The proposed mechanism of the opening of the E-ring is based on the studies of Kishi et al. and is shown in Scheme 216.[343]

Scheme 216



8.7.1) Epimerization at C-7 of isoalstonoxine A (890) into the natural oxindole (–)-alstonoxine A (19)

Since it was possible to achieve the diastereospecific hydrolysis of the E-ring in the C7-(*R*) series isoalstonisine (**27**) into the non-natural isoalstonoxine (**890**) in high yield, attention turned to access to two more natural sarpagine/macroline oxindole alkaloids.

Thus, when oxindole (**890**) was treated with the conditions for epimerization of the 7*R*-series to the 7*S*-series (Section 8.6.1), *e.g.* pyridine-DCM (8:2) at 100-110 °C for 60 hours, (–)-alstonoxine A (**19**) was obtained in 81% isolated yield and 18% starting oxindole (**890**) was recovered (**890**/**19** mol ratio = 1:4 in the equilibrium, Scheme 217). When the reverse epimerization, *e.g.* 7*S*-series to 7*R*-series (Section 8.6.1), was executed utilizing a pure synthetic sample of alstonoxine A (**19**) in acetonitrile at 80-85 °C with 3 equivalents of DIEA for 2 days, a mixture was reached in which the mol ratio was [**890**/**19** = 64:36, Scheme 217].

The spectral ^{1}H NMR (see Table 21 below) and ^{13}C NMR (see Table 22 below) data as well as IR spectrum [dry film on KBr: 3357, 3240, 1701 cm^{-1}, literature[12] IR (dry film) 3390, 3288, 1694 cm^{-1}], the physical properties including the specific optical rotation value {[α]$^{23}_{D}$ = –40.0° (*c* 0.15, $CHCl_3$), literature[12] [α]$^{23}_{D}$ = –34° (*c* 0.19, $CHCl_3$)]}, and HRMS were in good agreement with those published in the literature by Kam et al.[12] Selected NOE-NMR experiments were then carried out on synthetic (–)-alstonoxine A (**19**). The diagnostic H-9 hydrogen-atom effected enhancement of H-15 by 5% and *vice versa* when irradiated in a NOE NMR experiment, thus, confirming the 7***S*** configuration of the spiro center.

Scheme 217

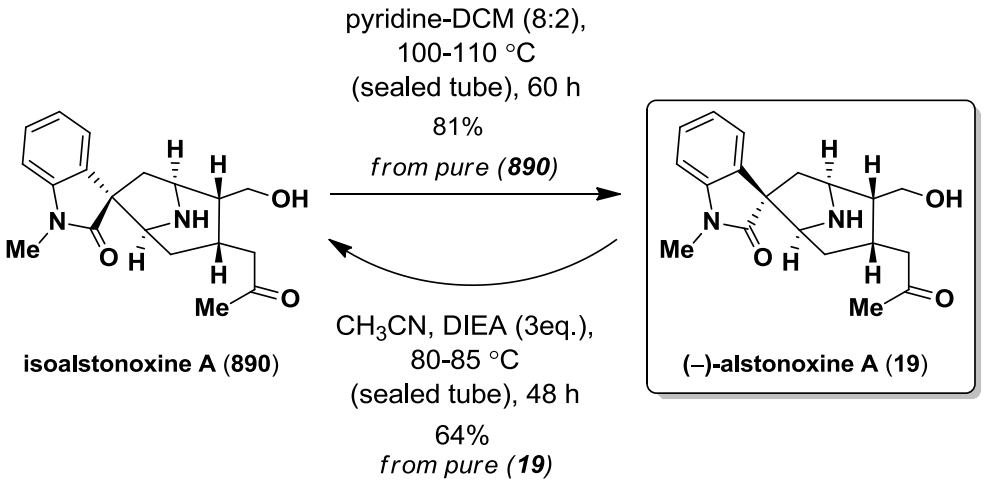


Table 21. Comparison of the ^{1}H NMR spectral data for synthetic (–)-alstonoxine A (**19**) to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

	Proton NMR	
Position	Natural sample[12]	Synthetic sample (**19**)
N_a-CH_3	3.20 s	3.19 s
3	3.25 brs	3.22 brm
5	3.90 brd (8)	3.86 d (7)
6	2.15 dd (13,2) 2.43 dd (13,8)	2.09 dd (13,2) 2.40 dd (12,8)
9	7.84 brd (8)	7.81 brd (8)
10	7.20 td (8,1)	7.17 td (8,1)
11	7.37 td (8,1)	7.31 td (8,1)
12	6.87 brd (8)	6.84 brd (8)

14	1.71 m 1.87 ddd (14,6,2)	1.66 m 1.85 m
15	3.05 m	3.00 m
16	1.71 m	1.66 m
17	3.80 dd (12,2) 4.02 dd (12,1)	3.76 dd (12,1) 4.00 dd (12,1)
18	2.21 s	2.19 s
20	2.72 dd (18,6) 2.79 dd (18,7)	2.69 dd (18,6) 2.74 dd (18,6)

Table 22. Comparison of the ^{13}C NMR spectral data for synthetic (–)-alstonoxine A (**19**) to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

	Carbon NMR	
Position	Natural sample[12]	Synthetic sample (**19**)
N_a-CH_3	26.2	26.3
2	182.3	182.7
3	63.1	63.4
5	61.7	61.9
6	40.7	41.1
7	57.2	57.8
8	129.0	129.6
9	125.0	125.4
10	123.1	123.7
11	128.1	128.5
12	108.1	108.7

13	144.1	144.5
14	33.0	33.6
15	26.1	26.7
16	41.4	41.9
17	65.8	66.1
18	30.8	30.9
19	208.4	208.7
20	47.0	47.7

8.7.2) Diastereospecific synthesis of (–)-macrogentine (31) from isoalstonoxine A (890)

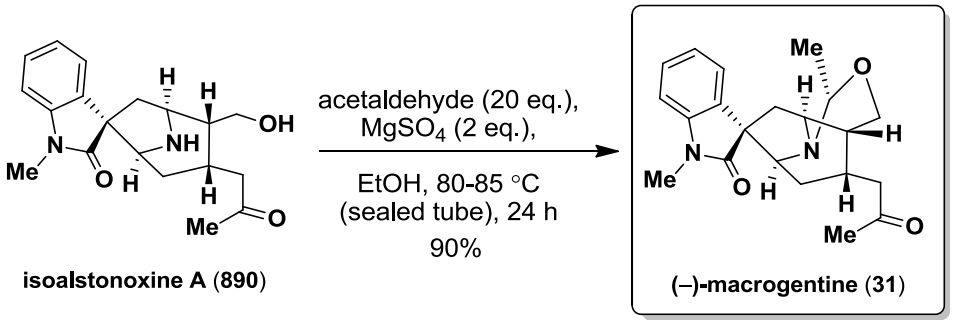
The oxindole alkaloid macrogentine (**31**) possesses a carbon skeleton in which the A, B, C, and D rings of a macroline oxindole system are essentially intact, however, cleavage and rearrangement have occurred involving the E ring. More specifically, the E-ring is a 6-member oxazolidine with the 2-position of the oxazolidine system substituted with a methyl group in the equatorial position.[12]

Oxazolidines can be synthesized by several routes, with the direct route being the condensation of amino alcohols with either aldehydes or ketones. There are many examples in the literature where amino alcohols are reacted with a ketone or aldehyde to form a 2-mono substituted oxazolidine.[344]

The most common procedure for the formation of oxazolidines from amino alcohols involves the heating of the latter in the presence of an excess of aldehyde and a dehydrating agent. Thus, when alstonoxine A (**19**) was treated with 20 equivalents of

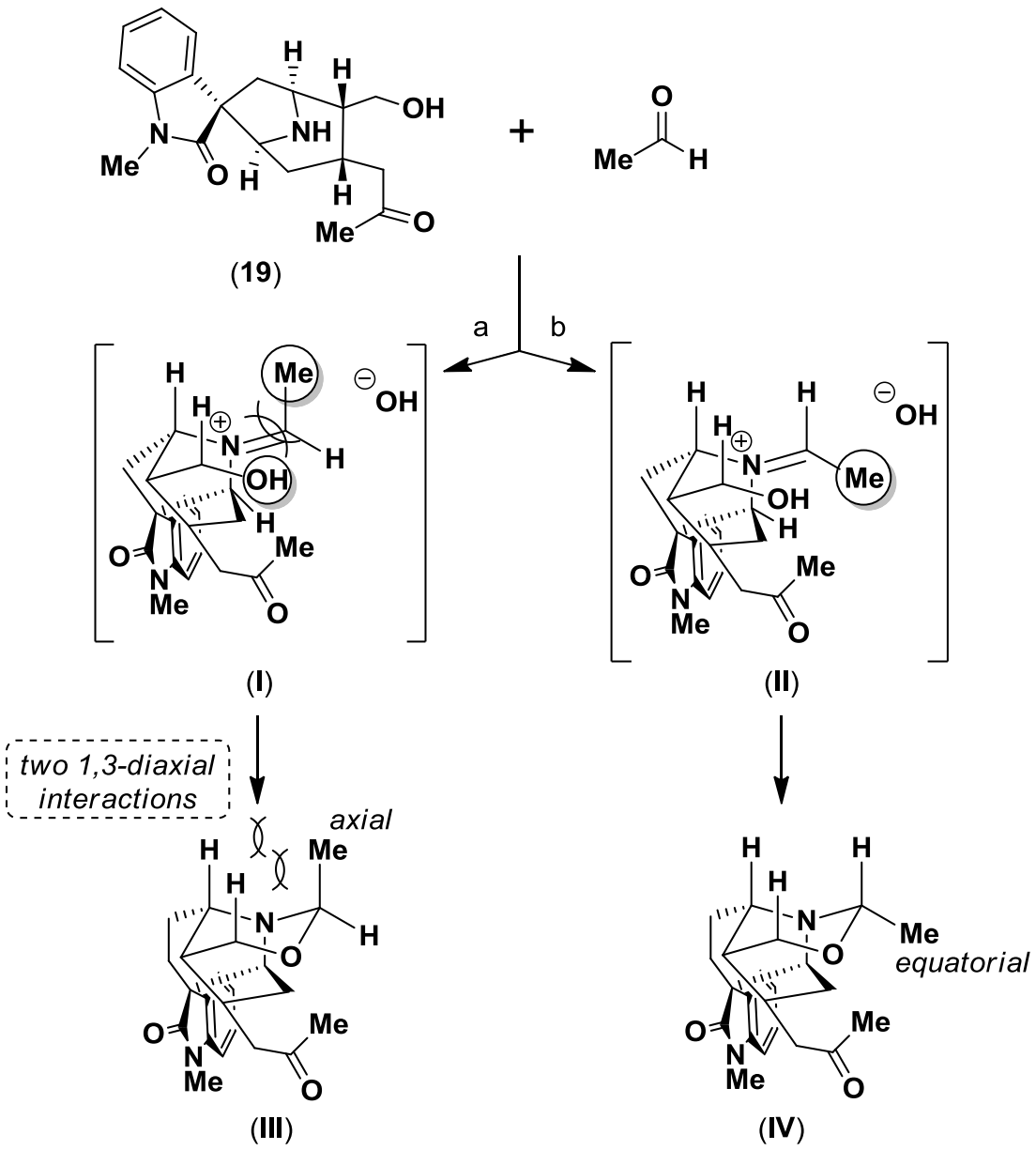
acetaldehyde, 2 equivalents of anhydrous $MgSO_4$ in absolute ethanol at 80-85 °C (in a sealed tube) for 24 hours (Hitchcock et al.[345]), the oxazolidine E-ring formed in a gratifying 90% yield, as shown in Scheme 218. The use of other solvents failed to provide a high yield under the same conditions: in DCM or $CHCl_3$ (traces of product detected); in toluene or benzene (<20% yield). Replacing the $MgSO_4$ with molecular sieves did not change the above results.

Scheme 218



As was expected from previous studies of molecular models, the newly formed C-21 stereocenter (2-position in the oxazolidine ring) had a *S* configuration with the methyl group occupying the equatorial position of the 6-member ring, as shown in Scheme 219. A proposed sequence of events, consistent with studies done by Wrackmeyer et al.;[344g] Rizk et al.;[344h] Jones et al.;[344i] Neelakantan et al.;[344j,344k] and Hagopian et al.,[344l] is shown in Scheme 219.

Scheme 219



The stereospecific formation of the equatorial methyl group was rationalized mainly by the two unfavorable 1,3-diaxial interactions between the methyl group and the protons H-5 and H-17 in the epimeric oxindole (**III**, path a, Scheme 219). Such steric interactions

are not present in the equatorial epimer (**IV**). Additionally, intermediate (**I**, Scheme 219) leading to intermediate (**III**), is more sterically hindered than intermediate (**II**) where the methyl group is located far away from the hydroxy methyl moiety. This hypothesis was confirmed by NOE NMR studies in which irradiation of the methyl group caused an increase in the H-14 signal by 13%; however, there was no enhancement in the intensity of H-5 or H-17 signals (Figure 30).

Figure 30. NOE NMR, Macrogentine

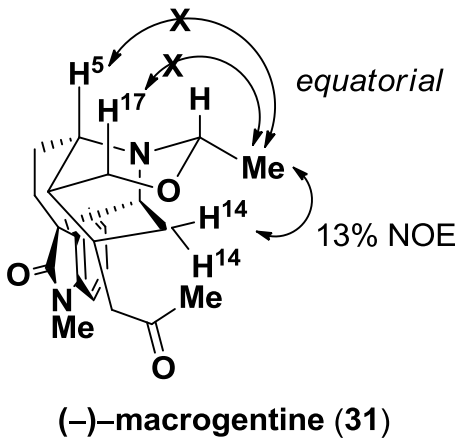


Table 23. Comparison of the ^{1}H NMR spectral data for synthetic (−)-macrogentine (**31**) to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

	Proton NMR	
Position	Natural sample[12]	Synthetic sample (**31**)
N_a-CH_3	3.22 s	3.25 s
3	3.52 d (4)	3.56 d (3)
5	3.74 dd (7,2)	3.77 d (7)
6	2.40 dd (13,2) 2.26 dd (13,7)	2.43 dd (12,2) 2.30 dd (13,6)
9	7.57 dd (8,1)	7.59 dd (8,1)
10	7.00 td (8,1)	7.05 td (8,1)
11	7.25 td (8,1)	7.30 td (8,1)
12	6.79 dd (8,1)	6.86 dd (8,1)
14	1.88 ddd (13,11,4) 1.74 ddd (13,6)	1.89 ddd (13,10,3) 1.76 ddd (13,7)
15	3.44 m	3.43 m
16	1.49 dd (5,2)	1.50 d (5)
17	3.84 d (12) 4.19 dd (12,2)	3.87 dd (12,1) 4.22 dd (12,1)
18	2.25 s	2.25 s
20	2.51 dd (15,7) 2.56 dd (15,8)	2.50 dd (15,7) 2.57 dd (15,7)
21	4.90 q (6)	4.93 q (6)
22	1.29 d (6)	1.33 d (6)

Table 24. Comparison of the ^{13}C NMR spectral data for synthetic (−)-macrogentine (**31**) to that obtained from *Alstonia angustifolia* var. *latifolia* by Kam et al.[12]

	Carbon NMR	
Position	Natural sample[12]	Synthetic sample (**31**)
N_a-CH_3	26.3	26.6
2	177.4	177.7
3	62.6	63.1
5	60.0	60.5
6	39.1	39.6
7	55.0	55.4
8	138.1	138.7
9	123.6	123.9
10	122.6	122.7
11	127.5	127.8
12	107.1	107.6
13	141.9	142.3
14	29.8	30.3
15	27.7	28.5
16	34.7	35.2
17	68.4	68.8
18	31.0	31.2
19	208.8	209.4
20	48.7	49.1
21	85.1	85.6
22	19.8	20.2

9) Conclusions

The (7***R***)-sarpagine/macroline related oxindole alkaloids (–)-isoalstonisine (**27**) and (–)-macrogentine (**31**) together with the (7***S***)-sarpagine/macroline related oxindole alkaloids (–)-affinisine oxindole (**24**), (–)-alstonoxine A (**19**), (+)-alstonisine (**8**, second generation total synthesis), (+)-N_a-demethylalstonisine (**17**) and (+)-alstofoline (**18**) were concisely synthesized during these studies.

A highly enantio- and diastereoselective general strategy to access any member of the sarpagine/macroline family of oxindole alkaloids was developed from cheap, commercially-available and optically active **D-(+)-tryptophan**. This *chiral-pool* starting material was manipulated through successive enantioselective reactions, using achiral reagents, to obtain the desired target molecules. The built-in chirality in D-(+)-tryptophan was used and expanded, *via intramolecular asymmetric induction*, to form new enantio rich compounds. Although the routes were usually stereospecific any diastereomeric byproducts enabled their facile separation by methods such as column chromatography or crystallization. This only occurred in a few instances but was the reason the chirality was built in from the beginning.

At the heart of this approach was the diastereospacific generation of the spiro[pyrrolidine-3,3′-oxindole] moiety at an early stage of the route via a *tert*-butyl hypochlorite-promoted oxidative rearrangement of chiral tetrahydro-*β*-carbolines derivatives. This key branching point determined the spatial configuration at the C-7 spiro center to be either **7*R*** or **7*S***. Other key enantiospecific initial reactions were the asymmetric Pictet–Spengler and Dieckmann cyclization which were scalable 300-600

gram levels. This early construction of the spiro oxindole moiety had the important advantage that there was no need to perfom complex studies for every single target molecule at the end of the route which involved the optimization of reaction conditions to the particular system under study, *e.g.* finding the suitable oxindole-generating reaction or screening of chiral catalysts to obtain the desired stereochemistry at C-7. On the other hand, it was well-known that oxindoles at C-7 could equilibrate between 7*R* and 7*S* through a Mannich-type process. Consequently, the careful confirmation of the diastereomeric outcome of oxindole reactions had to be realized. As a consecuance of our studies on this topic, we were able to find a set of two reaction conditions that enabled the 7R,7S-interconversion validated by X-ray crystallography in many cases as well as 1D NOE-NMR studies.

The utility of a mild Pd-promoted enolate-driven cross-coupling at room temperature, that generated the chiral center at C-14, was demostrated in . Also, the application of the Wacker–Cook (termed this by Maldonado et al.) oxidation process for the generation of the E-ring of some oxindole systems was expanded.

Finally, the complete structural elucidation of all the final products corroborated the studies by Kam et al who performed the alkaloid isolation process and initial structure determination from plant material in many cases by X-ray crystallography.

10) Experimental Section

10.1) General Characteristics

All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from Na/benzophenone ketyl prior to use. Dichloromethane was distilled from calcium hydride prior to use. Methanol was distilled over magnesium sulfate prior to use. Benzene and toluene were distilled over Na prior to use. Acetonitrile was distilled over CaH_2 prior to use. Reagents were purchased of the highest commercial quality and used without further purification unless otherwise stated. Thin layer chromatography (TLC) was performed using Dynamic Adsorbents Inc. UV active silica gel, 200 µm, plastic backed plates; Dynamic Adsorbents Inc. UV active alumina N, 200 µm, F-254 plastic backed. Flash and gravity chromatography were performed using silica gel P60A, 40-63 µm purchased from Silicycle. Basic alumina (Act I, 50-200 µm) for chromatography was purchased from Dynamic Adsorbents. Neutral alumina (Brockman I, ~150 mesh) for chromatography was purchased from Sigma-Aldrich. TLC plates were visualized by exposure to short wavelength UV light (254 nm). Indoles were visualized with a saturated solution of ceric ammonium sulfate in 50% sulfuric acid.[97] Alkynes were visualized by immersing the TLC plate in a permanganate solution,[97] followed by gentle heating with a heat gun; these compounds appeared as either yellow or light brown spots on a light purple or pink background. Elemental analyses were performed on a Carlo Erba model EA-1110 carbon, hydrogen, and nitrogen analyzer. All samples submitted for

CHN analyses were first dried under high vacuum for a minimum of six hours using a drying pistol with isopropyl alcohol or benzene as the solvent with potassium hydroxide pellets in the drying bulb. Melting points were taken on a Stuart melting point apparatus SMP3 manufactured by Barloworld Scientific US Ltd. Proton (^{1}H NMR) and carbon high resolution nuclear magnetic resonance spectra (^{13}C NMR) were obtained on a Bruker 300-MHz or a GE 500-MHz NMR spectrometer. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, sex = sextet, m = multiplet), integration, and coupling constants (Hz). ^{13}C NMR data are reported in parts per million (ppm) on the δ scale. The low resolution mass spectra (LRMS) were obtained as electron impact (EI, 70eV), which were recorded on a Hewlett-Packard 5985B gas chromatography-mass spectrometer, while high resolution mass spectra (HRMS) were recorded on a VG Autospec (Manchester, England) mass spectrometer. HRMS recorded by electrospray ionization (ESI) methods were performed at the Laboratory for Biological Mass Spectrometery at Texas A&M University on an API QStar Pulsar model manufactured by MDS Sciex. Optical rotations were measured on a JASCO Model DIP-370 digital polarimeter. Infra-red spectra were recorded on a Thermo Nicolet Nexus 870 FT-IR or a Perkin Elmer 1600 series FT-IR spectrometer.

10.2) Synthetic Procedures

D-(–)-Tryptophan methyl ester (828) from D-(+)-tryptophan.

To a (22 L)-round bottom flask which contained a freshly saturated solution of anhydrous methanolic hydrogen chloride (6000 mL) was added D-(+)-tryptophan (1,000 g, 4.90 mol). The suspension which resulted was heated to reflux for 8 h (it became a clear solution) and then allowed to cool to rt. The crystalline product which formed upon cooling was filtered out and washed with cold anhydrous diethyl ether to provide D-(–)-tryptophan methyl ester•HCl. The free base (**828**) was prepared by treatment of the corresponding HCl salt with cold aq NH_4OH (10%), followed by extraction with a solution of CH_2Cl_2-methanol (4:1, 3 x 1000 mL). The solvent was then removed under reduced pressure, after which the solid was redissolved in CH_2Cl_2 and dried (K_2CO_3). The CH_2Cl_2 was removed under reduced pressure to provide D-(–)-tryptophan methyl ester (**828**, 972 g, 91%). **m.p.** = 92-93 °C (free base); $\mathbf{[\alpha]_D^{27}}$ = –37.2° (*c* 1.0 in MeOH); **IR** (KBr) 1730 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, free base) δ 8.24 (s, 1H), 7.61 (d, 1H, *J* = 7.5 Hz), 7.35 (d, 1H, *J* = 7.5 Hz), 7.23-7.04 (m, 3H), 3.86 (dd, 1H, *J* = 7.5, 4.8 Hz), 3.74 (s, 3H), 3.29 (dd, 1H, *J* = 14.6, 5.8 Hz), 3.05 (dd, 1H, *J* = 14.5, 7.5 Hz), 1.62 (s, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$, free base) δ 175.71, 136.37, 127.57, 122.87, 122.11, 119.49, 118.73, 111.19, 55.06, 51.86, 30.83; **EIMS** (*m/e*, relative intensity) 218 ($M^{+\bullet}$, 78), 159 (57), 130 (100), 117 (33). **Anal.** calcd. for $C_{12}H_{14}O_2N_2$: C, 66.06; H, 6.42, N, 12.84, found: C, 66.14; H, 6.33; N, 12.77. This material was identical to an authentic sample.[267]

D-(+)-N_b-Benzyl tryptophan methyl ester (743) from (828).

To a round bottom flask (3000 mL) which contained a solution of D-(–)-tryptophan methyl ester (**828**, 408 g, 2.0 mol) in dry EtOH (1500 mL) was added benzaldehyde (260 g, 2.3 mol). The solution which resulted was stirred with an overhead stir for 5 h at 23 °C, until examination by TLC (silica gel) indicated the disappearance of the starting material. The mixture was then cooled in an ice-salt bath to -8 °C [It was much easier to maintain the inside temperature between -10 °C to -5 °C by the employment of a dry ice bath (without solvent)]. If the temperature falls below -15 °C, a large amount of solid will appear and it is very difficult to stir the reaction mixture. Sodium borohydride (42 g, 1.1 mol) was then added portionwise at -8 °C over a period of 3 h [The slow addition and low temperature of this process are critical to avoid racemization of the chiral center]. The solution was allowed to stir for 4 h and was then followed by the addition of ice water (50 mL). The solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (2000 mL) and washed with brine (2 x 500 mL). The organic layer was dried (K_2CO_3) and the solvent was removed under reduced pressure to give the free base (**743**, 525 g, 90%), which could be further purified by crystallization from EtOH. **m.p.** = 109-110 °C; **$[\alpha]_D^{22}$** = + 9.02° (*c* 1.0 in CH_3OH); **IR** (film) 1745 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 8.2 Hz), 7.25 (m, 7H), 7.10 (1H, m), 6.90 (s, 1H), 3.80 (m, 3H), 3.65 (s, 3H), 3,15 (m, 2H), 2.10 (s, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 175.36, 139.79, 136.30, 128.32, 128.19, 127.62, 127.03, 122.88, 122.07, 119.45, 118.84, 111.18, 61.38, 52.20, 51.68, 29.35; **EIMS** (*m/e*, relative intensity) 308 ($M^{+\bullet}$, 28), 249

(22), 178 (57), 130 (100). **Anal**. calcd. for $C_{19}H_{20}O_2N_2$: C, 74.03; H, 6.49; N, 9.08, found: C, 73.99; H, 6.56; N, 8.99. This material was identical to an authentic sample.[267]

Preparation of methyl 4,4-dimethoxybutanoate (830).

To a round bottom flask (12 L) equipped with an overhead stir which contained a solution of methyl acrylate (1075 g, 12.5 mol) and nitromethane (762.5 g, 12.5 mol) in CH_2Cl_2 (2500 mL) at 0 °C was added a solution of NaOH (60 g) in water (2500 mL) at 0 °C. The mixture which resulted was stirred at 23 °C for 2 days. The organic layer was separated and washed with water (2 x 500 mL) and dried ($MgSO_4$). The solvent was then removed under reduced pressure and the residue was distilled under reduced pressure (95-100 °C/8 mm of Hg) to give the pure methyl methyl-4-nitrobutanoate (540 g, 30%).[265] This was dissolved in methanolic sodium methoxide [5400 mL, 0.8 *N*, freshly prepared from 173 g of NaH (60% dispersion in mineral oil)] and the solution which resulted was added dropwise with an overhead stir at a rate of 1 drop per second to a round bottom flask (12 L) which contained a solution of conc sulfuric acid (1350 mL) in methanol (4 L) at -45 to -50 °C. After the addition was completed the reaction mixture was poured into CH_2Cl_2 (8 L). The organic layer was separated and washed with ice water (2 x 1000 mL), aq 4 *N* NaOH (2 x 600 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure and the residue was distilled (110-115 °C/8 mm of Hg) to provide methyl 4,4-dimethoxybutanoate (**830**, 540 g, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.38 (1H, t, *J* = 15.8 Hz), 3.66 (s, 3H), 3.31 (s, 6H), 2.37 (2H, t, *J* = 7.5 Hz), 1.92 (2H, q, *J* = 7.5 Hz); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 103.14, 53.14, 51.45, 29.07,

27.92; **CIMS** (*m/e*, relative intensity) 375 (M^+ + 1, 100). The spectral data for (**830**) were identical to the published values.[265]

Diastereospecific preparation of the *trans*-(1*S*,3*R*)-(–)-2-benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indole (484) via the modified Pictet–Spengler reaction from benzyl tryptophan (743).

To a round bottom flask (5 L) which contained a solution of optically active N_b-benzyl-D-tryptophan methyl ester (**743**, 400 g, 1.3 mol) in CH_2Cl_2 (2500 mL) was added methyl 4,4-dimethoxybutanoate (**830**, 315 g, 1.9 mol) and TFA (180 g, 2.4 eq) at 0 °C with stirring. The reaction mixture which resulted was stirred at 23 °C for 10 d and then cooled in an ice bath and brought to pH = 8 with a cold aq solution of NaOH (3 *N*). The aq layer was separated and extracted with CH_2Cl_2 (3 x 1500 mL). The combined organic layers were washed with brine (2 x 600 mL) and dried (K_2CO_3). The volume of the solution was reduced to 300 mL under reduced pressure and EtOAc (100 mL) and hexanes (300 mL) were added to the above solution. The solution was cooled to -20 °C. The *trans* diester (**484**, 402 g, 76%) precipitated out as white crystals and the mother liquor was concentrated. The residue which resulted was purified by flash chromatography (silica gel, EtOAc/hexane, 3:1) to provide additional (**484**, 83 g, 16%). The combined yield of the product was 92%. **m.p.** = 152-153 °C; $\mathbf{[\alpha]_D^{27}}$ = –35.7° (*c* 1.4, in $CHCl_3$); **IR** (film) 3310, 1731, 1707 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.43 (d, 1H, *J* = 7.2 Hz), 7.35-7.07 (m, 8H), 3.98 (dd, 1H, *J* = 8.8, 5.3 Hz), 3.93-3.87 (m, 1H), 3.84 (d, 1H, *J* = 13.6 Hz), 3.75 (s, 3H), 3.59 (d, 1H, *J* = 13.6 Hz), 3.48 (s, 3H), 3.12

(dd, 1H, J = 15.8, 8.8 Hz), 3.03 (dd, 1H, J = 15.8, 5.3 Hz), 2.50-2.20 (m, 2H), 2.15-1.85 (m, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 174.18, 173.42, 139.41, 136.50, 134.26, 129.13, 128.28, 127.13, 127.08, 121.77, 119.51, 118.16, 110.99, 107.51, 56.79, 54.81, 53.51, 51.85, 51.45, 29.88, 28.94, 21.39; **EIMS** (*m/e*, relative intensity) 406 ($M^{+\bullet}$, 60), 347 (45), 319 (100), 169 (50). **Anal.** calcd. for $C_{24}H_{26}O_4N_2$: C, 70.91; H, 6.45; N, 6.89, found: C, 70.88; H, 6.47; N, 6.91. This material was identical to an authentic sample.[267]

<u>One pot process</u> for converting D-(–)-tryptophan methyl ester (828) into *trans*-(1*S*,3*R*)-(–)-2-benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indole (484).

To a round bottom flask (12 L) which contained a solution of D-(–)-tryptophan methyl ester (**828**, 400 g, 1.83 mol) in CH_3OH (5 L) was added benzaldehyde (230 g, 2.2 mol) with overhead stirring. The solution which resulted was stirred for 6 h at 23 °C. The mixture was then cooled to -10 °C and sodium borohydride (55 g, 1.3 mol) was added portionwise over a period of 3 h. The internal reaction temperature was kept between -10 and -5 °C with a dry ice bath (solid dry ice). After analysis by TLC (silica gel, EtOAc/hexane, 1:1) indicated the disappearance of the imine, the mixture was allowed to stir for an additional 0.5 h, followed by the slow addition of CF_3COOH (260 mL) at 0 °C. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (3 L). After the solution which resulted was cooled to 0 °C, methyl 4,4-dimethoxybutanoate (**830**, 430 g, 2.8 mol) and TFA (250 g, 2.4 eq) were added to this vessel at 0 °C. The reaction mixture was stirred at 23 °C for 10 d after which it was

cooled in an ice bath and brought to pH = 8 with a cold aq solution of NaOH (3 *N*). The aq layer was separated and extracted with CH_2Cl_2 (3 x 5 L). The combined organic layers were washed with brine (2 x 200 mL) and dried (K_2CO_3). The volume of the solution was reduced to 300 mL under reduced pressure and EtOAc (100 mL) and hexanes (300 mL) were added to the above solution. The solution was cooled to -20 °C. The *trans* diester (**484**, 510 g, 69%) precipitated as white crystals and the mother liquor was concentrated and the residue which resulted was purified by flash chromatography (silica gel, EtOAc/hexane, 3:1) to provide additional (**484**, 114 g, 14%). The combined yield of product was 83% and the solid was identical to the *trans* diester (**484**) obtained from N_b-benzyl-D-tryptophan methyl ester (**743**) in the earlier experiment.

Dieckmann cyclization of the N_a-H diester (484) to provide (6*S*,10*S*)-(−)-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (−)-(837).

To a round bottom flask (2 L) which contained a suspension of sodium hydride (8.5 g, 0.21 mol, 60% in mineral oil) in dry toluene (100 mL) with stirring (overhead stir) was added a solution of N_a-H, *trans* diester (**484**, 40.6 g, 0.10 mol) in toluene (650 mL) which had been predried by azeotropic removal of H_2O by a DST (refluxed for 3 h). The reaction mixture which resulted was heated to reflux under an atmosphere of argon, after which a solution of dry CH_3OH (4 mL) in toluene (16 mL) was added dropwise over 1 h. The solution was held at reflux for an additional 72 h (**the flask was covered with aluminum foil on the top to maintain the temperature at reflux to retard**

carbonization of the lactam intermediate). After the reaction mixture was cooled to 0 °C, glacial acetic acid (15 mL) was added to the solution and this was followed by neutralization with a cold saturated aq solution of $NaHCO_3$. The mixture was extracted with toluene (3 x 400 mL) and the combined organic extracts were washed with brine (2 x 200 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure was followed by purification by flash chromatography (silica gel, EtOAc/hexane, 3:1) to provide the *N*$_a$-H, *β*-enolester (–)-(**837**) (33.8 g, 88%). **m.p.** = 149-150 °C; **[α]$_D^{27}$** = –177.4° (*c*, 1.0 in $CHCl_3$); **IR** (KBr) 1670, 1630cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 2.30 (1 H, d, *J* = 15.6 Hz), 2.82 (1H, dd, *J* = 15.5, 5.6 Hz), 2.90 (1H, d, *J* = 15.3 Hz), 3.18 (1H, dd, *J* = 15.9, 5.9 Hz), 3.66 (s, 3 H), 3.71 (1H, d, *J* = 13.4 Hz), 3.77 (1H, d, *J* = 5.3 Hz), 3.82 (1H, d, *J* = 13.4 Hz), 3.98 (1H, d, *J* = 5.4 Hz), 7.11 (1H, t, *J* = 7.1 Hz), 7.16 (1H, t, *J* = 7.0 Hz), 7.24-7.39 (6H, m), 7.50 (1H, d, *J* = 7.1 Hz), 7.63 (1H, s), 11.98 (1H, s); **^{13}C NMR** (75.5 MHz, $CDCl_3$) *δ* 22.2, 28.6, 49.7, 51.3, 55.2, 55.9, 94.3, 106.2, 110.8, 118.1, 119.5, 121.6, 127.0, 127.2, 128.4, 128.7, 133.4, 135.7, 138.3, 171.6, 172.5; **CIMS** (CH_4) (*m/e*, relative intensity) 389 (M^+ + 1, 100). **Anal.** calcd. for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48, found: C, 74.19; H, 6.23; N, 7.35. This material was identical to an authentic sample.[267]

Preparation of (6*S*,10*S*)-(–)-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (–)-(215) via hydrolysis of the *N*$_a$-H, *β*-enolester (–)-(837).

To a round bottom flask (500 mL) which contained the *N*$_a$-H, *β*-enolester [(–)-**837**, 45 g, 0.12 mol] was added glacial acetic acid (167 mL), aq hydrochloric acid (245 mL, conc.)

and water (65 mL) with stirring (magnetic stir). The solution which resulted was heated at reflux for 8 h. After removal of the solvent under reduced pressure, the residue was brought to pH = 9 with a cold aq solution of NaOH (3 *N*). The mixture which resulted was extracted with CH_2Cl_2 (4 x 250 mL) and the combined organic extracts were washed with a saturated aq solution of NH_4Cl (100 mL), brine (2 x 100 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded an oil. After a short wash column on silica gel, the N_a-H, N_b-benzyl tetracyclic ketone (–)-(**215**) (24.5 g, 64%) was crystallized from EtOAc/hexane (1:4, 30 mL). The mother liquor was concentrated under reduced pressure and the residue was chromatographed on silica gel with EtOAc/hexane (1:4) to provide additional [(–)-(**215**), 10.5 g, 27%]. The combined yield of the product was 91%. $\mathbf{[\alpha]_D^{27}}$ = –240.0° (*c* 1.0 in $CHCl_3$); **IR** (KBr) 2933, 1715 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.02(1 H, m), 2.15 (1 H, m), 2.49 (2 H, m), 2.71 (1 H, d, *J* = 16.9 Hz), 3.27 (1 H, dd, *J* = 16.9, 6.8 Hz), 3.78 (2 H, s), 3.80 (1 H, s), 4.02 (1 H, s), 7.17 (1 H, dt, *J* = 7.3, 1.0 Hz), 7.23 (1 H, dt, *J* = 7.6, 1.0 Hz), 7.30-7.38 (5 H, m), 7.54 (1 H, d, *J* = 7.6 Hz), 7.81 (1 H, s); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 20.40, 30.37, 34.51, 49.40, 56.13, 65.22, 106.73, 110.94, 118.21, 119.72, 122.01, 126.86, 127.42, 128.43, 128.60, 131.98, 135.85, 138.25, 210.40; **CIMS** (*m/e*, relative intensity) 317 (M^+ + 1). **Anal.** calcd. for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85, found: C, 79.51; H, 6.37; N, 8.85. This material was identical to an authentic sample.[267]

<u>One pot process</u> for converting trans-(1*S*,3*R*)-(–)-2-benzyl-3-methoxy carbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (484) into (6*S*,10*S*)-(–)-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*] indole (–)-(215).

The *trans* diester (**484**) (26.0 g, 64 mmol) was dissolved in dry toluene (100 mL) in a round bottom flask (250 mL) which was equipped with a Dean Stark trap (DST) and a reflux condenser. The solution which resulted was heated to reflux for 3 h with stirring (magnetic stir). The above predried solution was cooled and added to a suspension of sodium hydride (7.6 g of 60% NaH, washed twice with dry hexane) and dry toluene (650 mL) in a round bottom flask (3 L) under an atmosphere of argon. Dry CH_3OH (8 mL) was added carefully (**a large amount of H_2 gas was evolved at this point**). The mixture was stirred at 23 °C for 0.5 h, and then heated to reflux for an additional 72 h. After analysis by TLC (silica gel, EtOAc/hexane, 1/4) indicated the disappearance of starting material, the reaction mixture was cooled to 0 °C and then quenched carefully with glacial acetic acid (15 mL). The solvent was removed under reduced pressure and glacial acetic acid (167 mL), aq hydrochloric acid (245 mL, conc.) and water (65 mL) were added to the above vessel. The mixture which resulted was heated at reflux for 8 h. After removal of the solvent under reduced pressure, the residue was brought to *p*H = 9 by addition of an aq solution of cold NaOH (3 *N*). The mixture which resulted was extracted with CH_2Cl_2 (4 x 250 mL) and the combined organic extracts were washed with a saturated aq solution of NH_4Cl (100 mL), brine (2 x 100 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded an oil which was

chromatographed on silica gel with EtOAc/hexane (3:7) to provide the tetracyclic ketone (**215**, 16.4 g, 82%), which was identical to the ketone obtained from enolester (**837**, see above).

Catalytic debenzylation of (6*S*,10*S*)-(–)-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (215) to provide (6*S*,10*S*)-(–)-9-oxo-12-H-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (217) over Pd/C, H_2.

The N_a-H, N_b-benzyl tetracyclic ketone (**215**, 10 g, 31.7 mmol) was suspended in anhydrous EtOH (100 mL), and saturated ethanolic HCl (15 mL) was added dropwise to form a clear solution. The solvent was removed under reduced pressure. Then the residue was dissolved again in dry EtOH (80 mL), and the solvent was removed under vacuum. This process was repeated three times after which EtOH (50 mL) and Pd/C (10%, 2.0 g) were added. The mixture that resulted was allowed to stir at 23 °C under an atmosphere of hydrogen for 5 h. Analysis by TLC (silica gel) indicated the absence of starting material. The catalyst was removed by filtration and was washed with EtOH (3 x 50 mL). The solvent was removed under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 and aq NH_4OH (5:1, 100 mL). The layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (20 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded the crude product, which was purified by chromatography on silica gel [$CHCl_3$/MeOH (20:1)] to provide pure N_a-H, N_b-H tetracyclic ketone (**217**, 6.2 g, 88%): **FTIR** (NaCl) 3390, 3384, 1709 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.08-2.15 (2H, m), 2.39-2.50 (3H, m), 2.80 (1H, d, J = 16.4

Hz), 3.08 (1H, dd, *J* = 16.5, 6.8 Hz), 3.97 (1H, d, *J* = 6.7 Hz), 4.27 (1H, d, *J* = 3.9 Hz), 7.10 (1H, d, *J* = 7.4 Hz), 7.16 (1H, d, *J* = 7.4 Hz), 7.29 (1H, d, *J* = 7.9 Hz), 7.44 (1H, d, *J* = 7.6 Hz), 8.06 (1H, bs); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 25.78, 31.96, 35.02, 46.06, 59.75, 107.50, 110.90, 118.14, 119.76, 122.09, 126.85, 133.95, 135.71, 210.95; **CIMS** (*m*/*e*, relative intensity) 227 (M+ 1, 100). **Anal.** calcd for $C_{14}H_{14}N_2O$: C, 74.34; H, 6.26; N, 12.32, found: C, 74.36; H, 6.38; N, 12.44. This material was identical to an authentic sample.[267]

Preparation of *tert*-butyl hypochlorite.

To around bottom flask (500 mL) which contained a stirred mixture of Clorox® (167 mL, 5.25% in NaOCl) and ice (30 g) was added a mixture of pure *tert*-butanol (12.3 mL) and concentrated AcOH (8.2 mL) at 0 °C. The reaction mixture which resulted was stirred at 0 °C for an additional 10 min. The organic layer was then separated and washed quickly with an aq solution of cold $NaHCO_3$ (10 mL), brine (10 mL) and dried (Na_2SO_4) to provide *tert*-butyl hypochlorite (7.9 g, 80%). It was directly employed for the next step. **This reagent must be kept cold**, **managed in dim light, and avoid contact with rubber. If store in the refrigerator, it must be in a brown bottle at or below 0 °C.**[269]

Diastereospecific conversion of the N_a-H, N_b-benzyl ketone (215) into the N_a-H, N_b-benzyl ketooxindole (216) *via tert*-butyl hypochlorite oxidation.

To a round bottom flask (100 mL) which contained a stirred solution of N_a-H, N_b-benzyl ketone (**215**, 816 mg, 2.5 mmol) and Et_3N (0.28 g, 1.1 equivalents) in DCM (30 mL) was added the freshly prepared *tert*-butyl hypochlorite (0.36 g, 0.4 mL, 3 mmol) at 0 °C. The reaction mixture which resulted was stirred at 0 °C for 12 h. The solvent was removed under reduced pressure and the solid which resulted was dissolved in a solution of MeOH-10% AcOH (1:1, 20 mL). The reaction mixture which resulted was heated to reflux for 2 hours and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and the organic layer was washed with an aq solution of $NaHCO_3$ (20 mL), brine (2 x 20 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (silica gel, EtOAc/hexane, 3/7) to provide the N_a-H, N_b-benzyl ketooxindole (**216**, 770 mg, 93%). **m.p.** = 203-204 °C; $\mathbf{[\alpha]_D^{27}}$ = +182.3° (*c* 0.95, in $CHC1_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.30-2.41(2H, m), 2.41-2.43 (1H, m), 2.43-2.56 (2H, m), 3.15 (1H, d, *J* = 2.56 Hz), 3.41 (1H, dt, *J* = 8.8, 10.4 Hz), 3.55 (1H, d, *J* = 7.20 H z), 3.89 (2H, dd, *J* = 4.1, 13.1 Hz), 6.89 (1H, d, *J* = 7.5 Hz), 7.11 (1H, t, *J* = 7.5 Hz), 7.24 (1H, t, *J* = 7.5 Hz), 7.26-7.42 (5H, m), 7.77 (1H, d, *J* = 7.5 Hz), 8.66 (1H, s); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 23.67, 34.27, 39.61 , 51.67, 55.71, 65.26, 67.51, 109.05, 122.87, 123.96, 127.33, 127.88, 128.38, 128.80, 137.49, 137.65, 139.14, 179.56, 212.59; **IR** (KBr) 3236, 1707, 1676,1466 cm^{-1}; **MS(EI)** m/z (%) 333 (M^+ + 1,100%), 304 (7%), 189(6%). **Anal.** calcd. for $C_{21}H_{20}N_2O_2$: C, 75.90; H, 6.02; N, 8.43, found: C, 76.22; H, 6.40; N, 8.10.

Diastereospecific conversion of the N_a-H, N_b-H, ketone (217) into the N_a-H, N_b-H ketooxindole (218) *via* tert-butyl hypochlorite oxidation.

To a round bottom flask (50 mL) which contained a stirred solution of N_a-H, N_b-H ketone (**217**) (113 mg, 0.5 mmol) and Et_3N (0.1 g, 1.2 equivalents) in DCM (20 mL) was added the freshly prepared *tert*-butyl hypochlorite (72 mg, 80 µL, 0.6 mmol) at 0 °C. The reaction mixture which resulted was stirred at 0 °C for 12 hours. The solvent was removed under reduced pressure and the solid which resulted was dissolved in a solution of MeOH-10% AcOH (1:1, 15 mL). The solution which resulted was heated to reflux for 2 hours and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and the organic layer was washed with an aqueous solution of $NaHCO_3$ (10 mL), brine (2 x 10 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude oxindole was purified by flash chromatography (silica gel, EtOAc/hexane, 3/5) to provide the N_a-H, N_b-H ketooxindole (**218**, 97 mg, 80%). $[\alpha]_D^{27}$ = –65.9° (*c* 1.0, $CHC1_3$); **IR** (KBr): 3400-3100,1700,1610 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 192-215 (3H, m), 2.51-2.62 (3H, m), 2.53 (1H, d, J = 6.6 Hz), 3.90 (1H, d, J = 8.7 Hz), 6.95 (1H, d, J = 8.7 Hz), 8.95 (1H, s); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 24.82, 34.42, 40.35, 58.18, 63.25, 66.64, 110.40, 122.68, 123.96, 128.46, 141.47, 184.30, 207.24; **MS(CI)** m/z (%) 243 (M +l, 100%). **Anal.** calc. for $C_{14}H_{14}N_2O_2$: C, 69.14; H, 5.79; N, 11.57, found: C, 68.86; H, 6.01; N, 11.37.

Synthesis of N_a-methyl, N_b-H tetracyclic ketone oxindole (849) from oxindole (218).

To a round bottom flask (1000 mL) which contained a solution of pure N_a-H, N_b-H tetracyclic ketone oxindole (**218**, 3 g, 12.4 mmol) in dry THF (300 ml) under argon at 0 °C, was added NaH (0.545 g, 13.6 mmol, 60% dispersion in mineral oil). The slurry which resulted was allowed to stir at 0 °C for 5 min and then CH_3I (2.1 g, 14.8 mmol) was added to the reaction flask through a syringe. The reaction solution was allowed to reach rt and this was followed by TLC analysis (SiO_2 gel, EtOAc-hexanes = 3:1) until disappearance of starting material (**218**). The solution was quenched by careful addition of cold water (10 mL) and then concentrated under reduced pressure to a third of its volume. Then CH_2Cl_2 (500 mL) was added to the mixture and the solution was successively washed with 10% aq $NaHCO_3$ (2 x 100 mL), brine (100 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded the crude solid, which was purified by flash chromatography (SiO_2 gel, EtOAc-hexanes = 1:1) to provide the pure oxindole (**849**) as an amorphous pale yellow solid (2.54 g, 80% yield): **m.p.** = 80-82 °C; $\mathbf{[\alpha]_D^{27}}$ = +26.4° (*c* 0.25, $CHCl_3$); **IR** (KBr) 3300, 2937, 1695, 1611, 1493, 1471, 1374, 1349, 752 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 (td, *J* = 7.5, 1 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.15 (td, *J* = 7.5, 1 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 3.95 (d, *J* = 8 Hz, 1H), 3.48 (d, *J* = 5.3 Hz, 1H), 3.25 (s, 3H), 2.62 (m, 3H), 2.11 (m, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 207.1 (C), 182.1 (C), 154.6 (C), 144.3 (C), 128.4 (CH), 123.6 (CH), 122.7 (CH), 108.5 (CH), 60.1 (C), 40.5 (CH_2), 32.4 (CH_2), 26.4 (CH_3), 24.8 (CH_2); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{15}H_{16}N_2O_2$ $(M+H)^+$ = 257.1212, found 257.1208.

Large scale one-pot synthesis of (*Z*)-2-iodobuten-1-ol (852) from crotonoaldehyde (848).

To a cold (using dry ice) stirred solution of crotonaldehyde (200 g, 234 mL, 2.85 mol) in 1:1 THF-H_2O (10 L) was added K_2CO_3 (480 g, 3.47 mol), I_2 (1095 g, 4.31 mol) and DMAP (70 g, 0.57 mol) successively. The reaction mixture was gradually allowed to come to rt and stirred for a total of 5 h. Upon completion by TLC, the reaction mixture was again cooled (using dry ice). Small portions of $NaBH_4$ (54 g, 1.43 mol) were gradually added to the reaction mixture and the reaction was constantly monitored for completion. The mixture was subsequently extracted with EtOAc and dried over Na_2SO_4, before concentration and purification by flash column chromatography (EtOAc-hexanes, 1:4) afforded 530 g (95%) of the (*Z*)-2-iodobuten-1-o1. The ^1H and ^{13}C NMR data were identical to those reported in the literature.[273b,273c]

Synthesis of (*Z*)-1-bromo-2-iodo-2-butene (847) from (*Z*)-2-iodobuten-1-ol (852).

To a cold, stirred solution of alcohol (**847**, 52 g, 0.26 mol) in dry diethyl ether (1000 mL at 0 °C) was added PBr_3 (0.4 equivalents, 28.5 g) slowly. After the addition was complete, the reaction solution was slowly allowed to reach rt and stirred for a total of 22 hours. Cold water (200 mL, 0 °C) was then slowly added to the solution to quench the reaction. The layers were separated and the aq layer was further extracted with diethyl ether (3 x 200 mL). The organic layers were combined and dried (Na_2SO_4). The solvent was later removed under vacuum to afford 62 g (93% yield) of (*Z*)-1-bromo-2-iodo-2-

butene (**847**) as a light yellow clear oil. No further purification was needed. The ^{1}H and ^{13}C NMR data were identical those reported in the literature.[273a,273d]

Synthesis of N_b-allyl-tetracyclic ketone oxindole (846) from oxindole (849).

The N_a-methyl, N_b-H ketooxindole (**849**, 2 g, 7.8 mmol), (*Z*)-1-bromo-2-iodo-2-butene (**847**, 16.3 g, 62.5 mmol) and *N*,*N*-diisopropylethylamine (DIEA, 1.31 g, 10.1 mmol) were added to a 1-neck round-bottom flask with a stirring bar such that the flask was half full. The flask was closed with a rubber septum and the air evacuated using a stream of argon. The reaction flask was then placed inside an oil bath at 50 °C and the reaction progress monitored by TLC [SiO_2 gel, EtOAc-hexanes = 1:1 to check for the disappearance of (**849**); EtOAc-hexanes = 1:3 to check for the formation of oxindole (**846**)]. After the starting material (**849**) was completely consumed, the reaction mixture was allowed to cool to rt. The crude mixture was then directly subjected to flash chromatography (SiO_2 gel, hexanes + 1% Et_3N was used first to recover unreacted excess of (**847**), then the solvent was switched to CH_2Cl_2 + 1% Et_3N to recover the pure oxindole **846**). The expected pure allyl oxindole (**846**) was obtained as an amorphous yellow solid (3.1 g, 90% yield): **m.p.** = 58-60 °C; $\mathbf{[\alpha]^{26}_D}$ = +39.7° (*c* 2.3, $CHCl_3$); **IR** (KBr) 2933, 1700, 1611, 1471, 1374, 1349, 754 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 7.04 (td, *J* = 7.5, 1 Hz, 1H), 6.99 (dd, *J* = 7.5, 1 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.04 (qt, *J* = 6.4, 1 Hz, 1H), 4.00 (dt, *J* = 14, 1 Hz, 1H), 3.75 (brd, *J* = 7.3 Hz, 1H), 3.68 (dt, *J* = 14, 1 Hz, 1H), 3.62 (brd, *J* = 6.9 Hz, 1H), 3.21 (s, 3H), 2.90 (m, 1H), 2.81 (q, *J* = 7.4 Hz, 1H), 2.46 (ddd, *J* = 17.4, 8.9, 3.6 Hz, 1H), 2.24 (m,

1H), 2.13 (d, *J* = 13.5 Hz, 1H), 1.82 (d, *J* = 6.4 Hz, 3H), 1.69 (m, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.7 (C), 181.4 (C), 143.7 (C), 132.6 (CH), 130.2 (C), 128.1 (CH), 124.0 (CH), 122.4 (CH), 109.8 (C), 107.9 (CH), 71.2 (CH), 66.4 (CH), 62.6 (CH_2), 58.2 (C), 41.2 (CH_2), 34.2 (CH_2), 26.4 (CH_3), 23.1 (CH_2), 21.7 (CH_3); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{19}H_{21}IN_2O_2$ $(M+H)^+$ = 437.0648, found 437.0697.

Synthesis of N_b-allyl oxindole (846) by epimerization at C-7 of N_b-allyl oxindole (854).

In a 10 mL screw-cap glass tube with a magnetic sitrrer, oxindole (**854**, 10 mg, FW = 436.29, 0.023 mmol) was placed into a pyridine- CH_2Cl_2 (8:2, 5 mL) mixture. The vessel was capped with a rubber septum, then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 100-110 °C [external temperature (or oil bath temperature)] and allowed to run for 60 h with vigorous magnetic stirring. The vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was chromatographed (SiO_2 gel, CH_2Cl_2-EtOAc = 7:3 + 1% Et_3N). The expected oxindole (**846**) was obtained as an amorphous yellow solid (6 mg, 60% yield). *Note 1*: the reaction was also carried out at reflux with a condenser with the same experimental results. *Note 2*: see the latter procedure for the complete characterization data of this oxindole.

Synthesis of N_a-methyl, N_b-benzyl tetracyclic ketone oxindole (855) from oxindole (216).

To a round bottom flask (3000 mL) which contained a solution of pure N_a-H, N_b-benzyl tetracyclic ketone oxindole (**216**, 29 g, 87.2 mmol) in dry THF (1000 mL) under argon at 0 °C, NaH (3.7 g, 91.6 mmol, 60% dispersion in mineral oil) was slowly added in portions. The slurry which resulted was allowed to stir at 0 °C for 5 min and then CH_3I (13.6 g, 95.8 mmol) was added to the reaction flask through a syringe. The reaction solution was allowed to reach rt and this was followed by analysis on TLC (SiO_2 gel, CH_2Cl_2) until disappearance of starting oxindole (**216**) was realized. The solution was then quenched by careful addition of cold water (50 mL) and then concentrated under reduced pressure to a third of its volume. The CH_2Cl_2 (2000 mL) was added to the mixture and the solution was successively washed with 10% aq $NaHCO_3$ (2 x 500 mL), brine (500 mL) and dried (K_2CO_3). The removal of the solvent under reduced pressure afforded the crude product, which was purified by flash chromatography (SiO_2 gel, CH_2Cl_2 + 1% Et_3N) to provide the pure oxindole (**855**) as an amorphous pale yellow solid (25.4 g, 87% yield): **m.p.** = 86-88 °C; $\mathbf{[\alpha]^{24}_D}$ = +112.4° (*c* 0.93, CH_2Cl_2); **IR** (KBr) 2926, 1701, 1610, 1491, 1469, 1374, 1351, 1123, 1084, 749, 700 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.4, 1H), 7.42-7.26 (m, 6H), 7.13 (td, *J* = 7.5, 1 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 3.92 (dd, *J* = 18.3, 13 Hz, 2H), 3.58 (d, *J* = 7 Hz, 1H), 3.52 (m, 1H), 3.25 (s, 3H), 3.14 (d, *J* = 2.5 Hz, 1H), 2.48-2.44 (m, 2H), 2.39 (m, 1H), 2.34-2.24 (m, 2H); ^{13}**C NMR** (75.5 MHz, $CDCl_3$) δ 212.6 (C), 177.2 (C), 142.1 (C), 137.5 (C), 137.1 (C), 128.1 (CH), 128.4 (CH), 127.9 (CH), 127.3 (CH), 123.5 (CH), 122.9 (CH), 107.5 (CH), 67.5

(CH), 65.1 (CH), 55.3 (C), 51.7 (CH_2); 39.6 (CH_2); 34.3 (CH_2); 26.4(CH_3); 23.7 (CH_2); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{22}H_{22}N_2O_2$ $(M+H)^+$ = 347.1760, found 347.1772.

Synthesis of N_a-methyl, N_b-H tetracyclic ketone oxindole (856) from oxindole (855).

Pure N_a-methyl, N_b-benzyl tetracyclic ketone oxindole (**855**, 1 g, 2.89 mmol) was dissolved in a mixture of MeCN-H_2O (5:1, 200 mL) at rt. Ceric ammonium nitrate (CAN, 3.49 g, 6.36 mmol) was then added portionwise to the above solution and the reaction progress was monitored by TLC (SiO_2 gel, EtOAc-hexanes = 1:1). Once the starting material, oxindole (**855**), was completely consumed (do not keep the product in the reaction mixture for a longer time otherwise the yield decreases), the reaction solution was quenched by addition of saturated aq $NaHCO_3$ solution (50 mL) and stirred vigorously for 10 min. The solution was concentrated to a third of its initial volume and then brine (300 mL) was added to the mixture. The solution was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were dried (K_2CO_3). The removal of the solvent afforded a crude solid which was purified by flash chromatography (SiO_2 gel, EtOAc-hexanes = 1:4) to provide pure oxindole (**856**) as a white crystalline solid (0.44 g, 60% yield): **m.p.** = 98-101°C; $\mathbf{[\alpha]^{23}_D}$ = +112.0° (*c* 0.1, $CHCl_3$); **IR** (KBr) 3288, 2944, 1695, 1610, 1493, 1470, 1352, 1085, 752 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.5, 1 Hz, 1H), 7.31 (td, *J* = 7.5, 1 Hz, 1H), 7.09 (td, *J* = 7.5, 1 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 3.91 (brt, *J* = 4 Hz, 1H), 3.47 (dt, *J* = 17, 9.6 Hz, 1H), 3.36 (d, *J* = 4.3 Hz, 1H), 3.28 (s, 3H), 2.49-2.41 (m, 3H), 2.33 (dd, *J* = 14, 9.4 Hz, 1H), 2.00-1.88 (m, 1H); **^{13}C**

NMR (75.5 MHz, $CDCl_3$) δ 208.7 (C), 177.0 (C), 142.0 (C), 136.9 (C), 127.9 (CH), 122.9 (CH), 122.6 (CH), 107.7 (CH), 65.6 (CH), 63.8 (CH), 56.1 (CH), 40.3 (CH_2), 33.7 (CH_2), 30.5 (CH_2), 26.4 (CH_3); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{15}H_{16}N_2O_2$ $(M+H)^+$ = 257.1212, found 257.1285.

Synthesis of N_b-allyl-tetracyclic ketone oxindole (854) from oxindole (856): Method (A).

Method (A) from oxindole (**856**): The N_a-methyl, N_b-H ketooxindole (**856**, 3.7 g, 14.4 mmol), (*Z*)-1-bromo-2-iodo-2-butene (**847**, 30 g, 115.5 mmol) and *N*,*N*-diisopropylethylamine (DIEA, 2.2 g, 17.3 mmol) were added to a 1-neck round-bottom flask with a stirring bar such that the flask was half full. The flask was closed with a rubber septum and the air evacuated using a stream of argon. The reaction flask was placed inside an oil bath at 50 °C and the reaction progress was monitored by TLC [SiO_2 gel, EtOAc-hexanes = 1:1 to check for the disappearance of (**856**), EtOAc-hexanes = 1:3 to check for the formation of oxindole (**854**)]. After the starting material (**856**) was completely consumed, the reaction mixture was allowed to cool to rt. The crude mixture was then directly subjected to flash chromatography [SiO_2 gel, CH_2Cl_2 was used first to recover unreacted excess of (**847**); then was switched to CH_2Cl_2-EtOAc = 7:3 + 1% Et_3N to recover pure product]. The expected pure oxindole (**854**) was recovered a an amorphous yellow solid (5.7 g, 91% yield, see Method (b), below, for full structural characterization).

Synthesis of N_b-allyl-tetracyclic ketone oxindole (854) from oxindole (856): Method (B).

Method (B) from oxindole (**856**): The N_a-methyl, N_b-H ketooxindole (**856**, 2 g, 7.8 mmol), (*Z*)-1-bromo-2-iodo-2-butene (**847**, 2.2 g, 8.6 mmol) and *N*,*N*-diisopropylethylamine (DIEA, 1.1 g, 8.6 mmol) were dissolved in CH_3CN (200 mL) in a 2-neck round-bottom flask with a stirring bar under argon. The flask was heated to reflux for 48 h and the reaction progress monitored by TLC [SiO_2 gel, EtOAc-hexanes = 1:1 to check for the disappearance of (**856**); EtOAc-hexanes = 1:3 to check for the formation of (**854**)]. After starting material (**856**) was completely consumed, the reaction mixture was allowed to cool to rt. The solvent was removed under reduced pressure and the residue was chromatographed (SiO_2 gel, CH_2Cl_2-EtOAc = 7:3 + 1% Et_3N). The expected pure oxindole (**854**) was recovered as an amorphous yellow solid (3.4 g, 90% yield): **m.p.** = 73-75 °C; $\mathbf{[\alpha]^{26}_D}$ = +58.7° (*c* 0.15, $CHCl_3$); **IR** (KBr) 2946, 1704, 1611, 1471, 1374, 1351, 753 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.4, 1 Hz, 1H), 7.31 (td, *J* = 7.4, 1 Hz, 1H), 7.12 (td, *J* = 7.4, 1 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 5.87 (qt, *J* = 6.4, 1 Hz, 1H), 3.61 (m, 3H), 3.58 (d, *J* = 1.5 Hz, 1H), 3.27 (s, 3H), 3.18 (d, *J* = 4 Hz, 1H), 2.50 (d, *J* = 7.8 Hz, 1H), 2.43 (d, *J* = 1 Hz, 1H), 2.37 (m, 1H), 2.32 (d, *J* = 8.2 Hz, 1H), 2.27 (d, *J* = 9.4 Hz, 1H), 1.80 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.0 (C), 177.2 (C), 141.9 (C), 136.8 (C), 134.1 (CH), 127.9 (CH), 125.1 (CH), 123.1 (CH), 107.3 (CH), 105.5 (C), 66.7 (CH), 65.6 (CH), 59.4 (CH_2), 55.4 (C), 39.6 (CH_2), 34.3 (CH_2), 26.4 (CH_3), 24.6 (CH_2), 21.7 (CH_3); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{19}H_{21}IN_2O_2$ $(M+H)^+$ = 437.0648, found 437.0683.

Synthesis of N_b-allyl oxindole (854) by epimerization at C-7 of N_b-allyl oxindole (846).

In a 10 mL screw-cap glass tube with a magnetic sitrrer, alstonisine (**846**, 20 mg, FW = 436.29, 0.046 mmol) and diisopropylethylamine (DIEA, 3 equivalents, 0.138 mmol, 18 mg) were placed into acetonitrile (10 mL). The vessel was capped with a rubber septum and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 80-85 °C [external temperature (or oil bath temperature)] and allowed to run for 48 h with vigorous magnetic stirring. The vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was chromatographed (SiO_2 gel, CH_2Cl_2-EtOAc = 7:3 + 1% Et_3N). The expected pure oxindole (**854**) was obtained as an amorphous yellow solid (19 mg, 95% yield). *Note*: the reaction was also carried out at reflux with a condenser with the same experimental results. *Note*: see the latter procedure for the complete characterization data of this oxindole.

Synthesis of pentacyclic ketone oxindole (857) from oxindole (846).

Method A: A mixture of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**846**, 1.0 g, 2.3 mmol), $Pd(PPh_3)_4$ (0.265 g, 0.23 mmol) and $PhONa•3H_2O$ (0.975 g, 5.7 mmol) was dissolved in THF (previously distilled over Na/benzophenone ketyl, 250 mL), and then the system was degassed (freeze-pump-thaw degassed, 3-5 cycles). The solution was then

heated to reflux under argon for 2 h. Analysis by TLC (SiO_2 gel, EtOAc-hexanes = 4:1) indicated the disappearance of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**846**) and the presence of a new oxindole component of lower *Rf* value. The solution was allowed to warm to rt and then was concentrated to a third of its original volume under reduced pressure. The residue was dissolved in CH_2Cl_2 (500 mL) and washed with 10% aq $NaHCO_3$ (2 x 100 mL), brine (100 mL) and then dried (K_2CO_3). Removal of the solvent provided a mixture which was subjected to flash chromatography (SiO_2 gel, EtOAc-hexanes = 4:1) to afford the expected oxindole (**857**) as an amorphous pale yellow solid (0.46 g, 65% yield).

Method B: A mixture of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**846**, 1.0 g, 2.3 mmol), Pd_2dba_3 (0.842 g, 0.92 mmol) and NaHMDS (2 equivalents, 0.843 g, 4.6 mmol) was dissolved in THF (previously distilled over Na/benzophenone ketyl, 250 mL), and then the system was degassed (freeze-pump-thaw degassed, 3-5 cycles, to remove all the oxygen from the solution). The solution was then stirred under argon for 8 h at rt. Analysis by TLC (SiO_2 gel, EtOAc-hexanes = 4:1) indicated the absence of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**846**) and the presence of a new oxindole component of lower *Rf* value. The solution was then concentrated to a third of its original volume under reduced pressure. The residue was dissolved in CH_2Cl_2 (500 mL) and washed with 10% aq $NaHCO_3$ (2 x 100 mL), brine (100 mL) and dried (K_2CO_3). The removal of the solvent under reduced pressure provided a mixture which was subjected to flash chromatography (SiO_2 gel, EtOAc-hexanes = 4:1) to afford the expected pure oxindole (**857**) as an amorphous pale yellow solid (1.84 mmol, 567 mg, 80% yield): **m.p.** = 61-64 °C; $\mathbf{[\alpha]^{27}_D}$ = –6.12° (*c* 8.5, $CHCl_3$); **IR** (KBr) 2923, 1716, 1610, 1493, 1373,

1345, 1197, 1119 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 (td, *J* = 8, 2 Hz, 1H), 7.02 (td, *J* = 8, 2 Hz, 1H), 6.89 (brd, *J* = 8 Hz, 1H), 6.79 (brd, *J* = 8 Hz, 1H), 5.44 (qt, *J* = 7, 2 Hz, 1H), 3.73 (brd, *J* = 1.5 Hz, 2H), 3.69 (brd, *J* = 8 Hz, 1H), 3.51 (brd, *J* = 8 Hz, 1H), 3.44 (d, *J* = 4.5 Hz, 1H), 3.18 (s, 3H), 2.75 (ddd, *J* = 13, 8, 1.5 Hz, 1H), 2.23 (ddd, *J* = 14, 4.5, 1.5 Hz, 1H), 1.97 (d, *J* = 13 Hz, 1H), 1.84 (dd, *J* = 14, 9 Hz, 1H), 1.64 (dt, *J* = 7, 2 Hz, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) *δ* 216.4 (C), 180.7 (C), 143.9 (C), 133.8 (C), 129.4 (C), 128.5 (CH), 125.9 (CH), 122.1 (CH), 120.6 (CH), 108.0 (CH), 69.0 (CH), 62.4 (CH), 55.6 (C), 48.4 (CH_2), 43.9 (CH), 38.5 (CH_2), 26.5 (CH_3), 25.4 (CH_2), 12.4 (CH_3); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{19}H_{21}N_2O_2$ $(M+H)^+$ = 309.1603, found 309.1605.

Synthesis of (−)-affinisine oxindole (24) from oxindole (857).

A mixture of anhydrous *tert*-BuOK (0.292 g, 2.6 mmol) and methoxy methyl triphenyl phosphonium chloride (0.881 g, 2.57 mmol) in dry benzene (10 mL) was allowed to stir at rt for 45 min. The pentacyclic ketone oxindole (**857**, 0.113 g, 0.367 mmol) was dissolved in dry THF (4 mL) was then added to the above orange solution dropwise at rt (23 °C). The mixture that resulted was stirred at rt for 1 d. The mixture was diluted with EtOAc (50 mL) then washed with 10% aq $NaHCO_3$ (2 x 10 mL), brine (10 mL) and dried (K_2CO_3). The solution was concentrated under reduced pressure and the baseline materials were removed by a quick wash column on silica gel. The solvent was removed under reduced pressure and the residue [containing a mixture of enol ethers (**858**)] was dissolved (without further purification) in a solution of aq HCl (2 *N*)-THF (1:1, 10 mL).

The solution which resulted was stirred at 55 °C (oil bath temperature) under an argon atmosphere for 5 h. The reaction mixture was cooled to 0 °C, diluted with EtOAc (20 mL) and brought to *p*H = 8 with an ice cold solution of aq NaOH (1 *N*). The aqueous layer was then extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with 10% aq $NaHCO_3$ (2 x 10 mL), brine (10 mL) and then dried (K_2CO_3). The removal of the solvent under reduced pressure provided a crude mixture [containing aldehyde (**859**)] which was dissolved in EtOH (200 proof, 25 mL) and then $NaBH_4$ (0.015 g, 0.4 mmol) was added to the above solution in one portion at 0 °C. The mixture was then allowed to reach rt and was stirred for a total of 8 h. The reaction mixture concentrated under reduced pressure (not to dryness) and the residue was diluted with CH_2Cl_2 (150 mL) and poured into ice cooled water (20 mL). The aq layer was extracted with additional CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with brine (10 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford a crude mixture which was chromatographed (SiO_2 gel, EtOAc) to provide (–)-affinisine oxindole (**24**) as a clear oil (0.040 g, 34% yield over three steps): $\mathbf{[\alpha]^{23}_D}$ = –66.0° (*c* 0.3, $CHCl_3$); **IR** (KBr) 3375, 2933, 1711, 1610, 1470 cm^{-1}; $^{\mathbf{1}}$**H NMR** (300 MHz, $CDCl_3$) δ 7.37 (brd, *J* = 8 Hz, 1H), 7.31 (td, *J* = 8, 1 Hz, 1H), 7.09 (td, *J* = 8, 1 Hz, 1H), 6.83 (brd, *J* = 8 Hz, 1H), 5.32 (qt, *J* = 7, 2 Hz, 1H), 3.78 (m, 2H), 3.62 (m, 2H), 3.37 (dd, *J* = 10, 2 Hz, 1H), 3.31 (dd, *J* = 6, 3 Hz, 1H), 3.21 (s, 3H), 2.88 (brs, 1H), 2.77 (dd, *J* = 13, 6 Hz, 1H), 2.18 (ddd, *J* = 14, 4, 2 Hz, 1H), 2.05 (m, 1H), 1.82 (d, *J* = 13 Hz, 1H), 1.61 (dt, *J* = 7, 2 Hz, 3H), 1.56 (ddd, *J* = 14, 10, 2 Hz, 1H); $^{\mathbf{13}}$**C NMR** (75.5 MHz, $CDCl_3$) δ 181.8 (C), 144.4 (C), 136.0 (C), 130.4 (C), 128.1 (CH), 126.6 (CH), 121.5 (CH), 114.8 (CH), 107.8 (CH), 65.7 (CH_2), 62.8 (CH), 59.1 (CH), 56.7 (C), 48.8 (CH_2),

47.9 (CH), 44.6 (CH_2), 28.8 (CH_2), 26.5 (CH_3), 26.1 (CH), 12.4 (CH_3); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{20}H_{25}N_2O_2$ $(M+H)^+$ = 325.1916, found 325.1927.

Preparation of α-chloromethyl phenyl sulfoxide.

A solution of sulfuryl chloride (22.9 g, 0.166 mol) in CH_2Cl_2 (125 mL) was added dropwise to a stirred mixture of wet silica gel (12.5 g silic acid, 12.5 g H_2O) and α-chloromethyl phenylsulfide (25 g, 0.158 mol) in CH_2Cl_2 (125 mL) at 23 °C. The mixture was allowed to stir for an additional 2 h and then poured into an aq solution of $NaHCO_3$ (10%, 50 mL). This was then followed by extraction with CH_2Cl_2 (3 x 70 mL). The combined extracts were washed with water (30 mL), brine (2 x 50 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide an oil. The oil was chromatographed (silica gel, EtOAc/hexane, 1:1) to provide the sulfoxide (20.5 g, 81%): **$bp_{0.2mm}$** = 120-123 °C, [lit.[73] $bp_{0.2mm}$ = 120-123 °C]; **IR** (NaCl) 3100, 3000, 1480 cm^{-1}; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 4.38 (2 H, s), 7.55 (3 H, m), 7.65 (2 H, m); **CIMS** (*m/e*, relative intensity) 175 (M^+ + 1, 100). The data was identical in all respects to the published values.[267,282,283]

Synthesis of α,β-unsaturated aldehyde oxindole (863) from (7*R*)-N_a-methyl, N_b-benzyl tetracyclic ketone oxindole (855).

A solution of lithium diisopropylamide [145 mmol, from dry diisopropylamine (14.6 g, 145 mmol) in dry THF (200 mL) and *n*-butyl lithium (60.0 mL, 2.5 M solution in

hexanes)] was cooled to -78 °C under an atmosphere of argon. A solution of α-chloromethyl phenylsulfoxide (25 g, 145 mmol) in dry THF (50 mL) was added to the solution of LDA. The yellow mixture which resulted was stirred at -78 °C for 20 min, after which the ketone oxindole (**855**, 2 g, 5.8 mmol) in dry THF (50 mL) was added dropwise via a double ended needle over a 40 min period. The reaction mixture which resulted was stirred at -78 °C for 1 h, after which it was allowed to warm rt and then it was diluted with THF (400 mL). A 15 *N* aq solution of KOH (420 g in 500 mL of H_2O) was added and the heterogeneous mixture was stirred (overhead mechanical stir) for 16 h at rt. The organic layer was separated and the aqueous phase was extracted with EtOAc (4 x 250 mL). The combined organic layers were washed with a saturated aq solution of NH_4Cl (2 x 250 mL), brine (2 x 200 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude mass that resulted was quickly purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to obtained a brownish solid. To this residue, which resulted, was added dry toluene (600 mL) and lithium perchlorate (13.2 g, 124 mmol). The slurry which resulted was heated at 90 °C under an atmosphere of argon for 10 hours and then was allowed to cool to rt and diluted with EtOAc (500 mL). The organic solution was washed with an aq solution of NH_4OH (10%, 200 mL), brine (2 x 300 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure. The oil which resulted was chromatographed (basic Al_2O_3, CH_2Cl_2/hexanes, 2:1) to provide the α,β-unsaturated aldehyde (**863**) as an amorphous solid (1.2 g, 60% yield). $\mathbf{[\alpha]_D^{27}}$ = +209^o (*c* 0.19 in CH_2Cl_2); **IR** (KBr) 2934, 1705, 1663, 1611, 1349, 750 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.22 (1 H, d, *J* = 9.00 Hz), 2.45 (1 H, dd, *J* = 6.60, 5.70 Hz), 2.56 (2 H, m), 3.19 (3 H, s), 3.23 (1 H, bm), 3.70 (1 H, d, *J* = 13.2 Hz), 3.80 (1 H, d, *J* =

13.2), 4.21 (1 H, d, *J* = 6.30 Hz), 6.79 (1 H, d, *J* = 7.80 Hz), 7.03 (1 H, bt, *J* = 3.00 Hz), 7.12 (1 H, dt, *J* = 7.50, 0.90 Hz), 7.24-7.28 (2 H, bm), 7.29-7.33 (2 H, m), 7.40-7.42 (2 H, bm), 7.81 (1 H, dd, J = 7.50, 0.60 Hz), 9.56 (1 H, s); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 24.3 (CH_2), 26.3 (CH3), 47.1 (CH2), 50.9 (CH2), 53.6 (CH), 56.6 (C), 64.8 (CH), 107.4 (CH), 123.0 (2 x CH), 127.2 (CH), 127.7 (CH), 128.3 (2 x CH + C), 128.7 (2 x CH), 137.6 (C), 138.6 (C), 142.0 (C), 147.8 (CH), 177.6 (C), 192.6 (C). **HRMS** (+TOF MS, *m/z*, relative intensity) calc. for $C_{23}H_{23}N_2O_2$ $(M+1)^+$.= 359.1760, found 359.1768.

Preparation of *trans*-1-bromo-2-pentene.

The *trans*-2-penten-3-ol (2.0 g, 23.2 mmol) was dissolved in dry ethyl ether (15 ml) in a round bottom flask (50 mL) and the solution which resulted was cooled to 0 °C with an ice-bath. Phosphorus tribromide (0.85 ml, 8.97 mmol) was then injected into the above solution dropwise via a syringe under an argon atmosphere. The mixture which resulted was stirred at 0 °C for 2 h. The reaction was carefully quenched by adding CH_3OH (0.5 mL) at 0 °C. The mixture which resulted was then poured into an ice-H_2O mixture. The aqueous layer was separated and extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed quickly with an ice-cold saturated aq solution of $NaHCO_3$, then brine, and finally dried ($MgSO_4$). The solvent was removed under reduced pressure at a temperature lower than 20 °C to provide the desired *trans*-1-bromo-2-pentene (3.3 g. 95%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 11.9 Hz), 2.30 (2H, m), 3.91 (2H, d, *J* = 6.7 Hz), 5.66 (1H, m), 5.77 (1H, m); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 13.01, 25.23,

33.52, 125.37, 137.05. The spectral data for this material were identical to the reported data.[55b] This material was directly employed in the next experiment.

Attempted protocol for the 1,2-addition of *trans*-1-bromo-2-pentene to oxindole (863) to provide (875) by the method of Yamamoto et al. (*α*-selective allylation process).

A mixture of lithium metal (30 mg, 4.3 mmol) and biphenyl (680 mg, 4.4 mmol) in freshly distilled THF (100 mL) was stirred at rt overnight under argon. Freshly flame dried BaI_2 (880 mg, 2.1 mmol) was then added to the above dark blue solution, and the mixture which resulted was stirred at rt for 1 h. The dark red solution which formed was cooled to -78 °C in a cooling bath of dry ice-EtOAc. A solution of *α,β*-unsaturated aldehyde (**863**, 180 mg, 0.5 mmol) and *trans*-1-bromo-2-pentene (690 mg, 4.6 mmol) in THF (50 mL) was added at -78 °C dropwise to the above chilled solution of barium metal, after which the mixture was stirred at -78 °C for an additional 2 h. The reaction mixture was poured into an ice cold aq solution of NH_4OH (10%, 100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water (100 mL), brine (100 mL) and then dried (K_2CO_3). The solvent was removed under reduced pressure to give a crude oil which was purified by flash chromatography (EtOAc-hexane = 1:4). None of the desired oxindole (**875**) was observed.

Synthesis of pentacyclic ketone oxindole (879) from tetracyclic ketone oxindole (854).

A mixture of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**854**, 1.0 g, 2.3 mmol), Pd_2dba_3 (0.842 g, 0.92 mmol) and NaHMDS (2 equivalents, 0.843 g, 4.6 mmol) was dissolved in THF (previously distilled over Na/benzophenone ketyl, 250 mL), and then the system was degassed (freeze-pump-thaw degassed, 3-5 cycles, to remove all the oxygen from the solution). The solution was then stirred under argon for 8 h at rt. Analysis by TLC (SiO_2 gel, EtOAc-hexanes = 4:1) indicated the absence of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**854**) and the presence of a new oxindole component of lower *Rf* value. The solution was then concentrated to a third of its original volume under reduced pressure. The residue was dissolved in CH_2Cl_2 (500 mL) and washed with 10% aq $NaHCO_3$ (2 x 100 mL), brine (100 mL) and dried (K_2CO_3). The removal of the solvent under reduced pressure provided a mixture which was subjected to flash chromatography (SiO_2 gel, EtOAc-hexanes = 4:1) to afford the expected pure oxindole (**879**) as an amorphous pale yellow solid (1.84 mmol, 567 mg, 80% yield). **m.p.** = 68-70 °C; $\mathbf{[\alpha]^{26}_D}$ = +9.1° (*c* 0.11, CH_2Cl_2); **IR** (KBr) 2932, 1731, 1705, 1610, 1491, 1375, 1349, 753, 731 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8 Hz, 1H), 7.29 (t, *J* = 8 Hz, 1H), 7.07 (t, *J* = 8 Hz, 1H), 6.82 (d, *J* = 8 Hz, 1H), 5.40 (m, 1H), 3.68 (brm, 3H), 3.45 (m, 1H), 3.30 (d, *J* = 9 Hz, 1H), 3.22 (s, 3H), 3.08 (dt, *J* = 14, 2 Hz, 1H), 2.48 (dd, *J* = 14, 9 Hz, 1H), 2.31 (brd, *J* = 14 Hz, 1H), 1.74 (m, 1H), 1.67 (m, 3H); ^{13}**C NMR** (75.5 MHz, $CDCl_3$) δ 216.0 (C), 176.8 (C), 142.2 (C), 136.8 (C), 135.6 (C), 127.9 (CH), 124.0 (CH), 122.9 (CH), 119.5 (CH), 107.5 (CH), 68.1 (CH), 64.7 (CH), 54.3 (C), 48.6

(CH_2), 43.7 (CH), 39.7 (CH_2), 26.4 (CH_3), 22.0 (CH_2), 12.5 (CH_3); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{19}H_{21}N_2O_2$ $(M+H)^+$ = 309.1603, found 309.1602.

Synthesis of isoaffinisine oxindole (878) from pentcyclic ketone oxindole (879).

A mixture of anhydrous *tert*-BuOK (0.584 g, 5.2 mmol) and methoxy methyl triphenyl phosphonium chloride (1.76 g, 5.14 mmol) in dry benzene (20 mL) was allowed to stir at rt for 45 min. The pentacyclic ketone oxindole (**879**, 226 mg, 0.734 mmol) was dissolved in dry THF (10 mL) was then added to the above orange solution dropwise at rt (23 °C). The mixture which resulted was allowed to stir at rt for 1 d. The mixture was diluted with EtOAc (100 mL) then washed with 10% aq $NaHCO_3$ (2 x 20 mL), brine (20 mL) and dried (K_2CO_3). The solution was concentrated under reduced pressure and baseline materials were removed by a quick wash column on silica gel (EtOAc/hexanes 1:1). The solvent was removed under reduced pressure and the residue [containing a mixture of enol ethers (**880**)] was dissolved (without further purification) in a solution of aq HCl (2 *N*)-THF (1:1, 20 mL). The solution which resulted was stirred at 55 °C (oil bath temperature) under an argon atmosphere for 5 h. The reaction mixture was cooled to 0 °C, diluted with EtOAc (40 mL) and brought to *p*H = 8 with an ice cold solution of aq NaOH (1 *N*). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with 10% aq $NaHCO_3$ (2 x 20 ml), brine (20 mL) and then dried (K_2CO_3). The removal of the solvent under reduced pressure provided a crude mixture [containing aldehyde (**881**)] which was dissolved in EtOH (200 proof, 50 mL) and then $NaBH_4$ (0.030 g, 0.8 mmol) was added to the above solution in one portion

at 0 °C. The mixture was stirreed and allowed to warm to rt and was stirred for a total of 8 h. The reaction mixture was concentrated under reduced pressure (not to dryness) and the residue was diluted with CH_2Cl_2 (300 mL) and poured into cold water (50 mL). The aq layer was extracted with additional CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with brine (20 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford a crude mixture which was chromatographed (SiO_2 gel, EtOAc) to provide isoaffinisine oxindole (**878**) as a yellowish solid (167 mg, 0.514 mmol, 70% yield). **m.p.** = 71-74 °C; $\mathbf{[\alpha]^{23}_D}$ = –54.0° (*c* 0.10, $CHCl_3$); **IR** (KBr) 3390, 2941, 1710, 1465 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8 Hz, 1H), 7.25 (t, *J* = 8 Hz, 1H), 7.04 (t, *J* = 8 Hz, 1H), 6.80 (d, *J* = 8 Hz, 1H), 5.27 (brq, *J* = 7 Hz, 1H), 3.58 (m, 4H), 3.23 (s, 3H), 3.14 (m, 2H), 2.81 (brm, 1H), 2.75 (dt, *J* = 14, 3 Hz, 1H), 2.42 (dd, *J* = 13, 7 Hz, 1H), 2.16 (m, 1H), 2.07 (d, *J* = 12 Hz, 1H), 1.62 (d, *J* = 7 Hz, 3H), 1.42 (m, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 178.3 (C), 142.1 (C), 138.4 (C), 137.6 (C), 127.4 (CH), 123.4 (CH), 122.8 (CH), 114.2 (CH), 107.2 (CH), 66.2 (CH_2), 65.8 (CH), 59.1 (CH), 55.4 (C), 49.0 (CH_2), 48.1 (CH), 46.3 (CH_2), 26.8 (CH), 26.4 (CH_3), 26.1 (CH_2), 12.4 (CH_3); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{20}H_{25}N_2O_2$ $(M+H)^+$ = 325.1916, found 325. 1912.

Synthesis of triisopropylsilyl ether oxindole (882) from isoaffinisine oxindole (878).

A solution of isoaffinisine oxindole (**878**, 1.5 g, 4.6 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C, after which 2,6-lutidine (4 equivalents, 2.1 mL, 18.4 mmol) was added, and this was followed by addition of TIPSOTf (2 equivalents, 2.5 mL, 9.2 mmol) to the

stirred solution. The mixture was then allowed to stir for an additional 2 h at rt, after which ice cooled water (5 mL) was added to quench the reaction mixture. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and poured into cold water (50 mL). The aq layer was extracted with additional CH_2Cl_2 (2 × 50 mL), and the combined organic layer was washed with brine (30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product, which was dried in vacuo to remove the excess 2,6-lutidine before the solid was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:4] to provide oxindole (**882**, 4.14 mmol, 1.99 g, 90%). $\mathbf{[\alpha]^{23}_D}$ = –84.0° (*c* 0.15, $CHCl_3$); **IR** (KBr) 2937, 1713, 1488, 1120 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8 Hz, 1H), 7.24 (td, *J* = 8, 1 Hz, 1H), 7.03 (td, *J* = 8, 1 Hz, 1H), 6.79 (d, *J* = 8 Hz, 1H), 5.24 (m, 1H), 3.58 (m, 4H), 3.24 (s, 3H), 3.10 (m, 2H), 2.80-2.71 (brm, 2H), 2.41 (dd, *J* = 13, 7 Hz, 1H), 2.14 (m, 1H), 2.07 (d, *J* = 12 Hz, 1H), 1.59 (dt, *J* = 7, 2 Hz, 3H), 1.39 (m, 1H), 1.07 (s, 21H); ^{13}**C NMR** (75.5 MHz, $CDCl_3$) δ 178.3, 142.2, 138.7, 137.5, 127.3, 123.5, 122.7, 113.9, 107.1, 66.3, 65.9, 59.3, 55.4, 49.2, 48.5, 46.5, 26.6, 26.4, 18.1, 17.7, 12.5, 12.3, 12.0; **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{29}H_{45}N_2O_2Si$ $(M+H)^+$ = 481.3172, found 481.3175.

Synthesis of pentacyclic ketone oxindole (884) from pentacyclic olefin oxindole (882).

To a solution of triisopropylsilyl ether oxindole (**882**, 500 mg, 1.04 mmol) in dry THF (30 mL) was added BH_3-DMS complex (1 *M* in THF, 9.4 mL, 9.36 mmol) at rt. The

mixture which resulted was stirred at rt for 3 h. The reaction mixture was then quenched by careful addition of water (5 mL) at 0 °C. At this point aq NaOH (3 *N*, 18 mL, 57 mmol) was added to the mixture, followed by addition of H_2O_2 (30% in water, 5.0 mL, 43 mmol). The mixture which resulted was allowed to stir at rt for 3 h after which EtOAc (500 mL) and H_2O (80 mL) were added. The organic layer was separated and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure and the residue was purified by a short flash column chromatography (wash column) with EtOAc/hexanes (4:6) to provide a mixture of sec-ol diastereomers which was used directly in the next step.

The mixture of isomers was dissolved in CH_2Cl_2 (30 mL) and the tetrapropylammonium perruthenate (2 equivalents, 2.08 mmol, 731 mg) was quickly added to the solution. The reaction was stirred at rt for approximately 2 h. Water (30 mL) was then added and the layers were separated. The organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide pentacyclic oxindole (**884**, 0.676 mmol, 336 mg, 65%). $\mathbf{[\alpha]^{23}_D}$ = –53.0° (*c* 0.25, $CHCl_3$); **IR** (KBr) 2941, 1720, 1711, 1355, 1206 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8 Hz, 1H), 7.24 (t, *J* = 8 Hz, 1H), 7.03 (t, *J* = 8 Hz, 1H), 6.78 (d, *J* = 8 Hz, 1H), 3.87 (dd, *J* = 11, 7 Hz, 1H), 3.77 (t, *J* = 10 Hz, 1H), 3.62 (dd, *J* = 14, 5 Hz, 1H), 3.21 (s, 3H), 3.05 (dd, *J* = 10, 2 Hz, 1H), 2.94-2.86 (m, 2H), 2.77-2.70 (m, 1H), 2.45-2.33 (m, 4H), 2.14 (s, 3H), 2.10-2.05 (m, 1H), 2.10 (d, *J* = 13 Hz, 1H), 1.12-1.10 (m, 21H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 210.7, 178.1, 142.1, 138.2, 127.4, 123.6, 122.8, 107.2, 64.8, 64.7, 58.1, 55.2, 46.7, 46.1, 42.9, 41.0, 29.7, 28.8, 26.4, 25.7, 21.2, 18.1, 11.9;

HRMS (ESI, *m/z*, relative intensity) calcd for $C_{29}H_{45}N_2O_3Si$ $(M+H)^+$ = 496.3121, found 496.3126.

Synthesis of tetracyclic enone oxindole (886) from pentacyclic ketone (884).

Oxindole (**884**, 100 mg, FW = 496.76, 0.20 mmol) was mixed with MeI (employed as the solvent, 5 mL) and the solution which resulted was heated at 70 °C (external temperature, oil bath) in a closed round bottom flask (scew-cap) for 24 h. The solution was then allowed to cool to rt and the MeI was removed under reduced pressure (inside the hood!), to provide the methyl ammonium salt (**886**) as a crude solid, which was used without further purification: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8 Hz, 1H), 7.19 (t, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8 Hz, 1H), 4.81-4.73 (m, 1H), 4.41 (t, *J* = 10 Hz, 1H), 4.28 (dd, *J* = 14, 7 Hz, 1H), 4.06-4.00 (m, 1H), 3.89 (s, 3H), 3.80 (m, 1H), 3.71-3.65 (m, 1H), 3.60-3.52 (m, 2H), 3.47-3.42 (m, 1H), 3.24 (s, 3H), 2.93 (dd, *J* = 14, 6 Hz, 1H), 2.74 (brs, 1H), 2.47 (dd, *J* = 14, 6 Hz, 1H), 2.24 (s, 3H), 1.82 (dd, J = 15, 9 Hz, 1H), 1.19-0.95 (brs, 21H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 205.7, 176.5, 143.2, 130.3,129.9, 124.2, 124.1, 109.3, 68.0, 61.8, 55.9, 54.8, 51.0, 43.0, 42.0, 41.8, 29.7, 28.1, 27.2, 24.1, 23.6, 18.0, 11.9.

The crude salt (**886**) was dissolved in dry THF and NaHMDS (2 equivalents, 0.40 mmol, 74 mg) were quickly added under a stream of argon. The solution was stirred an additional 30 min at rt. The solution was concentrated to a third of its original volume and the ice cooled water was added to the solution. The EtOAc was used to extract the aq layer (3 x 50 mL) and the combined organic layers were washed once with brine and

dried (K_2CO_3). The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 2:3] to provide tetracyclic oxindole (**886**, 0.16 mmol, 82 mg, 80%). **$[\alpha]^{23}_{D}$** = +95.0° (*c* 0.12, $CHCl_3$); **IR** (KBr) 2942, 2865, 1709, 1645, 1125, 1096 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7 Hz, 1H), 7.25 (t, *J* = 7 Hz, 1H), 7.02 (t, *J* = 7 Hz, 1H), 6.78 (d, *J* = 7 Hz, 1H), 6.04 (s, 1H), 5.64 (s, 1H), 3.93 (brm, 1H), 3.69 (t, *J* = 9 Hz, 1H), 3.45 (m, 1H), 3.24-3.18 (m, 4H), 3.07 (s, 1H), 2.81 (s, 3H), 2.41 (d, *J* = 4 Hz, 1H), 2.35 (s, 3H), 2.18 (m, 1H), 2.06 (m, 1H), 1.69-1.61 (m, 1H), 1.37-1.31 (m, 1H), 1.13-0.85 (m, 21H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 198.8, 177.9, 151.4, 141.9, 139.1, 127.3, 123.4, 122.6, 122.4, 106.9, 68.3, 64.1, 58.6, 55.3, 44.1, 42.9, 35.5, 30.1, 29.7, 26.3, 20.66, 18.1, 11.9; **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{30}H_{47}N_2O_3Si$ $(M+H)^+$ = 511.3278, found 511.3271.

Synthesis of pentacyclic enone oxindole (887) from enone oxindole (886)

To a solution of oxindole (**886**, 50 mg, FW = 510.78, 0.098 mmol) in a dioxane/water (6:1) mixture (7 mL) were added Na_2PdCl_4 (40 mol%, 0.039 mmol, 12 mg) and *tert*-butyl hydroperoxide (70% in water, 1.5 equivalents, 0.147 mmol) at rt and the mixture was stirred at 85 °C for approximately 6 h. After the mixture was cooled to rt, ice-cooled water (3 mL) and a saturated solution of aq $NaHCO_3$ (10 mL) were added to the mixture and this was followed by addition of EtOAc (50 mL). After separation, the aq layer was extracted with additional EtOAc (2 x 30 mL). The combined organic layers were washed with a saturated solution of aq $NaHCO_3$, then brine, and dried (K_2CO_3). The solvent was

removed under reduced pressure and the residue was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide the pentacyclic oxindole (**887**, 0.064 mmol, 22 mg, 65%). **[α]$^{23}_{D}$** = +184° (*c* 0.10, $CHCl_3$); **IR** (KBr) 2933, 1713, 1695, 1357, 1233 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.16 (td, *J* = 8, 1 Hz, 1H), 7.00 (dd, *J* = 8, 1 Hz, 1H), 6.86 (td, *J* = 8, 1 Hz, 1H), 6.73 (dd, *J* = 8, 1 Hz, 1H), 4.19 (t, *J* = 12 Hz, 1H), 3.94 (ddd, *J* = 12, 4, 1 Hz, 1H), 3.70 (m, 1H), 3.45 (brd, *J* = 6 Hz, 1H), 3.22 (s, 3H), 2.89 (brs, 1H), 2.81 (s, 3H), 2.49 (d, *J* = 11 Hz, 1H), 2.37 (dd, *J* = 14, 8 Hz, 1H), 2.17 (s, 3H), 1.98 (m, 1H), 1.81 (m, 1H), 1.42-1.53 (m, 1H).; **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 196.0 (C), 177.7 (C), 155.4 (CH), 141.7 (C), 136.7 (C), 127.0 (CH), 121.7 (C), 119.8 (CH), 117.9 (CH), 106.9 (CH), 70.9 (CH_2), 62.3 (CH), 55.4 (C), 49.5 (CH), 41.6 (CH_2), 36.9 (CH), 34.4 (CH_3), 31.7 (CH_2), 26.7 (CH_3), 25.6 (CH_3), 22.4 (CH); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{21}H_{25}N_2O_3$ $(M+H)^+$ = 353.1787, found 353.1780.

Procedure for the N_b-demethylation of oxindole (887) to provide isoalstonisine (27).

Oxindole (**887**, 5 mg, 0.014 mmol) was dissolved in dry 1,2-dichloroethane (3 mL) in a vessel that can be sealed with cap. ACE-Cl (from a new bottle, 20 mg, 0.14 mmol) was added to the solution at 0 °C under argon. The reaction vessel was closed and was heated in oil bath at 85-90 °C (external temperature) for 24 h with stirring. The mixture was then allowed to reach ambient temperature and the solvent was removed under vacuum. Distilled, dried methanol (5 mL) was added to the residue and the mixture was heated to reflux for 5 h with stirring. The solvent was removed in vacuo and distilled EtOAc was

added to the residue and then cold aq 1 *N* NaOH (5 mL) was added to neutralize the HCl salt which had formed. The layers were separated and the aq layer was washed with EtOAc (3 x 5 mL). The combined organic layers were washed with brine until neutrality (*p*H = 7) and dried (K_2CO_3). After the solvent was removed under reduced pressure, the residue was purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 2:3] to provide isoalstonisine (**27**, 4 mg, 80%). $\mathbf{[\alpha]^{23}_D}$ = +201° (*c* 0.15, $CHCl_3$), [lit.[12] $\mathbf{[\alpha]^{23}_D}$ = +207° (*c* 0.07, $CHCl_3$)]; **IR** (KBr) 3411 (weak), 2933, 1701, 1690, 1257 cm^{-1}, [lit.[12] **IR** (dry film) 1704 cm^{-1} (C=O, lactam, ketone)]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.25 (td, *J* = 8, 1 Hz, 1H), 7.13 (dd, *J* = 8, 1 Hz, 1H), 6.98 (td, *J* = 8, 1 Hz, 1H), 6.80 (dd, *J* = 8, 1 Hz, 1H), 4.24 (t, *J* = 11 Hz, 1H), 4.14 (ddd, *J* = 11, 4, 1 Hz, 1H), 3.99 (m, 1H), 3.73 (brd, *J* = 7 Hz, 1H), 3.22 (s, 3H), 3.11 (brt, *J* = 3 Hz, 1H), 2.58 (dd, *J* = 14, 2 Hz, 1H), 2.34 (m, 2H), 2.22 (s, 3H), 1.96 (brm, 1H), 1.47 (brdt, *J* = 12, 4 Hz, 1H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 197.0 (C), 177.4 (C), 155.8 (CH), 142.3 (C), 137.4 (C), 127.7 (CH), 122.2 (CH), 121.8 (C), 120.6 (CH), 107.6 (CH), 67.6 (CH_2), 66.8 (CH), 57.1 (C), 56.8 (CH), 42.2 (CH_2), 37.5 (CH), 32.5 (CH_2), 26.3 (CH_3), 25.6 (CH_3), 23.7 (CH); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{20}H_{23}N_2O_3$ $(M+H)^+$ = 339.1630, found 339.1635. The spectral data was in excellent agreement to that reported by Kam et al.[12]

Synthesis of isoalstonisine (27) by epimerization at C-7 of (+)-alstonisine (8).

In a 10 mL screw-cap glass tube with a magnetic sitrrer, alstonisine (**8**, 7 mg, FW = 338.40, 0.021 mmol) and diisopropylethylamine (DIEA, 3 equivalents, 0.062 mmol, 8

mg) were placed into acetonitrile (5 mL). The vessel was capped with a rubber septum, and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 80-85 °C [external temperature (or oil bath temperature)] and allowed to run for 48 h with vigorous magnetic stirring. The vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide isoalstonisine (**27**, 0.018 mmol, FW = 338.40, 6 mg, 85%). *Note*: see the latter procedure for the complete characterization data of this oxindole.

Synthesis of (+)-alstonisine (8) by epimerization at C-7 of isoalstonisine (27).

In a 10 mL screw-cap glass tube with a magnetic sitrrer, isoalstonisine (**27**, 8 mg, FW = 338.40, 0.024 mmol) was placed into a pyridine-DCM (8:2, 5 mL) mixture. The vessel was capped with a rubber septum, and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 100-110 °C [external temperature (or oil bath temperature)] and allowed to run for 60 h with vigorous magnetic stirring. The vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-Hexanes (distilled both), 1:1] to provide alstonisine (**8**, 0.015 mmol, FW = 338.40, 5.6 mg, 70%). $\mathbf{[\alpha]^{23}_D}$ = +195° (*c* 0.2, EtOH); **IR** (KBr)

1692, 1643, doblets at 1616 and 1611 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7, 1 Hz, 1H), 7.64 (s, 1H), 7.36 (td, *J* = 7, 1 Hz, 1H), 7.32 (td, J = 7, 1 Hz, 1H), 6.89 (dd, *J* = 7, 1 Hz, 1H), 4.56 (t, *J* = 11 Hz, 1H), 4.29 (ddd, *J* = 11, 4, 1 Hz, 1H), 3.77 (brd, *J* = 7 Hz, 1H), 3.41 (m, 1H), 3.22 (s, 3H), 3.20 (m, 1H), 2.56 (dd, *J* = 13, 7 Hz, 1H), 2.28 (m, 1H), 2.26 (s, 3H), 2.20 (d, *J* = 13 Hz, 1H), 2.06 (brm, 1H), 1.67 (m, 1H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 196.9 (C), 182.8 (C), 158.0 (CH), 144.4 (C), 129.5 (C), 128.3 (CH), 125.9 (CH), 123.7 (CH), 122.2 (C), 108.3 (CH), 68.7 (CH_2), 64.2 (CH), 57.2 (C), 56.7 (CH), 42.3 (CH_2), 37.4 (CH), 31.4 (CH_2), 26.6 (CH_3), 25.3 (CH_3), 24.6 (CH); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{20}H_{23}N_2O_3$ $(M+H)^+$ = 339.1630, found 339.1627. This spectral data and optical rotation were in excellent agreement with that of Wearing et al.[267] and Elderfield et al.[7]

Synthesis of (+)-N_a-demethylalstonisine (17) from (+)-alstonisine (8).

A solution of alstonisine (**8**, 17 mg, FW = 338.40, 0.05 mmol) and benzoylperoxide (>98% Aldrich, 0.1 mmol, 24 mg) in CH_2Cl_2 (3 mL) was heated in a sealed tube (the inside air was removed under vacuum and then filled with an argon atmosphere) for 24 h at 85 °C. After concentrating the reaction mixture under vacuum, a saturated solution of NH_3 (g) in methanol (8 mL) was added, and the mixture was stirred for 24 h at rt. After concentrating the reaction mixture under vacuum, saturated aq solution of $NaHCO_3$ was added. The mixture was extracted with EtOAc and the combined organic layers were washed with brine and dried (Na_2SO_4). The removal of the solvent under reduced pressure afforded a crude product, which was purified by flash chromatography [silica

gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 2:1] to provide (+)-N_a-demethylalstonisine (**17**, 0.033 mmol, FW = 324.37, 10 mg, 65%). $\mathbf{[\alpha]^{23}_D}$ = +176° (*c* 0.15, MeOH), [lit.[12]: not reported]; **IR** (KBr) 3260 (weak), 1703, 1689 cm^{-1}, [lit.[12]: not reported]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.28 (dd, *J* = 7, 3 Hz, 1H), 7.68 (s, 1H), 7.31 (td, *J* = 6, 1 Hz, 1H), 7.24 (td, J = 6, 1 Hz, 1H), 6.92 (dd, *J* = 7, 3 Hz, 1H), 4.51 (t, *J* = 11 Hz, 1H), 4.25 (ddd, *J* = 10, 4, 2 Hz, 1H), 3.74 (brd, *J* = 6 Hz, 1H), 3.40 (m, 1H), 3.27 (brs, 1H), 2.63 (dd, *J* = 13, 7 Hz, 1H), 2.32 (ddd, *J* = 14, 6, 2 Hz, 1H), 2.30 (s, 3H), 2.23 (d, *J* = 12 Hz, 1H), 2.01 (brm, 1H), 1.65 (m, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 197.1 (C), 184.5 (C), 158.0 (CH), 141.3 (C), 129.9 (C), 128.5 (CH), 126.4 (CH), 123.7 (CH), 122.3 (C), 109.8 (CH), 69.0 (CH_2), 64.3 (CH), 57.7 (C), 56.6 (CH), 42.3 (CH_2), 37.5 (CH), 31.3 (CH_2), 25.3 (CH_3), 24.6 (CH); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{19}H_{21}N_2O_3$ $(M+H)^+$ = 325.1474, found 325.1469. The spectral data (^{1}H and ^{13}C NMR) was in excellent agreement to that reported by Kam et al.[12]

Synthesis of (+)-alstofoline (18) by N_b-formylation of (+)-alstonisine (8).

In a 10 mL screw-cap glass tube with a magnetic stirrer, oxindole (**8**, 10 mg, FW = 338.40, 0.029 mmol) and 2,2,2-trifluoroethyl formate (TFEF, 5 equivalents, 0.145 mmol, 19 mg, *free of formic acid*) were placed into dry 1,2-dichloroethane (3 mL). The vessel was capped with a rubber septum and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 65 °C [external temperature (or oil bath temperature)] and allowed to run for 24 h with vigorous magnetic stirring. The reaction

vessel was then removed from the oil bath and the mixture was allowed to cool to rt. The solvent was removed under vacuum. The residue was directly purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide alstofoline as a mixture of rotamers (**18**, 3:1 ratio by ^{1}H NMR, 0.026 mmol, FW = 366.41, 9.6 mg, 90%). $[\alpha]^{23}_D$ = +32.0° (*c* 0.10, $CHCl_3$), [lit[12]: $[\alpha]^{23}_D$ = +39.0° (*c* 0.21, $CHCl_3$)]; **IR** (KBr) 2945, 1713, 1705, 1651 cm^{-1}, [lit.[12] **IR** (dry film) 1706, 1662 cm^{-1}]; **^{1}H NMR Major conformer**,(300 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 7, 1 Hz, 1H), 8.11 (s, 1H), 7.66 (s, 1H), 7.44 (td, *J* = 8, 1 Hz, 1H), 7.35 (td, *J* = 8, 1 Hz, 1H), 6.91 (dd, *J* = 7, 1 Hz, 1H), 4.97 (brd, *J* = 6 Hz, 1H), 4.50 (ddd, *J* = 10, 4, 1 Hz, 1H), 3.93 (t, *J* = 10 Hz, 1H), 3.84 (brs, 1H), 3.63 (td, *J* = 12, 6 Hz, 1H), 3.19 (s, 3H), 2.72 (dd, *J* = 13, 7 Hz, 1H), 2.56 (ddd, *J* = 13, 6, 2 Hz, 1H), 2.28 (s, 3H), 2.23 (m, 2H), 1.61 (m, 1H); **^{1}H NMR Minor conformer**,(300 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7, 1 Hz, 1H), 8.11 (s, 1H), 7.63 (s, 1H), 7.44 (td, *J* = 8, 1 Hz, 1H), 7.35 (td, *J* = 8, 1 Hz, 1H), 6.89 (dd, *J* = 7, 1 Hz, 1H), 4.33 (brd, *J* = 6 Hz, 1H), 4.27 (ddd, *J* = 10, 4, 1 Hz, 1H), 4.01 (t, *J* = 10 Hz, 1H), 4.53 (s, 1H), 3.63 (dt, *J* = 12, 6 Hz, 1H), 3.17 (s, 3H), 2.81 (dd, *J* = 13, 7 Hz, 1H), 2.46 (ddd, *J* = 13, 6, 2 Hz, 1H), 2.28 (s, 3H), 2.23 (m, 2H), 1.51 (m, 1H); **^{13}C NMR Major conformer,** (75.5 MHz, $CDCl_3$) δ 196.0 (C), 179.3 (C), 159.7 (CH), 157.3 (CH), 143.7 (C), 128.4 (C), 126.4 (CH), 125.1 (CH), 123.1 (CH), 120.0 (C), 107.8 (CH), 66.0 (CH_2), 60.5 (CH), 53.0 (C), 49.8 (CH), 39.1 (CH_2), 36.5 (CH), 32.3 (CH_2), 25.4 (CH_3), 24.3 (CH_3), 23.7 (CH); **^{13}C NMR Minor conformer,** (75.5 MHz, $CDCl_3$) δ 196.0 (C), 179.1 (C), 159.4 (CH), 156.9 (CH), 143.3 (C), 128.4 (C), 126.1 (CH), 125.1 (CH), 122.8 (CH), 120.3 (C), 107.8 (CH), 65.6 (CH_2), 55.9 (CH), 54.8 (CH), 52.7 (C), 38.5 (CH_2), 36.4 (CH), 31.6 (CH_2), 25.8 (CH_3), 24.0 (CH_3), 23.8 (CH); **HRMS** (ESI, *m/z*, relative

intensity) calcd for $C_{19}H_{23}N_2O_4$ $(M+H)^+$ = 367.1580, found 367. 1571. The spectral data and optical rotation were in excellent agreement to that reported by Kam et al.[12]

Preparation of 2,2,2-trifluoroethyl formate (TFEF).

In a 50 mL jacketed flask fitted with a reflux condenser and temperature probe, 2,2,2,-trifluoroethanol (12 g, 0.12 mol, 0.10 equivalents) was combined with >95% formic acid (23.2 g, 0.48 mol, 4.0 equiv). The mixture was then heated at an internal temperature of 80 °C for 18 h. The analysis of a sample by NMR spectroscopy taken after 18 h indicated a 1.4:1 ratio of trifluoroethanol/trifluoroethyl formate. The mixture was then subjected to fractional distillation through a 10 inch Vigreux column and the fraction boiling at 55-70 °C (1 atmosphere) was collected. The distillate contained a 70% yield of trifluoroethyl formate: **^{1}H NMR** (300 MHz, CDCl3) δ 8.10 (s, 1H, HC=O), 4.55 (q, 2H, CH_2). The spectral data was in excellent agreement with that reported in the literature.[343,334]

Synthesis of isoalstonoxine A (890) by acidic hydrolysis of isoalstonisine (27)

Isoalstonisine (**27**, 6 mg, 0.018 mmol) was heated to reflux (in a round bottom flask with condenser) in a solution of 2 *N* aq HCl (5 mL) for 24 h. The solution was allowed to reach rt and then was brougth to *p*H = 7.5 with an ice-cold solution of 2 *N* NaOH very slowly. The solution which resulted was then extracted with $CHCl_3$ (3 x 10 mL). The extract was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-

hexanes (distilled both), 3:1 then EtOAc] to provide isoalstonoxine A (**890**, 0.014 mmol, FW = 328.41, 4.7 mg, 80%). $[\alpha]^{23}_{D}$ = –28.0° (*c* 0.10, $CHCl_3$); **IR** (KBr) 3361, 3248, 1708, 1690, cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 (td, *J* = 8, 1 Hz, 1H), 7.16 (td, *J* = 8, 1 Hz, 1H), 7.07 (brd, *J* = 8 Hz, 1H), 6.85 (brd, *J* = 8 Hz, 1H), 4.01 (d, *J* = 8 Hz, 1H), 3.78 (dd, *J* = 12, 1 Hz, 1H), 3.64 (dd, *J* = 12, 1 Hz, 1H), 3.51 (m, 1H), 3.26 (brm, 1H), 3.20 (s, 3H), 2.71 (dd, *J* = 18, 6 Hz, 1H), 2.63 (dd, *J* = 18, 6 Hz, 1H), 2.44 (dd, *J* = 13, 2 Hz, 1H), 2.31 (dd, *J* = 12, 8 Hz, 1H), 2.23 (s, 3H), 1.90 (m, 1H), 1.61-1.77 (m, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.5 (C), 179.1 (C), 143.8 (C), 138.2 (C), 127.85 (CH), 122.9 (CH), 122.3 (CH), 108.3 (CH), 66.5(CH), 65.4 (CH_2), 62.5 (CH), 58.1 (C), 48.5 (CH_2), 42.2 (CH_2), 41.8 (CH), 33.7 (CH_2), 31.6 (CH_3), 26.5 (CH_3), 26.2 (CH); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{19}H_{25}N_2O_3$ $(M+H)^+$ = 329.1787, found 329.1792.

Synthesis of isoalstonoxine A (890) by epimerization at C-7 of (–)-alstonoxine A (19).

In a 10 mL screw-cap glass tube with a magnetic stirrer, oxindole (**19**, 5 mg, FW = 328.41, 0.015 mmol) and diisopropylethylamine (DIEA, 3 equivalents, 0.045 mmol, 6 mg) were placed into acetonitrile (4 mL). The reaction vessel was capped with a rubber septum and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 80-85 °C [external temperature (or oil bath temperature)] and was allowed to run for 48 h with vigorous magnetic stirring. The reaction vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was purified by flash column chromatography [silica gel (washed

with pure EtOAc), EtOAc-hexanes (distilled both), 3:1] to provide isoalstonoxine A (**890**, 0.010 mmol, FW = 328.41, 3.2 mg, 64%). *Note*: see the latter procedure for the complete characterization data of this oxindole.

Synthesis of (–)-alstonoxine A (19) by epimerization at C-7 of isoalstonoxine A (890).

In a 10 mL screw-cap glass tube with a magnetic stirrer, oxindole (**890**, 6 mg, FW = 328.41, 0.019 mmol) was placed into a pyridine-CH_2Cl_2 (8:2, 4 mL) mixture. The vessel was capped with a rubber septum, and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 100-110 °C [external temperature (or oil bath temperature)] and was allowed to run for 60 h with vigorous magnetic stirring. The reaction vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 3:1] to provide alstonoxine A (**19**, 0.015 mmol, FW = 328.41, 4.8 mg, 81%). $\mathbf{[\alpha]^{23}_D}$ = –40.0° (*c* 0.15, $CHCl_3$), [lit.[12]: $\mathbf{[\alpha]^{23}_D}$ = –34.0° (*c* 0.19, $CHCl_3$)]; **IR** (KBr) 3357, 3240, 1701, 1694, cm^{-1}, [lit.[12]: **IR** (dry film) 3390, 3288, 1694, cm^{-1}]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (brd, *J* = 8 Hz, 1H), 7.31 (td, *J* = 8, 1 Hz, 1H), 7.17 (td, *J* = 8, 1 Hz, 1H), 6.84 (brd, *J* = 8 Hz, 1H), 4.00 (dd, *J* = 12, 1 Hz, 1H), 3.86 (d, *J* = 7 Hz, 1H), 3.76 (dd, *J* = 12, 1 Hz, 1H), 3.22 (brm, 1H), 3.19 (s, 3H), 3.00 (m, 1H), 2.74 (dd, *J* = 18, 6 Hz, 1H), 2.69 (dd, *J* = 18, 6 Hz, 1H), 2.40 (dd, *J* = 12, 8 Hz, 1H), 2.19 (s, 3H), 2.09 (dd, *J* = 13, 2 Hz, 1H), 1.85 (m, 1H), 1.66 (m, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 208.7 (C), 182.7

(C), 144.5 (C), 129.6 (C), 128.5 (CH), 125.4 (CH), 123.7 (CH), 108.7 (CH), 66.1(CH_2), 63.4 (CH), 61.9 (CH), 57.8 (C), 47.7 (CH_2), 41.9 (CH), 41.1 (CH_2), 33.6 (CH_2), 30.9 (CH_3), 26.7 (CH_3), 26.3 (CH); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{19}H_{25}N_2O_3$ $(M+H)^+$ = 329.1787, found 329.1781. The spectral data was in excellent agreement to that reported by Kam et al.[12]

Synthesis of (−)-macrogentine (31) from isoalstonoxine A (890).

In a 10 mL screw-cap glass tube with a magnetic stirrer, oxindole (**890**, 12 mg, FW = 328.41, 0.037 mmol) and acetaldehyde (20 equivalents, 0.73 mmol, 32 mg) were placed into absolute ethanol (3 mL) and dry $MgSO_4$ (2 equivalents, 0.074 mmol, 9 mg). The reaction vessel was capped with a rubber septum and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 80-85 °C [external temperature (or oil bath temperature)] and was allowed to run for 24 h with vigorous magnetic stirring. The reaction vessel was then removed from the oil bath and it was allowed to cool to rt. The reaction mixture was gravity filtered to remove $MgSO_4$. The filtrate was collected and the solvent was removed under vacuum. The residue was purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide macrogentine (**31**, 0.033 mmol, FW = 354.44, 11 mg, 90%). $\mathbf{[\alpha]^{23}_D}$ = −27.0° (*c* 0.10, $CHCl_3$), [lit.[12]: $\mathbf{[\alpha]^{23}_D}$ = −21.0° (*c* 0.15, $CHCl_3$)]; **IR** (KBr) 2957, 1708, 1702, 1210, 1104 cm^{-1}, [lit.[12]: **IR** (dry film) 1704 cm^{-1}]; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8, 1 Hz, 1H), 7.30 (td, *J* = 8, 1 Hz, 1H), 7.05 (td, *J* = 8, 1 Hz, 1H),

6.86 (dd, *J* = 8, 1 Hz, 1H), 4.93 (q, *J* = 6 Hz, 1H), 4.22 (dd, *J* = 12, 1 Hz, 1H), 3.87 (dd, *J* = 12, 1 Hz, 1H), 3.77 (d, *J* = 7 Hz, 1H), 3.56 (d, *J* = 3 Hz, 1H), 3.43 (m, 1H), 3.25 (s, 3H), 2.57 (dd, *J* = 15, 7 Hz, 1H), 2.50 (dd, *J* = 15, 7 Hz, 1H), 2.43 (dd, *J* = 12, 2 Hz, 1H), 2.30 (dd, *J* = 13, 6 Hz, 1H), 2.25 (s, 3H), 1.89 (ddd, *J* = 13, 10, 3 Hz, 1H), 1.76 (dd, *J* = 13, 7 Hz, 1H), 1.50 (d, *J* = 5 Hz, 1H), 1.33 (d, *J* = 6 Hz, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.4 (C), 177.7 (C), 142.3 (C), 138.7 (C), 127.8 (CH), 123.9 (CH), 122.7 (CH), 107.6 (CH), 85.6 (CH), 68.8 (CH_2), 63.1 (CH), 60.5 (CH), 55.4 (C), 49.1 (CH_2), 39.6 (CH_2), 35.2 (CH), 31.2 (CH_3), 30.3 (CH_2), 28.5 (CH), 26.6 (CH_3), 20.2 (CH_3); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{21}H_{27}N_2O_3$ $(M+H)^+$ = 355.1946, found 355. 1949. The spectral data was in excellent agreement to that reported by Kam et al.[12]

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12) Appendix A: ^{1}H and ^{13}C NMR spectra of selected oxindole alkaloids

12.1) Alkaloid **846**

12.2) Alkaloid **849**

12.3) Alkaloid **854**

12.4) Alkaloid **855**

12.5) Alkaloid **856**

12.6) Alkaloid **857**

12.7) *Affinisine oxindole* **24**

12.8) Alkaloid **863**

12.9) Alkaloid **879**

12.10) Alkaloid **878**

12.11) Alkaloid **882**

12.12) Alkaloid **884**

12.13) Alkaloid **885** (crude)

12.14) Alkaloid **886**

12.15) Alkaloid **887**

12.16) *Isoalstonisine* **27**

12.17) *Alstonisine* **8**

12.18) N_a*-demethylalstonisine* **17**

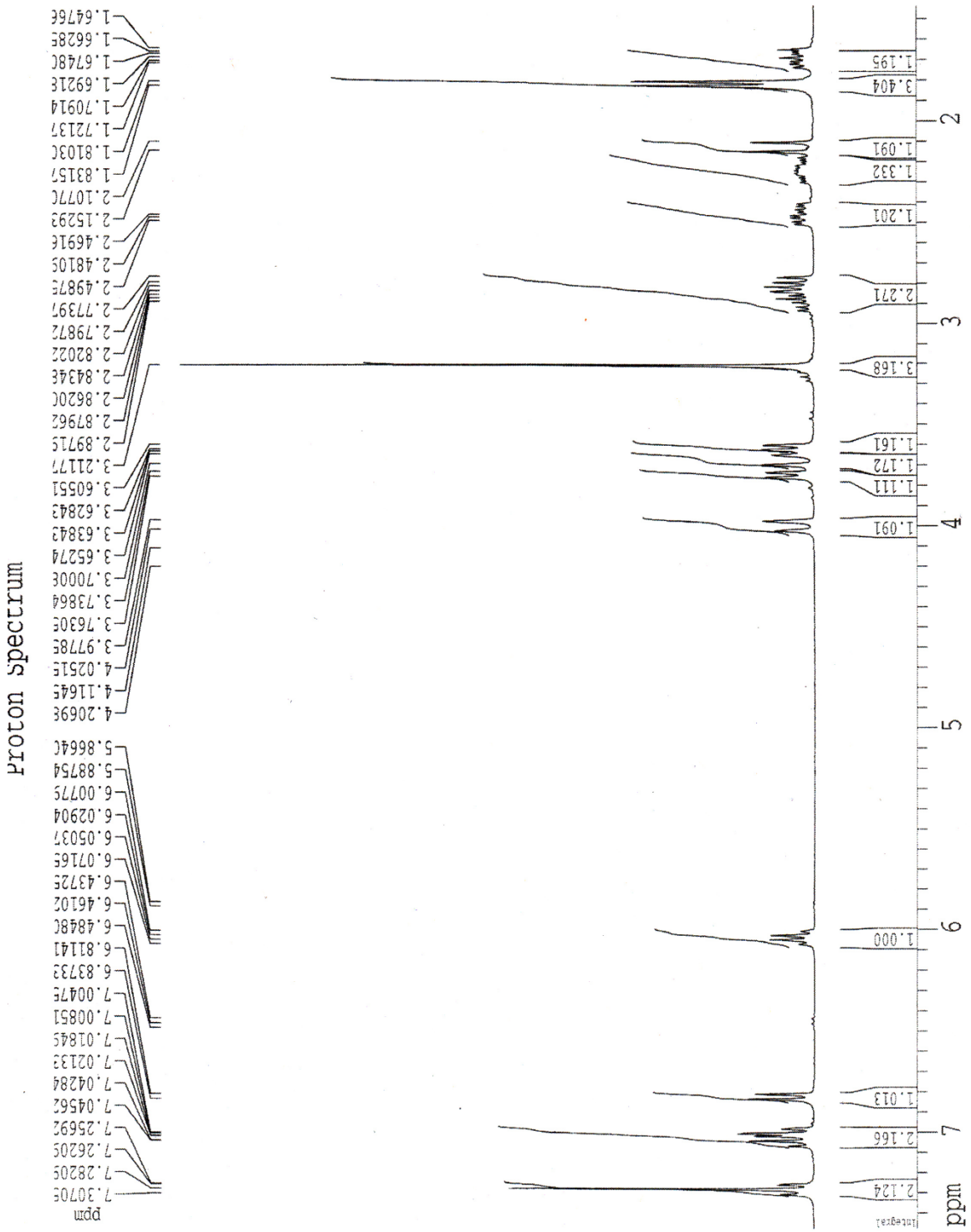
12.19) *Alstofoline* **18**

12.20) Alkaloid **890**

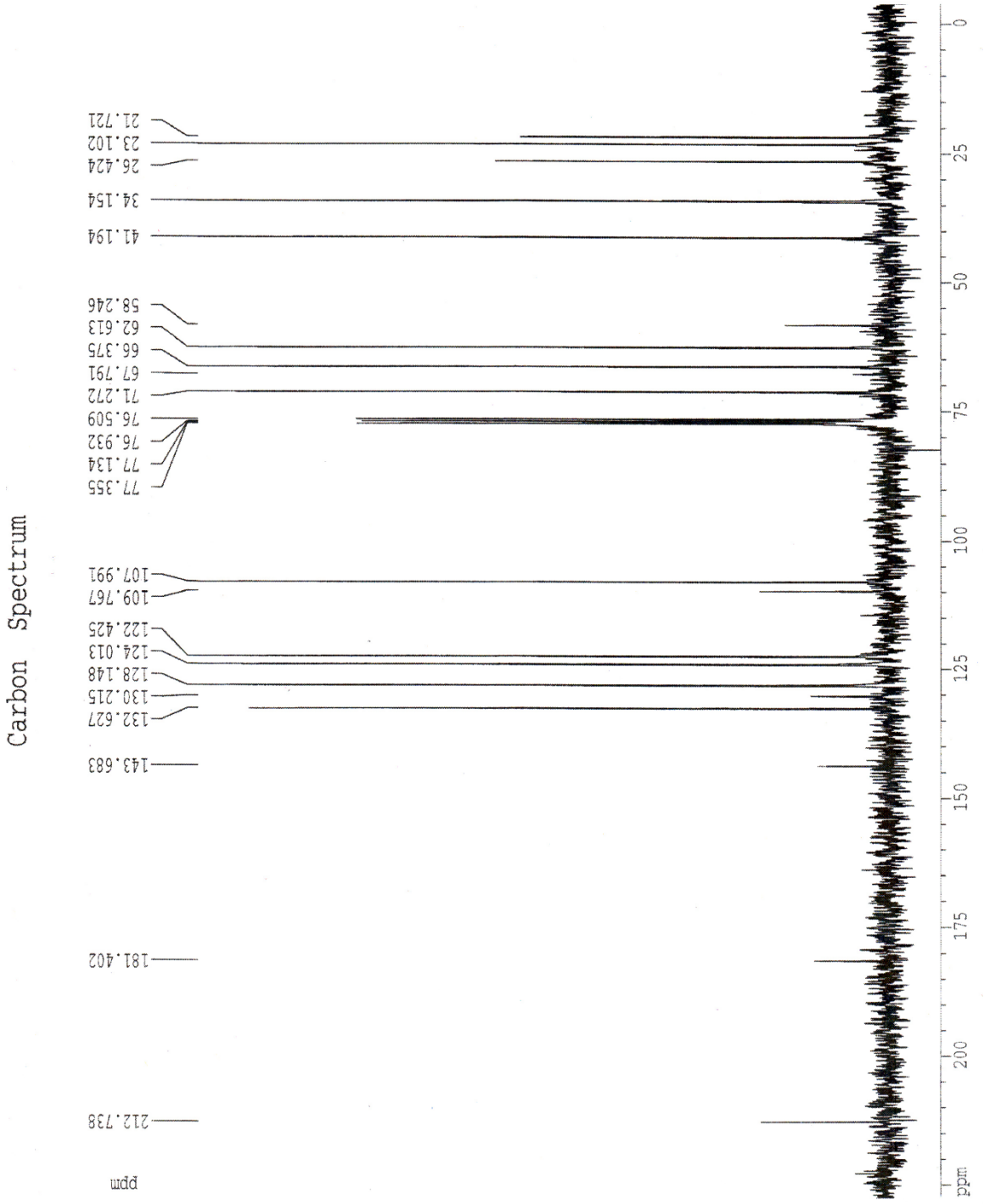
12.21) *Alstonoxine A* **19**

12.22) *Macrogentine* **31**

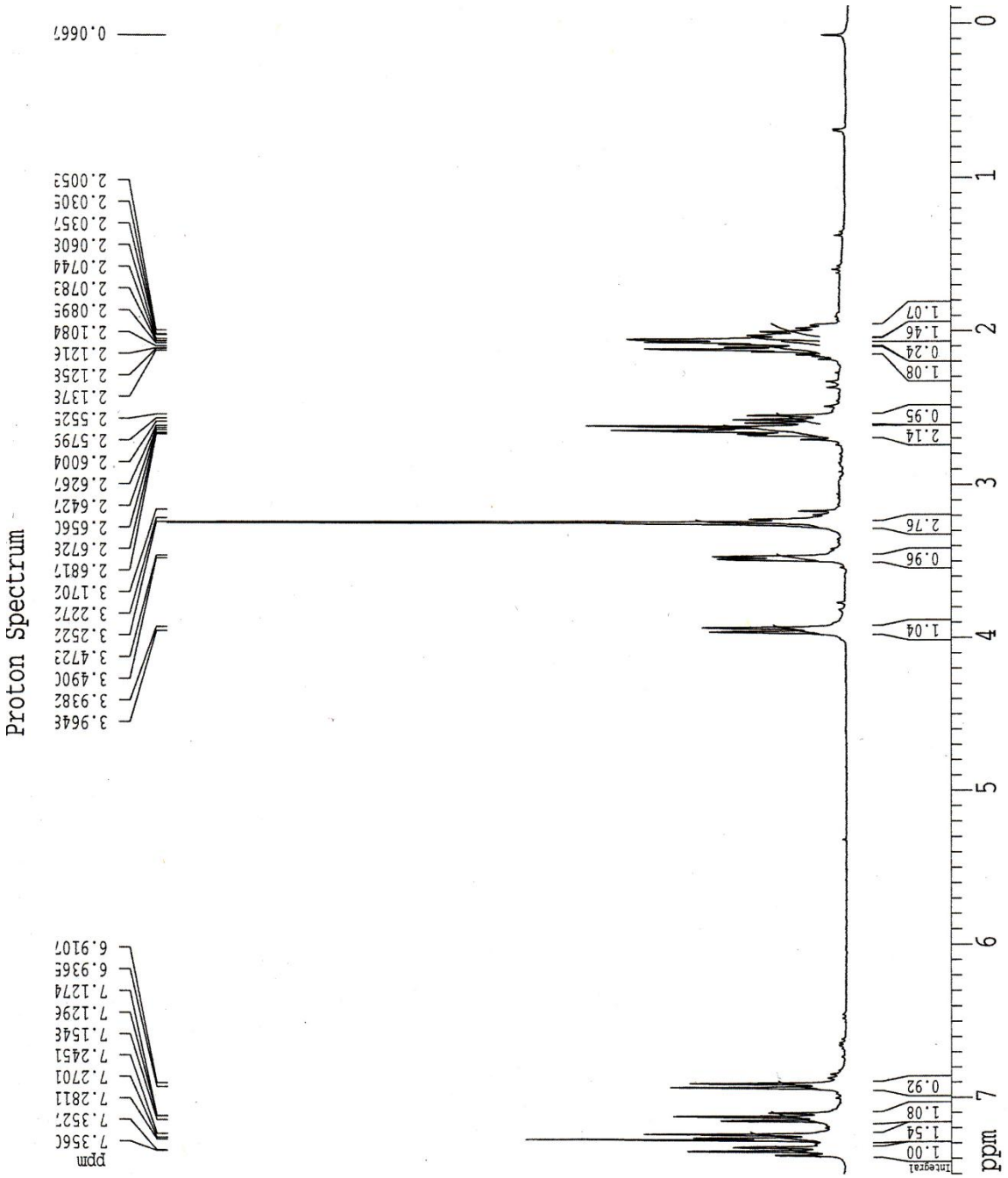
12.1) ^{1}H NMR: alkaloid **846** (solvent: $CDCl_3$)



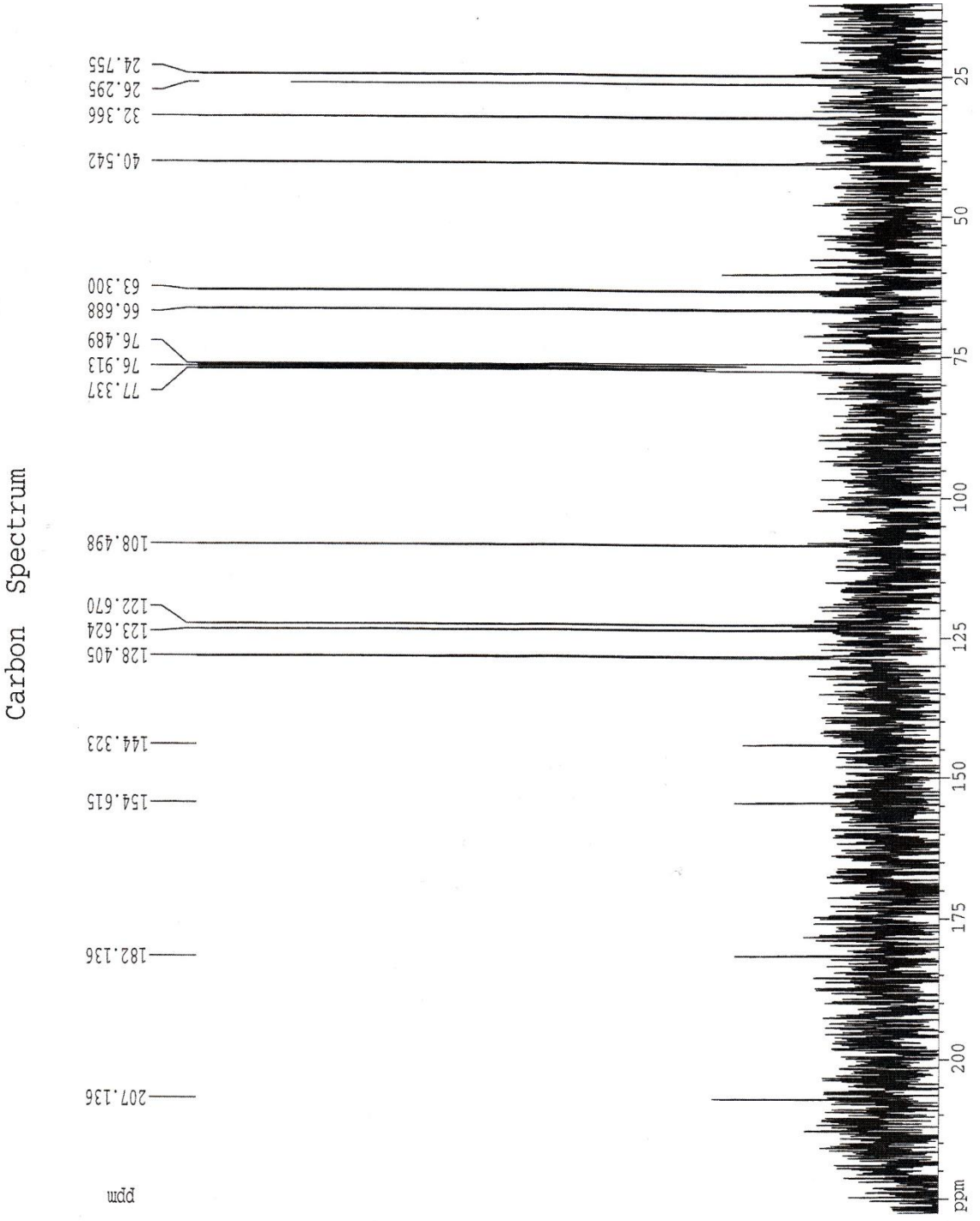
12.1) ^{13}C NMR: alkaloid **846** (solvent: $CDCl_3$)



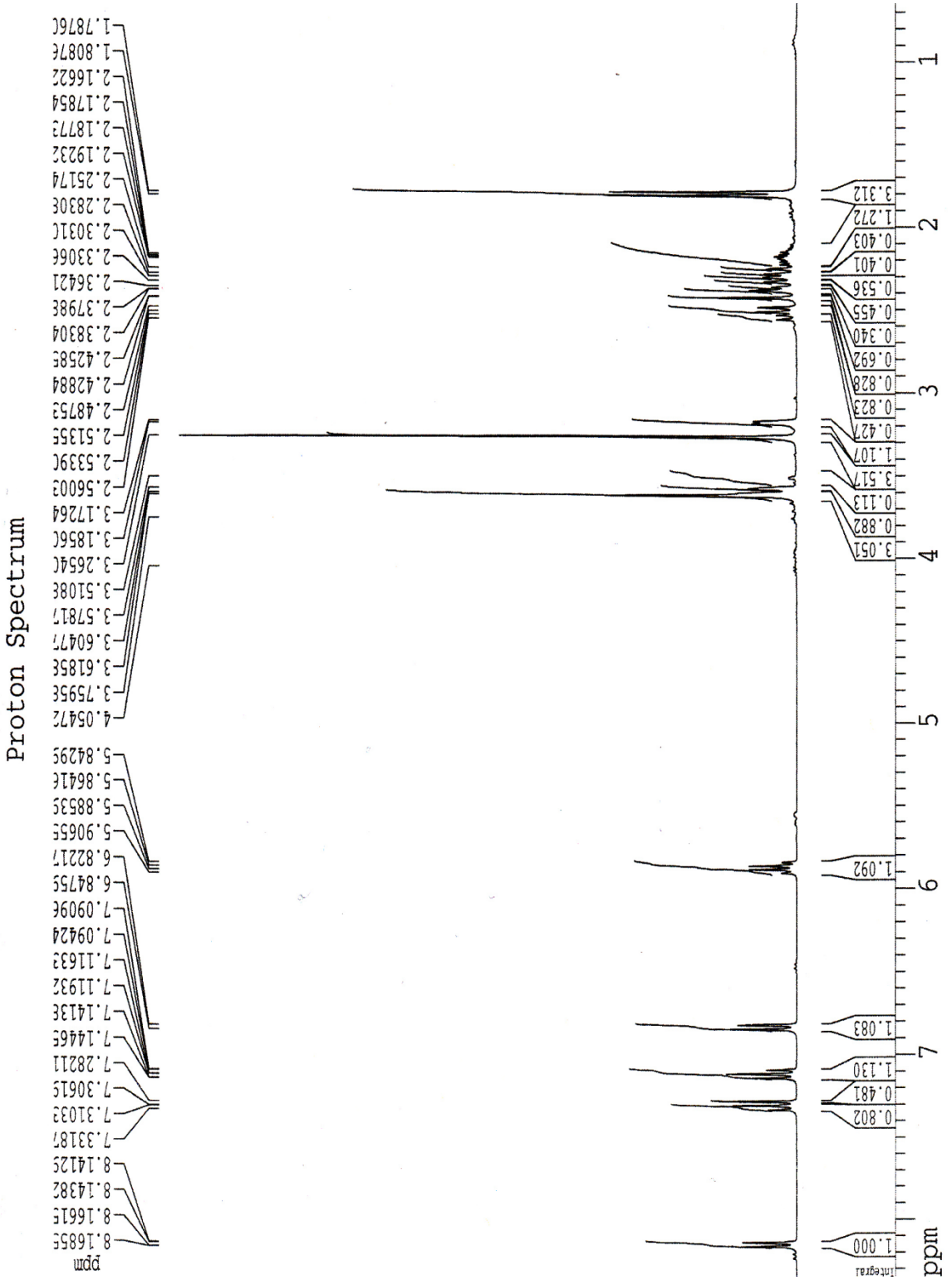
12.2) ^{1}H NMR: alkaloid **849** (solvent: $CDCl_3$)



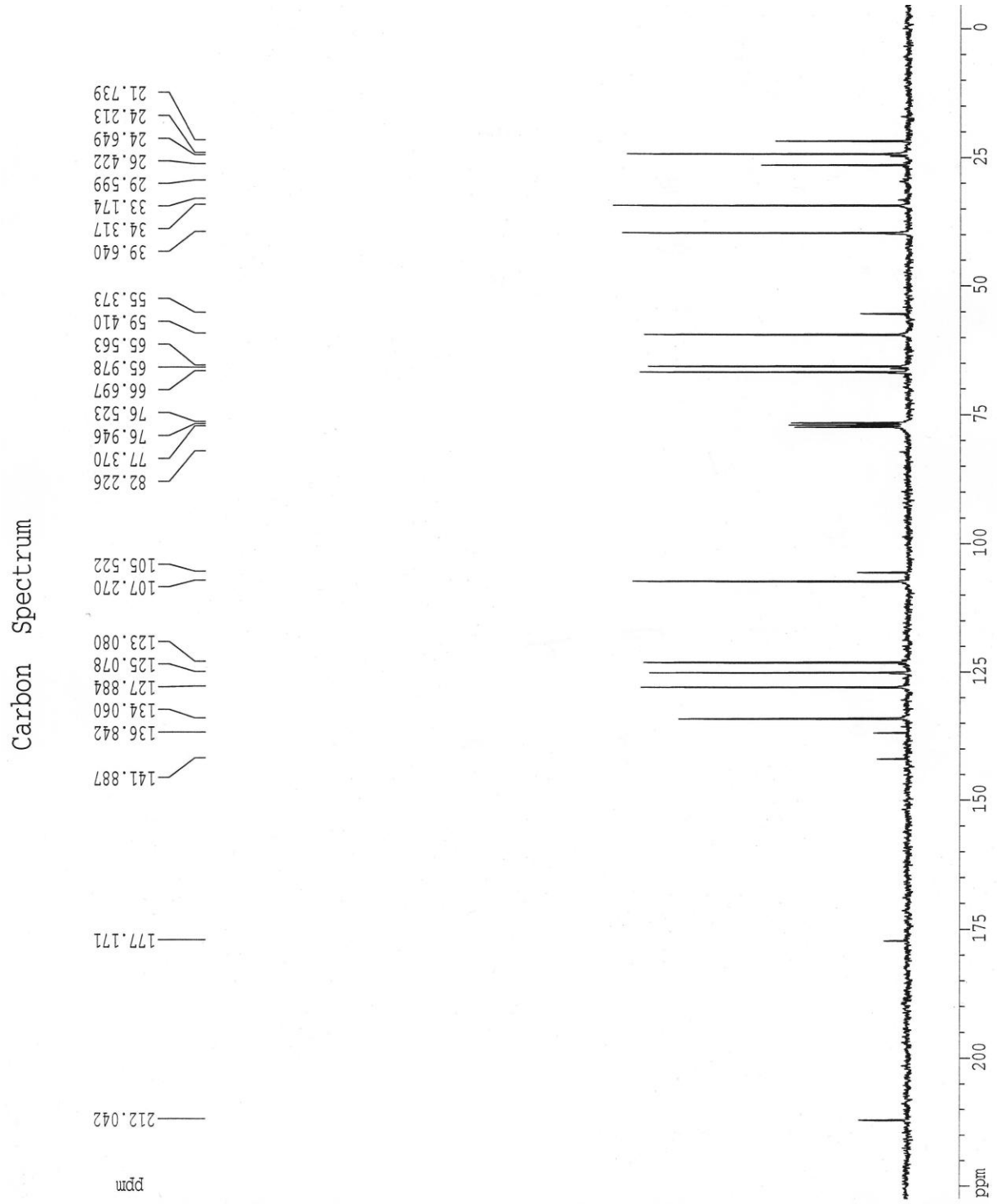
12.2) ^{13}C NMR: alkaloid **849** (solvent: $CDCl_3$)



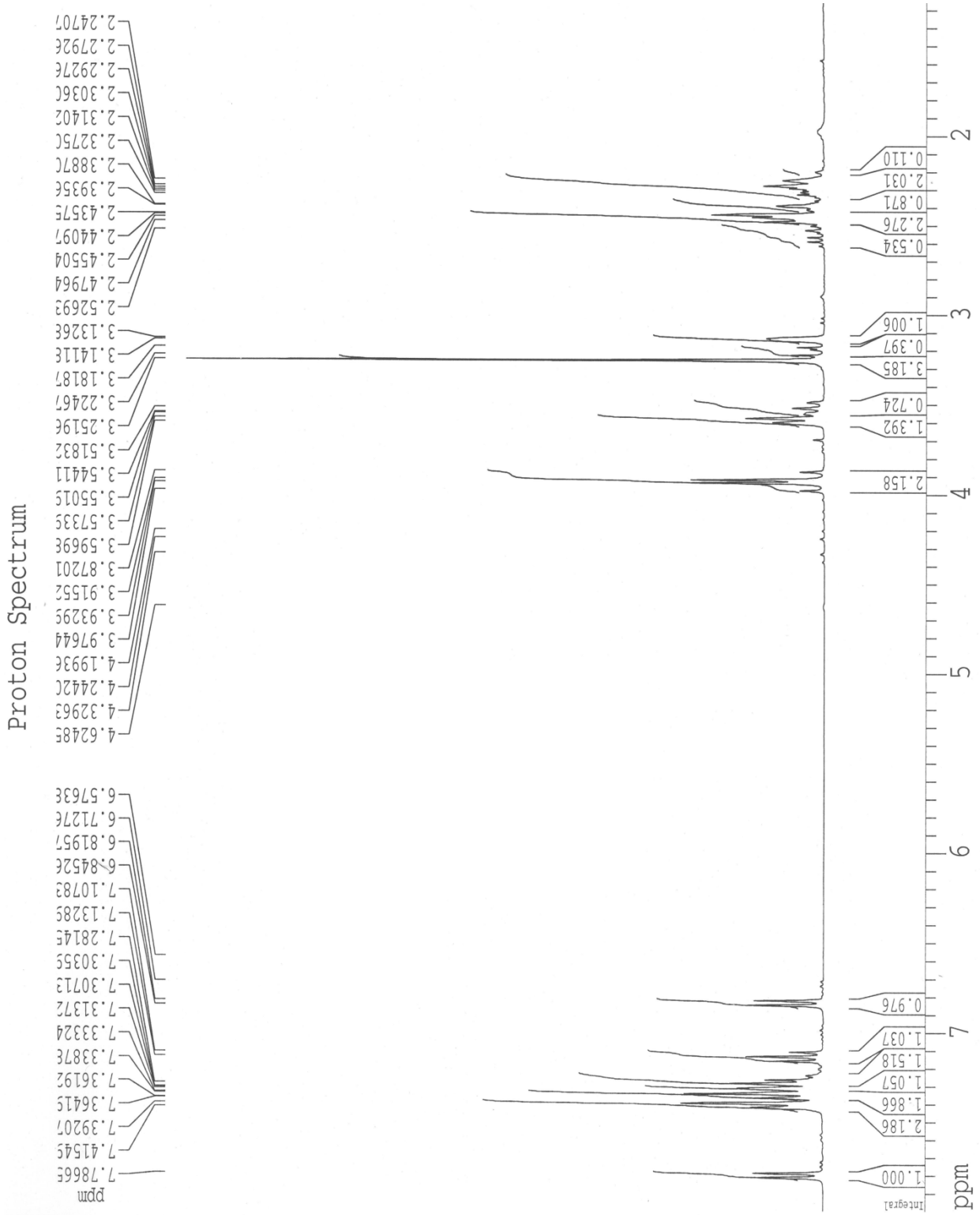
12.3) ^{1}H NMR: alkaloid **854** (solvent: $CDCl_3$)



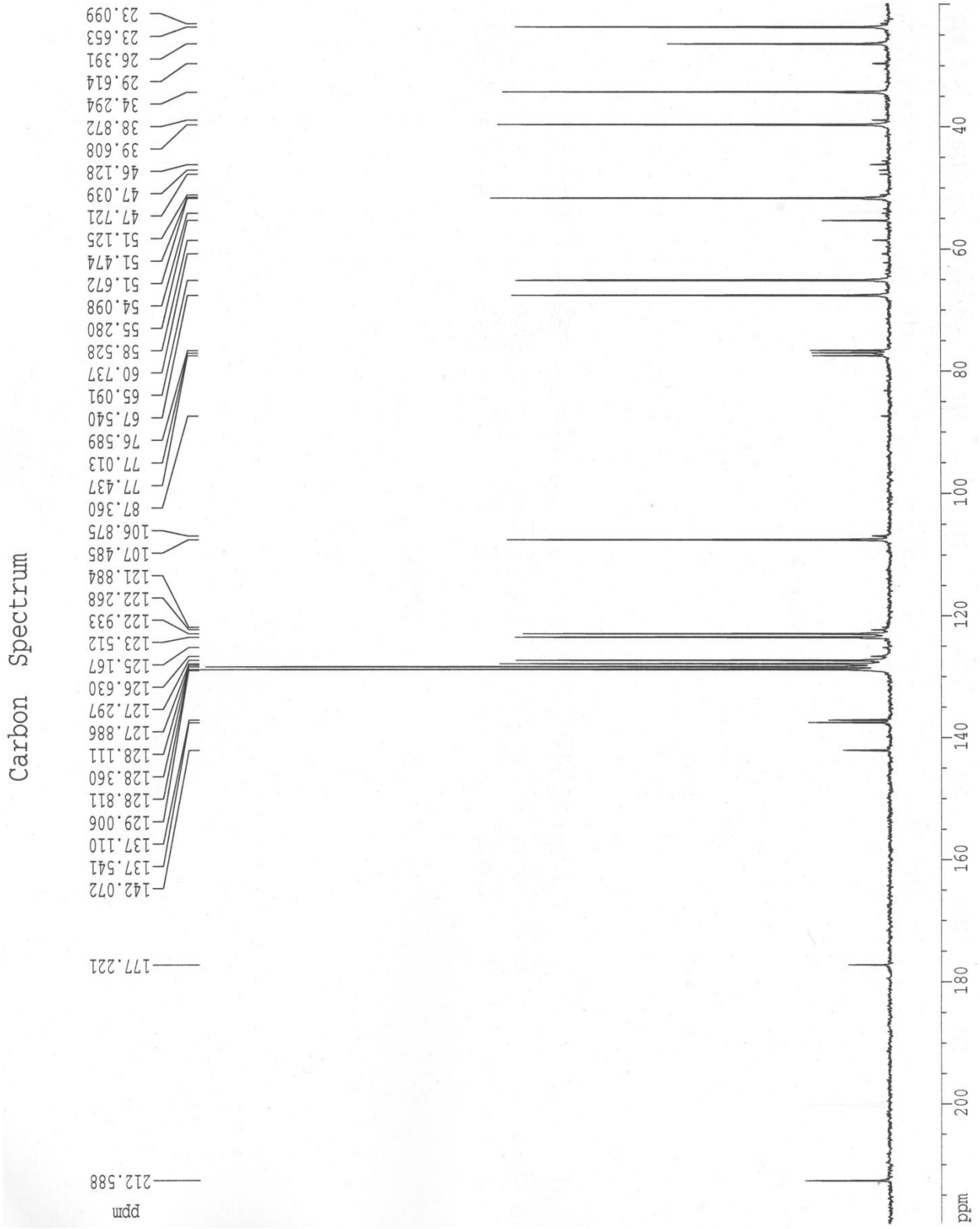
12.3) ^{13}C NMR: alkaloid **854** (solvent: $CDCl_3$)



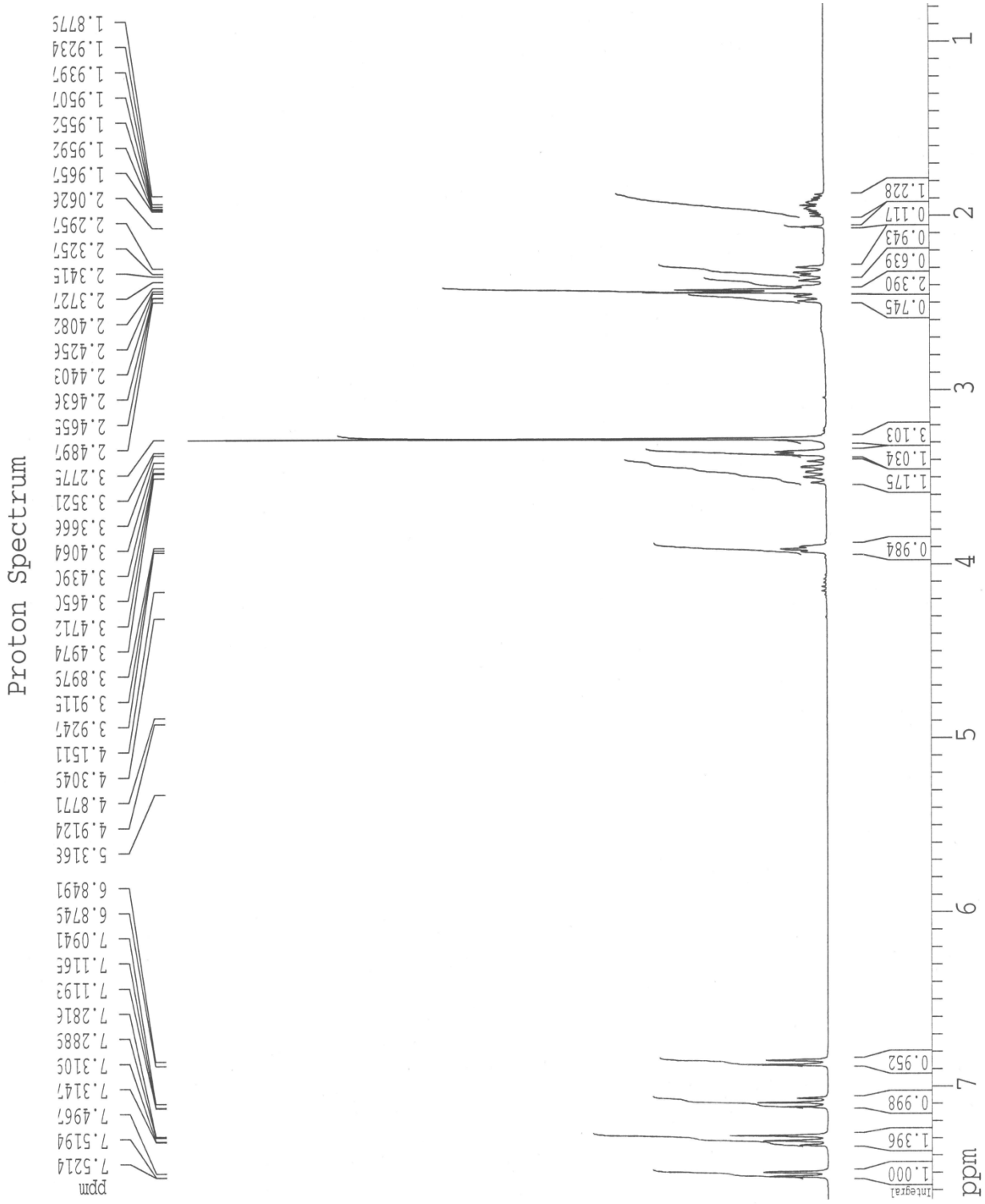
12.4) ^{1}H NMR: alkaloid **855** (solvent: $CDCl_3$)



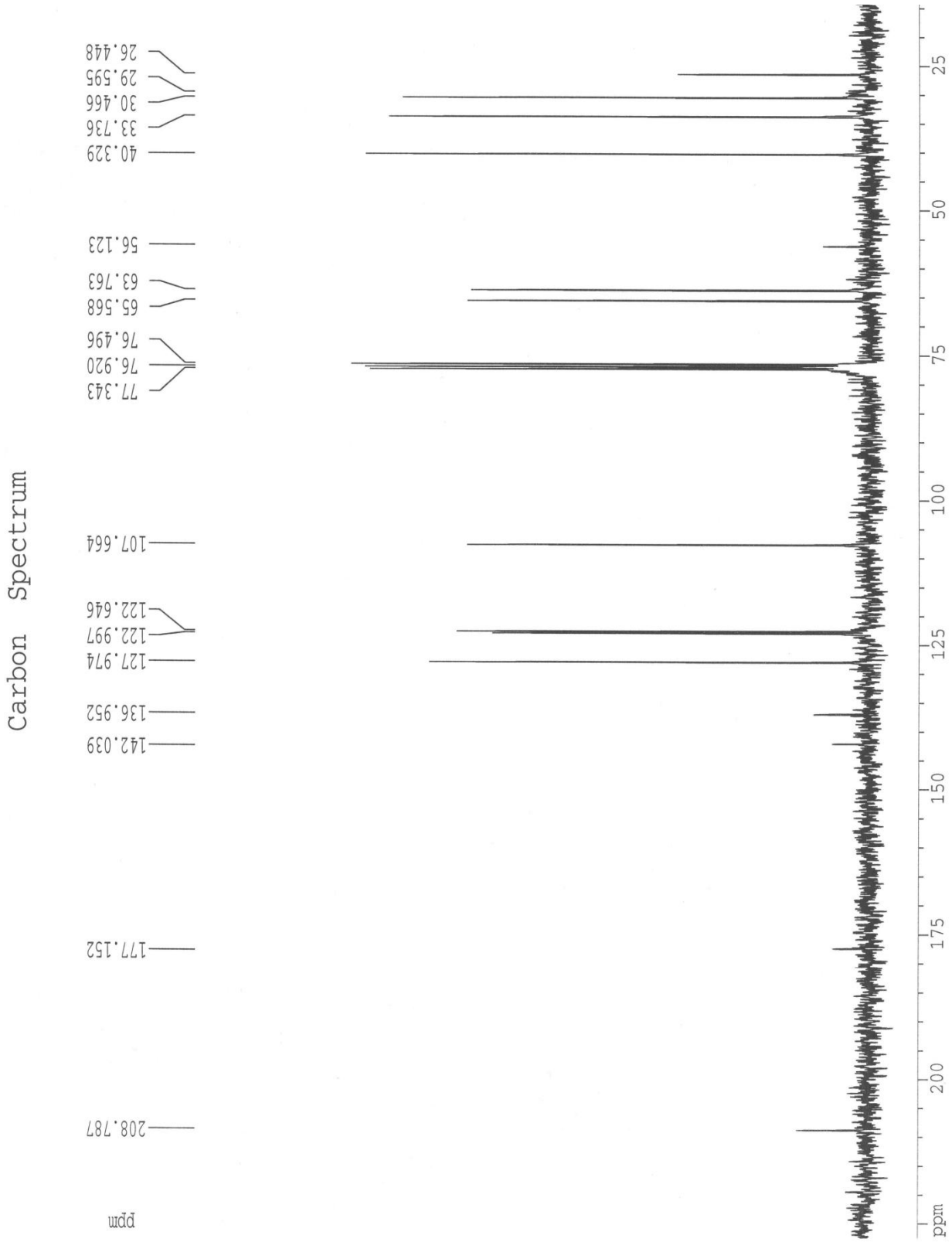
12.4) ^{13}C NMR: alkaloid **855** (solvent: $CDCl_3$)



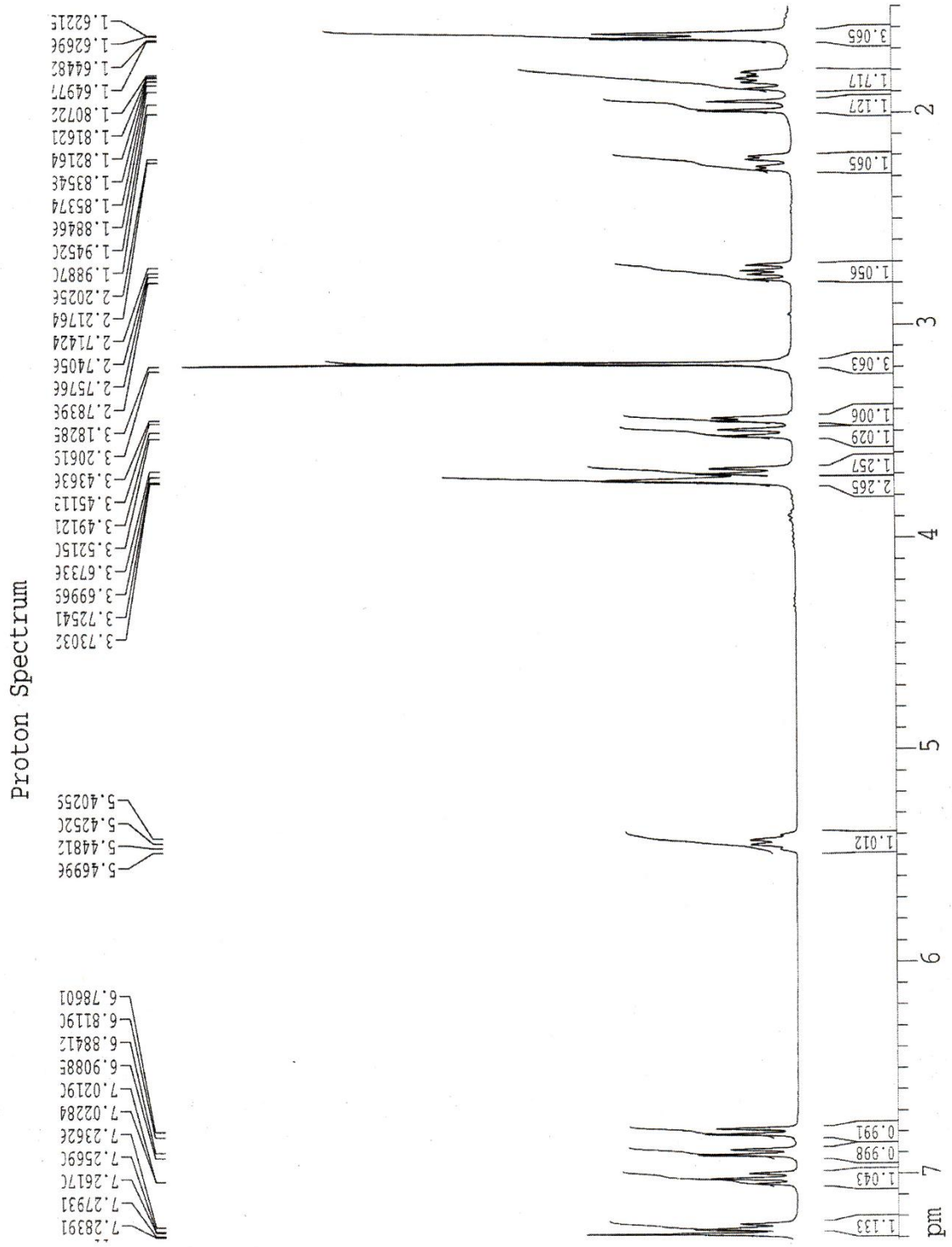
12.5) ^{1}H NMR: alkaloid **856** (solvent: $CDCl_3$)



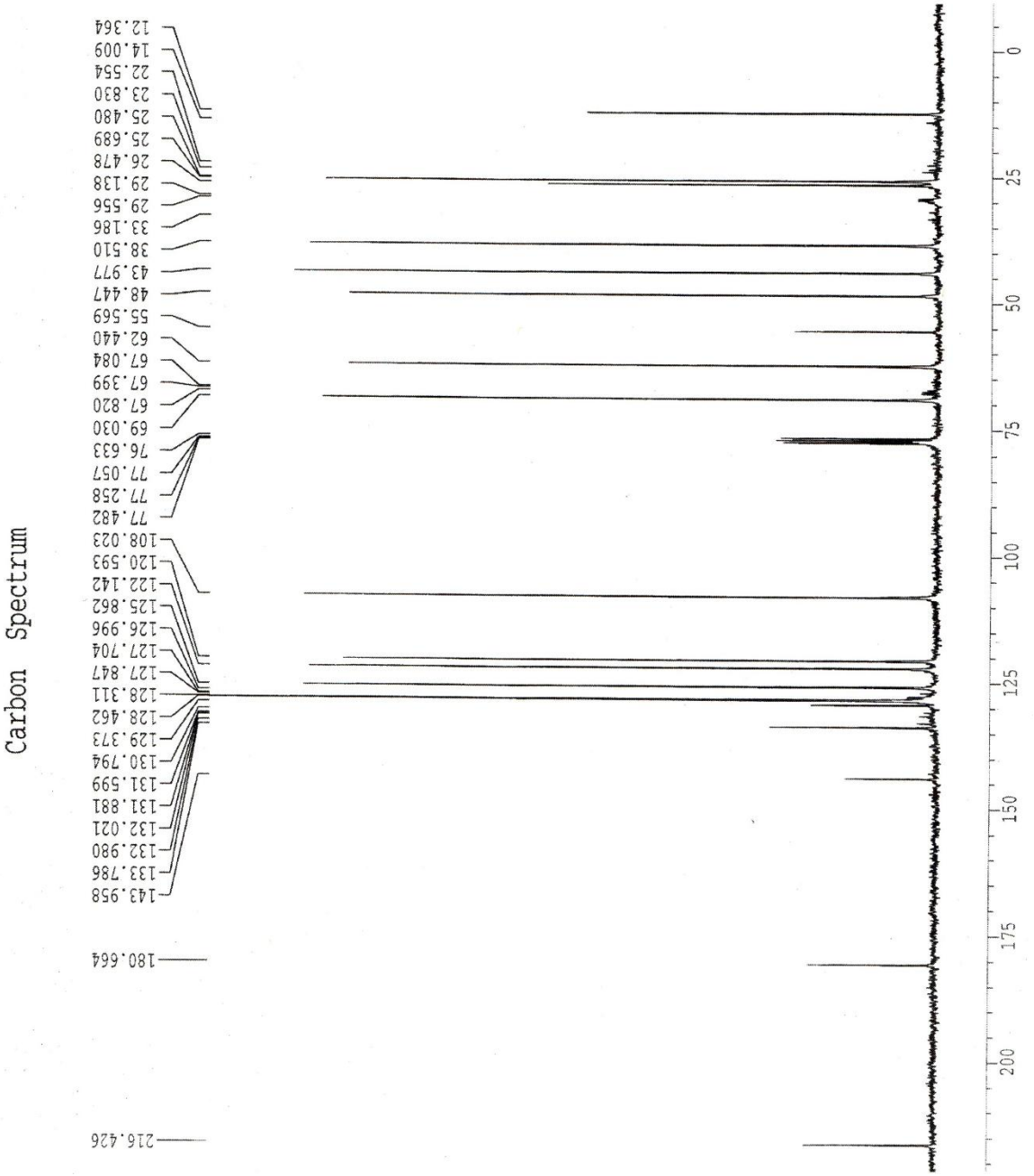
12.5) ^{13}C NMR: alkaloid **856** (solvent: $CDCl_3$)



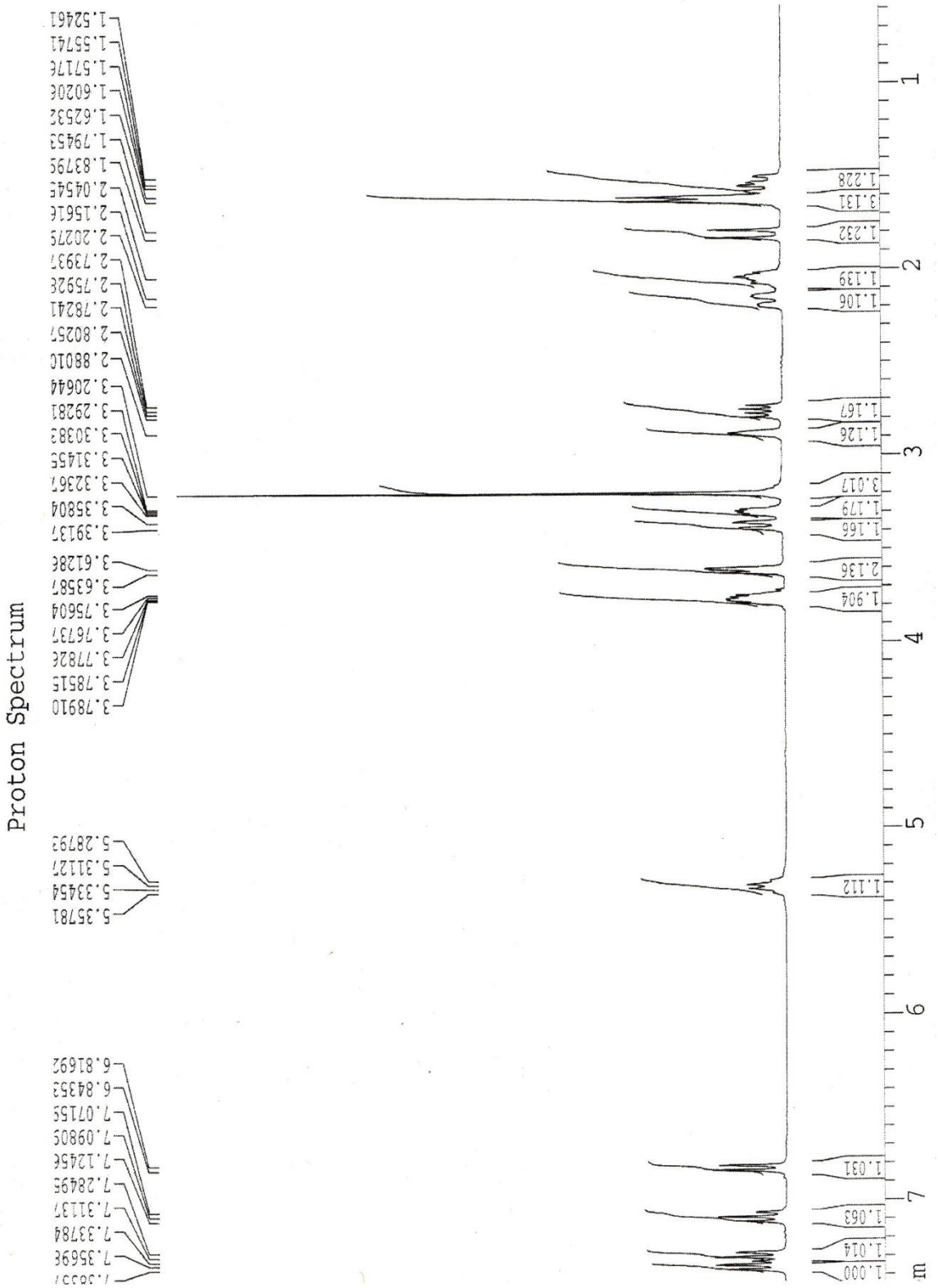
12.6) ^{1}H NMR: alkaloid **857** (solvent: $CDCl_3$)



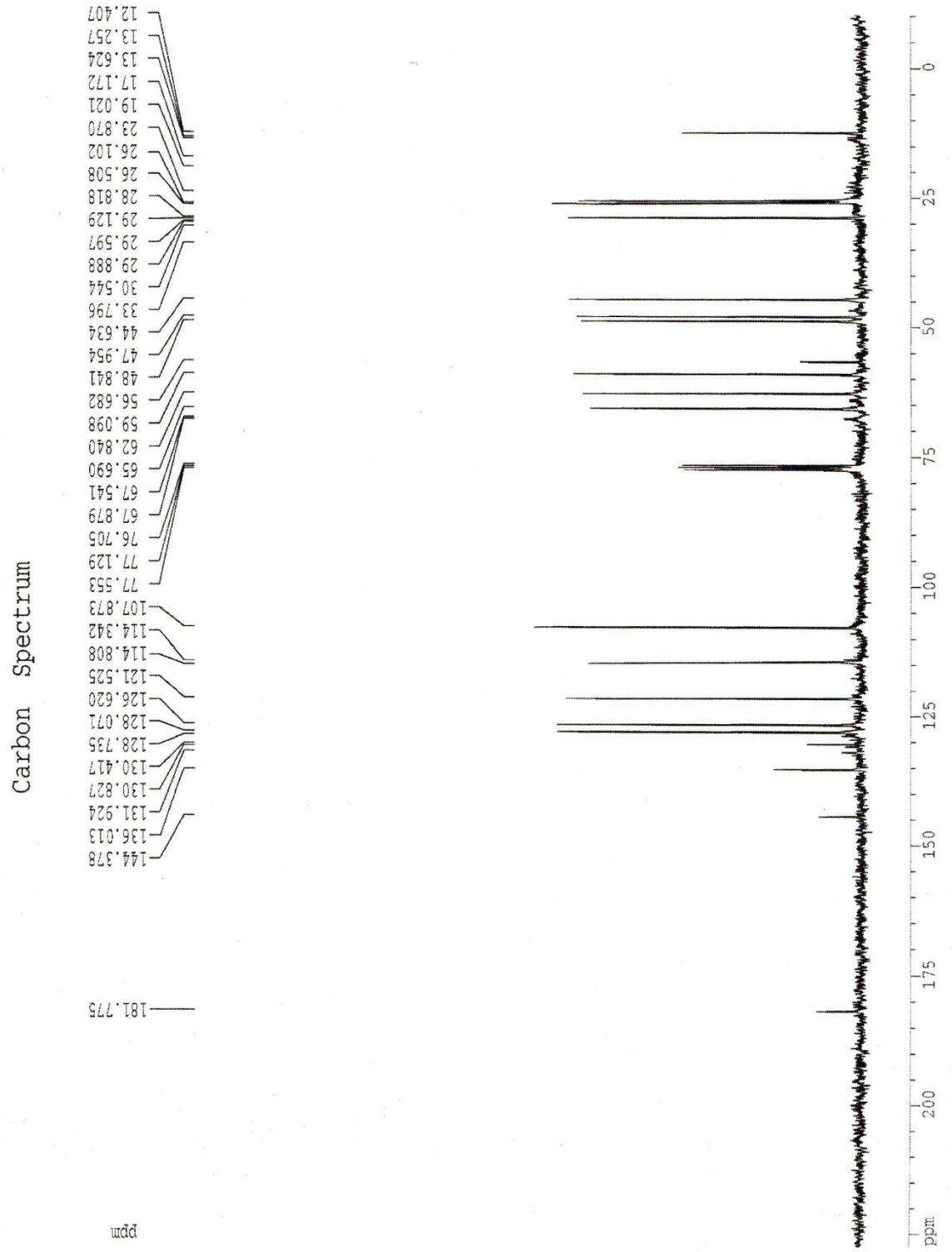
12.6) ^{13}C NMR: alkaloid **857** (solvent: $CDCl_3$)



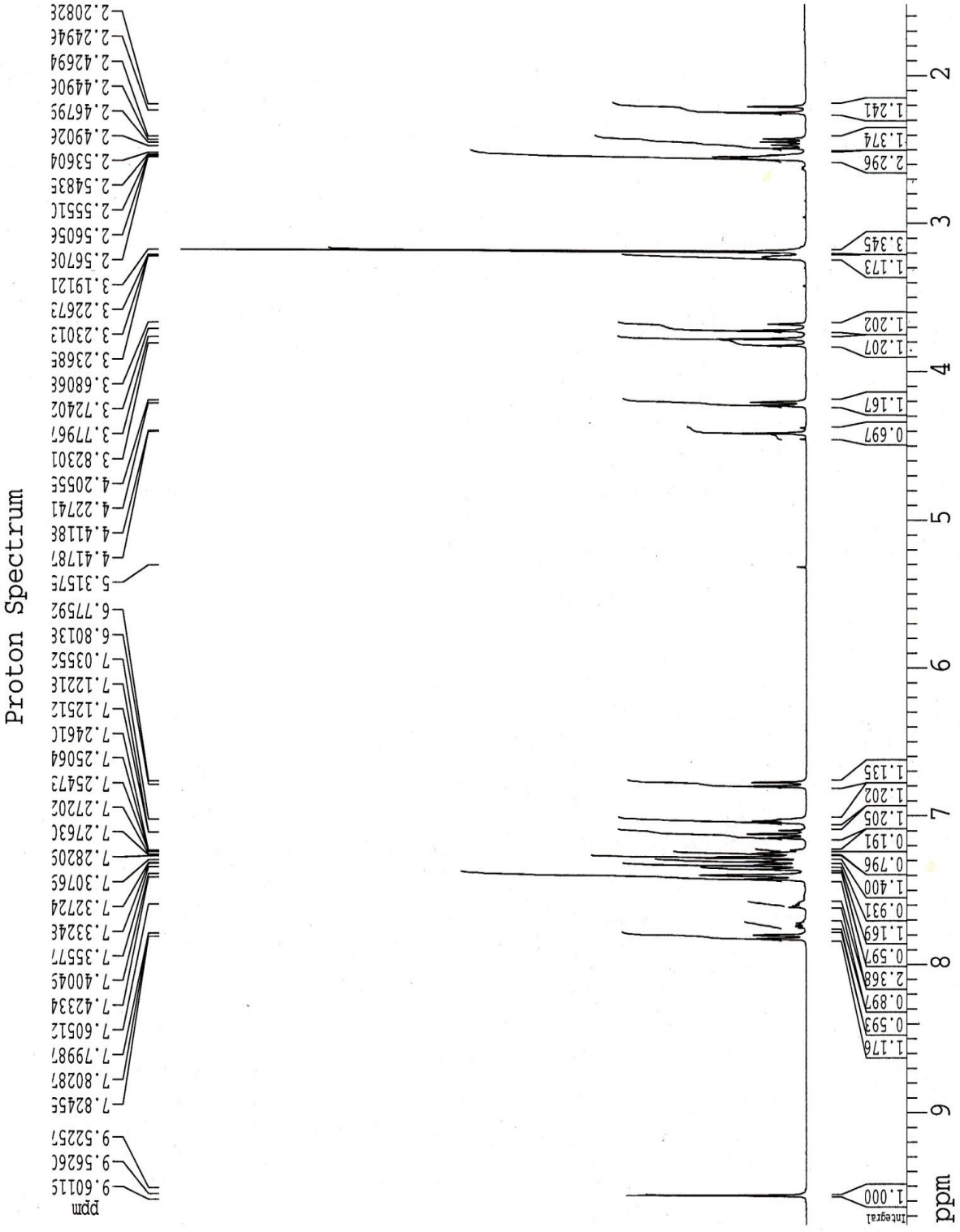
12.7) ^{1}H NMR: affinisine oxindole **24** (solvent: $CDCl_3$)



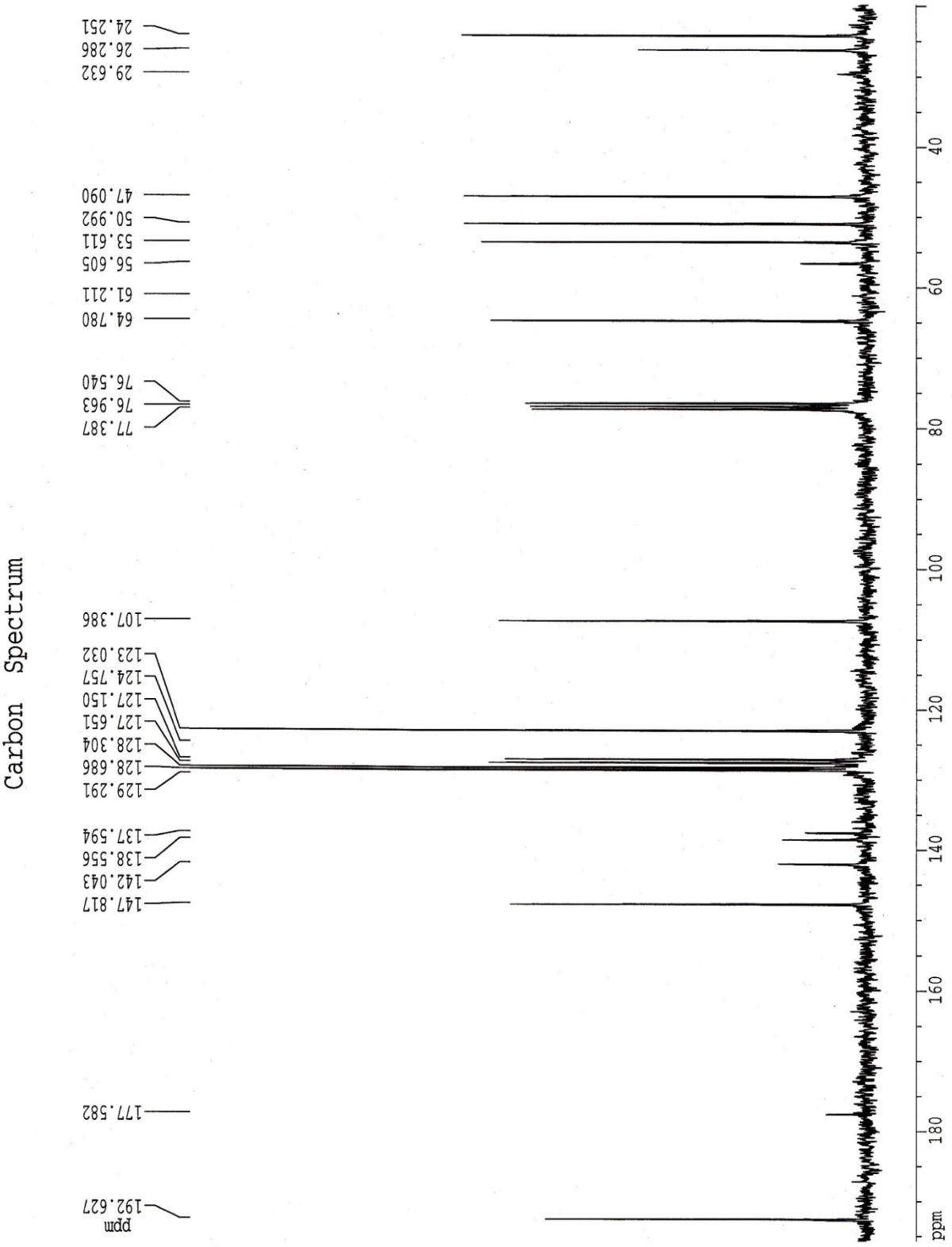
12.7) ^{13}C NMR: affinisine oxindole **24** (solvent: $CDCl_3$)



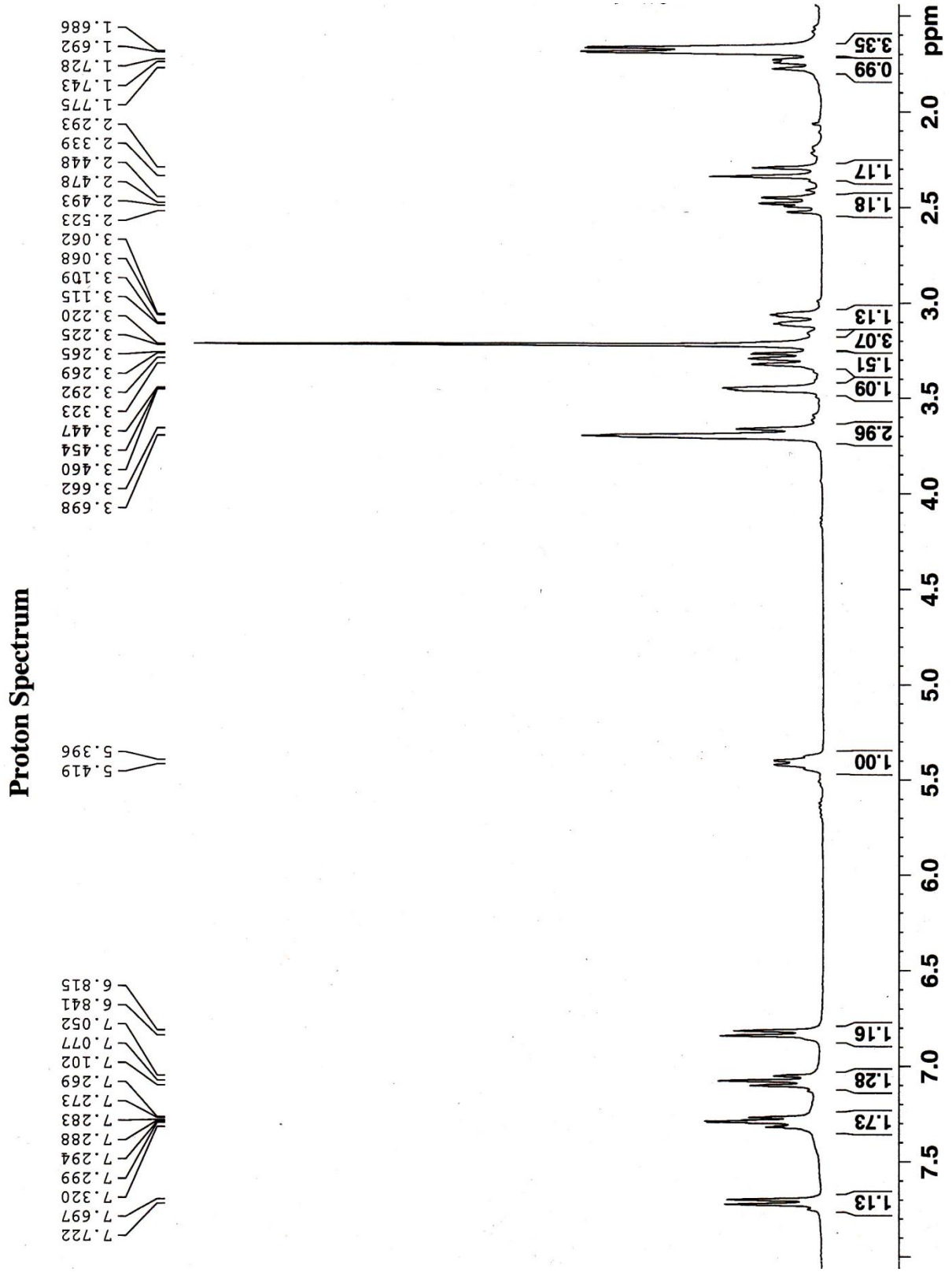
12.8) ^{1}H NMR: alkaloid **863** (solvent: $CDCl_3$)



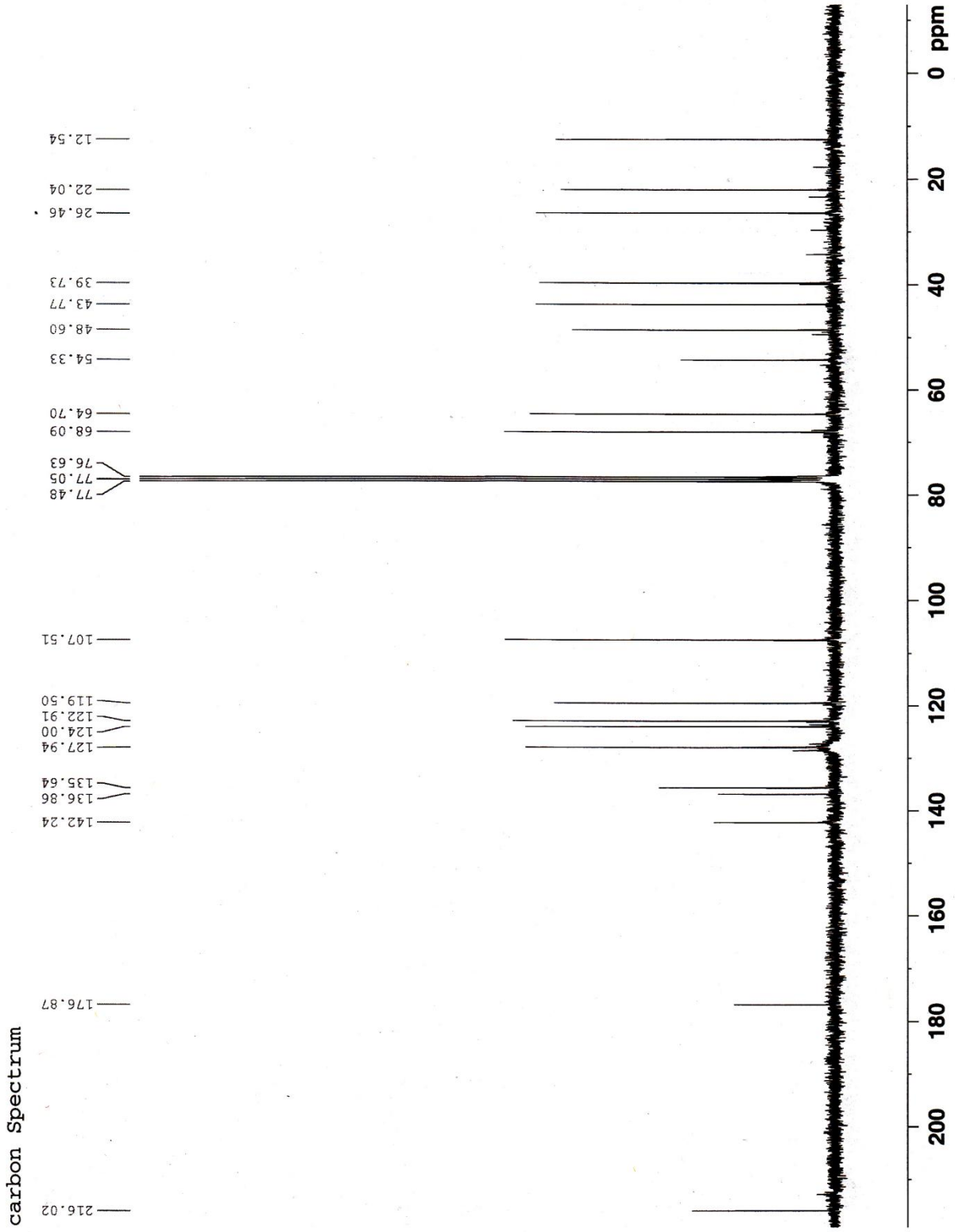
12.8) ^{13}C NMR: alkaloid **863** (solvent: $CDCl_3$)



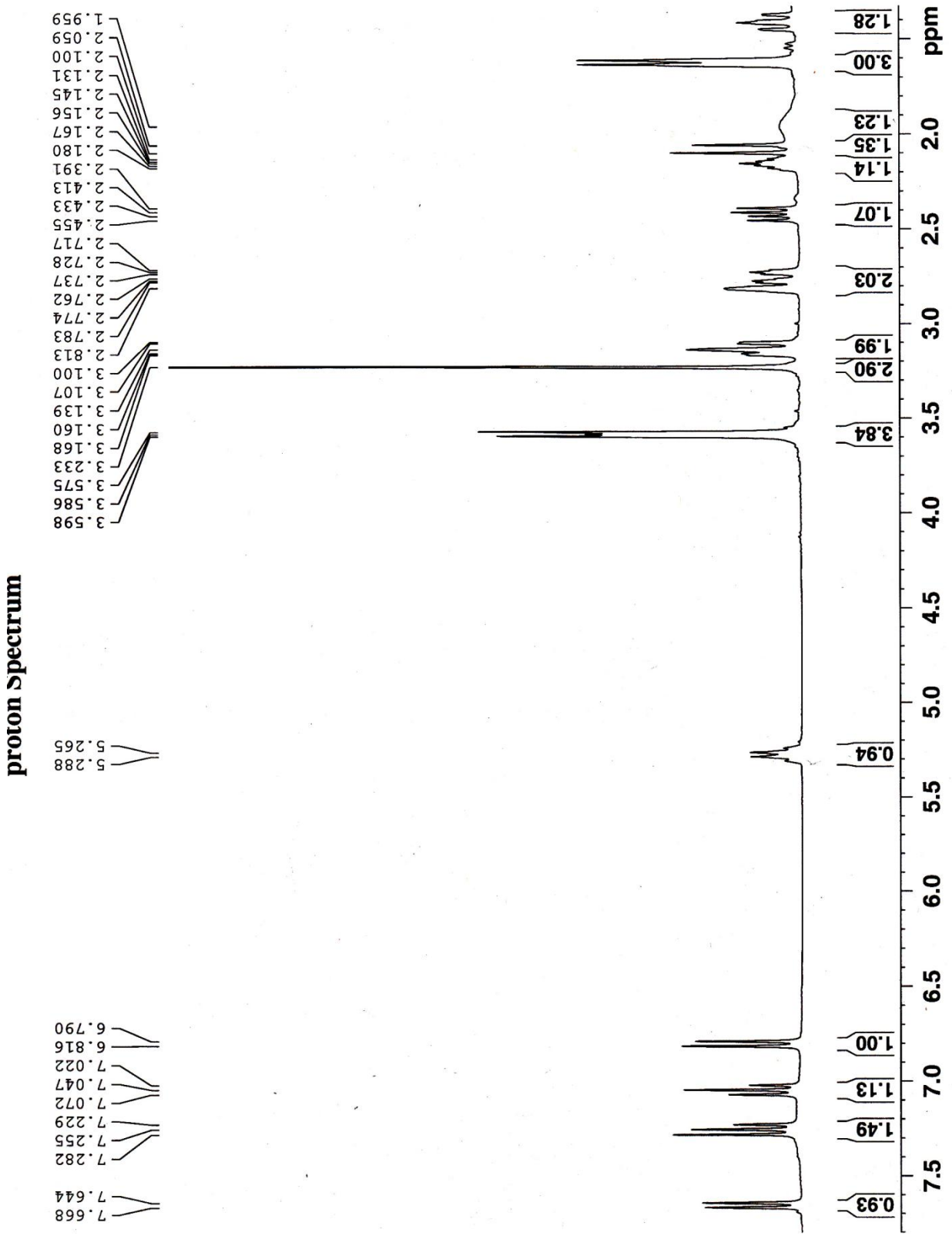
12.9) ^{1}H NMR: alkaloid **879** (solvent: $CDCl_3$)



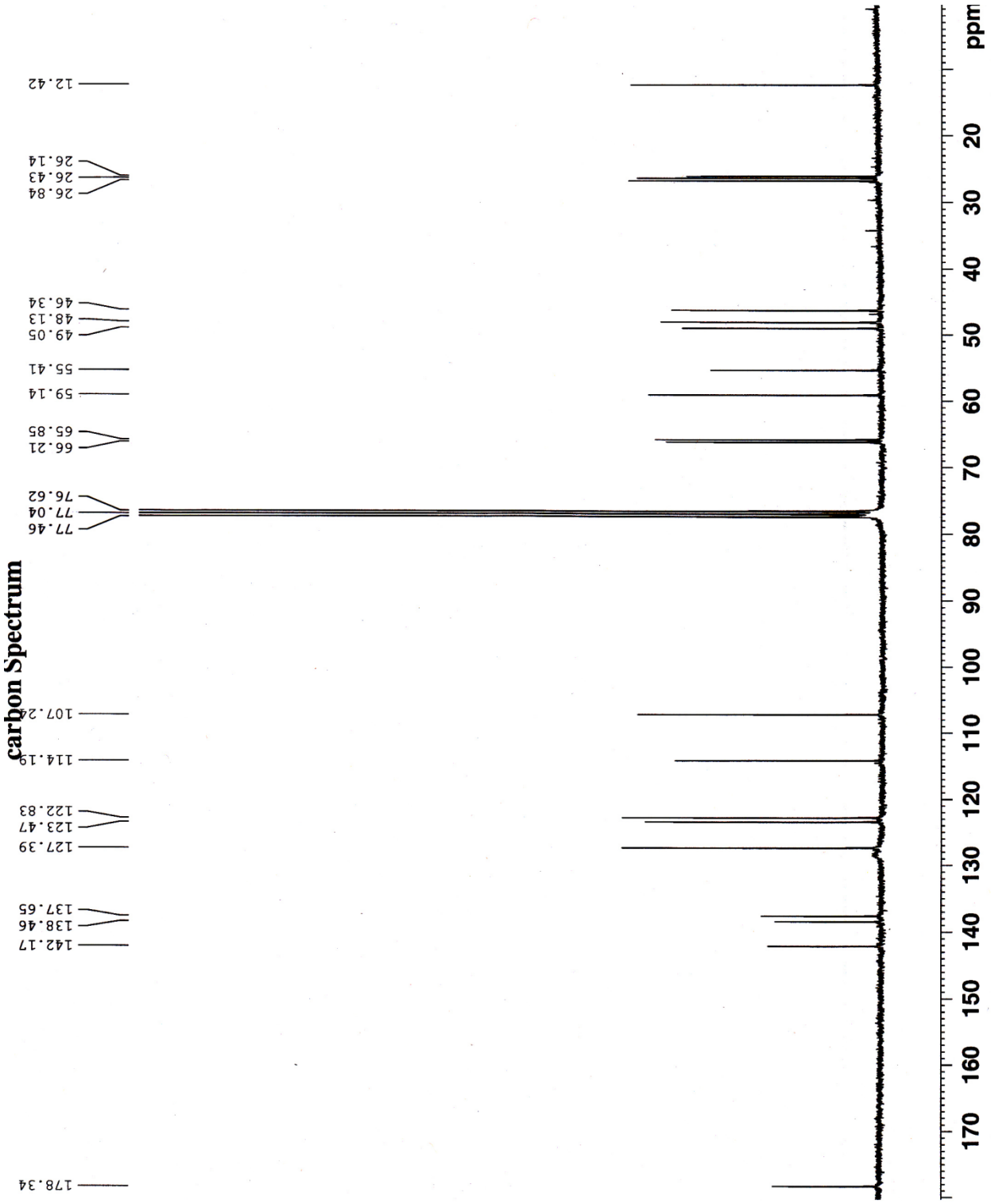
12.9) ^{13}C NMR: alkaloid **879** (solvent: $CDCl_3$)



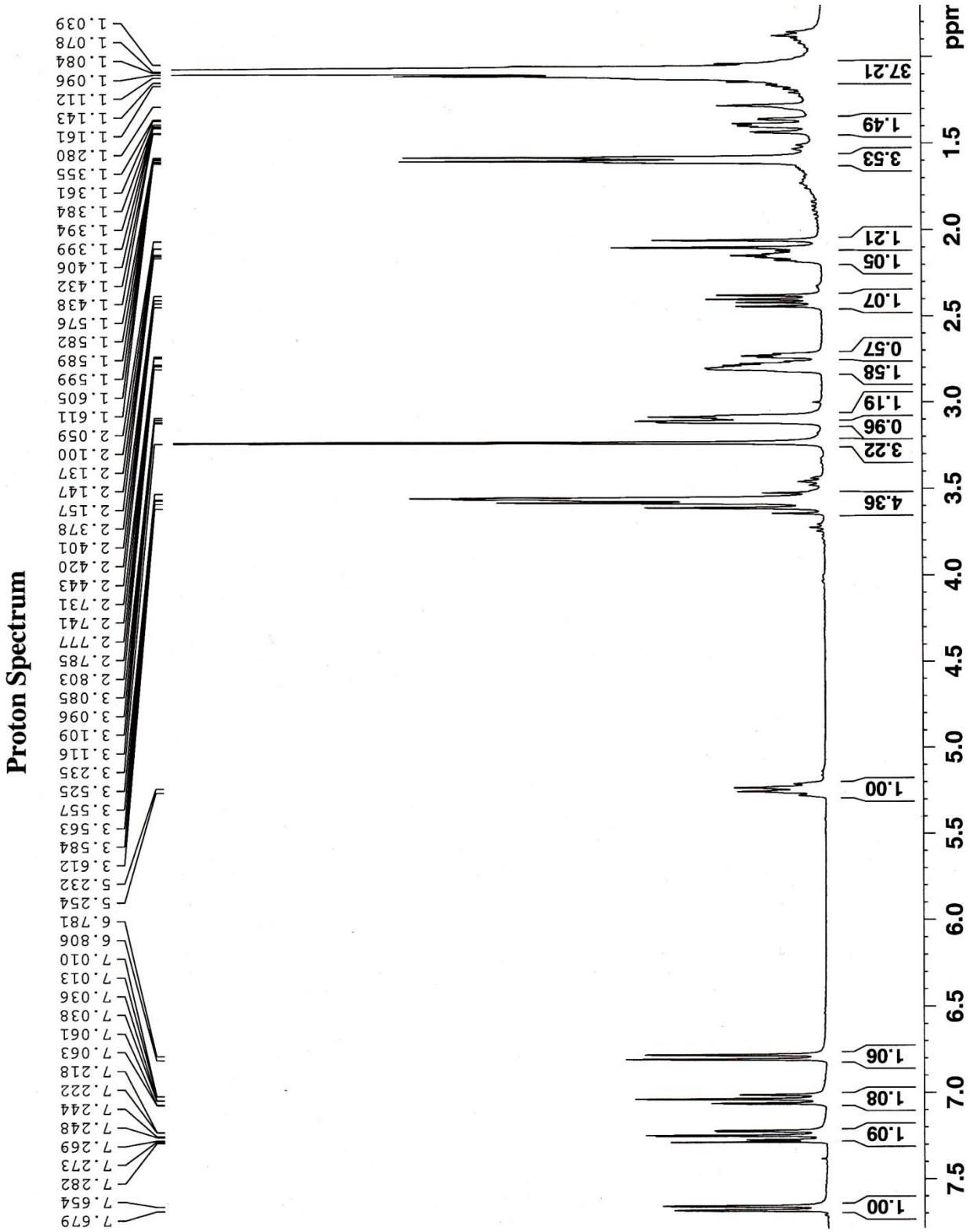
12.10) ^{1}H NMR: alkaloid **878** (solvent: $CDCl_3$)



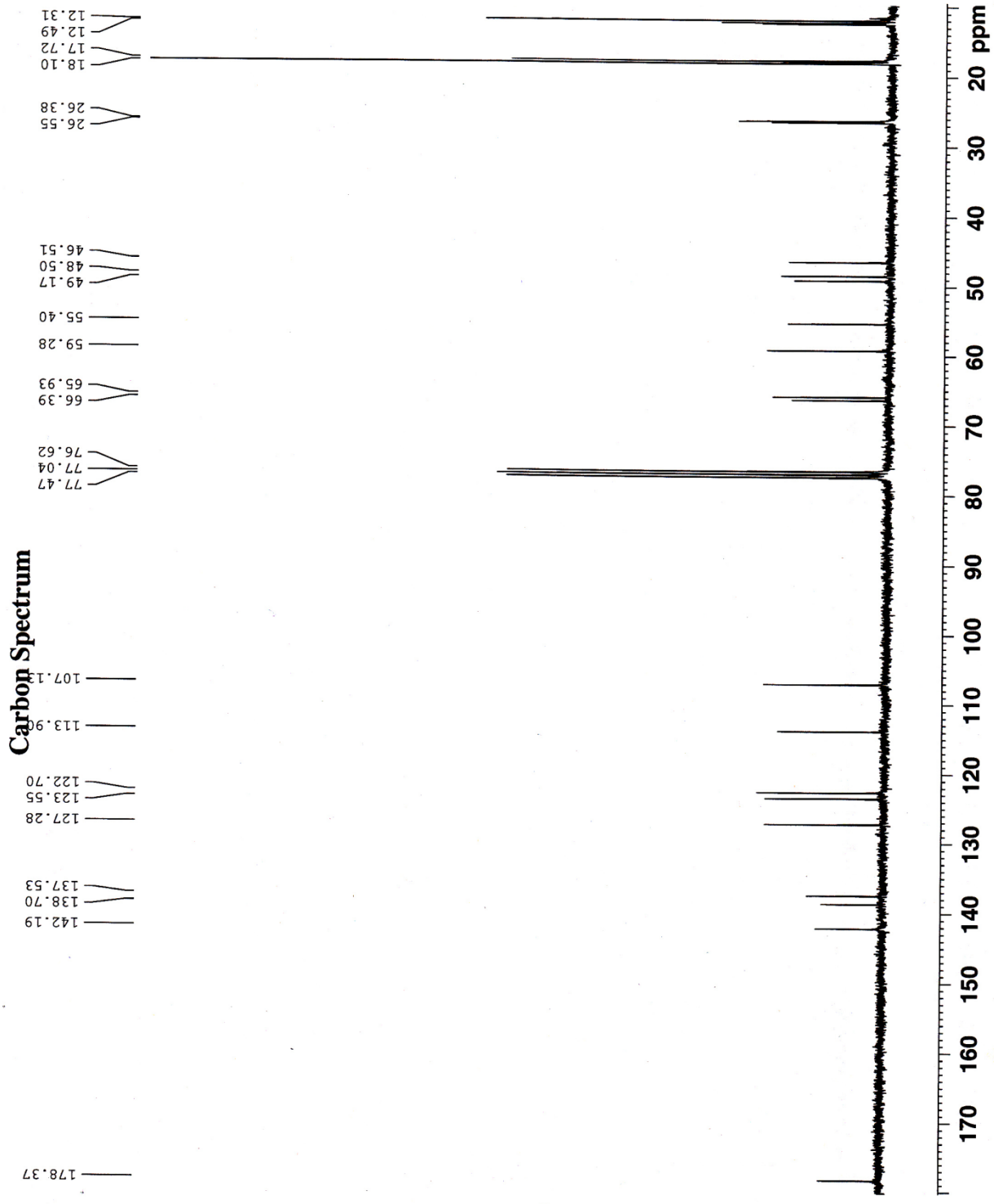
12.10) ^{13}C NMR: alkaloid **878** (solvent: $CDCl_3$)



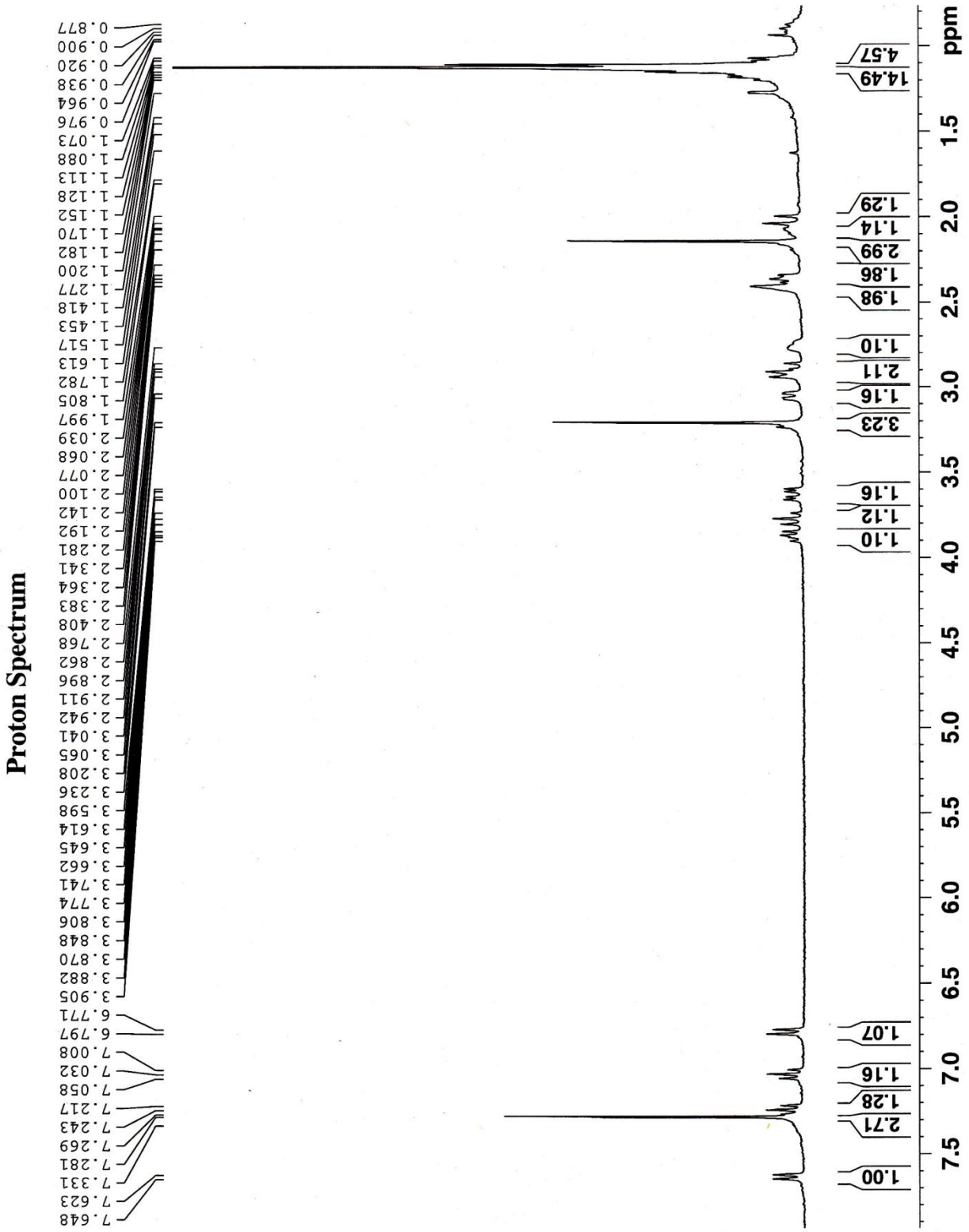
12.11) ^{1}H NMR: alkaloid **882** (solvent: $CDCl_3$)



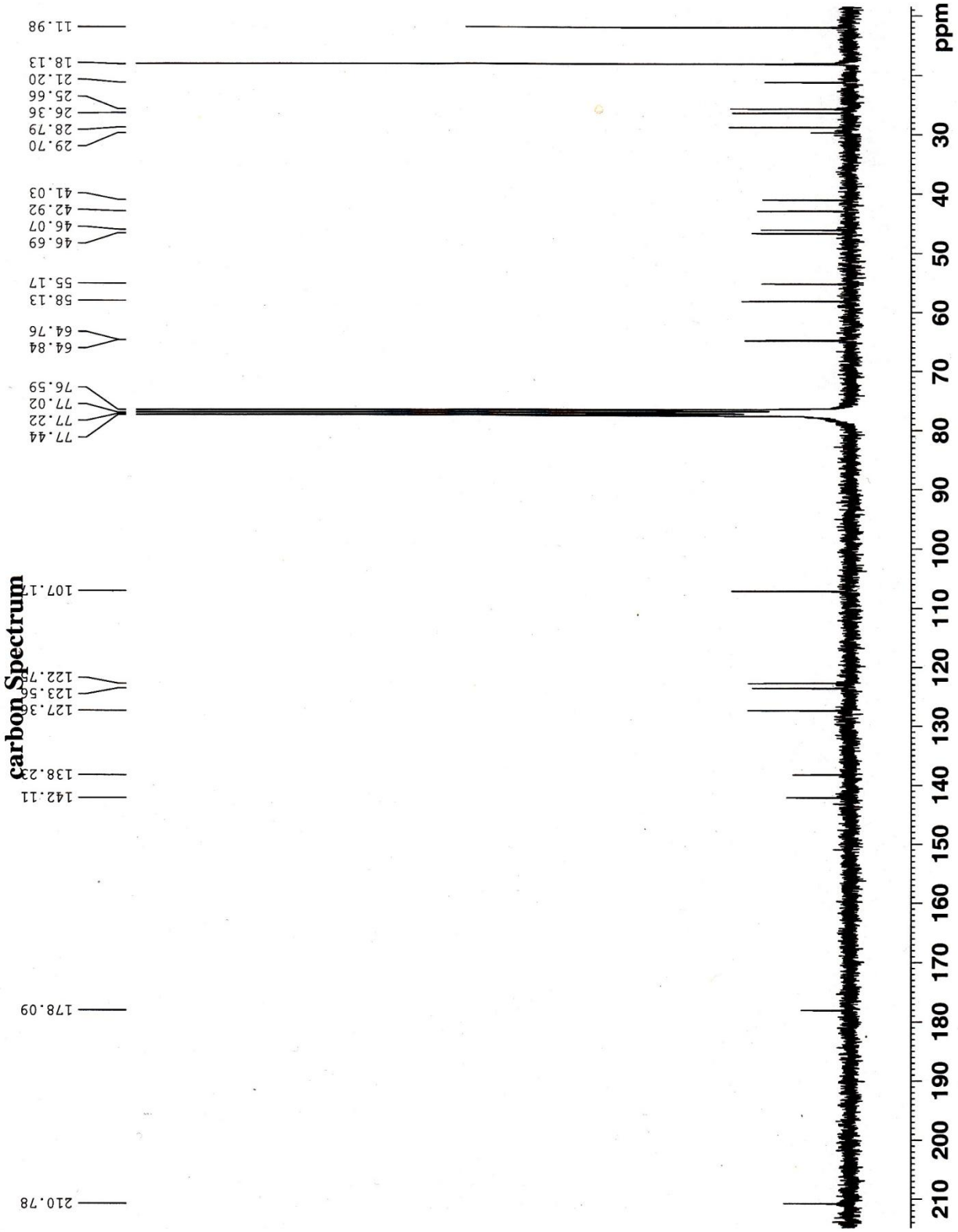
12.11) ^{13}C NMR: alkaloid **882** (solvent: $CDCl_3$)



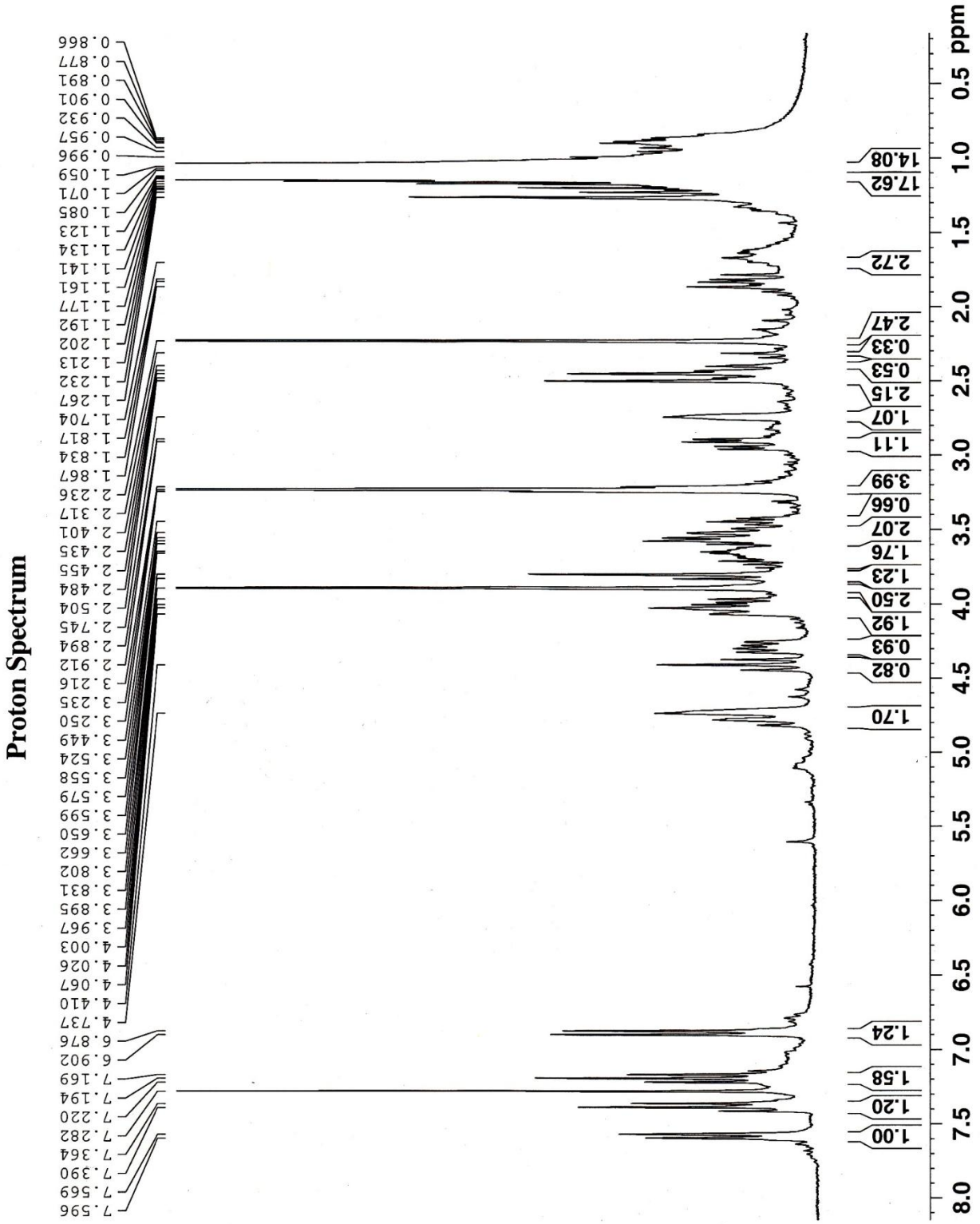
12.12) ^{1}H NMR: alkaloid **884** (solvent: $CDCl_3$)



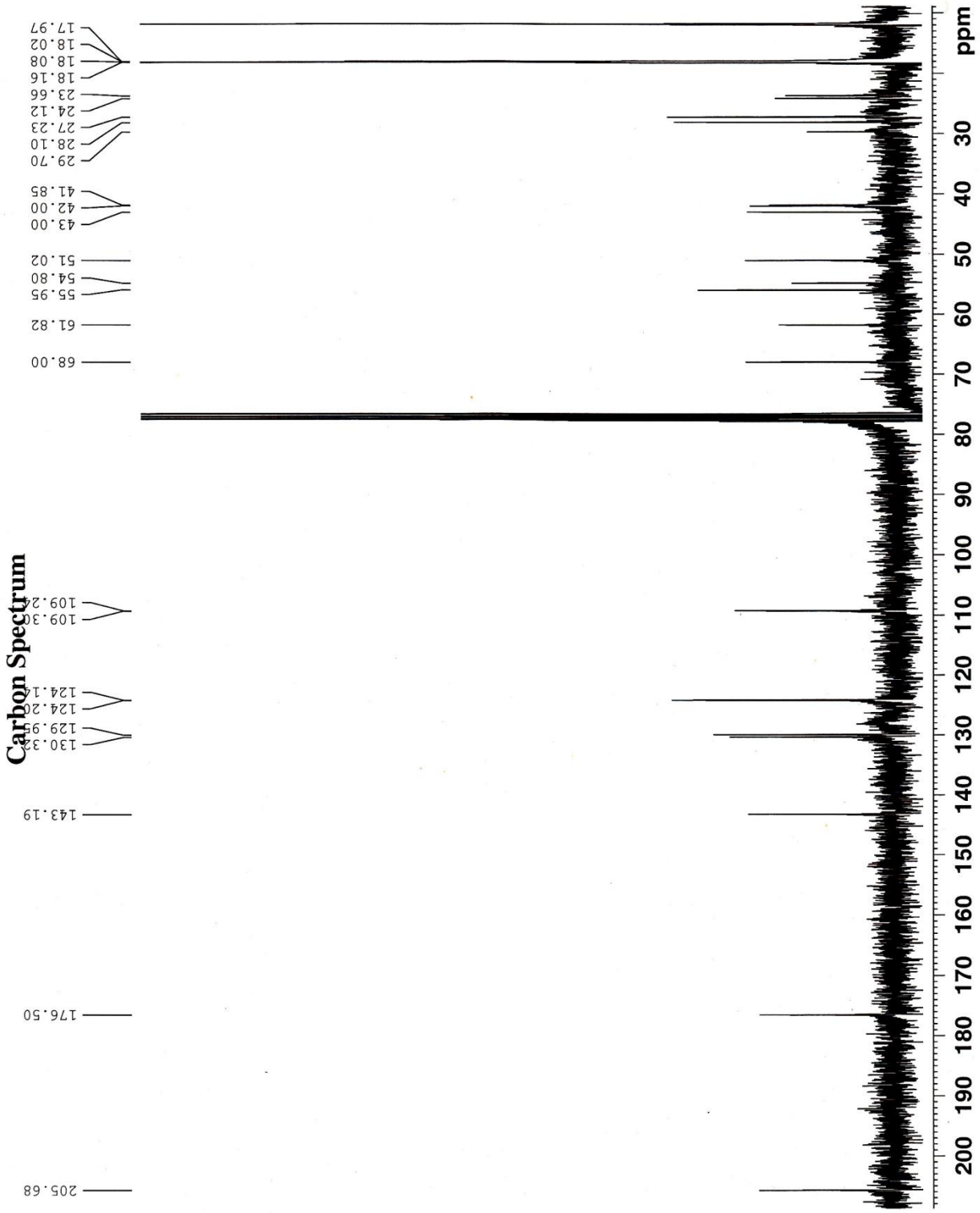
12.12) ^{13}C NMR: alkaloid **884** (solvent: $CDCl_3$)



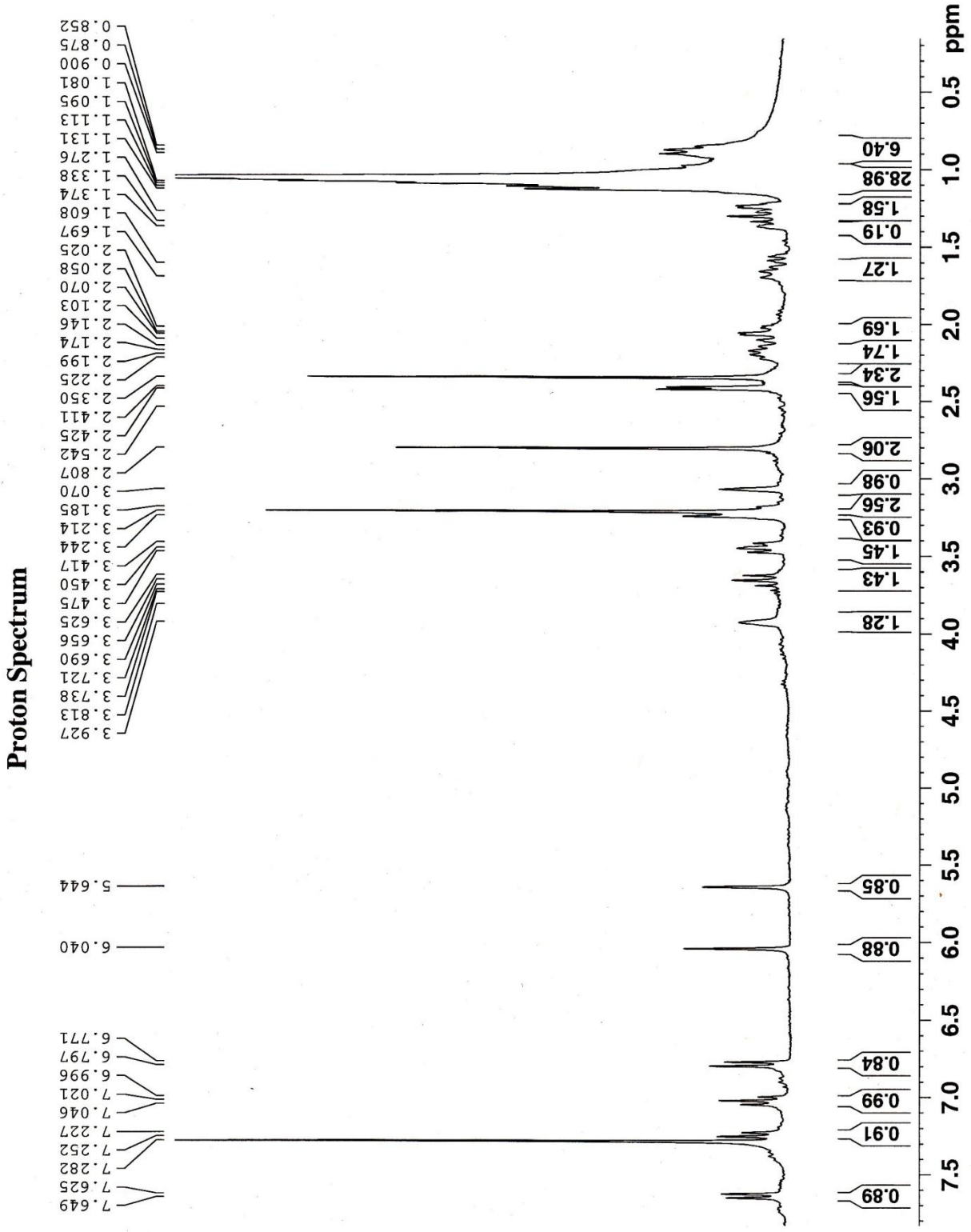
12.13) ^{1}H NMR: alkaloid **885** (**crude**, solvent: $CDCl_3$)



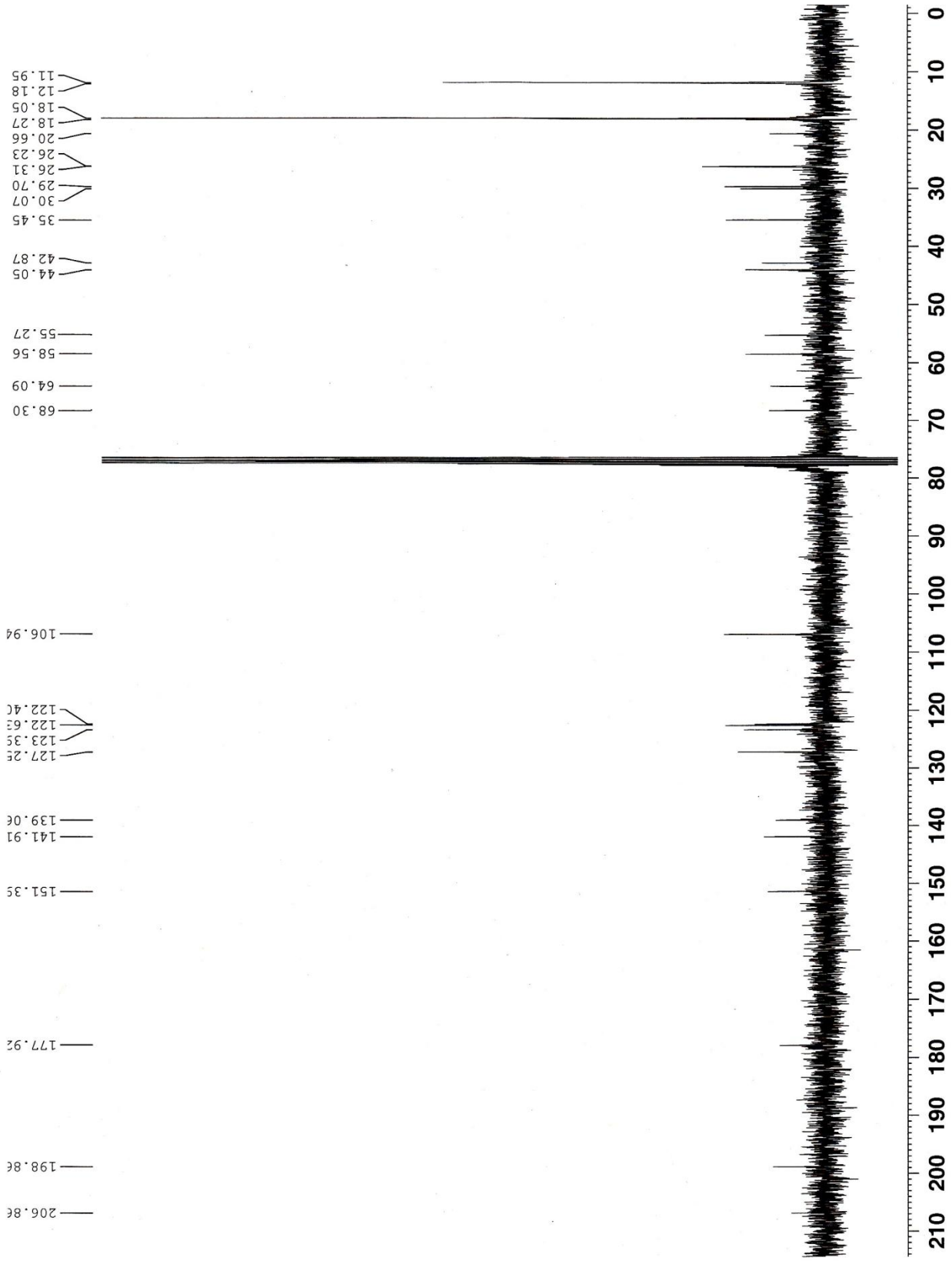
12.13) ^{13}C NMR: alkaloid **885** (**crude**, solvent: $CDCl_3$)



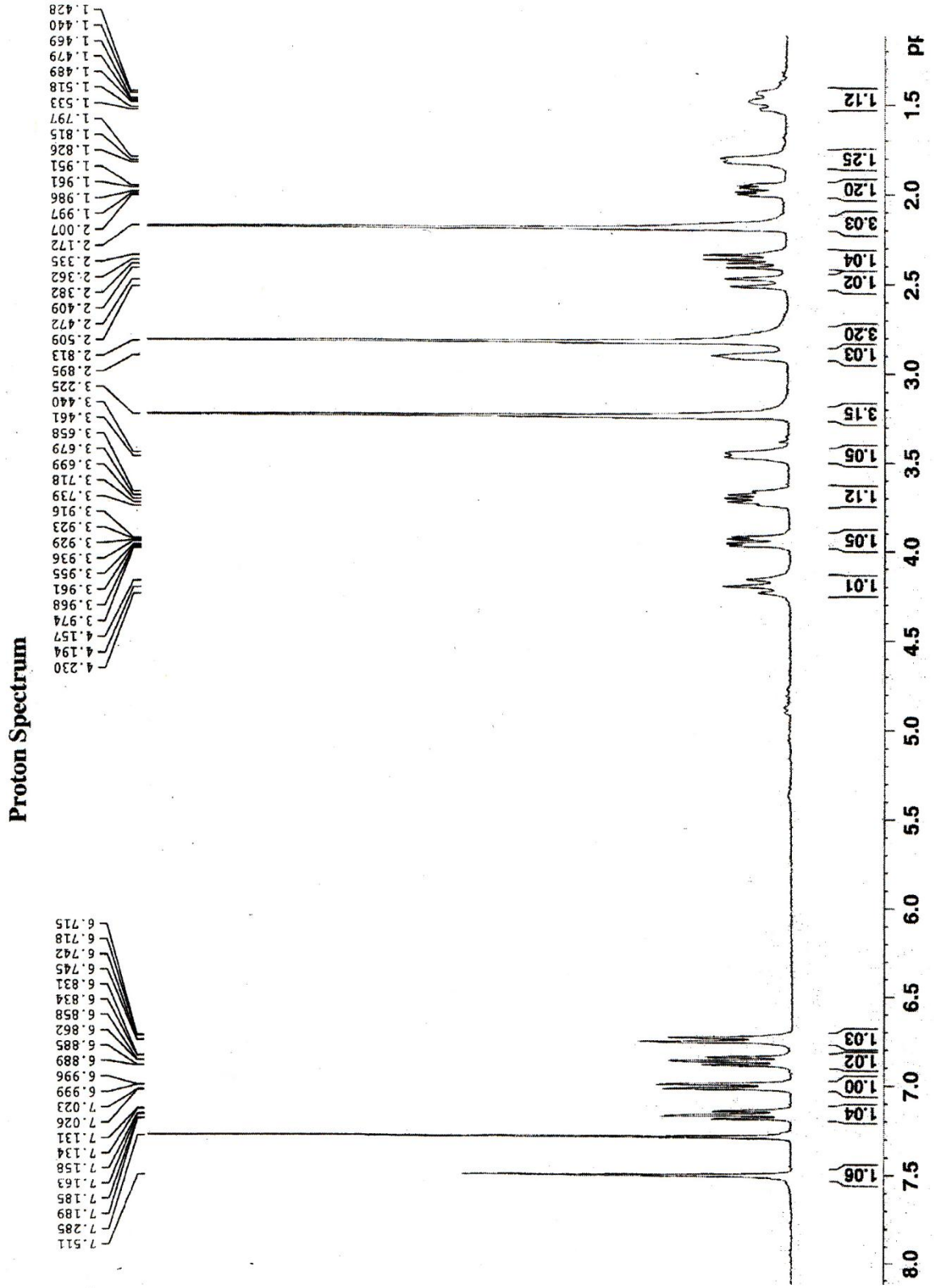
12.14) ^{1}H NMR: alkaloid **886** (solvent: $CDCl_3$)



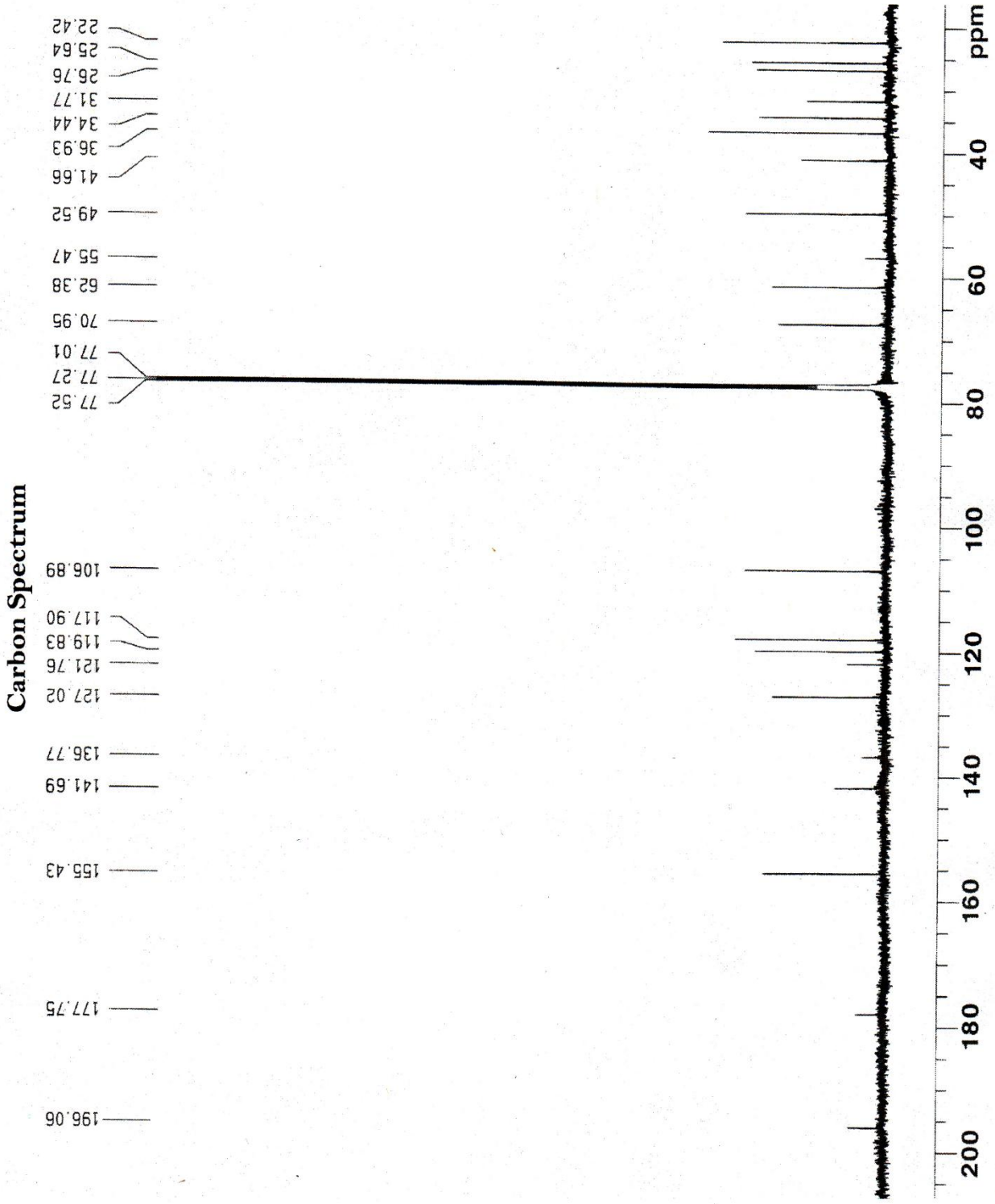
12.14) ^{13}C NMR: alkaloid **886** (solvent: $CDCl_3$)



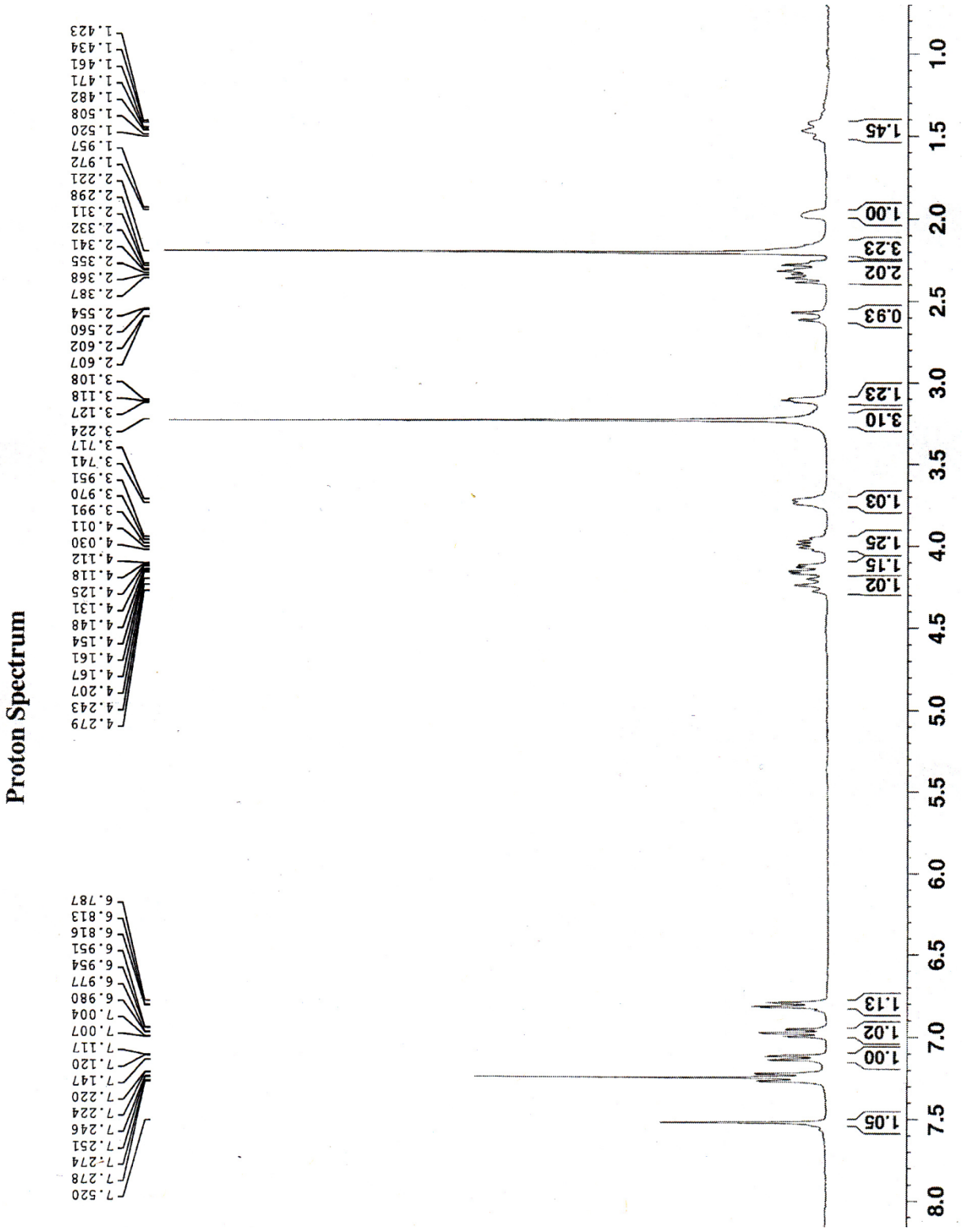
12.15) ^{1}H NMR: alkaloid **887** (solvent: $CDCl_3$)



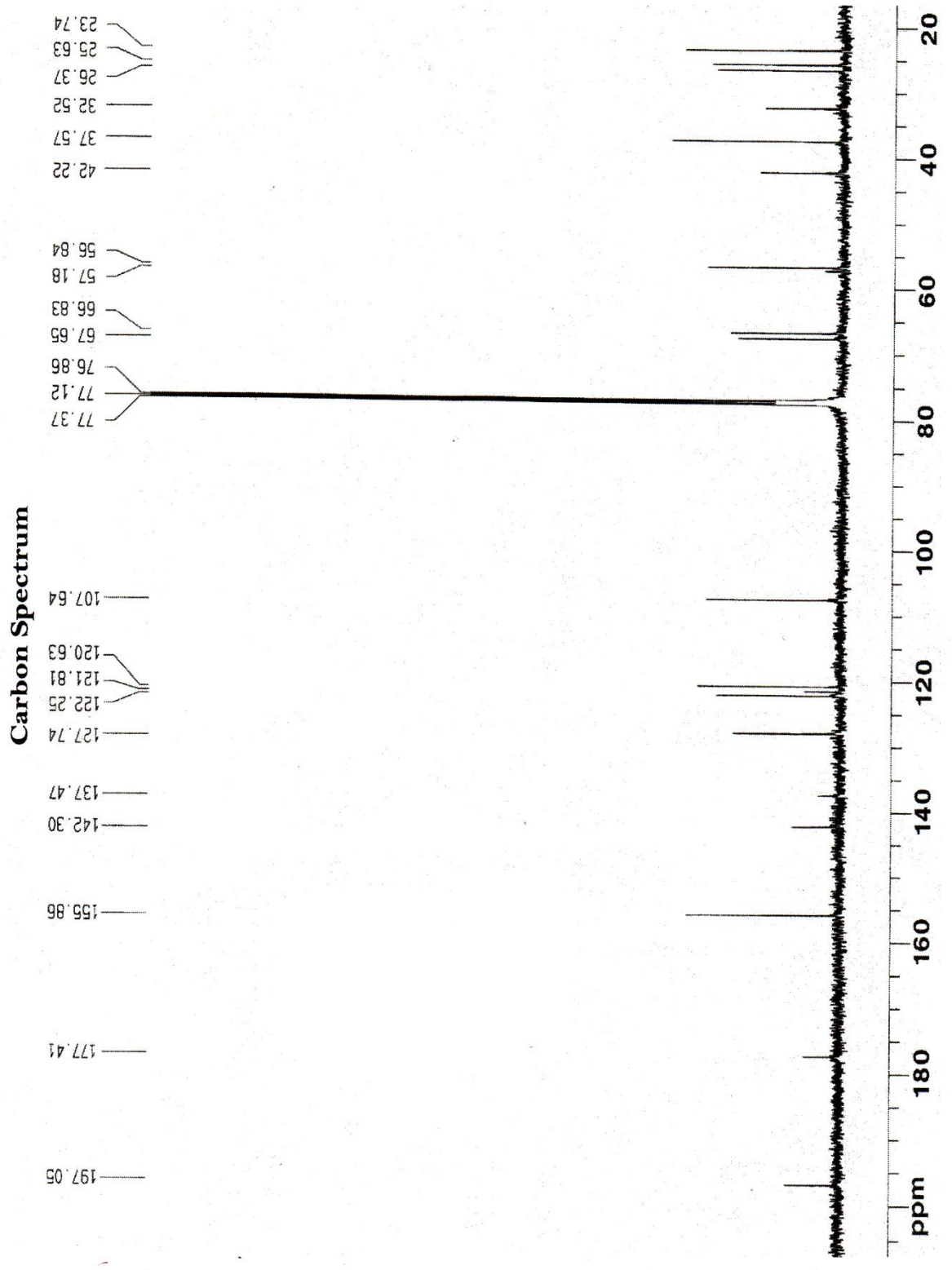
12.15) ^{13}C NMR: alkaloid **887** (solvent: $CDCl_3$)



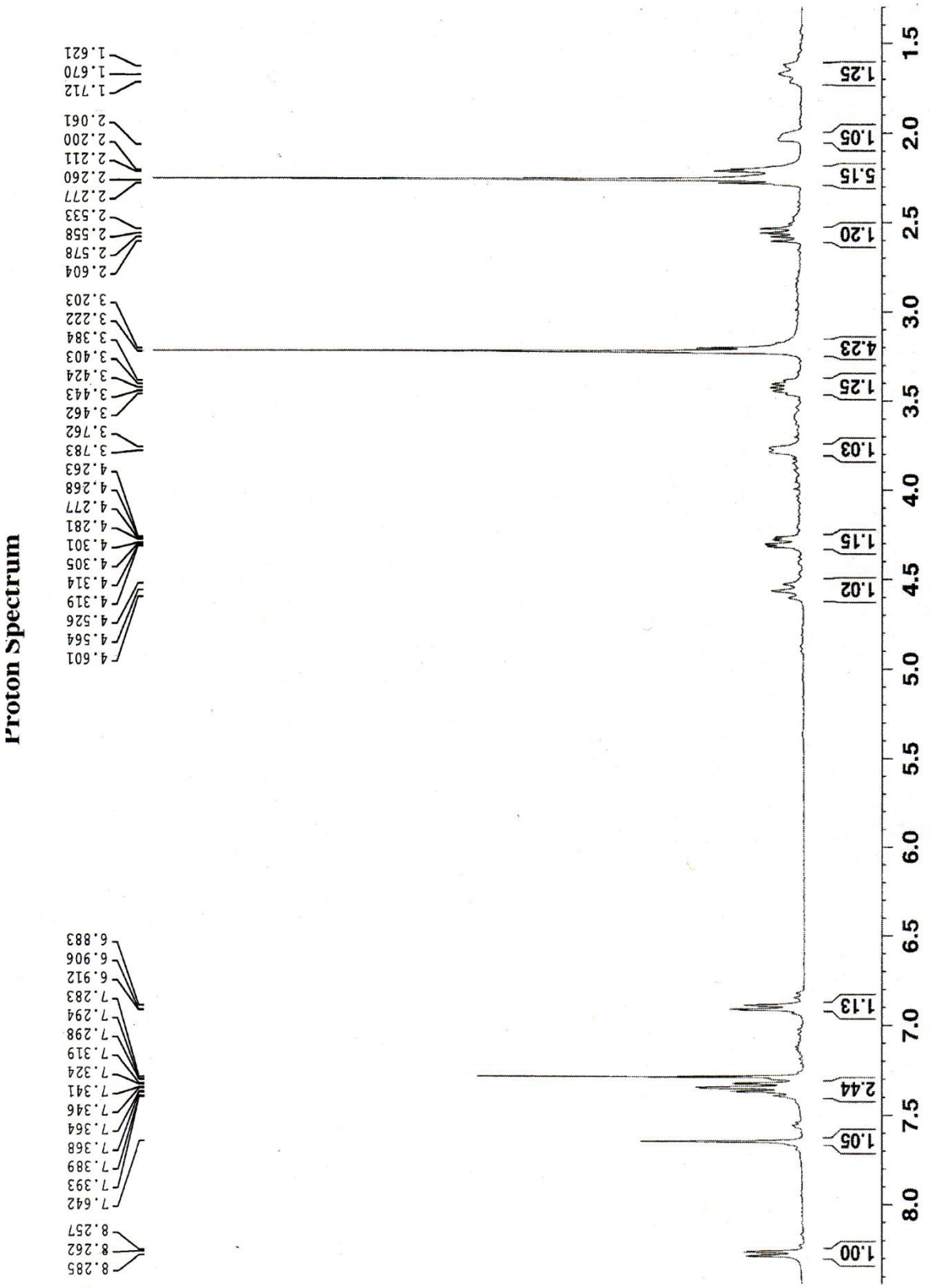
12.16) ^{1}H NMR: isoalstonisine **27** (solvent: $CDCl_3$)



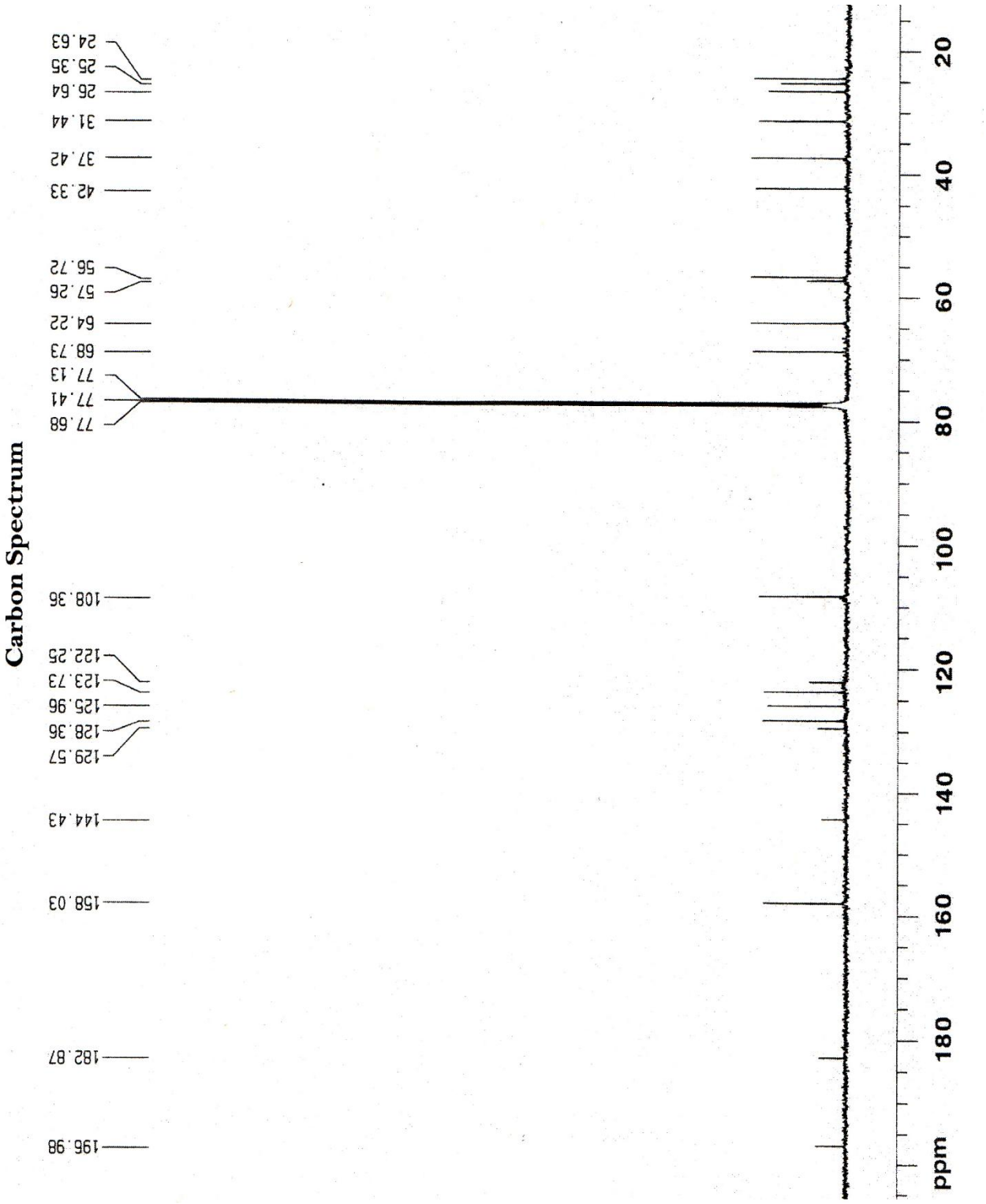
12.16) ^{13}C NMR: isoalstonisine **27** (solvent: $CDCl_3$)



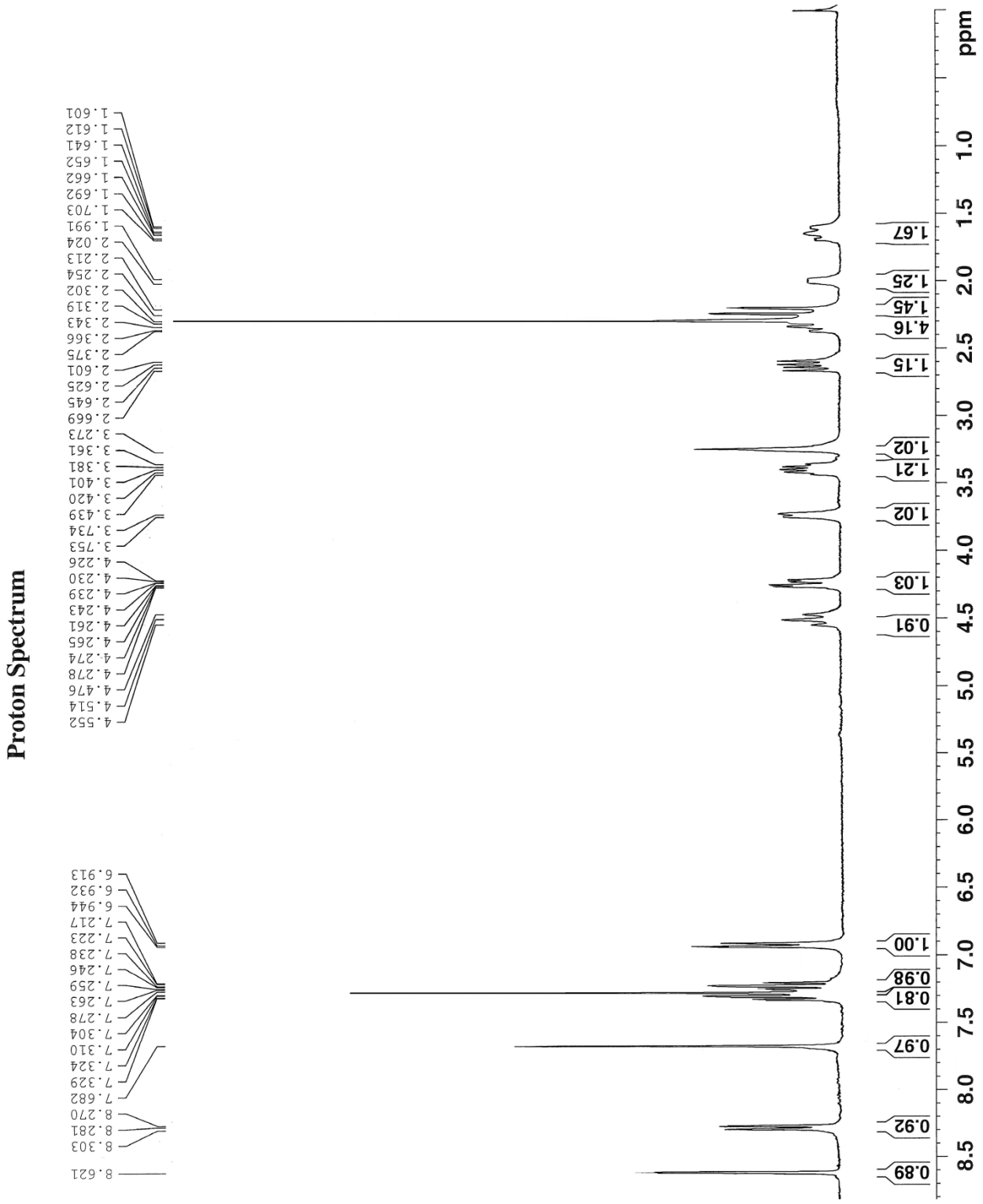
12.17) ^{1}H NMR: alstonisine **8** (solvent: $CDCl_3$)



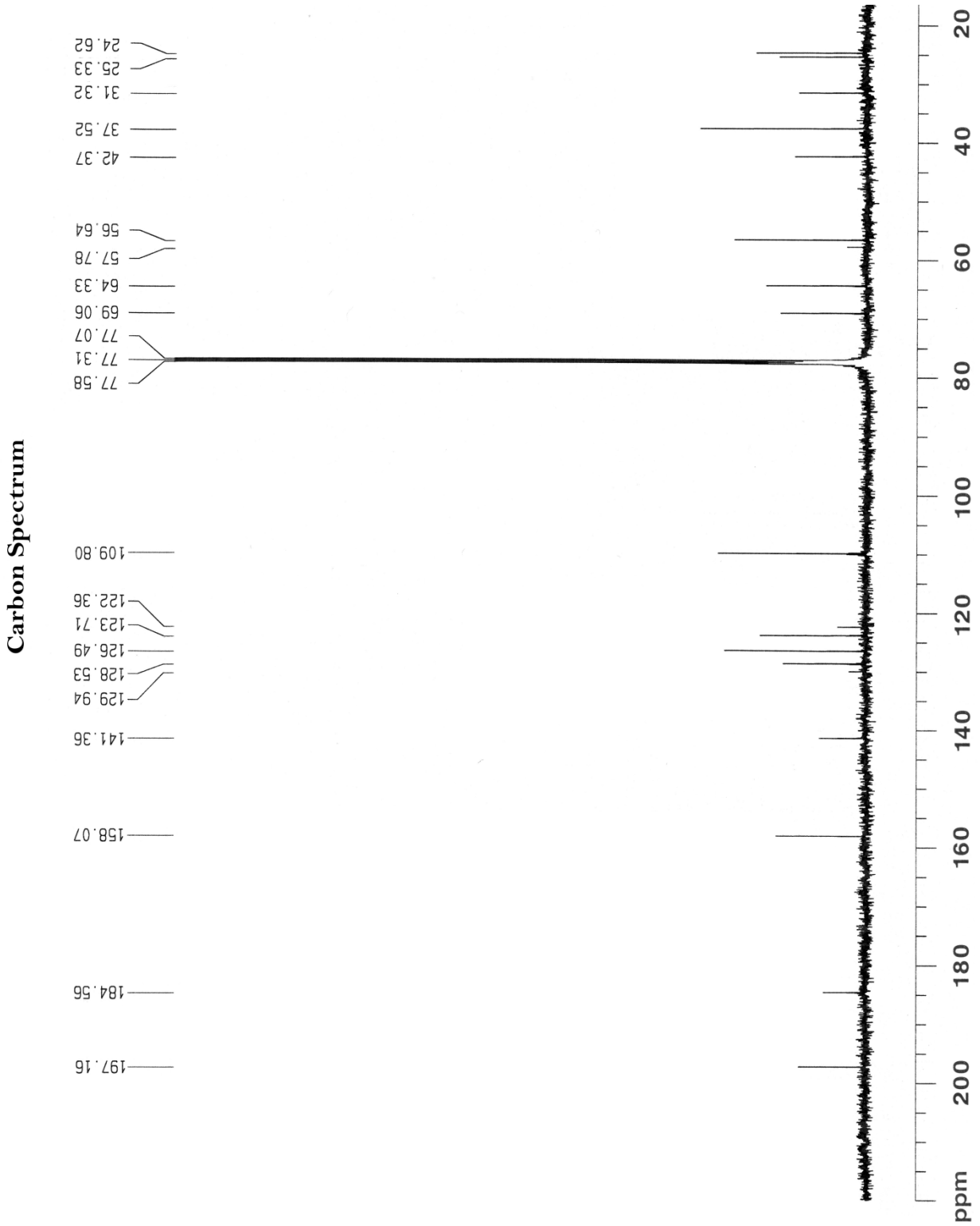
12.17) ^{13}C NMR: alstonisine **8** (solvent: $CDCl_3$)



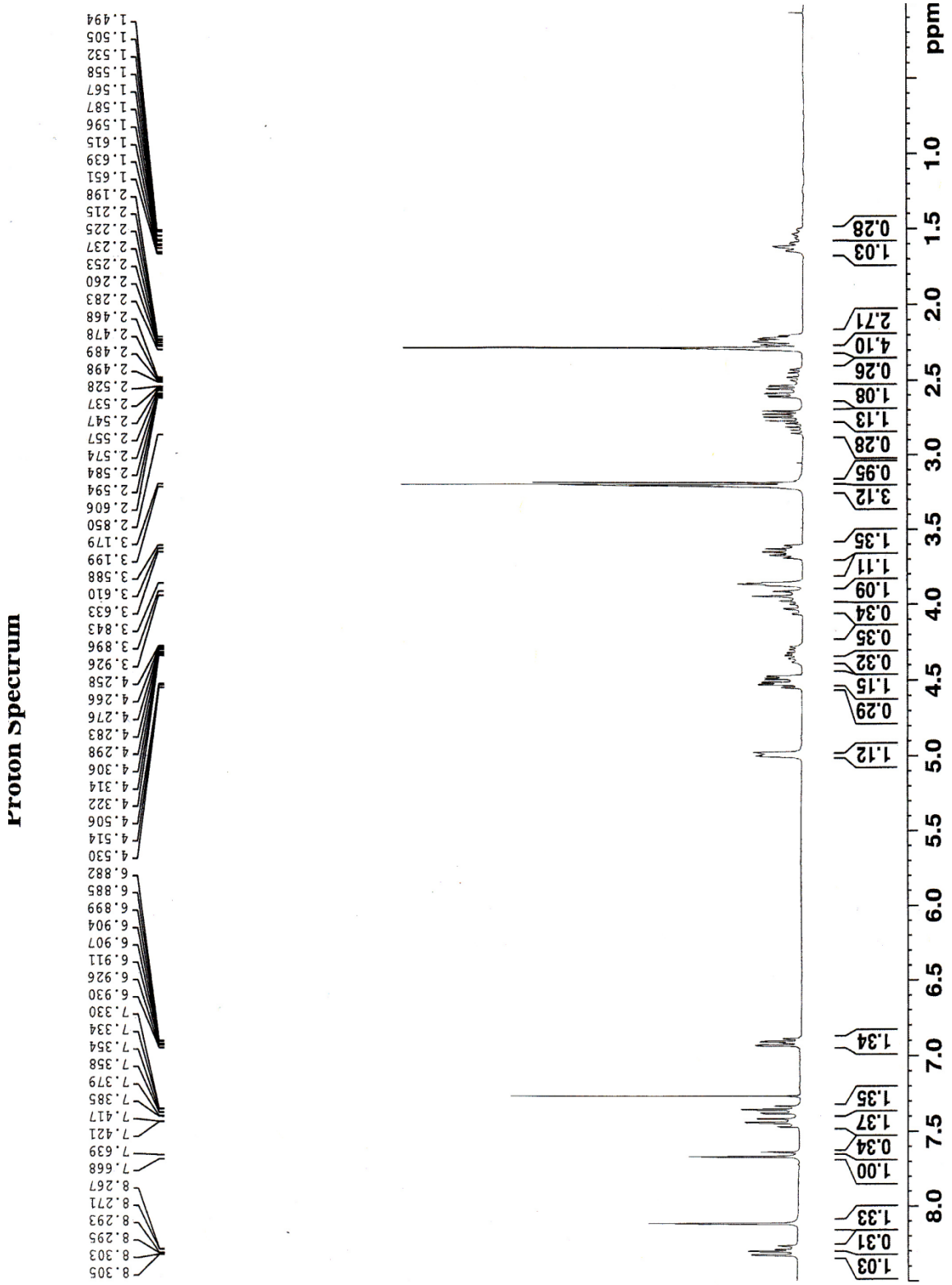
12.18) ^{1}H NMR: N_a-demethylalstonisine **17** (solvent: $CDCl_3$)



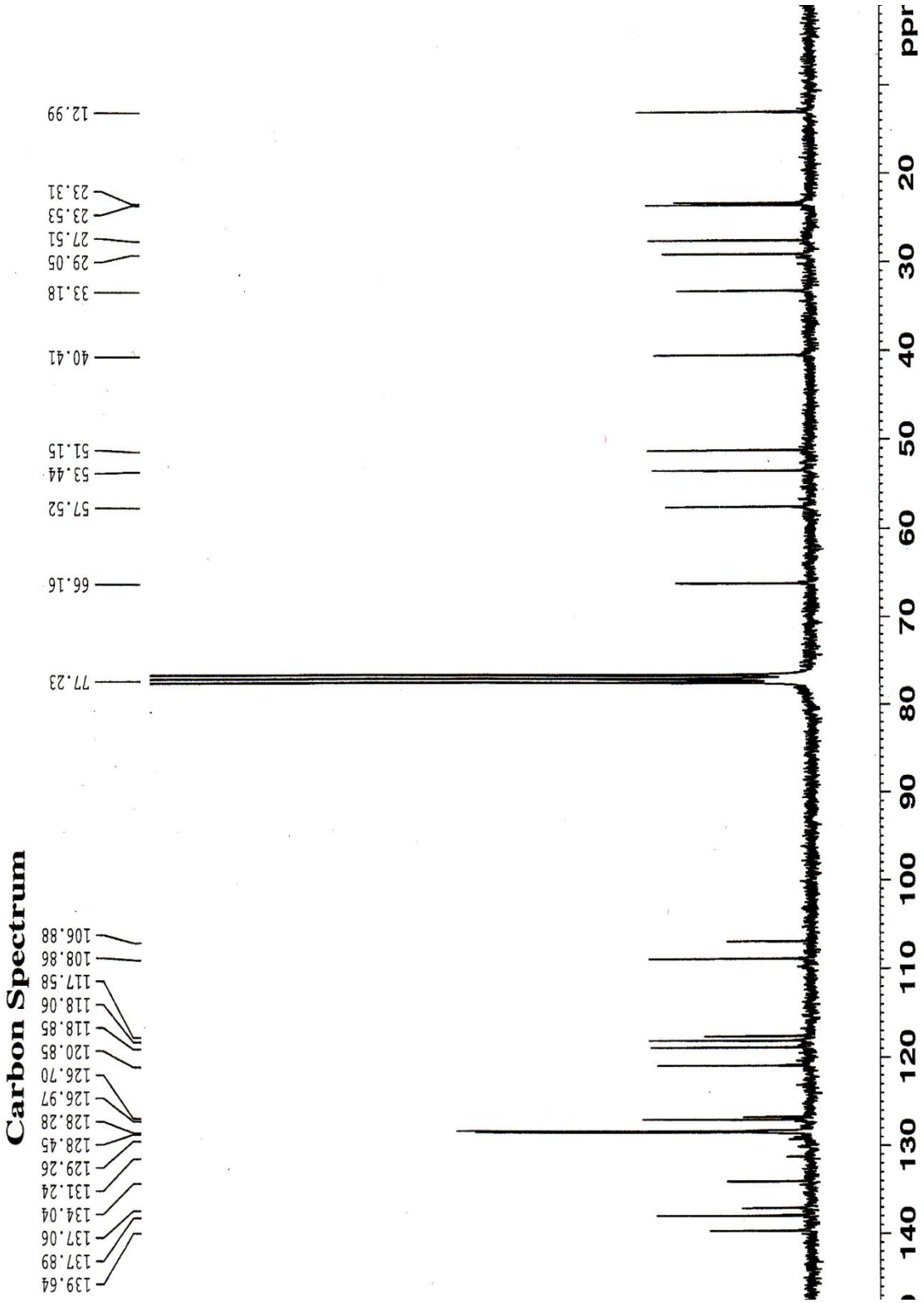
12.18) ^{13}C NMR: N_a-demethylalstonisine **17** (solvent: $CDCl_3$)



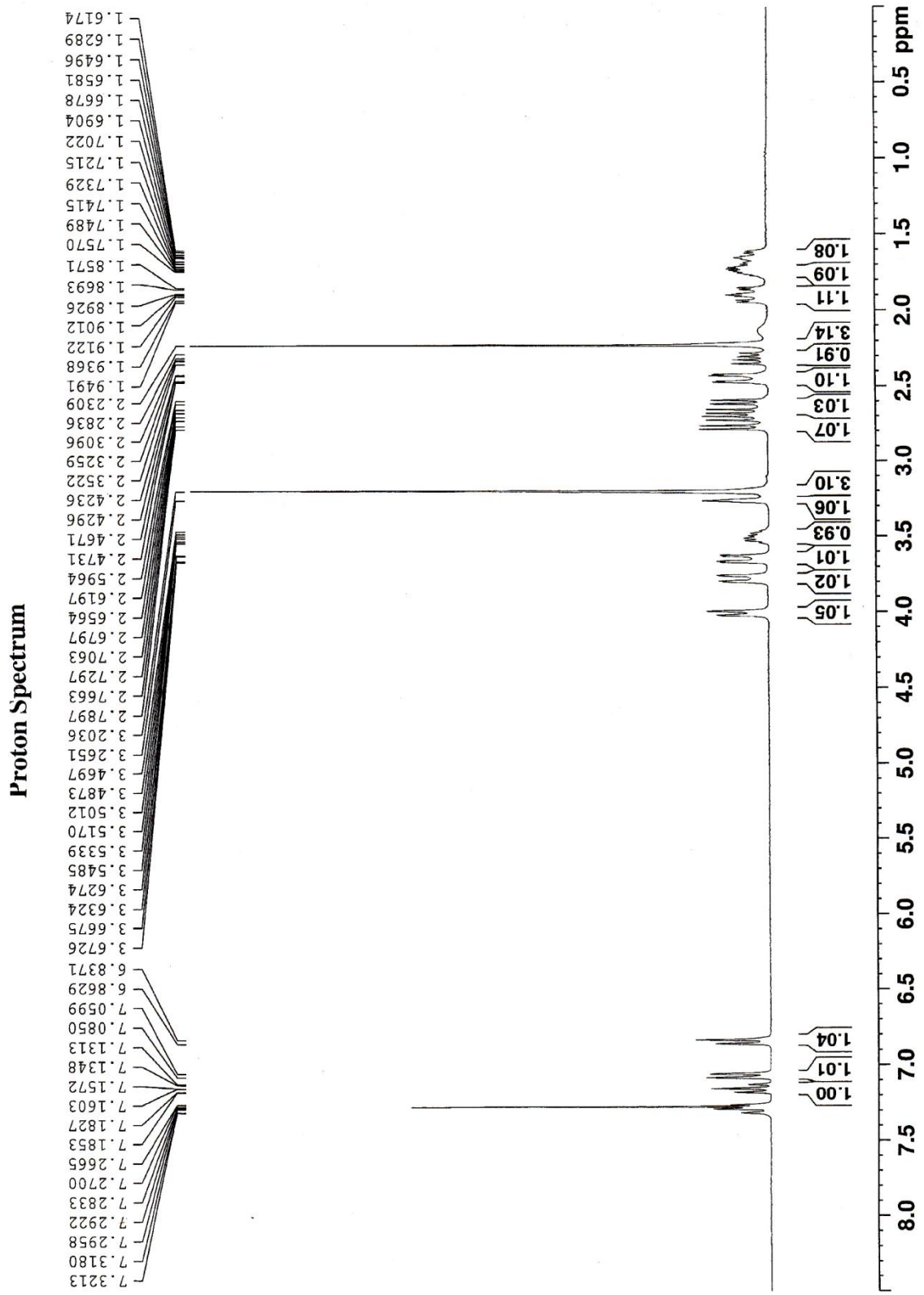
12.19) ^{1}H NMR: alstofoline **18** (solvent: $CDCl_3$)



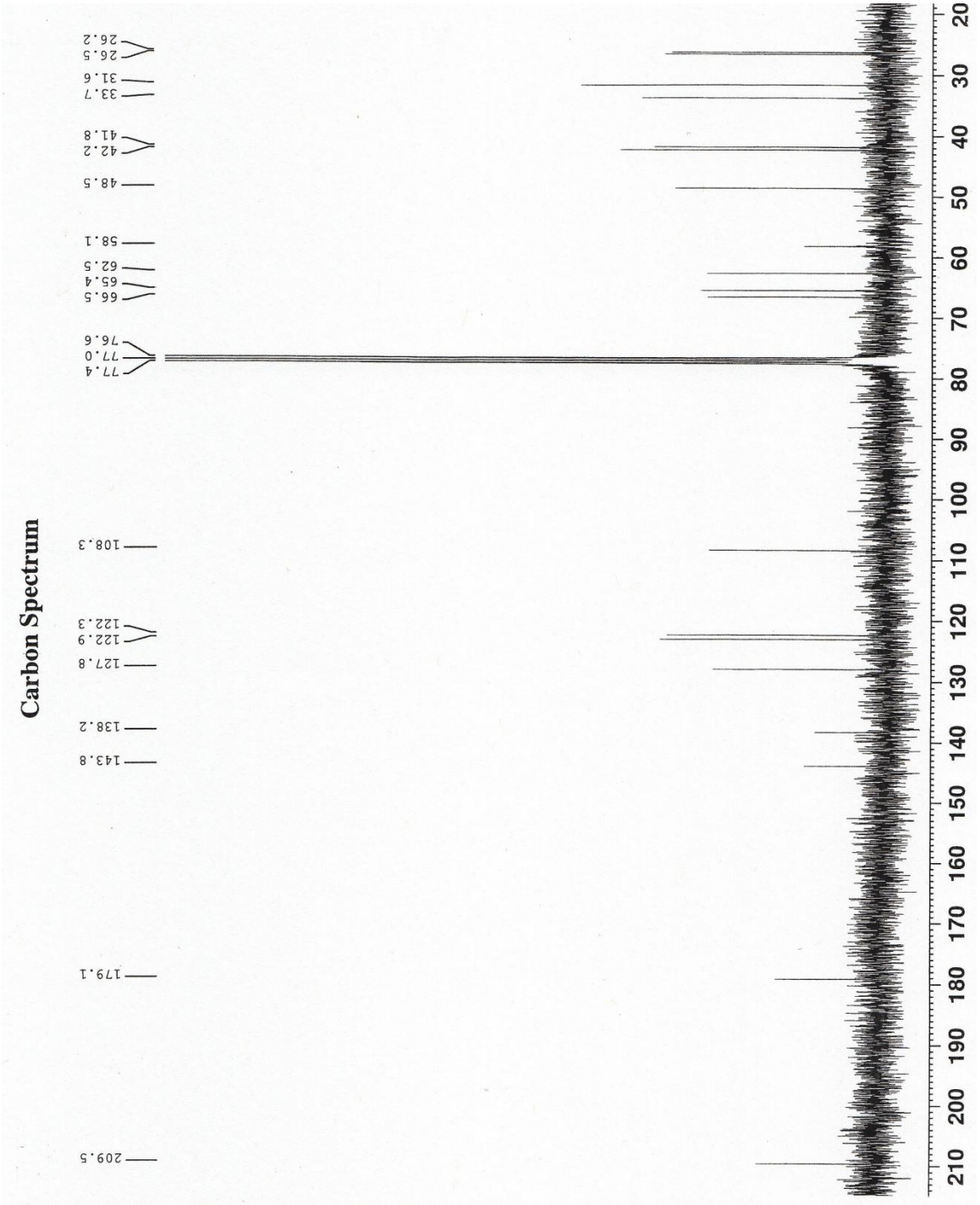
12.19) ^{13}C NMR: alstofoline **18** (solvent: $CDCl_3$)



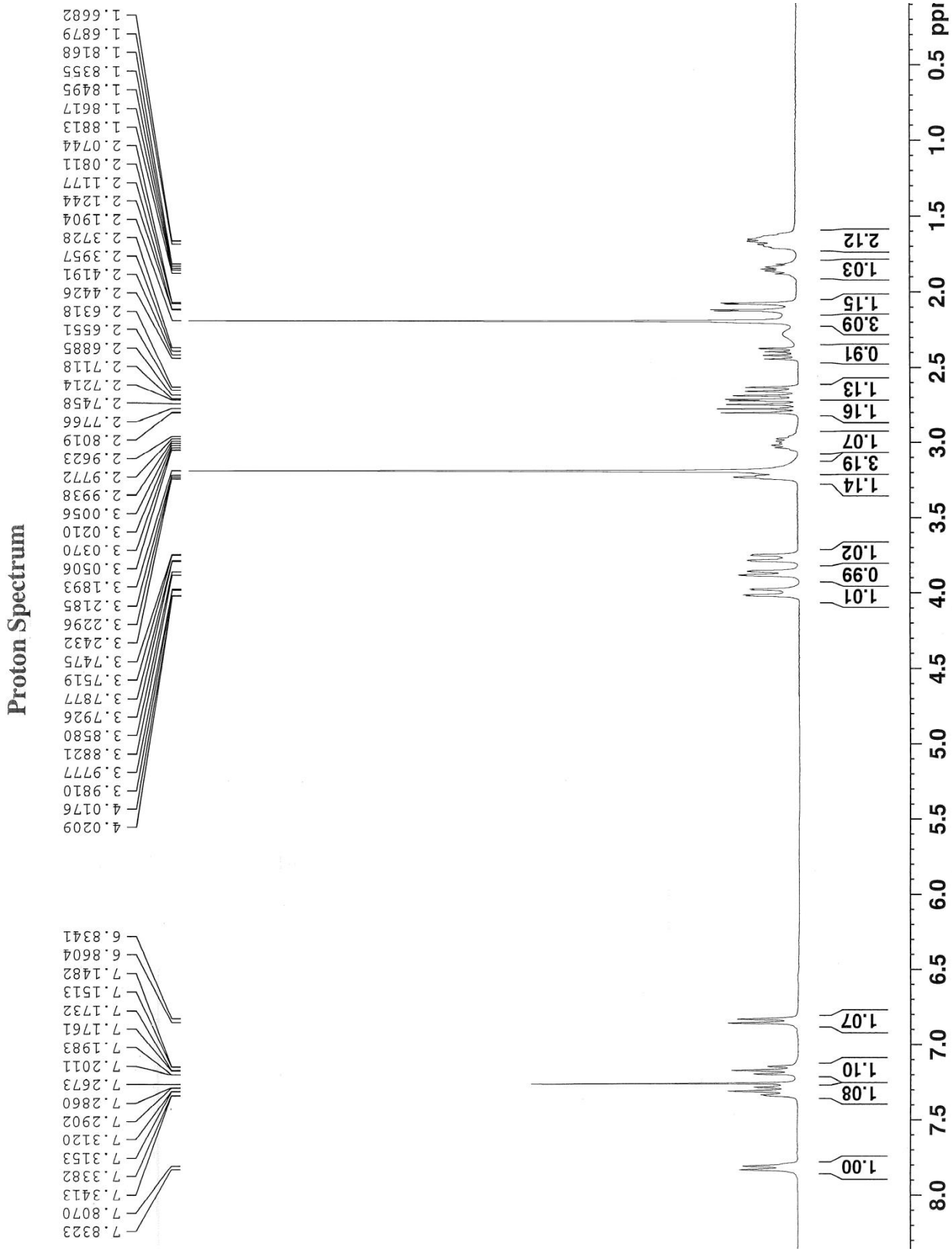
12.20) ^{1}H NMR: alkaloid **890** (solvent: $CDCl_3$)



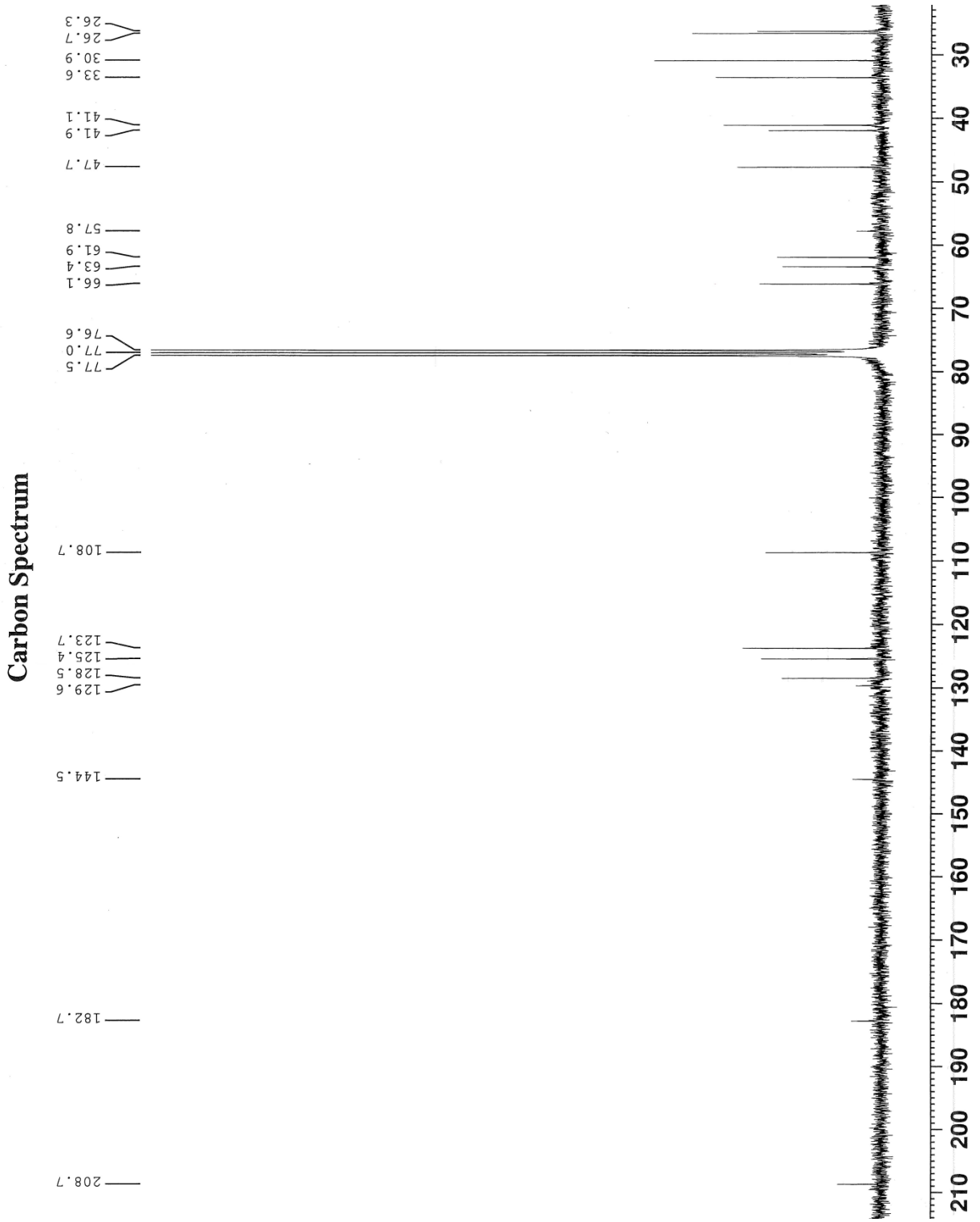
12.20) ^{13}C NMR: alkaloid **890** (solvent: $CDCl_3$)



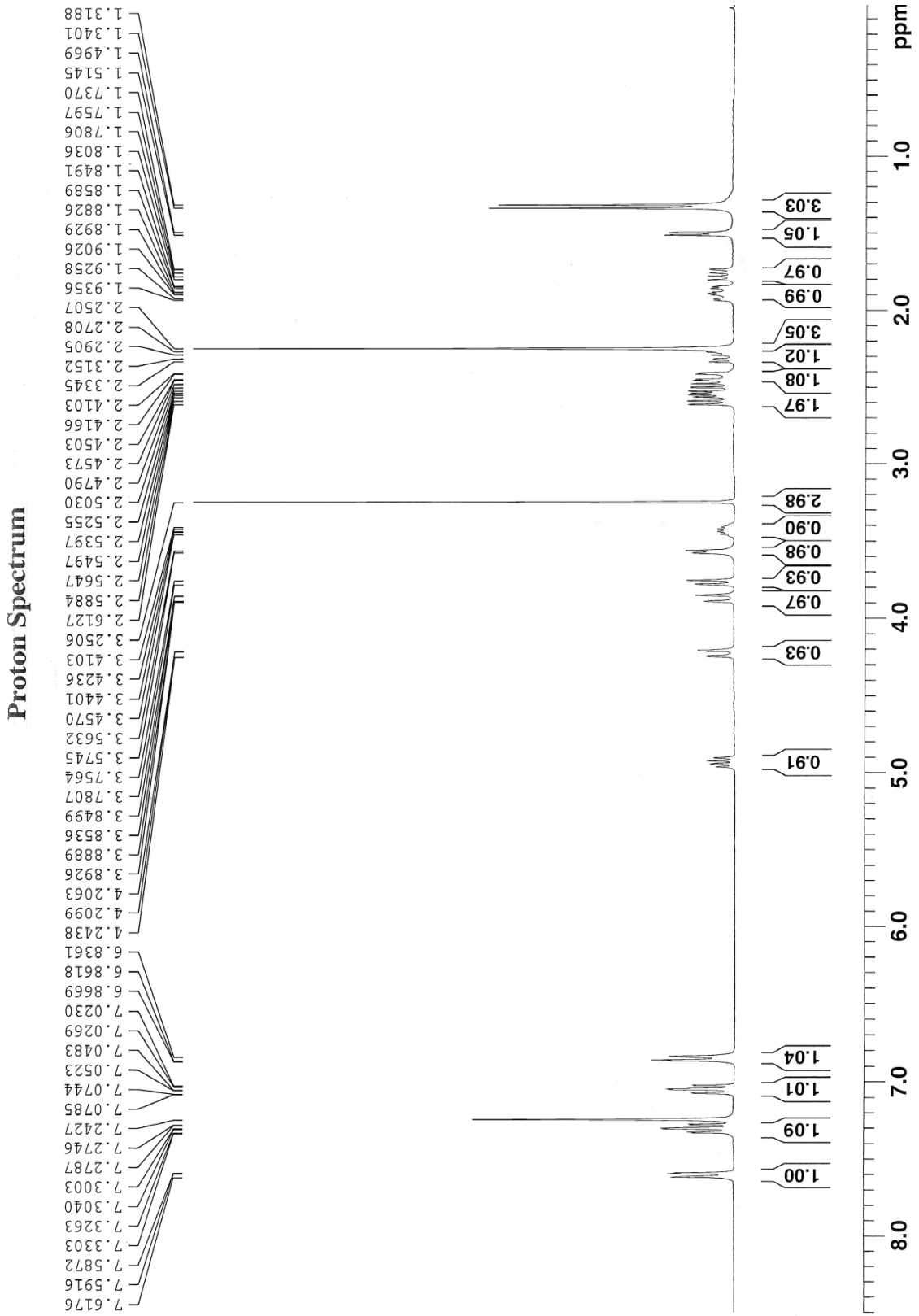
12.21) ^{1}H NMR: alstonoxine A **19** (solvent: $CDCl_3$)



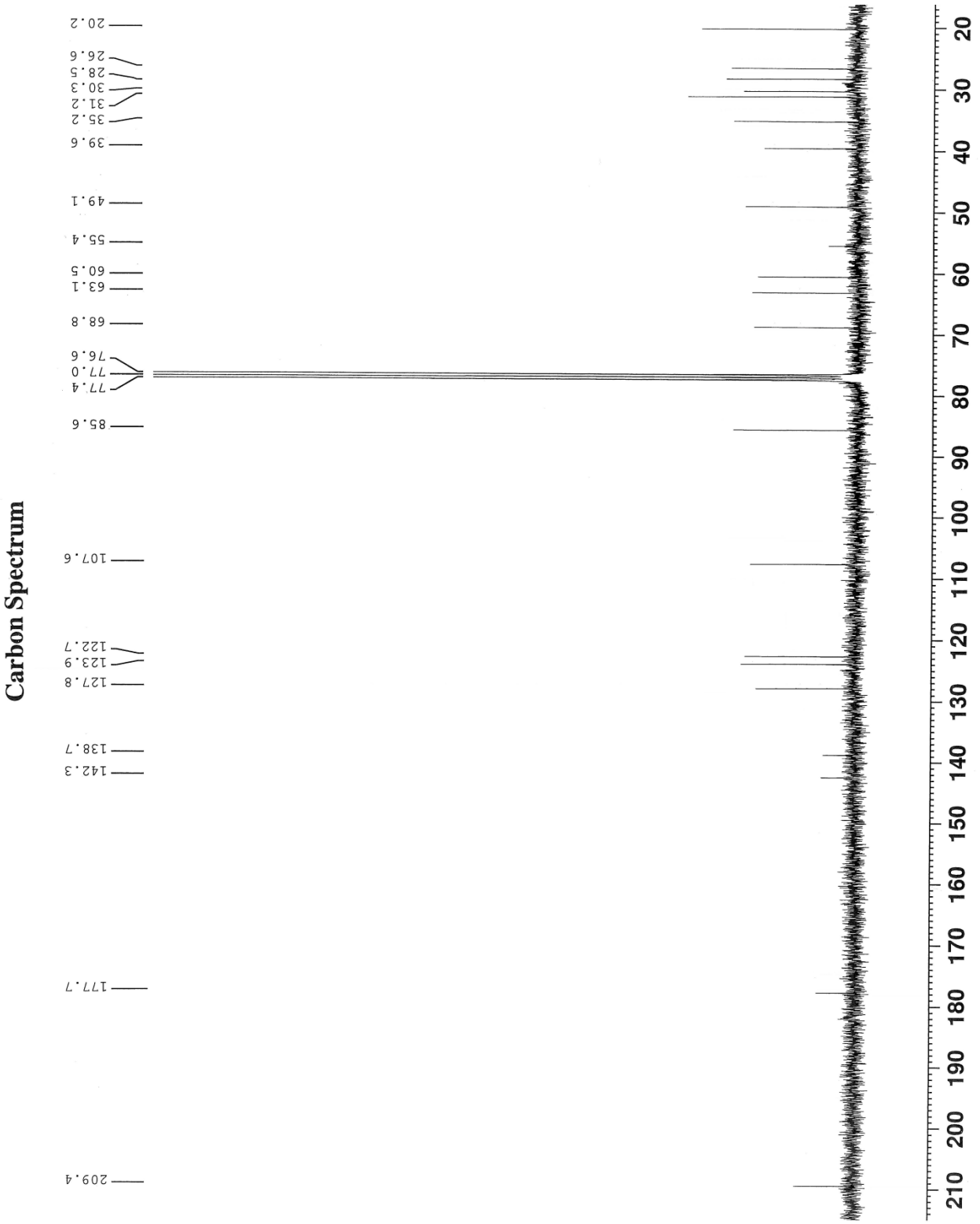
12.21) ^{13}C NMR: alstonoxine A **19** (solvent: $CDCl_3$)



12.22) ^{1}H NMR: macrogentine **31** (solvent: $CDCl_3$)



12.22) ^{13}C NMR: macrogentine **31** (solvent: $CDCl_3$)



13) Appendix B: X-ray crystal structure data and tables of oxindoles 854, 216, 846, 857, and 878.

13.1) X-ray crystal structure: METHODS

X-ray crystal data on oxindole 854, 216, 846, 857

Single-crystal X-ray diffraction data on **854**, **216**, **846**, and **857** were collected at 296, 273, 100, and 100 °K respectively. All data were collected using MoKα radiation (λ = 0.71073 Å) and a Bruker APEX 2 CCD area detector. Samples were prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a MicroMesh mount (MiTeGen, Inc.) and transferred immediately to the diffractometer. Corrections were applied for Lorentz, polarization, and absorption effects. All structures were solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å.

The 0.79 x 0.55 x 0.36 mm^3 crystal of **854** was monoclinic in space group $P2_1/n$ with unit cell dimensions a = 12.7298(8) Å, b = 9.9647(6) Å, c = 14.7212(9) Å, and β = 106.790(2)°. Data were 100% complete to 25.00° θ (approximately 0.75 Å) with an average redundancy of 3.89. The asymmetric unit contains a single molecule.

The 0.46 x 0.17 x 0.09 mm^3 crystal of **216** was orthorhombic in space group $P2_12_12_1$ with unit cell dimensions a = 6.8433(4) Å, b = 8.3450(4) Å, and c = 29.1138(13. Data were 100% complete to 25.00° θ (approximately 0.75 Å) with an average redundancy of 5.59. The asymmetric unit contains a single molecule.

The 0.51 x 0.13 x 0.01 mm^3 crystal of **846** was monoclinic in space group $P2_1$ with unit cell dimensions a = 10.4533(9) Å, b = 6.9333(6) Å, c = 15.6135(12) Å, and β = 106.712(3)°. Data were 98.7% complete to 25.00° θ (approximately 0.75 Å) with an average redundancy of 3.97. The asymmetric unit contains a single molecule along with a co-crystallized solvent (chloroform) molecule.

The 0.41 x 0.38 x 0.19 mm^3 crystal of **857** was triclinic in space group P-1 with unit cell dimensions a = 9.6047(6) Å, b = 12.5723(9) Å, c = 14.8500(13) Å, α = 104.090(4)°, β = 103.346(4)°, and γ = 109.298(3)°. Data were 98.6% complete to 25.00° θ (approximately 0.75 Å) with an average redundancy of 1.76. The asymmetric unit contains two molecules.

Full information on data collection, refinement, and results of the x-ray studies are given in Tables A1 to A25.

Atomic coordinates for **854**, **216**, **846**, and **857** have been deposited with the Cambridge Crystallographic Data Centre). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

X-ray crystal data on oxindole 878

Single-crystal X-ray diffraction data on compound **878** was collected using CuKα radiation and a Bruker Platinum-135 CCD area detector. Crystals were prepared for data collection by coating with high viscosity microscope oil. The oil-coated crystal was mounted on a micro-mesh mount (Mitergen, Inc.) and transferred to the diffractometer and data collected at 150°K. The 0.102 x 0.065 x 0.011 mm^3 crystal was monoclinic in space group P 2_1, with unit cell dimensions a = 11.7475(3), b = 6.0992(1), c = 11.9622(3) Å, and β = 97.397(2)°. Data was 86.8% complete to 68.10° θ (~ 0.83 Å) with an average redundancy of 2.58. The final anisotropic full matrix least-squares refinement on F^2 with 219 variables converged at R1 = 3.40%, for the observed data and wR2 = 9.18% for all data. The structure was solved by direct methods and refined by full-matrix least squares on F2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI).[18] Corrections were applied for Lorentz, polarization, and absorption effects. Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å. Complete information on data collection and refinement is available in the supplemental material, Tables A26-A31.

Absolute configuration was determined using the method of Hooft et al. (Hooft, R.W.W., Straver, L.H., Spek, A.L.J., *Appl. Crystallogr.*, **41**, 96−103 (2008)) as implemented in PLATON(Spek, A.L., PLATON (v 1.15), Utrecht University, Utrecht, The Netherlands (2011)). Based on the analysis of 1077 Bijovet pairs (approximately 90% coverage for

this dataset) the Hooft y parameter was 0.02(14) indicated that the probability that the configuration was wrong was 0.4×10^{-10}. The absolute configuration at C9 is R.

13.2) X-RAY CRYTAL STRUCTURE: TABLES

Table A1. Crystal data and structure refinement for **854**.

Empirical formula	$C_{19}H_{21}IN_2O_2$	
Formula weight	436.28	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/n	
Unit cell dimensions	a = 12.7298(8) Å	α= 90°
	b = 9.9647(6) Å	β= 106.790(2)°
	c = 14.7212(9) Å	γ = 90°
Volume	1787.76(19) $Å^3$	
Z	4	
Density (calculated)	1.621 Mg/m^3	
Absorption coefficient	1.805 mm^{-1}	
F(000)	872	
Crystal size	0.792 x 0.554 x 0.361 mm^3	
Theta range for data collection	1.87 to 29.21°	
Index ranges	-17<=h<=17, -13<=k<=13, -20<=l<=20	
Reflections collected	19436	
Independent reflections	4815 [R(int) = 0.0199]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5619 and 0.3290	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4815 / 0 / 219	
Goodness-of-fit on F^2	1.021	
Final R indices [I>2sigma(I)]	R1 = 0.0288, wR2 = 0.0643	
R indices (all data)	R1 = 0.0311, wR2 = 0.0655	
Largest diff. peak and hole	3.019 and -1.697 $e.Å^{-3}$	

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **854**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	2387(2)	1639(2)	490(1)	24(1)
C(1)	2776(2)	542(3)	25(2)	33(1)
O(2)	1399(2)	410(2)	1277(1)	32(1)
C(2)	1708(2)	1486(2)	1056(2)	24(1)
C(3)	200(2)	3266(2)	1009(2)	20(1)
N(4)	194(1)	4383(2)	1664(1)	18(1)
C(5)	713(2)	3796(2)	2607(2)	21(1)
C(6)	1713(2)	3059(2)	2456(2)	22(1)
C(7)	1438(2)	2889(2)	1361(2)	19(1)
C(8)	2122(2)	3784(2)	930(1)	19(1)
C(9)	2293(2)	5153(2)	988(2)	21(1)
C(10)	3009(2)	5716(2)	528(2)	25(1)
C(11)	3529(2)	4910(3)	21(2)	27(1)
C(12)	3359(2)	3527(3)	-50(2)	27(1)
C(13)	2659(2)	2992(2)	420(2)	22(1)
C(14)	-597(2)	2145(2)	1085(2)	25(1)
C(15)	-465(2)	1711(3)	2124(2)	32(1)
O(16)	-341(2)	2894(2)	3572(2)	43(1)
C(16)	-70(2)	2805(3)	2846(2)	29(1)
C(17)	-1203(3)	7420(3)	3549(2)	45(1)
C(18)	-1227(2)	6284(3)	2887(2)	32(1)
I(19)	89(1)	7825(1)	1810(1)	27(1)
C(19)	-790(2)	6219(2)	2171(2)	23(1)
C(20)	-879(2)	5002(2)	1555(2)	20(1)

Table A3. Bond lengths [Å] and angles [°] for **854**.

N(1)-C(2)	1.371(3)	N(1)-C(13)	1.403(3)
N(1)-C(1)	1.451(3)	C(1)-H(1A)	0.9600
C(1)-H(1B)	0.9600	C(1)-H(1C)	0.9600
O(2)-C(2)	1.219(3)	C(2)-C(7)	1.537(3)
C(3)-N(4)	1.475(3)	C(3)-C(14)	1.534(3)
C(3)-C(7)	1.556(3)	C(3)-H(3A)	0.9800
N(4)-C(20)	1.464(3)	N(4)-C(5)	1.475(3)
C(5)-C(16)	1.516(3)	C(5)-C(6)	1.539(3)
C(5)-H(5A)	0.9800	C(6)-C(7)	1.557(3)
C(6)-H(6A)	0.9700	C(6)-H(6B)	0.9700
C(7)-C(8)	1.507(3)	C(8)-C(9)	1.380(3)
C(8)-C(13)	1.397(3)	C(9)-C(10)	1.400(3)
C(9)-H(9A)	0.9300	C(10)-C(11)	1.388(3)
C(10)-H(10A)	0.9300	C(11)-C(12)	1.394(4)
C(11)-H(11A)	0.9300	C(12)-C(13)	1.384(3)
C(12)-H(12A)	0.9300	C(14)-C(15)	1.551(4)
C(14)-H(14A)	0.9700	C(14)-H(14B)	0.9700
C(15)-C(16)	1.504(4)	C(15)-H(15A)	0.9700
C(15)-H(15B)	0.9700	O(16)-C(16)	1.218(3)
C(17)-C(18)	1.488(4)	C(17)-H(17A)	0.9600
C(17)-H(17B)	0.9600	C(17)-H(17C)	0.9600
C(18)-C(19)	1.328(3)	C(18)-H(18A)	0.9300
I(19)-C(19)	2.107(2)	C(19)-C(20)	1.499(3)
C(20)-H(20A)	0.9700	C(20)-H(20B)	0.9700
C(2)-N(1)-C(13)	111.35(18)	C(2)-N(1)-C(1)	124.3(2)
C(13)-N(1)-C(1)	124.3(2)	N(1)-C(1)-H(1A)	109.5
N(1)-C(1)-H(1B)	109.5	H(1A)-C(1)-H(1B)	109.5
N(1)-C(1)-H(1C)	109.5	H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5	O(2)-C(2)-N(1)	124.7(2)
O(2)-C(2)-C(7)	127.3(2)	N(1)-C(2)-C(7)	107.98(19)
N(4)-C(3)-C(14)	111.91(17)	N(4)-C(3)-C(7)	99.24(16)
C(14)-C(3)-C(7)	115.34(18)	N(4)-C(3)-H(3A)	110.0
C(14)-C(3)-H(3A)	110.0	C(7)-C(3)-H(3A)	110.0
C(20)-N(4)-C(3)	115.29(16)	C(20)-N(4)-C(5)	114.85(16)
C(3)-N(4)-C(5)	103.31(16)	N(4)-C(5)-C(16)	109.33(18)
N(4)-C(5)-C(6)	102.61(16)	C(16)-C(5)-C(6)	110.39(19)
N(4)-C(5)-H(5A)	111.4	C(16)-C(5)-H(5A)	111.4
C(6)-C(5)-H(5A)	111.4	C(5)-C(6)-C(7)	104.68(17)
C(5)-C(6)-H(6A)	110.8	C(7)-C(6)-H(6A)	110.8
C(5)-C(6)-H(6B)	110.8	C(7)-C(6)-H(6B)	110.8
H(6A)-C(6)-H(6B)	108.9	C(8)-C(7)-C(2)	102.19(17)
C(8)-C(7)-C(3)	111.70(17)	C(2)-C(7)-C(3)	114.34(17)
C(8)-C(7)-C(6)	112.76(18)	C(2)-C(7)-C(6)	113.49(17)
C(3)-C(7)-C(6)	102.76(16)	C(9)-C(8)-C(13)	119.8(2)
C(9)-C(8)-C(7)	131.29(19)	C(13)-C(8)-C(7)	108.85(18)
C(8)-C(9)-C(10)	118.7(2)	C(8)-C(9)-H(9A)	120.6
C(10)-C(9)-H(9A)	120.6	C(11)-C(10)-C(9)	120.4(2)
C(11)-C(10)-H(10A)	119.8	C(9)-C(10)-H(10A)	119.8
C(10)-C(11)-C(12)	121.6(2)	C(10)-C(11)-H(11A)	119.2
C(12)-C(11)-H(11A)	119.2	C(13)-C(12)-C(11)	116.9(2)
C(13)-C(12)-H(12A)	121.6	C(11)-C(12)-H(12A)	121.6
C(12)-C(13)-C(8)	122.5(2)	C(12)-C(13)-N(1)	127.9(2)

Table A3. (continued)

C(8)-C(13)-N(1)	109.51(19)	C(3)-C(14)-C(15)	112.96(19)
C(3)-C(14)-H(14A)	109.0	C(15)-C(14)-H(14A)	109.0
C(3)-C(14)-H(14B)	109.0	C(15)-C(14)-H(14B)	109.0
H(14A)-C(14)-H(14B)	107.8	C(16)-C(15)-C(14)	114.39(19)
C(16)-C(15)-H(15A)	108.7	C(14)-C(15)-H(15A)	108.7
C(16)-C(15)-H(15B)	108.7	C(14)-C(15)-H(15B)	108.7
H(15A)-C(15)-H(15B)	107.6	O(16)-C(16)-C(15)	123.5(2)
O(16)-C(16)-C(5)	121.9(3)	C(15)-C(16)-C(5)	114.6(2)
C(18)-C(17)-H(17A)	109.5	C(18)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5	C(18)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5	H(17B)-C(17)-H(17C)	109.5
C(19)-C(18)-C(17)	128.5(3)	C(19)-C(18)-H(18A)	115.7
C(17)-C(18)-H(18A)	115.7	C(18)-C(19)-C(20)	123.0(2)
C(18)-C(19)-I(19)	122.51(18)	C(20)-C(19)-I(19)	114.52(15)
N(4)-C(20)-C(19)	111.66(17)	N(4)-C(20)-H(20A)	109.3
C(19)-C(20)-H(20A)	109.3	N(4)-C(20)-H(20B)	109.3
C(19)-C(20)-H(20B)	109.3	H(20A)-C(20)-H(20B)	107.9

Table A4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **854**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	26(1)	23(1)	23(1)	-1(1)	8(1)	7(1)
C(1)	37(1)	31(1)	32(1)	-6(1)	10(1)	13(1)
O(2)	34(1)	20(1)	44(1)	3(1)	13(1)	3(1)
C(2)	22(1)	22(1)	26(1)	0(1)	4(1)	4(1)
C(3)	18(1)	19(1)	22(1)	0(1)	5(1)	1(1)
N(4)	16(1)	19(1)	18(1)	1(1)	4(1)	2(1)
C(5)	21(1)	25(1)	18(1)	3(1)	7(1)	3(1)
C(6)	21(1)	27(1)	19(1)	5(1)	7(1)	5(1)
C(7)	19(1)	18(1)	20(1)	1(1)	6(1)	2(1)
C(8)	16(1)	23(1)	17(1)	1(1)	4(1)	1(1)
C(9)	19(1)	25(1)	19(1)	-2(1)	6(1)	-2(1)
C(10)	20(1)	29(1)	24(1)	2(1)	4(1)	-5(1)
C(11)	18(1)	42(1)	23(1)	6(1)	7(1)	1(1)
C(12)	21(1)	39(1)	21(1)	2(1)	9(1)	8(1)
C(13)	19(1)	26(1)	19(1)	0(1)	4(1)	5(1)
C(14)	21(1)	19(1)	35(1)	-3(1)	9(1)	-3(1)
C(15)	29(1)	24(1)	49(2)	10(1)	18(1)	-1(1)
O(16)	49(1)	48(1)	43(1)	16(1)	32(1)	8(1)
C(16)	26(1)	31(1)	33(1)	12(1)	14(1)	9(1)
C(17)	43(2)	52(2)	49(2)	-22(1)	26(1)	-5(1)
C(18)	29(1)	33(1)	38(1)	-7(1)	15(1)	-1(1)
I(19)	25(1)	20(1)	37(1)	-5(1)	8(1)	-2(1)
C(19)	19(1)	23(1)	27(1)	-3(1)	6(1)	3(1)
C(20)	16(1)	21(1)	23(1)	1(1)	6(1)	1(1)

Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **854**.

	x	y	z	U(eq)
H(1A)	2519	-294	205	50
H(1B)	3564	545	213	50
H(1C)	2504	651	-650	50
H(3A)	15	3598	355	23
H(5A)	938	4493	3094	25
H(6A)	1811	2192	2769	26
H(6B)	2376	3584	2702	26
H(9A)	1941	5691	1325	25
H(10A)	3137	6636	563	30
H(11A)	4003	5302	-279	32
H(12A)	3700	2989	-398	32
H(14A)	-476	1373	727	30
H(14B)	-1343	2452	802	30
H(15A)	-1168	1388	2169	39
H(15B)	48	969	2281	39
H(17A)	-1934	7750	3458	68
H(17B)	-750	8126	3425	68
H(17C)	-908	7116	4191	68
H(18A)	-1597	5519	2988	39
H(20A)	-1362	4353	1720	24
H(20B)	-1201	5255	897	24

Table A6. Torsion angles [°] for **854**.

C(13)-N(1)-C(2)-O(2)	-175.7(2)	C(1)-N(1)-C(2)-O(2)	4.1(4)
C(13)-N(1)-C(2)-C(7)	3.4(2)	C(1)-N(1)-C(2)-C(7)	-176.8(2)
C(14)-C(3)-N(4)-C(20)	-56.7(2)	C(7)-C(3)-N(4)-C(20)	-178.88(16)
C(14)-C(3)-N(4)-C(5)	69.4(2)	C(7)-C(3)-N(4)-C(5)	-52.77(18)
C(20)-N(4)-C(5)-C(16)	54.7(2)	C(3)-N(4)-C(5)-C(16)	-71.7(2)
C(20)-N(4)-C(5)-C(6)	171.90(17)	C(3)-N(4)-C(5)-C(6)	45.5(2)
N(4)-C(5)-C(6)-C(7)	-19.1(2)	C(16)-C(5)-C(6)-C(7)	97.3(2)
O(2)-C(2)-C(7)-C(8)	175.6(2)	N(1)-C(2)-C(7)-C(8)	-3.4(2)
O(2)-C(2)-C(7)-C(3)	-63.5(3)	N(1)-C(2)-C(7)-C(3)	117.4(2)
O(2)-C(2)-C(7)-C(6)	53.9(3)	N(1)-C(2)-C(7)-C(6)	-125.1(2)
N(4)-C(3)-C(7)-C(8)	-82.55(19)	C(14)-C(3)-C(7)-C(8)	157.77(18)
N(4)-C(3)-C(7)-C(2)	162.02(17)	C(14)-C(3)-C(7)-C(2)	42.3(3)
N(4)-C(3)-C(7)-C(6)	38.59(19)	C(14)-C(3)-C(7)-C(6)	-81.1(2)
C(5)-C(6)-C(7)-C(8)	108.4(2)	C(5)-C(6)-C(7)-C(2)	-136.04(19)
C(5)-C(6)-C(7)-C(3)	-12.0(2)	C(2)-C(7)-C(8)-C(9)	-175.9(2)
C(3)-C(7)-C(8)-C(9)	61.4(3)	C(6)-C(7)-C(8)-C(9)	-53.7(3)
C(2)-C(7)-C(8)-C(13)	2.3(2)	C(3)-C(7)-C(8)-C(13)	-120.32(19)
C(6)-C(7)-C(8)-C(13)	124.54(19)	C(13)-C(8)-C(9)-C(10)	0.0(3)
C(7)-C(8)-C(9)-C(10)	178.1(2)	C(8)-C(9)-C(10)-C(11)	0.4(3)
C(9)-C(10)-C(11)-C(12)	0.1(3)	C(10)-C(11)-C(12)-C(13)	-0.9(3)
C(11)-C(12)-C(13)-C(8)	1.3(3)	C(11)-C(12)-C(13)-N(1)	-177.3(2)
C(9)-C(8)-C(13)-C(12)	-0.9(3)	C(7)-C(8)-C(13)-C(12)	-179.4(2)
C(9)-C(8)-C(13)-N(1)	177.99(19)	C(7)-C(8)-C(13)-N(1)	-0.5(2)
C(2)-N(1)-C(13)-C(12)	176.9(2)	C(1)-N(1)-C(13)-C(12)	-2.9(4)
C(2)-N(1)-C(13)-C(8)	-1.9(3)	C(1)-N(1)-C(13)-C(8)	178.3(2)
N(4)-C(3)-C(14)-C(15)	-49.1(2)	C(7)-C(3)-C(14)-C(15)	63.4(2)
C(3)-C(14)-C(15)-C(16)	29.5(3)	C(14)-C(15)-C(16)-O(16)	147.4(2)
C(14)-C(15)-C(16)-C(5)	-33.3(3)	N(4)-C(5)-C(16)-O(16)	-124.9(2)
C(6)-C(5)-C(16)-O(16)	122.9(2)	N(4)-C(5)-C(16)-C(15)	55.7(2)
C(6)-C(5)-C(16)-C(15)	-56.4(3)	C(17)-C(18)-C(19)-C(20)	-179.9(3)
C(17)-C(18)-C(19)-I(19)	0.2(4)	C(3)-N(4)-C(20)-C(19)	-173.74(18)
C(5)-N(4)-C(20)-C(19)	66.3(2)	C(18)-C(19)-C(20)-N(4)	-114.6(2)
I(19)-C(19)-C(20)-N(4)	65.4(2)		

Table A7. Crystal data and structure refinement for **216**.

Empirical formula	$C_{21}H_{20}N_2O_2$	
Formula weight	332.39	
Temperature	273(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.8433(4) Å	α= 90°
	b = 8.3450(4) Å	β= 90°
	c = 29.1138(13) Å	γ = 90°
Volume	1662.61(15) $Å^3$	
Z	4	
Density (calculated)	1.328 Mg/m^3	
Absorption coefficient	0.086 mm^{-1}	
F(000)	704	
Crystal size	0.456 x 0.169 x 0.088 mm^3	
Theta range for data collection	1.40 to 29.14°	
Index ranges	-8<=h<=9, -10<=k<=11, -39<=l<=39	
Reflections collected	14639	
Independent reflections	4484 [R(int) = 0.0171]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9925 and 0.9618	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4484 / 0 / 226	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0336, wR2 = 0.0875	
R indices (all data)	R1 = 0.0354, wR2 = 0.0890	
Absolute structure parameter	0.9(8)	
Largest diff. peak and hole	0.349 and -0.192 $e.Å^{-3}$	

Table A8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **216**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	5477(1)	9216(1)	228(1)	15(1)
O(2)	7542(1)	7096(1)	334(1)	19(1)
C(2)	6992(2)	8454(1)	434(1)	14(1)
C(3)	8043(2)	8941(1)	1290(1)	14(1)
N(4)	9636(1)	9972(1)	1472(1)	15(1)
C(5)	11201(2)	9767(1)	1128(1)	15(1)
C(6)	10091(2)	9991(1)	670(1)	15(1)
C(7)	7916(2)	9601(1)	790(1)	13(1)
C(8)	6606(2)	11061(1)	744(1)	13(1)
C(9)	6641(2)	12548(1)	959(1)	17(1)
C(10)	5260(2)	13704(1)	828(1)	18(1)
C(11)	3906(2)	13388(1)	481(1)	18(1)
C(12)	3878(2)	11903(1)	257(1)	16(1)
C(13)	5217(2)	10769(1)	401(1)	14(1)
C(14)	8554(2)	7155(1)	1334(1)	17(1)
C(15)	10574(2)	6734(1)	1130(1)	19(1)
O(16)	13801(1)	7827(1)	1150(1)	23(1)
C(16)	12054(2)	8076(1)	1146(1)	17(1)
C(17)	10287(2)	9623(2)	1943(1)	17(1)
C(18)	8675(2)	9801(1)	2296(1)	17(1)
C(19)	7148(2)	10895(2)	2246(1)	21(1)
C(20)	5712(2)	11034(2)	2583(1)	26(1)
C(21)	5785(2)	10085(2)	2974(1)	25(1)
C(22)	7300(2)	8998(2)	3029(1)	25(1)
C(23)	8735(2)	8863(2)	2693(1)	20(1)

Table A9. Bond lengths [Å] and angles [°] for **216**.

N(1)-C(2)	1.3556(14)	N(1)-C(13)	1.4022(14)
N(1)-H(1A)	0.8600	O(2)-C(2)	1.2292(14)
C(2)-C(7)	1.5460(15)	C(3)-N(4)	1.4859(14)
C(3)-C(14)	1.5362(16)	C(3)-C(7)	1.5607(14)
C(3)-H(3A)	0.9800	N(4)-C(17)	1.4713(14)
N(4)-C(5)	1.4760(14)	C(5)-C(16)	1.5274(16)
C(5)-C(6)	1.5463(14)	C(5)-H(5A)	0.9800
C(6)-C(7)	1.5628(15)	C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700	C(7)-C(8)	1.5179(15)
C(8)-C(9)	1.3894(15)	C(8)-C(13)	1.4003(14)
C(9)-C(10)	1.4029(16)	C(9)-H(9A)	0.9300
C(10)-C(11)	1.3944(16)	C(10)-H(10A)	0.9300
C(11)-C(12)	1.4002(16)	C(11)-H(11A)	0.9300
C(12)-C(13)	1.3820(16)	C(12)-H(12A)	0.9300
C(14)-C(15)	1.5449(16)	C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700	C(15)-C(16)	1.5108(16)
C(15)-H(15A)	0.9700	C(15)-H(15B)	0.9700
O(16)-C(16)	1.2138(14)	C(17)-C(18)	1.5161(16)
C(17)-H(17A)	0.9700	C(17)-H(17B)	0.9700
C(18)-C(19)	1.3953(17)	C(18)-C(23)	1.3962(16)
C(19)-C(20)	1.3937(17)	C(19)-H(19A)	0.9300
C(20)-C(21)	1.3875(18)	C(20)-H(20A)	0.9300
C(21)-C(22)	1.387(2)	C(21)-H(21A)	0.9300
C(22)-C(23)	1.3915(17)	C(22)-H(22A)	0.9300
C(23)-H(23A)	0.9300		

C(2)-N(1)-C(13)	111.80(9)	C(2)-N(1)-H(1A)	124.1
C(13)-N(1)-H(1A)	124.1	O(2)-C(2)-N(1)	124.22(10)
O(2)-C(2)-C(7)	127.15(10)	N(1)-C(2)-C(7)	108.59(9)
N(4)-C(3)-C(14)	111.41(9)	N(4)-C(3)-C(7)	99.71(8)
C(14)-C(3)-C(7)	115.61(9)	N(4)-C(3)-H(3A)	109.9
C(14)-C(3)-H(3A)	109.9	C(7)-C(3)-H(3A)	109.9
C(17)-N(4)-C(5)	112.95(9)	C(17)-N(4)-C(3)	116.06(9)
C(5)-N(4)-C(3)	102.94(8)	N(4)-C(5)-C(16)	111.15(9)
N(4)-C(5)-C(6)	102.40(8)	C(16)-C(5)-C(6)	109.23(9)
N(4)-C(5)-H(5A)	111.2	C(16)-C(5)-H(5A)	111.2
C(6)-C(5)-H(5A)	111.2	C(5)-C(6)-C(7)	104.48(8)
C(5)-C(6)-H(6A)	110.9	C(7)-C(6)-H(6A)	110.9
C(5)-C(6)-H(6B)	110.9	C(7)-C(6)-H(6B)	110.9
H(6A)-C(6)-H(6B)	108.9	C(8)-C(7)-C(2)	101.36(8)
C(8)-C(7)-C(3)	113.41(8)	C(2)-C(7)-C(3)	115.49(9)
C(8)-C(7)-C(6)	112.08(9)	C(2)-C(7)-C(6)	111.62(9)
C(3)-C(7)-C(6)	103.24(8)	C(9)-C(8)-C(13)	119.16(10)
C(9)-C(8)-C(7)	131.89(10)	C(13)-C(8)-C(7)	108.87(9)
C(8)-C(9)-C(10)	118.73(10)	C(8)-C(9)-H(9A)	120.6
C(10)-C(9)-H(9A)	120.6	C(11)-C(10)-C(9)	120.92(10)
C(11)-C(10)-H(10A)	119.5	C(9)-C(10)-H(10A)	119.5
C(10)-C(11)-C(12)	120.89(10)	C(10)-C(11)-H(11A)	119.6
C(12)-C(11)-H(11A)	119.6	C(13)-C(12)-C(11)	117.10(10)
C(13)-C(12)-H(12A)	121.4	C(11)-C(12)-H(12A)	121.4
C(12)-C(13)-C(8)	123.17(10)	C(12)-C(13)-N(1)	127.44(10)
C(8)-C(13)-N(1)	109.35(9)	C(3)-C(14)-C(15)	113.14(9)
C(3)-C(14)-H(14A)	109.0	C(15)-C(14)-H(14A)	109.0

Table A9. (continued)

C(3)-C(14)-H(14B)	109.0	C(15)-C(14)-H(14B)	109.0
H(14A)-C(14)-H(14B)	107.8	C(16)-C(15)-C(14)	114.78(10)
C(16)-C(15)-H(15A)	108.6	C(14)-C(15)-H(15A)	108.6
C(16)-C(15)-H(15B)	108.6	C(14)-C(15)-H(15B)	108.6
H(15A)-C(15)-H(15B)	107.5	O(16)-C(16)-C(15)	122.23(11)
O(16)-C(16)-C(5)	122.35(11)	C(15)-C(16)-C(5)	115.32(9)
N(4)-C(17)-C(18)	113.14(9)	N(4)-C(17)-H(17A)	109.0
C(18)-C(17)-H(17A)	109.0	N(4)-C(17)-H(17B)	109.0
C(18)-C(17)-H(17B)	109.0	H(17A)-C(17)-H(17B)	107.8
C(19)-C(18)-C(23)	118.39(11)	C(19)-C(18)-C(17)	122.57(10)
C(23)-C(18)-C(17)	119.02(11)	C(20)-C(19)-C(18)	120.60(11)
C(20)-C(19)-H(19A)	119.7	C(18)-C(19)-H(19A)	119.7
C(21)-C(20)-C(19)	120.29(12)	C(21)-C(20)-H(20A)	119.9
C(19)-C(20)-H(20A)	119.9	C(22)-C(21)-C(20)	119.72(12)
C(22)-C(21)-H(21A)	120.1	C(20)-C(21)-H(21A)	120.1
C(21)-C(22)-C(23)	119.93(11)	C(21)-C(22)-H(22A)	120.0
C(23)-C(22)-H(22A)	120.0	C(22)-C(23)-C(18)	121.06(12)
C(22)-C(23)-H(23A)	119.5	C(18)-C(23)-H(23A)	119.5

Table A10. Anisotropic displacement parameters ($Å^2$ x 10^3) for **216**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	14(1)	17(1)	14(1)	-2(1)	-2(1)	-2(1)
O(2)	17(1)	19(1)	21(1)	-5(1)	3(1)	1(1)
C(2)	12(1)	17(1)	14(1)	-1(1)	3(1)	-3(1)
C(3)	10(1)	16(1)	15(1)	1(1)	0(1)	-2(1)
N(4)	10(1)	19(1)	14(1)	0(1)	-1(1)	-2(1)
C(5)	9(1)	18(1)	17(1)	0(1)	0(1)	-2(1)
C(6)	11(1)	20(1)	15(1)	2(1)	0(1)	-2(1)
C(7)	10(1)	14(1)	14(1)	-1(1)	-1(1)	-1(1)
C(8)	11(1)	15(1)	13(1)	1(1)	1(1)	-1(1)
C(9)	17(1)	17(1)	16(1)	-1(1)	-2(1)	-2(1)
C(10)	21(1)	15(1)	18(1)	-1(1)	1(1)	0(1)
C(11)	16(1)	18(1)	19(1)	4(1)	1(1)	3(1)
C(12)	12(1)	20(1)	15(1)	3(1)	-1(1)	-2(1)
C(13)	12(1)	16(1)	13(1)	0(1)	1(1)	-2(1)
C(14)	13(1)	17(1)	21(1)	3(1)	0(1)	-2(1)
C(15)	15(1)	16(1)	26(1)	1(1)	-2(1)	1(1)
O(16)	12(1)	29(1)	28(1)	3(1)	1(1)	3(1)
C(16)	14(1)	21(1)	16(1)	1(1)	0(1)	0(1)
C(17)	14(1)	21(1)	16(1)	0(1)	-2(1)	1(1)
C(18)	16(1)	19(1)	15(1)	-3(1)	-2(1)	-3(1)
C(19)	21(1)	24(1)	18(1)	1(1)	-1(1)	3(1)
C(20)	23(1)	31(1)	23(1)	-2(1)	0(1)	7(1)
C(21)	26(1)	32(1)	18(1)	-4(1)	5(1)	0(1)
C(22)	32(1)	25(1)	17(1)	1(1)	2(1)	-2(1)
C(23)	24(1)	19(1)	18(1)	0(1)	-1(1)	1(1)

Table A11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for **216**.

	x	y	z	U(eq)
H(1A)	4762	8798	16	18
H(3A)	6823	9167	1454	17
H(5A)	12223	10579	1165	18
H(6A)	10582	9263	437	18
H(6B)	10219	11082	559	18
H(9A)	7561	12773	1185	20
H(10A)	5249	14695	974	22
H(11A)	3010	14173	398	21
H(12A)	2997	11690	22	19
H(14A)	7561	6529	1178	20
H(14B)	8535	6858	1656	20
H(15A)	11098	5822	1296	23
H(15B)	10399	6410	813	23
H(17A)	11350	10341	2021	20
H(17B)	10787	8536	1955	20
H(19A)	7088	11538	1986	25
H(20A)	4700	11767	2546	31
H(21A)	4823	10177	3198	30
H(22A)	7356	8360	3291	30
H(23A)	9751	8136	2733	24

Table A12. Torsion angles [°] for **216**.

C(13)-N(1)-C(2)-O(2)	-178.21(10)	C(13)-N(1)-C(2)-C(7)	-0.48(12)
C(14)-C(3)-N(4)-C(17)	-53.44(12)	C(7)-C(3)-N(4)-C(17)	-175.99(9)
C(14)-C(3)-N(4)-C(5)	70.46(10)	C(7)-C(3)-N(4)-C(5)	-52.09(10)
C(17)-N(4)-C(5)-C(16)	56.70(12)	C(3)-N(4)-C(5)-C(16)	-69.22(10)
C(17)-N(4)-C(5)-C(6)	173.24(9)	C(3)-N(4)-C(5)-C(6)	47.31(10)
N(4)-C(5)-C(6)-C(7)	-22.77(11)	C(16)-C(5)-C(6)-C(7)	95.13(10)
O(2)-C(2)-C(7)-C(8)	179.07(10)	N(1)-C(2)-C(7)-C(8)	1.42(11)
O(2)-C(2)-C(7)-C(3)	-57.92(15)	N(1)-C(2)-C(7)-C(3)	124.43(10)
O(2)-C(2)-C(7)-C(6)	59.60(14)	N(1)-C(2)-C(7)-C(6)	-118.06(10)
N(4)-C(3)-C(7)-C(8)	-85.74(10)	C(14)-C(3)-C(7)-C(8)	154.75(9)
N(4)-C(3)-C(7)-C(2)	157.89(9)	C(14)-C(3)-C(7)-C(2)	38.37(13)
N(4)-C(3)-C(7)-C(6)	35.77(10)	C(14)-C(3)-C(7)-C(6)	-83.74(11)
C(5)-C(6)-C(7)-C(8)	114.23(9)	C(5)-C(6)-C(7)-C(2)	-132.85(9)
C(5)-C(6)-C(7)-C(3)	-8.18(11)	C(2)-C(7)-C(8)-C(9)	-178.42(11)
C(3)-C(7)-C(8)-C(9)	57.16(15)	C(6)-C(7)-C(8)-C(9)	-59.27(15)
C(2)-C(7)-C(8)-C(13)	-1.89(10)	C(3)-C(7)-C(8)-C(13)	-126.31(9)
C(6)-C(7)-C(8)-C(13)	117.27(9)	C(13)-C(8)-C(9)-C(10)	0.83(15)
C(7)-C(8)-C(9)-C(10)	177.07(11)	C(8)-C(9)-C(10)-C(11)	-1.53(17)
C(9)-C(10)-C(11)-C(12)	0.46(17)	C(10)-C(11)-C(12)-C(13)	1.28(16)
C(11)-C(12)-C(13)-C(8)	-2.02(16)	C(11)-C(12)-C(13)-N(1)	-179.41(10)
C(9)-C(8)-C(13)-C(12)	0.99(15)	C(7)-C(8)-C(13)-C(12)	-176.06(10)
C(9)-C(8)-C(13)-N(1)	178.79(10)	C(7)-C(8)-C(13)-N(1)	1.75(11)
C(2)-N(1)-C(13)-C(12)	176.89(10)	C(2)-N(1)-C(13)-C(8)	-0.80(12)
N(4)-C(3)-C(14)-C(15)	-51.60(12)	C(7)-C(3)-C(14)-C(15)	61.29(12)
C(3)-C(14)-C(15)-C(16)	29.17(14)	C(14)-C(15)-C(16)-O(16)	154.53(11)
C(14)-C(15)-C(16)-C(5)	-28.96(14)	N(4)-C(5)-C(16)-O(16)	-132.76(11)
C(6)-C(5)-C(16)-O(16)	114.98(12)	N(4)-C(5)-C(16)-C(15)	50.73(12)
C(6)-C(5)-C(16)-C(15)	-61.53(12)	C(5)-N(4)-C(17)-C(18)	-178.90(9)
C(3)-N(4)-C(17)-C(18)	-60.36(13)	N(4)-C(17)-C(18)-C(19)	-30.87(16)
N(4)-C(17)-C(18)-C(23)	150.63(10)	C(23)-C(18)-C(19)-C(20)	-0.55(18)
C(17)-C(18)-C(19)-C(20)	-179.06(11)	C(18)-C(19)-C(20)-C(21)	0.1(2)
C(19)-C(20)-C(21)-C(22)	0.2(2)	C(20)-C(21)-C(22)-C(23)	-0.1(2)
C(21)-C(22)-C(23)-C(18)	-0.40(19)	C(19)-C(18)-C(23)-C(22)	0.71(18)
C(17)-C(18)-C(23)-C(22)	179.27(11)		

Table A13. Hydrogen bonds for **216** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1A)...O(2)#1	0.86	1.98	2.8118(12)	163.7

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y+3/2,-z

Table A14. Crystal data and structure refinement for **846**.

Empirical formula	$C_{20}H_{22}Cl_3IN_2O_2$	
Formula weight	555.65	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 10.4533(9) Å	α= 90°
	b = 6.9333(6) Å	β= 106.712(3)°
	c = 15.6135(12) Å	γ = 90°
Volume	1083.81(16) Å	
Z	2	
Density (calculated)	1.703 Mg/m^3	
Absorption coefficient	1.866 mm^{-1}	
F(000)	552	
Crystal size	0.51 x 0.13 x 0.01 mm^3	
Theta range for data collection	1.36 to 29.15°	
Index ranges	-14<=h<=14, -9<=k<=9, -21<=l<=21	
Reflections collected	12545	
Independent reflections	5731 [R(int) = 0.0339]	
Completeness to theta = 25.00°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9816 and 0.4496	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5731 / 1 / 255	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2sigma(I)]	R1 = 0.0346, wR2 = 0.0715	
R indices (all data)	R1 = 0.0427, wR2 = 0.0750	
Absolute structure parameter	0.010(16)	
Largest diff. peak and hole	1.383 and -1.179 $e.Å^{-3}$	

Table A15. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **846**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	10115(3)	3093(4)	5870(2)	15(1)
C(1)	8723(3)	3059(5)	5893(2)	22(1)
O(2)	11112(2)	2925(5)	7382(2)	22(1)
C(2)	11178(3)	2996(5)	6616(2)	16(1)
C(3)	13382(4)	4802(5)	6781(3)	13(1)
N(4)	14445(3)	4017(4)	7529(2)	14(1)
C(5)	14730(3)	2185(4)	7171(2)	15(1)
O(16)	15829(3)	1291(4)	6078(2)	25(1)
C(6)	13361(4)	1247(5)	6728(3)	15(1)
C(7)	12472(3)	3013(5)	6324(2)	14(1)
C(8)	11913(3)	3040(4)	5316(2)	14(1)
C(9)	12511(3)	2955(6)	4641(2)	18(1)
C(10)	11725(4)	2980(5)	3744(2)	20(1)
C(11)	10344(4)	3026(5)	3539(2)	23(1)
C(12)	9714(4)	3074(5)	4217(2)	23(1)
C(13)	10511(3)	3069(4)	5090(2)	15(1)
C(14)	14120(4)	5807(5)	6177(2)	17(1)
C(15)	15383(4)	4670(5)	6147(3)	18(1)
C(16)	15383(3)	2584(7)	6424(2)	17(1)
C(17)	14152(4)	3862(5)	8391(2)	17(1)
I(18)	15553(1)	7704(1)	8992(1)	26(1)
C(18)	13902(4)	5812(5)	8731(2)	19(1)
C(19)	12743(4)	6358(7)	8850(3)	29(1)
C(20)	12403(5)	8257(7)	9177(3)	44(1)
C(1S)	10778(4)	7291(6)	1465(2)	24(1)
Cl(1S)	11923(1)	9224(2)	1623(1)	39(1)
Cl(2S)	11654(1)	5089(2)	1568(1)	35(1)
Cl(3S)	9575(1)	7460(2)	424(1)	33(1)

Table A16. Bond lengths [Å] and angles [°] for **846**.

N(1)-C(2)	1.361(4)	N(1)-C(13)	1.394(4)
N(1)-C(1)	1.466(4)	C(1)-H(1A)	0.9600
C(1)-H(1B)	0.9600	C(1)-H(1C)	0.9600
O(2)-C(2)	1.220(4)	C(2)-C(7)	1.547(4)
C(3)-N(4)	1.466(5)	C(3)-C(14)	1.546(5)
C(3)-C(7)	1.600(5)	C(3)-H(3A)	0.9800
N(4)-C(5)	1.453(4)	N(4)-C(17)	1.467(4)
C(5)-C(16)	1.535(4)	C(5)-C(6)	1.543(5)
C(5)-H(5A)	0.9800	O(16)-C(16)	1.208(5)
C(6)-C(7)	1.556(5)	C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700	C(7)-C(8)	1.514(4)
C(8)-C(9)	1.373(4)	C(8)-C(13)	1.406(4)
C(9)-C(10)	1.404(4)	C(9)-H(9A)	0.9300
C(10)-C(11)	1.386(5)	C(10)-H(10A)	0.9300
C(11)-C(12)	1.399(5)	C(11)-H(11A)	0.9300
C(12)-C(13)	1.378(5)	C(12)-H(12A)	0.9300
C(14)-C(15)	1.550(5)	C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700	C(15)-C(16)	1.510(6)
C(15)-H(15A)	0.9700	C(15)-H(15B)	0.9700
C(17)-C(18)	1.503(5)	C(17)-H(17A)	0.9700
C(17)-H(17B)	0.9700	I(18)-C(18)	2.113(4)
C(18)-C(19)	1.332(5)	C(19)-C(20)	1.492(6)
C(19)-H(19A)	0.9300	C(20)-H(20A)	0.9600
C(20)-H(20B)	0.9600	C(20)-H(20C)	0.9600
C(1S)-Cl(3S)	1.750(4)	C(1S)-Cl(2S)	1.763(4)
C(1S)-Cl(1S)	1.766(4)	C(1S)-H(1SA)	0.9800
C(2)-N(1)-C(13)	111.9(3)	C(2)-N(1)-C(1)	123.4(3)
C(13)-N(1)-C(1)	124.6(3)	N(1)-C(1)-H(1A)	109.5
N(1)-C(1)-H(1B)	109.5	H(1A)-C(1)-H(1B)	109.5
N(1)-C(1)-H(1C)	109.5	H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5	O(2)-C(2)-N(1)	125.4(3)
O(2)-C(2)-C(7)	126.2(3)	N(1)-C(2)-C(7)	108.4(3)
N(4)-C(3)-C(14)	104.9(3)	N(4)-C(3)-C(7)	106.5(3)
C(14)-C(3)-C(7)	114.4(3)	N(4)-C(3)-H(3A)	110.3
C(14)-C(3)-H(3A)	110.3	C(7)-C(3)-H(3A)	110.3
C(5)-N(4)-C(3)	102.1(3)	C(5)-N(4)-C(17)	114.2(3)
C(3)-N(4)-C(17)	116.6(3)	N(4)-C(5)-C(16)	108.7(3)
N(4)-C(5)-C(6)	105.9(3)	C(16)-C(5)-C(6)	107.1(3)
N(4)-C(5)-H(5A)	111.6	C(16)-C(5)-H(5A)	111.6
C(6)-C(5)-H(5A)	111.6	C(5)-C(6)-C(7)	102.6(3)
C(5)-C(6)-H(6A)	111.2	C(7)-C(6)-H(6A)	111.2
C(5)-C(6)-H(6B)	111.2	C(7)-C(6)-H(6B)	111.2
H(6A)-C(6)-H(6B)	109.2	C(8)-C(7)-C(2)	101.4(2)
C(8)-C(7)-C(6)	116.0(3)	C(2)-C(7)-C(6)	110.2(3)
C(8)-C(7)-C(3)	117.2(3)	C(2)-C(7)-C(3)	109.4(3)
C(6)-C(7)-C(3)	102.7(3)	C(9)-C(8)-C(13)	118.7(3)
C(9)-C(8)-C(7)	132.3(3)	C(13)-C(8)-C(7)	108.9(3)
C(8)-C(9)-C(10)	120.0(3)	C(8)-C(9)-H(9A)	120.0
C(10)-C(9)-H(9A)	120.0	C(11)-C(10)-C(9)	120.2(3)
C(11)-C(10)-H(10A)	119.9	C(9)-C(10)-H(10A)	119.9
C(10)-C(11)-C(12)	120.7(3)	C(10)-C(11)-H(11A)	119.6
C(12)-C(11)-H(11A)	119.6	C(13)-C(12)-C(11)	117.8(3)

Table A16. (continued)

C(13)-C(12)-H(12A)	121.1	C(11)-C(12)-H(12A)	121.1
C(12)-C(13)-N(1)	128.0(3)	C(12)-C(13)-C(8)	122.6(3)
N(1)-C(13)-C(8)	109.4(3)	C(3)-C(14)-C(15)	111.6(3)
C(3)-C(14)-H(14A)	109.3	C(15)-C(14)-H(14A)	109.3
C(3)-C(14)-H(14B)	109.3	C(15)-C(14)-H(14B)	109.3
H(14A)-C(14)-H(14B)	108.0	C(16)-C(15)-C(14)	114.1(3)
C(16)-C(15)-H(15A)	108.7	C(14)-C(15)-H(15A)	108.7
C(16)-C(15)-H(15B)	108.7	C(14)-C(15)-H(15B)	108.7
H(15A)-C(15)-H(15B)	107.6	O(16)-C(16)-C(15)	123.4(3)
O(16)-C(16)-C(5)	121.2(4)	C(15)-C(16)-C(5)	115.3(3)
N(4)-C(17)-C(18)	111.2(3)	N(4)-C(17)-H(17A)	109.4
C(18)-C(17)-H(17A)	109.4	N(4)-C(17)-H(17B)	109.4
C(18)-C(17)-H(17B)	109.4	H(17A)-C(17)-H(17B)	108.0
C(19)-C(18)-C(17)	124.2(4)	C(19)-C(18)-I(18)	121.5(3)
C(17)-C(18)-I(18)	114.3(2)	C(18)-C(19)-C(20)	127.9(4)
C(18)-C(19)-H(19A)	116.0	C(20)-C(19)-H(19A)	116.0
C(19)-C(20)-H(20A)	109.5	C(19)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5	C(19)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5	H(20B)-C(20)-H(20C)	109.5
Cl(3S)-C(1S)-Cl(2S)	111.0(2)	Cl(3S)-C(1S)-Cl(1S)	110.8(2)
Cl(2S)-C(1S)-Cl(1S)	109.3(2)	Cl(3S)-C(1S)-H(1SA)	108.6
Cl(2S)-C(1S)-H(1SA)	108.6	Cl(1S)-C(1S)-H(1SA)	108.6

Table A17. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **846**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	12(1)	17(2)	16(1)	-1(1)	1(1)	1(1)
C(1)	9(1)	25(3)	28(2)	1(2)	1(1)	-1(1)
O(2)	15(1)	34(2)	15(1)	-4(1)	3(1)	-3(1)
C(2)	14(1)	18(2)	14(1)	-2(1)	1(1)	-3(1)
C(3)	10(2)	15(2)	11(2)	1(1)	-3(1)	1(1)
N(4)	14(1)	15(1)	10(1)	0(1)	-1(1)	2(1)
C(5)	14(2)	14(2)	13(2)	2(1)	-2(1)	3(1)
O(16)	21(2)	31(2)	23(2)	-4(1)	8(1)	5(1)
C(6)	16(2)	14(2)	15(2)	-1(1)	4(2)	-3(1)
C(7)	12(1)	17(2)	12(1)	0(1)	2(1)	0(1)
C(8)	15(1)	9(2)	12(1)	-1(1)	-3(1)	0(1)
C(9)	20(2)	19(2)	15(1)	3(2)	4(1)	-2(2)
C(10)	30(2)	16(2)	10(1)	-2(1)	2(1)	1(2)
C(11)	30(2)	16(2)	14(2)	0(1)	-6(1)	2(1)
C(12)	21(2)	22(2)	18(2)	1(1)	-6(1)	0(1)
C(13)	15(2)	12(2)	14(2)	1(1)	-1(1)	-1(1)
C(14)	19(2)	17(2)	14(2)	2(1)	3(1)	-3(1)
C(15)	16(2)	24(2)	14(2)	2(1)	6(2)	-3(1)
C(16)	11(1)	24(2)	13(1)	0(2)	-1(1)	1(2)
C(17)	18(2)	23(2)	9(2)	-1(1)	0(1)	-5(1)
I(18)	28(1)	21(1)	24(1)	-4(1)	1(1)	-4(1)
C(18)	23(2)	22(2)	11(2)	0(1)	3(2)	-2(1)
C(19)	29(2)	34(2)	25(2)	-4(2)	7(2)	3(2)
C(20)	39(3)	58(4)	35(2)	-19(2)	12(2)	7(2)
C(1S)	20(2)	37(3)	14(2)	-1(2)	4(1)	-1(2)
Cl(1S)	38(1)	42(1)	31(1)	-3(1)	-1(1)	-15(1)
Cl(2S)	38(1)	38(1)	24(1)	3(1)	0(1)	11(1)
Cl(3S)	24(1)	39(1)	27(1)	2(1)	-6(1)	1(1)

Table A18. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **846**.

	x	y	z	U(eq)
H(1A)	8688	3368	6485	32
H(1B)	8355	1797	5731	32
H(1C)	8215	3991	5477	32
H(3A)	12848	5741	7000	16
H(5A)	15293	1360	7639	18
H(6A)	13024	584	7165	18
H(6B)	13414	342	6265	18
H(9A)	13436	2881	4776	22
H(10A)	12132	2966	3288	23
H(11A)	9831	3025	2943	27
H(12A)	8788	3107	4083	27
H(14A)	14376	7097	6401	21
H(14B)	13521	5920	5576	21
H(15A)	15461	4722	5543	21
H(15B)	16163	5301	6536	21
H(17A)	14899	3253	8824	21
H(17B)	13371	3054	8323	21
H(19A)	12064	5444	8713	35
H(20A)	11548	8677	8806	66
H(20B)	13071	9189	9153	66
H(20C)	12371	8127	9783	66
H(1SA)	10325	7351	1934	28

Table A19. Torsion angles [°] for **846**.

C(13)-N(1)-C(2)-O(2)	-177.3(4)	C(1)-N(1)-C(2)-O(2)	-2.1(6)
C(13)-N(1)-C(2)-C(7)	3.2(4)	C(1)-N(1)-C(2)-C(7)	178.4(3)
C(14)-C(3)-N(4)-C(5)	-84.6(3)	C(7)-C(3)-N(4)-C(5)	37.1(3)
C(14)-C(3)-N(4)-C(17)	150.3(3)	C(7)-C(3)-N(4)-C(17)	-88.1(3)
C(3)-N(4)-C(5)-C(16)	68.6(3)	C(17)-N(4)-C(5)-C(16)	-164.7(3)
C(3)-N(4)-C(5)-C(6)	-46.2(3)	C(17)-N(4)-C(5)-C(6)	80.6(3)
N(4)-C(5)-C(6)-C(7)	36.3(3)	C(16)-C(5)-C(6)-C(7)	-79.5(3)
O(2)-C(2)-C(7)-C(8)	178.1(4)	N(1)-C(2)-C(7)-C(8)	-2.5(3)
O(2)-C(2)-C(7)-C(6)	54.7(5)	N(1)-C(2)-C(7)-C(6)	-125.9(3)
O(2)-C(2)-C(7)-C(3)	-57.6(5)	N(1)-C(2)-C(7)-C(3)	121.9(3)
C(5)-C(6)-C(7)-C(8)	116.8(3)	C(5)-C(6)-C(7)-C(2)	-128.7(3)
C(5)-C(6)-C(7)-C(3)	-12.2(3)	N(4)-C(3)-C(7)-C(8)	-143.0(3)
C(14)-C(3)-C(7)-C(8)	-27.6(4)	N(4)-C(3)-C(7)-C(2)	102.4(3)
C(14)-C(3)-C(7)-C(2)	-142.2(3)	N(4)-C(3)-C(7)-C(6)	-14.6(3)
C(14)-C(3)-C(7)-C(6)	100.8(3)	C(2)-C(7)-C(8)-C(9)	-175.7(4)
C(6)-C(7)-C(8)-C(9)	-56.3(5)	C(3)-C(7)-C(8)-C(9)	65.3(5)
C(2)-C(7)-C(8)-C(13)	0.9(3)	C(6)-C(7)-C(8)-C(13)	120.3(3)
C(3)-C(7)-C(8)-C(13)	-118.0(3)	C(13)-C(8)-C(9)-C(10)	2.6(5)
C(7)-C(8)-C(9)-C(10)	179.0(3)	C(8)-C(9)-C(10)-C(11)	-2.1(6)
C(9)-C(10)-C(11)-C(12)	0.8(6)	C(10)-C(11)-C(12)-C(13)	-0.1(5)
C(11)-C(12)-C(13)-N(1)	-179.4(3)	C(11)-C(12)-C(13)-C(8)	0.7(5)
C(2)-N(1)-C(13)-C(12)	177.4(3)	C(1)-N(1)-C(13)-C(12)	2.2(5)
C(2)-N(1)-C(13)-C(8)	-2.7(4)	C(1)-N(1)-C(13)-C(8)	-177.8(3)
C(9)-C(8)-C(13)-C(12)	-2.0(5)	C(7)-C(8)-C(13)-C(12)	-179.1(3)
C(9)-C(8)-C(13)-N(1)	178.1(3)	C(7)-C(8)-C(13)-N(1)	0.9(3)
N(4)-C(3)-C(14)-C(15)	37.1(4)	C(7)-C(3)-C(14)-C(15)	-79.2(4)
C(3)-C(14)-C(15)-C(16)	19.8(4)	C(14)-C(15)-C(16)-O(16)	142.9(4)
C(14)-C(15)-C(16)-C(5)	-35.2(4)	N(4)-C(5)-C(16)-O(16)	173.0(3)
C(6)-C(5)-C(16)-O(16)	-73.1(4)	N(4)-C(5)-C(16)-C(15)	-8.8(4)
C(6)-C(5)-C(16)-C(15)	105.2(3)	C(5)-N(4)-C(17)-C(18)	178.5(3)
C(3)-N(4)-C(17)-C(18)	-62.6(4)	N(4)-C(17)-C(18)-C(19)	116.3(4)
N(4)-C(17)-C(18)-I(18)	-62.5(3)	C(17)-C(18)-C(19)-C(20)	-179.6(4)
I(18)-C(18)-C(19)-C(20)	-0.8(6)		

Table A20. Crystal data and structure refinement for **857**.

Empirical formula	$C_{19}H_{20}N_2O_2$	
Formula weight	308.37	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.6047(6) Å	α= 104.909(4)°
	b = 12.5723(9) Å	β= 103.346(4)°
	c = 14.8500(13) Å	γ = 109.298(3)°
Volume	1534.2(2) $Å^3$	
Z	4	
Density (calculated)	1.335 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	656	
Crystal size	0.409 x 0.379 x 0.186 mm^3	
Theta range for data collection	1.51 to 29.21°	
Index ranges	-13<=h<=11, -17<=k<=16, -20<=l<=20	
Reflections collected	14624	
Independent reflections	7995 [R(int) = 0.0194]	
Completeness to theta = 25.00°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9839 and 0.9651	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7995 / 0 / 419	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0440, wR2 = 0.1118	
R indices (all data)	R1 = 0.0552, wR2 = 0.1192	
Largest diff. peak and hole	0.614 and -0.201 $e.Å^{-3}$	

Table A21. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **857**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	9104(1)	12228(1)	3995(1)	21(1)
C(1)	10471(2)	13369(1)	4340(1)	26(1)
O(2)	10226(1)	10934(1)	3471(1)	27(1)
C(2)	9088(2)	11114(1)	3572(1)	20(1)
C(3)	7557(2)	9386(1)	3981(1)	19(1)
N(4)	7681(1)	8347(1)	3314(1)	19(1)
C(5)	6370(2)	7992(1)	2394(1)	20(1)
C(6)	6742(2)	9196(1)	2230(1)	20(1)
C(7)	7412(1)	10149(1)	3299(1)	18(1)
C(8)	6522(2)	10921(1)	3489(1)	19(1)
C(9)	4928(2)	10622(1)	3255(1)	22(1)
C(10)	4405(2)	11536(1)	3495(1)	24(1)
C(11)	5490(2)	12734(1)	3964(1)	25(1)
C(12)	7097(2)	13059(1)	4180(1)	24(1)
C(13)	7584(2)	12137(1)	3922(1)	20(1)
C(14)	6152(2)	8924(1)	4332(1)	21(1)
C(15)	5023(1)	7612(1)	3627(1)	19(1)
O(16)	3528(1)	7188(1)	1921(1)	30(1)
C(16)	4792(2)	7552(1)	2563(1)	20(1)
C(17)	7528(2)	7390(1)	3731(1)	23(1)
C(18)	5874(2)	6799(1)	3731(1)	19(1)
C(19)	5255(2)	5680(1)	3727(1)	21(1)
C(20)	3631(2)	4990(1)	3692(1)	25(1)
N(1')	10251(1)	7175(1)	2650(1)	23(1)
C(1')	11269(2)	8362(1)	3405(1)	32(1)
O(2')	10621(1)	6055(1)	3611(1)	30(1)
C(2')	9995(2)	6121(1)	2825(1)	22(1)
C(3')	9701(2)	4282(1)	1501(1)	19(1)
N(4')	9330(1)	3379(1)	1987(1)	20(1)
C(5')	7614(2)	2974(1)	1724(1)	21(1)
C(6')	7472(2)	4176(1)	2082(1)	22(1)
C(7')	8811(1)	5063(1)	1868(1)	19(1)
C(8')	8319(1)	5715(1)	1218(1)	19(1)
C(9')	7153(2)	5301(1)	308(1)	23(1)
C(10')	6959(2)	6143(1)	-117(1)	27(1)
C(11')	7921(2)	7365(1)	370(1)	29(1)
C(12')	9083(2)	7800(1)	1296(1)	26(1)
C(13')	9246(2)	6957(1)	1707(1)	21(1)
C(14')	9149(2)	3620(1)	363(1)	20(1)
C(15')	7943(2)	2305(1)	68(1)	21(1)
O(16')	5368(1)	1985(1)	196(1)	34(1)
C(16')	6776(2)	2354(1)	594(1)	23(1)
C(17')	9792(2)	2397(1)	1595(1)	24(1)
C(18')	8746(2)	1620(1)	527(1)	22(1)
C(19')	8488(2)	471(1)	106(1)	25(1)
C(20')	7461(2)	-363(1)	-935(1)	31(1)

Table A22. Bond lengths [Å] and angles [°] for **857**.

N(1)-C(2)	1.3728(17)	N(1)-C(13)	1.4025(17)
N(1)-C(1)	1.4526(16)	C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800	C(1)-H(1C)	0.9800
O(2)-C(2)	1.2215(16)	C(2)-C(7)	1.5427(17)
C(3)-N(4)	1.4811(16)	C(3)-C(14)	1.5464(17)
C(3)-C(7)	1.5777(16)	C(3)-H(3A)	1.0000
N(4)-C(17)	1.4699(15)	N(4)-C(5)	1.4730(16)
C(5)-C(6)	1.5326(16)	C(5)-C(16)	1.5365(17)
C(5)-H(5A)	1.0000	C(6)-C(7)	1.5520(16)
C(6)-H(6A)	0.9900	C(6)-H(6B)	0.9900
C(7)-C(8)	1.5078(17)	C(8)-C(9)	1.3827(18)
C(8)-C(13)	1.3970(17)	C(9)-C(10)	1.3980(18)
C(9)-H(9A)	0.9500	C(10)-C(11)	1.388(2)
C(10)-H(10A)	0.9500	C(11)-C(12)	1.393(2)
C(11)-H(11A)	0.9500	C(12)-C(13)	1.3857(18)
C(12)-H(12A)	0.9500	C(14)-C(15)	1.5483(18)
C(14)-H(14A)	0.9900	C(14)-H(14B)	0.9900
C(15)-C(18)	1.5204(17)	C(15)-C(16)	1.5224(17)
C(15)-H(15A)	1.0000	O(16)-C(16)	1.2107(16)
C(17)-C(18)	1.5148(17)	C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900	C(18)-C(19)	1.3315(17)
C(19)-C(20)	1.4946(18)	C(19)-H(19A)	0.9500
C(20)-H(20A)	0.9800	C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800	N(1')-C(2')	1.3689(17)
N(1')-C(13')	1.4048(17)	N(1')-C(1')	1.4521(17)
C(1')-H(1'A)	0.9800	C(1')-H(1'B)	0.9800
C(1')-H(1'C)	0.9800	O(2')-C(2')	1.2207(16)
C(2')-C(7')	1.5378(17)	C(3')-N(4')	1.4859(15)
C(3')-C(14')	1.5498(16)	C(3')-C(7')	1.5763(17)
C(3')-H(3'A)	1.0000	N(4')-C(17')	1.4732(16)
N(4')-C(5')	1.4749(17)	C(5')-C(6')	1.5301(18)
C(5')-C(16')	1.5359(17)	C(5')-H(5'A)	1.0000
C(6')-C(7')	1.5558(17)	C(6')-H(6'A)	0.9900
C(6')-H(6'B)	0.9900	C(7')-C(8')	1.5097(16)
C(8')-C(9')	1.3813(17)	C(8')-C(13')	1.3991(18)
C(9')-C(10')	1.4039(18)	C(9')-H(9'A)	0.9500
C(10')-C(11')	1.386(2)	C(10')-H(10B)	0.9500
C(11')-C(12')	1.393(2)	C(11')-H(11B)	0.9500
C(12')-C(13')	1.3842(18)	C(12')-H(12B)	0.9500
C(14')-C(15')	1.5470(17)	C(14')-H(14C)	0.9900
C(14')-H(14D)	0.9900	C(15')-C(16')	1.5149(18)
C(15')-C(18')	1.5170(17)	C(15')-H(15B)	1.0000
O(16')-C(16')	1.2110(17)	C(17')-C(18')	1.5166(17)
C(17')-H(17C)	0.9900	C(17')-H(17D)	0.9900
C(18')-C(19')	1.3280(18)	C(19')-C(20')	1.4970(19)
C(19')-H(19B)	0.9500	C(20')-H(20D)	0.9800
C(20')-H(20E)	0.9800	C(20')-H(20F)	0.9800
C(2)-N(1)-C(13)	111.15(10)	C(2)-N(1)-C(1)	124.44(11)
C(13)-N(1)-C(1)	123.83(11)	N(1)-C(1)-H(1A)	109.5
N(1)-C(1)-H(1B)	109.5	H(1A)-C(1)-H(1B)	109.5
N(1)-C(1)-H(1C)	109.5	H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5	O(2)-C(2)-N(1)	125.19(12)

Table A22. (continued)

O(2)-C(2)-C(7)	126.85(12)	N(1)-C(2)-C(7)	107.91(10)
N(4)-C(3)-C(14)	109.74(10)	N(4)-C(3)-C(7)	101.43(9)
C(14)-C(3)-C(7)	116.14(10)	N(4)-C(3)-H(3A)	109.7
C(14)-C(3)-H(3A)	109.7	C(7)-C(3)-H(3A)	109.7
C(17)-N(4)-C(5)	113.55(10)	C(17)-N(4)-C(3)	110.83(9)
C(5)-N(4)-C(3)	101.58(9)	N(4)-C(5)-C(6)	101.12(9)
N(4)-C(5)-C(16)	110.38(10)	C(6)-C(5)-C(16)	111.27(10)
N(4)-C(5)-H(5A)	111.2	C(6)-C(5)-H(5A)	111.2
C(16)-C(5)-H(5A)	111.2	C(5)-C(6)-C(7)	103.53(9)
C(5)-C(6)-H(6A)	111.1	C(7)-C(6)-H(6A)	111.1
C(5)-C(6)-H(6B)	111.1	C(7)-C(6)-H(6B)	111.1
H(6A)-C(6)-H(6B)	109.0	C(8)-C(7)-C(2)	101.70(10)
C(8)-C(7)-C(6)	114.80(10)	C(2)-C(7)-C(6)	113.86(10)
C(8)-C(7)-C(3)	116.76(9)	C(2)-C(7)-C(3)	106.22(9)
C(6)-C(7)-C(3)	103.57(9)	C(9)-C(8)-C(13)	119.55(12)
C(9)-C(8)-C(7)	131.29(11)	C(13)-C(8)-C(7)	109.02(11)
C(8)-C(9)-C(10)	119.58(12)	C(8)-C(9)-H(9A)	120.2
C(10)-C(9)-H(9A)	120.2	C(11)-C(10)-C(9)	119.65(13)
C(11)-C(10)-H(10A)	120.2	C(9)-C(10)-H(10A)	120.2
C(10)-C(11)-C(12)	121.73(12)	C(10)-C(11)-H(11A)	119.1
C(12)-C(11)-H(11A)	119.1	C(13)-C(12)-C(11)	117.47(12)
C(13)-C(12)-H(12A)	121.3	C(11)-C(12)-H(12A)	121.3
C(12)-C(13)-C(8)	121.91(12)	C(12)-C(13)-N(1)	128.53(12)
C(8)-C(13)-N(1)	109.50(11)	C(15)-C(14)-C(3)	109.55(10)
C(15)-C(14)-H(14A)	109.8	C(3)-C(14)-H(14A)	109.8
C(15)-C(14)-H(14B)	109.8	C(3)-C(14)-H(14B)	109.8
H(14A)-C(14)-H(14B)	108.2	C(18)-C(15)-C(16)	102.71(10)
C(18)-C(15)-C(14)	108.46(10)	C(16)-C(15)-C(14)	108.07(10)
C(18)-C(15)-H(15A)	112.4	C(16)-C(15)-H(15A)	112.4
C(14)-C(15)-H(15A)	112.4	O(16)-C(16)-C(15)	124.79(12)
O(16)-C(16)-C(5)	123.74(11)	C(15)-C(16)-C(5)	111.45(10)
N(4)-C(17)-C(18)	111.20(10)	N(4)-C(17)-H(17A)	109.4
C(18)-C(17)-H(17A)	109.4	N(4)-C(17)-H(17B)	109.4
C(18)-C(17)-H(17B)	109.4	H(17A)-C(17)-H(17B)	108.0
C(19)-C(18)-C(17)	123.13(11)	C(19)-C(18)-C(15)	126.59(11)
C(17)-C(18)-C(15)	109.99(10)	C(18)-C(19)-C(20)	127.90(12)
C(18)-C(19)-H(19A)	116.1	C(20)-C(19)-H(19A)	116.1
C(19)-C(20)-H(20A)	109.5	C(19)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5	C(19)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5	H(20B)-C(20)-H(20C)	109.5
C(2')-N(1')-C(13')	111.01(11)	C(2')-N(1')-C(1')	123.28(12)
C(13')-N(1')-C(1')	125.15(12)	N(1')-C(1')-H(1'A)	109.5
N(1')-C(1')-H(1'B)	109.5	H(1'A)-C(1')-H(1'B)	109.5
N(1')-C(1')-H(1'C)	109.5	H(1'A)-C(1')-H(1'C)	109.5
H(1'B)-C(1')-H(1'C)	109.5	O(2')-C(2')-N(1')	124.86(12)
O(2')-C(2')-C(7')	126.88(12)	N(1')-C(2')-C(7')	108.27(10)
N(4')-C(3')-C(14')	109.60(10)	N(4')-C(3')-C(7')	101.29(9)
C(14')-C(3')-C(7')	115.98(10)	N(4')-C(3')-H(3'A)	109.9
C(14')-C(3')-H(3'A)	109.9	C(7')-C(3')-H(3'A)	109.9
C(17')-N(4')-C(5')	113.17(10)	C(17')-N(4')-C(3')	110.94(9)
C(5')-N(4')-C(3')	101.23(9)	N(4')-C(5')-C(6')	101.75(10)
N(4')-C(5')-C(16')	110.97(10)	C(6')-C(5')-C(16')	109.65(10)
N(4')-C(5')-H(5'A)	111.4	C(6')-C(5')-H(5'A)	111.4

Table A22. (continued)

C(16')-C(5')-H(5'A)	111.4	C(5')-C(6')-C(7')	103.37(10)
C(5')-C(6')-H(6'A)	111.1	C(7')-C(6')-H(6'A)	111.1
C(5')-C(6')-H(6'B)	111.1	C(7')-C(6')-H(6'B)	111.1
H(6'A)-C(6')-H(6'B)	109.1	C(8')-C(7')-C(2')	101.89(10)
C(8')-C(7')-C(6')	116.11(10)	C(2')-C(7')-C(6')	111.39(10)
C(8')-C(7')-C(3')	116.63(10)	C(2')-C(7')-C(3')	106.94(10)
C(6')-C(7')-C(3')	103.71(10)	C(9')-C(8')-C(13')	119.58(11)
C(9')-C(8')-C(7')	131.73(11)	C(13')-C(8')-C(7')	108.64(10)
C(8')-C(9')-C(10')	118.75(12)	C(8')-C(9')-H(9'A)	120.6
C(10')-C(9')-H(9'A)	120.6	C(11')-C(10')-C(9')	120.54(13)
C(11')-C(10')-H(10B)	119.7	C(9')-C(10')-H(10B)	119.7
C(10')-C(11')-C(12')	121.42(12)	C(10')-C(11')-H(11B)	119.3
C(12')-C(11')-H(11B)	119.3	C(13')-C(12')-C(11')	117.17(13)
C(13')-C(12')-H(12B)	121.4	C(11')-C(12')-H(12B)	121.4
C(12')-C(13')-C(8')	122.50(12)	C(12')-C(13')-N(1')	127.80(12)
C(8')-C(13')-N(1')	109.64(11)	C(15')-C(14')-C(3')	109.57(10)
C(15')-C(14')-H(14C)	109.8	C(3')-C(14')-H(14C)	109.8
C(15')-C(14')-H(14D)	109.8	C(3')-C(14')-H(14D)	109.8
H(14C)-C(14')-H(14D)	108.2	C(16')-C(15')-C(18')	103.12(10)
C(16')-C(15')-C(14')	107.41(10)	C(18')-C(15')-C(14')	109.35(10)
C(16')-C(15')-H(15B)	112.2	C(18')-C(15')-H(15B)	112.2
C(14')-C(15')-H(15B)	112.2	O(16')-C(16')-C(15')	125.86(12)
O(16')-C(16')-C(5')	123.12(12)	C(15')-C(16')-C(5')	110.99(11)
N(4')-C(17')-C(18')	110.87(10)	N(4')-C(17')-H(17C)	109.5
C(18')-C(17')-H(17C)	109.5	N(4')-C(17')-H(17D)	109.5
C(18')-C(17')-H(17D)	109.5	H(17C)-C(17')-H(17D)	108.1
C(19')-C(18')-C(15')	126.23(12)	C(19')-C(18')-C(17')	123.45(11)
C(15')-C(18')-C(17')	110.05(10)	C(18')-C(19')-C(20')	126.89(12)
C(18')-C(19')-H(19B)	116.6	C(20')-C(19')-H(19B)	116.6
C(19')-C(20')-H(20D)	109.5	C(19')-C(20')-H(20E)	109.5
H(20D)-C(20')-H(20E)	109.5	C(19')-C(20')-H(20F)	109.5
H(20D)-C(20')-H(20F)	109.5	H(20E)-C(20')-H(20F)	109.5

Table A23. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **857**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	20(1)	17(1)	22(1)	8(1)	6(1)	4(1)
C(1)	24(1)	20(1)	26(1)	10(1)	4(1)	2(1)
O(2)	23(1)	29(1)	35(1)	14(1)	13(1)	11(1)
C(2)	21(1)	21(1)	20(1)	10(1)	7(1)	8(1)
C(3)	21(1)	17(1)	18(1)	7(1)	7(1)	8(1)
N(4)	21(1)	18(1)	23(1)	9(1)	8(1)	9(1)
C(5)	23(1)	18(1)	19(1)	6(1)	9(1)	9(1)
C(6)	24(1)	18(1)	17(1)	7(1)	8(1)	9(1)
C(7)	19(1)	17(1)	19(1)	7(1)	7(1)	7(1)
C(8)	23(1)	18(1)	17(1)	8(1)	8(1)	9(1)
C(9)	23(1)	22(1)	22(1)	9(1)	9(1)	9(1)
C(10)	27(1)	29(1)	23(1)	12(1)	11(1)	15(1)
C(11)	36(1)	26(1)	22(1)	11(1)	12(1)	20(1)
C(12)	34(1)	19(1)	20(1)	8(1)	8(1)	11(1)
C(13)	24(1)	20(1)	16(1)	8(1)	6(1)	9(1)
C(14)	28(1)	20(1)	20(1)	9(1)	11(1)	11(1)
C(15)	19(1)	19(1)	23(1)	10(1)	10(1)	10(1)
O(16)	23(1)	35(1)	28(1)	14(1)	3(1)	8(1)
C(16)	21(1)	17(1)	23(1)	8(1)	7(1)	9(1)
C(17)	21(1)	24(1)	35(1)	17(1)	13(1)	13(1)
C(18)	19(1)	21(1)	21(1)	9(1)	8(1)	10(1)
C(19)	21(1)	20(1)	23(1)	8(1)	7(1)	10(1)
C(20)	21(1)	19(1)	31(1)	9(1)	7(1)	7(1)
N(1')	20(1)	21(1)	24(1)	4(1)	8(1)	8(1)
C(1')	22(1)	24(1)	36(1)	-1(1)	9(1)	5(1)
O(2')	33(1)	36(1)	20(1)	5(1)	3(1)	20(1)
C(2')	20(1)	25(1)	22(1)	4(1)	8(1)	12(1)
C(3')	20(1)	19(1)	19(1)	7(1)	7(1)	10(1)
N(4')	24(1)	20(1)	19(1)	8(1)	7(1)	12(1)
C(5')	24(1)	22(1)	20(1)	10(1)	8(1)	10(1)
C(6')	24(1)	26(1)	23(1)	12(1)	12(1)	13(1)
C(7')	19(1)	20(1)	18(1)	7(1)	6(1)	10(1)
C(8')	19(1)	21(1)	22(1)	10(1)	10(1)	12(1)
C(9')	21(1)	26(1)	24(1)	11(1)	9(1)	12(1)
C(10')	26(1)	39(1)	28(1)	19(1)	12(1)	20(1)
C(11')	36(1)	32(1)	38(1)	23(1)	23(1)	24(1)
C(12')	31(1)	22(1)	36(1)	13(1)	21(1)	14(1)
C(13')	21(1)	22(1)	26(1)	8(1)	13(1)	12(1)
C(14')	23(1)	20(1)	19(1)	8(1)	9(1)	11(1)
C(15')	23(1)	20(1)	17(1)	6(1)	5(1)	10(1)
O(16')	24(1)	41(1)	30(1)	11(1)	6(1)	9(1)
C(16')	24(1)	22(1)	23(1)	10(1)	7(1)	9(1)
C(17')	30(1)	23(1)	19(1)	7(1)	5(1)	16(1)
C(18')	26(1)	21(1)	18(1)	8(1)	7(1)	10(1)
C(19')	30(1)	22(1)	23(1)	9(1)	7(1)	11(1)
C(20')	38(1)	22(1)	26(1)	5(1)	5(1)	11(1)

Table A24. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **857**.

	x	y	z	U(eq)
H(1A)	11397	13211	4315	39
H(1B)	10645	13842	5025	39
H(1C)	10292	13823	3912	39
H(3A)	8550	9858	4569	23
H(5A)	6391	7364	1831	23
H(6A)	5780	9216	1827	24
H(6B)	7528	9334	1895	24
H(9A)	4193	9800	2933	26
H(10A)	3312	11338	3338	29
H(11A)	5127	13347	4142	30
H(12A)	7832	13882	4491	29
H(14A)	6538	8947	5018	26
H(14B)	5584	9453	4332	26
H(15A)	4005	7328	3748	23
H(17A)	8281	7742	4420	28
H(17B)	7792	6771	3335	28
H(19A)	5928	5271	3750	25
H(20A)	3689	4779	4286	37
H(20B)	3102	4249	3098	37
H(20C)	3037	5490	3667	37
H(1'A)	11651	8279	4043	47
H(1'B)	10678	8865	3466	47
H(1'C)	12165	8745	3215	47
H(3'A)	10859	4793	1767	22
H(5'A)	7189	2437	2078	25
H(6'A)	7629	4441	2800	27
H(6'B)	6431	4111	1708	27
H(9'A)	6494	4463	-25	27
H(10B)	6161	5871	-743	33
H(11B)	7784	7919	64	34
H(12B)	9737	8639	1632	32
H(14C)	8660	4050	14	24
H(14D)	10063	3616	164	24
H(15B)	7417	1890	-668	25
H(17C)	9712	1889	2008	28
H(17D)	10900	2748	1632	28
H(19B)	9010	144	509	30
H(20D)	8070	-705	-1266	47
H(20E)	7069	89	-1299	47
H(20F)	6570	-1018	-922	47

Table A25. Torsion angles [°] for **857**.

C(13)-N(1)-C(2)-O(2)	174.83(11)	C(1)-N(1)-C(2)-O(2)	3.29(19)
C(13)-N(1)-C(2)-C(7)	-7.60(13)	C(1)-N(1)-C(2)-C(7)	-179.14(10)
C(14)-C(3)-N(4)-C(17)	-45.89(13)	C(7)-C(3)-N(4)-C(17)	-169.26(9)
C(14)-C(3)-N(4)-C(5)	75.05(11)	C(7)-C(3)-N(4)-C(5)	-48.32(11)
C(17)-N(4)-C(5)-C(6)	172.65(10)	C(3)-N(4)-C(5)-C(6)	53.62(11)
C(17)-N(4)-C(5)-C(16)	54.78(13)	C(3)-N(4)-C(5)-C(16)	-64.25(11)
N(4)-C(5)-C(6)-C(7)	-36.42(11)	C(16)-C(5)-C(6)-C(7)	80.79(12)
O(2)-C(2)-C(7)-C(8)	-174.10(12)	N(1)-C(2)-C(7)-C(8)	8.38(12)
O(2)-C(2)-C(7)-C(6)	-50.05(16)	N(1)-C(2)-C(7)-C(6)	132.43(10)
O(2)-C(2)-C(7)-C(3)	63.27(15)	N(1)-C(2)-C(7)-C(3)	-114.25(10)
C(5)-C(6)-C(7)-C(8)	-121.34(11)	C(5)-C(6)-C(7)-C(2)	122.00(11)
C(5)-C(6)-C(7)-C(3)	7.11(12)	N(4)-C(3)-C(7)-C(8)	151.60(10)
C(14)-C(3)-C(7)-C(8)	32.72(15)	N(4)-C(3)-C(7)-C(2)	-95.86(11)
C(14)-C(3)-C(7)-C(2)	145.26(10)	N(4)-C(3)-C(7)-C(6)	24.37(11)
C(14)-C(3)-C(7)-C(6)	-94.51(12)	C(2)-C(7)-C(8)-C(9)	169.06(12)
C(6)-C(7)-C(8)-C(9)	45.64(17)	C(3)-C(7)-C(8)-C(9)	-75.86(16)
C(2)-C(7)-C(8)-C(13)	-6.41(12)	C(6)-C(7)-C(8)-C(13)	-129.83(11)
C(3)-C(7)-C(8)-C(13)	108.67(11)	C(13)-C(8)-C(9)-C(10)	-2.90(17)
C(7)-C(8)-C(9)-C(10)	-177.98(11)	C(8)-C(9)-C(10)-C(11)	0.15(18)
C(9)-C(10)-C(11)-C(12)	1.84(18)	C(10)-C(11)-C(12)-C(13)	-0.99(18)
C(11)-C(12)-C(13)-C(8)	-1.85(18)	C(11)-C(12)-C(13)-N(1)	175.18(11)
C(9)-C(8)-C(13)-C(12)	3.83(17)	C(7)-C(8)-C(13)-C(12)	179.92(11)
C(9)-C(8)-C(13)-N(1)	-173.71(10)	C(7)-C(8)-C(13)-N(1)	2.38(13)
C(2)-N(1)-C(13)-C(12)	-173.89(12)	C(1)-N(1)-C(13)-C(12)	-2.29(19)
C(2)-N(1)-C(13)-C(8)	3.44(13)	C(1)-N(1)-C(13)-C(8)	175.04(10)
N(4)-C(3)-C(14)-C(15)	-18.61(13)	C(7)-C(3)-C(14)-C(15)	95.63(12)
C(3)-C(14)-C(15)-C(18)	65.62(12)	C(3)-C(14)-C(15)-C(16)	-45.04(13)
C(18)-C(15)-C(16)-O(16)	119.95(13)	C(14)-C(15)-C(16)-O(16)	-125.53(13)
C(18)-C(15)-C(16)-C(5)	-59.04(12)	C(14)-C(15)-C(16)-C(5)	55.48(13)
N(4)-C(5)-C(16)-O(16)	-178.70(12)	C(6)-C(5)-C(16)-O(16)	69.87(16)
N(4)-C(5)-C(16)-C(15)	0.31(14)	C(6)-C(5)-C(16)-C(15)	-111.13(11)
C(5)-N(4)-C(17)-C(18)	-45.01(14)	C(3)-N(4)-C(17)-C(18)	68.57(13)
N(4)-C(17)-C(18)-C(19)	155.55(12)	N(4)-C(17)-C(18)-C(15)	-18.64(14)
C(16)-C(15)-C(18)-C(19)	-104.38(14)	C(14)-C(15)-C(18)-C(19)	141.39(13)
C(16)-C(15)-C(18)-C(17)	69.56(12)	C(14)-C(15)-C(18)-C(17)	-44.67(13)
C(17)-C(18)-C(19)-C(20)	-177.76(12)	C(15)-C(18)-C(19)-C(20)	-4.6(2)
C(13')-N(1')-C(2')-O(2')	-174.31(12)	C(1')-N(1')-C(2')-O(2')	-2.5(2)
C(13')-N(1')-C(2')-C(7')	6.03(14)	C(1')-N(1')-C(2')-C(7')	177.86(11)
C(14')-C(3')-N(4')-C(17')	46.01(13)	C(7')-C(3')-N(4')-C(17')	169.05(10)
C(14')-C(3')-N(4')-C(5')	-74.35(11)	C(7')-C(3')-N(4')-C(5')	48.69(11)
C(17')-N(4')-C(5')-C(6')	-172.06(9)	C(3')-N(4')-C(5')-C(6')	-53.29(11)
C(17')-N(4')-C(5')-C(16')	-55.48(13)	C(3')-N(4')-C(5')-C(16')	63.29(12)
N(4')-C(5')-C(6')-C(7')	35.38(11)	C(16')-C(5')-C(6')-C(7')	-82.16(12)
O(2')-C(2')-C(7')-C(8')	172.98(13)	N(1')-C(2')-C(7')-C(8')	-7.37(13)
O(2')-C(2')-C(7')-C(6')	48.54(17)	N(1')-C(2')-C(7')-C(6')	-131.82(11)
O(2')-C(2')-C(7')-C(3')	-64.12(16)	N(1')-C(2')-C(7')-C(3')	115.52(11)
C(5')-C(6')-C(7')-C(8')	123.68(11)	C(5')-C(6')-C(7')-C(2')	-120.31(11)
C(5')-C(6')-C(7')-C(3')	-5.62(12)	N(4')-C(3')-C(7')-C(8')	-154.63(10)
C(14')-C(3')-C(7')-C(8')	-36.09(15)	N(4')-C(3')-C(7')-C(2')	92.18(11)
C(14')-C(3')-C(7')-C(2')	-149.28(10)	N(4')-C(3')-C(7')-C(6')	-25.65(11)
C(14')-C(3')-C(7')-C(6')	92.89(11)	C(2')-C(7')-C(8')-C(9')	-171.39(13)
C(6')-C(7')-C(8')-C(9')	-50.17(18)	C(3')-C(7')-C(8')-C(9')	72.58(17)
C(2')-C(7')-C(8')-C(13')	6.23(13)	C(6')-C(7')-C(8')-C(13')	127.46(11)

Table A25. (continued)

C(3')-C(7')-C(8')-C(13')	-109.79(12)	C(13')-C(8')-C(9')-C(10')	1.75(18)
C(7')-C(8')-C(9')-C(10')	179.16(12)	C(8')-C(9')-C(10')-C(11')	0.0(2)
C(9')-C(10')-C(11')-C(12')	-1.2(2)	C(10')-C(11')-C(12')-C(13')	0.5(2)
C(11')-C(12')-C(13')-C(8')	1.34(19)	C(11')-C(12')-C(13')-N(1')	-175.49(12)
C(9')-C(8')-C(13')-C(12')	-2.50(19)	C(7')-C(8')-C(13')-C(12')	179.54(11)
C(9')-C(8')-C(13')-N(1')	174.84(11)	C(7')-C(8')-C(13')-N(1')	-3.12(14)
C(2')-N(1')-C(13')-C(12')	175.23(12)	C(1')-N(1')-C(13')-C(12')	3.6(2)
C(2')-N(1')-C(13')-C(8')	-1.93(14)	C(1')-N(1')-C(13')-C(8')	-173.57(12)
N(4')-C(3')-C(14')-C(15')	18.22(13)	C(7')-C(3')-C(14')-C(15')	-95.64(12)
C(3')-C(14')-C(15')-C(16')	46.35(13)	C(3')-C(14')-C(15')-C(18')	-64.89(13)
C(18')-C(15')-C(16')-O(16')	-123.45(14)	C(14')-C(15')-C(16')-O(16')	121.11(14)
C(18')-C(15')-C(16')-C(5')	58.08(12)	C(14')-C(15')-C(16')-C(5')	-57.37(12)
N(4')-C(5')-C(16')-O(16')	-177.22(12)	C(6')-C(5')-C(16')-O(16')	-65.60(16)
N(4')-C(5')-C(16')-C(15')	1.31(14)	C(6')-C(5')-C(16')-C(15')	112.92(12)
C(5')-N(4')-C(17')-C(18')	43.88(14)	C(3')-N(4')-C(17')-C(18')	-69.11(13)
C(16')-C(15')-C(18')-C(19')	103.67(15)	C(14')-C(15')-C(18')-C(19')	-142.28(13)
C(16')-C(15')-C(18')-C(17')	-70.49(13)	C(14')-C(15')-C(18')-C(17')	43.56(14)
N(4')-C(17')-C(18')-C(19')	-154.58(13)	N(4')-C(17')-C(18')-C(15')	19.77(15)
C(15')-C(18')-C(19')-C(20')	5.7(2)	C(17')-C(18')-C(19')-C(20')	179.10(14)

Table A26. Crystal data and structure refinement for **878**.

Empirical formula	$C_{20}H_{24}N_2O_2$	
Formula weight	324.41	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 11.7475(3) Å	α= 90°
	b = 6.09920(10) Å	β= 97.397(2)°
	c = 11.9622(3) Å	γ = 90°
Volume	849.96(3) $Å^3$	
Z	2	
Density (calculated)	1.268 Mg/m^3	
Absorption coefficient	0.651 mm^{-1}	
F(000)	348	
Crystal size	0.102 x 0.065 x 0.011 mm^3	
θ range for data collection	3.73 to 68.10°	
Index ranges	-12<=h<=11, -7<=k<=7, -12<=l<=14	
Reflections collected	4426	
Independent reflections	2316 [R(int) = 0.0198]	
Completeness to θ = 68.10°	86.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9929 and 0.9365	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2316 / 1 / 219	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2σ(I)]	R1 = 0.0340, wR2 = 0.0899	
R indices (all data)	R1 = 0.0367, wR2 = 0.0918	
Absolute structure parameter	0.2(3)	
Largest diff. peak and hole	0.141 and -0.160 $e.Å^{-3}$	

Table A27. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **878**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6560(2)	2417(3)	1289(2)	29(1)
O(1)	6911(1)	3634(2)	598(1)	39(1)
N(2)	5467(2)	2444(3)	1549(1)	32(1)
C(2)	4585(2)	3910(4)	1027(2)	45(1)
C(3)	5277(2)	689(3)	2270(2)	31(1)
C(4)	4271(2)	148(4)	2693(2)	41(1)
C(5)	4314(2)	-1671(4)	3402(2)	48(1)
C(6)	5301(2)	-2900(4)	3654(2)	47(1)
C(7)	6297(2)	-2329(4)	3200(2)	39(1)
C(8)	6287(2)	-505(3)	2522(2)	29(1)
C(9)	7224(2)	586(3)	1969(2)	27(1)
C(10)	7893(2)	-918(3)	1233(2)	31(1)
C(11)	9102(2)	-1098(3)	1882(2)	28(1)
C(12)	9977(2)	559(3)	1502(2)	28(1)
C(13)	10144(2)	2409(3)	2382(2)	28(1)
C(14)	8949(2)	3296(3)	2545(2)	31(1)
C(15)	8200(2)	1378(3)	2897(2)	28(1)
N(16)	8879(2)	-667(3)	3048(1)	27(1)
C(17)	9940(2)	-411(4)	3831(2)	33(1)
C(18)	10670(2)	1472(3)	3488(2)	29(1)
C(19)	11602(2)	2160(4)	4135(2)	35(1)
C(20)	12354(2)	4038(4)	3919(2)	45(1)
C(21)	11084(2)	-556(4)	1315(2)	35(1)
O(21)	11818(1)	965(3)	873(1)	48(1)

Table A28. Bond lengths [Å] and angles [°] for **878**.

C(1)-O(1)	1.222(2)	C(1)-N(2)	1.359(3)
C(1)-C(9)	1.535(3)	N(2)-C(3)	1.411(3)
N(2)-C(2)	1.447(3)	C(2)-H(2A)	0.9800
C(2)-H(2B)	0.9800	C(2)-H(2C)	0.9800
C(3)-C(4)	1.384(3)	C(3)-C(8)	1.392(3)
C(4)-C(5)	1.394(4)	C(4)-H(4A)	0.9500
C(5)-C(6)	1.381(4)	C(5)-H(5A)	0.9500
C(6)-C(7)	1.396(3)	C(6)-H(6A)	0.9500
C(7)-C(8)	1.376(3)	C(7)-H(7A)	0.9500
C(8)-C(9)	1.509(3)	C(9)-C(10)	1.554(3)
C(9)-C(15)	1.566(3)	C(10)-C(11)	1.533(3)
C(10)-H(10A)	0.9900	C(10)-H(10B)	0.9900
C(11)-N(16)	1.475(3)	C(11)-C(12)	1.550(3)
C(11)-H(11A)	1.0000	C(12)-C(21)	1.510(3)
C(12)-C(13)	1.538(3)	C(12)-H(12A)	1.0000
C(13)-C(18)	1.499(3)	C(13)-C(14)	1.540(3)
C(13)-H(13A)	1.0000	C(14)-C(15)	1.555(3)
C(14)-H(14A)	0.9900	C(14)-H(14B)	0.9900
C(15)-N(16)	1.479(2)	C(15)-H(15A)	1.0000
N(16)-C(17)	1.468(3)	C(17)-C(18)	1.521(3)
C(17)-H(17A)	0.9900	C(17)-H(17B)	0.9900
C(18)-C(19)	1.325(3)	C(19)-C(20)	1.490(3)
C(19)-H(19A)	0.9500	C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800	C(20)-H(20C)	0.9800
C(21)-O(21)	1.415(3)	C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900	O(21)-H(21C)	0.8400
O(1)-C(1)-N(2)	124.0(2)	O(1)-C(1)-C(9)	127.42(19)
N(2)-C(1)-C(9)	108.55(16)	C(1)-N(2)-C(3)	111.05(17)
C(1)-N(2)-C(2)	123.60(18)	C(3)-N(2)-C(2)	124.86(18)
N(2)-C(2)-H(2A)	109.5	N(2)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	109.5	N(2)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2C)	109.5	H(2B)-C(2)-H(2C)	109.5
C(4)-C(3)-C(8)	122.7(2)	C(4)-C(3)-N(2)	127.9(2)
C(8)-C(3)-N(2)	109.39(18)	C(3)-C(4)-C(5)	116.6(2)
C(3)-C(4)-H(4A)	121.7	C(5)-C(4)-H(4A)	121.7
C(6)-C(5)-C(4)	121.8(2)	C(6)-C(5)-H(5A)	119.1
C(4)-C(5)-H(5A)	119.1	C(5)-C(6)-C(7)	120.2(2)
C(5)-C(6)-H(6A)	119.9	C(7)-C(6)-H(6A)	119.9
C(8)-C(7)-C(6)	119.1(2)	C(8)-C(7)-H(7A)	120.4
C(6)-C(7)-H(7A)	120.4	C(7)-C(8)-C(3)	119.5(2)
C(7)-C(8)-C(9)	131.6(2)	C(3)-C(8)-C(9)	108.89(17)
C(8)-C(9)-C(1)	101.75(16)	C(8)-C(9)-C(10)	116.01(16)
C(1)-C(9)-C(10)	112.90(16)	C(8)-C(9)-C(15)	109.52(16)
C(1)-C(9)-C(15)	115.28(16)	C(10)-C(9)-C(15)	101.91(15)
C(11)-C(10)-C(9)	105.00(16)	C(11)-C(10)-H(10A)	110.7
C(9)-C(10)-H(10A)	110.7	C(11)-C(10)-H(10B)	110.7
C(9)-C(10)-H(10B)	110.7	H(10A)-C(10)-H(10B)	108.8
N(16)-C(11)-C(10)	101.53(16)	N(16)-C(11)-C(12)	111.48(16)
C(10)-C(11)-C(12)	114.26(16)	N(16)-C(11)-H(11A)	109.8
C(10)-C(11)-H(11A)	109.8	C(12)-C(11)-H(11A)	109.8
C(21)-C(12)-C(13)	113.25(18)	C(21)-C(12)-C(11)	111.43(16)
C(13)-C(12)-C(11)	107.98(15)	C(21)-C(12)-H(12A)	108.0

Table A28. (continued)

C(13)-C(12)-H(12A)	108.0	C(11)-C(12)-H(12A)	108.0
C(18)-C(13)-C(14)	107.46(16)	C(18)-C(13)-C(12)	109.05(17)
C(14)-C(13)-C(12)	107.81(17)	C(18)-C(13)-H(13A)	110.8
C(14)-C(13)-H(13A)	110.8	C(12)-C(13)-H(13A)	110.8
C(13)-C(14)-C(15)	109.13(16)	C(13)-C(14)-H(14A)	109.9
C(15)-C(14)-H(14A)	109.9	C(13)-C(14)-H(14B)	109.9
C(15)-C(14)-H(14B)	109.9	H(14A)-C(14)-H(14B)	108.3
N(16)-C(15)-C(14)	110.58(16)	N(16)-C(15)-C(9)	99.23(15)
C(14)-C(15)-C(9)	115.38(17)	N(16)-C(15)-H(15A)	110.4
C(14)-C(15)-H(15A)	110.4	C(9)-C(15)-H(15A)	110.4
C(17)-N(16)-C(11)	112.49(16)	C(17)-N(16)-C(15)	112.88(16)
C(11)-N(16)-C(15)	101.20(15)	N(16)-C(17)-C(18)	111.68(17)
N(16)-C(17)-H(17A)	109.3	C(18)-C(17)-H(17A)	109.3
N(16)-C(17)-H(17B)	109.3	C(18)-C(17)-H(17B)	109.3
H(17A)-C(17)-H(17B)	107.9	C(19)-C(18)-C(13)	127.6(2)
C(19)-C(18)-C(17)	122.2(2)	C(13)-C(18)-C(17)	110.11(18)
C(18)-C(19)-C(20)	127.3(2)	C(18)-C(19)-H(19A)	116.3
C(20)-C(19)-H(19A)	116.3	C(19)-C(20)-H(20A)	109.5
C(19)-C(20)-H(20B)	109.5	H(20A)-C(20)-H(20B)	109.5
C(19)-C(20)-H(20C)	109.5	H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5	O(21)-C(21)-C(12)	109.77(18)
O(21)-C(21)-H(21A)	109.7	C(12)-C(21)-H(21A)	109.7
O(21)-C(21)-H(21B)	109.7	C(12)-C(21)-H(21B)	109.7
H(21A)-C(21)-H(21B)	108.2	C(21)-O(21)-H(21C)	109.5

Table A29. Anisotropic displacement parameters ($Å^2$ x 10^3) for **878**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	32(1)	24(1)	31(1)	-1(1)	4(1)	-2(1)
O(1)	43(1)	36(1)	40(1)	10(1)	9(1)	-3(1)
N(2)	26(1)	30(1)	39(1)	2(1)	3(1)	2(1)
C(2)	39(2)	40(1)	54(1)	8(1)	-1(1)	8(1)
C(3)	30(1)	31(1)	32(1)	-3(1)	4(1)	-4(1)
C(4)	26(2)	49(1)	51(1)	-4(1)	10(1)	-7(1)
C(5)	40(2)	56(2)	51(1)	1(1)	14(1)	-21(1)
C(6)	47(2)	48(1)	45(1)	12(1)	2(1)	-22(1)
C(7)	38(2)	37(1)	40(1)	9(1)	-4(1)	-11(1)
C(8)	27(1)	29(1)	31(1)	0(1)	1(1)	-7(1)
C(9)	24(1)	24(1)	33(1)	2(1)	4(1)	-1(1)
C(10)	31(1)	25(1)	36(1)	-5(1)	3(1)	-3(1)
C(11)	29(1)	21(1)	35(1)	-2(1)	4(1)	0(1)
C(12)	28(1)	28(1)	28(1)	4(1)	4(1)	-1(1)
C(13)	25(1)	24(1)	38(1)	2(1)	7(1)	-5(1)
C(14)	28(1)	21(1)	42(1)	-2(1)	4(1)	-3(1)
C(15)	29(1)	26(1)	29(1)	-1(1)	5(1)	0(1)
N(16)	25(1)	24(1)	33(1)	3(1)	2(1)	-3(1)
C(17)	32(1)	35(1)	32(1)	5(1)	2(1)	-4(1)
C(18)	30(1)	30(1)	30(1)	-4(1)	9(1)	-2(1)
C(19)	32(1)	42(1)	33(1)	-4(1)	4(1)	-5(1)
C(20)	38(2)	47(1)	49(1)	-10(1)	8(1)	-10(1)
C(21)	37(2)	34(1)	36(1)	-5(1)	9(1)	-3(1)
O(21)	49(1)	44(1)	57(1)	-1(1)	29(1)	-6(1)

Table A30. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **878**.

	x	y	z	U(eq)
H(2A)	4905	4842	477	68
H(2B)	4309	4831	1607	68
H(2C)	3946	3050	645	68
H(4A)	3587	975	2510	50
H(5A)	3644	-2078	3721	58
H(6A)	5302	-4136	4137	56
H(7A)	6973	-3190	3357	47
H(10A)	7527	-2381	1137	37
H(10B)	7919	-262	480	37
H(11A)	9397	-2626	1823	33
H(12A)	9632	1214	769	34
H(13A)	10637	3602	2129	34
H(14A)	8580	3959	1834	37
H(14B)	9025	4442	3136	37
H(15A)	7876	1753	3606	33
H(17A)	10389	-1788	3850	39
H(17B)	9744	-139	4599	39
H(19A)	11814	1365	4813	42
H(20A)	13158	3569	4037	67
H(20B)	12241	5239	4438	67
H(20C)	12157	4542	3141	67
H(21A)	11465	-1150	2038	42
H(21B)	10919	-1793	783	42
H(21C)	12208	316	433	72

Table A31. Torsion angles [°] for **878**.

O(1)-C(1)-N(2)-C(3)	172.88(19)	C(9)-C(1)-N(2)-C(3)	-5.1(2)
O(1)-C(1)-N(2)-C(2)	0.5(3)	C(9)-C(1)-N(2)-C(2)	-177.41(19)
C(1)-N(2)-C(3)-C(4)	-178.4(2)	C(2)-N(2)-C(3)-C(4)	-6.2(3)
C(1)-N(2)-C(3)-C(8)	1.7(2)	C(2)-N(2)-C(3)-C(8)	173.9(2)
C(8)-C(3)-C(4)-C(5)	0.4(3)	N(2)-C(3)-C(4)-C(5)	-179.5(2)
C(3)-C(4)-C(5)-C(6)	-1.2(4)	C(4)-C(5)-C(6)-C(7)	0.3(4)
C(5)-C(6)-C(7)-C(8)	1.4(4)	C(6)-C(7)-C(8)-C(3)	-2.2(3)
C(6)-C(7)-C(8)-C(9)	176.2(2)	C(4)-C(3)-C(8)-C(7)	1.4(3)
N(2)-C(3)-C(8)-C(7)	-178.76(18)	C(4)-C(3)-C(8)-C(9)	-177.4(2)
N(2)-C(3)-C(8)-C(9)	2.5(2)	C(7)-C(8)-C(9)-C(1)	176.3(2)
C(3)-C(8)-C(9)-C(1)	-5.1(2)	C(7)-C(8)-C(9)-C(10)	53.4(3)
C(3)-C(8)-C(9)-C(10)	-128.03(19)	C(7)-C(8)-C(9)-C(15)	-61.2(3)
C(3)-C(8)-C(9)-C(15)	117.36(19)	O(1)-C(1)-C(9)-C(8)	-171.8(2)
N(2)-C(1)-C(9)-C(8)	6.1(2)	O(1)-C(1)-C(9)-C(10)	-46.7(3)
N(2)-C(1)-C(9)-C(10)	131.14(17)	O(1)-C(1)-C(9)-C(15)	69.8(3)
N(2)-C(1)-C(9)-C(15)	-112.30(19)	C(8)-C(9)-C(10)-C(11)	-111.20(19)
C(1)-C(9)-C(10)-C(11)	131.93(17)	C(15)-C(9)-C(10)-C(11)	7.67(18)
C(9)-C(10)-C(11)-N(16)	25.07(18)	C(9)-C(10)-C(11)-C(12)	-95.05(18)
N(16)-C(11)-C(12)-C(21)	113.65(19)	C(10)-C(11)-C(12)-C(21)	-131.96(18)
N(16)-C(11)-C(12)-C(13)	-11.3(2)	C(10)-C(11)-C(12)-C(13)	103.06(19)
C(21)-C(12)-C(13)-C(18)	-60.0(2)	C(11)-C(12)-C(13)-C(18)	63.9(2)
C(21)-C(12)-C(13)-C(14)	-176.34(17)	C(11)-C(12)-C(13)-C(14)	-52.5(2)
C(18)-C(13)-C(14)-C(15)	-60.7(2)	C(12)-C(13)-C(14)-C(15)	56.7(2)
C(13)-C(14)-C(15)-N(16)	4.0(2)	C(13)-C(14)-C(15)-C(9)	-107.5(2)
C(8)-C(9)-C(15)-N(16)	85.92(18)	C(1)-C(9)-C(15)-N(16)	-160.09(15)
C(10)-C(9)-C(15)-N(16)	-37.46(17)	C(8)-C(9)-C(15)-C(14)	-155.96(16)
C(1)-C(9)-C(15)-C(14)	-42.0(2)	C(10)-C(9)-C(15)-C(14)	80.66(19)
C(10)-C(11)-N(16)-C(17)	-171.24(15)	C(12)-C(11)-N(16)-C(17)	-49.2(2)
C(10)-C(11)-N(16)-C(15)	-50.52(17)	C(12)-C(11)-N(16)-C(15)	71.55(19)
C(14)-C(15)-N(16)-C(17)	54.0(2)	C(9)-C(15)-N(16)-C(17)	175.61(15)
C(14)-C(15)-N(16)-C(11)	-66.5(2)	C(9)-C(15)-N(16)-C(11)	55.16(17)
C(11)-N(16)-C(17)-C(18)	59.4(2)	C(15)-N(16)-C(17)-C(18)	-54.3(2)
C(14)-C(13)-C(18)-C(19)	-115.8(2)	C(12)-C(13)-C(18)-C(19)	127.5(2)
C(14)-C(13)-C(18)-C(17)	61.6(2)	C(12)-C(13)-C(18)-C(17)	-55.0(2)
N(16)-C(17)-C(18)-C(19)	172.44(19)	N(16)-C(17)-C(18)-C(13)	-5.1(2)
C(13)-C(18)-C(19)-C(20)	0.1(4)	C(17)-C(18)-C(19)-C(20)	-177.0(2)
C(13)-C(12)-C(21)-O(21)	-63.3(2)	C(11)-C(12)-C(21)-O(21)	174.75(17)

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