New Small Molecule Precursors with Labile Protecting Groups for the Synthesis of Riccardin C Analogs

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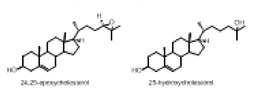
Liver X Receptor

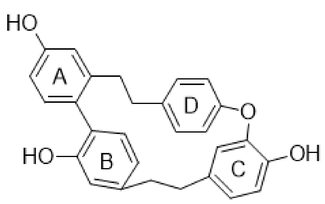
- Member of a nuclear receptor superfamily, proteins activating transcription of genes in response to binding of a small molecule
- Two subtypes
  - α expressed in liver, adipose tissue, macrophages
  - B expressed ubiquitously
- Cholesterol sensor: endogenous ligand are products of cholesterol metabolism



- Activation leads to ↑ HDL cholesterol
  ↓ LDL cholesterol
- Target for atherosclerosis and cardiovascular disease
- Obstacle: increase in fatty acid synthesis leads to hypertriglyceridemia
- Mice lacking LXR α has no resistance to cholesterol- rich diet

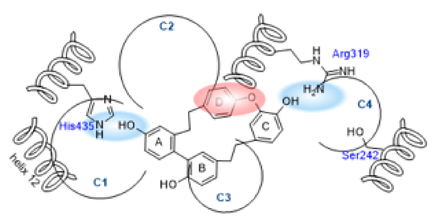
Could difference in tissue distribution of the receptor subtypes by utilized to achieve selective activation of certain families of genes?

Riccardin C



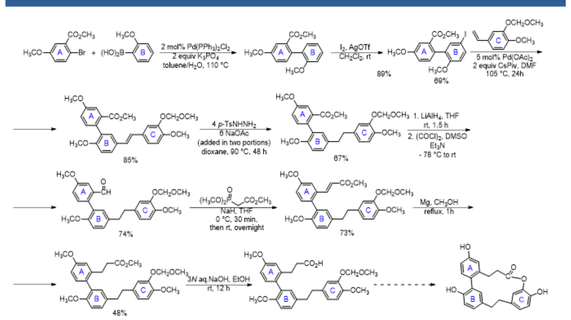
- Liver X receptor ligand
- Activates only one subtype (α)
- Mechanism of selectivity unclear, since ligand- binding pockets are very similar
- Low potency
- The strained structure makes synthesis of a large number of analogs difficult

Proposed Riccardin C Analogs



It is proposed that ring D does not make any significant interactions with the ligand- binding pocket and can be replaced with a flexible and easy to synthesize tether (highlighted in red)

Synthesis of the Model System



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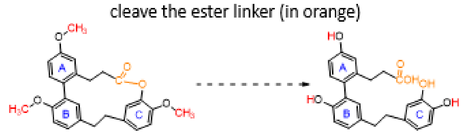
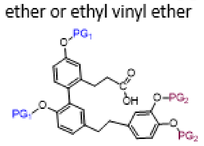
Modification of the Model Synthesis

Removal of the methyl protecting groups (in red) on the last step of the synthesis occurs under harsh conditions, which would also cleave the ester linker (in orange)



Solution:

Exchange methyls of more labile protecting groups, such as silyl ether or ethyl vinyl ether



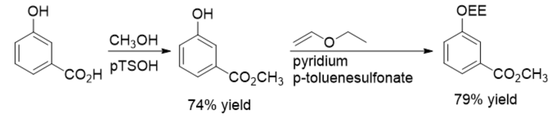
Research Questions

- I. Will it prove more efficient to switch the ether groups to the new protecting groups during synthesis
- II. Will it prove to be more efficient to prepare the starting materials with the new protecting groups
  - Attach new protecting groups to both starting materials
  - Conjoin rings with coupling reaction
  - Complete the synthesis

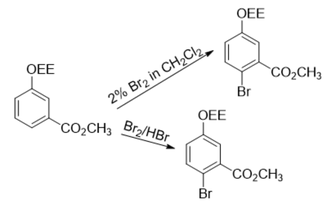
Preliminary Results

Synthesis of Ring A Staring Material

Starting Material and Addition of Protecting Group

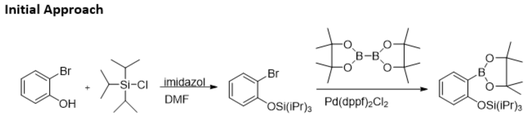


Bromination

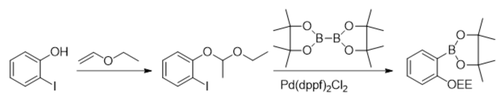


Synthesis of Ring B Starting material

Initial Approach

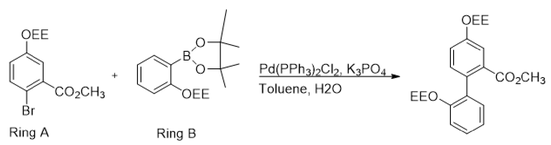


New Protecting Group and Starting Material



Coupling Reaction with New Starting Materials

Conjoining the rings with new protecting groups



Conclusion

- Synthesis of rings A and B is nearly complete
- Will soon begin attempts at coupling
- Future directions
  - Attachment of the ring C and completion of the linker
  - Removal of ethyl vinyl ether groups

Acknowledgements

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