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
  - a: expressed in liver, adipose tissue, macrophages
  - b: expressed ubiquitously
- Activation leads to upregulation of cholesterol synthesis
- Targets for atherosclerosis and cardiovascular disease
- Dose-dependent increase in fatty acid synthesis leads to insulin resistance
- Mild deficiency in B causes no resistance to cholesterol-rich diet
- Could difference in tissue distribution of the receptor subtypes be utilized for selective activation of certain families of genes?

Riccardin C
- Liver X receptor ligand
- Activates only one subtype (b)
- 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)

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 methyl 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

Synthesis of Ring A Starting Material

Synthesis of Ring B Starting Material

Coupling Reaction with New Starting Materials

Preliminary Results

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

Synthesis of the Model System

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