Chem 242b Chemical Synthesis
Scott Virgil, California Institute of Technology, Feb. 6, 2013

Lecture 13 Arene-Olefin Cycloaddition and Azomethine Ylide Cyclizations

13A. α-Cedrene (Wender JACS 1981, 103, 688)

The Oxa-Di-π-Methane reaction was brought to the synthetic community by Wender’s classic synthesis of α-cedrene. The photosubstrate was prepared in three steps in racemic form. The existing benzylic stereocenter enforces the stereoselectivity by allylic strain (as shown) to give exclusive attack from the front face for the enantiomer shown. Two regioisomers are obtained which together are converted to the ketone shown (fragmentation of bromonium ion occurs). Two isomeric photoadducts are obtained which both afford the same ketone upon bromine-induced cleavage and tributyltin hydride reduction.

13B. Miroestrol (Corey JACS 1993, 115, 9237)

Corey’s miroestrol project was initially envisaged as a arene-olefin cyclization strategy. After about 2 years of painstaking attempts to get the arene-olefin photoreaction to occur failed completely, an intramolecular Diels-Alder strategy was discovered to be highly effective for the synthesis.
13C. Retigeranic Acid (Wender TL 1990, 31, 2517)

Wender chose to apply the arene-olefin cycloaddition to the synthesis of retigeranic acid. As one can see, the triquinane portion of the molecule maps on very nicely to one of the arene-olefin regioisomers from the above cedrene synthesis. The Diels-Alder reaction was expected to give the isomer shown which of course had to be isomerized.

The photosubstrate is easily made, but the photocycloaddition gave a 2:1 mixture of cycloadducts in 72% yield with only the minor isomer useful for the synthesis. Fortunately, the mixture could be separated and re-equilibrated photochemically thus “offering easy access to multigram quantities of cycloadduct” needed for the synthesis. The subsequent steps of the synthesis involve a peculiar formamido radical addition to the vinylcyclopropane and selenium dioxide oxidation. As it turned out, the Diels-Alder reaction favored the cis-hydrindane fusion and the minor trans-hydrindane component was carried to the end.
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13D. **Deoxyharringtonine** (Gin JACS 2006, 128, 10370)

The synthesis of deoxyharringtonine utilizes a novel divinylaziridine [3,3] rearrangement to access the tetracyclic precursor. The aziridine is prepared by a reductive Neber rearrangement.

![Chemical structures](image)

The fifth ring of the deoxyharringtonine is assembled by a azomethine ylide cycloaddition. It is important to consider both resonance structures of the ylide when evaluating the regiochemistry of the cycloaddition. Although the ylide is generated by removal of the trimethylsilyl group, the other resonance structure is predominant and correctly predicts the observed regiochemistry.
13D. Deoxyharringtonine (cont.)

The authors note that the observed product appears to have arisen from a “contrasteric” approach of the vinyl sulfone to the convex face of the [5,5]-system. Footnote 12 suggests that possibly the addition initially occurred to the less hindered β-face and that this adduct rearranged to the observed product.

Proposed Isomerization: