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Synthetic Studies on the Ingenane Diterpenes. Construction of an ABC Tricycle Exhibiting *trans*-Intrabridgehead Stereochemistry

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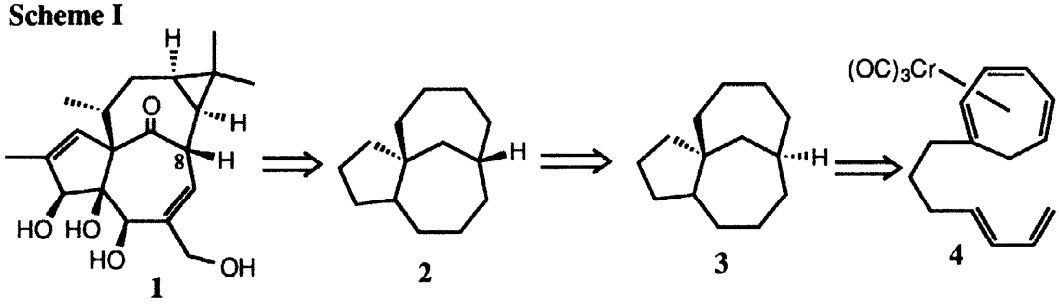
Abstract: Intramolecular, metal-promoted [6π+4π] cycloaddition followed by alkoxide accelerated 1,5-H sigmatropy affords a functionalized ingenane tricycle possessing the critical *in,out*-intrabridgehead stereochemical relationship.

Ingenol (**1**), a highly oxygenated diterpene isolated from the genus *Euphorbia*,[1] has been the subject of considerable study in recent years due to its intricate structural features as well as to the potent tumor-promoting activity exhibited by many of its derivatives.[2,3] While construction of the unusual bicyclo[4.4.1]undecanone unit comprising the BC ring substructure of the ingenanes is a significant challenge, a more formidable task is the incorporation of the highly strained "inside-outside" or *trans*-intrabridgehead stereochemical relationship within that bicyclic array.[4] To date, four strategically distinct approaches for addressing this crucial issue have been disclosed by Winkler[5], Funk[6], Rigby[7] and Tanino-Kuwajima[8], however, the natural product itself has yet to succumb to total synthesis.

Scheme I



Recently, alkoxide accelerated 1,5-H sigmatropy has been employed in a model study to effect a net isomerization of a simple "outside-outside" or *cis*-bicyclo[4.4.1]undecane into the highly strained *trans*-isomer.[7] Cognizant of the strict spatial requirements for successful delivery of the requisite bridgehead hydrogen via this process, it became imperative to demonstrate the viability of the transformation in a context more relevant to the ingenol target molecule itself. Studies directed toward bringing this "isomerization" protocol to practice in an appropriate tricyclic intermediate were thus initiated. It was envisioned that intramolecular [6π+4π] cycloaddition[9] could rapidly produce an appropriately functionalized tricyclic substrate upon which the "outside-outside to inside-outside" conversion could be tested. Scheme I depicts the salient features of this strategy.

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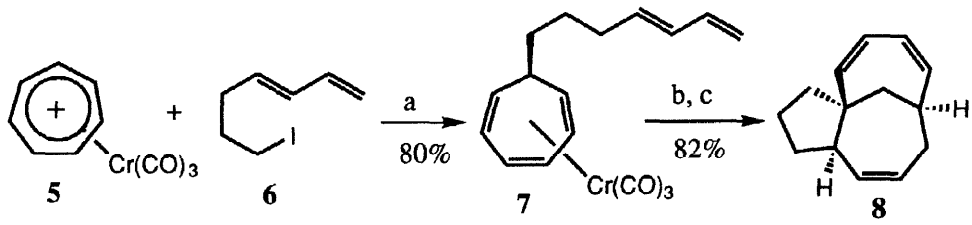
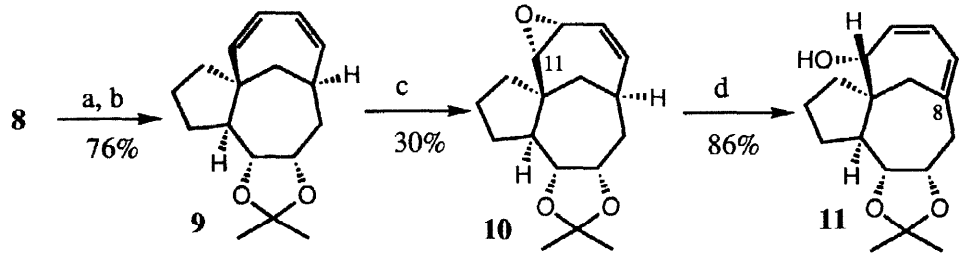


(1)

a) CuCN, LiCl; b) 1,4-dioxane, reflux; c) hν (pyrex), hexanes

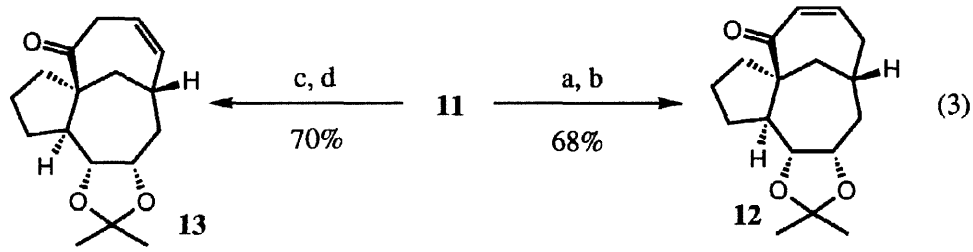
Treatment of readily available tricarbonyl(tropylium)chromium(0) fluoroborate (**5**)[10] with the organocopper derivative[11] of iodide **6**[12] afforded the 7-exo adduct **7**[13] in good yield. Heating this substrate briefly in refluxing 1,4-dioxane effected a series of Cr(0)-promoted 1,5-H shifts that afforded primarily the corresponding complex with the side-chain located at C-1 as required for the cycloaddition step.[14] Irradiation (pyrex filter) of this material provided tricyclic adduct **8**[13] as a single diastereomer after demetalation. As with most metal-promoted cycloadditions in this series, compound **8** was derived from an *endo* ring forming event.[9b] Alternatively, complex **7** can be converted directly into **8** with somewhat lower efficiency by heating in a sealed tube at 150 °C for two days.[15]



(2)

a) OsO_4; b) DMP/H^+; c) mClPBA; d) $LiNEt_2$/THF

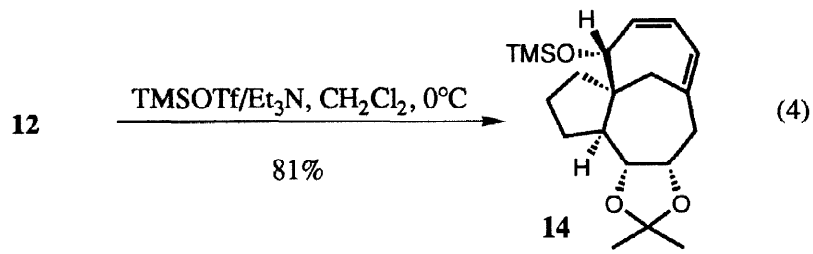
With the desired scaffolding in place, routine *cis*-dihydroxylation and protection of the isolated alkene in **8** afforded **9**[13] as a single diastereomer in 76% yield. The stereochemical course of this set of transformations illustrates a key feature of the projected isomerization protocol. Most external reagents are known to approach the bicyclo[4.4.1]undecane system exclusively from the more accessible convex surface. Next, attention turned to processing the diene into the dienol required for the projected 1,5-H sigmatropic rearrangement. The quickest route into this functionality involved epoxidation of the more hindered double bond of the diene from the more accessible *exo*-face, thus forcing the crucial proton at C-11 into a β-oriented configuration. Molecular models suggested that the $\Delta^{11,12}$ position was, in fact, reasonably accessible to an incoming reagent. In the event, treatment of **9** with m-ClPBA provided a serviceable, easily separable quantity of the desired epoxide **10**[13] along with significant amounts (70%) of the alternative α-epoxide. Opening of the epoxide in vinylogous fashion with $LiNEt_2$ proceeded without incident to afford dienol **11**[13] in excellent yield.



(3)

a) KH, 18-cr-6, THF, 0°C; b) NH_4Cl(aq); c) KH, 18-cr-6, THF, 0°C; d) SiO_2, -78°C

Efforts to carry out the anticipated 1,5-H shift on **11** employing the standard conditions (KH, 18-crown-6, dioxane, reflux)[16] that were previously successful in the simple bicyclic system[7] yielded only a modest quantity of rearranged product **12** along with substantial amounts of decomposition. At this point, it was noted during a particular run that the reaction could proceed to the desired product without application of heat. *Remarkably, it was ultimately determined that conversion to* **12**[13] *(mp:113-5 °C, ν = 1666 cm^{-1}) could best be achieved by performing the rearrangement at 0°C!* The stereochemical outcome of the reaction was ascertained by single crystal x-ray analysis of **12**;[17] however, a rationale for the facility of this transformation is obscure at this juncture. Of further note, careful quenching of this reaction at low temperature allows for the isolation of the interesting and potentially significant deconjugated enone **13**[13] (ν = 1697 cm^{-1}). The positioning of the double bond in this compound has important implications for eventual D-ring installation if a method for "locking" this unsaturation in place can be identified.



(4)

Initial efforts in this regard, while not successful, revealed the highly reversible nature of the hydrogen sigmatropy in this system. Thus, exposing **12** to TMSOTf/Et3N at 0 °C did not give the expected extended enolsilyl ether but produced, instead, the dienol derivative **14**[13] in excellent yield. Based on this observation, care must always be exercised while manipulating these substrates so as to maintain the integrity of the in,out-topography in the BC ring substructure.

In summary, rapid entry into an advanced ingenane tricycle exhibiting the strained inside, outside intrabridgehead stereochemical relationship has been achieved. The mildness of the key sigmatropic rearrangement step suggests that the protocol will be compatible with more highly functionalized substrates. Application of this methodology to the total synthesis of ingenol are currently underway in our laboratory and results of this endeavor will be reported in due time.

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