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Stereoselective Approach to the Dihydroagarofuran Framework via Directed Intramolecular Radical Addition

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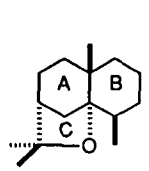
Abstract: The radical derived from bromoacetal **12** undergoes intramolecular addition to give predominantly the cyclic acetal **13** in which the C12 methyl substituent is *endo*.

The dihydroagarofuran skeleton **1** is present in a wide array of polyhydroxylated sesquiterpenes,[1] including maytol (**2**)[2] and euonyminol (**3**).[3] These sesquiterpene polyols are found as their esters in plants of the *Celastraceae*, where they constitute core units of complex structures such as the cathedulins.[4]



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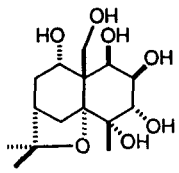

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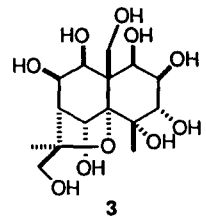
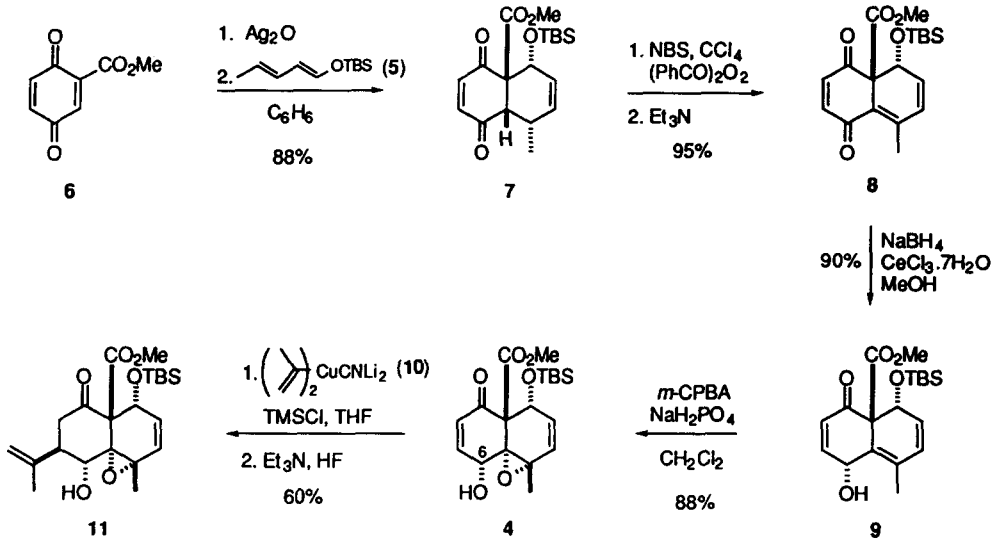


3

In the course of studies directed towards synthesis of members of this class,[5,6] the bicyclic ketone **4** was identified as a pivotal intermediate in the hope that this functionalized decalin would serve as a template from which rings A and B of **2** and **3** could be fabricated. An efficient synthesis of **4** was devised (Scheme 1) via Diels-Alder addition of diene **5**[7] to the quinone **6** (prepared *in situ* by oxidation of methyl gentisate[8]), allylic bromination of the resultant adduct **7** and *in situ* elimination to the homoannular diene **8**, stereoselective Luche reduction[9] to give **9**, and a final directed epoxidation. Unfortunately, further progress from **4** towards **2** and **3** was obstructed by difficulties associated with introduction of the three carbons of the heterocyclic ring in the correct configuration. Thus, conjugate addition of the isopropenylcuprate **10** to enone **4** in the presence of trimethylsilyl chloride, followed by cleavage of the resultant silyl enol ether, gave exclusively the product **11** in which the isopropenyl substituent had entered with the undesired β orientation.

Reasoning that the C6 hydroxyl group of **4** could be employed to steer conjugate addition of a suitable nucleophile to the α face of the unsaturated ketone, a plan was conceived that attached a functional group to this alcohol in anticipation that cyclization would be forced to occur in *syn* fashion. However, neither the propionate of **4** nor a malonyl ester derivative could be induced to undergo base-catalyzed, intramolecular Michael reaction. We therefore turned to a radical cyclization pathway, cognizant of the fact that intramolecular conjugate addition of radicals to α,β unsaturated ketones is a well precedented process.[10]



Scheme 1

Bromoacetal **12** was prepared by treatment of **4** with N-bromosuccinimide and 1-ethoxypropene,[11] and was obtained as an inseparable mixture of four stereoisomers. Exposure of this mixture of bromoacetals to tri-*n*-butylstannane and AIBN in benzene at reflux led in good yield to cyclized products **13** and **14** in the ratio 5:2, respectively. In addition, a small quantity of the epimeric acetal **15**, isolated as an inseparable mixture of C11 stereoisomers was obtained. Stereochemical assignments to **13** and **14** were made on the basis of nuclear Overhauser experiments. Thus, irradiation of the signals due to the C12 methyl protons of **13** produced signal enhancement of the equatorial H8α proton (1.1%) and the α proton H13 (1.4%) but not H7. By contrast, irradiation of the C12 methyl signal of **14** caused enhancement only of H7 (3.1%) and H11 (3.5%). Energy minimized conformations of **13** and **14** that accommodate these data are shown in Figure 1.

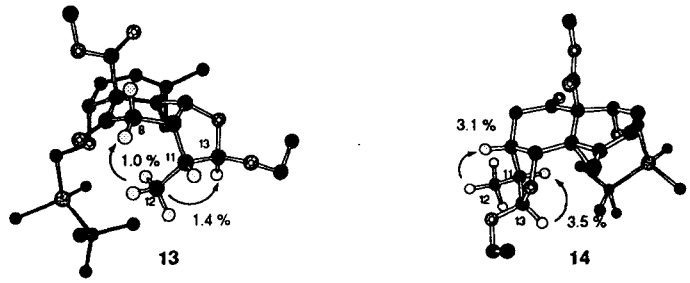
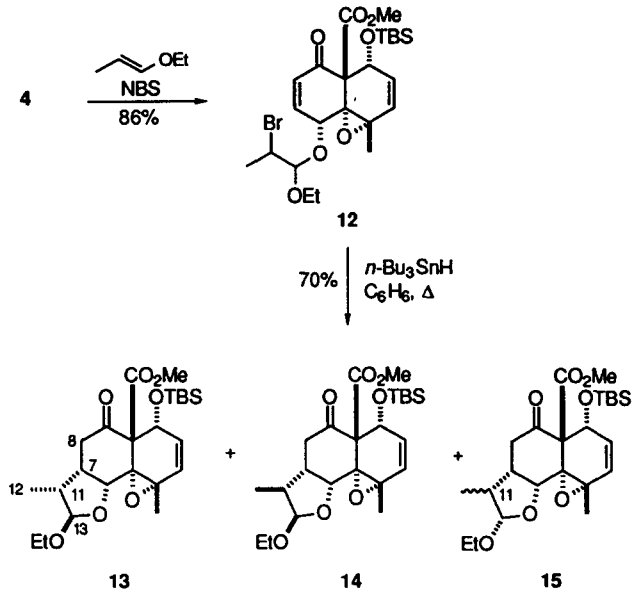


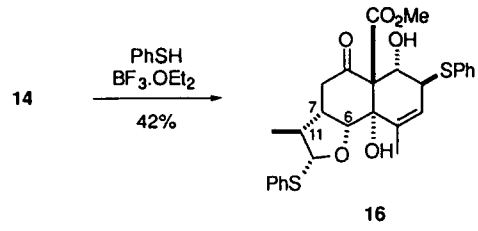
Figure 1. Energy Minimized Conformations and NOE Data for **13** and **14**

These results indicate that **13** and **14** are *cis* fused, and that the two stereoisomers differ only in the configuration of the C12 methyl group. Further support for the assignment made to **14** was acquired when this

acetal was treated with thiophenol in the presence of boron trifluoride etherate. A crystalline bis(thiophenyl) adduct was obtained whose X-ray crystallographic analysis showed it to be **16** (Figure 2).



Aside from confirming the configuration at C6, 7, and 11 of **14**, the structure of **16** gave evidence of characteristic reactivity in ring B of **4** that was later used to advantage in our route to **3**.[6] Although ^{1}H NMR spectroscopy strongly suggested that the acetal (C13) configuration of both stereoisomers of **15** was opposite to that in **13** and **14**, ambiguity with respect to the center at C11 in this structure prevented a firm conclusion to be drawn regarding the orientation of the C12 methyl substituent.



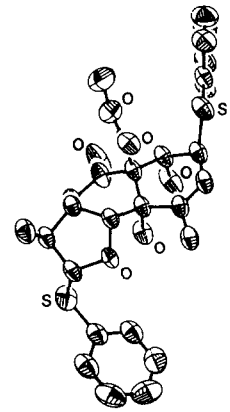


Figure 2. X-ray Crystal Structure of **16**

The formation of **13**, which possesses the more sterically crowded *endo* methyl substituent, as the major product from **12** has little direct precedent, although high *endo* selectivity for an alkyl substituent has been noted in other types of radical cyclization,[12] including one involving a bromoacetal and an *exo* olefin.[13] Our result can be accommodated within the mechanistic guidelines of Beckwith[14] and the theoretical framework of Houk,[15] assuming the transition state shown in Figure 3. This view of the reaction pathway postulates that the preferred conformation of the radical species generated from **12** will be chair-like, with the methyl substituent "equatorial."

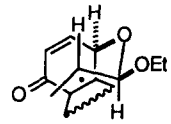


Figure 3. Proposed Transition State for the Cyclization of **12** to **13**

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