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An approach to the aromadendrane carbon skeleton by a radical fragmentation/3-*exo*-trig cyclization sequence

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Abstract

A radical fragmentation/cyclization sequence of a [2+2] photoadduct derivative leads to the formation of the aromadendrane ring system. The 5,7 fused rings of this sesquiterpenoid family are formed in the fragmentation step and the cyclopropane moiety is the result of a 3-*exo*-trig cyclization. The cyclization step is facilitated by the use of SmI_2 as the electron donor and by an ester group to stabilize the resultant strained intermediate.

Keywords: cyclization; cyclopropanes; fragmentation reactions; radical reactions; terpenoids.

Radical cyclizations have been employed extensively in the synthesis of natural products[1] while the use of radical fragmentations is becoming increasing important.[2] We have employed radical fragmentation/reduction[3] and fragmentation/elimination[4] sequences in the synthesis of a number of terpenoids. In this Letter we report our successful attempts to generate the 5,7 ring system and the strained cyclopropane moiety of the aromadendrane family of sesquiterpenoids by a radical fragmentation/cyclization sequence.

The driving force in the fragmentation step of our sequence is the relief of strain upon breaking a cyclobutane bond in a [2+2] photoadduct derivative. Subsequent formation of a cyclopropane ring by a radical cyclization, normally a contra-thermodynamic process, requires significant stabilization of the resultant cyclopropyl carbinyl radical. Previous investigations have shown that cyclizations to yield strained cyclopropane or cyclobutane rings were possible if the resultant radical was stabilized by an ester,[5] a ketone,[6] a nitrile,[7] an aryl[8] or a phenylthio[9] group. An elimination step after the cyclization can also be employed to drive the reaction to completion.[10] In our study an ester group was chosen to stabilize the intermediate (a radical or carbanion?) formed after the cyclization.

The substrate required for the fragmentation/cyclization sequence was prepared from known photoadduct **1**[11] (Scheme 1). The plan was to attach an α,β-unsaturated ester moiety at C-8 via an aldehyde

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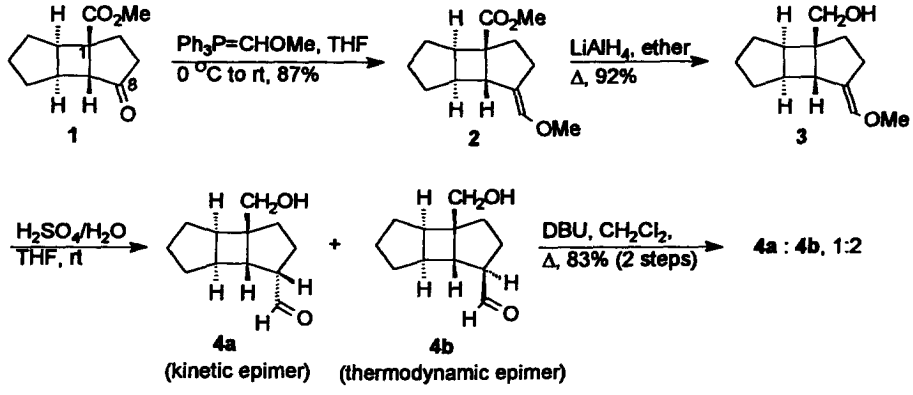
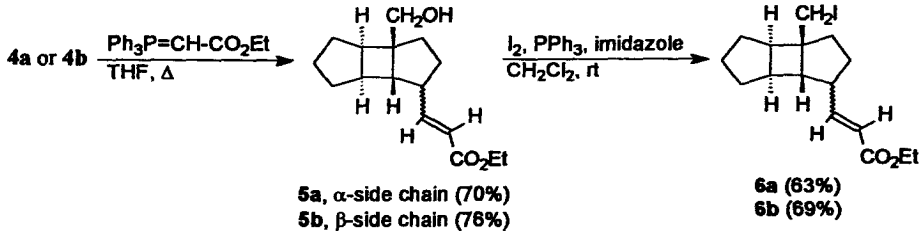
function. The first step in aldehyde homologation of **1** was effected by a Wittig reaction to afford **2**, which was reduced with $LiAlH_4$ to give alcohol **3**. Hydrolysis of the enol ether in **3** gave a 2:1 mixture of epimers **4a** and **4b**, respectively. Treatment of this mixture with DBU resulted in epimerization to give a 1:2 mixture of these aldehydes.[12] Protonation of enol ether **3** from the less hindered β-face would be expected to give primarily the kinetic product **4a** while epimerization would then lead to a preponderance of the thermodynamic product **4b**. Epimers **4a** and **4b** were separated by flash chromatography and subsequent reactions were conducted on each isomer.

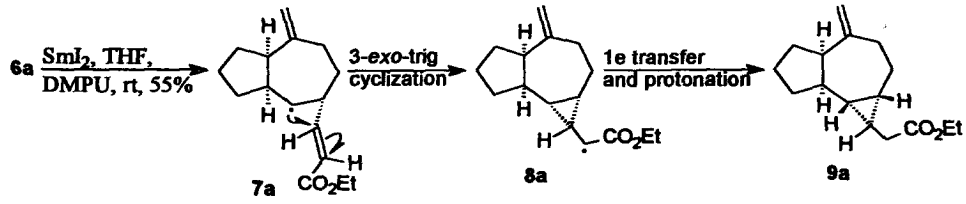


Scheme 1.

Reaction of α-aldehyde **4a** with a carboethoxymethylene ylide gave the (*E*)-alkene **5a** which was converted to iodide **6a** using our standard protocol (I_2, Ph_3P, imidazole)[13](Scheme 2). Compound **6a** contained the structural features and functionality necessary to test our fragmentation/cyclization methodology. Treatment of **6a** with SmI_2 in THF/DMPU gave in 55% yield **9a**[14] (Scheme 3) which possesses the desired aromadendrane ring system, i.e. the 5,7 fused ring system with a cyclopropyl moiety. Also, the exocyclic methylene group in **9a** is often encountered at this position in these sesquiterpenoids. Formation of **9a** can be rationalized as outlined in Scheme 3. Abstraction of iodide from **6a** followed by radical fragmentation gave **7a**. A 3-*exo*-trig cyclization then yields the stabilized cyclopropyl carbinyl radical **8a**. Simple cyclopropyl carbinyl systems in which the radical is stabilized



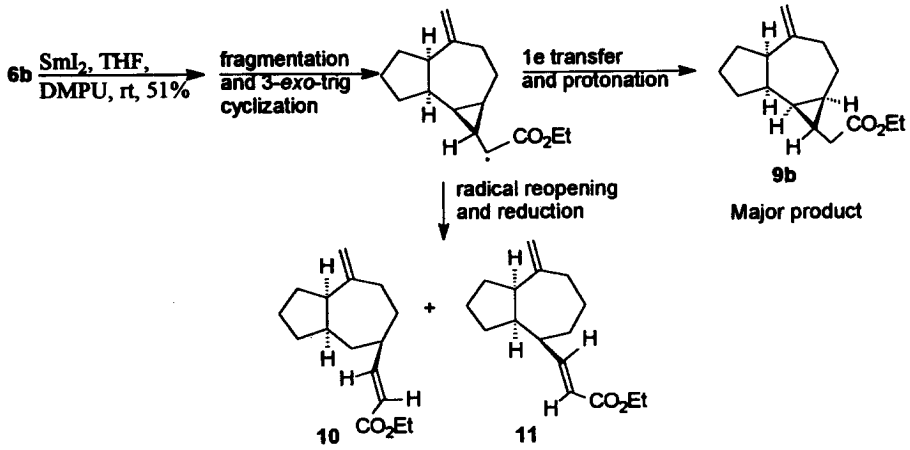
Scheme 2.



Scheme 3.

by a *t*-butyl ester moiety fragment at a rate of about 10^4 s^{-1}.[15] Thus we suggest that **8a** accepts another electron from SmI_2 to give the enolate of **8a** which is then protonated. It is also possible that **7a** could accept an additional electron and the resultant carbanion could undergo a Michael addition to give the same enolate of **8a**.[16] When *n*-Bu_3SnH rather than SmI_2 was employed in the reaction with **6a** only a modest yield of the product derived from reduction of **7a** was obtained.

Conversion of β-epimer **4b** to unsaturated ester **6b** was effected in a manner similar to that employed for the preparation of **6a** from **4a** (Scheme 2). Treatment of **6b** with SmI_2 gave in 51% overall yield a mixture of three products (Scheme 4). The major product **9b** (25% yield) was formed again by 3-*exo*-trig cyclization and possessed the aromadendrane ring system. The other two products **10** and **11** (each obtained in ~13% yield) were formed by cyclization followed by opening on either side of the cyclopropyl carbinyl system. A related cyclization/fragmentation equilibrium process has been reported in a diterpenoid synthesis.[17]



Scheme 4.

This study has shown that it is possible to form the aromadendrane ring system using a radical fragmentation/cyclization sequence if the proper electron donor (SmI_2) and the proper stabilizing group are employed. Use of a ketene dithioacetal moiety [RCH=C(SR′)$_2$] rather than an α,β-unsaturated ester resulted only in reduction of the fragmented radical and decomposition. Work is now in progress to exploit this new methodology in the synthesis of a specific aromadendrane target.

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