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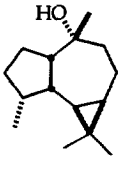
Bridged to Fused Ring Interchange. The Total Synthesis of (±)-Ledol

Stephen L. Gwaltney, II and Kenneth J. Shea*
University of California, Irvine, CA 92717

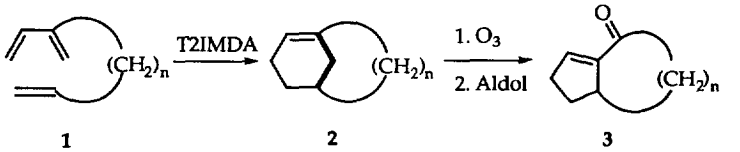
Abstract: *The type two intramolecular Diels-Alder reaction, when coupled with bridged to fused ring interchange, provides an efficient stereoselective route to fused 5,7- and 5,8-ring systems. This methodology has been utilized in the total synthesis of (±)-ledol, an aromadendrane sesquiterpene.*

The aromadendranes are a class of sesquiterpene natural products found in a number of plant species.[1] Structurally, they are characterized by a dimethyl cyclopropane unit fused to a hydroazulene core. Ledol is representative of this class and shows antifungal activity against *Coriolus renatus*.[2]



ledol

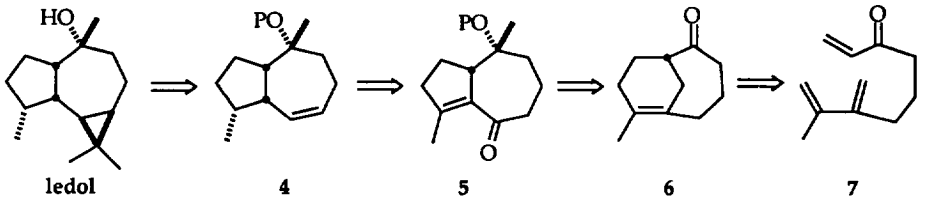
The type two intramolecular Diels-Alder reaction, when coupled with bridged to fused ring interchange, provides an efficient, stereoselective route to fused 5,7 and 5,8 ring systems.[3] The overall transformation is shown in eq. 1. A type 2 intramolecular Diels-Alder cyclization of triene **1** affords bridged bicycle **2**. Following oxidative cleavage of the bridgehead double bond, simple aldol condensation results in the formation of enone **3**.



1 **2** **3** (1)

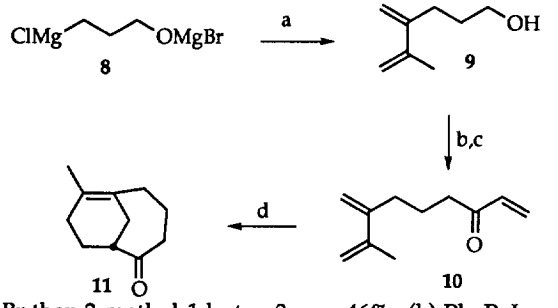
Setting stereochemistry in medium rings can be difficult due to their conformational flexibility.[4] An attractive feature of the above methodology is that it provides an opportunity to take advantage of the conformational rigidity of the bridged bicyclic intermediate (**2**) to set stereochemistry in the medium sized ring *prior* to oxidative cleavage.

In this communication, we report the use of this methodology for the total synthesis of (±)-ledol from triene **7** (Scheme 1). The approach exploits the concave nature of cycloadduct **6** and hydroazulenes **4** and **5** to direct the delivery of reagents in a stereocontrolled manner.



Scheme 1

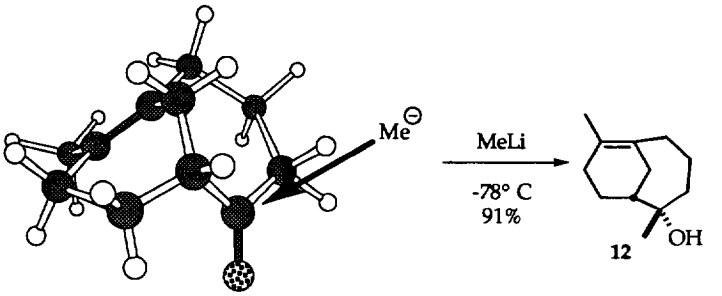
The synthesis begins with commercially available 3-chloropropanol and 2-methyl-1-buten-3-yne (Scheme 2). Generation of the Normant Grignard[5] **8**, transmution, and addition of the enyne[6] results in formation of alcohol **9**. Although this reaction proceeds in moderate yield, it represents a convenient entry to this 2-substituted diene. Synthesis of the iodide is accomplished using Ph_3P, iodine, and pyridine in CH_2Cl_2. Alkylation of lithio methoxyallene[7] followed by hydrolysis gives triene **10** in good yield. The type two intramolecular Diels-Alder reaction is carried out using Et_2AlCl (20 mole %) in CH_2Cl_2.



Reagents: (a) CuBr then 2-methyl-1-buten-3-yne, 46%; (b) Ph_3P, I_2, pyridine, 70-80%; (c) lithio methoxyallene, THF, 77%; (d) Et_2AlCl, CH_2Cl_2, 70%.

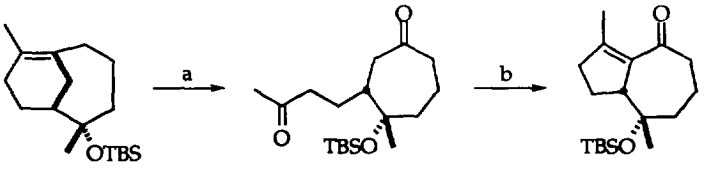
Scheme 2

When cycloadduct **11** is treated with MeLi at -78° C, **12** is formed exclusively in 91% yield. The origin of this stereoselection can be understood by examining the conformational bias of the ketone (eq. 2).[8] The lowest energy conformation[9] presents the exo face of the carbonyl to reagents. This results in high levels of stereocontrol. The tertiary alcohol thus formed can be efficiently protected (94% yield) using TBSOTf in pyridine / CH_2Cl_2.



(2)

The bridged to fused ring interchange is initiated by treating the protected alcohol with ozone at -78° C (Scheme 3). After a reductive workup with trimethyl phosphite, the diketone **14** is obtained. Cyclization is accomplished with KOH in MeOH to give enone **15**.

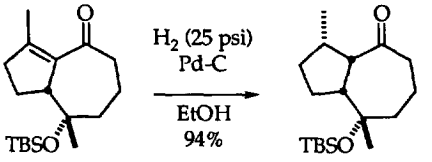


13 **14** **15**

Reagents: (a) O_3, MeOH, 67%; (b) KOH, MeOH, 97%.

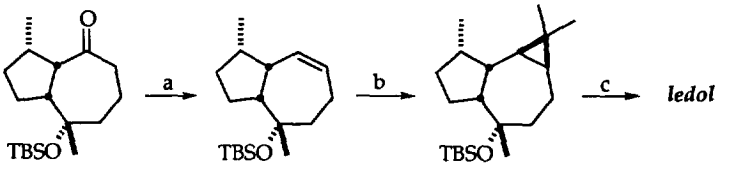
Scheme 3

The ring fusion stereochemistry of ledol requires a cis addition of hydrogen to **15**. An example from the literature suggested that this ring system would be amenable to medium pressure catalytic hydrogenation.[10] In the event, treatment of **15** with 25 psi of hydrogen in EtOH over Pd-C afforded 94% of a single diastereomer which was assigned as structure **16** based on ^1H NMR coupling constants and NOESY spectra.



15 **16** (3)

Installation of the dimethyl cyclopropane moiety was accomplished as follows. Conversion of **16** to the enol phosphate, followed by reduction with lithium in ammonia,[11] gave alkene **17** (Scheme 4). Dibromocyclopropanation employed Seyferth's reagent.[12] Gem-dimethylation was best performed with the mixed cuprate derived from MeLi and CuCN.[13] Removal of the TBS protecting group with TBAF in refluxing THF gave (±)-ledol which had spectroscopic properties consistent with the assigned structure and was found to be identical to an authentic sample.[14]



16 **17** **18**

Reagents: (a) i: LDA, then $(EtO)_2POCl$, ii: Li, NH_3, 45%;
(b) i: $PhHgCBr_3$, PhH, reflux, ii: MeLi, CuCN, 69%; (c) TBAF, THF, reflux, 59%.

Scheme 4

This work demonstrates that the type two intramolecular Diels-Alder reaction, when coupled with bridged to fused ring interchange, is an effective method for the stereoselective formation of 5,7 fused ring systems and that the methodology is amenable to the synthesis of terpene natural products. Development of this methodology for the synthesis of other fused polycyclic natural products continues in our lab.

Acknowledgment

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