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The Total Synthesis of (±)-Barbatusol§1

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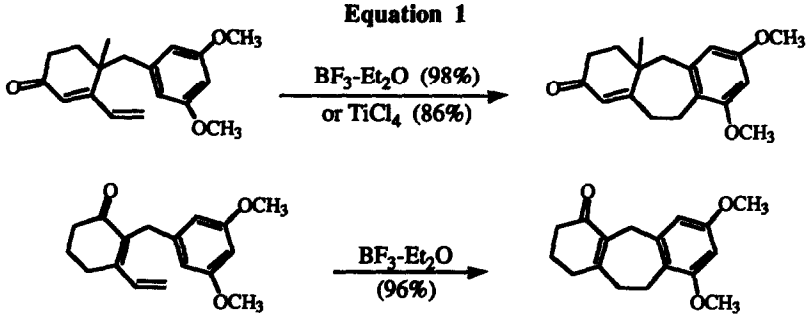
Abstract: An eight-step synthesis of the naturally occurring hypotensive diterpene barbatusol (3) featuring a Friedel-Crafts annulation is reported.

In the preceding Letter, we reported that tricyclic systems containing a central cycloheptane ring can be easily prepared by Lewis acid-catalyzed intramolecular alkylation of electron-rich arenes with conjugated dienones (Equation 1).[2]

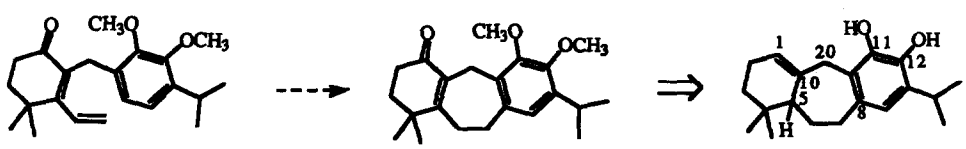
Equation 1



This study suggested a simple approach to barbatusol (3),[3,4] a diterpene known to lower blood pressure in mice (Equation 2).[5] Enone 2 is an attractive synthetic intermediate because it contains the entire carbocyclic framework of barbatusol and because the ring fused enone allows the introduction of the sensitive trisubstituted C(1),C(10)-double bond with complete control. Accordingly, we sought an efficient means to prepare arene-dienone 1.

Our synthesis began with 2,3-dimethoxy-4-isopropylbenzyl alcohol (5), readily prepared by quenching the ortho metalated anion of 3-isopropylveratrole (4)[4] with gaseous formaldehyde (Scheme 1).[6]

Equation 2

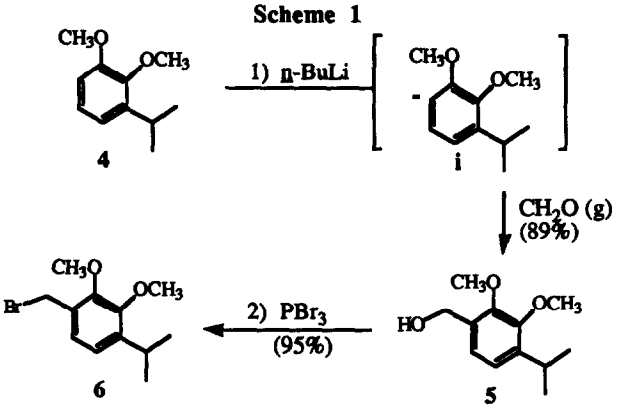


1 2 Barbatusol (3)

§ Dedicated to the memory of Professor Philip Southwick [1916-1992]

The conversion of **5** to benzyl bromide **6** was accomplished in 95% yield by using phosphorus tribromide.

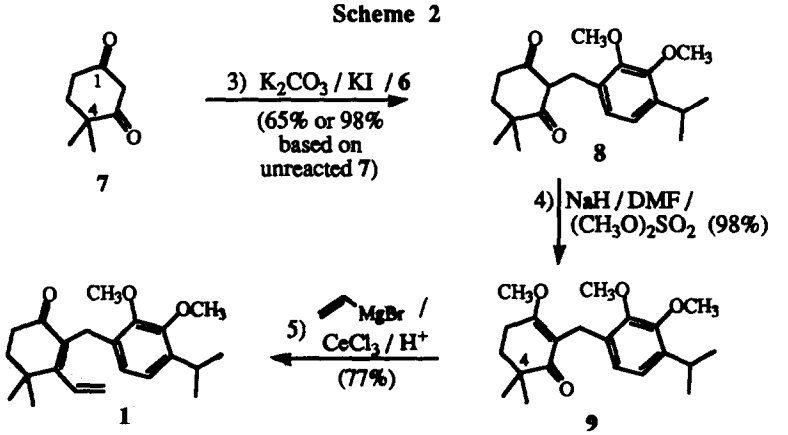
Scheme 1



The next step required the carbon alkylation of 4,4-dimethylcyclohexane-1,3-dione (**7**) with bromide **6**. The use of typical conditions for the C-alkylation of cyclic 1,3-diones gave predominantly O-alkylation or *bis*-alkylation. However, the use of a concentrated solution of **7** in 20% potassium carbonate yielded *mono*-alkylated dione **8** in 65% yield or 98% based on recovered **7** (Scheme 2).[7] Because of the steric congestion of the *gem*-dimethyls at C(4), we expected that only the C(1) carbonyl would undergo O-alkylation. Indeed, treatment of dione **8** with sodium hydride and dimethyl sulfate in DMF gave exclusively enone **9**.[8] 1,2-Addition of vinylmagnesium bromide to **9**, followed by mild acid hydrolysis, completed the preparation of our cyclization precursor. Not surprisingly, the *gem*-dimethyls at C(4) required activation of the carbonyl to facilitate 1,2-addition.[9]

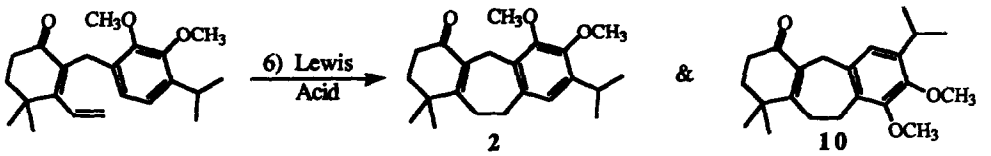
Mild Lewis acids, such as trimethylaluminum or zinc bromide, failed to promote reaction. In light of model studies,[2] we expected that titanium tetrachloride and boron trifluoride etherate would give only enone **2**. Instead, these catalysts gave isomeric products with opposing selectivity (Equation 3).[10] Note that tricyclic enone **10** is the result of an acid-promoted rearrangement and is not useful as a potential

Scheme 2



barbatusol precursor. Re-exposure of enone **2** to excess Lewis acid does not result in the formation of enone **10**, nor does enone **10** rearrange to isomer **2** under identical conditions.

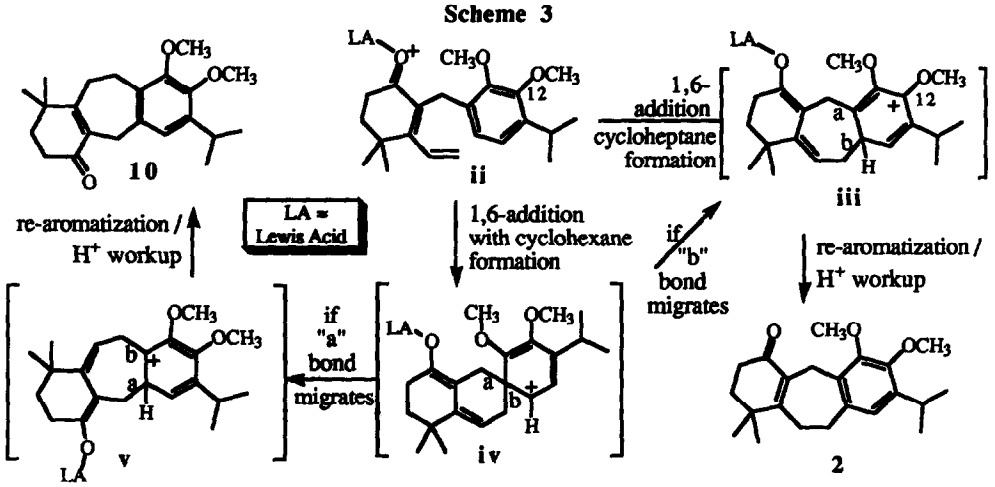
Equation 3



Scheme 3 presents two mechanisms which account for the products observed. In the simpler mechanism, electrophilic addition of the activated conjugated dienone (**ii**) occurs para to the C(12) methoxy group to form a seven-membered ring and resonance-stabilized intermediate **iii** which loses a proton to re-establish aromaticity. Although this mechanism is consistent with the results of our model study and the formation of enone **2**, it does not readily explain the formation of enone **10**. The alternative mechanism accounts for the formation of both products. A basic tenet of ring closures holds that six-membered rings form more easily than seven-membered rings. Thus, *ipso*-attack on the arene by the activated dienone leads to the formation of a new cyclohexane ring and cationic intermediate **iv**, which generates either intermediate **v** or **iii** by migration of the "a" or "b" bond, respectively. Since both bonds are allylic and primary, they are equally likely to migrate. We therefore conclude that the choice of catalyst determines which bond migrates.[11]

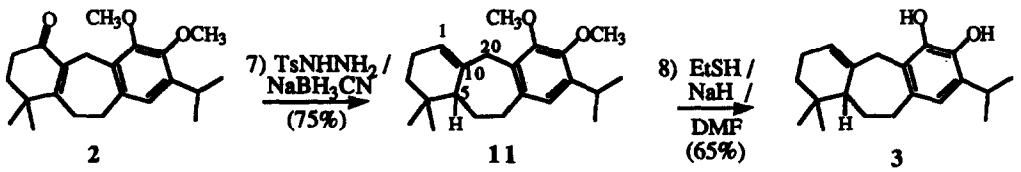
We postulate that for reactive arene-dienones Lewis acid catalysis results in rapid cycloheptane annulation via the first mechanism or "normal" addition pathway. In contrast, less reactive arene-dienones may cyclize by means of an "abnormal" pathway involving *ipso*-addition. Moreover, the use of too weak a Lewis acid to promote cyclization may trigger the "abnormal" mechanism and can lead to the formation of rearranged products.

Scheme 3



The best way to verify our structural assignments for enones **2** and **10** was to complete a synthesis of barbatusol. This was achieved by a modified Wolff-Kishner reduction of enone **2**,[12] removing the C(1) carbonyl and migrating the C(5),C(10)-double bond to theC(1),C(10)-position (Equation 4). The final step of the synthesis benefitted from Koft's determination that demethylation of the methyl ethers could be achieved under basic conditions without isomerization of the C(1),C(10)-trisubstituted double bond to the more stable C(5),C(10)- or C(10),C(20)-positions.[3,4] Hence, heating dimethyl ether **11** with EtSNa in DMF resulted in the isolation of racemic barbatusol in 65% yield, along with 15% of a *mono*-demethylated product. The NMR (300 MHz), infrared and mass spectra were identical with those reported by both Koft and Kelecom, thereby confirming our synthesis.

Equation 4



2 **11** **3**

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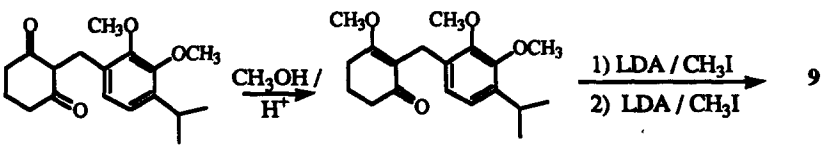
References and Notes:

1. Taken in part from the MS thesis of Mr. T. Lee Feltman, *The University of Georgia* (1992).
2. Majetich, G.; Zhang, Y. Feltman, T. L; Belfoure, V. *The Use of Conjugated Dienones in Friedel-Crafts Annulations*, preceding Letter.
3. *Isolation:* Kelecom, A. Tetrahedron **1983**, *39*, 3603.
4. For the first synthesis of barbatusol, see: Koft, E. R. Tetrahedron **1987**, *43*, 5775.
5. a) Steven, R. V.; Bisacchi, G. S. J. Org. Chem. **1982**, *47*, 2396. b) Edwards, J. D.; Cashaw, J. L. Ibid. **1955**, *26*, 847.
6. a) All structures drawn here represent racemates, with only one enantiomer shown. b) The spectroscopic data obtained for all new compounds [^{1}H NMR, ^{13}C NMR, IR and MS] were fully consistent with the assigned structures. c) Reaction conditions have not been optimized. d) All yields are isolated yields.
7. Stettler, H.; Dierichs, W. Chem. Ber. **1952**, *85*, 1061.
8. The specificity of enol formation was confirmed as shown:



9. Imamoto, T.; Kusumoto, T.; Yokoyama, M. J. C. S. Chem. Commun. **1982**, 1042.
10. Enones **2** and **10** defied modern 2-D NMR techniques, as the resonances for the aromatic methine and the methylene unit linking the rings consisted of singlets, devoid of long-range couplings. After a synthesis of **3** had been achieved, an X-ray crystal study confirmed our structural assignment for tricyclic enone **10**.
11. An analogue of dienone **1**, lacking the C(4) *gem*-dimethyl group, gave similar cyclization results.
12. Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. J. Am. Chem. Soc. **1973**, *95*, 3662.

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