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Total Synthesis of (±)-Dictamnol by a Free Radical Fragmentation/Elimination Sequence. Confirmation of its Revised Structure.

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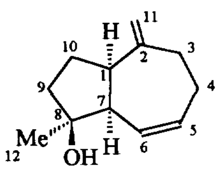
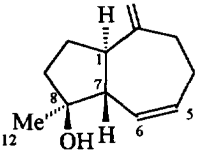
Abstract: The trinor-guaiane sesquiterpenoid (±)-dictamnol **2** was synthesized, in only 6 steps, from photoadduct **5**. The crucial step involved a SmI_2-mediated tandem free radical fragmentation/elimination reaction of diiodide **10**. Support for the recently revised structure of dictamnol is presented. © 1997 Elsevier Science Ltd.

Dictamnol, a trinor-guaiane sesquiterpenoid, was isolated from the roots of *Dictamnus dasycarpus* TURCZ. On the basis of a detailed NMR study, structure **1** with a *cis* ring fusion was proposed for the natural product.[1] Recently, a total synthesis of this compound was claimed.[2] In the same year a stereospecific synthesis of **1** was reported and it was discovered that the spectral properties of **1** differed from those of dictamnol.[3] After further NMR analyses the latter investigators suggested that dictamnol possessed structure **2** with a *trans*-fused ring junction.[3] Compound **2** was prepared in low yield by air oxidation of pregeijerene.[3] In this letter we describe efficient total syntheses of **1** and **2** employing a free radical fragmentation/elimination sequence of a photoadduct derivative. On the basis of our study we support the revised structure **2** proposed for dictamnol.



1

Initially proposed structure for dictamnol



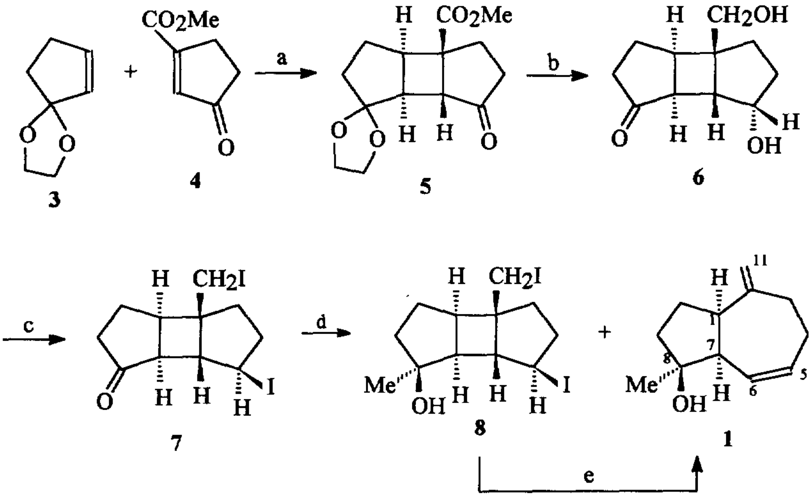
2

Dictamnol

We previously reported that radical-mediated fragmentations of strained cyclobutane systems derived from photoadducts resulted in the preparation of a variety of bicyclic ketones[4] and in the formal synthesis of the angular triquinane pentalenene.[5, 6] More recently, the first total synthesis of the guaiane sesquiterpenoid alismol employed a free radical fragmentation/elimination sequence of an iodoxanthate.[7] In the syntheses of both **1** and **2** reported herein a diiodide was used in the critical fragmentation/elimination reaction.

In the first step of our syntheses, the head-to-head *cis-anti-cis* adduct **5** was prepared by [2+2] photoaddition of excess ketal **3** with enone **4** (Scheme 1). Reduction of the ester and ketone functions in **5** with lithium aluminum hydride followed by hydrolysis of the ketal gave diol **6** which was converted to diiodide **7** using our previously reported protocol.[8] Reaction of **7** with methyl Grignard gave primarily the desired alcohol **8** along with a significant amount of the ultimate fragmentation product **1**! Presumably an equilibrium was established between MeMgBr and the primary iodide of **8** and the resultant Grignard reagent of **8** then underwent free radical fragmentation to give **1**.[9] Treatment of **8** with SmI_2 effected the tandem fragmentation/elimination to give **1** in good yield. Because the ketone in **7** was reacted prior to the fragmentation there was no opportunity for epimerization at C-7 and thus the ring fusion in **1** must be *cis*. Comparison of the ^{1}H- and ^{13}C - NMR spectra of **1** with dictamnol[1] indicated clearly that the compounds were different while the comparison of **1** with the *cis*-isomer recently synthesized showed that these two compounds were identical.[3]

Scheme 1

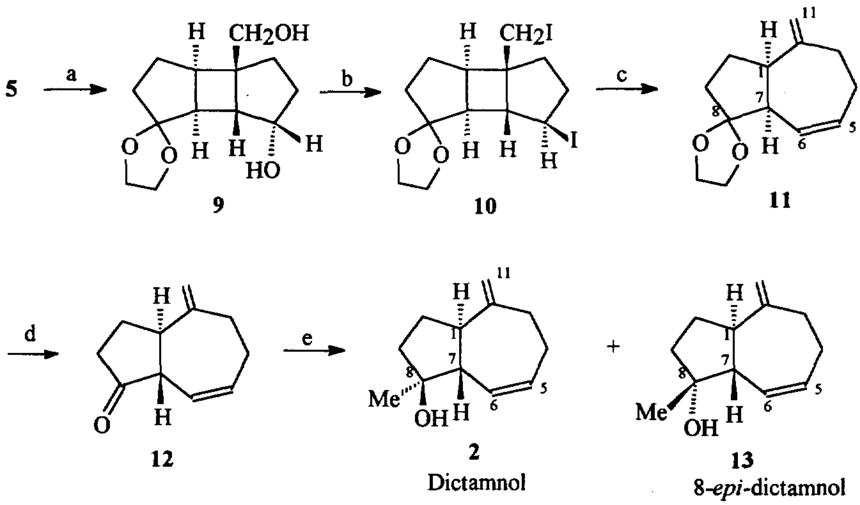


(a) hν, CH_2Cl_2(47%); (b) $LiAlH_4$, ether, Δ; 1M HCl, ether, r.t.(60%); (c) I_2, PPh_3 , imidazole, CH_2Cl_2, Δ(77%); (d) MeMgBr, THF, r.t.(**8**, 63%; **1**, 14%); (e) SmI_2 , DMPU, THF, r.t.(73%).

In our approach to the synthesis of **2**, photoadduct **5** was reduced to diol **9** which was then converted to diiodide **10**. Treatment of **10** with SmI_2 resulted in fragmentation/elimination to afford in excellent yield the *cis*-fused 5/7 ring system **11** (Scheme 2). Removal of the protective group under mild transketalization conditions was accompanied by C-7 epimerization[10] to give the *trans*-fused ketone **12**. Treatment of **12** with methyl Grignard gave a mixture of **2** and **13**. This lack of stereoselectivity is not surprising upon examination of a molecular model of **12**. Comparison of the NMR spectral data of **2** and dictamnol indicated these compounds were identical and thus **13** must be the C-8 epimer of dictamnol.

Detailed NOESY studies of **1**, **2** and **13** support the structural assignments proposed. In **1**, cross peaks were evident between H-1 and H-7 as well as between H-7 and 8-Me. For dictamnol, **2**, a cross peak was observed between H-1 and 8-Me while no such peaks were noted between H-7 and 8-Me or between H-1 and H-7. In **13**, a cross peak was evident between H-7 and 8-Me but not between H-1 and 8-Me.[11]

Scheme 2



(a) $LiAlH_4$, ether, Δ(63%); (b) I_2, PPh_3 , imidazole, CH_2Cl_2, Δ(80%); (c) SmI_2 , DMPU, THF, r.t.(85%); (d) 4M H_2SO_4, acetone, r.t.(84%); (e) MeMgI, ether, 0^oC(**2**, 28%; **13**, 22%).

In conclusion, we have shown that a SmI_2-mediated fragmentation/elimination sequence is a highly efficient method for converting diiodides **8** and **10** into 5/7 ring systems **1** and **11** with regioselective introduction of two double bonds. Using this methodology, short total syntheses of **1** (5 steps) and dictamnol, **2** (6 steps),[12] have been achieved and support is offered for the revised structure[3] of natural product **2**.

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References and Notes

1. Takeuchi, N.; Fujita, T.; Goto, K.; Morisaki, N.; Osone, N.; Tobinaga, S. *Chem. Pharm. Bull.* **1993**, *41*, 923.
2. Koike, T.; Yamazaki, K.; Fukumoto, N.; Yashiro, K.; Takeuchi, N.; Tobinaga, S. *Chem. Pharm. Bull.* **1996**, *44*, 646.
3. Piet, D.P.; Orru, R.V.A.; Jenniskens, L.H.D.; van de Haar, C.; van Beek, T.A.; Franssen, M.C.R.; Wijnberg, J.B.P.A.; de Groot, A. *Chem. Pharm. Bull.* **1996**, *44*, 1400.
4. Lange, G.L.; Gottardo, C. *Tetrahedron Lett.* **1990**, *31*, 5985.
5. Lange, G.L.; Gottardo, C. *J. Org. Chem.* **1995**, *60*, 2183.
6. Free radical fragmentation of other cyclobutyl carbinyl systems has been reported: (a) Ziegler, F. E.; Zheng, Z.-L. *J. Org. Chem.* **1990**, *55*, 1416. (b) Ranu, B. C.; Das, A. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 921. (c) Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519.
7. Lange, G.L.; Gottardo, C. *Tetrahedron Lett.* **1994**, *35*, 8513.
8. Lange, G.L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473.
9. Free radicals have been suggested as intermediates in the formation of Grignard reagents: (a) Ashby, E. C.; Oswald, J. *J. Org. Chem.* **1988**, *53*, 6068. (b) Walling, C. *Acc. Chem. Res.* **1991**, *24*, 255.
10. If concentrated sulfuric acid in acetone is employed, ketal removal is accompanied by C_6-C_7 double bond migration into conjugation.
11. NOE difference experiments have been reported for **1** and **2**.[3]
12. Both previous syntheses of **1**[3] and **2**[2] required 13 steps.

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