Pergamon

Tetrahedron Letters, Vol. 35, No. 30, pp. 5351-5354, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01058-7

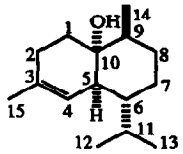
Total Synthesis of (±)-Epicubenol

David E. Cane* and Manish Tandon

Department of Chemistry, Box H, Brown University, Providence, RI 02912, U. S. A.

Abstract: The sesquiterpenoid microbial metabolite (±)-epicubenol (**1**) has been synthesized in 8 steps from a readily available diene aldehyde (**7**) using an intramolecular Diels-Alder reaction.

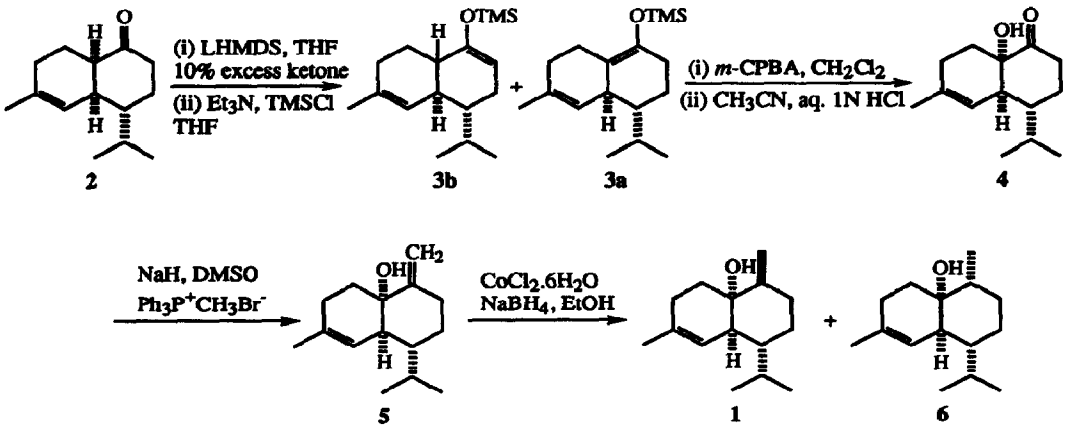
Some 20 years ago Gerber reported the isolation of a cadinene-type sesquiterpene alcohol, (+)-epicubenol (**1**), from *Streptomyces* sp. LL-B7, sp. LL-B5a, and sp. LL-100-1 (Eren).[1] It was shown by NMR, IR, GC, and polarimetric comparison to be the enantiomer of (-)-epicubenol previously isolated from cubeb oil[2a] and a variety of other plant sources.[2b,c] Biosynthetic studies[3] with cell-free extracts have established that **1** is derived from farnesyl diphosphate and have provided evidence for a mechanism of formation involving a germacradienyl cation intermediate and the operation of a 1,3-hydride shift. In this communication we wish to report the first total synthesis of **1**.



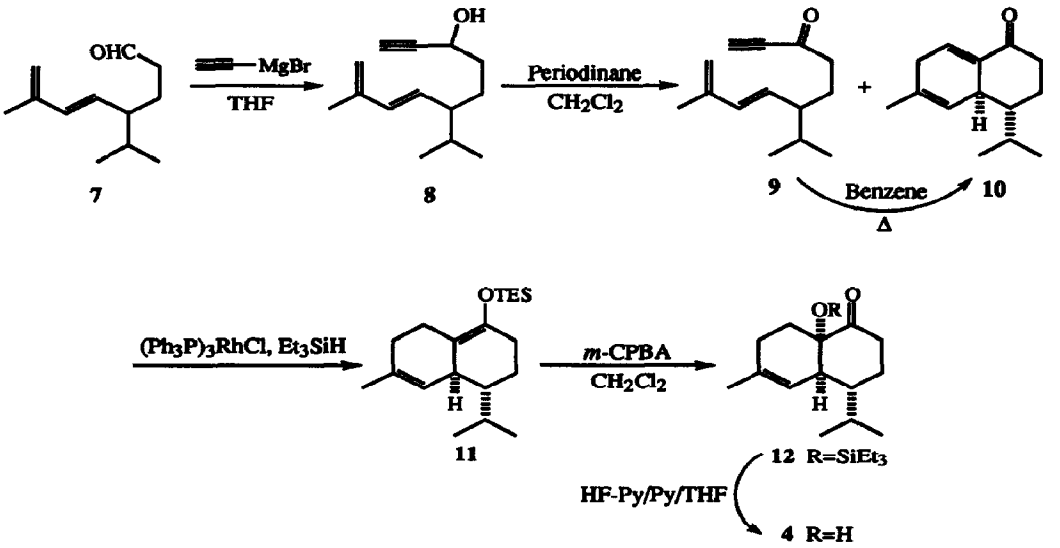
1

The bicyclic ketone **2**, which had been earlier synthesized as an intermediate in the total synthesis of (±)-torreyol by Taber *et al.*,[4] was initially selected as the starting material for the synthesis of **1** because it possesses

the correct relative stereochemistry of the isopropyl group and the ring junction hydrogen H-5. In preparation for the introduction of the hydroxyl group at C-10, **2** was converted into the trimethylsilylenol ethers **3a** and **3b** in a ratio of 45:55 (LHMDS, 10% excess ketone, -78°C, 15 min, rt, 16 h; 1.5 equiv TMSCl, 0.85 equiv Et_3N, 4.5 ml THF, rt, 10 min). All attempts to improve the ratio of **3a**:**3b** by forming the enolate under thermodynamic conditions failed. The enol ethers **3a** and **3b** were separated by repeated chromatography in 75% overall yield.[5] Reaction of **3a** with *m*-CPBA (1.0 equiv, CH_2Cl_2, rt, 1 h)[6] followed by treatment of the resulting crude product with aqueous 1N HCl in acetonitrile afforded the α-hydroxyketone **4** with the expected *cis*-fused[7] ring in 70% yield. Wittig olefination[8] of **4** with triphenylphosphonium methyl bromide (4.2 equiv) in NaH (4.0 equiv) and DMSO (rt, 5 h) resulted in the formation of the α-hydroxyalkene **5** in 78% yield. The exocyclic double bond was then reduced[9] in preference over the internal trisubstituted double bond with a mixture of $NaBH_4$ (3.0 equiv) and $CoCl_2.6H_2O$ (1.0 equiv) in ethanol (rt, 14 h). The reduction resulted in the formation of **1** and its diastereomer syn-epicubenol (**6**), in a 1:1 ratio with a combined yield of 75% for the two isomers which were separated by repeated SiO_2 flash column chromatography and individually characterized. The relative stereochemistry of **1** was verified by X-ray crystallographic studies on a triol obtained by treatment of **1** with OsO_4.[3] The synthetic sample of (±)-epicubenol was identical in spectroscopic properties and chromatographic behavior with an authentic sample of **1** obtained from mycelial extracts of *Streptomyces* sp. LL-B7.



While exploring ways to improve the proportion of **3a**, we postulated that an intramolecular Diels-Alder reaction between the alkynone and a diene moieties in **9** would result in the formation of bicyclic enone **10**, which could be converted into a silylenol ether *via* a 1,4-hydride reduction. The silylenol ether could then be further elaborated into epicubenol. In fact the diene aldehyde **7**, which had been synthesized as an intermediate in the synthesis of **2** by Taber *et al.*,[4] was converted into the alkyne alcohol **8** by a Grignard reaction with ethynl magnesium bromide (2 equiv, THF, rt, 1 h) in 90% yield. Dess-Martin periodinane oxidation[10] of **8** resulted in the formation of the alkynone **9** which slowly underwent an intramolecular Diels-Alder reaction to **10**. The mixture of **9** and **10** was heated in a sealed tube at 120 °C in benzene for 2 h to complete the cyclization with an overall yield of 73% over both steps. The 1,4-hydride reduction[11] was subsequently carried out by heating **10** with Wilkinson's catalyst (0.4 equiv) and triethylsilane (1.05 equiv, 93 °C, 5 min), resulting in the formation of the triethylsilyl enol ether **11** in 66% yield.[12] Hydroxylation of **11** with *m*-CPBA (1.0 equiv, CH_2Cl_2, rt, 1 h) resulted in the formation of **4** and the α-silyloxyketone **12** which could be readily converted into **4** by treatment with HF-Py/Py/THF (0.25 ml).[13] The overall yield for the conversion of **11** to **4** was 65%. The α-hydroxyketone produced by hydroxylation of **11** was identical to that produced in the original synthesis of **1**. Based on this more direct route, (±)-1 can therefore be readily prepared in 8 steps from the diene aldehyde **7**.



Acknowledgments: This work was supported by a grant from the National Institutes of Health (GM30301). We thank Dr. Mike Nichols for carrying out the X-ray structure determination on the crystalline derivative of **1**. We also thank Jason Silvers for carrying out preliminary studies.

References and Notes

1. Gerber, N. N. *Phytochemistry* **1971,** *10*, 185. Although epicubenol (cadin-4-en-1-ol) was properly identified, the stereochemistry of **1** was incorrectly depicted as that of the isomeric cubenol.
2(a). Ohta, Y.; Hirose, Y. *Tetrahedron Lett.* **1967,** 2073. (b) Tomita, B.; Hirose, Y. *Phytochemistry* **1972,** *11*, 3355 and refs. 1-6 therein. (c) Talvite, A.; Borg-Karlson, A.-K. *Finn. Chem. Lett.* **1979,** 93.
3. Cane, D. E.; Tandon, M.; Prabhakaran, P. C. *J. Am. Chem. Soc.* **1993,** *115*, 8103.
4. Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979,** *101*, 3992.
5. All new compounds were fully characterized by ^{1}H and ^{13}C NMR, IR, and high resolution mass spectroscopy.
6. Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975,** *40*, 3427.
7. Johnson, W. S.; Allen, D. S. Jr.; Hindersinn, R. R.; Sausen, G. N.; Pappo, R. *J. Am. Chem. Soc.* **1962,** *84*, 2181.
8. Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963,** *28*, 1128.
9. Chung, S.-K. *J. Org. Chem.* **1979,** *44*, 1014.
10. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983,** *48*, 4155.
11. Ojima, I.; Kogure, T. *Organometallics*, **1982,** *1*, 1390.
12. The bicyclic ketone **2** was also produced in 15% yield.
13. Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990,** *112*, 7001.

(*Received in USA* 16 *May* 1994; *accepted* 31 *May* 1994)