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Synthesis of the Sesquiterpene (±)-Ceratopicanol: Use of Radicals Derived from Epoxides

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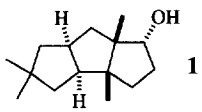
Summary: The sesquiterpene (±)-ceratopicanol [(±)-**1**] was synthesized by a route based on Claisen rearrangement (**7** → **8**) and radical cyclization (**16**α, **16**β → **17**α, **17**β). Certain limitations on vinyl radical cyclization were observed, and so the required radical was generated by titanium-induced opening of an epoxide.

Ceratopicanol (**1**)[1] has a noteworthy place in biogenetic theory as its structure represents evidence for generation *in vivo* of carbonium ion **2** — a species suggested[2] to be a precursor of hirsutene and related natural products. We report the synthesis[3] of (±)-**1** by a route that involves radical cyclization. Several of our experiments have exposed some limitations to certain types of radical closure.



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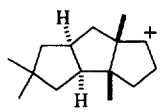
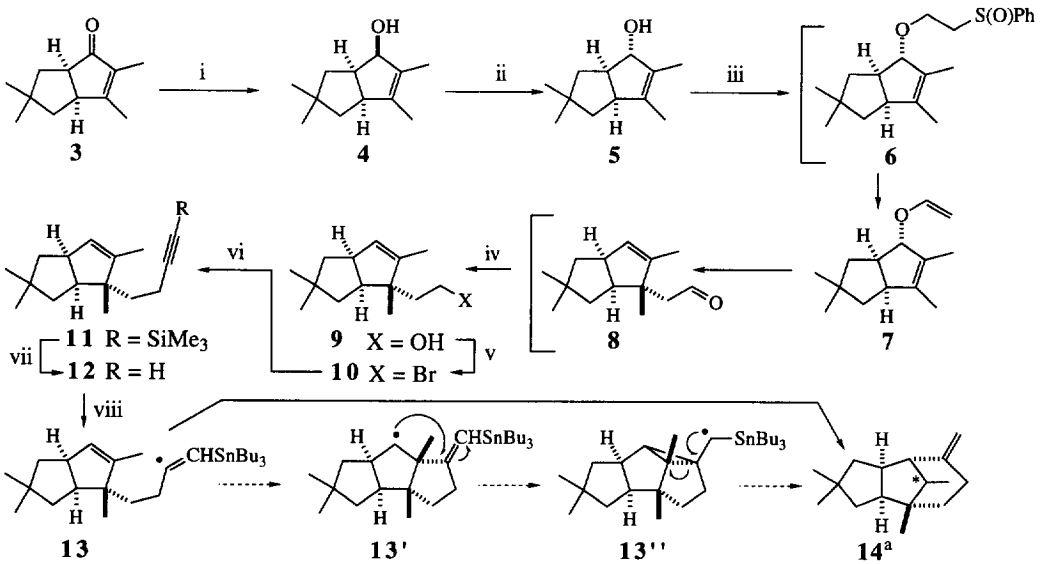


2

Enone **3** (Scheme 1), readily available by a reported method,[4] was reduced (**3** → **4**; DIBAL, 89%), and Mitsunobu inversion under carefully controlled conditions[5] (Ph_3P, $ClCH_2CO_2H$, DEAD; $LiAlH_4$; 58% overall), then gave the *exo* alcohol **5**. This was converted successively into vinyl ether **7**, then the product of Claisen rearrangement **8** and, finally, the reduction product **9**. These transformations were best done (73% overall) by treating **5** with phenyl vinyl sulfoxide (**5** → **6**) and heating the product (150°C).[6] Under these conditions **7** was generated and it rearranged *in situ* to **8**, which was reduced (**8** → **9**; $LiAlH_4$) without purification. Alcohol **9** was converted efficiently into bromide **10** (Ph_3P, CBr_4; 94%), and the bromine was then displaced (**10** → **11**) with lithium trimethylsilylacetylide. Exposure of **11** (which was not isolated) to 1 M methanolic sodium hydroxide gave the key acetylene **12** (94% from **10**). When this compound was treated in refluxing benzene with Bu_3SnH (0.01-0.07 M), in the presence of AIBN, the intermediate vinyl radical **13** was formed, but it gave **14**,[7] the formal result of 6-*endo* trigonal closure. None of the product of the desired 5-*exo* closure, which we had observed as the exclusive pathway in model studies,[8] was isolated. Use of a higher stannane concentration (1.1 M) again led to **14**, and hydrostannylation of the triple bond now became a serious competing reaction; consequently, we were unable to establish if the observed product is the result of initial 5-*exo* cyclization (**13** → **13'**), followed by rearrangement (**13'** → **13"** → **14**).[9] If the rate of hydrogen abstraction by the initial (hindered) radical (from 5-*exo* closure) is slow, the rearrangement (**13'** → **13"** → **14**) need not be unusually fast, but the possibility remains that formation of **14** is an example of kinetically preferred

Scheme 1



[a]Stereochemistry at starred atom in **14** not established; material is a single isomer. *Reagents and conditions*: i, DIBAL, CH_2Cl_2, 0°C, 2 h (89%); ii, PPh_3, $ClCH_2CO_2H$, DEAD, benzene, 3 h; $LiAlH_4$, THF, 0°C → 25°C, (58% overall); iii, $CH_2CHS(O)Ph$, NaH, KH, THF, 3 h; decalin, 150°C, 40 h; iv, $LiAlH_4$, THF, -78°C → 25°C, (73% from **5**); v, Ph_3P, CBr_4, CH_2Cl_2, 0°C → 25°C, 1.5 h (94%); vi, $LiC{\equiv}CSiMe_3$, HMPA, THF, -78°C → 25°C, 4 h; vii, 1 M methanolic NaOH, 6 h (94% from **10**); viii, Bu_3SnH, AIBN, benzene, 80°C, 1-4 h; silica gel (*ca* 75%).

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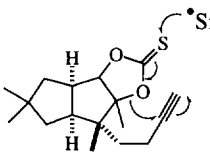
direct 6-*endo* closure.[10,11] Several examples are known of vinyl radicals cyclizing onto proximally substituted non-conjugated double bonds,[12] and so it was disappointing to see none of the desired 5-*exo* closure product in our case.[11] We tried, therefore, to generate the radical at a different position so as to effect closure *onto* the triple bond.

To that end, alcohol **9** was converted into the thionocarbonates shown in **15**,[13] with which we hoped to induce the radical process summarized by the arrows (see **15**). Some work has been reported on stannane

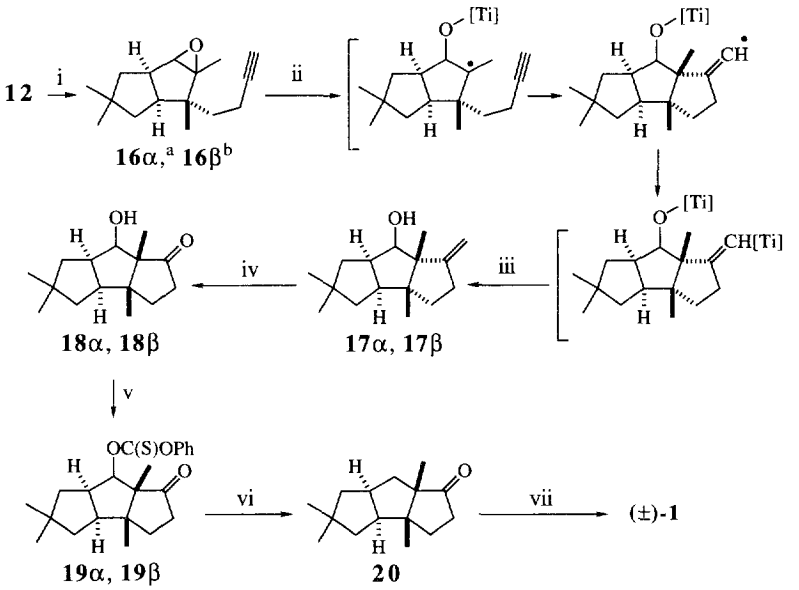


15

reduction of unsymmetrical thionocarbonates,[14] and formation of either the less substituted or the more substituted radical (as in **15**) has been observed; however, the factors that control regiochemistry are not entirely clear but must include[14] other important considerations besides the status (primary, secondary, or tertiary) of the potential carbon radical products. In any event, we were unable to explore this point, as our attempts to reduce **15**[15] with stannanes (Ph_3SnH or Bu_3SnH) gave quite complex mixtures in which products of the desired type

were not present (as judged by 200 MHz ^{1}H NMR spectra of the reaction mixtures). Fortunately, the ring closure problem posed by the thionocarbonates was easily dealt with as soon as we recognized that an epoxide can be made to behave (see Scheme 2) in a synthetically equivalent manner to that expressed in diagram **15**.

Scheme 2



[a]Oxygen *syn* to acetylenic chain. [b]Oxygen *anti* to acetylenic chain. *Reagents and Conditions*: i, MCPBA, CH_2Cl_2, 0°C, 2 h (**16α** 75%; **16β** *ca* 25%; ii, Cp_2TiCl, THF, room temperature, 7 h for **17α**, 2 h for **17β**; iii, 10% H_2SO_4 workup (**17α**: 82% from **16α**; **17β**: 81% from **16β**); iv, Ac_2O, AcCl, DMAP, pyridine, 25°C, 2-4 h; OsO_4, 4-methylmorpholine *N*-oxide, 10:1 acetone-H_2O, *ca* 12 h; K_2CO_3, MeOH, 1 h; $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, 0°C → 25°C, (**18α** 80%, **18β** 75%); v, ClC(S)OPh, DMAP, CH_3CN, 8 h (**19α** 84%, **19β** 74%); vi, Bu_3SnH, Et_3B, air, hexane, 0°C, 1 h, workup, and treat again with stannane/borane system (72% from **19α**, 73% from **19β**); vii, $NaBH_4$, MeOH, -20°C, 20 min (81%).

Epoxidation of acetylene **12** (MCPBA) gave two epoxides, **16α** (oxygen *syn* to acetylenic chain, 75%) and **16β** (oxygen *anti* to acetylenic chain, *ca* 25%[16]). The compounds were separated chromatographically and each was treated with bis(cyclopentadienyl)titanium(III) chloride[17] in tetrahydrofuran to afford **17α** (82%) and **17β** (81%), respectively, as shown in Scheme 2. From this point, completion of the synthesis required deoxygenation of **17α** and **17β**, and stereoselective replacement of the exocyclic methylene by a hydroxyl ($C{=}CH_2 \rightarrow C{=}O \rightarrow CHOH$). Direct radical deoxygenation of **17α** or **17β** via the derived phenoxythiocarbonyl esters[18] led to rearrangement product **14**. Accordingly, **17α** and **17β** were individually acetylated (AcCl, pyridine, DMAP; 94% and 95%, respectively), hydroxylated (OsO_4), hydrolyzed (MeOH, K_2CO_3), and treated with $Pb(OAc)_4$, to afford hydroxy ketones **18α** and **18β** (80% and 75%, respectively, from the acetates). These were converted[18] into the corresponding phenoxythiocarbonyl esters **19α** and **19β** (84% and 74%, respectively) and deoxygenated (**19α** and **19β** → **20**) at 0°C with Bu_3SnH in the presence of Et_3B and air.[19] The stannane reduction must be done by the borane method as standard thermal conditions (Bu_3SnH, AIBN,

boiling toluene) led to appreciable ring expansion.[20] Finally, reduction of **20** with $NaBH_4$ afforded crystalline (±)-ceratopicanol (81%, mp 67-68°C), whose 300 MHz ^1H NMR spectrum matched the reported[1] data.

All new compounds were characterized by spectroscopic measurements (including mass measurements) and, usually, also by combustion analysis.

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References and Footnotes

1 Hanssen, H.-P.; Abraham, W.-R. *Tetrahedron* **1988**, *44*, 2175.
2 Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Helv. Chim. Acta* **1981**, *64*, 1347. Comer, F.W.; McCapra, F.; Qureshi, I.H.; Scott, A.I. *Tetrahedron* **1967**, *23*, 4761.
3 For synthesis of the unnatural antipode, see: Mehta, G.; Karra, S.R. *J. Chem. Soc., Chem. Commun.* **1991**, 1367.
4 Tobe, Y.; Yamashita, D.; Takahashi, T.; Inata, M.; Sato, J.; Kakiuchi, K.; Kobiro, K.; Odaira, Y. *J. Am. Chem. Soc.* **1990**, *112*, 775 and references cited therein.
5 Saïah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317.
6 Mandai, T.; Ueda, M.; Hasegawa, S.; Kawada, M.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1990**, *31*, 4041.
7 Stereochemistry at starred atom in **14** not established; material is a single isomer.
8 Clive, D.L.J.; Manning, H.W. *J. Chem. Soc., Chem. Commun.* **1993**, 666.
9 Beckwith, A.L.J.; O'Shea, D.M. *Tetrahedron Lett.* **1986**, *27*, 4525. Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529. Denis, R.C.; Rancourt, J.; Ghiro, É.; Boutonnet, F.; Gravel, D. *Tetrahedron Lett.* **1993**, *34*, 2091.
10 *Cf.* Berkowitz, W.F.; Wilson, P.J. *J. Org. Chem.* **1991**, *56*, 3097.
11 *Cf.* Kataoka, T.; Yoshimatsu, M.; Noda, Y.; Sato, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 121.
12 E.g. Stork, G.; Baine, N.H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. G. Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720. Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829.
13 Each of the two isomers corresponding to the structure shown in **15** (oxygens *cis*, and either *syn* or *anti* to the acetylenic chain) was examined. The thionocarbonates were obtained by acetylation of **9** followed by vicinal hydroxylation (OsO_4), and separation of the resulting diols. The diols were individually ketalized (2,2-dimethoxypropane, pyridinium *p*-toluenesulfonate), and then the acetate was hydrolyzed (MeOH, K_2CO_3). The resulting primary alcohols were each homologated by the same method as had been used to convert **9** into **12**. Finally, the ketal was hydrolyzed (I_2, MeOH) and the liberated diols were treated with thiophosgene in the presence of DMAP.
14 E.g. Barton, D.H.R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718. Redlich, H.; Sudau, W.; Paulsen, H. *Tetrahedron* **1985**, *41*, 4253. Ziegler, F.E.; Zheng, Z. *J. Org. Chem.* **1990**, *55*, 1416 and references cited therein.
15 We studied both isomers.
16 This isomer was not obtained absolutely pure, and was used as such.
17 RajanBabu, T.V.; Nugent, W.A. *J. Am. Chem. Soc.* **1994**, *116*, 986.
18 Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.
19 Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 6127. Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. Barton, D.H.R.; Jang, D.O.; Jasberenyi, J.Cs. *Tetrahedron Lett.* **1990**, *31*, 4681.
20 *Cf.* Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

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