

Total Syntheses of (\pm)- α -Biotol, (\pm)- β -Biotol, and (\pm)-4-Epi- α -biotol

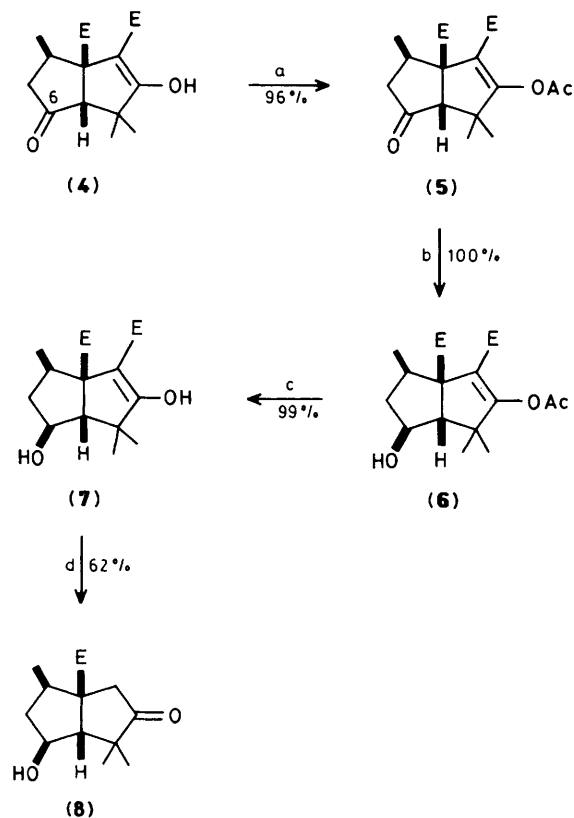
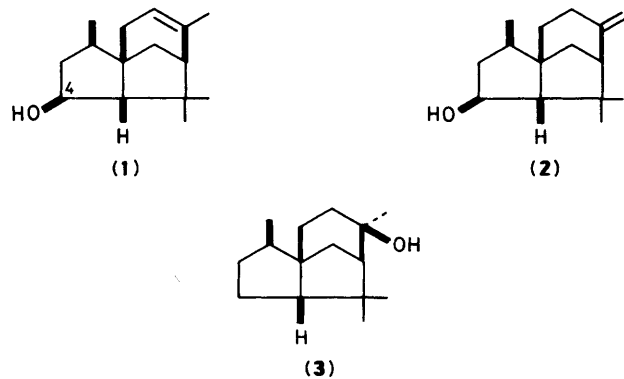
Rupinder S. Grewal, Peter C. Hayes, Jeffery F. Sawyer, and Peter Yates*

Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario, Canada M5S 1A1

Total syntheses of (\pm)- α -biotol, (\pm)- β -biotol, and (\pm)-4-epi- α -biotol from dimethyl 3-hydroxy-6-oxo-4,4,exo-8-trimethyl-*cis*-bicyclo[3.3.0]oct-2-ene-1,2-dicarboxylate are reported.

α -Biotol (**1**) and β -biotol (**2**) are cedranoid sesquiterpenes isolated from the essential oil of the wood of *Biota orientalis* together with cedrol (**3**).¹ The original structural assignment¹ for (**1**) has been corroborated by its partial synthesis from (**3**) by dog metabolism and subsequent laboratory processing.^{2,3} We now report the total synthesis of (\pm)-(**1**) and (\pm)-(**2**) via the bicyclo[3.3.0]octene derivative (**4**), whose preparation has been described earlier.⁴

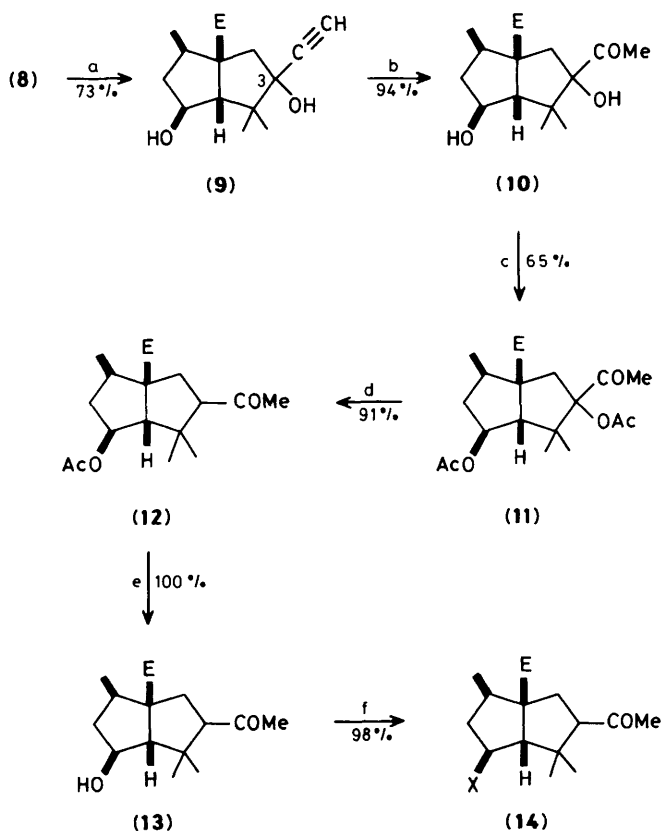
Highly chemo- and stereo-selective reduction of the C-6 carbonyl group of (**4**) was achieved (Scheme 1) by its conversion into the acetate (**5**), reduction of (**5**) with NaBH₄ to give (**6**), and hydrolysis of (**6**) to give (**7**). The configuration at C-6 in (**6**) and (**7**) was established by monodemethoxycarbonylation of (**7**) to (**8**), whose relative stereochemistry at C-6 was established by X-ray crystallography.^{5†}



E = CO₂Me

Scheme 1. Reagents: a, Ac₂O-C₅H₅N; b, NaBH₄-MeOH, 0°C; c, K₂CO₃-MeOH; d, NaCl-H₂O-dimethyl sulphoxide, heat.

† The exclusive formation of the *exo* isomer (**6**) on reduction of (**5**) with NaBH₄ is noteworthy, since such reduction of bicyclo[3.3.0]octan-2-ones usually gives the *endo* product preferentially.⁵

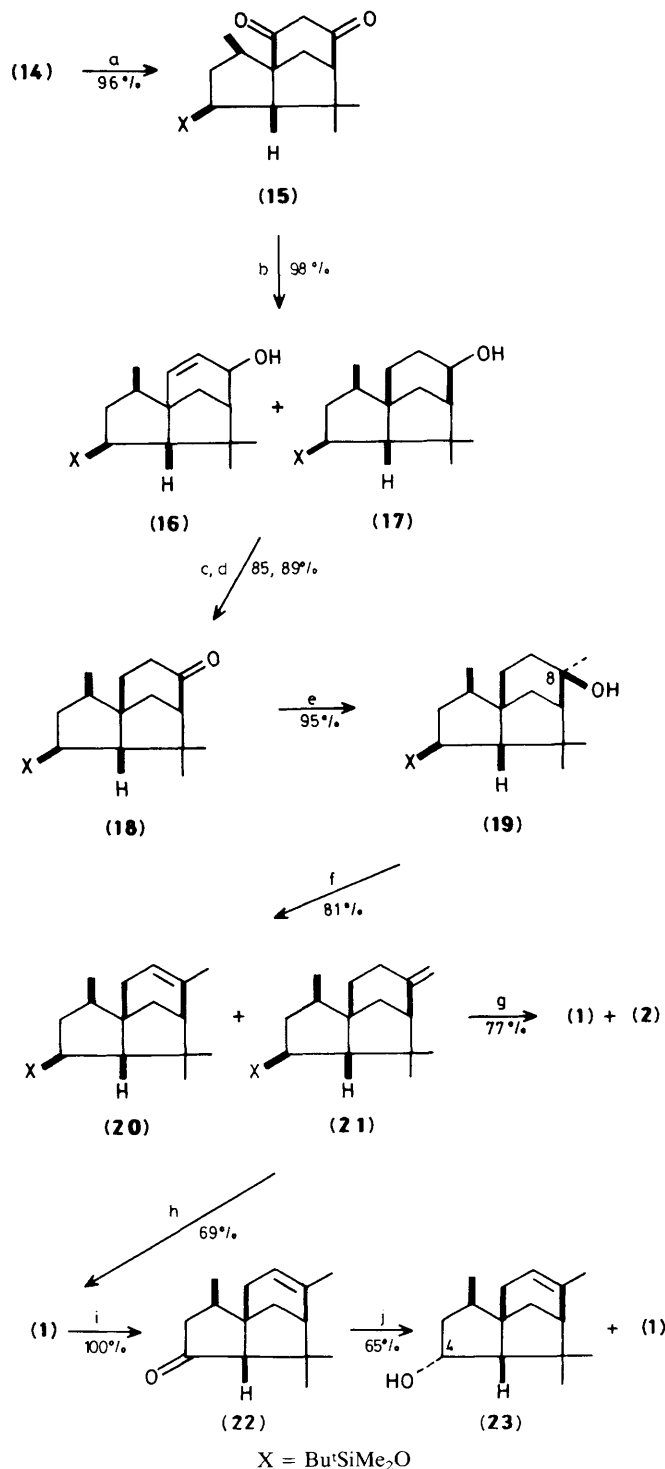


E = CO₂Me, X = Bu^tSiMe₂O

Scheme 2. Reagents: a, LiC≡CH-CeCl₃-tetrahydrofuran (THF), -78°C; b, HgO-3M H₂SO₄-THF; c, Ac₂O-DMAP-CH₂Cl₂, (DMAP = 4-*N,N*-dimethylaminopyridine); d, Bu₃SnH-AIBN-PhMe, heat; e, K₂CO₃-MeOH; f, Bu^tSiMe₂OSO₂CF₃-2,6-Me₂C₅H₃N-CH₂Cl₂, 0°C.

Treatment of (8) with lithium acetylide in the presence of CeCl₃⁶ gave the propynylic alcohol (9) (Scheme 2). Hydration of the acetylenic bond gave (10), which was acetylated to give (11). Highly selective reductive removal of the tertiary acetoxy group with tri-*n*-butyltin hydride and azoisobutyronitrile (AIBN)⁷ gave (12). Hydrolysis to (13) followed by silylation yielded (14). The relative configuration at C-3 in compounds (9)–(14) was not established; it is of no consequence insofar as the final synthetic goals are concerned (*vide infra*).

Compound (14) was converted into (19) by a route (Scheme 3) patterned on that used by Stork and Clarke in their synthesis of cedrol (3).⁸ Ring closure of (14) to the β-diketone (15) was effected under conditions that permitted epimerization at C-3, allowing ring closure whatever the configuration at C-3 in (14). Reduction of (15) with LiAlH₄ gave a mixture of the allyl and saturated alcohols (16) and (17) which, on oxidation followed by hydrogenation, gave the single ketone (18). Treatment of (18) with methyl-lithium gave a single tertiary alcohol (19), which was assigned the relative configuration shown at C-8 by analogy to cedrol (3).⁸ This was dehydrated to give a mixture of (20) and (21). Desilylation of the mixture of (20) and (21) with HF gave a 2:1 mixture of (±)-(1) and (±)-(2), which were separated on SiO₂ to give (±)-(1), m.p. 68–70°C, and (±)-(2), m.p. 95–97°C. Desilylation of the mixture of (20) and (21) with HCl was accompanied by isomerization of the exocyclic ethylenic double bond and gave solely (±)-α-biotol (1). Oxidation of this to (±)-α-biotone (22)^{1–3} followed by reduction with



X = Bu^tSiMe₂O

Scheme 3. Reagents: a, Bu^tOK-Bu^tOH, heat; b, LiAlH₄-Et₂O, heat; c, CrO₃-C₅H₅N; d, H₂-Pd-C-EtOH; e, MeLi-Et₂O, heat; f, SOCl₂-C₅H₅N, 0°C; g, 5% aq. HF-MeCN, 0°C; h, HCl-MeOH; i, pyridinium chlorochromate-CH₂Cl₂; j, LiAlH₄-Et₂O, heat.

LiAlH₄ gave a 1:1 mixture of (±)-(1) and (±)-4-epi-α-biotol (23),^{1,3} which were separated on SiO₂ to provide pure (±)-(23), m.p. 57–59°C.‡

‡ The identities of (±)-(1) and (±)-(23) were established by comparison of their solution i.r. and ¹H and ¹³C n.m.r. spectra with those of (1) and (23) kindly provided by Dr. Pierre Brun, Université d'Aix-Marseille.

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