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

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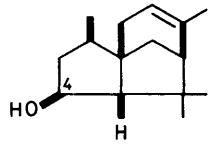
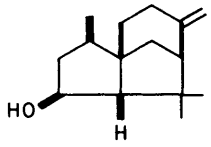
Total syntheses of (±)-α-biotol, (±)-β-biotol, and (±)-4-epi-α-biotol from dimethyl 3-hydroxy-6-oxo-4,4,*exo*-8-trimethyl-*cis*-bicyclo[3.3.0]oct-2-ene-1,2-dicarboxylate are reported.

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 assignment[1] 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 (±)-(**1**) and (±)-(**2**) *via* the bicyclo[3.3.0]octene derivative (**4**), whose preparation has been described earlier.[4]

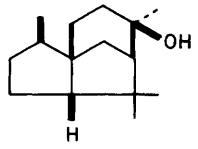
Highly chemo- and stereo-selective reduction of the C-6 carbonyl group of (**4**) was achieved (Scheme 1) by its conversion into the acetate (**5**), reduction of (**5**) with $NaBH_4$ to give (**6**), and hydrolysis of (**6**) to give (**7**). The configuration at C-6 in (**6**) and (**7**) was established by monodemethoxycarbonylation of (**7**) to (**8**), whose relative stereochemistry at C-6 was established by *X*-ray crystallography.[5]†



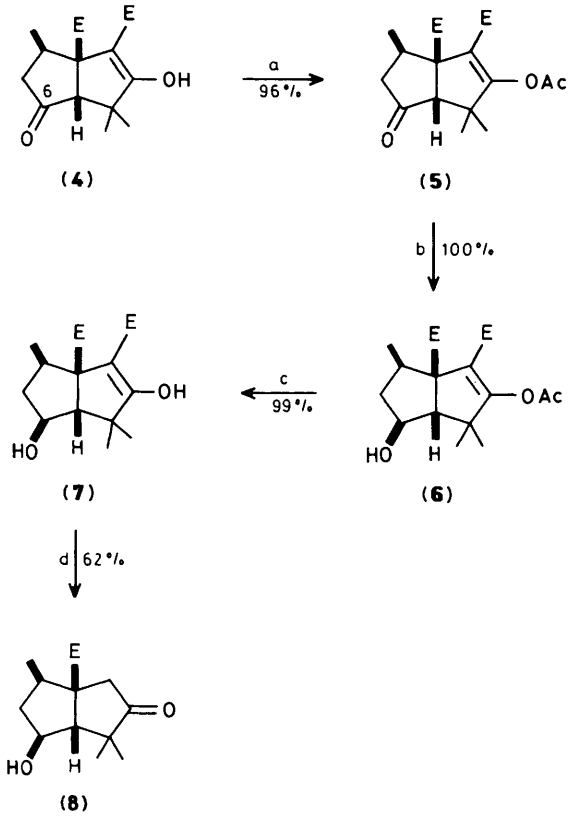
(**1**)



(**2**)



(**3**)

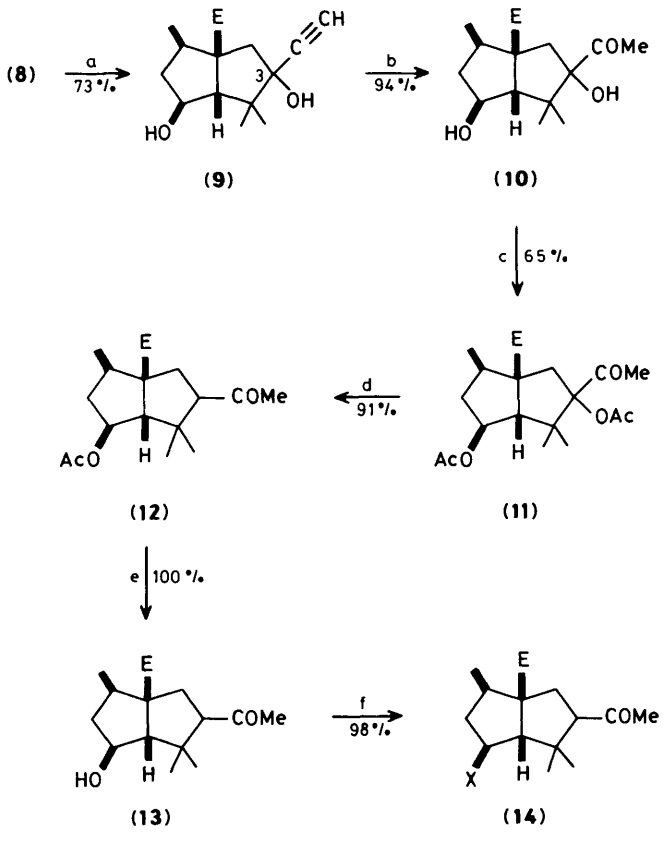


(**4**) (**5**) (**6**) (**7**) (**8**)

E = CO_2Me

Scheme 1. *Reagents:* a, Ac_2O–C_5H_5N; b, $NaBH_4$–MeOH, 0 °C; c, K_2CO_3–MeOH; d, NaCl–H_2O–dimethyl sulphoxide, heat.

† The exclusive formation of the *exo* isomer (**6**) on reduction of (**5**) with $NaBH_4$ is noteworthy, since such reduction of bicyclo[3.3.0]-octan-2-ones usually gives the *endo* product preferentially.[5]



E = CO_2Me, X = Bu^tSiMe_2O

Scheme 2. *Reagents:* a, $LiC{\equiv}CH$–$CeCl_3$–tetrahydrofuran (THF), −78 °C; b, HgO–3M H_2SO_4–THF; c, Ac_2O–DMAP–CH_2Cl_2, (DMAP = 4-*N*,*N*-dimethylaminopyridine); d, Bu_3SnH–AIBN–PhMe, heat; e, K_2CO_3–MeOH; f, $Bu^tSiMe_2OSO_2CF_3$–2,6-$Me_2C_5H_3N$–CH_2Cl_2, 0 °C.

Treatment of (**8**) with lithium acetylide in the presence of $CeCl_3$[6] 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 $LiAlH_4$ 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 SiO_2 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 $LiAlH_4$ gave a 1 : 1 mixture of (±)-(**1**) and (±)-4-epi-α-biotol (**23**),[1,3] which were separated on SiO_2 to provide pure (±)-(**23**), m.p. 57—59 °C.‡

X = Bu^tSiMe_2O

Scheme 3. *Reagents:* a, Bu^tOK–Bu^tOH, heat; b, $LiAlH_4$–Et_2O, heat; c, CrO_3–C_5H_5N; d, H_2–Pd–C–EtOH; e, MeLi–Et_2O, heat; f, $SOCl_2$–C_5H_5N, 0 °C; g, 5% aq. HF–MeCN, 0 °C; h, HCl–MeOH; i, pyridinium chlorochromate–CH_2Cl_2; j, $LiAlH_4$–Et_2O, heat.

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

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