An Enantiospecific Synthesis of Longiborneol and Longifolene

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(+)-8-Bromocamphor (7) is readily converted into a chiral enol ether acetal (8) which undergoes TiCl₄-promoted cyclization to provide a tricyclic intermediate that can serve as a synthetic precursor of longibornane and longifolane sesquiterpenoids.

In previous reports¹ we outlined a general synthetic plan for the construction of a series of structurally and perhaps biosynthetically related bicyclic, tricyclic, and tetracyclic sesquiterpenoids in which (+)-camphor (1) or its enantiomer could be regarded as an important chiral starting material. Included in this proposal was the assumption that (+)longicamphor (2)[†] could be synthesized from (+)-camphor (1), and then serve as the synthetic precursor of the naturally occurring sesquiterpenoids, (+)-longiborneol (3), $\ddagger (+)$ -longifolene (5), \ddagger and (+)-longicyclene (6). Recent studies in our laboratory have shown that the bicyclic trimethylsilyl ether (8), derived from (+)-8-bromocamphor (7)⁵ (Scheme 1), undergoes facile intramolecular cyclization when treated with titanium tetrachloride⁶ at -78 °C for 45 minutes. The product of this reaction, isolated in \sim 85% yield, was a mixture (\sim 3:1) of diastereoisomeric methoxyketones (9a,b)§ and the structure and absolute configuration of the major epimer (9a) was confirmed by X-ray crystallographic analysis.⁷ Subsequent functional group transformations {reduction [Ca/NH₃(l)], acetylation [Ac₂O, 4-N,N-dimethylaminopyridine(DMAP), C₅H₅N], demethylation (BBr₃, 15-crown-5, NaI, CH₂Cl₂),⁸ and oxidation (pyridinium dichromate (PDC), CH₂Cl₂, $72 h^{9}$ provided the keto acetate (11)¶ in ~75% overall yield. Conversion of the ketone group in (11) to the required





⁺ Several synthetic routes to racemic or optically active forms of longicamphor,² longiborneol,² longifolene,³ longicyclene,² and culmorin⁴ have been reported previously.

 \ddagger The naturally occurring enantiomers of (3) and (5) would of course, be accessible using commercially available (-)-camphor as starting material.

§ Diastereoisomeric hydroxyethoxyketones were obtained in \sim 75% yield when the ethylene acetal corresponding to (8) was cyclized in a similar way.

¶ Attempts to convert methoxy-acetate (10) to keto acetate (11) by reaction with nitronium tetrafluoroborate¹⁰ provided a low yield of the corresponding diketone.

gem-dimethyl group|| was accomplished by an efficient 3-step procedure (methylenation, cyclopropanation, and hydrogenolysis)^{3d,11} and, when this was coupled with reductive removal of the acetate group, (+)-longiborneol (**3**)¹² [α]_D +15.8° (*c* 0.54, CHCl₃), was obtained in ~70% overall yield. The n.m.r. spectrum [400 MHz; δ 0.84 (3H, s), 0.86 (3H, s), 0.94 (6H, s), 3.77 (1H, dd, *J* 2 Hz, 5 Hz)] and capillary g.l.c.



Scheme 1. Reagents and conditions: i, Br₂, HBr, HOAc, 110 °C; ii, Br₂, ClSO₃H; iii, Zn, HOAc, Et₂O, 0 °C; iv, KI, dimethyl sulphoxide (DMSO), 110 °C, 3 days; v, Me₃SiCl, HOCH₂CH₂OH; vi, NaCN, DMSO, 70 °C, 2 days; vii, lithium di-isopropylamide (LDA), THF, -78 °C; Bu^tMe₂SiOCH₂CH₂CH₂Br; viii, K, hexamethylphosphoramide (HMPA), Et₂O, Bu^tOH, 0 °C; ix, HCl, Me₂CO; x, PDC, CH₂Cl₂; xi, HC(OMe)₃, CeCl₃, MeOH; xii, LDA, THF, -78 °C; Me₃SiCl; xiii, TiCl₄, CH₂Cl₂, -78 °C; xiv, Ca/NH₃(l), Et₂O; xvi, Ac₂O, DMAP, C₃H₅N; xvi, BBr₃, 15-crown-5, NaI, CH₂Cl₂; xvii, Ph₃MePBr, BuLi, $-78 \rightarrow 20$ °C; xviii, Et₂Zn, CH₂I₂, prMe; xix, H₂/Pt, HOAc, 2.5 atm; xx, LiAlH₄, THF; xxi, PCC, CH₂Cl₂; xxii, MeSO₂Cl, C₅H₅N, DMAP, 100 °C, 16 h.

^{||} We are currently investigating the possibility of converting ketoacetate (11) directly to (12) by the procedure (Me_2TiCl_2 , CH_2Cl_2) developed by Reetz and coworkers.^{11a}

retention times were identical to those of authentic longiborneol. Oxidation of (+)-longiborneol (3) with pyridinium chlorochromate (PCC)¹³ gave (+)-longicamphor (2)** which was converted into isolongiborneol (4) by reduction with LiAlH₄, tetrahydrofuran (THF). Subsequent treatment of isolongiborneol (4) with methanesulphonyl chloride and DMAP, pyridine at ~100 °C provided (+)-longifolene (5)^{3d} {[α]_D +51.78 (*c* 0.89, CHCl₃); δ (400 MHz, CDCl₃), 0.9 (3H, s), 0.95 (3H, s), 1.00 (3H, s), 4.5 (1H, s), 4.75 (1H, s)} in ~65% yield.

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** Unsuccessful attempts to construct the longicamphor structure by photochemical, thermal, base-protonated, or Lewis acid-catalysed cyclization of campherenone, campherenone hydrochloride, campherenone enol trimethylsilyl ether, and campherenone enol acetate will be described in a future paper. Campherenone was synthesized by prenylation of 8-cyanocamphor ethylene acetal¹⁴ followed by reductive decyanation.¹⁵ This is a less hazardous and more convenient synthetic route than the one previously reported¹ by us. J. CHEM. SOC., CHEM. COMMUN., 1986

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