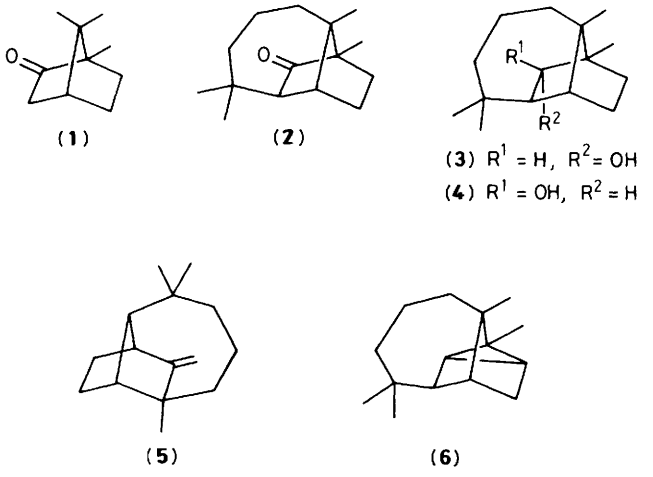
An Enantiospecific Synthesis of Longiborneol and Longifolene

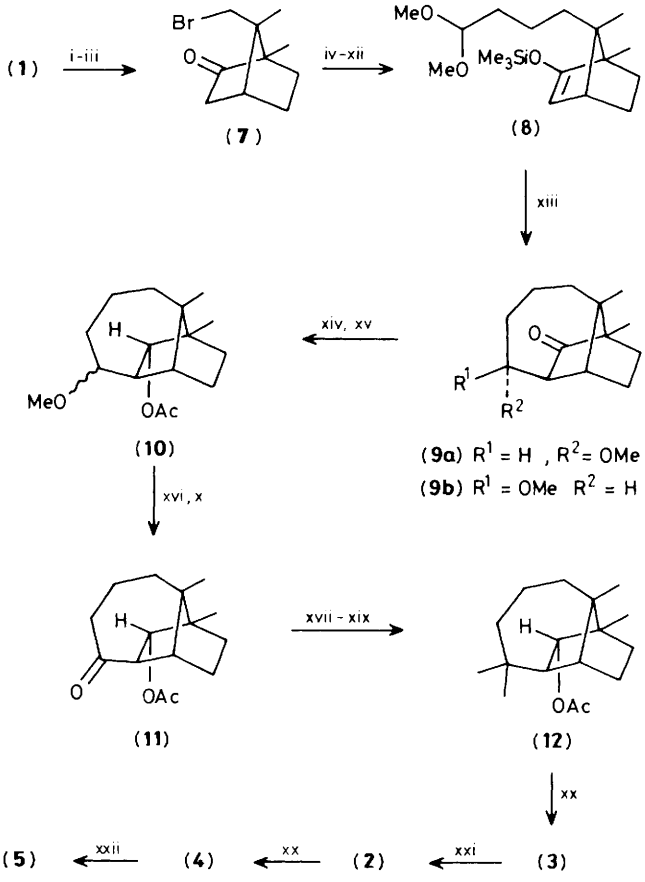
David L. Kuo and Thomas Money*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, B.C., Canada V6T 1Y6

(+)-8-Bromocamphor (**7**) is readily converted into a chiral enol ether acetal (**8**) which undergoes $TiCl_4$-promoted cyclization to provide a tricyclic intermediate that can serve as a synthetic precursor of longibornane and longifolane sesquiterpenoids.

In previous reports[1] 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**),‡ (+)-longifolene (**5**),‡ 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 tetrachloride[6] at −78 °C for 45 minutes. The product of this reaction, isolated in ~85% yield, was a mixture (~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 [$Ca/NH_3(l)$], acetylation [Ac_2O, 4-*N*,*N*-dimethylaminopyridine(DMAP), C_5H_5N], demethylation (BBr_3, 15-crown-5, NaI, CH_2Cl_2),[8] and oxidation [pyridinium dichromate (PDC), CH_2Cl_2, 72 h][9]} provided the keto acetate (**11**)¶ in ~75% overall yield. Conversion of the ketone group in (**11**) to the required *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] $[\alpha]_D$ +15.8° (*c* 0.54, $CHCl_3$), 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, Br_2, HBr, HOAc, 110 °C; ii, Br_2, $ClSO_3H$; iii, Zn, HOAc, Et_2O, 0 °C; iv, KI, dimethyl sulphoxide (DMSO), 110 °C, 3 days; v, Me_3SiCl, $HOCH_2CH_2OH$; vi, NaCN, DMSO, 70 °C, 2 days; vii, lithium di-isopropylamide (LDA), THF, −78 °C; $Bu^tMe_2SiOCH_2CH_2CH_2Br$; viii, K, hexamethylphosphoramide (HMPA), Et_2O, Bu^tOH, 0 °C; ix, HCl, Me_2CO; x, PDC, CH_2Cl_2; xi, $HC(OMe)_3$, $CeCl_3$, MeOH; xii, LDA, THF, −78 °C; Me_3SiCl; xiii, $TiCl_4$, CH_2Cl_2, −78 °C; xiv, $Ca/NH_3(l)$, Et_2O; xv, Ac_2O, DMAP, C_5H_5N; xvi, BBr_3, 15-crown-5, NaI, CH_2Cl_2; xvii, Ph_3MePBr, BuLi, −78 → 20 °C; xviii, Et_2Zn, CH_2I_2, PhMe; xix, H_2/Pt, HOAc, 2.5 atm; xx, $LiAlH_4$, THF; xxi, PCC, CH_2Cl_2; xxii, $MeSO_2Cl$, C_5H_5N, DMAP, 100 °C, 16 h.

† Several synthetic routes to racemic or optically active forms of longicamphor,[2] longiborneol,[2] longifolene,[3] longicyclene,[2] and culmorin[4] have been reported previously.

‡ 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 ~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 tetrafluoroborate[10] provided a low yield of the corresponding diketone.

‖ 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 $LiAlH_4$, tetrahydrofuran (THF). Subsequent treatment of isolongiborneol (**4**) with methanesulphonyl chloride and DMAP, pyridine at ~100 °C provided (+)-longifolene (**5**)[3d] {$[\alpha]_D$ +51.78 (*c* 0.89, $CHCl_3$); δ (400 MHz, $CDCl_3$), 0.9 (3H, s), 0.95 (3H, s), 1.00 (3H, s), 4.5 (1H, s), 4.75 (1H, s)} in ~65% yield.

We are grateful to Professor Steven C. Welch (University of Houston) and Professor Niels H. Anderson (University of Washington) for samples of longiborneol and n.m.r. spectra, and we acknowledge financial support for this research from the N.S.E.R.C. Canada.

Received, 8th July 1986; Com. 937

References

1 C. R. Eck, G. L. Hodgson, D. F. MacSweeney, R. W. Mills, and T. Money, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1938; *cf.* G. L. Hodgson, D. F. MacSweeney, and T. Money, *ibid.*, 1973, 2113.
2 S. C. Welch and R. L. Walters, *Synth. Commun.*, 1973, **3**, 15, 419; *J. Org. Chem.*, 1974, **39**, 2665.
3 (a) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Am. Chem. Soc.*, 1964, **86**, 478; (b) J. E. McMurry and S. J. Isser, *ibid.*, 1972, **94**, 7132; (c) R. A. Volkman, G. C. Andrews, and W. S. Johnson, *J. Am. Chem. Soc.*, 1975, **97**, 4777; (d) W. Oppolzer and T. Godel, *ibid.*, 1978, **100**, 2538; *Helv. Chim. Acta*, 1984, **67**, 1154; (e) A. G. Schultz and S. Puig, *J. Org. Chem.*, 1985, **50**, 915.
4 B. W. Roberts, M. S. Poonian, and S. C. Welch, *J. Am. Chem. Soc.*, 1969, **91**, 3400.
5 We have not been able to repeat the yield quoted in our original paper (C. R. Eck, R. W. Mills, and T. Money, *J. Chem. Soc., Perkin Trans. 1*, 1975, 251) and now find that (+)-8-bromocamphor (**7**) can be prepared from (+)-camphor (**1**) in ~35% overall yield; see also, P. Cachia, N. Darby, C. R. Eck, and T. Money, *J. Chem. Soc., Perkin Trans. 1*, 1976, 359; W. M. Dadson and T. Money, *J. Chem. Soc., Chem. Commun.*, 1982, 112.
6 T. Mukaiyama, *Org. React.*, 1982, **28**, 203 and references cited; P. Brownbridge, *Synthesis*, 1983, 1; *ibid.*, 1983, 85; G. S. Cockerill and P. Kocienski, *J. Chem. Soc., Chem. Commun.*, 1983, 705 and references cited to intramolecular Mukaiyama reaction; T. H. Chan and M. A. Brook, *Tetrahedron Lett.*, 1985, **26**, 2943.
7 S. J. Rettig and J. Trotter (Chemistry Dept., University of British Columbia, Vancouver), unpublished results.
8 H. Niwa, T. Hida, and K. Yamada, *Tetrahedron Lett.*, 1981, **22**, 4239.
9 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
10 T.-L. Ho and G. A. Olah, *J. Org. Chem.*, 1977, **42**, 3097.
11 (a) M. T. Reetz, J. Westermann, and S.-H. Kyung, *Chem. Ber.*, 1985, **118**, 1050 and references cited; (b) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, 1968, **24**, 53; *cf.* S. Miyano and H. Hashimoto, *Chem. Commun.*, 1971, 1418; B.M. Trost and H. Hiemstra, *J. Am. Chem. Soc.*, 1982, **104**, 886 and references cited.
12 H. Erdtman and B. R. Thomas, *Chem. Ind.*, 1955, 384; K. Doi and T. Shibuya, *Phytochemistry*, 1972, **11**, 1174; S. C. Bisarya and S. Dev, *Tetrahedron Lett.*, 1964, 3751; S. Akiyoshi, H. Erdtmann, and T. Kubota, *Tetrahedron*, 960, **9**, 237.
13 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647; E. J. Corey and D. L. Boger, *ibid.*, 1978, 2461.
14 P. Cachia, N. Darby, T. C. W. Mak, T. Money, and J. Trotter, *Can. J. Chem.*, 1980, **58**, 1172.
15 T. Cuvigny, M. Larcheveque, and H. Normant, *Bull. Soc. Chim. France*, 1973, 1174; M. Larcheveque and T. Cuvigny, *Tetrahedron Lett.*, 1975, 3851; A. Debal, T. Cuvigny, and M. Larcheveque, *Synthesis*, 1976, 391; *cf.* D. Heissler and J.-J. Riehl, *Tetrahedron Lett.*, 1980, **21**, 4711; T. Ohsawa, T. Kobayashi, Y. Mizuguchi, T. Saitoh, and T. Oishi, *ibid.*, 1985, **26**, 6103.

** 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 acetal[14] followed by reductive decyanation.[15] This is a less hazardous and more convenient synthetic route than the one previously reported[1] by us.