Preparation of (2*R*,3*S*)-1,2-Epoxypent-4-en-3-ol, a New Chiral Building Block for the Synthesis of (+)-*endo*- and (−)-*exo*-Brevicomin

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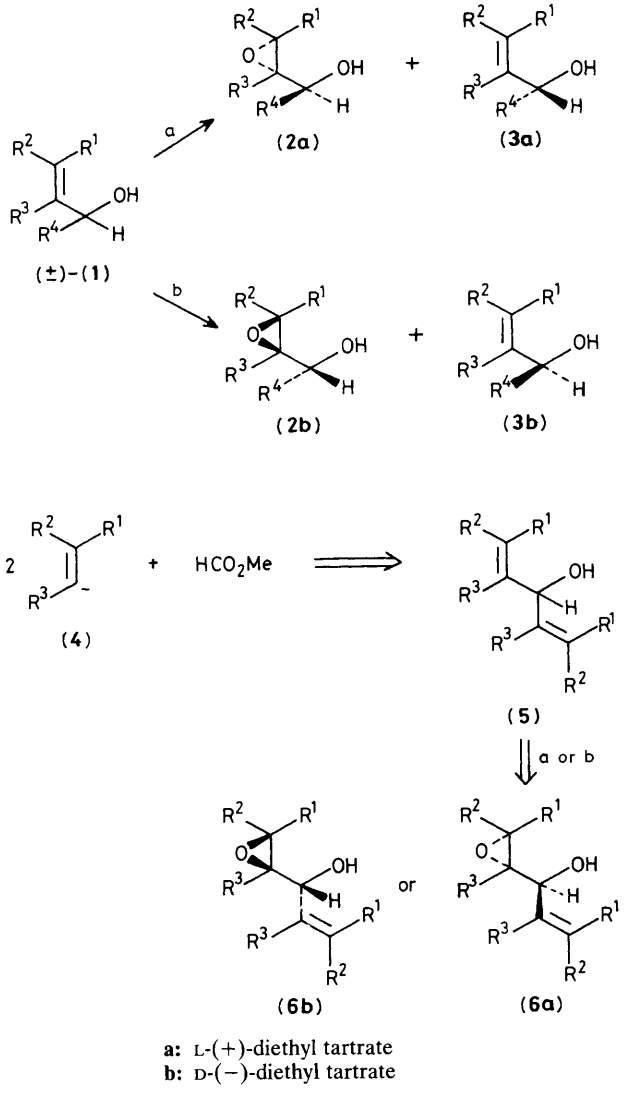
Asymmetric epoxidation of the divinylcarbinol (**7**) using L-(+)-diethyl tartrate gave (2*R*,3*S*)-1,2-epoxypent-4-en-3-ol (**8**), which was utilized as a chiral building block in the synthesis of (+)-*endo*- and (−)-*exo*-brevicomin.

Sharpless and co-workers[1] demonstrated that the titanium tartrate mediated asymmetric epoxidation of racemic secondary alcohols (**1**) proceeds with enantio- and diastereoselectivity to produce mainly one stereoisomer (**2**) of the four possible stereoisomers, together with the kinetically resolved starting alcohol (**3**). On the basis of this reactivity pattern (*lk*-attack with *ul*-1,2-induction),[2] we assumed that this type of asymmetric epoxidation using a prochiral divinylcarbinol (**5**), accessible from addition of a vinyl anion (**4**) to methyl formate, would lead to a chiral epoxy alcohol (**6**) which is expected to serve as a chiral building block in the synthesis of various natural products (Scheme 1). We now report the asymmetric synthesis of (2*R*,3*S*)-1,2-epoxypent-4-en-3-ol (**8**) and its transformation into (+)-*endo*- (**15**)† and (−)-*exo*-brevicomin (**18**).[3]

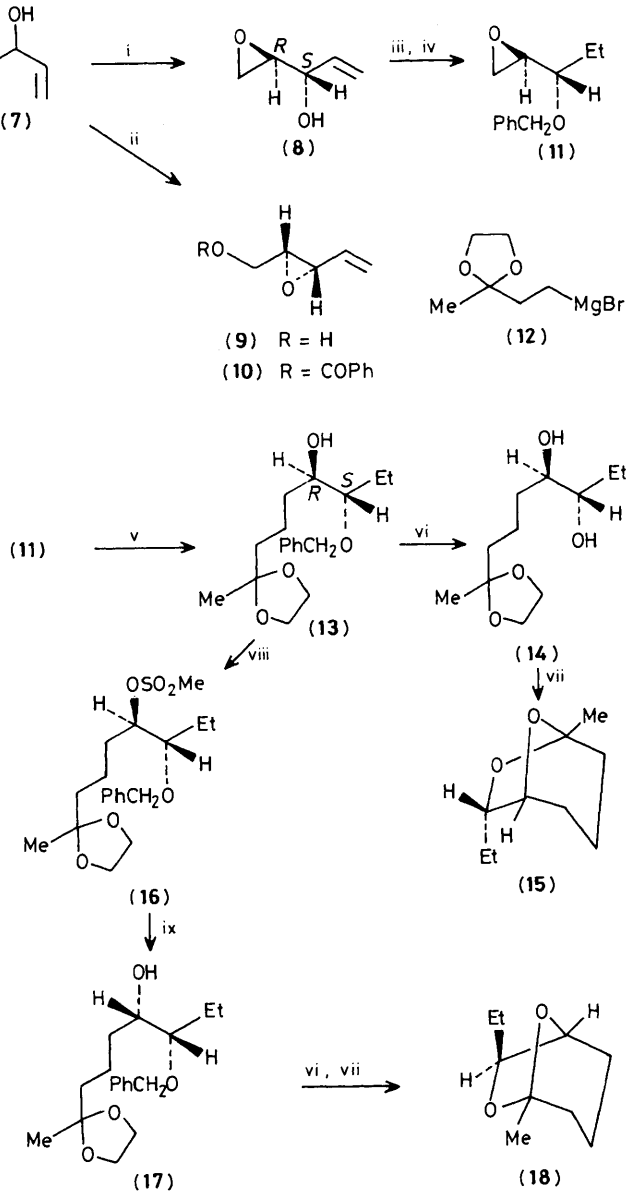
Epoxidation of the divinylcarbinol (**7**)[4] with t-butyl hydroperoxide and titanium tetraisopropoxide in the presence of L-(+)-diethyl tartrate at −20 °C for 3 days, followed by work up with 2.7% aqueous acetone[5] and distillation gave the epoxide (**8**),‡ b.p. 78 °C (18 mm Hg), $[\alpha]_D^{22}$ +46.7° (*c* 1.38,

† Very recently, both enantiomers of *endo*-brevicomin were synthesized by Mori and Seu and the (+)-isomer was shown to be biologically active.[3c]

‡ All new compounds exhibited satisfactory spectral (^1H n.m.r., i.r., and high resolution mass) data.



Scheme 1



Scheme 2. *Reagents and conditions:* i, Bu^{t}OOH (1.2 equiv.), Ti(OPr^i)$_4$ (1.0 equiv.), L-(+)-diethyl tartrate (1.0 equiv.), CH_2Cl_2, −20 °C, then 2.7% aqueous acetone; ii, Bu^{t}OOH (1.2 equiv.), Ti(OPr^i)$_4$ (1.0 equiv.), L-(+)-diethyl tartrate (1.0 equiv.), CH_2Cl_2, −20 °C, then 10% tartaric acid, 1 M NaOH; iii, $PhCH_2Br$, NaH, Bu$^n_4$NI (10 mol%), tetrahydrofuran (THF), 25 °C; iv, H_2, 10% Pd–C, n-hexane; v, (**12**), CuI, THF, −78 °C; vi, Li, NH_3–THF, −33 °C; vii, 0.1 M $HClO_4$, 25 °C; viii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; ix, KO_2, dicyclohexano-18-crown-6, dimethyl sulphoxide, 25 °C.

$CHCl_3$), in 50—60% yield. On the other hand, usual work up including hydrolysis of diethyl tartrate[6] led to Payne rearrangement[7] to give the isomeric epoxide (**9**) which was characterised as the benzoate (**10**), b.p. 70 °C (12 mm Hg, Kugelrohr), $[\alpha]_D^{19}$ −36.3° (*c* 1.86, $CHCl_3$). Although the (2*R*,3*S*)-isomer (**8**) was the expected product, the absolute stereochemistry and the enantiomeric purity of (**8**) could not be determined at this stage.§

Benzylation[8] of (**8**) followed by catalytic hydrogenation gave the benzyl ether (**11**), b.p. 100 °C (0.25 mm Hg, Kugelrohr), $[\alpha]_D^{22}$ −13.7° (*c* 1.08, $CHCl_3$), in 81% yield. Reaction of (**11**) with the Grignard reagent (**12**) in the presence of copper(I) iodide at −78 °C produced the alcohol (**13**), $[\alpha]_D^{26}$ +3.5° (*c* 1.08, $CHCl_3$), in 96% yield. The alcohol (**13**) was subjected to debenzylation to yield the diol (**14**) which, upon intramolecular acetalisation,[9] furnished (+)-*endo*-brevicomin (**15**),¶ b.p. 70 °C (18 mm Hg, Kugelrohr), $[\alpha]_D^{26}$ +74.6° (*c* 1.06, Et_2O) [lit.[3b] +74.0° (78.5% optical purity)], in 63% overall yield.

Furthermore, the hydroxy group of (**13**) was inverted *via* the methanesulphonate (**16**) by Corey's method[10] to give the alcohol (**17**), $[\alpha]_D^{24}$ +13.9° (*c* 1.02, $CHCl_3$), which was then converted into (−)-*exo*-brevicomin (**18**),¶ b.p. 100 °C (30 mm Hg, Kugelrohr), $[\alpha]_D^{25}$ −66.5° (*c* 1.112, Et_2O) [lit.[3a] −80.6° and +84.1° for (+)-*exo*-brevicomin], by intramolecular acetalisation after debenzylation in 56% overall yield. G.l.c. analysis revealed that synthetic *endo*-brevicomin (**15**) and *exo*-brevicomin (**18**) were contaminated with 3% of the corresponding *exo*- and *endo*-isomers, respectively. From

§ We could not determine the enantiomeric purity of (**8**) by ^{1}H n.m.r. analysis of (**8**) or the corresponding methoxy(trifluoromethyl)phenylacetyl ester using shift reagents.

¶ The spectral properties were identical with those previously published (ref. 3).

these results, it was ascertained that asymmetric epoxidation of the divinylcarbinol (**7**) had proceeded with 90:10 enantioselectivity and with 93:3 *threo–erythro* selectivity.

Since asymmetric epoxidation of (**7**) using D-(−)-diethyl tartrate afforded (2*S*,3*R*)-(**8**), b.p. 90 °C (20 mm Hg, Kugelrohr), $[\alpha]_D^{28}$ −50.0° (*c* 1.24, $CHCl_3$), in 50% yield, the synthetic route demonstrated above should enable us to synthesize a western pine beetle pheromone (+)-*exo*-brevicomin as well as (−)-*endo*-brevicomin.

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References

1 M. J. Schweiter and K. B. Sharpless, *Tetrahedron Lett.*, 1985, **26**, 2543; K. B. Sharpless, C. H. Behrens, T. Katsuki, A. W. M. Lee, V. S. Martin, M. Takatani, S. M. Viti, F. J. Walker, and S. S. Woodard, *Pure Appl. Chem.*, 1983, **55**, 589; K. B. Sharpless, S. S. Woodard, and M. G. Finn, *ibid.*, 1983, **55**, 1823.

2 D. Seebach, B. Weidmann, and L. Widler, in 'Modern Synthetic Methods,' ed. R. Scheffold, Salle and Sauerlander, Frankfurt am Main, 1983, Vol. 4, pp. 324—353.

3 For syntheses of optically enriched *endo*- and *exo*-brevicomin, see: (a) K. Mori, *Tetrahedron*, 1974, **30**, 4223; (b) R. Bernardi, C. Fuganti, and P. Grasselli, *Tetrahedron Lett.*, 1981, **22**, 4021; A. E. Sherk and B. Fraser-Reid, *J. Org. Chem.*, 1982, **47**, 932; B. D. Johnston and A. C. Oehlschlager, *ibid.*, 1982, **47**, 5384; R. J. Ferrier and P. Prasit, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1645; C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, S. Servi, and C. Zirotti, *Tetrahedron Lett.*, 1983, **24**, 3753; P. G. M. Wuts and S. S. Bigelow, *J. Chem. Soc., Chem. Commun.*, 1984, 736; R. J. Ferrier, P. Schmidt, and P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1*, 1985, 301; M. Larchevêque and J. Lalande, *J. Chem. Soc., Chem. Commun.*, 1985, 83; (c) K. Mori and Y.-B. Seu, *Tetrahedron*, 1985, **41**, 3429.

4 H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balint, and R. Cserr, *J. Org. Chem.*, 1957, **22**, 1602.

5 V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237.

6 T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974.

7 G. B. Payne, *J. Org. Chem.*, 1962, **27**, 3819; C. H. Behrens and K. B. Sharpless, *Aldrichimica Acta*, 1983, **16**, 67.

8 S. Czernecki, C. Georgoulis, and C. Provelenghiou, *Tetrahedron Lett.*, 1976, 3535.

9 P. J. Kocienski and R. W. Ostrow, *J. Org. Chem.*, 1976, **41**, 398.

10 E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 1975, 3183.