

Preparation of (2*R*,3*S*)-1,2-Epoxy-pent-4-en-3-ol, a New Chiral Building Block for the Synthesis of (+)-*endo*- and (–)-*exo*-Brevicomins

Susumi Hatakeyama, Kuniya Sakurai, and Seiichi Takano*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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

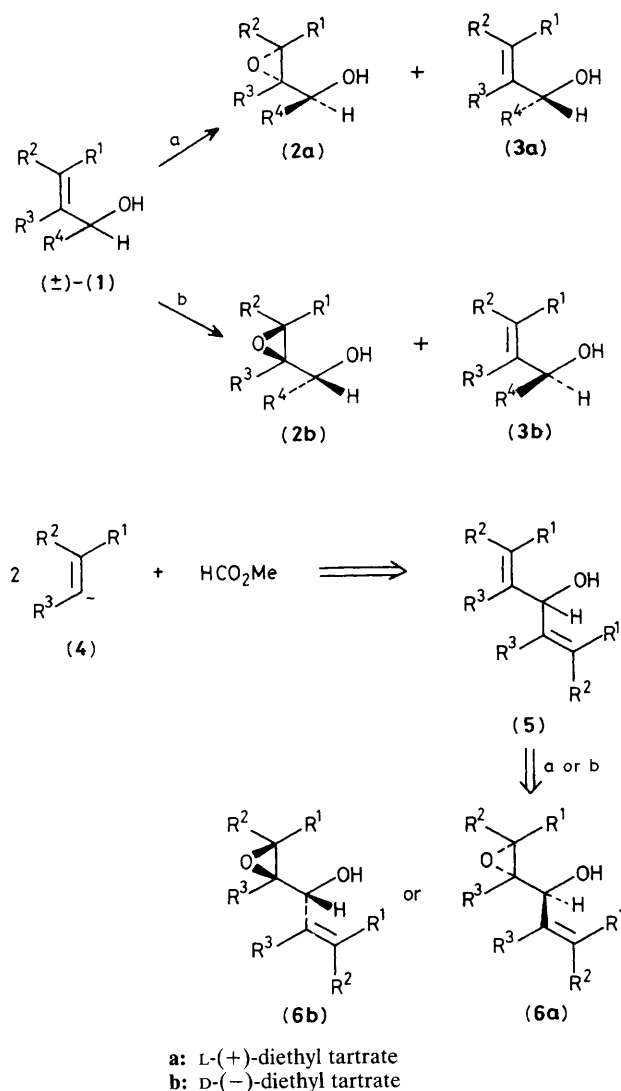
Sharpless and co-workers¹ demonstrated that the titanium tartrate mediated asymmetric epoxidation of racemic secondary alcohols (**1**) proceeds with enantio- and diastereoselectivity to produce mainly one stereoisomer (**2**) of the four possible stereoisomers, together with the kinetically resolved 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-epoxy-pent-4-en-3-ol (**8**)

and its transformation into (+)-*endo*- (**15**)[†] and (–)-*exo*-brevicomins (**18**).³

Epoxidation of the divinylcarbinol (**7**)⁴ with *t*-butyl hydroperoxide and titanium tetrakisopropoxide in the presence of L-(+)-diethyl tartrate at –20 °C for 3 days, followed by work up with 2.7% aqueous acetone⁵ and distillation gave the epoxide (**8**),[‡] b.p. 78 °C (18 mm Hg), [α]_D²² +46.7° (*c* 1.38,

[†] Very recently, both enantiomers of *endo*-brevicomins 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.



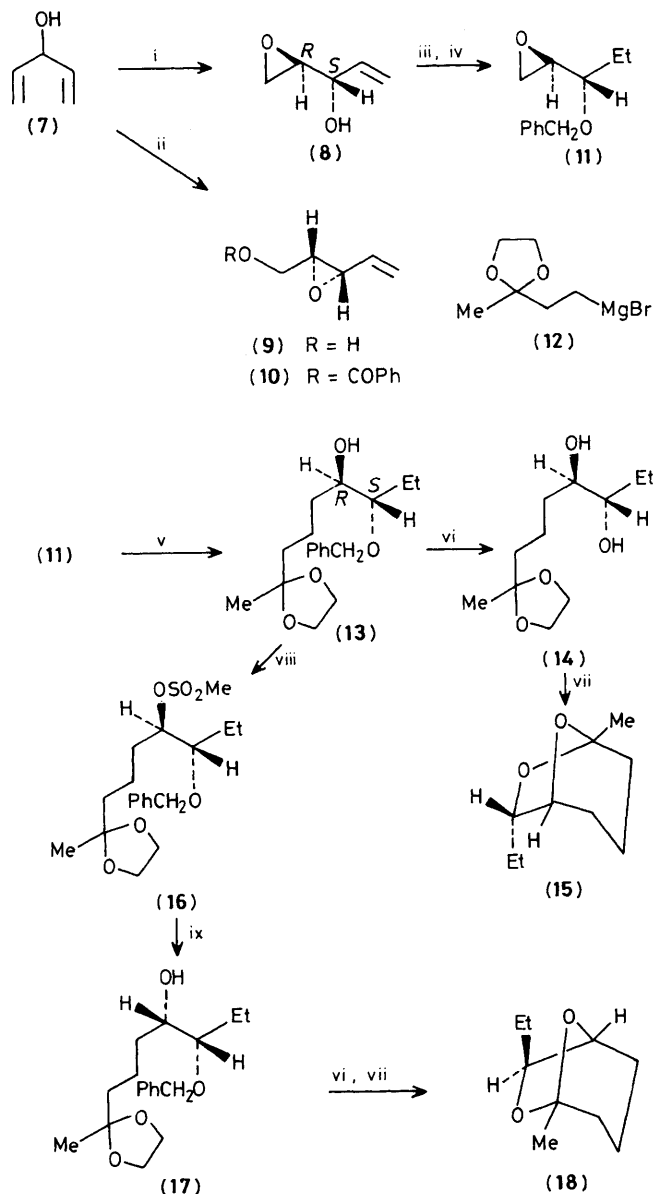
Scheme 1

CHCl₃), in 50–60% yield. On the other hand, usual work up including hydrolysis of diethyl tartrate⁶ led to Payne rearrangement⁷ to give the isomeric epoxide (9) which was characterised as the benzoate (10), b.p. 70 °C (12 mm Hg, Kugelrohr), [α]_D²² –36.3° (c 1.86, CHCl₃). 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. §

Benzylation⁸ of (8) followed by catalytic hydrogenation gave the benzyl ether (11), b.p. 100 °C (0.25 mm Hg, Kugelrohr), [α]_D²² –13.7° (c 1.08, CHCl₃), 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), [α]_D²⁶ +3.5° (c 1.08, CHCl₃), in 96% yield. The alcohol (13) was subjected to debenzoylation to yield the diol (14) which, upon intramolecular acetalisation,⁹ furnished (+)-*endo*-brevicomin (15), ¶ b.p. 70 °C (18 mm Hg, Kugelrohr),

§ We could not determine the enantiomeric purity of (8) by ¹H n.m.r. analysis of (8) or the corresponding methoxy(trifluoromethyl)phenyl-acetyl ester using shift reagents.

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



Scheme 2. Reagents and conditions: i, Bu^tOOH (1.2 equiv.), Ti(OPri)₄ (1.0 equiv.), L-(+)-diethyl tartrate (1.0 equiv.), CH₂Cl₂, –20 °C, then 2.7% aqueous acetone; ii, Bu^tOOH (1.2 equiv.), Ti(OPri)₄ (1.0 equiv.), L-(+)-diethyl tartrate (1.0 equiv.), CH₂Cl₂, –20 °C, then 10% tartaric acid, 1 M NaOH; iii, PhCH₂Br, NaH, Buⁿ₄Ni (10 mol%), tetrahydrofuran (THF), 25 °C; iv, H₂, 10% Pd–C, n-hexane; v, (12), CuI, THF, –78 °C; vi, Li, NH₃–THF, –33 °C; vii, 0.1 M HClO₄, 25 °C; viii, MeSO₂Cl, Et₃N, CH₂Cl₂, 0 °C; ix, KO₂, dicyclohexano-18-crown-6, dimethyl sulphoxide, 25 °C.

[α]_D²⁶ +74.6° (c 1.06, Et₂O) [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 method¹⁰ to give the alcohol (17), [α]_D²⁴ +13.9° (c 1.02, CHCl₃), which was then converted into (–)-*exo*-brevicomin (18), ¶ b.p. 100 °C (30 mm Hg, Kugelrohr), [α]_D²⁵ –66.5° (c 1.112, Et₂O) [lit.^{3a} –80.6° and +84.1° for (+)-*exo*-brevicomin], by intramolecular acetalisation after debenzoylation 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

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), $[\alpha]_{\text{D}}^{28} -50.0^\circ$ (*c* 1.24, CHCl₃), 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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