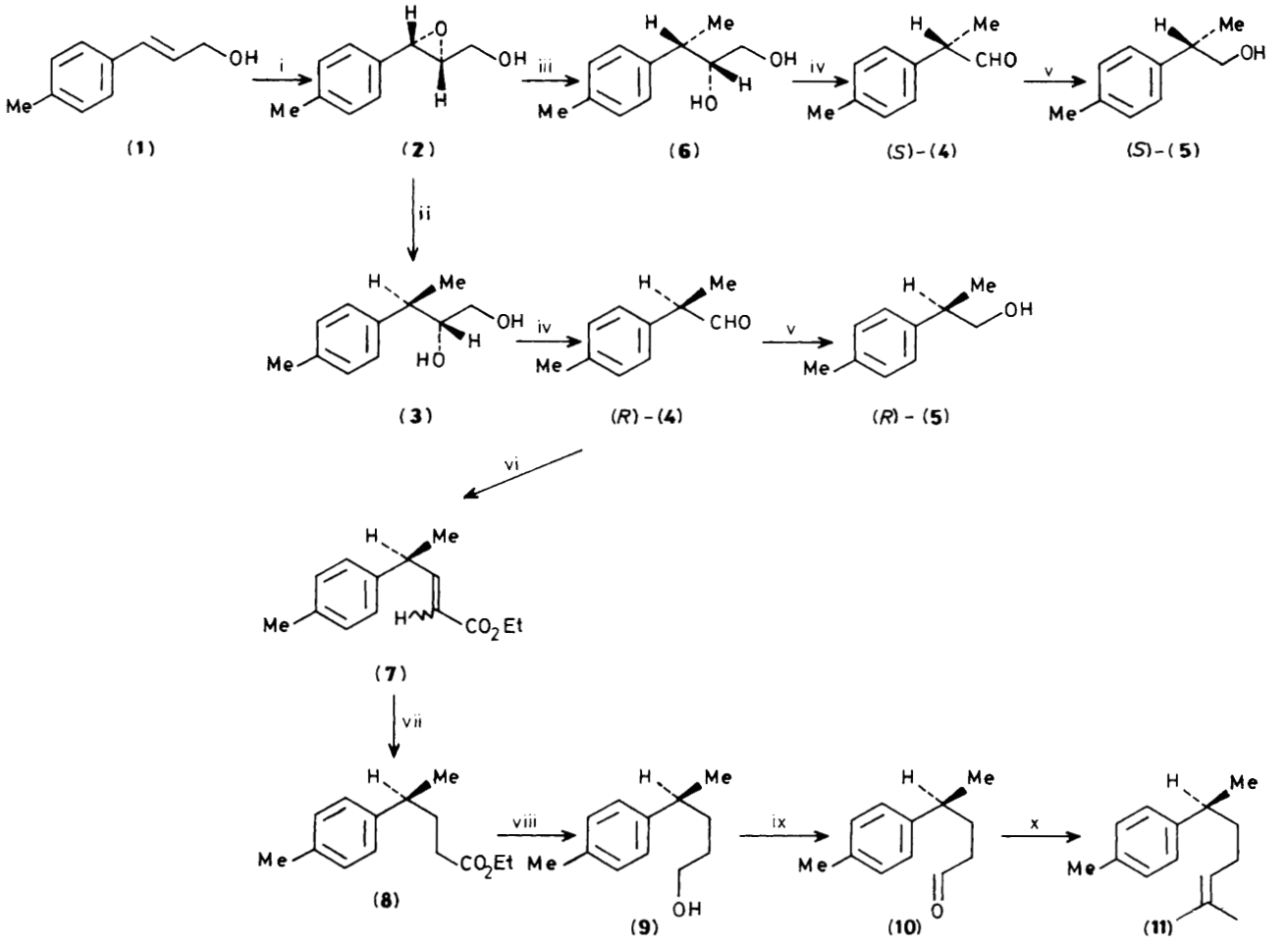
Enantiodivergent Route to the Aromatic Bisabolane Sesquiterpenes by Regio- and Stereo-controlled Epoxide Opening

Seiichi Takano,* Masashi Yanase, Takumichi Sugihara, and Kunio Ogasawara

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

An enantiodivergent route to aromatic bisabolane sesquiterpenes from a single chiral precursor has been established by employing regio- and stereo-controlled epoxide opening as the key step.

Transformation of optically active 2,3-epoxy alcohols is one of the most promising ways of constructing polyfunctional chiral organic molecules since optically active epoxy alcohols are now readily accessible from allylic alcohol precursors by the Sharpless chiral epoxidation.[1] We report here an efficient utilization of (−)-3-(*p*-tolyl)glycidol (**2**), obtained from *trans*-4-methylcinnamic alcohol (**1**) by the Sharpless epoxidation under catalytic conditions,[2] as the enantiodivergent chiral building block for the synthesis of both enantiomers of the aromatic bisabolane sesquiterpenes.



Scheme 1. *Reagents and conditions:* i, L-(+)-DIPT (15%), $Ti(OPr^i)_4$ (10%), Bu^tOOH (2.0 equiv.), CH_2Cl_2, −20 °C, 34 h; ii, $Me_2Cu(CN)Li_2$ (2.5 equiv.), Et_2O, −40 °C, 1.5 h; iii, (a) Me_3Al (1.5 equiv.), CH_2Cl_2, −72 °C, 36 h, (b) 2,2-dimethoxypropane (5.0 equiv.), acetone, pyridinium toluene-*p*-sulphonate, room temp., 9 h, then SiO_2 column (Et_2O/hexane 1:30 v/v), (c) 10% HCl–THF (1:2 v/v), room temp., 10 h; iv, $NaIO_4$ (1.5 equiv.) MeOH–H_2O (5:1), 0 °C, 0.5 h; v, $NaBH_4$ (3.0 equiv.), MeOH–H_2O (5:1) 0 °C, 10 min; vi, NaH (1.3 equiv.), $(EtO)_2P(O)CH_2CO_2Et$ (1.2 equiv.), tetrahydrofuran (THF), −10 °C, 100 min; vii, H_2, 10% Pd/C, EtOH, room temp., 1h; viii, $LiAlH_4$, THF, 0 °C, 35 min; ix, $(COCl)_2$, dimethyl sulphoxide (DMSO), Et_3N, CH_2Cl_2, −52 °C, x, $Ph_3\overset{+}{P}CH(CH_3)_2\bar{I}$ (2.2 equiv.), Bu^nLi (2.1 equiv.), THF, −15 °C to room temp., 16 h.

Oxidation of (**1**) using a catalytic amount of di-isopropyl L-tartrate (DIPT; 15% mol) and titanium isopropoxide (10% mol) afforded the crystalline 3-(*p*-tolyl)glycidol† (**2**) m.p. 57—58 °C, $[\alpha]_D^{24}$ −36.65° (*c* 2.03, $CHCl_3$), in 62% yield (Scheme 1). On reaction with lithium dimethylcyanocuprate (2.5 equiv.),[3] (**2**) afforded the single diol (**3**), $[\alpha]_D^{27}$ +25.04° (*c* 1.01, $CHCl_3$), in 73% yield, regio- and stereo-selectively, with inversion at the benzylic centre; the diastereoisomeric purity was estimated to be >99% diastereoisomeric excess (d.e.) by ^{1}H n.m.r. analysis‡ of both enantiomeric bis-MTPA [MTPA = methoxy(trifluoromethyl)phenylacetyl] acid esters. On the other hand, upon reaction with trimethylaluminium (1.5 equiv.) (CH_2Cl_2, −72 °C), (**2**) afforded the epimeric diol (**6**) with retention[4] at the benzylic centre accompanied by a small amount of the inverted diol (**3**) which were readily separated in 89.4 and 2.9% yield (94% d.e.) on a silica gel column after conversion into the acetonide followed by acid hydrolysis.

Each of the diols (**3**) and (**6**) was sequentially treated with sodium periodate and sodium borohydride in the same medium to give each corresponding alcohol (**5**)[(*R*)-(+)-(**5**), $[\alpha]_D^{24}$ +14.01° (*c* 1.26, $CHCl_3$) obtained in 98% yield from (**3**); (*S*)-(−)-(**5**), $[\alpha]_D^{24}$ −14.05° (*c* 1.22, $CHCl_3$) obtained in 97% yield from (**6**)] for comparison; each was shown to be formed in >98% enantiomeric excess (e.e.) by the MTPA method.

The (+)-diol (**3**) was cleaved with sodium periodate and the resulting (*R*)-aldehyde (**4**) was immediately converted into the unsaturated ester (**7**), $[\alpha]_D^{30}$ −13.6° (*c* 1.03, $CHCl_3$), in 79% yield by Horner–Emmons reaction. Catalytic hydrogenation of (**7**) followed by hydride reduction of the resulting saturated ester (**8**) gave the primary alcohol (**9**), $[\alpha]_D^{28}$ +14.6° (*c* 0.74, $CHCl_3$), quantitatively, which was estimated to be formed in >99% e.e. by the MTPA method. This indicated that no epimerization occurred during the transformation. Employing the established method,[5] (**9**) was converted into (+)-α-curcumene (**11**), $[\alpha]_D^{29}$ +44.4° (*c* 1.05, $CHCl_3$) {natural[6] $[\alpha]_D$ +45.10° (*c* 0.75, $CHCl_3$)}, in 61% overall yield *via* the aldehyde (**10**) by sequential oxidation and the Wittig reaction. The enantiomeric (−)-α-curcumene (**11**) may also be obtained from the diol (**6**) by employing the same method. Since

† Satisfactory spectral (i.r., ^{1}H n.m.r., mass) and analytical (combustion and/or high resolution mass) data were obtained for all new isolable compounds.

‡ ^{1}H N.m.r. analysis was carried out using a 500 MHz equipment.

sythesis of other aromatic bisabolane sesquiterpenes, such as nuciferol and nuciferal *via* (**10**)[5] as well as *ar*-turmerone *via* (**5**)[7] has been established, the present method constitutes their formal enantiodivergent synthesis.

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