An Enantio- and Stereo-controlled Synthesis of L-*erythro*- and D-*threo*-C_{18}-sphingosines *via* the Anomalous Version of the Katsuki–Sharpless Asymmetric Epoxidation Reaction

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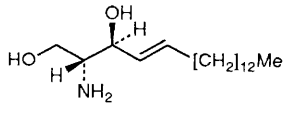
A new enantiocontrolled synthesis of L-*erythro*- and D-*threo*-sphingosines has been established starting from (*R,R*)- and *meso*-1,2-divinylethylene glycols *via* the anomalous version of the Katsuki–Sharpless asymmetric epoxidation reaction as the key step.

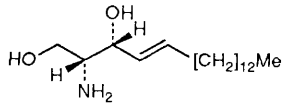
Recently, we discovered[1] that both DL- and *meso*-forms of 1,2-divinylethylene glycol afford the corresponding epoxides in an enantio- and diastereo-facial manner which was unexpected from an empirically established rule under the Katsuki–Sharpless asymmetric epoxidation conditions.[2] We report herein a new enantio- and stereo-controlled synthesis of L-*erythro*- and D-*threo*-C_{18}-sphingosines **1**,[3] which are interesting as basic components of the cerebrosides[4] as well as reversible inhibitors of protein kinase C,[5,6] starting from the epoxides obtained from the (*R,R*)- and *meso*-forms of 1,2-divinylethylene glycol.

The Katsuki–Sharpless asymmetric epoxidation of optically active (*R,R*)-1,2-divinylethylene glycol[7] [(*R,R*)-**2**], $[\alpha]_D^{30}$ +99.4° (*c* 1.04, $CHCl_3$), using diisopropyl D-(−)-tartrate (DIPT) (1.2 equiv.), titanium tetraisopropoxide [$Ti(OPr^i)_4$] (1.0 equiv.), and *tert*-butyl hydroperoxide (TBHP) (1.2 equiv.) in the presence of 4 Å molecular sieves[8] at −20 °C for 10 h afforded the monoepoxide **3** in 32% yield [42% yield based on consumed (*R,R*)-**2**] accompanied by a 19% yield [25% yield based on consumed (*R,R*)-**2**] of the readily separable diepoxide **4**, stereoselectively (Scheme 1). In this reaction the epoxidation occurred in an inversed enantio- and diastereo-facial selective mode[1] to those empirically predicted for simple allylic alcohols.[2] The monoepoxide **3** gave the acetonide† **5**, $[\alpha]_D^{30}$ −31.1° (*c* 1.00, $CHCl_3$), which was treated with potassium *p*-methoxyphenylmethoxide to afford the secondary alcohol **6**, $[\alpha]_D^{27}$ +1.03° (*c* 1.03, $CHCl_3$), in 81% overall yield, whose enantiomeric excess (e.e.) was determined to be ~100%.‡ On sequential mesylation, nucleophilic substitution, and acid-catalysed deketalization, **6** provided the diol **9**, $[\alpha]_D^{30}$ −45.1° (*c* 1.04, $CHCl_3$), in 55% overall yield *via* **7** and **8**, $[\alpha]_D^{27}$ −1.26° (*c* 1.06, $CHCl_3$).

Exposure of **9** to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of 4 Å molecular sieves brought about oxidative cyclization[9] to give the acetal **10**, $[\alpha]_D^{28}$ −26.1° (*c* 0.52, $CHCl_3$), in 85% yield as a single product. After several unsuccessful attempts, we found that the mesylate **11**



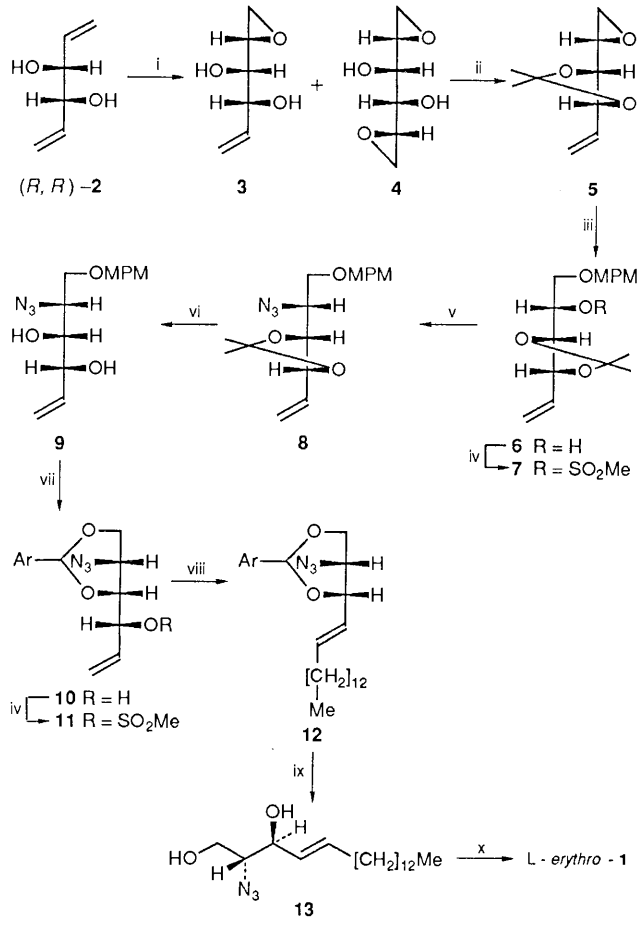
L-*erythro*-sphingosine **1**



D-*threo*-sphingosine **1**

† All new isolable compounds showed satisfactory spectral (IR, ^1H NMR, and mass) and analytical (combustion and/or high resolution MS) data.

‡ Optical purity was estimated by ^1H NMR analysis (500 MHz) of its methoxy(trifluoromethyl)phenylacetyl (MTPA) (both enantiomers) esters.

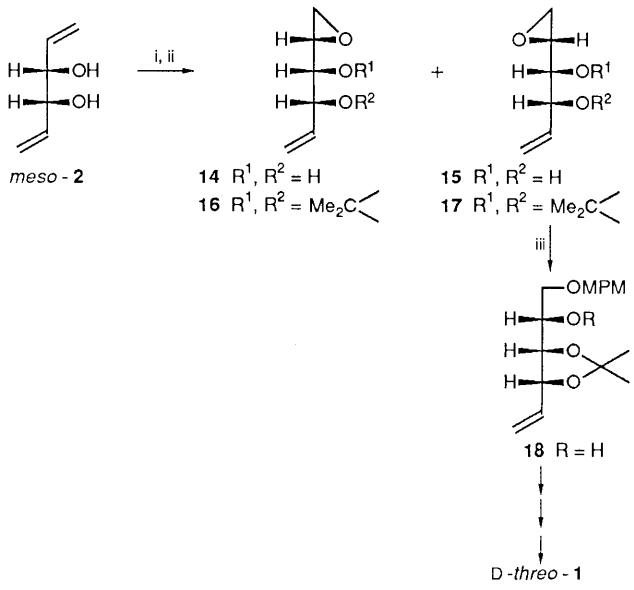


Scheme 1 *Reagents and conditions*: i, D-(−)-DIPT, $Ti(O^iPr)_4$, TBHP, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 10 h; ii, 2,2-dimethoxypropane, cat. PPTS, acetone, room temp., 90%; iii, KH, *p*-$MeOC_6H_4CH_2OH$, DMF, 0 °C, 90%; iv, MsCl, DMAP, CH_2Cl_2, 0 °C; v, NaN_3, DMF, 120 °C, 77%; vi, Amberlyst-15, MeOH, room temp., 72%; vii, DDQ, 4 Å molecular sieves, CH_2Cl_2, 0 °C, 88%; viii, laurylmagnesium bromide, CuI, THF, −30 to 0 °C, 77%; ix, dil. HCl, MeOH, room temp., 95%; x, $LiAlH_4$, THF, 85%. PPTS = pyridinium toluene-*p*-sulphonate; DMF = dimethylformamide; Ms = $MeSO_2$; DMAP = 4-*N*,*N*-dimethylaminopyridine.

afforded the *E*-alkene§ **12**, $[\alpha]_D^{27}$ +2.10° (*c* 1.05, $CHCl_3$), selectively, in 77% overall yield on exposure to the Grignard reagent in tetrahydrofuran (THF) in the presence of copper(I) iodide. Acid hydrolysis of **12** afforded the diol **13**, $[\alpha]_D^{26}$ +34.9° (*c* 0.98, $CHCl_3$), in 95% yield, which was reduced with lithium aluminium hydride to give L-*erythro*-sphingosine (L-*erythro*-**1**), m.p. 80–82 °C, $[\alpha]_D^{27}$ +2.87° (*c* 1.10, $CHCl_3$) {lit.:[3a] m.p. 81–82 °C, $[\alpha]_D^{24}$ +2.8° ($CHCl_3$)}, in 85% yield. The structure was further confirmed by preparation of the triacetyl derivative, m.p. 100–102 °C, $[\alpha]_D^{27}$ +11.9° (*c* 0.85, $CHCl_3$) {lit.:[3a] m.p. 101–102 °C, $[\alpha]_D^{24}$ +12.1° ($CHCl_3$)}.

Similar asymmetric epoxidation of *meso*-1,2-divinylethylene glycol[10] (*meso*-**2**) also proceeded predominantly in an inversed mode of enantiofacial selectivity to that predicted by the empirical rule[2] to afford an inseparable 7 : 1 diastereoisomeric mixture of the monoepoxides, **14** and **15** (Scheme 2). The epoxides **14** and **15** were separated as their acetonides: *syn*-epoxide **16**, $[\alpha]_D^{27}$ −20.1° (*c* 1.01, $CHCl_3$); *anti*-epoxide **17**, $[\alpha]_D^{28}$ −17.9° (*c* 1.15, $CHCl_3$), in 57 and 8% overall yields (71 and 10% based on consumed *meso*-**2**) from *meso*-**2**. The

§ Stereochemistry was confirmed by ^1H (500 MHz) and ^{13}C (125 MHz) NMR analyses.



Scheme 2 *Reagents and conditions*: i, L-(+)-DIPT, $Ti(OPr^i)_4$, TBHP, 4 Å molecular sieves, CH_2Cl_2, THF, −20 °C, 3 days; ii, 2,2-dimethoxypropane, cat. PPTS, acetone, room temp., 90%; iii, KH, *p*-$MeOC_6H_4CH_2OH$, DMF, 0 °C, 90%

major epoxide **16** was converted into D-*threo*-sphingosine (D-*threo*-**1**), m.p. 82–84 °C, $[\alpha]_D^{28}$ +2.6° (*c* 0.58, $CHCl_3$) {lit.:[3a] m.p. 84–85 °C, $[\alpha]_D^{24}$ +2.8° ($CHCl_3$)}, triacetyl derivative, m.p. 41–42 °C, $[\alpha]_D^{29}$ −8.5° (*c* 0.79, $CHCl_3$) {lit.:[3a] m.p. 41–42 °C, $[\alpha]_D^{24}$ −8.9° ($CHCl_3$)}, in 16% overall yield using the same procedure as for L-*erythro*-sphingosine above except that the azide displacement was accomplished on a trifluoromethanesulphonate ester instead of a mesylate.

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