

## Enantiodivergent Route to Conduritol C via Lipase-mediated Asymmetrization

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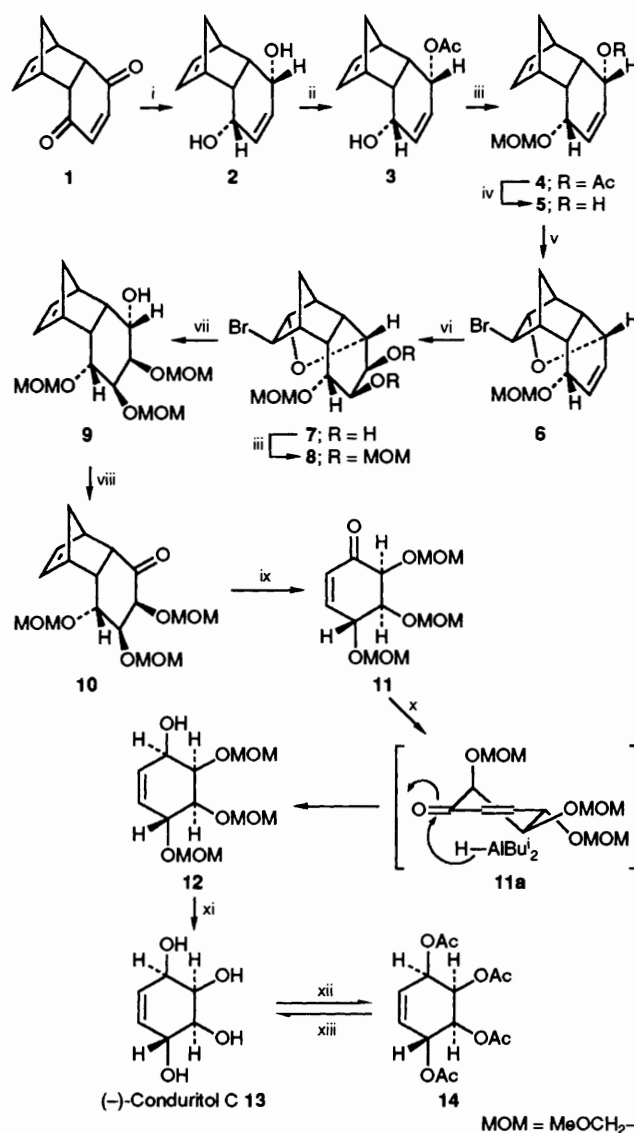
Enantiodivergent route to conduritol C **13** has been developed by utilizing the optically pure starting material **3** obtained from the *meso*-diol **2** by lipase-mediated asymmetrization.

Since we first demonstrated the synthetic potentiality of a diol substrate having *meso* structure as a convenient chiral starting material by employing microbial asymmetrization in 1976,<sup>1</sup> the utilization of *meso* substrates in enantiocontrolled syntheses has become a conventional procedure.<sup>2</sup> We report here the preparation and utilization of a new chiral building block **3** obtained by lipase-mediated asymmetric esterification of the *meso* diol **2**.

Treatment of the known *meso* diol **2**, obtained by sodium borohydride–ceric chloride reduction<sup>3†</sup> of the Diels–Alder adduct<sup>4</sup> **1** of cyclopentadiene and benzoquinone, with vinyl acetate (6 equiv.) and lipase PS (Amano) (same weight as **2**) in acetonitrile<sup>5</sup> at 30 °C for 2 weeks to furnish the optically pure monoacetate<sup>‡</sup> **3**, m.p. 87–88 °C,  $[\alpha]_D^{31} +72.2$  (*c* 1.00, CHCl<sub>3</sub>),§ in 87% yield. Methoxymethylation of **3** with methoxymethyl chloride (MOM-Cl) (1.5 equiv.) in the presence of ethyldiisopropylamine<sup>6</sup> gave the MOM ether **4**,  $[\alpha]_D^{30} +23.3$  (*c* 2.25, CHCl<sub>3</sub>), in 88% yield. Methanolysis of **4** followed by exposure of the resulting alcohol **5**, m.p. 39–40 °C,  $[\alpha]_D^{27} -39.0$  (*c* 1.05, CHCl<sub>3</sub>), to *N*-bromosuccinimide (NBS)<sup>7</sup> (1.1 equiv.) afforded the bromoether **6**, m.p. 47.5–49 °C,  $[\alpha]_D^{30} -110.6$  (*c* 1.09, CHCl<sub>3</sub>), in 67% yield. Owing to its biased tricyclic structure, glycolization of **6** with a catalytic amount of osmium tetroxide (3%) and *N*-methylmorphine *N*-oxide (NMO)<sup>7,8</sup> (1.5 equiv.) occurred selectively from the convex face of the molecule to give exclusively the *exo*-diol **7**, m.p. 104–105.5 °C,  $[\alpha]_D^{30} -154.9$  (*c* 1.06, CHCl<sub>3</sub>), in 85% yield. Methoxymethylation<sup>6</sup> of **7** followed by treating the resulting tri-MOM ether **8**,  $[\alpha]_D^{34} -39.5$  (*c* 1.28, CHCl<sub>3</sub>), with activated zinc powder (8 equiv.) in methanol in the presence of a catalytic amount of acetic acid<sup>7</sup> regenerated the olefinic bond and the hydroxy group to give the enol **9**,  $[\alpha]_D^{31} +22.4$  (*c* 0.91, CHCl<sub>3</sub>), in 77% yield. Since **9** was found to be stable at 250 °C, it was first oxidized with pyridinium chlorochromate (PCC) (1.6 equiv.) in dichloromethane to give the ketone **10**,  $[\alpha]_D^{31} +8.2$  (*c* 0.89, CHCl<sub>3</sub>), which in turn was thermolysed in diphenyl ether at 250 °C for 1.5 h to initiate the retro-Diels–Alder cleavage to give rise to the enone **11**,  $[\alpha]_D^{31} -194$  (*c* 0.63, CHCl<sub>3</sub>), in 60% yield. Treatment of **11** with diisobutylaluminium hydride (2 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C allowed stereoselective reduction to form the conduritol C tri-MOM ether **12**,  $[\alpha]_D^{32} -72.3$  (*c* 0.61, CHCl<sub>3</sub>), in 92% yield as a single product. The observed stereochemical outcome may be reasoned by assuming the stereoelectronically more stable conformation **11a** having an axial  $\alpha$ -alkoxy ketone structure in which the reduction occurred selectively from a less congested and stereoelectronically more favoured quasi-axial direction.<sup>9</sup> Hydrolysis of **12** with hot 10% hydrochloric acid in tetrahydrofuran (THF) (1:1) furnished crude (–)-conduritol C<sup>10,11</sup> **13**, which was transformed into the tetraacetate **14**,  $[\alpha]_D^{31} -188$  (*c* 0.28, CHCl<sub>3</sub>) [lit.<sup>11b,c</sup>  $[\alpha]_D^{24} +194$  (*c* 1.1,

CHCl<sub>3</sub>) for (+)-enantiomer], in 60% overall yield for purification. Reversion of **14** into (–)-**13** has already been carried out in a single step.<sup>11b</sup>

On the other hand, the monoacetate **3** was treated first with *tert*-butyldimethylsilyl (TBS) chloride in the presence of imidazole in dimethylformamide (DMF) to yield the TBS ether **15**,  $[\alpha]_D^{32} +30.5$  (*c* 1.49, CHCl<sub>3</sub>), which on sequential methanolysis, methoxymethylation and desilylation, furnished the *ent*-**5**,  $[\alpha]_D^{32} +37.6$  (*c* 0.81, CHCl<sub>3</sub>), in 74% overall yield *via* the alcohol **16**, m.p. 127.5–129 °C,  $[\alpha]_D^{31} -11.3$  (*c*

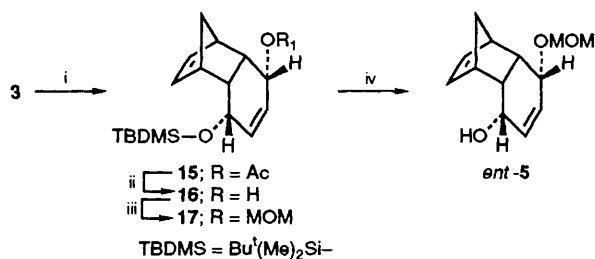


**Scheme 1 Reagents and conditions:** i, NaBH<sub>4</sub>–CeCl<sub>3</sub>, MeOH, 0 °C or Bu<sub>2</sub>AlH, CH<sub>2</sub>Cl<sub>2</sub>, room temp.; ii, lipase PS, MeCN, 30 °C, 2 weeks; iii, MOM-Cl, Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>; iv, K<sub>2</sub>CO<sub>3</sub>, MeOH, room temp.; v, NBS, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; vi, OsO<sub>4</sub> (cat.), NMO, 0 °C to room temp.; vii, Zn, AcOH (cat.), MeOH, reflux; viii, PCC, CH<sub>2</sub>Cl<sub>2</sub>, room temp.; ix, 250 °C, diphenyl ether, 1.5 h; x, Bu<sub>2</sub>AlH, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C; xi, 10% HCl–THF (1:1), 80 °C, 12 h; xii, Ac<sub>2</sub>O, pyridine, room temp.; xiii, K<sub>2</sub>CO<sub>3</sub>, MeOH, room temp. [ref. 11(b)]

† Diisobutylaluminium hydride was found to be more suitable for a large-scale preparation.

‡ All new compounds showed satisfactory analytical (combustion and/or high resolution mass) and spectral (IR, <sup>1</sup>H NMR and mass) data.

§ Optical purity was determined to be >99% enantiomeric excess (e.e.) by HPLC (Chiralcel OD, 5% Pr<sup>i</sup>OH–*n*-hexane) of the enone derived from **3**.



**Scheme 2** Reagents and conditions: i, TBS-Cl, imidazole, DMF, room temp.; ii,  $\text{K}_2\text{CO}_3$ , MeOH, room temp.; iii, MOM-Cl,  $\text{Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C to room temp.; iv,  $(\text{Bu}^n)_4\text{NF}$ , THF, room temp.

0.82,  $\text{CHCl}_3$ ) and the MOM ether **17**,  $[\alpha]_{\text{D}}^{30} +14.9$  ( $c$  1.25,  $\text{CHCl}_3$ ). This transformation constitutes a synthesis of (+)-conduiritol C **13** in a formal sense. Thus, the enantiodivergent route to conduiritol C **13** from the *meso*-diol **1** via the common chiral intermediate **3** has been developed. Further utilization of **3** as an enantiodivergent chiral building block is under investigation.

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