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

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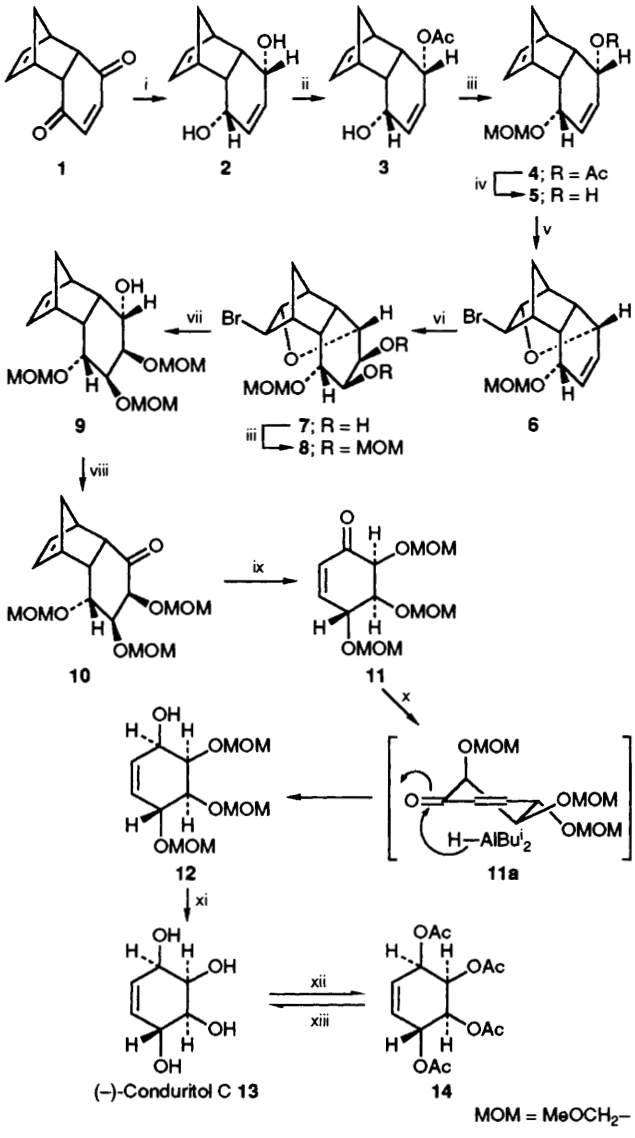
Enantiodivergent route to conduritol C **13** has been developed by utilizing the optically pure starting material **3** obtained from the *meso*-diol **2** by lipase-mediated asymmetrization.

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,[1] the utilization of *meso* substrates in enantiocontrolled syntheses has become a conventional procedure.[2] 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 [3]† of the Diels–Alder adduct[4] **1** of cyclopentadiene and benzoquinone, with vinyl acetate (6 equiv.) and lipase PS (Amano) (same weight as **2**) in acetonitrile[5] at 30 °C for 2 weeks to furnish the optically pure monoacetate‡ **3**, m.p. 87–88 °C, $[\alpha]_D^{31}$ +72.2 (*c* 1.00, $CHCl_3$),§ in 87% yield. Methoxymethylation of **3** with methoxymethyl chloride (MOM-Cl) (1.5 equiv.) in the presence of ethyldiisopropylamine[6] gave the MOM ether **4**, $[\alpha]_D^{30}$ +23.3 (*c* 2.25, $CHCl_3$), 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, $CHCl_3$), to *N*-bromosuccinimide (NBS)[7] (1.1 equiv.) afforded the bromoether **6**, m.p. 47.5–49 °C, $[\alpha]_D^{30}$ −110.6 (*c* 1.09, $CHCl_3$), 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)[7,8] (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, $CHCl_3$), in 85% yield. Methoxymethylation[6] of **7** followed by treating the resulting tri-MOM ether **8**, $[\alpha]_D^{34}$ −39.5 (*c* 1.28, $CHCl_3$), with activated zinc powder (8 equiv.) in methanol in the presence of a catalytic amount of acetic acid[7] regenerted the olefinic bond and the hydroxy group to give the enol **9**, $[\alpha]_D^{31}$ +22.4 (*c* 0.91, $CHCl_3$), 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, $CHCl_3$), 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, $CHCl_3$), in 60% yield. Treatment of **11** with diisobutylaluminium hydride (2 equiv.) in CH_2Cl_2 at −78 °C allowed stereoselective reduction to form the conduritol C tri-MOM ether **12**, $[\alpha]_D^{32}$ −72.3 (*c* 0.61, $CHCl_3$), 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 α-alkoxy ketone structure in which the reduction occurred selectivley from a less congested and stereoelectronically more favoured quasi-axial direction.[9] Hydrolysis of **12** with hot 10% hydrochloric acid in tetrahydrofuran (THF) (1:1) furnished crude (−)-conduritol C[10,11] **13**, which was transformed into the tetraacetate **14**, $[\alpha]_D^{31}$ −188 (*c* 0.28, $CHCl_3$) [lit.[11b,c] $[\alpha]_D^{24}$ +194 (*c* 1.1, $CHCl_3$) for (+)-enantiomer], in 60% overall yield for purification. Reversion of **14** into (−)-**13** has already been carried out in a single step.[11b].

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, $CHCl_3$), which on sequential methanolysis, methoxymethylation and desilylation, furnished the *ent*-**5**, $[\alpha]_D^{32}$ +37.6 (*c* 0.81, $CHCl_3$), in 74% overall yield *via* the alcohol **16**, m.p. 127.5–129 °C, $[\alpha]_D^{31}$ −11.3 (*c*

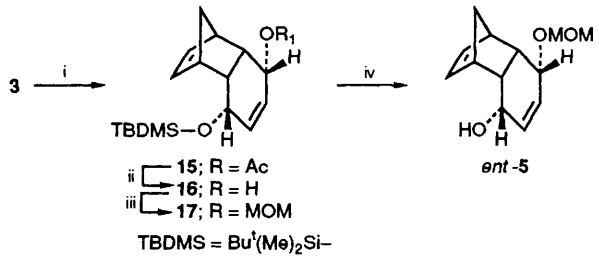


Scheme 1 *Reagents and conditions*: i, $NaBH_4$–$CeCl_3$, MeOH, 0 °C or Bu^i_2AlH, CH_2Cl_2, room temp.; ii, lipase PS, MeCN, 30 °C, 2 weeks; iii, MOM-Cl, Pr^i_2NEt, CH_2Cl_2; iv, K_2CO_3, MeOH, room temp.; v, NBS, CH_2Cl_2, 0 °C; vi, OsO_4 (cat.), NMO, 0 °C to room temp.; vii, Zn, AcOH (cat.), MeOH, reflux; viii, PCC, CH_2Cl_2, room temp.; ix, 250 °C, diphenyl ether, 1.5 h; x, Bu^i_2AlH, CH_2Cl_2, −78 °C; xi, 10% HCl–THF (1:1), 80 °C, 12 h; xii, Ac_2O, pyridine, room temp.; xiii, K_2CO_3, 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, H NMR and mass) data.

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



Scheme 2 *Reagents and conditions:* i, TBS-Cl, imidazole, DMF, room temp.; ii, K_2CO_3, MeOH, room temp.; iii, MOM-Cl, Pr^i_2NEt, CH_2Cl_2, 0 °C to room temp.; iv, $(Bu^n)_4NF$, THF, room temp.

0.82, $CHCl_3$) and the MOM ether **17**, $[\alpha]_D^{30}$ +14.9 (*c* 1.25, $CHCl_3$). This transformation constitutes a synthesis of (+)-conduritol C **13** in a formal sense. Thus, the enantiodivergent route to conduritol 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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