Stereocontrolled Synthesis of Dihydroxycyclopentane Derivative: Enantioselective Synthesis of (+)-Brefeldin A

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A novel enantioselective synthesis of (+)-brefeldin A was achieved *via* stereocontrolled one-pot synthesis of a dihydroxycyclopentane derivative from allyl phenyl sulfone and chiral diepoxide.

(+)-Brefeldin A[1] **1** has a variety of biological activities, including antifungal, antiviral and antimitotic effects.[2] Recently, it has been shown that brefeldin A blocks transport of secretory proteins between rough endoplasmic reticulum and golgi apparatus.[3] Since the first synthesis of (±)-brefeldin A, there have been numerous partial, formal and total syntheses.[4] We report a new total synthesis of (+)-brefeldin A, using our recently developed methodology for stereocontrolled synthesis of a dihydroxycyclopentane system (Scheme 1).[5]

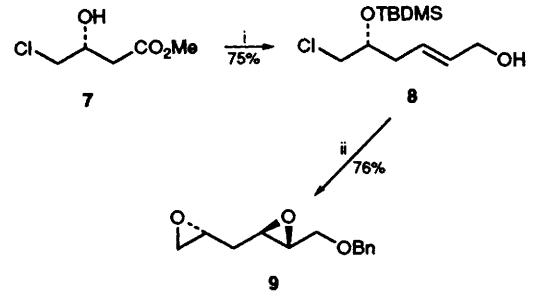
The coupling reaction of allyl phenyl sulfone **6** with the chiral diepoxide **5** gives the dihydroxycyclopentane derivative **4**. The acetylene **2** can be synthesized from **4** and then **1** derived by coupling with the side chain **3**.

The diepoxide **9** was synthesized as follows from (*R*)-methyl 4-chloro-3-hydroxybutyrate **7** [96.6% enantiomeric excess (e.e.)] (Scheme 2). The hydroxy group of **7** was protected, followed by reduction of the methyl ester, Wittig reaction, and reduction to give **8**. Asymmetric epoxidation[6] of **8**, followed by protection as the benzyl ether, deprotection of the silyl ether and treatment with K_2CO_3 in MeOH gave the diepoxide **9**.†

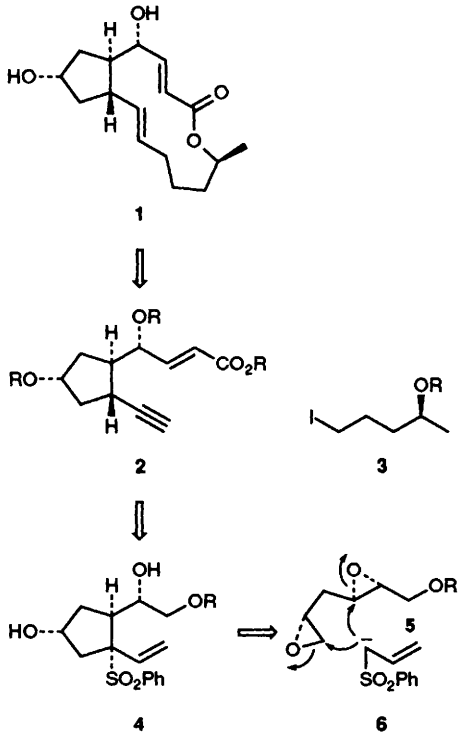
The lithio derivative of allyl phenyl sulfone was prepared from the sulfone (2.5 equiv.) and butyllithium (2.4 equiv.) in THF at −78 °C for 1 h. The diepoxide **9** (1.0 equiv.) in THF was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then at room temp. for 1 h. The reaction gave the dihydroxycyclopentane **10** as a single product in 95% yield; the stereochemistry was determined by an NOE experiment in the ^1H NMR spectrum. The hydroxy group of **10** was protected as the methoxyethoxymethyl (MEM) ether, the terminal olefin was oxidized to aldehyde, and the phenylsulfonyl group was removed by treatment with samarium(II) iodide (SmI_2) in the presence of hexamethylphosphoric triamide (HMPA). The formyl group was isomerized by treatment with K_2CO_3 in MeOH and the dibromoolefin **11** was obtained (Scheme 3).‡

The iodide **14** corresponding to the side chain moiety was prepared according to Scheme 4. The lithio derivative of 2,2,4-trimethyl-2-oxazoline[7] reacted with (*R*)-epichlorohydrin **12** (98% e.e.), and the oxazoline ring was hydrolysed with HCl to give the chlorolactone, which was reduced with $LiAlH_4$ to the triol **13**. The secondary hydroxy group of **13** was protected with silyl ether and the primary hydroxy group was converted to iodide to give **14** in 52% yield.§

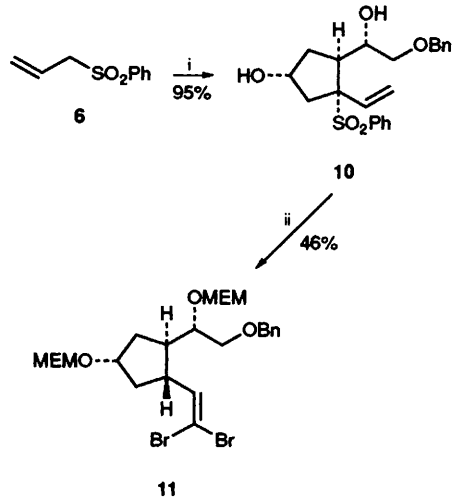
Treatment of **11** with butyllithium and then the iodide **14**



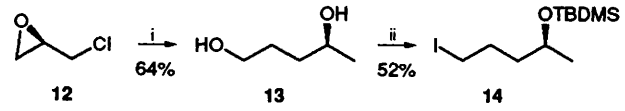
Scheme 2 *Reagents and conditions*: i, (a) TBDMSCl (TBDMS = *tert*-butyldimethylsilyl), imidazole, DMF, (b) diisobutylaluminum hydride (DIBAL), toluene, −78 °C, (c) $Ph_3PCH{=}CO_2Et$, benzene, room temp., (d) DIBAL, CH_2Cl_2, −78 °C, ii, (a) *tert*-butyl hydroperoxide (TBHP), $Ti(Pr^iO)_4$, D-(−)-diethyl tartrate, CH_2Cl_2, −20 °C, (b) Bn–Br, NaH, THF–DMF (4:1), room temp., (c) Bu_4NF, THF, room temp., (d) K_2CO_3, MeOH, room temp.



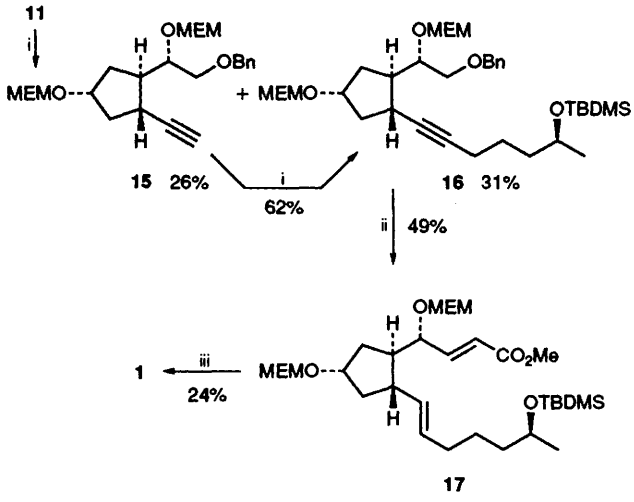
Scheme 1



Scheme 3 *Reagents and conditions*: i, BuLi, THF, −78 °C, then **9**, −78 °C to room temp., ii, (a) MEMCl, Pr^i_2NEt, CH_2ClCH_2Cl, 50 °C, (b) O_3, MeOH–CH_2Cl_2 (1:1), −78 °C, then Me_2S, room temp., (c) SmI_2, THF–HMPA (15:1), room temp., (d) K_2CO_3, MeOH, room temp., (e) CBr_4, Ph_3P, CH_2Cl_2, 0 °C



Scheme 4 *Reagents and conditions*: i, (a) 2,2,4-trimethyl-2-oxazoline, BuLi, THF, −78 °C, (b) 3 mol dm^{-3} HCl, 80 °C, (c) $LiAlH_4$, THF, room temp., ii, (a) Bu^tCOCl, Et_3N, CH_2Cl_2, room temp., (b) TBDMSCl, imidazole, DMF, room temp., (c) DIBAL, CH_2Cl_2, −78 °C, (d) Ts–Cl, py, CH_2Cl_2, room temp., (e) NaI, acetone, room temp.



Scheme 5 *Reagents and conditions*: i, BuLi, **14**, THF–HMPA (3:1), −78 °C, ii, (a) Na, liq. NH_3, THF, −33 °C, (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, (c) $(Pr^iO)_2P(O)CH_2CO_2Me$, Bu^tOK, THF, −78 °C, iii, (a) 75% AcOH, 25 °C, (b) 1 mol dm^{-3} LiOH, MeOH, 25 °C, (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, room temp., then DMAP, toluene, reflux, (d) $TiCl_4$, CH_2Cl_2, 0 °C

gave the coupling product **16** and the acetylene **15**. The acetylene **15** further reacted with the iodide **14** to give **16**. Treatment of **16** with sodium in liquid ammonia, followed by Swern oxidation, and Horner–Wittig reaction gave the α,β-unsaturated ester **17**. Conversion of **17** to (+)-brefeldin A **1**¶ {$[\alpha]_D$ + 93.4 (*c*. 0.35, MeOH)} was carried out by desilylation, hydrolysis of the methyl ester, Yamaguchi's lactonization[8] and treatment with titanium tetrachloride.

The present work illustrates the utility of our new methodology for the stereocontrolled synthesis of a dihydroxycyclopentane system. The reaction should also be applicable to synthesis of other natural products.

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Footnotes

† *Selected spectroscopic data* for **9**: $[\alpha]_D$ + 37.7 (*c* 1.00, $CHCl_3$); IR (neat) ν/cm^{-1} 3000, 1500, 1458; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (2H, m) 2.54 (1H, dd, *J* 5.0, 2.8 Hz), 2.81 (1H, dd, *J* 5.0, 4.1 Hz), 3.03 (2H, m), 3.09 (1H, m), 3.51 (1H, dd, *J* 11.3, 5.1 Hz), 3.73 (1H, dd, *J* 11.3, 3.1 Hz), 4.56 (1H, d, *J* 12.1 Hz), 4.60 (1H, d, *J* 12.1 Hz) 7.25–7.4 (5H, m).

‡ *Selected spectroscopic data* for **11**: $[\alpha]_D$ −23.0 (*c* 1.05, $CHCl_3$); IR (near) ν/cm^{-1} 2930, 2880, 1455, 1365; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (1H, m), 1.77 (1H, m), 1.84 (1H, m), 2.24 (1H, m), 2.30 (1H, m), 2.68 (1H, m), 3.37 (3H, s), 3.39 (3H, s), 3.45–3.55 (6H, m), 3.65–3.75 (5H, m), 4.19 (1H, m), 4.47 (1H, d, *J* 12.1 Hz), 4.54 (1H, d, *J* 12.1 Hz), 4.69 (1H, d, *J* 7.2 Hz), 4.70 (1H, d, *J* 7.2 Hz), 4.79 (1H, d, *J* 6.9 Hz), 4.86 (1H, d, *J* 6.9 Hz), 6.42 (1H, d, *J* 9.5 Hz), 7.25–7.4 (5H, m).

§ *Selected spectroscopic data* for **14**: $[\alpha]_D$ +8.8 (*c* 1.15, $CHCl_3$); IR (neat) ν/cm^{-1} 2930, 2855, 1470, 1375, 1255; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 1.14 (3H, d, *J* 6.2 Hz) 1.45–1.55 (2H, m), 1.75–2.0 (2H, m), 3.19 (2H, dt, *J* 1.5, 6.9 Hz), 3.82 (1H, m).

¶ Lit. $[\alpha]_D$ +90 (*c* 0.1, MeOH).[4b]

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