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TOTAL SYNTHESIS OF (+)-BREFELDIN C *VIA* LEWIS ACID MEDIATED CYCLIZATION OF AN EPOXY-ALLYLSILANE

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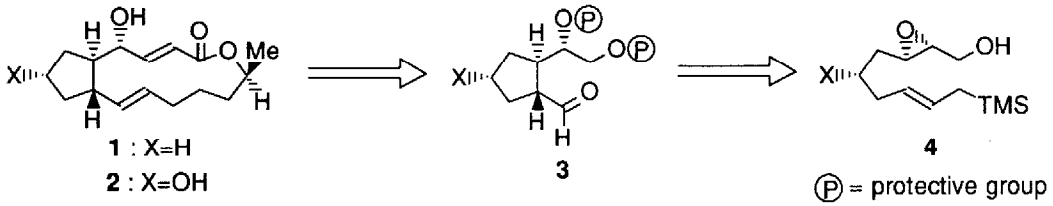
Summary: An enantioselective synthesis of (+)-brefeldin C has been achieved using Lewis acid mediated cyclization of a chiral epoxy-allylsilane as a key step.

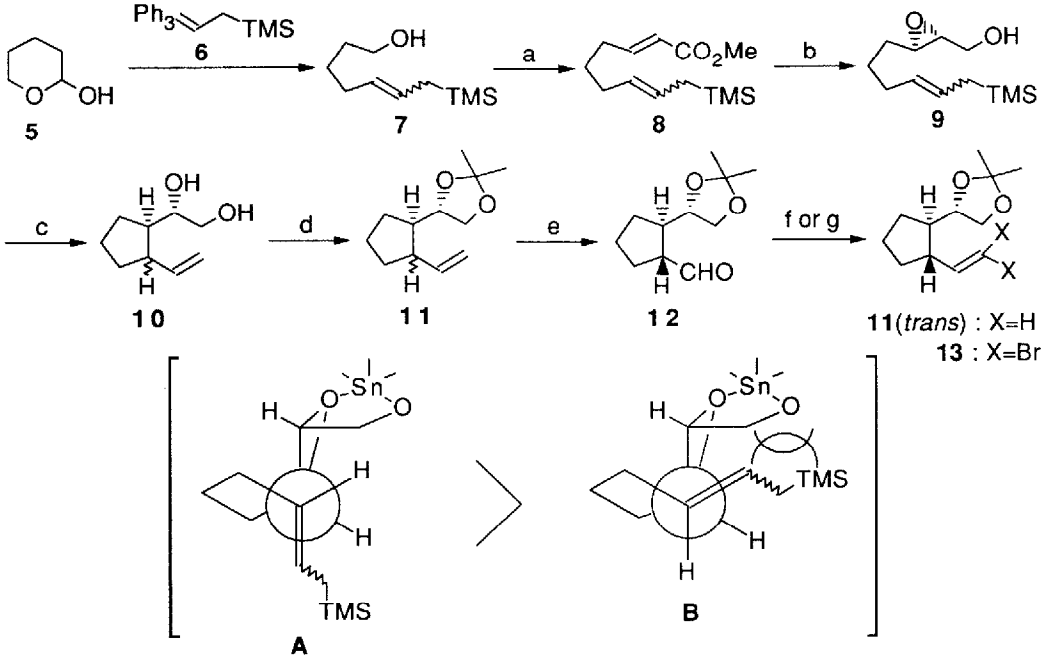
The stereoselective construction of substituted five membered ring systems continues to receive extensive attention.[1] One of the major reasons for this has been the search for synthetic routes to prostaglandins, steroids, cyclopentanoid terpenes, and so on. For the purpose of developing an effective enantioselective method for the construction of vicinally substituted cyclopentane units, we chose brefeldin C (**1**) as a synthetic target. Brefeldin C (**1**), a fungal metabolite isolated from *Eupenicillium brefeldianum* by Nozoe and co-workers,[2] is known to be a biosynthetic precursor[3] of brefeldin A (**2**),[4] a macrolide antibiotic possessing a wide range of biological activity. We now report an enantioselective synthesis[5] of (+)-brefeldin C (1) based on a new strategy which relys on Lewis acid mediated cyclization of a chiral epoxy-allylsilane[6,7] as depicted in Scheme I.



Scheme I

Our synthesis started with the known allylsilane **7**,[6] readily prepared as an isomeric mixture by Wittig reaction of the phosphorane **6**[8] with the lactol **5**. Swern oxidation of **7** followed by Horner-Emmons reaction[9] gave the ester **8**[10] in 72% yield. The ester **8** was then converted to the epoxy alcohol **9** by DIBAL reduction and subsequent Sharpless catalytic asymmetric epoxidation[11] in 96% yield. Upon treatment of **9** with 1.5 equiv of $SnCl_4$ at –90 °C in methylene chloride, instantaneous cyclization took place to give the diol **10** as an inseparable 4:1 isomeric mixture in 82% yield. After protection of the diol **10** as its acetonide, ozonolysis of **11** followed by base-catalyzed epimerization led to exclusive formation of the *trans*-aldehyde **12**. The optical purity of **12** was determined to be ≥93% ee by 500 MHz ^1H NMR analysis of the (*R*)- and (*S*)-MTPA esters[12] of the corresponding alcohol obtained from

$NaBH_4$ reduction of **12**. After conversion of **12** into the *trans*-olefin **11**(*trans*), $[\alpha]_D^{22}$ –17.6° (*c* 1.11, $CHCl_3$), by Wittig reaction, 500 MHz ^1H NMR analysis of **11** and **11**(*trans*) allowed us to conclude that the major component of **11** was the *trans*-isomer. This stereochemical outcome suggests that the $SnCl_4$ mediated cyclization predominantly proceeds through the transition state **A** rather than **B** by steric reasons. In order to introduce the requisite lower side chain, the *trans*-aldehyde **12** so obtained was transformed[13] into the dibromoolefin **13**, $[\alpha]_D^{26}$ –12.6° (*c* 0.93, $CHCl_3$), in 75% overall yield from the diol **10**.

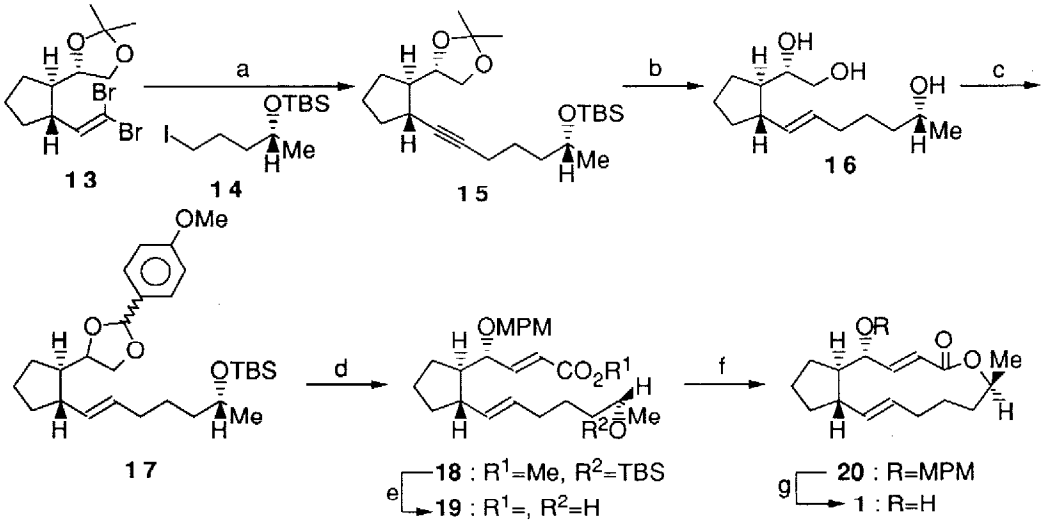


Scheme II. (a) (i) $(COCl)_2$/DMSO/Et_3N, –50 →0 °C, (ii) $(^iPrO)_2P(O)CH_2CO_2Me$, KO^tBu, THF, –78 °C, 72%; (b) (i) DIBAL, CH_2Cl_2, –78 °C, (ii) $Ti(O^iPr)_4$ (0.1 equiv), D-(–)-DIPT (0.15 equiv), ^{t}BuOOH (2 equiv), 4A molecular sieves, CH_2Cl_2, –25 °C, 96%; (c) $SnCl_4$ (1.5 equiv), CH_2Cl_2, –90 °C, 82% (*trans*:*cis*=4:1); (d) $Me_2C(OMe)_2$, CSA (catalyst), acetone; (e) (i) O_3. $NaHCO_3$, CH_2Cl_2-MeOH (5:1 v/v), –78 °C, then add Me_2S, (ii) NaOMe, MeOH; (f) $Ph_3P{=}CH_2$, THF, –78 °C; (g) Ph_3P (4 equiv), CBr_4 (2 equiv), CH_2Cl_2, 0 °C, 75% overall from **10**.

Treatment of **13** with 3 equiv of ^{n}butyllithium followed by *in situ* alkylation of the resulting lithium acetylide with the iodide **14**[14] afforded the acetylene **15**, $[\alpha]_D^{25}$ –46.9° (*c* 0.81, $CHCl_3$). Without purification, **15** was then successively subjected to reduction of the acetylenic bond and deprotection to give the triol **16**, $[\alpha]_D^{22}$ –28.8° (*c* 1.05, $CHCl_3$), in 81% overall yield from the dibromoolefin **13**.

The assembly of the upper side chain was achieved by taking advantage of regioselective cleavage of a benzylidene acetal with DIBAL previously developed by our group.[16] Thus, the triol **16** was converted to the *p*-methoxybenzylidene acetal **17** by acetalization followed by silylation in 94% yield. Upon sequential reductive cleavage of the acetal moiety, Swern oxidation, and Horner-Emmons reaction,[9] **17** afforded the ester **18**, $[\alpha]_D^{22}$ –70.6° (*c* 0.62, $CHCl_3$), in 72% overall yield.

After quantitative conversion of **18** to **19**, the hydroxy acid **19** was subjected to lactonization using Mitsunobu's procedure[17] giving the lactone **20** (85%), mp 117 °C, $[\alpha]_D^{19}$ –30.2° (*c* 0.66, $CHCl_3$), along with unidentified polymeric lactones (<5%). Finally, oxidative deprotection[18] of **20** furnished (+)-brefeldin C (**1**) in 97% yield. The synthetic substance, mp 162 °C, $[\alpha]_D^{19}$ +125.2° (*c* 1.06, $CHCl_3$),[19] was identical with natural brefeldin C (**1**), mp 160.5 – 161 °C,[2] $[\alpha]_D^{20}$ +130.6° (*c* 0.07, $CHCl_3$),[2] by spectroscopic (^1H NMR, IR, MS) and chromatographic comparisons.



Scheme III. (a) ^{n}BuLi (3 equiv), THF, –78 °C, then add **14** in HMPA, –78 °C → 0 °C; (b) (i) Li, ^{t}BuOH, NH_3, –33 °C, (ii) *p*-TsOH (catalyst), MeOH, 81% overall from **13**; (c) (i) *p*-$(MeO)C_6H_4CH(OMe)_2$, CSA (catalyst), (ii) TBSCl, imidazole, DMF, 94%; (d) (i) DIBAL, toluene, (ii) $(COCl)_2$/DMSO/Et_3N, CH_2Cl_2, –50 → 0 °C, (iii) $(^iPrO)_2P(O)CH_2CO_2Me$, KO^{t}Bu, THF, –78 °C, 72%; (e) (i) *p*-TsOH (catalyst), MeOH, (ii) LiOH, aq. MeOH; (f) DEAD (5 equiv), Ph_3P (5 equiv), toluene (2.5×10^{-3} M), 0 °C, 85% overall from **18**; (g) DDQ, aq. CH_2Cl_2, 97%.

The present study outlined in this report provides a new method for the preparation of *trans*-disubstituted cyclopentanes with high optical purity. The two adjacent 'masked aldehyde' functionality generated in the Lewis acid mediated cyclization offers an opportunity for further structural elaboration as illustrated in the synthesis of (+)-brefeldin C (**1**).

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