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# A Formal Synthesis of (+)-Brefeldin A

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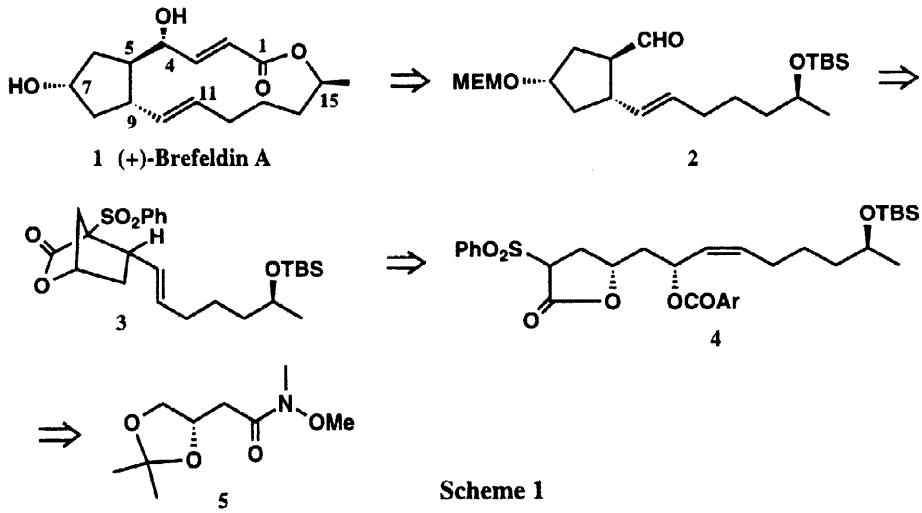
***Abstract:*** : A formal synthesis of (+)-brefeldin A has been achieved *via* stereoselective construction of hydroxycyclopentane skeleton possessing the requisite hydroxyheptenyl side chain. The highly advanced intermediate **2** has been synthesized from the known Weinreb amide in 19 % overall yield of 11 steps. 

Brefeldin A (**1**) has been one of the most attractive targets for the synthetic chemists during the last two decades due to its wide range of biological activities and characteristic structure.[1] Particularly, stereoselective synthesis of (+)-brefeldin A *via* construction of cyclopentane skeleton followed by alkylative chain elongation has merged as one of the versatile strategy.[2] However, the unsatisfactory yield in cyclopentane construction or moderate stereoselectivity in carbonyl reduction of cyclopentanone system has often limited the applicability of this approach.

We have recently reported stereoselective syntheses of *cis* and *trans*-disubstituted hydroxycyclopentanes.[3] We herein report a formal synthesis of (+)-brefeldin A as an extended application of this new variant of cyclopentane construction. Our synthetic strategy outlined in Scheme 1 employs the stereoselective construction of hydroxycyclopentane skeleton of brefeldin A possessing the requisite hydroxyheptenyl side chain *via* highly stereoselective palladium catalyzed cyclization of allylic benzoate as a key step. The stereochemistry of $C_9$ as well as the olefin geometry of $C_{10}$ are also established during this process.




**1** (+)-Brefeldin A **2** **3** **4** **5**

**Scheme 1**

Our synthesis was commenced by preparation of the cyclization precursor **4** from the known Weinreb amide **5**[4] as shown in Scheme 2. The amide **5** was treated with anion of silyloxyheptyne **6**[5] derived from (*S*)-

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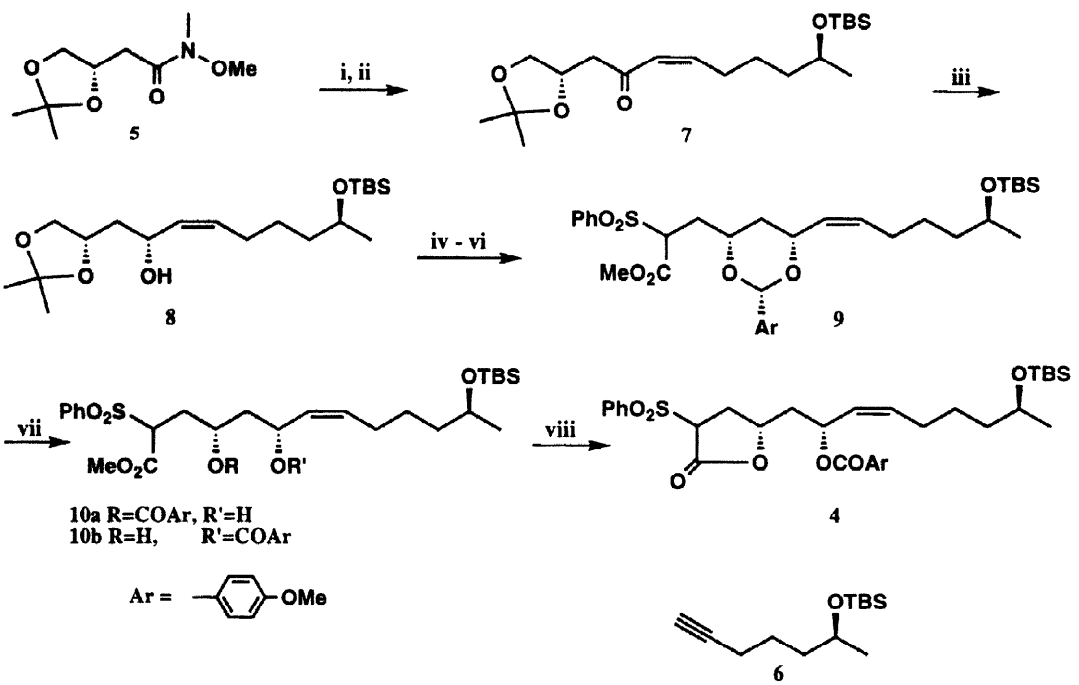
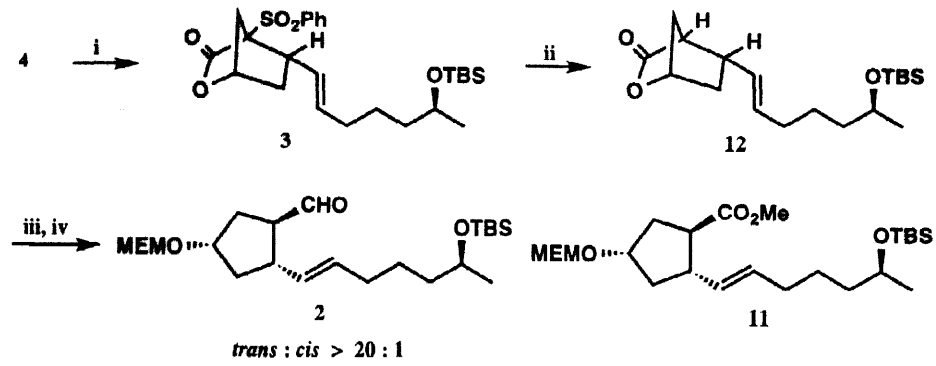
lactate and the resulting ynone was patially hydrogenated to afford enone **7**.[6] Stereoselective reduction of enone **7** was achieved by Suzuki procedure.[7] LAH reduction of enone **7** in the presence of lithium iodide afforded the alcohol **8** as a single diastereomer in 95 % yield. Subjection of alcohol **8** to the equilibrating exchange conditions[8] using dimethylacetal of anisaldehyde and tosylation of the resulting hydroxydioxane followed by benzenesulfonylacetate displacement furnished the alkylated dioxane **9**. Finally, sequential deprotection and lactonization of dioxane **9** provided the cyclization precursor **4**. Regioselective PMB deprotection of dioxane **9** by DDQ[9] initially liberated a mixture of hydroxy ester **10a** and **10b** in favor of the undesired isomer **10a**. However, DBU promoted lactonization of the isomeric mixture afforded the desired lactone **4** as an only product in 71 % of two step yield. The isomer **10a** seems to undergo initial intramolecular acyl transfer and then lactonization.




**i) 6, *n*-BuLi, THF, -78 °C, 81% ii) Lindlar catalyst, quinoline, $H_2$, MeOH, 95% iii) LAH, LiI, $Et_2O$, -78 °C, 95% iv) $(MeO)_2CHC_6H_4$(*p*-OMe), CSA, $CH_2Cl_2$, 84% v) TsCl, $Et_3N$, 4-DMAP, $CH_2Cl_2$, 99% vi) $PhO_2SCH_2CO_2Me$, NaH, DMF, 100 °C, 72% vii) DDQ, $CH_2Cl_2$-$H_2O$ (18 : 1) viii) DBU, $CH_3CN$, 71% for 2steps**

**Scheme 2**

The crucial cyclization of allylic benzoate **4** was carried out by DBU treatment in the presence of 5 mol % $Pd(PPh_3)_4$. The bicyclic lactone obtained in 88 % yield possesses the three requisite stereogenic centers and one *E*-olefin of (+)-brefeldin A at this stage. The final conversion of the bicyclic lactone **3** to the known advanced intermediate **2**[2a,10] was accomplished by the efficient three step sequence. Desulfonylation of the bicyclic lactone **3** under the modified Trost conditions[11] follwed by sequential DIBAL reduction, MEM protection of the resulting hydroxy aldehyde[12] and then DBU treatment afforded the aldehyde **2**[13] in 71 % overall yield. The bicyclic lactone **3** could be also converted to an alternative advanced intermediate **11**[14] as a 4 : 1 mixture of *trans* and *cis*-isomer by our previously reported procedure.[3] However, the present three step sequence turned out to be superior in point of diastereomeric ratio (more than 20 : 1 in favor of *trans*-isomer) and reaction steps.




**i) $Pd(PPh_3)_4$ (5 mol %), DBU, THF, reflux, 88% ii) 6% Na/Hg, $B(OH)_3$, MeOH, 87% iii) DIBAL, toluene, -78 °C, 91% based on 85% conversion iv) MEMCl, $iPr_2NEt$, $ClCH_2CH_2Cl$, 50 °C then DBU, 90%**

**Scheme 3**

In summary, the advanced synthetic intermediate **2** for (+)-brefeldin A has been efficiently synthesized from the known Weinreb amide **5** in 19 % overall yield of 11 steps. The key feature of this versatile synthetic route involves a highly stereoselective construction of hydroxycyclopentane skeleton of (+)-brefeldin A. In addition, the requisite hydroxyheptenyl side chain possessing correct stereochemistries and olefin geometry are also generated during this process. This versatile procedure would be widely utilized in the syntheses of variety of the related systems.

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## REFERENCES AND NOTES

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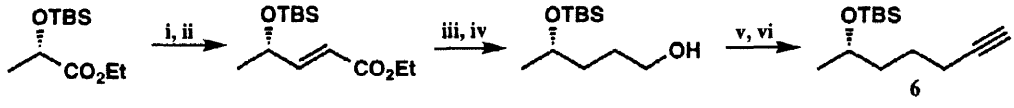
4. Tavares, F.; Lawson, J. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 3303.
5. Drian, C. L.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473. Nokami, J.; Ohkura, M.; Dan-Oh, Y.; Sakamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 2409. The known 6-silyloxy-1-heptyne (**6**) was straightforwardly prepared from (*S*)-lactate in 74 % overall yield by our own six step sequence.




**i) DIBAL, $CH_2Cl_2$, -78 °C ii) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, $iPr_2NEt$, $CH_3CN$, 94% for 2steps. iii) $H_2$, Pd/C, EtOH iv) DIBAL, $CH_2Cl_2$, -78 °C, 98% for 2steps v) TsCl, $Et_3N$, 4-DMAP, $CH_2Cl_2$, vi) Litium acetylide-EDA complex, DMSO, 81% for 2steps**

6. The unstable *Z*-olefinic enone **7** was utilized for the preparation of the corresponding cyclization precursor **4** due to synthetic efficiency although both *Z*-olefinc allylic benzoate **4** and its *E*-isomer with the requisite stereochemistry at allylic position would provide the same cyclization product **3**. For the *syn* and *anti* interconversion of $\pi$-allyl palladium complex, see: Trost, B. M. *Chem. Rev*, **1996**, *96*, 35 and references cited therein. Spectral data for **7**: IR (neat) 2930, 1693, 1616, 1472, 1372, 1254 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ -0.01 (s, 3H), 0.00 (s, 3H), 0.84 (s, 9H), 1.07 (d, 3H, J = 6.0 Hz), 1.32 (s, 3H), 1.37 (s, 3H), 1.34-1.54 (m, 4H), 2.54-2.59 (m, 2H), 2.59 (dd, 1H, J = 16.8, 7.6 Hz), 2.92 (dd, 1H, J = 16.8, 5.6 Hz), 3.52 (dd, 1H, J = 8.2, 6.8 Hz), 3.71-3.77 (m, 1H), 4.17 (dd, 1H, J = 8.2, 5.8 Hz), 4.40-4.48 (m, 1H), 6.05 (dd, 1H, J = 11.2, 6.0 Hz), 6.11 (d, 1H, J = 11.2 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ -4.9, -4.5, 18.0, 23.7, 25.1, 25.3, 25.8, 26.7, 29.3, 39.1, 48.2, 68.1, 69.4, 71.7, 108.5, 126.3, 149.6, 198.4; HRMS (CI) *m/z* calcd for $C_{20}H_{39}O_4Si$ 371.2618, found 371.2624 ($M^+$+H); $[\alpha]^{16}_D$ = +16.2 (c = 6.8, $CH_2Cl_2$).
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11. Unpublished results. The details for this extremely mild desulfonylation procedure will be reported soon in due courses. For Trost's conditions, see; Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *39*, 3477.
12. DIBAL reduction of bicyclic lactone **12** provided the hydroxy aldehyde rather than lactol.
13. Spectral data for **2**: IR (neat) 2928, 1725, 1462, 1372, 1254, 1046, 835, 774 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 0.00 (s, 6H), 0.84 (s, 9H), 1.07 (d, 3H, J = 6.0 Hz), 1.25-1.39 (m, 4H), 1.50-1.57 (m, 1H), 1.87-1.96 (m, 3H), 2.01-2.07 (m, 1H), 2.20-2.25 (m, 1H), 2.57-2.63 (m, 1H), 2.67 (qd, 1H, J = 9.0, 2.4 Hz), 3.35 (s, 3H), 3.51-3.53 (m, 2H), 3.64-3.66 (m, 2H), 3.71-3.75 (m, 1H), 4.14-4.18 (m, 1H), 4.68 (s, 2H), 5.39-5.42 (m, 2H), 9.58 (d, 1H, J = 2.4 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ -4.7, -4.4, 18.2, 23.8, 25.5, 25.9, 32.3, 33.0, 39.1, 40.0, 42.6, 55.9, 59.0, 67.0, 68.5, 71.8, 76.9, 94.3, 131.4, 131.8, 202.9; HRMS (CI) *m/z* calcd for $C_{23}H_{45}O_5Si$ 429.3036, found 429.3037 ($M^+$+H); $[\alpha]^{17}_D$ -23.5° (c = 0.14, $CH_2Cl_2$).
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