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A SIMPLIFIED SYNTHESIS OF (+)-BREFELDIN A

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Summary: An effective and enantioselective process for the total synthesis of (+)-brefeldin A (**1**) is described which starts from the dextrorotatory ketone **2**.

Brefeldin A[1] (**1**) has long been known to exhibit an extraordinary range of biological activities including antibiotic, antiviral, cytostatic and antimitiotic effects.[2] Recently, the underlying reason for such biological activities has been clarified by a number of important discoveries including the following: (1) **1** inhibits protein transport in mammalian cells from the endoplasmic reticulum (ER) to the golgi complex (GC)[3] and causes disassembly of the GC; (2) **1** inhibits sialation, fucosylation, and sulfation of glycoproteins as well as transport of proteins;[4] (3) **1** inhibits exocytosis and the presentation of viral proteins to cytotoxic T lymphocytes.[5] These are remarkable actions for such a small molecule.

Since the first synthesis of (±)-brefeldin A in 1976,[6] several groups have described syntheses of **1**, both in racemic and chiral form.[7] Because of a substantial current demand for experimental quantities of **1**, its commercial unavailability, and the impracticality of previously developed syntheses, we were led to develop a simplified and practically useful new synthetic route to **1** with the results which are described herein.

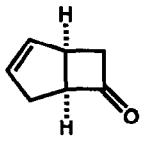
The starting point for synthesis was the readily available dextrorotatory form of bicyclo[3.2.0]heptenone **2**, $[\alpha]_D^{25}$ +61.4° (c=1, $CHCl_3$),[8] which was converted to bromo lactone **3** by (1) bromohydrin formation with 1 equiv of N-bromosuccinimide in 5 : 1 acetone-water at 23°C (60% yield)[9] and (2) Baeyer-Villiger oxidation with 30% H_2O_2 in HOAc at 5 °C for 4 h (67% yield, not optimized). Bromo lactone **3** was transformed into enone **4** by the sequence: (1) debromination with 1.15 equiv of Bu_3SnH and 0.2 equiv of bisazoisobutyronitrile in C_6H_6 at reflux for 24 h (92%), (2) oxidation by treatment with dimethyl sulfoxide (1.1 equiv) and $(CF_3CO)_2O$ (1.1 equiv) in CH_2Cl_2 at -65 °C followed by Et_3N (2.15 equiv), warming to 25 °C (1 h at 25 °C) to give **4**, and (3) esterification (CH_3I, K_2CO_3, DMF, 23 °C for 48 h) to

afford **5** (60% overall), $[\alpha]_D^{23}$ +120.8° (c=1.1, CH_2Cl_2). The next step, **5** → **7**, required the reagent **6** which was prepared by reaction of the *t*-butyldimethylsilyl (BMS) ether of (*S*)-hept-6-yn-2-ol[7b] with Cp_2ZrHCl[10] in THF.[11] A mixture of **5** and **6** (1.6 equiv) in THF at 0 °C was treated with a THF solution prepared from 0.4 equiv of $Ni(acac)_2$ and 0.4 equiv of diisobutylaluminum hydride at -10 °C[10] to give, after a reaction time of 8 h at 0 °C and isolation by silica gel chromatography, keto ester **7** in 72% yield as an oil, $[\alpha]_D^{23}$ -69.5° (c=2.6, CH_2Cl_2). Reduction of **7** with 1 equiv of Li-*sec*-Bu_3BH (L-Selectride) in THF at -78 °C for 2 h gave a 4 : 1 mixture of **8** and the C-7 epimer (brefeldin numbering) in 89% combined yield. Pure **8** was obtained by heating the mixture with 2 mole% of tosic acid in toluene at reflux for 10 h, to lactonize the minor diastereomer, followed by silica gel chromatography; oil, $[\alpha]_D^{23}$ -14.8° (c=0.3, CH_2Cl_2). Reaction of **8** with methoxyethoxymethyl chloride (MEM chloride, 3 equiv) and diisopropylethylamine (4.5 equiv) in methylene chloride at 23 °C for 10 h afforded the MEM ether **9** (97%), $[\alpha]_D^{23}$ -14.7° (c=1.9, CH_2Cl_2), reduction of which with 1 equiv of *i*-Bu_2AlH in CH_2Cl_2 at -78 °C for 1.5 h produced aldehyde **10** (98%), $[\alpha]_D^{23}$ -15.1° (c=1.4, CH_2Cl_2). Reaction of aldehyde **10** with 4 equiv of (*S*)-**11**[12] and 6 equiv of piperidine in CH_3CN at 5 °C for 48 h afforded after silica gel chromatography allylic alcohol **12** and its C(4) diastereomer in a ratio of 7.5 : 1 (94% total yield). Since the mixture was difficult to separate it was used as such, since the purification of the final product **1** was easily accomplished by chromatography.

Intermediate **12** was converted to the bis MEM ether as described above for **8** → **9** (90% yield) and then converted to hydroxy acid **13** by desilylation (3 : 1 HOAc-H_2O at 23 °C for 5 h, 87% yield) and saponification (0.15 M LiOH in 6 : 1 MeOH-H_2O at 23 °C for 24 h, 93% yield). Lactonization of **13** and MEM ether cleavage, as previously described,[6] provided after silica gel chromatography and recrystallization from ethyl acetate, (+)-brefeldin A (**1**), mp and mixture mp with an authentic sample 201-202 °C, $[\alpha]_D^{23}$ +90° (c=0.1, MeOH). Synthetic and authentic samples of brefeldin A were identical by infrared, 500 MHz ^1H NMR, and tlc comparison.[13]

In an effort to achieve and even shorter synthesis of **1**, esters **14** and **15** were synthesized from **4** and the corresponding (*S*)-α-*p*-toluenesulfinylacetate esters, as described above for **10** → **12**. Attempts to effect macrolactonization-conjugate addition from **14** using reagents such as $Bu_3Sn\bullet$ radical precursors or sources of Pd(0) were not successful. In addition attempts to hydrozirconate **15** with Cp_2ZrHCl (for Ni-catalyzed internal conjugation analogous to **5** + **6** → **7**) were thwarted by the facile reduction of the enone carbonyl by Cp_2ZrHCl.

We believe that the synthesis of (+)-**1** reported herein is substantially simpler and more effective than any previously described.[14]



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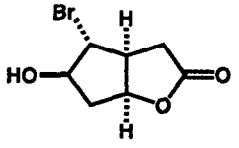

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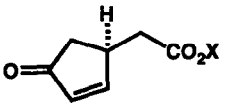
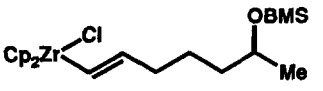


4 X = H

5 X = CH_3



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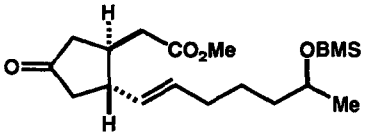

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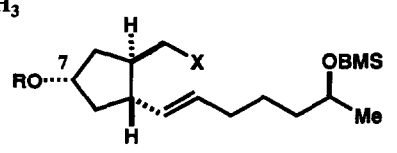
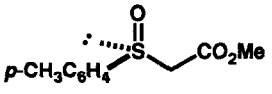


8 R = H; X = CO_2Me

9 R = MEM; X = CO_2Me

10 R = MEM; X = CHO



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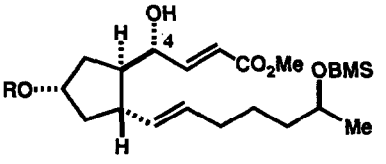

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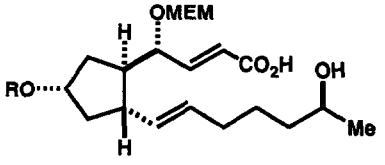

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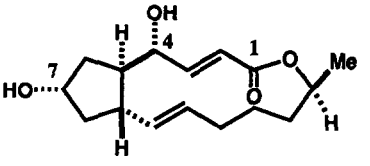
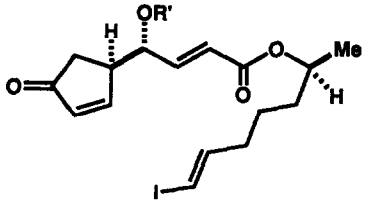
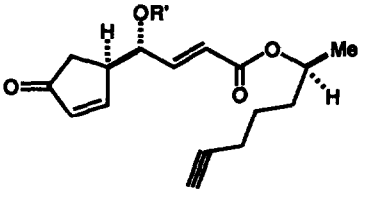


1



14 R' = *t*-$BuPh_2Si$



15

BMS - *t*-butyldimethylsilyl

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8. The dextro ketone **2** is readily available from (±)-**2** by resolution of the crystalline bisulfite addition product obtained from (±)-**2**, (–)-α-phenylethylamine, sulfur dioxide and 1 equiv of water; see E. W. Collington, C. J. Wallis, and I. Waterhouse, *Tetrahedron Letters*, **24**, 3125 (1983). We are grateful to Dr. Wallis for a generous supply of (+)-**2**.
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13. We are grateful to Dr. H. P. Sigg of Sandoz Ltd. for an authentic sample of brefeldin A.

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