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Total Synthesis of (+)-Brefeldin A

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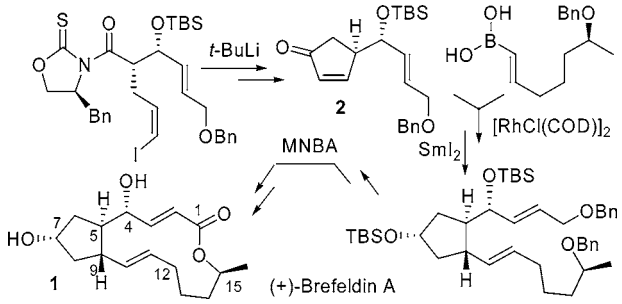
ABSTRACT



(+)-Brefeldin A was synthesized through an efficient route, which features (1) construction of the five-membered ring from a Crimmins aldol via tandem Li–I exchange and carbanion-mediated cyclization with concurrent removal of the chiral auxiliary, (2) introduction of the lower side chain (C10 to C16) via a Rh-catalyzed Michael addition of a vinyl boronic acid, (3) stereoselective reduction of the C7 ketone with SmI_2, and (4) a 2-methyl-6-nitrobenzoic anhydride-mediated (Shiina) lactonization.

(+)-Brefeldin A (BFA, **1**) is one of the naturally occurring compounds of lasting interest over the decades. Since its first isolation[1] in 1958, BFA has been a target of study for numerous chemists and bio-scientists. In particular, in the field of total synthesis more than 30 successful approaches have been documented during the past 30 years.[2] Apart from the natural compound itself, derivatives and analogues of BFA are also receiving more and more attention.[3]

In 2004 we reported an aldol approach to **1** and its 7-epimer.[2i,j] The same strategy has also been applied to the synthesis of the 15-demethyl analogues.[3i] While that approach is efficient in constructing the key C4/C5 stereogenic centers, the route to the key intermediate enone **2** and the lower side chain was rather lengthy. Establishment of the C7 stereogenic center was also unsatisfactory. Efforts to circumvent these drawbacks led to a much more efficient synthesis of **1**, which is presented here below.

(1) Singleton, V. L.; Bohonos, N.; Ullstrup, A. J. *Nature* (*London*) **1958**, *181*, 1072−1073.

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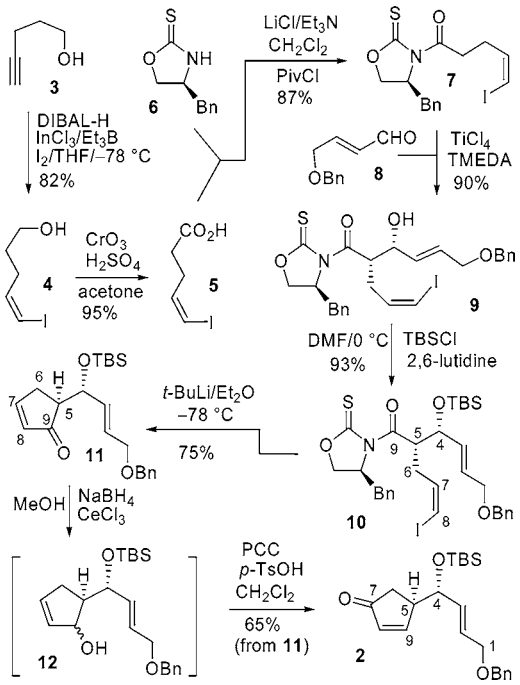
One of the factors that contributed to the efficiency of the present approach was an expeditious synthesis (Scheme 1) of enone **2**, which exploited a cyclization initiated by the

Scheme 1



attack of an in situ formed vinyl lithium onto an internally tethered carbonyl group with concurrent removal of the chiral auxiliary. Successful execution of this plan called for facile access to a vinyl halide building block of pure cis configuration. Consequently, quite a few known protocols[4] were examined, including decarboxylative elimination of α,β-dibromocarboxylic acids under microwave conditions,[4a] addition of catecholborane to a terminal alkyne followed by halogenation,[4b] conversion of vinyl 1,1-dibromide into a cis vinyl monobromide under the $Bu_3SnH/Pd(PPh_3)_4$ conditions,[4c] and Wittig reaction of $Ph_3P{=}CHI$[4d] with an aldehyde. However, none of them gave satisfactory results. The desired product was either formed in low yields or it was contaminated with the undesired trans isomers. Finally, the problem was solved using Oshima's[4e] protocol. Thus, by treating the commercially available alkynol **3** with DIBAL-H/$InCl_3$/Et_3B/I_2, very pure cis **4** was cleanly formed in 82% yield.[4f]

The alcohol **4** was oxidized into the known[5a] acid **5** by Jones oxidation in 95% yield. Use of PDC[5b] or IBX/oxone[5c] here was less satisfactory (82% and 62% yield, respectively). The resultant **5** was connected[6a] to the readily accessible[6b] chiral auxiliary **6** to afford the acyl oxazolidinthione **7**. Subsequent treatment of **7** with the known[2j] enal **8** under the Crimmins[7] conditions afforded the enantiopure syn aldol **9** in 90% isolated yield. Other diastereomers, formed in less than 3% yield altogether, were readily removed by chromatography. The newly formed hydroxyl group in **9** was then protected with TBSCl/2,6-lutidine/DMF, leading to the TBS ether **10**.

The tandem lithium−iodine exchange−cyclization reaction was first attempted using an equimolar amount of *n*-BuLi. The exchange was expected to work well because vinyl carbanions are more stable than alkyl carbanions in general. However, the product in this case was rather complex, containing several components apart from unreacted **10** and the expected chiral auxiliary **6**. Introduction of additional *n*-BuLi (<0.3 mol equiv with respect to **10**) did result in complete disappearance of the starting **10**. However, it also led to an even more complex product mixture. Later, we found in the literature that Negishi[8] had used *t*-BuLi to realize a smooth lithium−iodine exchange/ring closure from a simple amide precursor. Although the situation in our case appeared to be more complicated because of the presence of a chiral auxiliary and the high risk of subsequent elimination of the β-silyloxy group, to our gratification used *t*-BuLi instead of *n*-BuLi did indeed result in a great improvement. The number of components in the product mixture was remarkably reduced. Through careful optimization of the reaction conditions, we finally managed to obtain **11** in 75% yield.[9]

Transposition of the carbonyl group in **11** was executed following Carnell's[10] reduction−oxidation stratagem. The ketone was first reduced to the alcohol under Luche[11] conditions. The resultant **12** was then re-oxidized with PCC/*p*-TsOH, giving enone **2** in 63% yield (from **11**). PCC/SiO_2[10d] or PCC/4 Å MS[10e] also afforded **2** in 60−65% yield. However, IBX/DMSO[10f] oxidation did not lead to any **2** but only **11**.

Completion of a highly efficient route to enone **2** set the stage for introduction of the lower side chain. In our first

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(5) (a) Apparu, M.; Demenge, P.; Fagret, D.; Ghezzi, C.; Majid, S.; Mathieu, J.-P.; Manuclaire, L.; Pasqualini, R.; Vidal, M. PCT Int. Appl. WO 9600717 A1, Jan. 11, 1996, 56 pp.; *Chem. Absrt.* **1996**, *124*, 288981. (b) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *5*, 399−402. (c) Thottumkara, A. P.; Bowsher, M. S.; Vinod, T. K. *Org. Lett.* **2005**, *7*, 2933−2936.

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(8) Sawada, H.; Webb, M.; Stoll, A. T.; Negishi, E. I. *Tetrahedron Lett.* **1986**, *27*, 775−778.

(9) A similar lithium−iodine exchange has been reported to be failed, see: Morita, A.; Kuwahara, S. *Org. Lett.* **2006**, *8*, 1613−1616.

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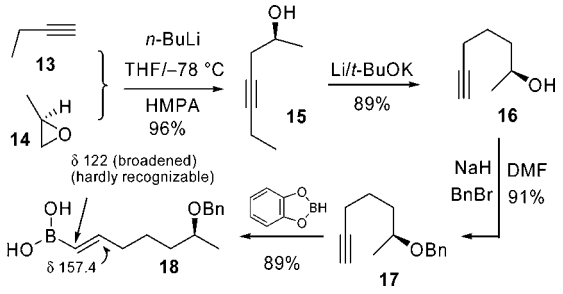
(11) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.

generation[2j] synthesis of BFA and many of previous ones, this was accomplished via a Michael addition of an in situ formed organolithium cuprate species. Although the best yield of that approach exceeded 90%, the operation was cumbersome and the outcome varied from run to run. Failure to meet the requirement for strict exclusion of oxygen/moisture and the precise stoichiometry of the reagents often led to formation of only undesired side products. Besides, waste of 2 equiv of the optically active lower side chain there was another shortcoming. During the present endeavor we found, in the literature, that similar Michael additions could also be achieved[12] using boronic acids and an appropriate Rh catalyst. Although the methodology was tested only on relatively simple compounds (to our knowledge), the impressive yields, the need for only a slight excess of the boronic acids, and its operational simplicity encouraged us to examine it on our substrate.

The requisite lower side chain **18** was synthesized by incorporating different literature steps, as shown in Scheme 2. The alcohol **15** was assembled from the commercially

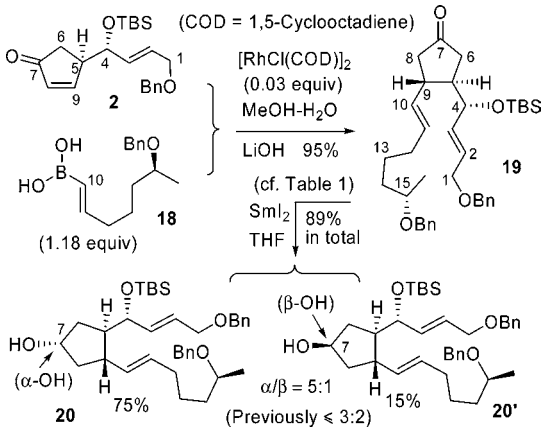
Scheme 2



available alkyne **13** and epoxide **14** as reported[13] by Nokami. However, in the subsequent zip reaction (migration of the triple bond) Lesot's[14] Li/*t*-BuOK/$H_2N(CH_2)_3NH_2$ conditions gave significantly higher yields than Nokami's[13] KH/$H_2N(CH_2)_2NH_2$ (89% vs 68%). Protection of the hydroxyl group in **16** with BnBr afforded the known[2j] **17**. Finally, treatment of **17** with catecholborane followed by alkaline hydrolysis yielded the desired boronic acid **18**.[15]

Addition of the boronic acid **18** to enone **2** was performed under the Csaky's[12b] conditions (Scheme 3). Despite the presence of additional labile functionalities in **2** compared

Scheme 3



with the simple substrates in the literature, the anticipated ketone **19** was obtained cleanly. Although the yield is only slightly higher than that in the previous lithium cuprate-mediated protocol, the present approach is much simpler and consumes less of the lower side chain.

It is noteworthy that although the rhodium catalyst is quite stable to air and moisture, it appears rather sensitive to catechol. Compound **18**, when contaminated by traces of catechol (which is difficult to completely remove by routine workup or/and chromatography), did not undergo the Michael addition at all.

Reduction of C7 in **19** was a challenge that remained from our previous[2j] work; where the best α/*β*-OH ratio achieved after screening a range of different reagents/conditions was 3:2 (by Corey−Bakshi−Shibata[16] reduction). In the hope of finding better conditions in the present endeavor, we examined three other reducing agents (Table 1), which are less common compared with those tested earlier.

Table 1. Reduction of the C7 Carbonyl Group in Ketone **19** under Different Conditions (cf. Scheme 3 for the Structures)

entry	conditions	α/*β* (total yield[a])
1	SmI_2/*i*-PrOH/0 °C/24 h	5:1[b] (89%)
2	Sm/cat. I_2/*i*-PrOH/0 °C/30 h	5:1[c] (77%)
3	*t*-BuLi/DIBAL-H/−78 °C/1 h	*β*-OH only (95%)
4	*n*-BuLi/DIBAL-H/−78 °C/1 h	1:5[c] (100%)

[a] Based on isolated products. [b] Calculated from isolated isomers. [c] Calculated from ^{1}H NMR of the crude mixture.

Interestingly, although the number of reagents examined in this work is much smaller than that in the previous[2i,j] study, the results turned out to be much better. The SmI_2/*i*-PrOH[17] (Entry 1) gave a very pleasing α/*β* ratio of 5:1, while the

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(13) Nokami, J.; Ohkura, M.; Dan-oh, Y.; Sakamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 2409−2412 (with only specific rotation reported).

(14) Parenty, A.; Campagne, J.-M.; Aroulanda, C.; Lesot, P. *Org. Lett.* **2002**, *4*, 1663−1666 (the antipode of **16**).

(15) It should be noted that the olefinic carbon directly bonded to boron in **18** appears in ^{13}C NMR as an almost unrecognizable lump (caused by ^{11}B) at around *δ* 122 as revealed by the HMQC experiment. The difficulty in detecting this signal presumably misled some investigators to report only one of the two olefinic carbones or to take the extra line (stemming from the trimer gradually formed on standing) for another olefinic carbon in similar cases, see, e.g.: (a) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031−6034. (b) Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lua, F.-J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285−4299. Cf. also the description in the Supporting Information section.

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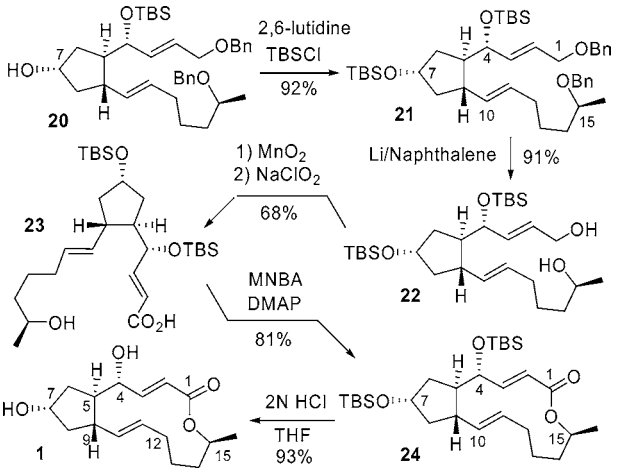
t-BuLi/DIBAL-H[18] (Entry 3) led exclusively to the β isomer. Thus, selective reduction of the C7 carbonyl group to either isomer of the alcohol becomes much more feasible now.

The subsequent steps were performed similarly to those in our previous[2i,j] work. The C7 hydroxyl group was masked as a TBS ether (using a different reagent here). The Bn groups were cleaved under the Liu[19] conditions. The newly released benzylic alcohol was selectively oxidized first with MnO_2[20] and then $NaClO_2/NaH_2PO_4$/methyl-2-butene,[21] providing the hydroxy acid **23** (Scheme 4).

Scheme 4



Yamaguchi[22] lactonization has been the method of choice for the ring-closure in all the relevant BFA syntheses since 1980. However, as in a recent[23] related transformation, Shiina's[24] MNBA (2-methyl-6-nitro-benzoic anhydride) was found to be superior. In the present work we also tried MNBA. The results were quite satisfactory. While the yield of **24** was essentially the same as the best achieved under the Yamaguchi conditions, the operation was remarkably simpler, and the yield no longer varied drastically from run to run.

Finally, the TBS protecting groups were removed with 2 N HCl to yield the end product (+)-BFA, **1**.

In summary, a concise enantioselective total synthesis of natural BFA has been completed. The potentially interesting elements encapsulated include (1) a facile access to pure cis vinyl iodo alkenol **4**,[25] (2) direct formation of an enone from a Crimmins aldol via tandem lithium−iodine exchange and intramolecular neucleophilic addition with concurrent removal of the chiral auxiliary, (3) use of a boronic acid as the lower side chain and the Michael addition mediated by a rhodium catalyst, (4) stereoselective reduction of the C7 ketone in an extremely difficult situation, and (5) a macrolactonization using MNBA, which is more convenient than the Yamaguchi protocol (the best choice up to now in all BFA syntheses involving similar lactonization).

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Supporting Information Available: Experimental procedures, physical and spectroscopic data for all new compounds, ^{1}H and ^{13}C NMR spectra of **2**, **4**, **7**, **9**, **10**, **11**, **16**, **17**, **18**, **19**, **20**, **20′**, **21**, **24**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) (a) Hillis, L. R.; Ronald, R. C. *J. Org. Chem*. **1985**, *50*, 470−473. (b) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

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(24) (a) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535−7539. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem*. **2004**, *69*, 1822−1830.

(25) Such pure cis-vinyl iodo alkenols (more difficult to obtain in pure form than the corresponding trans isomers) may find diverse uses as bifunctional building blocks in organic synthesis.