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# An aldol approach to the total synthesis of (+)-brefeldin A

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**Abstract**—A convergent selective route to (+)-brefeldin A (BFA) and 7-*epi*-BFA was developed, with the crucial C-4/C-5 stereogenic centers were established using Crimmins asymmetric aldolization.


Brefeldin A (BFA, **1a**) was first isolated[1] from *Penicillium decumbens* in 1958. The structure of BFA, however, was not fully[2] established until 1971. Early biological studies showed that BFA possesses antifugal,[3] antiviral,[4] antitumor,[5] and nematocidal[6] activities. Since the first[7] total synthesis of BFA by Corey, around 30 total/formal syntheses[8] have been recorded in the literature. Interest[9,10] in probing the mode of action as well as establishing the structure–activity relationship is also growing in recent years. Herein we wish to report a new selective route to (+)-BFA, which exploits Crimmins[11] asymmetric aldolization and Jacobsen[12] HKR (hydrolytic kinetic resolution) to establish the C-4/C-5 and C-15 stereogenic centers, respectively. Along with BFA, 7-*epi*-BFA[13] (**1b**, also a natural product with biological activity untested and has been synthesized[14] only once) was also synthesized.

The key intermediate cyclopentenone **12** was synthesized as shown in Scheme 1 from **3** (which was readily prepared in 95% yield from the corresponding acid[15]). Reaction of **3** with the known (*E*)-4-benzyloxy-2-butenal[16] (**4**) under the Crimmins[11] conditions gave aldol **5** (isolated as a single enantiomer) in 78% yield. Protection of **5** was first done in $CH_2Cl_2$ using TBSOTf (3 equiv) as reported[17] by Sulikowski. Later we found that TBSCl (2 equiv) also worked very well if using DMF instead of $CH_2Cl_2$ as the solvent. The auxiliary was then cleaved with $NaBH_4$/THF-$H_2O$[18] using Prashad's procedure, resulting in **7** in ca. 70% yield. Under the same conditions, the corresponding oxazolidinone failed to react. The yield of **7** was improved to 96% by using $LiBH_4$/ether (using MeOH instead of $H_2O$ in the original[19] recipe).

Due to the presence of the thiolane protecting group, oxidation of **7** could be realized in satisfactory yields only with $SO_3$·Py in DMSO/$CH_2Cl_2$. PCC, IBX, Dess-Martin, or Swern oxidation all led to drastically lowered yields. Further direct masking (ethylene glycol/PPTS) the carbonyl gave **9** in 60% yield. However, conversion of **8** to the corresponding dimethyl acetal ($(MeO)_3CH$/MeOH/TsOH) followed by treatment with ethylene glycol/PPTS afforded **9** in ca. 95% (two-step) yield. The first step was somewhat tricky, to prevent deprotection of the TBS while driving the acetal formation to completion, $(MeO)_3CH$ must be in large excess (used as solvent) and the MeOH (which accelerated the acetalization) content must be minimized. Hydrolysis of the thio protecting group in **9** was also troublesome. Various reagents (such as the classical NBS, NBS (or NCS)/$AgNO_2$ with or without 2,6-lutidine, or the recently reported $H_5IO_6$[20] and $PhI(OAc)_2$[21]) failed to give satisfactory results here. Finally, the problem was solved by using[22] $I_2$ in aq acetone in the presence of $NaHCO_3$ buffer. Under these conditions, ketone **10** could be obtained in 89% yield.

Subsequent formation of the five-membered ring using an intramolecular Mukaiyama[23] reaction was realized in 73% yield by conversion of **10** into corresponding silyl enol ether with LDA/TMSCl followed by treatment with $TiCl_4$ in $CH_2Cl_2$ at −78 °C. Elimination of the alkoxyl with DBU in MeOH at 0 °C proceeded rapidly and gave the key intermediate **12** in 97% yield within 1 h.

*Keywords*: cyclization; asymmetric aldolization; macrolides; lactones; natural products.
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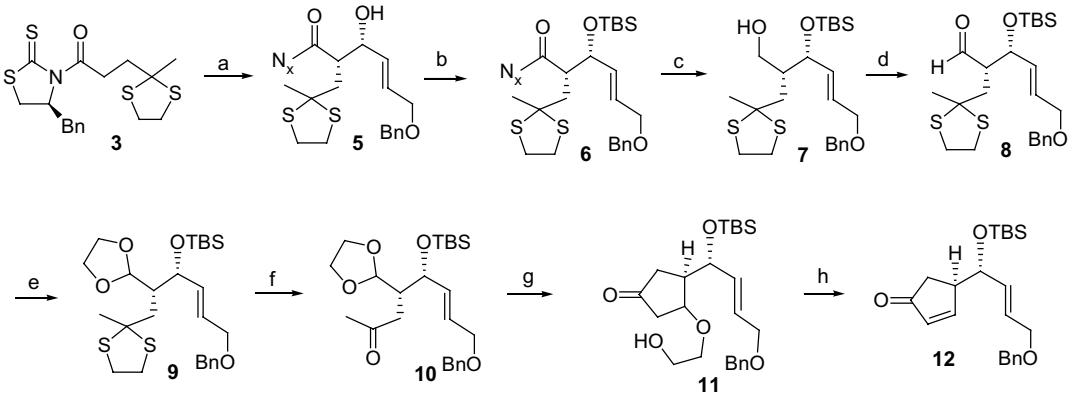


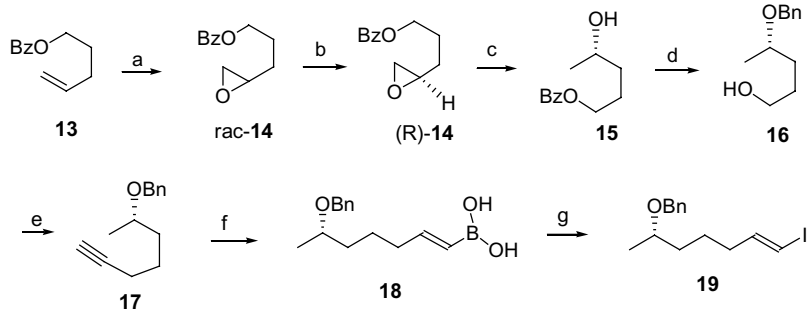
**Scheme 1.** Reagents and conditions: $N_x$ = the auxiliary; (a) $TiCl_4$/TMEDA/**4**, 78%; (b) TBSCl/2,6-lutidine, 97%; (c) $LiBH_4/Et_2O$–MeOH, 96% (d) $SO_3$·Py/$^i$Pr$_2$NEt/DMSO/$CH_2Cl_2$, 96%; (e) (i) excess $(MeO)_3CH$/traces MeOH/cat·TsOH/rt, 98%; (ii) PPTS/ethylene glycol/benzene/reflux, 97%; (f) $I_2/NaHCO_3$/acteone–$H_2O$, 89%; (g) (i) LDA/TMSCl/THF/−78 °C/1 h, then warmed to rt over 3 h, (ii) $TiCl_4/CH_2Cl_2$/−78 °C/1 h, 73% (from **10**); (h) DBU/MeOH, 97%.

The lower chain was constructed as shown in Scheme 2. The known alkene **13**[24] was converted to *rac*-**14** with *m*-CPBA (95% yield). A Jacobsen HKR using (*R,R*)-salenCo(III)OAc as the catalyst was then performed at 25 °C to afford (*R*)-**14** in 44% yield, with the ee value >99%. It is interesting to note that if using benzyl to replace the benzoyl protecting group, the ee value was lowered to 97% under the same conditions.

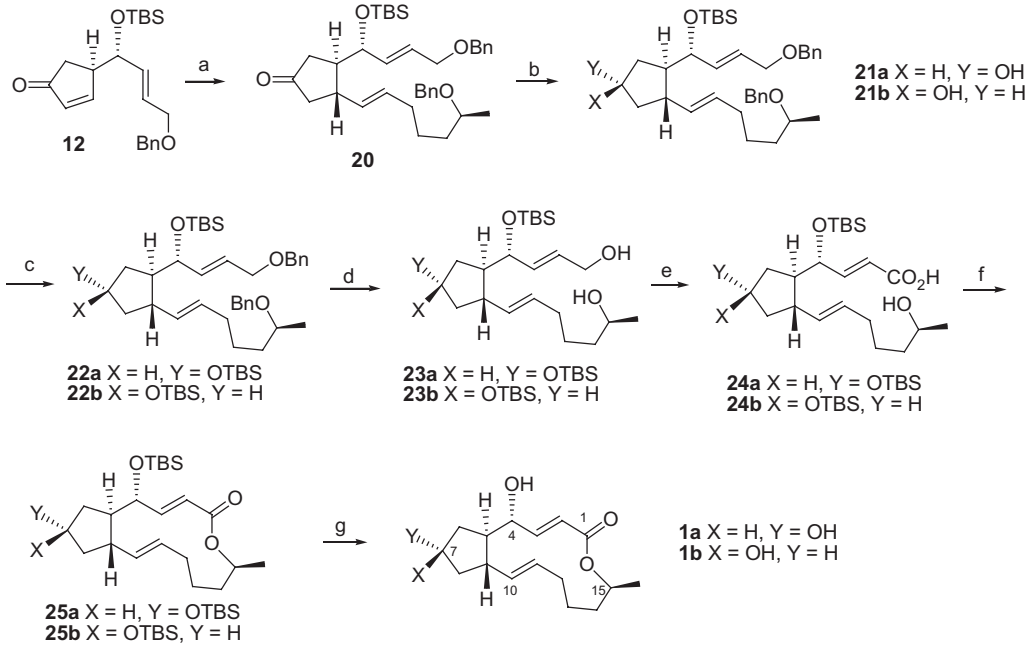
The (*R*)-**14** was then hydrogenated (90% yield) over 10% Pd–C and the resulting OH was protected using $BnOCNCCl_3$/TMSOTf[25] (other reagents/conditions always led to partial migration of the benzoyl group to the secondary OH). The benzoyl group was hydrolyzed and replaced by a tosyl. Treatment of the intermediate tosylate with LiC≡CH·EDA[26] gave **17** (86% from **16**). Finally, addition of catecholborane (72% yield) followed by substitution of the boron (95% yield) with iodine afforded **19**.

The vinyl iodide **19** was then transformed into the corresponding cuprate by sequential treatment with *n*-BuLi and CuCN/MeLi before the Michael addition to **12** to yield **20** (93%, Scheme 3). To achieve yields significantly higher than those for the comparable steps in the literature, 3 equiv of the cuprate must be utilized. Reduction of **20** with various reducing agents always afforded two epimers, with the β-OH isomer as the major product in most cases. The best selectivity for the β-OH was observed with L-Selectride (90% yield, **21b/21b** = 1:8). After screening many reducing agents/conditions, we found that (*S*)-2-methyl-CBS-oxazaborolidine/$BH_3$ gave more α-OH epimer than the β one. (96.4% yield, **21a/21b** = 3:2). The two epimers could be easily separated and the unwanted one could be re-oxidized back to **20** with Dess–Martin periodinane (92%) and recycled.

The OH at the five-membered ring was then masked with TBSOTf and the benzyl groups were removed with Li/naphthalene to furnish diols **23a** and **23b**, respectively. The allylic alcohols were oxidized into the corresponding carboxylic acids **24a** and **24b**, respectively, by sequential treatment with $MnO_2$ and $NaClO_2$ in 70–76% overall yields. Macro-ring closure of **24a** and **24b** using the Yamaguchi[27] procedure resulted in **25a** and **25b**, respectively, in 81–83% yields. Finally, the TBS groups were cleaved with 2 N HCl/THF, providing the end products[28] **1a** and **1b**, respectively.



**Scheme 2.** Reagents and conditions: (a) *m*-CPBA, 95%; (b) (*R,R*)-salenCo(III)OAc, 44%, ee>99%; (c) Pd–C/$H_2$, 90%; (d) (i) $BnOCNCCl_3$/TMSOTf, (ii) MeONa/MeOH, 94% (from **15**); (e) (i) *p*-TsCl/$NEt_3$, 73.7%; (ii) LiC≡CH·$H_2N(CH_2)_2NH_2$/DMSO, 86%; (f) Catecholborane, 72%; (g) NaOH/$I_2$, 95%.




**Scheme 3.** Reagents and conditions: (a) *n*-BuLi/**19**, CuCN/MeLi, 93% of **20**; (b) L-Selectride, 90% of **21a/21b** (1:8) or (*S*)-2-methyl-CBS-oxazaborolidine/$BH_3{\cdot}SMe_2$/THF/0 °C, 96.4% of **21a/21b** (3:2); (c) TBSOTf/$NEt_3$, 96% for **22a**, 95% for **22b**; (d) Li–naphthalene, 72% for **23a**, 70% for **23b**; (e) (i) $MnO_2/CH_2Cl_2$, (ii) $NaClO_2/NaH_2PO_4$/2-methyl-2-butene, 71% for **24a**, 76% for **24b** (2-step yields); (f) 2,4,6-trichlorobenzoyl chloride/$NEt_3$, DMAP, 81% for **25a**, 83% for **25b**; (g) 2 N HCl/THF, 91% for **1a**, 93% for **1b**.

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of five- or six-membered rings using Mukaiyama reaction in the literature.
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28. Physical and spectroscopic data for **1a**: mp 202–203 °C (lit.[29] 203–204 °C); $[\alpha]_D^{20}$ +92.7° (*c* 0.45, MeOH); (lit.[29] $[\alpha]_D^{20}$ +92.2° (*c* 0.51, MeOH)); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.45 (dd, $J = 3.0$, 15.6 Hz, 1H), 5.82 (dd, $J = 2.0$, 15.6 Hz, 1H), 5.75 (ddd, $J = 4.6$, 10.2, 15.0 Hz, 1H), 5.27 (dd, $J = 9.6$, 15.1 Hz, 1H), 4.78 (m, 1H), 4.21 (m, 1H), 4.03 (m, 1H), 2.38 (quintet, $J = 8.7$ Hz, 1H), 2.12 (ddd, $J = 5.4$, 8.7, 13.6 Hz, 1H), 2.05–1.97 (m, 2H), 1.90–1.70 (m, 5H), 1.55 (m, 1H), 1.42 (m, 1H), 1.23 (d, $J = 6.2$ Hz, 3H), 0.90 (m, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 168.7, 155.4, 138.4, 131.7, 118.1, 76.9, 73.5, 73.3, 53.5, 45.8, 44.4, 42.1, 35.3, 33.3, 28.3, 21.3; FT-IR (KBr) 3366, 1713, 1257 cm$^{-1}$; ESI-MS *m*/*z* 281 ([M+H]$^+$). Physical and spectroscopic data for **1b**: mp 126–127 °C (lit.[13] 124–125 °C); $[\alpha]_D^{23}$ +109.2° (*c* 1.15, MeOH); (lit.[13] $[\alpha]_D^{20}$ +108.6° (*c* 1.03)); $^1$H NMR(500 MHz, $CDCl_3$) $\delta$ 7.41 (dd, $J = 2.9$, 15.6 Hz, 1H, H-3), 5.91 (dd, $J = 1.6$, 15.6 Hz, 1H, H-2), 5.79 (ddd, $J = 4.6$, 10.2, 15.0 Hz, 1H, H-11), 5.16 (dd, $J = 9.6$, 15.1 Hz, 1H, H-10), 4.85 (m, 1H, H-15), 4.36 (m, 1H, H-7), 4.23 (d, $J = 1.0$ Hz, 1H, H-4), 2.72 (quintet, $J = 9.0$ Hz, 1H, H-9), 2.20 (ddd, $J = 4.7$, 10.1, 14.7 Hz, 1H, H-8α), 2.00 (m, 1H, H-12), 1.86 (m, 4H, H-6β, H-8β, H-12 and H-13), 1.74 (m, 1H, H-14), 1.66 (m, 1H, H-5), 1.58–1.50 (m, 2H, H-6α and H-14), 1.26 (d, $J = 6.2$ Hz, 3H, H-16), 0.94 (m, 1H, H-13); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.5 (C-1), 152.1 (C-3), 135.2 (C-10), 131.3 (C-11), 117.4 (C-2), 76.3 (C-4), 73.1 (C-7), 71.8 (C-15), 52.1 (C-5), 44.4 (C-9), 43.7 (C-6), 40.2 (C-8), 34.1 (C-14), 32.0 (C-12), 26.7 (C-13), 20.8 (Me at C-15). FT-IR (KBr) 3302, 1712, 1257 cm$^{-1}$; EI-MS *m*/*z* (%) 280 (M$^+$, 1), 262 (M$^+$−$H_2O$, 2), 119 (41), 55 (100). The assignments of the NMR signals were made with the aid of COSY, NOESY, DEPT, and HMQC experiments.
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