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Enantioselective Total Synthesis of (+)-Brefeldin A and 7-*epi*-Brefeldin A

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A convergent enantioselective route to brefeldin A (BFA) and 7-*epi*-BFA was developed. The key C-4/C-5 chiral centers were established by using chiral auxiliary induced intermolecular asymmetric aldolization in the presence of $TiCl_4$ and TMEDA. The results with the thiazolidinethione/$TiCl_4$ mediated intermolecular asymmetric aldolization added some new information about the scope and limitations to the existing knowledge of that type of reactions (which so far was essentially limited to the reactions with *N*-propionyl thiazolidinethiones). During the course a method for protecting the liable aldol hydroxyl groups by using inexpensive TBSCl in DMF with 2,6-lutidine as the base was developed to replace the otherwise unavoidable TBSOTf procedure. Due to the excessive steric hindrance, removal of the auxiliary was much more difficult than most literature cases. Cleavage of the oxazolidinone by reduction was almost impossible. The thiazolidinethione auxiliary was relatively easier to remove. However, several reactions reported for facile removal of thiazolidinethione auxiliaries in the literature still failed. Reductive removal of the thiazolidinethione auxiliary was most effectively realized with $LiBH_4$ in diethyl ether in the presence of 1 equiv of MeOH (a modification of a literature procedure for removal of oxazolidinone auxiliaries in less hindered substrates). Apart from the auxiliary removal, oxidation of the alcohol into aldehyde and the deprotection of the dithiolane protecting group were also rather difficult in the present context. A range of methods were screened before final solutions were found. The five-membered ring was constructed by employing an intramolecular Mukaiyama reaction after many attempts with the intramolecular aldolization under a variety of conditions failed. The rate of elimination of the alkoxyl to form the α,β-double bond of the key intermediate cyclopentenone **49** with DBU was highly solvent dependent (very sluggish in CH_2Cl_2 but rather fast in MeOH). Introduction of the lower chain (which was synthesized by using a Jacobsen KHR to establish the C-15 chirality) was achieved through a Michael addition similar to the precedents in the literature. It has not been noticed before that the yield of this Michael reaction could be dramatically raised by using 3 equiv of the copper−lithium reagent **55**. Reduction of the C-7 carbonyl was apparently more difficult than similar cases in the literature. After examination of many reagents under various conditions, it was found that the best reagent for yielding the α-isomer was (*S*)-2-methyl-CBS-borolidine/BH_3 and that for the β-isomer was L-Selectride. The α- and β-isomers were then further elaborated into (+)-brefeldin A and 7-*epi*-BFA, respectively. An unexpected yet very interesting solubility difference between BFA and 7-*epi*-BFA was also observed.

Introduction

Brefeldin A (BFA, **1a**) was first isolated from *Penicillium decumbens* in 1958[1] and subsequently from *Penicillium cyaneum*,[2a] *P. brefeldianum*,[2b] *P. simplicissiumum*,[2c] *Ascochyta imperfecta*,[2d] *Nectria radicicola*,[2e] *Curvularia launata*,[2f] *C. subulata*,[2f] *Phoma herbarum*,[2g] and *Phyllosticta medicaginis*.[2h] Although many other names (e.g., cyanein,[2a] ascotoxin,[2d] decumbin,[1] synergisidin,[2i] or nectrolide[2j]) were once given to this compound, since the 1980s brefeldin A (rather than the earliest "decumbin") gradually became the only one in use, presumably because the first complete structure with clearly defined absolute[3] configuration came with that name.

Early biological studies showed that BFA possesses antifugal,[4] antiviral,[5] antitumor,[6] and nematocidal[7] activities. Further reports appeared later, mostly in the late 1990s, including those on suppressing[8] prostatic carcinoma LNCaP cells through modulating AR expression,

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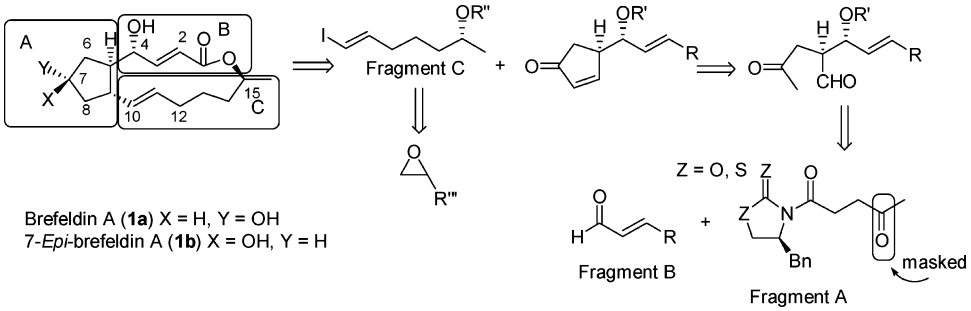

FIGURE 1. The retrosynthetic analysis of the present work.

inducing[9] enhanced GM3 expression associated with decreased invasiveness in bladder cancer cells, inhibiting[10] thrombin receptor regeneration in endothelial cells, inhibiting[11] de novo synthesis of poliovirus RNA replication in infected cells, and inducing[12] DNA fragmentation associated with apoptosis in cancer cells.

BFA has received remarkable attention in the synthetic community. Since the first[13] total synthesis of (racemic) BFA by Corey and Wollenberg, around 30 total/formal syntheses[14,15] have been reported in the literature. Interest[15d,16,17] in probing the mode of action as well as establishing the structure−activity relationship has also obviously grown in recent years. Herein we wish to detail[15g] a new route to enantiomerically pure natural BFA, which exploits Crimmins[18] asymmetric aldolization to establish the critical C-4/C-5 stereogenic centers and Jacobsen[19] HKR (hydrolytic kinetic resolution) to create the C15 chiral carbon. Apart from BFA, 7-*epi*-BFA[20] (**1b**, also a natural product with biological activity untested and synthesized only once[21] up to date) was also synthesized.

Results and Discussion

We planned (Figure 1) from the outset to derive the C-4/C-5 chiral carbons using chiral auxiliary-induced intermolecular asymmetric aldolization, a strategy that so far has never been employed in the synthesis of this compound of enduring interest. Using this strategy made it possible to introduce the C-1 to C-4 moiety in one go and created considerable flexibility in making analogues in future endeavors. The C-15 of BFA is an isolated stereogenic center. In the present work, we chose to utilize Jacobsen's KHR to generate this chiral carbon, because such an approach would not only add one more new alternative to the existing list of methodologies for synthesizing the lower chain of BFA, but also offer facile entries to analogues at the C-15 and the C-15 methyl.

It appeared to us at the beginning that the cyclopentenone (Figure 1) might be accessible from the corresponding aldehyde-methyl ketone via an intramolecular aldolization followed by elimination of the resulting hydroxyl group. An apparent risk of this approach was that the alkoxy group at the carbon β to the aldehyde group might be eliminated (or epimerized) if the deprotonation took place at the α carbon of the aldehyde carbonyl. Indeed, we were not able to find any precedents in the literature for such an annulation, although some examples[22] with a chiral aldehyde carrying an α-H were known. However, if both the alkoxyl group β to the aldehyde carbonyl and the base (such as LDA or LiHMDS) employed in the deprotonation were bulky enough, the steric hindrance for the deprotonation at the aldehyde

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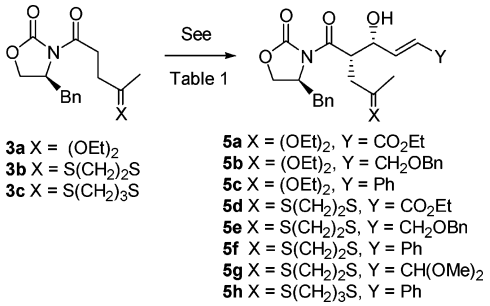
SCHEME 1



α-carbon might be sufficiently large and thus suppress the deprotonation of the α carbon of the aldehyde. This possibility, along with another apparent factor that there were three protons at the ketone methyl but only one proton at the α carbon to the aldehyde, might render the deprotonation to occur preferentially at the ketone methyl group. On the basis of these considerations, we decided to examine the feasibility of this aldehyde−ketone cyclization.

The first step was to establish the *syn* C-4/C-5 stereogenic centers. Since the early 1980s, Evans aldolization has found many successful applications in the asymmetric synthesis of natural products. Although not so explicitly at first sight, the C-4/C-5 of BFA do fit the Evans syn pattern (Figure 1). The facile[23] access to the otherwise rather expensive oxazolidinones recently developed by us also provided another reason for us to employ Evans auxiliary to induce the desired chirality (Scheme 1).

Aldehyde (*E*)-$EtO_2CCH{=}CHCHO$ (**2**)[24] was utilized as the fragment B in the first tries. However, due to the problems that arose at later stages, other aldehydes such as (*E*)-$BnOCH_2CH{=}CHCHO$[25] (**8**), (*E*)-$(MeO)_2CHCH{=}CHCHO$[26] (**9**), and (*E*)-PhCH=CHCHO (**10**) were also examined. The main results of the intermolecular aldolization step are outlined in Table 1. Most of these reactions were carried out with $TiCl_4$ (which is much cheaper and much easier to store than Bu_2OTf). In the beginning (*S*)-4-benzyloxazolidinone was used as the auxiliary. However, because the removal of this auxiliary from our substrates was extremely difficult (vide infra), the corresponding thiazolidinethione (Scheme 2) was utilized later.

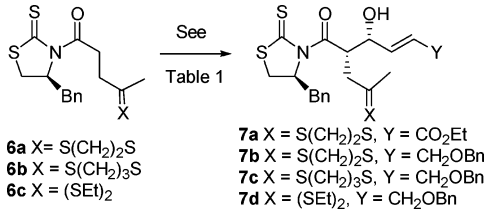
The condensation with aldehyde **2** proceeded rather fast and gave the desired aldols in good to excellent yields. The reactions with the other three aldehydes were slower. When the ketone functionality in the acyl auxiliaries was protected as a diethyl ketal (**3a**, prepared by protection of the corresponding methyl ketone **4**), only

TABLE 1. The Main Results of the $TiCl_4$-Mediated Intermolecular Asymmetric Aldolization of 3 and 6 (cf. Schemes 1 and 2)[a]

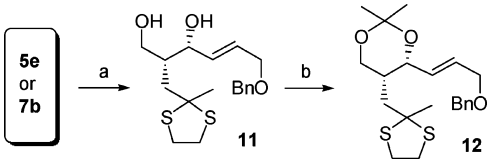
Nx-acyl	aldehyde	base	main product (yield)
3a	**2**	*i*-Pr_2NEt	none[b]
3a	**8**	*i*-Pr_2NEt	none[b]
3a	**10**	*i*-Pr_2NEt	none[b]
3b	**2**	*i*-Pr_2NEt	**5d** and **5d′** (6−7:1, 99%)
3b	**8**	*i*-Pr_2NEt	**5e** and **5e′** (1:1, ∼70%)
3b	**8**	TMEDA[d]	**5e** (84.3%)
3b[c]	**9**	NEt_3	**5g** (60.6%)
3b	**10**	*i*-Pr_2NEt	**5f** and **5f′**(1:1, ∼70%)
3b	**9**	*i*-Pr_2NEt	none[b]
3c	**10**	*i*-Pr_2NEt	**5h** (26%)
6a	**2**	*i*-Pr_2NEt	**7a** and **7a′** (2:1, 92.2%)
6a	**2**	TMEDA	**7a** (93.9%)
6a	**2**	TMPDA[e]	**7a** (75.1%)
6a	**8**	TMEDA	**7b** (78.7%)
6b	**8**	TMEDA	**7c** (65.4%)
6c	**8**	TMEDA	**7d** (75.6%)

[a] For detailed conditions, cf. those representative reactions given in the Experimental Section in the Supporting Information. The **5d′**, **5e′** **5f′**, and **7f′** were diastereoisomers of **5d**, **5e**, **5f**, and **7f**, respectively. [b] No expected aldols were formed in any significant amounts. [c] The reaction was mediated by Bu_2BOTf instead of $TiCl_4$. [d] *N*,*N*′-Tetramethylethylenediamine. [e] *N*,*N*′-Tetramethylpropylenediamine.

SCHEME 2



SCHEME 3[a]



[a] Reagents and conditions: (a) $NaBH_4$/THF−H_2O, 67.8% from **7b**; (b) $(MeO)_2CMe_2$/TsOH, 76%.

Bu_2BOTf promoted the intermolecular aldolization. Using $TiCl_4$ as the Lewis acid led to essentially no desired aldols at all, regardless of what base was utilized.

The stereoselectivity was strongly dependent on the base employed. A monoamine such as *i*-Pr_2NEt often led to formation of two major products. A diamine, such as TMEDA or TEPDA (*N*,*N*′-tetramethylpropylenediamine, which has not been tested in the Crimmins aldolization to date) gave much better results than those observed with the original Crimmins' substrates (the acyl thiazolidinethiones carrying only a small, nonhindered methyl group at the carbon α to the acyl carbonyl). In most cases, only one major product was formed.

To find some early evidence for the syn stereochemistry, we converted **7b** into acetonide **12** (Scheme 3). The conformations for the syn and anti isomers are shown in Figure 2. For the syn isomer, the two protons marked with an arrow in the figure are cis to each other. The *J* value therefore should be significantly smaller than that

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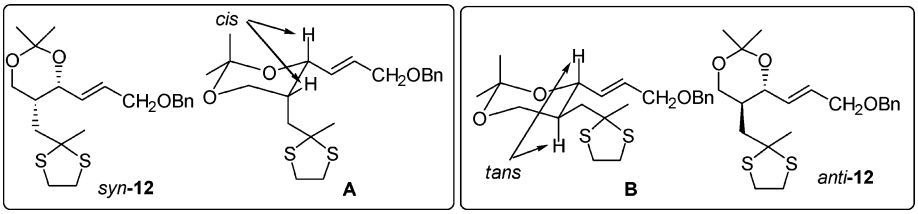
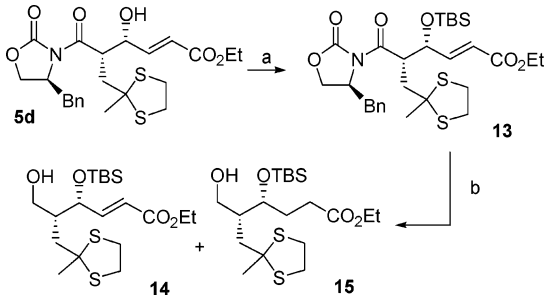


FIGURE 2. The syn and anti aldols have a large difference in the dihedral angle between the two protons marked with an arrow and therefore should be readily differentiated according to the *J* value. The absolute configurations were presumed as depicted here according to the well-established trends in Evans/Crimmins aldolization before they were confirmed in the end product **1a**/**1b**.

SCHEME 4[a]



[a] Reagents and conditions: (a) TBSCl/imidazole, 84%; (b) $NaBH_4/CaCl_2$/THF−EtOH, ca. 27%.

for the anti isomer (which is usually remarkably larger than 10 Hz). Judging from the line width at the half-peak height (<8 Hz) of the observed signal of the allylic methine group (unresolved multiplet), which was impossible to contain a coupling constant ≥10 Hz, we concluded that the aldol obtained must be a syn one.

Reductive removal of the oxazolidinone auxiliary in **13** was very difficult (presumably due to the excess steric hindrance). Many nice protocols in the literature are not applicable. The procedure of Prashad[27] ($NaBH_4$/THF−H_2O), for instance, led to no reaction at all. $CaCl_2/NaBH_4$ in THF−EtOH[28] afforded a nearly 1:1 mixture of **14** and **15** in ca. 27% total yield (Scheme 4). Replacing the ester group with a nonreducible substituent (benzoylmethyl or dimethoxymethyl), which allowed for using more powerful reducing agents such as $LiBH_4$, did not make the removal of the auxiliary any easier.

We next examined a different sequence (Scheme 5) targeting dicarbonyl species **20**. The aldol **5e** (prepared from **3b** and **8** in ca. 84% yield) was converted to its TBS ether **16** before the free ketone group was released with use of NBS in acetone−H_2O. Further treatment of the ketone **17** with $LiBH_4$ gave diol **19** in 93% yield. Under the same conditions, the auxiliary in **18** (prepared from **17** with cat. NBS/$CH(OMe)_3$/MeOH[29]) could not be cleaved at all, indicating that the hydroxyl group formed in situ from the methyl ketone played a critical role in the reductive removal of the auxiliary in **17**.

Oxidation of the diol **19** into the anticipated aldehyde−ketone **20** was unexpectedly difficult. PCC, NaClO, IBX, and Swern oxidation, for instance, all gave a rather complicated product mixture. Using Dess−Martin periodinane as the oxidant led[30] to **21**. Similarly, treatment of diol **19** with $NaBrO_3$[31] did not give[32] **20** but **22**. All these results[33] convinced us that the tough oxazolidinone auxiliary must be replaced by the corresponding thiazolidinethione auxiliary, which according to Crimmins[18] was significantly easier to remove.

Protection of the hydroxyl group in **7a** (derived[34] from (*S*)-4-benzylthiazolidinethione **26** and the 1,2-ethanedithiol-protected levulinic acid **27**[35] via **6a**) required 3 equiv of TBSOTf to achieve the quantitative conversion (Scheme 6).[36a] Treatment with $NaBH_4$ (with or without $CaCl_2$) in EtOH at the ambient temperature led to clean removal of the auxiliary. However, instead of the expected alcohol **14**, the intramolecular Michael addition product **29**[36b] was obtained exclusively, presumably due to the favor-

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(32) Because these compounds were useless to this work, no efforts were made to determine configurations of the newly formed stereogenic centers/the distereomeric ratios. It was possible that both **21** and **22** were mixtures of diatereomers.

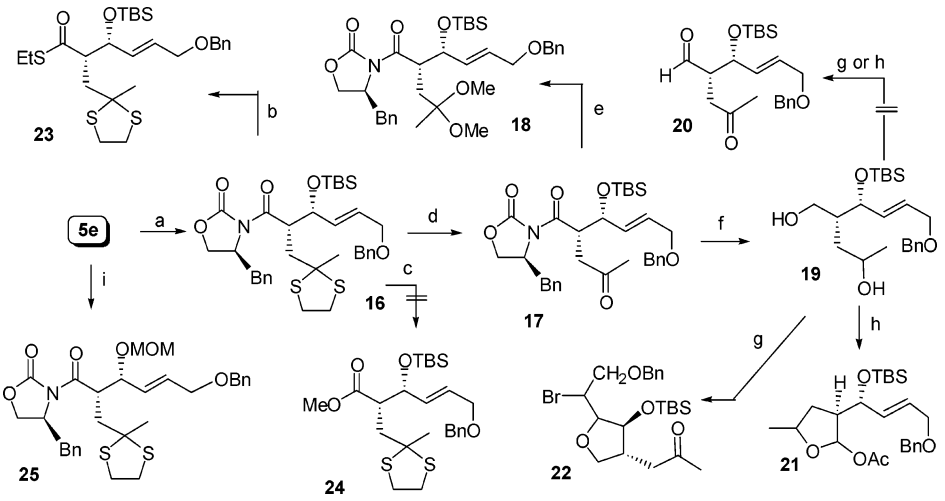
(33) While exploring the oxidation of diol **19**, we also attempted to remove the auxiliary with EtSLi because the thioester **23** should be able to be readily converted into the corresponding aldehyde. Unfortunately, the process did not work so well on our substrate either, giving **23** in only 32% yield. Attempts to use MeOMgBr to cut off the auxiliary also failed (cf. Scheme 5). The aldol **5e** could be smoothly converted to the MOM ether **25** in high yield, but neither direct reductive cleavage of the auxiliary nor hydrolysis of the dithiolane protecting group could give any useful results. The cleavage of the auxiliary with EtLi or MeOMgBr followed the procedures reported by Evans: (a) Evans, D. A.; Ng, H. P.; Rieger, D. *J. Am. Chem. Soc.* **1993**, *115*, 11446. (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151.

(34) The **26** and **27** were combined to give **6a** under the conditions reported for acylation of oxazolidinones developed by Ho and Mathre (Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271).

(35) Ahmad, S.; Ozaki, S.; Nagase, T.; Iigo, M.; Tokuzen, R.; Hoshi, A. *Chem. Pharm. Bull.* **1987**, *35*, 4137.

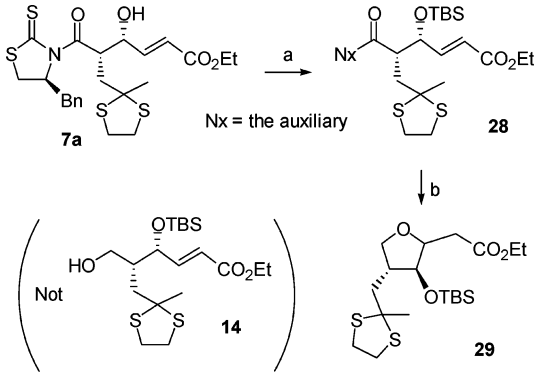
(36) (a) Due to the steric hindrance and interference of the labile elimination to form α,β-unsaturated species, protection of the hydroxyl groups in the Evans aldols (carrying an oxazolidinone auxiliary) with a bulky TBS group usually requires the most active (also rather expensive) TBS etherification reagent TBSOTf (which still cannot always guarantee success). Because the thiazolidinethione auxiliaries were introduced only for a few years, pertinent literature examples were relatively few. In fact, the only example that we found for protection of a Crimmins aldol as a TBS ether was that done by Sulikowski (Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu, B. *Org. Lett.* **2000**, *2*, 1439; we thank Prof. Sulikowski and Dr. Wu for providing the detailed procedure), which required 3 equiv of TBSOTf to drive the reaction to completion in our case. (b) Because **30** (a mixture of the diastereomers) was useless to this work, no efforts were made to determine configuration of the newly formed stereogenic center and the distereomeric ratio. It is noteworthy that lowering the reaction temperature to 0 °C could suppress the unwanted Michael addition, but the auxiliary removal was also greatly slowed. Prolonged reaction time at low temperature did not improve the reductive cleavage, but led to formation of more Michael addition product.

SCHEME 5[a]



[a] Reagents and conditions: (a) TBSOTf/2,6-lutidine/CH_2Cl_2, 98.9%; (b) EtSH/BuLi/THF, 32%; (c) MeOMgBr; (d) NBS/acetone−H_2O, 92.4%; (e) cat. NBS/$CH(OMe)_3$/MeOH, 52.3%; (f) $LiBH_4/Et_2O-H_2O$, 92.6%; (g) $NaBrO_3/NaHCO_3$; (h) Dess−Martin peroiodinane, 63.5%; (i) $CH_2(OMe)_2/i\text{-}Pr_2NEt$, 92.3%.

SCHEME 6[a]



[a] Reagents and conditions: (a) TBSOTf/2,6-lutidine/CH_2Cl_2, 100%; (b) $NaBH_4$ (with or without $CaCl_2$)/EtOH/0 °C to rt.

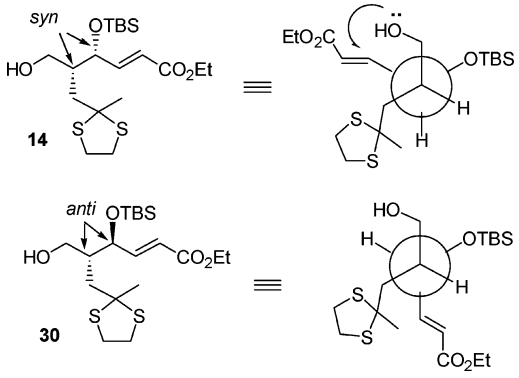
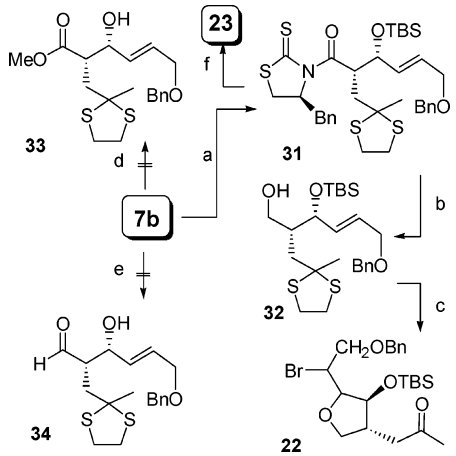


FIGURE 3. The Newman projections of the most stable conformers of **14** and the corresponding anti isomer **30**. Note that the OH in the most stable conformer of **30** is away from the double bond.

able spatial relationship between the newly generated OH and the C−C double bond in the syn aldol (Figure 3).

To avoid the undesired Michael addition, the aldehyde **8** was again employed in place of **2** to perform the

SCHEME 7[a]



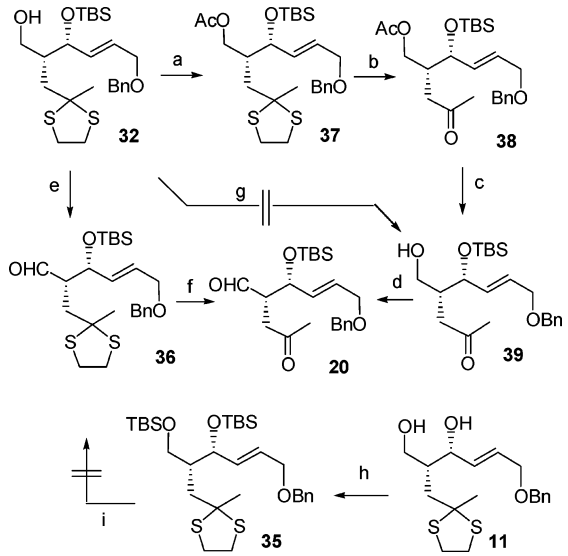
[a] Reagents and conditions: (a) TBSOTf (3 equiv)/2,6-lutidine/CH_2Cl_2, 97.6% or TBSCl (2 equiv)/2,6-lutidine/DMF, 96.7%; (b) $LiBH_4/Et_2O$−MeOH, 95.9%; (c) NBS/acetone−H_2O; (d) MeOH/imidazole; (e) DIBAL-H; (f) EtSLi/THF, 50%.

Crimmins aldolization. The aldol **7b** was then transferred (Scheme 7) into the corresponding TBS ether either as reported by Sulikowski[36a] or by using 2 equiv of TBSCl (which is much cheaper than TBSOTf) in DMF (developed in this work) instead of CH_2Cl_2 in excellent yields. The auxiliary was then cleaved with $NaBH_4$/THF−H_2O following Prashad's[27] procedure, resulting in **32** in ca. 70% yield. It should be noted that under the same conditions, the corresponding oxazolidinone failed to react completely. The yield of **32** was improved to 96% by using $LiBH_4$/ether (in the presence of MeOH instead of H_2O in the original[37] recipe). The following deprotection of the dithiolane **32** with NBS, however, led to the unwanted bromide **22** again.[38]

Finally, the anticipated aldehyde−ketone **20** was obtained via the routes shown in Scheme 8. Although direct

(37) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307.

SCHEME 8[a]



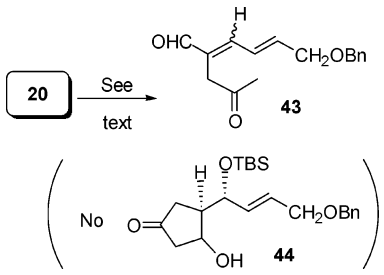
[a] Reagents and conditions: (a) Ac_2O/DMAP/NEt_3, 99.2%; (b) NBS/acetone/H_2O, 82%; (c) NaOMe/MeOH; (d) PCC, 46% (from **37**); (e) NaClO/Bu_4NBr or PCC, 57.9%, or SO_3·Py, 95.8%; (f) H_5IO_6, 81.1%; (g) NCS/$AgNO_3$/2,6-lutidine or $PhI(OAc)_2$; (h) TBSOTf/NEt_3, 63.3%; (i) QFC.

deprotection of the dithiolane in alcohol **32** was not successful, the reaction occurred nicely under the same conditions if the hydroxyl group was masked as an acetate. The hydroxyl group was then regenerated by treatment with MeONa in MeOH and the resulting alcohol was oxidized into aldehyde with PCC in 46% overall yield from **38**.

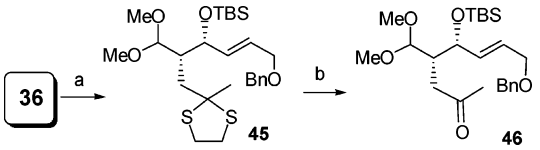
Alternatively, **32** could be first oxidized to aldehyde **36** with SO_3·Py[39] before deprotection of the dithiolane. For comparison, we also prepared the propane-1,3-dithol and bis-ethanethiol protected counterparts of **36** (i.e., **42a** and **42b**) via **40a**/**40b** and **41a**/**41b**.[40] However, neither **42a** nor **42b** was utilized in further transformations because they were inferior to **36** in terms of overall yields and cost.

In contrast to the smooth hydrolysis of **37**, conversion of **36** to **20** could not be realized with NBS. However, the problem was later overcome by using the H_5IO_6 method reported[41] by Rokach.

SCHEME 9



SCHEME 10[a]



[a] Reagents and conditions: (a) $CH(MeO)_3$/MeOH/TsOH, 97.8%; (b) see the text.

The cyclization of **20** was then examined under a variety of conditions[42] (e.g., aq NaOH, DBU, LiHMDA, $TiCl_4$/TMEDA, BF_3·OEt_2, $TiCl_4$/*i*-Pr_2NEt, LDA). Unfortunately, we only obtained the β-elimination product **43** or a complicated product mixture (Scheme 9). These results suggest that either the deprotonation at the α carbon of the aldehyde carbonyl occurred much easier than we thought or the initially formed ketone enolate underwent an efficient intramolecular attack at the α proton of the aldehyde carbonyl group and thus greatly facilitated the elimination of the TBSO group at the β carbon. Due to the limited time available to us to complete the whole synthesis, further explorations along this line were suspended and an intramolecular Mukaiyama approach, which did not involve any free aldehyde and thus avoided the elimination in the first place, was attempted.[43]

The aldehyde **36** was therefore transformed into its dimethyl acetal as shown in Scheme 10. This seemingly very simple reaction was in fact somewhat tricky. If using a few molar equivalents of $CH(OMe)_3$ as the reagent and running the reaction in MeOH with TsOH as the catalyst, the acetal **45** could be obtained only in less than 70% yield. Other acid catalysts (e.g., Amberlyst-15,[45] $CeCl_3$·H_2O,[46] or $LaCl_3$·H_2O[47]) did not lead to any significant improvement. However, when running the reaction in $CH(OMe)_3$ containing only traces of MeOH (which greatly

(38) (a) We attempted to convert the acyl-thiazolidinethione **7b** into the corresponding methyl ester or aldehyde as reported (ref 18b) by Crimmins. Testing the two conversions (using MeOH/imidazole or DIBAL-H to cleave the thiazolidinethione auxiliary) on **7b** resulted in neither **33** (at low temperatures no reactions occurred, while at higher temperatures a complicated product mixture was obtained) nor **34** (extremely slow, with prolonged reaction/more forcing conditions leading to substantial amounts of diol **11**), suggesting that the facile cleavage of the thiazolidinethione observed by Crimmins might be applicable only to those nonhindered acyl-thiazolidinethiones. (b) We tried (Scheme 8) to convert diol **11** into di-TBS ether **35** and further oxidize the primary TBS using QFC (quinolinium fluoro-chromate, cf.: Murugensan, V.; Pandurangan, A. *Ind. J. Chem.* **1992**, *31* (B), 377) preferentially in the presence of a secondary one. Unfortunately again, we failed to obtain any **36**.

(39) Sisler, H. H.; Audrieth, L. F. *Inorg. Synth.* **1946**, *2*, 173. It is noteworthy that using NaClO under phase transfer conditions (cf.: Mirafzal, G. A.; Lozeva, A. M. *Tetrahedron Lett.* **1998**, *39*, 7263), PCC, Dess−Martin periodinane, or IBX gave substantially lower yields while Swern oxidation resulted in epimermization.

(40) **42a** and **42b** (propane-1,3-dithol and bis-ethanethiol protected counterparts of **36**) were synthesized from TBS ethers **40a**/**40b** (derived from aldols **7c**/**7d**) via alcohols **41a**/**41b**. For structures and reaction details, see the Experimental Section in the Supporting Information.

(41) Shi, X.-X.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 4331.

(42) Use of proline ((a) Hojos, Z. C.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395.) in our case led to no reaction at all, although it was quite effective on other substrates.

(43) We only managed to find applications of this reaction to construction of seven-membered (see e.g.: (a) Kataoka, Y.; Nakamura, Y.; Morihira, K.; Arai, H.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1992**, *33*, 6979. (b) Soung, M.-G.; Matsui, M.; Kitahara, T. *Tetrahedron* **2000**, *56*, 7741) or larger (ref 44 below) rings in the literature.

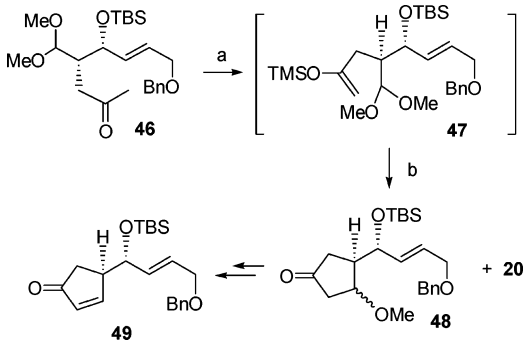
(44) Cockerill, G. S.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093 and 2101.

(45) Lorett, N. B.; Howard, W. L.; Brown, J. H. *J. Org. Chem.* **1959**, *24*, 1731.

(46) Smith, A. B., III; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 2071.

(47) Gemal, A. L.; Luche, J. L. *J. Org. Chem.* **1979**, *44*, 4187.

SCHEME 11[a]



[a] Reagents and conditions: (a) LDA/TMSCl/−78 °C; (b) $TiCl_4$/CH_2Cl_2/−78 °C.

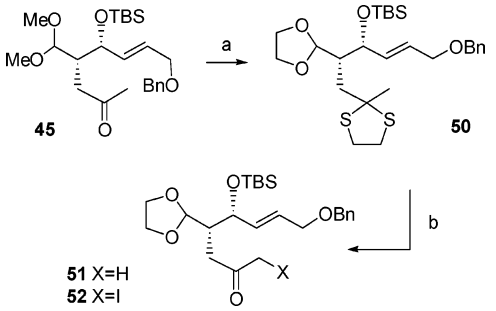
accelerated the reaction) conversion of **36** to **45** was realized in nearly quantitative yield in ca. 1 h.

Hydrolysis of the thioketal was again rather difficult. We tried a number of reagents/conditions (e.g., H_5IO_6[41] in THF/ether, $Hg(ClO_4)_2$[48] in THF−H_2O, $HgCl_2$[49] in acetone−H_2O, NBS/$AgNO_3$[49] in MeCN−H_2O in the presence of Na_2CO_3 or 2,6-lutidine NEt_3, $PhI(OAc)_2$)[50] but always got a mixture of **20** and **46** (ca. 75% yield). Separation of the two compounds was also very difficult. To push the synthesis forward as quick as we could, we did not spent more time on the optimization of the reaction conditions, but instead concentrated on the key cyclization.

Deprotonation of **46** with LDA at −78 °C (Scheme 11) followed by treatment with TMSCl produced the silyl enol ether **47**, which was directly treated with $TiCl_4$ to yield a mixture of cyclopentanone **48** and the aldehyde−ketone **20** as shown by ^1H NMR. These two compounds were again of similar polarity and thus inseparable on silica gel. Reduction of the mixture with $NaBH_4$ in MeOH offered a chance to separate the two. The pure cyclopentanol was reoxidized to **48** with IBX[51] and the latter was readily transformed into the key intermediate cyclopentenone **49** (a rather stable compound, which for instance did not lead to any decomposition/self-condensed products after heating in 1,4-dioxane at 100 °C for 12 h) on elimination of the methoxyl group by treatment with DBU. It is interesting to note that no epimerization at the C-4 occurred, perhaps the steric crowding caused by the OTBS at the adjecent carbon made further deprotonation at the C-4 difficult.

To eliminate the difficulties asociated with the dimethyl acetal, we next tested using ethylene glycol acetal. Direct preparation of **50** from **36** (ethylene glycol/TsOH/bezene with azeotropic removal of the water) was not so encouraging. The product **50** was inseparable from the starting aldehyde **36** and the yield was around 60%. Ketal exchange (Scheme 12) however, worked much better (with the overall yield >90%). Although superficially one more step was involved, the operations were in fact more convenient.

SCHEME 12[a]

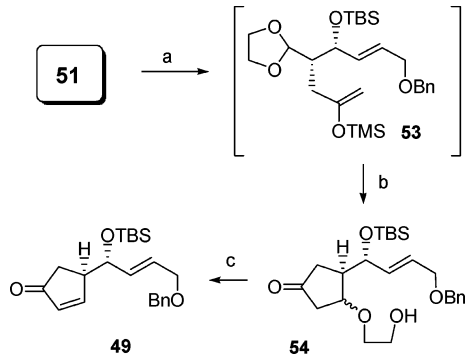


[a] Reagents and conditions: (a) PPTS/ethylene glycol/benzene/reflux, 97.1%; (b) I_2/$NaHCO_3$/acetone−H_2O, 89%, see also Table 2.

TABLE 2. Some Results of Deprotection of Dithiolane 50

reagent	solvent	base	product (yield)
NBS	acetone−H_2O	none	**51** (30%)
NBS/$AgNO_3$	CH_3CN−H_2O	2,6-lutidine	**51** (59%)
NCS/$AgNO_3$	CH_3CN−H_2O	2,6-lutidine	**51** (65%)
H_5IO_6	THF	none	**51** (75%) and **52** (traces)
$PhI(OAc)_2$	CH_3CN−H_2O	none	**51** (79%)
I_2	acetone−H_2O	$NaHCO_3$	**51** (89%)

SCHEME 13[a]



[a] Reagents and conditions: (a) LDA/TMSCl/−78 °C; (b) $TiCl_4$/CH_2Cl_2/−78 °C, 72.6% from **51**; (c) DBU/MeOH, 97%.

The next task was to convert the dithiolane into a free ketone functionality. As in the previous cases, deprotection of the thio ketal in **50** was not straightforward. The initial attempt with NBS in acetone−water resulted in **51** in only 30% yield. Several other reagents were also examined. Some of the results are listed in Table 2. Finally, a clean transformation was realized by using I_2/$NaHCO_3$[52] in acetone−water. Under this set of conditions, the desired ketone **51** was produced in 89% yield.

Once a feasible access to **51** was secured, our attention was turned to the Mukaiyama reaction again. Using the same procedure used for cyclization of **46**, we obtained the cyclopentanone **54** in 72.6% yield (2 steps). With an

(48) (a) Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1978**, *26*, 3743. (b) Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15.

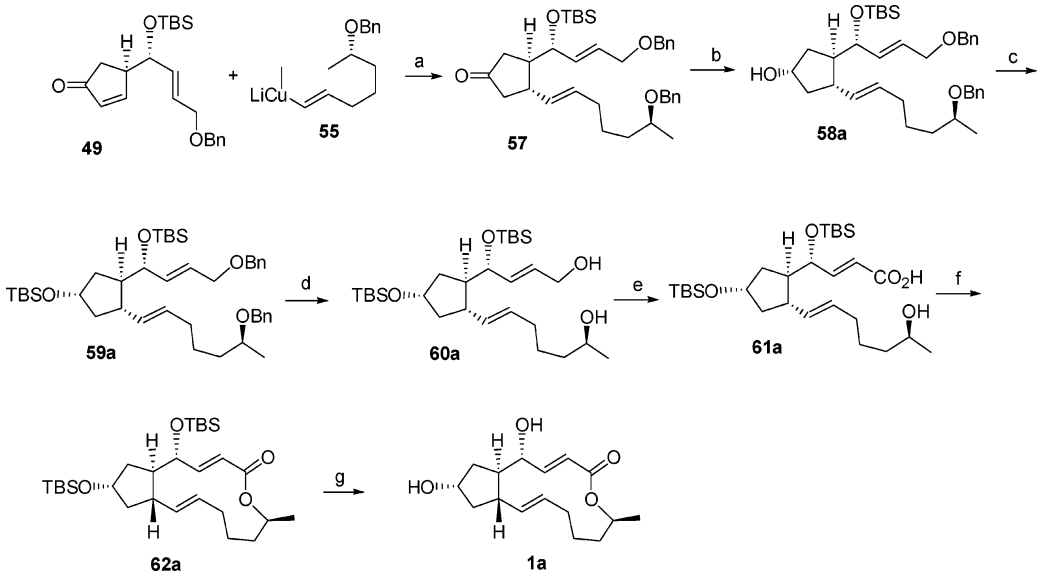
(49) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(50) Shi, X.-X.; Wu, Q. Q. *Synth. Commun.* **2000**, *30*, 4081.

(51) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (b) De Munari, S.; Frigreio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272. (c) Frigreio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

(52) (a) Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 599. (b) Russell, G. A.; Ochrymowy, L. A. *J. Org. Chem.* **1969**, *34*, 3618.

SCHEME 14[a]



[a] Reagents and conditions: (a) THF/−78 °C, 92.6%; (b) (*S*)-2-methyl-CBS-oxazaborolidine/BH_3·SMe_2/THF/0 °C, 96.4% of **58a**/**58b** (3:2); (c) TBSOTf/NEt_3, 96%; (d) Li-naphthalene, 72%; (e) (i) MnO_2/CH_2Cl_2, (ii) $NaClO_2$/NaH_2PO_4/2-methyl-2-butene, 71% from **60a**; (f) 2,4,6-trichlorobenzoyl chloride/NEt_3, DMAP, 81%; (g) 2 N HCl/THF, 91%.

additional hydroxyl group in the molecule, **54** could be readily separated from the side product **20**. The separation problem encountered with **48** was indeed eliminated. Further treatment of **54** (a very unstable compound that must be used immediately) with DBU in MeOH or CH_2Cl_2−MeOH led to **49** in 97% yield. It is interesting to note that if using CH_2Cl_2, a common solvent for DBU-mediated elimination reactions, as solvent for the elimination without adding any MeOH to the reaction system, the formation of **49** was very sluggish. Addition of small amounts of MeOH or use MeOH alone as the solvent accelerated the elimination dramatically. The reason for this phenomenon is not clear yet, but it does not seem to be related to the solubility because neither **48** nor **54** has difficulty in dissolving in CH_2Cl_2.

Introduction (Scheme 14) of the lower side chain was realized through a Michael addition of **55**, a reagent[53] similar to that employed by Olivo[54] but with an Bn instead of a TBS as the protecting group at the chiral hydroxyl group at C-15. It was noted that if using only slightly more than 1 equiv of **55**, the starting **49** could never be fully consumed (despite prolonged time or higher temperature), although the yield was comparable as those reported[55] for similar reactions in the literature. Addition of HMPA did not help. When the **55** was present in 3 equiv, however, the yield was raised dramatically.

The stereogenic center at C-7 was established by reduction of the corresponding ketone. There have been several syntheses[56] of BFA relying on this type of strategy to yield an α-OH. However, most of them did not use a fully (i.e., both upper and the lower side chains were complete) developed substrate. The best results were always obtained with those simpler precursors with only either the upper or the lower chain. A hydroxyl group present in the substrate at the C-4 position appeared to greatly enhance the stereoselectivity. Masked[54] OH did not seem to have the same efficiency in guiding the hydride to attack the carbonyl. The protecting group in our case (TBS) was even bulkier than that of Olivo's (MEM), and the reduction was therefore even more difficult. We tested a range of reducing agents, including $NaBH_4$, $LiBH_4$, DIBAL-H, L-Selectride, K-Selectride, Red-Al, (*i*-PrO)$_3$Al/*i*-PrOH (either using commercially available (*i*-PrO)$_3$Al or preparing[57] it in situ from $AlMe_3$), (*R*)-2-methyl-CBS-oxazaborolidine/BH_3,[58] or (*S*)-2-methyl-CBS-borolidine/BH_3, under a variety of reaction conditions (temperature, solvent, addition order, etc.) but always got a mixture of the two epimers. In most cases, the β isomer yield was higher than the α yield (even with $NaBH_4$ we could not obtain equal amounts of the two isomers). It appeared that due to the excess steric

(53) The stereogenic center at C-15 in this work was derived from a chiral epoxide of >99% ee (by chiral HPLC analysis) obtained by using Jacobsen HKR. For detailed information, see the Experimental Section, Part Two in the Supporting Information.

(54) (a) Casy, G.; Gorins, G.; McCague, R.; Olivo, H. F.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1085. (b) Carnell, A. J.; Casy, G.; Gorins, G.; Kompany-Saeid, A.; McCague, R.; Olivo, H. F.; Roberts, S. M.; Willets, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3431.

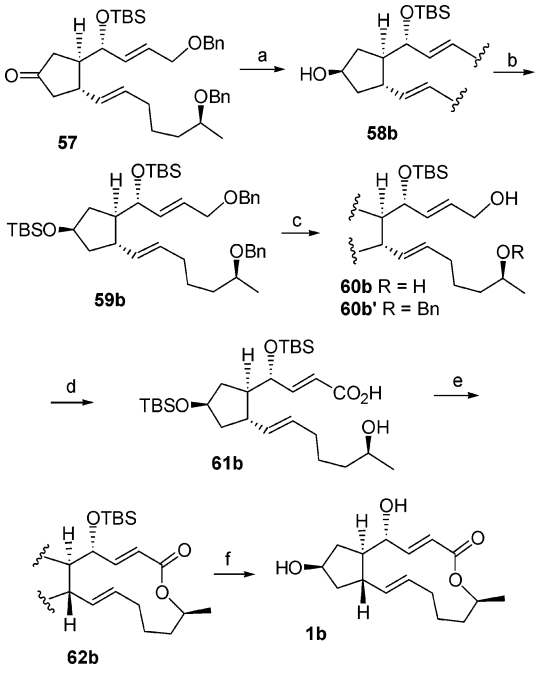
(55) The yield for introduction of the BFA lower chain via a Michael addition was usually in the range of 70−80%. See: (a) Reference 13 above (80%). (b) Baudouy, R.; Crabbé, P.; Greene, A. E.; Le Drian, C.; Orr, A. F. *Tetrahedron Lett.* **1977**, *34*, 2973 (82%). (c) Köksal, Y.; Raddatz, P.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 472 (76%). (d) Greene, A. E.; Le Drian, C.; Crabbé, P. *J. Am. Chem. Soc.* **1980**, *102*, 7584 (72%). (e) Le Drian, C.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473 (72%). (f) Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 7555 (72%). (g) Nokami, J.; Ohkura, M.; Dan-Oh, Y.; Sakamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 2409 (65%). (h) Casy, G.; Gorins, G.; McCague, R.; Olivo, H. F.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1085 (87%). (i) Bernades, V.; Kann, N.; Riera, A.; Moyano, A.; Pericas, M. A.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 6670 (89% or 76%).

(56) See e.g.: (a) Reference 51. (b) Reference 15a. (c) Solladié, G.; Lohse, O. *J. Org. Chem.* **1993**, *58*, 4555. (d) Nokami, J.; Ohkura, M.; Dan-Oh, Y.; Sakamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 2409. (e) Reference 55f. (f) Troast, B. M.; Lynch, J.; Renault, P.; Steinman, H. *J. Am. Chem. Soc.* **1986**, *108*, 284.

(57) Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 2391.

(58) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) For a review, see: Singh, V. K. *Synthesis* **1992**, 605.

SCHEME 15[a]



[a] Reagents and conditions: (a) L-Selectride/THF/0 °C, 90% of **58a**/**58b** (1:8); (b) TBSOTf/NEt_3, 95%; (c) Li-naphthalene, 70% for **60b**; (d) (i) MnO_2/CH_2Cl_2, (ii) $NaClO_2/NaH_2PO_4$/2-methyl-2-butene, 76% from **60b**; (e) 2,4,6-trichlorobenzoyl chloride/NEt_3, DMAP, 83%; (f) 2 N HCl/THF, 93%.

hindrance associated with the TBS group, the hydride preferred to attack from the α face of the cyclopentanone plan giving the *β*-isomer. However, the *β* face was also hindered by the long lower chain. The best conditions for the α isomer seemed to be BH_3/(*S*)-2-methyl-CBS-oxazaborolidine, which gave **58a**/**58b** in a 3:2 ratio in 96.4% total yield.

The two isomers were readily separated on silica gel and the *β*-isomer **58b** could be reoxidized back to ketone **57** with Dess−Martin periodinane in 92% yield. The **58a** was then protected as a TBS ether with TBSOTf in the presence of NEt_3. The two benzyl protecting groups were cleaved with Li-naphthalene[59] in 70% yield. Na metal in liquid NH_3 was less satisfactory. While the starting **59a** was not consumed, some side product without the TBS group was already formed.

The allylic hydroxyl group was then selectively oxidized with activated MnO_2[60] to yield an intermediate aldehyde, which was immediately oxidized with $NaClO_2$[61] to the known[15c] acid **61a**. The 13-membered ring was closed by using 2,4,6-trichlorobenzoic chloride[62] in the presence of NEt_3 and DMAP to give the known[16a] di-TBS ether **62a**. Finally, the TBS protecting groups were cleaved with 2 N HCl/THF, providing (+)-brefeldin A **1a** in 91% yield.

Compound **1b** (7-*epi*-BFA) is also a natural product with untested biological activity and it has been synthesized only once to date. Having noticed this, we decided to take the advantage of the unexpected (yet pretty good for the synthesis of **1b**) result of reduction of **57** with L-Selectride, which afforded **58a**/**58b** in 1:8 ratio (90% yield). Thus, the *β*-isomer **58b** was further transformed into **1b** under conditions similar to those employed for the synthesis of **1a** (Scheme 15). It is interesting to note that although the only difference between the natural BFA **1a** and 7-*epi*-BFA **1b** lies in the orientation of the C-7 hydroxyl group, their solubility in $CDCl_3$ differs remarkably. **1b** could be dissolved in $CDCl_3$ to give a concentrated enough solution for taking both the ^1H as well as the ^{13}C NMR spectra, whereas **1a** is only fairly soluble after heating. However, the solubility of **1a** in CD_3OD was large enough to allow for recording satisfactory NMR spectra.

In brief, we have developed an aldol approach to the total synthesis of BFA using Crimmins aldolization and Jacobsen HKR as the key reactions. (+)-BFA and 7-*epi*-BFA were obtained in 16 steps from acyl thiazolidinethione **6a** in 9.4% and 12% overall yields, respectively. The route was adaptable for preparing other analogues, because the three fragments utilized in the synthesis might vary independently without affecting the overall assembly strategy. The Crimmins aldolization and the oxidations of thio-containing intermediates as well as the hydrolysis of the thio-protecting groups were examined extensively in the present context and considerable knowledge about these reactions has been gained. A practical protocol for masking the *β*-hydroxyl group in the acyl thiazolidinethione type aldols with use of TBSCl was developed. Traces of MeOH were found to be very effective in facilitating the acetalization of aldehyde **36** and the DBU-initiated elimination of alkoxy groups leading to the key cyclopetenone **49**. A previous unknown effect of the quantity of the fragment C on the Michael addition was recorded, which rasied the yield to an unprecedented 92.6%. Finally an interesting solubility differentce between the natural brefeldin A and its 7-epimer was observed.

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Supporting Information Available: Experimental details; ^1H NMR spectra of **6c**, **7a**, **7b**, **7c**, **7d**, **28**, **5g**, **23**, **11**, **12**, **35**, **32**, **41a**, **41b**, **20**, **42a**, **42b**, **51**, **46**, **54**, **57**, **58a**, **58b**, **59a**, **59b**, **60a**, **60b**, **61a**, **61b**, **62a**, **62b**, **1a**, and **1b**; ^1H and ^{13}C NMR spectra of **1a**; and ^1H and ^{13}C, DEPT, COSY, and HMQC spectra of **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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