Enantioconvergent Formal Synthesis of Brefeldin A via Sakai-Catalyzed Cyclization

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Received March 23, 1999

Since the isolation of Brefeldin A (BFA) **1** in 1958,[1] much effort has been devoted to its study.[2] Initially, interesting biological activities including antitumor, antifungal, and antiviral effects, as well as the unique bicyclic macrolactone framework, stimulated synthetic efforts. Since the early 1990s, it has been found that BFA causes rapid redistribution of Golgi proteins into the endoplasmic reticulum, leaving no definable Golgi apparatus, and blocks transport of proteins into post-Golgi compartments in the cell.[3] Understanding the mechanism through which BFA acts on the Golgi should help explain how membrane organelles maintain their identity.[4] To answer this fundamental question, the identification of the biological target of BFA is necessary. Toward this end, we have developed a synthesis of BFA analogues that can either be linked to a solid support, for affinity chromatography, or, that would incorporate photoactivatable radioactive probes. We report here the synthesis of the key intermediate **3a** which could rapidly and efficiently lead to these derivatives, but also to **2** (Scheme 1). The latter could lead, in few steps, to BFA as described by Gais.[2f]

We developed an enantioconvergent synthesis of optically pure aldehyde **3a** starting from racemic pentenal **5** (Scheme 1). A catalytic asymmetric intramolecular hydroacylation of **5** in the first step should lead to optically pure cyclopentanones **4a** and **4b** in equal amounts.[5] Indeed, the stereochemistry of the newly created center should only depend on the chirality of the catalyst. (*S*)-BINAP, as rhodium ligand, should provide (3*R*) **4a** and **4b**. The hydroxyl group on this stereogenic center could then be used as a directing group in the asymmetric reduction of the ketone.[2n] A highly diastereoselective reduction is expected. Finally, epimerization should transform trans aldehyde **3b** into key intermediate **3a**.

Racemic pentenal **5** was obtained using a Heck reaction[6] between vinylic bromide **6** and *cis*-4,7-dihydro-1,3-dioxepin (Scheme 2). All attempts to perform this reaction asymmetrically were unsuccessful despite the report of Shibasaki[6b] who described a similar arylation with 72% ee. This result prompted us to develop the enantioconvergent strategy reported herein. The hydrolysis of **7** with aqueous HCl was followed by treatment with EtSH in a one-pot reaction to afford **8**. TBS protection of the hydroxyl group, followed by cleavage of the thioacetal, provided 4-pentenal **5**.[7]

Sakai cyclization using a catalytic amount (0.9%) of cationic Rh[(*S*)-BINAP]$^+$BF$_4^-$ proceeded smoothly to afford a 1:1 mixture of *trans*-(3*R*,4*R*)-cyclopentanone **4a** and *cis*-(3*R*,4*S*)-cyclopentanone **4b** in high yield (90%) and with high enantioenrichment (96% for each) (Scheme 3). An efficient transformation into aldehyde **3a** was then carried out starting from the **4a** + **4b** epimeric mixture. The hydrogenation of the benzyl ether was followed by the highly diastereoselective reduction of the resulting ketone using sodium triacetoxyborohydride.[2n] The primary hydroxyl group in **9a** and **9b** was acetylated and the secondary hydroxyl group protected with MEM chloride. After deacetylation, the primary hydroxyl was protected as MTM ether.[8] The TBS protecting group was then removed, and the resulting hydroxyl group was oxidized with PCC to furnish aldehydes **3a** and **3b**. Basic treatment converted the cis aldehyde **3b** to the thermodynamically favored chiral synthon **3a**.

Chloride **13**, corresponding to the side chain moiety, was prepared according to Scheme 4. Lithium acetylide was reacted with (*S*)-propylene oxide to give an alcohol which was benzyl-protected to afford **11**.[9] Dihydroboration of

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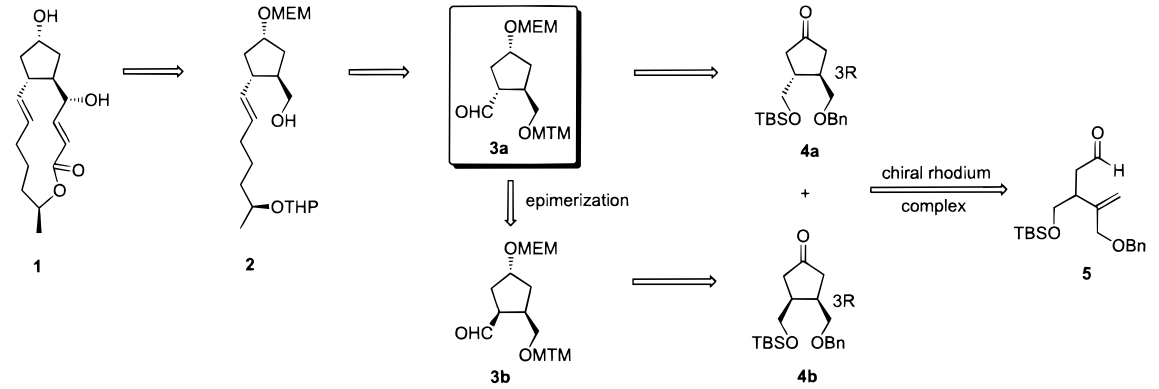
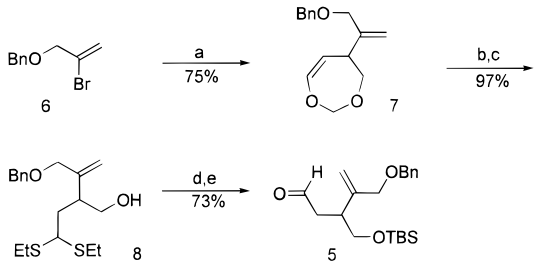
10.1021/jo990507w CCC: $18.00
Published on Web 05/06/1999

Scheme 1

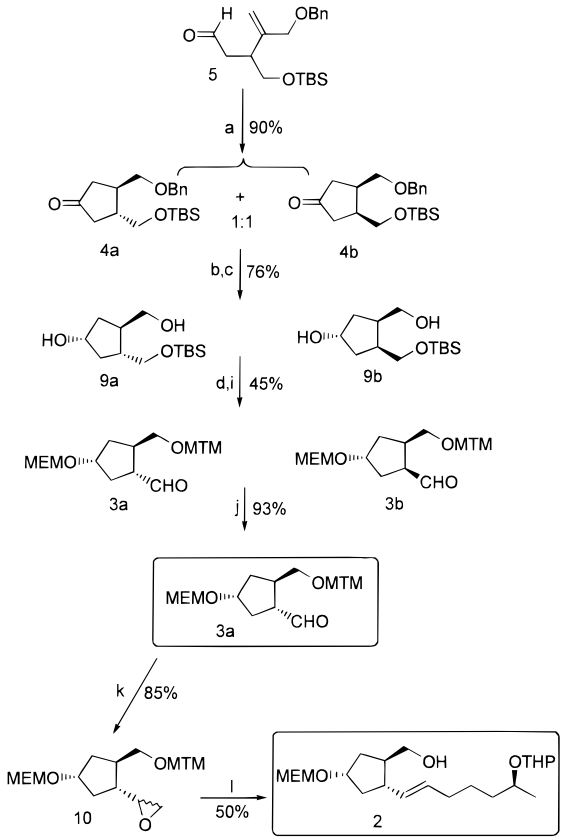


Scheme 2



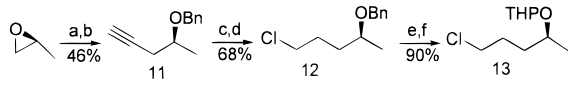
a) $Pd(OAc)_2$, P(*o*-Tol)$_3$, KOAc, $BnEt_3NBr$, *cis*-4,7-dihydro-1,3-dioxepin, CH_3CN reflux, 15 h; b) 2-butanone, HCl 1N, 50°C, 22h; c) EtSH, HCl conc., 0°C, 10 min, then rt 35 min; d) TBSCl, DMAP, imidazole, CH_2Cl_2, 0°C 30 min, then rt 30 min, 1h; e) MeI, Na_2CO_3, acetone/water, 65°C, 8h.

Scheme 3



a) Rh{(S)-BINAP}BF_4, CH_2Cl_2, rt, 3h, 96% ee; b) H_2, Pd/C, dioxane, rt, 1.5h; c) $NaBH(OAc)_3$, AcOH, THF, rt, 22h, 97% de; d) AcCl, NEt_3, DMAP, THF, 0°C, 2h; e) MEMCl, *i*Pr_2EtN, CH_2Cl_2, rt, 16h; f) MeONa, C_6H_6/CH_3OH, 0°C, 30 min then rt, 3h; g) NaH, DME, NaI, MTMCl, 0°C, 2h; h) TBAF, THF, 0°C 1h then rt 1.5h; i) PCC, KOAc, CH_2Cl_2, rt, 45 min; j) Na_2CO_3, MeOH, rt, 5h; k) Me_3SMeSO_4, NaOH/CH_2Cl_2, rt, 20h; l) **13**, Li metal, Et_2O/THF, -70°C then rt, 4h.

Scheme 4



a) C_2HLi-EDA, DMSO, rt, 4h; b) NaH, THF, rt, 45 min then BnBr, rt, 2h; c) 9-BBN, THF, rt, 18h then aq. NaOH, H_2O_2; d) $(COCl)_2$, DMF, CH_2Cl_2, rt, 12 min, then **11a**, reflux, 1.5h e) H_2, Pd/C, CH_2Cl_2, rt, 3h; f) DHP, PPTS, CH_2Cl_2, rt, 4h.

acetylene **11** and oxidation of the reaction mixture with alkaline hydrogen peroxide[10] afforded primary alcohol **12** which, upon treatment with oxalyl chloride, furnished the corresponding chloro compound. Debenzylation followed by THP protection afforded **13**.

Condensation of aldehyde **3a** with trimethylsulfonium methyl sulfate, under phase transfer conditions, gave the desired epoxide **10** (Scheme 3).[11] Reductive alkylation of **10** with the organolithium reagent[12] derived from halide **13**[13] afforded, with concomitant regeneration of the hydroxyl function, olefin **2**. The stereoselectivity of this process is better than that of classical olefination methods applied to BFA syntheses (E/Z = 90/10).

A formal, catalytic, and enantioconvergent synthesis of BFA is reported. Our approach utilizes, as the key steps, an asymmetric Sakai cyclization and a reductive alkylation of epoxide rendering this approach particularly attractive despite the large number of total or partial syntheses of (+) BFA described in the literature. This allows the conversion of racemic **5** into an optically pure product using only 0.9% of a chiral catalyst. These two reactions were, for the first time, applied to the total synthesis of a natural product.

Acknowledgment. We warmly thank Drs. François Képès, Catherine Jackson, and Eric Doris for hepful discussions. We also thank Ms Florence Pillon, Mrs Alain Valleix, Franck Sobrio, and Dr. Patrick Berthault for running important control experiments.

Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C spectra for all compounds including unnumbered intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990507W

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