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# Efficient enantioselective syntheses of chloramphenicol and (D)-*threo*- and (D)-*erythro*-sphingosine

E. J. Corey * and Soongyu Choi

*Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, USA*

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**Abstract**

The chiral diazaborolidine **1** has been applied to the enantioselective syntheses of chloramphenicol (**2**) and (D)-*threo*-*N*-acetylsphingosine (**3**), a synthetic precursor of the diastereomeric (D)-sphingosines. 

Optically active amino alcohols with vicinal stereocenters are important as drugs and natural products such as amino sugars,[1] peptides and peptide analogs,[2] enzyme inhibitors, such as glycosphingolipids, antibiotics, and alkaloids. The pharmacological utility demonstrated by these compounds themselves or as components of larger structures has recently stimulated the search for better methods for their synthesis.[3]

A previous paper described the use of the chiral, recoverable diazaborolidine reagent **1** to the promotion of highly enantio- and diastereoselective aldol reactions between various aldehydes and *t*-butyl bromoacetate to form α-bromo-β-hydroxy esters which can serve as versatile intermediates for the synthesis of countless chiral products.[4] Disclosed herein is the application of this methodology to the efficient synthesis of chloroamphenicol (**2**) (and analogs) and *threo*-*N*-acetylsphingosine (**3**).[5]

Since its discovery more than 50 years ago, the antibiotic chloramphenicol (**2**)[6] has been especially effective in the treatment of typhus, dysentery and ocular bacterial infections, and number of syntheses have been described.[7] Our synthesis of **2** (Scheme 1) started with the (2*R*,3*R*)-2-bromo-3-hydroxy ester **4** which was prepared in quantity via aldol reaction of *p*-nitrobenzaldehyde and *t*-butyl bromoacetate in the presence of (*S*,*S*)-bromoborane **1** (*S*,*S* form) and triethylamine (99% yield, *anti*:*syn*=96:4, *anti* 93% ee).[8] Protection of the β-hydroxy group in **4** as the *t*-butyldimethylsilyl ether (**5**), and reaction of **5** with sodium azide gave the α-azido-β-silyloxy ester **6** (DMF, 40°C, 1 day, 73% yield).[9] Reduction of the azido ester **6** was performed in two steps with $LiBH_4$ in ether followed by triphenylphosphine in $H_2O$–THF,[10] to form the amino alcohol **7**. *N*-Acylation of **7** with $Cl_2CHCOCl$ in $CH_2Cl_2$ at 0°C for 1 h and subsequent desilylation with $Bu_4NF$ in THF afforded chloroamphenicol which was recrystallized from

* Corresponding author.

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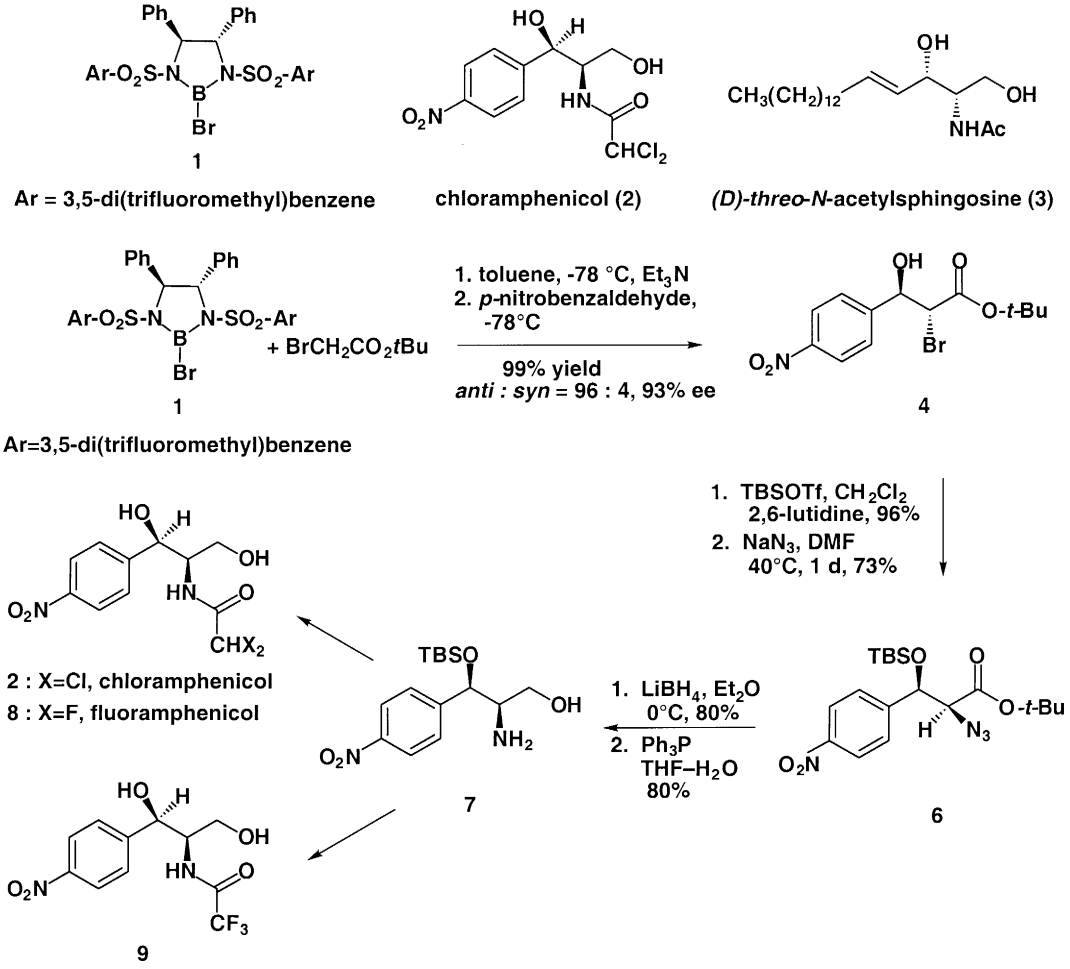
1,2-dichloroethane (83% recovery, as colorless plates), $[\alpha]_D^{23}$ −25.2 (*c* 0.33, EtOAc), mp 150–150.5°C, {lit.[6b] $[\alpha]_D^{23}$ −25.5° (EtOAc), mp 149.7–150.7°C}. The identity of synthetic **2** with known material was confirmed by comparison of chromatographic behavior and spectroscopic data with a commercial sample (Aldrich) of chloroamphenicol.

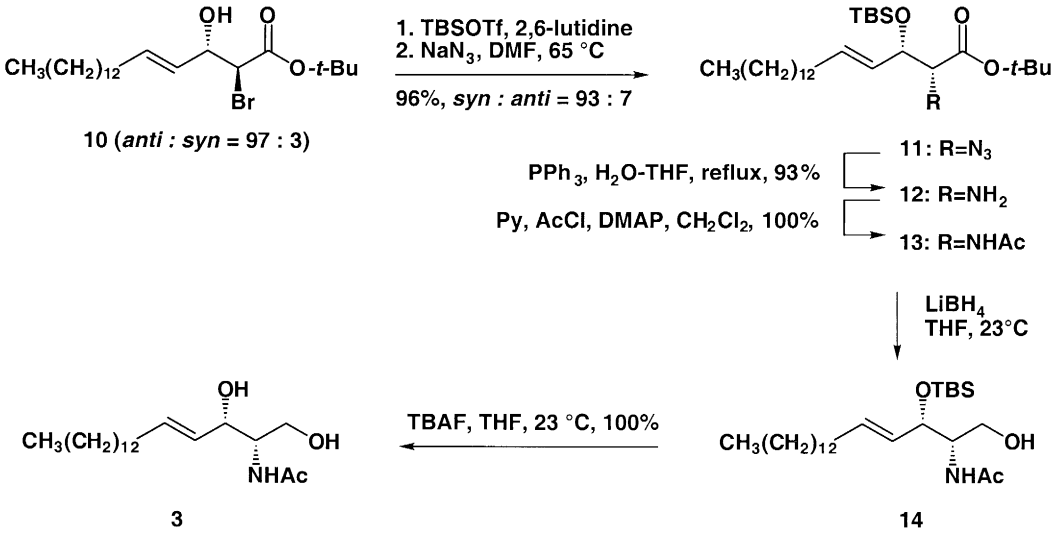



Scheme 1.

Similarly, the potent antibiotic (–)-fluoramphenicol (**8**) was prepared via the reaction of amino alcohol **7** and $F_2CHCOCl$,[11] followed by desilylation (TBAF, THF, 0°C, 94% yield), $[\alpha]_D^{23}$ −6.7 (*c* 0.9, EtOAc). Its enantiomer, (+)-fluoramphenicol, was also obtained starting from aldol reaction in the presence of (*R*,*R*)-bromoborane *ent*-**1** for biological evaluation. The trifluoromethyl analog **9**, potentially a safer antibiotic, was produced from the reaction of amino alcohol **7** and trifluoroacetic anhydride ($CH_2Cl_2$, 0°C), followed by desilylation (TBAF, THF, 89% yield) and trituration with hexane, $[\alpha]_D^{23}$ −7.2 (*c* 1.1, EtOAc), mp 116–117°C.

Sphingosine (D-*erythro*-1,3-dihydroxy-2-amino-4-octadecene)[12] is an important mammalian lipid which plays a critical role in signal transduction and cellular regulation.[12,13] It has been the target of a number of synthetic studies.[13,14] The objective of this work was the synthesis of (D)-*threo*-sphingosine and (D)-*threo*-*N*-acetylsphingosine (**3**) for biological evaluation and as an intermediate for the preparation of both (D)-*threo*- and (D)-*erythro*-sphingosine.[5]

The synthesis of (D)-*threo*-acetylsphingosine (Scheme 2) commenced with the diastereo- and enantioselective aldol reaction of *t*-butyl bromoacetate and (*E*)-hexadec-2-enal[12] with the (*R,R*)-bromoborane *ent*-**1** which afforded the α-bromo-β-hydroxy ester **10** in 75% yield and 94% de.[15] Silylation of hydroxy group in compound **10** and replacement of bromide by azide generated the α-azido-β-silyl ether **11**. Reduction of the azido group in **12** by triphenylphosphine in aqueous THF afforded the α-amino ester **12**. The pure *syn* amino ester **12**, which was separated from an impurity of *anti* diastereomer by flash chromatography, was treated with acetyl chloride to give amide ester **13** in quantitative yield (pyridine, AcCl, DMAP, $CH_2Cl_2$). Reduction of ester **13** to amino alcohol **14** with lithium borohydride and desilylation (TBAF, THF, 0°C) produced *threo-N*-acetylsphingosine in high yield. *threo-N*-Acetylsphingosine was transformed into the more stable di- or triacetyl derivatives of (D)-*threo*-sphingosine[16] to confirm absolute configuration {for the diacetyl derivative: $[\alpha]_D^{23}$ −21.9 (*c* 0.32, $CHCl_3$), lit. $[\alpha]_D$ −20.3 (*c* 1.1, $CHCl_3$);[5a] for triacetyl derivative: $[\alpha]_D^{23}$ +10.7 (*c* 0.28, $CHCl_3$), lit. $[\alpha]_D$ +10.4 (*c* 1.0, $CHCl_3$),[5b] $[\alpha]_D$ +8.78 (*c* 1.2, $CHCl_3$),[14a] $[\alpha]_D$ +8.43° ($CHCl_3$)[17]}. (D)-*threo*-Sphingosine is available from **3** by alkaline hydrolysis.[18]




Scheme 2.

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8. (a) The absolute configuration was assumed from the results in Ref. 4 and confirmed later by comparison of the optical rotation with that reported for chloramphenicol (**2**). (b) The enantiomeric purity (ee) was determined by HPLC analysis using a Daicel Chiralcel OJ column. (c) The diastereoselectivity was determined by $^1$H NMR analysis at 500 MHz in $CDCl_3$ solution.
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15. The diastereoselectivity was determined by $^1$H NMR analysis at 500 MHz in $CDCl_3$ solution. The enantiomeric purity (ee) was determined later from its derivative because **10** is readily converted into the corresponding α,β-epoxy ester under basic conditions. The absolute configuration was assumed from the results in Ref. 4 and confirmed later by comparison of the optical rotation with that reported for the final product, acetyl (D)-*threo*-sphingosine.
16. The enantiomeric purity of the alcohol **14** was confirmed by its conversion to (*R*)-(+)-MTPA ester followed by $^1$H NMR analysis at 500 MHz. There was no detectable amount of the other enantiomer.
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