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Stereoselective synthesis of β-amino alcohols: practical preparation of all four stereomers of *N*-PMB-protected sphingosine from L- and D-serine

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Abstract

Serine was efficiently converted to the *N*-*p*-methoxybenzyl (PMB) protected α′-amino enone derivative **6**, which was reduced with $Zn(BH_4)_2$ to the corresponding *anti*-β-amino alcohol in >96% de. On the other hand, *N*-PMB-*N*-Boc-protected α′-amino enone derivative **8** was reduced by $NaBH_4$ to *syn*-product with a diastereoselectivity of ca. 90%.

The stereoselective synthesis of β-amino alcohols is a topic of current interest, since a number of biologically important compounds contain this structural motif.[1] Diastereoselective synthesis of β-amino alcohols may in principle be approached by either the nucleophilic addition of organometallics to *N*,*N*-dibenzylamino aldehydes giving primarily *anti*-adducts,[2] or the reduction of the corresponding α-amino ketones. Recently, we described a highly efficient synthetic route to *syn*-β-amino alcohols via the diastereoselective reduction of α-*N*,*N*-dibenzylamino enones prepared from the corresponding α-amino acid.[3] Although the α-*N*,*N*-dibenzylamino moiety provides the bulkiness necessary for the diastereoselection, and a degree of resistance to possible racemization at the α-amino ketone stage, it is also a source of serious limitations to the subsequent functional group manipulation. In connection with our interests in developing practical synthetic routes to various sphingosine related structures, it was required to obviate the problems associated with the α-*N*,*N*-dibenzylamino-protecting method. We wish to report herein a divergent synthesis of all four stereomers of sphingosine as an illustration of the *syn/anti*-diastereoselectivity control in the synthesis of β-amino alcohols.

Naturally occurring D-*erythro*-sphingosine **1a** is the major backbone component of glycosphingolipids, important cell membrane constituents. The glycosphingolipids play crucial roles in cell recognition events such as growth, differentiation, the immune response,[4] and all of the sphingosine diastereomers have been reported to be potent inhibitors of protein kinase C.[5] In addition, certain glycosphingolipid analogues exhibit significant antiinflammatory,[6] immunosuppressive,[7] antiviral,[8] and

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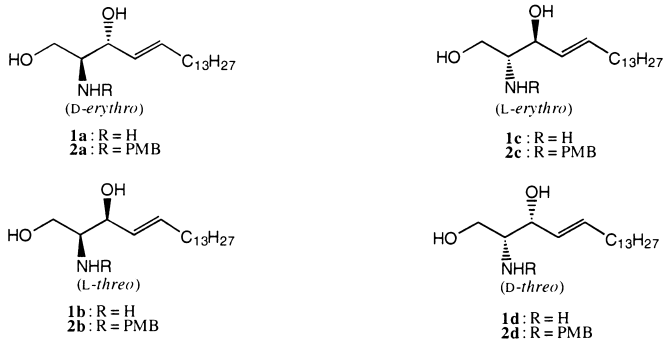
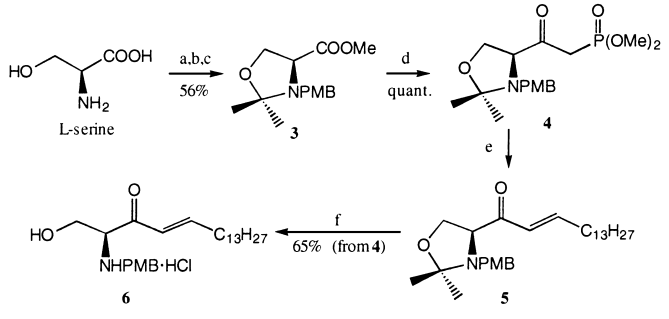
antifungal activities.[9] Various synthetic methods for the enantiomerically pure sphingosine diastereomers have been reported.[10] One of the most widely used methods involves the diastereoselective addition of organometallics to suitably protected serinal derivatives. In addition to the fact that chiral α-amino aldehydes are prone to racemization, obtaining a high level of diastereoselectivity by this method is still problematic.[11] Since α′-amino enones could be readily prepared from α-amino acids via the Horner–Wadsworth–Emmons procedure,[3] we have examined other *N*-protection methods than the *N*,*N*-dibenzylation in order to gain a direct access to either *syn*- or *anti*-β-amino alcohols by reduction. Initially, we examined the *N*-trityl protection, but diastereoselectivity of the reduction was found to vary widely depending on the structure of α′-amino enones. More successful results were obtained with the *N*-*p*-methoxybenzyl (*N*-PMB) protection.



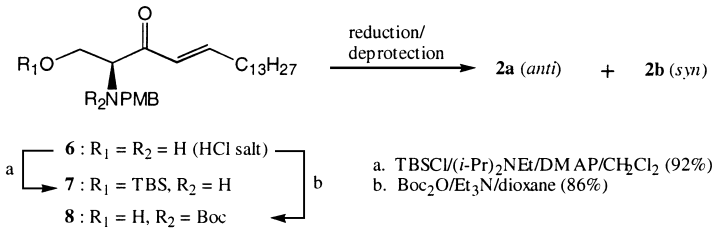
L-Serine was esterified with methanolic hydrogen chloride, the amino group protected as the *N*-PMB group with *p*-methoxybenzaldehyde followed by reduction of the imine intermediate,[12] and introduction of the acetonide gave **3** as a crystalline solid in 56% yield from serine (Scheme 1). The ester **3** was converted to the β-keto phosphonate **4** by treatment with 2.2 equiv. of lithium dimethyl methylphosphonate in THF at −78°C. The Horner–Wadsworth–Emmons olefination of **4** with tetradecylaldehyde under Masamune conditions[13] provided the *O*,*N*-protected enone **5**, which was subjected to one-pot deacetonidation to generate the *N*-protected α′-amino enones **6** as a stable HCl salt in 65% yield from **3**. The *E*-stereochemistry of compound **6** was assigned on the basis of ^{1}H NMR (*J*=15.8 Hz, *trans*-olefinic CH). The enantiomeric purity of **6** was determined to be >99% ee by a chiral HPLC (Daicel-OD, 10% *i*-PrOH in *n*-hexane), which also showed no epimerization at the stereogenic center throughout the entire sequence of transformation.



Scheme 1. Reagents: (a) AcCl/MeOH; (b) *p*-methoxybenzaldehyde/Et_3N/$MgSO_4$/MeOH then $NaBH_4$; (c) $(MeO)_2CMe_2$/PPTS/toluene; (d) $CH_3PO(OMe)_2$/*n*-BuLi/THF; (e) $C_{13}H_{27}CHO$/DBU/LiCl/THF; (f) 10% HCl–THF

Our initial attempts to obtain **2a** or **2b** from the *O*,*N*-protected enone **5** by stereoselective reduction and subsequent removal of the isopropylidene group resulted in poor yield and diasteroselectivity.[14] Thus, the diastereoselective reduction was examined on **6** and the results are shown in Table 1 (entries 1–6).

Table 1



Entry	Compound	Reductant	Yield (%)	**2a/2b**[a]
1	**6**	$NaBH_4$/EtOH	86	0.9/1
2	**6**	DIBAH/THF	68	2.6/1
3	**6**	DIBAH/$ZnCl_2$/THF	79	8/1
4	**6**	L-Selectride/THF	75	4.3/1
5	**6**	$Zn(BH_4)_2$/THF	84	**>49/1**
6	**6**	$Me_4NBH(OAc)_3$/CH_3CN-AcOH	77	1/7
7	**7**	$NaBH_4$/EtOH	82	3.8/1[b]
8	**7**	DIBAH/THF	67	>49/1[b]
9	**7**	DIBAH/$ZnCl_2$/THF	70	>49/1[b]
10	**7**	L-Selectride/THF	72	4.2/1[b]
11	**7**	$Zn(BH_4)_2$/THF	80	>49/1[b]
12	**7**	$Me_4NBH(OAc)_3$/CH_3CN-AcOH	72	8.5/1[b]
13	**8**	$NaBH_4$/MeOH	71	**1/19** [c]

a. by HPLC and ^1H NMR; b. after desilylation; c. after removal of the Boc group

Virtually all reducing agents examined except $Me_4NBH(OAc)_3$ (entry 6), provided the *anti*-diastereomer **2a** as the major product in accord with the expected α-chelated transition state.[15] The highest *anti*-diastereoselectivity (>96% de) was obtained with $Zn(BH_4)_2$, presumably due to the high chelating ability of zinc.[16] The *syn*-preference in the case of entry 6 with $Me_4NBH(OAc)_3$ is consistent with the β-hydroxy-directed reduction.[17] In order to assess the effect of the chelation by the free hydroxy group on the diastereoselectivity, the *O*-silylated ketone **7** was examined (entries 7–12). This modification was found generally to increase the *anti*-selectivity, probably due to the increased α-chelation. Finally, enone **6** was diprotected as the *N*-*p*-methoxybenzyl-*N*-*tert*-butoxycarbonyl derivative **8**. Reduction of **8** with $NaBH_4$ afforded the expected *syn*-amino alcohol **2b** in high yield and excellent diastereoselectivity (>90% de) after in situ removal of the Boc group with dil. HCl (entry 13). It is evident that the reduction proceeds through a non-chelated transition state, in which the bulky *N*-protecting groups both prevent the chelation and control the diastereoselectivity.

The stereochemical assignments for diastereomers **2a** and **2b** were made based on spectral analyses of the corresponding oxazolidinone derivatives.[18] The *erythro*-derivative showed $J_{\text{vicinal H}}$ value slightly larger (8.2 Hz) than that of the *threo*-isomer (6.5 Hz). The compounds **2a** and **2b** were also converted to the known triacetates by acetylation with Ac_2O, followed by removal of the PMB group with cerium ammonium nitrate in 70% and 65% overall yields, respectively.[19] Their physical properties were identical with the reported values.[20]

Employing the identical procedures, D-serine was also transformed to **2c** and **2d**. Thus, all four stereomers of the *N*-PMB-protected sphingosine were divergently synthesized in good yield and excellent enantiomeric excess (Table 2).

Table 2

	2a	2b	2c	2d
mp (°C)	49-50	71.5-73	49-50	73-74
$[\alpha]_D^{25}$ (in $CHCl_3$)	-5.72 (c 2.30)	+14.30 (c 1.16)	+5.80 (c 1.06)	-14.42 (c 0.70)

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20. Triacetyl-D-*erythro*-sphingosine: mp 101–102°C; $[\alpha]_D^{25}$ −13.18 (*c* 1.04, $CHCl_3$) [lit.[11a] mp 102.5–103°C; $[\alpha]_D$ −13.0 (*c* 1.08, $CHCl_3$), triacetyl-L-*threo*-sphingosine: mp 42–43°C; $[\alpha]_D^{25}$ +7.92 (*c* 1.28, $CHCl_3$) [lit.[11a] mp 42–44°C; $[\alpha]_D$ +7.02 (*c* 2.05, $CHCl_3$).