Dihydroxylation of 2-vinylaziridine: efficient synthesis of D-*ribo*-phytosphingosine†

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Received (in Cambridge, UK) 4th September 2006, Accepted 30th October 2006
First published as an Advance Article on the web 17th November 2006
DOI: 10.1039/b612740a

An efficient and highly stereoselective synthesis of D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine was accomplished in 62% overall yield starting from commercially available (2*S*)-hydroxymethylaziridine *via* osmium-catalyzed asymmetric dihydroxylation as a key step.

Sphingolipids along with glycerides are the main constituents of cell membranes and their metabolism is closely related to many inherited human diseases and to cell regulation. Sphingosine and phytosphingosine are two most important long-chain backbones of sphingolipids in the realm of nature (Fig. 1).[1] Recently, it has been revealed that phytosphingosine shows a great variety of biological activities such as cell differentiation, signal transduction, regulation, proliferation and induction of apoptosis.[2] Furthermore, phytosphingosine was shown to be widely distributed as one of the molecular species of sphingolipids in microorganisms, plants, and many mammalian tissues such as brain, hair, kidney, skin, liver, uterus, intestine and in blood plasma.[3]

Among all eight possible stereoisomers of phytosphingosine, (2*S*,3*S*,4*R*)-2-aminooctadecane-1,3,4-triol with D-*ribo*-stereochemistry, is the most common. Owing to interests in these vital biological activities many synthetic approaches to enantiomerically pure phytosphingosines have been reported in the literature.[4] However, most of them suffer from long synthetic steps and low overall yield. Recent success in the synthesis of sphingosine[5] and ceramide analogues[6] prompted us to aim for the efficient synthesis of phytosphingosine. In this communication we would like to report a remarkably efficient synthetic route to yield D-*ribo*-phytosphingosine from commercially available (2*S*)-hydroxymethylaziridine through a simple five-step transformations including stereoselective dihydroxylation.

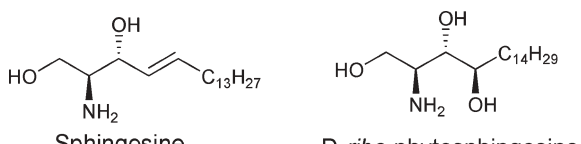
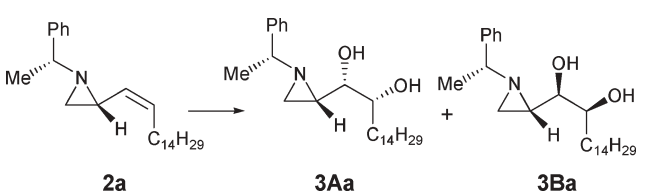


Fig. 1 Structure of sphingosine and D-*ribo*-phytosphingosine (**1**).

Aziridine-2(*S*)-carbaldehyde was readily prepared *via* Swern oxidation of the enantiomerically pure aziridine-2(*S*)-methanol which is commercially available.[7] The bromopentadecane was converted to the corresponding phosphonium salt in 80% yield by stirring with triphenylphosphine in acetonitrile at reflux for 30 h.[8] Treatment of the phosphonium salt with LiHMDS at −78 °C generated the ylide which was then reacted with aziridine-2(*S*)-carbaldehyde to provide 2(*S*)-[(*Z*)-hexadec-1-enyl]aziridine **2a** in 93% yield with the ratio of 99 : 1 (*Z* : *E*).

We studied the stereoselective dihydroxylations of the (*Z*)-2-alkenylaziridine (**2a**) under a variety of conditions (Scheme 1 and Table 1). The Sharpless asymmetric dihydroxylation with AD-mix α and AD-mix β was not completed after two days. Furthermore, the ratio of the vicinal diols **3Aa** and **3Ba** was poor in terms of stereoselectivity. We concluded that the reluctance of the dihydroxylation of the 2-vinylaziridine using AD-mix reagents is due to the steric congestion around the double bond of the aziridine which hinders the approach of the bulky oxidation catalyst to the double bond. This interaction between the catalyst and bulkiness of the substrate in stereoselective dihydroxylation has been reported in the literature.[9] When the 2-vinylaziridine was oxidized with 10 mol% of osmium tetraoxide in aqueous acetone with *N*-methylmorpholine oxide (NMO) as re-oxidant, we obtained the two vicinal diols **3Aa** and **3Ba** with high stereoselectivity (93 : 7) and high yield. A better ratio (99 : 1) was obtained by lowering the reaction temperature to −10 °C. The diastereomeric mixture of the diols was easily separated by flash column chromatography to remove trace amount of the other isomer. The identity of each diastereoisomeric diol was confirmed by ^{1}H NMR spectra in the literature after regioselective aziridine ring opening with AcOH and removing the benzyl group from the nitrogen. Once we obtained 2-(1,2-dihydroxyhexadecanyl)aziridine (**3Aa**) in high yield, we looked into the origin of the stereoselectivity and the scope of dihydroxylation reactions of the 2-vinylaziridine in general.



Scheme 1 Dihydroxylation reactions of **2a**.

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† Electronic supplementary information (ESI) available: Experimental details of all reactions and the calculated rotational energy barriers of **2a** and **2b**. See DOI: 10.1039/b612740a

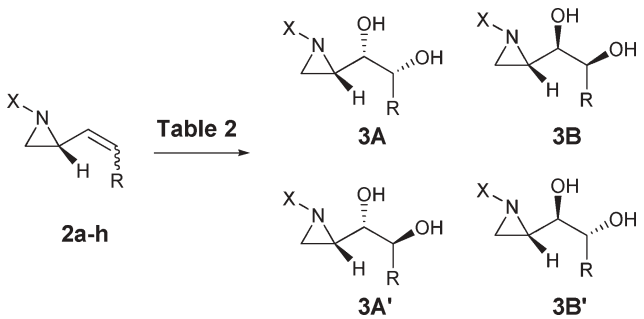
Table 1 Dihydroxylation conditions of the 2-vinylaziridine **2a**

Entry	Reagents	Solvent	Temp	Time	**3Aa** : **3Ba**[c]	Yield[d] (%)
1	AD-mix α (1.4 g/1 mmol)	*t*-BuOH–H_2O (1 : 1)	RT	2 days	2 : 3	<40
2	AD-mix β (1.4 g/1 mmol)	*t*-BuOH–H_2O (1 : 1)	RT	2 days	3 : 2	<40
3	OsO_4[a] (1.1 equiv.)–TMEDA[b] (1.1 equiv.)	Acetone–H_2O (1 : 1)	RT	2 days	ND	Trace
4	OsO_4[a] (1.1 equiv.)	Acetone	RT	2 days	ND	Trace
5	OsO_4[a] (0.1 equiv.)–NMO (3 equiv.)	Acetone–H_2O (9 : 1)	RT	2 h	5 : 1	80
6	OsO_4[a] (0.1 equiv.)–NMO (3 equiv.)	Acetone/H_2O (9 : 1)	0 °C	4 h	93 : 7	88
7	OsO_4[a] (0.1 equiv.)–NMO (3 equiv.)	Acetone/H_2O (9 : 1)	−10 °C	10 h	99 : 1	87

[a] 5 wt% in H_2O. [b] *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine. [c] Based on the integration of the crude ^{1}H NMR (300 MHz) spectra. [d] Total isolated yields.

The origin of this high stereoselectivity was investigated by changing the substrate structures to address the following questions. Is there any steric influence of the vinyl substituents R in **2a–h**? Will stereoselectivity be changed by double bond configuration? Is there any influence by the group X attached on the aziridine ring nitrogen? Thereby various 2-vinylaziridines (**2b–h**) were used to investigate the stereoselectivities of dihydroxylation reactions (Scheme 2) and the results were shown in Table 2.

The *Z* isomer of the olefins (**2a**, **2d** and **2f**) always showed better selectivity than *E* (**2b**, **2e** and **2g**). When we compare the reactions of *Z* isomeric substrates (**2a**, **2c**, **2d** and **2f**) we find that a longer alkyl chain gives better selectivity. Decrease of selectivity, from 93 : 7 to 83 : 17, was also observed by changing the alkyl group X attached on the nitrogen of the aziridine from phenylethyl (**2a**) to benzyl (**2h**). These observations can be explained by the conformational preference during the hydroxylation. In the literature, it has been reported that some ligands, especially tertiary amine group for asymmetric dihydroxylation, play an important role in controlling enantioselectivity by coordinating with OsO_4.[10] We assume that the two substituents on the nitrogen and the vinyl group at C-2 have an *anti* relationship[11] and OsO_4 may coordinate to the aziridine ring nitrogen. Two conformations (**A** and **B**, Fig. 2) from the *Z*-stereoisomer (**2a**, **2d** and **2f**) are possible by rotating the σ-bond for the double bond to get close to the oxygen atoms of OsO_4 for the dihydroxylation reactions. One pathway "b" leading to the conformer **B** is unfavorable due to nonbonding interaction between X and the bulky R groups while the other pathway "a" toward the conformer **A** is easily accessible. Therefore, the nitrogen bound OsO_4 can readily deliver oxygen atoms to the double bond with **A** conformer to result in the major dihydroxylation product **3Aa**. In the case of *E*-stereoisomers (**2b**, **2e** and **2g**) the rotation barrier difference to go to the possible conformers **A**′ and **B**′ are not as large as for **A** and **B** of the *Z*-isomers since the steric interaction between the bulky substituent of the *E*-double bond and X group is less than that of the *Z*-stereoisomer. Therefore, the *E*-stereoisomer shows decreased diastereoselectivity in the asymmetric dihydroxylation reaction. The decrease of the selectivity by changing the alkyl group X attached on the nitrogen of the aziridine from phenylethyl (**2a**) to the smaller benzyl (**2h**) also can be explained by the decrease of the nonbonding interaction of the reactive conformation **A** or **B**.



Scheme 2 Dihydroxylation reactions and their stereoselectivities of **2**.

Table 2 Selectivity of dihydroxylation of (2*S*)-vinylaziridine[a]

Subst.	X	R	Isomer	**3A** : **3B**[b]	**3A**′ : **3B**′[b]	Yield (%)
2a	(*R*)-Phenylethyl	$C_{14}H_{29}$	*Z*	93 : 7		88
2b	(*R*)-Phenylethyl	$C_{14}H_{29}$	*E*		72 : 28	90
2c	(*R*)-Phenylethyl	C_5H_{11}	*Z*	89 : 11		92
2d	(*R*)-Phenylethyl	Phenyl	*Z*	70 : 30		84
2e	(*R*)-Phenylethyl	Phenyl	*E*		58 : 42	79
2f	(*R*)-Phenylethyl	Benzyl	*Z*	84 : 16		88
2g	(*R*)-Phenylethyl	Benzyl	*E*		71 : 29	82
2h	Benzyl	$C_{14}H_{29}$	*Z*	83 : 17		85

[a] Under the reaction conditions of entry 6 in Table 1. [b] Based on the integration of the crude ^{1}H NMR (300 MHz) spectra.

Regioselective ring opening reaction of the aziridine diol **3Aa** by AcOH and hydrolysis of the acetate by KOH in ethanol provided the aminotriol **4** (Scheme 3). AcOH was used for the activation of

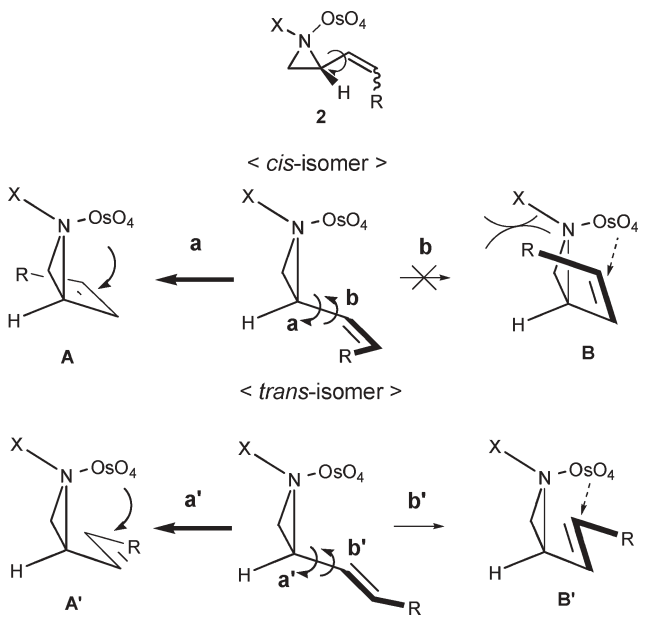
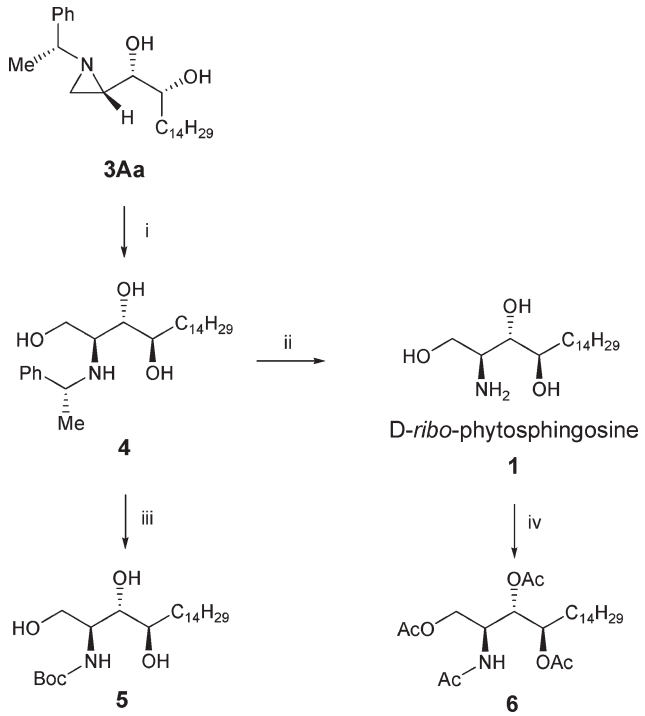


Fig. 2 Dihydroxylations of (*Z*)- and (*E*)-2-alkenylaziridine (**2**).



Scheme 3 Conversion of dihydroxyaziridine (**3Aa**) to D-*ribo*-phytosphingosine (**1**). *Reagents and conditions*: (i) (1) AcOH, CH_2Cl_2; (2) KOH, EtOH, rt, 93%; (ii) $Pd(OH)_2$, H_2(g) 100 psi, EtOH, rt, 92%; (iii) $Pd(OH)_2$, H_2(g) 100 psi, EtOH, rt, $(Boc)_2O$, 95%; (iv) acetic anhydride, pyridine, rt, 98%.

the basic ring nitrogen of the aziridine and was also used as the source of the acetate nucleophile to attack the less sterically hindered C-3 position of the aziridine.[5] Finally, enantiomerically pure D-*ribo*-phytosphingosine **1** was obtained by palladium catalyzed debenzylation reaction. We further synthesized and characterized *N*-Boc derivative **5** and tetraacetate **6** to confirm the absolute configuration of the C-3 and C-4 hydroxy group in D-*ribo*-phytosphingosine.

In summary, we efficiently synthesized enantiomerically pure D-*ribo*-phytosphingosine through a five-step sequence in 62% overall yield from commercially available (2*S*)-hydroxymethylaziridine using asymmetric dihydroxylation of the *Z*-vinylaziridine as the key step. This methodology also provides an efficient way for the preparation of structurally modified phytosphingosine analogs. Additional study regarding the relation between the stereoselectivity in the dihydroxylation and the chain length of the substituents will be reported in due course.

This work was supported by the following institutions: The Korea Science and Engineering Foundation (R01-2005-000-10032-0 and the Center for Bioactive Molecular Hybrids to HJH), Korea Research Foundation (KRF-2002-070-C00060 to WKL) and Imagene for providing enantiomerically pure chiral aziridines.

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