SHORT COMMUNICATION

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A General Synthesis of Sphinganines through Multicomponent Catalytic Asymmetric Aziridination

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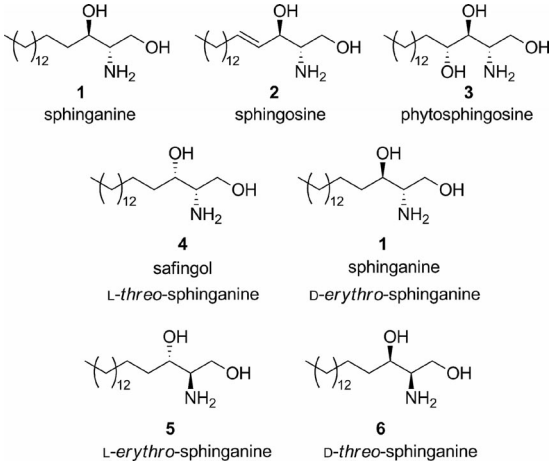
A catalytic asymmetric synthesis of all four stereoisomers of sphinganine is described starting from hexadecanal. Utilizing either the (*R*) or (*S*) enantiomer of a BOROX catalyst, a multicomponent reaction of this aldehyde with an amine and ethyl diazoacetate gives rise to enantiomeric aziridine-2-carboxylates. Access to all diastereomers of sphinganine is realized upon ring opening of the enantiopure aziridine-2-carboxylate at the C-3 position by direct S_N2 attack of an oxygen nucleophile, which occurs with inversion of configuration and by ring expansion of an *N*-acyl aziridine to an oxazolidinone and then hydrolysis. Overall, this process results in the formal ring opening of the aziridine with an oxygen nucleophile with retention of configuration.

Introduction

Sphingolipids consist of several subclasses of compounds that are involved in cell structure and regulation, and they are based on a structurally related family of hundreds of compounds known as sphingoid bases, often termed "long-chain bases".[1–3] The three major core units in sphingolipids are sphinganine, sphingosine, and phytosphingosine (Scheme 1). *N*-Acylated derivatives of the sphingoid bases are members of the ceramide family. Glycosphingolipids are ceramides with one or more sugar units attached to the hydroxy group at the 1-position. Members of this group include cerebrosides, which have a single glucose or galactose. Gangliosides have three sugars, one of which must be a sialic acid. The number of different head groups in the glycosphingolipids is enormous, and a variety of "omics" web sites are devoted to this class of compounds.[3] Phosphosphingolipids are ceramides in which a phosphate group is bound as a phosphate ester to the hydroxy group at the 1-position. For sphingomyelins, this phosphate group is either a phosphorylcholine or a phosphoroethanolamine.

Sphingolipids were recognized as far back as 1884, and much has since been learned about their biochemistry.[4] Errors in their metabolism has led to several inherited human diseases including diabetes,[5] cancers,[6] infection by microorganisms,[7] Alzheimer's disease,[8] heart disease, and an array of neurological syndromes.[9] They are involved in nearly all aspects of cell regulation including proliferation, differentiation, adhesion, neuronal repair, and signal transduction.[10] The natural configuration of both sphinganine and sphingosine is the D-*erythro* configuration; however, it has been found that for both classes of compounds (and their derivatives) the stereochemistry can play a large role in their bioactivity. For example, the L-*threo* diastereomer of sphinganine (safingol **4**) is an antineoplastic and antipsoriatic drug[11] and has been investigated for its ability to inhibit protein kinase C.[12] As a consequence of this and other differences in bioactivities, all four of the isomers of sphinganines and sphingosines have been prepared and their biological properties investigated.[1–3]



Scheme 1. Sphingoid bases and the four stereoisomers of sphinganine.

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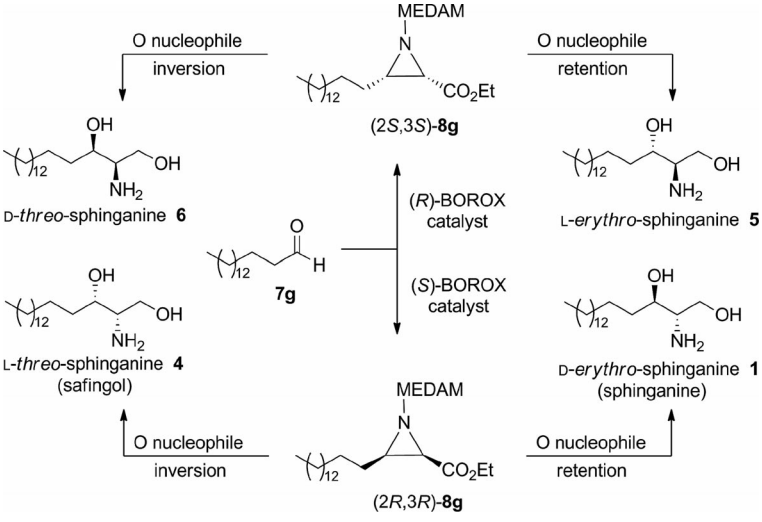
Background

The history of the syntheses of the sphinganines has been reviewed[13] and covers the period from the first synthesis in 1951 up to 2004, and many other syntheses have appeared subsequent to this review.[14] The earlier syntheses of sphinganines tended to be nonselective, which gave mixtures of diastereomers that needed to be separated and enantiomers that needed to be resolved. The most successful applications with asymmetric catalysis involved the use of Sharpless asymmetric dihydroxylation,[15] Sharpless asymmetric epoxidation,[16] and Sharpless kinetic resolution of allylic alcohols,[14n] although it has not been demonstrated if these methods can be used for all four of the stereoisomers of the sphinganines. Other catalytic asymmetric methods utilized in the synthesis of a specific sphinganine stereoisomer are the asymmetric hydrogenation of β-oxo esters[14m] and a proline-based Mannich reaction.[14p] As might be expected, the shortest synthesis (two steps from hexadecanal) involves an asymmetric catalytic reaction in which the chiral center at the nitrogen-substituted carbon atom is created in the stereogenic step. Shibasaki and co-workers reported that a 1,1′-bi-2-naphthol (BINOL)–lanthanum catalyst will effect the nitroaldol reaction (Henry reaction) between 2-nitroethanol and hexadecanal.[17a] Although this reaction gave good diastereoselectivity (91:9) and good asymmetric induction (97%*ee*), the reaction was limited in that it could produce only one diastereomer and prolonged reaction times were required: 10 turnovers required 6.8 d. Testimony to the impracticality of this method is found in a recent study that concluded that for the large-scale synthesis (100 g) of the same sphinganine, it was best to run the reaction without a chiral catalyst and separate the diastereomers and enantiomers.[14b] This reaction seems to have come full circle, as this approach with this reaction was first reported in 1951.[17b]

Our goal was to develop an asymmetric catalytic aziridination that would provide direct access to all four of the stereoisomers of sphinganine (Scheme 2). The plan was to involve a three-component asymmetric aziridination of hexadecanal with a BOROX catalyst for which the (*S*) enantiomer would give the (2*R*,3*R*) enantiomer of aziridine **8g** and the (*R*) enantiomer would give the (2*S*,3*S*) enantiomer of **8g**. Access to all four stereoisomers of sphinganine would result from stereocontrolled opening of each enantiomer of aziridine **8g** with both retention and inversion of configuration.

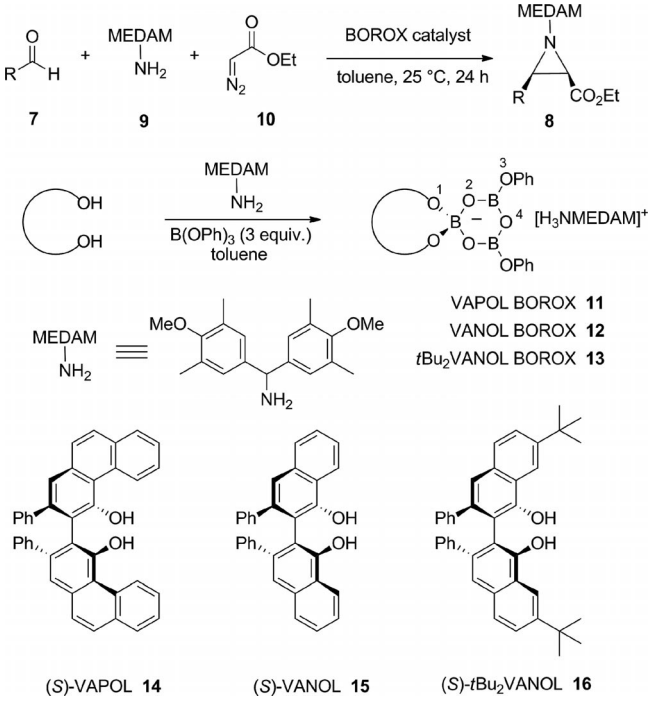
Results and Discussion

Three years ago, we introduced the first three-component catalytic asymmetric aziridination reaction (MCAZ) by bringing together an aldehyde, an amine, and a diazo compound (Scheme 3).[18a] The catalyst for this reaction was a chiral polyborate anion (BOROX catalyst) that was assembled in situ from a vaulted biaryl ligand and $B(OPh)_3$ by the amine substrate.[18b,19] This reaction was only reported with VAPOL–BOROX catalyst **11** for the multicomponent aziridination with MEDAM amine, and the results from a screening of catalysts **12** and **13** derived from VANOL and tBu$_2$VANOL with several aldehydes are presented in Table 1. The reactions in Table 1 were allowed to proceed for 24 h with the catalyst (5 mol-%) to ensure that all of the substrates were fully converted, but many of the substrates were undoubtedly converted in far less time. For example, the reaction of the VAPOL catalyst (5 mol-%) in Entry d of Table 1 was complete in 1 h.[18a] In previous studies on the aziridination of preformed imines, the VANOL catalyst gave essentially the same results as the VAPOL catalyst, but the catalyst derived from tBu$_2$VANOL **16** was found to give improved inductions with preformed benzhydryl imines derived from aliphatic and heteroarenecarbaldehydes.[20a] The results in Table 1 for the VAPOL catalyst are taken from ref.[18a] The data in the table reveal that all three ligands gave very high asymmetric inductions for arenecarbaldehydes and that tBu$_2$VANOL ligand **16** gave higher yields than unsubstituted VANOL ligand **15**.



Scheme 2. Proposed syntheses of all four sphinganines.

The tBu$_2$VANOL ligand gave higher asymmetric induction for aliphatic aldehydes than either VANOL or VAPOL. Note that the reactions of primary aliphatic aldehyde **7g** were performed at –10 °C rather than at 25 °C (Table 1, Entry g). It was previously observed for primary aliphatic aldehydes that the yields are much higher at lower temperatures.[18a] The reaction of aldehyde **7g** was also optimized with regard to temperature, concentration, and catalyst loading (see the Supporting Information). The higher asymmetric inductions with the tBu$_2$VANOL ligand could be useful for nonsolid aziridines, the optical purity of which cannot be enhanced by crystallization.[20b]



Scheme 3. Three-component catalytic asymmetric aziridination.

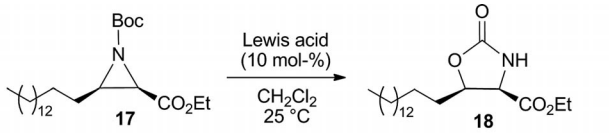
Thus, with ready access to either enantiomer of aziridine **8g** (Table 1), we viewed the biggest challenge to the realization of the proposed synthesis outlined in Scheme 2 as the opening of the aziridine ring with an oxygen nucleophile with retention of configuration.[21] The ring expansion of *N*-*tert*-butoxycarbonyl- (Boc-)aziridines to oxazolidinones has been reported to occur with retention of configuration and would represent a tidy solution to this problem.[22] We approached this with some trepidation, because in our experience the ring expansion of an *N*-Boc-*cis*-aziridine with a phenyl group in the 3-position is not selective and gives mixtures of *cis*- and *trans*-oxazolidinones.[23] The ring expansion of *trans*-aziridines has been reported to proceed with high stereoselectivity with Cu(OTf)$_2$ (Tf = trifluoromethylsulfonyl) as the optimum Lewis acid.[22] Under the same conditions, the ring expansion of *cis*-aziridines was also reported to be stereoselective, although no experimental procedures were given and no yields or data were presented for any *cis* product. In any event, the stage was set to test the ring expansion by removing the MEDAM group in aziridine **8g** with triflic acid in acetonitrile,[24] and the resulting *N*-H-aziridine was treated with Boc anhydride to give *N*-Boc-aziridine **17** in 80% yield. We found that *cis*-aziridine **17** could be ring-expanded to give only *cis*-oxazolidinone **18** in 90% yield, and the optimal Lewis acid was Sc(OTf)$_3$ (Table 2).

Table 1. Comparison of VAPOL, VANOL, and tBu$_2$VANOL BOROX catalysts.[a]

Entry	R	VAPOL[b]		VANOL		tBu$_2$VANOL	
		% yield **8**[c]	% *ee* **8**[d]	% yield **8**[c]	% *ee* **8**[d]	% yield **8**[c]	% *ee* **8**[d]
a	4-$O_2NC_6H_4$	92	99	77	99	100	99
b	4-MeC_6H_4	95	99	87	98	91	99
c	2-MeC_6H_4	96	>99	73	98	97	99
d	C_6H_5	98	98	87	98	100	99
e	4-$MeOC_6H_4$	78	98	82	97	93	99
f	2-pyridyl	96	90	95	96	97	99
g	*n*-pentadecyl[e]	85	96	60	95	97	98
h	cyclohexyl	95	90	94	94	100	96
i	*tert*-butyl	89	94	70	95	100	97

[a] Unless otherwise specified, all reactions were run at 0.5 M in amine in toluene on a 0.5 mmol scale with **10** (1.2 equiv.) and **7** (1.05 equiv.) at 25 °C for 24 h and went to 100% completion with the catalyst (5 mol-%). The catalyst was prepared by stirring a mixture of the ligand (5 mol-%), commercial B(OPh)$_3$ (15 mol-%), and **9** (100 mol-%) in toluene at 80 °C for 0.5 h. This was followed by the addition of 4 Å molecular sieves and **7** and then **10**. (*S*)-VANOL and (*R*)-tBu$_2$VANOL were used. [b] Data taken from ref.[18a] [c] Yield of isolated *cis*-aziridine **8** after silica gel chromatography. [d] Determined by HPLC on a chiral column. [e] Reaction was performed at –10 °C at 0.2 M and with **10** (2.0 equiv.).

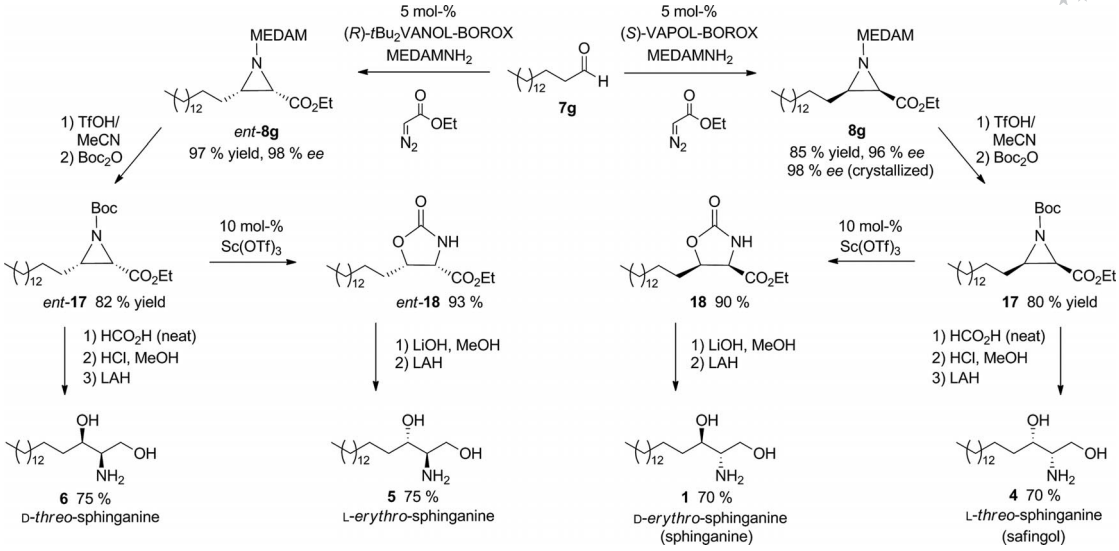
Table 2. Ring expansion of *N*-Boc-aziridine **17** with retention of configuration.



Entry	Lewis acid	Time [h]	% Yield **18**[b]
1	Cu(OTf)$_2$	48	60
2[c]	BF_3·OEt_2	48	n.d.[d]
3	Yb(OTf)$_3$	48	70
4	Sc(OTf)$_3$	30	93 (90)

[a] Unless otherwise specified, all reactions were performed with **17** (0.2 mmol) that was 0.2 M in CH_2Cl_2 with the Lewis acid (10 mol-%). [b] Determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy with Ph_3CH as an internal standard. n.d. = not determined. Yield of isolated product after silica gel chromatography is given in parentheses. [c] Catalyst 50 mol-%. [d] A complex mixture of unidentified products was observed.

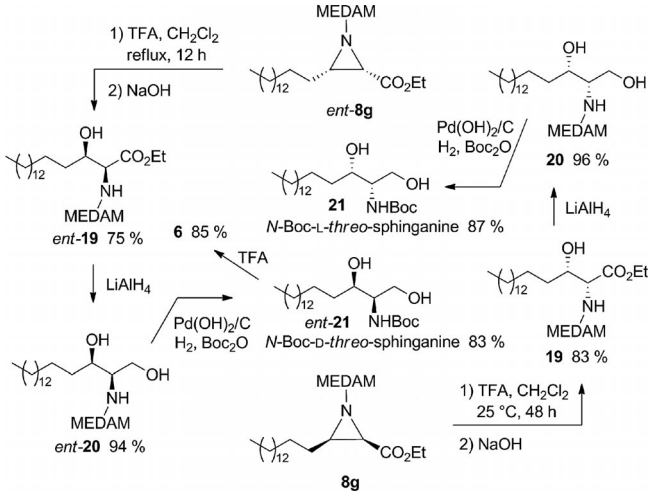
The synthesis of all four stereoisomers of sphinganine is summarized in Scheme 4. Aziridine **8g** is crystalline, and the optical purity could be enhanced to 98% by crystallization (80% recovery). Alternatively, the aziridination could be performed with (*R*)-tBu$_2$VANOL–BOROX catalyst **13** to give *ent*-**8g** in a higher yield (97 vs. 80%) with 98% *ee*. A comparison of the aziridination with preformed imine from aldehyde **7g** was also performed (see the Supporting Information, Section C). The MCAZ protocol was also success-



Scheme 4. Synthesis of all four stereoisomers of sphinganine.

fully performed at the gram scale (5 mmol, 1.5 g) with no effect on the yield (85% on 2.6 g of **8g**) or the *ee* (96%) by using the VAPOL–BOROX catalyst. The ring opening of aziridines with oxygen nucleophiles with inversion of configuration is known and typically requires an electron-withdrawing group on the nitrogen atom.[25] Thus, Boc-aziridine **17** was treated with neat formic acid at room temperature, which resulted in ring opening with formate and subsequent *O*- to *N*-formyl migration. The *N*-formyl group was removed with hydrochloric acid, and finally the ester was reduced to give L-*threo*-sphinganine isomer **4** (safingol) in 70% yield over the three steps. Instead of ring opening with inversion of configuration, *N*-Boc-aziridine **17** can be ring-expanded with retention of configuration with the aid of scandium triflate; this procedure resulted in oxazolidione **18** in 90% yield. From this oxazolidinone, the D-*erythro* isomer of sphinganine (**1**) was prepared in 70% yield by hydrolysis and reduction with lithium aluminum hydride (LAH). Enantiomeric sphinganines D-*threo*-sphinganine **6** and L-*erythro*-sphinganine **5** were prepared in an analogous fashion beginning with aldehyde **7g** and the (*R*)-BOROX catalyst.

Alternatively, the D-*threo* and L-*threo* isomers could be accessed by direct opening of unactivated aziridine **8g** and *ent*-**8g** (Scheme 5). Treatment of **8g** with trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature for 48 h resulted in ring opening with clean inversion of configuration. Hydrolysis of the trifluoroacetyl ester gave amino alcohol **19** in 83% yield. Reduction gave MEDAM-protected amino diol **20** in 96% yield. The MEDAM group in **20** was removed by hydrogenolysis in the presence of Boc anhydride to give *N*-Boc-protected L-*threo*-sphinganine **21** in 87% yield.[26] A similar set of transformations allowed the conversion of aziridine *ent*-**8g** into *N*-Boc-protected D-*threo*-sphinganine *ent*-**21** in four steps in 59% overall yield. The advantage of this route is that the large MEDAM group on the nitrogen atom greatly reduces the polarity of these intermediates, which facilitates purification.



Scheme 5. Alternative route by direct ring opening of unactivated MEDAM aziridines.

Conclusions

The syntheses described in this work represent the first use of a single catalytic asymmetric reaction to prepare all four stereoisomers of sphinganine. The key step is a multicomponent catalytic asymmetric aziridination of hexadecanal with an amine and ethyl diazoacetate. Aziridine **8g** and its enantiomer can be obtained with the proper enantiomer of the BOROX catalyst in 96–98%*ee* depending on the ligand used in the catalyst. The four stereoisomers of sphinganine follow from the ring opening of the each aziridine with an oxygen nucleophile under conditions that proceed selectively with inversion or retention of configuration.

Supporting Information (see footnote on the first page of this article): Procedures and spectroscopic data for all new compounds.

Acknowledgments

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