Asymmetric α-Chloroallylboration of Amino Aldehydes: A Novel and Highly Versatile Route to D- and L-*erythro*-Sphingoid Bases†

Christian Hertweck and Wilhelm Boland*

Max-Planck-Institute for Chemical Ecology, Tatzendpromenade 1a, D-07745 Jena, Germany

Received February 1, 1999

Serinal-derived vinyloxiranes represent versatile building blocks for synthesis of D-(or L-)*erythro*-sphingosine and its analogues. Asymmetric α-chloroallylation of the Garner aldehyde with chiral and achiral γ-(*Z*)-chloroallylboranes, followed by DBU-mediated cyclization of the corresponding chlorohydrins, provides a highly effective route to oxazolidine vinyloxiranes in high yield under mild conditions. Matched and mismatched cases of the double diastereoselective allylation were investigated. The vinyloxirane reacts with a variety of organocuprates by a S_N2' type nucleophilic substitution, yielding protected sphingoid bases as (*E*)-allylic alcohols exclusively. By the new approach, a multitude of different sphingoid core structures becomes available, from a uniform protocol, with high yield and efficiency.

Introduction

The sphingoid bases constitute a large group of structurally diverse, biologically active long chain amino alcohols. D-*erythro*-Sphingosine (**1**, R = R′ = H, *n* = 7), a PK C inhibitor,[1] is the most abundant core structure incorporated into highly complex sphingolipids (**1**, R = carbohydrate, phosphate; R′ = acyl), that have long been known as important constituents of the cell membranes.[2] More recently, the importance of sphingolipid metabolites has been recognized.[3] Sphingosine-1-phosphate (SPP, **1**, R = PO_2OH, R′ = H, *n* = 7) and ceramide (**1**, R = H, R′ = acyl, *n* = 7) play critical roles as secondary messengers in regulatory processes and cell signaling such as apoptosis[4] and cell proliferation and survival.[5] Sphingolipids, as a class, comprise 300−400 individual species with different substitution patterns, but common to all is a sphingoid backbone with a long aliphatic chain and a polar 2-amino-1,3-diol headgroup.[3a] In addition to D-*erythro*-sphingosine, more than 60 other sphingoid base structures were found in nature.[2a,6] Sphingosine analogues may differ in the configuration of the head (D- and L-, *erythro*-/*threo*-), type of tail (truncated, branched, unsaturated), and mode of substitution (methyl, hydroxyl). Marine organisms (algae, tunicata, etc.) provide a particularly rich source of exciting novel structures, often endowed with pharmaceutical activity such as antiviral,[7] antitumor,[8] and antibiotic properties.[9] The most common configuration of the headgroup is D-*erythro*, but the other isomers may also be bioactive, at least to a certain extent.[10] The (*E*)-configuration of the double bond (sphingosine backbone) and the resulting spatial alignment of the molecule are, however, essential for activity.

The biological significance of structural complexity is largely unknown and is thus a fascinating area of research. Since the isolation of distinctive sphingolipids from microheterogeneous mixtures can be very tedious, potent de novo syntheses are needed to provide novel structures and modifications, as tools to study the functions of individual sphingoid bases. To date, more than 50 total syntheses of sphingosine and its analogues have been reported, each of which possesses special advantages and drawbacks.[11] For rapid synthesis, and for screening a structurally diverse library of sphingoid bases, a highly convergent synthetic route is most practical. In this context, S_N2' substitutions such as copper-assisted alkylation of vinyloxiranes with general structure **5** (Scheme 2), employing different nucleophiles,[12] offer a unique approach toward this class of natural products with a minimum of synthetic effort. The configuration of the headgroup is already determined by the vinyloxirane building block and, following introduction

* Corresponding author. Phone: +49 (0)3641-643663. Fax: +49 (0)-3641-643670. E-mail: Boland@ice.mpg.de.

† Dedicated to Prof. K. Sandhoff on the occasion of his 60th birthday.

(1) (a) Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500. (b) Merrill, A. H.; Nimkar, S.; Menaldino, D.; Hannun, Y. A.; Loomis, C.; Bell, R. M.; Tyagi, S. R.; Lambeth, J. D.; Stevens, V. L.; Hunter, R.; Liotta, D. C. *Biochemistry* **1989**, *28*, 3138.

(2) (a) Kanfer, J. N.; Hakomori, S. *Handbook of Lipid Research, Vol. 3 Sphingolipid Biochemistry*; Hanahan, D. J., Ed.; Plenum Press: New York, 1983. (b) Merrill, A. H., Jr.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins and Membranes*; Vance, D. E., Vance, J. E., Eds.; Elsevier Science B. V.: Amsterdam, 1996; p 309.

(3) (a) Bell, R. M.; Hannun, Y. A. Merrill, A. H., Jr. (Eds.) *Advances in Lipid Research: Sphingolipids and their Metabolites*; Academic Press: Orlando, FL, 1993; Vols. 25 & 26. (b) Hannun, Y. A. *Sphingolipid-Mediated Signal Transduction*; Chapman & Hall: New York, 1997. (c) Pyne, S.; Tolan, D. G.; Conway, A. M.; Pyne, N. *Biochem. Soc. Trans.* **1997**, *25*, 549. (d) Igarashi, Y. *J. Biochem.* **1997**, *122*, 1080.

(4) (a)Ariga, T.; Jarvis, W. D.; Yu, R. K. *J. Lipid Res.* **1998**, *39*, 1. (b) Sweeney, E. A.; Sakakura, C.; Shirahama, T.; Masamune, A.; Ohta, H.; Hakomori, S.; Igarashi, Y. *Int. J. Cancer* **1996**, *66*, 358.

(5) Zhang, H.; Desai, N. N.; Olivera, A.; Seki, T.; Brooker, G.; Spiegel, S. *J. Cell Biol.* **1991**, *114*, 155.

(6) Karlsson, K.-A. *Lipids* **1970**, *5*, 878.

(7) For an example of an antiviral sphingosine derivative, isolated from green alga *Ulva fasciata*, see: Garg, H. S.; Sharma, M.; Bhakuni, D. S.; Pramanik B. N.; Bose, A. K. *Tetrahedron Lett.* **1992**, *33*, 1641.

(8) For an example of antitumor cerebrosides (agelaphins) from marine sponge *Agelas mauritianus*, see: Naroti, T.; Morita, M.; Akimoto, K.; Koezuka Y. *Tetrahedron* **1994**, *50*, 2771.

(9) For antibiotic properties of aplidiasphingosine (**4**), isolated from *Aplidium* sp. (tunicate), see: Carter, G. T.; Rinehart, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7441.

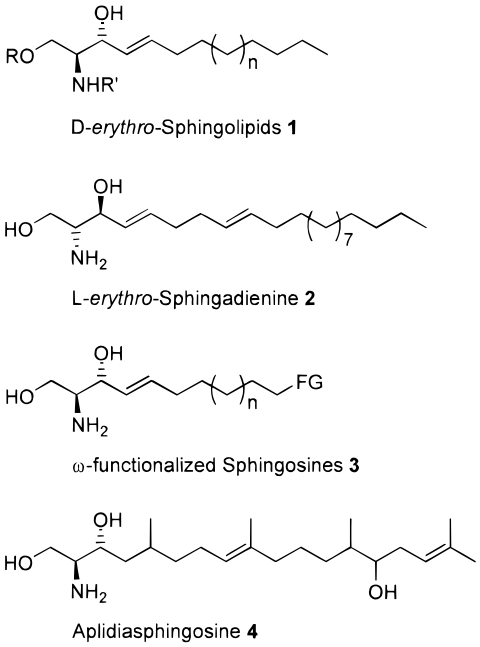
(10) Sachs, C. W.; Ballas, L. M.; Mascarella, S. W.; Safa, A. R.; Lewin, A. H.; Loomis, C.; Carroll, F. I.; Bell, R. M.; Fine, R. L. *Biochem. Pharmacol.* **1996**, *52*, 603.

(11) For a comprehensive review on sphingosine syntheses, see: (a) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075, and references cited herein. (b) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3979−3985. (c) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510.

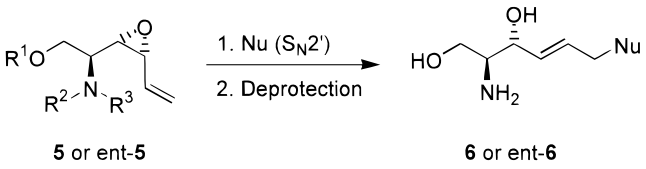
(12) Hertweck, C.; Boland, W. Recent Approaches Using Alkenyloxiranes in Organic Chemistry. In *Recent Research Developments in Organic Chemistry*; Pandalai, S. G., Ed.; Transworld Research Network: 1999, in print.

10.1021/jo990117+ CCC: $18.00
Published on Web 05/20/1999

Scheme 1. D- and L-*Erythro*-Sphingoid Bases



Scheme 2. Synthesis of Sphingoid Bases from Vinyloxiranes



of the nucleophile, no further manipulation of the side chain is required.

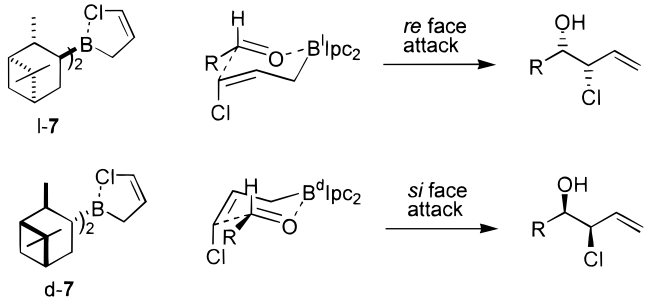
A first example of this approach has recently been published,[13] but while the stereospecificity and yield were high (94%, no (*Z*)-isomer detected), multistep preparation of the vinyloxirane from the chiral pool, utilizing D-glucosamine, proved to be cumbersome. An improved route[13b] still required eight individual transformations, each requiring chromatographic purification. Moreover, since L-glucosamine is not available, L-sphingoid bases,[14] such as **2**, are not accessible by this protocol.

In a previous communication,[15] we introduced serinal-derived vinyloxiranes as readily accessible and versatile building blocks for the stereoselective synthesis of D- and L-*erythro*-sphingosine. Here we extend the scope of the concept and present the double diastereoselective α-chloroallylation of amino aldehyde **8**, with chiral organoboron reagents, as a general synthetic pathway to vinyloxirane *erythro*-**10**, with a view to make structurally diverse sphingoid bases readily available by simple alkylation of *erythro*-**10** with different organocuprates.[12,16]

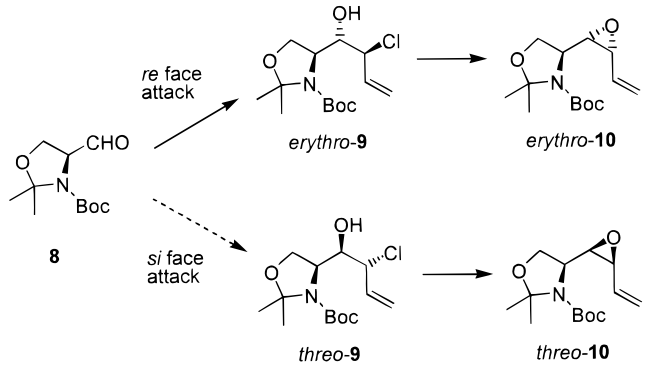
Results and Discussion

Asymmetric α-Chloroallylation. To transform a suitably protected serine aldehyde into the corresponding

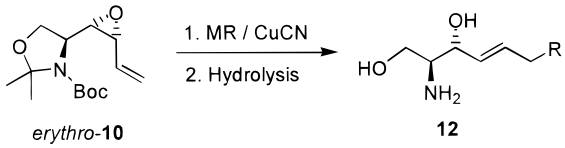
Scheme 3. Asymmetric α-Chloroallylboration



Scheme 4. Asymmetric α-Chloroallylboration of the Garner Aldehyde (Shown for L-Serinal; the D-Enantiomer Reacts Analogously)



Scheme 5. Cross-Coupling of *Erythro*-10 with Organocuprates Prepared in Situ



cis-vinyloxirane *erythro*-**10**, α-chloroallylation of protected serinal **8** and subsequent base-mediated ring closure of the ensuing chlorohydrin is an effective strategy. For this purpose, Oehlschlager and co-workers recently introduced chiral *γ*-(*Z*)-chloroallylboranes,[17] D-**7** and L-**7**, prepared in situ from $^{D}Ipc_2BOMe$ or $^{L}Ipc_2BOMe$,[18,19] allyl chloride, and lithium dicyclohexylamide at −95 °C. With achiral model substrates, *syn*-halohydrins (Scheme 3) and *cis*-vinyloxiranes were obtained with remarkably high diastereoselectivity and enantiomeric excess.[17]

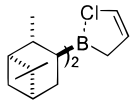
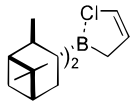
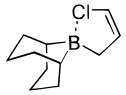
The Garner aldehyde[20] **8** or *ent*-**8** appeared to be an ideal substrate for this transformation, since the protected serinal is configurationally stable and readily available as L- and D-serinal on a multigram scale.[21] Double diastereoselective chloroallylation of **8** with chiral allylation agents such as L-**7** and D-**7** was anticipated to provide, after cyclization, vinyloxiranes *erythro*- and *threo*-**10** (Scheme 4) in high ee and yield. Such compounds are valuable precursors of the *erythro*- and the

(13) (a) Murakami, T.; Hato, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, *8*, 823. (b) Murakami, T.; Shimizu, T. *Synth. Commun.* **1997**, *27*, 4255.
(14) Nakagawa, M.; Tsuruoka, A.; Yoshida, J.; Hino, T. *J. Chem. Soc., Chem. Commun.* **1990**, *8*, 603.
(15) Hertweck, C.; Goerls, H.; Boland, W. *J. Chem. Soc., Chem. Commun.* **1998**, *18*, 1955−1956.
(16) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503, and references cited herein.
(17) (a) Jayaraman, S.; Hu, S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1995**, *36*, 4765. (b) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1996**, *61*, 7513.
(18) Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1.
(19) Hertweck, C.; Boland, W. *J. Prakt. Chem.* **1999**, *341*, 83.
(20) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
(21) (a) Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18. (b) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31. (c) Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527. (d) Meffre, P.; Durand, P.; Branquet, E.; Le Goffic, F. *Synth. Commun.* **1994**, *24*, 2147.

threo-series of sphingoid bases. While *re* facial attack of L-**7** would provide *erythro*-**9**, the diastereoisomeric *threo*-**9** was predicted to form by *si* facial chloroallylation of serinal **8** with D-**7**, providing the course of reaction is reagent controlled. The protected serinal **8** is commercially available or readily prepared from protected L- or D-serine ester by a sequence of reduction and oxidation[21c,d] without the need for chromatographic purification of intermediates.[21b,c] Epimerization of the amino aldehyde has not been observed.[22] To establish the carbon backbone, crude serinal was alkylated with the enantiomeric allylation agents D- and L-**7** under identical conditions. Oxidative workup with buffered H_2O_2,[23] or treatment with 8-hydroxyquinoline,[24] removed the boron auxiliary and provided α-chlorohydrins **9**. According to GC and ^{13}C and ^{1}H NMR analyses, the allylation with L-**7** (matched case) proceeded with extraordinarily high simple diastereoselectivity (*erythro*/*threo* = >97:3) and good yield (72% after cleavage of the borinic ester with 8-hydroxyquinoline, 68% after buffered oxidative workup). Alkylation of **8** with D-**7** (mismatched case) gave only poor yield (37%) and resulted in a low *erythro*/*threo* ratio (62:38). Unlike recently published results on excellent diastereoselectivities in the matched case and moderate to good diastereoselectivity in the mismatched case,[25] the chloroallylation of the Garner aldehyde (**8**) appeared not to be reagent-controlled but largely substrate-controlled.[26] This is corroborated by the alkylation of **8** with achiral γ-chloroallyl-BBN (**11**), which also provided the chlorohydrin *erythro*-**9** with a high degree of diastereoselectivity (*erythro*:*threo* = 95:5). Thus, use of 9-OMe-9-BBN is an inexpensive alternative to the pinene-based borane, provided that formation of *threo*-**10** (5%) and *trans*-**10** (4%) as byproducts is acceptable. However, recrystallization of the crude halohydrins (or epoxides) afforded isomerically pure material in both cases. Stereochemical assignments followed unambiguously from an X-ray crystallographic study of the corresponding epoxide *erythro*-**10** (vide infra).[15]

Cyclization of Halohydrins. For the cyclization of halohydrins,[27] and arylsulfoniumhydrins,[28] to the corresponding labile vinyloxiranes, we recently reported the use of nonnucleophilic, sterically hindered bases such as BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[29] Accordingly, treatment of *erythro*-**9** with DBU in DCM at 0 °C for 8 h afforded the vinyloxirane *erythro*-**10** in high yield (89%) under mild conditions and without isomerization. In addition, the entire allylation/cyclization sequence could be conducted as a "one-pot" synthesis with an overall yield of 48−57% starting from **8**, independent of the type of borane used.

Table 1. Asymmetric α-Chloroallylboration of the Garner Aldehyde (8)

entry	allylation agent	*erythro*/*threo*-**9**	*cis*/*trans* (epoxide)	yield (%)[b]
1	 l-**7**	> 97 : 3 [a]	> 98 : 2 [a]	72
2	 d-**7**	62 : 38	> 98 : 2	37
3	 **11**	95 : 5 [a]	96 : 4 [a]	68

[a] Upon recrystallization only a single isomer could be detected by NMR spectroscopy. [b] Isolated yield.

Recrystallization of *erythro*-**10** at low temperature (−30 °C) from pentane/ether afforded the vinyloxirane as colorless needles. Only a single isomer could be detected by GC and NMR analyses. An X-ray crystallographic study corroborated the stereochemical assignment.[15]

Synthesis of Protected Sphingoid Bases. To demonstrate the synthetic potential and the efficiency of the overall sequence, sphingoid bases of different chain length were synthesized by copper-assisted S_N2'-alkylation of vinyloxirane *erythro*-**10** with carbon nucleophiles (RLi, RMgCl).[16,30] The vinyloxirane *erythro*-**10** was simply added to in situ prepared organocuprates (ether, −78 °C) and slowly allowed to come to room temperature. The cuprates were obtained by adding an organolithium (e.g. ^{n}BuLi) to a suspension of CuCN in ether (Table 2, entry 1) or, alternatively, by adding CuCN to a solution of an organolithium previously prepared in situ by halogen/lithium exchange in ether at −100 °C (entry 2).[31] In the case of the Grignard reagent (entry 3), addition of only a catalytic amount of CuCN (10 mol %) achieved a complete S_N2' attack of the nucleophile, at the expense of S_N2 substitution. Thus, in all cases, introduction of the alkyl side chain via organocuprates occurred in a strict S_N2' fashion and proceeded with exclusive formation of the (*E*)-double bond, according to ^{13}C and ^{1}H NMR data ($^{3}J_{HH\,trans}$ = 16 Hz).[32] Yields were generally high (82−92%) and the transformations were essentially free from side reactions. Treatment of the oxazolidines **14**[33] and **15**[34] with 1 M HCl/THF[35] or TFA/water[34] is known to generate the native C_{18}- and C_{20}-D-*erythro*-sphingosines **12** (R =

(22) For mild oxidation of serinol using the Dess−Martin-reagent see: Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Synthesis* **1997**, 1146.

(23) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Malecha, J. W.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1240.

(24) Brown, H. C.; Racherla, U. S.; Liao, Y.; Khanna, V. V. *J. Org. Chem.* **1992**, *57*, 6608.

(25) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1998**, *63*, 8843.

(26) For other examples of substrate control in pinene based allylborations, see: (a) Burgess, K.; Henderson, I. *Tetrahedron Lett.* **1990**, *31*, 6949. (b) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243. (c) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P. Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677.

(27) Hertweck, C.; Boland, W. *Tetrahedron* **1997**, *53*, 14651.

(28) Hertweck, C.; Boland, W. *Eur. J. Org. Chem.* **1998**, *2143*, 3.

(29) Schwesinger, R. *Nachr. Chem. Technol. Lab.* **1990**, *38*, 1214.

(30) Marshall, J. A.; Crute, T. D., III; Hai, J. D. *J. Org. Chem.* **1992**, *57*, 115.

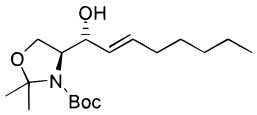
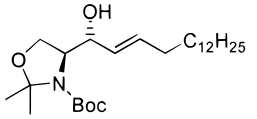
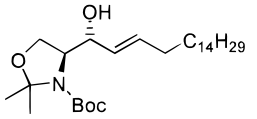
(31) Bailey, W. F.; Ovaska, T. V.; Leipert, T. K. *Tetrahedron Lett.* **1989**, *30*, 3901.

(32) For the influence of steric factors on cuprate additions see: (a) Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. J. *J. Org. Chem.* **1988**, *53*, 4274. For the influence of solvents see: (b) Schlecht, M. F. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1331. For electronic factors affecting (*E*)-stereospecificity and theoretical background of cuprate addition, see: (c) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063. (d) Hamon, L.; Levisalles, J. *Tetrahedron* **1989**, *45*, 489.

(33) Radunz, H.-E.;Devant, R. M.; Eiermann, V. *Liebigs Ann. Chem.* **1988**, 1103.

(34) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439.

Table 2. Crosscoupling of *erythro*-10 with Organocuprates Prepared in Situ

entry	reagent	Product	*E*/*Z*[a]	yield (%)[b]
1	*n*-BuLi/ CuCN	 **13**	> 99/1	92
2	$C_{12}H_{25}Br$/ *t*-BuLi/CuCN	 **14**	> 99/1	82
3	$C_{14}H_{29}MgCl$/ cat. CuCN	 **15**	> 99/1	91

[a] *E*/*Z* ratio determined by NMR of the crude reaction mixture. [b] Isolated yield.

$C_{12}H_{25}$, $C_{14}H_{29}$) in high yield. The truncated C_{12}-D-*erythro*-sphingosine **12** (R = C_4H_9), available from **13** by mild acid hydrolysis, has been previously incorporated into a water-soluble, short-chain sphingomyelin analogue to approach the catalytic mechanism of the sphingomyelinase.[36]

Summary. α-Chloroallylation of protected serinal **8**, mediated by organoboron reagents L-**7** and **11**, leads to enantiopure (crystalline) vinyloxiranes, which serve as highly versatile building blocks for the synthesis of sphingoid bases. The substrate aldehydes are readily available from L- and D-serine esters without tedious isolation of intermediates and, thus, provide a straightforward access to the D- and L-*erythro* series of sphingosines without serious constraints concerning the nature of the long chain aliphatic backbone. The introduction of ω-functionalized side chains[37] has been already demonstrated via transmetalation of organozinc precursors,[38] but has not yet been optimized. The introduction of isotopes at a late stage of synthesis is feasible and will be reported soon. Due to the multitude of catalytic and stoichiometric reactions possible with vinyloxiranes, serine and other amino acid derived vinyloxiranes may also employed as valuable precursors to azasugars and alkaloids.[39]

Experimental Section

General. All reactions were carried out under argon in flame-dried glassware using standard gastight syringes, cannulas, and septa. Solvents and reagents were dried prior to use.[17,25] Chemical shifts of ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) are given in ppm (δ) downfield relative to TMS as internal standard. Thin-layer chromatography was performed with silica gel plates. Column chromatographic separations were performed with silica gel (Merck) and Florisil (>200 mesh, Aldrich). ^{D}Ipc$_2$BOMe, ^{L}Ipc$_2$BOMe, and B-MeO-9BBN were purchased from Aldrich Co. Garner aldehyde (**8**) was prepared according to literature procedures.[21b,c]

(1*S*,2*S*,4*S*)-4-(2-Chloro-1-hydroxy-but-3-enyl)-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (*erythro*-9). A stirred solution of allyl chloride (0.49 mL, 6.0 mmol) and ^{l}Ipc$_2$BOMe (1.42 g, 4.5 mmol) in ether (20.0 mL) was gradually treated, at −95 °C, with a solution of LiN(^{c}Hex)$_2$ [prepared in THF (10.0 mL) from dicyclohexylamine (1.2 mL, 6.0 mmol) by deprotonation with ^{n}BuLi (3.75 mL, 1.6 M solution in hexane, 6.0 mmol) and stirring at 0 °C for 0.5 h]. The mixture was stirred at −95 °C for 1 h, and BF_3·OEt_2 (1.26 mL, 10.0 mmol) was added slowly. The organoboron reagent was stirred for 30 min more at −95 °C followed by slow addition of a solution of Garner aldehyde (**8**) (916 mg, 4.0 mmol). Stirring was continued for 6 h at −95 °C. After reaching rt, the organonboron reagent was removed either by complexation or oxidation as follows.

(i) 8-Hydroxyquinoline Workup.[24] Following removal of the solvents in vacuo at room temperature, the crude residue was treated with dry pentane (40 mL), filtered through a small pad of Celite under argon, and rinsed with dry pentane (2 × 30.0 mL). The combined filtrates were evaporated in vacuo at room temperature. The residual semisolid was dissolved in chilled ether (30.0 mL), and a solution of 8-hydroxyquinoline (2.3 g, 16.0 mmol) in ether (30.0 mL) was added slowly with concomitant formation of a strongly fluorescent suspension. Stirring was continued for 8 h at 0 °C, the precipitate was filtered off and the organic layer was extracted with water to remove inorganic and polar compounds. After drying (Na_2SO_4), the solvent was evaporated in vacuo at room temperature. Flash chromatography of the crude oil on silica using pentane/ether (v:v = 2:1) for elution afforded the chlorohydrin *erythro*-**9** as a colorless, viscous oil, which crystallized from pentane/ether (v:v = 3:1) at −40 °C. Yield, 1.32 g (72%); $[\alpha]^{23}_D = -57.5$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 330 K) δ 1.41 (s, 3H), 1.43 (s, 9H), 1.47 (s, 3H), 3.82 (dd, *J* = 7.0, 8.8 Hz, 1H), 3.87−3.96 (m, 2H), 4.08 (dd, *J* = 2.5, 8.8 Hz, 1H), 4.44 (dd, *J* = 5.0, 8.9 Hz, 1H), 5.19 (d, *J* = 10.1 Hz, 1H), 5.32 (d, *J* = 15.8 Hz, 1H), 5.96 (ddd, *J* = 8.9, 10.1, 15.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 330 K) δ 24.1, 26.3, 28.1 (3C), 58.9, 62.5, 66.1, 72.3, 79.3, 93.2, 117.9, 136.3, 151.5; IR (KBr, film) ν 3430 (br), 3091, 3005, 2922, 1687, 1409, 1315, 1261, 1115, 1097, 902, 791, 604 cm^{-1}; MS 70 eV; *m*/*z* (% rel int)] 250 ($M^{+\bullet}$ − 55, 6), 232 (2), 214 (36), 198 (39), 154 (8), 144 (11), 100 (31), 95 (5), 84 (57), 69 (13), 57 (100), 56 (51). Anal. Calcd for $C_{14}H_{24}ClNO_4$: C, 54.99; H, 7.91; N, 4.58. Found: C, 55.14; H, 7.93; N, 4.44.

(ii) Oxidative Workup.[23] The reaction mixture was allowed to come to −40 °C, treated with methanol (9.0 mL), saturated aqueous $NaHCO_3$ (4.5 mL), $NaHCO_3$ (1.8 g), and H_2O_2 (18 mL), and then stirred at room temperature for 12 h. The mixture was cooled to 0 °C and 10% aqueous NaS_2O_3 (15 mL) was added slowly. After stirring for 15 min at room temperature, the organic phase was separated and the aqueous layer extracted with ether (3 × 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (20 mL), dried over Na_2SO_4, and concentrated in vacuo.

(1*S*,2*R*,4*S*)-2,2-Dimethyl-4-(3-vinyloxiranyl)oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (*erythro*-10). A well-stirred and chilled solution of *erythro*-**9** (917 mg, 3 mmol) in dichloromethane (40 mL) was gradually treated with a solution of DBU (2.28 g, 15 mmol) in dichloromethane (25 mL). Stirring was continued for 8 h at 0 °C until TLC showed quantitative conversion of the halohydrin. Then, the mixture was poured into 10% $NaHCO_3$ solution (20 mL), the organic layer separated, and the aqueous phase extracted with ether (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on Florisil using a pentane/ether gradient for elution to yield a colorless oil. When crystallized from pentane/ether (v:v = 1:1) at −40 °C, colorless, low-melting needles (mp 49−50.5 °C) were obtained. Yield, 718

(35) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395.
(36) Murakami, M.; Iwama, S.; Fujii, S.; Ikeda, K.; Katsumara, S.; *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1725.
(37) Use of a ω-functionalized sphingoid base for affinity chromatography has been reported: Kozikowski, A. P.; Ding, Q.; Spiegel, S. *Tetrahedron Lett.* **1996**, *37*, 3279.
(38) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
(39) Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988.

mg (89%); $[\alpha]^{25}_D = +40.37$ (*c* 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 330 K) δ 1.46 (s, 9 H), 1.50 (s, 3H), 1.55 (s, 3H), 3.12 (m, 1H), 3.58 (m, 1H), 3.69 (m, 1H), 3.93 (m, 2H), 5.34 (d, $J = 10.7$ Hz), 5.43 (d, $J = 17$ Hz, 1H), 5.84 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 330 K) δ 23.9, 27.6, 28.1 (3C), 53.0, 57.6, 59.2, 65.7, 79.6, 93.8, 120.2, 132.7, 151.4; IR (KBr, film) ν 3094, 2987, 2936, 1698, 1388, 1365, 1254, 1102, 1058, 770 cm^{-1}; MS 70 eV; *m*/*z* (% rel int)] 270 ($M^{+\bullet} + 1$, 1), 214 (13), 200 (6), 170 (5), 154 (18), 144 (8), 138 (7), 100 (30), 83 (12), 67 (7), 57 (100), 56 (13). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.64; H, 8.53; N, 5.15.

(1*R*,4*S*)-4-(1-Hydroxyoct-2-enyl)-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester; *O*,*N*-Isopropylidene-*N*-(*tert*-butoxycarbonyl)-C$_{10}$-D-*erythro*-sphingosine (13).[40] *n*-Butyllithium (0.63 mL, 1.6 M solution in hexanes, 1 mmol) was added slowly to a cooled (−78 °C) suspension of CuCN (89 mg, 1 mmol) in ether (20 mL). The mixture was allowed to come slowly to −30 °C and a dark green suspension resulted within 2 h of further stirring. After recooling to −78 °C, vinyloxirane *erythro*-**10** (80 mg, 0.3 mmol) in ether (1.0 mL) was added dropwise and the reaction mixture was warmed to 0 °C over 2 h. After stirring at 0 °C for 6 h, saturated aqueous NH_4Cl (5.0 mL) was added and the aqueous phase extracted with ether (4 × 20 mL). The combined organic phases were dried (Na_2SO_4) and, after removal of the solvent in vacuo, the residue was purified by chromatography on silica with using pentane/ether (v:v = 2:1) for elution. Yield, 90.0 mg (92%); colorless, waxy solid; $[\alpha]^{22}_D = -5.2$ (*c* 0.27, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6, 330 K) δ 0.73 (t, $J = 6$ Hz, 3H), 1.03 (s, 3H), 1.06 (s, 3H), 1.08 (s, 9H), 1.16−1.49 (m, 6H), 1.97 (m, 2H), 3.63 (m, 1H), 3.79 (m, 2H), 4.30 (m, 1H), 5.52 (dd, $J =$ 16, 5 Hz, 1H), 5.74 (dt, $J = 16$, 7 Hz, 1H); ^{13}C NMR (500 MHz, C_6D_6, 330 K) δ 15.4, 22.8, 26.7, 27.9, 28.4(3C), 29.3, 31.8, 32.7, 65.8, 71.4, 73.8, 80.1, 94.6, 130.1, 132.6, 154.4; IR (KBr, film) ν 3382 (br), 2959, 2926, 2874, 1701, 1677, 1455, 1385, 1366, 1296, 1257, 1207, 1174, 1005, 967, 848 cm^{-1}; MS 70 eV; *m*/*z* (% rel int)] 327 ($M^{+\bullet}$, 1), 254 (43), 228 (35), 170 (6), 144 (14), 100 (74), 83 (18), 57 (100), 41 (57); HRMS for $C_{18}H_{33}NO_4$ calcd 327.2409, obsd 327.2413.

(1*R*,4*S*)-4-(1-Hydroxyhexadec-2-enyl)-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester; *O*,*N*-Isopropylidene-*N*-(*tert*-butoxycarbonyl)-C$_{18}$-D-*erythro*-sphingosine (14).[33,35] A cold solution (−100 °C) of dodecyl bromide (217.0 mg, 0.87 mmol) in ether (10 mL) was gradually treated with ^{t}BuLi (1.0 mL, 1.74 mmol, 1.7 M in pentane) within 10 min. After stirring for 2 h at −100 °C, the solution was briefly warmed to −20 °C (3 min) and recooled to −78 °C, and CuCN (78 mg, 0.87 mmol) was added. The mixture was slowly warmed to −40 °C, stirred at −40 °C for 1.5 h, and cooled to −78 °C after formation of a dark green suspension. Then, vinyloxirane *erythro*-**10** (79.0 mg, 0.29 mmol) in ether (2.0 mL) was added and the mixture was stirred for 30 min at −78 °C, warmed to −40 °C, and stirred at −40 °C for 2 h and at 0 °C for 4 h. After addition of saturated aqueous NH_4Cl (10 mL), the aqueous phase was extracted with ether (4 × 20 mL), and the combined organic phases were dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica using pentane/ether (v:v = 2:1) for elution. Yield, 104 mg (82%); colorless, waxy solid; $[\alpha]^{23}_D = +14.1$ (*c* 0.27, $CHCl_3$). Spectroscopic data were fully consistent with those reported.[33,35]

(1*R*,4*S*)-4-(1-Hydroxyoctadec-2-enyl)-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester; *O*,*N*-Isopropylidene-*N*-(*tert*-butoxycarbonyl)-C$_{20}$-D-*erythro*-sphingosine (15).[34] A solution of tetradecylmagnesium bromide (0.26 mmol, 0.26 mL, 1.0 M solution in ether) was slowly added to a cold (−78 °C) suspension of CuCN (13 mg, 0.013 mmol) in THF (5.0 mL) and vinyloxirane *erythro*-**10** (35 mg, 0.13 mmol). The mixture was stirred for 10 min at −78 °C and the temperature slowly raised over 2 h to −30 °C. Stirring was continued at −30 °C for 2 h, and the solution was slowly warmed to 0 °C and hydrolyzed with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether (4 × 20 mL), and the combined organic phases were dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was purified by flash chromatography silica using pentane/ether (v:v = 2:1) for elution. Yield, 55 mg (91%); $[\alpha]^{23}_D = +13.6$ (*c* 0.47, $CHCl_3$); colorless, waxy solid. Spectroscopic data are fully consistent with those reported.[34]

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft, Bonn, Germany, and the Fonds der Chemischen Industrie, Frankfurt, Germany, is gratefully acknowledged. We thank the BASF AG, Ludwigshafen, Germany, and the Bayer AG, Leverkusen, Germany, for generous supply of chemicals and solvents.

JO990117+

(40) Suzuki, K.; Hasegawa, T.; Imai, T.; Maeta, H.; Ohba, S. *Tetrahedron* **1995**, *51*, 4483.