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Chemoenzymatic Synthesis of All Four Stereoisomers of Sphingosine from Chlorobenzene: Glycosphingolipid Precursors[1a]

Thomas C. Nugent[†] and Tomas Hudlicky*

Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

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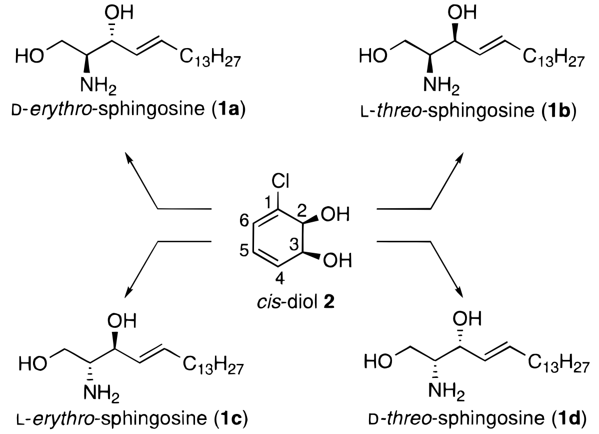
Advantageous use of homochiral cyclohexadiene-*cis*-1,2-diol **2**, available by means of biocatalytic oxidation of chlorobenzene with toluene dioxygenase, has enabled the synthesis of all four enantiomerically pure C_{18}-sphingosines **1**. The four requisite diastereomers of azido alcohols **4a**−**d** were accessed by regioselective opening of epoxides **7** and **8** with either azide or halide ions. The configuration of C4 and C5 in azides **4** defines the stereochemistry of the incipient sphingosine chain, liberated from **4** by the oxidative cleavage of the C1−C6 olefin. For L-*threo*-sphingosine (**1b**), lactol **20b** generated by this cleavage was converted by periodate oxidation to azido deoxy L-threose **22b**, which gave **1b** upon Wittig olefination and reduction. Similarly, D-*erythro*-sphingosine (**1a**) and L-*erythro*-sphingosine (**1c**) were generated from **4a**,**c**, respectively. The last sphingosine (**1d**) was synthesized from the silyl-protected azido alcohol **29d**. Subsequent transformations provided silyl-protected azido deoxy D-threose **32d**, which upon Wittig olefination and reduction gave D-*threo*-sphingosine (**1d**). Experimental and spectral data are provided for all new compounds.

Introduction

Sphingosines constitute a group of related long-chain aliphatic 2-amino-1,3-diols, of which 2-amino-D-*erythro*-4(*E*)-octadecene-1,3-diol (**1a**) (Chart 1) occurs most frequently in animal glycosphingolipids.[2] Sphingosines are known inhibitors of protein kinase C and are the backbone of glycosphingolipids. This larger family of biomolecules is involved in a plethora of processes related to cell growth, differentiation, adhesion, and neuronal repair.[3] Glycosphingolipids contain two basic structural motifs: carbohydrate and ceramide. The ceramide portion consists of a sphingoid base and an amide-linked fatty acyl chain, e.g., stearoyl (Chart 2) or palmitoyl. The structural variation in fatty acids (*N*-acyl portion), sphingosines, and carbohydrates results in a great variety of chemically distinct glycosphingolipids.[2]

Glycosphingolipids are found in the cell membrane of all animal and many plant cells, where they serve as identifying markers and regulate cellular recognition, growth, and development.[4a] They are thought to function by anchoring the hydrophobic ceramide portion (Chart 2) in the plasma membrane, exposing the hydrophilic carbohydrate portion to the surrounding exterior which specifies the intended biological function.[4b] Among their biological functions are (1) HIV binding to galactosyl ceramide receptor sites in cells lacking the principal CD4 cellular receptor,[5] (2) an unambiguous link between specific sphingolipids and malignant tumors which enables them to be used as 'biological markers' for possible early detection of cancer,[4a] and (3) potent and reversible inhibition of protein kinase C[6] by breakdown products of glycosphingolipids, e.g., sphingosine, sphinganine, and lysosphingolipids (Chart 2). The latter is particularly significant because protein kinase C mediates cellular responses for tumor promoters, hormones, and growth factors.[7] The ongoing recognition of glycosphingolipids as fundamental mediators of cellular interactions continues to sustain research in this field.

Chart 1. Four Stereoisomers of C_{18}-Sphingosine Synthesized from Arene-*cis*-diol 2



[†] Current address: Department of Chemistry, University of Arizona, Tucson, AZ 85721.

(1) Preliminary results of this work have been published; see: (a) Hudlicky, T.; Nugent, T. C.; Griffith, W. *J. Org. Chem.* **1994**, *59*, 7944. (b) Banwell, M. G.; Haddad, N.; Hudlicky, T.; Nugent, T. C.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1779.

(2) Hakomori, S. Sphingolipid Biochemistry. In *Handbook of Lipid Research*; Kanfer, J. N., Hakomori, S., Eds.; Plenum: New York, 1983; Vol. 3, p 1.

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(6) Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500.

(7) 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.

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Chart 2. Generic Structure of a Glycosphingolipid

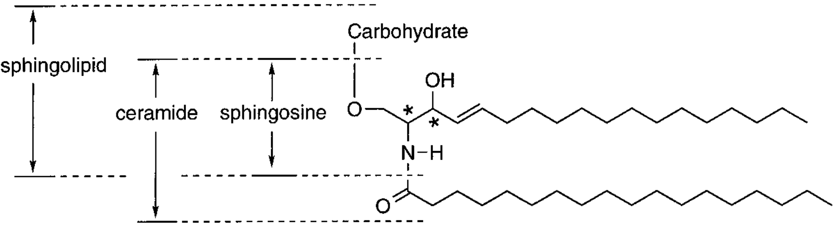
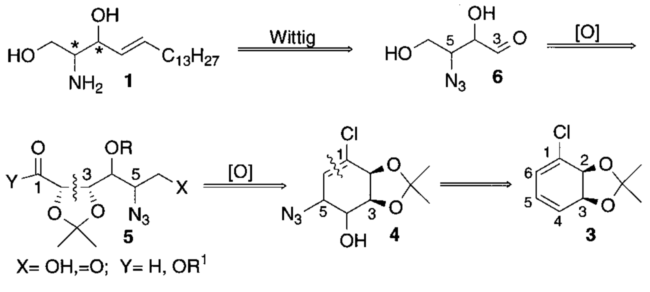


Chart 3. Retrosynthetic Analysis of Sphingosine



Of the four sphingosines, only one (D-*erythro*-sphingosine) is commercially available. We therefore envisioned a general synthetic plan that would rely on the functionalization of *cis*-diol **2** (Chart 1) at C4–C5 in such a way as to define the two chiral centers in sphingosines for all four stereoisomers. The introduction of azide and hydroxyl functionalities at C4–C5 of acetonide **3** would lead to azido alcohols **4**. Subsequently, the C1–C6 olefin of **4** would be oxidatively cleaved to **5**, followed by further oxidative cleavage of the C2–C3 diol to liberate the key synthon, azido deoxy threose or erythrose, **6** (Chart 3). In this fashion, the two stereocenters in sphingosines could be independently set prior to the double oxidative cleavage that provides the terminal alcohol as well as the aldehyde functionality required for the Wittig chain extension. In this article we report the synthesis of all four isomers by this strategy.

Results and Discussion

Many syntheses of enantiomerically pure sphingosines have relied on the use of carbohydrates or L-serine as chiral building blocks. The first such application was reported by Reist[8a] in 1970 using 3-amino-3-deoxy-1,2:5,6-diisopropylidene-α-D-allofuranose, which was followed 3 years later by Newman's[9a] synthesis of sphingosine from L-serine. Since then exhaustive studies on the use of L-serine derivatives and carbohydrates have culminated in highly efficient and diastereoselective syntheses of D-*erythro*-sphingosine (**1a**), the naturally occurring stereoisomer, and L-*threo*-sphingosine (**1b**). The most noteworthy to date is Polt's[9h] synthesis of L-*threo*-sphingosine[10] in five steps and in 60% overall yield from L-serine.

A survey of the remaining sphingosine literature[1a,11] reveals some of the more novel and efficient syntheses of D-*erythro*-sphingosine (**1a**), as well as the first synthesis by Shapiro and Segal in 1954.[11a,b] In 1983 Vasella employed the Katsuki–Sharpless asymmetric epoxidation to set the chirality of an enynol which ultimately led to a six-step synthesis of D-*erythro*-sphingosine (**1a**) in 50% overall yield.[11c,d] Among the other syntheses

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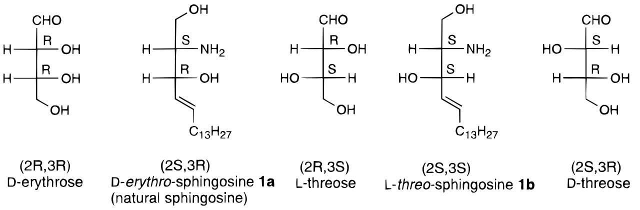
[8] Syntheses of sphingosine from carbohydrates: (a) Reist, E. J.; Christie, P. H. *J. Org. Chem.* **1970**, *35*, 4127. (b) Obayashi, M.; Schlosser, M. *Chem. Lett.* **1985**, 1715. (c) Schmidt, R. R.; Zimmermann, P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 725. (d) Schmidt, R. R.; Zimmermann, P. *Tetrahedron Lett.* **1986**, *27*, 481. (e) Kiso, M.; Nakamura, A.; Tomita, Y.; Hasegawa, A. *Carbohydr. Res.* **1986**, *158*, 101. (f) Kiso, M.; Nakamura, A.; Nakamura, J.; Tomita, Y.; Hasegawa, A. *J. Carbohydr. Chem.* **1986**, *5* (2), 335. (g) Koike, K.; Numata, M.; Sugimoto, M.; Nakahara, Y.; Ogawa, T. *Carbohydr. Chem.* **1986**, *158*, 113. (h) Zimmermann, P.; Schmidt, R. R. *Liebigs Ann. Chem.* **1988**, 663. (i) Sugawara, T.; Norisada, M. *Carbohydr. Res.* **1989**, *194*, 125. (j) Yadav, J. S.; Vidyanand, D.; Rajagopal, D. *Tetrahedron Lett.* **1993**, *34*, 1191. (k) Murakami, T.; Minamikawa, H.; Hato, M. *Tetrahedron Lett.* **1994**, *35*, 745. (l) Schmidt, R. R.; Wild, B. *Tetrahedron: Asymmetry* **1994**, *5*, 2195. (m) Li, Y. L.; Sun, X. L.; Wu, Y. L. *Tetrahedron* **1994**, *50*, 10727. (n) Schmidt, R. R.; Bär, T.; Wild, B. *Synthesis* **1995**, 869. (o) Murakami, T.; Hato, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 823. (p) Shinozaki, K.; Mizuno, K.; Masaki, Y. *Chem. Pharm. Bull.* **1996**, *44*, 927. (q) Synthesis from D-isoascorbic acid: Tuch, A.; Sanière, M.; Merrer, Y. L.; Depezay, J. C. *Tetrahedron: Asymmetry* **1996**, *7*, 897.

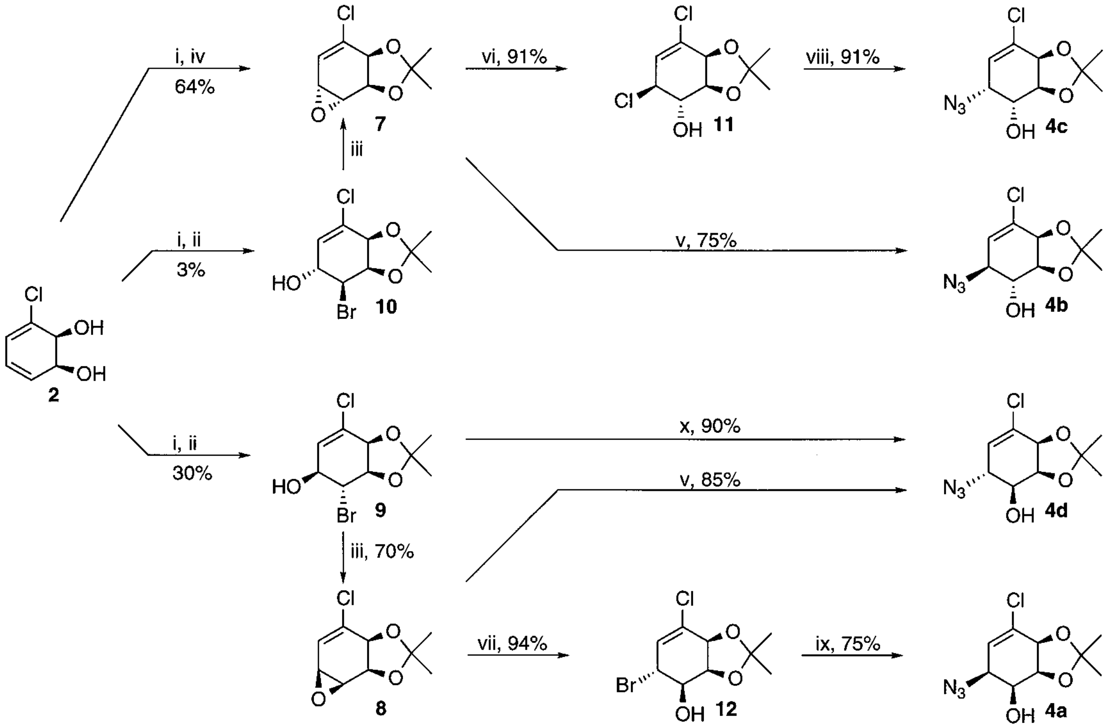
[9] Syntheses of sphingosine from L-serine: (a) Newman, H. *J. Am. Chem. Soc.* **1973**, *95*, 4098. (b) Tkaczuk, P.; Thornton, E. R. *J. Org. Chem.* **1981**, *46*, 4393. (c) Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5320. (d) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354. (e) Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037. (f) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395. (g) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439. (h) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469.

[10] Whereas all organic chemists seem to agree that D-*erythro*- and L-*erythro*-sphingosine have structures **1a**,**c**, respectively (Chart 1), the naming of the *threo* enantiomers lacks consistency. In general, carbohydrate chemists have adopted L-*threo*-sphingosine as **1b**, while non-carbohydrate chemists tend to refer to it as D-*threo*-sphingosine. For the reasons outlined below, we believe the L-*threo* assignment of **1b** is correct and that the D-*threo* descriptor should be discontinued for the assignment of sphingosine **1b**. The assignment of natural sphingosine (**1a**) is based on a Fischer projection in which the primary alcohol of **1a** is placed at the top of the projection.[9a] Once this reference point has been established, comparison of the Fischer projections of D-erythrose and sphingosine clearly shows their analogous spatial arrangement. This fact alone determines whether two vicinal chiral centers are described as *erythro* or *threo*, **not** their stereochemical *R* or *S* assignment; i.e., D-erythrose has the 2*R*,3*R* configuration, and D-*erythro*-sphingosine (**1a**) has the 2*S*,3*R* configuration, but it is irrelevant. When sphingosine **1b** is depicted in a Fischer projection, it resembles L-threose and not D-threose.



[11] Miscellaneous approaches to sphingosines: (a) Shapiro, D.; Segal, K. H. *J. Am. Chem. Soc.* **1954**, *76*, 5894. (b) Shapirio, D.; Segal, K. H.; Flowers, H. M. *J. Am. Chem. Soc.* **1958**, *80*, 1194. (c) Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491. (d) Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1985**, *69*, 368. (e) Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1986**, *42*, 917. (f) Findeis, M. A.; Whitesides, G. M. *J. Org. Chem.* **1987**, *52*, 2838. (g) Nicolaou, K. C.; Caufield, T.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910. (h) Shibuya, H.; Kawashima, K.; Ikeda, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 7205. (i) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1991**, 820. (j) Somfai, P.; Olsson, R. *Tetrahedron* **1993**, *49*, 6645. (k) Solladié-Cavallo, A.; Koessler, J. L. *J. Org. Chem.* **1994**, *59*, 3240. (l) Enders, D.; Whitehouse, D. L.; Runsink, J. *Chem. Eur. J.* **1995**, *1*, 382. (m) Davis, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 4349 and references cited therein.

Scheme 1[a]



[a] Reagents and conditions: (i) 2,2-dimethoxypropane, cat. *p*-TsOH, CH_2Cl_2; (ii) NBS, DME/H_2O (3:2), 0 °C; (iii) NaOH (1.1 equiv), Bu_4HNSO_4 (1.0 equiv), CH_2Cl_2 reflux; (iv) *m*-CPBA, CH_2Cl_2; (v) NaN_3, NH_4Cl, DME/EtOH/H_2O (3:3:2), 65 °C; (vi) LiCl (5.0 equiv), ethyl acetoacetate (3.0 equiv), THF, 45 °C; (vii) LiBr (1.1 equiv), ethyl acetoacetate (2.0 equiv), THF, 35 °C; (viii) NaN_3 (3.0 equiv), DMF; (ix) NaN_3 (15 equiv), DMSO; (x) NaN_3 (3.0 equiv), DMSO, 70 °C.

those by Nicolaou[11g] and Solladié[11k] are noteworthy for their brevity and elegance.

In recent years the use of enantiomerically pure cyclohexadiene-*cis*-1,2-diols in the total synthesis of carbohydrates, cyclitols, and oxygenated alkaloids has increased dramatically.[12,13] To further demonstrate the general utility of these dienediols, obtained by enzymatic oxidation of chlorobenzene with toluene dioxygenase from the whole cells of *Pseudomonas putida* 39D,[14] we envisioned the synthesis of all four stereoisomers of sphingosine from **3** (Chart 3). The two stereocenters of the title compounds would be established early, by means of a cyclic rather than acyclic intermediate, when a high degree of regio- and stereochemical control would still be possible.

Chemo- and Stereoselective Functionalization of the C4-C5 Olefin. *cis*-Diol **2** was protected as its acetonide **3**[15] and converted to epoxide **7**[12j] or **8**[1a] as desired (Scheme 1). Conversely exposure of **3** to *N*-bromosuccinimide (NBS), in the presence of H_2O, led predominantly to bromohydrin **9** in 30% yield. The minor diastereoisomer **10** was produced in 3% yield. The regiochemistry of bromohydrins **9** and **10** was confirmed by ^1H NMR irradiation studies and their stereochemistry by conversion to epoxides **8** and **7**, respectively.

trans-Azido alcohols **4b**,[1b] **d**[1a] were directly accessible, in high yield, from epoxides **7** and **8**, respectively, upon exposure to NaN_3 (Scheme 1). The synthesis of the two

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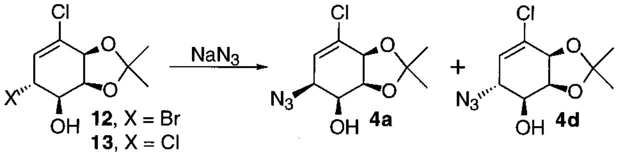
(12) For recent examples of arenediols in synthesis, see: (a) Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem.* **1989**, *54*, 4239. (b) Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683. (c) Downing, W.; Latouche, R.; Pitoll, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2613. (d) Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W. *Synlett* **1991**, 741. (e) Boyd, D. R.; Dority, M. R. J.; Hand, M. V.; Malone, J. F.; Sharma, N. D.; Dalton, H.; Gray, D. J.; Sheldrake, G. N. *J. Am. Chem. Soc.* **1991**, *113*, 666. (f) Carless, H. A. J. *Tetrahedron Lett.* **1992**, 6379. (g) Banwell, M. G.; Corbett, M.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1. (h) Hudlicky, T.; Mandel, M.; Kwart, L. D.; Whited, G. M. *J. Org. Chem.* **1993**, *58*, 2331. (i) Hudlicky, T.; Rouden, J.; Luna, H. *J. Org. Chem.* **1993**, *58*, 985. (j) Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc.* **1994**, *116*, 5099. (k) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752. (l) Gonzalez, D.; Schapiro, V.; Seoane, G.; Hudlicky, T. *Tetrahedron: Asymmetry* **1997**, *8*, 975.

(13) For comprehensive reviews of cyclohexadiene-*cis*-diol chemistry, see: (a) Widdowson, D. A.; Ribbons, D. W.; Thomas, S. D. *Jansen Chim. Acta* **1990**, *8*, 3. (b) Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795. (c) Brown, S. M.; Hudlicky, T. In *Organic Synthesis: Theory and Practice*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, p 113. (d) Hudlicky, T.; Reed, J. W. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 1, p 271. (e) Grund, A. D. *SIM NEWS* **1995**, *45*, 59. (f) Hudlicky, T.; Thorpe, A. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1993. (g) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3. (h) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195. (i) Hudlicky, T. In *Green Chemistry: Designing Chemistry for the Environment*; Anastas, P. T., Williamson, T., Eds.; ACS Symposium Series 626; American Chemical Society: Washington, DC, 1996; Chapter 14.

(14) (a) Commercially available from Genencor International, Inc., Palo Alto, CA. (b) Gibson, D. T.; Kock, J. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653. (c) Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kallio, R. E. *Biochemistry* **1968**, *7*, 3795. (d) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, J. J. *Biochemistry* **1970**, *9*, 1626. (e) Gibson, D. T. *Crit. Rev. Microbiol.* **1971**, *1*, 199. (f) Gibson, D. T. *Tox. Environ. Chem.* **1982**, *5*, 237. (g) Gibson, D. T.; Subramanian, V. In *Microbial Degradation of Organic Compounds*; Gibson, D. T., Ed.; Microbiology Series 13; Marcel Dekker: New York, 1984; Chapter 7. (h) Gibson, D. T.; Zylstra, G. J.; Chauhan, S. In *Pseudomonas: Biotransformations, Pathenogenesis and Evolving Biotechnology*; Silver, S., Ed.; American Society for Microbiology: Washington, DC, 1990; Chapter 13, p 121. (i) Zylstra, G. J.; Gibson, D. T. In *Genetic Engineering*; Setlow, J. A., Ed.; Pergamon: New York, 1991; Vol. 13, p 183.

(15) (a) Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439. (b) Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *Tetrahedron Lett.* **1989**, *30*, 4053. (c) Hudlicky, T.; Price, J. D. *Synlett* **1990**, 159.

Table 1. Control of Halogen Displacement



entry	SM[a]	molarity SM	molarity NaN$_3$	ratio[b] of NaN$_3$/SM	solvent	T (°C)[c]	yield (%) 4a	yield (%) 4d
1	**13**	0.18	0.70	3.9	DMF	85	13	77
2	**12**	0.20	0.80	4.0	DMF	90	14	76
3	**13**	0.19	5.70	30.0	DMSO	40[d]	0	0
4	**12**	0.61	9.70	16.0	DMSO	40[d]	75	22

[a] SM, starting material (halohydrin). [b] Molar ratio of sodium azide to halohydrin. [c] Temperature at which noticeable consumption of halohydrin began. [d] An ultrasound sonicator was used to maintain homogeneity; the temperature of the bath was a constant 40 °C.

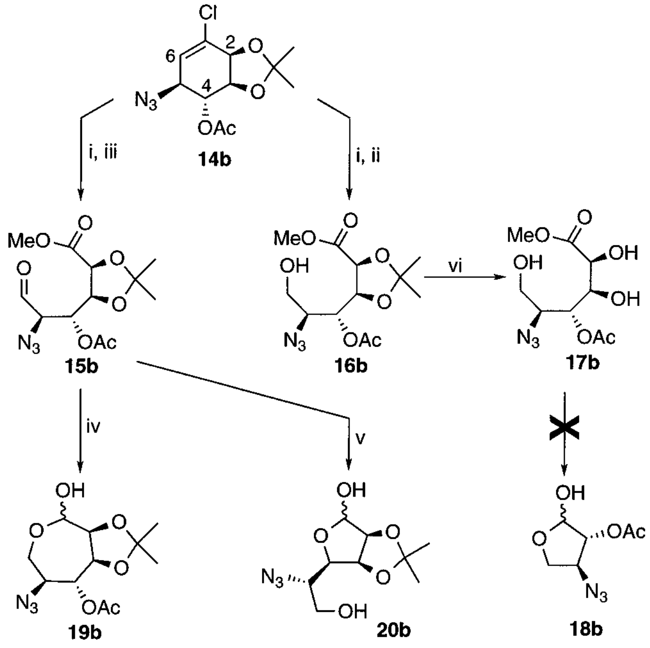
remaining azido alcohols (**4a**,**c**) presented a greater challenge. Earlier we reported[12j] the synthesis of *cis*-azido alcohol **4c** from chlorohydrin **11**[16] in 91% yield. In a similar manner epoxide **8** was treated with LiBr to give bromohydrin **12**, which gave **4a** upon exposure to a large excess of NaN$_3$.

Initial attempts to synthesize **4a** were unsuccessful. When chlorohydrin **13** was subjected to the same reaction conditions as those for the production of **4c** (from **11**), the epimeric azido alcohol **4d** was formed as the major product (Table 1, entry 1). It was only in the presence of a large excess of NaN$_3$ that **4a** was formed. Thus by varying the amount of NaN$_3$, bromohydrin **12** could be selectively converted to either **4a** or **4d**. This unique stereochemical outcome is understandable if one considers the two competing chemical processes. The first is the S$_N$2 displacement of halide by the azide; the second is the reconstitution of epoxide **8**, followed by its in situ opening with azide. The data (Table 1) clearly suggest that the former process prevails at high molar ratios of NaN$_3$ to halohydrin, while the latter predominates at low molar ratios.

Interestingly **4d** was synthesized directly when bromohydrin **9** was treated with NaN$_3$ in DMSO at 70 °C (Scheme 1).[17] The spectral data for the two independently synthesized azido alcohols **4d** were indistinguishable. Since the formation of **4d** from **9** must proceed via epoxide **8**, we also attempted the conversion of **9** to **12** with NaBr, expecting the intermediate epoxide to open regioselectively. Unfortunately, only decomposition was observed at elevated temperatures.

With the access to the required azido alcohols **4a**–**d** assured, we turned our attention to the synthesis of all four enantiomerically pure sphingosines. (*Note*: All compounds leading to the synthesis of a particular stereoisomer of sphingosine bear the same letter designation. When another stereoisomer of sphingosine is synthesized using stereoisomeric intermediates, it will have the same number but a different letter. For example, all compounds which could potentially lead to the synthesis of D-*erythro*-sphingosine (**1a**) will carry the letter "a".)

Scheme 2[a]



[a] Reagents and conditions: (i) O$_3$ (excess), MeOH, −78 °C; (ii) NaBH$_3$CN, pH ~3.0, 0 °C; (iii) NaBH$_4$, −30 °C or rt; (iv) NaBH$_4$, MeOH, 0 °C; (v) NaBH$_4$, MeOH, rt; (vi) Amberlyst 15 (wet) ion-exchange resin, strongly acidic in MeOH/H$_2$O.

Synthesis of L-*threo*-Sphingosine (1b) and D-*erythro*-Sphingosine (1a). For L-*threo*-sphingosine (**1b**) azido alcohol **4b** was protected as its acetate **14b** and subjected to a variety of ozonolysis conditions (Scheme 2). Ester aldehyde **15b** and hydroxy ester **16b** were isolated when the ozonide derived from **14b** was worked up under the reducing conditions of NaBH$_4$ and NaCNBH$_3$, respectively.[18] Ester **16b**, obtained in 82% yield, was converted to the free diol **17b**, with the expectation that the protected azido deoxy threose **18b** could be generated (Scheme 2). Unfortunately a nonspecific migration of the acetyl group in **17b** occurred; after several different acidic reaction conditions were examined, to no avail, this approach was abandoned.[19]

Treatment of the ozonide derived from **14b** with a large excess of NaBH$_4$, even at room temperature, failed to

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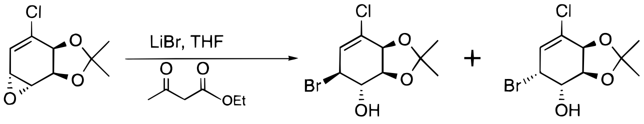
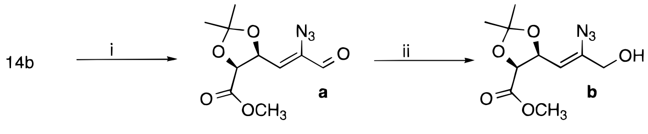
(16) Chlorohydrin **11** (0.09 M), NaN$_3$ (0.27 M), DMF, 12 h at 55 °C, then 12 h at rt, 91% yield. (*Note*: The corresponding bromohydrin of **11** could not be synthesized without scrambling the stereochemistry at the allylic site, i.e., a 1:1 mixture of epimeric products was observed. T. Nugent and T. Hudlicky, unpublished results.)



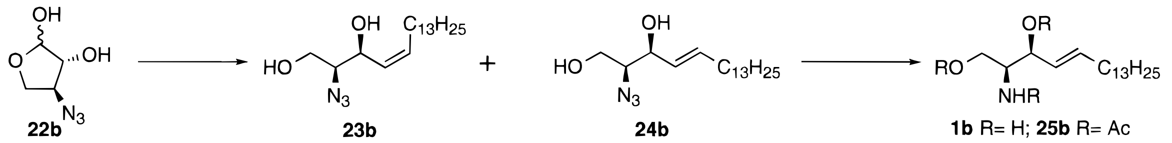
(17) J. Rouden and T. Hudlicky, unpublished results.

(18) Interestingly a vinyl azide was produced using the conditions shown below. While most of the data were collected for the alcohol **b** (^{1}H NMR, ^{13}C NMR, IR, MS), which was easier to handle (approximate half-life at room temperature of 24 h), the ^{1}H NMR of the aldehyde **a** showed the elimination had already occurred. Only one geometric isomer (not assigned) was observed. *Reagents and conditions*: (i) (1) O$_3$ (excess), NaHCO$_3$ (5.5 equiv), MeOH, −78 °C, (2) NaBH$_4$ (>10 equiv), CeCl$_3$·7H$_2$0, −20 °C; (ii) NaBH$_4$ (excess), MeOH, rt.



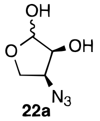
(19) For neutral deprotection conditions using 0.5–1.0% I$_2$ in MeOH (w/v), see: Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R. *Tetrahedron Lett.* **1986**, *27*, 3827. Unfortunately these neutral deprotection conditions were unknown to us when we were trying to synthesize **17b**.

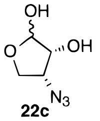
Table 2. Wittig Olefination of Lactol 22



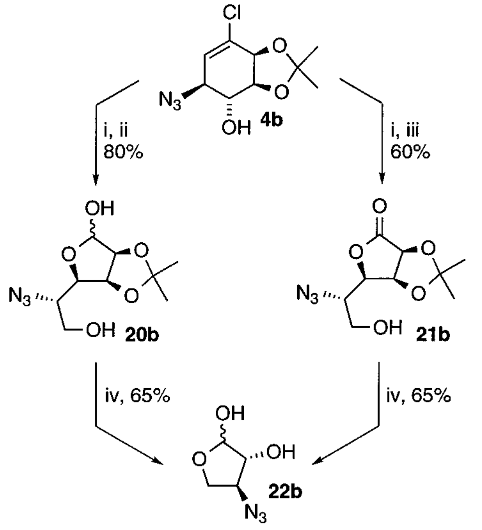
lactol	ref	equiv[a]	equiv of base	*T* (°C)	solvent	% yield *Z*/*E*
22b	12b	4.0	4.0 *n*-BuLi	rt	THF	*e*
22b	11j, 22a[b]	1.2	4.6 PhLi	−35	THF/toluene	1/2
22b	*b*	1.2	5.5 PhLi	−78	THF/toluene	*e*
22b	22b	4.0	8.0 dimsyl Na[c]	rt	DMSO	*e*
22b	23, 1a	2.0	2.0 Na amylate	rt	THF/toluene	10/7
22b		3.2	2.7 *n*-BuLi	rt	THF	24/6[d]
22a		3.2	2.7 *n*-BuLi	rt	THF	14/4

[a] Equiv of salt, refers to equivalents of tetradecyltriphenylphosphonium bromide. [b] Denotes modified Schlosser–Wittig conditions. [c] The dimsyl anion was generated by the addition of 8.0 equiv of NaH to DMSO (the reaction solvent). [d] Note this yield was not consistent; subsequent reactions gave yields very similar to those of lactol **22a**, i.e., combined yields (*Z* and *E*) of 20%. [e] Neither *cis*- nor *trans*-azidosphingosine was observed.


22a


22c

Scheme 3[a]



[a] Reagents and conditions: (i) O_3 (excess), MeOH, −78 °C; (ii) $NaBH_4$, −30 °C to rt; (iii) $NaBH_3CN$, pH ~3.0, 0 °C; (iv) (1) Amberlyst 15 (wet) ion-exchange resin, strongly acidic, H_2O, (2) $NaIO_4$, H_2O.

provide **19b** or **20b** directly. Only aldehyde **15b** was isolated. After workup, the crude aldehyde was reduced with $NaBH_4$. At 0 °C the seven-membered lactol **19b** was isolated in 55% yield, while at room temperature the five-membered lactol **20b** was obtained in 65% yield, because of apparent cleavage of the acetate at the higher temperature.[20]

We therefore turned to the ozonolysis of the unprotected azido alcohol **4b** (Scheme 3). To this end treatment of **4b** with ozone provided lactol **20b** in 80% yield, without the need of additional reduction. Alternatively, when the ozonide derived from **4b** was reduced with sodium cyanoborohydride ($NaBH_3CN$), lactone **21b** was observed, albeit in lower yield (60%). Fortuitously, in a one-pot procedure, acid-catalyzed hydrolysis of acetonide **20b** or **21b** followed by $NaIO_4$ cleavage provided in 65% overall yield[1a] lactol **22b**, the cyclic version of the key sphingosine synthon **6**, Chart 3. Note that the difference in oxidation states is inconsequential as the carbonyl atom is lost from both compounds during the periodate cleavage.

Direct olefination of lactol **22b** under optimized conditions[21] (Table 2) gave a chromatographically separable mixture of *cis*- (**23b**) and *trans*-azidosphingosine (**24b**) in 24% and 6% yield, respectively. The *cis*-azidosphingosine (**23b**) was photoisomerized to *trans*-azidosphingosine (**24b**) by means of a Hanovia 450-W lamp,[24] Pyrex filter,[25,26] and diphenyl disulfide in a 4:1 mixture of hexanes and dioxane.[8g,11h] Ultimately, the purified mixture of *cis*-**23b** and *trans*-**24b** was photolyzed to give a 21% yield of *trans*-azidosphingosine (**24b**) from **22b**. Reduction[8d,h] of the azide was accomplished with H_2S, pyridine, and H_2O to provide **1b** whose peracetylation

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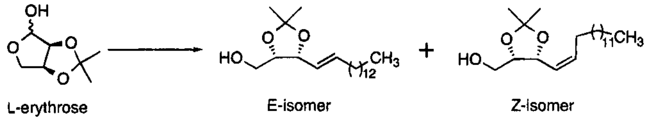
(20) We believe that the lactols **19b** and **20b** are the products of reduction of the corresponding lactones—for precedent, see refs 12i,j.

(21) To ensure the integrity of our Wittig protocol, acetonide-protected L-erythrose, available from *cis*-diol **2**,[12b] was subjected to our Wittig conditions.

ylide (equiv)	base (equiv)	*T* (°C)	solvent	% yield *E*/*Z*
2.20	2.25 (*n*-BuLi)	25	THF	15/80
2.20	4.12 (PhLi)	−35	THF	61/6



(22) (a) Schlosser, M.; Tuong, H. B.; Schaub, B. *Tetrahedron Lett.* **1985**, *26*, 311. (b) Bestmann, H. J.; Vostrowsky, O. In *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer-Verlag: New York, 1983; Vol. 109, p 106.

(23) (a) Conia, J. M.; Limasset, J. C. *Bull. Soc. Chem. Fr.* **1967**, *6*, 1936. (b) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103. (c) Short, R. P.; Ranu, B. C.; Revol, J. M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453.

(24) In our initial communication detailing the synthesis of D-*erythro*- and L-*threo*-sphingosine, we reported that a 400-W lamp was used; however, all photoisomerizations were carried out with a 450-W lamp.

(25) No special filter is needed, but Pyrex glassware is required. We used a Pyrex round-bottomed flask for all photoisomerizations. Pyrex filters out UV irradiation below 280 nm.[26]

(26) Moussebois, C.; Dale, J. *J. Chem. Soc. C* **1966**, 260.

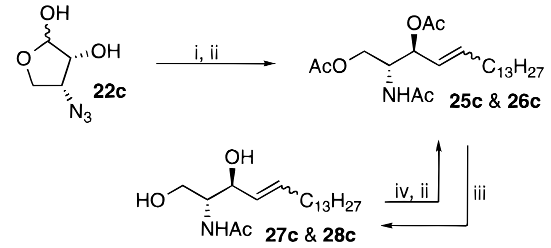
gave triacetyl-L-*threo*-sphingosine (**25b**), indistinguishable (vide ^{1}H NMR spectrum and optical rotation) from an authentic sample.[27]

Azido alcohol **4a**, the precursor of naturally occurring D-*erythro*-sphingosine (**1a**), was subjected to the same set of reactions as **4b** to yield lactol **22a** (Table 2) in 52% overall yield. Under optimized Wittig olefination conditions, outlined in Table 2, *cis*- (**23a**) and *trans*-azidosphingosine (**24a**) were observed in 14% and 4% yield, respectively. Photoisomerization resulted in a 12% yield of *trans*-azidosphingosine **24a** (from **22a**), displaying ^{1}H NMR spectrum and optical rotation ($[\alpha]^{25}_{D} = -34.2$ (*c* 1.6, CHCl$_3$)) in agreement with the literature values ($[\alpha]^{20}_{D} = -32.9$ (*c* 4.0, CHCl$_3$)[8h]). The attainment of *trans*-azidosphingosine (**24a**), a known compound, constitutes a formal synthesis of naturally occurring D-*erythro*-sphingosine (**1a**).[1a]

Electrophilic Nature of Azides. 1. Synthesis of L-*erythro*-Sphingosine (1c). It is known that aldehydes containing α-hydroxy groups are poor substrates for Wittig olefination.[9g] This alone could account for the poor yields we encountered. Although Wittig reactions of lactols abound in the literature,[22b] no precedent was found for successful olefination of lactols with the disposition of functionality and functional group type found in **22b**. In addition we failed to find an example in which an azide moiety was present during a Wittig olefination reaction. To explain the low yields ((*E*)- and (*Z*)-azidosphingosines), we turned to the electrophilic nature of azides in the presence of alkylidenephosphoranes. Examination of some of the alkylidenephosphorane literature[28a] confirmed that azides are attacked by Wittig reagents to form imines, nitrogen, and triphenylphosphine. Because triphenylphosphine is commonly used to reduce azides to amines via hydrolysis of the intermediate iminophosphoranes,[29] and because triphenylphosphine and octacos-14-ene (C$_{28}$H$_{56}$, alkylidenephosphorane dimer) were isolated, as byproducts from the Wittig reactions, the presence of imine and iminophosphorane intermediates is highly probable.[30] We reasoned that the Wittig reaction could be improved if the reaction conditions were adjusted to favor the final sphingosine product by a one-pot Wittig olefination and triphenylphosphine-mediated Staudinger reduction of azidosphingosine.

Expecting to improve the overall yield by channeling both azido- and iminophosphoranyl sphingosines into the final product, we initiated the synthesis of L-*erythro*-sphingosine (**1c**). Thus lactol **22c** (Table 2) was synthesized, in the same manner as **22b**, and subsequently treated with the Wittig ylide (prepared by addition of 4.5 equiv of *n*-BuLi in hexanes to 4.7 equiv of tetradecyltriphenylphosphonium bromide in THF at 0 °C → room temperature). After 4 h, water (3.0 mL) was added, and the reaction mixture was stirred for an additional 12 h. This modification enables the hydrolysis of any iminophosphoranes or imines present and maximizes the content of sphingosine **1c**. Workup provided the crude L-*erythro*-sphingosine (**1c**) product, as evidenced by TLC analysis (Scheme 4).

Scheme 4[a]



[a] Reagents and conditions: (i) tetradecyltriphenylphosphonium bromide, *n*-BuLi, THF; (ii) Ac$_2$O, pyridine; (iii) K$_2$CO$_3$, MeOH; (iv) PhSSPh, dioxane/hexane, Pyrex filter, Hanovia 450-W lamp.

A cursory analysis indeed indicated the yield of sphingosine **1c** was improved to 35−55%. Treatment of the waxy material with excess Ac$_2$O and pyridine provided triacetates *cis*-**26c** and *trans*-**25c** in a 6:1 ratio, respectively. The two geometric isomers proved inseparable by chromatography and were therefore converted to the corresponding acetamides *cis*-**27c** and *trans*-**28c**, which proved to be as inseparable as the triacetates. Acetamides *cis*-**27c** and *trans*-**28c** were synthesized in a combined yield of 5% (this low isolated yield may reflect the rather redundant and unsuccessful attempts at purification) from **22c** (Scheme 4) and were photoisomerized and peracetylated as a mixture to provide triacetate *trans*-**25c**, displaying optical rotation and an ^{1}H NMR spectrum in agreement with the literature.[31] No further attempt was made to optimize these conditions.

2. Synthesis of the Fourth Stereoisomer: D-*threo*-Sphingosine (1d). A second-generation approach was initiated in order to obviate some of the above problems. Because of our earlier experience with the acetyl migration observed in **17b**, we chose the *tert*-butyldiphenylsilyl (TBDPS) protecting group. Azido alcohol **4d** was protected as its *tert*-butyldiphenylsilyl ether **29d** (85%) and subsequently treated with ozone to provide methyl ester **30d** (91%) (Scheme 5). Upon treatment with 1% I$_2$ in MeOH (w/v),[19] **30d** provided the desired vicinal diol **31d** (80% yield).

In initial unoptimized reactions with Amberlyst 15 (wet) strongly acidic ion-exchange resin, the desired diol **31d** was isolated in 44% yield. The remaining mass

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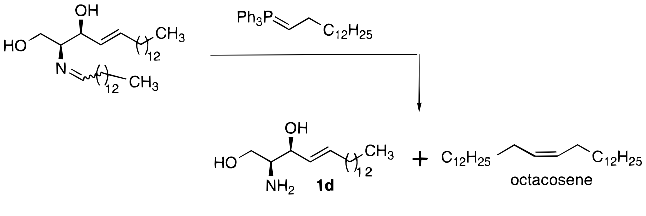
[27] The sample was kindly provided by Professor Robin Polt of the University of Arizona. (*Note*: In the Experimental Section of the Polt paper, ref 9h, sphingosine **1b** is referred to as the D-*threo* isomer; see ref 10 for further clarification.)

[28] (a) Trippett, S. *Chem. Soc. Rev.* **1963**, *17*, 406. For a more recent review on Wittig reactions, see: (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

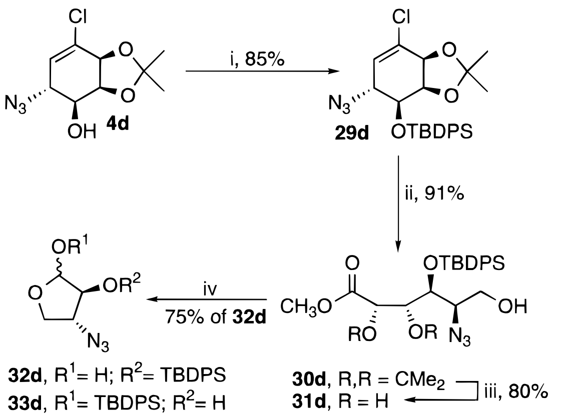
[29] (a) Pilard, S.; Vaultier, M. *Tetrahedron Lett.* **1984**, *25*, 1555. (b) Falck, J. R.; Manna, S.; Viala, J.; Siddhanta, A. K.; Moustakis, C. A.; Capdevila, J. *Tetrahedron Lett.* **1985**, *26*, 2287. (c) Lin, T. C.; Cheng, M. C.; Peng, S. M.; Liu, S. T.; Kiang, F. M. *J. Chin. Chem. Soc.* **1995**, *42*, 543.

[30] These products were not isolated until the synthesis of D-*threo*-sphingosine (**1d**). One possible reaction pathway for the formation of octacosene and sphingosine is shown below.



[31] A 1:1 mixture of *trans*-triacetyl-L-*erythro*- (**25c**) and *cis*-triacetyl-L-*erythro*-sphingosine (**26c**) was obtained after photoisomerization of the 6:1 mixture of acetamides *cis*-**27c** and *trans*-**28c**, followed by peracetylation. This 1:1 mixture of **25c** and **26c** had $[\alpha]^{27}_{D} = +8.2$ (*c* 0.9, CHCl$_3$). Pure *cis*-triacetyl-L-*erythro*-sphingosine (**26c**) (obtained by recrystallizing the original 6:1 mixture of *cis*- and *trans*-triacetates twice from hexane) has $[\alpha]^{27}_{D} = -4.4$ (*c* 1.1, CHCl$_3$), and pure *trans*-triacetyl-L-*erythro*-sphingosine (**25c**) has $[\alpha]^{24}_{D} = +12.1$ (CHCl$_3$).[11h]

Scheme 5[a]



[a] Reagents and conditions: (i) *tert*-butyldiphenylsilyl chloride (2.0 equiv), imidazole (2.4 equiv), THF; (ii) (1) O_3, MeOH, −78 °C, (2) $NaBH_4$ (excess), MeOH, 0 °C to rt; (iii) 1.0% I_2 in MeOH, 45 °C; (iv) $NaIO_4$ (2.0 equiv), MeOH/H_2O, 3:1.

balance consisted of three other compounds resulting from migration of the *tert*-butyldiphenylsilyl group and/or subsequent lactonization. These compounds were isolated and fully identified (see the Experimental Section, compounds **36**−**38**).[32] The ratio of these products changed only slightly when literature conditions for this type of deprotection (THF/H_2O/CH_3CO_2H, THF/H_2O/CF_3CO_2H, or CH_3OH/H_2O/HCl) were employed.[32]

When vicinal diol **31d** was treated with $NaIO_4$, lactol **32d** (75%) and its regioisomer **33d** (13%) were formed. Elaboration to the sphingosine skeleton was accomplished by coupling **32d** with the appropriate phosphonium ylide, as delineated in Table 3. The best conditions afforded a combined yield (13%) of *cis*- (**23d**) and *trans*-azidosphingosine (**24d**) after Wittig olefination and TBDPS deprotection of *cis*-**34** and *trans*-**35**. Note also the isolation of some *trans*-2-hexadecene originating from the base-induced decomposition of THF to acetaldehyde and ethylene. Photoisomerization of *cis*-**23d** provided *trans*-azidosphingosine (**24d**), whose ^1H NMR spectrum and optical rotation ($[\alpha]^{25}_D = -2.4$ (*c* 0.27, $CHCl_3$)) were in agreement with the literature values.[1a,11i]

Conclusion

The synthesis of all four sphingosine stereoisomers was accomplished from a common precursor, cyclohexadiene-*cis*-diol **2**, in 8−10-step sequences. All of the steps in these synthetic sequences proceeded in good to excellent yield with the exception of the Wittig olefination. We chose to pursue the olefinations with the azido deoxy tetroses as intermediates because of the known lack of nucleophilicity associated with sphingosines.[3a] In coupling the sphingosine units to biologically desirable electrophiles, the azido derivatives or the ceramide derivatives enjoy more widespread use. Even though the azido deoxy tetroses complicated the olefination protocols, the advantage of generating four isomers from a single source offsets this inconvenience. It is anticipated that the third-generation refinements in these procedures will address the Wittig step in more detail and will focus on generating the ceramides by optimizing the Staudinger component of the reaction and by maximizing the acetylsphingosine content in the reaction mixtures before the final purification. Other olefination alternatives, especially those involving softer anions, will also be examined in order to provide the useful azido analogues of sphingosine. The primary goal of this effort, provision of all four isomers from a simple intermediate, has been achieved. We will report on further solutions to the olefination protocol in due course.

Experimental Section

General Methods. All reactions were carried out in an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried under vacuum. All solvents were reagent grade. Anhydrous solvents were dried immediately before use. THF and toluene were distilled from sodium benzophenone ketyl.

Dry oxygen containing about 2.5% ozone was introduced at a speed of 4 L/min into a solution of substrate for the ozonolysis experiments.

TLC plates were visualized by immersion in a vanillin stain followed by warming on a hot plate. Flash chromatography was carried out on Merck Kieselgel 60 silica gel (230−400 mesh). Impure products purified by column chromatography were first impregnated onto silica gel.

^1H NMR and APT ^{13}C NMR spectra were recorded at 270 and 68 MHz. Proton and carbon chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (^1H NMR, 7.24 ppm; ^{13}C NMR, 77.0 ppm—middle peak of the triplet). Alcohol protons were identified by the addition of D_2O. Elemental

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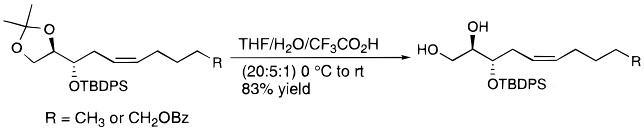
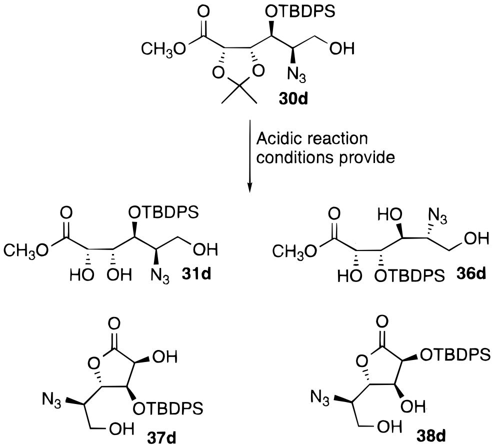
[32] For the following conversion, we used the procedure described in Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.* **1993**, *58*, 832.

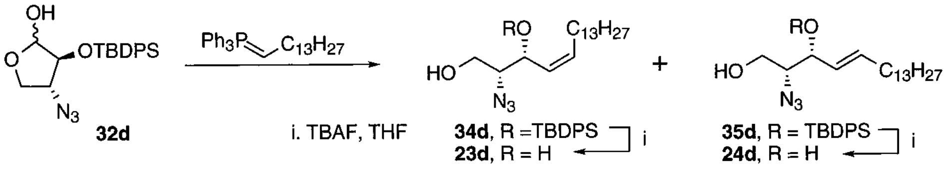


In our case, we observed three new compounds following the hydrolysis of **30d**. It seems that deprotection of the acetonide furnishes the desired vicinal diol **31d** first, followed by *tert*-butyldiphenylsilyl migration to the adjacent alcohol moieties (based on TOCSY and irradiation ^1H NMR experiments of **37d** and **38d**). When triol **36d** was stored neat or exposed to silica gel (short columns of silica gel and fast elution are advised for purification), lactones **37d** and **38d** slowly formed. Lactones **37d** and **38d** are stable, and each was fully characterized. Suprisingly, when either pure lactone **37d** or **38d** was dissolved in DMSO-d_6, it immediately equilibrated to a 1:1 mixture of the two lactones, as evidenced by ^1H NMR. This ratio remained unchanged even after 3 days. Silyl migration was not observed in $CDCl_3$ (^1H NMR analysis).



In an attempt to thwart the silyl migration of triol **31d**, we looked at some nontraditional deprotection reagents. Thus when acetonide **30d** was treated with dimethylaluminum chloride,[33] the results were very encouraging (TLC), but upon workup, the four products were found as usual. Finally, when 1% I_2 in MeOH (w/v)[19] was employed, at an optimized temperature (45 °C), **31d** was observed in an 80% yield.

Table 3. Wittig Olefination Conditions for Lactol 32d



				% yield				
equiv of salt	equiv of base	*T* (°C)	solvent	**34d** & **35d**	dimer[a]	silanol[b]	*trans*-2-hexadecene	PPh_3
2.2	4.4 PhLi	−50 to 0	THF	0	*c*	57	not present	*c*
1.8	1.8 Na amylate	rt	THF	9	*c*	43	*c*	*c*
1.8	1.8 Na amylate	0 to rt	THF	4[d]	20	47	*c*	*c*
3.5	3.5 Na amylate	0 to rt	THF	13[d]	19	≈19	12	12
2.2	2.0 *n*-BuLi	rt	THF	0	*c*	66	not present	*c*
3.0	2.7 *n*-BuLi	rt	THF[e]	≈5	≈5	≈40	not present	≈5
3.5	3.2 *n*-BuLi	-78 to rt	toluene	0[f]	20	*c*	not present	*c*
4.0	3.6 *n*-BuLi	rt	THF	0[g]	*c*	*c*	not present	*c*

[a] The dimer refers to octacos-14-ene ($C_{28}H_{56}$). [b] The silanol is *tert*-butyldiphenylsilanol. [c] Did not isolate. [d] Percent yield determined by treating the crude product **34d** and **35d** with *n*-Bu_4NF and isolating the corresponding azidosphingosine. [e] The solvent was deoxygenated. [f] 36% of the silyl-migrated product **33d** and 35% of starting lactol isolated. [g] TLC shows the silyl-migrated product **33d** in <5 min; after 15 h neither starting lactol **32d** nor **33d** remains.

analyses were performed by Atlantic Microlab, Inc., and the University of Florida.

(3*R*,4*S*,5*S*,6*S*)-3-Azido-1-chloro-5,6-*O*-isopropylidene-1-cyclohexene-4,5,6-triol (4d). NH_4Cl (264 mg, 4.94 mmol, 4.00 equiv) and NaN_3 (320 mg, 4.92 mmol, 4.00 equiv) were added to a solution of epoxide **8**[1a] (250 mg, 1.23 mmol) in 1,2-dimethoxyethane (13.0 mL), ethanol (10.0 mL), and H_2O (8.0 mL). The resulting mixture was then heated at 60 °C. After 1 h the reaction mixture was cooled to rt, H_2O (40.0 mL) was added, and the solution was extracted with EtOAc (×3). The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography using gradient elution (hexanes/EtOAc, 3:1 → 2:1) afforded **4d** (262.1 mg, 85%) as a clear oil. Within 5 h at rt the oil became dark-brown, yet no decomposition was noticeable by ^1H NMR. An analytical sample was obtained after column chromatography (1% acetone in CH_2Cl_2 → 2% acetone in CH_2Cl_2): $R_f = 0.45$ (hexanes/EtOAc, 2:1); $[\alpha]^{22}_D = -120.1$ (c 1.00, $CHCl_3$); IR (neat) ν 3430, 2995, 2930, 2100, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (d, $J = 2.0$ Hz, 1H), 4.57 (m, 2H), 4.27 (td, $J = 1.8$, 8.6 Hz, 1H), 3.81 (dt, $J = 2.1$, 8.1 Hz, 1H), 2.54 (d, $J = 7.5$ Hz, OH), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 134.2 (C), 111.1 (C), 123.9 (CH), 76.7 (CH), 76.3 (CH), 72.0 (CH), 60.9 (CH), 27.3 (CH_3), 26.3 (CH_3); MS (CI, 70 eV) m/z (rel. intensity) 246 ($M^+ + 1$, 3.0), 160 (3.0), 145 (20), 101 (15.0), 96 (15.0), 59 (100). Anal. Calcd for $C_9H_{12}ClN_3O_3$: C, 44.00; H, 4.92; N, 17.11. Found: C, 44.34; H, 4.96; N, 16.96.

(3*S*,4*R*,5*R*,6*S*)-4-Acetyl-3-azido-1-chloro-5,6-*O*-isopropylidene-1-cyclohexane-4,5,6-triol (14b). Azido alcohol **4b**[1b] (1.48 g, 6.04 mmol) was treated with acetic anhydride (5.0 equiv) and pyridine (2.0 mL) under N_2. After 2 h, the volatile components were removed (high vacuum, overnight). Column chromatography (hexanes/EtOAc, 7:3) of the resulting yellowish-white crystals afforded **14b** (1.73 g, 99% yield) as a white crystalline solid: $R_f = 0.58$ (hexanes/EtOAc, 1:1); $[\alpha]^{21}_D = +66.1$ (c 1.0, $CHCl_3$); mp = 55−56 °C; IR (neat) ν 2995, 2095, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.92 (d, $J = 2.7$ Hz, 1H), 5.18 (t, $J = 7.9$ Hz, 1H), 4.58 (dd, $J = 1.1$, 5.9 Hz, 1H), 4.25 (dd, $J = 5.9$, 8.0 Hz, 1H), 3.95 (ddd, $J = 1.0$, 2.7, 7.5 Hz, 1H), 2.12 (s, 3H), 1.53 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.5 (C), 133.0 (C), 125.1 (CH), 111.9 (C), 75.4 (CH), 75.2 (CH), 71.4 (CH), 59.1 (CH), 27.6 (CH_3), 26.2 (CH_3), 20.8 (CH_3); MS (CI, 70 eV) m/z (rel. intensity) 272 ($M^+ - 15$, 15), 245 (50), 230 (18), 187 (15), 160 (100), 142 (45). Anal. Calcd for $C_{11}H_{14}ClN_3O_4$: C, 45.92; H, 4.91. Found: C, 45.93; H, 4.94.

(2*S*,3*R*,4*R*,5*S*)-4-Acetyl-5-azido-2,3-*O*-isopropylidene-hexanoic Acid Methyl Ester 2,3,4,6-Tetrol (16b). Excess O_3/O_2 was bubbled through a solution of vinyl chloride **14b** (814 mg, 2.83 mmol) in MeOH (10.0 mL) at −78 °C. After 30 min the reaction mixture was purged with N_2 at −78 °C for 30 min. The solution was warmed to 0 °C, and methyl orange indicator (≤4 mg) was added. $NaBH_3CN$ (125 mg) was added, and the red/pink solution color was maintained throughout the reduction by the addition of 2.0 M aqueous HCl, as needed. After 30 min, two more portions of $NaBH_3CN$ (125 mg, 30 min apart) were added before warming to rt. Additional reductant (270, 250, and finally 100 mg, 30-min intervals between additions) was added at rt until TLC analysis showed only the title compound. Acetone (5.0 mL) was then added to consume the excess $NaBH_3CN$. The reaction solution was reduced to one-half of its original volume (rotary evaporator), and H_2O (40 mL) was added. The solution was extracted with EtOAc (×3), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography (Hex/EtOAc, 3:1) provided **16b** (739 mg, 82% yield) as an oil: $R_f = 0.25$ (hexanes/EtOAc, 1:1); IR (neat) ν 3505, 2995, 2955, 2110, 2095, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.17 (dd, $J = 2.7$, 5.4 Hz, 1H), 4.78 (d, $J = 7.5$ Hz, 1H), 4.65 (dd, $J = 2.7$, 7.4 Hz, 1H), 3.75 (m, 6H), 2.47 (t, $J = 6.6$ Hz, 1H), 2.12 (s, 3H), 1.63 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5 (C), 168.5 (C), 111.3 (C), 75.8 (CH), 75.3 (CH), 69.9 (CH), 63.4 (CH), 61.5 (CH_2), 52.3 (CH), 26.2 (CH_3), 25.4 (CH_3), 20.6 (CH_3); MS (CI, 70 eV) m/z (rel. intensity) 318 ($M^+ + 1$, 3), 290 (40), 260 (50), 142 (100), 114 (80). Anal. Calcd for $C_{12}H_{19}N_3O_7$: C, 45.42; H, 6.04. Found: C, 45.41; H, 6.06.

(2*S*,3*R*,4*R*,5*S*)-5-Azido-4-(acetyloxy)hexanal 2,3,4,6-Tetrol (19b). The title compound was synthesized using the same general procedure adopted for the synthesis of lactols **20a**−**c**. Conversion of crude **15b** to **19b** was accomplished by treatment with $NaBH_4$ (0.5 equiv at a time) in MeOH at 0 °C: yield 50−60%; $R_f = 0.46$ (hexanes/EtOAc, 1:1); IR (neat) 3440, 2990, 2960, 2105, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.45 (d, $J = 2.4$ Hz, 1H), 4.71 (dd, $J = 3.4$, 5.9 Hz, 1H), 4.65 (d, $J = 5.9$ Hz, 1H), 4.29 (m, 2H), 4.22 (m, 1H), 3.95 (m, 1H), 2.77 (d, $J = 2.5$ Hz, 1H), 2.12 (3H, s), 1.47 (3H, s), 1.30 (3H, s); ^{13}C NMR ($CDCl_3$) δ 172.0 (C), 113.9 (C), 101.1 (CH), 85.9 (CH), 79.9 (CH), 79.6 (CH), 63.5 (CH_2), 60.2 (CH), 26.1 (CH_3), 24.8 (CH_3), 20.2 (CH_3). Anal. Calcd for $C_{11}H_{17}N_3O_6$: C, 45.99; H, 5.97. Found: C, 45.88; H, 5.94.

General Procedure for the Formation of Lactols 20a−c. Excess O_3/O_2 was bubbled through a 0.4 M solution of azido alcohol **4** in methanol, cooled in a dry ice/acetone bath, until a persistent blue color was observed (≅30 min). After the solution had been purged with N_2 for 30 min at −78 °C, the reaction flask was placed in an ice bath. $NaBH_4$ (2.5 equiv, assuming 1 mol of hydride/mol of $NaBH_4$) was slowly added so that the reaction temperature did not exceed 10 °C. (*Note*: The reduction is routinely performed with the round-bottomed flask open to the atmosphere.) After 45 min the ice bath was removed, and stirring continued for another 15 min. If the reduction was not complete (TLC analysis) more $NaBH_4$ was added slowly at rt (0.3 equiv of $NaBH_4$, stir for 20 min, check by TLC). This routine was repeated until the reduction was complete. (*Note*: Overreduction can occur!) The reaction mixture was acidified with aqueous HCl (1.0 M), pH 4.5 (±0.5), and extracted with EtOAc (×4). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Column chromatography using gradient elution (hexanes/EtOAc, 65:35 → 1:1) provided **20** (70−80% yield) as a clear oil.

(2*S*,3*S*,4*S*)-2,3-*O*-Isopropylidene-4-(1(*S*)-azido-2-hydroxyethyl)-γ-butyrolactol (20a) (*Note*: Both anomeric lactols were evident in the ^{1}H and ^{13}C NMR spectra, but one anomeric form predominated (9:1 ratio, 10−20 mg in 0.5 mL of $CDCl_3$): $R_f = 0.29$ (hexanes/EtOAc, 1:1); $[\alpha]^{21}_D = +31.0$ (*c* 0.97, $CHCl_3$); IR (neat) 3400, 2995, 2940, 2115, 2095, 1755, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 1H), 4.73 (dd, $J = 5.9$, 3.6 Hz, 1H), 4.61 (d, $J = 5.9$ Hz, 1H), 4.24 (dd, $J = 8.8$, 3.4 Hz, 1H), 4.11 (br d, $J = 2.0$ Hz, 1H), 3.82 (m, 2H), 3.71 (m, 1H), 2.92 (br t, $J = 5.5$ Hz, 1H), 1.44 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 112.9 (C), 100.9 (CH), 85.9 (CH), 79.9 (CH), 79.5 (CH), 63.5 (CH), 62.1 (CH_2), 25.9 (CH_3), 24.8 (CH_3); MS (CI, 70 eV) *m*/*z* (rel. intensity) 246 ($M^+ + 1$, 0.5), 230 (12), 218 (2), 202 (2.5), 159 (20), 73 (25), 59 (100). Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.16; N, 17.13. Found: C, 44.25; H, 6.29; N, 17.09.

(2*S*,3*S*,4*R*)-2,3-*O*-Isopropylidene-4-(1(*S*)-azido-2-hydroxyethyl)-γ-butyrolactol (20b) (*Note*: Both anomeric lactols were evident in the ^{1}H and ^{13}C NMR spectra, but one anomeric form predominated (2:1 ratio, 15−20 mg in 0.5 mL of $CDCl_3$). This ratio changed to approximately 3:1 when 3 mg of **20b** was used. Because of the lactol equilibrium, the integration for individual resonance patterns in the ^{1}H NMR will not always correspond.): $R_f = 0.26$ (hexanes/EtOAc, 1:1); $[\alpha]^{23}_D = +11.7$ (*c* 0.94, $CHCl_3$); IR (neat) 3430, 2995, 2950, 2100, cm^{-1}; ^{1}H NMR ($CDC1_3$) δ 5.44 (s, 1H), 5.38 (d, $J = 3.83$ Hz, 0.5H), 4.83 (dd, $J = 6.0$, 1.1 Hz, 1H), 4.72 (dd, $J = 6.8$, 2.8 Hz, 0.5H), 4.67 (dd, $J = 6.9$, 3.9 Hz, 0.5H), 4.61 (d, $J = 5.92$ Hz, 1H), 4.1 (dd, $J = 5.5$, 2.8 Hz, 0.5H), 4.06 (dd, $J = 9.36$, 1.22 Hz, 1H), 3.97 (dd, $J = 11.8$, 4.0 Hz, 1H), 3.81 (m, 2.5 H), 3.62 (m, 1.5H), 1.55 (s, 1.5H), 1.46 (s, 3H), 1.38 (s, 1.5H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 115.2 (C), 112.9 (C), 103.2 (CH), 96.5 (CH), 86.0 (CH), 85.7 (CH), 82.3 (CH), 80.9 (CH), 80.7 (CH), 79.5 (CH), 64.6 (CH), 64.2 (CH), 62.9 (CH_2), 62.4 (CH_2), 26.5 (CH_3), 26.2 (CH_3), 24.9 (CH_3); MS (CI, 70 eV) *m*/*z* (rel. intensity) 246 ($M^+ + 1$, 4), 218 (23), 202 (25), 200 (25), 188 (41), 159 (64), 142 (61), 69 (69), 59 (100). Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.16; N, 17.13. Found: C, 43.93; H, 6.19; N, 17.31.

(2*S*,3*S*,4*R*)-2,3-*O*-Isopropylidene-4-(1(*R*)-azido-2-hydroxyethyl)-γ-butyrolactol (20c) (*Note*: Both anomeric lactols are evident in the ^{1}H and ^{13}C NMR spectra. One anomeric form predominates (15:1 ratio).): $R_f = 0.25$ (hexanes/EtOAc, 1:1); $[\alpha]^{24}_D = -13.7$ (*c* 1.0, $CHCl_3$); mp = 89−91 °C; IR (neat) 3425, 2995, 2945, 2105 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.39 (d, $J = 2.3$ Hz, 1H), 4.85 (dd, $J = 5.8$, 3.7 Hz, 1H), 4.62 (d, $J = 5.9$ Hz, 1H), 4.17 (dd, $J = 9.1$, 3.6 Hz, 1H), 3.94 (br d, 1H), 3.82 (m, 2H), 3.55 (br s, OH), 2.60 (br s, OH), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 112.9 (C), 101.3 (CH), 88.9 (CH), 85.5 (CH), 79.8 (CH), 62.9 (CH), 62.4 (CH_2), 25.9 (CH_3), 24.8 (CH_3); MS (CI, 70 eV) *m*/*z* (rel. intensity) 246 ($M^+ + 1$, 9), 230 (49), 218 (57), 202 (22). Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.16; N, 17.13. Found: C, 44.17; H, 6.21; N, 17.23.

General Procedure for the Formation of Lactols 22a−c. Amberlyst 15 (wet) ion-exchange resin (4.0 wt equiv with respect to **20**) was added to a 0.1 M solution of lactol **20** in distilled H_2O. After 5 h at 65 °C the reaction mixture was filtered through a glass sinter. The pH of the filtrate was adjusted to 7.0 (±0.5) with satd aq $NaHCO_3$, and H_2O was added until a 0.05 M (with respect to **20**) solution was achieved. $NaIO_4$ (1.0 equiv with respect to **20**) was added to the the reaction mixture, which had been protected from light. Depending on the diastereomer of **20** used, reaction times varied from 1 to 6 h. After the reaction solution was saturated with NaCl, the product was extracted with EtOAc/2-propanol (1:1) until no more product could be detected in the aqueous layer (TLC analysis). The combined organic extracts were saturated with NaCl, decanted, dried ($MgSO_4$), and concentrated. Column chromatography (hexanes/EtOAc, 1:3) provided **22** (55−65%) as a clear oil. (*Note*: The propensity of these lactols to interconvert between the two anomeric forms makes quantitative interpretation of the ^{1}H NMR data almost impossible; Aldehyde resonances were also observed.)

(2*S*,3*S*)-2-Hydroxy-3-azido-γ-butyrolactol (22a): obtained following the general procedure; $R_f = 0.35$ (CH_2Cl_2/acetone, 3:1); $[\alpha]^{23}_D = +39.6$ (*c* 1.2, acetone); IR (film) 3400, 2105, 1660, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.38 (m, 1H), 5.60 (d, $J = 4.39$ Hz, 1H), 5.30 (d, $J = 6.83$ Hz, 1H) 5.06 (t, $J = 5.42$, 4.52 Hz, 1H), 5.00 (dd, $J = 4.6$, 1.3 Hz, 1H), 4.02 (m, 3H), 3.80 (m, 2H), 3.70 (m, 1H), 3.40 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 102.5 (CH), 95.7 (CH′), 80.4 (CH), 75.8 (CH′), 65.3 (CH), 64.7 (CH′), 68.3 (CH_2), 66.7 (CH_2′); MS (CI 70 eV) *m*/*z* (rel. intensity) 128 ($M^+ - 17$, 15), 118 (8), 103 (6), 88 (93), 85 (54), 73 (30), 60 (100). Anal. Calcd for $C_4H_7N_3O_3$: C, 33.11; H, 4.86. Found: C, 33.37; H, 4.98.

(2*R*,3*S*)-2-Hydroxy-3-azido-γ-butyrolactol (22b): obtained following the general procedure; $R_f = 0.29$ (CH_2Cl_2/acetone, 3:1); $[\alpha]^{25}_D = +5.47$ (*c* 1.2, acetone); IR (film) 3400, 2950, 2900, 2500, 2105, 1725, 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.39 (d, $J = 5.2$ Hz, OH), 5.70 (d, $J = 5.1$ Hz, OH), 5.00 (dd, $J = 5.2$, 2.3 Hz, 1H), 3.95 (m, 3H), 3.63 (dd, $J = 9.0$, 4.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 101.8 (CH), 77.2 (CH), 67.5 (CH_2), 61.1 (CH); MS (CI 70 eV) *m*/*z* (rel. intensity) 128 ($M^+ - 17$, 45), 118 (8), 103 (12), 100 (13), 85 (68), 72 (46), 60 (100).

(2*R*,3*R*)-2-Hydroxy-3-azido-γ-butyrolactol (22c): obtained following the general procedure; $R_f = 0.32$ (CH_2Cl_2/acetone, 3:1); $[\alpha]^{23}_D$ = -35.8 (*c* 0.94, acetone); IR (film) 3400, 2105, 1660, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.40 (d, 1H), 6.2 (d, 1H), 5.75 (d, $J = 4.4$ Hz, 1H), 5.30 (m, 1H), 5.06 (m, 2H), 3.92 (m, 6H), 3.60 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 103.1 (CH), 95.9 (CH′), 80.7 (CH), 76.0 (CH′), 65.5 (CH), 64.9 (CH′), 68.6 (CH_2), 67.0 (CH_2′); MS (CI 70 eV) *m*/*z* (rel. intensity) 128 ($M^+ - 17$, 11), 118 (6), 88 (85), 85 (42), 60 (100).

General Procedure for the Formation of 23a,b and 24a,b. To a flame-dried round-bottomed flask under Ar was added *n*-tetradecyltriphenylphosphonium bromide (3.20 equiv). After 30 min under high vacuum, the flask was flooded with Ar, and THF was added until a 1.0 M solution was obtained. The solution was cooled in an ice bath, and *n*-BuLi (2.75 equiv, 2.0 M in hexanes) was added, resulting in an immediate color change (brown/yellow). After 5 min the ice bath was removed, the solution stirred for another 15 min, and then lactol **22** (1.0 equiv) in THF (0.7 M) was added. After 5 h the reaction was quenched with saturated NH_4Cl and the mixture extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and concentrated, providing a viscous residue. Column chromatography using gradient elution (15% EtOAc in hexanes → 30% EtOAc in hexanes) provided *cis*- (**23**) and *trans*-azidosphingosine (**24**) (4:1 ratio, respectively, ^{1}H NMR analysis).

D-*erythro*-(2*S*,3*R*,4*Z*)-2-Azidooctadecene-1,3-diol (23a): cis isomer isolated in 14% yield; $R_f = 0.43$ (hexanes/EtOAc, 2:1); ^{1}H NMR ($CDCl_3$) δ 5.67 (dtd, $J = 0.8$, 7.5, 11.0 Hz, 1H), 5.45 (tt, $J = 1.5$, 10.9 Hz, 1H), 4.58 (ddd, $J = 0.9$, 5.8, 8.8 Hz, 1H), 3.77 (m, 2H), 3.49 (q, $J = 5.4$ Hz, 1H), 2.19 (br s, 2H), 2.08 (m, 2H), 1.23 (m, >22H), 0.85 (t, $J = 6.8$ Hz, 3H).

D-*erythro*-(2*S*,3*R*,4*E*)-2-Azidooctadecene-1,3-diol (24a): trans isomer isolated in 3.8% yield; $R_f = 0.38$ (hexane/EtOAc, 2:1); $[\alpha]^{24}_D = -34.1$ (*c* 1.58, $CHCl_3$) (lit.[8h] $[\alpha]^{20}_D = -32.9$ (*c* 4.0, $CHCl_3$)); ^{1}H NMR ($CDCl_3$) δ 5.80 (dtd, $J = 0.7$, 6.7, 15.4 Hz, 1H), 5.51 (ddt, $J = 1.3$, 7.3, 15.4 Hz, 1H), 4.23 (t, $J = 6.4$ Hz, 1H), 3.77 (m, 2H), 3.45 (q, $J = 5.3$ Hz, 1H), 2.05 (q, $J = 7.0$ Hz, 2H), 1.94 (br s, 2H), 1.23 (m, >22H), 0.86 (t, $J = 6.8$ Hz, 3H).

L-*threo*-(2*S*,3*S*,4*Z*)-2-Azidooctadecene-1,3-diol (23b): cis isomer isolated in 24.4% yield; $R_f = 0.52$ (hexane/EtOAc, 2:1); ^{1}H NMR ($CDCl_3$) δ 5.64 (dt, $J = 7.5$, 11.1 Hz, 1H), 5.44 (tt, $J = 1.5$, 9.9 Hz, 1H), 4.53 (m, 1H), 3.79 (m, 1H), 3.65 (m, 1H), 3.44 (dt, J = 4.1, 6.3 Hz, 1H), 2.06 (m, 4H), 1.23 (m, >22H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$) δ 135.7 (CH), 127.7 (CH), 68.4 (CH), 68.1 (CH), 62.8 (CH$_2$), 31.9 (CH$_2$), 29.64 (CH$_2$), 29.56 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 28.0 (CH$_2$), 22.7 (CH$_2$), 14.0 (CH$_3$).

L-*threo*-(2*S*,3*S*,4*E*)-2-Azidooctadecene-1,3-diol (24b): trans isomer isolated in 6.1% yield; R_f = 0.45 (hexane/EtOAc, 2:1); [α]$^{24}_{\rm D}$ = +3.11 (c 0.53, CHCl$_3$); IR (neat) 3360, 2920, 2855, 2095, 1520 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 5.78 (dtd, J = 0.7, 6.7, 15.4 Hz, 1H), 5.50 (ddt, J = 1.4, 7.1, 15.4 Hz, 1H), 4.19 (t, J = 6.5 Hz, 1H), 3.80 (dd, J = 4.3, 11.5 Hz, 1H), 3.68 (dd, J = 6.3, 11.5 Hz, 1H), 3.45 (dt, J = 4.3, 6.0 Hz, 1H), 2.04 (q, J = 6.7 Hz, 2H), 1.63 (br s, >2H), 1.22 (m, >22H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$) δ 135.5 (CH), 128.4 (CH), 73.6 (CH), 67.8 (CH), 63.0 (CH$_2$), 32.3 (CH$_2$), 31.9 (CH$_2$), 29.7 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 22.7 (CH$_2$), 14.0 (CH$_3$). Anal. Calcd for $C_{18}H_{35}N_3O_2$: C, 66.42; H, 10.84; N, 12.91. Found: C, 66.87; H, 10.70; N, 12.41.

D-*threo*-(2*R*,3*R*,4*Z*)-2-Azido-4-octadecene-1,3-diol (23d) and D-*threo*-(2*R*,3*R*,4*E*)-2-Azido-4-octadecene-1,3-diol (24d). To a flame-dried round-bottomed flask under Ar was added *n*-tetradecyltriphenylphosphonium bromide (359 mg, 0.67 mmol, 3.50 equiv). After 30 min under high vacuum Ar was introduced. THF (2.50 mL) was added, and the solution was cooled in an ice bath. After 15 min, sodium amylate[34] (0.27 M, 2.5 mL, 3.5 equiv) was added. The solution immediately became orange. After 15 min the ice bath was removed. After 30 min at rt the ylide solution was cooled to 0 °C, and lactol **32d** (72.9 mg, 0.190 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise over 1 min. After 30 min the ice bath was removed, and the reaction mixture stirred for 1 h at rt. After the solution was cooled to −55 °C, the reaction was quenched with saturated NH$_4$Cl (10 mL), and the mixture was extracted with EtOAc (×3). The organic extracts were combined, dried (MgSO$_4$), and concentrated providing a viscous dark oil. Column chromatography using gradient elution (100% hexanes → hexanes/EtOAc, 6:1) provided 32 mg of impure sphingosine adducts **34d** and **35d**. Further attempts at purification were futile; the major impurity was *tert*-butyldiphenylsilanol. ^{1}H NMR of the impure silyloxy azidosphingosine indicated a 9:1 cis:trans ratio of olefinic isomers. (*Note*: When the lactol **32d** was added at rt, to the ylide, a 6:4 cis:trans ratio was found.)

34d and 35d: ^{1}H NMR (CDCl$_3$) δ 7.67 (m, 4H), 7.42 (m, 6H), 5.72 (m, 0.1H, trans), 5.55 (dt, J = 7.3, 11.0 Hz, 0.9H, cis), 5.38 (m, 1H), 4.43 (m, J = 4.8 Hz av, 0.9H, cis), 4.13 (q, J = 5.6 Hz, 0.1H, trans), 3.8 (m, 4H), 3.42 (m, 2H), 1.99 (m, 2H), 1.26 (s, 22H), 0.89 (t, J = 6.9 Hz, 3H).

The crude silyloxy azidosphingosine products (**34d** and **35d**) were treated with *n*-Bu$_4$NF-hydrate (40 mg) in THF (2.0 mL), followed by addition of H$_2$O, extraction (EtOAc), and concentration. The resulting oil was subjected to column chromatography (gradient elution, hexanes/EtOAc, 6:1 → 7:3) to provide **23d** and **24d** (8.3 mg, 13% yield from **32d**).

D-*threo*-(2*R*,3*R*,4*Z*)-2-Azido-4-octadecene-1,3-diol (23d): cis isomer isolated in 11.0% yield; ^{1}H NMR (CDCl$_3$) δ 5.66 (dtm, J = 7.7, 11.0 Hz, 1H), 5.46 (ddt, J = 1.5, 10.8, 10.8 Hz, 1H), 4.52 (m, 1H), 3.81 (m, 1H), 3.67 (m, 1H), 3.46 (ddd, J = 4.1, 6.4, 6.4 Hz, 1H), 2.08 (m, 2H), 1.90 (m, 2H), 1.24 (s, >20H), 0.90 (t, J = 7.0 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 135.8 (CH), 127.5 (CH), 68.3 (CH), 68.0 (CH), 62.8 (CH$_2$), 31.9 (CH$_2$), 29.6 (CH$_2$), 29.56 (CH$_2$), 29.5 (CH$_2$), 29.34 (CH$_2$), 29.28 (CH$_2$), 28.9 (CH$_2$), 27.9 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$).

D-*threo*-(2*R*,3*R*,4*E*)-2-Azido-4-octadecene-1,3-diol (24d): trans isomer isolated in 2% yield; R_f = 0.30 (hexane/EtOAc, 2:1); [α]$^{24}_{\rm D}$ = −2.40 (c 0.27, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.80 (dtd, J = 0.7, 6.7, 15.4 Hz, 1H), 5.52 (ddt, J = 1.4, 7.1, 15.4 Hz, 1H), 4.21 (t, J = 6.5 Hz, 1H), 3.81 (dd, J = 4.3, 11.5 Hz, 1H), 3.71 (dd, J = 6.3, 11.5 Hz, 1H), 3.44 (dt, J = 4.3, 6.0 Hz, 1H), 2.04 (q, J = 6.7 Hz, 2H), 1.63 (br s, >2H), 1.36 (m, 2H), 1.23 (m, >22H), 0.86 (t, J = 6.6 Hz, 3H).

General Photoisomerization Procedure: *cis*-23 → *trans*-24 or *cis*-27 → *trans*-28. To a mixture of *cis*- and *trans*-azidosphingosines under an Ar atmosphere were added 1 vol of dioxane and 3 vol of hexane by means of a syringe (molarity of solution, 0.01 M). The solution was degassed by bubbling Ar through it for 20 min. Diphenyl disulfide was added (0.3 equiv); the Pyrex round-bottomed flask was placed 2.5−5.0 cm from the photochemical lamp. The light source was a 450-W Canrad-Hanovia, medium-pressure, quartz, mercury lamp. (*Note*: In our initial communication[1a] we stated incorrectly that a 400-W light source had been used.) Exposure of this solution to the filtered light (Pyrex glass excludes light <280 nm)[26] for 3 h provided the thermodynamic cis−trans equilibrium. (*Note*: The solution turned light-green.) Additional diphenyl disulfide (0.15 equiv) was added if the isomerization proceeded slowly. The solution was concentrated under reduced pressure and purified as before. This provided an 80% combined yield of *trans*- and *cis*-azidosphingosine in a 3:1 ratio, respectively, with respect to the initial predominately cis mixture of olefins.

For further examples of this type of photoisomerization, albeit without an azide present, see refs 8g and 11h.

L-*erythro*-(2*S*,3*R*)-Triacetylsphingosine (*trans*-25c and *cis*-26c). A 1:1 (^{1}H NMR analysis) mixture of inseparable *cis*-**26c** and *trans*-**25c** was obtained after photoisomerization of the 6:1 cis:trans mixture of acetamides **27d** and **28c** and peracylation: [α]$^{27}_{\rm D}$ = +8.2 (c 0.9, CHCl$_3$).[31] See General Photoisomerization Procedure for experimental details.

(3*R*,4*S*,5*R*,6*S*)-3-Azido-4-(*tert*-butyldiphenylsilyl)-1-chloro-5,6-*O*-isopropylidenecyclohex-1-ene-4,5,6-triol (29d). To a solution of alcohol **4d**[1a] (2.30 g, 9.37 mmol) in THF (10.0 mL) were added *tert*-butyldiphenylsilyl chloride (5.07 g, 18.5 mmol, 2.00 equiv) and imidazole (1.52 g, 22.4 mmol, 2.39 equiv). After 4 h at reflux the reaction mixture was cooled to rt and stirred for another 12 h. (*Note*: As the reaction proceeds a white precipitate, which we assume to be the hydrochloride salt of imidazole, accumulates.) The solution was filtered through Celite (rinsed with CH$_2$Cl$_2$), and the filtrate was washed with saturated aq NH$_4$Cl and brine. The organic extracts were dried (MgSO$_4$) and evaporated to give 7.21 g of a viscous brown oil. Column chromatography using gradient elution (100% hexanes → 3% EtOAc in hexanes) provided **29d** (3.85 g, 85%) as a viscous clear oil: R_f = 0.45 (hexanes/EtOAc, 9:1); [α]$^{24}_{\rm D}$ = −62.5 (c 0.95, CHCl$_3$); IR (neat) ν 3075, 3050, 2985, 2930, 2105 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.78 (m, 4H), 7.40 (m, 6H), 5.73 (m, J = 1.7 Hz, 1H), 4.37 (dm, J = 8.7 Hz, 1H), 4.10 (m, 2H), 3.68 (dm, J = 8.8 Hz, 1H), 1.42 (s, 3H), 1.27 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (CDCl$_3$) δ 133.9 (C), 133.8 (C), 132.2 (C), 110.6 (C), 19.4 (C), 136.0 (CH), 135.9 (CH), 130.2 (CH), 129.9 (CH), 128.0 (CH), 127.6 (CH), 76.6 (CH), 76.4 (CH), 72.8 (CH), 61.7 (CH), 27.5 (CH$_3$), 26.8 (CH$_3$), 26.2 (CH$_3$); MS CI m/z (rel. intensity) 484 (M$^+$, 0.52), 426 (17), 398 (38), 385 (36), 383 (100), 378 (34), 305 (37). Anal. Calcd for $C_{25}H_{30}ClN_3O_3Si$: C, 62.03; H, 6.25; N, 8.68. Found: C, 62.41; H, 6.52; N, 8.35.

(2*S*,3*R*,4*S*,5*R*)-5-Azido-4-[(*tert*-butyldiphenylsilyl)oxy]-1,2-*O*-isopropylidenehexanoic Acid Methyl Ester 2,3,4,6-Tetrol (30d). Vinyl chloride **29d** (3.74 g, 7.73 mmol) was added to MeOH (50 mL) and gently heated to ensure dissolution. The reaction mixture was then cooled with a dry ice/acetone bath, and O$_3$/O$_2$ was bubbled through the solution. After 20 min the solution was saturated with O$_3$, indicated by a characteristic blue color, and TLC analysis indicated no starting material remained. The reaction mixture was then purged with N$_2$ for 20 min at −78 °C. The reaction flask was placed in an ice bath, and maintaining the temperature at 5 °C, three portions of NaBH$_4$ (580 (15.3 mmol, 2.00 equiv), 220, and finally 240 mg) were added, with 25-min intervals between additions. (*Note*: Use lumps of NaBH$_4$; if powdered NaBH$_4$ is used, add slowly over 3−5 min.) Thirty minutes after the last addition of NaBH$_4$ the ice bath was removed, and the reaction mixture stirred for another 20 min. Two more

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(33) Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832.

(34) For the preparation of sodium amylate, see: Short, R. P.; Ranu, J. M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453. The solution of sodium amylate must be heated to 65 °C and transferred quickly to the cooled solution of the phosphonium salt via syringe; otherwise, the amylate salt precipitates in the syringe.

portions of $NaBH_4$ (340 mg, wait 20 min, then 107 mg) were added. (*Note*: It is crucial to monitor the reaction by TLC after each addition of $NaBH_4$ (depending on the reaction, more or less $NaBH_4$ may be required).) Distilled H_2O (150 mL) was added, and the solution was acidified with 1.2 N HCl to pH 3.5 ± 0.5. The acidic solution was immediately extracted with EtOAc (×4); the combined organic extracts were washed with brine (×2), dried ($MgSO_4$), and evaporated to provide a yellow oil. Column chromatography (gradient elution, 15% → 40% EtOAc in hexanes) provided **30d** (3.59 g, 91%) as a viscous clear oil: $R_f = 0.33$ (hexanes/EtOAc, 2:1); $[\alpha]^{24}_{D} = +29.6$ (*c* 1.6, $CHCl_3$); IR (neat) ν 3500, 3070, 3050, 2980, 2950, 2100, 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (m, 4H), 7.41 (m, 6H), 4.40 (ddm, $J = 3.9$, 6.9 Hz, 1H), 4.22 (m, 2H), 3.52 (m, 6H), 1.57 (s, 3H), 1.31 (s, 3H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.3 (C), 133.3 (C), 133.0 (C), 110.6 (C), 19.6 (C), 136.0 (CH), 135.9 (CH), 130.0 (CH), 127.8 (CH), 127.7 (CH), 80.1 (CH), 75.4 (CH), 70.4 (CH), 64.6 (CH), 51.8 (CH), 62.3 (CH_2), 27.0 (CH_3), 26.4 (CH_3), 25.1 (CH_3); MS CI *m*/*z* (rel. intensity) 514 ($M^+ + 1$, 2), 487 (33), 486 (100), 428 (73.6), 408 (60), 379 (12), 378 (73), 358 (31), 291 (45), 220 (49). Anal. Calcd for $C_{26}H_{35}N_3O_6Si$: C, 60.80; H, 6.87; N, 8.18. Found: C, 61.16; H, 7.15; N, 7.87.

(2*S*,3*R*,4*S*,5*R*)-5-Azido-4-[(*tert*-butyldiphenylsilyl)oxy]hexanoic Acid Methyl Ester 2,3,4,6-Tetrol (31d). Acetonide **30d** (1.73 g, 3.37 mmol) was added to 1% I_2 in MeOH (30 mL, w/v) and heated at 45 °C with stirring for 46 h. The reaction was quenched with saturated sodium thiosulfate ($Na_2S_2O_3$) (80 mL) and the mixture extracted with EtOAc (×3). The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the ensuing viscous oil using gradient elution (25% → 50% EtOAc in hexanes) provided **31d** (1.28 g, 80% yield) as a white solid. (*Note*: Four inches of silica gel are sufficient and optimal. This product is prone to silyl migration and lactonization on prolonged exposure to silica gel. If the reaction is performed at higher temperatures, three new products (**36d**, **37d**, **38d**) appear.[32] Compound **36d** was judged to be too unstable for analysis; **37d** and **38d** were fully identified.) Vicinal diol **31d**: $R_f = 0.19$ (hexanes/EtOAc, 1:1); $[\alpha]^{24}_{D} = +13.4$ (*c* 1.00, $CHCl_3$); mp = 78−82 °C; IR (KBr) ν 3470, 3430, 3350, 3075, 3050, 3000, 2950, 2095, 1755 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.69 (m, 4H), 7.42 (m, 6H), 5.62 (d, $J = 5.9$ Hz, OH), 5.31 (d, $J = 5.8$ Hz, OH), 4.91 (t, $J = 5.2$ Hz, OH), 4.27 (t, $J = 6.1$ Hz, 1H), 3.83 (t, $J = 4.3$ Hz, 1H), 3.76 (q, $J = 5.4$ Hz, 1H), 3.66 (q, $J = 5.7$ Hz, 1H), 3.52 (s, 3H), 3.37 (t, $J = 5.6$ Hz, 2H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.9 (C), 132.8 (C), 19.5 (C), 136.0 (CH), 130.2 (CH), 127.9 (CH), 75.4 (CH), 71.8 (CH), 71.6 (CH), 64.5 (CH), 52.5 (CH), 61.4 (CH_2), 27.0 (CH_3).

(2*S*,3*R*)-3-Azido-2-[(*tert*-butyldiphenylsilyl)oxy]-γ-butyrolactol (32d). $NaIO_4$ (1.15 g, 5.40 mmol, 2.00 equiv) was added to a solution of vicinal diol **31d** (1.28 g, 2.70 mmol) in CH_3OH/H_2O (80 mL, 3:1). The reaction mixture was protected from light and stirred. (*Note*: A white precipitate accumulates as the reaction proceeds; it is not the product.) After 3 h CH_2Cl_2 (80 mL) was added, and the resulting solution was passed through a plug of Celite. H_2O (80 mL) was added to the filtrate, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were dried ($MgSO_4$) and evaporated to provide an oil. Column chromatography (gradient elution, 20% → 35% EtOAc/hexanes) provided **32d** (778 mg, 75%) as a viscous clear oil. In addition **33d** (134 mg, 13%), the product of silyl migration, was isolated. (*Note*: Both anomeric lactols are evident in the ^{1}H and ^{13}C NMR spectra of **32d**. The two anomers exist in an approximate ratio of 1:1.2 (10−20 mg in 0.5 mL of $CDCl_3$).) TOCSY NMR established the separate lactol resonances: $R_f = 0.28$ (hexanes/EtOAc, 4:1); $[\alpha]^{25}_{D} = -2.22$ (*c* 1.35, $CHCl_3$); IR (neat) ν 3435, 3080, 2980, 2950, 2100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (m, 4H), 7.45 (m, 6H), 5.28 (dd, $J = 4.0$, 9.8 Hz, 1H′), 5.25 (d, $J = 7.9$ Hz, 1H), 4.28 (dd, $J = 5.2$, 9.8 Hz, 1H), 4.18 (dd, $J = 4.6$, 9.8 Hz, 1H′; d, $J = 1.5$ Hz, 1H), 4.12 (dd, $J = 2.2$, 4.0 Hz, 1H′), 4.01 (dd, $J = 2.3$, 9.8 Hz, 1H), 3.96 (d, $J = 9.8$ Hz, OH′), 3.76 (dt, $J = 1.7$, 5.0 Hz, 1H), 3.66 (ddd, $J = 0.5$, 2.1, 9.8 Hz, 1H′), 3.62 (m, $J = 2.1$, 4.6 Hz, 1H′), 2.63 (d, $J = 7.9$ Hz, OH), 1.13 (s, 9H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 132.7 (C), 132.4 (C), 132.0 (C), 131.4 (C), 19.1 (C), 19.0 (C), 135.6 (CH), 135.58 (CH), 130.6 (CH), 130.5 (CH), 130.24 (CH), 130.19 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 103.5 (CH), 97.0 (CH), 81.1 (CH), 76.5 (CH), 66.2 (CH), 65.9 (CH), 71.2 (CH_2), 68.2 (CH_2), 26.9 (CH_3), 26.8 (CH_3).

(2*S*,3*R*)-3-Azido-1-[(*tert*-butyldiphenylsilyl)oxy]-2-hydroxy-γ-butyrolactol (33d): The procedure used to make lactol **32d** also provided 134.4 mg (0.350 mmol, 13%) of the anomeric silyloxy-protected lactol **33d**; $R_f = 0.45$ (hexanes/EtOAc, 4:1); $[\alpha]^{25}_{D} = -86.2$ (*c* 1.30, $CHCl_3$); IR (neat) ν 3505, 3070, 3050, 2955, 2100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.67 (m, 4H), 7.43 (m, 6H), 5.41 (d, $J = 3.7$ Hz, 1H), 4.20 (dd, $J = 5.7$, 9.7 Hz, 1H), 4.13 (m, 2H), 3.66 (dd, $J = 4.4$, 9.0 Hz, 1H), 2.91 (d, $J = 7.5$ Hz, OH), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 132.5 (C), 132.4 (C), 19.2 (C), 135.6 (CH), 135.5 (CH), 130.2 (CH), 130.1 (CH), 127.9 (CH), 127.8 (CH), 97.2 (CH), 77.2 (CH), 66.1 (CH), 68.6 (CH_2), 26.8 (CH_3).

(2*S*,3*R*,4*S*)-2-Hydroxy-3-[(*tert*-butyldipenylsilyl)oxy]-4-(1(*R*)-azido-2-hydroxyethyl)-γ-butyrolactone (37d): procedure used to synthesize diol **31d** also provided lactone **37d**; $R_f = 0.45$ (hexanes/EtOAc, 1:1); $[\alpha]^{24}_{D} = -45.3$ (*c* 1.03, $CHCl_3$); mp = 104−105 °C; IR (KBr) ν 3350, 3070, 3045, 2940, 2105, 1790, 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (m, 4H), 7.46 (m, 6H), 4.57 (m, 1H) (*Note*: When a drop of D_2O is added the multiplet is simplified to a d, $J = 6.0$ Hz, 1H), 4.34 (d, $J = 5.9$ Hz, 1H), 3.99 (d, $J = 2.1$ Hz, 1H), 3.61 (dd, $J = 7.7$, 11.2 Hz, 1H), 3.44 (dd, $J = 5.4$, 11.2 Hz, 1H), 2.92 (br s, 1H, OH), 2.69 (m, 1H) (*Note*: When a drop of D_2O is added the multiplet is simplified to a septet, $J = 2.2$, 5.4, 7.6 Hz, 1H), 1.64 (br s, 1H, OH), 1.09 (s, 9H) (*Note*: If the ^{1}H NMR solvent is DMSO-d_6 or acetone-d_6, a 1:1 mixture of **37d** and **38d** results almost immediately.); ^{13}C NMR ($CDCl_3$) δ 174.8 (C), 132.5 (C), 131.4 (C), 19.2 (C), 135.7 (CH), 130.8 (CH), 130.6 (CH), 128.3 (CH), 83.2 (CH), 71.7 (CH), 68.2 (CH), 62.15 (CH), 62.24 (CH_2), 26.9 (CH_3); MS CI *m*/*z* (rel. intensity) 442 ($M^+ + 1$, 2). Anal. Calcd for $C_{22}H_{27}N_3O_5Si$: C, 59.84; H, 6.16; N, 9.52. Found: C, 59.46; H, 6.15; N, 9.34.

(2*S*,3*S*,4*S*)-2-[(*tert*-Butyldipenylsilyl)oxy]-3-hydroxy-4-(1(*R*)-azido-2-hydroxyethyl)-γ-butyrolactone (38d): procedure used to synthesize diol **31d** also provided lactone **38d**; $R_f = 0.28$ (hexanes/EtOAc, 1:1); $[\alpha]^{24}_{D} = -77.2$ (*c* 1.00, $CHCl_3$); mp = 121−123 °C; IR (KBr) ν 3350, 3070, 2960, 2935, 2105, 1785, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82 (m, 2H), 7.69 (m, 2H), 7.47 (m, 6H), 4.65 (d, $J = 5.5$ Hz, 1H), 4.44 (d, $J = 2.4$ Hz, 1H), 3.81 (d, $J = 6.4$ Hz, 1H), 3.78 (dd, $J = 0.8$, 5.5 Hz, 1H), 3.61 (ddd, $J = 2.5$, 6.4 Hz, 1H), 2.98 (br s, OH), 2.05 (br s, OH), 1.16 (s, 9H) (*Note*: If the ^{1}H NMR solvent is DMSO-d_6, a 1:1 mixture of lactones **37d** and **38d** immediately ensues.); ^{13}C NMR ($CDCl_3$) δ 173.3 (C), 132.2 (C), 131.0 (C), 19.3 (C), 135.9 (CH), 135.5 (CH), 130.6 (CH), 130.5 (CH), 128.1 (CH), 128.0 (CH), 82.1 (CH), 70.2 (CH), 69.5 (CH), 62.3 (CH), 62.8 (CH_2), 26.8 (CH_3); MS CI *m*/*z* (rel. intensity) 442 ($M^+ + 1$, 2.5), 385 (11), 384 (43), 364 (100), 308 (83), 199 (34), 60 (52). Anal. Calcd for $C_{22}H_{27}N_3O_5Si$: C, 59.84; H, 6.16; N, 9.52. Found: C, 59.83; H, 6.23; N, 9.42.

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