A solution of LDA [prepared from diisopropylamine (16 mg, 0.16 mmol) and 0.1 mL (0.16 mmol) of *n*-butyllithium (100 mg/mL in hexane)] in THF (1 mL) was added dropwise to a stirred solution of **30** (58 mg, 0.149 mmol) in THF (1 mL) at −78 °C. After stirring had been continued for 20 min, a solution of **53** (39 mg, 0.15 mmol) in THF (0.5 mL) was added to this solution, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was then treated with acetyl chloride (0.011 mL), poured into water, and extracted with ether (10 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (97:3 v/v) as an eluant to give 85 mg of **54** as a colorless oil, which was used immediately for the next reaction.

To a stirred solution of **54** (85 mg) in THF–MeOH (1:1) (3 mL) was added 5% sodium amalgam (300 mg) at −20 °C, and stirring was continued for 2 h at the same temperature. After stirring had been continued for 7 h at room temperature, the reaction mixture was poured into water and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The crude product, **55**, obtained by the evaporation of the solvent was dissolved in THF (2 mL), treated with 0.13 mL of *n*-Bu_4NF (1.0 M in THF), and stirred for 2 h at room temperature. The mixture was then poured into water and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The residue resulted from the evaporation of the solvent was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (17:3 v/v) as an eluant to give 29.2 mg (51%) of vitamin D_3 (**29**) as a colorless oil: $[\alpha]^{20}_D$ +49.5° (*c* 0.5) [authentic sample, $[\alpha]^{20}_D$ +51.2° (*c* 0.63)]. This sample was identical with an authentic sample in spectral comparisons.

3,5-Dinitrobenzoate of Vitamin D_3. To a solution of triethylamine (0.08 mL) and 3,5-dinitrobenzoyl chloride (10 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) was added a solution of **29** (5 mg, 0.013 mmol) and stirring was continued for 1 h at room temperature. The reaction mixture was then poured into water and extracted with ether (10 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Evaporation of the solvent gave a crude product, which was chromatographed on neutral alumina (1 g) by using hexane–ethyl acetate (19:1 v/v) as an eluant to give 6 mg (80%) of **56** as yellow needles: mp 129–130 °C (acetone–MeOH); $[\alpha]^{20}_D$ +95.9° (*c* 0.34). This was identical with the authentic sample[30,31] in all aspects.

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α-Amino Acid Derivatives as Chiral Educts for Asymmetric Products. Synthesis of Sphingosine from α′-Amino-α,β-ynones

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The utility of α′-amino-α,β-ynones in the chirospecific synthesis of sphingosine is demonstrated. Thus, a protected L-serine isoxazolidide has been converted to sphingosine by two routes, both via α,β-ynones. The first route is very short and high yielding, merely involving two selective reductions after synthesis of the appropriate α,β-ynone. The second route involves alkylation of a β-unsubstituted ynone and illustrates the synthetic versatility of the α′-amino-α,β-ynone system. Further routes through conjugate 1,4 additions to ynones are demonstrated but are limited by the highly reactive nature of this system.

The chirospecific synthesis of natural products from simple, readily available components of the chiral pool as educts has become a major objective for organic chemists. Previous work from this laboratory has demonstrated the conversion of suitably protected amino acids into optically pure amino ketones by acylation of aromatic rings[1] and by reaction with organometallic reagents.[2] A modification of this methodology, using isoxazolidides, has produced optically pure α′-amino-α,β-ynones.[3] This modification was necessary because the less reactive organometallics derived from acetylenic precursors would not react with the carboxylate functionality of protected amino acids. The use of an isoxazolidide "activating" group gave good yields of the desired α,β-ynones.

To demonstrate the α′-amino-α,β-ynone system's utility, we have synthesized the amino lipid sphingosine (1). Presented here are two chirospecific routes to sphingosine from L-serine. Both routes involve the use of α′-amino-α,β-ynones and exploit the flexibility inherent in these synthetic intermediates. The carbon chain can be introduced directly via lithium pentadecyne, followed by a diastereoselective reduction of the ketone. This produces sphingosine (1) in five steps from CBZ-serine in an overall yield of 22% (Scheme I and II). An alternative path is to form an α,β-unsubstituted acetylenic ketone (**17**; Scheme III) using lithium acetylide. Reduction of the ketone followed by alkylation with 1-iodotridecane (Scheme IV) then leads to sphingosine (1).

Sphingosine has been the target of several syntheses in the past.[4] Recently, interest has greatly increased, with methodology centering on enantiospecific routes. Attempts have been made at utilizing the 2*S* stereochemistry of L-serine as a chiral precursor;[5] however, this route involves an intermediate α-amino aldehyde, whose chiral integrity is questionable.[6] Sphingosine has also been synthesized

(1) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157–6163.

(2) (a) Kundsen, C. G.; Rapoport, H., *J. Org. Chem.* **1983**, *48*, 2260–2266. (b) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095–1098. (c) Maurer, P. J.; Knudsen, C. G.; Palkowitz, A. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 325–330.

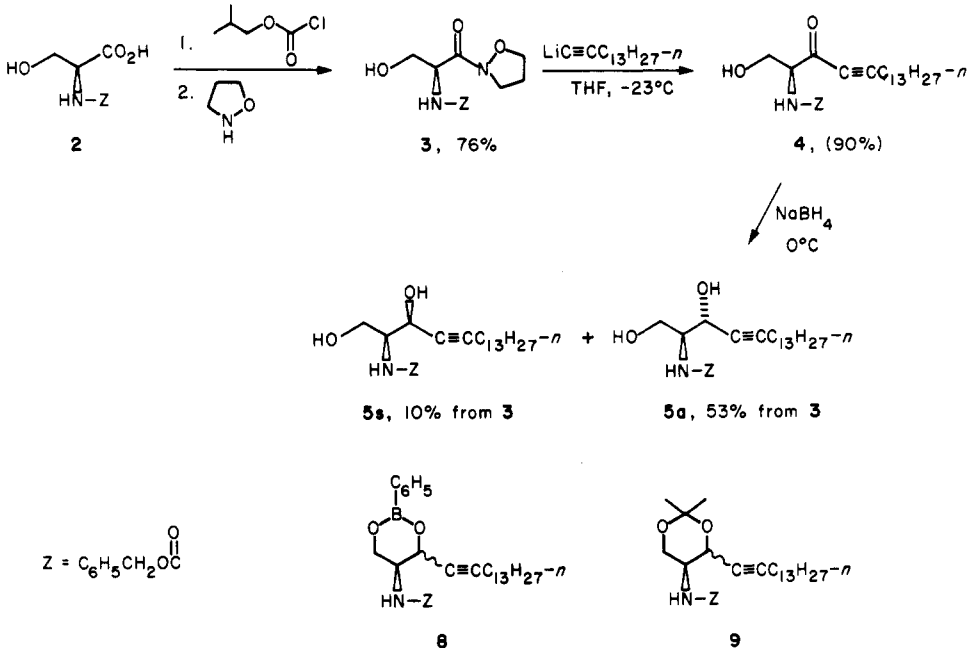
(3) Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972–3979.

(4) Syntheses of sphingosine are reviewed to 1967 by: Shapiro, D. In *Chemistry of Sphingolipids*; Hermann: Paris, 1969.

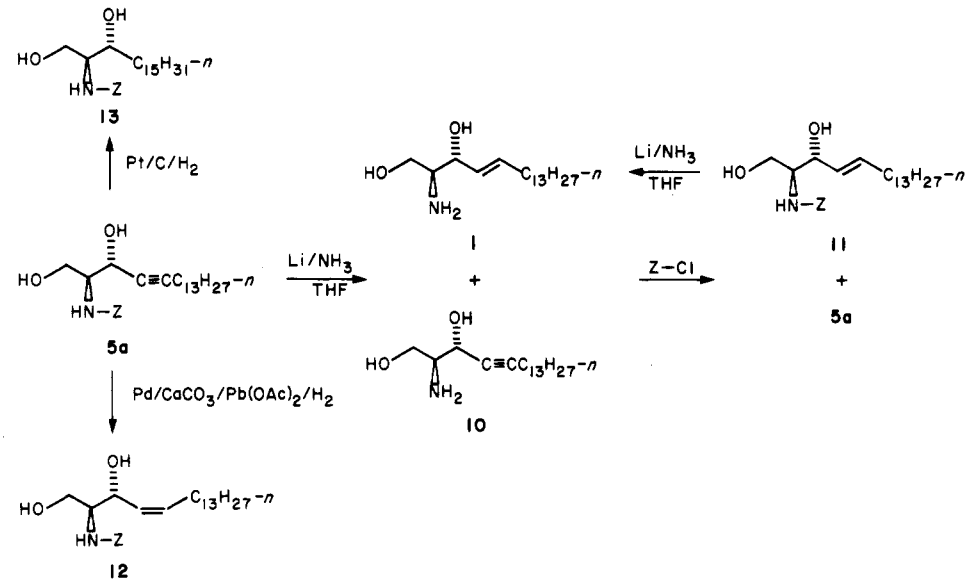
(5) (a) Newman, H. *J. Am. Chem. Soc.* **1973**, *95*, 4098–4099. (b) Tkaczuk, P.; Thornton, E. R. *J. Org. Chem.* **1981**, *46*, 4393–4398.

0022-3263/86/1951-5320$01.50/0

Scheme I

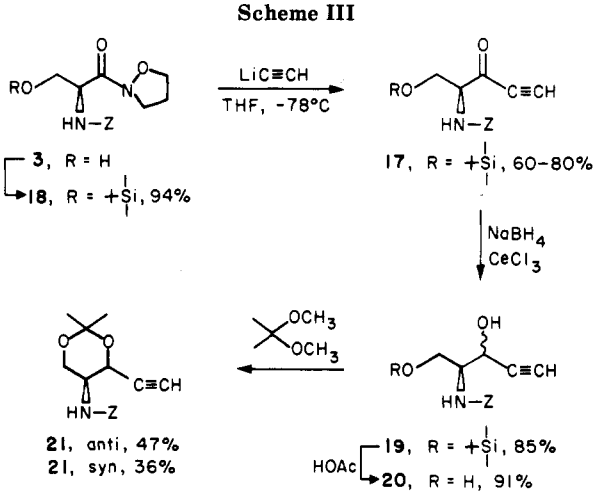


Scheme II



from carbohydrate precursors; an early attempt required eight steps from 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose.[7a] A somewhat lengthly approach from D-mannose has recently been reported,[7b] as well as an efficient synthesis from D-galactose.[7c] In the latter, a key trihydroxy aldehyde was condensed with a long-chain Wittig reagent to form "practically exclusively" the *trans*-trihydroxyalkene. Common to all these synthetic efforts is introduction of the trans double bond by Wittig olefination,[5,7] requiring the use of a potentially configurationally labile α-substituted aldehyde. More recently a short and efficient synthesis has appeared[8a,8c] in which the necessary chirality at both C-2 and C-3 is introduced through a Sharpless expoxidation. A virtually identical

Scheme III

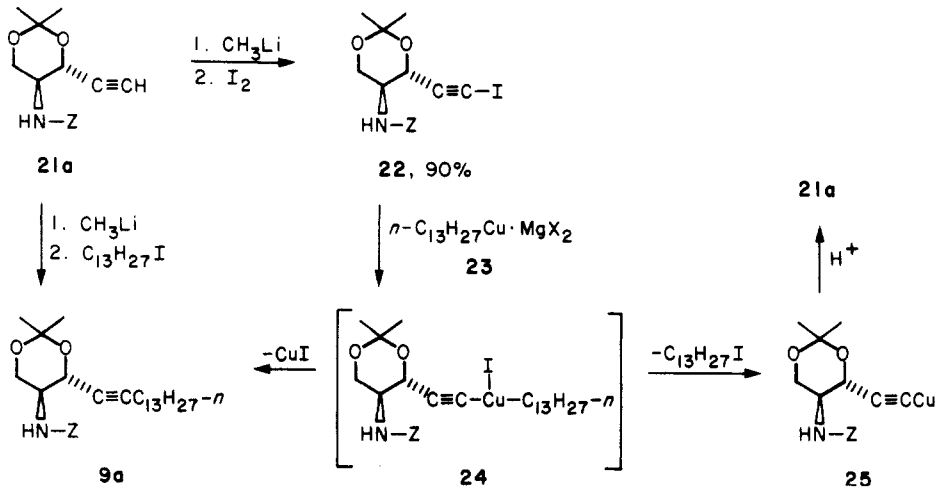


(6) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624–3626.

(7) (a) Reist, E. J.; Christie, P. H., *J. Org. Chem.* **1970**, *35*, 4127–4130. (b) Obayashi, M.; Schlosser, M. *Chem. Lett.* **1985**, 1715–1718. (c) Schmidt, R. R.; Zimmermann, P. *Tetrahedron Lett.* **1986**, *27*, 481–484.

(8) (a) Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491–5494. (b) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1986**, *50*, 3752–3757. (c) Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 368–373.

Scheme IV



series of reactions has been used to synthesize dihydrosphingosine.[8b] Introduction of the stereochemical centers via such epoxidations avoids the intermediacy of a chirally labile aldehyde but presents a new problem with asymmetric induction.

The synthesis of sphingosine presented here has several considerable advantages. The stereochemistry at C-2 is introduced directly from L-serine. This stereocenter is then used to induce the stereochemistry at C-3. All four stereoisomeric sphingosines can be prepared by a single synthetic strategy depending only on the choice of starting amino acid (D or L) and ketone reducing agent. The stereochemistry of the double bond can also be easily and completely controlled by the mode of reduction of the triple bond. The carbon chain can be varied considerably and introduced at either a direct or a subsequent stage. Acylation of the acetylenic lipid chain occurs under relatively mild conditions, and in this way any acetylenic lipid chain stable to *n*-butyllithium at −23 °C can be incorporated. Direct addition of the carbon chain is also an attractive feature as it involves a minimal use of protecting groups.

We were not merely interested in the synthesis of natural sphingosine but wanted to demonstrate the synthetic versatility of the α′-amino-α,β-ynone system. Toward this goal some further chemistry has been explored. Alkylation of a β-unsubstituted alkyne, derived from an α′-amino-α,β-ynone, and 1,4 additions to the ynone were chosen as examples of potentially useful transformations. The alkylation reaction is a key step in our second route to sphingosine and allows even more latitude in designing side chains for the synthesis of analogues. The Michael additions reflect further reactivity of the α′-amino-α,β-ynone system and underscore some important limitations on their use.

Results and Discussion

Previous work has shown that an *N*-alkylcarbamate-protected amino acid isoxazolidide provided the best yield of ynone with retention of optical purity.[3] The starting material delineated by these criteria was *N*-CBZ-L-serine isoxazolidide (**3**; Scheme I), prepared from *N*-CBZ-L-serine (**2**) with isoxazolidine in 76% yield by a minor modification of our previous method.[3] Reaction of **3** with 500 mol % of lithium pentadecyne produced the ynone **4** in 90% yield while the excess pentadecyne was easily and quantitatively recovered.

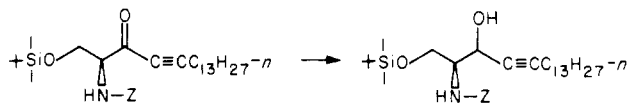
Reduction of ynone **4**, to give the 1,3-diol **5**, was extensively examined and the results are presented in Table I. The reducing agents were chosen on the basis of literature examples of diastereoselectivity and/or regioselectivity (1,2 vs. 1,4 addition). All of the reducing agents and conditions examined formed the anti diastereomer **5a** as the major product. The highest diastereoselectivity was obtained

Table I. Diastereoselectivity in the Reduction of Ynone 4 to *anti*- and *syn*-1,3-Diols 5a and 5s

entry	reducing agent[a]	diastereoselectivity,[b] 5a/5s
1	$NaBH_4$	80/20
2	$LiBH_4$/*i*-PA	78/22
3	$LiBH_4$/THF	77/23
4	$NaBH_3CN$/pH 4.5[c]	83/17
5	$Zn(BH_4)_2$/0°C[d]	77/23
6	$Zn(BH_4)_2$/−78 °C	86/14
7	$LiHAl(O\text{-}t\text{-}Bu)_3$[e]	67/33
8	φ-$Si(CH_3)_2H$/TBAF[f]	95/5
9	$Al[OCH(CH_3)_2]_3$	50/50
10	DIBAL[g]	41/59
11	9-BBN[h]	ND[i]

[a] Abbreviations: *i*-PA, isopropyl alcohol; TBAF, tetra-*n*-butylammonium fluoride; DIBAL, diisobutylaluminum hydride; 9-BBN, 9-borabicyclo[3.3.1]nonane. [b] Ratio of diols **5a**/**5s** determined by HPLC. [c] Reference 9. [d] Reference 10. [e] Reference 11. [f] Reference 12. [g] Reference 13. [h] Reference 14. [i] No diols detected by HPLC.

Table II. Diastereoselectivity in the Reduction of O-Protected Ynone 6



6 7

entry	reducing agent	diastereoselectivity,[a] 7 anti/7 syn
1	$NaBH_4$	44/56
2	$Zn(BH_4)_2$	57/43
3	DIBAL	80/20

[a] Ratio of **7a** to **7s** determined by HPLC.

(9) Hutchins, R. O.; Kandasamy, D. *J. Org. Chem.* **1975**, *40*, 2530–2533.
(10) (a) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411–1415. (b) Takahashi, T.; Miyazawa, M.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 5139–5142.
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(14) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197–1201.

with dimethylphenylsilane; however, this reductant gave a poor chemical yield. For practical purposes the best reducing agent was sodium borohydride, which gave an 80/20 mixture in a combined yield of 92%.

One of the factors potentially controlling diastereoselectivity in the reduction of ketone **4** is chelation by the free hydroxyl group or the carbamate.[15] The silyl ether protected ketone **6** (Table II) was examined as a possible means of reversing the anti/syn ratio. This modification did influence the diastereoselectivity observed for the three reagents tested, and the anti/syn ratio did decrease. Protection of the hydroxyl group, however, did not lead to formation of the syn alcohol **7s** as the major isomer.

The diastereomeric diols **5a** and **5s** were difficult to separate on silica gel. Preparative HPLC gave an adequate separation only with very low column loadings. Formation of the cyclic phenylboronic diester[16] **8** or the isopropylidene derivative **9** did not lead to any improvement. Since modification of the diols proved ineffective, a modification of the adsorbent was examined. Boric acid impregnated silica gel has been used to differentiate diastereomeric 1,2-diols by TLC.[17] This technique has been extended to column chromatography for the separation of prostaglandin intermediates.[18] We have found that the use of sodium borate impregnated silica gel leads to a preparatively useful gravity column separation of diols **5a** and **5s**. When subsequent experiments demonstrated that silica gel purification of ynone **4** resulted in extensive (60%) racemization, this loss could be circumvented by reducing the mixture of crude **4** and excess pentadecyne, followed by borate-treated silica gel chromatography. This yielded an 89% recovery of distilled pentadecyne, pure crystalline diol **5a** (53% from **3**), and pure crystalline diol **5s** (10% from **3**).

Conversion of **5a** to sphingosine (**1**) requires the removal of the CBZ protecting group and reduction of the acetylene to a trans double bond. This was achieved simultaneously by dissolved metal reduction. Sodium in liquid ammonia/THF quantitatively removed the CBZ group[19] but gave a 1/1 mixture of sphingosine and alkyne **10** (Scheme II). The best reducing conditions were lithium (2500 mol %) in liquid ammonia/THF followed by resubjecting the crude product to the reducing conditions to attain an 88% crude yield. Formation of CBZ derivative **11** revealed the persistence of 25% of the acetylenic bond. Difficulties in obtaining quantitative conversions of triple bonds to trans olefins by dissolving metal reductions also have been noted by others.[8a,c,20] Purification was readily accomplished by chromatography of the CBZ derivatives (**5a**, **11**), obtaining a 50% yield of pure **11**. Diol **5a** was recovered in 21% yield and was available for recycling. Olefinic diol **11** was treated with lithium in liquid ammonia/THF to remove the CBZ group in 90% yield and directly gave pure sphingosine (**1**; 56% from **5a**, including recycle).

Sphingosine (**1**), as the free base, is difficult to handle and subject to air-oxidation. In contrast, the CBZ derivative **11** is stable, is easy to handle, and has the added virtue of incorporating a chromophore. The generally accepted method for purification and characterization of sphingosine is as the triacetyl derivative.[21] We find the *N*-CBZ derivative **11** to be superior. It is easily formed and amenable to HPLC and column chromatography. The CBZ protecting group can be quantitatively removed under mild conditions. Another interesting facet of the chemistry of these 1,3-dihydroxy-2-amino compounds is the occurrence of *N*- to *O*-acyl migrations. These have been observed for some amides (e.g., **15**) but not for the *N*-CBZ derivatives **5a**, **5s**, and **11–13**.

The *N*-CBZ sphingosine **11** was utilized in a quantitative assessment of the reduction of the triple bond. Sodium and lithium in liquid ammonia result in predominant trans stereoselectivity. We quantitatively analyzed trans alkene **11** for the presence of cis alkene **12** and alkane **13** (Scheme II). Thus, crude **1** from the reduction of **5a** was acylated with benzyl chloroformate and analyzed by HPLC for the presence of **5a** and **11–13**. Samples of **12** and **13** were prepared from **5a** by catalytic hydrogenation using Pd/$CaCO_3$/$Pb(OAc)_2$ and Pt/C, respectively. Crude trans alkene **11** contained 25% of alkyne **5a**, <1% of cis alkene **12**, and no detectable levels of alkane **13**. A commercial sample of sphingosine (from a natural source), treated with benzyl chloroformate and analyzed by HPLC in the same way, contained **11** and a small amount (~10%) of the threo isomer.

The accepted literature method for testing the optical purity of sphingosine is the specific rotation of the triacetyl derivative.[21] This procedure suffers from an inherent low sensitivity ($[\alpha]^{24}_D$ −12.8°) and a lack of specificity. To develop a more reliable assay, we treated sphingosine (**1**) with *N*-(phenylsulfonyl)prolyl chloride (**14**) as a chiral auxiliary to form the diastereomeric amides **15**. However, these were not separable by HPLC, and the HPLC analysis suggested that an *N*- to *O*-acyl migration was occurring. This problem was overcome by reaction of the diastereomeric amides **15** with chlorotrimethylsilane, affording bis-*O*-(trimethylsilyl) ethers **16** well suited for HPLC analysis. Use of a chiral auxiliary and HPLC of the resulting diastereomeric derivatives is inherently more sensitive than determination of the optical rotation. The use of *N*-(phenylsulfonyl)prolyl chloride (**14**) allows the detection of as little as 1% racemization. As noted above, purification of ynone **4** by silica gel led to extensive racemization. Direct reduction of **4** to diol **5** prior to chromatography yielded sphingosine, which is >99% optically pure by our method.

Our alternate route to sphingosine begins with the β-unsubstituted acetylenic ketone **17** (Scheme III). Attempts at forming an ynone using lithium acetylide and isoxozolidide **3** containing an unprotected hydroxyl group were unsuccessful. Therefore, isoxazolidide **3** was protected as the *tert*-butyldimethylsilyl ether (TBDMS) **18** in 94% yield. Reaction of **18** with an excess of lithium acetylide in THF[22] gave ketone **17**. This reaction was somewhat erratic, giving 60–80% yields of **17** contaminated with unreacted **18** and occasionally with deprotected alcohol **3**.

Removal of the reactive ketone functionality was necessary prior to alkylation of the acetylenic carbon. In contrast to ynone **4**, the reduction of **17** with sodium borohydride gave only a 50% yield. The addition of cerium chloride[23] produced the alcohols **19** in 85% yield as a 6/4 ratio of diastereomers. The TBDMS ether was then quantitatively hydrolyzed to give diols **20** (Scheme III). Routinely, formation and reduction of ynone **17**, as well

(15) (a) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367–1371. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2204.
(16) Sugihara, J. M.; Bowman, C. M. *J. Am. Chem. Soc.* **1958**, *80*, 2443–2446.
(17) Morris, L. J. *J. Chromatogr.* **1963**, *12*, 321–328.
(18) (a) Lincoln, F. H.; Schnieder, W. P.; Pike, J. E. *J. Org. Chem.* **1973**, *38*, 951–956. (b) Miyano, M.; Dorn, C. R.; Mueller, N. A. *J. Org. Chem.* **1972**, *37*, 1810–1818.
(19) Sifferd, R. H.; de Vigneaud, V. *J. Biol. Chem.* **1935**, *108*, 753–761.
(20) Warthen, J. D.; Jacobsen, M. *Synthesis* **1973**, 616–617.
(21) Shapiro, D.; Segal, H.; Flowers, H. M. *J. Am. Chem. Soc.* **1958**, *80*, 1194–1197.
(22) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250–2252.
(23) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

as removal of the TBDMS ether, were preformed without purification of intermediates and with no loss in yield or purity of **20**. Protection of the hydroxyl groups was necessary prior to alkylation, and this was achieved by formation of acetonides **21a** and **21s** in 85% yield.

The major isomer, **21a**, was converted to isopropylidene **9a** by dianion formation with methyllithium followed by alkylation with 1-iodotridecane in HMPA. This sequence forms the alkylated isopropylidene **9a** in 35% yield (Scheme IV). Variation in cation and solvent did not improve the yield. An alternative to alkylation of an acetylenic anion is addition–elimination of an organocuprate with an iodo-substituted acetylene (Scheme IV). This reaction produces good yields with simple acetylenes.[24] Formation of the iodo derivative **22** proceeded smoothly and in 90% yield; however, reaction with the organocuprate **23** gave only a 12% yield of the cross-coupling product **9a** and a 79% yield of returned acetonide **21a**. Creation of the dehalogenated **21a** is probably due to reductive elimination of $C_{13}H_{27}$ and I from the addition intermediate **24**. This gives the acetylenic cuprate **25**, which is hydrolyzed to **21a** on isolation. The product **9a** is formed by the competing reductive elimination of CuI and the acetylenic ligand. The low yield of cross-coupling can perhaps be explained by the electron-withdrawing groups on the acetylenic ligand. These electronic effects will decrease the acetylene's ability to transfer to $C_{13}H_{27}$, making the halogen–metal exchange compound **25** the major product. The cyclic ketal of **9** was quantitatively removed to give diol **5a**, identical with that produced by the first route.

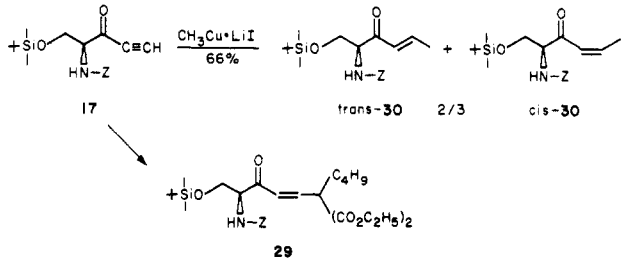
Conversion of **21a** to **9a** proved more difficult than originally envisioned. Direct alkylation of the acetylenic anion gives a higher yield (35%), but no recovery of starting material. The cross-coupling reaction provides a much better mass balance (90% for each step), but only a 12% yield of alkylated material. In designing a synthesis of sphingosine derivatives, one could use the anion alkylation reaction if recovery of **21a** was not important. Conversely, proceeding through the iodoacetylene **22** makes the most efficient use of **21a** but requires recycling to obtain better conversions.

The optical purity of isopropylidene **21s** was determined by hydrogenation and hydrogenolysis of **21s** by palladium on carbon to amine **26** (Scheme III). The free amine was then acylated, without isolation, with *N*-(phenylsulfonyl)alanyl chloride (**27**) to give the diastereomeric amides **28**. Ready separation by HPLC revealed an optical purity of >99%.

Assignment of the relative stereochemistry of **21a** and **21s** rests on the conversion of **21a** to **9a**, and the stereochemistry of **9a** is based on the transformation of **5a**, the precursor to **9a**, to sphingosine (**1**). NMR spectra of **21a**/**21s** and **9a**/**9s** were not readily assigned with respect to the relative coupling constants of the C-2 and C-3 protons. The major isomers (**21a**, **9a**) gave broad multiplets for the C-3 proton. The minor isomers (**21s**, **9s**) have a 2.1-Hz coupling constant for the C-3 proton. This is consistent with an axial–equatorial relationship. Previous reports of compounds directly related to **9** and **21** indicate a 2-Hz coupling for the syn isomer and a 9-Hz coupling for the anti isomer.[25]

To pursue further the synthetic possibilities inherent in ynone **17**, aside from alkylation of the acetylenic carbon, Michael additions to the α,β-ynone system appeared potentially useful. The models chosen were the addition of

Scheme V



a malonate[26] and a cuprate[27] (Scheme V). Addition of diethyl *n*-butylmalonate to **17**, either as the sodium salt or in the presence of a catalytic amount of sodium ethoxide, returned very poor (<5%) yields of enone **29**. The reaction mixtures were complex, and no starting material was recovered. On the other hand, addition of methylcopper ($CH_3Cu\cdot LiI$) to **17** gave enones **30** in a combined 66% yield. Enone **30** was a 60/40 mixture of cis and trans isomers that required repetitive chromatography for purification. Reactions with lithium dimethyl cuprate produced approximately the same ratio of products, but in lower yield.

Conclusions

Our initial study on the synthesis of optically active α'-amino-α,β-ynones has been extended to the synthesis of sphingosine (**1**). One route adds the necessary carbon chain in one portion as lithium pentadecyne[6] and gives sphingosine of >99% optical purity in four steps and 22% yield. The second process adds the carbon chain in two steps via an unsubstituted acetylenic ketone. Both strategies are very flexible, in terms of the nature of the added carbon chain as well as the stereochemistry possible for the double bond and chiral centers. Michael additions to the α'-amino-α,β-ynone give an acceptable yield with methyl cuprate, but as a mixture of cis and trans products. The α'-amino-α,β-ynones synthesized as part of this study are labile with respect to racemization and are best handled by reduction to stable propargyllic alcohols, which are amenable to a variety of synthetic transformations.

Experimental Section

Acetylene was purified by slow passage through two cold traps (dry ice/acetone), a sulfuric acid trap, and a KOH/Drierite drying column. THF was distilled from sodium benzophenone immediately prior to use. *n*-Butyllithium was used as a 1.5 M solution in hexanes. ^{1}H NMR spectra were recorded in $CDCl_3$ and are reported in ppm (δ) downfield of internal tetramethylsilane. Melting points are uncorrected. Organic solvent solutions of isolated products were dried over Na_2SO_4 and evaporated in vacuo from a rotary evaporator.

***N*-(Benzyloxycarbonyl)-L-serine Isoxazolidide (3).** Isoxazolidine hydrochloride[3] (3.67 g, 33.5 mmol) was dissolved in 50 mL of THF and 2 mL of water, giving a two-phase mixture. To this mixture was added anhyrous K_2CO_3 (9.25 g, 66.9 mmol), and the mixture was stirred at room temperature for 3 h. In a separate flask *N*-CBZ-L-serine (6.66 g, 27.9 mmol) was dissolved in 200 mL of THF and the mixture cooled to −15 °C under nitrogen. To the *N*-CBZ-L-serine solution was added 3.06 mL of *N*-methylmorpholine (27.9 mmol), followed by 3.62 mL (27.88 mmol) of isobutyl chloroformate. After 1 min the isoxazolidine solution was added rapidly via cannula and the mixture was stirred for 45 min at −15 °C and then quenched by the addition of 30 mL of water. The solvents were evaporated, leaving a clear oil to which 100 mL of 5% aqueous citric acid was added and the mixture

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extracted with EtOAc (2 × 150 mL). The combined EtOAc extracts were washed with 5% citric acid (1 × 100 mL) and saturated $NaHCO_3$ (2 × 100 mL) and then dried and evaporated. Crystallization of the residue from EtOAc/isooctane gave **3** as fine white needles: 6.25 g, 21.2 mmol (76%); mp 134–135 °C; TLC R_f 0.17 (EtOAc); $[\alpha]^{21}_D$ −4.89° (*c* 1.78, CH_3OH); IR (KBr) 1720, 1630 cm^{-1}; ^1H NMR δ 2.33 (m, 2 H), 3.59 (m, 1 H), 3.90 (m, 4 H), 4.10 (m, 1 H), 4.84 (m, 1 H), 5.11 (s, 2 H), 6.06 (br d, *J* = 8 Hz, 1 H), 7.33 (s, 5 H). Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.1; H, 6.2; N, 9.5. Found: C, 57.0; H, 6.2; N, 9.4.

(2*S*)-2-[(Benzyloxycarbonyl)amino]-1-hydroxy-3-oxo-4-octadecyne (4) and Reduction to (2*S*,3*R*)-2-[(Benzyloxycarbonyl)amino]-1,3-dihydroxy-4-octadecyne (5a) and (2*S*,3*S*)-2-[(Benzyloxycarbonyl)amino]-1,3-dihydroxy-4-octadecyne (5s). 1-Pentadecyne (4.37 g, 21.0 mmol) was dissolved in 150 mL of THF, the resultant mixture was cooled to −23 °C under nitrogen, and to this solution was added 14.0 mL of *n*-BuLi (1.5 M in hexanes, 21.0 mmol) over a 5-min period. The lithium pentadecyne solution was stirred at −23 °C for 20 min and then transferred via cannula to a solution of *N*-CBZ-L-serine isoxazolidide (**3**; 1.24 g, 4.2 mmol) in 50 mL of THF at −23 °C. This was then stirred at −23 °C for 45 min, poured onto 100 mL of 1 M NaH_2PO_4 while stirring vigorously, and extracted with EtOAc (2 × 150 mL). The combined EtOAc extracts were washed with 1 M NaH_2PO_4 (1 × 50 mL) and saturated NaCl (2 × 50 mL), then dried, and evaporated. The residue was dissolved in 100 mL of isopropyl alcohol, the solution was cooled to 0 °C, sodium borohydride (0.48 g, 12.6 mmol) was added, and the heterogeneous mixture was stirred at 0 °C for 1 h. The solvent was evaporated to a mixture of oil and solid that was dissolved in 100 mL of CH_3OH and cooled to 0 °C, and 20 mL of 1 N HCl was added dropwise. The solvents were evaporated again, EtOAc (100 mL) and 1 N HCl (50 mL) were added, and the mixture was shaken. The aqueous layer was washed with 100 mL of EtOAc; the combined organic layers were washed with 1 N HCl (50 mL) and saturated $NaHCO_3$ (2 × 50 mL), then dried, and evaporated to a residue containing pentadecynes **5a** and **5s**. The diols **5a** and **5s** were separated by sodium borate impregnated silica gel (below).

Ynone **4** can be isolated in *partially racemic form* by flash chromatography on silica gel, eluting with EtOAc/hexanes (1/2). This leaves **4** as a white waxy solid after evaporation of solvent: 1.60 g, 3.73 mmol (89%); mp 48–50 °C; TLC R_f 0.33 (EtOAc/hexanes, 1/1); IR (KBr) 2220, 1675 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 7.1 Hz, 3 H), 1.27 (m, 22 H), 2.38 (t, *J* = 7.2 Hz, 2 H), 4.13 (m, 2 H), 4.49 (m, 1 H), 5.13 (s, 2 H), 5.84 (br d, *J* = 8 Hz, 1 H), 7.37 (s, 5 H). Anal. Calcd for $C_{26}H_{39}NO_4$: C, 72.7; H, 9.1; N, 3.3. Found: C, 72.8; H, 9.1 N, 2.9. Reduction of partially racemic ketone **4** (210 mg, 0.49 mmol) with 55 mg of $NaBH_4$ by the procedure above gave an 8/2 mixture of diols **5**, 195 mg, 0.45 mmol (92%).

Sodium Borate Impregnated Silica Gel Purification of 5. Sodium borate impregnated silica gel was prepared by mixing 150 g of silica gel (230–400 mesh, Merck) with 250 mL of saturated $Na_2B_4O_7{\cdot}H_2O$ in water (5.5 g/100 mL). Most of the water was evaporated, followed by drying in an oven at 110 °C for 24 h. The treated silica gel was placed in a crystallization dish and allowed to equilibrate with the atmosphere for a minimum of 72 h. This gave a free-flowing powder visually indistinguishable from untreated silica gel. The equilibration with atmospheric moisture is necessary to deactivate the silica gel, since without this deactivation diol **5s** will not elute from the column. The column was poured using a slurry of 150 g of impregnated silica gel in 400 mL of chloroform, and the diols **5** were loaded onto the column in 6 mL of chloroform. Unreacted 1-pentadecyne was eluted with 100 mL of chloroform (1/2 column volume). Diol **5a** was eluted with 750 mL of 3% 2-propanol in chloroform, and diol **5s** was eluted with 250 mL of 5% 2-propanol in chloroform. Fractions (50 mL) were analyzed for the presence of **5a** and **5s** by HPLC: normal-phase Microsorb 5-μm column, 4.6 mm id × 250 mm, eluting with 1.0 mL/min 2.5% 2-propanol in chloroform; **5a** t_R 12 min, **5s** t_R 15 min. Fractions 5–9 contained pentadecyne [3.10 g after Kugelrohr distillation, 14.9 mmol (89%)]. Fractions 11–17 contained **5a** and Fractions 19–23 contained **5s**. The diols contained traces of a borate ester, which were removed by rotary evaporation with methanol (2 × 40 mL) to give **5a** and **5s** as white, waxy solids.

5a: crystallized from isooctane, 964 mg, 2.23 mmol (53%); mp 81–83 °C; TLC R_f 0.42 (EtOAc/hexanes, 1/1), 0.31 ($CHCl_3$/2-propanol 95/5); $[\alpha]_D^{21}$ −4.29° (*c* 1.7, $CHCl_3$); IR (KBr) 2210, 1690 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.26 (m, 20 H), 1.50 (m, 2 H), 2.21 (dt, *J* = 2.0, 7.0, CCC*H*$_2$, and br m, O*H*, 3 H total), 2.69 (br d, *J* = 6 Hz, O*H*, 1 H), 3.83 (m, 2 H), 4.14 (m, 1 H), 4.63 (m, 1 H), 5.13 (s, 2 H), 5.57 (m, 1 H), 7.36 (m, 5 H). Anal. Calcd for $C_{26}H_{41}NO_4$: C, 72.3; H, 9.6; N, 3.2. Found: C, 72.3; H, 10.0; N, 3.2.

5s: crystallized from isooctane, 187 mg, 0.43 mmol (10%); mp 67–69 °C; TLC R_f 0.42 (EtOAc/hexanes, 1/1), 0.31 ($CHCl_3$/2-propanol, 95/5); $[\alpha]_D^{21}$ −8.88° (*c* 3.2, $CHCl_3$); IR (KBr) 2205, 1680 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.25 (m, 20 H), 1.49 (m, 2 H), 2.18 (dt, *J* = 1.8, 7.0 Hz, CCCH_2, 2 H), 2.26 (br m, O*H*, 1 H), 2.61 (br m, O*H*, 1 H), 3.86 (m, 3 H), 4.64 (m, 1 H), 5.13 (s, 2 H), 5.36 (br m, 1 H), 7.36 (m, 5 H). Anal. Calcd for $C_{26}H_{41}NO_4$: C, 72.3; H, 9.6; N, 3.2. Found: C, 72.6; H, 9.8; N, 3.3.

(2*S*,3*R*,4*E*)-2-[(Benzyloxycarbonyl)amino]-1,3-dihydroxy-4-octadecene, *N*-CBZ-sphingosine (11). Liquid ammonia (~50 mL) was distilled into a 100-mL flask equipped with a cold-finger condenser (dry ice/acetone) and blanketed with a slow stream of nitrogen. Lithium metal (0.10 g, 14.41 mmol) was added to give a uniform blue solution, and diol **5a** (250 mg, 0.58 mmol) was added as a solution in 5 mL of THF. The blue solution was refluxed under nitrogen for 2 h, then excess NH_4Cl was added, and the solvents allowed to evaporate overnight. The white residue was suspended in 50 mL of water and extracted thoroughly with $CHCl_3$ (4 × 50 mL), the extracts were dried and evaporated, and the residue was dissolved in 5 mL of THF and resubjected to the reduction conditions (0.10 g of Li/50 mL of NH_3). The resulting mixture of **1** and **10** was dissolved in 10 mL of THF; 0.22 mL of triethylamine (1.57 mmol) and 0.11 mL of benzyl chloroformate (0.79 mmol) were added, and the resultant mixture was stirred for 1 h at room temperature. EtOAc (100 mL) was added, and after washing with 5% citric acid (2 × 20 mL) followed by saturated $NaHCO_3$ (2 × 20 mL), the EtOAc was dried and evaporated. The residue was purified by chromatography on silica gel, eluting with EtOAc/hexanes (2/3) to give **5a** [52 mg, 0.12 mmol (21%)] and **11** [125 mg, 0.29 mmol (50%)].

11: mp 78–79 °C; TLC R_f 0.37 (EtOAc/hexanes, 1/1), 0.28 ($CHCl_3$/2-propanol, 95/5); $[\alpha]_D^{21}$ 2.29° (*c* 2.8, $CHCl_3$); IR (KBr) 1690, 965 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.26 (m, 22 H), 2.03 (q, *J* = 6.9 Hz, 2 H), 2.40 (br m, O*H*, 2 H), 3.69 (m, 2 H), 3.99 (m, 1 H), 4.34 (m, 1 H), 5.12 (s, 2 H), 5.55 (m, N*H* and C=C*H*, 2 H), 5.75 (dt, *J* = 6.8, 15.2 Hz, 1 H), 7.36 (m, 5 H). Anal. Calcd for $C_{26}H_{43}NO_4$: C, 72.0; H, 10.0; N, 3.2. Found: C, 71.8; H, 10.2; N, 3.3.

(2*S*,3*R*,4*E*)-2-Amino-1,3-dihydroxy-4-octadecene, Sphingosine (1). *N*-CBZ-sphingosine (**11**; 90 mg, 0.21 mmol) in 4 mL of THF was added to lithium (0.05 g, 7.20 mmol) in 50 mL of NH_3 by the procedure described above for the reduction of **5a**. Isolation gave **1** as a white, waxy solid to which extensive handling in air imparted a yellow color: 55 mg, 0.18 mmol (88%); mp 72–75 °C (lit. mp 80–84 °C,[21] 82.5 °C[28]); $[\alpha]_D^{21}$ −1.3° (*c* 3.5, $CHCl_3$) [lit.[29] $[\alpha]^{22}_D$ −3.4° (*c* 2, $CHCl_3$)]; IR (film) 1690, 965 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.27 (m, 22 H), 2.05 (q, *J* = 7.0 Hz, 2 H), 2.88 (q, *J* = 5.2 Hz, 1 H), 3.66 (m, 2 H), 4.05 (t, *J* = 6.8 Hz, 1 H), 5.46 (dd, *J* = 7.1, 16 Hz, 1 H), 5.74 (dt, *J* = 7, 16 Hz, 1 H). Anal. Calcd For $C_{18}H_{37}NO_2$: C, 72.2; H, 12.5; N, 4.7. Found: C, 72.3; H, 12.5; N, 4.5.

(2*S*,3*R*,4*Z*)-2-[(Benzyloxycarbonyl)amino]-1,3-dihydroxy-4-octadecene, *N*-CBZ-*cis*-sphingosine (12). Diol **5a** (150 mg, 0.35 mmol) was dissolved in 4 mL of CH_3OH, Lindlar's catalyst [5% $Pd/CaCO_3/Pb(OAc)_2$, 15 mg] was added, and the mixture was stirred under 1 atm of H_2 for 1 h. The catalyst was removed by filtration through Celite, the Celite was washed with CH_3OH (75 mL), and the CH_3OH was evaporated. The residue was purified by chromatography on silica gel, eluting with $CHCl_3$/2-propanol (95/5) to give **12**: 100 mg, 0.23 mmol (66%); mp 69–69.5 °C; TLC R_f 0.26 ($CHCl_3$/2-propanol, 95/5); $[\alpha]_D^{21}$ −4.86° (*c* 2.9, $CHCl_3$); IR (KBr) 1680 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.25 (m, 22 H), 2.09 (m, 2 H), 2.31 (m, O*H*, 1 H), 2.47 (m, O*H*, 1 H), 3.64 (m, 1 H), 3.77 (m, 1 H), 4.02 (m, 1 H),

(29) *Beilstein*, Vol. IV, Supplement III, 1962, 854.

4.70 (m, 1 H), 5.12 (s, 2 H), 5.53 (m, CH=CH, NH, 3 H), 7.36 (m, 5 H). Anal. Calcd for $C_{26}H_{43}NO_4$: C, 72.0; H, 10.0; N, 3.2. Found: C, 71.7; H, 9.9; N, 3.3.

(2*S*,3*R*)-2-[(Benzyloxycarbonyl)amino]-1,3-dihydroxyoctadecane, *N*-CBZ-dihydrosphingosine (13). Diol **5a** (150 mg, 0.35 mmol) was dissolved in 5 mL of CH_3OH, catalyst (5% Pt/C, 10 mg) was added, and the mixture stirred under 1 atm of H_2 for 45 min. This produced a very stiff gel to which was added 25 mL of EtOAc, and the catalyst was removed by filtration through Celite. The Celite was washed with an additional 75 mL of EtOAc. The filtrate and washings were evaporated, and the residue was chromatographed on silica gel, eluting with $CHCl_3$/2-propanol (95/5) to give **13**: 144 mg, 0.33 mmol (95%); mp 98–100 °C; TLC R_f 0.25 ($CHCl_3$/2-propanol, 95/5); $[\alpha]_D^{21}$ +8.5° (*c* 3.3, $CHCl_3$); IR (KBr) 1680 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.26 (s, 26 H), 2.33 (m, 2 H), 3.59 (m, 1 H), 3.79 (m, 2 H), 4.01 (m, 1 H), 5.12 (s, 2 H), 5.64 (br d, *J* = 9 Hz, 1 H), 7.36 (m, 5 H). Anal. Calcd for $C_{26}H_{45}NO_4$: C, 71.7; H, 10.4; N, 3.2. Found: C, 71.9; H, 10.3; N, 3.3.

HPLC of CBZ-sphingosine Derivatives 5a and 11–13. The *N*-CBZ-sphingosine derivatives were separable by HPLC using an IBM normal-phase pell sil 5-μm silica gel column (4.6 mm i.d. × 250 mm). Compounds were eluted with EtOAc/hexanes (45/55) at 1.0 mL/min. t_R: **5a** 8.7 min; **11**, 12.6 min; **12**, 12.0 min; **13**, 13.8 min.

Optical Purity of Synthetic Sphingosine. *N*-(Phenylsulfonyl)prolyl chloride (**14**) was prepared form *N*-(phenylsulfonyl)proline.[2b] Crude synthetic sphingosine (25 mg, 0.08 mmol) was dissolved in 3 mL of $CHCl_3$, the solution was cooled to 0 °C, and triethylamine (23 μL, 0.17 mmol) was added, followed by the acid chloride (34 mg, 0.13 mmol) in 1 mL of $CHCl_3$. The heterogeneous mixture was stirred for 2 h at 0 °C, then it was added to 50 mL of 5% citric acid and extracted twice with EtOAc (50 mL). The combined extracts were washed with 5% citric acid (25 mL) followed by saturated $NaHCO_3$ (2 × 25 mL), then dried, and evaporated to give 40 mg (90%) of **15** as a very pale yellow oil. The prolyl derivative **15** was dissolved in 5 mL of THF, the solution was cooled to 0 °C, triethylamine (23 μL, 0.17 mmol) and imidazole (11 mg, 0.17 mmol) were added, and the solution was stirred for 20 min at 0 °C. Chlorotrimethylsilane (53 μL, 0.42 mmol) was then added, and after 1 h at 0 °C the reaction mixture was diluted with 100 mL of EtOAc and washed with 5% citric acid (2 × 10 mL), followed by saturated $NaHCO_3$ (2 × 10 mL). The EtOAc solution was dried and evaporated, and the resulting diastereomeric amides **16** from DL-(phenylsulfonyl)proline were separable by HPLC on an IBM pell sil 5-μm silica gel column (4.6 mm i.d. × 250 mm), eluting at 1.0 mL/min with EtOAc/hexanes (30/70); t_R 6.0, 7.2 min. Reaction with *N*-(phenylsulfonyl)-L-proline acid chloride gave t_R 7.2 min and a trace (<1%) of t_R 6.0 min.

***O*-(*tert*-Butyldimethylsilyl)-*N*-(benzyloxycarbonyl)-L-serine Isoxazolidide (18).** *N*-CBZ-L-serine isoxazolidide (**3**; 5.20 g, 17.7 mmol) was dissolved in 50 mL of DMF. To this solution were added imidazole (1.80 g, 26.5 mmol) and *tert*-butyldimethylsilyl chloride (4.0 g, 26.5 mmol). The mixture was stirred at room temperature for 4 h and then evaporated (0.2 mmHg, bath temperature 30 °C). EtOAc (100 mL) and 5% citric acid (50 mL) were added, the layers were separated, and the aqueous phase was washed with an additional 100 mL of EtOAc. The combined EtOAc layers were washed with 5% citric acid (50 mL) followed by saturated $NaHCO_3$ (2 × 50 mL), then dried, and evaporated to give **18** as an oil. This oil was chromatographed on silica gel, eluting with EtOAc/hexanes (2/5); **18** was isolated as an oil that solidified under vacuum (0.05 mmHg, room temperature, 5 days): 6.80 g, 16.6 mmol (94%); mp 48–51, 56–57 °C after recrystallization from isooctane; TLC R_f 0.51 (EtOAc/hexanes, 1/2); $[\alpha]_D^{21}$ −0.67° (*c* 3.3, $CHCl_3$); IR (KBr) 1720, 1650 cm^{-1}; ^1H NMR δ 0.016 (s, 3 H), 0.019 (s, 3 H), 0.86 (s, 9 H), 2.32 (m, 2 H), 3.53 (m, 1 H), 3.95 (m, 4 H), 4.07 (m, 1 H), 4.79 (m, 1 H), 5.10 (s, 2 H), 5.72 (br d, *J* = 8 Hz, 1 H), 7.35 (m, 5 H). Anal. Calcd for $C_{20}H_{39}N_2O_5Si$: C, 58.8; H, 7.9; N, 6.9. Found: C, 58.8; H, 8.1; N, 6.8.

(2*S*,3*RS*)-2-[(Benzyloxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy] 3-hydroxy-4-pentyne (19). Lithium acetylide[22] was prepared as follows. THF (200 mL) was presaturated with acetylene at −78 °C under nitrogen (20 min). *n*-Butyllithium (59 mL, 1.5 M in hexanes, 88.1 mmol) was added over a 20-min period, and the acetylene addition was continued for an additional 30 min. A solution of **18** (3.60 g, 8.81 mmol) in 75 mL of THF was then added and the reaction stirred at −78 °C for 45 min and then poured onto 100 mL of 1 M NaH_2PO_4 with vigorous stirring. Water (100 mL) was added and the mixture extracted with EtOAc (2 × 150 mL). The combined EtOAc extracts were washed with 1 M NaH_2PO_4 (1 × 100 mL) and saturated NaCl (2 × 100 mL), then dried, and evaporated to give crude **17** as a yellow oil; 3.0 g, 8.3 mmol (94% mass balance). TLC showed product, a trace of starting material and more polar impurities. ^1H NMR was used to ascertain the amount of **17** present by the integration of the acetylenic CC*H* at δ 3.34.

The ynone **17** could be isolated *in racemic form* by chromatography on Florosil. Crude **17** (1.46 g, 60% **17**) was purified on 100 g of Florosil, eluting with EtOAc/hexanes (1/3). This gave 0.77 g of ynone **17** (2.14 mmol), 51% from **18**). Continued elution with EtoAc/hexanes (1/1) gave recovered **18** [0.40 g, 0.98 mmol (23%)]. The purified ynone **17** was initially a colorless oil but decomposed to polar, highly colored material at 2 °C under nitrogen: TLC R_f 0.71 (EtOAc/hexanes, 1/2); ^1H NMR δ 0.027 (s, 6 H), 0.85 (s, 9 H), 3.34 (s, CC*H*, 1 H), 3.90 (dd, *J* = 3.1, 10.5 Hz, 1 H), 4.34 (dd, *J* = 2.3, 10.5 Hz, 1 H), 4.47 (m,1 H), 5.14 (s, 2 H), 5.67 (br d, *J* = 8 Hz, 1 H), 7.37 (s, 5 H).

Crude ynone **17** (1.88 g, 70% ynone **17** by NMR) was dissolved in 100 mL of CH_3OH and the solution cooled to 0 °C. Cerium chloride ($CeCl_3 \cdot 5H_2O$; 0.46 g, 1.30 mmol) was added, and when solution was complete, sodium borohydride (0.20 g, 5.22 mmol) was added and gave an immediate gas evolution. The solution was stirred for 20 min at 0 °C; then, the solvent was evaporated (bath temperature <25 °C), and the residue was suspended in 50 mL of 1 N HCl and extracted with EtOAc (2 × 100 mL). The combined extracts were washed with 1 N HCl (50 mL) and saturated $NaHCO_3$ (2 × 50 mL), then dried, and evaporated. Chromatography of the residue on silica gel, eluting with EtOAc/hexanes (1/3), gave pure **19** as a colorless, stiff oil: 1.06 g, 2.92 mmol (85%); TLC R_f 0.37 (EtOAc/hexanes, 1/3); IR ($CHCl_3$) 2120, 1710 cm^{-1}; ^1H NMR δ 0.071 (s, 3.6 H), 0.087 (s, 2.4 H), 0.89 (2 s, 9 H), 2.47 (d, CC*H*, *J* = 2.1 Hz, 0.4 H), 2.53 (d, CC*H*, *J* = 2.2 Hz, 0.6 H), 3.35 (d, *J* = 5.2 Hz, 0.4 H), 3.57 (d, *J* = 9.3 Hz, 0.6 H), 3.80 (m, 2.4 H), 4.23 (dd, *J* = 2.7, 10.4 Hz, 0.6 H), 4.61 (m, 1 H), 5.13 (2 s, 2 H), 5.27 (br, d, *J* = 10 Hz, 0.4 H), 5.46 (br, d, *J* = 10 Hz, 0.6 H), 7.36 (m, 5 H). Anal. Calcd for $C_{19}H_{29}NO_4Si$: C, 62.8; H, 8.0; N, 3.9. Found: C, 62.7; H, 8.2; N, 3.9.

(2*S*,3*RS*)-2-[(Benzyloxycarbonyl)amino]-1,3-dihydroxy-4-pentyne (20). Compound **19** (1.68 g, 4.62 mmol) was dissolved in 150 mL of acetic acid/water (80/20) and the resultant mixture stirred at room temperature overnight. The solvents were evaporated, and the residue was chromatographed on silica gel, eluting with EtOAc/hexanes (2/1). Diols **20** were isolated as a colorless, stiff oil: 1.05 g, 4.21 mmol (91%); TLC R_f 0.42 (EtOAc/hexanes, 2/1); IR ($CHCl_3$) 2120, 1710 cm^{-1}; ^1H NMR δ 2.34 (br s, O*H*, 1 H), 2.49 (d, CC*H*, *J* = 1.4 Hz, 0.4 H), 2.56 (d, CC*H*, *J* = 2.1 Hz, 0.6 H), 3.07 (br s, O*H*, 0.4 H), 3.18 (br m, O*H*, 0.6 H), 3.90 (m, 3 H), 4.15 (m, 1 H), 4.65 (m, 1 H), 5.13 (s, 2 H), 5.43 (br m, N*H*, 0.4 H), 5.60 (br m, N*H*, 0.6 H), 7.36 (s, 5 H). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.6; H, 6.1; N, 5.6. Found: C,62.5; H, 6.0; N, 5.6.

(4*R*,5*S*)-5-[(Benzyloxycarbonyl)amino]-2,2-dimethyl-4-ethynyl-1,3-dioxane (21a) and (4*S*,5*S*)-5-[(Benzyloxycarbonyl)amino]-2,2-dimethyl-4-ethynyl-1,3-dioxane (21s). To diols **20** (0.70 g, 2.81 mmol) dissolved in 20 mL of CH_2Cl_2 were added pyridinium *p*-toluenesulfonate (0.70 g, 2.79 mmol) and 2,2-dimethoxypropane (10 mL, 81 mmol), and the clear solution for 6 h at room temperature. Saturated $NaHCO_3$ (50 mL) was added, the mixture was extracted with $CHCl_3$ (3 × 75 mL), and the combined extracts were dried and evaporated. The residue of diastereomers **21a** and **21s** was separated by chromatography on silica gel, eluting with EtOAc/hexanes/triethylamine (1/3/0.1).

21a: 0.38 g, 1.31 mmol (47%); mp 79–80, 88–89 °C from Et_2O/isooctane; TLC R_f 0.56 ($CHCl_3$/2-propanol, 95/5), 0.46 (EtOAc/hexanes, 1/2); $[\alpha]^{21}_D$ 46.8° (*c* 3.2, $CHCl_3$); IR (KBr) 2120, 1730, 1700 cm^{-1}; ^1H NMR, δ 1.44 (s, 3 H), 1.57 (s, 3 H), 2.53 (s, CC*H*, 1 H), 3.77 (m, 2 H), 4.20 (m, 1 H), 4.62 (m, 1 H), 5.12 (s, 2 H), 5.27 (br s, 1 H), 7.36 (s, 5 H). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.4; H, 6.6; N, 4.8.

21s: 0.29 g, 1.00 mmol (36%); very stiff oil; TLC R_f 0.56 ($CHCl_3$/2-propanol, 95/5), 0.37 (EtOAc/hexanes, 1/2); $[\alpha]^{21}_D$ 2.32° (*c* 1.85, $CHCl_3$); IR ($CHCl_3$) 2120, 1710 cm^{-1}; ^1H NMR δ 1.45 (s, 3 H), 1.49 (s, 3 H), 2.40 (d, CC*H*, *J* = 2.1 Hz, 1 H), 3.83 (m, 2 H), 4.07 (dd, *J* = 2.5, 12.7 Hz, 1 H), 4.84 (overlapping dd, *J* = 2.1 Hz, 1 H), 5.10 (d, ϕ-CH_2O, *J* = 12.3 Hz, 1 H), 5.17 (d, ϕ-CH_2O, *J* = 12.3 Hz, 1 H), 5.73 (br d, N*H*, *J* = 9.5 Hz, 1 H), 7.36 (m, 5 H). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.1; H, 6.7; N, 4.8.

(4*R*,5*S*)-5-[(Benzyloxycarbonyl)amino]-2,2-dimethyl-4-(1-pentadecynyl)-1,3-dioxane (9a). From 21a: Acetonide **21a** (308 mg, 1.07 mmol) was dissolved in 10 mL of THF and the resultant mixture cooled to −78 °C under nitrogen. Methyllithium (1.56 mL, 1.5 M in ether, 2.34 mmol) was added over a 5-min period, and the yellow solution was stirred at −78 °C for 30 min. A solution of 1-iodotridecane (396 mg, 1.28 mmol) in 2 mL of hexamethylphosphoric triamide was added to give a thick, white slurry. The cooling bath was removed, the solution was stirred under nitrogen for 3 h at room temperature, and 10 mL of 1 M NaH_2PO_4 and 40 mL of water were added followed by extraction with EtOAc (2 × 50 mL). The combined extracts were washed with water (3 × 50 mL), dried, and evaporated. Chromatography of the residue on silica gel, eluting with EtOAc/hexanes/triethylamine (1/4/0.1), gave pure **9a**: 175 mg, 0.37 mmol (36%); mp 60–61 °C from isooctane; TLC R_f 0.55 (EtOAc/hexanes, 1/3); $[\alpha]^{21}_D$ 31.8° (*c* 2.15, $CHCl_3$); IR (KBr) 2240, 1700 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.25 (s, 20 H), 1.42 (s, 3 H), 1.49 (m, 2 H), 1.57 (s, 3 H), 2.19 (dt, *J* = 1.3, 6.6 Hz, 2 H), 3.70 (m, 2 H), 4.22 (m, 1 H), 4.55 (m, 1 H), 5.11 (s, 2 H), 5.22 (m, N*H*, 1 H), 7.36 (s, 5 H). Anal. Calcd for $C_{29}H_{45}NO_4$: C, 73.8; H, 9.6; N, 3.0. Found: C, 74.2; H, 9.9; N, 3.0.

From 5a: Diol **5a** (50 mg, 0.12 mmol) was treated with pyridinium *p*-toluenesulfonate (29 mg, 0.12 mmol) and 2 mL of 2,2-dimethoxypropane in 4 mL of CH_2Cl_2, as described above for the synthesis of **21a**/**21s**. Isolation gave 52 mg of a crystalline solid chromatographed on silica gel, eluting with EtOAc/hexanes/triethylamine (1/5/0.1) to give pure **9a**: 43 mg, 0.09 mmol (76%); spectra, TLC, and HPLC identical with that of **9a** from **21a**.

Deketalization of 9a to 5a. Acetonide **9a** (256 mg, 0.54 mmol) was dissolved in 15 mL of methanol, and to this solution was added pyridinium *p*-toluenesolfonate (27 mg, 0.11 mmol). The clear solution was stirred for 24 h at room temperature, saturated $NaHCO_3$ (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried and evaporated. HPLC showed only one diol, indicating no epimerization at the **3s** stereocenter. Chromatography on silica gel, eluting with EtOAc/hexanes (2/3), gave pure **5a**; 167 mg, 0.39 mmol (71%).

(4*R*,5*S*)-5-[(Benzyloxycarbonyl)amino]-2,2-dimethyl-4-(2-iodoethynyl)-1,3-dioxane (22). To acetonide **21a** (411 mg, 1.42 mmol) in 10 mL of THF, cooled to −23 °C under nitrogen, was added methyllithium (2.10 mL, 1.5 M in ether, 3.13 mmol) over a 5-min period, and the solution was stirred at −23 °C for 30 min. A solution of iodine (860 mg, 3.41 mmol) in 5 mL of THF was added, the dark solution was stirred for an additional 30 min at −23 °C, and the reaction was quenched by pouring onto 10 mL of 1 M NaH_2PO_4 and then extracted with EtOAc (100 mL). The EtOAc solution was washed with 1 M NaH_2PO_4 (10 mL), 1% $NaHSO_3$ (2 × 25 mL), and saturated $NaHCO_3$ (2.25 mL), then dried, and evaporated to give **22** as a white solid: 532 mg, 1.28 mmol (90%); mp 150–151 °C from EtOAc/isooctane; TLC R_f 0.36 (EtOAc/hexanes, 1/3); $[\alpha]_D^{21}$ 67.9° (*c* 3.5, $CHCl_3$); IR (KBr) 2180, 1690 cm^{-1}; ^1H NMR δ 1.42 (s, 3 H), 1.59 (s, 3 H), 3.73 (m, 2 H), 4.23 (m, 1 H), 4.78 (m, 1 H), 5.12 (s, 2 H), 5.28 (m, 1 H), 7.37 (m, 5 H). Anal. Calcd for $C_{16}H_{18}INO_4$: C, 46.3; H, 4.4; N, 3.4. Found: C, 46.3; H, 4.4; N, 3.4.

9a from 22. Copper(I) iodide[30] (303 mg, 1.59 mmol) was suspended in 5 mL of THF, the mixture was cooled to −45 °C under nitrogen, a solution of 1-tridecanylmagnesium bromide (7.10 mL, 0.22 M in THF) was added, and the heterogeneous mixture was stirred at −45 °C for 1 h. Compound **22** (300 mg, 0.72 mmol) in 10 mL of THF was added; the heterogeneous mixture was stirred for 3 h at −45 °C, then poured onto 20 mL of 1 N HCl, and extracted with EtOAc (100 mL). The EtOAc layer was washed with 1 N HCl (20 mL) and saturated $NaHCO_3$ (2 × 20 mL), then dried, and evaporated. The residue was chromatographed on silica gel, eluting with EtOAc/hexanes/triethylamine (1/4/0.1). **9a**: 42 mg, 0.09 mmol (12%). **21a**: 166 mg, 0.57 mmol (79%).

Optical Purity of 21s. Acetonide **21s** (100 mg, 0.35 mmol) was dissolved in 10 mL of EtOAc, catalyst (5% Pt/C, 10 mg) was added, the mixture was stirred under 1 atm of H_2 at room temperature for 1 h, and then 10 mg of 5% Pd/C was added and stirring continued under 1 atm of H_2 for an additional 1 h. Triethylamine (0.19 mL, 1.38 mmol) was added along with *N*-(phenylsulfonyl)alanyl chloride [**27**; 257 mg, 1.04 mmol, prepared from *N*-(phenylsulfonyl)alanine by the procedure described for *N*-(phenylsulfonyl)proline[2b]]. The heterogeneous mixture was stirred for 2 h at room temperature and then filtered through Celite. The Celite was washed with 75 mL of EtOAc, and the washings and filtrate were washed with saturated $NaHCO_3$ (2 × 50 mL), dried, and evaporated to give **28** as a white solid. HPLC on an IBM pell sil 5-μm silica gel column (4.6 mm i.d. × 250 mm), eluting at 1.0 mL/min with EtOAc/hexanes (50/50), gave the two diastereomers from DL-*N*-(phenylsulfonyl)alanine at t_R 10.8 and 14.1 min. The L acid derivative gave t_R 14.1 min and a trace (<1%) of t_R 10.8 min.

(2*RS*)-2-[(Benzyloxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-3-oxo-4-hexene (30). To copper(I) iodide[30] (174 mg, 0.91 mmol) suspended in 3 mL of THF and cooled to 0 °C under nitrogen was added methyllithium (0.60 mL, 1.5 M in ether, 0.90 mmol) and the mixture stirred for 20 min at 0 °C. The methylcopper solution was then cooled to −78 °C, ynone **17** (racemic, purified by Florisil chromatography, 300 mg, 0.83 mmol) in 5 mL of THF was added, and the reaction was stirred for 2 h at −78 °C under nitrogen and then quenched by pouring onto 50 mL of 1 N HCl. The mixture was extracted with EtOAc (100 mL), and the EtOAc layer was washed with 1 N HCl (50 mL) and saturated $NaHCO_3$ (2 × 50 mL), then dried, and evaporated. The residue was chromatographed on silica gel, eluting with EtOAc/hexanes (1/9), and the enones **30** were isolated as a 2/3, cis/trans mixture; 206 mg, 0.55 mmol (66%). The cis/trans mixture could be separated by taking enriched fractions from the above chromatography and repeating the chromatography, eluting with EtOAc/hexanes (1/9).

***trans*-30**: colorless oil; TLC R_f 0.28 (EtOAc/hexanes, 1/6); IR (film) 1720, 1680, 1630 cm^{-1}; ^1H NMR δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.94 (d, *J* = 8 Hz, 1 H), 3.84 (dd, *J* = 6, 10 Hz, 1 H), 4.02 (dd, *J* = 4, 10 Hz, 1 H), 4.62 (m, 1 H), 5.12 (s, 2 H), 5.82 (br d, *J* = 6 Hz, 1 H), 6.33 (d, *J* = 16 Hz, 1 H), 7.00 (m, 1 H), 7.36 (m, 5 H). Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.6; H, 8.3; N, 3.7. Found: C, 63.7; H, 8.4; N, 3.5.

***cis*-30**: colorless oil; TLC R_f 0.23 (EtOAc/hexanes, 1/6); IR (film) 1720, 1680, 1620 cm^{-1}; ^1H NMR δ 0.03 (s, 6 H), 0.88 (s, 9 H), 2.14 (d, *J* = 6 Hz, 3 H), 3.88 (dd, *J* = 5, 10 Hz, 1 H), 4.05 (dd, *J* = 4, 10 Hz, 1 H), 4.42 (m, 1 H), 5.12 (s, 2 H), 5.85 (br d, *J* = 6 Hz, 1 H), 6.31 (m, 2 H), 7.37 (m, 5 H). Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.6; H, 8.3; N, 3.7. Found: C, 63.6; H, 8.1; N, 3.7.

(30) Purification of CuI was by the method of: Kauffman, G. B.; Teter, L. A. In *Inorganic Syntheses*; Kleinberg, J., Ed.; McGraw-Hill: New York, 1963; Vol. VII, pp 9–12.