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Synthesis of D-*erythro*-Sphingosine and D-*erythro*-Sphinganine Via 3-Ketosphinganine

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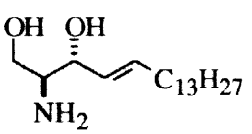
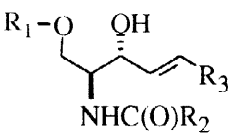
Abstract: D-*erythro*- sphingosine and D-*erythro*-sphinganine can be produced in protected form from serine by a synthetic approach in which the normal biological intermediate 3-ketosphinganine in protectyed form, is a key synthetic intermediate. The sequence is short and convergent, proceeds in good overall yields (≈ 30% for 6 steps) and with excellent stereocontrol (>91% de, >95% ee).

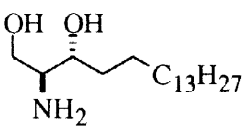
The finding that sphingolipids are involved in "essentially all aspects of cell regulation"[1] has led to an explosion of interest in sphingolipid chemistry.[1-4] Sphingosine **1** is the core structure of most sphingolipids **2**, which can vary in the nature of the head group R_1, the structure of the N-acyl group R_2 (if one is present), and the structure of the sphingosine tail R_3.[5] For example, the saturated analog sphinganine **3** lacks the biological activity of sphingosine highlighting the importance of the double bond.



Sphingosine, **1**
(D-*erythro*)



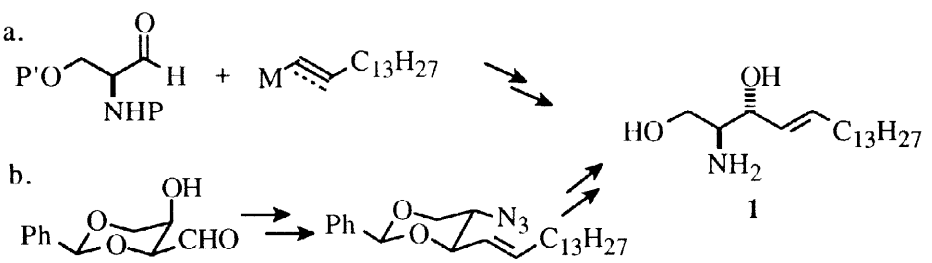
Sphingolipid, **2**
(D-*erythro*)



Sphinganine, **3**
(D-*erythro*)

Since most sphingolipids are prepared from sphingosine, quite a number of syntheses of sphingosine and its derivatives have been reported. In general these syntheses fall into three main categories.[6] The first uses stereoselective addition of an organometallic reagent (often a lithium acetylide) to a protected serinal. This approach forms the 3,4 carbon-carbon bond and sets the stereochemistry of the C-3 hydroxyl group in one step (Scheme 1a).[7] The second major strategy uses carbohydrate precursors as the source of stereochemistry at C-2 and C-3. The tail is then attached by an anionic addition of some type (Scheme 1b).[6,8] The third major category

Scheme 1



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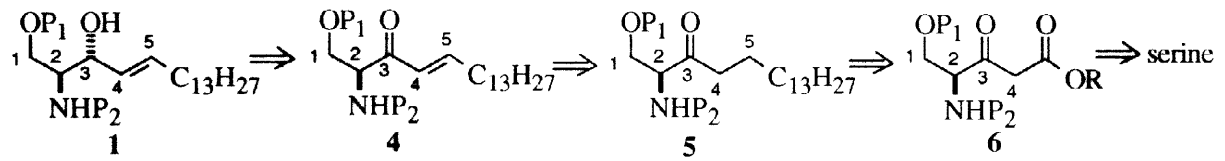
uses a variety of chiral precursors to build up the structure by nucleophilic addition processes.[9] All these approaches set the stereochemistry of the head groups early and attach the tail as a nucleophile.

The D-*erythro* stereochemistry of **1** is most common, but all four possible diastereomers of the 2,3-amino alcohol unit are known and are all bioactive to different degrees.[10] Thus stereochemical control at C-2 and C-3 is crucial to any synthesis. Moreover, the *trans* geometry of the sphingosine $C_{13}H_{27}$ alkene tail is crucial for both activity and ease of purification since the separation of *cis* and *trans*-sphingosines is very tedious.

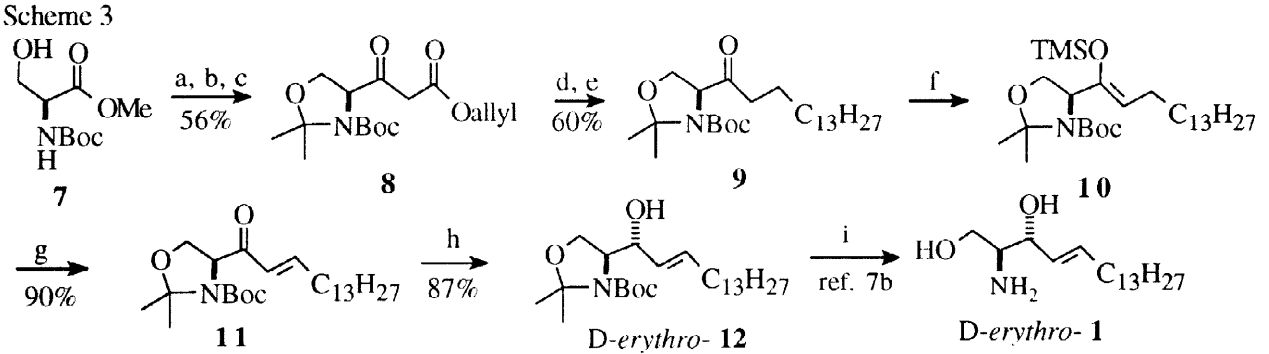
Our interest in the synthesis of densely functionalized molecules[11] led to the retrosynthetic scheme for protected D-*erythro*-sphingosine **1** shown in Scheme 2. This strategy is fundamentally different from previous syntheses in both sequence and polarity. The tail is attached as an electrophile to **6**. After introduction of the double bond in ketosphinganine **5**, stereoselective reduction of the ketone group of 3-ketosphingosine **4** sets the stereochemistry of the C-3 hydroxyl group in the last stage of the synthesis. This approach mimics to some degree the biological route to sphingosines which also passes through 3-ketosphinganine **5** ($P_1 = P_2 = H$) as a key intermediate.[4a,12] Formation of the *erythro* diastereomer of the protected sphingosine **1** requires that the reduction of **5** proceeds by a chelated transition state. Chelation control using an N-Boc oxazolidine for P_1 and P_2 provides a means to cleanly control the stereochemical outcome of the reduction.[7a]

Scheme 2



This strategy was successfully reduced to practice as seen in Scheme 3. Commercially available L-(*N*-Boc) serine methyl ester **7** was cyclized to the corresponding 2,2-oxazolidine with 2,2-dimethoxypropane.[13] Conversion to β-ketoester **8** in 56% yield with CDI and lithio allyl acetate followed a standard procedure.[14] Ketoester **8** was alkylated by treatment with NaH followed by 1-tetradecyl triflate at room temperature for 6 h. 1-Bromotetradecane could also be used to alkylate the enolate of **8** by refluxing in THF-HMPA (5:1) with 10% NaI for 6 h.The milder triflate alkylation procedure is preferred in order to minimize the chances of epimerization. Treatment of the crude alkylation product with $Pd(PPh_3)_4$ and morpholine gave deallylation and decarboxylation

Scheme 3

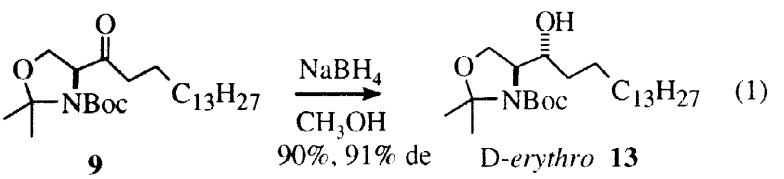


a. $(CH_3)_2CH(OCH_3)_2$, TsOH; b. LiOH; c. (i) CDI, (ii) $LiCH_2CO_2allyl$;
d. (i) NaH, (ii) $TfOCH_2C_{13}H_{27}$; e. $Pd(PPh_3)_3$, morpholine;
f.(i) NaHMDS, -78°C, (ii)TMSCl; g. $Pd(OAc)_2$, CH_3CN; h. $NaBH_4$, $CeCl_3$, -20°C; i. 1N HCl

to 3-ketosphinganine derivative **9** in 60% yield. The use of allyl esters in β-ketoester **8** is a significant improvement over *t*-butyl esters used earlier.[11b] Palladium [0] not only removes the allyl group under mild, neutral conditions, but it also catalyzes the decarboxylation of the resulting β-keto acid which occurs smoothly at room temperature.

Treatment of **9** with NaHMDS followed by TMSCl gave TMS-enol ether of **10**[15] which was oxidized with $Pd(OAc)_2$ to the α,β-unsaturated ketone **11** (90%).[16] The nmr spectrum of **11** had only one set of vinyl signals with J= 15.7 Hz indicating that the *trans* isomer was produced exclusively. In practice, **11** was not purified but carried on as the crude product. Reduction with $NaBH_4$/ $CeCl_3$ (87%) gave the known D-*erythro*-sphingosine derivative **12**.[7b] The $CeCl_3$ was needed to suppress conjugate reduction of **11** which occurred to the extent of 25% in its absence. The diastereoselectivity of the reduction was excellent (92% de) and the *anti*-stereochemistry results from the expected chelation controlled reduction. An LIS study ($Eu(hfc)_3$) of the major diastereomer **12** showed the sequence was highly enantioselective (>95% ee). Deprotection of **12** to D-*erythro*-sphingosine **1** using 1 N HCl is straightforward.[7b]

As expected, reduction of 3-ketosphinganine **9** with sodium borohydride gave D-*erythro*-sphinganine derivative **13** (90% yield, 91% de) without the need for $CeCl_3$ because conjugate reduction is not an issue (eq 1).



9 D-*erythro* **13** (1)

In summary, D-*erythro*- sphingosine and D-*erythro*-sphinganine can be produced in protected form from serine by a synthetic approach in which 3-ketosphinganine is a key synthetic intermediate and thus mimics to some degree the biological route. The relatively short sequence proceeds in good overall yields (≈ 30% for 6 steps) and with excellent stereocontrol (>91% de, >95% ee). The extension of this methodology to the synthesis of other sphingosine derivatives and analogs is currently underway.

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References and Notes

1. For an excellent overview of sphingolipid functions see Merrill, A. H., J.r; Sweeley, C. C. in "Biochemistry of Lipids, Lipoproteins and Membranes", Vance, D. E.; Vance, J. E. Eds.; Elsevier Science B. V.: Amsterdam, **1996**; Cpt. 12, pp 309-339.
2. Hannun, Y. A.; Loomis, C. R.; Merrill, A. H., Jr.; Bell, R. M. *J. Biol. Chem.* **1986**, *261*, 12604.
3. Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500.
4. a. Merrill, A. H., Jr.; Hannun, Y. A.; Bell, R. M. in "Advances in Lipid Research, Vol. 25 *Sphingolipids Part A: Functions and Breakdown Products*" Bell, R. M.; Hannun, Y. A.; Merrill, A. H., Jr., Eds.; Academic Press: San Diego, CA; 1993, pp 1-23. b. Bell, R. M.; Hannun, Y. A.; Merrill, A. H., Jr., Eds."Advances in

Lipid Research, Vol. 25 *Sphingolipids Part A: Functions and Breakdown Products*" ; Academic Press: San Diego, CA; 1993. c. Cevc, G, Ed. "Phospholipids Handbook"; Marcel Dekker: New York, 1993.

5. Karlsson, K.-A. *Lipids* **1970**, *5*, 878.
6. For an excellent discussion of synthetic approaches see a. Schmidt, R. R.; Bar, T.; Wild, R. *Synthesis* **1995**, 868. b. Schmidt, R. R. in "Synthesis in Lipid Chemistry", Tyman, J. H. P., Ed; Royal Society of Chemistry: Cambridge, UK; **1996**, pp 93-118 and references therein.
7. For example: a. Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037. b. Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395. c. Herold, P. *Helv. Chim. Acta.* **1988**, *71*, 354. d. Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469 and references therein. e. Soai, K.; Takahashi, K. *J. Chem. Soc., Perkins Trans. 1* **1994**, 1258. f. Dondoni, A.; Perrone, D.; Turturici, E. *J. Chem. Soc., Perkins Trans. 1* **1997**, 2389.
8. For example: a. Hirata, N.; Yamagiwa, Y.; Kamikawa, T. *J. Chem. Soc., Perkins Trans. 1* **1991**, 2279. b. Li, Y.-L.; Wu, Y.-L. *Liebigs Ann.* **1996**, 2079. c. Murakami, T.; Hato, M. *J. Chem. Soc. Perkins Trans. 1* **1996**, 823.
9. See for example: a. Katsumura, S.; Yamamoto, N.; Fukuda, E.; Iwama, S. *Chem. Lett.* **1995**, 393 and references therein. b. Davis, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 4349. c. Hudlicky, T.; Nugent, T.; Griffith, W. *J. Org. Chem.* **1994**, *59*, 7944. d. Garigipati, R. S.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 4499. e. Spanu, P.; Rassu, G.; Pinna, L.; Battistini, L.; Casiraghi, G. *Tetrahedron: Assym.* **1997** *8*, 3237. f. Solladié-Cavallo, A.; Koessler, J. L. *J. Org. Chem.* **1994**, *59*, 3240.
10. Sachs, C. W.; Ballas, L. M.; Mascarella, S. W.; Safa, A. R.; Lewin, A. H.; Loomis, C.; Carroll, F. I.; Bell, R. M.; Fine, R. L. *Biochem. Pharmacol.* **1996**, *52*, 603.
11. a. Hoffman, R. V.; Tao, J.-H. *J. Org. Chem.* **1997**, *62*, 2292. b. Tao, J.-H, Hoffman, R. V.; *J. Org. Chem.* **1997**, *62*, 6240.
12. Geeraert, L.; Mannaerts, G. P.; Van Veldhoven, P. P. *Biochem. J.* **1997**, *327*, 125.
13. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
14. Harris, B. D.; Joullie, M. M.; . *Tetrahedron* **1988**, *44*, 3489.
15. It is known that bulky substituents on the nitrogen of α-aminoketones promote enolization at the α'-position. Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *110*, 7447. b. Alexander, C. W.; Liotta, D. C. *Tetrahedron Lett.* **1996**, *37*, 1961 and references therein.
16. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.