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Enantioselective Syntheses of D-*erythro*-Sphingosine and Phytosphingosine from Simple Achiral Aldehydes Using Catalytic Asymmetric Aldol Reactions as Key Steps

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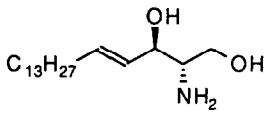
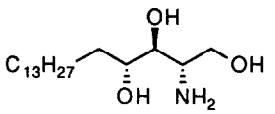
Abstract: D-*erythro*-sphingosine and phytosphingosine were prepared from simple achiral aldehydes, trimethylsilylpropynal and acrolein, by using chiral tin(II) Lewis acid-catalyzed asymmetric aldol reactions as key steps.

Recently, much attention has been paid to the sphingomyelin cycle and the second messenger function of ceramide.[1] After the discovery of protein kinase C inhibition by sphingosine,[2] attension has been focused on the lipid components of sphingolipids and indirect evidence led to the hypothesis that sphingolipid-derived products may function as second messengers.[3] Efforts are now being made to define a novel ceramide-dependent pathway of signal transduction, and development of an efficient method for the preparation of sphingosine and its derivatives is strongly desired.[4] In this paper, we report the facile and efficient syntheses of D-*erythro*-sphingosine and phytosphingosine from simple achiral aldehydes, trimethylsilylpropynal and acrolein, by using chiral tin(II) Lewis acid-catalyzed asymmetric aldol reactions as key steps.



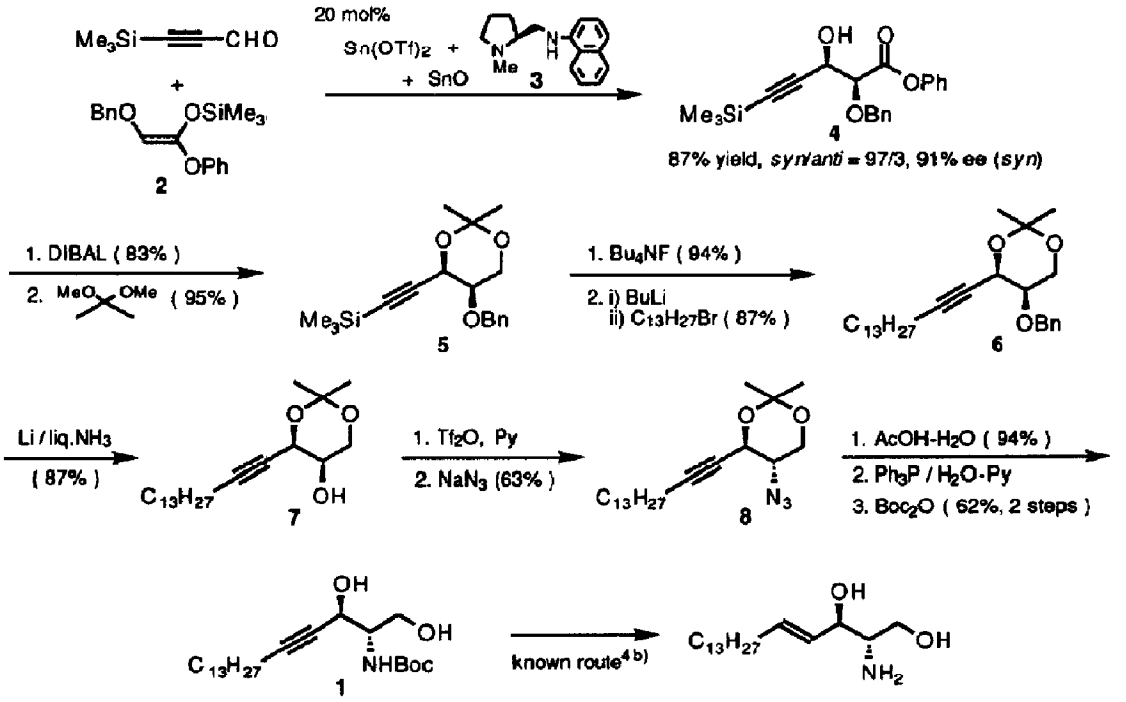
D-*erythro*-sphingosine



phytosphingosine

The synthetic pathway for the preparation of key intermediate **1** to D-*erythro*-sphingosine is shown in Scheme 1. The key asymmetric aldol reaction of trimethylsilylpropynal with the

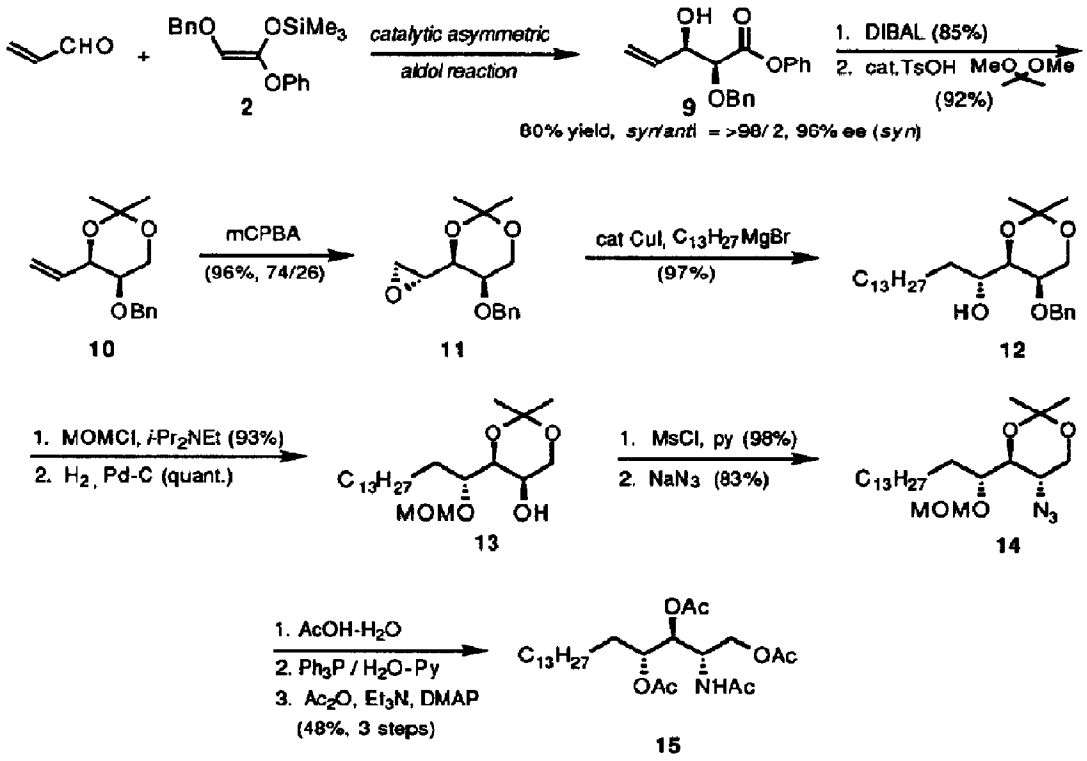
ketene silyl acetal (**2**) derived from phenyl α-benzyloxyacetate was carried out by using 20 mol% of tin(II) triflate, chiral diamine **3**, and tin(II) oxide.[5] Slow addition of the substrates to the catalyst in propionitrile gave the best results, and the desired aldol adduct (**4**) was obtained in high diastereo- and enantioselectivities (*syn*/*anti* = 97/3, 91% ee for *syn*). Reduction of **4** with DIBAL, followed by protection of the diol part with 2,2-dimethoxypropane, gave **5**. After the trimethylsilyl group of **5** was deprotected and then alkylated, the benzyl group of **6** was removed under Birch conditions.[6] An azide group was introduced via an SN_2 process by successive treatment of **7** with triflic anhydride/pyridine and sodium azide.[7] At this stage, the basic skeleton of D-*erythro*-sphingosine was constructed. Deprotection of the acetonide group of **8**,[8] followed by reduction of the azide to an amino group[9] and then protection of the amino group with a *t*-butoxycarbonyl group, gave the key intermediate (**1**) for the preparation of D-*erythro*-sphingosine. The ^1H NMR spectrum and the optical rotation of synthetic **1** were completely consistent with those in the literature.[4b]



Scheme 1. Synthesis of D-*erythro*-Sphingosine

Phytosphingosine was prepared from acrolein according to the equations shown in Scheme 2. The key catalytic asymmetric aldol reaction of acrolein with **2** proceeded smoothly under standard conditions to afford the desired adduct (**9**) in excellent selectivities (*syn*/*anti* =

>98/2, 96% ee for *syn*).[5] After **9** was reduced and protected, **10** was oxidized with *m*-chloroperbenzoic acid (mCPBA) to give epoxide **11**. Regioselective ring opening of **11** using copper iodide and a Grignard reagent, followed by protection of the resulting alcohol (**12**) with a MOM group and deprotection of the benzyl group, gave alcohol **13**. An azide group was introduced by using sodium azide via an SN2 process after derivation of **13** to its mesylate. The basic skeleton of phytosphingosine was constructed at this stage. After the MOM and acetonide groups of **14** were removed, the azide group was reduced to afford phytosphingosine. Its structure was confirmed after derivation to tetraacetate **15** by comparison of its ^{1}H and ^{13}C NMR spectra and optical rotation with those in the literature.[4h]



Scheme 2. Synthesis of Phytosphingosine

In summary, D-*erythro*-sphingosine and phytosphingosine were synthesized from trimethylsilylpropynal and acrolein, respectively, using chiral tin(II) Lewis acid-catalyzed asymmetric aldol reactions as key steps. The total yields were 15% (10 steps, **1** from trimethylsilylpropynal) and 21% (13 steps, **15** from acrolein). Since we have developed diastereo- and enantioselective aldol reactions,[10] various stereoisomers of sphingosine and phytosphingosine can be prepared according to these synthetic routes.

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References and Notes

1) a) Kanfer, J. N.; Hakomori, S. *Sphingolipid Biochemistry;* Plenum Press: New York, 1983. b) Hannun, Y. A. *J. Biol. Chem.* **1994**, *269*, 3125.
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) For synthesis of D-*erythro*-sphingosine and/or phytosphingosine, a) Kiso, M.; Nakamura, A.; Tomita, Y.; Hasegawa, A. *Carbohydr. Res.* **1986**, *158*, 101. b) Herold, P. *Helv. Chim. Acta.* **1988**, *71*, 354. c) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395. d) Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta.* **1986**, *69*, 368. e) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 239. f) Sugawara, T.; Narisada, M. *Carbohydr. Res.* **1989**, *194*, 125. g) Fujita, S.; Sugimoto, M.; Tomita, K.; Nakahara, Y.; Ogawa, T. *Agric. Biol. Chem.* **1991**, *55*, 2561. h) Murakami, T.; Minamikawa, H.; Hato, K.; Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1994**, *35*, 745, and references cited therein.
5) a) Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911. b) Kobayashi, S.; Kawasuji, T, Mori, N. *Chem. Lett.* **1994**, 217.
6) Boeckman, R. K., Jr.; Thomas, E. W. *J. Am. Chem. Soc.* **1987**, *100*, 2806.
7) Zimmermann, P.; Schmidt, R. R. *Liebigs Ann. Chem.* **1988**, 663.
8) Lewbart, M. L.; Schneider, J. J. *J. Org. Chem.* **1969**, *34*, 3505.
9) Dong, Z.; Butcher, J. A., Jr. *Tetrahedron Lett.* **1991**, *32*, 5291.
10) a) Kobayashi, S.; Kawasuji, T. *Tetrahedron Lett.* **1994**, *35*, 3329. b) Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*. 1708.

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