Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2983–2985

TETRAHEDRON LETTERS

The first total synthesis of the 6-hydroxy-4*E*-sphingenines☆

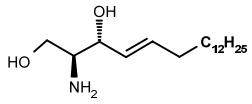
J. S. Yadav,* V. Geetha, A. Krishnam Raju, D. Gnaneshwar and S. Chandrasekhar

Organic Chemistry Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

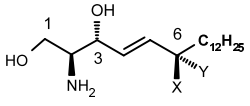
Received 11 December 2002; revised 30 January 2003; accepted 7 February 2003

Abstract—Ceramides containing the 6-hydroxy-4*E*-sphingenines, previously unknown long-chain bases, have recently been found in human skin. A total synthesis of 6-hydroxy-4*E*-sphingenines has been achieved. © 2003 Elsevier Science Ltd. All rights reserved.

Sphingolipids, e.g. **1** (e.g. ceramides, sphingomyelin, gangliosides) constitute a broad class of biologically important compounds. They are ubiquitous membrane components of essentially all eukaryotic cells and are abundantly located in all plasma membranes as well as in some intracellular organelles (endoplasmic reticulum (ER), golgi complex and mitochondria).[1–4]



1

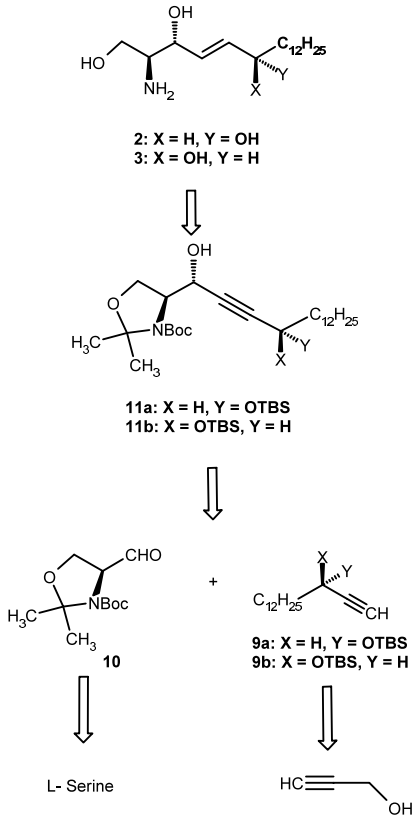


2: X = H, Y = OH
3: X = OH, Y = H

Ceramides containing the 6-hydroxy-4*E*-sphingenines **2** and **3**, previously unknown long-chain bases, have recently been found in human skin.[5,6] They occur in the stratum corneum, not as the free base, but as ceramides (the *N*-acylated base). These 6-hydroxy sphingosines ranged from 17 to 22 carbons in length, with 18–20 carbon species predominating.

Our group has been actively involved in the synthesis of sphingosine[7] and therefore stimulated by its biological significance and activity, we were encouraged to initiate studies directed towards the total synthesis of 6-hydroxy-4*E*-sphingenines **2** (2-amino-(2*S*,3*R*,4*E*,6*S*)-4-octadecene-1,3,6-triol) and **3** (2-amino-(2*S*,3*R*,4*E*,6*R*)-4-octadecene-1,3,6-triol) for the first time. The retrosynthetic analysis for **2** and **3** is as shown in Scheme 1.

Initially, propargyl alcohol was treated with dodecyl bromide in liquid ammonia using lithium amide at liquid ammonia temperature, to give compound **4** in 70% yield.[8] Acetylenic alcohol **4** was reduced with 2 equiv. of $LiAlH_4$ in refluxing THF to afford the *trans*-allylic alcohol **5** in 95% yield.[9]



Scheme 1.

Keywords: sphingolipids; 6-hydroxy-4*E*-sphingenines; Sharpless asymmetric epoxidation; Garner aldehyde.

☆ IICT Communication No. 030125.

* Corresponding author. Fax: +91-40-2716-0512; e-mail: yadav@iict.ap.nic.in

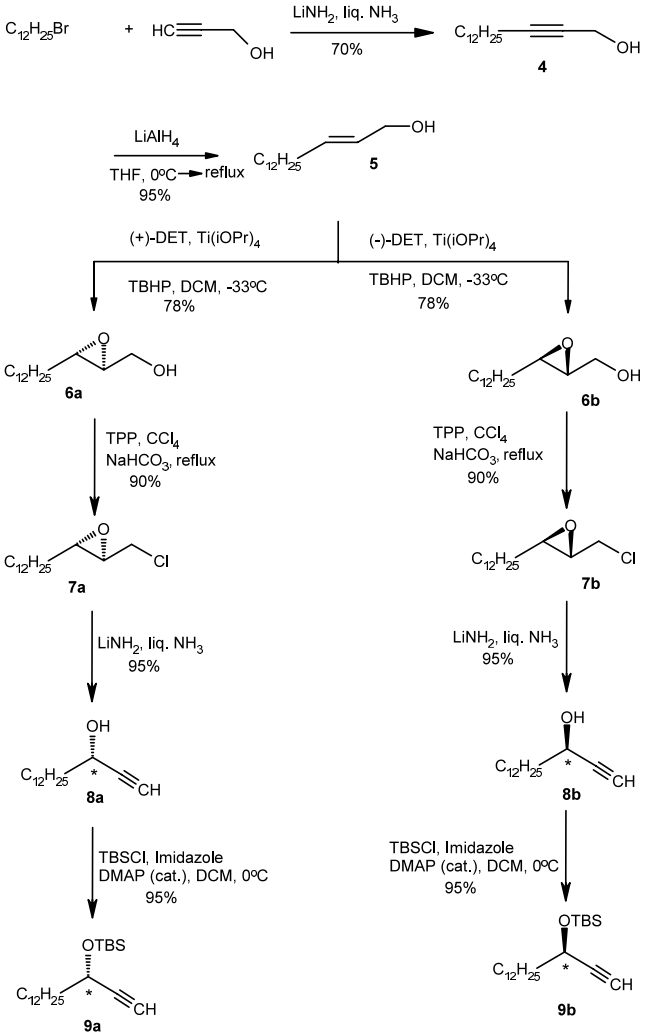
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00390-3

The *E*-allyl alcohol **5** was subjected to the Sharpless asymmetric epoxidation protocol.[10] Accordingly, treatment of **5** with (+)-DET, titanium tetraisopropoxide and TBHP in dry CH_2Cl_2 at −30°C gave the epoxy alcohol **6a**. The optical rotation was found to be −25.6 (*c* 1.15, $CHCl_3$).[11] The epoxy alcohol **6a** was converted to epoxy chloride **7a** using triphenylphosphine and $NaHCO_3$ in refluxing CCl_4. The key-step was the execution of the earlier approach for the preparation of the chiral propargyl alcohol from chiral 2,3-epoxy chloride **7a** using LDA or $LiNH_2$ in liquid ammonia. Accordingly **7a** was subjected to our reaction conditions,[12] in liquid ammonia using lithium amide to afford the chiral propargyl alcohol **8a**. The structure of compound **8a** was confirmed by its ^1H NMR spectrum, which gave a signal at 2.4 ppm as a doublet for one proton corresponding to the newly arisen acetylenic proton (Scheme 2).

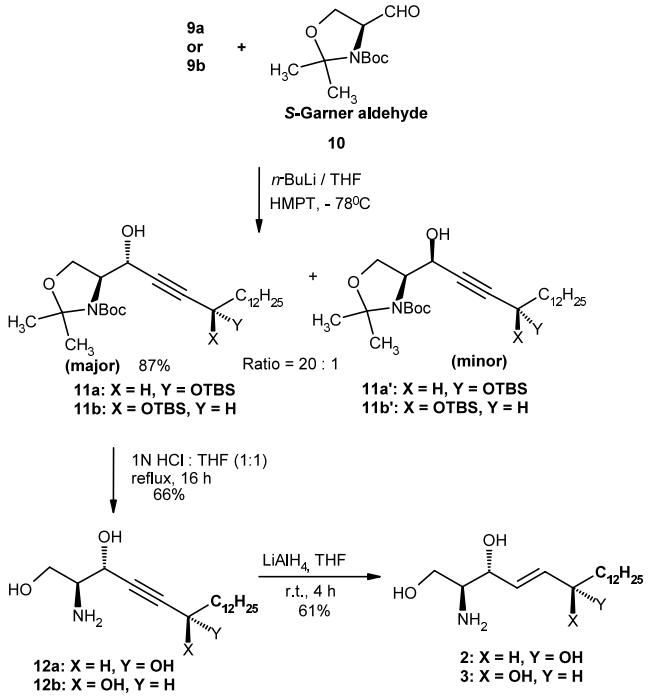
The secondary hydroxyl functionality of compound **8a** was protected as its TBDMS ether using 2 equiv. of imidazole, a catalytic amount of DMAP and 1.2 equiv. of TBDMS-Cl in anhyd. CH_2Cl_2 at 0°C to afford compound **9a** in 95% yield. In a similar manner **9b** was synthesised using (−)-DET in the Sharpless asymmetric epoxidation reaction (Scheme 2). A preparation of the (*S*)-Garner aldehyde **10** was achieved starting from L-serine by the procedure reported in literature.[13]

After the successful completion of the syntheses of the two fragments **9a** and **10**, our next aim was to couple together the fragments. Lithium acetylide additions to the Garner aldehyde proceed with high selectivity in the Felkin–Anh sense.[14] Of particular relevance is the demonstration by Jurczak and co-workers[15] that TBS-protected pentadecyne behaves in a similar manner with high selectivity. Thus the TBS protected pentadecyne **9a** was lithiated using *n*-BuLi and treated with 2.1 equiv. of HMPT at −78°C followed by Garner aldehyde **10** to afford a 20:1 mixture of compounds in favour of **11a** in 87% yield.[14,16] The ^1H NMR spectrum of compound **11a** showed the absence of the terminal acetylenic proton at 2.3 ppm of compound **9a** and the presence of peaks between 3.90 and 4.40 ppm corresponding to five protons (-N**CH**, **CH$_2$**O, **CH**OH and **CH**OTBS).

The deprotection of the Boc, acetonide and TBS groups of compound **11a** to yield the alkynic amino triol **12a** was achieved by using 1N HCl:THF (1:1) under reflux conditions for 16 h.[17] Our final aim was to convert the triple bond to a *trans* double bond and this was achieved using $LiAlH_4$ in THF at 0°C. The ^1H NMR spectrum of compound **2**[18] showed resonances at 5.5 and 5.7 ppm as two double doublets corresponding to the olefinic protons, which was consistent with its FABMS *m*/*z* 316 (M+1) (Scheme 3).



Scheme 2.



Scheme 3.

Synthesis of the other diastereomer **3** was achieved by coupling **9b** with **10** and a similar procedure for the rest of the steps as shown in Scheme 3.

Thus, a total synthesis of the 6-hydroxy-4*E*-sphingenines was achieved for the first time. Further work on the synthesis of other analogues of the 6-hydroxy-4*E*-sphingenines utilizing the above method is in progress. Their biological evaluation and the absolute stereochemistry of the synthetic samples in comparison with the natural products will be reported in due course.

Acknowledgements

V.G. thanks the CSIR, New Delhi, for a research fellowship.

References

1. Thudichum, J. L. W. *A Treatise on the Chemical Constitution of the Brain*; Lontoo: Bailliere, 1884; New edition 1962, Archon Books, Hamden, CT, USA.
2. Hakomori, S. *J. Biol. Chem.* **1990**, *5*, 878.
3. Van Meer, G.; Burger, K. N. J. *Trends Cell Biol.* **1992**, *2*, 332.
4. For recent studies on D-*erythro*-sphingosine synthesis, see: (a) Review: Koskinene, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075; (b) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3939; (c) Yin, J.; Liu, H.; Pidgeon, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 179; (d) Khiar, N.; Singh, K.; Garcia, M.; Martin-Lomas, M. *Tetrahedron Lett.* **1999**, *40*, 5779; (e) Hertweck, C.; Boland, W. *J. Org. Chem.* **1999**, *64*, 4426; (f) Nakamura, T.; Shiozaki, M. *Tetrahedron Lett.* **1999**, *40*, 9063; (g) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem.* **2000**, *65*, 3538; (h) Nakamura, T.; Shiozaki, M. *Tetrahedron* **2001**, *57*, 9087.
5. (a) Stewart, M. E.; Downing, D. T. *J. Invest. Dermatol.* **1995**, *105*, 613 and references cited therein; (b) Bouwstra, J. A.; Gooris, G. S.; Dubbelaar, F. E. R.; Ponec, M. *J. Lipid Res.* **2001**, *42*, 1759.
6. Wakita, H.; Nishimura, K.; Takigawa, M. *J. Invest. Dermatol.* **1992**, *99*, 617.
7. (a) Yadav, J. S.; Vidyanand, D.; Rajagopal, D. *Tetrahedron Lett.* **1993**, *34*, 1191; (b) Mohamed Takhi, Ph.D. Dissertation, Osmania University, 1997.
8. Yadav, J. S.; Dutta, D.; Bhanu, L. R. M. *Tetrahedron* **1998**, *54*, 3929.
9. (a) Yadav, J. S.; Bandhopadhayay, A.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 4907; (b) Yadav, J. S.; Mishra, R. K. *Tetrahedron Lett.* **2002**, *43*, 1739.
10. (a) Katzuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5954; (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464; (c) Sharpless, K. B.; Woodward, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823.
11. van Aar, M. P. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1995**, *41*, 112223.
12. Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033.
13. (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361; (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149; (c) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609.
14. (a) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354; (b) Van Brunt, M. P.; Standaert, R. F. *Org. Lett.* **2000**, *2*, 705.
15. Gruza, H.; Kiciak, K.; Kraninski, A.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2627.
16. No effort was made to characterize **11a′** and **11b′**, which were minor constituents.
17. Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395.
18. *Spectral data for selected compounds*:
Compound **8a** (colourless solid): $[\alpha]_D = -1.8$ (*c* 1.6, $CHCl_3$). mp 36.0–36.5°C. ^1H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, $J = 4.4$ Hz, 3H), 1.22–1.78 (m, 22H), 2.40 (d, $J = 3.6$ Hz, 1H), 4.25 (m, 1H).
Compound **8b**: $[\alpha]_D = +1.3$ (*c* 1.05, $CHCl_3$).
Compound **11a** (viscous liquid): $[\alpha]_D = -40.5$ (*c* 1.45, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 6H), 0.9 (s, 12H), 1.22–1.75 (m, 37H), 3.90–4.19 (m, 3H), 4.30 (bt, 1H), 4.44 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.1 and −4.5 [$(CH_3)_2$-Si], 14.0 (C-18), 18.1, 22.6, 25.1, 25.2, 25.7, 28.3, 29.1, 29.2, 29.4, 29.5, 31.8, 38.5 (C-7), 62.3 (C-6), 62.8 (C-2), 63.5 (C-3), 64.7 (C-1), 81.9, 82.0 (C-2), 89.0 (C-5), 94.9 [$\underline{C}$-$(CH_3)_2$], 154.0 (C=O). FABMS (*m*/*z*): 380, 200, 144, 100, 84, 73, 57.
Compound **11b** (viscous liquid): $[\alpha]_D = -46.5$ (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 0.04 (s, 6H), 0.88 (s, 12H), 1.22–1.60 (m, 37H), 3.90–4.20 (m, 3H), 4.39 (bt, 1H), 4.60 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.1 and −4.5 [$(CH_3)_2$-Si], 13.9, 18.0, 22.5, 25.1, 25.2, 25.7, 28.3, 29.1, 29.2, 29.4, 29.5, 31.8, 38.5, 62.3, 62.8, 63.7, 64.5, 80.5, 81.0 (C-2), 88.0 (C-5), 94.9 [$\underline{C}$-$(CH_3)_2$], 154.0 (C=O).
Compound **12a** (viscous liquid): $[\alpha]_D = -10.6$ (*c* 1.65, CH_3OH). ^1H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, $J = 2.4$ Hz, 3H), 1.15–2.0 (m, 23H), 3.45–3.95 (m, 3H), 4.32–4.50 (m, 4H). FABMS (*m*/*z*): 314 (M+1), 278, 264, 248, 182, 178, 107.
Compound **12b** (viscous liquid): $[\alpha]_D = -14.9$ (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, $J = 2.1$ Hz, 3H), 1.20–1.95 (m, 23H), 3.50–3.95 (m, 3H), 4.33–4.40 (m, 2H), 4.75–4.80 (m, 2H).
Compound **2** (semi-solid): $[\alpha]_D = -24.6$ (*c* 0.65, CH_3OH). ^1H NMR (DMSO-d_6, 500 MHz): δ 0.9 (t, $J = 7.3$ Hz, 3H), 1.22–1.40 (m, 22H), 2.98 (bs, 1H), 3.42–3.70 (m, 2H), 4.0–4.10 (m, 4H), 5.65 (dd, $J = 16.4$ and 7.2 Hz, 1H), 5.78 (dd, $J = 16.4$ and 7.2 Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.8 (C-18), 22.0, 24.9, 28.6, 29.0, 31.2, 37.3, 39.3, 39.5, 39.8, 40.0, 40.1, 57.4 (C-2), 62.5 (C-1), 70.4 (C-6), 72.1 (C-3), 129.4 (C-4), 134.9 (C-5). FABMS (*m*/*z*): 316 (M+1), 284, 280, 250, 133, 109.
Compound **3** (semi-solid): $[\alpha]_D = -30.5$ (*c* 0.90, CH_3OH). ^1H NMR (DMSO-d_6, 300 MHz): δ 0.85 (t, $J = 5.8$ Hz, 3H), 1.10–1.40 (m, 22H), 3.02 (bs, 1H), 3.60–3.70 (m, 2H), 3.80–4.30 (m, 4H), 5.50 (dd, $J = 15.0$ and 5.8 Hz, 1H), 5.70 (dd, $J = 15.0$ and 5.8 Hz, 1H), ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.2 (C-18), 21.7, 24.6, 28.3, 28.7, 30.9, 36.2, 38.6, 38.9, 39.2, 39.4, 39.7, 56.5 (C-2), 58.3 (C-1), 68.9 (C-6), 70.5 (C-3), 127.0 (C-4), 136.8 (C-5). FABMS (*m*/*z*): 316.5 (M+1), 118.2.