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An Expeditious and Practical Synthetic Process for Phytosphingosine and Tetrahydroxy-LCB from D-Glutamic Acid

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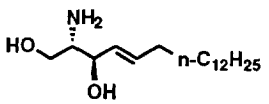
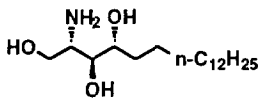
Abstract: For the asymmetric synthesis of phytosphingosine and 2-amino-1,3,4,5-tetrahydroxyoctadecene, the long chain base (LCB) part of novel cerebrosides, a simple and short synthetic route is described featuring the elabortion of the functionalized homochiral lactam derived from D-glutamic acid as a common structural unit.

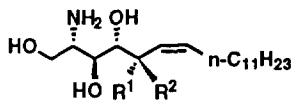
Marine sponges contain unusual lipid components such as phospholipids with long-chain or branched fatty acids[1] and sterols with unconventional side chains.[2] In particular, sphingosine **1** and phytosphingosine **2** are major backbone building blocks of glycosphingolipids and phosphosphingolipids, important membrane constituents composed of ceramides and phosphorous or sugar residues.[3] They play a significant role in biological processes on cell surfaces.[4] The presence of phytosphingosine in mammalian tissues, for example, in kidney,[5a] liver,[5b] uterus,[5c] intestine,[5d] skin,[5e] and blood plasma[5f] is also well known. In addition, due to the recent interesting discovery of protein kinase C inhibition by **1**,[6] considerable attention has been focussed on the lipid parts of sphingolipids and indirect evidence led to the hypothesis that sphingolipid-derived products may function as second messangers.[7]



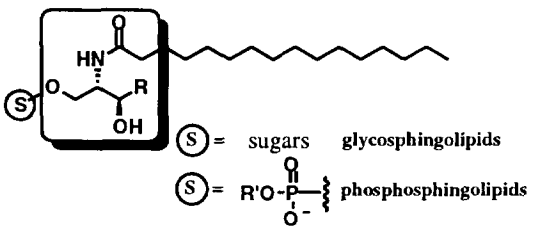
sphingosine 1

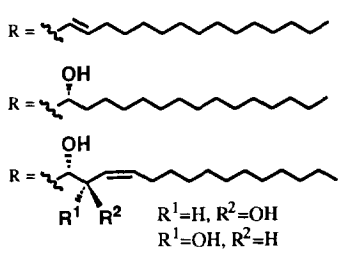


phytosphingosine 2



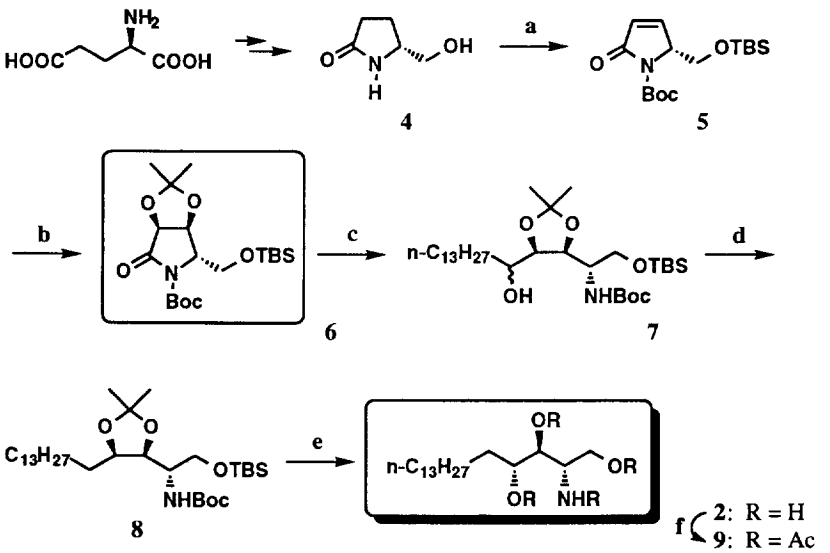
tetrahydroxy-LCB 3a: R^1=H, R^2=OH
3b: R^1=OH, R^2=H





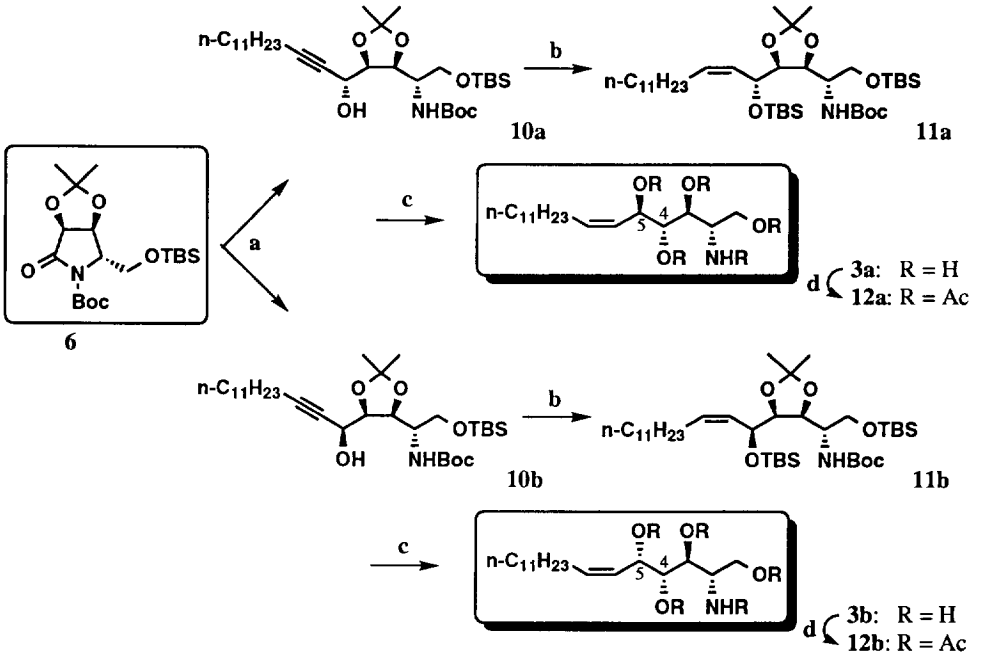
Although many synthetic strategies have appeared for the construction of such compounds, these require multistep reactions or crucial techniques and were not necessarily satisfactory. Thus, further development of much more convenient and practical ways is strongly desired.[8] Herein we wish to communicate the details of an expeditious method for the synthesis of phytosphingosine **2** and tetrahydroxy-LCB **3a** of new cerebrosides and its (5*S*)-isomer **3b** through a homochiral lactam intermediate as a common material. The latter compound, **3a** recently isolated from the latex *Euphorbia characias* L. was inferred from analogy with spectral data of asteriacerebrosides[9] and during our synthetic studies the first method was reported in 1995 from D-mannose.[10]

Hydroxylactam **4** easily obtained from D-glutamic acid[11] (99% e.e. determined by Chiral HPLC) was protected with TBSCl and $(Boc)_2O$ successively, followed by olefination with selenoxide-elimination to afford the unsaturated lactam **5** in high yield (Scheme 1). Dihydroxylation of **5** in the presence of cat. OsO_4 and subsequent acetonide-protection proceeded smoothly, leading to the single product **6**.[12] Treatment of **6** with tridecanylmagnesium bromide, followed by reduction of the corresponding tautomer of keto- and hydroxy pyrrolidine form[13] resulted in the preparation of the alcohol **7** as a diastereomeric mixture. Then, formation of thioimidazolide with (thiocarbonyl)diimidazole and successive reaction with Bu_3SnH under radical conditions[14] cleanly provided the deoxygenated product **8** in 85% yield (2 steps). Finally, **8** was effected by simultaneous deprotection of TBS and Boc groups with TFA-H_2O to complete the synthesis of **2**, $[\alpha]_D^{20}$ +11.6 (c 0.28, pyridine). Furthermore, the structure was confirmed by direct conversion from **7** to the known tetraacetate **9**, $[\alpha]_D^{19}$ +24.7 (c 1.14, $CHCl_3$), whose physical data were identical with the reported values in all respects.[8f]



Scheme 1. Reagents and conditions: (a) 1, TBSCl, imidazole, DMF; 88%; 2, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; 90%; 3, LDA, THF, then PhSeBr, -78 °C; 4, MCPBA, -78 °C; (b) 1, OsO_4, NMO, acetone-H_2O (1:1); 55% (3 steps); 2, $(CH_3)_2C(OCH_3)_2$, *p*-TsOH; quant.; (c) 1, $C_{13}H_{27}MgBr$, -78 °C; 60%; 2, $NaBH_4$, EtOH; 88%; (d) 1, (thiocarbonyl)diimidazole, 50 °C; 98%; 2, Bu_3SnH, AIBN, toluene, 100 °C; 87%; (e) TFA-H_2O (9:1), then KOH, MeOH; quant.; (f) Ac_2O, pyridine, DMAP; 70%.

On the other hand, the syntheses of (5*R*)-tetrahydroxy-LCB **3a** and its (5*S*)-stereoisomer **3b** of new cerebrosides were established as follows: nucleophilic addition of acetylide anion to the common lactam **6** and then reduction with $NaBH_4$ afforded the two diastereomers of **10a** and **10b**[15] in 59% and 22% isolated yield, respectively. After silylation of the hydroxyl group in **10a** and **10b**, these were reduced effectively by partial hydrogenation over Lindlar's catalyst leading to the *cis*-olefinic **11a** and **11b**, respectively, since accompanying formation of small amounts of saturated products were observed in the case of direct hydrogenation of **10**. Finally, deprotection of **11a** and **11b** were submitted with TFA-H_2O simultaneously as described above to produce the desired **3a** and **3b**, respectively. Those structures were characterized after derivatisation to the pentaacetate derivatives **12a**, $[\alpha]_D^{20}$ -15.8 (c 1.44, $CHCl_3$) and **12b**, $[\alpha]_D^{20}$ -12.9 (c 0.57, $CHCl_3$).[16]



Scheme 2. Reagents and conditions: (a) 1, $C_{11}H_{23}C{\equiv}CLi$, THF, -78 °C; 2, $NaBH_4$, *i*-PrOH; **10a**: 59% (2 steps); **10b**: 22% (2 steps); (b) 1, TBSCl, imidazole, DMF; 2, H_2, Lindlar, quinoline, MeOH; **11a**: 60% (2 steps); **11b**: 67% (2 steps): (c) TFA-H_2O (9:1), then KOH, MeOH; (d) Ac_2O, Et_3N, DMAP; **12a**: 68% (2 steps); **12b**: 51% (2 steps).

This process starting from D-glutamic acid to these membrane components represents a short and easily accessible alternative to existing synthetic methods of the long chain bases.

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15. The absolute configuration of the generated stereogenic center was assigned based on the spectral data of synthetic **12a** and **12b**.
16. The spectral data of the synthetic **12a** were completely identical with those of the reported compound except the value of the specific rotation (lit. $[\alpha]_D^{20}$-29.3 (c 0.15, $CHCl_3$)[10]). It is not clear at present the reasons for such a difference, since we confirmed the absence of the other stereoisomers using chiral HPLC. The physical data of **12b** were as follows: ^1H and ^{13}C NMR data ($CDCl_3$) for **8a** and **9a**. **8a**: ^1H NMR δ 0.88 (3H, t, J = 6.6 Hz), 1.17-1.42 (20H, m), 2.00 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.14 (3H, s), 4.10 (1H, dd, J = 2.6, 8.4 Hz), 4.18-4.75 (2H, m), 5.14 (1H, dd, J = 4.2, 4.2 Hz), 5.27-5.75 (3H, m), 5.88 (1H, dd, J = 4.0, 9.0 Hz), 6.12 (1H, d, J = 9.6 Hz). ^{13}C NMR δ 14.1, 20.8, 21.0, 22.7, 23.3, 28.2, 29.4, 29.7, 31.9, 48.2, 62.2, 67.3, 71.5, 72.3, 122.7, 137.3, 169.7, 170.2, 170.5, 170.9.

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