Communications

Synthesis of D-*erythro*-Sphingosine from D-*ribo*-Phytosphingosine

Hyun-Joon Ha,*,†,‡ Doo-Ha Yoon,†,‡ Lae-Sung Kang,†,‡ Myeng Chan Hong,† and Won Koo Lee*,§

†*Department of Chemistry and Protein Research Centre for Bio-Industry, Hankuk University of Foreign Studies, Yongin, Kyunggi 449-719, Korea. *E-mail: hjha@hufs.ac.kr*
‡*Center for Bioactive Molecular Hybrids, Yonsei University, Seoul 120-749, Korea*
§*Department of Chemistry and Interdisciplinary Program of Integrated Biotechnology, Sogang University, Seoul 121-742, Korea. *E-mail: wonkoo@sogang.ac.kr*
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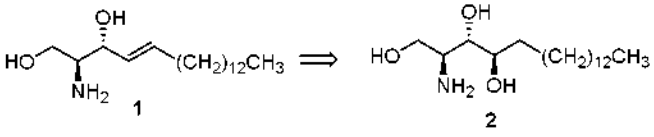
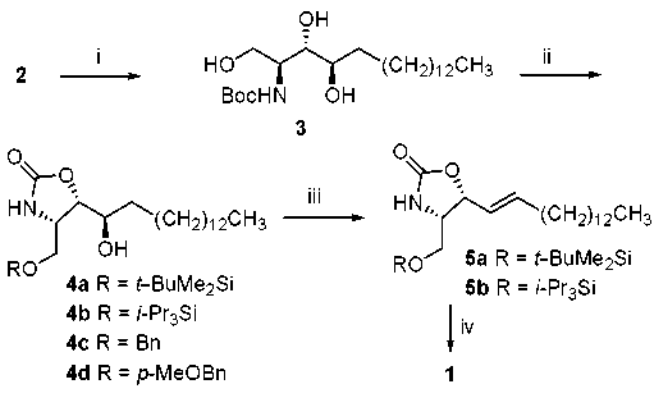
Understanding the role of sphingolipids metabolism in the transduction of the extracellular signals gives an opportunity to develop many novel biologically active molecules including anticancer, anti-inmflamatory and immunosuppressant agents.[1] All of sphingolipids consists of sphingoid backbone and the diverse pendants on hydroxides and/or amine groups(s) including fatty acids, sugars, phosphate etc.[1,2] The most important sphingoid backbone occurring all mammalian cells is D-*erythro*-sphingosine [[(2*S*,3*R*,4*E*)-2-amino-3-hydroxyoctadec-4-ene-1-ol (**1**)].[2] Ample examples of synthetic methods toward D-*erythro*-sphingosine were reported, most of which required several steps to introduce 2-amino-1,3,-dihydroxy moieties with right configurations.[3] D-*ribo*-phytosphingosine [(2*S*,3*S*,4*R*)-2-amino-1,3,4-octadecanetriol (**2**)] available in large quantity from fermentation, possesses all eighteen carbons and 2-amino-1,3-diols for D-*erythro*-sphingosine with one extra-hydroxyl group at C4.[4] Thereby, dehydrative removal of one extra-hydroxide at C4 along with one hydrogen at C5 in stereoselective manner may afford D-*erythro*-sphingosine. Though a few methods[5] were already available for the preparation of D-*erythro*-sphingosine form D-*ribo*-phytosphingosine, a more reliable large scale and cheap synthetic route is still needed.

Herein, we would like to report a facile synthetic method for the synthesis of D-*erythro*-sphingosine form D-*ribo*-phytosphingosine with versatile synthetic intermediate with relatively cheap reagents for an industrial application. Considering many natural and unnatural bioactive analogs[6] including spisulosine[7] bear amine and hydroxide at C2 and C3 with different substituents at C1, the synthetic intermediate being useful toward diverse sphingosine analogs should have properly protected C1-hydroxide group independent to the C2-amine and C3-hydroxy group protections. Thereby, an appropriate protection strategy must be devised to allow protection of amine and hydroxide groups at C2 and C3 while the hydroxide at C1 is blocked independently to leave one extra hydroxide at C4 naked. At first the substrate D-*ribo*-phytosphingosine was reacted with $(Boc)_2O$ to yielded *N*-Boc-protected phytosphingosine (**3**) in quantitative yield, which was then treated with silyl or alkylhalide to block the hydroxide at C1 without purification. This was then treated with two mole equivalents of NaH to yield oxazolidine-2-one (**4**) with various protecting groups at C1-hydroxy group such as *t*-butyldimtheylsilyl, triisopropylsilyl, benzyl and *p*-methoxybenzyl in high yields.[8] Preparation of **4** was succeeded as a one-pot process starting from *N*-Boc-protected phytosphingosine (**3**) by adding 2 equivalents of base in the same reaction vessel after protection of C1 alcohol with the same base NaH. Once we got the crude product crystallization form diethyl ether yielded analytically pure product without chromatographic separation.

Dehydration of **4** proceeded via chlorination followed by dehydrochlorination with proper base.[9] Treatment of **4a** with $POCl_3$ at room temperature in pyridine yielded white precipi-



Figure



Scheme. Reagents and conditions: i. $(Boc)_2O$, 96%; ii. (1) RX, NaH, (2) NaH, **4a** (87%); **4b** (81%); **4c** (78%); **4d** (63%). iii. (1) $POCl_3$, Pyridine, (2) DBU, **5a** (41%); **5b** (62%); iv. $LiAlH_4$, 71%.

tates, solubilized upon addition of DBU. The reaction mixture was then headed at 90 °C to yield dehydrated product **5a** without detectable accumulation of *cis*-isomer in 41% yield. The same reaction starting from **4b** afforded the product in 62% yield. resulted from the more robust nature[10] of triisopropylsilyl over *t*-butyldimethylsilyl group either employed for the protection of the C1-hydroxide group. The compound **5a** or **5b** were treated with five equivalents of $LiAlH_4$ to afford D-*erythro*-sphingosine with removal of all protecting groups in over 70% yield.

In conclusion we synthesized D-*erythro*-sphingosine from D-*ribo*-phytosphingosine whose process is applicable in large scale. Also developed were the intermediates with orthogonally protected amine at C2 and hydroxides at C1 and C3.

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8. Physical data of compound **4a**. R_f = 0.1 (EtOAc : Hexane , 1:3). $[\alpha]_D$ = +0.6 (c = 4.47, CH_2Cl_2). ^{1}H NMR (200 MHz; $CDCl_3$; *J*/Hz) δ 0.07 (6H, s), 0.56 - 1.75 (39H, m), 3.42 - 3.84 (5H, m), 4.42 - 4.44 (1H, m), 5.32 (1H, s). ^{13}C NMR (50.3 MHz ; $CDCl_3$; *J*/Hz) δ -5.7, -5.5, 14.2, 18.2, 22.8, 24.9, 25.8, 25.9, 29.4, 29.7, 32.0, 33.7, 55.9, 61.6, 68.1, 81.5, 159.7. MS (m/z) 458 (M^++1, 100%), 400 (15), 339 (3), 312 (4), 265 (8), 218 (12), 174 (32), 158 (9). HRMS (EI) calcd for $C_{25}H_{51}NO_4Si$: 457.3587, found 457.3580. **5a**. R_f = 0.5 (EtOAc:Hexane, 1:3). $[\alpha]_D$ = -39.9 (c = 1.06, EtOAc). ^{1}H NMR (200 MHz; $CDCl_3$; *J*/Hz) δ 0.04 - 2.08 (42H, m), 3.47 (1H, dd, *J* = 11 Hz, 3.4 Hz), 3.51 (1H, dd, *J* = 11 Hz, 7.4 Hz), 4.42 (1H, dt, *J* = 8.8 Hz, *J* = 5.6 Hz), 5.14 (1H, t, *J* = 8.8 Hz), 5.65 (1H, s). ^{13}C NMR (50.3 MHz ; $CDCl_3$; *J*/Hz) δ -5.3, 14.2, 18.3, 22.8, 25.7, 25.8, 29.2, 29.4, 29.5, 29.6, 29.7, 30.1, 32.0, 56.7, 64.9, 77.7, 104.8, 145.5, 156.9. MS (m/z) 440 (M^++1, 100%), 382 (17), 339 (6), 294 (3), 264 (3), 149 (6), 115 (13). HRMS (EI) calcd for $C_{25}H_{49}NO_4Si$: 439.3482, found 439.3477.
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