Novel Synthon of *N*-Boc-Phytosphingosine-3,4-thiocarbonate for the Synthesis of Sphingosine Derivatives

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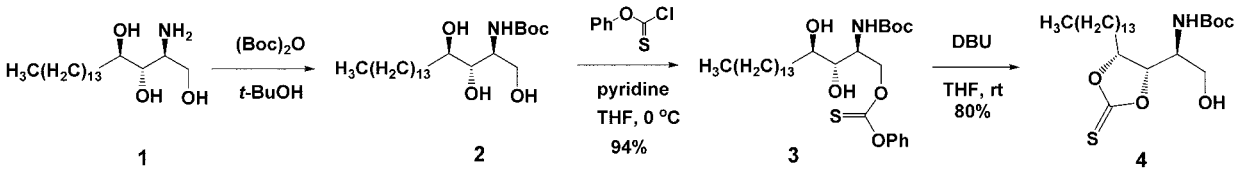
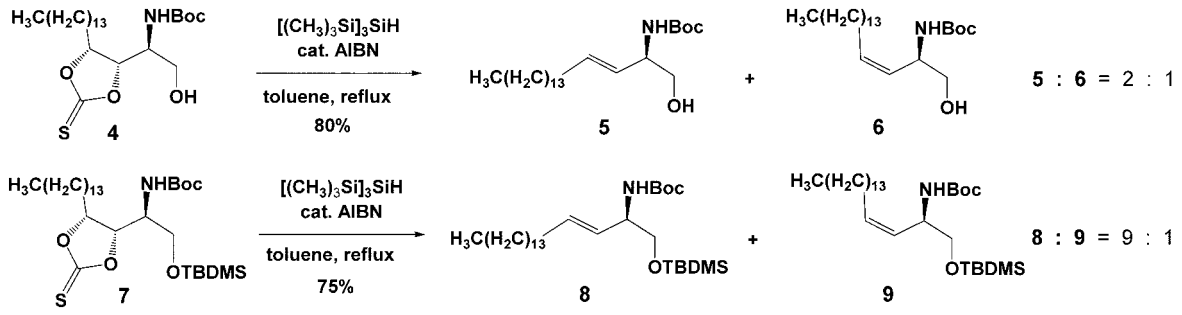
Phytosphingosine, one of the major sphingosine derivatives was found in microorganisms, yeast, plants, and fungi as a major membrane component, and also found in many mammalian tissues[1] and interestingly in some cancer cell-types.[2] The roles of sphingosine derivatives have been enigmatic but they are recently proved to be essential in cell communications and regulation of cell growth.[3] Sphingosine-1-phosphate, the most focused compound in sphingosine derivatives is known to affect fundamental cellular functions.[4] it can also reduce mortality in hypoxic cardiac myocytes.[5] and proved to be crucial in cancer development and progression.[6] Much attention has also been paid to KRN7000, one of α-galactosylceramides as an interesting immunomodulator, which will be useful for treatment of immune related diseases.[7] Since the sphingosine derivatives are very interesting both biologically and synthetically, recently many attempts have been tried to synthesize not only natural sphingosine derivatives[8] but also new modifications of sphingosine derivatives for the evaluation of biological activities.[9]

Previously, we reported a novel synthesis of *N*-Boc-phytosphingosine-3,4-carbonate as an intermediate for the synthesis of new phytosphingosine derivatives, however we could only modify 1-position of phytosphingosine from the intermediate.[10] Here we wish to report a new synton for the synthesis of various sphingosine derivatives. *N*-Boc-Phytosphingosine (**2**)[10] was reacted with phenyl chlorothionocarbonate and pyridine at 0 °C in THF to afford **3** in good yield. To the reaction mixture was added 1.2 equiv of DBU at 25 °C, the thiocarbonate at 1-position was migrated to 3-position, and then the cyclic thiocarbonate **4** was formed as sticky solid in 65% yield as shown in Scheme 1.[11]

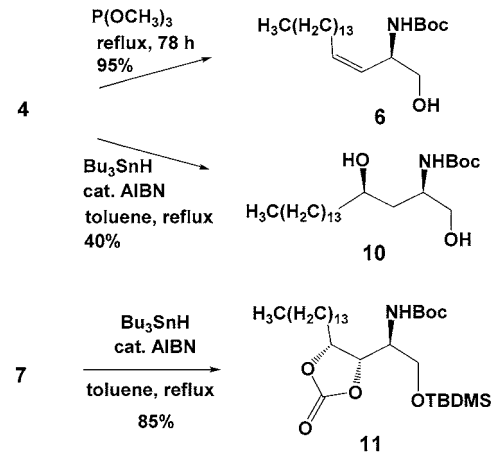
Hydrolysis of **4** with potassium carbonate in 95% methanol afforded *N*-Boc-phytosphingosine (**2**) quantitatively. For the reductive elimination of **4**, first we examined tributyltin hydride or triphenyltin hydride in the presence of triethylborane, but the reaction did not occur at all. When **4** was heated in toluene with tri(trimethylsilyl)silane in the presence of *cat.* AIBN, the thiocarbonate group in **4** was reduced to the double bond to form **5** and **6**[12] in a ratio of 2 : 1 in total 80% yields, while after protection of hydroxyl group of **4** with TBDMS, the *trans* double bond (**8**) was formed as a major in a ratio of 9 : 1 as shown in Scheme 2. The aminoalcohols, **5** and **6** showed potent biological



Scheme 1



Scheme 2



Scheme 3

activities[13] and these compounds could be easily converted to other sphingosine derivatives.[14]

When **4** was heated in trimethyl phosphite for 78 h, only *cis* double bond was formed to give **6** in 95% yield as shown in Scheme 3. Interestingly, when tributyltin hydride was used with AIBN, **10** was separated in 40% yield from a complicated mixture. **5** and **6** were not formed in the reaction but any other compounds could not be isolated. The structure of **10**[15] was confirmed by COSY and NOE experiment. Moreover, **7** afforded only desulfurized product **11**, the spectral data of which were in accordance with those previously reported.[10]

In summary, phytosphingosine was protected by the formation of novel cyclic thiocarbonate in two steps, which could be useful for the derivatization of phytosphingosine by reductive cleavage of the thiocarbonate ring.

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11. **3**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.9 Hz), 1.24-1.53 (m, 24H), 1.47 (s, 9H), 1.53-1.63 (m, 2H), 2.14 (br, 1H, -OH), 2.90 (br, 1H, -OH), 3.66-3.75 (m, 2H), 4.12-4.18 (m, 1H), 4.70-4.85 (m, 2H), 5.10 (d, 1H, J = 6.2 Hz, -NH). 7.08-7.45 (m, 5H). **4**: ^{1}H NMR ($CDCl_3$) δ0.88 (t, 3H, J = 6.2 Hz), 1.24-1.48 (m, 24H), 1.45 (s, 9H), 1.76-1.82 (m, 2H), 1.85 (br, 1H, -OH), 3.75-3.81 (m, 1H), 3.93-4.10 (m, 2H), 4.86-4.95 (m, 2H), 5.02 (br, 1H, -NH).
12. **5**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.20-1.45 (m, 24H), 1.45 (s, 9H), 1.94-2.05 (m, 2H), 2.25 (br, 1H, -OH), 3.50-3.72 (m, 2H), 4.10-4.22 (m, 1H), 4.78 (br, 1H, -NH), 5.36 (dd, 1H, J = 6.1, 15.4Hz), 5.62-5.78 (m, 1H); Anal. calcd for $C_{23}H_{45}NO_3$: C, 72.01; H, 11.82; N, 3.65; O, 12.51. Found: C, 72.051; H, 11.918; N, 3.646. **6**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.5 Hz), 1.18-1.40 (m, 24H), 1.45 (s, 9H), 2.05-2.225 (m, 2H), 2.50 (br, 1H, -OH), 3.50-3.65 (m, 2H), 4.40-4.56 (m, 1H), 4.62 (br, 1H, -NH), 5.18-5.35 (m, 1H), 5.50-5.68 (m, 1H); Anal. calcd for $C_{23}H_{45}NO_3$: C, 72.01; H, 11.82; N, 3.65; O, 12.51. Found: C, 72.1938; H, 11.796; N, 3.643.
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15. **10**: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.0 Hz), 1.20-1.57 (m, 27H), 1.42 (s, 9H), 1.75-1.85 (m, 1H), 2.32 (br, 1H), 3.29 (br, 1H), 3.55-3.78 (m, 3H), 5.20 (br, 1H); Anal. calcd for $C_{33}H_{67}NO_4$: C, 68.78; H, 11.80; N, 3.49; O, 15.93. Found: C, 68.64; H, 11.78; N, 3.48.