SYNTHESIS OF SPHINGOSINE ANALOGUES: STEREOSELECTIVE SYNTHESIS OF 3-DEOXYSPHINGOSINE AND *cis*-ISOMERS

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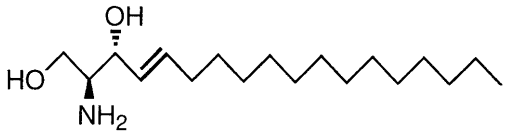
Both enantiomers of 3-deoxysphingosine as well as their *cis*-isomers were synthesized stereoselectively from L- and D-serine.
KEY WORDS 3-deoxysphingosine; sphingosine analogue; primase inhibitor; serine

Sphingosine has been well known as a major component of ceramides. Recently, sphingosine itself has been found to have an inhibiting property toward protein kinase C[1] and inhibitory activity toward DNA primase.[2] These biological activities are important for signal transduction, cell recognition, and cell growth. Sphingosine consists of one amino group, two hydroxy groups, one *trans* C=C double bond, and a long non-branched aliphatic chain. The amino group is usually condensed with aliphatic carboxylic acid, as found in ceramides and cerebrosides. The role of the primary hydroxy group is as a glycosyl acceptor in cerebrosides as well as a phosphate component in sphingosine-1-phosphate and sphingomyelin. Among these functionalities, the function of the C-3 secondary hydroxy group is still unknown.[3] In connection with our interest in the structure-activity relationship of sphingosine analogues in DNA primase inhibition,[4] we became interested in the biochemical activity of 3-deoxysphingosine in order to determine the role of the 3-hydroxy group of sphingosine. Therefore, the synthesis of all four diastereoisomers of 3-deoxysphingosine was required. Although there are more than 20 reports on the synthesis of sphingosine,[5] only two reports are available on the synthesis of 3-deoxysphingosine. Bittman and co-workers prepared racemic 3-deoxysphingosine from allylic iodide and tris(trimethylsilyl)glycine followed by $LiAlH_4$ reduction.[6] Kinsho and Mori synthesized (*R*)- and (*S*)-3-deoxysphingosine using enzymatic resolution of the intermediate.[7] In this paper we report our results on the stereoselective synthesis of all four possible diastereisomers of 3-deoxysphingosine, namely the (*R*,*E*)-, (*R*,*Z*)-, (*S*,*E*)-, (*S*,*Z*)-isomers, from easily available chiral sources, L- and D-serines.



D-*erythro*-sphingosine

4-Vinyl-oxazoline (*R*)-**3** was prepared from L-serine in 5 steps according to the literature.[8] Hydroboration of (*R*)-**3** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by H_2O_2 oxidation

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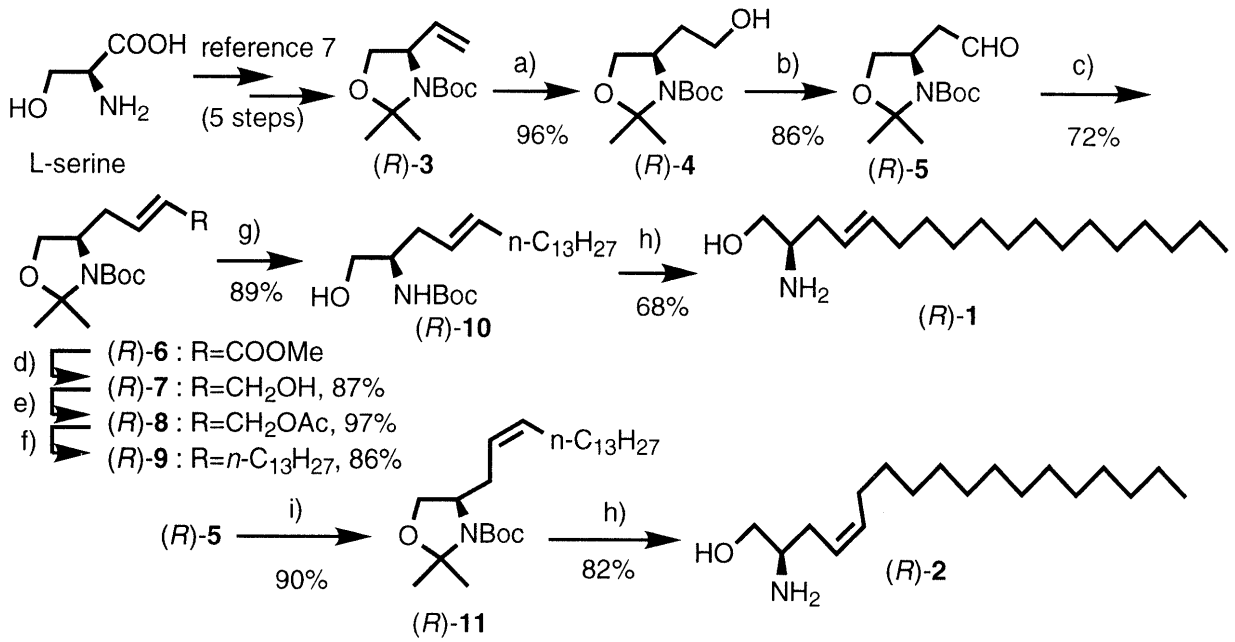

Reagents and conditions: a) i) 9-BBN, THF, rt, 12 h; ii) H_2O_2, NaOH, rt, 4 h, b) Dess-Martin periodinane, CH_2Cl_2, rt, 0.3 h, c) $Ph_3P{=}CHCO_2Me$, PhMe, reflux, 0.5 h, d) DIBAH, THF, -78°C, 10 h, e) Ac_2O, pyridine, rt, 12.5 h, f) *n*-$C_{12}H_{25}MgBr$, Li_2CuCl_4, THF, -15~0°C, 5 h, g) Amberlyst-15, MeOH, rt, 26 h, h) *c*.HCl, AcOEt, rt, 22 h for (*R*)-**10**, 1 h for (*R*)-**11** , i) *n*-$C_{14}H_{29}P^+Ph_3$ Br^-, *n*-BuLi, THF, rt, 2.5 h.

gave primary alcohol (*R*)-**4** in 96% yield as a single product.[9] Oxidation of alcohol (*R*)-**4** with Dess-Martin periodinane[10] provided aldehyde (*R*)-**5** in 86% yield. Wittig reaction of (*R*)-**5** with methoxycarbonyltriphenylphosphorane in refluxing toluene gave *trans*-alkene (*R*)-**6** in 72% yield with a trace amount of *cis*-isomer.[11] Reduction of (*R*)-**6** with diisobutylaluminum hydride (DIBAH) gave allylic alcohol (*R*)-**7** in 87% yield, which was acylated with Ac_2O in pyridine to give allylic acetate (*R*)-**8** in 97% yield. Aliphatic chain extension was performed by means of copper-catalyzed allylic substitution with Grignard reagent.[12] Thus acetate (*R*)-**8** was treated with *n*-$C_{12}H_{25}MgBr$ in the presence of 4 mol% of Li_2CuCl_4 to give alkene (*R*)-**9** in 86% yield. Stirring of MeOH solution of (*R*)-**9** with Amberlyst-15™ gave a primary alcohol (*R*)-**10** in 89% yield. Final deprotection of Boc with concentrated HCl in AcOEt furnished (*R*)-3-deoxysphingosine (*R*)-**1** in 68% yield in the form of tiny colorless plates.[13] The overall yield of (*R*)-**1** from (*R*)-**3** was 26% in 8 steps.[13,14] *cis*-Diastereoisomer (*R*)-**2** was prepared as follows. Wittig reaction of (*R*)-**5** with *n*-$C_{13}H_{27}CH{=}PPh_3$ gave *cis*-alkene (*R*)-**11** in 90% yield. Double deprotection of (*R*)-**11** with *c*. HCl gave (*R*)-(*E*)-3-deoxysphingosine (*R*)-**2** in 82% and 61% overall yield from (*R*)-**3**.[16,17]

With a similar synthetic sequence starting from D-serine, (*S*)-enantiomers (*S*)-**1** and (*S*)-**2** were also synthesized in 31% and in 49% overall yield from (*S*)-**3**, respectively.[18]

Experiments on the biological activity of these analogues are underway and will be reported in due course.

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17) (*R*)-**2**: tiny colorless plates, mp 64.0-65.0°C (hexane). $[\alpha]_D^{17}$ -8.5° (c 2.08, $CHCl_3$).
18) (*S*)-**1**: tiny colorless plates, mp 70.0-71.5°C (hexane). $[\alpha]_D^{24}$ -1.9° (c 0.42, MeOH), (*S*)-**2**: tiny colorless plates, mp 64.0-65.0°C (hexane). $[\alpha]_D^{23}$ +8.0° (c 0.50, $CHCl_3$).

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