Efficient Enantioselective Total Synthesis of *arabino*-Phytosphingosine

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Abstract: Enantioselective total synthesis of *arabino*-phytosphingosine has been achieved in 8 steps employing Claisen rearrangement and Fleming–Tamao oxidation as key steps. Installation of all chiral centers present in *arabino*-phytosphingosine was achieved through the use of asymmetric catalysis. This synthesis provides one of the most efficient routes to prepare 2-amino-1,3,4-triol moiety.

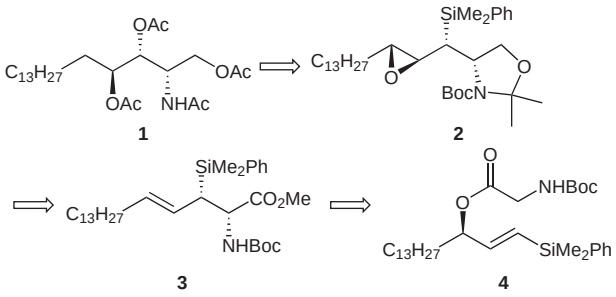
Key words: amino alcohol, enantioselective synthesis, total synthesis, sphingolipids, Claisen rearrangement

Sphingolipids and glycosphingolipids are important elements of eukaryotic cell membranes and are known to regulate several biological processes, such as cell proliferation, differentiation, adhesion, neuronal repair, and signal transduction.[1] Additionally, many glycosphingolipids from marine organisms display remarkable antitumor,[2] antiviral,[3] antifungal,[4] antiinflammatory,[5] immunosuppressive,[6] immunostimulatory,[2] neuritogenic,[7] and cytotoxic activities.[8] Phytosphingosines are one of the major long chain components of glycosphingolipids with an 18-carbon chain and a terminal 2-amino-1,3,4-triol moiety. Like many members of sphingolipids, phytosphingosine itself is a bioactive lipid and its analogues also show significant bioactivities. Due to these biochemical importance, along with the fact that natural supply of phytosphingosines are fairly limited, there is a continuing interests in developing efficient methods for the synthesis of phytosphingosines.

Many methods have been reported for the synthesis of phytosphingosines.[9–11] Most of them, however, are based on a chiral pool strategy that usually employs carbohydrates[9] or amino acid[10] derived starting material to install chiral centers present in the final product. Also, very few methods employing asymmetric synthesis to install chiral centers are reported.[11] However, except for some cases,[9a] they often suffer from the drawbacks of being a multistep synthesis with a poor overall yield. To overcome the problems inherent in the previous synthetic routes, new retrosynthetic analysis of *arabino*-phytosphingosine was made (Scheme 1).

The *arabino*-phytosphingosine **1** can be thought to derive from the epoxide **2** through regioselective reduction of epoxide[10b,c,12] and subsequent Fleming–Tamao oxidation[13] which occurs under acidic conditions and will result in the formation of fully deprotected *arabino*-phytosphingosine. In turn, the epoxide **2** can be prepared from the allyl silane **3**, which may result from the Claisen rearrangement of allylic ester **4**.

To prepare **4**, we started from tetradecanal (Scheme 2). According to our retrosynthetic analysis and preceding experimental evidences about the stereochemistry of Claisen rearrangement, to prepare natural enantiomer of *arabino*-phytosphingosine, *R*-form of *E*-allylic alcohol **6** should be prepared. Enantio-enriched allylic alcohol **6** can be prepared by many ways, including kinetic resolution with Sharpless procedure, chromatographic separation of diastereomeric derivatives of *rac*-**6**, and probably enzymatic resolution of *rac*-**6**.[14] However, it is important that for an asymmetric synthesis to be practical, the stereochemistry should be installed by asymmetric catalysis involving carbon–carbon bond formation. Thus, tetradecanal was reacted with dimethylphenylsilyl acetylene under the conditions of Pu.[15] Treatment of tetradecanal with (*S*)-BINOL, $Ti(O\textit{i}\text{-}Pr)_4$, Et_2Zn and dimethylphenylsilyl acetylene gave the corresponding propargyl alcohol **5** in 85% yield with 98% ee. It was partially reduced with Red-Al to give allylic alcohol **6** in high yield in an almost enantiomerically pure form (98% ee). The coupling of **6** with Boc-glycine gave **4** in good yield. Allylic alcohol like **6** has been prepared in many ways, however to our knowledge, it is the first time to employ asymmetric catalysis to establish the stereochemistry of **6**.



Scheme 1 Retrosynthetic analysis for *arabino*-phytosphingosine.

The Claisen rearrangement of amino acid derived allylic ester is known.[16] However, only one report[17] has been written regarding the Claisen rearrangement of allylic ester in which the allylic component is vinyl silane. To investigate the key rearrangement step, we first employed

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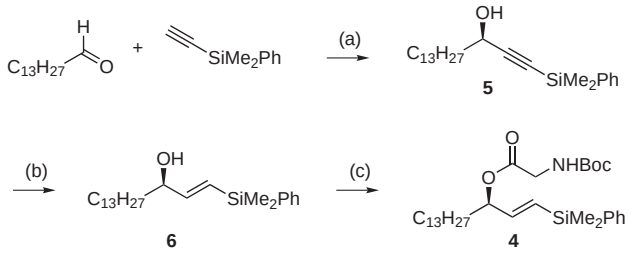
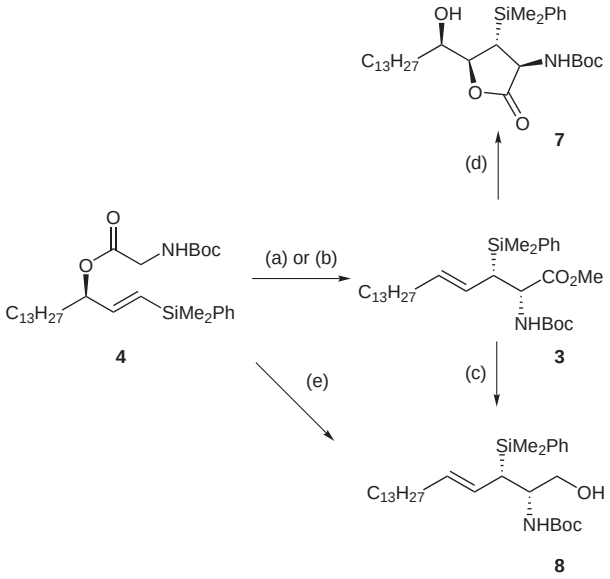


Scheme 2 *Reagents and conditions*: (a) Et_2Zn (6 equiv), dimethylphenylsilyl acetylene (6 equiv), toluene, reflux, 1 h; then, (*S*)-BINOL (0.5 equiv), Ti(O*i*-Pr)$_4$ (1.5 equiv), tetradecanal in Et_2O, 75%, 98% ee; (b) Red-Al (2.1 equiv), Et_2O, 0 °C to r.t., 87%, 98% ee; (c) EDCI (1.1 equiv), Boc-Gly-OH (1.1 equiv), DMAP (0.3 equiv), 95%.

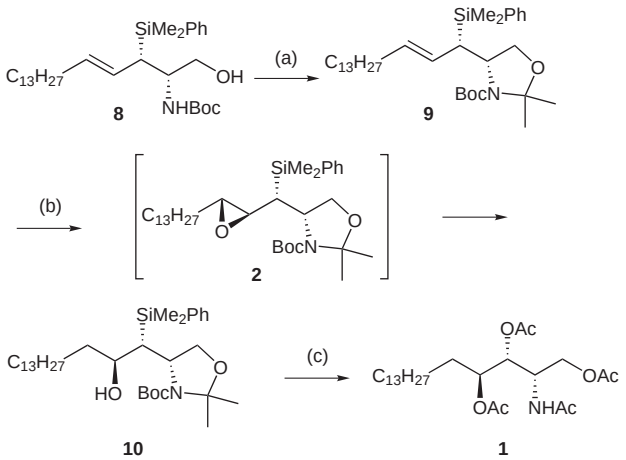
conditions reported by Kazmaier et al. (Scheme 3).[16] In the presence of LDA and $ZnCl_2$, **3** can be obtained in moderate yield with excellent stereoselectivity [ca. 60% yield, *syn*:*anti* > 95:5, (*S*,*S*):(*R*,*R*) > 95:5]. To improve the yield, the conditions of Brook was employed.[17] Thus, by treating lithium enolate, generated from **4** by treatment with LDA, with TMSCl, we could induce the more efficient Claisen rearrangement with the same degree of stereoselectivity [77% yield, *syn*:*anti* > 95: 5, (*S*,*S*): (*R*,*R*) > 95:5]. The *syn*-relation of amino- and silyl-groups have been established by transforming the allyl silane to the lactone **7** and taking NOE spectra.[18] To adjust the oxidation state of C-1 carbon, the ester **3** was reduced to give amino alcohol **8**. We also tried the one pot reaction of **4** to **8**. The completion of the rearrangement was confirmed by TLC, the reaction mixture was treated with excess amount of $LiAlH_4$ to give **8**. The yield improved significantly compared with the two-step procedure one-step reaction (77%).

The deoxygenation of lactone **7** could be a possible option for introducing C-4 hydroxyl group though, it would require two additional steps and in view of atom economy, it should be avoided. Thus, instead we chose to epoxidize the double bond in **8** and then make a reductive cleavage of the epoxide to synthesize the key intermediate (Scheme 4). Thus, **8** was protected as the corresponding acetonide **9**.[19] Treatment of **9** with four equivalents of MCPBA followed by reduction by lithium triethylborohydride (super-hydride) gave **10** as a sole diastereomer, presumably through the key epoxide **2**. In spite of the effort to isolate the epoxide **2**, it decomposed readily and has to be employed directly in the next reaction. The **10** was then subjected to the Fleming–Tamao oxidation, under which the Boc- and acetonide protection of **10** were also deprotected.[14] The crude *arabino*-phytosphingosine was then acetylated to give the known tetra-acetyl *arabino*-phytosphingosine **1**.[22]

The high diastereoselectivity of epoxidation step could be rationalized by the following model, suggested by Fleming et al. (Scheme 5).[20] The dimethylphenylsilyl group of allyl silane should take the position vertical to the plane of olefin double bond to ensure maximum overlap of orbitals. Theoretically, two transition states **A** and **B** are possible. However, the presence of bulky R group in this case



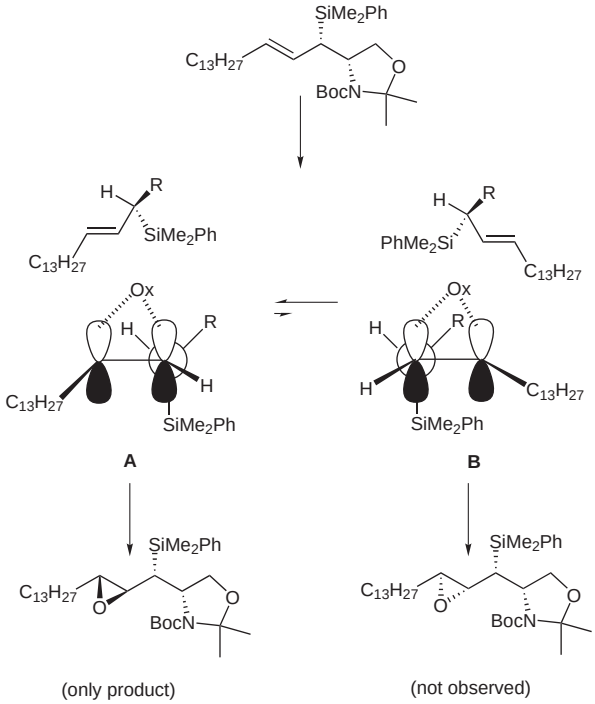
Scheme 3 *Reagents and conditions*: (a) LDA (2.5 equiv), $ZnCl_2$ (1.3 equiv), THF, –78 °C to r.t., 60%; (b) LDA (2.1 equiv), TMSCl (3 equiv), THF, –78 °C to r.t., 77%; (c) $LiAlH_4$ (2 equiv), THF, 0 °C, 80%; (d) OsO_4 (5 mol%), NMO (2.1 equiv), acetone–H_2O = 20:1, r.t.; (e) LDA (2.1 equiv), TMSCl (3 equiv), THF, –78 °C to r.t., then, $LiAlH_4$ (2 equiv), THF, 0 °C, 78%.



Scheme 4 *Reagents and conditions*: (a) 2,2-dimethoxypropane, acetone, $BF_3{\cdot}OEt_2$, r.t., ca. 100%;[19] (b) MCPBA (4 equiv), $NaHCO_3$ (6 equiv), CH_2Cl_2, 0 °C, then, $LiEt_3BH$ (2 equiv), THF, 0 °C, 81%; (c) $Hg(TFA)_2$ (1.1 equiv), TFA–HOAc = 1:1, 25 °C, then, peracetic acid (3 equiv); then, Ac_2O (6 equiv), pyridine (10 equiv), 70%.

made **B** unfavorable and oxidation reaction would proceed through the transition state **A**. This kind of stereoselection has well-established precedents.

In conclusion, we have developed a short, efficient, and conceptually novel synthesis of *arabino*-phytosphingosines starting from easily obtainable starting materials. This synthesis provides phytosphingosines in only eight steps starting from tetradecanal. The overall yield of synthesis reaches nearly 30% and the all the stereocenters of *arabino*-phytosphingosine are derived from the stereo-



Scheme 5 Stereochemical model for epoxidation.

chemistry of the propargyl alcohol **5**, prepared through an asymmetric catalysis. Also, it is the first time to synthesize allyl silane such as **3**[21] without depending on chiral resolution.

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(21) **Experimental Procedure for the Synthesis of Allylsilane 3**.
A freshly prepared solution of LDA (2.1 equiv) in THF under argon was cooled down to –78 °C. To the above solution, the allylic ester **4** was added rapidly. The resulting mixture was left to stir for 3 min and then treated with 3.0 equiv of TMSCl. This solution was allowed to warm to r.t. and stirred for further 2 h. The reaction was quenched with dilute aq HCl and extracted with EtOAc. The extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude carboxylic acid. The crude product was dissolved in the mixed solvent of MeOH–benzene (1:1) and treated with TMS-diazomethane (2.0 equiv). The mixture was stirred for 30 min at r.t. and concentrated in vacuo to give crude γ,δ-unsaturated methyl ester **3**. The crude ester **3** was purified by silica gel column chromatography using EtOAc–*n*-hexane = 1:8 as eluents. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.48 (m, 2 H), 7.24–7.33 (m, 3 H), 5.29 (m, 1 H), 5.14 (m, 1 H), 4.87 (br d, 1 H), 4.31 (br t, 1 H), 3.52 (s, 3 H), 2.05 (m, 1 H), 1.95 (m, 2 H), 1.38 (s, 9 H), 1.24 (br s, 24 H), 0.86 (t, 3 H), 0.31 (d, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3, 1.1, 12.9, 22.8, 23.1, 28.4, 30.1, 30.6, 30.7, 32.5, 33.7, 50.4, 53.5, 71.0, 127.8, 128.4, 128.9, 133.6, 133.9, 140.4, 158.1, 170.9. MS (EI): *m/z* calcd for $C_{31}H_{53}NO_4Si$: 544.29; found: 545.3900.
(22) **Experimental Procedure for the Synthesis of *arabino*-Phytosphingosine.**
To a solution of acetonide **9** in CH_2Cl_2, 8 equiv of $NaHCO_3$ was added. The resulting mixture was cooled to 0 °C and

then, 4 equiv of MCPBA were added in one portion. The resulting mixture was allowed to warm to r.t. over 6 h. The reaction was quenched by the addition of sat. aq Na_2SO_3 solution and extracted with CH_2Cl_2. The resulting organic layer was washed twice with sat. aq $NaHCO_3$ solution, dried over anhyd $MgSO_4$, filtered and concentrated in vacuo. The crude epoxide **2** was dissolved in anhyd THF and cooled to 0 °C. It was treated with 2 equiv of lithium triethylborohydride and allowed to stir for additional 2 h. The reaction was quenched with dilute aq HCl and extracted with EtOAc. The extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude alcohol **10**. The resulting crude alcohol **10** was purified by silica gel column chromatography using EtOAc–*n*-hexane = 1:4 as eluents. The alcohol **10** was placed in a round-bottom flask and the mixture of TFA–HOAc (1: 1) was added. To the above mixture was added 2.0 equiv of mercury trifluoroacetate. After 15 min of stirring, 4 equiv of peracetic acid (40 wt% in acetic acid) were added and stirring was continued overnight with exclusion of light. The reaction mixture was diluted with Et_2O and washed successively with excess amount of aq $NaHCO_3$ solution and aq Na_2SO_3 solution. The combined aqueous layer was again extracted with Et_2O several times. The resulting organic layer was washed with sat. aq $NaHCO_3$ solution twice, dried over anhyd $MgSO_4$, filtered and concentrated in vacuo. To the resulting crude *arabino*-phytosphingosine was added THF and it was treated with excess pyridine and Ac_2O. The reaction was quenched with dilute aq HCl and extracted with EtOAc. The extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude tetraacetyl *arabino*-phytosphingosine (**1**). The resulting crude **1** was purified by silica gel column chromatography using EtOAc–*n*-hexane = 1:5 as eluents to give pure tetraacetyl *arabino*-phytosphingosine whose spectral data are identical with those reported in literature.[10b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.63 (d, 1 H), 5.19 (dd, 1 H), 5.00 (dt, 1 H), 4.60 (m, 1 H), 4.00 (d, 2 H), 2.11 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.99 (s, 3 H), 1.54 (br s, 2 H), 1.24 (br s, 24 H), 0.88 (t, 3 H). $[\alpha]_D^{25}$ –24.7 (*c* 1.0, $CHCl_3$); lit. $[\alpha]_D^{25}$ –25.1 (*c* 1.5, $CHCl_3$).