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Oxazine formation by MsCl/Et_3N as a convenient tool for the stereochemical interconversion of the hydroxyl group in *N*-acetyl 1,3-aminoalcohols. Asymmetric synthesis of *N*-acetyl L-*xylo*- and L-*arabino*-phytosphingosines

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Abstract—Use of MsCl/Et_3N was proven to provide a convenient synthetic tool for the stereochemical intercoversion of the hydroxyl group in *N*-acetyl 1,3-aminoalcohols. Thus, under these conditions, the alcohols **4** and **6** smoothly converted to the oxazines **5** and **7**, respectively, which were hydrolyzed to generate the corresponding inverted alcohols **6** and **4** in one pot. Further elaboration of **4** and **6** led to the efficient asymmetric synthesis of *N*-acetyl L-*xylo*- and L-*arabino*-phytosphingosines (**11** and **15**), respectively, via olefin cross metathesis reactions.

Along with sphingosines and sphinganines, phytosphingosines (PS) constitute the three most abundant core structures for the sphingolipids, which are ubiquitous membrane components in eukaryotic cells and in all plasma membranes. In addition to their passive structural roles as membrane constituents, sphingolipids are also dynamically involved in essentially all aspects of cell regulation covering cellular recognition, growth, and development.[1] Phytosphingosines are major membrane components in plants and yeasts, and have also been discovered in mammalian tissues and marine organisms.[2]

Among these, of particular interest is D-*ribo*-phytosphingosine with 18-carbons, since it is the most frequently occurring in nature and has been shown to play an important role as a potential heat stress signal in yeast cells,[3] as a modulator for the activity of the Ca^{2+} release channel,[4] and as an inhibitor for calf thymus DNA primase as well as a cytotoxic agent against human leukemic cell lines.[5] Furthermore, D-*ribo*-phytosphingosine is an essential part of more complex bioactive molecules such as KRN7000, which is believed to be involved in the activation of natural killer T cells and is currently under clinical trial for the treatment of liver tumors.[6] Phytosphingosines with other chain lengths as well as different stereochemistries of the amino and hydroxyl groups are also known and bioactive to varying degrees.[2]

As a consequence of these diverse biological roles of phytosphingosines, a considerable number of methodologies have been developed for the synthesis of phytosphingosines, most of which rely upon use of chiral starting materials such as α-amino acids and carbohydrates.[2,7] Asymmetric approaches have scarcely been reported, and/or are quite lengthy.[8]

Recently we became interested in the asymmetric synthesis of phytosphingosines, since it was envisioned that the reactions between the aldehyde **1** and various Grignard reagents would provide the most direct and flexible asymmetric route for their production (Eq. 1). Indeed, this approach worked out well for the asymmetric synthesis of phytosphingosines with *syn*-diol stereochemistry at C3 and C4. However, for the cases in which R is longer than a five carbon chain, inversion of the C4 hydroxyl group of **2** using either Mitsunobu[9] or Burgess[10] conditions was not possible, limiting the flexibility and general applicability of this approach (Eq. 1 of Fig. 1).

Keywords: Phytosphingosine; Regioselective asymmetric aminohydroxylation; Olefin cross metathesis; Oxazine.
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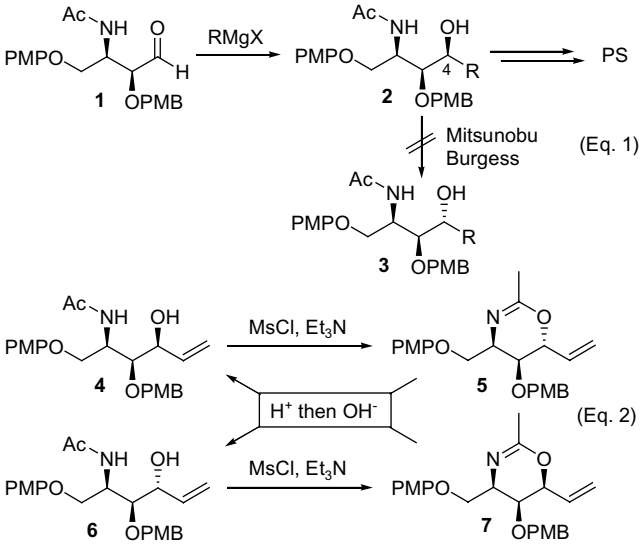


Figure 1. Formation and hydrolysis of the oxazines **5** and **7**.

During the course of other research projects in the laboratory, it was observed that treating the *N*-acetyl 1,3-aminoalcohols **4** and **6** with MsCl and Et_3N in THF resulted in the formation of the oxazines **5** and **7**, respectively, with the stereochemical inversion at the allylic carbons, which were hydrolyzed to generate the corresponding inverted *N*-acetyl 1,3-aminoalcohols **6** and **4** (Eq. 2 of Fig. 1). Formation and subsequent hydrolysis of the oxazines **5** and **7** could be done in one pot, making it possible to interconvert between the *syn*- and *anti*-diol stereochemistries at the C3 and C4 of these phytosphingosines.

Then, as shown in Figure 2, it was envisioned that combining the present oxazine chemistry with an olefin cross metathesis (CM) reaction[11] could lead to an extremely efficient and flexible methodology for the asymmetric synthesis of phytosphingosines. The C2 and C3 stereocenters of phytosphingosines could be installed by the regioselective asymmetric aminohydroxylation (RAA) reaction[12] of the readily available achiral olefin **VI**.

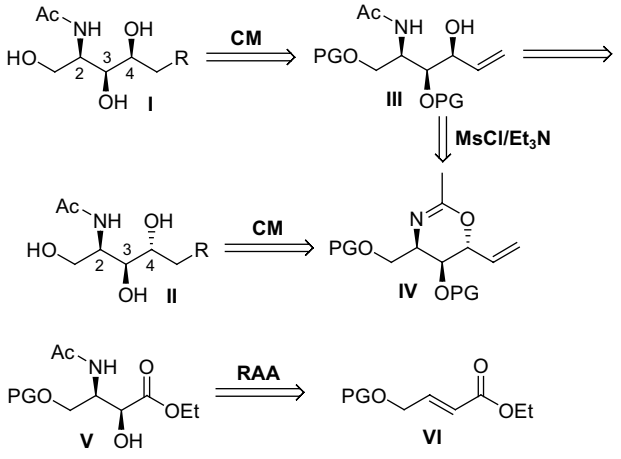
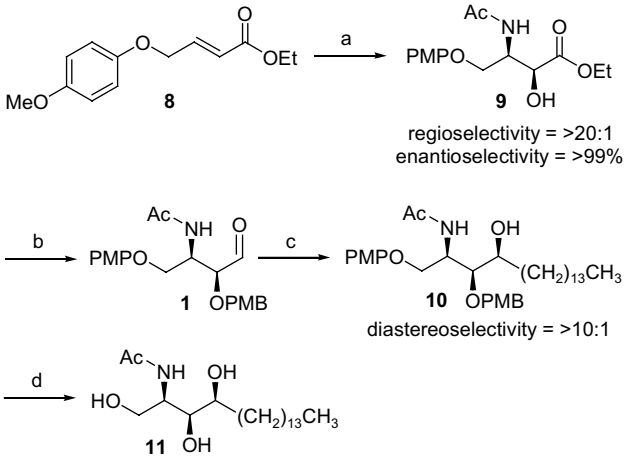


Figure 2. Retrosynthetic analysis for phytosphingosines.

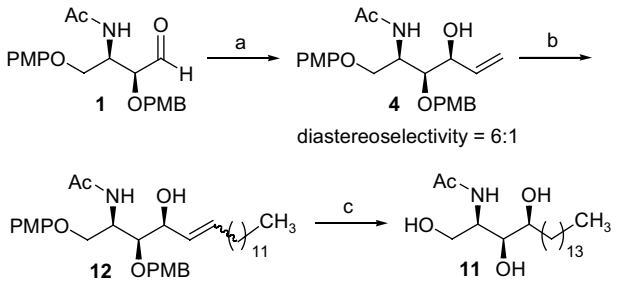


Scheme 1. Asymmetric synthesis of *N*-acetyl L-*xylo*-(2*R*,3*S*,4*S*)-phytosphingosine using Grignard reagents. Reagents and conditions: (a) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, LiOH, AcNHBr, *t*-BuOH–H_2O 2:1, 4 °C, 70%; (b) (i) NaH, PMBCl, DMF, 0 °C, 80%; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 60%; (c) $C_{14}H_{29}MgBr$, THF, −30 °C, 1 h then 25 °C, 2 h, 88%; (d) CAN, MeCN–H_2O 4:1, 0 °C to room temperature, 75%.

Scheme 1 describes the asymmetric synthesis of *N*-acetyl L-*xylo*-(2*R*,3*S*,4*S*)-phytosphingosine (**11**) with the *syn*-3,4-diol stereochemistry via the RAA reaction of the achiral olefin **8** and the reaction of the aldehyde **1** with Grignard reagents. The RAA reaction of **8** using the $(DHQD)_2PHAL$ as a ligand and *N*-bromoacetamide as a nitrogen source/oxidant afforded the *syn*-aminoalcohol **9** with excellent regio- (>20:1) and enantioselecivity (>99% after one recrystallization from ethyl acetate). Protection of the hydroxyl group of **9** by *p*-methoxybenzyl (PMB) chloride and sodium hydride in DMF[13] and the partial reduction of the resulting ester by slow addition of DIBAL at −78 °C[14] generated the aldehyde **1**. Reactions of the aldehyde **1** with tetradecylmagnesium bromide were examined under various conditions. Slow addition of the Grignard reagent to the reaction mixture at −30 °C in THF followed by the slow warm-up of the reaction mixture to room temperature proved to provide optimal conditions in terms of both diastereoselectivity and reaction yield, providing the alcohol **10** as a major product in a ratio of >10:1 and 88% yield.[7f] Simultaneous deprotection of the PMP and PMB groups of **10** by CAN[15] gave *N*-acetyl L-*xylo*-(2*R*,3*S*,4*S*)-phytosphingosine (**11**).

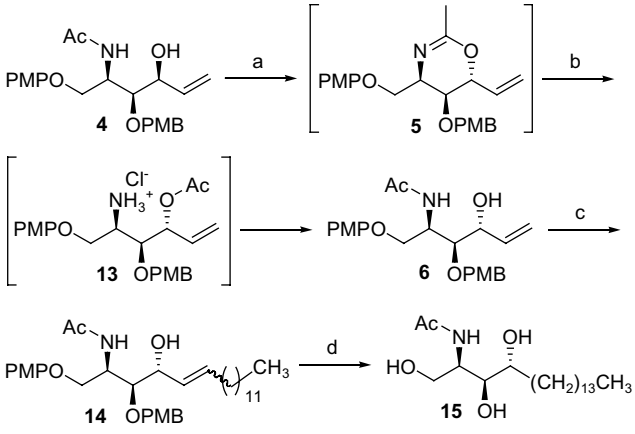
N-Acetyl L-*xylo*-(2*R*,3*S*,4*S*)-phytosphingosine (**11**) was also prepared using a nuclophilic addition reaction of the aldehyde **1** with vinylmagnesium bromide and a cross metathesis reaction of the resulting olefin **4** with 1-tetradecene (Scheme 2). The second generation Grubbs' catalyst {Tricyclohexylphosphine[1,3-bis(2,4,6-trimethyl-phenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]-ruthenium (IV) dichloride} was used for the cross metathesis reaction. Hydrogenation of the olefin **12** and deprotection of the PMP group by CAN yielded *N*-acetyl L-*xylo*-(2*R*,3*S*,4*S*)-phytosphingosine (**11**).[17]

To prepare *N*-acetyl L-*arabino*-(2*R*,3*S*,4*R*)-phytosphingosine (**15**) with *anti*-3,4-diol stereochemistry, the allylic



Scheme 2. Asymmetric synthesis of **11** using olefin cross metathesis reaction. Reagents and conditions: (a) vinylmagnesium bromide, THF, −50 °C to room temp, 74%; (b) 1-tetradecene, second generation Grubbs' catalyst, CH_2Cl_2, 40 °C, 8 h, 80%; (c) (i) H_2, Pd/C, ethyl acetate, quantitaive; (ii) CAN, MeCN–H_2O 4:1, 0 °C, 80%.

hydroxyl group of the alcohol **4** was inverted to give the alcohol **6** in a three-step, one-pot operation: treatment of **4** with MsCl and Et_3N followed by the sequential additions of 0.5 N HCl and K_2CO_3 after the complete disappearance of **4** and **5**, respectively.[10,16] Use of MsCl and Et_3N (0 °C to ambient temperature) transformed the alcohol **4** to the corresponding mesylate, under which conditions the alcohol **4** underwent an S_N2 type intramolecular cyclization to give the oxazine **5**. Acidic hydrolysis of the oxazine **5** by 0.5 N HCl at ambient temperature generated the *O*-acetyl ester **13**, which upon treatment with K_2CO_3 at 60 °C underwent a 1,5-shift of the acetyl group to provide the inverted alcohol **6**. Similarly the alcohol **6** with *anti*-diol stereochemistry could be transformed back to the alcohol **4** with *syn*-diol stereochemistry. The oxazine **5** could also be prepared by using Mitsunobu reaction or Burgess reagent. However, the former method suffered from interference by a triphenylphosphine oxide by-product during column chromatography, and the latter reagent is commercially available but expensive. Notably, a clean one-pot operation was possible only with the reaction conditions involving MsCl and Et_3N. As with the olefin **4**, a sequence of cross metathesis reaction of **6** with 1-tetradecene in the presence of the second generation Grubbs' catalyst, the hydrogenation of **14**, and final deprotection of the PMP group by CAN finished the asymmetric synthesis of *N*-acetyl L-*arabino*-(2*R*,3*S*,4*R*)-phytosphingosine (**15**) (Scheme 3).[17]



Scheme 3. Asymmetric synthesis of *N*-acetyl L-*arabino*-(2*R*,3*S*,4*R*)-phytosphingosine (**15**) using olefin cross metathesis reaction and oxazine chemistry. Reagents and conditions: (a) MsCl, TEA, 0 °C to room temperature, 6 h; (b) 0.5 N HCl, THF, 30 min then K_2CO_3, 60 °C, 8 h, 70% in two steps; (c) 1-tetradecene, second generation Grubbs' catalyst, CH_2Cl_2, 40 °C, 8 h, 80%; (d) (i) H_2, Pd/C, ethyl acetate, quantitaive; (ii) CAN, MeCN–H_2O 4:1, 0 °C, 75%.

In summary, we have shown that MsCl/Et_3N can be conveniently used for the stereochemical intercoversion of the hydroxyl group in *N*-acetyl 1,3-aminoalcohols through the formation of the corresponding oxazines. Also demonstrated is that, combined with the regioselective asymmetric aminohydroxylation (RAA) and olefin cross metathesis (CM) reactions, the developed oxazine chemistry provides an extremely efficient and flexible route for the asymmetric synthesis of phytosphingosines. Asymmetric synthesis of other phytosphingosine derivatives is currently in progress, and will be reported in the full paper version of this letter.

Acknowledgements

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16. One pot procedure for the conversion of **4** to **6**: MsCl (172 mg, 1.5 mmol) was slowly added to a solution of the alcohol **4** (415 mg, 1 mmol) and Et_3N (350 μL, 2.5 mmol) in THF (20 mL) at 0 °C. After the addition, the reaction mixture was brought to room temperature, and further stirred until the alcohol **4** disappeared on TLC. At this point, 0.5 N HCl (5 mL) was added, and the resulting mixture was stirred for 30 min. Then, solid potassium carbonate was added in small portions until pH of the reaction mixture became ~9.5 (as measured by pH paper). Temperature was raised to 60 °C, and the reaction mixture was stirred at this temperature for 8 h. After cooling to room temperature, the reaction mixture was partitioned between water and CH_2Cl_2. The aqueous phase was further extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, and dried over anhydrous sodium sulfate. Evaporation of all volatile solvents and recrystallization of the remaining residue from ethyl acetate/hexane gave the inverted alcohol **6** as a white crystalline compound (291 mg, 70%): mp 118–19 °C; $[\alpha]_{589}$ −11.67 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, 2H, J = 8.5 Hz), 6.88–6.76 (m, 6H), 6.02 (ddd, 1H, J = 6.0, 10.5, and 16.5 Hz), 5.89 (d, 1H, J = 8.5 Hz), 5.44 (dt, 1H, J = 1.5 and 17.0 Hz), 5.28 (dt, 1H, J = 1.5, 10.5 Hz), 4.66–4.62 (m, 1H), 4.59 (d, 1H, J = 11.0 Hz), 4.41 (d, 1H, J = 11.0 Hz), 4.02 (br t, 1H), 3.92 (dd, 1H, J = 5.0 and 9.5 Hz), 3.84 (dd, 1H, J = 7.0 and 9.5 Hz), 3.81–3.76 (br s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.60 (dd, 1H, J = 1.5 and 7.0 Hz), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.44, 159.58, 154.19, 152.33, 137.33, 130.10, 129.78, 116.82, 115.49, 114.71, 113.90, 80.70, 74.32, 71.93, 67.50, 55.72, 55.24, 49.08, 23.23; HRMS *m/z* 415.1993 (calcd for $C_{23}H_{29}NO_6$ 415.1995). Similarly the alcohol **6** was converted back to **4**: $[\alpha]_{589}$ −37.4 (*c*, 5.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.5 Hz). 6.81 (s, 4H), 5.98–5.89 (m, 2H), 5.36 (dt, 1H, J = 1.5 and 17.0 Hz), 5.22 (dt, 1H, J = 1.5 and 10.5 Hz), 4.68 (d, 1H, J = 11.0 Hz), 4.57 (d, 1H, J = 11.0 Hz), 4.52–4.46 (m, 1H), 4.22–4.18 (m, 1H), 3.93 (dd, 1H, J = 5.0 and 9.0 Hz), 3.82–3.73 (m, 8H), 2.62 (br s, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.09, 159.58, 154.07, 152.32, 136.64, 130.02, 129.62,117.00, 115.44, 114.67, 113.96, 79.59, 74.87, 73.03, 67.01, 55.69, 55.22, 48.69, 23.31; HRMS *m/z* 415.1991 (calcd for $C_{23}H_{29}NO_6$ 415.1995). The oxazine intermediates **5** and **7** were isolated and characterized. **5**: $[\alpha]_{589}$ +38.33 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, 2H, J = 8.4 Hz), 6.82 (s, 4H), 6.76 (d, 2H, J = 8.4 Hz), 5.83–5.72 (ddd, 1H, J = 4.5, 11.0, and 15.5 Hz), 5.31–5.23 (m, 2H), 4.82–4.78 (m, 1H), 4.60 (d, 1H, J = 11.0 Hz), 4.47 (d, 1H, J = 11.0 Hz), 4.11–4.00 (m, 2H), 3.77 (s, 3H), 3.76–3.75 (m, 4H), 3.71–3.63 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.16, 157.01, 153.65, 152.65, 134.11, 130.01, 129.66, 117.11, 115.11, 114.48, 113.62, 75.35, 71.19, 69.48, 67.65, 55.56, 55.04, 50.39, 21.39; HRMS *m/z* 397.1880 (calcd for $C_{23}H_{27}NO_5$ 397.1889). **7**: $[\alpha]_{589}$ −9.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, 2H, J = 8.5 Hz), 6.84 (s, 4H), 6.75 (d, 2H, J = 8.5 Hz), 5.95 (ddd, 1H, J = 6.5, 10.0, 15.6 Hz), 5.42 (dt, 1H, J = 1.5 and 16.0 Hz), 5.29 (br d, 1H, J = 10.0 Hz), 4.57 (d, 1H, J = 6.5 Hz), 4.54 (d, 1H, J = 12.0 Hz), 4.47 (d, 1H, J = 12.0 Hz), 4.11 (dd, 1H, J = 5.0, 9.0 Hz), 3.97–3.94 (m 2H), 3.85–3.80 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.16, 158.23, 153.73, 152.41, 134.13, 130.03, 129.88, 118.06, 114.98, 114.59, 113.45, 77.98, 74.39, 70.17, 67.86, 55.59, 55.49, 55.04, 21.34; HRMS *m/z* 397.1884 (calcd for $C_{23}H_{27}NO_5$ 397.1889). For other approaches for the formation of oxazines and oxazolines, see: (a) Lee, S.-H.; Yoon, J.; Nakamura, K.; Lee, Y.-S. *Org. Lett.* **2000**, *2*, 1243–1246; (b) Aguilera, B.; Fernandez-Mayoralas, A. *J. Org. Chem.* **1998**, *63*, 2719–2723; (c) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524–2536; (d) Yoshimura, J.; Iwakawa, M.; Ogura, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2506–2510.
17. *N*-Acetyl L-*xylo*-(2*R*,3*S*,4*S*)-phytosphingosine (**11**): mp 106–07 °C; $[\alpha]_{589}$ −3.15 (*c* 0.67, MeOH–CH_2Cl_2); ^{1}H NMR (300 MHz, MeOH-d_4) δ 4.07–3.99 (m, 1H), 3.66–3.55 (m, 3H), 3.50–3.44 (m, 1H), 1.97 (s, 3H), 1.29 (s, 26H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 173.38, 73.59, 72.88, 62.68, 53.83, 34.19, 33.08, 30.79, 30.48, 26.73, 23.73, 22.68, 14.46; HRMS *m/z* 359.3034 (calcd for $C_{20}H_{41}NO_4$ 359.3036). *N*-Acetyl L-*arabino*-(2*R*,3*S*,4*R*)-phytosphingosine (**15**): mp 129–30 °C; $[\alpha]_{589}$ +34.2 [*c*, 0.7, $CHCl_3$–MeOH (1:2)]; ^{1}H NMR (500 MHz, $CDCl_3$–MeOH-d_4) δ 4.11 (dt, 1H, J = 1.5 and 5.75 Hz, H-2), 3.67 (dd, 1H, J = 5.5 and 11.0 Hz, H-1), 3.63 (dd, 1H, J = 6.0 and 11.0 Hz, H-1′), 3.44 (dd, 1H, J = 1.5 and 8.5 Hz, H-3), 3.21–3.17 (m, 1H, H-4), 1.99 (s, 3H), 1.71–1.65 (m, 1H), 1.52–1.44 (m, 1H), 1.20 (s, 24H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.53, 75.42, 71.88, 63.84, 51.86, 33.53, 32.51, 30.29, 29.91, 26.36, 23.23, 23.08, 14.49; HRMS *m/z* 359.3039 (calcd for $C_{20}H_{41}NO_4$ 359.3036).