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A common and stereoselective strategy for the synthesis of *N,O,O,O*-tetra-acetyl D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine and 2-*epi*-jaspine B

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ABSTRACT

A common and stereoselective strategy for the synthesis of *N,O,O,O*-tetra-acetyl D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine and 2-*epi*-jaspine B was achieved by using Grignard addition on *N*-benzyl sugar lactamine and Wittig olefination as key steps.

Sphingoids are long-chain amino-diol and -triol bases that form the backbone and the characteristic structural unit of sphingolipids, which are important membrane constituents and play a vital role in cell regulation as well as signal transduction.[1] Furthermore, glycosphingolipids show important biological activities, such as antitumor,[2a] antiviral,[2b] antifungal,[2c] and cytotoxic properties.[2d] Phytosphingosines, one of the major classes of sphingoids, have been isolated and identified either separately or as parts of sphingolipids from plants,[3a] marine organisms,[3b,c] fungi,[3d] yeasts[3e] and even mammalian tissues[3f–k] of kidney,[3g] liver,[3h] uterus,[3i] intestine,[3j] and skin.[3k] In addition to being base components of sphingolipids in membranes, phytosphingosines themselves are found to be bioactive lipids. For example, *ribo*-phytosphingosine **1** is a potential heat stress signal in yeast cells.[4] It has also been established that various diastereomers of sphingosines exhibit different activities and metabolism.[5] Some of its derivatives exhibit important physiological activities.[6] For instance KRN 7000 (Fig. 1) which is a glucosphingolipid exhibits natural killer activity and strongly inhibits tumor metastasis in mice.[6b] Since it is costly to isolate these lipids from the natural sources, and also not possible to obtain homogeneous material for biological studies, a great work has been carried out for the synthesis of these compounds. Among all the eight possible stereoisomers of phytosphingosine (2*S*,3*S*,4*R*)-2-aminooctadecane-1,3,4-triol **1** with D-*ribo*-stereochemistry is the most common one. Owing to their interesting biological activities many synthetic approaches to enantiomerically pure D-*ribo*-phytosphingosine **1** have been reported in the literature.[7]

Jaspine B, also known as pachastrissamine (**2a**, Fig. 1), is a cyclic anhydro-phytosphingosine derivative, which was initially isolated from a marine sponge *Pachastrissa* sp. (family Calthropellidae) in 2002 by Higa and co-workers,[8] and found to have cytotoxicity at a level of IC_{50} 0.01 μg/mL against P388, A549, HT29, and MEL28 cell lines. Later, Debitus and co-workers[9] isolated the same compound from a Vanuatuan marine sponge genus *Jaspis* and named it as jaspine B **2a**. This compound displayed remarkable bioactivity (IC_{50} 0.24 μM) against the A549 human lung carcinoma cell line using the ATPlite assay and represented as the most potent anticancer agent on this cell line. Delgado and co-workers reported that the potency of cytotoxicity is dependent on the stereochemistry of the tetrahydrofuran moiety.[10]

The novel structural features and interesting biological activity of pachastrissamine have prompted chemists to develop several syntheses for jaspine B **2a** and its isomers.[11] Our group published the first total synthesis of jaspine B **2a** and its C2 epimer **2b**.[12a] We also published the synthesis of the C2 and C3 epimer **2c** and an enantiomer of jaspine B **2d** and their biological activity in comparison to jaspine B **2a**[12b] and 3-*epi* jaspine **2e**.[12c]

In continuation of our efforts in this area, we envisaged a concise, efficient, and common method for the synthesis of *N,O,O,O*-tetra-acetyl *ribo*-(2*S*,3*S*,4*R*)-phytosphingosine **3** and 2-*epi*-jaspine B **2b**. The starting material for our approach is D-ribose, which is an inexpensive sugar and possesses desired chirality. The retrosynthetic analysis of *N,O,O,O*-tetra-acetyl D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine **3** and 2-*epi*-jaspine **2b** is depicted in Scheme 1. Compound **4** is a common intermediate for the synthesis of **3** and **2b** and it can be obtained from compound **5** after appropriate manipulations. The amino group can be introduced by nucleophilic addition on ribosylamine **6** and the required lipid chain can be introduced by Wittig olefination.

Earlier we explored stereoselective Grignard addition on chiral-imines for the synthesis of polyhydroxylated pyrrolidines[13] and carbasugrs.[14] In this report we expanded the utility of this sugar-imine Grignard addition, for the synthesis of *N,O,O,O*-tetra-acetyl *ribo*-phytosphingosine **3** and 2-*epi*-jaspine **2b**.

The starting material 5-*O*-*tert*-butyl dimethylsilyl-2,3-*O*-isopropylidene-D-ribofuranose **7**, required for our synthesis was prepared from D-ribose using our earlier procedure (Scheme 2).[15] Reaction on **7** with benzylamine gave ribosylamine **6**. Treatment of the crude ribosylamine **6** with vinylmagnesium bromide at −78 °C

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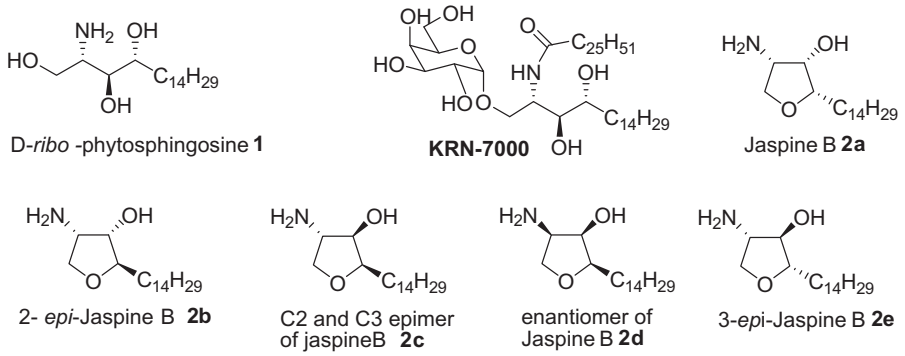
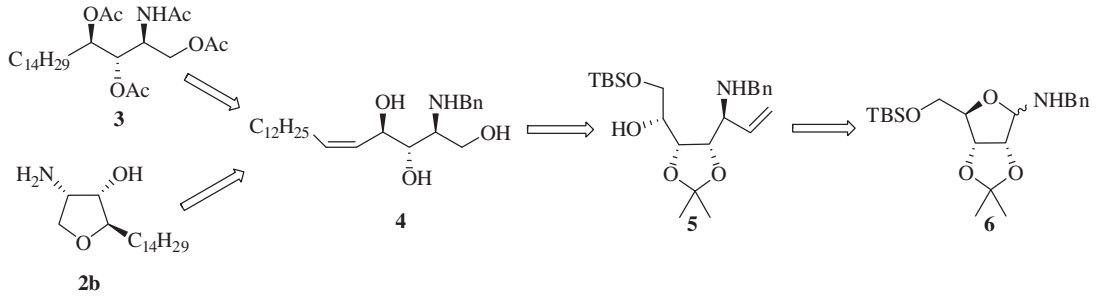
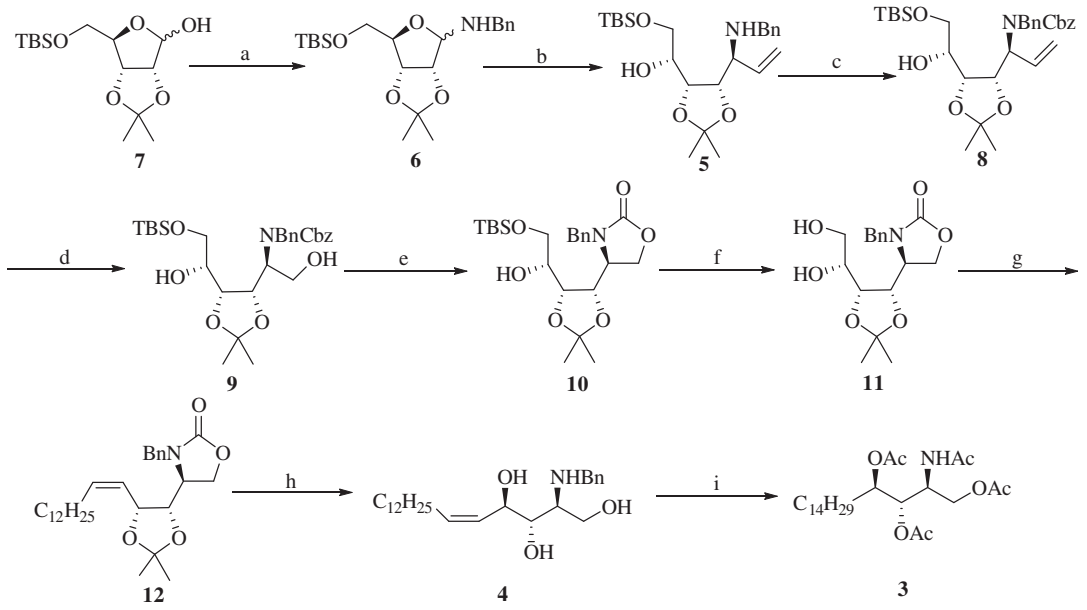


Figure 1. Structures of D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine, KRN 7000, jaspine B, and its isomers.



Scheme 1. Retrosynthetic analysis of *N*,*O*,*O*,*O*-tetra-acetyl D-*ribo*-phytosphingosine **3** and 2-*epi*-jaspine B **2b**.



Scheme 2. Synthesis of *N*,*O*,*O*,*O*-tetra-acetyl D-*ribo*-phytosphingosine **3**. Reagents and conditions: (a) $BnNH_2$, MeOH, reflux; (b) vinylmegnesium bromide, THF, −78 °C, 2 h, 72%; (c) Cbz-Cl, $NaHCO_3$, MeOH, 1 h, 98%; (d) (i) O_3, CH_2Cl_2, −78 °C, 30 min and DMS, (ii) $NaBH_4$, MeOH, 1 h (85% for two steps); (e) NaH, THF, 30 min, 92%; (f) TBAF, THF, 2 h, 96%; (g) (i) $NaIO_4$, CH_2Cl_2, H_2O, rt, 4 h, (ii) $C_{13}H_{27}Ph_3P^+Br^-$, *n*-BuLi, THF, 1 h (90% for two steps); (h) 6 N HCl, EtOH, reflux, 6 h, 94%; (i) (i) H_2, Pd/C, MeOH, 6 h, (ii) $(Ac)_2O$, $N(Et)_3$, CH_2Cl_2, 6 h (85% for two steps).

gave exclusively **5** as a single isomer**.** The absolute configuration of the newly generated stereo center was not confirmed at this stage, but as per our earlier observation it should give the *erythro*-isomer.[14] The formation of *erythro*-isomer can be explained via seven membered transition state **A**[16] or Felkin-Anh model **B** (Fig. 2). In fact the formation of *erythro*-isomer shows that chelation between sugarimine and isopropylidene group has not taken place due to steric strain.

The amino functionality in **5** was converted into carbamate with CbzCl to give **8**. Oxidative degradation of the alkene functionality in **8** with ozone afforded the aldehyde, which on treatment with $NaBH_4$ in MeOH gave alcohol **9.** In order to protect the primary hydroxyl group, compound **9** was treated with sodium hydride to give the cyclic carbamate **10**. Deprotection of silylether in **10** with TBAF gave diol **11**. The diol functionality of compound **11** was oxidatively cleaved to aldehyde using $NaIO_4$ in CH_2Cl_2/

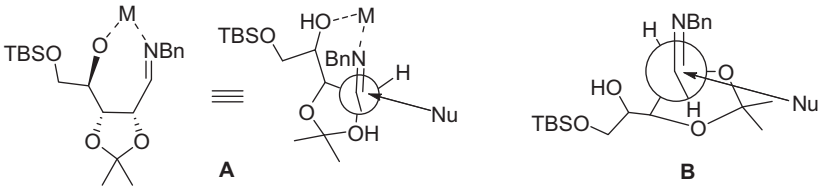
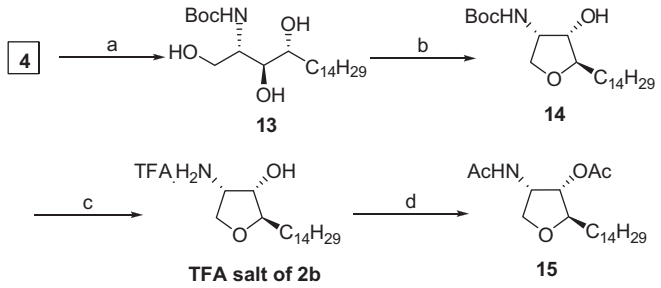


Figure 2. Seven-membered transition state (A) and Felkin Anh Model (B).



Scheme 3. Synthesis of TFA salt of 2-*epi*-jaspine B **2b**. Reagents and conditions: (a) (i) H_2, Pd/C, MeOH, 6 h, (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 2 h (95% over two steps); (b) (i) TsCl, Et_3N, DMAP, CH_2Cl_2, 86%; (c) TFA, CH_2Cl_2, 2 h; 89%; (d) $(Ac)_2O$, Et_3N, CH_2Cl_2, 4 h, 94%.

H_2O**,** which was carried to the next step without any purification. Wittig reaction on crude aldehyde with $C_{13}H_{27}PPh_3^+Br^-$ gave **12**. Global deprotection of carbamate and acetonide in **12** with 6 N HCl in EtOH under reflux conditions gave **4**. Hydrogenation of **4** gave the D-*ribo*-phytosphingosine **1**. For the sake of characterization, it was converted as such into *N*,*O*,*O*,*O*-tetra-acetyl D-*ribo*-phytosphingosine **3**,[17] by treating with acetic anhydride and Et_3N, whose physical properties are in good agreement with the reported values.[18]

To convert the compound **4** into 2-*epi*-jaspine B **2b** the following reactions were carried out (Scheme 3). Hydrogenation of compound **4** using Pd/C in MeOH followed by treatment of the resultant amino functionality with $(Boc)_2O$ afforded carbamate **13**. Regioselective tosylation of the primary hydroxy group of **13** prompted spontaneous cyclization to give the tetrahydrofuran derivative **14**.[11b] Deprotection of the Boc group in **14** with TFA/CH_2Cl_2 provided the desired 2-*epi*-jaspine B **2b** as TFA salt[19a] and TFA salt of **2b** on acetylation with acetic anhydride in the presence of excess Et_3N gave the acetyl derivative **15**.[19b] The physical properties of the TFA salt of 2-*epi*-jaspine B **2b**[13a] and its diacetate derivative **15**[12b] were in good agreement with the reported values.

In conclusion we have successfully demonstrated a general strategy for the synthesis of *N*,*O*,*O*,*O*-tetra-acetyl D-*ribo*-phytosphingosine **3** and 2-*epi*-jaspine B **2b** and its diacetate derivative **15** by using stereoselective vinyl Grignard on ribosylamine. Application of this strategy to make some more analogs of phytosphingosine and jaspine B are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.032.

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17. Spectral data of compound **3**: $[\alpha]_D^{26}$ + 23.1 (*c* 0.62, $CHCl_3$); {lit.[18] $[\alpha]_D^{20}$ +21.9 (*c* 1.1, $CHCl_3$)}; IR ν_{max}: 2924, 2854, 1741, 1659, 1543, 1370, 1221, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.00 (d, 1H, *J* = 9.4 Hz), 5.04 (dd, 1H, *J* = 3.0 and 8.3 Hz), 4.83–4.91 (m, 1H), 4.40 (m, 1H), 4.22 (dd, 1H, *J* = 4.7 and 11.5 Hz), 3.94 (dd, 1H, *J* = 3.0 and 11.5 Hz), 2.01 (s, 3H), 1.99 (s, 6H), 1.96 (s, 3H), 1.76 (m, 1H), 1.51 (m, 1H), 1.05–1.31 (m, 24H), 0.80 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.1, 170.8, 170.0, 169.7, 72.9, 71.9, 62.8, 47.6, 31.9, 29.6, 29.5, 29.4, 29.3, 29.3, 28.1, 25.5, 23.3, 22.6, 21.0, 20.7, 14.1; ESIMS *m*/*z*: 486 $[M+H]^+$; HRMS (ESI): calcd for $C_{26}H_{48}NO_7$ $[M+H]^+$ 486.3430, found 486.3441.
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19. (a) Spectral data of compound of **2a** as TFA salt: $[\alpha]_D^{26}$ +16.2 (*c* 1.1, EtOH),{lit.[12a] $[\alpha]_D^{25}$ +14.46 (*c* 1.5, EtOH)}; IR ν_{max}: 2920, 2851, 1669, 1209, 1147 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): δ 4.14 (m, 1H), 4.03 (t, 3H, *J* = 5.7 Hz), 3.65–3.80 (m, 3H), 1.17–1.70 (m, 26H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 85.3, 74.4, 69.4, 53.7, 47.9, 34.1, 33.1, 30.8, 30.7, 30.6, 30.5, 26.9, 23.7, 14.4; ESIMS *m*/*z*: 300 (M^++1−CF_3COOH); HRMS (ESI): calcd for $C_{18}H_{38}NO_2$ $[M+H]^+$ 300.2902, found 300.2902.
(b) Spectral data of compound **15**: $[\alpha]_D^{26}$ −15.1 (*c* 1.2, $CHCl_3$), {lit.[11b] $[\alpha]_D^{22}$ −15.4 (*c* 1.0, $CHCl_3$)}; IR ν_{max}: 3298, 2920, 2851, 1740, 1658, 1557, 1376, 1232, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.68 (br d, 1H, *J* = 7.7 Hz), 4.66 (m, 1H), 4.18 (t, 1H, *J* = 7.7 Hz), 3.84–3.90 (m, 1H), 3.52 (t, 1H, *J* = 8.5 Hz), 2.14 (s, 3H), 2.02 (s, 3H), 1.49–1.68 (m, 2H), 1.15–1.47 (m, 26H), 0.88 ((t, 1H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1, 169.9, 84.0, 76.7, 69.7, 49.9, 33.5, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 25.5, 23.2, 22.7, 21.0, 14.1; ESIMS *m*/*z*: 406 $(M+Na)^+$; HRMS (ESI): calcd for $C_{22}H_{41}NO_4Na$ $[M+Na]^+$ 406.2933, found 406.2933.