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Asymmetric synthesis of *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine, jaspine B (pachastrissamine) and its C(2)-epimer

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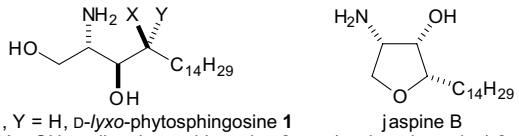
Abstract—The highly diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to a γ-silyloxy-α,β-unsaturated ester and in situ enolate oxidation with (+)-(camphorsulfonyl)oxaziridine has been used as the key step in the asymmetric synthesis of *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine, jaspine B (pachastrissamine) and its C(2)-epimer.

1. Introduction

The vicinal amino alcohol motif is a recurring structural component in a diverse range of biologically active natural products and synthetic molecules.[1] Among this molecular class the sphingoid bases D-*lyxo*- and D-*ribo*-phytosphingosine, **1** and **2** respectively, are ubiquitous components of biomolecules that occur in eukaryotic cells,[2] and as such have received considerable synthetic attention.[3] Recent studies on the marine sponge *Pachastrissa* sp. by Higa and co-workers[4] led to the isolation of the cyclic anhydrophytosphingosine pachastrissamine **3**. Subsequently, Debitus and co-workers independently reported the isolation of jaspine B **3** from the marine sponge *Jaspis* sp.;[5] pachastrissamine and jaspine B being identical (Fig. 1).

To date, 10 enantiospecific syntheses of jaspine B **3** have been reported,[6–15] utilising L-serine,[6,7] D-xylose,[8,9] (*R*)-glycidol,[10] D-*ribo*-phytosphingosine,[11,12] D-glucose,[13] D-galactose[14] and D-tartaric acid[15] as the sources of chirality. Additionally, an asymmetric entry to jaspine B **3** employing Sharpless asymmetric dihydroxylation was recently disclosed,[16] and two syntheses of 'truncated' analogues (bearing C_5 and C_8 side-chains), based upon manipulation of L-xylose,[17] and Sharpless asymmetric epoxidation,[18] have also appeared.



X = OH, Y = H, D-*lyxo*-phytosphingosine **1**
X = H, Y = OH, D-*ribo*-phytosphingosine **2**
jaspine B
(pachastrissamine) **3**

Figure 1. Phytosphingosines **1** and **2**, and jaspine B (pachastrissamine) **3**.

Previous investigations from this laboratory have shown that conjugate addition of a homochiral lithium amide (derived from α-methylbenzylamine)[19] and enolate oxidation with (camphorsulfonyl)oxaziridine (CSO) represents an efficient entry to *anti*-α-hydroxy-β-amino esters.[20] This methodology has been utilised as the key synthetic strategy for a number of natural product syntheses,[21] and herein we delineate the application of this useful transformation to the asymmetric synthesis of the *N*,*O*,*O*,*O*-tetra-acetyl derivative of D-*lyxo*-phytosphingosine **1**, jaspine B **3** and its C(2)-epimer.

2. Results and discussion

γ-Tri-*iso*-propylsilyloxy-α,β-unsaturated methyl ester **4** was synthesised from *cis*-but-2-ene-1,4-diol in three steps based on literature protocols.[22] Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and enolate oxidation with (+)-CSO[20] gave *anti*-α-hydroxy-β-amino-γ-silyloxy ester (2*S*,3*S*,α*S*)-**5** in >98% de,[23] isolated in 75%

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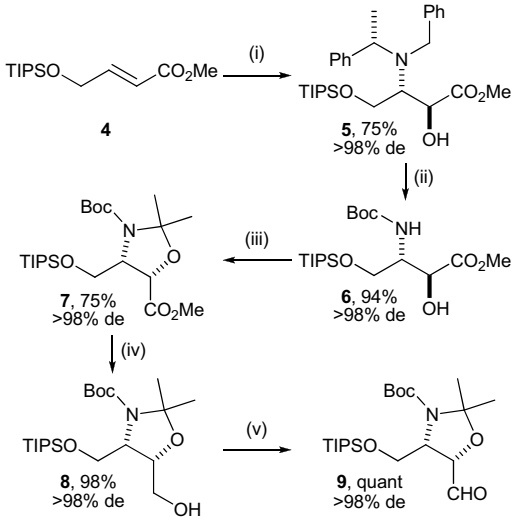
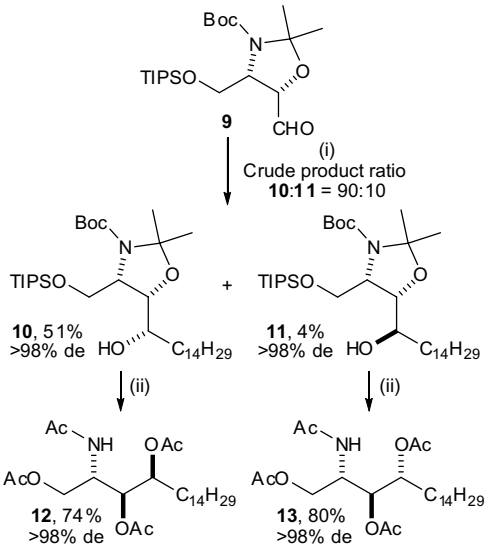
yield and >98% de. The configurations of C(2) and C(3) within **5**, relative to the α-methylbenzyl stereocentre, were assigned by analogy to the well-established stereochemical outcome resulting from the addition of this class of lithium amide to α,β-unsaturated esters,[24] with enolate oxidation occurring *anti* to the amino group.[20] Hydrogenolysis of **5** with Pearlman's catalyst [$Pd(OH)_2$/C] in EtOAc in the presence of Boc_2O gave **6** in 94% yield. Treatment of **6** with 2,2-dimethoxypropane and $BF_3{\cdot}Et_2O$ in refluxing acetone[25] gave 80% conversion to oxazolidine **7**, which was isolated in 75% yield.[26] Treatment of **7** with DIBAL-H gave alcohol **8** in 98% yield, with oxidation of **8** with IBX[27] giving aldehyde **9** in quantitative yield (Scheme 1).



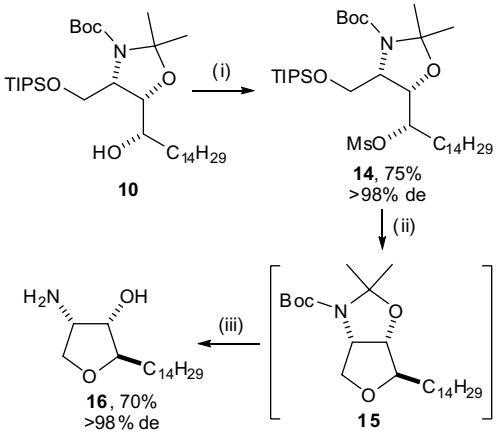
Scheme 1. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (ii) H_2 (5 atm), $Pd(OH)_2$/C, Boc_2O, EtOAc, rt, 12 h; (iii) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, reflux, 12 h; (iv) DIBAL-H, DCM, 0 °C, 6 h; (v) IBX, DMSO, rt, 12 h.

Addition of tetradecylmagnesium bromide[28] to aldehyde **9** gave a chromatographically separable 90:10 mixture of alcohols **10** and **11**,[29,30] which were isolated in 51% and 4% yield, respectively, and in >98% de in each case. Hydrolysis of **10** and subsequent peracetylation gave *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine **12** in 74% yield and >98% de {$[\alpha]_D^{21} = -3.1$ (*c* 0.7 in $CHCl_3$); lit.[31] $[\alpha]_D^{21} = -3.1$ (*c* 1.1 in $CHCl_3$)}, whilst analogous treatment of **11** gave *N*,*O*,*O*,*O*-tetra-acetyl D-*ribo*-phytosphingosine **13** in 80% yield and >98% de {$[\alpha]_D^{21} = +18.2$ (*c* 1.0 in $CHCl_3$); lit.[31] $[\alpha]_D^{21} = +21.9$ (*c* 1.1 in $CHCl_3$)}, with spectroscopic properties in excellent agreement with those of the literature[31] (Scheme 2).

Mesylation of the major diastereoisomeric alcohol **10** gave **14** in 75% yield. Treatment of **14** with TBAF promoted desilylation and concomitant intramolecular cyclisation via an S_N2-type displacement of the mesylate by the primary hydroxyl, giving **15**, with subsequent hydrolysis giving **16** (the C(2)-epimer of jaspine B)[32] in 70% yield and >98% de (Scheme 3).



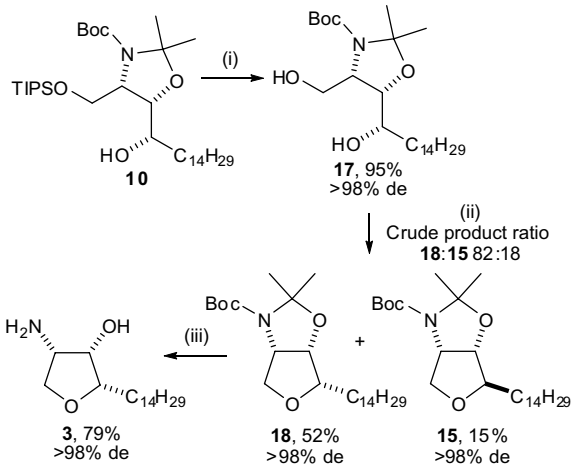
Scheme 2. Reagents and conditions: (i) $C_{14}H_{29}MgBr$, THF, 0 °C to rt, 6 h; (ii) HCl (2 M, aq), MeOH, 50 °C, 6 h then Ac_2O, pyridine, DMAP.



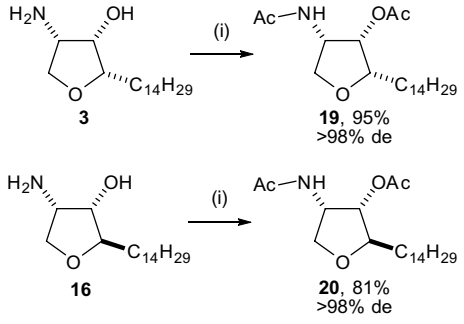
Scheme 3. Reagents and conditions: (i) MsCl, Et_3N, DCM, rt, 12 h; (ii) TBAF, THF, rt, 12 h; (iii) HCl (2 M, aq), MeOH, 50 °C, 6 h, then KOH (2 M, aq).

Alternatively, desilylation of **10** with TBAF gave diol **17** in 95% yield. Subsequent treatment of **17** with tosyl chloride enabled the preferential tosylation of the primary hydroxyl group, promoting intramolecular cyclisation, giving a chromatographically separable 82:18 mixture of **18**:**15** from which the major diastereoisomer **18** was isolated in 52% yield, and **15** in 15% yield. Hydrolytic deprotection of **18** followed by basification and recrystallisation then gave jaspine B **3** in 79% yield, with spectroscopic properties in excellent agreement with those originally reported for the natural product by Higa and co-workers[4] {$[\alpha]_D^{23} = +17.5$ (*c* 0.3 in EtOH); lit.[4] $[\alpha]_D^{25} = +18.0$ (*c* 0.1 in EtOH)}[33] (Scheme 4).

To further confirm the configurations of our samples of jaspine B **3** and its C(2)-epimer **16**, they were converted to the corresponding *N*,*O*-diacetyl derivatives **19** and **20** (Scheme 5). NOE analyses of **19** and **20** were supportive of the assigned relative configurations of the tetrahydrofuran



Scheme 4. Reagents and conditions: (i) TBAF, THF, rt, 12 h; (ii) TsCl, DMAP, pyridine, reflux, 8 h; (iii) HCl (2 M, aq), MeOH, 50 °C, 6 h, then KOH (2 M, aq).



Scheme 5. Reagents and conditions: (i) Ac_2O, DMAP, pyridine, rt, 12 h.

rings.[4] Furthermore, single crystal X-ray analysis of **19** unambiguously confirmed the all-*cis* relationship of the substituents around the ring,[34,35] and determination of a Flack parameter[36] for the structure of −0.04(15), which satisfies the criterion for a reliable assignment of absolute configuration of a material known to be homochiral,[36] allowed the reported absolute (2*S*,3*S*,4*S*)-configuration of the natural product (originally determined by Higa et al.[4] using the Mosher method)[37] to be confirmed unambiguously (Fig. 2).

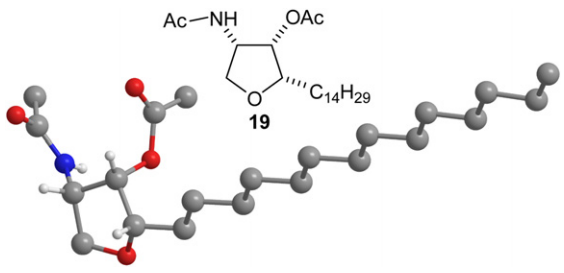


Figure 2. Chem 3D representation of the X-ray structure of *N*,*O*-diacetyl jaspine B **19** (some H atoms removed for clarity).

3. Conclusion

In conclusion, highly concise asymmetric syntheses of *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine **12**, jaspine B (pachastrissamine) **3** and its C(2)-epimer **16** have been achieved from γ-tri-*iso*-propylsilyloxy-α,β-unsaturated ester **4**. The overall yields were *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine **12**, 20% over 7 steps; jaspine B **3**, 10% over 9 steps; and the C(2)-epimeric compound **16**, 14% over 9 steps from γ-tri-*iso*-propylsilyloxy-α,β-unsaturated ester **4**. The absolute configuration of jaspine B **3** has been unambiguously proven by X-ray crystal structure analysis of the corresponding *N*,*O*-diacetate **19**.

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28. Tetradecylmagnesium bromide was prepared as a solution in THF from 1-bromotetradecane and magnesium turnings.
29. The rotameric nature of **10** and **11** precluded the direct determination of the reaction diastereoselectivity from the ^{1}H NMR spectrum of the crude reaction product. However, hydrolysis of the crude reaction mixture followed by peracetylation gave a 90:10 mixture of the corresponding *N*,*O*,*O*,*O*-tetra-acetyl phytosphingosines **12** and **13**.
30. The configurations of **10** and **11** could not be assigned a priori; they were determined by correlation to the corresponding *N*,*O*,*O*,*O*-tetra-acetyl phytosphingosines **12** and **13**. The (4*S*,5*S*,1′*S*)-configuration of the major diastereoisomeric product **10** is consistent with *Si* face attack of the Grignard on aldehyde **9** via a chelated Cram model; see: Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828; Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.
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33. Data for jaspine B **3**: mp 90–92 °C (Et_2O/heptane); $[\alpha]_D^{23} = +17.5$ (*c* 0.3 in EtOH); ν_{max} (KBr) 3340, 3074, 2921, 2849; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.7, C(14′)H_3), 1.18–1.50 (24H, m, C(2′)-C(13′)H_2), 1.55–1.70 (2H, m, C(1′)H_2), 3.50 (1H, dd, *J* 8.4, 7.2, C(5)H_A), 3.61–3.69 (1H, m, C(4)*H*), 3.74 (1H, td, *J* 7.2, 4.0, C(2)*H*), 3.87 (1H, t, *J* 4.0, C(3)*H*), 3.91 (1H, t, *J* 7.7, C(5)H_B); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 26.3, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9, 54.4, 71.8, 72.4, 83.1; *m*/*z* (ESI^+) 300 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{38}NO_2^+$ ($[M+H]^+$) requires 300.2897; found, 300.2900.
34. Data were collected using an Oxford Diffraction Gemini R diffractometer with graphite monochromated Cu Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[35] X-ray crystal structure data for **19** [$C_{22}H_{41}NO_4$]: $M = 383.57$, monoclinic, space group $P12_11$, $a = 7.3304(2)$ Å, $b = 9.2479(2)$ Å, $c = 17.2441(4)$ Å, $\beta = 101.220(2)°$, $V = 1146.65(5)$ Å^3, $Z = 2$, $\mu = 0.075$ mm^{-1}, colourless prism, crystal dimensions $= 0.13 \times 0.13 \times 0.24$ mm^3. A total of 16,073 reflections were measured for $5 < \theta < 27$, of which 2008 were unique, and 3510 reflections were used in the refinement. The final parameters were $wR_2 = 0.046$ and $R_1 = 0.037$ [$I > 3\sigma(I)$], Flack enantiopole $= -0.04(15)$.[36] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 616170. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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