Asymmetric Synthesis of Jaspine B (Pachastrissamine) via an Organocatalytic Aldol Reaction as Key Step

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Abstract: The asymmetric synthesis of jaspine B (pachastrissamine) using a (R)-proline-catalyzed enantioselective aldol reaction as key step is described. Jaspine B was synthesized from the commercially available and inexpensive 1-pentadecanal and the dihydroxyacetone equivalent 2,2-dimethyl-1,3-dioxan-5-one in nine steps, good overall yield (23.6%) and excellent stereoselectivity (de >98%, ee = 95%).

Key words: pachastrissamine (jaspine B), asymmetric synthesis, aldol reaction, organocatalysis, proline

The naturally occurring, cyclic anhydrophytosphingosine derivative jaspine B (pachastrissamine, 1) was first isolated from the Okinawan marine sponge Pachastrissa sp. (family Calthropellidae) in 2002 by Higa et al.¹ and later from a different marine sponge, Jasps sp., by Debitus and co-workers.²

Due to the significant cytotoxic activity of jaspine B (IC₅₀ 0.01 µg/mL against P388, A549, HT29 and MEL28 tumour cell lines), there is increasing interest within the chemical community regarding its total synthesis.¹

Indeed, several stereoselective syntheses of jaspine B have been reported. Most of these routes are based on chiral pool strategies and use L-serine,³ Garner’s aldehyde,⁴,⁵ D-xylose,⁶ L-xylose⁷ (to obtain a truncated phytosphingosine (e.g. 2)) derived from the chiral substrates (R)-glycidol¹¹ or other epoxides,¹² generated by asymmetric Sharpless epoxidation, have also been described. The research groups of Yakura¹³ and Srinivasan¹⁴ have independently disclosed the synthesis of 1 using the asymmetric Sharpless dihydroxylation as a key step. Very recently Davis et al. described an elegant asymmetric synthesis via an azo-Michael addition/enolate oxidation sequence.¹⁵

As a cyclic anhydrophytosphingosine derivative, the structure of jaspine B is similar to that of phytosphingosines, e.g. D-ribo-phytosphingosine (2), with characteristic sub-units present in the ubiquitous sphingolipids. Both 1 and 2 possess common structural elements, namely, 18 carbon atoms, three contiguous stereogenic centers, a non-polar aliphatic ‘tail’ and a polar aminoalcohol ‘head’ (Figure 1).

Recently reported syntheses of 1 and its analogues by the groups of Overkleeft¹⁶ and Kim¹⁷ have taken advantage of this structural similarity and transformed phytosphingosine (2) into jaspine B.

Our research group has developed a proline-catalyzed aldol reaction that allows access to D- and L-phytosphingosines (e.g. 2) in a highly enantioselective manner.¹⁸ Herein we report an efficient asymmetric synthesis of jaspine B, which employs this diastereo- and enantioselective aldol reaction as a key step. Retrosynthetically, we envisaged the preparation of the title compound by reduction of the cyclic azide 12, which could be traced back to the tosylate 11 via a one-pot acid-catalyzed deprotection/intramolecular nucleophilic substitution reaction (Scheme 1). In turn, the tosylate 11 could be obtained from the known acetone and TBS-protected triol 7 in an azidation/tosylation sequence. The asymmetric aldol reaction of dioxanone 3 with 1-pentadecanal, catalyzed by proline, would give access to the protected chiral anti-diol 5 that contains two of the required stereocenters of jaspine B (1).¹⁸ Furthermore, the asymmetric organocatalytic aldol reaction of dioxanone 3 and 1-pentadecanal would assemble all 18 carbons of jaspine B in one synthetic step.

To commence the synthesis of the jaspine B target, the silyl ether 7 was prepared from dioxanone 3¹⁹ using (R)-proline for the organocatalytic aldol reaction (Scheme 2). This five-step procedure is similar to that reported previously which used (S)-proline.¹⁸,²⁰ Thus, the aldol product 5 was prepared using the diastereo- and enanto-selective (R)-proline-catalyzed aldol reaction of dioxanone 3 and 1-pentadecanal (4). Next, protection of the alcohol as a tert-butyldimethylsilyl (TBS) ether to form 6 and subsequent diastereoselective reduction with L-Selectride afforded the protected anti-1,3-diol 7 in multi-gram quantities. The free hydroxy group of alcohol 7 was then transformed into...
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the mesylate \(8\) in 98% yield. Reaction of \(8\) with sodium azide in the presence of 18-crown-6 proceeded with virtually complete inversion of configuration and gave the desired TBS-protected syn-1,3-azido alcohol \(9\) in 79% yield (de > 98% by NMR and GC). After deprotection of the silyl ether \(9\) with tetra-n-butylammonium fluoride (TBAF), the secondary alcohol of the syn-1,3-azido alcohol \(10\) was tosylated to afford \(11\) in 81% yield. Treatment of this tosylate in a methanol/tetrahydrofuran solution with an acidic resin (Amberlyst 15) at room temperature installed the tetrahydrofuran ring present in jaspine B. Mechanistically, the one-pot, acid-catalyzed formation of tetrahydrofuran \(12\) likely involves an initial acid-catalyzed acetal solvolysis reaction within tosylate \(11\) to form the transient diol intermediate \(13\) (Scheme 3). A subsequent intramolecular nucleophilic displacement reaction of intermediate \(13\) then affords the tetrahydrofuran \(12\) and sets the appropriate relative and absolute stereochemistry. To complete the synthesis, the azide group of the tetrahydrofuran \(12\) was subjected to a catalytic hydrogenation reaction, which afforded jaspine B (1) in 98% yield.

In summary, we have developed an efficient asymmetric synthesis of jaspine B (pachastrissamine, 1) using an organocatalytic aldol reaction as a key step. The title compound was obtained in nine steps with a good overall yield (23.6%) starting from the readily available achiral precursors dioxanone \(3\) and 1-pentadecanal (4), in excellent diastereo- and enantiomeric excesses (de >98%, ee = 95%). This method allows access to both enantiomers of jaspine B depending on whether \((R)\)- or \((S)\)-proline is used as catalyst. Furthermore, the pro-chiral ketone function of \(6\) can be easily functionalized into epimeric amino groups. In theory, this route allows access to various stereoisomers of jaspine B, which is the subject of current investigations in our laboratories.

All solvents were dried by conventional methods. Starting materials and reagents were purchased from commercial suppliers and used without further purification. THF was freshly distilled from Na–Pb alloy under argon. CH₂Cl₂ was freshly distilled from CaH under argon. Preparative column chromatography was performed using silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC was carried out employing silica gel 60 F254 plates from Merck, Darmstadt. Visualization of the developed chromatograms was performed by staining with phosphomolybdic acid solution in EtOH. Optical rotation values were measured on a Perkin-
CH2). CHCl3). action mixture was quenched with sat. NH4Cl (10 mL), extracted

Yield: 1.62 g (59%); colourless oil; de >99% (NMR, GC, HPLC);

1H NMR (400 MHz, CDCl3): δ = 0.08 (t, J = 6.9 Hz, 3 H, CH3), 1.28
(24 H, CH2), 1.43 (s, 3 H, CH3), 1.44 (s, 3 H, CH3), 1.58 (m, 2 H, CH2), 3.85 (dd, J = 12.2, 1.7 Hz, 1 H, CH3), 3.91 (m, 1 H, CH3), 3.98 (dd, J = 12.2, 1.0 Hz, 1 H, CH3).

13C NMR (100 MHz, CDCl3): δ = 14.1 (CH), 22.7 (CH2), 23.5 (2 × CH2), 26.0 (CH2), 29.7 (3 × CH2), 31.9 (CH2), 32.3 (CH2), 46.7 (CH), 70.6 (CH), 76.0 (CH), 100.9 (C), 211.2 (C=O).

MS (CI): m/z (%): 340 (22) [M+ – 16], 339 (100) [M+ – 17], 338 (8).

Anal. Calcd for C21H46O4Si: C, 68.59; H, 11.94. Found: C, 68.35; H, 11.36.

(R,R)-4-[1-(tert-Butyldimethylsiloxy)pentadecyl]-2,2-dimethyl-1,3-dioxan-5-one (6)
To a solution of the aldol product 5 (1.50 g, 4.21 mmol) in CH2Cl2 (15 mL) at –20 °C was added sequentially, 2.6-lutidine (2.0 mL, 16.8 mmol) and TBSOTf (2.9 mL, 12.6 mmol)dropwise via syringe. After 2 h the reaction mixture was quenched with sat. NaHCO3 solution (10 mL) and warmed to r.t. The aqueous phase was extracted with CH2Cl2 (3 × 30 mL) and the combined organic layers were dried over MgSO4 and the solvent was removed under reduced pressure. Purification by flash chromatography (silica gel, n-pentane–CH2Cl2, 1:1) afforded the desired product 6.

Yield: 1.88 g (95%); colourless oil; de >99% (NMR); [α]D23 +88.5 (c 2.4, CHCl3).

IR (CHCl3): 2926, 2856, 1750, 1465, 1378, 1252, 1225, 1096, 838, 763 cm–1.

1H NMR (400 MHz, CDCl3): δ = 0.88 (t, J = 6.9 Hz, 3 H, CH3), 0.89 (s, 9 H, (CH3)2Si), 1.26 (m, 24 H, 12 × CH2), 1.29 (m, 2 H, CH2), 1.45 (s, 3 H, CH3), 1.46 (s, 3 H, CH3), 1.51 (d, J = 15.8 Hz, 1 H, CH3), 4.07 (m, 1 H, CH3), 4.20 (dd, J = 15.8, 1.5 Hz, 1 H, CH3), 4.23 (m, 1 H, CH).

13C NMR (100 MHz, CDCl3): δ = –46.8 (CH3), –44.4 (CH2), 14.1 (CH2), 18.1 (C), 22.7 (CH2), 23.4 (CH3), 24.5 (CH3), 25.9 (CH3), 26.0 (CH3), 29.4 (CH2), 29.6 (2 × CH2), 29.7 (4 × CH2), 32.0 (CH3), 32.7 (CH3), 67.3 (CH2), 72.2 (CH), 78.5 (CH), 100.5 (C), 207.9 (C=O).

MS (CI): m/z (%): 471 (2.1) [M+ + 1], 413 (10), 343 (7), 342 (27), 341 (100), 339 (7), 129 (18).

Anal. Calcd for C27H56O4Si: C, 68.88; H, 11.56. Found: C, 68.88; H, 11.32.

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To a solution of 1 (0.20 g, 0.52 mmol) in CH2Cl2 (5 mL) was added DMAP (127 mg, 1.04 mmol) and p-toluenesulfonyl chloride (148 mg, 0.78 mmol) at 0 °C. The reaction was stirred at r.t. for 4 h then quenched with H2O (5 mL), extracted with CH2Cl2 (3 × 10 mL) and dried over MgSO4. Evaporation of the solvent gave the crude product, which was purified by flash chromatography (silica gel, CH2Cl2–Et2O, 9:1) to give 11.

Yield: 0.27 g (97%); de >98% (NMR); [α]D23 +30.0 (c 2.4, CHCl3).

IR (film): 3531, 2925, 2856, 2106, 1598, 1461, 1370, 1269, 1180, 1099, 920, 814, 766, 672, 577 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 8.08 (s, 1, H, CH 3), 7.81 (d, J = 8.1 Hz, 2 H, ArH), 7.29 (d, J = 8.0 Hz, 2 H, ArH), 7.18 (d, J = 8.1 Hz, 1 H, 1H), 6.38 (dd, J = 9.4, 2.5 Hz, 1 H, CH 3), 3.92 (dd, J = 14.1, 6.9 Hz, 1 H, CH 2), 3.73 (m, 2, H, 2 × CH 2), 3.29 (dd, J = 14.5, 7.9 Hz, 1 H, CH 3).

13C NMR (125 MHz, CDCl3): δ = 141.0 (CH3), 121.7 (CH 2), 119.6 (CH 3), 119.2 (CH 2), 116.5 (CH 2), 115.6 (CH 2), 113.3 (CH 3), 112.6 (CH 3), 106.8 (CH 2), 84.0 (CH 3), 78.5 (CH 2), 72.1 (CH 2), 68.6 (CH 3), 55.6 (CH 2), 46.5 (CH 2), 29.7 (CH 2), 22.7 (CH 2), 18.5 (CH 2), 17.2 (CH 3).

HRMS: m/z calcd for [C28H47N3O5S – CH3]: 522.3001; found: 522.3006.

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Yield: 74 mg (76%); colourless solid; de >98% (NMR); [α]D23 +15.9 (c 1.1, CHCl3). Lit.7 [α]D23 +16.7 (c 1.0, CHCl3). Lit.10 [α]D23 +17 (c 1.0, CHCl3).

IR (CHCl3): 3332, 2920, 2825, 2106, 1467, 1340, 1261, 1121, 759 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 8.33 (s, 1, H, CH 3), 7.60 (d, J = 9.0 Hz, 2 H, ArH), 7.46 (d, J = 8.1 Hz, 1 H, 1H), 6.23 (dd, J = 9.4, 2.5 Hz, 1 H, CH 3), 3.87 (dd, J = 14.5, 7.9 Hz, 1 H, CH 3).

13C NMR (125 MHz, CDCl3): δ = 141.7 (CH3), 122.9 (CH 2), 119.6 (CH 3), 119.2 (CH 2), 116.6 (CH 2), 115.5 (CH 2), 113.3 (CH 3), 112.5 (CH 3), 106.7 (CH 2), 83.8 (CH 3), 78.4 (CH 2), 72.1 (CH 2), 68.4 (CH 3), 55.5 (CH 2), 46.5 (CH 2), 29.7 (CH 2), 22.7 (CH 2), 18.5 (CH 2), 17.2 (CH 3).

HRMS: m/z calcd for [C18H23N3O2]: 273.1708; found: 273.1713.
Yield: 144 mg (98%); de >98% (NMR); ee = 95%; [α]D21 +20.2 (c 0.55, MeOH) [lit.1] [α]D18 +18 (c 0.1, EtOH), Lit.10 [α]D18 +17.5 (c 0.4, EtOH), Lit.15 [α]D123 +17.5 (c 0.3, EtOH).

IR (KBr): 3343, 2822, 2742, 2342, 1584, 1471, 1383, 1037, 719 cm–1.

1H NMR (CDCl3, 300 MHz): δ = 0.88 (t, J = 6.8 Hz, 3 H, CH3), 1.25 (m, 24 H, 12 × CH2), 1.65 (m, 2 H, CH2-5), 2.08 (br s, 3 H, NH2, OH), 3.51 (dd, J = 8.4, 6.7 Hz, 1 H, H-1a), 3.61–3.68 (br m, 1 H, H-2), 3.74 (ddd, J = 3.7, 6.9, 6.9 Hz, 1 H, H-4), 3.85–3.96 (m, 2 H, H-3, H-1b).

13C NMR (75 MHz, CDCl3): δ = 14.1 (CH3), 22.7, 26.3, 29.3, 29.4, 29.6, 29.7, 29.8 (CH2, C6-17), 31.9 (CH2, C5-), 54.4 (CH, C-2), 71.8 (CH, C-3), 72.4 (CH2, C-1), 83.2 (CH, C-4).

MS (EI): m/z (%) = 299 (5) [M+], 252 (2), 226 (43), 83 (41), 71 (60), 60 (100), 59 (46), 57 (9).

HRMS: m/z: calcd for C18H37NO2: 299.2824; found: 299.2826.

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