Concise synthesis of truncated pachastrissamine (jaspine B) and its enantiomer

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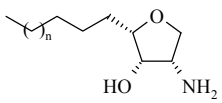
Abstract
A short and efficient stereoselective synthesis of truncated pachastrissamine and its enantiomer have been achieved using the Wittig olefination, azidation through imidazole sulfonate ester and one-pot reductive hydrogenation as the key steps.

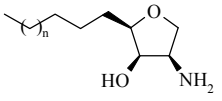
Keywords: Pachastrissamine, Wittig olefination, azidation, imidazole sulfonate ester, one-pot reductive hydrogenation

Introduction

(+)-Pachastrissamine **1a**, a naturally occurring novel anhydrosphingosine derivative, has been isolated recently from the Okanawa marine sponge *Pachastrissa sp* (family calthropellidae) by Higa and co-workers[1] and found to posses cytotoxicity at a level of IC_{50} 0.01 μg/mL against P388, A549, HT29 and Mell 28 cell lines. Shortly thereafter, the Debitus research group[2] reported the isolation of the same natural product from a different marine sponge *Jaspis sp*. Pachastrissamine represents the first example of an anhydrosphingosine structural feature in a natural product. In anticancer assays, this novel sphingosine derivative exhibited submicromolar cytotoxic activity against human lung carcinoma cell line using the ATP lite assay. Jaspine B **1a** proved to be the most potent compound yet isolated from the *Jaspis* genus on this cell lines, *cf*. pectenotoxin II (IC_{50} > 10 μM),[3] bengamide Y (IC_{50} = 12.8 μM),[4] bengamide Z (IC_{50} = 10.5 μM).[5]



n = 10: (+)-pachastrissamine (1a)
n = 1: (+)-truncated pachastrissamine (2a)

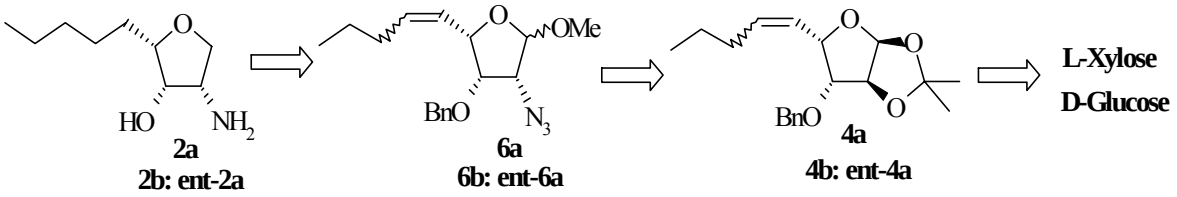


n = 10: (-)-pachastrissamine (1b)
n = 1: (-)-truncated pachastrissamine (2b)

It has been reported that sphingosine 1-phosphate induces a rapid and relevant release of arachidonic acid and increase phospholipase D activity in A549 cells.[6] The marine sponges even though have provided several bioactive leads, the consistent supply of these compounds has been limited. In order to gain rapid access to these products of biological interests, we have initiated a programme[7] to synthesise these scarce natural products and their analogues efficiently so that the supply for screening is uninterrupted. Herein we wish to report the concise synthesis of a truncated version of titled compound **2a** and its enantiomer **2b**. The same strategy can be also applied for the synthesis of jaspine B with original side chain. The present approach allows one to use various commercially available sugars and design new stereoanalogs with ease. To the best of our knowledge only three syntheses have been reported.[8]

Results and Discussion

The retrosynthetic analysis depends on the conversion of hydroxyl group at C-2 to sulfuryl imidazylate followed by S_N2 displacement with N_3 group in the furanose sugar normally a difficult step owing to its vicinity to anomeric carbon. For (+) and (-) Jaspine (truncated), we began with commercially available L-xylose and D-glucose respectively which were converted to key aldehydes **3a** and **3b**. Our retrosynthetic approach is outlined in scheme 1.

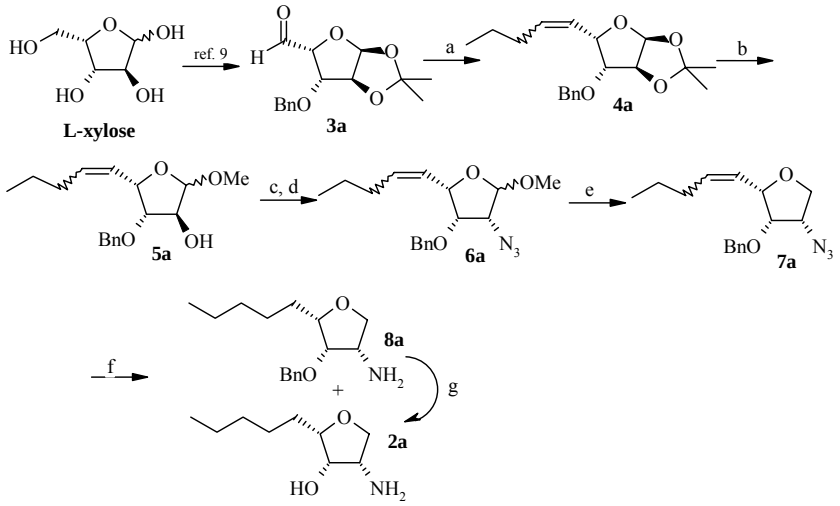


Scheme 1

The (+) isomer, L-xylose was converted to aldehyde **3a** through known sequence of reactions.[9] The aldehyde **3a** was subjected to Wittig olefination[10] with n-butyl triphenylphosphonium bromide in THF-HMPA and n-butyl lithium at – 40 ^oC to give olefin **4a** with **Z/E** ratio of more than 10:1 in 86 % yield. The hydrolysis of acetonide linkage and *in situ* formation of the methyl glycoside **5a** was successfully achieved using catalytic CH_3COCl in methanol.[11]

With the alcohol **5a** in hand, we tried several methods e.g. tosylation and mesylation for the S_N2 displacement of hydroxyl group at C-2 with N_3 group. But all efforts failed. Even more reactive triflate did not give good yield in nucleophilic substitution and resulted mainly in the elimination product. This problem was circumvented by treating **5a** with N, N'-sulfuryldiimidazole[12] and sodium hydride in DMF at - 40 ^oC to give imidazole sulfonate ester. Heating this sulfonate ester with NaN_3 in DMF gave the desired product **6a** but in poor yield.

This situation was overcome by using Bu_4NN_3 in place of NaN_3 giving **6a** in 68 % overall yield for two steps. Bu_4NN_3[13] was generated by the reaction of tetrabutylammonium chloride and NaN_3 as it is not commercially available. (Scheme 2)

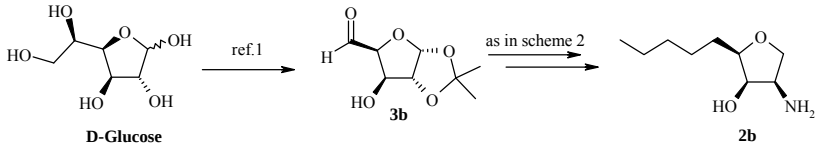


Reagents and conditions: $C_4H_9P^+Ph_3Br^-$, *n*-BuLi, THF-HMPA, -40 °C, 4 h, 86 %; b) CH_3COCl (cat), MeOH, 60 °C, 8 h, 95%; c) SO_2Im_2, NaH, DMF, -40 °C, 3 h; d) NaN_3, TBACl, DMF, 110 °C, 12 h, 58% (for two steps); e) $BF_3.OEt_2$, Et_3SiH, CH_2Cl_2, 0 °C-rt, 2 h, 94%; f) Pd/C, H_2, MeOH, rt, 6 h, 70%; g) Pd/C, H_2, MeOH, rt, 6 h

Scheme 2

The reductive removal of the methoxy group of **6a** with triethylsilane in the presence of $BF_3.OEt_2$[14] proceeded smoothly to give the tetrahydrofuran derivative **7a** in 94 % yield. Finally, reduction of the azide group as well as olefin hydrogenation and cleavage of the benzyl ether was successfully achieved in one-pot.[15] A mixture of **7a** and Pd / C in methanol was stirred under hydrogen atmosphere to furnish the target molecule **2a** in good yield along with the formation of a minor product as benzyl ether **8a**. The benzyl ether **8a** was again subjected to hydrogenation under the same conditions to yield final compound **2a** in complete conversion (scheme 2).

The (-)-enantiomer of truncated pachastrissamine **2b** was also synthesized from D-glucose as a replenishable starting material. Initially D-glucose was transformed to aldehyde derivative **3b** employing already known set of reactions.[16] All above reactions were strategically applied to this aldehyde **3b** to furnish the (-)-enantiomer of truncated pachastrissamine, **2b** in a stereoselective manner (scheme 3).



Scheme 3

Conclusions

In conclusion, a practical and stereoselective total synthesis of truncated pachastrissamine **2a** and its enantiomer **2b** has been achieved using Wittig olefination, azidation through imidazole sulfonate ester and one-pot reductive hydrogenation as the key steps. Moreover, this synthetic approach is flexible and can be applied for the synthesis of other analogues with variety of side chain and different stereocentres.

Experimental Section

General Procedures. Optical rotations were measured with a JASCO DIP-360 Polarimeter at 26 ^{o}C and IR spectra were recorded with a Perkin Elmer FTIR spectrophotometer. ^{1}H NMR spectra were carried out using a Varian Gemini 200 or Varian Unity 400 or Bruker Avance 300 MHz spectrophotometer using TMS as an internal standard in $CDCl_3$. Mass spectra were recorded on Micro mass VG-7070H for EI and VG Autospec M for FABMS mass spectrometers. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel $60F_{254}$ to a thickness of 0.25mm (Merck). Column chromatography was conducted by elution of columns with silica gel 60-120 mesh using ethyl acetate and hexane as eluents.

4–Benzyloxy-2,2-dimethyl-5-[1-pentenyl]-(3a*S*,5*S*,6*R*,6a*S*)-perhydrofuro[2,3-d][1,3]-dioxole (4a). To a well stirred solution of n-butyl riphenylphosphonium bromide (14.2 g, 35.8 mmol) in freshly distilled THF (50 mL) was added HMPA (4.18 g, 23.3 mmol) at room temperature. The mixture was cooled to – 40 ^{o}C and a solution of n-BuLi in hexane (18.7 mL, 26.8 mmol, 1.5M) was added dropwise. The resultant red brick coloured solution was stirred at – 40 ^{o}C for 30 min. A solution of aldehyde **3a** (5 g, 17.9 mmol) in THF was added slowly over a period of 20 min at – 40 ^{o}C. The reaction mixture was further stirred for a period of 1hour at – 40 ^{o}C and then allowed to warm up to room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3X60 mL). The combined extract was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to yield **4a** (4.9 g, 86 %) as colourless oil: $[\alpha]_D^{25}$ + 77.33 (c 2.6, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$); δ 7.32-7.23 (m, 5H), 5.88 (d, 1H, J = 3.2Hz), 5.68-5.62 (m, 2H),

4.90-4.84 (m, 1H), 4.62-4.55 (m, 3H), 3.74 (d, 1H, *J* = 3.2 Hz), 2.17-1.98 (m, 2H), 1.33-1.27 (m, 8H), 0.91 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.04, 128.33, 127.7, 127.4, 123.5, 111.3, 104.6, 83.3, 83.0, 75.8, 72.0, 30.0, 26.8, 26.2, 22.5, 13.7; IR (neat) cm^{-1} 3415, 2960, 2933, 2871, 1617, 1376, 1076, 1025; MS (ESI): *m/z* 315 $(M+Na)^+$, 243, 201, 150; HRMS: Calcd for $C_{19}H_{26}O_4Na$ $(M+Na)^+$: 341.1728 Found 341.1713

4-Benzyloxy-2-methoxy-5-[1-pentenyl]-(3*S*,4*R*,5*S*)-tetrahydro–3-furanol (5a). A catalytic amount of CH_3COCl was added to a solution of **4a** (4 g, 12.4 mmol) in methanol (20 mL). The reaction mixture was refluxed for overnight and then solvent was removed in vacuo. The residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$, brine, dried with Na_2SO_4 and concentrated. The organic residue was purified by column chromatography to give both anomers of **5a** (3.5 g, 95 %) in 1:1ratio. $[\alpha]_D^{25}$ - 41.36 (c 2.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$); δ 7.32 - 7.22 (m, 5H), 5.69-5.59 (m, 2H), 4.95 (d, 1H, *J* = 4.5 Hz), 4.88 (q, 1H, *J* = 5.2 Hz), 4.58 (q, 2H, *J* = 12.0 Hz), 4.24 - 4.18 (m, 1H), 3.80 (q, 1H, *J* = 3.0 Hz), 3.49 (s, 3H), 2.66 (d, 1H ,*J* = 6.0), 2.15 -2.01 (m, 2H), 1.48 - 1.35 (m, 2H), 0.92 (t, 2H, *J* = 7.5Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 134.8, 128.2, 127. 5,127.5, 124.8, 101.7, 84.8, 77.2, 74.1, 71.8, 55.6, 29.8, 22.6, 13.6; IR (neat) cm^{-1} 3416, 2931, 1617, 1113, 1040; MS(ESI): *m/z* 315 $(M + Na)^+$, 243, 201, 150

3-Azido-4-benzyloxy-2-methoxy-5-[1-penyenyl]-(3*R*,4*S*,5*S*)-tetrahydro furan (6a). To a well stirred suspension of freshly activated NaH (0.51 g, 12.9 mmol, 60% w/v dispersion in mineral oil) in anhydrous DCM (5mL), a solution of alcohol **5a** (2.5g, 8.6 mmol) in dry DCM was added dropwise at 0 ^{o}C and stirred for 30 min at room temperature. The reaction mixture was cooled to – 40 ^{o}C and to this added a solution of sulfuryl diimidazole (2.5g, 12.9 mmol) in dry DCM (5 mL) at – 40 ^{o}C and stirred for one hour at this temperature. To this added 0.01 mL of methanol at – 40 ^{o}C and further stirred for 30 min at – 40 ^{o}C. The reaction mixture was allowed to warm up to 0 ^{o}C and quenched with ice. The aqueous layer was extracted with DCM (3X20 mL). The combined organic extract was washed with water, brine, dried over Na_2SO_4 and concentrated. To the solution of this crude product in dry DMF was added NaN_3 (0.046 g, 7.1 mmol) and tetrabutylammonium chloride (1.9 g, 7.1 mmol) and stirred for overnight at 110 ^{o}C. The reaction mixture was diluted with water and the aqueous layer extracted with ether (3X20 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography to give **6a** (0.71 g, 58 % for both steps) as colourless oil. $[\alpha]_D^{25}$ - 2.7 (*c* 1.10, $CHCl_3$) ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 - 7.24 (m, 5H), 5.70 - 5.64 (m, 2H), 4.94-4.82 (m, 2H), 4.58 (q, 2H, *J* = 11.8 Hz), 4.19 (t, 1H *J* = 5.9 Hz), 3.74 - 3.68 (m, 1H), 3.37 (s, 3H), 2.16 - 2.01 (m, 2H), 1.49 - 1.36 (m, 2H), 9.28 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.2, 135.0, 128.2, 127.7, 127.6, 124.7, 105.6, 79.8, 74.7, 73.3, 66.4, 55.4, 29.7, 22.6, 13.6; IR (neat) cm^{-1} 2929, 2107, 1737, 1455,1265, 1102, 1045; MS (ESI): 318 $(M+H)^+$, 283, 255; HRMS Calcd for $C_{17}H_{23}N_3O_3Na$ $(M+Na)^+$ 340.1637 Found : 340.1647.

4-Azido-2-[1-pentenyl]-(2*S*,3*S*,4*S*)-tetrahydro-3-furanyl benzyl ether (7a). A catalytic amount of $BF_3.OEt_2$ was added to a solution of **6a** (0.13 g, 0.42 mmol) in anhydrous DCM (5mL)

at 0 ^{o}C and stirred for 15 min at the same temperature. To this added triethylsilane (0.15 g, 1.26 mmol) at 0 ^{o}C and further stirred for 2 h at room temperature. The reaction mixture was diluted with water and aqueous layer was extracted with DCM (3X15 mL). The combined organic extract was washed with water, brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography to afford **7a** (0.11g, 94 %) as colourless oil. $[\alpha]_D^{25}$ + 83.1 (*c* 1.45, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$); δ 7.35-7.29 (m, 5H), 5.71-5.63 (m, 2H), 4.72-4.57 (m, 3H), 4.05 (t, 1H, *J* = 5.2 Hz), 3.95-3.80 (m, 3H), 2.17-1.95 (m, 2H), 1.51-1.32 (m, 2H), 0.92 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 134.7, 128.3, 127.8, 127.7, 125.2, 80.4, 75.9, 73.7, 68.6, 61.6, 29.7, 22.6, 13.6; IR (neat) cm^{-1} 2959, 2871, 2103, 1454, 1267, 1121, 1060, 982; MS (ESI): *m/z* 305.1 $(M+NH_4)^+$, 310.1 $(M+Na)^+$; HRMS: Calcd. for $C_{16}H_{21}N_3O_2Na$ $(M+Na)^+$: 310.1531, Found: 310.1541.

Jaspine B (2a). A mixture of **7a** (0.11g, 0.3 mmol) and 10 % Pd-C (0.05 g) in methanol (5 mL) was stirred for overnight at room temperature under H_2 atmosphere (3atm). The catalyst was filtered off and filtrate concentrated in vacuo to give a residue which was purified by column chromatography to give **2a** (0.06 g) in 92 % yield as a yellowish oil; $[\alpha]_D^{25}$ +55.7 (*c* 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$); δ 3.95-3.85 (m, 2H), 3.76-3.61 (m, 2H), 3.56-3.48 (m, 1H), 2.01-1.89 (bs, 3H), 1.73-1.60 (m, 2H), 1.44-1.25 (m, 6H), 0.89 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 83.1, 70.1, 69.8, 58.3, 31.9, 29.6, 25.8, 22.5, 14.0; IR (neat) cm^{-1} 3485, 3414, 1618, 618; MS (ESI): *m/z* 174 $(M+H)^+$, 102 $(M-71)^+$, HRMS: Calcd for $C_9H_{20}NO_2$ $(M+H)^+$: 174.1494, Found: 174.1495.

NOTE: For all the intermediates arising from D-glucose reaction procedure, physical properties and spectral datas are same corresponding to L- xylose intermediates except specific rotation with opposite sign.

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References and Footnotes

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