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The first synthesis of the anhydrophytosphingosine pachastrissamine (jaspine B) from Garner's aldehyde☆

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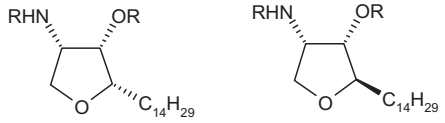
Abstract—The synthesis of the natural anhydrophytosphingosine pachastrissamine (jaspine B) **1a** from Garner's aldehyde is described.

Pachastrissamine **1a**, the first natural anhydrophytosphingosine derivative was recently isolated from a marine sponge, *Pachastrissa* sp. (family calthropellidae) by Higa and co-workers[1] and found to possess cytotoxicity at a level of IC_{50} 0.01 μg/mL against P388, A549, HT29 and Mell 28 cell lines. Later Debitus and co-workers[2] isolated the same compound from a marine sponge, genus jaspis, which is a main source of many cytotoxic compounds such as jaspamides,[3] jaspisamides,[4] isomalabaricane,[5] toyocamycin and 5-methoxy carbonyltubercidine,[6] and named as **1a**.

Jaspamides possess interesting biological activities such as antiproliferative (cytotoxic and antimicrobial), anthelminthic, insecticidal and ichthyototoxic activities.[7]



1a R = H
2a R = Ac

1b R = H
2b R = Ac

Jaspine B **1a** displayed marked cytotoxicity (IC_{50} = 0.24 μM) against the A549 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 line, cf. pectenotoxin II (IC_{50} > 10 μM),[8] bengamide Y (IC_{50} = 12.8 μM),[9] bengamide Z (IC_{50} = 10.5 μM).[10] The important biological activity and the novel structural features of **1a** prompted us to undertake its total synthesis.

The convergent total synthesis of **1a** started from the Garner's aldehyde.[11] Stereoselective addition of vinylmagnesium bromide to **3** afforded a 6:1 mixture of allylic alcohols **4** and **5**, which were separated by column chromatography.[12] The alcohol functionality of compound **4** was protected as it's *O*-benzyl ether to give **6**. Oxidative degradation of the alkene functionality with ozone afforded the aldehyde, which then underwent Grignard addition using $C_{14}H_{29}MgBr$ in THF to give compounds **7a** and **7b** as an inseparable diastereomeric mixture (ratio 7:3 by ^1H NMR), which was carried further as such (Scheme 1).

Deprotection of the acetonide group in compound **7** was achieved using 80% AcOH to give compounds **8a** and **8b**, which were converted into the *O*-silyl ethers **9a**,**b**. The hydroxyl groups in compounds **9a**,**b** were converted into mesylates, which were treated with TBAF to give the five membered cyclic compounds **10** and **11** in a 7:3 ratio, which were easily separable by column chromatography. The confirmation of structures and assignments for the tetrahydrofurans **10** and **11** was achieved by detailed 1D and 2D NMR studies including DQF-COSY and NOESY experiments. For **10** strong NOE

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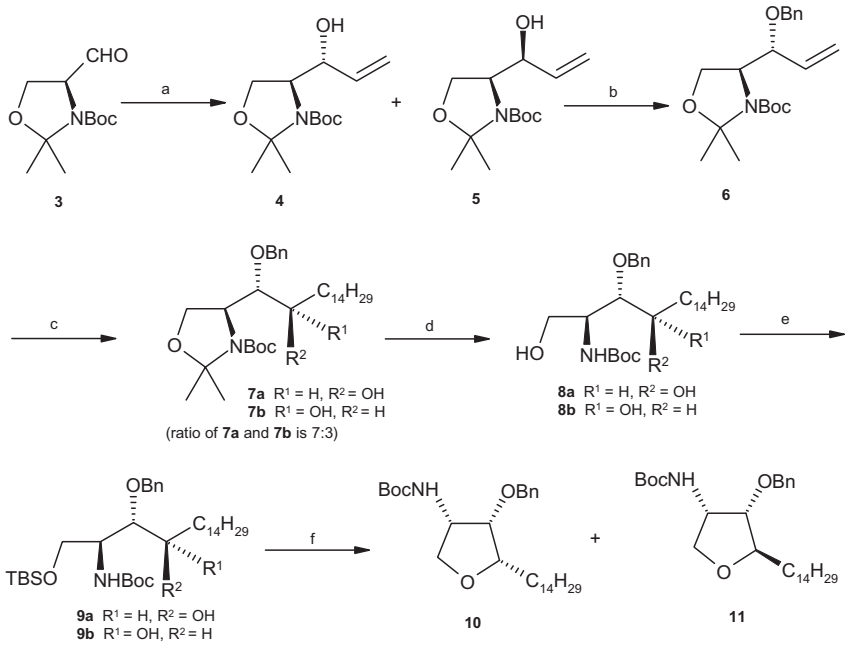


Scheme 1. Reagents and conditions: (a) vinylmagnesium bromide, THF, 0 °C–rt, 12 h, (b) BnBr, THF, NaH (60% w/w), 0 °C–rt, 12 h, 92%, (c) (i) O_3, DCM, −78 °C, 1 h, $(CH_3)_2S$, (ii) $C_{14}H_{29}MgBr$, THF, 12 h, rt (83% for two steps), (d) 80% AcOH, 0 °C–rt, 12 h, 91%, (e) TBDMS-Cl, imidazole, dry DCM, DMAP, 0 °C–rt, 12 h, 86%, (f) (i) MsCl, Et_3N, DCM, 0 °C–rt, 2 h, (ii) TBAF, THF, rt, 2 h, 88% (overall yield 28.3% for compound **10** and 12.1% for compound **11**), (7:3 diastereoisomeric mixture for **10** and **11**).

cross peaks were observed between NH–H1′, H2–H4 and H5–H6, whereas for **11** the NOE cross peaks between NH–H1′, H2–H5, H3–H5 and H4–H6 confirmed the structures as shown in Figure 1.

The *O*-benzyl ether in compound **10** was cleaved under Na/liq. NH_3 conditions to afford alcohol **12**. Compound **12** on treatment with 50% TFA–DCM gave the target molecule pachastrissamine (jaspine B) **1a** as it's TFA salt (Scheme 2).

The diacetate derivative of pachastrissamine **2a** was synthesized from compound **1a** using Et_3N and Ac_2O. The ^1H NMR of the TFA salt of **1a** [it's optical rotation $[\alpha]_D^{25}$ +17.1 (*c* 0.4, EtOH)], {lit.[1] $[\alpha]_D^{25}$ +18 (*c* 0.1, EtOH)} and electrospray analysis: *m*/*z* 300 (M^++1−CF_3COOH) and for the diacetate derivative were identical with the reported values.[1,2]

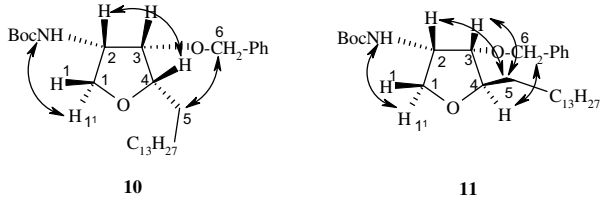


Figure 1. NOEs observed in compounds **10** and **11**.

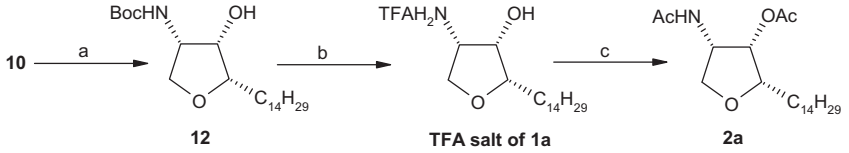
Compound **11** was also converted into the C-2 epimer of **1a** as it's TFA salt **1b** and the di-acetate derivative **2b** was prepared using the same strategy (Scheme 3). The spectral data of diacetate **2b** is matched with the C-12 side chain derivative, which was synthesized earlier.[13] Compound **1b** is also reported as synthetic derivative of phytosphingosine.[14]

In conclusion we have developed a strategy for the synthesis of pachastrissamine (jaspine B) **1a** and its diacetate derivative **2a** from Garner's aldehyde. The C-2 epimer of pachastrissamine (jaspine B) was also synthesized.

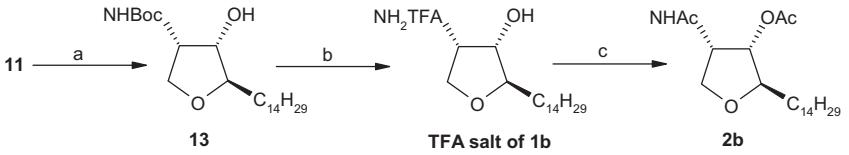
1. Spectral data

1.1. TFA salt of 1b

$[\alpha]_D^{25}$ +14.46 (*c* 1.5, EtOH); (^1H NMR, 300 MHz, CD_3OD): δ 0.89 (t, 3H, J = 7.3 Hz), 1.22–1.39 (m,



Scheme 2. Reagents and conditions: (a) Na/liq. NH_3, THF, −78 °C, 30 min, 96%, (b) 50% TFA–DCM, rt, 6 h, 87%, (c) Et_3N, Ac_2O, DCM, 0 °C–rt, 4 h, 94% (overall yield for **2a** is 22.3%).



Scheme 3. Reagents and conditions: (a) Na/liq. NH_3, THF, −78 °C, 30 min, 96%, (b) 50% TFA–DCM, rt, 6 h, 89%, (c) Et_3N, Ac_2O, DCM, 0 °C–rt, 4 h, 94% (overall yield for **2b** is 9.8%).

22H), 1.41–1.67 (m, 4H), 3.64–3.75 (m, 3H), 3.98–4.04 (m, 1H), 4.10–4.17 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz): δ 85.20, 74.33, 69.36, 53.65, 34.02, 32.95, 30.67, 30.65, 30.59, 30.55, 30.35, 26.76, 23.61, 14.34; electrospray analysis: *m/z* 300 (M^++1−CF_3COOH).

1.2. Compound 10

$[\alpha]_D^{25}$ +1.08 (*c* 1.1, $CHCl_3$); (^{1}H NMR, 500 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 6.85 Hz), 1.26 (br s, 24H), 1.44 (br s, 9H, CH_3-Boc), 1.62 (m, 2H, H-5), 3.61 (dd, 1H, $J_{1,1'} = 8.3$ Hz, $J_{1'2} = 7.2$ Hz, H-1′), 3.80 (dt, 1H, $J_{3,4}$ = 4.5 Hz, $J_{4,CH2}$ = 6.4 Hz, H-4), 3.91 (dd, 1H, $J_{1,1'} = 8.3$ Hz, $J_{1,2}$ = 7.7 Hz, H-1), 3.95 (dd, 1H, $J_{3,4}$ = 4.5 Hz, $J_{2,3}$ = 6.0 Hz, H-3), 4.35 (dddd, $J_{1,2}$ = 6.7 Hz, $J_{1'2} = 7.4$ Hz, $J_{2,3}$ = 6.2 Hz, $J_{NH,2}$ = 7.2 Hz, H-2), 4.58 (s, 2H, H-6), 5.0 (d, 1H, J = 8.3 Hz, NH), 7.30-7.40 (m, 5H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.55, 137.79, 128.47, 127.91, 81.90, 79.56, 79.14, 74.24, 70.56, 53.21, 31.89, 29.63, 29.56, 29.30, 28.37, 26.33, 22.63, 14.01; FABMS: *m/z* 490 (M^++1).

1.3. Compound 11

$[\alpha]_D^{25}$ +5.1 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 6.9 Hz), 1.26 (br s, 24H), 1.45 (br s, 9H, CH_3-Boc), 1.47 (m, 2H, H-5), 3.57 (dd, 1H, $J_{1,1'} = 8.7$ Hz, $J_{1',2} = 7.4$ Hz, H-1′), 3.66 (dd, 1H, $J_{3,4}$ = 4.3 Hz, $J_{2,3}$ = 6.2 Hz, H-3), 3.83 (dt, 1H, $J_{3,4}$ = 4.3 Hz, $J_{4,CH2}$ = 6.3 Hz, H-4), 4.10 (dd, 1H, $J_{1,1'} = 8.7$ Hz, $J_{1,2}$ = 6.7 Hz, H-1), 4.22 (dddd, $J_{1,2}$ = 6.7 Hz, $J_{1',2} = 7.4$ Hz, $J_{2,3}$ = 6.2 Hz, $J_{NH,2}$ = 7.2 Hz, H-2), 4.53 (s, 2H, H-6), 5.10 (d, 1H, J = 7.2 Hz, NH), 7.28–7.40 (m, 5H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.64, 137.51, 128.48, 127.99, 127.90, 82.50, 81.58, 79.58, 72.24, 71.12, 51.54, 33.92, 31.90, 29.64, 29.54, 29.32, 28.37, 25.72, 22.65, 14.05; FABMS: *m/z* 490 (M^++1).

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