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Expeditious synthesis of nitrogenated spongianes: 4-methyldecarboxy-spongolactams

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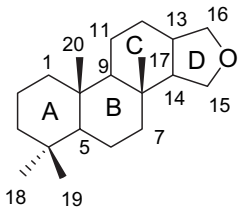
ABSTRACT

Herein, the synthesis of 4-methyldecarboxyhaumanamide (**9**) and 4-methyldecarboxyspongolactams A (**11**) and C (**13**) is presented. (−)-Sclareol is the starting material and the chloroderivative **7** is the common intermediate. Moreover, this synthesis represents a new strategy for the preparation of pyrrolinones.

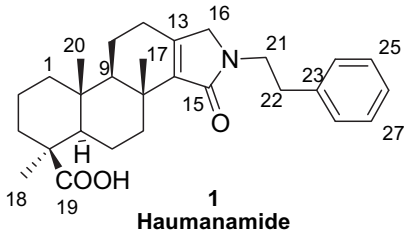
1. Introduction

Spongianes are a group of tetracyclic diterpenes isolated from marine organisms,[1] some of which display an interesting range of biological activities.[2]



Spongiane skeleton

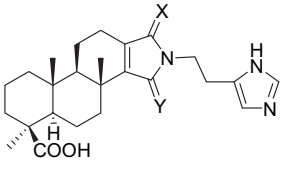
Haumanamide[3] **1** is a nitrogenous derivative isolated from a Pohnpei *Spongia sp*. It is active in the KB (MIC 5 μg/mL) and LoVO (MIC 10 μg/mL) bioassays.



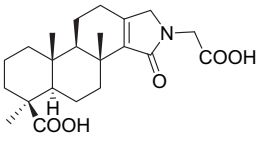
1
Haumanamide

Structurally, haumanamide is a terpenoid with two clearly distinguished parts: a phenylethylamine part and a terpenic moiety, which belong to the nitrospongiane family. This compound is the first one of this class to be isolated.

Recently,[4] novel nitrogenous diterpenoids, spongolactams A–C (**2**–**4**) were isolated as trace compounds from an Okinawan marine sponge, *Spongia sp*. They showed Farnesyl Transferase Inhibition activity.



2 X=H_2, Y=O, Spongolactam A
3 X=O, Y=H_2, Spongolactam B



4 Spongolactam C

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Spongolactams have a pyrrolinone core in common.

Pyrrolinones are the predominant tautomeric form of the α-hydroxypyrroles. Traditionally,[5] they have be synthesized either directly by oxidation of the corresponding pyrroles or by ring synthesis. Those latter include the reduction and cyclization of cyanohydrins derived from β-keto-esters, the cyclization of acyl-succinic esters with ammonia or primary amines, or the Michael addition of nucleophiles to acetylenic carbonyls.

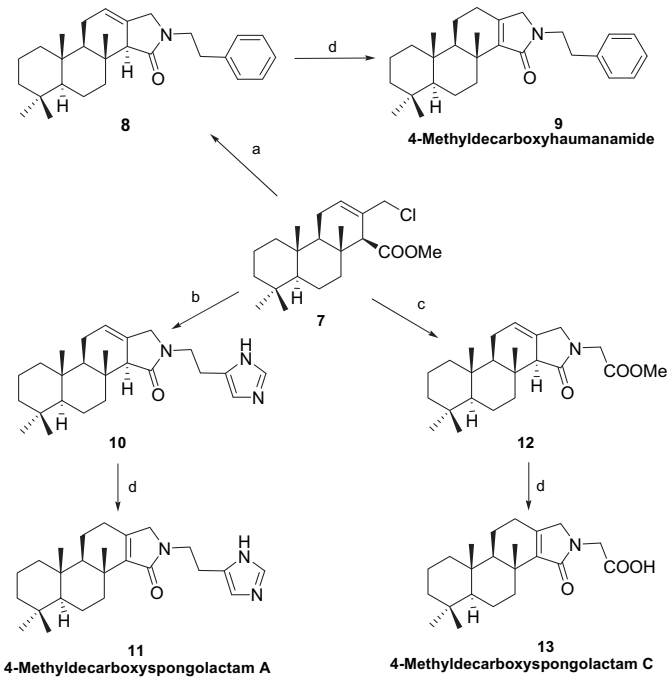
Recently, new strategies have been reported. Many synthetic routes to these compounds introduce the nitrogen heteroatom into a carbon framework via azide, cyanide or ammonia substitution reactions,[6] via reduction of imine derivatives, or they are based on a coupling promoted by a metal catalyst.[7] Ring expansion of cyclobutanones[8] and biomimetic studies have also been reported.[9]

The synthetic route that we present offers an alternative method of preparation of this moiety by condensation of the allylic halide/ester with an amine followed by isomerisation of the olefin. Besides, it is a useful way of achieving a series of spongolactams depending on the amine chosen.

In this work, the synthesis of 4-methyldecarboxyhaumanamide, **9**, and 4-methyldecarboxyspongolactams A, **11**, and C, **13**, is described.

The synthesis of this kind of molecules is interesting in order to build an even wider portfolio of spongianes on which the oxygen in ring D has been replaced by a nitrogen atom.

On the other hand the synthesis of 4-methyldecarboxy-compounds will help to establish the influence of carboxylic group in the biological activity.



Scheme 2. Reagents and conditions: (a) β-phenylethylamine, NaCN, 45 °C, 24 h (81%); (b) Histamine, MeOH, 80 °C, 24 h (42%); (c) Glycine methyl ester hydrochloride, MeOH, Et_3N, 80 °C, 24 h (38%); (d) 10% KOH/MeOH, rt (82% **9**, 91% **11**, 93% **13**).

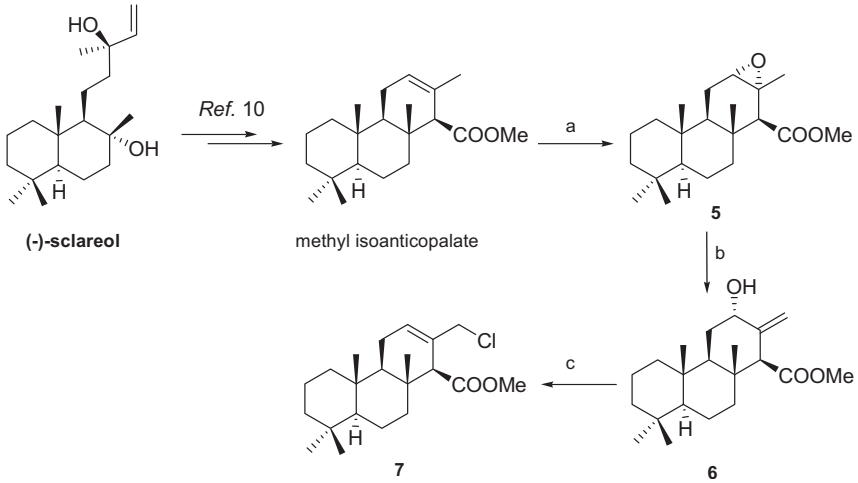
2. Results and discussion

The key intermediate in the synthesis of the targeted spongolactams is the halogenated compound **7**. This compound is obtained throughout the reaction sequence shown in Scheme 1, using methyl isoanticopalate as the starting material. Methyl isoanticopalate, obtained from sclareol,[10] is an excellent precursor for the synthesis of bioactive natural compounds.[11]

Treatment of methyl isoanticopalate with *m*CPBA gives the expected epoxide **5**. Reaction of **5** with Al(*i*PrO)$_3$[12] leads to alcohol **6**. From **6**, an allylic rearrangement[13] of the double bond and nucleophilic substitution of the hydroxyl group by a chlorine atom yields the desired chloroderivative **7**. With the key intermediate **7** in hand, the synthesis of the 4-metyldecarboxyspongolactams is carried out following the reaction sequence described in Scheme 2.

Treatment of **7** with β–phenylethylamine in presence of NaCN[14] affords the lactamic ring of **8**. The reaction of **7** with histamine in MeOH at 80 °C leads to **10**. When the same conditions are applied to **7** and glycine methyl ester hydrochloride, the desired compound **12** is obtained. Double bond isomerization from Δ^{12}–Δ^{13} tested with LDA and *t*-BuOK gave no satisfactory results. However, treatment of **8**, **10** and **12** with KOH/MeOH, respectively yielded **9**, **11** and **13**.

Compounds **9**, **11** and **13** did not inhibit tumour cell growth of a number of established human tumour cell lines, including HeLa (epitheloid cervix carcinoma), MCF-7 (breast adenocarcinoma), NCI-H460 (non-small lung carcinoma), and SF-268 (glioblastoma), when used in a molar range of 10^{-5}–10^{-9} M, as assessed by Alamar Blue assay.[15] This fact indicates that the IC_{50} (50% inhibitory concentration, drug concentration causing 50% inhibition in cell proliferation) values for these compounds were higher than



Scheme 1. Reagents and conditions: (a) *m*CPBA, DCM, 0 °C, 2 h (78%); (b) (*i*PrO)$_3$Al, toluene, 110 °C, 12 h (86%); (c) $SOCl_2$, C_6H_6, 0 °C, 15 min (52%).

1×10^{-5} M, whereas Taxol, used as a positive control, rendered IC_{50} values of $3.8\pm0.5\times10^{-9}$ M (HeLa), $8.4\pm0.7\times10^{-9}$ M (MCF-7), $3.9\pm0.2\times10^{-9}$ M (NCI-H460), and $4.9\pm0.2\times10^{-9}$ M (SF-268) (data are mean values±SD of three independent determinations).

All these results seem to show that the presence of the carboxylic group in C-4, as in **1**, **2** and **4**, is essential for the activity of these compounds.

3. Conclusions

The synthesis of three 4-methyldecarboxyspongolactams **9**, **11** and **13** has been accomplished. The chloroderivative **7** is the key intermediate to get to this kind of compounds. This synthesis offers a novel, rapid, and metal-free strategy for the construction of pyrrolinones. The presence of a carbonyl group in C-4 is essential for the activity of these compounds.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FTIR or an AVATAR 370 FTIR Thermo Nicolet spectrophotometers. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^{1}H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ ppm and coupling constants (*J*) are given in hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as *m*/*z* (% rel int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

4.2. Epoxidation of methyl isoanticopalate to yield 5

To a solution of methyl isoanticopalate (960 mg, 3.0 mmol) in CH_2Cl_2 (33 mL), cooled at 0 °C, *m*CPBA (938 mg, 5.4 mmol) was added. The reaction was controlled by TLC. After stirring for 2 h the solution was diluted with ether, washed with $NaHSO_3$ 10%, $NaHCO_3$ 10% and brine. It was dried with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by chromatography on silica gel to give the colourless oil **5** (789 mg, 2.36 mmol, 78% yield).

*4.2.1. Methyl 12,13-α-epoxy-isoanticopal-15-oate (**5**).* $[\alpha]_D^{22}$ −23.0 (*c* 0.85, $CHCl_3$); IR (film): 1737, 1443, 1329, 1268, 1163, 1103, 1007 cm^{-1}; ^{1}H NMR (200 MHz) δ: 3.64 (3H, s), 3.02 (1H, br s), 2.45 (1H, s), 2.1–0.92 (14H, m), 1.26 (3H, s), 1.05 (3H, s), 0.87 (3H, s), 0.81 (3H, s), 0.77 (3H, s); ^{13}C NMR (50 MHz) δ: 172.6, 62.1, 60.3, 57.0, 56.5, 51.2, 50.3, 41.9, 40.4, 39.5, 37.4, 36.2, 33.6, 33.3, 22.6, 21.9, 21.9, 18.5, 18.5, 15.9, 15.2; EIHRMS: calcd for $C_{21}H_{34}O_3Na$ (M+Na): 357.2400, found 357.2401.

4.3. Reaction of 5 with (*i*PrO)$_3$Al to yield 6

To a solution of **5** (530 mg, 1.59 mmol) in toluene (52 mL), (*i*PrO)$_3$Al (312 mg, 1.53 mmol) was added. The mixture was refluxed for 12 h. Then, it was allowed to reach room temperature. After dilution with ether, it was washed with $NaHCO_3$ and brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. Silica gel chromatography gave **6** as a colourless oil (457 mg, 1.37 mmol, 86% yield).

*4.3.1. Methyl 12-α-hydroxy-isoanticopal-13-(16)-en-15-oate (**6**).* $[\alpha]_D^{22}$ −32.2 (*c* 0.82, $CHCl_3$); IR (film): 3424, 2936, 1737, 1435, 1387, 1194, 1163, 1043, 1005, 911 cm^{-1}; ^{1}H NMR (200 MHz) δ: 5.03 (1H, s), 4.84 (1H, s), 4.38 (1H, s), 3.64 (3H, s), 3.34 (1H, s), 1.88–0.87 (14H, m), 1.02 (3H, s), 0.86 (3H, s), 0.84 (3H, s), 0.80 (3H, s), OH not observed; ^{13}C NMR (50 MHz) δ: 172.2, 145.3, 111.5, 73.1, 57.6, 56.9, 51.9, 51.2, 42.2, 40.4, 40.3, 39.9, 37.5, 33.5, 33.3, 29.3, 21.7, 18.9, 18.7, 16.3, 14.4; EIHRMS: calcd for $C_{21}H_{34}O_3Na$ (M+Na): 357.2400, found 357.2393.

4.4. Rearrangement of 6 with $SOCl_2$ to yield 7

A solution of **6** (145 mg, 0.43 mmol) in C_6H_6 (1.1 mL) was cooled to 0 °C and $SOCl_2$ (2.2 mL, 30 mmol) was added. The mixture was stirred for 15 min at this temperature. Then, it was quenched with ice and extracted with EtOAc. The organics were washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue purified by chromatography on silica gel afforded the yellowish oil **7** (80 mg, 0.23 mmol, 52% yield).

*4.4.1. Methyl 16-chloro-isoanticopal-12-en-15-oate (**7**).* IR (film): 1730, 1450, 1430, 1390, 1190, 1160 cm^{-1}; ^{1}H NMR (200 MHz) δ: 5.93 (1H, br s), 4.32 (1H, d, *J*=11.1 Hz), 3.99 (1H, d, *J*=11.1 Hz), 3.71 (3H, s), 3.22 (1H, br s), 2.10–0.90 (14H, m), 0.91 (3H, s), 0.88 (3H, s) 0.87 (3H, s), 0.82 (3H, s); ^{13}C NMR (50 MHz) δ: 172.7, 131.1, 129.8, 58.6, 57.5, 56.9, 51.3, 49.1, 42.1, 41.8, 40.1, 37.7, 36.8, 33.3, 33.3, 23.2, 21.8, 18.9, 18.6, 15.8, 15.8; EIHRMS: calcd for $C_{21}H_{33}O_2NaCl$ (M+Na): 375.2061, found 375.2076.

4.5. Reaction of 7 to yield 8

Compound **7** (30 mg, 0.08 mmol) was dissolved in phenylethylamine (2.8 mL, 22 mmol) and 0.42 mg (0.008 mmol) of NaCN were added to the reaction mixture. It was stirred at 45 °C under argon atmosphere for 24 h. Then, ether was added and the solution was washed with 2 N HCl, $NaHCO_3$ 10% and brine. The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude was purified by chromatography on silica gel affording **8** as a yellowish oil (28 mg, 0.07 mmol, 81% yield).

*4.5.1. 13-iso-4-Methyldecarboxyhaumanamide (**8**).* $[\alpha]_D^{22}$ −23.0 (*c* 0.84, $CHCl_3$); IR (film): 1690, 1560, 1450, 1390, 1270 cm^{-1}; ^{1}H NMR (200 MHz) δ: 7.30–7.20 (5H, m, C_6H_5), 5.55 (1H, br s), 3.80–3.35 (3H, m), 2.82 (2H, t, *J*=7.4 Hz), 2.61 (2H, br s), 2.10–0.90 (14H, m), 0.88 (6H, s), 0.83 (3H, s), 0.75 (3H, s); ^{13}C NMR (50 MHz) δ: 173.5, 139.0, 128.9, 128.7, 128.7, 128.7, 128.7, 128.6, 120.5, 57.4, 56.9, 54.5, 51.2, 43.8, 42.1, 40.6, 40.0, 37.8, 34.8, 34.0, 33.7, 33.2, 23.0, 21.9, 18.7, 18.7, 15.4, 14.9; EIHRMS: calcd for $C_{28}H_{40}NO$ (M+H): 406.3104, found 406.3106.

4.6. Reaction of 8 with KOH/MeOH to yield 9

To a solution of **8** (18 mg, 0.04 mmol) in MeOH (0.3 mL), 0.1 mL of 10% KOH in MeOH were added. The reaction mixture was stirred at room temperature for 3 h. Then the solvent was removed under reduced pressure. The residue was diluted with ether and washed with water. The organics were dried over Na_2SO_4 and concentrated. Purification by chromatography on silica gel afforded the desired 4-methyldecarboxyhaumanamide **9** (15 mg, 0.04 mmol, 82% yield).

*4.6.1. 4-Methyldecarboxyhaumanamide (**9**).* $[\alpha]_D^{22}$ −30.5 (*c* 0.41, $CHCl_3$); IR (film): 1670, 1455, 1410, 1380 cm^{-1}; ^{1}H NMR (200 MHz)

δ: 7.30–7.20 (5H, m, C_6H_5), 3.75–3.40 (3H, m), 3.58 (1H, d, J=5.9 Hz), 3.50 (1H, d, J=5.9 Hz), 2.90 (3H, m), 2.25–1.10 (14H,m), 1.16 (3H, s), 0.88 (3H, s), 0.85 (3H, s), 0.83 (3H, s); ^{13}C NMR (50 MHz) δ: 170.8, 147.2, 141.5, 139.3, 128.7, 128.7, 128.5, 128.5, 126.3, 57.0, 57.0, 52.7, 43.6, 42.2, 40.0, 37.6, 36.6, 36.0, 35.2, 33.3, 33.3, 21.3, 21.3, 21.3, 18.6, 18.3, 17.5, 16.5; EIHRMS: calcd for $C_{28}H_{40}NO$ (M+Na): 406.3104, found 406.3106.

4.7. Reaction of 7 to yield 10

Compound **7** (64 mg, 0.18 mmol) was dissolved in MeOH (6 mL) and histamine (300 mg, 2.7 mmol) was added. The reaction mixture was stirred at 80 °C under argon atmosphere for 24 h. Then it was allowed to reach room temperature, and the MeOH was removed under reduced pressure. After addition of water the solution was extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on silica gel affording **10** as a yellowish oil (22 mg, 0.06 mmol, 42% yield).

*4.7.1. 13-iso-4-Methyldecarboxyspongolactam A (**10**).* $[\alpha]_D^{22}$ −29.4 (*c* 0.16, $CHCl_3$); IR (film): 2998, 2929, 1669, 1478, 1270, 1091 cm^{-1}; ^{1}H NMR (400 MHz) δ: 7.54 (1H, br s), 6.81 (1H, br s), 5.60 (1H, br s), 3.90–3.55 (3H, m), 2.88 (2H, t, J=6.8 Hz), 2.65–2.55 (2H, m), 2.05–1.05 (14H, m), 0.87 (6H, s), 0.82 (3H, s), 0.71 (3H, s), NH not observed; ^{13}C NMR (100 MHz) δ: 174.4, 134.6, 132.6, 129.0, 120.7, 118.9, 57.2, 56.6, 54.1, 50.7, 41.8, 41.1, 40.4, 39.7, 37.5, 34.7, 33.4, 33.1, 24.6, 22.7, 21.6, 18.4, 18.3, 15.1, 14.7; EIHRMS: calcd for $C_{25}H_{38}N_3O$ (M+H): 396.3009, found 396.3020.

4.8. Reaction of 10 with KOH/MeOH to yield 11

Compound **10** (22 mg, 0.06 mmol) was dissolved in 2.2 mL of 10% KOH/MeOH. The reaction mixture was stirred at room temperature for 6 h. Then the solvent was removed and water was added. After extraction with EtOAc, the organics were washed with brine. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography on silica gel afforded 20 mg of 4-methyldecarboxyspongolactam A, **11** (0.05 mmol, 91% yield).

*4.8.1. 4-Methyldecarboxyspongolactam A (**11**).* $[\alpha]_D^{22}$ −41.4 (*c* 0.07, $CHCl_3$); IR (film): 2905, 2850, 1663, 1458, 1408, 1224 cm^{-1}; ^{1}H NMR (400 MHz) δ: 7.58 (1H, br s), 6.83 (1H, br s), 3.71 (2H, t, J=6.4 Hz), 3.64 (2H, d, J=2.6 Hz), 2.93 (2H, t, J=6.4 Hz), 2.76 (2H, d, J=12.9 Hz), 2.7–1.4 (14H, m), 1.13 (3H, s), 0.88 (3H, s), 0.85 (3H, s), 0.83 (3H, s), NH not observed; ^{13}C NMR (100 MHz) δ: 171.6, 148.3, 141.0, 134.6, 132.6, 118.9, 56.8, 56.8, 52.5, 42.1, 40.7, 39.8, 37.5, 36.5, 35.9, 33.3, 33.3, 26.4, 25.9, 21.3, 21.2, 18.5, 18.2, 17.3, 16.4; EIHRMS: calcd for $C_{25}H_{38}N_3O$ (M+H): 396.3009, found 396.3004.

4.9. Reaction of 7 to yield 12

Glycine methyl ester hydrochloride (105 mg, 0.84 mmol) was dissolved in 0.5 mL of MeOH and Et_3N (0.12 mL, 0.84 mmol) was added. To this mixture a solution of **7** (27 mg, 0.08 mmol) in MeOH was added. The reaction mixture was stirred overnight at 80 °C under argon atmosphere. Then it was allowed to reach room temperature and water was added. After extraction with EtOAc the organic phase was washed with 2 N HCl, $NaHCO_3$10 % and brine. It was dried over Na_2SO_4 and the solvent evaporated. The crude was purified by chromatography to yield **12** as a yellowish oil (9 mg, 0.03 mmol, 38%).

*4.9.1. 13-iso-4-Methyldecarboxyspongolactam C (**12**).* $[\alpha]_D^{22}$ −21.4 (c 0.27, $CHCl_3$); IR (film): 2923, 2847, 1752, 1688, 1434, 1273, 1209 cm^{-1}; ^{1}H NMR (200 MHz) δ: 5.65 (1H, br s), 4.14 (1H, d, J=17.6 Hz), 3.99 (1H, d, J=17.6 Hz), 3.89 (1H, s), 3.72 (3H, s), 2.61 (1H, s), 2.70 (1H, s), 2.20–1.05 (14H, m), 0.89 (3H, s), 0.88 (3H,s), 0.83 (3H,s), 0.81 (3H, s); ^{13}C NMR (50 MHz) δ: 174.5, 169.4, 128.5, 121.0, 56.9, 56.8, 54.5, 52.4, 51.4, 43.8, 42.1, 40.5, 40.0, 37.8, 35.0, 33.7, 33.4, 23.0, 21.9, 18.7, 18.6, 15.4, 15.0; EIHRMS: calcd for $C_{23}H_{35}NO_3Na$ (M+Na): 396.2509, found 396.2522.

4.10. Reaction of 12 with KOH/MeOH to yield 13

Compound **12** (8 mg, 0.02 mmol) was dissolved in 0.8 mL of 10% KOH/MeOH. The reaction mixture was stirred at room temperature for 8 h. Then methanol was removed and water was added. It was extracted with EtOAc, and the organic phase was washed with brine. It was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give 6 mg of the 4-methyldecarboxyspongolactam C, **13** (0.02 mmol, 93% yield).

*4.10.1. 4-Methyldecarboxyspongolactam C (**13**).* $[\alpha]_D^{22}$ −56.0 (*c* 0.05, $CHCl_3$); IR (film): 2922, 2850, 1737, 1632, 1441, 1383, 1177, 1014 cm^{-1}; ^{1}H NMR (400 MHz) δ: 4.18 (2H, s), 3.86 (1H, d, J=14.4 Hz), 3.80 (1H, d, J=14.4 Hz), 2.72 (1H, dt, J=12.8, 1.5 Hz), 2.33 (1H, dd, J=18.0, 4.8 Hz), 2.25 (1H, ddd, J=18.0, 11.5, 6.5 Hz), 2.10–1.20 (13H, m), 1.15 (3H , s), 0.87 (3H, s), 0.85 (3H, s), 0.82 (3H, s), COOH signal not observed; ^{13}C NMR (100 MHz) δ: 172.1, 165.7, 150.0, 140.6, 56.8, 56.7, 53.3, 42.1, 39.8, 38.7, 37.5, 36.4, 35.9, 33.3, 29.7, 26.5, 21.3, 21.2, 18.5, 18.2, 17.2, 16.4; EIHRMS: calcd for $C_{22}H_{33}NO_3Na$ (M+Na): 382.2353, found 382.2345.

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