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Synthesis of the Arctic sponge alkaloid viscosaline and the marine sponge alkaloid theonelladin C

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Abstract—The synthesis of Arctic sponge alkaloid viscosaline (**1**) is achieved by using the Zincke reaction as the penultimate step. A key synthetic intermediate theonelladin C (**6**), itself a marine sponge natural product, is synthesised efficiently using a four-step sequence.

1. Introduction

Marine sponges have always fascinated natural product chemists due to the wide variety of natural products that are present in this relatively simple organism.[1] While most of the sponges examined by natural product chemists have been from tropical and temperate waters, the chemical composition of Arctic sponges has not been extensively investigated.[2]

3-Alkyl pyridine alkaloids are commonly found in the marine sponges of the order Haplosclerida.[3] In 2004, Volk and Köck reported the isolation and structural characterisation of an acyclic 1,3-dialkylpyridinium alkaloid viscosaline (**1**), from the sponge *Haliclona viscosa* collected off the coast of Blomstrandhalvøya, near Hansneset.[4] The isolation of **1** from *H. viscosa* was guided by antimicrobial assays and it was observed that the *n*-butanol extract of *H. viscosa* that contained **1** showed high antimicrobial activity against several bacteria.

The structure of **1** was established via the use of high-resolution mass spectrometry and NMR spectroscopy and was found to contain a β-alanine unit attached to the terminal of an alkyl bis-pyridinium salt. The authors suggested that **1** might be a biosynthetic precursor of cyclic bis-pyridinium alkaloids, cyclostellettamines, and related compounds.[5] The interesting structure of **1** and its strong antimicrobial activity prompted us to investigate its synthesis. We report here the successful execution of our plan.

2. Results and discussion

Retrosynthetically, **1** can be derived from the basic building block **2**. Compound **2** has been used previously in the synthesis of cyclostellettamines[6] and recently in the synthesis of viscosamine,[7] a trimeric pyridinium alkaloid also isolated from *H. viscosa*.[8] Usually, compound **2** is prepared in four steps from 1,12-dodecanediol **3**,[6a,c,14] which entails monobromination, protection of alcohol, alkylation with lithiated 3-picoline and deprotection. To obtain an ample supply of **2**, we decided to streamline its synthesis. 1,12-Dodecanediol **3** was selectively brominated to give an 80% yield of bromoalcohol **4** with aqueous hydrobromic acid and toluene under reflux.[9] Compound **4** was then treated with 4 equiv of lithiated 3-picoline to deliver building block **2** in 69% yield, demonstrating that compound **2** could be synthesised directly from **4** without the use of a protecting group. Alcohol **2** was subjected to a Mitsunobu reaction with phthalimide[10] to afford **5** in 79% yield and removal of the phthaloyl protecting group from **5** with hydrazine hydrate in ethanol[10] gave amine **6** in 96% yield (Scheme 1).

Interestingly, compound **6** is itself a natural product called theonelladin C. It is an antineoplastic alkaloid that was previously isolated by Kobayashi et al.[11] from the marine sponge *Theonella swinhoei* and its synthesis has been reported in the literature.[12,14] Rao et al. reported two slightly different synthesis of **6**[12a] from 3-(3-pyridyl)-1-propanol, using the Wittig reaction as the key C–C bond forming reaction. Teubner and Gerlach completed a six-step synthesis of **6**,[12b] using the Grignard reaction as the key C–C bond forming reaction. An interesting palladium catalysed three component coupling reaction was utilised by Larock et al. in the synthesis of **6**,[12c,d] however, all these components needed to be synthesised separately. The Marazano group[14] prepared compound **6** in five steps from

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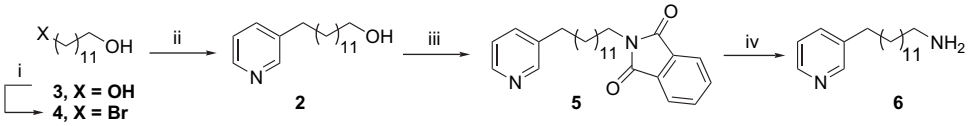


Scheme 1. Reagent and conditions: (i) $HBr_{(aq)}$, toluene, reflux, 80%; (ii) 3-picoline (4 equiv), LDA (4 equiv), DMPU (4 equiv), THF, −78 °C to rt, 69%; (iii) PPh_3, DIAD, phthalimide, 0 °C to rt, 79%; (iv) $N_2H_4 \cdot H_2O$, ethanol, reflux, 96%.

13-bromo-1-(tetrahydropyranyloxy)tridecane, a compound that is not commercially available. The synthesis of compound **6** presented in Scheme 1 is possibly the shortest as it is only a four-step synthesis and all the required reagents are commercially available.

The synthesis of viscosaline (**1**) continued with the conjugate addition of amine **6** to *tert*-butyl acrylate, in toluene[13] under reflux, to give crude **7**. Compound **7** was not purified but treated with di-*tert*-butyl dicarbonate, in dichloromethane, to afford **8** in 85% yield over two steps. Reaction of pyridine **8** with 1-chloro-2,4-dinitrobenzene in methanol[14] under reflux delivered Zincke salt **9** in 89% yield. Upon mixing solutions of Zincke salt **9** and amine **6**, in *n*-butanol, a red solution was formed, which quickly decolourised upon heating under reflux. Purification of the crude reaction mixture, through gradient elution chromatography, gave pyridinium salt **10** in 61% yield. The global deprotection of **10** was effected by stirring **10** in neat trifluoroacetic acid to afford viscosaline (**1**), in near quantitative yield, which was found to be spectroscopically pure (Scheme 2).

The ^{1}H NMR of synthetic **1** in DMSO-d_6 was indistinguishable from that of the literature spectra between the region of δ 0–5. However some differences were observed between the two spectra in the region of δ 6.8–9.2. This was not surprising as Volk and Köck observed that the ^{1}H NMR chemical shifts of the protonated pyridine ring varied between all the investigated samples of natural viscosaline.[15] To prove that synthetic **1** was identical to natural viscosaline, synthetic **1** was subjected to an ESI-MS/MS experiment. The mass spectra obtained showed good match with that of the literature spectra. Thus, this confirmed that the structure of synthetic **1** is identical to that of natural viscosaline (Fig. 1).

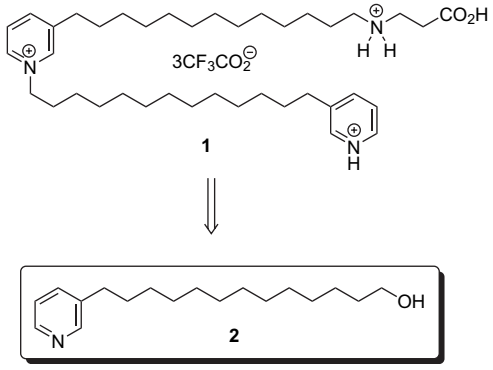


Figure 1. Retrosynthetic analysis of viscosaline (**1**).

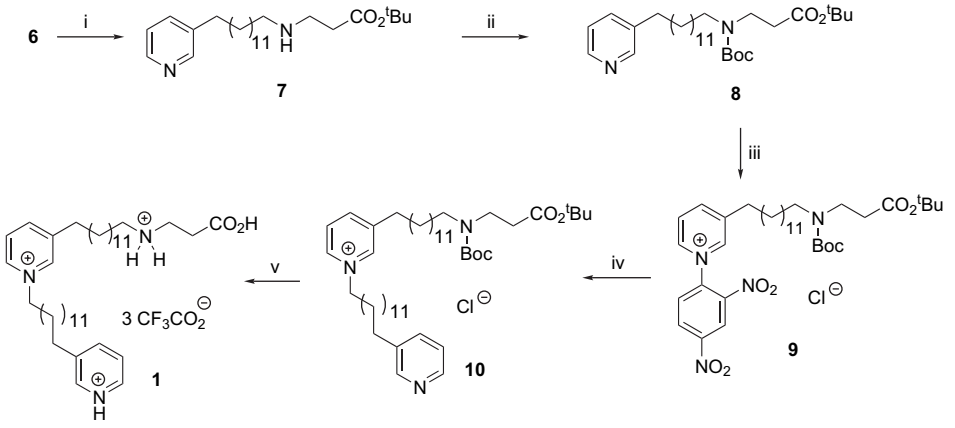
3. Conclusion

An expeditious synthesis of the marine sponge alkaloid theonelladin C (**6**) has been completed. The synthesis of the Arctic sponge alkaloids viscosaline (**1**) has been achieved through the use of Zincke salt/amine coupling chemistry. In addition we have streamlined the preparation of known compound **2** from four to two steps. This modified protocol should be applicable to the preparation of the homologues of **2** and thereby potentially improving the efficiency for the synthesis of various 3-alkyl pyridine or 3-alkylpyridinium alkaloids.

4. Experimental

4.1. General

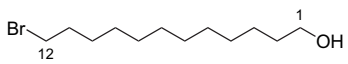
All melting points were measured on a Leica Galen III micro hot stage microscope and are uncorrected. IR spectra



Scheme 2. (i) *tert*-Butyl acrylate, toluene, reflux; (ii) (^{t}BuOC═O)$_2$O, CH_2Cl_2, 85% over two steps; (iii) 1-chloro-2,4-dinitrobenzene, MeOH, reflux, 89%; (iv) **6**, ^{n}BuOH, heat, 61%; (v) CF_3CO_2H, rt, 99%.

were recorded on a Bruker Tensor 27 Fourier transform spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using Bruker DQX400 or Bruker AVC500 spectrometers, respectively, in $CDCl_3$, CD_3OD or DMSO-d_6. Low-resolution mass spectra (LRMS) were recorded on a Fisons Platform mass spectrometer for ESI mode spectra and a Micromass GCT mass spectrometer for CI mode spectra. High-resolution mass spectra (HRMS) were recorded on either a Bruker MicroTOF electrospray mass spectrometer, a Bruker ApexQ FTICR mass spectrometer or a Micromass GCT mass spectrometer. Column chromatography was accomplished using silica gel (Prolabo silica gel 60, 35–75 mm particle size, 200–400 mesh) as the stationary phase.

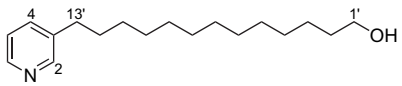
4.1.1. 12-Bromododecan-1-ol (4).



To a solution of 1,12-dodecanediol **3** (2.01 g, 9.9 mmol) in toluene (30 mL), was added an aqueous solution of HBr (1.33 mL, 9.0 M, 12 mmol) and the resulting mixture heated at reflux until the reaction was shown to be complete by TLC analysis (ca. 18 h). During reaction a flat balloon was used to create a sealed but expandable system to prevent the escape of HBr and ensure complete reaction. The mixture was washed with $NaOH_{(aq)}$ (1 M, 30 mL), brine (30 mL) and a phosphate buffer (pH 7, 30 mL). The resulting organic phase was dried over anhydrous Na_2SO_4 and the solvents removed in vacuo to give a pale yellow oil, which slowly solidified upon standing. The crude oil was purified through flash column chromatography (Et_2O/petroleum ether 2:3) to give the desired bromoalcohol **4** as a colourless oil (2.11 g, 80%), which slowly solidified upon standing.

R_f 0.28 (Et_2O/petroleum ether 1:1); mp 28–30 °C; IR ν_{max} (KBr disc) cm^{-1} 3297 (br s, O–H), 2919 (s, C–H), 2854 (s, C–H), 1462 (s), 1335 (w), 1288 (w), 1255 (w), 1232 (w), 1207 (w), 1185, 1122 (w), 1072 (s), 1029 (s), 985 (w), 938 (w), 892 (w), 719 (s), 650 (s); ^{1}H NMR (400.2 MHz, $CDCl_3$) δ: 1.25–1.48 (m, 16H, CH_2), 1.53–1.61 (m, 2H, H-2), 1.81–1.91 (m, 2H, H-11), 3.41 (t, J=7.0 Hz, 2H, H-12), 3.65 (t, 2H, J=6.5 Hz, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 25.72, 28.16, 28.74, 29.40, 29.49, 29.50, 29.56, 32.79, 32.82 (10C, CH_2), 34.06 (C-12), 63.07 (1C, C-1); LRMS (CI, NH_3) m/z found 284 (MNH_4^+, ^{81}Br, 98%), 282 (MNH_4^+, ^{79}Br, 98%), 137 (39), 135 (38), 97 (32), 83 (27), 69 (23); HRMS found $C_{12}H_{25}Br^{79}NaO$ [M+Na$^+$] at 287.0981 (calculated 287.0981) and $C_{12}H_{25}Br^{81}NaO$ [M+Na$^+$] at 298.0964 (calculated 289.0961).

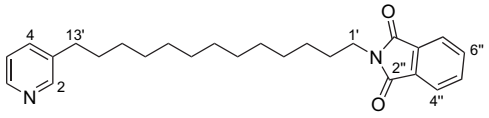
4.1.2. 3-(1′-Hydroxytridec-13′-yl)pyridine (2).



To a solution of ^{i}PrNH$_2$ (11.1 mL, 79 mmol) in anhydrous THF (30 mL) and under argon, was added ^{n}BuLi (1.4 M, 57 mL, 79 mmol) dropwise at 0 °C. The resulting solution was stirred for 30 min at the same temperature after which DMPU (9.6 mL, 79 mmol) was added, and the mixture stirred at 0 °C for a further 15 min. To the resulting solution was added 3-methylpyridine (7.7 mL, 79 mmol) in anhydrous THF (30 mL) and the mixture stirred at 0 °C for 30 min. At this point the reaction was cooled to −78 °C and a solution of 12-bromododecan-1-ol **4** (5.3 g, 20 mmol) in anhydrous THF (30 mL) was added over a period of 5 min. The mixture was allowed to warm to room temperature whilst stirring for a further 18 h after which the reaction was quenched through addition of a solution of NH_4Cl (40 mL, satd) and water (40 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The organic phases were combined and dried over $MgSO_4$, then concentrated in vacuo. The resulting crude residue was purified through flash column chromatography (EtOAc/petroleum ether 3:7) to give the desired alkyl pyridine **2** as a pale yellow solid (3.8 g, 69%).

R_f 0.29 (EtOAc/petroleum ether 4:6); mp 47–49 °C; IR ν_{max} (KBr disc) cm^{-1} 3271 (m), br (OH), 2924 (s), 2852 (s), 1575 (m), 1467 (m), 1423 (m), 1074 (m), 1026 (m); ^{1}H NMR (400.2 MHz, $CDCl_3$) δ: 1.21–1.40 (m, 18H, CH_2), 1.52–1.68 (m, 4H, H-2′,12′), 2.61 (t, J=7.5 Hz, 2H, H-13′), 3.64 (t, J=6.5 Hz, 2H, H-1′), 7.22 (dd, J=5.0, 8.0 Hz, 1H, H-5), 7.46–7.55 (m, 1H, H-4), 8.37–8.50 (m, 2H, H-2,6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 25.76, 29.09, 29.36, 29.43, 29.48, 29.53, 29.55, 29.57, 31.09, 32.85, 33.00 (12C, CH_2), 62.98 (1C, C-1′), 123.33 (1C, C-5), 136.09 (1-C, C-4), 138.16 (1C, C-3), 146.83 (1C, C-6), 149.62 (1C, C-2); LRMS (ESI +ve) m/z 278 ([M+H]$^+$, 100%); HRMS found $C_{18}H_{32}NO$ [M+H$^+$] at 278.2486 (calculated 278.2484).

4.1.3. 3-(1′-[Isoindoline-2″,9″-dione]tridec-13′-yl)pyridine (5).

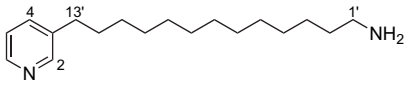


A solution of 3-(1′-hydroxytridec-13′-yl)pyridine **2** (0.25 g, 0.9 mmol), triphenylphosphine (0.35 g, 1.4 mmol) and phthalimide (0.16 g, 1.1 mmol) in THF (5.5 mL) was cooled to 0 °C and to this was added DIAD (0.19 mL, 1.0 mmol) in THF (2.7 mL). The mixture was allowed to warm to room temperature and stirred for a total of 18 h. At this point the mixture was concentrated to remove the majority of the solvent then triturated with Et_2O (3×10 mL) to remove triphenylphosphine oxide. The resulting solution was concentrated in vacuo, and the crude residue purified through flash column chromatography (EtOAc/petroleum ether 1:1), to afford the desired phthalimide derivative **5** as a white solid (0.29 g, 79%).

R_f 0.32 (EtOAc/petroleum ether 1:1); mp 59–61 °C; IR ν_{max} (KBr disc) cm^{-1} 2919 (s, C–H), 2849 (s, C–H), 1769 (s, C═O), 1716 (s, C═O), 1573 (w), 1467 (m), 1433 (m), 1397 (s), 1367 (m), 1337 (m), 1188 (m), 1055 (m), 1028 (w), 993 (w), 901 (w), 871 (w), 791 (w), 721 (s), 627 (w), 529 (m); ^{1}H NMR (400.2 MHz, $CDCl_3$) δ: 1.19–1.37 (m,

18H, CH_2), 1.54–1.71 (m, 4H, H-2′,12′), 2.58 (t, J=7.5 Hz, 2H, H-13′), 3.66 (t, J=7.0 Hz, 2H, H-1′), 7.18 (dd, J=8.0, 5.0 Hz, 1H, H-5), 7.47 (dt, J=8.0, 2.0 Hz, 1H, H-4), 7.69 (dd, J=5.5, 3.0 Hz, 2H, H-4″,7″), 7.82 (dd, J=5.5, 3.0 Hz, 2H, H-5″,6″), 8.39–8.45 (m, 2H, H-2,6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 26.86, 28.61, 29.15, 29.19, 29.40, 29.47, 29.53, 29.57, 31.15 (11C, CH_2), 33.02 (1C, C-13′), 38.07 (1C, C-1′), 123.12 (3C, C-5, C-4″,7″), 132.17 (2C, C-3″,8″), 133.82 (2C, C-5″,6″), 135.77 (1C, C-4), 137.98 (1C, C-3), 147.12 (1C, C-6), 149.94 (1C, C-2), 168.45 (2C, C-2″,9″); LRMS (ESI +ve) m/z 407 ([M+H]$^+$, 100%); HRMS found $C_{26}H_{35}N_2O_2$ at 407.2698 (calculated 407.2699).

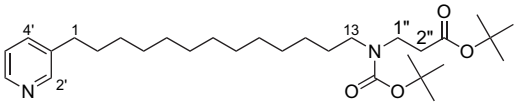
4.1.4. 3-(1′-Amino-tridec-13′-yl)pyridine (6).



3-(1′-[Isoindoline-1″,3″-dione]tridec-13′-yl)pyridine **5** (0.12 g, 0.3 mmol) was dissolved in EtOH (5 mL) and to this solution was added hydrazine hydrate (0.17 mL, 3.5 mmol). The mixture was heated at reflux for 18 h at which point TLC analysis showed the starting material to be consumed. A white precipitate formed during the reaction dissolved upon dilution with $NaOH_{(aq)}$ (1 M, 15 mL). The aqueous solution was extracted with DCM (5×15 mL), and the organic extracts combined, washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The solvents were removed in vacuo to give the desired amine **6** as a waxy solid (0.08 g, 96%), which required no further purification.

Mp 69–70 °C; IR ν_{max} (KBr) cm^{-1} 3363 (m, N–H), 3290 (m, N–H), 3028, 2927, 2854, 1575, 1466, 1309, 1026; ^{1}H NMR (400.2 MHz, $CDCl_3$) δ: 1.22–1.37 (m, 18H, CH_2), 1.48 (quintet, J=7.0 Hz, 2H, H-2′), 1.61 (quintet, J=7.5 Hz, 2H, H-12′), 1.80 (br s, 2H, NH_2), 2.60 (t, J=7.5 Hz, 2H, H-13′), 2.71 (br s, 2H, H-1′), 7.20 (dd, J=8.0, 5.0 Hz, 1H, H-5), 7.49 (dt, J=8.0, 2.0 Hz, 1H, H-4), 8.41–8.45 (m, 2H, H-2,6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 26.82, 29.11, 29.37, 29.40, 29.50, 29.56, 29.57, 29.58, 31.11, 32.80, 32.98 (13C, CH_2), 123.18 (1C, C-5), 135.74 (1C, C-4), 137.94 (1C, C-3), 147.09 (1C, C-6), 149.90 (1C, C-2); LRMS (ESI +ve) m/z 277 ([M+H]$^+$, 100%); HRMS found $C_{18}H_{33}N_2$ at 277.2644 (calculated 277.2644).

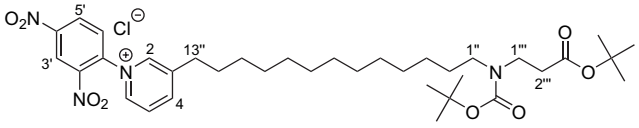
4.1.5. 3-(1′-[{3″-*tert*-Butoxy-3″-oxopropyl}{*tert*-butoxycarbonyl}amino]tridec-13′-yl)pyridine (8).



To a solution of 3-(1′-amino-tridec-13′-yl)pyridine **6** (1.00 g, 3.6 mmol) in toluene (30 mL) was added *tert*-butyl acrylate (0.53 mL, 3.6 mmol, 1.0 equiv) and the solution heated at reflux for 4 h. The solution was allowed to cool and the solvent partially removed in vacuo. To this crude mixture were added DCM (20 mL) and di-*tert*-butyl dicarbonate (1.19, 5.5 mmol). The reaction was stirred at room temperature for 17 h then the reaction was diluted with water, and extracted into DCM (3×15 mL). The organic extracts were combined and washed with $KHSO_4$ (15 mL, aq 10%) and brine (15 mL) and dried over anhydrous $MgSO_4$. The solvents were removed in vacuo and the crude residue purified through flash column chromatography (MeOH/DCM ether 2:8) to yield the desired product **8** as a yellow oil (1.54 g, 85%).

R_f 0.18 (MeOH/DCM 2:8); IR ν_{max} (thin film) cm^{-1} 2980 (s, C–H), 2925 (s, C–H), 2855 (s, C–H), 1798 (s, C=O), 1758 (s, C=O), 1715 (s, C=O), 1680 (s, C=O), 1560 (w), 1450 (s), 1277 (s), 1350 (s), 1230 (s), 1135 (s), 1005 (s), 928 (w), 823 (w), 750 (w), 688 (w); ^{1}H NMR (400.2 MHz, CD_3OD) δ: 1.24–1.37 (m, 18H, CH_2), 1.44 (s, 9H OC(CH_3)$_3$), 1.45 (s, 9H, OC(CH_3)$_3$), 1.47–1.56 (m, 2H, H-12), 1.58–1.67 (m, 2H, H-2), 2.47 (t, J=7.0 Hz, 2H, H-2″), 2.64 (t, J=8.0 Hz, 2H, H-1), 3.20 (t, J=7.5 Hz, 2H, H-13), 3.43 (t, J=7.0 Hz, 2H, H-1″), 7.33 (ddd, J=8.0, 5.0, 0.5 Hz, 1H, H-5′), 7.66 (ddd, J=8.0, 2.0, 1.5 Hz, 1H, H-4′), 8.35 (dd, J=5.0, 1.5 Hz, 1H, H-6′), 8.37 (d, J=1.5 Hz, 1H, H-2′); ^{13}C NMR (100.6 MHz, CD_3OD) δ: 27.94, 30.36, 30.56, 30.63, 30.79, 30.80, 30.82, 30.85, 32.40 (11C, CH_2), 28.60 (3C, OC(CH_3)$_3$), 28.98 (3C, OC(CH_3)$_3$), 33.93 (1C, C-1), 35.58 (1C, C-2″), 44.54 (1C, C-1″), 48.75 (1C, C-13), 80.76 (1C, OC(CH_3)$_3$), 81.62 (1C, OC(CH_3)$_3$), 125.09 (1C, C-5′), 138.08 (1C, C-4′), 140.07 (1C, C-3′), 147.55 (1C, C-6′), 150.13 (1C, C-2′), 156.91 (1C, NC(=O)O), 172.61 (1C, CC(=O)O); LRMS (ESI +ve) m/z 505 ([M+H]$^+$, 100%); HRMS found $C_{30}H_{53}N_2O_4$ at 505.3995 (calculated 505.4000).

4.1.6. 1-(2′,4′-Dinitrophenyl)-3-(1″-[{3‴-*tert*-butoxy-3‴-oxopropyl}{*tert*-butoxycarbonyl}amino]tridec-13″-yl)-pyridinium chloride (9).

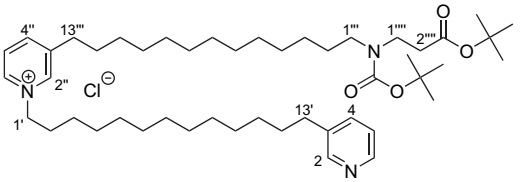


A solution of 3-(1′-[{3″-*tert*-butoxy-3″-oxopropyl}{*tert*-butoxycarbonyl}amino]tridec-13′-yl)pyridine **8** (0.23 g, 0.46 mmol) in MeOH (1.0 mL) was treated with 2,4-dinitrochlorobenzene (0.19 g, 0.94 mmol, 2.0 equiv) and the mixture heated under reflux for 18 h. Removal of the solvent from the resulting mixture gave a yellow oil, which was purified through flash column chromatography (5–20% MeOH in DCM) to give the desired pyridinium salt **9** as a thick yellow oil (0.29 g, 89%).

R_f 0.20 (MeOH/DCM 2:8); IR ν_{max} (thin film) cm^{-1} 2926 (s, C–H), 2851 (s, C–H), 1723 (s, C=O), 1609 (s, C=O), 1458 (m), 1411 (m), 1248 (w), 1153 (s); ^{1}H NMR (400.2 MHz, CD_3OD) δ: 1.25–1.50 (m, 18H, CH_2), 1.47 (s, 18H, OC(CH_3)$_3$), 1.50–1.59 (m, 2H, H-2″), 1.76–1.90 (m, 2H, H-12″), 2.45–2.56 (m, 2H, H-2‴), 3.03 (t, 2H, J=7.5 Hz, H-13″), 3.22 (t, 2H, J=7.5 Hz, H-1″), 3.45 (t, 2H, J=7.0 Hz, H-1‴), 8.37 (dd, 1H, J=8.0, 6.0 Hz, H-5), 8.39 (d, 1H, J=8.5 Hz, H-6′), 8.85 (d, 1H, J=8.0 Hz, H-4), 8.93 (dd, 1H, J=8.5, 2.5 Hz, H-5′), 9.23 (s, 1H, H-6), 9.24 (d, 1H, J=2.5 Hz, H-3′), 9.33 (s, 1H, H-2); ^{13}C NMR

(100.6 MHz, CD_3OD) δ: 27.78, 29.97, 30.41, 30.60, 30.63, 30.65, 30.67, 30.70 (10C, CH_2), 28.61 (3C, $OC(CH_3)_3$), 29.02 (3C, $OC(CH_3)_3$), 31.43 (1C, C-12″), 33.61 (1C, 13″), 35.64 and 36.32 (rotamers, 1C, C-2‴), 44.32 and 44.56 (rotamers, 1C, C-1‴), 48.64 (1C, C-1″), 80.87 (1C, $OC(CH_3)_3$), 81.96 (1C, $OC(CH_3)_3$), 123.15 (1C, C-3′), 129.22 (1C, C-5), 131.42 (1C, C-5′), 132.83 (1C, C-6′), 139.98 (1C, C-1′), 144.33 (1C, C-3), 144.49 (1C, C-6), 145.70 (1C, C-2′), 146.10 (1C, C-2), 149.88 (1C, C-4′), 150.79 (1C, C-4), 156.93 (1C, NC(=O)O), 172.92 (1C, CC(=O)O); LRMS (ESI +ve) *m/z* 671 (M^+, 100%), 505 ([M+H−DNB]$^+$, 50%); HRMS found $C_{36}H_{55}N_4O_8$ at 671.4014 (calculated 671.4014).

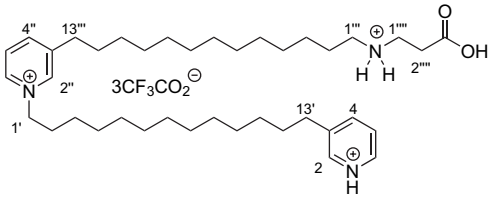
4.1.7. 3-(1′-[3″-{1‴-([3⁗-*tert*-Butoxy-3⁗-oxopropyl]-[*tert*-butoxycarbonyl]amino)tridec-13‴-yl}pyridinium-1‴-yl chloride]tridec-13′-yl)pyridine (10).



A solution of 1-(2′,4′-dinitrophenyl)-3-(1″-[{3‴-*tert*-butoxy-3‴-oxopropyl}{*tert*-butoxycarbonyl}amino]tridec-13″-yl)-pyridinium chloride **9** (0.29 g, 0.41 mmol) in ^{n}BuOH (8 mL) was treated with a solution of 3-(1′-amino-tridec-13′-yl)pyridine (0.13 g, 1.2 equiv, 0.47 mmol) in ^{n}BuOH (2 mL) upon which a deep red solution was formed. This solution was heated under reflux for 20 min after which the red colour had disappeared. The solvents were removed from the mixture in vacuo and the resulting crude oil was purified by flash column chromatography (5–20% MeOH in DCM) to give the desired adduct **10** as a thick yellow oil (0.20 g, 61%).

R_f 0.21 (MeOH/DCM 2:8); IR ν_{max} (thin film) cm^{-1} 2976 (m, C–H), 2927 (s, C–H), 2855 (s, C–H), 1728 (s, C=O), 1695 (s, C=O), 1614 (s), 1545 (s), 1458 (m), 1416 (m), 1366 (s), 1345 (s), 1253 (m), 1155 (s), 909 (w); ^{1}H NMR (400.2 MHz, CD_3OD) δ: 1.25–1.41 (m, 36H, CH_2), 1.45 (s, 9H, $OC(CH_3)_3$), 1.46 (s, 9H, $OC(CH_3)_3$), 1.48–1.57 (m, 2H, H-2‴), 1.59–1.69 (m, 2H, H-12′), 1.63 (quintet, 2H, *J*=7.5 Hz, H-12‴), 1.98–2.08 (m, 2H, H-2′), 2.47 (t, 2H, *J*=7.0 Hz, H-2⁗), 2.65 (t, 2H, *J*=7.5 Hz, H-13′), 2.90 (t, 2H, *J*=7.5 Hz, H-13‴), 3.20 (t, 2H, *J*=7.5 Hz, H-1‴), 3.43 (t, 2H, *J*=7.0 Hz, H-1⁗), 4.66 (t, 2H, *J*=7.5 Hz, H-1′), 7.36 (dd, 1H, *J*=8.0, 5.0 Hz, H-5), 7.69 (dt, 1H, *J*=8.0, 2.0 Hz, H-4), 8.05 (dd, 1H, *J*=8.0, 6.0 Hz, H-5″), 8.33–8.40 (m, 2H, H-2,6), 8.48 (d, 1H, *J*=8.0 Hz, H-4″), 8.91 (d, 1H, *J*=6.0 Hz, H-6″), 9.00 (s, 1H, H-2″); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 27.26, 27.96, 30.22, 30.33, 30.56, 30.62, 30.73, 30.79, 30.82, 30.84, 30.86, 31.69, 32.41, 32.64 (22C, CH_2), 28.55 (3C, $OC(CH_3)_3$), 28.94 (3C, $OC(CH_3)_3$), 33.61 (1C, C-13‴), 33.92 (1C, C-13′), 35.64 (1C, C-2⁗), 44.51 (1C, C-1⁗), 48.78 (1C, C-1‴), 62.97 (1C, C-1′), 80.92 (1C, $OC(CH_3)_3$), 81.79 (1C, $OC(CH_3)_3$), 125.24 (1C, C-5), 129.11 (1C, C-5″), 138.25 (1C, C-4), 140.24 (1C, C-3), 143.47 (1C, C-6″), 145.34 (1C, C-2″), 145.72 (1C, C-3″), 146.70 (1C, C-4″), 147.57 (1C, C-6), 150.11 (1C, C-2), 157.07 (1C, NC(=O)O), 172.78 (1C, CC(=O)O); LRMS *m/z* 764 (M^+, 100%); HRMS found $C_{48}H_{82}N_3O_4$ at 764.6296 (calculated 764.6300).

4.1.8. Viscosaline (1).



3-(1′-[3″-{1‴-([3⁗-*tert*-Butoxy-3⁗-oxopropyl][*tert*-butoxy-carbonyl]amino)tridec-13‴-yl}pyridinium-1″-yl chloride]-tridec-13′-yl)pyridine **10** (19.4 mg, 0.0024 mmol) was treated with neat trifluoroacetic acid (4 mL) and stirred at room temperature for 4 h. The excess trifluoroacetic acid was removed in vacuo. The residue obtained was dissolved in water (ca. 2 mL) and subjected to freeze drying. This process was repeated twice to give the desired product (22.7 mg, 99%).

R_f 0.1 (MeOH/DCM 2:8); IR ν_{max} (thin film) cm^{-1} 2927 (s, C–H), 2855 (s, C–H), 1679 (s, C=O), 1428 (w), 1203 (s), 1133 (s), 835 (w), 801 (m), 722 (m); ^{1}H NMR (400.2 MHz, CD_3OD) δ: 1.26–1.43 (m, 36H, CH_2), 1.63–1.78 (m, 6H, H-2‴,12′,12‴), 1.96–2.04 (m, 2H, H-2′), 2.74 (t, 2H, *J*=7.0 Hz, H-2⁗), 2.82–2.92 (m, 4H, H-1‴,13′), 3.01 (t, 2H, *J*=8.0 Hz, H-13‴), 3.25 (t, 2H, *J*=6.5 Hz, H-1⁗), 4.59 (t, 2H, *J*=7.5 Hz, H-1′), 7.97–8.05 (m, 2H, H-5,5″), 8.44 (d, 1H, *J*=8.0 Hz, H-4), 8.52 (d, 1H, *J*=8.0 Hz, H-4″), 8.71 (d, 1H, *J*=5.0 Hz, H-6), 8.76 (s, 1H, H-2), 8.82 (d, 1H, *J*=6.0 Hz, H-6″), 8.90 (s, 1H, H-2″); ^{13}C NMR (100.6 MHz, CD_3OD) δ: 27.25, 27.33, 27.66, 30.24, 30.29, 30.31, 30.35, 30.58, 30.65, 30.67, 30.79, 30.87 (19C, CH_2), 31.19 (1C, C-2⁗), 31.74 and 31.77 (2C, C-12′,12‴), 32.67 (1C, C-2′), 33.64 (2C, C-1‴,13′), 33.68 (2C, C-1‴,13′), 44.52 (1C, C-1⁗), 49.28 (1C, C-13‴), 63.11 (1C, C-1′), 128.42 and 129.10 (2C, C-5,5″), 140.41 (1C, C-6), 142.24 (1C, C-2), 143.43 (1C, C-6″), 145.10 (1C, C-3), 145.34 (1C, C-3″), 145.96 (1C, C-2″), 146.73 (1C, C-4), 148.13 (1C, C-4″), 158.88 (1C, C-3⁗); HRMS found $C_{39}H_{66}N_3O_2$ at 608.5153 (calculated 608.5150).

^{1}H NMR (500.3 MHz, DMSO-d_6) δ: 1.18–1.31 (m, 36H, CH_2), 1.51–1.59 (m, 4H, H-12′,2‴), 1.59–1.66 (m, 2H, H-12‴), 1.86–1.95 (m, 2H, H-2′), 2.55–2.64 (m, 4H, H-13′, 2⁗), 2.78 (t, *J*=7.5 Hz, 2H, H-13‴), 2.88 (t, *J*=7.0 Hz, 2H, H-1‴), 3.09 (t, *J*=7.0 Hz, 2H, H-1⁗), 4.54 (t, *J*=7.0 Hz, 2H, H-1′), 7.30 (br s, 1H, H-5), 7.61 (d, *J*=7.5 Hz, 1H, H-4), 8.07 (dd, *J*=8.0, 6.0 Hz, 1H, H-5″), 8.40 (br s, 2H, H-2,6), 8.47 (d, *J*=8.0 Hz, 1H, H-4″), 8.93 (d, *J*=6.0 Hz, 1H, H-6″), 9.02 (s, 1H, H-2″); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ: 25.30, 25.45, 25.88, 28.29, 28.48, 28.74, 28.83, 28.93, 28.96, 29.06, 29.75, 30.56, 30.59, 31.62, 32.06, 39.01, 39.18, 39.34, 39.51, 39.68, 39.84, 40.01 (25C, CH_2), 42.56 (1C, C-1⁗), 46.80 (1C, C-1‴), 60.64 (1C, C-1′), 123.43 (1C, C-5), 127.55 (1C, C-5″), 135.74 (1C, C-4), 137.64 (1C, C-3), 142.24 (1C, C-6″), 143.02 (1C, C-3″), 143.94 (1C, C-2″), 145.07 (1C, C-4″), 146.97 (1C, C-6), 149.47 (1C, C-2), 171.9 (1C, CC(=O)O).

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Supplementary data

The ^{1}H, ^{13}C NMR spectra and ESI-MS/MS analysis of synthetic viscosaline (**1**) can be found in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.04.020.

References and notes

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15. See supporting information of Ref. 4. It should be noted that although viscosaline (**1**) was depicted as a singly charged cationic compound in Ref. 4, this is slightly incorrect. Viscosaline was isolated by preparative HPLC using an acetonitrile/water gradient elution profile of 5% acetonitrile (containing 0.1% trifluoroacetic acid) to 35% acetonitrile. Therefore natural viscosaline should be isolated as its tris-trifluoroacetate salt with all the available basic nitrogen sites being protonated.