Supporting Information

First Total Synthesis and Structural Confirmation of Fluvirucinine A_2 via an Iterative Ring Expansion Strategy

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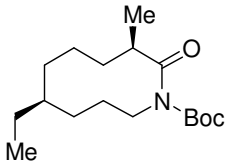
Contents

General Experimental

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and Et_2O were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, acetonitrile and pyridine were freshly distilled from calcium hydride. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100 °C. Air and moisture sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using direct visualization, UV at 254 nm or 356 nm, p-anisaldehyde, ceric ammonium molybdate, potassium permanganate, and iodine vapor over sand. Melting points were measured on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with JASCO DIP-1000 digital polarimeter using 100 mm cell of 2 mL capacity. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Low-resolution electrospray ionization (ESI) mass spectra were obtained with Finnigan LCQ mass spectrometer. Low and high-resolution fast atom bombardment (FAB) and electron impact (EI) mass spectra were obtained with JEOL JMS-700 instrument. High-resolution chemical ionization (CI) mass spectra were obtained with JEOL JMS-AX 505WA instrument. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 (600 MHz), Avance 500 (500 MHz), Avance 400 (400 MHz), or JEOL JNM-LA 300 spectrometer as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$: ^1H-NMR, δ 7.24 ppm, ^{13}C-NMR, δ 77.0 ppm). ^1H-NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad and/or multiple resonances), number of protons, and coupling constant in hertz (Hz).

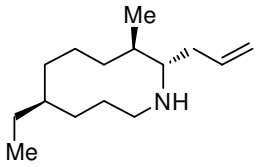
Total Synthesis of Fluvirucinine A_2

***tert*-butyl (3*R*,7*S*)-7-ethyl-3-methyl-2-oxo-1-azecanecarboxylate (4)**



To a solution of lactam **8**[1] (450 mg, 2.3 mmol) in THF (40 mL) was added *n*-BuLi (1.6M in hexane, 1.7 mL, 2.7 mmol) at –78 °C . After the mixture was stirred at –78 °C for 10 min, a solution of *t*-butyl dicarbonate (746 mg, 3.4 mmol) in THF (10 mL) was added and the mixture was stirred at –78 °C for 2 h. The reaction was quenched with saturated NH_4Cl, and the mixture was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane only to 5% EtOAc in hexane) to afford the N-Boc-Lactam **4** (670 mg, 2.3 mmol, 98%) as a colorless oil; $[\alpha]_D^{20}$ –72.6 (0.45, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 2933, 1729, 1697, 1456 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.19 (ddd, 1H, *J* = 13.4, 8.8, 4.3 Hz), 3.61 (ddd, *J* = 17.8, 10.7, 6.6 Hz), 3.48 (ddd, *J* = 13.9, 6.1, 4.2 Hz), 1.79 – 1.56 (m, 5H), 1.52 (s, 9H), 1.43 – 1.15 (m, 8H), 1.12 (d, 3H, *J* = 6.8 Hz), 0.84 (t, 3H, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 181.3, 153.7, 82.3, 45.8, 41.1, 37.4, 31.2, 30.4, 29.4, 28.9, 28.0, 23.3, 20.5, 16.6, 11.8; HR-MS (CI+) calcd for $C_{17}H_{32}NO_3$ ($M+H^+$) 298.2382; found 298.2380.

***tert*-butyl (2*S*,3*R*,7*S*)-2-allyl-7-ethyl-3-methyl-1-azecanecarboxylate (3)**



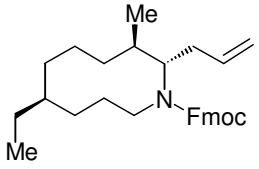
To a solution the lactam **4** (670 mg, 2.3 mmol) in CH_2Cl_2 (25 mL) was added DIBAL (1.0 M solution in toluene, 4.1 mL, 4.1 mmol) dropwise at –78 °C. After 1h, the reaction mixture was treated with pyridine (0.6 mL, 6.8 mmol) and then TMSOTf (1.0 mL, 5.6 mmol). The mixture was stirred at –78 °C for 10 min, and then slowly warmed to 0 °C, quenched with 15% aqueous sodium potassium tartrate (10 mL), and diluted with Et_2O.

[1] Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3545.

The resultant mixture was warmed to room temperature and stirred vigorously until two layers were completely separated. The mixture was extracted with Et_2O and combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5 to 10% EtOAc in hexane, silica gel deactivated with Et_3N) to afford *N,O*-acetal TMS ether **9** (769 mg, 2.0 mmol, 92%) as colorless oil.

To a solution of *N,O*-acetal TMS ether **9** (689 mg, 1.86 mmol) in CH_2Cl_2 (20 mL) were added tributylallyltin (1.2 mL, 3.7 mmol) and $BF_3 \cdot OEt_2$ (0.2 mL, 1.9 mmol) at – 78 °C. The reaction mixure was stirred for 30min, and then slowly warmed to room temperature. The mixture was stirred for 24 h, quenched with triethylamine and concentrated under reduced pressure. The residue was purified by flash column chromatography (17% EtOAc in hexane) to afford **3** (395 mg, 1.77 mmol, 95%) as colorless oil. This procedure directly afforded amine **3** from the *N,O*-acetal TMS ether **9** without Boc-deprotection step ; $[\alpha]_D^{20}$ +12.4 (*c* 0.21, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 2956, 2918, 1640, 1460, 1129 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.81 (ddt, 1H, *J* = 15.8, 11.3, 5.3 Hz), 5.04 – 4.99 (m, 2H), 3.07 (ddd, 1H, *J* = 12.6, 6.8, 3.9 Hz), 2.47 – 2.28 (m, 3H), 2.09 (dtd, 1H, *J* = 12.6, 6.6, 1.1 Hz), 1.82 – 1.05 (m, 15H), 0.91 (d, 3H, *J* = 6.8 Hz), 0.85 (t, 3H, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 135.6, 116.8, 61.3, 49.5, 37.3, 36.3, 35.6, 33.1, 33.0, 30.4, 29.2, 27.9, 19.4, 17.8, 12.0; HR-MS (FAB+) calcd. for $C_{15}H_{30}N$ ($M+H^+$) 224.2378; found 224.2385.

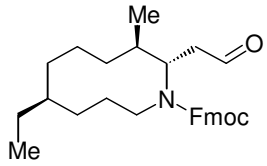
9*H*-fluoren-9-ylmethyl(2*S*,3*R*,7*S*)-2-allyl-7-ethyl-3-methyl-1-azecanecarboxylate (10)



To a solution of the amine **3** (288 mg, 1.29 mmol) in THF/H_2O (3:1, 36 mL) were added *N*-(9-Fluorenylmethoxy -carbonyl)succinimide (435 mg, 1.29 mmol) and Na_2CO_3 (273 mg, 2.58 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h, and THF was then removed under reduced pressure. The remaining aqueous

suspension was extracted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (17% EtOAc in hexane) to afford **10** (530 mg, 1.19 mmol, 92%) as a colorless oil; $[\alpha]_D^{20}$ + 4.74 (*c* 0.26, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 2957, 2919, 1695, 1469, 1419 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.74 – 7.73 (m, 2H), 7.59 – 7.53 (m, 2H), 7.38 – 7.26 (m, 4H), 5.65 (m, 0.5H), 5.41 (m, 0.5H), 4.96 – 4.74 (m, 2.5H), 4.51 (m, 1.5H), 4.20 (m, 1H), 3.76 (m, 0.3H), 3.51 (m, 0.5H), 2.81 (m, 0.2H), 2.36 (m, 1.5H), 1.94 (m, 0.5H), 1.78 – 0.97 (m, 13H), 1.56 (d, 3H, *J* = 6.6 Hz), 0.79 nd 0.45 (m, 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 157.2, 156.8, 144.2, 144.0, 141.5, 141.3, 141.2, 136.2, 134.9, 127.3, 126.9, 126.8, 124.6, 124.5, 124.0, 123.8, 119.6, 116.6, 116.4, 66.8, 66.1, 65.2, 57.4, 47.4, 47.2, 40.0, 37.7, 36.2, 35.8, 35.7, 35.4, 33.3, 32.8, 31.9, 31.4, 30.6, 30.1, 29.7, 28.8, 27.1, 26.7, 24.7, 23.6, 22.5, 18.8, 17.9, 17.2, 14.0, 11.9, 11.6; HR-MS (FAB+) calcd for $C_{30}H_{40}NO_2$ ($M+H^+$) 446.3059; found 446.3052.

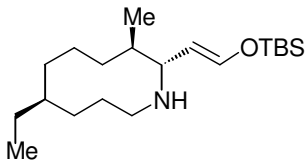
9*H*-fluoren-9-ylmethyl(2*S*,3*R*,7*S*)-7-ethyl-3-methyl-2-(2-oxoethyl)-1-azecanecarboxylate (18)



To a stirred solution of α-allylazacycle **10** (280 mg, 0.63 mmol) and 4-methylmorpholine *N*-oxide (221 mg, 1.89 mmol) in acetone/H_2O (3:1, 24 mL) at 0 °C was added OsO_4 (0.05 M in toluene, 0.4 mL, 0.019 mmol). The reaction mixture was allowed to room temperature, and stirred for additional 5 h. $NaIO_4$ (404 mg, 1.89 mmol) was added and the mixture was stirred at room temperature for 30 min. The reaction was quenched with Na_2SO_3 (5 eq) and extracted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (17% EtOAc in hexane) to afford aldehyde **18** (278 mg, 0.62 mmol, 98%) as a colorless oil; $[\alpha]_D^{20}$ –20.3 (*c* 0.24, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 2958, 2921, 1722, 1695, 1453 cm^{-1}; ^{1}H-

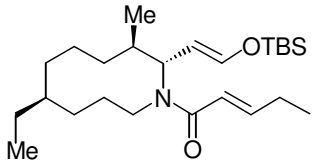
NMR ($CDCl_3$, 400 MHz) δ 9.62 (s, 0.5H), 9.22 (s, 0.5H), 7.73 (d, 2H), 7.56 (t, 2H), 7.39 – 7.29 (m, 4H), 4.80 (bs, 1H), 4.60 (dd, 0.5H, *J* = 8.5, 4.7 Hz), 4.47 (dd, 0.5H, *J* = 8.4, 4.1 Hz), 4.19 and 4.18 (s, 1H), 3.71 (bs, 0.5H), 3.12 (bs, 0.5H), 2.86 (bs, 0.5H), 2.65 (m, 1H), 2.15 (bs, 0.5H), 1.81 (bs, 0.5H), 1.64 (bs, 1H), 1.41 – 0.76 (m, 14H), 0.87 (d, 2.5H, *J* = 6.8 Hz), 0.78 (t, 3H, *J* = 7.0 Hz), 0.39 (bs, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ201.2, 200.8, 156.8, 156.5, 144.2, 144.1, 143.7, 141.7, 141.5, 141.4, 141.3, 127.5, 127.1, 127.0, 126.9, 126.8, 124.7, 124.5, 124.2, 124.1, 119.7, 119.6, 66.4, 65.6, 59.5, 58.8, 47.5, 47.2, 46.2, 36.9, 35.3, 31.8, 31.5, 30.0, 26.8, 20.1, 17.7, 17.1, 14.1, 14.0, 11.9, 11.7; HR-MS (FAB+) calcd for $C_{29}H_{38}NO_3$ ($M+H^+$) 448.2852; found 448.2857.

(2*R*,3*R*,7*S*)-2-((*E*)-2-[*tert*-butyl(dimethyl)silyl]oxyethenyl)-7-ethyl-3-methylazecane (11)



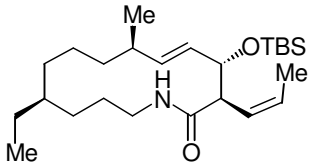
A mixture of aldehyde **18** (110 mg, 0.25 mmol), TBSCl (75 mg, 0.50 mmol) and DBU (0.37 mL, 2.5 mmol) in CH_2Cl_2 (7 mL) were stirred at 40 °C for 1 h. The reaction mixture was concentrated under reduced pressure to 0.5 mL. The residue was purified by flash chromatography on silica gel (only hexane to 10% EtOAc in hexane, silica gel deactivated with Et_3N) to give only (*E*)-enol ether **11** (82 mg, 0.24 mmol, 96%) as a colorless oil; $[\alpha]_D^{20}$ –18.1 (*c* 0.03, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 2925, 2856, 1650, 1539, 1458, 1257 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ6.22 (d, 1H, *J* = 11.9 Hz), 4.65 (dd, 1H, *J* = 11.6, 9.4 Hz), 2.89 (ddd, 1H, *J* = 9.9, 8.7, 2.6 Hz), 2.65 (t, 1H, *J* = 9.9 Hz), 2.55 (m, 1H), 1.94 (m, 1H), 1.83 (bs, 1H), 1.72 (m, 1H), 1.57 – 1.51 (m, 3H), 1.40 – 1.23 (m, 8H), 1.14 – 1.08 (m, 3H), 0.90 (s, 9H), 0.87 (d, 3H, *J* = 6.9 Hz), 0.86 (t, 3H, *J* = 7.4 Hz), 0.31 (s, 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) 141.1, 115.3, 60.1, 47.7, 37.8, 36.6, 33.2, 31.9, 30.3, 27.9, 25.7, 25.6, 19.8, 18.4, 17.4, 12.0, –5.2; HR-MS (FAB+) calcd for $C_{20}H_{42}NOSi$ ($M+H^+$) 340.3036; found 340.3041.

(*E*)-1-[(2*R*,3*R*,7*S*)-2-((*E*)-2-[*tert*-butyl(dimethyl)silyl]oxyethenyl)-7-ethyl-3-methylazecanyl]-2-penten-1-one (2b)



A mixture of *trans*-2-pentenoic acid (81 mg, 0.81 mmol) and 1-hydroxybenzotriazole (109 mg, 0.81 mmol) was suspended in CH_2Cl_2 (15 mL), cooled at 0 °C and treated with EDCI (155 mg, 0.81 mmol) and triethylamine (0.14 mL, 1.1 mmol). After the reaction mixture was stirred at room temperature for 30 min, amine **11** (92 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) was added by cannula. The reaction mixture was concentrated under reduced pressure to ca. 0.5 mL. The residue was purified by flash chromatography on silica gel (9% EtOAc in hexane, silica gel deactivated with Et_3N) to afford amide **2b** (109 mg, 0.26 mmol, 96%) as a colorless oil; $[\alpha]_D^{20}$ –57.5 (*c* 0.28, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 2926, 2856, 1656, 1462, 1258, 1168 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.87 and 6.81 (td, 1H, *J* = 15.2, 6.4 Hz), 6.31 (bs, 0.8H), 6.22 (d, 0.2H, *J* = 12.0 Hz), 6.19 and 6.17 (d, 1H, *J* = 15.2, 6.4 Hz), 5.28 (bs, 0.6H), 4.90 (dd, 0.4H, *J* = 12.0, 9.2 Hz), 3.68 – 2.68 (bm, 2H), 2.19 (qd, 2H, *J* = 7.2, 6.4 Hz), 2.02 – 1.10 (m, 16H), 1.03 (t, 3H, *J* = 7.2 Hz), 1.01 – 0.84 (m, 3H), 0.88 and 0.87 (s, 9H), 0.84 and 0.83 (t, 3H, *J* = 6.8 Hz), 0.10 and 0.09 (s, 3H), 0.09 and 0.08 (s, 3H); HR-MS (FAB+) calcd for $C_{25}H_{48}NO_2Si$ ($M+H^+$) 422.3454; found 422.3457.

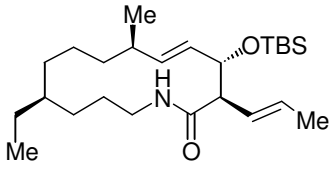
(3*R*,4*S*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-7-methyl-3-[(*Z*)-1-propenyl]-1-aza-5-cyclotetradecen-2-one (12a)



To a solution of silyl enol ether **2b** (105 mg, 0.25 mmol) in toluene (5 mL) was added dropwise LHMDS (1.0 M solution in hexane, 0.5 mL, 0.5 mmol) at 130 °C and resulting solution was refluxed for 20 min. After addition of water, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (9% EtOAc in hexane) to afford the lactam (*Z*)-isomer **12a** (71 mg, 0.17 mmol, 68%) and (*E*)-isomer **12b** (6.7 mg, 0.016 mmol, 6.4%) as a white solid.; $[\alpha]_D^{20}$ + 49.2 (*c* 0.20, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 3342, 2927, 2858, 1647, 1517, 1460, 1370,

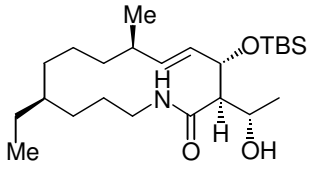
1253 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.33 (bs, 1H), 5.87 (qd, 1H, *J* = 10.9, 6.8 Hz), 5.59 (td, 1H, *J* = 10.6, 1.8 Hz), 5.41 (dd, 1H, *J* = 15.4, 7.3 Hz), 5.33 (dd, 1H, *J* = 15.4, 6.5 Hz), 4.81 (dd, 1H, *J* = 6.4, 3.7 Hz), 3.84 (m, 1H), 3.55 (dd, 1H, *J* = 10.2, 3.7 Hz), 2.45 (m, 1H), 2.02 (m, 1H), 1.66 (dd, 3H, *J* = 6.8, 1.8 Hz), 1.43 – 1.15 (m, 10H), 0.93 (d, 3H, *J* = 6.8 Hz), 0.89 – 0.85 (m, 3H), 0.85 (s, 9H), 0.83 (t, 3H, *J* = 7.3 Hz), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 170.8, 138.5, 130.8, 128.1, 124.7, 74.2, 51.7, 39.9, 37.9, 37.8, 37.7, 36.2, 32.0, 27.3, 26.7, 25.8, 24.2, 21.8, 21.1, 18.1, 12.1, -4.2, -4.7; HR-MS (FAB+) calcd for $C_{25}H_{48}NO_2Si$ ($M+H^+$) 422.3454; found 422.3457.

(3*R*,4*S*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-7-methyl-3-[(*E*)-1-propenyl]-1-aza-5-cyclotetradecen-2-one (12b)



FT-IR (thin film, neat) ν_{max} 2926, 2856, 1743, 1649, 1536, 1460, 1256 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.56 (bs, 1H), 5.63 (dd, 1H, *J* = 14.8, 6.2 Hz), 5.52 (dd, 1H, *J* = 14.8, 10.0 Hz), 5.43 (dd, 1H, *J* = 15.6, 7.4 Hz), 5.31 (dd, 1H, *J* = 15.6, 6.0 Hz), 4.61 (m, 1H), 3.81 (m, 1H), 3.10 (dd, 1H, *J* = 8.8, 3.2 Hz), 2.49 (m, 1H), 2.06 (m, 1H), 1.81 (m, 1H), 1.73 (d, 3H, *J* = 6.0 Hz), 1.65 – 1.14 (m, 12H), 0.93 (d, 3H, *J* = 6.8 Hz), 0.87 (s, 9H), 0.83 (t, 3H, *J* = 7.2 Hz), 0.04 (s, 3H), 0.01 (s, 3H); HR-MS (FAB+) calcd for $C_{25}H_{48}NO_2Si$ ($M+H^+$) 422.3454; found 422.3440.

(3*R*,4*S*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-3-[(1*S*)-1-hydroxyethyl]-7-methyl-1-aza-5-cyclotetradecen-2-one (14a)

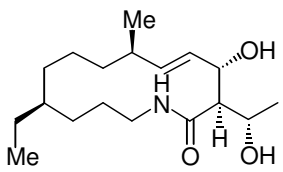


To a stirred solution of **12** (63 mg, 0.15 mmol) and 4-methylmorpholine *N*-oxide (52 mg, 0.45 mmol) in acetone/H_2O (3:1, 9 mL) at 0 °C was added OsO_4 (0.1 M in toluene, 0.15 mL, 0.015 mmol). The reaction mixture was allowed to room temperature, and stirred for additional 5 h. $NaIO_4$ (96 mg, 0.45 mmol) was added and the mixture was stirred at room temperature for 30 min. The reaction

was quenched with Na_2SO_3 (5 eq) and extracted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure.

To an ice-cooled solution of the resulting aldehyde in ethyl ether (10 mL) was added dropwise methylmagnesium iodide (3.0 M in diethyl ether, 0.10 mL, 0.30 mmol), and the mixture was stirred for 30 min at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with Et_2O. The organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (25% EtOAc in hexane) to afford alcohol **14a** (58 mg, 0.14 mmol, 93%) as a white solid.; $[\alpha]_D^{20}$ +37.2 (*c* 0.06, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 3304, 2927, 2858, 1629, 1542, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 5.94 (bs, 1H), 5.34 (dd, 1H, *J* = 15.3, 8.7 Hz), 5.21 (dd, 1H, *J* = 15.3, 8.0 Hz), 4.53 (t, 1H, *J* = 8.7 Hz), 3.85 (bs, 1H), 3.84 (d, 1H, *J* = 9.3 Hz), 2.55 (t, 1H, *J* = 10.1 Hz), 2.13 (dd, 1H, *J* = 9.3, 2.7 Hz), 1.98 (m, 1H), 1.43 – 1.15 (m, 12H), 1.19 (d, 3H, *J* = 6.5 Hz), 0.95 (d, 3H, *J* = 6.7 Hz), 0.96 – 0.86 (m, 2H), 0.87 (s, 9H), 0.83 (t, 3H, *J* = 7.4 Hz), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 172.7, 139.2, 130.2, 72.5, 65.7, 59.7, 39.9, 38.0, 37.9, 36.3, 31.9, 27.2, 27.0, 25.9, 24.4, 22.1, 21.8, 21.1, 18.1, 12.1, –3.8, –4.8; HR-MS (FAB+) calcd for $C_{24}H_{48}NO_3Si$ ($M+H^+$) 426.3403; found 426.3400.

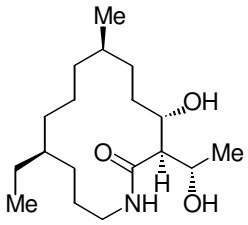
(3*R*,4*S*,7*R*,11*S*)-11-ethyl-4-hydroxy-3-[(1*S*)-1-hydroxyethyl]-7-methyl-1-aza-5-cyclotetradecen-2-one (19)



To a solution of lactam **14a** (24 mg, 0.056 mmol) in THF (3 mL) was added TBAF (1.0 M solution in THF, 11 μL, 0.11 mmol) and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (only EtOAc) to afford diol **19** (17 mg, 0.055 mmol, 98%) as a white solid; $[\alpha]_D^{20}$ +85.2 (*c* 0.05, CH_3OH); FT-IR (thin film, neat) ν_{max} 3325, 2920, 2857, 1639, 1555, 1456 cm^{-1}; ^{1}H-

NMR ($CDCl_3$, 600 MHz) δ 5.97 (bs, 1H), 5.44 (dd, 1H, *J* = 15.2, 8.8 Hz), 5.33 (dd, 1H, *J* = 15.2, 8.3 Hz), 4.55 (td, 1H, *J* = 9.2, 3.1 Hz), 4.24 (m, 1H), 3.80 (m, 1H), 3.61 (d, 1H, *J* = 9.9 Hz), 2.66 (ddd, 1H, *J* = 13.4, 5.0, 2.9 Hz), 2.19 (d, 1H, *J* = 3.5 Hz), 2.17 (dd, 1H, *J* = 9.6, 3.0 Hz), 2.00 (m, 1H), 1.48 – 1.17 (m, 10H), 1.24 (d, 3H, *J* = 6.5 Hz), 0.97 (d, 3H, *J* = 6.7 Hz), 0.95 – 0.88 (m, 3H), 0.84 (t, 3H, *J* = 7.4 Hz); HR-MS (FAB+) calcd for $C_{18}H_{34}NO_3$ ($M+H^+$) 312.2539; found 312.2545.

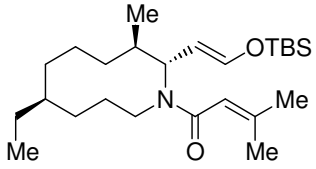
(3*R*,4*S*,7*R*,11*S*)-11-ethyl-4-hydroxy-3-[(1*S*)-1-hydroxyethyl]-7-methyl-1-azacyclotetradecan-2-one (1, Fluvirucinine A_2)



A solution of lactam **19** (13 mg, 0.042 mmol) and 10% Pd/C in 9 mL of anhydrous MeOH was placed under an atmosphere of hydrogen. After stirring for 12 h, the reaction mixture was diluted with EtOAc, filtered through celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (only EtOAc) to afford Fluvirucinine A_2 (**1**) (13 mg, 0.041 mmol, 98%) as a white solid; $[\alpha]_D^{20}$ + 55.7 (*c* 0.015, CH_3OH); FT-IR (thin film, neat) ν_{max} 3295, 2920, 2853, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 5.91 (bs, 1H), 4.19 (bs, 1H), 4.00 (t, 1H, *J* = 8.9 Hz), 3.71 (m, 1H), 3.69 (d, 1H, *J* = 9.5 Hz), 2.95 (m, 1H), 2.24 (bs, 1H), 2.06 (dd, 1H, *J* = 9.5, 2.7 Hz), 1.69 – 1.21 (m, 12H), 1.21 (d, 3H, *J* = 6.3 Hz), 1.13 – 0.95 (m, 6H), 0.89 (d, 3H, *J* = 6.9 Hz), 0.83 (t, 3H, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 173.4, 71.1, 65.4, 59.9, 38.8, 37.2, 32.6, 32.1, 31.6, 31.3, 31.1, 27.7, 26.9, 26.8, 21.6, 21.2, 18.5, 11.3; HR-MS (FAB+) calcd for $C_{18}H_{36}NO_3$ ($M+H^+$): 314.2695; found 314.2685.

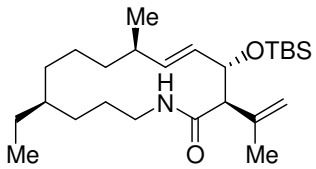
Total Synthesis of *epi*-Fluvirucinine A_2

1-[(2*R*,3*R*,7*S*)-2-((*E*)-2-[*tert*-butyl(dimethyl)silyl]oxyethenyl)-7-ethyl-3-methylazecanyl]-3-methyl-2-buten-1-one (2c)



A mixture of 3,3-dimethylacrylic acid (30 mg, 0.30 mmol) and 1-hydroxybenzotriazole (41 mg, 0.30 mmol) was suspended in CH_2Cl_2 (8 mL), cooled at 0 °C and treated with EDCI (58 mg, 0.30 mmol) and triethylamine (56 μL, 0.40 mmol). After the reaction mixture was stirred at room temperature for 30 min, amine **11** (35 mg, 0.10 mmol) in CH_2Cl_2 was added by cannula. The reaction mixture was concentrated under reduced pressure to ca. 0.5 mL. The residue was purified by flash chromatography on silica gel (9 % EtOAc in hexane, silica gel deactivated with Et_3N) to afford amide **2c** (40 mg, 0.095 mmol, 95%) as colorless oil; FT-IR (thin film, neat) ν_{max} 2926, 2857, 1652, 1463, 1258, 1162 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.35 (bd, 0.6H, J = 10.8 Hz), 6.21 (d, 0.4H, J = 11.9 Hz), 5.77 (s, 1H), 5.23 (bs, 0.5H), 4.98 (dd, 0.4H, J = 11.9, 9.2 Hz), 3.78 and 2.65 (bs, 1H), 1.88 and 1.86 (s, 3H), 1.81 and 1.79 (s, 3H), 1.34 – 1.09 (m, 16H), 0.88 (s, 9H), 0.88 – 0.81 (m, 3H), 0.83 (t, 3H, J = 6.6 Hz), 0.11 and 0.10 (s, 6H); HR-MS (FAB+) calcd for $C_{25}H_{48}NO_2Si$ ($M+H^+$) 422.3454; found 422.3458.

(3*R*,4*S*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-3-isopropenyl-7-methyl-1-aza-5-cyclotetradecen-2-one (13a)

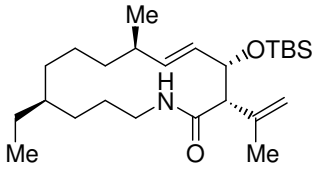


To a solution of silyl enol ether **2c** (23 mg, 0.055 mmol) in toluene (3 mL) was added dropwise 2-Mesitylmagnesium bromide[2] (1.0 M solution in THF, 11 μL, 0.11 mmol) at 130 °C and resulting solution was refluxed for 20 min. After addition of water (0.2 mL), the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (9% EtOAc in hexane) to afford lactam **13a**

[2] For a report on the Claisen rearrangement under these conditions, see: (a) Arnold, R. T.; Searles, S. *J. Am. Chem. Soc.* **1949**, *71*, 1150. (b) Arnold, R. T.; Parham, W. E.; Dodson, R. M. *J. Am. Chem. Soc.* **1949**, *71*, 2489.

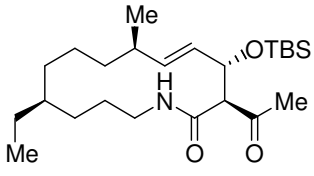
(9.3 mg, 0.022 mmol, 40%) and diastereomer **13b** (8.9 mg, 0.021 mmol, 38%) as a white solid; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.58 (bs, 1H), 5.33 (dd, 1H, J = 15.2, 9.2 Hz), 5.17 (dd, 1H, J = 15.2, 7.8 Hz), 4.87 (s, 1H), 4.81 (s, 1H), 4.51(dd, 1H, J = 9.9, 7.9 Hz), 3.70 (m, 1H), 2.75 (d, 1H, J = 9.9 Hz), 2.45 (m, 1H), 1.90 (m, 1H), 1.77 (s, 3H), 1.56 – 1.19 (m, 10H), 0.95 (d, 3H, J = 6.8 Hz), 0.87 – 0.80 (m, 3H), 0.82 (t, 3H, J = 7.5 Hz), 0.81 (s, 9H), 0.00 (s, 3H), –0.03 (s, 3H).

(3*S*,4*S*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-3-isopropenyl-7-methyl-1-aza-5-cyclotetradecen-2-one (13b)



FT-IR (thin film, neat) ν_{max} 2927, 2857, 1649, 1536, 1459, 1254 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.31 (bs, 1H), 5.49 (dd, 1H, J = 15.8, 6.7 Hz), 5.40 (dd, 1H, J = 15.8, 4.6 Hz), 5.04 (s, 1H), 4.90 (s, 1H), 4.61 (s, 1H), 3.86 (m, 1H), 3.13 (d, 1H, J = 2.5 Hz), 2.56 (td, 1H, J = 8.5, 4.6 Hz), 1.85 (s, 3H), 1.52 – 0.86 (m, 14H), 0.94 (d, 3H, J = 6.8 Hz), 0.89 (s, 9H), 0.83 (t, 3H, J = 7.4 Hz), 0.03 (s, 6H); HR-MS (FAB+) calcd for $C_{25}H_{48}NO_2Si$ ($M+H^+$) 422.3454; found 422.3440.

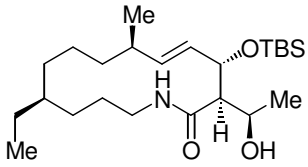
(3*S*,4*S*,7*R*,11*S*)-3-acetyl-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-7-methyl-1-aza-5-cyclotetradecen-2-one (20a)



To a stirred solution of **13a** (24 mg, 0.057 mmol) and 4-methylmorpholine *N*-oxide (20 mg, 0.17 mmol) in acetone/H_2O (3:1, 6 mL) at 0 °C was added OsO_4 (0.1 M in toluene, 57 μL, 0.006 mmol). The reaction mixture was allowed to room temperature, and stirred for additional 5 h. $NaIO_4$ (36 mg, 0.17 mmol) was added and the mixture was stirred at room temperature for 30 min. The reaction was quenched with Na_2SO_3 (5 eq) and extracted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (33% EtOAc in hexane) to afford ketone **20a** (23 mg, 0.054 mmol, 95%) as a white solid; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.10 (d, 1H, J = 11.1 Hz), 6.22 (dd, 1H, J = 15.4, 11.7 Hz), 6.05

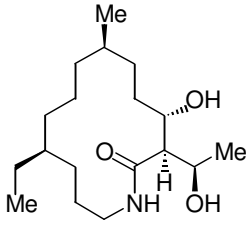
(dd, 1H, *J* = 15.4, 6.7 Hz), 5.82 (bs, 1H), 3.73 (m, 1H), 3.11 (m, 1H), 2.39 (m, 1H), 2.31 (s, 3H), 1.69 (m, 1H), 1.54 – 1.10 (m, 10H), 1.03 (d, 3H, *J* = 6.9 Hz), 0.89 (s, 9H), 0.87 – 0.80 (m, 3H), 0.85 (t, 3H, *J* = 6.9 Hz), 0.08 (s, 6H); HR-MS (FAB+) calcd for $C_{24}H_{46}NO_3Si$ ($M+H^+$) 424.3247; found 424.3249.

(3*R*,4*S*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-3-[(1*R*)-1-hydroxyethyl]-7-methyl-1-aza-5-cyclotetradecen-2-one (14b)



To a solution of ketone **20** (20 mg, 0.047 mmol) in ethanol (3 mL) was added $NaBH_4$ (3.6 mg, 0.094 mmol) at –78 °C. The reaction mixture was stirred for 2 h and allowed to 0 °C, quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The organic layers was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 to 33% EtOAc in hexane) to afford alcohol **14b** (19 mg, 0.045 mmol, 96%) as a white solid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.70 (bs, 1H), 5.28 (dd, 1H, *J* = 15.2, 9.0 Hz), 5.19 (dd, 1H, *J* = 15.2, 8.1 Hz), 4.65 (dd, 1H, *J* = 8.2, 1.4 Hz), 4.14 (qd, 1H, *J* = 7.2, 6.3 Hz), 3.83 (m,1H), 2.49 (ddd, 1H, *J*= 9.2, 4.9 Hz), 2.06 (dd, 1H, *J* = 9.6, 7.6 Hz), 1.85 (m, 1H), 1.40 – 1.10 (m, 12H), 1.11 (d, 3H, *J* = 6.6 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 0.93 – 0.71 (m, 2H), 0.87 (s, 9H), 0.83 (t, 3H, *J* = 7.3 Hz), 0.13 (s, 3H), 0.06 (s, 3H); HR-MS (FAB+) calcd for $C_{24}H_{48}NO_3Si$ ($M+H^+$) 426.3403; found 426.3404.

(3*R*,4*S*,7*R*,11*S*)-11-ethyl-4-hydroxy-3-[(1*R*)-1-hydroxyethyl]-7-methyl-1-azacyclotetradecan-2-one (*epi*-Fluvirucinine A_2) (21)

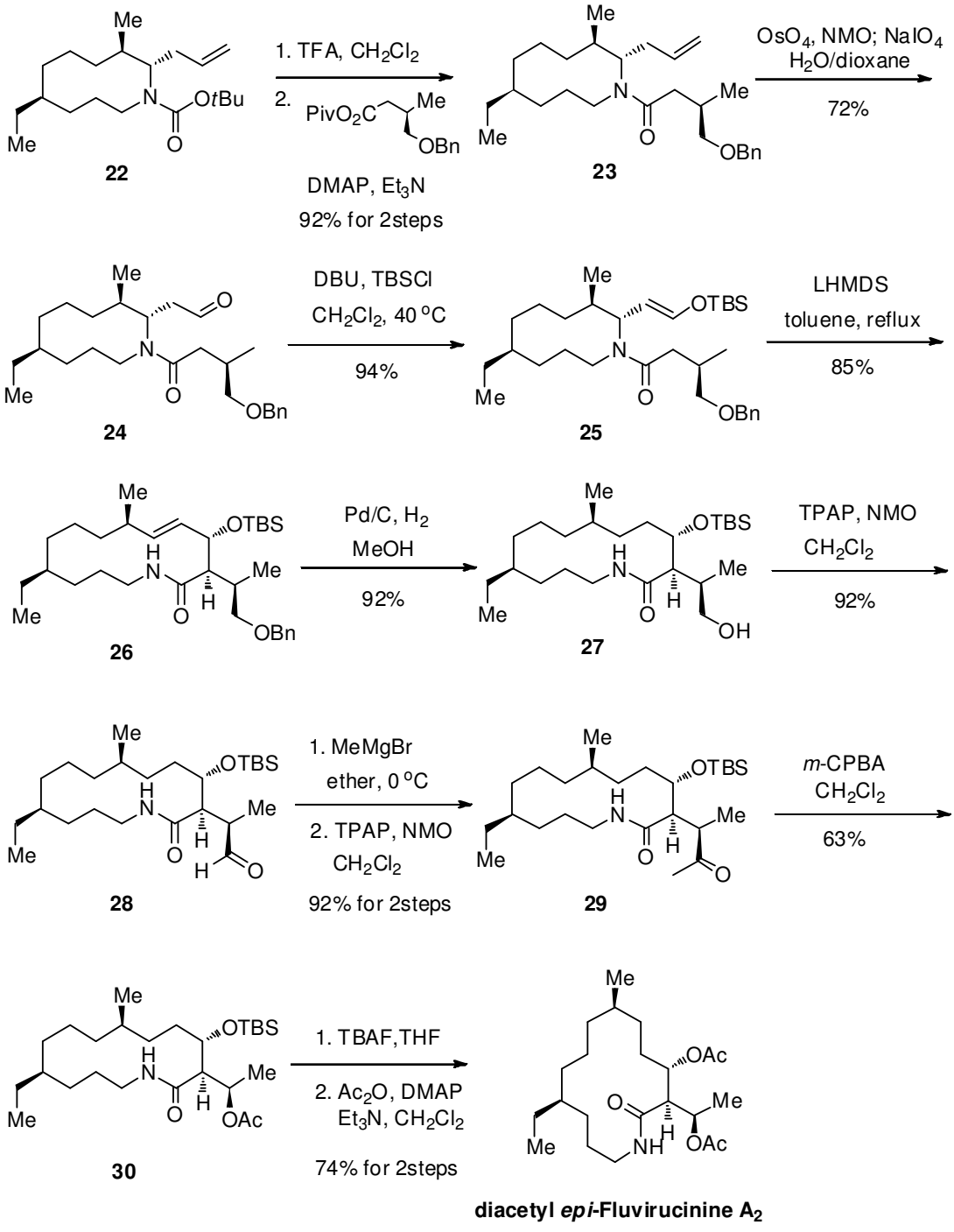


To a solution of lactam **14b** (19 mg, 0.045 mmol) in THF (2 mL) was added TBAF (1.0 M solution in THF, 90 μL, 0.09 mmol) and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure.

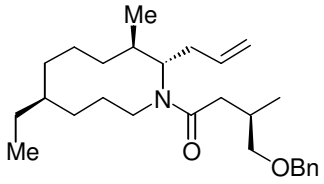
To a solution containing the above lactam and 10% Pd/C in 5 mL

of anhydrous MeOH was placed under an atmosphere of hydrogen. After stirring for 12 h, the reaction mixture was diluted with EtOAc, filtered through celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 to 33% hexane in EtOAc) to afford *epi*-Fluvirucinine A_2 (**21**) (13 mg, 0.041 mmol, 91%) as a white solid; FT-IR (thin film, neat) ν_{max} 3301, 2934, 2864, 1643, 1550, 1458 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.22 (bs, 1H), 3.88 (bd, 1H, J = 8.0 Hz), 3.59 (m, 1H), 3.44 (q, 1H, J = 6.5 Hz), 2.87 (m, 1H), 2.31 (ddd, 1H, J = 14.5, 7.3, 2.2 Hz), 1.69 – 1.54 (m, 2H), 1.44 – 1.09 (m, 14H), 1.34 (d, 3H, J = 7.3 Hz), 1.01 – 0.97 (m, 2H), 0.90 (d, 3H, J = 7.0 Hz), 0.83 (t, 3H, J = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 176.3, 77.2, 74.9, 44.1, 39.1, 37.7, 33.4, 32.0, 31.0, 30.7, 29.7, 27.3, 27.0, 24.4, 21.6, 20.8, 16.4, 11.7; HR-MS (FAB+) calcd for $C_{18}H_{36}NO_3$ ($M+H^+$) 314.2695; found 314.2696.

Total Synthesis of *epi*-Fluvirucinine A_2 via Baeyer-Villiger Reaction



(3*R*)-1-[(2*S*,3*R*,7*S*)-2-allyl-7-ethyl-3-methylazecanyl]-4-(benzyloxy)-3-methyl-1-butanone (23)



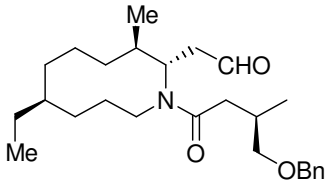
To a solution of carbamate **22** (230 mg, 0.7 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.6 mL, 7.1 mmol) at 0 °C and the ice bath was removed. The mixture was stirred for 5 h at room temperature. The reaction mixture was concentrated under reduced pressure to afford ammonium salt.

To a solution of (3*R*)-4-benzyloxy-3-methyl butyric acid[3] (296 mg, 1.4 mmol) and triethylamine (0.8 mL, 5.7 mmol) in THF (20 mL) was added pivaloyl chloride (0.1 mL, 1.1 mmol) at 0 °C. After the mixture was stirred for 2 h, THF was removed under reduced pressure.

To a solution of crude ammonium salt and DMAP (cat. amount) in CH_2Cl_2 (20 mL) was added triethylamine (0.5 mL, 3.6 mmol) and a solution of acid anhydride in CH_2Cl_2 (20 mL). The resulting solution was stirred for 24 h. After evaporation of solvent, the residue was diluted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (17% EtOAc in hexane) to afford amide **23** (270 mg, 0.65 mmol, 92%) as colorless oil; $[\alpha]_D^{20}$ +27.5 (*c* 0.48, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 2921, 1642, 1455, 1419, 1098 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.31 – 7.26 (m, 5H), 5.60 (m, 0.7H), 5.07 - 4.89 (m, 2H), 4.61 (bs, 0.2H), 4.48 and 4.47 (s, 1H), 3.72 (m, 0.4H), 3.43 (m, 0.6H), 3.39 – 3.30 (m, 2H), 3.10 (bs, 0.2H), 2.77 (m, 0.4H), 2.50 (m, 0.5H), 2.44 – 2.37 (m, 2H), 2.18 – 2.02 (m, 2H), 1.78 – 1.19 (m, 16H), 0.98 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.4 Hz), 0.85 (t, 3H, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.5, 138.6, 138.5, 134.3, 128.0, 127.1, 127.0, 117.7, 117.6, 74.8, 74.6, 72.5, 57.5, 39.6, 37.8, 37.6, 35.3, 32.1, 31.0, 30.8, 30.2, 29.2, 24.8, 24.4, 18.6, 17.4, 11.8; HR-MS (FAB+) calcd for $C_{27}H_{44}NO_2$ ($M+H^+$) 414.3372; found 414.3372.

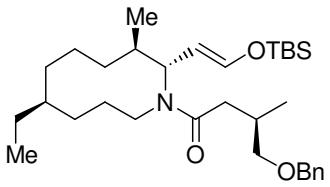
[3] Smith, A. B.; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123* , 5925.

2-(2*S*,3*R*,7*S*)-1-[(3*R*)-4-(benzyloxy)-3-methylbutanoyl]-7-ethyl-3-methylazecanylacetaldehyde (24)



To a solution of **23** (270 mg, 0.7 mmol) in H_2O/dioxane (1:2, 30 mL) was added OsO_4 (0.05 M in toluene, 0.6 mL, 0.03 mmol) and 4-methylmorpholine *N*-oxide (240 mg, 2.0 mmol) at room temperature and stirred for 1 h. $NaIO_4$ (417 mg, 2.0 mmol) was added in one portion and the reaction mixture stirred 5 h. Na_2SO_3 (6eq) was added, to reduce the remaining Os(VIII), and stirred for additional 1 h. After evaporation of solvent, the residue was diluted with EtOAc. The organic phase was washed with 1*N* HCl and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (17% EtOAc in hexane) to afford aldehyde **24** (195 mg, 0.47 mmol, 72%) as colorless oil; $[\alpha]_D^{20}$ +27.4 (*c* 0.60, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 2923, 2724, 1723, 1641, 1455, 1097 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.69 and 9.62 (s, 1H), 7.33 – 7.22 (m, 5H), 4.48 and 4.47 (m, 2H), 4.03 (m, 0.2H), 3.80 (m, 0.2H), 3.41 – 3.27 (m, 4.6H), 2.78 – 2.55 (m, 3H), 2.50 (dd, 1H, *J* = 15.1, 5.5 Hz), 2.34 (m, 1.5H), 2.21(m, 0.5H), 2.13 – 2.07 (m, 2H), 1.75 – 1.18 (m, 11H), 1.01 and 0.96 (d, 3H, *J* = 6.7 Hz), 0.89 (d, 3H, *J* = 6.6 Hz), 0.85 (t, 5H, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 201.2, 199.4, 174.1, 173.3, 173.0, 138.6, 138.5, 128.6, 128.1, 127.6, 127.4, 127.3, 127.2, 74.7, 74.6, 72.7, 57.4, 56.3, 45.9, 45.7, 38.3, 37.7, 36.8, 34.9, 31.4, 30.8, 30.7, 30.3, 30.0, 29.3, 29.1, 26.1, 24.8, 18.6, 18.0, 17.5, 17.2, 11.9; HR-MS (FAB+) calcd for $C_{26}H_{42}NO_3$ ($M+H^+$) 416.3165; found 416.3175.

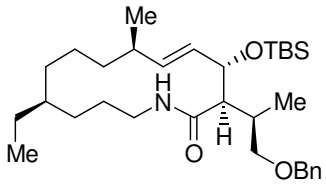
(3*R*)-4-(benzyloxy)-1-((2*R*, 3*R*, 7*S*)-7-ethyl-3-methyl-2-(*E*)-2-[*tert*-butyl(dimethylsilyl)oxy]ethenylazecanyl)-3-methyl-1-butanone (25)



A mixture of aldehyde **24** (71 mg, 0.2 mmol), TBSCl (51 mg, 0.3 mmol) and DBU (0.04 mL, 0.3 mmol) in CH_2Cl_2 (7 mL) were stirred at 40 °C for 1 h. The reaction mixture

was concentrated under reduced pressure to ca. 0.5 mL. The residue was purified by flash chromatography on silica gel (only hexane to 9% EtOAc in hexane, silica gel deactivated with Et_3N,) to give only (*E*)-enol ether **25** (85 mg, 0.2 mmol, 94%) as colorless oil; $[\alpha]_D^{20}$ –3.1 (*c* 0.90, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 2957, 1647, 1462, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.31 – 7.26 (m, 5H), 6.33 and 6.27 (d, 1H, *J* = 12.1 Hz), 5.12 (bs, 0.5H), 4.97 (dd, 0.5H), 4.49 and 4.47 (s, 2H), 3.82 (bs, 0.4H), 3.38 – 3.32 (m, 2.6H), 2.82 – 2.36 (m, 2.2H), 2.05 (m, 1H), 1.63 – 1.23 (m, 16H), 0.98 (t, 3H, *J* = 6.5 Hz), 0.89 and 0.88 (s, 9H), 0.86 – 0.80 (m, 3H), 0.82 (d, 3H, *J* = 6.4 Hz), 0.10 and 0.09 (s, 6H); HR-MS (FAB+) calcd for $C_{32}H_{56}NO_3Si$ ($M+H^+$) 530.4029; found 530.4031.

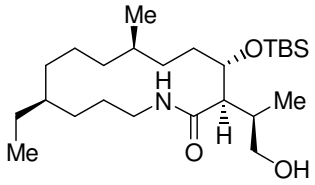
(3*R*,4*S*,7*R*,11*S*)-3-[(1*R*)-2-(benzyloxy)-1-methylethyl]-11-ethyl-7-methyl-4-[*tert*-butyl (dimethylsilyl)oxy]-1-aza-5-cyclotetradecen-2-one (26)



To a solution of (*E*)-enol ether **25** (67 mg, 0.13 mmol) was added dropwise LHMDS (1.0 M solution in hexane, 0.3 mL, 0.3 mmol) in toluene (6 mL) at 130 °C and resulting solution was refluxed for 20 min. After addition of water, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (9% EtOAc in hexane) to afford the pure lactam **26** (53 mg, 0.11 mmol, 85%) as a white solid; $[\alpha]_D^{20}$ +131.5 (*c* 0.11, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3324, 2928, 2857, 1644, 1538, 1458 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39 – 7.30 (m, 5H), 5.69 (t, 1H, *J* = 5.7 Hz), 5.24 (dd, 1H, *J* = 15.2, 8.9 Hz), 5.14 (dd, 1H, *J* = 15.2, 7.7 Hz), 4.59 (d, 1H, *J* = 11.9 Hz), 4.40 (dd, 1H, *J* = 10.2, 7.8 Hz), 4.31 (d, 1H, *J* = 11.9 Hz), 3.62 (m, 1H), 3.37 (dd, 1H, *J* = 9.7, 5.0 Hz), 3.16 (dd, 1H, *J* = 11.0, 9.7 Hz), 2.58 (m, 1H), 2.45 (dd, 1H, *J* = 10.3, 3.6 Hz), 2.07 (m, 1H), 1.89 (m, 1H), 1.47 - 1.03 (m, 10H), 0.93 (d, 3H, *J* = 6.6 Hz), 0.86 (d, 3H, *J* = 6.6 Hz), 0.86 (s, 9H), 0.83 (d, 3H, *J* = 6.8 Hz), 0.81 (t, 3H, *J* = 7.1 Hz), 0.02, (s, 3H), 0.01 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.9, 138.6, 138.3, 132.1, 128.7, 128.0, 127.9, 73.6, 72.8, 72.3, 53.2, 39.7, 38.6, 38.2, 37.1, 32.3, 31.1, 27.4, 26.6, 26.0, 25.0, 21.4, 21.2, 18.1, 12.2, 11.6, –3.2, –4.8;

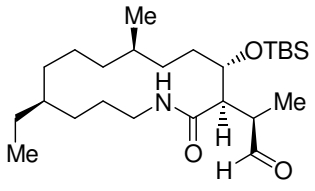
HR-MS (FAB+) calcd for $C_{32}H_{56}NO_3Si$ ($M+H^+$) 530.4029; found 530.4037.

(3*R*,4*S*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-3-[(1*R*)-2-hydroxy-1-methylethyl]-7-methyl-1-azacyclotetradecan-2-one (27)



A solution of lactam **26** (52 mg, 0.1 mmol) and 10% Pd/C in anhydrous MeOH (9 mL) was placed under an atmosphere of hydrogen. After stirring for 12 h, the reaction mixture was diluted with EtOAc, filtered through celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (33% EtOAc in hexane) to afford the hydrogenated lactam **27** (41 mg, 0.09 mmol, 92 %) as a white solid; $[\alpha]_D^{20}$ +94.1 (*c* 0.10, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3294, 2928, 2857, 1634, 1545, 1462, 1251 cm^{-1} ; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.35 (bs, 1H), 4.20 (m, 1H), 3.87 (m, 1H), 3.64 (dd, 1H, *J* = 10.8, 5.0 Hz), 3.31 (t, 1H, *J* = 10.2 Hz), 2.67 (dd, 1H, *J* = 9.0, 3.8 Hz), 2.47 (m, 1H), 2.24 (m, 1H), 1.67 – 1.09 (m, 16H), 0.89 – 0.80 (m, 3H), 0.88 (s, 9H), 0.86 (d, 3H, *J* = 7.0 Hz), 0.85 (d, 3H, *J* = 6.8 Hz), 0.83 (t, 3H, *J* = 7.1 Hz), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 172.2, 69.8, 66.2, 50.7, 39.1, 38.3, 34.7, 33.8, 32.2, 30.9, 29.7, 27.1, 27.0, 26.0, 24.8, 24.0, 22.7, 20.6, 18.1, 12.8, 12.1, –3.9, –4.8; HR-MS (FAB+) calcd for $C_{25}H_{52}NO_3Si$ ($M+H^+$) 442.3716; found 442.3719.

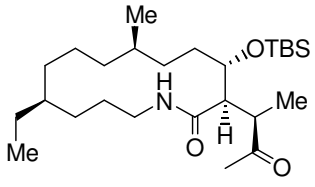
(2*R*)-2-(3*R*,4*S*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-7-methyl-2-oxo-1-azacyclotetradecanyl)propanal (28)



To a solution of alcohol **27** (30 mg, 0.07 mmol) in CH_2Cl_2 (10 mL) at room temperature was added 4-methylmorpholine *N*-oxide (9.6 mg, 0.08 mmol) and tetrapropylammonium perruthenate (2.4 mg, 6.8 mmol), and the mixture was stirred for 2 h. The resultant mixture was filtered through celite pad, concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (17% EtOAc in hexane) to afford aldehyde **28** (27 mg, 0.06 mmol, 92%) as a white

solid; FT-IR (thin film, neat) ν_{max} 3292, 2953, 2857, 1724, 1636 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.65 (s, 1H), 6.25 (bs, 1H), 4.18 (dt, 1H, *J* = 9.5, 2.4 Hz), 3.82 (m, 1H), 2.98 (dd, 1H, *J* = 9.5, 4.0 Hz), 2.88 (ddd, 1H, *J* = 11.6, 7.3, 4.1 Hz), 2.40 (m, 1H), 1.66 – 1.16 (m, 12H), 1.05 (d, 3H, *J* =7.7 Hz), 0.91 – 0.81 (m, 3H), 0.87 (s, 9H), 0.86 (d, 3H, *J* = 7.7 Hz), 0.85 (d, 3H, *J* =6.8 Hz), 0.83 (t, 3H, *J* =7.1 Hz), 0.06 (s, 3H), 0.05 (s, 3H).

(3*S*,4*R*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-3-[(1*R*)-2-hydroxy-1-methylethyl]-7-methyl-1-azacyclotetradecan-2-one (29)

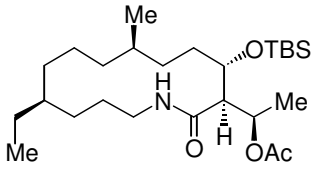


To an ice-cooled solution of aldehyde **28** (60 mg, 0.14 mmol) in ethyl ether (20 mL) was added dropwise methylmagnesium iodide (3.0 M in diethyl ether, 0.10 mL, 0.28 mmol), and the mixture was stirred for 30 min at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with ethyl ether. The organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure.

To a solution containing the above alcohol in CH_2Cl_2 (10 mL) were added 4-methylmorpholine *N*-oxide (20 mg, 0.17 mmol) and tetrapropylammonium perruthenate (4.9 mg, 0.014 mmol) at room temperature, and the mixture was stirred for 2 h. The resultant mixture was filtered through celite pad, concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (17% EtOAc in hexane) to afford ketone **29** (57 mg, 0.13 mmol, 92%) as a white solid; $[\alpha]_D^{20}$ +123.6 (*c* 0.13, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3306, 2952, 2858, 1708, 1641, 1542, 1462, 1358 cm^{-1} ; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.54 (bs, 1H), 4.11 (m, 1H), 3.82 (m, 1H), 3.05 (dd, 1H, *J* = 7.5, 3.6 Hz), 2.96 (dd, 1H, *J* = 9.3, 3.6 Hz), 2.45 (m, 1H), 2.15 (s, 3H), 1.68 – 1.17 (m, 15H), 1.16 (d, 3H, *J* = 7.5 Hz), 0.92 – 0.88 (m, 3H), 0.89 (s, 9H), 0.85 (d, 3H, *J* = 6.9 Hz), 0.84 (t, 3H, *J* = 7.3 Hz), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 212.8, 171.4, 69.7, 49.4, 45.3, 39.3, 38.7, 34.9, 32.5, 31.0, 28.4,

27.3, 27.1, 26.0, 25.6, 24.6, 24.3, 22.6, 20.5, 18.1, 13.2, 12.0, –4.1, –4.9 ; HR-MS (FAB+) calcd for $C_{26}H_{52}NO_3Si$ (M+H$^+$) 454.3716; found 454.3717.

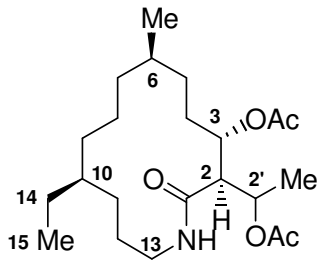
(1*R*)-1-(3*S*,4*R*,7*R*,11*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-11-ethyl-7-methyl-2-oxo-1-azacyclotetradecanyl)ethyl acetate (30)



To a stirred solution of ketone **29** (27 mg, 0.060 mmol) in CH_2Cl_2 (6 mL) at room temperature was added *m*-chloroperoxy benzoic acid (54 mg, 0.24 mmol).[4] The reaction was stirred for 24 h and quenched with 10% Na_2SO_3-doped saturated $NaHCO_3$ solution. After stirring for 10 min, the layers were separated and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (17% EtOAc in hexane) to afford acetate **30** (18 mg, 0.038 mmol, 63%) as a white solid; FT-IR (thin film, neat) ν_{max} 3294, 2929, 2857, 1740, 1641, 1462, 1369, 1247 cm^{-1} ; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.12 (bs, 1H), 5.27 (t, 1H, J = 6.2 Hz), 4.13 – 3.94 (m, 2H), 2.58 (t, 1H, J = 6.8 Hz), 2.50 (m, 1H), 2.02 (s, 3H), 1.72 – 1.22 (m, 15H), 1.27 (d, 3H, J = 7.5 Hz), 0.91 – 0.81 (m, 3H), 0.91 (s, 9H), 0.85 (d, 3H, J = 6.8 Hz), 0.83 (t, 3H, J = 7.3 Hz), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.3, 169.7, 70.4, 69.8, 55.8, 39.5, 38.9, 35.0, 32.2, 30.9, 27.6, 27.2, 26.3, 25.9, 25.4, 23.8, 23.4, 21.3, 20.6, 18.1, 17.5, 11.9, –4.1, –4.7; HR-MS (FAB+) calcd for $C_{26}H_{52}NO_4Si$ (M+H$^+$) 470.3666; found 470.3686.

[4] (a) Hunt, K. W.; Grieco, P. A. *Org. Lett.* **2000**, *2*, 1717. (b) For a recent reviews on the Baeyer-Villiger reaction, see; ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A.*Chem. Rev*. **2004**, *104*, 4105. (c) For a selective metal-catalyzed Baeyer-Villiger reaction, see; Gottlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Syn.Lett*. **1997**, 971.

Table. Comparison of ^{1}H-NMR data for Synthetic and Natural Diacetylfluvirucinine A_2.

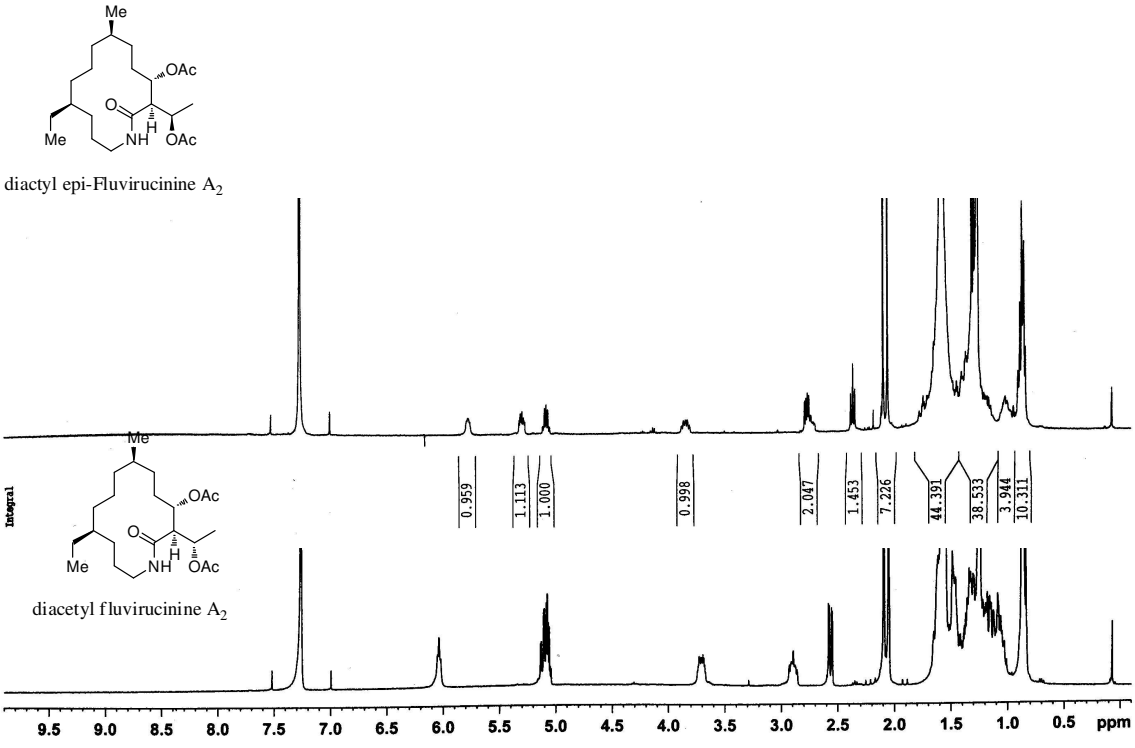


	Natural Fluvirucinine A_2[a]	Synthetic Fluvirucinine A_2	Synthetic *Epi*- Fluvirucinine A_2
	δ[b] (mult, *J*)	δ (mult, *J*)	δ (mult, *J*)
2-CH_3	1.24 (d, 6.4)	1.24 (d, 6.5)	1.29 (d, 6.5)
6-CH_3	0.86 (t, 6.8)	0.87 (t, 6.8)	0.88 (t, 6.8)
15-CH_3	0.85 (t, 7.7)	0.85 (t, 7.3)	0.85 (t, 6.9)
2-H	2.56 (dd, 10.6, 3.4)	2.56 (dd, 11.2, 3.6)	2.76 (dd, 10.4, 5.1)
3-H	5.10 (td, 10.6, 1.9),	5.10 (td, 10.8, 2.0)	5.29 (m)
2'-H		5.07 (qd, 6.5, 3.4)	5.07 (qd, 5.4, 0.91)
13-H	2.89 (dddd, 13.7, 5.7, 5.1, 1.3) 3.70 (ddt, 13.7, 3.0, 5.7)	2.89 (dddd, 13.1, 9.1, 5.3, 1.8) 3.70 (ddt, 13.1, 3.0, 6.3)	2.72 (m) 3.84 (m)
NH	6.04 (brt, 5.7)	6.04 (brt, 5.7)	5.77 (brt, 6.0)
Ac	2.05	2.05	2.05
Ac	2.09	2.09	2.09

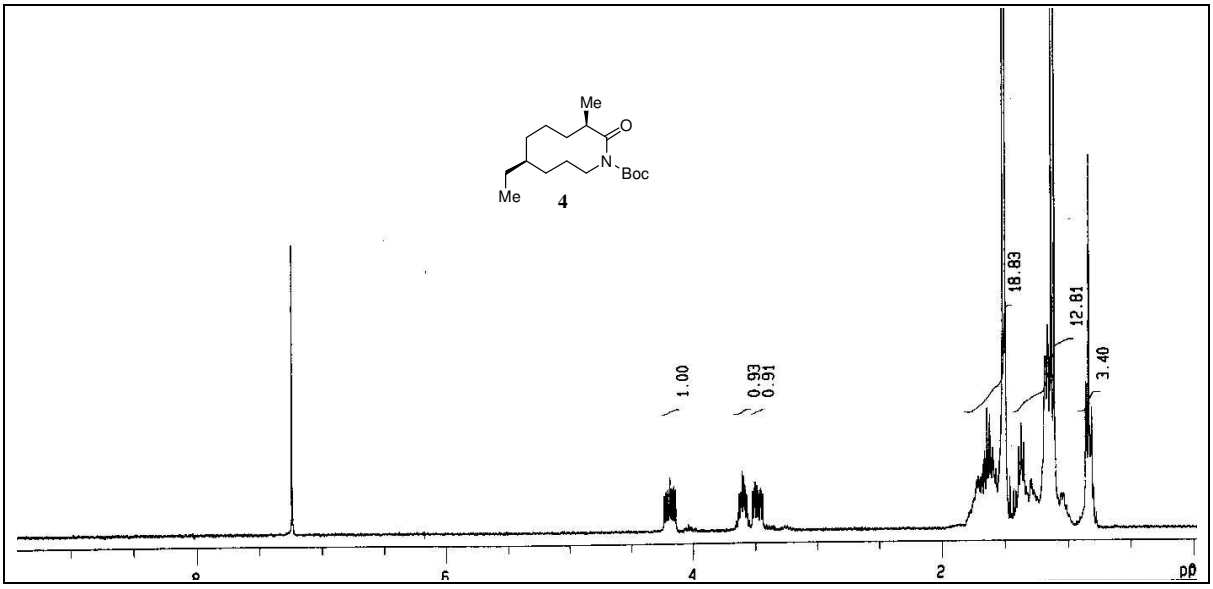
[a] Naruse, N.; Tsuno, T.; Sawada, Y.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 741.

[b] Chemical shifts in ppm relative to $CDCl_3$ as solvent reference (7.26 ppm)

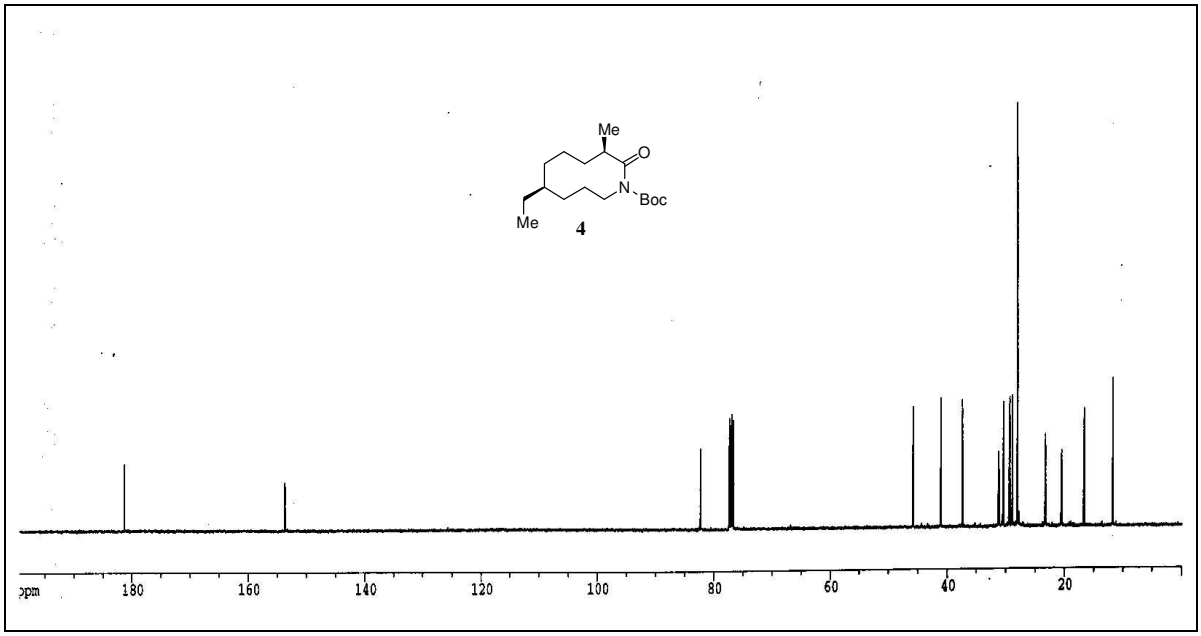
Comparison of ^{1}H-NMR data for diacetyl epi-fluvirucinine A_2 and diacetyl fluvirucinine A_2



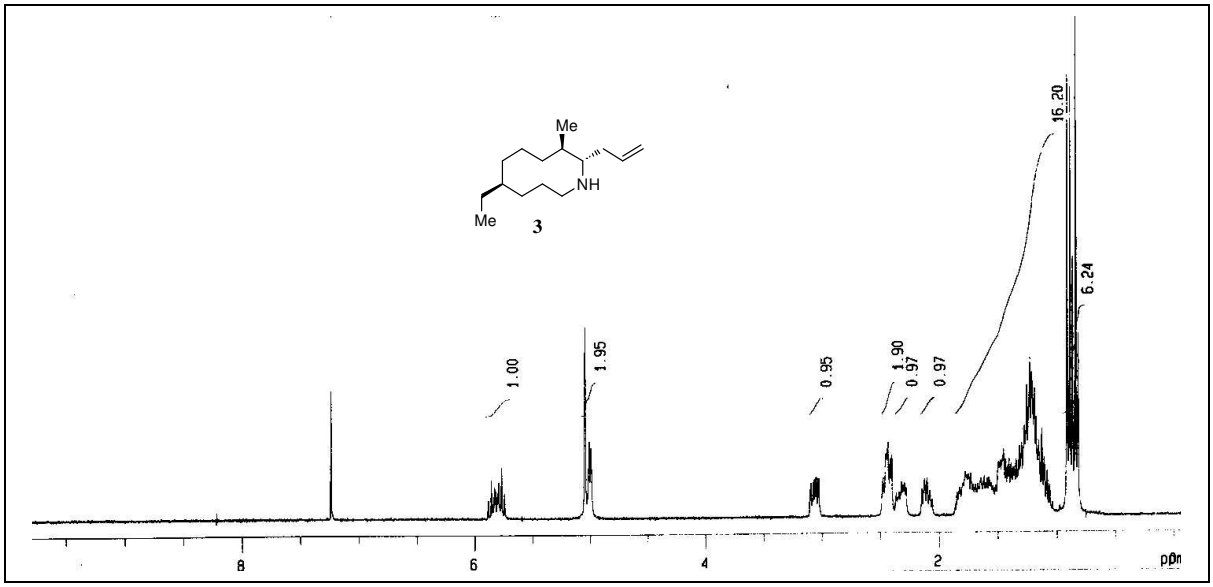
^{1}H- and ^{13}C-NMR Spectra



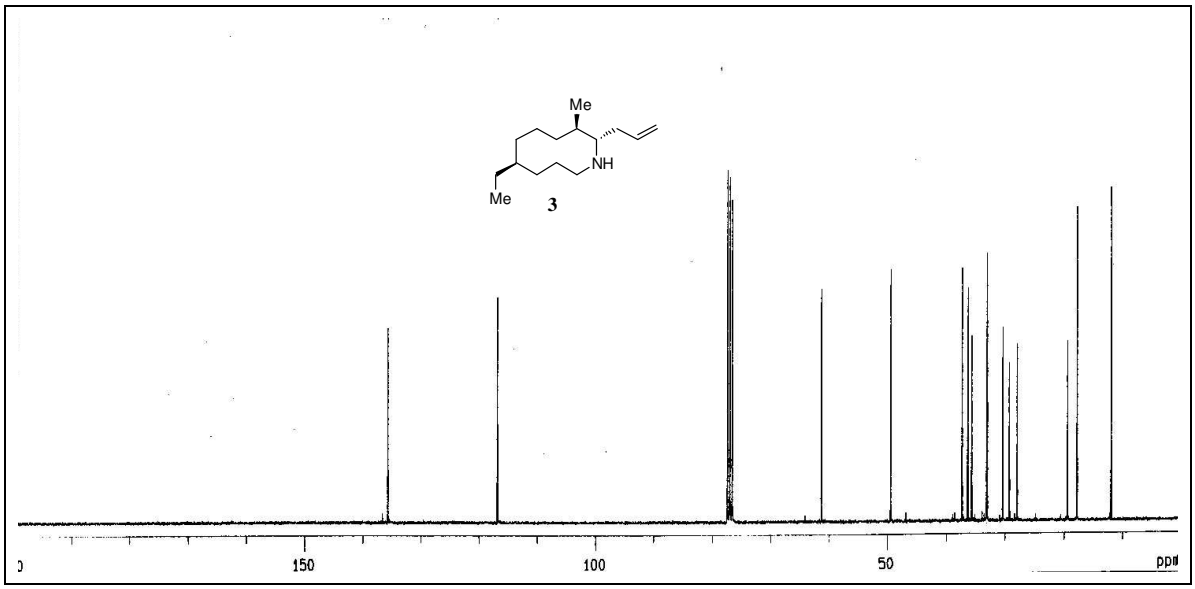
▲ ^{1}H-NMR (300 MHz, $CDCl_3$)



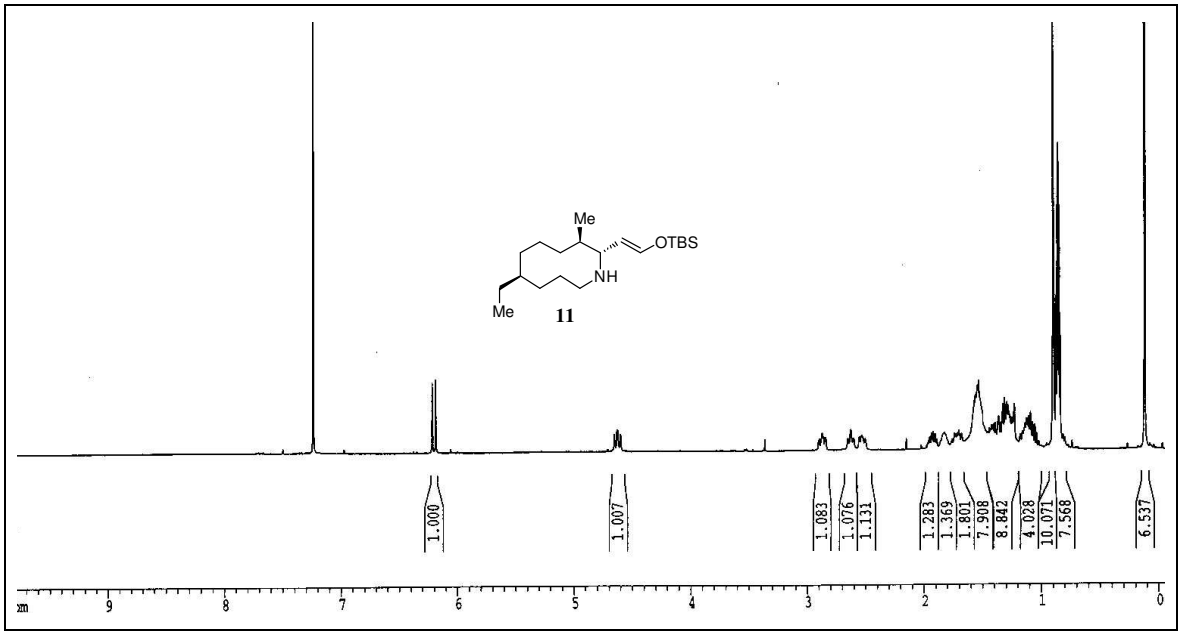
▲ ^{13}C-NMR (100 MHz, $CDCl_3$)



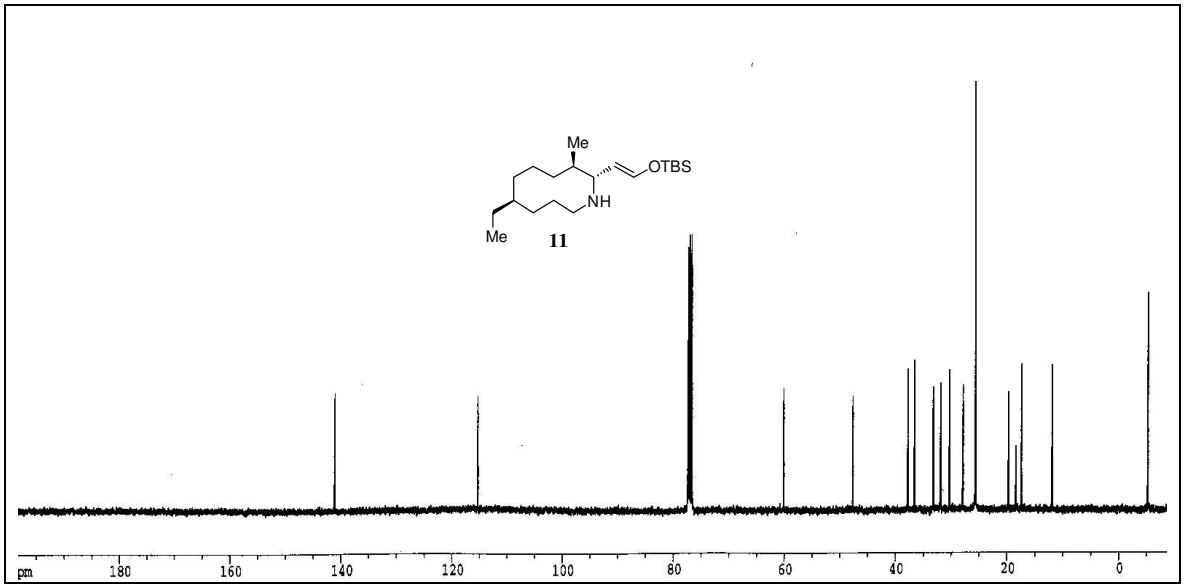
▲ ^{1}H-NMR (300 MHz, $CDCl_3$)



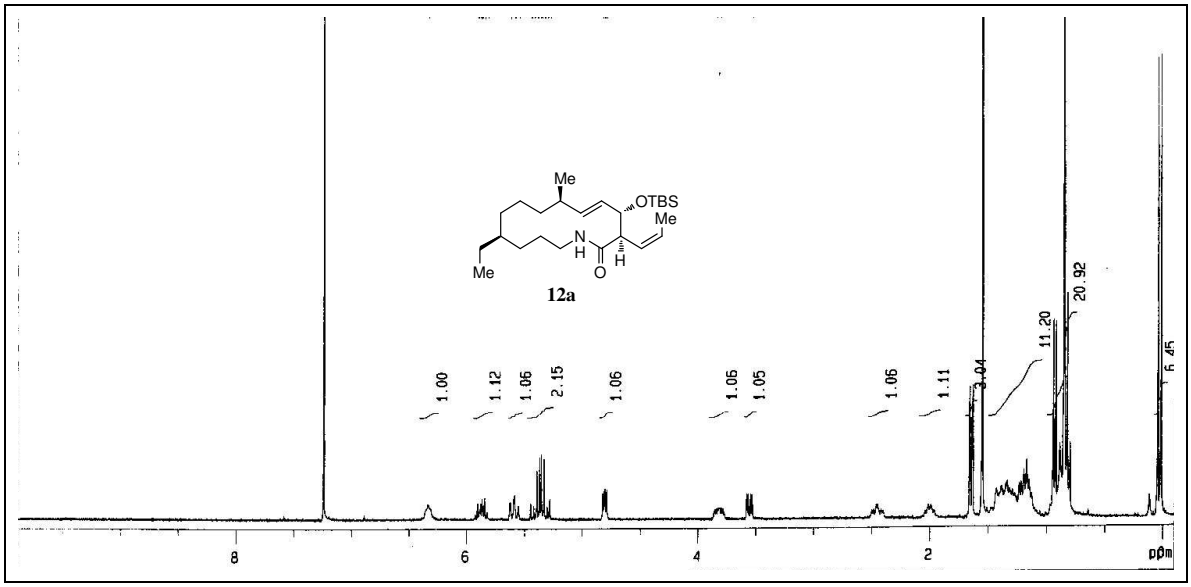
▲ ^{13}C-NMR (75 MHz, $CDCl_3$)



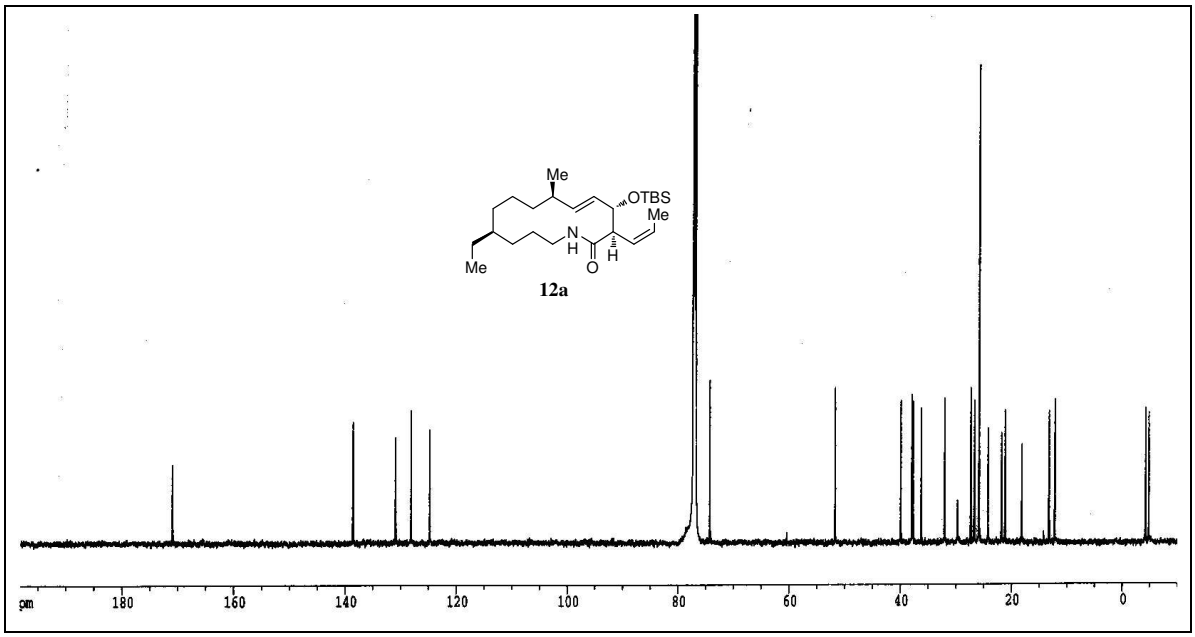
▲ ^{1}H-NMR (400 MHz, $CDCl_3$)



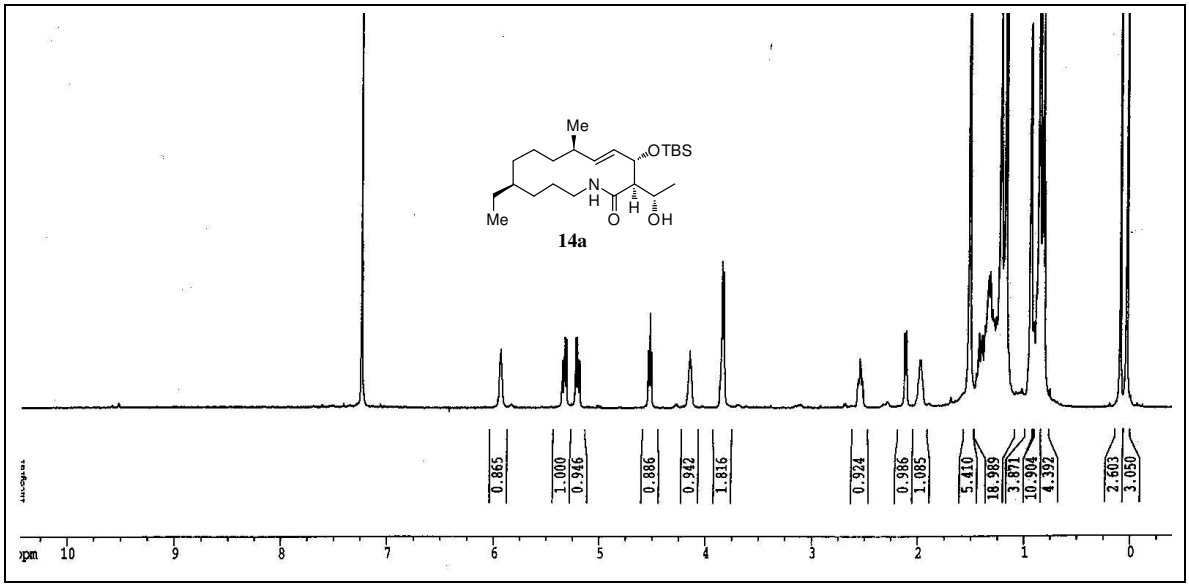
▲ ^{13}C-NMR (75 MHz, $CDCl_3$)



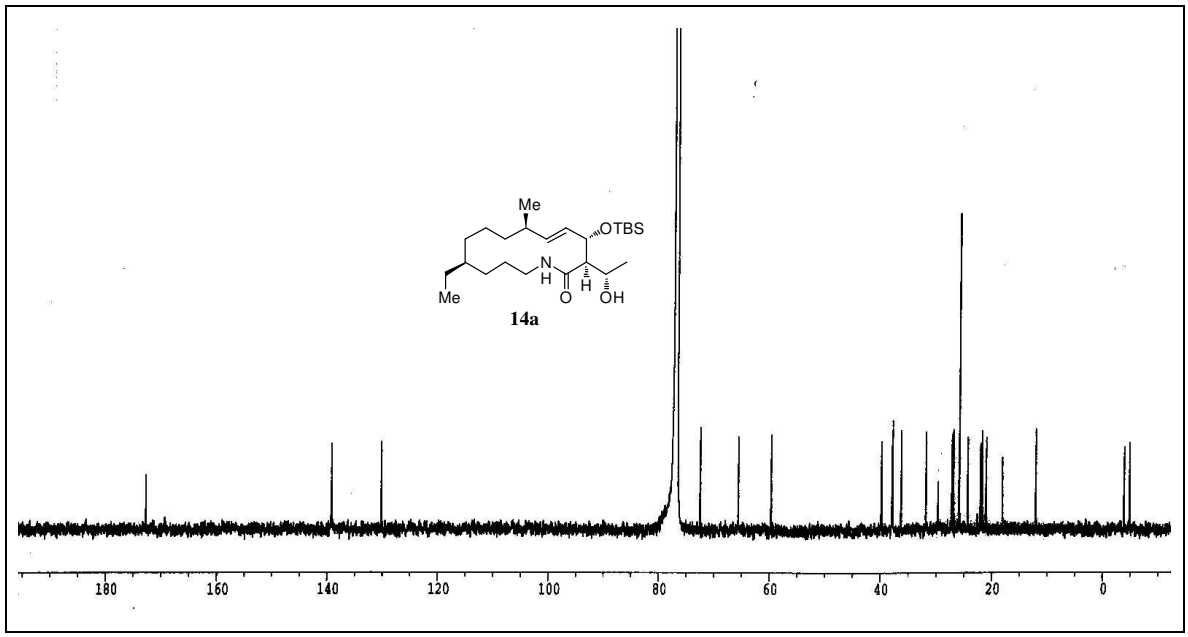
▲ ^{1}H-NMR (300 MHz, $CDCl_3$)



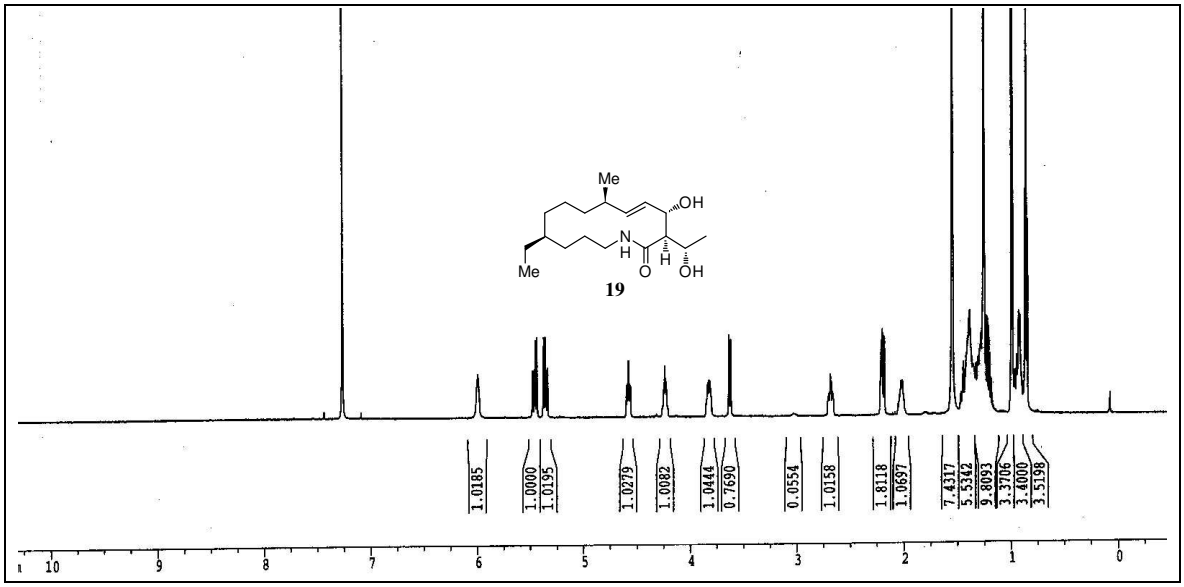
▲ ^{13}C-NMR (150 MHz, $CDCl_3$)



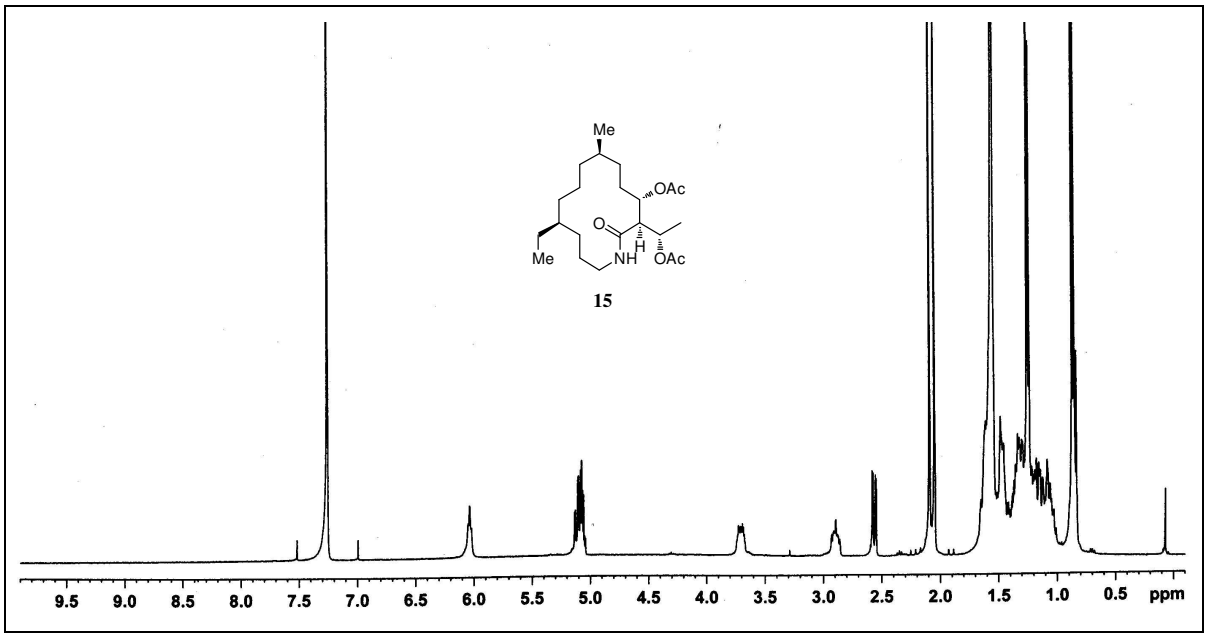
▲ ^{1}H-NMR (600 MHz, $CDCl_3$)



▲ ^{13}C-NMR (150 MHz, $CDCl_3$)

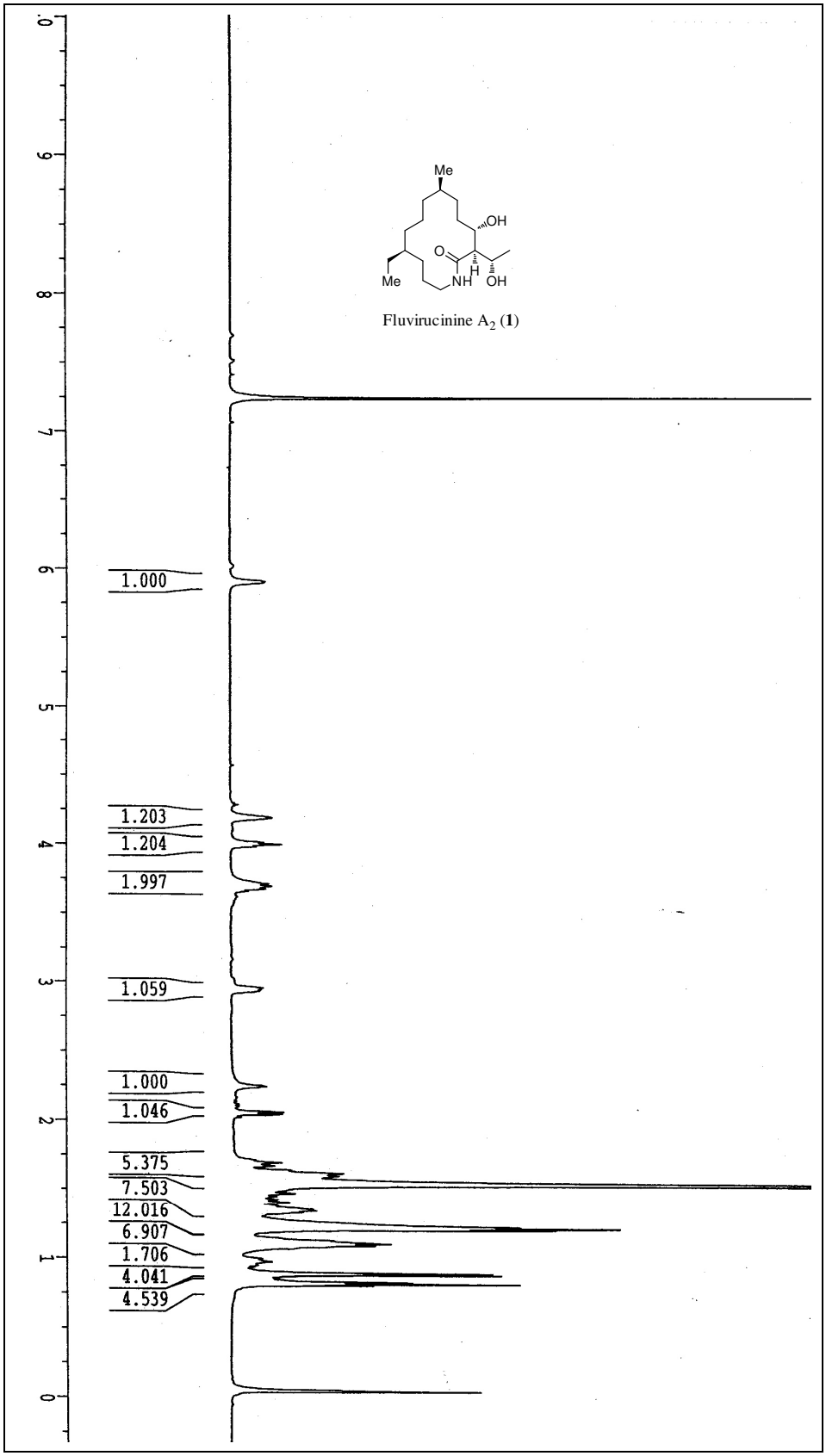


▲ ^{1}H-NMR (600 MHz, $CDCl_3$)



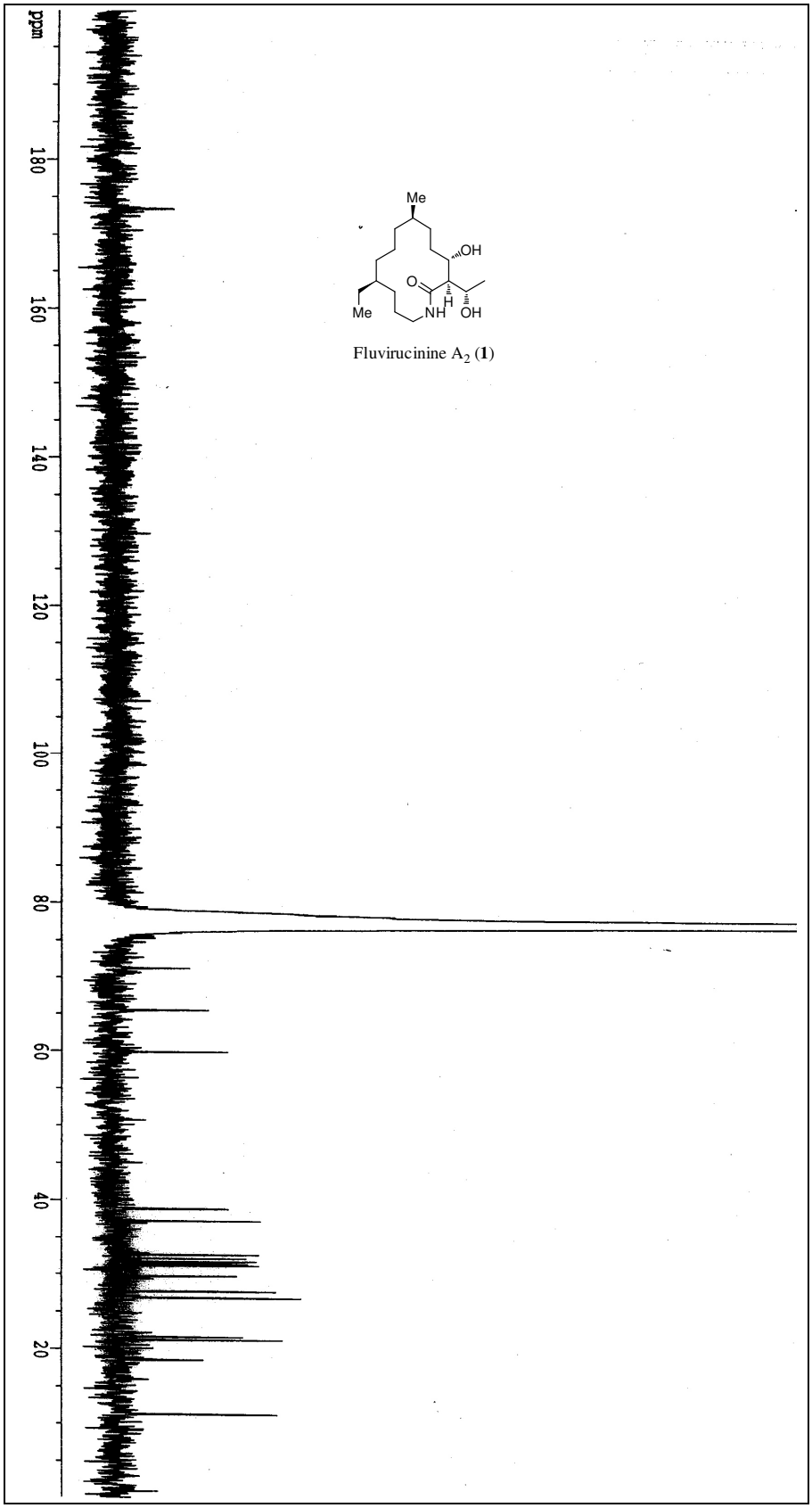
▲ ^{1}H-NMR (400 MHz, $CDCl_3$)

▲ ^{1}H-NMR (600 MHz, $CDCl_3$)



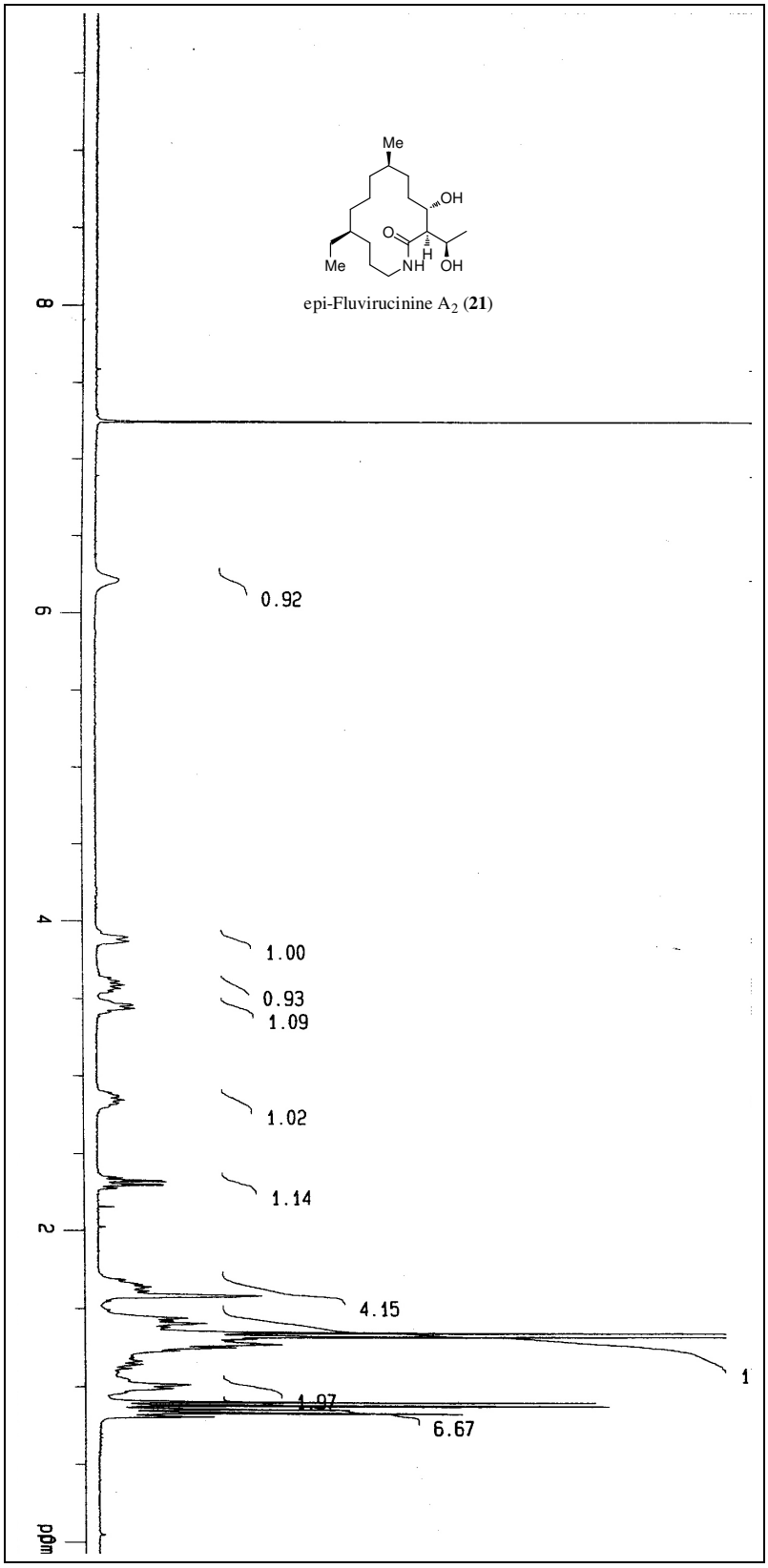
Fluvirucinine A_2 (**1**)

▲ ^{13}C-NMR (150 MHz, $CDCl_3$)

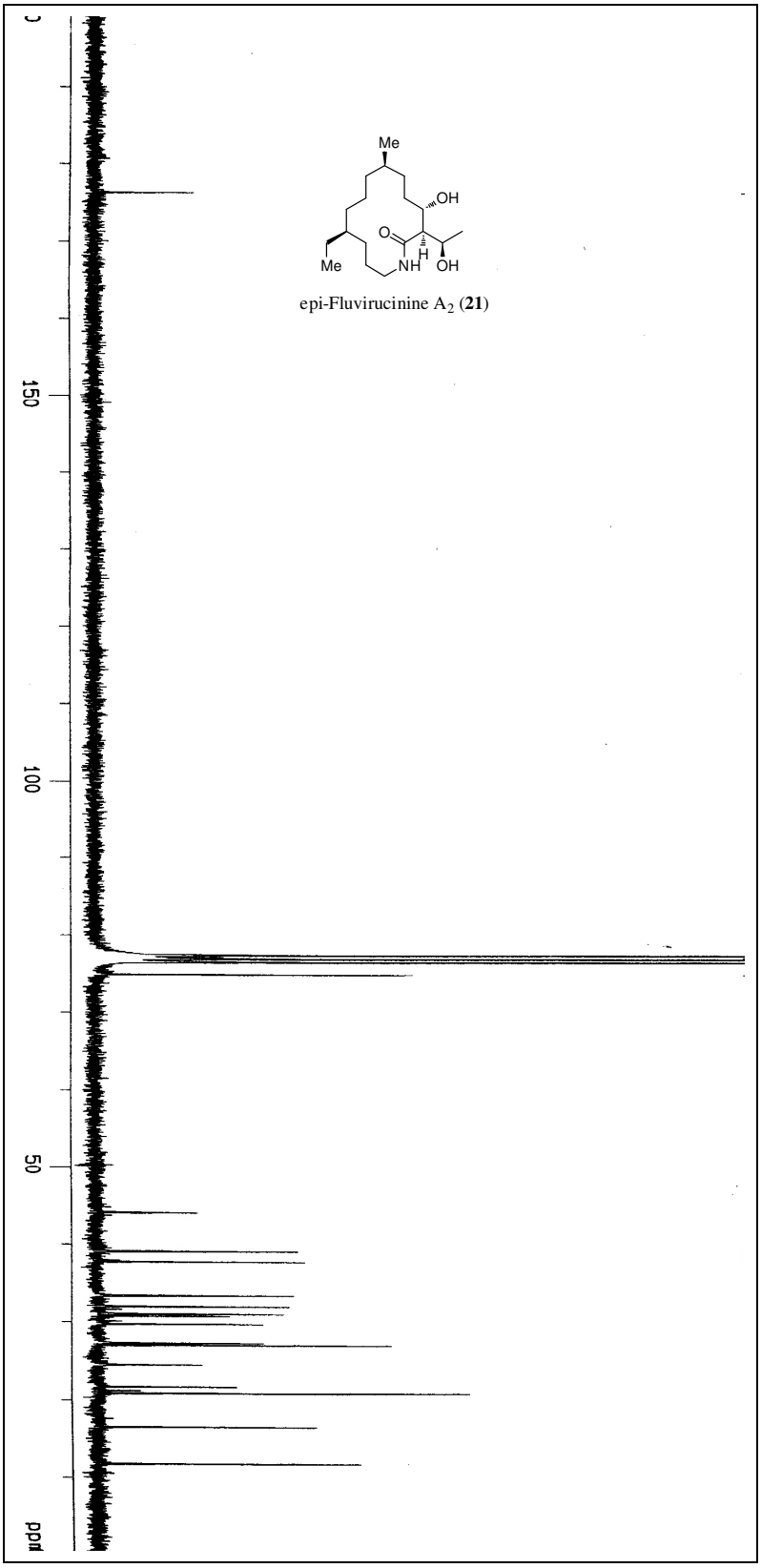


Fluvirucinine A_2 (**1**)

▲ ^{1}H-NMR (300 MHz, $CDCl_3$)



▲ ^{13}C-NMR (75 MHz, $CDCl_3$)



epi-Fluvirucinine A_2 (**21**)