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PAPER

A stereo-controlled access to functionalized macrolactams *via* an aza-Claisen rearrangement†

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A novel and stereo-controlled method for the preparation of functionalized macrolactams was developed. The process involves stereoselective enol ether formation, followed by an azacyclic ring expansion *via* an aza-Claisen rearrangement. Herewith, we describe a systematic investigation of an aza-Claisen rearrangement-induced ring expansion of azacycles prepared by appending *E*/*Z*-enol ethers to the medium-sized lactams as well as the stereochemical outcome. In addition, the strategy was successfully applied to the total synthesis of fluvirucinine A_1 and 3-*epi*-fluvirucinine A_1. This method offers an attractive alternative to the intramolecular amide–aldol reaction for the elaboration of β-alkoxy-α-substituted motifs.

Introduction

Macrolactams and related azacycles are often encountered in biologically active natural products,[1,2,3] and especially in drug candidates such as bioisosteres of macrolides.[4] However, direct cyclization approaches to the synthesis of macrocyclic rings are often limited because of entropic considerations, highly diluted conditions and the lack of functional diversity. A potential method to produce these heterocycles is to employ a lactam-ring-expansion strategy using the aza-Claisen rearrangement (ACR).[5] ACR-induced ring expansion, which offers an opportunity for the rapid assembly of complex alkaloids, such as macrolactams has been under emphasized, partly as a result of limited access to the requisite precursors.[1] In particular, the direct ring-expansion of medium-sized lactam precursors (*e.g.*, **1b**) *via* ACR has been limited, primarily because of the susceptibility of their lactam carbonyl to ring-opening during the requisite amidoalkylation.[6]

Our ring expansion strategy arises from the facile and stereoselective production of the β-alkoxy-α-substituted macrolactams **4** of diverse ring sizes[7] *via* ACR of the geometry-defined enol ether **3** as highly ordered intramolecular amide–aldol equivalents, as shown in Fig. 1. Furthermore, the ring-expanded macrolactams with an internal olefin were anticipated to serve as a scaffold for functionalized 1-azabicyclic systems (*e.g.*, **5**) with various ring sizes *via* an appropriate transannulation.[5,7c]

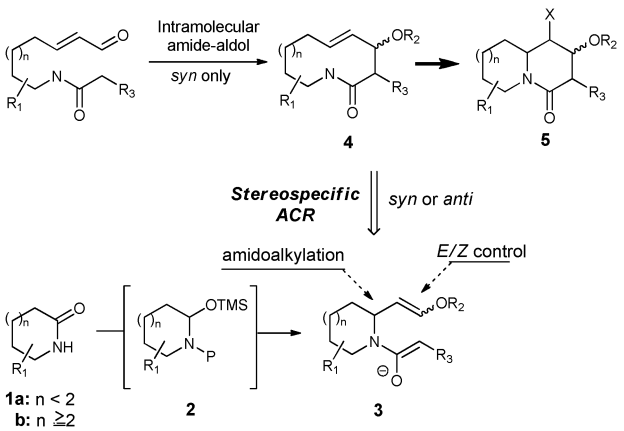

Fig. 1 Lactam ring expansion *via* ACR.

Recently, we reported the synthesis of bioactive natural products containing β-alkoxy-α-substituted azacyclic moieties.[7c,7d] Taking advantage of a highly stereospecific remote control of ACR-induced ring expansion, (*E*)-vinyl ether was successfully utilized to provide the *anti*-β-alkoxy-α-substituted azacycle,[7c] and this strategy was proven to be quite useful for a macrocyclic lactam *via* a vinylogous amide enolate-induced ring expansion.[7d] The successful applications of our strategy prompted us to undertake a systematic investigation of ACR-induced ring expansions of the larger ring-sized lactams to the corresponding functionalized macrolactams, as well as their stereochemical outcome, in view of both synthetic and bio-medicinal interests.

Herein, we describe a stereocontrolled approach for the synthesis of functionalized macrolactams that relies on efficient preparation of the medium-sized ACR precursors and a highly stereospecific ACR-induced ring expansion.[1,5,7]

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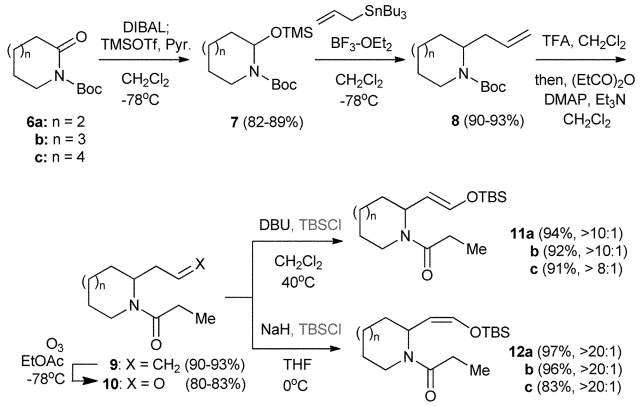
Results and discussion

We initially attempted to prepare medium-sized azacycles possessing an (*E*)- or (*Z*)-enol ether (Scheme 1). On the basis of extensive experimentation, it was eventually concluded that the direct and selective generation of the (*E*)- and (*Z*)-enol ethers **11** and **12** from the corresponding aldehyde **10** would be most effective in terms of functional diversity. Allylation of the *N*,*O*-acetal TMS ethers **7** provided the α-allylated azacycles **8** in excellent yield.[6] Boc-deprotection of **8** followed by amidation with propionic anhydride was carried out prior to the formation of the enol ether because of its lability in acidic conditions. Thus, removal of the Boc group with TFA and subsequent treatment of the resulting amine salt with propionic anhydride produced the requisite amide **9**. The aldehyde **10**, obtained from **9** by ozonolysis, could be converted into the (*E*)- and (*Z*)-silyl enol ethers **11** and **12**, respectively. Surprisingly, silylation under quite mild conditions (TBSCl, DBU, CH_2Cl_2, reflux) [7c,8a] resulted in the stereoselective formation of the desired (*E*)-enol ether **11** in excellent yield, along with a small amount of the corresponding (*Z*)-enol ether **12**. On the other hand, NaH treatment of **10** afforded exclusively the (*Z*)-enol ether **12** (>20 : 1).[8b,8d]

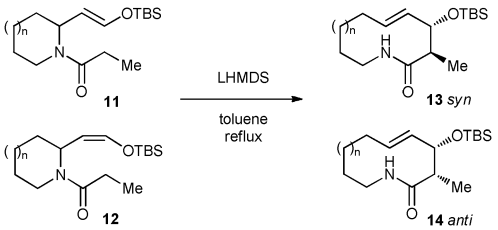


Scheme 1 Stereocontrolled silyl enol ether formation.

Examples of preferential (*E*)-silyl enol ether formation over the (*Z*)-silyl enol ether from the starting aldehyde are well known.[8a] However, the particularly high selectivity of the enol formation is noteworthy. The mechanistic basis for this excellent stereoselectivity is not yet entirely clear, although a plausible explanation based on the sterically less encumbered (*E*)-enolate silylation has been proposed.[7c,8c] For a sterically demanding (*Z*)-enolate silylation, Ukaji and Inomata proposed that the σ–π* interaction in the eclipsed conformation and/or 6π-electron homoaromacity stabilizes the *syn*-conformation against the steric hindrance in the transition state of deprotonation.[8d]

With the functionalized precursors **11** and **12** in hand, the projected ACR reactions were executed using established reaction conditions (LHMDS, toluene, reflux),[7] and the ring-expansion results are summarized in Table 1. To our delight, stereospecific aza-Claisen rearrangements of all substrates proceeded smoothly to afford the macrolactams **13** and **14** in good yields. Interestingly, the reaction was generally completed within 1 h, probably because of the beneficial effect of the electron-rich alkoxy substituent.[9] As anticipated, the (*E*)-enol ether substrates **11a–c** underwent ACR-induced ring expansion reactions to provide the *syn* diastereomers

Table 1 ACR of 1-acyl-2-alkoxyvinyl-azacycles



Entry	**10/11**	*n* (*E* : *Z*)	Product (**12/13**)[a]	Yield (%)[b]	*syn* : *anti*[c]
1	**11a**	2 (>10 : 1)	**13a**	70	>10 : 1
2	**11b**	3 (>10 : 1)	**13b**	78	>10 : 1
3	**11c**	4 (>8 : 1)	**13c**	73	>8 : 1
4	**12a**	2 (1 : <20)	**14a**	74	1 : <20
5	**12b**	3 (1 : <20)	**14b**	80	1 : <20
6	**12c**	4 (1 : <20)	**14c**	62	1 : <20

[a] All *N*,*O*-acetal TMS ethers were sufficiently stable for storage at room temperature. [b] Isolated yields. [c] Determined by ^{1}H-NMR spectra of the diastereomeric mixture or isolation yield of each isomer by flash column chromatography.

13a–c with nearly complete chirality transfer (Table 1, entries 1–3). The *anti* diastereomers **14a–c** were also obtained from the (*Z*)-enol ether substrates **12a–c** (Table 1, entries 4–6). The stereochemistry of the internal olefin in the ring expanded lactams **13** and **14** was confirmed to be (*E*) regardless of ring size, based on the ^{1}H-NMR coupling constant (~15 Hz) between the two olefinic protons. In addition, the relative stereochemistries of the newly created stereocenters for both rearrangement products were established by comparison of the coupling constants of the protons at the two stereocenters (~10 Hz for the *syn* diastereomer **13** *vs.* ~5 Hz for the *anti* diastereomer **14**). The complete chirality transfer and the confirmed internal (*E*)-olefin geometry of the present ACR were supported by the highly ordered chair-like transition state, as shown in Fig. 2.

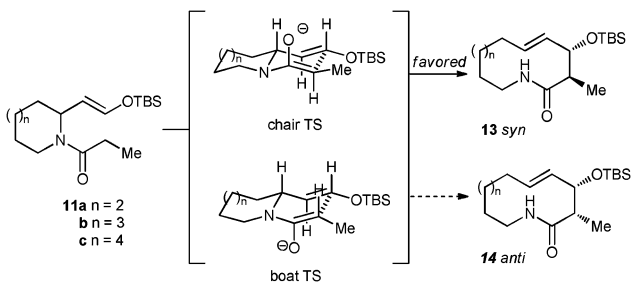
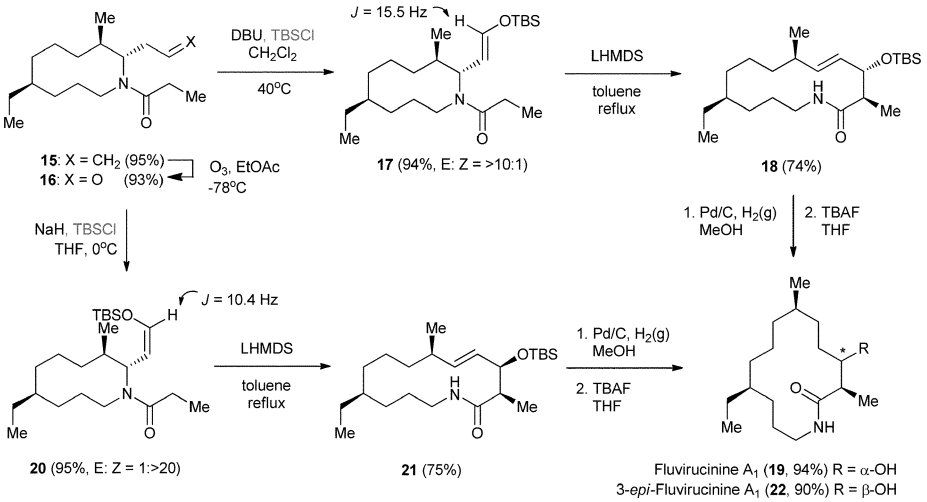


Fig. 2 Plausible transition states.

With a reliable protocol established for the synthesis of functionalized macrolactams, we turned our attention to the application of this method to the second-generation total synthesis of fluvirucinine A_1, an aglycon belonging to a potent antibiotic macrolactam family[3] (Scheme 2). It should be noted that when we reported the first total synthesis of fluvirucinine A_1,[7a] because of the lack of methods and knowledge, the direct preparation of the requisite functionalized azacycles from the corresponding lactams was not possible. The α-allyl azacycle **15** was prepared as previously reported[7d] by highly stereoselective amidoalkylation, with no detectable *cis*-isomer in high yield, *via* an *N*,*O*-acetal TMS



Scheme 2 Application to the total synthesis of fluvirucinine A_1.

ether intermediate. Subsequently, the azacycle **15** was converted into the aldehyde **16** by ozonolysis, and the resulting aldehyde **16** was then subjected to stereocontrolled silyl enol ether formation to afford the requisite ACR precursors **17** and **20**. Upon DBU treatment in the presence of TBSCl in refluxing CH_2Cl_2, highly stereoselective silylation afforded the (*E*)-enol ether **17**, and NaH treatment in the presence of TBSCl in THF afforded exclusively the (*Z*)-enol ether **20**. As anticipated, the (*E*)-enol ether **17** smoothly underwent stereospecific ACR to provide the *syn*-substituted 14-membered macrolactam **18**, possessing all four stereocenters of fluvirucinine A_1 in place. Finally, catalytic hydrogenation of the internal olefin followed by TBS removal with TBAF furnished synthetic fluvirucinine A_1 (**19**), which was identical in all aspects to the natural compound, **1**.[3] The (*Z*)-enol ether **20** also provided the corresponding macrolactam **21** under the standard ACR conditions,[7] which yielded to 3-*epi*-fluvirucinine A_1 (**22**) in a manner analogous to the synthesis of fluvirucinine A_1 (**19**).

Conclusions

In summary, a novel and stereocontrolled method for the preparation of functionalized macrolactams with defined stereogenic centers was developed. The process employs a versatile and stereoselective (*E*)- and (*Z*)-enol ether formation, with subsequent lactam-ring-expansion *via* ACR of the medium-sized 1-acyl-2-alkoxyvinyl-azacycles. This approach could offer an attractive alternative to the intramolecular amide–aldol reaction for the elaboration of β-alkoxy-α-substituted motifs. We believe our strategy could also serve as a new tool for the preparation of structurally diverse alkaloids, including functionalized macrolactams.

Experimental section

General

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 over sodium benzophenone ketyl. Dichloromethane, triethylamine and pyridine were freshly distilled over 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. 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 a JEOL JMS-700 instrument. High-resolution chemical ionization (CI) mass spectra were obtained with a JEOL JMS-AX 505WA instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500, Avance 400, or JEOL JNM-LA 300 spectrometer as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$: ^{1}H-NMR, δ 7.24 ppm, ^{13}C-NMR, δ 77.0 ppm). ^{1}H-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 resonance), number of protons, and coupling constants in hertz (Hz).

General procedure for the synthesis of 8a–c

N,*O*-Acetal TMS ethers **7a–c** were prepared from **6a–c** according to the reported procedure.[6a] To a solution of *N*,*O*-acetal TMS ether **7a** (962 mg, 3.4 mmol) in CH_2Cl_2 (20.0 mL) were added allyltributyltin (2.6 mL, 10.0 mmol) and $BF_3{\cdot}OEt_2$ (0.4 mL, 3.4 mmol) at –78 °C. The reaction mixture was stirred for 30 min, and then slowly warmed to 0 °C. The mixture was quenched with triethylamine (2.0 mL) and concentrated under reduced pressure. The residue was purified by flash column chromatography (9% EtOAc in hexane) to afford **8a** as a colorless oil. Azacycles **8b–c** were synthesized by analogy with **8a**.

***tert*-Butyl 2-(prop-2-en-1-yl)azepane-1-carboxylate (8a).** Yield: 93% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max}

2925, 1685, 1408, 1165 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.74 (m, 1H), 5.01–4.94 (m, 2H), 4.01–3.58 (m, 2H), 2.66 (m, 1H), 2.15–2.02 (m, 2H), 1.74–1.18 (m, 17H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 155.5, 155.2, 135.1, 116.3, 116,0, 78.7, 78.4, 78.4, 77.2, 55.3, 54.0, 41.6, 41.1, 39.5, 39.2, 33.7, 33.4, 29.5, 28.9, 28.6, 28.2, 25.0, 24.7; LR-MS (FAB^+) m/z 240 ($M + H^+$).

***tert*-Butyl 2-(prop-2-en-1-yl)azocane-1-carboxylate (8b).** Yield: 90% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2922, 1691, 1406, 1364, 1147 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.72 (m, 1H), 4.99–4.90 (m, 2H), 4.06 and 3.80 (m, 1H), 3.32 (m, 1H), 2.96 and 2.82 (m, 1H), 2.14–1.22 (m, 21H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 155.3, 154.8, 155.1, 116.2, 115.9, 78.2, 77.2, 59.8, 55.6, 54.4, 40.7, 39.1, 39.0, 29.5, 28.7, 28.0, 27.5, 26.4, 26.0, 25.8, 24.4, 24.0; LR-MS (FAB^+) m/z 254 ($M + H^+$).

***tert*-Butyl 2-(prop-2-en-1-yl)azonane-1-carboxylate (8c).** Yield: 92% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2919, 1693, 1167 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.70 (m, 1H), 4.95 (m, 2H), 4.06 (m, 1H), 3.22 and 2.83 (m, 2H), 2.09 (m, 2H), 1.80–1.23 (m, 21H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 156.5, 155.9, 135.6, 135.4, 116.6, 116.2, 78.9, 78.7, 56.6, 55.4, 41.4, 39.1, 28.9, 28.4, 27.1, 26.6, 26.4, 25.0, 24.1, 23.8; HR-MS (FAB^+) calcd for $C_{16}H_{30}NO_2$ ($M + H^+$): 268.2277; found 268.2277.

General procedure for the synthesis of 9a–c

To a solution of **8a** (187 mg, 0.8 mmol) in CH_2Cl_2 (4 mL) was added TFA (0.3 mL) at 0 °C, and the reaction 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 crude ammonium salt and DMAP (cat. amount) in CH_2Cl_2 (4.0 mL) was added triethylamine (0.3 mL, 2.5 mmol) and propionic anhydride (0.16 mL, 1.3 mmol). The resulting solution was stirred for 24 h. Volatiles were removed under reduced pressure, and the remaining 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 (30% EtOAc in hexane) to afford **9a** as a colorless oil. Amides **9b–c** were synthesized by analogy with **9a**.

1-[2-(Prop-2-en-1-yl)azepan-1-yl]propan-1-one (9a). Yield: 91% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2928, 2855, 1639, 1424 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.24 (m, 1H), 5.56–5.43 (m, 2H), 5.02 and 4.18 (m, 1H), 4.59 and 4.01 (m, 1H), 3.45 and 3.07 (m, 1H), 2.92–1.65 (m, 12H), 1.63 (td, 3H, J = 7.3, 2.0 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.3, 172.8, 134.1, 133.1, 116.8, 115.6, 77.1, 55.3, 52.2, 41.6, 39.5, 38.9, 38.1, 33.4, 32.0, 29.3, 29.0, 28.5, 26.8, 26.4, 23.9, 23.8, 8.2; LR-MS (ESI) m/z 196.2 ($M + H^+$), 218.2 ($M + Na^+$).

1-[2-(Prop-2-en-1-yl)azocan-1-yl]propan-1-one (9b). Yield: 93% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2928, 1731, 1639, 1420 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.69 (m, 1H), 5.03–4.90 (m, 2H), 4.51 and 3.78 and 3.37 and 3.15 and 2.75 (m, 3H), 2.33 (m, 2H), 2.16–1.95 (m, 2H), 1.70–1.28 (m, 10H), 1.10 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 174.6, 173.5, 135.3, 133.9, 117.7, 116.2, 57.1, 40.3, 39.3, 38.9, 29.4, 29.2, 28.8, 27.5, 27.4, 27.1, 26.7, 26.6, 26.5, 26.4, 26.0, 25.9, 25.8, 24.1, 23.9, 20.7, 13.9, 13.3, 9.6, 9.2, 8.8; LR-MS (ESI) m/z 210.6 ($M + H^+$), 232.8 ($M + Na^+$).

1-[2-(Prop-2-en-1-yl)azonan-1-yl]propan-1-one (9c). Yield: 90% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2921, 1641, 1418, 1352 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.69 (m, 1H), 5.01–4.87 (m, 2H), 3.68 and 3.28 and 3.04 (m, 2H), 2.64 and 2.31 (m, 1H), 2.37 (q, 2H, J = 14.8, 7.5 Hz), 2.15–1.14 (m, 14H), 1.08 (td, 3H, J = 7.3, 1.5 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 174.2, 135.7, 134.2, 117.8, 116.4, 58.0, 42.0, 39.2, 29.7, 27.9, 27.7, 27.2, 27.1, 26.5, 26.2, 25.6, 24.8, 23.8, 23.3, 17.5, 13.5, 9.8, 9.4, 8.9; LR-MS (ESI) m/z 224.2 ($M + H^+$), 246.1 ($M + Na^+$).

General procedure for the synthesis of 10a–c

Ozone was bubbled through a solution of **9a** (190 mg, 1.0 mmol) in EtOAc (10.0 mL) at −78 °C until the solution turned light blue. To this solution was added Ph_3P (1.3 g, 4.9 mmol) at −78 °C. After the reaction mixture was stirred at room temperature for 12 h, volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (30 to 33% EtOAc in hexane) to afford **10a** as a colorless oil. **10b–c** were synthesized in analogy to **10a**.

(1-Propanoylazepan-2-yl)acetaldehyde (10a). Yield: 82% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2928, 2855, 1721, 1629, 1427, 1375 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.71 and 9.63 (m, 1H), 4.80 and 4.21 (m, 1H), 4.06 and 3.49 (m, 1H), 2.96 and 2.43–2.21 (m, 5H), 2.03–1.11 (m, 8H), 1.06 (t, 3H, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 199.9, 199.2, 173.6, 172.3, 50.5, 49.2, 48.7, 41.9, 40.2, 34.4, 33.3, 29.7, 29.2, 27.1, 26.0, 25.9, 245, 24.1, 13.6, 8.9; HR-MS (FAB^+) calcd for $C_{11}H_{20}NO_2$ ($M + H^+$) 198.1494; found 198.1499.

(1-Propanoylazocan-2-yl)acetaldehyde (10b). Yield: 80% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2929, 2857, 1720, 1635, 1422 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.73 and 9.66 (m, 1H), 4.70 and 4.24 and 3.81 and 3.42–3.19 and 2.69 (m, 3H), 2.60–2.26 (m, 4H), 2.02–1.22 (m, 10H), 1.10 (t, 3H, J = 7.3 Hz);^{13}C-NMR ($CDCl_3$, 100 MHz) δ 200.6, 199.4, 174.4, 173.0, 51.5, 50.3, 49.0, 48.8, 43.6, 40.8, 30.0, 29.5, 28.2, 26.6, 26.1, 25.9, 25.8, 25.7, 25.5, 25.0, 24.3, 23.9, 9.3, 9.1; HR-MS (FAB^+) calcd for $C_{12}H_{22}NO_2$ ($M + H^+$) 212.1651; found 212.1650.

(1-Propanoylazonan-2-yl)acetaldehyde (10c). Yield: 83% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2923, 2725, 1721, 1638, 1420 cm^{-1}; ^{1}H-NMR (CDCl3, 300 MHz) δ 9.66 and 9.60 (m, 1H), 4.62 and 4.26 and 3.71 and 3.28 (m, 3H), 2.72 and 2.46 (m, 2H), 2.39–2.24 (q, 2H, J = 14.8, 7.3 Hz), 1.99–1.33 (m, 12H), 1.05 (t, 3H, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 200.8, 199.3, 175.0, 173.7, 52.2, 48.8, 48.7, 42.5, 30.5, 30.4, 27.7, 27.3, 27.2, 27.1, 26.7, 26.4, 25.9, 25.4, 24.7, 24.5, 23.7, 23.6, 9.3, 9.2; HR-MS (FAB^+) calcd for $C_{13}H_{24}NO_2$ ($M + H^+$): 226.1807; found 226.1807.

General procedure for the synthesis of (*E*)-enol ethers 11a–c

A mixture of **10a** (30 mg, 0.2 mmol), TBSCl (35 mg, 0.2 mmol) and DBU (68 µL, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was 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 column

chromatography on silica gel (5 to 10% EtOAc in hexane, silica gel deactivated with Et_3N) to give an inseparable mixture of *E*- and *Z*-enol ether **11a** as a colorless oil. The *E*/*Z* ratio of 10 : 1 was determined by integration of signals for 6.34 and 6.10 (d, 10H, J = 12.1 Hz) and 6.04 (d, 1H, J = 5.9 Hz) of the ^{1}H-NMR spectrum. Enol ethers **11b–c** were synthesized by analogy with **11a**.

1-{2-[(*E*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethenyl]azepan-1-yl}propan-1-one (11a). Yield: 94% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2931, 2857, 1642, 1467, 1417, 1254, 1169 cm-1; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.34 and 6.10 (d, 1H, J = 12.1 Hz), 4.84 (dd, 1H, J = 12.1. 6.2 Hz), 4.78 and 4.01 and 3.38 and 2.87 and 2.49 (m, 3H), 2.28–2.17 (m, 2H), 1.92–1.13 (m, 8H), 1.02 (t, 3H, J = 7.3 Hz), 0.79 (s, 9H), 0.02 and 0.00 (s, 6H); HR-MS (FAB$^+$) calcd for $C_{17}H_{34}NO_2Si$ (M + H$^+$): 312.2359; found 312.2352.

1-{2-[(*E*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethenyl]azocan-1-yl}propan-1-one (11b). Yield: 89% (isolated); colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.31 and 6.10 (d, 1H, J = 12.1 Hz), 4.84 (dd, 1H, J = 12.1, 5.7 Hz), 4.89 and 4.02 and 3.70 and 3.32 and 3.07 and 2.70 (m, 3H), 2.34–2.17 (m, 2H), 1.97–1.18 (m, 10H), 1.05 (t, 3H, J = 7.3 Hz), 0.82 (s, 9H), 0.02 and 0.00 (s, 6H); HR-MS (FAB$^+$) calcd for $C_{18}H_{36}NO_2Si$ (M + H$^+$): 326.2515; found 326.2506.

1-{2-[(*E*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethenyl]azonan-1-yl}propan-1-one (11c). Yield: 91% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2931, 2857, 1637, 1466, 1425, 1255, 1177 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.27 and 6.11 (d, 1H, J = 12.1 Hz), 4.81 (dd, 1H, J = 12.1, 6.0 Hz), 4.91 and 4.08 and 3.61 and 3.27 and 2.99 and 2.61 (m, 3H), 2.36–2.15 (m, 2H), 1.92–1.13 (m, 12H), 1.06–0.98 (m, 3H), 0.79 (s, 9H), 0.00 (s, 6H); HR-MS (FAB$^+$) calcd for $C_{19}H_{38}NO_2Si$ (M + H$^+$) 340.2672; found 340.2668.

General procedure for the synthesis of (*Z*)-enol ethers 12a–c

Amide **10a** (41.0 mg, 0.2 mmol) was added to a suspension NaH (60% suspension in mineral oil, 50 mg, 1.3 mmol) in THF (1.0 mL) at 0 °C. TBSCl (160.0 mg, 1.0 mmol) was then added, and the bath was removed. Stirring was continued for 1 h, and the reaction mixture was concentrated under reduced pressure to *ca.* 0.5 mL. 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 (*Z*)-enol ether **12a** exclusively, as a colorless oil. Enol ethers **12b–c** were synthesized by analogy with **12a**.

1-{2-[(*Z*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethenyl]azepan-1-yl}propan-1-one (12a). Yield: 97% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2932, 2857, 1643, 1422, 1258, 1230, 1126 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.02 (d, 1H, J = 5.9 Hz), 4.54 (m, 1H), 4.29 (dd, 1H, J = 8.6, 5.9 Hz), 3.98 (m, 1H), 2.50 (m, 1H), 2.24 (m, 2H), 1.91–1.03 (m, 8H), 0.98 (t, 3H, J = 7.3 Hz), 0.79 (s, 9H), 0.01 and –0.04 (s, 6H); HR-MS (FAB$^+$) calcd for $C_{17}H_{34}NO_2Si$ (M + H$^+$) 312.2359; found 312.2364.

1-{2-[(*Z*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethenyl]azocan-1-yl}propan-1-one (12b). Yield: 96% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2930, 2857, 1620, 1466, 1253 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.10 (dd, 1H, J = 5.9, 0.9 Hz), 4.66 (m, 1H), 4.43 (dd, 1H, J = 11.9, 3.5 Hz), 2.43 (q, 2H, J = 7.5 Hz), 2.27 (q, 0.3H, J = 7.3 Hz), 1.96 (m, 1H), 1.79–1.40 (m, 10H), 1.12 (td, 3H, J = 7.5, 2.4 Hz), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); HR-MS (FAB$^+$) calcd for $C_{18}H_{36}NO_2Si$ (M + H$^+$) 326.2515; found 326.2515.

1-{2-[(*Z*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethenyl]azonan-1-yl}propan-1-one (12c). Yield: 83% (isolated); colorless oil; FT-IR (thin film, neat) ν_{max} 2929, 2857, 1645, 1256, 840 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.00 (dd, 1H, J = 5.8, 0.9 Hz), 4.64 (m, 1H), 4.35 (dd, 1H, J = 8.2, 5.8 Hz), 3.65 (m, 1H), 2.65 (m, 1H), 2.41 (q, 2H, J = 7.5 Hz), 1.75–1.30 (m, 12H), 1.03 (t, 1H, J = 7.3 Hz), 0.82 (s, 9H), 0.03 (s, 9H); HR-MS (FAB$^+$) calcd for $C_{19}H_{38}NO_2Si$ (M + H$^+$) 340.2672; found 340.2672.

General procedure for the synthesis of 13a–c and 14a–c

Lactams **13a–c** and **14a–c** were prepared from **11a–c** and **12a–c** respectively according to the standard procedure.[7] Representative procedure: to a solution of **11a** (35.0 mg, 0.1 mmol) in toluene (2.0 mL) was added dropwise LHMDS (1.0 M solution in hexane, 0.2 mL, 0.2 mmol) at 130 °C, the resulting solution was refluxed for 30 min. After addition of water, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (15% EtOAc in hexane) to afford **13a** as a white solid.

3,4-*syn*-(5*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylazacycloundec-5-en-2-one (13a). Yield: 70% (isolated); white solid; m.p. 156–157 °C; FT-IR (thin film, neat) ν_{max} 3293, 2930, 1643, 1552 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.61 (bs, 1H), 5.37 (ddd, 1H, J = 15.5, 9.9, 4.2 Hz), 5.25 (dd, 1H, J = 15.7, 7.3 Hz), 3.9 (dd, 1H, J = 8.0 Hz), 3.65 (m, 1H), 2.48 (m, 1H), 2.23–2.02 (m, 2H), 1.78–1.02 (m, 6H), 1.14 (d, 3H, J = 6.6 Hz), 0.81 (s, 9H), 0.02 and –0.04 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.6, 133.5, 130.8, 77.4, 49.9, 39.1, 33.2, 28.0, 25.8, 25.2, 22.6, 18.1, 13.7, –4.1, –4.8; HR-MS (FAB$^+$) calcd for $C_{17}H_{34}NO_2Si$ (M + H$^+$) 312.2359; found 312.2359.

3,4-*syn*-(5*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylazacyclododec-5-en-2-one (13b). Yield: 78% (isolated); white solid; m.p. 183–184 °C; FT-IR (thin film, neat) ν_{max} 3286, 2931, 1641, 1555 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.37 (ddd, 1H, J = 15.3, 10.1, 3.8 Hz), 5.25 (dd, 1H, J = 15.7, 7.3 Hz), 5.20 (bd, 1H, J = 10.4 Hz), 4.00 (dd, 1H, J = 8.3 Hz), 3.90 (m, 1H), 2.72 (m, 1H), 2.18–1.92 (m, 3H), 1.58–1.06 (m, 8H), 1.21 (d, 3H, J = 6.8 Hz), 0.86 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.9, 132.3, 132.2, 76.8, 50.3, 35.8, 30.0, 26.6, 25.8, 24.9, 23.9, 20.9, 18.0, 14.5, –4.0, –4.8; HR-MS (FAB$^+$) calcd for $C_{18}H_{36}NO_2Si$ (M + H$^+$) 326.2515; found 326.2520.

3,4-*syn*-(5*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylazacyclotridec-5-en-2-one (13c). Yield: 73% (isolated); white solid; m.p. 160–161 °C; FT-IR (thin film, neat) ν_{max} 3346, 2929, 1646, 1537 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.89 (bs, 1H), 5.63 (dt, 1H, J = 15.2, 6.0 Hz), 5.35 (dd, 1H, J = 15.4, 5.7 Hz), 4.04 (dd, 1H, J = 12.6, 5.8 Hz), 3.60 (m, 1H), 2.68 (m, 1H), 2.21 (dt, 1H, J = 14.1, 7.1 Hz), 1.95(m, 2H), 1.55–1.03 (m, 10H), 1.11 (d, 3H, J = 7.0 Hz), 0.82 (s, 9H), 0.00 and –0.04 (s, 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.7, 133.3, 130.1, 74.9, 48.4, 38.8, 31.1, 27.3, 27.1, 26.6, 26.4, 25.8, 24.9, 18.1, 14.5, –4.4, –4.9; HR-MS (FAB$^+$) calcd for $C_{19}H_{38}NO_2Si$ (M + H$^+$) 340.2672; found 340.2674.

3,4-*anti*-(5*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylazacycloundec-5-en-2-one (14a). Yield: 74% (isolated); colorless oil;

FT-IR (thin film, neat) ν_{max} 3342, 2927, 2857, 1635, 1533, 1461, 1254, 1077 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.89 (bs, 1H), 5.43 (dt, 1H, J = 13.5, 6.8 Hz), 5.37 (dd, 1H, J = 15.0, 6.4 Hz), 4.38 (dd, 1H, J = 5.1 Hz), 3.62 (m, 1H), 2.58 (m, 1H), 2.12–1.97 (m, 2H), 1.82–1.20 (m, 6H), 1.13 (d, 3H, J = 7.1 Hz), 0.87 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.6, 130.9, 130.4, 74.3, 49.5, 48.5, 38.9, 33.5, 29.7, 25.9, 25.5, 22.3, 18.1, –4.4. –4.8; HR-MS (FAB$^+$) calcd for $C_{17}H_{34}NO_2Si$ (M + H$^+$) 312.2359; found 312.2352.

3,4-*anti*-(5*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylazacyclododec-5-en-2-one (14b). Yield: 80% (isolated); white solid; FT-IR (thin film, neat) ν_{max} 3338, 2927, 2856, 1633, 1538, 1072 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.06 (bs, 1H), 5.59 (dtd, J = 15.3, 7.2, 1.3 Hz), 5.44 (ddt, J = 15.3, 5.3, 1.3 Hz), 4.38 (m, 1H), 3.77 (dtd, J = 13.2, 9.7, 3.5 Hz), 2.74 (m, 1H), 2.59 (m, 1H), 2.14–2.09 (m, 2H), 1.42–1.25 (m, 8H), 1.20 (d, 3H, J = 7.3 Hz), 0.92 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.5, 133.1, 129.0, 73.7, 47.7, 37.3, 31.3, 26.8, 26.2, 25.9, 24.8, 22.6, 18.2, 13.2, –4.4, –4.8; HR-MS (FAB$^+$) calcd for $C_{18}H_{36}NO_2Si$ (M + H$^+$) 326.2515; found 326.2509.

3,4-*anti*-(5*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylazacyclotridec-5-en-2-one (14c). Yield: 62% (isolated); white solid; m.p. 74–76 °C; FT-IR (thin film, neat) ν_{max} 3361, 2928, 2856, 1644, 1536, 1462, 1253, 1065 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.64 (bs, 1H), 5.67 (m, 1H), 5.39 (m, 1H), 4.17 (s, 1H), 3.58 (m, 1H), 2.65 (m, 1H), 2.45 (m, 1H), 1.95–0.64 (m, 19H), 0.05 (s, 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 174.7, 132.0, 13.0, 73.3, 47.1, 38.1, 31.5, 27.8, 27.1, 26.6, 26.5, 25.9, 24.0, 18.0, 16.4, –4.4, –4.7; HR-MS (FAB$^+$) calcd for $C_{19}H_{38}NO_2Si$ (M + H$^+$) 340.2672; found 340.2670.

Total synthesis of fluvirucinin A$_1$

2-[(2*S*,3*R*,7*S*)-7-Ethyl-3-methyl-1-propionylazecanyl] acetaldehyde (16). Amide **15** were prepared according to the reported procedure.[7d] A solution of **15** (640.0 mg, 2.3 mmol) in EtOAc (25.0 mL) was cooled to –78 °C, and ozone was bubbled until the solution turned light blue. To this solution was added Ph_3P (6.9 mmol) at –78 °C. After the reaction mixture was stirred at room temperature for 12 h, it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (17% EtOAc in hexane) to afford **16** (602.0 mg, 2.2 mmol, 93%) as a colorless oil; $[\alpha]_D^{20}$ +11.8 (*c* 0.24, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 2960, 2925, 1723, 1644, 1464, 1422 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.68 and 9.61 (s, 1H), 4.16 (bs, 0.6H), 3.96 (m, 0.2H), 3.78 (m, 0.2H), 3.24 (m, 2H), 2.66 (m, 3H), 2.41 (m, 0.1H), 2.32 (m, 1H), 2.26 (qd, 2H, J = 7.4, 1.4 Hz), 1.78–1.10 (m, 12H), 1.05 (t, 3H, J = 7.4 Hz), 0.86 (t, 3H, J = 6.6 Hz), 0.80 (t, 3H, J = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 201.5, 199.5, 175.7, 57.4, 46.2, 45.9, 40.2, 38.0, 36.9, 35.1, 31.6, 30.7, 30.0, 29.8, 29.2, 27.9, 27.3, 26.1, 25.0, 24.0, 18.8, 18.0, 12.0, 11.9, 9.5, 9.4; HR-MS (EI$^+$) calcd for $C_{17}H_{31}NO_2$ (M$^+$) 281.2355; found 281.2345.

1-[(2*R*,3*R*,7*S*)-2-((*E*)-2-[*tert*-Butyl(dimethyl)silyl]oxyethenyl)-7-ethyl-3-methylazecanyl]-1-propanone (17). A mixture of **16** (375.0 mg, 1.3 mmol), TBSCl (401.0 mg, 2.7 mmol) and DBU (0.3 mL, 2.0 mmol) in CH_2Cl_2 (10.0 mL) was 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 column chromatography on silica gel (9% EtOAc in hexane, silica gel deactivated with Et_3N) to give an inseparable diastereomeric mixture of (*E*)-enol ether **17** (494.0 mg, 1.3 mmol, 94%). The *E*/*Z* ratio of >10 : 1 was determined by integration of signals for C3–H of the ^{1}H-NMR spectrum (6.25 and 6.18 (d, J = 11.9 Hz, 22.3H, C3-H(*E*)), 6.17 (d, J = 5.5 Hz, 1H, C3–H (*Z*)); $[\alpha]_D^{20}$ –18.4 (*c* 0.18, CH_2Cl_2); FT-IR (thin film, neat) ν_{max} 2957, 2930, 1651, 1465, 1361, 1171 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.25 and 6.18 (d, 1H, J = 11.9 Hz), 5.13 (bs, 0.6H), 4.90 (dd, 0.4H, J = 11.9, 9.3 Hz), 3.68–3.52 (bm, 1H), 3.30 (bs, 1H), 3.06 and 2.78 (s, 1H), 2.21 (qd, 2H, J = 7.3, 2.2 Hz), 1.87–1.11 (m, 14H), 1.03 and 1.02 (t, 3H, J = 7.3 Hz), 0.82 and 0.81 (s, 9H), 0.75 (t, 3H, J = 6.6 Hz), 0.81–0.73 (m, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 174.6, 142.7, 110.3, 109.8, 36.3, 34.8, 31.5, 29.5, 28.0, 27.5, 25.6, 25.5, 25.4, 22.6, 19.5, 18.3, 18.2, 17.9, 14.1, 12.0, 11.9, 9.5, 9.4, –3.6, –5.2, –5.3; HR-MS (EI$^+$) calcd for $C_{23}H_{45}NO_2Si$ (M$^+$) 395.3220; found 395.3218.

(3*R*,4*S*,7*R*,11*S*)-4-[*tert*-Butyl (dimethyl)silyl]oxy-11-ethyl-3,7-dimethyl-1-aza-5-cyclotetradecen-2-one (18). To a solution of **17** (105.0 mg, 0.3 mmol) in toluene (5.0 mL) was added dropwise LHMDS (1.0 M solution in hexane, 0.5 mL, 0.5 mmol) at 130 °C and the 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 **18** (79.0 mg, 0.2 mmol, 74%) as a white solid; $[\alpha]_D^{20}$ +87.7 (*c* 0.11, CH_3OH); FT-IR (thin film, neat) ν_{max} 3295, 2928, 2858, 1643, 1549, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.78 (s, 1H), 5.26 (dd, 1H, J = 15.3, 8.3 Hz), 5.13 (dd, 1H, J = 15.3, 8.3 Hz), 4.10 (d, 1H, J = 8.8 Hz), 3.76 (m, 1H), 2.43 (td, 1H, J = 8.8, 4.9 Hz), 2.08 (ddd, 1H, J = 15.8, 13.6, 6.8 Hz), 1.44–1.10 (m, 14H), 1.13 (d, 3H, J = 6.8 Hz), 0.88 (d, 3H, J = 6.7 Hz), 0.83 (q, 2H, J = 6.8 Hz), 0.81 (s, 9H), 0.01 (s, 3H), –0.04 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 174.4, 138.3, 130.5, 75.6, 49.3, 39.9, 37.9, 36.2, 31.9, 27.2, 26.7, 25.9, 25.6, 24.2, 21.9, 21.1, 18.1, 16.0, 12.1, –3.9, –4.8; HR-MS (EI$^+$) calcd for $C_{23}H_{45}NO_2Si$ (M$^+$) 395.3220; found 395.3221.

(3*R*,4*S*,7*R*,11*S*)-11-Ethyl-4-hydroxy-3,7-dimethyl-1-azacyclotetradecan-2-one (19, fluvirucinine A$_1$). A solution of **18** (75.0 mg, 0.2 mmol) and 10% Pd/C in 8.0 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 a celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (only EtOAc) to afford the corresponding hydrogenated lactam (76.0 mg, 0.2 mmol, 99%) as white solid; $[\alpha]_D^{20}$ +125.0 (*c* 0.08, CH_3OH); FT-IR (thin film, neat) ν_{max} 3320, 1636, 1556 cm^{-1}; ^{1}H-NMR ($CDCl^3$, 300 MHz) δ 6.63 (bd, 1H, J = 7.6 Hz), 4.01 (m, 1H), 3.74(m, 1H), 2.57–2.41 (m, 2H), 1.78–0.81 (m, 18H), 1.10 (d, 3H, J = 7.1 Hz), 0.91 (s, 9H), 0.84 (d, 3H, J = 6.8 Hz), 0.83 (t, 3H, J = 7.1 Hz), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.8, 74.8, 46.0, 38.9, 38.8, 35.0, 32.1, 30.6, 27.5, 27.0, 25.9, 24.1, 23.8, 23.4, 20.8, 18.0, 14.4, 11.9, –4.5, –4.6; HR-MS (EI$^+$) calcd for $C_{23}H_{47}NO_2Si$ (M$^+$) 397.3220; found 397.3221.

To a solution of above hydrogenated lactam (76.0 mg, 0.2 mmol) in THF (5.0 mL) was added TBAF (1.0 M solution in THF, 0.2 mL, 0.2 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 (9% MeOH in EtOAc) to afford fluvirucinine A$_1$ **19** (50.0 mg,

0.2 mmol, 95%) as a white solid; $[\alpha]_D^{20}$ +140.5 (*c* 0.1, CH_3OH); FT-IR (thin film, neat) ν_{max} 3305, 2918, 1637, 1541 cm^{-1}; ^{1}H-NMR ($CDCl_3$: CD_3OD = 1 : 1, 300 MHz) δ 3.50 (m, 1H), 3.38 (m, 1H), 2.71 (m, 1H), 2.09 (dq, 1H, J = 9.5, 6.8 Hz), 1.55–0.89 (m, 18H), 1.05 (d, 3H, J = 6.8 Hz), 0.78 (d, 3H, J = 7.1 Hz), 0.72 (t, 3H, J = 7.1 Hz); ^{13}C-NMR ($CDCl_3$: CD_3OD = 1 : 1, 100 MHz) δ 176.1, 73.1, 48.0, 38.3, 36.8, 31.9, 31.7, 31.3, 30.8, 30.1, 26.9, 26.2, 25.5, 20.3, 18.8, 14.1, 10.5; HR-MS (EI^+) calcd for $C_{17}H_{33}NO_2$ (M^+) 283.2511; found 283.2514.

Total synthesis of 3-*epi*-fluvirucinin A_1

1-[(2*R*,3*R*,7*S*)-2-((*Z*)-2-[*tert*-Butyl(dimethyl)silyl]oxyethenyl)-7-ethyl-3-methylazecanyl]-1-propanone (20). Aldehyde **16** (219.0 mg, 0.8 mmol) was added to a suspension of NaH (60% suspension in mineral oil, 148.0 mg, 3.7 mmol) in THF (6.0 mL) at 0 °C. TBSCl (460.0 mg, 3.1 mmol) was then added, and the bath was removed. Stirring was continued for 1 h, and 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 (*Z*)-enol ether **20** (293 mg, 0.74 mmol, 95%) as a colorless oil; FT-IR (thin film, neat) ν_{max} 2957, 2928, 2858, 1650, 1464 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.25 and 6.17 (d, 1H, J = 5.5 Hz), 4.87 (bs, 0.4H), 4.41 and 4.38 (dd, 1H, J = 5.5, Hz), 4.01 (bs, 0.2H), 3.72 (bs, 0.5H), 3.46 (m, 0.5H), 3.14 (m, 0.5H), 2.84 (bs, 0.4H), 2.57 (m, 0.6H), 2.37 and 2.30 (q, 2H, J = 7.3 Hz), 2.02–1.14 (m, 14H), 1.08 (t, 3H, J = 7.3 Hz), 0.90 and 0.89 (s, 9H), 0.86 and 0.81 (t, 3H, J = 7.1 Hz), 0.09 and 0.07 (s, 6H); HR-MS (FAB^+) calcd for $C_{23}H_{46}NO_2Si$ ($M + H^+$) 396.3298; found 396.3296.

(3*R*,4*R*,7*R*,11*S*)-4-[*tert*-Butyl(dimethyl)silyl]oxy-11-ethyl-3,7-dimethyl-1-aza-5-cyclotetradecen-2-one (21). To a solution of **20** (32.0 mg, 0.1 mmol) in toluene (5.0 mL) was added dropwise LHMDS (1.0 M solution in hexane, 0.16 mL, 0.2 mmol) at 130 °C and the 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 **21** (24.0 mg, 0.1 mmol, 75%) as a white solid; FT-IR (thin film, neat) ν_{max} 3365, 2929, 2857, 1648, 1536, 1459 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.86 (bd, 1H, J = 5.2 Hz), 5.50 (ddd, 1H, J = 15.6, 6.2, 1.3 Hz), 5.42 (dd, 1H, J = 15.6, 3.7 Hz), 4.26 (s, 1H), 3.72 (dtd, 1H, J = 10.8, 8.3, 2.7 Hz), 2.68 (m, 1H), 2.49 (dq, 1H, J = 7.4, 2.7 Hz), 2.16 (m, 1H), 1.42–1.06 (m, 14H), 1.25 (d, 3H, J = 7.4 Hz), 0.94 (s, 9H), 0.93 (d, 3H, J = 7.6 Hz), 0.83 (t, 2H, J = 6.7 Hz), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.8, 136.7, 129.0, 73.6, 47.4, 38.5, 37.0, 35.9, 35.7, 31.2, 28.2, 27.4, 25.9, 25.8, 21.2, 20.7, 18.1, 16.6, 11.8, –4.3, –4.8; HR-MS (FAB^+) calcd for $C_{23}H_{46}NO_2Si$ ($M + H^+$) 396.3298; found 396.3291.

(3*R*,4*R*,7*R*,11*S*)-11-Ethyl-4-hydroxy-3,7-dimethyl-1-azacyclotetradecan-2-one (22, 3-*epi*-fluvirucinine A_1). A solution of **21** (19.0 mg, 0.05 mmol) and 10% Pd/C in 4.0 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 a celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (17% EtOAc in hexane) to afford the corresponding hydrogenated lactam (18.0 mg, 0.05 mmol, 94%) as a white solid; FT-IR (thin film, neat) ν_{max} 2928, 1737, 1647, 1538, 1460, 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.14 (bs, 1H), 3.80 (m, 1H), 3.69 (td, 1H, J = 10.4, 2.5 Hz), 2.64 (m, 1H), 2.37 (ddd, 1H, J = 14.8, 7.3, 2.2 Hz), 1.70–0.93 (m, 18H), 1.22 (d, 3H, J = 7.4 Hz), 0.93 (s, 9H), 0.87 (d, 3H, J = 6.9 Hz), 0.82 (t, 3H, J = 7.4 Hz), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 175.3, 74.8, 48.2, 38.6, 36.6, 32.6, 31.3, 30.6, 30.5, 29.7, 28.1, 26.8, 26.7, 26.1, 20.8, 18.2, 17.2, 16.7, 11.2, –3.7; HR-MS (FAB^+) calcd for $C_{23}H_{48}NO_2Si$ ($M + H^+$) 398.3454; found 398.3456.

To a solution of above hydrogenated lactam (32.0 mg, 0.1 mmol) in THF (5.0 mL) was added TBAF (1.0 M solution in THF, 0.2 mL, 0.2 mmol) and the reaction mixture 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 (9% MeOH in EtOAc) to afford 3-*epi*-fluvirucinine A_1 **22** (22.0 mg, 0.1 mmol, 96%) as a white solid; FT-IR (thin film, neat) ν_{max} 3298, 2933, 2862, 1639, 1550, 1457 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.29 (bs, 1H), 3.94 (s, 1H), 3.57 (m, 1H), 3.45 (s, 1H), 2.85 (m, 1H), 2.34 (ddd, 1H, J = 14.3, 7.2, 2.1 Hz), 1.55–0.89 (m, 18H), 1.34 (d, 3H, J = 7.2 Hz), 0.90 (d, 3H, J = 6.9 Hz), 0.81 (t, 3H, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 176.4, 74.9, 44.0, 39.1, 37.7, 33.3, 32.0, 31.0, 30.6, 29.7, 27.2, 27.0, 24.4, 21.7, 20.8, 16.5, 11.7; HR-MS (FAB^+) calcd for $C_{17}H_{34}NO_2$ ($M + H^+$) 284.2590; found 284.2581.

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