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Asymmetric Synthesis of (−)-6-Desmethyl-Fluvirucinine A_1 via Conformationally-Controlled Diastereoselective Lactam-Ring Expansions

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Received: 1 September 2018; Accepted: 10 September 2018; Published: 14 September 2018

Abstract: The versatile synthesis of (−)-6-desmethyl-fluvirucinine A_1 was accomplished at a 24% overall yield through a thirteen-step process from a known vinylpiperidine. The key part involved the elaboration of the distal stereocenters and a macrolactam skeleton via conformationally-induced diastereocontrol and the iterative aza-Claisen rearrangements of lactam precursors.

Keywords: fluvirucinine; aza-Claisen rearrangement; amidoalkylation

1. Introduction

Fluvirucins, a class of macrolactam alkaloids, including fluvirucin $A_{1\text{-}2}$ and $B_{1\text{-}5}$ (**1**–**7**) (Figure 1) were isolated in the 1990s [1–6]. These macrolactam antibiotics have drawn significant attention due to their considerable inhibitory activities against the influenza A virus in Madin—Darby canine kidney (MDCK) cells [3,4]. They commonly consist of 2,6-dialkyl-10-ethyl-3(or 9)-hydroxy-13-tridecanelactam as an aglycon called fluvirucinine, which possesses four stereogenic centers and is connected to a carbohydrate by a glycosidic linkage. The synthesis of fluvirucinines has continuously attracted the attention of organic chemists [7–15] due to the difficult stereocontrol during the creation of distant stereogenic centers. Recently, three new macrolactams, including 6-desmethyl-*N*-methylfluvirucin A_1 (**8**), *N*-methylfluvirucin A_1 (**9**), and fluvirucin B_0 (**10**), were isolated from *Nonomuraea terkmeniaca* MA7364 [16] and *Nonomuraea terkmeniaca* MA7381 [17], respectively. In particular, 6-desmethyl-*N*-methylfluvirucin A_1 (**8**) exhibited in vitro activity (EC_{90} 15 ± 5 μg/mL) against *Haemonchus contortus* larvae. The absolute configurations of C_2, C_3, and C_{10} of **8** and **9** have not been determined yet, although the relative stereochemistry of C_2 and C_3 has been disclosed. The stereochemistries of C_2, C_3, and C_{10} of **8** and **9** have been considered the same as those reported for the fluvirucin A series [16].

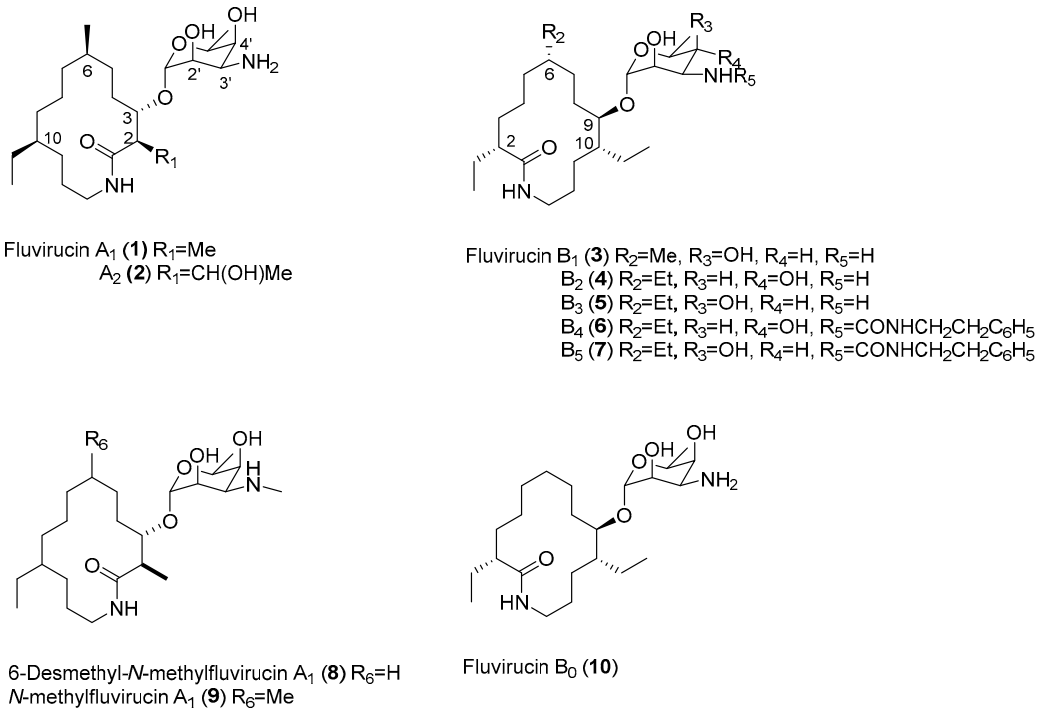


Figure 1. Structures of fluvirucins.

Recently, we have been interested in 6-desmethyl-*N*-methylfluvirucin A_1 (**8**) since it has biological activities even though 6-desmethyl-fluvirucinine A_1 (**11**), which is an aglycon of **8**, is devoid of the characteristic C_6-alkyl substituent of the fluvirucin family [16]. In particular, our interests are focused on the effect of the stereochemistry of 6-desmethyl-fluvirucinine A_1 on biological activities (Figure 2). Along this line, we have been working on the synthesis of **13** as an antipode of 6-desmethyl-fluvirucinine A_1 (**11**) [16]. Herein, we describe synthesis and structural confirmation of (−)-6-desmethyl-fluvirucinine A_1 (**13**).

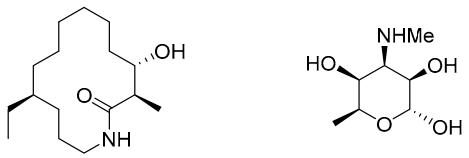
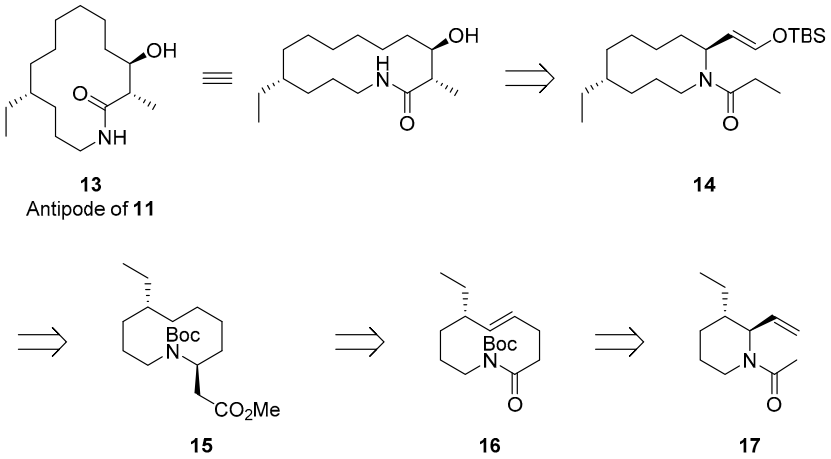


Figure 2. 6-Desmethyl-fluvirucinine A_1 (**11**) and the carbohydrate part (**12**) of 6-desmethyl-*N*-methylfluvirucin A_1 (**8**).

2. Results and Discussion

2.1. Synthetic Strategy for (−)-6-Desmethyl-Fluvirucinine A_1 (13)

Our synthetic strategy for **13** was based on the amide enolate-induced lactam ring expansion strategy [18–20], which was established by us for the synthesis of macrolactam alkaloids (Scheme 1) [14,15,21–29]. However, the diastereoselective aza-Claisen rearrangement (ACR) of **14**, which does not possess the characteristic C_6-methyl substituent, remains a formidable task because the C_6-substituent seemed to influence the formation of a chair-like transition state in the key ACR [14,15].



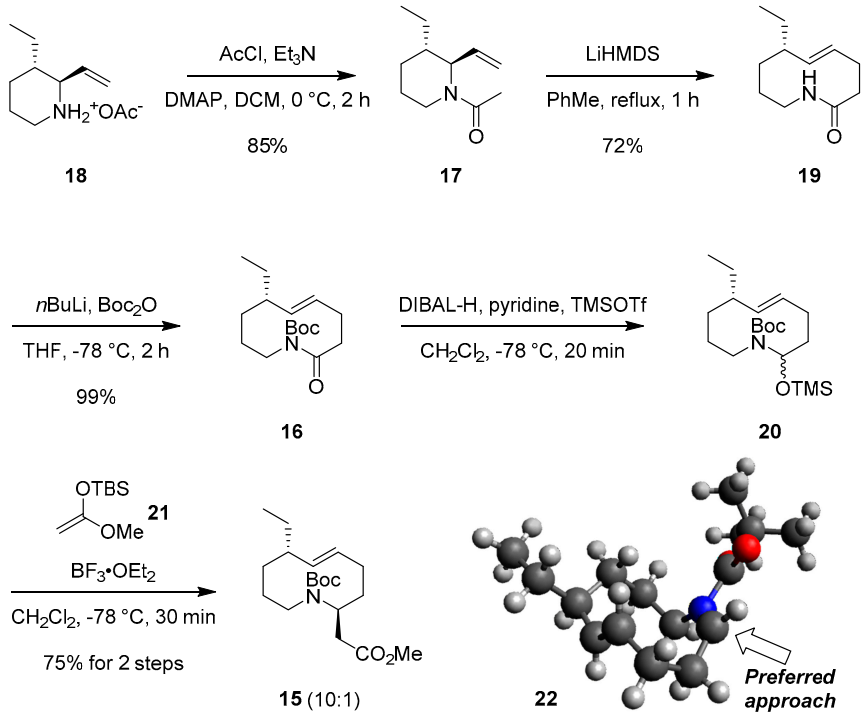
Scheme 1. Retrosynthetic analysis for synthesis of **13** as an antipode of **11**.

2.2. The First ACR and Diastereoselective Amidoalkylation for Synthesis of Ester 15

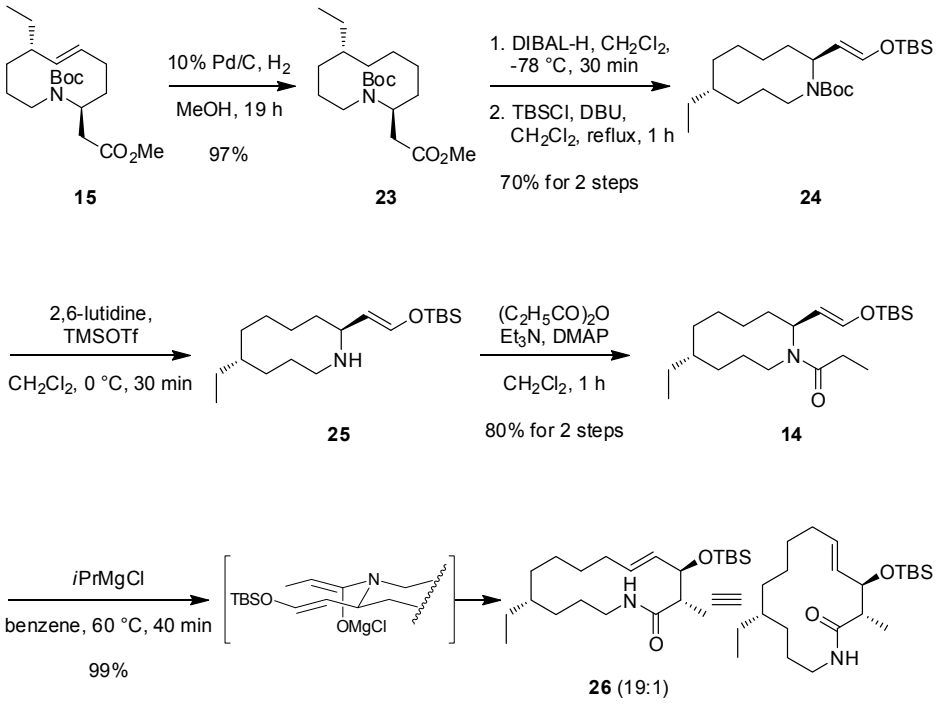
Our synthesis was commenced with the preparation of azacycle **17**, which is the first ACR precursor, through the acetylation of the known and optically active vinylpiperidine **18** [**14**], as shown in Scheme 2. The subjection of **17** to the first ACR (LiHMDS, toluene, reflux) [14,15,21–24] produced the ring-expanded lactam **19** with a 72% yield. Our initial attempt for the amidoallylation of **19**, which was commonly utilized to prepare a second ACR precursor in our previous syntheses [15,23,30–33], was not successful. We encountered difficult diastereocontrol in the amidoallylation of **19**, which was likely due to the absence of the 2-methyl substituent [15]. We anticipated that the ring-olefin in a medium sized-lactam system can induce an intrinsic ring strain that results in an improved diastereoselective amidoalkylation. In addition, we decided to execute an amidoalkylation with ketene acetal **21** as a bulky nucleophile [34]. After the Boc-protection of lactam **19**, the resulting lactam **16** was subjected to a sequence [15,23,30–34] of DIBAL-H reduction followed by the trapping of the resulting alkoxide with TMSOTf and the addition of ketene acetal **21** to the unstable *N*,*O*-acetal TMS-ether **20** in the presence of $BF_3{\cdot}OEt_2$. Indeed, a highly diastereoselective amidoalkylation of **16** was observed, which afforded methyl ester **15** with a 75% yield for three steps and a small amount of diastereoisomer (10:1). The excellent diastereoselectivity was likely due to the sterically favored *Si*-face attack of the bulky ketene acetal **21** in the energetically favorable (*Z*)-*N*-acyl iminium intermediate **22** that was generated from *N*,*O*-acetal TMS ether **20** [34,35].

2.3. The Second ACR and Completion of the Synthesis

For the preparation of the second ACR precursor, olefin hydrogenation of **15** produced ester **23** as show in Scheme 3. DIBAL-H reduction of **23** and treatment of the resulting aldehyde with TBSCl in the presence of DBU in dichloromethane [36,37] selectively produced (*E*)-enol ether **24** with a 67% yield for three steps. Boc deprotection of **24** and propionylation of the resulting amine **25** afforded the second ACR precursor **14** with a 80% yield for three steps. Finally, subjection of **14** to the standard ACR conditions (*i*PrMgCl in benzene, 60 °C) [25–29] produced the desired ring-expansion product **26** with a 99% yield in favor of the *anti*-stereoisomer (19:1). The ACR with other bases, including LiHMDS, resulted in a low diastereoselectivity (≈1.1–1.2:1) for the *anti*-product. It is noteworthy that the *anti*-stereoisomer **26** in the absence of the 6-methyl substituent, which was considered important for the diastereoselective ACR, was selectively produced [15,23]. The stereochemistry of **26** was confirmed by X-ray crystallographic analysis (Figure 3) [38].



Scheme 2. Preparation and diastereoselective amidoalkylation of **16**.



Scheme 3. Synthesis of macrolactam **26**.

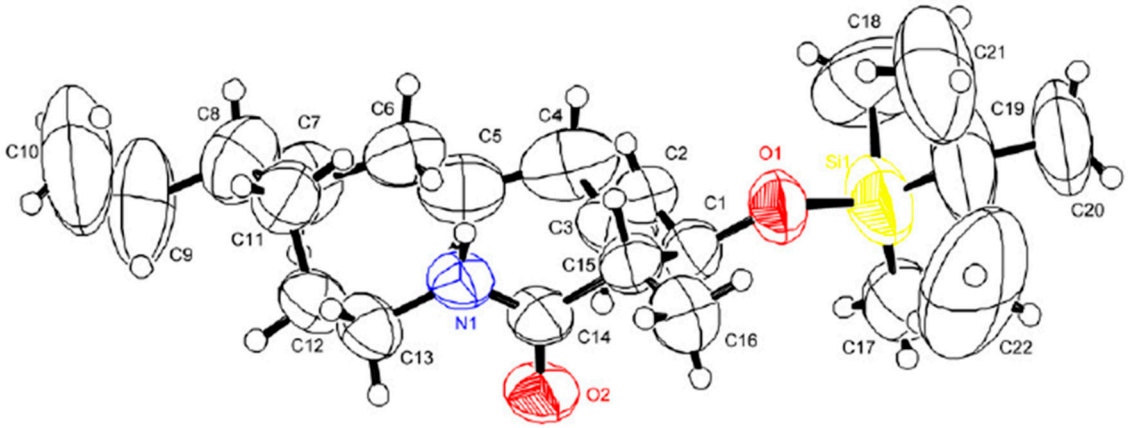
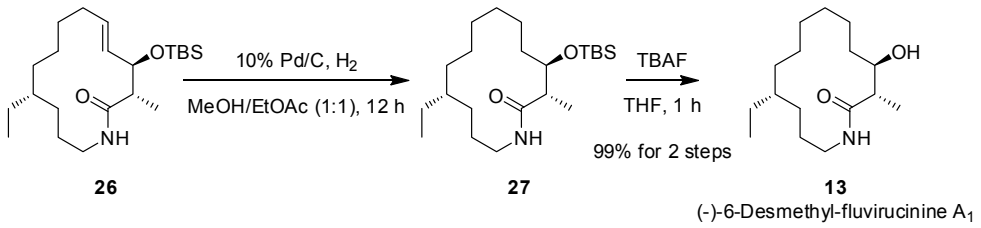


Figure 3. X-ray crystallographic structure of **32**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii; black = carbon, red = oxygen, blue = nitrogen, and yellow = silicon.

For the completion of the synthesis, macrolactam **26** was hydrogenated and then desilylated to produce **14** with a 99% yield for two steps (Scheme 4).



Scheme 4. Completion of the (−)-6-demethyl-fluvirucinine A_1 (**13**) synthesis.

3. Materials and Methods

3.1. General Information

Unless stated otherwise, all reactions were performed under an argon atmosphere with dry solvents under anhydrous conditions. Tetrahydrofuran (THF) and Et_2O were distilled immediately before use in sodium benzophenone ketyl. Dichloromethane, chloroform, triethylamine, acetonitrile, and pyridine were freshly distilled from calcium hydride. All starting materials and reagents were obtained from commercial suppliers and were used without further purification, unless otherwise noted. Solvents for routine isolation of products and chromatography were reagent grade and glass distilled. Silica gel 60 (230–400 mesh, Merck, Kenilworth, NJ, USA) was used for flash column chromatography. Reaction progress was monitored by thin-layer chromatography (TLC), which was performed using 0.25 mm silica gel plates (Merck, Kenilworth, NJ, USA). Optical rotations were measured with a P-2000 digital polarimeter (JASCO, Easton, MD, USA) at ambient temperature using a 100 mm cell of 2 mL capacity. ^{1}H- and ^{13}C-NMR spectra were recorded on a JNM-LA 300 (JEOL, Tokyo, Japan), AVANCE-500 (Brucker, Billerica, MA, USA), AVANCE-400 (Brucker, Billerica, MA, USA), and JNM-ECA-600 (JEOL, Tokyo, Japan). ^{1}H-NMR data were reported as follows: chemical shift (parts per million, δ), multiplicity (br, broad signal; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet and/or multiple resonances), coupling constant in hertz (Hz), and number of protons. Infrared spectra were recorded on a JASCO FT-IR-4200 spectrometer and are reported in the frequency of absorption (cm^{-1}). High resolution mass spectra (HR-MS) were obtained with a JMS-700 (JEOL, Tokyo, Japan) instrument and Q TOF 6530 (Agilent, Santa Clara, CA, USA).

3.2. Experimental Part

1-((2R,3S)-3-Ethyl-2-vinylpiperidin-1-yl)ethan-1-one (**17**). To a cooled (0 °C) solution of piperidine **18** (1.0 g, 5.0 mmol) in CH_2Cl_2 (15 mL) were added DMAP (catalytic amount), Et_3N (2.0 mL, 15.0 mmol), and acetyl chloride (0.5 mL, 7.5 mmol). The mixture was stirred for 2 h at room temperature, quenched with water, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified uisng flash column chromatography (EtOAc/Hexane = 1:2) to provide 770 mg (85%) of **17**. $[\alpha]_D^{20} = -33.66$ (*c* 1.08, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 5.82–5.73 (m, 1H), 5.23–5.19 (m, 1.5H), 5.07–5.01 (m, 1H), 4.46 (d, *J* = 11.3 Hz, 0.5H), 4.18 (s, 0.5H), 3.54 (d, *J* = 13.1 Hz, 0.5H), 3.17 (t, *J* = 11.8 Hz, 0.5H), 2.64 (t, *J* = 12.8 Hz, 0.5H), 2.11 (s, 1.5H), 2.05 (s, 1.5H), 1.64 (m, 3H), 1.50–1.43 (m, 3H), 1.40–1.28 (m, 1H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz, mixture of rotamers) δ 170.7, 137.0, 136.7, 116.1, 115.9, 115.8, 59.6, 53.6, 53.5, 42.4, 42.3, 39.7, 38.7, 37.0, 24.1, 23.4, 23.3, 23.1, 21.3, 20.8, 19.6, 12.2; IR (thin film, neat) ν_{max} 3477, 2937, 1651, 1423, 1267 cm^{-1}; HR-MS (ESI+) calcd. for $C_{11}H_{19}NNaO$ $[M + Na]^+$ 204.1359; found 204.1360.

(S,E)-7-Ethyl-3,4,7,8,9,10-hexahydroazecin-2(1H)-one (**19**). To a refluxing solution of amide **17** (750 mg, 4.1 mmol) in toluene (40 mL) was added lithium bis(trimethylsilyl)amide (LiHMDS) (1.0 M in toluene, 12.4 mL, 12.4 mmol). The mixture was stirred for 1 h at the same temperature, cooled to room temperature, quenched with water, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified using flash column chromatography (EtOAc/Hexane = 1:1) to provide 540 mg (72%) of **19**. $[\alpha]_D^{20} = +15.07$ (*c* 0.55, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 5.76 (br s, 1H), 5.27 (ddd, *J* = 15.1, 10.1, 5.0 Hz, 1H), 5.00 (dd, *J* = 15.6, 9.6 Hz, 1H), 3.39 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.76 (dd, *J* = 12.8, 8.2 Hz, 1H), 2.22–2.11 (m, 3H), 1.95 (td, *J* = 11.3, 5.5 Hz, 1H), 1.74–1.70 (quint, *J* = 6.6 Hz, 2H), 1.59–1.57 (m, 1H), 1.25–1.14 (m, 3H), 1.13–1.06 (m, 1H), 0.69 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 173.0, 138.7, 126.6, 45.8, 40.5, 38.5, 35.7, 29.5, 28.2, 26.7, 11.8; IR (thin film, neat) ν_{max} 3309, 2926, 1645, 1554 cm^{-1}; HR-MS (ESI+) calcd. for $C_{11}H_{20}NO$ $[M + H]^+$ 182.1539; found 182.1532.

tert-Butyl (S,E)-5-ethyl-10-oxo-3,4,5,8,9,10-hexahydroazecine-1(2H)-carboxylate (**16**). To a cooled (−78 °C) solution of lactam **19** (530 mg, 2.9 mmol) in THF (9 mL) was slowly added *n*BuLi (2.5 M in hexane, 1.8 mL, 4.5 mmol). The mixture was stirred for 10 min at the same temperature and a solution of Boc_2O (2.8 mL, 6.1 mmol) in THF (3 mL) was added. The reaction mixture was stirred for 1 h 50 min at the same temperature, quenched with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified using flash column chromatography (EtOAc/Hexane = 1:20) to provide 814 mg (99%) of **16**. $[\alpha]_D^{20} = -16.08$ (*c* 0.98, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.36–5.26 (m, 1H), 5.01(br s, 1H), 3.70–3.56 (m, 2H), 3.21 (br s, 1H), 2.80 (br s, 1H), 2.80–2.31 (m, 2H), 1.71–1.67 (m, 2H), 1.56 (s, 1H), 1.53 (s, 10H), 1.34–1.22 (m, 3H), 0.80 (t, *J* = 8.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz, mixture of rotamers) δ 177.5, 153.5, 146.7, 138.9, 126.0, 85.1, 82.5, 47.1, 46.3, 39.3, 33.4, 33.1, 30.9, 29.2, 28.9, 28.1, 27.8, 27.6, 27.4, 24.8, 24.7 12.1; IR (thin film, neat) ν_{max} 2961, 1726, 1691, 1369, 1148 cm^{-1}; HR-MS (ESI+) calcd. for $C_{16}H_{27}NNaO_3$ $[M + Na]^+$ 304.1883; found 304.1867.

tert-Butyl (5S,10S,E)-5-ethyl-10-(2-methoxy-2-oxoethyl)-3,4,5,8,9,10-hexahydroazecine-1(2H)-carboxylate (**15**). To a cooled (−78 °C) solution of lactam **16** (860 mg, 3.1 mmol) in CH_2Cl_2 (9 mL) was slowly added diisobutylaluminium hydride (DIBAL-H) (1.0 M in toluene, 5.5 mL, 5.5 mmol). After stirring for 10 min at the same temperature, pyridine (1.2 mL, 15.3 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1.4 mL, 7.7 mmol) were added. The reaction mixture was stirred for 10 min at the same temperature, quenched with saturated Rochelle's solution, and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified using flash column chromatography (EtOAc/Hexane = 1:20, silica gel deactivated with Et_3N) to afford unstable *N*,*O*-acetal TMS ether **20**. To a cooled (−78 °C) solution of **20** in CH_2Cl_2 (9 mL) were

added 1-(*tert*-butyldimethylsilyloxyl)-1-methoxyethane (1.1 mL, 4.9 mmol) **21** and $BF_3{\cdot}OEt_2$ (0.3 mL. 2.7 mmol). After stirring for 30 min at the same temperature, the reaction mixture was allowed to warm to 0 °C. The reaction mixture was quenched with Et_3N and concentrated *in vacuo*. The residue was purified using flash column chromatography (EtOAc/Hexane = 1:10) to provide 783 mg of **15** as a diastereomeric mixture (75% for 2 steps, 68% for desired diastereomer). $[\alpha]_D^{20}$ = +37.66 (*c* 2.36, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 5.51–5.42 (m, 1H), 5.20–5.13 (m, 1H), 3.71 (m, 0.5H), 3.61 (s, 3H), 3.20 (br s, 0.5H), 3.11–3.10 (m, 1H), 2.82 (dd, *J* = 15.0, 8.8 Hz, 0.5H), 2.53–2.47 (m, 1H), 2.43–2.37 (m, 0.5H), 2.31–2.26 (m, 1.5H), 2.19 (br s, 0.5H), 2.08 (br s, 0.5H), 1.98–1.89 (m, 1.5H), 1.83–1.76 (m, 1H), 1.67–1.62 (m, 1H), 1.45–1.39 (m, 10.5H), 1.36–1.29 (m, 1.5H), 1.27–1.15 (m, 2H), 0.93 (t, *J* = 12.2 Hz, 1H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz, mixture of rotamers) δ 173.0, 172.4, 155.3, 155.0, 135.2, 134.6, 131.5, 130.9, 79.6, 78.9, 64.4, 56.0, 51.6, 51.4, 48.3, 48.1, 40.3, 38.5, 35.9, 35.8, 34.4, 34.1, 33.5, 31.6, 30.6, 29.2, 28.6, 28.5, 28.4, 25.6, 22.6, 14.0, 12.2; IR (thin film, neat) ν_{max} 2961, 2930, 1740, 1692, 1365, 1172 cm^{-1}; LR-MS (FAB+) *m*/*z* 340 $[M + H]^+$; HR-MS (FAB+) calcd. for $C_{19}H_{34}NO_4$ $[M + H]^+$ 340.2488; found 340.2484.

tert-Butyl (2S,7R)-7-ethyl-2-(2-methoxy-2-oxoethyl)azecane-1-carboxylate (**23**). To a solution of ester **15** (705 mg, 2.1 mmol) in MeOH (10 mL) was added 10% Pd/C (71 mg) and the mixturre was stirred under H_2 (balloon pressure) for 19 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The residue was purified using flash column chromatography (EtOAc/Hexane = 1:10) to provide 688 mg (97%) of **23**. $[\alpha]_D^{20}$ = +23.72 (*c* 2.29, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.75 (br s, 1H), 3.61 (s, 3H), 3.49 (br s, 1H), 2.99–2.65 (m, 2H), 2.44–2.40 (m, 1H), 2.06–1.91 (m, 1H), 1.67 (br s, 2H), 1.41 (br s, 15H), 1.30 (s, 2H), 1.25–1.20 (m, 2H), 1.09 (br s, 2H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 172.5, 155.9, 79.7, 79.2, 56.1, 51.6, 39.1, 38.3, 37.0, 32.8, 30.8, 30.1, 28.5, 27.8, 26.7, 22.7, 11.9; IR (thin film, neat) ν_{max} 2959, 2925, 1741, 1696, 1365, 1171 cm^{-1}; LR-MS (FAB+) *m*/*z* 342 $[M + H]^+$; HR-MS (FAB+) calcd. for $C_{19}H_{36}NO_4$ $[M + H]^+$ 342.2644; found 342.2644.

tert-Butyl (2S,7R)-2-((E)-2-((tert-butyldimethylsilyl)oxy)vinyl)-7-ethylazecane-1-carboxylate (**24**). To a cooled (−78 °C) solution of ester **23** (645 mg, 1.9 mmol) in CH_2Cl_2 (8 mL) was slowly added DIBAL-H (1.0 M in toluene, 2.4 mL, 2.4 mmol). The reaction mixture was stirred for 30 min at the same temperature, quenched with saturated Rochelle's solution, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude aldehyde was directly used for the next reaction without further purification. To a stirred solution of aldehyde in CH_2Cl_2 (9 mL) were added *tert*-butyldimethylsilyl chloride (TBSCl) (570 mg, 3.8 mmol) and DBU (0.9 mL, 6.0 mmol). The reaction mixture was refluxed for 1 h and concentrated *in vacuo*. The residue was purified using flash column chromatography (EtOAc/Hexane = 1:30, silica gel deactivated with Et_3N) to provide 563 mg (70% for 2 steps) of **24**. $[\alpha]_D^{20}$ = +26.68 (*c* 1.25, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.31 (dd, *J* = 15.8, 9.4 Hz, 1H), 5.10 (m, 1H), 3.64 (m, 1H), 2.85–2.78 (m, 1H), 2.04 (m, 1H), 1.74 (br s, 1H), 1.66–1.63 (m, 1H), 1.54 (s, 1H), 1.44 (s, 11H), 1.35 (m, 3H), 1.25–1.18 (m, 4H), 1.14 (br s, 2H), 0.89 (s, 9H), 0.86–0.84 (m, 4H), 0.11 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 156.3, 141.3, 138.6, 111.9, 79.2, 78.8, 57.2, 36.4, 32.6, 30.0, 28.5, 26.2, 25.7, 25.6, 22.8, 18.4, 18.1, 11.9, −3.0, −4.8; IR (thin film, neat) ν_{max} 2958, 2929, 1695, 1655, 1170, 839 cm^{-1}; LR-MS (FAB+) *m*/*z* 426 $[M + H]^+$; HR-MS (FAB+) calcd. for $C_{24}H_{48}NO_3Si$ $[M + H]^+$ 426.3403; found 426.3394.

1-((2S,7R)-2-((E)-2-((tert-Butyldimethylsilyl)oxy)vinyl)-7-ethylazecan-1-yl)propan-1-one (**14**). To a cooled (0 °C) solution of silyl enol ether **24** (69.4 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) were added 2,6-lutidine (0.1 mL, 0.64 mmol) and TMSOTf (0.1 mL, 0.48 mmol). The mixture was stirred for 30 min at the same temperature, quenched with MeOH, and concentrated *in vacuo*. The crude amine **25** was directly used for the next reaction without further purification. To a stirred solution of amine **25** in CH_2Cl_2 (2 mL) were added DMAP (catalytic amount), Et_3N (0.1 mL, 0.48 mmol), and propionic anhydride (0.04 mL, 0.32 mmol). The reaction mixture was stirred for 1 h and concentrated *in vacuo*. The residue was purified using flash column chromatography (EtOAc/Hexane = 1:10, silica gel deactivated with Et_3N) to provide 49.8 mg (80% for 2 steps) of **14**. $[\alpha]_D^{20}$ = +12.16 (*c* 2.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ

6.31 (d, *J* = 15.5 Hz, 1H), 6.22 (d, *J* = 15.5 Hz, 1H), 5.23 (br s, 1H), 4.93 (dd, *J* = 12.1, 6.6 Hz, 1H), 4.13 (t, *J* = 8.6 Hz, 1H), 3.49–3.37 (m, 2H), 3.08–2.92 (m, 2H), 2.38–2.27 (m, 2H), 2.24 (qd, *J* = 7.5, 2.4 Hz, 3H), 2.03 (m, 1H), 1.89–1.86 (m, 1H), 1.75 (br s, 1H), 1.65–1.55 (m, 2H), 1.49–1.47 (m, 1H), 1.39 (m, 1H), 1.26–1.13(m, 2H), 1.11–1.06 (m, 2H), 0.85 (s, 9H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.07 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz, mixture of rotamers) δ 175.0, 174.8, 174.5, 142.6, 142.0, 141.7, 111.8, 111.7, 111.6, 56.6, 56.1, 41.8, 39.4, 37.4, 36.7, 32.7, 31.6, 31.0, 31.0, 30.8, 30.7, 30.5, 29.8, 29.7, 29.7, 29.5, 29.4, 29.4, 29.3, 29.2, 28.2, 28.0, 27.8, 27.5, 27.4, 25.7, 25.6, 25.5, 25.5, 25.2, 25.0, 24.8, 24.5, 24.2, 23.8, 23.3, 18.3, 11.9, 9.4, −5.3; IR (thin film, neat) ν_{max} 2956, 2930, 1653, 839 cm^{-1}; LR-MS (FAB+) *m*/*z* 382 $[M + H]^+$; HR-MS (FAB+) calcd. for $C_{22}H_{44}NO_2Si$ $[M + H]^+$ 382.3141; found 382.3139.

(3S,4R,11R,E)-4-((tert-Butyldimethylsilyl)oxy)-11-ethyl-3-methylazacyclotetradec-5-en-2-one (**26**). To a heated (60 °C) solution of amide **14** (46.6 mg, 0.13 mmol) in benzene (3 mL) was slowly added *i*PrMgCl (1.0 M in hexane, 0.5 mL, 0.5 mmol). The reaction mixture was stirred for 40 min at the same temperature, cooled to room temperature, quenched with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified using flash column chromatography (EtOAc/Hexane = 1:10) to provide 46.1 mg of **26** as a diastereomeric mixture (99%, 95% for desired diastereomer). $[\alpha]_D^{20} = -62.95$ (*c* 0.62, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.25 (s, 1H), 5.59–5.54 (m, 1H), 5.37 (dd, *J* = 15.5, 5.8 Hz, 1H), 4.18 (t, *J* = 6.5 Hz, 1H), 3.89–3.83 (m, 1H), 2.51 (m, 1H), 2.27 (quint, *J* = 7.1 Hz, 1H), 2.01 (m, 2H), 1.56 (s, 1H), 1.48–1.38 (m, 2H), 1.36–1.20 (m, 8H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.07–0.99 (m, 2H), 0.89 (s, 9H), 0.83 (t, *J* = 7.3 Hz, 3H), 0.06 (s, 3H), 0.02 (s,3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 173.9, 131.8, 130.7, 75.0, 48.4, 39.4, 37.7, 31.0, 30.9, 27.2, 27.1, 26.4, 25.9, 23.8, 23.6, 18.1, 15.1, 12.0, −4.3, −4.9; IR (thin film, neat) ν_{max} 3279, 2928, 1638, 775 cm^{-1}; LR-MS (FAB+) *m*/*z* 382 $[M + H]^+$; HR-MS (FAB+) calcd. for $C_{22}H_{44}NO_2Si$ $[M + H]^+$ 382.3141; found 382.3140.

Crystal Data for **26**. $C_{22}H_{43}NO_2Si$ (M = 381.67 g/mol), orthorhombic, space group $P2_12_12$ (no. 18), a = 9.4913(8) Å, b = 31.653(3) Å, c = 8.524(1) Å, V = 2560.9(5) $Å^3$, Z = 4, T = 300 K, μ(MoKa) = 1.052 mm^{-1}, D_{calc} = 0.990 g/cm^3, 25442 reflections measured, 5869 unique (R_{int} = 0.1257) which were used in all calculations. The final R1 was 0.1071 ($I > 2\sigma(I)$) and wR2 was 0.2824 (all data).

(−)-6-Desmethyl-fluvirucinine A$_1$ (**13**). To a solution of lactam **26** (39.8 mg, 0.10 mmol) in a mixture of EtOAc and MeOH (1:1, 2 mL) was added 10% Pd/C (4.0 mg) and the mixture was stirred under H_2 (balloon pressure) for 12 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The crude lactam **27** was directly used for the next reaction without further purification. To a stirred solution of lactam **27** in THF (1 mL) was added tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 0.2 mL, 0.20 mmol) at room temperature. The mixture was stirred for 1 h at the same temperature, quenched with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane/MeOH = 25:25:1) to provide 27.8 mg (99% for 2 steps) of **13**. $[\alpha]_D^{20} = -76.61$ (*c* 0.18, MeOH); ^{1}H-NMR (MeOD, 500 MHz) δ 4.58 (s, 1H), 3.68–3.62 (m, 2H), 2.69 (ddd, *J* = 13.6, 7.7, 1.7 Hz, 1H), 2.37–2.31(m, 1H), 1.62–1.52 (m, 2H), 1.50–1.45 (m, 4H), 1.43–1.41 (m, 4H), 1.39–1.32 (m, 3H), 1.30–1.26 (m, 2H), 1.24–1.10 (m, 4H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (MeOD, 150 MHz) δ 178.7, 74.6, 48.8, 40.3, 38.5, 35.3, 32.6, 29.8, 28.9, 28.7, 27.8, 27.5, 24.2, 22.7, 16.8, 12.7; IR (thin film, neat) ν_{max} 3388, 3305, 1637, 790 cm^{-1}; HR-MS (ESI+) calcd. for $C_{16}H_{31}NO_2$ $[M + H]^+$ 270.2428; found 270.2426.

4. Conclusions

The versatile synthesis of (−)-6-desmethyl-fluvirucinine A_1 (**13**) was accomplished through 13 steps with a 24% overall yield from the known vinylpiperidine **18**. The key part of the synthesis included the highly diastereoselective ACR of the 10-membered lactam intermediate for the elaboration of the 14-membered lactam framework via the conformationally-induced diastereocontrol of the distal

stereocenters. The stereochemical effect of 6-desmethyl-fluvirucinine A_1 on the biological activities and the synthesis of the carbohydrate moiety will be reported in future research.

Supplementary Materials: The supplementary materials are available online.

Author Contributions: Y.-G.S., S.-H.K., H.M., H.Y., and J.J. conceived and designed the experiments; H.M., H.Y., J.J., and C.L. performed the experiments; J.-J.Y., J.K.L., J.L., Y.N., and W.S.S. analyzed the data; Y.-G.S., S.-H.K., H.M., H.Y., and C.L. wrote the paper; all authors read and approved the final manuscript.

Funding: This work was supported by the GRRC program of Gyeonggi province (GRRC-CHA2018-B02).

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of compounds are available from the authors.

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