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Total synthesis of fluvirucinine A_1

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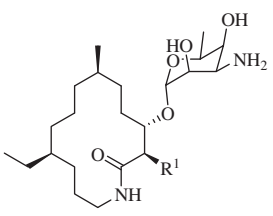
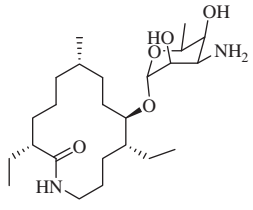
ABSTRACT

An efficient and highly stereocontrolled convergent synthesis of fluvirucinine A_1 is reported herein. In fluvirucinine A_1 both C_5–C_{13} and C_1–C_4 fragments were accessed from a common intermediate **6** derived from (*S*)-Roche ester in 15 and 7 steps, respectively. The key steps involve Evans asymmetric alkylation, Sharpless asymmetric epoxidation, amidation and a ring-closing metathesis reaction (RCM) for macrocyclization.

In 1991, Naruse et al.[1–3] reported the isolation and structural determination of fluvirucins A_1, A_2, B_1–B_5 from the fermentation broth of actinomycete strains. Fluvirucines are a family of macrolactam antibiotics and are potent inhibitors of influenza A virus.[1–4] Among all aglycones of fluvirucin series, fluvirucinine A_1 (**1**) and A_2 (aglycone of **II**) are particularly important because of their low toxicity[3] and more potent inhibitory activity against influenza A virus.[1–4] Fluvirucinine A_1 is aglycone of fluvirucin A_1. To date, three synthesis of fluvirucinine A_1 have been reported.[5–7] Of all, the one reported by Suh et al.[5] by an innovative iterative lactam ring-expansion to access the 14-membered lactam skeleton is note-worthy. Yet another equally significant synthesis by Negishi and co-worker[6] employing zirconium catalyzed asymmetric carboalumination of alkenes-Lipase catalyzed acetylation tandem process as the key step was recently reported.



I. Fluvirucin A_1 $R^1 = CH_3$
II. Fluvirucin A_2 $R^1 = CH(OH)CH_3$



III. Fluvirucin B_1

Due to their promising biological activity and interesting structural features, we designed a flexible synthetic strategy suitable for accessing both fluvirucinine A_1 (**1**) and A_2 (aglycone of **II**), as they share close structural similarities. We envisioned that the second fragment (compound **4**), which is the point of structural difference, could be synthesized by a related strategy. Thus, the present approach (Scheme 1) involves an independent synthesis of fragments **3** and **4**, their connection through amidation and macrocyclization via ring-closing metathesis[6,8] (RCM)/hydrogenation afforded the important C–C bond, a saturated C_4–C_5 linked macrocycle.

Accordingly, the retrosynthetic strategy anticipated for fluvirucinine A_1 (**1**) is delineated in Scheme 1. The standard disconnection of **1** at C_4–C_5 and C_1–N bonds revealed two fragments **3** and **4**. We visualized that **1** could be obtained from fragments **3** and **4** by utilizing amidation and ring-closing metathesis strategy. Both fragments **3** and **4** in turn could be readily accessed from the commercially available (*S*)-Roche ester **5**, wherein the naturally endowed methyl stereogenic center could be correlated to C_2 and C_6 of the target molecule **1**. The stereochemistry at C_{10} was derived by invoking the highly diastereoselective Evans asymmetric alkylation,[9] while the hydroxyl functionality at C_3 (of fragment **4**) was achieved through Sharpless asymmetric epoxidation.[10]

Thus, the synthesis of **3** commenced with **6**[10] that was easily accessed in four steps from **5** (Scheme 2). Treatment of **6** with TPP in presence of iodine and imidazole in THF produced allyl iodide **7** in 76% yield and set the stage for highly diastereoselective Evans asymmetric alkylation[9] to install the C_{10} ethyl group with the desired stereochemistry. Accordingly, *N*-butyryl oxazolidinone was treated with LiHMDS in dry THF at −78 °C to furnish an enolate intermediate that was reacted with allylic iodide **7** to afford the corresponding ethylated product **9** in good yield of 86% and in high diastereoselectivity. An excess of enolate (1.6) was found necessary

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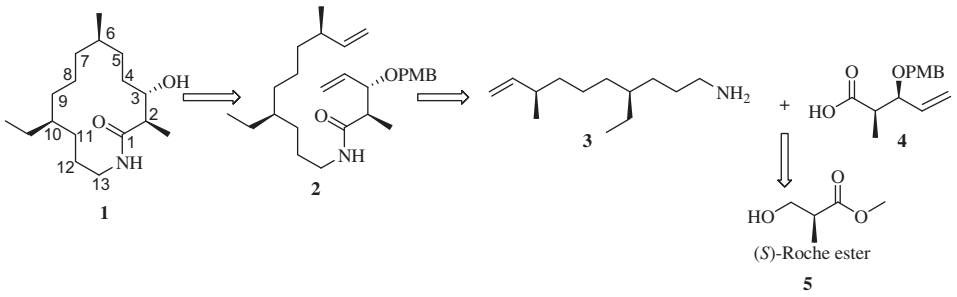
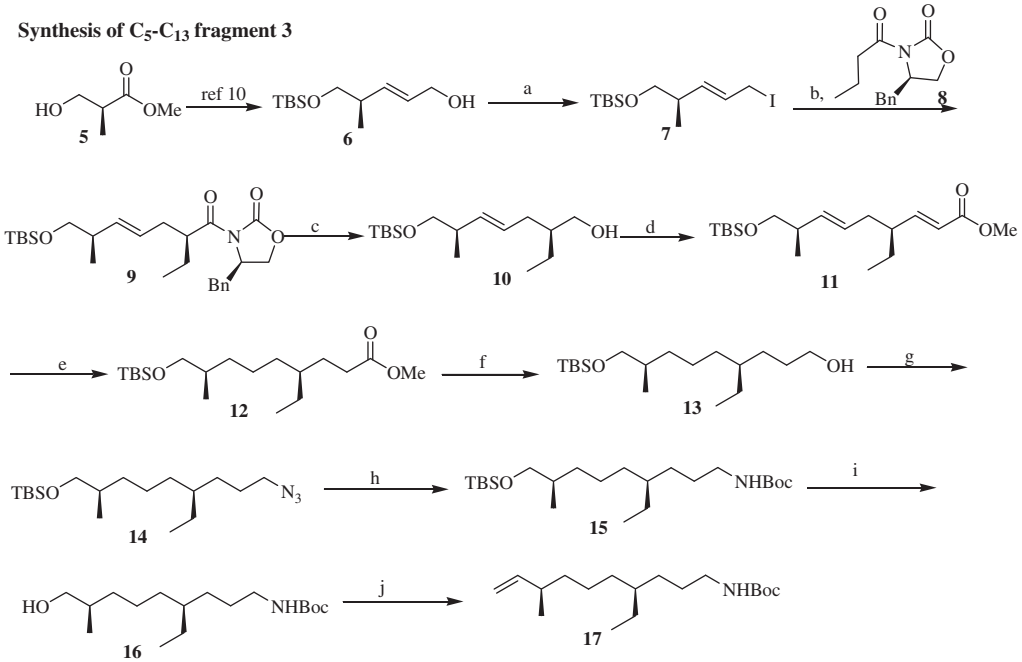


Scheme 1. Retrosynthetic analysis.



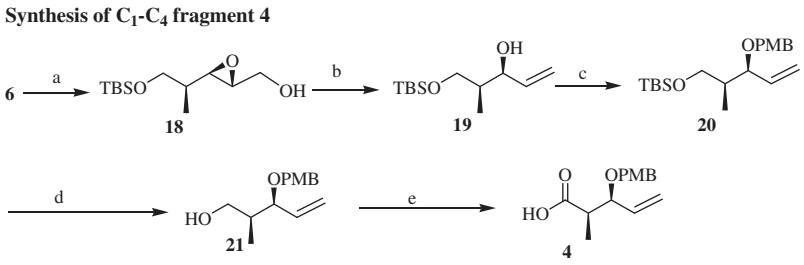
Scheme 2. Reagents and conditions: (a) TPP, I_2, imidazole, THF, 0.5 h, 76%; (b) **8**, LiHMDS, −78 °C, 1 h, **7** after 6 h, −20 °C, 14 h; (c) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 81%; (d) (i) IBX, CH_2Cl_2, DMSO, 0°C to rt, 4 h; (ii) Ph_3P CHCOOEt, C_6H_6, 70°C, 4 h, 85% (over two steps) (e) H_2 Pd/C, EtOAc, 4 h, 92%; (f) DIBAL-H, CH_2Cl_2, −40 °C, 1 h, 84%; (g) (i) TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; (ii) NaN_3, DMF, 80 °C, 4 h, 85% (over two steps); (h) (i) H_2, Pd/C, EtoAc, 9 h; (ii) $(Boc)_2O$, Et_3N,CH_2Cl_2, 1 h, 83% (over two steps); (i) TBAF, THF, 3 h, 78%; (j) (i) $(COCl)_2$, DMSO, Et_3N, −78 °C, 1 h (ii) Ph_3 PCH_3^+ I^-, ^{t}BuOK, THF, −10 °C to rt, 4 h, 65% (over two steps).

to achieve completion of the reaction. The second diastereoisomer was not detected either by ^1H or ^{13}C NMR of crude reaction mixture, thus suggesting high selectivity and diastereoselectivity and hence assumed to be >95:5.

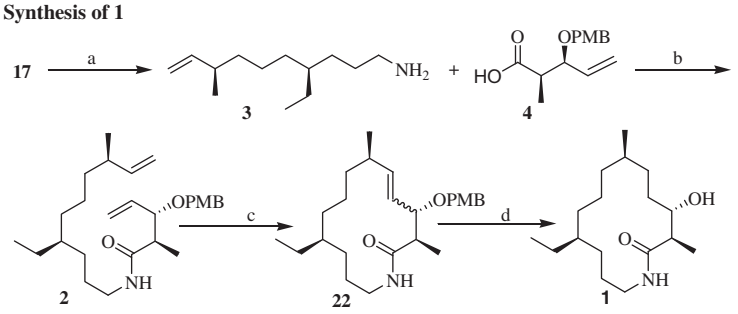
Next, reductive cleavage ($NaBH_4$/MeOH/0 °C to rt/1 h) of the chiral auxiliary gave alcohol **10** (81%). Oxidation of **10** with IBX provided the corresponding aldehyde, which was subjected to Wittig olefination to afford **11** (85% yield over two steps). Exposure of **11** to hydrogenation in the presence of Pd/C in EtOAc produced the corresponding saturated ester **12** (92%), which upon treatment with DIBAL-H in CH_2Cl_2 gave alcohol **13** (84%). Alcohol **13** was converted to its corresponding tosylate ($TsCl/Et_3N/CH_2Cl_2$/0 °C to rt/3 h), which was subsequently transformed into the corresponding azide **14** (85%, over two steps) under conventional conditions (NaN_3/DMF/80 °C/4 h). The resulting azide **14** was converted to *N*-Boc derivative **15** in 83% yield by a two-step process, firstly reduction of the azide to the amine via hydrogenation (Pd/C–H_2/rt/9 h) followed by the bocylation reaction {$(Boc)_2O/Et_3N/CH_2Cl_2$/0 °C to rt/1 h}. Later, deprotection (TBAF/THF/0 °C to rt/3 h) of silyl ether in **15** furnished alcohol **16** (78%). Alcohol **16** was transformed into alkene **17** by Swern oxidation and one carbon Wittig olefination in 65% yield over two steps.

As outlined in Scheme 3, the synthesis of C_1–C_4 fragment (compound **4**) began with **6**.[10] Sharpless asymmetric epoxidation[10] of **6** using (−)-DIPT afforded epoxy alcohol **18**. Compound **18** was treated with TPP, iodine and imidazole to give the corresponding iodo derivative, which on treatment with Zn in ethanol[11], gave allylic alcohol **19** (78% yield over two steps). The resulting allylic alcohol **19** was protected (NaH/PMBBr/THF/0 °C to rt/14 h) as its PMB ether **20** (74%). Later, deprotection (TBAF/THF/0 °C to rt/3 h) of TBS ether gave alcohol **21** (79%). The oxidation of the resultant primary alcohol **21** under Swern conditions furnished the aldehyde which on subsequent oxidation[12] ($NaClO_2/NaH_2PO_4{\cdot}2H_2O$/2-methyl 2-butene/12 h) afforded acid **4** (75%).

Compound **17** was treated with TFA in CH_2Cl_2 to liberate the free amine **3** which was immediately used for the amidation reaction (Scheme 4). With the requisite fragments **3** and **4** in hand, the coupling reaction was undertaken. Thus, coupling of **3** and **4** was achieved by treating the acid **4** with EDCI/HOBT followed by addition of amine **3** to afford amide **2** (98%). The resulting diene **2** was



Scheme 3. Reagents and conditions: (a) (−)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide (CHP), CH_2Cl_2, −20 °C, 4–5 h, 86%; (b) (i) TPP, I_2, imidazole, THF, 0.5 h; (ii) Zn, EtOH, 80 °C, 3 h, 78% (over two steps); (c) NaH, PMBBr, THF, 0 °C to rt, 14 h, 74%; (d) TBAF, THF, 3 h, 79%; (e) (i) $(COCl)_2$, DMSO, Et_3N, −78 °C, 1 h; (ii) $NaClO_2$ $NaH_2PO_4{\cdot}2H_2O$, 2-Methyl 2-butene, $^tBuOH/H_2O$ (3:1), 0 °C to rt, 12 h, 75% (over two steps).



Scheme 4. Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C, 15 min; (b) EDCI, HOBT, CH_2Cl_2, 98% (over two steps); (c) Grubbs-II, CH_2Cl_2, 45 °C, 12 h, 79%; (d) H_2Pd/C, EtOAc, 3 h, 89%.

exposed to the RCM reaction using Grubbs-II catalyst in refluxing dichloromethane to produce the desired macrolactam **22** (79%) as an *E/Z* mixture. Since the isomeric status was irrelevant, no attempts were made to purify compound **22** into separate entities. Compound **22** was subjected to a hydrogenation reaction (Pd/C–H_2/rt/3 h) wherein both the saturation of the C_4–C_5 olefinic bond and C_3-OPMB-deprotection occurred in one-pot to furnish **1** (89%).[13] The spectroscopic data (^1H and ^{13}C NMR) and specific rotation of the synthetic material **1** was in good agreement with the reported data.[1–3,13]

In summary, we have accomplished a stereoselective synthesis of **1** from the common intermediate **6**,[10] using Evans asymmetric alkylation,[9] Sharpless asymmetric epoxidation,[10] amidation and RCM[6,8] in an overall yield of 10.5%. Further application of this strategy toward synthesis of fluvirucinine A_2 and B_1 is under progress and will be reported elsewhere.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.087.

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13. Spectral data for selected compounds. Compound **10**: Colorless liquid; $[\alpha]_D^{25}$ +1.1 (*c* 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.67–5.47 (m, 2H), 3.71–3.50 (m, 4H), 2.47–2.38 (m, 1H), 1.67–1.40 (m, 2H), 1.14–1.08 (m, 9H), 1.05 (s, 9H), 0.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.8, 128.3, 68.3, 65.1, 42.7, 39.6, 34.5, 26.2, 23.3, 18.3, 16.8, 11.5, −4.9. ESIMS: *m/z* 309 $[M+Na]^+$, HRMS *m/z*: Calcd for $C_{16}H_{34}O_2NaSi$: 309.2225. Found: 309.2224. Compound **17**: Pale yellow liquid; $[\alpha]_D^{25}$ −7.1 (*c* 0.57, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.64–5.47 (m, 1H), 4.90–4.83 (m, 2H), 4.42 (br. s, 1H), 3.04–3.03 (m, 2H), 2.06–2.04 (m, 1H), 1.40 (s, 9H), 1.24–1.20 (m, 13H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.6, 112.9, 78.9, 41.0, 38.7, 37.8, 37.1, 33.2, 30.3, 28.5, 27.4, 25.9, 24.3, 20.6, 10.9. ESIMS: *m/z* 320 $[M+Na]^+$, HRMS *m/z*: Calcd for $C_{18}H_{35}NO_2Na$: 320.2565. found: 320.2559. Compound **4**: Colorless liquid; $[\alpha]_D^{25}$ +50.6 (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 5.84–5.69 (m, 1H), 5.36–5.25 (m, 2H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.02–3.85 (m, 1H), 3.77 (s, 3H), 2.66–2.57 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.4, 159.1, 135.5, 129.3, 120.1, 119.2, 113.7, 80.4, 70.1, 55.1, 44.7, 13.3. ESIMS: *m/z* 273 $[M+Na]^+$, HRMS *m/z*: Calcd for $C_{14}H_{18}O_4Na$: 273.1102. found: 273.1093. Compound **2**: Colorless liquid; $[\alpha]_D^{25}$ +2.5 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.22 (t, *J* = 5.5 Hz, 1H), 5.76–5.57 (m, 2H), 5.29 (d, *J* = 9.8 Hz, 2H), 4.88 (d, *J* = 8.3 Hz, 2H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.25 (d, *J* = 11.3 Hz, 1H), 3.89–3.83 (m, 1H), 3.79 (s, 3H), 3.25–3.13 (m, 2H), 2.50–2.41 (m, 1H), 2.12–2.03 (m, 1H), 1.47–1.33 (m, 1H), 1.28–1.14 (m, 12H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.81 (t, *J* = 7.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 158.9, 135.2, 129.4, 119.5, 113.9, 112.5, 81.7, 70.7, 55.2, 45.6, 39.7, 38.6, 37.9, 37.2, 33.2, 30.4, 26.9, 25.8, 24.3, 20.3, 12.8, 10.9. ESIMS: *m/z* 430 $[M+H]^+$, 452 $[M+Na]^+$, HRMS *m/z*: Calcd for $C_{27}H_{44}NO_3$: 430.3321. Found: 430.3388. Compound **1**: white solid; mp 229–236 °C. $[\alpha]_D^{25}$ +138.3 (*c* 0.69, MeOH); ^1H NMR (500 MHz, $CDCl_3$: CD_3OD = 1:1): 7.89 (br. s, 1H), 3.61–3.48 (m, 1H), 3.46–3.40 (m, 1H), 2.66–

2.56 (m, 1H), 2.28–2.15 (m, 1H), 1.56–1.18 (m, 18H), 1.05 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H), 0.77 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$:CD_3OD = 1:1): δ 175.7, 72.8, 47.8, 38.3, 36.0, 34.0, 31.8, 31.5, 30.7, 30.0, 27.5, 26.4, 25.2, 20.1, 16.4, 14.0, 10.6. ESIMS: m/z 284 $[M+H]^+$, 306 $[M+Na]^+$, HRMS: m/z $[M+Na]^+$ Calcd for $C_{17}H_{33}NO_2Na$: 306.2408. Found: 306.2405.