Enantioselective Synthesis of 6-nor-Fluvirucinin B_1

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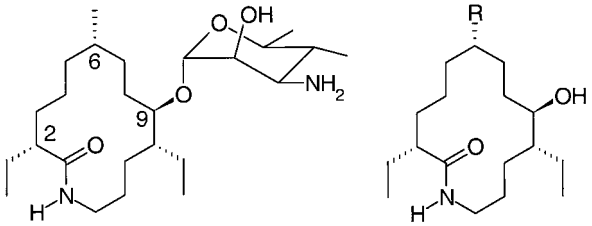
Abstract: An enantioselective synthesis of the 6-nor-derivative **3** of the antiviral macrocyclic lactam fluvirucinin B_1 (**2**) is presented. Key steps are two regioselective ring opening reactions of chiral epoxides, and a ring-closing metathesis with Grubbs' catalyst. The choice of appropriate protective groups was essential for the success and efficiency of the synthesis.

Key words: asymmetric synthesis, epoxides, fluvirucin, natural products, metathesis

In 1990 and 1991 two independent groups at Schering–Plough[1] and Bristol–Myers–Squibb[2] described the isolation and structure elucidation of a novel group of 14-membered lactams called fluvirucines from fermentation broths of the actinomycete *Actinomadura vulgaris*. These macrolactams, especially fluvirucin B_1 (= Sch 38516; **1**), exhibit potent antifungal and antiviral activities. The aglycones, e. g. fluvirucinin B_1 (**2**) still retain significant activity against influenza A virus.

A first total synthesis of the aglycone fluvirucinin B_1 (**2**, Figure 1) was reported by Hoveyda with one key step being a ring-closing metathesis (RCM) with Schrock's molybdenum catalyst to connect C-5 and C-6 of the macrolactam. Later this method was extended to the total synthesis of the glycoside fluvirucin B_1 (**1**, Scheme 1).[3] Meanwhile a few other approaches to the fluvirucinines have been published using different macrolactamization methods to build up the macrocycles.[4]

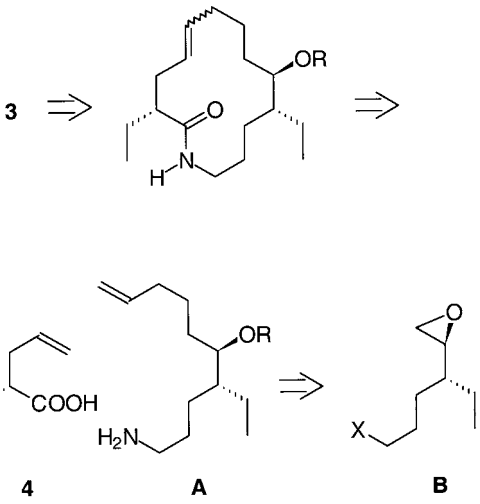


1 **2** R = CH_3 **3** R = H

Figure 1

In this letter we present a new enantioselective access to the fluvirucinin skeleton, again utilizing RCM.[5] But in our case Grubbs' ruthenium-catalyst [benzylidene-bis(tricyclohexylphosphine)dichlororuthenium], which is easier to handle than Schrock's catalyst, can be used to connect C-4 and C-5 of the lactam.

In order to work out a general approach to the fluvirucinin skeleton first, we decided to omit the methyl group at C-6 of the lactam. The target compound, 6-nor-fluvirucinin B_1 (**3**) was disconnected into two main fragments, (*R*)-2-ethyl-4-pentenoic acid (**4**) and an amino olefin **A**. The 14-membered ring should be constructed by amide synthesis from the two building blocks, followed by RCM, and subsequent reduction of the double bond (Scheme 1). The main challenge was the enantioselective synthesis of building block **A**. This should be accomplished by ring opening of a chiral epoxide of type **B** with an appropriate metalated butene.



4 **A** **B**

Scheme 1 Retrosynthetic analysis of **3** (X = protected amino group or a precursor of a primary amine).

Building block **4**[6] was prepared in two steps in enantiopure form from Oppolzer's *N*-crotyl-(+)-camphorsultam **5** (Scheme 2).[7] Conjugate hydride addition with L-selectride,[8] followed by trapping of the resulting enolate with allyl bromide gave, after recrystallization, pure **6** in 71% yield. Carboxylic acid **4** was obtained from **6** in 93% yield using Yamamoto's optimized hydrolysis procedure.[9] The standard protocol (LiOH, H_2O_2)[8] gave dramatically lower yields.

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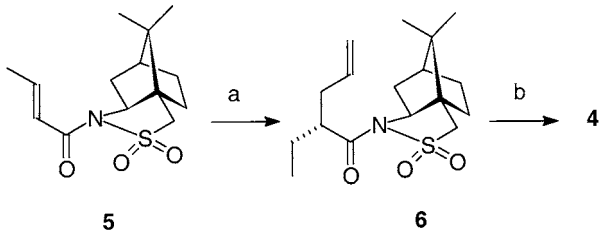


Scheme 2 a) L-Selectride, THF, –78 °C, 30 min; then allyl bromide, 90 min (71%); b) tetrabutylammonium hydroxide, H_2O_2, 2-methyl-2-butene, 1,2-dimethoxyethane, 0 °C, 2 h (93%).

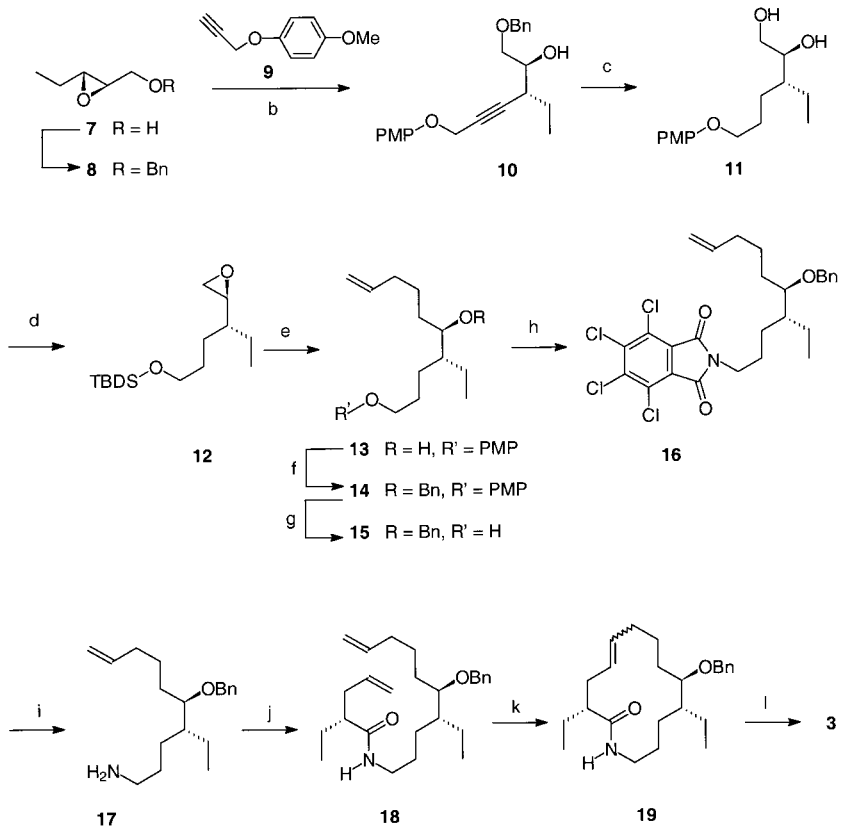
For the synthesis of building block **A** *R*,*R*-configurated epoxy alcohol **7**, prepared by Sharpless epoxidation of (*E*)-pent-2-en-1-ol,[10] was first converted to the benzyl ether **8**.[11] This intermediate should be subjected to a regio- and stereoselective nucleophilic ring opening reaction with a C_3-synthon covering C-11 to C-13 of the target compound.

It appeared reasonable to use propargylamine or propynol derivatives for this purpose, since these compounds bear an acidic alkyne group and a terminal functional group that should enable us to introduce the ring nitrogen. By examining numerous C_3-building blocks of these types, we found that propargyl 4-methoxyphenylether (**9**) gave the best results in the ring opening reaction. The rarely used 4-methoxyphenyl (PMP) protective group[12] was found to be ideal for our purpose, since it is stable to organometallic reagents and to catalytic hydrogenation, as needed for the selective removal of a O-benzyl group later. On the other hand, PMP ethers can be removed by Ce^{4+}-oxidation without affecting benzyl ethers and olefins.

Under carefully controlled conditions[13] epoxide **8** was opened in a regioselective manner by treatment with an alkynyl alanate prepared from **9** and *n*-butyllithium–Me_3Al, in the presence of BF_3, to give **10** in 49% yield.

In the absence of BF_3 we obtained no conversion of the epoxide at all. Catalytic hydrogenation of **10** resulted in reduction of the alkyne group and removal of the benzyl protective group. The diol **11** was obtained in 85% yield.

In order to allow the introduction of a C-5→C-7 fragment, the diol was converted to the epoxide **12** under complete retention at the stereocentres in a single operation with *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole (*N*-TrisIm) and NaH.[14] Next, this epoxide was opened with 3-butenylmagnesium bromide–CuI to give the secondary alcohol **13**. But it was even more efficient to perform these two steps consecutively in one flask, and so **13** was obtained from **11** in 58% overall yield. After benzylation of the



Scheme 3 a) NaH, THF, 30 min; then benzyl bromide, 24 h (71%); b) **9**, *n*-BuLi, THF, –20 °C; then Me_3Al–heptane; then **8** and $BF_3{\cdot}OEt_2$, –30 °C, 2 h (49%); c) H_2, Pd/C, MeOH, 2 h (85%); d) NaH, THF, 0 °C, 1 h; then *N*-TrisIm, 1 h; e) $H_2C{=}CH{-}CH_2{-}CH_2MgBr$, CuI, –30 °C, 2 h (58% from **11**); f) NaH, THF, 30 min; then benzyl bromide, 48 h (79%); g) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, H_2O, –20 °C, 20 min (75%); h) 4,5,6,7-tetrachlorophthalimide, Ph_3P, DEAD, THF, 12 h (60%); i) ethylenediamine, EtOH, THF, 60 °C, 4 h (79%); j) **4**, CH_2Cl_2, DCC, HOBT, 5 min; then **17**, 12 h (63%); k) Ti(*i*-PrO)$_4$, CH_2Cl_2, 1 h; then Grubbs' catalyst, reflux, 4 d (72%); l) H_2, Pd/C, MeOH, 2 h (83%).

secondary alcohol, the PMP protective group was selectively removed by oxidation with CAN in 75% yield. Transformation of the resulting primary alcohol **15** to the primary amine **17** (building block **A**) was performed by coupling with 4,5,6,7-tetrachlorophthalimide under Mitsunobu conditions, followed by deprotection with ethylenediamine.[15] The analogous phthalimide derivative was readily obtained from **15** under identical conditions, but could not be hydrolyzed to the primary amine **17** in acceptable yield under various conditions.

Finally, amine **17** was converted to the amide **18** with carboxylic acid **4** and DCC/HOBT[16] in 63% yield. First attempts to perform a RCM of diene **18** with Grubbs' catalyst gave absolutely no conversion. A literature search revealed, that the γ,δ-unsaturated amide might form an unproductive Ru-chelate with the catalyst. In accordance with Fürstner's observations,[17] addition of 30 mol% Ti(*i*-PrO)$_4$ to the reaction mixture resulted in a clean conversion of the diene to the unsaturated 14-membered lactam **19**.[18] RCM reactions leading to macrocyclic compounds give mixtures of *E*- and *Z*-olefins in most cases. We did not have to care about the stereochemistry around the double bond, since in the final step of the synthesis **19** was subjected to catalytic hydrogenation with a Pd-catalyst resulting in reduction of the double bond and concomitant removal of the O-benzyl group to give the target compound 6-nor-fluvirucinin B$_1$ (**3**) in 83% yield (Scheme 4).[19]

In conclusion, we have worked out a new approach to the fluvirucinin ring system. Use of chiral 2-substituted Grignard reagents derived from1-bromo-3-butenes should also open the possibility to introduce alkyl groups at C-6. Since our synthesis starts from readily available chiral precursors, it should allow the free variation of stereochemistry at each chiral center and the modification of substituents on the ring to prepare further analogs of fluvirucinin B$_1$ for detailed investigation of structure-activity relationships.

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(18) *Ring-closing metathesis*: A solution of diene **18** (30 mg, 0.075 mmol) and Ti(*i*-PrO)$_4$ (6 mg, 0.02 mmol) in 50 mL anhydrous CH_2Cl_2 was refluxed under N_2 for 1 hour. Then 2 mg (0.002 mmol) benzylidene-bis(tricyclohexylphosphine)dichlororuthenium, dissolved in 0.5 mL CH_2Cl_2, was added and the mixture was refluxed for 4 days. Purification by flash column chromatography (silica, hexanes–ethyl acetate 5:2) gave 20 mg (72%) **19** as colorless crystals, mp 176 °C. $[\alpha]_D^{20}$ = +35.4 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.84 (t, *J* = 7.4 Hz, 3 H), 0.90 (t, *J* = 7.5 Hz, 3 H), 1.20–1.60 (m, 13 H), 2.00 (m, 2 H), 2.08 (m, 1 H), 2.39 (m, 1 H), 2.65 (m, 1 H), 3.21 (m, 1 H), 3.50 (m, 1 H), 3.75 (m, 1 H), 4.42 (d, *J* = 11.1 Hz, 1 H), 4.54 (d, *J* = 11.1 Hz, 1 H), 5.38 (m, 1 H), 5.42 (m, 2 H), 7.30 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 11.0, 12.2, 21.9, 23.4, 24.8, 25.1, 26.9, 29.7, 31.5, 35.3, 39.4, 42.5, 50.3, 72.1, 81.5, 127.4, 127.8 (2 C), 128.3 (2 C), 131.5, 131.7, 139.0, 175.0. MS (EI, 70 eV): *m/z* 371 (6, M^+), 280 (100), 263 (12), 100 (12), 91 (91).
(19) Analytical data of **3**: Mp 208 °C. $[\alpha]_D^{20}$ = +50.8 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD 1:1) δ (ppm) 0.88 (t, *J* = 7.5 Hz, 3 H), 0.89 (t, *J* = 7.1 Hz, 3 H), 1.20–1.75 (m, 22 H), 2.15 (m, 1 H), 2.71 (dt, *J* = 4.4 and 13.7 Hz, 1 H), 3.48 (m, 1 H), 3.65 (m, 1 H), 5.40 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD 1:1) δ (ppm) 10.9, 12.3, 21.7, 22.1, 26.0 (2 C), 26.3, 26.4, 27.4, 27.6, 32.4, 33.5, 39.6, 44.9, 52.9, 73.7, 178.2. MS (EI, 70 eV): *m/z* 283 (44, M^+), 265 (51), 212 (22), 184 (30), 171 (49), 156 (26), 128 (51), 115 (43), 100 (38), 81 (29), 69 (46), 55 (100), 43 (50).