Synthesis of Fluvirucins and Their Aglycons, the Fluvirucinins

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Abstract Fluvirucins are bioactive macro lactam glycosides isolated from actinomycetes. This review gives an overview of this family of natural products, covering isolation, biological activities, biosynthesis, and total synthesis. The synthesis of fluvirucins and their aglycons, the fluvirucinins, is presented, paying special attention to the synthetic strategy and stereochemical aspects.

1 Introduction

Fluvirucins are a family of naturally occurring glycosides structurally characterized by the presence of an amino sugar attached at the C-3 or C-9 position of a 14-membered macrocycle lactam aglycon. They also incorporate a methyl or ethyl substituent at C-2 [(S)-1-hydroxyethyl in fluvirucin A2], C-6 (absent in some members), and C-10 of the core lactam nucleus. The amino sugar moiety can be 3-amino-3,6-dideoxy-α-L-talopyranose, e.g. in fluvirucins A1 and B1, or its 4-epimer [(S)-mycosamine], e.g. in fluvirucin B2, or an N-substituted derivative of either.

2 Isolation, Biological Activity, and Biosynthesis

The first member of the fluvirucin family (Sch 38516) was reported in 1990 by scientists at Schering–Plough, who obtained it by extraction from the fermentation broth of the actinomycete Actinomadura vulgaris.1 Its structure was established by X-ray crystallographic analysis. In the following years, the same group reported the isolation of several other glycosides (Sch 38511–38513, Sch 38518, and their C-4′ epimers) produced by various species of Actinomadura.2,3 (Figure 1). All these compounds were found to exhibit antifungal activity against various strains of Candida sp. and dermatophytes.

Almost simultaneously, scientists at Bristol–Myers Squibb described seven macro lactam glycosides, named fluvirucins A1, A2, and B1–B5, from several actinomycete strains. The fluvirucinins possess inhibitory activity against the influenza A virus,4 which is partially retained in the corresponding fluvirucinins.4b

Fluvirucin B2 also acts as an inhibitor of phosphatidylinositol-specific phospholipase C.5 The structures of some of these fluvirucins coincided with those previously reported by the Schering–Plough researchers.

More recently, researchers at Merck have reported the isolation of fluvirucin B06 and two new N-methyl derivatives of fluvirucin A4,7 from the actinomycete Nonomuraea turkmenica, all of which show anthelmintic activity.

By 13C feeding experiments, it was demonstrated that the aglycon moiety of fluvirucins is biosynthesized from acetate and propionate via a combination of polyketide and tricarboxylic acid mechanisms.4b,8 In this context, the identification and characterization of the putative polyketide
3 Synthetic Approaches

The synthesis of fluvirucins has been little explored. In fact, only one total enantioselective synthesis of a member of this group, fluvirucin B₁, has been reported to date. In contrast, fluvirucins have received considerable attention from the synthetic standpoint, which has resulted in enantioselective syntheses of fluvirucins A₁, A₂, B₀, B₁, and B₂–S, the latter being the aglycon common to fluvirucins B₂, B₃, B₄, and B₅.

Two key issues in the synthesis of fluvirucins and fluvirucins are the closure of a 14-membered lactam ring and the control of the configuration of its stereocenters.

As outlined in Figure 2, three main strategies have been used for the construction of the macrocyclic ring: 1. olefin ring-closing metathesis reaction (bond formed Cₓ–Cᵧ, Cᵧ–Cₓ, Cₓ–Cₓ, or Cₓ–Cₓ); 2. macro lactamization (bond formed N–Cₓ); and 3. amide–enolate-induced ring expansion viaaza-Claisen rearrangement of a 10-membered 1-acyl-2-alkoxyvinyl-aza-cyclyc (bond formed Cₓ–Cₓ).

For the sake of clarity, the carbon numbering used in this review for the synthetic intermediates corresponds to that of the fluvirucinin system. In addition, to facilitate its visualization, the fluvirucinin ring skeleton has been drawn with the same orientation throughout the review, both in the A and B series.

3.1 Closure of the 14-Membered Ring by Ring-Closing Metathesis

3.1.1 Hoveyda’s Approach to Fluvirucinin B₁ and Fluvinucin B₁

The first synthesis of a fluvirucinin was reported by Hoveyda in 1995. Two relevant aspects of the synthesis are the use of a ring-closing metathesis (RCM) reaction to promote stereoselective macrocyclization from a conformationally mobile acyclic diene, and the use of macrocyclic stereocentrality to establish the remote stereochemistry at C-6 by catalytic hydrogenation. Thus, closure of the 14-membered ring was efficiently accomplished (bond formed Cₓ–Cₓ) under smooth conditions, using the Schrock Mo catalyst, from amido diene 3, which was convergently prepared by coupling of acid 1 with amine 2 (Scheme 1). Catalytic hydrogenation of the resulting trisubstituted Z olefin 4 stereoselectively installed the C-6 stereo center to afford, after deprotection, fluvirucinin B₁, which was converted into the corresponding acetate.

The required starting materials 1 and 2 (Cₓ–Cₓ and Cₓ–N fragments, respectively, of fluvirucinin B₁), which incorporate the C-2, C-9, and C-10 stereo centers of fluvirucinin B₁, were prepared as outlined in Scheme 2. Acid 1, with the required R configuration, was prepared from

...synthase genes associated with fluvirucin B₁ aglycon biosynthesis in Actinomadura vulgaris has recently been reported.\(^9\)
drofuran 5 via a sequence of three metal-catalyzed steps. Enantioselective Zr-catalyzed ethylmagnesation of 5 gave homoallylic alcohol 6, which was subjected to a tandem Ti- and Ni-catalyzed hydrovinylation by hydromagnesation of the olefin, followed by in situ cross-coupling reaction of the resulting Grignard reagent 7 with vinyl bromide. Ru-catalyzed oxidation of the resulting alcohol 8 completed the synthesis of acid 1.

In turn, homoallylic alcohol 9 was converted into enantiopure allylic alcohol 10 (>99% ee) via kinetic Sharpless resolution of the corresponding racemate. Subsequent one-pot double alkylation of the monosubstituted olefin moiety of 10, involving a diastereoselective Zr-catalyzed ethylmagnesation, and in situ trapping of the resulting alkylmagnesium halide intermediate 11 with N-tosylaziridine, afforded 12 (dr = 97:3). Final protection–deprotection steps led to amine 2 in 12% overall yield for the six-step procedure.

The same strategy was employed for the synthesis of fluvirucin B 1 (Sch 38516), which incorporates a novel carbohydrate moiety identified for the first time in a natural product. However, all attempts to glycosylate the deprotected alcohol derived from 4 with a variety of carbohydrate derivatives failed, probably due to the low solubility of the macrocyclic alcohol in organic solvents.

This problem was circumvented using the more readily soluble alcohol resulting from deprotection of acyclic diene 3, which underwent stereoselective glycosylation with fluoroglycoside 13 to give 14 in excellent yield (Scheme 3). Subsequent RCM, followed by stereoselective hydrogenation of the resulting Z-unsaturated macrolactam 15 and deprotection of the sugar moiety, afforded fluvirucin B 1 (Sch 38516). This was the first, and to date the only, synthesis of a member of the fluvirucin family.
The carbohydrate fragment 20 of fluvirucin B1 was prepared from ethyl sorbate (16) as illustrated in Scheme 4. Key steps of the synthesis are catalytic Sharpless asymmetric (80% ee) dihydroxylation of 16, which ensured the optical purity, diastereoselective dipolar [3+2] cycloaddition between (R)-α-methylbenzylamine-derived nitrone 18 and vinylene carbonate, and the removal of the protecting groups from the resulting cycloaddition product 19 by controlled acid hydrolysis and hydrogenolysis. The stereochemical identity of 20 was established through conversion into the corresponding O, O, N-triacetyl methyl glycoside, which proved identical to the material obtained from degradation of natural fluvirucin B1.

To perform the crucial glycosylation reaction, 20 was protected as an O, O-diacetyl-N-trifluoroacetyl derivative and then activated as a fluoroglycoside 13 via acetoxyglycoside 21 and a thioglycoside.11–13

### 3.1.2 Bracher’s Approach to Fluvirucinin B0

In 2002, Bracher reported14 the enantioselective synthesis of 6-norfuvirucinin B1 before it was known that this nor derivative was the aglycon of fluvirucin B0. The closure of the macro lactam ring was also achieved by RCM reaction,
although, in this case, involving the formation of the C₄–C₅ bond.

The required amido diene 24, which incorporates the three stereocenters of fluvirucinin B₀, was synthesized by coupling acid 22 with amine 23 (C₁–C₄ and C₅–N fragments of fluvirucinin B₀). The RCM of 24 was satisfactorily performed with Grubbs’ catalyst, in the presence of Ti(O-i-Pr)₄ to avoid the formation of an unproductive Ru chelate with the γ,δ-unsaturated amide. Subsequent catalytic hydrogenation of the resulting diene 25 led to fluvirucinin B₀ (Scheme 5).

![Scheme 5](image)

Enantiopure acid 22 was prepared in two steps from Oppolzer’s N-crotyl-(+)-camphorsultam 26, by conjugate hydride addition followed by trapping of the resulting enolate with allyl bromide and subsequent hydrolysis of N-acylsultam 27 (Scheme 6).

In turn, amine 23 was obtained from epoxy alcohol 28, which was accessible by Sharpless oxidation of the corresponding (E)-pentenol. After protection of the hydroxy group, regio- and stereoselective ring-opening reaction with an alkylnl alanate derived from 29 gave alcohol 30, which was converted into saturated epoxide 31. Regioselective opening of 31 with 3-butenylmagnesium bromide, followed by protection–deprotection steps and conversion of the primary alcohol function of 32 into a primary amino group, completed the synthesis of the amine half 23 (Scheme 7).

### 3.1.3 Radha Krishna’s Approach to Fluvirucinin A₁

In 2011, Radha Krishna reported an enantioselective synthesis of fluvirucinin A₁ involving the same C₄–C₅ bond disconnection. Closure of the macrocyclic ring was also achieved by RCM reaction, in this case from diene 35, which was prepared in nearly quantitative yield by amidation between carboxylic acid 33 and amine 34 (C₁–C₄ and C₅–N fragments of fluvirucinin A₁). Hydrogenation of the resulting unsaturated macro lactam 36 (Z/E mixture) brought about both the reduction of the olefinic bond and the deprotection of the alcohol function to furnish fluvirucinin A₁ (Scheme 8).

Both fragments, 33 and 34, were accessed from a common intermediate 38 derived from (S)-Roche ester 37, which provided the C-2 and C-6 stereogenic centers of fluvirucinin A₁. Conversion of ester 37 into allylic alcohol 38 followed by Sharpless asymmetric epoxidation afforded epoxy alcohol 39 which was converted into allylic alcohol 40 by Zn reduction of the corresponding iodide. Subsequent protecting group interconversions and oxidation of the primary alcohol function afforded O-protected hydroxy acid 33 (Scheme 9).

![Scheme 6](image)

![Scheme 7](image)
The preparation of amino-alkene 34 started with a highly diastereoselective (dr > 95:5) Evans asymmetric alkylation of N-butyryloxazolidinone 41 with the allylic iodide derived from 38, which installed the C-10 stereogenic center of fluvirucinin A1 (bond formed C9–C10). Reductive cleavage of the chiral auxiliary, followed by a two-carbon homologation of the resulting alcohol 43 gave alcohol 44, which was converted into N-Boc-amino alcohol 45. Finally, Swern oxidation and one-carbon Wittig olefination completed the C5–N fragment 34.

3.1.4 Negishi’s Approach to Fluvirucinin A1

An alternative enantioselective synthesis of fluvirucinin A1, also using an RCM reaction to promote the macrocyclization, was reported in 2008 by Negishi, although, unlike other syntheses, in this approach the bond formed was C8–C9.

The required diene 48 was prepared in excellent yield by amidation of acid 46 with amine 47 (C1–C8 and C9–N fragments of fluvirucinin A1), and the RCM was performed, also in excellent yield, using Grubbs I catalyst. Subsequent hydrogenation of the olefinic double bond and deprotection afforded fluvirucinin A1 (Scheme 10).
O-Protected hydroxy acid 46 was synthesized in nine steps from (–)-(S)-β-citronellol (50), which provided the C-6 stereogenic center of the target macrocycle. The two other stereocenters of 46 were stereoselectively (dr ≥ 98%) generated by Brown crotylboration\(^2\) of aldehyde 51, which led to homoallylic alcohol 52 (Scheme 11). The synthesis of the C1–C8 fragment was completed by oxidative cleavage of the alkene moiety of 52, protection–deprotection steps, and one-carbon Wittig olefination of the aldehyde resulting from oxidation of alcohol 53.

Amino alkene 47 was obtained by two alternative routes, both of them involving a Zr-catalyzed asymmetric carboalumination reaction, followed by purification by lipase-catalyzed acetylation, starting from either 3-buten-1-ol (54a) or 4-penten-1-ol (54b). The resulting enantiomerically pure (≥98% ee) (R)-2-ethyl-1-alkanols 56a and 56b, containing the C-10 asymmetric center of fluvirucinin A, were converted into the C\(_9\)–N fragment 47 in six conventional steps, via alkenols 57a and 57b, as shown in Scheme 12.

### 3.1.5 The Vilarrasa–Urpí Approach to Fluvirucinin B\(_2\)–B\(_5\)

In 2009, Vilarrasa and Urpí reported the first, and to date the only, enantioselective synthesis of fluvirucinin B\(_2\)–B\(_5\), the aglycon common to fluvirucins B\(_2\)–B\(_5\), via an RCM reaction involving the formation of the C\(_6\)–C\(_7\) bond.\(^2\) The macrocyclization was performed in the presence of the Hoveyda–Grubbs (H–G) II catalyst using diene 60 as the substrate, which was prepared by direct coupling of carboxylic acid 58 with azide 59 using the Staudinger–Vilarrasa reaction (Scheme 13).

Hydrogenation of the trisubstituted double bond of the resulting unsaturated lactam 61 (1:1.2 mixture of Z/E isomers) stereoselectively installed the C-6 stereogenic center (9:1 dr); subsequent hydrolysis afforded fluvirucinin B\(_2\)–B\(_5\). The corresponding acetate was found to be identical to the reported acetylated aglycon derived from fluvirucin B\(_2\) (Sch 38518).

Both the ethyl-branched acid 58 and azide 59 (the C\(_1\)–C\(_6\) and C\(_7\)–N fragments of fluvirucinin B\(_2\)–B\(_5\)) were stereoselectively prepared from the same starting material, the known\(^2\) allylated N-acyloxazolidinone 62 (Scheme 14), which provided the C-2 and C-10 ethyl-substituted stereogenic centers of fluvirucinin B\(_2\)–B\(_5\).

Cross-metathesis of 62 with ethyl vinyl ketone, followed by hydrogenation of the resulting carbon–carbon double bond of enone 63 and selective Petasis ketone methylenation...
tion using DMF as a scavenger, afforded 64. Finally, hydrolytic removal of the chiral auxiliary provided acid 58 in excellent overall yield.

The conversion of 62 into azide 59 commenced with a one-pot hydroboration–iodination process, followed by replacement of the iodine atom by an azide anion. After reductive removal of the auxiliary in 65 and oxidation of the resulting alcohol, stereoselective (dr ≥ 98:2) allylation of aldehyde 66 using the (S,S)-Leighton reagent installed the C-9 stereogenic center to give syn alcohol 67, which was protected as its TBS ether.

3.1.6 The Amat–Bosch Approach to Fluvirucinin B₁

Our group has recently disclosed 23 the enantioselective synthesis of fluvirucinin B₁, also employing an RCM reaction to form the strategic C₆–C₇ bond in the key macrocyclization step.

This was accomplished from amido diene 70 (Scheme 15), which was prepared by coupling acid 68 with amine 69 (the C₁–C₆ and C₇–N fragments of fluvirucinin B₁). The C-6 stereocenter was generated, as in previous syntheses, by stereoselective hydrogenation of the trisubstituted double bond of the macrocyclic alkene 71 (1.2:1 E/Z ratio), leading to the O-protected fluvirucinin B₁ derivative 72 (absolute configuration unambiguously confirmed by X-ray crystallographic analysis). Finally deprotection gave fluvirucinin B₁.

A distinctive feature of the synthesis is the use of (S)-phenylglycinol-derived amino diol 75 as the common starting material for the preparation of acid 68 and amine 69. This amino diol provides the C-2 and C-10 ethyl substituents of the target aglycon, with the required absolute ste-
After protection of the two hydroxy groups, amino diol 75 was converted into the O-protected hydroxy acid 76 by an unprecedented m-CPBA-promoted transformation involving the regioselective oxidation of a phenylglycinol-derived secondary amine to a carboxylic acid. Alternatively, 75 was converted into nitrile 78 by I2/NH3-mediated oxidative cleavage of the secondary amino group (Scheme 17).

The synthesis of the C1–C6 fragment 68 from 76 was completed, via iodide 77, by copper-catalyzed cross-coupling reaction with 2-propenylmagnesium bromide, followed by conversion of the alcohol function into a carboxy group. In turn, the C7–N fragment 69 was synthesized from nitrile 78, via aldehyde 79, by a diastereoselective Leighton allylation (dr = 9:1), which introduced the stereogenic center at C-9, and subsequent protection and reduction steps from the resulting alcohol 80.

3.2 Closure of the 14-Membered Ring by Macrolactamization

3.2.1 Trost’s Approach to Fluvirucinin B1

In 1997, Trost reported a synthesis of fluvirucinin B1 using a conceptually different approach, in which the macrocyclic ring was assembled by lactamization. Starting from N-acylimidazolidinone 87, two key intermediates, Meldrum’s acid derivative 81 and epoxide 82 (C1–C5 and C6–N fragments of fluvirucinin B1), were synthesized in enantiopure form. Coupling of these two building blocks (bond formed C5–C6) by palladium-catalyzed addition of the pronucleophile 81 to alkenyl epoxide 82 occurred with complete transfer of chirality, via a π-allylpalladium species, thus creating the proper configuration at C-6. The resulting allylic alcohol 83, which incorporates all stereogenic centers of fluvirucinin B1, was obtained as a single diastereomer (Scheme 18). Then, simultaneous hydrogenolysis of...
the benzyl ester and azide functionalities and subsequent macrolactamization of the resulting amino acid took place under the reaction conditions depicted in Scheme 18 to give macrolactam 84.

Once the macrocyclic ring system of fluvirucinin B₁ was assembled, the 1,3-dicarbonyl ester moiety was removed stepwise by base-catalyzed hydrolysis–decarboxylation of 84 and, after hydrogenation of the olefinic bond, by radical decarboxylation of the acyl phenylselenide derived from ester 85. The resulting O-silyl derivative 86 had previously been desilylated to fluvirucinin B₁.

The synthesis of the key fragments 81 and 82 is outlined in Scheme 19. Stereospecific alkylation (de >95%) of N-butyrylimidazolidinone 87, followed by removal of the chiral auxiliary from imidazolidinone 88, afforded ester 89. After ozonolysis of the olefinic bond of 89, the Meldrum’s acid moiety was introduced on the resulting aldehyde 90 by reductive alkylation under Knoevenagel conditions to afford 81.

On the other hand, the synthesis of azide 82 started with stereoselective alkylation of 87 (≥95% de) leading to imidazolidinone 91. Reductive removal of the chiral auxiliary followed by oxidation of the resulting alcohol 92 and a two-carbon homologation-reduction sequence gave allylic alcohol 93. Asymmetric epoxidation afforded a single diastereomeric epoxide, thus defining the C-9 absolute configuration. Subsequent oxidation and a stereoselective Wittig olefination (7:1 Z/E ratio) of the resulting aldehyde 94 gave the Cₛ–N fragment 82.

### 3.2.2 The Vilarrasa–Urpi Approach to Fluvirucinin B₁

In 1999, Vilarrasa and Urpi published an alternative synthesis of fluvirucinin B₁, also involving a lactamization reaction to construct the 14-membered ring. The crucial open-chain precursor 98 was prepared by stereoselective aldol-like reaction (bond formed C₈–C₉) between aldehyde 96 and the boron enolate generated from ketone 95 and the menthone-derived boryl bromide 97 (Scheme 20). Alcohol 98 incorporates all carbon atoms of the target aglycon with the natural configuration in all stereocenters. After the subsequent conversion of syn alcohol 98 (20:1 syn/anti ratio) into ω-azido acid 99, the macrolactamization to 100 was performed via an S-2-pyridyl ester by reduction of the azido group.

A three-step reduction of the ketone carbonyl and deprotection of the alcohol function afforded fluvirucinin B₁. The spectroscopic data of the corresponding acetate matched those reported in the literature.

Both ketone 95 and aldehyde 96 (C₁–C₈ and C₉–N fragments of fluvirucinin B₁) were synthesized from a common intermediate 103, which provided the C-2 and C-10 ethyl-substituted stereocenters of the target aglycon. Compound 103 was accessible in five steps from the known Evans N-acyloxazolidinone 101, via alcohol 102 as outlined in Scheme 21.

The preparation of ketone 95 featured a diastereoselective alkylation of the N-propanoyl derivative of (−)-pseudoephedrine with the iodide derived from 103, a process that installed the C-6 methyl-substituted stereocenter of fluvirucinin B₁. Removal of the chiral auxiliary with MeLi gave methyl ketone 95.
In turn, azido aldehyde 96 was obtained from 103 in three conventional steps: introduction of the azido group, deprotection, and Swern oxidation.

### 3.2.3 Suh’s Approach to Fluvirucinin A₁

The synthesis of fluvirucinin A₁ by Suh in 1999 was the first synthesis of a member of the fluvirucinin A series.²⁷ Before the final lactamization of amino acid 114, the key steps were diastereoselective vinyl addition to a 2-piperidone derivative, amide–enolate aza-Claisen rearrangement to generate the 10-membered lactam 109, and stereoselective condensation of an aldehyde with the boron enolate of N-propionyloxazolidinone 112.

The synthesis begins with the Evans asymmetric alkylation of 40–45% of 104, to install the initial stereogenic center corresponding to C-10 of fluvirucinin A₁, and the conversion of the alkylated product 105 into 2-piperidone 106 (Scheme 22). The corresponding N-benzyl derivative was converted into trans-2,3-disubstituted piperidine 107 via a diastereoselective (95:5 trans/cis ratio) vinylation at the lactam carbonyl with the assistance of LiAl(OEt)₃H. Exchange of the benzyl group for propionyl gave amide 108, which underwent stereoselective amide–enolate-induced aza-Claisen rearrangement (bond formed C₆–C₇), leading to the ring-expanded lactam 109, which possesses a new stereogenic center, corresponding to C-6 of fluvirucinin A₁. The reaction occurs via a Z-enolate in a chair–chair-like transition state bearing an equatorial ethyl substituent.
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After unsaturated lactam 109 was hydrogenated and N-protected, reductive ring-opening of lactam 110, followed by a two-carbon Wittig olefination and two reduction steps, afforded saturated aldehyde 111 (Scheme 23). The two remaining stereocenters (C-2 and C-3) were stereoselectively introduced following the Evans protocol by an aldol-type reaction between aldehyde 111 and N-propionyloxazolidinone 112. Hydrolytic removal of the auxiliary and protecting–deprotecting steps converted the resulting alcohol 113 into amino acid 114. Subsequent lactamization and deprotection provided synthetic fluvirucinin A1, which was identical in all respects to the natural aglycon.

3.2.4 Fu’s Approach to Fluvirucinin A1

In 2008, Fu reported a formal total synthesis of fluvirucinin A1, using two sequential Ni-catalyzed asymmetric C(sp3)–C(sp3) Negishi cross-coupling reactions of allylic chlorides as the key steps.

The synthesis started from ethyl (E)-4-oxo-2-butenoate, which was converted in two steps into racemic secondary allylic chloride 116a (Scheme 24).

Nickel(II)-catalyzed cross-coupling of 116a with alkylzinc reagent 115 in the presence of Pybox ligand 117 provided compound 118 in excellent yield and almost complete regio- (>20:1) and enantioselectivity (96% ee). Compound 118 was converted into bromide 119 and then into the corresponding alkylzinc derivative, which was subjected to a second nickel(II)-catalyzed asymmetric cross-coupling reaction with racemic allylic chloride 116b to generate unsaturated ester 120 in excellent diastereomeric ratio (15:1 ratio) and enantioselectivity (>98% ee). A subsequent reduction–amination sequence provided N-protected amino aldehyde 111, an advanced intermediate in Suh’s synthesis of fluvirucinin A1.

3.3 Construction of the 14-Membered Ring by Aza-Claisen Ring Expansion

3.3.1 Suh’s Approach to Fluvirucinin A2

In 2010, Suh contributed the first total synthesis of fluvirucinin A2 by iterative lactam ring expansion via an amide–enolate-induced aza-Claisen rearrangement that provided the 14-membered lactam skeleton with the required absolute configuration at all ring stereogenic centers.

The 10-membered lactam 109, an early intermediate in Suh’s synthesis of fluvirucinin A1, prepared by an initial amide–enolate-induced aza-Claisen rearrangement, was converted into N-Boc saturated lactam 121 (Scheme 25). After partial reduction of the lactam carbonyl and trapping of the resulting N,O-hemiacetal as a silyl ether, stereoselective amidoalkylation led to allyl azacycle 122, which was protected as the Fmoc derivative 123. Oxidative cleavage of the allyl group to an aldehyde, followed by silylation stereoselectively afforded the required (E)-silyl enol ether 124 (E/Z > 10:1).
The corresponding (E)-2-pentenamide 125a underwent regio- and stereoselective (dr >10:1) vinylogous amide-enolate-induced aza-Claisen rearrangement, via a highly favorable transition state, leading to lactam 126 (bond formed C₂⁻C₃), with generation of the C-2 and C-3 stereoergic centers. Selective oxidation of the propenyl appendage of 126, followed by a stereoselective Grignard addition to the resulting aldehyde, left the (S)-1-hydroxyethyl chain at C-2. Deprotection of the C-3 hydroxy group and hydrogenation of the olefinic double bond completed the synthesis of fluvirucinin A₂, whose diacetate exhibited spectral data identical to those of the diacetate derived from the natural aglycone.

The stereoselectivity of the aza-Claisen rearrangement was dependent on the substitution at the unsaturated N-acyl moiety. Thus, when starting from N-(3,3-dimethylacryloyl) derivative 125b, the rearrangement was not stereoselective, leading to a 1:1 mixture of macrolactam 127 and its C-2 epimer, probably due to a nonselective formation of the Z-enolate (Scheme 26).

Compound 127 was converted into epi-fluvirucinin A₂ by manipulation of the isopropenyl chain at C-2 and subsequent deprotection and hydrogenation steps. The R configuration of the 1-hydroxyethyl moiety was attained by stereoselective NaBH₄ reduction of a ketone generated by selective oxidative cleavage of the isopropenyl double bond.

The structures of the synthetic fluvirucinin A₂ and its epi-derivative were confirmed by an alternative synthesis of epi-fluvirucinin A₂ employing a Baeyer–Villiger oxidation to ensure the R configuration of the 1-hydroxyethyl chain.

After acylation of the 10-membered amine intermediate 122 with the R-configurated mixed anhydride 128 and conversion of the allyl chain into an (E)-silyl enol ether, treatment of 129 under aza-Claisen rearrangement conditions afforded the 14-membered lactam 130 (Scheme 27). The (R)-benzylxoxymethyl substituent in the C-2 chain of 130 was converted into (R)-acetyl in 131 and then to (R)-acetoxy in 132, via a Baeyer–Villiger oxidation with retention of configuration.

The spectral data of epi-fluvirucinin A₂ prepared by this approach were identical to those of epi-fluvirucinin A₂ synthesized by the route depicted in Scheme 26.

In the context of a systematic investigation of the aza-Claisen rearrangement induced ring expansion of azacycles and its stereochemical outcome, in 2012 Suh and Jung reported an alternative synthesis of fluvirucinin A₁. Based on a stereoselective (E)- and (Z)-silyl enol ether formation and subsequent ring expansion of the resulting 10-membered 1-acetyl-2-alkoxyvinyl azacycles, it provides stereoselective access to both fluvirucinin A₁ and its C-3 epimer.

After acylation of the allyl acyloxymethyl substituent in the C-2 chain of 133 gave aldehyde 134, which was then converted with al-
most complete stereoselectivity into either the (E)-silyl enol ether E-135 or the Z-isomer Z-135, depending on the reaction conditions (Scheme 28).

These silyl enol ethers underwent a stereospecific amide–enolate-induced aza-Claisen rearrangement (bond formed C2–C3), via the chair-like transition states depicted in Scheme 28, providing the respective C-3 isomeric 14-membered lactams 136 and 3-epi-136, which were then converted into fluvirucinin A1 and its C-3 epimer.

4 Conclusion

Considerable work remains to be done on the synthesis of fluvirucins. To date, the only member of this family of natural products to have been synthesized is fluvirucin B1, which incorporates 3-amino-3,6-dideoxy-α-L-talopyranose as the aminosugar moiety. No syntheses of fluvirucins bearing L-mycosamine as the carbohydrate fragment have been reported.

In contrast, the synthesis of fluvirucinins has attracted considerable attention and a variety of strategies and procedures have been employed to assemble the macrocyclic ring system. Table 1 summarizes the synthetic strategies used for the construction of the 14-membered ring of fluvirucinins, showing the bond formed in the macrocyclization step in each case. Except when the 14-membered ring is assembled by expansion of a 10-membered ring, the table also indicates the bond formed to complete the open-chain skeleton before the macrocyclization step, as well as the length of the two fragments used and the ring atoms they incorporate.

All the reported syntheses are enantioselective and most of them highly convergent, in many cases accessing both key intermediates from a single enantiopure building block. By an appropriate selection of the starting materials, many of the strategies developed could be applied to the synthesis of other members of the fluvirucinin family.

Finally, it should be noted that the synthetic activity in this area has stimulated the development and extensive application of new synthetic methodologies such as RCM macrocyclizations, as well as the use of metal-catalyzed transformations in crucial synthetic steps.

Scheme 27  Alternative synthesis of epi-fluvirucinin A2

Scheme 28  The Suh–Jung synthesis of fluvirucinin A1 and 3-epi-fluvirucinin A1
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(3) A macro lactam disaccharide (Sch 42729; α-D-GlcP-(1→2)-α-L-myco samine) and a macro lactam trisaccharide (Sch 42282; β-D-GlcP-(1→4)-α-D-GlcP-(1→2)-α-L-mycosamine) bearing the same aglycon as Sch 38518 were also isolated: (a) Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Horan, A. C.; King, A. H.; Gentile, F.; Wagman, G. H.; Puar, M. S.; Loebenberg, D. J. Antibiot. 1993, 46, 1109. (b) Hegde, V. R.; Patel, M. G.; Horan, A. C.; King, A. H.; Gentile, F.; Puar, M. S.; Loebenberg, D. J. Antibiot. 1998, 51, 464.


