assuming a nonchelated transition state,[17] as observed in similar reactions.[18] These results reflect a very high degree of substrate control in the aldol addition of achiral boron enolates to chiral aldehydes.[18]

It is worth pointing out that the three-component coupling reaction described here represents an interesting alternative to the aldol reaction where the main problem of the lack of regioselectivity for nearly symmetrical ketones is solved (Figure 2). Further studies on the mechanism and synthetic applications of this novel transformation will be reported in due course.

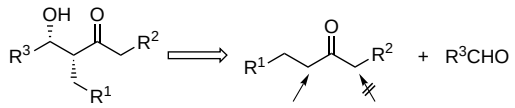

Figure 2. Regio and diastereoselective aldol reaction.

Experimental Section.

Preparation of **4** and **6**: $BF_3 \cdot OEt_2$ (0.36 mL, 3 mmol) was slowly added at $-60\,^{\circ}C$ to a solution of **1**, generated by reaction of hexacarbonylmolybdenum (3 mmol) and the corresponding organolithium compound (3 mmol), in diethyl ether (30 mL), and the mixture stirred for 10 min. The vinyl ketone **2** and the aldehyde **3** or **5** were then added dropwise at the same temperature. Stirring was continued while the temperature reached room temperature (compounds **4**) or $-20\,^{\circ}C$ (compounds **6**). The mixture was hydrolyzed with water (30 mL), extracted with diethyl ether (3×10 mL), and the organic layer dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the crude product purified by column chromatography (silica gel, hexane/ethyl acetate 40/1). All compounds gave satisfactory analytical data, including elemental analysis, mass and NMR spectra.

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High-Yielding Enantioselective Synthesis of the Macrolactam Aglycon of Sch 38516 from Two Units of (2*R*)-2-Ethyl-4-penten-1-ol**

Manuel Martín, Gemma Mas, Fèlix Urpí,* and Jaume Vilarrasa*

Dedicated to Professor Elias J. Corey and in memory of Felix Serratosa

The tridecanelactam antifungal agents Sch 38516, Sch 38518, and Sch 39185 isolated by researchers at Schering – Plough[1] from *Actinomadura vulgaris*, shown to be active

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against *Candida* sp. and dermatophytes, and the 14-membered lactams fluvirucins A_1, A_2, B_1, B_2, B_3, B_4, and B_5 isolated by scientists at Bristol–Myers Squibb[2] from different strains of actinomycetes, shown to be active against influenza A virus, belong to the same family of compounds.[1, 2] Fluvirucin B_2 was also isolated from *Streptomyces* sp. MJ677-72F5 and found to inhibit phosphatidylinositol-specific phospholipase C (among ca. 3000 samples screened).[3] Most fluvirucin aglycons (called fluvirucinins) have structures similar to the representative examples shown in Figure 1.[4]

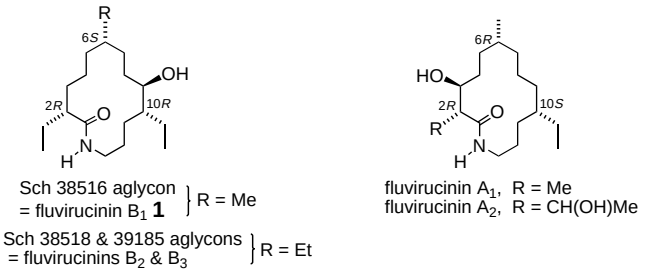
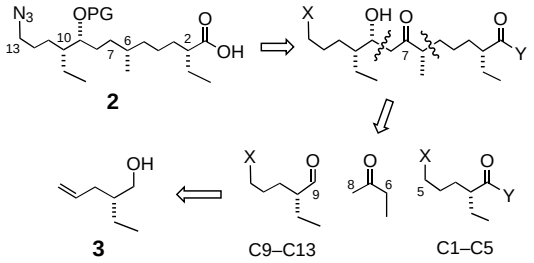


Figure 1. Schematic representations of various fluvirucinins.

The novelty of these macrolactams, which are not strictly macrolide-like antibiotics,[1, 2, 5] their variety of biological roles, and the difficulty of controlling the creation of the distant stereocenters during total synthesis drew the attention of several research groups. So far, two brilliant syntheses of **1** (Figure 1) have been reported, the first one by Hoveyda et al.[6] and the second one by Trost et al.[7] Both syntheses are primarily based on the application of transition metal mediated C–C bond formations. By contrast, our synthesis of **1** relies upon the direct macrolactamization reaction of a 13-azidotridecanoic acid derivative and a peculiar asymmetric aldol-like reaction as key steps.

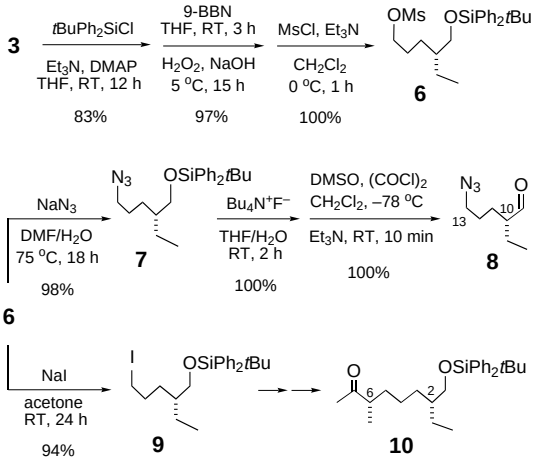
Our retrosynthetic analysis began with the disconnection of the amide bond to **2** (Scheme 1). Formal introduction of an oxo group at C7 and disconnection of the ketone between C5



Scheme 1. The retrosynthetic analysis for the synthesis of **1**. PG = protecting group.

and C6 and between C8 and C9 led to synthetically equivalent fragments C1–C5 and C9–C13. Both fragments could be readily prepared from enantiopure (2*R*)-2-ethyl-4-penten-1-ol (**3**) or its carboxyl or carbonyl derivatives. The essential points were to form the C5–C6 bond by a stereoselective alkylation and the C8–C9 bond by a stereoselective aldol reaction. The versatility of this simple strategy is remarkable since, for example, use of 2-pentanone derivatives instead of butanone-related derivatives should afford an entry to fluvirucinins B_2–B_5. However, the "state of the art" of synthetic methodology does not yet permit such flexible and straightforward manipulations in a controlled fashion.

The synthesis of **1** started from the phenylalanine-derived oxazolidinone (20 g) of Evans et al., which was converted as reported into enantiopure **3** in excellent overall yield.[8] Protection of the hydroxyl group of **3**, hydroboration with 9-BBN followed by oxidation, and reaction with methanesulfonyl chloride afforded **6**, also in excellent overall yield (Scheme 2). A fraction of **6** was converted into azide **7**,



Scheme 2. Synthesis of ketone **10** from **3**. 9-BBN = 9-borabicyclo[3.3.1]-nonane, DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl.

deprotected with tetrabutylammonium fluoride, and oxidized to aldehyde **8**. The other portion of **6** was transformed to iodo derivative **9** by reaction with NaI in acetone. After careful optimization of all steps, **8** and **9** were obtained in about 60% overall yield each from the oxazolidinone.

The challenge at this stage was the diastereoselective alkylation of Aux*-CO-Et (Aux* = chiral auxiliary) with **9** to establish the C5–C6 bond.[9] Myers et al. have demonstrated that enolates from pseudoephedrine-derived amides react efficiently with alkyl iodides and that removal of the auxiliary is feasible.[10] Therefore, we treated the *N*-propanoyl derivative of (−)-pseudoephedrine with lithium diisopropylamide (LDA, 2.25 equiv) and LiCl (6 equiv) and then with **9** (0.5 equiv) to give the alkylation product in 87% yield; addition of MeLi (3.0 equiv) afforded the desired methyl ketone **10** (only one stereoisomer by 500-MHz ^{1}H NMR) in 92% yield. To summarize, **10** was available in three high-yielding steps from **6**.

We anticipated difficulties in the aldol-like reaction between **8** and **10**, since the two Cα substituents of aldehyde **8** are sterically very similar. Moreover, it was presumed that the Cα methyl group of **10** would not be sufficient to discriminate the two faces of its enolate. A series of experiments with lithium, sodium, or titanium(IV) enolates of **10** under different conditions afforded, as expected, almost equimolar mixtures of the "Felkin" (*syn* OH and Et groups) and "anti-Felkin" aldols (*anti*). So, we had to rely on a "triple asymmetric approach".

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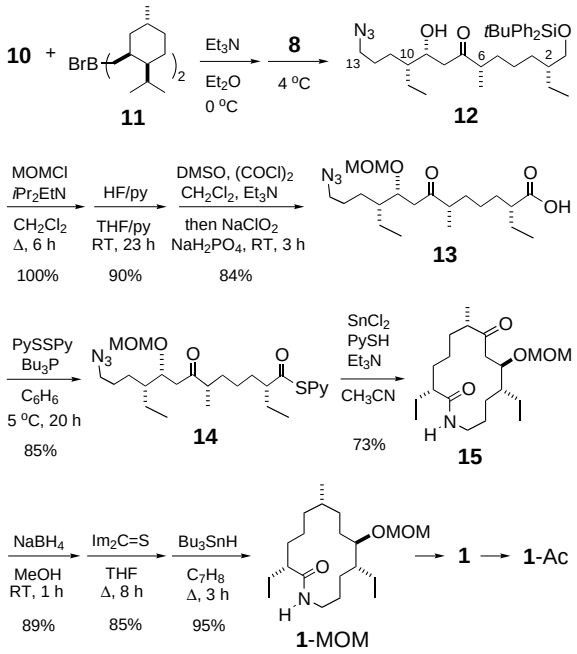
Boron enolates of **10**—generated by using either (−)-Ipc$_2$BCl, (+)-Ipc$_2$BCl, (−)-Ipc$_2$BBr, (−)-Ipc$_2$BOTf[11] (Ipc = isopinocamphenyl), or the menthone-derived boryl bromide of Gennari et al.[12] (**11**)—were allowed to react under different conditions with equimolar amounts of **8** (Scheme 3). The



Scheme 3. Synthesis of **1**. Im = imidazole, MOM = methoxymethyl, py = pyridine, Py = 2-pyridyl.

best results were 1) 61 % conversion with a 6.6:1 *syn*:*anti* ratio by using (−)-Ipc$_2$BCl and *i*Pr$_2$EtN in Et$_2$O for after 4 d at 4 °C, and 2) 79 % conversion with a 20.6:1 *syn*:*anti* ratio by using **11** and Et$_3$N in Et$_2$O for 4 d at 4 °C. Pure *syn* aldol **12**[13] could be isolated by flash column chromatography (in 40 – 45 % yield), and unchanged starting materials (**8** and **10**) were easily recovered in the first eluted fractions.

Protection of the hydroxyl group of **12** was accomplished in quantitative yield with methoxymethyl chloride and *i*Pr$_2$EtN in refluxing CH$_2$Cl$_2$. Deprotection of the hydroxyl group at C1 with HF/pyridine and oxidation of the primary alcohol afforded the carboxylic acid **13**. Thus, in 75 % overall yield from **12**, we obtained an ω-azido acid amenable to the cyclization, which is in principle the last key step of our synthetic strategy. The carboxylic acid moiety was activated as its *S*-2-pyridyl ester (**14**) in 85 % yield.[14] Cyclization of **14** by slow addition (over 6 h) to a large volume of refluxing acetonitrile containing SnCl$_2$ (20 equiv), Et$_3$N (80 equiv), and 2-thiopyridone[15] (80 equiv) afforded the desired macrolactam **15** in 73 % yield. The ketone functionality of **15** was removed by reduction to the corresponding alcohol, followed by reaction with 1,1′-thiocarbonyldiimidazole and radical reduction with Bu$_3$SnH,[16] to yield the desired MOM-protected **1** (**1**-MOM). A very small amount of **1**-MOM was hydrolyzed with aqueous HCl (MOM removal), and the evaporation residue (**1**), after confirmation of its structure by NMR spectroscopy and FAB-MS, was heated in the presence of excess acetic anhydride and pyridine; the spectroscopic data of the resulting product were identical to those previously reported for the *O*-acetyl derivative of **1** (**1**-Ac).[6]

In summary, a simple and efficient strategy to reach the aglycon of Sch 38516/fluvirucin B$_1$ (i.e., fluvirucinin B$_1$, **1**), which is readily amenable to the synthesis of related targets, has been demonstrated. The challenging acetate aldol reaction to form the C8–C9 bond has been achieved with a conversion of 79 % and a diastereomeric ratio of 20:1 by using the chiral boron derivative of Gennari et al. Another key step, macrolactamization, proceed in a gratifying 73 % yield from a *S*-2-pyridyl 13-azidothioester by reduction (with Sn^{II} – PySH complexes) and cyclization in situ.

Experimental Section

12: To a solution of **11** in CH$_2$Cl$_2$ (432 μL, 0.4 M solution, 0.177 mmol), at 0 °C and under N$_2$, were added by means of a syringe Et$_3$N (24 μL, 0.173 mmol) and a solution of ketone **10** (44 mg, 0.104 mmol) in Et$_2$O (1 mL). The reaction mixture was stirred for 5 h. Aldehyde **8** (16 mg, 0.103 mmol) in Et$_2$O (1 mL) was then added dropwise. After stirring for 4 d at 4 °C, the reaction was quenched with phosphate buffer (pH 7, 10 mL), and the mixture extracted with Et$_2$O (3 × 10 mL). The volatile components were removed in vacuo, and the crude product was diluted with MeOH (2 mL), phosphate buffer (0.5 mL), and 30 % aqueous H$_2$O$_2$ (0.5 mL). The resulting mixture was stirred at 0 °C for 1.5 h, diluted with H$_2$O (15 mL), and extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic extracts were washed with saturated aqueous NaHCO$_3$ (15 mL) and brine (15 mL), and then dried over Na$_2$SO$_4$. Analysis by HPLC (hexanes/EtOAc 95/5, Tracer Spherisorb S3W column, 4.6 mm × 25 cm, 9 mL min^{-1}) of the product indicated a 20.6:1 ratio of the stereoisomers 5*R* (t_r = 17.1 min) and 5*S* (t_r = 12.2 min). Separation by flash chromatography on silica gel (CH$_2$Cl$_2$) afforded first **10** (20 mg) and finally ketone **12** (26 mg, 44 %, 79 % based on recovered starting material) as a colorless oil: R_f = 0.33 (hexanes/EtOAc 85/15); $[\alpha]_D^{20}$ = +25.43 (c = 0.98 in CHCl$_3$); IR (film): $\tilde{\nu}$ = 3600 – 3200, 3100 – 2800, 2100, 1700, 1450 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 7.7 – 7.6 (m, 4H; ArH), 7.4 – 7.3 (m, 6H; ArH), 4.1 – 4.0 (m, 1H; C*H*OH), 3.51 (d, J = 2.5 Hz, 2H; CH$_2$OSi), 3.3 – 3.2 (m, 2H; CH$_2$N$_3$), 3.0 (d, J = 4.0 Hz, 1H; CHO*H*), 2.52 (d, J = 9.5 Hz, 2H; COCH$_2$), 2.47 (h, J = 7.0 Hz, 1H; CH$_3$C*H*), 1.7 – 1.1 (m, 16H), 1.04 (d, J = 7.0 Hz, 3H; C*H*$_3$CH), 1.03 (s, 9H; *t*Bu), 0.89 (t, J = 7.2 Hz, 3H; CH$_3$), 0.79 (t, J = 7.2, 3H; CH$_3$); ^{13}C NMR (CDCl$_3$, 50.3 MHz): δ = 216.6, 135.6, 133.9, 129.5, 127.5, 68.5, 65.6, 51.7, 47.0, 44.0, 43.7, 41.8, 33.1, 30.6, 26.8, 26.4, 26.0, 24.5, 23.5, 22.0, 19.3, 16.0, 11.7, 11.2; MS (FAB): 602 [*M*+Na]; HPLC analysis of the Mosher ester of **12**: t_r = 5.9 min (hexanes/EtOAc 95/5).

15: To a stirred mixture of SnCl$_2$ (120 mg, 0.62 mmol), PySH (277 mg, 2.44 mmol), and Et$_3$N (340 μL, 2.45 mmol) in acetonitrile (20 mL), heated at 80 °C under argon atmosphere, was added by means of a syringe pump over 3 h a solution of **14** (15.0 mg, 0.030 mmol) in toluene (20 mL). Heating was maintained for one further hour, and the flask was then cooled externally. The solvent was evaporated in vacuo. The residue was treated with CH$_2$Cl$_2$/MeOH (95/5, 40 mL) and washed with aqueous KOH (2 M, 2 × 40 mL). The aqueous layers were extracted with CH$_2$Cl$_2$ (2 × 40 mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The resulting colorless oil was dissolved in Et$_2$O (20 mL) and extracted twice with 1 M HCl (20 mL). The aqueous phase was extracted with Et$_2$O (3 × 20 mL). The extracts were dried (MgSO$_4$) and purified by chromatography on silica gel (CH$_2$Cl$_2$, CH$_2$Cl$_2$/EtOAc 3/1 → 1/1) to give lactam **15** (8.0 mg, 73 %) as a white foam: R_f = 0.29 (CH$_2$Cl$_2$/EtOAc 3/1); $[\alpha]_D^{20}$ = +6.8 (c = 0.6 in CHCl$_3$); IR (film): $\tilde{\nu}$ = 2850, 1710, 1640, 1560, 1460, 1420 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 5.4 – 5.3 (br s, 1H; NH), 4.64 (d, J = 6.5 Hz, 1H; OC*H*$_a$H$_b$O), 4.59 (d, J = 6.5 Hz, 1H; OCH$_a$*H*$_b$O), 3.89 (dt, J = 9.0 Hz, J = 4.5 Hz, 1H; CHO), 3.8 – 3.6 (m, 1H; C*H*$_a$H$_b$NH), 3.30 (s, 3H; CH$_3$O), 3.0 – 2.9 (m, 1H; CH$_a$*H*$_b$NH), 2.77 (d, J = 4.5 Hz, 2H; CH$_2$CO), 2.6 – 2.4 (m, 1H; CH$_3$C*H*), 1.9 – 1.8 (m, 1H; C*H*CONH), 1.7 – 1.1 (m, 15H), 1.02 (d, J = 7.0 Hz, 3H; C*H*$_3$CH), 0.85 (t, J = 7.2 Hz, 3H; C*H*$_3$CH$_2$), 0.84 (t, J = 7.5 Hz, 3H; C*H*$_3$CH$_2$); ^{13}C NMR (CDCl$_3$, 75.4 MHz): δ = 212.7, 175.2, 97.0, 74.6, 55.9,

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50.6, 48.7, 46.6, 43.7, 38.9, 34.4, 33.0, 29.7, 26.7, 26.1, 25.4, 21.2, 17.3, 12.2, 9.6; MS (CI, NH_3): 356 [M+1], 373 [M+18]; HR-MS (CI, CH_4) calcd for $C_{20}H_{37}NO_4$ [M+H]: 355.2723, found: 355.2715.

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Enantioselective Total Synthesis of Avarol and Avarone**

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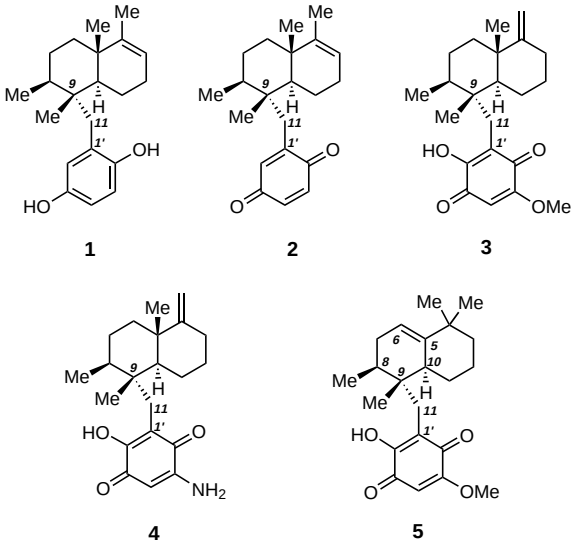
In memory of Sir Derek H. R. Barton

Quinone and hydroquinone subunits are featured in a variety of natural products,[1] including a family of marine metabolites represented by avarol (**1**),[2] avarone (**2**),[2] ilimaquinone (**3**),[3] smenospongine (**4**),[4] and mamanuthaquinone (**5**).[5] Among the exciting and diverse biological properties exhibited by all members of this family, the antimitotic, antileukemic, and antiviral effects reported for **1** and **2** are particularly noteworthy.[6] Although the chemical origins of



these biological properties remain obscure, the redox properties of the hydroquinone – quinone system present in **1** and **2** may be held accountable for such a profile.[7]

The combination of attractive structure and biological activity displayed by the above family has spurred the development of multiple syntheses for some of these compounds.[8, 9] A common element in all reported strategies is the early assembly of the entire skeleton of the natural products

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