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Efficient Approach to Fluvirucins B_2−B_5, Sch 38518, and Sch 39185. First Synthesis of their Aglycon, via CM and RCM Reactions

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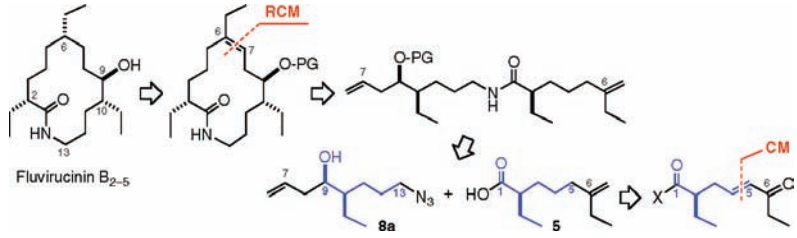
ABSTRACT



A route to fluvirucinins B_{2-5} (the common aglycon of fluvirucins B_2−B_5, Sch 38518, and Sch 39185) is reported for the first time. A ring-closing metathesis (RCM) generated the C6−C7 double bond, which by catalytic hydrogenation (in toluene) gave the desired epimer with a 9:1 diastereoselection. Azide 8a and carboxylic acid 5 came from ethyl-branched fragments C9−C13 (CHO at C9) and C1−C5 via an asymmetric allylation of the former and a cross metathesis (CM) followed by a ketone methylenation (with 20 mol % of DMF as a sacrificial additive) of the latter.

Compounds Sch 38516, Sch 38518, Sch 39185, and related derivatives (antifungal agents isolated by Schering-Plough from *Actinomadura vulgaris*)[1] as well as fluvirucins A_1, A_2, and B_1−B_5 (antibiotics active against influenza A viruses isolated from diverse *Actinomycetes* at Bristol-Myers Squibb)[2] share a 14-membered lactam skeleton or scaffold to which various 3-aminosaccharides (e.g., 3-amino-3,6-didesoxitalopyranose, micosamine, and related sugars) are appended through a hydroxyl group (see Figure 1). Fluvirucin B_2 was also isolated from a *Streptomyces* culture broth and exhibited phospholipase C inhibition.[3]

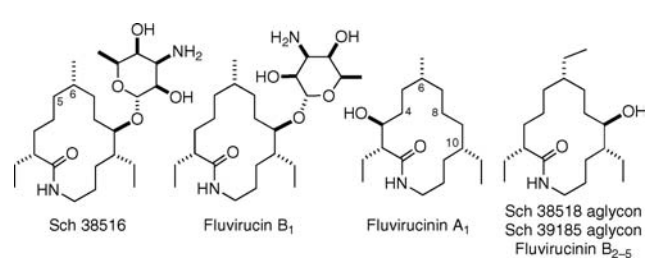


Figure 1. Representative fluvirucins and fluvirucinins.

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(1) (a) Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Ganguly, A. K.; Sarre, O.; Puar, M. S.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6403. (b) Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Puar, M. S. *J. Chem. Soc., Chem. Commun.* **1991**, 810. (c) Hegde, V. R.; Patel, M. G.; Horan, A.; Gullo, V.; Marquez, J.; Gunnarsson, I.; Gentile, F.; Loebenberg, D.; King, A.; Puar, M. S.; Pramanik, B. *J. Antibiot.* **1992**, *45*, 624. (d) Cooper, R.; Truumees, I.; Yarborough, R.; Loebenberg, D.; Marquez, J.; Horan, A.; Patel, M.; Gullo, V.; Puar, M. S.; Pramanik, B. *J. Antibiot.* **1992**, *45*, 633 (5 new analogues discovered). (e) Puar, M. S.; Gullo, V.; Gunnarsson, I.; Hegde, V.; Patel, M. G.; Schwartz, J. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 575 (biosynthesis). (f) 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 (a Sch 38518-derived disaccharide). (g) Hegde, V. R.; Patel, M. G.; Horan, A. C.; King, A. H.; Gentile, F.; Puar, M. S.; Loebenberg, D. *J. Antibiot.* **1998**, *51*, 464 (a trisaccharide related with Sch 38518).

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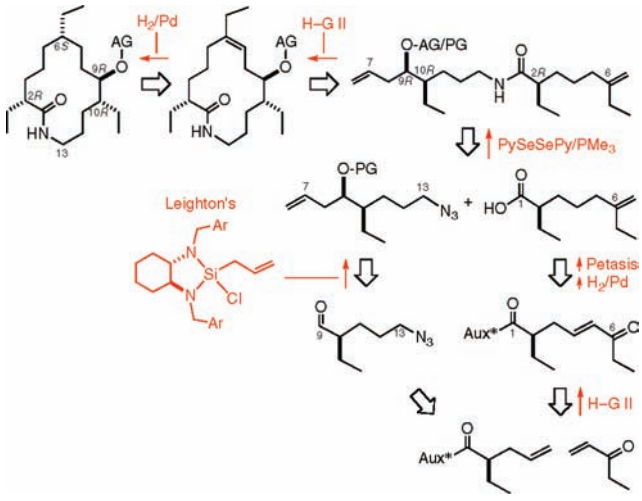
Syntheses of some of these structures have been reported.[4−10] The first one, that of the aglycon of Sch 38516 and fluvirucin B_1 (that is, of fluvirucinin B_1) by Hoveyda et al.,[4a] is remarkable historically as, to our knowledge, it was the first application of a RCM to a complex enantioselective synthesis of a natural product. Very recently, new members have been added to this family of antibiotics, for which further biological properties are being disclosed.[11]

In particular, we were attracted by fluvirucins B_2−B_5 for which no synthesis has been described to date. Our purpose was to reach sufficient amounts of their common aglycon (fluvirucinins B_{2-5}, no synthesis reported either) by a convergent strategy, to prepare series of aminosaccharide and/or aminodiol derivatives amenable to QSAR studies.

Our strategy is summarized in Scheme 1. Provided that the reduction of the double bond between C6 and C7 gives

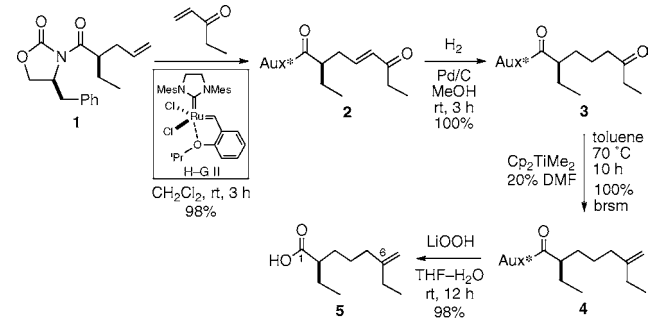
Scheme 1. Retrosynthetic Analysis of Fluvirucins B_2−B_5 (AG = 3-Aminoglycosides) and Their Fluvirucinins (AG = H)



mainly the desired 6*S*-Et derivative, disconnection between C6 and C7 via RCM would afford the linear amide indicated on top. Disconnection of the amide group would then give rise to two fragments: an azide (in a fragment containing carbon atoms C7 to C13) and a carboxylic acid (containing carbons C1 and C6). The first could come from an asymmetric (nucleophilic) allylation of aldehyde C9−C13, while the second fragment could come via a cross metathesis (CM), followed by hydrogenation of the double bond and a methylenation. Both fragments can arise from the same starting material, that is, from the product of the electrophilic allylation of Aux*-CO-$CH_2CH_2CH_3$.

In practice, we started the synthesis from the known oxazolidinone derivative of 2-ethyl-4-pentenoic acid, **1**.[12] Cross metathesis of **1** with an excess of ethyl vinyl ketone (2-penten-3-one, 4 equiv) in the presence of Hoveyda−Grubbs II initiator (0.05 equiv),[13] for 3 h at room temperature (rt), afforded 98% of **2** (see Scheme 2).[14,15] Simple catalytic

Scheme 2. Synthesis of Carboxylic Acid **5**



hydrogenation of the double bond of **2** gave **3** quantitatively. For the selective methylenation of **3**, only the dimethyltitanocene of Petasis[16] gave acceptable yields in preliminary trials. The endocyclic CO group (of the Evans chiral auxiliary) was also partially methylenated. To tame the reactivity of dimethyltitanocene (of the active carbene

(2) (a) Naruse, N.; Tenmyo, O.; Kawano, K.; Tomita, K.; Ohgusa, N.; Miyaki, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 733. (b) Naruse, N.; Tsuno, T.; Sawada, Y.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 741. (c) Tomita, K.; Oda, N.; Hoshino, Y.; Ohkusa, N.; Chikazawa, H. *J. Antibiot.* **1991**, *44*, 940.

(3) Ui, H.; Imoto, M.; Umezawa, K. *J. Antibiot.* **1995**, *48*, 387.

(4) (a) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943 (Schrock's catalyst, installation of a trisubstituted C5−C6 double bond). (b) Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926 (Sch 38516 total synthesis). (c) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302. (d) Xu, Z.; Johannes, C. W.; La, D. S.; Hofilena, G. E.; Hoveyda, A. H. *Tetrahedron* **1997**, *53*, 16377.

(5) Trost, B. M.; Ceschi, M. A.; König, B. *Angew. Chem., Int. Ed.* **1997**, *36*, 1486 (fluvirucinin B_1, formation of the key C5−C6 bond by a Pd-catalyzed reaction of a C1−C4-substituted Meldrum's acid with an alkenyl epoxide).

(6) Martín, M.; Mas, G.; Urpí, F.; Vilarrasa, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3086 (fluvirucinin B_1, via an asymmetric aldol reaction, assisted by a temporal carbonyl group at C7, and a direct macrolactamization from the appropriate ω-azido acid).

(7) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3545 (fluvirucinin A_1, starting from enantiopure 3-ethylpentanolactam).

(8) Baltrusch, A. W.; Bracher, F. *Synlett* **2002**, 1724. (6-nor-fluvirucinin B_1, formation of a C4−C5 double bond by RCM). The absence of the stereocenter at C6 simplifies the synthesis considerably.

(9) Liang, B.; Negishi, E. *Org. Lett.* **2008**, *10*, 193 (fluvirucinin A_1, RCM between C8 and C9, ethyl-metalation and lipase resolution to give the C9−C13 chain-containing amine).

(10) Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756 (formal synthesis of fluvirucinin A_1, two Ni-catalyzed cross couplings to generate the C5−C6 and C10−C11 bonds).

(11) (a) Ayers, S.; Zink, D. L.; Mohn, K.; Powell, J. S.; Brown, C. M; Murphy, T.; Grund, A.; Genilloud, O.; Salazar, O.; Thompson, D.; Singh, S. B. *J. Nat. Prod.* **2007**, *70*, 1371 (6-desmethyl-*N*-methylfluvirucin A_1 and *N*-methylfluvirucin A_1, *Nonomuraea turkmeniaca* MA7364, anti-helmintic). (b) Ayers, S.; Zink, D. L.; Powell, J. S.; Brown, C. M; Grund, A.; Genilloud, O.; Salazar, O.; Thompson, D.; Singh, S. B. *J. Antibiot.* **2008**, *61*, 59 (6-desmethylfluvirucin B_1/B_3, or fluvirucin B_0, *N. turkmeniaca* MA7381; the compound of ref 8 is therefore a natural product).

(12) We prepared **1** in quantitative yield and dr >98% by standard treatment at −78 °C of the corresponding *N*-butyryl oxazolidinone with NaHMDS and an excess of allyl iodide. See: (a) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260. (b) Clive, D. L. J.; Murthy, K. S. K.; George, R.; Poznansky, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2099. (c) Kowashi, S.; Ogamino, T.; Kamei, J.; Ishikawa, Y.; Nishiyama, S. *Tetrahedron Lett.* **2004**, *45*, 4393. (d) Freixas, G.; Urpí, F.; Vilarrasa, J. *Lett. Org. Chem.* **2006**, *3*, 183.

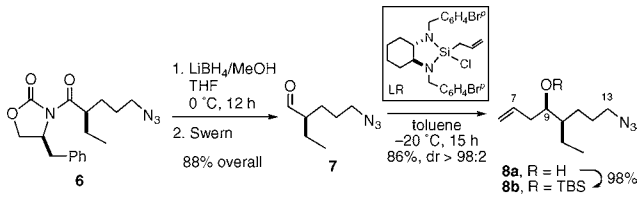
species, $Cp_2Ti{=}CH_2$), we examined the effect of possible scavengers or additives with sacrificial CO groups[17] such as *tert*-butyl acetate, *N*-butyryl-4-benzyl-1,3-oxazolidin-2-one, or DMF. DMF (20 mol %) turned out to be the scavenger of choice: although the conversion was incomplete (76%, with 1.2 equiv of Cp_2TiMe_2),[18] only the methylenated compound, **4**, was formed and the remaining starting material was fully recovered (100% yield brsm). It is worth noting that the chiral auxiliary survived (was amenable to) the cross metathesis conditions and methylenation reaction. Finally, standard removal of the chiral auxiliary gave carboxylic acid **5** in practically quantitative yield. Therefore, we had achieved carboxylic acid **5** in ≥95% overall yield from **1**.

The C7−C13 fragment was synthesized from azide **6**, according to Scheme 3. We prepared this azide by the one-pot hydroboration (with cyclohexene and $PhNEt^iPr\text{-}BH_3$) and iodination of **1** (86% overall),[12d] followed by the quantitative replacement of the iodine atom by azide anion in DMSO at rt.[19] The standard reductive removal of the auxiliary of **6**, followed by the Swern reaction (DMSO/ClCOCOCl, −78 °C, then Et_3N),[20] afforded the desired azido-aldehyde **7** in high overall yield from **1** (≥75%). Among several alternatives for the allylation[21] of **7**, we chose the allylsilane derivative reported by Leighton et al.,[22] shown in Scheme 3, mainly because it had given us excellent results in another total synthesis. Reaction of **7** with freshly prepared (*S*,*S*)-siladiazolidine (Leighton reagent, LR) afforded the *syn* adduct **8a** in 86% yield as a single product by ^1H NMR (dr >98:2).[23] The hydroxyl group of **8a** was protected as its TBS ether **8b**.

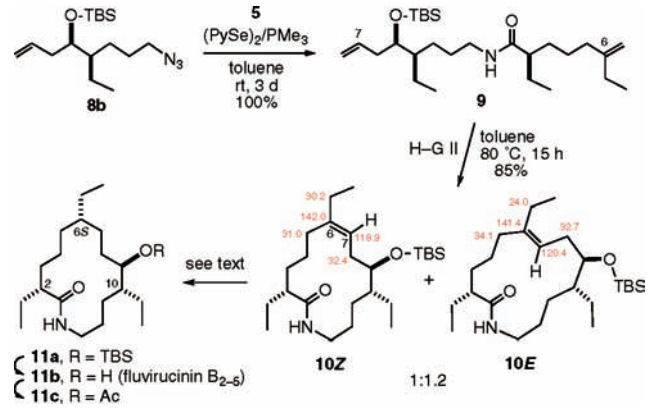
The direct coupling of the azide group of **8b** with carboxylic acid **5** gave amide **9** quantitatively (Scheme 4) by using a catalytic variant of the Staudinger−Vilarrasa reaction.[24] However, as this particular reaction was too slow at rt, with catalytic amounts of 2,2′-dipyridyl diselenide (PySeSePy), we effected it stoichiometrically.

We were ready to subject amide **9** to a RCM. To generate a macrocycle-embedded trisubstituted double bond with the desired configuration by RCM is a difficult task.[25] In light of our previous studies with other macrocyclic substrates,[25e] we used 20 mol % of H-G II initiator in toluene at 80 °C.

Scheme 3. Synthesis of Azides **8**



Scheme 4. RCM and Hydrogenation



(13) Representative review: Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243.

(14) In this case, the Grubbs II initiator gave only 50% of conversion after 5 h in refluxing CH_2Cl_2 (18% after 5 h at rt).

(15) For CM studies with propenal (acrolein), alkyl acrylates, vinyl ketones, and related derivatives, see: (a) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1091. (b) Blanco, O. M.; Castedo, L. *Synlett* **1999**, 557. (c) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58. (d) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (e) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *634*, 216. (f) Dreher, S. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 341. (g) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451. (h) Cossy, J.; Bargiggia, F.; BouzBouz, S. *Org. Lett.* **2003**, *5*, 459. (i) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (j) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (k) Lee, C.-H. A.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 809. (l) Lipshutz, B. H.; Aguinaldo, G. T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* **2008**, *10*, 1325. (m) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2008**, *10*, 4489.

(16) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392. For a review of Ti-based alkylidenations, see: (b) Hartley, R. C.; Li, J.; Main, C. A.; McKiernan, G. J. *Tetrahedron* **2007**, *63*, 4825.

(17) (a) 1,1-Dimethyl-2-phenylethyl acetate has been used as a sacrificial additive: Payack, J. F.; , M. A.; Cai, D.; Hughes, D. L.; Collins, P. C.; Johnson, B. K.; Cottrel, I. F.; Tuma, L. D. *Org. Process Res. Dev.* **2004**, *8*, 256. For the use of ethyl pivalate, cf. : (b) Smith, A. B.; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T.; Meis, R. M. *J. Org. Chem.* **2008**, *73*, 1192. (c) Smith, A. B.; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T. *Org. Lett.* **2005**, *7*, 4399, and references cited therein.

(18) This is the optimum conversion yield (and the maximum recovery of **3**) we found, after various experiments with higher ratios of DMF and/or Cp_2TiMe_2.

(19) Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.

(20) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(21) For illustrative reviews, see: (a) Kargbo, R. B.; Cook, G. R. *Curr. Org. Chem.* **2007**, *11*, 1287. (b) Zanoni, G.; Pontiroli, A.; Marchetti, A.; Vidari, G. *Eur. J. Org. Chem.* **2007**, 3599. (c) Hall, D. G. *Synlett* **2007**, 1644. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (e) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732.

(22) (a) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946. (b) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596. (c) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375. (d) Zhang, X.; Houk, K. N.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 938. For a recent application, see: (e) Guo, H.; Mortensen, M. S.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3149.

(23) The allylsilane reagent derived from (*R*,*R*)-pseudoephedrine gave, under identical conditions, yields around 60% and a 88:12 dr (*syn*/*anti*).

(24) Burés, J.; Martín, M.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **2009**, *74*, 2203.

(25) Very recent reviews on RCM: (a) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125. (b) Kotha, S.; Lahiri, K. *Synlett* **2007**, 2767. (c) Reference 13. (d) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. For a review of cyclizations leading to trisubstituted olefins, see ref 10 in: (e) Rodríguez-Escrich, C.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 5191. Also see: (f) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073.

We soon achieved conversion percentages of 85% plus 5−10% of the CM dimer of **9**, at C7; the latter could be cyclized by heating with additional amounts of catalyst. Mixtures of *Z* and *E* isomers were formed typically in ratios between 1:1.1 and 1:1.3.[26] The isomers were readily separable by flash chromatography on silica gel. They were characterized by ^{13}C NMR.

Even more surprising was the fact that the independent catalytic reductions of pure **10*Z***, pure **10*E***, and the 1:1.2 *Z*/*E* mixture gave products with identical NMR spectra, where **11a** was the major compound. Both *Z* and *E* isomers appear to have interacted with the metal surface and undergone H_2 addition mainly through the upper face (on the drawings of **10*Z*** and **10*E*** in Scheme 4 and Figure 2).[27]

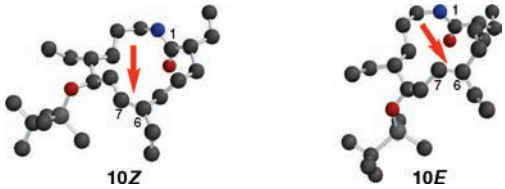


Figure 2. Lowest energy conformers of **10*Z*** and **10*E***, with the hydrogen atoms omitted for clarity. The upper faces of **10*Z*** (*Re*,*Si*) and of **10*E*** (*Re*,*Re*) are more accessible.

In other words, the experimental results agree with the models if hydrogen additions on the catalyst surface take place preferably as indicated by the arrows; both isomers would then give rise mainly to the macrolactams of configuration 6*S*.

The use of Pd/C in toluene (Table 1, entry 5) gave the highest stereoselectivity in favor of the desired product, **11a**, which was purified to ≥97:3 by a simple crystallization in 1:9 EtOAc/C_6H_{14}. To confirm the structure of **11a**, it was quantitatively deprotected with 1% HCl in EtOH to **11b** and a sample was then converted to **11c** (with Ac_2O/pyridine). The ^{13}C NMR spectrum of **11c** in $CDCl_3$ was identical with that reported for the acetylated natural product Sch 38518.[1b] Hydrogenation of pure **10*E*** in toluene also afforded the best selectivity (Table 1, entry 6).

Table 1. Hydrogenation (H_2, 1 atm) of **10*Z*** and **10*E***, at Room Temperature

entry	substrate	conditions	time (h)[a]	**11a**/epimer ratio
1	**10*Z***	PtO_2, 20% w/w, EtOH	4	62:38
2	**10*E***	PtO_2, 20% w/w, EtOH	4	60:40
3	**10*Z***	10% Pd/C, 10% w/w, EtOH	4	82:18
4	**10*E***	10% Pd/C, 10% w/w, EtOH	4	79:21
5	**10*Z***	10% Pd/C, 10% w/w, toluene	24	90:10
6	**10*E***	10% Pd/C, 10% w/w, toluene	24	88:12

[a] Time required for full conversion (complete hydrogenation) of the substrates, at 0.02 M concentrations.

In summary, the first synthesis of fluvirucinins B_{2-5} (**11b**), in 13 chemical steps from **1**, has been achieved. We have optimized most of these to attain yields ranging between 85% and 100%. Even the methylenation with the Petasis reagent (for which we disclose that DMF is a suitable scavenger) and the RCM, with the H-G II catalyst, gave excellent yields. Hydrogenation of the *Z*/*E* mixture of macrolactam **10** in toluene favored largely the desired product, with the "natural" configuration at C6 (**11a**). We plan to adapt and scale this synthesis to provide fluvirucins B_2−B_5, Sch 38518, and Sch 39185 (see **11**, R = diverse 3-aminoglycosides), for which no total synthesis has been described to date.

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Supporting Information Available: Experimental procedures and copies of the ^1H and ^{13}C NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) In this regard, it is worth noting that parallel experiments carried out with the methyl analogue of **9** (with a Me group at C6 instead of an Et) gave a 5:1 Z/*E* ratio. Therefore, in this 14-membered ring the preference for the *Z* isomer disappears when a Me group is replaced by an Et group.

(27) Full MacroModel-based conformational analyses and ab initio calculations of these systems will be reported independently.