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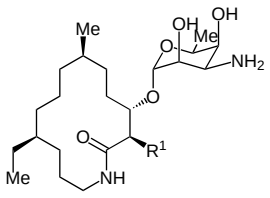
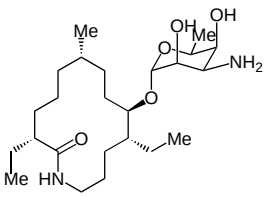
Asymmetric Total Synthesis of Fluvirucinine A_1**

Young-Ger Suh,* Soon-Ai Kim, Jae-Kyung Jung, Dong-Yun Shin, Kyung-Hoon Min, Bon-Am Koo, and Hwa-Soon Kim

Fluvirucins, a class of macrolactam antibiotics produced by actinomycete strains, have attracted considerable attention owing to their interesting structural features and promising biological properties.[1] Fluvirucins A_1 (**1a**) and A_2 (**1b**) are particularly attractive within the fluvirucin A series because of their low toxicity;[2] however, they show less potent antiinfluenza virus activity than fluvirucin B_1 (**2**), a representative of the fluvirucin B series. In addition, none of the members of the fluvirucin A series has been synthesized yet, while two recent syntheses have focused on fluvirucin B_1.[3] We herein report the first, asymmetric total synthesis of



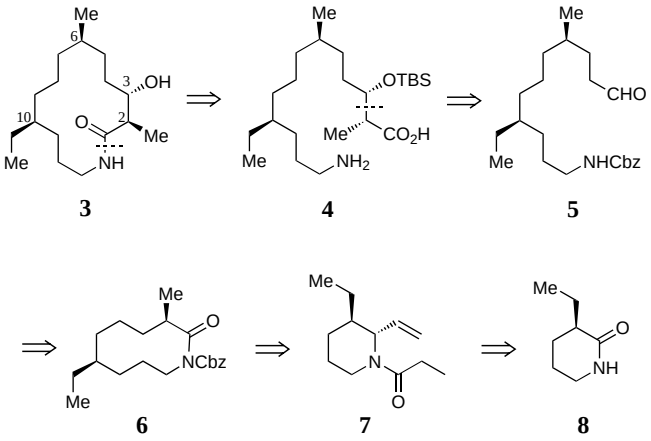
Fluvirucin A_1 $R^1 = CH_3$: **1a**
A_2 $R^1 = CH(OH)CH_3$: **1b**



Fluvirucin B_1 **2**

fluvirucinine A_1 (**3**; see Scheme 1), an aglycon of fluvirucin A_1, by our unique strategy, which is capable of readily introducing a variety of substituents at all chiral centers.

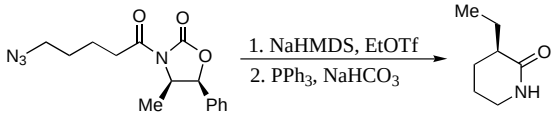
Our approach (Scheme 1) envisions efficient, remote stereocontrol of the C6 stereocenter by a key two-step sequence. The stereoselective vinyl addition to the carbonyl group of lactam **8**, possessing the initially established C10 chiral unit, and the subsequent amide enolate induced aza-Claisen rearrangement[4] of **7** provides the ultimate 1,5-chiral



Scheme 1. Strategy for the asymmetric total synthesis of fluvirucinine A_1 (**3**). Cbz = benzyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.

transfer for the C6 chiral unit. Moreover, the chiral centers C2 and C3 are efficiently introduced by the protocol of Evans et al.[5] For the cyclization in the final stage, we employed macrolactamization, which is one of the most attractive processes for the preparation of a 14-membered lactam skeleton, from the viewpoint of synthetic versatility and generality.[6]

Our synthesis was commenced by preparation of the optically active *trans*-2,3-disubstituted piperidine **7**, as a precursor for the aza-Claisen rearrangement, from 3-ethylvalerolactam (**8**), which is readily accessible from 3-azidopentanoyl-4-methyl-5-phenyl-oxazolidinone by a two-step sequence [Eq. (1)].[7] The initial stereogenic center corresponding to C10 of fluvirucinine A_1, which ultimately controls



(1)

8, 90%
$[\alpha]_D^{25} = -64.1$
(c = 2.6, CH_2Cl_2)

the configuration at C6, is conveniently introduced during the preparation of **8**. For the synthesis of the key lactam intermediate **6**, **8** was protected with benzyl bromide and then efficiently converted into the *trans*-disubstituted piperidine **9** (Scheme 2). After numerous attempts, we developed the direct diastereoselective vinyl addition to the lactam carbonyl group with the assistance of $LiAl(OEt)_3H$,[8] which provides the desired and separable *trans* isomer **9** along with

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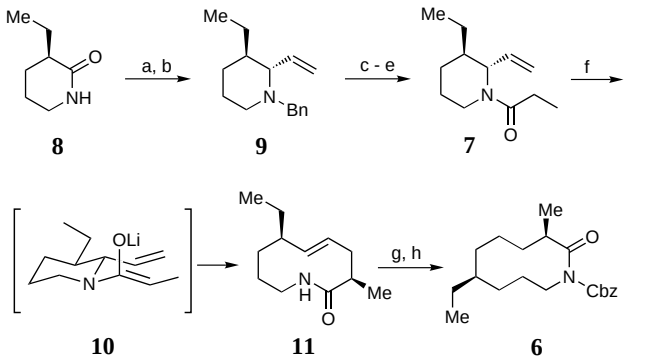
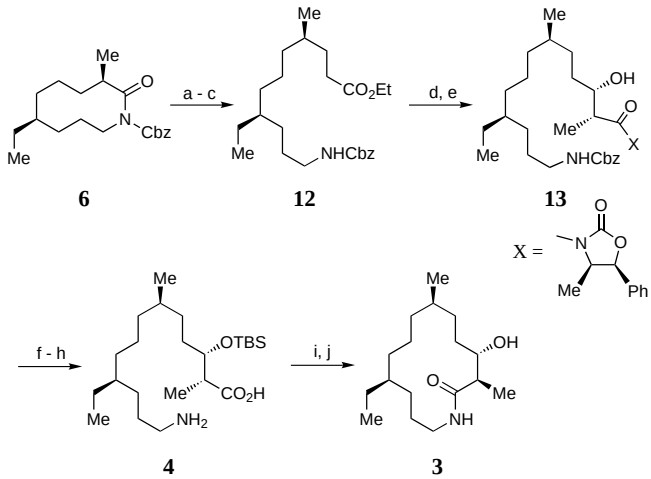


Scheme 2. Synthesis of the key lactam intermediate **6** from **8**. a) NaH, BnBr, THF, 0→25 °C, 79%; b) $LiAl(OEt)_3H$, Et_2O then $CH_2CHMgBr$, 0 °C, 70%; c) Cl_3CCH_2OCOCl, CH_3CN, reflux, 74%; d) Zn, AcOH; e) DMAP, $(CH_3CH_2CO)_2O$, Et_3N, CH_2Cl_2, 78% over two steps; f) LHMDS, toluene, reflux, 74%; g) H_2, Pd/C, MeOH; h) *n*BuLi, CbzCl, THF, 94% from **11**. Bn = benzyl, DMAP = 4-(dimethylamino)pyridine, LHMDS = lithium bis(trimethylsilyl)amide.

the minor *cis* isomer in a 95:5 ratio.[9] The aza-Claisen rearrangement precursor **7** was readily obtained by debenzylation of **9** followed by propionylation of the resulting amine. Facile aza-Claisen rearrangement of **7**, induced by an amide enolate, afforded the ring-expanded lactam **11** as the sole product, which possesses the second requisite stereogenic center corresponding to C6 of the target molecule. This excellent diastereoselectivity can be understood by the combination of the favorable chair–chair-like transition state **10** with an equatorial ethyl substituent and the formation of the preferred amide (*Z*)-enolate.[4] The lactam **6** was finally obtained by hydrogenation of the ring olefin moiety of **11** and exchange of the benzyl protecting group for the benzyloxycarbonyl group (Scheme 2).

The lactam **6** was converted into the ester **12** by a three-step sequence (Scheme 3): Reduction with DIBAL[10] of Cbz-protected **6**, followed by direct Wittig olefination of the resulting aldehyde and then reduction of the olefin[11] with $NaBH_4$, afforded **12**, which is extended by two carbon atoms compared to **6**. The C2 and C3 chiral units with the requisite configurations were effectively elaborated by DIBAL reduction of **12**, followed by condensation[5] of the resulting aldehyde with the boron enolate of propionyloxazolidinone. The ω-amino acid intermediate **4** was straightforwardly derived from **13** by protection of the hydroxy group as *tert*-butylsilyl, removal of the oxazolidinone auxiliary,[12] and then removal of the Cbz protecting group. For the completion of the synthesis, **4** was cyclized by treatment with pentafluorophenol[13] in the presence of dimethylaminopropylethyl carbodiimide to furnish fluvirucinine A_1 (**3**) after desilylation. The synthetic fluvirucinine A_1 was identical in all respects to natural fluvirucinine A_1.[2, 14]



Scheme 3. Synthesis of fluvirucinine A_1 (**3**) from **6**. a) DIBAL, CH_2Cl_2, −78 °C; b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 70% from **6**; c) $NaBH_4$, CuCl, THF/MeOH, 0 °C, 95%; d) DIBAL, CH_2Cl_2, −78 °C; e) (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyloxazolidinone, Bu_2BOTf, Et_3N, CH_2Cl_2, −78→0 °C, 79% from **12**; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 67%; g) LiOH, 30% H_2O_2, THF/H_2O, 72%; h) H_2, Pd/C, MeOH, 100%; i) dimethylaminopropylethyl carbodiimide, C_6F_5OH, CH_2Cl_2; j) $(n\text{Bu})_4N^+F^-$, THF, 62% from **4**. DIBAL = diisobutylaluminum hydride; TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

In summary, the first, asymmetric synthesis of fluvirucinine A_1 has been accomplished, starting from the readily accessible 3-ethylvalerolactam (**8**). This unique synthetic procedure, which employs diastereoselective vinyl addition to the amide carbonyl group and amide enolate induced aza-Claisen rearrangement as the key steps, offers a concise synthetic route to this important antiviral drug prospect.

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[8] To the best of our knowledge, our procedure is the first direct diastereoselective vinylation at a lactam carbonyl group. The reported cyanide addition to a lactam carbonyl group and the subsequent substitution by a vinyl group was not adopted, because partial epimerization during the cyanide addition was consistently observed: R. D. Gless, H. Rapoport, *J. Org. Chem.* **1979**, *44*, 1324; M. Rubiralta, E. Giralt, A. Diez, *Piperidine*, Elsevier, New York, **1991**, pp 235–244; for related α-alkylations of piperidine, see a) L. Gottlieb, A. I. Meyers, *Tetrahedron Lett.* **1990**, *31*, 4723; b) M. Yamaguchi, I. Hirao, *Tetrahedron Lett.* **1983**, *24*, 1719; Y. C. Hwang, M. Chu, F. W. Fowler, *J. Org. Chem.* **1985**, *50*, 3885; c) D. S. Brown, P. Charreau, T. Hansson,

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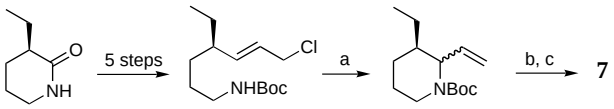

8 *trans* : *cis* = 10 : 1

Scheme 4. Alternative synthetic route to intermediate **7**. a) nBu$_4$NI, NaH, [Pd(Ph$_3$P)$_4$], THF; b) CF_3CO_2H, CH_2Cl_2; c) $(CH_3CH_2CO)_2O$, Et_3N, CH_2Cl_2.

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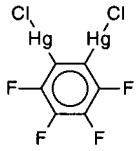
[14] The structure of the synthetic fluvirucinine A$_1$ was also confirmed by comparison of the spectral data of the methoxy(trifluoromethyl)phenylacetic acid (MTPA) esters of synthetic and natural fluvirucinine A$_1$.[1c] We thank Professor Takenori Kusumi of Tokushima University and Professor Hiroshi Kakisawa of the University of Tsukuba for kindly providing spectral data of the fluvirucins.

Micropore Decoration with Bidentate Lewis Acids: Spontaneous Assembly of 1,2-Bis(chloromercurio)tetrafluorobenzene**

Martin Tschinkl, Annette Schier, Jürgen Riede, and François P. Gabbaï*

Dedicated to Professor Hubert Schmidbaur on the occasion of his 65th birthday

Polydentate Lewis acids constitute a rapidly growing class of molecular compounds made up of simple bidentate derivatives[1–8] as well as more elaborate polydentate macrocycles.[9–11] The importance of these derivatives is coming to light in several aspects of chemistry including activation of organic reactions,[1] organometallic catalysis,[2] and molecular[3, 5–10] and anion recognition.[6–11] It occurred to us that the incorporation of polydentate Lewis acid functionalities in supramolecular nanoporous structures[12] could also be of interest for the design of new materials with unusual guest affinity[13] or catalytic activity.[14] We now report that 1,2-bis(chloromercurio)tetrafluorobenzene (**1**), a rigid bifunctional Lewis acid,[15] assembles into a microporous solid with internal Lewis acidic sites while retaining the integrity of its bidentate character. In addition, we report that guest exchange is readily observed within the host lattice. This work is part of our current interest in the chemistry of bifunctional Lewis acids as supramolecular synthons.[16]



1

Slow evaporation of a solution of **1** in DMSO affords crystals of composition **1**·(DMSO)$_3$ (**2**), as determined by elemental analysis.[17] The IR spectrum of this novel compound revealed an unresolved broad absorption in the S=O stretching frequency region, suggesting the presence of chemically nonequivalent DMSO molecules.[17] Solid-state MAS NMR spectroscopy confirmed this view, as two sets of methyl resonances could be detected in the ^{13}C NMR spectrum.[17]

As determined by single-crystal X-ray diffraction analysis,[18] the asymmetric unit of **2** consists of one molecule of **1**·(μ_2-DMSO)$_2$ and one noncoordinating solvate DMSO molecule (Figure 1). Each of the coordinated DMSO molecules is chelated by the bidentate Lewis acidic pincer. The resulting Hg–O bonds (av 2.70 Å) are shorter than the sum of

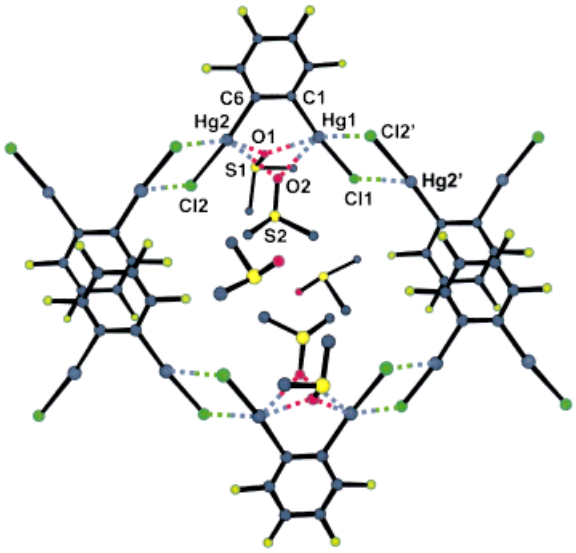


Figure 1. Ball-and-stick diagram showing the structure of **2**. The Hg···Cl and π–π contacts are evident from this view. Selected bond lengths [Å] and angles [°]: Hg1–C1 2.063(7), Hg1–Cl1 2.315(2), Hg1–O1 2.689(6), Hg1–O2 2.785(5), Hg2–C6 2.050(6), Hg2–Cl2 2.319(2), Hg2–O1 2.623(5), Hg2–O2 2.686(5), S1–O1 1.497(6), S2–O2 1.521(2); C1-Hg1-Cl1 173.6(2), C1-Hg1-O1 89.9(2), Cl1-Hg1-O1 94.67(13), C1-Hg1-O2 87.2(2), Cl1-Hg1-O2 98.28(11), O1-Hg1-O2 73.6(2), C6-Hg2-Cl2 174.9(2), C6-Hg2-O1 91.6(2), Cl2-Hg2-O1 91.10(13), C6-Hg2-O2 89.3(2), Cl2-Hg2-O2 95.53(11).

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