Synthesis of (±)-Fomannosin

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Fomannosin (**1**) has been isolated from the wood-rotting fungus, *Fomes annosus* (Fr) Karst. It was shown to be toxic toward *Pinus taeda* seedlings, *Chlorella pyrenoidosa*, and some bacteria.[1] It was obtained as a noncrystalline semisolid and initially partially characterized by IR, UV, and ^{1}H NMR spectroscopic studies. X-ray diffraction studies on crystalline dihydro derivatives revealed structure **2** and led to the postulation of structure **1** for fomannosin,[2] with the 7*S*,9*R* absolute configuration.[3] It is the only natural product with the methylene cyclobutene functionality and is unstable, especially toward base, due to the reactive doubly unsaturated lactone unit.[1,2] The first synthesis of the fomannosan skeleton was reported in 1974,[4] and 5,6-dihydrofomannosin acetate was synthesized in 1977;[5] however, no synthesis of fomannosin (**1**) has appeared. The biosynthesis connection (Figure 1) between fomannosin and illudol (**3**) has been defined[6] and provides the key element of our synthesis strategy. Disconnection at C-3/C-13 in **3** and lactonization at C-3/C-8 converts the illudol skeleton to the fomannosin arrangement; the rigid fused tricyclic system in **3** is useful in assembling the proper stereochemical relationships at C-7 and C-9 (identical in **1** and **3**). We prepared[7] illudol (**3**) from intermediate **4** and now report successful conversion of **4** to fomannosin by using this biosynthesis strategy.

Diels–Alder reaction of **5** and **6** produced a single product, **4**, in 72% yield (Scheme I). Reduction of the ester with excess lithium aluminum hydride at 0 °C was followed by hydrolysis of the enol silyl ether unit with a suspension of 3-Å molecular sieves in methanol at 25 °C for 4.5 h. The ketone **7** was obtained exclusively with the trans ring fusion, apparently the kinetic product from internal delivery of the proton during hydrolysis.[8] Baeyer–Villiger oxidation using *m*-chloroperbenzoic acid in a suspension of sodium bicarbonate in dichloromethane produced a single isomer, the acid-sensitive seven-membered lactone **8**. Hydrolysis of the ketal (acetone/concentrated HCl, 0 °C for 0.5 h) followed by protection of the hydroxyl group afforded ketolactone **9**. Since the cyclobutanone unit is prone to fragmentation as soon as the C-2/C-4 double bond is in place,[9] the keto group

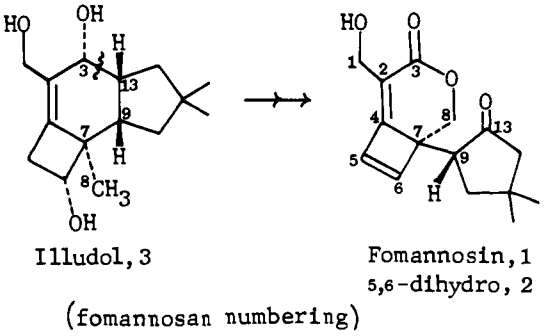
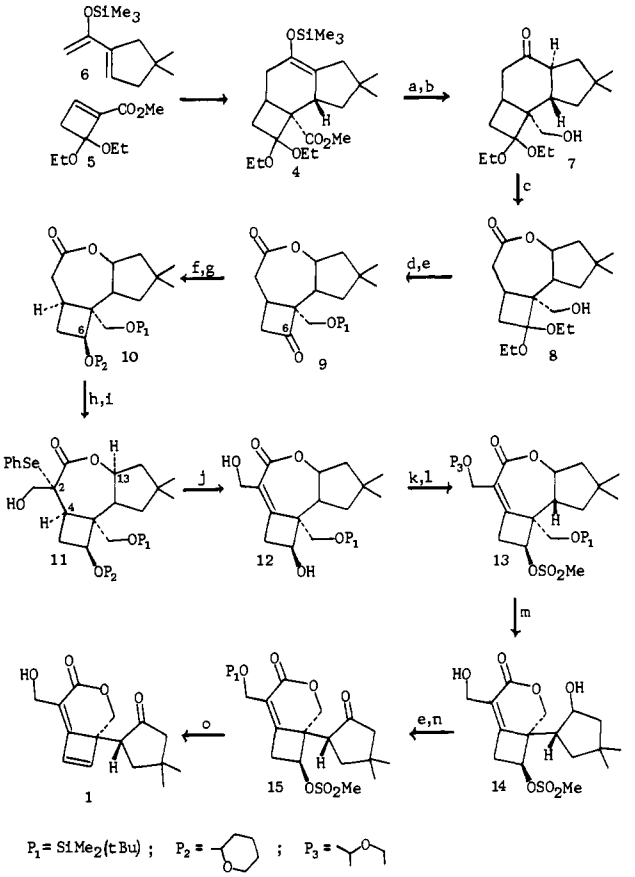


Figure 1. Biosynthesis connection.

Scheme I. Synthesis of Fomannosin[a]



[a] (a) $LiAlH_4$, 96%; (b) 3-Å sieves, MeOH, 98%; (c) *m*-$ClC_6H_4CO_3H$, 96%; (d) HCl, Me_2CO, 91%; (e) $ClSiMe_2$-*t*-Bu, imidazole, 88–92%; (f) $NaBH_4$, 94%; (g) dihydropyran, *p*-TsOH, 98%; (h) $LiNR_2$, then CH_2O, 98%; (i) $LiNR_2$, then PhSeCl, 48%; (j) *p*-TsOH-py, MeOH, then H_2O_2, 71%; (k) CH_2=$CHOCH_2CH_3$, *p*-TsOH, 87%; (l) $MeSO_2Cl$, Et_3N, 93%; (m) 48% HF, CH_3CN, 72%; (n) CrO_3·Py_2, 96%; (o) $(n\text{-}Bu)_4NF$, THF, 22 °C, 81%.

was immediately reduced to the alcohol (excess sodium borohydride in methanol at 0 °C) and the tetrahydropyranyl protecting group was added (**10**). The configuration of the hydroxyl group at C-6 in **10** has not been established; however, a single isomer is obtained, and the product from optimum hydride approach is expected to be **10**.

Addition of the lactone enolate anion of **10** (from lithium diisopropylamide in THF added to **10** in THF at −78 °C) to a vigorously stirred solution of excess monomeric formaldehyde in ether at −78 °C introduced the hydroxymethyl unit at C-2. Without purification, this product was treated with a solution of lithium diisopropylamide in THF (2.2 mol equiv). The resulting dianion was added to phenylselenyl chloride (2.2 mol equiv in THF) at −78 °C. Column chromatography produced **11**, apparently a single isomer (^{13}C NMR) in 48% yield, and recovered

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(2) J. A. Kepler, M. E. Wall, J. E. Mason, C. Basset, A. T. McPharil, and G. A. Seni, *J. Am. Chem. Soc.*, **89**, 1260 (1967).

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(4) K. Miyano, Y. Ohfune, S. Azuma, and T. Matsumoto, *Tetrahedron Lett.*, 1545 (1974).

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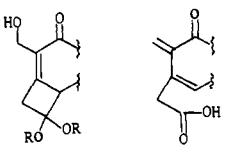
(6) (a) D. S. Cane and R. S. Nachbar, *J. Am. Chem. Soc.*, **100**, 3208 (1978); (b) the biosynthesis relationship between illudol and formannosin was proposed to us by Professor D. Arigoni (ETH-Zurich) during seminar discussions at Cornell in 1974 and led to the strategy developed here.

(7) M. F. Semmelhack, Shuji Tomoda, and K. M. Hurst, *J. Am. Chem. Soc.*, **102**, 7567 (1980).

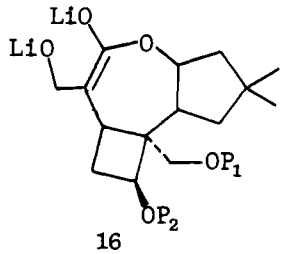
(8) In the illudol synthesis,[7] it was established that the cis ring fusion for **8** (and related derivatives) is slightly more stable. The configuration at C-13 is not important except for the convenience of working with a single isomer.

(9) All attempts to hydrolyze the ketal unit in structures represented by i resulted in cleavage of the four-membered ring tog give products with structures of type ii.



i ii

starting material (the hydroxymethyl compound **17**; 40%). The success of the next stage, selenoxide elimination, depends upon the correct order of introduction of the hydroxymethyl group and the phenylselenyl unit, in order to produce the proper configuration at C-2 (as in **11**). From our experience with a related sequence in the synthesis of illudol,[7] it was expected that reaction of the enolate anion at C-2 with electrophiles would occur syn to the hydrogen at C-4 in **10**. Structure **11** is also based on the strong downfield shift (more than 1 ppm) shown by the ^{1}H NMR signal for the proton at C-13, attributed to anisotropic shielding by the phenylselenyl unit. Of course, the successful selenoxide elimination under mild conditions (86% yield, CH_2Cl_2, 20 °C, 20 min) to form **12** is consistent with the syn arrangement of the phenyl–selenyl unit and the hydrogen at C-13.[10] The step of lowest efficiency is the reaction of enolate **16** with phenylselenyl chloride, which proceeds to give **11** in 48% yield under the best conditions, but



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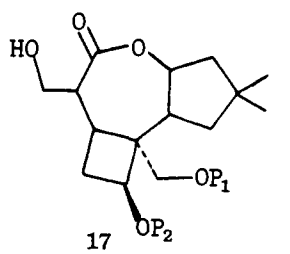

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a large amount of the reactant (**17**) is recovered (ca. 40%) and can be recycled.

Selective reaction of the primary hydroxyl group in **12** with ethyl vinyl ether at −22 °C by using pyridinium tosylate as catalyst in CH_2Cl_2 was followed by formation of the methanesulfonate ester at C-6, to produce **13**. With aqueous hydrofluoric acid at 20 °C in acetonitrile, cleavage of the silyl ether and spontaneous trans lactonization was observed, to afford **14**. The primary hydroxyl was protected again as the *tert*-butyldimethylsilyl ether in order to allow oxidation (Collins procedure)[11] of the secondary hydroxyl to give **15**. Then tetra-*n*-butylammonium fluoride (1.0 mol equiv, THF, 0 °C for 10 min) brought about cleavage of the silyl ether and induced elimination of methanesulfonic acid which resulted in formation of (±)-fomannosin (**1**). Rapid chromatography on silica gel provided a pure sample which is a rather unstable semisolid. The sample appears to be homogeneous by TLC and ^{13}C NMR spectral data analysis, and to have the correct relative configuration. There is an opportunity for equilibration of configuration via enolization toward C-9, but no evidence for 9-*epi*-fomannosin has been obtained.[12] The ^{1}H NMR spectrum of the synthesized sample was identical with the published spectrum[2] and a spectrum of a sample of natural material. In addition, ^{13}C NMR, TLC, and IR data comparison of synthetic and natural material showed no differences. The overall yield from **4** is 9.2%.

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(10) H. J. Reich, F. Chou, and S. K. Shah, *J. Am. Chem. Soc.*, **101**, 6638 (1979), and reference therein.

(11) Professor David Cane (Brown University) has informed us that fomannosin slowly epimerizes during prolonged contact with silica gel, but characterization of 9-*epi*-fomannosin had not been reported.

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(13) Fellow of the John Simon Guggenheim Foundation, 1978–1979.

(14) On leave from the Department of Chemistry, University of Tokyo, Komaba, Meguro, Tokyo 153, Japan.

Stereochemical Features of the 1,3-Chloropalladation of Bicyclic Methylenecyclopropanes

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The role of transition metals in promoting electrocyclic organic reactions has received renewed scrutiny in the last year. Theoretical analyses, at the extended Hückel level, of the opening of the 2,3-σ bond of a methylenecyclopropane coordinated to either a $[Fe(CO)_3]$[1] or a $[Pt(PPh_3)_2]$[2] fragment, to give a trimethylenemethane ligand, have been reported. These calculations suggest that conrotatory opening should be the most favored mode of ring cleavage; of the two possible disrotatory modes, both of which are formally forbidden by orbital–symmetry considerations, that which involves the breaking bond bending away from the metal (disrotatory away) should be more favored.[1,2]. Experimental data are sparse, but the ring openings of substituted methylenecyclopropanes coordinated to $[Fe(CO)_3]$[3] and $[Mo(CO)_3(\eta\text{-}C_5H_5)]^+$[4] fragments have been shown to occur in the disrotatory away mode, to the exclusion of conrotatory opening. In both cases the final products are η^4-trimethylenemethane complexes. We have described the regiochemistry of a unique 1,3 chloropalladation of alkyl-[5] and aryl methylenecyclopropanes[6] which involves cleavage of the same bond in the three-membered ring to yield η^3-allyl compounds. This communication describes the intimate stereochemistry of this reaction in which the disrotatory away opening is preferred to the exclusion of the conrotatory mode.

Previous attempts to elucidate the stereochemical features of the 1,3 chloropalladation of *cis*- and *trans*-2,3-dimethylmethylenecyclopropane failed because of rapid $\eta^3 \rightarrow \eta^1 \rightarrow \eta^3$ interconversion of the allyl ligand subsequent to the chloropalladation step; compound **1** was the only product from either of the isomeric methylenecyclopropanes.[5] In contrast *cis*-9-methylenebicyclo[6.1.0]nonane **2**[7a] reacted almost instantaneously with $PdCl_2(PhCN)_2$ ($CDCl_3$ or C_6D_6 solution; 20 °C) to afford a quantitative yield of a single isomer **3**.[8] The acetylacetonato derivative of **3**[9] was subjected to a single-crystal X-ray crystallographic analysis and was shown to have the structure shown in Figure 1.[10] The corresponding chloropalladation of *trans*-9-

† Alfred P. Sloan Research Fellow, 1980–1982.

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(3) Pinhas, A. R.; Carpenter, B. K. *J. Chem. Soc. Chem. Commun.* **1980**, 17–19.

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(7) (a) Arora, S.; Binger, P. *Synthesis* **1974**, 801–803. (b) Prepared from *trans*-cyclooctene by the method of ref 7a.

(8) Satisfactory microanalytical data were obtained for all compounds described. The ^{1}H NMR spectra of the allylic complexes are sufficient to characterize them structurally. Pertinent ^{1}H NMR data (δ, downfield from Me_4Si, $CDCl_3$, 270 MHz, 25 °C) have been incorporated into structural drawings for clarity. Protons on the unsubstituted allylic terminus appear as singlets while the protons on the substituted allylic carbon and the CHCl carbon appear as doublets of doublets (J = 7, 2) due to coupling with the adjacent CH_2 groups. Compound **3**, **5**, and **6** are all yellow, air-stable, crystalline solids.

(9) Prepared from **3** in 90% yield by treatment with Tl(acac). Corresponding acac derivatives of all compounds reported here have been prepared. The ^{1}H NMR spectra of the organic ligands are identical with those of their chloride precursors except that the three allylic proton resonances are shifted upfield by ~0.2 ppm; the C*H*Cl resonance remains unchanged in each case.

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