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A SYNTHETIC APPROACH TO FOMANNOSIN

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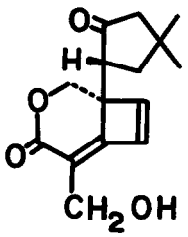
The unique structural features of fomannosin 1, a biologically active metabolite from Fomes annosus, have been elucidated from the X-ray analysis of a heavy atom derivative.[1] We describe here the first synthesis of the fomannosane skeleton.[2]

trans-1,2-Dibromo-4,4-dimethylcyclopentane 2[3] was converted to a dinitrile 3[4,5] (mp 81-82°) by treatment with sodium cyanide in dimethylsulfoxide (80°, 6hr). Hydrolysis of 3 with aqueous sodium hydroxide (reflux, 18hr) led to a dicarboxylic acid 4[4,5] (mp 175-176°), which was alkylated to bismethylketone 5[4,5] (bp 90°/5mmHg) with methyllithium in abs ether. The intramolecular aldol condensation of 5 with potassium tert-butoxide in tert-butanol (0°, 1hr) yielded a cis-bicyclo[3,3,0]octane derivative 6.[4,5] Oxidation of the vinylic methyl of 6 with selenium dioxide in bromobenzene gave an aldehyde 7[4] (140°, 1hr). Selective reduction of the aldehyde group of 7 with sodium borohydride afforded a hydroxyenone 8[4,5] (mp 76-77°), which on treatment with acetic anhydride in pyridine gave an acetate 9.[4,5]

Photochemical cycloaddition of the acetate 9 and ethylene in methylene chloride (5hr, 0°, 75W high pressure mercury lamp) gave a cis-anti-cis[6] cycloadduct 10[4] $C_{15}H_{22}O_3$[5] (62%) and a cis-syn-cis[6] isomer 11[4] $C_{15}H_{22}O_3$[5] (24%). The cis-anti-cis cycloadduct 10 was converted to a lactone 12[4] $C_{15}H_{22}O_4$[5] (50%) and a regioisomer 13[4] $C_{15}H_{22}O_4$[5] (18%) by peracetic acid (25°, 80hr). Reduction of 12 with sodium dihydro-bis(2-methoxyethoxy)aluminate in benzene (25°, 18hr) gave an essentially quantitative yield of a triol 14[4] $C_{13}H_{24}O_3$[5] (mp 91-92°) which on treatment with acetone and a trace of p-toluenesulfonic acid (reflux,



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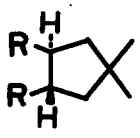
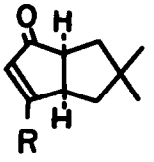
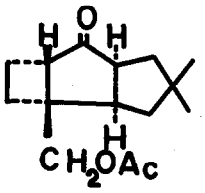


2 R=Br
3 R=CN
4 R=CO_2H
5 R=CO_2CH_3



6 R=CH_3
7 R=CHO
8 R=CH_2OH
9 R=CH_2OAc



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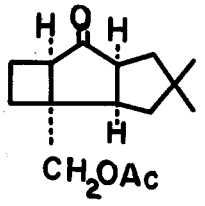

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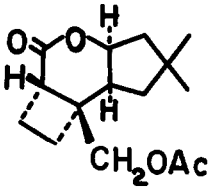

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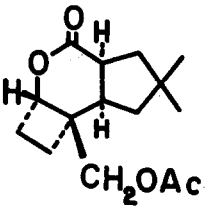

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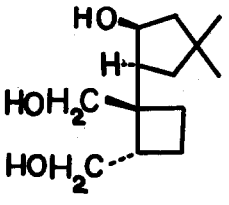

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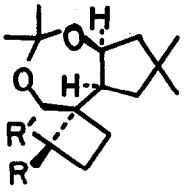
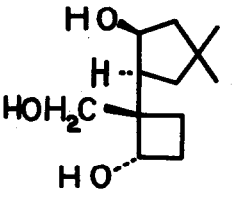


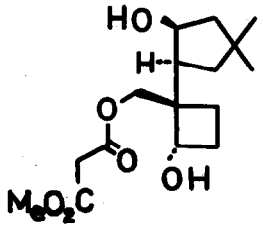
15 R=H, R'=CH_2OH

16 R=H, R'=CHO
17 R, R'= =C-N O
18 R, R'= =O



19 R=H, R'=OH

20



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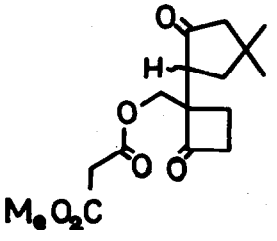

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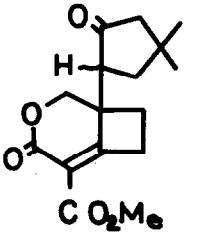


23

16hr) resulted in a nearly quantitative yield of an acetonide 15[4,7] $C_{16}H_{28}O_3$[5] [mp 58-59°; nmr($CDCl_3$)δ 3.05, 4.90 (each 1H, AB, J=11Hz)]. Unprotected hydroxy group of 15 was oxidized with silver carbonate in xylene[8] (reflux, 16hr) to give an aldehyde 16[4,7] $C_{16}H_{26}O_3$[5] [92%; mp 102-103°; nmr($CDCl_3$)δ 3.19, 4.95 (each 1H, AB, J=11Hz) 9.87 (1H, d, J=2Hz, -CHO)]. Treatment of the aldehyde 16 with morpholine and p-toluenesulfonic acid in toluene (reflux, 18hr, generated water was removed with molecular sieves 4A) led to an enamine 17 and subsequent photooxidative cleavage with singlet oxygen (25°, 18hr, rose bengal as sensitizer, 15W fluorescent lamp)[9] afforded a ketone 18[4] $C_{15}H_{24}O_3$[5] [62%; mp 88-89°; ir(nujol) 1780cm^{-1}]. Reduction of 18 with sodium borohydride in ethanol (0°, 1.5hr) resulted in the formation of 19[4,7] $C_{15}H_{26}O_3$[5] [83%; mp 108-109°; nmr($CDCl_3$)δ 3.00, 3.89 (each 1H, AB, J=12Hz)]. The acetonide group of 19 was removed with 6N hydrochloric acid in aqueous ethanol (0°, 1hr) to yield a triol 20[4] $C_{12}H_{22}O_3$[5] (96%; mp 107-108°). Selective esterification of 20 with methyl malonyl chloride (1.1 equiv) and pyridine (1.1 equiv) in abs ether (-70°, 1.5hr)[10] led to a monoester 21[4] $C_{16}H_{26}O_6$[5] (72%) which upon oxidation with Jones reagent (0°, 1hr) gave a diketone 22[4,11] $C_{16}H_{22}O_6$[5] [68%; m/e 310(M^+); ir(neat) 1785, 1750, 1738cm^{-1}; nmr($CDCl_3$)δ 1.05, 1.17 (each 3H, s) 3.23 (2H, s, $-CO_2CH_2CO_2Me$) 3.65 (3H, s) 4.06 (2H, s)]. The intramolecular aldol condensation of 22 proceeded in the refluxing pyridine-benzene (2:1) solution (18hr; generated water was removed with molecular sieves 4A) and the final product 23,[4,11] which has the fomannosane skeleton, was obtained in 36% yield [$C_{16}H_{20}O_5$[5]; m/e 292(M^+); ir(neat) 1742, 1720, 1690cm^{-1}; nmr($CDCl_3$)δ 1.07, 1.13 (each 3H, s) 3.71 (3H, s) 4.13, 4.34 (each 1H, AB, J=11Hz)]. The compound 23 is suitably functionalized and is hoped to be a promising intermediate for the total synthesis of fomannosin.

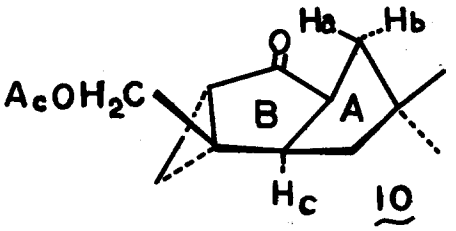
REFERENCES AND FOOTNOTES

1. J. A. Kepler, M. E. Wall, J. E. Mason, C. Basset, A. T. McPhail, and G. A. Sim, J. Amer. Chem. Soc., 89, 1260 (1967).

2. For the synthesis of a biogenetically related compound illudin M, see T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S.

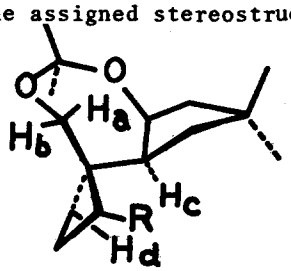
Matsumoto, and S. Nishida, J. Amer. Chem. Soc., 90, 3280 (1968).

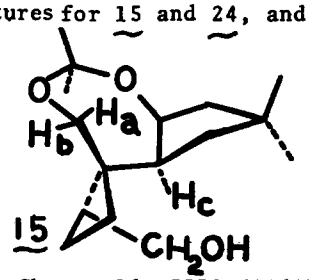
3. H. Kwart and J. A. Ford, Jr., J. Org. Chem., 24, 2060 (1959).
4. Reasonable ir, nmr and mass spectra have been obtained for this compound.
5. Satisfactory elemental analyses were obtained.
6. The nmr spectrum of 10 showed that the proton Ha (δ=0.86, t, J=12Hz) was shifted to unusually high field by the diamagnetic anisotropy of the carbonyl group and double resonance experiments revealed a long-range coupling (Jbc=1.5Hz) between the protons Hb and Hc. However the nmr spectrum of the syn-isomer 11 did not show such high field peaks and a long-range coupling, indicating conformational change of A-B rings due to steric crowdedness in 11.



7. In the nmr spectrum of 15 a long-range coupling (Jbc=1.5Hz) was observed. Similar couplings were observed in the spectra of 16 and 19. By contrast the nmr spectra of the isomers (24,[4,5] 25,[4,5] and 26[4,5]) derived from the syn-cycloadduct 11 showed a pair of long-range couplings (Jad and Jbd=1.5Hz). All these data support the assigned stereostructures for 15 and 24, and hence for 10 and 11.

24 R=CH_2OH
25 R=~CHO
26 R=~OH





8. W. King, W. G. Penprase, and M. C. Kloetzel, J. Org. Chem., 26, 3558 (1961)
9. C. S. Foote and J. Wei-Ping Lin, Tetrahedron Lett., 3267 (1968).
10. D. S. Breslow, E. Baumgarten, and C. R. Hauser, J. Amer. Chem. Soc., 66, 1286 (1944).
11. Although the product was homogeneous by TLC and by elemental analysis, accessory peaks in the nmr spectrum showed the product to contain a small amount (less than 7%) of an epimer.