Synthesis of (±)-Dihydrofomannosin Acetate[1)]

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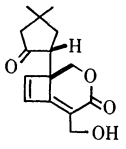
The synthesis of (±)-dihydrofomannosin acetate [5-acetoxymethyl-1-(4,4-dimethyl-2-oxocyclopentyl)-3-oxabicyclo[4.2.0]oct-5-en-4-one] is described. Photocycloaddition of 4-(2-acetoxy-4,4-dimethylcyclopentyl)-2(5*H*)-furanone to ethylene gave 5-(2-acetoxy-4,4-dimethylcyclopentyl)-3-oxabicyclo[3.2.0]heptan-2-one, which was converted into ethyl [2-acetoxymethyl-2-(2-acetoxy-4,4-dimethylcyclopentyl)cyclobutyl]glyoxylate by the reaction with 2-methylthio-1,3-dithiane, followed by acetylation and ethanolysis. Introduction of an additional one carbon unit to the glyoxylate was accomplished by the Wittig reaction, and the subsequent hydrolysis and lactonization afforded 1-(2-hydroxy-4,4-dimethylcyclopentyl)-5-methylene-3-oxabicyclo[4.2.0]octan-4-one, which was transformed into 5-acetoxymethyl-5-hydroxy-1-[4,4-dimethyl-2-(tetrahydropyranyloxy)cyclopentyl]-3-oxabicyclo[4.2.0]-octan-4-one. Mesylation followed by elimination and oxidation led to (±)-dihydrofomannosin acetate.

Fomannosin (**1**) is a biologically active sesquiterpene first isolated from the still culture of the wood-rotting fungus Basidiomycete *Fomes annosus* (Fr.) Karst[2)] and subsequently from *Fomitopsis insularis*,[3)] and has been found toxic toward *Pinus tadea* seedlings, *Chlorella pyrenoidosa*, and some bacteria.[4)] The unusual B-*seco*-protoilludane structure of fomannosin was determined by an X-ray study of the *p*-bromobenzoylurethane derivative of dihydrofomannosin (**2**).[2)] Recently, X-ray crystallography of the (−)-camphenate of **2** led to the establishment of its absolute configuration.[5)] The synthesis of fomannosin and its derivative seems to be of interest from structural and biological points of view. However, fomannosin is very unstable,[2)] and our initial efforts in synthetic studies have been directed towards the synthesis of dihydrofomannosin (**2**) or its acetate **3**. In view of the recent work on



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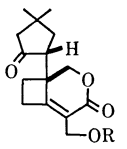
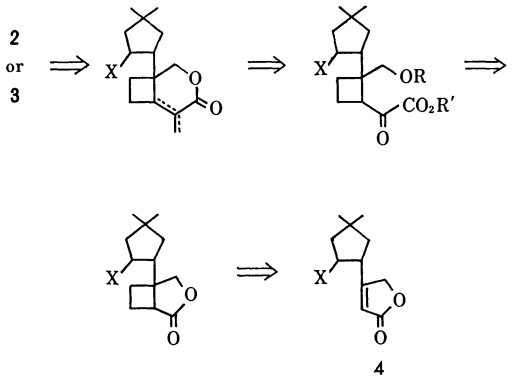


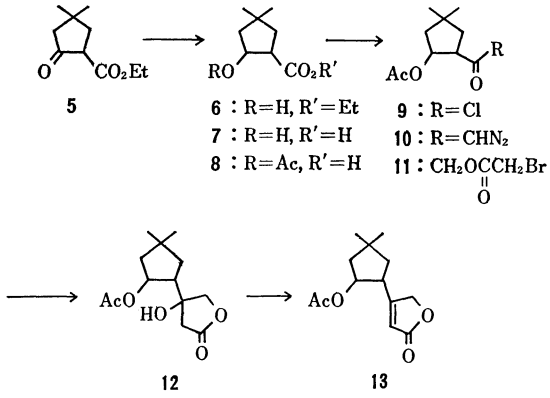
2 : R=H
3 : R=Ac

the photocycloaddition reaction of $\Delta^{\alpha,\beta}$-butenolides [2(5*H*)-furanones] with ethylene,[6)] we adopted Scheme 1 involving the photo-process on a suitably substituted butenolide **4** and the ring enlargement of a γ-lactonic photo-adduct to a δ-lactone system for construction of the fomannosin skeleton.[7)]

Our first step was to prepare the β-substituted $\Delta^{\alpha,\beta}$-butenolide **13** as a key intermediate. Three routes (Schemes 2—4) were examined for this purpose. Firstly, the intramolecular Reformatsky reaction of (bromoacetoxy)methyl ketones,[8)] a method for the synthesis of β-substituted butenolides, was applied. 2-Ethoxycarbonyl-4,4-dimethylcyclopentanone (**5**) was converted into the acetoxy carboxylic acid **8** by the usual procedure. The carboxyl group of **8** could be then transformed into the (bromoacetoxy)methyl ketone function through the standard steps[8)] to give the desired ketone **11** (Scheme 2). The Reformatsky reaction of **11** in the presence of ethyl bromoacetate[8)] followed by dehydration of the resulting hydroxy lactone **12** with alumina afforded the key butenolide **13** in 60% yield. In practice, however, this route appeared to be disadvantageous because of the low yield (<9.6% overall from **5**), requiring multistage operations and separation.

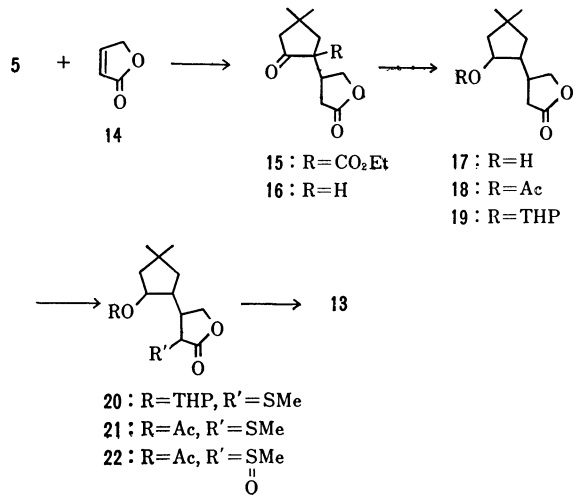


Scheme 1.



Scheme 2.

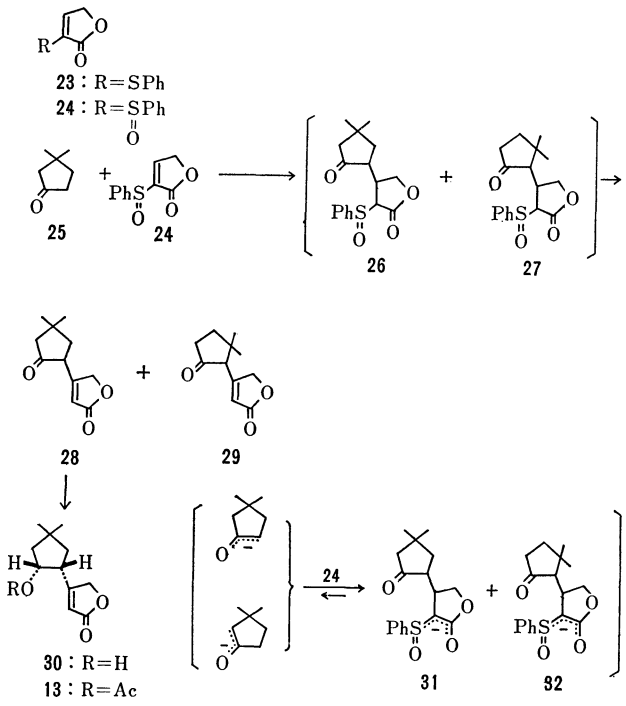
We adopted, as the second Scheme, introduction of the double bond at the α,β-position of a suitable γ-butyrolactone derivative such as **18** or **19**. The Michael reaction of **5** with γ-crotonolactone (**14**) afforded the adduct **15** in 66% yield, use of excess **14** being essential for a good yield of **15**. The adduct **15** was decarboxylated to give the keto lactone **16** in 74% yield, which was reduced to the hydroxy lactone **17**. Attempt to introduce unsaturation to the lactone moiety of the acetate **18** by the usual bromination-dehydrobromination was unsuccessful; bromination gave an intractable mixture. We examined the sulfenylation-dehydrosulfenylation procedure recently developed by Trost *et al.*[9)] Reaction of the enolate of the tetrahydropyranyl ether derivative **19** with



Scheme 3.

dimethyl disulfide afforded the α-methylthio lactone **20** in 60% yield. From the fact that a tetrahydropyranyloxy group is somewhat sensitive to UV irradiation (partial decomposition) at this stage, the protecting group was exchanged by an acetyl group. Oxidation of the acetoxy derivative **21** and subsequent pyrolysis of the resulting sulfoxide **22** gave **13** in 60% yield from **20** (Scheme 3). Thus, the desired compound **13** was available in moderate yield. However, the route also seems to be practically inconvenient for the preparation of **13** on a larger scale.

During the course of this study, it was found that α-phenylthio- (**23**) or α-phenylsulfinyl-$\Delta^{\alpha,\beta}$-butenolide (**24**) is an efficient carbanion acceptor in the Michael reactions and the use of **23** or **24** provides a high-yield and convenient method for the synthesis of butenolides having various substituents at the β-position.[10] The method should be applicable to the present case. Reaction of the enolate of **5** with either of **23** or **24** resulted in the formation of only self-polymerization product of **23** or **24**, indicating that the enolate of **5** acts as a base rather than the Michael addend.[10] This suggests that a much stronger nucleophilic enolate should be employed as an addend to achieve the Michael reaction. 3,3-Dimethylcyclopentanone (**25**) was chosen for this purpose. The Michael reaction of **24** with the lithium enolate of **25** proceeded smoothly at −68 °C, as expected, to produce the adduct **26** and **27**, which was dehydrosulfenylated, without separation, in refluxing toluene giving two separable keto butenolides **28** and **29** in 54 and 18% yields, respectively (Scheme 4). In the NMR spectra, the methine proton α to the keto group was observed as a broad triplet (J=10.5 Hz) at δ 3.45 in the major product **28**, but as a broad singlet at δ 3.40 in the minor one **29**, indicating that **28** is the desired compound and **29** the regioisomer. On the other hand, the reaction of the α-phenylthio lactone **23** with **25** gave a singel adduct (38% yield), which was confirmed to be the phenylthio analogue of **26** by transformation into **13** *via* **28**. The precursor **27** of the minor isomer **29** should be sterically less favorable than the major precursor **26**. The actual formation of **27** can be attributed to the formation of

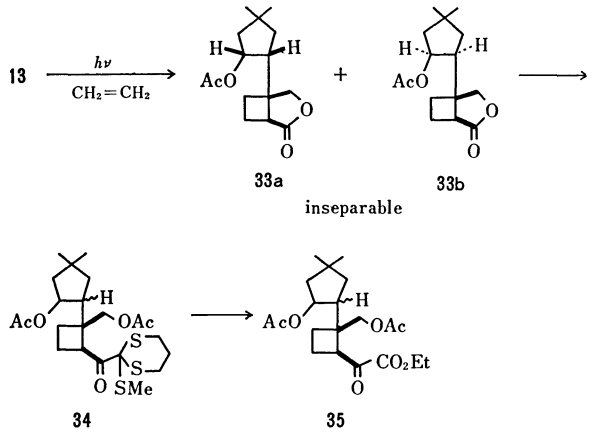


Scheme 4.

the relatively tight bonding between lithium cation and the effectively stabilized carbanion intermediate **32** together with **31**[10] from the equilibrated enolate of **25**. Such a tight bonding would prevent the reversible process (**32**→**24**+**25**) under the conditions employed, resulting in slight loss of the regioselectivity in the reaction. Reduction of **28** with sodium borohydride afforded the single crystalline hydroxy butenolide **30**, mp 36—37 °C, which was acetylated to give **13** in 74% yield. The spectral properties were compatible with the assigned structure **13**. Assignment of the *cis* configuration of two vicinal substituents on the cyclopentane ring of **13** follows from the steric course of the reaction and the NMR coupling pattern of the proton at the carbon atom bearing the acetoxyl group: doublet (J=6.0 Hz, *trans* coupling) of triplet (J=7.5 Hz, *cis* coupling) at δ 5.12.

According to the procedure of Kosugi *et al.*,[6] a solution of **13** in acetone with moderately rapid introduction of ethylene was irradiated at −50— −60 °C with a 500 W high-pressure mercury lamp without filter giving an 85% yield of the 1:1 photoadduct **33** (Scheme 5). From the NMR spectrum, the photoadduct was found to be a mixture of stereoisomers **33a** and **33b**. The ratio of **33a** and **33b** could not be determined at this stage, since the product was homogeneous on thin layer chromatography, and the NMR spectrum revealed no distinctly separated signals. Actual separation of the stereoisomers was carried out at a later stage.

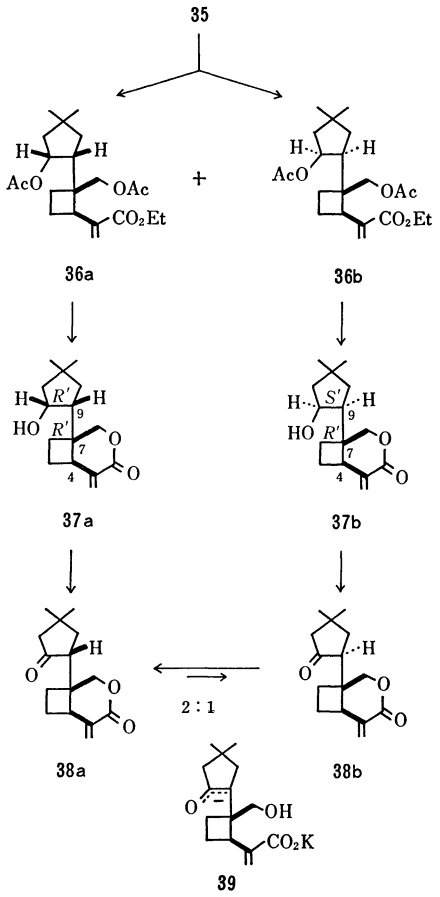
The next step to elaborate the fomannosin skeleton was one carbon elongation of the lactone-carbonyl position. Among a number of agents, 2-methylthio-1,3-dithiane[11] was chosen as a carboxyl equivalent. The photoadduct **33** was treated with lithiated 2-methylthio-1,3-dithiane, followed by acetylation giving the ring-opened product **34** in 74% yield. Mercury(II) ion-



Scheme 5.

catalyzed ethanolysis of **34** gave the glyoxylate **35** in high yield, which apparently consists of about equal amounts of two stereoisomers as detected by the NMR spectrum. The prominent peaks were observed as the pairs with about equal intensities. Although an α-methylene-δ-lactone structural unit has been found to a lesser extent than an α-methylene-γ-lactone unit in naturally occurring compounds, it is of growing importance from the viewpoint of its biological activities, *e.g.*, vernolepin. The glyoxylate **35** can be easily converted into an α-methylene-δ-lactone derivative **37**. The sequential reactions developed in the present study [(i) nucleophilic attack of the anion of 2-methylthio-1,3-dithiane, (ii) acetylation and ethanolysis, (iii) a Wittig reaction, and (iv) hydrolysis and lactonization] would provide a convenient method for the synthesis of α-methylene-δ-lactones from readily available γ-lactones.[12]

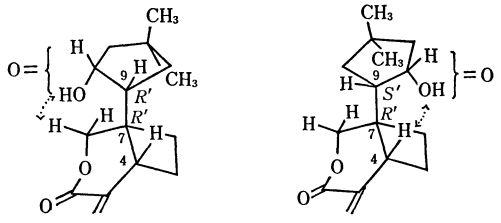
The next step was to extend the keto group of **35** by an additional one-carbon unit. A methylene function would be most suitable for leading to the final functionality, an allylic hydroxy- or acetoxymethyl grouping, of the synthetic targets, and would be introduced easily by the Wittig reaction.[13] However, it was found that the reaction of **35** with methylenetriphenylphosphorane in the standard way (generated by dimsylsodium in dimethyl sulfoxide or butyllithium in ether) is unsatisfactory because of very low yields of the product. Observation of the rapid consumption of the starting material **35** and of the low recovery after work-up in the above experiments suggests that the use of polar media probably caused further undesirable side reactions. A less polar medium, benzene, was employed as a co-solvent for the reaction. Inverse slow addition of a reagent solution in dimethyl sulfoxide to a solution of **35** in benzene afforded a high yield of the product **36**. At this stage, the stereoisomers could be separated by preparative thin layer chromatography to give the α-methylene esters **36a** and **36b** in 33 and 32% yields, respectively. Each isomer **36a** or **36b** was hydrolyzed with potassium hydroxide, and the resulting dihydroxy carboxylic acid was treated with *p*-toluenesulfonic acid in refluxing benzene giving, without double bond isomerization, the α-methylene-δ-lactone **37a** or **37b** in a high yield. The observed significant differences in the physical properties of



Scheme 6.

these isomers were the NMR coupling patterns of the lactonic methylene protons (–CH_2–O–CO–): an AB type quartet (J=12 Hz) at δ 4.20 in **37a** and a singlet at δ 4.07 in **37b**, and the chemical shift values of the allylic methine protons: δ 3.14 (dd) in **37a** and 3.43 (dd) in **37b**. Such characteristics were also observed in the corresponding keto lactones **38**: the lactonic methylene protons appeared as an AB type quartet (J=11 Hz) at δ 4.16 in **38a**, while a singlet at δ *ca.* 3.90 in **38b**, and the allylic methine protons appeared at δ 3.10 (br s) in **38a** and at δ *ca.* 3.80 (br s) in **38b**, respectively.

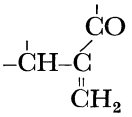
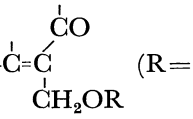
We now considered the stereochemical features of these isomeric lactone derivatives with Dreiding models, in order to establish whether the a-series or b-series lactone would possess the same stereochemistry as that of fomannosin. As shown in Scheme 6, one series has the same (7*R*′,9*R*′)[14] configuration as that of fomannosin,[16] the other having the (7*R*′,9*S*′) configuration. In both series, the conformations, in which the cyclopentane ring (especially the part of

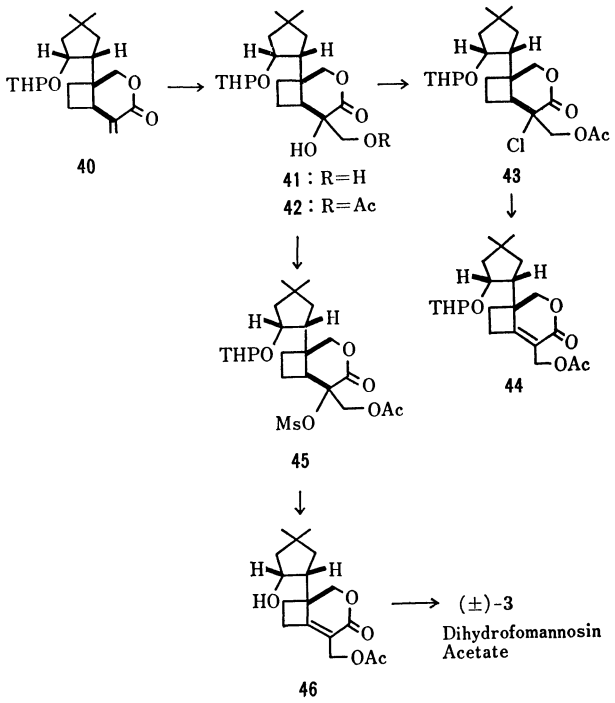


37a, 38a **37b, 38b**

the dimethyl groups) is so oriented as to be far from the bicyclic lactone ring system, the lactone ring being bisected by the methine hydrogen on the cyclopentane ring, could be postulated to be the sterically favorable conformations as shown by the stereoformulae. If so, in the (7*R*′,9*R*′)-series compounds the hydroxyl or carbonyl group on the cyclopentane ring is located close to the lactonic methylene group and apart from the allylic methine hydrogen at C-4, and therefore, the anisotropic effect of the oxygen-functions may cause a somewhat large difference in the chemical shifts of two methylene protons, resulting in the appearance as an AB type quartet. Almost no shift would be expected in the signal of the allylic methine proton upon conversion of the hydroxyl into the keto group. Contrary to the (7*R*′,9*R*′)-series, in the case of the (7*R*′,9*S*′)-series compounds the hydroxyl or carbonyl group on the cyclopentane ring should be far from the lactonic methylene group, approaching to the allylic methine hydrogen. Thus, lactonic methylene protons would appear as a singlet (alomost same chemical shifts), and the allylic proton signal at a lower field than that of the corresponding (7*R*′,9*R*′)-isomer, shifting markedly upon conversion of the hydroxyl into the keto group. The compounds (a-series) exhibiting an AB type quartet methylene signal should be the desired (7*R*′,9*R*′)-stereoisomers **37a** and **38a**. The assignment was confirmed by completion of the synthesis of dihydrofomannosin acetate from **37a**.[17] The spectral properties of the b-series compounds **37b** and **38b** were also in good agreement with expectation for the (7*R*′,9*S*′)-configuration.

At this point a remark regarding the relative stabilities between the stereoisomers is appropriate. After treatment of pure **38b** with excess potassium hydroxide in aqueous dioxane–methanol at room temperature overnight, the keto lactone **38** was recovered through acidification and lactonization. The recovered material was found to be a *ca.* 2:1 mixture of **38a** and **38b** as determined by a comparison of the NMR peak areas of the respective lactonic methylene protons. Thus, in the ring-opened state **39** the (7*R*′,9*R*′)-stereoisomer leading to **38a** was slightly more stable than the (7*R*′,9*S*′)-one.

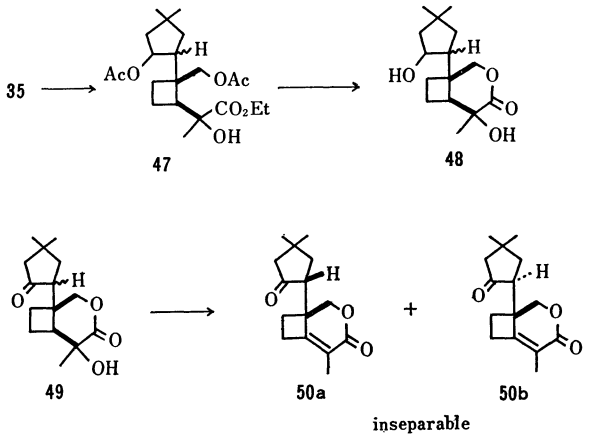
Of the compounds **37a** and **38a**, both having the proper stereochemistry and functionalities for the synthesis, **37a** appeared to be the better precursor, since the use of **38a** would cause some complexity (epimerization *etc.*) upon subsequent operations. For the remaining functional group manipulation,  ⟶  (R=H or Ac), allylic oxidation-rearrangement with singlet oxygen[18] or selenium dioxide[19] would be the most promising procedure. However, all attempts to achieve the allylic oxidation-rearrangement of **37a** or the acetate with singlet oxygen or selenium dioxide under various conditions were unsuccessful. Thus, a stepwise scheme (Scheme 7) was adopted.



Scheme 7.

The tetrahydropyranyl ether **40**, derived from **37a**, was hydroxylated with osmium tetraoxide-pyridine in ether, and the resulting dihydroxy lactone **41** was acetylated to the monoacetate **42** in 69% yield. Dehydration of **42** with the common agents (thionyl chloride or phosphoryl chloride in pyridine) was found to be quite troublesome. The reactions were extremely slow and the chloride **43** initially formed resisted subsequent dehydrochlorination enormously giving only a trace of the unsaturated lactone **44**. Compound **42** was then treated with methanesulfonyl chloride in the presence of triethylamine to give quantitatively the unstable mesylate **45**. Demesylation of crude **45** was accomplished by heating with lithium chloride-lithium carbonate in *N*,*N*-dimethylformamide, providing directly the unsaturated hydroxy lactone **46** along with several by-products. The Jones oxidation of **46**, without isolation, gave after chromatographic separation, (±)-dihydrofomannosin acetate (**3**), mp 102—103 °C, in 20% yield from **45**. The spectral [IR, NMR (60 and 100 MHz), and mass] and chromatographic behaviors were identical with those of the authentic sample prepared from dihydrofomannosin derived from natural fomannosin. Furthermore, we examined the preparation of (±)-dihydrofomannosin (**2**) itself. It was found that **3** and **2** seem to be base-sensitive; saponification of **3** resulted in the formation of a complex mixture.

An attempt to synthesize (±)-deoxydihydrofomannosin (**50a**) should be mentioned (Scheme 8). Treatment of the glyoxylate **35** with methyllithium gave the hydroxy ester **47**, which was converted into the dihydroxy lactone **48** through hydrolysis and lactonization in the same manner; there was no indication of cyclization to a tetrahydrofuran derivative. The Jones oxidation of **48** afforded the hydroxy keto lactone **49**. In the case of **49**, dehydration with thionyl chlo-



Scheme 8.

ride–pyridine proceeded well to give selectively the *endo*-unsaturated lactone. The product was apparently a *ca.* 1:1 mixture of the stereoisomers **50a** and **50b**, which were inseparable. In the NMR spectrum, the signals due to the lactonic methylene protons were observed as a set of an AB type quartet and a singlet. The isomer revealing an AB type quartet should be (±)-deoxydihydrofomannosin (**50a**).

Experimental

All melting points were taken on a Yamato melting point apparatus and are uncorrected. Small amounts of liquid products were purified by evaporative short-path distillation; oil-bath temperatures are recorded. IR spectra were obtained with a Hitachi EPI-S2 or G2 spectrophotometer, NMR spectra with a JEOL PMX-60 (60 MHz), C-60HL (60 MHz), or PS-100 (100 MHz) instrument with TMS as an internal standard, coupling constants being given in Hz, and mass spectra with a Shimadzu LKB-9000 spectrometer at 70 eV. Silica gel (Merck GF-254) was used for preparative and analytical thin-layer chromatography (TLC); solvent systems are indicated in parentheses. Microanalyses were carried out at this Institute.

*4-(2-Acetoxy-4,4-dimethylcyclopentyl)-2(5H)-furanone (**13**).* *Route a*: 2-Acetoxy-4,4-dimethylcyclopentyl (bromoacetoxy)-methyl ketone (**11**) was prepared from 2-ethoxycarbonyl-4,4-dimethylcyclopentanone (**5**)[20] in 16% overall yield through six steps by a procedure similar to that reported.[8] Activated zinc powder (1.56 g, 3 equiv) was added portionwise under stirring and gentle refluxing to a solution of **11** (2.65 g, 8 mmol), ethyl bromoacetate (1.0 g, 0.6 mmol), and iodine (a catalytic amount) in anhydrous benzene (40 ml). After vigorous reaction ceased, refluxing and stirring were continued for 2 h. Acetic acid (2 ml) and methanol (1 ml) were added in succession to the cooled reaction mixture, and the resulting mixture was diluted with water. The water layer was extracted with ether. The combined organic layers were washed with an aqueous solution of sodium hydrogencarbonate, water, and saturated brine, and dried over anhydrous sodium sulfate. After removal of the solvent, the oily residue (1.6 g) was dissolved in acetic anhydride (20 ml) and heated under reflux for 24 h. Concentration of the solution under reduced pressure and chromatography of the concentrate on silica gel (50 g) using $CHCl_3$ as an eluant gave **13** (437 mg, 48%).

Route b: To a slurry of potassium *t*-butoxide (4.93 g, 44 mmol) in anhydrous benzene (25 ml) was added dropwise a solution of **5** (7.4 g, 40 mmol) in anhydrous benzene (35 ml) at room temperature under nitrogen. After stirring at room temperature for 2 h, the solution was concentrated under reduced pressure, and the concentrated enolate was dissolved in DMSO (25 ml). To this solution was added dropwise a solution of γ-crotonolactone (**14**) (8.2 g, 0.1 mol, 2.5 equiv) in DMSO (25 ml) with ice-water cooling under nitrogen. After being stirred at room temperature for 12 h, the reaction mixture was poured into ice-water, neutralized with 10% sulfuric acid, and extracted with ether. The combined extracts were washed with water and brine, and dried. Evaporation of the solvent gave a stereoisomeric mixture of 4-(1-ethoxycarbonyl-4,4-dimethyl-2-oxocyclopentyl)tetrahydro-2-furanone (**15**) (6.06 g, 66%): bp 160—165 °C/1.5 Torr; IR ($CHCl_3$) 1780, 1750, 1720, 1180, and 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (6H, s) 1.28 (3H, t, J=7.0), 1.70—3.40 (7H, m), 4.20—4.75 (2H, m), and 4.25 (2H, q, J=7.0). Found: *m/e* 268 (M^+). Calcd for $C_{14}H_{20}O_5$: M 268.

A mixture of **15** (3.82 g) and an aqueous 20% perchloric acid solution was heated at 80—90 °C with vigorous stirring for 12 h and then at the refluxing temperature for 1 h. After cooling, the product was extracted with ether. The combined extracts were washed with water and brine, and freed from the solvent. Distillation of the oil remaining afforded 4-(4,4-dimethyl-2-oxocyclopentyl)tetrahydro-2-furanone (**16**): bp 135—145 °C/1.5 Torr; IR (CCl_4) 1780, 1740, 1170, and 1030 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (3H, s), 1.20 (3H, s), and 3.90—4.90 (2H, m). Found: C, 67.21; H, 7.90%. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%.

To a solution of **16** (2.0 g, 10 mmol) in methanol (80 ml) was added portionwise sodium borohydride (550 mg, 15 mmol) under cooling in an ice–water bath, and the reaction mixture was stirred at 0 °C for 1.5 h and at room temperature for 1 h. After the reaction was quenched by the addition of dilute hydrochloric acid (2 M), the solution was concentrated under reduced pressure. The residual semi-solid was dissolved in $CHCl_3$, the resulting solution being washed with brine. Evaporation of the solvent and distillation of the residue gave 4-(2-hydroxy-4,4-dimethylcyclopentyl)tetrahydro-2-furanone (**17**) (1.52 g, 77%): bp 145—155 °C/1.5 Torr; IR ($CHCl_3$) 3450 and 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (3H, s), 1.10 (3H, s), 2.40 (1H, s, OH), and 3.70—4.70 (3H, m). Found: C, 66.75; H, 8.95%. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%.

A solution of tetrahydropyranyl ether **19** (2.83 g, 10 mmol), prepared from **17** by the standard method, in THF (6 ml) was added dropwise at −60 °C over a period of 10 min under nitrogen to a solution of lithium diisopropylamide (20 mmol) in anhydrous ether (14 ml) and THF (5 ml). After stirring at −60 °C to −40 °C for 1 h, the reaction mixture was added dropwise to a solution of dimethyl disulfide (2 ml, 20 mmol) in THF (6 ml) at −35 °C, and the resulting mixture was allowed to warm slowly to room temperature over a period of 2 h with stirring. A saturated aqueous solution of ammonium chloride was added, the water layer being separated and extracted with ether. The combined organic layers were washed with water and brine, dried, and freed from ether. Chromatography of the residue (3.26 g) on silica gel (75 g) using petroleum ether–ether (the amount of ether was gradually increased, the final ratio being 2:1.) as an eluant gave 4-[4,4-dimethyl-2-(tetrahydropyranyloxy)cyclopentyl]-3-(methylthio)tetrahydro-2-furanone (**20**) (1.88 g, 60%): IR ($CHCl_3$) 1760, 1025, and 1015 cm^{-1}; NMR (CCl_4) δ 1.04 and 1.10 (total 6H, each s), 2.15 and 2.25 (total 3H), and 3.00—4.80 (7H, m). Found: C, 62.44; H, 8.92%. Calcd for $C_{17}H_{28}O_4S$: C, 62.17; H, 8.59%.

A solution of **20** (3.1 g) and hydrochloric acid (1 M, 4 ml)

in methanol (50 ml) was allowed to stand at room temperature for 4 h. The reaction mixture subjected to the usual work-up (dilution with water and extraction with ether) gave 4-(2-hydroxy-4,4-dimethylcyclopentyl)-3-(methylthio)tetrahydro-2-furanone (1.95 g, 84%): bp 120 °C/0.5 Torr; IR ($CHCl_3$) 3400, 1760, 1160, and 1015 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (3H, s), 1.07 (3H, s), 2.25 and 2.27 (total 3H, each s), and 3.80—4.70 (3H, m). Found: C, 59.02; H, 8.55%. Calcd for $C_{12}H_{20}O_3S$: C, 59.00; H, 8.25%.

The above hydroxy lactone was acetylated in the usual way with acetic anhydride and pyridine to afford 4-(2-acetoxy-4,4-dimethylcyclopentyl)-3-(methylthio)tetrahydro-2-furanone (**21**): IR ($CHCl_3$) 1770, 1725, and 1020 cm^{-1}; NMR (CCl_4) δ 1.07 (6H, s), 1.98 (3H, s), 2.22 (3H, s), 3.20 (1H, m), 3.90—4.70 (2H, m), and 5.00 (1H, m).

A solution of sodium periodate (1.7 g, 8 mmol) in water (15 ml) was added dropwise at 0 °C to a solution of **21** (1.94 g, 6.8 mmol) in methanol (15 ml), and the reaction mixture was stirred at room temperature overnight. After removal of inorganic material by filtration, the filtrate was extracted with $CHCl_3$ three times. The combined extracts were washed with water and brine, dried, and evaporated. The residual oil was dissolved in pyridine (20 ml), and the resulting solution was heated under reflux for 3 h and evaporated under reduced pressure. The residue was dissolved in ether, the ethereal solution being washed with dilute hydrochloric acid, water, and brine, and evaporated. The residue was passed through a short column of silica gel with the aid of 1:1 petroleum ether–ether and distilled to give **13** (1.23 g, 76% from **21**): bp 140 °C/1 Torr.

Route c: To a solution of lithium diisopropylamide (0.03 mol) in anhydrous THF (20 ml) and hexane (20 ml) was added dropwise a solution of 3,3-dimethylcyclopentanone (**25**)[21] (3.36 g, 0.03 mol) in anhydrous THF (10 ml) at −60 °C under nitrogen, and the reaction mixture was stirred at −60 °C for 1 h. A solution of 3-phenylsulfinyl-2(5*H*)-furanone (**24**)[10] (6.9 g, 0.03 mol) in anhydrous THF (35 ml) was added to the above solution at −78 °C with stirring. After stirring at this temperature for 2 h, a saturated aqueous solution of ammonium chloride was added. The resulting solution was then neutralized with dilute sulfuric acid and extracted with ether three times. The combined extracts were washed with water and brine, dried, and evaporated. The residue was dissolved in toluene (150 ml), and the solution was heated under reflux for 30 min. Evaporation of the solvent under reduced pressure and chromatography on silica gel (150 g) using 4:6 petroleum ether–ether as an eluant gave 4-(4,4-dimethyl-2-oxocyclopentyl)-2(5*H*)-furanone (**28**) (3.17 g, 54%, faster eluted fraction): IR ($CHCl_3$) 1790, 1758, 1750, and 1638 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (3H, s), 1.26 (3H, s), 2.24 (2H, s), 1.80—2.50 (2H, m), 3.45 (1H, br t, J=10.5), 4.80 (1H, a part of AB type q, finely split, J=18.0), 5.12 (1H, a part of AB type q, finely split, J=18.0), and 5.88 (1H, q, J=2.2), and 4-(2,2-dimethyl-5-oxocyclopentyl)-2(5*H*)-furanone (**29**): IR ($CHCl_3$) 1785, 1765, 1745, and 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (3H, s), 1.30 (3H, s), 1.70—2.70 (4H, m), 3.40 (1H, br s), 4.76 (1H, a part of AB type q, finely split, J=18.0), 5.00 (1H, a part of AB type q, finely split, J=18.0), and 5.96 (1H, q, J=2.2). Both **28** and **29** were fairly unstable, decomposing on storage, giving no satisfactory analytical data.

To a solution of **28** (2.31 g, 12 mmol) in anhydrous methanol (60 ml) was added portionwise sodium borohydride (464 mg, 12 mmol) at −15 °C over a period of 30 min, and the reaction mixture was stirred at −15 °C for 30 min. A few drops of glacial acetic acid was added, and the resulting solution was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, and the solution successively washed with dilute sulfuric acid, water, and brine. Evaporation of the solvent left the single crystalline product, 4-(2-hydroxy-4,4-dimethylcyclopentyl)-2(5*H*)-furanone (**30**) (2.01 g, 89%). An analytical sample was purified by preparative TLC (1:1 $CHCl_3$–ether) and then by recrystallization from 4:1:1 CCl_4–ether–petroleum ether: mp 36—38 °C; IR ($CHCl_3$) 3450, 1780, 1745, 1630, and 1030 cm^{-1}; NMR ($CDCl_3$) δ 1.12 (3H, s), 1.19 (3H, s), 1.30—2.20 (4H, m), 2.97 (1H, m), 3.55 (1H, OH), 4.13 (1H, q, J=9.5), 4.92 (2H, t, J=2.5), and 5.85 (1H, q, J=2.5). Found: C, 66.90; H, 8.39%. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%.

Compound **30** (1.79 g) was treated with pyridine (20 ml) and acetic anhydride (20 ml), and the reaction mixture was allowed to stand at 0 °C overnight. The usual work-up and purification by chromatography on silica gel (50 g) using 1:1 petroleum ether–ether as an eluant gave **13** (1.78 g, 82%): bp 120—130 °C/1 Torr; IR (CCl_4) 1785, 1745, and 1640 cm^{-1}; NMR (CCl_4) δ 1.12 (3H, s), 1.15 (3H, s), 2.00 (3H, s), 3.16 (1H, dt, J=10.5 and 7.5), 4.77 (2H, d, J=2.2), 5.12 (1H, td, J=7.5 and 6.0), and 5.83 (1H, td, J=2.2 and 1.2). Found: C, 65.45; H, 7.64%. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61%.

*5-(2-Acetoxy-4,4-dimethylcyclopentyl)-3-oxabicyclo[3.2.0]heptan-2-one (**33**).* A solution of **13** (1.9 g) in freshly distilled acetone (600 ml) was irradiated with a 500 W high-pressure mercury lamp (immersed, no filter) at −50—−60 °C with continuous introduction of finely dispersed ethylene. On this scale, the reaction was essentially completed within 3—5 h. Evaporation of the solvent left the product (2.4 g) which was chromatographed on silica gel (70 g) using petroleum ether–ether (the amount of ether was gradually increased, the final ratio being 6:4.) as an eluant to give an inseparable stereoisomeric mixture of **33** (1.80 g, 85%): bp 110—120 °C/1 Torr; IR (CCl_4) 1775, 1732, 1233, and 1020 cm^{-1}; NMR (CCl_4) δ 1.08 and 1.12 (total 6H, each s), 2.00 (total 3H, two singlets), 4.10 (2H, m), and 5.00 (1H, m). Found: C, 68.03; H, 8.10%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

*Ethyl [2-Acetoxymethyl-2-(2-acetoxy-4,4-dimethylcyclopentyl)cyclobutyl]glyoxylate (**35**).* 2-Methylthio-1,3-dithiane was prepared according to the procedure given by Ellison *et al.*:[11] bp 130—150 °C/4—5 Torr; NMR (CCl_4) δ 2.10 (3H, s) and 4.75 (1H, s). To a solution of 2-methylthio-1,3-dithiane (1.80 g, 11 mmol) in anhydrous THF (10 ml) was added dropwise a solution of butyllithium in hexane (5.7 ml of 1.9 M solution, 11 mmol) at −60 °C under nitrogen, and the mixture was stirred at −60 °C for 0.5 h. A solution of **33** (850 mg, 3.2 mmol) in anhydrous THF (8 ml) was added dropwise to the above solution at −60 °C, and the reaction mixture was allowed to warm to 0 °C over a period of several hours with stirring. A saturated aqueous solution of ammonium chloride was added, and the product was extracted with ether. The combined extracts were washed with water and brine, and dried. Evaporation of the solvent left an oily material which was treated with a mixture of acetic anhydride (18 ml) and pyridine (18 ml) at room temperature overnight. The mixture was evaporated to dryness under reduced pressure. Chromatography of the oil remaining on silica gel (50 g) using 2:1 petroleum ether–ether as an eluant gave the ring-opened product **34** (1.08 g, 71%): IR ($CHCl_3$) 1725 cm^{-1}; NMR (CCl_4) δ 1.10 (6H), 1.87 (3H), 2.04 (3H), 4.05 (2H), and 4.30—5.50 (1H). Found: *m/e* 474 (M^+). Calcd for $C_{22}H_{34}O_5S_3$: M 474.

To a slurry of mercury(II) chloride (3.31 g, 12.2 mmol) and mercury(II) oxide (1.35 g, 6.2 mmol) in 95% ethanol

(50 ml)[11] was added a solution of **34** (1.43 g, 3.0 mmol) in 95% ethanol (20 ml), and the reaction mixture was vigorously stirred at 80—90 °C for 2 h. After cooling to room temperature, inorganic material was removed by filtration and the filtrate concentrated under reduced pressure. The residue was dissolved in ether, the ethereal solution being washed with water and brine. Evaporation of the ether gave colorless oily **35** (990 mg, 85%), which was sufficiently pure to be used for subsequent treatment. An analytical sample was purified by preparative TLC (6:4 petroleum ether–ether) and then distilled: bp 120—130 °C/0.5 Torr; IR ($CHCl_3$) 1730 (sh) and 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.07, 1.13, and 1.18 (total 6H, each s), 1.38 and 1.41 (total 3H, each t, J=7.0), 1.95 and 2.12 (total 6H, each s), 3.60—4.20 (3H, m), 4.35 (2H, q, J=7.0), and 4.77 and 5.33 (total 1H, each m). Found: C, 62.76; H, 8.02%. Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.90%.

*Ethyl 2-[2-Acetoxymethyl-2-(2-acetoxy-4,4-dimethylcyclopentyl)-cyclobutyl]propenoate (**36**).* A solution of methylenetriphenylphosphorane in DMSO (2.8 ml of 0.5 M solution, 1.4 mmol), prepared according to the procedure given by Greenwald *et al.*,[22] was added to a solution of **35** (420 mg, 1.1 mmol) in anhydrous benzene (10 ml) at 0 °C under nitrogen. After stirring at room temperature for 1—2 h, the reaction mixture was poured into ice–water containing a few drops of 2 M sulfuric acid, and the product was extracted with ether. The combined extracts were washed with water and brine, dried and freed from ether. Preparative TLC (6:4 petroleum ether–ether) of the residue (710 mg) gave **36a** (R_f 0.58, 137 mg, 33%) and **36b** (R_f 0.67, 124 mg, 32%). The analytical samples were purified by distillation, bp 110—120 °C/0.5 Torr. Isomer **36a** had IR ($CHCl_3$) 1720, 1624, and 1035 cm^{-1}; NMR (CCl_4) δ 1.10 (3H, s), 1.13 (3H, s), 1.32 (3H, t, J=7.5), 1.85 (6H, s), 2.70 (1H, m), 3.30 (1H, br t, J=*ca.* 8.0), 3.84 (2H, s), 4.17 (2H, q, J=7.5), 4.63 (1H, m), 5.40 (1H, m), and 6.13 (1H, m). Found: C, 66.04; H, 8.73%. Calcd for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48%. Isomer **36b** had mp 51—53 °C (crystallized sample); IR ($CHCl_3$) 1718, 1625, and 1030 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (3H, s), 1.13 (3H, s), 1.33 (3H, t, J=7.0), 1.90 (3H, s), 1.97 (3H, s), 3.47 (1H, br t, J=7.5), 3.70 and 4.00 (1H each, AB type q, J=7.0), 4.22 (2H, q, J=7.0), 5.47 (2H, br s), and 6.13 (1H, br s). Found: C, 66.55; H, 8.44%.

*1-(2-Hydroxy-4,4-dimethylcyclopentyl)-5-methylene-3-oxabicyclo-[4.2.0]octan-4-one (**37**).* A solution of **36a** (221 mg) in a mixture of dioxane (4 ml), an aqueous solution of potassium hydroxide (200 mg in 4 ml of water), and methanol (1 ml) was allowed to stand at room temperature overnight. After acidification with dilute sulfuric acid, the product was thoroughly extracted with $CHCl_3$. The combined extracts were washed with brine, and evaporated. The residue was dissolved in benzene (5 ml) containing a catalytic amount of fused *p*-toluenesulfonic acid, and the resulting solution was heated under reflux for 1 h. The reaction mixture was diluted with ether and washed successively with an aqueous solution of sodium hydrogencarbonate, water, and brine, and dried. Evaporation of the solvent under reduced pressure gave **37a** (146 mg, quantitative). A pure sample was obtained by preparative TLC (1:4 petroleum ether–ether), but further purification by distillation caused decomposition. Compound **37a** had IR ($CHCl_3$) 3400, 1720, 1628, 1030, and 940 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (3H, s), 1.18 (3H, s), 2.50 (1H, OH), 3.14 (1H, dd, J=9.0 and 6.0), 4.10 (1H, m), 4.02 and 4.38 (1H each, AB type q, J=10.0), 5.36 (1H, br s), and 5.95 (1H, br s). Found: *m/e* 250 (M^+). Calcd for $C_{15}H_{22}O_3$: M 250.

In the same manner, isomeric **37b** was obtained from **36b** and had IR ($CHCl_3$) 3400, 1720, 1625, 1030, and 940 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (3H, s), 1.15 (3H, s), 2.42 (1H, OH), 3.43 (1H, dd, J=9.9 and 6.0), 4.07 (2H, s), 4.20 (1H, m), 5.43 (1H, br s), and 5.96 (1H, br s). Found: *m/e* 250 (M^+).

*1-(4,4-Dimethyl-2-oxocyclopentyl)-5-methylene-3-oxabicyclo-[4.2.0]octan-4-one (**38**).* The hydroxy lactone **37a** (90 mg) was oxidized with Jones reagent[23] in the standard way to afford **38a** (81 mg, 91%). Similarly, isomeric **38b** (74 mg, 90%) was obtained from **37b** (81 mg). The analytical samples were purified by preparative TLC (1:1 petroleum ether–ether) and by distillation, bp 130—140 °C/0.1 Torr. Isomer **38a** had IR ($CHCl_3$) 1730, 1725, 1640, 1625, 1140, 1040, and 950 cm^{-1}; NMR (CCl_4) δ 1.06 (3H, s), 1.23 (3H, s), 3.10 (1H, br s), 3.94 and 4.38 (1H each, AB type q, J=11.0), 5.26 (1H, br s), and 5.83 (1H, br s). Found: C, 72.77; H, 7.99%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%. Isomer **38b** had IR ($CHCl_3$) 1740, 1730, 1640, 1625, 1140, 1042, and 950 cm^{-1}; NMR (CCl_4) δ 1.03 (3H, s), 1.10 (3H, s), *ca.* 3.90 [total 3H, br, two singlets of 2H and 1H (centered at *ca.* 3.80) were overlapped], 5.30 (1H, br s), and 5.90 (1H, br s). Found: C, 72.47; H, 7.77%.

A solution of **38b** (50 mg, 0.2 mmol) in a mixture of dioxane (1 ml), methanol (2 ml), and water (2 ml) containing potassium hydroxide (56 mg, 1 mmol, 5 equiv) was left at room temperature overnight. Work-up and the subsequent lactonization of the acidic product (52 mg) in the same way as described in the preceding experiment gave a *ca.* 2:1 mixture of **38a** and **38b** [total product (50 mg) isolated by passing through a short column of silica gel with the aid of ether] as determined by the NMR spectrum.

*1-[4,4-Dimethyl-2-(tetrahydropyranyloxy)cyclopentyl]-5-methylene-3-oxabicyclo[4.2.0]octan-4-one (**40**).* A solution of **37a** (59 mg, 0.23 mmol), dihydropyrane (21 mg, 0.28 mmol), fused *p*-toluenesulfonic acid (a catalytic amount) in CH_2Cl_2 (2 ml) was stirred at 0 °C for 1 h. After addition of a few drops of pyridine, the usual work-up and purification by chromatography on silica gel with ether gave **40** (70 mg, 92%): IR ($CHCl_3$) 1720, 1630, 1150, 1130, and 1028 cm^{-1}; NMR (CCl_4) δ 1.07 and 1.12 (total 6H, each s), 4.47 (1H), 5.27 (1H, br s), and 5.83 (1H, br s). Found: *m/e* 334 (M^+). Calcd for $C_{20}H_{30}O_4$: M 334.

*(±)-Dihydrofomannosin Acetate (**3**).* To a solution of **40** (180 mg, 0.53 mmol) and pyridine (536 mg, 6.5 mmol) in ether (3 ml) was added dropwise a solution of osmium tetraoxide (165 mg, 0.65 mmol) in ether (1.5 ml) at 0 °C under nitrogen,[24] and the reaction mixture was stirred at room temperature overnight. Pyridine (2.5 ml) and then an aqueous solution of sodium hydrogensulfite (270 mg in 3.5 ml) were added to the stirred mixture at 0 °C, and the stirring was continued at room temperature for 1 h. Water was added, and the product was thoroughly extracted with a 1:2:1 mixture of $CHCl_3$–ether–ethyl acetate. The combined extracts were successively washed with dilute sulfuric acid, water, and brine, and dried. The solvent was evaporated to leave the diol **41** (225 mg): IR ($CHCl_3$) 3500—3200 and 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.03 and 1.11 (total 6H, each s).

This crude diol **41**, without further purification, was dissolved in a mixture of acetic anhydride (0.6 ml) and pyridine (1 ml) at 0 °C, and the mixture was allowed to stand at the same temperature for 1 h. The usual work-up and purification by preparative TLC (2:3 petroleum ether–ether) gave 5-acetoxymethyl-5-hydroxy-1-[4,4-dimethyl-2-(tetrahydropyranyloxy)cyclopentyl]-3-oxabicyclo[4.2.0]octan-4-one (**42**) (148 mg, 68%) as a mixture of stereoisomers:

IR ($CHCl_3$) 3300 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.03 and 1.12 (total 6H, each s), 2.10 (3H, s), and 3.20—5.50 (9H). Found: *m/e* 410 (M^+). Calcd for $C_{22}H_{34}O_7$: M 410.

To a solution of **42** (144 mg, 0.35 mmol) and triethylamine (54 mg, 0.53 mmol) in CH_2Cl_2 (2 ml) was added dropwise a solution of methanesulfonyl chloride (48 mg, 0.42 mmol) in CH_2Cl_2 (1 ml) at 0 °C, and the reaction mixture was stirred at 0 °C for 45 min. The mixture was poured into ice–water, and the water layer was extracted with a 2:1:1 mixture of ether–CH_2Cl_2–ethyl acetate. The combined organic layers were washed with water and brine, and dried. Removal of the solvent gave the unstable mesylate **45** (180 mg, quantitative): IR ($CHCl_3$) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.10 and 1.17 (total 6H), 2.13 (3H, s), and 3.17 (3H, s).

A mixture of **45** (187 mg, 0.38 mmol), lithium chloride (160 mg), and lithium carbonate (112 mg) in DMF (3.5 ml)[25] was heated with stirring at 110 °C for 1 h and then at 160 °C for 2 h. After cooling, the reaction mixture was poured into ice–water and acidified with dilute sulfuric acid, and the product was extracted with a 1:1 mixture of ether–ethyl acetate. The extracts were washed with water and brine, and dried. Removal of the solvent left an oily **46** (128 mg), which was immediately dissolved in acetone and treated with Jones reagene at 0 °C by the standard procedure. The reaction mixture was diluted with water and extracted with a 1:1 mixture of ether–ethyl acetate. The combined extracts were washed with water and brine, dried, and evaporated to dryness. Preparative TLC (4:6 petroleum ether–ether) of the residue gave (±)-**3** (23 mg, 20%): mp 102—103 °C. The IR, NMR, and mass spectra and chromatographic behavior were identical with those of the authentic sample, which was prepared by acetylation of dihydrofomannosin (2 mg), derived from natural fomannosin, with acetic anhydride (0.1 ml) and pyridine (0.1 ml) at room temperature for 4 h.

*Deoxydihydrofomannosin (**50a**) and the Stereoisomer (**50b**).* To a solution of **35** (413 mg, 1.04 mmol) in anhydrous ether (10 ml) was added dropwise a solution of methyllithium in ether (1.5 ml of 1.0 M solution, 1.5 mmol) at −60 °C under nitrogen. The reaction mixture was stirred at −60 °C for 1 h and the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride. After the usual work-up, the crude product **47** (400 mg) was dissolved in dilute methanol (75%, 4 ml) containing potassium hydroxide (290 mg), and the resulting solution was heated at 68—70 °C for 2 h. Acidification with 4 M sulfuric acid to pH 1—2 and the usual work-up gave an acidic product (280 mg). A solution of this product in benzene (10 ml) containing a catalytic amount of fused *p*-toluenesulfonic acid was heated under reflux for 2 h. The solution was diluted with ether and washed with an aqueous solution of sodium hydrogencarbonate, water, and brine. Evaporation of the solvent left the dihydroxy lactone **48** (243 mg): IR ($CHCl_3$) 3580, 3500, 1730, and 1160 cm^{-1}.

The total crude **48** was oxidized with Jones reagent by the standard procedure gave the hydroxy keto lactone **49** (240 mg). An analytical sample was purified by preparative TLC (1:3 petroleum ether–ether) and then by distillation: bp 160—170 °C/0.05 Torr; IR ($CHCl_3$) 3520, 1735, 1160, 1140, and 1035 cm^{-1}; NMR ($CDCl_3$) δ 1.03 and 1.10 (total 3H), 1.25 and 1.27 (total 3H), 1.42 and 1.46 (total 3H), 3.65 (1H, OH), and 4.00 (d, J=12.0), 4.25 (d, J=12.0), 4.57 (d, J=12.0), and 4.68 (d, J=12.0) [total 2H, two pairs of AB type q]. Found: C, 67.44; H, 8.45%; *m/e* 266 (M^+). Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.86%, M 266.

Thionyl chloride (0.2 ml) was added to a solution of **49** (227 mg) in pyridine (2 ml) and the reaction mixture was heated at 60 °C for 1 h. The usual work-up gave an inseparable stereoisomeric mixture (*ca.* 1:1) of **50** (171 mg, 81%). An analytical sample was purified by preparative TLC (1:2 petroleum ether–ether) and then by distillation: bp 130—140 °C/0.05 Torr; IR ($CHCl_3$) 1730 and 1030 cm^{-1}; NMR (CCl_4) δ 1.10 and 1.12 (total 3H, each s), 1.25 (3H, s), 1.72 (3H, br. s), and 4.10 and 4.72 (a pair of AB type q, J=10.5, isomer **50a**) and 4.10 (s, isomer **50b**) [total 2H]. Found: C, 72.35; H, 8.05%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

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