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STUDIES DIRECTED TOWARDS THE SYNTHESIS OF FOMANNOSIN. A SYNTHESIS OF (±)-DIHYDROFOMANNOSIN ACETATE

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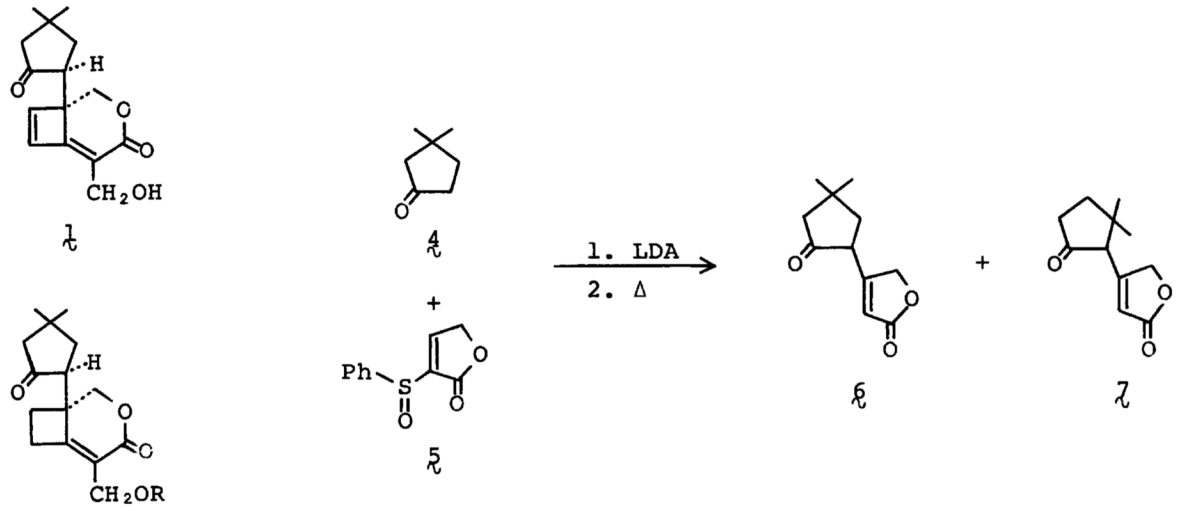
(±)-Dihydrofomannosin acetate has been synthesized by a reaction sequence involving the photocycloaddition of a $\Delta^{\alpha,\beta}$-butenolide derivative and the ring enlargement of a γ- to a δ-lactone system.

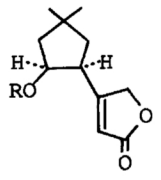
Fomannosin (1)[1] is a phytotoxic,[2] B-seco-protoilludane sesquiterpene first isolated from a still culture of the wood-rotting fungus Fomes annosus (Fr.) Karst[1] and subsequently from Basidiomycetes (Fomitopsis insularis),[3] and the structure has been established by X-ray crystallographic analysis of the p-bromobenzoylurethan derivative of dihydrofomannosin (2).[1] Photocycloaddition reaction of α,β-unsaturated lactones with olefins recently reported from our laboratory[4] appears suitable for the construction of the carbon skeleton of fomannosin or dihydrofomannosin, and we have firstly adopted the synthesis of dihydrofomannosin derivatives since fomannosin (1) has been reported to be chemically very unstable. This communication deals with a synthesis of dihydrofomannosin acetate (3).[5]

Our initial approach to dihydrofomannosin acetate involved the photocycloaddition of ethylene to the key intermediate butenolide 9, which was synthesized in the following manner. Michael addition of the enolate of dimethylcyclopentanone (4)[6] to α-phenylsulfinylbutenolide (5)[7] (lithium diisopropylamide in tetrahydrofuran, 1 hr at -65°C) followed by pyrolysis of the adduct in refluxing toluene gave the regioisomeric

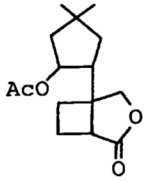


butenolides 6 and 7 in 54% and 18% yields based on the butenolide 5, respectively.[8] In the NMR spectra the methine proton α to the ketone appeared as broad triplet (J = 10.5 Hz) in the major isomer 6, whereas as broad singlet in the minor one 7. Thus, it was apparent that the major product 6 was the desired compound. The butenolide 6 was transformed to the key intermediate 9 in 82% yield by reduction with sodium borohydride in methanol (1 hr at -15°C) followed by acetylation of the resulting single (probably cis)[9] alcohol 8 (mp 36–38°C) with acetic anhydride–pyridine (10 hr at 0°C).

Irradiation of the butenolide 9 in acetone solution with moderately rapid introduction of a finely dispersed stream of ethylene (500-W high-pressure mercury lamp without a filter; 2–3 hr at -60– -50°C) gave a diastereoisomeric mixture of the photoadduct 10 in 85% yield. Separation of the diastereomers was carried out at a later stage. Introduction of one carbon unit to the lactone moiety was accomplished by



8: R=H
9: R=Ac



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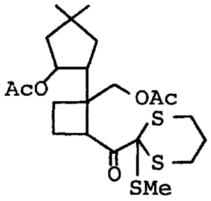

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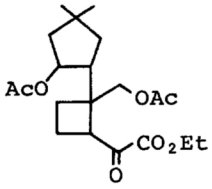

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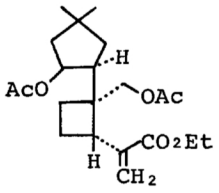
the use of 2-methylthio-1,3-dithiane.[10] Thus, the lactone 10 was allowed to react with the lithio derivative of 2-methylthio-1,3-dithiane, generated with n-butyl lithium (30 min at -50°C), in tetrahydrofuran (10 hr at -50– 22°C) and the resulting alcohol, without isolation, was subjected to the action of acetic anhydride–pyridine (10 hr at 22°C), affording the ring-opened diacetoxy ketone 11 in 93% yield. Treatment of 11 with mercuric chloride–mercuric oxide in 95% ethanol (2 hr at 80–90°C) gave diacetoxy α-ketoester 12 in 80% yield.

Wittig reaction of the ketoester 12 with methylenetriphenylphosphorane was quite troublesome, giving rise to a low yield of the product under several standard conditions. From a number of experiments, the dropwise addition of a solution of the Wittig reagent in dimethyl sulfoxide to a solution of the ketoester 12 in benzene (1 hr at 22°C) achieved a good yield of the diastereoisomeric Wittig products, which were easily separated by preparative thin layer chromatography on silica gel to give the pure diastereomers 13 and 14 in 33 and 32% yields, respectively. Saponification of each isomer 13 or 14 with potassium hydroxide in dioxane–methanol–water (10 hr at 22°C) followed by lactonization with refluxing benzene containing a catalytic amount of p-toluenesulfonic acid provided quantitatively α-methylene-δ-lactone 15 or 16.



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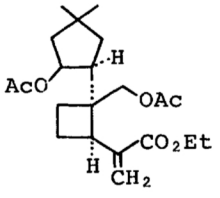

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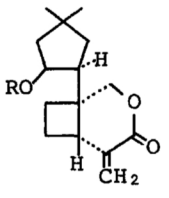
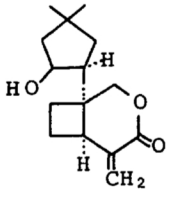


15: R=H
17: R=THP



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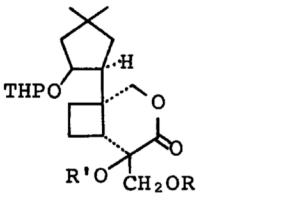
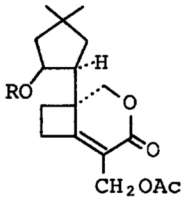
The most clear difference in the physical properties of both isomers is the NMR coupling patterns of the lactonic methylene protons ($-CH_2-O-CO-$): AB type quartet in 15 and singlet in 16. In all compounds derived subsequently from the isomer 15, including dihydrofomannosin acetate, the signal of these methylene protons always appeared as AB type quartet, and that 15 is the desired diastereomer was finally confirmed by completion of the synthesis of dihydrofomannosin acetate. The isomer 15 was transformed to the tetrahydropyranyl ether 17 by the action of dihydropyran in dichloromethane containing a catalytic amount of p-toluenesulfonic acid (1 hr at 0°C) in quantitative yield.

All attempts to introduce directly a hydroxyl group to the α-methylene-lactone 17, including sensitized photooxidation and oxidation with selenium dioxide or NBS etc, were failed. Treatment of 17 with osmium tetroxide–pyridine in ether (10 hr at 22°C) produced glycol 18 which was converted to the monoacetate 19 by exposure to acetic anhydride–pyridine (1 hr at 0°C) in 70% overall yield from 15. Difficulties were again encountered at the next stage. Direct dehydration of the monoacetate 19 to olefinic lactone 21 with either thionyl chloride–pyridine or phosphorous oxychloride–pyridine resulted in an extremely low yield of the product.



18: R=R'=H
19: R=Ac, R'=H
20: R=Ac, R'=Ms



21: R=THP
22: R=H

Treatment of 19 with methanesulfonyl chloride–triethylamine in dichloromethane (45 min at 0°C) produced the unstable mesylate 20 in quantitative yield, which, without purification, was subjected to the action of lithium chloride–lithium carbonate in dimethylformamide (2 hr at 110°C and then 2 hr at 160°C), giving directly unsaturated hydroxy lactone 22 along with several by-products. Oxidation of total crude 22 with Jones reagent, after preparative thin layer chromatography on silica gel, gave (±)-dihydrofomannosin acetate (3), mp 102–103°C, in 20% yield from 20, identical with that prepared from naturally derived dihydrofomannosin (2)[11] by tlc behavior, and IR (CS_2), ^{1}HNMR ($CDCl_3$, 60 and 100 MHz), and mass spectra.[12]

References and Notes

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8) All intermediates were characterized by IR and NMR (60 and 100 MHz) spectroscopy and the spectral data are fully consistent with the structures assigned. All new compounds except the keto-butenolides 6 and 7 (polymerized easily on distillation or standing) gave satisfactory combustion analyses or mass data (THP ethers). Yields reported are for isolated pure substances.
9) The cis configuration of two substituents on the cyclopentane ring was assigned from the NMR coupling pattern of the proton at the carbon atom bearing the acetoxyl group in 9: doublets (J = 6.0 Hz, trans coupling) of triplet (J = 7.5 Hz, cis coupling).
10) P. A. Ellison, W. D. Woessner, and G. C. Williams, J. Org. Chem., 37, 2757 (1972).
11) We are grateful to Dr. J. A. Kepler, Research Triangle Institute, for a valuable sample of dihydrofomannosin derived from natural fomannosin, which we acetylated with acetic anhydride–pyridine (4 hr at 22°C) and purified by preparative thin layer chromatography on silica gel.
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