A SIMPLE SYNTHESIS OF SHOWDOMYCIN

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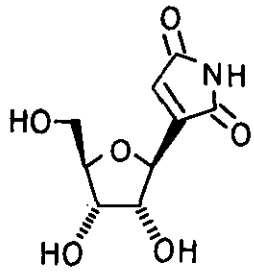
Abstract —— Showdomycin has been synthesized from the methyl β-D-ribofuranosylacetate 4a which can be readily prepared by Wittig reaction of the protected D-ribose 2 with the chlorophosphorane 3a.

Showdomycin (1) is a *C*-nucleoside, isolated from *Streptomyces showdoensis*,[1] having antibacterial and antitumor activities.[2,3] There have been several reports concerning the synthesis of 1.[4-9] We now report a simple synthesis of 1 from the β-D-ribofuranosylacetate derivative 4a. Our starting material (4a) was easily obtained by condensation of the protected D-ribose 2 with the chlorophosphorane 3a. Condensation of 2 with 3a in acetonitrile under reflux for 6 h gave the *C*-glycoside 4a in almost quantitative yield.[10] Examination of the ^{13}C-nmr spectrum indicated clearly that the compound had the β-configuration and was diastereomeric (*ca.* 2:1) only at the carbon bearing chlorine. 4a: ^{13}C-nmr δ ($CDCl_3$) 25.60, 27.36, and 27.48 (isopropylidene-Me).[11] In this reaction no trace of α-isomers was detected.[12]

Compound 4a was treated with potassium acetate in the presence of 18-crown-6 in dimethylsulfoxide (DMSO) at 50°C for 4 h to give the 2-acetoxy derivative 4b[13] in 82% yield. 4b: $\nu_{max.}$ ($CHCl_3$) 1750 cm^{-1}; ^{1}H-nmr δ ($CDCl_3$) 1.32, 1.34, 1.50, 1.54 (isopropylidene-Me), 1.87, 1.92 (OCOMe), 3.65, 3.77 (OMe), 5.22 (1H×*ca.*2/3) d, *J* 3.5 Hz, 2-H), and 5.30 (1H×ca.1/3, d, *J* 3.5 Hz, 2-H); ^{13}C-nmr δ ($CDCl_3$) 25.71 and 27.65 (isopropylidene-Me). Epimerization was not observed under the conditions used for the acetoxylation. Treatment of 4b with 28% ammonium hydroxide in methanol for 2 h at room temperature gave a 53% yield of the two diastereomeric esters 4c, which could be separated by chromatography on a column of silica gel. Less polar 4c: $\nu_{max.}$ ($CHCl_3$) 3525 and 1742 cm^{-1}; ^{1}H-nmr δ ($CDCl_3$)



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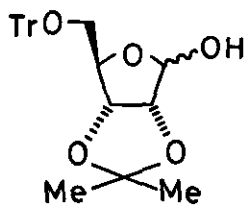

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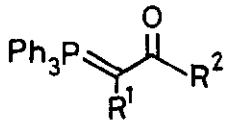

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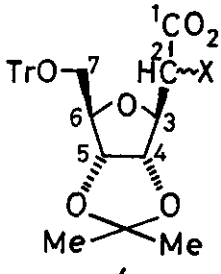
a: R^1=Cl, R^2= OMe
b: R^1=H, R^2= NH_2



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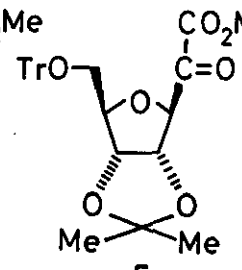
a: X = Cl
b: X = OCOMe
c: X = OH



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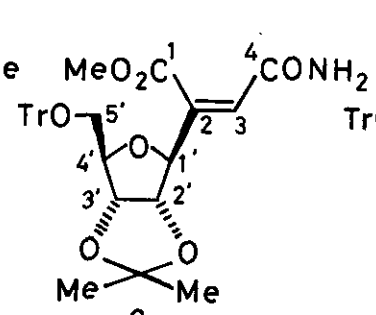

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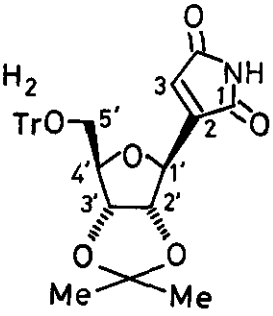

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1.29, 1.49 (isopropylidene-Me), 3.75 (OMe), and 3.35 (OH); ^{13}C-nmr δ ($CDCl_3$) 25.49 and 27.48 (isopropylidene-Me). More polar 4c: ^{1}H-nmr δ ($CDCl_3$) 1.28, 1.48 (isopropylidene-Me), 3.62 (OMe), and 3.36 (OH); ^{13}C-nmr δ ($CDCl_3$) 25.60 and 27.48 (isopropylidene-Me).

Oxidation of 4c (a mixture of diastereoisomers) by DMSO-acetic anhydride at room temperature for 16 h afforded the α-keto ester 5 [$\nu_{max.}$ ($CHCl_3$) 1750 and 1740 cm^{-1}], which, without further purification, was treated with (carbamoylmethylene)triphenylphosphorane (3b) in dry chloroform at room temperature to give a 32% yield of methyl 2-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-maleamate (6) and a trace of the protected showdomycin 7 (*vide infra*). 6: $\nu_{max.}$ ($CHCl_3$) 3470, 3400, 1725, 1680, and 1645 cm^{-1}; ^{1}H-nmr δ ($CDCl_3$) 1.30, 1.53

(isopropylidene-Me), 3.75 (OMe), 5.60 (NH_2), and 6.30 (1H, d, *J* 2 Hz, 3-H); ^{13}C-nmr δ ($CDCl_3$) 25.66 and 27.53 (isopropylidene-Me).

The configuration with respect to the C=C bond of 6 was determined by ^{1}H-nmr spectrum. Thus, the allylic coupling constant (*J* 2 Hz) indicating *Z*-form was observed between an olefinic proton (3-H) and an anomeric proton (1'-H).[7]

Compound 6, on treatment with 4-dimethylaminopyridine in benzene, was transformed into 7 in 28% yield. 7: $\nu_{max.}$ ($CHCl_3$) 3450, 1780, 1730, and 1635 cm^{-1}; ^{1}H-nmr δ ($CDCl_3$) 1.35, 1.58 (isopropylidene-Me), 3.23 (2H, m, 5'-H), 4.2-4.8 (3H, m, 2',3',4'-H), 4.87 (1H, dd, *J* 4, 2 Hz, 1'-H), 6.47 (1H, dd, *J* 2, 2 Hz, 3-H), and 7.1-7.5 (16H, m, NH and Tr); ^{13}C-nmr δ ($CDCl_3$) 25.48 and 27.36 (isopropylidene-Me).

Deprotection of 7 with 90% trifluoroacetic acid gave showdomycin (1) in 56% yield. The ir spectrum of 1 was identical in every respect with that of authentic sample of showdomycin.

Our method could be also applied for the synthesis of showdomycin analogs because the key intermediate 5 can be easily prepared.[14]

REFERENCES AND NOTES

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10. Quite recently, Secrist and Clingerman have also reported the synthesis of 4a by the reaction of 2 with 3a in toluene, followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). M. C. Clingerman and J. A. Secrist III, *J. Org. Chem.*, 1983, 48, 3141.
11. H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, 1975, 97, 4602.
12. Other protected D-riboses such as 2,3,5-tri-*O*-benzylribofuranose and 5-*O*-*t*-butyldimethylsilyl-2,3-*O*-isopropylideneribofuranose also reacted with the phosphorane 3a to give exclusively the corresponding β-*C*-ribofuranosylglycosides. These results will be reported as a full paper in near future.
13. Satisfactory analytical data were obtained for all new compounds herein reported.
14. The synthesis of showdomycin from the α-keto ester or α-keto lactone intermediate, which was prepared by somewhat cumbersome method, was reported by several workers. Cf. references 4, 5, 6, and 8.

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