

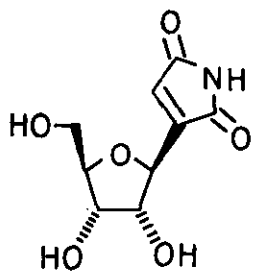
## A SIMPLE SYNTHESIS OF SHOWDOMYCIN

Nobuya Katagiri, • Toru Haneda, and Naoko Takahashi  
 Pharmaceutical Institute, Tohoku University,  
 Aobayama, Sendai 980, Japan

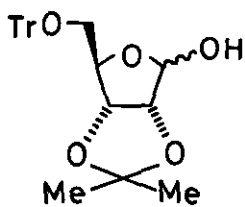
*Abstract* — Showdomycin has been synthesized from the methyl  $\beta$ -D-ribofuranosylacetate 4a which can be readily prepared by Wittig reaction of the protected D-ribose 2 with the chlorophosphorane 3a.

Showdomycin (1) is a C-nucleoside, isolated from *Streptomyces showdoensis*,<sup>1</sup> having antibacterial and antitumor activities.<sup>2,3</sup> There have been several reports concerning the synthesis of 1.<sup>4-9</sup> We now report a simple synthesis of 1 from the  $\beta$ -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.<sup>10</sup> Examination of the <sup>13</sup>C-nmr spectrum indicated clearly that the compound had the  $\beta$ -configuration and was diastereomeric (ca. 2:1) only at the carbon bearing chlorine. 4a: <sup>13</sup>C-nmr  $\delta$  (CDCl<sub>3</sub>) 25.60, 27.36, and 27.48 (isopropylidene-Me).<sup>11</sup> In this reaction no trace of  $\alpha$ -isomers was detected.<sup>12</sup>

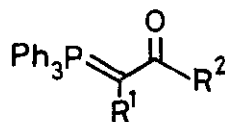
Compound 4a was treated with potassium acetate in the presence of 18-crown-6 in dimethylsulfoxide (DMSO) at 50°C for 4 h to give the 2-acetoxy derivative 4b<sup>13</sup> in 82% yield. 4b:  $\nu_{\max}$ . (CHCl<sub>3</sub>) 1750 cm<sup>-1</sup>; <sup>1</sup>H-nmr  $\delta$  (CDCl<sub>3</sub>) 1.32, 1.34, 1.50, 1.54 (isopropylidene-Me), 1.87, 1.92 (OCOMe), 3.65, 3.77 (OMe), 5.22 (1H $\times$ ca.2/3 d,  $J$  3.5 Hz, 2-H), and 5.30 (1H $\times$ ca.1/3, d,  $J$  3.5 Hz, 2-H); <sup>13</sup>C-nmr  $\delta$  (CDCl<sub>3</sub>) 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<sub>3</sub>) 3525 and 1742 cm<sup>-1</sup>; <sup>1</sup>H-nmr  $\delta$  (CDCl<sub>3</sub>)



1

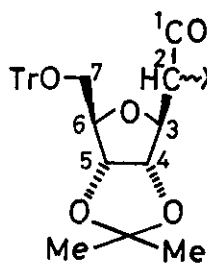


2



3

a: R<sup>1</sup>=Cl, R<sup>2</sup>=OMe  
b: R<sup>1</sup>=H, R<sup>2</sup>=NH<sub>2</sub>

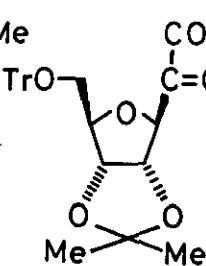


4

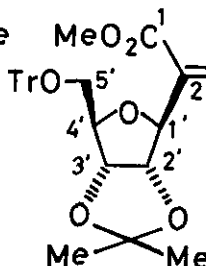
a: X = Cl

b: X = OCOMe

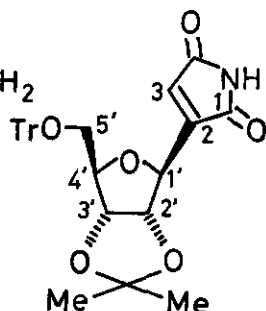
c: X = OH



5



6



7

1.29, 1.49 (isopropylidene-Me), 3.75 (OMe), and 3.35 (OH); <sup>13</sup>C-nmr δ (CDCl<sub>3</sub>) 25.49 and 27.48 (isopropylidene-Me). More polar 4c: <sup>1</sup>H-nmr δ (CDCl<sub>3</sub>) 1.28, 1.48 (isopropylidene-Me), 3.62 (OMe), and 3.36 (OH); <sup>13</sup>C-nmr δ (CDCl<sub>3</sub>) 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 [ν<sub>max.</sub> (CHCl<sub>3</sub>) 1750 and 1740 cm<sup>-1</sup>], 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: ν<sub>max.</sub> (CHCl<sub>3</sub>) 3470, 3400, 1725, 1680, and 1645 cm<sup>-1</sup>; <sup>1</sup>H-nmr δ (CDCl<sub>3</sub>) 1.30, 1.53

(isopropylidene-Me), 3.75 (OMe), 5.60 (NH<sub>2</sub>), and 6.30 (1H, d, *J* 2 Hz, 3-H); <sup>13</sup>C-nmr δ (CDCl<sub>3</sub>) 25.66 and 27.53 (isopropylidene-Me).

The configuration with respect to the C=C bond of 6 was determined by <sup>1</sup>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).<sup>7</sup> Compound 6, on treatment with 4-dimethylaminopyridine in benzene, was transformed into 7 in 28% yield. 7: ν<sub>max.</sub> (CHCl<sub>3</sub>) 3450, 1780, 1730, and 1635 cm<sup>-1</sup>; <sup>1</sup>H-nmr δ (CDCl<sub>3</sub>) 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); <sup>13</sup>C-nmr δ (CDCl<sub>3</sub>) 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.<sup>14</sup>

#### REFERENCES AND NOTES

1. H. Nishimura, M. Mayama, Y. Komatsu, H. Kato, N. Shimaoka, and Y. Tanaka, *J. Antibiotics, Ser. A.*, 1964, 17, 148. For studies concerning the elucidation of structure, see: Y. Nakagawa, H. Kano, Y. Tsukuda, and H. Koyama, *Tetrahedron Lett.*, 1967, 4105. K. R. Darnall, L. B. Townsend, and R. K. Robins, *Proc. Nat. Acad. Sci. U.S.A.*, 1969, 57, 548.
2. R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Inter-Science, New York, 1970, p. 354.
3. G. D. Danes and C. C. Cheng, *Progr. Medicin. Chem.*, 1976, 13, 303.
4. L. Kalvoda, J. Farkaš, and F. Šorm, *Tetrahedron Lett.*, 1970, 2297.
5. G. Trummlitz and J. G. Moffatt, *J. Org. Chem.*, 1973, 38, 1841.
6. R. Noyori, T. Sato, and Y. Hayakawa, *J. Am. Chem. Soc.*, 1978, 100, 2561.
7. J. G. Buchanan, A. R. Edgar, M. J. Power, and C. T. Shanks, *J. Chem. Soc., Perkin Trans. I*, 1979, 225.
8. G. Just, T. J. Liak, M. -I. Lim, P. Potvin, and Y. S. Tsantrizos, *Can. J.*

*Chem.*, 1980, 58, 2024.

9. A. P. Kozikowski and A. Ames, *J. Am. Chem. Soc.*, 1981, 103, 3923.
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-ribose 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  $\beta$ -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  $\alpha$ -keto ester or  $\alpha$ -keto lactone intermediate, which was prepared by somewhat cumbersome method, was reported by several workers. Cf. references 4, 5, 6, and 8.

Received, 25th May, 1984