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STEREOCONTROLLED SYNTHESIS OF SHOWDOMYCIN AND 6-AZAPSEUDOURIDINES[1]

T. Sato, R. Ito, Y. Hayakawa, and R. Noyori*

Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

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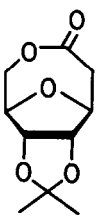
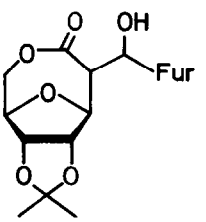
The lactone acetonide 1, having a C-β-glycoside structure, can be prepared in a stereospecific manner starting from acetone and furan.[2,3] Alternatively, this compound may be obtained by lactonization[2,4] of the corresponding seco-acid prepared from D-ribose.[5] Here we describe an aldol route to certain C-nucleoside antibiotics[6] starting with such lactone.

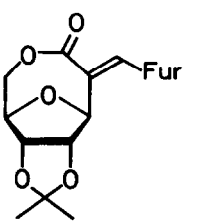
Reaction of the lactone 1 and furfural aided by lithium cyclohexylisopropylamide (THF, -78 °C, 1 hr) afforded the aldol adduct 2 (Fur = α-furyl, a single threo isomer),[7] mp 136–137 °C, in 90% yield. Dehydration of 2 was then affected by treatment with pivaloyl chloride in pyridine (25 °C, overnight) followed by heating in the same solvent at 90 °C, yielding 3[8] quantitatively. Subsequent treatment with 0.05 M methanolic sodium methoxide (0 °C, 30 min) gave the methyl ester 4 in 86% yield, whose hydroxyl group was protected by a silyl group to afford 5[9] (t-butyldimethylsilyl chloride/imidazole,[10] DMF, 25 °C, 1 hr, 100% yield).



1



2



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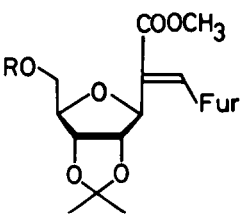
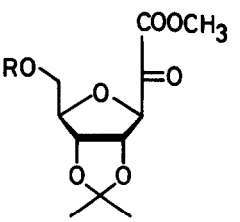
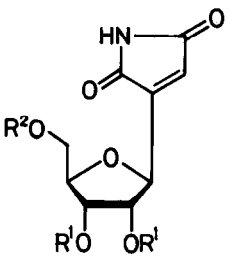


4, R = H

5, R = t-$C_4H_9(CH_3)_2Si$



6, R = t-$C_4H_9(CH_3)_2Si$



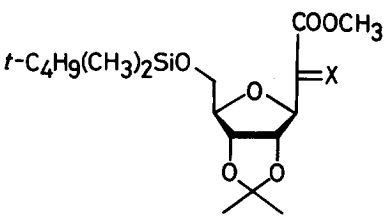
7, R^1–R^1 = $(CH_3)_2C$;
R^2 = t-$C_4H_9(CH_3)_2Si$

8, R^1 = R^2 = H

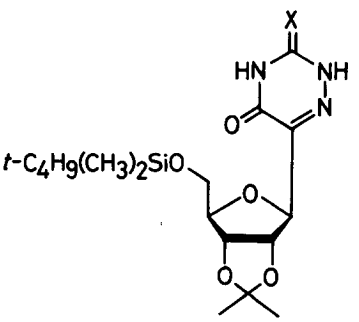
9, R^1 = $(CH_3)_2C$; R^2 = H

Ozonolysis of 5 in ethyl acetate at -78 °C followed by reductive workup with dimethyl sulfide[11] produced unstable keto ester 6,[12] which without purification was subjected to Wittig reaction with $(C_6H_5)_3PCHCONH_2$ ($CHCl_3$, 25 °C, 3.5 hr),[13] leading to 7[14] in 29% yield (based on 5). Finally, removal of the protective groups with 50% aqueous trifluoroacetic acid (25 °C, 10 min) produced showdomycin (8), identical in all respects with authentic sample.[16] Such overall transformation has been achieved without any epimerization at the anomeric center (C-1 position of ribose skeleton). Ozonolysis of 3 followed by Wittig condensation with $(C_6H_5)_3PCHCONH_2$ also gave showdomycin acetonide (9) but the yield was only 15%.

Further, the keto ester 6 serves as a precursor of certain 6-azapseudouridines.[17] For instance, condensation of crude 6 with semicarbazide hydrochloride in aqueous methanol containing sodium acetate (12 hr at 25 °C and then 6 hr at 60 °C) gave the semicarbazone 10 (syn/anti = 1:1,[18] 32% based on 5), which upon exposure to 0.1 M ethanolic sodium ethoxide (reflux, 3 hr) furnished the 6-azauracil derivative 12 in 44% yield.[19] In a similar manner, reaction of 6 and thiosemicarbazide (CH_3OH, reflux, 12 hr) afforded the thiosemicarbazone 11[20] (26% based on 5). Its cyclization with sodium ethoxide in ethanol (reflux, 3 hr) produced the 6-aza-2-thiouracil derivative 13[21] in 59% yield. Again the construction of the heterocyclic nuclei was performed under complete stereochemical control with retention of the original β configuration.



10, X = NH_2CONHN
11, X = NH_2CSNHN



12, X = O
13, X = S

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7. IR ($CHCl_3$) 3200—3600 (OH), 1728 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.48 (dd, J = 9 and 5 Hz, CHCH(OH)Fur), 5.25 (dd, J = 9 and 7 Hz, CHCH(OH)Fur).
8. IR ($CHCl_3$) 1715 (C=O), 1627 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.24 (s, =CHFur).
9. IR ($CHCl_3$) 1709 (C=O), 1634 (C=C), 831 cm^{-1} (Si—O); NMR (C_6D_6) δ 3.38 (s, OCH_3), 7.44 (s, =CHFur).
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12. IR ($CHCl_3$) 1752, 1725 cm^{-1} (C=O).
13. (a) G. Trummlitz and J. G. Moffatt, J. Org. Chem., 38, 1841 (1973); (b) S. Trippett and D. M. Walker, J. Chem. Soc., 3874 (1959).
14. IR ($CHCl_3$) 3220--3480 (NH), 1775, 1720, 1620 cm^{-1} (C=O); UV λ_{max} (CH_3OH) 221 nm (log ε 4.14); NMR ($CDCl_3$) δ 1.37, 1.59 (s, 3 H each, CH_3), 6.57 (s, =CH). Difference in chemical shift due to the acetonide methyls, $\Delta\delta_{CH_3}$ = 0.22 ppm, indicates the β configuration at the C-1 position.[15]
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17. Such C-nucleosides have been prepared only by transformation of pseudouridine: M. Bobek, J. Farkas, and F. Sorm, Tetrahedron Lett., 1543 (1968); Collect. Czech. Chem Commun., 34, 1690 (1969).

18. NMR ($CDCl_3$) δ 10.21, 11.29 (1:1 ratio, anti and syn =NNHCO protons, respectively).

19. The cyclization was carried out according to the method of G. Just and S. Kim, Can. J. Chem., 55, 427 (1977).

20. IR ($CHCl_3$) 3520, 3380, 3280 (NH), 1731, 1715 cm^{-1} (C=O); UV λ_{max} (CH_3OH) 268 (log ε 3.83), 314 nm (3.72).

21. NMR ($CDCl_3$) δ 1.38, 1.59 (s, 3 H each, CH_3), $\Delta\delta_{CH_3}$ = 0.21 ppm[15]), 9.90, 10.6 (br s, 1 H each, NH); UV λ_{max} (0.1 N HCl) 213 (log ε 3.87), 269 nm (4.15), λ_{max} (CH_3OH) 213 (log ε 3.57), 272 nm (4.08), λ_{max} (0.1 N NaOH) 226 (log ε 4.21), 258 (4.06), 313 nm (3.51).