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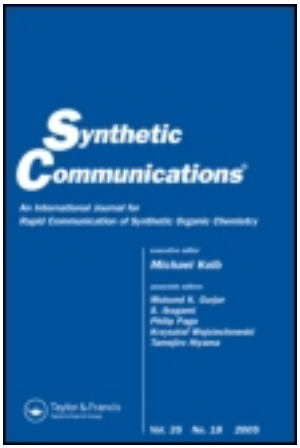

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Stereospecific C=β-Glycosidation and Synthesis of 4,7-Anhydro-5,6-isopropylidene-4 (S), 5(S), 6(R), 7(R)-Tetrahydroxyoxocan-2-one

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SYNTHETIC COMMUNICATIONS, 23(9), 1239-1244 (1993)

STEREOSPECIFIC C-β-GLYCOSIDATION AND SYNTHESIS OF 4,7-ANHYDRO-5,6-ISOPROPYLIDENE-4 (S), 5(S), 6(R), 7(R)-TETRAHYDROXYOXOCAN-2-ONE

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Abstract : Wittig reaction of 2,3-O-isopropylidene-5-O-p-anisyldiphenylmethyl-β-D-ribofuranose (2) with methoxycarbonylmethylene triphenylphosphorane was accompanied by spontaneous cyclization to generate 3 stereospecifically. Deprotection of 5-OH followed by mild base hydrolysis and cyclization with Py-Ac_2O-DBU then yielded 4,7-anhydro-5,6-isopropylidene-4(S), 5(S), 6(R), 7(R)-tetrahydroxyoxocan-2-one (5) in good overall yield.

C-Nucleosides with a carbon-carbon ribosidic linkage constitute a class of compounds having potent antitumor and antiviral properties[1]. Available methodologies[2] for C-glycosidation usually give a mixture of difficultly separable α-and β-anomers (except in Reformatsky reaction where exclusively β-ribosidation is reported[3]), though in some cases column chromatography and preparative TLC have been used to separate the anomers.

For an improved synthesis of showdomycin, an antitumor agent and other related compounds we sought a convenient method of introducing a methoxycarbonylmethyl group in C-β-orientation for the preparation of 4,7-anhydro-5,6-O-isopropylidene-4(S), 5(S),

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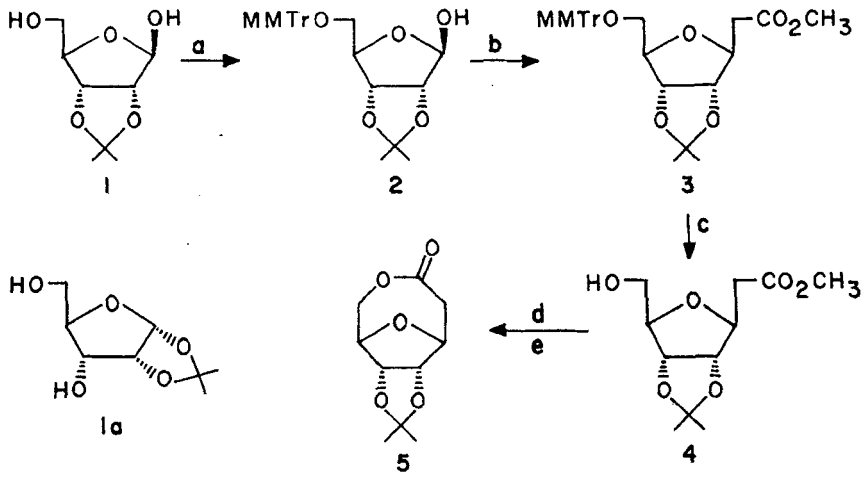
6(R), 7(R)-tetrahydroxyoxocan-2-one (5), a key intermediate[4,5a] used in the synthesis of several nucleosides.

As outlined in Scheme 1, 2,3-O-Isopropylidene-β-D-ribofuranose (1), prepared from D-ribose and acetone by modification of Levene's procedure[6], was treated with p-anisyldiphenylchloromethane (MMTrCl) in pyridine at 37°C for C-5-OH protection to furnish 2. Stereospecific Wittig reaction of the latter with methoxycarbonylmethylene triphenylphosphorane afforded exclusively C-β-glycosylated product 3 in very good yield. Methanesulphonic acid treatment of 3 in dry $CHCl_3$ at rt smoothly furnished 4 without epimerization of C-3. Subsequent attempts to hydrolyze the ester group in 4 (using sodium hydroxide in different conditions) to the intermediate hydroxy-acid followed by cyclization with Py-

Scheme I



a: MMTrCl,Py; b: $Ph_3P{=}CHCO_2CH_3$,CH_3CN; c: CH_3SO_3H,$CHCl_3$; d: NaOH (0.9 eqv, 0.1N), MeOH; e: Py-Ac_2O-DBU, 80°C

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Ac_2O to the desired bicyclic lactone 5 proved ineffective due to epimerization of the carboxymethyl group from C-β to C-α configuration. Nevertheless, the target compound 5 could be obtained in 56% yield by hydrolyzing 4 with sodium hydroxide (0.9 eqv, 0.1N , 65°C, 5 min), followed by neutralization with Dowex-50W(H^+) and dehydrative cyclization with Py-Ac_2O-DBU. The anomeric purity of 3 was evident from the observed single set of NMR signals. The β-configuration being concluded from the successful cyclization reaction of 4 affording 5.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a JASCO – 700 spectrophotometer. ^1H NMR spectra were measured on a JEOL FX-100 FT spectrometer using TMS as internal standard and the mass spectra (FI) were taken on a Hitachi RMU-6L spectrometer at 70 eV.

2,3-O-Isopropylidene-β-D-ribofuranose (1)

Concentrated H_2SO_4 (0.3 ml) was added dropwise to the stirring mixture of anhydrous ribose (5.0g) and freshly fused $CuSO_4$ in dry acetone (100 ml) cooled to -5°C. The mixture was allowed to come to rt within 2 h time period and then stirred at 40°C for 10h. It was filtered, the filtrate was neutralized with $CaCO_3$ and filtered again. The filtrate was evaporated to a syrupy residue which after purification by column chromatography [elution with EtOAc-pet.ether (9:1)] afforded 1 (3.70g, 56%) as a thick oil. Elution with pure EtOAc furnished 1a (600 mg, 9%) which was recrystallized from MeOH.

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1: 140-148°C/0.1 mm [Lit[6] 110-117°C/0.05 mm]; IR ν_{max} (Neat) : 3530 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.32 and 1.48 (2xs, 6H), 3.48-4.08 (m, 4H, CH_2OH, OH), 4.40 (brt, 1H, H-4), 4.58 (d, 1H, J=6Hz, H-3), 4.86 (d, 1H, J=6Hz, H-2), 5.42 (s, 1H, H-1).

1a: mp 60-62°C (Lit[6] 61-62°C); IR ν_{max} (KBr) : 3520 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.36 and 1.56 (2xs, 6H), 3.60-4.16 (m, 4H), 4.80 (t, 1H, J=4Hz, H-2), 5.82 (d, 1H, J=4Hz, H-1).

5-O-p-Anisyldiphenylmethyl-2,3-O-isopropylidene-β-D-ribofuranose (2)

p-Anisyldiphenylchloromethane (6.3g, 22 mmol) was added portionwise to the compound 1 (4.0g, 21 mmol) in pyridine (25 ml) and stirred at 37°C for 20h. The solvent was removed to give a syrup which was purified by column chromatography [Elution with CH_2Cl_2-MeOH (49:1)] afforded a thick sticky gum 2 (9.0g, 94%), $[\alpha]_D^{25}$ -11.5° (c 2.3, $CHCl_3$); IR ν_{max} (Neat) : 3474 (OH), 1607 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.32 and 1.48 (2xs, 6H), 3.38 (m, 2H), 4.00 (d, 1H, J=10Hz, OH), 4.34 (brt, 1H, H-4), 4.64 and 4.80 (2xd, 2H, J=6Hz, H-2, H-3), 5.33 (d, 1H, J=10Hz, H-1), 6.84 (d, 2H, Ar-H), 7.28 (m, 12H, Ar-H).

Methyl-3,6-Anhydro-2-deoxy-4,5-O-isopropylidene-7-O-p-anisyldiphenylmethyl-D-allo-heptanoate (3)

Methoxycarbonylmethylene triphenylphosphorane (8.0g, 22.8 mmol) was added portionwise to 2 (5.0g, 10.8 mmol) in dry CH_3CN (100 ml) and the mixture was heated at reflux under N_2 for 12h. The solvent removed and the desired product from the crude residue was purified by column chromatography (CH_2Cl_2-pet.ether=1:1) to furnish 3 (5.0g, 89%) as a thick stick gummy material, $[\alpha]_D^{25}$ +1.6°

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(c 2.5, $CHCl_3$); IR ν_{max} (Neat) : 1740 (CO), 1606 (Ar), 1510, 1445, 1377, 831, 762, 704 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.32 and 1.52 (2xs, 6H), 2.72 (t-like, 2H, CH_2CO), 3.20 (t-like, 2H, CH_2O-), 3.68 (s, 3H, CO_2CH_3), 3.78 (s, 3H, OCH_3), 4.08-4.72 (m, 4H, H-3, H-4, H-5, H-6), 6.88 (d, 2H, Ar-H), 7.30 (m, 12H, Ar-H); Anal. Calcd. for $C_{31}H_{34}O_7$ (518.61) : C, 71.80; H, 6.61. Found : C, 71.75; H, 6.63.

Methyl-3,6-Anhydro-2-deoxy-4,5-O-isopropylidene-D-allo-heptanoate (4)

Methanesulphonic acid (211 mg, 2.2 mmol) was added to 3 (1.04g, 2 mmol) in dry $CHCl_3$, stirred for 1.5h at rt. The $CHCl_3$ solution was washed with saturated solution of $NaHCO_3$, water, dried (Na_2SO_4) and evaporated to a crude mixture which was purified by column chromatography (CH_2Cl_2-MeOH=19:1) to give the product 4 (438 mg, 89%) as a foamy mass, $[\alpha]_D^{25}$+5.8° (c 2.0, $CHCl_3$) [Lit[5b] + 5.4° (c 1.0, $CHCl_3$)]; IR ν_{max} (Neat) : 3520 (OH), 1735 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32 and 1.53 (2xs, 6H), 2.48-2.96 (m, 3H, CH_2CO, OH), 3.70 (s, 3H, CO_2CH_3), 3.60-3.96 (m, 2H, CH_2O-), 4.02-4.40 (m, 2H, H-3, H-6), 4.50 (dd, 1H, J=8,4Hz, H-5), 4.74 (dd, 1H, J=8,4Hz, H-4).

4,7-Anhydro-5,6-O-isopropylidene-4(S), 5(S), 6(R), 7(R)-tetrahydroxyoxocan-2-one (5)

A mixture was made by adding MeOH (10.6 ml) to NaOH (44 mg, 1.1 mmol) dissolved in 0.4 ml water. The compound 4 (300 mg, 1.22 mmol) was dissolved in the above mixture, heated at 65°C for 5 min, neutralized with Dowex-50W(H^+), filtered and evaported in

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vacuo. The gummy mass after dried over P_2O_5 overnight under vacuum was dissolved in hot (80°C) pyridine (2 ml) and then treated with Ac_2O (153 mg, 1.5 mmol) and DBU (228 mg, 1.5 mmol) and kept for 30 min at 80°C. The solvent was removed and the residue was purified by column chromatography (CH_2Cl_2-pet.ether=1:9) to yield 5 (140 mg, 54%), mp 170°C (Lit[4b] 161-163°C), $[\alpha]_D^{25}$+83.75° (c 0.64, $CHCl_3$) [Lit[4b]+84° (c 0.3, $CHCl_3$)]; IR ν_{max} (KBr) : 1732 (CO), 1455, 1384, 1186, 1074, 867 cm^{-1}; ^1H NMR ($CDCl_3$); δ1.32 and 1.48 (2xs, 6H), 2.98 (d, 1H, J=4Hz, CH_2CO), 4.20-4.52 (m, 4H, CH_2O-, H-1, H-4), 4.64 (d, 1H, J=6Hz, H-3), 4.96 (d, 1H, J=6Hz, H-2), MS: M^+ at m/z 214.

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