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SYNTHESIS OF PSEUDO-*C*-NUCLEOSIDES*

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ABSTRACT

Whereas the reaction of 1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranuronamide (**1**) with the Wittig reagent ethoxycarbonylmethylenetriphenylphosphorane gave 3-(1,2-*O*-isopropylidene-β-L-threofuranos-4-yl)maleimide (**2**, 15%) and ethyl 5-carbamoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enofuranuronate (**3**, 76%), a similar reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-5-hexulofuranuronamide (**4**) gave only 3-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-erythrofuranos-4-yl)maleimide (**5**, 80%), and that of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranuronamide (**6**) gave only ethyl 3-*O*-benzyl-5-carbamoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enofuranuronate (**7**, 85%). The formation of the maleimide ring depended on the orientation and substitution of HO-3′. Compounds **2** and **5** are analogous of showdomycin.

INTRODUCTION

Pseudo-*C*-nucleosides[1] possess a C–C linkage between C-4 of the carbohydrate moiety and the heterocyclic moiety. Showdomycin[2] is a *C*-nucleoside having antitumor and antibacterial activities[2,3], which has been synthesised[4,5] as have analogues with antitumor activity[6]. We now report the synthesis of analogues of showdomycin.

RESULTS AND DISCUSSION

As part of a search for showdomycin analogues having biological activity, we have synthesized the pseudo-*C*-nucleosides 3-(1.2-*O*-isopropylidene-β-L-

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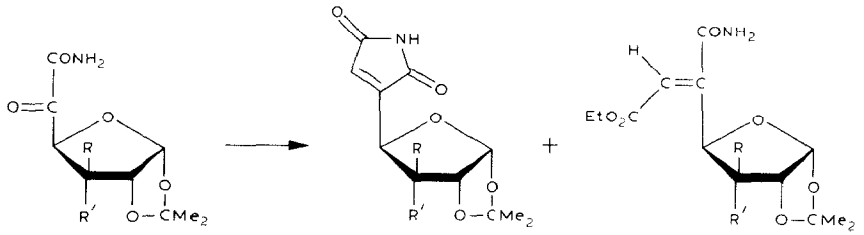


1 R = OH, R′ = H
4 R = H, R′ = OBn
6 R = OBn, R′ = H

2 R = OH, R′ = H
5 R = H, R′ = OBn

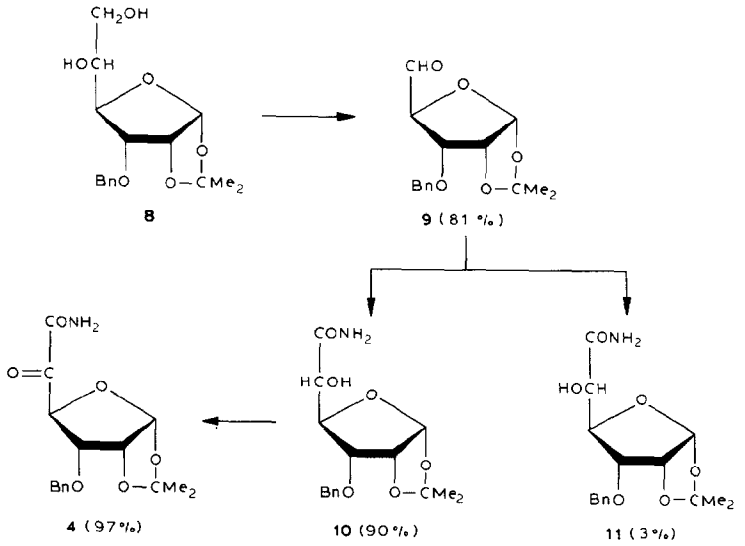
3 R = OH, R′ = H
7 R = OBn, R′ = H

threofuranos-4-yl)maleimide (**2**) and 3-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-erythrofuranos-4-yl)maleimide (**5**) *via* a Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane[7] at room temperature during 30 min in *N*,*N*-dimethylformamide (for **2**) or tetrahydrofuran–chloroform (for **5**). The substrates used were 1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranuronamide (**1**), obtained by ammonolysis in methanol at 0° of 1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranurono-6,3-lactone[8], and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-5-hexulofuranuronamide (**4**). The spontaneous cyclisation[9] of the *Z*-adduct from **4** gave the corresponding maleimide **5** in 80% yield. The orientation of HO-3 in **1** was probably responsible for the low yield (15%) of **2**, the main product (76%) being the *E*-acyclic compound **3**. The possible steric hindrance of the formation of the *Z*-intermediate was confirmed by the Wittig reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranuronamide[10] (**6**) in which no cyclisation occurred and an 85% yield of **7** was obtained.

The ^{1}H-n.m.r. spectra of **2** and **5** (see Table II) each contained a singlet for NH at δ 13.25 and 11.89, respectively. The signals for the olefinic protons appeared at δ 5.66 (d, $J_{4,4'}$ 1.5 Hz) and 5.79 (s), respectively. The unexpectedly high value (8.79 Hz) of $J_{3',4'}$ for **5** could reflect the conformation in which the interaction of the heterocyclic moiety and the benzyl group is minimised. The presence of two carbonyl groups in these molecules was confirmed by their ^{13}C-n.m.r. spectra (see Table III), which contained singlets at δ 171.29 and 171.20 for **2** and at δ 174.89 and 175.76 for **5**. The resonances of the olefinic carbons appeared at δ 130.78 (C-4) and 145.88 (C-3) for **2**, and at δ 131.77 (C-4) and 143.52 (C-3) for **5**.

The ^{1}H-n.m.r. spectra of the *E* isomers **3** and **7** each contained two singlets (δ 7.84 and 7.74, and δ 7.41 and 6.05, respectively) corresponding to the two protons of the amide group. The olefinic protons resonated at δ 6.04 ($J_{CH=,4}$ 2.3 Hz) and 6.33 ($J_{CH=,4}$ 1.8 Hz), respectively. The presence of the ethoxycarbonyl group in the molecules was also confirmed by triplets at δ 1.22 (*J* 8.2 Hz) and 1.20 (*J* 7.2 Hz) for CH_3CH_2.

The ^{13}C-n.m.r. spectrum of **3** contained signals typical for the carbonyl function of the amide and ester groups, at δ 170.31 and 165.17, respectively. The olefinic carbons resonated at δ 132.47 (C-6) and 147.99 (C-5).



Synthesis of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-5-hexulofuranuronamide (**4**) was accomplished using the procedure described[10] for **6**. Partial deacetonation of 3-*O*-benzyl-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose[11] with aqueous acetic acid gave 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose (**8**), oxidation of which to 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanose (**9**) was achieved with sodium metaperiodate. Treatment of a 1,4-dioxane solution of **9** with aqueous sodium cyanide/potassium carbonate, to give the cyanohydrins, followed immediately by the addition of hydrogen peroxide gave a mixture of the hydroxyamides **10** and **11** in a one-pot reaction. Column chromatography (10:1 ethyl acetate–methanol) of the mixture on silica gel gave 90% of 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-talofuranuronamide (**10**) and 3% of its 5-epimer **11**. Oxidation of **10** with pyridinium chlorochromate/3Å molecular sieve powder[10,12] in dichloromethane gave **4** in 97% yield.

EXPERIMENTAL

General. — Melting points were determined on a melting-point apparatus (Tottoli) and are uncorrected. The ^{1}H- and ^{13}C-n.m.r. spectra (internal Me_4Si) were recorded at 300 and 22.5 MHz, respectively, with Bruker CXP 300 and Jeol FX 90Q spectrometers. Optical rotations were determined with a Perkin–Elmer 141 polarimeter and i.r. spectra were recorded on a Perkin–Elmer 577 spectrometer. T.l.c. was performed on Silica Gel 60 F_{254} (Merck) with detection using u.v. light (254 nm) and/or 3% vanillin–sulfuric acid. Column chromatography was performed on silica gel (Merck, 230–400 mesh).

Wittig Reaction. — A solution of ethoxycarbonylmethylenetriphenylphosphorane[7] (320 mg, 1 mmol) in dry chloroform (5 mL) was added to a solution of

TABLE I

DATA FOR **1–5, 7, 9,** AND **10**

Compound	*Yield (%)*	R_F[a]	$[\alpha]_D^{20}$[e] *(degrees)*	*M.p. (degrees)*
1	99	0.21	−12[f]	70
2	15	0.60	−63.5[g]	Syrup
3	76	0.30	+13.5[g]	Syrup
4	97	0.70[b]	−1.4	Syrup
5	80	0.49	+56[h]	Syrup
7	85	0.51[c]	−31	Syrup
9	81	0.60	+87	Syrup
10	90	0.37[d]	+89[i]	142–144

[a]Ethyl acetate–toluene (2:1). [b]Ethyl acetate–methanol (10:1). [c]Ethyl acetate–toluene (1:1). [d]Ethyl acetate. [e]In chloroform (*c* 1). [f]In acetone (*c* 2). [g]In chloroform (*c* 4). [h]In chloroform (*c* 1.2). [i]In methanol (*c* 1).

TABLE II

^{1}H-N.M.R. DATA ($CDCl_3$; δ IN P.P.M., J IN Hz) FOR **1–5, 7, 9,** AND **10**

1[a] δ 7.83 (s, 1 H, NH_2), 7.72 (s, 1 H, NH_2), 5.78 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.40 (d, 1 H, $J_{HO\text{-}3,3}$ 4.1 Hz, HO-3), 5.21 (d, 1 H, $J_{3,4}$ 3.4 Hz, H-4), 4.20 (d, 1 H, H-2), 3.90 (dd, 1 H, H-3), 1.42 (s, 3 H, CMe_2), 1.27 (s, 3 H, CMe_2).

2[a] δ 13.25 (s, 1 H, NH), 5.66 (d, 1 H, $J_{4,4'}$ 1.5 Hz, H-4), 5.21 (d, 1 H, $J_{1',2'}$ 3.4 Hz, H-1'), 4.85 (d, 1 H, $J_{HO\text{-}3',3'}$ 4.2 Hz, HO-3'), 4.34 (dd, 1 H, $J_{3',4'}$ 3.0 Hz, H-4'), 4.01 (d, 1 H, H-2'), 3.78 (dd, 1 H, H-3'), 1.42 (s, 3 H, CMe_2), 1.28 (s, 3 H, CMe_2).

3[a] δ 7.84 (s, 1 H, NH_2), 7.74 (s, 1 H, NH_2), 6.04 (d, 1 H, $J_{CH=,4}$ 2.3 Hz, CH=), 5.36 (d, 1 H, $J_{HO\text{-}3,3}$ 4.1 Hz, HO-3), 4.83 (dd, 1 H, H-4), 4.59 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.31–4.00 (m, 4 H, H-2, H-3, CH_3CH_2), 1.42 (s, 3 H, CMe_2), 1.25 (s, 3 H, CMe_2), 1.22 (t, 3 H, *J* 8.2 Hz, CH_3CH_2).

4 δ 7.87 (s, 1 H, NH_2), 7.54 (s, 1 H, NH_2), 7.63–7.32 (m, 6 H, Ph, H-4), 5.87 (d, 1 H, $J_{1,2}$ 2.7 Hz, H-1), 4.93 (s, 2 H, CH_2Ph), 4.70 (t, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 4.22 (d, 1 H, H-3), 1.56 (s, 3 H, CMe_2), 143 (s, 3 H, CMe_2).

5 δ 11.89 (s, 1 H, NH), 7.37–7.34 (m, 5 H, Ph), 5.79 (s, 1 H, H-4), 4.79 and 4.75 (part A of AB system, 1 H, J_{AB} 12 Hz, CH_2Ph), 4.60–4.50 (m, 3 H, H-1', H-2', part B of AB system CH_2Ph), 4.22 (d, 1H, $J_{3',4'}$ 8.79 Hz, H-4'), 3.93 (dd, 1 H, $J_{2',3'}$ 4.2 Hz, H-3'), 1.59 (s, 3 H, CMe_2), 1.36 (s, 3 H, CMe_2).

7[b] δ 7.41 (s, 1 H, NH_2), 7.23–7.20 (m, 5 H, Ph), 6.33 (d, 1 H, $J_{CH=,4}$ 1.8 Hz, CH=), 6.05 (s, 1 H, NH_2), 5.89 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.07 (dd, 1 H, $J_{3,4}$ 3.3 Hz, H-4), 4.54, 4.49, 4.45, and 4.40 (AB system, 2 H, J_{AB} 10 Hz, CH_2Ph), 4.53 (d, 1 H, H-2), 4.21 (d, 1 H, H-3), 4.10 (q, 2 H, *J* 7.2 Hz, CH_3CH_2), 1.41 (s, 3 H, CMe_2), 1.24 (s, 3 H, CMe_2), 1.20 (t, 3 H, CH_3CH_2).

9 δ 9.61 (s, 1 H, CHO), 7.37–7.35 (m, 5 H, Ph), 5.76 (d, 1 H, $J_{3,4}$ 3.6 Hz, H-4), 4.79–4.73 (m, 2 H, H-1, part A of AB system CH_2Ph), 4.65 and 4.61 (part B of AB system, 1 H, J_{AB} 12 Hz, CH_2Ph), 4.55 (dd, 1 H, $J_{2,3}$ 9 Hz, H-3), 3.85 (dd, 1 H, $J_{1,2}$ 4.2 Hz, H-2), 1.59 (s, 3 H, CMe_2), 1.37 (s, 3 H, CMe_2).

10[c] δ 7.42–7.26 (m, 5 H, Ph), 7.10 (s, 1 H, NH_2), 6.68 (s, 1 H, NH_2), 5.74 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.07 (d, 1 H, $J_{HO\text{-}5,5}$ 4.5 Hz, HO-5), 4.73 (t, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 4.70, 4.66, 4.58, and 4.54 (AB system, 2 H, J_{AB} 12 Hz, CH_2Ph), 4.39 (d, 1 H, $J_{3,4}$ 8.70 Hz, H-4), 4.29 (d, 1 H, H-5), 4.17 (dd, 1H, H-3), 1.47 (s, 3 H, CMe_2), 1.30 (s, 3 H, CMe_2).

[a]In $(CD_3)_2SO$. [b]Recorded at 200 MHz with a Bruker WP-200 SY spectrometer. [c]In acetone-d_6.

TABLE III

^{13}C-N.M.R. DATA ($CDCl_3$; δ IN P.P.M.) FOR **1–5** AND **10**

Atom	**1**	**2**[a]	**3**	**4**	**5**[a]	**10**[b]
CH_3CH_2			14.13			
CH_2C	26.42	28.30	26.38	26.87	26.34	26.60
	27.20	28.95	27.07	28.07	26.71	26.88
CH_3CH_2			61.14			
$PhCH_2$				72.93	71.52	72.17
C-2,3,4	84.74	75.00	75.84	76.54	74.60	77.56
	85.66	77.00	81.98	76.47	76.44	78.28
	86.05	85.53	85.13	77.75	77.37	79.05
C-5	192.87[c]		147.99[d]	192.67[c]		81.71
C-1	105.36	104.70	105.09	101.48	103.54	105.16
CH_3C	112.77	112.84	112.25	115.89	112.91	112.97
CH (arom.)				128.52	127.11	128.03
				128.63	127.38	128.26
				128.95	127.59	128.41
C-arom.				138.21	138.92	138.51
HC=C		130.78	132.47		131.77	
C=CH		145.88			143.52	
C=O	165.38	171.29	165.17	172.08	174.89	168.30
	(amide)	171.20	(ester)	(amide)	175.76	
			170.31			
			(amide)			

[a]C-1/4 correspond to C-1′/4′. [b]In acetone-d_6. [c]C=O. [d]*C*=CH.

TABLE IV

I.R. SPECTRA[a] AND ELEMENTAL ANALYSES FOR **1–5, 7, 9,** AND **10**

Compound	$\nu_{C=O}$	$\nu_{C=C(arom.)}$	$\nu_{NH_2/NH}$	*Formula*	*Analysis*	
					Calc.	*Found*
1	1725		3500	$C_9H_{13}NO_6$	C 46.75	46.82
	1760				H 5.66	5.60
					N 6.05	5.98
2	1725	1630	3420	$C_{11}H_{13}NO_6$	C 51.76	51.59
	1775				H 5.13	5.25
					N 5.48	5.55
3	1680		3480	$C_{13}H_{19}NO_7$	C 51.82	51.67
	1725				H 6.35	6.48
					N 4.64	4.53
4	1730	1595	3450	$C_{16}H_{19}NO_6$	C 59.80	59.93
	1765				H 5.95	5.89
					N 4.35	4.33
5	1730	1635	3400	$C_{18}H_{19}NO_6$	C 62.60	62.73
	1780	1590			H 5.54	5.48
					N 4.05	4.15
7	1680	1600	3450	$C_{20}H_{25}NO_7$	C 61.37	61.44
	1730				H 6.43	6.39
					N 3.57	3.65
9	1730	1605		$C_{15}H_{18}O_5$	C 64.73	64.61
					H 6.51	6.58
10	1690	1595	3325[b]	$C_{16}H_{21}NO_6$	C 59.43	59.45
			3375		H 6.54	6.49
					N 4.33	4.36

[a]Film on NaCl (cm^{-1}). [b]NH_2/OH.

0.6 mmol of 5-hexulofuranuronamide in dry tetrahydrofuran (5 mL; *N,N*-dimethylformamide when reacting with **1**). The mixture was stirred for 30 min at room temperature and then concentrated, and the residue was subjected to column chromatography (ethyl acetate for the separation of **2** and **3**, or 1:10 ethyl acetate–toluene).

*1,2-O-Isopropylidene-α-*D-xylo-*5-hexulofuranuronamide* (**1**). — To a solution of 1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranurono-6,3-lactone[8] (928 mg, 4 mmol) in dry methanol (5 mL) at 0° was added methanol (20 mL) saturated with ammonia; after 20 min at 0°, the reaction was complete. The solvent was evaporated at 0° and **1** was recrystallised from acetone–benzene.

The procedures used to obtain **4** and **9–11** were exactly those described[10].

The data for all the compounds synthesised are given in Tables I–IV.

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