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A NEW METHOD OF OLIGOSACCHARIDE SYNTHESIS: RHAMNOBIOSES

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ABSTRACT

A semi-synthetic approach to (1→2)-α- and (1→3)-α-linked rhamnobioses is presented. The method involves condensation of benzyl 2-*O*- or 3-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranoside (**5**) with 1-*O*-acetyl-2,3,6-trideoxy-α,β-DL-*glycero*-hex-2-enopyranos-4-ulose (**6**), isolation of the L-L and D-L forms of the resulting disaccharide derivatives, reduction of the carbonyl groups to give α-*erythro* unsaturated products, and *cis*-hydroxylation to form the rhamnobiose derivatives. Removal of the protecting groups then gave α-L-Rha*p*-(1→2)-L-Rha*p*, α-L-Rha*p*-(1→3)-L-Rha*p*, and the corresponding D-L stereoisomers. The ^{1}H- and ^{13}C-n.m.r. data are of diagnostic value in differentiating the stereoisomers. 1-(2-Furyl)ethanol was resolved into its enantiomers, and the (+)-form was converted into (+)-**6** which in turn was condensed with **5**. The structure of the products indicated that (+)-1-(2-furyl)ethanol has the *R* configuration.

INTRODUCTION

Achmatowicz and his co-workers demonstrated the utility of 2-furylmethanols (**1**) for the synthesis of C_5–C_8 sugars[1,2]. The key intermediates in these syntheses were ald-2-enopyranos-4-uloses (**2**), which were transformed by stereocontrolled steps into the desired stereoisomeric monosaccharide.

Enulose **2** must be converted into a glycoside before the dihydropyranone ring can be modified. Glycosidation of **2** based on reactions with a trialkyl orthoformate[3] or alkyl halide in the presence of silver oxide[4] are limited to simple glycosides. However, the 1-*O*-acetyl derivative **3** can form glycosides in moderate to good yields when treated with various alcohols in the presence of stannic chloride[5]. Thus, the reaction of **3** with a protected sugar derivative containing a single, unsubstituted hydroxyl group offers a route to disaccharide derivatives[5,6]. Separation of the resulting diastereoisomers and appropriate modification of the dihydropyranone moiety constitutes a new approach to disaccharides in which the non-reducing unit can be of any required stereochemistry and be D or L. Using this approach, Grynkiewicz[6a] obtained the first semi-synthetic disaccharides, namely, the 1,2:5,6-di-*O*-isopropylidene-3-*O*-(2,3,4-tri-*O*-acetyl-α-D- and -α-L-lyxopyranosyl)-α-D-glucofuranoses.

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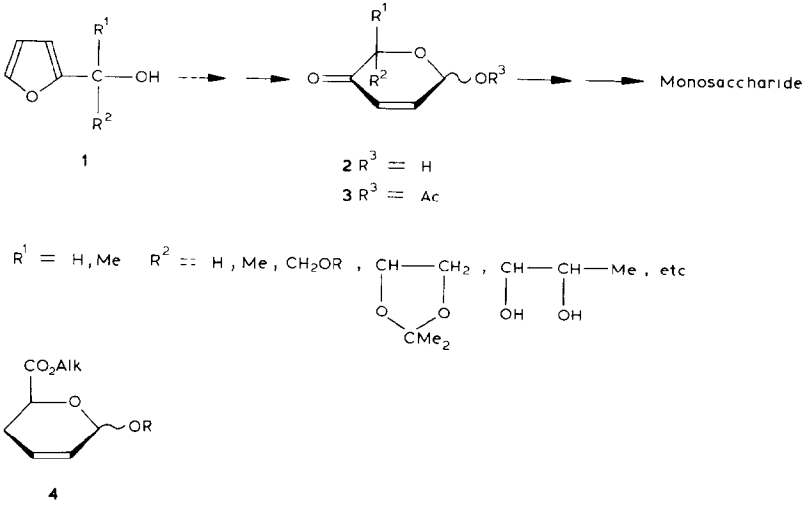


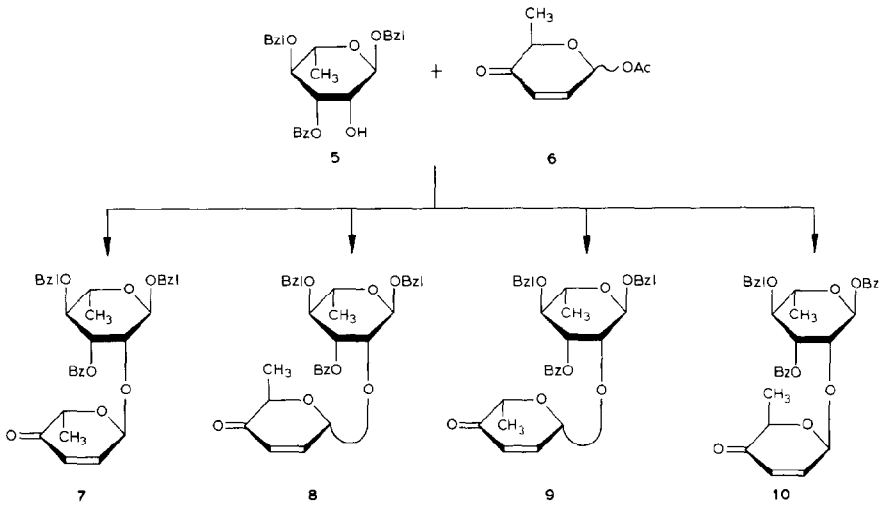
Another semi-synthetic route to oligosaccharides has been developed by David[7], in which a dihydro-2*H*-pyran derivative (**4**, where R is a protected saccharide or disaccharide) is transformed into a new sugar unit.

We have applied the 2-furylmethanol approach in the synthesis of (1→2)- and (1→3)-linked rhamnobioses. Disaccharides of this type are often encountered as structural units in bacterial polysaccharides, and several syntheses have been described[8–19].

RESULTS AND DISCUSSION

Synthesis of 2-O-α-L- *and* -D-*rhamnopyranosyl*-L-*rhamnopyranose.* — Condensation of benzyl 3-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranoside (**5**) with 1-*O*-acetyl-2,3,6-trideoxy-α,β-DL-*glycero*-hex-2-enopyranos-4-ulose[3,20] (**6**) in the presence of stannic chloride gave four isomeric products (**7**–**10**, 91% combined yield) which could be isolated by flash chromatography[21]. The ratios of products **7**–**10*** were 10:10:1:1, and the presence of (1→2) linkages in these disaccharide derivatives was indicated by ^{1}H-n.m.r. data. The signals associated with the enulose system were readily discernible in the spectra of **7**–**10**. The α linkages in **7** and **8** were reflected in the $J_{1',2'}$ and $J_{1',3'}$ values of ~3.5 and <0.5 Hz, respectively, and the β linkages in **9** and **10** by the $J_{1',2'}$ and $J_{1',3'}$ values of ~1.7 and ~1.6 Hz, respectively. However, at this stage, it was not possible to differentiate between the L-L and D-L forms (these terms are used to denote the configurations of the sugar units in the disaccharide derivatives). Compound **7**, chosen first for further modification, was shown later to be the L-L isomer.

*2,3,6-Trideoxy-L-*glycero*-hex-2-enopyranos-4-ulose (L-aculose) occurs[22] as a component of the antibiotic aclacinomycin Y1

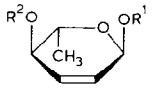


Borohydride reduction of **7** gave the expected allylic alcohol **11** in almost quantitative yield, which was characterised as the acetate **12**. Although the configuration of **11** could not be established at this stage, it was expected[20] to be *erythro*.

cis-Hydroxylation[20b] of the double bond in **12** with osmium tetraoxide afforded 90% of **13**. Acetylation then gave **14**, which was identical with benzyl 3-*O*-benzoyl-4-*O*-benzyl-2-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside obtained by condensation of **5** with 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide in the presence of mercuric cyanide. Hydrogenation (Pd/C) of **14** followed by Zemplén de-esterification gave 2-*O*-α-L-rhamnopyranosyl-L-rhamnopyranose[15].

The foregoing results establish the L-L structure for **7**, and this configuration has been confirmed by an X-ray structure determination[23]. Therefore, **8** must be the D-L isomer. The isomer **8** was subjected to the reaction sequence applied to **7**. Borohydride reduction of **8** afforded **15** and **16** in the ratio 4.6:1 (78% combined yield). The ^{1}H-n.m.r. data (Table II) of the 4-acetates (**17** and **18**) of **15** and **16** indicated the former to be the *α-erythro* and the latter to be *α-threo*. Hydroxylation of **17** with osmium tetraoxide afforded 78% of **19** which was characterised as the triacetate **20**. Deprotection of **20** yielded the hitherto unknown 2-*O*-α-D-rhamnopyranosyl-L-rhamnopyranose. The L-L and D-L (1→2)-α-linked rhamnobioses exhibited the same R_F values in t.l.c. (di-isopropyl ether–methanol, 2:1), but differed markedly in optical rotation and in ^{13}C-n.m.r. spectra (see below).

Synthesis of 3-O-α-L- *and* -α-D-*rhamnopyranosyl*-L-*rhamnopyranose.* — For the synthesis of the (1→3)-linked rhamnobioses, benzyl 2-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranoside (**21**) was condensed with **6** to afford four stereoisomeric products (77.6% combined yield). Only the main products **22** (36%) and **23** (38%) could be isolated by chromatography. These products were the L-L and D-L α-linked disaccharide derivatives, respectively. Borohydride reduction of **22** gave 80% of



11 R^1 = A, R^2 = H
12 R^1 = A, R^2 = Ac
24 R^1 = B, R^2 = H
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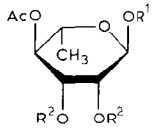

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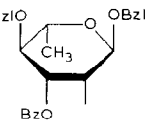

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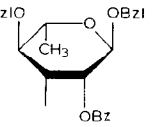
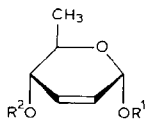
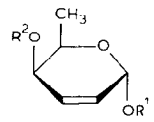




15 R^1 = A, R^2 = H
17 R^1 = A, R^2 = Ac
28 R^1 = B, R^2 = H
29 R^1 = B, R^2 = Ac



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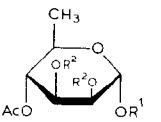
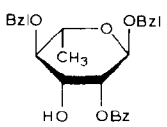


19 R^1 = A, R^2 = H
20 R^1 = A, R^2 = Ac
30 R^1 = B, R^2 = H
31 R^1 = B, R^2 = Ac



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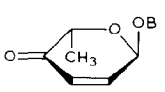

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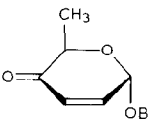


23

the *α-erythro* alcohol **24**, whereas reduction with lithium aluminum hydride, successfully employed in a similar reaction[20b], gave only 24% of **24**; the main product was **21** formed by reductive cleavage of the glycosidic bond. The *α-erythro* configuration of **24** was indicated by the ^{1}H-n.m.r. data of the acetylated derivative **25** (Table II). Hydroxylation of **25** with *N*-methylmorpholine *N*-oxide in the presence of a catalytic amount of OsO_4 yielded the expected product **26**, which was acetylated to give **27** identical with benzyl 2-*O*-benzoyl-4-*O*-benzyl-3-*O*-(2,3,4-tri-*O*-acetyl-*α*-L-rhamnopyranosyl)-L-rhamnopyranoside (obtained by condensation of 2,3,4-tri-*O*-acetyl-*α*-L-rhamnopyranosyl bromide with **21**). Thus, **22** was the L-L stereoisomer. Deprotection of **27** in the usual way gave known[15] 3-*O*-*α*-L-rhamnopyranosyl-L-rhamnopyranose.

Application to **23** of the reaction sequence described above for **22** gave the *α-erythro* alcohol **28** (characterised as the 4-acetate **29**), the *cis*-hydroxylated product **30** (characterised as the triacetate **31**), and 3-*O*-*α*-D-rhamnopyranosyl-*α*-L-rhamnopyranose.

TABLE I

^{13}C-N.M.R. DATA FOR 2-*O*-α- AND 3-*O*-α-RHAMNOPYRANOSYL-L-RHAMNOPYRANOSES[a]

	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-1'*	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*
α-L-Rha*p*-(1→2)-L-Rha*p*	93.4	79.9	70.8	73.1	69.2	17.6	102.9	70.5	70.8	72.8	69.9	17.4
$\Delta\delta^b$	−1.4	+8.3	0	+0.1	+0.1	—	+8.1	—	—	—	—	—
α-D-Rha*p*-(1→2)-L-Rha*p*	91.7	76.5	70.9	72.8	69.4	17.6	99.1	71.2	70.0	72.8	69.6	17.3
$\Delta\delta^b$	−3.1	+4.9	+0.1	−0.2	+0.3	—	+4.3	—	—	—	—	—
α-L-Rha*p*-(1→3)-L-Rha*p*	94.7	70.9	78.5	72.4	69.2	17.4	103.1	71.4	70.9	72.8	69.8	17.6
$\Delta\delta^b$	−0.1	−0.7	+7.7	−0.6	+0.1	—	+8.3	—	—	—	—	—
α-D-Rha*p*-(1→3)-L-Rha*p*	94.6	71.2	75.1	72.8	69.1	17.3	97.2	71.2	71.0	72.8	69.4	17.7
$\Delta\delta^b$	−0.2	−0.4	+4.3	−0.2	0	—	+2.4	—	—	—	—	—

[a]For solutions in D_2O. The assignment of signals for D-L compounds was based on comparison with the spectra of L-L compounds. [b]$\Delta\delta = \delta_{C(disaccharide)} - \delta_{C(L\text{-rhamnose})}$.

TABLE II

^{1}H-N M R DATA (100 MHZ, $CDCl_3$) FOR THE BENZYL RHAMNOSIDE DERIVATIVES **5** AND **21**, DISACCHARIDE PRECURSORS, AND RHAMNOBIOSE DERIVATIVES[a]

Compound	*Unit*	*Chemical shifts (δ)*						*Coupling constants (Hz, first order)*					
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
5	—	4.84	4.24	5.54	3 71	3 96	1 37	2 0	—	3 0	9 3	9 3	6 0
21	—	4.94	5 39	4 27	3 49	3.84	1.38	1.7	—	3.3	9.0	9.5	6.0
7	N[b]	5.15	6 70	6.07	—	4.55	1.21	3.5	<0.5	10.5	—	—	6.0
	R[b]	4.89	4.31	5.64	3 69	3.89	1 41	2.0	—	3.5	9 0	9 5	6.0
8	N	5.12	6.75	6.02	—	4.60	0.75	3.5	<0.5	10.5	—	—	6.0
	R	4.88	4.60	5.61	3.73	3 92	1 37	1 75	—	3.5	9.0	9.0	6.0
9	N	5 37	6 77	6.00	—	4.5–4.9	0.92	1.8	1 6	10.5	—	—	6.5
	R	4.91	4.41	5.51	3.73	3.83	1.36	1 75	—	3.5	9.0	9 0	6.0
10	N	5.32	6.84	6.06	—	4.4–5.0	1.25	1.7	1.6	10.5	—	—	6.5
	R	5 03	4.32	5.53	3 73	3.0	1.36	1.75	—	3.3	9.5	9.5	6.0
12	N	4.97	5.80	5.80	4 7–5.1	3.83	1.01	[c]	[c]	[c]	[c]	[c]	6.5
	R	4 88	4.24	5.57	3.68	3.83	1.41	[c]	—	3.5	9.0	9.0	6.0
14	N	4.5–4.9	5.2	5.9	5.02	3 88	1 04	[c]	[c]	[c]	9 25	9 25	6 0
	R	4.5–4.9	4.16	5.64	3.76	3 88	1 34	[c]	—	3.5	9 5	9.5	6.0
16	N	4.5–5.0	5.84	6 13	4.5–5.0	3.91	0.69	1.9	—	9.8	9.3	—	6.5
	R	4.5–5.0	4.47	5 57	3.70	3 91	1.34	[c]	—	3.5	9.0	9.0	6.0
17	N	4 95	5.89	5.89	4.5–5.0	3.87	0.61	[c]	[c]	[c]	[c]	[c]	6.5
	R	4 86	4.44	5.58	3.74	3.87	1.38	[c]	—	3.5	9.0	9.0	6.0
18	N	4.5–5.0	6.03	6.03	4.5–5 0	3.95	0.59	[c]	[c]		[c]	[c]	6.2
	R	4.5–5.0	4.47	5.59	3.73	3.95	1.34	[c]	—	3.5	9.0	9.0	6.0
20	N	4.7–4.9	5.30	5.38	4 91	3.84	0.71	[c]	—	3.3	9 3	9.3	6.0
	R	4.7–4.9	4.32	5.53	3.78	3.84	1.35	[c]	—	3.5	9.0	9.0	6.0
22	N	5.39	6.54	5.93	—	4.47	1.35	3.5	<0.5	10.3	—	—	6 0
	R	4.95	5 57	4.35	3.61	3 84	1 41	1 75	—	3.5	9.0	9.5	6.0
23	N	5.41	6.70	5.98	—	4.49	1.17	3.5	<0.5	10.5	—	—	6.0
	R	4.92	5.64	4.45	3.51	3.96	1.40	[c]	—	3.5	9.5	9.0	6 0
25	N	5.21	5.6	5.8	4.94	3.85	1 19	[c]	[c]	[c]	[c]	9.3	6.0
	R	4.94	5.54	4 33	3.60	3.85	1.35	[c]	—	3.5	9.5	9.3	6.0
27	N	4.9–5 3	4.9		5.5	3.83	1.06	[c]	—	[c]	[c]	[c]	6.0
	R	4 9–5.3	5.38	4 28	3.63	3.83	1.34	[c]	—	3.5	9.0	9 5	6.0
29	N	5.25	5.67	5.78	5.00	3.93	0 98	[c]	[c]	[c]	[c]	9.0	6.5
	R	5.09	5.59	4 54	3.48	3.93	1.36	[c]	—	3.5	9.5	9 5	6.0
31	N	4.8–5 2	4.80		5.40	3 96	1.05	[c]	—	[c]	—	[c]	6.0
	R	4.8–5.2	5 54	4.31	3.53	3.96	1.40	[c]	—	3.5	9.0	9 0	6.0

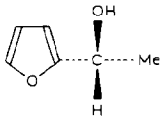
[a]Signals of acetyl, benzoyl, and benzyl protons are omitted [b]N, non-reducing unit; R, reducing unit. [c]Not determined.

Table I contains the ^{13}C-n.m.r. data for the four rhamnobioses. The markedly reduced α-shifts of the signals for carbon atoms participating in the glycoside linkage in the case of the D-L disaccharides is noteworthy.

The ^{1}H-n.m.r. data recorded in Table II show that, whereas the Me-5 protons (reducing unit) resonate within a narrow range (δ 1.35–1.41), the chemical shift of the Me-5′ protons (non-reducing unit) depends on whether the sugar moiety is D or L. Thus, for (1→2)-α-linked L-L compounds, the Me-5′ doublet occurs in the range δ 1.01–1.21; for the D-L compounds, it is in the range δ 0.61–0.75. For the (1→3)-α-linked compounds, these differences occur but they are less pronounced. Dreiding models with φ and ψ angles of ~35° and ~10°, respectively (*cf.* 33° and 13° estimated from the X-ray determination[23] of **7**) reveal that, for the (1→2)-α-linked D-L compounds, Me-5′ approaches BzO-3 very closely, whereas there is no such interaction for the L-L series. For the (1→3)-α-linked D-L disaccharides, Me-5 approaches BzO-1; however, the distance from the aromatic ring is greater than in the former compounds. Similar upfield shifts of the Me-5 resonances of rhamnose units in oligosaccharides protected with aromatic groups have been observed[18,24,25] and interpreted in terms of anisotropic shielding of the aromatic rings. In our work, this upfield shift helped in identifying the D-L configuration during the synthesis of rhamnotrioses[26].

The syntheses described above would be simplified by using one enantiomer of the enulose **6**. 1-(2-Furyl)ethanol, the starting substance for the synthesis of **6**, was resolved into enantiomers[27] by fractional crystallisation of the phthalic acid ester salt with quinine. Racemic **1** (R^1 = H, R^2 = Me) was resolved by crystallisation of its (−)-ω-camphanyl ester[28], and (+)-1-(2-furyl)ethanol was then converted into (+)-**6**. Condensation of (+)-**6** with **5** gave **8** (major) and **10** (minor), thereby establishing the *R* configuration of (+)-1-(2-furyl)ethanol (**32**), and the D-L configuration of **10**.

In the synthesis described above, the pyranone unit was modified by reduction of the 4′-carbonyl group and *cis*-hydroxylation of the double bond to give the rhamnopyranose structure, but other types of reaction can be readily envisaged, leading to a variety of other structures. Also, following hydroxylation of the non-reducing unit, selective protection should be possible, thereby providing a route for the synthesis of trisaccharides. This strategy is described in the following paper[26].



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EXPERIMENTAL

N.m.r. spectra were recorded with Jeol JNM-4H-100 (^{1}H) and 90-Q (^{13}C)

spectrometers. I.r. spectra were recorded with Unicam SP-200 and Beckman IR 4240 spectrophotometers. Optical rotations were measured with a Perkin–Elmer 141 polarimeter at 18°.

For column chromatography, MN silica gel (<0.8) and Merck silica gel 60 (230–400 mesh) were used. Merck silica gel was used for t.l.c.

Acetylations were performed conventionally with acetic anhydride and pyridine.

1-(2-Furyl)ethanol (b.p. 60–61°/10 Torr) was obtained (89%) from 2-furaldehyde and methylmagnesium bromide. 1-*O*-Acetyl-2,3,6-trideoxy-α,β-DL-*glycero*-hex-2-enopyranos-4-ulose (**6**) was prepared by a reported method[20].

Resolution of 1-(2-furyl)ethanol. — A solution of 1-(2-furyl)ethanol (8 g) in dry pyridine (150 mL) was treated with (−)-ω-camphanyl chloride[28] (21 g). After 22 h at room temperature, the mixture was poured into cold water and extracted with chloroform. The extract was washed with water, aqueous 5% hydrochloric acid, and water, dried, and concentrated. The residue (~15.2 g) was eluted from a short column of silica gel with light petroleum–ethyl acetate (4:1), to give the crystalline ester (14.8 g, 97.4%), which gave six ^{1}H-n.m.r. signals for camphanyl methyl groups representing both diastereoisomeric forms. Five recrystallisations of the mixture from light petroleum–ether (2:1) gave a pure diastereoisomer (7.1 g), m.p. 74–75.5°, $[\alpha]_D$ −89° (*c* 0.7, chloroform); ν_{max}^{KBr} 1790, 1740, 1500, 1010, 880, and 740 cm^{-1}. N.m.r. data ($CDCl_3$): δ 1.09, 0.98, and 0.90 (3 Me). From the mother liquors, the second diastereoisomer was isolated (6 g); m.p. 73.5–75°, $[\alpha]_D$ +66° (*c* 0.6, chloroform); ν_{max}^{KBr} 1775, 1735, 1505, 1010, 890, and 750 cm^{-1}. N.m.r. data: δ 1.10, 1.02, and 0.83 (3 Me).

Anal. Calc. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.72; H, 6.96.

(+)-1R-*(2-Furyl)ethanol* (**32**). — The above (+)-diastereoisomer (5.2 g) was treated with boiling 2M NaOH in 1:1 ethanol–water (50 mL) for 1.5 h. The cooled mixture was extracted with ether, the extract was dried and concentrated, and the residue was distilled at 60–61°/10 Torr to give **32** (1.39 g, 70.2%) $[\alpha]_D$ +15° (*c* 1.4, chloroform).

From (+)-1*R*-(2-furyl)ethanol, 1-*O*-acetyl-2,3,6-trideoxy-α,β-D-*glycero*-hex-2-enopyranos-4-ulose, $[\alpha]_D$ +90° (*c* 1.95, chloroform), was obtained according to the reported procedure[20].

Benzyl 3-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside (**5**), *benzyl 2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside* (**21**), *and benzyl 2,3-di-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside.* — To a solution of benzyl 4-*O*-benzyl-α-L-rhamnopyranoside[29] (16 g, 46.5 mmol) in dichloromethane (92 mL) was added benzoic anhydride (14.4 g, 69.7 mmol). The mixture was cooled to 5° and triethylamine (9.28 mL) was added. The mixture was left at room temperature for 16 h, washed with water, dried, and concentrated. The residue was eluted from a column of silica gel with light petroleum–ethyl acetate (9:1).

Eluted first was **21** (6.3 g, 30.3%), m.p. 99–100°, $[\alpha]_D$ −1° (*c* 1.8, chloroform); $\nu_{max}^{CHCl_3}$ 3580, 1720, 1600, 1580, 1490, 1265, 1110, 1090, 1060, and 1022 cm^{-1}. See Table II for ^{1}H-n.m.r. data.

Anal. Calc. for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 72.27; H, 6.20.

Eluted second was **5** (6.2 g, 29.8%), m.p. 83–83.5° (from light petroleum–ether, 7:3), $[\alpha]_D$ −2° (*c* 2.6, chloroform); $\nu_{max}^{CHCl_3}$ 3590, 1720, 1600, 1580, 1450, 1270, 1110, 1090, 1060, and 1020 cm^{-1}. See Table II for ^{1}H-n.m.r. data.

Anal. Found: C, 72.02; H, 6.27.

Eluted third was starting material (6.5 g).

When the reaction mixture was left for 72 h, then, in addition to **21**, **5**, and the starting material, benzyl 2,3-di-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranoside (3.3%) was obtained; m.p. 75–77° $[\alpha]_D$ +53° (*c* 1.7, chloroform); $\nu_{max}^{CHCl_3}$ 1720, 1690, 1600, 1580, 1490, 1450, 1270, 1260, 1100, 1090, and 1060 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.79 (q, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 9.0 Hz, H-3), 5.69 (q, 1 H, $J_{1,2}$ 1.75 Hz, H-2), 5.0 (d, 1 H, H-1), 4.06 (dq, 1 H, $J_{4,5}$ 9.3, $J_{5,6}$ 6.0 Hz, H-5), 3.81 (t, 1 H, H-4), and 1.45 (d, 3 H, Me-5).

Anal. Calc. for $C_{34}H_{32}O_7$: C, 73.89; H, 5.84. Found: C, 73.69; H, 5.95.

Benzyl 3-O-benzoyl-4-O-benzyl-2-O-(2,3,6-trideoxy-α-L-, -α-D-, -β-L-, and -β-D-hex-2-enopyranosyl-4-ulose)-α-L-rhamnopyranosides (**7–10**). — To a solution of **5** (2.95 g, 6.5 mmol) and **6** (1.33 g, 7.8 mmol) in 1,2-dichloroethane (15 mL) was added stannic chloride (0.45 mL; a M solution in 1,2-dichloroethane). After 3 h at room temperature, the mixture was diluted with dichloromethane (60 mL) and quickly washed with aqueous 5% sodium hydrogencarbonate and twice with water, dried, and concentrated. The oily residue (3.5 g) was subjected to flash chromatography with light petroleum–ethyl acetate (4:1).

Eluted first was **7** (1.504 g, 41%), m.p. 98–100° (from aqueous ethanol), $[\alpha]_D$ +31° (*c* 2.1, chloroform); ν_{max}^{KBr} 1720, 1695, 1460, 1270, 1110, 1090, 1060, 1025, 750, 710, and 700 cm^{-1}.

Anal. Calc. for $C_{33}H_{34}O_8$: C, 70.95; H, 6.14. Found: C, 70.74; H, 6.15.

Eluted second was **8** (1.522 g, 41%) as a syrup, $[\alpha]_D$ −12° (*c* 1.7, chloroform); ν_{max}^{film} 1722, 1700, 1460, 1280, 1110, 1090, 1070, 1030, 740, and 695 cm^{-1}.

Anal. Found: C, 71.20; H, 6.31.

Eluted third was **9** (0.144 g, 3.9%) as a syrup, $[\alpha]_D$ −28° (*c* 1.6, chloroform); ν_{max}^{film} 1722, 1700, 1460, 1270, 1100, 1060, 1030, 750, 730, 710, and 695 cm^{-1}.

Anal. Found: C, 70.77; H, 6.30.

Eluted fourth was **10** (0.156 g, 4.3%) as a syrup, $[\alpha]_D$ ~0° (*c* 1.2, chloroform); ν_{max}^{film} 1720, 1700, 1460, 1270, 1100, 1060, 1030, 750, 740, 710, and 695 cm^{-1}.

Anal. Found: C, 70.91; H, 6.31.

Condensation of **5** (879 mg) with (+)-**6** (357 mg), according to the above method, gave, after chromatography, **8** (803 mg, 72%), $[\alpha]_D$ −13° (*c* 0.8, chloroform), and **10** (109 mg, 16.9%).

Benzyl 2-O-(4-O-acetyl-2,3,6-trideoxy-α-L-erythro-hex-2-enopyranosyl)-3-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside (**12**). — To a solution of sodium borohydride (2.2 g) in water (4 mL) and tetrahydrofuran (15 mL) was added, dropwise, a solution of **2** (1.32 g) in tetrahydrofuran (10 mL). The mixture was stirred for 1.5 h, poured into cold water, and extracted with ether, and the extract was dried and concentrated to give **11** (1.28 g, 96%), m.p. 145–146° (from methanol).

Acetylation of **11** gave **12** (1.38 g, 97%) as a syrup, $[\alpha]_D$ −29° (*c* 1.5, chloroform); ν_{max}^{film} 1742, 1730, 1660, 1460, 1278, 1240, 1110, 1070, 1060, 1030, 750, 740, 710, and 695 cm^{-1}.

Anal. Calc. for $C_{35}H_{38}O_9$: C, 69.75; H, 6.36. Found: C, 69.26; H, 6.48.

Benzyl 3-O-benzoyl-4-O-benzyl-2-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**14**). — (*a*) A solution of osmium tetraoxide (300 mg) in pyridine (1.2 mL) was added to a solution of **12** (551 mg) in pyridine (3 mL), and the mixture was stirred at room temperature for 3 days. A solution of sodium hydrogensulphite (600 mg) in pyridine (6 mL) and water (9 mL) was then added and the stirring was continued for 2 days. The mixture was diluted with water (100 mL) and extracted with several portions of dichloromethane. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. The resulting, thick syrup was eluted from a short column of silica gel with light petroleum–ethyl acetate (2:1) to give **13** (520 mg), which was acetylated to yield **14** as a syrup, $[\alpha]_D$ −42° (*c* 1.4, chloroform); ν_{max}^{film} 1755, 1725, 1460, 1270, 1250, 1220, 1100, 1080, 1055, 1045, 740, 730, 700, and 690 cm^{-1}.

Anal. Calc. for $C_{39}H_{44}O_{13}$: C, 64.99; H, 6.15. Found: C, 64.79; H, 6.38.

(*b*) To a solution of **5** (2.88 g) and mercuric cyanide (1.62 g) in nitromethane–benzene (1:1, 50 mL) was added a solution of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide (2.43 g) in benzene (3 mL), with stirring under nitrogen. Stirring was continued for 2 days at room temperature and then for 5 h at 65–70°. The mixture was concentrated under reduced pressure and a solution of the residue in chloroform (100 mL) was filtered, washed several times with aqueous 5% potassium iodide and water, dried, and concentrated. The residue was eluted from a column of silica gel with 9:1 benzene–ether. Two fractions were obtained. Eluted first was **14** (1.47 g, 34.7%) as a syrup, $[\alpha]_D$ −45° (*c* 0.6, chloroform). Eluted second was a mixture of two compounds (0.86 g) which was not analysed further.

2-O-α-L-Rhamnopyranosyl-L-rhamnose. — A solution of **14** (650 mg) in ethanol (15 mL) was hydrogenated at 1 atm. in the presence of 10% Pd/C. The catalyst was then filtered off and the solution was concentrated to dryness. To a solution of the residue in methanol (40 mL) was added sodium (240 mg), and the mixture was left for 12 h, neutralised with Amberlite IR-120 (H^+) resin, and concentrated to dryness. The residue was eluted from a column of silica gel with benzene to remove methyl benzoate, and then with methanol to give the title product (233 mg, 83.5%), $[\alpha]_D$ −29° (*c* 0.8, water), R_F 0.24 (t.l.c.; di-isopropyl ether–methanol, 2:1), lit. $[\alpha]_D$ −24° (*c* 0.8, water)[15] and −28.7° (water)[9]. See Table I for ^{13}C-n.m.r. data.

*Benzyl 2-O-(4-O-acetyl-2,3,6-trideoxy-α-D-*erythro- *and -α-D-*threo*-hex-2-enopyranosyl)-3-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside* (**17** and **18**). — Reduction of **8** (1.1 g) with sodium borohydride, as described above for **7**, followed by column chromatography (light petroleum–ethyl acetate, 7:2) of the product, gave, first, the *α-erythro* compound **15** (639 mg, 64%), acetylation of which afforded

17 as a syrup, $[\alpha]_D$ +51° (*c* 1.9, chloroform); ν_{max}^{film} 1740, 1720, 1650, 1460, 1270, 1234, 1100, 1065, 1025, 745, 730, 705, and 690 cm^{-1}.

Anal. Calc. for $C_{35}H_{38}O_9$: C, 69.75; H, 6.36. Found: C, 70.10; H, 6.72.

Eluted second was the *α-threo* compound **16** (138 mg, 13.8%), acetylation of which gave **18** as a syrup, $[\alpha]_D$ −41° (*c* 1.7, chloroform); ν_{max}^{film} 1720, 1460, 1280, 1240, 1100, 1070, 1020, 750, 710, and 690 cm^{-1}.

Anal. Found: C, 69.43; H, 6.45.

Benzyl 3-O-benzoyl-4-O-benzyl-2-O-(2,3,4-tri-O-acetyl-α-D-rhamnopyranosyl)-α-L-rhamnopyranoside (**20**). — *cis*-Hydroxylation of **17** (2.15 g), as described for **12**, and elution of the product from a column of a silica gel with 1:1 light petroleum–ethyl acetate gave the diol **19** (1.79 g, 78%), which was acetylated to give **20** as a thick syrup, $[\alpha]_D$ +51° (*c* 1.05, chloroform); ν_{max}^{film} 1750, 1720, 1460, 1270, 1240, 1220, 1100, 1085, 1070, 1050, 1020, 740, 730, 705, and 690 cm^{-1}.

Anal. Calc. for $C_{39}H_{44}O_{13}$: C, 64.99; H, 6.15. Found: C, 64.84; H, 6.22.

2-O-α-D-Rhamnopyranosyl-L-rhamnose. — Deprotection of **20**, as described for the L-L stereoisomer, gave the amorphous title disaccharide (86%); $[\alpha]_D$ +49° (*c* 0.6, ethanol), R_F 0.24 (t.l.c.; di-isopropyl ether–methanol, 2:1). See Table I for the ^{13}C-n.m.r. data.

The hexa-acetate had $[\alpha]_D$ +30° (*c* 0.3, chloroform).

Anal. Calc. for $C_{24}H_{34}O_{15}$: C, 51.24; H, 6.09. Found: C, 51.43; H, 6.34.

Benzyl 2-O-benzoyl-4-O-benzyl-3-O-(2,3,6-trideoxy-α-L- and -α-D-glycero-hex-2-enopyranosyl-4-ulose)-α-L-rhamnopyranoside (**22** and **23**). — A solution of **21** (2.5 g) and **6** (1.22 g) in 1,2-dichloroethane (16 mL) was treated with M stannic chloride in 1,2-dichloroethane (0.25 mL). After 2 h at room temperature, the mixture was diluted with dichloromethane (50 mL) and worked-up as described for **7–10**. Flash chromatography afforded, first, **23** (1.16 g, 37.7%), m.p. 65–67° (from light petroleum–ether–methanol, 90:10:2), $[\alpha]_D$ +5° (*c* 1.2, chloroform); ν_{max}^{KBr} 1730, 1695, 1460, 1110, 1080, 1060, 1020, 740, 700, and 680 cm^{-1}.

Anal. Calc. for $C_{33}H_{34}O_8$: C, 70.95; H, 6.14. Found: C, 71.18; H, 6.41.

Eluted second was **22** (1.09 g, 35.5%) as an oil, $[\alpha]_D$ +22° (*c* 2.7, chloroform); $\nu_{max}^{CHCl_3}$ 1715, 1700, 1455, 1260, 1100, 1060, 1035, 1020, and 1000 cm^{-1}.

Anal. Found: C, 70.88; H, 6.34.

Eluted third was a mixture (0.14 g, 4.4%) of two compounds which was not analysed further.

*Benzyl 3-O-(4-O-acetyl-2,3,6-trideoxy-α-L-*erythro-*hex-2-enopyranosyl)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside* (**25**). — Compound **22** (3.19 g) was reduced with sodium borohydride, as described for **7**, to give **24** (2.57 g, 80%). Acetylation afforded **25** as a thick syrup, $[\alpha]_D$ −20° (*c* 2.6, chloroform); ν_{max}^{film} 1720, 1700, 1620, 1460, 1265, 1230, 1100, 1060, 1040, 1000, 740, 730, 700, and 690 cm^{-1}.

Anal. Calc. for $C_{35}H_{38}O_9$: C, 69.75; H, 6.36. Found: C, 70.01; H, 6.36.

Benzyl 2-O-benzoyl-4-O-benzyl-3-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**27**). — (*a*) The *cis*-hydroxylation reagent was prepared from *N*-methylmorpholine (300 mg), *tert*-butyl alcohol (3 mL), water (1 mL), and a few crystals of osmium tetraoxide.

A solution of **25** (622 mg) in tetrahydrofuran (3 mL) was added, and the mixture was stirred at room temperature for 3 days and then diluted with water (30 mL). Aqueous 40% sodium hydrogensulfite (0.3 mL) was added, followed by Florisil (0.2 g), and stirring was continued for 2 h. The mixture was filtered and extracted with ethyl acetate, and the extract was dried and concentrated. The residue was eluted from a column of silica gel with 1:1 light petroleum–ethyl acetate to give **26** (393 mg, 60%) as a syrup. Acetylation gave **27**, m.p. 45–49°, $[\alpha]_D$ −31° (*c* 1, chloroform); ν_{max}^{KBr} 1755, 1720, 1460, 1260, 1240, 1215, 1100, 1080, 1060, 740, 730, and 690 cm^{-1}.

Anal. Calc. for $C_{39}H_{44}O_{13}$: C, 64.99; H, 6.15. Found: C, 64.94; H, 6.18.

(*b*) Condensation of **21** (2.67 g) and 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide (2.26 g) in the presence of mercuric cyanide (as described for **14**) gave **27** (2.1 g, 62.7%), $[\alpha]_D$ −32° (*c* 1.1, chloroform).

3-O-α-L-Rhamnopyranosyl-L-rhamnose. — Deprotection of **27** (484 mg), as described for **14**, gave the title disaccharide (200 mg, 95.3%) as a glass, $[\alpha]_D$ −39° (*c* 0.3, water); lit.[10] $[\alpha]_D$ −41° (*c* 0.9, water). See Table I for the ^{13}C-n.m.r. data.

Benzyl 3-O-(4-O-acetyl-2,3,6-trideoxy-α-D-erythro-hex-2-enopyranosyl)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside (**29**). — Reduction of **23** (4.72 g) with sodium borohydride, as described for **7**, and elution of the products from a column of silica gel with 2:1 light petroleum–ethyl acetate gave, first, **28** (3.34 g, 70%), acetylation of which gave **29**, $[\alpha]_D$ +31° (*c* 1.5, chloroform); ν_{max}^{film} 1735, 1720, 1460, 1265, 1230, 1110, 1090, 1050, 1030, 730, 700, and 690 cm^{-1}.

Anal. Calc. for $C_{35}H_{38}O_9$: C, 69.75; H, 6.36. Found: C, 69.80; H, 6.60.

Eluted second was a mixture (0.95 g) of **28** and another product, possibly the *α-threo* stereoisomer of **28**.

Eluted third was unchanged **23** (0.22 g).

Benzyl 2-O-benzoyl-4-O-benzyl-3-O-(2,3,4-tri-O-acetyl-α-D-rhamnopyranosyl)-α-L-rhamnopyranoside (**31**). — Compound **28** (583 mg) was *cis*-hydroxylated as described for **12**, to give **30** (507 mg, 83%), m.p. 146–147°. Acetylation gave amorphous **31**, $[\alpha]_D$ +56° (*c* 0.8, chloroform); ν_{max}^{KBr} 1750, 1725, 1460, 1265, 1242, 1220, 1110. 1090, 1050, 750, 730, 710, and 690 cm^{-1}.

Anal. Calc. for $C_{39}H_{44}O_{13}$: C, 64.99; H, 6.15. Found: C, 64.63; H, 6.10.

3-O-α-D-Rhamnopyranosyl-L-rhamnose. — Removal of the protecting groups from **31** gave the amorphous title disaccharide (84.3%), $[\alpha]_D$ +44° (*c* 0.35, ethanol). See Table I for the ^{13}C-n.m.r. data.

The hexa-acetate had $[\alpha]_D$ +24.5° (*c* 0.4, chloroform); ν_{max}^{KBr} 1765, 1230, 1100, and 1060 cm^{-1}.

Anal. Calc. for $C_{24}H_{34}O_{15}$: C, 51.38; H, 6.16. Found: C, 52.00; H, 6.44.

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