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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF SUBSTITUTED 2,6-DIOXABICYCLO[3.1.1.]HEPTANES: 1,3-ANHYDRO-2,4-DI-*O*-BENZYL- AND -2,4-DI-*O*-(*p*-BROMOBENZYL)-β-L-RHAMNOPYRANOSE*

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ABSTRACT

The synthesis of 1,3-anhydro-2,4-di-*O*-benzyl- and 1,3-anhydro-2,4-di-*O*-(*p*-bromobenzyl)-β-L-rhamnopyranose was achieved *via* 8 steps, with L-rhamnose as the starting material. The key intermediates for the synthesis were 3-*O*-acetyl-2,4-di-*O*-benzyl- and 3-*O*-acetyl-2,4-di-*O*-(*p*-bromobenzyl)-α-L-rhamnopyranosyl chloride that were transformable into the target compounds by ring closure with potassium *tert*-butoxide. Vicinal and long-range proton–proton coupling-constants suggested that the conformation of the 1,3-anhydro sugar ethers is essentially $B^{2,5}$(L) with some lowering of the boat head at C-5 for the pyranose ring, and a chair for the 1,3-dioxane ring.

INTRODUCTION

The synthesis and conformation of 1,3-anhydro-2,4-di-*O*-benzyl- (**14**) and 1,3-anhydro-2,4-di-*O*-(*p*-bromobenzyl)-β-L-rhamnopyranose (**15**) are of interest as their stereoregular polymerization can be expected to produce an α-(1→3)-linked L-rhamnopyranan. It has been found that α-(1→3)-linked L-rhamnopyranosyl residues occur in several Klebsiella K and pneumococcal capsular polysaccharides[1]. The syntheses of α-(1→3)-linked L-rhamno-oligosaccharides[2,3] and of a polysaccharide[4] have been reported. Also, the title compounds are of the 2,6-dioxabicyclo[3.1.1]heptane class, occurring[5,6] in thrombaxane A_2 (TXA_2), a compound of substantial importance in biological chemistry. 1,3-Anhydroglycopyranose derivatives are useful model compounds for investigating the highly strained nature of the bicyclic, oxetane acetal system in TXA_2. The preparation of

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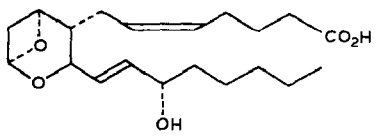
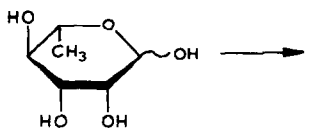


TXA2



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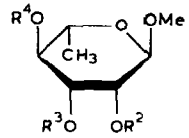
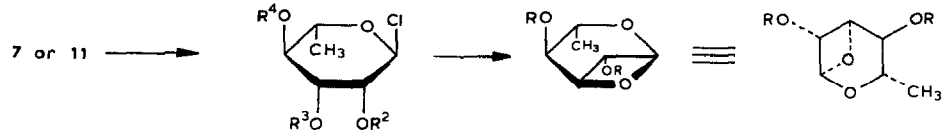


Bn = $C_6H_5CH_2$

BBn = p-$BrC_6H_4CH_2$

	R^4	R^3	R^2
2	H	H	H
3	H	CMe_2	
4	Bn	CMe_2	
5	Bn	H	H
6	Bn	H	Bn
7	Bn	Ac	Bn
8	BBn	CMe_2	
9	BBn	H	H
10	BBn	H	BBn
11	BBn	Ac	BBn



	R^4	R^3	R^2
12	Bn	Ac	Bn
13	BBn	Ac	BBn

14 R = Bn

15 R = BBn

1,3-anhydro-gluco-[7,8] and -mannopyranose[9,10] derivatives has been described. We now report the synthesis and conformational analysis of 1,3-anhydro-2,4-di-*O*-benzyl- and 1,3-anhydro-2,4-di-*O*-(*p*-bromobenzyl)-β-L-rhamnopyranose.

RESULTS AND DISCUSSION

L-Rhamnose (**1**) was converted[11] into a mixture of methyl α- and β-L-rhamnopyranoside and α- and β-L-rhamnofuranoside [thin-layer chromatography

(t.l.c.) and liquid chromatography (l.c.)]. Without purification, it was acetalated with ethyl orthoformate and acetone, to give a mixture of products which was readily resolved by column chromatography. The methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3**) obtained was benzylated, to afford methyl 4-*O*-benzyl-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**4**). Similar (*p*-bromobenzyl)ation of **3** gave **8**. To prevent hydrolysis of the acid-labile protecting groups in **4** and **8**, sodium hydrogencarbonate was used to neutralize the hydrogen bromide formed during removal of the excess of the alkylating reagents by steam distillation. It appears that the glycosidic linkages in methyl 4-*O*-benzyl- and methyl 4-*O*-(*p*-bromobenzyl)-α-L-rhamnopyranoside are much more acid-labile than those in the corresponding α-D-mannopyranosides. Therefore, cleavage of the *O*-isopropylidene groups from **4** and **8** must be carried out under carefully controlled conditions[12], in order to avoid losses due to the formation of reducing L-rhamnose derivatives.

Selective benzylation and *p*-bromobenzylation of compounds **5** and **9** was performed under phase-transfer conditions[13], to afford the desired 2,4-di-*O*-substituted L-rhamnopyranosides **6** and **10**. Subsequent acetylation of **6** and **10** gave **7** and **11**, respectively. The conversion of **7** and **11** into 3-*O*-acetyl-2,4-di-*O*-benzyl- (**12**) and 3-*O*-acetyl-2,4-di-*O*-(*p*-bromobenzyl)-α-L-rhamnopyranosyl chloride (**13**) was carried out essentially as described[10] for the conversion of methyl 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside into 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride. However, due to the pronounced susceptibility of the present substrates towards acid hydrolysis, the rather basic solvent diethyl ether was used in this conversion, rather than a 1:1 mixture of dichloromethane and acetic acid[10].

Compounds **12** and **13** were found to be moisture-sensitive and to decompose during monitoring of the reactions by t.l.c. However, they were stable and purifiable by analytical l.c. after the excess of HCl had been removed. The L-rhamnopyranosyl chlorides **12** and **13** were used as the key intermediates for the synthesis of the title compounds by a ring-closure reaction. This was conducted with potassium *tert*-butoxide in oxolane at room temperature, to yield **14** and **15**, respectively, readily. Compared with the corresponding 1,3-anhydro-β-D-mannopyranose derivatives, compounds **14** and **15** were found to be more acid-labile. They decompose during chromatography on common silica gel (t.l.c. or l.c.), and a column packed with Lichrosorb-NH_2 had to be used for this purification. Pure compounds **9** and **15** were stable for several weeks at −20°.

1,3-Anhydro-2,4-di-*O*-benzyl-β-L-rhamnopyranose (**14**) was identified by its i.r., mass, and ^{1}H-n.m.r. spectra, and by elemental analysis. The i.r. spectrum showed strong absorption for the ether linkage, and no absorption for a C=C bond. The mass spectrum showed a parent peak of moderate intensity at *m/z* 326, consistent with a molecular formula of $C_{20}H_{22}O_4$. Its ^{1}H-n.m.r. spectrum showed features similar, except for H-6,6, to those of the corresponding D-mannopyranose derivative. The same holds for 1,3-anhydro-2,4-di-*O*-(*p*-bromobenzyl)-β-L-rhamnopyranose, which was obtained crystalline.

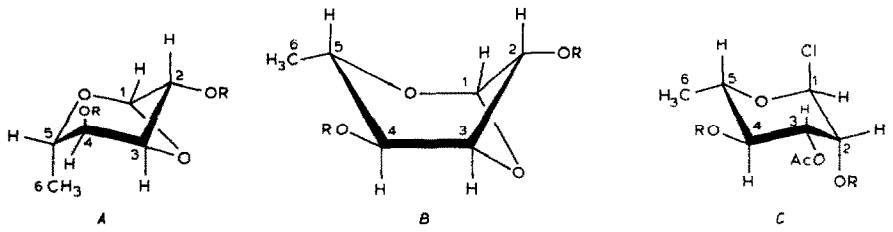


Fig. 1. Two possible conformations, *A* and *B*, for the 1,3-anhydro-L-rhamnopyranose ethers (**14**, R = $C_6H_5CH_2$; **15**, R = *p*-$BrC_6H_4CH_2$) and conformation *C* for the chlorides (**12**, R = $C_6H_5CH_2$; **13**, R = *p*-$BrC_6H_4CH_2$).

A detailed conformational analysis of the benzyl and *p*-bromobenzyl ethers of the 1,3-anhydro sugar was performed with the aid of a 400-MHz spectrometer in conjunction with calculations by the Karplus[14] and a modified Karplus equation[15].

The ring protons and benzyl methylene protons of the title compounds comprise a complex spin system. However, at 400 MHz, ^{1}H-spectral dispersions were sufficient for approximate first-order analysis.

Two conformations, *A* and *B*, may be considered for the ring-closure products **14** and **15** from the corresponding chlorides **12** and **13**, as shown in Fig. 1. Forms *A* and *B* can each be described in terms of the shape of two six-membered rings. Conformation *A* consists of the pyranose ring in the $^4C_1$(L) conformation, with C-6 axial, and a 1,3-dioxane ring in a $B_{5,O\text{-}3}$ form. Conformation *B* consists of a 1,3-dioxane ring in the $^1C_4$ and the pyranose ring in the $^{2,5}B$(L) conformation, with C-6 equatorial. Judgment as to the conformation of the ring-closure products requires consideration of the relative thermodynamic stability of the proposed conformations. In conformation *A*, both the OBn-4 and the CH_3-5 group are in disfavored, axial positions that are sterically hindered by a 1,3-nonbonding interaction between OBn-4 and H-2, and also by a crowding interaction between nonbonding electrons of oxygen and the CH_3-5 group on the "bottom" side of the 1,3-dioxane ring. In contrast to *A*, the two large groups in *B* are in equatorial positions. Therefore, conformation *B* is favored. This postulate was confirmed by the experimental results, as indicated later.

The ^{1}H-n.m.r. spectrum of compound **14** was assigned by use of single-frequency decoupling and a two-dimensional, homonuclear correlated spectrum. The anomeric proton (H-1) appeared as a doublet at δ 5.295 with a coupling constant of 4.4 Hz. In either conformation, *A* or *B*, the dihedral angle $\phi_{1,2}$ was close to 95°; thus, $^3J_{1,2}$ must be at the minimum, and only $^4J_{1,3}$ = 4.4 Hz was oberved. Such a large value of $^4J_{1,3}$ is probably caused by coupling through two W paths, as found in cyclobutane derivatives[16].

Because the resonance of H-2 at δ 4.449 and that of H-3 at δ 4.457 were very close, their assignment needed to be verified. This was done with a two-dimensional, heteronuclear-correlated spectrum and the fully proton-coupled, ^{13}C-

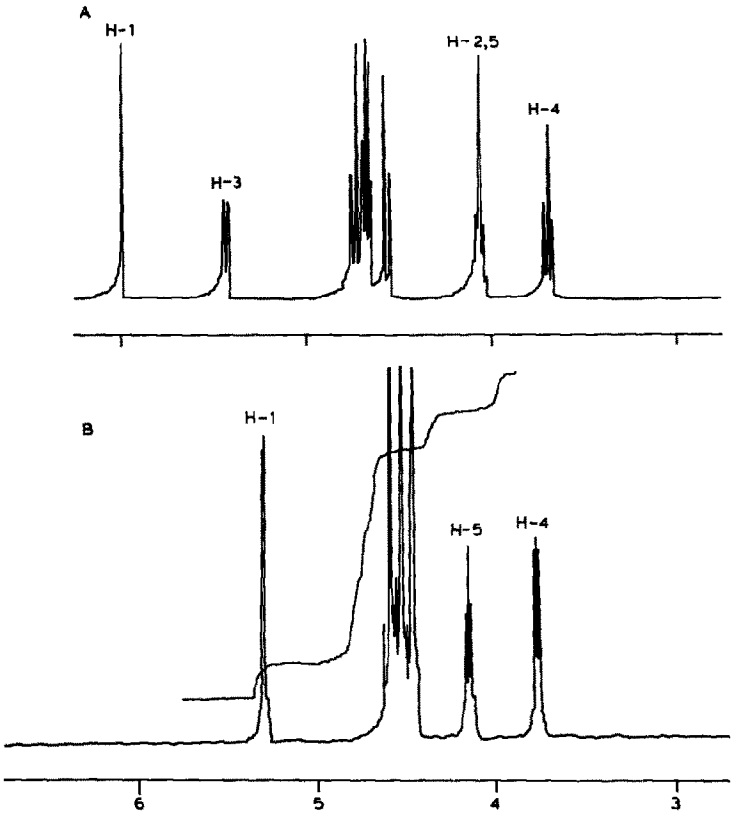


Fig. 2. The 400 MHz, ^{1}H-n.m.r. spectra (3–6 p.p.m.) of compounds **12** (A) and **14** (B).

n.m.r. spectrum of compound **14**. The resonance at δ 4.457, being correlated with the ^{13}C signal at δ 81.74, was assigned to H-3. In a bicyclic system, the ^{13}C–^{1}H coupling-constants observed for bridge-head carbon atoms (C-1 and C-3) are generally greater than those for other ring-carbon atoms[17]. Although the ^{13}C–^{1}H coupling constant for the signal at δ 81.74 was smaller than that for C-1, it was larger than those measured for the remaining carbon atoms. Therefore, the resonance at δ 4.449 was assigned to H-2, and δ 4.457 to H-3.

The assignment of compounds **8, 12, 13**, and **15** was achieved by inter-comparison of their ^{1}H-n.m.r. spectra and by comparison with the assignments for **14**. The results are given in Tables I and II.

For both conformations *A* and *B*, $^4J_{1,3}$ should be the same, but $^3J_{4,5}$ and $^3J_{3,4}$ should each be quite different. In conformation *B*, according to inspection of a model, H-4 and H-5 have an antidiaxial correlation, with a dihedral angle of 160°, which would give $^3J_{4a,5a}$ a value near 9 Hz, similar to the values in the spectra of compounds **12** and **13**. Meanwhile, H-3 and H-4 have a *quasi e-a* correlation, with a dihedral angle 80°, which would show a very small coupling constant. For con-

TABLE I

^{1}H CHEMICAL SHIFTS (δ) FOR COMPOUNDS **8** AND **12–15**

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*Benzyl methylene groups*				*Other groups*
							on O-4		*on O-2*		
							H_A	H_B	H_A	H_B	
8	4.828 (s)	4.106 (d)	4.206 (d,d)	3.156 (d,d)	3.631 (m)	1.256 (d)	4.818 (d)	4.553 (d)			1.481 (s), 1.345 (s), (isopropylidene) 3.345 (s), (OMe)
12	5.958 (d)	4.049 (d,d)	5.420 (d,d)	3.678 (d,d)	4.049 (m)	1.360 (d)	4.669 (d)	4.554 (d)	4.728 (d)	4.653 (d)	1.962 (s), (CH_3CO)
13	5.958 (d)	4.010 (d,d)	5.396 (d,d)	3.608 (d,d)	4.022 (m)	1.334 (d)	4.601 (d)	4.478 (d)	4.650 (d)	4.593 (d)	1.952 (s), (CH_3CO)
14	5.295 (d)	4.449 (s)	4.457 (d,d)	3.757 (d,d)	4.147 (m)	1.339 (d)	4.535 (d)	4.495 (d)	4.600 (d)	4.555 (d)	
15	5.305 (d)	4.419 (s)	4.438 (d,d)	3.746 (d,d)	4.134 (m)	1.356 (d)	4.476 (s)	4.476 (s)	4.573 (d)	4.505 (d)	

TABLE II

^{1}H COUPLING CONSTANTS (Hz) FOR COMPOUNDS **8** AND **12–15**

Compound	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{A,B}$ *for benzyl* CH_2	
							on O-4	*on O-2*
8	0		5.6	7.1	9.6	6.4	−11.7	
12	1.7		3.4	9.8	9.5	6.3	−12.2	−11.2
13	1.5		3.4	9.8	9.4	6.3	−12.2	−11.5
14	0	4.4	0	3.3	6.6	6.6	−11.7	−11.7
15	0	4.2	0	3.3	6.6	6.2		−12.0

formation *A*, H-4 and H-5 have an *e-e gauche* correlation, which should lead to a small vicinal coupling near $^3J_{1,2}$ (0–1.7 Hz) in the spectra of compounds **8, 12,** and **13**, and H-3 and H-4, having a *quasi e-e* correlation should also give a small coupling constant[15].

However, the spectrum of compound **14** showed $^3J_{4,5}$ 6.6 and $^3J_{3,4}$ 3.3 Hz. These values are closer to the data calculated for *B* than for *A*, as the latter cannot show a large value of $^3J_{4,5}$.

It was found that H-2 and H-5 in a model of *B* are closer to each other, with a crowding interaction, than in a normal $^{2,5}B$ conformation. Thus, possibly, the boat-head C-5 atom would be lowered to some extent, to decrease the crowding interaction; namely, the boat head in *B* is depressed to such an extent that $\phi_{4,5}$ and $\phi_{3,4}$ reach 140° and 65°, respectively, angles which are very close to the values 143°

TABLE III

DIHEDRAL BOND ANGLES (DEGREES) FOR COMPOUNDS **14** AND **15**

	$\phi_{1,2}$	$\phi_{2,3}$	$\phi_{3,4}$	$\phi_{4,5}$
Measured from model of *A*	95	95	35	75
Measured from model of *B*	95	95	80	160
Measured from model *B* with some flattening of C-5	95	95	65	140
Calculated, from the coupling constants, by the Karplus equation[14]	78/99	78/99	49	148
Calculated, from the coupling constants, by the modified Karplus equation[15]	78	87	64	143

TABLE IV

^{13}C CHEMICAL SHIFTS (p.p.m.) FOR COMPOUNDS **12–15**, AND ^{13}C–^{1}H COUPLING CONSTANTS (Hz) FOR COMPOUNDS **14** AND **15**

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Benzyl methylene*	*Other groups*
12	90.48 (d)	(70.72, (d)	78.83, (d)	78.31)[a] (d)	72.14 (d)	17.62 (q)	73.27, 75.07 (t) (t)	20.91 (q), 169.9 (s), (CH_3CO)
13	90.23 (d)	(70.60, (d)	79.20, (d)	78.48)[a] (d)	72.04 (d)	17.67 (q)	72.65, 74.16 (t) (t)	20.89 (q), 169.8 (s), (CH_3CO)
14	107.00 (d) 186.2	79.46 (d) 160.2	81.74 (d) 164.8	79.66 (d) 138.8	73.02 (d) 146.5	20.92 (q) 127.2	71.99, 72.24 (t) (t) 142.7, 145.0	
15	106.93 (d) 185.0	79.63 (d) 161.3	81.67 (d) 165.6	79.82 (d) 139.6	73.01 (d) 148.8	21.04 (q) 127.4	71.50, 71.26 (t) (t) 142.2, 143.1	

[a]The values for C-2,3,4 may be interchangeable.

and 64° calculated from the observed coupling constants by means of the modified Karplus equation[15]. Accordingly, compound **14** essentially adopts conformation *B*, with some lowering of the boat head, to give a skew form.

There was an alternative proof for the suggested conformation. Namely, there was found to be only a small difference (~0.1 p.p.m.) in the chemical shifts of H-4, H-5, and H-6 as between compounds **12** and **14** (which were the starting material and the product of the ring-closure reaction, respectively). Large differences between **12** and **14** (or **13** and **15**) were that H-2 shifted downfield ~0.4 p.p.m. and changed from a doublet of doublets to a single peak, while H-1 and H-3 shifted upfield ~0.6 and 1 p.p.m. respectively, because of the oxetane-ring formation.

It was known that compounds **12** and **13** have the $^1C_4$(L) conformation *C*, with an antidiaxial relation between H-4 and H-5 similar to that between H-4 and H-5 in conformation *B*. The fact that the chemical shifts of H-4, -5, and -6 in compounds **14** and **12** are close indicated that the two compounds have a similar partial conformation in the moiety consisting of C-4, C-5, and C-6.

Dihedral angles for compounds **14** and **15** calculated from coupling constants by the Karplus[14] and the modified Karplus equation[15], and measured from molecular models, are listed in Table III.

The ^{13}C-n.m.r. spectrum of compound **14** was assigned by use of a two-dimensional, heteronuclear-correlated spectrum and a fully proton-coupled spectrum, in conjunction with use[18] of the "Fingerprint technique". The ^{13}C spectrum assignment of **15** was carried out by comparison with the assignment of **14**. The assignment of the ^{13}C spectra was simplified by use of the first-order, approximate, analytical method. The data for the ^{13}C chemical shifts and coupling constants ($^1J_{C,H}$) for the anhydro sugar ethers are listed in Table IV.

EXPERIMENTAL

General methods. — Optical rotations were determined at 20° with a Perkin–Elmer Model 241-MC automatic polarimeter. Melting points were determined with a "Mel-Temp" apparatus. Analytical l.c. was carried out by using stainless-steel columns packed with silica gel (10 × 150 mm) or Lichrosorb-NH_2 (4.6 × 250 mm), a differential refractometer (Model 1107L, made by LDC, Division of Milton Roy Company, Florida, U.S.A.), and ethyl acetate–petroleum ether (b.p. 60–90°) as the eluant, at a flow rate of 1 to 4 mL/min. Thin-layer chromatography (t.l.c.) was performed on Silica Gel G, detection being effected by charring with 30% (v/v) sulfuric acid in methanol. Column chromatography was performed by elution of columns (16 × 240, 18 × 300, and 35 × 400 mm) of silica gel (100–200 mesh). I.r. spectra were recorded with a Perkin–Elmer 125 spectrometer. For most of the compounds involved in the synthesis, ^{1}H-n.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian XL-200 spectrometer. For conformational analysis, ^{1}H- and ^{13}C-n.m.r. spectra, recorded with a JEOL GX-400 MHz n.m.r.

spectrometer, were measured in the pulsed, Fourier-transform mode for solutions in $CDCl_3$ at 27°, with Me_4Si as the internal standard. Chemical shifts are given in p.p.m. (δ) downfield from the internal Me_4Si absorption. The spectrometer was controlled by means of a computer. A Varian spin-simulation program was used in the assignment of the ^1H-n.m.r. spectra. The working frequencies were 399.78 MHz for ^1H, and 100.4 MHz for ^{13}C. Sweep widths were 4000 Hz at 2.048 s, p.d. 1.0 s, p.w. 2.8 μs for ^1H; and 25000 Hz at 0.655 s, p.d. 5 s, p.w. 4.8–9.6 μs for ^{13}C. Mass spectra were recorded with a JMS-D 3005 mass spectrometer, using a direct sample introduction technique.

3-O-Acetyl-2,4-di-O-benzyl-α-L-rhamnopyranosyl chloride (**12**). — For preparation of **12**, the precursor methyl 3-*O*-acetyl-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (**7**) was prepared from L-rhamnose monohydrate (**1**) *via* compounds **2**–**6**. The overall yield was 50.5%. Optical rotations, $[\alpha]_D^{20}$, observed, and reported, for those compounds which were separated, were as follows: **3**, −24.5° (*c* 1, chloroform), −16° (*c* 1.3, acetone); lit.[14] −15.9° (*c* 1.6, acetone); **5**, −68.5° (*c* 1, chloroform); lit.[20] −68.3° (*c* 1.6, chloroform, 25°); **6**, −15.2° (*c* 1.8, chloroform); lit.[13] −15° (*c* 1, chloroform); **7**, +3.8° (*c* 1.4, chloroform). Compound **5** was obtained as white crystals with m.p. 106–107°; lit.[20] m.p. 107–109°. ^1H-N.m.r. spectra of compounds **3**, **5**, and **6** were consistent with the reported data; for **7**: δ 7.50–7.20 (m, 10 H, aromatic H), 5.18 (m, 1 H, $J_{3,4}$ 9.0, $J_{2,3}$ 3.2 Hz, H-3), 4.78–4.43 (m, 5 H, 2 CH_2Ph and H-1), 3.90–3.58 (m, 3 H, H-2,4,5), 3.38 (s, 3 H, OCH_3), 1.98 (s, 3 H, CH_3CO), and 1.36 (d, 3 H, $J_{5,6}$ 6 Hz, 3 H-6).

Compound **7** (199 mg, 0.5 mmol) was dissolved in dry ether (10 mL). Hydrogen chloride gas was bubbled in to saturation (under nitrogen and in an ice-bath). The mixture was kept for 6 h at room temperature, and then evaporated under diminished pressure to a syrup which was dissolved in dichloromethane (2 mL), and the solution evaporated. This procedure was repeated 7 or 8 times, to decrease the HCl to the minimum. Then, the product was purified by analytical l.c. (silica-gel column, 1:4 ethyl acetate–petroleum ether), to give pure **12** (125 mg, 62%); $[\alpha]_D^{20}$ −55.9° (*c* 1, chloroform); and the starting material **7** (36.5 mg) was recovered; ^1H-n.m.r. data are given in Tables I and II; *m/z* 404 (M^+), 368 (M^+ − HCl), 361 (M^+ − CH_3CO), 313 (M^+ − CH_2Ph), and 207 (M^+ − 2 CH_2Ph − CH_3).

Anal. Calc. for $C_{22}H_{25}ClO_5$: C, 65.26; H, 6.22. Found: C, 65.27; H, 6.24.

1,3-Anhydro-2,4-di-O-benzyl-β-L-rhamnopyranose (**14**). — Potassium *tert*-butoxide (56 mg, 0.5 mmol) was added to a solution of **12** (103 mg, 0.25 mmol) in dry oxolane (10 mL), and the mixture was stirred for 2 h at room temperature. After evaporation, a solution of the residue in dichloromethane (10 mL) was washed with ice–water (5 mL × 3), dried (sodium sulfate), and evaporated, and the crude product purified by analytical l.c. (1:3 ethyl acetate–petroleum ether) in a column packed with Lichrosorb-NH_2, to yield **14** (71.2 mg, 86%); $[\alpha]_D^{20}$ −62.7° (*c* 0.44, chloroform); ^1H-n.m.r. data are indicated in Tables I and II; i.r.: 1100 and 1080 cm^{-1} (C–O); *m/z* 326 (M^+).

Anal. Calc. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.61; H, 6.85.

Methyl 2,3-O-isopropylidene-4-O-(p-bromobenzyl)-α-L-rhamnopyranoside (**8**). — To a solution of **3** (3.37 g, 15.5 mmol) in dry oxolane (25 mL) was added sodium hydride (in oil, 80%; 2 g, 66 mmol). A solution of *p*-bromobenzyl bromide (6 g, 24 mmol) in oxolane (15 mL) was added dropwise during 30 min, while the mixture was refluxed and stirred vigorously. Heating under reflux was continued for 6–8 h, when t.l.c. (1:2 ethyl acetate–petroleum ether) indicated that the starting material had disappeared. The remaining sodium hydride was filtered off and the filtrate was evaporated. Toluene (8 mL) followed by sodium hydrogencarbonate (0.5 g) were added to the residue, and the mixture was steam distilled to remove the excess of *p*-bromobenzyl bromide. The mixture was repeatedly extracted with dichloromethane, and the extracts were combined, dried, and evaporated. The residue crystallized from ether–petroleum ether, to give **8** (5.39 g, 90%); m.p. 80–80.5°, $[\alpha]_D^{20}$ −47.6° (*c* 0.89, chloroform); ^{1}H-n.m.r. data are given in Tables I and II.

Anal. Calc. for $C_{17}H_{23}BrO_5$: C, 52.73; H, 5.99. Found: C, 52.54; H, 5.96.

Methyl 4-O-(p-bromobenzyl)-α-L-rhamnopyranoside (**9**). — To compound **8** (3 g, 7.8 mmol) was added 7:3 (v/v) acetic acid–water (12 mL). The mixture was boiled under reflux for 20 min, at which time t.l.c. (1:1 ethyl acetate–petroleum ether) showed that no starting material remained. After evaporation of the solution, the product crystallized from ethyl acetate–petroleum ether, to afford **9** (2.52 g, 93.5%); m.p. 120–120.5°, $[\alpha]_D^{20}$ −53.6° (*c* 1.9, chloroform); ^{1}H-n.m.r.: δ 7.48–7.18 (m, 4 H, aromatic H), 4.72–4.62 (m, 3 H, C*H*$_2$Ph and H-1), 3.91–3.60 (m, 3 H, H-2,3,5), 3.33 (s, 3 H, OC*H*$_3$), 3.28 (m, 1 H, H-4), 2.20 (s, 2 H, 2 O*H*), and 1.30 (d, 3 H, $J_{5,6}$ 6.4 Hz, 3 H-6).

Anal. Calc. for $C_{14}H_{19}BrO_5$: C, 48.43; H, 5.51. Found: C, 48.60; H, 5.45.

Methyl 2,4-di-O-(p-bromobenzyl)-α-L-rhamnopyranoside (**10**). — Aqueous sodium hydroxide (10%, 4 mL) was added to a solution of compound **9** (700 mg, 2 mmol), tetrabutylammonium bromide (161 mg, 0.5 mmol) and *p*-bromobenzyl bromide (550 mg, 2.2 mmol) in dichloromethane (20 mL), and the mixture was vigorously stirred for 6 h at room temperature. The crude product, obtained after conventional processing, was purified on a column of silica gel (16 × 240 mm; 1:3 ethyl acetate–petroleum ether), to afford **10** (685 mg, 66.7%) and 141 mg of crystalline starting-material **9**; compound **10** had $[\alpha]_D^{20}$ −3.1° (*c* 0.8, chloroform); ^{1}H-n.m.r.: δ 7.48–7.15 (m, 8 H, aromatic H), 4.90–3.24 (m, 9 H, 2 C*H*$_2$Ph and H-1,2,3,4,5), 3.32 (s, 3 H, OC*H*$_3$), 2.08 (s, 1 H, O*H*), and 1.31 (d, 3 H, $J_{5,6}$ 6.8 Hz, 3 H-6).

Anal. Calc. for $C_{21}H_{24}Br_2O_5$: C, 48.86; H, 4.69. Found: C, 48.85; H, 4.69.

Methyl 3-O-acetyl-2,4-di-O-(p-bromobenzyl)-α-L-rhamnopyranoside (**11**). — Compound **10** (540 mg, 0.97 mmol) was acetylated with acetic anhydride and pyridine by the standard procedure, to give **11** in theoretical yield; $[\alpha]_D^{20}$ +15.9° (*c* 1.4, chloroform); ^{1}H-n.m.r.: δ 7.54–7.16 (m, 8 H, aromatic H), 5.16 (m, 1 H, $J_{3,4}$ 9.4, $J_{2,3}$ 3.7 Hz, H-3), 4.68–4.50 (m, 5 H, 2 C*H*$_2$Ph and H-1), 3.85–3.52 (m, 3 H, H-2,4,5), 3.34 (s, 3 H, OC*H*$_3$), 1.95 (s, 3 H, C*H*$_3$CO), and 1.32 (d, 3 H, $J_{5,6}$ 5.8 Hz, 3 H-6).

Anal. Calc. for $C_{23}H_{26}Br_2O_6$: C, 49.48; H, 4.70. Found: C, 49.69; H, 4.82.

3-O-Acetyl-2,4-di-O-(p-bromobenzyl)-α-L-rhamnopyranosyl chloride (**13**). — Compound **11** (195 mg, 0.35 mmol) was converted into **13** (145 mg, 73.6%); $[\alpha]_D^{20}$ −25.5° (*c* 1.5, chloroform), as described for the preparation of **12**; ^{1}H-n.m.r. data are given in Tables I and II.

Anal. Calc. for $C_{22}H_{23}Br_2ClO_5$: C, 46.96; H, 4.12. Found: C, 46.73; H, 4.08.

1,3-Anhydro-2,4-di-O-(p-bromobenzyl)-β-L-rhamnopyranose (**15**). — Compound **13** (141 mg, 0.25 mmol) was dissolved in dry oxolane (10 mL), and potassium *tert*-butoxide (62 mg, 0.55 mmol) was added. After being stirred for 2 h at room temperature, the mixture was processed as described for the preparation of **14**, and compound **15** (97 mg, 80%) crystallized from ether–petroleum ether; m.p. 67°, $[\alpha]_D^{20}$ −35.2° (*c* 0.42, chloroform); ^{1}H-n.m.r. data are given in Tables I and II.

Anal. Calc. for $C_{20}H_{20}Br_2O_4$: C, 49.61; H, 4.16. Found: C, 49.45; H, 4.16.

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