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Preliminary communication

A new and efficient synthesis of β-L-rhamnopyranosides

TOMMY IVERSEN and DAVID R. BUNDLE
Division of Biological Sciences, National Research Council of Canada, Ottawa, Ontario K1A 0R6 (Canada)

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A systematic approach to the synthesis of β-L-rhamnopyranosides has not been reported, and, as this structural unit occurs in bacterial antigens[1,2], an effective synthesis of oligosaccharides containing residues thereof is of practical significance. We report here the synthesis of β-L-rhamnopyranosides in good yield, utilizing the readily accessible α-L-rhamnopyranosyl bromide (3).

The problem of synthesis of 1,2-*cis*-hexosides possessing the *manno* configuration has received attention by several groups[3–7]. The approach has, in general, been similar, *i.e.*, selection of a nonparticipating, protecting group for O-2, in conjunction with activation at C-1. Currently, the most practical exemplification of these principles is the procedure of Garegg and co-workers[5,7], which takes advantage of the fact that acetalation of D-mannose under kinetic control gives rise to pyranose 2,3:4,6-acetals[8].

In contrast to D-mannose, L-rhamnose undergoes acetalation with 1-ethoxycyclohexene, followed by acetylation, to yield a furanose derivative, namely, 1,5-di-*O*-acetyl-2,3-*O*-cyclohexylidene-α-L-rhamnofuranose. In order to obtain a pyranose derivative, methyl α-L-rhamnopyranoside (**1**) was chosen as the starting material. A solution of **1** in acetonitrile containing a catalytic amount of *p*-toluenesulfonic acid was treated with 1-ethoxycyclohexene (2 mol. equiv.), and the crude product was benzoylated, to afford 72% of crystalline methyl 4-*O*-benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranoside (**2**), m.p. 95.5–97° (from Skellysolve B), $[\alpha]_D^{20}$ +2.2° ($CHCl_3$). Reaction of **2** in chloroform solution with zinc bromide (1 mol. equiv.) and dibromomethyl methyl ether (2 mol. equiv.)[9,10] for 45 min at 50°, filtration, and evaporation, afforded crude, syrupy rhamnosyl bromide **3**, $[\alpha]_D^{20}$ –26.1° ($CHCl_3$). Judged by its ^{13}C-N.M.R. spectrum the product was >90% pure, and it was used immediately, without purification.

Treatment of **3** with methanol containing triethylamine gave a 69% yield of crystalline methyl 4-*O*-benzoyl-2,3-*O*-cyclohexylidene-β-L-rhamnopyranoside (**4**), m.p. 149.5–151.5° (from ethanol). Reactions of **3** with three selectively protected pyranosides (**8–10**), chosen for their moderate to low reactivity, were performed under standard Koenigs–Knorr conditions. A solution of bromide **3** (4 mmol) in dichloromethane (5 mL) was added dropwise to a stirred suspension of silver carbonate (8 mmol), molecular sieve 4A (10 g), and the aglycon (1 mmol) in dichloromethane

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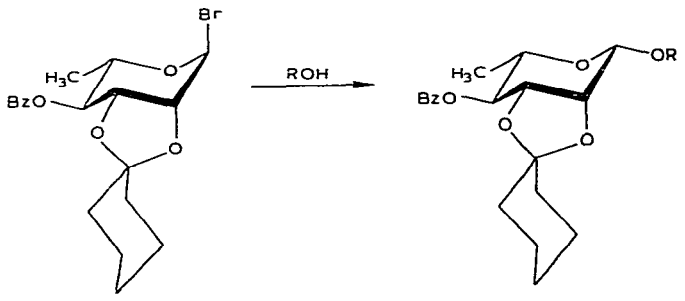
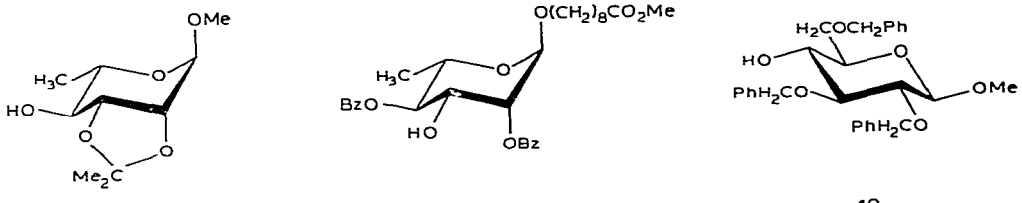


3

4 ROH = MeOH
5 ROH = 8
6 ROH = 9
7 ROH = 10



8 9 10

(10 mL). After 2 h, the reactions were processed by filtration followed by chromatography.

Both rhamnose disaccharides, namely, methyl 4-*O*-(4-*O*-benzoyl-2,3-*O*-cyclohexylidene-β-L-rhamnopyranosyl)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**5**) and 8-(methoxycarbonyl)octyl 2,4-di-*O*-benzoyl-3-*O*-(4-*O*-benzoyl-2,3-*O*-cyclohexylidene-β-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**6**), were obtained with high stereoselectivity in yields of 87 and 62%, respectively. With the particularly unreactive[11] aglycon **10**, the stereoselectivity was lowered, and both anomers were obtained, namely, methyl 4-*O*-(4-*O*-benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**11**) in 33% yield, and methyl 4-*O*-(4-*O*-benzoyl-2,3-di-*O*-cyclohexylidene-β-L-rhamnopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**7**) in 23% yield. That the stereoselectivity is lowered in glycosidations with unreactive aglycons has also been observed[7] in the synthesis of β-D-mannopyranosides.

Removal of protecting groups was accomplished in the usual ways, by transesterification of benzoic esters, hydrogenolysis of benzyl ethers, and acid hydrolysis of acetals by trifluoroacetic acid[7]. The physical constants and anomeric-shift data for the fully protected and de-protected glycosides are listed in Table I.

The readily accessible bromide **3** has been shown to be an effective intermediate for the synthesis of β-L-rhamnopyranosides. In this regard, its use for sequential synthesis[12,13] of the oligosaccharides of bacterial O-antigens is receiving further attention

TABLE I

SOME PHYSICAL PROPERTIES OF THE COMPOUNDS LISTED

Compound	$[\alpha]_D^{20}$ (degrees)	*H-1*	*H'-1* [a,b]	*C-1*	*C'-1* [a,b]
4	+79.8 [c]	–	–	100.0	– [d]
5	+19.0 [c]	–	–	98.9	98.2 [d]
6	+65.3 [c]	–	–	97.9	95.5 [d]
11	−12.6 [c]	–	–	96.8	104.9 [d]
7	+52.8 [c]	–	–	99.9	104.6 [d]
Methyl β-L-rhamnopyranoside	+95.2 [e,f]	4.52		102.2	– [g]
Methyl 4-*O*-β-L-rhamnopyranosyl-α-L-rhamnopyranoside	−12.1 [e]	4.71	4.71	101.6	101.8 [g]
8-(Methoxycarbonyl)octyl 3-*O*-β-L-rhamnopyranosyl-α-L-rhamnopyranoside	+5.0 [e]	4.78	4.72	101.0	98.5 [g]
Methyl 4-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside	−54.3 [e]	4.91	4.37	102.0	104.3 [g]
Methyl 4-*O*-β-L-rhamnopyranosyl-β-D-glucopyranoside	+31.5 [e]	4.86	4.37	101.8	104.4 [g]

[a] Primes refer to the anomeric proton of the aglyconic saccharide. [b] For ^{1}H-n.m.r. spectra, chemical shifts were measured at 90°, and are referenced to sodium trimethylsilyl propionate. ^{13}C- n.m.r. spectra are referenced to external Me_4Si for solutions in D_2O, and to internal Me_4Si for solutions in $CDCl_3$. [c] In $CHCl_3$. [d] In $CDCl_3$. [e] In H_2O. [f] Lit. $[\alpha]_D$ +95.4°; m.p. 140.5–141.5° (from ethyl acetate) [lit. [14] m.p. 138–140°]. [g] In D_2O.

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