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Benzylidene Acetal Fragmentation Route to 6-Deoxy Sugars: Direct Reductive Cleavage in the Presence of Ether Protecting Groups, Permitting the Efficient, Highly Stereocontrolled Synthesis of β-D-Rhamnosides from D-Mannosyl Glycosyl Donors. Total Synthesis of α-D-Gal-(1→3)-α-D-Rha-(1→3)-β-D-Rha-(1→4)-β-D-Glu-OMe, the Repeating Unit of the Antigenic Lipopolysaccharide from *Escherichia hermannii* ATCC 33650 and 33652

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Abstract: An approach to the stereocontrolled synthesis of β-D-rhamnopyranosides is described in which 2,3-*O*-benzyl or related 4,6-*O*-[α-(2-(2-iodophenyl)ethylthiocarbonyl)benzylidene]-mannosyl thioglycosides are first used to introduce the β-D-mannopyranoside linkage in high yield and stereoselectivity. Following glycosylation, treatment with tributyltin hydride in toluene at reflux brings about reductive radical fragmentation directly to the 6-deoxy sugar in high yield. A variation of these donors bearing a carboxylated donor on O3 is a highly α-selective mannosyl and, after radical fragmentation, α-D-rhamnosyl donor. Using this stereoselective glycosylation/radical-fragmentation approach, a concise synthesis of the title tetrasaccharide is realized in which both the β-D- and α-D-rhamnopyranosyl units are obtained in a single step by a double radical fragmentation of the modified benzylidene acetals.

Introduction

Rhamnopyranosides are frequent components of antigenic bacterial capsular polysaccharides and exopolysaccharides. As such, they play important roles in the propagation of disease states and may be viewed as components of vaccines against pneumococcal infections.[1] While the L-rhamnopyranosides are the most common of the two antipodes in bacterial polysaccharides, increasing numbers of the D-modification[2] are being located in the form of α- and β-glycosidic linkages. In terms of chemical synthesis, the two enantiomeric series present very different problems, with the readily available L-rhamnose being the obvious starting point for both the α- and β-L-rhamnopyranosides and the lack of a facile, large-scale source of D-rhamnose[3,4] dictating an indirect approach to the D-rhamnosides. This paper concentrates on the synthesis of the D-rhamnopyranosides, with particular focus on the β-D-series, while ongoing work in our laboratory addresses the problem of the β-L-family.[5] The effectiveness of the method developed here is illustrated by a concise synthesis of the tetrasaccharide repeating unit **1** of the antigenic lipopolysaccharide from *Escherichia hermannii* ATCC 33650 and 33652, an atypical biogroup of *Escherichia coli*, isolated from human wounds, lungs, and stools.[2l] The synthetic challenge of **1** is heightened by the presence of a total of four different types of glycosidic bond, including an α-D-rhamnopyranoside directly linked to the

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(4) Bundle has previously developed a synthesis of *S*-ethyl 2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-thiorhamnopyranoside from D-mannose as an α-rhamnosyl donor: Kihlberg, J.; Eichler, E.; Bundle, D. R. *Carbohydr. Res.* **1991**, *211*, 59−75.

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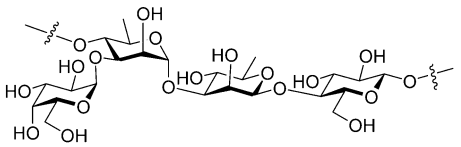
β-D-rhamnopyranoside, all of which must be assembled with a high degree of stereocontrol.



1: → 4)-α-D-Rha-(1→ 3)-β-D-Rha-(1→ 4)-β-D-Glu-(1→
|
(3→1)-α-D-Gal

The obvious approach to β-D-rhamnosides in terms of both directness and availability of starting materials is the selective deoxygenation of D-mannose derivatives at position 6. This deoxygenation might conceivably be achieved either prior to or after glycosylation. Deoxygenation prior to glycosylation is effectively a synthesis of a D-rhamnosyl donor and brings the problem in line with that of the L-rhamnosides. Deoxygenation after glycosylation simplifies the problem to one of stereocontrolled β-mannoside synthesis and regioselective protection. Both approaches are associated with the considerable problem of the stereoselective synthesis of the 1,2-cis-equatorial-type glycosidic bond[6] for which the 4,6-*O*-benzylidene β-directed glycosylations initially developed in this laboratory,[7,8] which are finding increasing application in complex oligosaccharide synthesis,[9] provide effective solutions, at least in the mannose series. The obvious solution to the β-D-rhamnopyranoside then becomes one of employing a 4,6-*O*-benzylidene-protected β-D-mannosyl donor followed by a Hanessian-type[10] fragmentation of the benzylidene acetal leading to a 4-*O*-benzoyl-6-bromo-6-deoxy-β-D-mannoside, that is, a 4-*O*-benzoyl-6-bromo-β-D-rhamnoside, followed by removal of the extraneous bromine atom. Closer examination, however, reveals this approach to be less than ideal owing (i) to the facile cleavage of benzyl ethers, important components of many oligosaccharide syntheses, on exposure to *N*-bromosuccinimide[11] and (ii) to the requirement of the extra debromination step after glycosylation. A more direct reductive fragmentation route from benzylidene acetals to 6-deoxy sugars, developed by Roberts and co-workers,[12] following earlier work by Pedersen,[12f] also suffers from the problem of competing benzyl ether cleavage.[13] With this background, the initial goal of the research described here became the development of an alternative approach to the fragmentation of 4,6-*O*-benzylidene acetals, leading directly to 6-deoxy sugars, that is fully compatible with the presence of benzyl and other ethers.[14]

Results and Discussion

Regioselective Fragmentation of Benzylidene Acetals. The incompatibility of the Hanessian *N*-bromosuccinamide (NBS)-mediated benzylidene acetal fragmentation and benzyl and similarly protected carbohydrates stems from the intermolecular hydrogen-atom abstraction, which is insufficiently discriminatory between a single benzylidene C−H bond and the typical multiplicity of benzyl C−H bonds.[10] Roberts's method, employing a thiyl radical as an intermolecular hydrogen-abstracting species, fails similarly.[12,13] This leads to the notion that chemoselectivity might be enforced by the application of an intramolecular hydrogen-abstraction step. Accordingly, substrate **2** was prepared and subjected to treatment with tributylstannane under conditions likely to permit 1,5-hydrogen-atom abstraction. Surprisingly, despite repeated attempts, only traces of the desired abstraction and ensuing fragmentation were observed, with the majority of the product being that of simple reductive deiodination. The contrast between these failures and the highly successful radical translocations achieved by Curran and others[15] with related but less constrained systems calls to mind the difficulties experienced earlier by this[16] and the Curran group[17] in the intramolecular abstraction of anomeric hydrogens with radical-bearing protecting groups on O2. Apparently, the transition state for 1,5-hydrogen-atom abstraction by aryl

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(11) The majority of NBS-mediated cleavage of carbohydrate-based benzylidene acetals has been conducted with the residual alcohols either unprotected or protected as esters. Reports occasionally surface on the application of the reaction in the presence of benzyl-type ethers, but yields are generally low and difficult to reproduce: Liotta, L. J.; Dombi, K. L.; Kelley, S. A.; Targontsidis, S.; Morin, A. M. *Tetrahedron Lett.* **1997**, *38*, 7833−7834.

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(13) There are no published reports of this chemistry in the presence of benzyl ethers. Certainly, in our hands, benzyl ether cleavage is competitive with benylidene acetal fragmentation.

(14) For a preliminary communication see: Crich, D.; Yao, Q. *Org. Lett.* **2003**, *5*, 2189−2191.

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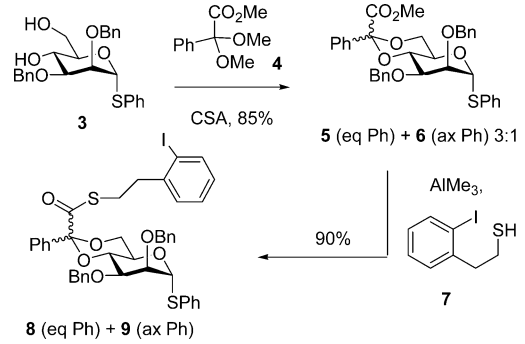
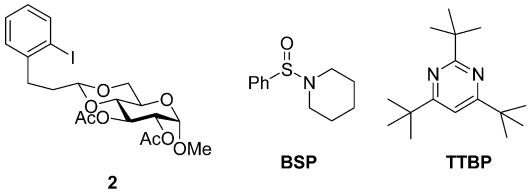
Scheme 1. Synthesis of Glycosyl Donors **8** and **9**



radicals from acetals is not sufficiently flexible to enable juxtaposition with a rigid cyclic acetal.



Attention was therefore refocused on a fragmentation approach to a benzylidene radical, in particular one based on the decarbonylation of an acyl radical. Among the available methods for acyl radical generation,[18] the use of a 2-(2-iodophenyl)-ethylthio ester[19] was the method of choice, as preliminary experiments demonstrated this functionality to be stable under the conditions intended for the activation of thioglycosides in the eventual synthesis of **1**.

Reaction of known diol **3**[7e] with the dimethyl acetal **4**[20] afforded the carbohydrate acetals **5** and **6** in 85% yield in the form of a 3/1 mixture favoring the less polar isomer (Scheme 1). Analytical quantities of the two pure isomers were obtained by preparative TLC for characterization purposes and the less-polar major isomer was tentatively assigned as having the carbomethoxy group in the less-exposed axial position. Some support for this assignment was gleaned from parallels between the spectroscopic data and those of crystallographically assigned, carbohydrate-based pyruvate acetals.[21] Analogous to methodology from the Gennari group,[22] the mixture of methyl esters **5** and **6** was treated with a reagent preformed from 2-(2-iodophenyl)ethanethiol, **7**[19], and trimethylaluminum to give the desired thiol esters **8** and **9**; the optimized conditions for this transesterification required heating to reflux in toluene, reflective of the hindered nature of the substrate, to give a yield of 90% (Scheme 1). Although not strictly necessary, the isomers were separated chromatographically and used pure in the subsequent glycosylations to facilitate subsequent spectral interpretation.

Scheme 2. Stereocontrolled Glycosylation

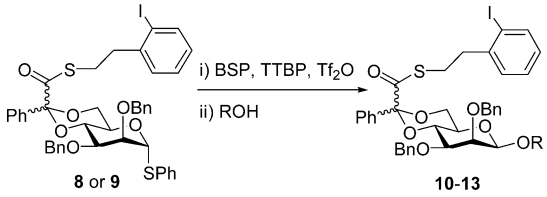
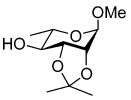
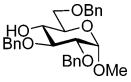
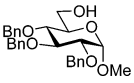
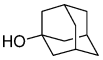


Table 1. Glycosylation and Cleavage in the Mannose Series

donor	acceptor	β-mannoside (% yield)	β-rhamnoside (% yield)	acetal (% yield)
8		**10** (94)	**14** (78)	**18** (8)
8		**11** (71)	**15** (74)	**19** (13)
9		**12** (77)	**16** (78)	**20** (8)
8		**13** (84)	**17** (80)	**21** (9)

Following our standard thioglycoside activation protocol, isomers **8** and **9** were coupled to a selection of primary, secondary, and tertiary alcohols with the aid of 1-benzenesulfinyl piperidine (BSP)[7d] and the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[23] to give the corresponding β-mannosides (Scheme 2, Table 1). Two points are of note in these coupling reactions. First, as expected on the basis of simple exploratory experiments, the thiol ester is stable under the conditions of the thioglycoside activations. Second, in line with expectations from previous 4,6-*O*-benzylidene directed mannosylations,[7,8] the couplings are highly β-selective, with only the one anomer being observed. The assignment of anomeric stereochemistry reposes on the characteristic, somewhat upfield chemical shift (typically δ 3.0−3.2 in $CDCl_3$) of the mannose H5 in the β-series,[7c] which we have consistently found to be a reliable diagnostic and which has been independently verified by means of nuclear Overhauser measurements and anomeric $^1J_{CH}$ coupling constants[24] on many occasions.

As expected, dropwise addition of tributyltin hydride and AIBN to mannosides **10**−**13** in toluene at reflux afforded the corresponding β-D-rhamnosides **14**−**17** in good yield, as well as the simple 4,6-*O*-benzylidene-protected mannosides **18**−**21** (Scheme 3, Table 1). In each reaction, the sole fragmentation product was the 6-deoxy sugar, with none of the alternative 4-deoxy products being observed in the crude reaction mixtures. The benzylidene acetal byproducts, arising from premature quenching of the benzylidene radical intermediates, were formed as single isomers with the depicted stereochemistry. Stereochemical assignment of the acetals was made by comparison with the spectral data of authentic standards and is consistent with axial quenching of the intermediate σ-radical.[25]

Tetrasaccharide Synthesis. In designing the synthesis of tetrasaccharide **1**, as its β-methyl glycoside, emphasis was placed

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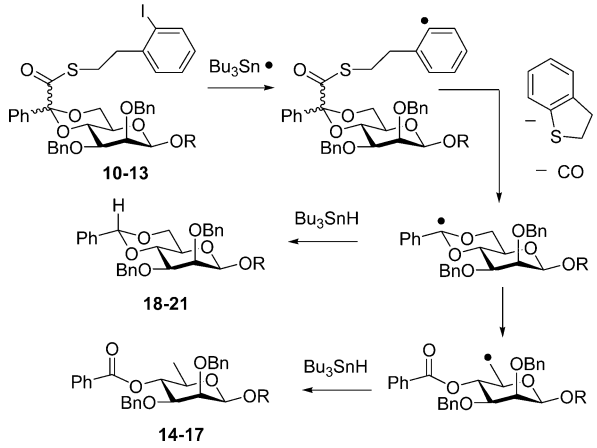
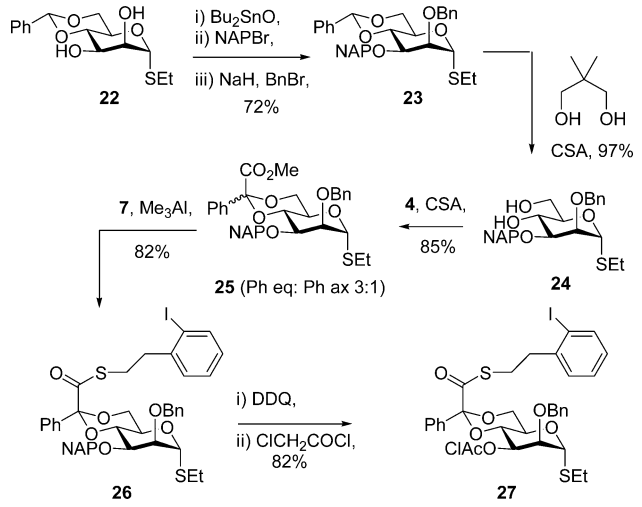
Scheme 3. Reductive Radical Fragmentation



on using, as closely as possible, a set of standard glycosylation conditions for the formation of all glycosidic bonds, for which the BSP/triflic anhydride activation of thioglycosides was selected,[7d,9i,26] and on obtaining the β-D- and α-D-rhamnopyranosidic units with a minimum of steps from a common building block. Toward this end, diol **22**[9f] was converted to the 3-*O*-(2-naphthyl)methyl ether[27] by treatment with dibutyltin oxide[28] and then 2-naphthylmethyl bromide. Standard benzylation with benzyl bromide and sodium hydride then afforded the fully protected thioglycoside **23**. The benzylidene acetal was selectively removed by treatment with neopentyl glycol and camphor sulfonic acid in methylene chloride, giving diol **24**. Exposure to acetal **4** in the presence of camphorsulfonic acid enabled introduction of the modified benzylidene acetal **25** as a mixture of stereoisomers, of which only the less polar isomer, presumed to have an equatorial phenyl group (vide supra), was employed in the subsequent work to facilitate spectral interpretation. Treatment of **25** with thiol **7** and trimethylaluminum then gave the β-D-rhamnosyl donor **26** (Scheme 4). This substance was converted in two steps: selective naphthylmethyl ether removal with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and esterification to the presumed α-D-rhamnosyl donor **27** (Scheme 4). The 3-*O*-chloroacetate **27** was selected as the α-rhamnosyl donor on the basis of previous observations, whereby an ester at the 3-position was found to be strongly α-directing and to overcome the strong β-directing influence of the 4,6-*O*-benzylidene acetal in the mannose series,[29] and the presumption that it could be selectively removed in the presence of the hindered thiol ester function.

Methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside **28**, obtained by reduction of the corresponding 4,6-*O*-benzylidene acetal with sodium cyanoborohydride in the presence of HCl,[30] was coupled to donor **26** on a 2 g scale, following preactivation with BSP and Tf_2O in the presence of TTBP in dichloromethane at −60 °C to give an 85% yield of the β-mannoside **29** along with a

Scheme 4. Preparation of Donors **26** and **27**



7% yield of the α-anomer **30** (Scheme 5). The stereochemistry of **29** is readily apparent from the characteristic upfield chemical shift of the mannose H5 residue (δ 3.20), which is shifted considerably downfield in the α-anomer. Exposure to wet DDQ then removed the naphthylmethyl ether, providing alcohol **31** for the next coupling. Interestingly, attempts at the activation of donor **27** with BSP and Tf_2O failed, and we therefore turned to the even more potent combination of diphenyl sulfoxide and Tf_2O, subsequently developed by van Boom and co-workers[8e,31] following initial work by Gin on the activation of hemiacetals.[32] This reagent combination performed excellently and permitted coupling of **27** with disaccharide acceptor **31**, giving trisaccharide **32** in 75% yield. As anticipated,[29] only α-glycoside **32** was formed in this reaction. In this trisaccharide, only one mannose H5 resonance was found in the region δ 3.0−3.2, consistent with the presence of only one of two possible β-mannosides; moreover, in the gated CH coupled ^{13}C NMR spectrum, three anomeric carbon resonances were located with $^1J_{CH}$ coupling constants of 154.6, 153.3, and 175.1 Hz, in agreement with the presence of two equatorial and one axial glycosidic linkages.[24] Removal of the chloroacetate protecting group with ethylenediamine[33,34] provided alcohol **33** (Scheme 5) and set the stage for the conversion of the two mannoside groups to the corresponding rhamnosides.

Dropwise addition of tributyltin hydride and AIBN to a solution of **33** at reflux in toluene provided bis rhamnosyl trisaccharide **34** in 54% isolated yield. The final coupling was accomplished by the standard BSP/Tf_2O activation protocol, using galactosyl donor **35**, whose α-selectivity under similar conditions had been previously established.[26] In this coupling, tetrasaccharide **36** was formed as a single α-anomer, as was clear from the gated CH coupled ^{13}C NMR spectrum, which exhibited four anomeric carbon signals with $^1J_{CH}$ coupling constants of 160.4, 159.1, 173.1, and 168.9 Hz, consistent with the presence of two equatorial and two axial glycosidic linkages,

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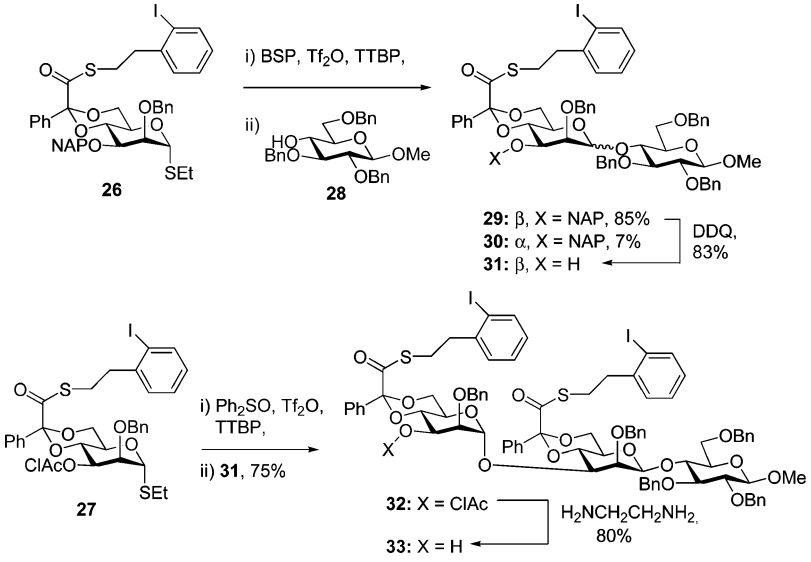
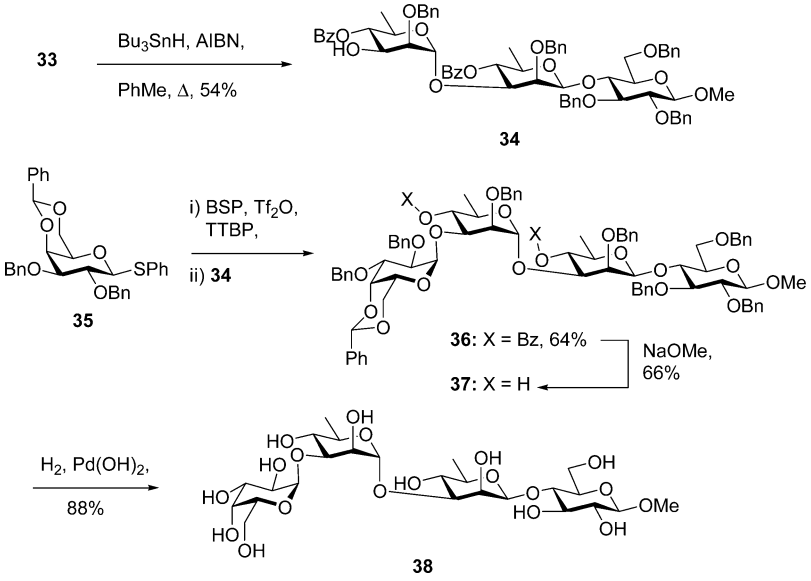
(34) Note that it was necessary to remove the chloroacetate group prior to the radical reaction to prevent competitive reduction of the relatively weak chloroacetate C−Cl bond by the stannane.

Scheme 5. Stereocontrolled Trisaccharide Formation



Scheme 6. Double Radical Fragmentation and Completion of the Synthesis



respectively. Saponification of the two benzoate esters provided diol **37**, which finally was converted to the target **38**, the methyl glycoside of **1**, by hydrogenolysis over Pearlman's catalyst (Scheme 6). The fully deprotected tetrasaccharide displayed a molecular ion in the high-resolution ESIMS, consistent with the assigned structure. In the ^{1}H NMR spectrum, four clearly resolved anomeric hydrogen signals were present at δ 4.20 (d, J = 8.0 Hz, β-Glu), 4.64 (br s, β-Rha), 4.99 (br s, α-Rha), and 5.17 (d, J = 3.5 Hz, α-Gal), while the ^{13}C NMR spectrum presented four anomeric carbon resonances at δ 103.9 (d, $^1J_{CH}$ = 157.3 Hz, β-Glu), 100.0 (d, $^1J_{CH}$ = 158.8 Hz, β-Rha), 102.8 (d, $^1J_{CH}$ = 169.5 Hz, α-Rha), and 100.8 (d, $^1J_{CH}$ = 167.2 Hz, α-Gal), in complete agreement with structure **38**.

In summary, a method for the stereocontrolled synthesis of β-D-rhamnopyranosidic linkages has been developed. This method consists of a stereocontrolled β-mannoside synthesis, directed by a modified benzylidene acetal, followed by a single-step reductive radical fragmentation to the 6-deoxy sugar. Operation of the method in the presence of a 3-*O*-carboxylate ester in the donor permits the equally direct and stereocontrolled synthesis of α-D-rhamnopyranosides. The single-step radical-fragmentation method has been conducted in the presence of up to five benzyl ethers without detriment. In the synthesis of the tetrasaccharide repeating unit of the *Escherichia hermannii* ATCC 33650 and 33652, both the α-D- and β-D-rhamnopyranosidic units were obtained in a single step by a double radical fragmentation of the corresponding mannosides.

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Supporting Information Available: Full experimental and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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