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The 4,6-*O*-[α-(2-(2-Iodophenyl)ethylthiocarbonyl)benzylidene] Protecting Group: Stereoselective Glycosylation, Reductive Radical Fragmentation, and Synthesis of β-D-Rhamnopyranosides and Other Deoxy Sugars

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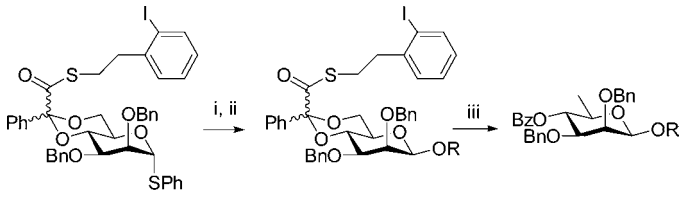
ABSTRACT



i) BSP, TTBP, Tf_2O, -60 °C; ii) ROH; iii) Bu_3SnH, AIBN, Δ

In the thioglycoside/BSP/Tf_2O glycosylation method, the 4,6-*O*-[α-(2-(2-iodophenyl)ethylthiocarbonyl)benzylidene] group enforces β-selectivity in mannopyranosylations. Following glycosylation, treatment with Bu_3SnH in toluene at reflux affords regioselective, reductive fragmentation to the 6-deoxy-β-mannosides (β-rhamnosides). Applied to glucosides, the radical fragmentation provides 6-deoxyglucosides, whereas 4-deoxygalactosides are the preferred products in the galactose series. The radical fragmentation is fully compatible with the presence of benzyl and *p*-methoxybenzyl ethers and with acetate esters

The β-rhamnopyranosides are frequent components of bacterial polysaccharides and thus constitute important synthetic targets. They differ from the β-mannopyranosides only by the replacement of the 6-hydroxy group by a C−H bond and therefore present a comparable synthetic challenge.[1,2] Both enantiomeric modifications exist in nature but, by virtue of the differing availability of the sugars themselves, present significantly different synthetic challenges.[3,4] L-Rhamnose itself, but not L-mannose, is readily available and is therefore the obvious starting point for the β-L-rhamnopyranosides,[5]

(1) Pozsgay, V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, p 319.

(2) Recent developments: (a) Abdel-Rahman, A. A.-H.; Jonke, S.; El Ashry, E. S. H.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2972. (b) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc*. **2001**, *123*, 8477.

(3) β-L-Rhamnosides are components of the repeating unit of the antigenic capsular polysaccharides from *Streptococcus pneumoniae*. For example, see: Jones, C.; Whitley, C.; Lemercinier, X. *Carbohydr. Res.* **2000**, *325*, 192.

(4) β-D-Rhamnosides are found in the repeating unit of the antigenic exopolysaccharide common to *Escherichia hermannii* ATCC 33650 and 33652 isolated from human wounds, sputum, lungs, and stools: Beynon, L. M.; Bundle, D. R.; Perry, M. B. *Can. J. Chem.* **1990**, *68*, 1456. The ultimate challenge in terms of β-D-rhamnoside synthesis is probably the antigenic polysaccharide from *Escherichia hermannii* ATCC 33651, a β-D-rhamnan: Perry, M. B.; Richards, J. C. *Carbohydr. Res.* **1990**, *205*, 371.

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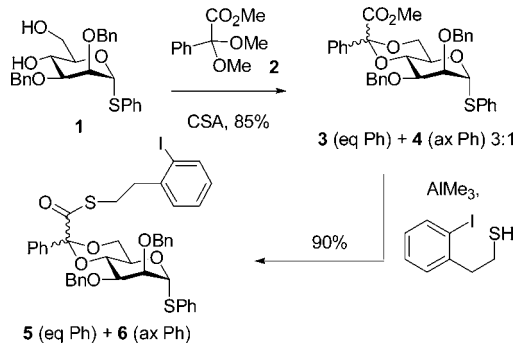
while in the D-series the converse is true and mannose must be used as a starting material. The direct synthesis of β-D-mannopyranosides, both in solution and on the solid phase, is straightforward provided that the donor is protected by the 4,6-*O*-benzylidene moiety or by a surrogate such as the 4,6-*O*-polystyrylboronate group.[6] The problem of the β-D-rhamnopyranosides therefore reduces to that of the reductive regioselective cleavage of the 4,6-*O*-benzylidene group to the 6-deoxy system. Here, we introduce the 4,6-*O*-[α-(2-(2-iodophenyl)ethylthiocarbonyl)benzylidene] group as a surrogate for the 4,6-*O*-benzylidene group that is capable of enforcing high β-selectivity in direct mannosylations and which is subsequently cleaved in a single step to the β-D-rhamnopyranoside system.

The cleavage of 4,6-*O*-benzylidene-protected sugars to their 4-*O*-benzoyl-6-bromo-6-deoxy congeners by *N*-bromosuccinimide is an established reaction in carbohydrate chemistry.[7,8] Unfortunately, the reaction is not suitable for use in the presence of benzyl and allyl-type protecting groups due to the competing cleavage of these groups, which significantly reduces yields and complicates isolation.[9] This incompatibility precludes the use of the NBS cleavage in the synthesis of β-D-rhamnosides from the corresponding β-D-mannnosides as ethers are the protecting groups of choice for the 2- and 3-hydroxy groups in direct β-mannosylation. A further disadvantage of the NBS reaction is the obvious need to remove the bromide atom in a subsequent reduction. As recognized from the outset by Hanessian,[7a−c] the actual cleavage of the 6-C−O bond in the NBS cleavage reaction can be envisaged as proceeding by either a radical or an ionic fragmentation. Roberts developed an alternative based on his catalysis of radical chain reactions by thiols, which leads directly to the 6-deoxy system, and in doing so demonstrated the key fragmentation to be radical in nature.[10] The contrathermodynamic regioselectivity in these radical fragmentations was explained on the basis of MO calculations as arising from the less strained transition state for cleavage of the 6-C−O bond.[11,12] Unfortunately, in our hands, even the very mild Roberts' conditions proved to be incompatible with the presence of benzyl ethers. We were therefore led to contemplate alternative entries into the key α-benzylidene radical and ultimately turned to cyclic acetals derived from benzoylformic acid with the α-benzylidene radical generation through decarbonylation. The need to minimize transformations after glycosylation indicated that the radical precursor itself be stable to the glycosylation conditions; thus, 2-(2-iodophenyl)ethylthio esters[13] became the precursors of choice.

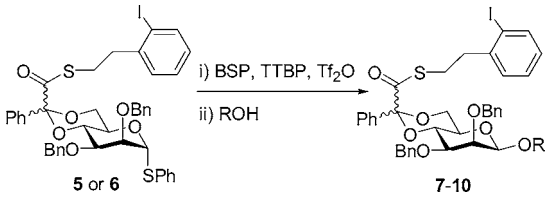
Reaction of **1**[6] with **2**[14] gave the acetals **3** and **4** as a 3/1 mixture in 85% yield, favoring the less polar isomer with the axial carbomethoxy group.[15] Treatment with a reagent formed from 2-(2-iodophenyl)ethylthiol[15] and $AlMe_3$ in toluene at reflux then afforded the separable thioesters **5** and **6** (Scheme 1).[16] It is possible to perform all of the ensuing

Scheme 1. Preparation of Glycosyl Donors



chemistry with the isomeric mixture, but to simplify the spectra at the stage of the glycosylation reaction, we have worked with pure isomers. The action of *N*-benzenesulfinyl piperidine (BSP),[17,18] 2,4,6-tri-*tert*-butylpyrimidine (TTBP),[18,19] and triflic anhydride on **5** at −60 °C in dichloromethane followed by addition of methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside as acceptor gave **7** in 94% yield as a single anomer. It is noteworthy that the BSP/Tf_2O combination cleanly activates the thioglycoside toward coupling but leaves the thioester unchanged. Three further coupling reactions were similarly conducted, each providing the desired β-mannoside in excellent yield and selectivity (Scheme 2, Table 1).

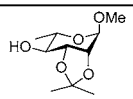
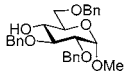
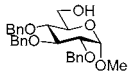
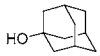
Scheme 2. Stereoselective Formation of Mannosides



Radical fragmentation was achieved by dropwise addition of tributyltin hydride and AIBN to the substrates in toluene

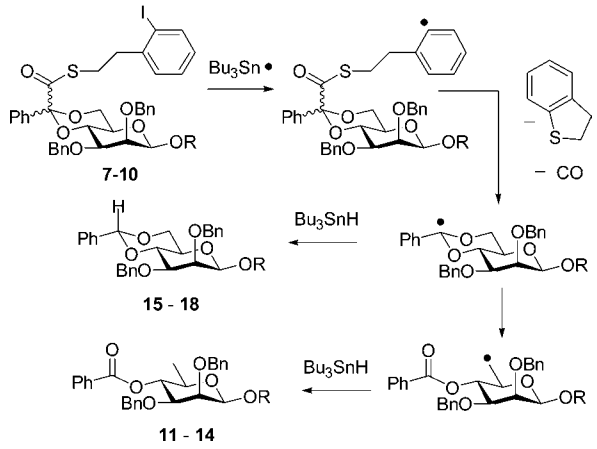
(5) Synthesis of L-rhamnosides: Crich, D.; Picione, J. *Org. Lett.* **2003**, *5*, 781.
(6) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867.
(7) (a) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035. (b) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1045. (c) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1053. (d) Hullar, T. L.; Siskin, S. B. *J. Org. Chem.* **1970**, *35*, 225. (e) Chana, J. S.; Collins, P. M.; Farnia, F.; Peacock, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 94.
(8) Ionic cleavage: Binkley, R. W.; Goewey, G. S.; Johnston, J. C. *J. Org. Chem.* **1984**, *49*, 992.
(9) Reported cleavage of benylidene acetals in the presence of benzyl ethers: Liotta, L. J.; Dombi, K. L.; Kelley, S. A.; Targontsidis, S.; Morin, A. M. *Tetrahedron Lett.* **1997**, *38*, 7833.
(10) Roberts, B. P.; Smits, T. M. *Tetrahedron Lett.* **2001**, *42*, 3663.
(11) Fielding, A. J.; Franchi, P.; Roberts, B. P.; Smits, T. M. *J. Chem. Soc., Perkin Trans. 2* **2002**, 155.
(12) Other contrathermodynamic radical ring openings and a similar explanation: Ziegler, F. E.; Zheng, Z. L. *J. Org. Chem.* **1990**, *55*, 1416.
(13) Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566.
(14) Chan, T. H.; Brook, M. A.; Chaly, T. *Synthesis* **1983**, 203.
(15) Stereochemistry of **3** and **4** was assigned by parallels in the ^{13}C NMR chemical shifts and the relative polarities with the pyruvate acetals. Garegg, P. J.; Janesson, P.-E.; Lindberg, B.; Lindh, F.; Lonngren, J.; Kvarnstrom, I.; Nimmich, W. *Carbohydr. Res.* **1980**, *78*, 127 and references therein.
(16) Gennari, C.; Carcano, M.; Donghi, M.; Mongelli, N.; Vanotti, E.; Vulpetti, A. *J. Org. Chem.* **1997**, *62*, 4746.

Table 1. Glycosylation and Cleavage in the Mannose Series

donor	acceptor	β-mannoside (% yield)	β-rhamnoside (% yield)	acetal (% yield)
5		**7** (94%)	**11** (78%)	**15** (8%)
5		**8** (71%)	**12** (74%)	**16** (13%)
6		**9** (77%)	**13** (78%)	**17** (8%)
5		**10** (84%)	**14** (80%)	**18** (9%)

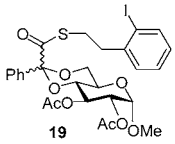
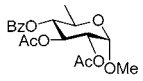
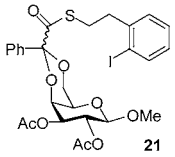
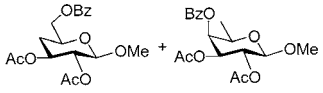
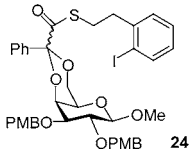
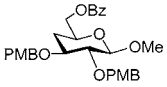
at reflux when the β-D-rhamnosides were obtained in high yield (Scheme 3, Table 1). As expected, the regioselectivity of all reactions was very high such that the alternative 6-*O*-benzoyl-4-deoxy-type products were not detected. The byproducts are the known 4,6-*O*-benzylidene-protected β-mannosides[20] arising from competing quenching of the benzylidene radical by the stannane.[21]

Scheme 3. Reductive Radical Fragmentation



Our focus has been on the synthesis of the β-D-rhamnosides, and thus we have emphasized the reductive fragmentation of the 4,6-*O*-type acetals in the mannopyranose series. There is no reason, in view of the common fragmentation step, why the new protecting group should not function as an effective precursor to other deoxy sugars with the same regioselectivity[7] as the NBS-mediated cleavage of other known benzylidene acetals. Indeed, Table 2 sets out examples

Table 2. Cleavage in the Glucose and Galactose Series

substrate[a]	product (% yield)
 **19**	 **20** (82)
 **21**	 **22** (89) + **23** (9)
 **24**	 **25** (70)

[a] Substrate preparation is described in Supporting Information.

of application in both the glucopyranose and galactopyranose series, wherein the regioselectivity is consistent with that obtained by previous workers in the field.[7,10,11] Furthermore, it is demonstrated that, as expected, the radical chemistry may be satisfactorily conducted in the presence of acetate esters and even *p*-methoxybenzyl ethers.

In summary, we have demonstrated a very direct entry into 6-deoxy sugars using a highly stereoselective glycosylation followed by a clean, regioselective, reductive radical cleavage of an acetal. Most importantly, these radical fragmentation reactions were compatible with the presence of up to six benzyl ethers.

Acknowledgment. We thank the NIH (GM 57335) for support of this work.

Supporting Information Available: Full experimental details and copies of spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034741R

(17) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.
(18) Available from Lakeview Synthesis, Chicago, IL (www.lakeviewsynthesis.com).
(19) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323.
(20) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321.
(21) Formed with high selectivity for the isomer shown due to the preferred axial quenching of the intermediate σ-type radical. Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, Germany, 1996.