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Direct Synthesis of the β-L-Rhamnopyranosides

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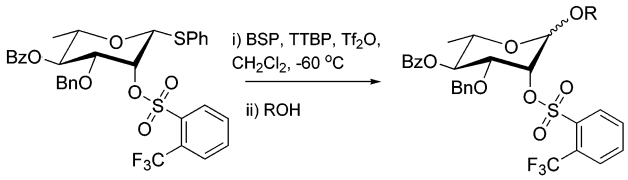
ABSTRACT



The direct formation of β-L-rhamnopyranosides by means of thioglycoside donors protected with a 2-*O*-sulfonate ester and, ideally, a 4-*O*-benzoyl ester, is reported. Activation is achieved with the combination of 1-benzenesulfinyl piperidine and triflic anhydride in the presence of 2,4,6-tri-*tert*-butylpyrimidine. Selectivities vary from moderate to good, and the sulfonyl group is easily removed post-glycosylation with sodium amalgam in 2-propanol.

The chemical synthesis of the β-L-rhamnopyranosides is a cognate problem to that of the β-D-mannopyranosides[1] insofar as both are cis-equatorial type glycopyranosidic bonds for which, until recently, there has been no viable direct approach other than the use of 2,3-*O*-carbonate-[2] or 2,3-*O*-alkylidene-protected[3] glycosyl bromides in conjunction with insoluble silver-based promoters. Closer inspection, however, reveals the rhamnoside problem to be the more complex of the two. First, our recent solution to the β-mannoside problem involving torsionally disarmed, 4,6-*O*-benzylidene-protected donors, thioglycosides,[4] or glycosyl sulfoxides[5] and triflate counterions cannot be applied in the rhamnose series because of the 6-deoxy function. Second, the 6-deoxy system influences any equilibrium between covalently bound donors and contact and solvent separated ion pairs and therefore impinges directly on the glycosylation mechanism. We describe here a direct entry to the β-L-rhamnosides by means 2-*O*-sulfonyl-protected rhamnosyl thioglycosides, activated with the combination of 1-benzenesulfinyl piperidine (**BSP**)[6,7] and triflic anhydride.

Embarking on this project, we took our cue from the work of Schuerch in which it was demonstrated that the 2-*O*-sulfonyl group is capable of stabilizing α-mannosyl and α-rhamnosyl sulfonate esters and of directing glycosylation, albeit with a very limited range of acceptors, to the β-position.[8,9,10] Preliminary investigations soon revealed the instability of trans-diaxial 2-*O*-sulfonyl-α-glycosyl thioglycosides and directed our attention to the β-thiorhamnosides as donors. A number of 2-*O*-sulfonates were prepared as outlined in Scheme 1 and were screened for their ability to promote the β-glycosylation of 3β-cholestanol as set out in

(1) (a) Pozsgay, V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, p 319. (b) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471. (c) Barresi, F.; Hindsgaul, O. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood: Amsterdam, 1996; p 251.

(2) Backinovsky, L. V.; Balan, N. F.; Shashkov, A. S.; Kochetkov, N. K. *Carbohydr. Res.* **1980**, *84*, 225.

(3) Iversen, T.; Bundle, D. R. *Carbohydr. Res.* **1980**, *84*, C13.

(4) (a) Crich, D.; de la Mora, M.; Cruz, R. *Tetrahedron* **2002**, *58*, 35. (b) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867. Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640.

(5) (a) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321. (b) Crich, D.; Li, H.; Yao, Q.; Wink, D. W.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 5826. (c) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263.

(6) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.

(7) BSP and TTBP are available from www.lakeviewsynthesis.com.

(8) (a) Srivastava, V. K.; Schuerch, C. *J. Org. Chem.* **1981**, *46*, 1121. (b) Awad; L. F.; El Ashry, E. S. H.; Schuerch, C. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1587.

(9) Reviewed in: Crich, D. In *Glycochemistry: Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Eds; Dekker: New York, 2001; p 53. Crich, D. *J. Carbohydr. Chem.* **2002**, *21*, 663.

(10) During the later stages of this investigation an isolated example of β-mannosylation with a 2-*O*-sulfonate protected trichloroacetimidate donor was described: Abdel-Rahman, A. A.-H.; Jonke, S.; El Ashry, E. S. H.; Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2972.

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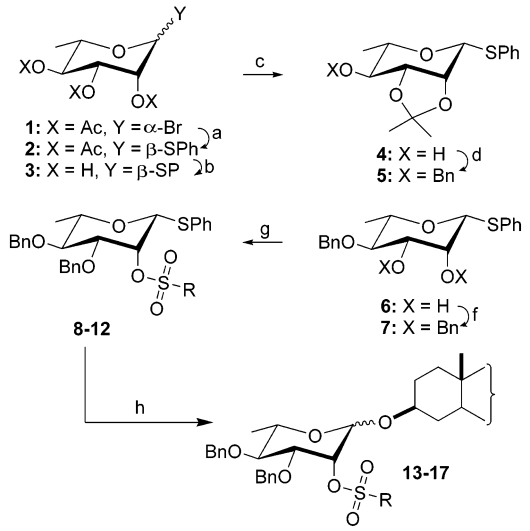
Scheme 1. Screening of Sulfonates for Propensity to β-Rhamnoside Formation[a]



[a] Key: (a) PhSH, NaH, HMPA, 78%; (b) NaOMe (cat.), MeOH, 95%; (c) PTSA (cat.), 2,2-dimethoxypropane, acetone, 79%; (d) BnBr, NaH, THF, 87%; (e) MeOH/H_2O, AcOH, reflux, 90%; (f) (i) Bu_2SnO, benzene, (ii) BnBr, CsF, DMF, 71%; (g) Et_3N, RSO_2Cl, CH_2Cl_2, 60−89%; (h) (i) BSP, Tf_2O, TTBP, −60 °C, CH_2Cl_2, (ii) cholestanol/CH_2Cl_2.

Table 1. All couplings were carried out by a standard protocol involving activation of a mixture of glycosyl donor, **BSP**,

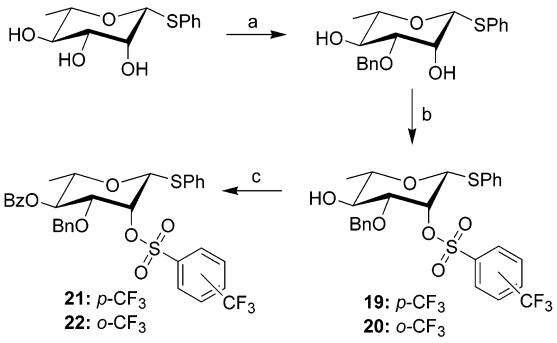
Table 1. β-Rhamnosylation of 3β-Cholestanol with Donors **8**−**12**

donor	SO_2R	product (% yield)	β/α ratio
8	p-C_6H_4Br	**13** (74)	2:1
9	p-C_6H_4F	**14** (81)	2:1
10	p-C_6H_4CN	**15** (69)	4:1
11	p-$C_6H_4CF_3$	**16** (75)	5.5:1
12	CH_2CF_3	**17** (70)	4.4:1

and 2,4,6-tri-*tert*-butylpyrimidine (**TTBP**)[7,11] in dichloromethane at −60 °C with triflic anhydride followed by addition of the acceptor alcohol. It is assumed, based on extensive work in the mannose series, that the combination of thioglycoside, **BSP**, and triflic anhydride results in the rapid formation of a co-valent glycosyl triflate[12] which is the actual glycosyl donor.

The optimal combination of yield and selectivity was obtained with the *p*-trifluoromethylbenzenesulfonate **11** but it was apparent that even this highly disarmed donor was unlikely to be sufficiently selective with less-reactive, carbohydrate-based acceptors. We reasoned that a further increase in β-selectivity could be obtained by the introduction of a second electron-withdrawing protecting group, i.e., with an even more strongly disarmed system. Mindful of the need for maximum orthogonality of protection in any donor, we elected to introduce a carboxylate ester, rather than a further sulfonate group, to fulfill this function. It having been previously shown that 3-*O*-benzoyl groups are strongly α-directing in mannosylation by the glycosyl triflate method,[13] presumably through neighboring group participation, the only option was a 4-*O*-carboxylate ester. Toward this end, regioselective 3-*O*-monobenzylation of α-thiorhamnoside **3** was conveniently achieved through treament with dibutyltin oxide and then benzyl bromide. Sulfonylation then afforded **19**, benzoylation of which gave the requisite donor **21** (Scheme 2). Unfortunately, the highly crystalline nature of

Scheme 2. Preparation of Donors **21** and **22**[a]

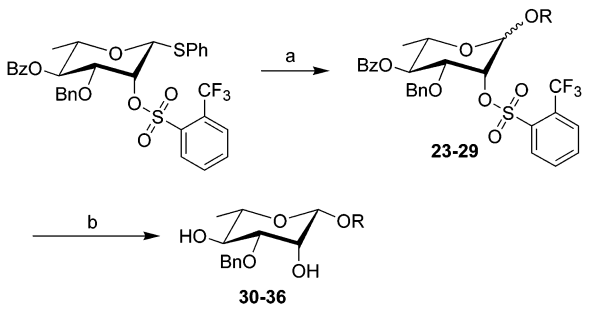


[a] Key: (a) (i) Bu_2SnO, benzene, (ii) BnBr, CsF, DMF, 71%; (b) RSO_2Cl, Ag_2O, KI, *sym*-collidine, CH_2,Cl_2, **19**: 55%, **20**: 52%; (c) Et_3N, BzCl, CH_2Cl_2, **21**: 90%, **22**: 88%.

this substance, and of the corresponding acetate, rendered it all but insoluble in dichloromethane at −60 °C and, so, of no use as a glycosyl donor in our system. This problem was circumvented through preparation of the *o*-trifluoromethyl analogue **22**, which proved much more pliable, via **20** (Scheme 2).

A series of glycosylations were then conducted with **22** as donor (Scheme 3) under the standard conditions with the results reported in Table 2. Comparison of the last entry of

Scheme 3. β-Rhamnosylation with Donor **22** and Subsequent Desulfonylation[a]



[a] Key: (a) (i) BSP, TTBP, Tf_2O, CH_2Cl_2, (ii) ROH/CH_2Cl_2; (b) Na/Hg, 2-propanol, THF.

(11) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323.
(12) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.

Table 2. β-Rhamnosylation with Donor **22** and Subsequent Desulfonylation

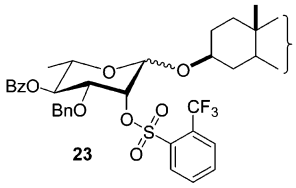
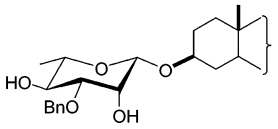
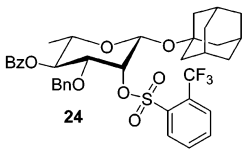
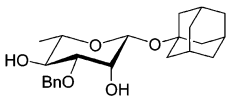
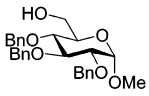
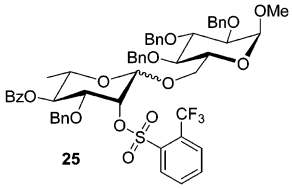
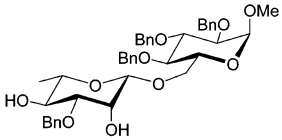
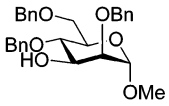
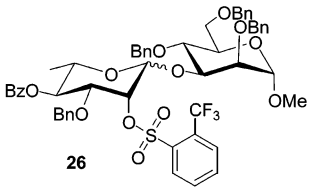
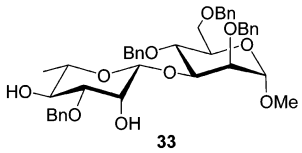
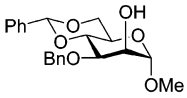
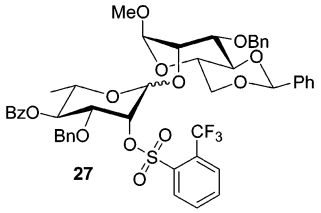
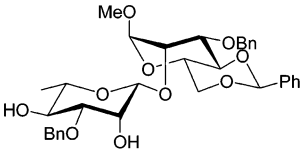
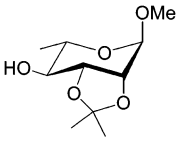
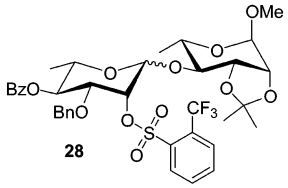
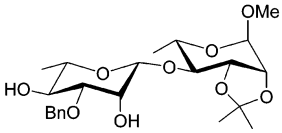
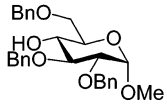
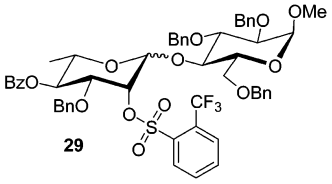
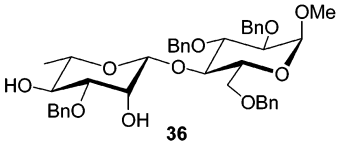
Acceptor	Product	% Yield (β:α ratio)	Desulfonylation Product	% Yield
3β-Cholestanol	 **23**	71 (9:1)	 **30**	75
1-Adamantanol	 **24**	81 (β-only)	 **31**	73
	 **25**	68 (5:1)	 **32**	80
	 **26**	75 (3:1)	 **33**	65
	 **27**	72 (3:1)	 **34**	61
	 **28**	63 (2:1)	 **35**	70
	 **29**	66 (1:1)	 **36**	77

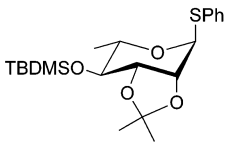
Table 1 with the first in Table 2, for which the only difference is the exchange of a benzyl ether for a benzoate ester, reveals a significant increase in selectivity with the more highly disarmed system. In general, β-rhamnosylation with donor **22** proceeds well with primary and more-reactive secondary acceptors. With the less reactive secondary acceptors the stereoselectivity falls off reaching a minimum for the systems studied for the difficult case of the glucose 4-OH acceptor. It is noteworthy that, as in our β-mannosylations, tertiary alcohols, represented here by 1-adamantanol, are extremely β-selective.

Finally, attention was turned to removal of the sulfonyl group. Among the many methods known for the removal of sulfonate esters, simple treatment with sodium amalgam in 2-propanol was selected for reasons of ease of operation and mildness of conditions. All the β-rhamnosides prepared from donor **13** were thus exposed to this reagent (Scheme 3), resulting in the isolation of the desulfonylated glycosides **30**-**36** which had also undergone removal of the benzoate ester (Table 2).

(13) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291.

Concerning the assignment of stereochemistry, differentiation between the β- and α-2-*O*-sulfonyl protected rhamnosides was made on the basis of the $^1J_{CH}$ coupling at the anomeric carbon[14] with the former typically having a value in the range 152.3−159.8 Hz and the latter 167.2−172.3 Hz.

Combined with the ability to form α-rhamnosides directly and in high yield from donors **37** and **38**, the present work extends the scope of our standardized thioglycoside/sulfonamide/triflic anhydride coupling to one of the more difficult classes of glycosidic bond. For all but the least reactive of acceptors the methodology we describe compares favorably with other approaches to β-rhamnosides involving either indirect methods[15] or intramoleclar aglycone delivery,[16] both of which are necessarily less efficient. Further optimization studies are in progress and will be reported in due course.



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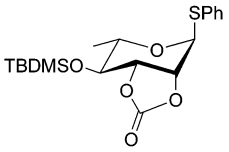

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Supporting Information Available: Synthetic details and characterization for all new molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.
(15) Lichtenthaler, F. W.; Metz, T. W. *Tetrahedron Lett.* **1997**, *38*, 5477.
(16) Lau, R.; Schüle, G.; Schwaneberg, U.; Ziegler, T. *Liebigs* **1995**, 1745.