JOC Article

The 3,4-*O*-Carbonate Protecting Group as a *β*-Directing Group in Rhamnopyranosylation in Both Homogeneous and Heterogeneous Glycosylations As Compared to the Chameleon-like 2,3-*O*-Carbonates

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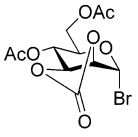
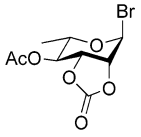
It is demonstrated that the *β*-selectivity observed in the insoluble silver salt mediated couplings of 2,3-*O*-carbonate-protected rhamnosyl bromides is uniquely due to the heterogeneous nature of the reaction. In homogeneous solution these same donors are α-selective, a fact that is attributed to the half-chair conformation of these substances which reduces the energy barrier to oxacarbenium ion formation. It is suggested that the 2,3-*O*-carbonate group be dubbed torsionally arming in the manno- and rhamnopyranose series. When the carbonate group is removed to the 3,4-*O*-position a *β*-selective system is formed, in both homogeneous and heterogeneous conditions, and it is demonstrated that this selectivity arises from the combination of the electron-withdrawing nature of the carbonate and its inability to take part in neighboring participation.

Introduction

In the realm of carbohydrate chemistry, the cyclic carbonate protecting group for vicinal diols has earned a reputation as being one of the few groups capable of enforcing *β*-glycosylations in the manno- and rhamnopyranose series. Thus, as reported originally by Gorin and Perlin,[1] a 2,3-*O*-carbonate-protected mannosyl bromide **1** affords *β*-mannosides with high diastereoselectivity when presented with an acceptor alcohol in the presence of an insoluble silver salt as promoter. The corresponding effect was reported by Kochetkov and co-workers for the rhamnosyl bromide **2**,[2] and numerous subsequent examples have been collated in reviews.[3]



1



2

The effect is usually explained by a combination of two factors. First, the strongly electron-withdrawing carbonate destabilizes any potential oxacarbenium ions derived by expulsion of the anomeric leaving group, thereby limiting the α-face selective S_N1 process. Second, it is supposed that the absorption of the bromide on the promoter surface occurs in such a way as to shield the α-face.[3ab,4] The first argument is supported by the demonstrated and widely applied principle that the disarming effect[5] of an electron-withdrawing protecting group is stronger the closer it is to the reactive center,[6] i.e, a 2,3-*O*-carbonate should be highly effective at oxacarbenium ion destabilization. The second reason, the preferential shielding of the α-face by the insoluble promoter, though widely accepted and quoted, does not appear to be supported by any published evidence. The first indication that one or the other of these reasons was flawed arose from the glycosylation of **3** with the mannosyl donor **4** promoted by benzenesulfenyl triflate, which contrary to our expectations afforded only the α-anomer **5** (Scheme 1).[7]

This result was in contrast to our expectation, based on our earlier work with *β*-selective 4,6-*O*-benzylidene-protected mannosyl donors,[8] that the two protecting groups would reinforce each other providing for a highly *β*-selective system. In a subsequent synthesis we noted

(1) Gorin, P. A. J.; Perlin, A. S. *Can. J. Chem.* **1961**, *39*, 2474−2485. (2) Backinowsky, L. V.; Balan, N. F.; Shashkov, A. S.; Kochetkov, N. K. *Carbohydr. Res.* **1980**, *84*, 225−235.

(3) (a) Barresi, F.; Hindsgaul, O. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic Publishers: Amsterdam, The Netherlands, 1996; pp 251−276. (b) Pozsgay, V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 319−343. (c) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471−1491.

(4) van Boeckel, C. A. A.; Beetz, T.; van Aelst, S. F. *Tetrahedron* **1984**, 4097−4107.

(5) (a) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584. (b) Andrews, C. W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280−5289.

(6) (a) Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51−65. (b) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (c) Green, L. G.; Ley, S. V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 427−448.

(7) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291−1297.

(8) (a) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348. (b) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

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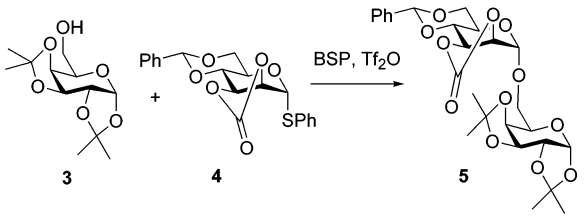
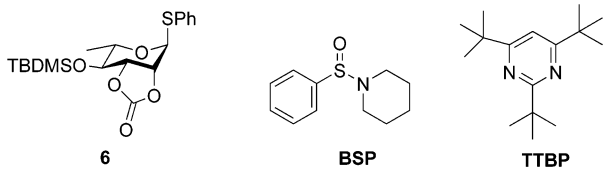
SCHEME 1. α-Selective Mannosylation Directed by a 2,3-*O*-Carbonate



that a 2,3-*O*-carbonate-protected rhamnosyl thioglycoside **6** was similarly an α-selective donor[9] in our powerful 1-benzenesulfinyl piperidine (BSP)/TTBP/triflic anhydride mediated system.[10−12]

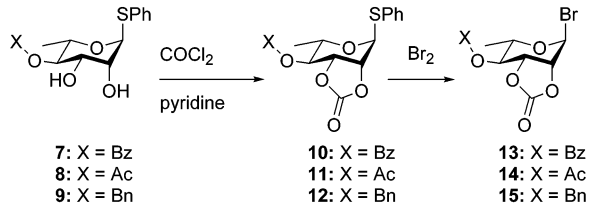


We report here on our attempts to resolve this apparent paradox which have led to the discovery of the 3,4-*O*-carbonate as a superior *β*-directing protecting group in homogeneous glycosylations in the rhamnose field, a contravention of the common wisdom that the more remote electron-withdrawing groups have less effect on the outcome of glycosylation reactions.[6]

Results and Discussions

In attempting to rationalize the observations of Scheme 1 we hypothesized that the α-selectivity was a case of ground-state destabilization. More precisely, we suggested that the glycosyl triflate,[8b] formed on activation of **4**, adopted the $^{O}H_5$ half-chair conformation and that this reduced the energy gap between the covalent triflate and the sofa conformation oxacarbenium ion thereby facilitating formation of the α-selective cation.[7] Moreover, it was obvious that this effect was not a small one as it completely overrode the normal *β*-directing effect of the 4,6-*O*-benzylidene group. Our argument was supported by NMR analyses of 2,3-*O*-carbonate-protected mannosides reported by Kunz which indicated the $^{O}H_5$ conformation.[13] This being the case, it was evident that the success of the insoluble silver method with donors **1** and **2** was not due to any strongly disarming effect of the carbonate but must be related to the promoter. Evidence

SCHEME 2. Preparation of 2,3-*O*-Carbonate-Protected Rhamnosyl Donors



in support of the critical insoluble nature of the promoter in glycosylations with **2** was provided by a series of couplings with donors **10**−**15**, prepared by reaction of the corresponding known diols **7**−**9**[14] with phosgene and then bromine as set out in Scheme 2, to cholestanol activated with either silver oxide (insoluble), silver triflate (soluble), or BSP/Tf_2O (soluble) for the thioglycosides (Table 1). The stereochemistry of the coupled products was assigned on the basis of the $^3J_{H1,H2}$ coupling constant in the rhamnose system, which was typically 3.0 Hz for the *β*-glycosides and 0 in the α-series. This assignment follows from our earlier work in the mannose series,[7] that of Kunz in the mannose series,[13] and from our own synthetic work with **6** in the rhamnose series.[9a] It is important to note (Table 1) that the common $^1J_{C1,H1}$ coupling constant method[15] of assigning anomeric stereochemistry in the manno- and rhamnopyranoside series breaks down here and should not be used. This, again, is a consequence of the half-chair conformation adopted in the 2,3-*O*-carbonates.

It is evident from Table 1 that when a homogeneous, soluble promoter system is used, i.e., silver triflate with the bromides or BSP/Tf_2O with the thioglycosides, the 2,3-*O*-carbonate is highly α-directing whereas the insoluble silver oxide promoter leads to *β*-selective couplings. Clearly, the *β*-selective couplings widely reported in the literature with **1** and **2** do derive their selectivity from their heterogeneous nature which, in reality, overcomes the true α-directing effect of the 2,3-*O*-carbonate in homogeneous solution.[16] Further inspection of Table 1 reveals that the nature of the protecting group on *O*-4, be it ester or ether, has little influence on the outcome of the couplings, homogeneous or heterogeneous, thereby eliminating the possibility of neighboring group participation by esters at that position having a role to play in the *β*-selective couplings.[4,17,18]

(9) (a) Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640−4646. (b) For a related observation with other 2,3-*O*-carbonyl rhamnosyl donors in homogeneous solution see: Codée, J. D. C.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519−1522.

(10) (a) **BSP**: Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020. (b) **TTBP**: Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323−326.

(11) **BSP** and **TTBP** are commercially available from Lakeviewsynthesis.com.

(12) A related reversal of selectivity was reported for the coupling of the *O*-benzoyloxime of 1-bromo-1-deoxy-α-D-arabino-hexopyranos-2-ulose 3,4,6-tribenzoate to a typical glucopyranose 4-OH acceptor. In a heterogeneous system mediated by silver carbonate the coupling was *β*-selective, whereas with silver triflate and tetramethylurea in dichloromethane solution the *β*-anomer was obtained: Kaji, E.; Matsui, E.; Kobayashi, M.; Zen, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1449−1454.

(13) Guenther, W.; Kunz, H. *Carbohydr. Res.* **1992**, *228*, 217−241.

(14) (a) **7**: Pozsgay, V. *Carbohydr. Res.* **1992**, *235*, 295−302. (b) **8**: Pozsgay, V. *J. Org. Chem.* **1998**, *63*, 5983−5999. (c) **9**: Kim, S.-H.; Augeri, D.; Yang, D.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 1766−1775.

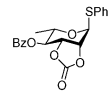
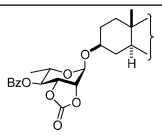
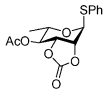
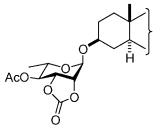
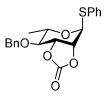
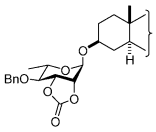
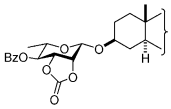
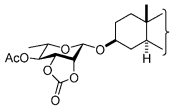
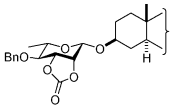
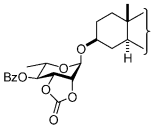
(15) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293−297.

(16) The magnitude of the anomeric effect in mannose (and by extension rhamnose) is such that any mechanism involving S_N2-like displacement of transient *β*-rhamnosyl triflates in the formation of *β*-rhamnosides from **10**−**12** and **13** in homogeneous solution in the presence of triflate anion is highly unlikely. The same situation pertains with donors **26** and **40**. Note that pentaacetyl α-mannopyranose is favored over its *β*-anomer by 1.69 kcal·mol^{-1} whereas in the glucose series the equilibrium only favors the α-anomer by 1.10 kcal·mol^{-1}: Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2214.

(17) (a) Demchenko, A. V.; Rousson, E.; Boons, G.-J. *Tetrahedron Lett.* **1999**, *40*, 6523−6536. (b) Kimura, Y.; Suzuki, M.; Matsumoto, T.; Abe, R.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 423−431. (c) Yamanoi, T.; Nakamura, K.; Takeyama, H.; Yanagihara, K.; Inazu, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1359−1366.

(18) For an actual example of neighboring group participation involving a seven-membered cyclic intermediate see: Wilen, S. H.; Delguzzo, L.; Saferstein, R. *Tetrahedron* **1987**, *43*, 5089−5094.

TABLE 1. Glycosylation of 3β-Cholestanol with 2,3-*O*-Carbonate-Protected Rhamnosyl Donors

Donor	Method /Conditions	Nature	Product (% yield)	$^3J_{H1,H2}$ (Hz)	$^1J_{C1,H1}$ (Hz)
	**BSP/TTBP**/Tf_2O, CH_2Cl_2, -60 °C	Homogeneous		0	169.1
10			**16** (72)		
	**BSP/TTBP**/Tf_2O, CH_2Cl_2, -60 °C	Homogeneous		0	168.9
11			**17** (67)		
	**BSP/TTBP**/Tf_2O, CH_2Cl_2, -60 °C	Homogeneous		0	168.5
12			**18** (59)		
	Ag_2O, CH_2Cl_2, Room temp	Heterogeneous		3.0	165.5
13			**19** (76)		
	Ag_2O, CH_2Cl_2, Room temp	Heterogeneous		3.0	166.5
14			**20** (71)		
	Ag_2O, CH_2Cl_2, Room temp	Heterogeneous		3.0	166.2
15			**21** (51)		
	AgOTf, **TTBP**, CH_2Cl_2, -60 to 25 °C	Homogeneous		0	169.1
13			**16** (56) [+ **19** (10)]		

The above results, wherein the electron-withdrawing nature of the 2,3-*O*-carbonate is more than compensated for by a conformational effect, which merits the name torsionally arming, led us to consider the possibility of employing a 3,4-*O*-carbonate group in rhamnosylation. Thus, we hypothesized that the conformational trap of the 2,3-*O*-carbonates, with their half-chair conformation predisposed to oxacarbenium ion formation, could be escaped by removing the carbonate from the anomeric center by one carbon to the 3,4-position where it would have a trans-fused ring junction to the pyranose ring. To test this possibility donors **26**, **27**, and **28** were prepared from β-phenyl thiorhamnoside **22**[19,20] as set out in Scheme 3 and coupled to a selection of acceptor alcohols by the BSP/Tf_2O method with the results indicated in Table 2. The tri-*O*-benzyl rhamnosyl donor **29**[21] was also included in this study for comparison purposes.

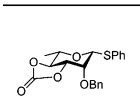
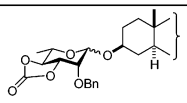
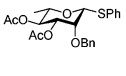
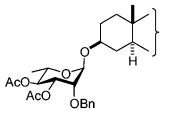
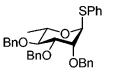
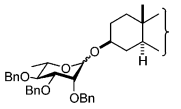
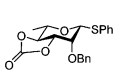
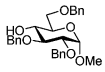
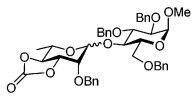
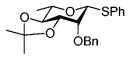
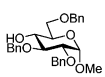
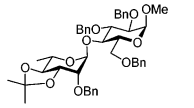
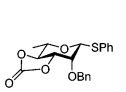
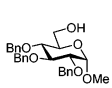
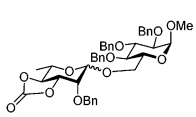
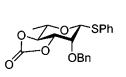
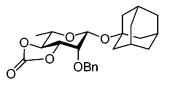
It is immediately evident from the couplings of cholestanol to donors **26**, **27**, and **29** that the 3,4-*O*-carbonate, unlike the 2,3-*O*-carbonates of Table 1, is uniquely β-directing in these homogeneous glycosylation reactions. The contrast between the β-selective nature

(19) Crich, D.; Picione, J. *Org. Lett.* **2003**, *5*, 781−784.

(20) The α-phenylthio analogue of **26** was also prepared by a directly analogous route but the β-anomer illustrated was generally superior owing to the more crystalline nature of several intermediates which facilitate isolation and thereby improve the overall yield. Coupling of the β-phenylthio analogue of **26** to cholestanol by the BSP method in dichloromethane solution gave a 61% yield of **30** with a β:α ratio of 6:1, indicating the β-directing effect of **26** is not a function of the initial stereochemistry of the thioglycoside.

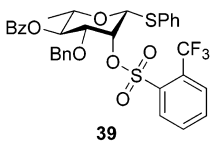
(21) Qiu, D.; Schmidt, R. R. *Synthesis* **1990**, 875−877.

TABLE 2. Rhamnosylations with Donors 26−29 by the BSP/Tf_2O Method

Donor	Acceptor	Product (% yield)	Ratio (β:α)	$^3J_{H1,H2}$ (Hz)	$^1J_{C1,H1}$ (Hz)
			6:1	β: 0 α: 0	β: 156.6 α: 171.1
26		**30** (62)			
			α only	α: 0	α: 167.2
27		**31** (57)			
			1:8	β: 1.2 α: 0	β: 151.9 α: 165.9
29		**32** (70)			
			1:1.5	β: 0 α: 0	β: 160.9 (170.3)[a] α: 173.2 (167.0)[a]
26	**33**	**34** (61)			
			α only	α: 0	α: 169.6 (166.4)[a]
28	**33**	**35** (66)			
			4.5:1	β: 2.0 α: 0	β: 157.8 (165.3)[a] α: 172.3 (170.0)[a]
26	**36**	**37** (77)			
			β only	β: 1.2	β: 152.6
26		**38** (56)			

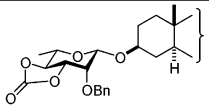
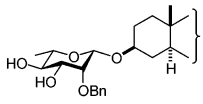
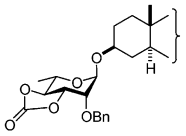
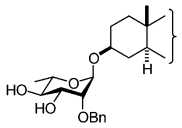
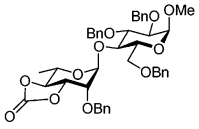
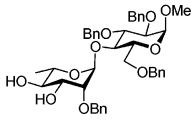
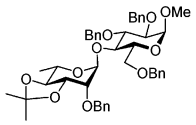
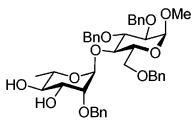
[a] The values in parentheses refer to the coupling constants for the anomeric carbon of the sugar at the reducing end of disaccharides.

of the coupling with the 3,4-*O*-carbonate **26** and that with the 3,4-di-*O*-acetyl donor **27** illustrates the need for the inclusion of the electron-withdrawing carbonyl group in a ring rendering it incapable of neighboring group participation. We have previously observed[7] a 3-*O*-carboxylate group to be α-directing in the closely related mannose series even in the presence of a 4,6-*O*-benzylidene acetal and, so, the α-selective coupling with diacetate **27** was not unexpected. When donor **26** was coupled to the glucose 4-OH acceptor (**33**) the anomeric selectivity was understandably much reduced in view of the relatively poor reactivity of this alcohol. However, when the same alcohol was coupled to the 3,4-*O*-isopropylidene acetal **28**, the reaction was completely α-selective indicating the *β*-selectivity of cyclic carbonate **26** was not due in any major way to a conformational effect arising from the cyclic nature of the protecting group.[22] Overall, it is clear that the *β*-selectivity of **26** is due both to its electron-withdrawing nature destabilizing the anomeric oxacarbenium ion and its cyclic nature, which prevents neighboring group participation. With the less hindered, more reactive glucose 6-OH acceptor (**36**) a return to significant *β*-selectivity was observed as anticipated. Finally, in this series of reactions, the coupling of **26** to 1-adamantanol was conducted resulting in the formation of the *β*-anomer as the only coupling product detected. This high *β*-selectivity with the tertiary alcohol acceptor mirrors that seen in the 4,6-*O*-benzylidene-protected mannosyl donors[8a] and, indeed, with the 4-*O*-benzoyl-2-*O*-sulfonylrhamnosyl donor **39**.[19]



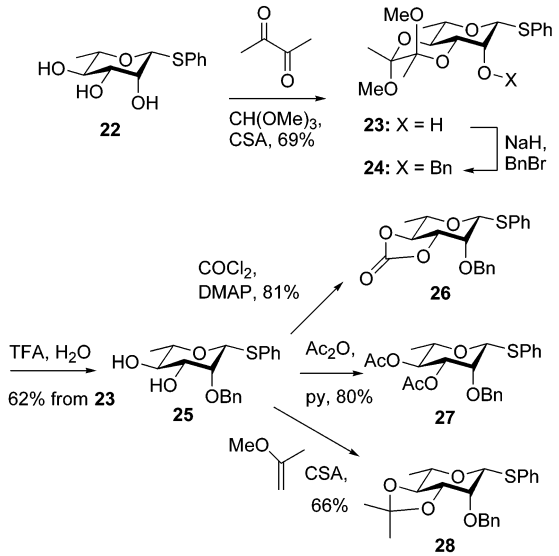
39

TABLE 3. Selected Deprotections in the 3,4-*O*-Carbonate and Isopropylidene Series

Substrate	Product (% yield)	$^3J_{H1,H2}$ (Hz)	$^1J_{C1,H1}$ (Hz)
		0	156.5
30β	**41β** (81)		
		0	165.7
30α	**41α** (76)		
		1.0	166.6 (166.7)[a]
34α	**42α** (68)		
		1.0	166.6 (166.7)[a]
35α	**42α** (89)		

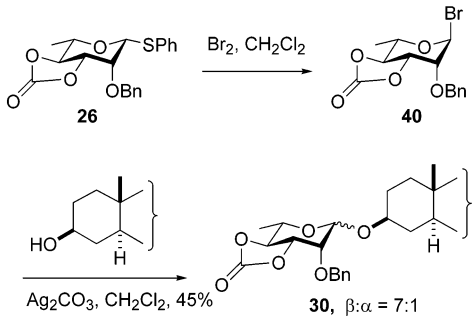
[a] The values in parentheses refer to the coupling constants for the anomeric carbon of the sugar at the reducing end of disaccharide.

SCHEME 3. Preparation of Rhamnosyl Donors 26−28



Donor **26** was converted to the somewhat unstable corresponding α-bromide **40**, which was coupled with cholestanol in dichloromethane by means of silver carbonate, i.e., by the insoluble silver salt method (Scheme 4). The product (**30**) was isolated as 7:1 *β*:α mixture thereby demonstrating that the 3,4-*O*-carbonate system, unlike the 2,3-*O*-carbonates of Table 1, functions analogously whether in homogeneous or heterogeneous coupling reactions.

SCHEME 4. Preparation and Coupling of a 3,4-*O*-Carbonate-Protected Rhamnosyl Bromide



Overall, the *β*-selectivity observed with donor **26** (and **40**) falls short, with the exception of coupling to 1-adamantanol, of that seen with the alternative *β*-rhamnosyl donor **39**, but this is to be expected given that the electron-withdrawing group in **26** is further removed from the site of reactivity. It remains to be seen whether a combination of **26** and **39**, i.e., a 3,4-*O*-carbonyl-2-*O*-sulfonyl donor, will provide enhanced selectivity over the present donors.

With respect to the assignment of configuration in the 3,4-*O*-carbonate-protected products, we examined both the rhamnose $^3J_{H1,H2}$ proton and the $^1J_{C1H1}$ coupling constants collected in Table 2. Unlike the 2,3-*O*-carbonate

(22) Both Danishefsky and Roush have previously employed 3,4-*O*-carbonyl-protected *β*-selective galactosyl donors, which they attributed to greatly enhanced conformational rigidity in the donor. Our results clearly show the effect not to be conformational but rather due to the blocking of neighboring group participation coupled to the electron-withdrawing effect of the carbonate: (a) Randolph, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5693−5700. (b) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1871−1874.

series, there is no useful pattern in the $^3J_{H1,H2}$ proton coupling constants, with both anomers typically displaying the anomeric proton as a broad singlet, or as a doublet with a minimal coupling constant. However, the usual pattern[15] in the anomeric $^1J_{C1H1}$ coupling constants, whereby the α-anomer, with its equatorial hydrogen, has the larger numerical value was observed. To recapitulate, this is distinct from the $^1J_{C1H1}$ coupling constants in the 2,3-*O*-carbonate series (Table 1) which are not reliable because of the half-chair conformation of the pyranoside ring in those cases. Final verification of the anomeric stereochemistry in the 3,4-*O*-carbonate series was achieved by removal of the carbonate group in selected examples by means of saponification. As seen from Table 3, the resulting 2-*O*-benzyl rhamnosides display a completely normal pattern of $^1J_{C1H1}$ coupling constant variation between the two anomers. The identity of the product (**42**α) from the saponification of **34**α and from the removal of the acetonide group in **35**α confirms the α-selective nature of the coupling to the acetonide-protected donor **28**.

In summary, it has been demonstrated that the *β*-selectivity observed in the insoluble silver salt mediated couplings of 2,3-*O*-carbonate-protected rhamnosyl bromides is uniquely due to the heterogeneous nature of the reaction. Indeed, in homogeneous solution these same donors are α-selective, a fact that is attributed to the half-chair conformation of these substances, which reduces the energy gap to oxacarbenium ion formation. When the carbonate group is removed to the 3,4-*O*-position a *β*-selective system is formed, in both homogeneous and heterogeneous conditions, and it is demonstrated that this selectivity arises from the combination of the electron-withdrawing nature of the carbonate and its inability to take part in neighboring participation. Although it has not been explicitly demonstrated here, we fully expect that the results observed and conclusions drawn will translate uneventfully to the closely analogous mannopyranoside series.

Acknowledgment. We thank the NIH (GM 57335, GM 62160) for financial support.

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

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