JOC*Article*

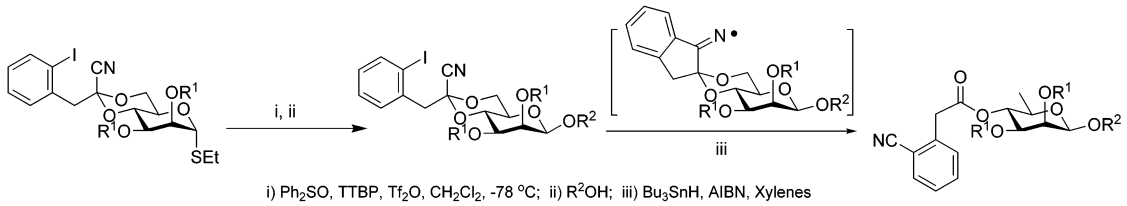
4,6-*O*-[1-Cyano-2-(2-iodophenyl)ethylidene] Acetals. Improved Second-Generation Acetals for the Stereoselective Formation of *β*-D-Mannopyranosides and Regioselective Reductive Radical Fragmentation to *β*-D-Rhamnopyranosides. Scope and Limitations

David Crich* and Albert A. Bowers

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

dcrich@uic.edu

Received December 29, 2005



The [1-cyano-2-(2-iodophenyl)]ethylidene group is introduced as an acetal-protecting group for carbohydrate thioglycoside donors. The group is easily introduced under mild conditions, over short reaction times, and in the presence of a wide variety of other protecting groups by the reaction of the 4,6-diol with triethyl (2-iodophenyl)orthoacetate and camphorsulfonic acid, followed by trimethylsilyl cyanide and boron trifluoride etherate. The new protecting group conveys strong *β*-selectivity with thiomannoside donors and undergoes a tin-mediated radical fragmentation to provide high yields of the synthetically challenging *β*-rhamnopyranosides. The method is also applicable to the glucopyranosides when high α-selectivity is observed in the coupling reaction and α-quinovosides are formed selectively in the radical fragmentation step. In the galactopyranoside series, *β*-glycosides are formed selectively on coupling to donors protected by the new system, but the radical fragmentation is unselective and gives mixtures of the 4- and 6-deoxy products. Variable-temperature NMR studies for the glycosylation step, which helped define an optimal protocol, are described.

Introduction

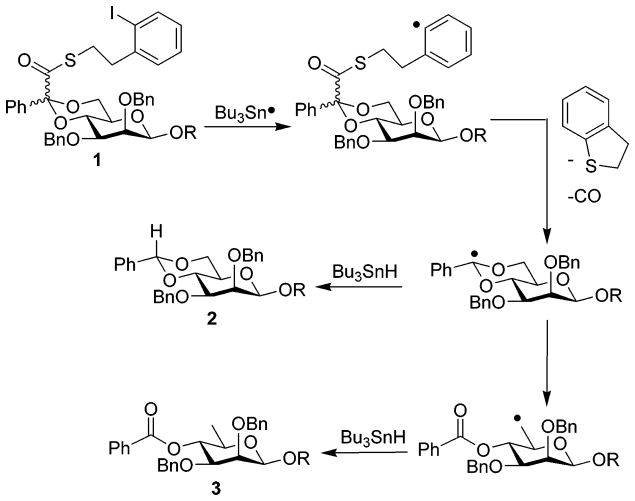
Rhamnopyranosides are significant components of bacterial capsular polysaccharides, which are involved in the propagation of disease states. Their synthesis presents a means of understanding these biointeractions and routes to possible vaccines against them. While L-rhamnose and its glycosides are widespread, the D-series is being found with greater frequency and the preparation of oligosaccharides bearing this novel subunit has become the object of increasing interest from standpoints of characterization and biophysical investigation.[1] The scarcity of D-rhamnose itself distinguishes the problem of D-rhamnoside synthesis from that of the L-series, for which the obvious starting point is the readily available L-rhamnose. The issue of glycosidic bond formation in the two enantiomeric series may be reconciled to a single problem by the chemical synthesis of D-rhamnose or of a suitably protected derivative. Indeed, this has been the method of choice in other laboratories, with approaches to D-rhamnopyranosyl donors beginning from D-mannose and including an iodination/reduction sequence at the C6 hydroxyl or a Hanessian-type NBS-mediated cleavage of the 4,6-*O*-benzylidene-protected mannosides.[2,3] We reason, however, given

(1) (a) Beynon, L. M.; Bundle, D. R.; Perry, M. B. *Can. J. Chem.* **1990**, *68*, 1456−1466. (b) Perry, M. B.; Richards, J. C. *Carbohydr. Res.* **1990**, *205*, 371−376. (c) Vinogradov, E. V.; Shashkov, A. S.; Knirel, Y. A. *Carbohydr. Res.* **1991**, *212*, 307−311. (d) Vinogradov, E. V.; Campos-Portuguez, S.; Yokota, A.; Mayer, H. *Carbohydr. Res.* **1994**, *261*, 103−109. (e) Winn, A. M.; Wilkinson, S. G. *Carbohydr. Res.* **1996**, *294*, 109−115. (f) Cerantola, S.; Montrozier, H. *Eur. J. Biochem.* **1997**, *246*, 360−366. (g) Senchenkova, S. y. N.; Shashkov, A. S.; Kecskes, M. L.; Ahohuendo, B. C.; Knirel, Y. A.; Rudolph, K. *Carbohydr. Res.* **2000**, *329*, 831−838. (h) Spitali, M.; Smith, A. R. W. *J. Phytopathol.* **2000**, *148*, 563−568. (i) Knirel, Y. A.; Shashkov, A. S.; Senchenkova, S. Y. N.; Ajiki, Y.; Fukuoka, S. *Carbohydr. Res.* **2002**, *337*, 1589−1591. (j) Molinaro, A.; Silipo, A.; Lanzetta, R.; Newman, M.-A.; Dow, J. M.; Parilli, M. *Carbohydr. Res.* **2003**, *338*, 277−281. (k) Hirooka, M.; Yoshimura, A.; Saito, I.; Ikawa, F.; Uemoto, Y.; Koto, S.; Takabatake, A.; Taniguchi, A.; Shinoda, Y.; Morinaga, A. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1409−1421.

10.1021/jo0526688 CCC: $33.50
Published on Web 03/25/2006

the present state of the art in the synthesis of the β-L-rhamnopyranosides,[4] that this is a less than ideal approach to the β-D-rhamnopyranosides. This is amply documented by a recent synthesis of a β-D-rhamnopyranoside at the core of a trisaccharide by means of a 2-*O*-sulfonyl-protected rhamnosyl donor, when the anomeric selectivity was limited to 1.1:1 in favor of the β-anomer.[5] Rather, we have preferred an approach in which the β-D-rhamnopyranosidic linkage is introduced in the form of a β-D-mannopyranoside which, taking advantage of the β-directing effect of the 4,6-*O*-benzylidene acetal protecting group, is currently one of the easier types of glycosidic bond to prepare with reproducibly high stereoselectivity.[6] Once the glycosidic bond has been formed, the 4,6-*O*-benzylidene acetal is then cleaved reductively to afford the β-D-rhamnopyranoside. The most obvious approach to the reductive cleavage of the 4,6-*O*-benzylidene acetal is the Hanessian−Hullar *N*-bromosuccinimide-mediated cleavage to the 6-bromo-6-deoxymannoside followed by hydrogenolytic cleavage of the bromine atom, or the more recent Roberts' radical cleavage with a catalytic thiol, which leads directly to the 6-deoxy system.[7] However, neither system is really compatible with the presence of benzyl ethers and the like, owing to essential hydrogen atom abstraction step from the acetal.[8] One rare exception to this rule is the high-yield cleavage of a benzylidene acetal of a 1,2-diol in the presence of benzyl ethers with NBS on a significant scale and in excellent yield reported in the course of a synthesis of a cyclosporine component.[9] It should be noted, however, that the rate of hydrogen atom abstraction from the acetal position of 1,3-dioxolanes is approximately 1 order of magnitude faster than that from the comparable position in 1,3-dioxanes,[10] which accounts for the selectivity over benzylic hydrogen atom abstraction in this example.

SCHEME 1. 4,6-*O*-[α-(2-(2-Iodophenyl)ethylthiocarbonyl)-benzylidene] Radical Fragmentation



The central role of benzyl ether type protecting groups in modern oligosaccharide synthesis and their incompatibility with the Hanessian−Hullar and Roberts' 4,6-*O*-benzylidene acetal fragmentations spurred the search in our laboratory for an alternative means of generation of 2-substituted 1,3-dioxan-2-yl-type radicals, not dependent on hydrogen atom abstraction, suitable for use in stereoselective glycosylation reactions. This search led to our development of a first-generation solution in the form of the 4,6-*O*-[α-(2-(2-iodophenyl)ethylthiocarbonyl)-benzylidene] group as a surrogate for the 4,6-*O*-benzylidene acetal (Scheme 1) and its subsequent employment in the total synthesis of the lipopolysaccharide from *E. hermanii* ATCC 33650/33652 (Scheme 2).[11] In this synthesis, both α- and β-rhamnosyl linkages were formed from donors equipped with the novel acetal protecting group, and a single radical reaction step was used to uncover the two latent rhamnopyranosides simultaneously. This protecting group provided excellent β-selectivities in coupling reactions, and the high yields in the fragmentations are decreased only to a minor extent by formation of a byproduct from reduction of the intermediate benzylidene radical to the benzylidene radical itself. Notwithstanding this success, the method suffers from two limitations: the lengthy sequence required to prepare the thiol and the transesterification required to introduce the thiol ester, which limits functional group compatibility.

(2) (a) Haskins, W. T.; Hann, R. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1946**, *68*, 628−632. (b) Zorbach, W. W.; Tio, C. O. *J. Org. Chem.* **1961**, *26*, 3543−3545. (c) Bundle, D. R.; Eichler, E.; Kihlberg, J. *Carbohydr. Res.* **1991**, *211*, 59−75. (d) Ramm, M.; Lobe, M.; Hamburger, M. *Carbohydr. Res.* **2003**, *338*, 109−112.

(3) (a) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035−1044. (b) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1045−1053. (c) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1053−1058. (d) Chana, J. S.; Collins, P. M.; Farnia, F.; Peacock, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, *2*, 94−96. (e) Binkley, R. W.; Goewey, G. S.; Johnston, J. C. *J. Org. Chem.* **1984**, *49*, 992−996. (f) Hanessian, S. *Org. Synth.* **1987**, *65*, 243−247. (g) Hullar, T. L.; Siskin, S. B. *J. Org. Chem.* **1970**, *35*, 225−227. (e) Hanessian, S. *Adv. Chem. Ser.* **1968**, *74*, 159−201. (h) Szarek, W. A. *Adv. Carbohydr. Chem. Biochem.* **1973**, *28*, 225−306. (i) Paulsen, H. *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 127−195. (j) Gelas, J. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 71−156.

(4) (a) Crich, D.; Picione, J. *Org. Lett.* **2003**, *5*, 781−784. (b) Crich, D.; Vinod, A. U.; Picione, J. *J. Org. Chem.* **2003**, *68*, 8453−8458. (c) Crich, D.; Hutton, T.; Banerjee, A.; Jayalath, P.; Picione, J. *Tetrahedron: Asymmetry* **2005**, *16*, 105−119.

(5) (a) Bedini, E.; Carabellese, A.; Barone, G.; Parilli, M. *J. Org. Chem.* **2005**, *70*, 8064−8070. (b) Bedini, E.; De Castro, C.; Erbs, G.; Manogoni, L.; Dow, J. M.; Newman, M.-A.; Parilli, M.; Unverzagt, C. *J. Am. Chem. Soc.* **2005**, *127*, 2414−2416.

(6) (a) Crich, D.; Li, H.; Yao, Q.; Wink, D. J.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *121*, 5826−5828. (b) Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640−4646. (c) Crich, D.; Dai, Z. *Tetrahedron* **1999**, *55*, 1569−1580. (d) Crich, D.; Barba, G. R. *Tetrahedron Lett.* **1998**, *39*, 9339−9342. (e) Crich, D.; de la Mora, M. A.; Cruz, R. *Tetrahedron* **2002**, *58*, 35−44. (f) Crich, D.; Banerjee, A.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 14930−14934. (g) Crich, D.; Banerjee, A. *Org. Lett.* **2005**, *7*, 1935−1938. (h) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263−2266. (i) Dudkin, V. Y.; Crich, D. *Tetrahedron Lett.* **2003**, *44*, 1787−1789. (j) Dudkin, V. K.; Miller, J. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 736−738. (k) Miller, J. S.; Dudkin, V. Y.; Lyon, G. J.; Muir, T. W.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 431−434. (l) Nicolaou, K. C.; Mitchell, H. J.; Rodriguez, R. M.; Fylaktakidou, K. C.; Suzuki, H.; Conley, S. R. *Chem. Eur. J.* **2000**, *6*, 3149−3165. (m) Kim, K. S.; Kang, S. S.; Seo, Y. S.; Kim, H. J.; Jeong, K.-S. *Synlett* **2003**, 1311−1314. (n) Wu, X.; Schmidt, R. R. *J. Org. Chem.* **2004**, *69*, 1853−1857. (o) Kwon, Y. T.; Lee, Y. J.; Lee, K.; Kim, K. S. *Org. Lett.* **2004**, *6*, 3901−3904. (p) Tanaka, S.-i.; Takashina, M.; Tokimoto, H.; Fujimoto, Y.; Tanaka, K.; Fukase, K. *Synlett* **2005**, 2325−2328.

(7) (a) Roberts, B. P.; Smits, T. M. *Tetrahedron Lett.* **2001**, *42*, 3663−3666. (b) Roberts, B. P.; Smits, T. M. *Tetrahedron Lett.* **2001**, *42*, 137−140. (c) Dang, H.-S.; Roberts, B. P.; Sekhon, J.; Smits, T. M. *Org. Biomol. Chem.* **2003**, *1*, 1330−1341. (d) Fielding, A. J.; Franchi, P.; Roberts, B. P.; Smits, T. M. *J. Chem. Soc., Perkin Trans. 2* **2002**, 155−163. (e) Cai, Y.; Dang, H. S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2449−2458. (f) Jeppesen, L. M.; Lundt, I.; Pedersen, C. *Acta Chem. Scand.* **1973**, *27*, 3579−3585.

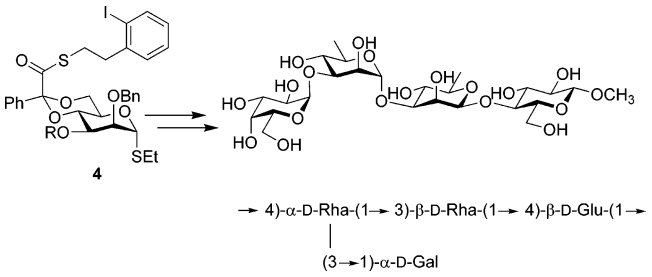
(8) For a rare exception see: Liotta, L. J.; Dombi, K. L.; Kelley, S. A.; Targontsidis, S.; Morin, A. M. *Tetrahedron. Lett.* **1997**, *38*, 7833−7834.

(9) Wenger, R. M. *Helv. Chim. Acta* **1983**, *66*, 2308−2321.

(10) (a) Ingold, K. U.; Malatesta, V. *J. Am. Chem. Soc.* **1981**, *103*, 609−614. (b) Beckwith, A. L. J.; Easton, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 615−619.

(11) (a) Crich, D.; Yao, Q. *Org. Lett.* **2003**, *5*, 2189−2191. (b) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 8232−8236.

SCHEME 2. Synthesis of a Lipopolysaccharide from *E. hermanii* ATCC 33650/33652



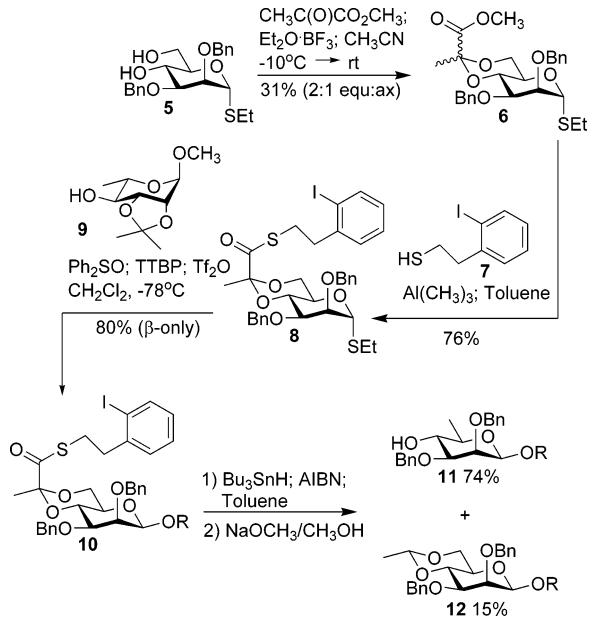
It was hoped that broader versatility could be achieved by another radical methodology, perhaps also capable of decreasing the reduction byproduct observed with the first-generation system. On the basis of seminal work by Beckwith on the radical migration of cyano groups, and subsequent applications to synthesis by Rychnovsky and co-workers,[12] we hypothesized that a 2-cyano-1,3-dioxane would serve as a suitable precursor to the 1,3-dioxan-2-yl radical by intramolecular transfer of the cyano group to an appropriately placed radical. The successful implementation of this second-generation method is described herein.

Results and Discussion

Acetal Design and Development. Before embarking on the development of the second generation system it was necessary to ascertain the effect of the 2-substituent on the fragmentation, more especially the regioselectivity, of substituted 1,3-dioxan-2-yl radicals. Additionally, it was reasoned that substitution of a methyl group for the phenyl group of the traditional benzylidene fragmentation could destabilize the incipient radical at the acetal carbon leading to a faster rate of fragmentation and diminishing amounts of reduced product.

To this end, we prepared a modified first-generation system beginning with the diol **5**. Collins et al. observed that acetal exchange with the methyl pyruvate dimethyl acetal provides high yields of an undesired isomerization product; in our hands, similar results were observed and the byproduct proved all but intractable in most solvent systems.[13] Of the literature methods surveyed, Ziegler's proved the most workable, yielding 31% of a 2:1 (equatorial methyl/axial methyl) mixture of isomers,[14,15] with the remainder of the starting material undergoing decomposition during the course of reaction, a result observed by other groups in use of the method.[16] The separated isomer with an equatorial methyl group was then smoothly transesterified at room temperature to give the new donor **8** in 76% yield.

SCHEME 3. Preparation and Fragmentation of a Pyruvate-Based Mannosyl Donor



Benzenesulfinylpiperidine (BSP)-mediated coupling[17] of donor **8** in the presence of the hindered base, tri-*tert*-butyl pyrimidine (TTBP),[18] proceeded to give disaccharide **10** in 76% yield with 5% recovered starting material, whereas coupling with the stronger thiophile generated from the Ph_2SO/Tf_2O combination[19] saw complete activation with an 80% yield. In both instances, only the β-isomer could be isolated by silica gel chromatography, in keeping with observations made with the first- generation system itself. Dropwise addition of AIBN and tributyltin hydride to substrate **10** in refluxing toluene, according to the procedure used with the first-generation system, provided the β-D-rhamnoside **11** in 74% yield with 15% of the ethylidene acetal byproduct **12** isolated after deacylation and column chromatography (Scheme 3). This result parallels very closely those obtained earlier with the first-generation series and indicates that the 1,3-dioxan-2-yl radical need not carry a 2-phenyl substituent for a highly regioselective cleavage favoring fragmentation of the primary C−O bond. The analogous observation was also made by the Roberts' group with their thiyl radical-based hydrogen atom abstraction/fragmentation system. The fact that results with the methyl group prove similar to those with a phenyl group suggests that the transition state for fragmentation is late and the contribution from destabilization of the radical is equally countered by loss of the delocalization obtained in the conjugated benzoate ester, again in accord with theoretical calculations performed by Roberts.[7]

Turning to the use of nitriles as radical precursors, we first investigated briefly the intermolecular abstraction of this group by a stannyl radical, based on the demonstration of Curran and co-workers of radical monodecyanation of *gem*-dicyano acetals using AIBN/Bu_3SnH.[20] Accordingly, donor **14** was synthesized

(12) (a) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565−2575. (b) Rychnovsky, S. D.; Swenson, S. S. *Tetrahedron* **1997**, *53*, 16489−16502.

(13) (a) Hind, C. R. K.; Collins, P. M.; Renn, D.; Cook, R. B.; Caspi, D.; Baltz, M. L.; Pepys, M. B. *J. Exp. Med.* **1984**, *159*, 1058−1069. (b) Liptak, A.; Szabo, L. *Carbohydr. Res.* **1984**, *184*, C5−C8. (c) Hashimoto, H.; Hiruma, K.; Tamura, J.-I. *Carbohydr. Res.* **1988**, *177*, C9−C12. (d) Collins, P. M.; McKinnon, A. C.; Manro, A. *Tetrahedron Lett.* **1989**, *30*, 1399−1400.

(14) For a review of methods, see: Ziegler, T. *Top. Curr. Chem.* **1997**, *186*, 203−229.

(15) For the $BF_3(OEt)_2$-promoted method, see: (a) Ziegler, T.; Herold, G. *Liebigs. Ann. Chem.* **1994**, 859−866. (b) Ziegler, T. *Tetrahedron Lett.* **1994**, *35*, 6857−6860.

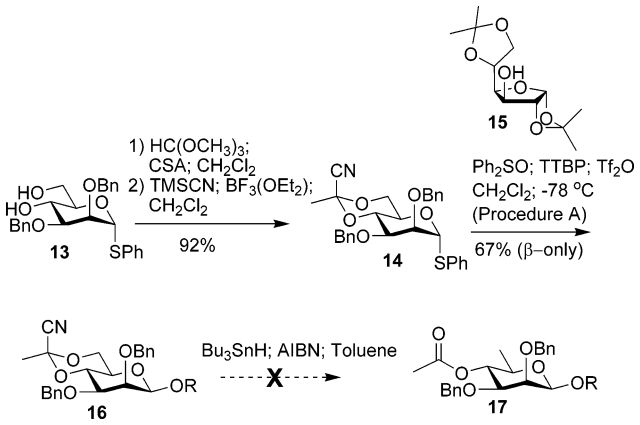
(16) (a) Wardrop, D. J.; Velter, A. I.; Forslund, R. E. *Org. Lett.* **2001**, *3*, 2261−2264. (b) Wardrop, D. J.; Forslund, R. E.; Landrie, C. L.; Velter, A. I.; Wink, D.; Surve, B. *Tetrahedron: Asymmetry* **2003**, *14*, 929−940.

(17) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020.

(18) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323−326.

(19) (a) 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. (b) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057−1064.

SCHEME 4. Radical Decyanation-Based Ethylidene Fragmentation



via Utimoto's Lewis acid assisted TMSCN protocol.[21] From a mixture of diastereomers of the preformed ortho ester, the latter reaction provided a single isomer cleanly and in good yield. The diphenyl sulfoxide/Tf_2O coupling protocol yielded 67% of the pure β-anomer **16** with 20% of the unactivated donor recovered. The incomplete activation was unexpected given use of the strong thiophile; the cause was not investigated at this stage, however, due to uncertainty of how the product would behave under conditions of radical fragmentation. Unfortunately, repeated attempts at heating in toluene with AIBN/Bu_3SnH induced no fragmentation, and the disaccharide was recovered quantitatively each time (Scheme 4). Evidently, the generation of a somewhat stabilized 2-methyl-1,3-dioxan-2-yl radical is insufficient to promote the desired intermolecular nitrile abstraction reaction.

We turned, therefore, to intramolecular nitrile abstraction following the precedent of the Beckwith and Rychnovsky groups.[12] Thus, the requisite ortho ester **19** was prepared according to standard Pinner synthesis via the imidate salt **18** of 2-iodophenylacetonitrile in 57% over two steps with the known carboxylate ester as the major byproduct.[22] Acid-catalyzed ortho ester exchange in the presence of the acid ester, followed directly by $BF_3.OEt_2$-promoted cyanation, without prior purification provided the desired donor in 80% yield after silica gel chromatography. The presumed stereochemical outcome of cyanation of **20**, based on stereoelectronic effects,[23] was rigorously proven by X-ray crystallographic analysis (Figure 1) of the β-mannoside **21** after coupling to methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside by the Ph_2SO/Tf_2O protocol (Scheme 5). Dropwise addition of tributyltin hydride and AIBN to a solution of mannoside **21** in toluene at reflux finally gave the β-rhamnopyranoside **22** in 76% yield, with no indication of the formation of the regioisomeric 4-deoxy product (Scheme 5).

Glycosylation and Radical Fragmentation. With proof of principle for the complete second-generation sequence in hand, a series of VT-NMR experiments, described in detail below, helped definite an optimal protocol for preparative-scale couplings in which the mixture of thioglycoside and diphenyl sulfoxide was warmed to −20 °C after addition of triflic anhydride then cooled back to −78 °C before the acceptor was introduced. In this manner, a number of couplings were conducted in high yield, with excellent β-selectivity as reported in Table 1.

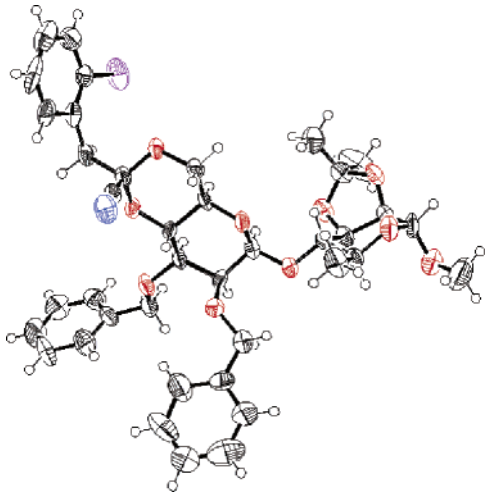


FIGURE 1. X-ray structure of disaccharide **21**.

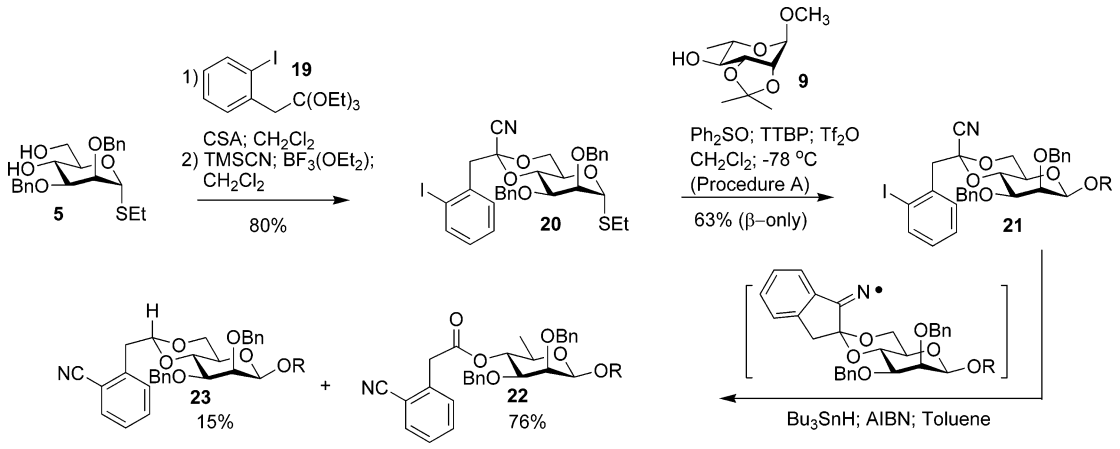
With the couplings in hand, other measures were then considered to favor the desired fragmentation pathway. To this end, tris(trimethylsilyl)silane was employed as a weaker hydrogen donor and addition times and temperatures were adjusted until optimized parameters were found,[24] as summarized in Table 2. Of note, the silane proved an inefficient propagator, and an amount of starting material was recovered in all such trials. Also, it was found that the pathway leading to the 6-deoxy sugars was favored at higher temperature, though no conditions were obtained which eliminated formation of the reduced acetal altogether. No 4-deoxy sugars were observed in the ^1H NMR spectra of the crude reaction mixtures indicating complete regioselectivity of radical fragmentation in the mannose series. Overall, therefore, the 4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene group provides the β-D-rhamnopyranosides rapidly and in high yields from thiomannosides.

Subsequently, the optimized fragmentation conditions were applied to the complete series of β-D-mannosides, resulting in each case in high isolated yields of the corresponding β-D-rhamnopyranosides, as set out in Table 3, entries 1−5.

To probe the scope and limitations of this second-generation system, the glucopyranose and galactopyranose systems were also investigated. In the glucose series four donors were prepared, equipped with 2-naphthylmethyl, *p*-methoxybenzyl, and standard benzyl protecting groups as outlined in Scheme 6. Contrary to our expectations, couplings to glucosyl donors **29**, **30**, and **32** resulted in relatively complex reaction mixtures and, ultimately, low yields of the coupled products (Table 1, entries 7 and 8). Neither the use of higher equivalents of activator nor variation of temperature was able to increase these coupling yields. Only the 2,3-di-*O*-benzyl-protected donor **31**

(20) Curran, D. P.; Seong, C. M. *Synlett* **1991**, 107−108.
(21) Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967−973.
(22) For a review of ortho ester formation: DeWolfe, R. H. *Synthesis* **1974**, 153−172.
(23) (a) Eliel, E.; Nader, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 584−589. (b) Eliel, E.; Nader, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 3050−3055. (c) Rychnovsky, S. D.; Kim, J. *Tetrahedron Lett.* **1991**, *32*, 7223−7224. (d) Cf. ref 16 and references therein.
(24) (a) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641−3642. (b) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194. (c) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1989**, *54*, 2492−2494. (d) Giese, B.; Kopping, B. *Tetrahedron Lett.* **1989**, *30*, 681−684.

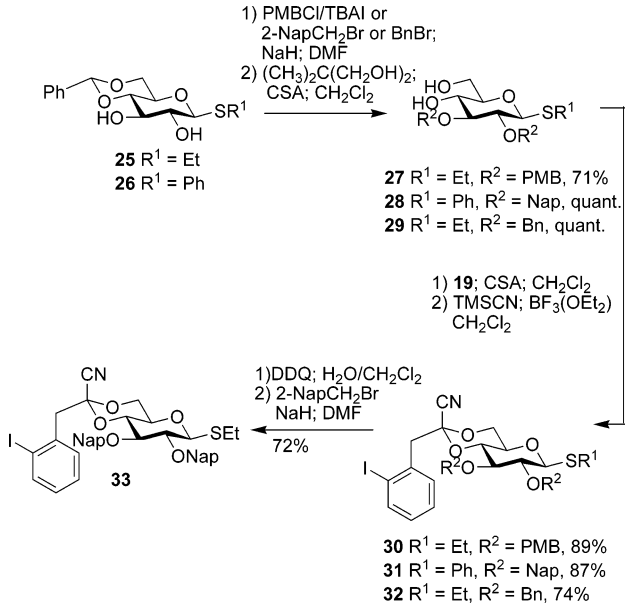
SCHEME 5. Nitrile Transfer-Based Fragmentation



produced satisfactory yields and only upon employing protocol B, as developed with the mannose donor **20**. In line with the precedent for coupling to 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-protected glucosyl donors, the reactions were α-selective.[25] As discussed below, VT-NMR experiments were again conducted in an attempt to understand the problematic couplings.

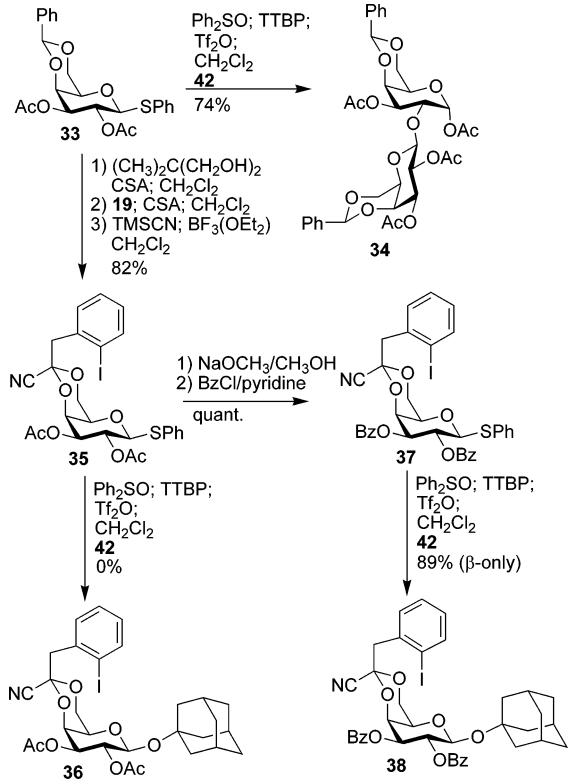
Only two examples of the radical fragmentation were studied in the glucose series; nevertheless, excellent selectivities for fragmentation of the primary bond leading to the 6-deoxy-D-glucoside, or D-quinovoside, were obtained (Table 3, entries 7 and 8). This selectivity parallels exactly that seen with the first-generation system in the glucose series, as well as that seen by Roberts and Hanessian in their fragmentation of standard 4,6-*O*-benzylidene acetals in the glucopyranose series. In other words, the radical fragmentation in the glucose series is no different from that in the mannose case with very high selectivity for formation of the 6-deoxy isomer.

SCHEME 6. Preparation of Glucosyl Donors



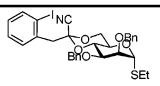
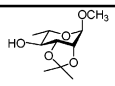
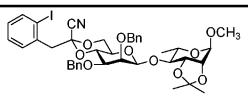
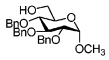
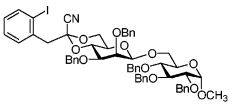
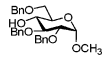
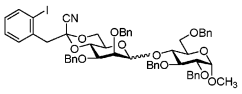
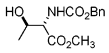
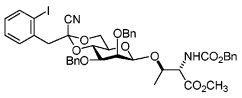
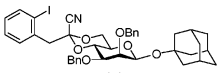
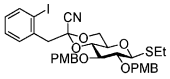
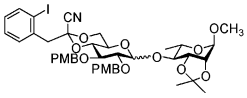
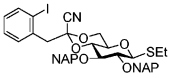
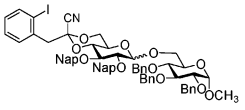
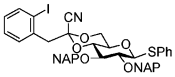
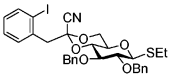
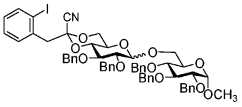
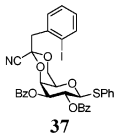
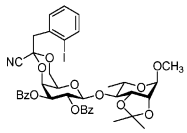
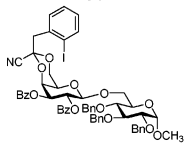
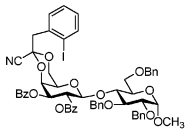
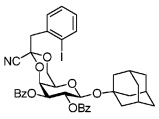
Working in the galactopyranose series, we began with the known benzylidene acetal proctected thioglycoside **33**,[26] which was converted to the second-generation acetal by a three-step protocol including removal of the benzylidene group with neopentyl glycol and catalytic camphorsulfonic acid, introduction of the ortho ester, and finally, the nitrile (Scheme 7). As expected for the more reactive galactopyranoside series, activation of this donor was efficient. However, the addition of 1-adamantanol, usually an excellent glycosyl acceptor, resulted not in the isolation of the anticipated *β*-galactoside **36** but in the formation of a relatively complex mixture. To elucidate this problem, we returned to the more plentiful benzylidene acetal **33**, which on activation and attempted coupling delivered a 74% yield of an unexpected disaccharide **34**.[27] We were able to circumvent this problem, with its obvious roots in acetoxy migration and neighboring group participation, simply by switching to the corresponding benzoate ester **37** when the adamantanyl *β*-galactopyranoside **38** was formed in 89% yield.

SCHEME 7. Preparation and Coupling of Galactoside Donors



(25) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926−4930.
(26) Deng, S.; Yu, B.; Guo, Z.; Hui, Y. *J. Carbohydr. Chem.* **1998**, *17*, 439−452.

TABLE 1. Glycosylation Reactions with [1-Cyano-2-(2-iodophenyl)]ethylidene-Protected Donors

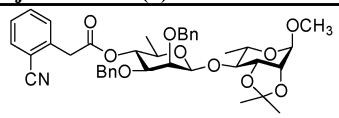
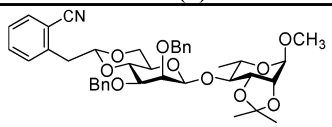
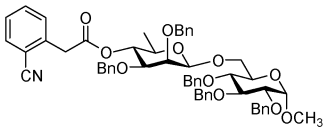
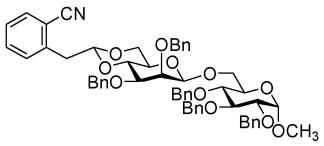
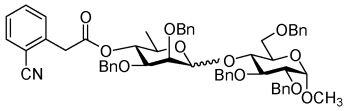
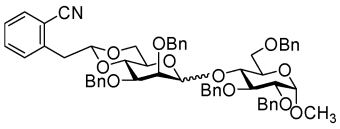
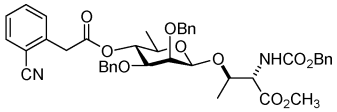
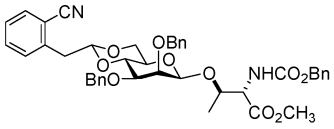
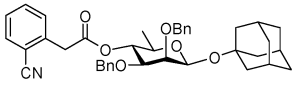
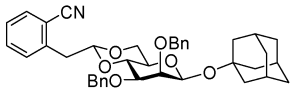
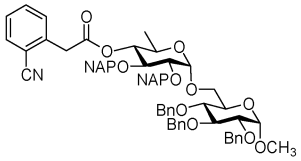
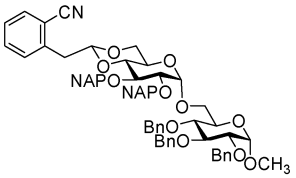
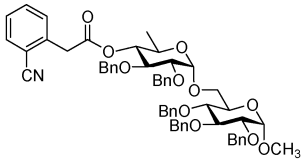
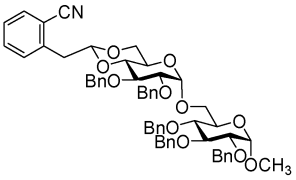
Entry	Donor	Acceptor	Product	$^1J_{CH}$ (Hz)	Procedure[a] (% yield, β: α selectivity)
1	 **20**	 **9**	 **21**	β: 158.6	A: 63 % (β-only) B: 92 % (β-only)
2	**20**	 **39**	 **43**	β: 156.1	B: 77 % (β-only)
3	**20**	 **40**	 **44**	β: 157.1 α: 173.7	B: 72% (8.4:1)
4	**20**	 **41**	 **45**	β: 154.9	B: 71% (β-only)
5	**20**	 **42**	 **46**	β: 153.5	B: 82% (β-only)
6	 **29**	**9**	 **47**	β: 164.9 α: 175.0	A: 41% (1:5)
7	 **32**	**39**	 **48**	β: 159.9 α: 171.2	A: 33% (1:4) B: 25% (1:5)
8	 **30**	**39**	**48**	-	A: 31% (1:4)
9	 **31**	**39**	 **49**	β: 164.9 α: 169.2	B: 65% (1:10)
10	 **37**	**9**	 **50**	β: 164.9	A: 96% (β-only)
11	**37**	**39**	 **51**	β: 159.9	A: 75% (β-only)
12	**37**	**40**	 **52**	β: 159.9	A: 86% (β-only)
13	**37**	**42**	 **38**	β: 160.9	A: 89% (β-only)

[a] Isolated yields of analytically pure material. Procedure A: Tf_2O added at −78 °C and reaction maintained at −78 °C until ∼1.5 h after addition of acceptor. Procedure B: Tf_2O added at −78 °C and reaction mixture warmed to −20 °C for ∼20 min. Mixture then cooled to −78 °C, acceptor added, and resulting mixture stirred at −78 °C for ∼1.5 h.

TABLE 2. Optimization of the Radical Fragmentation with Disaccharide 21

entry	solvent	initiator	propagator	addition (h)	6-deoxy **22** yield (%)	acetal **23** yield (%)	recovered **21** (%)
1	toluene	AIBN	Bu_3SnH	3	76	15	0
2	toluene	AIBN	$((CH_3)Si)_3SiH$	3	68	6	15
3	xylenes	AIBN	Bu_3SnH	3	56	2	30
4	xylenes	AIBN	Bu_3SnH	2	81	5	0
5	xylenes	Bz_2O_2	Bu_3SnH	2	61	10	0
6	xylenes	AIBN	$((CH_3)Si)_3SiH$	2	70	5	20

TABLE 3. Radical Fragmentations of Coupled β-D-Mannopyranosides and α-D-Glucopyranosides

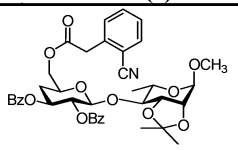
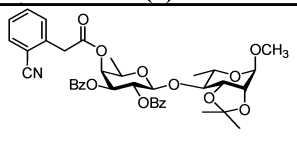
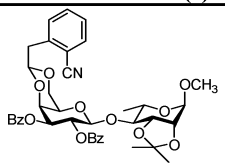
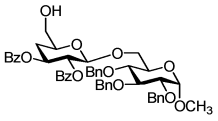
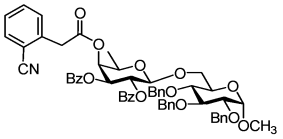
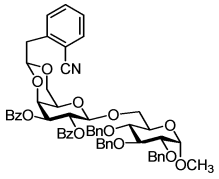
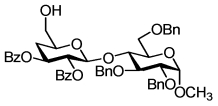
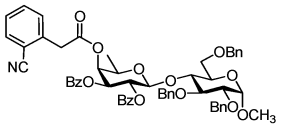
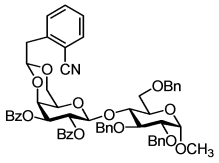
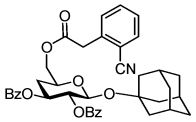
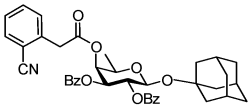
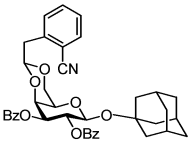
Entry	Substrate	Major Product (a)	Reduction Product (b)	% Yield (a:b)[a]
1	**21**	 **22**	 **23**	86% (16:1)
2	**43**	 **53**	 **54**	89% (14:1)
3	**44**	 **55**	 **56**	66% (6:1)
4	**45**	 **57**	 **58**	83% (trace b)
5	**46**	 **59**	 **60**	94% (8:1)
7	**48**	 **61**	 **62**	72% (trace b)
8	**49**	 **63**	 **64**	69% (trace b)[b]

[a] All yields refer to isolated yields from 2 h addition of 1.5 equiv of Bu_3SnH and 0.2 equiv of AIBN in refluxing xylenes. [b] 17% unreacted starting material recovered.

A series of further couplings were then conducted with this donor as reported in Table 1 (entries 12−15), all of which proceeded in high yield and with excellent β-selectivity. The synthesis of donor **37** (Scheme 7) serves to highlight two advantages of the second-generation radical precursor over and above the first-generation system (Scheme 1), both of which revolve around compatibility with ester protecting groups. First, the second-generation system may be introduced in the presence of esters, whereas the transesterification step required for the

(27) Precedent for the formation of similar substances combining two molecules of a glycosyl donor, with migration of a single ester to the anomeric position, can be found in the work of Whitfield and co-workers: Nukada, T.; Berces, A.; Whitfield, D. M. *J. Org. Chem.* **1999**, *64*, 9030−9045.

TABLE 4. Radical Fragmentations of β-D-Galactopyranosides

Entry	Substrate	Product (a)	Product (b)	Reduction Product (c)	% Yield (a:b:c)[a]
1	**50**	 **78**	 **79**	 **80**	79% (7.5:7.5:1)
2	**51**	 **81**	 **82**	 **83**	73% (2.8:1.8:1)[b]
3	**52**	 **84**	 **85**	 **86**	70% (3.2:2.8:1)[b]
4	**38**	 **87**	 **88**	 **89**	83% (5:4.5:1)

[a] All yields refer to isolated yields from 2 h addition of 1.5 equiv of Bu_3SnH and 0.2 equiv of AIBN in refluxing xylenes. [b] Yields after radical reaction and selective saponification of the ester on the primary hydroxyl with 1 equiv of guanidine in CH_2Cl_2/EtOH (1:9).

first generation system precluded their use. Second, saponification may be readily carried out in the presence of the second-generation system under standard conditions, which was obviously not possible for the first-generation, thiol ester-based radical precursor.[28]

Radical fragmentation of the galactosides prepared in this manner led to mixtures of the 6-deoxy (fucopyranosides) products and the 4-isomers, typically with a slight excess of the 4-deoxy regioisomer (Table 4). To facilitate separation of the mixture of regioisomers, chemoselective saponification of the primary ester in the 4-deoxy product was achieved with guanidine in ethanol.[29] The lack of regioselectivity in these galactoside fragmentations matches well that found by Roberts in his thiyl radical-mediated cleavage of galactose-based benzylidene acetals.[30] The observed regioselectivity and the high degree of agreement with the Roberts work prompted a reinspection of our earlier work on the application of the first-generation radical trigger to the galactose series. Thus, we reported previously that acetals **65** afforded an 89/9 mixture of **67** and **69** and that acetal **66** gave exclusively the 4-deoxy product **68**.[11a] Scrutiny of the spectral data for **65**−**69** revealed these structures to have been misassigned in the original publication, and we now revise these structures, along with their precursors described in the original Supporting Information, to the galactofuranoside substrates **70** and **71** and the 5- and 6-deoxygalactofuranoside products **72**, **73**, and **74**. The error in assignment of these structures arose because of a methyl galactopyranoside to methyl galactofuranoside rearrangement[31,32] that had gone undetected during the Lewis acid (TMSOTf) mediated acetalization of **75**, which it is now clear gave the furanosides **76** and not the pyranosides **77**. The sequence employed originally in the intended synthesis of **65** and **66** was predicated on the need to introduce the acetal and complete the subsequent transesterification step to the thiol ester before introduction of any ester protecting groups. It serves to highlight, therefore, one of the significant advantages of the second-generation series presented here, namely the full compatibility with esters as apparent in Scheme 7 and as discussed above.

VT NMR Studies on Glycosylation Intermediates. The unexpectedly incomplete activation of the glycosyl donor **20** at −78 °C, with 20% unchanged thioglycoside recovered from the example reported in Scheme 5, prompted an investigation by

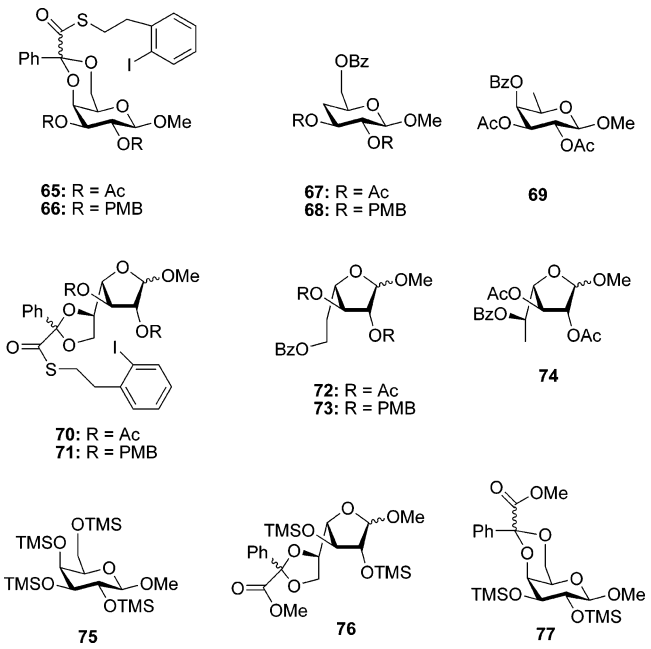
(28) However, it did prove possible to selectively cleave a chloroacetate ester in the presence of the first-generation radical precursor with ethylenediamine, cf. ref 11b.

(29) Kunesch, N.; Miet, C.; Poisson, J. *Tetrahedron Lett.* **1987**, *28*, 3569−3572.

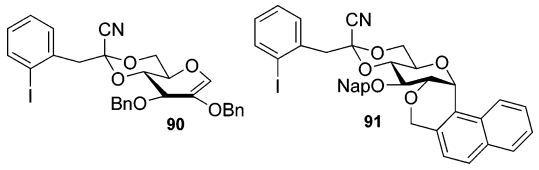
(30) Comparison with the Hanessian−Hullar NBS mediated cleavage reveals significant differences between the two reactions in the galactopyranose series, but this is due to the operation of different mechanisms. The work described here, like that of Roberts, is a pure radical fragmentation, whereas the Hanessian−Hullar reaction is a nucleophilic ring opening by the bromide ion: McNulty, J.; Wilson, J.; Rochon, A. C. *J. Org. Chem.* **2004**, *69*, 563−565.

(31) Precedent exists in the literature for this type of Lewis acid mediated methyl galactopyranoside to methyl galactofuranoside rearrangement. Ziegler, T.; Eckhardt, E.; Herold, G. *Liebigs Ann. Chem.* **1992**, 441−451.

(32) This galactopyranoside to furanoside rearrangement is readily apparent from the downfield shifts of the anomeric hydrogen and carbon in the ^1H and ^{13}C NMR spectra, respectively, as well as from the collapse of the anomeric proton signal to a broad singlet in the furanose, as discussed by Ziegler.[31]



variable-temperature NMR spectroscopy, our method of choice for probing such questions.[33] Accordingly, a CD_2Cl_2 solution of donor **20** and diphenyl sulfoxide was treated at −78 °C and the spectrum recorded. The anomeric peak of donor **20** at δ 5.26 (Figure 2a) was immediately consumed after addition of Tf_2O, giving rise to two new peaks, the first at δ 6.09 and the second at δ 5.90 (Figure 2b). Upon warming in 10° intervals to −30 °C, it was observed that the first peak decreased and then disappeared altogether as the second peak increased relative to the methylene chloride peak present at δ 5.32 (Figure 2c). Further warming witnessed the disappearance of the peak at δ 5.90 and emergence of a new peak at δ 6.28 at 0 °C. In a subsequent experiment, it was observed that, after enriching the peak at δ 5.90 by warming to −20 °C, the reaction mixture could be recooled to −78 °C with no detriment and then quenched with methanol to give the anomeric mixture of methyl glycosides. The last result suggests that the peak at δ 5.90 is the active species, the glycosyl triflate, in such couplings, which decomposes at 0 °C to be replaced by a signal at δ 6.28. We tentatively assign this signal to glycal **90** (H1) on the basis of the previous isolation of such 2-alkoxyglycals from this type of experiment.[25]



Exactly analogous results were observed with the 2,3-di-*O*-benzyl-protected glucosyl donor **31** (see the Supporting Information for VT-spectra). Thus, on addition of Tf_2O to a CD_2Cl_2 mixture of **31** and Ph_2SO at −78 °C, the substrate was consumed and two new anomeric signals were formed at δ 6.02 (d, J = 3.3 Hz) and δ 5.63 (d, J = 9.6 Hz), representing an α- and a β-derivative, respectively. On warming, the signal at δ 5.63 was converted to that at δ 6.02 by −20 °C, which we assign to the α-triflate. This triflate was stable to −10 °C at which temperature the onset of decomposition was observed. If the reaction mixture was warmed to −20 °C and then recooled to −78 °C (Table 1, protocol B) a good yield of the coupled product could be obtained. Addition of triflic anhydride to donor **32** likewise led to the formation of two new peaks at δ 5.95 (d, J = 2.7 Hz) and δ 5.70 (d, J = 9.0 Hz), indicative of an α- and a β-derivative, respectively (see the Supporting Information for VT-spectra). Quenching of the mixture at −78 °C with methanol resulted in the loss of the signal at δ 5.95 in favor of an anomeric mixture of methyl glucosides, which suggests this resonance to be that of the α-glucosyl triflate. However, in contrast to the di-*O*-benzyl system **31**, and to the mannosyl donor **20**, on warming of the mixture from the activation of **32** to −50 °C the upfield peak (δ 5.70) was observed to have decreased, relative to the methylene chloride peak at δ 5.32, in favor of a new, poorly resolved peak at δ 5.61. By −30 °C, the δ 5.70 peak had disappeared completely and the anomeric triflate peak at δ 5.95 was diminished in size, while the resonance at δ 5.61 had both increased in intensity and was better resolved into a doublet with coupling constant of 4.0 Hz, consistent with an α-glucosyl derivative. Finally, at −20 °C, the downfield peak had disappeared completely, leaving only the δ 5.61 resonance.

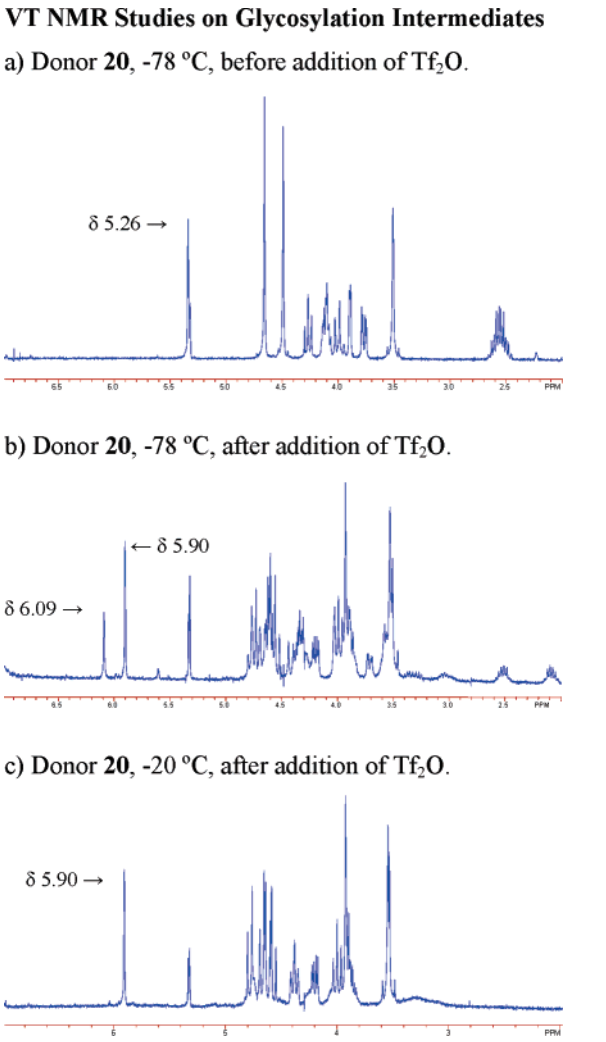


FIGURE 2. Low-temperature NMR spectra for (a) thiomannoside **20** at −78 °C, before activation, (b) glycosyl triflate (δ 5.90) and byproduct (δ 6.09) at −78 °C, and(c) the glycosyl triflate alone at −20 °C, after conversion of the other intermediate.

(33) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

The product corresponding to this last anomeric signal was isolated and characterized as decomposition product **91**, arising from electrophilic aromatic substitution by the anomeric oxacarbenium ion on the naphthylmethyl protecting group. The difference between the performance of the 2,3-di-*O*-benzyl donor **31** and the 2,3-di-*O*-naphthylmethyl donors **30** and **32**, apparent from the preparative scale coupling reactions (Table 1) is therefore seen to be the result of the more facile aromatic substitution onto the naphthalene ring, which competes with the conversion of the unknown intermediate at δ 5.70 to the anomeric triflate on warming. Although no VT-NMR experiments were conducted, a parallel problem presumably underlies the poor yield obtained with the 2,3-di-*O*-(4-methoxybenzyl) donor **29** (Table 1, entry 6).

The one remaining unknown is the identity of the substances characterized by anomeric resonances at δ 6.09 in the mannose series and δ 5.63 (J = 9.6 Hz, 2,3-di-*O*-benzyl system) and δ 5.70 (J = 9.7 Hz, 2,3-di-*O*-naphthylmethyl system) in the glucose series and which is slowly converted to the corresponding α-anomeric triflates on warming. We considered *O*-glycosyl sulfoxonium ions, as observed by Gin,[34] but excluded this possibility with the aid of an experiment in which the diphenyl sulfoxide was preactivated at −78 °C with triflic anhydride, thereby removing all nucleophilic sulfoxide from the reaction mixture, before addition of the thioglycoside, when the same resonances were displayed as in the normal mode of activation. We also considered the possibility of glycosyl thiosulfonium salts, such as might arise from reaction of a glycosyl triflate or an oxacarbenium ion with disulfide formed in situ from reaction between the thioglycoside and the activating mixture.[35] However, the addition of diethyl disulfide to the initial reaction mixture arising from activation of **32** resulted in loss of both the anomeric triflate signal at δ 5.95 and the signal in question at δ 5.70, giving a spectrum devoid of resonances in the region δ 5.4−7.0. That this occurrence was not simply due to decomposition, but to the formation of a third, likely thiosulfonium intermediate, was confirmed by subsequently increasing the probe temperature to −20 °C, where the familiar decomposition product due to electrophilic aromatic substitution was observed to appear. The identities of the products, with anomeric peaks at δ 6.09 in mannose and δ 5.70 in glucose, therefore remain unknown at present, but it appears likely that they are initial intermediates formed on reaction between the thioglycoside and the activated diphenyl sulfoxide and persist due to the somewhat disarmed nature of the donors. These results call to mind the work of Lowary and co-workers who observed a number of intermediates by VT-NMR spectroscopy during the activation of a series of 2,3-anhydrothiofuranoside sulfoxides with Tf_2O, which only coalesced to the apparent glycosyl triflate on warming to −40 °C.[36] If, as Bols has demonstrated in recent work, the effect of 4,6-*O*-acetals in disarming sugar donors is partially torsional and partially electronic, it must be assumed that an apical nitrile or other, more severely electron-withdrawing group could be capable of enhancing the electron-withdrawing, disarming effect,[37] leading to enhanced stability of any intermediate sulfonium salts along the pathway to the glycosyl triflate. By a similar token, once formed the glycosyl triflates should be more stable than those observed with simple benzylidene acetal protecting groups as is reflected in the decomposition temperature of 0 °C. This in turn leads to tighter transient oxacarbenium triflate ion pairs and enhanced β-selectivity[38] over that seen with the simple benzylidene acetals.

(34) Gin, D. Y.; Garcia, B. A. *J. Am. Chem. Soc.* **2000**, *122*, 4269−4279.

(35) Such intermediates are well-known in DMTST activations. For a recent example, see: Davis, B. G.; Grayson, E. J.; Ward, S. J.; Hall, A. L.; Rendle, P. M.; Gamblin, D. P.; Batsanov, A. S. *J. Org. Chem.* **2005**, *70*, 9740−9754.

(36) Callam, C. S.; Gadikota, R. R.; Krein, D. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 13112−13119.

Conclusion

The [1-cyano-2-(2-iodophenyl)]ethylidene group, an acetal protecting group for carbohydrate thioglycoside donors, has been developed. The group is easily introduced under mild conditions, over short reaction times, and in the presence of a wide variety of other protecting groups. It conveys strong β-selectivity with thiomannoside donors and undergoes a tin-mediated radical fragmentation to provide high yields of the synthetically challenging β-rhamnopyranosides.

Experimental Section

Ethyl (2-Iodophenyl)iminoacetate Hydrochloride (18). To 5.00 g of dry 2-iodophenylacetonitrile was added 1.400 mL (1.2 equiv) of absolute ethanol under inert atmosphere. The solution was cooled to 0 °C, saturated with anhydrous HCl gas, and then allowed to stand at 0 °C overnight. The resultant white solid was triturated with ethyl ether, filtered, and dried under vacuum, providing the product in 92% yield. White solid. Mp: 125−128 °C (sublimes). ^{1}H NMR (DMSO-d_6): δ 7.86 (d J = 8.0 Hz, 1H), 7.43 (d J = 6.5 Hz, 1H), 7.38 (t J = 7.0 Hz, 1H), 7.06 (dt J = 1.0, 7.5 Hz, 1H), 4.44 (q J = 7.0 Hz, 2H), 4.20 (s, 2H), 1.20 (t J = 7.0 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 176.7, 139.8, 135.9, 131.7, 130.4, 129.2, 101.9, 70.2, 43.7, 13.8. Anal. Calcd for $C_{10}H_{13}ClINO$: C, 36.89; H, 4.02. Found: C, 36.79; H, 3.91.

Triethyl (2-Iodophenyl)orthoacetate (19). A 6.00 g portion of imidate **18** was dissolved in 40 mL of absolute ethanol and stirred under inert atmosphere for 2 days at room temperature. A volume of ethyl ether equal to that of ethanol used (40 mL) was added to the reaction mixture. The reaction was then filtered through Celite to remove the precipitated ammonium chloride, and solvents were evaporated to yield the crude ortho ester together with the byproduct carboxylate ester in 62% yield by NMR. The ortho ester was best used as the crude mixture itself.

General Procedure for Preparation of 4,6-*O*-[1-Cyano-2-(2-iodophenyl)ethylidene]-Protected Donors. One equivalent of relevant diol and 0.05 equiv of CSA were dissolved in dry CH_2Cl_2 (to ∼0.1 M) and stirred under inert atmosphere at 0 °C. Crude ortho ester **19** (1.2 equiv based on NMR) in a sparing amount of CH_2Cl_2 was then added dropwise to the reaction mixture over ∼10 min. The reaction was allowed to warm to room temperature and left to stir for ∼3 h, after which time TLC showed that no starting material remained. The mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of solvents and azeotropic removal of water with benzene provided the crude ortho ester as a mixture of isomers, which was reacted without further purification. The crude ortho ester was taken up in CH_2Cl_2 (to ∼0.1 M), and 4 equiv of TMSCN was added in one portion. The mixture was stirred at 0 °C while 0.4 equiv of $BF_3(OEt_2)$ in a sparing amount of CH_2Cl_2 was added dropwise. The reaction mixture was stirred at room temperature ∼1.5 h further, after which time TLC showed that all starting material had been converted to a slightly more polar compound. Solid K_2CO_3 was added and the mixture stirred ∼10 min before being diluted with

(37) Jensen, H. H.; Nordstrom, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205−9213.

(38) Crich, D.; Chandrasekera, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386-5389.

CH_2Cl_2, washed with aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Column chromatography provided the donors in 74−89% yield from the diols.

Ethyl 2,3-Di-*O*-benzyl-4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene-α-D-thiomannopyranoside (20). A 0.72 g (1.8 mmol) portion of dry diol **5** and 0.77 g (2.1 mmol, 1.2 equiv) of crude ortho ester **19** were combined according to the general procedure to give 0.93 g of **20** (80% over two steps) after column chromatography (eluent 10:1 hexanes/EtOAc). $[\alpha]^{24}_D$: +90.7 (*c* 1, $CHCl_3$). IR (thin film): 2251 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.90 (dd J = 1.0, 8.5 Hz, 1H), 7.52 (dd J = 1.0, 7.5 Hz, 1H), 7.39−7.29 (m, 11H), 6.99 (dd J = 1.5, 8.0 Hz, 1H), 5.26 (d J = 1.5 Hz, 1H), 4.77 (d, J = 12.5 Hz, 1H), 4.69 (d J = 12.5 Hz, 1H), 4.66 (d J = 11.5 Hz, 1H), 4.55 (d J = 11.5 Hz, 1H), 4.52−4.49 (m, 1H), 4.12−4.09 (m, 3H), 3.89 (dd J = 1.0, 3.0 Hz, 1H), 3.82 (dd J = 3.5, 9.5 Hz, 1H), 3.56 (dd J = 6.5, 14.5 Hz, 2H), 2.63−2.53 (m, 2H), 1.25 (t J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 139.9, 138.3, 137.8, 135.8, 131.6, 129.4, 128.5, 128.4, 128.3, 128.2, 127.9, 127.70, 127.65, 114.6, 103.1, 96.9, 83.9 ($^1J_{CH}$ = 166.2 Hz), 78.0, 76.7, 76.3, 73.24, 73.18, 65.8, 63.6, 49.0, 25.5, 14.9. HRMS (ESI): *m*/*z* calcd for $C_{31}H_{32}INO_5S$ $(M + Na)^+$ 680.0944, found 680.0936.

General Procedure for Coupling of Thiogalactopyranoside 37 (Protocol A). Dry donor (1 equiv), together with 1.3 equiv of diphenyl sulfoxide, 1 equiv of TTBP, and freshly activated molecular sieves, was taken up in dry CH_2Cl_2 (0.05 M in substrate) and brought to −70 °C under inert atmosphere. 0.080 mL (0.477 mmol, 1.4 equuiv) Triflic anhydride was then added. After the mixture was stirred at −70 °C for ∼30 min, 2 equiv of the acceptor alcohol dissolved in dry CH_2Cl_2 was added all at once. The mixture was allowed to stir at −70 °C for 2 h before being filtered, quenched with $NaHCO_3$, washed with brine, and dried over Na_2SO_4. Evaporation of solvent and column chromatography provided the coupled products.

General Procedure for Coupling of Thiomannopyranoside 20 (Protocol B). Dry donor (1.0 equiv), together with 1.5 equiv of diphenyl sulfoxide and 3 equiv of TTBP, was dissolved in dry CH_2Cl_2 (0.05 M to substrate with the thiomannosides and 0.01 M to substrate with the thioglucosides) and brought to −70 °C under inert atmosphere. Triflic anhydride (1.7 equiv) was then added and the mixture allowed to rise to −20 °C over 30 min. After being stirred at −20 °C for ∼15 min, the mixture was then brought back to −70 °C, and 2 equiv of the acceptor alcohol dissolved in 1 mL of dry CH_2Cl_2 was added all at once. The mixture was allowed to stir at −70 °C for 2 h before being quenched with $NaHCO_3$, washed with brine, and dried over Na_2SO_4. Evaporation of solvent and column chromatography provided the coupled products.

Methyl 4-*O*-(2,3-Di-*O*-benzyl-4,6-*O*-[1-cyano-2-(2-iodophenyl)]-ethylidene-β-D-mannopyranosyl)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (21). Coupling of 0.100 g (0.15 mmol) of **20** with 0.066 g (0.30 mmol) of **9** according to protocol B afforded 0.114 g (0.14 mmol, 92%) of **21** as a white solid. $[\alpha]^{24}_D$: −42.4 (*c* 1, $CHCl_3$). Mp: 112−115 °C. IR (KBr pellet): 2230 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.87 (dd J = 1.0, 8.0 Hz, 1H), 7.49 (dd J = 1.5, 7.5 Hz, 1H), 7.39−7.22 (m, 11H), 6.97 (dt J = 2.0, 8.0, 1H), 4.94 (s, 1H), 4.86 (s, 1H), 4.84 (d J = 12.0 Hz, 1H), 4.79 (d J = 12.0 Hz, 1H), 4.54 (d J = 12.5 Hz, 1H), 4.48 (d J = 12.5 Hz, 1H), 4.38 (t J = 10.0 Hz, 1H), 4.14 (s, 1H), 4.12 (d J = 2.5 Hz, 1H), 4.08 (d J = 1.5 Hz, 1H), 3.91 (d J = 2.5 Hz, 1H), 3.63−3.62 (m, 2H), 3.56−3.49 (m, 3H), 3.40 (s, 3H), 3.20 (m, 1H), 1.51 (s, 3H), 1.34 (s, 3H), 1.31 (d J = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 139.8, 138.4, 138.3, 135.8, 131.4, 129.4, 128.4, 128.3, 128.2, 128.1, 127.6, 127.53, 127.46, 114.7, 109.3, 103.0, 100.1 ($^1J_{CH}$ = 158.6 Hz), 97.8 ($^1J_{CH}$ = 168.7 Hz), 96.7, 78.3, 78.1, 76.3, 76.2, 76.1, 74.8, 72.5, 66.6, 65.9, 64.1, 55.0, 49.0, 27.9, 26.4, 17.7. Anal. Calcd for $C_{39}H_{44}INO_{10}$: C, 57.57; H, 5.45. Found: C, 57.34; H, 5.57.

General Procedure for Radical Fragmentation of Glycopyranosides. Substrate (1 equiv) was dissolved in degassed xylenes (to ∼0.006 M) and brought to reflux under argon. Over 2 h, 1.5 equiv of Bu_3SnH and 0.20 equiv of AIBN in degassed xylenes (to ∼0.025 M in Bu_3SnH) was added via syringe pump to the refluxing reaction mixture. Upon completion of the addition, the mixture was cooled to room temperature and solvent evaporated and taken up in 5 mL of ethanol. $NaBH_4$ (2.0 equiv) was added and the reaction stirred for ∼15 min. The ethanol was removed under vacuum, and the mixture was diluted with CH_2Cl_2 and washed with water and brine. Evaporation of solvents followed by column chromatography provided the deoxygenated sugars.

Methyl 4-*O*-(2,3-Di-*O*-benzyl-4-*O*-(2-cyanophenyl)acetyl-β-D-rhamnopyranosyl)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (22) and Byproduct Methyl 4-*O*-(2,3-Di-*O*-benzyl-4,6-*O*-[2-(2-cyanophenyl)]ethylidene-β-D-mannopyranosyl)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (23). According to the general procedure, 0.093 g (0.114 mmol) of **21** yielded 0.062 g (0.092 mmol, 81%) of **22** and 0.004 g (0.006 mmol, 5%) of **23**. **22.** Clear oil. $[\alpha]^{24}_D$: −56.2 (*c* 0.5, $CHCl_3$). IR (thin film): 2229 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.60 (dd J = 1.5, 7.5 Hz, 1H), 7.42 (dd J = 1.0, 7.0 Hz, 1H), 7.38−7.16 (m, 12H), 5.23 (t J = 10.0 Hz, 1H), 4.89 (s, 1H), 4.88 (d J = 13.0 Hz, 1H), 4.87 (s, 1H), 4.73 (d J = 12.5 Hz, 1H), 4.37 (d J = 12.5 Hz, 1H), 4.20 (d J = 12.5 Hz, 1H), 4.14−4.08 (m, 2H), 3.90 (d J = 2.5 Hz, 1H), 3.81 (q J = 15.5 Hz, 2H), 3.70−3.64 (m, 2H), 3.44 (dd J = 3.5, 10.0 Hz, 1H), 3.39 (s, 3H), 3.39−3.35 (m, 1H), 1.51 (s, 3H), 1.34 (d J = 6.0 Hz, 3H), 1.23 (d J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 168.8, 138.7, 138.1, 137.5, 132.9, 132.8, 130.6, 128.3, 128.1, 128.0, 127.8, 127.5, 127.4, 127.1, 117.7, 113.3, 109.4, 99.3 ($^1J_{CH}$ = 157.4 Hz), 97.9 ($^1J_{CH}$ = 171.2 Hz), 79.4, 78.5, 77.5, 77.2, 76.1, 74.1, 74.0, 71.0, 70.6, 64.3, 54.9, 39.7, 27.9, 26.5, 17.7, 17.5. HRMS (ESI): *m*/*z* calcd for $C_{39}H_{45}NO_{10}$ $(M + Na)^+$ 710.2941, found 710.2937. **23.** Clear oil. $[\alpha]^{24}_D$: −41.2 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.60 (dd J = 1.0, 8.0 Hz, 1H), 7.49 (dt J = 1.5, 7.5 Hz, 1H), 7.42−7.20 (m, 12H), 4.93 (s, 1H), 4.88−4.84 (m, 3H), 4.76 (d J = 12.5 Hz, 1H), 4.54 (d J = 12.5 Hz, 1H), 4.48 (d J = 12.5 Hz, 1H), 4.13−4.06 (m, 3H), 3.90 (t J = 10.0 Hz, 1H), 3.89 (d J = 3.0 Hz, 1H), 3.71 (t J = 5.0 Hz, 1H), 3.61 (m, 2H), 3.53 (dd J = 3.5, 10.0 Hz, 1H), 3.38 (s, 3H), 3.23−3.19 (m, 3H), 1.50 (s, 3H), 1.33 (s, 3H), 1.30 (d J = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 139.9, 138.5, 132.8, 132.5, 131.0, 128.4, 128.3, 128.1, 127.5, 127.4, 127.2, 118.2, 113.7, 109.4, 101.3 ($^1J_{CH}$ = 156.1 Hz), 100.1 ($^1J_{CH}$ = 158.6 Hz), 97.9 ($^1J_{CH}$ = 167.4 Hz), 78.6, 78.4, 78.0, 77.8, 76.3, 76.1, 74.7, 72.4, 68.3, 54.9, 39.4, 27.9, 26.4, 17.7. HRMS (ESI): *m*/*z* calcd for $C_{39}H_{45}NO_{10}$ $(M + Na)^+$ 710.2941, found 710.2933.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-[2,3-di-*O*-benzoyl-4-deoxy-6-*O*-(2-cyanophenyl)acetyl-β-D-galactopyranosyl]-α-D-glucopyranoside (81), Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-[2,3-di-*O*-benzoyl-4-*O*-(2-cyanophenyl)acetyl-β-D-fucopyranosyl]-α-D-glucopyranoside (82), and Byproduct Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-[2,3-di-*O*-benzoyl-4,6-*O*-(2-cyanophenyl)ethylidene-β-D-galactopyranosyl]-α-D-glucopyranoside (83). According to the general procedure, 0.086 g (0.079 mmol) of **51** yielded after column chromatography 0.045 g (0.047 mmol, 61%) of a 1.5:1 mixture of 6-deoxy and 4-deoxy products as determined by NMR, together with 0.010 g (0.010 mmol, 13%) of **83**. The mixture of deoxy sugars was dissolved in 2 mL of EtOH/CH_2Cl_2 (9:1), and 0.003 g (1 equiv) of guanidine (obtained by neutralization of the HCl salt with NaOEt and filtration under argon) was added. The mixture was stirred for 15 min, after which time TLC showed complete disappearance of one of the two isomers and emergence of a more polar compound. Aqueous workup with extraction into CH_2Cl_2 and column chromatography afforded 0.027 g of **82** (36% from **51**) and 0.015 g of **81** (24% from **51**). **81.** Clear oil. $[\alpha]^{24}_D$: +21.6 (*c* 0.25, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.93−7.88 (m, 4H), 7.51−7.48 (m, 1H), 7.40−7.17 (m, 18H), 7.03 (m, 2H), 5.45 (dd J = 7.5, 10.0 Hz, 1H), 5.37 (dt J = 5.5, 11.0 Hz, 1H), 4.88 (d J = 11.0 Hz, 1H), 4.75 (d J = 12.0 Hz, 1H), 4.69 (d J = 11.0 Hz, 1H), 4.66 (d J = 7.5 Hz, 1H), 4.60 (d J = 12.5 Hz, 1H), 4.49 (d J = 4.0 Hz, 1H), 4.45 (d J = 11.0 Hz,1H), 4.28 (d J = 11.0 Hz, 1H), 4.10 (dd J =

1.5, 10.5 Hz, 1H), 3.88 (t J = 9.5 Hz, 1H), 3.80−3.66 (m, 2H), 3.46−3.35 (m, 2H), 3.24 (s, 3H), 2.27 (ddd J = 1.0, 5.0, 12.0 Hz, 1H), 2.06 (t J = 6.5 Hz, 1H), 1.82 (q J = 11.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 166.0, 165.3, 138.8, 138.2, 133.3, 133.0, 129.73, 129.70, 129.4, 129.3, 128.5, 128.4, 128.3, 128.2, 127.9, 127.6, 1275, 101.4 ($^1J_{CH}$ = 155.4 Hz), 98.1 ($^1J_{CH}$ = 170.2 Hz), 81.9, 79.7, 79.1, 77.3, 77.2, 75.6, 74.7, 73.5, 72.6, 72.4, 71.7, 69.5, 68.3, 64.8, 55.1, 32.0, 25.7. HRMS (ESI): m/z calcd for $C_{48}H_{50}NO_{12}$ $(M + Na)^+$ 841.3200, found 841.3206. **82.** Clear oil. $[\alpha]^{24}_D$: +10.0 (c 0.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.88 (dd J = 1.0, 7.5 Hz, 2H), 7.78 (d J = 7.5 Hz, 2H), 7.61 (d J = 7.5 Hz, 1H), 7.47 (q J = 8.0 Hz, 2H), 7.40 (t J = 6.5 Hz, 1H), 7.36−7.24 (m, 17H), 7.21 (t J = 7.5 Hz, 2H), 7.11 (d J = 6.0 Hz, 2H), 5.69 (dd J = 8.0, 10.5 Hz, 1H), 5.50 (d J = 3.0 Hz, 1H), 5.40 (dd J = 3.0, 10.0 Hz, 1H), 4.89 (d J = 11.0 Hz, 1H), 4.73 (d J = 12.0 Hz, 1H), 4.69 (d J = 10.5 Hz, 1H), 4.68 (d J = 8.0 Hz, 1H), 4.58 (d J = 12.0 Hz, 1H), 4.55 (d J = 11.0 Hz, 1H), 4.46 (d J = 3.0 Hz, 1H), 4.37 (d J = 11.0 Hz, 1H), 4.15 (d J = 9.0 Hz, 1H), 4.03 (d J = 17.0 Hz, 1H), 3.95 (d J = 17.0 Hz, 1H), 3.92−3.89 (m, 2H), 3.74−3.69 (m, 2H), 3.41 (dd J = 3.5, 9.5 Hz, 1H), 3.37 (t J = 9.5 Hz, 1H), 3.20 (s, 3H), 1.30 (d J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 169.4, 165.6, 165.2, 138.8, 138.2, 137.1, 133.3, 133.1, 132.9, 130.5, 129.7, 128.5, 128.41, 128.37, 128.34, 128.1, 127.9, 127.8, 127.7, 127.6, 117.4, 113.5, 101.4 ($^1J_{CH}$ = 157.4 Hz), 97.9 ($^1J_{CH}$ = 173.2 Hz), 82.0, 79.8, 77.6, 75.6, 74.7, 73.4, 72.1, 71.6, 69.6, 69.4, 68.3, 55.0, 39.1, 16.2. HRMS (ESI): m/z calcd for $C_{57}H_{55}NO_{13}$ $(M + Na)^+$ 984.3571, found 984.3568. **83.** Clear oil. $[\alpha]^{24}_D$: +8.6 (c 0.5, $CHCl_3$). IR (thin film): 2224 (CN), 1728 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.91 (dd J = 1.0, 8.5 Hz, 2H), 7.88 (dd J = 1.0, 8.5 Hz, 2H), 7.54−7.40 (m, 4H), 7.36 (t J = 7.0 Hz, 2H), 7.33−7.23 (m, 15H), 7.18−7.10 (m, 4H), 5.84 (dd J = 8.0, 10.0 Hz, 1H), 5.23 (dd J = 3.5, 10.0 Hz, 1H), 4.90 (d J = 11.0 Hz, 1H), 4.79 (dd J = 4.0, 6.5 Hz, 1H), 4.71 (d J = 12.0 Hz, 1H), 4.70 (d J = 10.5 Hz, 1H), 4.68 (d J = 8.5 Hz, 1H), 4.61 (d J = 12.0 Hz, 1H), 4.58 (d J = 12.0 Hz, 1H), 4.43 (d J = 4.0 Hz, 1H), 4.42 (d J = 11.0 Hz, 1H), 4.28 (d J = 4.0 Hz, 1H), 4.22 (dd J = 1.0, 12.5 Hz, 1H), 4.16 (dd J = 1.5, 11.0 Hz, 1H), 3.90 (t J = 8.5 Hz, 1H), 3.88 (dd J = 2.0, 13.0 Hz, 1H), 3.74 (ddd J = 1.5, 5.0, 10.0 Hz, 1H), 3.67 (dd J = 5.0, 11.0 Hz, 1H), 3.49 (d J = 1.5 Hz, 1H), 3.38 (dd J = 3.5, 9.5 Hz, 1H), 3.34 (dd J = 8.5, 9.5 Hz, 1H), 3.30−3.20 (m, 2H), 3.19 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 165.8, 165.2, 139.6, 138.8, 138.3, 138.2, 133.4, 133.0, 132.4, 132.2, 132.0, 129.9, 129.7, 128.5, 128.39, 128.37, 128.1, 127.92, 127.90, 127.6, 127.5, 126.9, 118.1, 113.0, 101.4 ($^1J_{CH}$ = 163.7 Hz), 100.1 ($^1J_{CH}$ = 170.0 Hz), 97.8 ($^1J_{CH}$ = 171.2 Hz), 82.0, 79.8, 77.8, 75.6, 74.7, 73.3, 72.9, 72.5, 69.7, 69.0, 68.4, 68.1, 66.5, 55.0, 39.4. HRMS (ESI): m/z calcd for $C_{57}H_{55}NO_{13}$ $(M + Na)^+$ 984.3571, found 984.3535.

Acknowledgment. We thank the NIH (GM 57335) for support, Professor Duncan Wardrop for helpful discussions, and Professor Donald Wink for the X-ray structure.

Supporting Information Available: Complete experimental details, copies of spectra of all new compounds, copies of VT-NMR spectra, and crystallographic data for disaccharide **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0526688