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Direct Stereocontrolled Synthesis of 3-Amino-3-deoxy-β-Mannopyranosides: Importance of the Nitrogen Protecting Group on Stereoselectivity

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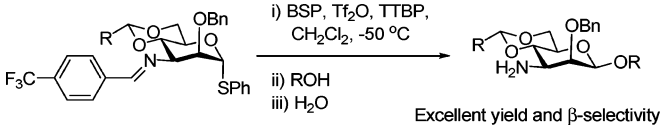
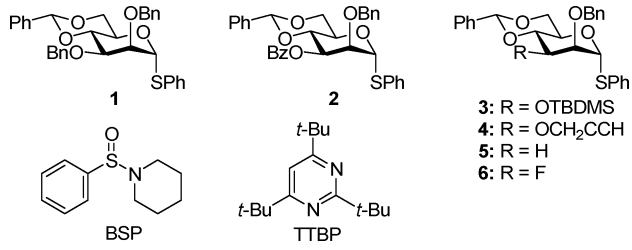


The highly stereocontrolled synthesis of the 3-amino-3-deoxy-β-mannopyranosides is achieved by means of thioglycoside donors protected with a 4,6-*O*-benzylidene or alkylidene acetal and a benzylidene imine group. Among the various nitrogen protecting groups investigated only the Schiff's base was found to give high β-selectivity. *N*-Phthalimido and *N*-acetamido protected donors were found to be highly α-selective, whereas 3-azido-3-deoxy glycosyl donors gave intermediate selectivity. The reasons for the protecting group dependency are discussed in terms of the change in the O2−C2−C3−N3 torsional interaction on conversion of the covalent glycosyl triflates to the transient oxacarbenium ions.

Introduction

It is becoming increasingly apparent in the 4,6-*O*-benzylidene directed β-mannopyranosylation developed in our laboratories[1,2] that the substituent at the mannose 3-position plays a critical role in determining the stereochemical outcome of the reaction. Thus, while the 3-*O*-benzyl donor **1** and related benzylic-type ethers are highly β-selective,[3−5] 3-*O*-carboxylate esters such as **2** give essentially pure α-glycosides.[6,7] On the other hand, intermediate selectivity, namely the formation of α/β mixtures, is seen with a broad spectrum of compounds including the 3-*O*-*tert*-butyldimethylsilyl ether **3**,[8] the 3-*O*-propargyl ether **4**,[9] the 3-deoxy system **5**,[10] and the 3-deoxy-3-fluoro system **6**.[11] This variation of selectivity is seen irrespective of whether a thioglycoside is activated with the combination of 1-benzenesulfinyl piperidine (BSP) and trifluoromethanesulfonic anhydride,[5] with that of diphenyl sulfoxide and trifluoromethanesulfonic anhydride,[12] or by oxidation to the corresponding glycosyl sulfoxide followed by activation with trifluoromethanesulfonic anhydride,[3,4] and in other glycosylation systems functioning by a similar mechanism.[13]



With exception of the ester **2** and its analogues, for which we do not have a satisfactory explanation at present, these effects are understood in terms of our general glycosylation mechanism involving initial conversion of the donor to a demonstrable α-mannosyl triflate intermediate[14] that is in equilibrium with a

(1) Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115−251.
(2) Crich, D. In *Glycochemistry*: *Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Dekker: New York, 2001; pp 53−75.
(3) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−1199.
(4) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348.
(5) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020.
(6) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291−1297.
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(8) Crich, D.; Dudkin, V. *Tetrahedron Lett.* **2000**, *41*, 5643−5646.
(9) Crich, D.; Jayalath, P.; Hutton, T. K. *J. Org. Chem.* **2006**, *71*, 3064−3070.
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(11) Crich, D.; Li, L. *J. Org. Chem.* **2007**, *72*, 1681−1690.
(12) 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.
(13) Codée, J. D. C.; Hossain, L. H.; Seeberger, P. H. *Org. Lett.* **2005**, *7*, 3251−3254.

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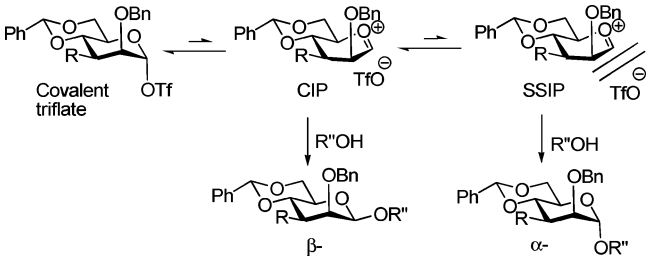
SCHEME 1. Glycosylation Mechanism



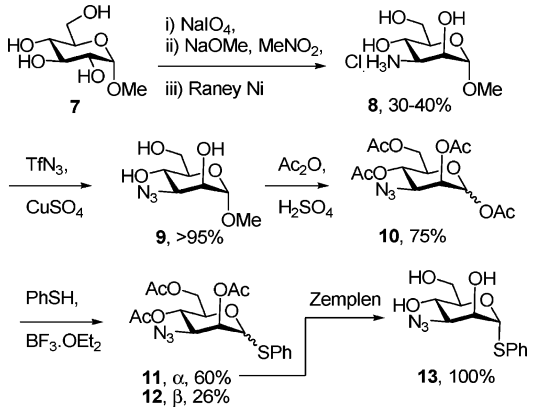
transient β-selective contact ion pair (CIP)[15] and thereby with an α-selective solvent separated ion pair (SSIP) (Scheme 1).[16] β-Selectivity is obtained when the series of equilibria is shifted as far as possible toward the covalent triflate, thereby minimizing the concentration of the α-selective SSIP. The role of the 4,6-*O*-benzylidene acetal, or its surrogates, is to fix the C5−C6 bond of the donor in the most electron-withdrawing *tg* conformation thereby destabilizing any glycosyl oxacarbenium ions and favoring the covalent glycosyl triflate.[17,18] As the covalent triflate, with its $^4C_1$ conformation, collapses to the CIP, with the oxacarbenium ion in the likely $^4H_3$ conformation,[19,20] the O2−C2−C3−R torsion angle is compressed from 60° to 45°.[10] When R is benzyloxy this results in an increase in steric strain, which further destabilizes the oxacarbenium ion and favors the covalent triflate. When R is hydrogen, fluoride, or propargyloxy the increase in steric strain is smaller and lower selectivity is the result.[11] The effect of the large *tert*-butyldimethylsiloxy group, on the other hand, is explained by a steric buttressing interaction with the O-2 protecting group, which results in increased shielding of the β-face, resulting in reduced selectivity:[8] the effect of the 3-*O*-*tert*-butyldimethylsilyl ether can be thwarted when it is employed in conjunction with a sterically minimal 2-*O*-propargyl ether.[9]

In this paper we report on the synthesis and glycosylation reactions of a series of 4,6-*O*-alkylidene protected 3-amino-3-deoxymannopyranosyl donors and provide further insight into the range of acceptable substituents at the 3-position.

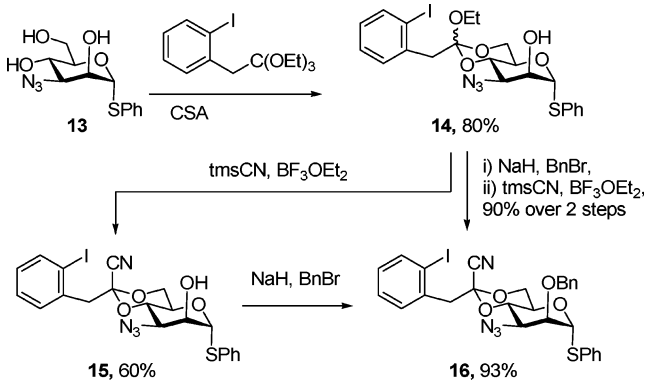
Results

Synthesis of Substrates. Methyl 3-amino-3-deoxy-α-D-mannopyranoside **8** was most expediently prepared from methyl α-D-glucopyranoside **7** by periodate cleavage followed by double Henry reaction with nitromethane, as described by Baer and Fischer,[21] and as improved by Richardson.[22] Metal-catalyzed

SCHEME 2. Thioglycoside Synthesis



SCHEME 3. Introduction of the 1-Cyano-2-(2-iodophenyl)ethylidene Acetal



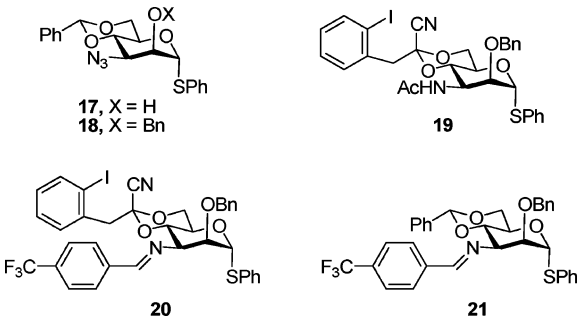
diazo transfer[23] from trifluoromethanesulfonyl azide[24] gave the corresponding azide **9**, which was converted to a mixture of the peracetylated α- and β-thioglycosides **11** and **12** by standard methods. X-ray crystallography confirmed the configuration of **12**, and saponification of **11** gave the triol **13** (Scheme 2).

Our recent interest in the use of modified 4,6-*O*-acetal protecting groups, particularly those suitable for subsequent radical fission to give the 6-deoxy sugars, prompted the employment of the 1-cyano-2-(2-iodophenyl)ethylidene acetal,[25] with previous work having established the β-directing ability of this group.[25,26] Thus, reaction of triol **13** with triethyl 2-(2-iodophenyl)orthoacetate[25] gave an unstable orthoester **14**, which was converted in 62% yield to the stable cyanoacetal **15** by treatment with trimethylsilyl cyanide and BF_3 ethereate.[25] Benzylation then gave the donor **16** in 93% yield. Interestingly, a higher overall yield of **16** was obtained when the sequence of cyanide introduction and benzylation was inverted (Scheme 3). The complete stereochemical assignment of **15** was confirmed crystallographically.

The analogous benzylidene acetal **18** was also prepared in the standard manner via the intermediacy of **17**. Treatment of **16** with triphenylphosphine in the presence of water, followed by acetylation provided an acetamide **19**. Reaction of both **16** and **18** with triphenylphosphine under anhydrous conditions with subsequent reaction of the intermediate iminophosphoranes with

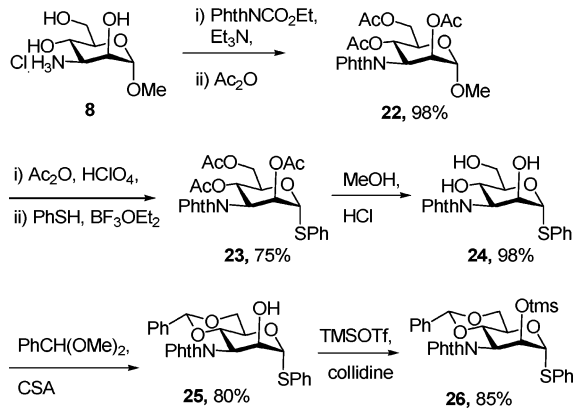
(14) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.
(15) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386−5389.
(16) As suggested by a reviewer of a recent manuscript, whom we thank, an S_Ni mechanism cannot be completely excluded from consideration for the formation of the α-mannosides.
(17) Jensen, H. H.; Nordstrom, M.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205−9213.
(18) Torsional effects also potentially contribute to the benzylidene acetal effect. (a) Fraser-Reid, B.; Wu, Z. C.; Andrews, W.; Skowronski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434−1435. (b) Andrews, C. W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280−5289.
(19) Nukada, T.; Berces, A.; Whitfield, D. M. *Carbohydr. Res.* **2002**, *337*, 765−774.
(20) Nukuda, T.; Bérces, A.; Wang, L.; Zgierski, M. Z.; Whitfield, D. M. *Carbohydr. Res.* **2005**, *340*, 841−852.
(21) Baer, H. H.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1960**, *82*, 3709−3713.
(22) Richardson, A. C. *J. Chem. Soc.* **1962**, 373−374.
(23) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6029−6032.
(24) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073−2077.
(25) Crich, D.; Bowers, A. A. *J. Org. Chem.* **2006**, *71*, 3452−3463.
(26) Crich, D.; Bowers, A. A. *Org. Lett.* **2006**, *8*, 4327−4330.

p-trifluoromethylbenzaldehyde gave the imines **20** and **21**, respectively, both with yields in the range of 60−80%.[27]



Finally, a phthalimido protected donor **26** was prepared by the route outlined in Scheme 4, the longer route being necessary because introduction of the phthalimido group directly on the amines derived from **16** and/or **18** failed, presumably for steric reasons. In this scheme the use of methanolic HCl to effect cleavage of the acetate groups in **23** was dictated by incompatibility of the phthalimido group under the standard Zemplen deacetylation conditions. Likewise, the use of the trimethylsilyl ether as the protecting group for O-2 arose from difficulties in attempted benzylation reactions.

SCHEME 4. Preparation of a Phthalimido Protected Donor



Glycosylation Reactions. Our preferred candidate for the 3-position was the azide group and, thus, glycosylation studies began with donor **16**. A number of experiments were carried out with 1-adamantanol as acceptor, with activation by the diphenyl sulfoxide/trifluoromethanesulfonic anhydride couple[12] in the presence of the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[28] in dichloromethane. Previous work had indicated the 1-cyano-2-(2-iodophenyl)ethylidene acetal to be somewhat disarming and to retard clean activation at −78 °C,[25] thus a series of experiments were conducted in which the donor/diphenyl sulfoxide/trifluoromethanesulfonic anhydride/TTBP was warmed to different temperatures before the acceptor was added. The results presented in Table 1 indicate that warming to −50 °C before addition of the acceptor and quenching at that temperature provided the optimum results in terms of yield and selectivity (entry 3). Using BSP in place of diphenyl sulfoxide gave essentially analogous results (Table 1, entry 4), and the attempted use of the nitrile effect[29−33] was found to be disappointing in line with previous observations in the mannose[34] and rhamnose series (Table 1, entry 5).[35] Initial stereochemical assignments for **27**α and **27***β*, and for all subsequent coupling products, were based on the diagnostic chemical shift (δ 3.0−3.3) of the *β*-mannose H5 resonance in the ^{1}H NMR spectra,[4] and were subsequently verified by determination of the $^1J_{CH}$ coupling constants for the anomeric carbon.[36−38]

Donors **16**, **19**−**21**, and **26** were then coupled to 1-adamantanol with activation by the diphenyl sulfoxide/trifluoromethanesulfonic anhydride protocol with activation at −65 °C and warming to −50 °C before addition of the acceptor (Table 2).

From the results presented in Table 2 it is evident that the Schiff's base is the ideal protecting group for N-3 in these glycosylation reactions, being readily formed from the azide in a single step, giving outstanding *β*-selectivity, and being hydrolyzed directly to the amine in the course of the workup. Equally, it is apparent that the nature of the acetal spanning O4 and O6 has little effect on the yield or stereochemical outcome of the reaction, as had been anticipated from previous work.[25] One interesting feature of this series of reactions was the sulfenylation of the amide nitrogen of donor **19**, ultimately leading to glycoside **28**α, whose structure rests on HRMS data, and the absence of an NH resonance in the ^{1}H NMR spectrum. This *N*-acetylsulfenamide arises from the reaction of the amide group with the byproducts of the thioglycoside activation process.

On the basis of these results, further reactions were carried out in which the more typical glycosyl acceptors methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside **32** and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **33** were coupled to donors **20** and **21** under the optimium conditions, resulting in the highly *β*-selective formation of the products in each case (Table 3).

Overall, the picture that emerges for the 3-amino-3-deoxy-mannopyranoside series closely follows that established by the mannopyranosides themselves. Thus, the optimum protecting group for N3 is a benzylidene imine group that mimics the steric properties of a benzyl ether (steric *A* value = 1.39).[9] It is appropriate to point out here that no attempt was made to prepare or conduct glycosylation reactions with the reduced version of the benzylidene imines, namely the *N*-benzylamines, as it was considered that these would be protonated under the reaction conditions. The smaller azide (steric *A* value = 0.45−0.62),[39,40] like fluoride (steric *A* value = 0.25−0.42),[39,41−45] is insufficiently bulky for the compression of the O2−C2−C3−X

(27) For previous application of benzylidene imines as amine protecting groups in oligosaccharide synthesis see: Madsen, R.; Udodonge, U. E.; Roberts, C.; Mootoo, D. R.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 1554−1565. Also see: Khiar, N.; Fernandez, I.; Araujo, C. S.; Rodriguez, J. A.; Suarez, B.; Alvarez, E. *J. Org. Chem.* **2003**, *68*, 1433−1442.

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

(29) Majumdar, D.; Boons, G.-J. In *Handbook of Reagents for Organic Synthesis*: *Reagents for Glycoside, Nucleotide, and Peptide Synthesis*; Crich, D., Ed.; Wiley: Chichester, UK, 2005; pp 11−15.

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(31) Pougny, J.-R.; Sinaÿ, P. *Tetrahedron Lett.* **1976**, *17*, 4073−4076.

(32) Braccini, J.; Derouet, C.; Esnault, J.; de Penhoat, C. H.; Mallet, J.-M.; Michon, V.; Sinaÿ, P. *Carbohydr. Res.* **1993**, *246*, 23−41.

(33) Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 747−750.

(34) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694−696.

(35) Crich, D.; Patel, M. *Carbohydr. Res.* **2006**, *341*, 1467−1475.

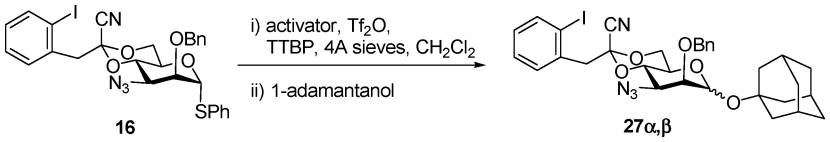
(36) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293−297.

(37) Tvaroska, I.; Taravel, F. R. *Adv. Carbohydr. Chem. Biochem.* **1995**, *51*, 15−61.

(38) Duus, J. O.; Gotfredsen, C. H.; Bock, K. *Chem. Rev.* **2000**, *100*, 4589−4614.

(39) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866−3873.

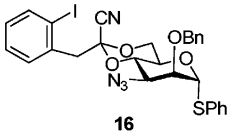
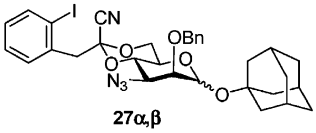
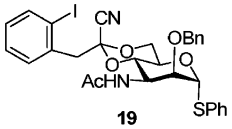
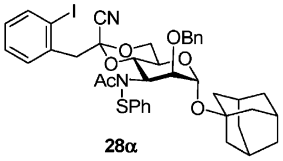
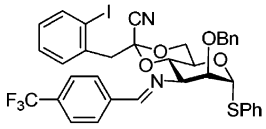
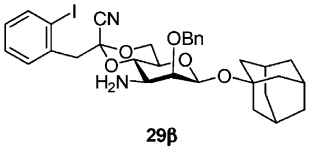
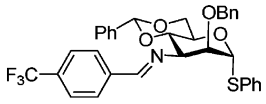
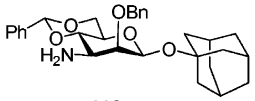
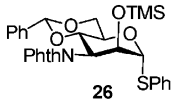
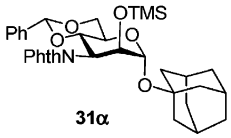
TABLE 1. Exploratory Coupling Reactions with Donor 16 and 1-Adamantanol[a]



entry	activator	solvent	method	yield, %	α:β ratio
1	Ph_2SO	CH_2Cl_2	A	97	1:1.7
2	Ph_2SO	CH_2Cl_2	B	94	1:1.5
3	Ph_2SO	CH_2Cl_2	C	98	1:3.3
5	BSP	CH_2Cl_2	D	99	1:3.2
6	Ph_2SO	CH_2Cl_2/MeCN (95/5)	E	65	1:1.2

[a] Method A: Activation at −78 °C followed, after 30 min at −78 °C, by the addition of adamantanol then warming to 0 °C before quenching. Method B: Activation at −78 °C followed, after 30 min at −78 °C, by the addition of adamantanol then quenching at −78 °C. Method C: Activation at −65 °C, followed by warming to −50 °C over 30 before addition of 1-adamantanol, and final quenching at −50 °C after 1 h. Method D: Same as for method C except that BSP was used as the activator in place of diphenyl sulfoxide. Method E: Activation at −65 °C, followed by warming to −30 °C over 30 min before addition of 1-adamantanol, and final quenching at −30 °C after 1 h

TABLE 2. Investigation of Different N-3 Protecting Groups[a]

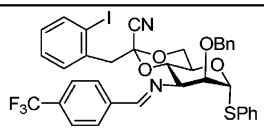
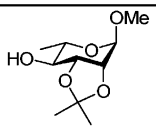
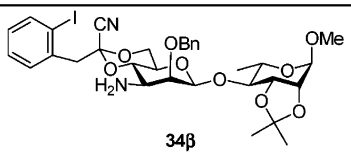
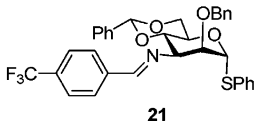
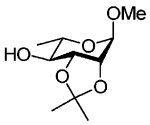
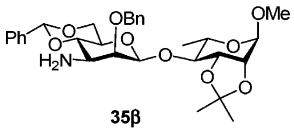
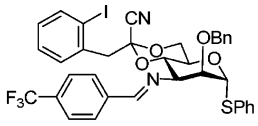
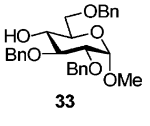
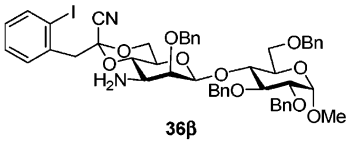
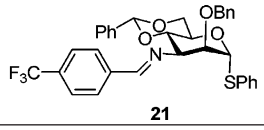
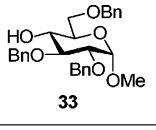
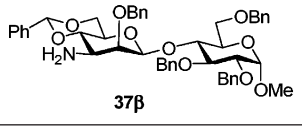
entry	donor	method	product	yield, %	α:β ratio
1	 **16**	C	 **27α,β**	98	1:3.3
2	 **19**	C	 **28α**	56	α only
3	 **20**	F	 **29β**	83	β only
4	 **21**	F	 **30β**	78	β only
5	 **26**	F	 **31α**	77%	α only

[a]Method C: Activation at −65 °C, followed by warming to −50 °C over 30 min before addition of 1-adamantanol, and final quenching at −50 °C after 1 h. Method F: As in method C except that the reaction mixture was allowed to warm to −10 °C before quenching.

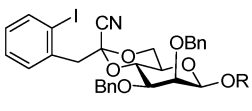
torsion angle to impact significantly the covalent triflate−CIP equilibrium (Scheme 1) resulting in a loss of β-selectivity. The acetamide and phthalimido protected systems behave exactly as the 3-*O*-carboxylate esters and lead to essentially complete α-selectivity. We note that the bulk of the 2-*O*-trimethylsilyl ether in donor **26** is unlikely to be a major factor in the α-selectivity of this system as related 2-*O*-silyl-3-*O*-benzylmannopyranosyl donors have been shown previously to exhibit good β-selectivity.[4,8]

Radical Fragmentation Reactions. In contrast to the clean radical fragmentations observed previously with glycosides **38**,[25,26] attempted radical fragmentations of the various glycosides prepared in this study with the 1-cyano-2-(2-iodophenyl)-ethylidene acetals were disappointing. Typically relatively complex reaction mixtures were observed and significant amounts of initiator were required to drive the reactions to completion irrespective of the nitrogen protecting group. By way of example the 6-deoxy glycoside **39** could only be isolated

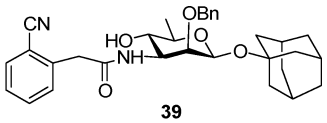
TABLE 3. Further Couplings to Donors 20 and 21

entry	donor	acceptor	product	yield, %	α:β ratio
1	 **20**	 **32**	 **34β**	76	β only
2	 **21**	 **32**	 **35β**	82	β only
3	 **20**	 **33**	 **36β**	82	β only
4	 **21**	 **33**	 **37β**	92	β only

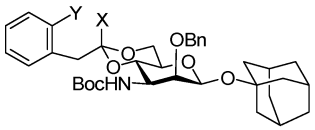
in 20% yield even though TLC indicated it to be the major product from the reaction of **29***β* with tributyltin hydride and AIBN in toluene at reflux. In addition to the radical fragmentation sequence **29***β* has undergone an O to N shift of the (2-cyano)phenylacetate group, which is the obligatory product of the radical reaction. To prevent this migration **29***β* was converted to the *N*-Boc derivative **40** in good yield by standard means, but subsequent radical reactions continued to afford complex mixtures with the isolation of the premature reduction product **41** in 10% yield, along with the desired deoxy sugar **42** in yields ranging from 10% to 15%. Unfortunately, the reason for the disappointing nature of the radical fragmentation reactions remains unclear at this time.



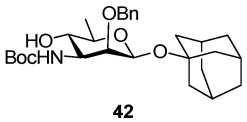
38



39



40, X = CN, Y = I
41, X = H, Y = CN



42

Conclusion

Among the various protecting groups investigated for the 3-amino group in the 3-amino-3-deoxy mannopyranoside series the *p*-trifluoromethylbenzylidene imine was by far the best, affording high yields of coupled product and excellent *β*-selectivity. The comparable steric bulk of this benzylidene imine to the 3-*O*-benzyl ethers typically employed at the 3-position in the mannopyranoside series provides considerable support for our hypothesis of the importance of the O2−C2−C3−R3 torsional interaction in the stereocontrolled synthesis of *β*-mannopyranosides and related compounds. The benzylidene imine methodology should facilitate the introduction of 3-amino-3-deoxy-*β*-mannopyranosides into antibiotics, an area of current interest,[46,47] and other molecules. Unfortunately, at least at the present stage of development, the unexpectedly poor results in the radical fragmentation mean that the method is not suitable for the introduction of the *β*-mycosamine (3-amino-3,6-dideoxy) unit into macrolide antibiotics such as the amphotericins, the nystatins, and the rimocidins.[48−50]

Experimental Section

Methyl 3-Amino-3-deoxy-α-D-mannopyranoside Hydrochloride (8). Sodium metaperiodate (55 g) was slowly added in 30 min to a stirred solution of methyl α-D-glucopyranoside (25 g) in iced water (30 mL) at <10 °C. The mixture was then stirred for 1 h, and the released formic acid was carefully neutralized with sodium

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bicarbonate (10 g). The mixture, from which much sodium iodate had crystallized, was then poured into ethanol (150 mL) and the precipitate was filtered off and washed with ethanol (100 mL). The filtrate was condensed under vacuum at <10 °C and the residal syrup, which contained solid, was taken up with ethanol. The solid was filtered off and washed with ethanol and the filtrate was again condensed under vacuum at <10 °C, and the same procedure was repeated 4 to 6 times until a clear syrup (not contaminated with visible solid) was obtained. Nitromethane (7.0 mL) was added to the solution of the syrup in dry methanol (75 mL), followed by the addition of a solution of sodium methoxide (30 mL, 25% w in methanol) at −10 °C. The stirred mixture was brought to rt slowly over 2 h, and was kept at rt for another 6 h. Amberlite-120H ion-exchange resin was added to neutralize the reaction mixture, then was removed by filtration, and the filtrate was condensed to give an orange oil. This oil was shaken under hydrogen (50 psi) with Raney Nickel (2.0 g) as the catalyst in ethanol (50 mL) for 24 h. The catalyst was removed by filtration and the filtrate was condensed to approximately 30 mL. To this brown solution was added HCl in ether (70 mL, 2M) with vigorously stirring. Ether was removed under vacuum and the residue was cooled in a refrigerator overnight. The so formed crystals were collected by filtration to give the product as a white powder (10−12 g, 30−40%): $[\alpha]_D$ +68.4 (*c*, 1.0, H_2O); mp 208 °C dec [lit.[21,22] $[\alpha]_D$ +60 (*c*, 2.0, H_2O); mp 210−240 °C dec]; ^{1}H NMR (500 MHz, D_2O) δ 4.66 (s, 1H), 3.96 (m, 1H), 3.78 (d, J = 12.0 Hz, 1H), 3.63−3.72 (m, 2H), 3.55−3.60 (m, 1H), 3.38 (dd, J = 10.0, 2.5 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 99.7, 72.2, 66.6, 63.3, 60.3, 54.7, 53.2.

Methyl 3-Azido-3-deoxy-α-D-mannopyranoside (9). To a stirred mixture of salt **8** (3.4 g, 15 mmol), Na_2CO_3 (3.2 g, 30 mmol), and $CuSO_4 \cdot 5H_2O$ (50 mg) in dry methanol (100 mL) was added a solution of trifluoromethanesulfonyl azide in dichloromethane, prepared from sodium azide (8 g, 123 mmol) and triflic anhydride (4.1 mL, 25 mmol) in dichloromethane (50 mL) according to Vasella's protocol,[24] in 6 h by syringe pump. When the addition was complete, the mixture was stirred overnight before the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (dichloromethane/MeOH: 10/1) to give a colorless oil (3.2 g, 97%). $[\alpha]_D$ +160 (*c*, 1.0, MeOH); ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.60 (d, J = 1.5 Hz, 1H), 3.78−3.86 (m, 3H), 3.72 (dd, J = 11.5, 6 Hz, 1H), 3.53 (ddd, J = 9.5, 6.0, 2.0 Hz, 1H), 3.43 (dd, J = 10, 3.5 Hz, 1H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 100.6, 73.3, 69.9, 64.2, 63.4, 61.3, 53.8; HRMS(ESI) *m*/*z* calcd for $C_7H_{13}N_3NaO_5$ $[M + Na]^+$ 242.0748, found 242.0743.

Phenyl 2,4,6-Tri-*O*-acetyl-3-azido-3-deoxy-α-1-thio-D-mannopyranoside (11) and Phenyl 2,4,6-Tri-*O*-acetyl-3-azido-3-deoxy-β-1-thio-D-mannopyranoside (12). A mixture of triol **9** (1.15 g, 5.25 mmol), Ac_2O (6.0 mL), and concentrated H_2SO_4 (0.5 mL) was stirred at rt for 12 h. Then ice (15 g) was added followed by cold water (30 mL). The resulting mixture was extracted with ether (3 × 40 mL). The combined extracts were washed with saturated $NaHCO_3$ until the aqueous layer was neutral, then with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate: 2/1) to give a mixture of isomers **10** (1.54 g, 75%) as an oil. The major component of this mixture was the α-isomer, which had the following characteristics: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (d, J = 1.5 Hz, 1H), 5.34 (t, J = 10.5 Hz, 1H), 5.20 (m, 1H), 4.26 (dd, J = 12.5, 5.0 Hz, 1H), 3.99 (m, 1H), 3.85 (dd, J = 10.5, 3.5 Hz, 1H), 2.19 (s, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 169.6, 169.5, 167.8, 89.9, 70.5, 69.5, 66.3, 62.1, 58.7, 20.83, 20.76, 20.72. To this mixture of isomers (1.54 g, 4.0 mmol) and thiophenol (0.6 mL, 6.0 mmol) in dry dichloromethane (20 mL) was added dropwise $BF_3 \cdot OEt_2$ (1.0 mL, 7.8 mmol) at 0 °C in 10 min. The reaction mixture was stirred overnight and monitored by TLC, before cold saturated $NaHCO_3$ (30 mL) was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined dichloromethane layers were dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography (hexanes/ethyl acetate: 5/2) was applied to the residue to give two compounds: α-1-thio-D-mannopyranoside **11** (1.1 g, 60%) and β-1-thio-D-mannopyranoside **12** (0.44 g, 26%). **11**: oil, $[\alpha]_D$ +109.2 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 Mz, $CDCl_3$) δ 7.47 (m, 2H), 7.32 (m, 3H), 5.50 (s, 1H), 5.42 (dd, J = 3.0, 1.0 Hz, 1H), 5.33 (td, J = 5.0, 2.5 Hz, 1H), 4.50 (m, 1H), 4.28 (dd, J = 12.5, 6.0 Hz, 1H), 4.12 (dd, J = 12.0, 2.5 Hz, 1 H), 3.81 (dd, J = 10.5, 3.0 Hz, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.8, 169.6, 132.25, 132.17, 129.3, 128.3, 85.5 ($^1J_{CH}$ = 168.8 Hz), 72.2, 69.4, 67.1, 62.4, 59.5, 20.9, 20.8, 20.7; HRMS(ESI) *m*/*z* calcd for $C_{18}H_{21}N_3NaO_7S$ $[M + Na]^+$ 446.0998; found 446.1005. **12**: white solid; $[\alpha]_D$ −62.4 (*c*, 1.0, ethyl acetate); mp 121 °C; ^{1}H NMR (500 Mz, $CDCl_3$) δ 7.52 (m, 2H), 7.31 (m, 3H), 5.70 (dd, J = 7.5, 0.5 Hz, 1H), 5.21 (t, J = 10.0 Hz, 1H), 4.85 (d, J = 1.5 Hz, 1H), 4.26 (dd, J = 12.0, 6.5 Hz, 1H), 4.17 (dd, J = 12.0, 2.5 Hz, 1H), 3.68 (ddd, J = 10.0, 6.5, 2.5 Hz, 1H), 3.63 (dd, J = 10.0, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.0, 169.6, 133.0, 132.1, 129.1, 128.2, 86.0 ($^1J_{CH}$ = 152.5 Hz), 70.8, 66.9, 63.0, 62.8, 20.8, 20.7, 20.6. Anal. Calcd for $C_{18}H_{21}N_3O_7S$: C, 51.06; H, 5.00. Found: C, 50.94; H, 4.93.

Phenyl 3-Azido-3-deoxy-α-1-thio-D-mannopyranoside (13). To a stirred solution of **11** (1.06 g, 2.5 mmol) in methanol (20 mL) was added one drop of NaOMe in methanol (25% w/w). The reaction mixture was followed by TLC and, after 4 h, Amberlite I-120H ion-exchange resin was added to neutralize the base and then removed by filtration. Methanol was removed under vacuum to give the triol as a syrup (0.72 g, 100%). $[\alpha]_D$ +254.6 (*c*, 0.5, MeOH); ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.51−7.54 (m, 2H), 7.26−7.33 (m, 3H), 5.39 (d, J = 1.0 Hz, 1H), 4.15 (dd, J = 3.0, 1.5 Hz, 1H), 4.08 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H), 3.95 (t, J = 10.0 Hz, 1H), 3.76−3.83 (m, 2H), 3.47 (dd, J = 10.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 134.0, 131.7, 128.8, 127.3, 88.7 ($^1J_{CH}$ = 166.3 Hz), 74.4, 71.5, 65.4, 63.8, 61.0; HRMS(ESI) *m*/*z* calcd for $C_{12}H_{15}N_3NaO_4S$ $[M + Na]^+$ 320.0676, found 320.0668.

Phenyl 3-Azido-2-*O*-benzyl-3-deoxy-4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene-α-1-thio-D-mannopyranoside (16). A mixture of triol **13** (0.72 g, 2.42 mmol), triethyl 2-iodophenylorthoacetate (1.5 equiv about 50% purity), prepared from 2-iodophenyl acetonitrile,[25] and camphorsufonic acid (20 mg) in dry dichloromethane (20 mL) was stirred at rt for 12 h. Triethylamine (drops) was added to quench the reaction before removal of the solvent under vacuum to afford an oily residue, which on silica gel chromatography (hexanes/ethyl acetate: 10/3) gave a mixture of orthoester isomers **14** (1.1 g, 80%) as an oil. The major component had the following characteristics: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, J = 8.0, 1.0 Hz, 1H), 7.52 (dd, J = 8.0, 2.0 Hz, 1H), 7.40−7.43 (m, 2H), 7.27−7.33 (m, 4H), 6.91 (td, J = 8.0, 2.0 Hz, 1H), 5.48 (s, 1H), 4.40 (t, J = 10.0 Hz, 1H), 4.22 (td, J = 3.0, 1.0 Hz, 1H), 4.10−4.15 (m, 1H), 4.02 (t, J = 10.0 Hz, 1H), 3.80 (dd, J = 10.5, 3.0 Hz, 1H), 3.77 (dd, J = 9.5, 5.0 Hz, 1H), 3.69 (q, J = 7.0 Hz, 2H), 3.34 (d, J = 15.0 Hz, 1H), 3.31 (d, J = 15.0 Hz, 1H), 2.74 (d, J = 3.0 Hz, 1H), 1.26 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 138.2, 133.1, 131.6, 131.0, 129.3, 128.3, 127.9, 113.3, 102.7, 88.0 ($^1J_{CH}$ = 167.5 Hz), 71.9, 69.9, 64.8, 61.4, 61.0, 59.1, 45.5, 15.1.

Two sequences of transformations were applied to orthoester **14** to obtain donor **16**:

Sequence A: To a stirred mixture of **14** (1.0 g, 1.76 mmol) and TMSCN (1.2 mL, 8.8 mmol) in dry dichloromethane (15 mL) was added $BF_3 \cdot OEt_2$ (111 uL, 0.88 mmol) under Argon at 0 °C. After 2 h of stirring, the reaction was quenched by saturated aqueous $NaHCO_3$ (10 mL), washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and condensed under vacuum to give an oily residue. Purification by silica gel chromatography (hexanes/ethyl acetate: 10/3) afforded **15** as white crystals (0.60 g, 62%). $[\alpha]_D$

184.2 (*c*, 0.5, $CHCl_3$); mp 191−192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 1H), 7.45 (m, 3H), 7.33 (m, 4H), 6.99 (td, J = 8.0, 1.5 Hz, 1H), 5.51 (s, 1H), 4.37 (t, J = 10.0 Hz, 1H), 4.28 (td, J = 10.0, 5.0 Hz, 1H), 4.24 (s, 1H), 4.12 (dd, J = 11.0, 5.0 Hz, 1H), 4.02 (t, 10.5 Hz, 1H), 3.92 (dd, J = 9.5, 3.0 Hz, 1H), 3.55 (s, 3H), 2.54 (d, J = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 135.2, 132.6, 131.7, 131.6, 129.6, 129.4, 128.3, 128.1, 114.1, 102.8, 97.1, 87.8,75.2, 71.8, 65.7, 63.8, 60.7, 48.7. Anal. Calcd for $C_{21}H_{19}IN_4O_4S$: C, 45.83; H, 3.48; N, 10.18; S, 5.83. Found: C, 45.84; H, 3.51; N, 10.04; S, 5.70. A mixture of **15** (0.41 g, 0.745 mmol), benzyl bromide (260 uL, 2.2 mmol), and 60% NaH (90 mg, 2.2 mmol) in dry THF (20 mL) was heated to reflux under Argon for 2 h. The reaction mixture was cooled to rt before it was passed through a short silica gel pad. Removal of the solvent then afforded an oily residue that was purified by silica gel chromatography (hexanes/ethyl acetate: 10/1) to give thiomannopyranoside **16** (0.45 g, 93%) as an oil. $[\alpha]_D$ +100.6 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.0, 1.0 Hz, 1H), 7.47 (dd, J = 7.5, 1.5 Hz, 1H), 7.30−7.35 (m, 6H), 6.90 (td, J = 7.5, 1.5 Hz, 1H), 5.38 (d, J = 1.0 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.60 (d. J = 12.0 Hz, 1H), 4.47 (t, J = 10.0 Hz, 1H), 4.19 (td, J = 10.0, 4.5 Hz, 1H), 4.11 (dd, J = 10.5, 5.0 Hz, 1H), 4.02 (t, J = 10.0 Hz, 1H), 4.01 (dd, J = 3.0, 1.0 Hz, 1H), 3.71 (dd, J = 10.5, 3.0 Hz, 1H), 3.55 (s, 2H); ^{13}C (125 MHZ, $CDCl_3$) δ 140.0, 136.8, 135.3, 133.0, 131.7, 131.6, 129.5, 129.3, 128.6, 128.3, 128.2, 128.0, 114.0, 102.8, 97.0, 86.5 ($^1J_{CH}$ = 167.5 Hz), 78.8, 74.2, 73.4, 65.6, 64.2, 59.4, 48.7; HRMS(ESI): *m*/*z* calcd for $C_{28}H_{25}IN_4NaO_4S$ [M + Na]$^+$ 663.0534, found 663.0518.

Sequence B: A mixture of **14** (2.0 g, 3.6 mmol), benzyl bromide (0.64 mL, 6.4 mmol) and 60% NaH (200 mg, 5.0 mmol) in dry THF (30 mL) was heated to reflux for 3 h under Argon, then cooled to rt. The reaction mixture was filtered through a thin silica gel pad, and the filtrate was concentrated to afford a crude product, which was used directly for the next reaction without further purification. To a stirred mixture of this crude product and TMSCN (1.2 mL, 9.0 mmol) in dry dichloromethane (20 mL) was added $BF_3{\cdot}OEt_2$ (50 uL, 0.4 mmol) under Argon at 0 °C. The reaction was kept at 0 °C for 2 h before being quenched by $NaHCO_3$ (20 mL), washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent under vacuum furnished an oily residue that was purified by silica gel chromatography (hexanes/ethyl acetate: 10/1) to afford **16** (2.1 g, 90% for two steps).

Phenyl 3-Azido-4,6-*O*-benzylidene-3-deoxy-α-1-thio-D-mannopyranoside (17). A mixture of **11** (550 mg, 1.85 mmol), benzaldehyde dimethylacetal (300 mg, 1.97 mmol), and camphorsufonic acid (10 mg) in dry dichloromethane (10 mL) was stirred at rt overnight. Triethylamine (drops) then was added before the solvent was removed under vacuum. The residue was purified by silica gel chromatography (hexanes/ethyl acetate/dichloromethane: 10/3/2) to give **17** (605 mg, 85%) as a white solid. $[\alpha]_D$ +221 (*c*, 0.5, $CHCl_3$); mp 134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.52 (m, 4H), 7.30−7.41 (m, 6H), 5.67 (s, 1H), 5.53 (s, 1H), 4.41 (td, J = 10.0, 5.0 Hz, 1H), 4.20−4.27 (m, 3H), 4.05 (dd, J = 10.5, 3.0 Hz, 1H), 3.88 (t, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 132.9, 131.9, 129.3, 129.1, 128.3, 128.0, 125.9, 101.7, 87.9, 77.9, 71.7, 68.6, 64.9, 60.9; HRMS(ESI) *m*/*z* calcd for $C_{19}H_{19}N_3NaO_4S$ [M + Na]$^+$ 408.0989, found 408.0978.

Phenyl 3-Azido-2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-1-thio-D-mannopyranoside (18). A solution of **17** (542 mg, 1.41 mmol) and benzyl bromide (0.7 g, 4.09 mmol) together with 60% NaH (112 mg, 2.8 mmol) in dry THF (30 mL) was heated to reflux for 3 h. After cooling to rt, the solution was passed through a thin silica gel pad then concentrated. The residue was purified by silica gel chromatography (hexanes/ethyl acetate 10/1) to give **18** (670 mg, 100%) as a crystalline solid. $[\alpha]_D$ +143 (*c*, 0.5, ethyl acetate); mp 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.53 (m, 2H), 7.30−7.40 (m, 13H), 5.67 (s, 1H), 5.48 (s, 1H), 4.71 (s, 2H), 4.23−4.38 (m, 3H), 4.05 (d, J = 2.5 Hz, 1H), 3.84−3.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 133.2, 131.9, 129.3, 129.1, 128.6, 128.3, 128.22, 128.16, 128.0, 126.0, 101.7, 86.3, 79.0, 76.9, 73.3, 68.5, 65.3, 59.6. Anal. Calcd for $C_{26}H_{25}N_3O_4S$: C, 65.67; H, 5.30; N, 8.84; S, 6.74. Found: C, 65.68; H, 5.27; N, 8.69; S, 6.54.

Phenyl 3-Acetamido-2-*O*-benzyl-3-deoxy-4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene-α-1-thio-D-mannopyranoside (19). A mixture of azide **16** (157 mg, 0.25 mmol), triphenylphosphine (77 mg, 0.29 mmol), and water (10 uL, 0.56 mmol) in THF (5 mL) was stirred at rt overnight, after which Ac_2O (53 uL, 0.56 mmol) was added, followed by pyridine (50 uL, 0.62 mmol). The mixture was allowed to stir for 12 h at rt before the solvent was removed to afford an oily residue that was purified by silica gel chromatography (hexanes/ethyl acetate: 10/3) to give donor **19** (120 mg, 75%) as an oil. $[\alpha]_D$ +71.4 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.0, 1.0 Hz, 1H), 6.93−7.43 (m, 12H), 6.95 (td, J = 8.0, 1.5 Hz, 1H), 5.60 (d, J = 9.5 Hz, 1H), 5.53 (s, 1H), 4.71 (d, J = 11.5 Hz, 1H), 4.56 (td, J = 9.5, 3.5 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.29 (td, J = 9.5, 4.5 Hz, 1H), 4.10 (dd, J = 11.0, 5.0 Hz, 1H), 3.93−4.04 (m, 3H), 3.40 (d, J = 14.5 Hz, 1H), 3.20 (d, J = 14.0 Hz, 1H), 1.86 (s, 3H); ^{13}C (125 MHZ, $CDCl_3$) δ 169.7, 139.8, 136.7, 135.4, 133.4, 132.4, 131.6, 129.5, 129.3, 128.9, 128.6, 128.4, 128.0, 127.9, 114.3, 102.8, 96.8, 85.6 ($^1J_{CH}$ = 166.5 Hz), 78.9, 74.3, 72.7, 65.6, 64.3, 48.4, 48.2, 23.4; HRMS-(ESI) *m*/*z* calcd for $C_{30}H_{29}IN_2NaO_5S$ [M + Na]$^+$ 679.0734, found 679.0720.

Phenyl 2-*O*-Benzyl-4,6-*O*-(1-cyano-2-[2-iodophenyl])ethylidene-3-(4-trifluoromethyl)benzylideneimino-3-deoxy-α-1-thio-D-mannopyranoside (20). A solution of azide **16** (128 mg, 0.2 mmol) and triphenylphosphine (58 mg, 0.22 mmol) in dry dichloromethane (6 mL) was stirred at rt overnight before 4-trifluoromethylbenzaldehyde (52 mg, 0.30 mmol) was added. The reaction mixture then was stirred for 24 h before the solvent was evaporated. The residue was purified by flash chromatography on neutral alumina (hexanes/ethyl acetate/triethylamine: 100/10/1) to give **20** (60−80%) as an oil. $[\alpha]_D$ +87.3 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.70−7.73 (m, 2H), 7.40−74.1 (m, 2H), 7.23−7.34 (m, 9H), 7.01 (dd, J = 2.5, 1.5 Hz, 1H), 6.80 (dd, J = 2.5, 1.5 Hz, 1H), 5.53 (d, J = 1.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.68 (d, J = 11.5 Hz, 1H), 4.66 (t, 9.5 Hz, 1H), 4.29 (td, J = 10.0, 5.0 Hz, 1H), 4.16 (dd, J = 11.0, 5.0 Hz, 1H), 4.11 (t, J = 10.5 Hz, 1H), 4.03 (dd, J = 3.0, 1.0 Hz, 1H), 3.93 (dd, J = 10.0, 2.5 Hz, 1H), 3.47(d, J = 14.5 Hz, 1H), 3.46 (d, J = 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 139.7, 138.9, 137.6, 135.6, 133.7, 131.4, 131.3, 129.9,129.3, 129.2, 128.8, 128.4, 128.0, 127.94, 127.88, 127.7, 125.5, 114.5, 102.7, 96.9, 87.4, 79.5, 73.9, 69.0, 66.0, 64.3, 48.7; HRMS(ESI) *m*/*z* calcd for $C_{36}H_{30}F_3IN_2NaO_4S$ [M + Na]$^+$ 793.0816, found 793.0800.

Phenyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-3-(4-trifloromethyl)benzylideneimino-α-1-thio-D-mannopyranoside (21). The protocol preparation of **20** was applied to azide **18** to give imine **21** (60−80%) as an oil. $[\alpha]_D$ +72.0 (*c*, 0.5, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.91 (d, J = 3.0 Hz, 2H), 7.70 (d, J = 3.0 Hz, 2H), 7.26−7.45 (m, 15 H), 5.62 (s, 1H), 5.60 (s, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.41−4.50 (m, 2H), 4.29 (dd, J = 10.5, 4.5 Hz, 1H), 3.99−4.02 (m, 2H), 3.94 (t, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 139.1, 137.7, 137.4, 134.0, 131.6, 129.2, 128.9, 128.7, 128.4, 128.2, 128.1, 127.9, 127.7, 126.0, 125.6, 101.5, 87.2, 80.0, 76.7, 73.7, 69.5, 68.7, 65.5; HRMS(ESI) *m*/*z* calcd for $C_{34}H_{31}F_3NO_4S$ [M + H]$^+$ 606.19204, found 606.19200.

Methyl 2,4,6-Tri-*O*-acetyl-3-deoxy-3-phthalimido-α-D-mannopyranoside (22). A mixture of **8** (1.15 g, 5 mmol), *N*-ethoxyphthalimide (1.15 g, 5.25 mmol), and triethylamine (0.55 g, 5.4 mmol) in dry DMF (10 mL) was stirred at 100 °C for 12 h. The solvent was removed under vacuum and the residue was mixed with acetic anhydride (2.3 g, 22.8 mmol) and pyridine (3.5 g, 45.4 mmol) and stirred at rt for 12 h. Cold water (20 mL) was added to the reaction mixture and the mixture was stirred for 3 h before it was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed by aqueous HCl (1.0 M) and saturated

$NaHCO_3$, dried over Na_2SO_4, and concentrated to give an oily residue that was purified by silica gel chromatography (hexanes/ethyl acetate: 1/1) to give **22** (2.2 g, 98%) as a colorless oil. $[\alpha]_D$ +23.2 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79−7.83 (m, 2H), 7.70−7.72 (m, 2H), 6.21 (t, J = 10.5 Hz, 1H), 5.17 (dd, J = 3.0, 1.5 Hz, 1H), 4.91 (dd, J = 11.5, 3.0 Hz, 1H), 4.70 (d, J = 1.5 Hz, 1H), 4.27 (dd, J = 12.0, 6.0 Hz, 1H), 4.19 (dd, J = 12.0, 3.0 Hz, 1H), 3.99 (ddd, J = 12.0, 6.0, 3.0 Hz, 1H), 3.45 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 169.2, 167.8, 134.3, 131.4, 123.5, 98.4, 71.0, 70.0, 64.1, 63.2, 55.2, 50.9, 21.0, 20.8, 20.6; HRMS(ESI) *m*/*z* calcd for $C_{21}H_{23}NNaO_{10}$ $[M + Na]^+$ 472.1215, found 472.1217.

Phenyl 2,4,6-Tri-*O*-acetyl-3-deoxy-3-phthalimido-α-1-thio-D-mannopyranoside (23). To a solution of **22** (2.25 g, 5 mmol) in acetic anhydride (10 mL) was added $HClO_4$ (two drops) at 0 °C, followed by stirring at rt for 24 h before cold water (50 mL) was added. The resulting mixture was allowed to stir for 2 h before it was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water (50 mL), aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum to afford a crude product as an oil. $BF_3{\cdot}Et_2O$ (2 mL, 18.6 mmol) and PhSH (0.8 mL, 7.8 mmol) were added to this crude product in dry dichloromethane (30 mL) at 0 °C and the reaction mixture was stirred overnight before $NaHCO_3$ (30 mL) was added. The dichloromethane phase was separated and washed with brine (20 mL), dried over Na_2SO_4, and concentrated to a residue that was purified by silica gel chromatography (hexanes/ethyl acetate/dichloromethane: 10/10/3) to give **23** (2.0 g 75%) as a white solid. $[\alpha]_D$ +82.4 (*c*, 0.5, ethyl acetate); mp 195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, J = 5.5, 3.0 Hz, 2H), 7.74 (dd, J = 5.5, 3.0 Hz, 2H), 7.30−7.35 (m, 2H), 7.30−7.35 (m, 3H), 6.32 (t, J = 10.5 Hz, 1H), 5.52 (d, 1.0 Hz, 1H), 5.45 (dd, J = 2.5, 1.0 Hz, 1H), 4.92 (dd, J = 11.0, 2.5 Hz, 1H), 4.58 (m, 1H), 4.31 (dd, J = 12.0, 6.5 Hz, 1H), 4.21 (dd, J = 12.0, 2.5 Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H); ^{13}C (125 MHZ, $CDCl_3$) δ 170.62, 170.55, 169.2, 167.7, 134.4, 132.6, 132.2, 131.3, 129.2, 128.1, 123.7, 85.9 ($^1J_{CH}$ = 168.8 Hz), 72.5, 71.2, 64.2, 63.1, 51.9, 21.0, 20.8, 20.7; HRMS(ESI) *m*/*z* calcd for $C_{26}H_{25}NNaO_9S$ $[M + Na]^+$ 550.1543, found 550.1545.

Phenyl 3-Deoxy-3-phthalimido-α-1-thio-D-mannopyranoside (24). Peracetyl thioglycoside **23** (1.24 g, 2.35 mmol) and HCl in ether (3 mL, 2M) were mixed in dry methanol (30 mL) at rt and stirred overnight. The solvent was removed by rotary evaporation at rt and the residue was purified by silica gel chromatography (dichloromethane/MeOH: 5/1) to give triol **24** (0.92 g, 98%) as a solid. $[\alpha]_D$ +82.8 (*c*, 1.0, $CHCl_3$); mp 95 °C; ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.76−7.89 (m, 4H), 7.54−7.59 (m, 2H), 7.27−7.36 (m, 3H), 5.45 (d, J = 0.9 Hz, 1H), 5.13 (dd, J = 11.1, 9.9 Hz, 1H), 4.51 (dd, J = 11.1, 3.0 Hz, 1H), 4.14−4.20 (m, 2H), 3.85 (m, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 168.9, 134.0, 133.9, 131.9, 131.8, 128.8, 127.3, 122.7, 88.8, 75.6, 72.2, 61.2, 60.8, 57.0; HRMS(ESI) *m*/*z* calcd for $C_{20}H_{19}NNaO_6S$ $[M + Na]^+$ 424.0826, found 424.0815.

Phenyl 4,6-*O*-Benzylidene-3-deoxy-3-phthalimido-α-1-thio-D-mannopyranoside (25). Triol **24** (305 mg, 0.76 mmol), benzaldehyde dimethylacetal (127 mg, 125 uL), and camphorsufonic acid (5 mg) were stirred in dry dichloromethane (10 mL) overnight before triethylamine (1 drop) was added. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (hexanes/ethyl acetate: 1/1) to give compound **25** (298 mg, 80%) as an oil. $[\alpha]_D$ +41.2 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.87 (m, 2H), 7.72−7.75 (m, 2H), 7.51−7.53 (m, 2H), 7.26−7.37 (m, 8H), 5.59 (d, J = 1.5 Hz, 1H), 5.58 (s, 1H), 4.92−5.01 (m, 2H), 4.52 (td, J = 10.0, 5.0 Hz, 1H), 4.39−4.41 (m, 1H), 4.31 (d, J = 4.5 Hz, 1H), 4.25 (dd, J = 10.5, 5.5 Hz, 1H), 3.93 (t, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 134.5, 133.2, 132.0, 129.2, 129.1, 128.2, 127.8, 126.3, 123.8, 102.1, 89.2, 73.7, 72.7, 68.6, 67.0, 53.4; HRMS(ESI) *m*/*z* calcd for $C_{27}H_{23}NNaO_6S$ $[M + Na]^+$ 512.1139, found 512.1126.

Phenyl 4,6-*O*-Benzylidene-3-deoxy-3-phthalimido-2-*O*-trimethylsilyl-α-1-thio-D-mannopyranoside (26). TMSOTf (130 uL, 0.72 mmol) was added to a mixture of **25** (178 mg, 0.36 mmol) and *sym*-collidine (142 uL, 1.08 mmol) in dichloromethane (4 mL) at 0 °C. The resulting mixture was stirred for 30 min at rt before it was washed with aqueous $NaHCO_3$ and brine then dried over Na_2SO_4 and condensed under vacuum. Purification of the residue on silica gel (hexanes/ethyl acetate/triethylamine 100/30/0.5) gave **26** (168 mg, 83%) as an oil. $[\alpha]_D$ +20.8 (*c*, 0.5, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.72 (m, 2H), 7.54 (m, 2H), 7.28−7.43 (m, 8H), 5.70 (s, 1H), 5.43 (dd, J = 11.5, 9.5 Hz, 1H), 5.33 (s, 1H), 4.72 (dd, J = 11.5, 3.0 Hz, 1H), 4.42 (td, J = 9.5, 4.5 Hz, 1H), 4.36 (d, J = 3.0 Hz, 1H), 4.26 (dd, J = 10.5, 5.0 Hz, 1H), 3.97 (t, 10.0 Hz, 1H), −0.10 (s, 9H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 168.8, 167.6, 137.4, 134.2, 133.9, 133.4, 132.4, 129.3, 129.0, 128.2, 127.9, 126.3, 123.2, 101.8, 89.4 ($^1J_{CH}$ = 166.0 Hz), 72.5, 72.3, 68.7, 66.8, 54.3, −0.4; HRMS(ESI) *m*/*z* calcd for $C_{30}H_{31}NNaO_6SSi$ $[M + Na]^+$ 584.1534, found 584.1535.

General Procedure for Coupling of Donors 16, 19, and 26 with Adamantanol. A mixture of donor **16**, **19**, or **26** (0.10 mmol), 1-benzenesulfinyl piperidine or diphenyl sulfoxide (0.11 mmol), and 2,4,6-tri-*tert*-butylpyrimidine (50 mg, 0.20 mmol) in dry dichloromethane (4 mL) was stirred with 4 Å MS (30 mg) at rt for 30 min, then cooled to −78 or −65 °C. Trifluoromethanesulfonic anhydride (20 uL, 0.12 mmol) was added in one portion under Argon and the reaction mixture was kept at this temperature for 30 min. 1-Adamantanol (30 mg, 0.20 mmol) in dichloromethane (1 mL) was added at either −78 or −50 °C, and after being stirred for the requisite time the reaction mixture was quenched with saturated $NaHCO_3$ (2 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography.

1-Adamantanyl 3-Azido-2-*O*-benzyl-3-deoxy-4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene-α-D-mannopyranoside (27α) and 1-Adamantanyl 3-Azido-2-*O*-benzyl-3-deoxy-4,6-*O*-[1-cyano-2-(2-iodophenyl)ethylidene-β-D-mannopyranoside (27β). Coupling of **16** with adamantanol, after column chromatography on silica gel (hexanes/ethyl acetate: 10/1), gave two stereoisomers: **27**α and **27**β. **27**α: oil, $[\alpha]_D$ +39.8 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.0, 1.0 Hz, 1H), 7.48 (dd, J = 8.0, 1.5 Hz, 1H), 7.25−7.55 (m, 6H), 6.80 (td, J = 8.0, 1.5 Hz, 1H), 4.96 (d, J = 1.5 Hz, 1H), 4.79 (d, 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.35 (t, J = 10.0 Hz, 1H), 4.07 (dd, J = 10, 5.0 Hz, 1H), 3.96 (t, 10.5 Hz, 1H), 3.87 (td, J = 10.0, 5.0 Hz, 1H), 3.78 (dd, J = 10.5, 3.0 Hz, 1H), 3.55 (dd, J = 3.0, 2.0 Hz, 1H), 3.53 (s, 2H), 2.10 (s, 3H), 1.52−1.61 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 137.4, 135.5, 131.7, 129.4, 128.6, 128.4, 128.2, 128.1, 114.2, 102.8, 97.0, 91.6 ($^1J_{CH}$ = 167.5 Hz), 78.6, 75.3, 74.6, 73.8, 66.1, 62.8, 59.1, 48.8, 42.1, 36.1, 30.5; HRMS(ESI) *m*/*z* calcd for $C_{32}NaH_{35}IN_4O_5$ $[M + Na]^+$ 705.1545, found 705.1527. **27**β: oil, $[\alpha]_D$ −16.7 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.0, 1.5 Hz, 1H), 7.42−7.45 (m, 3H), 7.28−7.35 (m, 4H), 6.97 (td, J = 8.0, 1.5 Hz, 1H), 4.97 (d, J = 12.0 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.78 (s, 1H), 4.34 (t, J = 10.0 Hz, 1H), 4.05−4.16 (m, 2H), 3.69 (d, 3.0 Hz, 1H), 3.51 (s, 2H), 3.39 (dd, J = 10.5, 3.0 Hz, 1H), 3.28 (td, J = 10.0, 5.0 Hz, 1H), 2.16 (s, 3H), 1.57−1.82 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 137.6, 135.5, 131.7, 129.4, 128.8, 128.1, 127.8, 114.2, 102.9, 96.7, 94.9 ($^1J_{CH}$ = 151.3 Hz), 77.9, 75.8, 75.4, 73.6, 66.9, 65.9, 61.8, 48.6, 42.3, 36.1, 30.6; HRMS(ESI): *m*/*z* calcd for $C_{32}H_{35}IN_4NaO_5$ $[M + Na]^+$ 705.1545, found 705.1528.

1-Adamantanyl 3-Acetamido-2-*O*-benzyl-3-deoxy-4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene-α-D-mannopyranoside (28α). Coupling of **19** with adamantanol gave **28**α (56%), which was separated by silica gel chromatography (hexanes/ethyl acetate: 10/3): oil, $[\alpha]_D$ +31.4 (*c*, 0.5, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$, −40 °C) δ 7.77 (d, J = 7.5 Hz, 1H), 6.93−7.42 (m, 13H),

5.09 (s, 1H), 4.96 (d, J = 11.0 Hz, 1H), 4.72 (t, J = 10.5 Hz, 1H), 4.65 (d, J = 12.5 Hz, 1H), 4.36 (d, J = 12.0 Hz, 1H), 3.85−3.99 (m, 2H), 3.78 (t, J = 10.5 Hz, 1H), 3.72 (s, 1H), 2.59 (d, J = 14.0 Hz, 1H), 2.37 (d, J = 14.5, 1H), 2.10 (m, 3H), 2.05 (s, 3H), 1.40−1.66 (m, 12H); ^{13}C (125 MHZ, $CDCl_3$) δ 177.7, 139.9, 139.7, 137.3, 135.7, 131.6, 129.1, 128.8, 128.72, 128.65, 128.2, 128.0, 125.5, 122.0, 113.9, 102.6, 96.6, 91.0 ($^1J_{CH}$ = 165.0 Hz), 75.1, 73.3, 73.0, 66.3, 62.8, 56.4, 47.6, 42.2, 36.2, 30.6, 22.4; HRMS-(ESI) m/z calcd for $C_{40}H_{43}IN_2NaO_6S$ $[M + Na]^+$ 829.1779, found 829.1777.

1-Adamantanyl 4,6-*O*-Benzylidene-3-deoxy-3-phthalimido-2-*O*-trimethylsilyl-α-D-mannopyranoside (31α). Coupling of **26** with adamantanol gave **31**α (77%), which was separated by silica gel chromatography (hexanes/ethyl acetate: 10/3). **31**α: oil; $[\alpha]_D$ −30.0 (*c*, 0.5, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−7.82 (m, 2H), 7.67−7.70 (m, 2H), 7.40−7.42 (m, 2H), 7.26−7.29 (m, 3H), 5.68 (s, 1H), 5.33 (dd, J = 11.5, 9.5 Hz, 1H), 5.04 (d, J = 1.0 Hz, 1H), 4.74 (dd, J = 11.0, 3.0 Hz, 1H), 4.25 (dd, J = 10.0, 5.0 Hz, 1H), 4.16 (td, J = 10.0, 5.0, 1H), 3.93 (m, 1H), 3.90 (t, J = 10.5 Hz, 1H), 2.17 (br s, 3H), 1.81−1.89 (m, 6H), 1.61−1.69 (m, 6H), −0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 134.0, 128.9, 128.1, 126.3, 123.0, 101.7, 94.1 ($^1J_{CH}$ = 166.3 Hz), 74.7, 73.0, 72.5, 69.1, 65.1, 53.8, 42.4, 36.3, 30.6, −0.4; HRMS-(ESI) m/z calcd for $C_{34}H_{42}NO_7Si$ $[M + H]^+$ 604.2725, found 604.2726.

General Procedure of the Coupling Reaction of Donors 20 and 21 with Acceptors 32 and 33 and Adamantanol. A mixture of donor **20** or **21** (0.10 mmol), diphenyl sulfoxide (0.11 mmol), and 2,4,6-tri-*tert*-butylpyrimidine (50 mg, 0.20 mmol) in dry dichloromethane (4 mL) was stirred together with 4 Å MS (30 mg) at rt for 30 min, then cooled to −78 °C. Trifluoromethanesulfonic anhydride (20 uL, 0.12 mmol) then was added in one portion under Argon. Then the reaction mixture was raised to −65 °C over 15 min before the acceptor (0.20 mmol for adamantanol, 0.15 mmol for **32** and **33**) in dichloromethane (1.5 mL) was added. The resulting mixture was allowed to rise to −10 °C gradually before it was quenched with $NaHCO_3$. The resulting mixture was extracted with dichloromethane and the extracts concentrated to give a residue, which was mixed with silica gel (1.5 g) then loaded onto a silica gel column. Elution of the products was achieved with a solution of 5% ethyl acetate in hexanes (100 mL), then a solution of 20% ethyl acetate in hexanes (100 mL), and then a mixture of hexanes/ethyl acetate/MeOH (10/5/1).

1-Adamantanyl 3-Amino-2-*O*-benzyl-3-deoxy-4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene-β-D-mannopyranoside (29β). Coupling of **20** with 1-adamantanol gave **29**β (83%) as an oil. $[\alpha]_D$ −129.2 (*c*, 0.25, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 7.5 Hz, 1H), 7.26−7.41 (m, 7H), 6.96 (td, J = 7.5, 1.5 Hz, 1H), 5.09 (d, J = 11.5 Hz, 1H), 4.84 (s, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.11 (dd, J = 11.0, 5.0 Hz, 1H), 4.01 (t, J = 10.5 Hz, 1H), 3.79 (t, 9.5 Hz, 1H), 3.69 (d, 3.0 Hz, 1H), 3.47 (s, 2H), 3.15 (td, J = 10.0, 5.0 Hz, 1H), 2.78 (dd, J = 10.0, 3.0 Hz, 1H), 2.16 (s, 3H), 1.76−1.86 (m, 6H), 1.59−1.67 (m, 6H); ^{13}C NMR δ (125 MHz, $CDCl_3$) δ 139.9, 138.4, 135.8, 131.8, 129.3, 128.5, 128.4, 128.0, 127.8, 114.7, 102.8, 96.8, 95.9 ($^1J_{CH}$ = 151.3 Hz), 80.4, 76.0, 75.4, 67.2, 65.9, 54.4, 48.7, 42.4, 36.2, 30.6; HRMS(ESI) m/z calcd for $C_{32}H_{38}IN_2O_5$ $[M + H]^+$ 657.1820, found 657.1830.

1-Adamantanyl 3-Amino-2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-β-mannopyranoside (30β). Coupling of **21** with 1-adamantanol gave **30**β (78%) as an oil. $[\alpha]_D$ −50.0 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.51 (m, 10H), 5.50 (s, 1H), 5.16 (d, J = 12.0 Hz, 1H), 4.91 (s, 1H), 4.65 (d, 11.5 Hz, 1H), 4.25 (dd, J = 10.0, 5.0 Hz, 1H), 3.85 (t, J = 10.0 Hz, 1H), 3.73 (d, J = 3.0 Hz, 1H), 3.61 (t, J = 9.5 Hz, 1H), 3.35 (td, J = 10.0, 5.0 Hz, 1H), 2.91 (dd, J = 10.0, 3.0 Hz, 1H), 2.19 (s, 3H), 1.89 (d, J = 11.5 Hz, 3H), 1.83 (d, J = 11.0 Hz, 3H), 1.62−1.70 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 137.6, 129.1, 128.5, 128.3, 127.7, 126.2, 102.0, 95.8 ($^1J_{CH}$ = 151.3 Hz), 81.1, 80.3, 76.2, 75.2, 68.9, 68.4, 54.7, 42.4, 36.2, 30.6; HRMS(ESI) m/z calcd for $C_{30}H_{37}NNaO_5$ $[M + Na]^+$ 514.2564, found 514.2561.

Methyl 4-*O*-{3-Amino-2-*O*-benzyl-3-deoxy-4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene-β-D-mannopyranosyl}-(1→4)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (34β). Coupling of **20** with **32** gave **34**β (76%) as an oil. $[\alpha]_D$ −52.8 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.26−7.34 (m, 6H), 6.97 (t, J = 7.5 Hz, 1H), 5.04 (s, 1H), 4.96 (d, 11.0 Hz, 1H), 4.86 (s, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.10−4.18 (m, 3H), 4.01 (t, J = 11.0 Hz, 1H), 3.86 (d, J = 3.0 Hz, 1H), 3.77 (t, J = 9.5 Hz, 1H), 3.63 (m, 2H), 3.47 (m, 2H), 3.37 (s, 3H), 3.15 (td, J = 10.0, 5.0 Hz, 1H), 2.82 (dd, J = 10.0, 3.5 Hz, 1H), 1.51 (s, 3H), 1.35 (s, 3H), 1.29 (d, J = 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 138.3, 135.7, 131.8, 129.4, 128.4, 128.14, 128.10, 127.8, 114.7, 109.4, 102.7, 101.4 ($^1J_{CH}$ = 157.5 Hz), 97.9, 96.9, 79.1, 78.32, 78.27, 77.7, 76.1, 75.8, 67.4, 65.9, 64.1, 54.9, 54.1, 48.7, 28.0, 26.4, 17.7; HRMS(ESI) m/z calcd for $C_{32}H_{40}IN_2O_9$ $[M + H]^+$ 723.1779, found 723.1773.

Methyl (3-Amino-2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-β-D-mannopyranosyl)-(1→4)-2,3-O-isopropylidene-α-L-rhamnopyranoside (35β). Coupling of **21** with **32** gave **35**β (82%) as an oil. $[\alpha]_D$ −86.8 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.50 (m, 2H), 7.30−7.40 (m, 8H), 5.52 (s, 1H), 5.13 (s, 1H), 5.02 (d, J = 11.5 Hz, 1H), 4.88 (s, 1H), 4.60 (d, J = 11.5 Hz, 1H), 4.26 (dd, J = 10.5, 5.0 Hz, 1H), 4.21 (dd, J = 7.0, 5.5 Hz, 1H), 4.11 (d, J = 5.5 Hz, 1H), 3.90 (d, J = 5.0 Hz, 1H), 5.87 (t, J = 10.0 Hz, 1H), 3.72 (dd, J = 10.0, 2.5 Hz, 1H), 3.66 (m, 1H), 3.61 (t, J = 10.0 Hz, 1H), 3.39 (s, 3H), 3.34 (m, 1H), 2.93 (dd, J = 10.0, 3.0 Hz, 1H), 1.54 (s, 3H), 1.36 (s, 3H), 1.33 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 137.5, 129.1, 128.4, 128.3, 128.1, 127.8, 126.2, 109.4, 102.0, 101.3 ($^1J_{CH}$ = 157.5 Hz), 97.9, 80.6, 79.6, 78.4, 77.9, 76.1, 75.8, 68.7,68.6, 64.2, 54.9, 54.4, 27.9, 26.5, 17.7; HRMS(ESI) m/z calcd for $C_{30}H_{40}NO_9$ $[M + H]^+$ 558.2698, found 558.2694.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-{3-amino-2-*O*-benzyl-3-deoxy-4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene-β-D-mannopyranosyl}-α-D-glucopyranoside (36β). Coupling of **20** with **33** gave **36**β (82%) as an oil. $[\alpha]_D$ +0.8 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, J = 8.0, 1.5 Hz, 1H), 7.24−7.39 (m, 22H), 7.00 (td, J = 8.0, 1.5 Hz, 1H), 4.95 (d, J = 11.0 Hz, 1H), 4.94 (d, J = 10.5 Hz, 1H), 4.86 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 4.74 (d, J = 10.0, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 3.5 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.33 (d, J = 12.0 Hz, 1H), 4.28 (s, 1H), 3.92 (t, 9.0 Hz, 1H), 3.80−3.87 (m, 2H), 3.45−3.69 (m, 9H), 3.42 (s, 3H), 2.73 (td, J = 10.0, 5.0 Hz, 1H), 2.36 (dd, J = 10.0, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 139.1, 138.4, 138.1, 137.5, 135.9, 132.1, 129.5, 128.7, 128.6, 128.4, 128.3, 128.13, 128.09, 128.0, 127.9, 127.8, 127.5, 114.8, 102.9, 102.2 ($^1J_{CH}$ = 155.0 Hz), 98.5, 96.7, 80.2, 79.3, 79.0, 77.0, 76.0, 75.6, 73.7, 69.7, 68.1, 67.0, 65.7, 55.5, 53.9, 48.7; HRMS(ESI) m/z calcd for $C_{50}H_{54}IN_2O_{10}$ $[M + H]^+$ 969.2823, found 969.2827.

Methyl (3-Amino-2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-β-D-mannopyranosyl)-(1→4)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (37β). Coupling of **21** with **33** gave **37**β (92%) as a colorless oil. $[\alpha]_D$ −36.1 (*c*, 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.47 (m, 25H), 5.43 (s, 1H), 5.07 (d, J = 11.0 Hz, 1H), 5.00 (d, J = 11.0 Hz, 1H), 4.82 (d, 12.0 Hz, 1H), 4.53−4.75 (m, 6H), 4.42 (d, J = 12.0 Hz, 1H), 4.11 (dd, J = 10.5, 5.0 Hz, 1H), 3.98 (t, J = 9.0 Hz, 1H), 3.85 (t, 9.0 Hz, 1H), 3.64−3.71 (m, 4H), 3.55 (dd, J = 10.0, 4.0 Hz, 1H), 3.49 (dd, J = 18.0, 10.5 Hz, 2H), 3.41 (s, 3H), 3.07 (td, J = 10.0, 5.0 Hz, 1H), 2.63 (dd, J = 10.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 138.5, 138.4, 137.5, 129.2, 128.7, 128.41, 128.36, 128.2, 128.1, 127.82, 127.76, 127.3, 126.2, 102.5, 102.0 ($^1J_{CH}$ = 162.5 Hz), 98.5, 80.4, 80.2, 79.7, 78.9, 77.5, 76.0, 75.4, 73.7, 69.8, 68.7, 68.4, 68.3, 55.4, 54.2; HRMS-(ESI) m/z calcd for $C_{48}H_{54}NO_{10}$ $[M + H]^+$ 804.3742, found 804.3727.

1-Adamantanyl 3-*N*-(*tert*-Butyloxycarbonylamino)-2-*O*-ben-

zyl-3-deoxy-4,6-*O*-[1-cyano-2-(2-iodophenyl)]ethylidene-β-D-mannopyranoside (40). To a solution of amine **29**β (75 mg, 0.11 mmol) and $(Boc)_2O$ (30 mg, 0.14 mmol) was added triethylamine (30 uL, 0.23 mmol) in dry THF (5 mL). The reaction mixture was stirred at rt for 4 h, then concentrated under vacuum to give a residue, which was purified by chromatography on silica gel (hexanes/ethyl acetate: 10/1) to give **40** (89 mg, 100%) as a white solid. $[\alpha]_D$ −42.6 (*c*, 0.5, ethyl acetate); mp 202−203 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.0, 1.0 Hz, 1H), 7.40, (dd, J = 8.0, 1.5 Hz, 1H), 7.24−7.37 (m, 6H), 6.94 (td, J = 8.0, 1.5 Hz, 1H), 5.01 (d, J = 12.0 Hz, 1H), 4.87 (s, 1H), 4.79 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.11 (dd, J = 11.0, 6.0 Hz, 1H), 4.00 (t, J = 10.5 Hz, 1H), 3.83−3.92 (m, 2H), 3.67 (d, 2.5 Hz, 1H), 3.48 (d, J = 14.5 Hz, 1H), 3.43 (d, J = 14.5 Hz, 1H), 3.28 (m, 1H), 2.17 (s, 3H), 1.84 (d, J = 10.5 Hz, 3H), 1.76 (d, J = 11.5 Hz, 3H), 1.6 (d, J = 12.5 Hz, 3H), 1.61 (d, J = 12.0 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 139.8, 138.0, 135.7, 131.8, 129.3, 128.9, 128.6, 128.0, 114.5, 102.9, 96.8, 95.3 ($^1J_{CH}$ = 156.3 Hz), 79.6, 78.5, 75.6, 73.9, 67.3, 65.9, 52.5, 48.7, 42.4, 36.2, 30.6, 28.4; HRMS(ESI) *m*/*z* calcd for $C_{37}H_{46}IN_2O_7$ $[M + H]^+$ 757.2344, found 757.2347.

General Procedure for Radical Fragmentation. A solution of substrate (0.006 M) in dry toluene or xylenes was deoxygenated by sparging with Argon at rt with stirring for 2 h then was heated to reflux with stirring under Argon while a mixture of initiator (azoisobutyronitrile or 1,1′-azobis(cyanocyclohexane) (0.2 equiv)) and hydrogen donor (tributyltin hydride or tris(trimethylsilylsilane) (1.6 equiv)) in the same deoxygenated solvent (0.025 M) was added by syringe pump in 2 h. The reaction mixture was cooled, the solvent was removed under vacuum, and the residue was dissolved in acetonitrile and washed with hexanes (5 times). The acetonitrile phase was concentrated under vacuum and the residue subjected to silica gel chromatography.

1-Adamantanyl 3-Amino-2-*O*-benzyl-3-deoxy-3-*N*-(2-cyanophenyl)acetyl-β-D-rhamnopyranoside (39). With **29**β as substrate the radical reaction was executed in xylenes, with addition of the reagents over 2 h. Silica gel chromatography (hexanes/ethyl acetate/MeOH: 10/5/1) then preparative HPLC were applied to give compound **39** in 20% yield: $[\alpha]_D$ −59.8 (*c*, 0.5, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 1H), 7.51 (td, J = 7.5, 1.5 Hz, 1H), 7.30−7.42 (m, 7H), 6.01 (d, J = 8.0 Hz, 1H), 5.08 (d, J = 12.5 Hz, 1H), 4.82 (s, 1H), 4.58 (d, J = 12.0 Hz, 1H), 3.87−3.92 (m, 1H), 3.56 (d, J = 3.0 Hz, 1H), 3.49 (d, J = 16.0 Hz, 1H), 3.41 (d, J = 15.5 Hz, 1H), 3.27−3.34 (m, 2H), 2.79 (br s, 1H), 2.18 (s, 3H), 1.89 (d, J = 11.0 Hz, 3H), 1.81 (d, J = 11.0 Hz, 3H), 1.61−1.68 (m, 6H), 1.33 (d, J = 6.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.4, 138.6, 138.2, 133.1, 132.8, 130.6, 128.9, 128.7, 128.2, 127.8, 117.8, 112.9, 94.3 ($^1J_{CH}$ = 151.3 Hz), 77.9, 75.2, 73.5, 73.4, 55.2, 42.5, 41.3, 36.3, 30.7, 17.9; HRMS-(ESI) *m*/*z* calcd for $C_{32}H_{39}N_2O_5$ $[M + H]^+$ 531.2854, found 531.2855.

1-Adamantanyl 2-*O*-Benzyl-3-*N*-(*tert*-butyloxycarbonylamino)-3-deoxy-4,6-*O*-[2-(2-cyanophenyl)]ethylidene-β-D-mannopyranoside (41) and 1-Adamantanyl 2-*O*-Benzyl-3-*N*-(*tert*-butyloxycarbonylamino)-3-deoxy-β-D-rhamnopyranoside (42). Under a variety of conditions of solvent, temperature, reductant, and initiator for the radical reaction, **40** gave mixtures of two isomers after silica gel chromatography (hexanes/ethyl acetate: 5/1) in low yield. Saponification of these mixtures with catalytic MeONa in methanol followed by silica gel chromatography (hexanes/ethyl acetate: 5/1 then 3/1) enabled the separation of **41** and **42**. Reduction product **41**: $[\alpha]_D$ −20.4 (*c*, 0.5, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.0, Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.27−7.35 (m, 6H), 5.01 (d, J = 12.0 Hz, 1H), 4.86 (s, 1H), 4.76 (d, J = 9.0 Hz, 1H), 4.71 (t, J = 5.0 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.06 (dd, J = 11.0, 5.0 Hz, 1H), 3.83 (td, J = 8.0, 3.5 Hz, 1H), 3.69 (d, J = 2.0 Hz, 1H), 3.56 (t, J = 10.5 Hz, 1H), 3.44 (t, J = 10.5 Hz, 1H), 3.26 (td, J = 9.5, 5.0 Hz, 1H), 3.16 (d, J = 5.0 Hz, 1H), 2.16 (s, 3H), 1.83 (d, J = 11.5 Hz, 3H), 1.76 (d, J = 11.5 Hz, 3H), 1.63 (m, 6H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 140.0, 132.9, 132.6, 132.4, 131.6, 128.7, 128.5, 127.9, 127.1, 118.1, 113.4, 101.0, 95.1, 79.4, 79.0, 76.3, 75.8, 75.4, 68.4, 68.3, 52.9, 42.4, 39.2, 36.2, 30.6, 28.4; HRMS-(ESI) *m*/*z* calcd for $C_{37}H_{46}N_2NaO_7$ $[M + Na]^+$ 653.3203, found 653.3177. Fragmentation product **42**: $[\alpha]_D$ −37.9 (*c*, 1.0, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.37 (m, 5H), 5.70 (d, J = 12.5 Hz, 1H), 4.96 (d, J = 8.0 Hz, 1H), 4.79 (s, 1H), 4.63 (d, J = 12.5 Hz, 1H), 3.50−3.54 (m, 2H), 3.32 (t, J = 9.5 Hz, 1H), 3.22−3.27 (m, 1H), 2.95 (s, 1H), 2.17 (s, 3H), 1.88 (d, J = 11.5 Hz, 3H), 1.80 (d, J = 11.5 Hz, 3H), 1.63 (m, 6H), 1.38 (s, 9H), 1.33 (d, J = 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 138.5, 128.6, 127.9, 94.6 ($^1J_{CH}$ = 151.3 Hz), 80.1, 77.9, 75.0, 73.6, 73.4, 55.9, 42.5, 36.3, 30.7, 28.3, 17.9; HRMS(ESI) *m*/*z* calcd for $C_{28}H_{41}NNaO_6$ $[M + Na]^+$ 510.2832, found 510.2837.

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Supporting Information Available: Copies of spectra of all compounds, and CIF files for compounds **12** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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