Thiazole-Based Synthesis of Formyl C-Glycosides

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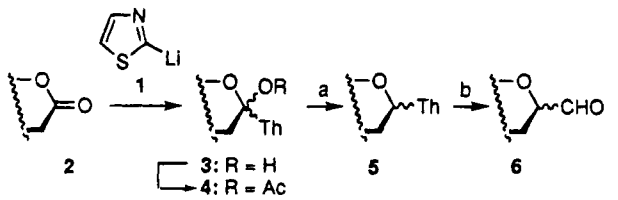
A method for the installation of the formyl group at the anomeric position of pyranoses and furanoses starting from the corresponding lactones has been developed. The strategy involves the addition of 2-lithiothiazole to the sugar lactone, followed by the silane reduction of the acetylated resultant ketol and the unmasking of the formyl group from the thiazole ring. All steps have been studied in some details to improve chemical efficiency and stereochemical control. Hence, reversed α:β ratios of ketols were found in kinetic and thermodynamic mixtures, the former being consistent with a steric effect control of the substituents and the latter by the electronic effect of the ring oxygen. Seven sugar aldehydes with different D-pyranosidic (2,3,4,6-tetra-*O*-benzyl-*gluco*, -*galacto*, and -*manno*, 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-*galacto*) and D-furanosidic moieties (5-*O*-benzyl-2,3-isopropylidene-*ribo*; 2,3,5-tri-*O*-benzyl-*ribo*; 2,3:5,6-di-*O*-isopropylidene-*manno*) were prepared in 52–65% isolated overall yield from the corresponding lactone.

An efficient protocol for incorporating a formyl group at the anomeric position of sugars may serve as a tool toward the synthesis of more or less complex *C*-glycosides of biological relevance.[1] Herein we report a method that is centered on the use of thiazole as a formyl group equivalent,[2] for the synthesis of β-linked formyl *C*-glycopyranosides and α- and β-linked formyl *C*-glycofuranosides. The first and key step of the procedure[3] (Scheme 1) consists on the stereoselective addition of 2-lithiothiazole (2-LTT, **1**) to the sugar lactone **2** to give the ketol **3**. This hemiketal is converted into a kinetic or a thermodynamic derivative **4** by acetylation of its hydroxy group either in situ or after isolation of the product. Then, in the second step the trimethylsilyl triflate-promoted silane reduction of the acetate **4** gives the thiazolyl *C*-glycoside **5** from which in the third and final step the formyl derivative **6** is released by hydrolytic cleavage of the thiazole ring. The choice of the thiazole ring as a masked formyl group stemmed from its remarkable efficiency based on previous work from this laboratory.[2] However other reagents available in the repertoire of formyl anion equivalents[4] can be candidates to the same role in this synthetic approach to glycosyl aldehydes **6** from sugar lactones **2**.[5]

Scheme 1[a]



[a] Th = 2-thiazolyl. Reagents and conditions: (a) Et_3SiH (10 eq.), TMSOTf (2.8 eq.), 4 Å MS, CH_2Cl_2. (b) MeOTf, CH_3CN; then $NaBH_4$, MeOH; then $HgCl_2$, H_2O-CH_3CN.

Syntheses of specific formyl *C*-furanosides by ring contraction of an amino pyranose,[6] by reductive hydrolysis of a furanosyl cyanide,[1a,7] or by acidic rearrangement of an hexofuranose,[8] have been described in the past. Quite recently, an approach to *C*-pyranosyl aldehydes by ozonolysis of *C*-glycosyl allenes[9] has been reexamined by Bednarski and co-workers,[10] wherein the base-catalyzed epimerization of the α-D into the more stable β-D isomer was also described. However several drawbacks appear to be associated with this methodology. First of all, it requires the quite expensive propargyltrimethylsilane as a reagent for the installation of the allenyl group. Second, the quite harsh oxidizing conditions under which this group is cleaved to formyl are hardly tolerated by common hydroxyl protective groups such as the benzyl which is readily oxidized to benzoate.[11] In our hands this methodology gave β-D-linked glycosyl aldehydes in somewhat lower yields than the quoted values.[10] Hence, the search for an alternative and more practical formylating method is examined in this paper.

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(1) For the synthetic use of formyl *C*-glycosides see: (a) Trummlitz, G.; Moffatt, J. G. *J. Org. Chem.* **1973**, *38*, 1841. (b) Bertozzi, C. R.; Hoeprich, P. D., Jr.; Bednarski, M. D. *J. Org. Chem.* **1992**, *57*, 6092. (c) Bertozzi, C. R.; Cook, D. G.; Kobertz, W. R.; Gonzales-Scarano, F.; Bednarski, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 10639. (d) Dietrich, H.; Schmidt, R. R. *Carbohydr. Res.* **1993**, *250*, 161.

(2) For overviews and recent papers on the "thiazole–aldehyde synthesis", see: (a) Dondoni, A. *Pure Appl. Chem.* **1990**, *62*, 643. (b) Dondoni, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, 1992; pp 377–437. (c) Dondoni, A. In *Antibiotics and Antiviral Compounds, Chemical Synthesis and Modification*; Krohn, K., Kirst, H., Maas, H., Eds.; VCH: Weinheim, 1993; pp 57–73. (d) Dondoni, A.; Merino, P. *Org. Synth.* **1993**, *72*, 21. (e) Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162. (f) Dondoni, A. Marra, A.; Merino, P. *J. Am. Chem. Soc.* **1994**, *116*, 3324.

(3) For a preliminary account, see: Dondoni, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7319.

(4) Dondoni, A.; Colombo, L. In *Advances in The Use Of Synthons in Organic Chemistry*; Dondoni, A., Ed.; JAI Press Ltd.: London, 1993; Vol. 1, p 1.

(5) Exploratory experiments were carried out with 2-lithio-1,3-dithiane which in fact added to sugar lactones to give the corresponding ketols in comparable yields to those obtained with 2-lithiothiazole. However, silane reductive deoxygenation of the ketols or their acetates gave numerous unidentified products in low yield.

(6) Horton, D.; Philips, K. D. *Carbohydr. Res.* **1973**, *30*, 367.

(7) Albrecht, H.; Repke, D. B.; Moffatt, J. G. *J. Org. Chem.* **1973**, *38*, 1836.

(8) Ogawa, T.; Kikuchi, Y.; Matsui, M.; Ohrui, H.; Kuzuhara, H.; Emoto, S. *Agr. Biol. Chem.* **1971**, *35*, 1825.

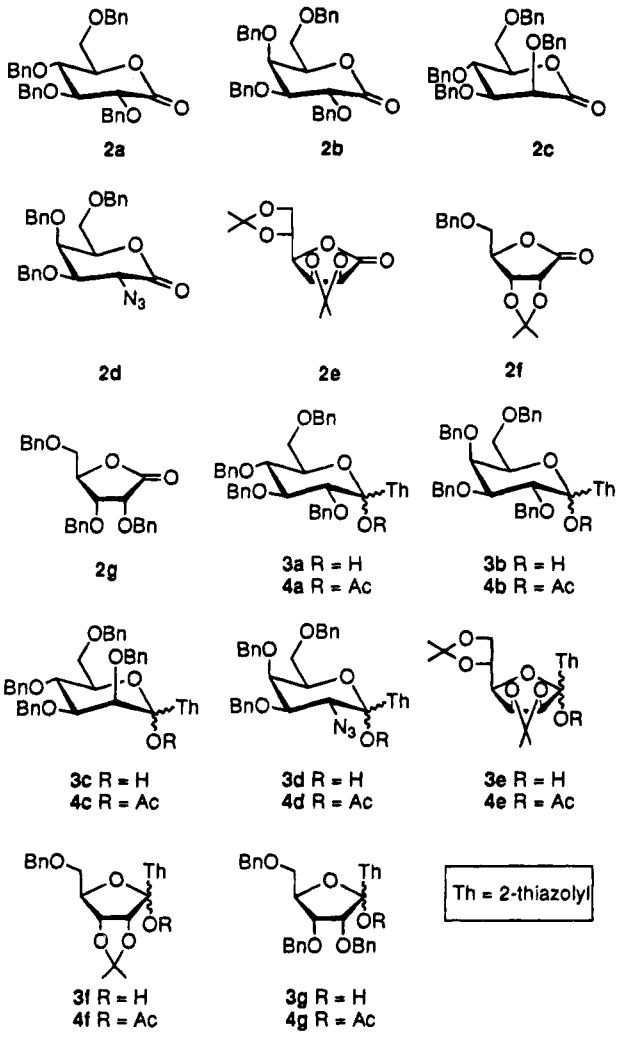
(9) The synthesis of *C*-glycosyl allenes and their ozonolysis to aldehydes were previously reported by others. See: (a) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370. (b) Wang, Y.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468. (c) Haneda, T.; Goekjian, P. G.; Kim, S. H. Kishi, Y. *J. Org. Chem.* **1992**, *57*, 490.

(10) (a) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 737. (b) Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 3109.

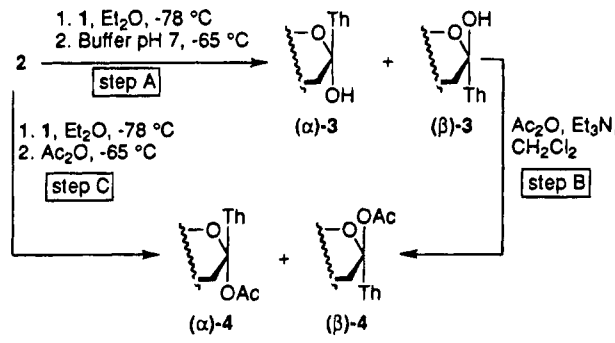
(11) Dondoni, A.; Marra, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7323 and references cited therein.

0022-3263/94/1959-6404$04.50/0

Chart 1



Scheme 2[a]



[a] Th = 2-thiazolyl

Results and Discussion

Addition of 2-Lithiothiazole (2-LTT, 1) to Sugar Lactones 2a–g. Of the various methods that were considered for the introduction of the thiazole ring at the anomeric position of sugars, the addition of a 2-metalated thiazole to a sugar lactone seemed particularly qualified. We reached this conclusion after failure of C-glycosylation[12] of thiazole at C-2 under different conditions.[13] On the other hand, sugar lactones were known to add alkyl, alkynyl, aryl, and heteroaryl organometallics to form ketols which were in some cases[11,14] reduced to the corresponding C-glycosides. Hence, although from parallel work in our laboratory we were quite familiar with various C-2 metalated thiazoles,[15] an initial addition model was generated from 2-LTT (**1**) and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranolactone (**2a**) (Chart 1). Thus, treatment of **2a** with **1** in diethyl ether[16] at −78 °C and quenching with a pH 7 buffer gave exclusively the 2-thiazolyl C-glucopyranose derivative (α)-**3a** in 80% isolated yield (Scheme 2, step A). Essentially quantitative conversion of this ketol into the acetate (α)-**4a** (Chart 1, Table 1) was carried out by reaction with acetic anhydride in the presence of triethylamine at room temperature (step B). It became quite soon apparent that the observed stereochemistry at the anomeric center of the hemiketal (α)-**3a** was the manifestation of the product stability very likely controlled by the electronic effect of the ring oxygen (anomeric effect). In fact upon treatment of **2a** with **1** as above and then quenching the reaction mixture with acetic anhydride (step C), the main product that was isolated was the isomer (β)-**4a**[17] (Table 1). The configuration at the anomeric center obtained in this case is in agreement with a diastereoselective attack of the nucleophile **1** to the less hindered face of the sugar lactone **2a** and trapping of the resultant kinetic lactol (β)-**3a** by acetic anhydride. These same sequences A–B and C were also performed starting from the tetra-*O*-benzyl-D-galacto- and D-mannopyranolactones **2b** and **2c**

Table 1. Addition of 2-Lithiothiazole (1) to Lactones 2a–g

lactone[a]	ketol acetate[b]	condtn[c]	α:β (yield)[d]
2a	**4a**	A–B	1:0 (80)
		C	1:7 (87)
2b	**4b**	A–B	1:0 (78)
		C	1:10 (75)
2c	**4c**	A–B	1:0 (73)
		C	0:1 (78)
2d	**4d**	A–B	1:0 (77)
		C	0:1 (80)
2e	**4e**	A–B	1:0 (76)
		C	0:1 (90)
2f	**4f**	A–B	1:7 (76)
		C	15:1 (80)
2g	**4g**	A–B	1:1 (73)
		C	4:1 (60)

[a] For references to the preparation of these compounds see the Experimental Section. [b] Th = 2-thiazolyl. [c] See Scheme 2. In the case of **4f** (method A–B), the acetylation was carried out with pyridine–Ac_2O. [d] α:β Ratios determined by NMR before purification; yields refer to isolated mixtures.

(12) For recent up-to-day reviews on C-glycosidation methods, see: (a) Postema, M. H. *Tetrahedron* **1992**, *48*, 8545. Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1.

(13) C-Glycosylation of thiazole and 4,5-dimethylthiazole was attempted using 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl acetate or trichloroacetimidate as glycosyl donors and boron trifluoride etherate or trimethylsilyl triflate as promoters. We believe that the failure of this approach is due to both the electron-poor character of the thiazole ring (see: Noyce, D. S.; Fike, S. D. *J. Org. Chem.* **1973**, *38*, 3316) and the basicity of the nitrogen atom. Since most of the glycosidation procedures require the activation of the anomeric leaving group by a Lewis acid, the interaction of the latter with the basic thiazole site further reduces the reactivity of the substrate. Also the attempts to introduce the thiazole ring by nucleophilic displacement of anomeric nitrate or tosylate by 2-LTT gave unreacted material.

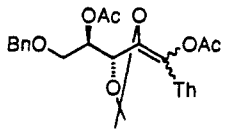
(14) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Lancelin, J.-M.; Zollo, P. H. A.; Sinaÿ, P. *Tetrahedron Lett.* **1983**, *24*, 4833. (c) Wilcox, C. S.; Cowart, M. D. *Carbohydr. Res.* **1987**, *171*, 141. (d) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752. (e) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610. (f) Rosenblum, S. B.; Bihovsky, R. *J. Am. Chem. Soc.* **1990**, *112*, 2746. (g) Krohn, K.; Heins, H.; Wielkens, K. *J. Med. Chem.* **1992**, *35*, 511.

(15) Dondoni, A.; Franco, S.; Merchan, F.; Merino, T.; Tejero, T. *Synlett* **1993**, 78 and *Tetrahedron Lett.* **1993**, *34*, 5475.

and from the 2-azido-tri-*O*-benzyl-2-deoxy-D-galactopyranolactone **2d** (Chart 1). In all cases the extent of stereoselectivity was very good and the sense was identical to that observed for **2a** under the same conditions (Table 1). The stereochemistry at the anomeric center of compounds **4a–c** was assigned on the basis of the previous observation[18] that the chemical shift of the H-3 proton lies downfield in α-isomers because of the 1,3-diaxial interaction between this proton and the anomeric C–O bond. This trend did not hold for the 2-azido derivative **4d** whose configuration, however, was tentatively assigned from other similarities of the NMR spectra of its α- and β-isomer to those of **4b**.[19]

The reaction of **1** with the bis-acetonide mannofuranolactone **2e** under the conditions of route A–B afforded the ketol acetate (α)-**4e** in good isolated yield. The unequivocal proof of the structure of this compound was obtained from X-ray crystallography,[20] thus showing that our previous assignment to the precursor lactol (α)-**3e** based on ^{1}H NMR data was incorrect.[21] Accordingly, route C led to the kinetic epimer (β)-**4e** in agreement with the expectation that steric effects would direct the attack of the nucleophile to the less hindered face of the lactone in this case as well. On a similar basis, the reactions of ribofuranolactone derivatives **2f** and **2g** through route C afforded the expected isomers (α)-**4f** and (α)-**4g** as major products. On the other hand, route A–B led to (β)-**4f** as major product and to **4g** as 1:1 anomeric mixture. The anomeric configuration of compounds **4g** and **4f** was deduced from the ^{13}C NMR resonances of the anomeric carbon. Downfield chemical shifts have been reported[22] for the isomers having a trans orientation of the C–O bonds at C-1 and C-2. This observation was in line with the X-ray structure of compound (α)-**4e**.

From a practical point of view, it is important to note that routes A–B and C furnish ketol acetates **4a–f** in either epimeric form with high stereoselectivity and good isolated yields. It is worth adding a few comments that may serve to better illustrate the conditions employed in each step and reveal the side-products formation. First of all, the reactions of **1** with the sugar lactone **2** gave better yields when carried out on 5–10 mmol scale of the latter reagent. Ketopyranoses **3a–d** were exclusively isolated as stable α-anomers and conveniently acetylated in dichloromethane using acetic anhydride (10 equiv) and triethylamine (10 equiv) as a base. The use of neat pyridine and acetic anhydride induced both anomerization and formation of open-chain products.[23] Also the ketofuranose **3e** was isolated as a pure α-isomer[21] and transformed into the corresponding acetate under the above standard conditions. Compounds **3f** and **3g** appeared by NMR to be mixtures of α- and β-ketofuranoses along with the open-chain ketose in the case of **3g**. Acetylation of **3f** (Chart 1) in dichloromethane with acetic anhydride and triethylamine afforded a 1:7 mixture of α and β acetates **4f** along with 30% of the enol ether **7** (stereochemistry not assigned). Quite interestingly, when the acetylation of **3f** was carried out with neat pyridine and acetic anhydride, only the acetates **4f** were obtained whereas under the same conditions the *ribo* derivative **3g** gave a 1:1 mixture of acetates **4g** and ketone **8** in 60 and 36% isolated yields, respectively.



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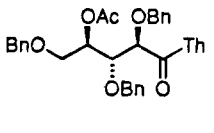

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Reduction of Ketol Acetates 4a–g. While unsuccessful reductive dehydroxylation of the ketol **3a** under either polar and radical conditions[24] was experienced at the early stage of the work, the removal of the acetoxy group by reduction with excess triethylsilane (10 equiv) and trimethylsilyl triflate (2.8 equiv) in dichloromethane at room temperature proved to be feasible with high efficiency for all compounds **4a–g** (Table 2). Considering that these substrates incorporate the basic thiazole moiety,[25] crucial to a successful and high-yield operation was the substrate–silane–TMSOTf ratio. However we have found that a larger excess of the Lewis acid considerably increased the formation of anhydro derivative byproducts. Quite detrimental was also the use of acetonitrile as a solvent which gave rise to 1-acetamido derivatives through anomeric acetonitrilium ions.[26] Finally the reaction did not proceed at low temperature (−20 to 0 °C). It is noteworthy that the stereoselectivity

(16) 2-LTT (**1**) was generated from 2-bromothiazole and butyllithium at −78 °C in diethyl ether. Successful lithiation of the heterocycle is shown by the formation of an homogeneous and slightly yellow solution whereas a brown red solution and eventually the presence of a precipitate are indicative of decomposition products. This organometallic can be also prepared in THF as a solvent where, however, it is less soluble giving rise to a milky mixture. Care should be taken to generate **1** from freshly distilled 2-bromothiazole and a good stock of butyllithium and to use a well-purified and anhydrous solvent.

(17) This compound adopts a $^4H_3$ conformation as proven by the small $J_{2,3}$ value shown by its ^{1}H NMR spectrum (see Experimental Section). Upon deacetylation (MeONa/MeOH or Et_3N/H_2O/MeOH), (β)-**4a** quantitatively gave pure (α)-**3a** which, after treatment with Ac_2O/Et_3N in CH_2Cl_2, afforded pure (α)-**4a** in a $^4C_1$ conformation.

(18) This effect is well established; for early reference see: Paulsen, H.; Holger, T. *Carbohydr. Res.* **1984**, *125*, 47.

(19) In the NMR spectra of (α)-**4b** and (α)-**4d**, the chemical shifts of H-2 is very close to that of H-3: (α)-**4b**), $\delta_{H-2} \sim \delta_{H-3} = 4.04–4.12$ ppm; (α)-**4d**, $\delta_{H-2} = 3.92$, $\delta_{H-3} = 4.00$ ppm. For the β anomers, the signal of H-2 is shifted downfield: (β)-**4b**, $\delta_{H-2} = 4.24$ ppm; (β)-**4d**, $\delta_{H-2} = 5.05$ ppm. Furthermore, the δ_{C-1} values of (β)-**4b** and (β)-**4d** are downfield compared to those of the corresponding α anomers.

(20) Bertolasi, V. (University of Ferrara, Italy), private communication. The atomic coordinates for (α)-**4e** have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2, 1EZ, UK. The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Center.

(21) In our preliminary report (ref 3) we assigned the structure (β)-**3e** to the isolated lactol. The reason was that we had in our hands only a single isomer whose rather low-field OH signal (5.44 ppm) suggested hydrogen bonding with the vicinal O-2 atom. Later, we observed that this compound slowly equilibrated in solution of chloroform to give a mixture of α and β anomers (α:β = 2.2/1, 24 h) which were characterized by NMR by comparison of their δ_{C-1} values.[22]

(22) (a) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602. (b) Boschetti, A.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. *J. Chem. Soc. Perkin Trans. 1* **1988**, 3353.

(23) The formation of an open-chain product under these conditions has already been described for a *galacto*-keto-derivative. See: Heskamp, B. M.; Noort, D.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1992**, 713.

(24) Reaction of **3a** with phenyl chlorothionoformate and pyridine in dichloromethane failed (Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059). Anomeric methyl oxalyl ester was obtained in 70% yield by reaction of **3a** with methyl oxalyl chloride in THF (Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588), but upon treatment of this compound with AIBN and $(Me_3Si)_3SiH$ in toluene at 80 °C, a complex mixture of products was obtained. Attempt to dehydroxylate **3a** with triethylsilane in presence of TMSOTf or $BF_3{\cdot}Et_2O$ gave unaltered material. Similar combinations of silane and Lewis acid were known to reduce ketols. See for instance refs 9, 11, and 14.

(25) Metzger, J. V.; Vincent, E. J. In *Thiazole and its Derivatives*; Metzger, J. V., Ed.; Wiley: New York, 1979; Part 1, p 91.

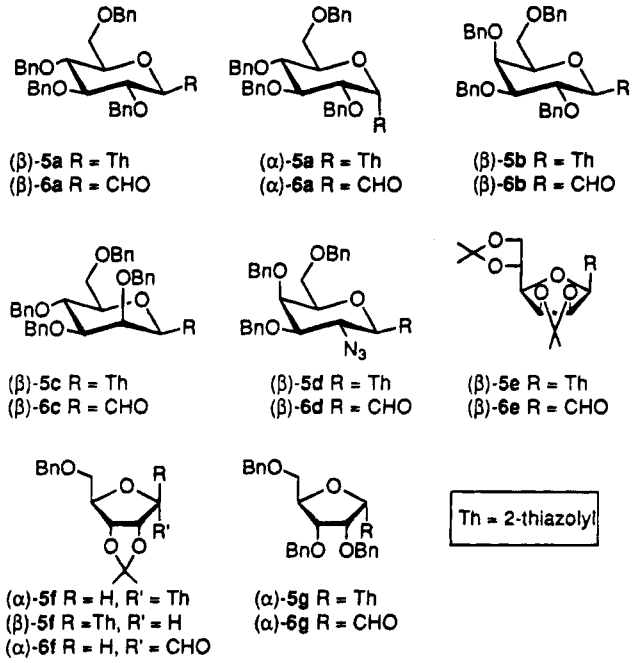
(26) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244.

Table 2. Reduction of Ketol Acetates 4 to Thiazolyl C-Glycosides 5 and Unmasking of Aldehydes 6[a]

ketol acetate[b]	thiazolyl C-glycoside (yield, %)	aldehyde (yield, %)
4a	**5a** (94)[c]	**6a** (74)[c] (60)[d]
4b	**5b** (96)	**6b** (80) (59)[d]
4c	**5c** (97)	**6c** (75) (57)[d]
4d	**5d** (97)	**6d** (72) (56)[d]
4e	**5e** (92)	**6e** (78) (65)[d]
4f	**5f** (93)[e]	**6f** (76) (56)[d]
4g	**5g** (96)	**6g** (74) (52)[d]

[a] Reagents and conditions: see Scheme 1. [b] From either route A–B or C (see Table 1). [c] Mixture (1:1) of anomers. [d] Overall yield from lactone **2**. [e] Mixture (4:1) of anomers.

Chart 2



of the reduction did not depend upon the configuration at C-1 of the substrate **4** since either the α- or β-isomer or mixture of them produced the same thiazolyl C-glycoside **5**. This result is in agreement with a pyran oxonium ion intermediate which accepts the hydride ion from the α (axial) side in a chair-like transition state and therefore leads to a β-linked C-glycoside. In only one case, the reduction of the gluco derivative **4a**, was this stereocontrol not observed as a 1:1 mixture of α- and β-linked thiazolyl C-glycosides **5a** was obtained (Chart 2). Under identical conditions, phenyldimethylsilane produced a 2:1 ratio of α:β isomers, but the selectivity again disappeared with tri-*n*-propylsilane.[27] The anomeric configuration of compound (α)-**5a**, (β)-**5b**, and (β)-**5d** (Chart 2) was assigned by ^{1}H NMR on the base of the $J_{1,2}$ values (6.0, 9.4, and 10.0 Hz, respectively) indicating an equatorial–axial ((α)-**5a**) and an axial–axial ((β)-**5b** and (β)-**5d**) arrangement in $^4C_1$ conformations. For the mannopyranoside derivative **5c**, the β configuration was supported by the substantial nuclear Overhauser effect between H-1 and H-3, and H-1 and H-5. Along the same line a furan oxonium ion intermediate should be involved for the reduction of furanoses **4e–g**. In this case the configuration of the resulting thiazolyl C-glycofuranosides **5e–g** can be rationalized by steric bias of the two faces of the oxycarbenium ion. The anomeric configuration for (β)-**5e** and (α)-**5g** was deduced from the $J_{1,2}$ values in their ^{1}H NMR spectra[22a] and confirmed by a NOE between H-1 and H-4 observed for (β)-**5e** and not for (α)-**5g**. The α and β configuration of compound **5f** was attributed by comparison in their NMR spectra of $J_{H\text{-}3,H\text{-}4}$ and $\delta_{C\text{-}1}$ values.[22a] Furthermore, (β)-**5f** showed a NOE between H-1 and H-4.

Formyl Group Deblocking. Synthesis of C-Glycosyl Aldehydes 6. The final step of the methodology required the conversion of the thiazole ring to the formyl group without affecting the configuration at the anomeric position of the substrate **5** employed. The essentially neutral and mild one-pot protocol[28] involving *N*-methylation with methyl trifluoromethanesulfonate (methyl triflate), reduction with sodium borohydride, and a metal-mediated hydrolysis[29] appeared quite suitable for that purpose. Hence application of this procedure to the individual isomer thiazolyl C-glucopyranoside derivatives (α)-**5a** and (β)-**5a** afforded the corresponding aldehydes (α)-**6a** (72%) and (β)-**6a** (76%) (Chart 2, Table 2). While (β)-**6a** was obtained essentially pure, (α)-**6a** appeared by NMR contaminated by 10% of the β-isomer[30] and could not be purified by flash chromatography due to major decomposition and further epimerization. Using the Bednarski procedure of epimerization under mild basic conditions[10] (10% solution of Et_3N in 1:1 *i*-PrOH–CH_2Cl_2), the crude aldehyde (α)-**6a** was transformed into an equilibrium α/β ratio of 1:20. Hence, the application of the $HgCl_2$-based deblocking protocol to the 1:1 mixture of α- and β-thiazolyl C-glycosides **5a** as obtained by the silane reduction of the ketol acetate **4a** gave the α- and β-aldehydes **6a** with the same 1:1 ratio. This material by base-catalyzed equilibration as above afforded the β-formyl C-glucopyranosyl derivative (β)-**6a** in 60% overall yield from the glucopyranolactone **2a**. As reported by Bednarski and co-workers,[10a] we also observed in this reaction a byproduct (3–10%) arising from β-elimination of the benzyloxy group at C-2.

The same deblocking sequence was also performed starting from the C-1 stereoisomerically pure thiazolyl C-glycopyranosides **5b–d** and C-glycofuranosides[31] **5e–g**. In all cases the procedure afforded the corresponding formyl derivatives **6b–g** in very good yields and without any apparent epimerization by NMR analysis. It is worth pointing out that in some cases, the ^{1}H NMR spectra of these products in $CDCl_3$ at room temperature appeared to be very complex due to the presence of the hydrate form of the aldehyde. Simple spectra were obtained in DMSO-d_6 at high temperature. Overall yields of isolated aldehydes from lactones were in the range 52–65%. Among the compounds prepared, it is worth mentioning the 2-azido derivative **6d**, a quite attractive precursor to more complex 2-azido C-glycosyl sugars.[10b] Aldehydes **6a–g** were stable enough to handling at room temperature and storage at −20 °C for

(27) It is known that the stereoselectivity of the silane reduction of carbohydrates is both silane and substrate dependent giving in some cases the unexpected α (axial) product. See refs 9a and 9b.

(28) Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275.

(29) Since, in the case of (α)-**5a**, the use of mercury(II) chloride in the last step of the procedure gave a better yield of aldehyde than copper(II) chloride, the former halide was used in all cases.

(30) From the various chiral aldehydes prepared in our laboratory by this route without any apparent loss of chiral integrity, we believe that the observed epimerization of (α)-**6a** is due to its intrinsic instability rather than to the conditions employed for thiazole cleavage.

(31) In the case of **5f** which formed as a mixture of α and β anomers in 4:1 ratio from the silane reduction of **4f**, the aldehyde was revealed only from the pure major isomer isolated by chromatography.

several days but appeared to decompose partially on silica gel chromatography. Nonetheless, crude compounds were found to be enough pure and quite suitable for further synthetic elaborations.[32]

Conclusions

We have developed a thiazole-based practical route to *C*-glycopyranosyl and *C*-glycofuranosyl aldehydes from sugar lactones. The flexibility of the synthesis is demonstrated by its application to seven different substrates while its efficiency is supported by the good overall yields of isolated products (52–65%). The sugar aldehydes are delicate compounds whereas their thiazolyl-masked precursors from which they can be readily generated are indefinitely stable. Hence the thiazole ring also serves in this methodology as an excellent formyl group equivalent since it is easily installed in the sugar moiety, tolerates the subsequent synthetic elaboration of the product, and finally provides the formyl group quite rapidly under mild and neutral conditions. The scope of this methodology appears large enough since it has been applied to both pyranose and furanose systems having different types of hydroxyl-protecting groups.

Experimental Section

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. All solvents were dried over standard drying agents[33] and freshly distilled prior to use. Flash column chromatography[34] was performed on silica gel 60 (230–400 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C in chloroform at $c = 1$. ^1H (300 MHz) and ^{13}C (75 MHz) NMR were recorded at room temperature for $CDCl_3$ solutions, unless otherwise specified. Decoupling and/or homo- and heteronuclear two-dimensional experiments were carried out for configurational assignments (see supplementary material). With the exception of **2f**, all sugar lactones were prepared by oxidation of the corresponding hemiacetal with pyridinium chlorochromate[35] in 80–100% yield. Lactone **2a**[36] was obtained from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. Lactone **2c**[37] was obtained from 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose[38] prepared as described. Lactone **2e**[39] was obtained from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose[40] conveniently prepared from mannose. Lactone **2f**[41] was prepared as reported.[42] Lactone **2g**[43] was obtained from 2,3,5-tri-*O*-benzyl-D-ribofuranose.[44] Although 2-bromothiazole is commercially available, its cost is appreciable. We found it convenient to prepare this compound on a multigram scale (0.1 mol) in 65–70% yield from 2-aminothiazole at considerable cost saving according to a published method.[2b,45]

2,3,4,6-Tetra-*O*-benzyl-D-galactonolactone (2b). A mixture of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose[38] (2.00 g, 3.70 mmol), activated 4-Å powdered molecular sieves (3.70 g), and dry CH_2Cl_2 (56 mL) was stirred at room temperature for 15 min, and then pyridinium chlorochromate (3.70 g, 17.10 mmol) was added. The suspension was stirred for 45 min and then were added 56 mL of cyclohexane and 112 mL of Et_2O. The mixture was filtered through silica gel (30 g) and concentrated to give pure **2b** (1.99 g, 100%) as an oil: $[\alpha]_D = +75.2°$; ^1H NMR δ 3.69 (dd, 1 H, J = 5.7, 9.0 Hz), 3.74 (dd, J = 8.8, 9.0 Hz), 3.91 (dd, 1 H, J = 2.1, 9.0 Hz), 4.19 (dd, 1 H, J = 1.1, 2.1 Hz), 4.36 (ddd, 1 H, J = 1.1, 5.7, 8.8 Hz), 4.47 and 4.54 (2 d, 2 H, J = 11.1 Hz), 4.51 (d, 1 H, J = 9.0 Hz), 4.64 and 4.97 (2 d, 2 H, J = 11.1 Hz), 4.72 and 4.79 (2 d, 2 H, J = 11.4 Hz), 4.82 and 5.22 (2 d, 2 H, J = 10.8 Hz), 7.22–7.45 (m, 20 H); ^{13}C NMR δ 67.4, 72.3, 72.4, 73.2, 74.4, 74.9, 77.0, 79.7, 127.2–128.2, 137.2–137.8, 169.7. Anal. Calcd for $C_{34}H_{34}O_6$: C, 75.81; H, 6.36. Found: C, 75.73; H, 6.43.

2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactonolactone (2d). 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose[46] (2.00 g, 4.20 mmol) was treated as described for the preparation of **2b** to give pure **2d** (1.99 g, 100%) as an oil: $[\alpha]_D = +63.4°$; ^1H NMR δ 3.65 (dd, 1 H, J = 5.6, 9.5 Hz), 3.68 (dd, 1 H, J = 1.9, 10.4 Hz), 3.72 (dd, 1 H, J = 8.1, 9.5 Hz), 4.17 (dd, 1 H, J = 1.4, 1.9 Hz), 4.32 (ddd, 1 H, J = 1.4, 5.6, 8.1 Hz), 4.46 and 4.52 (2 d, 2 H, J = 11.7 Hz), 4.61 (d, 1 H, J = 10.4 Hz), 4.62 and 4.92 (2 d, 2 H, J = 11.2 Hz), 4.71 (s, 2 H), 7.20–7.45 (m, 15 H); ^{13}C NMR δ 61.5, 67.2, 71.1 72.5, 73.7, 74.8, 77.8, 78.8, 127.8–128.7, 137.0–137.4, 167.5. Anal. Calcd for $C_{27}H_{27}N_3O_5$: C, 68.48; H, 5.74; N, 8.87. Found: C, 68.64; H, 5.75; N, 8.84.

2,3,4,6-Tetra-*O*-benzyl-1-(2-thiazolyl)-α-D-glucopyranose ((α)-3a). To a cooled (−78 °C) and stirred solution of *n*BuLi (7.6 mL, 12.10 mmol of a 1.6 M solution in hexane) in dry Et_2O (17 mL) was added dropwise a solution of freshly distilled 2-bromothiazole (1.80 g, 11.10 mmol) in dry Et_2O (4.3 mL) over a 30 min period. After the yellow solution had been stirred at −78 °C for 20 min, a solution of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**2a**) (5.00 g, 9.29 mmol) in dry THF (17 mL) was added slowly (25 min). After an additional 20 min, the mixture was allowed to warm to −65 °C in 30 min and poured into 200 mL of a 1 M phosphate buffer (pH = 7). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (5:2 petroleum ether–ethyl acetate) of the residue gave 4.60 g (80%) of the ketose **3a** as a white solid: mp 96–97 °C (from AcOEt–hexane); $[\alpha]_D = +10.8°$; ^1H NMR δ 3.72 (dd, 1 H, J = 1.6, 11.6 Hz), 3.83 (dd, 1 H, J = 4.2, 11.6 Hz), 3.86 (dd, 1 H, J = 9.0, 10.0 Hz), 4.01 (d, 1 H, J = 9.0 Hz), 4.08 (t, 1 H, J = 9.0 Hz), 4.16–4.24 (m, 1 H), 4.19 and 4.57 (2 d, 2 H, J = 10.6 Hz), 4.53 and 4.64 (2 d, 2 H, J = 12.2 Hz), 4.58 (s, 1 H), 4.65 and 4.87 (2 d, 2 H, J = 10.6 Hz), 4.91 (s, 2 H), 6.95–7.40 (m, 20 H), 7.40 and 7.80 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 68.5, 72.9, 73.2, 74.9, 75.0, 75.5, 77.9, 83.2, 83.9, 96.8, 121.3, 127.7–128.6, 137.8–138.9, 142.3, 171.9. Anal. Calcd for $C_{37}H_{37}NO_6S$: C, 71.24; H, 5.97; N, 2.24. Found: C, 71.45; H, 6.07; N, 2.30.

2,3,4,6-Tetra-*O*-benzyl-1-(2-thiazolyl)-α-D-galactopyranose ((α)-3b). The lactone **2b** (2.00 g, 3.70 mmol) was treated with **1** as described for the preparation of **3a**. Flash chromatography (5:2 petroleum ether–ethyl acetate) of the residue gave 1.80 g (78%) of the ketose **3b** as a syrup: $[\alpha]_D = +6.4°$; ^1H NMR δ 3.64 (dd, 1 H, J = 5.6, 9.3 Hz), 3.72 (dd, 1 H, J = 7.5, 9.3 Hz), 4.09 (dd, 1 H, J = 2.5, 9.7 Hz), 4.15 (dd, 1 H, $J \sim$ 0.8, 2.5 Hz), 4.33 and 4.72 (2 d, 2 H, J = 10.6 Hz), 4.37 (ddd, 1 H, $J \sim$ 0.8, 5.6, 7.5 Hz), 4.46 and 4.52 (2 d, 2 H, J = 11.8 Hz), 4.53 (d, 1 H, J = 9.7 Hz), 4.74 and 5.07 (2 d, 2 H, J = 11.8 Hz), 4.79 (s, 2 H), 4.94 (s, 1 H), 7.00–7.50 (m, 21 H), 7.80 (d, 1 H, J = 3.3 Hz); ^{13}C NMR δ 68.3, 71.5, 72.6, 73.3, 74.1,

(32) Some of these aldehydes are currently being used in our laboratory in synthetic routes to various *C*-glycosides through reactions of the formyl group.

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74.3, 75.2, 80.0, 80.5, 97.2, 120.8, 127.5–128.4, 137.8–138.9, 142.1, 171.7. Anal. Calcd for $C_{37}H_{37}NO_6S$: C, 71.24; H, 5.97; N, 2.24. Found: C, 71.33; H, 5.98; N, 2.21.

2,3,4,6-Tetra-*O*-benzyl-1-(2-thiazolyl)-α-D-mannopyranose ((α)-3c). The lactone **2c** (500 mg, 0.93 mmol) was treated with **1** as described for the preparation of **3a**. Flash chromatography (5:3 cyclohexane–ethyl acetate) of the residue gave 423 mg (73%) of the ketose **3c** as a white solid: mp 93–95 °C (from iPr_2O), $[\alpha]_D$ = +2.5°; ^1H NMR δ 3.78 (dd, 1 H, J = 1.2, 11.5 Hz), 3.89 (dd, 1 H, J = 4.5, 11.5 Hz), 4.11–4.18 (m, 3 H), 4.22 and 4.72 (2 d, 2 H, J = 11.0 Hz), 4.31 (dd, 1 H, J = 2.3, 9.6 Hz), 4.46 (s, 1 H), 4.57 and 4.76 (2 d, 2 H, J = 12.0 Hz), 4.63 and 4.92 (2 d, 2 H, J = 11.3 Hz), 4.75 (s, 2 H), 7.05–7.45 (m, 21 H), 7.75 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 69.4, 72.3, 73.3, 73.7, 74.5, 74.6, 75.0, 78.4, 81.0, 97.4, 121.6, 127.3–128.3, 138.2–138.7, 141.2, 170.7. Anal. Calcd for $C_{37}H_{37}NO_6S$: C, 71.24; H, 5.97; N, 2.24. Found: C, 71.32; H, 6.03; N, 2.25.

2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-galactopyranose ((α)-3d). The lactone **2d** (600 mg, 1.26 mmol) was treated with **1** as described for the preparation of **3a**. Flash chromatography (5:2 cyclohexane–ethyl acetate) of the residue gave 545 mg (77%) of syrupy **3d** contaminated by an unknown product (~5%): ^1H NMR δ 3.58 (dd, 1 H, J = 5.9, 9.1 Hz), 3.65 (dd, 1 H, J = 7.4, 9.1 Hz), 4.08 (dd, 1 H, J = 2.1, 9.8 Hz), 4.10 (d, 1 H, J = 2.1 Hz), 4.22 (d, 1 H, J = 9.8 Hz), 4.34 (dd, 1 H, J = 5.9, 7.4 Hz), 4.43 and 4.49 (2 d, 2 H, J = 11.9 Hz), 4.62 and 4.96 (2 d, 2 H, J = 11.2 Hz), 4.74 and 4.78 (2 d, 2 H, J = 11.2 Hz), 5.16 (s, 1 H), 7.20–7.50 (m, 16 H), 7.75 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 65.1, 68.4, 71.7, 72.4, 73.1, 73.4, 74.5, 78.5, 96.8, 121.6, 127.6–128.6, 137.6–138.6, 141.7, 169.8.

2,3:5,6-Di-*O*-isopropylidene-1-(2-thiazolyl)-α,β-D-mannofuranose (3e). The lactone **2e** (2.00 g, 7.75 mmol) was treated with **1** as described for the preparation of **3a**. Flash chromatography (5:3 petroleum ether–ethyl acetate) of the residue gave 2.02 g (76%) of the ketose (α)-**3e** as a white solid: mp 139–140 °C (from Et_2O–hexane); $[\alpha]_D$ (2 min) = +43.6°; ^1H NMR δ 1.31, 1.40, 1.47, and 1.50 (4 s, 12 H), 4.08 (dd, 1 H, J = 5.0, 8.3 Hz), 4.14 (dd, 1 H, J = 5.8, 8.3 Hz), 4.32 (dd, 1 H, J = 4.1, 7.5 Hz), 4.48 (ddd, 1 H, J = 5.0, 5.8, 7.5 Hz), 4.79 (d, 1 H, J = 5.8 Hz), 5.03 (dd, 1 H, J = 4.1, 5.8 Hz), 5.44 (s, 1 H), 7.46 and 7.80 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 24.1, 25.2, 25.4, 26.7, 66.7, 73.1, 79.6, 80.3, 86.1, 103.7, 109.2, 113.4, 122.2, 141.2, 167.1. Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.46; H, 6.16; N, 4.07. Found: C, 52.28; H, 6.08; N, 3.97.

The compound (α)-**3e** in a solution of $CDCl_3$ slowly equilibrated into α- and β-anomers (α:β = 2.2:1; 24 h). (β)-**3e**: ^1H NMR δ 1.36, 1.42, 1.44, and 1.62 (4 s, 12 H), 3.87 (dd, 1 H, J = 3.1, 8.6 Hz), 3.98 (dd, 1 H, J = 3.9, 8.6 Hz), 4.09 (dd, 1 H, J = 5.5, 8.6 Hz), 4.42 (ddd, 1 H, J = 3.9, 5.5, 8.6 Hz), 4.78 (s, 1 H), 4.99 (dd, 1 H, J = 3.1, 5.4 Hz), 5.15 (d, 1 H, J = 5.4 Hz), 7.38 and 7.76 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 24.6, 25.0, 25.8, 26.8, 67.1, 72.9, 79.6, 80.1, 81.9, 101.7, 109.4, 113.7, 120.3, 142.6, 169.8.

5-*O*-Benzyl-2,3-*O*-isopropylidene-1-(2-thiazolyl)-α,β-D-ribofuranose (3f). The lactone **2f** (1.60 g, 5.70 mmol) was treated with **1** as described for the preparation of **3a**. Flash chromatography (5:2 petroleum ether–ethyl acetate) of the residue gave 1.58 g (76%) of the ketose **3f** as a syrup: ^1H NMR δ 1.26 and 1.42 (2 s, 6 H), 3.62 (dd, 0.3 H, J = 4.6, 9.4 Hz), 3.67 (dd, 0.3 H, J = 4.6, 9.4 Hz), 3.72 (dd, 0.7 H, J = 3.7, 10.1 Hz), 3.78 (dd, 0.7 H, J = 4.6, 10.1 Hz), 4.47 (ddd, 0.3 H, J = 3.7, 4.6, 9.4 Hz), 4.50 and 4.54 (2 d, 0.6 H, J = 11.0 Hz), 4.57 (ddd, 0.7 H, J = 1.1, 3.7, 4.6 Hz), 4.61 and 4.67 (2 d, 1.4 H, J = 11.0 Hz), 4.79 (d, 0.7 H, J = 5.5 Hz), 4.84 (s, 0.3 H), 4.88 (dd, 0.3 H, J = 3.7, 7.2 Hz), 4.95 (dd, 0.7 H, J = 1.1, 5.5 Hz), 5.18 (d, 0.3 H, J = 7.2 Hz), 5.44 (s, 0.7 H), 7.25–7.40 (m, 6 H), 7.77 (d, 0.3 H, J = 3.2 Hz), 7.82 (d, 0.7 H, J = 3.2 Hz); ^{13}C NMR selected data δ 101.3 (C-1α) and 106.0 (C-1β). Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.49; H, 5.82; N, 3.85. Found: C, 59.51; H, 5.78; N, 3.83.

2,3,5-Tri-*O*-benzyl-1-(2-thiazolyl)-α,β-D-ribofuranose (3g). The lactone **2g** (500 mg, 1.20 mmol) was treated with **1** as described for the preparation of **3a**. Flash chromatography (5:2 petroleum ether–ethyl acetate) of the residue gave 439 mg (73%) of the ketose **3g** as a syrup. The ^1H NMR spectrum of this compound was very complex due to its existence as a mixture of α and β anomers and the presence of the open-chain hydroxy ketone. This compound was characterized as the acetate **4g**.

1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-1-(2-thiazolyl)-α,β-D-glucopyranose (4a). Route A–B. To a solution of **3a** (4.00 g, 6.41 mmol) in CH_2Cl_2 (15 mL) were added at rt 6 mL of Et_3N and 6 mL of Ac_2O. After standing overnight at rt, the solution was concentrated to give 4.20 g (100%) of (α)-**4a** as a syrup: $[\alpha]_D$ = +35.0°; ^1H NMR δ 2.21 (s, 3 H), 3.60 (d, 1 H, J = 9.7 Hz), 3.76–3.86 (m, 2 H), 3.90 (dd, 1 H, J = 2.7, 11.7 Hz), 3.96 (t, 1 H, J = 9.6 Hz), 4.10 and 4.41 (2 d, 2 H, J = 10.4 Hz), 4.16 (dd, 1 H, J = 9.6, 9.7 Hz), 4.61 and 4.74 (2 d, 2 H, J = 11.7 Hz), 4.65 and 4.86 (2 d, 2 H, J = 10.4 Hz), 4.88 and 4.95 (2 d, 2 H, J = 11.0 Hz), 7.15–7.45 (m, 21 H), 7.80 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 21.5, 67.9, 73.5, 74.1, 75.2, 75.6, 77.2, 82.5, 84.0, 100.3, 120.4, 127.6–128.5, 137.5–138.5, 142.5, 167.1, 168.0. Anal. Calcd for $C_{39}H_{39}NO_7S$: C, 70.35; H, 5.90; N, 2.10. Found: C, 70.57; H, 5.74; N, 2.03.

Route C. 2,3,4,6-Tetra-*O*-benzyl-D-gluconolactone (**2a**) (1.00 g, 1.85 mmol) was treated with 2-lithiothiazole (**1**) at −78 °C as described for the preparation of **3a**. Then the reaction mixture was allowed to warm to −65 °C in 30 min and 10 equiv (1.8 mL) of Ac_2O were added. The mixture was stirred for an additional 1 h at −65 °C and then worked up as described for the preparation of **3a**. Flash chromatography (5:2 petroleum ether–ethyl acetate) of the residue gave first 946 mg (77%) of (β)-**4a**: $[\alpha]_D$ = −19.4°; ^1H NMR ($CDCl_3$) δ 1.85 (s, 3 H), 3.81 (bd, 1 H, J = 11.0 Hz), 3.88 (bd, 1 H, J = 11.0 Hz), 3.95 (m, 1 H), 4.26 and 4.33 (2 d, 2 H, J = 11.2 Hz), 4.29–4.33 (m, 2 H), 4.36 (d, 1 H, J = 2.6 Hz), 4.52 and 4.65 (2 d, 2 H, J = 11.1 Hz), 4.68 and 4.83 (2 d, 2 H, J = 10.7 Hz), 6.97–7.42 (m, 21 H), 7.78 (d, 1 H, J = 3.2 Hz); ^1H NMR (C_6D_6, 70 °C) δ 1.70 (s, 3 H), 3.73 (dd, 1 H, J = 1.8, 11.5 Hz), 3.83 (dd, 1 H, J = 4.0, 11.5 Hz), 4.25 (dd, 1 H, J = 3.8, 7.5 Hz), 4.35 (s, 2 H), 4.41 and 4.63 (2 d, 2 H, J = 12.0 Hz), 4.48 (dd, 1 H, J = 7.5, 10.5 Hz), 4.51 and 4.55 (2 d, 2 H, J = 12.0 Hz), 4.58 (ddd, 1 H, J = 1.8, 4.0, 10.5 Hz), 4.74 and 4.89 (2 d, 2 H, J = 12.0 Hz), 4.77 (d, 1 H, J = 3.8 Hz), 6.75 and 7.57 (2 d, 2 H, J = 3.2 Hz), 7.00–7.40 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 21.7, 68.4, 72.1, 73.1, 73.3, 74.4, 74.7, 76.4, 80.4, 83.4, 100.4, 120.6, 127.5–128.5, 137.3–138.6, 142.1, 167.6, 169.5. Anal. Calcd for $C_{39}H_{39}NO_7S$: C, 70.35; H, 5.90; N, 2.10. Found: C, 70.11; H, 5.70; N, 2.05.

Eluted second was (α)-**4a** (120 mg, 10%).

1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-1-(2-thiazolyl)-α,β-D-galactopyranose (4b). Route A–B. 3b (1.50 g, 2.40 mmol) was treated as described for the preparation of **4a** to give (α)-**4b** (1.60 g, 100%): $[\alpha]_D$ = +34.7°; ^1H NMR δ 2.20 (s, 3 H), 3.65 (dd, 1 H, J = 5.0, 9.0 Hz), 3.82 (t, 1 H, J = 9.0 Hz), 3.99 (ddd, 1 H, J ~ 1.0, 5.0, 9.0 Hz), 4.04–4.12 (m, 2 H), 4.14 (m, 1 H), 4.22 and 4.49 (2 d, 2 H, J = 10.5 Hz), 4.44 and 4.52 (2 d, 2 H, J = 11.5 Hz), 4.64 and 4.98 (2 d, 2 H, J = 12.0 Hz), 4.74 and 4.79 (2 d, 2 H, J = 11.5 Hz), 7.20–7.40 (m, 21 H), 7.75 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 21.7, 67.8, 72.6, 72.9, 73.6, 74.1, 74.6, 75.5, 79.7, 79.8, 101.0, 120.4, 127.4–128.7, 137.6–138.8, 142.4, 167.2, 168.2. Anal. Calcd for $C_{39}H_{39}NO_7S$: C, 70.35; H, 5.90; N, 2.10. Found: C, 70.20; H, 5.91; N, 2.10.

Route C. 2b (700 mg, 1.30 mmol) was treated as described for the preparation of **4a** to afford, after flash chromatography (5:1 to 5:2 petroleum ether–ethyl acetate), first (β)-**4b** (590 mg, 68%): $[\alpha]_D$ = +40.0°; ^1H NMR δ 1.95 (s, 3 H), 3.80 (d, 2 H, J = 7.0 Hz), 3.86 (dd, 1 H, J = 2.5, 9.0 Hz), 4.13 (dd, 1 H, J = 2.0, 2.5 Hz), 4.45 and 4.54 (2 d, 2 H, J = 11.0 Hz), 4.59 and 4.65 (2 d, 2 H, J = 11.5 Hz), 4.64 and 4.92 (2 d, 2 H, J = 12.0 Hz), 4.67 (d, 1 H, J = 9.0 Hz), 4.75 (s, 2 H), 4.94 (dt, 1 H, J = 2.0, 7.0 Hz), 7.20–7.37 (m, 20 H), 7.37 and 7.77 (2 d, 2 H, J = 3.3 Hz); ^{13}C NMR δ 21.9, 68.3, 72.6, 73.2, 73.6, 74.1, 74.4, 75.4, 78.5, 78.9, 101.7, 120.7, 127.3–128.3, 138.0–138.7, 141.5, 167.0, 167.3. Anal. Calcd for $C_{39}H_{39}NO_7S$: C, 70.35; H, 5.90; N, 2.10. Found: C, 70.17; H, 5.82; N, 2.07.

Eluted second was (α)-**4b** (60 mg, 7%).

1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-1-(2-thiazolyl)-α,β-D-mannopyranose (4c). Route A–B. 3c (100 mg, 0.16 mmol) was treated as described for the preparation of **4a** to afford 106 mg (100%) of syrupy (α)-**4c**: $[\alpha]_D$ = +34.1°; ^1H NMR δ

2.05 (s, 3 H), 3.83–4.93 (m, 2 H), 4.00 (dd, 1 H, J = 4.0, 12.0 Hz), 4.04 and 4.52 (2 d, 2 H, J = 11.3 Hz), 4.19 (dd, 1 H, J = 2.6, 9.5 Hz), 4.28 (t, 1 H, J = 9.5 Hz), 4.44 (d, 1 H, J = 2.6 Hz), 4.65 and 4.91 (2 d, 2 H, J = 10.8 Hz), 4.66 and 4.86 (2 d, 2 H, J = 11.5 Hz), 4.74 and 4.81 (2 d, 2 H, J = 11.7 Hz), 6.90–7.42 (m, 21 H), 7.75 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 21.3, 68.5, 72.1, 73.5, 73.8, 75.0, 75.3, 75.9, 78.0, 80.2, 100.7, 120.9, 127.4–128.4, 137.8–138.7, 141.9, 167.2, 169.4. Anal. Calcd for $C_{39}H_{39}NO_7S$: C, 70.35; H, 5.90; N, 2.10. Found: C, 70.54; H, 5.89; N, 2.09.

Route C. 2c (500 mg, 0.92 mmol) was treated as described for the preparation of **4a** to afford, after flash chromatography (5:2 cyclohexane–ethyl acetate), (β)-**4c** (482 mg, 78%) as a syrup: $[\alpha]_D$ = +3.0°; ^{1}H NMR δ 1.93 (s, 3 H), 3.52 (dt, 1 H, J = 4.0, 9.5 Hz), 3.78 (d, 2 H, J = 4.0 Hz), 4.07 (t, 1 H, J = 9.5 Hz), 4.24 (dd, 1 H, J = 2.6, 9.5 Hz), 4.51 and 4.83 (2 d, 2 H, J = 11.0 Hz), 4.56 and 4.64 (2 d, 2 H, J = 12.0 Hz), 4.71 and 4.88 (2 d, 2 H, J = 12.0 Hz), 4.74 and 5.09 (2 d, 2 H, J = 11.5 Hz), 5.44 (d, 1 H, J = 2.6 Hz), 7.05–7.44 (m, 20 H), 7.45 and 7.76 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 21.5, 68.9, 72.1, 73.1, 74.0, 74.7, 75.1, 75.5, 75.9, 80.9, 101.0, 121.9, 127.2–128.1, 137.9–138.6, 141.7, 167.6, 168.1. Anal. Calcd for $C_{39}H_{39}NO_7S$: C, 70.35; H, 5.90; N, 2.10. Found: C, 70.54; H, 5.89; N, 2.09.

1-*O*-Acetyl-2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α,β-D-galactopyranose (4d). Route A–B. 3d (500 mg, 0.89 mmol, contaminated by ~5% of a unknown product) was treated as described for the preparation of **4a** to afford, after flash chromatography (5:2 cyclohexane–ethyl acetate), 510 mg (95%) of syrupy (α)-**4d**: $[\alpha]_D$ = +60.8°; ^{1}H NMR δ 2.15 (s, 3 H), 3.67 (dd, 1 H, J = 5.0, 9.0 Hz), 3.82 (t, 1 H, J = 9.0 Hz), 3.92 (d, 1 H, J = 10.0 Hz), 4.00 (dd, 1 H, J = 2.5, 10.0 Hz), 4.01 (ddd, 1 H, J ~ 0.8, 5.0, 9.0 Hz), 4.15 (dd, 1 H, J ~ 0.8, 2.5 Hz), 4.46 and 4.53 (2 d, 2 H, J = 11.5 Hz), 4.61 and 4.92 (2 d, 2 H, J = 11.5 Hz), 4.77 and 4.81 (2 d, 2 H, J = 12.0 Hz), 7.23–7.47 (m, 16 H), 7.81 (d, 1 H, J = 3.3 Hz); ^{13}C NMR δ 21.5, 64.6, 67.7, 72.4, 72.5, 72.7, 73.6, 74.6, 78.0, 99.8, 120.6, 127.7–128.5, 137.5, 137.6, 138.4, 142.8, 166.8, 167.6. Anal. Calcd for $C_{32}H_{32}N_4O_6S$: C, 63.98; H, 5.37; N, 9.32. Found: C, 64.15; H, 5.39; N, 9.29.

Route C. 2d (900 mg, 1.9 mmol) was treated as described for the preparation of **4a** to afford, after flash chromatography (10:3 cyclohexane–ethyl acetate), (β)-**4d** (910 mg, 80%) as a syrup: $[\alpha]_D$ = +35.5°; ^{1}H NMR δ 2.17 (s, 3 H), 3.62 (dd, 1 H, J = 5.5, 8.9 Hz), 3.72 (dd, 1 H, J = 8.2, 8.9 Hz), 4.10 (dd, 1 H, J ~ 0.8, 2.4 Hz), 4.27 (dd, 1 H, J = 2.4, 10.4 Hz), 4.41 and 4.48 (2 d, 2 H, J = 11.0 Hz), 4.62 and 4.97 (2 d, 2 H, J = 11.7 Hz), 4.69 (s, 2 H), 4.70 (ddd, 1 H, J ~ 0.8, 5.5, 8.2 Hz), 5.05 (d, 1 H, J = 10.4 Hz), 7.20–7.43 (m, 15 H), 7.43 and 7.77 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 22.0, 62.6, 67.9, 72.3, 72.5, 73.2, 74.0, 74.5, 78.2, 101.2, 120.7, 127.5–128.3, 137.5, 137.7, 138.4, 141.8, 166.1, 167.1. Anal. Calcd for $C_{32}H_{32}N_4O_6S$: C, 63.98; H, 5.37; N, 9.32. Found: C, 64.10; H, 5.42; N, 9.51.

1-*O*-Acetyl-2,3:5,6-di-*O*-isopropylidene-1-(2-thiazolyl)-α,β-D-mannofuranose (4e). Route A–B. 3e (1.50 g, 4.30 mmol) was treated as described for the preparation of **4a** to afford 1.65 g (100%) of the ketose (α)-**4e** as a white solid: mp 131–132 °C (from hexane); $[\alpha]_D$ = +115.9°; ^{1}H NMR δ 1.29, 1.34, 1.41, and 1.50 (4 s, 12 H), 2.10 (s, 3 H), 4.15 (dd, 1 H, J = 4.1, 8.7 Hz), 4.20 (dd, 1 H, J = 5.8, 8.7 Hz), 4.23 (dd, 1 H, J = 3.5, 7.6 Hz), 4.54 (ddd, 1 H, J = 4.1, 5.8, 7.6 Hz), 5.02 (dd, 1 H, J = 3.5, 5.8 Hz), 5.09 (d, 1 H, J = 5.8 Hz), 7.35 and 7.80 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 21.4, 24.0, 25.0, 25.2, 26.7, 66.8, 72.8, 79.7, 81.9, 87.1, 107.6, 109.5, 113.6, 120.1, 142.7, 166.2, 168.0. Anal. Calcd for $C_{17}H_{23}NO_7S$: C, 52.97; H, 6.01; N, 3.63. Found: C, 53.12; H, 6.04; N, 3.57.

Route C. Lactone **2e** (3.50 g, 13.5 mmol) was treated as described for the preparation of **4a**. Flash chromatography (5:2 petroleum ether–ethyl acetate) of the residue gave 4.70 g (90%) of (β)-**4e** as a white solid: mp 136–137 °C (from iPr$_2$O); $[\alpha]_D$ = +70.9°; ^{1}H NMR δ 1.35, 1.40, 1.43, and 1.56 (4 s, 12 H), 2.17 (s, 3 H), 3.61 (dd, 1 H, J = 3.6, 8.5 Hz), 3.94 (dd, 1 H, J = 3.6, 8.5 Hz), 4.08 (dd, 1 H, J = 6.0, 8.5 Hz), 4.48 (ddd, 1 H, J = 3.6, 6.0, 8.5 Hz), 5.01 (dd, 1 H, J = 3.6, 6.0 Hz), 5.82 (d, 1 H, J = 6.0 Hz), 7.41 and 7.72 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 20.5, 24.6, 25.0, 25.5, 26.5, 66.4, 72.4, 77.4, 79.4, 81.7, 104.9, 109.1, 113.2, 120.6, 141.6, 167.6, 168.0. Anal. Calcd for $C_{17}H_{23}NO_7S$: C, 52.97; H, 6.01; N, 3.63. Found: C, 52.93; H, 6.05; N, 3.47.

1-*O*-Acetyl-5-*O*-benzyl-2,3-*O*-isopropylidene-1-(2-thiazolyl)-α,β-D-ribofuranose (4f). Route A–B. 3f (500 mg, 1.37 mmol) was treated as described for the preparation of **4a** to afford, after flash chromatography (2:1 petroleum ether–ethyl acetate), first 229 mg of **7** contaminated by 21% of (α)-**4f**. Eluted second was (β)-**4f** (344 mg, 62%).

When **3f** (100 mg, 0.27 mmol) was treated with 0.6 mL of pyridine and 0.6 mL of acetic anhydride overnight, only the two anomers **4f** in a 1:7 α/β ratio were obtained (111.5 mg, 100%).

Route C. 2f (1.50 g, 5.40 mmol) was treated as described for the preparation of **4a**. Flash chromatography (2:1 petroleum ether–ethyl acetate) of the residue afforded 1.64 g (75%) of (α)-**4f** and 109 mg (5%) of (β)-**4f**.

7: ^{1}H NMR δ 1.50 and 1.67 (2 s, 6 H), 2.15 and 2.45 (2 s, 6 H), 3.62 (dd, 1 H, J = 2.6, 10.2 Hz), 3.79 (dd, 1 H, J = 7.8, 10.2 Hz), 4.46 and 4.55 (2 d, 2 H, J = 11.3 Hz), 5.14 (d, 1 H, J = 2.0 Hz), 5.62 (ddd, 1 H, J = 2.0, 2.6, 7.8 Hz), 7.20–7.30 (m, 5 H), 7.32 and 7.80 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 20.4, 20.9, 25.2, 25.3, 67.2, 70.9, 72.9, 78.5, 115.8, 118.6, 127.5, 127.6, 128.3, 137.7, 142.1, 169.4, 170.7.

(α)-**4f**: mp 85–86 °C (from iPrO$_2$), $[\alpha]_D$ = +16.9°; ^{1}H NMR δ 1.40 and 1.72 (2 s, 6 H), 2.15 (s, 3 H), 3.70 (d, 2 H, J = 3.5 Hz), 4.53 and 4.59 (2 d, 2 H, J = 12.0 Hz), 4.60 (dd, 1 H, J = 2.5, 3.5 Hz), 4.87 (dd, 1 H, J = 2.5, 6.5 Hz), 5.01 (d, 1 H, J = 6.5 Hz), 7.23–7.36 (m, 6 H), 7.75 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 21.5, 25.4, 25.9, 69.4, 73.5, 80.9, 83.4, 85.9, 104.2, 105.6, 119.8, 127.6, 127.7, 128.4, 137.7, 142.7, 168.5, 168.6. Anal. Calcd for $C_{20}H_{23}NO_6S$: C, 59.29; H, 5.71; N, 3.45. Found: C, 59.46; H, 5.53; N, 3.42.

(β)-**4f**: mp 91–92 °C (from AcOEt–hexane); $[\alpha]_D$ = −119.3°; ^{1}H NMR δ 1.25 and 1.32 (2 s, 6 H), 1.92 (s, 3 H), 3.59 (dd, 1 H, J = 7.2, 9.7 Hz), 3.65 (dd, 1 H, J = 5.1, 9.7 Hz), 4.56 and 4.61 (2 d, 2 H, J = 11.3 Hz), 4.68 (ddd, 1 H, J = 1.5, 5.1, 7.2 Hz), 4.97 (dd, 1 H, J = 1.5, 5.6 Hz), 5.04 (d, 1 H, J = 5.6 Hz), 7.25–7.43 (m, 6 H), 7.80 (d, 1 H, J = 3.3 Hz); ^{13}C NMR δ 21.3, 24.6, 25.8, 69.7, 73.1, 81.9, 86.5, 87.3, 108.4, 113.4, 120.1, 127.5, 127.7, 128.3, 137.4 142.5, 167.0, 167.8. Anal. Calcd for $C_{20}H_{23}NO_6S$: C, 59.29; H, 5.71; N, 3.45. Found: C, 59.61; H, 5.80; N, 3.57.

1-*O*-Acetyl-2,3,5-tri-*O*-benzyl-1-(2-thiazolyl)-α,β-D-ribofuranose (4g). Route A–B. 3g (300 mg, 0.59 mmol) was treated as described for the preparation of **4a** to afford, after flash chromatography (5:2 cyclohexane–ethyl acetate), first 15 mg (5%) of **8**: $[\alpha]_D$ = −6.8°; ^{1}H NMR δ 1.96 (s, 3 H), 3.73 (d, 1 H, J = 3.7 Hz), 4.39 and 4.48 (2 d, 2 H, J = 12.0 Hz), 4.52 and 4.79 (2 d, 2 H, J = 12.1 Hz), 4.62 (s, 2 H), 4.63 (dd, 1 H, J = 3.5, 7.1 Hz), 5.38 (d, 1 H, J = 3.5 Hz), 5.41(dd, 1 H, J = 3.7, 7.1 Hz), 7.13–7.38 (m, 15 H), 7.68 and 8.01 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR δ 20.9, 68.4, 71.1, 72.5, 72.7, 73.0, 78.4, 79.6, 126.2, 127.5–128.3 and 137.5–138.2, 144.9, 166.1, 169.9, 190.5.

Eluted second was a 1:1 mixture of (α)- and (β)-**4g** (304 mg, 94%). (α)-**4g**: ^{1}H NMR δ 2.14 (s, 3 H), 3.55 (dd, 1 H, J = 3.5, 11.0 Hz), 3.68 (dd, 1 H, J = 4.0, 11.0 Hz), 4.10 (dd, 1 H, J = 5.0, 5.5 Hz), 4.34 (d, 1 H, J = 5.5 Hz), 4.44 and 4.54 (2 d, 2 H, J = 12.0 Hz), 4.51 and 4.71 (2 d, 2 H, J = 12.0 Hz), 4.51 (ddd, 1 H, J = 3.5, 4.0, 5.0 Hz), 4.70 and 4.80 (2 d, 2 H, J = 11.5 Hz), 7.16–7.34 (m, 16 H), 7.78 (d, 1 H, J = 3.3 Hz); ^{13}C NMR δ 21.7, 68.9, 72.5, 73.2, 76.7, 82.3, 83.2, 104.6, 120.2, 127.5–128.3, 137.6, 137.9, 138.0, 142.5, 169.1, 169.7.

(β)-**4g**: ^{1}H NMR selected data δ 2.18 (s, 3 H), 3.61 (dd, 1 H, J = 2.0, 11.5 Hz), 3.86 (dd, 1 H, J = 1.6, 11.5 Hz), 4.05 and 4.10 (2 d, 2 H, J = 10.0 Hz), 4.27 (d, 1 H, J = 4.0 Hz), 4.57–4.62 (m, 2 H), 6.95–7.40 (m, 15 H), 7.42 and 7.80 (2 d, 2 H, J = 3.2 Hz); ^{13}C NMR selected data δ 21.1, 67.8, 106.8.

When **3g** (100 mg, 0.19 mmol) was treated with 0.6 mL of pyridine and 0.6 mL of acetic anhydride overnight, flash chromatography afforded 65 mg (60%) of **8** and 39 mg (36%) of a 1:1 mixture of (α)- and (β)-**4g**.

Route C. 2g (800 mg, 1.90 mmol) was treated as described for the preparation of **4a**. Flash chromatography (5:2 cyclo-

hexane–ethyl acetate) of the residue afforded 625 mg (60%) of a 4:1 mixture of (α)- and (β)-**4g**.

2-(2,3,4,6-Tetra-*O*-benzyl-α,β-D-glucopyranosyl)thiazole (5a). To a stirred mixture of (α)-**4a** (1.00 g, 1.50 mmol) and activated 4-Å powdered molecular sieves (1 g) in dry CH_2Cl_2 (12 mL) were added Et_3SiH (2.4 mL, 15 mmol) and TMSOTf (775 μL, 4.2 mmol). The mixture was stirred at room temperature for 30 min and then neutralized with Et_3N, diluted with CH_2Cl_2, filtered through Celite, and concentrated. The residue was eluted from a column of silica gel with petroleum ether–ethyl acetate (5:2) to give a 1:1 mixture of the two anomers (α)-**5a** and (β)-**5a** (856 mg, 94%). Pure samples of (α)-**5a** and (β)-**5a** were obtained by flash chromatography (30:1 toluene–acetone). Eluted first was (α)-**5a** as a syrup: $[\alpha]_D$ = +38.3°; ^1H NMR δ 3.66 (dd, 1 H, J = 2.0, 10.6 Hz), 3.73 (dd, 1 H, J = 3.3, 10.6 Hz), 3.79 (dd, 1 H, J = 8.7, 10.0 Hz), 3.96 (ddd, 1 H, J = 2.0, 3.3, 10.0 Hz), 4.03 (dd, 1 H, J = 6.0, 8.7 Hz), 4.30 (t, 1 H, J = 8.7 Hz), 4.47 and 4.62 (2 d, 2 H, J = 12.0 Hz), 4.50 and 4.81 (2 d, 2 H, J = 10.7 Hz), 4.68 and 4.76 (2 d, 2 H, J = 12.0 Hz), 4.80 and 4.95 (2 d, 2 H, J = 11.3 Hz), 5.29 (d, 1 H, J = 6.0 Hz), 7.05–7.40 (m, 21 H), 7.85 (d, 1 H, J = 3.1 Hz). Anal. Calcd for $C_{37}H_{37}NO_5S$: C, 73.12; H, 6.13; N, 2.30. Found: C, 73.07; H, 6.02; N, 2.41.

Eluted second was (β)-**5a** as a white solid: mp 112–113 °C (from AcOEt–hexane); $[\alpha]_D$ = +10.4°; ^1H NMR δ 3.62–3.88 (m, 6 H), 4.15 and 4.52 (2 d, 2 H, J = 10.1 Hz), 4.56 and 4.62 (2 d, 2 H, J = 11.5 Hz), 4.60 and 4.86 (2 d, 2 H, J = 10.8 Hz), 4.71 (m, 1 H), 4.89 and 4.95 (2 d, 2 H, J = 10.8 Hz), 7.00–7.40 (m, 20 H), 7.40 and 7.84 (2 d, 2 H, J = 3.1 Hz). Anal. Calcd for $C_{37}H_{37}NO_5S$: C, 73.12; H, 6.13; N, 2.30. Found: C, 73.25; H, 6.15; N, 2.28.

When Me_2PhSiH was used instead of Et_3SiH, a 2:1 mixture of the two anomers (α)-**5a** and (β)-**5a** was obtained in 93% yield. The use of nPr_3SiH did not improve the selectivity.

The reduction of (β)-**4a** with Et_3SiH, nPr_3SiH, and Me_2PhSiH showed initial partial conversion into the anomer (α)-**4a** and was completed after 50 min.

2-(2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)thiazole ((β-5b). (β)-**4b** (1.50 g, 2.25 mmol) was treated for 50 min as described for the preparation of **5a**. Flash chromatography (5:2 cyclohexane–ethyl acetate) of the residue afforded 1.30 g (96%) of (β)-**5b**: $[\alpha]_D$ = 0°, $[\alpha]_{436}$ = −3.9°; ^1H NMR δ 3.63 (d, 2 H, J = 6.5 Hz), 3.73 (dd, 1 H, J = 2.9, 9.4 Hz), 3.75 (dt, 1 H, J ~ 0.6, 6.5 Hz), 4.05 (dd, 1 H, J ~ 0.6, 2.9 Hz), 4.24 (t, 1 H, J = 9.4 Hz), 4.28 and 4.66 (2 d, 2 H, J = 10.6 Hz), 4.41 and 4.47 (2 d, 2 H, J = 11.8 Hz), 4.66 (d, 1 H, J = 9.4 Hz), 4.67 and 5.01 (2 d, 2 H, J = 11.8 Hz), 4.73 and 4.78 (2 d, 2 H, J = 10.6 Hz), 7.20–7.40 (m, 21 H), 7.80 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 68.6, 72.5, 73.4, 73.8, 74.4, 75.0, 77.7, 78.7, 79.4, 84.0, 119.8, 127.5–128.4, 137.9–138.9, 142.5, 167.9. Anal. Calcd for $C_{37}H_{37}NO_5S$: C, 73.12; H, 6.13; N, 2.30. Found: C, 72.91; H, 6.15; N, 2.29.

2-(2,3,4,6-Tetra-*O*-benzyl-β-D-mannopyranosyl)thiazole ((β-5c). (β)-**4c** (300 mg, 0.45 mmol) was treated for 50 min as described for the preparation of **5a**. Flash chromatography (5:2 cyclohexane–ethyl acetate) of the residue afforded 265 mg (97%) of (β)-**5c**: $[\alpha]_D$ = −19.8°; ^1H NMR δ 3.70 (dt, 1 H, J = 3.6, 9.5 Hz), 3.82 (dd, 1 H, J = 2.9, 9.5 Hz), 3.85 (d, 2 H, J = 3.6 Hz), 4.05 (t, 1 H, J = 9.5 Hz), 4.27 and 4.61 (2 d, 2 H, J = 11.5 Hz), 4.42 (dd, 1 H, J = 0.9, 2.9 Hz), 4.62 and 4.93 (2 d, 2 H, J = 11.0 Hz), 4.64 and 4.75 (2 d, 2 H, J = 12.0 Hz), 4.65 and 4.77 (2 d, 2 H, J = 11.5 Hz), 4.86 (d, 1 H, J = 0.9 Hz), 6.95–7.42 (m, 21 H), 7.75 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 69.4, 71.9, 73.6, 74.6, 75.2, 76.5, 78.5, 80.4, 83.7, 119.4, 127.3–128.5, 138.2–138.6, 142.0, 169.5. Anal. Calcd for $C_{37}H_{37}NO_5S$: C, 73.12; H, 6.13; N, 2.30. Found: C, 72.95; H, 6.09; N, 2.32.

2-(2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)thiazole ((β-5d). (β)-**4d** (210 mg, 0.35 mmol) was treated for 50 min as described for the preparation of **5a**. Flash chromatography (5:2 cyclohexane–ethyl acetate) of the residue afforded 184 mg (97%) of (β)-**5d**: $[\alpha]_D$ = −2.6°; ^1H NMR δ 3.59 (dd, 1 H, J = 2.5, 10.0 Hz), 3.62 (d, 2 H, J = 6.5 Hz), 3.74 (dt, 1 H, J ~ 0.8, 6.5 Hz), 4.03 (dd, 1 H, J ~ 0.8, 2.5 Hz), 4.21 (t, 1 H, J = 10.0 Hz), 4.42 and 4.48 (2 d, 2 H, J = 11.5 Hz), 4.48 (d, 1 H, J = 10.0 Hz), 4.62 and 4.94 (2 d, 2 H, J = 11.5 Hz), 4.72 and 4.78 (2 d, 2 H, J = 11.7 Hz), 7.25–7.45 (m, 16 H), 7.82 (d, 1 H, J = 3.2 Hz); ^{13}C NMR 63.3, 68.4, 72.2, 73.5, 74.5, 77.7, 77.8, 82.3, 120.2, 127.7–128.6, 137.5–138.5, 142.7, 167.1. Anal. Calcd for $C_{30}H_{30}N_4O_4S$: C, 66.40; H, 5.57; N, 10.32. Found: C, 66.24; H, 5.55; N, 10.36.

2-(2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl)-thiazole ((β-5e). (α)-**4e** (400 mg, 1.03 mmol) was treated as described for the preparation of **5a**. Flash chromatography (1:1 petroleum ether–ethyl acetate) of the residue afforded 312 mg (92%) of (β)-**5e** as a syrup: $[\alpha]_D$ = +52.8°; ^1H NMR δ 1.31, 1.41, 1.46, and 1.48 (4 s, 12 H), 3.78 (dd, 1 H, J = 3.5, 7.0 Hz), 4.16 (d, 2 H, J = 5.6 Hz), 4.51 (dt, 1 H, J = 5.6, 7.0 Hz), 4.91 (dd, 1 H, J = 3.5, 5.6 Hz), 4.99 (dd, 1 H, J = 3.5, 5.6 Hz), 5.05 (d, 1 H, J = 3.5 Hz), 7.36 and 7.81 (2 d, 2 H, J = 3.3 Hz); ^{13}C NMR δ 24.2, 25.2, 25.3, 26.7, 66.8, 73.0, 80.8, 81.6, 81.7, 81.9, 109.2, 113.2, 119.9, 142.1, 165.8. Anal. Calcd for $C_{15}H_{21}NO_5S$: C, 55.02; H, 6.46; N, 4.27. Found: C, 54.96; H, 6.48; N, 4.20.

2-(5-*O*-Benzyl-2,3-*O*-isopropylidene-α,β-D-ribofuranosyl)thiazole (5f). (α)-**4f** (518 mg, 1.03 mmol) was treated for 40 min as described for the preparation of **5a**. Flash chromatography (5:2 cyclohexane–ethyl acetate with 0.1% of Et_3N) of the residue afforded 101 mg (23%) of (β)-**5f** as an oil: $[\alpha]_D$ = −40.6°; ^1H NMR δ 1.37 and 1.61 (2 s, 6 H), 3.58 (dd, 1 H, J = 4.5, 10.0 Hz), 3.62 (dd, 1 H, J = 4.5, 10.0 Hz), 4.40 (dt, 1 H, J = 3.0, 4.5 Hz), 4.49 and 4.53 (2 d, 2 H, J = 12.0 Hz), 4.75 (dd, 1 H, J = 3.0, 6.5 Hz), 5.03 (dd, 1 H, J = 4.0, 6.5 Hz), 5.27 (d, 1 H, J = 4.0 Hz), 7.20–7.40 (m, 6 H), 7.76 (d, 1 H, J = 3.3 Hz); ^{13}C NMR δ 25.3, 27.2, 70.3, 73.4, 82.4, 84.5, 85.6, 114.4, 119.3, 127.6, 128.4, 137.8, 142.9, 170.4. Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.22; H, 6.09; N, 4.03. Found: C, 62.06; H, 6.10; N, 4.02.

Eluted second was oily (α)-**5f** (310 mg, 70%): $[\alpha]_D$ = −63.2°; ^1H NMR δ 1.29 and 1.42 (2 s, 6 H), 3.65 (dd, 1 H, J = 3.5, 10.5 Hz), 3.75 (dd, 1 H, J = 3.5, 10.5 Hz), 4.72 (dd, 1 H, J ~ 0.5, 3.5 Hz), 4.50 and 4.59 (2 d, 2 H, J = 12.0 Hz), 4.96 (dd, 1 H, J ~ 0.5, 6.0 Hz), 5.04 (dd, 1 H, J = 4.5, 6.0 Hz), 5.64 (d, 1 H, J = 4.5 Hz), 7.25–7.40 (m, 6 H), 7.80 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 24.3, 25.6, 71.6, 73.4, 82.3, 82.7, 83.1, 83.2, 112.6, 119.2, 127.4, 127.7, 128.3, 137.4, 141.9, 168.0. Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.22; H, 6.09; N, 4.03. Found: C, 62.37; H, 6.08; N, 4.02.

2-(2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl)thiazole ((α)-5g). (α)-**4g** (120 mg, 0.22 mmol) was treated for 40 min as described for the preparation of **5a**. Flash chromatography (5:2 cyclohexane–ethyl acetate) of the residue afforded 103 mg (96%) of (α)-**5g** as an oil: $[\alpha]_D$ = +18.0°; ^1H NMR δ 3.65 (dd, 1 H, J = 4.7, 10.5 Hz), 3.75 (dd, 1 H, J = 3.5, 10.5 Hz), 3.96 (dd, 1 H, J = 5.0, 6.5 Hz), 4.24 (dd, 1 H, J = 3.6, 5.0 Hz), 4.42 (ddd, 1 H, J = 3.5, 4.7, 6.5 Hz), 4.45 and 4.59 (2 d, 2 H, J = 11.7 Hz), 4.56 and 4.63 (2 d, 2 H, J = 12.0 Hz), 4.66 and 4.78 (2 d, 2 H, J = 12.0 Hz), 5.42 (d, 1 H, J = 3.6 Hz), 7.25–7.40 (m, 16 H), 7.78 (d, 1 H, J = 3.3 Hz); ^{13}C NMR δ 69.8, 71.8, 72.0, 73.2, 77.4, 81.2, 81.7, 81.8, 119.3, 127.5–128.3, 137.6–138.1, 142.9, 171.2. Anal. Calcd for $C_{29}H_{29}NO_4S$: C, 71.43; H, 5.99; N, 2.87. Found: C, 71.28; H, 6.01; N, 2.88.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-*aldehydo*-D-*glycero*-D-*ido*-heptopyranose ((α)-6a). A mixture of (α)-**5a** (92 mg, 0.15 mmol) and activated 4-Å powdered molecular sieves (300 mg) in dry CH_3CN (1.4 mL) was stirred at room temperature for 10 min, and then methyl triflate (22 μL, 0.19 mmol) was added. The suspension was stirred for 15 min and then concentrated to dryness. The crude *N*-methylthiazolium salt was suspended in MeOH (1.4 mL), cooled to 0 °C, and then treated with $NaBH_4$ (13 mg, 0.34 mmol). The mixture was stirred at room temperature for an additional 10 min, diluted with acetone (2 mL), filtered through Celite, and concentrated. To the solution of the crude thiazolidine in 10:1 CH_3CN–H_2O (1.4 mL) was added $HgCl_2$ (41 mg, 0.15 mmol). The mixture was stirred for 15 min and then filtered through Celite. Acetonitrile was evaporated (bath temperature not exceeding 40 °C). The residue was suspended in CH_2Cl_2 (5 mL) and washed with 20% aqueous KI (3 × 5 mL) and water (5 mL); the organic layer was dried (Na_2SO_4) and concentrated to give a syrup, which was diluted with 4 mL of Et_2O and filtered through a short pad of Florisil (100–200 mesh) to afford a

colorless solution. After a further washing of Florisil with AcOEt (1.5 mL), the organic phase was concentrated to yield 60 mg (72%) of the syrupy aldehyde (α)-**6a** contaminated by 10% of (β)-**6a**.

(α)-**6a**: ^{1}H NMR selected data δ 4.40 (d, 1 H, J = 6.0 Hz), 9.98 (s, 1 H).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-*aldehydo*-D-*glycero*-D-*gulo*-heptopyranose ((β)-6a). (β)-**5a** (100 mg, 0.16 mmol) was treated as described for the preparation of (α)-**6a** to afford 69 mg (76%) of almost pure (NMR analysis) (β)-**6a** as an oil: ^{1}H NMR δ 3.48 (m, 1 H), 3.58–3.80 (m, 5 H), 3.84 (dd, 1 H, J = 1.3, 9.1 Hz), 4.56 and 4.63 (2 d, 2 H, J = 12.1 Hz), 4.65 and 4.82 (2 d, 2 H, J = 9.9 Hz), 4.90 (s, 2 H), 7.11–7.44 (m, 20 H), 9.65 (d, 1 H, J = 1.6 Hz).

A 1:1 mixture of (α)-**5a** and (β)-**5a** (400 mg, 0.65 mmol) was treated as described for the preparation of (α)-**6a** to give a mixture of (α)-**6a** and (β)-**6a**. This mixture was dissolved in 7 mL of CH_2Cl_2, 5.5 mL of *i*PrOH, and 1.3 mL of Et_3N. After 24 h, at room temperature, the solution was concentrated to afford a 1:20 mixture of (α)-**6a** and (β)-**6a** contaminated by 10% of a byproduct probably derived from the elimination of the benzyloxy group at C-2. Flash chromatography on a short pad of silica gel (5:3 cyclohexane–ethyl acetate) afforded 219 mg (60%) of (β)-**6a**.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-*aldehydo*-D-*glycero*-L-*manno*-heptopyranose ((β)-6b). (β)-**5b** (1.00 g, 1.64 mmol) was treated as described for the preparation of (α)-**6a** to give 727 mg (80%) of almost pure (NMR analysis) (β)-**6b** as an oil: ^{1}H NMR (DMSO-d_6, 180 °C) δ 3.64 (dd, 1 H, J = 6.4, 9.6 Hz), 3.70 (dd, 1 H, J = 5.3, 9.6 Hz), 3.80–3.88 (m, 3 H), 4.03 (t, 1 H, J = 8.6 Hz), 4.08 (dd, 1 H, J ~ 0.8, 2.3 Hz), 4.50 and 4.54 (2 d, 2 H, J = 10.7 Hz), 4.69 and 4.84 (2 d, 2 H, J = 11.8 Hz), 4.64 and 4.77 (2 d, 2 H, J = 10.7 Hz), 7.20–7.40 (m, 20 H), 9.60 (d, 1 H, J = 1.4 Hz).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-*aldehydo*-D-*glycero*-D-*galacto*-heptopyranose ((β)-6c). (β)-**5c** (100 mg, 0.16 mmol) was treated as described for the preparation of (α)-**6a** to give 68 mg (75%) of almost pure (NMR analysis) (β)-**6c** as an oil: ^{1}H NMR (DMSO-d_6, 140 °C) δ 3.56 (ddd, 1 H, J = 2.3, 4.6, 9.2 Hz), 3.73 (dd, 1 H, J = 4.6, 11.5 Hz), 3.79 (dd, 1 H, J = 2.3, 11.5 Hz), 3.80 (dd, J = 2.8, 9.2 Hz), 3.88 (t, 1 H, J = 9.2 Hz), 4.06 (d, 1 H, J = 1.0 Hz), 4.45 (dd, 1 H, J = 1.0, 2.8 Hz), 4.48–4.83 (m, 8 H), 7.15–7.45 (m, 20 H), 9.55 (s, 1 H).

2,6-Anhydro-3-azido-4,5,7-tetra-*O*-benzyl-3-deoxy-*aldehydo*-D-*glycero*-L-*manno*-heptopyranose ((β)-6d). (β)-**5d** (150 mg, 0.25 mmol) was treated as described for the preparation of (α)-**6a** to give 98 mg (72%) of almost pure (NMR analysis) (β)-**6d** as an oil: ^{1}H NMR (DMSO-d_6, 140 °C) δ 3.58–3.70 (m, 2 H), 3.74 (dd, 1 H, J = 1.1, 9.9 Hz), 3.77 (dd, 1 H, J = 2.7, 9.9 Hz), 3.84 (dt, J = 1.0, 5.5 Hz), 3.89 (t, 1 H, J = 9.9 Hz), 4.08 (dd, 1 H, J = 1.0, 2.7 Hz), 4.48 and 4.53 (2 d, 2 H, J = 11.5 Hz), 4.55 and 4.79 (2 d, 2 H, J = 11.3 Hz), 4.71 and 4.81 (2 d, 2 H, J = 11.5 Hz), 7.20–7.45 (m, 15 H), 9.58 (d, 1 H, J = 1.1 Hz).

2,5-Anhydro-3,4:6,7-di-*O*-isopropylidene-*aldehydo*-D-*glycero*-D-*galacto*-heptofuranose ((β)-6e). (β)-**5e** (300 mg, 0.91 mmol) was treated as described for the preparation of (α)-**6a** to give 195 mg (78%) of almost pure (NMR analysis) (β)-**6e** as an oil: ^{1}H NMR δ 3.65 (dd, 1 H, J = 3.2, 7.6 Hz), 4.02 (dd, 1 H, J = 1.0, 4.3 Hz), 4.08–4.18 (m, 2 H), 4.45 (dt, 1 H, J = 5.3, 7.6 Hz), 4.83 (dd, 1 H, J = 3.2, 5.4 Hz), 5.06 (dd, 1 H, J = 4.3, 5.4 Hz), 9.64 (d, 1 H, J = 1.0 Hz).

2,5-Anhydro-6-*O*-benzyl-3:4-*O*-isopropylidene-*aldehydo*-D-*altro*-hexofuranose ((α)-6f). (α)-**5f** (300 mg, 0.86 mmol) was treated as described for the preparation of (α)-**6a** to give 192 mg (76%) of almost pure (NMR analysis) (α)-**6f** as an oil: ^{1}H NMR δ 1.30 and 1.45 (2 s, 6 H), 3.59 (dd, 1 H, J = 3.0, 10.2 Hz), 3.68 (dd, 1 H, J = 2.5, 10.2 Hz), 4.43 (ddd, 1 H, J ~ 0.4, 2.5, 3.0 Hz), 4.47 and 4.54 (2 d, 2 H, J = 11.5 Hz), 4.60 (dd, 1 H, J = 1.2, 5.0 Hz), 4.86 (dd, 1 H, J ~ 0.4, 6.0 Hz), 5.10 (dd, 1 H, J = 5.0, 6.0 Hz), 7.25–7.40 (m, 5 H), 9.59 (d, 1 H, J = 1.2 Hz); ^{13}C NMR δ 24.3, 25.8, 71.9, 73.6, 82.7, 82.9, 84.0, 86.7, 113.2, 127.5, 127.9, 128.5, 137.5, 199.2.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*aldehydo*-D-*altro*-hexofuranose ((α)-6g). (α)-**5g** (100 mg, 0.20 mmol) was treated as described for the preparation of (α)-**6a** to give 65 mg (74%) of almost pure (NMR analysis) (α)-**6g** as an oil: ^{1}H NMR (DMSO-d_6, 140 °C) δ 3.60 (dd, 1 H, J = 4.7, 11.0 Hz), 3.66 (dd, 1 H, J = 3.6, 11.0 Hz), 3.97 (dd, 1 H, J = 4.9, 5.2 Hz), 4.24 (ddd, 1 H, J = 3.6, 4.7, 4.9 Hz), 4.27 (dd, 1 H, J = 4.8, 5.2 Hz), 4.36 (dd, 1 H, J = 1.5, 4.8 Hz), 4.54 (s, 2 H), 4.56 and 4.64 (2 d, 2 H, J = 11.7 Hz), 4.63 (s, 2 H), 7.20–7.40 (m, 15 H), 9.58 (d, 1 H, J = 1.5 Hz).

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Note added in proof: We recently became aware (Sept 1994) of a similar strategy to ours (present work and *Tetrahedron Lett.* **1993**, *34*, 7319) wherein 1,3-dithiane and phenylacetylene have been employed as precursors to the formyl group (Lasterra Sanchez, M. E.; Michelet, V.; Besnier, I.; Genêt, J. P. *Synlett* **1994**, 705). These approaches were applied to tetrabenzylgluconolactone and mannonolactone diacetonide to give the corresponding *C*-glycosyl aldehydes in lower yields (40–58 and 14–33%, respectively) than those reported here (60 and 65%).

Supplementary Material Available: A listing of ^{1}H and ^{13}C NMR data with peak assignments for compounds **2b**, **2d**, **3a–f**, **4a–g**, **5a–g**, and **6a–g** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.