Methyl (±)-[1*R,5*R**,9*S**(*R**)]-9-(1-Bromoethyl)-2,8-dioxabicyclo[3.3.1]nona-3,6-diene-4-carboxylate (19).** Hemiacetal **18** (6 mg, 0.020 mmol) and CSA (5 mg, 0.022 mmol) in $CDCl_3$ were held at 80 °C for 7 h. The mixture was directly purified by MPLC (3:1 hexanes/EtOAc) to give the ester **19** (5.0 mg, 87%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, *H*C=CCO$_2$R), 6.42 (d, *J* = 5.8 Hz, HC=C*H*OR), 6.05 [dd, *J* = 2 and 2 Hz, (RO)$_2$C*H*], 5.15 (ddd, *J* = 7.0, 5.8, and 1.4 Hz, *H*C=CHOR), 4.06 (dq, *J* = 10.7 and 6.7 Hz, C*H*Br), 3.74 (s, CO$_2$C*H*$_3$), 3.34 [ddd, *J* = 6.9, 2.4, and 2.4 Hz, (=CR)$_2$C*H*], 2.01 (ddd, *J* = 10.8, 2, and 2 Hz, BrCC*H*), and 1.77 (d, *J* = 6.7 Hz, RC*H*$_3$); IR ($CDCl_3$) 2965, 2940, 1710, 1655, 1640, 1445, 1305, 1230, 1160, 1095, and 1055 cm^{-1}; MS [CI (NH_3)], *m/z* (relative intensity) negative ion 306 (M + NH_2^-, 11.6), 304 (M + NH_2^-, 11.3), 226 (38.3), 225 (38.3), 81 (96.8), and 79 (100), positive ion 308 (M + NH_4^+, 99.1), 306 (M + NH_4^+, 100), and 244 (94.3).[10b]

Methyl (±)-[1*R,5*S**,7*R**,9*S**(*S**)]-7-Hydroxy-9-(1-methoxyethyl)-2,8-dioxabicyclo[3.3.1]non-3-ene-4-carboxylate (22).** The diene esters **12** (109 mg, 0.36 mmol) were dissolved in MeOH (5 mL) and cooled to −78 °C. A stream of ozone in oxygen was bubbled through the solution until a blue color persisted. Dimethyl sulfide (3 mL) was added, and the reaction was allowed to stand at room temperature for 24 h. Concentration and purification by MPLC (2:1 hexanes/EtOAc) gave the hemiacetal **22** (56 mg, 60%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, =C*H*OR), 5.70 [dd, *J* = 2 and 2 Hz, RC*H*(OR)$_2$], 5.18 (dd, *J* = 9.7 and 3.6 Hz, C*H*OH), 3.74 (s, CO$_2$C*H*$_3$), 3.39 (s, ROC*H*$_3$), 2.89 (dq, *J* = 3 and 6.1 Hz, C*H*OCH$_3$), 2.9 (m, =CC*H*R$_2$), 2.1 (m, R$_2$C*H*COMe), 1.84 (ddd, *J* = 13.6, 3.6, and 3.6 Hz, R$_2$C*H*H), 1.57 (ddd, *J* = 13.6, 9.7, and 3.6 Hz, R$_2$CH*H*), and 1.24 (d, *J* = 6.2 Hz, RC*H*$_3$); IR ($CDCl_3$) 3500 (br), 3000, 2980, 2960, 2840, 1700, 1630, 1440, 1300, 1150, 1100, 1050, 1020, 948, 905, and 875 cm^{-1}; MS (EI), *m/z* (relative intensity) 258 (0.2), 226 (2.1), 181 (6.3), 180 (4.5), 165 (3.6, 139 (6.7), and 59 (100). Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.86; H, 7.05.

Methyl (±)-[1*R,5*R**,9*R**(*R**)]-9-(1-Methoxyethyl)-2,8-dioxabicyclo[3.3.1]nona-3,6-diene-4-carboxylate (23).** Ester **22** (5 mg, 0.02 mmol) and CSA (5 mg, 0.02 mmol) were warmed to 100 °C in $CDCl_3$ (0.5 mL) for 2 h. The mixture was directly purified by MPLC (4:1 hexanes/EtOAc) to give the ester **23** (3.0 mg, 63%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, *H*C=CCO$_2$R), 6.39 (d, *J* = 5.8 Hz, HC=C*H*OR), 5.96 [dd, *J* = 2.3 and 2.3 Hz, (RO)$_2$C*H*], 5.15 (dd, *J* = 6.4 and 6.4 Hz, *H*C=CHOR), 3.73 (s, CO$_2$C*H*$_3$), 3.33 (s, ROC*H*$_3$), 3.30 (dq, *J* = 10.2 and 6.0 Hz, C*H*OMe), 3.12 [ddd, *J* = 6.9, 2.7, and 2.2 Hz, (=CR)$_2$C*H*], 1.4 [m, R$_2$C*H*CH(OR)$_2$], and 1.18 (d, *J* = 6.1 Hz, RC*H*$_3$).[10b]

(±)-Sarracenin (1). Hemiacetal **22** (5 mg, 0.02 mmol) was dissolved in CH_2Cl_2 (50 μL) and treated with boron tribromide (20 μL, 0.02 mmol) at room temperature. After 4 h, the solution was concentrated and purified by MPLC (3:1 hexanes/EtOAc) to provide (±)-sarracenin (**1**, 1.4 mg, 31%).

As an alternative, the ester alcohol **13** (35 mg, 0.133 mmol) was dissolved in MeOH (5 mL), cooled to −78 °C, and treated with an ozone stream until a blue color persisted. Dimethyl sulfide (1 mL) was added, and the mixture was warmed to room temperature and allowed to stand for 12 h. The solution was concentrated, and the residue was dissolved in 90% AcOH (0.5 mL). After 1 h at 60 °C, the AcOH was removed under reduced pressure and the material purified by MPLC to provide **1** (14.1 mg, 47%). Recrystallization from hexanes/EtOAc gave the following: mp 108–109 °C (lit.[3a] mp 107–108 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, RO*H*C=CCO$_2$R), 5.78 [br s, RC*H*OR(OC=C)], 4.98 [d, *J* = 3.2 Hz, RC*H*(OR)$_2$], 4.21 (q, *J* = 6.4 Hz, R$_2$C*H*CH$_3$), 3.75 (s, CO$_2$C*H*$_3$), 2.97 (m, *J* values include 10.7 and 2 Hz, =CC*H*R$_2$), 2.37 (br dd, *J* = 13.9 and 10.6 Hz, R$_2$C*H*H), 1.71 [m, R$_2$CH*H* and R$_2$C*H*CH(OR)$_2$], and 1.34 (d, *J* = 6.5 Hz, RC*H*$_3$); IR ($CDCl_3$) 2900, 2600, 1709, 1647, 1442, 1303, 1254, 1174, 1111, 1097, 1080, 935, and 905 cm^{-1}; MS (EI), *m/z* (relative intensity) 227 (4.1), 226 (29.6), 180 (50.2), 165 (36.7), 148 (41.2), 139 (40.1), 137 (30.7), 123 (46.1), 121 (40.8), 109 (24.7), 96 (41.9), 95 (50.6), 69 (55.8), 59 (61.8), and 41 (100); HRMS calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0836. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 57.96; H, 6.14.

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Iterative, Stereoselective Homologation of Chiral Polyalkoxy Aldehydes Employing 2-(Trimethylsilyl)thiazole as a Formyl Anion Equivalent. The Thiazole Route to Higher Carbohydrates[1]

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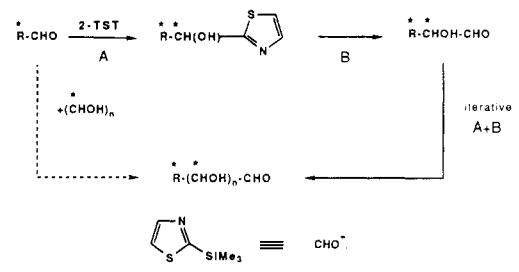
A new approach to long-chain sugars is demonstrated by the stereoselective conversion of D-glyceraldehyde acetonide (**2a**), L-threose acetonide (**2b**), and dialdogalactopyranose diacetonide (**2h**) into higher homologues up to C_9, C_7, and C_{10} terms, respectively, and with an all-anti configuration of vicinal hydroxy groups in the constructed chain. The methodology consists of the iterative repetition of a linear one-carbon chain extension that involves two very efficient (chemically and stereochemically) key operations: (A) the anti diastereoselective addition of 2-(trimethylsilyl)thiazole (**1a**) to the chiral alkoxy aldehyde; (B) the unmasking of the formyl group from the thiazole ring in the resulting adduct. The conversion of thiazole D-ribose **9a** into protected 2-deoxy- and 2,5-dideoxy-D-ribose (**28** and **30**) demonstrates the synthetic potential of thiazole masked sugars.

We report here a new and effective protocol[2] that is centered on the use of 2-(trimethylsilyl)thiazole (2-TST) (**1a**) as a synthetic equivalent to the formyl anion synthon[3] for the construction of long-chain polyhydroxylated aldehydes (carbohydrate-like materials) with high stereoselectivity and chemical efficiency starting from relatively simple and readily available chiral alkoxy aldehydes and dialdoses. The strategy, in essence, consists of repetition of sequence A and B (Scheme I), which involves as a whole a linear one-carbon chain elongation by creating a new chiral hydroxymethylene center. The chemical and stereochemical efficiency of this protocol is based on the high reactivity and stereoselectivity of **1a** in sequence A and the ready and effective aldehydic release in sequence B.

(1) Thiazole Route to Carbohydrates: Synthesis of Building Blocks or Precursors to Carbohydrates with the Use of Functionally Substituted Thiazoles as Auxiliaries.

0022-3263/89/1954-0693$01.50/0

Scheme I



Polyhydroxylated carbon compounds such as carbohydrates and related materials own a significant importance for their biological activity[4] and/or for their use as chiral precursors[5] to a variety of complex natural products in which they are incorporated such as macrolides[6] and antitumor[7] antibiotics, nucleosides,[8] and palytoxin-type compounds.[9] Since rare or unnatural target molecules of this type are often the most important, many efforts have been made in recent years to develop new and general approaches for de novo stereoselective total synthesis of carbohydrates as well as related polyhydroxylated natural products starting from non-carbohydrate materials. Thus, various methods leading to units with more than two consecutive hydroxymethylene centers via carbon–carbon and carbon–heteroatom bond formation reactions in stereoselective acyclic and cyclic manner[10,11] have been reported. However, since only few approaches involve processes that can be reiterated,[12] relatively small molecular fragments are frequently obtained. Thus, alternative methods are desiderable. We now report in full the results of a new, efficacious, and wide scope approach to 1,2-polyhydroxyacyclic chains with anti configuration of hydroxy groups in the constructed chain. In the first part of the report we present results relating to the scope of the addition of 2-TST (**1a**) to chiral alkoxy aldehydes as well as to the convenience of the thiazole ring as a masked formyl group. In the second part we show the application of the thiazole addition–unmasking sequence to two α,β-dialkoxy aldehydes and a dialdose to give in each case a series of higher homologues with up to ten carbon atoms (Thiazole Route to Carbohydrates).[1]

Results and Discussion

Stereochemical Studies. For an efficacious and tactically novel methodology for chain-lengthening of alkoxy aldehydes via nucleophilic addition of an organometal, one essentially needs to have a reagent that, in addition of being readily available and enough reactive, owns a fragment that can be converted into the formyl group. Following our earlier work on the synthesis of functionally substituted thiazoles through their silyl and stannyl derivatives,[13] we thought that 2-(trimethylsilyl)thiazole (**1a**) could be used as a convenient synthetic auxiliary[14] since (i) it can be easily and economically prepared;[15] (ii) it may be stored indefinitely without particular care; (iii) it is a very effective reagent for the 2-thiazolyl donor synthon toward various carbon electrophiles, including aldehydes;[15] and (iv) the thiazole[16a] or thiazoline ring[16b] can release the

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(12) Iterative homologation of aldehydes: (a) Masamune–Sharpless olefination–epoxidation (ref 11f). (b) Danishefsky cyclocondensation (ref 10i). (c) Solladié olefination–condensation (ref 11n). Hanessian replicating lactonization–hydroxylation (ref 11g). Matteson haloalkyl insertion in benzyloxy-substituted boronic esters (ref 11o).

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(14) For conceptually related approaches to carbohydrates or related polyoxygenated compounds that rely on formation of the carbon–carbon bond of a vicinal diol by nucleophilic addition of metalated heterocycles (lithiofurans) to hydroxy aldehydes, see ref 10e, 11a, and 11m.

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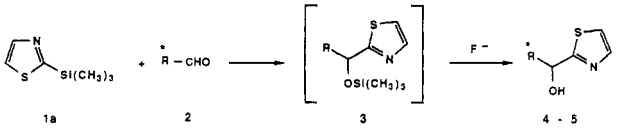
Table I



1a 2 3 4 - 5

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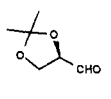
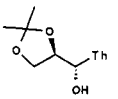
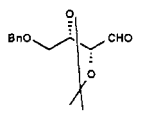
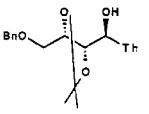
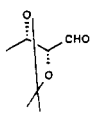
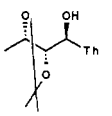
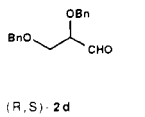
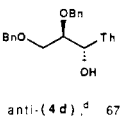
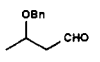
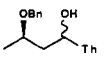
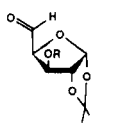
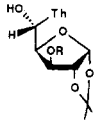
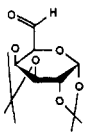
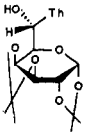
 2a	0	 anti-(4a), ≥95	96
 2b	0	 anti-(4b), 90	89
 2c	rt	 anti-(4c), ≥95	76
 (R,S)-2d	0	 anti-(4d),[d] 67	75
 (R,S)-2e	rt	 anti-(4e) + syn-(5e),[d,e] 50 : 50	70
 2f, R = Me 2g, R = Bn	0	 4f, R = Me, ≥95 4g, R = Bn, ≥95	84 80
 2h	0	 4h, ≥95	85

[a] Th = 2-thiazolyl. Only the major diastereoisomer is shown, the minor one having the opposite configuration at the newly formed diastereogenic center. Syn–anti nomenclature notation is employed (ref 21). [b] Degree of diastereoselectivity (ds %) (ref 20). Product ratios from integrated methine signals (see Experimental Section) of anti and syn isomers in the crude reaction mixture after desilylation. [c] Values refer to isolated total yields. [d] Racemic product. [e] Unassigned stereochemistry to these products.

formyl group. Further insights on points iii and iv given in this and the next section reaffirm our choice of **1a**.

Results on the reactivity and stereoselectivity of **1a** toward chiral alkoxy aldehydes are collected in Table I. The addition of **1a** to 2,3-*O*-isopropylidene-D-glyceraldehyde (**2a**),[10e,17] 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose (**2b**),[17,18] and (2*R*,3*S*)-4-deoxy-2,3-*O*-isopropylidene-L-threose (**2c**),[17,19] which are quite common compounds for stereochemical tests and useful starting material for stereoselective synthesis, occurred smoothly under very mild conditions and with high levels of diastereofacial selectivity[20] to give after in situ desilylation of the resulting adducts **3a–c**, the anti (α-hydroxyalkyl)thiazoles **4a–c** as major products (90–95% ds) in excellent isolated yields. The anti configuration[21] about the newly formed 1,2-diol unit in polyols **4a–c** was assigned on the basis of various arguments. First, it is that expected on the basis of the Felkin–Anh open-chain model for asymmetric induction[22] and corresponds to that which is obtained in nucleophilic addition of nonchelating organometals to α,β-dialkoxy aldehydes,[23] including of course **2a–c**. Second, compounds **4a–c** can be transformed[24] through the corresponding ketones (OH oxidation, CO reduction) into the minor isomers **5a–c** under conditions that usually provide syn selectivity. Third, the NMR spectra of compounds **4a–c** (see Experimental Section) show significant and similar differences from those of **5a–c**.[24] For instance, the chemical shifts of the methine proton of the newly formed hydroxymethylene center in **4a–c** were uniformly at lower field than those in **5a–c**. Finally, the stereochemistry of **4a** was confirmed by X-ray crystal structure determination and NMR studies of higher homologues (vide infra). Hence, assuming the Felkin–Anh open-chain model for asymmetric induction[22] and the stepwise mechanism via thiazolium 2-ylide as an intermediate that we have suggested for the reaction of **1a** with C-electrophiles including aldehydes,[15] a schematic transition state for the addition of **1a** to **2a** is presented in Figure 1. The interaction

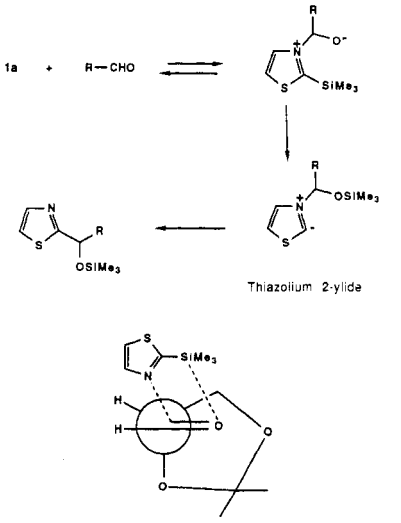
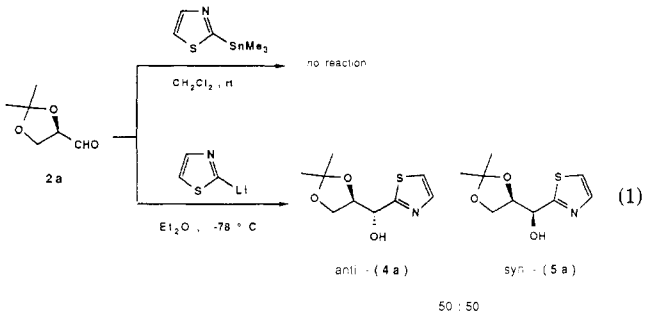


Figure 1. Proposed mechanism (ref 15) for the reaction of **1a** with aldehydes and Felkin–Anh transition-state model for the addition of **1a** to **2a**.

(17) For references to the use of aldehydes **2a–c** in the synthesis of carbohydrates and related natural products, see ref 10a.
(18) Mukaiyama, T.; Suzuki, K.; Yamada, T. *Chem. Lett.* **1982**, 929.
(19) Servi, S. *J. Org. Chem.* **1985**, *50*, 5866.
(20) Throughout the paper, the degree of diastereoselectivity is given as % ds, that is the percentage of the *major* diastereomer in the mixture. See, for instance: Seebach, D.; Helmchen, G.; Brown, A. C. "Synthesis of Enantiomerically Pure Compounds" in *Modern Synthetic Methods 1986*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; p 125.
(21) The relative configuration is assigned as anti or syn according to the definition of Masamune (Masamune, S.; Ali, A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521).
(22) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(23) For reviews and recent studies, see ref 10a and (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. Reetz, M. T.; Kesseler, K. *J. Org. Chem.* **1985**, *50*, 5435. (b) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (c) Mead, K.; McDonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.
(24) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.*, accompanying note in this issue.

between silicon of the trimethylsilyl group and oxygen of the carbonyl as shown provides an additional factor for a very tight transition state that should favor the high degree of diastereoselectivity observed.[25] Consistent with this hypothesis, the reaction of 2-lithiothiazole (**1b**) with **2a** was found to be nonselective and 2-(trimethylstannyl)thiazole (**1c**) was unreactive[26] (eq 1). Hence the trimethylsilyl group at C-2 of the thiazole ring is essential for both good reactivity and stereoselectivity.



(1)

In contrast to that observed for the α,β-dihydroxy aldehyde acetonides **2a–c**, the addition of 2-TST (**1a**) to (*R,S*)-di-*O*-benzylglyceraldehyde (**2d**) afforded the Felkin–Anh anti isomer **4d** with poor selectivity[27] (ds 67%) and the addition to the β-alkoxy aldehyde (*R,S*)-3-(benzyloxy)butyraldehyde (**2e**) was fairly unselective (**4e**:**5e** = 50:50) (Table I). On the other hand, usually high levels of diastereofacial selectivity were observed in the addition of **1a** to the D-xylose- and D-galactose-derived aldehydes **2f,g** and **2h** to give, after desilylation, the corresponding thiazole–sugar adducts **4f,g** and **4h** in very good yields. Substantially lower levels of diastereoselectivity have been reported[28] in the addition of other organometallic reagents to dialdoses **2f,g** and **2h**. We have already provided[2d] experimental evidence supporting the assigned stereochemistry at the newly formed hydroxymethylene center in **4f–h** and commented that this stereochemical outcome is in agreement with the non-chelate Felkin–Anh model for asymmetric induction.[22] Specifically the attack of 2-TST (**1a**) should occur on the aldehyde conformer shown in Table I and from the *re* face. In conclusion, from the above results it appears that silylthiazole **1a** is a very effective nucleophile toward α,β-dialkoxy aldehydes and dialdoses to give the expected Felkin–Anh–Houk adducts[29] in quite high diastereomeric excess.

Formyl Group Deblocking. The next step for the success of the homologation protocol of Scheme I was the aldehydic release from the chiral (α-hydroxyalkyl)thiazole. Methods for the conversion of 2-alkyl-substituted thiazoles[16a] and thiazolines[16b] have been reported, dealing however with compounds not bearing asymmetric centers in the alkyl chain. On the other hand, it is evident that the methodology required here must be efficient and leave intact the chirality at the various hydroxymethylene centers that are constructed through the homologation process. Hence, each step for the formyl group deblocking in the adduct **4a** was examined for a complete evaluation of the efficiency of the method (Scheme II). First, the hydroxy group was protected[30] as the *O*-benzyl ether **4a′**. The subsequent step, viz. the formation of the thiazolium N-quaternary salt, was quite crucial since we found the methylation under the conditions described by Altman and Richheimer[16a] ($MeO^+BF_4^-$, SO_2) unpractical for large scale preparations and producing a gummy material difficult to handle and purify. After several attempts under a variety of conditions using dimethyl sulfate and methyl iodide as alkylating agents in polar solvents, the best results were obtained with an 8–10 M excess of methyl iodide in refluxing acetonitrile. Under these conditions the alkylthiazole *O*-benzyl ether **4a′** was transformed into the corresponding *N*-methylthiazolium iodide **6a**, which was isolated as pure crystalline material in almost quantitative yield. The sodium borohydride exhaustive reduction of **6a** gave the thiazolidine **7a** (1:1 mixture of diastereoisomers), which was hydrolyzed in the presence of mercuric chloride to the trialkoxybutanal **8a** (D-threose). A careful examination of the NMR spectra of intermediates **4a′**, **6a**, and **7a** as well as of the final product **8a** showed that these compounds were *diastereomerically pure*,[31] thus proving that no substantial racemization occurs at the chiral hydroxymethylene group in the course of the aldehyde-releasing sequence.[32] In addition to that, on repeating the deblocking sequence by a one-pot procedure, viz. without the isolation and purification of intermediates, the aldehyde **8a** was obtained from **4a** in 62% overall yield. The same thiazole–formyl deblocking procedure was successfully applied to thiazole–dialdose adducts[2d] **4f,g** and **4h** and more recently to the thiazole–serinal adduct[2e] as well as to a thiazole aminofuranoside.[33] Hence it appears that the thiazole ring is an excellent latent formyl group equivalent since it associates the properties of stability toward hydrolysis in both acid and base and toward oxidation and reduction[34] to the ability of yielding the aldehydic group under conditions that do not affect functional groups[35] and chiral centers. Hence, the thiazole nucleus appears to be a convenient alternative to other precursors for the formyl group that are currently employed.[36]

Linear Iterative Homologation. Encouraged by the above results showing the effective equivalence between 2-TST (**1a**) and the formyl anion through the two sequences A (addition) and B (unmasking) (Scheme I), we

(25) This hypothesis implies that the new asymmetric center is created in the early equilibrium leading to the thiazolium N-quaternary intermediate and that the chirality is maintained throughout the subsequent steps, i.e., the formation of the 2-ylide and the rearrangement of the latter into the product by 1,2-shift of the *N*-alkyl chain. However, since at present we cannot exclude that the latter step occurs by a bimolecular process (ref 15) involving the diastereoselective addition of the ylide to another molecule of aldehyde, other work is underway in our laboratory to better define this mechanistic scheme.

(26) No reaction was observed (THF, −78 °C) by addition of zinc chloride (1 equiv) to 2-lithiothiazole and with the use of 2-thiazolylmagnesium bromide.

(27) The identical sense of diastereoselectivity (anti) has been reported (ref 23c) in the addition to **2a** and **4a** by a nonchelating titanium reagent ($MeTi(O\text{-}i\text{-}Pr)_3$) (ref 23a). Results from further studies on the diastereoselectivity of addition of **1a** to various chiral aldehydes will appear in a forthcoming paper.

(28) For leading references, see 2c.

(29) Recently Houk and co-workers have reported ab initio calculations supporting the Felkin–Anh model for asymmetric induction: Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. Wu, Y.-D.; Houk, K. N. *Ibid.* **1987**, *109*, 906 and 908.

(30) Other protecting groups were used in parallel studies: $OSiPh_2$-(*tert*-butyl), $OCOCH_3$. We also observed that the hydroxy group protection is not a prerequisite in the deblocking procedure.

(31) Only occasionally was the formation of the epimer of **4a′** (5–10%) observed in the benzylation step.

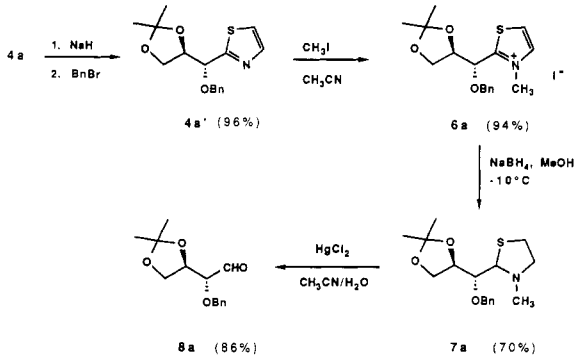
(32) The most pessimistic event that cannot be ruled out on the basis of this simple NMR study is that inversion had occurred at *both* chiral centers. However, this is very unlikely on the basis of parallel experiments carried out in our laboratory. For instance: (*S*)-*O*-benzyllactaldehyde can be released from (*S*)-*O*-benzyl-(2-hydroxyethyl)thiazole without racemization.

(33) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 3215.

(34) For a review on thiazole chemistry, see also: Metzger, A. I. *The Chemistry of Heterocyclic Compounds. Thiazole and its Derivatives*; Wiley: New York, 1979; Vol. 34.

(35) An inconvenient exception occurs with 2-vinylthiazoles that lead to saturated aldehydes instead of α,β-enals. See: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 2021.

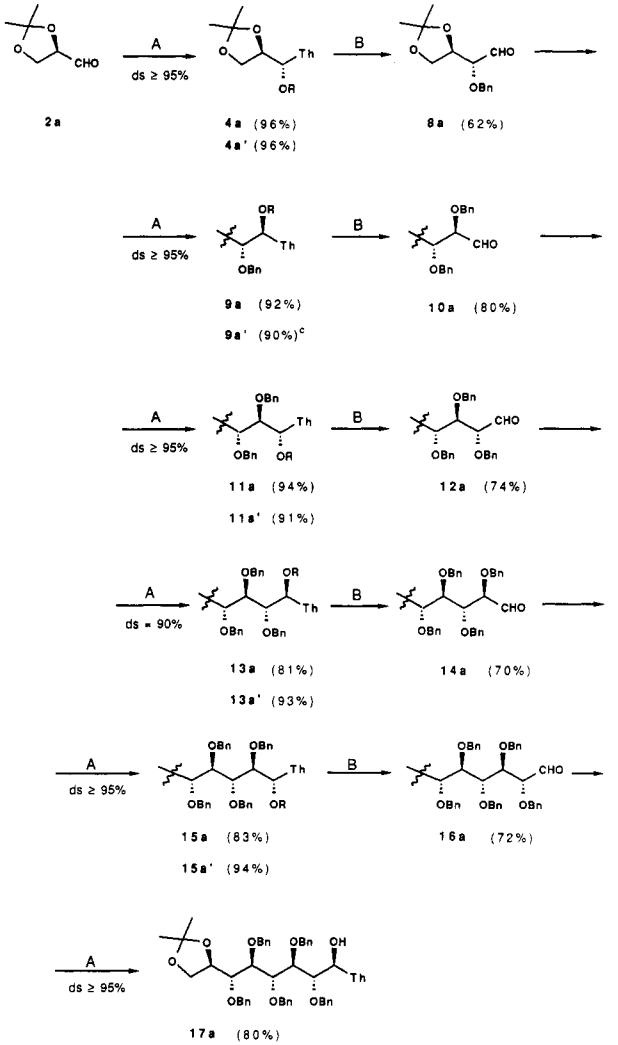
Scheme II



decided to apply iteratively this principle in order to define its scope toward long-chain polyhydroxylated aldehydes. Thus, it was extremely gratifying to find that repetition of the linear one-carbon chain-elongation sequence A and B over six consecutive cycles transformed D-glyceraldehyde acetonide (**2a**) into a series of higher homologues up to the *nine* carbon atom compound **17a**[37] (Scheme III). In the general procedure adopted, sequences A and B involved the following sequential operations: (A) (i) reaction of the aldehyde with 2-TST (**1a**), (ii) O-benzylation; (B) (i) N-quaternization, (ii) reduction, (iii) hydrolysis. The fairly good chemical yields of the products reported in Scheme III indicated that the various transformations in each sequence occured as a rule with great chemical and stereochemical effectiveness. In particular, the addition of 2-TST (**1a**) to each aldehyde over the six consecutive cycles maintained high levels of anti diastereoselectivity (ds 90–95%) in agreement with the aforementioned Felkin–Anh–Houk open-chain model for asymmetric induction.[29] Hence, the formation of the thiazole D-nonose **17a** does not appear to be the upper limit of application of this chain-elongation methodology. Two pieces of experimental evidence proved the all-anti configuration for 1,2-polyols **4a** and **8a**–**17a**. The first consisted of the X-ray structure analysis of the thiazole *D*-ribose **9a**.[38] The second was provided by the elaboration of the thiazole *D*-octose **15a** into the *meso*-octitol (**20**) (Scheme IV) whose configuration is supported by its optical inactivity and the very simple patterns of ^1H and ^{13}C NMR spectra.

The same chain-elongation protocol A and B was successfully applied to the protected L-threose **2b** (Scheme V), thus giving rise to a series of L sugars up to the seven carbon atom compound **11b**. The major diastereoisomer (ds 86–95%) obtained in each cycle was reasonably assigned the anti relationship at the newly formed 1,2-diol system on the basis of that observed in the iterative homologation of **2a**. It is worth mentioning that also in this case the chain lengthening should be repeatable with compound **11b**, thus providing access to higher carbohydrates of the L series.

Scheme III[a,b]



[a] Th = 2-thiazolyl; Bn = benzyl; ds values determined on the crude reaction mixture; yields refer to isolated products. [b] Sequence A: (i) 2-TST addition and desilylation; (ii) O-benzylation (compounds **4**, **9**, **11**, **13**, and **15**: **a**, R = H; **a'**, R = Bn. Sequence B: (i) N-methylation; (ii) reduction; (iii) hydrolysis. [c] Lower yields (70–75%) were occasionally obtained owing to the formation of another product, which was isolated as the *O*-benzyl derivative.

Finally in view of the importance of constructing a polyhydroxylated carbon chain attached to a sugar moiety as shown by the work of Danishefsky and his co-workers en route to the total synthesis of natural products,[10i] we decided to apply our methodology to the side-chain elongation of the dialdogalactopyranoside **2h** (Scheme VI). Thus, iterative repetition of the sequence A and B over four consecutive cycles provided a series of long-chain dialdogalactopyranosides (carbon–carbon-linked disaccharides)[39] in good chemical yields and diastereoselectivity[40] up to ten carbon atoms as in **26h**. The anti selectivity was assigned to the major isomer on the basis of the logical assumption that the Felkin–Anh–Houk[29] model for asymmetric induction was followed also in this case. Hence, the validity of the "Thiazole Route" to

(36) Benzothiazole, which has been employed as a masked formyl group (Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 5), appears to be a less convenient auxiliary in our methodology since 2-(trimethylsilyl)benzothiazole reacts sluggishly and in low selectivity with the aldehyde **2a** (ref 2a) and the formyl deblocking (N-quaternization step) is more difficult. For a compilation of references of formyl and acyl anion synthons, see: Hase, T. A.; Koskimilo, J. K. *Aldrichimica Acta* **1981**, *14*, 73. See also ref 33 and 35 and references cited therein.

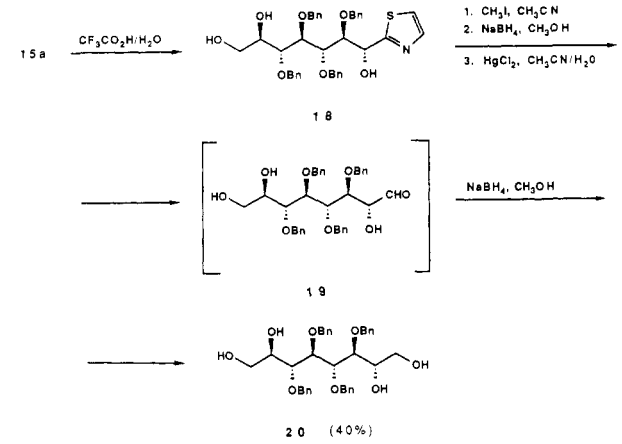
(37) By virtue of the thiazolyl–formyl equivalence the polyhydroxyalkylthiazoles are considered as "thiazole sugars". Hence, a simplified name is given to these compounds by combining the word thiazole with that of the carbohydrate (OH protection is ignored) that is formed by formyl deblocking.

(38) Crystals of **9a** are acentric, space group $P2_12_12_1$, this showing that this compound is a pure homochiral species. We thank Professor G. Gilli (University of Ferrara) for the X-ray structure determination of **9a**.

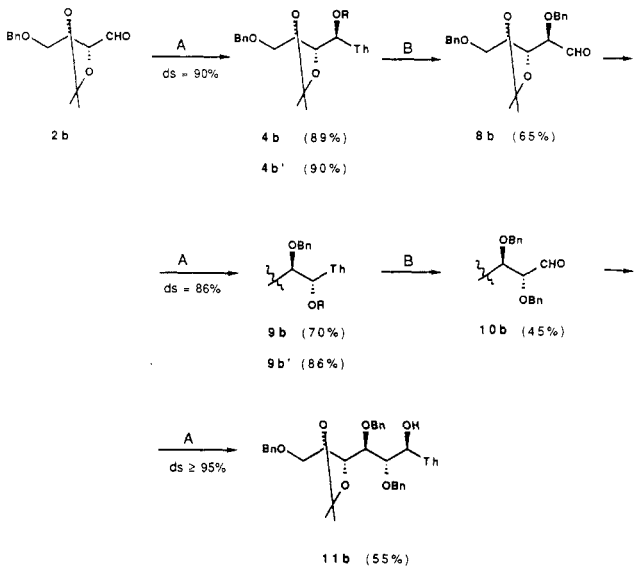
(39) For earlier work on *C*-disaccharides, see: Danishefsky, S. J.; Maring, C. J.; Barbachyn, M. R.; Segmuller, B. E. *J. Org. Chem.* **1984**, *49*, 4564 and references cited therein.

(40) The disappointing lack of facial diastereoselectivity resulting in the addition of **1a** to dialdose **21h** under the usual conditions (CH_2Cl_2, room temperature) was overcome by using THF as a solvent (see ref 2c).

Scheme IV



Scheme V[a,b]

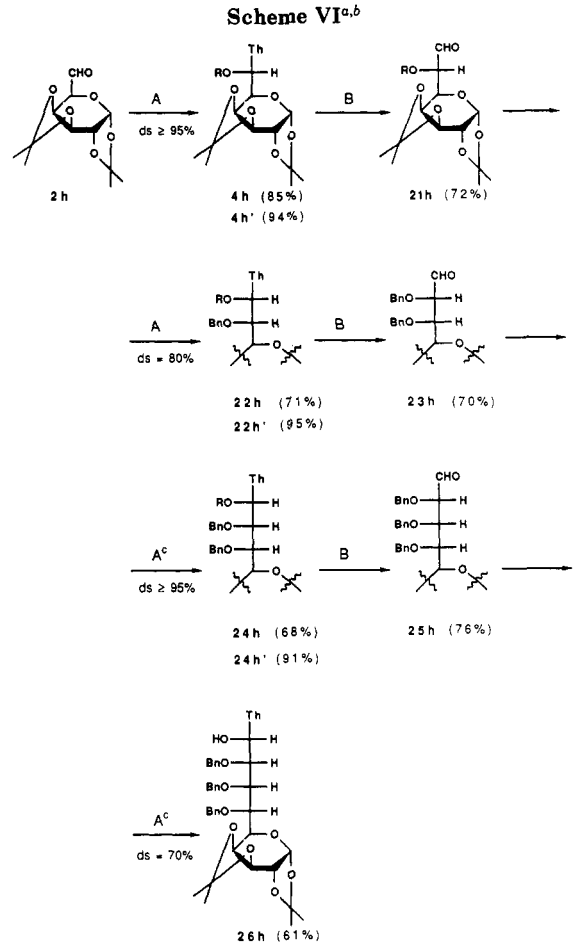


[a] Th = 2-thiazolyl; Bn = benzyl; ds values determined in the crude reaction mixtures; yields refer to isolated products. [b] Sequence A: (i) 2-TST addition and desilylation; (ii) O-benzylation (compounds **4** and **9**: **b**, R = H; **b'**, R = Bn). Sequence B: (i) N-methylation; (ii) reduction; (iii) hydrolysis.

long-chain carbohydrates appears to be sufficiently demonstrated!

Synthetic Elaborations. The above protocol, which leads to a polyhydroxyalkyl chain by creating *one* hydroxymethylene group in each cycle, gives the possibility of differentiating the various hydroxy groups[30] by different protections. This feature may be conveniently exploited for selective elaborations of these molecules as illustrated here for thiazole D-ribose **9a** (Scheme VII). The removal of the unprotected hydroxy group at C_2 via the (thiocarbonyl)imidazolide by the Barton deoxygenation procedure using *tert*-butyltin hydride[41] gave compound **27**, which through the usual thiazole–formyl deblocking sequence produced the 2-deoxy-D-ribose derivative **28** in good yield. Alternatively, the 1,3-dioxolane ring opening in **27** followed by selective mesylation of the primary hydroxy group gave the alcohol **29**, which upon treatment with lithium aluminum hydride was demesylated into **30**, an ultimate precursor to 2,5-dideoxy-D-ribose, a key intermediate for the boromycin synthesis.[42] Other elaborations of thiazole sugars based on this concept and leading to *C*-glycosyl thiazoles are in progress in our laboratory.

Scheme VI[a,b]



[a] Th = 2-thiazolyl; Bn = benzyl; ds values determined in the crude reaction mixtures; yields refer to isolated products. [b] Sequence A: (i) 2-TST addition and desilylation; (ii) O-benzylation (compounds **4**, **22**, and **24**: **h**, R = H; **h'**, R = Bn). Sequence B: (i) N-methylation; (ii) reduction; (iii) hydrolysis. [c] The addition of **1a** to the aldehyde was carried out without solvent.

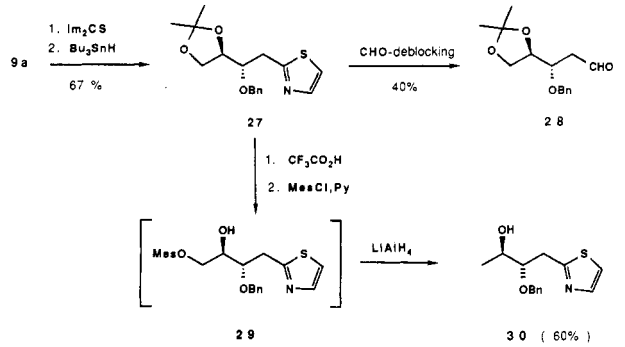
Conclusions

The foregoing results demonstrate that a highly stereoselective protocol for the chain-elongation of alkoxy aldehydes into all-anti 1,2-polyalkoxy higher homologues has been developed (Thiazole Route). This is centered on the use of 2-TST (**1a**) as the source of the carbon chain through two very effective sequences that essentially involve the anti-diastereoselective addition of **1a** to the aldehyde and the racemization-free conversion of the thiazole ring into the formyl group. As a whole, 2-TST (**1a**) appears to be a *suitable synthetic equivalent to the formyl anion synthon*. A quite remarkable feature of this methodology is the iterative repetition of the linear chain-extension sequences over several cycles with very high degree of acyclic stereoselectivity and very good chemical yields in each cycle. In fact, the C_9 thiazole sugar **17a** (Scheme III), the C_7 thiazole sugar **11b** (Scheme V), and the C_{10} thiazole sugar **26** (Scheme VI) do not appear to constitute the upper limits to the repetition of the homologation se-

(41) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574. Reviews: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609. Neuman, W. P. *Synthesis* **1987**, 665.

(42) See ref. 5a and Hanessian, S.; Delorme, D.; Tyler, P. G.; Demaily, G.; Charplens, Y. *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: Oxford, 1983; p 205.

Scheme VII[a]



[a] Mes = (2,4,6-trimethylphenyl)sulfonyl.

quences. Hence, the access to 1,2-polyols having even longer chains should be possible. Further work, however, is required to better define the actual synthetic utility of the Thiazole Route in respect to other iterative methodologies.[12] A synthetic value of this method is already evident when considering the various advantages associated with the use of the thiazole nucleus as a latent formyl group equivalent. On the other hand, total stereocontrol in the addition sequence A is still missing due to the profound anti selectivity of the addition of **1a** to α,β-dialkoxy aldehydes. Fortunately, this drawback can be overcome through an oxidation–reduction pathway, which allows the syn 1,2-diastereoisomers to be equally available in very good yields.[24] Finally in light of the various analogies between the cyanide ion and the thiazole nucleus (*pseudocyanide*[43]), the 2-TST-mediated route to carbohydrates can be considered as an extension of the milestone Fisher–Kiliani cyanohydrin synthesis.[44]

Experimental Section

General Comments. All melting and boiling points are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a 80-MHz WP 80 Bruker spectrometer. Chemical shifts are given in parts per million downfield from tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 297 grating spectrometer. Elemental analyses were performed on a Model 1106 microanalyzer (Carlo Erba).

Starting Materials. 2-(Trimethylsilyl)thiazole (**1a**) [bp 58–60 °C (16 mmHg)] was prepared from 2-lithiothiazole and trimethylchlorosilane as described.[15] (*R*)-2,3-*O*-Isopropylideneglyceraldehyde[45] (**2a**), 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[46] (**2b**), 4-deoxy-2,3-*O*-isopropylidene-L-threose[11b] (**2c**), (*R,S*)-2,3-di-*O*-benzylglyceraldehyde[45] (**2d**), (*R,S*)-3-(benzyloxy)butanal[47] (**2e**), 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*-pentodialdofuranose[48] (**2g**), and 1,2,3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose[49] (**2h**) were prepared according to literature procedures. 1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdofuranose (**2g**) was commercially available.

Addition Reactions of 2-(Trimethylsilyl)thiazole (1a) to Aldehydes 2a–h. General Procedure. A solution of the aldehyde **2** (5 mmol) and **1a** (1.17 g, 7.5 mmol) in dry dichloromethane (25 mL) was stirred for 12 h (temperature is given in Table I). The solvent was evaporated under vacuum and the residue was treated with a 1 M solution of tetra-*n*-butylammonium fluoride (7.5 mmol) in tetrahydrofuran (30 mL). After 2 h of stirring, the solvent was removed under vacuum and water was added. The solution was extracted with dichloromethane and dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was chromatographed (silica gel, 7:3 cyclohexane/ethyl acetate) to give the anti adduct **4** and in some cases the syn isomer **5**.

(1*R*)-2,3-*O*-Isopropylidene-1-(2-thiazolyl)-D-glycitol (4a) (1.03 g, 96%): mp 114–116 °C (from dichloromethane–*n*-hexane); ^1H NMR ($CDCl_3$–D_2O) δ 1.40 (s, 3 H), 1.47 (s, 3 H), 4.0 (m, 2 H), 4.45 (m, 1 H), 5.07 (d, 1 H, *J* = 5.1 Hz), 7.30 (d, 1 H, *J* = 3.2 Hz), 7.73 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.25; H, 6.11; N, 6.53.

(1*R*)-4-*O*-Benzyl-2,3-*O*-isopropylidene-1-(2-thiazolyl)-L-threitol (4b) (1.49 g, 89%): oil; ^1H NMR ($CDCl_3$–D_2O) δ 1.41 (s, 6 H), 3.2 (m, 2 H), 4.1–4.5 (m, 2 H), 4.45 (s, 2 H), 5.11 (d, 1 H, *J* = 4.4 Hz), 7.21 (m, 6 H), 7.62 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.96; H, 6.24; N, 4.11.

The degree of diastereoselectivity was determined by integrating the 5.11 (d, anti isomer) and 4.97 (m, syn isomer) signals.

(1*R*)-4-Deoxy-2,3-*O*-isopropylidene-1-(2-thiazolyl)-L-threitol (4c) (0.87 g, 76%): syrup; ^1H NMR ($CDCl_3$–D_2O) δ 0.99 (d, 3 H, *J* = 5.7 Hz), 1.38 (s, 3 H), 1.42 (s, 3 H), 3.87–4.25 (m, 2 H), 5.15 (d, 1 H, *J* = 4.4 Hz), 7.27 (d, 1 H, *J* = 3.2 Hz), 7.72 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.90; H, 6.60; N, 6.11. Found: C, 53.01; H, 6.52; N, 6.20.

Mixture of the diastereomeric 1,2-di-*O*-benzyl-3-(2-thiazolyl)-1,2,3-propanetriols (4d and 5d) (1.24 g, 75%): oil; ^1H NMR ($CDCl_3$–D_2O) δ 3.72 (m, 2 H), 4.03–4.72 (m, 5 H), 5.15 (m, 1 H), 7.00–7.4 (m, 11 H), 7.7 (d, 1 H, *J* = 3.2 Hz). The methine proton for the anti (**4d**) (major) product is centered at δ 5.11 (*J* = 2.85 Hz) and for the syn (**5d**) (minor) product at δ 5.21 (*J* = 5.1 Hz).

Anal. Calcd for $C_{20}H_{21}NO_3S$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.71; H, 6.04; N, 3.99.

Mixture of the diastereomeric 3-*O*-benzyl-1-(2-thiazolyl)-1,3-butanediols (4e and 5e) (70%): oil; ^1H NMR ($CDCl_3$–D_2O) δ 1.28 (d, 3 H, *J* = 5.8 Hz), 2.2 (m, 2 H), 3.85 (m, 1 H), 4.48 (m, 2 H), 5.16 (m, 1 H), 7.26 (m, 6 H), 7.62 (d, 0.5 H, *J* = 3.2 Hz), and 7.65 (d, 0.5 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.60; N, 5.26.

(5*S*)-1,2-*O*-Isopropylidene-3-*O*-methyl-5-(2-thiazolyl)-α-D-*xylo*-pentofuranose[2c] (4f) (1.2 g, 84%): colorless syrup; ^1H NMR ($CDCl_3$–D_2O) δ 1.32 (s, 3 H), 1.48 (s, 3 H), 3.33 (s, 3 H), 3.86 (d, 1 H, *J* = 3.4 Hz), 4.58 (m, 2 H), 5.3 (d, 1 H, *J* = 5.6 Hz), 6.02 (d, 1 H, *J* = 3.8 Hz), 7.3 (d, 1 H, *J* = 3.2 Hz), 7.75 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{12}H_{17}NO_5S$: C, 50.17; H, 5.97; N, 4.88. Found: C, 50.29; H, 6.03; N, 4.79.

(5*S*)-1,2-*O*-Isopropylidene-3-*O*-benzyl-5-(2-thiazolyl)-α-D-*xylo*-pentofuranose[2c] (4g) (1.45 g, 80%); colorless syrup; ^1H NMR (C_6D_6–D_2O) δ 1.1 (s, 3 H), 1.34 (s, 3 H), 4.16–4.41 (m, 3 H), 4.81 (dd, 1 H, *J* = 7 Hz, *J* = 3.8 Hz), 5.5 (d, 1 H, *J* = 7 Hz), 5.9 (d, 1 H, *J* = 3.8 Hz), 6.58 (d, 1 H, *J* = 3.2 Hz), 7.12 (br s, 5 H), 7.43 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.49; H, 5.83; N, 3.86. Found: C, 59.35; H, 5.90; N, 3.81.

(6*S*)-1,2:3,4-Di-*O*-isopropylidene-6-(2-thiazolyl)-α-D-*galacto*-hexo-1,5-pyranose[2c] (4h) (1.45 g, 85%): mp 170–172 °C (from ethyl acetate–*n*-hexane); ^1H NMR ($CDCl_3$–D_2O) δ 1.32 (s, 3 H), 1.35 (s, 3 H), 1.48 (s, 3 H), 1.51 (s, 3 H), 4.02–4.76 (m, 4 H), 5.12 (d, 1 H, *J* = 7 Hz), 5.6 (d, 1 H, *J* = 4.6 Hz), 7.3 (d, 1 H, *J* = 3.2 Hz), 7.7 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.47; H, 6.17; N, 4.08. Found: C, 52.49; H, 6.20; N, 4.06.

Addition of 2-Lithiothiazole to the Aldehyde 2a. To a cooled solution (−78 °C) of thiazole (0.5 g, 5.9 mmol) in dry diethyl ether (20 mL) was added a solution of *n*-BuLi (6.4 mmol) under nitrogen. After 20 min of stirring, the aldehyde **2a** (0.7 g, 5.9 mmol) in the same solvent (20 mL) was added. After 1 h at −78 °C and warm up to room temperature, a saturated solution of $NaHCO_3$ (20 mL) was added. The reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4 and the

(43) For a list of formal similarities see ref 15.

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solvent was removed in vacuo. The residue was chromatographed (silica gel, 1:1 cyclohexane/diethyl ether) to give 0.6 g (47%) of a 1:1 mixture of the diastereoisomers **4a** and **5a**.[24]

Formyl Deblocking from the Thiazole Ring in 2-Thiazolyl-D-glycitol 4a. A. O-Benzylation. To the compound **4a** (1 g, 4.6 mmol) in dry THF (50 mL) was added portionwise NaH 50% (0.25 g, 5.1 mmol) at room temperature. The reaction mixture was gently refluxed for 20 min and then tetra-*n*-butylammonium iodide (0.17 g, 0.46 mmol) and benzyl bromide (0.88 g, 5.1 mmol) were added sequentially. The solution was allowed to stand at room temperature overnight. The solvent was concentrated at reduced pressure, saturated $NaHCO_3$ was added (30 mL), and the mixture was extracted with dichloromethane. After drying (anhydrous Na_2SO_4), the solvent was removed under vacuum and the residue was chromatographed (silica gel, 95:5 dichloromethane/diethyl ether) to give the *O*-benzyl derivative **4a'** (1.35 g, 96%): oil; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.37 (s, 3 H), 4.0 (m, 2 H), 4.4–4.66 (m, 3 H), 4.8 (d, 1 H, J = 5.2 Hz), 7.31 (br s, 6 H), 7.87 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.85; H, 6.21; N, 4.66.

B. N-Methylation. The *O*-benzyl derivative **4a'** (1 g, 3.3 mmol) was treated with methyl iodide (4.68 g, 33 mmol) in acetonitrile (30 mL). The solution was refluxed until total disappearance of **4a'** by TLC (7 h). The solvent was concentrated at reduced pressure and diethyl ether was added to precipitate the *N*-methylthiazolium salt, which was filtered off. The crude salt was crystallized from methanol–diethyl ether to give 1.38 g (94%) of the pure *N*-methylthiazolium iodide **6a**: mp 181–183 °C dec (from methanol–diethyl ether); ^1H NMR (CD_3OD) δ 1.33 (s, 3 H), 1.51 (s, 3 H), 3.95–4.51 (m, 3 H), 4.17 (s, 3 H), 4.79 (d, 2 H), 5.36 (d, 1 H, J = 7.2 Hz), 7.34 (s, 5 H), 8.27 (m, 2 H).

Anal. Calcd for $C_{17}H_{22}INO_3S$: C, 45.64; H, 4.96; N, 3.13. Found: C, 45.69; H, 4.98; N, 3.11.

C. Reduction. The *N*-methylthiazolium salt **6a** (1 g, 2.24 mmol) was dissolved in methanol (40 mL) and treated with sodium borohydride (0.16 g, 4.48 mmol) at −10 °C. After 30 min, acetone (2 mL) was added and the solvent was evaporated. The residue was treated with a saturated aqueous solution of NaCl and extracted with dichloromethane. The organic layer was dried (anhydrous Na_2SO_4), the solvent was removed in vacuo, and the residue was chromatographed (silica gel, 95:5 dichloromethane/diethyl ether) to give 0.5 g (70%) of the thiazolidine **7a** (1:1 mixture of diastereoisomers): oil; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.42 (s, 3 H), 2.31 (s, 1.5 H), 2.33 (s, 1.5 H), 2.77–3.25 (m, 4 H), 3.66 (m, 1 H), 3.9–4.55 (m, 4 H), 4.77 (s, 2 H), 7.32 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.6 (q), 26.8 (q), 30.3 (q), 30.8 (q), 42.7 (t), 43.5 (t), 59.65 (t), 65.12 (t), 66.11 (t), 76.06 (d), 78.05 (d), 78.29 (d), 83.27 (d), 83.76 (d), 109.86 (s), 128.51 (d), 129.25 (d), 129.75 (d), 140.19 (s).

Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.31; H, 7.65; N, 4.37.

D. Hydrolysis. The thiazolidine **7a** (0.5 g, 1.54 mmol) was dissolved in acetonitrile (5 mL) and treated with a solution of $HgCl_2$ (0.5 g, 1.8 mmol) in a 4:1 mixture of acetonitrile/water (20 mL). After being stirred at room temperature for 15 min, the reaction mixture was filtered and the solvent was removed under vacuum. The residue was treated with a saturated solution of NaCl and extracted with dichloromethane. After drying (anhydrous Na_2SO_4), the solvent was removed in vacuo and the residue was chromatographed (silica gel, 95:5 dichloromethane/diethyl ether) to give 0.33 g (86%) of the protected D-erythrose **8a**: oil; $[\alpha]^{20}_D$ = +29.5° (*c* 1.70, $CHCl_3$); IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.42 (s, 3 H), 3.8 (dd, 1 H, J = 6.4 Hz, J = 2 Hz), 3.87–4.48 (m, 3 H), 4.65 (d, 2 H), 7.32 (s, 5 H), 9.65 (d, 1 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 25.22 (q), 26.55 (q), 66.37 (t), 73.51 (t), 75.22 (d), 83.31 (dd), 110.24 (s), 128.38 (d), 128.76 (d), 137.23 (s), 201.4 (d).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.28; H, 7.32.

Iterative Homologation. General Procedure. A solution of the aldehyde (1 equiv) and 1.5 equiv of **1a** in dry dichloromethane (20 mL) was stirred for 12 h at room temperature. Usual workup and treatment with 1.5 equiv of tetra-*n*-butylammonium fluoride gave the crude thiazole sugar, which was examined (^1H NMR) for the evaluation of ds values. To this material in tetrahydrofuran (50 mL) was added portionwise 50% NaH (1.2 equiv) at room temperature. The reaction mixture was gently refluxed for 20 min and then tetra-*n*-butylammonium iodide (0.1 equiv) and benzyl bromide (1.2 equiv) were added sequentially. The solution was allowed to stand at room temperature overnight. After workup as described above (see deblocking procedure of **4a**) and eventual chromatographic separation of the two diastereoisomers, the major product was treated with 10 equiv of methyl iodide in acetonitrile (30 mL). The solution was refluxed for an appropriate time (ca. 12–24 h). The solvent was evaporated in vacuo and the residue, dissolved in methanol (40 mL), was treated with 2 equiv of sodium borohydride at −10 °C. After 30 min, usual workup (see above) gave the crude thiazolidine, which was dissolved in acetonitrile (4 mL) and was thus added to a solution of 1.2 equiv of $HgCl_2$ in a 4/1 acetonitrile/water mixture (20 mL). After being stirred at room temperature for 15 min, the reaction mixture was worked up as above. Distillation of the solvent gave the crude aldehyde, which was purified by column chromatography (silica gel, 7:3 cyclohexane/ethyl acetate).

A. Homologation of 2a. 2-Thiazolyl-D-glycitol **4a** (96%), (1*R*)-1-*O*-benzyl-2,3-*O*-isopropylidene-1-(2-thiazolyl)-D-glycitol (**4a'**) (96%), and 2-*O*-benzyl-3,4-*O*-isopropylidene-D-erythrose (**8a**) (62%) are described above.

(1*R*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-1-(2-thiazolyl)-D-erythritol (9a) (92%, ds ≥ 95%); mp 105–107 °C; ^1H NMR ($CDCl_3$–D_2O) δ 1.32 (s, 3 H), 1.38 (s, 3 H), 3.82–4.31 (m, 4 H), 4.68 (m, 2 H), 5.22 (d, 1 H, J = 4.6 Hz), 7.34 (m, 6 H), 7.78 (d, 1 H, J = 3.4 Hz); ^{13}C NMR ($CDCl_3$) δ 25.35 (q), 26.34 (q), 66.1 (t), 73.1 (d), 74.57 (t), 76.31 (d), 82.27 (d), 109.37 (s), 119.8 (d), 128.1 (d), 128.19 (d), 128.57 (d), 138.45 (s), 142.36 (d), 171.24 (s).

Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.85; H, 6.33; N, 4.19.

(1*R*)-1,2-Di-*O*-benzyl-3,4-*O*-isopropylidene-1-(2-thiazolyl)-D-erythritol (9a') (90%): oil; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.31 (s, 3 H), 3.8–4.21 (m, 4 H), 4.42–4.96 (m, 4 H), 5.07 (d, 1 H, J = 2.2 Hz), 7.28 (m, 11 H), 7.75 (d, 1 H, J = 3 Hz).

Anal. Calcd for $C_{24}H_{27}NO_4S$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.63; H, 6.47; N, 3.25.

2,3-Di-*O*-benzyl-4,5-*O*-isopropylidene-D-ribose (10a) (80%): oil; $[\alpha]^{20}_D$ = +45.1° (*c* 1.20, $CHCl_3$); IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 6 H), 3.6–4.28 (m, 5 H), 4.32–4.9 (m, 4 H), 7.28 (m, 10 H), 9.65 (d, 1 H, J = 1.15 Hz).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.51; H, 7.16.

(1*R*)-2,3-Di-*O*-benzyl-3,4-*O*-isopropylidene-1-(2-thiazolyl)-D-ribitol (11a) (94%, ds ≥ 95%): oil; ^1H NMR ($CDCl_3$–D_2O) δ 1.33 (s, 3 H), 1.38 (s, 3 H), 3.52–4.58 (m, 7 H), 4.68 (s, 2 H), 5.25 (d, 1 H, J = 5.7 Hz), 7.25 (m, 11 H), 7.75 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{25}H_{29}NO_5S$: C, 65.92; H, 6.42; N, 3.08. Found: C, 66.18; H, 6.48; N, 3.00.

(1*R*)-1,2,3-Tri-*O*-benzyl-3,4-*O*-isopropylidene-1-(2-thiazolyl)-D-ribitol (11a') (91%): oil; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.37 (s, 3 H), 3.7–4.57 (m, 9 H), 4.66 (s, 2 H), 5.07 (d, 1 H, J = 5.4 Hz), 7.22 (m, 16 H), 7.72 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{32}H_{35}NO_5S$: C, 70.44; H, 6.47; N, 2.57. Found: C, 70.28; H, 6.39; N, 2.51.

2,3,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-D-allose (12a) (74%): oil; $[\alpha]^{20}_D$ = +38.7° (*c* 1.45, $CHCl_3$); IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.34 (s, 3 H), 3.48–4.9 (m, 12 H), 7.25 (m, 15 H), 9.37 (d, 1 H, J = 1 Hz).

Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.66; H, 7.08.

(1*R*)-2,3,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-1-(2-thiazolyl)-D-allitol (13a) (81%, ds = 90%): oil; ^1H NMR ($CDCl_3$–D_2O) δ 1.27 (s, 3 H), 1.37 (s, 3 H), 3.52–4.75 (m, 12 H), 5.3 (d, 1 H, J = 5 Hz), 7.22 (m, 16 H), 7.71 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{33}H_{37}NO_6S$: C, 68.85; H, 6.48; N, 2.43. Found: C, 68.77; H, 6.55; N, 2.38.

Degree of diastereoselectivity from the methine protons of the O-benzylated products: anti isomer (**13a'**) δ 5.2 (d, J = 4 Hz) and syn isomer δ 5.18 (d, J = 3.3 Hz).

(1*R*)-1,2,3,4-Tetra-*O*-benzyl-5,6-*O*-isopropylidene-1-(2-thiazolyl)-D-allitol (13a') (93%): oil; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.35 (s, 3 H), 3.62–4.9 (m, 14 H), 5.2 (d, 1 H, J = 4 Hz), 7.2 (m, 21 H), 7.75 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{40}H_{43}NO_6S$: C, 72.16; H, 6.51; N, 2.10. Found: C, 72.01; H, 6.44; N, 2.15.

2,3,4,5-Tetra-*O*-benzyl-6,7-*O*-isopropylidene-D-*allo*-D-

***glycero*-heptose (14a)** (70%): oil; $[\alpha]^{20}_D$ = +32.2° (*c* 1.13, $CHCl_3$); IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.37 (s, 3 H), 3.87–4.81 (m, 15 H), 7.2 (m, 20 H), 9.32 (s, 1 H).

Anal. Calcd for $C_{38}H_{42}O_7$: C, 74.73; H, 6.93. Found: C, 74.89; H, 6.98.

(1*R*)-2,3,4,5-Tetra-*O*-benzyl-6,7-*O*-isopropylidene-1-(2-thiazolyl)-D-*allo*-D-*glycero*-heptitol (15a) (83%, ds ≥ 95%)): oil; $[\alpha]^{20}_D$ = +15.1° (*c* 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$–D_2O) δ 1.26 (s, 3 H), 1.31 (s, 3 H), 3.68–4.66 (m, 15 H), 5.23 (d, 1 H, *J* = 5.2 Hz), 7.19 (m, 21 H), 7.67 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{41}H_{45}NO_7S$: C, 70.77; H, 6.25; N, 2.01. Found: C, 70.65; H, 6.18; N, 2.06.

(1*R*)-1,2,3,4,5-Penta-*O*-benzyl-6,7-*O*-isopropylidene-1-(2-thiazolyl)-D-*allo*-D-*glycero*-heptitol (15a′) (94%): oil; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.33 (s, 3 H), 3.47–4.78 (m, 17 H), 5.18 (d, 1 H, *J* = 5.6 Hz), 7.12 (m, 26 H), 7.71 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{48}H_{51}NO_7S$: C, 73.35; H, 6.54; N, 1.78. Found: C, 73.18; H, 6.47; N, 1.82.

2,3,4,5,6-Penta-*O*-benzyl-7,8-*O*-isopropylidene-D-*allo*-D-*erythro*-octose (16a) (72%): oil; $[\alpha]^{20}_D$ = +28.5° (*c* 2.79, $CHCl_3$); IR (film) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.36 (s, 3 H), 3.37–4.81 (m, 18 H), 7.18 (m, 25 H), 9.34 (s, 1 H).

Anal. Calcd for $C_{46}H_{50}O_8$: C, 75.60; H, 6.90. Found: C, 75.82; H, 6.83.

(1*R*)-2,3,4,5,6-Penta-*O*-benzyl-7,8-*O*-isopropylidene-1-(2-thiazolyl)-D-*allo*-D-*erythro*-octitol (17a) (80%, ds ≥ 95%): oil; $[\alpha]^{20}_D$ = +17.3° (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$–D_2O) δ 1.25 (s, 3 H), 1.31 (s, 3 H), 3.67–4.66 (m, 18 H), 5.25 (d, 1 H, *J* = 4.8 Hz), 7.17 (m, 26 H), 7.62 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{49}H_{53}NO_8S$: C, 72.13; H, 6.55; N, 1.72. Found: C, 72.01; H, 6.49; N, 1.77.

B. Homologation of 2b. (1*R*)-4-*O*-Benzyl-2,3-*O*-isopropylidene-1-(2-thiazolyl)-L-threitol (4b) (80%) is described above.

(1*R*)-1,4-Di-*O*-benzyl-2,3-*O*-isopropylidene-1-(2-thiazolyl)-L-threitol (4b′) (90%): oil; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.41 (s, 3 H), 3.4 (m, 2 H), 4.17–4.7 (m, 6 H), 4.92 (d, 1 H, *J* = 4.2 Hz), 7.25 (m, 11 H), 7.62 (d, 1 H, *J* = 3.5 Hz).

Anal. Calcd for $C_{24}H_{27}NO_4S$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.66; H, 6.49; N, 3.34.

2,5-Di-*O*-benzyl-3,4-*O*-isopropylidene-L-lyxose (8b) (65%): oil; IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 6 H), 3.53 (m, 2 H), 3.81–4.75 (m, 7 H), 7.28 (s, 10 H), 9.62 (d, 1 H, *J* = 1.6 Hz).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.18; H, 7.14.

(1*R*)-2,5-Di-*O*-benzyl-3,4-*O*-isopropylidene-1-(2-thiazolyl)-L-lyxitol (9b) (70%, ds = 86%): oil; ^1H NMR (C_6D_6–D_2O) δ 1.37 (s, 3 H), 1.42 (s, 3 H), 3.32–4.6 (m, 9 H), 5.35 (d, 1 H, *J* = 4.8 Hz), 6.65 (d, 1 H, *J* = 3.4 Hz), 7.2 (m, 10 H), 7.55 (d, 1 H, *J* = 3.4 Hz).

Anal. Calcd for $C_{25}H_{29}NO_6S$: C, 65.92; H, 6.42; N, 3.08. Found: C, 66.03; H, 6.36; N, 3.03.

Degree of diastereoselectivity from the methine protons (C_6D_6) of the benzylated products: anti isomer δ 5.47 (d, *J* = 2 Hz) and syn isomer δ 5.37 (d, *J* = 3.4 Hz).

(1*R*)-1,2,5-Tri-*O*-benzyl-3,4-*O*-isopropylidene-1-(2-thiazolyl)-L-lyxitol (9b′) (86%): oil; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.37 (s, 3 H), 3.52 (m, 2 H), 4.02–4.85 (m, 9 H), 5.12 (d, 1 H, *J* = 6 Hz), 7.3 (m, 16 H), 7.8 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{32}H_{35}NO_5S$: C, 70.44; H, 6.47; N, 2.57. Found: C, 70.56; H, 6.53; N, 2.53.

2,3,6-Tri-*O*-benzyl-4,5-*O*-isopropylidene-L-talose (10b) (45%): oil; IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.39 (s, 3 H), 3.43–4.75 (m, 12 H), 7.28 (m, 15 H), 9.65 (d, 1 H, *J* = 1.25 Hz).

Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.64; H, 7.06.

(1*R*)-2,3,6-Tri-*O*-benzyl-4,5-*O*-isopropylidene-1-(2-thiazolyl)-L-talitol (11b) (55%, ds ≥ 95%): oil; ^1H NMR ($CDCl_3$–D_2O) δ 1.32 (s, 3 H), 1.42 (s, 3 H), 3.5–4.7 (m, 12 H), 5.3 (d, 1 H, *J* = 6 Hz), 7.3 (m, 16 H), 7.75 (d, 1 H, *J* = 3.4 Hz).

Anal. Calcd for $C_{33}H_{37}NO_6S$: C, 68.85; H, 6.48; N, 2.43. Found: C, 68.99; H, 6.41; N, 2.37.

C. Homologation of 2h. (6*S*)-1,2:3,4-Di-*O*-isopropylidene-6-(2-thiazolyl)-α-D-*galacto*-hexo-1,5-pyranose (4h) is described above.

(6*S*)-6-*O*-Benzyl-1,2:3,4-di-*O*-isopropylidene-6-(2-thiazolyl)-α-D-*galacto*-hexo-1,5-pyranose (4h′) (94%): oil; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.51 (s, 3 H), 3.97–4.73 (m, 6 H), 5.01 (d, 1 H, *J* = 9.4 Hz), 5.41 (d, 1 H, *J* = 5.0 Hz), 7.28 (s, 5 H), 7.36 (d, 1 H, *J* = 3.3 Hz), 7.76 (d, 1 H, *J* = 3.3 Hz).

Anal. Calcd for $C_{22}H_{27}NO_6S$: C, 69.96; H, 6.28; N, 3.23. Found: C, 69.81; H, 6.34; N, 3.27.

6-*O*-Benzyl-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-D-*glycero*-heptodialdo-1,5-pyranose (21h)[50] (72%): oil; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.3 (s, 3 H), 1.36 (s, 3 H), 1.45 (s, 3 H), 1.48 (s, 3 H), 4.08 (m, 2 H), 4.33 (dd, 1 H, *J* = 4.9 Hz, *J* = 2.4 Hz), 4.42 (dd, 1 H, *J* = 8.1 Hz, *J* = 1.6 Hz), 4.57 (d, 1 H, *J* = 11.3 Hz), 4.65 (dd, 1 H, *J* = 8.1 Hz, *J* = 2.4 Hz), 4.73 (d, 1 H, *J* = 11.3 Hz), 5.52 (d, 1 H, *J* = 5.0 Hz), 7.25–7.40 (m, 5 H), 9.8 (d, 1 H, *J* = 1.76 Hz).

Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.37; H, 6.98.

(7*S*)-6-*O*-Benzyl-1,2:3,4-di-*O*-isopropylidene-7-(2-thiazolyl)-α-D-*galacto*-D-*glycero*-heptulo-1,5-pyranose (22h) (71%, ds = 80%): mp 82–85 °C; ^1H NMR ($CDCl_3$–D_2O) δ 1.27 (s, 3 H), 1.35 (s, 3 H), 1.4 (s, 3 H), 1.45 (s, 3 H), 3.77–4.62 (m, 7 H), 5.31 (d, 1 H, *J* = 3.6 Hz), 5.43 (d, 1 H, *J* = 4.8 Hz), 7.22 (m, 6 H), 7.71 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{23}H_{29}NO_7S$: C, 59.60; H, 6.31; N, 3.02. Found: C, 59.63; H, 6.29; N, 3.00.

The degree of diastereoselectivity was determined by integrating the 5.31 (d, *J* = 3.6 Hz, anti isomer) and 5.28 (d, *J* = 1.2 Hz, syn isomer) signals.

(7*S*)-6,7-Di-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-7-(2-thiazolyl)-α-D-*galacto*-D-*glycero*-heptulo-1,5-pyranose (22h′) (95%): oil; ^1H NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.35 (s, 3 H), 1.48 (s, 3 H), 3.65 (m, 1 H), 4.17–4.62 (m, 6 H), 4.95 (AB quartet, 2 H, *J* = 10.4 Hz), 5.33 (d, 1 H, *J* = 1.6 Hz), 5.51 (d, 1 H, *J* = 5 Hz), 7.33 (m, 11 H), 7.75 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{30}H_{35}NO_7S$: C, 65.08; H, 6.37; N, 2.53. Found: C, 64.91; H, 6.44; N, 2.48.

6,7-Di-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-D-*erythro*-octodialdo-1,5-pyranose (23h) (70%): oil; IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.32 (s, 3 H), 1.40 (s, 3 H), 1.48 (s, 3 H), 3.97–4.75 (m, 10 H), 5.4 (d, 1 H, *J* = 5 Hz), 7.29 (s, 10 H), 9.65 (d, 1 H, *J* = 1 Hz).

Anal. Calcd for $C_{28}H_{34}O_8$: C, 67.45; H, 6.87. Found: C, 67.31; H, 6.99.

(8*S*)-6,7-Di-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-8-(2-thiazolyl)-α-D-*galacto*-D-*erythro*-octulo-1,5-pyranose (24h) (68%, ds ≥ 95%): oil; ^1H NMR ($CDCl_3$–D_2O) δ 1.28 (s, 3 H), 1.32 (s, 3 H), 1.4 (s, 6 H), 3.85–4.82 (m, 11 H), 5.31 (d, 1 H, *J* = 7.0 Hz), 5.53 (d, 1 H, *J* = 5.0 Hz), 7.25 (m, 11 H), 7.73 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{31}H_{37}NO_8S$: C, 63.79; H, 6.39; N, 2.40. Found: C, 63.62; H, 6.47; N, 2.36.

(8*S*)-6,7,8-Tri-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-8-(2-thiazolyl)-α-D-*galacto*-D-*erythro*-octulo-1,5-pyranose (24h′) (97%): oil; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.3 (s, 3 H), 1.35 (s, 3 H), 1.47 (s, 3 H), 3.98–4.85 (m, 12 H), 5.22 (d, 1 H, *J* = 8 Hz), 5.47 (d, 1 H, *J* = 5 Hz), 7.03–7.38 (m, 16 H), 7.77 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{38}H_{43}NO_8S$: C, 67.15; H, 6.55; N, 2.12. Found: C, 67.22; H, 6.47; N, 2.16.

6,7,8-Tri-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-D-*ribo*-nonodialdo-1,5-pyranose (25h) (76%): oil; IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.34 (s, 6 H), 1.46 (s, 3 H), 3.22–4.78 (m, 13 H), 5.5 (d, 1 H, *J* = 5.2 Hz), 7.28 (m, 15 H), 9.76 (d, 1 H, *J* = 1.5 Hz).

Anal. Calcd for $C_{36}H_{42}O_9$: C, 69.88; H, 6.84. Found: C, 70.01; H, 6.77.

(9*S*)-6,7,8-Tri-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-9-(2-thiazolyl)-α-D-*galacto*-D-*ribo*-nonulo-1,5-pyranose (26h) (61%, ds = 70%): syrup; ^1H NMR ($CDCl_3$–D_2O) δ 1.26 (s, 6 H), 1.37 (s, 3 H), 1.45 (s, 3 H), 4.06–4.98 (m, 13 H), 5.42 (d, 1 H, *J* = 5.9 Hz), 5.53 (d, 1 H, *J* = 4.8 Hz), 7.26 (m, 16 H), 7.77 (d, 1 H, *J* = 3.2 Hz).

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Anal. Calcd for $C_{39}H_{45}NO_9S$: C, 66.55; H, 6.44; N, 1.99. Found: C, 66.69; H, 6.50; N, 1.95.

Degree of diastereoselectivity from the methine protons (300 MHz, C_6D_6): anti isomer δ 5.86 (d, J = 4.6 Hz) and syn isomer δ 5.88 (brs).

Elaboration of 15a into *meso*-Octitol 20. The thiazole sugar **15a** (0.5 g, 0.72 mmol) was treated with 90% trifluoroacetic acid (2 mL) at room temperature for 15 min. The mixture was concentrated in vacuo, and a saturated solution of $NaHCO_3$ was added. Extraction with ethyl acetate gave 0.44 (95%) of the crude alcohol **18**: syrup; ^1H NMR ($CDCl_3$–D_2O) δ 3.43–4.68 (m, 15 H), 5.27 (d, 1 H, J = 5 Hz), 7.17 (m, 21 H), 7.62 (d, 1 H, J = 3.2 Hz).

The formyl deblocking of the alcohol **18** according to the general procedure gave the aldehyde **19** whose NMR spectrum showed the CHO proton at δ 9.28 whereas the other signals were unresolved.

The crude aldehyde was treated with 1.5 equiv of $NaBH_4$ in methanol (5 mL) at room temperature for 30 min. Acetone (0.5 mL) was added and the solution was concentrated and a saturated solution of NaCl (20 mL) was added. The mixture was extracted with ethyl acetate and after drying (Na_2SO_4) the solvent was removed in vacuo. The residue was chromatographed (silica gel, 6:2:2 ethyl acetate/diethyl ether/dichloromethane) to give *meso*-octitol **20** (overall yield 40%): mp 75–78 °C; optically inactive (c = 0.95, MeOH or $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (br, 2 H), 3.27 (br, 2 H), 3.61 (m, 4 H), 3.84 (s, 4 H), 4.05 (s, 2 H), 4.57 (AB quartet, 4 H, J = 10.8 Hz), 4.64 (AB quartet, 4 H, J = 10.8 Hz), 7.26 (s, 20 H); ^{13}C NMR (C_6D_6) δ 64.41 (t), 72.56 (d), 73.70 (d), 74.01 (d), 80.01 (t), 80.27 (t), 138.36 (s), 138.93 (s).

Anal. Calcd for $C_{36}H_{42}O_8$: C, 71.74; H, 7.02. Found: C, 71.81; H, 6.96.

3-*O*-Benzyl-2-deoxy-4,5-*O*-isopropylidene-D-ribose (28). A stirred solution of the thiazole D-ribose **9a** (1.8 g, 5.37 mmol) and (thiocarbonyl)diimidazole (1.9 g, 10.7 mmol) was refluxed for 5 h. The solvent was removed in vacuo and the imidazolyl(thiocarbonyl) intermediate was separated through a short column (silica gel, 3:7 cyclohexane/ethyl acetate). This was dissolved in dry toluene and the solution was added dropwise over 30 min to a stirred solution of tri-*n*-butyltin hydride (2.34 g, 8.05 mmol) in refluxing toluene (200 mL) and under N_2. When the reduction was completed (6 h), the solution was cooled and then concentrated in vacuo. Flash chromatography of the residue (silica gel, 7:3 cyclohexane/ethyl acetate) gave 1.15 g (67%) of the thiazole 2-deoxy-D-ribose **27**: oil; $[\alpha]^{25}_D$ = +9.6° (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.42 (s, 3 H), 3.32 (m, 2 H), 3.8–4.2 (m, 4 H), 4.52 (s, 2 H), 7.20 (m, 6 H), 7.66 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.78; H, 6.56; N, 4.44.

The formyl deblocking from the thiazole ring in compound **27** according to the general procedure (see above) gave the protected 2-deoxy-D-ribose **28** (0.39 g, 41%): oil; IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.40 (s, 3 H), 2.72 (dd, 2 H, J = 5.3 Hz, J = 2 Hz), 3.71–4.18 (m, 4 H), 4.58 (s, 2 H), 7.26 (s, 5 H), 9.76 (t, 1 H, J = 2 Hz).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.03; H, 7.69.

2-*O*-Benzyl-1-(2-thiazolyl)-2,3-butanediol (Masked 2,5-Dideoxy-D-ribose) (30). A solution of trifluoroacetic acid (2 mL) and water (0.2 mL) was added to thiazole 2-deoxy-D-ribose **27** (0.5 g, 1.6 mmol) at 0 °C. Usual workup (see above for the *meso*-octitol) gave the 1,2-diol, which was treated with 2-mesitylenesulfonyl chloride (1.1 equiv) and pyridine (10 mL) at room temperature. After 12 h of stirring, pyridine was evaporated in vacuo and a saturated solution of $NaHCO_3$ was added to the residue. After extraction with ethyl acetate and drying, the solvent was removed at reduced pressure. The crude *O*-mesityl derivative **29** was dissolved in dry THF (10 mL) and the solution was slowly added to a suspension of $LiAlH_4$ (2 equiv) in the same solvent (10 mL). After 2 h of stirring at room temperature, water was added dropwise and the precipitate was filtered off. The solvent was removed in vacuo and the residue chromatographed (silica gel, 7:3 cyclohexane/ethyl acetate) to give 0.25 g (60% overall yield) of masked 2,5-dideoxy-D-ribose **30**: oil; ^1H NMR ($CDCl_3$–D_2O) δ 1.22 (d, 3 H, J = 6.2 Hz), 3.28 (m, 2 H), 3.57–3.92 (m, 2 H), 4.50 (s, 2 H), 7.17 (m, 6 H), 7.60 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.99; H, 6.59; N, 5.26.

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Supplementary Material Available: Crystal data, tables of bond distances, positional parameters, and bond angles, and an ORTEP drawing of **9a** (7 pages). Ordering information is given on any current masthead page.

Notes

Hydroxy Group Inversion in Thiazole Polyols by an Oxidation–Reduction Sequence. An Entry to Syn 1,2-Diol Fragments in Masked Carbohydrates

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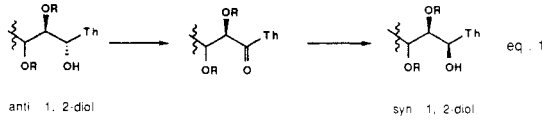
We recently described in a preliminary form[1] the anti-diastereoselective addition of 2-(trimethylsilyl)thiazole (**1**) to the protected L-serinal (**2**) to give the thiazole amino alcohol *anti*-**3a** (ds = 92%), which was converted into the diastereoisomer *syn*-**3c** (ds = 94%) through the ketone **3b** (Scheme I). Thus, the hydroxy group inversion sequence made the individual anti and syn isomers **3a** and **3c** and consequently the corresponding aldehydes by virtue of the thiazolyl–formyl equivalence[1,2] equally available in multigram quantities. Since the same problem exists in the construction of polyhydroxy aldehydes (carbohydrate-like materials) through our thiazole-mediated strategy (Thiazole Route) because of the profound anti selectivity of the addition of **1** to α,β-dialkoxy aldehydes, we have decided to extend this oxidation–reduction methodology to other thiazole polyols, in order to convert anti 1,2-diol fragments into the syn isomers (eq 1). Although various methods



have been described for the inversion of the configuration of secondary alcohols,[3] very few deal with an oxidation–

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