Installation of the Pyruvate Unit in Glycidic Aldehydes via a Wittig Olefination–Michael Addition Sequence Utilizing a Thiazole-Armed Carbonyl Ylid. A New Stereoselective Route to 3-Deoxy-2-Ulosonic Acids and the Total Synthesis of DAH, KDN, and 4-*epi*-KDN

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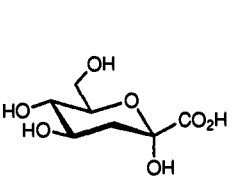
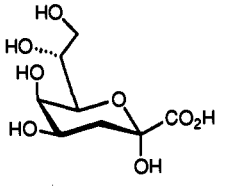
Received November 16, 1993®

Abstract: A method for the installation of the (2-thiazolylcarbonyl)methylene group, i.e. a masked pyruvate unit owing to the thiazole to formyl equivalence, in sugar-derived aldehydes has been developed. The strategy involves stereoselective carbon–carbon and carbon–oxygen bond formation, the former consisting of a Wittig olefination with a thiazole-armed carbonyl ylid, the latter involving a conjugate addition of the benzyl oxide anion to the resultant *E* α,β-enone. This addition was mainly anti (ds 78–85%) to a resident γ-benzyloxy group in the enone, but changed to syn (ds 70–95 %) with a chiral 1,3-dioxolane or 1,3-dioxane ring. The removal of the hydroxy-protecting groups and the consequent cyclization via intramolecular ketalization gave 2-thiazolyl-substituted pyranoses at C-1. The unmasking of the formyl group from the thiazole ring in these compounds afforded 3-deoxy-2-aldopyranosuloses, which were quantitatively oxidized to pyranosulonic acids. Applications of this strategy to the total synthesis of DAH (D-*arabino*-heptulosonic), KDN (D-*glycero*-D-*galacto*-nonulosonic), and its D-*glycero*-D-*talo* epimer, 4-*epi*-KDN, are described.

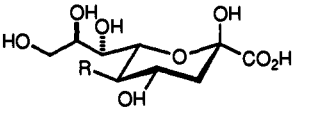
Higher 3-deoxy-2-ulosonic acids are widely diffuse natural carbohydrates which participate in various important biological processes. For example, the 7-phosphate of the seven-carbon compound 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH, **1**) is a key intermediate in the biosynthesis of aromatic amino acids from glucose in plants (shikimate pathway);[1] the well-known eight-carbon compound 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **2**)[2] occurs in the lipopolysaccharide region of the cell surface of all Gram-negative bacteria and is an essential component for their replication;[3] the nine-carbon compound *N*-acetyl-5-amino-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (*N*-acetylneuraminic acid, Neu5Ac or NANA, **3**)[4] is a widely encountered member of a large class of aminononulosonic acids (sialic acids)[5] which are incorporated at the terminal positions of glycoproteins, glycolipids, and oligosaccharides. These sialyl conjugates, which are often found in cellular membranes and in nerve tissues of various living organisms, play an essential role in biological molecular recognition processes, such as cell adhesion and differentiation phenomena.[6] The deaminated analog of Neu5Ac (**3**), namely, 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN, **4**),[7] has been isolated from polysialoglycoproteins of rainbow trout eggs. The unique occurrence of KDN (**4**) at the nonreducing termini in polysialoglycoproteins (PSGP) protects oligopolysialyl chains from exosialidases, thereby allowing those polysialoglycoproteins to perform some important functions in egg activation.



DAH, **1**



KDO, **2**



Neu5Ac, **3** : R = NHAc
KDN, **4** : R = OH

The biosynthesis of compounds **1-4**, as well as of sialic and ulosonic acids in general, is thought to involve the stereoselective aldol condensation of pyruvic acid, in the form of phosphoenol pyruvate, with aldoses catalyzed by the appropriate aldolase enzyme.[3a,8] Either *R* or *S* configuration at the newly formed stereocenter, i.e. C-4 of the resultant ulosonic acid, is obtained as required. The simplicity of this bioconversion methodology has stimulated enzymatic syntheses of ulosonic acids **1-4** employing variably protected aldoses and pyruvic acid derivatives.[9] On the other hand, the coupling of these moieties by chemical means is problematical. Therefore, chemical syntheses of **1-4** employing sugar-derived aldehydes and various surrogates for the pyruvate unit have been reported.[10-13] Recent exploratory

* Abstract published in *Advance ACS Abstracts*, March 1, 1994.

(1) Ganem, B. *Tetrahedron* **1978**, *34*, 3353. Dewick, P. M. *Nat. Prod. Rep.* **1988**, *5*, 73. Haslam, E. *Shikimic Acid. Metabolism and Metabolites*; Wiley: New York, 1993.

(2) Isolated and initially referred to as 2-keto-3-deoxyoctonic acid (KDO). See: Levin, D. H.; Racker, E. *J. Biol. Chem.* **1959**, *234*, 2532.

(3) (a) Unger, F. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323. (b) *Bacterial Lipopolysaccharides: Structure, Synthesis, and Biological Activities*; Anderson, L., Unger, F. M., Eds.: ACS Symposium Series 231; American Chemical Society: Washington, DC, 1983.

(4) First isolation: Gottschalk, A. *Nature* **1951**, *167*, 845. For a recent review on the synthesis and reactivity of Neu5Ac, see: DeNinno, M. P. *Synthesis* **1991**, 583.

(5) Sialic Acids. Chemistry, Metabolism, and Function. In *Cell Biography Monographs*; Schauer, R., Ed.; Springer Verlag: Wien, New York, 1982; Vol. 10.

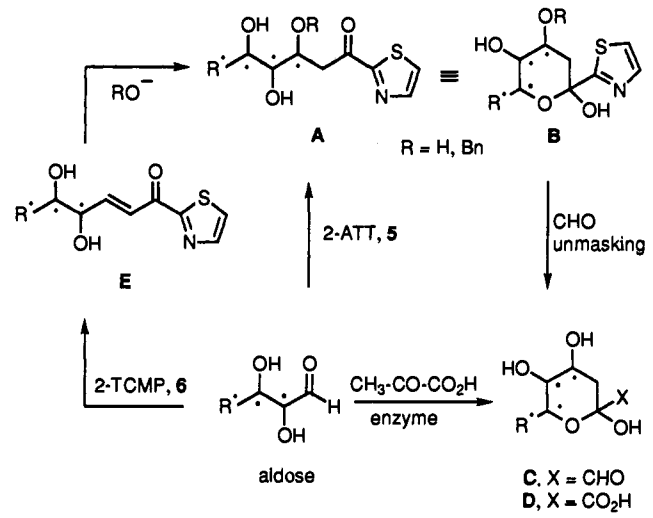
(6) McGuire, E. J. In *Biological Roles of Sialic Acids*; Rosenberg, R. A., Schengrund, C. L., Eds.; Plenum: New York, 1976; Chapter 4. Suzuki, Y.; Nagano, Y.; Kato, H.; Matsumoto, M.; Nerome, K.; Nakajima, K.; Nobusawa, E. *J. Biol. Chem.* **1986**, *261*, 17057. Hanai, N.; Dohi, T.; Nores, G. A.; Hakomori, S. *Ibid.* **1988**, *263*, 6296.

(7) Nadano, D.; Iwasaki, M.; Endo, S.; Kitajima, K.; Inoue, S.; Inoue, Y. *J. Biol. Chem.* **1986**, *261*, 11550.

(8) Schauer, R. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 131.

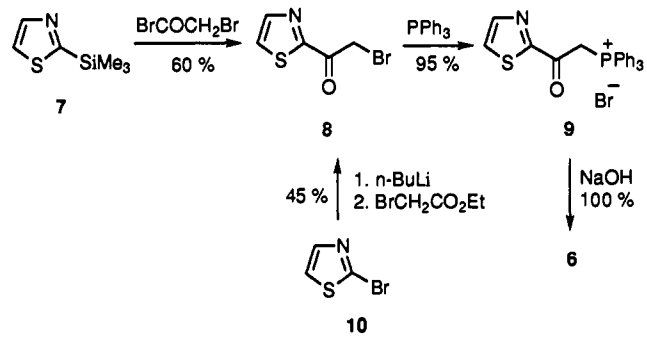
0002-7863/94/1516-3324$04.50/0

Scheme 1

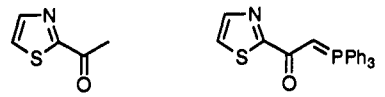


studies have appeared dealing with the development of new pyruvate equivalents, which, however, were tested with rather simple nonsugar substrates.[14] We have also addressed this problem in the context of the application of the thiazole–aldehyde synthesis in carbohydrate chemistry[15] and focused on the enolate chemistry of 2-acetylthiazole (2-ATT, **5**) as a route to the 2-thiazolyl polyhydroxyalkyl ketone **A**, which in the form of its cyclic hemiketal equivalent **B** is an advanced intermediate to the 2-ulosonic acid **D** via the aldosulose **C** (Scheme 1). The application of this strategy led to a new synthesis of KDO (**2**) from D-arabinose.[11c,d] In this and other thiazole-based strategies, the thiazole ring serves as an excellent precursor to the formyl group,[16] whereas its direct conversion to the carboxylate group is still unsatisfactory.[17] The required extra step, i.e. the oxidation (quantitative) of **C** to **D**, is largely compensated by the numerous advantages associated with the use of the thiazole ring as a masked functionality, including its remarkable chemical stability and the ease of cleavage to the formyl group under mild and essentially neutral conditions.

Scheme 2



It appeared from earlier[11c,d] and recent work[18] that the addition of the lithium enolate of 2-ATT (**5**) to sugar-derived aldehydes (aldol route) leads to the β-hydroxy ketone **A** with good levels of antiselectivity. We have recently reported[19] a reversal of diastereoselectivity favoring the syn isomer by a two-step route involving the Wittig olefination of the aldose with the thiazole-armed carbonyl ylid **6**, followed by the Michael-type addition of an alkoxide anion to the resultant α,β-enone **E** (Wittig–Michael route). In this full account, we describe experiments illustrating this strategy and culminating in the total synthesis of DAH (**1**), KDN (**4**), and its epimer at C-4 (**4a**).



5 **6**

Results and Discussion

Preparation and Reactivity of ((2-Thiazolylcarbonyl)methylene)triphenylphosphorane (2-TCMP, 6). In a route to the key intermediate 2-(bromoacetyl)thiazole[20] (**8**) for the preparation of **6** (Scheme 2), the efficient 2-thiazolyl carbanion equivalent 2-(trimethylsilyl)thiazole (2-TST, **7**)[21] was readily acylated with bromoacetyl bromide following the widely explored procedure described earlier.[22] A second route to **8** involved ethoxide displacement from ethyl bromoacetate by 2-lithiothiazole gen-

(9) (a) Kim, M.-J.; Hennen, W. J.; Sweers, H. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 6481. (b) Simon, E. S.; Bednarski, M. D.; Whitesisdes G. M. *J. Am. Chem. Soc.* **1988**, *110*, 7159. (c) Bednarski, M. D.; Crans, D. C.; DiCosimo, R.; Simon, E. S.; Stein, P. D.; Whitesides, G.; Schneider, M. J. *Tetrahedron Lett.* **1988**, *29*, 427. (d) Toone, E. J.; Simon, E. S.; Bednarski, M. D.; Whitesides, G. M. *Tetrahedron* **1989**, *45*, 5365. (e) Augé, C.; Bouxom, B.; Cavayé, B.; Gautheron, C. *Tetrahedron Lett.* **1989**, *30*, 2217. (f) Augé, C.; Gautheron, C.; David, S.; Malleron, A.; Cavayé, B.; Bouxom, B. *Tetrahedron* **1990**, *46*, 201. (g) Kragl, U.; Gygax, D.; Ghisalba, O.; Wandrey, C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 827. (h) Lin, C.-H.; Sugai, T.; Halcomb, R. L.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 10138. (i) Sugai, T.; Shen, G.-J.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 413.

(10) DAH: (a) Herrmann, K. M.; Poling, M. D. *J. Biol. Chem.* **1975**, *250*, 6817. (b) Frost, J. W.; Knowles, J. R. *Biochemistry* **1984**, *23*, 4465. (c) Ramage, R.; MacLeod, A. M.; Rose, G. W. *Tetrahedron* **1991**, *47*, 5625.

(11) KDO: (a) Enhsen, A.; Schmidt, R. R. *Liebigs Ann. Chem.* **1989**, 69. (b) Esswein, A.; Betz, R.; Schmidt, R. R. *Helv. Chim. Acta* **1989**, *72*, 213. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *Tetrahedron Lett.* **1990**, *31*, 4513. (d) Dondoni, A.; Merino, P. *J. Org. Chem.* **1991**, *56*, 5294. (e) Giese, B.; Carboni, B.; Göbel, T.; Muhn, R.; Wetterich, F. *Tetrahedron Lett.* **1992**, *33*, 2673. (f) Giese, B.; Linker, T. *Synthesis* **1992**, 46.

(12) Neu5Ac: (a) Csuk, R.; Hugener, M.; Vasella, A. *Helv. Chim. Acta* **1988**, *71*, 609. (b) Yamamoto, T.; Teshima, T.; Inami, K.; Shiba, T. *Tetrahedron Lett.* **1992**, *33*, 325.

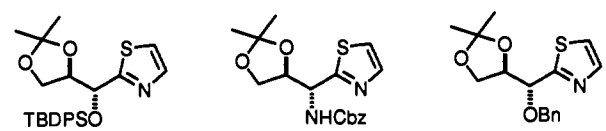
(13) KDN: (a) Shirai, R.; Ogura, H. *Tetrahedron Lett.* **1989**, *30*, 2263. (b) Chan, T.-H.; Li, C.-J. *J. Chem. Soc., Chem. Commun.* **1992**, 747.

(14) Chen, C.; Crich, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1289. Enders, D.; Dyker, H.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 618; **1993**, *32*, 421.

(15) Thiazole–Aldehyde Synthesis: Preparation of aldehydes from C-2 substituted thiazoles by thiazole-to-formyl conversion. For recent overviews in carbohydrate chemistry, see: Dondoni, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, 1992; p 377. Dondoni, A. In *New Aspects of Organic Chemistry II*; Yoshida, Z., Ohshiro, Y., Eds.; Kodansha: Tokyo, and VCH: Weinheim, 1992, p 105.

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

(17) The cleavage of the thiazole ring to amide via reaction with singlet oxygen has been occasionally reported (Matsuura, T.; Saito, I. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2973. Wasylyk, J. M.; Biskupiak, J. E.; Costello, C. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 4445). This method appears to be rather unpractical and requires workup operations which are hardly compatible with the integrity of stereocenters and acid sensitive protective groups in the substrate. Hence, we explored the oxidation with ruthenium tetroxide (Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936) since this reagent has been reported to cleave efficiently heteroaromatic rings to the carboxylate group (Kasai, M.; Ziffer, H. *J. Org. Chem.* **1983**, *48*, 2346. Danishefsky, S. J. Pearson, W. H.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 1280. Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *Ibid.* **1988**, *110*, 3929). The application of this oxidative cleavage (1 equiv of RuO_2, 4 equiv of $NaIO_4$, MeCN–CCl_4–H_2O 3:2:2, room temperature, 30 min) to the three substrates shown below gave the corresponding amides in 25–30% yield to the best and scarce reproducibility.



(18) Dondoni, A.; Merino, P. *Synthesis* **1993**, 903.

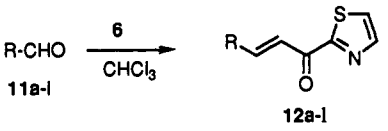
(19) Dondoni, A.; Merino, P.; Orduna, J. *Tetrahedron Lett.* **1991**, *32*, 3247.

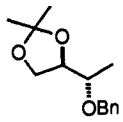
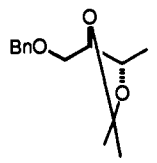
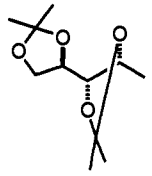
(20) Although the synthesis of this compound was previously reported by bromination of 2-acetylthiazole (**5**) (Erlenmeyer, H.; Weber, O.; Schmidt, P.; Küng, G.; Zinsstag, C.; Prijs, B. *Helv. Chim. Acta* **1948**, *31*, 1142), we have developed two alternative routes.

(21) Dondoni, A. *Pure Appl. Chem.* **1990**, *62*, 643.

(22) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1988**, *53*, 1748. (b) Dondoni, A.; Merino P. *Org. Synth.* **1993**, *72*, 21.

Table 1. Wittig Reaction of Aldehydes[a] **11a-i** with 2-TCMP (**6**) in $CHCl_3$



R	aldehyde	α,β-enone	time (h)	temp (°C)	yield[b] (%)
C_6H_5	**11a**	**12a**	24	reflux	60
i-C_3H_7	**11b**	**12b**	72	25	76
	**11c**	**12c**	96	25	72
	**11d**	**12d**	72	25	71
	**11e**	**12e**	24	25	74
	**11f**	**12f**	24	25	87
	**11g**	**12g**	48	reflux	82
	**11h**	**12h**	36	25	83
	**11i**	**12i**	24	25	88

[a] For references to the preparation of these compounds, see the Experimental Section. [b] Isolated yield after chromatography of the crude reaction mixture.

erated in situ from 2-bromothiazole (**10**) and butyllithium. The crude bromoketone **8** prepared by either route proved to be suitable for the next step, whereas the chromatographic purification resulted in a considerable loss of material. Treatment of crude **8** with PPh_3 in toluene afforded the phosphonium salt **9** as a solid (57% from **7**), which on treatment with aqueous sodium hydroxide gave 2-TCMP (**6**) in almost quantitative yield. This ylid is a slightly hygroscopic solid which can be stored indefinitely in a desiccator at room temperature without appreciable decomposition.

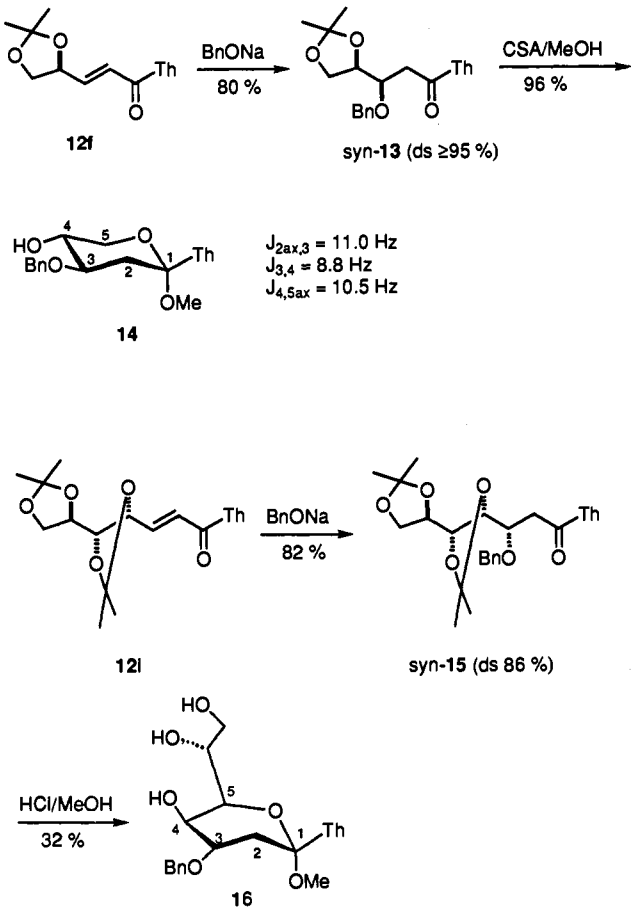
The Wittig olefination of various aldehydes **11a-i** with 2-TCMP (**6**) in chloroform (Table 1) proceeded smoothly and selectively to give good isolated yields of the corresponding *E* 2-thiazolyl α,β-enones **12a-i**. The formation of the *E*-olefin in this Wittig reaction[23] was expected on the basis of the reaction conditions adopted and the stabilized nature of the carbonyl ylid **6**. Although only one isomer was isolated, the stereochemistry of α,β-enones **12a-i** was assigned with confidence on the basis of the olefinic protons' coupling constants measured for some of them,[24] i.e. values (J = 16 Hz) in the range of trans ethylenic protons.[25] Hence, the phosphorane **6** appeared to be a convenient reagent for the execution of the first step in the synthetic strategy to 2-ulosonic acids outlined above.

Conjugate Addition of Benzyl Oxide Anion to Polyalkoxy α,β-Enones. Having secured an entry to *E* α,β-enones, attention was focused on a stereoselective Michael-type addition of an alkoxide anion to these compounds.[26] Benzyl oxide was chosen as the nucleophile, so that the resultant benzyl ether would serve as a readily removable protecting group for the hydroxyl function. The α,β-enone **12f** derived from D-glyceraldehyde acetonide **11f** was chosen as the initial model for an exploratory stereochemical study. We recently reported[27] the syn diastereoselective addition of benzylamine to **12f**. The same sense of asymmetric induction was observed by other workers for the addition of organolithium reagents,[28] benzylamine,[29] sodium benzyl oxide,[30] and silicon-centered radicals[31] to γ-alkoxy *E*-enoates derived from the aldehyde **11f**. This stereochemical outcome is that expected on the basis of a Felkin–Anh transition-state model[32] whose application in conjugate and Michael additions is supported by molecular orbital[33] and molecular mechanics[34] calculations. Accordingly, the reaction of sodium benzyl oxide with **12f** at −50 °C in THF proceeded with exclusive 1,4-regioselectivity and a high degree of diastereoselectivity to give the adduct *syn*-**13** (ds ≥ 95%)[35] in good isolated chemical yield (Scheme 3). At higher temperatures, yields were much lower due to the instability of the adduct. Also, changing the metal cation with lithium and potassium associated to the benzyl oxide anion gave lower yields but had no effect on the diastereoselectivity. For the assignment of the configuration, *syn*-**13** was converted to the cyclic acetal **14** by acid-catalyzed removal of the isopropylidene protecting group. The ^1H NMR spectrum of **14** showed large coupling constant values for the pyranoside ring protons, thus indicating a trans-diequatorial arrangement of benzyloxy and hydroxy groups. The substantial nuclear Overhauser effect (NOE) between the methoxy group and the axial proton at C-5 supported the α-anomeric structure of **14**.

As a second example of this study, the addition of BnONa to the α,β-enone **12i** derived from D-arabinose diacetonide **11i** occurred smoothly under the above conditions to give the corresponding 1,4-adduct *syn*-**15** (ds 86%) as major isomer.[19] Also this adduct was converted to the corresponding methyl pyranoside **16** for the configurational assignment. Unfortunately, the ^1H NMR spectrum of **16** did not permit a first-order analysis of the coupling constants. Nevertheless, the close and downfield signals of C-2 protons (2.73 and 2.54 ppm) suggested a half-chair conformation of the ring, which avoids the unfavorable trans-diaxial arrangement between the benzyloxy and hydroxy groups. Indirect support of the structure of **16** came from the

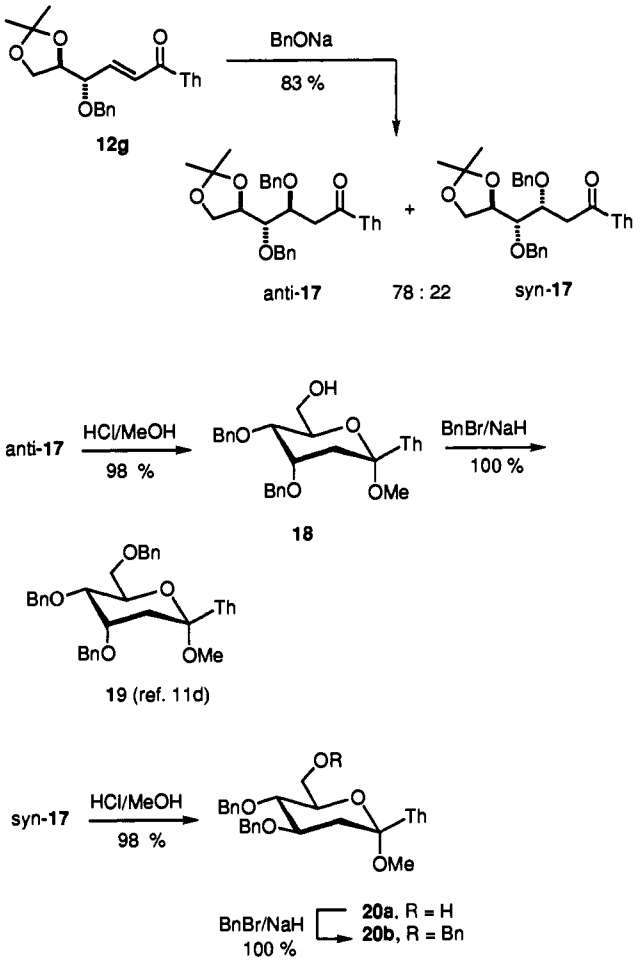
(23) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(24) These coupling constants could not be measured for **12a**, **12c**, and **12d** due to the overlap of the corresponding signals with other signals. In these cases the stereochemistry was assigned by analogy to the other vinyl ketones.
(25) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon: Oxford, 1969; p 301. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; Wiley: New York, 1991; p 221.
(26) A more precise definition of this reaction is "conjugate addition" or "1,4-addition". For a recent overview on Michael and Michael-type reactions, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press: Oxford, 1992.
(27) Dondoni, A.; Boscarato A.; Marra, A. *Synlett* **1993**, 256.
(28) Leonard, J.; Mohialdin, S.; Reed, D.; Jones, M. F. *Synlett* **1992**, 741.
(29) Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009.
(30) Mulzer, J.; Kappert, M.; Huttner, G.; Jibril, I. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 704.
(31) Smadja, W.; Zahouily, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 5511.
(32) This model for carbonyl and alkene addition predicts that the large α substituent is oriented antiperiplanar to the forming new bond and the medium-size substituent is on the inside position.
(33) For a review, see: Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108.
(34) Bernardi, A.; Capelli, A. M.; Gennari, C.; Scolastico, C. *Tetrahedron: Asymmetry* **1990**, *1*, 21.
(35) It is worth recalling the convenient use of the notation % ds instead of % de to quote the diastereoselectivity of a given transformation. For a more extensive comment on this matter, see: Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7407.

Scheme 3[a]



[a] Th = 2-thiazolyl.

Scheme 4[a]



[a] Th = 2-thiazolyl.

observation that the ^1H NMR spectrum of the epimer[36] at C-3 obtained by addition of the lithium enolate of 2-ATT (**5**) to the aldehyde **11i** (aldol route) showed small (J = 2.5 Hz) H_3–H_4 and large (J = 12.0 Hz) H_3–H_2 coupling constants, which were consistent with the cis equatorial–axial disposition of the two hydroxy groups at C-3 and C-4 in a $^4C_1$ conformation. As this compound was an intermediate in the synthesis of KDO (**2**), the methyl pyranoside **16** can serve as an advanced precursor to a C-4 epimer, that is 3-deoxy-D-*gluco*-2-octulosonic acid.

These results indicate that the above olefination–conjugate addition sequence (Wittig–Michael route) is stereochemically complementary to the aldol route. Starting from the same glycidic aldehyde, two polyhydroxyalkyl ketones of type **A** (Scheme 1) having opposite configuration at the stereocenter that is β to the carbonyl can be prepared. Consequently, various couples of C-4 epimer 3-deoxy-2-aldosuloses and ulosonic acids should be, in principle, accessible.

Total Synthesis of 3-Deoxy-D-*arabino*-2-heptulosonic Acid (DAH, 1). As the aldol route was employed[11d] for the synthesis of 3-deoxy-D-*ribo*-2-heptulosonic acid (DRH) from D-erythrose, the above Wittig–Michael route was considered for the synthesis of the *arabino*-isomer DAH (**1**) from the same tetrose. Application of this route relied on stereoselective syn-addition of benzyl oxide anion to the α,β-enone obtained by carbonylolefination with 2-TCMP (**6**) of a suitable protected D-erythrose derivative. Unbeknown to us, the protection of the γ-hydroxy group was critical in that respect. Surprisingly, the addition of benzyl oxide anion to the α,β-enone **12g**, derived from 2-*O*-benzyl-3,4-isopropylidene-*aldehydo*-D-erythrose **11g** (see Table 1), afforded a 78:22 mixture of adducts *anti*-**17** and *syn*-**17** (Scheme 4). After chromatographic separation of these diastereoisomers, their configuration was established through the corresponding cyclic ketals. Specifically, *anti*-**17** treated with HCl–MeOH at room temperature afforded the α-methyl pyranoside **18**, whereas *syn*-**17** gave the C-3 epimer **20a**. Interestingly enough, the tri-*O*-benzyl derivative **19** showed ^1H and ^{13}C NMR data identical to those of the *major* product obtained from **11g** via the aldol route.[37] The structure of the pyranoside **20a** related to the minor adduct *syn*-**17** was easily assigned on the basis of significant NMR data such as $J_{2ax,3}$ = 11.2 Hz and $J_{3,4}$ = 8.8 Hz.

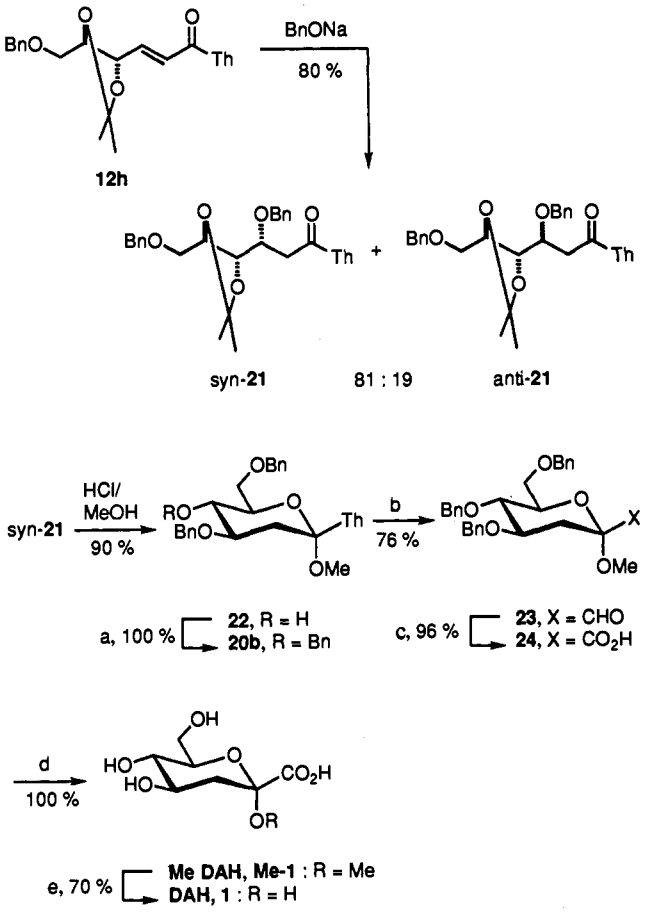
Hence, it appeared that unlike the 1,4-addition of BnONa to the polyalkoxy α,β-enones **12f** and **12i**, the reaction with **12g** was anti-selective. While various conjectures can be made to account for this reversal of diastereofacial selectivity,[38] it remained to us to find the way to control the syn-addition of benzyl oxide anion to the resident γ-hydroxy group in the α,β-enone derived from D-erythrose. To this aim we decided to modify the protecting group arrangement of this tetrose and employ compound **12h** (Scheme 5), which similarly to polyalkoxy vinyl ketones **12f** and **12i** featured O-3 and O-4 bonds incorporated into a 1,3-dioxolane isopropylidene ring. It is worth mentioning that the precursor aldehyde **11h** can be easily prepared in multigram quantities by one-carbon homologation of D-glyceraldehyde acetonide (**11f**)

(36) See compound **13** in ref 11d.

(37) See compound **8b** in ref 11d.

(38) The stereoselectivity of conjugate addition to γ-alkoxy enones and enoates highly depends on the substrate structure and the reagent type. Other models besides the modified Felkin–Anh have been formulated to explain the observed selectivities. For theoretical (a) and experimental (b) papers strictly related to this topic, see: (a) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524. (b) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *Ibid.* **1992**, *114*, 7652. Hence, while it may be convenient to apply one of these models to our case, we intend to approach the problem by further experimental and theoretical studies.

Scheme 5[a]



[a] Th = 2-thiazolyl. Reagents: (a) BnBr–NaH; (b) TfOMe, then $NaBH_4$, then $CuCl_2$–CuO–H_2O; (c) Ag_2O; (d) H_2–Pd/C; (e) AcOH–H_2O.

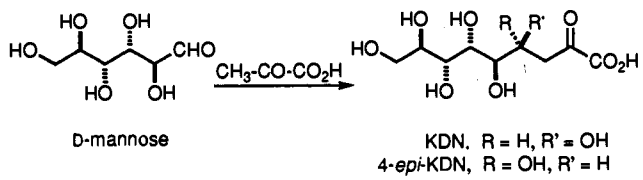
via a published procedure.[39] Hence it was gratifying to observe that the addition of BnONa to **12h** afforded a mixture of products *syn*-**21** and *anti*-**21** in a 81:19 ratio and 80% overall yield. Also in this case the stereoisomers were separated by chromatography, and the major adduct *syn*-**21** converted via acid-catalyzed methanolysis and benzylation into the *O*-methyl *C*-thiazolyl pyranoside **20b**, identical in all respects to the compound obtained by cyclization of the minor adduct *syn*-**17** of Scheme 4. The application of the thiazole–aldehyde synthesis to **20b** furnished the aldosulose **23** (76%), which by oxidation with Ag_2O gave the protected heptulosonic acid **24** in nearly quantitative yield (35% overall yield from **11h**). The synthesis of **24** has been previously reported,[40] but no yield nor physical data which could now be used for comparison were provided. Hence, the *O*-benzyl and the *O*-methyl groups were removed from **24** by hydrogenolysis and acid hydrolysis, respectively, to give DAH (**1**), which was characterized as its barium salt.[10c]

Total Synthesis of 3-Deoxy-D-*glycero*-D-*galacto*-2-nonulosonic Acid (KDN, 4) and D-*glycero*-D-*talo* Isomer 4-*epi*-KDN (4a). The synthesis of the 2-nonulosonic acids **4** and **4a** from D-mannose requires the stereocontrolled introduction of the pyruvate unit with formation of the new stereocenter in *R* and *S* configurations, respectively (Scheme 6).

Following the above Wittig–Michael route, the syn-addition of BnONa to a suitably protected α,β-enone of type **E** derived from D-mannose will give a precursor of **4**, whereas the anti-addition will lead to **4a**. Hence, we first decided to employ a substrate bearing O-3 and O-4 incorporated in a 1,3-dioxolane isopropylidene ring. Attempts to convert efficiently mannose

(39) Dondoni, A.; Merino, P. *Synthesis* **1992**, 196.
(40) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Chem. Commun.* **1988**, 985.

Scheme 6

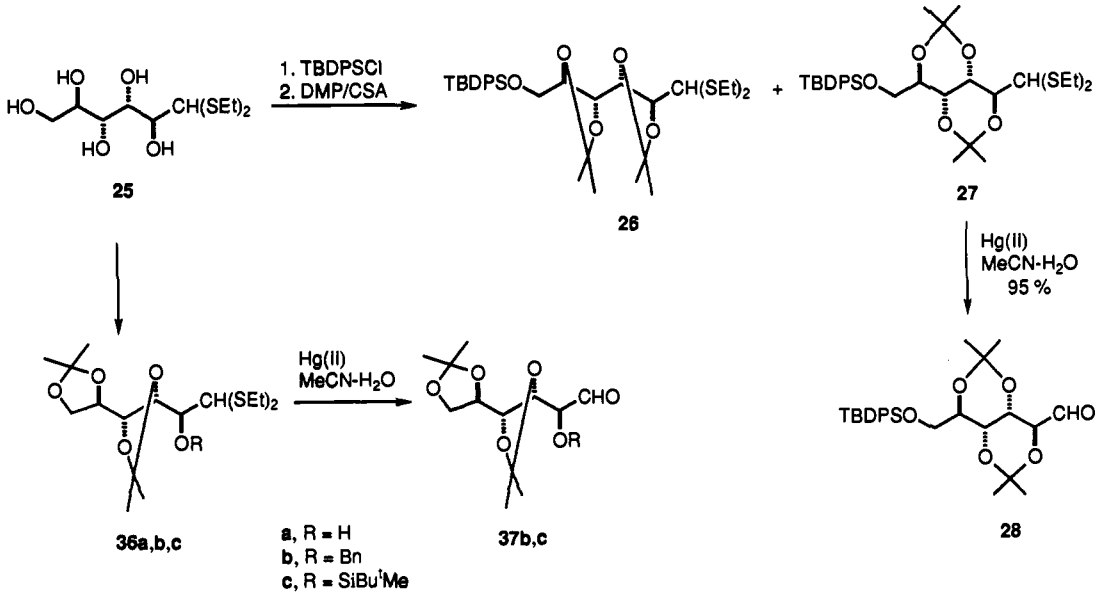


diethyl dithioacetal **25** into the diacetonide derivative **26** (Scheme 7) gave this compound in very low yield,[41] whereas the 1,3-dioxane isopropylidene derivative **27** was obtained (DMP, CSA, room temperature, 4 h) in an acceptable yield (56%). The structure of each of these products was assigned from the ^{13}C chemical shifts of methyl and quaternary acetonide carbons. The signals of compound **26** (23.6–26.7 ppm, 108.6 and 108.7 ppm) were in the range of those reported[42] for 1,3-dioxolane isopropylidenes (23–28 and 108–111 ppm), whereas the signals of **27** (23–28 ppm, 100.8 and 101.2 ppm) were consistent with those reported for 1,3-dioxane rings in a skew-boat conformation (24.6 ± 0.76 and 100.6 ± 0.25 ppm).[43] The aldehyde **28** was then generated from **27** by the standard Hg(II)-mediated hydrolysis. Also, the carbonylolefination of **28** with 2-TCMP (**6**) proceeded with excellent selectivity to give the *E* α,β-enone **29** in good isolated yield (82%) (Scheme 8). Quite surprisingly, the addition of BnONa to this olefin in THF at low temperature (−30 °C) turned out to be essentially unselective, leading to *anti*-**30** and *syn*-**30** in a 1:1 ratio. We attempted to find conditions that would give some selectivity to this reaction, but unfortunately, several limitations associated with the low solubility and instability of the nucleophile prevented a study of the reaction in different solvents. The use of lithium instead of sodium benzyl oxide had also no effect on the diastereoselectivity. On the other hand, change of the temperature proved to be quite helpful since at 0 °C the adducts *syn*-**30** and *anti*-**30** formed in a 70:30 ratio and were isolated as individual products in 54 and 21% yield, respectively. This product distribution is likely to be under thermodynamic control via retro-Michael reaction since treatment of *anti*-**30** with BnONa in THF at 0 °C afforded also in this case a 70:30 equilibrium mixture of *syn*-**30**:*anti*-**30**. Hence, it is in principle possible to achieve by this equilibration the total transformation of the *E*-enone **29** into the required isomer *syn*-**30**. The configuration at the newly formed stereocenter of this compound was assigned following its conversion to a cyclic derivative. To this end, the removal of the silyl and acetonide protecting groups by treatment with methanolic hydrochloric acid followed by benzylation (Scheme 9) furnished the methyl penta-*O*-benzyl pyranoside **31** whose NMR spectrum was consistent with the $^1C_4$ conformation and 3,4-diequatorial benzyloxy groups. The application of the thiazole–aldehyde synthesis to **31** and oxidation of the resultant aldehyde **32** afforded the carboxylic acid **33a** (66%). The synthesis was completed by reductive debenzylation of **33a** to **33b** and acid-catalyzed glycosidic hydrolysis (aqueous acetic acid) of the latter to KDN (**4**), which was isolated as its ammonium salt (14% from **28**). The physical and spectroscopic data of ammonium KDN compared quite well with those of the literature (see the Experimental Section).

Although the conversion of the thiazole to the formyl group and the oxidation of the latter to carboxylate occurred under mild conditions with good overall yield, we envisaged the ketoester-armed phosphorane[44] **34** as an alternative reagent to **6** in a

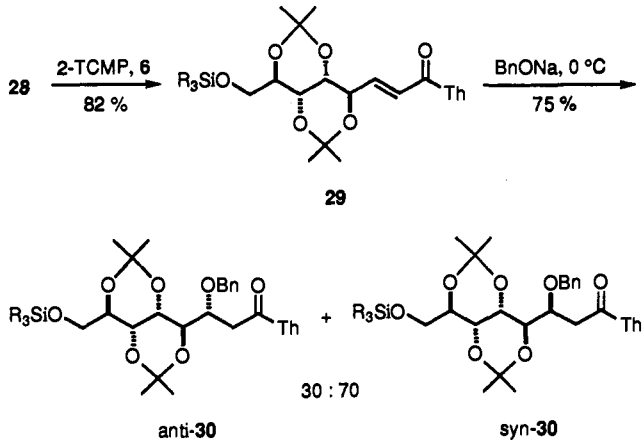
(41) The resultant aldehyde which formed by removal of the dithioacetal protective group proved to be quite unstable and decomposed considerably when submitted to the Wittig olefination with 2-TCMP (**6**).
(42) Buchanan, J. G.; Chacón-Fuertes, M. E.; Edgar, A. R.; Moorhouse, S. J.; Rawson, D. I.; Wightman, R. H. *Tetrahedron Lett.* **1980**, *21*, 1793.
(43) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.
(44) Zhdanov, Y. A.; Uzlova, L. A. *J. Gen. Chem. USSR* **1966**, *36*, 1225. For an improved preparation of phosphorane **34** and its use in the synthesis of KDO analogs, see: Shing, T. K. M. *Tetrahedron* **1992**, *48*, 6777.

Scheme 7



25 26 27 36a,b,c 37b,c 28

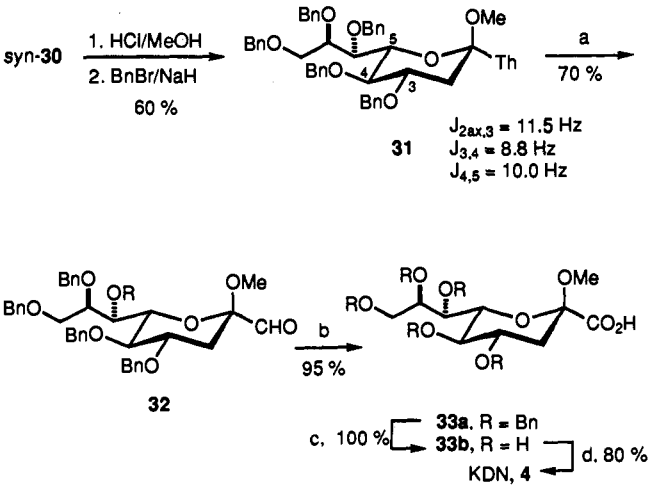
Scheme 8[a]



29 anti-30 syn-30

[a] Th = 2-thiazolyl; R_3 = TBDP.

Scheme 9

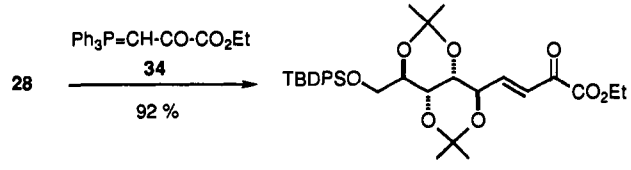


31 32

[a] Th = 2-thiazolyl. Reagents: (a) TfOMe, then $NaBH_4$, then $CuCl_2$–CuO–H_2O; (b) Ag_2O; (c) H_2–Pd/C; (d) AcOH–H_2O.

variation of the Wittig–Michael sequence leading to KDN (**4**). Indeed the reaction of the mannose-derived aldehyde **28** with **34** afforded the *E* α-ketoenoate **35** in good isolated chemical yield (Scheme 10). Unfortunately, the carbethoxy group proved to be

Scheme 10



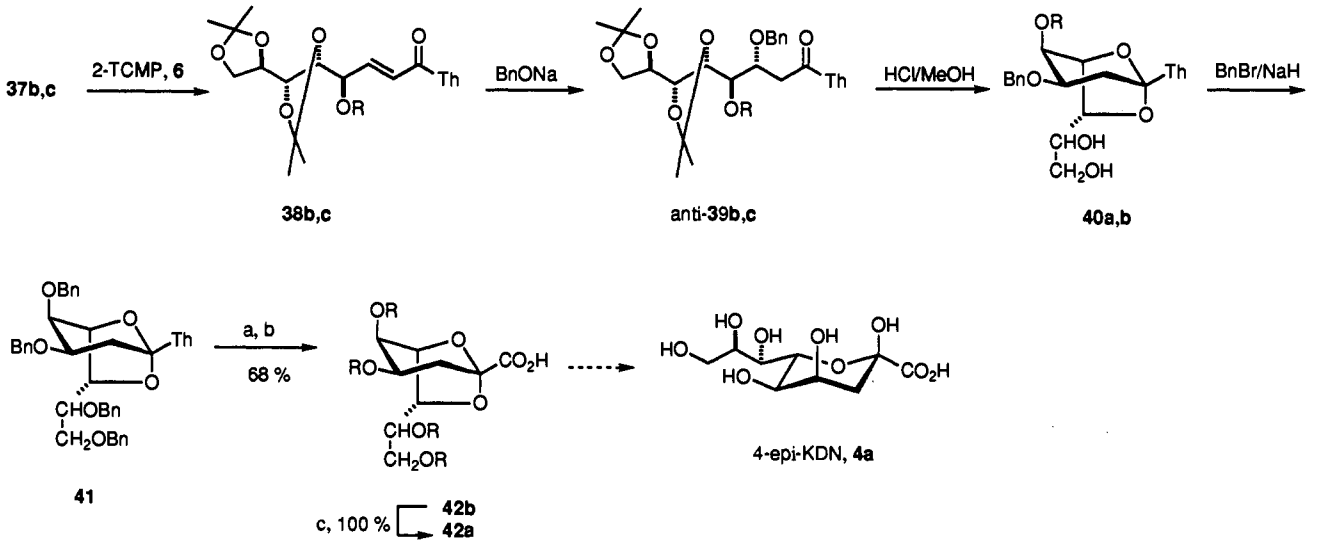
28 35

detrimental to the execution of an efficient conjugate addition since the reaction of **35** with sodium benzyl oxide under the usual conditions produced several products, each one in very small yield, which discouraged us to further develop this synthetic route. The considerable drawback in the conjugate addition of alkoxides to enoates due to the occurrence of side reactions, such as transesterification and lactonization, has been already reported.[30]

Mindful of the anti-selective addition of BnONa to the enone **12g** bearing a γ-OBn group, we decided to exploit a similar route for building up the required intermediate of type **A** precursor to 4-epi-KDN (**4a**). To aim, 2-*O*-benzyl-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-mannose **37b** (Scheme 7) was prepared from D-mannose diethyl dithioacetal **25** via diacetonization and benzylation to **36b** and Hg(II)-promoted hydrolysis of the latter compound. The carbonylolefination of **37b** (Scheme 11) with 2-TCMP (**6**) under the usual conditions afforded the polyalkoxy enone **38a** in good isolated yield (83%). The addition of BnONa to this compound in THF at −30 °C occurred with a good level of diastereoselectivity (ds 85%) in favor of the required isomer *anti*-**39b**, which was isolated in 74% yield by chromatography. The change of benzyl with *tert*-butyldimethylsilyl as the hydroxy protective group made this approach quite inefficient. In fact, the olefination of the aldehyde **37c** (52%) was very difficult and the addition of BnONa to the resultant enone **38c** was almost unselective (anti:syn 1.5:1).[45] Hence, the elaboration of *anti*-**39b** only was continued. The removal of the isopropylidene groups of this compound by either methanolic hydrochloric acid at room temperature or aqueous acetic acid at reflux afforded the *C*-thiazolyl 1,6-anhydro derivative **40b** as the main product. The structure of this compound was assigned on the basis of its ^1H NMR spectrum. Quite significant were the absence of the methyl

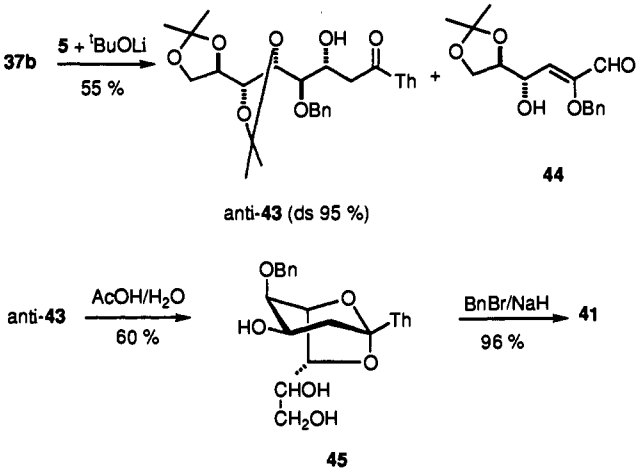
(45) For recent examples of change of diastereofacial selectivity induced by *O*-alkyl and *O*-silyl groups in Michael-type reactions, see: (a) Larchevêque, M.; Tamagnan, G.; Petit, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 31. (b) Jeroncic, L. O.; Cabal, M.-P.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 387.

Scheme 11[a]



[a] Th = 2-thiazolyl; **a**, R = H; **b**, R = Bn; *c*, R = SiBu^{t}Me$_2$. Reagents: (a) TfOMe, then $NaBH_4$, then $CuCl_2$–CuO–H_2O; (b) Ag_2O; (c) H_2–Pd/C.

Scheme 12[a]



[a] Th = 2-thiazolyl.

group signal and by contrast the presence of signals corresponding to C-7 and C-8 hydroxy groups only, as proven upon addition of trichloroacetyl isocyanate.[46] Overall, these results indicate that an intramolecular ketalization occurred to give a 1,6-anhydro pyranoside in a $^4C_1$ conformation ($J_{2ax,3}$ = 11.0 Hz, $J_{3,4}$ = 4.0 Hz). The diol **40b** was benzylated to **41**, which, via thiazole cleavage to aldehyde, oxidation of the latter to carboxylic acid (68%), and reductive debenzylation (quantitative), afforded compound **42a**, which corresponded to the 2,7-anhydro form of 4-epi-KDN (**4a**). The anhydro sugar **42a** proved to be quite stable and resistant to conversion to **4a** even by treatment with aqueous trifluoroacetic acid. Only a partial decomposition of **42a** occurred under these conditions.

The approach to **4a** via the complementary aldol route was also examined. The addition of the lithium enolate of 2-ATT (**5**) to the aldehyde **37b** (THF, −50 °C) (Scheme 12) afforded the adduct *anti*-**43** with high selectivity (ds 95%) but relatively low chemical yield (52%). A side product of this reaction was the enal **44** (11%), arising from the base-catalyzed deacetonization of **37b**. The cyclization of *anti*-**43** by removal of the acetonide protecting groups (*anti*-**43** to **45**) and benzylation afforded a compound identical in all respects to the intermediate **41** obtained by the Wittig–Michael route described above (see Scheme 11).

(46) Goodlett, V. W. *Anal. Chem.* **1965**, *37*, 431.

Conclusions

The carbonylolefination of polyalkoxyaldehydes with the thiazole-armed phosphorane **6** followed by the addition of benzyl oxide anion to the resultant α,β-enone provides an efficient sequence for the synthesis of advanced intermediates to aldosuloses and ulosonic acids. In this strategy the thiazole ring serves as a masked formyl group, which once revealed by a simple and high yield protocol can be easily oxidized to the carboxyl group. The role of thiazole as a stable yet easily convertible precursor to these functionalities should not be underestimated, as shown by the failure to achieve a shorter synthesis of KDN (**4**) by the replacement of the thiazole-armed carbonyl ylid **6** with the phosphorane **34** bearing a ketoester moiety. This more direct approach was unsuccessful due to various side reactions which occur at the ester group when performing the conjugate addition of the benzyl oxide anion to the α-ketoenoate. Hence, the Wittig–Michael approach to ulosonic acids employing the ylid **6** as a key reagent appears of considerable interest.

Experimental Section

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. All solvents were dried over standard drying agents[47] and freshly distilled prior to use. Flash column chromatography[48] 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 the stated solvent. ^1H (300 MHz) and ^{13}C (75 MHz) NMR were recorded at room temperature for $CDCl_3$ solutions, unless otherwise specified. Assigments were aided by decoupling and/or homo- and heteronuclear two-dimensional experiments. The anomeric configuration of the methyl pyranosides was established by NOE experiments. 2-Acetylthiazole (**5**) and 2-(trimethylsilyl)thiazole (**7**), although commercially available, were conveniently prepared[11d,22] in multigram scale from 2-bromothiazole[49] (**10**). D-Mannose diethyl dithioacetal (**25**) was prepared as reported.[50] Aldehydes **11a-c** and **11e** were commercially available. 2-Thiazolecarboxaldehyde (**11d**) was prepared as described.[51]

(47) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.
(48) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(49) Although 2-bromothiazole (**10**) 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 the following: Roussel, P.; Metzger, J. *Bull. Soc. Chim. Fr.* **1962**, 2075.
(50) Levene, P. A.; Meyer, G. M. *J. Biol. Chem.* **1927**, *74*, 695.
(51) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis*, **1987**, 998.

2,3-*O*-Isopropylidene-D-glyceraldehyde (**11f**) was prepared from D-mannitol by the literature procedure.[52] 2-*O*-Benzyl-3,4-*O*-isopropylidene-*aldehydo*-D-erythrose[22b,53] (**11g**) and its 4-*O*-benzyl-2,3-*O*-isopropylidene isomer[39] (**11h**) were prepared by homologation of **11f** as described. Finally, 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose (**11i**) was prepared by a literature procedure.[54]

2-(Bromoacetyl)thiazole (8). Method A. To a solution of 2-(trimethylsilyl)thiazole (**7**) (22.0 g, 22.3 mL, 0.140 mol) in dry CH_2Cl_2 (450 mL) was added a solution of 2-bromoacetyl bromide (56.6 g, 0.28 mol) in the same solvent (250 mL). Stirring was continued for 3 h at room temperature, and then the mixture was neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to afford 20.2 g (85% pure by ^1H NMR analysis) of crude **8**. Purification by column chromatography on silica gel (9:1 petroleum ether–diethyl ether) gave an analytical sample of bromo ketone **8** as a white solid: mp 48–49 °C; IR ($CHCl_3$) ν cm^{-1} 1690; ^1H NMR δ 8.05 and 7.77 (2 d, 2 H, J = 3.0 Hz, Th), 4.71 (s, 2 H).

Anal. Calcd for C_5H_4BrNOS: C, 29.14; H, 1.96; N, 6.80. Found: C, 28.92; H, 2.18; N, 6.67.

Method B. To a stirred, cooled (–80 °C) solution of butyllithium (38 mL of a 1.6 M solution in hexanes, 61 mmol) in dry Et_2O (60 mL) were slowly added (45 min) a solution of freshly distilled 2-bromothiazole (10.0 g, 61 mmol) in dry Et_2O (40 mL) and then a solution of freshly distilled ethyl bromoacetate (11.2 g, 67 mmol) in dry Et_2O (40 mL). During both additions the internal temperature was kept below -60 °C and then allowed to reach –30 °C in 2 h. The mixture was stirred with saturated aqueous $NaHCO_3$ (100 mL), warmed to room temperature, and extracted with Et_2O (200 mL). The organic layer was dried (Na_2SO_4) and concentrated to afford crude **8** (7.29 g, 80% pure by ^1H NMR analysis) as a brown syrup.

((2-Thiazolylcarbonyl)methyl)triphenylphosphonium Bromide (9). To a solution of 2-(bromoacetyl)thiazole (**8**) (2.37 g, 11.5 mmol) in toluene (75 mL) was added portionwise triphenylphosphine (3.14 g, 12 mmol), and the mixture was stirred at room temperature for 3 h. The precipitate was removed by filtration and washed several times with toluene and then petroleum ether to afford 5.11 g (95%) of the salt **9** as a hygroscopic white solid: mp 120–122 °C; IR ($CHCl_3$) ν cm^{-1} 1680; ^1H NMR δ 8.07–7.66 (m, 17 H), 6.38 (d, 2 H, J_{HP} = 13.5 Hz).

Anal. Calcd for $C_{23}H_{19}BrNOPS$: C, 58.98; H, 4.09; N, 2.99. Found: C, 58.70; H, 3.80; N, 2.88.

When the same reaction was performed using crude **8** as the starting material, brownish **9** (almost pure by NMR analysis) was recovered in 57% yield from **7** and 43% yield from **10**.

((2-Thiazolylcarbonyl)methylene)triphenylphosphorane (6). A well-stirred suspension of the phosphonium salt **9** (5.00 g, 10.7 mmol) in water (100 mL) was treated drop by drop with 1 N NaOH up to pH = 10. The mixture was stirred for 30 min, and the precipitate was removed by filtration, washed several times with water, and dried at 40 °C/0.1 mbar to give 3.94 g (95%) of the phosphorane **6** as a white solid: mp 188–190 °C; IR ($CHCl_3$) ν cm^{-1} 1540; ^1H NMR δ 7.88–7.30 (m, 17 H), 4.96 (d, 1 H, J_{HP} = 23.6 Hz).

Anal. Calcd for $C_{23}H_{18}NOPS$: C, 71.30; H, 4.68; N, 3.62. Found: C, 71.26; H, 4.63; N, 3.84.

6-(*O*-*tert*-Butyldiphenylsilyl)-2,3:4,5- (26) and 6-(*O*-*tert*-Butyldiphenylsilyl)-2,4:3,5-di-*O*-isopropylidene-D-mannose Diethyl Dithioacetal (27). To a solution of **25** (5.73 g, 20 mmol) and triethylamine (4.2 mL, 30 mmol) in DMF (30 mL) was slowly added *tert*-butyldiphenylsilyl chloride (5.72 mL, 22 mmol). The mixture was stirred for 1 h at room temperature and then concentrated. The residue was diluted with AcOEt (300 mL), washed with water (50 mL), and dried (Na_2SO_4), and the solvent was evaporated. The crude product was treated at room temperature for 6 h with 2,2-dimethoxypropane (200 mL) and 10-camphorsulfonic acid (0.5 g), then neutralized with triethylamine, and concentrated. The residue was dissolved in CH_2Cl_2 (300 mL), washed with water (50 mL), and dried (Na_2SO_4), and the solvent was evaporated to give a white solid. Crystallization from MeOH afforded **27** (5.81 g, 48%): mp 116–117 °C; $[\alpha]_D$ = –3° (*c* 1, $CHCl_3$); ^1H NMR δ 7.72–7.67 and 7.42–7.30 (2 m, 10 H, 2 Ph), 4.24 (dd, 1 H, J = 8.3, 4.7 Hz), 3.98 (dd, 1 H, J = 8.3, 2.9 Hz), 3.89–3.72 (m, 5 H), 2.77–2.61 (m, 4 H, 2 CH_2CH_3), 1.36, 1.35, 1.31, and 1.23 (4 s, 12 H, 4 Me), 1.24 and 1.22 (2 t, 6 H, J = 7.2 Hz, 2 CH_2CH_3), 1.02 (s, 9 H, *t*-Bu). ^{13}C NMR selected data: δ 101.2 and 100.8 (2 OCO), 64.3 (C-6), 52.8 (C-1), 26.4 (CMe_3), 25.0, 24.8, 24.3, 24.2, 23.7, and 23.4 (4 CH_3, 2 SCH_2CH_3), 18.9 (CMe_3), 14.3 and 14.1 (2 SCH_2CH_3).

Anal. Calcd for $C_{32}H_{48}O_5S_2Si$: C, 63.53; H, 8.00. Found: C, 63.66; H, 8.12.

The mother liquors were concentrated and eluted from a column of silica gel with petroleum ether–diethyl ether (from 20:1 to 10:1, containing 0.2% Et_3N) to yield **27** (0.97 g, 8%). Second eluted was **26** (0.72 g, 6%) as a colorless oil: $[\alpha]_D$ = –16° (*c* 1, $CHCl_3$); ^1H NMR δ 7.71–7.63 and 7.44–7.32 (2 m, 10 H, 2 Ph), 4.74 (dd, 1 H, $J_{3,4}$ = 2.8, $J_{4,5}$ = 6.7 Hz, H-4), 4.53 (dd, 1 H, $J_{2,3}$ = 6.1 Hz, H-3), 4.37 (ddd, 1 H, $J_{5,6a}$ = 7.7, $J_{5,6b}$ = 4.9 Hz, H-5), 4.22 (dd, 1 H, $J_{1,2}$ = 9.4 Hz, H-2), 4.13 (d, 1 H, H-1), 3.99 (dd, 1 H, $J_{6a,6b}$ = 10.2 Hz, H-6a), 3.70 (dd, 1 H, H-6b), 2.85–2.55 (m, 4 H, 2 CH_2CH_3), 1.47, 1.39, 1.32, and 1.29 (4 s, 12 H, 4 Me), 1.25 and 1.24 (2 t, 6 H, J = 7.3 Hz, 2 CH_2CH_3). ^{13}C NMR selected data: δ 108.7 and 108.6 (2 OCO), 63.3 (C-6), 50.2 (C-1), 26.7, 26.4, 26.1, 24.8, 24.6, and 23.6 (4 CH_3, 2 SCH_2CH_3), 26.5 (CMe_3), 18.8 (CMe_3), 14.0 and 13.8 (2 SCH_2CH_3).

Anal. Calcd for $C_{32}H_{48}O_5S_2Si$: C, 63.53; H, 8.00. Found: C, 63.75; H, 8.15.

3,4:5,6-Di-*O*-isopropylidene-D-mannose Diethyl Dithioacetal (36a). To a suspension of D-mannose (10.00 g, 55.4 mmol) in concentrated HCl (6.0 mL) was added, under vigorous magnetic strirring, ethanethiol (12.4 mL, 166 mmol). Stirring was continued at room temperature until the two-layer mixture gave an amorphous, white solid (usually after 15 min), which was immediately treated with acetone (200 mL). After 5 h the solution was neutralized with Amberlyst A-26 resin and filtrated, and the solvent was evaporated. The residue was eluted from a column of silica gel with petroleum ether–diethyl ether (from 10:1 to 5:1) to give syrupy **36a** (10.5 g, 52%): $[\alpha]_D$ = +19.3° (*c* 1, $CHCl_3$); lit.[55] $[\alpha]_D$ = +17.8°. ^1H NMR: δ 4.20–4.05 (m, 4 H), 3.99 (dd, 1 H, J = 7.9, 4.9 Hz), 3.91 (dt, 1 H, J = 7.9, 2.2 Hz), 3.68 (m, 2 H), 2.73 and 2.71 (2 q, 4 H, J = 7.3 Hz, 2 CH_2CH_3), 1.42, 1.35, and 1.33 (3 s, 12 H, 4 Me), 1.28 and 1.26 (2 t, 6 H, J = 7.3 Hz, 2 CH_2CH_3). ^1H NMR ($CDCl_3$ + trichloroacetyl isocyanate): δ 8.42 (s, 1 H, NH), 5.33 (dd, 1 H, $J_{1,2}$ = 3.9, $J_{2,3}$ = 7.3 Hz, H-2), 4.44 (dd, 1 H, $J_{3,4}$ = 5.8 Hz, H-3), 4.24 (d, 1 H, H-1), 4.14 (dd, 1 H, $J_{5,6a}$ = 5.6, $J_{6a,6b}$ = 8.2 Hz, H-6a), 4.04 (ddd, 1 H, $J_{4,5}$ = 8.0 Hz, H-5), 3.97 (dd, 1 H, H-4), 3.91 (dd, 1 H, $J_{5,6b}$ = 5.7 Hz, H-6b), 2.80–2.64 (m, 4 H, 2 CH_2CH_3), 1.39, 1.35, and 1.32 (3 s, 12 H, 4 Me), 1.29 and 1.27 (2 t, 6 H, J = 7.3 Hz, 2 CH_2CH_3). ^{13}C NMR selected data: δ 110.3 and 109.6 (2 OCO), 67.5 (C-6), 54.5 (C-1), 26.6, 26.5, 26.0, 25.2, 25.1, and 24.8 (4 CH_3, 2 SCH_2CH_3), 14.3 and 14.0 (2 SCH_2CH_3).

2-*O*-Benzyl-3,4:5,6-di-*O*-isopropylidene-D-mannose Diethyl Dithioacetal (36b). A stirred, cooled (0 °C) solution of **36a** (3.66 g, 10 mmol) in DMF (50 mL) was treated with NaH (0.80 g, 20 mmol, of a 60% dispersion in oil) and, after 10 min, with benzyl bromide (1.78 mL, 15 mmol). Stirring was continued for an additional 30 min at room temperature, and then the mixture was diluted with methanol and concentrated in high vacuum. The residue was suspended in water (50 mL) and extracted with CH_2Cl_2 (300 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The crude product was eluted from a column of silica gel with 10:1 petroleum ether–diethyl ether to give syrupy **36b**: $[\alpha]_D$ = +2° (*c* 1, $CHCl_3$). ^1H NMR: δ 7.38–7.25 (m, 5 H, Ph), 4.96 and 4.70 (2 d, 2 H, J = 10.9 Hz, $PhCH_2$), 4.24 (t, 1 H, J = 6.2 Hz), 4.21 (d, 1 H, J = 4.0 Hz), 4.17 (t, 1 H, J = 5.9 Hz), 4.13 (t, 1 H, J = 5.5 Hz), 4.00 (dd, 1 H, J = 8.0, 5.9 Hz), 3.88 (dd, 1 H, J = 8.0, 6.7 Hz), 3.82 (dd, 1 H, J = 6.7, 4.0 Hz), 2.76–2.62 (m, 4 H, 2 CH_2CH_3), 1.37, 1.36, 1.35, and 1.29 (4 s, 12 H, 4 Me), 1.27 and 1.22 (2 t, 6 H, J = 7.3 Hz, 2 CH_2CH_3).

Anal. Calcd for $C_{23}H_{36}O_5S_2$: C, 60.49; H, 7.95. Found: C, 60.30; H, 8.06.

2-(*O*-*tert*-Butyldimethylsilyl)-3,4:5,6-di-*O*-isopropylidene-D-mannose Diethyl Dithioacetal (36c). To a stirred solution of **36a** (0.73 g, 2 mmol) and 4-(dimethylamino)pyridine (20 mg) in pyridine (10 mL) was slowly added *tert*-butyldimethylsilyl triflate (0.70 mL, 3 mmol). The mixture was stirred for 4 h at room temperature and then concentrated. The residue was eluted from a column of silica gel with 15:1 petroleum ether–diethyl ether to afford **36c** (0.87 g, 91%) as a white solid: mp <40 °C; $[\alpha]_D$ = +37.2° (*c* 0.9, $CHCl_3$). ^1H NMR: δ 4.28–4.07 (m, 5 H), 4.00 (dd, 1 H, J = 6.7, 2.6 Hz), 3.91 (t, 1 H, J = 7.6 Hz), 2.75–2.55 (m, 4

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H, 2 CH_2CH_3), 1.43, 1.40, 1.39, and 1.35 (4 s, 12 H, 4 Me), 1.28 and 1.27 (2 t, 6 H, J = 7.0 Hz, 2 CH_2CH_3), 0.93 (s, 9 H, *t*-Bu), 0.23 and 0.16 (2 s, 6 H, Me_2Si).

Anal. Calcd for $C_{22}H_{44}O_5S_2Si$: C, 54.96; H, 9.22. Found: C, 55.20; H, 9.33.

6-(*O*-*tert*-Butyldiphenylsilyl)-2,4:3,5-di-*O*-isopropylidene-*aldehydo*-D-mannose (28). A stirred solution of **27** (4.84 g, 8 mmol) in CH_2Cl_2 (24 mL) was diluted with CH_3CN (40 mL) and then water (4 mL), treated at room temperature for 30 min with yellow mercury(II) oxide (6.93 g, 32 mmol) and mercury(II) chloride (4.34 g, 16 mmol), filtered through a pad of Celite, and concentrated. The residue was suspended in CH_2Cl_2 (300 mL) and washed with 20% aqueous KI (3 × 50 mL) and water (30 mL); the organic layer was dried (Na_2SO_4) and concentrated to give 3.79 g (95%) of almost pure (NMR analysis) syrupy aldehyde **28** suitable for the next step. An analytical sample was obtained by chromatography on a Sephadex LH-20 column (2 × 80 cm) with CH_2Cl_2 as the eluent: $[\alpha]_D$ = –8.4° (*c* 1, $CHCl_3$). ^1H NMR: δ 9.71 (s, 1 H, CHO), 7.75–7.68 and 7.47–7.35 (2 m, 10 H, 2 Ph), 4.18 (dd, 1 H, J = 9.1 Hz), 4.10 (dd, 1 H, J = 9.1, 4.0 Hz), 3.98 (m, 1 H), 3.84–3.75 (m, 3 H), 1.40, 1.39, 1.34, and 1.30 (4 s, 12 H, 4 Me), 1.02 (s, 9 H, *t*-Bu).

Anal. Calcd for $C_{28}H_{38}O_6Si$: C, 67.44; H,7.68. Found: C, 67.19; H, 7.72.

In the presence of $CuCl_2$–CuO the hydrolysis of the diethyl dithioacetal in 10:1 CH_3CN–H_2O did not occur after 2 h at room temperature.

2-*O*-Benzyl-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-mannose (37b). A solution of **36b** (4.57 g, 10 mmol) in CH_3CN (100 mL) and H_2O (10 mL) was stirred at room temperature with yellow mercury(II) oxide (5.41 g, 25 mmol) and mecury(II) chloride (5.43 g, 20 mmol). After 20 min the mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was suspended in CH_2Cl_2 (300 mL) and washed with 20% aqueous KI (3 × 50 mL) and water (30 mL); the organic layer was dried (Na_2SO_4) and concentrated to give 3.29 g (94%) of almost pure (NMR analysis) syrupy aldehyde **37b** suitable for the next step. An analytical sample was obtained by chromatography on a silica gel column (5:1 petroleum ether–diethyl ether): $[\alpha]_D$ = –10.5° (*c* 1, $CHCl_3$). ^1H NMR: δ 9.67 (dd, 1 H, J = 1.9, 0.6 Hz, CHO), 7.39–7.31 (m, 5 H, Ph), 4.76 and 4.71 (2 d, 2 H, J = 11.9 Hz, $PhCH_2$), 4.29 (dd, 1 H, J = 7.4, 2.5 Hz), 4.14–3.95 (m, 5 H), 1.37, 1.36, 1.34, and 1.29 (4 s, 12 H, 4 Me).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.39; H, 7.62.

2-(*O*-*tert*-Butyldimethylsilyl)-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-mannose (37c). Hydrolysis of **36c** (1.44 g, 3 mmol) as described for the preparation of **37b** afforded syrupy aldehyde **37c** (1.07 g, 95%), almost pure by NMR analysis. An analytical sample was obtained by chromatography on a silica gel column (10:1 petroleum ether–diethyl ether): $[\alpha]_D$ = –4° (*c* 1, $CHCl_3$). ^1H NMR: δ 9.58 (s, 1 H, CHO), 4.29 (dd, 1 H, J = 2.1, 1.3 Hz), 4.15 (dd, 1 H, J = 7.3, 2.1 Hz), 4.13–3.91 (m, 4 H), 1.36, 1.35, 1.34, and 1.29 (4 s, 12 H, 4 Me), 0.92 (s, 9 H, *t*-Bu), 0.11 and 0.10 (2 s, 6 H, Me_2Si).

Anal. Calcd for $C_{18}H_{34}O_6Si$: C, 57.72; H, 9.15. Found: C, 57.89; H, 9.21.

Wittig Reaction between ((2-Thiazolylcarbonyl)methylene)-triphenylphosphorane (6) and Aldehydes 11. General Procedure. A solution of phosphorane **6** (3.10 g, 8 mmol) and aldehyde **11** (8 mmol) in dry $CHCl_3$ (40 mL) was kept under the conditions reported in Table 1, and then the solvent was removed *in vacuo*. The residue was chromatographed on a silica gel column (2:1 diethyl ether–petroleum ether) to give the enone **12**.

3-Phenyl-1-(2-thiazolyl)-2(*E*)-propen-1-one (12a): (1.03 g, 60%) mp 69-70 °C; IR ($CHCl_3$) ν cm^{-1} 1660; ^1H NMR: δ 8.09 (d, 1 H, J =3.1 Hz), 8.02 (m, 2 H), 7.74 (m, 3 H), 7.46 (m, 3 H).

Anal. Calcd for $C_{12}H_9NOS$: C, 66.95; H, 4.21; N, 6.51. Found: C, 66.73; H, 4.34; N, 6.49.

4-Methyl-1-(2-thiazolyl)-2(*E*)-penten-1-one (12b): (1.10 g, 76%) oil; IR ($CHCl_3$) ν cm^{-1} 1660; ^1H NMR δ 8.04 (d, 1 H, J = 3.1 Hz), 7.68 (d, 1 H, J = 3.1 Hz), 7.32 (dd, 1 H, J = 5.7, 15.5 Hz), 7.25 (d 1 H, J = 15.5 Hz), 2.60 (dd, 1 H, J = 5.7, 6.8 Hz), 1.16 (d, 6 H, J = 6.8 Hz).

Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.28. Found: C, 59.87; H, 6.11; N, 7.55.

3-(2-Furyl)-1-(2-thiazolyl)-2(*E*)-propen-1-one (12c): (1.18 g, 72%) mp 67–68 °C; IR ($CHCl_3$) ν cm^{-1} 1655; ^1H NMR δ 8.06 (d, 1 H, J = 3.1 Hz), 7.79 (m, 2 H), 7.70 (d, 1 H, J = 3.1 Hz), 7.57 (d, 1 H, J = 1.8 Hz), 6.82 (d, 1 H, J = 3.5 Hz), 6.53 (dd, 1 H, J = 3.5, 1.8 Hz).

Anal. Calcd for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82. Found: C, 58.48; H, 3.52; N, 6.59.

1,3-Di-(2-thiazolyl)-2(*E*)-propen-1-one (12d): (1.28 g, 71%) mp 118–119 °C; IR ($CHCl_3$) ν cm^{-1} 1660; ^1H NMR: δ 8.15 (m, 2 H), 8.10 (d, 1 H, J = 3.0 Hz), 7.98 (d, 1 H, J = 3.0 Hz), 7.76 (d, 1 H, J = 3.0 Hz), 7.52 (d, 1 H, J = 3.0 Hz).

Anal. Calcd for $C_9H_6N_2OS_2$: C, 48.63; H, 2.72; N, 12.60. Found: C, 48.42; H, 2.95; N, 12.55.

3-(3,4-Dihydro-2*H*-pyranyl)-1-(2-thiazolyl)-2(*E*)-propen-1-one (12e): (1.30 g, 74%) mp 48–50 °C; IR ($CHCl_3$) ν cm^{-1} 1665; ^1H NMR δ 8.07 (d, 1 H, J = 3.1 Hz), 7.81 (d, 1 H, J = 3.1 Hz), 7.55 (d, 1 H, J = 15.4 Hz), 7.33 (dd, 1 H, J = 15.4, 4.9 Hz), 6.48 (d, 1 H, J = 6.5 Hz), 4.78 (m, 1 H), 4.66 (m, 1 H), 2.12 (m, 3 H), 1.84 (m, 1 H).

Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.51; H, 5.06; N, 6.23.

(4*S*)-4,5-Dihydroxy-4,5-*O*-isopropylidene-1-(2-thiazolyl)-2(*E*)-penten-1-one (12f): (1.66 g, 87%) oil; $[\alpha]_D$ = +21.9° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) ν cm^{-1} 1670. ^1H NMR: δ 8.05 (d, 1 H, J = 3.1 Hz), 7.72 (d, 1 H, J = 3.1 Hz), 7.57 (d, 1 H, J = 15.6 Hz), 7.26 (dd, 1 H, J = 15.6, 5.6 Hz), 4.81 (ddd, 1 H, J = 7.3, 6.9, 5.6 Hz), 4.26 (dd, 1 H, J = 8.3, 6.9 Hz), 3.76 (dd, 1 H, J = 8.3, 7.3 Hz), 1.50 (s, 3 H), 1.44 (s, 3 H). ^{13}C NMR: δ 182.35, 168.59, 146.90, 145.55, 127.08, 127.57, 110.85, 75.79, 69.08, 26.53, 25.79.

Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.05; H, 5.62; N, 5.72.

(4*S*,5*S*)-4-*O*-Benzyl-4,5,6-trihydroxy-5,6-*O*-isopropylidene-1-(2-thiazolyl)-2(*E*)-hexen-1-one (12g): (2.36 g, 82%) oil; $[\alpha]_D$ = +20.4° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) ν cm^{-1} 1665. ^1H NMR: δ 8.04 (d, 1 H, J = 3.3 Hz), 7.68 (d, 1 H, J = 3.3 Hz), 7.52 (dd, 1 H, J = 15.8, 1.0 Hz), 7.35 (m, 5 H), 7.30 (dd, 1 H, J = 15.8, 6.1 Hz), 4.68 (d, 1 H, J = 11.7 Hz), 4.46 (d, 1 H, J = 11.7 Hz), 4.19 (ddd, 1 H, J = 6.3, 6.2, 5.2 Hz), 4.12 (ddd, 1 H, J = 6.3, 6.1, 1.0 Hz), 4.09 (dd, 1 H, J = 8.5, 6.2 Hz), 3.94 (dd, 1 H, J = 8.5, 5.2 Hz), 1.41 (s, 3 H), 1.32 (s, 3 H). ^{13}C NMR: δ 181.92, 168.56, 147.01, 145.34, 138.05, 128.87, 128.38, 128.32, 127.04, 126.85, 110.18, 79.62, 77.10, 72.09, 68.80, 26.42, 25.06.

Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.50; H, 6.02; N, 3.79.

(4*S*,5*R*)-6-*O*-Benzyl-4,5,6-trihydroxy-4,5-*O*-isopropylidene-1-(2-thiazolyl)-2(*E*)-hexen-1-one (12h): (2.38 g, 83%) oil; $[\alpha]_D$ = –23.5° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) ν cm^{-1} 1665. ^1H NMR: δ 8.03 (d, 1 H, J = 3.0 Hz), 7.71 (d, 1 H, J = 3.0 Hz), 7.57 (dd, 1 H, J = 15.6, 1.5 Hz), 7.30 (m, 6 H), 4.95 (ddd, 1 H, J = 6.7, 5.3, 1.5 Hz), 4.53 (m, 2 H), 4.46 (d, 1 H, J = 11.8 Hz), 3.52 (dd, 1 H, J = 9.4, 6.0 Hz), 3.44 (dd, 1 H, J = 9.4, 6.4 Hz), 1.59 (s, 3 H), 1.44 (s, 3 H). ^{13}C NMR: δ 181.25, 167.78, 144.58, 144.24, 137.35, 128.00, 127.52, 127.33, 125.99, 124.89, 109.19, 76.51, 76.27, 72.91, 68.39, 26.79, 24.33.

Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.39; H, 5.80; N, 3.72.

(4*R*,5*S*,6*R*)-4,5,6,7-Tetrahydroxy-4,5:6,7-di-*O*-isopropylidene-1-(2-thiazolyl)-2(*E*)-hepten-1-one (12i): (2.39 g, 88%) oil; $[\alpha]_D$ = +3.7° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) ν cm^{-1} 1660. ^1H NMR: δ 8.06 (d, 1 H, J = 3.1 Hz), 7.71 (d, 1 H, J = 3.1 Hz), 7.62 (dd, 1 H, J = 15.7, 1.6 Hz), 7.40 (dd, 1 H, J = 15.6, 4.3 Hz), 4.70 (ddd, 1 H, J = 7.8, 4.3, 1.6 Hz), 4.17 (m, 2 H), 3.99 (m, 1 H), 3.78 (m, 1 H), 1.48 (s, 6 H), 1.43 (s, 3 H), 1.38 (s, 3 H). ^{13}C NMR: δ 182.38, 168.87, 147.50, 145.53, 127.36, 124.90, 111.21, 110.69, 81.90, 80.11, 77.67, 68.14, 27.28, 27.06 (2C), 25.51.

Anal. Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96; N, 3.94. Found: C, 53.88; H, 6.08; N, 4.14.

(4*R*,5*R*,6*S*,7*S*)-8-(*O*-*tert*-Butyldiphenylsilyl)-4,5,6,7,8-pentahydroxy-4,6:5,7-di-*O*-isopropylidene-1-(2-thiazolyl)-2(*E*)-octen-1-one (29). A mixture of aldehyde **28** (2.99 g, 6 mmol), phosphorane **6** (2.80 g, 7.2 mmol), activated 4-Å powdered molecular sieve (1.80 g), and dry $CHCl_3$ (60 mL) was refluxed for 14 h, then cooled to room temperature, filtered through Celite, and concentrated. The residue was eluted from a column of silica gel with 5:1 petroleum ether–ethyl acetate (containing 0.2% Et_3N) to give syrupy **29** (2.99 g, 82%): $[\alpha]_D$ = –17° (*c* 1, $CHCl_3$). ^1H NMR: δ 8.03 and 7.67 (2 d, 2 H, J = 3.0 Hz, Th), 7.72–7.67 and 7.40–7.32 (2 m, 11 H), 7.52 (dd, 1 H, J = 15.8, 1.9 Hz), 4.41 (ddd, 1 H, J = 9.2, 3.4, 1.9 Hz), 3.95 (m, 1 H), 3.85–3.75 (m, 4 H), 1.40, 1.38, 1.33, and 1.31 (4 s, 12 H, 4 Me), 1.02 (s, 9 H, *t*-Bu).

Anal. Calcd for $C_{33}H_{41}NO_6SSi$: C, 65.21; H, 6.80; N, 2.30. Found: C, 65.40; H, 6.91; N, 2.42.

(4*R*,5*R*,6*S*,7*R*)-4-*O*-Benzyl-4,5,6,7,8-pentahydroxy-5,6:7,8-di-*O*-isopropylidene-1-(2-thiazolyl)-2(*E*)-octen-1-one (38b). The aldehyde **37b** (2.80 g, 8 mmol) was treated (48 h refluxing) with **6** (3.71 g, 9.6 mmol), as described for the preparation of **29**. Column chromatography (5:1 petroleum ether–ethyl acetate, containing 0.2% Et_3N) of the residue afforded syrupy **38b** (3.05 g, 83%): $[\alpha]_D$ = –20.5° (*c* 1, $CHCl_3$). ^1H

NMR: δ 8.02 and 7.68 (2 d, 2 H, *J* = 3.1 Hz, Th), 7.46 (d, 1 H, *J* = 16.2 Hz), 7.37–7.24 (m, 6 H), 4.70 and 4.48 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.27 (dd, 1 H, *J* = 6.6, 4.0 Hz), 4.16 (dd, 1 H, *J* = 6.7, 4.0 Hz), 4.11–4.04 (m, 2 H), 3.92–3.84 (m, 2 H), 1.36, 1.31, and 1.28 (3 s, 12 H, 4 Me).

Anal. Calcd for $C_{24}H_{29}NO_6S$: C, 62.72; H, 6.36; N, 3.05. Found: C, 62.50; H, 6.48; N, 3.20.

(4*R*,5*R*,6*S*,7*R*)-4-(*O*-*tert*-Butyldimethylsilyl)-4,5,6,7,8-pentahydroxy-5,6:7,8-di-*O*-isopropylidene-1-(2-thiazolyl)-2(*E*)-octen-1-one (38c). The aldehyde **37c** (0.75 g, 2 mmol) was treated (72 h refluxing) with **6** (1.16 g, 3 mmol), as described for the preparation of **29**. Column chromatography (petroleum ether–diethyl ether, from 10:1 to 5:1, containing 0.2% Et_3N) of the residue afforded unreacted **37c** (0.30 g, 40%). Eluted second was syrupy **38c** (0.50 g, 52%): $[\alpha]_D$ = +12.4° (*c* 1, $CHCl_3$). ^1H NMR: δ 8.01 and 7.65 (2 d, 2 H, *J* = 3.0 Hz, Th), 7.46 (dd, 1 H, *J* = 15.8, 1.2 Hz), 7.34 (dd, 1 H, *J* = 15.8, 5.2 Hz), 4.61 (ddd, 1 H, *J* = 5.4, 3.7, 1.2 Hz), 4.12–3.86 (m, 5 H), 1.38, 1.36, and 1.28 (3 s, 12 H, 4 Me), 0.95 (s, 9 H, *t*-Bu), 0.11 and 0.09 (2 s, 6 H, Me_2Si).

Anal. Calcd for $C_{23}H_{37}NO_6SSi$: C, 57.11; H, 7.71; N, 2.90. Found: C, 57.33; H, 7.82; N, 2.96.

Ethyl (5*R*,6*R*,7*S*,8*S*)-9-(*O*-*tert*-butyldiphenylsilyl)-5,6,7,8,9-pentahydroxy-5,7:6,8-di-*O*-isopropylidene-2-oxo-3(*E*)-nonenoate (35). A mixture of aldehyde **28** (0.50 g, 1 mmol), phosphorane **34** (0.75 g, 2 mmol), activated 4-Å powdered molecular sieve (0.50 g), and dry toluene (5 mL) was refluxed for 14 h, then cooled to room temperature, filtered through Celite, and concentrated. The residue was eluted from a column of silica gel with CH_2Cl_2 (containing 0.2% Et_3N) to give syrupy **35** (0.55 g, 92%): $[\alpha]_D$ = −11° (*c* 1, $CHCl_3$). ^1H NMR: δ 7.74–7.68 and 7.45-7.34 (2 m, 10 H, 2 Ph), 7.24 (dd, 1 H, *J* = 16.0, 3.4 Hz), 6.94 (dd, 1 H, *J* = 16.0, 1.9 Hz), 4.38 (m, 1 H), 4.36 (q, 2 H, *J* = 7.0 Hz, CH_2CH$_3$), 3.97 (m, 1 H), 3.84–3.76 (m, 4 H), 1.41, 1.38, 1.33, and 1.31 (4 s, 12 H, 4 Me), 1.38 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{33}H_{44}O_8Si$: C, 66.41; H, 7.43. Found: C, 66.20; H, 7.28.

Conjugate Addition of Benzyl Oxide Anion to Enones 12. General Procedure. To a stirred suspension of NaH (0.56 g, 14 mmol, of a 60% dispersion in mineral oil) in dry THF (10 mL) was added a solution of anhydrous benzyl alcohol (1.51 g, 14 mmol) in dry THF (20 mL); then the mixture was cooled to −50 °C, and a solution of the enone **12** (7 mmol) in dry THF (70 mL) was added over a 30-min period. Stirring was continued for 5 h at −50 °C, and then the mixture was quenched with saturated aqueous NH_4Cl (50 mL), allowed to warm to room temperature, diluted with water (50 mL), and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated, and the excess of benzyl alcohol was removed by Kugelrohr distillation. The diastereoselectivity (% ds) was determined on the residue by ^1H and/or ^{13}C NMR analysis. The crude product was purified by column chromatography on silica gel (9:1 petroleum ether–diethyl ether).

(3*R*,4*S*)-3-*O*-Benzyl-3,4,5-trihydroxy-4,5-*O*-isopropylidene-1-(2-thiazolyl)-1-pentanone (*syn*-13): (0.83 g, 80%, ds > 95%) oil; $[\alpha]_D$ = +27.7° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) ν cm^{-1} 1680. ^1H NMR: δ 8.01 (d, 1 H, *J* = 3.1 Hz), 7.68 (d, 1 H, *J* = 3.1 Hz), 7.28 (m, 5 H), 4.66 (m, 2 H), 4.37 (m, 2 H), 4.05 (dd, 1 H, *J* = 8.6, 6.6 Hz), 3.91 (dd, 1 H, *J* = 8.6, 6.2 Hz), 3.52 (dd, 1 H, *J* = 16.6, 8.0 Hz), 3.29 (dd, 1 H, *J* = 16.6, 3.7 Hz), 1.44 (s, 3 H), 1.37 (s, 3 H). ^{13}C NMR: δ 192.45, 145.45, 138.96, 128.89, 128.84, 128.41, 128.17, 126.83, 110.12, 76.88, 75.99, 73.35, 65.80, 39.88, 26.35, 25.14.

Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.20; H, 6.48; N, 4.08.

(3*S*,4*R*,5*S*,6*R*)-3-*O*-Benzyl-3,4,5,6,7-pentahydroxy-4,5:6,7-di-*O*-isopropylidene-1-(2-thiazolyl)-1-hexanone (*syn*-15): (1.11 g, 82%, ds = 86%) oil; $[\alpha]_D$ = −2.5° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν cm^{-1} 1670. ^1H NMR: δ 8.02 (d, 1 H, *J* = 3.2 Hz), 7.68 (d, 1 H, *J* = 3.2 Hz), 7.25 (m, 5 H), 4.72 (d, 1 H, *J* = 11.5 Hz), 4.66 (d, 1 H, *J* = 11.5 Hz), 4.37 (m, 1 H), 4.10 (m, 4 H), 3.90 (m, 1 H), 3.75 (dd, 1 H, *J* = 17.4, 7.5 Hz), 3.46 (dd, 1 H, *J* = 17.4, 4.8 Hz), 1.41 (s, 3 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.33 (s, 3 H). ^{13}C NMR: δ 191.78, 167.23, 144.47, 138.07, 127.83, 127.31, 127.08, 125.76, 109.22, 109.16, 81.75, 76.87, 76.54, 73.99, 72.34, 66.88, 40.23, 26.34, 25.99, 25.52, 24.32.

Anal. Calcd for $C_{23}H_{29}NO_6S$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.92; H, 6.89; N, 2.96.

(3*S*,4*S*,5*S*)-3,4-di-*O*-Benzyl-3,4,5,6-tetrahydroxy-5,6-*O*-isopropylidene-1-(2-thiazolyl)-1-hexanone (*anti*-17): (0.90 g, 65%, ds = 78%) oil; $[\alpha]_D$ = +11.5° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) ν cm^{-1} 1675. ^1H NMR: δ 7.96 (d, 1 H, *J* = 3.2 Hz), 7.63 (d, 1 H, *J* = 3.2 Hz), 7.30 (m, 10 H), 4.80 (d, 1 H, *J* = 11.4 Hz), 4.71 (d, 1 H, *J* = 11.4 Hz), 4.64 (m, 2 H), 4.43 (ddd, 1 H, *J* = 7.7, 4.7, 3.3 Hz), 4.24 (ddd, 1 H, *J* = 6.5, 6.4, 5.9 Hz), 3.96 (dd, 1 H, *J* = 8.4, 6.4 Hz), 3.89 (dd, 1 H, *J* = 8.4, 6.5 Hz), 3.77 (dd, 1 H, *J* = 5.9, 3.3 Hz), 3.65 (dd, 1 H, *J* = 16.8, 7.7 Hz), 3.41 (dd, 1 H, *J* = 16.8, 4.7 Hz), 1.37 (s, 3 H), 1.32 (s, 3 H). ^{13}C NMR: δ 193.10, 168.54, 145.77, 139.45, 139.30, 129.60, 129.31, 129.19, 128.82, 128.64, 128.56, 127.13, 109.94, 81.60, 77.17, 76.13, 74.53, 73.39, 67.21, 40.60, 27.04, 25.69.

Anal. Calcd for $C_{26}H_{29}NO_5S$: C, 66.79; H, 6.25; N, 3.00. Found: C, 66.50; H, 6.38; N, 3.39.

(3*R*,4*S*,5*S*)-3,4-di-*O*-Benzyl-3,4,5,6-tetrahydroxy-5,6-*O*-isopropylidene-1-(2-thiazolyl)-1-hexanone (*syn*-17): (0.26 g, 18%, ds = 22%) oil; $[\alpha]_D$ = +3.6° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) ν cm^{-1} 1670. ^1H NMR: δ 7.98 (d, 1 H, *J* = 3.0 Hz), 7.67 (d, 1 H, *J* = 3.0 Hz), 7.38 (m, 10 H), 4.76 (d, 1 H, *J* = 11.6 Hz), 4.67 (d, 1 H, *J* = 11.6 Hz), 4.63 (d, 1 H, *J* = 11.4 Hz), 4.57 (d, 1 H, *J* = 11.4 Hz), 4.34 (m, 2 H), 4.08 (dd, 1 H, *J* = 8.0, 6.4 Hz), 4.03 (dd, 1 H, *J* = 8.0, 7.4 Hz), 3.91 (m, 1 H), 3.47 (m, 2 H), 1.45 (s, 3 H), 1.33 (s, 3 H). ^{13}C NMR: δ 193.12, 168.30, 145.83, 139.30, 139.14, 129.35, 129.30, 129.08, 129.05, 128.94, 128.65, 127.14, 109.27, 80.55, 77.04, 76.64, 75.21, 73.49, 66.71, 40.53, 26.95, 25.60.

Anal. Calcd for $C_{26}H_{29}NO_5S$: C, 66.79; H, 6.25; N, 3.00. Found: C, 66.83; H, 6.09; N, 2.82.

(3*R*,4*S*,5*R*)-3,6-di-*O*-Benzyl-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylidene-1-(2-thiazolyl)-1-hexanone (*syn*-21): (0.91 g, 65%, ds = 81%) oil; $[\alpha]_D$ = +7.0° (*c* 0.5, MeOH); IR ($CHCl_3$) ν cm^{-1} 1675. ^1H NMR: δ 7.96 (d, 1 H, *J* = 3.1 Hz), 7.64 (d, 1 H, *J* = 3.1 Hz), 7.25 (m, 10 H), 4.72 (d, 1 H, *J* = 11.1 Hz), 4.67 (d, 1 H, *J* = 11.1 Hz), 4.52 (d, 1 H, *J* = 11.8 Hz), 4.46 (d, 1 H, *J* = 11.8 Hz), 4.38 (m, 3 H), 3.71 (dd, 1 H, *J* = 9.7, 6.2 Hz), 3.61 (m, 2 H), 3.49 (m, 1 H), 1.51 (s, 3 H), 1.42 (s, 3 H). ^{13}C NMR: δ 191.17, 166.6, 144.35, 138.33, 137.45, 127.88, 127.76, 127.41, 127.39, 127.20, 126.95, 125.69, 108.36, 79.31, 75.39, 73.13, 72.83, 72.27, 68.44, 40.59, 26.75, 24.60.

Anal. Calcd for $C_{26}H_{29}NO_5S$: C, 66.79; H, 6.25; N, 3.00. Found: C, 66.84; H, 6.57; N, 2.73.

(3*S*,4*S*,5*R*)-3,6-di-*O*-Benzyl-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylidene-1-(2-thiazolyl)-1-hexanone (*anti*-21): (0.21 g, 15%, ds = 19%) oil; $[\alpha]_D$ = +8.2° (*c* 0.4, MeOH); IR ($CHCl_3$) ν cm^{-1} 1670. ^1H NMR: δ 8.01 (d, 1 H, *J* = 3.1 Hz), 7.68 (d, 1 H, *J* = 3.1 Hz), 7.28 (m, 10 H), 4.62 (d, 1 H, *J* = 12.4 Hz), 4.59 (d, 1 H, *J* = 10.9 Hz), 4.51 (d, 1 H, *J* = 12.4 Hz), 4.45 (ddd, 1 H, *J* = 8.1, 5.8, 3.5 Hz), 4.38 (d, 1 H, *J* = 10.9 Hz), 4.35 (m, 1 H), 4.20 (dd, 1 H, *J* = 8.2, 6.2 Hz), 3.78 (dd, 1 H, *J* = 10.3, 3.4 Hz), 3.69 (dd, 1 H, *J* = 16.1, 5.0 Hz), 3.54 (dd, 1 H, *J* = 10.3, 7.9 Hz), 3.44 (dd, 1 H, *J* = 16.1, 5.4 Hz), 1.38 (s, 3 H), 1.23 (s, 3 H). ^{13}C NMR: δ 191.63, 167.02, 144.37, 139.12, 138.82, 127.98, 127.93, 127.50, 127.39, 127.24, 127.19, 125.76, 108.20, 77.43, 76.10, 73.87, 72.85, 70.90, 68.15, 40.36, 26.43, 24.35.

Anal. Calcd for $C_{26}H_{29}NO_5S$: C, 66.79; H, 6.25; N, 3.00. Found: C, 66.43; H, 6.48; N, 3.32.

(3*S*,4*R*,5*R*,6*S*,7*S*)-3-*O*-Benzyl-8-(*O*-*tert*-butyldiphenylsilyl)-3,4,5,6,7,8-hexahydroxy-4,6:5,7-di-*O*-isopropylidene-1-(2-thiazolyl)-1-octanone (*syn*-30) and 3-Epimer (*anti*-30). The enone **29** (2.43 g, 4 mmol) was treated with sodium benzyl oxide (see the above-mentioned General Procedure) at 0 °C for 5 h to afford a 70:30 syn/anti mixture of adducts. The crude product was eluted from a column of silica gel with 8:1 petroleum ether–ethyl acetate (containing 0.2% Et_3N) to give first *anti*-**30** (0.60 g, 21%) as a syrup: $[\alpha]_D$ = +5° (*c* 1, $CHCl_3$). ^1H NMR: δ 7.95 and 7.63 (2 d, 2 H, *J* = 3.1 Hz, Th), 7.72–7.66 and 7.43–7.19 (2 m, 15 H, 3 Ph), 4.72 and 4.59 (2 d, 2 H, *J* = 11.4 Hz, PhCH_2), 4.37 (ddd, 1 H, *J* = 8.3, 5.0, 3.2 Hz), 4.10 (dd, 1 H, *J* = 8.5, 4.3 Hz), 3.87 (dd, 1 H, *J* = 8.5, 2.9 Hz), 3.85–3.72 (m, 4 H), 3.52 (dd, 1 H, *J* = 16.9, 8.3 Hz), 3.33 (dd, 1 H, *J* = 16.9, 5.0 Hz), 1.35, 1.34, 1.31, and 1.20 (4 s, 12 H, 4 Me), 1.02 (s, 9 H, *t*-Bu).

Anal. Calcd for $C_{40}H_{49}NO_7SSi$: C, 67.10; H, 6.90; N,1.96. Found: C, 67.32; H, 6.99; N, 2.19.

Eluted second was *syn*-**30** (1.55 g, 54%) as a syrup: $[\alpha]_D$ = −21° (*c* 1, $CHCl_3$). ^1H NMR: δ 8.00 and 7.67 (2 d, 2 H, *J* = 3.1 Hz, Th), 7.75–7.69 and 7.43-7.19 (2 m, 15 H, 3 Ph), 4.69 and 4.65 (2 d, 2 H, *J* = 11.3 Hz, PhCH_2), 4.35 (dt, 1 H, *J* = 7.4, 5.0 Hz), 4.14 (t, 1 H, *J* = 7.2 Hz), 4.10 (dd, 1 H, *J* = 8.7, 4.7 Hz), 3.93–3.75 (m, 4 H), 3.62 (dd, 1 H, *J* = 16.6, 7.4 Hz), 3.37 (dd, 1 H, *J* = 16.6, 5.0 Hz), 1.36, 1.33, 1.26, and 1.23 (4 s, 12 H, 4 Me), 1.05 (s, 9 H, *t*-Bu).

Anal. Calcd for $C_{40}H_{49}NO_7SSi$: C, 67.10; H, 6.90; N,1.96. Found: C, 67.29; H, 6.81; N, 2.15.

When pure *anti*-**30** was stirred at 0 °C for 1 h in the presence of 2 equiv of sodium benzyl oxide, a 70:30 syn/anti mixture of **30** was recovered after the usual workup.

(3*R*,4*R*,5*R*,6*S*,7*R*)-3,4-di-*O*-Benzyl-3,4,5,6,7,8-hexahydroxy-5,6:7,8-di-*O*-isopropylidene-1-(2-thiazolyl)-1-octanone (*anti*-39b) and 3-Epimer (*syn*-39b). The enone **38b** (1.38 g, 3 mmol) was treated with sodium benzyl oxide (see the above-mentioned General Procedure) at −30 °C for 2 h to afford a 15:85 syn/anti mixture of adducts. The crude product was eluted from a column of silica gel with 12:1 toluene–ethyl acetate (containing 0.2% Et_3N) to give first *anti*-**39b** (1.26 g, 74%) as a syrup: $[\alpha]_D$ = +16.3° (*c* 1, $CHCl_3$). ^1H NMR: δ 7.96–7.62 (2 d, 2 H, *J* = 3.1 Hz, Th), 7.30–7.20 (m, 10 H, 2 Ph), 4.81 and 4.74 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.62 (s, 2 H, PhCH_2), 4.60 (m, 1 H), 4.18–4.04 (m, 4 H), 3.94–3.87 (m, 2 H), 3.67 (dd, 1 H, *J* = 16.9, 7.1 Hz), 3.54 (dd, 1 H, *J* = 16.9, 4.5 Hz), 1.40, 1.35, 1.34, and 1.33 (4 s, 12 H, 4 Me).

Anal. Calcd for $C_{31}H_{37}NO_7S$: C, 65.59; H, 6.57; N, 2.47. Found: C, 65.82; H, 6.63; N, 2.61.

Eluted second was *syn*-**39b** (0.19 g, 11%) as a syrup: $[\alpha]_D$ = +8.3° (*c* 1, $CHCl_3$). ^1H NMR: δ 8.00 and 7.67 (2 d, 2 H, *J* = 3.2 Hz, Th), 7.35–7.19 (m, 10 H, 2 Ph), 4.78 and 4.74 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.73 and 4.67 (2 d, 2 H, *J* = 11.0 Hz, PhCH_2), 4.46 (ddd, 1 H, *J* = 7.6, 6.5, 4.9 Hz), 4.26 (dd, 1 H, *J* = 6.3 Hz), 4.18-4.05 (m, 3 H), 3.91 (dd, 1 H, *J* = 8.0, 6.7 Hz), 3.85 (dd, 1 H, *J* = 6.5, 5.2 Hz), 3.62 (dd, 1 H, *J* = 16.8, 7.6 Hz), 3.50 (dd, 1 H, *J* = 16.8, 4.9 Hz), 1.42, 1.40, 1.33, and 1.28 (4 s, 12 H, 4 Me).

Anal. Calcd for $C_{31}H_{37}NO_7S$: C, 65.59; H, 6.57; N, 2.47. Found: C, 65.78; H, 6.60; N, 2.39.

(3*R*,4*R*,5*S*,6*S*,7*R*)-3-*O*-Benzyl-4-(*O*-*tert*-butyldimethylsilyl)-3,4,5,6,7,8-hexahydroxy-5,6:7,8-di-*O*-isopropylidene-1-(2-thiazolyl)-1-octanone (*anti*-39c). The enone **38c** (0.48 g, 1 mmol) was treated with sodium benzyl oxide (see General Procedure) at −30 °C for 4 h to afford a 40:60 syn/anti mixture of adducts. The crude product was eluted from a column of silica gel with 15:1 toluene–diethyl ether (containing 0.2% Et_3N) to give first *anti*-**39c** (0.26 g, 44%) as a syrup: $[\alpha]_D$ = +30.1° (*c* 1, $CHCl_3$). ^1H NMR: δ 7.99 and 7.65 (2 d, 2 H, *J* = 3.1 Hz, Th), 7.30–7.20 (m, 5 H, Ph), 4.62–4.52 (2 d, 2 H, *J* = 11.3 Hz, PhCH_2), 4.49 (ddd, 1 H, *J* = 8.5, 3.5, 2.4 Hz), 4.21–4.06 (m, 4 H), 3.97 (dd, 1 H, *J* = 6.0 Hz), 3.90 (dd, 1 H, *J* = 8.0, 6.9 Hz), 3.66 (dd, 1 H, *J* = 17.5, 8.5 Hz), 3.46 (dd, 1 H, *J* = 17.5, 3.5 Hz), 1.43, 1.36, and 1.34 (3 s, 12 H, 4 Me), 0.93 (s, 9 H, *t*-Bu), 0.13 and 0.15 (2 s, 6 H, Me_2Si).

Anal. Calcd for $C_{30}H_{45}NO_7SSi$: C, 60.88; H, 7.66; N, 2.37. Found: C, 60.61; H, 7.72; N, 2.51.

Eluted second was the syn-adduct together with a byproduct (0.18 g). This mixture was not purified further.

(3*R*,4*R*,5*R*,6*S*,7*R*)-4-*O*-Benzyl-3,4,5,6,7,8-hexahydroxy-5,6:7,8-di-*O*-isopropylidene-1-(2-thiazolyl)-1-octanone (*anti*-43). To a stirred solution of *tert*-butyl alcohol (0.74 g, 10 mmol) in dry THF (20 mL) was added *n*-butyllithium (6.2 mL, 10 mmol, of a 1.6 M solution in hexanes); then the mixture was cooled to −50 °C, and a solution of the aldehyde **37b** (3.50 g, 10 mmol) and 2-acetylthiazole (1.27 g, 10 mmol) in dry THF (15 mL) was added over a 30-min period. Stirring was continued for 2 h at −50 °C, and then the mixture was quenched with saturated aqueous NH_4Cl (50 mL), allowed to warm to room temperature, diluted with water (50 mL), and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to afford a 5:95 syn/anti mixture of adducts. The residue was eluted from a column of silica gel with 7:1 CCl_4–THF (containing 0.2% Et_3N) to give first unreacted aldehyde **37b** (0.74 g, 21%). Eluted second was syrupy *anti*-**43** (2.48 g, 52%): $[\alpha]_D$ = +35.6° (*c* 1, $CHCl_3$). ^1H NMR: δ 7.99 and 7.64 (2 d, 2 H, *J* = 3.1 Hz, Th), 7.35–7.23 (m, 5 H, Ph), 4.92–4.68 (2 d, 2 H, *J* = 11.4 Hz, PhCH_2), 4.49–4.41 (m, 2 H), 4.21–4.09 (m, 3 H), 3.98 (dd, 1 H, *J* = 8.1, 5.8 Hz), 3.82 (dd, 1 H, *J* = 7.9, 3.6 Hz), 3.78 (d, 1 H, *J* = 5.4 Hz, OH), 3.52 (dd, 1 H, *J* = 16.8, 8.6 Hz), 3.41 (dd, 1 H, *J* = 16.8, 3.3 Hz), 1.45, 1.42, 1.37, and 1.36 (4 s, 12 H, 4 Me).

Anal. Calcd for $C_{24}H_{31}NO_7S$: C, 60.36; H, 6.54; N,2.93. Found: C, 60.45; H, 6.61; N, 3.01.

Eluted third was the syn-adduct contaminated by *anti*-**43** (0.14 g, 3%). Eluted next was the enal **44** (0.32 g, 11%) as a syrup: $[\alpha]_D$ = −4.9° (*c* 1, $CHCl_3$). ^1H NMR: δ 9.29 (s, 1 H, CHO), 7.40–7.30 (m, 5 H, Ph), 5.97 (d, 1 H, $J_{3,4}$ = 7.0 Hz, H-3), 5.18 and 5.14 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.58 (ddd, 1 H, $J_{4,5}$ = 5.4, $J_{4,OH}$ = 3.5 Hz, H-4), 4.03 (ddd, 1 H, $J_{5,6a}$ = 6.5, $J_{5,6b}$ = 5.9 Hz, H-5), 3.92 (dd, 1 H, $J_{6a,6b}$ = 8.4 Hz, H-6a), 3.82 (dd, 1 H, H-6b), 2.50 (d, 1 H, OH), 1.41 and 1.32 (2 s, 6 H, 2 Me). ^{13}C NMR selected data: δ 189.4 (CHO), 154.2 (C=*C*O), 136.2 (*C*=CO), 109.7 (OCO), 73.0 (Ph*C*H_2), 65.4 (C-6), 26.0 and 24.6 (2 CH_3).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 66.03; H, 6.86.

Methyl 3-*O*-Benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*threo*-pentopyranoside (14). A solution of *syn*-**13** (0.5 g, 1.44 mmol) and 10-camphorsulfonic acid (10 mg) in dry MeOH (15 mL) was refluxed for 1 h, then saturated aqueous $NaHCO_3$ (2 mL) was added, the solvent was evaporated, and the residue was partitioned between brine (20 mL) and CH_2Cl_2 (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (6:4 petroleum ether–diethyl ether) to give 0.44 g (96%) of **14**: oil; $[\alpha]_D$ = −8.5° (*c* 0.8, $CHCl_3$). ^1H NMR: δ 7.84 (d, 1 H, *J* = 3.2 Hz, Th), 7.38 (m, 6 H, Ph, Th), 4.72 and 4.51 (2 d, 2 H, *J* = 11.4 Hz, PhCH_2), 4.06 (dd, 1 H, $J_{5eq,5ax}$ = 10.6, $J_{4,5eq}$ = 5.3 Hz, H-5eq), 3.93 (ddd, 1 H, $J_{2ax,3}$ = 11.0, $J_{3,4}$ = 8.8, $J_{2eq,3}$ = 4.6 Hz, H-3), 3.80 (dddd, 1 H, $J_{4,5ax}$ = 10.5, $J_{4,OH}$ = 2.3 Hz, H-4), 3.62 (dd, 1 H, H-5ax), 3.11 (s, 3H, MeO), 2.95 (dd, 1 H, $J_{2eq,2ax}$ = 13.0 Hz, H-2eq), 2.59 (d, 1 H, OH), 1.68 (dd, 1 H, H-2ax). ^{13}C NMR: δ 170.30, 143.29, 138.39, 128.68, 128.02, 127.99, 120.10, 100.56, 77.41, 70.84, 69.85, 63.30, 49.40, 39.62.

Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36. Found: C, 60.02; H, 5.65; N, 4.24.

Methyl 3-*O*-Benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*gluco*-heptopyranoside (16). The adduct *syn*-**15** (0.5 g, 1.19 mmol) was treated with 8% w/w methanolic HCl (8 mL) at 0 °C for 2 h. Then the solvent was evaporated and the residue dissolved in 1:1 MeOH–H_2O (10 mL). The solution was neutralized with Amberlyst A-26 resin, filtrated, and evaporated at a temperature not exceeding 40 °C. The residue was purified by flash chromatography on silica gel (40:1 diethyl ether–methanol) to give **16** (0.15 g, 32%): oil; $[\alpha]_D$ = −4.0° (*c* 0.4, MeOH). ^1H NMR ($CDCl_3$ + D_2O): δ 7.83 (d, 1 H, *J* = 3.2 Hz, Th), 7.38–7.20 (m, 6 H, Ph, Th), 4.58 (m, 2 H), 4.52 and 4.41 (2 d, 2 H, *J* = 11.7 Hz, PhCH_2), 4.10–3.84 (m, 4 H), 3.21 (s, 3 H, MeO), 2.73 (m, 1 H, H-2), 2.54 (m, 1 H, H-2'). ^{13}C NMR: δ 170.04, 142.79, 136.82, 128.23, 127.75, 127.37, 119.74, 105.88, 79.33, 79.35, 71.38, 71.24, 71.09, 63.49, 49.99, 44.81.

Anal. Calcd for $C_{18}H_{23}NO_6S$: C, 56.68; H, 6.08; N, 3.67. Found: C, 56.72; H, 6.26; N, 3.38.

Methyl 3,4-Di-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*ribo*-hexopyranoside (18). The adduct *anti*-**17** (0.5 g, 1.10 mmol) was treated with 8% w/w methanolic HCl (10 mL) at room temperature for 16 h, then neutralized with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 25 mL). After drying (Na_2SO_4), the solvent was evaporated and the residue was purified by column chromatography on silica gel (1:9 petroleum ether–diethyl ether) to give 0.48 g (98%) of **18**: oil; $[\alpha]_D$ = +53.8° (*c* 0.8, $CHCl_3$). ^1H NMR: δ 7.82 (d, 1 H, *J* = 3.2 Hz, Th), 7.30 (m, 11 H, 2 Ph, Th), 4.93 and 4.47 (2 d, 2 H, *J* = 12.3 Hz, PhCH_2), 4.65 and 4.60 (2 d, 2 H, *J* = 10.0 Hz, PhCH_2), 4.39 (ddd, 1 H, $J_{4,5}$ = 9.7, $J_{5,6b}$ = 4.1, $J_{5,6a}$ = 3.3 Hz, H-5), 4.03 (ddd, 1 H, $J_{2eq,3}$ = 3.4, $J_{2ax,3}$ = 3.3, $J_{3,4}$ = 3.1 Hz, H-3), 3.99 (dd, 1 H, $J_{6a,6b}$ = 12.0 Hz, H-6a), 3.93 (dd, 1 H, H-6b), 3.66 (dd, 1 H, H-4), 3.18 (s, 3 H, MeO), 2.92 (dd, 1 H, $J_{2eq,2ax}$ = 15.2 Hz, H-2eq), 2.08 (bs, 1 H, OH), 1.74 (dd, 1 H, H-2ax). ^{13}C NMR: δ 171.12, 144.07, 139.89, 138.91, 129.57, 129.44, 129.14, 128.98, 128.93, 128.65, 120.24, 100.10, 75.39, 71.56, 71.16, 70.29, 63.25, 50.47, 37.67, 30.28.

Anal. Calcd for $C_{24}H_{27}NO_5S$: C, 65.28; H, 6.16; N, 3.17. Found: C, 65.48; H, 5.96; N, 3.14.

When a solution of *anti*-**17** in MeOH was refluxed in the presence of acid, a 1,6-anhydro-D-*ribo*-hexopyranose derivative was the sole product formed; this finding was not unexpected: see ref 11d. Benzylation of **18** afforded in quantitative yield known[11d] **19**.

Methyl 3,4-Di-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*arabino*-hexopyranoside (20a). The adduct *syn*-**17** (0.20 g, 0.44 mmol) was processed as described for the synthesis of **18** to give, after column chromatography on silica gel (9:1 petroleum ether–diethyl ether), compound **20a** (0.19 g, 98%): oil; $[\alpha]_D$ = +37.3° (*c* 0.5, $CHCl_3$). ^1H NMR: δ 7.85 (d, 1 H, *J* = 3.2 Hz, Th), 7.35 (m, 11 H, 2 Ph, Th), 5.01 and 4.72 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.74 and 4.66 (2 d, 2 H, *J* = 11.0 Hz, PhCH_2), 4.21 (ddd, 1 H, $J_{2ax,3}$ = 11.2, $J_{3,4}$ = 8.8, $J_{2eq,3}$ = 4.9 Hz, H-3), 3.97 (dd, 1 H, $J_{6a,6b}$ = 11.9, $J_{5,6a}$ = 2.7 Hz, H-6a), 3.88 (dd, 1 H, $J_{5,6b}$ = 4.0 Hz, H-6b), 3.78 (ddd, 1 H, $J_{4,5}$ = 9.8 Hz, H-5), 3.66 (dd, 1 H, H-4), 3.12 (s, 3 H, MeO), 2.93 (dd, 1 H, $J_{2eq,2ax}$ = 13.0 Hz, H-2eq), 2.25 (bs, 1 H, OH), 1.79 (dd, 1 H, H-2ax). ^{13}C NMR: δ 170.81, 143.74, 139.16, 139.10, 129.10, 129.06, 128.72, 128.48, 128.35, 128.29, 120.62, 100.69, 78.05, 76.69, 75.39, 73.94, 71.97, 62.43, 50.03, 41.25.

Anal. Calcd for $C_{24}H_{27}NO_5S$: C, 65.28; H, 6.16; N, 3.17. Found: C, 65.47; H, 6.23; N, 3.35.

Methyl 3,4,6-Tri-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*arabino*-hexopyranoside (20b). Compound **20a** (0.15 g, 0.34 mmol) was benzylated as described for the preparation of **36b** to give, after column chromatography on silica gel (6:4 petroleum ether–diethyl ether), 0.18 g (100%)

of **20b**: oil; $[\alpha]_D$ = +58.1° (*c* 0.5, $CHCl_3$). ^1H NMR: δ 7.84 (d, 1 H, *J* = 3.2 Hz, Th), 7.40–7.25 (m, 16 H, 3 Ph, Th), 4.95 and 4.62 (2 d, 2 H, *J* = 10.9 Hz, PhCH_2), 4.72 and 4.66 (2 d, 2 H, *J* = 12.4 Hz, PhCH_2), 4.69 and 4.60 (2 d, 2 H, *J* = 11.6 Hz, PhCH_2), 4.17 (ddd, 1 H, $J_{2ax,3}$ = 11.3, $J_{3,4}$ = 8.9, $J_{2eq,3}$ = 4.9 Hz, H-3), 3.90–3.80 (m, 3H), 3.65 (dd, 1 H, $J_{4,5}$ = 9.2 Hz, H-4), 3.08 (s, 3 H, MeO), 2.95 (dd, 1 H, $J_{2eq,2ax}$ = 13.1 Hz, H-2eq), 1.77 (dd, 1 H, H-2ax). ^{13}C NMR: δ 169.98, 124.80, 138.36, 138.28, 138.23, 127.99 (4C), 127.95 (2C), 127.56 (2C), 127.33 (2C) 127.21, 127.17, 127.13 (2C), 127.10, 119.51, 99.44, 77.16 (2C), 74.30, 72.81, 72.68, 70.86, 68.47, 48.88, 39.81.

Anal. Calcd for $C_{31}H_{33}NO_5S$: C, 70.03; H, 6.26; N, 2.64. Found: C, 69.90; H, 6.08; N, 2.87.

Methyl 3,6-Di-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*arabino*-hexopyranoside (22). The adduct *syn*-**21** (0.90 g, 1.92 mmol) was processed as described for the synthesis of **18** to give, after column chromatography on silica gel (2:1 petroleum ether–ethyl acetate), compound **22** (0.76 g, 90%): oil; $[\alpha]_D$ = +22.6° (*c* 0.8, $CHCl_3$). ^1H NMR: δ 7.86 (d, 1 H, *J* = 3.2 Hz, Th), 7.41–7.25 (m, 11 H, 2 Ph, Th), 4.70 and 4.53 (2 d, 1 H, *J* = 11.6 Hz, PhCH_2), 4.73 and 4.68 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2) 3.99 (ddd, 1 H, $J_{2ax,3}$ = 11.2, $J_{3,4}$ = 8.9, $J_{2eq,3}$ = 4.8 Hz, H-3), 3.90–3.65 (m, 4 H), 3.12 (s, 3 H, MeO), 2.97 (dd, 1 H, $J_{2eq,2ax}$ = 13.2 Hz, H-2eq), 2.81 (bs, 1 H, OH), 1.74 (dd, 1 H, H-2ax). ^{13}C NMR: δ 169.89, 142.80, 138.07, 137.91, 128.14 (2C), 128.05 (2C), 127.44 (4C), 127.24, 127.16, 119.61, 99.62, 76.51, 72.99, 72.39, 72.55 (2 C), 69.38, 48.97, 33.09.

Anal. Calcd for $C_{24}H_{27}NO_5S$: C, 65.28; H, 6.16; N, 3.17. Found: C, 65.46; H, 6.22; N, 3.37.

The benzylation of compound **22** gave **20b** in quantitative yield, identical to the compound obtained from cyclization of *syn*-**17** and benzylation (Scheme 4).

Methyl 3,4,6,7,8-Penta-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-β-D-*glycero*-D-*galacto*-octopyranoside (31). The adduct *syn*-**30** (1.43 g, 2 mmol) was treated with 2% w/w methanolic HCl (60 mL) at room temperature for 13 h. Then the solvent was evaporated and the residue dissolved in 9:1 MeOH–H_2O (20 mL). The solution was neutralized with Amberlyst A-26 resin, filtrated, and evaporated at a temperature not exceeding 40 °C. The crude product was benzylated in DMF with benzyl bromide and sodium hydride, as described for the preparation of **36b**. Purification by column chromatography on silica gel (10:1 toluene–ethyl acetate) afforded **31** (0.93 g, 60%) as a syrup: $[\alpha]_D$ = −15.5° (*c* 1, $CHCl_3$). ^1H NMR: δ 7.84 (d, 1 H, *J* = 3.2 Hz, Th), 7.37–7.20 (m, 26 H, 5 Ph, Th), 5.02 and 4.62 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.83 and 4.55 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.82 and 4.55 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.67 and 4.51 (2 d, 2 H, *J* = 11.3 Hz, PhCH_2), 4.54 and 4.51 (2 d, 2 H, *J* = 12.2 Hz, PhCH_2), 4.30 (dd, 1 H, $J_{5,6}$ = 1.6, $J_{6,7}$ = 5.7 Hz, H-6), 4.24 (ddd, 1 H, $J_{2eq,3}$ = 4.9, $J_{2ax,3}$ = 11.5, $J_{3,4}$ = 8.8 Hz, H-3), 4.13 (dd, 1 H, $J_{7,8a}$ = 2.0, $J_{8a,8b}$ = 11.0, H-8a), 4.07 (ddd, 1 H, $J_{7,8b}$ = 1.6 Hz, H-7), 4.05 (dd, 1 H, $J_{4,5}$ = 10.0 Hz, H-5), 3.80 (dd, 1 H, H-8b), 3.78 (dd, 1 H, H-4), 2.96 (dd, 1 H, $J_{2eq,2ax}$ = 13.0 Hz, H-2eq), 2.94 (s, 3 H, MeO), 1.76 (dd, 1 H, H-2ax).

Anal. Calcd for $C_{47}H_{49}NO_7S$: C, 73.13; H, 6.40; N, 1.81. Found: C, 73.35; H, 6.48; N, 1.71.

1,6-Anhydro-3,4-di-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*glycero*-D-*talo*-octopyranoside (40b). A solution of *anti*-**39b** (1.13 g, 2 mmol) in 4:1 acetic acid–water (60 mL) was refluxed for 30 min, then cooled to room temperature, and concentrated. The residue was eluted from a column of silica gel with 2:1 ethyl acetate–petroleum ether to give **40b** (0.61 g, 65%) as a white solid: mp 139–140 °C (from AcOEt–hexane); $[\alpha]_D$ = +34.4° (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$ + D_2O): δ 7.82 (d, 1 H, *J* = 3.2 Hz, Th), 7.46–7.28 (m, 11 H, 2 Ph, Th), 4.90 (bd, 1 H, $J_{4,5}$ = 2.4 Hz, H-5), 4.86 (s, 2 H, PhCH_2), 4.61 and 4.56 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.00 (ddd, 1 H, $J_{2eq,3}$ = 5.9, $J_{2ax,3}$ = 11.0, $J_{3,4}$ = 4.0 Hz, H-3), 3.83 (bd, 1 H, $J_{6,7}$ = 7.5 Hz, H-6), 3.78 (dd, 1 H, H-4), 3.76 (dd, 1 H, $J_{8a,8b}$ = 11.0, $J_{7,8a}$ = 3.5 Hz, H-8a), 3.70 (dd, 1 H, $J_{7,8b}$ = 4.1 Hz, H-8b), 3.61 (ddd, 1 H, H-7), 2.82 (dd, 1 H, $J_{2eq,2ax}$ = 12.8 Hz, H-2eq), 2.73 (dd, 1 H, H-2ax). ^1H NMR ($CDCl_3$ + trichloroacetyl isocyanate) selected data: 8.41 and 8.37 (2 s, 2 H, 2 NH), 5.06 (ddd, 1 H, H-7), 4.79 (dd, 1 H, H-8a), 4.76 (bd, 1 H, H-5), 4.35 (dd, 1 H, H-8b), 4.18 (bd, 1 H, H-6), 3.98 (ddd, 1 H, H-3), 3.84 (dd, 1 H, H-4), 2.93 (dd, 1 H, H-2eq), 2.51 (dd, 1 H, H-2ax).

Anal. Calcd for $C_{25}H_{27}NO_6S$: C, 63.95; H, 5.80; N, 2.98. Found: C, 63.76; H, 5.91; N, 2.87.

Different conditions (CSA–MeOH, HCl–MeOH) led to similar results.

1,6-Anhydro-3,4,7,8-tetra-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*glycero*-D-*talo*-octopyranoside (41). Route a. Benzylation of the diol **40b** (0.94 g, 2 mmol) as described for the preparation of **36b** afforded, after column chromatography on silica gel (3:1 petroleum ether–ethyl acetate), **41** (1.23 g, 95%) as a syrup: $[\alpha]_D$ = +18.3° (*c* 1, $CHCl_3$). ^1H NMR: d.7.81 (d, 1 H, *J* = 3.8 Hz, Th), 7.43–7.28 (m, 21 H, 4 Ph, Th), 4.82 (s, 2 H, PhCH_2), 4.79 (bd, 1 H, $J_{4,5}$ = 2.4 Hz, H-5), 4.73 and 4.50 (2 d, 2 H, *J* = 11.4 Hz, PhCH_2), 4.60 and 4.49 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.58 (s, 2 H, PhCH_2), 3.97 (ddd, 1 H, $J_{2eq,3}$ = 5.8, $J_{2ax,3}$ = 10.8, $J_{3,4}$ = 4.0 Hz, H-3), 3.92 (bd, 1 H, $J_{6,7}$ = 8.6 Hz, H-6), 3.80 (dd, 1 H, $J_{7,8a}$ = 1.7, $J_{8a,8b}$ = 10.6 Hz, H-8a), 3.74 (dd, 1 H, H-4), 3.58 (dd, 1 H, $J_{7,8b}$ = 4.3 Hz, H-8b), 3.54 (ddd, 1 H, H-7), 2.83 (dd, 1 H, $J_{2eq,2ax}$ = 13.1 Hz, H-2eq), 2.55 (dd, 1 H, H-2ax).

Anal. Calcd for $C_{39}H_{39}NO_6S$: C, 72.09; H, 6.05; N, 2.16. Found: C, 72.32; H, 6.14; N, 2.28.

Route b. The adduct *anti*-**39c** was refluxed for 1 h in 6:4 AcOH–H_2O to give crude 1,6-anhydro-3-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*glycero*-D-*talo*-octopyranoside (**40a**), which, after benzylation and column chromatography purification, afforded **41** in 58% total yield.

Route c. The adduct *anti*-**43** (1.43 g, 3 mmol) was refluxed in 4:1 AcOH–H_2O as described for the preparation of **40b** to give, after column chromatography on silica gel (AcOEt), 1,6-anhydro-4-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*glycero*-D-*talo*-octopyranoside (**45**) (0.68 g, 60%) as a syrup: $[\alpha]_D$ = +66.3° (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$ + D_2O): δ 7.82 (d, 1 H, *J* = 3.2 Hz, Th), 7.43–7.28 (m, 6 H, Ph, Th), 5.00 (bd, 1 H, $J_{4,5}$ = 2.2 Hz, H-5), 4.88 and 4.63 (2 d, 2 H, *J* = 11.4 Hz, PhCH_2), 4.16 (ddd, 1 H, $J_{2eq,3}$ = 6.1, $J_{2ax,3}$ = 10.5, $J_{3,4}$ = 2.6 Hz, H-3), 3.93 (bd, 1 H, $J_{6,7}$ = 8.0 Hz, H-6), 3.84 (dd, 1 H, $J_{7,8a}$ = 3.7, $J_{8a,8b}$ = 11.5 Hz, H-8a), 3.76 (dd, 1 H, $J_{7,8b}$ = 4.3 Hz, H-8b), 3.71 (dd, 1 H, H-4), 3.66 (ddd, 1 H, H-7), 2.72 (dd, 1 H, $J_{2eq,2ax}$ = 13.1 Hz, H-2eq), 2.29 (dd, 1 H, H-2ax). Anal. Calcd for $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69. Found: C, 56.75; H, 5.66; N, 3.60. This triol was submitted to benzylation and column chromatography purification to give **41** in 96% yield.

Methyl 4,5,7-Tri-*O*-benzyl-3-deoxy-α-D-*arabino*-2-heptosulopyranoside (23). A mixture of **20b** (0.80 g, 1.5 mmol), activated 4-Å powdered molecular sieve (3.0 g), and dry CH_3CN (15 mL) was stirred at room temperature for 10 min, and then methyl triflate (0.20 mL, 1.8 mmol) was added. The suspension was stirred for 15 min and then concentrated to dryness. The crude methylthiazolium salt was suspended in MeOH (15 mL), cooled to 0 °C, and treated with $NaBH_4$ (125 mg, 3.3 mmol). The mixture was stirred at room temperature for an additional 10 min, diluted with acetone (15 mL), filtered through Celite, and concentrated. To a solution of the crude thiazolidines in 10:1 CH_3CN–H_2O (15 mL) were added CuO (0.95 g, 12 mmol) and then, portionwise and under vigorous stirring, $CuCl_2 \cdot 2H_2O$ (0.26 g, 1.5 mmol). The mixture was stirred for 15 min and then filtered through Celite. Acetonitrile and most of the water were evaporated (bath temperature not exceeding 40 °C) to give a brown syrup, which was triturated with Et_2O (5 × 15 mL), and the liquid phase was pipetted and filtered through a pad (1 × 3 cm, h × d) of Florisil (100–200 mesh) to afford a colorless solution. After a further washing of Florisil with AcOEt (15 mL) the combined organic phases were concentrated to yield almost pure (NMR analysis) syrupy aldehyde **23** (0.54 g, 76%). An analytical sample was obtained by column chromatography on silica gel (2:1 diethyl ether–petroleum ether): $[\alpha]_D$ = +34.6° (*c* 0.7, $CHCl_3$). ^1H NMR: δ 9.51 (s, 1 H, CHO), 7.40–7.19 (m, 15 H, 3 Ph), 4.90 and 4.56 (2 d, 2 H, *J* = 11.0 Hz, PhCH_2), 4.68–4.58 (4 d, 4 H, 2 PhCH_2), 4.02 (ddd, 1 H, $J_{3ax,4}$ = 10.9, $J_{4,5}$ = 8.6, $J_{3eq,4}$ = 5.1 Hz, H-4), 3.84–3.74 (m, 3 H), 3.62 (dd, 1 H, $J_{5,6}$ = 8.8 Hz, H-5), 3.26 (s, 3 H, MeO), 2.26 (dd, 1 H, $J_{3eq,3ax}$ = 13.0 Hz, H-3eq), 1.58 (dd, 1 H, H-3ax). ^{13}C NMR: δ 197.78, 142.46, 137.98, 137.91, 128.00 (6C), 127.52 (3C), 127.30 (6C), 99.30, 74.28, 72.82, 72.33, 71.13, 71.11, 68.86, 68.22, 49.69, 28.74.

Anal. Calcd for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77. Found: C, 73.37; H, 6.82.

Methyl 4,5,7,8,9-Penta-*O*-benzyl-3-deoxy-β-D-*glycero*-D-*galacto*-2-nonosulopyranoside (32). Treatment of the thiazole derivative **31** (0.77 g, 1 mmol) as described for the preparation of **23** gave almost pure (NMR analysis) syrupy aldehyde **32** (0.52 g, 70%). An analytical sample was obtained by column chromatography on silica gel (2:1 diethyl ether–petroleum ether): $[\alpha]_D$ = −30° (*c* 1, $CHCl_3$). ^1H NMR: δ 9.40 (s, 1 H, CHO), 7.39–7.21 (m, 25 H, 5 Ph), 4.96 and 4.43 (2 d, 2 H, *J* = 11.4 Hz, PhCH_2), 4.80 and 4.60 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.77 and 4.53 (2 d, 2 H, *J* = 11.9 Hz, PhCH_2), 4.61 and 4.53 (2 d, 2 H, *J* = 11.6 Hz, PhCH_2), 4.58 and 4.49 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.27 (dd, 1 H, $J_{6,7}$ = 1.6, $J_{7,8}$ = 5.6 Hz, H-7), 4.05 (ddd, 1 H, $J_{3eq,3}$ = 4.6, $J_{3ax,3}$ = 10.9, $J_{4,5}$ = 8.2 Hz, H-4), 4.03-3.94 (m, 3 H), 3.79–3.69 (m, 2 H), 3.10 (s, 3 H, MeO), 2.25 (dd, 1 H, $J_{3eq,3ax}$ = 12.9 Hz, H-3eq), 1.57 (dd, 1 H, H-3ax).

Anal. Calcd for $C_{45}H_{48}O_8$: C, 75.40; H, 6.75. Found: C, 75.14; H, 6.88.

(Methyl 4,5,7-tri-*O*-benzyl-3-deoxy-α-D-*arabino*-2-heptulopyranosid)-onic Acid (24). To a vigorously stirred mixture of silver nitrate (0.34 g, 2 mmol), NaOH (0.16 g, 4 mmol), and water (10 mL) was added a solution of **23** (0.48 g, 1 mmol) in freshly distilled THF (20 mL). Stirring was continued for 24 h at room temperature, then acetic acid was added up to pH = 5, and the mixture was filtered through Celite. The solution was concentrated, the residue was dissolved in CH_2Cl_2 (60 mL), washed with water (5 mL), and dried (Na_2SO_4), and the solvent was evaporated to give almost pure (NMR analysis) acid **24** (0.47 g, 96%) as a syrup. An analytical sample was obtained by chromatography on a Sephadex LH-20 column (2 × 80 cm) with 1:1 MeOH–CH_2Cl_2 as the eluent: $[\alpha]_D$ = +53° (*c* 0.9, $CHCl_3$). ^1H NMR: δ 7.38–7.15 (m, 15 H, 3 Ph), 4.90 and 4.52 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.66 and 4.58 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.60 and 4.51 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.02 (ddd, 1 H, $J_{3ax,4}$ = 11.2, $J_{4,5}$ = 8.4, $J_{3eq,4}$ = 4.7 Hz, H-4), 3.81–3.70 (m, 3 H), 3.60 (dd, 1 H, $J_{5,6}$ = 9.0 Hz, H-5), 3.25 (s, 3 H, MeO), 2.60 (dd, 1 H, $J_{3eq,3ax}$ = 13.2 Hz, H-3eq), 1.75 (dd, 1 H, H-3ax). ^{13}C NMR: δ 168.54, 138.95, 137.90, 137.76, 128.23, 128.07, 128.03, 127.81, 127.76, 127.71, 127.67, 127.51, 127.39, 98.47, 74.22, 72.89, 72.84, 72.10, 72.04, 71.01, 67.85, 50.19, 32.88.

Anal. Calcd for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55. Found: C, 70.58; H, 6.68.

(Methyl 4,5,7,8,9-penta-*O*-benzyl-3-deoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onic Acid (33a). The aldehyde **32** (0.36 g, 0.5 mmol) was oxidized as described for the preparation of **24** to afford almost pure (NMR analysis) acid **33a** (0.35 g, 95%) as a syrup. An analytical sample was obtained by chromatography on a Sephadex LH-20 column (2 × 80 cm) with 1:1 MeOH–CH_2Cl_2 as the eluent: $[\alpha]_D$ = –25.9° (*c* 0.9, $CHCl_3$). ^1H NMR: δ 7.38–7.20 (m, 25 H, 5 Ph), 4.94 and 4.65 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.68 and 4.44 (2 d, 2 H, *J* = 11.4 Hz, PhCH_2), 4.63 and 4.34 (2 d, 2 H, *J* = 11.4 Hz, PhCH_2), 4.55 and 4.51 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.19 (dd, 1 H, $J_{6,7}$ = 1.4, $J_{7,8}$ = 4.8 Hz, H-7), 4.06 (ddd, 1 H, $J_{3ax,4}$ = 10.9, $J_{3eq,4}$ = 4.3, $J_{4,5}$ = 8.3 Hz, H-4), 3.98–3.86 (m, 3 H), 3.73–3.66 (m, 2 H), 3.08 (s, 3 H, MeO), 2.61 (dd, 1 H, $J_{3eq,3ax}$ = 13.2 Hz, H-3eq), 1.74 (dd, 1 H, H-3ax).

Anal. Calcd for $C_{45}H_{48}O_9$: C, 73.75; H, 6.60. Found: C, 73.50; H, 6.69.

(2,7-Anhydro-4,5,8,9-tetra-*O*-benzyl-3-deoxy-α-D-*glycero*-D-*talo*-2-nonulopyranosid)onic Acid (42b). The thiazole derivative **41** (0.65 g, 1 mmol) was treated as described for the preparation of **23** to give the crude aldehyde, which was immediately oxidized with Ag_2O (see the synthesis of **24**). The crude product was eluted from a Sephadex LH-20 column (3 × 90 cm) with 1:1 MeOH–CH_2Cl_2 to give **42b** (0.41 g, 68%) as a syrup: $[\alpha]_D$ = +23.2° (*c* 1, $CHCl_3$). ^1H NMR: δ 7.40–7.18 (m, 20 H, 4 Ph), 4.75 and 4.71 (2 d, 2 H, *J* = 12.6 Hz, PhCH_2), 4.59 (bs, 1 H, H-6), 4.57 and 4.36 (2 d, 2 H, *J* = 11.6 Hz, PhCH_2), 4.54 (s, 2 H, PhCH_2), 4.53 and 4.49 (2 d, 2 H, *J* = 12.2 Hz, PhCH_2), 3.80 (bd, 1 H, $J_{7,8}$ = 7.6 Hz, H-7), 3.76 (ddd, 1 H, $J_{3ax,4}$ = 11.0, $J_{3eq,4}$ = 6.3, $J_{4,5}$ = 4.1 Hz, H-4), 3.64 (dd, 1 H, $J_{9a,9b}$ = 10.1, $J_{8,9a}$ = 6.4 Hz, H-9a), 3.62 (bd, 1 H, H-5), 3.57 (dd, 1 H, $J_{8,9b}$ = 2.3 Hz, H-9b), 3.48 (ddd, 1 H, H-8), 2.38 (dd, 1 H, $J_{3ax,3eq}$ = 13.1 Hz, H-3eq), 2.29 (dd, 1 H, H-3ax).

Anal. Calcd for $C_{37}H_{38}O_8$: C, 72.77; H, 6.27. Found: C, 72.60; H, 6.41.

(Methyl 3-deoxy-α-D-*arabino*-2-heptulopyranosid)onic Acid (Me-1). A vigorously stirred mixture of **24** (0.20 g, 0.4 mmol) and 10% palladium on activated carbon (50 mg) in 9:1 MeOH–H_2O (10 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred for an additional 3 h at room temperature under a slightly positive pressure of H_2, then filtered through a plug of cotton, and concentrated to afford in quantitative yield Me-**1** as a syrup: $[\alpha]_D$ = +68.6° (*c* 1, MeOH). ^1H NMR (D_2O): δ 3.95 (ddd, 1 H, $J_{3ax,4}$ = 11.8, $J_{3eq,4}$ = 5.1, $J_{4,5}$ = 9.5 Hz, H-4), 3.92 (dd, 1 H, $J_{6,7a}$ = 2.3, $J_{7a,7b}$ = 12.5 Hz, H-7a), 3.84 (dd, 1 H, $J_{6,7b}$ = 5.4 Hz, H-7b), 3.70 (ddd, 1 H, $J_{5,6}$ = 10.2 Hz, H-6), 3.42 (dd, 1 H, H-5), 3.26 (s, 3 H, MeO), 2.36 (dd, 1 H, $J_{3eq,3ax}$ = 13.3 Hz, H-3eq), 1.94 (dd, 1 H, H-3ax).

Anal. Calcd for $C_8H_{14}O_7 \cdot H_2O$: C, 40.00; H, 6.71. Found: C, 39.95; H, 6.67.

(Methyl 3-deoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onic Acid (33b). The acid **33a** (0.37 g, 0.5 mmol) was treated as described for the preparation of Me-**1** to give in quantitative yield **33b** as a syrup: $[\alpha]_D$ = –44.1° (*c* 1, MeOH). ^1H NMR (D_2O): δ 3.98 (ddd, 1 H, $J_{3ax,4}$ = 11.5, $J_{3eq,4}$ = 5.0, $J_{4,5}$ = 9.4 Hz, H-4), 3.94-3.70 (m, 5 H), 3.58 (dd, 1 H, $J_{5,6}$ = 9.6 Hz, H-5), 3.27 (s, 3 H, MeO), 2.33 (dd, 1 H, $J_{3eq,3ax}$ = 13.4 Hz, H-3eq), 1.72 (dd, 1 H, H-3ax).

Anal. Calcd for $C_{10}H_{18}O_9 \cdot 2H_2O$: C, 37.74; H, 6.97. Found: C, 37.67; H, 7.03.

(2,7-Anhydro-3-deoxy-α-D-*glycero*-D-*talo*-2-nonulopyranosid)onic Acid (42a). The acid **42b** (0.31 g, 0.5 mmol) was treated as described for the preparation of Me-**1** to give in quantitative yield **42a** as a syrup: $[\alpha]_D$ = +62.5° (*c* 1.5, MeOH). ^1H NMR (D_2O): δ 4.72 (bd, 1 H, $J_{5,6}$ = 2.4 Hz, H-6), 4.15–3.50 (m, 6 H), 2.30 (dd, 1 H, $J_{3eq,3ax}$ = 13.1, $J_{3eq,4}$ = 5.8 Hz, H-3eq), 1.85 (dd, 1 H, $J_{3ax,4}$ = 11.2 Hz, H-3ax).

Anal. Calcd for $C_9H_{14}O_8 \cdot H_2O$: C, 40.30; H, 6.01. Found: C, 40.21; H, 6.05.

3-Deoxy-D-*arabino*-2-heptulopyranosonic Acid (1). A solution of Me-**1** (67 mg, 0.3 mmol) in 4:1 AcOH–H_2O (5 mL) was refluxed for 1 h, then cooled to room temperature, and concentrated. The residue was eluted from a Sephadex G-10 column (1 × 80 cm) with 1:1 MeOH–H_2O to give the acid **1** (44 mg, 70%), homogeneous by TLC analysis (6:2:0.6:1 ethyl acetate–pyridine–acetic acid–water). To a solution of this product in 1:1 MeOH–H_2O (2 mL) was added a freshly prepared (in an argon atmosphere) solution of barium hydroxide octahydrate (33 mg, 0.11 mmol) in H_2O (5 mL). After 1 h at room temperature the solution was partially concentrated under vacuum and then lyophilized to afford DAH barium salt as a white solid: mp 180 °C (dec); $[\alpha]_D$ = +31° (*c* 0.6, H_2O); lit.[10c] mp 185 °C (dec); $[\alpha]_D$ = +33° (*c* 1, H_2O). The ^1H NMR data were in agreement with those reported.[10c]

3-Deoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonic Acid (4). A solution of **33b** (85 mg, 0.3 mmol) in 4:1 AcOH–H_2O (5 mL) was refluxed for 1 h, then cooled to room temperature, and concentated. The residue was eluted from a Sephadex G-10 column (1 × 80 cm) with 1:1 MeOH–H_2O to give the acid **4** (68 mg, 80%), homogeneous by TLC analysis (5:5:1:3 ethyl acetate–pyridine–acetic acid–water). A solution of this product in H_2O (2 mL) was treated with 0.5 M ammonium hydroxide up to pH = 7 and then lyophilized to give KDN ammonium salt as a white solid: $[\alpha]_D$ = –42° (*c* 0.8, H_2O); lit.[56] $[\alpha]_D$ = –41° (H_2O). The ^1H NMR data were in agreement with those reported.[56]

Acknowledgment. This work was supported by a grant from Progetto Finalizzato Chimica Fine e Secondaria 2, CNR (Roma). We are also grateful to the Ministerio de Educacion y Ciencia (Spain) for awarding a postdoctoral fellowship to P.M.

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