Chemistry of the Enolates of 2-Acetylthiazole: Aldol Reactions with Chiral Aldehydes To Give 3-Deoxy Aldos-2-uloses and 3-Deoxy 2-Ulosonic Acids. A Short Total Synthesis of 3-Deoxy-D-*manno*-2-octulosonic Acid (KDO)[1]

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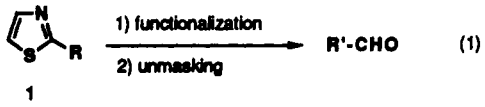
The acetyl group of 2-acetylthiazole (2-ATT) was selectively metalated by treatment with lithium *tert*-butoxide (the lithium enolate was formed) or triethylamine/zinc chloride/trimethylsilyl chloride (the silyl enol ether was formed). The use of strong bases (LDA, TMP) resulted in substantial deprotonation of the thiazole ring. The lithium enolate of 2-ATT, formed under conditions of kinetic control, reacted with aliphatic and aromatic aldehydes to give the corresponding aldols (β-hydroxyalkyl 2-thiazolyl ketones) in isolated yields of 51–65%. The reaction of the lithium enolate with chiral compounds, i.e., various alkoxy-substituted aldehydes and one amino aldehyde derivative, occurred with a high degree of anti diastereoselectivity (80–92%), an outcome that was in accord with the Felkin–Ahn model for asymmetric induction. Hemiketalization of the aldols that resulted from the reaction of the enolate with D-glyceraldehyde acetonide and 2-*O*-benzyl D-erythrose acetonide and subsequent liberation of the formyl group by hydrolytic cleavage of the thiazole ring afforded the corresponding aldosuloses. Oxidation converted these to ulosonic acids. The application of this three-carbon-chain elongation to D-arabinose diacetonide afforded the octulosonic acid KDO in 6.8% overall yield.

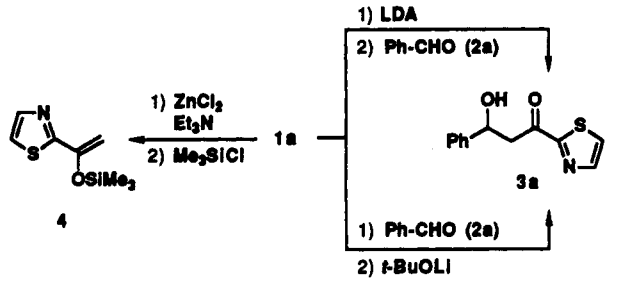
The use of thiazoles (1) as the synthetic equivalent of a formyl group has been demonstrated in the synthesis of carbohydrates.[3] Access to various functionalized aldehydes was provided, in essence, by two key operations (eq 1): (1) the construction of a functionalized carbon chain



at C-2 of the thiazole ring by the reaction of the substituent (R) at C-2 with a suitable substrate (*functionalization*); (2) the generation of the aldehyde by cleavage of the thiazole ring (*unmasking*).[4] Reagents that have been designed and extensively employed for this purpose include 2-(trimethylsilyl)thiazole (2-TST, **1b**),[5] (2-thiazolylmethylene)triphenylphosphorane (2-TMP, **1c**),[6] and 2-thiazolyl carbonitrile *N*-oxide (2-TNO, **1d**).[7] The advantages of using such compounds 1, i.e., high reactivity, the formation of products that are stable to isolation and purification, the ease of cleaving the thiazole ring under neutral conditions, induced us to explore the possibility of utilizing other substituted thiazoles to extend the scope of this methodology in synthesis.

How to construct a 1,3-dioxygenated carbon fragment remains one of the most important problems in the synthesis of natural products, especially those, like polyene and polyol macrolide antibiotics,[8] that arise via the polyacetate and polypropionate biosynthetic pathways. Synthetic approaches to such compounds have employed β-hydroxy carbonyl compounds as key intermediates. The latter are accessible from aldehydes by aldol-type condensations[9] or by the ring-opening of Δ^2-isoxazolines, which in turn are prepared by the cycloaddition of nitrile oxides to olefins.[10] Alternative synthetic approaches, which lead

Scheme I



(1) Presented in part by the senior author (A.D.) at the Royal Society of Chemistry Carbohydrate Group Annual Symposium (Cardiff, U.K., March 1990) and at the Royal Society of Chemistry Annual Chemical Congress (Belfast, N. Ireland, April 1990).

(2) Postdoctoral Research Associate [Grant PF-89-17871707 from the Ministerior de Educacion y Ciencia (Spain)].

(3) Thiazole route to carbohydrates: synthesis of building blocks or precursors to carbohydrates and related compounds using functionally substituted thiazoles at C-2 as auxiliaries. For recent accounts see: Dondoni, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1989**, *43*, 25. Dondoni, A. *Pure and Appl. Chem.* **1990**, *62*, 643.

(4) Examples of syntheses performed in this manner include (a) higher carbohydrates: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693. (b) Amino sugars and sphingosines: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439. (c) Higher ene sugars: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *J. Carbohydr. Chem.* **1990**, *9*, 735. (d) Epidaunosamine and lincosamine analogues: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *Tetrahedron* **1990**, *46*, 6167.

(5) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1988**, *53*, 1748. Dondoni, A. *Org. Synth.*, submitted for publication.

(6) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 2121.

(7) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, 998. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 3215.

(8) *Macrolide Antibiotics. Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984. Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. For recent papers: Mori, Y.; Takeuchi, A.; Kageyama, H.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5423. Mori, Y.; Suzuki, M. *Ibid.* **1989**, *30*, 4383. Nakata, T.; Hata, N.; Oishi, T. *Ibid.* **1990**, *31*, 381. Maehr, H.; Yang, R.; Hong, L.-N.; Liu, C.-M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1989**, *54*, 3817. Prandi, J.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 4517 and 4521. Driver, M. J.; MacLachlan, W. S.; MacPherson, D. T. Readshaw, S. A. *J. Chem. Soc., Chem. Commun.* **1990**, 636.

(9) For leading references on aldol condensations, see: (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3. (c) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. (d) For recent selected papers, see: Masamune, S.; Sato, T.; Kim, B.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 827. Enders, D.; Lohray, B. B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 581. Yamazaki, T.; Yamamoto, T.; Kitazume, T. *J. Org. Chem.* **1989**, *54*, 83. Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997. Yu, K.-L.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1442. Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357. Dandan, H.; Hausen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173. Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481.

(10) For leading references, see: Torssell, K. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*; VCH: New York, 1988. Curran, D. P. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: New York, 1988; Vol. 1, p 129. Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253. For recent selected papers see: Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585. Kozikowski, A. P.; Park, P. *Ibid.* 4668.

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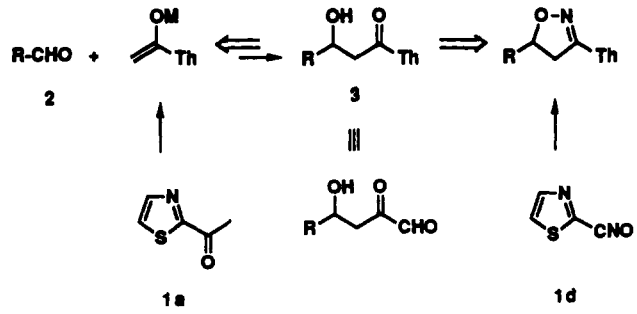


Figure 1.

to protected aldols, have also been presented.[11] Thus, we sought an access to aldols bearing a masked formyl group, i.e., 2-oxo-4-hydroxybutanal fragments,[12] by combining the methods outlined above with one based on thiazole chemistry (Figure 1). The incorporation of a reactive functionality like the formyl group at one terminus of the aldol would increase the aldol's synthetic value. Results of an attempt to achieve this end via the cycloaddition of 2-TNO (**1d**) to olefins have been reported in part.[7] This paper describes in full[13a] the aldol-type reactions of the lithium enolate of 2-acetylthiazole (2-ATT, **1a**) with various aldehydes **2** to give β-hydroxyalkyl 2-thiazolyl ketones **3** (thiazole aldols). The conversion of suitably substituted derivatives to 3-deoxy aldos-2-uloses and 2-ulosonic acids, one of which is a compound of biological relevance, i.e., KDO,[13b] is also described.

Results and Discussion

Aldol Reactions of the Lithium Enolate of 2-Acetylthiazole. The chemistry of the enolates of 2-ATT (**1a**) has hitherto been largely unexplored.[14] Therefore, methods for the generation of a metal enolate of **1a** were explored to find the conditions whereby an efficiently directed aldol reaction could be performed.[9a] Attempts to perform an aldol reaction by treating **1a** with a THF solution of a slight excess of LDA at −70 °C and then introducing benzaldehyde (**2a**) gave a complex mixture of products (TLC analysis) from which aldol **3a** was isolated in 10% yield.[15] (Scheme I). Very likely, under these conditions, unselective deprotonation of **1a** took place.[16]

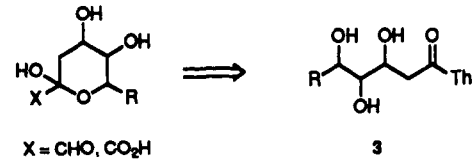
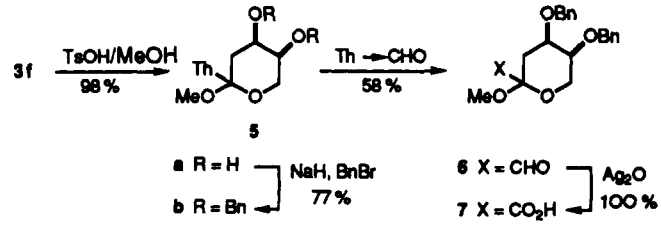


Figure 2.

Scheme II[a,b]



[a] Th = 2-Thiazolyl. [b] Th → CHO: (a) MeI; (b) $NaBH_4$; (c) $HgCl_2$–H_2O.

In fact, quenching a THF solution of **1a** and LDA with D_2O at −78 °C gave a complex mixture of deuterated products as the complex ^1H NMR spectrum of the reaction mixture showed. Similar results were obtained when an attempt was made to prepare the silyl enol ether **4** by treating a mixture of **1a** and LDA with trimethylsilyl chloride.[17] However, satisfactory results were obtained by generating the lithium enolate of **1a** under conditions of kinetic control, i.e., by treating **1a** with a hindered base in the presence of the aldehyde.[18] Thus, the reaction that ensued on introducing a THF solution of 2-ATT (**1a**) and benzaldehyde (**2a**) into a THF solution of lithium *tert*-butoxide at −50 °C afforded the aldol **3a** in 54% isolated yield (after chromatographic purification). This method was also applied successfully with various other aldehydes **2** and gave the corresponding aldols **3** in satisfactory yields (Table I). Among the achiral products, the aldols **3b** and **3c** are worthy of note because, in the former, both termini of the carbon chain are latent formyl groups and, in the latter, each terminus represents a different masked functionality.[19] From the chiral aldehydes **2f–j** the corresponding anti-aldols **3f–j** were obtained as the major products (diastereoselectivity = 80–92%). This result was consistent with a reaction via a nonchelation-controlled process and with the Felkin–Anh–Houk model for asymmetric induction.[20] Anti selectivity was reported[12b,21] for the addition under nonchelating conditions of ketone enolates to various α,β-dialkoxy aldehydes, one of which was the D-glyceraldehyde acetonide **2f**. The stereochemistry assigned tentatively to the products was established by ^1H NMR analysis of the cyclic products derived from **3h** and **3i** (vide infra). In a similar manner, the stereo-

(11) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827. Ireland, R. E.; Wipf, P.; Miltz, W.; Vanasse, B. *J. Org. Chem.* **1990**, *55*, 1423.

(12) Access to these functionalized aldehyde units should also be possible via the aldol reactions of metal enolates of pyruvic aldehyde dimethyl acetal. To our knowledge only a few descriptions of the enolates of that compound have appeared. See: (a) Ito, M.; Iwata, T.; Tsukida, K. *Chem. Pharm. Bull.* **1986**, *34*, 4346. (b) Narasaka, K.; Pai, F.-G. *Tetrahedron* **1984**, *40*, 2233.

(13) Preliminary communications: (a) Dondoni, A.; Fantin, G.; Fogagnolo, M. *Tetrahedron Lett.* **1989**, *30*, 6063. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *Ibid.* **1990**, *31*, 4513.

(14) For a compilation of the condensation reactions of heteroaryl methyl ketones with aldehydes, see: Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1.

(15) Low yields of **3a** were obtained by deprotonation of **1a** with LDA in the presence of HMPA (−70 °C) or with lithium 2,2,6,6-tetramethylpiperidine (TMP). Quenching the LDA-generated enolate at −70, −30, or −10 °C did not improve the yield.

(16) It is likely that the high kinetic acidity of the C-5 proton of the thiazole ring is increased by the presence of the electron-withdrawing acetyl group at C-2. For leading references on the acidity of thiazoles and the hydrogen–metal exchange reactions of thiazoles, see: Metzger, J. V.; Vincent, E.-J.; Chouteau, J.; Mille, J. In *Thiazole and Its Derivatives*; Metzger, J. V., Ed.; Wiley: New York, 1979; Part 1, pp 113–124. For recent examples of metalation of thiazoles see: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Mastellari, A.; Medici, A.; Negrini, E.; Pedrini, P. *Gazz. Chim. Ital.* **1988**, *118*, 211. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1988**, *53*, 1748.

(17) The silyl enol ether **4** (an oil, bp 120 °C (17 mmHg)) was prepared by treating **1a** with Me_3SiCl in the presence of Et_3N and $ZnCl_2$. See: Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. A study of the aldol reactions of **4** and other metal derivatives of **1a** is currently underway.

(18) Kuwajima, I.; Sato, T.; Arai, M.; Minami, N. *Tetrahedron Lett.* **1976**, 1817.

(19) For the use of furan as a synthetic equivalent group of a 1,4-dicarbonyl compound, carboxylic acid, etc., see: Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. See also: Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15.

(20) Cherest, M; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Anh, N. *J. Top. Curr. Chem.* **1980**, *88*, 145. Wu, Y.-D.; Houk, N. K. *J. Am. Chem. Soc.* **1987**, *109*, 908.

(21) (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. (b) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.

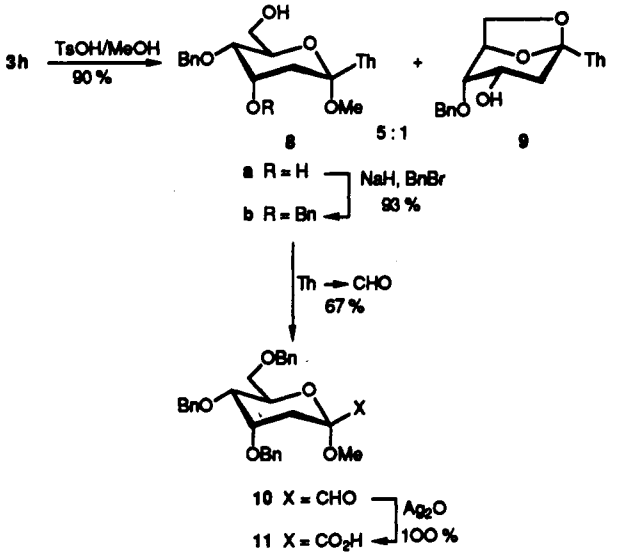
Table I. Aldol Condensation of Lithium Enolate[a] of 2-Acetylthiazole (1a) with Various Aldehydes 2

entry	aldehyde 2	aldol,[b] ds[c] %	yield,[d] %
1	Ph-CHO **2a**	**3a**	54
2	**2b**	**3b**	53
3	**2c**	**3c**	58
4	i-C_3H_7-CHO **2d**	**3d**	58
5	n-C_6H_{13}-CHO **2e**	**3e**	55
6	**2f**	**3f**, 90	58
7	**2g**	**3g**, 92	60
8	**2h**	**3h**, 90	51
9	**2i**	**3i**, 90	54
10	**2j**	**3j**, 80	65

[a] Generated by treatment of 1a with LiOBu-*t*/THF at −50 °C in the presence of the aldehyde. [b] Th = 2-thiazolyl; Fu = 2-furyl. [c] ds = diastereoselectivity. Determined by integration of the ^{1}H NMR spectrum of the crude mixture of products. [d] Isolated yields after column chromatography.

chemistry of the aldol **3j** derived from the protected L-serinal **2j** was also established.[22] This result is in agreement with the observations[4b,23] that, under nonchelating

Scheme III[a,b]



[a,b] See Scheme II.

conditions,[24] other nucleophiles also add anti selectively to amino aldehyde **2j**.

3-Deoxy Aldos-2-uloses and 3-Deoxy 2-Ulosonic Acids. We envisioned that the polyoxygenated aldols **3** could serve as intermediates in a synthesis of cyclic 3-deoxy aldosuloses and ulosonic acids via hemiketalization followed by liberation and oxidation of the formyl group (Figure 2). One reason for attempting such a synthesis is that the 3-deoxy 2-ulosonic functionality occurs in a variety of important natural products like the sialic acids,[25] i.e., *N*-acetylneuraminic acid and its derivatives, and various higher monosaccharides like 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP)[26] and 3-deoxy-D-*manno*-octulosonic acid (KDO).[27]

A preliminary experiment used the aldol **3f** derived from readily available D-glyceraldehyde acetonide (**2f**)[21b] (Table I, entry 6). Cleavage of the 1,3-dioxolane ring of **3f** (Scheme II) by TsOH-catalyzed methanolysis[28] and benzylation of the resulting oil afforded a mixture of the anomers of pyranose **5b**. These were separated by preparative TLC and were characterized by ^{1}H NMR spectroscopy. The mixture was subjected to one-pot thiazole-to-formyl unmasking (N-methylation, reduction, hydrolysis) to produce the aldosulose **6** in 58% isolated yield (after chromatographic purification). At this stage, the structure of the product was not known due to its partially unresolved ^{1}H NMR spectrum. Nevertheless, the spectrum did show two singlets at 3.41 and 3.29 ppm, which could be attributed to the protons of the anomeric methoxy

(22) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1990**, 854.

(23) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609. Garner, P.; Park, J. M. *Ibid.* **1990**, *55*, 3772.

(24) We are not aware of any earlier reports of aldol condensations involving *N*-Boc L-serinal acetonide (**2j**). For examples of the aldol reactions of other N-protected amino aldehydes, see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. Reetz, M. T.; Rivadeneira, E.; Niemeyer, C. *Tetrahedron lett.* **1990**, *31*, 3863. Mikami, K.; Kaneko, M.; Loh, T.-P.; Terada, M.; Nakai, T. *Ibid.* 3909.

(25) *Sialic Acids*; Schauer, R., Ed.; Springer-Verlag: Wien, 1982.

(26) Haslam, E. *The Shikimate Pathway*; Wiley: New York, 1974. Ganem, B. *Tetrahedron* **1978**, *34*, 3353.

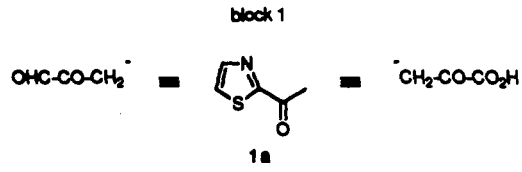
(27) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323. *Bacterial Lipopolysaccharides: Structure, Synthesis, and Biological Activities*; Anderson, L.; Unger, F. M., Eds.; ACS Symposium Series no. 231; American Chemical Society: Washington DC, 1983.

(28) Because of the nondescript nature of the ^{1}H NMR spectrum of this material, the possibility that, in addition to pyranose **5a**, furanoses were present cannot be excluded. See, for example: Assarsson, A.; Theander, O. *Acta Chem. Scand.* **1963**, *17*, 47.

groups, and two singlets at 9.43 and 9.52 ppm, which could be attributed to two different CHO groups. Oxidation of **6** with wet Ag_2O gave the 3-deoxy 2-ulosonic acid **7** in virtually quantitative yield. Thus, despite some uncertainty about the structures of intermediate compounds, a method whereby a polyhydroxyalkyl 2-thiazolyl ketone could be converted to aldosulose and ulosonic acid structures was developed.

Application of the above reaction sequence to the aldol **3h** (Table I, entry 8) gave more conclusive results (Scheme III). TsOH-catalyzed hemiketalization of **3h** in methanol solution afforded after chromatographic purification a 5:1 mixture, as clearly shown by ^1H NMR analysis, of methyl α-hexopyranoside **8a** ($^4C_1$ ring conformation) and its 1,6-anhydro derivative **9** in 90% combined yield.[29] The magnitude of the vicinal H_3–H_4 coupling constant (J = 3.1 Hz) in the spectrum of **8a** indicated a cis axial–equatorial disposition of the hydroxy and benzyloxy groups (erythro configuration) and furthermore confirmed that the configuration of the aldol **3h** was anti. That **8a** was the α-anomer was inferred from the results of an NOE experment performed with the *O*-benzyl derivative **8b**. A substantial enhancement of the H-5 signal was observed upon irradiation at the frequency of the methoxy group protons. That the 1,6-anhydro pyranose **9** was formed can be explained in terms of the $^1C_4$ conformation of **8a**, which permitted an acid-catalyzed internal acetalization via an S_N2cA reaction.[30] Thus, only compound **9** was isolated after prolonged heating of **3h** in the presence of TsOH.[31] The fully protected *O*-benzyl derivative **8b**, when subjected to the usual unmasking conditions, gave the 3-deoxyheptosulose **10** (ribo configuration) in 67% isolated yield. Compound **10** was then oxidized with Ag_2O to the O-protected 3-deoxy-D-*ribo*-heptulosonic acid **11** (DRH) in virtually quantitative yield[32] (24% overall from **3h**). The seven-carbon sugar **11** is the C-4 epimer of natural 3-deoxy-D-*arabino*-heptulosonic acid (DAH), a key intermediate in the biosynthesis of shikimic acid from glucose.[26]

In conclusion, the results demonstrated that 2-acetylthiazole (**1a**) can serve as an effective equivalent of the enolate of pyruvic aldehyde or pyruvic acid in the synthesis of aldosuloses and ulosonic acids. That **1a** can be conveniently used in place of other protected derivatives of pyruvic aldehyde like, for example, the dimethyl acetal,[12] is a consequence of the stability of the thiazole ring toward the various reaction conditions for converting the aldols to the final products.



3-Deoxy-D-*manno*-2-octulosonic Acid (KDO, 12). This well-known eight-carbon sugar is an essential component of the lipopolysaccharides that exist in the outer membrane of all Gram-negative bacteria.[27] Various approaches[33] to the synthesis of **12** have been reported over the years. These include the biomimetic aldol condensation[34] of D-arabinose (ARA) and pyruvic acid or one of its activated synthetic equivalents (Figure 3). One chemical[33f] and two enzymatic[33d,e] syntheses that employ such intermediates have been very recently reported. Each, however, suffers some shortcomings. Hence, the development of a synthesis of KDO starting from the new pyruvic acid equivalent **1a** appeared worthy of investigation (Scheme IV).

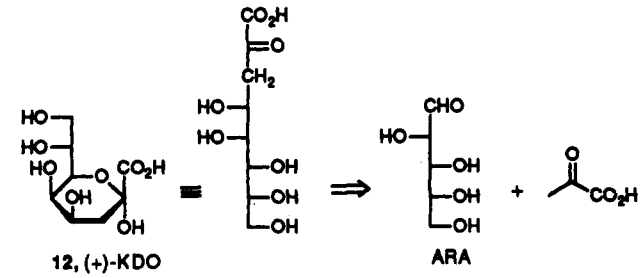
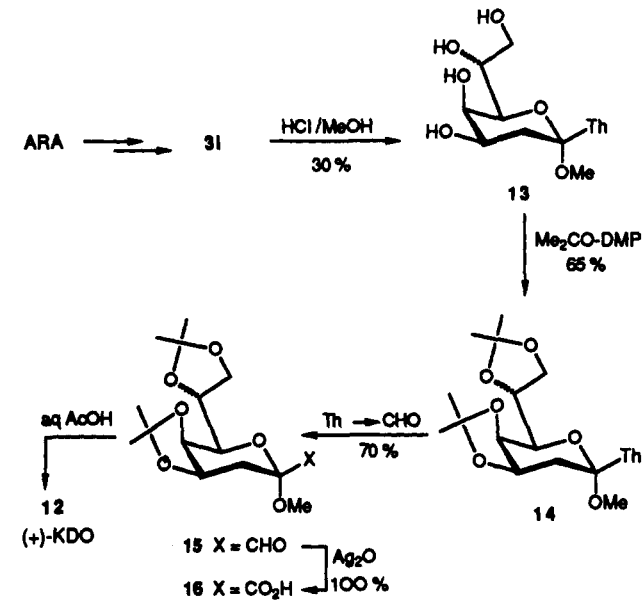


Figure 3.

Scheme IV[a,b]



[a,b] See Scheme II.

The aldol condensation of the lithium enolate of 2-ATT (**1a**) and the diacetonide of the aldehydo D-arabinose **2i** (Table I, entry 9) occurred with a high degree of anti selectivity to give the ulose **3i**, which possessed the required KDO manno configuration. This result and the fact that **2i** can be prepared in multigram quantities from com-

(29) The ^1H NMR spectrum of the crude reaction mixture revealed only one signal, at 3.18 ppm, attributable to the OMe group.

(30) For IUPAC recommendations on the use of symbols to denote reaction mechanisms, see: Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343.

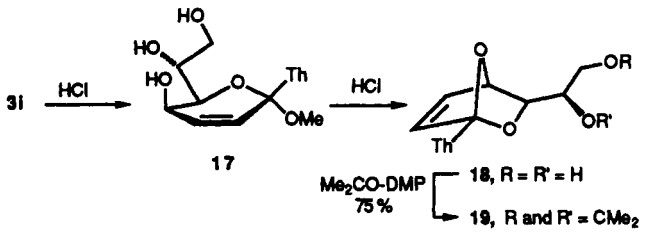
(31) We have recently reported[22] the conversion, under similar conditions, of aza sugars to the corresponding 1,6-anhydro derivatives. For the synthesis of 1,6-anhydrohexopyranoses via the tosyl derivatives of aldoses, see: Zottola, M. A.; Alonso, R.; Vite, G. D.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 6123.

(32) For an early nonstereospecific synthesis of 3-deoxy-D-*ribo*-heptulosonic acid 7-phosphate by the metal-catalyzed condensation of oxaloacetate and erythrose 4-phosphate, see: Herrmann, K. M.; Poling, M. D. *J. Biol. Chem.* **1975**, *250*, 6817.

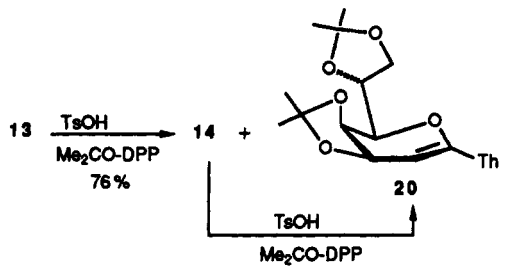
(33) (a) Shiba, T.; Kusumoto, S.; Imoto, M. *Tetrahedron Lett.* **1987**, *28*, 6235. (b) Itoh, H.; Kaneko, T.; Tanami, K.; Yoda, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3356. (c) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1989**, *110*, 3929. (d) Bednarski, M. D.; Crans, D. C.; Dicosimo, R.; Simon, E. S.; Stein, P. D.; Whitesides, G.; Scheider, M. J. *Tetrahedron lett.* **1988**, *29*, 427. (e) Augé, C.; Bouxom, B.; Cavayé, B.; Gautheron, C. *Ibid.* **1989**, *30*, 2217. (f) Enhsen, A.; Schmidt, R. R. *Liebigs Ann. Chem.* **1989**, 69. (g) Van der Klein, P. A. M.; Boons, G. J. P. H.; Veenenan, G. H.; van der Mael, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1989**, *30*, 5477.

(34) KDO synthetase (E.C.4.1.2.16) catalyzes the formation of KDO-8-P (3-deoxy-D-*manno*-2-octulosonate 8-phosphate) from arabinose 5-phosphate (ARA-5-P) and phosphoenol pyruvate. See: ref 27. Toone, E. J.; Simon, E. S.; Bednarski, M. D.; Whitesides, G. M. *Tetrahedron* **1989**, *45*, 5365 and references cited therein.

Scheme V



Scheme VI



mercial D-arabinose[35] (three steps, 45% overall yield) ensured that the key intermediate **3i** was readily accessible. However, the TsOH-catalyzed methanolysis of **3i** in the manner described above for **3h** did not induce hemiketalization. Only cleavage of the terminal 1,3-dioxolane ring occurred. When more acidic conditions, i.e., 8% methanolic HCl, were employed, the pyranose **13** was produced in 30% isolated yield.[36] The structure of **13** was inferred from its ^{1}H NMR spectrum. In particular, the magnitudes of the H_3–H_4 and one of the H_3–H_2 coupling constants (J = 2.5 and 12.0 Hz, respectively) indicated a cis equatorial–axis disposition of the two hydroxy groups at C-3 and C-4 ($^4C_1$ chair conformation). Consequently, an anti configuration for the aldol **3i** was also confirmed. Finally, the axial disposition of the methoxy group (α-anomer) was demonstrated by the results of an NOE experiment performed with the diacetonide **14**. An enhancement of the H-5 signal occurred upon irradiation at the frequency of the methoxy group protons. One side product (ca. 15%) was isolated. It was tentatively identified (^{1}H NMR) as the unsaturated [2.2.1] bicyclic compound **18** (Scheme V). The structure of **18** was confirmed by converting it to the acetonide **19**, the ^{1}H NMR spectrum of which was consistent with its structure. Acid-catalyzed loss of water from aldol **3i** and hemiketalyzation of the product would yield the unsaturated sugar **17**. An intramolecular S_N2cA reaction[30] of **17** would give the 1,4-anhydro derivative **18**.

The next transformation, i.e., the unmasking of the formyl group and its oxidation to a carboxylic acid, occurred in very high yields. The first step was the TsOH-catalyzed conversion of **13** into the diacetonide **14**, which was isolated (65% yield) along with the glycal **20** (11%)[37] (Scheme VI). That the latter arose from either **13** or **14** by the acid-catalyzed 1,2-elimination of methanol was shown by an independent experiment. The application of the thiazole-to-formyl unmasking sequence to **14** afforded the octosulose **15** (70% yield). By oxidation with silver oxide, **15** was converted, in virtual quantitative yield, into the protected octulosonic acid **16**. Deprotection of all the hydroxy groups of **16** by treatment with aqueous acetic acid at 90 °C gave (+)-KDO **12**, which was isolated as the crystalline ammonium salt (89%). The salt was identical (mp, optical rotation, spectra) with an authentic sample of ammonium (+)-KDO.[38] The overall yield of the (+)-KDO ammonium salt (6.8%) starting from the protected D-arabinose **2i** was the highest obtained by any reported chemical synthesis of KDO.

Conclusions

The results demonstrate that the lithium enolate of 2-acetylthiazole (**1a**) can serve effectively to install pyruvic aldehyde and pyruvic acid units into aldehydes. Thus, a new synthetic route from protected acyclic polyhydroxy aldehydes to cyclic aldosuloses and ulosonic acids having six, seven, and eight carbon atoms has been opened. The application of the methods described here to suitably substituted aldehydes should provide access to higher homologues of such compounds. Because of its stability under the reaction conditions employed and the ease with which it can subsequently be unmasked, the thiazole ring plays a key role, as a convenient synthetic equivalent of the formyl group, in such syntheses. The use of thiazolyl-substituted intermediates allows chemical manipulations that would be risky in the presence of more labile aldehyde-protecting groups like acetal or thioacetal. Moreover, as has been reported[33c] in another heterocycle-based, i.e., furan, route to KDO, the thiazole ring may prove useful in the synthesis of disaccharides via intermediates like **13** and **14**.

Experimental Section

General Comments. Melting points are uncorrected. Preparative thin-layer chromatography (TLC) was performed with 20 cm × 20 cm × 2 mm glass silica gel coated plates (Merck No. 5717). Analytical thin-layer chromatography was performed with glass microscope slides coated with Merck Kiesel gel 60 F254. Preparative column chromatography was performed with Merck 70–230 mesh silica gel. All experiments were carried out under nitrogen atmosphere and with freshly distilled and dry solvents.

Starting Materials. 2-Acetylthiazole (**1a**) was prepared by the reaction of 2-(trimethylsilyl)thiazole (**1b**) and acetyl chloride[5] or by the reaction of 2-bromothiazole and ethyl acetate as described below. (*R*)-2,3-*O*-Isopropylideneglyceraldehyde[21b] (**2f**), 4-deoxy-2,3-*O*-isopropylidene-D-threose[39] (**2g**), 2-*O*-benzyl-3,4-*O*-isopropylidene-D-erythrose[4a] (**2h**), 2,3:4,5-diisopropylidene-D-arabinose[35] (**2i**), and *N*-(*tert*-butoxycarbonyl)-*N*,*O*-isopropylidene-L-serinal[40] (**2j**) were prepared according to literature procedures.

2-Acetylthiazole (2-ATT, 1a). A solution of 2-bromothiazole (25 g, 0.15 mol) in Et_2O (200 mL) was added drop-by-drop over 0.5 h to a stirred solution of BuLi (0.16 mol, prepared by diluting 100 mL of a 1.6 M solution in hexane to 150 mL) at −78 °C. After being stirred for 0.5 h, the yellow solution was treated with a solution of freshly distilled EtOAc (25 g, 0.28 mol) in Et_2O (50 mL) added drop-by-drop. After being stirred for 1 h at −78 °C, the solution was allowed to warm to room temperature and was then treated with saturated aqueous $NaHCO_3$. The two liquid layers were separated. The organic layer was washed with water, dried (Na_2SO_4), and concentrated in vacuo. Distillation of the residue gave 17.76 g (92%) of **1a**: bp 89–91 °C (12 mmHg); IR ($CHCl_3$) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1 H, J = 3.2 Hz), 7.73 (d, 1 H, J = 3.2 Hz), 2.72 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.82,

(35) Zinner, H.; Wittenburg, E.; Rembarz, G. *Chem. Ber.* **1959**, *92*, 1614.

(36) Other conditions employed were: (a) 2% methanolic HCl, rt; (b) a catalytic amount of TFA in MeOH; (d) Dowex H$^+$/MeOH, reflux.

(37) In view of the potent enzymatic inhibitory activity displayed by 2-deoxy KDO, compound **20** appears to be a very attractive intermediate for use in the synthesis of 2-deoxy analogues of KDO. For recent work and leading references on KDO analogues, see: Luthman, K.; Orbe, M.; Waglund, T.; Claesson, A. *J. Org. Chem.* **1987**, *52*, 3777. Anderson, F. O.; Classon, B.; Samuelsson, B. *Ibid.* **1990**, *55*, 4699.

(38) Purchased from Sigma Chemical Co.

(39) Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, 3883.

(40) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.

167.43, 144.72, 126.31, 25.68. Anal. Calcd for C_5H_5NOS: C, 47.23; H, 3.96; N, 11.01. Found: C, 46.89; H, 3.76; N, 11.65.

Aldol Reaction of 2-Acetylthiazole (1a) and Aldehydes 2a–j. General Procedure. To a well-stirred solution of tert-butyl alcohol (0.74 g, 10 mmol) in anhydrous THF (15 mL) was added, drop-by-drop, BuLi (10.24 mmol, 6.4 mL of a 1.6 M solution in hexane) at room temperature. Stirring was continued for 30 min. The mixture was then cooled to −50 °C, and a solution of aldehyde 2 (10 mmol) and 2-acetylthiazole (1a, 1.3 g, 10.24 mmol) in anhydrous THF (40 mL) was added drop-by-drop. After 2 h, saturated aqueous NH_4Cl (40 mL) was added. The mixture was stirred for an additional 10 min at −50 °C and then was allowed to warm to room temperature. Water (20 mL) was added, and the two liquid layers were separated. The aqueous layer was extracted with Et_2O (4 × 25 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (Et_2O/hexane (1:1)) to give aldol 3. In the case of the chiral compounds 3f–j, the diastereomeric ratio of the products (Table I) was determined before chromatographic purification by integration of the signals in the 8.0–7.0 ppm range (H-4 and H-5 thiazole protons) of the corresponding ^1H NMR spectrum.

3-Hydroxy-3-phenyl-1-(2-thiazolyl)-1-propanone (3a) (1.26 g, 54%): an oil; IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (d, 1 H, J = 3.2 Hz), 7.66 (d, 1 H, J = 3.2 Hz), 7.33 (m, 5 H), 5.34 (dd, 1 H, J = 7.0, 5.0 Hz), 3.60 (dd, 1 H, J = 16.9, 7.0 Hz), 3.57 (dd, 1 H, J = 16.9, 5.0 Hz), 2.96 (br s, 1 H, exchangeable with D_2O). Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.42; H, 4.96; N, 6.32.

3-Hydroxy-1,3-di(2-thiazolyl)-1-propanone (3b) (1.27 g, 53%): mp 114–116 °C; IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, 1 H, J = 3.2 Hz), 7.75 (d, 1 H, J = 3.2 Hz), 7.69 (d, 1 H, J = 3.2 Hz), 7.33 (d, 1 H, J = 3.2 Hz), 5.66 (dd, 1 H, J = 7.0, 4.8 Hz) 3.93 (dd, 1 H, J = 17.0, 4.8 Hz), 3.70 (dd, 1 H, J = 17.0, 7.0 Hz), 3.18 (br s, 1 H, exchangeable with D_2O). Anal. Calcd for $C_9H_8N_2O_2S_2$: C, 44.98; H, 3.36; N, 11.66. Found: C, 45.08; H, 3.24; N, 11.87.

3-(2-Furyl)-3-hydroxy-1-(2-thiazolyl)-1-propanone (3c) (1.29 g, 58%): oil; IR ($CHCl_3$) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, 1 H, J = 3.1 Hz), 7.72 (d, 1 H, J = 3.1 Hz), 7.41 (m, 1 H), 6.34 (m, 2 H), 5.39 (ddd, 1 H, J = 8.7, 5.2, 3.5 Hz), 3.81 (dd, 1 H, J = 17.1, 8.7 Hz), 3.64 (dd, 1 H, J = 17.1, 3.5 Hz), 3.48 (d, 1 H, J = 5.2 Hz, exchangeable with D_2O). Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27. Found: C, 53.36; H, 3.97; N, 6.48.

3-Hydroxy-4-methyl-1-(2-thiazolyl)-1-pentanone (3d) (1.16 g, 58%): oil; IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99 (d, 1 H, J = 3.2 Hz), 7.65 (d, 1 H, J = 3.2 Hz), 3.97 (m, 1 H), 3.30 (dd, 1 H, J = 16.5, 4.4 Hz), 3.26 (dd, 1 H, J = 16.5, 7.1 Hz), 2.74 (br s, 1 H, exchangeable with D_2O), 1.76 (m, 1 H), 1.02 (d, 6 H, J = 6.6 Hz). Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58; N, 7.03. Found: C, 54.63; H, 6.91; N, 6.82.

3-Hydroxy-1-(2-thiazolyl)-1-nonanone (3e) (1.33 g, 55%): oil; IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (d, 1 H, J = 3.2 Hz), 7.72 (d, 1 H, J = 3.2 Hz), 4.22 (m, 1 H), 3.38 (dd, 1 H, J = 17.2, 2.8 Hz), 3.24 (dd, 1 H, J = 17.2, 8.9 Hz), 3.18 (d, 1 H, J = 4.5 Hz, exchangeable with D_2O), 1.55 (m, 2 H), 1.30 (m, 8 H), 0.88 (t, 3 H, J = 7.0 Hz). Anal. Calcd for $C_{12}H_{19}NO_2S$: C, 59.72; H, 7.94; N, 5.80. Found: C, 59.56; H, 7.54; N, 5.37.

(3*S*,4*R*)-4,5-*O*-Isopropylidene-3,4,5-trihydroxy-1-(2-thiazolyl)-1-pentanone (3f) (1.49 g, 58%): oil; $[\alpha]^{20}_D$ = −9.2° (*c* 5.26, $CHCl_3$); IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, 1 H, J = 3.2 Hz), 7.73 (d, 1 H, J = 3.2 Hz), 4.26–3.38 (m, 4 H), 3.52 (dd, 1 H, J = 16.8, 2.8 Hz), 3.34 (dd, 1 H, J = 16.8, 8.8 Hz), 2.94 (br s, 1 H, exchangeable with D_2O), 1.44 (s, 3 H), 1.36 (s, 3 H). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.42; H, 6.18; N, 5.79.

(3*R*,4*S*,5*R*)-4,5-*O*-Isopropylidene-3,4,5-trihydroxy-1-(2-thiazolyl)-1-hexanone (3g) (1.63 g, 60%): an oil; $[\alpha]^{20}_D$ = −10.2° (*c* 1.49, $CHCl_3$); IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, 1 H, J = 3.2 Hz), 7.73 (d, 1 H, J = 3.2 Hz), 4.26 (ddd, 1 H, J = 8.8, 6.5–3.0 Hz), 4.12 (dq, 1 H, J = 7.6, 6.9 Hz), 3.61 (dd, 1 H, J = 6.9, 6.5 Hz), 3.54 (dd, 1 H, J = 17.0, 3.0 Hz), 3.39 (dd, 1 H, J = 17.0, 8.8 Hz), 2.76 (br s, 1 H, exchangeable with D_2O), 1.45 (s, 3 H), 1.43 (s, 3 H), 1.38 (d, 3 H, J = 7.6 Hz). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16. Found: C, 53.24; H, 5.96; N, 5.34.

(3*S*,4*R*,5*R*)-4-*O*-Benzyl-5,6-*O*-isopropylidene-3,4,5,6-tetrahydroxy-1-(2-thiazolyl)-1-hexanone (3h) (1.93 g, 51%): an oil; $[\alpha]^{20}_D$ = +3.6° (*c* 5.73, $CHCl_3$); IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (d, 1 H, J = 3.2 Hz), 7.69 (d, 1 H, J = 3.2 Hz), 7.30 (m, 5 H), 4.74 (d, 1 H, J = 12.0 Hz), 4.71 (d, 1 H, J = 12.0 Hz), 4.47 (m, 1 H), 4.30 (ddd, 1 H, J = 6.9, 6.5, 6.3 Hz), 4.20 (dd, 1 H, J = 8.4, 6.5 Hz), 3.88 (dd, 1 H, J = 8.4, 6.3 Hz), 3.70 (dd, 1 H, J = 6.9, 4.2 Hz), 3.48 (m, 2 H), 3.30 (br s, 1 H, exchangeable with D_2O), 1.40 (s, 3 H), 1.35 (s, 3 H). Anal. Calcd for $C_{19}H_{23}NO_5S$: C, 60.46; H, 6.14; N, 3.71. Found: C, 60.62; H, 6.21; N, 3.97.

(3*R*,4*R*,5*R*,6*R*)-4,5:6,7-Di-*O*-isopropylidene-3,4,5,6,7-pentahydroxy-1-(2-thiazolyl)-1-heptanone (3i) (1.93 g, 54%): an oil; $[\alpha]^{20}_D$ = +15.4° (*c* 1.43, $CHCl_3$); IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, 1 H, J = 3.2 Hz), 7.70 (d, 1 H, J = 3.2 Hz), 4.39 (m, 1 H), 4.22–3.38 (m, 4 H), 3.84 (m, 1 H), 3.73 (br s, 1 H, exchangeable with D_2O), 3.50 (m, 2 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.33 (s, 3 H). Anal. Calcd for $C_{16}H_{23}NO_6S$: C, 53.77; H, 6.49; N, 3.92. Found: C, 53.82; H, 6.73; N, 3.61.

(3*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4,5-*N*,*O*-isopropylidene-4-amino-3,5-dihydroxy-1-(2-thiazolyl)-1-pentanone (3j) (2.30 g, 65%): an oil; $[\alpha]^{20}_D$ = −8.0° (*c* 0.65, $CHCl_3$); IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (d, 1 H, J = 3.2 Hz), 7.70 (d, 1 H, J = 3.2 Hz), 4.47–3.90 (m, 4 H), 3.34 (m, 1 H), 3.32 (m, 1 H), 3.28 (br s, 1 H, exchangeable with D_2O), 1.61 (s, 3 H), 1.53 (s, 3 H), 1.50 (s, 9 H). Anal. Calcd for $C_{16}H_{24}N_2O_5S$: C, 53.92; H, 6.79; N, 7.86. Found: C, 54.01; H, 6.39; N, 7.97.

Methyl 2-Deoxy-1-(2-thiazolyl)-D-*erythro*-pentapyranoside (5a). To a solution of aldol 3f (1.0 g, 3.9 mmol) in anhydrous MeOH (20 mL) was added *p*-TsOH (7 mg, 0.04 mmol). The mixture was heated at 50 °C. After 3 h, saturated aqueous $NaHCO_3$ (2 mL) was added. The solvent was then evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/MeOH (49:1)) to give 5a (0.88 g, 98%): an oil, ^1H NMR ($CDCl_3$) (mixture of isomers) δ 7.81, 7.37 (overlapping thiazole doublets, 2 H total), 4.70–4.40 (br m, 1 H total), 4.18–3.80 (br m, 3 H total), 3.35, 3.30 (methoxy singlets, 3 H total), 3.10 (m, 1 H total), 2.80 (m, 1 H total), 2.46 (m, 1 H total), 2.18–1.96 (br m, 1 H total). Anal. Calcd for $C_9H_{13}NO_4S$: C, 46.74; H, 5.67; N, 6.06. Found: C, 46.51; H, 5.30; N, 5.92.

Methyl 3,4-Di-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-D-*erythro*-pentapyranoside (5b). To a solution of 5a (0.8 g, 3.46 mmol) in dry THF (30 mL) was added, in small portions, NaH (50% dispersion in mineral oil, 0.34 g, 7 mmol) at room temperature. The reaction mixture was gently refluxed for 20 min, and then *n*-Bu_4NI (0.14 g, 0.37 mmol) and BnBr (1.2 g, 7 mmol) were added sequentially. The solution was allowed to stand at room temperature overnight. The solution was concentrated in vacuo, saturated aqueous $NaHCO_3$ (20 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The extract was dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane/Et_2O (3:2)) to give 1.1 g (77%) of 5b as a mixture of anomers. Preparative TLC on silica gel (hexane/Et_2O (4:1); 6 developments) of a portion of this material separated the two. More mobile isomer: ^1H NMR ($CDCl_3$) δ 7.81 (d, 1 H, J = 3.2 Hz), 7.40–7.25 (m, 11 H), 4.86 (d, 1 H, J = 11.2 Hz), 4.71 (m, 3 H), 4.09 (ddd, 1 H, J = 11.3, 8.3, 5.0 Hz), 3.96 (m, 1 H), 3.62 (m, 2 H), 3.06 (s, 3 H), 2.88 (dd, 1 H, J = 13.1, 5.0 Hz), 1.71 (dd, 1 H, J = 13.1, 11.3 Hz). Less mobile isomer: ^1H NMR ($CDCl_3$) δ 7.72 (d, 1 H, J = 3.2 Hz), 7.43–7.26 (m, 11 H), 4.71 (br s, 1 H), 4.6 (m, 3 H), 4.34 (ddd, 1 H, J = 11.8, 6.8, 6.4 Hz), 4.08 (m, 1 H), 3.76 (m, 1 H), 3.68 (m, 1 H), 3.15 (s, 3 H), 2.86 (dd, 1 H, J = 13.2, 6.8 Hz), 2.41 (dd, 1 H, J = 13.2, 6.4 Hz). Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40. Found: C, 66.82; H, 6.45; N, 3.57.

Methyl 4,5-Di-*O*-benzyl-3-deoxy-D-*erythro*-2-hexosulo-2,6-pyranoside (6). A solution of 5b (1 g, 2.43 mmol) in freshly distilled CH_3CN (30 mL) was treated with MeI (3.45 g, 24.3 mmol). The solution was refluxed until the starting material disappeared (ca. 8 h by TLC analysis). The solution was concentrated in vacuo, then Et_2O was added to precipitate the *N*-methylthiazolium salt, which was collected by filtration. The crude salt was dissolved in MeOH (40 mL), and the solution was treated with $NaBH_4$ (0.13 g, 3.65 mmol) at −10 °C. After 30 min, acetone (2 mL) was added and the solvent was evaporated. Brine (30 mL) was added, and

the mixture was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), and the solvent was concentrated in vacuo. The residue of crude thiazolidine was dissolved in CH_3CN (5 mL), and the solution was treated with $HgCl_2$ (0.72 g, 2.6 mmol) dissolved in 20 mL of a 4:1 mixture of CH_3CN and water. This solution was stirred at room temperature for 15 min. The solution was then filtered, and the solvent was evaporated from the filtrate in vacuo. The residue was treated with brine (30 mL) and was extracted with $CHCl_3$ (3 × 30 mL). The extract was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (hexane/Et_2O (1:1)) to give 0.5 g (58%) of **6**: an oily mixture of isomers; IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.52, 9.43 (aldehyde singlets, 1 H total), 7.40–7.25 (m, 10 H total), 4.52 (m, 4 H total), 4.41 (m, 2 H total), 3.54 (m, overlapping diastereotopic C_6-H, 2 H total), 3.41, 3.29 (methoxy singlets, 3 H total), 2.40–2.28 (m, overlapping diastereotopic C_3-H, 2 H total). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.89, H, 7.07.

4,5-Di-*O*-benzyl-2-*O*-methyl-3-deoxy-D-*erythro*-2-hexulopyranosonic Acid (7). To a solution of $AgNO_3$ (0.56 g, 3.28 mmol) in water (10 mL) was added, sequentially, a solution of NaOH (0.27 g, 6.73 mmol) in water (10 mL). A precipitate of Ag_2O formed. Then was added a solution of the aldehyde **6** (0.5 g, 1.4 mmol) in THF (15 mL). The mixture was stirred for 7 days at room temperature. The mixture was filtered through Celite, and the filtrate was extracted with $CHCl_3$ (2 × 15 mL). The pH of the aqueous solution that remained was adjusted to 5 with 1 N aqueous HCl and then was extracted with $CHCl_3$ (3 × 20 mL). The combined $CHCl_3$ extracts were extracted with saturated aqueous $NaHCO_3$ (2 × 20 mL). The aqueous extract was washed with CH_2Cl_2 (1 × 20 mL) and then was acidified to pH 5 with 1 N aqueous HCl and was extracted with $CHCl_3$ (3 × 20 mL). The various organic extracts were combined and dried (Na_2SO_4). The solvent was evaporated in vacuo to give 0.52 g (100%) of diastereomers of acid **7**: an oil, IR ($CHCl_3$) 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.21 (m, 10 H total), 6.12 (br s, 1 H total, exchangeable with D_2O), 4.50 (m, 4 H total), 4.36 (m, 2 H total), 3.71 (m, 2 H total), 3.39, 3.30 (methoxy singlets, 3 H total), 2.52–2.43 (m, overlapping diastereotopic C_3-H, 2 H total). Anal. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.41; H, 6.46.

Methyl 4-*O*-Benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*ribo*-hexopyranoside (8a) and 1,6-Anhydro-4-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-D-*ribo*-hexopyranose (9). The method described above for converting **3f** to **5a** was applied to aldol **3h** (0.7 g, 1.86 mmol) to give, after column chromatography on silica gel (EtOAc/hexane (9:1)), pyranose **8a**, and 1,6-anhydropyranose **9**.

Compound **8a** (0.49 g, 75%): an oil that solidified on standing; $[\alpha]^{20}_D$ = +72.2° (*c* 1.54, $CHCl_3$); ^1H NMR ($CDCl_3$ + D_2O) δ 7.82 (d, 1 H, *J* = 3.2 Hz), 7.33 (m, 6 H), 4.79 (d, 1 H, *J* = 11.7 Hz), 4.58 (d, 1 H, *J* = 11.7 Hz), 4.30 (ddd, 1 H, *J* = 3.4, 3.3, 3.1 Hz), 4.11 (ddd, 1 H, *J* = 9.9, 4.3, 2.8 Hz), 4.03 (dd, 1 H, *J* = 12.6, 2.8 Hz), 3.93 (dd, 1 H, *J* = 12.6, 4.3 Hz), 3.59 (dd, 1 H, *J* = 9.9, 3.1 Hz), 3.18 (s, 3 H), 2.72 (dd, 1 H, *J* = 14.8, 3.3 Hz), 1.95 (dd, 1 H, *J* = 14.8, 3.4 Hz); ^{13}C NMR ($CDCl_3$ + D_2O) δ 169.82, 143.46, 138.02, 128.81, 128.27, 120.38, 100.24, 73.83, 70.66, 69.13, 63.96, 62.27, 50.04, 40.34. Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99. Found: C, 57.61; H, 6.26; N, 3.91.

Compound **9** (0.09 g, 15%): an oil; $[\alpha]^{20}_D$ = −30.4° (*c* 1.56, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.81 (d, 1 H, *J* = 3.1 Hz), 7.52–7.28 (m, 6 H), 4.91 (ddd, 1 H, *J* = 5.6, 2.6, 1.1 Hz), 4.87 (d, 1 H, *J* = 11.7 Hz), 4.68 (d, 1 H, *J* = 11.7 Hz), 4.18 (ddd, 1 H, *J* = 10.1, 6.6, 4.6 Hz), 4.03 (dd, 1 H, *J* = 7.8, 5.6 Hz), 3.86 (dd, 1 H, *J* = 7.8, 1.1 Hz), 3.66 (dd, 1 H, *J* = 4.6, 2.6 Hz), 2.75 (dd, 1 H, *J* = 13.0, 6.6 Hz), 2.60 (br s, 1 H, exchangeable with D_2O), 2.31 (dd, 1 H, *J* = 13.0, 10.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.75, 142.64, 137.11, 128.26, 127.77, 127.61, 120.11, 104.69, 74.85, 74.59, 71.30, 65.71, 63.54, 40.03. Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 59.94; H, 5.82; N, 4.02.

Methyl 3,4,6-Tri-*O*-benzyl-2-deoxy-1-(2-thiazolyl)-α-D-*ribo*-hexopyranoside (8b). The method described above for benzylating **5a** to give **5b** was applied to compound **8a** (0.4 g, 1.14 mmol). After the usual workup, the residue was purified by column chromatography on silica gel (EtOAc/hexane (9:1)) to give 0.56 g (93%) of **8b**: an oil; $[\alpha]^{20}_D$ = −127.2° (*c* 0.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.84 (d, 1 H, *J* = 3.2 Hz), 7.44–7.21 (m, 16 H), 4.90 (d, 1 H, *J* = 12.6 Hz), 4.74 (d, 1 H, *J* = 12.2 Hz), 4.67 (d, 1 H, *J* = 12.2 Hz), 4.59 (m, 2 H), 4.44 (m, 2 H), 3.97 (m, 1 H), 3.91 (dd, 1 H, *J* = 11.2, 6.6 Hz), 3.86 (dd, 1 H, *J* = 11.2, 2.0 Hz), 3.70 (dd, 1 H, *J* = 9.8, 3.1 Hz), 3.15 (s, 3 H), 2.94 (dd, 1 H, *J* = 15.2, 3.6 Hz), 1.75 (dd, 1 H, *J* = 15.2, 3.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.05, 143.39, 139.21, 139.01, 138.65, 128.55, 128.27, 128.04, 127.82, 127.70, 119.88, 99.24, 74.25, 73.47, 70.88, 70.20, 69.59, 69.54, 69.52, 49.71, 36.40. Anal. Calcd for $C_{31}H_{33}NO_5S$: C, 70.03; H, 6.26; N, 2.63. Found: C, 70.21; H, 6.38; N, 2.58.

Methyl 4,5,7-Tri-*O*-benzyl-3-deoxy-α-D-*ribo*-2-heptosulo-2,6-pyranoside (10). The unmasking method described above for converting **5b** to **6** was applied to the methyl pyranoside **8b** (0.5 g, 0.94 mmol). Column chromatography on silica gel (hexane/EtOAc (4:1)) gave 0.30 g (67%) of pure aldehyde **10**: an oil; $[\alpha]^{20}_D$ = +82.3° (*c* 1.52, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.47 (s, 1 H), 7.40–7.20 (m, 15 H), 4.77 (d, 1 H, *J* = 12.5 Hz), 4.53 (m, 4 H), 4.42 (d, 1 H, *J* = 12.5 Hz), 4.37 (m, 1 H), 3.98 (m, 1 H), 3.81 (m, 2 H), 3.63 (dd, 1 H, *J* = 9.6, 3.0 Hz), 3.33 (s, 3 H), 2.26 (dd, 1 H, *J* = 14.8, 3.4 Hz), 1.53 (dd, 1 H, *J* = 14.8, 3.3 Hz); ^{13}C NMR ($CDCl_3$) δ 198.61, 142.51, 138.77, 138.44, 128.60, 128.12, 128.05, 127.94, 127.81, 98.84, 74.21, 73.56, 71.05, 70.65, 69.45, 69.35, 69.00, 50.46, 30.06. Anal. Calcd for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77. Found: C, 72.67; H, 7.04.

4,5,7-Tri-*O*-benzyl-2-*O*-methyl-3-deoxy-α-D-*ribo*-2-heptulopyranosonic Acid (4,5,7-Tri-*O*-benzyl-2-*O*-methyl DRH, 11). The method described above for oxidizing aldehyde **6** to acid **7** was applied to aldehyde **10** (0.2 g, 0.42 mmol) to give, after the usual workup, 0.21 g (100%) of the pure acid **11**: an oil; $[\alpha]^{20}_D$ = +88.1° (*c* 2.76, $CHCl_3$); IR ($CHCl_3$) 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–7.18 (m, 15 H), 5.15 (br s, 1 H, exchangeable with D_2O), 4.80 (d, 1 H, *J* = 12.0 Hz), 4.55 (m, 4 H), 4.39 (d, 1 H, *J* = 12.0 Hz), 4.35 (ddd, 1 H, *J* = 9.9, 3.8, 2.0 Hz), 3.97 (ddd, 1 H, *J* = 3.2, 3.1, 2.8 Hz), 3.86 (dd, 1 H, *J* = 10.8, 3.8 Hz), 3.79 (dd, 1 H, *J* = 10.8, 2.0 Hz), 3.64 (dd, 1 H, *J* = 9.9, 2.8 Hz), 3.28 (s, 3 H), 2.63 (dd, 1 H, *J* = 15.1, 3.2 Hz), 1.65 (dd, 1 H, *J* = 15.1, 3.1 Hz); ^{13}C NMR ($CDCl_3$) δ 170.33, 138.62, 138.23, 138.04, 128.78, 128.61, 128.21, 128.16, 128.04, 127.86, 98.45, 73.62, 73.53, 70.83, 70.40, 69.11, 69.07, 68.86, 51.12, 33.22. Anal. Calcd for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55. Found: C, 70.95; H, 6.11.

Methyl 2-Deoxy-1-(2-thiazolyl)-α-D-*manno*-heptopyranoside (13) and 1,4-Anhydro-2,3-dideoxy-1-(2-thiazolyl)-α-D-*manno*-hept-2-enopyranose (18). Aldol **3i** (1.63 g, 4.55 mmol) was treated with ca. 8% methanolic HCl (15 mL). The mixture was stirred for 16 h. The solvent was evaporated in vacuo and the residue dissolved in water (25 mL). The solution was neutralized by the introduction of Amberlyst A-26 basic ion-exchange resin. The resin was removed by filtration. The water was evaporated in vacuo from the filtrate at a temperature not exceeding 50 °C. The residue was purified by column chromatography on silica gel (EtOAc/methanol (9:1)) to give tetrol **13** and diol **18**.

13 (0.4 g, 30%): mp 105–107 °C; $[\alpha]^{20}_D$ = +65° (*c* 0.65, CH_3OH); ^1H NMR (D_2O) δ 7.67 (d, 1 H, *J* = 3.3 Hz), 7.46 (d, 1 H, *J* = 3.3 Hz), 4.01 (ddd, 1 H, *J* = 12.0, 4.9, 2.5 Hz), 3.93 (m, 1 H), 3.86 (ddd, 1 H, *J* = 9.0, 6.5, 2.5 Hz), 3.82 (dd, 1 H, *J* = 12.3, 2.5 Hz), 3.62 (dd, 1 H, *J* = 9.0, 1.1 Hz), 3.59 (dd, 1 H, *J* = 12.3, 6.5 Hz), 2.86 (s, 3 H), 2.17 (dd, 1 H, *J* = 13.0, 4.9 Hz), 1.77 (dd, 1 H, *J* = 13.0, 12.0 Hz); ^{13}C NMR (D_2O) δ 177.72, 149.50, 128.57, 106.85, 78.35, 75.87, 72.52 (2C), 69.59, 56.44, 43.07. Anal. Calcd for $C_{11}H_{17}NO_6S$: C, 45.35; H, 5.88; N, 4.81. Found: C, 45.13; H, 5.85; N, 4.66.

18 (0.16 g, 15%): an oil; ^1H NMR (D_2O) δ 7.62 (d, 1 H, *J* = 3.2 Hz), 7.36 (d, 1 H, *J* = 3.2 Hz), 6.72 (d, 1 H, *J* = 3.6 Hz), 6.41 (d, 1 H, *J* = 3.6), 4.58 (m, 2 H), 3.89 (ddd, 1 H, *J* = 7.4, 6.4, 3.5 Hz), 3.66 (dd, 1 H, *J* = 12.1, 3.5 Hz), 3.51 (dd, 1 H, *J* = 12.1, 6.4 Hz). Anal. Calcd for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.60; N, 5.81. Found: C, 49.62; H, 4.84; N, 5.96.

Methyl 3,4:6,7-Di-*O*-isopropylidene-2-deoxy-1-(2-thiazolyl)-α-D-*manno*-heptopyranoside (14) and 3,4:6,7-Di-*O*-isopropylidene-1,2-dideoxy-1-(2-thiazolyl)-α-D-*manno*-hept-1-enopyranose (20). To a solution of tetrol **13** (0.4 g, 1.37 mmol) in anhydrous acetone (20 mL) and 2,2-dimethoxypropane (5 mL) were added, sequentially, anhydrous $MgSO_4$ (0.63 g) and *p*-TsOH (4 mg). After the mixture was stirred for 16 h, the solvent was evaporated in vacuo. Saturated aqueous $NaHCO_3$ (10 mL) was added to the residue, and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The extract was dried (Na_2SO_4), the solvent was evaporated, and the residue was purified by column chroma-

tography on silica gel (Et_2O/hexane (1:1)) to give **14** and **20**.

14 (0.33 g, 65%): an oil; $[\alpha]^{20}_D$ = +45.3° (*c* 1.72, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.85 (d, 1 H, *J* = 3.4 Hz), 7.33 (d, 1 H, *J* = 3.4 Hz), 4.57 (ddd, 1 H, *J* = 7.2, 4.7, 4.1 Hz), 4.45 (ddd, 1 H, *J* = 8.7, 6.3, 5.7 Hz), 4.29 (dd, 1 H, *J* = 7.2, 2.0 Hz), 4.22 (dd, 1 H, *J* = 8.7, 6.3 Hz), 4.14 (dd, 1 H, *J* = 8.7, 5.7 Hz), 3.91 (dd, 1 H, *J* = 6.3, 2.0 Hz), 3.05 (s, 3 H), 2.79 (dd, 1 H, *J* = 15.2, 4.7 Hz), 2.29 (dd, 1 H, *J* = 15.2, 4.1 Hz), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.38, 143.84, 120.38, 109.70, 99.76, 99.58, 74.89, 72.07, 71.37, 70.75, 67.02, 49.87, 36.46, 26.96, 26.31, 25.70, 24.90. Anal. Calcd for $C_{17}H_{25}NO_6S$: C, 54.97; H, 6.78; N, 3.77. Found: C, 55.16; H, 6.71; N, 3.93.

20 (0.05 g, 11%): an oil; $[\alpha]^{20}_D$ = +119.7° (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.72 (d, 1 H, *J* = 3.2 Hz), 7.38 (d, 1 H, *J* = 3.2 Hz), 6.01 (d, 1 H, *J* = 3.3 Hz), 4.92 (dd, 1 H, *J* = 6.2, 3.3 Hz), 4.53 (m, 2 H), 4.27 (m, 2 H), 4.01 (m, 1 H), 1.50 (s, 3 H), 1.43 (br s, 9 H); ^{13}C NMR ($CDCl_3$) δ 164.06, 148.13, 144.64, 120.41, 111.64, 110.38, 101.35, 77.42, 74.68, 72.43, 69.68, 67.07, 28.38, 27.22, 27.13, 25.63. Anal. Calcd for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13. Found: C, 56.01; H, 6.11; N, 4.46.

More of compound **20** was produced, as TLC and ^1H NMR analysis showed, when the reaction time was increased.

1,4-Anhydro-6,7-*O*-isopropylidene-2,3-deoxy-1-(2-thiazolyl)-α-D-*manno*-hept-2-enopyranose (19). The method described above for the acetonization of **13** was applied to **18** (0.1 g, 0.41 mmol) to give, after column chromatography on silica gel (Et_2O/hexane (2:3)), 0.086 g (75%) of **19**: a white solid; mp 114-116 °C; $[\alpha]^{20}_D$ = +35.0° (*c* 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.81 (d, 1 H, *J* = 3.2 Hz), 7.31 (d, 1 H, *J* = 3.2 Hz), 6.97 (d, 1 H, *J* = 3.6 Hz), 6.51 (dd, 1 H, *J* = 3.6, 0.8 Hz), 4.93 (dd, 1 H, *J* = 5.1, 3.5 Hz), 4.49 (ddd, 1 H, *J* = 6.7, 5.6, 5.1 Hz), 4.15 (dd, 1 H, *J* = 9.8, 5.6 Hz), 4.08 (dd, 1 H, *J* = 9.8, 6.7 Hz), 2.62 (dd, 1 H, *J* = 3.5, 0.8 Hz), 1.50 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.74, 155.23, 149.31, 144.14, 118.48, 110.49, 110.19, 110.07, 77.36, 68.07, 65.49, 26.49, 25.06. Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98. Found: C, 55.61; H, 5.95; N, 4.70.

Methyl 4,5:7,8-Di-*O*-isopropylidene-3-deoxy-α-D-*manno*-2-octosulo-2,6-pyranoside (15). The method described above for converting **5b** to **6** was applied to methyl pyranoside **14** (0.33 g, 0.88 mmol). After column chromatography on silica gel (hexane/Et_2O (1:1)), 0.2 g (73%) of the pure aldehyde **15** was obtained: an oil; $[\alpha]^{20}_D$ = +47.8° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.49 (s, 1 H), 4.52 (ddd, 1 H, *J* = 7.8, 3.6, 2.6 Hz), 4.40 (ddd, 1 H, *J* = 7.8, 6.3, 4.5 Hz), 4.33 (dd, 1 H, *J* = 7.8, 1.9 Hz), 4.18 (dd, 1 H, *J* = 8.8, 6.3 Hz), 4.04 (dd, 1 H, *J* = 8.8, 4.5 Hz), 3.67 (dd, 1 H, *J* = 7.8, 1.9 Hz), 3.28 (s, 3 H), 2.50 (dd, 1 H, *J* = 15.7, 3.6 Hz), 1.82 (dd, 1 H, *J* = 15.7, 2.6 Hz), 1.45 (s, 6 H), 1.40 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.71, 110.21, 109.98, 99.24, 74.14, 72.60, 72.20, 70.07, 67.34, 50.93, 32.40, 27.09, 26.23, 26.37, 24.94. Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.78; H, 7.83.

4,5:7,8-Di-*O*-isopropylidene-2-*O*-methyl-3-deoxy-α-D-*manno*-2-octulopyranosonic Acid (16). The method described above for oxidizing aldehyde **6** to acid **7** was applied to aldehyde **15** (0.2 g, 0.64 mmol) to give, after the usual workup, 0.21 g (100%) of pure acid **16**: an oil; $[\alpha]^{20}_D$ = +23.2° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 1790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (br s, 1 H, exchangeable with D_2O), 4.57 (m, 1 H), 4.36 (m, 2 H), 4.18 (dd, 1 H, *J* = 9.0, 6.0 Hz), 4.00 (dd, 1 H, *J* = 9.0, 4.5 Hz), 3.65 (dd, 1 H, *J* = 7.8, 1.9 Hz), 3.34 (s, 3 H), 2.77 (dd, 1 H, *J* = 15.9, 3.3 Hz), 1.93 (dd, 1 H, *J* = 15.9, 3.0 Hz), 1.50 (s, 3 H), 1.47 (s, 3 H), 1.41 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.28, 110.18, 110.13, 98.56, 73.89, 72.56, 72.03, 70.22, 67.19, 51.39, 32.50, 27.06, 25.53, 25.28, 24.34. Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 54.13; H, 7.08.

(+)-3-Deoxy-D-*manno*-2-octulosonic Acid (12, KDO). A solution of acid **16** (0.2 g, 0.60 mmol) in 90% aqueous AcOH (20 mL) was heated at 90 °C for 30 min. The solution was then concentrated in vacuo, at a temperature not exceeding 50 °C, to afford free KDO, a very hygroscopic white solid, in quantitative yield. This was dissolved in water (15 mL), and the solution was made basic (pH 10) by the introduction of concentrated aqueous NH_3. Evaporation of the solvent in vacuo, at a temperature not exceeding 50 °C, gave a solid residue. This was passed through a reversed-phase column packed with C_{18}-bonded silica gel to give 0.138 g (89%) of the pure KDO ammonium salt: mp 123-126 °C, $[\alpha]^{20}_D$ = +40.9° (*c* 1.05, H_2O) [lit.[32a] mp 125-127 °C, $[\alpha]^{20}_D$ = +41.6° (*c* 2.0, H_2O); lit.[32g] mp 121-124 °C, $[\alpha]^{20}_D$ = +40.3° (*c*, 1.9, H_2O)]. The ammonium salt thus obtained showed TLC behavior ($MeOH/CHCl_3/H_2O$ (10:10:3) and $EtOH/H_2O$/AcOH (4:1:1)) and ^1H and ^{13}C NMR spectra identical with those of an authentic sample.[37]

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Evidence for Ketene Intermediates in the Decarbonylation of 2,4-Dioxo Acids and Esters and 2-Oxobutanedioic Acid Esters

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The mechanism by which α,γ-dioxo carboxylic acid esters **1** and 2-oxobutanedioic acid diesters **2** lose CO was explored. The compounds, 5,5-dimethyl-2,4-dioxohexanoic acid ethyl ester, **1a**, α,2-dioxocyclohexaneacetic acid ethyl ester, **1b**, and α,1-dioxotetrahydro-2-naphthaleneacetic acid ethyl ester, **1c**, lose CO at 170-190 °C to yield the corresponding β-keto esters **3a-c**. When compounds **1** or the parent acids **4** were heated to 170-190 °C with water in a sealed reactor, they yielded ketones resulting from replacement by H of $C(O)CO_2R$ from **1** or $C(O)CO_2H$ from **4**. β-Keto esters suffered replacement by H of the carbethoxy group to yield the corresponding ketones when heated with water at about 105 °C. Acylketenes, such as 4,4-dimethyl-1-pentene-1,3-dione, **6a**, 2-oxocyclohexylidenemethanone, **6b**, 1-oxotetrahydro-2-naphthylidenemethanone, **6c**, 3-methyl-1-butene-1,3-dione, **6d**, and 1-butene-1,3-dione, **6e**, are implicated as the common intermediates that react with water to form β-keto acids that subsequently decarboxylate to yield the ketones **5**. Intense IR frequencies in the region of 2120-2140 cm^{-1}, characteristic of ketenes, are observed when **1**, **2**, or **3** is subjected to GC-FTIR analysis with the injector and light pipe at 280 °C. Loss of carbon monoxide and alcohol at high temperature is required to form **6** from **1**, while only the loss of alcohol at lower temperature is needed to form **6** from **3**.

The quest for a plausible mechanism for the decarbonylation of 2,4-dioxo carboxylic acid esters **1** and 2-oxobutanedioic acid esters **2**, a useful synthetic reaction,[1] has intrigued four generations of chemists. Many useful facts

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