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

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

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

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

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

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

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

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

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

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

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

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

Acknowledgment. We thank Professor S. Hanessian (Université de Montréal) for helpfull discussions. The financial support by CNR (Rome) is greatly appreciated.

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

Notes

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

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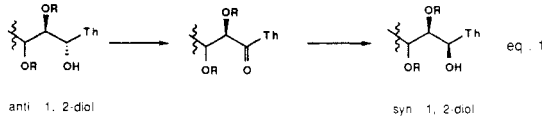
We recently described in a preliminary form[1] the anti-diastereoselective addition of 2-(trimethylsilyl)thiazole (**1**) to the protected L-serinal (**2**) to give the thiazole amino alcohol *anti*-**3a** (ds = 92%), which was converted into the diastereoisomer *syn*-**3c** (ds = 94%) through the ketone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

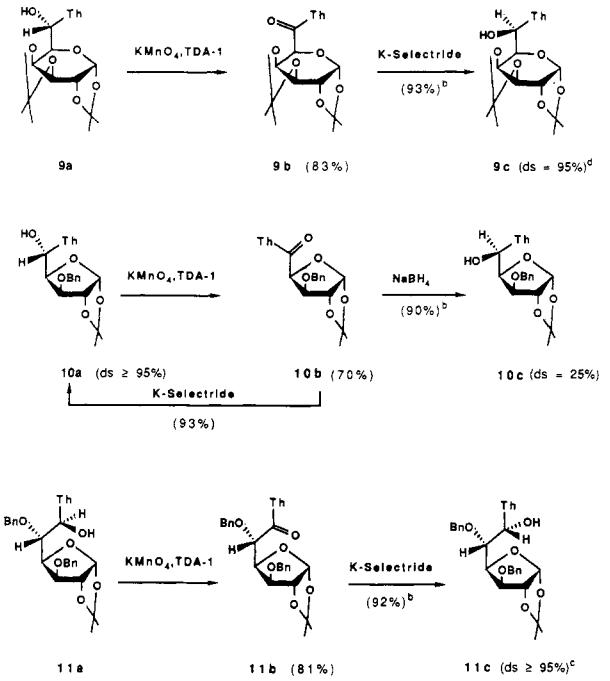


have been described for the inversion of the configuration of secondary alcohols,[3] very few deal with an oxidation–

(1) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *J. Chem. Soc., Chem. Commun.* **1988**, 10.

0022-3263/89/1954-0702$01.50/0

Chart I[a]

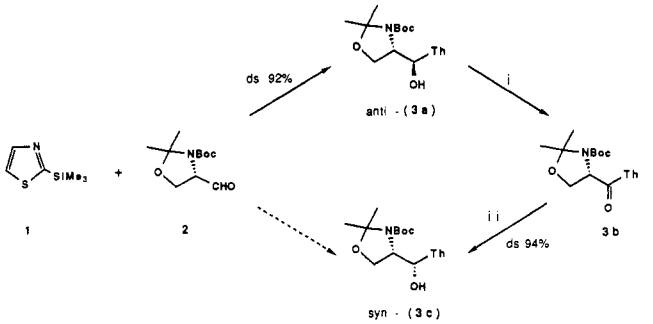


[a] Th = 2-thiazolyl; Bn = benzyl; ds values determined on the crude reaction mixtures; yields refer to the isolated products.

reduction sequence; moreover, the scope of these methods is still undefined since they have been applied to a limited number of structures.[4] We give here a full report of our own results in this area.

The oxidation of the secondary unprotected hydroxy group in thiazole aldoses[5,6] **3a–8a** (Table I) and thiazole dialdoses[5,6] **9a–11a** (Chart I) to give the corresponding uloses **3b–8b** and aldosuloses **9b–11b** was conveniently carried out in dry dichloromethane with potassium permanganate[7] partly solubilized with TDA-1 (tris[2-(2-methoxyethoxy)ethyl]amine. In all cases examined the reaction was completed within 12–20 h at room temperature and produced the corresponding ketose, which was isolated in good yield and high purity. No appreciable racemization occurred via exchange of the proton at the secondary carbon α to the carbonyl under the reaction conditions and workup operations. In fact, compounds **3b** and **4b** appeared to possess enantiomeric purity ≥95% by ^{1}H NMR analysis of the corresponding alcohols **3c** and **4c** using the chiral shift reagent Eu(hfc)$_3$ and the Mosher reagent MTPA, respectively.[8] The examples reported in Table I sufficiently demonstrate that this neutral nonaqueous oxidation procedure of the unprotected α-hydroxy group in polyoxygenated alkylthiazoles employing heptavalent manganese in the presence of TDA-1 is a quite convenient method showing an high degree of generality. Very likely the procedure may be equally well extended to other primary and secondary aryl and heteroaryl alcohols.[9] It is worth pointing out that despite the availability of various effective oxidizing agents for the conversion of the hydroxy group into the carbonyl function,[10] there is still a need for new methods especially for complex and highly sensitive substrates where selectivity and mild conditions are prerequisites.

Scheme I[a]



[a] Reagents: (i) $KMnO_4$, TDA-1; (ii) $NaBH_4$.

The hydride reduction[11] of the carbonyl with sodium borohydride or Selectride (Aldrich) into the hydroxy group in thiazole uloses **3b–8b** occurred smoothly with high levels of syn-distereofacial selectivity to give the protected aldoses **3c–8c** as major isomers[12] in very good chemical yields (Table I). The preference for the syn isomer corresponds to that observed for the reduction of other α,β-dialkoxy ketones with the same hydride releasing reagents[11] and it is that expected on the basis of the Felkin–Anh open-chain model for asymmetric induction.[13] Hence a procedure for the α-hydroxy group inversion of anti thiazole aldoses **3a–8a** into syn isomers **3c–8c** with good chemical and stereochemical efficiency appears to be at hand. On the other hand, the reduction of **4b** with Red-Al (Vitride) produced compound **4a** as major isomer having the anti 1,2-diol unit. As already suggested for the hydride reduction of other α,β-dialkoxy ketones where the opposite stereochemical outcome was obtained using Vitride instead of Selectride,[4a] the anti selectivity can be explained by assuming the α-chelate model, which is favored by the coordinating ability of aluminum of the metal hydride.

Next we turned our attention to the carbonyl reduction of thiazole aldosuloses **9b–11b** (Chart I). Treatment of the thiazole *galacto*-heptosulose **9b** with sodium borohydride afforded both dialdoses **9a** and **9c** in nearly 50:50 ratio

(2) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.*, accompanying article in this issue. (b) Dondoni, A.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron Lett.* **1985**, *26*, 5477. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 835. (d) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Tetrahedron* **1987**, *43*, 3533.

(3) See, for instance, the following. (a) Mitsunobu inversion: Mitsunobu, O.; Sano, T.; Wada, M., *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2833. Mitsunobu, O., *Synthesis* **1981**, 1. (b) Via nitroesters: Cainelli, G.; Manescalchi, F.; Martelli, G.; Panunzio, M.; Plessi, L. *Tetrahedron Lett.* **1985**, *26*, 3369. (c) Via isourea esters: Kaulen, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *109*, 3981.

(4) (a) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769. (b) Pikul, S.; Raczko, J.; Ankner, K.; Jurczak, J. *J. Am. Chem. Soc.* **1987**, *109*, 3981.

(5) By virtue of the thiazolyl–formyl equivalence, thiazole polyols are considered as masked carbohydrates. See ref 37 of ref 2a.

(6) The relative stereochemistry in compound **4a** stems from an X-ray structure determination (ref 2a), while in compound **8a** and **10a** it was assigned on the basis of chemical transformations (ref 2a and 2d).

(7) Reviews on potassium permanganate as oxidant: Fatiadati, A. J. *Synthesis* **1987**, 85. Lee, D. G. *Oxidation in Organic Chemistry, Part D*; Trahanovsky, W. S., Ed.; Academic Press: New York, 1982.

(8) *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic Press: New York, 1983; Vol. 1 Chapters 7 and 9.

(9) A Rhone-Poulenc catalog reports the permanganate oxidation in the presence of TDA-1 of benzyl alcohol, (α-hydroxymethyl)thiophene and (α-hydroxymethyl)pyridine to the corresponding aldehydes.

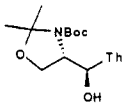
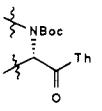
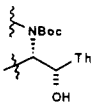
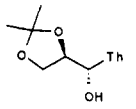
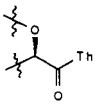
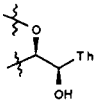
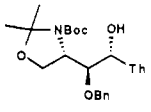
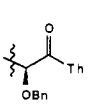
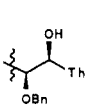
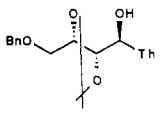
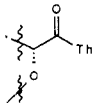
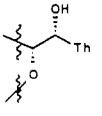
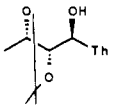
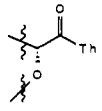
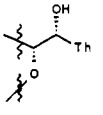
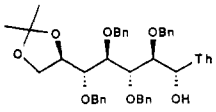
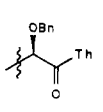
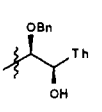
(10) House, H. *Modern Synthetic Reactions*; Brewlow, R., Ed.; Benjamin, W. A., Inc.: Menlo Park, CA, 1972; Chapter 5. Butterworth, R. F.; Hanessian, S. *Synthesis* **1971**, 70. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399 and references therein.

(11) Review on the hydride reduction of carbonyls: Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338. See also: ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(12) The stereochemistry of **5c** has been unequivocally assigned by an X-ray structure determination analysis.

(13) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. For a rationale by ab initio calculations of the Felkin–Anh model for asymmetric induction, see: Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.

Table I. Oxidation[a]-Reduction[b] Sequence of Thiazole Aldoses 3a–7a

Aldose (anti)	Ulose (Yield %)[c]	Aldose (syn)	Reducing Agent	Ratio[d] syn : anti	Yield[e] (%)
 3a	 3b (87)	 3c	$NaBH_4$	94 : 4	90
 4a	 4b (80)	 4c	$NaBH_4$ L-Selectride K-Selectride Red-Al	83 : 17 89 : 11 95 : 5 6 : 94	90 90 95 80
 5a	 5b (73)	 5c	$NaBH_4$ L-Selectride	70 : 30 91 : 9	88 90
 6a	 6b (70)	 6c	K-Selectride L-Selectride	85 :15 93 : 7	90 90
 7a	 7b (71)	 7c	K-Selectride	90 : 10	92
 8a	 8b (85)	 8c	L-Selectride	95 : 5	95

[a] Oxidant: $KMnO_4$ (TDA-1) in CH_2Cl_2. [b] Reducing agent: $NaBH_4$ (MeOH, room temperature); M-Selectride = $MBH(Bu\text{-}sec)_3$ (THF, −78 °C); Red-Al (Vitride) = $NaAlH_2(OCH_2CH_2OCH_3)_2$ (toluene, 0 °C). [c] Isolated yields. [d] Determined on the basis of 80-MHz ^1H NMR spectrum. [e] Values refer to isolated total yields.

whereas the employment of K-Selectride produced essentially the Felkin–Anh product **9c** (ds = 95%) in accord with the nonchelation control[14] observed with other ketones **3b–8b**. This provides the desired hydroxy group inversion in the dialdose **9a**. On the other hand the reduction of the thiazole *xylo*-hexosulose **10b** with either K- or L-Selectride afforded essentially the dialdose **10a** (ds 95%) in accord with the α-chelation control[14] instead of the expected epimer **10c** and the reduction with sodium borohydride produced only a minor amount of **10c** (ds 25%). Hence, the oxidation–reduction sequence fails to provide the hydroxy group inversion at C-5 in the thiazole dialdofuranose **10a**. The identical sense of diastereofacial selectivity arising from α-chelation has been reported for the reduction of another *xylo*-hexulofuranose[15] structurally similar to **10b**. Interestingly enough, moving the carbonyl away from the furanose ring by one carbon atom restored the nonchelation controlled diastereofacial selectivity as shown by the reduction of the thiazole *gluco*-heptosulose **11b** to the dialdose **11c** (ds ≥ 95%) having the syn 1,2-diol unit in the side chain. The reasons for the anomalous behavior of **10b** with respect to the other uloses described above are open to conjecture.

In conclusion, the above results demonstrate that one can invert the configuration of the hydroxy group that is α to the thiazole ring in thiazole aldoses and dialdoses via sequential oxidation with heptavalent manganese and then hydride reduction of the resulting carbonyl back to the hydroxy group. In particular this protocol allows for conversion of anti 1,2-diol fragments into the syn isomers in good-to-excellent yields and diastereoselectivities, thus providing preparatively useful reactions for building up new thiazole-protected carbohydrates.

Experimental Section

All melting points are uncorrected. ^1H NMR spectra were obtained on a 80-MHz WP80 Bruker spectrometer. Chemical shifts are given in parts per million from Me_4Si as internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 297 grating spectometer.

Material. Thiazole aldoses (anti isomers) **4a**, **7a**, and **8a** (ref 2a) and aldosuloses **9a–11a** (ref 2d) were prepared by addition of 2-(trimethylsilyl)thiazole (**1**) to the appropriate aldehydes as described.

Thiazole 3-deoxy-3-amino-L-erythrose **3a**[1] was prepared from *N*-(*tert*-butoxycarbonyl)-L-serinal (**2**) (1.14 g, 5 mmol) and 2-(trimethylsilyl)thiazole (**1**) (1.17 g, 7.5 mmol) according to the general procedure for the addition of **1** to chiral aldehydes.[2a]

(14) The major product **9c** arises from the attack by the hydride on the *si* face of the ketone conformer implied in structure **9b** whereas **10a** arises from attack on the *re* face in structure **10b**.

(15) Reitsen, B.; Kilaas, L.; Anthonsen, T. *Acta Chem. Scand.* **1986**, *B40*, 440.

Crystallization from dichloromethane–*n*-hexane gave 1.22 g (78%) of **3a**: mp 168–171 °C (dichloromethane–*n*-hexane); ^{1}H NMR ($CDCl_3$–D_2O) δ 1.47 (s, 15 H), 3.87–4.58 (m, 3 H), 5.22 (d, 1 H, J = 2.8 Hz), 7.30 (d, 1 H, J = 3.2 Hz), 7.76 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{14}H_{22}N_2O_4S$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.45; H, 7.01; N, 8.94.

Thiazole 4-Deoxy-4-amino-L-ribose **5a**. *O*-Benzylation and formyl deblocking from the thiazole ring[2a] of the adduct **3a** gave the corresponding (2*S*,3*S*)-2,4-dihydroxy-3-aminobutanal[1] (73%): oil; IR (film) 1740, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 1.50 (s, 3 H), 1.59 (s, 3 H), 3.68–4.20 (m, 4 H), 4.60 (AB quartet, 2 H, J = 8.8 Hz), 7.34 (br s, 5 H), 9.63 (d, 1 H, J = 3.2 Hz).

The reaction of 2-(trimethylsilyl)thiazole (**1**) (0.36 g, 2.28 mmol) with this aldehyde (0.38 g, 1.14 mmol) and in tetrahydrofuran (15 mL) at 0 °C for 20 h gave after the usual workup[2a] a mixture of *anti*-**5a** and syn adduct (85:15) (0.37 g, 75%). Flash chromatography (silica gel, 7:3 petroleum ether/ethyl acetate) gave the anti isomer **5a** (0.3 g, 61%): syrup; ^{1}H NMR ($CDCl_3$–D_2O) δ 1.40 (s, 9 H), 1.45 (s, 6 H), 3.77–4.75 (m, 4 H), 4.67 (s, 2 H), 5.16 (d, 1 H, J = 3.6 Hz), 7.32 (m, 6 H), 7.71 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{22}H_{30}N_2O_5S$: C, 60.81; H, 6.96; N, 6.45. Found: C, 60.92; H, 6.88; N, 6.50.

General Procedure for the Oxidation of the Alcohols 3a–11a. To a stirred solution of the appropriate alcohol (3 mmol) and TDA-1 (0.1 g, 0.3 mmol) in dry dichloromethane (50 mL) was added portionwise powdered $KMnO_4$ (0.95 g, 6 mmol), and the suspension was vigorously stirred until TLC indicates the absence of the starting material (12–20 h). The reaction mixture was filtered through Celite and the solvent was removed in vacuo. The residue was chromatographed through a short column (silica gel, 7:3 petroleum ether/ethyl acetate) to give the ketoses **3b–11b**.

Thiazole ketose **3b** (0.81 g, 87%): mp 115–117 °C (*n*-hexane–diethyl ether); IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR (C_6D_6, 84 °C) δ 1.35 (s, 9 H), 1.60 (br s, 3 H), 1.91 (br s, 3 H), 3.80–4.15 (m, 2 H), 5.67 (m, 1 H), 6.70 (d, 1 H, J = 3.2 Hz), 7.44 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{14}H_{20}N_2O_4S$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.88; H, 6.41; N, 8.95.

The NMR spectrum at room temperature indicated the presence of two conformers in ca. 2:1 ratio.

Thiazole ketose **4b** (0.51 g, 80%): mp 70–72 °C (*n*-hexane–diethyl ether); IR (film) 1710 cm^{-1}; ^{1}H NMr ($CDCl_3$) δ 1.50 (s, 3 H), 1.55 (s, 3 H), 4.02–4.72 (m, 2 H), 5.6 (dd, 1 H, J = 5.2 Hz, J = 7.8 Hz), 7.75 (d, 1 H, J = 3.2 Hz), 8.05 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.70; H, 5.20; N, 6.57. Found: C, 50.66; H, 5.23; N, 6.55.

Thiazole ketose **5b** (0.94 g, 73%): syrup; IR ($CHCl_3$) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 1.5 (s, 3 H), 1.65 (s, 3 H), 3.8–4.75 (m, 5 H), 5.37 (d, 1 H, J = 7 Hz), 7.25 (s, 5 H), 7.63 (d, 1 H, J = 3.2 Hz), 7.97 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{22}H_{28}N_2O_5S$: C, 61.10; H, 6.53; N, 6.48. Found: C, 61.21; H, 6.60; N, 6.41.

Thiazole ketose **6b** (0.7 g, 70%): oil; IR (film) 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 3 H), 1.56 (s, 3 H), 3.70–3.96 (m, 2 H), 4.4–4.66 (m, 1 H), 4.62 (s, 2 H), 5.46 (d, 1 H, J = 6.4 Hz), 7.3 (s, 5 H), 7.7 (d, 1 H, J = 3.2 Hz), 7.96 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.36; H, 5.81; N, 4.13.

Thiazole ketose **7b** (0.48 g, 71%): oil; IR (film) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 9 H), 4.08–4.45 (m, 1 H), 5.19 (d, 1 H, J = 7.2 Hz), 7.70 (d, 1 H, J = 3.2 Hz), 8.0 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.71; H, 5.70; N, 6.22.

Thiazole ketose **8b** (1.76 g, 85%): syrup; IR ($CHCl_3$) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.32 (s, 3 H), 3.62–4.96 (m, 14 H), 5.28 (d, 1 H, J = 3.6 Hz), 7.22 (m, 20 H), 7.50 (d, 1 H, J = 3.2 Hz), 7.83 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{41}H_{43}NO_7S$: C, 70.98; H, 6.25; N, 2.02. Found: C, 71.25; H, 6.31; N, 1.98.

Thiazole ketose **9b** (0.84 g, 83%): mp 169–171 °C (dichloromethane–*n*-hexane); IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.38 (s, 3 H), 1.47 (s, 3 H), 1.60 (s, 3 H), 4.51 (dd, 1 H, J = 3 Hz, J = 5 Hz), 4.77 (dd, 1 H, J = 3 Hz, J = 8 Hz), 5.15 (dd, 1 H, J = 3 Hz, J = 8 Hz), 5.56 (d, 1 H, J = 3 Hz), 5.82 (d, 1 H, J = 5 Hz), 7.77 (d, 1 H, J = 3.2 Hz), 8.08 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{15}H_{19}NO_6S$: C, 52.78; H, 5.61; N, 4.10. Found: C, 52.73; H, 5.64; N, 4.07.

Thiazole ketose **10b** (0.75 g, 70%): oil; IR (film) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.56 (s, 3 H), 4.37 (AB quartet, 2 H, J = 11.8 Hz), 4.77 (m, 2 H), 5.8 (d, 1 H, J = 4.2 Hz), 6.2 (d, 1 H, J = 3.6 Hz), 6.82–7.42 (m, 5 H), 7.68 (d, 1 H, J = 3.2 Hz), 7.87 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{18}H_{19}NO_5S$: C, 59.83; H, 5.30; N, 3.88. Found: C, 59.96; H, 5.21; N, 3.94.

Thiazole ketose **11b** (1.16 g, 81%): oil; IR (film) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.45 (s, 3 H), 4.07–4.87 (m, 7 H), 5.51 (d, 1 H, J = 9.4 Hz), 5.85 (d, 1 H, J = 3.8 Hz), 7.21 (s, 5 H), 7.32 (s, 5 H), 7.65 (d, 1 H, J = 3.2 Hz), 8.02 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{26}H_{27}NO_6S$: C, 64.85; H, 5.65; N, 2.91. Found: C, 64.70; H, 5.58; N, 2.96.

General Procedure for the Reduction of Ketoses 3b–11b. A. With $NaBH_4$. To a stirred solution of the appropriate ketone (0.2 mmol) in methanol (10 mL) was added $NaBH_4$ (0.4 mmol) at room temperature. After 15–30 min, acetone (1 mL) was added to the reaction mixture and the solvent was removed in vacuo. A saturated solution of NaCl (20 mL) was added to the residue and the product was taken up in ethyl acetate (2 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was chromatographed through a short column (silica gel, 7:3 petroleum ether/ethyl acetate) to give a mixture of the diastereoisomeric alcohols (NMR spectrum gave the ratio) (see Table I).

B. With L- or K-Selectride. To a stirred and cooled (−78 °C) solution of the ketone (0.2 mmol) in THF (10 mL) was added 0.4 mL (0.4 mmol) of a 1 M solution of L- or K-Selectride in THF, and the mixture was stirred at −78 °C for 1 h. The reaction was quenched with a solution of 10% NaOH (1 mL) and 30% H_2O_2 (0.5 mL). The reaction mixture was stirred at room temperature for additional 2 h and worked up in a similar manner to that described in A.

C. With Red-Al. To a stirred and cooled (0 °C) solution of the appropriate ketone (0.2 mmol) in toluene (10 mL) was added 0.3 mL (1 mmol) of 3.4 M Red-Al in toluene. The reaction mixture was stirred at 0 °C for 20 min and then at room temperature for 10 min. The reaction was quenched by addition of water (1 mL) and the resultant mixture was extracted with toluene (3 × 10 mL) and worked up in a similar manner to that described in A.

Thiazole 3-deoxy-3-amino-*L*-threose[1] **3c**: mp 86–88 °C (dichloromethane–*n*-hexane); IR (KBr) 3200, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$–D_2O) δ 1.47 (s, 3 H), 1.52 (s, 9 H), 1.61 (s, 3 H), 3.77–4.55 (m, 3 H), 5.10 (d, 1 H, J = 8.7 Hz), 7.34 (d, 1 H, J = 3.2 Hz), 7.77 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{14}H_{22}N_2O_4S$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.53; H, 7.00; N, 8.89.

Thiazole D-threose[2a] **4c**: oil; ^{1}H NMR ($CDCl_3$–D_2O) δ 1.38 (s, 3 H), 1.46 (s, 3 H), 3.93–4.60 (m, 3 H), 5.0 (d, 1 H, J = 6.0 Hz), 7.38 (d, 1 H, J = 3.2 Hz), 7.8 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.32; H, 6.16; N, 6.60.

Thiazole 4-deoxy-4-amino-L-arabinose[1] **5c**: mp 99–102 °C (dichloromethane–*n*-hexane); IR ($CHCl_3$) 3350, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$–D_2O) δ 1.51 (s, 9 H), 1.55 (s, 3 H), 1.65 (s, 3 H), 3.8–4.4 (m, 6 H), 5.02 (br s, 1 H), 6.9–7.4 (m, 6 H), 7.81 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{22}H_{30}N_2O_5S$: C, 60.81; H, 6.96; N, 6.45. Found: C, 60.76; H, 6.91; N, 6.44.

Thiazole L-xylose **6c**: oil; ^{1}H NMR ($CDCl_3$–D_2O) δ 1.35 (s, 6 H), 3.38 (m, 2 H), 4.17–4.57 (m, 2 H), 4.45 (s, 2 H), 4.97 (m, 1 H), 7.21 (s, 6 H), 7.61 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.88; H, 6.31; N, 4.18. Found: C, 61.02; H, 6.37; N, 4.11.

Thiazole 5-deoxy-L-xylose **7c**: oil; ^{1}H NMR ($CDCl_3$–D_2O) δ 1.09 (d, 3 H, J = 5.8 Hz), 1.35 (s, 6 H), 3.80–4.26 (m, 2 H), 4.89 (d, 1 H, J = 4.1 Hz), 7.26 (d, 1 H, J = 3.2 Hz), 7.70 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.50; H, 6.37; N, 6.20.

Thiazole D-*allo*-D-*threo*-octose **8c**: syrup: ^{1}H NMR ($CDCl_3$–D_2O) δ 1.3 (s, 3 H) 1.4 (s, 3 H), 3.55–4.81 (m, 15 H), 5.26 (d, 1 H, J = 2 Hz), 7.27 (m, 21 H), 7.70 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{41}H_{45}NO_7S$: C, 70.77; H, 6.52; N, 2.01. Found: C, 70.89; H, 6.44; N, 1.97.

Thiazole D-*galacto*-D-*glycero*-hepto-1,5-pyranose **9c**: mp 98–100 °C (*n*-hexane–dichloromethane); ^1H NMR ($CDCl_3$–D_2O) δ 1.31 (s, 3 H), 1.38 (s, 3 H), 1.5 (s, 3 H), 1.53 (s, 3 H), 4.1–4.75 (m, 4 H), 5.36 (d, 1 H, J = 5.0 Hz), 5.61 (d, 1 H, J = 4.8 Hz), 7.36 (d, 1 H, J = 3.2 Hz), 7.81 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.47; H, 6.17; N, 4.08. Found: C, 52.44; H, 6.20; N, 4.05.

Thiazole L-*ido*-1,4-furanose **10c**: oil; ^1H NMR ($CDCl_3$–D_2O) δ 1.32 (s, 3 H), 1.45 (s, 3 H), 4.13–4.76 (m, 5 H), 5.32 (d, 1 H, J = 4.4 Hz), 5.96 (d, 1 H, J = 3.4 Hz), 7.22 (m, 6 H), 7.67 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.49; H, 5.83; N, 3.86. Found: C, 59.58; H, 5.76; N, 3.81.

Thiazole D-*gluco*-L-*glycero*-1,4-furanose **11c**:[2] syrup; ^1H NMR ($CDCl_3$–D_2O) δ 1.32 (s, 3 H), 1.48 (s, 3 H), 3.97–4.76 (m, 8 H), 5.32 (d, 1 H, J = 1.1 Hz), 5.96 (d, 1 H, J = 3.7 Hz), 7.26 (m, 11 H), 7.78 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{26}H_{29}NO_6S$: C, 64.58; H, 6.05; N, 2.90. Found: C, 64.49; H, 6.11; N, 2.85.

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Supplementary Material Available: Crystal data, tables of bond distances, positional parameters, and bond angles, and an ORTEP drawing of **5c** (8 pages). Ordering information is given on any current masthead page.

Electron-Deficient Isoxazoles: 1,3-Dipolar Cycloadditions of Ethyl 4-Nitro-3-phenylisoxazole-5-carboxylate with Diazoalkanes[1]

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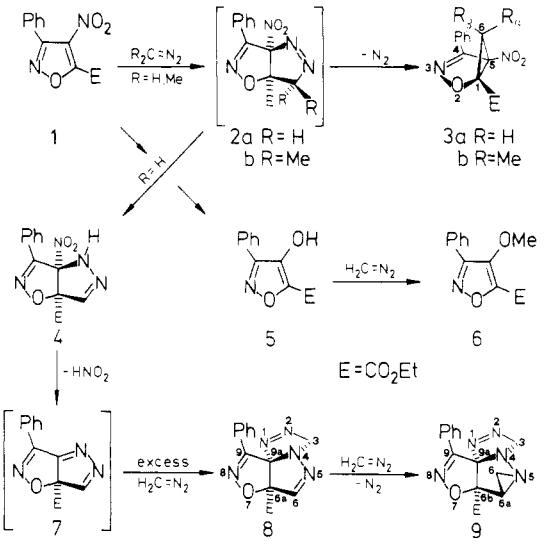
In an earlier note we reported that ethyl 4-nitro-3-phenylisoxazole-5-carboxylate (**1**) reacts with diazoalkanes as dipolarophile to give adducts that lose nitrogen, leading to the 2-oxa-3-azabicyclo[3.1.0]hex-3-enes **3**.[1] Both nitro and ester groups are required for the cycloaddition. We have now found that the reaction of **1** with excess diazomethane gives rise to the unusual tricyclic and tetracyclic products **8** and **9** (Scheme I).

Results and Discussion

When the nitro ester **1** was allowed to react with diazomethane, the reaction course strongly depended on the relative proportions of the two reagents; thus, in the presence of an equimolecular amount of the dipole, a partial conversion of **1** was achieved, affording the bicyclic

Scheme I



derivatives **3a** and **4** as the largely predominant reaction products.

The structure of **3a**, isolated by flash chromatography, followed from analytical and spectral evidence. In particular, the cyclopropane moiety was recognized by an IR absorption at 3115 cm^{-1} for the methylene at position 6; on the other hand, the ^1H NMR spectrum characteristically displayed an AX system at δ 1.60 and 3.33, attributable to the strongly diastereotopic protons of the same group, which, in turn, gave rise to a doublet of doublets at δ 19.8 in the proton-coupled ^{13}C NMR pattern.

Although repeated efforts to isolate ethyl (3a*R**,6a*S**)-3a,6a-dihydro-3a-nitro-3-phenyl-4*H*-pyrazolo[3,4-*d*]isoxazole-6a-carboxylate (**4**) were completely unsuccessful, its presence in the original reaction mixture was firmly established spectroscopically: careful comparison of the rapidly taken spectra of the crude product with those of compounds **1** and **3a** enabled us to detect all the most diagnostic signals of **4**.

Among these, an IR absorption was observed at 3380 cm^{-1} for the NH group, which gave rise to an exchangeable peak at δ 7.90 in the ^1H NMR spectrum; on the other hand, the latter was also characterized by a singlet at δ 6.99 for the H-6 proton, whereas the off-resonance ^{13}C pattern clearly showed, besides a doublet at δ 139.0 (CH), four singlets at δ 161.8, 152.2, 117.0, and 104.0 for the CO, C-3, C-3a, and C-6a carbons, respectively. Furthermore, on the basis of the relative intensities of the proton singlets of **4** with respect to those of the doublets at higher field of **3a**, it could be easily ascertained that the crude product contained nearly equimolecular quantities of these compounds.

After chromatographic workup, we isolated a small amount of the isoxazole derivative **5**, at first absent in the reaction mixture; the structure of this compound, which probably arises from the unreacted **1** through an acid-catalyzed Michael addition of water to the C(4)–C(5) double bond of the latter, followed by elimination of nitrous acid, was determined by spectral data and conversion into the corresponding methoxy derivative **6** with diazomethane.

Failure to isolate **4** can be imputed to its tendency to lose nitrous acid, affording the isopyrazole system **7**, which is unstable, probably due to the presence of a strained exocyclic C=N double bond. This explanation was strongly supported by the behavior of **1** with an excess (molar ratio 1:3) of diazomethane: under these conditions,

(1) For a preliminary communication on a part of this work, see: Nesi, R.; Giomi, D.; Quartara, L.; Bracci, S.; Papaleo, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1077.

0022-3263/89/1954-0706$01.50/0