and TLC behavior identical with that[5b] of authentic (±)-24;[5] mass spectrum, m/e 467 (M^+).

Epimerization of the Cis Lactam Acid (-)-16 to the Trans Isomer 20. (-)-16 (4.56 g, 10 mmol) was heated neat at 180 °C for 80 min to give a brown solid. Recrystallization of the solid from AcOEt–hexane (1:1, v/v) produced almost colorless prisms (4.10 g, 90%), mp 118–119 °C, presumed to be a 37:63 mixture[19] of (-)-16 and 20.[21] A portion (3.00 g, 6.59 mmol) of the mixture was esterified [10% (w/w) ethanolic HCl (60 mL), 17 °C, 12 h] as described above for (+)-17, giving a mixture of 15 and 19 as a pale yellow oil (3.01 g, 95%): IR (neat) 1730 (ester C=O), 1643 (lactam C=O) cm^{-1}. The oil (2.98 g, 6.16 mmol) was subjected to the Bischler–Napieralski cyclization [$POCl_3$ (5.35 g, 34.9 mmol), boiling benzene (30 mL), 2.5 h] followed by catalytic hydrogenation [Adams catalyst (200 mg), EtOH (20 mL), atmospheric pressure, 20 °C, 150 min] as described above for (-)-24, and the basic product obtained was chromatographed [silica gel, AcOEt–hexane (1:2, v/v)] to afford (-)-24 (170 mg, 10% overall yield based on 20) as a yellow oil which was identical (by comparison of TLC behavior and IR and NMR spectra) with authentic (-)-24.

(2*R*,3*R*,11b*S*)-(-)-8-(Benzyloxy)-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-ethanol [(-)-25]. To a stirred, ice-cooled suspension of $LiAlH_4$ (140 mg, 3.7 mmol) in dry ether (10 mL) was added dropwise a solution of (-)-24 (865 mg, 1.85 mmol) in dry ether (10 mL) over a period of 15 min. After the mixture had been heated under reflux for 4 h, H_2O (0.15 mL), 10% aqueous NaOH (0.2 mL), and H_2O were sequentially added under ice cooling. The supernatant ethereal solution was separated from the resulting insoluble inorganic materials by decantation, dried (K_2CO_3), and concentrated in vacuo to give (-)-25 (725 mg, 92%) as an unstable, pale yellow oil: $[\alpha]^{20}_D$ -33.4° (*c* 1.00, EtOH); IR ($CHCl_3$) and NMR ($CDCl_3$) spectra superimposable with those[5b] of authentic (±)-25.[5]

(2*R*,3*R*,11b*S*)-(-)-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-ethanol (Ankorine) [(-)-1]. A solution of (-)-25 (660 mg, 1.55 mmol) in EtOH (25 mL) was hydrogenated over 10% Pd–C (300 mg) at ordinary pressure and 20 °C for 60 min. Removal of the catalyst by filtration and concentration of the filtrate under reduced pressure furnished (-)-1 (515 mg, 99%) as a colorless solid, mp 173–177 °C. Recrystallization of the solid from acetone yielded an analytical sample as colorless prisms: mp 176–177 °C; $[\alpha]^{16}_D$ -58 ± 1° (*c* 0.23, $CHCl_3$); UV max (99% EtOH) 273 nm (log ε 2.98); UV max (0.1 M aqueous NaOH) 287 (3.37); IR ($CHCl_3$) 3630, 3530 (OH), 2800, 2750 (*trans*-quinolizidine ring)[22] cm^{-1}; NMR ($CDCl_3$) δ 0.91 (t, 3, *J* = 6.5 Hz, CH_2CH_3), 3.84 and 3.87 (s each, 6, CH_3O's), 5.90 (br, OH's), 6.33 (s, 1, C_{11} H); mass spectrum, m/e (relative intensity) 335 (M^+) (75), 334 (100), 320 (32), 318 (43), 306 (10), 304 (8), 290 (17), 278 (15), 262 (67), 248 (10), 221 (54), 207 (54). Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.24; H, 8.56; N, 4.19. This sample was identical [by mixture melting point test (mmp 175–177 °C) and comparison of UV, IR ($CHCl_3$ or KBr), NMR, and mass spectra, TLC behavior, and specific rotation] with a natural sample of ankorine [mp 175–177 °C; $[\alpha]^{16}_D$ -54 ± 2° (*c* 0.18, $CHCl_3$)].[3,20]

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Registry No. (-)-1, 13849-54-2; (+)-3, 56246-53-8; 5, 118-10-5; (-)-9, 57103-62-5; 10, isomer 1, 73090-15-0; 10, isomer 2, 73090-16-1; 11, isomer 1, 73090-17-2; 11, isomer 2, 73090-18-3; 12, isomer 1, 73090-19-4; 12, isomer 2, 73090-20-7; 12, isomer 3, 73090-21-8; 12, isomer 4, 73090-22-9; (-)-13, 57130-36-6; (-)-14, 65929-06-8; (-)-16, 57103-66-9; (±)-17, 56774-69-7; (+)-17, 65942-29-2; (±)-18, 73173-72-5; (+)-18, 65929-07-9; (+)-19, 57130-38-8; 20, 57103-67-0; *trans*-23, 73136-35-3; (-)-24, 57130-35-5; (-)-25, 73136-36-4.

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Carbohydrate Models of α-Methylene-γ-butyrolactones[1]

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The α-methylene-γ-butyrolactone moiety is a characteristic component of a large class of sesquiterpenes many of which possess marked cytotoxic, antitumor, and other biological activities. The activity of these lactones apparently derives from their chemical affinity for the thiol groups of sulfhydryl enzymes. Although the enone component is essential for biological activity, there are additional factors which may enhance these properties. These enhancement factors include the presence of hydroxyl groups in stereochemically strategic positions and the presence of various conjugated ester side chains. The built-in functionality of carbohydrates was utilized for the synthesis of such analogues. The target molecule was 2-deoxy-2-*C*-methylene-D-*threo*-pentono-1,4-lactone (2), the D-xylose analogue of α-methylene-γ-butyrolactone. Synthesis of 2 commenced with the protection of D-xylose at the 1, 3, and 5 positions to give methyl 3,5-*O*-isopropylidene-α-D-xylofuranoside (3). Compound 3 was oxidized with RuO_4 to the 2-keto sugar which was condensed with $NaCH_2NO_2$. Treatment of the resulting nitro alcohols with Ac_2O in Me_2SO followed by quantitative reduction with $NaBH_4$ gave the protected 2-deoxy-2-*C*-nitromethyl derivative of D-xylose. Removal of the protecting groups followed by oxidation with bromine in water–acetic acid and then treatment with $BaCO_3$ gave the target molecule 2 as evidenced by IR, ^1H NMR, and ^{13}C NMR data. The reaction of 2 was carried out with the model sulfhydryl compounds cysteine and glutathione. In each case the reaction was complete in less the 15 min and gave crystalline adducts quantitatively. In addition, these sulfhydryl compounds added stereospecifically, as evidenced by ^{13}C NMR data.

The potent cytotoxic action of many sesquiterpene plant products and their ability to inactivate certain selected enzymes have been attributed to the presence of the α-methylene-γ-butyrolactone moiety.[2-5] The activity of these compounds apparently derives from the extreme ease

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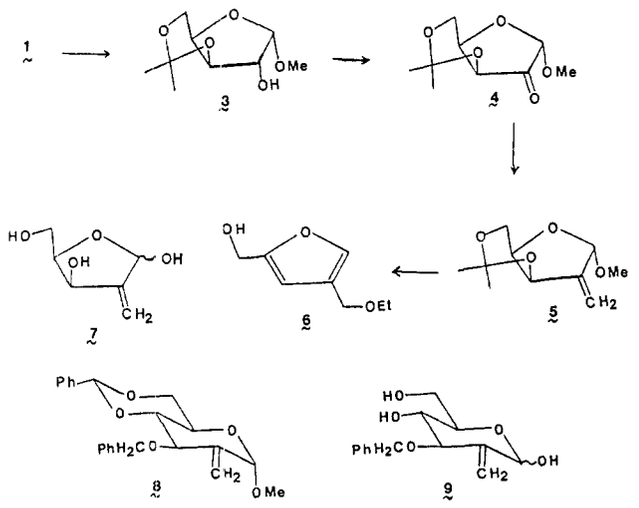
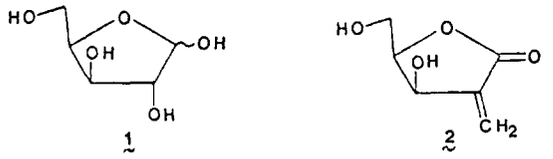
Scheme I



with which this functionality reacts with thiols.[3,6,7] Interest in α-methylene-γ-butyrolactones as medicinal agents has been stimulated by the possibility that some of these might show enough selective toxicity against neoplastic cells to be of therapeutic value as anticancer agents.[4,7-11] Although the presence of the α-methylene-γ-butyrolactone unit is essential for biological activity,[3,12] there are other factors which may enhance these properties.[7] These enhancement factors include the presence of hydroxyl groups in stereochemically strategic positions and the presence of various conjugated ester side chains. A conjugated ester moiety, if present in a sesquiterpene lactone, not only increases lipophilicity of the molecule but also may constitute an additional functionality reactive toward thiols.[3,4] Although their exact role is not clear, the presence of hydroxyl groups adjacent to the α-methylene group is a common feature among a number of sesquiterpene lactones showing in vivo antitumor activity.[3,4,7] Presence of such hydroxyl groups apparently increases the rate of cysteine addition to these molecules.[3,12] It has been suggested that the hydroxyl groups might be involved in direct binding of these compounds to receptor sites in tumor cells.[7,13] It should be mentioned, however, that the biological activity of α-methylene-γ-butyrolactones is not confined to the complex polyfunctional sesquiterpene lactones only. For example, it has been shown that synthetic α-methylene-γ-butyrolactone derivatives containing no other reactive functionality can in some instances have growth-inhibitory activity comparable to that of multifunctional natural products.[14,15]

Although intense interest has been shown in the synthesis of α-methylene-γ-butyrolactone derivatives,[16-18] no study involving the effects of the enhancement factors on synthetic models has been made. As α-methylene-γ-butyrolactones, either synthetic or natural, are expected to have some biological properties,[7] a rational approach toward the development of new SH alkylating antitumor agents is the synthesis of model compounds which incorporate both active centers and enhancement factors. Compounds which by virtue of their built-in functionality appear to be ideal starting materials for the synthesis of such model compounds are the carbohydrates. For example, the α-methylene-γ-butyrolactone derivative that is obtainable by the minimum structural alteration of D-xylose (1) (shown in the furanose form) is 2. Either of the



remaining hydroxyl groups of 2 can be suitably esterified to give model compounds incorporating the active center as well as enhancement factors. In this report we wish to describe the synthesis of the D-xylose model of α-methylene-γ-butyrolactone and to discuss its reactions with model biological thiols.

Results and Discussion

In terms of functional group transformation, conversion of 1 to 2 involves oxidation of a lactol to a lactone and replacement of a secondary hydroxyl group by an exocyclic methylene group. A reaction sequence that appears to be relatively simple involves introduction of the methylene group by the Wittig reaction of a suitably protected 2-keto sugar followed by deprotection and oxidation at C-1. Another reasonable sequence involves generation of the exocyclic methylene group in the last step of the synthesis from a suitable branched-chain lactone. In either pathway, a 2-keto sugar is the key intermediate.

Synthesis of the 2-keto sugar necessitates prior protection of the other hydroxyl groups of D-xylose. This was done by reacting D-xylose with methanolic hydrogen chloride followed by treatment with acetone/*p*-TsOH·H_2O/$CuSO_4$ to give methyl 3,5-*O*-isopropylidene-α,β-D-xylofuranosides.[19] The mixture was separated by fractional distillation to give α-(3) and the β isomer in 33 and 21% overall yield, respectively. The structure of 3 and its β isomer was confirmed by ^1H NMR data. In the α isomer (3), H-1 occurred as a doublet with coupling constant $J_{1,2}$ = 4.0 Hz, characteristic of vicinal cis coupling in furanose rings, while H-1 of the β isomer, where H-1 and H-2 are trans, occurred as expected as a singlet.[20] Although either isomer could be used in the subsequent steps, only the α isomer was used here mainly because it was produced in higher yields. Oxidation of the xyloside 3 with RuO_2/KIO_4/K_2CO_3 in water–carbon tetrachloride proceeded smoothly to give the keto sugar 4 in 80% yield (Scheme I). The product obtained initially was a mixture of 4 and its hydrate. Pure ketone was obtained by azeotropic distillation of the water of hydration with benzene. Pure

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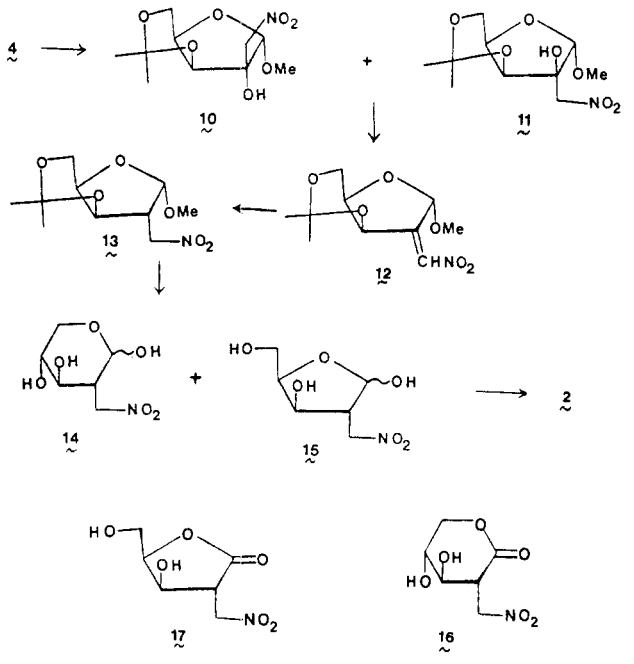
Scheme II



4 showed absorption in the infrared at 1790 cm^{-1}. As the keto sugar was unstable and darkened on storage, it was utilized immediately after its synthesis. Interestingly, dimethyl sulfoxide based reagents such as Me_2SO/Ac_2O and $Me_2SO/DCC/H_3PO_4$/pyridine were found to be unsatisfactory for this oxidation reaction.[31]

Treatment of the keto sugar 4 with methylenetriphenylphosphorane,[21] generated in situ, in toluene at 0 °C gave the unsaturated sugar 5 in 28% yield. The yields were lower in THF or ether or at higher temperatures. Removal of the protecting groups of 5, both of which are acid labile, was then attempted. However, treatment of 5 in ethanol–water with dilute HCl led to the formation of the furan derivative 6. The desired hydrolysis product 7 was not detected. This is in contrast to our earlier observation[22] that compound 8 can be hydrolyzed quantitatively in ethanol–water which is 0.1 N in HCl at 85 °C for 1 h to give the expected hydrolysis product 9. It is apparent that had the 3-OH been protected by an acid-stable protecting group, formation of the furan derivative 6 could have been avoided. However, the nature of the Wittig reaction[21] and the Wittig product precluded the use of other common protecting groups, namely, those labile to hydrogenolysis or base.

Attention was then turned toward the reaction sequence involving generation of the exocyclic methylene group in the last step of the synthesis from a branched-chain lactone. The branched chain that appeared suitable for this purpose was a nitromethyl group. The problem then was the replacement of the 2α-OH of 3 by CH_2NO_2. The keto sugar 4 again served as the starting material. Condensation of 4 with $NaCH_2NO_2$ in excess CH_3NO_2 gave an isomeric mixture of nitro alcohols 10 and 11 in 83% yield (Scheme II). The ratio of xylo (10) to lyxo (11) was 70:30 as evidenced by ^1H NMR data. As the 2β-OH of 11 is cis to H-1, a shielding is expected in the chemical shift of H-1 of 11 compared to that of 10. Thus the singlet at δ 4.98 in the NMR spectrum was assigned to the lyxo isomer (11) and the singlet at δ 5.20 to the xylo isomer (10). The nitro alcohols were dehydrated with Ac_2O/Me_2SO at 25 °C to give the nitro alkene 12. The crude nitro alkene was reduced with $NaBH_4$ in ethanol–water at 0 °C for 2 h whereby the nitro alkane 13 was obtained in 81% yield as a syrup. Interestingly, this reduction is stereospecific, as shown by NMR studies.[31,32] The ^1H noise-decoupled PFT ^{13}C NMR spectrum of 13 showed the presence of a single compound with C-2 resonance at δ 49.6. Its ^1H NMR spectrum exhibited a coupling constant, $J_{1,2}$ = 5.0 Hz, consistent with the α stereochemistry of the nitromethyl group.[20]

The synthetic plan then involved removal of the protecting groups (of 13), oxidation at C-1, and subsequent generation of the exocyclic methylene group at C-2. Removal of protecting groups was accomplished quantitatively by treating 13 with Dowex 50-W (H^+ form) in ethanol–water at 65 °C for 3 h. The syrupy product appeared to be a mixture consisting of the pyranose (14) and furanose (15) forms of 2-deoxy-2-C-(nitromethyl)-D-xylose as evidenced by ^{13}C NMR data. As expected, the pyranose forms 14 were predominant, and detailed ^{13}C NMR data analysis suggested that compounds 14 accounted for about 77% of the product mixture.[23] Oxidation of the free sugar (14 + 15) was carried out with bromine in 30% acetic acid for 24 h in the dark. After removal of excess bromine, the mixture was stirred with excess $BaCO_3$ for 2 h to neutralize the acids. Extractive workup gave not the expected nitromethyl lactones 16 and 17 but the target D-xylose model of α-methylene-γ-butyrolactone (2) directly in 52% yield. The structure of the α-methylene lactone 2 was confirmed by its IR, ^1H NMR, and ^{13}C NMR spectral data. The infrared spectrum showed the presence of a strong absorption at 1768 cm^{-1}, characteristic of γ-lactones.[24] The absorption due to a NO_2 group was absent, and the occurrence of two peaks at 915 and 1650 cm^{-1} suggested the presence of an exocyclic methylene group.[24] The ^{13}C NMR spectrum indicated the presence of only one compound with a characteristic C-4 resonance at δ 83.4 similar to that found in other γ-lactone structures.[23] In the ^1H NMR spectrum, each hydrogen of the exocyclic methylene group occurred as a doublet with J_{gem} = 2.0 Hz.

The direct formation of 2 can be explained by considering the mechanistic details of bromine oxidation and the stabilities of γ- and δ-aldonolactones toward acids and bases. In neutral and acidic media, bromine oxidizes aldoses directly to the corresponding aldonolactones and in the process 2 mol of HBr are produced for each mole of aldose oxidized.[25] This HBr probably catalyzed the equilibration of 16 and 17, ultimately favoring the γ-lactone, 17, because of its greater thermodynamic stability.[26] During the treatment with $BaCO_3$, the δ-lactone 16 (or the α-methylene δ-lactone derived from 16) is removed from the solution as an insoluble barium salt because of its greater reactivity toward base.[27] Elimination of the elements of HNO_2 from 17 was possibly mediated by $BaCO_3$. This is reasonable as nitromethyl groups when positioned α to an ester or lactone carbonyl carbon undergo facile elimination reactions to give unsaturated esters or lactones.[28]

As mentioned earlier, the biological activity of α-methylene lactones apparently derives from their affinity for

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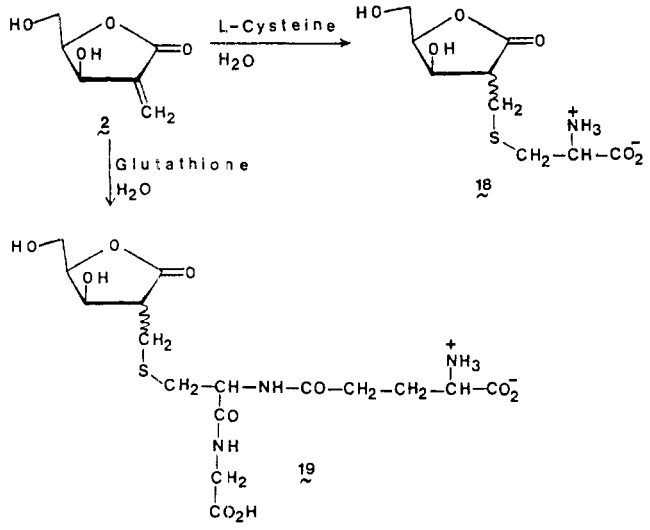
Scheme III



the thiol groups of sulfhydryl enzymes. Accordingly, biomimetic reactions of 2-deoxy-2-*C*-methylene-D-*threo*-pentono-1,4-lactone (**2**) with model sulfhydryl systems such as cysteine and glutathione were next attempted. In both cases, the reaction was quantitative and complete in less than 15 min in neutral aqueous medium to give the cysteine adduct **18** and the glutathione adduct **19**, respectively, as crystalline solids (Scheme III). The reactions were very conveniently monitored by ^{1}H NMR by observing the disappearance of the signals due to the exocyclic methylene group of **2**. The reaction time compares very favorably with that of some of the reactive naturally occurring α-methylene-γ-butyrolactones. For example, the reaction of eupatundin with cysteine at pH 7.4 was complete in 30 min, whereas reaction of helenalin with glutathione in water was complete in 4 h.[6,29] The assignment of peaks in the ^{1}H NMR spectra of the adducts was not possible due to considerable overlapping of signals. Thus it was not possible to deduce the stereochemistry of the adducts. However, ^{13}C NMR data indicated the formation of a single isomer in each case and that it was the SH group that had added to the C=CH_2 group of the α-methylene lactone **2**.

Since the reaction sequence developed for the synthesis of **2** appears to be of general applicability, this approach should lead to other carbohydrate analogues of α-methylene-γ-butyrolactones with various stereostructural characteristics. Synthesis of various esters of **2** and the biological evaluation of **2** and its esters are currently in progress.

Experimental Section

Methyl 3,5-*O*-Isopropylidene-α-D-xylofuranoside (3) and Its β Anomer. The crude syrup obtained in two steps from D-xylose by the method of Baker and co-workers[19] was distilled through a Vigreux column to give the α anomer **3** as a colorless syrup (33%): bp 83–88 °C (0.1 mm) [lit.[19] bp 85–88 °C (0.1 mm)]; $[\alpha]^{25}_D$ +17.6° (*c* 2, H_2O); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.41 (s, 3 H), 3.28 (br s, OH), 3.52 (s, 3 H, OMe), 3.92–4.18 (m, 5 H), 5.15 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1); ^{13}C NMR (Me_4Si, $CDCl_3$): δ 19.6, 28.5, 56.3, 60.5, 71.3, 75.5, 76.8, 97.7, 103.4. The Vigreux column was replaced by a Claisen head, and the residue was distilled to give the β anomer (21%): bp 107–109 °C (0.1 mm); $[\alpha]^{25}_D$ –64.2° (*c* 2, H_2O) [lit.[19] bp 108–110 °C (0.1 mm); $[\alpha]^{24}_D$ –64.2° (*c* 2, H_2O)]; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.38 (s, 3 H), 3.40 (s, 3 H, OMe), 3.82–4.27 (m, 6 H), 4.86 (s, 1 H, H-1); ^{13}C NMR (Me_4Si, $CDCl_3$): δ 21.0, 27.0, 55.2, 60.9, 75.0, 75.3, 80.2, 98.4, 110.5.

Methyl 3,5-*O*-Isopropylidene-α-D-*threo*-pentofuranosid-2-ulose (4). To a well-stirred solution of methyl 3,5-*O*-isopropylidene-α-D-xylofuranoside (**3**; 14.1 g, 70 mmol) in 200 mL of carbon tetrachloride were added water (200 mL), ruthenium dioxide (225 mg, 50–60% hydrated reagent, Engelhard Industries), potassium carbonate (2.48 g, 18 mmol), and potassium metaperiodate (23 g, 100 mmol). The mixture was stirred vigorously at 25 °C for 15 h. The oxidation was then terminated by adding 2-propanol (10 mL) and stirring the mixture for 10 min. The mixture was then filtered through a pad of Celite, and the filter was washed with two 20-mL portions of carbon tetrachloride. The organic layer was separated, and the aqueous layer was evaporated in vacuo at >40 °C to dryness. The residue was stirred with 100 mL of warm (50 °C) chloroform for 5 min and filtered. The process was repeated once. The chloroform solutions were combined with the carbon tetrachloride solution, dried (Na_2SO_4), and evaporated in vacuo to dryness to give the keto sugar predominantly as its hydrate as a syrup to partly solidified material (12.02 g). The syrup or the partly solidified material was crystallized from ether–hexane (40:60 by volume) to give pure hydrate, mp 69–70 °C (lit.[30] mp 69–70 °C). Anhydrous keto sugar was obtained by dissolution of the hydrate in boiling dry benzene and evaporation of the solution in vacuo to dryness. This process, when repeated two to three more times, gave essentially pure keto sugar as a syrup: 11.32 g (80%); $[\alpha]^{25}_D$ +111° (*c* 1, $CHCl_3$); IR (neat) 1790 (C=O) cm^{-1}; ^{1}H NMR δ 1.46 (s, 6 H), 3.56 (s, 3 H), 3.94–4.27 (m, 4 H), 4.92 (s, 1 H, H-1); ^{13}C NMR (Me_4Si, $CDCl_3$): δ 19.4, 28.7, 56.7, 60.8, 71.4, 73.6, 98.2, 106.4, 203.9.

Methyl 3,5-*O*-Isopropylidene-2-deoxy-2-*C*-methylene-α-D-*threo*-pentofuranoside (5). To a stirred suspension of methyltriphenylphosphonium bromide (5 g, 14 mmol) in dry toluene (70 mL) under nitrogen was added through a septum port 9 mL of 1.56 M *n*-butyllithium in hexane. The bright yellow mixture was stirred at 25 °C for 30 min. A solution of methyl 3,5-*O*-isopropylidene-α-D-*threo*-pentofuranosid-2-ulose (**4**; 1.42 g, 7 mmol) in 30 mL of dry toluene was then added dropwise through the septum port. The reaction mixture was then stirred at 25 °C under nitrogen for 18 h. Excess methylenetriphenylphosphorane was destroyed by addition of acetone (2 mL) and then stirring for 30 min. Evaporation of solvent gave a light red gum. The gum was extracted with boiling hexane (5 × 30 mL). The hexane solutions were combined and evaporated in vacuo to dryness. The residue was chromatographed on a column of silica gel (30 g) and eluted with 1:1 ether–hexane to give the title compound as a colorless oil (395 mg, 28%): ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3 H), 1.45 (s, 3 H), 3.41 (s, 3 H), 3.90–4.31 (m, 4 H), 4.53 (br s, 1 H), 5.45 and 5.51 (2 s, 2 H); ^{13}C NMR (Me_4Si, $CDCl_3$) δ 19.8, 28.5, 55.4, 60.3, 71.2, 78.6, 97.8, 103.7, 115.8, 148.4.

Attempted Hydrolysis of Methyl 3,5-*O*-Isopropylidene-2-deoxy-2-*C*-methylene-α-D-*threo*-pentofuranoside (5). To a solution of **5** (280 mg, 1.4 mmol) in 15 mL of ethanol was added 15 mL of 0.2 N hydrochloric acid. The mixture was heated with stirring at 65 °C for 20 min. The mixture was cooled to 25 °C, neutralized with Dowex 1-X8 (HCO_3^- form) to pH 7, and then evaporated in vacuo to dryness to give 4-(ethoxymethyl)-2-(hydroxymethyl)furan (**6**) as a pale yellow oil: 210 mg (~98%); ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 3 H), 3.1 (br s, 1 H, OH), 3.5 (q, J = 7 Hz, 2 H), 4.31 (s, 2 H), 4.51 (s, 2 H), 6.30 (s, 1 H), 7.35 (s, 1 H).

Methyl 3,5-*O*-Isopropylidene-2-*C*-(nitromethyl)-α-D-xylo- and -lyxofuranosides (10 and 11, Respectively). To a stirred solution of methyl 3,5-*O*-isopropylidene-α-D-*threo*-pentofuranosid-2-ulose (**4**; 5.05 g, 25 mmol) in a mixture of 50 mL of dry nitromethane and 25 mL of dry methanol at –50 to –40 °C (dry ice–acetone bath) under nitrogen was added a solution of sodium methoxide (1.35 g, 25 mmol) in 25 mL of dry methanol. The cooling bath was then allowed to attain room temperature in ca. 1.5 h. The mixture was then stirred at 25 °C for 4 h. The light yellow solution was neutralized to pH 7 with Dowex 50W-X8 (H^+ form), and the resin was removed by filtration immediately

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after neutralization. The filtrate was evaporated in vacuo to dryness to give a light red syrup. The syrup was dissolved in 30 mL of ether and applied on a column of neutral alumina (activity I, 20 g). The column was eluted with 200 mL of ether. The ether solution on evaporation to dryness gave the isomeric nitro alcohols as a very pale yellow syrup: 5.4 g (82.4%); IR (neat) 3450 (OH), 1550 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 and 1.45 (2 s, 6 H, CMe_2), 3.40 and 3.60 (2 s, 3 H, OMe of lyxo and xylo isomer, respectively), 3.8–5.8 (m, 7 H, OH, H-3, H-4, H-5, CH_2NO_2), 4.98 and 5.20 (2 s, 1 H, H-1 of lyxo and xylo isomer, respectively), approximate ratio of xylo to lyxo isomer of 70:30; ^{13}C NMR (Me_4Si, $CDCl_3$) xylo isomer: δ 21.9, 26.7, 55.4, 60.3, 70.9, 71.6, 77.7, 79.9, 99.7, 108.6; lyxo isomer: δ 18.8, 28.8, 57.0, 60.5, 71.6, 75.0, 76.9, 80.5, 97.9, 104.2.

Anal. Calcd for $C_{10}H_{17}NO_7$: C, 45.63; H, 6.46; N, 5.32. Found: C, 45.85; H, 6.36; N, 5.10.

Methyl 2-Deoxy-3,5-*O*-isopropylidene-2-*C*-(nitromethyl)-α-D-xylofuranoside (13). To a solution of methyl 3,5-*O*-isopropylidene-2-*C*-nitromethyl-α-D-xylo- and -lyxofuranosides (**10** and **11**; 7.89 g, 30 mmol) in 65 mL of dry dimethyl sulfoxide was added 50 mL of freshly distilled acetic anhydride. The mixture was stirred at 25 °C for 24 h while being protected from moisture. The pale yellow solution turned light red at the end of the reaction. The solvent was then removed by distillation at reduced pressure (boiling point up to 48 °C at 0.1 mm). The residue, a red gum, containing the nitroalkene **12**, was dissolved in 80 mL of absolute ethanol and the solution was cooled in an ice–water bath. To the cooled, stirred solution was added a solution of sodium borohydride (2.28 g, 60 mmol) in 20 mL of water in small aliquots over a period of 5 min. The mixture was stirred at 0–5 °C for 1 h and then at 25 °C for 1 h. The color of the reaction mixture changed from light red to pale yellow at the end of the reaction. The reaction mixture was then neutralized to pH 6–7 by careful addition of glacial acetic acid and filtered, and the filtrate was evaporated in vacuo to dryness. To the residue was added water (50 mL) and $CHCl_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and passed through a column of neutral alumina (activity I, 25 g). The column was then washed with 100 mL of $CHCl_3$. The combined $CHCl_3$ solutions were evaporated in vacuo to dryness to give **13** as a colorless syrup: 6.0 g (81%); $[\alpha]^{26}_D$ +111.5° (*c* 0.7, C_2H_5OH); IR (neat) 1550 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.39 (s, 3 H), 2.87–3.09 (m, 1 H, H-2), 3.88 (s, 3 H, OMe), 3.69–4.92 (m, 6 H), 4.96 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1); ^{13}C NMR (Me_4Si, $CDCl_3$): δ 19.0, 28.6, 49.6, 56.4, 60.4, 69.8, 70.7, 72.9, 97.9, 106.6.

Anal. Calcd for $C_{10}H_{17}NO_6$: C, 48.57; H, 6.80; N, 5.64. Found: C, 48.84; H, 6.74; N, 5.68.

2-Deoxy-2-*C*-(nitromethyl)-D-xyloses 14 and 15. To a solution of methyl 2-deoxy-3,5-*O*-isopropylidene-2-*C*-(nitromethyl)-α-D-xylofuranoside (**13**; 2.47 g, 10 mmol) in 20 mL of ethanol were added 50 mL of water and 15 g of Dowex 50W-X8 (H^+ form). The mixture was heated with stirring at 65 °C for 3 h. The mixture was then filtered, and the resin was washed with ethanol (3 × 15 mL). The combined filtrates were evaporated in vacuo at 35 °C to dryness. The residue was then dried over phosphorous pentoxide overnight to give 2-deoxy-2-*C*-nitromethyl-D-xylose as a pale yellow gum: 1.89 g (97%); IR (neat) 3350 (OH), 1550 (NO_2) cm^{-1}; ^1H NMR (D_2O) δ 2.66–3.16 (m, 1 H, H-2). ^{13}C NMR data indicated presence of anomeric mixtures of furanose and pyranose forms. The major form had the following chemical shifts in parts per million from Me_4Si in D_2O: 42.3, 65.0, 69.1, 72.0, 73.8, 93.6.

Anal. Calcd for $C_6H_{11}NO_6$: C, 37.30; H, 5.70; N, 7.25. Found: C, 37.10; H, 5.82; N, 7.10.

2-Deoxy-2-*C*-methylene-D-*threo*-pentono-1,4-lactone (2). 2-Deoxy-2-*C*-(nitromethyl)-D-xyloses (**14** and **15**; 775 mg, 4.0 mmol) were dissolved in 30 mL of 30% acetic acid in water. Bromine (1 mL) was added, and the mixture was swirled to dissolve the bromine. The flask was stoppered and allowed to stand in the dark at 25 °C for 24 h. Excess bromine was then removed by aeration, and the resulting clear colorless solution was diluted with 30 mL of water. Barium carbonate (17.73 g, 90 mmol) was then added in small portions with stirring over a period of 30 min. After the addition was over, the mixture was stirred at 25 °C for 2 h and filtered, and the filtrate was evaporated in vacuo at 35 °C to dryness. The residue was taken up in 100 mL of acetone, the resulting mixture was stirred at 25 °C for 15 min and filtered, and the precipitate was washed with acetone (3 × 50 mL). The acetone solutions were combined and evaporated to dryness in vacuo. The residue was redissolved in 100 mL of acetone, the solution was filtered to remove inorganic materials, and the filtrate was evaporated to dryness. This process was repeated until a clear pale yellow syrup was obtained. The syrup was then dissolved in 10 mL of acetone, and CH_2Cl_2 was added until the precipitation of a fluffy white solid was complete. The mixture was filtered, and the filtrate was evaporated to dryness to give 2-deoxy-2-*C*-methylene-D-*threo*-pentono-1,4-lactone (**2**) as a very pale yellow syrup: 297 mg (52%); IR (neat) 3365 (OH), 1768 (C=O), 1650 and 915 (C=CH_2) cm^{-1}; ^1H NMR (D_2O) δ 4.18–4.60 (m, 3 H, H-4, H-5), 5.60 (2 t, $J_{3,4}$ = 6.47 Hz, $J_{3,5}$ = 1.83 Hz, 1 H, H-3), 6.62 (d, J_{gem} = 2 Hz, 1 H, H-2′), 6.93 (d, J_{gem} = 2 Hz, 1 H, H-2′); ^{13}C NMR (Me_4Si, D_2O): δ 60.6, 68.5, 83.4, 128.2, 138.4, 172.6.

Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.55. Found: C, 49.75; H, 5.45.

Reaction of 2 with L-Cysteine. L-Cysteine (120.7 mg, 1.0 mmol) was dissolved in hot water (0.6 mL) and then cooled to 25 °C. A solution of 2-deoxy-2-*C*-methylene-D-*threo*-pentono-1,4-lactone (**2**; 144 mg, 1.0 mmol) in 0.4 mL of water was then added under nitrogen. (The reaction was complete in less than 15 min as evidenced by ^1H NMR in a run carried out in D_2O.) The mixture was allowed to stand at 25 °C for 1 h. Acetone was added to the solution until precipitation was complete. The solid was collected by filtration and recrystallized from acetone–ethanol–water. The recrystallized product was dried over P_2O_5 at 0.1 mm overnight to give the cysteine adduct **18** as white plates: 238 mg (90%); mp 180–185 °C dec; ^{13}C NMR (Me_4Si, D_2O): δ 25.5, 26.1, 33.6, 54.4, 60.5, 69.9, 85.0, 173.4, 179.5.

Anal. Calcd for $C_9H_{15}NO_6S$: C, 40.75; H, 5.66; N, 5.28. Found: C, 40.52; H, 5.23; N, 4.99.

Reaction of 2 with Glutathione. Glutathione (184.3 mg, 0.6 mmol) was dissolved in hot water (0.4 mL) and then cooled to 25 °C. A solution of 2-deoxy-2-*C*-methylene-D-*threo*-pentono-1,4-lactone (**2**; 86.4 mg, 0.6 mmol) in 0.3 mL of water was then added under nitrogen. (The reaction was complete in less than 15 min as evidenced by ^1H NMR in a run carried out in D_2O.) The mixture was allowed to stand at 25 °C for 1 h and was then evaporated in vacuo to dryness. The residue was scratched under 20 mL of acetone and filtered. The precipitate was dried over P_2O_5 at 0.1 mm overnight to give the glutathione adduct **19** as a granular solid: 264 mg (~99%); mp 145 °C dec; ^{13}C NMR (Me_4Si, D_2O): δ 26.3, 26.9, 31.1, 32.0, 42.3, 54.5, 56.4, 60.6, 70.3, 82.4; 173.1, 174.3, 175.6, 179.0.

Anal. Calcd for $C_{16}H_{25}N_3O_{10}S$: C, 42.57; H, 5.54; N, 9.09. Found: C, 42.20; H, 5.84; N, 9.12.

Registry No. 1, 58-86-6; **2**, 73230-64-5; α-**3**, 7045-40-1; β-**3**, 51754-99-5; **4**, 65247-31-6; **5**, 73230-65-6; **6**, 73230-66-7; **10**, 70448-59-8; **11**, 73230-67-8; **12**, 73230-68-9; **13**, 70448-61-2; α-**14**, 73230-69-0; β-**14**, 73230-70-3; α-**15**, 73230-71-4; β-**15**, 73230-72-5; **18**, 73230-73-6; **19**, 73230-74-7; L-cysteine, 52-90-4; glutathione, 70-18-8.