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Vitamin C and Isovitamin C Derived Chemistry. 3. Chiral Butenolides via Efficient 2,3-Didehydroxylations of L-Gulono-, D-Mannono-, and D-Ribono-1,4-lactones†

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Efficient, operationally simple procedures for preparing the chiral butenolides **3a**, **4a**, **13a,b**, and **16a-d** from the commercial L-ascorbic acid (L-threo-hex-2-enono-1,4-lactone) and D-isoascorbic acid (D-erythro-hex-2-enono-1,4-lactone) are described. The concept centers on the novel NaHSO_3 -induced regiospecific *trans*- β -bromo-acetoxy elimination of the readily accessible O-acetylated bromodeoxyaldono-1,4-lactones **10a,b** to compounds **13a,b**. These, on deacetylation and treatment of the resulting bromohydrins **16a,b** with Ag_2O , afford the enantiomerically pure epoxides **16c,d** and thence, in boiling water, the corresponding diols **3a** and **4a**. In a similar manner NaHSO_3 causes the D-ribono-1,4-lactone-derived bromo acetate mixture **17a,b** to undergo elimination to the corresponding butenolides **18a,b**, which, on subsequent hydrolysis and chromatographic purification, has given compound **1a** in 48% overall yield.

Introduction

Enantiomerically pure 4-substituted α,β -unsaturated and saturated γ -lactones occur widely in nature, i.e., as flavor components and as constituents of insect and mammalian pheromonal systems.^{1a,b} Butyrolactones are often found annelated onto lignan frameworks.² The biological activity of L-ascorbic acid (vitamin C) is due mainly to the 2,3-diol functionality on the butenolide system.³ Publications describing the preparation of some of these molecules have illustrated the potential of simple butenolides as chiral synthons in natural product syntheses. Compounds **1a-d** and **2** have been particularly useful in this respect and have served in the construction of (+)- and (-)-eldanolide,^{4a,b} the antileukemic lignans (+)-*trans*-burseran,⁵ (-)-isostegane,⁵ (+)- and (-)-steganacin,^{6a,b} (-)-verrucarinolactone⁷ and analogues of prostacyclin^{8a} and chrysanthemic acid,^{8a} chiral oxabicyclic systems,^{8b} and 15(*RS*)-11-deoxy-11-oxacarbacyclin methyl ester.^{8c} Compound **3c** has been utilized in a recent synthesis of polyoxin J.⁹

Considerable effort has been expended on preparing butenolide chiral synthons from chiral and nonchiral sources. When starting with nonchiral materials asymmetry has been introduced via (a) resolution of intermediates

somewhere in the sequence,^{4a,b} (b) asymmetric transformations resulting from the treatment of an optically inactive precursor with chiral reagents,^{10a,b} and (c) the use of bulky, detachable chiral auxiliaries for steering the processes toward the production of the least sterically encumbered asymmetric systems.^{11a,b}

Method a is exemplified by the preparation of **2** via resolution of the acid phthalate-(*S*)- α -methylbenzylamine salt, derived from the racemic intermediate $\text{PhCH}_2\text{OCH}_2\text{C}(\text{H})(\text{OH})\text{C}\equiv\text{CH}$.^{4a,b} Related optically pure acetylenic carbinols have resulted from the asymmetric reduction of the corresponding ketones with chiral agents such as the LiAlH_4 /*N*-methylephedrine/3,5-dimethylphenol complex^{10a} or *B*-3-pinalyl-9-borabicyclo[3.1.1]nonane^{10b} (method b). The chiral epoxidation of the readily prepared (*Z*)-4-(benzyloxy)-2-butenol using an L-tartrate ester has highlighted an approach to **1a**.^{10c} Method c is illustrated by the addition of the dianion of (+)-(*R*)-3-[(4-methylphenyl)sulfinyl]propionic acid to aldehydes,

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resulting in the formation of unequal amounts of two diastereomeric β -sulfinyl γ -lactones; their separation and subsequent pyrolysis then gave enantiomerically pure 4-substituted butenolides.^{11a} Optically active (*R*)- and (*S*)-4-octyl- and (*R*)- and (*S*)-4-tridecylbutenolides were prepared via the reaction of the dianions of chiral *N*-monosubstituted 3-(phenylsulfonyl)propionamides with aldehydes.^{11b}

Syntheses of chiral butenolides from naturally occurring materials are illustrated by the following examples. (–)-Eldanolide has been obtained from (–)- β -pinene by a route featuring a cyclobutyl-cyclopropylmethyl-homoallyl cation rearrangement.¹² A procedure starting from L-glutamic acid has given carboxylic acid lactone **5a** with complete retention of configuration.¹³ This was reduced to the carbinol **5b**¹³ and then converted into ethers **5c,d**. Introduction of the C-2–C-3 double bond was then achieved via the C-2 phenylselenation and the subsequent NaIO_4 -induced PhSeOH elimination to give **1b,c**.^{6a,b}

- 5 a:** R = COOH
b: R = CH₂OH
c: R = CH₂OCH₂Ph
d: R = CH₂OCH₂Ph₃

Various approaches to chiral butenolides from carbohydrates via formal C-2–C-3 didehydroxylations¹⁴ of aldono-1,4-lactones have been reported. D-Ribono-1,4-lactone and its derivatives have provided **1a–c** by pyrolysis of the cyclic orthoformates **6a,b**.^{15a,b} Raney nickel desulfuriza-

- 6 a:** R = H, X = CHOEt
b: R = CH₂Ph, X = CHOEt
c: R = CPh₃, X = CHOEt
d: R = CPh₃, X = (C=S)
e: R = Si(Ph)₂(t-Bu), X = (C=S)

tion transformed the corresponding thionocarbonates **6d**¹⁶ and **6e**⁸ into **1c** and **1d**, respectively. The 6-*O*-benzyl ether of the homologous hex-2-enono-1,4-lactone **3c** was afforded by lactonizing the olefination product produced from 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose and $\text{Ph}_3\text{P}=\text{CHCOOEt}$.⁹ Recently butenolides **1a**, **1c**, and **1d** were obtained from D-mannitol via an analogous approach^{17a} or via the intermediate dehydration of a 2-deoxy-D-ribono-1,4-lactone derivative.^{17b}

Scheme 1^a

^a (a) H_2/Pd ; (b) $\text{Me}_2\text{C}(\text{OMe})_2$, SnCl_2 ; (c) $\text{Me}_2\text{NCH}(\text{OMe})_2$; (d) MeI .

In part 1 of this series¹⁸ convenient syntheses of compounds **3a** and **4a** from the ascorbic acids **7a,b** were described. The method involved the thermolysis in boiling MeCN of the *N*-methyl-quaternized 2-(dimethylamino)-1,3-dioxolane derivatives **9a,b**, prepared from 5,6-*O*-isopropylidene-L-gulono-1,4-lactone and -D-mannono-1,4-lactone (**8c,d**) (Scheme I).

Chiral butenolides have also been generated from aldono-1,4-lactone derivatives via trans-2-bromo-3-*O*-benzoyl or -3-*O*-acetyl eliminations. In this manner 3-*O*-benzoyl-2-bromo-2,5-dideoxy-D-arabino-1,4-lactone yielded (–)-5-(*R*)-methyl-2(5*H*)-furanone on treatment with zinc in ethanol.¹⁹ A recent paper from these laboratories described a facile synthesis of **1a** in three steps via a procedure centering on the NaHSO_3 -induced trans-2-Br-3-OAc elimination of material obtained on treatment of D-ribono-1,4-lactone with HBr in AcOH.²⁰ Extended studies of this methodology and its application to the large-scale production of **1a**, **3a**, and **4a** are reported here.

Results and Discussion

O-Acetylated bromodeoxyaldono-1,4-lactones, prepared by treatment of the lactones with HBr in acetic acid (HBA), are valuable intermediates in carbohydrate synthesis.²¹ The selective formation of the C-2 inverted 2,6-dibromo lactone **10b**²² from D-mannono-1,4-lactone implies the intermediacy of acetoxonium ions. Many 2-substituted γ -lactones with leaving groups at C-3 undergo elimination readily under weakly basic conditions to give the 2-substituted α,β -unsaturated γ -lactones.²³ The C-2 debromination of **10b** to **11b** using NaI in acetone in the presence of trifluoroacetic acid has been reported.²⁴ Attention was directed initially to the development of conditions suitable for producing butenolide **13b** from **11b** without the product undergoing a second elimination to dienone **12**. The susceptibility of 2-unsubstituted chiral

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Scheme II^a

^a (a) NaI, acetone, CF₃CO₂H; (b) aqueous NaOAc; (c) NaHCO₃ in H₂O-Et₂O; (d) NaHSO₃; aqueous alcohol.

butenolides to racemization at C-4 or elimination at C-4-C-5 is well documented.^{18,25} A brief study of the behavior of 11b under mildly basic conditions and in various solvent systems was, therefore, undertaken; the reactions were monitored by TLC and NMR. A two-phase system of ether-aqueous NaHCO₃ led to mixtures of 11b, 12a, and 13b. Treatment of 11b with aqueous NaOAc produced only an *E/Z* mixture of 12a. The substrate 11b was unaffected by aqueous PbCO₃-Pb(OH)₂ at room temperature but gave a mixture of products on heating.

Attention was thereafter shifted toward the preparation of 13b from 10b directly. This decision was based partly on an observation²⁶ that 14 was transformed quantitatively into butenolide 15 via a NaHSO₃-induced *trans*-AcOH elimination (eq 1), suggesting that the butenolide is stable to the action of NaHSO₃.

The effect of NaHSO₃ on the C-2 epimeric bromolactone 10b was therefore examined. The reaction, conducted in 87.5% aqueous propan-2-ol at room temperature proceeded sluggishly but produced, most gratifyingly, after 100 h, in quantitative yield the thermally unstable, oily, unsaturated γ -lactone 13b, which was characterized spectrally. The method was extended subsequently and required compound 10a. This was prepared from L-gulonono-1,4-lactone¹⁸ and HBr-AcOH in the manner described for 10b.²² Similarly, lactone 10a when treated with NaHSO₃ in 90% aqueous methanol at room temperature afforded crystallizable butenolide 13a in high yield after 100 h (Scheme II).

The NaHSO₃-mediated elimination of 10a,b merits further comment. Whereas β -eliminations involving halogen and a hetero group are not uncommon,²⁷ there seems

Figure 1. Conformation and NaHSO₃-induced 2-Br-3-OAc elimination of dibromo diacetates 10a,b.

to be no precedent for NaHSO₃ bringing about such a transformation.²⁸ This would be substantiated by the stability of the 5-bromo-6-acetoxy groups of 13a,b and 15 toward the reagent. The fact that NaHSO₃ does cause 10a,b to undergo a *trans*- β -bromo-acetoxy elimination may either reflect the enhanced electrophilicity of halogens located α to the carbonyl or the actual participation of the carbonyl group in facilitating the process. Although aldehydes and some ketones are known to give crystalline addition compounds with NaHSO₃, no comparable adducts have apparently been derived from esters or lactones, albeit that [2,2'-bifuran]-5,5'-dione is claimed to yield adducts with NaHSO₃.²⁹ The interaction in solution of NaHSO₃ with the lactone carbonyl may therefore not be precluded. An additional aspect to be considered concerns the conformational-configurational relationships of the reactive species participating in the process. Spectral studies of lactones in solution have suggested them to exist as equilibrium mixtures of two envelope forms, ³E₁ and ¹E₃, with the substituents occupying pseudoequatorial and -axial positions.³⁰ These data also showed decreases in the H-2 and H-3 coupling constants on going from axial-axial to axial-equatorial and equatorial-equatorial orientations, the respective values being 10 $\pm$ 3, 6 $\pm$ 3, and 2 $\pm$ 2 Hz. The spectrum of 10b shows no evidence of coupling between H-2 and H-3; these protons are assumed to be equatorially disposed. The C-2 bromo and C-3 acetoxy groups would then be *trans*-diaxially orientated with the most bulky C-4 substituent adopting an equatorial position (I). If the carbonyl group is intimately involved through complex formation, reversible attack of NaHSO₃ on the *si* face of the C=O of this conformer would be nonproductive, whereas complexation from the *re* face would leave the reagent suitably positioned for initiating an antiperiplanar β -bromo-acetoxy elimination to provide 13b. Compound 10a, in contrast, exhibits an H-2-H-3 coupling constant of ca. 5 Hz. This is higher than would be expected for an equatorial-equatorial coupling but is insufficient

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to account for an axial-axial one. These data may be accommodated by assuming the presence at room temperature of two readily interconvertible conformers I and II. Structure II, with two of its three bulky substituents being directed equatorially, might be more stable than I; its elimination to **13a** would, however, require a prior equilibrium shift to I (Figure 1).

Some reagents resembling NaHSO_3 but unlikely to participate in $\text{C}=\text{O}$ complexation, such as Na_2SO_4 , sodium hydrogen oxalate, Na_2HPO_3 , or the reducing agent NaH_2PO_2 , failed to bring about the conversions of **10a,b** to **13a,b** under the cited reaction conditions. Aqueous NaH_2PO_4 caused partial deacetylation and fully eliminated products resulted from treatment with aqueous NaHCO_3 alone or in combination with NaH_2PO_2 . The substrates were also inert toward the action of sodium iodide in aqueous methanol but did undergo elimination in acetone. Altogether, the regio- and stereoselective NaHSO_3 -induced elimination may well occur via a concerted, ionic E_2 mechanism, be it with or without direct carbonyl participation.

Variations in the reaction conditions indicated the need for at least 3 equiv of NaHSO_3 (eq 2).

Optimal results were, in practice, attained on using 4 equiv of reagent. The reaction rate was shown to be critically pH dependent and adversely affected by an accumulation of the produced acidic components: the formation of SO_2 was established by passing N_2 through the reaction medium and observing the discoloration of aqueous KMnO_4 by the effluent gases. This aspect was considered to be of great importance and the NaHSO_3 -promoted eliminations were subsequently conducted in a NaHCO_3 -buffered system at pH ~ 6 . This resulted in a 50-fold increase in the reaction rate, producing **13a,b** cleanly, efficiently, and quantitatively after 2 h rather than 100 h. The system NaHSO_3 - Na_2SO_3 (1:2), being equivalent to the NaHSO_3 - NaHCO_3 (3:2) mixture, served equally well to bring about the elimination and was thereafter chosen for preparing the butenolides.

In principle the aforementioned dibromo-D-mannono-lactone **14**, obtained in one step from the very cheap calcium D-gluconate, could also represent a good precursor for butenolide **13b** and hence for diol **4a**, provided that $\text{S}_\text{N}2$ inversion at C-2 could be realized in high yield. Treatment of **14** with NaI in acetone (neutral conditions) at room temperature yielded a 4:1 mixture of 2-bromobutenolide **15** and the desired product **13b**. The former derives from trans 2-H-3-OAc elimination, as observed with methanolic NaHSO_3 , and the latter from $\text{S}_\text{N}2$ inversion with iodide and subsequent trans 2-I-3-OAc elimination. Since elimination proceeded faster than substitution, **14** was no longer considered as a practical precursor for **4a**. Conversely reaction of 2-deoxy derivative **11** with NaHSO_3 - Na_2SO_3 (1:2), as described for dibromo diacetates **10a,b**, gave after 100 h only limited amounts of butenolide **13b**, together with substantial amounts of starting material, indicating that both acidity and steric factors may well contribute to the formation of **15** or **13b**.

The documented instability^{18,25} of chiral butenolides toward basic, nucleophilic agents (addition to or opening of the ring system, deprotonation at C-4 followed by expulsion of a C-5 leaving group with loss of chirality or by reprotonation with loss of chiral integrity) imposes con-

siderable restrictions for achieving the seemingly straightforward conversions of **13a,b** to **3a** and **4a**. Conditions for conducting these transformations under mild, neutral or slightly acidic circumstances were therefore devised. Heating compounds **13a,b** under reflux in acidic MeOH produced deacetylated materials in addition to considerable amounts of the diene **12a**. When the hydrolyses were conducted at 5 °C for 48 h, however, high yields of the bromohydrins **16a,b** were obtained. These, on heating in boiling water, slowly produced mixtures of unidentified materials. The need for milder reaction conditions suggested the use of aqueous Ag_2O (Ag^+OH^-) for a silver ion assisted epoxide formation and also for neutralizing the HBr produced. An ice-cold aqueous solution of **16b** was consequently treated with slightly less than 1 equiv of Ag_2O to give an oily product in high yield. This was essentially devoid of OH functions and was characterized spectrally as the epoxide **16d**, contaminated with traces of the dienone **12b**. The product was stable

to silica gel chromatography and vacuum distillation. Its sensitivity to base was, however, convincingly demonstrated during an NMR-monitored experiment in which the addition of 0.1 equiv of Et_3N to a 0.5 M solution of **16d** in CDCl_3 produced more than 50% of **12b** within 1 min. The reaction of bromohydrin **16a** with Ag_2O , in the manner described for **16b**, produced the crystalline epoxide **16c**.³¹ The structurally related 5,6-anhydro-L-ascorbic acid has been shown to be the reactive intermediate in the formation of 6-substituted L-ascorbic acid derivatives from the corresponding 6-bromo compound. Attempts to isolate the intermediate epoxide were unsuccessful owing to the rapid autohydrolysis to L-ascorbic acid.³² Epoxides are known³³ to undergo ring opening preponderantly at the least hindered site under neutral or basic conditions. Whereas the epoxides **16c,d** had been unaffected by water at room temperature, the action of boiling water brought about their exclusive conversion to the previously¹⁸ described diols **3a** and **4a**. In contrast with Ag_2O , an aqueous suspension of Cu_2O , at or below room temperature, is unable to induce epoxide formation from bromohydrin **16a**. Heating under reflux for 2 days, however, led to the direct production of the compound **3a** in less than 40% yield. The formation of the epoxide is clearly slower than its ring opening to the diol.

The reaction conditions for preparing compounds **3a** and **4a** on a large scale were ultimately optimized and reduced to their simplest terms. The O-acetylated dibromo dideoxy 1,4-lactones **10a,b** were obtained from vitamin and isovitamin C in two steps on a 2-mol scale in 75% and 40%

(31) Ag_2O has also brought about the conversion of 2-bromo-3-hydroxy-1-indanone to 2,3-epoxyindanone: Undheim, K.; Nilsen, B. P. *Acta Chem. Scand., Ser. B* 1975, B29, 503.

(32) Andrews, G. C. *Carbohydr. Res.* 1984, 134, 321.

(33) Synthetically useful reactions of epoxides have been reviewed in depth: Gorzynski Smith, J. *Synthesis* 1984, 629.

Scheme III^a

^a (a) HBr in AcOH; (b) MeOH/HCl.

overall yields by treating the respective hydrogenation products with HBr–AcOH. The subsequent NaHSO₃–Na₂SO₃-promoted elimination of 0.2 mol of 10a gave 13a, which, without purification, was deacetylated to bromohydrin 16a in 85% yield on treatment with 1 M HCl in MeOH. Compound 3a resulted on hydrolysis of the intermediately produced (Ag₂O–H₂O) epoxide 16c in 65% overall yield from 10a. The C-5 epimeric diol 4a was obtained similarly in 69% overall yield from 10b on a 0.2-mol scale without purification of the oily intermediates 13b, 16b, and 16d.

The methodology was subsequently extended to include a three-step synthesis of 1a from D-ribo-1,4-lactone, not requiring purification of any of the intermediates.²⁰ Treatment of the lactone with 33% HBr in AcOH gave an oily 6/1 mixture of 17a,b.³⁴ This material in *i*-PrOH produced, on stirring with aqueous NaHSO₃–Na₂SO₃ for 3 h at room temperature, an oil consisting of 18a,b in a similar ratio. Subsequent hydrolysis (MeOH–HCl) then furnished mainly 1a contaminated with minor amounts of the corresponding bromide 18b. Column chromatography afforded essentially pure, oily 1a in 48% overall yield, which, on Kugelrohr distillation, gave material solidifying at room temperature (Scheme III). The product yielded the triphenylmethyl ether 1c, the optical rotation (–94°) of which agreed with the previously reported values of –96°, starting from 5d,^{6a} and –95°, starting from 6a,^{15b} but not with the value (–50°) reported for the product obtained by the Raney nickel desulfurization of 6d,¹⁶ probably implying that the material suffered considerable loss of optical purity during its synthesis.

During the course of ongoing investigations another way to prepare 3a was noted and will be mentioned briefly. Treatment of 10a with HBr in propan-2-ol yielded a compound C₈H₇BrO₄, the spectral characteristics of which were consistent with the 3,6-anhydro structure 19.³⁵ Boiling aqueous NaHSO₃ transformed this material partly (25%) to 3a via a β-bromo-ether elimination, resembling the β-bromo-acetoxy elimination described earlier (Scheme IV).

Concluding Remarks

In spite of their potential as chiral building blocks, the use of large amounts of optically active butenolides in synthesis has been limited owing to difficulties in their preparation. The present route offers a novel and operationally simple way for producing the chirons 1a, 3a, 4a, 10a,b, 13a,b, and 16a–d from the relatively inexpensive, industrially produced L-ascorbic and D-isoascorbic acids or from moderately priced D-ribo-1,4-lactone. The approach involves high-yield processes conducted in water or alcohol mostly at ambient temperatures and may well

Scheme IV^a

^a (a) Propan-2-ol–HBr; (b) aqueous NaHSO₃, reflux.

constitute the method of choice for preparing generous amounts of these valuable starting materials.

Experimental Section

General Methods. These were identical with those described in a previous paper in this series (*J. Org. Chem.* 1987, 52, 1093).

3,5-Di-O-acetyl-2,6-dibromo-2,6-dideoxy-L-idono-1,4-lactone (10a). L-Gulono-1,4-lactone (8a) (310 g, 1.74 mol), derived from L-ascorbic acid¹⁸ (7a) (352.2 g, 2.00 mol), was treated with stirring with HBr in glacial acetic acid (33%, 1.75 L, ~10 mol of HBr), at ca 30 °C for 3.5 h. The mixture was cooled and then treated dropwise over 30 min with acetic anhydride (675 mL, ~7 mol) with the temperature kept below 30 °C. The mixture was allowed to stir for an additional hour when it was poured slowly into vigorously stirred ice–water (10 L). The precipitate was collected by filtration and washed with more water (3.5 L) and then with propan-2-ol (5 × 375 mL) and diisopropyl ether (3 × 375 mL). The solid residue on trituration with propan-2-ol (1.5 L) gave the pure title compound 10a (552 g, 71%), mp 114–116 °C. A second crop (31 g, 4%), mp 117–119 °C, was obtained by concentrating the combined washings and mother liquor. Recrystallization from propan-2-ol gave analytically pure material: mp 118–120 °C; [α]_D²⁰ +39° (c 2.02, CHCl₃); IR (KBr, cm^{–1}) ν_{max} 1820 (C=O, lactone), 1760 (C=O, acetates); ¹H NMR (CDCl₃) δ 2.14 (s, 6 H), 3.49 (dd, J = 11.5 and 6 Hz, 1 H), 3.50 (d, J = 11.5 and 5.5 Hz, 1 H), 4.47 (d, J = 5.5 Hz, 1 H), 5.1–5.4 (m, 2 H), 5.56 (t, J = 5.5 Hz, 1 H). Anal. Calcd for C₁₀H₁₂Br₂O₆ (MW 388.02): C, 30.94; H, 3.12. Found: C, 31.3; H, 3.1.

5-O-Acetyl-6-bromo-2,3,6-trideoxy-L-threo-hex-2-enono-1,4-lactone (13a). A stirred suspension of compound 10a (77.6 g, 0.20 mol) in methanol–water (9:1, 720 mL) was treated with NaHSO₃ (20.8 g, 0.20 mol) and then portionwise with Na₂SO₃ (50.4 g, 0.40 mol) at a rate that did not cause the temperature to exceed 27.5 °C. The mixture was then allowed to stir for 3 h, whereupon 1 M HCl (600 mL) and dichloromethane (750 mL) were added. The aqueous phase was separated and reextracted with dichloromethane (3 × 250 mL). The combined extracts were washed with water (500 mL), dried (MgSO₄), and concentrated in vacuo to give an oil (50 g, ~100%), which solidified on storage at 0 °C. The ¹H NMR spectrum of the crude product indicated that it was the essentially pure butenolide 13a. Trituration of this material with diisopropyl ether gave analytical material (~50%): mp 42.5–43 °C; ¹H NMR (CDCl₃) δ 2.07 (s, 3 H), 3.59 (dd, J = 11 and 6 Hz, 1 H), 3.66 (dd, J = 11 and 6.5 Hz, 1 H), 5.32 (td, J = 6.25 and 3 Hz, 1 H), 5.47 (td, J = 1.5 and 3 Hz, 1 H), 6.19 (dd, J = 6 and 1.5 Hz, 1 H), 7.46 (dd, J = 6 and 1.5 Hz, 1 H). Anal. Calcd for C₈H₉BrO₄ (MW 249.07): C, 38.58; H, 3.64. Found: C, 38.6; H, 3.4.

6-Bromo-2,3,6-trideoxy-L-threo-hex-2-enono-1,4-lactone (16a). A solution of the crude butenolide 13a (49.8 g, 0.20 mol) in 1 M methanolic HCl (400 mL, 0.40 mol of HCl) was maintained at 5 °C for 2 days. Concentration of this solution in vacuo at 30 °C yielded a solid residue (40.2 g, 97%), which upon trituration with dichloromethane gave the pure, white bromo alcohol 16a (35.1 g, 85%), mp 105–106 °C. Recrystallization from chloroform gave analytically pure material, as needles: mp 105.5–106 °C; [α]_D²⁰ –107° (c 1.51, water); IR (KBr, cm^{–1}) ν_{max} 3400 (OH), 1740 (C=O), 1600 (C=C); ¹H NMR (CDCl₃) δ 2.8 (br s, 1 H), 3.49 (d, J = 7 Hz, 1 H), 3.52 (d, J = 5 Hz, 1 H), 4.03 (m, 1 H), 5.36 (td, J = 1.75 and 3.5 Hz, 1 H), 6.19 (dd, J = 6 and 1.75 Hz, 1 H), 7.55 (dd, J = 6 and 1.75 Hz, 1 H). Anal. Calcd for C₈H₉BrO₃ (MW 207.03): C, 34.81; H, 3.41. Found: C, 35.0; H, 3.3.

5,6-Anhydro-2,3-dideoxy-L-threo-hex-2-enono-1,4-lactone (16c). A stirred suspension of compound 16a (51.8 g, 0.25 mol)

(34) Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* 1981, 90, 17.

(35) The reactivity of 19 and its congeners is under current investigation.

in water (200 mL) at 0 °C was treated with moist, neutral, and freshly prepared Ag₂O (0.25 mol). The mixture was maintained at this temperature for 4 h, when HBr (48%, 1 mL) was added and the precipitated AgBr was removed by filtration and washed with dichloromethane (500 mL). The filtrate and washings were mixed thoroughly with vigorous stirring and separated. The aqueous phase was extracted exhaustively with dichloromethane (5 × 200 mL), and the combined organic phases were dried (MgSO₄) and concentrated in vacuo below 30 °C to give an oily residue (31.5 g, 99%). This material crystallized on storage at 0 °C and was shown (¹H NMR) to be essentially pure. A sample recrystallized from ether gave analytically pure **16c** (72%) as needles: mp 48–49 °C; [α]_D²⁰ –79° (c 1.01, water); IR (KBr, cm^{–1}) ν_{max} 1780–1760 (C=O), 1560 (C=C), 820 (C–O, epoxide); ¹H NMR (CDCl₃) δ 2.83 (d, *J* = 2.5 Hz, 1 H), 2.84 (d, *J* = 4 Hz, 1 H), 3.18 (td, *J* = 4.25 and 1.75 Hz, 1 H), 5.05 (dt, *J* = 4.5 and 1.75 Hz, 1 H), 6.20 (dd, *J* = 5.5 and 1.75 Hz, 1 H), 7.50 (dd, *J* = 5.5 and 1.75 Hz, 1 H). Anal. Calcd for C₆H₈O₃ (MW 126.11): C, 57.14; H, 4.80. Found: C, 57.2; H, 4.9.

2,3-Dideoxy-L-threo-hex-2-enono-1,4-lactone [2,3-Dideoxy-L-ascorbic Acid] (3a). a. **From Epoxide 16c.** A stirred solution of compound **16c** (31.5 g, 0.25 mol) in water (375 mL) was heated under reflux for 2 h. The mixture was concentrated in vacuo, and propan-2-ol was then distilled in vacuo from the residue to give a syrup, which solidified on seeding with authentic butenolide **3a**.¹⁸ Trituration of this material with ether (125 mL) gave the title compound **3a** (27.1 g, 75%), mp 82–83 °C, which was recrystallized from acetonitrile–diisopropyl ether (2:1) or ethyl acetate (23.1 g, 54%): mp 85–86 °C; [α]_D²⁰ –119° (c 1.01, water); IR (KBr, cm^{–1}) ν_{max} 3460 (OH, secondary), 3340 (OH, primary), 1755 (C=O), 1605 (C=C); ¹H NMR (deuterioacetone) δ 3.6–4.0 (m, 3 H), 4.1 (t, *J* = 5.5 Hz, 1 H), 4.3 (d, *J* = 5.5 Hz, 1 H), 5.25 (ddd, *J* = 3, 2 and 1.75 Hz, 1 H), 6.14 (dd, *J* = 6 and 2 Hz, 1 H), 7.72 (dd, *J* = 6 and 1.75 Hz, 1 H). Anal. Calcd for C₆H₈O₄ (MW 144.13): C, 50.00; H, 5.59. Found: C, 49.9; H, 5.7.

b. **From Bromo Alcohol 16a.** A stirred suspension of compound **16a** (1.035 g, 5 mmol) and copper(I) oxide (1.42 g, 10 mmol) in water (10 mL) was heated under reflux for 48 h; the transient formation of epoxide **16c** was observed (TLC) during this period. At the end of this time the mixture was treated with HBr (48%, 2.5 mL) concentrated in vacuo and the residue dissolved in chloroform–methanol (7:1, 12.5 mL). This solution was chromatographed (silica gel) by using the same solvent mixture for elution. Evaporation of the eluent in vacuo gave the NMR and TLC pure diol **3a** (281 mg, 39%), mp 80–82 °C [α]_D²⁰ –117° (c 0.98, water).

c. **From Dibromo Diacetate 10a.** The four-stage reaction sequence from compound **10a** to the title butenolide **3a** could be conducted consecutively, without the isolation or purification of the intermediates. The overall yield (60%) was of consequence lower than for the stepwise procedure (65%) and the final product required chromatographic purification.

d. **From Bicyclic Compound 19.** A mixture of bicyclic lactone **19** (vide infra; 112 mg, 0.50 mmol) in propan-2-ol–water (7:1, 2 mL) containing NaHSO₃ (208 mg, 2.0 mmol) was heated under reflux with stirring for 2.5 h. TLC (CHCl₃–MeOH, 9:1) then showed the absence of compound **19** (*R*_f 0.56) and the presence of two, more polar, components: A (*R*_f 0.39) and B (*R*_f 0.17), the latter being identical with the diol **3a**. Acetone (5 mL) was then added and the precipitated material removed by filtration. The filtrate was concentrated in vacuo to give a colorless oil (60 mg), which, on chromatography (CHCl₃–MeOH, 7:1) gave the diol **3a** (18 mg, 25%) (¹H NMR, TLC), corresponding to component B. Component A (37 mg) was not identified, but ¹H NMR showed it not to contain vinylic protons.

3,6-Anhydro-2-bromo-2-deoxy-L-idono-1,4-lactone (19). A stirred suspension of the dibromo lactone **10a** (3.88 g, 10 mmol) in 96% aqueous propan-2-ol (20 mL), that was 0.5 M with respect to HBr, was heated under reflux for 2 h. Propan-2-ol and other volatile material were then removed slowly by distillation, with continuous replenishment of the propan-2-ol (6 mL/h). After a total period of 8 h, the mixture was concentrated in vacuo to give a syrupy residue (2.25 g), which was purified by column chromatography (dichloromethane–ethyl acetate, 3:1), and yielded (¹H NMR) pure compound **19** as an oil (1.21 g, 54%). The addition of chloroform–diisopropyl ether (1:1) induced crystal-

lization and recrystallization from the same mixture afforded the title compound: mp 98–100 °C (0.74 g, 33%); [α]_D²⁰ –15° (c 1.12, CHCl₃); ¹H NMR (CDCl₃–CD₃OD, 3:1) δ 3.96 (dd, *J* = 11 and 1.5 Hz, 1 H), 4.03 (dd, *J* = 11 and 3 Hz, 1 H), 4.24 (s, 1 H), 4.25 (s, 1 H), 4.47 (dd, *J* = 3 and 1.5 Hz, 1 H), 4.81 (d, *J* = 3.5 Hz, 1 H), 5.00 (d, *J* = 3.5 Hz, 1 H). Anal. Calcd for C₆H₇BrO₄ (MW 223.04): C, 32.31; H, 3.16. Found: C, 32.0; H, 3.0.

3,5-Di-O-acetyl-2,6-dibromo-2,6-dideoxy-D-glucono-1,4-lactone (10b). Compound **10b** was obtained, on a 1-molar scale, in 40% yield from D-isoascorbic acid (**7b**) in the manner described for compound **10a**: mp 94.5–95.5 °C; [α]_D²⁰ +54° (c 2.01, CHCl₃) [lit.²² mp 93–95 °C; [α]_D²⁰ +51.4° (c 2.3, CHCl₃)]; IR (KBr, cm^{–1}) ν_{max} 1805 (C=O, lactone), 1760 (C=O, acetates); ¹H NMR (CDCl₃) δ 2.10 (s, 6 H), 3.69 (dd, *J* = 12 and 3 Hz, 1 H), 3.73 (dd, *J* = 12 and 3.75 Hz, 1 H), 4.15 (s, 1 H), 5.03 (dd, *J* = 9.75 and 3.5 Hz, 1 H), 5.29 (ddd, *J* = 9.75, 3.75 and 3 Hz, 1 H), 5.48 (d, *J* = 3.5 Hz, 1 H).

2,3-Dideoxy-D-erythro-hex-2-enono-1,4-lactone (4a). A stirred suspension of compound **10b** (38.8 g, 0.10 mol) in methanol–water (9:1, 360 mL) was treated with NaHSO₃ (10.4 g, 0.10 mol), followed by the portionwise addition of Na₂SO₃ (25.2 g, 0.20 mol) in the same manner as described for compound **10a** (vide supra) to give the oily butenolide **13b** (25 g, 100%). This was shown to be essentially pure by ¹H NMR spectroscopy [(CDCl₃) δ 2.14 (s, 3 H), 3.63 (d, *J* = 4.5 Hz, 2 H), 5.06 (td, *J* = 4.5 and 6.5 Hz, 1 H), 5.29 (td, *J* = 1.5 and 6.5 Hz, 1 H), 6.21 (dd, *J* = 6 and 1.5 Hz, 1 H), 7.58 (dd, *J* = 6 and 1.5 Hz, 1 H)]. The susceptibility of this material to elimination of acetic acid rendered further purification undesirable, and it was treated in the following manner. A solution of the oil in 1 M methanolic HCl (200 mL) was kept at 5 °C for 2 days. The mixture was evaporated in vacuo and propan-2-ol was then distilled from the residue in portions to give the bromo alcohol **16b** (21 g, ~100%) as an oil. This material could not be purified further due to dehydration. Column chromatographic purification resulted in considerable loss. [α]_D²⁰ –111° (c 1.28, water); IR (neat, cm^{–1}) ν_{max} 3400 (OH), 1760 (C=O), 1610 (C=C); ¹H NMR (CDCl₃) δ 3.4 (br s, 1 H), 3.64 (d, *J* = 4 Hz, 2 H), 3.82 (td, *J* = 6 and 4 Hz, 1 H), 5.11 (dt, *J* = 6 and 1.75 Hz, 1 H), 6.19 (dd, *J* = 6 and 1.75 Hz, 1 H), 7.72 (dd, *J* = 6 and 1.75 Hz, 1 H)]. A stirred solution of the bromo alcohol **16b** (21 g) in ice-cold water (80 mL) was treated with moist, neutral, and freshly prepared Ag₂O (0.10 mol). The mixture was stirred at 0 °C for 3 h, when TLC (CHCl₃–EtOAc, 7:1) indicated the absence of compound **16b** and the presence of a new and less polar component, identified as epoxide **16d** (vide infra) together with traces of more polar dienes (**12b**, *E/Z*). HBr (48%, 0.5 mL) was then added, the precipitated silver salts were removed by filtration and washed with water (50 mL) and the combined filtrate and washings heated under reflux for 2 h. The mixture was concentrated in vacuo, propan-2-ol was distilled from the residue, and the resulting solid material was triturated with ether (50 mL) to afford crude butenolide **4a** (9.9 g, 69%), mp 89–90 °C. Recrystallization from ethyl acetate gave the pure compound **4a** (8.2 g, 57%): mp 95–96 °C; [α]_D²⁰ –186° (c 1.01, water); IR (KBr, cm^{–1}) ν_{max} 3460 (OH, secondary), 3320 (OH primary), 1755 (C=O), 1605 (C=C); ¹H NMR (deuterioacetone) δ 3.6–3.8 (m, 3 H), 3.9 (t, *J* = 5 Hz, 1 H), 4.3 (d, *J* = 5 Hz, 1 H), 5.13 (ddd, *J* = 4.5, 2.25, and 1.75 Hz, 1 H), 6.11 (dd, *J* = 6 and 2.25 Hz, 1 H), 7.75 (dd, *J* = 6 and 1.75 Hz, 1 H). Anal. Calcd for C₆H₈O₄ (MW 144.13): C, 50.00; H, 5.59. Found: C, 50.0; H, 5.4.

5-O-Acetyl-6-bromo-2,3,6-trideoxy-D-erythro-hex-2-enono-1,4-lactone (13b). a. **From Dibromo-D-glucono Diacetate 10b.** See directions for compound **4a** (vide supra).

b. **From 3,5-Di-O-acetyl-2,6-dibromo-2,6-dideoxy-D-mannono-1,4-lactone (14).** A solution of lactone **14**²² (3.88 g, 10 mmol) in acetone (25 mL) containing sodium iodide (3.0 g, 20 mmol) was allowed to stir at room temperature for 6 h. The mixture was concentrated in vacuo and the residue shaken with a mixture of water (25 mL) and dichloromethane (50 mL). The organic extract was washed successively with 5% Na₂S₂O₃ solution and water, dried (MgSO₄), and evaporated in vacuo. The resulting yellow oil (2.7 g) was shown (TLC, CHCl₃–EtOAc, 7:1) to consist of two major components which were identified as the title butenolide **13b** and the less polar 5-O-acetyl-2,6-dibromo-2,3,6-trideoxy-D-erythro-hex-2-enono-1,4-lactone (**15**)²⁶ by comparison with authentic samples. [¹H NMR 15 (CDCl₃) δ 2.13 (s, 3 H), 3.64

(d, $J = 4.5$ Hz, 2 H), 5.08 (td, $J = 4.5$ and 6.5 Hz, 1 H), 5.28 (dd, $J = 6.5$ and 1.5 Hz, 1 H), 7.64 (d, $J = 2$ Hz, 1 H)]. From the relative peak intensities of the vinylic proton absorptions in ^1H NMR, a 1:4 molar ratio for **13b**/**15** could be deduced, thus indicating that this procedure was not of preparative value for the synthesis of **13b** and hence of **4a**.

5,6-Anhydro-2,3-dideoxy-D-erythro-hex-2-enono-1,4-lactone (16d). The crude aqueous epoxide **16d**, described in the four-stage preparation of **4a** (vide supra), was—after removal of insoluble silver salts by filtration—extracted exhaustively with dichloromethane (1×200 , 5×100 mL). The combined organic layers were dried (MgSO_4) and concentrated in vacuo below 30°C to give an essentially pure (^1H NMR) colorless oil (12.5 g, 99%), which could be distilled (bp 110°C , 1 mm) to give analytically pure **16d** (8.3 g, 66%): $[\alpha]_D^{20} -143^\circ$ (c 1.09, water); IR (neat, cm^{-1}) ν_{max} 1790–1750 (C=O), 1610 (C=C), 820 (C–O, epoxide); ^1H NMR (CDCl_3) δ 2.83 (d, $J = 2.5$ Hz, 1 H), 2.88 (d, $J = 3.5$ Hz, 1 H), 3.10 (ddd, $J = 5$, 3.5 and 2.5 Hz, 1 H), 4.85 (dt, $J = 5$ and 1.75 Hz, 1 H), 6.21 (dd, $J = 5.5$ and 1.75 Hz, 1 H), 7.56 (dd, $J = 5.5$ and 1.75 Hz, 1 H).

5(S)-(Hydroxymethyl)-2(5H)-furanone [2,3-Dideoxy-D-pent-2-enono-1,4-lactone] (1a). A suspension of D-ribo-1,4-lactone (50 g, 0.33 mol) in HBr–AcOH (33%, 250 mL, ~ 1.4 mol of HBr) was stirred at 30°C for 3 h. The resulting solution was then treated dropwise with acetic anhydride (100 mL, ~ 10 mol) over 1 h, with the temperature kept below 30°C . The mixture was allowed to stir at room temperature for 1 h more, when it was treated with a mixture of water (1.5 L) and dichloromethane (500 mL). The organic layer was separated after 15 min, and the aqueous phase was extracted with additional dichloromethane (3×250 mL). The combined extracts were washed with water (2×250 mL), dried (MgSO_4), and concentrated in vacuo to yield a mixture (93 g) (6:1) of the monobromo diacetate **17a** [^1H NMR (CDCl_3) δ 2.12 (s, 3 H), 2.15 (s, 3 H), 4.2–4.7 (m, 4 H), 5.36 (t, $J = 3.5$ Hz, 1 H)] and the dibromo monoacetate **17b** [^1H NMR (CDCl_3) δ 3.72 (d, $J = 6$ Hz, CH_2Br)]. A stirred solution of this product mixture (93 g) in propan-2-ol–water (3:1, 1 L) was treated with NaHSO_3 (35 g, 0.33 mol) in one portion and then portionwise with Na_2SO_3 (84 g, 0.67 mol), with the temperature prevented from exceeding 30°C . After a period of 3 h at room temperature the solution was poured into a vigorously stirred mixture of ice-cold 2 M HCl (500 mL) and dichloromethane (750 mL). The separated aqueous phase was further extracted with dichloromethane (2×375 mL), and the combined extracts were washed with brine, dried

(MgSO_4), and evaporated in vacuo. The residual oil (50 g, 96%) was shown (^1H NMR) to be a mixture (6:1) of butenolides **18a** [^1H NMR (CDCl_3) δ 2.08 (s, 3 H), 4.34 (d, $J = 4.5$ Hz, 2 H), 6.19 (dd, $J = 5.5$ and 2 Hz, 1 H), 5.27 (tdd, $J = 4.5$, 2 and 1.5 Hz, 1 H), 7.50 (dd, $J = 5.5$ and 1.5 Hz, 1 H)] and **18b** [δ 3.62 (d, $J = 5$ Hz, CH_2Br)]. A solution of this mixture (50 g) in 1 M methanolic HCl (600 mL) was stirred at 5°C for 18 h and evaporated in vacuo to give an oil, which was composed (TLC; CH_2Cl_2 –EtOAc, 4:1) of the title furanone **1a** and the 5-bromo compound **18b**. Column chromatography (silica gel, 150 g, eluted with the same solvent mixture) gave **18b**; continued elution with EtOAc gave pure **1a** as a colorless oil, which solidified on storage at 0°C (18.7 g, 48%). A portion of this product was distilled in vacuo, bp 140°C (0.3 mm), which crystallized spontaneously on standing: mp 39 – 41°C ; $[\alpha]_D^{20} -140^\circ$ (c 3.0, H_2O) [lit.^{15b} mp 37 – 39°C ; $[\alpha]_D^{20} -143^\circ$ (c 1.14, water)]; ^1H NMR (CDCl_3 – CD_3OD , 3:1) δ 3.75 (dd, $J = 12$ and 4 Hz, 1 H), 3.85 (dd, $J = 12$ and 4 Hz, 1 H), 4.3 (s, 1 H), 5.15 (tdd, $J = 4$, 2 and 1.5 Hz, 1 H), 6.13 (dd, $J = 5.5$ and 2 Hz, 1 H), 7.58 (dd, $J = 5.5$ and 1.5 Hz, 1 H). Anal. Calcd for $\text{C}_5\text{H}_6\text{O}_3$ (MW 114.10): C, 60.06; H, 6.05. Found: C, 60.0; H, 6.2.

5(S)-[(Triphenylmethoxy)methyl]-2(5H)-furanone (1c). A stirred solution of butenolide **1a** (257 mg, 2.25 mmol) in dichloromethane–pyridine (4:1, 5 mL) was treated with triphenylmethyl chloride (700 mg, 2.50 mmol) and the mixture allowed to stir at room temperature for 4 h. The solution was diluted with ether (12.5 mL) and washed repeatedly with water and the dried (MgSO_4) extract concentrated in vacuo to yield a semisolid residue, which was triturated with pentane to give the title product (710 mg, 88%). Recrystallization from propan-2-ol yielded analytically pure material (400 mg, 50%): mp 152 – 154°C [lit.^{6a} mp 153 – 154°C ; lit.^{15b} mp 152 – 154°C ; lit.¹⁶ mp 151 – 153°C]; $[\alpha]_D^{20} -94^\circ$ (c 2.01, CHCl_3) [lit.^{6a} $[\alpha] -95.9^\circ$; lit.^{15b} $[\alpha] -95.1^\circ$; lit.¹⁶ $[\alpha] -50.2^\circ$ (CHCl_3)]; ^1H NMR (CDCl_3) δ 3.35 (d, $J = 5$ Hz, 2 H), 4.99 (tdd, $J = 5$, 2, and 1.5 Hz, 1 H), 6.07 (dd, $J = 6$ and 2 Hz, 1 H), 7.1–7.5 (m, 16 H). Anal. Calcd for $\text{C}_{24}\text{H}_{20}\text{O}_3$ (MW 356.42): C, 80.88; H, 5.66. Found: C, 81.0; H, 5.6.

Registry No. **1a**, 78508-96-0; **1c**, 76236-32-3; **3a**, 102335-47-7; **4a**, 102335-56-8; **7a**, 50-81-7; **7b**, 89-65-6; **8a**, 1128-23-0; **10a**, 111975-45-2; **10b**, 69617-71-6; **13a**, 111975-46-3; **13b**, 111975-50-9; **14**, 69617-82-9; **15**, 71671-99-3; **16a**, 111975-47-4; **16b**, 111975-51-0; **16c**, 111975-48-5; **16d**, 111975-52-1; **17a**, 71671-95-9; **17b**, 78139-04-5; **18a**, 85846-83-9; **18b**, 85694-09-3; **19**, 111975-49-6; D-ribo-1,4-lactone, 5336-08-3.

Methyldiphenylsilylation of Ester and Lactone Enolates¹

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The reactions of a variety of ester and lactone enolates with methyldiphenylchlorosilane were studied. The C- versus O-silylation, leading to the α -silyl ester or lactone and silyl ketene acetal, respectively, was studied as a function of the structure of the ester or lactone and the reaction conditions. It was found that all simple acetates are C-silylated irrespective of the steric demands of the alcohol portion of the ester. Esters that are monosubstituted in the α -position are cleanly C-silylated with the notable exceptions of ethyl phenylacetate and ethyl phenoxyacetate, both of which give mixtures of C- and O-silylation. The α,α -disubstituted esters give only O-silylation, but the α,α -substituted α -silyl esters are readily prepared by the alkylation of the appropriate monosubstituted α -silylated ester. The reaction of the lithium enolate of ethyl acetate and *tert*-butyl acetate with (S)-(-)-1-naphthylphenylmethylchlorosilane showed the reaction to occur with inversion of configuration at silicon. Methylation of *tert*-butyl (1-naphthylphenylmethylsilyl)acetate gave a 91:9 mixture of diastereomeric α -silyl propionates, which could not be separated. It was found that only the γ -lactones gave C-silylation with δ -valerolactone and ϵ -caprolactone giving O-silylation.

The silylation of ester or lactone enolates can occur to produce the silyl ketene acetals or the α -silyl esters or

lactones, all synthetically useful classes of compounds, as a result of silylation at the O- or C-terminus of the enolate