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†

Jozef A. J. M. Vekemans, Gabriel A. M. Franken, Cornelis W. M. Dapperens, and Erik F. Godefroi*

Department of Chemical Technology, Section Technical Organic Synthesis, University of Technology, 5600 MB Eindhoven, The Netherlands

Gordon J. F. Chittenden

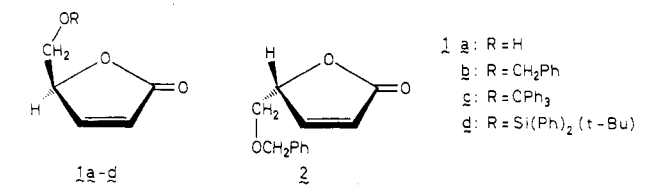
Department of Organic Chemistry, The University, Toernooiveld, 6525 ED Nijmegen, The Netherlands

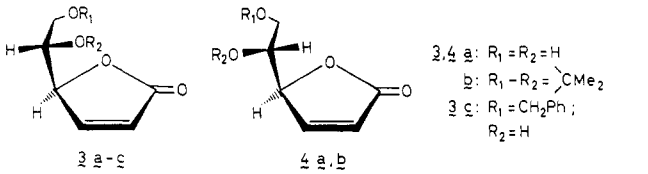
Received February 18, 1987

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] (−)-verrucarinolactone[7] 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 chirons 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 $PhCH_2OCH_2C(H)(OH)C{\equiv}CH$.[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,

† For part 2 of this series, see: Vekemans, J. A. J. M.; de Bruyn, R. G. M.; Caris, R. C. H. M.; Kokx, A. J. P. M.; Konings, J. J. H. G.; Godefroi, E. F.; Chittenden, G. J. F. *J. Org. Chem.* **1987**, *52*, 1093.

(1) For useful compilations of some naturally occurring γ-lactones, see: (a) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449. (b) Cardellach, J.; Font, J.; Ortuño, R. M. *J. Heterocycl. Chem.* **1984**, *21*, 327.

(2) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75.

(3) Seib, P. A.; Tolbert, B. M. *Ascorbic Acid: Chemistry, Metabolism, and Uses*; Advances in Chemistry 200; American Chemical Society: Washington, DC, 1982.

(4) (a) Vigneron, J. P.; Meric, R.; Larchevêque, M.; Debal, A.; Kunesch, G.; Zagetti, P.; Gallow, M. *Tetrahedron Lett.* **1982**, *23*, 5051. (b) Vigneron, J. P.; Meric, R.; Larchevêque, M.; Deral, A.; Lallemand, J. Y.; Kunesch, G.; Zagetti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521.

(5) Tomioka, K.; Ishiguro, T.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 652.

(6) (a) Tomioka, K.; Ishiguro, T.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2973. (b) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303.

(7) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982**, *17*, 311.

(8) (a) Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737. (b) Drew, M. G. B.; Mann, J.; Thomas, A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 2279. (c) Mann, J.; Thomas, A. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 2287.

(9) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405.

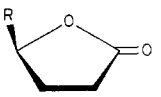
(10) (a) Vigneron, J. P.; Blanchard, J. M. *Tetrahedron Lett.* **1980**, *21*, 1739. (b) Midland, M. M.; Tramontano, A. *Ibid.* **1980**, *21*, 3549. (c) Takano, S.; Morimoto, M.; Ogasawara, K. *Synthesis* **1984**, 834.

(11) (a) Bravo, P.; Carrera, P.; Resnati, G.; Ticozzi, C. *J. Chem. Soc., Chem. Commun.* **1984**, 19. (b) Tanaka, K.; Wakita, H.; Yoda, H.; Kaji, A. *Chem. Lett.* **1984**, 1359.

0022-3263/88/1953-0627$01.50/0

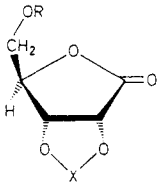
resulting in the formation of unequal amounts of two diastereomeric β-sulfinyl γ-lactones; their separation and subsequent pyrolysis then gave enantiomerically pure 4-substituted butenolides.[11a] Optically active (*R*)- and (*S*)-4-octyl- and (*R*)- and (*S*)-4-tridecylbutenolides were prepared via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

Syntheses of chiral butenolides from naturally occuring 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 = CH_2OH
c: R = CH_2OCH_2Ph
d: R = CH_2OCPh_3

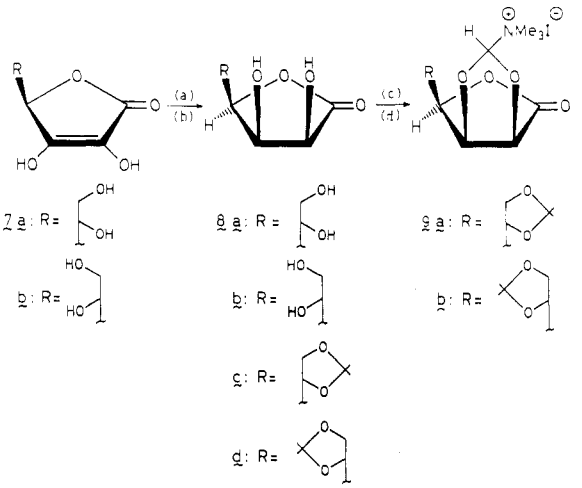
Various approaches to chiral butenolides from carbohydrates via formal C-2–C-3 didehydroxylations[14] of aldono-1,4-lactones have been reported. D-Ribono-1,4-lactone and its derivatives have provided **1a-c** by pyrolysis of the cyclic orthoformates **6a,b**.[15a,b] Raney nickel desulfuriza-



6 a: R = H, X = CHOEt
b: R = CH_2Ph, X = CHOEt
c: R = CPh_3, X = CHOEt
d: R = CPh_3, X = (C=S)
e: R = $Si(Ph)_2(t\text{-}Bu)$, 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 $Ph_3P{=}CHCOOEt$.[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 I[a]



[a] (a) H_2/Pd; (b) $Me_2C(OMe)_2$, $SnCl_2$; (c) $Me_2NCH(OMe)_2$; (d) MeI.

In part 1 of this series[18] 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).

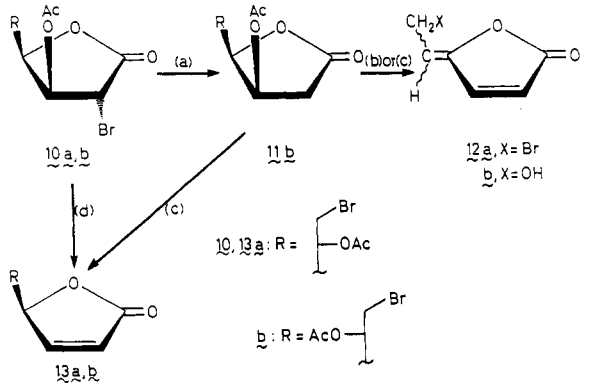
Chiral butenolides have also been generated from aldono-1,4-lactone derivatives via trans-2-bromo-3-*O*-benzoyl or -3-*O*-acetyl eliminations. In this manner 3-*O*-benzoyl-2-bromo-2,5-dideoxy-D-arabino-1,4-lactone yielded (−)-5-(*R*)-methyl-2(5*H*)-furanone on treatment with zinc in ethanol.[19] A recent 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

(12) Yokoyama, Y.; Yunokihara, M. *Chem. Lett.* **1983**, 1245.
(13) Červinka, O.; Hub, L. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2927.
(14) The synthesis of olefins from vicinal diols has been reviewed: Block, E. *Organic Reactions*; Vol. 30, chapter 2, Dauben, W. G., Ed.; Wiley: New York, 1984; Vol. 30, Chapter 2, p 457.
(15) (a) Camps, P.; Font, J.; Ponsati, O. *Tetrahedron Lett.* **1981**, *22*, 1471. (b) Camps, P.; Cardellach, J.; Font, J.; Ortuño, R. M.; Ponsati, O. *Tetrahedron* **1982**, *38*, 2395.
(16) Ireland, R. E.; Anderson, R. G.; Badoub, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.
(17) (a) Häfele, B.; Jäger, V. *Liebigs Ann. Chem.* **1987**, 85. (b) Danilova, G. A.; Mel'nikova, V. I.; Pivnitsky, K. K. *Tetrahedron Lett.* **1986**, *27*, 2489.
(18) Vekemans, J. A. J. M.; Boerekamp, J.; Godefroi, E. F.; Chittenden, G. J. F. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 266. Based on: Andrews, G. C.; Crawford, T. C.; Bacon, B. E. *J. Org. Chem.* **1981**, *46*, 2976.
(19) Chen, S.-Y.; Joullié, M. M. *J. Org. Chem.* **1984**, *49*, 2168.
(20) Vekemans, J. A. J. M.; Franken, G. A. M.; Chittenden, G. J. F.; Godefroi, E. F. *Tetrahedron Lett.* **1987**, *28*, 2299.
(21) Bock, K.; Lundt, I.; Pedersen, C. *Acta Chem. Scand., Ser. B.* **1986**, *B40*, 163 and references cited therein.
(22) Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1979**, *68*, 313.
(23) See part 2 of this series (*J. Org. Chem.* **1987**, *52*, 1093) and citations 7–13.
(24) Paulsen, H.; Eberstein, K. *Chem. Ber.* **1976**, *109*, 3907.

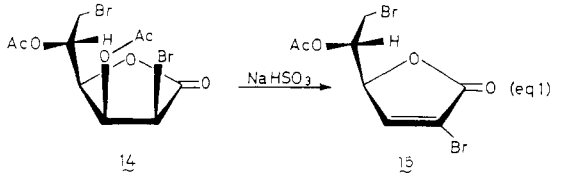
Scheme II[a]



[a] (a) NaI, acetone, CF_3CO_2H; (b) aqueous NaOAc; (c) $NaHCO_3$ in H_2O–Et_2O; (d) $NaHSO_3$; 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 $NaHCO_3$ 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 $PbCO_3$·$Pb(OH)_2$ 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 observation[26] that **14** was transformed quantitatively into butenolide **15** via a $NaHSO_3$-induced trans-AcOH elimination (eq 1), suggesting that the butenolide is stable to the action of $NaHSO_3$.



The effect of $NaHSO_3$ 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-gulono-1,4-lactone[18] and HBr–AcOH in the manner described for **10b**.[22] Similarly, lactone **10a** when treated with $NaHSO_3$ in 90% aqueous methanol at room temperature afforded crystallizable butenolide **13a** in high yield after 100 h (Scheme II).

The $NaHSO_3$-mediated elimination of **10a,b** merits further comment. Whereas β-eliminations involving halogen and a hetero group are not uncommon,[27] there seems

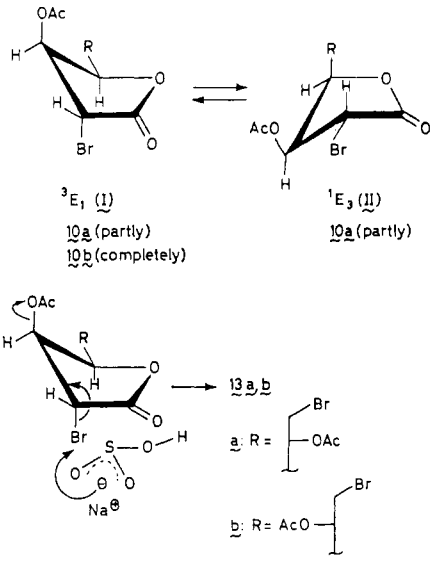


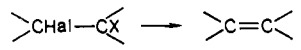
Figure 1. Conformation and $NaHSO_3$-induced 2-Br-3-OAc elimination of dibromo diacetates **10a,b**.

to be no precedent for $NaHSO_3$ 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 $NaHSO_3$ 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 $NaHSO_3$, 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 $NaHSO_3$.[29] The interaction in solution of $NaHSO_3$ 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, $^3E_1$ and $^1E_3$, 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 ± 3, 6 ± 3, and 2 ± 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 $NaHSO_3$ 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

(25) Camps, P.; Cardellach, J.; Corbera, J.; Font, J.; Ortuño, R. M.; Ponsati, O. *Tetrahedron* **1983**, *39*, 395.

(26) Pedersen, C.; Bock, K.; Lundt, I. *Pure Appl. Chem.* **1978**, *50*, 1385.

(27) For eliminations of the type



see among others; the following. (a) X = OCOR or OTos: Cristol, S. J.; Rademacher, L. E. *J. Am. Chem. Soc.* **1959**, *81*, 1600. Also ref 19. (b) X = NR_2: Gurien, H. *J. Org. Chem.* **1963**, *28*, 878 (c) X = SR; Amstutz, E. D. *J. Org. Chem.* **1944**, *9*, 310. The reactions are generally brought about by Zn, Mg, or Na.

(28) As indicated by referee 1, $NaHSO_3$ and related reagents are able to reduce α-dihalo carbonyl into α-monohalo carbonyl derivatives: Pirie, D. K.; et al. *Tetrahedron Lett.* **1986**, *27*, 1549. Pirie, D. K.; Weeks, P. D. US Patent 4 468 351, 1984. Lehmann, H. G. *Tetrahedron Lett.* **1976**, *17*, 987.

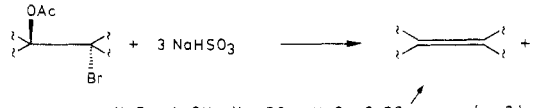
(29) Walker, I. F. U.S. Patent 2 849 458, 1958, *Chem. Abstr.* **1959**, *53*, 4299.

(30) Horton, D.; Walaszek, Z. *Carbohydr. Res.* **1982**, *105*, 131.

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 C=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 E2 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).

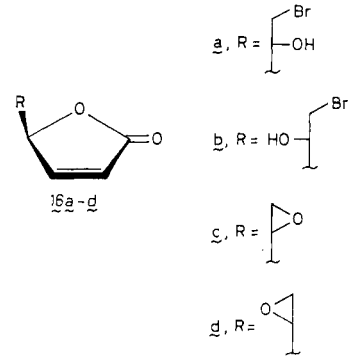


(eq 2)

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-mannonolactone **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 S_N2 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 S_N2 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 considerable 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

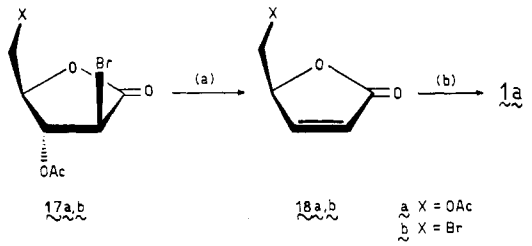


to silica gel chromatography and vacuum distillation. Its sensitivity to base was, however, convincingly demonstrated during an NMR-monitored experiment in which the addition of 0.1 equiv of Et_3N to a 0.5 M solution of **16d** in $CDCl_3$ produced more than 50% of **12b** within 1 min. The reaction 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 known[33] 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 previously[18] 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 $NaHSO_3$–Na_2SO_3-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 (Ag_2O–H_2O) 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-ribono-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 $NaHSO_3$–Na_2SO_3 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.

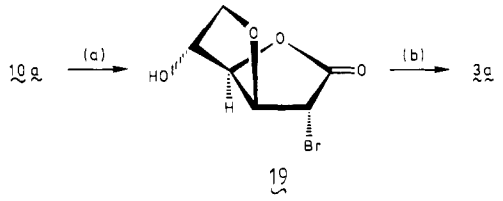
During the course of ongoing investigations another way to prepare **3a** was noted and will be mentioned briefly. Treatment of **10a** with HBr in propan-2-ol yielded a compound $C_6H_7BrO_4$, the spectral characteristics of which were consistent with the 3,6-anhydro structure **19**.[35] Boiling aqueous $NaHSO_3$ 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-ribono-1,4-lactone. The approach involves high-yield processes conducted in water or alcohol mostly at ambient temperatures and may well constitute the method of choice for preparing generous amounts of these valuable starting materials.

(34) Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1981**, *90*, 17.
(35) The reactivity of **19** and its congeners is under current investigation.

Scheme IV[a]



[a] (a) Propan-2-ol–HBr; (b) aqueous $NaHSO_3$, reflux.

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 acid[18] (**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; $[\alpha]^{20}_D$ +39° (*c* 2.02, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1820 (C=O, lactone), 1760 (C=O, acetates); ^1H NMR ($CDCl_3$) 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 $C_{10}H_{12}Br_2O_6$ (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 $NaHSO_3$ (20.8 g, 0.20 mol) and then portionwise with Na_2SO_3 (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 ($MgSO_4$), and concentrated in vacuo to give an oil (50 g, ~100%), which solifidied 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 ($CDCl_3$) 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 $C_8H_9BrO_4$ (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; $[\alpha]^{20}_D$ −107° (*c* 1.51, water); IR (KBr, cm^{-1}) ν_{max} 3400 (OH), 1740 (C=O), 1600 (C=C); ^1H NMR ($CDCl_3$) 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 $C_6H_7BrO_3$ (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)

in water (200 mL) at 0 °C was treated with moist, neutral, and freshly prepared Ag_2O (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 ($MgSO_4$) 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; $[\alpha]^{20}_D$ −79° (*c* 1.01, water); IR (KBr, cm^{-1}) ν_{max} 1780–1760 (C=O), 1560 (C=C), 820 (C–O, epoxide; ^1H NMR ($CDCl_3$) 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 $C_6H_6O_3$ (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; $[\alpha]^{20}_D$ −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 $C_6H_8O_4$ (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 $[\alpha]_D$ −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 $NaHSO_3$ (208 mg, 2.0 mmol) was heated under reflux with stirring for 2.5 h. TLC ($CHCl_3$–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 ($CHCl_3$–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 crystallization and recrystallization from the same mixture afforded the title compound: mp 98–100 °C (0.74 g, 33%); $[\alpha]^{20}_D$ −15° (c 1.12, $CHCl_3$); ^1H NMR ($CDCl_3$–CD_3OD, 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 $C_6H_7BrO_4$ (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; $[\alpha]^{20}_D$ +54° (*c* 2.01, $CHCl_3$) [lit.[22] mp 93–95 °C; $[\alpha]^{20}_D$ +51.4° (*c* 2.3, $CHCl_3$)]; IR (KBr, cm^{-1}) ν_{max} 1805 (C=O, lactone), 1760 (C=O, acetates); ^1H NMR ($CDCl_3$) 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 $NaHSO_3$ (10.4 g, 0.10 mol), followed by the portionwise addition of Na_2SO_3 (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 [($CDCl_3$) 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 a 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. [$[\alpha]^{20}_D$ −111° (c 1.28, water); IR (neat, cm^{-1}) ν_{max} 3400 (OH), 1760 (C=O), 1610 (C=C); ^1H NMR ($CDCl_3$) 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 Ag_2O (0.10 mol). The mixture was stirred at 0 °C for 3 h, when TLC ($CHCl_3$–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 dienones (**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; $[\alpha]^{20}_D$ −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 $C_6H_8O_4$ (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% $Na_2S_2O_3$ solution and water, dried ($MgSO_4$), and evaporated in vacuo. The resulting yellow oil (2.7 g) was shown (TLC, $CHCl_3$–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** ($CDCl_3$) 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 adsorptions in ^{1}H 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 (^{1}H 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%): $[\alpha]^{20}_D$ −143° (*c* 1.09, water); IR (neat, cm^{-1}) ν_{max} 1790–1750 (C=O), 1610 (C=C), 820 (C–O, epoxide; ^{1}H 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(5*H*)-furanone [2,3-Dideoxy-D-pent-2-enono-1,4-lactone] (1a). A suspension of D-ribono-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** [^{1}H 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** [^{1}H 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 (^{1}H NMR) to be a mixture (6:1) of butenolides **18a** [^{1}H 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; $[\alpha]^{20}_D$ −140° (*c* 3.0, H_2O) [lit.[15b] mp 37–39 °C; $[\alpha]^{20}_D$ −143° (*c* 1.14, water)]; ^{1}H 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 $C_5H_6O_3$ (MW 114.10): C, 60.06; H, 6.05. Found: C, 60.0; H, 6.2.

5(*S*)-[(Triphenylmethoxy)methyl]-2(5*H*)-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[; $[\alpha]^{20}_D$ −94° (*c* 2.01, $CHCl_3$) [lit.[6a] [α] −95.9°; lit.[15b] [α] −95.1°; lit.[16] [α] −50.2° ($CHCl_3$)]; ^{1}H 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 $C_{24}H_{20}O_3$ (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-ribono-1,4-lactone, 5336-08-3.

Methyldiphenylsilylation of Ester and Lactone Enolates[1]

Gerald L. Larson,*[2a] Veronica Cruz de Maldonado,[2b] Lelia M. Fuentes,[2c] and Luz E. Torres[3]

Department of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931, and Petrarch Systems, Bartram Road, Bristol, Pennsylvania 19007

Received May 1, 1987

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

0022-3263/88/1953-0633$01.50/0