Vitamin C and Isovitamin C Derived Chemistry. 4. Synthesis of Some Novel Furanone Chirons

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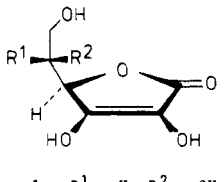
The utility of the vitamin C and isovitamin C derived dibromo diacetates **3a,b** for preparing synthetically useful chirons is further examined. Methodologies for transforming the readily accessible compounds **3a,b** into 3,6- and 5,6-anhydrohexono-1,4-lactones **10a,b** and **6a,b** are presented. Elaboration of the lactone epoxides **6a–c** has provided optically pure (*S,S*)-, *meso*-, and (*R,R*)-4,4′-bis-γ-butyrolactones **18a–c**. The difference in reactivity between some isomeric intermediates was related to the spatial arrangement at the reactive sites.

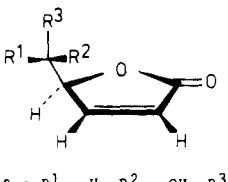
Introduction

Unequivocal stereocontrol constitutes the center piece of modern natural product synthesis. Most frequently the absolute configuration of the desired product has stemmed from the judiciously timed incorporation of chirally defined building blocks (chirons) during the synthesis and the subsequent configurational control of the asymmetric centers introduced. Carbohydrate-based schemes leading to a host of chirons have been especially rewarding in this respect; most of the desired routes have relied on the restructuring of furanoside and pyranoside systems.

Our recent studies have demonstrated some relevant advantages of utilizing aldono-1,4-lactones, rather than the corresponding lactols, towards these ends. In practice aldono-1,4-lactones are highly crystalline, easily manipulated, and readily characterized substances. Large amounts of starting lactones may be prepared from inexpensive, commercially available materials. Publications from these laboratories have described the production of chirally defined butenolides **2a–k**[1,2] from the ascorbic acids **1a,b** and from D-ribono-1,4-lactone. The preparation of three enantiomerically pure 4,5,6-trihydroxy-nor-D-leucines from **1a,b** has also been reported.[3]



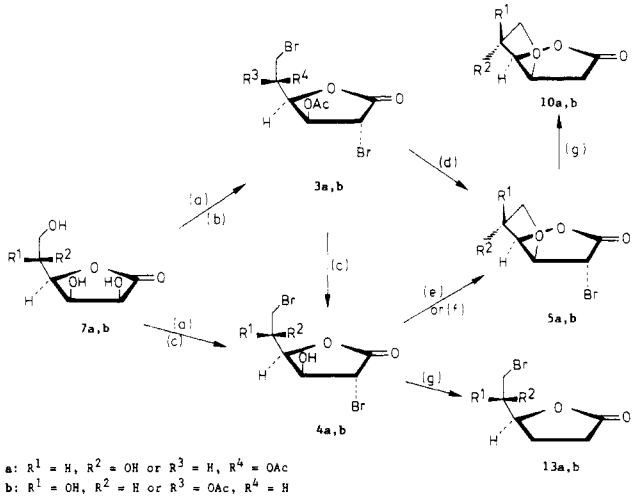
1a: R^1 = H, R^2 = OH
1b: R^1 = OH, R^2 = H



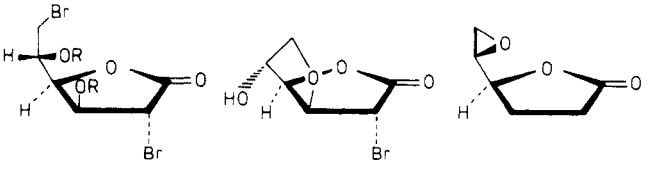
2a: R^1 = H, R^2 = OH, R^3 = CH_2OH
2b: R^1 = H, R^2 = OAc, R^3 = CH_2Br
2c: R^1 = H, R^2 = OH, R^3 = CH_2Br
2d: R^1 = H, R^2R^3 = O-CH_2
2e: R^1 = OH, R^2 = H, R^3 = CH_2OH
2f: R^1 = OAc, R^2 = H, R^3 = CH_2Br
2g: R^1 = OH, R^2 = H, R^3 = CH_2Br
2h: R^1R^3 = O-CH_2, R^2 = H
2i: R^1 = R^2 = H, R^3 = OH
2j: R^1 = R^2 = H, R^3 = OAc
2k: R^1 = R^2 = H, R^3 = Br

The creation of chirons originating from vitamin C and isovitamin C was further investigated. Attention was focused on their versatile educts, the dibromo diacetates **3a,b**, which may be regarded as fully protected γ-hexono-1,4-lactones. The acid-catalyzed deacetylation of L-idono dibromo diacetate **3a** was found to produce, in addition to diol **4a**, significant amounts of a byproduct. The latter became the main product on altering the reaction conditions and was assigned the 3,6-anhydrohexono-1,4-lactone structure **5a**. It was also found that compound **3a** could serve as precursor for L-threo butanolide epoxide **6a**, via *trans*-2-bromo-3-*O*-acetyl elimination to **2b**[2] and subsequent, consecutive catalytic reduction and base treatment.

Scheme I[a]



[a] Key: (a) HBr–HOAc; (b) Ac_2O; (c) $MeOH_2^+$; (d) *i*-PrOH–HBr, –HBr; (e) *t*-AmOH, Δ, –HBr; (f) Ag_2O–H_2O; (g) Pd–C, H_2.



3a: R = Ac
4a: R = H

5a

6a

The optimized preparation of the novel and potentially useful chiral furanones **5a** and **6a**, which may be considered

† E.F.G. supervised the experimental work that was conducted at the Technical University of Eindhoven, The Netherlands.

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Table I. Relevant ^1H Nuclear Magnetic Resonance Data of 3,6-Anhydro Sugar Derivatives[a]

entry	confign	H-2α	H-2β	H-3	H-4	H-5	H-6$_{endo}$	H-6$_{exo}$	$J_{2\alpha,2\beta}$	$J_{2\alpha,3}$	$J_{2\beta,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6_{endo}}$	$J_{5,6_{exo}}$	$J_{6,6}$
8a[b,c]	α-L-*ido*	–	4.14	4.59	4.68	4.42	4.24	3.82	–	–	~0	4.4	<0.5	3.8	<0.5	10.2
8b[b,c]	β-D-*gluco*	–	4.16	4.47	4.80	4.39	3.83	3.94	–	–	~0	4.7	5.1	7.5	7.0	8.5
5a[d]	L-*ido*	–	4.45	4.87	5.07	4.51	4.02	3.94	–	–	~0	3.3	~0	3.5	~0	10.2
5b[d]	D-*gluco*	–	4.51	4.82	5.15	4.52	3.71	4.06	–	–	1.4	4.3	4.35	7.4	6.4	8.8
10a[d]	L-*xylo*	2.90	2.55	4.88–4.89		4.53	4.03	3.80	18.4	8.1	~0	4.3	~0	3.9	1.9	10.1
10b[d]	D-*arabino*	2.93	2.57	4.77	4.98	4.42	3.65	3.92	18.3	6.5	1.3	5.1	4.4	7.0	6.2	8.8
15a[e]	L-*xylo*	2.75	2.61	4.86	4.95	5.02	4.07	3.93	18.7	5.1	1.2	4.5	~0	4.3	2.4	11.2
15b[e]	D-*arabino*	2.79	2.64	4.76	4.95	5.02	3.83	3.95	18.9	6.4	1.75	4.8	5.0	6.7	6.0	9.75

[a] δ values are expressed in parts per million, *J* values in hertz. [b] From ref 11. [c] In D_2O. [d] In CD_3OD. [e] In $CDCl_3$.

Table II. Relevant ^{13}C Nuclear Magnetic Resonance Data of 3,6-Anhydro Sugar Derivatives[a]

entry	solvent	confign	C-1	C-2	C-3	C-4	C-5	C-6
8a[b]	D_2O	α-L-*ido*	104.0	75.3	86.6	88.8	75.3	74.3
8b[b]	D_2O	β-D-*gluco*	103.9	75.7	86.5	83.1	71.3	70.6
5a	CD_3OD	L-*ido*	174.4	40.8	85.45	88.9	77.25	74.75
5b	CD_3OD	D-*gluco*	175.0	42.45	86.0	84.7	73.7	72.9
10a	CD_3OD	L-*xylo*	178.8	37.45	79.3	90.8	76.1	75.4
	pyridine-d_5		178.2	36.3	78.1	89.5	74.7	74.5
10b	CD_3OD	D-*arabino*	179.3	38.2	79.2	85.5	72.7	73.35
	pyridine-d_5		178.5	37.1	77.9	83.7	71.6	72.1
15a	$CDCl_3$	L-*xylo*	175.1	36.1	78.1	86.2	82.1	71.85
	pyridine-d_5		175.0	35.5	77.8	86.0	82.5	71.1
15b	$CDCl_3$	D-*arabino*	175.5	36.9	77.6	81.0	77.3	69.2
	pyridine-d_5		175.5	36.2	77.4	80.9	77.7	68.8

[a] δ values are expressed in parts per million. [b] From ref 11.

as "naked sugars",[4] together with their derivatization is now described. In addition the synthesis and the comparable modifications of the corresponding D-glucono and D-erythro isomers **5b** and **6b** and of enantiomeric D-threo epoxide **6c** are presented.

Results and Discussion

1. **3,6-Anhydrohexono-1,4-lactones (2,6-Dioxabicyclo[3.3.0]octan-3-ones).** Consecutive treatment of D-mannono-1,4-lactone (**7b**) with 33% HBr in HOAc and with methanol afforded crystalline 2,6-dibromo-2,6-dideoxy-D-glucono-1,4-lactone (**4b**)[5] (Scheme I). On similar treatment of L-gulono-1,4-lactone (**7a**), the expected compound **4a** could not be obtained crystalline from the syrupy product. Analysis (^1H NMR; TLC) of the material showed the presence of a byproduct possibly interfering with crystallization. Investigations into alternative deacetylation procedures, such as in situ treatment of pure diacetate **3a** with acidified methanol, did not furnish crystalline material, and even column chromatography (SiO_2; $CHCl_3$–MeOH, 9:1) failed to yield uncontaminated **4a**, despite the lower polarity of the byproduct. This suggested partial conversion of **4a** into the other product to have occurred during or after the chromatography. Increased reaction temperatures favored the formation of the byproduct. Thus, heating **3a** in propan-2-ol–HBr, with slow removal of volatiles and replenishment of the solvent, resulted in the complete conversion of intermediate **4a**. The ^1H NMR spectrum of the pure material ($C_6H_7BrO_4$) confirmed the presence of only seven protons instead of the expected eight for **4a**. The lack of signals above 5.1 and below 3.9 ppm precluded the presence of a vinylic system, a CH_2Br group, or a monosubstituted oxirane ring in the compound. The 3,6-anhydro structure **5a** was therefore assigned to the material.

3,6-Anhydro sugars featuring a hemiacetal system in place of a lactone function have been described.[6] It has been shown that 3,6-anhydropyranosides, easily obtainable from the corresponding 6-*O*-tosylates, undergo facile acid-catalyzed transformations into the thermodynamically more stable 3,6-anhydrofuranosides.[7] Conformational and configurational data for all of the possible 3,6-anhydrofuranose isomers supported the assigned lactone structure **5a**.[8] The NMR spectra of **5a** and 3,6-anhydro-α-L-idofuranose **8a** bear a very close resemblance (Tables I and II) (vide infra).

3,6-Anhydro-L-gulono- and -L-idono-1,4-lactones have been previously described.[9a,b] They were obtained by the Pt-catalyzed oxidation of 1,4-anhydro-D-sorbitol and -L-iditol, respectively. No ^1H NMR data were recorded for the compounds. D-Glucurono-1,4-lactone, D-mannaro-1,4:6,3-dilactone,[9c] and 3,6-anhydro-L-*xylo*-2-hexulosono-1,4-lactone[9a,b] are typical examples of other anhydro monosaccharide derivatives in a higher oxidation state.

Attempts were made to optimalize the production of **5a**, in view of its synthetic potential. This was achieved in the following manner. Treatment of the dibromo diacetate **3a** with hot propan-2-ol–HBr or heating of the crude dibromo diol **4a** in *tert*-amyl alcohol led to the desired result. The presence of catalytic amounts of HBr during the thermolysis of **4a** probably favors the ring closure. It was, however, found necessary to remove the majority of the HBr as it was formed for successful completion of the reaction.[10] This was achieved by the continuous, slow distillation of the solvent from the mixture with replenishment when necessary. The overall yields of **5a** from **7a** were 54% from the former and 63% from the latter approach. It was then demonstrated that **5a** could be obtained efficiently from the diol **4a** by treatment with an aqueous suspension of

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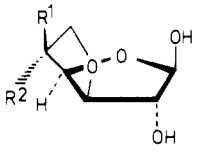
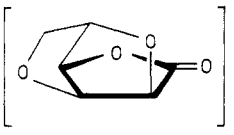
(9) (a) Heyns, K.; Linkies, A. *Chem. Ber.* **1968**, *101*, 4199; (b) **1968**, *101*, 4209; (c) **1975**, *108*, 3633.
(10) As was kindly suggested by reviewer 2, it is not excluded that **3a** and **5a** are interconverting species. However, no evidence was found for the intermediacy of **5a** (or its 5-acetate) in the preparation of **3a** (87% isolated yield) from **7a** and HBr–HOAc.

Ag_2O. The yield here was 90%, and it illustrates the preferred formation of the five-membered anhydro ring under almost neutral conditions. It was known[2] that the 5-bromo-5-deoxy derivatives **2c** and **2g**, which are incapable of 3,6-anhydro ring closure, yield the oxiranes **2d** and **2h** under the same conditions. The formation of **5a** from **4a** could also be achieved by using NaH in THF, but it was not sufficiently clean for practical purposes. Treatment of **4a** with mildly basic sodium hydrogen carbonate failed to yield the bicyclic lactone. The formation of compound **5a** from the lactone **7a** was eventually accomplished on a 0.25-molar scale to give the material in 56% yield. The procedure involved consecutive bromoacetylation, in situ deacetylation with methanol, and thermolysis in *tert*-amyl alcohol.

Attention was directed also toward the synthesis of the isomeric bicyclic lactone **5b**. In contrast to the behavior of compound **3a**, the dibromo diacetate **3b** was smoothly deacetylated to give the crystalline diol **4b**. Analysis of the crude reaction product (^{1}H NMR; TLC) indicated only traces of the desired **5b**. Compound **5b** was successfully obtained by thermolysis of the dibromo diol **4b** in excess *tert*-amyl alcohol, to give the bicyclic lactone in 48% yield. The length of time required to complete the reaction (60 h vs 6 h for its C-5 epimer **5a**) and the volume of solvent needed to be distilled from the mixture reflected the reluctance of **4b** to undergo cyclization. There was no evidence for double dehydrobromination to yield the corresponding 3,6:2,5-bis-anhydro-D-mannono derivative **9**, by analogy with the corresponding furanosides.[11] Double anhydro ring formation in the L-idono series, e.g., derived from **5a**, is impossible due to the anti orientation of the C-5-OH and the lactone ring. Treatment of the dibromo diacetate **3b** with boiling propan-2-ol–HBr or of the dibromo diol **4b** with an aqueous suspension of Ag_2O could not be brought to a successful conclusion and again reflected the nonreactivity of the system.



8a: R^1 = H, R^2 = OH
8b: R^1 = OH, R^2 = H



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A better understanding of the differing rates of formation of the isomers **5a** and **5b** is obtained by comparing the ^{1}H NMR spectral data of the two isomers with those of compounds **8a** and **8b** (Table I). A close spectral correlation exists between **5a** and **8a** (ido configuration) and of **5b** and **8b** (gluco configuration). In all four compounds a very small coupling constant $J_{2\beta,3}$ is observable, suggesting a quasi-axial relationship between the C-2-Br (or C-2-OH) and O-3. In the idono series H-4 is more shielded (~0.1 ppm), and in the glucono derivatives H-6_{endo} absorbs at lower field than H-6_{exo} (δ 0.35 and 0.1 ppm) while this is reversed in the idono series (δ 0.1 and 0.4 ppm). The most relevant differences are, however, observed with the coupling constants of H-5. The idono compounds have values approximating 0 Hz for $J_{4,5}$ and $J_{5,6_{exo}}$, while in the corresponding glucono compounds values >4 and >6 Hz were determined, respectively, for the same coupling constants. Newman projections along the C-2–C-3 and C-4–C-5 axes indicating the approximate dihedral angles between H-2–C-2 and C-3–H-3 and between H-4–C-4 and C-5–H-5 in compounds **5a** and **5b** (in parentheses) are

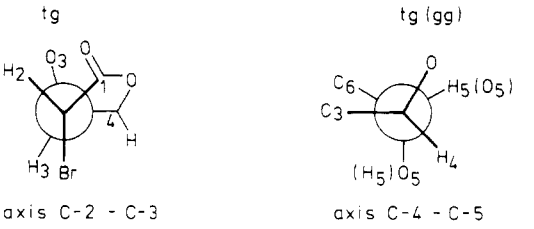

Figure 1. Newman projections indicating the approximate dihedral angles along the C-2–C-3 and C-4–C-5 axes in **5a** and **5b**. Where different from those in **5a**, conformations in **5b** are given in brackets.

depicted in Figure 1. A quasi-axial orientation is adopted by O-3 with respect to the lactone ring, in both isomers. The angle between H-2 and H-3 should approach 90° more closely in the L-idono compound **5a** than in D-glucono isomer **5b**, according to the Karplus rule ($J_{2,3}$ = 0 Hz vs 1.4 Hz). The C-5-OH and the lactone oxygen have an almost antiperiplanar relationship (dihedral angle ~150°) in the former and a synclinal one (~30°) in the latter series.

The dehydrobromination of diols **4a** and **4b** to the bicyclic lactones **5a,b** could occur without developing additional strain. The transition state derived from compound **4a** must have OH-5 and the lactone ring in opposition, which reduces the resultant dipole moment of the system. The comparable transformation of **4b** supposedly involves a transition state with an enhanced resultant moment because of the obligatory gauche disposition of the same two oxygens. The differences in the rates of cyclization of **4a,b** to **5a,b** are related therefore to conformationally imposed electronic factors and not to steric hindrance (cf. alditols[12]) or to stabilization resulting from hydrogen bonding which would favor the formation of the opposite epimer. The situation could be likened to the anomeric effect displayed by aldose derivatives. The ^{13}C NMR data (Table II) also reflect the close relationship between **5a,b** and the anhydrides **8a,b**. It is interesting that the signals assigned to C-4, C-5, and C-6 appear at higher field (3–6 ppm) in the D-glucono derivatives than in their L-idono counterparts. This is not observed for the corresponding monocyclic γ-hexonolactones.[13]

Attention was then directed toward the chemical reactivity of the bicyclic lactones **5a,b**. The effect of "aqueous" $NaHSO_3$ was examined initially. This reagent had previously induced quantitative bromoacetate elimination from the dibromo diacetates **3a,b**.[2] Compound **5a** was unreactive toward $NaHSO_3$ in 87.5% propan-2-ol at room temperature. When the mixture was heated under reflux for 2 h, two products, more polar (TLC) than the starting compound, were produced. The minor component (R_f 0.17) was identified as the butenolide **2a**, and to the major product (R_f 0.39) was assigned structure **10a** (^{1}H NMR spectroscopy). It was also shown that compounds **2a** and **10a** were not interconverting under the reaction conditions. Heating of both compounds, separately, up to 150 °C, did not lead to detectable amounts of the other, although the melting points of both are very close (85–86 vs 83–84 °C). Compound **10a**, which represents the internal Michael adduct of **2a**, could therefore be useful as a protected butenolide which is not susceptible to epimerization at C-4. The competition between elimination of

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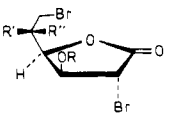
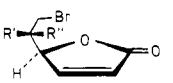
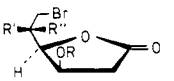
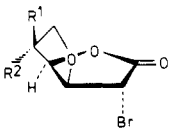
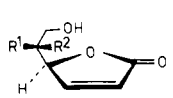
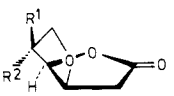
Table III. Competition between *trans*-3-OX Elimination and Enolization Accompanying C-2 Debromination of *trans*-2-Br-3-OX γ-Lactones

entry	R	R′	R″	conditns	eliminatn product	enoliztn product	ratio
				 + 			
3a[a]	Ac	H	OAc	$NaHSO_3$–Na_2SO_3–ROH	**2b**	–	≫
3b[a]	Ac	OAc	H	$NaHSO_3$–Na_2SO_3–ROH	**2f**	–	≫
3a[b]	Ac	H	OAc	NaI–acetone	**2b**	–	≫
3b[b]	Ac	OAc	H	NaI–acetone	**2f**	–	≫
3b[c]	Ac	OAc	H	NaI–acetone–CF_3CO_2H	**2f**	**11b**	~1:4
4b[d]	H	OH	H	Pd–C/H_2/ROH	(**2g**)[e]	**12b**	~4:1

entry	R^1	R^2	conditns	eliminatn product	enolizatn product	ratio
			 + 			
5a	H	OH	$NaHSO_3$–ROH–Δ	**2a**	**10a**	~1:2
5a	H	OH	NaI–acetone–CF_3CO_2H–Δ	**2a**	**10a**	~1:3
5a	H	OH	Pd–C/H_2/H_2O/H^+	(**2a**)[e]	**10a**	~1:3
5a	H	OH	Pd–C/H_2/NEt_3/EtOAc	–	**10a**	≪
5b	OH	H	Pd–C/H_2/NEt_3/EtOAc	–	**10b**	≪

[a] From ref 2. [b] Unpublished results. [c] From ref 14a. [d] From ref 15. [e] Upon formation, the butenolides are saturated at the carbon–carbon double bond to afford **13b** from **2g** and **14a** from **2a**, respectively.

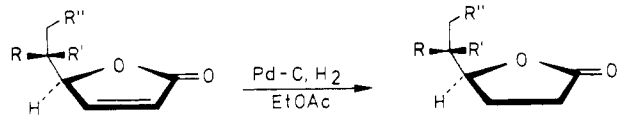
C-3-OR and enolization upon nucleophilic attack at C-2-Br suggests a mechanistic explanation for the course of this reaction and the others included in Table III. The dibromo diacetates **3a,b** both have a good leaving group at C-3. Hence, the formation of compounds **11a,b** could not be detected upon reaction with $NaHSO_3/Na_2SO_3$ in aqueous alcohol. Treatment of **3b** with NaI in acetone led mainly to butenolide **2f**. However, in the presence of excess trifluoroacetic acid, butanolide **11b** has been obtained in 71% yield.[14a] Presumably initial protonation of the lactone carbonyl group is followed by nucleophilic attack at the strongly activated C-2-Br with concomitant electron delocalization in the direction of O-1.[14b] Repeat of this experiment yielded besides butanolide **11b** also considerable quantities of butenolide **2f** (^{1}H NMR: vinylic protons). The elimination reactions occurred less readily with **5a,b** than with **3a,b**, apparently due to the less active C-3 substituent. Protonation of the C-3 ether function is achieved more readily than that of the ester function in **3a**. This explains why compounds **2a** and **10a** are formed in a comparable ratio (~1:3) as observed for the reaction of **3a** with $NaHSO_3$ (~1:2). The competitive vicinal E2 elimination and C-2 reduction observed recently during the Pd–C catalyzed hydrogenation of the dibromo diol **4b** may be viewed as a similar reaction pathway.[15] The catalyst probably enhances the leaving-group character of OH-3, thereby facilitating the elimination of HOBr.

The production of the 2-deoxy-3,6-anhydro 1,4-lactones **10a,b** was considered desirable. The Pd-catalyzed reduction of **5a,b** was subsequently investigated. The reduction of **5a** in aqueous media led not only to the expected bicyclic lactone **10a** but also to the dideoxy lactone **14a**. This was probably due to concomitant ring opening of the tetrahydrofuranyl moiety with attendant Pd-catalyzed C-2-Br–C-3-OH elimination and subsequent addition of hydrogen to the intermediate butenolide **2a**. Crystalline **10a** was obtained in 69% yield when the same reduction was carried out in ethyl acetate in the presence of Et_3N. The C-5 epimer **10b** was similarly obtained in almost equivalent yield (67%). The ^{1}H NMR spectral data (Table I) show that in both compounds the geminal protons on C-2 occur at ~2.9 and 2.55 ppm, with coupling constants >18 Hz. The former signal is assigned to the new H-2α, whereas the latter results from the large upfield shift of H-2β (1.9 ppm) when the C-2-Br is replaced by hydrogen. The H-2α signal in **10a** appeared as a 12-peak multiplet. This complexity was not due to long-range couplings as evidenced by the irradiation of selected proton signals. Irradiation of the multiplet at 4.89 ppm, assigned to H-3 and H-4, resolved the multiplet into a double (J ~ 18 Hz), originating from the geminal coupling with H-2β. When the H-2α proton was irradiated, the multiplet assigned to H-3 and H-4 became a very narrow AB system for which $J_{3,4}$ = 4.3 ± 0.4 Hz was found. The H-2α signal represents the X part of an ABX system which, even at 200 MHz, displayed all possible six peaks. Comparison of the ^{13}C NMR data (Table II) derived from **5a,b** and **10a,b** reflected the influence of the bromine substituent. It induces downfield shifts at C-2 (~4 ppm) and C-3 (~6.5 ppm) and an upfield shift of the lactone carbon C-1 (4.5 ppm).

The toluene-*p*-sulfonylation of OH-5 in **5a** and **10a** was then investigated. Under the usual conditions (pyridine–*p*-toluenesulfonyl chloride), compound **5a** reacted slowly and nonselectively. The L-xylo compound **10a**, however, reacted smoothly under these conditions to give the crystalline tosylate **15a** (60%) after four days at room temperature. Attempts to enhance the reaction rate, e.g., with CH_2Cl_2–Et_3N or catalytic amounts of 4-(dimethylamino)pyridine, were unsuccessful. The low reactivity of **10a** coincides with earlier attempts[16] to selectively tosylate the 3,6-anhydrofuranosides, which also required several days to obtain complete reaction. The corresponding D-arabino tosylate **15b** was obtained in comparable yield under similar conditions. Interestingly, in this case the reaction was complete within 1 day. A competition experiment carried out in pyridine-d_5 indicated that, upon addition of 0.6 equiv of *p*-toluenesulfonyl chloride, **15a** and **15b** are formed in a 1:2 ratio, which corresponds to a

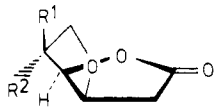
(14) (a) Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1979**, *68*, 313. (b) Meyer, K. H. *Justus Liebigs Ann. Chem.* **1911**, *380*, 212.
(15) Lundt, I.; Pedersen, C. *Synthesis* **1986**, 1052.
(16) Köll, P.; Komander, H. *Liebigs Ann. Chem.* **1983**, 1332.

Scheme II



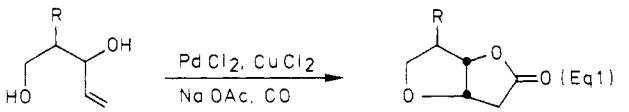
2a	(R = H, R' = R'' = OH)	14a
2b	(R = H, R' = OAc, R'' = Br)	16a
2c	(R = H, R' = OH, R'' = Br)	13a
2d	(R = H, R'R'' = O)	6a
2g	(R = OH, R' = H, R'' = Br)	13b
2h	(RR'' = O, R' = H)	6b

relative rate constant of ~1:3.25 for these second-order processes. The difference in reactivity between **10a** and **10b** has no steric reasons but may be explained by the enhanced acidity of OH-5 in **10b**, due to hydrogen bonding with the lactonic oxygen.



15a: R^1 = H, R^2 = OTs
15b: R^1 = OTs, R^2 = H

Optically active 2-deoxy-3,6-anhydrohexono-1,4-lactones have not been described hitherto. The preparation of some racemic analogues of **10a,b** was achieved recently by the Pd-catalyzed oxycarbonylation of the corresponding 4-pentene-1,3-diols[17] (eq 1).

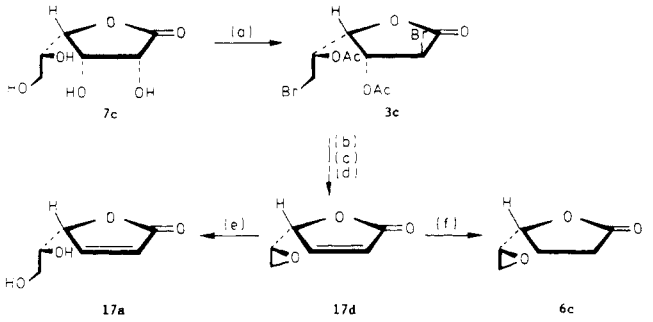


R = H, CH_2Ph, CH_2CH_2OH

2. 5,6-Anhydrohexono-1,4-lactones (5-(2'-Oxiranyl)dihydro-2(3*H*)-furanones). The $NaHSO_3/Na_2SO_3$ induced[2] trans elimination of the bromoacetates **3a,b** provides access to the Δ^2-butenolides **2b,f** and thence to compounds **2c,g**, **2d,h**, and **2a,e**. Catalytic hydrogenation of these unsaturated lactones should furnish the corresponding butanolides (Scheme II). Δ^2-Butenolides are prone to base-catalyzed epimerization at C-4[1a] and to H-4–X-5 elimination when there is a suitable leaving group at C-5. Most nucleophilic displacements at the side chain at C-4 are incompatible with conservation of optical purity.[18] The corresponding butanolides in contrast show no tendency to epimerize at C-4 and are capable of undergoing functionalization at C-2 or side-chain elongation without loss of chiral integrity. They do, however, undergo ring opening in acidic or basic protic media.

Chiral five-carbon butanolides are conveniently available from inexpensive L-glutamic acid[19] or from D-mannitol.[20] The six-carbon homologues are more difficultly accessible, which makes the current approach attractive, an additional advantage of this pathway being that it should also permit

Scheme III[a]



[a] Key: (a) HBr–HOAc; Ac_2O; (b) $NaHSO_3$–Na_2SO_3 in MeOH–H_2O, 9:1; (c) MeOH–HCl, 0 °C; (d) Ag_2O–H_2O, 0 °C; (e) H_2O, reflux; (f) Pd–C, H_2, EtOAc.

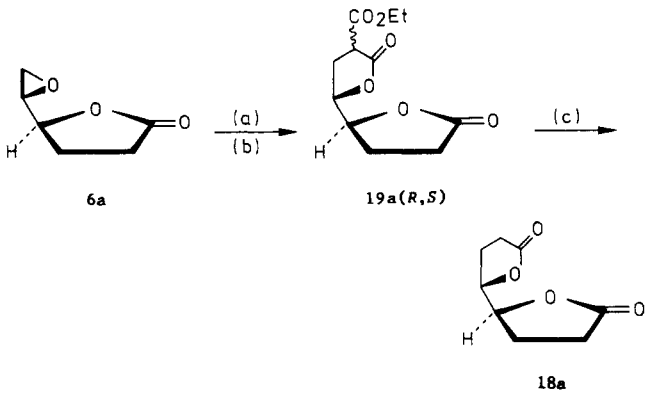
annulation at C-2 and C-3, via Diels–Alder cycloadditions, cis-vicinal hydroxylation, or stereoselective deuteration. The hitherto unknown and enantiomerically pure epoxy lactones **6a–c** were thus chosen as target molecules because of their structural simplicity and versatility. They may be considered as chiral combinations of oxirane and γ-butyrolactone. Apart from their synthetic applicability, they may also be useful for comparative reactivity studies of epoxide and γ-lactone functions with soft and hard nucleophiles.

The most direct route to epoxy lactone **6a** entails catalytic reduction of **2b** to **16a** (Scheme II) followed by base-catalyzed deacetylation and concomitant oxirane ring closure. Complete catalytic reduction (Pd/C) of **2b** was difficult to achieve, probably due to the presence of bisulfite-derived impurities which poisoned the catalyst. Conversion of **16a** into **6a** with methanolic sodium methoxide at 0 °C was accompanied by lactone ring opening. Acidic deacetylation of **16a** also resulted in considerable lactone ring opening. The stability of butenolides toward acid-catalyzed ring opening suggested therefore deacetylation of **2b** prior to carbon–carbon double bond reduction. Reaction of the resulting product with methanolic HCl (1 M) at 10 °C gave the pure, crystalline bromo alcohol **2c**, which on catalytic reduction gave **13a** in good yield. Treatment of this product with NaH in THF afforded the epoxide **6a** (56% after distillation). In another approach the reduction was postponed until the penultimate stage. The unsaturated bromo alcohol **2c** was transformed into the crystalline epoxide **2d** with an aqueous suspension of Ag_2O. This then gave 71% of oily **6a** on catalytic reduction (Pd/C) at atmospheric pressure. Distilled or chromatographed epoxy butanolide **6a** crystallized on standing at 0 °C, but liquefied at room temperature. Efforts were also undertaken to short-circuit the reaction sequence by using a one-pot procedure for the conversion of L-gulono-1,4-lactone (**7a**) into saturated bromo alcohol **13a** (Scheme I, paths a, c, and g). They were not of preparative value due to contamination with 2-deoxy sugar lactone **12a** and bicyclic lactone **10a** (Table III). In the C-5 epimeric series (**2f**, **2g**, **2h**, **13b**), no crystalline intermediates could be isolated. The pure epoxy butanolide **6b** was obtained in 43% overall yield from **3b**, via the reaction sequence that postponed the catalytic reduction to the last step (via **2h**).

The NMR data of the 4-oxiranyl-γ-butyrolactones merit some comments. In contrast to comparable threo and erythro systems,[1a,2] $^3J_{H\text{-}4\text{-}H\text{-}5}$ is not significantly different in **6a** and **6b**. However, in the threo isomer **6a** the signal attributed to H-5 appears at higher field (3.13 vs 3.24 ppm) and that assigned to H-6β at lower field (2.80 vs 3.24 ppm) than in the corresponding erythro isomer **6b**. ^{13}C NMR reveals a relative shielding in the erythro isomer both for

(17) Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 3207.
(18) (a) Camps, P.; Cardellach, J.; Font, J.; Ortuño, R. M. *Tetrahedron* **1982**, *38*, 2359. (b) Camps, P.; Cardellach, J.; Corbera, J.; Font, J.; Ortuño, R. M.; Ponsati, O. *Tetrahedron* **1983**, *39*, 395.
(19) (a) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547. (b) Tomioka, K.; Ishiguro, T.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2973. (c) Hanessian, S.; Sahoo, S. P.; Murray, P. J. *Tetrahedron Lett.* **1985**, *26*, 5631.
(20) (a) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 381; (b) **1981**, *16*, 951.

Scheme IV[a]

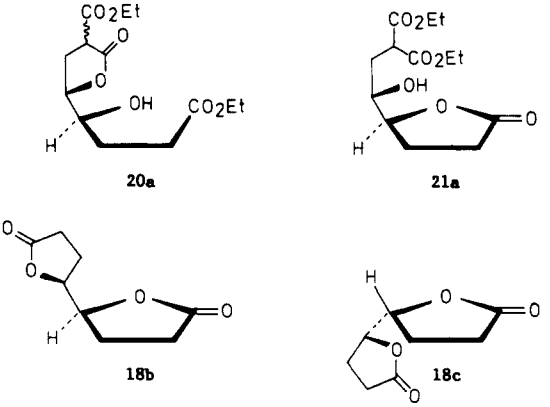


[a] Key: (a) $Na^+{}^-CH(CO_2Et)_2$, PhH, reflux; (b) CF_3CO_2H, CH_2Cl_2; (c) $MgCl_2{\cdot}6H_2O$, CH_3CONMe_2, reflux.

C-3 (22.8 vs 25.15 ppm) and for C-5 (52.1 vs 53.4 ppm). C-4 by contrast appears slightly downfield in **6b** as compared with **6a** (79.6 vs 78.9 ppm). Enantiomeric **6c** was obtained in five stages from commercial D-gulono-1,4-lactone (**7c**) via oxiranylbutenolide **17d** (Scheme III). Hydrolysis of **17d** gave the 2,3-dideoxy derivative **17a**. Complete regioselectivity, with retention of configuration at C-5, was achieved. Compound **17a** completes the series of 2,3-dideoxyhex-2-enone-1,4-lactones.[1a,2]

The pure enantiomeric epoxy butanolides **6a–c** should be versatile chiral intermediates, due to their potential for elaboration at C-6, C-2, and the γ-lactone function. The first of these options was illustrated by the synthesis of the hitherto unknown, enantiomerically pure 4,4′-bis-γ-butyrolactones **18a** and **18c**. A boiling solution of compound **6a** in benzene was treated with diethyl monosodiomalonate for 2 h. Analysis (^{1}H NMR: CH_3 and *H*-4) of the neutralized crude product showed the presence of the monoester **19a(R,S)** and the diesters **20a(R,S)** and/or **21a** (Scheme IV). The ethoxide ions produced during ring closure to the bis-lactone presumably induced ring opening of the original lactone ring to give some **20a**.

The formation of γ-butyrolactones from oxiranes by using dilithiocarboxylates[21] or dialkyl sodiomalonates[20a,22] is well documented. The former reagents lead directly to the γ-lactone and are applied primarily for the synthesis of C-2-substituted γ-lactones. These are frequently precursors to the corresponding butenolides. The second reagents yield α-carbalkoxy-γ-lactones as intermediates. These have to be subsequently decarboxylated. The inexpensive diethyl ester is commonly used when γ-lactones unsubstituted at C-2 or C-3 are required. Ethanolic sodium ethoxide[21a–e] and metallic sodium in benzene[21e] were used most frequently as solvent–base systems. Benzene was preferred in our case because of the probable susceptibility of the parent γ-lactone ring to strongly basic, protic conditions. The minimal differences in polarity between **19a(R,S)**, **20a**, and **21a** precluded their chromatographic separation. Treatment of a solution of the crude reaction product with trifluoroacetic acid (1.5 equiv) overnight at room temperature[23] fortunately resulted in complete lactonization thus affording compound **19a(R,S)** in 70% yield. This thermodynamically controlled equilibrium mixture must have arisen from protonation of the planar enol form. Heating of a solution of the oily product mixture in *N,N*-dimethylacetamide in the presence of $MgCl_2{\cdot}6H_2O$[20a] yielded 78% of the optically pure (*S,S*)-bis-γ-lactone **18a**. Only the racemic form of this double



lactone has been described[24,25] hitherto. The melting point (78–79 °C) of pure **18a** was considerably higher than that reported[25] for the racemic material (55–56 °C). Treatment of the D-erythro epoxy lactone **6b** in the same manner furnished the *meso*-bis-γ-lactone **18b** in 50% yield, presumably via similar intermediates. The corresponding diastereomeric (*R,R*)-bis-γ-lactone **18c** was likewise obtained in 55% yield from epoxy lactone **6c** and has the same melting point and opposite $[\alpha]_D$ value (−82°) as compared with **18a** ($[\alpha]_D$ = +83°). The physical constants of compound **18b** (mp 104–105 °C, $[\alpha]_D$ = 0°) are in agreement with those published previously for this compound. It was obtained via catalytic reduction of *cis*-bifurandione[24] or double lactonization of *cis*-octene-4-dioic acid (or its salts).[25] The formation of compound **18b** from **6b** demonstrated the stereospecificity of this route to the bis-γ-lactones. The optically active bis-γ-lactone **18a** and its meso isomer **18b** feature extremely complex ^{1}H NMR spectra. Only the H-4 (and H-4′) absorptions appear in both isomers isolated at around 4.6 ppm. They are characterized by a five-peak multiplet (width 16.5 Hz) in the threo isomer and by an 11-peak multiplet (width 21 Hz) in the erythro isomer. In the corresponding ^{13}C NMR spectra, composed of only four signals, both C-4 (80.4 vs 80.8 ppm) and C-3 (23.3 vs 24.4 ppm) appear at higher field in meso isomer **18b** than in optically active **18a**. The ^{13}C NMR data obtained for **6a,b** and **18a,b** indicate that the γ-shielding effect exerted by oxygen (at C-5 in **6** or C-4′ in **18**) on C-3 is a spatial effect governed by the dihedral angles between C-3–C-4 and C-5–O-5 or C-4′–O-4′.

Concluding Remarks

Optically pure 3,4-cis-fused γ-lactones, 4-oxiranyl-γ-lactones, and 4,4′-bis-γ-lactones have been obtained by chirality transfer from easily accessible sugar lactones, e.g., L- and D-gulono-1,4-lactones (**7a,c**) and D-mannono-1,4-lactone (**7b**). The versatility of the optically pure 2,6-di-

(21) See, inter alia: (a) Iwai, K.; Kawai, M.; Kosugi, H.; Uda, H. *Chem. Lett.* **1974**, 385. (b) Creger, P. L. *J. Org. Chem.* **1972**, *37*, 1907. (c) Fujita, T.; Watanabe, S.; Suga, K. *Aust. J. Chem.* **1974**, *27*, 2205. (d) Grieco, P. A.; Ang, C.-L. J.; Burke, S. D. *J. Chem. Soc., Chem. Commun.* **1975**, 537. (e) Hanessian, S.; Hodges, P. J.; Murray, P. J.; Sahoo, S. P. *J. Chem. Soc., Chem. Commun.* **1986**, 754.

(22) See, inter alia: (a) Cardellach, J.; Estopa, C.; Font, J.; Moreno-Maños, M.; Ortuño, R. M.; Sanchez-Ferrando, F.; Valle, S.; Vilamajo, L. *Tetrahedron* **1982**, *38*, 2377. (b) Satyamurthy, N.; Berlin, K. D.; Powell, D. R.; van der Helm, D. *Phosphorus Sulfur Relat. Elem.* **1984**, *19*, 137.

(23) Baldwin, J. E.; Adlington, R. M.; Sweeney, J. B. *Tetrahedron Lett.* **1986**, *27*, 5423.

(24) Holmquist, H. E.; Marsh, F. D.; Sauer, J. C.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1959**, *81*, 3681.

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oxabicyclo[3.3.0]octan-3-ones **5a,b**, **10a,b**, and **15a,b** becomes obvious on inspection of their reactive sites: S_N2 inversion of the 5-tosylate, transformation of the lactone ring into a hemiacetal, ring opening of the lactone with reducing agents or amines, and C-2 oxidation to afford 3,6-anhydroascorbic acid derivatives represent some possible future applications. Considering the presence of two chiral centers and the reactivities of the epoxide and γ-lactone functions, the 4-oxiranyl-γ-butyrolactones **6a–c** are real chiral synthons. Their synthetic potential was illustrated by their stereoselective transformation into optically pure 4,4′-bis-γ-lactones **18a,c**. The latter are in principle precursors for optically active polyamides and/or polyurethanes. They could also serve as key intermediates for the preparation of optically active crown ethers and, in combination with the condensation with bis-amines, for the construction of chirally defined, tubular, polyamidic crown ethers. Taking advantage of the double bifunctionality present in **18a,c**, immobilization on a support, for example, through the carboxyl functions, and transformation into a chiral reagent, for example, a boron derivative, could be envisaged.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R 24 B spectrometer (60 MHz) or on a Bruker AC 200 instrument (200 MHz) (Me_4Si internal standard). ^{13}C NMR spectra were recorded on a Bruker AC 200 instrument (50.4 MHz). Optical rotations were determined on an Optical Activity AA-10 polarimeter. Column chromatography was performed on silica gel (Merck, Kieselgel 60, Art 7734) and thin-layer chromatography (TLC) on aluminum sheets precoated with silica gel (Merck, Art. 5554).

2,6-Dibromo-2,6-dideoxy-L-idono-1,4-lactone (4a). L-Gulono-1,4-lactone[1] (**7a**, 44.5 g, 0.25 mol) was dissolved with stirring in HBr in glacial acetic acid (33%, 250 mL, ~1.4 mol of HBr) and kept at 30 °C for 4.5 h. Methanol (625 mL) was then added and the mixture kept overnight at room temperature. The solution was concentrated to ca. 125 mL, diluted with water (500 mL), and extracted with diethyl ether (4 × 250 mL). The dried ($MgSO_4$) extracts were concentrated in vacuo to yield **4a** (68.7 g, 90%) as a pale yellow syrup. Column chromatography (CH_2Cl_2–EtOAc, 3:1) was unsuccessful in removing a byproduct, identified as **5a** (vide infra). ^{1}H NMR (CD_3COCD_3): δ 3.61 (d, J = 6 Hz, 2 H, CH_2), 4.41 (td, J = 6 and 3 Hz, 1 H, H-5), 4.60 (d, J = 4 Hz, 1 H, H-2), 4.2–5.1 (m, 4 H, H-3, H-4, OH-3, OH-5). The crude product was sufficiently pure for transformation into **5a** (vide infra).

3,6-Anhydro-2-bromo-2-deoxy-L-idono-1,4-lactone (5a). a. By Thermolysis of Compound 4a in *tert*-AmOH. Crude compound **4a** (67.5 g, ~0.22 mol) dissolved in *tert*-amyl alcohol (500 mL) was heated to boiling. Volatile material (inter alia, HBr) was removed by continuous distillation (375 mL/h) with replenishment of *tert*-amyl alcohol during 6 h. The reaction mixture was then evaporated to dryness and the residue (~50 g) extracted with boiling water (4 × 125 mL). The cooled combined aqueous solution was then extracted with diethyl ether (4 × 250 mL), and the dried ($MgSO_4$), combined extracts were concentrated in vacuo to afford pure, solid **5a** (31.2 g, 56%, mp 96–98 °C) after trituration with cold diisopropyl ether. Recrystallization from chloroform gave analytically pure material: mp 99–100 °C; $[\alpha]^{20}_D$ −15° (c 1.12, $CHCl_3$). ^{1}H NMR: see Table I. ^{13}C NMR: see Table II. Anal. Calcd for $C_6H_7BrO_4$ (MW 223.04): C, 32.31; H, 3.16. Found: C, 32.1; H, 3.1.

b. By the Reaction of Compound 4a with Ag_2O. An ice-cooled, vigorously stirred solution of crude **4a** (1.216 g, ~4 mmol) in water was treated with Ag_2O (~2 mmol, freshly prepared from $AgNO_3$, 0.68 g, 4 mmol) in water (4 mL) and the mixture stirred at 0 °C for 3 h. Insoluble material was removed by filtration and then washed with diethyl ether (25 mL). The combined filtrate and washing was shaken vigorously and separated, and the aqueous layer was reextracted with more diethyl ether (3 × 15 mL). The combined, dried ($MgSO_4$) ethereal extracts were evaporated in vacuo to yield compound **5a** (0.816 g, 91%, mp 98–99 °C), which was identical with the material obtained by procedure a.

c. From Dibromo Diacetate 3a[2] and Propan-2-ol–HBr. Bicyclic compound **5a** was also obtained by deacetylation of **3a**, followed by in situ dehydrobromination in propan-2-ol of the intermediate **4a** in 54% yield.[2]

3,6-Anhydro-2-bromo-2-deoxy-D-glucono-1,4-lactone (5b). A solution of dibromo lactone **4b**[5] (3.04 g, 10 mmol) in *tert*-amyl alcohol (20 mL) was heated under reflux. Volatile material (inter alia, HBr) was removed by distillation (15 mL/h) with continuous replenishment of the solvent during 60 h. The mixture was then evaporated in vacuo and the residue (2.15 g) purified by column chromatography (CH_2Cl_2–EtOAc, 3:1) to afford white, crystalline **5b** (1.42 g, 64%, mp 98–100 °C) upon trituration with cold diisopropyl ether. Recrystallization form chloroform–diisopropyl ether (1:1) gave analytically pure material: mp 101–103 °C; $[\alpha]^{20}_D$ +7° (c 1.11, $CHCl_3$). ^{1}H NMR and ^{13}C NMR: see Tables I and II, respectively. Anal. Calcd for $C_6H_7BrO_4$ (MW 223.04): C, 32.31; H, 3.16. Found: C, 32.2; H, 3.0.

3,6-Anhydro-2-deoxy-L-*xylo*-hexono-1,4-lactone (10a). Palladized charcoal (10%, 0.500 g) was suspended in a solution of idono derivative **5a** (4.46 g, 0.020 mmol) and Et_3N (2.8 mL, 0.020 mol) in ethyl acetate (100 mL), and the mixture was hydrogenated (2 atm, 4 h). The catalyst was removed by filtration and washed with EtOAc (25 mL), and the combined filtrates and washings were evaporated to dryness under reduced pressure to furnish semisolid material (3.0 g). Filtration of a solution in EtOAc through silica gel (20 g) gave pure **10a** (2.55 g, 89%), mp 82–83 °C, which upon recrystallization from diisopropyl ether–chloroform (1:1) was analytically pure: mp 84–85 °C; $[\alpha]^{20}_D$ +80° (c 1.07, $CHCl_3$). ^{1}H NMR and ^{13}C NMR: see Tables I and II, respectively. Anal. Calcd for $C_6H_8O_4$ (MW 144.13): C, 50.00; H, 5.59. Found: C, 49.8; H, 5.4.

3,6-Anhydro-2-deoxy-D-*arabino*-hexono-1,4-lactone (10b). Catalytic reduction of compound **5b** (1.135 g, 0.005 mol) afforded crude **10b** (0.75 g) (vide supra, preparation of **10a**). Column chromatography (SiO_2, 25 g; EtOAc) gave pure **10b** (0.644 g, 89%) after recrystallization from diisopropyl ether–chloroform (1:1): mp 77–78 °C; $[\alpha]^{20}_D$ +89° (c 1.0, $CHCl_3$). ^{1}H NMR and ^{13}C NMR: see Tables I and II, respectively. Anal. Calcd for $C_6H_8O_4$ (MW 144.13): C, 50.00; H, 5.59. Found: C, 49.9; H, 5.6.

C-2 Debromination of 3,6-Anhydro-2-bromo-2-deoxy-L-idono-1,4-lactone (5a): 3-OR Elimination versus Enolization. a. With $NaHSO_3$. A stirred mixture of the bicyclic lactone **5a** (223 mg, 1.00 mmol) in propan-2-ol–water (7:1, 4 mL) containing $NaHSO_3$ (416 mg, 4.0 mmol) was heated under reflux for 2.5 h. TLC ($CHCl_3$–MeOH, 9:1) then showed the absence of the starting compound (R_f 0.56) and the presence of two more polar compounds A (R_f 0.39) and B (R_f 0.17). The mixture was treated with acetone (10 mL) and the precipitated material removed by filtration. The filtrate was concentrated in vacuo to give a colorless oil (121 mg), which on chromatography ($CHCl_3$–MeOH, 7:1) gave L-*xylo*-hexonolactone **10a** (vide supra, component A, 75 mg, 52%) and its isomer 2,3-dideoxy-L-ascorbic acid (**2a**,[2] component B, 36 mg, 25%) (^{1}H NMR, TLC).

b. With Trifluoroacetic Acid–NaI. Trifluoroacetic acid (~0.4 mL, 0.57 g, 5 mmol) and NaI (0.75 g, 5 mmol) were added to a solution of the bicyclic lactone **5a** (112 mg, 0.50 mmol) in acetone (4 mL). The reaction mixture was heated under reflux for 18 h, whereon volatile material was removed in vacuo. The crude product was shown (^{1}H NMR) to be a mixture of **10a** and **2a** (3:1).

c. By Catalytic Reduction in Water. Catalytic reduction (Pd–C/H_2) of an aqueous solution (10 mL) of **5a** (446 mg, 2 mmol) afforded a 3:1 mixture of **10a** and **14a** (vide infra) as indicated by ^{1}H NMR.

2,3-Dideoxy-L-*threo*-hexono-1,4-lactone (14a). A solution of 2,3-dideoxy-L-ascorbic acid (**2a**, 0.360 g, 2.5 mmol) in EtOAc (20 mL), treated with palladized charcoal (10%, 0.050 g), was reduced quantitatively within 2 h at 2 atm. Removal of the catalyst by filtration and concentration of the filtrate in vacuo gave a colorless, homogeneous syrup (TLC, ^{1}H and ^{13}C NMR, 0.361 g, 99%), which could not be distilled or brought to crystallization: ^{1}H NMR (D_2O) δ 4.8 (m, 3 H, 2 OH, H-4), 3.9–3.6 (m, 3 H, H-5, H-6, H-6′); 2.71 (dd, J = 7 and 9 Hz, 2 H, H-2α and H-2β), 2.43

(dq, J = 13 and 7 Hz, 1 H, H-3α), 2.23 (m, 1 H, H-3β), ^{13}C NMR (D_2O) δ 182.6 (C-1), 82.75 (C-4), 74.0 (C-5), 63.2 (C-6), 29.5 (C-2), 24.4 (C-1).

3,6-Anhydro-2-deoxy-5-*O*-tosyl-L-*xylo*-hexono-1,4-lactone (15a). A solution of compound **10a** (1.44 g, 10.0 mmol) in dry pyridine (16 mL) was treated with *p*-toluenesulfonyl chloride (2.15 g, 11.25 mmol) and the mixture set aside at room temperature for 4 days. The reaction mixture was poured into ice–water (100 mL) and the precipitated material collected by filtration and washed thoroughly with water. The material was dissolved in CH_2Cl_2 (50 mL) and the solution dried ($MgSO_4$) and then concentrated in vacuo to give **15a** (1.76 g, 59%) on recrystallization from methanol: mp 118–119 °C; TLC ($CHCl_3$–EtOAc, 3:1) R_f (**10a**) 0.10, R_f (**15a**) 0.61; $[\alpha]^{20}_D$ +72° (c 1.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (cf. Table I) δ 7.83 (d, J = 8 Hz, 2 H), 7.40 (d, J = 8 Hz, 2 H), 2.48 (s, 3 H, Me); ^{13}C NMR ($CDCl_3$) (cf. Table II) δ 145.7 (C-4′), 132.3 (C-1′), 130.1 (C-3′) 127.7 (C-2′), 21.5 (Me). Anal. Calcd for $C_{13}H_{14}O_6S$ (MW 298.32): C, 52.34; H, 4.73. Found: C, 52.6; H, 4.9.

3,6-Anhydro-2-deoxy-5-*O*-tosyl-D-*arabino*-hexono-1,4-lactone (15b). A solution of compound **10b** (288 mg, 2.0 mmol) in dry pyridine (3 mL) was treated with *p*-toluenesulfonyl chloride (429 mg, 2.25 mmol) at room temperature for 18 h and processed as described for the preparation of **15a** (vide supra) to give compound **15b** (411 mg, 69%, mp 96–98 °C). Analytically pure material was obtained after crystallization from methanol (325 mg, 55%): mp 99–100 °C; TLC ($CHCl_3$–EtOAc, 3:1) R_f (**10b**) 0.06, R_f (**15b**) 0.41; $[\alpha]^{20}_D$ +117° (c 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (cf. Table I) δ 7.84 (d, J = 8 Hz, 2 H), 7.38 (d, J = 8 Hz, 2 H), 2.46 (s, 3 H, Me); ^{13}C NMR ($CDCl_3$) (cf. Table II) δ 145.6 (C-4′), 132.5 (C-1′), 130.0 (C-3′), 127.9 (C-2′), 21.55 (Me). Anal. Calcd for $C_{13}H_{14}O_6S$ (MW 298.32): C, 52.34; H, 4.73. Found: C, 52.5; H, 4.7.

Competitive Tosylation of 10a and 10b. An equimolar mixture of **10a** and **10b** (each 18 mg, 0.125 mmol) in dry pyridine-d_5 (0.5 mL) was treated with *p*-toluenesulfonyl chloride (32 mg, 0.167 mmol), and the course of the reaction was followed via ^{1}H NMR: the signals attributable to H-3, H-4, and H-5 (4.7–5.8 ppm) were separated sufficiently, and integration of signals indicated after 6 h the presence of ~0.050 mmol of **15a** and ~0.100 mmol of **15b**. A second-order rate constant ratio k_{15b}/k_{15a} of 3.25 was deduced.

5,6-Anhydro-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (6a).
a. From Oxiranylbutenolide 2d.[2] A suspension of butenolide **2d** (3.148 g, 0.025 mol) and palladized charcoal (10%, 0.50 g, 0.5 mmol) in EtOAc (200 mL) was hydrogenated at 1.5 atm during 1.5 h. Removal of the catalyst and evaporation of the filtrate gave **6a** (3.16 g, 98%) as an oil, which was sufficiently pure for further transformation. Analytical material was obtained by distillation, bp 101 °C, 0.4 mm: $[\alpha]^{20}_D$ +58° (c 1.97, H_2O), +37° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.57 (td, J = 7.0 and 3.6 Hz, 1 H, H-4), 3.13 (ddd, J = 3.9, 3.5, and 2.9 Hz, 1 H, H-5), 2.83 (dd, J = 4.9 and 3.9 Hz, 1 H, H-6α), 2.80 (dd, J = 4.9 and 2.9 Hz, 1 H, H-6β), 2.75–2.15 (m, 4 H, H-2α,β, H-3α,β); ^{13}C NMR ($CDCl_3$) δ 177.3 (C-1), 78.9 (C-4), 53.4 (C-5), 44.1 (C-6), 28.15 (C-2), 25.15 (C-3).

b. From Bromo Alcohol 13a. (Vide infra.) A stirred solution of the bromo alcohol **13a** (20.9 g, 0.10 mol) in dry tetrahydrofuran (125 mL) was treated with NaH (80%, 3.3 g, 0.11 mol) at 0 °C for 2 h. The reaction mixture was poured into 5 M NH_4Cl (100 mL). After extraction with CH_2Cl_2 (4 × 125 mL), the dried (Na_2SO_4), combined extracts were evaporated in vacuo to give the crude epoxy butanolide **6a** (9.1 g, 71%), which on distillation under reduced pressure gave pure **6a** (6.2 g, 48%), bp 105 °C, 0.8 mm.

c. From Bromo Acetate 16a. (Vide infra.) Treatment of an ice-cold methanolic (20 mL) solution of **16a** (2.51 g, 10 mmol) with a solution of sodium methoxide in methanol (0.5 M, 20 mL) resulted in the rapid consumption of starting material (GLC, ^{1}H NMR) to yield a mixture from which epoxide **6a** was obtained by fractional distillation (bp 102 °C, 5 mm) (0.15 g, 12%).

6-Bromo-2,3,6-trideoxy-L-*threo*-hexono-1,4-lactone (13a). From Bromo Alcohol 2c.[2] A suspension of the unsaturated bromo alcohol **2c** (20.7 g, 0.10 mol) and palladized charcoal (10%, 2.0 g, 0.002 mol) in EtOAc (250 mL) was exhaustively hydrogenated for 3 h at 3 atm. Removal of the catalyst and concentration of the filtrate in vacuo gave compound **13a** (19.9 g, 95%), mp 71–73 °C. Recrystallization from chloroform gave analytically pure material: mp 72–74 °C; $[\alpha]^{20}_D$ +31° (c 1.96, H_2O); ^{1}H NMR ($CDCl_3$) δ 4.73 (td, J = 7.0 and 2.0 Hz, 1 H, H-4), 4.0–3.6 (m, 1 H, H-5), 3.49 (d, J = 6.0 Hz, 1 H, H-6α), 3.48 (d, J = 7.0 Hz, 1 H, H-6β), 3.4 (br s, 1 H, OH), 2.8–2.1 (, 4 H, H-2α,β, H-3α,β).

b. One-Pot Synthesis from 7a. L-Gulono-1,4-lactone[1] (**7a**, 4.45 g, 0.025 mol) was treated with HBr in acetic acid (33%, 25 mL, ~0.14 mol of HBr) at 30 °C for 4 h. Methanol (150 mL) was added and the mixture set aside overnight. Palladized charcoal (10%, 0.55 g) was then added and the mixture exhaustively hydrogenated at 5 atm for 6 h. The catalyst was removed by filtration and the filtrate concentrated in vacuo to ca. 25 mL, diluted with water (75 mL), and extracted with CH_2Cl_2–EtOAc, 1:1 (5 × 50 mL). Concentration of the combined, dried ($MgSO_4$) extracts gave a crude residue (3.53 g) from which on trituration with diethyl ether–diisopropyl ether (2:1, 10 mL) pure compound **13a** (1.2 g, 23%), mp 70–72 °C, was obtained.

5-*O*-Acetyl-6-bromo-2,3,6-trideoxy-L-*threo*-hexono-1,4-lactone (16a). A mixture of butenolide **2b**[2] (24.9 g, 0.10 mol) and palladized charcoal (10%, 2.5 g, 2.5 mmol) in EtOAc (225 mL) was exhaustively hydrogenated at 2 atm for 24 h, whereon removal of the catalyst and concentration of the filtrate gave an oily residue (25.0 g). This was shown (^{1}H NMR) to be composed of **16a** (~95%) and **2b** (5%). Repeat of the reduction (1.25 g of catalyst) afforded pure, oily **16a** after 48 h: ^{1}H NMR ($CDCl_3$) δ 5.07 (td, J = 6.0 and 3.0 Hz, 1 H, H-5), 4.87 (dt, J = 7.0 and 3.0 Hz, 1 H, H-4), 3.51 (d, J = 6 Hz, 2 H, H-6α,β), 2.14 (s, 3 H, Me), 2.7–2.0 (m, 4 H, H-2α,β, H-3α,β).

5,6-Anhydro-2,3-dideoxy-D-*erythro*-hexono-1,4-lactone (6b). Catalytic reduction of compound **2h**[2] (3.15 g, 0.025 mol) in the presence of palladized charcoal as described for **6a** (vide supra, entry a) gave crude **6b** (3.16 g, 98%), which was purified by chromatographic filtration (CH_2Cl_2–EtOAc, 19:1, R_f 0.33) (2.80 g, 87%). An analytical sample of **6b** was obtained by fractional distillation, bp 95 °C (0.2 mm): $[\alpha]^{20}_D$ +14° (c 1.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.57 (td, J = 7.0 and 3.75 Hz, 1 H, H-4), 3.24 (ddd, J = 4.15, 3.75, and 2.6 Hz, 1 H, H-5), 2.89 (dd, J = 4.65 and 4.15 Hz, 1 H, H-6α), 2.67 (dd, J = 4.65 and 2.6 Hz, 1 H, H-6β), 2.6–2.0 (m, 4 H, H-2α,β, H-3α,β); ^{13}C NMR ($CDCl_3$) δ 177.2 (C-1), 79.6 (C-4), 52.1 (C-5), 44.7 (C-6), 28.45 (C-2), 22.8 (C-3).

3,5-Di-*O*-acetyl-2,6-dibromo-2,6-dideoxy-D-idono-1,4-lactone (3). The title compound was prepared from D-gulono-1,4-lactone (**7c**) as described previously for its optical antipode **3a**[2] in 87% yield: mp 116–118 °C; $[\alpha]^{20}_D$ −45° (c 0.958 EtOAc) [lit.[2] $[\alpha]^{20}_D$ (**3a**) +46° (c 1.95, EtOAc)].

6-Bromo-2,3,6-trideoxy-D-*threo*-hex-2-enono-1,4-lactone (17c). The title compound was prepared in two steps (NaHSO_3–Na_2SO_3; MeOH–HCl) from **3c** in 85% yield, via the procedure described for the synthesis of **2c**.[2] The corresponding, intermediate 5-acetate (**17b**) was used without purification. Solid **17c** has mp 104–106 °C; $[\alpha]^{20}_D$ +108° (c 1.05, H_2O) [lit.[2] mp (**2c**) 105–106 °C; $[\alpha]^{20}_D$ −107° (H_2O)]. Anal. Cacld for $C_6H_7BrO_3$ (MW 207.03): C, 34.81; H, 3.41. Found: C, 34.8; H, 3.8.

5,6-Anhydro-2,3-dideoxy-D-*threo*-hex-2-enono-1,4-lactone (17d). The unsaturated epoxide **17d** was obtained from the bromo alcohol **17c** in the manner described for **2d**,[2] at a 0.1-mol scale in 84% yield: mp 48–49 °C (diethyl ether); $[\alpha]^{20}_D$ +120° (c 0.963, $CHCl_3$), $[\alpha]^{20}_D$ +88° (c 1.05, H_2O). Anal. Calcd for $C_6H_6O_3$ (MW 126.11): C, 57.14; H, 4.80. Found: C, 57.4; H, 5.0.

2,3-Dideoxy-D-*threo*-hex-2-enono-1,4-lactone (17a). Compound **17a** was obtained in 97% yield on hydrolysis of **17d** in the manner described for its enantiomer **2a**:[2] mp 86–87 °C; $[\alpha]^{20}_D$ +118° (c 1.00, H_2O); ^{13}C NMR (D_2O) δ 173.8 (C-1), 159.4 (C-3), 124.1 (C-2), 87.5 (C-4), 73.0 (C-5), 65.0 (C-6). Anal. Calcd for $C_6H_8O_4$ (MW 144.13): C, 50.00; H, 5.59. Found: C, 50.2; H, 5.8.

5,6-Anhydro-2,3-dideoxy-D-*threo*-hexono-1,4-lactone (6c). Crystalline **17d** was reduced quantitatively to oily **6c**, in the manner described for its enantiomer **6a** (vide supra, entry a): $[\alpha]^{20}_D$ −57 ° (c 1.5, H_2O).

(2*S*,2′*S*)-4(*R*,*S*)-Carbethoxytetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione [19a(R,S)]. A boiling stirred solution of diethyl sodiomalonate in benzene (6%, 66.0 g, 0.022 mol) was treated dropwise with the epoxy butanolide **6a** (2.56 g, 0.020 mol), also dissolved in benzene (20 mL). The mixture was further heated under reflux for 2 h, cooled, treated with trifluoroacetic acid (3 mL, ~2 equiv), and evaporated under reduced pressure. The

resultant pasty residue was dissolved in CH_2Cl_2 (12.5 mL) containing CF_3CO_2H (3 mL, ~2 equiv) and the solution set aside at room temperature overnight. After concentration in vacuo and column chromatography (CH_2Cl_2–EtOAc, 1:1), diastereomeric bis-lactone **19a(R,S)** (3.42 g, 71%) was obtained as an oil: TLC ($CHCl_3$–EtOAc, 1:1) R_f 0.26; ^1H NMR ($CDCl_3$) δ 4.76 (ddd, J = 8.2, 5.4, and 2.0 Hz, H-4′$_A$), 4.68–4.52 (m, H-4′$_B$, H-2$_A$, H-4$_B$), 4.27 (q, J = 7.1 Hz, CH_2 ester$_B$), 4.25 (4, J = 7.1 Hz, CH_2 ester$_A$), 3.78 (dd, J = 9.8 and 7.1 Hz, 1 H, H-2′$_A$), 3.72 (t, J = 10.1 Hz, H-2′$_B$), 2.9–2.1 (m, H-2α,β, H-3α,β, H-3′α,β_{A+B}), 1.29 (t, J = 7.1 Hz, CH_3 ester$_{A+B}$); ^{13}C NMR ($CDCl_3$) δ 177.1 (C-1), 172.2 and 171.8 (C-1′), 168.45 and 167.9 (CO ester), 80.6, 79.9, 79.8, and 79.7 (C-4, C-4′), 63.1 (CH_2 ester), 47.2 and 46.8 (C-2′), 29.05, 28.6, and 28.2 (C-2, C-3′), 24.4 (C-3), 14.8 (CH_3 ester).

(*S,S*)-Tetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione (18a). The foregoing product **19a(R,S)** (2.42 g, 0,010 mol), dissolved in *N,N*-dimethylacetamide (30 mL), containing $MgCl_2 \cdot 6H_2O$ (10.15 g, 0.050 mol) and water (3 drops), was heated under reflux (137 °C) with stirring for 7 h. Most of the solvent was distilled in vacuo (80 °C, 0.5 mm), and the residue was treated with water (40 mL). The aqueous phase was exhaustively extracted with $CHCl_3$–EtOAc (1:2, 4 × 75 mL), and the combined extracts were evaporated in vacuo. Column chromatography (EtOAc) of the residue yielded pure, crystalline bis-γ-lactone **18a** (1.33 g, 78%): TLC (EtOAc) R_f 0.33. Analytical material was obtained by recrystallization from ethyl acetate–diisopropyl ether, 2:1: mp 78–79 °C; $[\alpha]^{20}_D$ +82° (*c* 1.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.60 (5-peak multiplet, width 16.5 Hz, 2 H, H-4), 2.8–2.5 (m, 4 H, H-2), 2.5–2.15 (m, 4 H, H-3); ^{13}C NMR ($CDCl_3$) δ 177.2 (C-1), 80.8 (C-4), 28.6 (C-2), 24.4 (C-3). Anal. Calcd for $C_8H_{10}O_4$ (MW 170.16): C, 56.47; H, 5.92. Found: C, 56.4; H, 5.8.

(2*R*,2′*S*)-4(*R,S*)-Carbethoxytetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione [19b(R,S)]. Diastereomers **19b(R,S)** were prepared from epoxide **6b** (0.701 g, 0.005 mol) as described for **19a(R,S)** (vide supra) to afford, after chromatography ($CHCl_3$–EtOAc, 1:1, R_f 0.33), a solid 1:1 mixture of diastereomers (0.813 g, 67%): ^1H NMR ($CDCl_3$) δ 4.8–4.6 (m, H-4$_{A,B}$, H-4′$_{A,B}$), 4.28 (q, J = 7.1 Hz, CH_2 ester$_B$), 4.26 (q, J = 7.1 Hz, CH_2 ester$_A$) 3.73 (t, J = 9.9 Hz, H-2′$_B$), 3.7 (dd, J = 9.8 and 5.9 Hz, H-2′$_A$), 2.8–2.0 (m, H-2α,β, H-3α,β, H-3′α,$\beta_{A,B}$), 1.33 (t, J = 7.1 Hz, CH_3 ester$_B$), 1.31 (t, J = 7.1 Hz, CH_3 ester$_A$); ^{13}C NMR ($CDCl_3$) δ 177.0 and 176.85 (C-1), 171.9 (C-1′), 168.2 (CO ester), 80.3, 79.9, and 79.2 (C-4, C-4′), 63.2 (CH_2 ester), 47.1 and 47.0 (C-2′), 28.6, 28.5, 28.4, and 27.7 (C-2 and C-3′), 24.0 and 23.5 (C-3), 14.8 (CH_3 ester).

***meso*-Tetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione (18b).** The diastereomer mixture **19b(R,S)** (0.605 g, 0.0025 mol) was decarboxylated as described for **19a(R,S)** (vide supra). Column chromatography with a gradient elution (CH_2Cl_2–EtOAc, 1:1, to EtOAc) afforded pure **18b** (0.315 g, 75%): TLC ($CHCl_3$–EtOAc, 1:1) R_f 0.39. Recrystallization from ethyl acetate–diisopropyl ether gave analytically pure material: mp 104–105 °C (lit.[25] mp 105 °C); $[\alpha]^{20}_D$ 0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.58 (11-peak multiplet, width 21 Hz, 2 H, H-4), 2.7–2.55 (m, 2 H, H-2), 2.55–2.3 (m, 2 H, H-3α), 2.2–2.0 (m, 2 H, H-3β); ^{13}C NMR ($CDCl_3$) δ 176.9 (C-1), 80.4 (C-4), 28.4 (C-2), 23.3 (C-3).

(2*R*,2′*R*)-4(*R,S*)-Carbethoxytetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione [19c(R,S)]. The epoxy butanolide **6c** (2.56 g, 0.020 mol) was converted into the title compounds in the manner described for the preparation of **19a(R,S)**. The product was a diastereomeric mixture (1:1), 3.24 g (70%), featuring the same R_f value and ^1H and ^{13}C NMR spectra as described for **19a(R,S)**.

(*R,R*′)-Tetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione (18c). Decarboxylation of the diastereomers **19c(R,S)** (2.42 g, 0.010 mol) by the procedure described for the preparation of enantiomer **18a** afforded white, crystalline compound **18c** (1.23 g, 73%): TLC (EtOAc) R_f 0.34; mp 78–79 °C; $[\alpha]^{20}_D$ −81° (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_8H_{10}O_4$ (MW 170.16): C, 56.47; H, 5.92. Found: C, 56.3; H, 6.0.

Cleavage of 2-Quinolinylmethyl Ethers with Copper Salts: Potential Use as a Protecting Group for Alcohols

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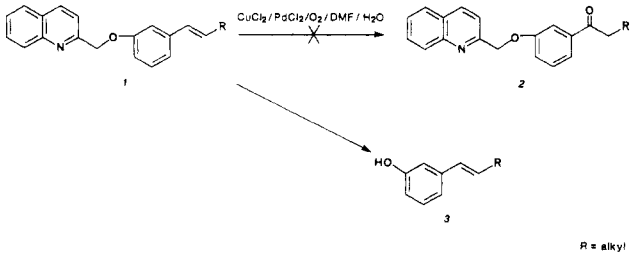
A variety of 2-quinolinylmethyl ethers were efficiently cleaved by $CuCl_2$ in DMF/H_2O to regenerate the corresponding alcohols. The same cleavage also takes place with the 4-regioisomer. On the other hand, the 2- and 4-pyridinylmethyl analogues were found to be stable under these reaction conditions. A mechanistic scheme for this cleavage is proposed.

In the last decades, the advent of many protecting groups[1] for alcohols have given the synthetic organic chemists important tools in the elaboration of complex molecules. Among these protecting groups, the benzyl group has found much use since it is easily introduced and can be removed under various conditions.[1] Surprisingly, there are only a few reports on the use of the pyridinylmethyl group[2,3] and none to our knowledge on the quinolinylmethyl group, although they are direct analogues of the benzyl group. Both pyridinylmethyl and quinolinylmethyl ethers, like benzyl ethers, can be prepared through the Williamson synthesis.[2,3] The methods published on the deprotection of pyridinylmethyl ethers involve electrolysis[2,3] or hydrogenolysis under acidic conditions.[2]

Scheme I



As part of our ongoing LTD_4 antagonists drug program, we became interested in the synthesis of ketones having the general structure **2** (Scheme I). It was envisaged that these ketones could be derived from the available styrenes

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(3) Wieditz, S.; Schafer, H. J. *Acta Chem. Scand.* **1983**, *6*, 475–483.

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