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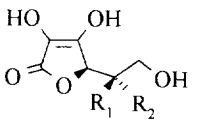
Organoalane-mediated Isomerization of Ascorbic and Isoascorbic Acid Derivatives

Josef Schachtner and Hans-Dietrich Stachel*

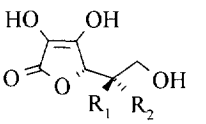
Institut für Pharmazie und Lebensmittelchemie der Universität München,
Sophienstraße 10, D-80333 München, Germany

Abstract: Derivatives of L-ascorbic acid **2a**, **10a/11a** and D-isoascorbic acid **2b**, **10b/11b**, when treated with triisobutylaluminium, partly epimerize to give the corresponding derivatives of L-isoascorbic acid ***ent*-2b**, ***ent*-10b** or D-ascorbic acid ***ent*-2a**, ***ent*-10a**, ***ent*-11a**, respectively. Complete removal of the protecting groups is effected by hydrogenolysis of the benzylidene acetals ***ent*-10** and ***ent*-11a**. This reaction leads to D-ascorbic acid ***ent*-1a** or L-isoascorbic acid ***ent*-1b**, respectively. Furthermore, the four acetonides **2** were converted by ozonolysis, transesterification and finally catalytic hydrogenation to the threonic and erythronic acid ketals **9**.

Over the past three decades L-ascorbic acid (L-*xylo*-ascorbic acid) **1a** and D-isoascorbic acid (D-*arabo*-ascorbic acid) **1b** have emerged as versatile constituents of nature's chiral pool[1] by providing simple and inexpensive access to various highly functionalized synthons. The commercially unavailable enantiomers ***ent*-1a** and ***ent*-1b**, respectively, are accessible *via* enzymatic reactions or C-4 epimerization with bases.[2] Our previous efforts to modify the lactone moiety incorporated in L-ascorbic acid were directed towards the *de novo* synthesis of its thia, aza and carba analogues[3], with the inherent disadvantage that we obtained only racemic ascorbic and isoascorbic acid heterologues. We recently envisaged a direct approach to the corresponding enantiomerically pure lactams and thiolactones utilizing a ring-opening recyclization sequence.



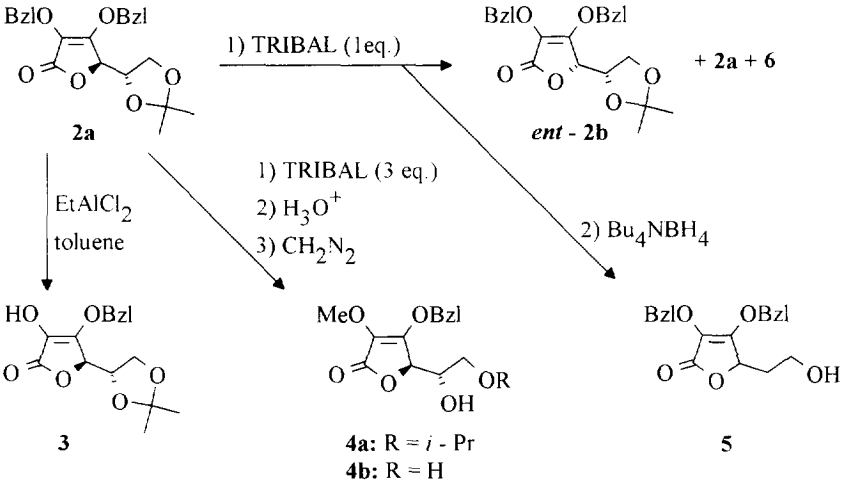
1a: R_1 = H, R_2 = OH
1b: R_1 = OH, R_2 = H



***ent* - 1a:** R_1 = OH, R_2 = H
***ent* - 1b:** R_1 = H, R_2 = OH

In order to evaluate this concept we conducted experiments with the dibenzylated L-ascorbic acid acetonide **2a**[4] and the corresponding D-isoascorbic acid derivative **2b**.[5] After heating a toluene solution of **2a** with

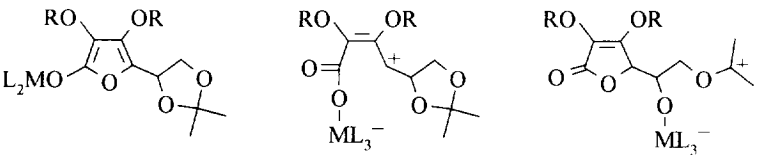
diethylaluminium *N*-methoxy-*N*-methylamide to 100°C over the course of three days, we expected a ring-opening according to the findings of *Weinreb*[6], however, to our surprise we obtained a mixture of **2a** and an isomer. The ^{1}H NMR, IR and MS spectra of the new compound resembled closely those of educt **2a**, indicating that the lactone moiety and the protecting groups remained intact. By comparison of these data with the corresponding set of spectra of the known D-isoascorbic acid derivative **2b**[5] and its specific rotation, the isomerization product was identified as ***ent*-2b**. Hence the reagent has caused in part stereoinversion at C-4 (scheme 1).



Scheme 1

The same isomerization occurred upon treatment of **2a** with dimethylaluminium benzylamide[7], dimethylaluminium *tert*-butylthiolate[8] and commercially available organoalanes such as trimethyl-, triethyl-, triisopropyl- and trioctylaluminium, albeit with different yields and reaction times. The use of triisobutylaluminium ("TRIBAL") in equimolar amounts gave the best results in terms of yield and cleanliness. This reaction gave rise to a mixture of the C-4 epimers, predominantly consisting of the educt **2a** and ***ent*-2b** in a ratio of 2:1, according to HPLC analysis.

There are only few literature reports concerning cleavage reactions of lactones with organoalanes[6,9], producing either alkylated or reduced products. However, base-promoted C-4 epimerization of ascorbic and isoascorbic acid, apparently *via* a mesomeric trianion, has long been known.[2b] If we assume a sufficient acidity at C-4, amphiphilic TRIBAL[10] might similarly deprotonate **2a** during the course of the reaction forming intermediate **A** (scheme 2) with loss of isobutane or isobutene and hydrogen. In this case, hydrolysis of the reaction mixture with deuterated sulfuric acid should cause deuterium incorporation into both the starting material **2a** and the epimer ***ent*-2b**. But actually no such thing was observed.



A **B** **C**

Scheme 2

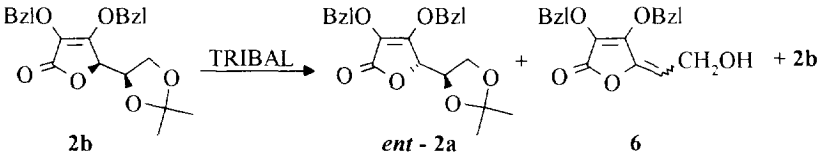
So intermediate **A** may account for the formation of the allylic alcohols **6**, but for the epimerization of **2a** we have to consider the possibility that the initially formed complex between the alane and either of the lactone oxygens of **2a** is in equilibrium with zwitterion **B** (scheme 2) as a prerequisite of the thermodynamically controlled stereoinversion at C-4. A competing reaction may be an attack of the oxygenophilic alane upon the neighbouring ketal oxygen, possibly forming an equilibrium with zwitterionic **C** (scheme 2), which, however, does not influence the second stereogenic center. The proposed pathway makes allowance for the fact that equivalent amounts of organoalane are required for the isomerization of **2a**. However, various attempts to trap the hypothetical intermediates with suitable electrophiles and nucleophiles were unsuccessful. So there is no definite proof that the actual intermediate is **B**. The *in situ*-reduction of the **2a**/organoalane mixture with tetrabutylammonium borohydride led to success giving rise to the known 5-desoxy ascorbic acid derivative **5**, which was, however, racemic.[11] We found that **2a** is also reduced with borohydride to a small extent; however, the hydrogenation is greatly facilitated by the presence of the organoalane.

More complex is the reaction of **2a** with three equivalents of TRIBAL. Methylation of the crude reaction mixture with diazomethane gave rise to lactone **4a** as the main product. The structure was elucidated by comparison of its ^{1}H NMR, IR and MS data with those of O^3-benzyl-O^2-methyl ascorbic acid **4b**, which in turn was obtained by sequential etherification of vitamin C with phenyldiazomethane and diazomethane. Hence in the course of this reaction of **2a** a reductive cleavage of the ketal has taken place[12], with zwitterion **C** as a likely intermediate. The reducing agent apparently is DIBALH, originated by the known TRIBAL/DIBALH interconversion.[13] The hydroalumination is accompanied by monodebenzylation at O-2. The benzyl group is transferred to the solvent toluene in a *Friedel-Crafts*-like reaction. Consequently a mixture of the isomeric phenyl(tolyl)methanes[14] was easily detected by GC analysis.

Reaction of **2a** with the significantly stronger Lewis acid ethylaluminium dichloride resulted solely in regioselective debenzylation[15] to give the enol **3**[16] and a mixture of the above mentioned isomeric phenyl(tolyl)methanes. Due to its participation in the reaction, the use of toluene as a solvent is essential.

Exposure of the corresponding isoascorbic acid derivative **2b** to equimolar amounts of TRIBAL gave rise to a mixture of educt and the isomeric lactone ***ent*-2a** in a ratio of 1:2, according to HPLC analysis (scheme 3). The structure of the new compound was determined by comparison of its spectral and chiroptical data with those of its enantiomer **2a**. In addition to ***ent*-2a**, an inseparable mixture of the *E*- and *Z*-allylic alcohols **6**[17] was

isolated, originating from either lactone by deketalization, presumably *via* vinylogous β-elimination from metallated dienolate **A** or *via* a dehydration-hydrolysis sequence from zwitterion **C** (scheme 2). In summary, the organoalane-induced epimerization of both the diastereomeric lactones **2a** and **2b** leads to equilibria which favour the formation of *xylo*-configured ascorbic acid derivatives.



2b ***ent*** **- 2a** **6**

Scheme 3

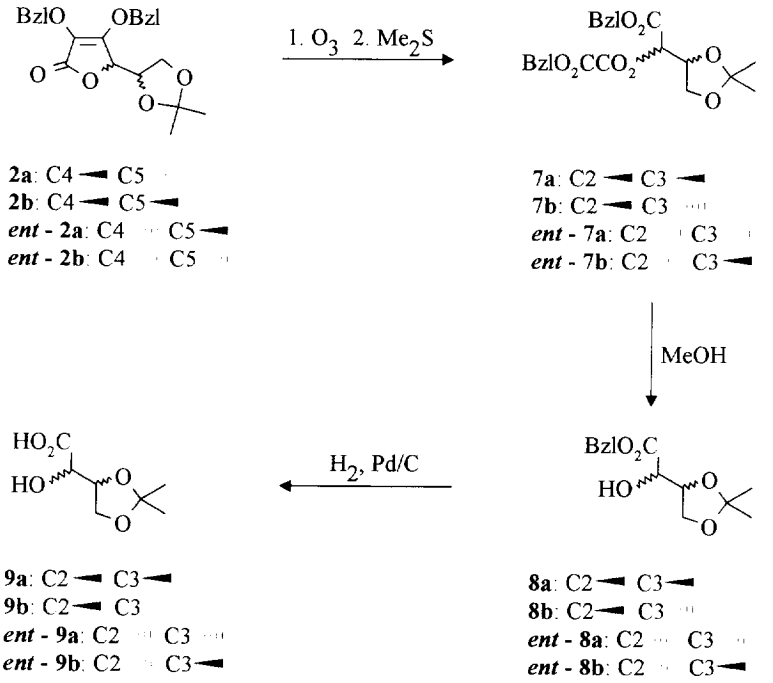
In order to provide additional proof for the assigned structures, we subjected all four lactones **2a**, **2b**, ***ent*-2a** and ***ent*-2b** to ozonolysis to produce the fully protected threonates and erythronates 7 in good yield. The benzoxalyl residue of all compounds 7 was smoothly removed by regioselective partial transesterification in boiling methanol to give the α-hydroxy esters **8**. Finally, catalytic debenzylation with Pd/C produced the hitherto unknown threonic and erythronic acid ketals **9** with an overall yield exceeding 50 % for the acids **9** (scheme 4). This reaction sequence favourably contrasts with the deprotection procedure employing the ozonization product of ascorbic acid dimethyl ether which is reported to be troublesome.[18, 19]

We now surmised that the reaction of TRIBAL with the sterically more demanding ascorbic acid benzylidene acetals **10** and **11** would lead to an enhancement of the observed stereochemical differentiation and thus provide easy access to direct precursors of hitherto scarcely known D-ascorbic acid ***ent*-1a** and L-isoascorbic acid ***ent*-1b**.

The preparation of compounds **10a**/**11a** was accomplished by benzylidenation of L-ascorbic acid dibenzyl ether[4] giving rise to a mixture of the diastereomers in a ratio of 55:45 as evidenced by HPLC analysis of the crude reaction mixture. The minor constituent was identified as **11a** by NOE experiments, indicating the *cis*-dipseudoaxial position of the two methine protons of the dioxolane ring. Isovitamin C **1b** was first acetalized[20] and then dibenzylated in a one-pot procedure yielding the diastereomeric endiol ethers **10b** and **11b** in a ratio of 53:47 and an overall yield of 46%. Again the absolute stereochemistry was established by NOE experiments with **11b**. Another proof of the structural assignment is provided by the occurrence of a significant diamagnetic shift of the benzylidene proton resonances of the H-2/H-4 *cis*-configured dioxolanes **11a** and **11b** in comparison with their diastereomers **10a** and **10b**.[21]

Treatment of pure **10a** with equimolecular amounts of TRIBAL resulted in the formation of a mixture of **10a**, its diastereomer **11a** and another isomer, later shown to be ***ent*-10b**, in a ratio of 55:26:19, accompanied by minor amounts of a mixture of the allylic alcohols **6** (scheme 5). Precisely the same product distribution was obtained by action of TRIBAL upon the epimeric acetal **11a**. Thus the two vitamin C-derived dioxolanes **10a** and **11a** could conveniently be employed here as a mixture. TRIBAL causes the stereoisomerization in both the

2-phenyldioxolane moiety[22] and the lactone unit consistent with the supposed zwitterionic intermediates (scheme 2). In comparison with the vitamin C-derived acetonide **2a**, the ratio of *xylo- vs. arabo*-configured products was markedly enhanced to roughly 4:1.



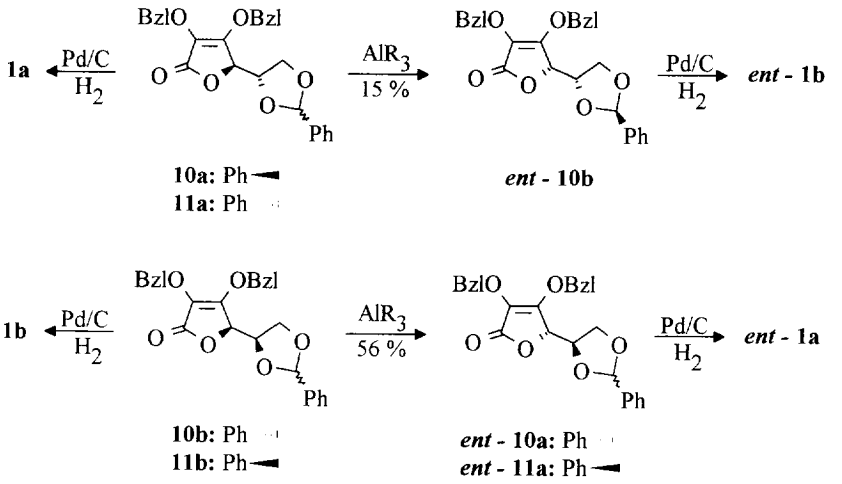
2a: C4 ◄ C5
2b: C4 ◄ C5 ◄
***ent* - 2a**: C4 C5 ◄
***ent* - 2b**: C4 C5

7a: C2 ◄ C3 ◄
7b: C2 ◄ C3
***ent* - 7a**: C2 C3
***ent* - 7b**: C2 C3 ◄

9a: C2 ◄ C3 ◄
9b: C2 ◄ C3
***ent* - 9a**: C2 C3
***ent* - 9b**: C2 C3 ◄

8a: C2 ◄ C3 ◄
8b: C2 ◄ C3
***ent* - 8a**: C2 C3
***ent* - 8b**: C2 C3 ◄

Scheme 4



10a: Ph ◄
11a: Ph

***ent* - 10b**

10b: Ph
11b: Ph ◄

***ent* - 10a**: Ph
***ent* - 11a**: Ph ◄

Scheme 5

The isomerization of both isovitamin C-derived acetals **10b** or **11b** proceeded analogously giving rise to a mixture of **10b**, ***ent*-10a** and ***ent*-11a** in a ratio of 28:53:19, accompanied by minor amounts of the allylic alcohols **6**. Once again the separation of the epimeric acetals **10b/11b** proved unnecessary. Compared to the isovitamin C-derived acetonide **2b** the ratio of *xylo- vs. arabo*-configured products was raised to roughly 3:1. Hence this reaction represents a novel access to the D-ascorbic acid skeleton.

For the purpose of final structural proof, the benzylidene acetals **10a**, **11a** and **10b** were hydrogenated in a one-step procedure to give vitamin C **1a** or isovitamin C **1b**, i.e. the unchanged corresponding starting materials. Analogously, the hydrogenolytic deprotection of the diastereomeric endiol ethers ***ent*-10a**/***ent*-11a** and ***ent*-10b** gave rise to D-ascorbic acid ***ent*-1a** or L-isoascorbic acid ***ent*-1b**, respectively. Thus, by this three-step reaction sequence, D-ascorbic acid ***ent*-1a** is accessible from D-isoascorbic acid **1b** in an overall yield of almost 25%. This equals the well-known base-promoted C-4 epimerization of D-isoascorbic acid in yield but certainly not in simplicity. However, due to the favorable *xylo/arabo*-ratio, the organoalane-mediated isomerization may prove beneficial in direct syntheses of D-ascorbic acid derivatives.

Experimental Section

General Methods. Melting points were determined using a Gallenkamp Melting Point apparatus and are uncorrected. Flash chromatography was performed using silica gel (230 - 400 mesh) from Merck. ^{1}H NMR spectra were recorded at 400 MHz using Me_4Si as internal standard on a JEOL GSX 400. Mass spectra were obtained with a Hewlett Packard 5989A Mass Spectrometer employing both EI and CI mode. GC analysis was performed on a Hewlett Packard Series II 5890 Gas Chromatograph. Infrared spectra were measured as KBr plates for solids and neat with oils using a FT-IR-Spectrometer PARAGON 1000 (Perkin-Elmer). UV analysis was performed in methanolic solutions on Uvikon 810 Anakomp 220. HPLC analysis was made employing Merck-Hitachi L-6000A/L-4000A and LiChrospher® 100 DIOL, 10 µm (Merck). Optical rotations were determined on a Polarimeter 241 (Perkin-Elmer). Microanalyses were carried out applying an Analysator CHN-O-Rapid from Heraeus. Toluene, ethyl acetate and dichloromethane were distilled from CaH_2, methanol from magnesium turnings under N_2. THF was distilled from sodium benzophenone ketyl under N_2 immediately prior to use. All reactions were run with flame-dried glassware.

General Procedure for TRIBAL-induced isomerization reactions:

TRIBAL (*1M* in toluene, 10.0 ml, 10 mmol) is added under N_2 *via syringe* to a solution of dibenzylated ascorbic acid acetonide or benzylidene acetal (10 mmol) in dry toluene (20 ml). The mixture is warmed to 100

°C for three days and, after cooling to r.t., quenched by addition of *2N* - HCl (20 ml). After extraction with CH_2Cl_2 (3 x 20 ml) the organic layer is dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue is purified by flash chromatography using hexane/ethyl acetate mixtures.

O^2,O^3-Dibenzyl-O^5,O^6-(1-methylethylidene)-D-ascorbic acid *ent*-2a.

Reaction of **2b** (396 mg, 1 mmol) with TRIBAL (*1M* in toluene, 1.0 ml, 1 mmol) according to the *General Procedure* gives 200 mg (50 %) ***ent*-2a** besides 106 mg (27 %) recovered starting material **2b** and 38 mg (11 %) allylic alcohols **6**. Diastereomeric ratio (***ent*-2a** : **2b** = 65 : 35). R_f 0.21 (hexane/ethyl acetate, 4:1). Colourless crystals, mp 127 °C (diisopropyl ether/ethyl acetate). $[\alpha]^{20}_D$ - 43.0 (*c* 1.01, $CHCl_3$); Anal. Calcd for $C_{23}H_{24}O_6$ (396.44): C, 69.68; H, 6.10. Found: C, 69.78; H, 5.91. MS: 396 [M$^+$].

O^2,O^3-Dibenzyl-O^5,O^6-(1-methylethylidene)-L-isoascorbic acid *ent*-2b.

Reaction of **2a** (396 mg, 1 mmol) with TRIBAL (*1M* in toluene, 1.0 ml, 1 mmol) according to the *General Procedure* gives 107 mg (27 %) ***ent*-2b** along with 198 mg (50 %) recovered **2a** and 37 mg (11 %) allylic alcohols **6**.. Diastereomeric ratio (***ent*-2b** : **2a** = 35 : 65). R_f 0.30 (hexane/ethyl acetate, 4:1). Colourless crystals, mp 83 °C (hexane/diisopropyl ether). $[\alpha]^{20}_D$ - 18.4 (*c* 1.03, $CHCl_3$); Anal. Calcd for $C_{23}H_{24}O_6$ (396.44): C, 69.68; H, 6.10. Found: C, 69.49; H, 6.32. MS: 396 [M$^+$].

O^3-Benzyl-O^5,O^6-(1-methylethylidene)-L-ascorbic acid 3.

$EtAlCl_2$ (*1.8 M* in toluene, 0.6 ml, 1.08 mmol) is added dropwise under N_2 *via syringe* to a solution of **2a** (396 mg, 1 mmol) in dry toluene (10 ml). After stirring for 2 h at r.t. the mixture is acidified by addition of *2N* - HCl (10 ml) and extracted with ethyl acetate (3 x 15 ml). The combined organic layers are dried (Na_2SO_4), filtered and evaporated to dryness. The resulting residue is purified by flash chromatography. R_f 0.31 (hexane/ethyl acetate, 3:2), colourless crystals, mp 116 °C (lit.[16]: 105 - 106 °C), greenish ferric chloride test, yield 184 mg (60 %). $[\alpha]^{20}_D$ + 20.0 (*c* 1.02, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 7.41 - 7.36 (m, 5 H), 5.9 - 5.7 (s. br., 1 H, OH), 5.53 (d, 1 H, *J* = 12.0 Hz), 5.48 (d, 1 H, *J* = 12.0 Hz), 4.57 (d, 1 H, *J* = 3.8 Hz), 4.26 (m, 1 H), 4.10 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 8.5 Hz), 4.02 (dd, 1 H, J_1 = 6.4 Hz, J_2 = 8.5 Hz), 1.39 (s, 3 H), 1.36 (s, 3 H). IR ν 3329, 1758, 1699 cm^{-1}, λ_{max}(lg ε) = 246 nm (4.109). Anal. Calcd for $C_{16}H_{18}O_6$ (306.31): C, 62.74; H, 5.92. Found: C, 62.51; H, 6.17. MS 306 [M$^+$]

O^3-Benzyl-O^2-methyl-O^6-isopropyl-L-ascorbic acid 4a.

A solution of **2a** (396 mg, 1 mmol) in dry toluene (10 ml) is charged with TRIBAL (*1M* in toluene, 3.0 ml, 3 mmol) and heated to 100 °C for three days. The cooled mixture is acidified with *2N* - HCl (30 ml) and extracted with CH_2Cl_2 (3 x 15 ml). The dried (Na_2SO_4) organic extracts are evaporated to dryness, redissolved in methanol (30 ml) and chilled in an ice-water bath. A slight excess of ethereal diazomethane solution is added dropwise. After completion of the reaction the volatiles are removed *in vacuo* and the resulting residue is purified by flash chromatography to furnish **4a** (84 mg, 26 %). R_f 0.30 (hexane/ethyl acetate, 3 : 2), colourless crystals, mp 70 °C (diisopropyl ether). $[\alpha]^{20}_D$ + 38.4 (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38 - 7.34 (m, 5 H),

5.12 (s, 2 H), 4.69 (d, 1 H, J = 2.1 Hz), 3.95 (m, 1 H), 3.91 (s, 3 H), 3.56 (m, 2 H), 3.54 (m, 1 H), 2.02 (d, 1 H, OH, J = 7.3 Hz), 1.14 (d, 6 H, J = 6.0 Hz); IR ν 3430, 1734, 1669 cm^{-1}; λ_{max}(lg ε) 234 nm (3.979); Anal. Calcd for $C_{17}H_{22}O_6$ (322.35): C, 63.34; H, 6.88. Found: C, 63.08; H, 6.83. MS: 322 [M^+].

O^3-Benzyl-O^2-methyl-L-ascorbic acid 4b.

An ethereal solution of phenyldiazomethane is added dropwise to an ice-cooled solution of L-ascorbic acid (1.76 g, 10 mmol) in MeOH (100 ml) until TLC analysis (R_f 0.5, ethyl acetate, blue ferric chloride test) indicates complete consumption of the starting material. The mixture is concentrated to a volume of about 100 ml and recooled in an ice-water bath. A slight excess of ethereal diazomethane solution is added slowly through a dropping funnel. After gas evolution has ceased the volatiles are removed *in vacuo* and the resulting residue is purified by flash chromatography to give **4b** (1.20 g, 43 %). R_f 0.25 (ethyl acetate/hexane, 2 : 1); viscous oil. $[\alpha]^{20}_D$ + 26.5 (*c* 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37 - 7.32 (m, 5 H), 5.45 (d, 1 H, J = 12.0 Hz), 5.42 (d, 1 H, J = 12.0 Hz), 4.68 (d, 1 H, J = 2.1 Hz), 3.95 (m, 1 H), 3.75 (m, 2 H), 3.70 (s, 3 H), 3.38 (s, 1 H, br., OH), 3.12 (s, 1 H, br., OH); IR ν 3416, 1760, 1674 cm^{-1}; UV λ_{max}(lg ε) 234 nm (4.081); Anal. Calcd for $C_{14}H_{16}O_6$ (280.27): C, 60.00; H, 5.75. Found: C, 59.76; H, 5.99; MS: 280 [M^+].

DL-O^2,O^3-Dibenzyl-5-desoxyascorbic acid 5.

A solution of **2a** (444 mg, 1 mmol) in toluene (10 ml) is charged under N_2 with TRIBAL according to the *General Procedure* given above. After cooling to r.t. tetrabutylammonium borohydride (500 mg, 2 mmol) is added in one portion and the solution heated to 60 °C for 3 h. The chilled mixture is hydrolyzed by addition of *2N* - H_2SO_4 (10 ml) and extracted with CH_2Cl_2 (3 x 15 ml). The dried organic layer is evaporated and the resulting residue purified by flash chromatography to give **5** (155 mg, 46 %). R_f 0.15 (hexane/ethyl acetate, 3 : 2); colourless crystals, mp 81 °C. Anal. Calcd for $C_{20}H_{20}O_5$ (340.37): C, 70.58; H, 5.92. Found: C, 70.46; H, 6.01.

***E/Z*-[3,4-Bis(benzyloxy)-2,5-dihydro-2-oxo-5-furanylidene]ethanol 6a,b.**

DBN (150 mg, 1.2 mmol) is added to a solution of **2a** (396 mg, 1 mmol) in dry THF (10 ml) under N_2 at r.t. After 24 h the mixture is acidified with *2N* - H_2SO_4 (10 ml) and extracted with ethyl acetate (3 x 15 ml). The combined organic layers are adsorbed onto silica gel and purified by flash chromatography to give **6a,b** (288 mg, 85 %), shown by HPLC and ^{1}H NMR analysis to be a mixture of the geometric isomers (*E*:*Z* = 1 : 6). R_f 0.36 (hexane/ethyl acetate, 3 : 2). Colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.31 - 7.15 (m, 10 H), 5.69 (t, 1 H, J = 7.3 Hz, *E*-isomer), 5.44 (t, 1 H, J = 7.3 Hz, *Z*-isomer), 5.19 - 5.09 (m, 4 H), 4.34 (m, 2 H); IR ν 3425, 1769, 1649 cm^{-1}; UV λ_{max}(lg ε) 258 br. nm (4.105), 280 sh (4.006); Anal. Calcd for $C_{20}H_{18}O_5$ (338.36): C, 71.00; H, 5.36. Found: C, 70.72; H, 5.60. MS: 338 [M^+].

Benzyl O^2-Benzyloxycarbonylcarbonyloxy-O^3,O^4-(1-methylethylidene)-L-threonate 7a.

A solution of **2a** (7.13 g, 18 mmol) in dry CH_2Cl_2 (100 ml) is immersed in a dry-ice acetone bath and the calculated amount of O_3 is bubbled through, monitoring the reaction for completeness by TLC. Thereupon Me_2S (3 ml) is slowly added dropwise and the mixture is allowed to reach r.t. The solution is washed with

water, dried (Na_2SO_4) and concentrated to dryness. The resulting residue is purified by flash chromatography to furnish **7a** (6.58 g, 85 %). R_f 0.31 (hexane/ethyl acetate, 4 : 1); colourless crystals, mp 49 °C (hexane/diisopropyl ether). $[\alpha]^{20}_D$ + 22.3 (*c* 1.12, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.41 - 7.34 (m, 10 H), 5.33 (s, 2 H), 5.24 (d, 1 H, *J* = 4.7 Hz), 5.23 (s, 2 H), 4.61 (m, 1 H), 4.09 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 9.0 Hz), 3.97 (dd, 1 H, J_1 = 5.6 Hz, J_2 = 9.0 Hz), 1.39 (s, 3 H), 1.35 (s, 3 H); IR ν 1784, 1756 cm^{-1}; UV λ_{max}(lg ε) 208 nm (4.311); Anal. Calcd for $C_{23}H_{24}O_8$ (428.44): C, 64.48; H, 5.65. Found: C, 64.46; H, 5.70. MS: 428 [M$^+$].

Benzyl O^2-Benzyloxycarbonylcarbonyloxy-O^3,O^4-(1-methylethylidene)-D-erythronate 7b.

A solution of **2b** (7.13 g, 18 mmol) is ozonized according to the procedure described above to give after flash chromatography **7b** (7.01 g, 91 %). R_f 0.33 (hexane/ethyl acetate, 4 : 1), colourless oil, bp 215 °C, 0.1 Torr. $[\alpha]^{20}_D$ − 21.6 (*c* 1.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.39 - 7.34 (m, 10 H), 5.34 (d, 1 H, *J* = 12.0 Hz), 5.29 (d, 1 H, *J* = 12.0 Hz), 5.27 (d, 1 H, *J* = 4.7 Hz), 5.23 (d, 1 H, *J* = 12.4 Hz), 5.19 (d, 1 H, *J* = 12.4 Hz), 4.53 (m, 1 H), 4.01 (m, 2 H), 1.34 (s, 6 H); IR ν 1775, 1749 cm^{-1}; UV λ_{max}(lg ε) 208 nm (4.224), Anal. Calcd for $C_{23}H_{24}O_8$ (428.44): C, 64.48; H, 5.65. Found: C, 64.32; H, 5.81. MS: 428 [M$^+$].

Benzyl O^2-Benzyloxycarbonylcarbonyloxy-O^3,O^4-(1-methylethylidene)-D-threonate *ent*-7a.

Ozonization of ***ent*-2a** (1.98 g, 5 mmol) in dry CH_2Cl_2 (50 ml) followed by Me_2S (1 ml) according to the procedure described above gives ***ent*-7a** (1.80 g, 84 %). Colourless crystals, mp 48 °C (hexane/diisopropyl ether). $[\alpha]^{20}_D$ - 22.6 (*c* 1.27, $CHCl_3$). Anal. Calcd for $C_{23}H_{24}O_8$ (428.44): C, 64.48; H, 5.65. Found: C, 64.48; H, 5.65.

Benzyl O^2-Benzyloxycarbonylcarbonyloxy-O^3,O^4-(1-methylethylidene)-L-erythronate *ent*-7b.

Ozonization of ***ent*-2b** (1.98 g, 5 mmol) in dry CH_2Cl_2 (50 ml) followed by Me_2S (1 ml) according to the procedure described above gives ***ent*-7b** (1.92 g, 92 %). Colourless oil, bp 190 °C, 0.03 Torr. $[\alpha]^{20}_D$ - 21.3 (*c* 1.88, $CHCl_3$). Anal. Calcd for $C_{23}H_{24}O_8$ (428.44): C, 64.48; H, 5.65. Found: C, 64.77; H, 5.85.

Benzyl O^3,O^4-(1-Methylethylidene)-L-threonate 8a.

A solution of **7a** (2.14 g, 5 mmol) in dry MeOH (100 ml) is refluxed for 4 h. The volatiles are removed *in vacuo* and the resulting residue purified by flash chromatography to give **8a** (891 mg, 67 %). R_f 0.16 (hexane/ethyl acetate, 4 : 1). Colourless oil, that solidifies upon standing, bp 180 °C, 1.2 Torr; mp 42 °C (diisopropyl ether). $[\alpha]^{20}_D$ − 31.5 (*c* 1.41, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.33 - 7.29 (m, 5 H), 5.19 (s, 2 H), 4.34 (m, 1 H), 4.09 (dd, 1 H, J_1 = 2.6 Hz, J_2 = 8.1 Hz), 4.00 (dd, 1 H, J_1 = 6.4 Hz, J_2 = 8.1 Hz), 3.93 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 8.1 Hz), 2.89 (d, 1 H, OH, *J* = 8.1 Hz), 1.35 (s, 3 H), 1.28 (s, 3 H); IR ν 3486, 1745 cm^{-1}; UV λ_{max}(lg ε) 209 nm (3.933); Anal. Calcd for $C_{14}H_{18}O_5$ (266.29): C, 63.15; H, 6.81. Found: C, 63.16; H, 6.80. MS: 266 [M$^+$].

Benzyl O^3,O^4-(1-Methylethylidene)-D-erythronate 8b.

The compound is prepared in an analogous manner to **8a** from **7b** (2.14 g, 5 mmol) to give **8b** (1.04 g, 78 %). R_f 0.20 (hexane/ethyl acetate, 3 : 1). Colourless crystals, mp 38 °C (diisopropyl ether). $[\alpha]^{20}_D$ - 11.6 (*c* 1.11,

$CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.39 - 7.34 (m, 5 H), 5.24 (s, 2 H), 4.32 (m, 2 H), 4.02 (dd, 1 H, J_1 = 5.6 Hz, J_2 = 8.5 Hz), 3.97 (dd, 1 H, J_1 = 6.4 Hz, J_2 = 8.5 Hz), 2.85 (d, 1 H, OH, J = 6.4 Hz), 1.40 (s, 3 H), 1.34 (s, 3 H); IR ν 3442, 1738 cm^{-1}; UV λ_{max}(lg ε) 208 nm (3.911); Anal. Calcd for $C_{14}H_{18}O_5$ (266.29): C, 63.15; H, 6.81. Found: C, 63.10; H, 6.86. MS: 266 [M^+].

Benzyl O^3,O^4-(1-Methylethylidene)-D-threonate *ent*-8a.

Following the procedure described for **8a** transesterification of ***ent*-7a** (956 mg, 2 mmol) with dry methanol (30 ml) gives ***ent*-8a** (350 mg, 66 %). Colourless crystals, mp 43 °C (diisopropyl ether). $[\alpha]^{20}_D$ - 31.1 (*c* 1.29, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}O_5$ (266.29): C, 63.15; H, 6.81. Found: C, 63.01; H, 6.95.

Benzyl O^3,O^4-(1-Methylethylidene)-L-erythronate *ent*-8b.

Following the procedure described for **8a** transesterification of ***ent*-7b** (2.14 g, 5 mmol) with dry methanol (100 ml) gives ***ent*-8b** (1.02 g, 77 %). Colourless crystals, mp 38 °C (diisopropyl ether). $[\alpha]^{20}_D$ + 11.3 (*c* 1.13, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}O_5$ (266.29): C, 63.15; H, 6.81. Found: C, 63.06; H, 6.90.

O^3,O^4-(1-Methylethylidene)-L-threonic acid 9a.

Pd/C (75 mg) is added to a solution of **8a** (1.33 g, 5 mmol) in dry ethyl acetate (100 ml) and the resulting suspension is hydrogenated under atmospheric pressure at r.t. for 90 min. The mixture is filtered through a small pad of reversed phase silica gel (RP 18) and evaporated. The resulting residue is recrystallized from diisopropyl ether to furnish **9a** (801 mg, 91 %). Colourless crystals, mp 90 °C (diisopropyl ether). $[\alpha]^{20}_D$ + 14.4 (*c* 1.46, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.47 (m, 1 H), 4.20 (d, 1 H, J = 2.6 Hz), 4.15 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 8.5 Hz), 4.06 (dd, 1 H, J_1 = 6.4 Hz, J_2 = 8.5 Hz), 1.46 (s, 3 H), 1.38 (s, 3 H); IR ν 3505, 3400 - 2800 br., 1727 cm^{-1}; Anal. Calcd for $C_7H_{12}O_5$ (176.17): C, 47.73; H, 6.87. Found: C, 47.44; H, 7.25. MS: 176 [M^+].

O^3,O^4-(1-Methylethylidene)-D-erythronic acid 9b.

A solution of **8b** (2.66 g, 10 mmol) in dry ethyl acetate (100 ml) is hydrogenated as described above to give **9b** (1.58 g, 90 %). Colourless crystals, mp 63 °C (hexane/diisopropyl ether). $[\alpha]^{20}_D$ - 12.5 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.35 (m, 1 H), 4.27 (d, 1 H, J = 5.6 Hz), 4.11 (m, 2 H), 1.49 (s, 3 H), 1.39 (s, 3 H); IR ν 3417, 3300 - 2800 br., 1738 cm^{-1}; Anal. Calcd for $C_7H_{12}O_5$ (176.17): C, 47.73; H, 6.87. Found: C, 47.42; H, 7.18. MS: 176 [M^+].

O^3,O^4-(1-Methylethylidene)-D-threonic acid *ent*-9a.

Following the procedure described for **9a** hydrogenation of ***ent*-8a** (1.33 g, 5 mmol) gives ***ent*-9a** (792 mg, 90 %). Colourless crystals, mp 89 °C (diisopropyl ether). $[\alpha]^{20}_D$ - 14.1 (*c* 1.01, $CHCl_3$); Anal. Calcd for $C_7H_{12}O_5$ (176.17): C, 47.73; H, 6.87. Found: C, 47.40; H, 6.58. MS: 176 [M^+].

O^3,O^4-(1-Methylethylidene)-L-erythronic acid *ent*-9b.

Hydrogenation of a solution of ***ent*-8b** (1.33 g, 5 mmol) in dry ethyl acetate (50 ml) according to the procedure described for **9a** gives ***ent*-9b** (780 mg, 89 %). Colourless crystals, mp 62 °C (hexane/diisopropyl ether). $[\alpha]^{20}_D$ + 12.7 (*c* 1.14, $CHCl_3$); Anal. Calcd for $C_7H_{12}O_5$ (176.17): C, 47.73; H, 6.87. Found: C, 47.36; H, 7.11. MS:

176 [M$^+$].

O^2,O^3-Dibenzyl-O^5,O^6-phenylmethylidene-L-ascorbic acid 10a/11a.

A solution of O^2,O^3-dibenzyl L-ascorbic acid[4] (7.12 g, 20 mmol), benzaldehyde (2.65 g, 25 mmol) and *p*-toluenesulfonic acid (200 mg) in toluene (200 ml) is refluxed for 3 h using a Dean-Stark trap. The cooled mixture is adsorbed onto silica gel and purified by flash chromatography to give in the order of elution first **10a** (4.10 g, 46 %) and then **11a** (3.36 g, 38 %).

10a: R_f 0.20 (hexane/ethyl acetate, 4 : 1), colourless crystals, mp 102 °C (diisopropyl ether/ethyl acetate). $[\alpha]^{20}_D$ + 47.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39 - 7.10 (m, 15 H), 5.81 (s, 1 H), 5.12 (d, 1 H, *J* = 11.5 Hz), 5.06 (d, 1 H, *J* = 11.5 Hz), 5.02 (d, 1 H, *J* = 11.5 Hz), 4.98 (d, 1 H, *J* = 11.5 Hz), 4.55 (d, 1 H, J = 2.2 Hz), 4.40 (m, 1 H), 4.24 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 8.0 Hz), 4.04 (dd, 1 H, J_1 = 7.7 Hz, J_2 = 8.0 Hz), IR ν 1754, 1675 cm^{-1}; UV λ_{max}(lg ε) 208 nm (4.394), 237 nm (4.036); Anal. Calcd for $C_{27}H_{24}O_6$ (444.48): C, 72.96; H, 5.44. Found: C, 72.80; H, 5.58. MS: 444 [M$^+$].

11a: R_f 0.13 (hexane/ethyl acetate, 4 : 1), colourless crystals, mp 87 °C (diisopropyl ether/ethyl acetate). $[\alpha]^{20}_D$ + 112.6 (*c* 1.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46 - 7.06 (m, 15 H), 5.70 (s, 1 H), 5.08 (d, 1 H, *J* = 11.5 Hz), 4.94 (s, 2 H), 4.81 (d, 1 H, *J* = 11.5 Hz), 4.57 (d, 1 H, *J* = 3.0 Hz), 4.31 (m, 1 H), 4.18 (dd, 1 H, J_1 = 5.0 Hz, J_2 = 8.5 Hz), 4.02 (m, 1 H); NOE: 5.70/4.31; IR ν 1756, 1672 cm^{-1}; UV λ_{max}(lg ε) 207 nm (4.382), 237 nm (4.029); Anal. Calcd for $C_{27}H_{24}O_6$ (444.48): C, 72.96; H, 5.44. Found: C, 73.19; H, 5.55. MS: 444 [M$^+$].

O^2,O^3-Dibenzyl-O^5,O^6-phenylmethylidene-D-isoascorbic acid 10b/11b.

A mixture of **1b** (17.6 g, 100 mmol), benzaldehyde dimethyl acetal (16.7 g, 100 mmol) and trifluoroacetic acid (0.75 g) in dry DMF (50 ml) is stirred at r.t. for 120 h.[20] A total volume of about 10 ml is removed under reduced pressure and the solution charged with K_2CO_3 (30.4 g, 220 mmol) and benzyl bromide (34.2 g, 200 mmol). The resulting mixture is stirred under N_2 at 50 °C for 3 h, thereupon cooled to r.t. and cautiously (CO_2!) poured into ice-cold *2N* - H_2SO_4. The suspension is extracted with CH_2Cl_2 (3 x 100 ml), the organic layer washed with water, dried (Na_2SO_4) and adsorbed onto silica gel. Purification of the residue by flash chromatography gives in the order of elution first **10b** (10.82 g, 24 %) and then **11b** (9.60 g, 22 %).

10b: R_f 0.28 (hexane/ethyl acetate, 4 : 1), colourless crystals, mp 108 °C (diisopropyl ether/ethyl acetate). $[\alpha]^{20}_D$ + 74.0 (*c* 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37 - 7.16 (m, 15 H), 5.83 (s, 1 H), 5.17 (d, 1 H, *J* = 11.5 Hz), 5.14 (s, 2 H), 5.03 (d, 1 H, *J* = 11.5 Hz), 4.88 (d, 1 H, *J* = 3.4 Hz), 4.38 (m, 1 H), 3.80 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 8.5 Hz), 3.55 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 8.5 Hz); IR ν 1756, 1674 cm^{-1}; UV λ_{max}(lg ε) 207 nm (4.156), 238 nm (3.771); Anal. Calcd for $C_{27}H_{24}O_6$ (444.48): C, 72.96; H, 5.44. Found: C, 72.94; H, 5.46. MS: 444 [M$^+$].

11b: R_f 0.23 (hexane/ethyl acetate, 4 : 1), colourless crystals, mp 75 °C (diisopropyl ether/ethyl acetate). $[\alpha]^{20}_D$ + 18.2 (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.44 - 7.11 (m, 15 H), 5.71 (s, 1 H), 5.14 (d, 1 H, *J* = 11.5 Hz), 5.10 (d, 1 H, *J* = 11.5 Hz), 5.06 (d, 1 H, *J* = 11.5 Hz), 5.02 (d, 1 H, *J* = 11.5 Hz), 4.69 (d, 1 H, *J* = 4.7 Hz),

4.29 (m, 1 H), 3.90 (dd, 1 H, J_1 = 4.2 Hz, J_2 = 8.5 Hz), 3.80 (dd, 1 H, J_1 = 7.3 Hz, J_2 = 8.5 Hz); NOE: 5.71/4.29; IR ν 1757, 1676 cm^{-1}; UV λ_{max}(lg ε) 208 nm (4.424), 238 nm (4.091); Anal. Calcd for $C_{27}H_{24}O_6$ (444.48): C, 72.96; H, 5.44. Found: C, 72.94; H, 5.46. MS: 444 [M$^+$].

O^2,O^3-Dibenzyl-O^5,O^6-phenylmethylidene-D-ascorbic acid *ent*-10a/*ent*-11a.

TRIBAL-induced isomerization of **10b/11b** (4.44 g, 10 mmol) according to the *General Procedure* given above furnishes after purification by flash chromatography (solvent: hexane/ethyl acetate, 4 : 1) in the order of elution first ***ent*-10a** (1.81 g, 41 %) and then ***ent*-11a** (650 mg, 15 %), besides recovered educt **10b** (957 mg, 22 %) and a mixture (*E*:*Z* = 1:4) of the allylic alcohols **6a,b** (330 mg, 10 %).

***ent*-10a**: Colourless crystals, mp 102 °C (diisopropyl ether/ethyl acetate). $[\alpha]^{20}_D$ - 47.0 (*c* 1.02, $CHCl_3$); Anal. Calcd for $C_{27}H_{24}O_6$ (444.48): C, 72.96; H, 5.44. Found: C, 72.92; H, 5.48. MS: 444 [M$^+$].

***ent*-11a**: Colourless crystals, mp 87 °C (diisopropyl ether/ethyl acetate). $[\alpha]^{20}_D$ - 109.9 (*c* 0.98, $CHCl_3$); Anal. Calcd for $C_{27}H_{24}O_6$ (444.48): C, 72.96; H, 5.44. Found: C, 72.98; H, 5.42. MS: 444 [M$^+$].

O^2,O^3-Dibenzyl-O^5,O^6-phenylmethylidene-L-isoascorbic acid *ent*-10b.

TRIBAL-induced isomerization of **10a/11a** (4.44 g, 10 mmol) according to the *General Procedure* described above furnishes after purification by flash chromatography in the order of elution first ***ent*-10b** (650 mg, 15 %), then **10a** (1.88 g, 42 %) and finally **11a** (889 mg, 20 %), followed by a mixture (*E*:*Z* = 1:4) of the allylic alcohols **6a,b** (370 mg, 11 %). Colourless crystals, mp 108 °C (diisopropyl ether/ethyl acetate). $[\alpha]^{20}_D$ - 76.0 (*c* 1.01, $CHCl_3$); Anal. Calcd for $C_{27}H_{24}O_6$ (444.48): C, 72.96; H, 5.44. Found: C, 72.81; H, 5.59. MS: 444 [M$^+$].

Typical hydrogenation procedure for the deprotection of the benzylidene acetals 10 and 11.

Pd/C (100 mg) is added to a solution of **10** or **11** (4.44 g, 10 mmol) in dry methanol (150 ml) and the resulting suspension is hydrogenated under atmospheric pressure at r.t. for 90 min. The mixture is filtered with suction through a small pad of reversed phase silica gel (RP 18) and evaporated. The obtained residue is recrystallized from diethyl ether/methanol mixtures to give the endiols **1** or ***ent*-1**, respectively.

D-*xylo*-Ascorbic acid *ent*-1a.

Following the *Typical procedure* described above hydrogenation of ***ent*-10a** or ***ent*-11a** (4.44 g, 10 mmol) gives ***ent*-1a** (1.60 g, 91 %). Colourless crystals, mp 190-192 °C dec. (diethyl ether/methanol). $[\alpha]^{20}_D$ - 20.8 (*c* 2.10, H_2O); Anal. Calcd for $C_6H_8O_6$ (176.13): C, 40.92; H, 4.58. Found: C, 40.80; H, 4.60.

L-*arabo*-Ascorbic acid *ent*-1b.

Following the *Typical procedure* described above hydrogenation of ***ent*-10b** (2.22 g, 5 mmol) gives ***ent*-1a** (0.81 g, 92 %). Colourless crystals, mp 168-169 °C dec. (diethyl ether/methanol). $[\alpha]^{20}_D$ + 17.2 (*c* 1.88, H_2O); Anal. Calcd for $C_6H_8O_6$ (176.13): C, 40.92; H, 4.58. Found: C, 40.76; H, 4.72.

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