A Novel Synthesis of (*R*)- and (*S*)-4-Hydroxytetrahydrofuran-2-ones

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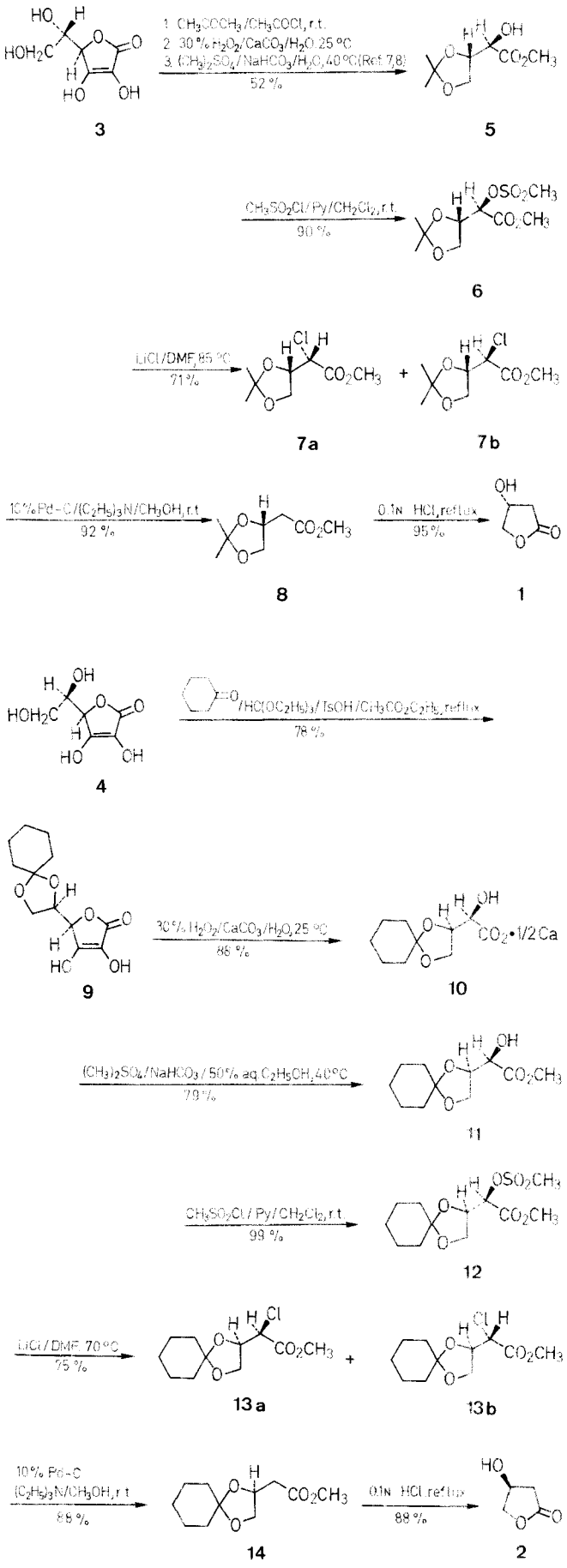
A practical synthesis of (*R*)- and (*S*)-4-hydroxytetrahydrofuran-2-ones is accomplished starting from L-ascorbic acid and D-isoascorbic acid, respectively.

Of the available chiral C_4 building blocks,[1] (*R*)- and (*S*)-4-hydroxytetrahydrofuran-2-ones [(*R*)- and (*S*)-dihydro-4-hydroxy-2(3*H*)-furanones, (**1**, **2**)] are a versatile class of chiral sources for the synthesis of optically active natural products.[2,3] The existing methods for preparing these hydroxylactones involve the chemical transformation of unnatural or natural malic acid.[2,4,5] However, especially the former unnatural substrate is very expensive and therefore unsuitable for large-scale preparation. Recently, an elegant asymmetric synthesis of compound **1** via baker's yeast reduction of substituted 3-oxobutanoates was reported.[6] We describe here a novel synthesis of compounds **1** and **2** starting from L-ascorbic acid (**3**) and D-isoascorbic acid (erythorbic acid, **4**), respectively, both of which are readily available and inexpensive.

The known hydroxy ester **5**[7] was prepared from L-ascorbic acid (**3**) by sequential treatment with acetone and acetyl chloride,[8] 30% hydrogen peroxide and calcium carbonate, and dimethyl sulfate. Then, ester **5** was treated with methanesulfonyl chloride and pyridine in dichloromethane providing the crystalline mesylate **6**. When heated at 85°C with lithium chloride in dimethylformamide, ester **6** furnished a mixture of the *erythro* and *threo* chloroesters **7a** and **7b**.[9] These are easily separable by column chromatography, although separation into the individual isomers is not necessary. Upon hydrogenolysis with 10% palladium on carbon in the presence of triethylamine, compounds **7** yielded the ester **8**,[10] which was finally treated with dilute hydrochloric acid giving a nearly quantitative yield of hydroxylactone **1** (29% overall yield from **3**;[11] $[\alpha]_D$: +88.9°). The (*S*)-enantiomer **2** was analogously prepared from D-isoascorbic acid (**4**). In contrast to 5,6-*O*-isopropylidene-L-ascorbic acid, however, the corresponding isopropylidene derivative of **4** has proven too moisture-sensitive to undergo the required oxidative cleavage.[12] Accordingly, the cyclohexylidene protective group was employed through a sequence of reactions. Thus, upon treatment with cyclohexanone and ethyl orthoformate in ethyl acetate in the presence of *p*-toluenesulfonic acid, compound **4** was converted into the cyclohexylidene derivative **9** which was subjected to oxidative cleavage with 30% hydrogen peroxide and calcium carbonate giving the calcium salt **10** in good overall yield. This was then allowed to react with dimethyl sulfate to furnish the methyl ester **11** which upon treatment with methanesulfonyl chloride as described for **5** yielded **12** as a viscous liquid. The substitution reaction with lithium chloride in dimethylformamide provided a separable mixture of the *erythro* and *threo* isomers **13a** and **13b**.[9] Hydrogenolysis of **13** followed by lactonization catalyzed by hydrochloric acid proceeded cleanly as in the synthesis of **1** giving an excellent yield of the (*S*)-enantiomer **2** (40% overall yield from **4**;[11] $[\alpha]_D$: −86.1°). In conclusion, the above sequence to hydroxylactones **1** and **2** is a practical alternative to the existing methods.

Melting and boiling points are uncorrected. Optical rotations were measured on a JASCO DIP-4 spectrometer. IR spectra were taken on a



JASCO IR-810 spectrometer and ^{1}H-NMR spectra were measured on a JEOL JNM FX-100 spectrometer (100 MHz). Column chromatography was carried out using silica gel unless otherwise stated.

Methyl (α*R*,4*S*)-α-Hydroxy-2,2-dimethyl-1,3-dioxolane-4-acetate (5):
This compound is prepared in three steps from L-ascorbic acid (**3**) by the literature procedures;[7,8] overall yield: 52%; $[\alpha]_D^{24}$: +16.8° (*c* = 1.92, $CHCl_3$) [Lit.,[7] $[\alpha]_D^{25}$: +18.39° (*c* = 1.0442, $CHCl_3$)].

Methyl (α*R*,4*S*)-2,2-Dimethyl-α-methylsulfonyloxy-1,3-dioxolane-4-acetate (6):
To a stirred solution of α-hydroxyester **5** (25.1 g, 0.132 mol) and pyridine (32 ml, 0.397 mol) in dichloromethane (200 ml) is added dropwise methanesulfonyl chloride (13.2 ml, 0.171 mol) at 0 °C and stirring is continued for 5 h at room temperature. The mixture is poured onto icewater (200 ml) whereby the product is partitioned between dichloromethane and water. The aqueous layer is extracted with dichloromethane (2 × 100 ml) and the combined organic solutions are washed successively with aqueous oxalic acid (100 ml), water (100 ml), and saturated sodium chloride solution (200 ml). The organic solution is dried with magnesium sulfate and evaporated to afford a crystalline solid which upon recrystallization from ethyl acetate gives **6**; yield: 31.9 g (90%); m.p. 105–106 °C; $[\alpha]_D^{21}$: +36.3° (*c* = 1.02, $CHCl_3$).

$C_9H_{16}O_7S$	calc.	C 40.29	H 6.01
(268.3)	found	40.32	5.97

IR (KBr): ν = 1760 (s); 1370 (s); 1340 (s); 1220 (s); 1175 (s); 1115 (s); 1065 (s); 990 (s); 870 (m) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.36 (s, 3H); 1.45 (s, 3H); 3.20 (s, 3H); 3.85 (s, 3H); 4.02 (dd, 1H, *J* = 6,9 Hz); 4.17 (dd, 1H, *J* = 6,9 Hz); 4.46 (dt, 1H, *J* = 5,6 Hz); 5.02 ppm (d, 1H, *J* = 5 Hz).

Methyl (α*S*,4*S*)- and (α*R*,4*S*)-α-Chloro-2,2-dimethyl-1,3-dioxolane-4-acetate (7a and 7b):
A mixture of mesyloxyester **6** (30 g, 0.112 mol) and lithium chloride (7.2 g, 0.17 mol) in dimethylformamide (100 ml) is stirred at 85 °C. After 7 h, water (300 ml) is added and the mixture is extracted with ether (3 × 100 ml). The ether layer is washed with water (100 ml) and with saturated sodium chloride solution (100 ml), and dried with magnesium sulfate. Evaporation of the solvent and distillation gives a mixture of **7a** and **7b**; yield: 17.8 g (71%); b.p. 85–87 °C/5 torr. A portion of this mixture is separated into the individual isomers (ratio 82:18) by column chromatography using ethyl acetate/hexane (1:10) as eluent.

Isomer **7a**; $[\alpha]_D^{20}$: −5.8° (*c* = 1.1, $CHCl_3$).

$C_8H_{13}ClO_4$	calc.	C 46.05	H 6.28
(224.6)	found	46.24	6.34

IR (film): ν = 1760 (s); 1390 (s); 1380 (s); 1280 (s); 1260 (s); 1235 (s); 1220 (s); 1170 (s); 1080 (s); 845 (m) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.35 (s, 3H); 1.45 (s, 3H); 3.83 (s, 3H); 4.11 (center of AB, 2H); 4.15 (d, 1H, *J* = 8 Hz); 4.49 ppm (dt, 1H, *J* = 4, 8 Hz).

Isomer **7b**; $[\alpha]_D^{20}$: +17.0° (*c* = 1, $CHCl_3$).

$C_8H_{13}ClO_4$	calc.	C 46.05	H 6.28
(224.6)	found	46.35	6.36

IR (film): ν = 1750 (s); 1390 (s); 1380 (s); 1260 (s); 1215 (s); 1170 (s); 850 (m) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.37 (s, 3H); 1.45 (s, 3H); 3.82 (s, 3H); 3.96 (dd, 1H, *J* = 6,9 Hz); 4.15 (dd, 1H, *J* = 6,9 Hz); 4.33 (d, 1H, *J* = 6 Hz); 4.54 ppm (q, 1H, *J* = 6 Hz).

Methyl (*R*)-2,2-Dimethyl-1,3-dioxolane-4-acetate (8):
Hydrogenolysis of the diastereoisomer mixture **7a** + **7b** (17.8 g, 0.0793 mol) is conducted at room temperature (3 h) using 10% palladium on carbon (2 g) and triethylamine (17.7 ml, 0.128 mol) in methanol (100 ml). After removal of the catalyst by filtration, the solvent is evaporated in vacuo giving a semisolid residue which is taken up in ether (100 ml) and filtered. Evaporation and distillation affords ester **8**; yield: 12.7 g (92%); b.p. 66–68 °C/5 torr; $[\alpha]_D^{24}$: −16.7° (*c* = 1.02, $CHCl_3$) [Lit.[10]: $[\alpha]_D$: +17.0° (*c* = 2, $CHCl_3$) for the (*S*)-enantiomer].

$C_8H_{14}O_4$	calc.	C 55.16	H 8.10
(174.2)		55.45	8.27

IR (film): ν = 1745 (s); 1385 (s); 1375 (s); 1255 (s); 1220 (s); 1180 (s); 1070 (s); 840 (m) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.36 (s, 3H); 1.42 (s, 3H); 2.50 (dd, 1H, *J* = 6, 16 Hz); 2.75 (dd, 1H, *J* = 6,16 Hz); 3.65 (dd, 1H, *J* = 6,8 Hz); 3.70 (s, 3H); 4.16 (dd, 1H, *J* = 6,8 Hz); 4.48 ppm (quin, 1H, *J* = 6 Hz).

(*R*)-4-Hydroxytetrahydrofuran-2-one [(*R*)-3-Hydroxy-4-butanolide, 1]:
A mixture of compound **8** (3.0 g, 0.0172 mol) in 0.1 normal hydrochloric acid (10 ml) is heated at reflux temperature for 2 h. Evaporation

followed by distillation gives lactone **1**; yield: 1.67 g (95%); b.p. 135–137°C/4 torr (Lit.[2], b.p. 103–105°C/0.4 torr; Lit.[6], b.p. 90–95°C/0.1 torr); $[\alpha]_D^{21}$: +88.9° (c = 1.36, ethanol [Lit.[2], $[\alpha]_D^{23}$: +77.3° (c = 2.0, ethanol); Lit.[6], $[\alpha]_D$: +94° (c = 1.5, ethanol)].

5,6-*O*-Cyclohexylidene-D-isoascorbic Acid (9):
A mixture of cyclohexanone (11.1 g, 0.113 mol), ethyl orthoformate (17.6 g, 0.119 mol), and *p*-toluenesulfonic acid monohydrate (100 mg, 0.526 mmol) in dry ethyl acetate (300 ml) is refluxed for 30 min. Then, D-isoascorbic acid (10.0 g, 0.0568 mol) is added and the mixture is refluxed for 5 h until all crystals of isoascorbic acid have disappeared. After slow distillation of ethyl acetate (200 ml) at atmospheric pressure, the residual solution is passed through a short column of neutral alumina (Merck, Aluminum oxide 90, activity grade III) in order to remove the acid catalyst. The crystalline product is deposited by the addition of hexane and collected by filtration; yield: 11.3 g (78%). Recrystallization from ethyl acetate/hexane gives pure **9**; m.p. 178–180°C; $[\alpha]_D^{21}$: −18.0° (c = 1, acetone).

$C_{12}H_{16}O_6$	calc.	C 56.24	H 6.29
(256.2)	found	56.45	6.49

IR (KBr): ν = 3350 (br.m); 1740 (m); 1640 (s); 1305 (m); 1165 (m); 1130 (m); 1110 (m); 935 (m) cm^{-1}.

^{1}H-NMR (acetone-d_6): δ = 1.17–1.86 (m, 10H); 3.01 (br.s, 2H); 3.75 (dd, 1H, J = 6.8 Hz); 4.01 (dd, 1H, J = 6,8 Hz); 4.43 (dt, 1H, J = 4,6 Hz); 4.83 ppm (d, 1H, J = 4 Hz).

Calcium (α*R*,2*R*)-α-Hydroxy-1,4-dioxaspiro[4.5]decane-2-acetate (10):
A suspension of acid **9** (10.1 g, 0.0395 mol), calcium carbonate (8.4 g, 0.084 mol), and 30% hydrogen peroxide (19 ml, 0.168 mol) in water (150 ml) is kept at 25°C with cooling. After the vigorous reaction has subsided, the mixture is heated at 40°C for 30 min and then treated with charcoal (2 g) and 10% palladium on carbon (0.1 g) on a boiling water for 1 h. The precipitate is filtered off and thoroughly washed with hot ethanol (3 × 40 ml). The combined solutions are evaporated to dryness in vacuo to afford the crude calcium salt which upon recrystallization from 50% aqueous ethanol provides pure **10**; yield: 8.5 g (88%); m.p. > 255°C; $[\alpha]_D^{21}$: +19.2° (c = 0.52, ethanol).

$C_{10}H_{15}O_5 \cdot \frac{1}{2}Ca \cdot \frac{1}{2}H_2O$	calc.	C 49.19	H 6.60
(244.3)	found	49.34	6.75

IR (KBr): ν = 3450 (br.s); 1610 (s); 1290 (m); 1170 (m); 1150 (m); 1105 (m); 1040 (m); 930 (m) cm^{-1}.

^{1}H-NMR (methanol-d_4): δ = 1.14–1.85 (m, 10H); 3.88 (d, 2H, J = 7 Hz); 4.37 (s, 1H, J = 3 Hz); 4.51 ppm (dt, 1H, J = 3,7 Hz).

Methyl (α*R*,2*R*)-α-Hydroxy-1,4-dioxaspiro[4.5]decane-2-acetate (11):
The calcium salt **10** (8.5 g, 0.0348 mol) is stirred with dimethyl sulfate (16.2 ml, 0.171 mol) and sodium hydrogen carbonate (14.6 g, 0.174 mol) in 50% aqueous ethanol (240 ml) at 40°C for 8 h. After removal of the precipitated salt by filtration, most of the ethanol is evaporated in vacuo and the aqueous solution is extracted with dichloromethane (3 × 100 ml). The organic layer is washed with saturated sodium chloride solution (100 ml) and dried with magnesium sulfate. Evaporation furnishes the crude product which upon column chromatography using ethyl acetate/hexane (1:5) as eluent gives pure **11**; yield: 6.3 g (79%); $[\alpha]_D^{23}$: −34.7° (c = 1.24, $CHCl_3$).

$C_{11}H_{18}O_5$	calc.	C 57.38	H 7.88
(230.2)	found	57.55	7.90

IR (film): ν = 3480 (m); 1750 (s); 1170 (m); 1100 (s); 1060 (m); 935 (m) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.26–1.83 (m, 10H); 2.86 (d, 1H, J = 6 Hz); 3.81 (s, 3H); 4.02 (d, 2H, J = 5 Hz); 4.28 ppm (m, 2H).

Methyl (α*R*,2*R*)-α-Methylsulfonyloxy-1,4-dioxaspiro[4.5]decane-2-acetate (12):
The hydroxy ester **11** (6.3 g, 0.0274 mol) is stirred with methanesulfonyl chloride (3.0 ml, 0.0389 mol) and pyridine (6.4 ml, 0.0794 mol) in dichloromethane (40 ml) at room temperature overnight. The same work-up procedure as that described for **6** affords the crude product which is purified by column chromatography using ethyl acetate/hexane (1:6) as eluent to give pure **12**; yield: 8.4 g (99%); $[\alpha]_D^{23}$: +14.6° (c = 3.14, $CHCl_3$).

$C_{13}H_{20}O_7S$	calc.	C 46.74	H 6.54
(308.3)	found	47.03	6.81

IR (film): ν = 1765 (s); 1375 (s); 1290 (m); 1185 (s); 1100 (s); 1050 (m); 970 (s) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.28–1.83 (m, 10H); 3.14 (s, 3H); 3.83 (s, 3H); 4.04 (d, 2H, J = 5 Hz); 4.48 (q, 1H, J = 5 Hz); 5.08 ppm (d, 1H, J = 5 Hz).

Methyl (α*R*,2*R*)- and (α*S*,2*R*)-α-Chloro-1,4-dioxaspiro[4.5]decane-2-acetate (13a and 13b):
A mixture of ester **12** (7.8 g, 0.0253 mol) and lithium chloride (1.6 g, 0.0377 mol) in dimethylformamide (40 ml) is heated at 70°C for 11 h. The product is obtained as a mixture of diastereoisomers after the same work-up as that described for **7**. Column chromatography using ethyl acetate/hexane (1:10) as eluent affords the *erythro* isomer **13a** and the *threo* isomer **13b**.

erythro Isomer **13a**; yield: 1.3 g (21%); $[\alpha]_D^{23}$: +6.9° (c = 2.92, $CHCl_3$).

$C_{11}H_{17}ClO_4$	calc.	C 53.12	H 6.89
(248.7)	found	52.97	7.06

IR (film): ν = 1760 (s); 1285 (m); 1170 (s); 1120 (m); 1100 (s); 1040 (m); 935 (m) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.23–1.83 (m, 10H); 3.82 (s, 3H); 4.09 (center of AB, 2H); 4.14 (d, 1H, J = 8 Hz); 4.48 ppm (dt, 1H, J = 4,8 Hz).

threo Isomer **13b**; yield: 3.4 g (54%); $[\alpha]_D^{22}$: −11.7° (c = 2.56, $CHCl_3$).

$C_{11}H_{17}ClO_4$	calc.	C 53.12	H 6.89
(248.7)	found	53.04	6.98

IR (film): ν = 1750 (s); 1285 (m); 1170 (s); 1105 (s); 1050 (s); 935 (m) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.27–1.83 (m, 10H); 3.81 (s, 3H); 3.95 (dd, 1H, J = 6,9 Hz); 4.13 (dd, 1H, J = 6,9 Hz); 4.33 (d, 1H, J = 6 Hz); 4.52 ppm (q, 1H, J = 6 Hz).

Methyl (*S*)-1,4-Dioxaspiro[4.5]decane-2-acetate (14):
The *threo* ester **13b** (3.3 g, 0.0133 mol) is subjected to hydrogenolysis using 10% palladium on carbon (0.8 g) and triethylamine (2.8 ml, 0.0202 mol) in methanol (25 ml). After 4 h, the mixture is worked up as described for **8**. Distillation gives product **14**; yield: 2.5 g (88%); b.p. 106–109°C/5 torr; $[\alpha]_D^{22}$: +10.9° (c = 1.84, $CHCl_3$).

$C_{11}H_{18}O_4$	calc.	C 61.66	H 8.47
(214.2)	found	61.38	8.72

IR (film): ν = 1745 (s); 1290 (m); 1170 (s); 1105 (s); 1045 (m); 940 (m) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.26–1.74 (m, 10H); 2.50 (dd, 1H, J = 6,16 Hz); 2.76 (dd, 1H, J = 6,16 Hz); 3.64 (dd, 1H, J = 6,8 Hz); 3.70 (s, 3H); 4.15 (dd, 1H, J = 6,8 Hz); 4.49 ppm (quin, 1H, J = 6 Hz).

(*S*)-4-Hydroxytetrahydrofuran-2-one [(*S*)-3-Hydroxy-4-butanolide, 2]:
A mixture of ester **14** (2.4 g, 0.0112 mol) and 0.1 normal hydrochloric acid (8 ml) is heated at reflux temperature for 2 h. Evaporation affords the crude product which is purified by column chromatography using ethyl acetate/hexane (1:3) as eluent to give pure **2**; yield: 1.0 g (88%); $[\alpha]_D^{21}$: −86.1° (c = 3.1, C_2H_5OH) [Lit.[5], $[\alpha]_D^{9}$: −85.9° (c = 2.2, ethanol)].

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(8) Jung, M.E., Shaw, T.J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.
(9) Stereochemistry of both isomers was deduced from the coupling patterns (^{1}H-NMR) characteristic of the *erythro* and *threo* derivatives; e.g. **11**, **12**, **5**, **6**.
(10) For the synthesis of **8** and its enantiomer via regioselective hydrolysis of (*R*)- and (*S*)-dimethyl malates using pig liver esterase, see: Papageorgiou, C., Benezra, C. *J. Org. Chem.* **1985**, *50*, 1145.

(11) Cf. reported overall yields:
Ref. 2, 20% from (*R*)-(+)-malic acid.
Ref. 6, 17% from 4-chloroacetoacetate derivatives.
Ref. 5, 79% from (*S*)-(−)-dimethyl malate.
Ref. 4, 23% from (*S*)-(−)-malic acid.

(12) The reason why 5,6-*O*-isopropylidene-D-isoascorbic acid is much more unstable than the corresponding derivatives of **3** cannot be simply explained.