144. A Non-Racemic Equivalent of Glycolic Acid: Preparation of Both Enantiomers from D-Mannitol

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A practical synthesis of both enantiomers of 2-(*tert*-butyl)-2-methyl-1,3-dioxolan-4-one starting from D-mannitol is reported. These compounds are chiral equivalents of glycolic acid (= hydroxyacetic acid) which are configurationally stable and can be alkylated *via* their enolates.

Introduction. – Recently, we became interested in producing glycolic-acid radicals and applying them for the synthesis of alkylated α-hydroxy- or α-alkoxy-acid derivatives [1]. Our final goal is the synthesis of enantiomerically pure cyclic α-hydroxy acids by enolate alkylations and radical cyclizations. For this purpose, we need an easily available non-racemic equivalent of glycolic acid (= hydroxyacetic acid). Several approaches to this problem have been reported in the literature. They are mainly based on acyclic derivatives bearing a chiral ester/amide group [2] or cyclic derivatives with chirality at the acetal

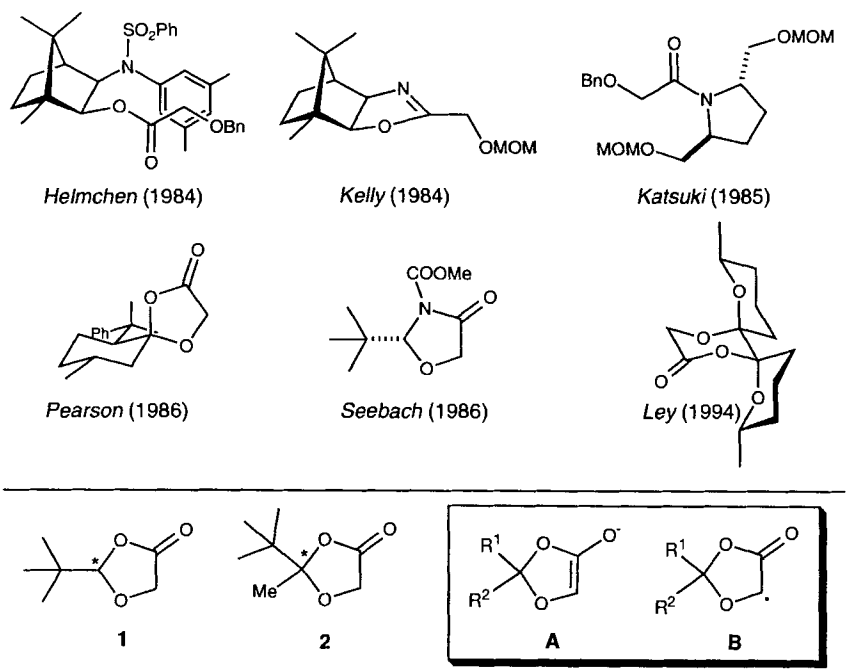
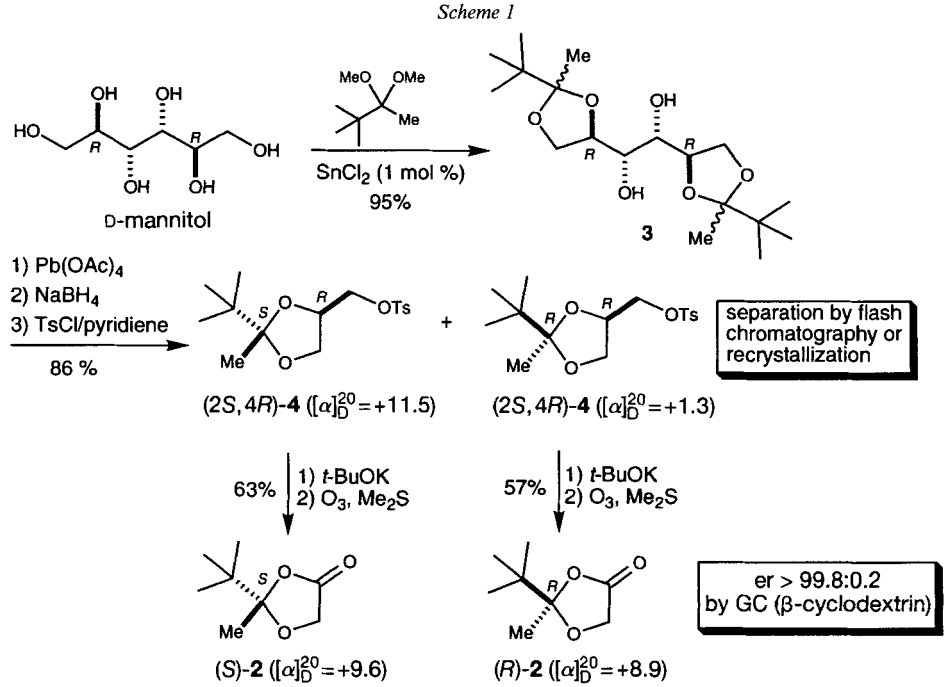


Figure. *Chiral non-racemic equivalents of glycolic acid used for the preparation of α-hydroxy acids by enolate alkylation*

center (*Fig.*) [3]. The approach of *Pearson* [3b] based on chiral 1,3-dioxolan-4-one derivatives seems to be the most promising in terms of ease of preparation and stereoselection for both anionic (type-**A** enolates) and radical reactions (type-**B** radicals). However, the preparation of this substrate is not suitable for a large-scale synthesis, since it requires a rather tedious separation of diastereoisomers by chromatography. Therefore, we decided to investigate a new approach for both enantiomers of a 1,3-dioxolan-4-one derivative. Preliminary studies with racemic 2-(*tert*-butyl)-1,3-dioxolan-4-one (**1**) revealed that the corresponding enolate is not sufficiently stable to be efficiently alkylated[1])[2]). So we decided to synthesize the 2-(*tert*-butyl)-2-methyl-1,3-dioxolan-4-one (**2**) which gives rise to a more stable enolate[3]).

Results. – From an economical point of view, cheap D-mannitol represents an attractive starting material. The reaction sequence is depicted in *Scheme 1*[4]). D-Mannitol was acetalized with pinacolone dimethyl acetal/$SnCl_2$ to give **3** as a mixture of diastereoisomers in 96% yield. The diastereoisomers could be separated by chromatography, at this stage. However, it proved advantageous to continue the reaction with the diastereoisomer

Scheme 1



[1]) Difficulties for the preparation of this substrate in optically pure form were already noticed by *Gander-Coquoz* [4]. Moreover, *Seebach* and coworkers have demonstrated that 2-aryl-1,3-dioxolan-4-one racemizes in solution at room temperature [5].

[2]) Racemic **1** has been brominated and used for radical reactions [6].

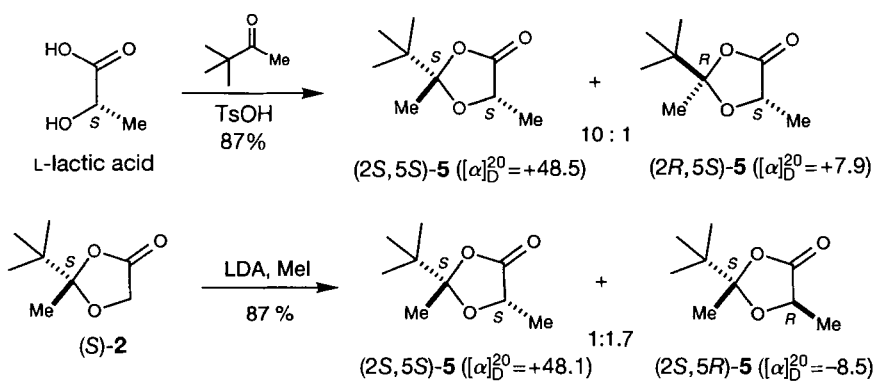
[3]) Optically active 2-ethyl-2-phenyl-1,3-dioxolan-4-one of unknown enantiomeric purity has been prepared by acidic rearrangement of [(1-phenylallyl)oxy]acetic acid [7].

[4]) For a previous attempt to synthesize optically pure **3** from D-mannitol, see [8]. We are very grateful to Prof. *P. Sinaÿ* and Dr. *E. Untersteller* for drawing our attention to this work.

mixture. Glycolic cleavage with lead tetraacetate followed by $NaBH_4$ reduction and tosylation (TsCl/pyridine) furnished a 1:1 mixture of (2*R*,4*R*)- and (2*S*,4*R*)-**4** in 86% yield. At this stage, the diastereoisomers were separaed by flash chromatography on a small scale or by recrystallization on a larger scale. Both diastereoisomers were then treated separately with *t*-BuOK/DMSO to give an enol ether which was directly submitted to ozonolysis (O_3/Me_2S) to afford (*S*)- and (*R*)-**2** in 63 and 57% yield, respectively[5]). The enantiomeric purity was checked at this stage by capillary GC on a chiral phase (β-cyclodextrin). The enantiomer ratio reflected exactly the *cis*/*trans* ratio measured at the previous stage. Very high enantiomer ratios (er > 99.8%) were obtained for both enantiomers (*S*)- and (*R*)-**2**.

The absolute configuration of **2** was determined by two independent approaches. Firstly, NOE measurements on both diastereoisomers **4** allowed us to determine their relative configuration, and since the absolute configuration at C(4) is known to be (*R*), it established the absolute configuration of **2** as depicted in *Scheme 1*. A second independent way to assign the configuration consisted in the preparation of (2*R*,5*S*)- and (2*S*, 5*S*)-**5** (1:10) from L-lactic acid according to *Greiner* and *Ortholand* who had also established without ambiguity their relative configuration by NOE measurements [9] (*Scheme 2*). Alkylation of (*S*)-**2** *via* its enolate furnished (2*S*,5*R*)- and (2*S*,5*S*)-**5** as a 1.7:1 mixture of diastereoisomers; this minor isomer was identical to the major one prepared from L-lactic acid. As expected, the major isomer, (2*S*,5*R*)-**5**, is the mirror image of (2*R*,5*S*)-**5** prepared from L-lactic acid.

Scheme 2



Conclusions. – We have reported here the easy preparation of a chiral glycolic acid equivalent in both enantiomeric forms and known absolute configuration from easily available and cheap D-mannitol. We are now investigating the combination of enolate and radical alkylations for the preparation of cyclic and acyclic optically pure α-hydroxy acids.

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[5]) The intermediate enol ether can be isolated in 80% yield but is quite volatile and extremely acid-sensitive. The yield of the ozonolysis varies between 75 and 85%. It is more convenient to run the ozonolysis and the elimination in a one-pot procedure (see *Exper. Part*).

Experimental Part

General. THF was freshly distilled from K under N_2, 1,2-dimethoxyethane (DME) and pyridine were distilled from CaH_2. Flash column chromatography (FC) and filtration: *Baker* silica gel (0.063–0.200 mm), AcOEt, Et_2O, and hexane as eluents. TLC: *Macherey-Nagel SIL G-25 UV$_{254}$* anal. plates; detection with UV, I_2, or by spraying with a soln. of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot 4\,H_2O$ (10 g), conc. H_2SO_4 soln. (60 ml), and H_2O (940 ml) with subsequent heating. GC: *Carlo Erba HRGC 5300*, *Supelco β DEX^{TM} 120*, 30-m capillary column. IR: *Perkin-Elmer 16PC*. FT-IR: *Mattson Unicam 5000*. NMR: *Bruker AM 360* (^{1}H 360 MHz, ^{13}C 90.5 MHz) and *Varian Gemini 200* (^{1}H 200 MHz, ^{13}C 50.3 MHz); chemical shifts δ in ppm rel. to $SiMe_4$ (= 0 ppm). MS: *Vacuum Generators Micromass VG 70/70E* and *DS 11-250*; CI (NH_3), EI (70 eV); *m/z* (%). Elementary analyses: *Ilse Beetz*, Mikroanalytisches Laboratorium, D–8640 Kronach, and *Ciba-Geigy*, Mikrolabor, CH–1723 Marly.

*1,2-Bis[2-(*tert*-butyl)-2-methyl-1,3-dioxolan-4-yl]ethane-1,2-diol* (**3**). D-Mannitol (18.2 g, 0,1 mol) and 2,2-dimethoxy-3,3-dimethylbutane [7] (33.6 g, 0.23 mol) were added to a soln. of $SnCl_2$ (378 mg, 2.0 mmol) in DME (100 ml), and the mixture was heated at reflux until the D-mannitol was completely dissolved (*ca.* 50 min). After evaporation of DME, the solid residue was recrystallized in hexane: mixture of 3 diastereoisomers (33.1 g, 96%). IR (film): 3433, 3394, 2912, 1495, 1392, 1168, 1148, 1066, 890, 609. CI-MS: 347.5 (82.6, $[M + 1]^+$), 331 (18), 289 (90), 247 (70), 147 (100), 101 (55). Anal. calc. for $C_{18}H_{34}O_6$ (346.47): C 62.40, H 9.89; found: C 62.36, H 9.95.

Diastereoisomer 1: ^{1}H-NMR (200 MHz, $CDCl_3$): 4.2 (*dd*, *J* = 5.7, 8.27, H–C(1), H–C(6)); 4.05 (*m*, H–C(2), H–C(5)); 3.9 (*t*, *J* = 8.55, H–C(1), H–C(6)); 3.76 (*m*, H–C(3), H–C(4)); 2.6 (*d*, *J* = 6.27, 2 OH); 1.28 (*s*, Me); 0.96 (*s*, *t*-Bu). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 114.9 (*s*); 77.9 (*d*); 72.3 (*d*); 67.6 (*t*); 39.3 (*s*); 25.2 (*q*); 20.5 (*q*).

Diastereoisomer 2: ^{1}H-NMR (200 MHz, $CDCl_3$): 4.18 (*m*, 4 H); 3.82 (*m*, 4 H); 2.57 (*d*, *J* = 4.28, 2 OH); 1.27 (*s*, Me); 0.97 (*s*, *t*-Bu). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 114.8 (*s*); 114.5 (*s*); 77.6 (*d*); 75.2 (*d*); 71.7 (*d*); 67.5 (*t*); 67.4 (*t*); 39.2 (*s*); 38.2 (*s*); 25.2 (*q*); 25.1 (*q*); 20.3 (*q*); 18.4 (*q*).

Diastereoisomer 3: ^{1}H-NMR (200 MHz, $CDCl_3$): 4.18 (*m*, 4 H); 3.84 (*m*, 4 H); 2.58 (*d*, *J* = 6.24, OH); 1.27 (*s*, Me); 0.97 (*s*, *t*-Bu). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 114.6 (*s*); 75.3 (*d*); 71.5 (*d*); 67.6 (*t*); 38.3 (*s*); 25.3 (*q*); 18.6 (*q*).

*[2-(*tert*-Butyl)-2-methyl-1,3-dioxolan-4-yl]methyl Toluene-4-sulfonate* (**4**). Dry $Pb(OAc)_4$ (44.3 g, 0.1 mol) was added to an ice-cooled soln. of **3** (32.1 g, 92 mmol) in THF (150 ml) with stirring ($T < 10°$). The soln. was stirred for 30 min at 0° and 90 min at r.t. After filtering through *Celite* and cooling to 0°, a soln. of $NaBH_4$ (7.56 g, 200 mmol) in 4% aq. NaOH soln. (130 ml) was added dropwise with vigorous stirring ($T < 10°$). After stirring for 30 min at 0° and for 90 min at r.t., the soln. was set to pH 8 by adding solid NH_4Cl. THF was removed under reduced pressure and the resulting aq. soln. saturated with NaCl. After extraction with AcOEt, the combined org. layers were washed with sat. $NaHCO_3$ soln. and dried (Na_2SO_4). Evaporation of the solvent gave crude 2-(*tert*-butyl)-2-methyl-1,3-dioxolan-4-methanol (30.0 g, 93%) as a mixture of 2 diastereoisomers which was used without further purification for the next step. IR ($CHCl_3$): 2978, 2964, 2877, 2359, 2342, 1393, 1374, 1162, 1058, 731. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.28 (*m*, 0.5 H); 4.06 (*m*, 1.5 H); 3.77 (*m*, 1.5 H); 3.59 (*m*, 1.5 H); 2.07 (br. *s*, OH); 1.29 (*s*, Me, diast. *1*); 1.27 (*s*, Me, diast. *2*); 0.98 (*s*, *t*-Bu, diast. *1*); 0.96 (*s*, *t*-Bu, diast. *2*). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 114.9 (*s*); 114.6 (*s*); 77.7 (*d*); 75.6 (*d*); 66.3 (*t*); 62.9 (*t*); 62.4 (*t*); 39.3 (*s*); 38.2 (*s*); 225.1 (*q*); 20.5 (*q*); 18.5 (*q*). CI-MS: 175.3 (100, $[M + 1]^+$), 147 (36), 129 (24), 117 (25), 101 (87). Anal. calc. for $C_9H_{18}O_3$ (174.24): C 62.04, H 10.41; found: C 62.06, H 10.65.

Toluene-4-sulfonyl chloride (34.2 g, 180 mmol) was added portionwise with stirring to an ice-cooled soln. of the previous alcohol (30.0 g, 172 mmol) in pyridine (100 ml). After stirring at r.t. for 5 h, Et_2O (400 ml) was added, and the mixture was washed with 1N HCl. The org. layer was dried (Na_2SO_4) and evaporated to give the crude product, which was crystallized from hexane to give **4** as a 1:1 mixture of diastereoisomers (52.0 g, 92%). IR (KBr): 2971, 1375, 1361, 1352, 1169, 982, 972, 813, 792, 559. CI-MS: 329 (46, $[M + 1]^+$), 271 (32), 229 (100), 157 (35), 101 (6). Anal. calc. for $C_{16}H_{24}O_5S$ (328.43): C 58.51, H 7.37, S 9.76; found: C 58.43, H 7.38, S 9.58.

The diastereoisomers were separated by FC (AcOEt/hexane 1:10), (2*S*, 4*R*)-**4** eluting first (R_f 0.26) followed by (2*R*,4*R*)-**4** (R_f 0.20). On a large scale, the diastereoisomers were separated by recrystallizations from AcOEt/hexane 1:10.

(2*S*,4*R*)-**4**: $[\alpha]_D^{20} = +11.5$ (*c* = 0.74, CH_2Cl_2). ^{1}H-NMR (360 MHz, $CDCl_3$): 7.79 (*d*, *J* = 8.3, 2 arom. H); 7.34 (*d*, *J* = 8.3, 2 arom. H); 4.1 (*m*, 4 H); 3.69 (*t*, *J* = 7.7, H–C(5)); 2.44 (*s*, *Me*C_6H_4); 1.18 (*s*, Me); 0.89 (*s*, *t*-Bu). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 144.9 (*s*); 133.0 (*s*); 129.8 (*d*); 127.9 (*d*); 115.7 (*s*); 74.2 (*d*); 69.6 (*t*); 67.2 (*t*); 39.3 (*s*); 25.1 (*q*); 21.6 (*q*); 20.4 (*q*).

(2*R*,4*R*)-**4**: $[\alpha]_D^{20} = +1.3$ (*c* = 0.79, CH_2Cl_2). ^{1}H-NMR (360 MHz, $CDCl_3$): 7.79 (*d*, *J* = 8.3, 2 arom. H); 7.34 (*d*, *J* = 8.3, 2 arom. H); 4.3 (*quint.*, *J* = 6.28, H–C(4)); 4.0 (*m*, CH_2OTs, 1 H–C(5)); 3.6 (*dd*, *J* = 6.28, 8.27, 1 H–C(5)); 2.44 (*s*, *Me*C_6H_4); 1.2 (*s*, Me); 0.88 (*s*, *t*-Bu). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 144.9 (*s*); 132.9 (*s*); 129.9 (*d*); 127.9 (*d*); 115.4 (*s*); 72.4 (*d*); 69.4 (*t*); 66.8 (*t*); 38.1 (*t*); 25.1 (*q*); 21.6 (*q*); 18.4 (*q*).

(S)-2-(tert-Butyl)-2-methyl-1,3-dioxolan-4-one ((*S*)-**2**). A soln. of (2*S*,4*R*)-**4** (6.56 g, 20 mmol) in DMSO (10 ml) was added at 50° to a soln. of *t*-BuOK (4.48 g, 40 mmol) in DMSO (40 ml). After 15 min, H_2O (50 ml) was added, the mixture extracted with pentane (4 × 50 ml), and the combined org. phase washed with H_2O (3 × 10 ml), dried (Na_2SO_4), and evaporated to give the crude enol ether. The enol ether was dissolved in CH_2Cl_2 (600 ml) and cooled to −78°. Ozone was passed through the soln. until persistence of a blue color. Excess of ozone was flushed out by bubbling O_2 through the soln. until decoloration. The mixture was then treated at −78° with Me_2S (10 ml), allowed to warm up to r.t., washed with H_2O (2 × 50 ml), dried (Na_2SO_4), and evaporated. The crude product was purified by FC (Et_2O/hexane 1:10): (*S*)-**2** (2.00 g, 63%). GC: t_R 771 s. $[\alpha]_D^{20} = +8.9$ ($c = 1$, CH_2Cl_2). IR (film): 3021, 3016, 2360, 2341, 1798, 1211, 745, 738. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.36 (*A* of *AB*, $J_{AB} = 14$); 4.33 (*B* of *AB*, $J_{AB} = 14$); 1.5 (*s*, Me); 1.02 (*s*, *t*-Bu). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 171.3 (*s*); 117.7 (*s*); 64.2 (*t*); 39.0 (*s*); 24.2 (*q*); 20.1 (*q*). CI-MS: 159 (100, $[M + 1]^+$), 101 (20), 99 (2), 84 (2), 83 (22). Anal. calc. for $C_8H_{14}O_3$ (158.20): C 60.74, H 8,92; found: C 60.73, H 9.12.

(R)-2-(tert-Butyl)-2-methyl-1,3-dioxolan-4-one ((*R*)-**2**). Starting from (2*R*,4*R*)-**4** (6.56 g, 20 mmol) according to the procedure for (*S*)-**2**. Optically pure (*R*)-**2** (1.88 g, 57%) was isolated. GC: t_R 742 s. $[\alpha]_D^{20} = -9.6$ ($c = 1.3$, CH_2Cl_2).

(2S,5R)- and (2S,5S)-2-(tert-Butyl)-2,5-dimethyl-1,3-dioxolan-4-one (**5**). *By Alkylation of (S)-***2**. A soln. of 1.6M BuLi in hexane (6.9 ml, 11 mmol) was added to a soln. of $(i\text{-}Pr)_2NH$ (1.56 ml, 11 mmol) in THF (50 ml) containing HMPA (2.5 ml) at −20°. After cooling at −78°, a soln. of (*S*)-**2** (1.58 g, 10 mmol) in THF (5 ml) was added dropwise. After 15 min, MeI (1.87 ml, 30 mmol) was added and the mixture stirred for 1 h at −78°. The reaction was quenched with sat. $NaHCO_3$ soln. (10 ml) and extracted with Et_2O (5 × 100 ml). The combined org. layer was washed with sat. $NaHCO_3$ soln. dried (Na_2SO_4), and evaporated. FC of the crude product (AcOEt/hexane 1:20) gave **5** (1.5 g, 87%) of (2*S*,5*R*)-**5**/(2*S*,5*S*)-**5** 1.7:1. IR (film): 2980, 2878, 1797, 1380, 1252, 1213, 1150, 1046, 929. CI-MS: 173.3 (100 $[M + 1]^+$), 141.2 (3), 115.1 (17), 101.1 (32), 83.15 (28). Anal. calc. for $C_9H_{16}O_3$ (172.27): C 62.77, H 9.36; found: C 62.86, H 9.23.

(2*S*,5*R*)-**5**: GC: t_R 376 s. $[\alpha]_D^{20} = -8.5$ ($c = 1.0$, CH_2Cl_2). ^{1}H-NMR (360 MHz, $CDCl_3$): 4.47 (*q*, $J = 6.86$, H–C(5)); 1.45 (*s*, Me–C(2)); 1.42 (*d*, $J = 6.86$, Me–C(5)); 0.99 (*s*, *t*-Bu). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 174.1 (*s*); 116.2 (*s*); 72.1 (*d*); 39.9 (*s*); 24.4 (*q*); 23.2 (*q*); 19.2 (*q*).

(2*S*,5*S*)-**5**: GC: t_R 413 s. $[\alpha]_D^{20} = +48.1$ ($c = 1.1$, CH_2Cl_2). ^{1}H-NMR (360 MHz, $CDCl_3$): 4.44 (*q*, $J = 6.9$, H–C(5)); 1.49 (*s*, Me–C(2)); 1.44 (*d*, $J = 6.9$, Me–C(5)); 0.97 (*s*, *t*-Bu). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 144.4 (*s*); 115.7 (*s*); 70.6 (*d*); 38.4 (*s*); 24.8 (*q*); 19.8 (*q*); 16.8 (*q*).

From L-*Lactic Acid.* From L-lactic acid (4.5 g, 50 mmol) and pinacolone (10.0 g, 100 mmol) according to [9]. (2*R*,5*S*)-**5**: GC: t_R 384 s. $[\alpha]_D^{20} = +7.9$ ($c = 1.1$, CH_2Cl_2). (2*S*,5*S*)-**5**: GC: t_R 413 s. $[\alpha]_D^{20} = +48.5$ ($c = 1$, CH_2Cl_2).

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