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A New Synthetic Route to β-Unsubstituted β-Lactones by Intramolecular Cyclization

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Abstract—When carboxylic acids β-substituted by a *tert*-butoxy group were treated with thionyl chloride, an intermediate acyl chloride β-substituted by a hydroxyl group was likely formed. Its subsequent intramolecular cyclization produced novel β-lactones in one step. Two enantiomerically enriched lactones could be prepared via intermediates obtained by enzymatic hydrolysis.

Introduction

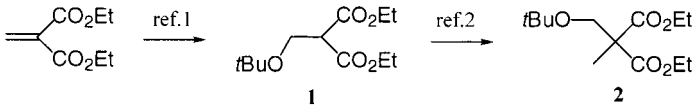
We recently obtained good results for the conjugate nucleophilic addition to diethyl methylenemalonate.[1] Compounds such as **1** thus became easily available. Several of these products could be reduced into diols then subjected to enzyme catalyzed acylation.[2] We also prepared **2** by alkylation of **1** with methyl iodide (Scheme 1).[2]

As β-lactones are compounds with versatile applicability,[3] we envisaged using **2** in preparation of functionalized compounds **3** with several centers likely to react with nucleophiles. Such 'polyalkylating agents' could find applications in organic synthesis. Their biological properties should also be evaluated (Scheme 2).

While numerous β-lactones can be obtained, the ones which are unsubstituted α to the oxygen are fairly scarce although several results in obtaining such compounds were pointed out in the case of spiro β-lactones,[4] serine β-lactones[5] and some simple β-lactones.[6] We then envisaged the possibility of preparing racemic lactones **3** in several steps starting from **2** via a cyclization to generate the lactone moiety. Extension to the non-racemic series should also be worth studying.[7]

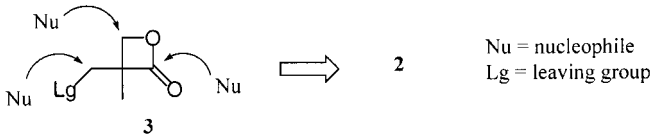
Results and Discussion

Saponification of **2** gave hemiester **4** and we were pleased to observe that when the latter was treated with thionyl chloride in refluxing CH_2Cl_2 the cyclization product **5** was obtained. This preparation of lactone **5**, in one step, involves nearly concomitant formation of an acid chloride moiety and deprotection of the *tert*-butoxy ether. Several experimental conditions were tested with the aim of minimizing



1 **2**

Scheme 1.



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Scheme 2.

Keywords: β-lactones; cyclization; reduction; enzymatic hydrolysis.

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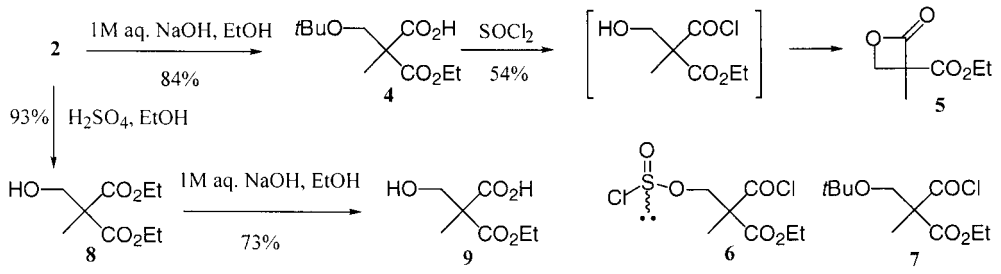


Scheme 3.

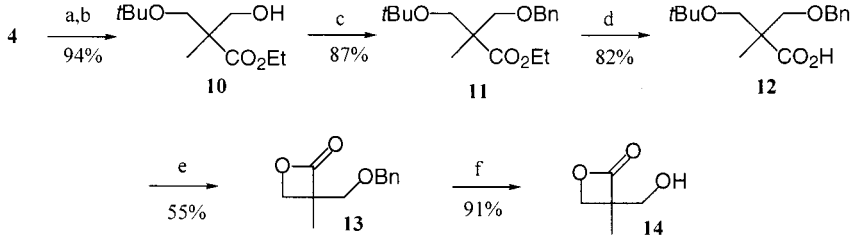
formation of the unwanted diastereomeric compounds **6** and of **7**. Finally when 2 equiv. of thionyl chloride were quickly added to a 1.7 M solution of **4** in refluxing CH_2Cl_2, a 54% yield was attained after 10 h at reflux (Scheme 3). This moderate yield is however interesting when taking into account the fact that such cyclizations to β-lactones unsubstituted α to the oxygen are usually very difficult, albeit possible in some cases via a Mitsunobu reaction.[5a,6c] On the other hand cyclization of compounds substituted by alkyl or aryl groups leads to good results by the usual methods due to the 'gem-dialkyl effect'.[8] Attempts to cyclize **9**, which is available from **2** by acidic treatment providing **8**, followed by saponification, did not lead to **5** by reaction with $PhSO_2Cl$/pyridine[4b,c,9] and using MsCl/Na_2CO_3 in CH_2Cl_2[10] mainly yielded unidentified products together with a very small amount of lactone **5**. This new method then appeared as complementary to the already known ones.

The good result with **4** prompted us to pursue our work towards preparation of lactones such as **3** but with the leaving group replaced by a hydroxyl group. Therefore compound **10** was prepared by reduction of a mixed anhydride.[11] Its benzylation with NaH/BnBr in THF led to poor results (30% yield) but use of benzyl 2,2,2-trichloroacetamidate in acidic medium[12] gave **11** in good yield. Saponification with LiOH, H_2O/THF or 1 M aq. NaOH/EtOH failed, probably because the molecule is too sterically crowded. Therefore **11** was saponified according to Gassman et al. conditions.[13] The first attempts of obtaining **13** by treatment with $SOCl_2$ led to a mixture of the expected product and of anhydride corresponding to **12**, or even only to the last one, depending on the experimental conditions. Fortunately when a solution of **12** in $CHCl_3$+$SOCl_2$ was added to refluxing $SOCl_2$ in the presence of a small amount of MeOH to acidify the reaction mixture, **13** was obtained in a reasonable yield after 16 h heating. Debenzylation gave lactone **14** (Scheme 4).

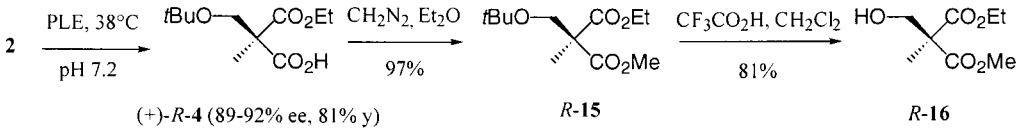
To extend our results to non-racemic products, we subjected **2** to PLE enzymatic hydrolysis. We thus obtained (+)-*R*-**4** in 87% yield and 89–92% ee (there were little variations of this ee according to the experimental conditions) measured by chiral gas phase chromatography or by ^{1}H NMR of the ammonium salt with (+)-*R*-α-methylbenzylamine. This result is comparable to the one obtained by Luyten et al. from the dimethyl ester.[14] The absolute configuration was assessed by chemical correlation leading to the known **16**[14] (Scheme 5).

Both enantiomers of lactone **14** could be obtained from a sample of (+)-*R*-**4** of 89% ee. The *S*-lactone was prepared through the β-hydroxyester, as in the racemic synthesis, whereas obtaining the *R*-lactone involved reduction of the ester group. We first used BH_3/Me_2S in THF as the reducing agent.[15] However, we obtained mixtures of β-hydroxyacid and of diol. We then replaced it by $Ca(BH_4)_2$ in EtOH[16] and we could thus prepare (−)-*R*-**17** in nearly quantitative yield (Scheme 6).

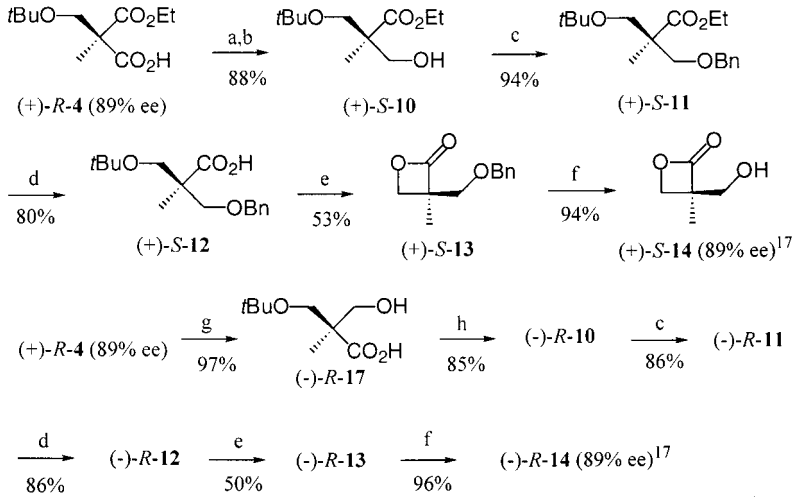
β-Lactones **5**, **13** and **14** were characterized by the spectral data and in particular by IR absorptions at 1813–1830 cm^{-1} (ν C=O). Difficulty of access to this kind of compounds is not due to their instability and these lactones could be kept



Scheme 4. (a) $ClCO_2/Et_3N$; (b) $NaBH_4$, MeOH; (c) $CCl_3CNHOBn$, CF_3SO_3H; (d) 8.0 equiv. of *t*BuOK, 2 H_2O, Et_2O; (e) $SOCl_2$; (f) H_2, 10% Pd/C.



Scheme 5.



Scheme 6. (a) $ClCO_2Me/Et_3N$; (b) $NaBH_4$, MeOH; (c) $CCl_3CNHOBn$, CF_3SO_3H; (d) 8 *t*BuOK, 2 H_2O, Et_2O; (e) $SOCl_2$; (f) H_2, 10% Pd/C; (g) $Ca(BH_4)_2$, EtOH; (h) EtOH, $SOCl_2$.

for several weeks at low temperature without decomposition.

Finally this new one step cyclization method was successful for obtaining several new β-lactones. It also could be applied to the synthesis of optically active compounds without damage to the enantiomeric excess.

Experimental

NMR spectra were recorded on a Bruker AC 400 instrument at 400 and 100.6 MHz for ^1H and ^{13}C, respectively, in $CDCl_3$ and using TMS as the internal reference. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. Optical rotations were measured with a Perkin–Elmer 343 polarimeter. Chromatographic analyses were performed with a Hewlett–Packard HP 6890 apparatus equipped with a 30 m Restek β-DEX-sm column. IR spectra were recorded with a Genesis Matteson infrared spectrophotometer. Melting points were measured on a Reichert apparatus and are uncorrected. Elemental analyses were performed by the service de microanalyse, CNRS, ISCN, Gif-sur-Yvette. Mass spectra were obtained by GPC/MS (Varian 3300 DB5 sm/ITD 800 Finnigan MAT). High-resolution mass measurements were performed at the CRMPO, Rennes.

2-(*tert*-Butoxymethyl)-3-ethoxy-2-methyl-3-oxopropanoic acid (4 and (+)-*R*-4). Preparation of the racemic monoester **4** was carried out by adding at room temperature a 1 M NaOH aqueous solution (5.9 mL) to a solution of diester **2**[2] (1.400 g, 5.38 mmol) in ethanol (3.5 mL). The reaction mixture was stirred overnight then ethanol was evaporated. The aqueous phase was extracted with ether (2×10 mL), acidified with a 10% HCl solution then extracted again with ether (3×15 mL). The last organic phases were dried ($MgSO_4$) and evaporated to afford the pure monoester **4** as a colorless oil (1.053 g, 84%). ^1H NMR δ 1.21 (s, 9H), 1.29 (t, 3H, J=7.1 Hz), 1.46 (s, 3H), 3.63 (d, 1H, J=8.4 Hz), 3.80 (d, 1H, J=8.4 Hz), 4.24 (q, 2H, J=7.1 Hz); ^{13}C NMR δ 13.9 (CH_3), 18.3 (CH_3), 27.1 (3C, CH_3), 54.5 (quat. C), 61.7 (CH_2), 65.1 (CH_2), 74.2 (quat. C), 171.4 (*C*O), 174.6 (*C*O); IR (film) cm^{-1} 3500–2500, 2979, 2937, 1747 (br.), 1365, 1302, 1257, 1193, 1083, 1025; anal. calcd. for $C_{11}H_{20}O_5{\cdot}0.4H_2O$: C, 55.12; H, 8.68, found: C, 55.14; H, 8.62. The optically active monoester (+)-*R*-**4** was obtained by enzymatic hydrolysis of diester **2** (3.102 g, 11.9 mmol) which was added to a pH 7 phosphate buffer (0.1 M KH_2PO_4, 30 mL). After adding of a 1 M NaOH aqueous solution to attain pH 7.2, then of PLE (250 μL, 937.5 units), the reaction mixture was stirred at 38°C overnight with maintaining pH at 7.2 by using a pH-stat to control addition of a 1 M NaOH aqueous solution. Extraction with ether (3×50 mL), acidification to pH 1–2 with a 10% HCl solution, another extraction with ether (3×100 mL), drying of the last organic phases ($MgSO_4$) and evaporation yielded (+)-*R*-(**4**) as an oil (2.523 g, 81%). This experiment led to a 89% ee. However, a 92% ee ($[\alpha]_D^{20}$ +4.1 (*c*=4.0, MeOH)) was obtained another time when working at a lower scale.

(±)-Ethyl 3-methyl-2-oxetanone-3-carboxylate (5). A solution of monoester **4** (199 mg, 0.86 mmol) in CH_2Cl_2 (0.5 mL) was heated to reflux under argon then $SOCl_2$ (124 μL, 1.7 mmol) was added through a septum. The reaction was stirred overnight at the same temperature. Cooling and evaporation left an oil. Purification by column chromatography on silica gel (cyclohexane/AcOEt 8:2) yielded pure **5** as a colorless oil (73 mg, 54%). ^1H NMR δ 1.32 (t, 3H, J=7.1 Hz), 1.71 (s, 3H), 4.13 (d, 1H, J=5.1 Hz), 4.28 (q, 2H, J=7.1 Hz), 4.67 (d, 1H, J=5.1 Hz); ^{13}C NMR δ 14.0 (CH_3), 16.9 (CH_3), 62.3 (quat. C), 62.5 (CH_2), 69.3 (CH_2), 167.29 (*C*O), 167.31 (*C*O); IR (film) cm^{-1} 2989, 1830, 1733, 1286, 1159, 1097; GPC/MS (EI) *m/z* (rel. int) 159 (MH^+, 5), 129 (9), 115 (14), 99 (23), 86 (27), 69 (100), 41 (88); anal. calcd. for $C_7H_{10}O_4$: C, 53.16, H, 6.37, found: C, 53.42, H, 6.48.

(±)-Ethyl 3-chloro-2-[(chlorosulfinyl)oxy]methyl-2-methyl-3-oxopropanoate (6) (both diastereomers). A mixture of monoester **4** (258 mg, 1.11 mmol) and of $SOCl_2$ (800 μL, 11.1 mmol) was heated to reflux under argon and without solvent and stirred at this temperature for 18 h. Cooling then evaporation left a yellow oil mainly consisting of crude **6**

(229 mg, 74%). ^{1}H NMR δ 1.33 (t, 3H, J=7.1 Hz), 1.66 (s, 3H, (dia 1)), 1.68 (s, 3H, (dia 2)), 4.31 (q, 2H, (dia 1), J=7.1 Hz), 4.32 (q, 2H, (dia 2), J=7.1 Hz), 4.63 (d, 1H, (dia 1), J=10.5 Hz), 4.71 (d, 1H, (dia 1), J=10.5 Hz), 4.90 (d, 1H, (dia 2), J=10.3 Hz), 4.96 (d, 1H, (dia 2), J=10.3 Hz); ^{13}C NMR δ 13.8 (CH_3), 18.5 (CH_3), 62.8 (quat. C (dia 1)), 62.9 (quat. C (dia 2)), 63.2 (CH_2), 66.5 (CH_2 (dia 1)), 66.6 (CH_2 (dia 2)), 166.5 (CO), 170.5 (CO); IR (film) cm^{-1} 2987, 1799, 1745, 1226, 962, 813.

(±)-Ethyl 2-(*tert*-butoxymethyl)-3-chloro-2-methyl-3-oxopropanoate (7). A solution of monoester **4** (1.022 g, 4.4 mmol) in CH_2Cl_2 (4.4 mL) was heated to reflux under stirring then a solution of $SOCl_2$ (950 μL, 13.2 mmol) in CH_2Cl_2 (2.6 mL) was added quickly. After 16 h stirring at the same temperature cooling then evaporation left a yellow oil mainly consisting of crude **7** (1.048 g, 95%). ^{1}H NMR δ 1.17 (s, 9H), 1.29 (t, 3H, J=7.1 Hz), 1.57 (s, 3H), 3.65 (d, 1H, J=8.7 Hz), 3.92 (d, 1H, J=8.7 Hz), 4.23 (m, 2H); ^{13}C NMR δ 14.1 (CH_3), 18.9 (CH_3), 27.2 (3C, CH_3), 62.1 (CH_2), 64.4 (CH_2), 64.5 (quat. C), 73.4 (quat. C), 168.6 (CO), 171.7 (CO); IR (film) cm^{-1} 2977, 2940, 1799, 1747, 1365, 1257, 1195, 1087.

(±)-Diethyl 2-(hydroxymethyl)-2-methylmalonate (8). 18 M H_2SO_4 (1.15 mL) was added dropwise with stirring to a solution of **2** (1.915 g, 7.36 mmol) in EtOH (20 mL). After 17 h refluxing the cooled solution was evaporated. Adding of water (10 mL), neutralization to pH 7 by adding of a saturated solution of $NaHCO_3$, extraction with ether (3×30 mL), drying ($MgSO_4$) and evaporation left practically pure **8** as a colorless oil which was used without further purification in the following step (1.397 g, 93%). This compound is also available by aldol condensation between diethyl methyl malonate and formaldehyde.[18] ^{1}H NMR δ 1.28 (t, 6H, J=7.1 Hz), 1.44 (s, 3H), 2.88 (t, 1H, J=7.1 Hz), 3.85 (d, 2H, J=7.1 Hz), 4.23 (q, 4H, J=7.1 Hz); ^{13}C NMR δ 13.9 (2 CH_3), 17.5 (CH_3), 55.8 (quat. C), 61.5 (2 CH_2), 66.7 (CH_2), 171.6 (CO); IR (film) cm^{-1} 3507, 2983, 1729, 1303, 1253, 1120, 1052; GPC/MS (EI) m/z (rel. int.) 205 (MH^+, 100), 187 (9), 175 (42), 174 (55), 129 (52), 115 (31), 100 (31), 100 (47), 85 (48), 57 (42).

(±)-3-Ethoxy-2-(hydroxymethyl)-2-methyl-3-oxopropanoic acid (9). A 1 M NaOH aqueous solution (1.22 mL) was added to a solution of **8** (250 mg, 1.22 mmol) in EtOH (1 mL). The reaction mixture was stirred at room temperature for 18 h. Ethanol was then evaporated and the aqueous phase was extracted with ether (2×5 mL), acidified with a 10% HCl solution then extracted again with ether (3×5 mL). The last organic phases were dried ($MgSO_4$) and evaporated to afford practically pure **9** as a colorless oil which was used without further purification in the following step (158 mg, 73%). ^{1}H NMR δ 1.30 (t, 3H, J=7.1 Hz), 1.48 (s, 3H), 3.89 (d, 1H, J=11.4 Hz), 3.93 (d, 1H, J=11.4 Hz), 4.26 (q, 2H, J=7.1 Hz); ^{13}C NMR δ 14.0 (CH_3), 17.6 (CH_3), 45.8 (quat. C), 62.1 (CH_2), 66.5 (CH_2), 171.6 (CO), 176.2 (CO); IR (film) cm^{-1} 3477, 3400–2600; 2987, 1712, 1253, 1126, 1045.

3-(*tert*-Butoxy)-2-(hydroxymethyl)-2-methylpropanoic acid ((−)-*R*-17). A solution of KOH (239 mg, 4.26 mmol) and of $CaCl_2$ (945 mg, 8.51 mmol) in EtOH (5.5 mL) was mixed to a solution of monoester (*R*)-**4** of 89% ee (449 mg, 1.93 mmol) in EtOH (20 mL). The mixture was cooled to 0°C then a suspension of $NaBH_4$ (439 mg, 11.61 mmol) in EtOH (4 mL) was added with stirring. The reaction was allowed to proceed for 17 h at room temperature then cooled to 0°C. Addition of a 10% HCl solution at the same temperature to attain pH 2–3, evaporation of EtOH, adding of water (10 mL), saturation with NaCl, extraction with CH_2Cl_2 (3×20 mL), drying ($MgSO_4$) then evaporation provided practically pure (−)-*R*-**17** as an oil that crystallized slowly on standing (358 mg, 97%), 89% ee, $[\alpha]_D^{20}$ −2.2 (c=21.7, $CHCl_3$). Mp 50.2–51.0°C, ^{1}H NMR δ 1.20 (s, 3H, H-5), 1.24 (s, 9H), 3.57 (d, 1H, J=8.9 Hz), 3.60 (d, 1H, J=8.9 Hz), 3.68 (d, 1H, J=11.4 Hz), 3.80 (d, 1H, J=11.4 Hz); ^{13}C NMR δ 18.1 (CH_3), 27.2 (3C, CH_3), 47.9 (quat. C), 66.0 (CH_2), 67.1 (CH_2), 74.7 (quat. C), 178.6 (CO); IR (nujol) cm^{-1} 3500–2500, 3311, 1698, 1463, 1365, 1195, 1085, 1031; anal. calcd. for $C_9H_{18}O_4$: C, 56.82; H, 9.54, found: C, 56.64; H, 9.51.

Ethyl 3-(*tert*-butoxy)-2-(hydroxymethyl)-2-methylpropanoate (10, (+)-*S*-10, (−)-*R*-10). Et_3N (945 μL, 6.82 mmol) was added at 0°C under argon to a stirred solution of **4** (1.535 g, 6.62 mmol) in THF (14 mL) then methyl chloroformate (525 μL, 6.82 mmol) was introduced dropwise at the same temperature. The reaction was allowed to proceed for 1 h then the reaction mixture was filtered and the precipitate was washed with cooled THF. Filtrate was cooled to −78°C, $NaBH_4$ (500 mg, 13.23 mmol) was introduced portionwise and methanol (2.7 mL) was added dropwise over 30 min. After 1 h more at the same temperature the cooling bath was removed then a 10% HCl solution (25 mL) was added slowly. Evaporation of THF, extraction with CH_2Cl_2 (3×20 mL), drying ($MgSO_4$), evaporation, and column chromatography on silica gel (cyclohexane/AcOEt 8:2), provided **10** as a colorless oil (1.35 g, 94%). ^{1}H NMR δ 1.15 (s, 3H), 1.17 (s, 9H), 1.27 (t, 3H, J=7.1 Hz), 2.98 (dd, 1H, OH, J=7.6, 5.4 Hz), 3.35 (d, 1H, J=8.4 Hz), 3.70 (dd, 1H, J=11.1, 7.6 Hz), 3.71 (d, 1H, J=8.4 Hz), 3.82 (dd, 1H, J=11.1, 5.4 Hz), 4.18 (m, 2H); ^{13}C NMR δ 14.1 (CH_3), 17.9 (CH_3), 27.2 (3C, CH_3), 48.1 (quat. C), 60.6 (CH_2), 66.3 (CH_2), 67.4 (CH_2), 73.2 (quat. C), 175.4 (CO); IR (film) cm^{-1} 3484, 2975, 2937, 1729, 1365, 1234, 1197, 1083, 1045; GPC/MS (EI) m/z (rel. int.) 203 (M^+–Me, 3), 185 (3), 163 (100), 145 (21), 132 (17), 100 (18), 71 (18), 57 (51), 41 (61); GPC/MS (CI) m/z (rel. int.) 219 (MH^+, 0.1), 163 (100); anal. calcd. for $C_{11}H_{22}O_4{\cdot}0.15H_2O$: C, 59.73; H, 10.09, found: C, 59.68; H, 10.01. The same reaction from a 89% ee sample of (+)-*R*-**4** (1.876 g, 8.08 mmol) provided (+)-*S*-**10** (1.589 g, 88%), $[\alpha]_D^{20}$ +0.8 (c=1.9, $CHCl_3$), 89% ee. Preparation of (−)-*R*-**10** was carried out starting from a solution of (−)-*R*-**17** (344 mg, 1.81 mmol) in EtOH (1.8 mL) that was added dropwise, at 0°C and under argon to a stirred mixture of $SOCl_2$ (200 μL, 2.71 mmol) and of EtOH (4.5 mL). The reaction mixture was stirred for 20 h at room temperature, EtOH was evaporated, ether was added (20 mL), this solution was successively washed with a saturated solution of $NaHCO_3$ then with brine, dried ($MgSO_4$), and evaporated to afford practically pure (−)-*R*-**10** as a colorless oil which was used without further purification in the following step (336 mg, 85%). $[\alpha]_D^{20}$ 0.5 (c=2.0, $CHCl_3$), 89% ee.

Ethyl 3-(benzyloxy)-2-(*tert*-butoxymethyl)-2-methylpropanoate (11, (+)-*S*-11 and (−)-*R*-11). To a stirred solution

of alcohol **10** (277 mg, 1.27 mmol) and of benzyl 2,2,2-trichoroacetamidate (472 μL, 2.54 mmol) in CH_2Cl_2 (2.5 mL), was added at 0°C a catalytic amount of trifuoromethanesulfonic acid (11 μL, 0.13 mmol). After stirring for 1 h, a saturated solution of $NaHCO_3$ (10 mL) was added. Extraction with CH_2Cl_2 (2×10 mL) then drying ($MgSO_4$) and evaporation of the organic layer left a residue. Adding of pentane, filtration, evaporation then column chromatography on silica gel (cyclohexane/ AcOEt 95/5) gave **11** as a colorless oil (339 mg, 87%). ^{1}H NMR δ 1.13 (s, 9H), 1.19 (s, 3H), 1.23 (t, 3H, J=7.1 Hz); 3.44 (d, 1H, J=8.2 Hz), 3.48 (d, 1H, J=8.2 Hz), 3.58 (s, 2H), 4.14 (q, 2H, J=7.1 Hz), 4.52 (s, 2H), 7.25–7.32 (m, 5H); ^{13}C NMR δ 14.2 (*C*H$_3$), 17.9 (*C*H$_3$), 27.4 (3C, *C*H$_3$), 48.1 (quat. C), 60.2 (*C*H$_2$), 63.7 (*C*H$_2$), 72.2 (quat. C), 72.4 (*C*H$_2$), 73.2 (*C*H$_2$), 127.3 (3C, *C*H), 128.4 (2C, *C*H), 138.7 (quat. C), 175.0 (*C*O); IR (film) cm^{-1} 3029, 2974, 2873, 1730, 1363, 1234, 1197, 1082, 736, 698; GPC/MS (EI) *m/z* (rel. int.) 253 (MH$^+$–*t*Bu, 17), 251 (20), 145 (29), 91 (100), 57 (29), 41 (28); GPC/MS (CI) *m/z* (rel. int.) 253 (MH$^+$–*t*Bu, 100), 161 (76), 131 (29), 91 (13); anal. calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15, found: C, 70.29; H, 9.11. The same reaction from a 89% ee sample of (+)-*S*-**10** (1.589 g, 7.15 mmol) provided (+)-*S*-**11** (2.102 g, 94%), $[\alpha]_D^{20}$ +1.3 (*c*=12.0 $CHCl_3$), 89% ee. The same reaction from a 89% ee sample of (−)-*R*-**10** (336 mg, 1.54 mmol) provided (−)-*R*-**11** (406 mg, 86%), $[\alpha]_D^{20}$ −1.6 (*c*=1.9 $CHCl_3$), 89% ee.

3-(Benzyloxy)-2-(*tert*-butoxymethyl)-2-methylpropanoic acid (12, (+)-*S*-12 and (−)-*R*-12). Water (42 μL, 2.32 mmol) was added under argon to a stirred suspension of potassium *tert*-butoxide (1.046 g, 9.32 mmol) in dry ether (18 mL), cooled to 0°C. This slurry was stirred for 5 min, then **11** (359 mg, 1.16 mmol) in dry ether (3 mL) was added. After 5 h stirring at room temperature the reaction mixture was quenched by adding cooled water until obtaining two clear layers. The aqueous phase was extracted with ether (2×10 mL), acidified with a 50% HCl solution and re-extracted with ether (3×15 mL). Drying of the last organic layers ($MgSO_4$), evaporation and column chromatography on silica gel (cyclohexane/AcOEt 8:2) provided **12** as a white solid (267 mg, 82%). Mp 72.6–76.8°C; ^{1}H NMR δ 1.20 (s, 9H), 1.24 (s, 3H), 3.47 (d, 1H, J=8.6 Hz), 3.54 (d, 1H, J=8.9 Hz), 3.57 (d, 1H, J=8.6 Hz), 3.64 (d, 1H, J=8.9 Hz), 4.54 (s, 2H), 7.25–7.32 (m, 5H); ^{13}C NMR δ 18.2 (*C*H$_3$), 27.3 (3C, *C*H$_3$), 47.6 (quat. C), 63.8 (*C*H$_2$), 72.3 (*C*H$_2$), 73.5 (*C*H$_2$), 74.1 (quat. C), 127.5 (2C, *C*H), 127.6 (*C*H), 128.3 (2C, *C*H), 138.1 (quat. C), 178.0 (*C*O); IR (film) cm^{-1} 3400–2600, 3066, 2971, 2877, 1712, 1456, 1363, 1251, 1197, 1087, 735, 698; GPC/MS (EI) *m/z* (rel. int) 281 (MH$^+$, 8), 223 (14), 107 (29), 91 (100); anal. calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63, found: C, 68.43; H, 8.59. The same reaction from a 89% ee sample of (+)-*S*-**11** (2.102 g, 6.82 mmol) provided (+)-*S*-**12** (1.539 g, 80%), $[\alpha]_D^{20}$ +2.4 (*c*=1.0 $CHCl_3$), 89% ee. The same reaction from a 89% ee sample of (−)-*R*-**11** (409 mg, 1.33 mmol) provided (−)-*R*-**12** (320 mg, 86%), $[\alpha]_D^{20}$ −3.1 (*c*=1.1 $CHCl_3$), 89% ee.

3-[(Benzyloxy)methyl]-3-methyl-2-oxetanone (13). A solution of **12** (118 mg, 0.42 mmol) in $CHCl_3$ (0.5 mL) was added under argon to a refluxing solution of $SOCl_2$ (1 mL) acidified with methanol (7 μL). Reflux was pursued for 16 h then cooling, evaporation and column chromatography on silica gel (CH_2Cl_2) led to **13** as a colorless oil (48 mg, 55%). ^{1}H NMR δ 1.39 (s, 3H), 3.46 (d, 1H, J=9.8 Hz), 3.64 (d, 1H, J=9.8 Hz), 4.03 (d, 1H, J=4.9 Hz), 4.48 (d, 1H, J=4.9 Hz), 4.55 (d, 1H, J=12.3 Hz), 4.62 (d, 1H, J=12.3 Hz), 7.29–7.38 (m, 5H); ^{13}C NMR δ 16.1 (*C*H$_3$), 58.2 (quat. C), 69.1 (*C*H$_2$), 69.8 (*C*H$_2$), 73.3 (*C*H$_2$), 127.6 (2C, *C*H), 127.8 (*C*H), 128.4 (2C, *C*H), 137.4 (quat. C), 173.3 (*C*O); IR (film) cm^{-1} 3051, 2977, 2864, 1824, 1101, 916, 738, 700; GPC/MS (EI) *m/z* (rel. int) 207 (MH$^+$, 2), 205 (3), 161 (7), 136 (7), 117 (5), 107 (21), 105 (18), 91 (100), 79 (21), 77 (15), 65 (27), 51 (19); anal. calcd. for $C_{12}H_{14}O_3$: C, 69.88, H, 6.84, found: C, 70.15, H, 6.86. The same reaction from a 89% ee sample of (+)-*S*-**12** (1.120 g, 3.98 mmol) provided (+)-*S*-**13** (437 mg, 53%), $[\alpha]_D^{20}$ +11.0 (*c*=7.3 $CHCl_3$), 89% ee.[17] The same reaction from a 89% ee sample of (−)-*R*-**12** (159 mg, 0.57 mmol) provided (−)-*R*-**13** (58 mg, 50%), $[\alpha]_D^{20}$ −11.5 (*c*=5.0 $CHCl_3$), 89% ee.[17]

3-(Hydroxymethyl)-3-methyl-2-oxetanone (14). A solution of **13** (48 mg, 0.23 mmol) in AcOEt (6 mL) was hydrogenated for 18 h under pressure (5 bars), at 40°C and with stirring in presence of 10% Pd on activated carbon (a few mg). Filtration, washing with AcOEt and evaporation left **14** as an oil (24.5 mg, 91%). ^{1}H NMR δ 1.41 (s, 3H), 2.6–3.0 (br s, 1H), 3.65 (d, 1H, J=11.6 Hz), 3.89 (d, 1H, J=11.6 Hz), 4.08 (d, 1H, J=4.8 Hz), 4.50 (d, 1H, J=4.8 Hz); ^{13}C NMR δ 15.7 (*C*H$_3$), 59.6 (quat. C), 62.9 (*C*H$_2$), 68.8 (*C*H$_2$), 171.1 (*C*O); IR (film) cm^{-1} 3454, 2975, 2937, 2879, 1813, 1159, 1101, 1051, 910. The same reaction from a 89% ee sample of (+)-*S*-**13** (286 mg, 1.24 mmol) provided, after column chromatography on silica gel (cyclohexane/AcOEt 1:1), (+)-*S*-**14** (135 mg, 94%) HRMS Calcd for $C_4H_5O_2$: (M–CH_2O)$^+$ 86.0367. Found: 86.0358, $[\alpha]_D^{20}$ +7.3 (*c*=1.0 $CHCl_3$), 89% ee. The same reaction from a 89% ee sample of (−)-*R*-**13** (50 mg, 0.24 mmol) provided (−)-*R*-**14** (27 mg, 96%), $[\alpha]_D^{20}$ −9.0 (*c*=3.0 $CHCl_3$), 89% ee.[17]

***R*-1-Ethyl-3-methyl-2-(*tert*-butoxymethyl)-2-methylmalonate (*R*-15).** A sample of *R*-**14** of 92% ee (89 mg, 0.38 mmol) in ether (5 mL) was esterified by adding a solution of diazomethane until obtaining a yellow solution then excess of diazomethane was destroyed by adding acetic acid until discoloration. Evaporation left pure R-**15** as a colorless oil (91 mg, 97%). ^{1}H NMR δ 1.14 (s, 9H), 1.24 (t, 3H, J=7.1 Hz), 1.48 (s, 3H), 3.70 (s, 2H), 3.72 (s, 3H), 4.18 (d, 2H, J=7.1 Hz); ^{13}C NMR δ 14.0 (*C*H$_3$), 18.4 (*C*H$_3$), 27.3 (3C, *C*H$_3$), 52.2 (*C*H$_3$), 54.8 (quat. C), 61.1 (*C*H$_2$), 64.7 (*C*H$_2$), 72.9 (quat. C), 170.9 (*C*O), 171.4 (*C*O); IR (film) cm^{-1} 2976, 1739, 1259, 1221, 1196, 1120, 1087.

***R*-1-Ethyl-3-methyl-2-(hydroxymethyl)-2-methylmalonate (*R*-16).** Trifluoracetic acid (150 μL) was added dropwise at 0°C to a solution of (*R*)-**15** (64 mg, 0.26 mmol) in CH_2Cl_2 (1.5 mL). After 1 h stirring at room temperature, adding of CH_2Cl_2 (15 mL), washings with a saturated solution of $NaHCO_3$ (1 mL) then with brine (1 mL), drying ($MgSO_4$) and evaporation yielded practically pure *R*-**16** as a colorless oil (40 mg, 81%). ^{1}H NMR δ 1.28 (t, 3H, J=7.1 Hz), 1.45 (s, 3H), 2.85 (t, 1H, OH, J=7.1 Hz), 3.77 (s, 3H), 3.86 (d, 2H, J=7.1 Hz), 4.23 (d, 2H, J=7.1 Hz); ^{13}C NMR δ 13.9 (*C*H$_3$), 17.5 (*C*H$_3$), 52.6 (*C*H$_3$), 55.8 (quat. C),

61.6 (CH_2), 66.7 (CH_2), 171.5 (*C*O), 172.1 (*C*O); IR (film) cm^{-1} 3498, 2987, 2956, 1730, 1303, 1253, 1214, 1120, 1051; GPC/MS (EI) *m/z* (rel. int) 191 (MH^+, 5), 160 (61), 132 (14), 131 (17), 129 (17), 128 (18), 116 (19), 115 (55), 101 (34), 100 (36), 88 (29), 85 (100), 83 (46); $[\alpha]_D^{20}$ +2.2 (c=3.7 $CHCl_3$) and $[\alpha]_D^{20}$ −1.0 (c=3.7 MeOH) 92% ee. Lit[14] $[\alpha]_D^{20}$ +0.95 (c=2.2, MeOH) for the *S*-**16** of 95% ee.

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