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Synthesis of $\alpha,\alpha,\beta,\beta$-Tetrasubstituted β-Lactones from Ketones, Ethyl α-Bromoisobutyrate, and Indium or Zinc. Factors Influencing the β-Lactone Formation in the Electrochemical and the Classical Procedure of the Reformatsky Reaction[1]

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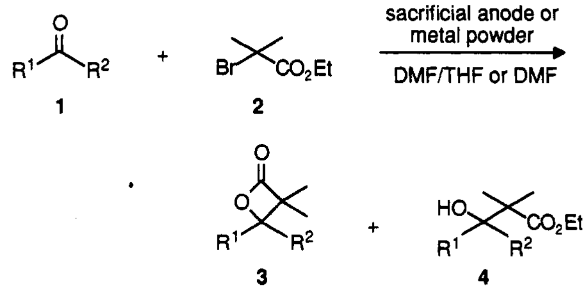
An efficient synthesis of $\alpha,\alpha,\beta,\beta$-tetrasubstituted β-lactones is achieved by an electrochemically supported Reformatsky reaction of aliphatic and aromatic ketones with ethyl α-bromoisobutyrate at a sacrificial indium anode. Under these conditions, in most cases the expected β-hydroxy esters are formed only in negligible amounts or not at all. β-Lactones are also obtained with a sacrificial zinc anode or even with indium or zinc powder. The substitution pattern of the reactants, the polarity of the solvent, and the applied metal are recognized as factors influencing the extent of the β-lactone formation.

The classical Reformatsky reaction of alkyl α-bromoalkanoates with zinc and aldehydes or ketones is the most often used procedure for the preparation of β-hydroxy esters.[2] In principle, the zinc can be replaced by many other metals such as magnesium,[3] cadmium,[4] nickel,[5] cerium,[6] manganese,[7] or indium[8] without significant influence on the general outcome of the reaction. Also the electrochemically supported Reformatsky reaction of ethyl α-chloroacetate with cyclohexanone at a sacrificial zinc anode in the presence of a catalytic amount of nickel bromide results in the formation of the expected β-hydroxy ester.[9] Therefore, we were very surprised that in a comparable electrochemical process at a sacrificial indium anode ethyl α-bromoisobutyrate and cyclohexanone reacted to the β-lactone **3e** in a yield of 80%. Having already reported in preliminary form on this observation,[10] we now would like to describe the full details as well as scope and limitations of this unexpected β-lactone formation.

Results

In a first series of experiments the α-bromo ester **2** was electrolyzed in the presence of the carbonyl compounds **1a–n** at an external voltage of 30 V and a temperature of 50 °C (Scheme 1). All these experiments were performed with DMF/THF (1:2) as solvent and tetrabutylammonium bromide as supporting electrolyte in an undivided cell equipped with an indium rod as sacrificial anode and a nickel net as cathode. The reaction was monitored by TLC. Workup of the reaction mixture afforded a crude product, from which the fraction containing the β-lactone **3** and the β-hydroxy ester **4** was separated by flash chromatography and analyzed by HPLC. The results are compiled in Table 1 (method A).

Scheme 1



Under these conditions the aliphatic ketones **1b–d** and the aromatic ketones **1h–k** were converted almost exclusively into the corresponding β-lactones **3** (entries 2–4 and 8–11). The cycloaliphatic ketones **1e–g** were transformed with high preference into the β-lactones **3e–g** (entries 5–7), whereas the aldehydes **1l–n** gave exclusively the corresponding β-hydroxy esters **4** (entries 12–14). In contrast to the other ketones, acetone (**1a**), the only methyl ketone investigated, afforded the β-hydroxy ester **4a** as the main product (entry 1).

In order to clarify whether the unexpected β-lactone formation was caused by the use of the sacrificial indium anode, the experiments were repeated under the same conditions with a zinc anode. The results are given in Table 1 (method B).

Acetone (**1a**) and the cycloaliphatic ketones **1e–g** were almost exclusively converted into the corresponding β-hydroxy esters **4** (entries 1 and 5–7). The aliphatic ketones **1b–d** gave mixtures of the β-lactones **3b–d** and the β-hydroxy esters **4b–d** with the latter as the main component (entries 2–4). The aromatic ketones **1h–k**, however, again afforded the β-lactones **3h–k** almost exclusively and in higher overall yield compared with method A (entries 8–11).

[●] Abstract published in *Advance ACS Abstracts,* April 15, 1994.

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Table 1. Synthesis of β-Lactones 3 and β-Hydroxy Esters 4 via Electrochemically Supported or Classical Reformatsky Reaction of α-Bromoisobutyrate and the Carbonyl Compounds 1 with Indium or Zinc

				indium anode method A		zinc anode method B		indium powder method C		zinc powder method D	
entry	1, 3, 4	R^1	R^2	yield (%) 3 + 4	ratio 3:4	yield (%) 3 + 4	ratio 3:4	yield (%) 3 + 4	ratio 3:4	yield (%) 3 + 4	ratio 3:4
1	a	Me	Me	36	7:93	35	0:100	59	19:81	43	0:100
2	b	Et	Et	61	>99:1	72	46:54	88	100:0	75	12:88
3	c	*n*-Pr	*n*-Pr	57	99:1	68	30:70	62	96:4	63	12:88
4	d	*n*-Bu	*n*-Bu	61	>99:1	79	40:60	68	98:2	93	8:92
5	e	$-(CH_2)_5-$		84	95:5	76	2:98	83	77:23	96	0:100
6	f	$-(CH_2)_2CHMe(CH_2)_2-$		66	91:9	78	2:98	77	66:34	88	0:100
7	g	$-(CH_2)_6-$		30	87:13	78	2:98	67	50:50	71	0:100
8	h	Et	Ph	46	>99:1	89	100:0	72	94:6	67	36:64
9	i	*n*-Pr	Ph	56	99:1	88	100:0	76	97:3	95	62:38
10	j	*n*-Bu	Ph	38	>99:1	85	99:1	78	99:1	53	96:4
11	k	Ph	Ph	61	100:0	92	100:0	62	96:4	57	84:16
12	l	Et	H	37	0:100						
13	m	*n*-Bu	H	50	0:100						
14	*n*	Ph	H	93	0:100						

Next, it was of interest to know whether the β-lactone formation was a consequence of the application of the electrochemical procedure. Therefore, the series of experiments was repeated under classical Reformatsky conditions with indium powder in DMF. The results are summarized in Table 1 (method C).

Again β-lactones were formed with high preference from the aliphatic ketones **1b–d** (entries 2–4) and the aromatic ketones **1h–k** (entries 8–11). In the case of the cycloaliphatic ketones **1e–g** the β-lactone formation was significantly reduced in comparison to method A (entries 5–7), whereas the ratio of β-lactone **3** to β-hydroxy ester **4** was only slightly diminished in the case of the aromatic ketones **1h–k** (entries 8–11).

Finally, we were interested in a comparison of the results so far described with the outcome of the classical Reformatsky reaction of the ketones **1a–k** with zinc powder in DMF. The results are compiled in Table 1 (method D).

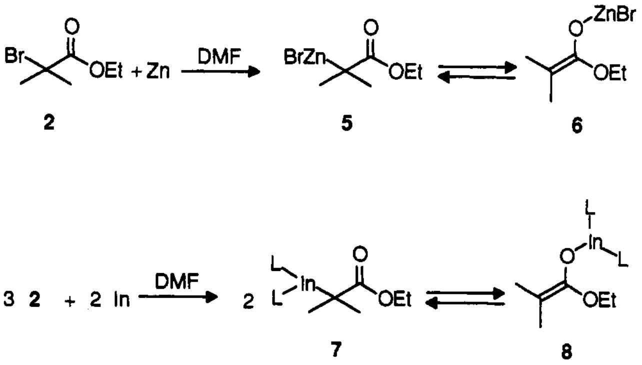
Acetone (**1a**) and the cycloaliphatic ketones **1e–g** were converted exclusively into the expected β-hydroxy esters **4** (entries 1 and 5–7). However, to our surprise even under these conditions the aliphatic ketones **1b–d** were at least partly (entries 2–4) and the aromatic ketones **1i–k** mainly transformed into the corresponding β-lactones **4** (entries 9–11).

Discussion

The results of the above-described four series of experiments reveal that the formation of β-lactones from ethyl α-bromoisobutyrate and different types of ketones depends on several factors. In all four series the aromatic ketones **1h–k** exhibit the highest tendency to form β-lactones. Unexpectedly, this holds even for the classical Reformatsky reaction with zinc powder in DMF. The cycloaliphatic ketones **1e–g** form the corresponding β-lactones **4** only with a sacrificial indium anode (method A) or indium powder (method C). With zinc powder (method D) or with a sacrificial zinc anode (method C), these ketones form exclusively or nearly exclusively the β-hydroxy esters **4** in accordance with the classical Reformatsky reaction. The aliphatic ketones **1b–d** provide the lactones **3b–d** with high preference only with a sacrificial indium anode or with indium powder. It is, however, remarkable that these ketones also form with a zinc anode or with zinc powder the β-lactones as an unnegligible byproduct.

In general, the outlined β-lactone synthesis seems to be restricted to those carbonyl compounds and ethyl α-bromoalkanoates which allow the formation of α,α,β,β-tetrasubstituted β-lactones. It has already been mentioned that the aldehydes **1l–n** are converted exclusively into the β-hydroxy esters **4l–n** (Table 1, method A, entries 12–14). The reaction of ethyl α-bromopropionate or ethyl α-bromobutanoate also gave only the corresponding β-hydroxy esters.

Scheme 2



L = Br, Me_2CCO_2Et, or $Me_2C{=}C(O)OEt$

In order to explain the reaction course, the generation of organometallic intermediates such as **5** and **7** or metal enolates such as **6** and **8** can be assumed for zinc and indium,[11] respectively (Scheme 2).

The formation of these intermediates should be possible in the electrochemically supported Reformatsky reaction as well as in the classical one. The nucleophilic attack of the α-carbon atom of the metal enolates **6** or **8** on the carbonyl carbon atom of the ketones **1** gives rise to the chelated metal derivatives **9** (Scheme 3). Elimination of a metal ethoxide from the metalated β-hydroxyalkanoate **9** results in β-lactone formation. The tendency for such an elimination proved to be greater for indium than for zinc. But nevertheless, with zinc this elimination is also the predominant or exclusive reaction path in the special cases discussed above. This metal ethoxide elimination occurs prior to the workup procedure, since β-lactone formation can already be recognized in the reaction mixture. The ^{13}C NMR spectra reveal the characteristic signal at 83–89 ppm for C-3 and the IR spectra exhibit the strong carbonyl absorption at 1800–1830 cm^{-1}.

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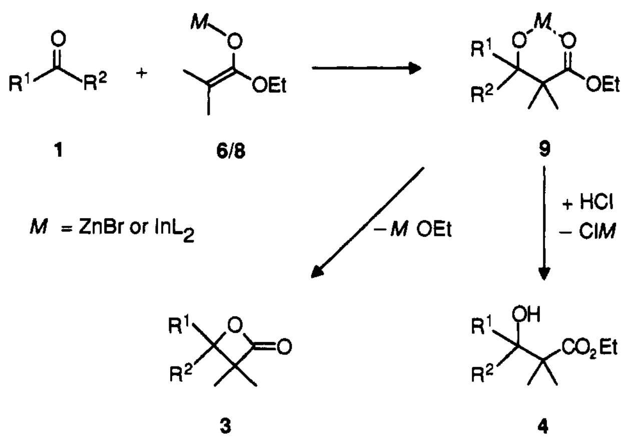
(11) Organoindium compounds of a similar structure have been discussed in refs 8a and 8b. The given formulae do not consider the possible aggregation of the organometallic species.

Scheme 3



The fact that only α,α,β,β-tetrasubstituted β-lactones are accessible under the described conditions may be explained by the *gem*-dialkyl effect.[12] Ring closure reactions are generally accelerated when hydrogen atoms in the cyclizing carbon chain are substituted by alkyl groups.[13]

The polarity of the solvent seems to be another important factor influencing the metal ethoxide elimination and thus the β-lactone formation. Reformatsky reactions traditionally performed in the unpolar solvent benzene have never been reported to result in β-lactone formation. Benzophenone (**1k**) and ethyl α-bromoisobutyrate (**2**) afforded in all of our experiments with DMF/THF (1:2) or in pure DMF predominantly the β-lactone **3k**; in methylal, however, this reaction is reported to provide the β-hydroxy ester **4k** in a yield of 50% as the sole product.[14,15]

Conclusion

In conclusion it has been shown that the formation of β-lactones by an electrochemically supported Reformatsky reaction is not restricted to the use of a sacrificial indium anode. β-Lactones are also accessible with a sacrificial zinc anode, or even by using indium or zinc powder under the classical conditions of the Reformatsky reaction with DMF as solvent. A prerequisite for the β-lactone formation is the substitution pattern of the carbonyl compound and the α-bromoalkanoate. Only α,α,β,β-tetrasubstituted β-lactones are accessible by the described procedure. Nevertheless, in many cases this new one-step β-lactone synthesis can compete well with the known methods.[16]

Experimental Section

General. The electrolysis cell was a thermostatable beaker with a diameter of 4 cm and a height of 8 cm, equipped with a four-necked cover and a magnetic stirrer bar. The electrosyntheses were performed without a diaphragm under dry nitrogen. A commercial dc voltage source (Statron, type 3218) was applied. The amount of electricity was measured with an electronic coulometer. A nickel net (40 × 40 mm) was used as cathode. Rods of indium or zinc were applied as sacrificial anode. DMF and THF, dried over molecular sieves, were purchased from Fluka. The other chemicals were purchased from Merck and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ at 80 and 75 MHz, respectively.

General Procedure for the Electrochemically Supported Reformatsky Reaction at a Sacrificial Indium Anode (Method A) or Zinc Anode (Method B). In the above-described cell equipped with an indium or a zinc anode, a solution of the carbonyl compound 1 (5 mmol), the α-bromo ester **2** (15 mmol), and tetrabutylammonium bromide (322 mg, 1 mmol) in DMF/THF (1:2, 10 mL) was electrolyzed at an external voltage of 30 V and a temperature of 50 °C. The course of the reaction was monitored by GLC or TLC. When the carbonyl compound or the bromo ester was consumed, the electrolysis was stopped and the reaction mixture was stirred for an additional 2 h. Then the reaction mixture was quenched by addition of ice (25 g) and diluted HCl (25 mL). Workup by extraction with EtOAc (5 × 20 mL), washing with water (3 × 10 mL), drying with Na_2SO_4, and removal of the solvent by distillation under reduced pressure afforded a crude product which was chromatographed on silica gel with hexane/EtOAc (10:1) as eluent. The fraction containing the β-lactone and the β-hydroxy ester was analyzed by HPLC on RP-18 with CH_3CN/H_2O (75:25) as eluent. The yield and the ratio of **3** and **4** are given in Table 1.

General Procedure for the Reformatsky Reaction with Indium (Method C) or Zinc Powder (Method D). Indium powder (574 mg, 5 mg-atom) or activated zinc powder (0.654 g, 10 mg-atom) was added to a solution of the α-bromo ester **2** (1.12 mL, 7.5 mmol) and a carbonyl compound 1 (5 mmol) in dry DMF (5 mL). The mixture was gently warmed to 60 °C in order to start the strongly exothermic reaction. Thereafter stirring was continued for an additional 2 h without external heating. Then the reaction mixture was poured onto ice (50 g) and aqueous HCl (50 mL, 5%) and extracted with EtOAc (5 × 30 mL). The combined extracts were washed with water (3 × 10 mL), dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with hexane/EtOAc (10:1) as eluent. The fraction containing the β-lactone and the β-hydroxy ester was analyzed by HPLC on RP-18 with CH_3CN/H_2O (75:25) as eluent. The yield and the ratio of **3** and **4** are given in Table 1.

3,3,4,4-Tetramethyl-2-oxetanone (3a).[17] Method C; a sample for the analytical characterization was obtained by column chromatography on silica gel with hexane/EtOAc (10:1) as a colorless solid: mp 129–130 °C: IR 1805 cm^{-1}; ^{1}H NNR δ 1.25 (6 H, s), 1.45 (6 H, s); ^{13}C NMR δ 19.3, 24.0, 54.6, 83.8, 176.1.

4,4-Diethyl-3,3-dimethyl-2-oxetanone (3b). Methods A and C; colorless oil: IR 1815 cm^{-1}; ^{1}H NMR δ 0.87 (6 H, t, J = 7 Hz), 1.29 (6 H, s), 1.71–1.94 (4 H, m); ^{13}C NMR δ 8.1, 18.7, 25.0, 54.6, 88.3, 176.1. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.99; H, 10.42.

3,3-Dimethyl-4,4-dipropyl-2-oxetanone (3c). Methods A and C; colorless oil: IR 1810 cm^{-1}; ^{1}H NMR δ 0.98 (6 H, t, J = 7 Hz), 1.24 (6 H, s), 1.26–1.42 (4 H, m), 1.69–1.91 (4 H, m); ^{13}C NMR δ 14.4, 17.4, 18.7, 35.1, 55.0, 87.5, 176.1. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.50; H, 11.04.

4,4-Dibutyl-3,3-dimethyl-2-oxetanone (3d). Methods A and C; coloress oil: IR 1810 cm^{-1}; ^{1}H NMR δ 0.87 (6 H, t, J = 7 Hz), 1.07–1.29 (8 H, m), 1.27 (6 H, s), 1.69–1.91 (4 H, m); ^{13}C NMR δ 13.9, 18.7, 23.0, 26.0, 32.6, 54.9, 87.6, 176.2. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.39; H, 11.42.

3,3-Dimethyl-1-oxaspiro[3.5]nonan-2-one (3e).[18,19] Method A; recrystallization from hexane afforded colorless crystals: mp 108–110 °C; IR 1810 cm^{-1}; ^{1}H NMR δ 1.25 (6 H, s), 1.51–1.77 (8 H, m), 1.81–1.93 (2 H, m); ^{13}C NMR δ 18.1, 22.7, 24.8, 32.3, 54.4, 85.1, 176.1.

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[15] It seems to be possible that the crystalline product with a mp of 101 °C isolated by Blaise and Courtot[27] in a yield of 2% from the reaction of benzophenone and ethyl α-bromoisobutyrate in benzene was the β-lactone **3k**. Erroneously this compound was regarded to be the β-hydroxy ester **4k**. Unfortunately, this experiment could not be reproduced.[14]

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3,3,6-Trimethyl-1-oxaspiro[3.5]nonan-2-one (3f).[20] Method A; recrystallization from hexane afforded colorless crystals of mp 94–96 °C: IR 1800 cm^{-1}; ^{1}H NMR δ 0.86 (3 H, d, J = 6 Hz), 1.22 (6 H, s), 1.31–2.01 (9 H, m); ^{13}C NMR δ 18.0, 22.0, 30.1, 31.2, 31.8, 54.3, 84.7, 176.2. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.82; H, 10.02.

3,3-Dimethyl-1-oxaspiro[3.6]decan-2-one (3g).[21] Method A; recrystallization from hexane afforded colorless crystals: mp 82–84 °C; IR 1810 cm^{-1}; ^{1}H NMR δ 1.27 (6 H, s), 1.31–1.74 (6 H, m), 1.94–2.06 (4 H, m); ^{13}C NMR δ 19.1, 22.1, 29.3, 35.4, 55.1, 88.5, 176.1.

(±)-4-Ethyl-3,3-dimethyl-4-phenyl-2-oxetanone (3h). Methods A and B; colorless oil: IR 1820 cm^{-1}; ^{1}H NMR δ 0.68 (3 H, t, J = 7 Hz), 0.83 (3 H, s), 1.39 (3 H, s), 2.00–2.13 (2 H, m), 7.16–7.36 (5 H, m); ^{13}C NMR δ 8.1, 17.7, 22.0, 29.9, 57.0, 89.1, 125.1, 127.5, 128.4, 138.6, 175.4. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.25; H, 8.01.

(±)-3,3-Dimethyl-4-phenyl-4-propyl-2-oxetanone (3i). Methods A and B; colorless oil: IR 1820 cm^{-1}; ^{1}H NMR δ 0.75–0.82 (6 H, m), 1.15–1.38 (2 H, m), 1.39 (3 H, s) 1.99 (2 H, t, J = 7 Hz), 7.15–7.36 (5 H, m); ^{13}C NMR δ 14.1, 17.3, 17.7, 21.9, 39.0, 57.2, 88.7, 124.9, 127.4, 128.4, 138.9, 175.5. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.33; H, 8.52.

(±)-4-Butyl-3,3-dimethyl-4-phenyl-2-oxetanone (3j). Methods A, B, and C; colorless oil: IR 1820 cm^{-1}; ^{1}H NMR δ 0.74 (3 H, t, J = 7 Hz), 0.82 (3 H, s), 1.16–1.31 (4 H, m), 1.39 (3 H, s), 2.01 (2 H, t, J = 7 Hz), 7.16–7.36 (5 H, m); ^{13}C NMR δ 13.8, 17.7, 21.8, 22.7, 26.0, 36.5, 57.2, 88.7, 124.9, 127.4, 128.4, 138.9, 175.5. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.34; H, 8.51.

3,3-Dimethyl-4,4-diphenyl-2-oxetanone (3k).[18] Methods A and B; recrystallization from hexane afforded colorless crystals: mp 101–102 °C; IR 1820 cm^{-1}; ^{1}H NMR δ 1.18 (6 H, s), 7.21–7.45 (10 H, m); ^{13}C NMR δ 21.5, 59.8, 88.5, 125.6, 127.7, 128.4, 139.7, 174.8.

Ethyl 3-Hydroxy-2,2,3-trimethylbutanoate (4a).[22] Methods B and D; colorless oil: ^{1}H NMR δ 1.13 (6 H, s), 1.16 (6 H, s), 1.23 (3 H, t, J = 7 Hz), 3.69 (1 H, s), 4.12 (2 H, q, J = 7 Hz); ^{13}C NMR δ 14.1, 21.3, 25.1, 49.6, 60.9, 73.5, 178.6.

Ethyl 3-Ethyl-3-hydroxy-2,2-dimethylpentanoate (4b). Method D; colorless oil: ^{1}H NMR δ 0.87 (6 H, t, J = 7 Hz), 1.16 (6 H, s), 1.29 (3 H, t, J = 7 Hz), 1.75–1.91 (4 H, m), 3.74 (1 H, s), 4.10 (2 H, q, J = 7 Hz); ^{13}C NMR δ 8.9, 14.0, 21.6, 28.1, 50.2, 60.9, 76.1, 179.1. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.52; H, 10.85.

Ethyl 3-Hydroxy-2,2-dimethyl-3-propylhexanoate (4c). Method D; colorless oil: ^{1}H NMR δ 0.81 (6 H, t, J = 7 Hz), 1.14 (6 H, s), 1.16–1.43 (11 H, m), 3.79 (1 H, s), 4.10 (2 H, q, J = 7 Hz); ^{13}C NMR δ 15.0, 17.6, 21.5, 38.9, 50.3, 60.8, 76.1, 179.1. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38. Found: C, 67.49; H, 11.08.

Ethyl 3-Butyl-3-hydroxy-2,2-dimethylheptanoate (4d). Method D; colorless oil: ^{1}H NMR δ 0.84 (6 H, t, J = 7 Hz), 1.15 (6 H, s), 1.17–1.49 (15 H, m), 3.77 (1 H, s), 4.11 (2 H, q, J = 7 Hz); ^{13}C NMR δ 14.1, 21.5, 23.7, 26.5, 36.1, 50.4, 60.9, 76.1, 179.2. Anal. Calcd for $C_{15}H_{30}O_2$: C, 69.72; H, 11.70. Found: C, 69.51; H, 11.54.

Ethyl 2-(1-Hydroxycyclohexyl)-2-methylpropanoate (4e).[23] Method D; colorless oil: ^{1}H NMR δ 1.15 (6 H, s), 1.21 (3 H, t, J = 7 Hz), 1.30–1.66 (10 H, m), 3.30 (1 H, s), 4.10 (2 H, q, J = 7 Hz); ^{13}C NMR δ 14.1, 20.8, 21.6, 25.9, 31.6, 50.0, 60.7, 74.0, 178.6.

Ethyl 2-(1-Hydroxy-4-methylcyclohexyl)-2-methylpropanoate (4f).[20] Methods B and D; colorless oil: ^{1}H NMR δ 0.82 (3 H, d, J = 6 Hz), 1.15 (6 H, s), 1.17–1.50 (12 H, m), 3.25 (1 H, s), 4.09 (2 H, q, J = 7 Hz); ^{13}C NMR δ 14.1, 20.9, 22.3, 30.2, 31.6, 32.3, 49.8, 60.8, 73.6, 178.6. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.47; H, 10.62.

Ethyl 2-(1-Hydroxycycloheptyl)-2-methylpropanoate (4g).[24] Methods B and D; colorless oil: ^{1}H NMR δ 1.15 (6 H, s), 1.22 (3 H, t, J = 7 Hz), 1.42–1.76 (12 H, m), 3.51 (1 H, s), 4.10 (2 H, q, J = 7 Hz); ^{13}C NMR δ 14.1, 21.2, 23.0, 29.7, 36.2, 51.1, 60.8, 77.3, 178.8.

Ethyl (±)-3-Hydroxy-2,2-dimethyl-3-phenylpentanoate (4h).[25] Method D; a sample for the analytical characterization was obtained by preparative HPLC on silica gel with hexane/EtOAc (20:1) as eluent in the form of a colorless oil: ^{1}H NMR δ 0.68 (3 H, t, J = 7 Hz), 0.94–1.26 (9 H, m), 1.48–1.66 (1 H, m), 2.13–2.28 (1 H, m), 4.07 (2 H, q, J = 7 Hz), 4.32 (1 H, s), 7.13–7.48 (5 H, m); ^{13}C NMR δ 8.0, 14.0, 21.4, 21.9, 28.3, 50.4, 61.1, 78.8, 126.6, 127.2, 128.1, 140.2, 179.9.

Ethyl (±)-3-Hydroxy-2,2-dimethyl-3-phenylhexanoate (4i). Method D; a sample for the analytical characterization was obtained by preparative HPLC on silica gel with hexane/EtOAc (20:1) as eluent in the form of a colorless oil: ^{1}H NMR δ 0.76–0.86 (6 H, m), 1.04 (3 H, s), 1.11 (3 H, s), 1.25–2.24 (4 H, m), 4.07 (2 H, q, J = 7 Hz), 4.39 (1 H, s), 7.14–7.38 (5 H, m); ^{13}C NMR δ 14.0, 14.6, 17.0, 21.5, 21.8, 38.1, 50.4, 61.1, 79.6, 126.6, 127.2, 127.9, 140.8, 178.9. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.77; H, 9.01.

Ethyl (±)-3-Hydroxy-2,2-dimethyl-3-phenylheptanoate (4j). Method D; colorless oil: ^{1}H NMR δ 0.75 (3 H, t, J = 7 Hz), 1.04 (3 H, s), 1.10 (3 H, s), 1.16 (3 H, t, J = 7 Hz), 1.21–1.43 (4 H, m), 1.52 (1 H, m), 2.15 (1 H, m), 4.07 (2 H, q, J = 7 Hz), 4.39 (1 H, s), 7.13–7.43 (5 H, m); ^{13}C NMR δ 13.99, 14.03, 21.5, 21.8, 23.2, 25.8, 35.5, 50.4, 61.1, 79.5, 126.6, 127.2, 127.9, 140.7, 178.9. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.47; H, 9.52.

Ethyl 3-Hydroxy-2,2-dimethyl-3,3-diphenylpropanoate (4k).[14] Method D; a sample for the analytical characterization was obtained by preparative HPLC on silica gel with hexane/EtOAc (20:1) as eluent in the form of a colorless oil: ^{1}H NMR δ 1.16 (3 H, t, J = 7 Hz), 1.27 (6 H, s), 4.12 (2 H, q, J = 7 Hz), 5.06 (1H, s), 7.12–7.30 (10 H, m).

Ethyl (±)-3-Hydroxy-2,2-dimethylpentanoate (4l).[26] Method A; colorless oil: ^{1}H NMR δ 0.96 (3 H, t, J = 7 Hz), 1.06–1.24 (11 H, m), 2.42 (1 H, d, J = 7 Hz), 3.45 (1 H, t, J = 7 Hz), 4.09 (2 H, q, J = 7 Hz); ^{13}C NMR δ 11.3, 14.1, 20.4, 22.4, 24.6, 46.2, 60.6, 78.4, 178.2.

Ethyl (±)-3-Hydroxy-2,2-dimethylheptanoate (4m). Method A; colorless oil: ^{1}H NMR δ 0.84 (3 H, t, J = 7 Hz), 1.10–1.41 (15 H, m), 2.44 (2 H, d, J = 7 Hz), 3.53 (1 H, t, J = 7 Hz), 4.10 (2 H, q, J = 7 Hz); ^{13}C NMR δ 14.0, 14.1, 20.5, 22.2, 22.6, 28.9, 31.4, 47.0, 60.6, 77.0, 177.8. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.36; H, 11.11.

Ethyl (±)-3-Hydroxy-2,2-dimethyl-3-phenylpropanoate (4n).[27] Method A; colorless oil: ^{1}H NMR δ 1.04 (3 H, s), 1.07 (3 H, s), 1.20 (3 H, t, J = 7 Hz), 3.14 (1 H, d, J = 4 Hz), 4.11 (2 H, q, J = 7 Hz), 7.20 (5 H, s); ^{13}C NMR δ 14.1, 19.0, 23.0, 47.5, 60.9, 78.6, 127.77, 140.0, 177.7.

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(20) This product is a mixture of two geometric isomers.

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