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α,β-Unsaturated diesters: radical acceptors in dialkylzinc-mediated tandem radical addition/aldol condensation. A straightforward synthesis of *rac*-nephrosteranic acid

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Abstract—The sequence involving conjugate radical addition/aldol condensation/lactonization is a high yielding route to di- and tri-substituted γ-lactones starting from fumaric or maleic diesters. The reactions are mediated with dialkylzincs. The domino process relies on the ability of dialkylzinc to transform α-alkoxycarbonylalkyl radicals into zinc enolates. Compared to diethylzinc, dimethylzinc enables the use of a wider range of alkyl radical precursors. In addition, dimethylzinc is a convenient source of methyl radical, which leads to a straightforward synthesis of methylated derivatives related to α-methyl-paraconic acids.

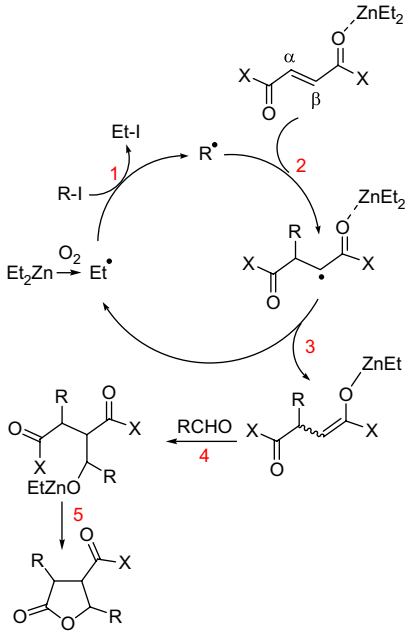
1. Introduction

Radical reactions using diethyl- or dimethylzinc as initiators,[1] as chain-transfer agents,[2,3] or as source of radicals[4] have been the focus of a growing interest over the last few years.[5] We have recently investigated tandem radical addition–aldol condensation processes mediated with diethylzinc.[6] This article emphasizes the possibility to use α,β-unsaturated esters as radical acceptors in these domino reactions.

The general mechanism of the multi-component reaction that leads to γ-lactones from protected fumaric acid is summarized in Scheme 1. It involves five elementary steps, i.e., iodine atom transfer (1), radical addition (2), homolytic substitution at zinc (3), aldol condensation (4) and lactonization (5).[6b]

The peculiar interest in using dialkylzincs as mediators lies in the opportunity that they offer to perform radical–polar crossover reactions. Homolytic substitutions at dialkylzincs leading to nucleophilic species (a zinc enolate in the above-mentioned reaction) are fast processes.[2,3,6,7]

We have shown that the use of chiral oxazolidinones as auxiliaries, already known to give incredibly high selectivities in conjugate radical additions carried out in the



Scheme 1.

Keywords: Diethylzinc; Dimethylzinc; Radical–polar crossover reaction; γ-Lactones; Conjugate addition.
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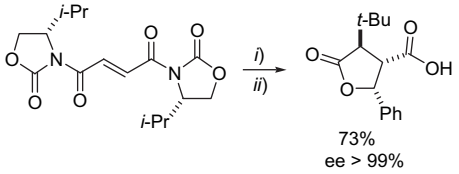
presence of Lewis acids,[8] led to enantiopure lactones in good yields (Scheme 2).[6b] However, in our particular case, only the reactions involving the initial addition of the bulky *tert*-butyl radical revealed themselves to have some interest in asymmetric synthesis.



Scheme 2. Reagents and conditions: (i) $ZnEt_2$ (2 equiv), PhCHO (1.1 equiv), *t*-BuI (45 equiv), CH_2Cl_2, air (20 mL), −10 °C; (ii) LiOH/H_2O_2 (30%), THF, H_2O.

The easy access to tri-substituted lactones through this one-pot procedure and the possibility to reach high diastereoselectivities through the epimerization of the enolizable centres have led us to investigate the scope of our process in the synthesis of racemic lactones.

2. Results and discussion

The necessity of employing a large number of equivalents of a radical precursor in order to avoid the competitive addition of ethyl radical (produced in the initiation step) is a severe limitation to the use of diethylzinc for synthetic purpose in the presence of highly reactive radical acceptors.[2a–d,6b] This difficulty was also encountered in triethylborane-mediated radical additions.[2f–h,9] Owing to the enthalpy factor being more favourable to the atom transfer elementary step, methyl radical, which is produced from the oxidation of dimethylzinc, offers a wider synthetic potential that has not been fully exploited except in radical additions to C=N bonds.[3] We have performed a comparative study of both mediators with respect to conjugate radical addition.

The multi-component methodology would gain interest if commercially available cheap reagents such as ethyl or methyl fumarate (or maleate) could be used as a starting material instead of fumaric acid protected with oxazolidinones. Our previous attempts to mediate tandem radical addition–aldol condensation with diethylzinc were unsuccessful when using methyl methacrylate as the radical acceptor.[2b,6] This result was misinterpreted in the sense that we initially thought that all α-alkoxycarbonylalkyl radicals would be reluctant to undergo homolytic substitution at zinc. The inability of tertiary α-alkoxycarbonylalkyl radicals to undergo S_H2 at dibutylzinc has been confirmed by Chemla and coworkers.[4] Such a behaviour with respect to dialkylzincs sounded quite consistent with the already known reactivity of these radicals with respect to trialkylboranes (α-alkoxycarbonylalkyl radicals do not react with triethylborane via S_H2 processes[9,10]).

However, several reports in the literature led us to suspect that slight structural changes, like for instance the possibility to chelate the metal, might influence the reactivity of dialkylzincs with respect to homolytic substitution.[2j,k,4,6a,11–13] Radical additions to fumaric or maleic esters, immediately

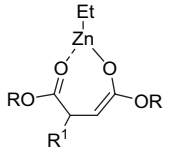


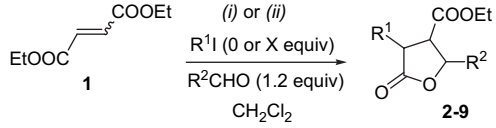
Figure 1. Chelated seven-membered zinc enolate.

followed by S_H2 at zinc, would lead to enolates stabilized through the formation of a seven-membered ring chelate (Fig. 1).[14] Even though the intermediate radical in this case is secondary, this additional stabilization might provide in itself the driving force for the radical–polar crossover reaction.

The experiments reported herein demonstrate that α,β-unsaturated diesters (**1**) behave similar to bis-oxazolidinones. According to Scheme 1, they lead to tri-substituted lactones by reacting with dialkylzincs in the presence (or in the absence) of an alkyl iodide, and in the presence of an aldehyde. So, contrary to their tertiary analogues, secondary α-alkoxycarbonylalkyl radicals react by homolytic substitution at dialkylzinc to give zinc enolates.[15]

The results are summarized in Table 1. We have first applied our initial procedure involving Et_2Zn to carry out radical additions to diethyl fumarate and diethyl maleate, in the presence of benzaldehyde and valeraldehyde (entries 1–5). It is to be noted that both diesters are far less reactive than the oxazolidinone-protected fumaric acid in Scheme 2, since 10 equiv of *tert*-butyl iodide are sufficient to make the reaction chemoselective in favour of the addition of the tertiary radical. It must also be noted that a mixture of diastereomeric lactones resulting from the competitive addition of ethyl radical was detected in the case of diethyl fumarate (three detectable diastereomers (**2a–c**) in 8:92 ratio with respect to lactones **3a–d**) (entry 2, footnote b). Owing to steric impediment to resonance stabilization, diethyl maleate

Table 1. Dialkylzinc-mediated lactonization of fumaric and maleic diesters



Entry	**1**	(i) or (ii), R^1I	R^2CHO	**2–9**	Yield (%)	d.r. **a**:**b**:**c**:**d**
1	***Z***	(i), None	PhCHO	**2**	93	19:23:50:8
2	***E***	(i), *t*-BuI (10 equiv)	PhCHO	**3**	89[b]	41:18:27:14
3	***Z***	(i), *t*-BuI (10 equiv)	PhCHO	**3**	90	46:15:25:14
4	***E***	(i), *t*-BuI (10 equiv)	*n*-BuCHO	**4**	97	13:9:12:66
5	***Z***	(i), *t*-BuI (10 equiv)	*n*-BuCHO	**4**	87	13:9:12:66
6	***E***	(ii), None	PhCHO	**5**	97	21:43:30:6
7	***Z***	(ii), EtI (10 equiv)	PhCHO	**2**	91	19:24:50:7
8	***Z***	(ii), *i*-PrI (2 equiv)	PhCHO	**6**	95	31:29:30:10
9	***Z***	(ii), *t*-BuI (2 equiv)	PhCHO	**3**	93	41:16:29:14
10	***E***	(ii) ICH_2OMe (5 equiv)[a]	PhCHO	**7**	43	45:27:13:15
11	***E***	(ii), None	*n*-BuCHO	**8**	79	39:50:11[c]
12	***E***	(ii), None	$(CH_2O)_n$	**9**	86	62:38[d]

Conditions: (i) $ZnEt_2$ (2 equiv), rt; (ii) $ZnMe_2$ (5 equiv), rt.
[a] −78 °C, $ZnMe_2$ (2 equiv).
[b] Three isomeric lactones (**2a–c**) were detected in a 8:92 ratio with respect to **3a–d**.
[c] (**a+c**):**b**:**d**.
[d] cis:trans.

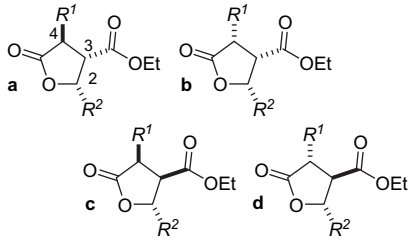
is slightly less reactive than diethyl fumarate.[16] No side product was detected in this case (entry 3). No competitive addition of ethyl radical was detected even with diethyl fumarate when the reaction was carried out in the presence of aliphatic aldehydes (entry 2/4). This sounds as if the nature of the aldehyde as a potential ligand in zinc(II) coordination sphere would influence the reactivity of the double bond in the complexed substrate.

In addition, we were interested in determining how much the number of equivalents of radical precursor necessary to perform a chemoselective reaction could be lowered when replacing diethylzinc by dimethylzinc (entries 7–10). When the addition of *tert*-butyl radical to diethyl maleate was performed in the presence of dimethylzinc, only 2 equiv of *tert*-butyl iodide was required (entry 9). Dimethylzinc enabled the use of a larger range of alkyl radical precursors ranging from the primary alkyl iodide (10 equiv of EtI, entry 7) to the secondary alkyl iodide (2 equiv of *i*-PrI, entry 8) up to the already discussed tertiary one. The addition of methoxymethyl radical could only be performed at −78 °C (entry 10).

In all cases, both aromatic and aliphatic aldehydes, such as valeraldehyde and formaldehyde, led to high yields. A mixture of four diastereomeric lactones (**2–8abcd**) (Fig. 2) was isolated in 43–97% yield (the stereochemistry was assigned, whenever possible, from the analysis of the coupling constants and chemical shifts of the ring protons, by reference to known compounds[6b,21a,22a]). The diastereomeric ratio was quite similar for the *Z* and the *E* diesters.

An interesting feature is that dimethylzinc could be used as a source of methyl radical (entries 6, 11 and 12).[17] The reaction carried out with formaldehyde led to a 62:38 mixture of *cis* and *trans* lactones in 86% yield (entry 12). The latter are formal precursors of *rac*-botryodiplodin and *rac-epi*-botryodiplodin.[18]

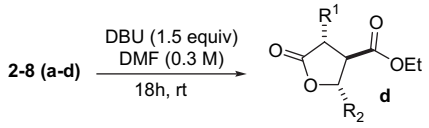
Epimerization was achieved in the presence of DBU (cf. Table 2). It led to a 55:45 mixture of **3a** and **3d** in the case of benzaldehyde (entry 2). In all the other cases, the *trans–trans*



2 : R^1 = Et, R^2 = Ph
3 : R^1 = *t*-Bu, R^2 = Ph
4 : R^1 = *t*-Bu, R^2 = *n*-Bu
5 : R^1 = Me, R^2 = Ph
6 : R^1 = *i*-Pr, R^2 = Ph
7 : R^1 = CH_2OMe, R^2 = Ph
8 : R^1 = Me, R^2 = *n*-Bu
9 : R^1 = Me, R^2 = H

Figure 2. Structures of diastereomeric lactones.

Table 2. Experimental and theoretical diastereomeric ratios after epimerization



Entry	Lactone	%[a]	d.r. **a**:**b**:**c**:**d**[b]
1	**2a–d**	81	6:2:4:88
2	**3a–d**	83	55:0:0:45 (1.3:0:0:98.7)[c]
3	**4a–d**	81	19:0:0:81 (2.7:0:0:97.3)[c]
4	**5a–d**		*partial degradation*
5	**6a–d**	88	25:7:trace:68
6	**8a–d**	92	14:6:80[d] (3.6:0.3:2.6:93.5)[c]

[a] Isolated yield.
[b] Experimental.
[c] Calculated at 298 K at the UB3LYP6-31+G(d,p) level of theory.
[d] (**a**+**c**):**b**:**d**.

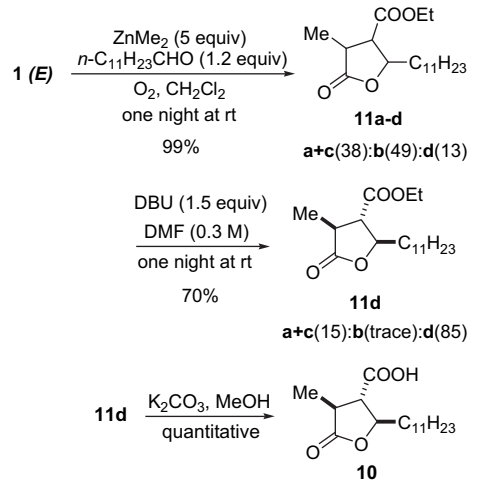
isomer **d** was predominant. DFT calculations performed for compounds **3**, **4** and **8** at the UB3LYP6-31+G(d,p) level of theory gave a theoretical estimate of the Boltzmann distribution of the different diastereomers at 298 K (Table 2). The theoretical calculations gave diastereomeric ratios quite different from the experimental ones; however, they indirectly confirmed the stereochemical assignments. The final ratio registered after epimerization for lactones **3** and **4** could be interpreted as follows. When a *t*-Bu group is present at C4, epimerization at C4 would readily transform isomer **b** into isomer **a** and isomer **c** into isomer **d**. Epimerization at C3 would be slow, in particular, owing to steric impediment, **a** would epimerize very slowly into **d** via **c** through proton abstraction at C3. A pure sample of **3b** submitted to epimerizing conditions led after three days, a 85:2:13 mixture of **a**:**b**:**d**.

The 62:38 cis:trans mixture of di-substituted lactones **9** was partially degraded under the conditions used for epimerization. Therefore, it was not possible to reach the 1.2:98.8 theoretical Boltzmann distribution of the two isomers calculated at 298 K.

Interestingly, when the reaction was performed in the presence of valeraldehyde, isomer **8d** accounted for 80% of the mixture after epimerization (Table 2). This led us to explore the potentiality of dimethylzinc to prepare naturally occurring nephrosteranic acid in racemic form (**10**) (Scheme 3).

γ-Butyrolactones with various ring appendages are frequently encountered in natural products, and most of them exhibit biological activities.[19] Among these, paraconic acids,[20] isolated from various species of lichens, moss and fungi, constitute a special class of γ-butyrolactones that are characterized by a methyl substituent (or methylene group) in the α-position and a carboxyl group in the β-position. The various members of the family differ in configuration at the vicinal chiral centres and in the nature of the substituent in the γ-position. Numerous strategies have been developed for the preparation of these natural products.[21] Only two of these syntheses are based on a free-radical key step.[22]

The addition of methyl radical proceeded readily at room temperature in the presence of oxygen. The results obtained



Scheme 3.

in the presence of dodecanal are summarized in Scheme 3. In this case, the four isomers were readily identified by comparing their ^{1}H NMR characteristic signals to those of known compounds.[21d–m,22] After epimerization in the presence of DBU (one night at room temperature), the thermodynamic 2,3-*trans*,3,4-*trans* isomer **11d** accounted for 85% of the mixture. The separation of the unwanted isomers was achieved via liquid chromatography. Thus racemic nephrosteranic ethyl ester **11d** was prepared in two steps according to Scheme 3. The selective saponification of the ester function was carried out using K_2CO_3 in methanol.

3. Conclusion

The dialkylzinc-mediated multi-component reactions described herein enable the preparation of tri-substituted γ-lactones in one step from diethyl fumarate and diethyl maleate. Epimerization of the enolizable centres improves the diastereoselectivity of the process in most cases. Dimethylzinc was used as a convenient source of methyl radical, and racemic nephrosteranic acid was prepared in three steps from diethyl fumarate and dodecanal.

These results support the assumption that spin density at the oxygen atom in secondary α-alkoxycarbonylalkyl radicals is sufficient for these radicals to react via homolytic substitution at zinc(II). The influence of additional steric effects, of the presence of the aldehyde as ligand in the zinc coordination sphere, and of the possibility to form chelated zinc enolates on the reactivity of dialkylzincs in the S_H2 step cannot be clearly evaluated. Further results will be reported in due course.

4. Experimental section

4.1. General

NMR and DEPT spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) using $CDCl_3$ as the solvent. The *J* values are given in hertz. Column chromatographies were performed on silica gel 60. The solvents for chromatography (*n*-hexane, 2-PrOH, EtOH) were HPLC grade. They were degassed and filtered on a 0.45 μm membrane before use. The HPLC analyses were performed on Chiralcel OD-H (250×4.6 mm), a cellulose tris-(3,5-dimethylphenylcarbamate) chiral stationary phase with UV and polarimetric detection.

4.2. General procedure for the synthesis of lactones

Method A: Aldehyde (1.2 equiv) and *t*-BuI (none or 10 equiv) were added under argon at room temperature to a 0.2 M solution of substrate in dichloromethane. Diethylzinc (2 equiv, 1 M solution in hexane) was then introduced and the reaction was stirred at the same temperature while air (20 mL) was injected through a needle into the solution over 1 h. After stirring overnight at room temperature, the reaction was quenched by aqueous saturated NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (FC).

Method B: Aldehyde (1.2 equiv) and alkyl iodide (none or *x* equiv) were added under argon at room temperature to a 0.2 M solution of substrate in dichloromethane. Dimethylzinc (5 equiv, 2 M solution in toluene) was then introduced and the reaction was stirred at the same temperature while O_2 (20 mL) was injected through a needle into the solution over 1 h. After stirring overnight at room temperature under O_2 atmosphere, the reaction was quenched by aqueous saturated NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by FC.

4.3. General procedure for the epimerization of lactones

Method C: DBU (1.5 equiv) was added under argon at room temperature to a 0.3 M solution of lactones in dry DMF. The reaction was stirred at the same temperature for overnight. After completion, the reaction was diluted in water and extracted with CH_2Cl_2 (×5). The organic layers were washed with HCl (1 M), dried, filtered and concentrated. The crude product was purified by FC.

NMR assignments follow from the analysis of enriched chromatographic fractions resulting from HPLC separation.

4.4. 2-(Hydroxy-phenyl-methyl)-4,4-dimethyl-pentanoic acid ethyl ester

Treating ethyl acrylate (50 mg, 0.5 mmol) according to method A in the presence of benzaldehyde (60 μL, 0.60 mmol) led to the desired product (114 mg, 0.44 mmol) isolated in 87% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (68:32) was determined from ^{1}H NMR.

Minor isomer—^{1}H NMR ($CDCl_3$): δ 0.78 (s, 9H), 1.06 (t, 3H, *J*=7.2), 1.59 (dd, 1H, *J*=1.7, 14.0), 1.79 (dd, 1H, *J*=10.2, 14.0), 1.88 (br s, 1H), 2.71 (ddd, 1H, *J*=1.7, 5.7, 10.2), 3.96 (q, 2H, *J*=7.2), 4.79 (d, 1H, *J*=5.7), 7.21–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3), 29.1 (CH_3), 30.2 (C), 40.3 (CH_2), 49.9 (CH), 60.4 (CH_2), 75.0 (CH), 126.3 (CH), 127.6 (CH), 128.1 (CH), 141.5 (C), 175.7

(C=O). *Major isomer*—^{1}H NMR ($CDCl_3$): δ 0.78 (s, 9H), 1.17 (t, 3H, J=7.2), 1.20 (dd, 1H, J=1.7, 14.2), 1.78 (dd, 1H, J=10.4, 14.2), 2.81 (ddd, 1H, J=1.7, 7.5, 10.2), 2.95 (br d, 1H, J=5.9), 4.09 (q, 2H, J=7.2), 4.65 (dd, 1H, J=5.9, 7.2), 7.21–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.9 (CH_3), 29.1 (CH_3), 30.4 (C), 43.1 (CH_2), 49.6 (CH), 60.5 (CH_2), 76.9 (CH), 126.5 (CH), 127.9 (CH), 128.3 (CH), 142.1 (C), 176.2 (C=O).

4.5. 4-Ethyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid ethyl ester (2)

Treating **(*Z*)-1** (100 mg, 0.58 mmol) according to method A in the presence of benzaldehyde (70 μL, 0.70 mmol) led to **2a–d** (142 mg, 0.54 mmol) isolated in 93% yield after purification by FC (5–25% EtOAc/pentane). The diastereomeric ratio (**a–d**=19:23:50:8) was determined from ^{1}H NMR. Treating **(*Z*)-1** (100 mg, 0.58 mmol) according to method B in the presence of ethyl iodide (45 μL, 0.58 mmol, 10 equiv) and benzaldehyde (70 μL, 0.70 mmol) led to **2a–d** (138 mg, 0.53 mmol) isolated in 91% yield after purification by FC (5–25% EtOAc/pentane). The diastereomeric ratio (**a–d**=19:24:50:7) was determined from ^{1}H NMR.

(2*R,3*S**,4*S**)-(2a)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 3.18 (dt, 1H, J=5.8, 8.0, H_4), 3.51 (pseudo t, 1H, J=8.5, H_3), 5.72 (d, 1H, J=8.1, H_2). **(2*R**,3*S**,4*R**)-(2b)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 2.89 (m, 1H, H_4), 3.68 (dd, 1H, J=5.7, 7.2, H_3), 5.60 (d, 1H, J=5.7, H_2). **(2*R**,3*R**,4*S**)-(2c)**—^{1}H NMR ($CDCl_3$): δ 1.07 (t, 3H, J=7.5), 1.29 (t, 3H, J=7.2), 1.53–1.67 (m, 1H), 1.82–1.93 (m, 1H), 2.84 (pseudo q, 1H, J=8.7, H_4), 3.40 (dd, 1H, J=6.0, 8.9, H_3), 4.16–4.29 (m, 2H), 5.73 (d, 1H, J=6.0, H_2), 7.19–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.6 (CH_3), 14.0 (CH_3), 20.2 (CH_2), 43.3 (CH), 52.6 (CH), 61.4 (CH_2), 79.8 (CH), 125.2 (CH), 128.7 (CH), 128.8 (CH), 138.0 (C), 169.8 (C=O), 176.0 (C=O). **(2*R**,3*R**,4*R**)-(2d)**—^{1}H NMR ($CDCl_3$): δ 1.02 (t, 3H, J=7.4), 1.26 (t, 3H, J=7.2), 1.69–1.85 (m, 1H), 1.87–2.02 (m, 1H), 3.04–3.14 (AB part of ABX, 2H, J_{AB}=10.8, H_3 and H_4), 4.22 (q, 2H, J=7.2), 5.50 (d, 1H, J=8.3, H_2), 7.30–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 10.6 (CH_3), 14.1 (CH_3), 20.4 (CH_2), 46.5 (CH), 54.4 (CH), 61.7 (CH_2), 80.4 (CH), 125.6 (CH), 128.8 (CH), 128.9 (CH), 137.8 (C), 170.9 (C=O), 175.9 (C=O).

Epimerization: Treating **2a–d** (99 mg) according to method C led to **2a–d** (80 mg) isolated in 81% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a–d**=6:2:4:88) was determined from ^{1}H NMR.

^{1}H and ^{13}C NMR are in accordance with those reported in the literature.[21]

4.6. 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid ethyl ester (3)

Treating **(*E*)-1** (100 mg, 0.58 mmol) according to method A in the presence of *tert*-butyl iodide (10 equiv, 700 μL, 5.8 mmol) and benzaldehyde (70 μL, 0.70 mmol) led to **3a–d** (149 mg, 0.52 mmol) isolated in 89% yield after purification by FC (5–25% EtOAc/pentane). The diastereomeric ratio (**a–d**=41:18:27:14) was determined from ^{1}H NMR (three isomeric lactones **2** were detected in a 8:92 ratio with respect to **3a–d**). Treating **(*Z*)-1** (100 mg, 0.58 mmol) according to method A in the presence of *tert*-butyl iodide (10 equiv, 700 μL, 5.8 mmol) and benzaldehyde (70 μL, 0.70 mmol) led to **3a–d** (151 mg, 0.53 mmol) isolated in 90% yield after purification by FC (5–25% EtOAc/pentane). The diastereomeric ratio (**a–d**=46:15:25:14) was determined from ^{1}H NMR. Treating **(*Z*)-1** (100 mg, 0.58 mmol) according to method B in the presence of *tert*-butyl iodide (2 equiv, 140 μL, 1.16 mmol) and benzaldehyde (70 μL, 0.70 mmol) led to **3a–d** (156 mg, 0.54 mmol) isolated in 93% yield after purification by FC (5–25% EtOAc/pentane). The diastereomeric ratio (**a–d**=41:16:29:14) was determined from ^{1}H NMR. **(2*R**,3*S**,4*R**)-(3a)**—^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, J=7.2), 1.11 (s, 9H), 3.10 (d, 1H, J=7.7, H_4), 3.65 (dd, 1H, J=9.3, 7.7, H_3), 3.68 (superimposed AB part of ABX_3, 2H), 5.65 (d, 1H, J=9.3, H_2), 7.19–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.5 (CH_3), 27.3 (CH_3), 33.1 (C), 49.3 (CH), 51.4 (CH), 61.2 (CH_2), 78.6 (CH), 125.9 (CH), 128.3 (CH), 128.7 (CH), 136.2 (C), 170.0 (C=O), 175.9 (C=O). **(2*R**,3*S**,4*S*)-(3b)**—^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J=7.2), 1.14 (s, 9H), 2.86 (d, 1H, J=6.8, H_4), 3.65 (dd, 1H, J=5.1, 6.8, H_3), 3.75 (q, 2H, J=7.2), 5.51 (d, 1H, J=5.1, H_2), 7.19–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.4 (CH_3), 28.3 (CH_3), 31.4 (C), 51.2 (CH), 55.3 (CH), 60.7 (CH_2), 78.4 (CH), 125.2 (CH), 128.1 (CH), 128.2 (CH), 135.1 (C), 169.3 (C=O), 173.4 (C=O). **(2*R**,3*R**,4*R**)-(3c)**—^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H, J=7.2), 1.12 (s, 9H), 2.69 (d, 1H, J=8.5, H_4), 3.33 (dd, 1H, J=4.2, 8.5, H_3), 4.21 (AB part of ABX_3, 2H), 5.66 (d, 1H, J=4.2, H_2), 7.19–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3), 28.1 (CH_3), 32.4 (C), 51.5 (CH), 52.1 (CH), 61.5 (CH_2), 79.2 (CH), 125.1 (CH), 128.5 (CH), 128.8 (CH), 137.9 (C), 171.3 (C=O), 174.2 (C=O). **(2*R**,3*R**,4*S**)-(3d)**—^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.23 (t, 3H, J=7.2), 3.10–3.13 (AB part of ABX_3, 2H), 4.21 (q, 2H, J=7.2), 5.27 (m, 1H, X part of an ABX, H_2 virtual coupling with H_4), 7.19–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 27.0 (CH_3), 32.7 (C), 53.0 (CH), 54.5 (CH), 61.7 (CH_2), 79.9 (CH), 125.4 (CH), 128.7 (CH), 128.9 (CH), 138.1 (C), 172.0 (C=O), 174.6 (C=O). HRMS calcd for $C_{17}H_{23}O_4$ [MH^+] 291.1596, found 291.1609.

Epimerization: Treating **3a–d** (157 mg) according to method C led to **3a**,**d** (131 mg) isolated in 83% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a**:**d**=55:45) was determined from ^{1}H NMR.

4.7. 2-Butyl-4-*tert*-butyl-5-oxo-tetrahydro-furan-3-carboxylic acid ethyl ester (4)

Treating **(*E*)-1** (100 mg, 0.58 mmol) according to method A in the presence of *tert*-butyl iodide (10 equiv, 700 μL, 5.8 mmol) and valeraldehyde (74 μL, 0.70 mmol) led to **4a–d** (153 mg, 0.57 mmol) isolated in 97% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a–d**=13:9:12:66) was determined from ^{1}H NMR. Treating **(*Z*)-1** (100 mg, 0.58 mmol) according to method A in the presence of *tert*-butyl iodide (10 equiv, 700 μL, 5.8 mmol) and valeraldehyde (74 μL, 0.70 mmol) led to **4a–d** (136 mg, 0.50 mmol) isolated in 87% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric

ratio (**a**–**d**=13:9:12:66) was determined from ^{1}H NMR. **(2*S**,3*S**,4*R**)-(4a)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 2.92 (d, 1H, J=8.1, H_4), 3.35 (pseudo t, 1H, J=8.5, H_3), 4.53 (dt, 1H, J=3.4, 8.8, H_2). ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 14.1 (CH_3), 27.3 (CH_3), 27.8 (CH_2), 29.6 (CH_2), 31.7 (CH_2), 32.9 (C), 47.1 (CH), 51.9 (CH), 61.3 (CH_2), 77.1 (CH), 170.9 (C=O), 175.6 (C=O). **(2*S**,3*S**,4*S**)-(4b)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 2.66 (d, 1H, J=6.8, H_4), 3.26 (dd, 1H, J=4.8, 6.8, H_3). **(2*S**,3*R**,4*R**)-(4c)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 2.72 (d, 1H, J=8.9, H_4), 3.06 (dd, 1H, J=4.3, 8.9, H_3). **(2*S**,3*R**,4*S**)-(4d)**—^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H, J=7.2), 1.05 (s, 9H), 1.29 (t, 3H, J=7.2), 1.24–1.59 (m, 4H), 1.64–1.85 (m, 2H), 2.86 (dd, 1H, J=10.7, 8.9, H_3), 2.99 (d, 1H, J=10.7, H_4), 4.17–4.28 (m, 1H, H_2), 4.22 (superimposed q, 2H, J=7.2). ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 14.0 (CH_3), 22.2 (CH_2), 27.0 (CH_3), 27.1 (CH_2), 32.5 (C), 34.7 (CH_2), 50.1 (CH), 54.0 (CH), 61.5 (CH_2), 79.0 (CH), 172.2 (C=O), 174.9 (C=O). HRMS calcd for $C_{15}H_{27}O_4$ [MH^+] 271.1906, found 271.1904.

Epimerization: Treating **4a**–**d** (153 mg) according to method C led to **4a**,**d** (124 mg) isolated in 81% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a**:**d**=19:81) was determined from ^{1}H NMR.

4.8. 4-Methyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid ethyl ester (5)

Treating **(*E*)-1** (100 mg, 0.58 mmol) according to method B in the presence of benzaldehyde (70 μL, 0.70 mmol) led to **5a**–**d** (139 mg, 0.56 mmol) isolated in 97% yield after purification by FC (5–25% EtOAc/pentane). The diastereomeric ratio (**a**–**d**=21:43:30:6) was determined from ^{1}H NMR. **(2*R**,3*S**,4*S**)-(5a)**—^{1}H NMR ($CDCl_3$): δ 0.99 (t, 3H, J=7.2), 1.38 (d, 3H, J=7.0), 3.28 (dq, 1H, J=9.5, 7.0, H_4), 3.45 (pseudo t, 1H, J=9.2, H_3), 3.85 (AB part of an ABX_3, 2H), 5.75 (d, 1H, J=8.7, H_2), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 14.6 (CH_3), 35.9 (CH), 53.9 (CH), 61.3 (CH_2), 78.7 (CH), 125.9 (CH), 128.3 (CH), 128.9 (CH), 135.4 (C), 168.8 (C=O), 178.0 (C=O). **(2*R**,3*S**,4*R**)-(5b)**—^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J=7.2), 1.34 (d, 3H, J=7.2), 3.10 (pseudo quint, 1H, J= 7.2, H_4), 3.66 (dd, 1H, J=5.6, 7.4, H_3), 3.77 (q, 2H, J= 7.2), 5.63 (d, 1H, J=5.6, H_2), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 10.5 (CH_3), 13.6 (CH_3), 39.3 (CH), 53.1 (CH), 60.8 (CH_2), 79.1 (CH), 125.2 (CH), 128.3 (CH), 128.5 (CH), 135.2 (C), 168.5 (C=O), 176.8 (C=O). **(2*R**,3*R**,4*S**)-(5c)**—^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, J=7.0), 1.32 (superimposed d, 3H, J=7.2), 3.08 (dq, 1H, J=9.1, 7.2, H_4), 3.40 (dd, 1H, J=6.6, 9.1, H_3), 4.25 (AB part of an ABX_3, 2H), 5.78 (d, 1H, J=6.7, H_2), 7.18–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.8 (CH_3), 14.2 (CH_3), 37.1 (CH), 53.1 (CH), 61.5 (CH_2), 79.7 (CH), 125.4 (CH), 128.7 (CH), 128.8 (CH), 138.0 (C), 169.7 (C=O), 177.1 (C=O). **(2*R**,3*R**,4*R**)-(5d)**—^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, J=7.0), 1.42 (d, 3H, J=7.0), 2.95 (dd, 1H, J=11.5, 9.4, H_3), 3.09 (dq, 1H, J=11.5, 7.0, H_4), 4.23 (q, 2H, J=7.0), 5.55 (d, 1H, J=9.4, H_2), 7.208–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 14.4 (CH_3), 40.5 (CH), 57.0 (CH), 61.7 (CH_2), 80.2 (CH), 125.8 (CH), 128.8 (CH), 128.9 (CH), 137.5 (C), 170.3 (C=O), 176.4 (C=O). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.26; H, 6.72.

4.9. 4-*iso*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid ethyl ester (6)

Treating **(*Z*)-1** (100 mg, 0.58 mmol) according to method B in the presence of *iso*-propyl iodide (2 equiv, 110 μL, 1.16 mmol) and benzaldehyde (70 μL, 0.70 mmol) led to **6a**–**d** (153 mg, 0.55 mmol) isolated in 95% yield after purification by FC (5–25% EtOAc/pentane). The diastereomeric ratio (**a**–**d**=31:29:30:10) was determined from ^{1}H NMR. **(2*R**,3*S**,4*S**)-(6a)**—^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H, J=7.2), 1.04 (d, 6H, J=7.0), 2.30 (dsept, 1H, J=5.1, 6.8), 3.21 (dd, 1H, J=8.0, 5.1, H_4), 3.59 (dd, 1H, J=8.0, 9.1, H_3), 3.71 (AB part of ABX_3, 2H), 5.68 (d, 1H, J=9.1, H_2), 7.19–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.5 (CH_3), 18.8 (CH_3), 19.9 (CH_3), 28.3 (CH), 47.5 (CH), 48.5 (CH), 61.1 (CH_2), 79.1 (CH), 125.8 (CH), 128.3 (CH), 128.7 (CH), 135.8 (C), 169.6 (C=O), 176.8 (C=O). **(2*R**,3*S**,4*R**)-(6b)**—^{1}H NMR ($CDCl_3$): δ 0.84 (t, 3H, J=7.2), 0.93 (d, 3H, J=6.8), 1.31 (d, 3H, J=6.4), 2.08–2.13 (m, 1H), 2.59 (dd, 1H, J=10.4, 6.8, H_4), 3.61 (dd, 1H, J=6.8, 5.5, H_3), 3.75 (AB part of ABX_3, 2H), 5.53 (d, 1H, J=5.5, H_2), 7.29–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.5 (CH_3), 21.2 (CH_3), 21.5 (CH_3), 26.1 (CH), 51.4 (CH), 51.9 (CH), 60.7 (CH_2), 78.7 (CH), 125.3 (CH), 128.2 (CH), 128.3 (CH), 134.9 (C), 168.9 (C), 175.3 (C). **(2*R**,3*R**,4*S**)-(6c)**—^{1}H NMR ($CDCl_3$): δ 1.08 (d, 3H, J=6.8), 1.16 (d, 3H, J=6.8), 1.30 (t, 3H, J=7.2), 2.08–2.13 (m, 1H), 2.74 (dd, 1H, J=9.1, 6.0, H_4), 3.40 (dd, 1H, J=9.1, 6.0, H_3), 4.24 (AB part of ABX_3, 2H), 5.70 (d, 1H, J=6.4, H_2), 7.29–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 19.5 (CH_3), 21.7 (CH_3), 27.3 (CH), 47.8 (CH), 52.8 (CH), 61.4 (CH_2), 79.8 (CH), 125.2 (CH), 128.5 (CH), 128.7 (CH), 138.2 (C), 170.0 (C), 175.2 (C). **(2*R**,3*R**,4*R**)-(6d)**—^{1}H NMR ($CDCl_3$): δ 1.00 (d, 3H, J=6.8), 1.02 (d, 3H, J=6.8), 1.25 (t, 3H, J=7.2), 2.34 (dsept, 1H, J=3.4, 6.8), 3.10 (dd, 1H, J=10.8, 8.3, H_3), 3.17 (dd, 1H, J=10.8, 3.4, H_4), 4.22 (q, 2H, J=7.2), 5.43 (d, 1H, J=8.3, H_2), 7.28–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 18.2 (CH_3), 19.7 (CH_3), 27.7 (CH), 51.1 (CH), 51.4 (CH), 61.7 (CH_2), 80.5 (CH), 125.4 (CH), 128.2 (CH), 128.8 (CH), 137.9 (C), 171.4 (C=O), 175.4 (C=O). HRMS calcd for $C_{16}H_{21}O_4$ [MH^+] 277.1440, found 277.1436.

Epimerization: Treating **6a**–**d** (160 mg) according to method C led to **6a**–**d** (140 mg) isolated in 88% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a**–**d**=25:7:trace:68) was determined from ^{1}H NMR.

4.10. 4-Methoxymethyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid ethyl ester (7)

Treating **(*E*)-1** (100 mg, 0.58 mmol) according to method B in the presence of benzaldehyde (295 μL, 2.91 mmol, 5 equiv), $MeOCH_2I$ (245 μL, 2.91 mmol, 5 equiv) and 2 equiv of dimethylzinc led to **7a**–**d** (70 mg, 0.25 mmol) isolated in 43% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a**–**d**=45:27:13:15) was determined from ^{1}H NMR. **(2*R**,3*S**,4*R**)-(7a)**—^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H, J=7.2), 3.39 (dt, 1H, J=7.7, 3.5, H_4), 3.39 (superimposed s, 3H), 3.62 (dd, 1H, J=3.4, 9.5),

3.75 (AB part of ABX_3, 2H, J_{AB}=10.8), 3.88 (dd, 1H, J=3.6, 9.6), 3.88 (superimposed dd, 1H, J=7.7, 8.9, H_3), 5.77 (d, 1H, J=8.9, H_2), 7.15–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.6 (CH_3), 43.2 (CH), 48.7 (CH), 59.3 (CH_3), 61.2 (CH_2), 69.7 (CH_2), 79.7 (CH), 126.0 (CH), 128.4 (CH), 128.8 (CH), 135.8 (C), 169.4 (C=O), 176.0 (C=O). **(2*R**,3*S**,4*S**)-(7b)**—^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3H, J=7.2), 3.33 (s, 3H), 3.37 (ddd, 1H, J=5.5, 7.2, 9.6, H_4), 3.65 (t, 1H, J=9.8), 3.70–3.78 (m, 3H), 3.92 (dd, 1H, J=5.5, 9.6), 5.64 (d, 1H, J=5.6, H_2), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.6 (CH_3), 45.0 (CH), 50.6 (CH), 59.1 (CH_3), 60.7 (CH_2), 68.4 (CH_2), 80.0 (CH), 125.4 (CH), 128.3 (CH), 128.5 (CH), 134.7 (C), 168.4 (C=O), 174.1 (C=O). **(2*R**,3*R**,4*R**)-(7c)**—Characteristic signal, ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, J=7.4), 5.83 (d, 1H, J=8.1, H_2). **(2*R**,3*R**,4*S**)-(7d)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, J=7.2), 3.24 (dt, 1H, J=10.8, 3.6, H_4), 3.51 (dd, 1H, J=10.6, 9.3, H_3), 5.52 (d, 1H, J=9.1, H_2). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.65; H, 6.69.

4.11. 2-Butyl-4-methyl-5-oxo-tetrahydro-furan-3-carboxylic acid ethyl ester (8)

Treating **(*E*)-1** (100 mg, 0.58 mmol) according to method B in the presence of valeraldehyde (74 μL, 0.70 mmol) led to **8a–d** (104 mg, 0.46 mmol) isolated in 79% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a+c**:**b**:**d**=39:50:11) was determined from ^{1}H NMR. **(2*S**,3*S**,4*S**)-(8a)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 3.04 (dq, 1H, J=9.8, 7.0, H_4), 3.17 (dd, 1H, J=8.1, 9.8, H_3), 4.64 (m, 1H, H_2). **(2*S**,3*S**,4*R**)-(8b)**—^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H, J=7.2), 1.28 (d, 3H, J=6.8), 1.29 (t, 3H, J=7.2), 1.33–1.69 (m, 5H), 1.70–1.87 (m, 1H), 2.90 (pseudo quint, 1H, J=7.2, H_4), 3.29 (dd, 1H, J=5.3, 7.4, H_3), 4.22 (AB part of ABX_3, 2H), 4.44 (dt, 1H, J=10.4, 5.3, H_2). ^{13}C NMR ($CDCl_3$): δ 10.3 (CH_3), 13.8 (CH_3), 14.2 (CH_3), 22.3 (CH_2), 27.8 (CH_2), 30.5 (CH_2), 39.1 (CH), 50.6 (CH), 60.9 (CH_2), 70.1 (CH), 169.5 (C=O), 177.1 (C=O). **(2*S**,3*R**,4*S**)-(8c)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 2.99 (dq, 1H, J=9.3, 7.4, H_4), 3.09 (dd, 1H, J=6.2, 9.3, H_3), 4.70 (q, 1H, J=6.2, H_2). **(2*S**,3*R**,4*R**)-(8d)**—^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, J=7.2), 1.30 (t, 3H, J=7.2), 1.33 (d, 3H, J=7.0), 1.20–1.54 (m, 4H), 1.61–1.87 (m, 2H), 2.63 (dd, 1H, J=11.5, 9.4, H_3), 2.95 (dq, 1H, J=11.5, 7.0, H_4), 4.23 (q, 2H, J=7.2), 4.45 (ddd, 1H, J=9.4, 8.1, 4.5, H_2). ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3), 14.1 (CH_3), 14.4 (CH_3), 22.3 (CH_2), 27.3 (CH_2), 34.5 (CH_2), 39.9 (CH), 54.3 (CH), 61.5 (CH_2), 79.5 (CH), 170.7 (C=O), 176.8 (C=O). HRMS calcd for $C_{15}H_{27}O_4$ [MH^+] 229.1440, found 271.1422.

Epimerization: Treating **8a–d** (170 mg) according to method C led to **8a–d** (156 mg) isolated in 92% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a+c**:**b**:**d**=14:6:80) was determined from ^{1}H NMR.

4.12. 4-Methyl-5-oxo-tetrahydro-furan-3-carboxylic acid ethyl ester (9)

Treating **(*E*)-1** (100 mg, 0.58 mmol) according to method B in the presence of formaldehyde (12 equiv, M_r $(30.03)_n$, 211 mg, 7 mmol) led to **9** (86 mg, 0.5 mmol) isolated in 86% yield after purification by FC (5–60% EtOAc/pentane). The diastereomeric ratio (*cis*:*trans*=62:38) was determined from ^{1}H NMR. ^{1}H and ^{13}C NMR are in accordance with those reported in the literature.[23]

4.13. 4-Methyl-5-oxo-2-undecyl-tetrahydro-furan-3-carboxylic acid ethyl ester (11)

Treating **(*E*)-1** (100 mg, 0.58 mmol) according to method B in the presence of dodecanal (129 mg, 0.70 mmol) led to **11a–d** (189 mg, 0.58 mmol) isolated in 99% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a+c**:**b**:**d**=38:49:13) was determined from ^{1}H NMR. **(2*S**,3*S**,4*S**)-(11a)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 3.04 (dq, 1H, J=9.8, 7.0, H_4), 3.16 (dd, 1H, J=8.3, 9.8, H_3), 4.66 (m, 1H, H_2). **(2*S**,3*S**,4*R**)-(11b)**—^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J=6.4), 1.15–1.85 (m, 26H), 2.89 (quint, 1H, J=7.2, H_4), 3.28 (dd, 1H, J=5.3, 7.6, H_3), 4.22 (m, 2H), 4.40 (dt, 1H, J=8.3, 5.3, H_2). ^{13}C NMR ($CDCl_3$): δ 10.2 (CH_3), 14.0 (CH_3), 14.2 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (2×CH_2), 30.8 (CH_2), 31.8 (CH_2), 39.1 (CH), 50.5 (CH), 60.9 (CH_2), 79.0 (CH), 169.5 (C=O), 177.0 (C=O). **(2*S**,3*R**,4*S**)-(11c)**—Characteristic signals, ^{1}H NMR ($CDCl_3$): δ 2.98 (dq, 1H, J=9.4, 7.2, H_4), 3.09 (dd, 1H, J=6.2, 9.4, H_3), 4.69 (q, 1H, J=6.4, H_2). **(2*S**,3*R**,4*R**)-(11d)**—^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, J=7.2), 1.10–1.85 (m, 26H), 2.63 (dd, 1H, J=9.5, 11.5, H_3), 2.95 (dq, 1H, J=11.5, 7.0, H_4), 4.23 (q, 2H, J=7.2), 4.44 (ddd, 1H, J=4.2, 7.7, 9.5, H_2). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 14.1 (CH_3), 14.4 (CH_3), 22.6 (CH_2), 25.2 (CH_2), 29.2 (2×CH_2), 29.3 (2×CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.8 (CH_2), 34.8 (CH_2), 39.9 (CH), 54.4 (CH), 61.5 (CH_2), 79.6 (CH), 170.7 (C=O), 176.8 (C=O). HRMS calcd for $C_{19}H_{35}O_4$ [MH^+] 327.2535; found 327.2531.

Epimerization: Treating **11a–d** (185 mg) according to method C led to **11a–d** (130 mg) isolated in 70% yield after purification by FC (5–20% EtOAc/pentane). The diastereomeric ratio (**a+c**:**b**:**d**=15:trace:85) was determined from ^{1}H NMR.

Saponification: Treating **11d** (56 mg, 0.172 mmol) by K_2CO_3 (119 mg, 0.86 mmol, 5 equiv) in MeOH (1.8 mL) at room temperature overnight, led to the corresponding carboxylic acid **10** (51 mg, 0.171 mmol) in 99% yield after evaporation of MeOH, acidic treatment (HCl 10%, pH=2) and AcOEt extraction (×4). ^{1}H and ^{13}C NMR are in accordance with those reported in the literature.[22a]

4.14. Computational details

All calculations were performed with Gaussian03 package.[24] The geometry optimizations were carried out without constraints at the B3LYP/6-31+G(d,p) level. Vibrational frequencies were calculated at the B3LYP/6-31+G(d,p) level to confirm that the geometries were minima. The harmonic frequencies were scaled by 0.9804 to calculate thermodynamic properties. B3LYP/6-31+G(d,p) computed enthalpies at 298.15 K, relative enthalpies respect to the more stable diastereoisomer, Boltzmann distribution at 298.15 K and Cartesian coordinates of isomers **3a–d**, **4a–d**, **8a–d** and **9a–b**. For

each isomer, we calculated two different positions of ester moiety (1: C═O bond directed towards the ring; 2: rotation by 180° of ester moiety).

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