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Masked ω-Lithio Ester Enolates: Synthetic Applications [§]

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[§] *Dedicated to Professor Ramón Mestres on the occasion of his 65th birthday.*

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Abstract: The protocol of lithiation by means of lithium and a catalytic (5% molar) amount of DTBB (4,4'-di-*tert*-butylbiphenyl), applied to ω-chloro ortho ester **6** under Barbier-type conditions gives, after final acid-catalyzed methanolysis, the corresponding functionalized esters **8** or **9** (for chlorotrimethylsilane as electrophile) or, after ortho ester deprotection and acid catalyzed treatment, the δ-lactones **11**. The procedure is also practical for bicyclic ortho esters **14**: the β-chloro OBO ester derivate generates the γ-lactones **15** and the γ-chloro OBO ester gives corresponding esters **8**.

Keywords: Chlorine-lithium exchange; functionalized ester; arene-catalyzed lithiation.

Introduction

Among organometallic reagents, organolithium compounds are the most reactive ones due to the high ionic nature of the carbon-lithium bond [1]. Functionalized organolithium compounds are very useful in synthetic organic chemistry in order to transfer their functionality to electrophiles in a single synthetic step, thus organolithium derivatives bearing a carboxylic moiety would transfer a carboxylic group to an electrophilic reagent. The corresponding α-derivatives (carboxylate enolate, **1**) [2] have been prepared by double deprotonation [2,3] using lithium dialkylamides [4] as bases (e.g. LDA). Recently, Parra *et al.* [5] have reported the generation of this intermediate (and the subsequent reaction

with carbonyl reagents) by using a sub-stoichiometric amount of an amine (Et$_2$NH or AZA: 1,3,3-trimethyl-6-azabicyclo-[3.2.1]-octane) and *n*-butyllithium to regenerate the amide. Our laboratory has approached the preparation of this organolithium reagent starting from α-chloroacetic acid by chlorine-lithium exchange using an excess of lithium in the presence of catalytic amount of DTBB (4,4'-di-*tert*-butylbiphenyl, 5% molar) [6].
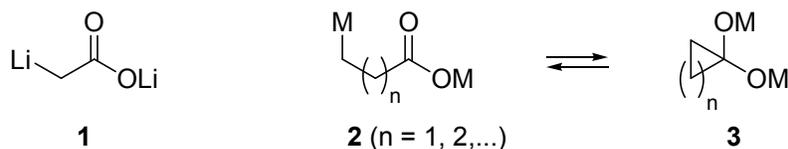
In general homoenolates (i.e. β-enolates, **2** with n = 1), bishomoenolates (i.e. γ-enolates, **2** with n = 2) and higher-order enolates (δ-, ε-, …) **2** are far more unstable because they can undergo cyclization to generate intermediates **3**. Carboxylate homoenolates can be prepared by deprotonation only when a stabilizing group is present at the β-position [7]. Another procedure to prepare these organolithium intermediates is via halogen-lithium exchange, either bromo-lithium [8] or chloro-lithium, the later being performed in our group using the same methodology as for the corresponding α-enolate (arene-catalyzed lithiation) [6]. To the best of our knowledge, there are few examples in the literature starting from the corresponding carboxylic acids, in all cases, being prepared by deprotonation with strong bases, at a carbon which bears a stabilizing group [9].

Our laboratory has been studying, during more than a decade, the preparation of functionalized organolithium intermediates [10] starting from different substrates (chlorinated, non-halogenated, or heterocyclic precursors [11]) by using an arene-catalytic lithiation under very mild reaction conditions [12-14]. Employing this methodology organolithium compounds bearing a masked carbonyl function (masked lithium ω-enolates) have been prepared [12,15]. We report herein the preparation of masked β-, γ-, and δ-lithium ester enolates starting from the corresponding ω-chloro ortho esters, by a chlorine-lithium exchange using the arene-catalyze lithiation process, and their reaction with electrophilic compounds [16].

Results and Discussion

Monocyclic ortho esters **6** (2-ethoxy-1,3-dioxolane derivatives) were easily prepared from the corresponding nitriles by the Pinner synthesis [17]. The reaction of 4-chlorobutyronitrile (**4a**) or 5-chlorovaleronitrile (**4b**) with ethanol in the presence of hydrogen chloride at -5ºC gave the corresponding imidates **5**, which by treatment with ethylene glycol in hexane yielded the corresponding ω-chloro ortho esters **6** (Scheme 1).

Scheme 1. Preparation of ω-chloro ortho esters **6**

4a (n = 2)   **5a**   **6a**
4b (n = 3)   **5b**   **6b**

The chlorine-lithium exchange from chlorinated ortho esters **6**, using an excess of lithium powder (5 eq) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 5% molar), to generate the organolithium intermediates **7** and their subsequent reaction with different electrophiles [E = Bu^{t}CHO, PhCHO, (CH$_2$)$_5$CO, Et$_2$CO, PhCOMe, PhCH=NPh, MeSiCl] had to be carried out under Barbier-type conditions (lithiation in the presence of the electrophile [18]) in THF at -78ºC in order to avoid decomposition of intermediate **7** under the tested reaction conditions. After hydrolysis with phosphate buffer and final treatment in dry methanol and a catalytic amount of *p*-toluensulfonic acid (PTSA), the corresponding functionalized methyl esters **8** were obtained (Scheme 2, Table 1) in all the cases, except when chlorotrimethylsilane was used as electrophile. In those cases, ω-trimethylsilyl hydroxyethyl alkanoates **9a** and **9b** (Table 1, entries 7 and 14) were the isolated products, their formation being explained by considering the anchimeric assistance of the silicon present in the structure during the hydrolysis step (see intermediate **10**).

Scheme 2. Preparation of compounds **8** and **9** from chloro ortho esters **6**

6a (n = 2)   **8aa-af**   **9a**
6b (n = 3)   **8ba-bf**   **9b**

Performing the reaction with the ortho ester **6a** and benzaldehyde as electrophile at higher temperature (0ºC) or under Grignard-type conditions (a two-step process), lower yields were obtained (Table 1, entry 2, footnotes c and d, respectively).

7   **10**

Table 1. Preparation of compounds **8** and **9** from chloro ortho esters **6**

Entry	Starting material	Electrophile (E)	Product **8** or **9**[a]			
			No.	n	X	Yield (%)[b]
1	**6a**	Bu^{t}CHO	**8aa**	2	Bu^{t}CHOH	58
2	**6a**	PhCHO	**8ab**	2	PhCHOH	63 (54)[c] (47)[d]
3	**6a**	(CH$_2$)$_5$CO	**8ac**	2	(CH$_2$)$_5$COH	59
4	**6a**	Et$_2$CO	**8ad**	2	Et$_2$COH	51
5	**6a**	PhCOMe	**8ae**	2	PhC(OH)Me	52
6	**6a**	PhCH=NPh	**8af**	2	PhCHNHPh	57
7	**6a**	Me$_3$SiCl	**9a**[e]	2	Me$_3$Si	40
8	**6b**	Bu^{t}CHO	**8ba**	3	Bu^{t}CHOH	62
9	**6b**	PhCHO	**8bb**	3	PhCHOH	66
10	**6b**	(CH$_2$)$_5$CO	**8bc**	3	(CH$_2$)$_5$COH	56
11	**6b**	Et$_2$CO	**8bd**	3	Et$_2$COH	52
12	**6b**	PhCOMe	**8be**	3	PhC(OH)Me	49
13	**6b**	PhCH=NPh	**8bf**	3	PhCHNHPh	54
14	**6b**	Me$_3$SiCl	**9b**[e]	3	Me$_3$Si	47

[a] All compounds **8** and **9** were ≥95% pure (GLC and/or 300 MHz ^{1}H-NMR); [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting chloro ortho ester **6**; [c] Yield corresponding to the reaction at 0ºC. [d] Yield corresponding to the Grignard-type reaction; [e] The corresponding 2-hydroxyethyl ester was isolated; see Scheme 2.

In the literature there are some examples for the synthesis of δ-lactones from the corresponding δ-hydroxy esters by treatment with catalytic amounts of an organic acid [e.g. camphorsulphonic acid, trifluoroacetic acid (TFA), etc.] in an inert solvent [19]. Thus, we decided to prepare the corresponding δ-lactones directly from the lithiation resulting mixture by acid catalyzed rearrangement. For the substrates **8ab**, **8ac** and **8ad** we tested different organic and inorganic acids (i.e. catalytic amounts of PTSA, TFA, HCl or H$_2$SO$_4$) in different solvents (i.e. CH$_2$Cl$_2$, benzene, toluene, THF) and at different temperatures (from room temperature to reflux). None of the different experiments gave the expected lactones **11b-d** in more than 10% yield, a wide range of decomposition byproducts being obtained in the reaction mixtures.

We therefore prepared the δ-lactones **11a-d** following the standard procedure for hydrolysis of the ortho ester protecting group [20] to generate the corresponding δ-hydroxy acid and converting this to the final δ-lactone. Hence, the ortho ester **6a** was lithiated as described above and, after hydrolysis, the reaction mixture was treated successively with KHSO$_4$ in a mixture of dimethoxyethane/water (5:1) at 0ºC and lithium hydroxide (basic pH) in the same solvent mixture at room temperature. Refluxing the

mixture obtained in benzene in the presence of a catalytic amount of PTSA resulted in formation of the corresponding δ-lactones **11a-d** with modest overall yields (Scheme 3, Table 2).

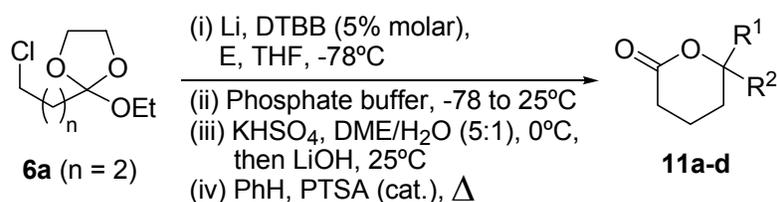**Scheme 3.** Preparation of δ-lactones **11** from ortho ester **6a**

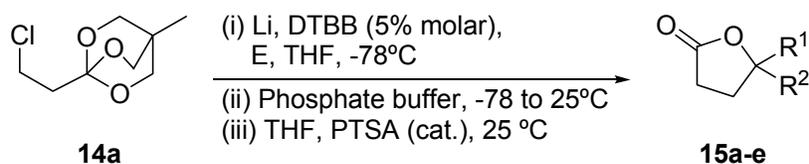**Table 2.** Preparation of δ-lactones **11** from ortho ester **6a**

| Entry	Carbonyl compound (E)	Product **11**[a]			
		No.	R^1	R^2	Yield (%)[b]
1	Bu^{t}CHO	**11a**	Bu^t	H	47
2	PhCHO	**11b**	Ph	H	33
3	$(CH_2)_5CO$	**11c**	$(CH_2)_5$		37
4	Et_2CO	**11d**	Et	Et	35

[a] All the lactones **11** were ≥95% pure (GLC and/or 300 MHz ^{1}H-NMR); [b] Isolated yield after chromatography (silica gel, hexane/ethyl acetate) based on the starting chloro ortho ester **6a**.

In order to generate the masked corresponding homoenolates (**7**, n = 1) we planned to use the same strategy starting from the corresponding β-chloro ortho ester, nevertheless, we could not obtain it in pure form. By employing the synthetic methodology described by Pinner and starting from 3-chloronitrile we obtained an inseparable mixture of the desired ortho ester and the corresponding dehydrochlorinated ortho ester (ca. 1:1 mixture). For this reason, we prepared the β-chloro bicyclic ortho ester **14a** (OBO ester: 2,6,7-trioxabicyclo[2.2.2]octane ester [17a, 20]). The ortho ester **14a** was prepared according to the synthetic path outlined in Scheme 4, starting from the commercially available 3-chloropropionyl chloride (**12a**), which was coupled with 3-hydroxymethyl-3-methyloxetane in the presence of pyridine to yield the ester **13a** (80%). Treatment of this oxetane ester with boron trifluoride etherate gave the isomeric bridged ortho ester **14a** in 63% yield. The corresponding γ-chloro OBO ester (**14b**) was also prepared following the same synthetic pathway, starting in this case from 4-chlorobutanoyl chloride (**12b**), which subsequently was coupled to generate the corresponding ester **13b** (92% isolated yield) and finally rearranged to the ortho ester **14b** (65% isolated yield from the ester **13b**).

Scheme 4. Preparation of ortho esters **14**

12a (n = 1)
12b (n = 2)

13a
13b

14a
14b
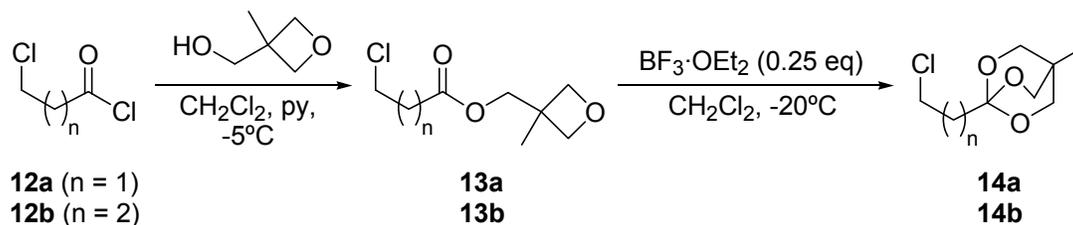
Performing the lithiation reaction with the OBO ester **14a** by means of the protocol used above for compounds **6** [using different carbonyl compounds as electrophiles: i.e. Bu^{t}CHO, PhCHO, (CH$_2$)$_5$CO, Et$_2$CO, PhCOMe], after hydrolysis and final treatment with a catalytic amount of PTSA in THF the corresponding lactones **15** were the only isolated products (Scheme 5, Table 3). If the final treatment with a catalytic amount of PTSA was carried out in dry methanol a mixture of the corresponding methyl esters and the corresponding γ-butyrolactones were obtained.

Scheme 5. Preparation of γ-lactones **15** from ortho ester **14a**

14a

(i) Li, DTBB (5% molar),
    E, THF, -78ºC

(ii) Phosphate buffer, -78 to 25ºC
(iii) THF, PTSA (cat.), 25 ºC

15a-e

Table 3. Preparation of γ-lactones **15** from ortho ester **14a**

Entry	Carbonyl compound (E)	Product **15**[a]			
		No.	R^1	R^2	Yield (%)[b]
1	Bu^{t}CHO	**15a**	Bu^t	H	45
2	PhCHO	**15b**	Ph	H	43
3	(CH$_2$)$_5$CO	**15c**	(CH$_2$)$_5$		39
4	Et$_2$CO	**15d**	Et	Et	38
5	PhCOMe	**15e**	Ph	Me	37

[a] All the γ-lactones **15** were ≥96% pure (GLC and/or 300 MHz ^{1}H-NMR); [b] Isolated yield after chromatography (silica gel, hexane/ethyl acetate) based on the starting chloro ortho ester **14a**.

When the corresponding γ-chloro OBO ester **14b** was lithiated using Bu^{t}CHO, PhCHO, PhCOMe as electrophiles and treated afterwards under the conditions depicted in Scheme 2, but at 0ºC, the corresponding methyl esters **8aa** (38% yield), **8ab** (41% yield) and **8ae** (37% yield) were isolated, respectively. For this type of ortho ester the lithiation process gave lower yield when the reaction was performed at lower temperature (-78ºC). For instance, the ester **8ab** was obtained in 30% yield, after

final methanolysis, performing the lithiation at -78ºC. For the reaction carried out via a two-step process (Grignard conditions), and using benzaldehyde as electrophile, a similar yield of the corresponding ester **8ab** was obtained (39%).

With the intention of studying the stability of the organolithium intermediates involved in these reactions we decided to carry out deuterolysis experiments with ortho esters **6a** and **14b**. After generating the corresponding organolithium intermediate through the DTBB-catalyzed methodology at -78ºC (for intermediate **7a**) or 0ºC (for intermediate **15b**), the final hydrolysis was carried out with deuterium oxide, yielding the corresponding ortho esters **16** and **17** with the yields and deuterium incorporation shown in Scheme 6.

Scheme 6. Deuterolysis of lithiated intermediates **7a** and **15b**
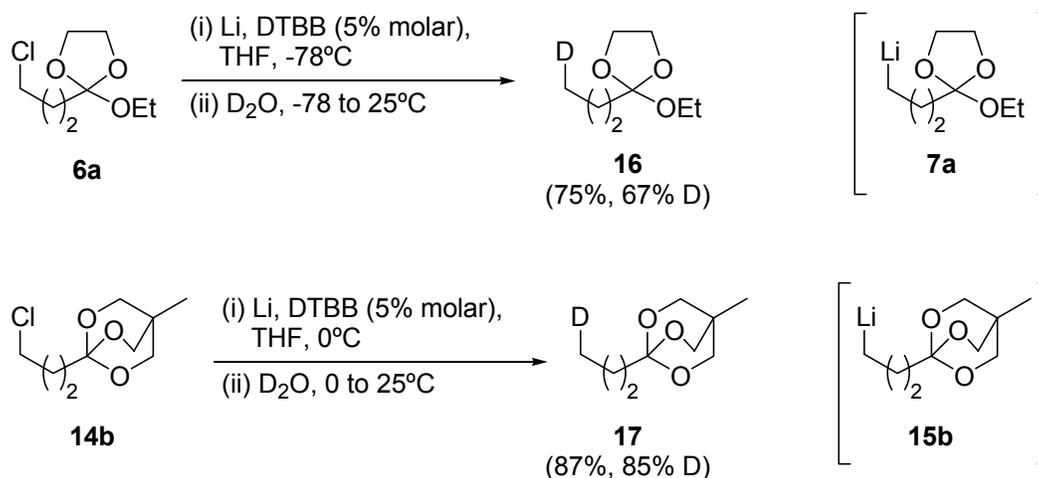
These observations indicate that ω-lithium OBO ester **15b** is more stable under the reaction conditions assayed than the corresponding monocyclic **7a**, which abstracts a proton from the reaction media more easily. These results are in agreement with the fact that monocyclic ortho esters gave better results under Barbier-type conditions whereas for OBO esters, regardless the conditions (Barbier-type or Grignard-type), gave the final product with almost the same yield.

Conclusions

We have demonstrated that the DTBB-catalyzed lithiation methodology can be applied to generate synthons of β-, γ-, and δ-lithio carboxylic acids by using an ortho ester protective group to mask the carboxylic moiety. These intermediates react with different electrophilic compounds (mainly carbonyl compounds) to generate remote functionalized carboxylic acid derivatives (i.e. hydroxy esters and/or lactones). Regarding to the stability we have verified that ω-lithium OBO ester intermediates are more stable than the corresponding monocyclic ortho esters ones. Albeit in general, better yields of the final

products have been obtained starting from 2-ethoxy-1,3-dioxolanes performing the reaction under Barbier-type conditions.

Acknowledgements

Experimental

General

All lithiation reactions were carried out under argon atmosphere in oven-dried glassware. All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification, except in the case of electrophiles, which were used freshly distilled. Commercially available anhydrous THF (99.9%, water content ≤0.006%, Acros) was used as solvent in all the lithiation reactions. IR spectra (thin film) were measured with a Nicolet Impact 400 D-FT Spectrometer. NMR spectra were recorded with a Bruker AC-300 using CDCl$_3$ as solvent (unless another solvent is indicated) and TMS as internal standard; chemical shifts are given in ppm and coupling constants (*J*) are given in Hz. LRMS were measured with Shimadzu GC/HS QP-5000 and Hewlett-Packard EM/CG-5973A spectrometers, and HRMS were measured with Finnigan MAT95 S spectrometer, fragment ions in *m/z* with relative intensities (%) in parentheses. The purity of volatile products and the chromatographic analyses (GLC) were determined with a flame ionization detector and a 30 m capillary column (0.32 mm diam.; 0.25 µm film thickness), using nitrogen (2 mL/min) as carrier gas, T_{injector} = 275ºC, T_{detector} = 300ºC, T_{column} = 60ºC (3 min) and 60 to 270ºC (15ºC/min), *P* = 40 KPa. Thin layer chromatography (TLC) was carried out on Merck plastic sheets coated with silica gel 60 F$_{254}$. Lithium powder was prepared from commercially available lithium granules (99%, high sodium content, Aldrich) as previously reported by us [21].

Preparation of ortho esters **6**.

Hydrogen chloride was bubbled through a cooled (-5ºC) solution of the starting nitrile **4** (0.1 mol) and ethanol (0.12 mol, 7 mL) in CH$_2$Cl$_2$ (150 mL) until the solution was saturated. The resulting solution was then allowed to stand at 0ºC for 4 days. The reaction mixture was concentrated to 2/3 of the original volume under vacuum and the precipitated imidate salt **5** was filtered, washed with several portions of diethyl ether (5 x 20 mL) and dried. Imidic ester hydrochlorides can be kept for several weeks if carefully protected from atmospheric moisture. To a solution of part of the corresponding imidate (50 mmol) in dry hexane (150 mL) was added ethylene glycol (150 mmol, 8.5 mL), and the

reaction was allowed to stir for 2 days. The resulting solid (ammonium chloride) was filtered out and the solvent was concentrated under vacuum. The ortho ester **6** was pure obtained as an oil by fractional distillation from anhydrous K_2CO_3.

2-(3-Chloropropyl)-2-ethoxy-1,3-dioxolane (**6a**): b.p.: 108ºC (0.1 mmHg); ^{1}H-NMR δ: 1.18 (3H, t, J = 7.0, CH_3), 1.96 (4H, m, CCH_2CH_2), 3.55 (2H, q, J = 7.0, CH_2CH$_3$), 3.60 (2H, m, CH_2Cl), 3.97, 4.11 (2H and 2H, 2m, OCH_2CH_2O); ^{13}C-NMR δ: 15.2 (CH$_3$), 27.3, 32.7 (CCH$_2$$CH_2$), 44.9 (CH$_2$Cl), 57.4 ($CH_2CH_3$), 64.95 (2C, O$CH_2$$CH_2$O), 122.3 (C).; IR cm^{-1}: 1193 (C-O); GC-MS (*m/z*): 151 (M$^+$+2-OEt, 32%), 149 (M$^+$-OEt, 94), 117 (29), 105 (44), 99 (24), 77 (27), 69 (30), 55 (45), 45 (57), 43 (27), 42 (34), 41 (100).

2-(3-Chlorobutyl)-2-ethoxy-1,3-dioxolane (**6b**): b.p.: 122ºC (0.1 mmHg); ^{1}H-NMR δ: 1.17 (3H, t, J = 7.0, CH$_3$), 1.58, 1.80 [2H and 4H, 2m, C(CH$_2$)$_3$], 3.53 (4H, m, CH_2CH$_3$ and CH$_2$Cl), 3.95, 4.09 (2H and 2H, 2m, OCH$_2$CH$_2$O; ^{13}C-NMR δ: 15.2 (CH$_3$), 21.2, 32.3, 34.6 [C(CH$_2$)$_3$], 44.8 (CH$_2$Cl), 57.3 (CH$_2$CH$_3$), 64.9 (2C, OCH$_2$$CH_2$O), 122.4 (C); IR cm^{-1}: 1191 (C-O); GC-MS (*m/z*): 165 (M$^+$+2-OEt, 17%), 163 (M$^+$-OEt, 52), 117 (27), 99 (42), 91 (16), 89 (57), 55 (100), 45 (43), 43 (19), 42 (20), 41 (22).

DTBB-catalyzed lithiation of ortho esters **6***: Preparation of esters* **8** *and* **9**.

A solution of the ortho ester **6** (2 mmol) and the electrophile (2.2 mmol) in THF (3 mL) was slowly added (ca. over 2 h) to a stirred green suspension of lithium powder (17.1 mmol, 120 mg) and DTBB (0.2 mmol, 53.2 mg) in THF (10 mL) at -78ºC under an argon atmosphere. The reaction mixture was stirred for 30 additional minutes at the same temperature and then quenched with phosphate buffer (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL), the organic phase was washed with brine (10 mL) and water (10 mL) and was dried over anhydrous sodium sulphate. The solvent was concentrated under vacuum (15 Torr) and the resulting crude was solved in dry methanol (20 mL), a catalytic amount of *p*-toluenesulphonic acid (10 mg) was added and the reaction was stirred at room temperature for 12 h. The reaction was hydrolyzed by adding water (20 mL) and then extracted with diethyl ether (4x20 mL). The organic phase was washed with NaOH (0.1 M, 10 mL) and water (10 mL), dried over anhydrous magnesium sulphate and concentrated under vacuum (15 Torr). Compounds **8** and **9** were isolated after column chromatography (silica gel, hexane/ethyl acetate mixtures).

Methyl 5-hydroxy-6,6-dimethylheptanoate (**8aa**): ^{1}H-NMR δ: 0.97 [9H, s, C(CH$_3$)$_3$], 1.43-1.59, 1.75-1.95 (2H and 2H, 2m, CHCH_2CH_2), 1.96 (1H, br s, OH), 2.37 (1H, m, CHHCO$_2$), 2.43 (1H, m, CHHCO$_2$), 3.47 (3H, s, OCH$_3$), 3.95 (1H, dd, J = 11.9, 2.7, HOCH); ^{13}C-NMR δ: 18.5, 22.5, 34.15 (3 x CH$_2$), 25.4 [3C, C(CH$_3$)$_3$], 33.8 (C), 51.4 (OCH$_3$), 79.3 (CH), 174.3 (CO$_2$); IR cm^{-1}: 3590-3201

(OH), 1737 (C=O), 1240 (C-O); GC-MS (*m/z*): 170 (M$^+$-H$_2$O, 0.2%), 131 (26), 99 (100), 74 (25), 71 (40), 57 (32), 55 (27), 43 (41), 41 (37).

Methyl 5-hydroxy-5-phenylpentanoate (**8ab**) [22]: ^{1}H-NMR δ: 1.57-1.83 (4H, m, CHC*H*$_2$C*H*$_2$), 2.31 (2H, def t, *J* = 6.4, C*H*$_2$CO$_2$), 2.37 (1H, br s, OH), 3.62 (3H, s, CH$_3$), 4.63 (1H, m, CH), 7.31 (5H, m, ArH); ^{13}C-NMR δ: 21.1, 33.6, 38.3 (3 x CH$_2$), 51.3 (CH$_3$), 73.8 (CH), 125.7, 127.3, 128.3, 144.6 (6C, ArC), 173.9 (CO$_2$); IR cm^{-1}: 3619-3173 (OH), 3086, 3061, 3028, 1434 (C=CH), 1722 (C=O), 1025 (C-O); GC-MS (*m/z*): 208 (M$^+$, 10%), 117 (20), 107 (99), 105 (16), 102 (22), 91 (17), 79 (76), 77 (47), 59 (100), 51 (19), 43 (33), 42 (25).

Methyl 4-(1-hydroxycyclohexyl)butanoate (**8ac**): ^{1}H-NMR δ: 1.37-1.61, 1.66-1.79 (11H and 4H, 2m, 7 x CH$_2$ and OH), 2.33 (2H, t, *J* = 7.3, C*H*$_2$CO$_2$), 3.67 (3H, s, OCH$_3$); ^{13}C-NMR δ: 18.45, 22.1, 25.7, 34.3, 37.3, 41.5 (8C, 8 x CH$_2$), 51.4 (CH$_3$), 71.1 (C), 174.1 (CO$_2$); IR cm^{-1}: 3644-3254 (OH), 1730 (C=O), 1240 (C-O); GC-MS (*m/z*): 200 (M$^+$, 0.2%), 125 (46), 112 (33), 99 (100), 98 (34), 97 (47), 84 (17), 83 (27), 81 (72), 79 (20), 74 (35), 67 (19), 59 (18), 55 (94), 43 (55), 42 (30), 41 (58); HRMS (CI) for C$_{11}$H$_{20}$O$_3$ (M$^+$): Calcd 200.1412; Found 200.1406.

Methyl 5-ethyl-5-hydroxyheptanoate (**8ad**) [23]: ^{1}H-NMR δ: 0.88 (6H, t, *J* = 7.3, 2xCH$_2$C*H*$_3$), 1.47 (4H, q, *J* = 7.3, 2 x C*H*$_2$CH$_3$), 1.53 (1H, br s, OH), 1.60-1.74 (4H, m, CC*H*$_2$C*H*$_2$), 2.33 (2H, t, *J* = 7.3, C*H*$_2$CO$_2$), 3.67 (3H, s, OCH$_3$); ^{13}C-NMR δ: 7.6 (2C, 2 x CH$_2$*C*H$_3$), 18.9, 30.85, 34.3, 37.4 (5C, 5 x CH$_2$), 51.4 (OCH$_3$), 74.3 (C), 174.1 (CO$_2$); IR cm^{-1}: 3624-3254 (OH), 1737 (C=O), 1172 (C-O); GC-MS (*m/z*): 187 (M$^+$-1, 0.2%), 127 (100), 99 (59), 87 (79), 74 (37), 69 (19), 57 (91), 55 (53), 45 (57), 43 (46), 41 (39).

Methyl 5-hydroxy-5-phenylhexanoate (**8ae**) [24]: ^{1}H-NMR δ: 1.56 (3H, s, CCH$_3$), 1.42-1.71, 1.79-1.88 (2H and 2H, 2m, CC*H*$_2$C*H*$_2$), 1.90 (1H, br s, OH), 2.26 (2H, t, *J* = 7.3, C*H*$_2$CO$_2$), 3.63 (3H, s, OCH$_3$), 7.23, 7.33, 7.43 (1H, 2H and 2H, 3m, ArH); ^{13}C-NMR δ: 19.5, 34.0, 43.3 (3 x CH$_2$), 30.3 (C*C*H$_3$), 51.5 (OCH$_3$), 74.4 (C), 124.7, 126.6, 128.2, 147.6 (6C, ArC), 174.0 (CO$_2$); IR cm^{-1}: 3600-3154 (OH), 3052, 3046, 1446 (C=CH), 1739 (C=O), 1025 (C-O); GC-MS (*m/z*): 207 (M$^+$-Me, 0.8%), 121 (43), 43 (100).

Methyl 5-anilino-5-phenylpentanoate (**8af**): ^{1}H-NMR δ: 1.76-1.91 (4H, m, C*H*$_2$C*H*$_2$CH), 2.33 (2H, t, *J* = 6.7, C*H*$_2$CO$_2$), 3.65 (3H, s, CH$_3$), 3.67 (1H, s, NH), 4.32 (1H, t, *J* = 6.5, CH), 6.51 (2H, dd, *J* = 8.6, 0.9, ArH), 6.63 (1H, def t, *J* = 7.4, ArH), 7.07, 7.19-7.27, 7.32 (2H, 2H and 3H, 3m, ArH); ^{13}C-NMR (CDCl$_3$) δ: 21.7, 33.6, 38.1, (3 x CH$_2$), 51.6 (CH$_3$), 57.9 (CH), 113.2, 115.1, 117.2, 126.3, 127.0, 128.6, 129.1, 129.3, 143.7, 147.3 (12C, ArC), 173.8 (CO$_2$); IR cm^{-1}: 3651-3100 (NH), 3018, 1433 (C=CH), 1728 (C=O); GC-MS (*m/z*): 283 (M$^+$, 4%), 183 (14), 182 (100), 117 (20), 104 (19), 93 (12), 91 (23), 77 (38), 55 (16), 51 (15); HRMS (CI) for C$_{18}$H$_{21}$NO$_2$ (M$^+$): Calcd 283.1572; Found 283.1536.

2-Hydroxyethyl 4-trimethylsilylbutanoate (**9a**): ^{1}H-NMR δ: -0.02 [9H, s, Si(CH$_3$)$_3$], 0.50 (2H, m, CH$_2$Si), 1.63 (2H, m, C*H*$_2$CH$_2$Si), 2.15 (1H, br s; OH), 2.36 (2H, t, *J* = 7.3, CH$_2$CO$_2$), 3.80, 4.19 (2H and 2H, 2m, OC*H*$_2$C*H*$_2$OH); ^{13}C-NMR (CDCl$_3$) δ: -1.8 [3C, Si(CH$_3$)$_3$], 16.4 (CH$_2$Si), 19.7 (CH$_2$), 37.7 (*C*H$_2$CO$_2$), 61.2, 65.8 (O*C*H$_2$*C*H$_2$OH), 174.1 (CO$_2$); IR cm^{-1}: 3600-3190 (OH), 1737 (C=O), 1118, 1025 (C-O); GC-MS (*m/z*): 189 (M$^+$-Me, 3%), 145 (20), 117 (36), 75 (100), 73 (98), 45 (54), 44 (29), 43 (86), 42 (31).

Methyl 6-hydroxy-7,7-dimethyloctanoate (**8ba**): ^{1}H-NMR δ: 0.89 [3C, C(CH$_3$)$_3$], 1.21-1.43, 1.47-1.75 [2H and 4H, 2m, CH(C*H*$_2$)$_3$], 1.69 (1H, br s, OH), 2.33 (2H, t, *J* = 7.3, CH$_2$CO$_2$), 3.18 (1H, dd, *J* = 10.4, 1.8, CH), 3.67 (3H, s, OCH$_3$); ^{13}C-NMR δ: 25.6 [3C, C(*C*H$_3$)$_3$], 24.9, 26.55, 31.0, 34.0 [(CH$_2$)$_4$], 34.9 (C), 51.4 (OCH$_3$), 79.6 (CH), 174.2 (CO$_2$); IR cm^{-1}: 3614-3214 (OH), 1739 (C=O), 1090 (C-O); GC-MS (*m/z*): 184 (M$^+$-H$_2$O, 0.4%), 145 (32), 113 (100), 95 (19), 87 (49), 85 (22), 67 (59), 57 (51), 55 (28), 43 (41), 41 (56).

Methyl 6-hydroxy-6-phenylhexanoate (**8bb**): ^{1}H-NMR δ: 1.26-1.53, 1.61-1.88 [2H and 4H, 2m, (CH$_2$)$_3$], 1.57 (1H, br s, OH), 2.30 (2H, t, *J* = 7.3, CH$_2$CO$_2$), 3.65 (3H, s, CH$_3$), 4.67 (1H, dd, *J* = 7.6, 5.8, CH), 7.33 (5H, m, ArH); ^{13}C-NMR δ: 24.7, 25.3, 33.9, 38.55 (4 x CH$_2$), 51.4 (CH$_3$), 74.2 (CH), 125.8, 127.5, 128.4, 144.7 (6C, ArC), 174.1 (CO$_2$); IR cm^{-1}: 3637-3207 (OH), 3093, 3060, 3026, 1454, 1441 (C=CH), 1737 (C=O), 1179 (C-O); GC-MS (*m/z*): 222 (M$^+$, 9%), 130 (39), 129 (16), 116 (31), 91 (28), 87 (100), 79 (59), 77 (38), 55 (25); HRMS (CI) for C$_{13}$H$_{18}$O$_3$ (M$^+$): Calcd 222.1256; Found 222.1264.

Methyl 5-(1-hydroxycyclohexyl)pentanoate (**8bc**) [25]: ^{1}H-NMR δ: 1.35-1.68 (17H, m, 8xCH$_2$ and OH), 2.33 (2H, t, *J* = 7.3, CH$_2$CO$_2$), 3.67 (3H, s, OCH$_3$); ^{13}C-NMR δ: 22.1, 22.3, 25.4, 25.7, 33.9, 37.3, 41.8 (9C, 9 x CH$_2$), 51.3 (CH$_3$), 71.1 (C), 174.1 (CO$_2$); IR cm^{-1}: 3617-3193 (OH), 1740 (C=O), 1106, 1023 (C-O); GC-MS (*m/z*): 196 (M$^+$-H$_2$O, 2%), 111 (16), 99 (93), 98 (39), 97 (22), 93 (19), 87 (39), 81 (67), 79 (17), 67 (27), 59 (21), 57 (18), 55 (100), 43 (67), 42 (23), 41 (81).

Methyl 6-ethyl-6-hydroxyoctanoate (**8bd**) [23]: ^{1}H-NMR δ: 0.85 (6H, t, *J* = 7.6, 2xCH$_2$C*H*$_3$), 1.25-1.49 (9H, m, 2 x C*H*$_2$CH$_3$, CC*H*$_2$C*H*$_2$C*H*$_2$ and OH), 1.64 (2H, m, CC*H*$_2$), 2.33 (2H, t, *J* = 7.3, CH$_2$CO$_2$), 3.67 (3H, s, OCH$_3$); ^{13}C-NMR δ: 7.7 (2C, 2 x CH$_2$*C*H$_3$), 22.9, 25.5, 30.9, 34.0, 37.8 (6C, 6 x CH$_2$), 51.4 (OCH$_3$), 74.4 (C), 174.1 (CO$_2$); IR cm^{-1}: 3629-3213 (OH), 1736 (C=O), 1169 (C-O); GC-MS (*m/z*): 184 (M$^+$-H$_2$O, 2%), 141 (34), 123 (22), 95 (90), 87 (100), 69 (21), 57 (80), 55 (46), 45 (46), 43 (35), 41 (39).

Methyl 6-hydroxy-6-phenylheptanoate (**8be**): ^{1}H-NMR δ: 1.12-1.36, 1.57 (2H and 2H, 2m, CH$_2$CH$_2$), 1.54 (3H, s, CC*H*$_3$), 1.80 (2H, m, CC*H*$_2$), 1.91 (1H, br s, OH), 2.24 (2H, t, *J* = 7.3, CH$_2$CO$_2$), 3.62 (3H, s, OCH$_3$), 7.23, 7.32, 7.41 (1H, 2H and 2H, 3m, ArH); ^{13}C-NMR δ: 23.5, 25.1, 33.9, 43.7 (4 x CH$_2$), 30.1 (C*C*H$_3$), 51.4 (OCH$_3$), 74.5 (C), 124.7, 126.5, 128.1, 147.8 (6C, ArC), 174.1 (CO$_2$; IR cm^{-1}: 3624-

3228 (OH), 3073, 3026, 1448 (C=CH), 1741 (C=O), 1172 (C-O; GC-MS (*m/z*): 218 (M$^+$-H$_2$O, 10%), 144 (31), 129 (52), 121 (81), 118 (32), 105 (19), 91 (28), 77 (19), 44 (23), 43 (100), 40 (33; HRMS (CI) for C$_{14}$H$_{20}$O$_3$ (M$^+$): Calcd 236.1412; Found 236.1402.

Methyl 6-anilino-6-phenylhexanoate (**8bf**): ^{1}H-NMR δ: 1.24-1.53, 1.66, 1.83 [3H, 2H and 2H, 3m, CH(C*H$_2$*)$_3$ and NH], 2.30 (2H, t, *J* = 7.3, CH$_2$CO$_2$), 3.66 (3H, s, CH$_3$), 4.31 (1H, t, *J* = 6.7, CH), 6.55 (2H, d, *J* = 7.9, 2 x NArH), 6.65 (1H, t, *J* = 7.3, NArH), 7.08, 7.25, 7.33 (2H, 1H and 4H, 3m, 2 x NArH and ArH); ^{13}C-NMR δ: 24.7, 25.8, 33.8, 38.3 (4 x CH$_2$), 51.5 (CH$_3$), 58.2 (CH), 113.4, 115.1, 117.4, 126.35, 126.95, 128.5, 129.0, 143.7, 147.1 (12C, ArC), 173.9 (CO$_2$); IR cm^{-1}: 3400 (NH), 3052, 3024, 1452, 1434 (C=CH), 1736 (C=O), 1154 (C-O); GC-MS (*m/z*): 297 (M$^+$, 4%), 182 (100), 104 (18), 91 (21), 77 (25); HRMS (CI) for C$_{19}$H$_{23}$NO$_2$ (M$^+$): Calcd 297.1729; Found 297.1732.

2-Hydroxyethyl 5-trimethylsilylpentanoate (**9b**): ^{1}H-NMR δ: -0.02 (9H, s, 3xCH$_3$), 0.50 (2H, m, CH$_2$Si), 1.31, 1.69 (2H and 2H, 2m, C*H$_2$*C*H$_2$*CH$_2$Si), 2.36 (2H, t, *J* = 7.5, CH$_2$CO$_2$), 3.85, 4.22 (2H and 2H, 2m, OCH$_2$CH$_2$O); ^{13}C-NMR δ: -1.76 (3C, 3 x CH$_3$), 16.3, 23.5, 28.6, 33.9 [(CH$_2$)$_4$], 61.2, 65.8 (OCH$_2$CH$_2$O), 174.2 (CO$_2$); IR (thin film) cm^{-1}: 3671-3154 (OH), 1739 (C=O), 1248, 1189 (C-O); GC-MS (*m/z*): 203 (M$^+$-Me, 4%), 99 (25), 75 (89), 73 (100), 57 (18), 56 (17), 55 (50), 45 (49), 44 (16), 43 (27).

Preparation of δ-lactones **11**.

A solution of the ortho ester **6a** (2 mmol) and the electrophile (2.2 mmol) in THF (3 mL) was slowly added (ca. over 2 h) to a stirred green suspension of lithium powder (17.1 mmol, 120 mg) and DTBB (0.2 mmol, 53.2 mg) in THF (10 mL) at -78ºC under an argon atmosphere. The reaction was stirred for an additional 30 minutes at the same temperature and then quenched with phosphate buffer (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL), the organic phase was washed with brine (10 mL) and water (10 mL) and was dried over anhydrous sodium sulphate. The solvent was concentrated under vacuum (15 Torr) and the resulting crude was treated with a 5:1 mixture of dimethoxyethane/KHSO$_4$ (sat. sol.) (12 mL) at 0ºC for 20 min. After this, lithium hydroxide was added to a basic pH and the reaction was stirred for 2 hours at room temperature. The aqueous phase was treated with HCl (3M) to an acidic pH, then it was extracted with diethyl ether (3 x 15 mL) and the resulting organic phase was washed with water (10 mL), dried over anhydrous magnesium sulphate and concentrated under vacuum (15 Torr). The resulting crude was dissolved in benzene (10 mL), a catalytic amount of *p*-toluenesulphonic acid (10 mg) was added and the reaction mixture was refluxed with stirring for 2 hours. Anhydrous potassium carbonate (15 mg) was added to the solution, then it was filtered out and the solvent was concentrated under vacuum (15 Torr). Lactones **11** were isolated after column chromatography (neutral silica gel, hexane/ethyl acetate mixtures).

*6-(tert-Butyl)tetrahydro-2*H*-2-pyranone* (**11a**) [26]: ^{1}H-NMR δ: 0.97 (9H, s, 3xCH$_3$), 1.41-1.59, 1.75-1.86, 1.88-1.99, 2.31-2.47, 2.56-2.66 (1H, 1H, 2H, 1H and 1H, 5m, 3 x CH$_2$), 3.93-3.98 (1H, dd, *J* = 11.8, 2.7, CH); ^{13}C-NMR δ: 18.5, 22.4, 29.3 (3C, 3 x CH$_2$), 25.3 (3C, 3 x CH$_3$), 34.1 (C), 88.0 (CH), 172.5 (CO$_2$); IR (thin film) cm^{-1}: 1732 (C=O), 1242 (C-O); GC-MS (*m/z*): 156 (M$^+$, 0.4%), 100 (51), 99 (100), 71 (51), 57 (45), 55 (29).

*6-Phenyltetrahydro-2*H*-2-pyranone* (**11b**) [26]: ^{1}H-NMR δ: 1.79-2.04, 2.12-2.21 (3H and 1H, 2m, 2 x CH$_2$), 2.51-2.76 (2H, m, CH$_2$CO), 5.33-5.37 (1H, dd, *J* = 10.4, 3.4, CH), 7.36 (5H, s, ArH); ^{13}C-NMR δ: 18.5, 29.4, 30.4 (3 x CH$_2$), 81.6 (CH), 125.6, 128.2, 128.5, 139.6 (6C, ArC), 171.3 (CO$_2$); IR cm^{-1}: 3064, 3034, 1456 (C=CH), 1731 (C=O), 1241 (C-O); GC-MS (*m/z*): 176 (M$^+$, 21%), 105 (51), 104 (100), 78 (16), 77 (26), 70 (40), 51 (16).

1-Oxaspiro[5.5]undecan-2-one (**11c**) [15d]: ^{1}H-NMR δ: 1.33-1.91 (14 H, m, 7 x ring CH$_2$), 2.50 (2H, def t, *J* = 6.9, CH$_2$CO); ^{13}C-NMR δ: 15.8, 21.4, 25.1, 29.3, 32.2, 37.1 (8C, 8x ring CH$_2$), 82.9 (C), 171.2 (CO$_2$); IR cm^{-1}: 1731 (C=O), 1241 (C-O); GC-MS (*m/z*): 168 (M$^+$, 22%), 126 (17), 125 (54), 112 (54), 98 (30), 97 (79), 96 (17), 84 (37), 83 (62), 81 (47), 79 (16), 70 (28), 67 (28), 55 (100).

*6,6-Diethyltetrahydro-2*H*-2-pyranone* (**11d**) [15d]: ^{1}H-NMR δ: 0.91 (6H, t, *J* = 7.4, 2 x CH$_3$), 1.60-1.78, 1.80-1.89 (6H and 2H, 2m, 4xCH$_2$), 2.48 (t, *J* = 6.9, CH$_2$CO); ^{13}C-NMR δ: 7.7 (2C, 2 x CH$_3$), 16.4, 28.8, 29.5, 30.7 (5C, 5xCH$_2$), 86.8 (C), 171.7 (CO$_2$); IR cm^{-1}: 1731 (C=O), 1252 (C-O); GC-MS (*m/z*): 156 (M$^+$, 0.3%), 127 (100), 99 (84), 69 (19), 57 (83), 55 (37).

Preparation of ortho esters **14**: *Preparation of esters* **13**.

To an ice-cooled solution of 3-hydroxymethyl-3-methyloxetane (20 mmol, 2 mL) and pyridine (24 mmol, 1.95 mL) in CH$_2$Cl$_2$ (10 mL) was added the acid chloride **12** (20 mmol). After the addition the reaction was allowed to stand at 0ºC for 2 days. The reaction mixture was dropped over crushed ice (5 g) and then extracted with CH$_2$Cl$_2$ (3x10 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated under vacuum (15 Torr). The esters **13** were obtained pure after column chromatography (neutral silica gel, hexane/ethyl acetate mixtures).

3-Methyl-3-oxetanylmethyl 3-chloropropanoate (**13a**): ^{1}H-NMR δ: 1.35 (3H, s, CH$_3$), 2.85 (2H, t, *J* = 6.6, C*H$_2$*CH$_2$Cl), 3.78 (2H, t, *J* = 6.6, CH$_2$Cl), 4.24 (2H, s, CO$_2$CH$_2$), 4.39 (2H, d, *J* = 6.0, 2 x ring C*H*H), 4.52 (2H, d, *J* = 6.0, 2x ring CH*H*); ^{13}C-NMR δ: 21.0 (CH$_3$), 37.4, 38.9 (CH$_2$CH$_2$Cl), 39.0 (C), 69.0 (CO$_2$*C*H$_2$), 79.4 (2C, 2 x ring CH$_2$), 170.2 (CO$_2$); IR cm^{-1}: 1740 (C=O), 1247, 1147 (C-O); GC-MS (*m/z*): 193 (M$^+$+1, 0.1%), 93 (19), 91 (53), 72 (100), 65 (23), 63 (60), 55 (60), 54 (29), 43 (19), 41 (31).

3-Methyl-3-oxetanylmethyl 4-chlorobutanoate (**13b**) [27]: ^{1}H-NMR δ: 1.34 (3H, s, CH$_3$), 2.12 (2H, m, ClCH$_2$C*H*$_2$), 2.57 (2H, t, *J* = 7.1, CH$_2$CO$_2$), 3.62 (2H, t, *J* = 6.2, ClCH$_2$), 4.19 (2H, s, OCH$_2$C), 4.39 (2H, d, *J* = 6.0, 2 x ring C*H*H), 4.51 (2H, d, *J* = 6.0, 2 x ring CH*H*); ^{13}C-NMR δ: 21.0 (CH$_3$), 27.5 (*C*H$_2$CH$_2$Cl), 31.0 (*C*H$_2$CO$_2$), 38.95 (*C*CH$_3$), 43.9 (CH$_2$Cl), 68.7 (CO$_2$*C*H$_2$), 79.4 (2C, 2 x ring CH$_2$), 172.6 (CO$_2$); IR cm^{-1}: 1740 (C=O), 1244, 1148 (C-O; GC-MS (*m/z*): 206 (M$^+$, 0.2%), 91 (43), 72 (100), 65 (19), 63 (61), 55 (62), 54 (24), 43 (19).

Rearrangement of esters **13:** *Preparation of ortho esters* **14**.

BF$_3$·OEt$_2$ (4 mmol, 0.5 mL) was added to a cooled (-20ºC) solution of the corresponding ester **13** (16 mmol) in CH$_2$Cl$_2$ (15 mL) under an argon atmosphere. The reaction was stirred for 24 h at the same temperature and a solution of Et$_3$N (16 mmol, 2.2 mL) in diethyl ether (20 mL) was then added to quench the reaction. The reaction mixture was filtered and the solvent was concentrated under vacuum (15 Torr). The resulting crude was filtered through a pad of neutral silica gel eluting with CH$_2$Cl$_2$ (150 mL), the solvent was concentrated under vacuum (15 Torr) to give the corresponding pure ortho ester **14**.

1-(2-Chloroethyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**14a**) [28]: ^{1}H-NMR (benzene-*d*$_6$) δ: 0.02 (3H, s, CH$_3$), 2.41 (2H, m, CCH$_2$), 3.46 (6H, s, 3 x CH$_2$O), 3.74 (2H, m, CH$_2$Cl); ^{13}C-NMR (benzene-*d*$_6$) δ: 13.8 (CH$_3$), 29.8 (*C*CH$_3$), 39.1, (CH$_2$Cl), 40.8 (*C*H$_2$C), 72.4 (3C, 3 x CH$_2$O), 107.9 [*C*(OCH$_2$)$_3$]; IR cm^{-1}: 1151, 1043 (C-O); GC-MS (*m/z*): 191 (M$^+$-H, 0.2%), 91 (39), 72 (100), 63 (47), 55 (52), 54 (24).

1-(3-Chloropropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**14b**) [29]: ^{1}H-NMR δ: 0.80 (3H, s, CH$_3$), 1.81, 1.93 (2H and 2H, 2m, C*H*$_2$CH$_2$CH$_2$Cl), 3.56 (2H, t, *J* = 6.6, CH$_2$Cl), 3.88 (6H, s, 3 x CH$_2$O); ^{13}C-NMR δ: 14.4 (CH$_3$), 26.7, 30.1, 44.8 [(CH$_2$)$_3$], 33.7 (*C*CH$_3$), 72.5 (3C, 3 x CH$_2$O), 108.6 [*C*(OCH$_2$)$_3$; IR cm^{-1}: 1150, 1040 (C-O); GC-MS (*m/z*): 206 (M$^+$, 0.1%), 176 (26), 107 (65), 105 (100), 79 (16), 77 (41), 72 (57), 55 (44), 54 (27), 43 (32), 41 (88).

DTBB-catalyzed lithiation of ortho esters **14**: *Preparation of γ-lactones* **15**.

A solution of the ortho ester **14a** (2 mmol) and the electrophile (2.2 mmol) in THF (3 mL) was slowly added to a stirred green suspension of lithium powder (17.1 mmol, 120 mg) and DTBB (0.2 mmol, 53.2 mg) in THF (10 mL) at -78ºC (ca. for 2 h) under an argon atmosphere. The reaction mixture was stirred for 30 additional minutes at the same temperature and then quenched with phosphate buffer (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL), the organic phase was washed with brine (10 mL) and water (10 mL) and dried over anhydrous sodium sulphate. The solvent was concentrated under vacuum (15 Torr) and the resulting crude product was dissolved in dry THF (20 mL), a catalytic amount of *p*-toluenesulphonic acid (10 mg) was added and

the reaction was stirred at room temperature for 12 h. The reaction was hydrolyzed by adding water (20 mL) and then extracted with diethyl ether (4 x 20 mL). The organic phase was washed with NaOH (0.1 M, 10 mL) and water (10 mL), dried over anhydrous magnesium sulphate and concentrated under vacuum (15 Torr). Compounds **15** were isolated after column chromatography (silica gel, hexane/ethyl acetate mixtures).

5-(tert-Butyl)tetrahydro-2-furanone (**15a**): ^{1}H-NMR δ: 0.95 (9H, s, 3 x CH$_3$), 1.90-2.17, 2.44-2.56, 2.73-2.80 (2H, 1H and 1H, 3m, 2 x CH$_2$), 4.17-4.23 (1H, m, CH); ^{13}C-NMR δ: 26.4 (3C, 3 x CH$_3$), 29.3, 34.6 (2xCH$_2$), 35.4 (C), 86.9 (CH), 177.4 (CO$_2$).; IR cm^{-1}: 1744 (C=O), 1229, 1209 (C-O); GC-MS (*m/z*): 142 (M$^+$, 1.2%), 87 (27), 86 (24), 85 (83), 57 (100), 56 (18), 55 (24), 44 (24), 43 (60), 41 (58; HRMS (CI) for C$_8$H$_{14}$O$_2$ (M$^+$): Calcd 142.0994; Found 142.0978.

5-Phenyltetrahydro-2-furanone (**15b**): ^{1}H-NMR δ: 2.12-2.28, 2.62-2.68 (1H and 3H, 2m, 2 x CH$_2$), 5.51 (1H, dd, *J* = 7.9, 6.1, CH), 7.31-7.42 (5H, m, ArH); ^{13}C-NMR δ: 28.9, 30.9 (2 x CH$_2$), 81.2 (CH), 125.2, 128.4, 128.6, 128.7, 139.3 (6C, ArC), 176.9 (CO$_2$); IR cm^{-1}: 3063, 3033, 1454 (C=CH), 1770 (C=O), 1024 (C-O); GC-MS (*m/z*): 162 (M$^+$, 64%), 117 (34), 107 (72), 105 (52), 91 (17), 79 (20), 78 (20), 77 (40), 56 (100), 51 (43), 50 (20); HRMS (CI) for C$_{10}$H$_{10}$O$_2$ (M$^+$): Calcd 162.0681; Found 162.0672.

1-Oxaspiro[4.5]decan-2-one (**15c**) [30]: ^{1}H-NMR δ: 1.37-1.84 (10H, m, 5 x ring CH$_2$), 2.00 (2H, def t, *J* = 8.5, CC*H*$_2$CH$_2$CO), 2.58 (2H, def t, *J* = 8.5, CCH$_2$C*H*$_2$CO); ^{13}C-NMR δ: 22.6, 25.0, 28.6, 32.9, 37.0 (7C, 7 x CH$_2$), 86.4 (C), 176.8 (CO$_2$); IR cm^{-1}: 1769 (C=O), 1193 (C-O); GC-MS (*m/z*): 154 (M$^+$, 18%), 112 (22), 111 (100), 98 (32), 83 (17), 67 (16), 56 (20), 55 (39), 42 (19), 41 (36).

5,5-Diethyltetrahydro-2-furanone (**15d**) [31]: ^{1}H-NMR δ: 0.94 (6H, t, *J* = 7.3, 2xCH$_3$), 1.66-1.74 (4H, m, 2 x C*H*$_2$CH$_3$), 2.01 (2H, def t, *J* = 8.5, C*H*$_2$CH$_2$CO), 2.58 (2H, def t, *J* = 8.5, CH$_2$C*H*$_2$CO); ^{13}C-NMR δ: 7.8 (2C, 2 x CH$_3$), 29.2, 29.8, 30.85 (4C, 4 x CH$_2$), 89.6 (C), 177.0 (CO$_2$); IR cm^{-1}: 1770 (C=O), 1203, 1163 (C-O); GC-MS (*m/z*): 143 (M$^+$+1, 0.4%), 113 (100), 95 (21), 87 (27), 85 (16), 69 (16), 57 (60), 56 (23), 55 (21), 41 (34).

5-Methyl-5-phenyltetrahydro-2-furanone (**15e**): ^{1}H-NMR δ: 1.72 (3H, s, CH$_3$), 2.36-2.68 (4H, m, CH$_2$CH$_2$), 7.31, 7.37 (1H and 4H, 2m, ArH); ^{13}C-NMR δ: 28.9, 36.1 (2 x CH$_2$), 29.4 (CH$_3$), 86.9 (C), 124.05, 127.6, 128.6, 144.3 (6C, ArC), 176.4 (CO$_2$).; IR cm^{-1}: 3060, 3029, 1446 (C=CH), 1770 (C=O), 1130, 1068 (C-O; GC-MS (*m/z*): 176 (M$^+$, 9%), 161 (100), 121 (35), 105 (44), 77 (29), 51 (21), 43 (52; HRMS (CI) for C$_{11}$H$_{12}$O$_2$ (M$^+$): Calcd 176.0837; Found 176.0845.

Preparation of esters **8aa**, **8ab** *and* **8ae**.

The same procedure as described above was used, but starting with ortho ester **14b** and carrying out the lithiation at 0ºC instead of -78ºC. The final step was performed in methanol. Compounds **8aa**, **8ab** and **8ae** were isolated after column chromatography (silica gel, hexane/ethyl acetate mixtures).

DTBB-catalyzed lithiation of ortho esters **6a** *and* **14b**.

Deuterolysis of lithiated intermediates. Preparation of compounds **16** *and* **17**.

The ortho ester **6a** or **14b** (2 mmol) was slowly added to a stirred green suspension of lithium powder (17.1 mmol, 120 mg) and DTBB (0.2 mmol, 53.2 mg) in THF (10 mL) at -78ºC (for **6a**) or at 0ºC (for **14b**) under an argon atmosphere. The reaction mixture was stirred for 30 additional minutes at the same temperature and then quenched with D_2O (0.2 mL) and the reaction mixture was allowed to warm up until room temperature. Phosphate buffer (10 mL) was added and the resulting mixture was extracted with diethyl ether (3 x 10 mL), the organic phase was washed with brine (10 mL) and water (10 mL) and dried over anhydrous magnesium sulphate. The solvent was removed under vacuum (15 Torr). Compounds **16** and **17** were isolated after column chromatography (neutral silica gel, hexane/ethyl acetate mixtures).

2-(3-Deuteropropyl)-2-ethoxy-1,3-dioxolane (**16**): ^{1}H-NMR δ: 0.92 (2H, m, CH_2D), 1.18 (3H, t, *J* = 7.02, CH_3), 1.46 (2H, m, CCH_2), 1.79 (2H, m, CCH_2CH_2), 3.54 (2H, q, *J* = 7.1, CH_2CH_3), 3.96, 4.10 (2H and 2H, 2m, OCH_2CH_2O); ^{13}C-NMR δ: 13.6 (t, *J* = 19.2, CH_2D), 15.2 (CH_3), 17.0, 37.3 (2C, CH_2CH_2), 57.3 (CH_2CH_3), 64.8 (2C, OCH_2CH_2O), 122.6 (C); IR cm^{-1}: 1148, 1047 (C-O); GC-MS (*m/z*): 161 (M$^+$, 0.02%), 117 (42), 116 (100), 115 (63), 99 (36), 89 (73), 87 (10), 72 (34), 71 (18), 55 (43).

1-(4-Deuteropropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**17**): ^{1}H-NMR δ: 0.79 (3H, s, CH_3), 0.90 (2H, m, CH_2D), 1.45, 1.65 (2H and 2H, 2m, CH_2CH_2), 3.89 (6H, s, 3 x CH_2O); ^{13}C-NMR δ: 13.7 (t, *J* = 19.2, CH_2D), 14.5 (CH_3), 16.5, 38.7 (CH_2CH_2), 30.2 (CCH_3), 72.5 (3C, 3xCH_2O), 109.0 [$C(OCH_2)_3$]; IR cm^{-1}: 1148, 1047 (C-O); GC-MS (*m/z*): 172 (M$^+$-H, 0.3%), 72 (100), 71 (21), 55 (20), 44 (73), 43 (27), 42 (21).

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