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Studies on the α-acetylation of δ-valerolactone and ε-caprolactone

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Abstract—The synthetic approach to α-acetylated δ-valero- (**7a**) and ε-caprolactone (**7b**) is reported. While **7a** was isolated in 21% yield from the respective iodoester **5a** by an alkylation sequence involving transesterification and Finkelstein reaction, **7b** was not obtained from **5b** but the dimer **8**. Also transesterification and olefin ring closing metathesis (RCM) failed to prepare **7b**. RCM resulted in the dimeric lactone **10**, showing that the formation of 14-membered rings is favored over that of seven-membered rings. A Mukaiyama-type Claisen reaction finally gave α-acetyl lactones **7a** and **7b** in practically useful quantity of about 10 g (62% yield): starting lactones **13a**,**b** were converted to silylenolethers **14a**,**b**, which were acetylated with acetic anhydride in presence of the Lewis acid catalyst $TiCl_4$. However, acetylation depends on the addition sequence of starting materials: if the mixture of $Ac_2O/TiCl_4$ is added to **14b**, lactone **7b** can be further converted to give bis-oxepanonyl ethanols **15a**,**b**. Both compounds **15** were characterized by X-ray crystallography and NMR.

1. Introduction

β-Dicarbonyl compounds such as 1,3-diketones and β-ketoesters are valuable substrates in organic synthesis. In the course of our investigations on the copper(II)-catalyzed asymmetric Michael reaction[1] we decided to extend the substrate range to heterocyclic donors such as lactams and lactones. The simplest representative of this kind of substrate, α-acetyl-γ-butyrolactone, is commercially available and frequently used as a building block. Both α-acetylated valerolactone and caprolactone had to be prepared. However, the reported yield of α-acetyl-δ-valerolactone obtained by direct acetylation of valerolactone[2] could not be reproduced by others.[3,4]

In a preliminary communication[5] we reported our attempts of a direct six- and seven-membered ring closure to give α-acetylated δ-valero- and ε-caprolactone by alkylation or olefin ring closing metathesis (RCM). Both methods, however, resulted in case of α-acetyl-ε-caprolactone in the formation of dimeric 14-membered products, which were studied intensively by NMR spectroscopy and X-ray crystallography.[5] The result of RCM disagrees with earlier reports. Of the six possible diastereoisomers, only the *meso*-*E*,*E*-isomer is obtained as a crystalline material. Other diastereoisomers have been detected as impurities of the major product. Formation of the obviously thermodynamically favored *E*,*E*-stereoisomer represents one of the rare cases of stereoselective double bond formation in olefin metathesis.

In this paper we wish to disclose in more detail two methods for the preparation of the β-dicarbonyl compounds α-acetyl-valerolactone and α-acetyl-caprolactone in practically useful quantity.

2. Results and discussion

2.1. Attempts of alkylation and transesterification

Alcohols **1a**,**b** were applied as starting materials for both pathways (Scheme 1). The first step in the alkylation sequence is the transesterification of alcohols **1a**,**b** with methyl acetylacetate following a protocol developed in our laboratory which allows for the azeotropic removal of methanol from the reaction mixture (Scheme 1).[6] The resulting chloroalkyl esters **3a** and **3b**[7] were converted to the corresponding iodoesters **5a**,**b** in a Finkelstein reaction.

Cyclization of ω-iodopropyl ester **5a** with DBU afforded α-acetyl-δ-valerolactone **7a** in moderate yield (21%), while the respective conversion of **5b**, in contrast, did not result in seven-membered ring formation. With stoichiometric amounts of base (NaH), only one chromatographically uniform product could be isolated which surprisingly turned out to be the dimeric *trans* isomer *trans*-**8a**, as stated by X-ray diffraction analysis.[5] A complete second set of ^{13}C

Keywords: acylation; β-dicarbonyl compounds; lactones; macrocycles; metathesis.

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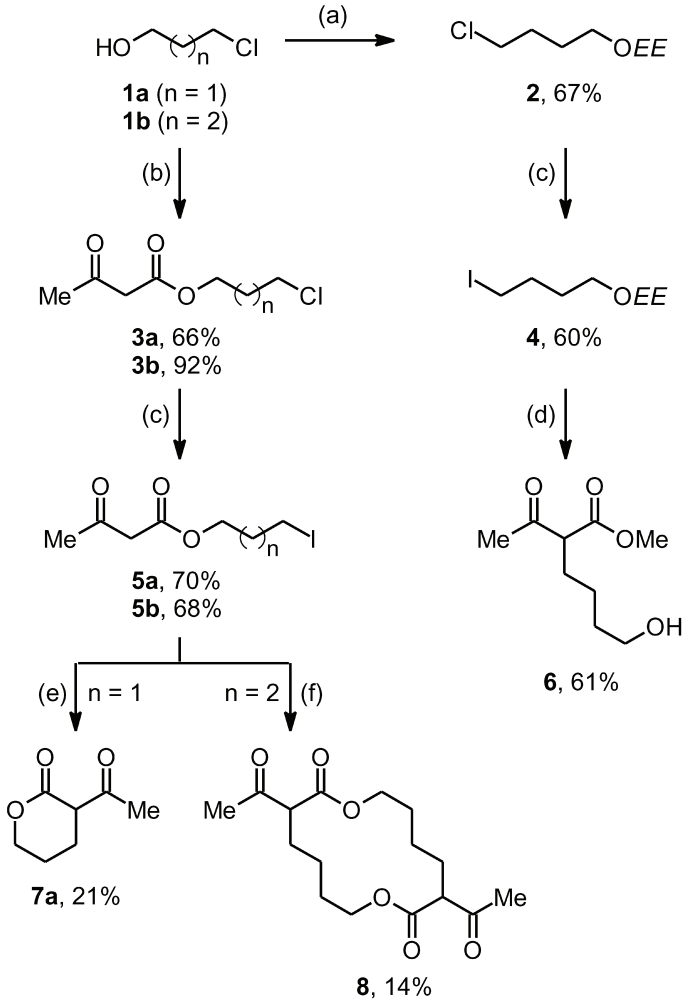


Scheme 1. Attempts of intramolecular alkylation and lactonization. *Reagents and conditions*: (a) ethyl vinyl ether, cat. TsOH, 0°C, 1.5 h. (b) $AcCH_2CO_2Me$, 5 mol% DMAP, cyclohexane, Dean–Stark trap, reflux, 16 h. (c) NaI, Na_2CO_3, acetone, reflux, 16 h. (d) (1) $AcCH_2CO_2Me$, NaH, THF, reflux, 16 h; (2) $HCl/NH_4Cl/H_2O$. (e) DBU, C_6H_6, reflux, 16 h. (f) NaH, THF, reflux, 16 h. *EE*=1-ethoxyethyl.

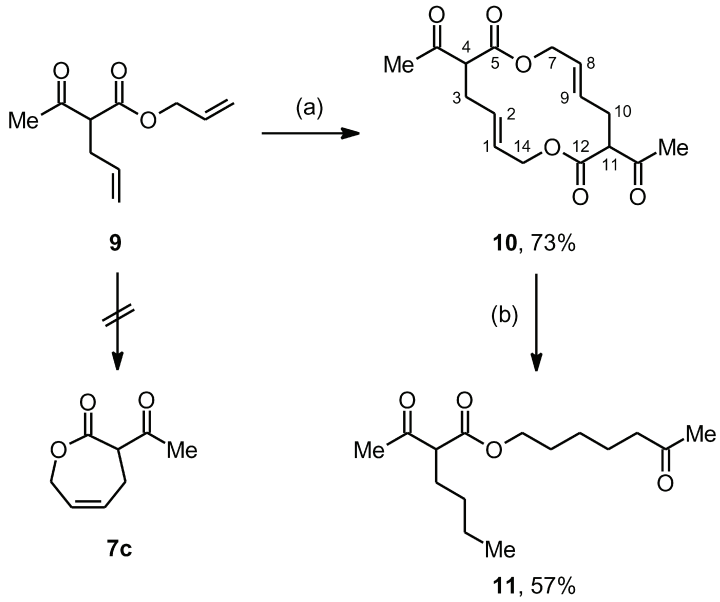
signals could be assigned to the corresponding minor *cis* isomer *cis*-**8b**.

The second route starts with the preparation of iodobutane **4** from chlorobutanol **1b** by a sequence of acetalization[8] and Finkelstein reaction. Both acetals **2** and **4** are extraordinarily acid-sensitive and need to be distilled from and stored over Na_2CO_3. Alkylation of methyl acetylacetate with **4** and hydrolytic cleavage of the protecting group furnished ω-hydroxyalkyl compound **6**, which seemed to be a reasonable starting material for lactonization. However, neither with catalytic amounts of DMAP and under conditions allowing for azeotropic removal of MeOH nor with Brönstedt acid catalysts (TsOH, H_2SO_4) the formation of lactone **7b** was observed. Only dehydration to an olefin and unspecific decomposition products could be observed. Intramolecular transesterification thus also proved an unsuitable strategy for closing the seven-membered ring of lactone **7b**.

2.2. Olefin metathesis

Olefin RCM is a recent preparative method which is increasingly applied for the synthesis of normal-, medium-sized, and large rings.[9–16] We consequently considered to likewise close the seven-membered ring by RCM of the corresponding diallyl precursor **9**,[17,18] catalyzed by benzylidenedichloro(1,3-dimesitylimidazolidine-2-ylidene)(tricyclohexylphosphane)ruthenium(II),[19] one of a new generation of Ru-catalysts with *N*-heterocyclic carbene ligands combining higher activity with improved stability.[20] RCM with 3 mol% Ru-catalyst in refluxing CH_2Cl_2 yielded, after column chromatography and recrystallization, a crystalline product with a predominant single set of ^1H and ^{13}C NMR resonances which were in perfect accordance with the constitution of the expected product **7c** (see Scheme 2).

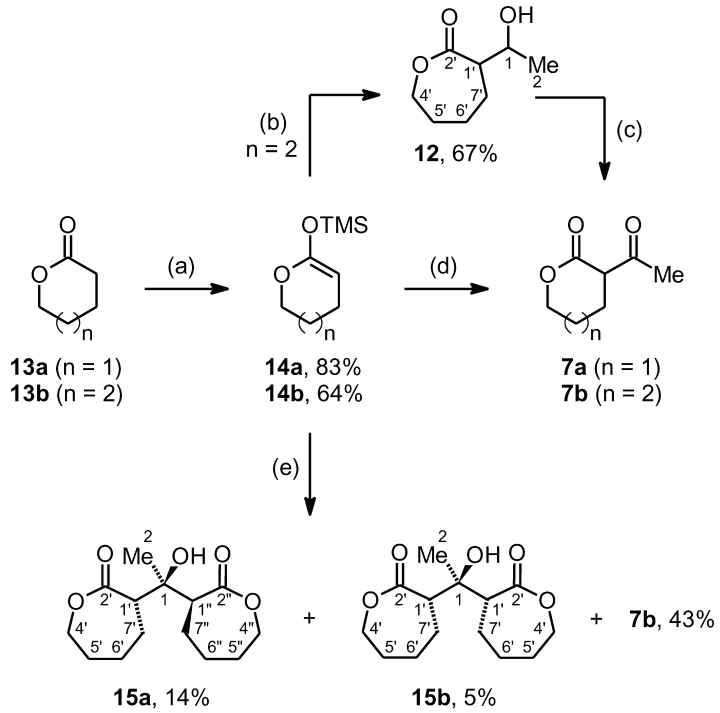
Two intense peaks at *m/z* 155 and 154 in the EI mass spectrum have been interpreted as the $[MH]^+$ and $[M]^{+\cdot}$ ions, respectively, of lactone **7c**. Formation of **7c** has been proposed in the literature.[21] Catalytic hydrogenation of the presumed RCM product **7c**, however, did not afford the lactone **7b** but rather the acyclic diketoester **11** as the only isolable hydrogenation product, apart from starting material. Its constitution was established unequivocally by 2D NMR



Scheme 2. 14-Membered-ring formation is favored over seven-membered ring formation. *Reagents and conditions*: (a) 3 mol% Ru-catalyst, CH_2Cl_2, 40°C, 1 day. (b) Pd–$BaSO_4$, H_2 (1 atm), EtOH, 23°C, 1 h.

(H,H-COSY, HMBC, HMQC).[5] Formation of **11** definitely refutes structure **7c** for the RCM product; GC–MS analysis of the crude RCM reaction mixture (after filtration) revealed not even traces of **7c**. Closer inspection of the mass spectrum of the RCM product in fact revealed two peaks of low intensity at *m/z* 308 (6%), 307 (2%), indicating a dimeric constitution. An X-ray diffraction analysis finally established the dimeric structure **10**.[5]

With two asymmetric carbon atoms and two C=C double bonds, the macrolactone **10** comprises four stereogenic elements; six diastereoisomers therefore are possible for compound **10**, four of them are chiral. The two stereocenters can be in either a *rac* (*R*,*R* or *S*,*S*) or *meso* (*R*,*S*) relationship, with the acetyl groups *cis* or *trans*, respectively; the two double bonds may have *E*,*E*; *E*,*Z*, or *Z*,*Z* configuration. To unequivocally correlate X-ray diffraction data, which established the structure of the single crystal as the *meso*-*E*,*E*-diastereoisomer **10a**,[5] with NMR solution stereochemistry,[22] another crystal was selected from the single crystal



Scheme 3. Mukaiyama-type aldol and Claisen reactions. *Reagents and conditions*: (a) LDA, THF, −78°C, TMSCl, −78°C→23°C, 16 h. (b) $BF_3{\cdot}OEt_2$, MeCHO, CH_2Cl_2, −78°C, 2 h. (c) DMP, 23°C, 1 h, 85% of **7b**. (d) Addition of **14** to $TiCl_4$, Ac_2O, CH_2Cl_2, −70°C, 1 h, 62% each of **7a** and **7b**. (e) As (d), but inverted order of addition (Ac_2O and $TiCl_4$ to **14b**).

Table 1. X-Ray crystal data collection and refinement for **7b**, **15a** and **15b**

	7b	**15a**	**15b**
Formula	$C_8H_{12}O_3$	$C_{14}H_{22}O_5$	$C_{14}H_{22}O_5$
FW	156.18	270.32	270.32
Crystal system	Orthorhombic	Triclinic	Orthorhombic
Space group	*Pbca*	$P\bar{1}$	*Pbca*
a (Å)	8.7045(3)	7.5515(11)	10.5120(12)
b (Å)	8.7402(6)	7.9466(15)	13.1811(9)
c (Å)	21.8142(11)	12.5579(19)	20.0925(17)
α (°)	90	74.623(12)	90
β (°)	90	79.888(13)	90
γ? (°)	90	79.441(14)	90
V (Å^3)	1659(15)	707.9(2)	2784.0(4)
Z	8	2	8
D_{calc} (mg m^{-3})	1.250	1.268	1.290
F(000)	672	292	1168
μ (mm^{-1})	0.790	0.789	0.803
θ range (°)	4.05–67.94	3.68–65.92	4.40–59.98
Reflections collected/unique	1379/1379	2991/2381	2031/2031
Data/restraints/parameters	1379/0/101	2381/0/177	2031/0/177
Goodness-of-fit on F^2	1.128	1.076	0.992
Final R indices			
[$I>2\sigma(I)$]	*R*1=0.0585	*R*1=0.0547	*R*1=0.0815
	w*R*2=0.1666	w*R*2=0.1519	w*R*2=0.2025
R indices (all data)	*R*1=0.0767	*R*1=0.0639	*R*1=0.1234
	w*R*2=0.2053	w*R*2=0.1619	w*R*2=0.2706
Largest diff.	0.220	0.317	0.282
Peak and hole (e Å^{-3})	−0.184	−0.182	−0.267

crystallization crop (0.5×0.3×0.05 mm^3). On the basis of 15 unique reflections, detected by rotation photograph, the $P2_1/c$ space group was determined for this crystal, definitely establishing its structural identity with *meso*-*E*,*E*-diastereoisomer **10a**. A ^{1}H NMR spectrum recorded immediately after dissolving the crystal (~10 μg) in $CDCl_3$ (0.3 ml; 10^{-5} mol dm^{-3} solution) displayed, apart from a minor impurity, a clean set of seven ^{1}H multiplets. Numerical analysis for the two olefinic resonances (1/8- and 2/9-H) afforded a coupling constant of 15.3_5 Hz which is clearly in the $^3J_{trans}$ range and thus unambiguously establishes the *E*,*E* configuration. The two diastereotopic protons 7/14-H_A,H_B appear well differentiated at 4.857 and 4.380 ppm.[5]

Upon standing at ambient temperature, however, a second signal set evolved in the NMR sample, with the O–CH_AH_B protons now almost isochronous around ~4.6 ppm while the resonances of the other five protons appear but slightly shifted. The corresponding *rac*-*E*,*E*-diastereoisomer **10b** is therefore presumed to be formed by epimerization of the stereocenters C-4 and C-11 via the respective enol tautomers. A ~1:1 equilibrium between **10a** and **10b** is established after 24 h. The position of this equilibrium, however, is matrix-dependent: if sufficient crystalline material is dissolved in $CDCl_3$, the ^{1}H NMR spectrum after two weeks integrates for 93:7 (**10a/10b**). An additional set of eight signals in the ^{13}C spectrum shows chemical shifts so close to those of the major isomer **10a** to absolutely rule out a change in double bond configuration.[5] A highly concentrated solution, after 30000 scans, displayed two additional signal sets (16 lines each) which were assigned, respectively, to the *meso*-*E*,*Z*-diastereoisomer (**10c**, *trans*) (the term '*meso*' is misleading, since **10c** is in fact chiral) and the *rac*-*E*,*Z*-diastereoisomer (**10d**, *cis*). Resonances of a *Z*,*Z*-isomer were not observed.[5]

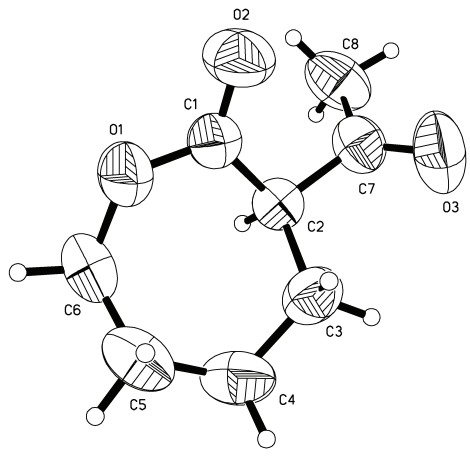


Figure 1. Molecular structure of the racemic lactone **7b**.

Generally macrocyclizations by RCM are not stereoselective with respect to C–C double bond configuration. Under certain conditions, however, reversibility of the RCM reaction results in exclusive formation of *E*-isomers.[23] A prerequisite for such high *E*-selectivity is strain or steric hindrance in the *Z*-isomer which probably holds also for the *E*,*Z*- and *Z*,*Z*-isomers of the bislactone **10**. With a simple RCM protocol and from readily available starting material, this 14-membered ring system is obtained in 73% isolated yield (after chromatographic purification) and with exceptional stereochemical purity. More than 95% of the crystalline material is *E*,*E*-configured, with C-4/C-11-configuration exclusively *R*,*S* (*meso*). This preparative approach is now being extended to larger ring systems.

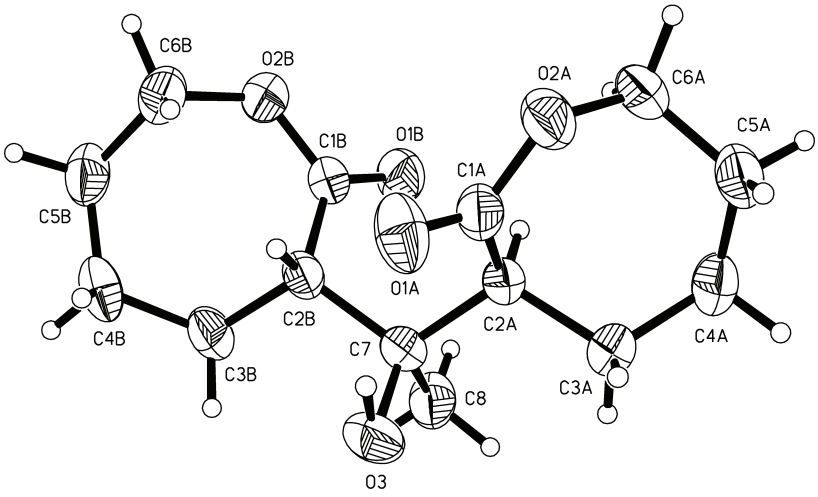


Figure 2. Molecular structure of the racemic *syn–anti* diastereoisomer (R^*,R^*)-**15a**.

2.3. Mukaiyama aldol and Claisen reactions

Because all attempts failed to prepare the seven-membered ring lactone **7b** by a direct seven-membered ring closure, we decided to start from the parent δ-valero- (**13a**) and ε-caprolactones (**13a**) as outlined in Scheme 3. The literature yields of trimethylsilylketene acetals **14a**,**b**, derived from **13a** and **13b**,[24] could be improved to 83% (**14a**) and 64% (**14b**). In a Mukaiyama aldol reaction, the silyl ether **14b** was converted with stoichiometric amounts of acetaldehyde and $BF_3{\cdot}OEt_2$ as Lewis acid in 67% yield to the hydroxy lactone **12** (mixture of two diastereoisomers).[25–27] Oxidation of **12** with the Dess–Martin periodinane (DMP)[28] gave the desired α-acetyl lactone **7b** in 85% yield.

Actually, the silyl ethers **14a**,**b** are acetylated directly, with acetic anhydride and $TiCl_4$ as Lewis acid catalyst, in a Mukaiyama-type Claisen reaction to give the α-acetylated lactones **7a** and **7b**. On an analytical scale, **7b** was isolated in this way in 85% yield. It must be noted, however, that a scale up following a literature procedure[29] is problematic: under the reaction conditions the products of the Mukaiyama–Claisen reaction, e.g. **7b**, are further converted with the silylenolether **14b** to give bis-oxepanonyl ethanols **15**, if acetic anhydride and $TiCl_4$ were added to **14b** [pathway (e), Scheme 3]. Under optimized reaction conditions [pathway (d)] we succeeded in a scale up giving both **7a** and **7b** in quantities of about 10 g (62% yield). Both, the concentration of the starting materials and the sequence of their addition, therefore have to be carefully controlled (for details see Section 3). Via this route, **7a** and **7b** are obtained in two steps from the parent lactones **13a** and **13b** [pathways (a) and (d), Scheme 3] in 40–50% overall yield.

2.4. Structural elucidation of 7b and 15a,b

From compound **7b**, single crystals suitable for X-ray structure elucidation were obtained (Table 1, Fig. 1). Two of the three possible diastereoisomers of **15** could be isolated and their relative configurations established by single crystal analysis (Table 1) as the racemic *syn–anti* diastereoisomer (R^*,R^*)-**15a** (Fig. 2) and the achiral *anti–anti* diastereoisomer (R^*,S^*)-**15b** (Fig. 3).

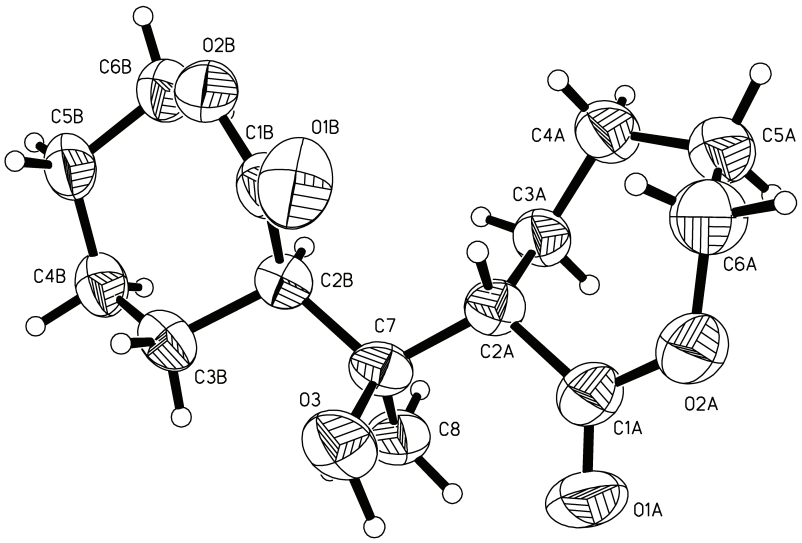


Figure 3. Molecular structure of the achiral *anti–anti* diastereoisomer (R^*,S^*)-**15b**.

Table 2. ^{13}C Chemical shifts of ethanols **12**, (R^*,R^*)-**15a**, and (R^*,S^*)-**15b** (0.5 M, $CDCl_3$, δ, ppm)

C atoms	**12** (major isomer)	**12** (minor isomer)	(R^*,S^*)-**15a**	(R^*,S^*)-**15b**
C1	68.73	66.92	74.36	75.07
C2	20.19	19.34	18.84	22.02
C1′/1″	48.46	50.29	49.72/46.76	49.81
C2′/2″	177.74	178.58	179.13/176.07	176.76
C4′/4″	68.75	68.96	68.65/69.17	67.99
C5′/5″	28.54	28.72	28.71/28.72	28.01
C6′/6″	27.86	28.08	24.51/24.98	24.69
C7′/7″	26.93	22.92	26.94/27.88	26.02

In Table 2, the ^{13}C chemical shifts of **15a**,**b** are collated with those of the corresponding 'mono' oxepanonyl ethanol **12**. As for the two diastereoisomers of **12**, a double signal set is observed for the two diastereotopic lactone moieties of the *syn–anti* isomer **15a**. The ^{13}C chemical shift differentiation appears sharply graded: 3.06/3.04 ppm for C1′,1″/C2′,2″, 0.92 ppm for C7′,7″ (for the corresponding lactone *O*, there is of course no signal), and 0.48/0.52 ppm for C6′,6″/C4′,4″. The C5′,5″ resonances, finally, can be resolved only with extreme Gaussian apodization. The crystal structure (Fig. 2) shows that the C═O function of one of the lactone rings (C1A═O1A) is oriented towards the O–H group, establishing a loose hydrogen bond or dipole contact (1.8 Å), while the C═O function of the other ring (C1B═O1B) is rotated 180° away from the O–H group. In this conformation, a pronounced γ-*cis* interaction becomes apparent between the protons of the methyl group and those at C7′ (C3A), explaining the 3 ppm high field shift of the CH_3 resonance for **15a** relative to that for **15b**.

For the *anti–anti* diastereoisomer **15b**, the ^{13}C spectrum (11.74 T, 198 K, $CDCl_3$) shows clear indications of beginning decoalescence. Thus, $\nu_{1/2}$ for the C1′ line is almost five times that for, e.g., the methyl carbon line. Apparently, there is a rapid reorientation in solution, by 180° rotation around the C7–O3 bond, between two energetically degenerate conformations where the OH group is aligned with the C═O function of either one or the other lactone ring. With the molecule frozen in one conformation, as in the crystalline state (Fig. 3), the two lactone subunits are diastereotopic. This holds also in solution, if the lifetime of the two conformers is long with respect to the NMR relaxation time.

3. Experimental

3.1. General

Compounds **6**, **7a**, **7b**, **8**, **10**, **12**, **14a**, and **14b** were prepared under anhydrous conditions in abs. solvents. Column chromatography was accomplished using SiO_2 60, grain size 0.063–0.200 mm (Merck) with hexanes (bp 40–60°C), EtOAc, or *tert*-butyl methyl ether (MTB) as eluents. All starting materials are commercially available. LDA (2.0 mol dm^{-3} in THF/heptane/ethylbenzene) was purchased from Aldrich Chemical Co. ^{13}C NMR multiplicities were determined with DEPT experiments. ^{13}C NMR spectra are proton decoupled.

3.1.1. 1-Chloro-4-(1-ethoxyethoxy)butane (2). To a solution of chlorobutanol **1b** (8.00 g, 73.7 mmol) in ethyl vinyl ether (80 ml) was added *p*-TsOH·H_2O (8 mg, 0.05 mmol) at 0°C. The mixture was stirred for 1.5 h at 0°C, diluted with MTB (30 ml), washed with saturated aqueous $NaHCO_3$ solution (3×100 ml), and dried over $MgSO_4$. The solvent was evaporated, and the crude product distilled from Na_2CO_3 through a 10 cm-Vigreux column (4–5 mbar, bp 45–46°C), yielding acetal **2** as a colorless oil (8.89 g, 49.2 mmol, 67%) which must be stored over Na_2CO_3. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.21 (t, *J*=7.1 Hz, 3H), 1.31 (d, *J*=5.3 Hz, 3H), 1.69–1.77 (m, 2H), 1.83–1.91 (m, 2H), 3.41–3.50 (m, 2H), 3.55–3.67 (m, 2H), 3.58 (t, *J*=6.8 Hz, 2H), 4.68 (q, *J*=5.3 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=15.32 (CH_3), 19.83 (CH_3), 27.24 (CH_2), 29.58 (CH_2), 44.94 (CH_2), 60.79 (CH_2), 64.20 (CH_2), 99.58 (CH) ppm. IR (neat): 2977 (vs), 2938 (vs), 2875 (vs), 1133 (vs), 1102 (vs), 1060 (vs) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 179 (1) [M^+−H], 91 (64), 73 (100). Anal. calcd for $C_8H_{17}ClO_2$: C, 53.18; H, 9.48; Cl, 19.62. Found: C, 53.10; H, 9.45; Cl, 19.50.

3.1.2. 3-Chloropropyl acetoacetate (3a). A solution of methyl acetoacetate (15.0 g, 129 mmol), chloropropanol **1a** (13.4 g, 142 mmol) and DMAP (158 mg, 1.29 mmol) in cyclohexane (50 ml) was heated to reflux overnight in a Dean–Stark trap. Saturated aqueous NH_4Cl solution (200 ml) and HCl (50 ml, 18%) were added, and the mixture was then extracted with MTB (3×100 ml). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated, and the crude product was chromatographed on SiO_2 (MTB/cyclohexane, 1:2, R_f=0.25) to give ester **3a** as a colorless oil (15.2 g, 85.1 mmol, 66%). ^1H NMR ($CDCl_3$, 200 MHz): δ=2.11 (quint, *J*=6.2 Hz, 2H), 2.27 (s, 3H), 3.47 (s, 2H), 3.62 (t, *J*=6.3 Hz, 2H), 4.31 (t, *J*=6.1 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=30.12 (CH_3), 31.28 (CH_2), 40.95 (CH_2), 49.86 (CH_2), 61.91 (CH_2), 166.88 (C), 200.35 (C) ppm. IR (ATR): 1741 (vs), 1715 (vs) cm^{-1}. HRMS (EI, 70 eV): Mol. mass calcd 178.0397 (for $C_7H_{11}ClO_3$), found 178.0400 (M^+). Anal. calcd for $C_7H_{11}ClO_3$: C, 47.07; H, 6.21. Found: C, 46.86; H, 6.34.

3.1.3. 4-Chlorobutyl acetoacetate (3b). A solution of methyl acetoacetate (10.0 g, 86.1 mmol), chlorobutanol **1b** (9.35 g, 86.1 mmol) and DMAP (530 mg, 4.34 mmol) in cyclohexane (100 ml) was heated to reflux overnight in a Dean–Stark trap. Saturated aqueous NH_4Cl solution (200 ml) and HCl (50 ml, 20%) were added, and the mixture was then extracted with MTB (3×50 ml). The organic layers were combined and dried over $MgSO_4$. The solvent was stripped off. Purification of the residual crude product by chromatography on SiO_2 (MTB/hexanes, 1:2, R_f=0.23) afforded ester **3b** as a colorless oil (15.2 g, 78.9 mmol, 92%). ^1H NMR ($CDCl_3$, 200 MHz): δ=1.82–1.87 (m, 4H), 2.27 (s, 3H), 3.46 (s, 2H), 3.54–3.60 (m, 2H), 4.17–4.21 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=25.91 (CH_2), 28.94 (CH_2), 30.20 (CH_3), 44.36 (CH_2), 50.02 (CH_2), 64.49 (CH_2), 167.04 (C), 200.41 (C) ppm. IR (ATR): 1739 (vs), 1713 (vs) cm^{-1}. HRMS (EI, 70 eV): Mol. mass calcd 192.0553 (for $C_8H_{13}ClO_3$), found 192.0551 (M^+). Anal. calcd for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80. Found: C, 49.60; H, 6.86.

3.1.4. 1-(1-Ethoxyethoxy)-4-iodobutane (4). Butylchloride **2** (3.10 g, 17.1 mmol) and Na_2CO_3 (0.50 g) were added to 100 ml of a saturated NaI solution in acetone. The mixture was heated to reflux overnight. After addition of saturated aqueous $NaHCO_3$ solution (150 ml), the mixture was extracted with hexanes (3×50 ml). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent yielded pure acetal **4** as a colorless oil (2.78 g, 10.2 mmol, 60%) which needed to be stored over Na_2CO_3 to prevent rapid decomposition. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.21 (t, J=7.1 Hz, 3H), 1.30 (d, J=5.3 Hz, 3H), 1.63–1.72 (m, 2H), 1.88–1.98 (m, 2H), 3.22 (t, J=7.0 Hz, 2H), 3.40–3.53 (m, 2H), 3.56–3.67 (m, 2H), 4.68 (q, J=5.3 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=6.70 (CH_2), 15.28 (CH_3), 19.77 (CH_3), 30.39 (CH_2), 30.71 (CH_2), 60.73 (CH_2), 63.76 (CH_2), 99.51 (CH) ppm. IR (neat): 2975 (vs), 2935 (vs), 2872 (vs), 1131 (vs), 1060 (vs) cm^{-1}. MS (EI, 70 eV), *m/z* (%): 271 (1) [M$^+$−H], 183 (45), 73 (100). Anal. calcd for $C_8H_{17}IO_2$: C, 35.31; H, 6.30; I, 46.63. Found; C, 35.39; H, 6.33; I, 46.36.

3.1.5. 3-Iodopropyl acetoacetate (5a). A mixture of chloroester **3a** (15.2 g, 85.1 mmol) and 100 ml of a saturated NaI solution in acetone was heated to reflux overnight. Saturated aqueous NH_4Cl solution (200 ml) was added, and the mixture was then extracted with MTB (3×100 ml). The combined organic layers were dried over $MgSO_4$, the solvent evaporated, and the crude product chromatographed on SiO_2 (MTB/cyclohexane, 1:2, R_f=0.23) to give iodoester **5a** as a colorless oil (16.0 g, 59.2 mmol, 70%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=2.16 (quint, J=6.3 Hz, 2H), 2.27 (s, 3H), 3.22 (t, J=6.8 Hz, 2H), 3.47 (s, 2H), 4.23 (t, J=6.0 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=1.19 (CH_2), 30.16 (CH_3), 32.02 (CH_2), 49.88 (CH_2), 64.84 (CH_2), 166.84 (C), 200.27 (C) ppm. IR (ATR): 1740 (vs), 1712 (vs) cm^{-1}. HRMS (EI, 70 eV): Mol. mass calcd 269.9753 (for $C_7H_{11}IO_3$), found 269.9751 (M$^+$). Anal. calcd for $C_7H_{11}IO_3$: C, 31.11; H, 4.11; found: C, 31.28; H, 4.06.

3.1.6. 4-Iodobutyl acetoacetate (5b). A mixture of chloroester **3b** (817 mg, 4.24 mmol) and 100 ml of a saturated NaI solution in acetone was heated to reflux overnight. After addition of a saturated aqueous NH_4Cl solution (100 ml), the mixture was extracted with MTB (3×50 ml). The organic layers were combined and dried over $MgSO_4$. The solvent was stripped off. Purification of the crude product by chromatography on SiO_2 [MTB/hexanes, 1:2, R_f (MTB/hexanes, 1:1)=0.34] gave ester **5b** as a colorless oil (823 mg, 2.90 mmol, 68%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=1.64–1.92 (m, 4H), 2.23 (s, 3H), 3.17 (t, J=6.5 Hz, 2H), 3.43 (s, 2H), 4.13 (t, J=6.1 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=5.84 (CH_2), 29.31 (CH_2), 29.68 (CH_2), 30.15 (CH_3), 49.93 (CH_2), 64.03 (CH_2), 166.96 (C), 200.36 (C) ppm. IR (ATR): 1740 (vs), 1715 (vs) cm^{-1}. HRMS (EI, 70 eV): Mol. mass calcd 283.9909 (for $C_8H_{13}IO_3$), found 283.9907 (M$^+$).

3.1.7. Methyl 2-acetyl-6-hydroxyhexanoate (6). A solution of methyl acetoacetate (14.4 g, 124 mmol) in THF (20 ml) was added dropwise to a suspension of NaH (55%, 5.56 g, 127 mmol) in THF (33 ml) at 0°C. The mixture was stirred for 1 h at 23°C, a solution of iodobutane **4** (8.45 g, 31.1 mmol) in THF (25 ml) added, and the mixture heated to reflux overnight. A saturated aqueous NH_4Cl solution (100 ml) and HCl (100 ml, 20%) were added successively at 0°C; the mixture was extracted with EtOAc (4×50 ml). The organic layers were combined and dried over $MgSO_4$. The solvent was stripped off. Purification of the crude product by chromatography on SiO_2 (hexanes/EtOAc, 1:2, R_f=0.23) yielded ester **6** as a colorless oil (3.60 g, 19.1 mmol, 61%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.33–1.41 (m, 2H), 1.53–1.62 (m, 2H), 1.83–1.91 (m, 2H), 2.24 (s, 3H), 2.84 (s, br, 1H), 3.47 (t, J=7.3 Hz, 1H), 3.62 (t, J=6.4 Hz, 2H), 3.74 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.45 (CH_2), 27.66 (CH_2), 28.71 (CH_3), 31.99 (CH_2), 52.21 (CH_3), 59.31 (CH), 61.85 (CH_2), 170.15 (C), 203.19 (C) ppm. IR (neat): 3422 (s), 1741 (vs), 1713 (vs) cm^{-1}. HRMS (EI, 70 eV): Mol. mass calcd 188.1049 (for $C_9H_{16}O_4$), found 188.1052 (M$^+$).

3.1.8. Preparation of α-acetyl-δ-valerolactone (7a). *By intramolecular alkylation*. A mixture of acetoacetate **5a** (16.0 g, 59.2 mmol), DBU (10.0 g, 65.7 mmol) and benzene (500 ml) was heated to reflux overnight. Saturated aqueous NH_4Cl solution (200 ml) was added, and the mixture then extracted with MTB (3×150 ml). The combined organic layers were dried over $MgSO_4$, the solvent evaporated, and the crude product chromatographed on SiO_2 (MTB/cyclohexane, 1:2, R_f=0.22) to give lactone **7a** as a colorless oil (1.78 g, 12.5 mmol, 21%).

By Mukaiyama–Claisen[30] *reaction*. To a mixture of Ac_2O (100 ml, 108 g, 1.06 mol) and molecular sieves (4 Å, 4 g) in CH_2Cl_2 (500 ml) at −78°C was slowly added dropwise $TiCl_4$ (20 ml, 34.5 g, 182 mmol), and the reaction mixture was stirred for 30 min. Silylenolether **14a** (18.4 g, 107 mmol) was added dropwise over a period of 5 h at −78°C (syringe pump). The mixture was then warmed to 23°C and stirred for another 16 h, subsequently poured onto ice (300 g) and extracted with EtOAc (3 × 200 ml). The combined organic layers were dried ($MgSO_4$), the solvent was evaporated and the residue distilled through a 10 cm Vigreux column (7 mbar, bp 88°C) to furnish lactone **7a** as a colorless solid (9.44 g, 66.4 mmol, 62%); mp 43–44°C. NMR spectra show only the enol tautomer. ^{1}H NMR ($CDCl_3$, 200 MHz): δ=1.86–1.96 (m, 2H), 1.98 (s, 3H), 2.39 (t, J=6.0 Hz, 2H), 4.24–4.29 (m, 2H), 13.68 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=18.72 (CH_3), 22.53 (CH_2), 22.63 (CH_2), 68.94 (CH_2), 93.15 (C), 172.65 (C), 175.80 (C) ppm. IR (ATR): 1736 (w), 1718 (w), 1636 (vs), 1416 (s), 1279 (s), 1250 (vs) cm^{-1}. HRMS (EI, 70 eV): Mol. mass calcd 142.0630 (for $C_7H_{10}O_3$), found 142.0622 (M$^+$). Anal. calcd $C_7H_{10}O_3$: C, 59.15; H, 7.09. Found: C, 59.43; H, 7.18.

3.1.9. α-Acetyl-ε-caprolactone (7b). To a mixture of Ac_2O (100 ml, 108 g, 1.06 mol) and molecular sieves (4 Å, 4 g) in CH_2Cl_2 (500 ml) at −78°C was slowly added dropwise $TiCl_4$ (20 ml, 34.5 g, 182 mmol), and the reaction mixture was stirred for 30 min. Silylenolether **14b** (20.0 g, 107 mmol) was added dropwise over a period of 5 h at −78°C (syringe pump). The mixture was then warmed to 23°C and stirred for another 16 h, subsequently poured onto ice (300 g) and extracted with EtOAc (3×200 ml). The combined organic layers were dried ($MgSO_4$), the solvent

was evaporated and the crude product chromatographed on SiO_2 [EtOAc/petroleum ether, 1:2→1:1, R_f (EtOAc/petroleum ether 1:1)=0.25] to give compound **7b** as a colorless solid (10.4 g, 66.4 mmol, 62%); mp 57°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.54–1.83 (m, 3H), 1.94–2.07 (m, 2H), 2.12–2.20 (m, 1H), 2.27 (s, 3H), 3.69 (dd, J=10.9, 1.9 Hz, 1H), 4.28 (ddd, J=12.8, 9.7, 0.7 Hz, 1H), 4.32–4.39 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.89 (CH_2), 27.06 (CH_2), 28.57 (CH_2), 28.66 (CH_3), 56.67 (CH), 69.38 (CH_2), 173.05 (C), 202.60 (C) ppm. IR (KBr): 1725 (vs), 1702 (vs), 1690 (vs) cm^{-1}. MS (CI, CH_4), m/z (%): 157 (100) [M$^+$+H]. Anal. calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.48; H, 7.71.

3.1.10. 3,10-Diacetyl-2,9-dioxo-1,8-dioxacyclotetradecane (8). A solution of iodoester **5b** (500 mg, 1.76 mmol) in THF (2 ml) was added dropwise at 0°C to a suspension of NaH (55%, 90.1 mg, 2.06 mmol) in THF (20 ml), and the reaction mixture was heated to reflux overnight. Aqueous citric acid solution (20 ml, 20%) was added, and the mixture extracted with hexanes (3×10 ml). The organic layers were combined and dried over $MgSO_4$. The solvent was stripped off, and the crude product chromatographed on SiO_2 (hexanes/EtOAc, 2:1, R_f=0.24), yielding lactone **6** as a colorless solid (37 mg, 0.12 mmol, 14%); mp 109–110°C. *trans*-**8a**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.36–1.50 (m, 4H), 1.57–1.65 (m, 2H), 1.68–1.75 (m, 2H), 1.77–1.84 (m, 2H), 1.91–1.99 (m, 2H), 2.22 (s, 6H), 3.43 (dd, J=11.6, 3.5 Hz, 2H), 4.19–4.23 (m, 2H), 4.27–4.31 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ=23.16 (C-2/9), 27.17 (C-3/10), 28.17 (C-1/8), 28.63 (CH_3), 60.47 (C-4/11), 63.99 (C-7/14), 169.68 (C-5/12), 202.38 (C=O). *cis*-**8b**: ^{13}C NMR ($CDCl_3$, 125 MHz): δ=23.19 (C-2/9), 27.26 (C-3/10), 28.05 (C-1/8), 28.67 (CH_3), 60.459.877 (C-4/11), 64.08 (C-7/14), 169.94 (C-5/12), 202.50 (C=O). IR (KBr): 1728 (vs), 1705 (vs) cm^{-1}. MS (EI, 70 eV), m/z (%): 312 (45) [M$^+$], 270 (44), 157 (91), 139 (60), 43 (100). Anal. calcd for $C_{16}H_{24}O_6$: C, 61.53; H, 7.74. Found: C, 61.33; H, 7.70.

3.1.11. Allyl 2-allyl-3-oxobutanoate (9). Allyl acetoacetate (15.0 g, 105 mmol) was added dropwise to a suspension of NaH (60%, 4.65 g, 116 mmol) in THF (450 ml) at 0°C. The mixture was stirred for 2 h at 23°C, allylbromide (9.90 ml, 14.2 g, 117 mmol) was added dropwise at 0°C, and the reaction mixture stirred overnight at 23°C. A saturated aqueous NH_4Cl solution (200 ml) and HCl (200 ml, 20%) were added successively at 0°C; the mixture was extracted with MTB (3×100 ml). The organic layers were combined and dried over $MgSO_4$. The solvent was stripped off, and the residual crude product purified by chromatography on SiO_2 (MTB/hexanes, 1:5, R_f=0.30), yielding **9** as a colorless oil (13.3 g, 73.0 mmol, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.24 (s, 3H), 2.61 (t, br, J=6.9 Hz, 2H), 3.56 (t, J=7.4 Hz, 1H), 4.64 (dt, J=5.8, 1.3 Hz, 2H), 5.06 (dq, J=10.2, 1.4 Hz, 1H), 5.11 (dq, J=17.2, 1.6 Hz, 1H), 5.26 (dq, J=10.4, 1.2 Hz, 1H), 5.33 (dq, J=17.2, 1.4 Hz, 1H), 5.75 (ddt, J=17.1, 10.2, 6.8 Hz, 1H), 5.90 (ddt, J=17.2, 10.5, 5.8 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=29.19 (CH_3), 32.18 (CH_2), 59.18 (CH), 65.98 (CH_2), 117.59 (CH_2), 119.01 (CH_2), 131.46 (CH), 134.1 (CH), 168.90 (C), 202.27 (C). IR (ATR): 1743 (vs), 1716 (vs) cm^{-1}. HRMS (EI, 70 eV): Mol. mass calcd 182.0943 (for $C_{10}H_{14}O_3$), found 182.0943 (M$^+$). Anal. calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.79; H, 7.84.

3.1.12. 4,11-Diacetyl-5,12-dioxo-6,13-dioxa-1,8-cyclotetradecadiene (10). To a solution of ester **9** (500 mg, 2.74 mmol) in CH_2Cl_2 (30 ml) Ru-catalyst (70 mg, 0.082 mmol) and CH_2Cl_2 (40 ml) were added. The reaction mixture was heated to reflux for 1 day, the solvent stripped off, and the residue was chromatographed on SiO_2 (MTB/hexanes, 1:1, R_f=0.14) to give **10** as a colorless solid (307 mg, 0.996 mmol, 73%); mp 119°C. Crystallization from MeOH afforded a crystalline material which consists predominantly of a single diastereoisomer **10a** (single ^{1}H and ^{13}C NMR signal set). In $CDCl_3$ solution, **10a** epimerizes to a matrix-dependent **10a/10b** equilibrium mixture. *meso-E,E*-**10a**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.242 (s, 3H; $COCH_3$), 2.46$_0$ (m, 1H; 3-H_B), 2.651 [dddd, J=(−)14.8, 11.3, 8.0, 0.9 Hz, 1H; 3-H_A], 3.542 (dd, J=11.3, 3.6 Hz, 1H; 4-H), 4.380 [ddt, J=(−)11.8$_5$, 5.7$_5$, 1.2 Hz, 1H; 7-H_B], 4.857 [ddd, J=(−)11.8$_5$, 7.5, 0.8 Hz, 1H; 7-H_A], 5.633 (ddddd, J=15.3$_5$, 7.5, 5.7$_5$, 1.6$_5$, J=0.9 Hz, 1H; 1-H), 5.725 (ddddd, J=15.3$_5$, 8.0, 5.2, 1.1, 0.8 Hz, 1H; 2-H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ=28.64 (CH_3), 30.74 (C-3/10), 58.72 (C-4/11), 65.34 (C-7/14), 126.72 (C-1/8), 132.26 (C-2/9), 168.74 (C-5/12), 201.60 (C=O). IR (ATR): 1733 (vs), 1709 (vs), 1641 (w) cm^{-1}. MS (EI, 70 eV), m/z (%): 308 (6) [M$^+$], 307 (2), 155 (63), 154 (50), 137 (24), 112 (24), 111 (30), 95 (40), 94 (28), 67 (32), 43 (100). Mol. mass calcd 308.1260 (for $C_{16}H_{20}O_6$), found 308.1265 (M$^+$). Anal. calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.02; H, 6.42.

3.1.13. 6-Oxoheptyl 2-acetylhexanoate (11). A degassed mixture of lactone **10** (20 mg, 0.065 mmol) and Pd (5%)–$BaSO_4$ (1.4 mg) in EtOH (1 ml) was stirred for 1 h at 23°C under 1 atm H_2. The reaction mixture was filtered with CH_2Cl_2, the solvent stripped off, and the residue chromatographed on SiO_2 (MTB/hexanes, 1:1, R_f=0.30), yielding ester **11** as a colorless oil (10 mg, 0.037 mmol, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ=0.89 (t, J=7.2 Hz, 3H), 1.24–1.37 (m, 6H), 1.55–1.67 (m, 4H), 1.76–1.90 (m, 2H), 2.13 (s, 3H), 2.21 (s, 3H), 2.43 (t, J=7.3 Hz, 2H), 3.39 (t, J=7.4 Hz, 1H), 4.10–4.13 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=13.76 (CH_3), 22.39 (CH_2), 23.21 (CH_2), 25.39 (CH_2), 27.91 (CH_2), 28.32 (CH_2), 28.74 (CH_3), 29.53 (CH_2), 29.87 (CH_3), 43.38 (CH_2), 59.87 (CH), 65.04 (CH_2), 169.94 (C), 203.32 (C), 208.58 (C) ppm. IR (ATR): 1739 (vs), 1714 (vs) cm^{-1}. MS (EI, 70 eV), m/z (%): 270 (1) [M$^+$], 228 (10), 213 (20), 141 (27), 131 (10), 113 (100), 98 (22), 55 (18). Mol. mass calcd 270.1831 (for $C_{15}H_{26}O_4$), found: 270.1833 (M$^+$).

3.1.14. 6-Trimethylsilyloxy-3,4-dihydro-2*H*-pyran (14a). Freshly distilled (7 mbar, bp 51°C) δ-valerolactone (**13a**) (16.3 ml, 18.0 g, 180 mmol) was added dropwise to a solution of LDA in THF (200 mmol, 100 ml of a commercial 2.0 mol dm^{-3} solution diluted with 170 ml THF) at −78°C. The reaction mixture was stirred for 1 h at −78°C, then TMSCl (30.0 ml, 25.8 g, 237 mmol) was added and after removal of the cooling bath, the mixture was further stirred overnight. After filtration and washing of the residue with CH_2Cl_2 (400 ml), the solvent was removed and the residue distilled through a 10 cm Vigreux column

(8 mbar, bp 27–30°C) to furnish the silylenolether **14a** (25.7 g, 149 mmol, 83%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.21 [s, d, $J(^1H,^{29}Si)$=6.6 Hz, 9H], 1.72–1.79 (m, 2H), 2.01–2.07 (m, 2H), 3.81 (t, J=3.6 Hz, 1H), 4.05 (t, J=5.1 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=-0.04 (CH_3), 19.85 (CH_2), 22.37 (CH_2), 67.14 (CH_2), 73.92 (CH), 154.47 (C) ppm. IR (neat): 2957 (s), 2850 (s), 1688 (vs), 1386 (s), 1336 (s), 1249 (vs), 1210 (vs), 1063 (s), 987 (s), 913 (vs), 849 (vs) cm^{-1}. Mol. mass calcd 171.0841 ($C_8H_{15}O_2Si$), found 171.0840 (M^+-H).

3.1.15. 2-Trimethylsilyloxy-4,5,6,7-tetrahydrooxepin (14b). Freshly distilled (8 mbar, bp 72°C) ε-caprolactone (**13b**) (19.0 ml, 20.5 g, 180 mmol) was added dropwise to a solution of LDA in THF (200 mmol, 100 ml of a commercial 2.0 mol dm^{-3} solution diluted with 140 ml THF) at −78°C. The reaction mixture was stirred for 1 h at −78°C, then TMSCl (30.0 ml, 25.8 g, 237 mmol) was added and after removal of the cooling bath, the mixture was further stirred overnight. After filtration and washing of the residue with EtOAc (400 ml), the solvent was removed and the residue distilled through a 10 cm Vigreux column (8 mbar, bp 39–41°C) to furnish the silylenolether **14b** (21.6 g, 116 mmol, 64%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.20 [s, d, $J(^1H,^{29}Si)$=6.8 Hz, 9H], 1.59–1.64 (m, 2H), 1.77–1.85 (m, 2H), 1.97–2.03 (m, 2H), 3.96–3.99 (m, 2H), 4.10 (t, J=5.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ=0.06 (CH_3), 23.25 (CH_2), 26.13 (CH_2), 31.25 (CH_2), 71.38 (CH), 83.00 (CH_2), 160.01 (C) ppm. IR (neat): 1680 (vs), 1251 (vs), 1236 (vs), 1201 (vs) cm^{-1}. HRMS (CI, CH_4): Mol. mass calcd 187.1154 (for $C_9H_{19}O_2Si$), found 187.1143 ($M+H^+$).

3.1.16. 2-(1-Hydroxyethyl)-6-hexanolide (12). A solution of $F_3B{\cdot}OEt_2$ (3.29 ml, 3.72 g, 26.2 mmol) in CH_2Cl_2 (26 ml) was added to a solution of silylenolether **14b** (4.88 g, 26.2 mmol) and MeCHO (1.23 ml, 0.96 g, 21.8 mmol) in CH_2Cl_2 (20 ml) at −78°C. The reaction mixture was stirred at −78°C for 2 h and warmed to 23°C. Saturated aqueous NH_4Cl (100 ml) was added, and the mixture extracted with EtOAc (3×100 ml). The organic layers were combined and dried over $MgSO_4$. The solvent was stripped off. Purification of the crude product by chromatography on SiO_2 (hexanes/EtOAc, 1:2, R_f=0.31) afforded **12** as a colorless oil (2.76 g, 17.4 mmol, 67%) which, on the NMR evidence, represents a 2:1 mixture of two diastereoisomers. ^{1}H NMR ($CDCl_3$, 300 MHz), major isomer: δ=1.30 (d, J=6.4 Hz, 3H), 1.42–2.08 (m, 6H), 2.52–2.64 (m, 1H), 3.44 (d, br, J=5.5 Hz, 1H), 3.93 (sextet, J=6.2 Hz, 1H), 4.19–4.35 (m, 2H) ppm; minor isomer: δ=1.24 (d, J=6.6 Hz, 3H), 1.42–2.08 (m, 6H), 2.52–2.64 (m, 1H), 3.14 (d, br, J=3.7 Hz, 1H), 4.19–4.35 (m, 3H) ppm. IR (neat): 3448 (vs, br), 1726 (vs, br) cm^{-1}. MS (CI, CH_4), m/z (%): 159 (100) [$M+H^+$]. Anal. calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.63; H, 9.03.

3.1.17. 1,1-Bis-(oxepan-2-on-1-yl)ethanol (15). A mixture of Ac_2O (3.00 ml, 3.24 g, 31.7 mmol), $TiCl_4$ (3.50 ml, 6.04 g, 31.8 mmol) and CH_2Cl_2 (60 ml) was stirred for 20 min at −78°C and then added to a solution of silylenolether **14b** (3.00 g, 16.1 mmol) in CH_2Cl_2 (1000 ml). After further stirring of the resulting mixture for 1 h at −78°C, it was warmed to 23°C overnight and then poured into saturated aqueous $NaHCO_3$ solution (700 ml), neutralized with HCl (20%) and extracted with EtOAc (4×100 ml). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated and the crude material was chromatographed on SiO_2 (EtOAc/hexanes, 1:1) to give 290 mg (1.07 mmol, 14%) of **15a** (R_f=0.375), 1.09 g (6.98 mmol, 43%) of lactone **7b** (R_f=0.25), and 98 mg (0.36 mmol, 5%) of **15b** (R_f=0.21) as colorless solids.

(R^*,R^*)-Isomer **15a**. Mp 125°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.32 (s, 3H), 1.39–1.46 (m, 1H), 1.52–1.81 (m, 5H), 1.88–1.97 (m, 3H), 2.04–2.08 (m, 1H), 2.18–2.21 (m, 1H), 2.39–2.42 (m, 1H), 3.32 (d, J=10.6 Hz, 1H), 3.45 (dd, J=10.3, 2.2 Hz, 1H), 3.62 (s, br, 1H), 4.18–4.31 (m, 4H) ppm. IR (KBr): 3510 (s), 2940 (s), 1730 (vs, br) cm^{-1}. MS (CI, CH_4), m/z (%): 271 (30) [$M+H^+$], 157 (100), 114 (74). Mol. mass calcd 271.1545 (for $C_{14}H_{22}O_5$), found 271.1549 ($M+H^+$).

(R^*,S^*)-Isomer **15b**. Mp 124–125°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.43 (s, 3H), 1.54–1.76 (m, 7H), 1.93–2.00 (m, 6H), 3.26 (dd, J=10.4, 3.2 Hz, 1H), 4.24 (dd, J=9.0, 1.7 Hz, 1H), 4.27 (dd, J=9.1, 1.9 Hz, 1H), 4.33 (s, 1H), 4.49 (dd, J=6.2, 2.8 Hz, 1H), 4.51 (dd, J=6.1, 2.6 Hz, 1H) ppm. IR (KBr): 3420 (s, br), 2920 (s), 1720 (vs) cm^{-1}. MS (CI, CH_4), m/z (%): 271 (78) [$M+H^+$], 157 (100). Anal. calcd for $C_{14}H_{22}O_5$: C, 62.21; H, 8.20. Found: C, 62.00; H, 8.06.

3.2. X-Ray crystallographic analysis

Crystallization from CH_2Cl_2/petroleum ether gave single crystals suitable for X-ray crystallographic analysis. Data were collected on a Siemens P4 diffractometer with graphite-monochromated Cu Kα radiation (λ=1.54178 Å) at 293 K. The structures were solved by direct methods and refined against F^2 for all observed reflections. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 196492 (**7b**), CCDC 196490 (**15a**), and CCDC 196591 (**15b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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