Synthesis of α-Acetyl Lactones; Access to 14-Membered Bislactones by Attempts at Direct Ring Closure

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Dedicated to Professor Robert G. Bergman on the occasion of his 60th birthday

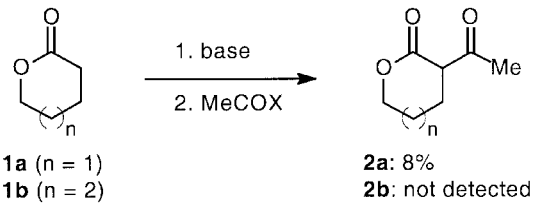
Abstract: α-Acetyl lactones are accessed by Mukaiyama–Claisen reactions. Attempts at direct 7-membered ring closure, by either intramolecular alkylation of 4-iodobutyl acetoacetate or olefin metathesis from allyl 2-allyl-3-oxobutanoate, afford exclusively dimeric 14-membered ring products instead of the expected caprolactones.

Key words: acylations, β-dicarbonyl compounds, lactones, macrocycles, metathesis

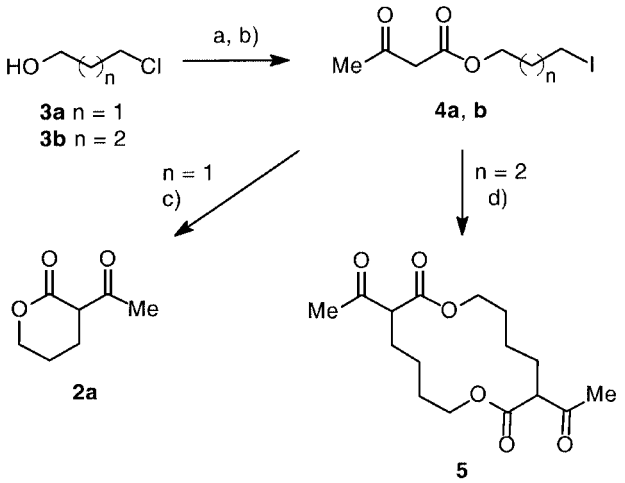
β-Ketoesters are valuable substrates in organic synthesis. α-Acetyl-γ-butyrolactone, prepared from acetylacetic esters and ethylene oxide, is commercially available and frequently used as a building block. The next higher homologue, α-acetyl-δ-valerolactone (**2a**), is accessible via acetylation of the ester enolate, generated by deprotonation of the parent 5-pentanolide (**1a**);[1] the yields, though, have been reported as not reproducible.[2] In fact, in all our attempts to prepare **2a**, the best result was an isolated yield of 8% obtained with NaH-KH-EtOAc in THF. Preparation of the seven-membered α-acetyl lactone **2b** from ε-caprolactone (**1b**) by an analogous deprotonation/acetylation sequence failed completely; bases applied were NaH, KH, LDA, *t*-BuOK, acetylating agents Ac_2O, AcCl, EtOAc (see Scheme 1). We hence decided on a direct ring closure approach for preparing lactones **2a** and **2b**, by either (1) intramolecular alkylation, (2) intramolecular transesterification, or (3) ring-closing olefin metathesis (RCM).

Alkylation. Transesterification of alcohols **3a**, **b** with methyl acetylacetate followed a protocol developed in our laboratory which allows for the azeotropic removal of methanol from the reaction mixture (Scheme 2).[3] The resulting chloroalkyl esters[4] were converted to the corresponding iodoesters **4a**,**b** in a Finkelstein reaction. Cyclization of ω-iodopropyl ester **4a** with DBU afforded valerolactone **2a** in moderate yield (21%); respective conversion of **4b**, 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 dimer **5**.[5] Crystallization from hexanes/EtOAc yielded one diastereoisomer, with a single NMR signal set, for which X-ray diffraction analysis established the achiral *trans* configuration[6] (cf. Figure 1). Closer inspection of the ^{13}C NMR spectrum, however, revealed a complete second set of signals (Table). The corresponding racemic *cis* configuration was assigned to this minor component on the basis of the ^{13}C chemical shifts, and a *trans*/*cis* ratio of 91:9 derived likewise from the NMR spectra. With these two diastereoisomeric 14-membered ring structures as the only products characterized, formation of the seven-membered ring obviously is disfavored over that of the 14-membered ring.

Transesterification. Iodobutane **6** was prepared from chlorobutanol **3b** by a sequence of acetalization[7] and Finkelstein reaction. Both acetals are extraordinarily acid-sensitive and need to be distilled from and stored over



Scheme 1 Attempts at α-acetylation of lactones. Conditions for **2a**: NaH, cat. KH, EtOAc in THF, 23 °C, 16 h.



Scheme 2 Intramolecular alkylation. a) $AcCH_2CO_2Me$, 5 mol% DMAP, cyclohexane, Dean–Stark trap, reflux, 16 h; 66% from **3a**, 92% from **3b**. b) NaI, acetone, reflux, 16 h; 70% (**4a**), 68% (**4b**). c) DBU, C_6H_6, reflux, 16 h, 21%. d) NaH, THF, reflux, 16 h, 14%.

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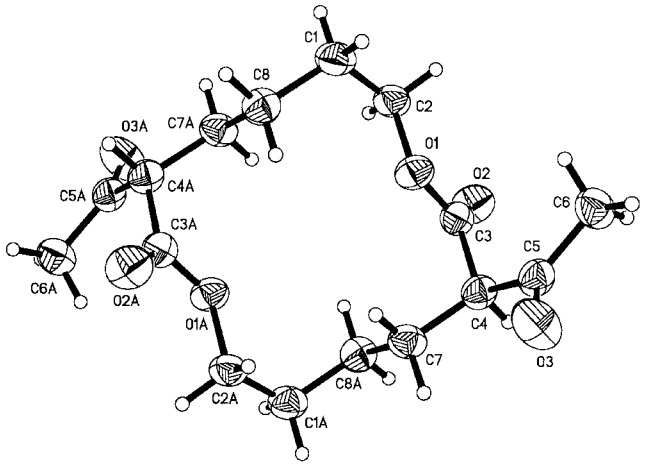
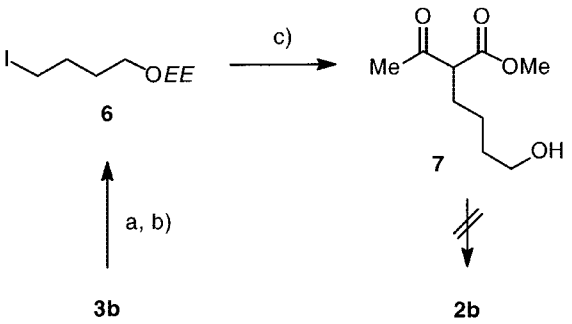


Figure 1 Molecular structure of the achiral 14-membered ring *trans*-**5a**.

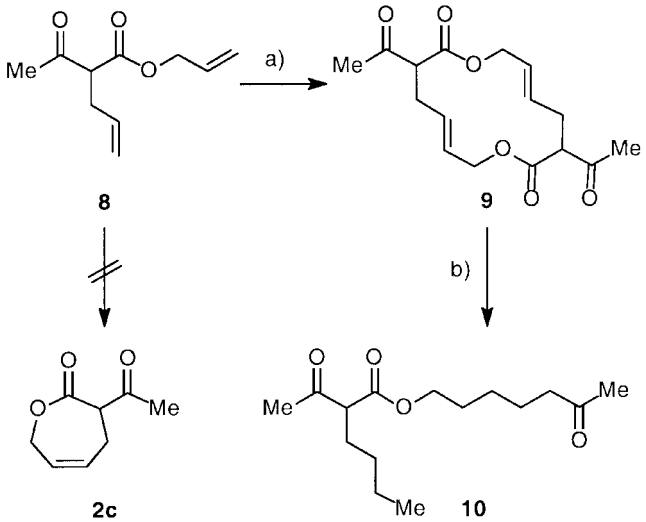
Na_2CO_3. Alkylation of methyl acetylacetate with **6** and subsequent hydrolysis of the protecting group furnished ω-hydroxyalkyl compound **7**, which seemed to be a reasonable starting material for lactonization. With catalytic amounts of DMAP and under conditions allowing for azeotropic removal of MeOH, however, no conversion was observed. With Brønsted acid catalysts (TosOH, H_2SO_4), no lactone **2b** was formed either. Intramolecular transesterification thus appears an unsuitable strategy for closing the seven-membered ring of lactone **2b** (Scheme 3).



Scheme 3 Attempt at intramolecular lactonization. a) ethylvinylether, cat. TosOH, 0 °C, 1.5 h; 67%. b) NaI, Na_2CO_3, acetone, reflux, 16 h; 60%. c) 1. $AcCH_2CO_2Me$, NaH, THF, reflux, 16 h; 2. HCl–NH_4Cl–H_2O; 61%. *EE* = 1-ethoxyethyl.

Olefin Metathesis. Ring closing olefin metathesis (RCM) is a recent preparative method which is increasingly applied for the synthesis of normal-, medium-sized, and large rings.[8,9] We consequently considered to likewise close the seven-membered ring by RCM of the corresponding diallyl precursor **8**.[10] Since Ru catalysts of the first generation showed no conversion with compound **8** at all,[11] we preferred to utilize benzylidenedichloro(1,3-dimesitylimidazolidine-2-ylidene)(tricyclohexylphosphane)ruthenium(II)[12] as metathesis catalyst. This is one of a new generation of Ru catalysts with *N*-heterocyclic carbene ligands which combine higher activity with improved stability.[13] RCM with 3 mol% Ru-catalyst in refluxing CH_2Cl_2 yielded, after column chromatography and recrystallization, a crystalline product with once again a predominant single set of ^1H and ^{13}C NMR resonances which were in perfect accord with the constitution of the expected product **2c** (see Scheme 4). The EI mass spectrum displayed two intense peaks at *m/z* 155 and 154 which we have erroneously interpreted as the $[MH]^+$ and $[M]^{+\bullet}$ ions, respectively, of lactone **2c**. Formation of **2c** has been proposed in the literature.[14] Catalytic hydrogenation of the presumed RCM product **2c** surprisingly did not afford the lactone **2b**, though, but rather the acyclic diketoester **10** as the only isolable hydrogenation product, apart from starting material. Its constitution was established unequivocally by 2D NMR (H,H-COSY, HMBC, HMQC). Formation of **10** definitely refutes structure **2c** for the RCM product.

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. Fortunately, single crystals of the RCM product could be grown from CH_2Cl_2/hexanes, and X-ray diffraction analysis established the dimeric structure **9**[15] (cf. Figure 2). Once again, closure of the 14-membered ring has prevailed over that of the seven-membered lactone. GC-MS analysis, moreover, of the crude RCM reaction mixture (after filtration) revealed no traces of the 'monomeric' cyclization product **2c**.



Scheme 4 14-Membered ring formation is favored over seven-membered ring formation. a) 3 mol% Ru-catalyst, CH_2Cl_2, 40 °C, 1 d; 73%. b) Pd–$BaSO_4$, H_2 (1 atm), EtOH, 23 °C, 1 h; 57%.

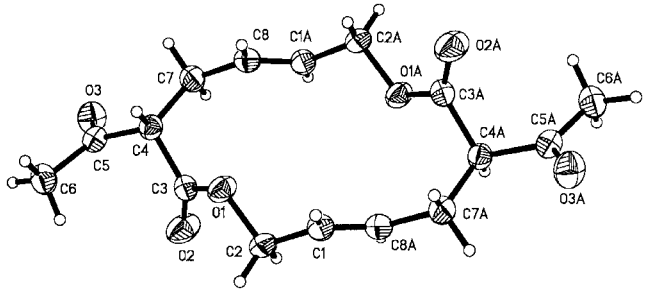


Figure 2 Molecular structure of *meso*-*E*,*E*-isomer **9a** (*trans*).

Of the six possible diastereoisomers of the macrolactone **9**, only the *meso*-*E*,*E*-form **9a** is realized in the crystalline state. From the ^{1}H NMR spectrum of another single crystal a complete set of δ/*J* data is derived for **9a**.[15] Upon standing in solution a concentration-dependent equilibrium is established between **9a** and the epimer *rac*-*E*,*E*-**9b**. The ^{13}C chemical shifts of **9a**,**b** as well as of the corresponding two *E*,*Z*-isomers **9c**,**d** are collected in the Table (Figure 3).[16]

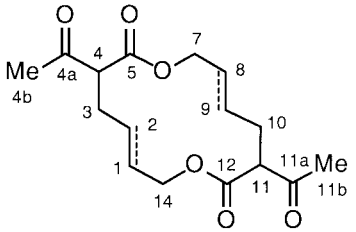


Figure 3 Numbering of compounds **5** and **9**.

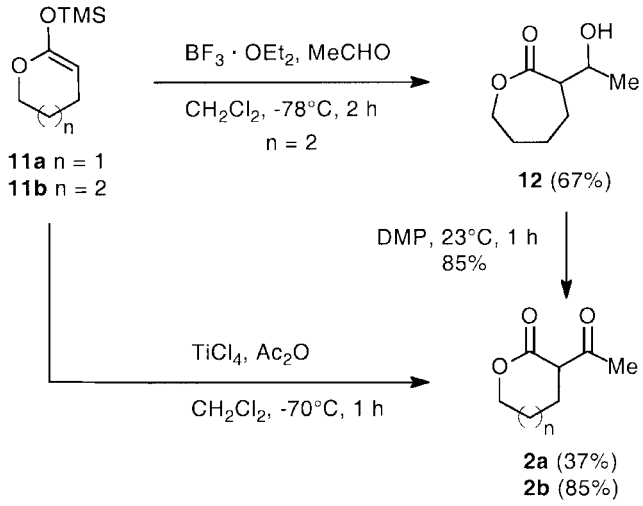
Synthetic Potential. Macrocyclizations by RCM generally are not stereoselective with respect to C-C double bond configuration. It was recently demonstrated, though, that the reversibility of the RCM reaction under certain conditions results in exclusive formation of *E*-isomers.[17] Prerequisite for 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 **9**. With a simple RCM protocol and from readily available starting material this 14-membered ring system thus 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*).

Mukaiyama Aldol and Claisen Reactions. Since all attempts at direct seven-membered ring closure had been unsuccessful, we finally decided, as originally planned, to start from the parent δ-valero (**1a**) and ε-caprolactone (**1b**). The trimethylsilylketene acetals **11a**,**b** derived from **1a**,**b** have been described;[18] the literature yields could be improved in our hands (83% **11a**, 66% **11b**). The silylether **11b** was converted with stoichiometric amounts of acetaldehyde and $BF_3{\cdot}OEt_2$ as Lewis acid in satisfying yield into the hydroxy lactone **12** in a Mukaiyama aldol reaction.[19] Oxidation of this material with the Dess–Martin periodinane (DMP)[20] at last gave the desired α-acetyl lactone **2b**.[21] Actually, the silylethers **11a**,**b** can be acetylated directly, with acetic anhydride and $TiCl_4$ as Lewis acid catalyst, in a Mukaiyama-type Claisen reaction. Via this route, **2a** and **2b** are obtained in two steps from the parent lactones **1a**,**b** in 50–60% overall yield (Scheme 5).

Table ^{13}C NMR Chemical Shifts[a,b] of Compounds **5** and **9** (Carbon Numbering of **5a**, **5b** follows that of **9a**)

	5a	**5b**	**9a**	**9b**	**9c**[c]	**9d**[c]
C-1/8	28.17	28.05	126.72	126.56	127.03 125.10	127.06 124.11
C-2/9	23.16	23.19	132.26	132.92	133.03 130.89	135.65 131.63
C-3/10	27.17	27.26	30.74	30.68	30.89 26.22	31.36 31.15
C-4/11	60.47	59.87	58.72	58.91	59.16 59.06	59.19 58.24
C-4a/11a	202.38	202.50	201.60	201.41	201.51 201.27	[d]
C-4b/11b	28.63	28.67	28.64	28.54	28.80 28.57	[d]
C-5/12	169.68	169.94	168.74	168.93	169.05 168.98	[d]
C-7/14	63.99	64.08	65.34	65.67	65.96 60.74	66.24 64.01

[a] δ/ppm relative to TMS as internal standard; 11.74 T, 298 K, 1.0 mol dm^{-3} in $CDCl_3$.
[b] FID 64 k, zero filled to size 512 k for a digital resolution of ±0.03 Hz, (<0.001 ppm).
[c] The double set is not differentiated as to *E*- or *Z*-hemisphere.
[d] Not detected.



Scheme 5 Mukaiyama-type aldol and Claisen reactions yield α-acetyl-δ-valero (**2a**) and ε-caprolactone (**2b**).

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(5) **3,10-Diacetyl-2,9-dioxo-1,8-dioxacyclotetradecane (5).** A solution of 500 mg (1.76 mmol) iodoester **4b** in 2 mL THF was added dropwise at 0 °C to a suspension of NaH (55%, 90.1 mg, 2.06 mmol) in 20 mL THF, and the reaction mixture heated to reflux overnight. Aq citric acid solution (20 mL, 20%) was added, and the mixture extracted with hexanes (3 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was stripped off, and the crude product purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1, R_f = 0.24), yielding lactone **5** as a colorless solid (37 mg, 0.12 mmol, 14%), mp 109–110 °C. Crystallization from hexanes/EtOAc afforded a product with one predominant diastereoisomer (single signal set in the NMR spectra) from which single crystals of the *meso*-diastereoisomer **5a** could be grown. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.36–1.50 (m, 4 H), 1.57–1.65 (m, 2 H), 1.68–1.75 (m, 2 H), 1.77–1.84 (m, 2 H), 1.91–1.99 (m, 2 H), 2.22 (s, 6 H), 3.43 (dd, *J* = 11.6 Hz, *J* = 3.5 Hz, 2 H), 4.19–4.23 (m, 2 H), 4.27–4.31 (m, 2 H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz) of the major (**5a**) and minor (**5b**) diastereoisomer: cf. Table. 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.

(6) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-176501 (**5a**) and no. CCDC-176500 (**9a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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(15) **4,11-Diacetyl-5,12-dioxo-6,13-dioxa-1,8-cyclotetradecadiene (9).** To a solution of 500 mg (2.74 mmol) ester **8** in 30 mL CH_2Cl_2, 70 mg (0.082 mmol) Ru catalyst and 40 mL CH_2Cl_2 were added. The reaction mixture was heated to reflux for 1 d, the solvent stripped off, and the residue purified by chromatography on SiO_2 (MTB/hexanes, 1:1, R_f = 0.14) to give **9** 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 **9a** (single ^{1}H and ^{13}C NMR signal set). From a CH_2Cl_2 solution of this material, single crystals of **9a** could be grown for the X-ray diffraction analysis. In $CDCl_3$ solution, **9a** epimerizes to a matrix-dependent **9a**/**9b** equilibrium mixture. ^{1}H NMR ($CDCl_3$, 500 MHz): **9a** – δ = 2.242 ($COCH_3$, s, 3 H), 2.46$_0$ (3-H$_B$, m, 1 H), 2.651 (3-H$_A$, dddd, *J* = (–) 14.8 Hz, *J* = 11.3 Hz, *J* = 8.0 Hz, *J* = 0.9 Hz, 1 H), 3.542 (4-H, dd, *J* = 11.3 Hz, *J* = 3.6 Hz, 1 H), 4.380 (7-H$_B$, ddt, *J* = (–)11.8$_5$ Hz, *J* = 5.7$_5$ Hz, *J* = 1.2 Hz, 1 H), 4.857 (7-H$_A$, ddd, *J* = (–)11.8$_5$ Hz, *J* = 7.5 Hz, *J* = 0.8 Hz, 1 H), 5.633 (1-H, ddddd, *J* = 15.3$_5$ Hz, *J* = 7.5 Hz, *J* = 5.7$_5$ Hz, *J* = 1.6$_5$ Hz, *J* = 0.9 Hz, 1 H), 5.725 (2-H, ddddd, *J* = 15.3$_5$ Hz, *J* = 8.0 Hz, *J* = 5.2 Hz, *J* = 1.1 Hz, *J* = 0.8 Hz, 1 H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz) of the major (**9a**) and minor (**9b**) *E*,*E*-diastereoisomers as well as of the two *E*,*Z*-diastereoisomers (**9c**, **9d**): cf. Table. 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. for $C1_{16}H_{20}O_6$: 308.1260; 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.

(16) **Structural Elucidation**. With two asymmetric carbon atoms and two C=C double bonds, the macrolactone **9** comprises four stereogenic elements; six diastereoisomers thence are possible for compound **9**, four of them 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. As Figure 2 shows, the single crystal obtained from the purified RCM product represents the *meso*-*E,E*-diastereoisomer **9a**, in accord with the predominant set of eight ^{13}C resonances. To unequivocally correlate X-ray diffraction with NMR solution stereochemistry,[22] another crystal was selected from the single crystal crystallization crop ($0.5 \times 0.3 \times 0.05$ mm). On the basis of 15 unique reflexes, detected by rotation photograph, $P2_1/c$ was determined as the space group for this crystal, which definitely established its structural identity with the single crystal on which the diffraction analysis was performed. The crystal (~10 μg) was dissolved in $CDCl_3$ (0.3 mL; 10^{-5} mol dm^{-3} solution), and a ^1H NMR spectrum recorded immediately. Apart from a minor impurity, the spectrum displayed a clean set of seven ^1H multiplets. For the two olefinic resonances at 5.725 and 5.633 ppm (1/8- and 2/9-H), numerical analysis afforded a coupling constant of 15.3_5 Hz which is clearly in the $^3J_{trans}$ range and thus unequivocally 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.
Upon standing at ambient temperature, though, 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 shifted but slightly. We thence presume that the corresponding *rac*-*E,E*-diastereoisomer **9b** is formed by epimerization of the stereocenters C-4 and C-11 via the respective enol tautomers. After 24 h, a ~1:1 equilibrium is established between **9a** and **9b**. The position of this equilibrium is matrix-dependent, however: if sufficient crystalline material is dissolved in $CDCl_3$ for a ^{13}C NMR spectrum, the ^1H NMR spectrum after two weeks integrates for 93:7 (**9a**:**9b**). The ^{13}C spectrum displays an additional set of eight signals (cf. Table), with chemical shifts so close to those of the major isomer **9a** that a change in double bond configuration is ruled out absolutely.
In an even more concentrated solution, and after 30,000 scans, two additional signal sets can be detected, in a 7:3 ratio (overall relative intensity ca. 5%) and with 16 lines each. Since this *per se* excludes a *Z,Z* configuration, these resonances were assigned to the *meso*-*E,Z*- (**9c**, *trans*)[23] and *rac*-*E,Z*-diastereoisomer (**9d**, *cis*), respectively (cf. Table). No resonances of a *Z,Z*-isomer were observed.
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(21) **α-Acetyl-ε-caprolactone (2b).** A solution of 0.50 mL (540 mg, 5.29 mmol) Ac_2O and 0.59 mL $TiCl_4$ (1.02 g, 5.37 mmol) in 10 mL CH_2Cl_2 was stirred for 20 min at –78 °C and then added to a solution of 500 mg (2.68 mmol) of silylenolether **11b** in 130 mL CH_2Cl_2. The reaction mixture was stirred at –70 °C for 1 h, warmed to 23 °C, stirred for another 0.5 h, and poured into a sat. aq $NaHCO_3$ solution (400 mL). The mixture was neutralized with HCl (20%) and extracted successively with CH_2Cl_2 (2×100 mL) and EtOAc (1×100 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was stripped off, and the crude product purified by filtration through SiO_2 with EtOAc, affording lactone **2b** as a colorless solid (354 mg, 2.27 mmol, 85%), mp 57 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.54–1.83 (m, 3 H), 1.94–2.07 (m, 2 H), 2.12–2.20 (m, 1 H), 2.27 (s, 3 H), 3.69 (dd, *J* = 10.9 Hz, *J* = 1.9 Hz, 1 H), 4.28 (ddd, *J* = 12.8 Hz, *J* = 9.7 Hz, *J* = 0.7 Hz, 1 H), 4.32–4.39 (m, 1 H) ppm. $^{13}C\{^1H\}$-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.
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