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Highly enantioselective synthesis of α-methylene-δ-valerolactones by an asymmetric Michael reaction

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Abstract—The synthesis of α-methylene-δ-valerolactones **7**, **13**, and **19** with enantiomeric excesses of 90–97% was achieved by the asymmetric Michael reaction of chiral imines **3**, **9**, and **15** with the acrylate **1**. Reduction of the carbonyl group of the resulting adducts followed by lactonization and HWE reaction with formaldehyde yielded the lactones as mixtures of diastereoisomers.

1. Introduction

In recent years the asymmetric Michael addition of imines derived from enantiomerically pure amines to electron-deficient olefins has been extensively exploited for enantioselective construction of quaternary stereocenters adjacent to a carbonyl group.[1]

Recently, we reported that dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate **1** can be used as particularly attractive acceptor in this type of reaction. We have demonstrated that the sequence involving the addition of imines derived from 2-methylcyclohexanone, 2-ethoxycarbonylcyclohexanone, and enantiomerically pure 1-phenylethylamine to acrylate **1**, followed by the diastereoselective reduction of the carbonyl group in the resultant 2-diethoxyphosphoryl-5-oxoalkanoic acids, lactonization of the reduction products, and finally Horner–Wadsworth–Emmons olefination of the α-phosphono-δ-valerolactones provides the corresponding α-methylene-δ-valerolactones with 97% enantiomeric excess.[2] It was also established that the 2-diethoxyphosphoryl-5-oxoalkanoic acids were mixtures of epimers that differ in configuration at the tertiary stereogenic center and their absolute configuration at the quaternary stereogenic center is in agreement with the transition-state model proposed for similar Michael reactions.[3]

Since optically active α-methylene-δ-valerolactones may serve as attractive building blocks for the construction of different natural products and their accessibility is limited,[4] we decided to clarify the generality of our synthetic method for the imines of both cyclic and acyclic ketones.

Herein we report on the effective and general protocol for the highly enantioselective preparation of α-methylene-δ-valerolactones derived from 2-methoxycyclohexanone **2** (Scheme 1), 2-ethoxycarbonylcyclopentanone **8** (Scheme 2), and 2-acetylbutyrolactone **14** (Scheme 3). We believed that using acyclic ketolactone **14** as a starting material would make it possible to obtain optically active spirocyclic bislactones.

2. Results and discussion

The starting (*R*)-α-imine **3**,[5] (*S*)-β-enaminoester **9**,[6] and (*R*)-β-enaminolactone **15**[6] were prepared by reported methods. Addition reactions of the imine **3** and enamines **9** and **15** to the salt **1** proceeded smoothly in benzene at room temperature. Complete consumption of salt **1** was observed after 2 days (^{31}P NMR). Ion-exchange chromatography of the crude Michael adducts gave 2-diethoxyphosphoryl-5-oxoalkanoic acids **4**, **10**, and **16**, respectively, each as a mixture of two diastereoisomers in a 1:1 ratio. Acids **4**, **10**, and

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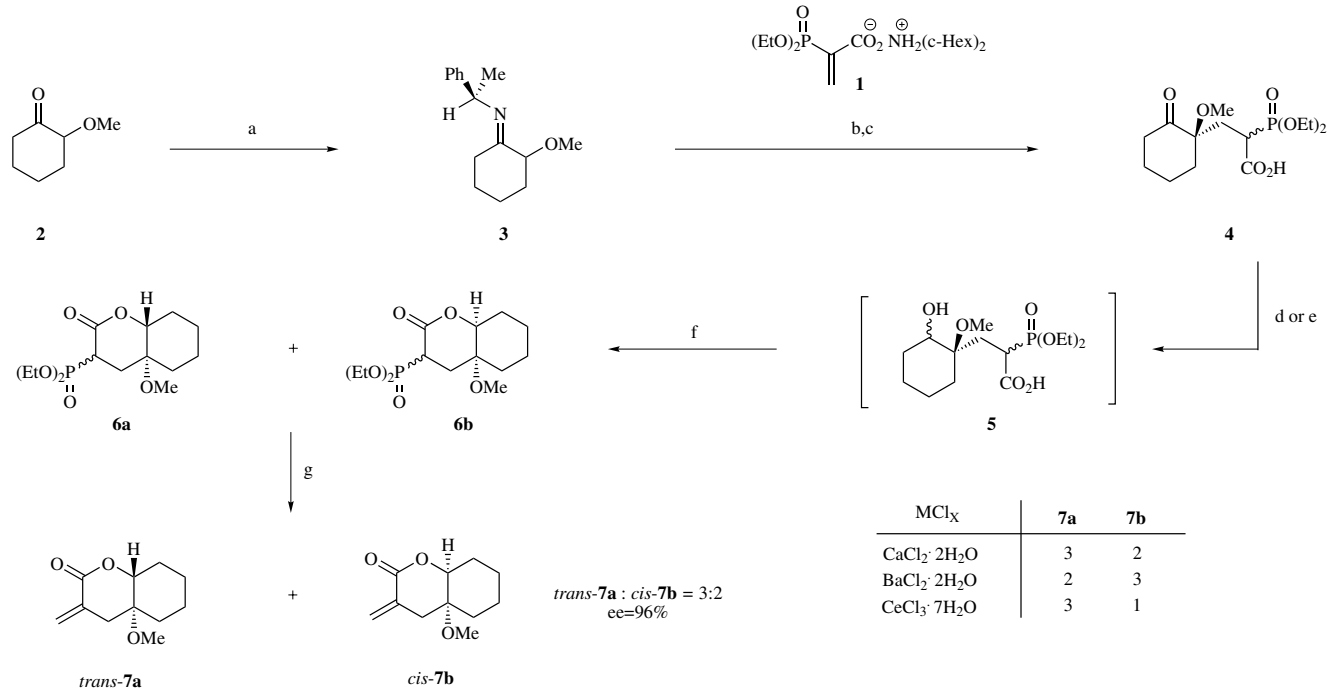
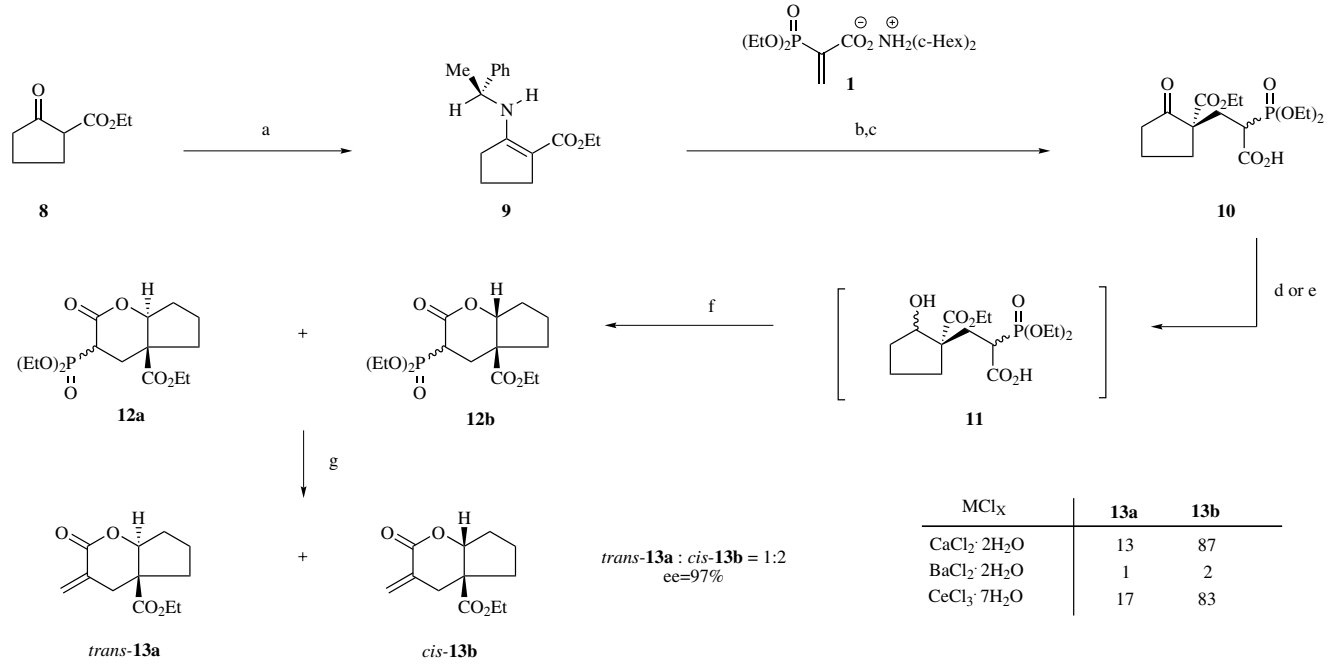
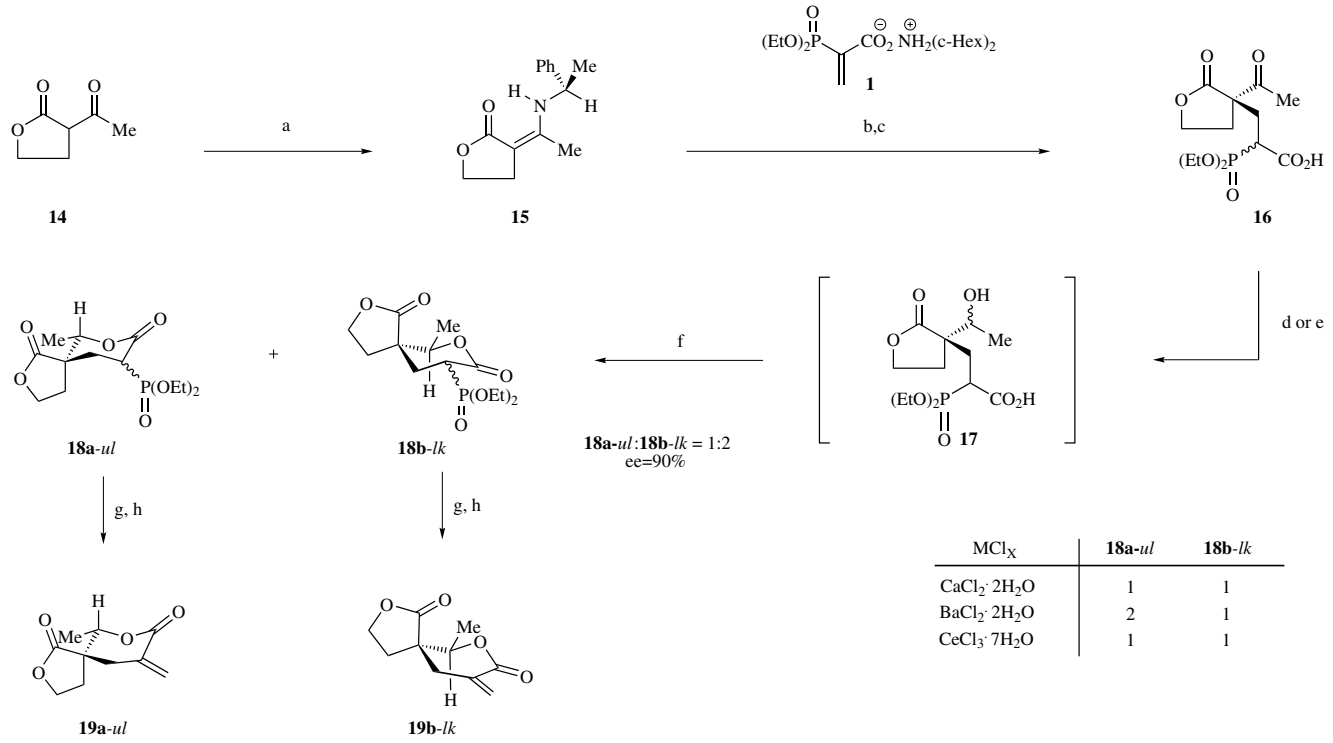


Scheme 1. Reagents and conditions: (a) (*R*)-phenylethylamine, SiO_2, Al_2O_3, molecular sieves 5 Å, rt, 6 days, 85%; (b) benzene, rt, 48 h; (c) Dowex 50W, acetone/water, 80%; (d) MeOH, KBH_4 (2 equiv), rt, 24 h; (e) MeOH, MCl_X (1 equiv), KBH_4 (2 equiv), −70 °C, 1 h, rt, 24 h; (f) TFAA (1 equiv), toluene, rt, 24 h, 70%; (g) *t*-BuOK (1 equiv), *t*-BuOH, $(HCHO)_n$ (5 equiv), Et_2O, rt, 1 h, 80%.



Scheme 2. Reagents and conditions: (a) (*R*)-phenylethylamine, $BF_3{\cdot}OEt_2$ (cat), benzene, reflux, 18 h, 90%; (b) benzene, rt, 48 h; (c) Dowex 50W, acetone/water, 86%; (d) MeOH, KBH_4 (2 equiv), rt, 24 h; (e) MeOH, MCl_X (1 equiv), KBH_4 (2 equiv), −70 °C, 1 h, rt, 24 h; (f) TFAA (1 equiv), toluene, rt, 24 h, 70%; (g) *t*-BuOK (1 equiv), *t*-BuOH, $(HCHO)_n$ (5 equiv), Et_2O, rt, 1 h, 75%.

16 were converted to α-methylene-δ-valerolactones **7**, **13**, and **19** by a standard procedure. Reduction of the carbonyl group was easily accomplished under mild conditions with KBH_4 in methanol. Lactonization of the hydroxyacids obtained **5**, **11**, and **17** was performed in toluene at room temperature in the presence of trifluoroacetic anhydride as the dehydrating agent,[7] and provided the phosphonolactones **6**, **12**, and **18**, each as a mixture of two diastereoisomers. ^{31}P NMR spectra of these compounds revealed the presence of two signals in ratios of 1:1, 2:1, and 2:1, respectively.



Scheme 3. Reagents and conditions: (a) (*R*)-phenylethylamine, $BF_3{\cdot}OEt_2$ (cat), benzene, reflux, 18 h, 90%; (b) benzene, rt, 48 h; (c) Dowex, acetone/water, 80%; (d) MeOH, KBH_4 (2 equiv), rt, 24 h; (e) MeOH, MCl_X (1 equiv), KBH_4 (2 equiv), −70 °C, 1 h, rt, 24 h; (f) TFAA (1 equiv), toluene, rt, 24 h, 85%; (g) column chromatography; (h) *t*-BuOK (1 equiv), *t*-BuOH, $(HCHO)_n$ (5 equiv), benzene, rt, 1 h, 85%.

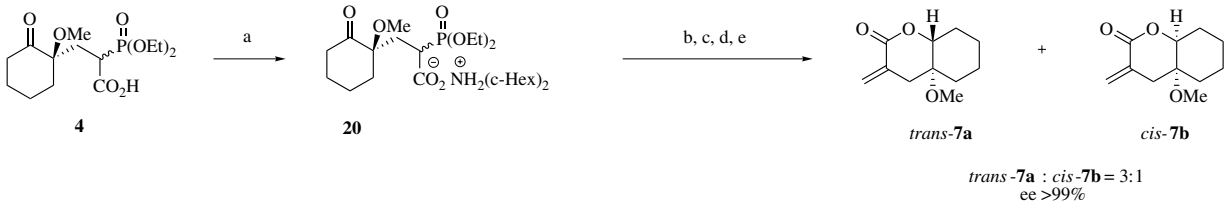
The mixtures of diastereoisomeric lactones **6** and **12** could not be separated by column chromatography. On the contrary, **18a**-*ul* and **18b**-*lk* diastereoisomers of lactone **18** were easily isolated by this method. Finally, the HWE reaction of the phosphonolactones **6**, **12**, **18a**-*ul*, and **18b**-*lk* afforded the corresponding α-methylene-δ-valerolactones **7**, **13**, **19a**-*ul*, and **19b**-*lk*. Lactones **7** and **13** were formed as mixtures of *trans*- and *cis*-diastereoisomers in ratios of 3:2 and 1:2, respectively. These ratios reflect the degree of diastereoselection, which is attained in the reduction of oxoacids **4** and **10**. On the other hand, the diastereoselectivity of the reduction of oxoacid **16** is expressed by the ratio of diastereoisomeric α-phosphonolactones **18a**-*ul*:**18b**-*lk* = 1:2.

In order to find an effective, alternative procedure for the highly diastereoselective synthesis of lactones **7**, **13**, and **19** we examined the stereoselectivity of reduction of the corresponding oxoacids **4**, **10**, and **16** with KBH_4 in the presence of metal chlorides such as $CaCl_2{\cdot}2H_2O$, $BaCl_2{\cdot}2H_2O$, and $CeCl_3{\cdot}7H_2O$.[8] Under these conditions, the reductions of acid **4** in the presence of $CeCl_3$ (*trans*-**7a**:*cis*-**7b** = 3:1) and acid **10** in the presence of $CaCl_2$ (*trans*-**13a**:*cis*-**13b** = 13:87) or $CeCl_3$ (*trans*-**13a**:*cis*-**13b** = 17:83) were more diastereoselective then those with KBH_4. On the other hand, reduction of **4** and **16** in the presence of $BaCl_2$ gave the expected products, but with reverse diastereoselectivity. No change of selectivity was observed in the reduction of **4** with $CaCl_2/KBH_4$ and **10** with $BaCl_2/KBH_4$ systems.

The mixtures of diastereoisomeric lactones **7** and **13** were separated by column chromatography. Pure diastereoisomers *trans*-**7a** and **19b**-*lk* were isolated as crystalline solids.

The enantiomeric purities of the lactones **7**, **13**, and **19** were established unambiguously by chiral GC analysis and in comparison with the authentic racemic samples. The highest level of enantiomeric excesses of 97% and 96% were obtained for the lactones **13** and **7**, respectively, while the enantiomeric excess of spirolactone **19** did not exceed 90%. In addition, the enantiomeric excess of acid **4** was further enhanced by a single recrystallization of its dicyclohexylammonium salt **20** (Scheme 4) from ethyl acetate. Salt **20** was converted by standard means into lactone **7** with 99% ee. The enantiomeric purity of lactone **19b**-*lk* was enhanced to 97% by a single recrystallization from diethyl ether.

The assignment of absolute configuration to the acids **4**, **10**, and **16** and lactones **7**, **13**, and **19** was based on X-ray crystallographic analysis of lactones *trans*-**7a** and **19**-*lk*. The absolute stereochemistry of lactone *trans*-**7a** was determined to be (4a*R*,8a*R*).[9] This result indicates that the quaternary stereogenic center of acid **4** has an (*R*)-configuration meaning that lactone *cis*-**7b** is undoubtedly the (4a*R*,8a*S*)-isomer. The absolute configuration of lactone **19b**-*lk* was determined to be (5*R*,6*R*) as shown in Figure 1. As a consequence, the stereochemistry at the quaternary stereogenic center in the acid **16** was assigned to be *R* and therefore the lactone **19a**-*ul* must be (5*R*,6*S*)-isomer.



Scheme 4. Reagents and conditions: (a) $(C_6H_{11})_2NH$, crystallization from EtOAc; (b) Dowex, 50W, acetone/water, 80%; (c) MeOH, KBH_4 (2 equiv), rt, 24 h; (d) TFAA (1 equiv), toluene, rt, 24 h; 70%; (e) *t*-BuOK (1 equiv), *t*-BuOH, $(HCHO)_n$ (5 equiv), Et_2O, rt, 1 h, 80%.

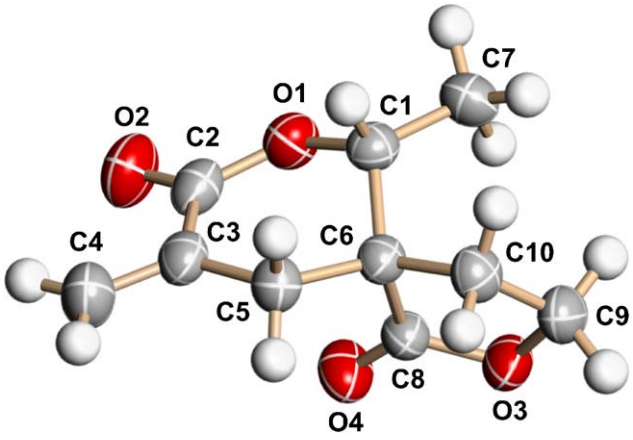


Figure 1. View of the **19b**-*lk* with atom numbering. Displacement ellipsoids were drawn at the 50% probability level.

The structure of **19b**-*lk* was determined by the single crystal X-ray diffraction analysis. The molecule investigated adopts an unusual spiro conformation with the γ-lactone and δ-lactone rings sharing the pivotal C6 atom and strongly twisted in respect to one another. While the single γ-lactone and δ-lactone fragments exist in a number of investigated crystal structures their combined arrangement is unique among crystal structures reported to date.[10] The former ring adopts an envelope conformation with the C9 atom shifted out of the O3, C8, C6, and C10 plane, while the δ-lactone ring exists in the distorted half-chair arrangement with the C1, O1, C2, C3, and C5 atoms approximately coplanar and the C6 atom situated at the flap. Within the δ-lactone fragment both exocyclic double bonds O2=C2 [1.212(2) Å] and C3=C4 [1.320(2) Å] are shorter than similar bonds observed in the O=C–C_α=C_β moiety[11] (1.222 and 1.340 Å). These bonds are separated by a relatively long C2–C3 bond [1.484(2), standard value 1.465 Å] and are not strictly coplanar, as shown by a non-zero value of the O2=C2–C3=C4 torsion angle [−7.9(2)°]. These results suggest that the highly polar character of the C2=O2 carbonyl group hinders π electron density delocalization within the O=C–C_α=C_β fragment of the molecule. The exocyclic O4 atom is involved in two intramolecular interactions, namely with atoms C2 and C3 of the O=C–C_α=C_β moiety, the respective interatomic distances: 3.060(2) and 3.064(2) Å are shorter than the sum of oxygen and carbon van der Waals radii: 3.22 Å.[12] As indicated by the natural bond orbital analysis[13] calculated at the RHF/6-311 + G(d,p) level (Gaussian 03[14]) those unusual, through space,[15] interactions follow from the overlapping of the occupied n_π lone pair orbital of the O4 atom with the vacant π* unoccupied of the C2=O2 and C3=C4 double bonds (Table 1 and Fig. 2). The molecular conformation is also affected by the mutual *anti* σ–σ* stereoelectronic interactions[16] of the endocyclic C2–O1 and exocyclic vinyl C3=C4 bond (9.17 and 5.03 kJ mol^{-1}).

Table 1. Energy of the selected non-bonding stereoelectronic interactions calculated with the natural bond orbital theory at the RHF/6-311+G(d,p) level of theory (Gaussian 03) for the X-ray determined coordinates

Interaction	Stabilization energy (kJ/mol)
n_π(O4)–π*(C2=O2)	1.31
n_π(O4)–π*(C3=C4)	1.80
σ(C3=C4)–σ*(C2–O1)	9.17
σ(C2–O1)–σ*(C3=C4)	5.03

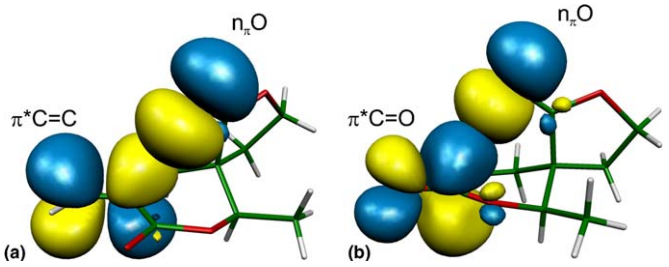


Figure 2. Natural bond orbitals involved in the stabilizing through space interactions: (a) n_π(O4)–π*(C2=O2); (b) n_π(O4)–π*(C3=C4).

The absolute configuration at the quaternary stereogenic center in adducts **4** and **16** is fully consistent with the transition-state model proposed for asymmetric Michael addition of chiral imines to electron-deficient alkenes[17] and with the results of our earlier studies.[2] The alkylation occurs preferentially on the less hindered π-face at the more substituted secondary enamine, in tautomeric equilibrium with the starting imine, *anti*- to the phenyl group. By analogy with the above results, the absolute configuration at the quaternary stereogenic center in adduct **10** was assigned to be *S*. Therefore, the absolute configuration of lactone *trans*-**13a** must be (4a*S*,7a*S*) while that of *cis*-**13b** which differs in configuration at around C-7a is 4a(*S*), 7a(*R*).

3. Conclusions

In summary, we have demonstrated that the asymmetric Michael reactions of chiral imines to acrylate **1** can be

exploited for highly enantioselective and diastereoselective synthesis of multifunctional α-methylene-δ-valerolactones containing adjacent quaternary and tertiary stereogenic centers.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for ^{1}H and 62.9 MHz for ^{13}C and 101.3 MHz for ^{31}P NMR, respectively, using tetramethylsilane as internal and 85% H_3PO_4 as external standard. The multiplicities of carbons were determined by DEPT experiments. IR spectra were measured on Specord M80 (Zeiss) instrument. Gas chromatographic analyses were obtained on Hewlett–Packard 5890 II instrument equipped with γ-Dex 225 column. Elemental analyses were performed on Perkin–Elmer PE 2400 analyzer. Melting points were determined in open capillaries and are uncorrected. Dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate **1** was prepared according to the literature procedure.[18]

4.2. General procedure for the preparation of phosphoalkanoic acids 4, 10, and 16

A mixture of acrylate **1** (3.89 g, 0.01 mol) and imine (0.011 mol) in benzene (50 ml) was stirred at room temperature for 48 h. After the reaction was completed (^{31}P NMR), the solvent was evaporated and the residue was subjected to ion-exchange chromatography performed on a glass column packed with Dowex 50W using H_2O/acetone, 1:1 as eluent. The eluent was evaporated to give the acid as colorless oil.

4.2.1. 2-(Diethoxyphosphoryl)-3-(1-methoxy-2-oxocyclohexyl)propanoic acid 4. (2.69 g, 80% yield); diastereoisomer ratio 1:1; colorless oil; IR (film) 1759, 1685, 1453, 1256 cm^{-1}; ^{31}P NMR ($CDCl_3$): $\delta = 24.48$, 24.86; ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (t, 6H, $^{3}J_{HH} = 7.0$, $2\times C\mathit{H}_3CH_2OP$), 1.44–1.76 (m, 2H, $C\mathit{H}_2$), 1.90–2.15 (m, 4H, $2\times C\mathit{H}_2$), 2.18–2.37 (m, 2H, $C\mathit{H}_2$), 2.48–2.71 (m, 2H, $C\mathit{H}_2$), 3.02–3.20 (m, 1H, C*H*P), 3.11 (s) and 3.13 (s), (3H, $C\mathit{H}_3$), 4.21 (m, 2H, $2\times C\mathit{H}_2OP$); ^{13}C NMR ($CDCl_3$): $\delta = 15.75$ (d, $^{3}J_{CP} = 6.1$, $2\times C\mathit{H}_3CH_2OP$), 20.14 and 20.50 ($C\mathit{H}_2$), 26.94 and 27.30 ($C\mathit{H}_2$), 28.22 (d, $^{2}J_{CP} = 4.1$) and 28.34 (d, $^{2}J_{CP} = 4.1$), ($C\mathit{H}_2$), 36.01 and 36.44 ($C\mathit{H}_2$), 38.88 and 39.16 ($C\mathit{H}_2$), 38.89 (d, $^{1}J_{CP} = 129.7$) and 38.96 (d, $^{1}J_{CP} = 129.7$), (*C*HP), 50.39 and 50.44 ($C\mathit{H}_3O$), 62.76 (d, $^{2}J_{CP} = 5.8$) and 62.85 (d, $^{2}J_{CP} = 5.8$), ($C\mathit{H}_2OP$), 63.12 (d, $^{2}J_{CP} = 5.9$) and 63.20 (d, $^{2}J_{CP} = 5.9$), ($C\mathit{H}_2OP$), 81.44 (d, $^{3}J_{CP} = 13.1$) and 81.55 (d, $^{3}J_{CP} = 13.5$), (C), 170.20 (d, $^{2}J_{CP} = 5.0$) and 170.68 (d, $^{2}J_{CP} = 5.0$), (*C*OOH), 211.04 and 211.57 (*C*O); Anal. Calcd for $C_{14}H_{25}O_7P$: C, 50.00; H, 7.49. Found: C, 50.53; H, 7.38.

4.2.2. 2-(Diethoxyphosphoryl)-3-(1-(ethoxycarbonyl)-2-oxocyclopentyl)propanoic acid 10. (3.13 g, 86% yield); diastereoisomer ratio 1:1; colorless oil; IR (film) 1735, 1713, 1222 cm^{-1}; ^{31}P NMR ($CDCl_3$) $\delta = 23.63$, 23.58; ^{1}H NMR ($CDCl_3$) $\delta = 1.23$ (t, $^{3}J_{HH} = 7.1$) and 1.24 (t, $^{3}J_{HH} = 6.9$), (3H, $C\mathit{H}_3CH_2OC$), 1.33 (t, $^{3}J_{HH} = 7.0$) and 1.35 (t, $^{3}J_{HH} = 7.0$), (3H, $2\times C\mathit{H}_3CH_2OP$), 1.90–2.10 (m, 4H, $2\times C\mathit{H}_2$), 2.21–2.58 (m, 4H, $2\times C\mathit{H}_2$), 3.21 (ddd, $^{3}J_{HH} = 1.5$, $^{3}J_{HH} = 10.2$, $^{2}J_{HP} = 25.9$) and 3.32 (ddd, $^{3}J_{HH} = 1.5$, $^{3}J_{HH} = 10.2$, $^{2}J_{HP} = 24.9$), (1H, C*H*P), 4.05–4.21 (m, 6H, $2\times C\mathit{H}_2OP$, $C\mathit{H}_2OC$); ^{13}C NMR ($CDCl_3$) $\delta = 13.64$ and 13.68 ($C\mathit{H}_3CH_2CO$), 15.92 (d, $^{3}J_{CP} = 6.3$) and 15.96 (d, $^{3}J_{CP} = 6.1$), ($2\times C\mathit{H}_3CH_2OP$), 19.22 and 19.43 ($C\mathit{H}_2$), 29.60 (d, $^{2}J_{CP} = 3.3$) and 29.80 (d, $^{2}J_{CP} = 4.4$), ($C\mathit{H}_2$), 32.00 and 33.93 ($C\mathit{H}_2$), 37.00 and 37.58 ($C\mathit{H}_2$), 41.62 (d, $^{1}J_{CP} = 126.6$) and 41.84 (d, $^{1}J_{CP} = 126.9$), (*C*HP), 59.11 (d, $^{3}J_{CP} = 13.1$) and 59.69 (d, $^{3}J_{CP} = 13.9$), (*C*), 61.24 and 61.30 ($C\mathit{H}_2OC$), 62.82 (d, $^{2}J_{CP} = 6.6$) and 63.00 (d, $^{2}J_{CP} = 6.6$), ($C\mathit{H}_2OP$), 63.13 (d, $^{2}J_{CP} = 6.6$) and 63.31 (d, $^{2}J_{CP} = 6.6$), ($C\mathit{H}_2OP$), 169.70 and 170.9 ($COOCH_2CH_3$), 170.6 (d, $^{2}J_{CP} = 5.1$) and 171.0 (d, $^{2}J_{CP} = 5.1$), (*C*OOH), 213.7 and 214.4 (*C*O). Anal. Calcd for $C_{15}H_{25}O_8P$: C, 49.45; H, 6.92. Found: C, 49.53; H, 6.86.

4.2.3. 3-(3-Acetyl-2-oxo-tetrahydrofuran-3-yl)-2-(diethoxyphosphoryl)propanoic acid 16. (2.69 g, 80% yield); diastereoisomer ratio 1:1; colorless oil; IR (film); 1759, 1696, 1245, 1150 cm^{-1}; ^{31}P NMR ($CDCl_3$) $\delta = 23.10$, 23.00; ^{1}H NMR ($CDCl_3$) $\delta = 1.30$ (t, 3H, $^{3}J_{HH} = 7.0$, $C\mathit{H}_3CH_2OP$), 1.34 (t, 3H, $^{3}J_{HH} = 7.0$, $C\mathit{H}_3CH_2OP$), 2.02–2.21 (m, 2H, $C\mathit{H}_2$), 2.32 (s, 3H, $C\mathit{H}_3$), 2.40–3.00 (m, 3H, $C\mathit{H}_2$, C*H*P), 4.08–4.38 (m, 6H, $C\mathit{H}_2O$, $2\times C\mathit{H}_2OP$); ^{13}C NMR ($CDCl_3$) $\delta = 16.00$ (d, $^{3}J_{CP} = 5.9$, $2\times C\mathit{H}_3CH_2OP$), 25.40 and 25.60 ($C\mathit{H}_3$), 28.51 and 29.72 ($C\mathit{H}_2$), 29.91 (d, $^{2}J_{CP} = 3.0$) and 30.93 (d, $^{2}J_{CP} = 3.2$), ($C\mathit{H}_2CHP$), 42.11 (d, $^{1}J_{CP} = 128.0$) and 42.64 (d, $^{1}J_{CP} = 129.0$), (*C*HP), 60.52 (d, $^{3}J_{CP} = 14.7$) and 60.71 (d, $^{3}J_{CP} = 15.2$), (*C*), 63.23 (d, $^{2}J_{CP} = 7.0$) and 63.41 (d, $^{2}J_{CP} = 7.0$), ($C\mathit{H}_2OP$), 63.62 (d, $^{2}J_{CP} = 6.8$) and 63.71 (d, $^{2}J_{CP} = 6.8$), ($C\mathit{H}_2OP$), 66.22 and 66.52 ($C\mathit{H}_2OC$), 170.21 (d, $^{2}J_{CP} = 4.4$) and 170.53 (d, $^{2}J_{CP} = 4.4$), (*C*OOH), 174.73 and 175.25 (*C*OO), 201.62 and 202.13 (*C*O). Anal. Calcd for $C_{13}H_{21}O_8P$: C, 46.43; H, 6.29. Found: C, 46.38; H, 6.37.

4.3. General procedure for the preparation of phosphonolactones 6, 12, and 18

To a stirred solution of **4** (2.69 g, 0.008 mol) in methanol (50 ml) was added KBH_4 (0.86 g, 0.016 mol). Stirring was continued for 24 h at room temperature. The resulting mixture was neutralized to pH ~3 with 5% HCl. The solvent was evaporated and the residue diluted with water (20 ml) and extracted with chloroform (3×20 ml). The organic layer was dried over $MgSO_4$ and evaporated. The oily residue was dissolved in toluene (20 ml) and trifluoroacetic anhydride (1.68 g, 0.008 mol) added. The resulting solution was stirred for 24 h at room temperature. The solvent was evaporated and the residue was dissolved in chloroform (50 ml), washed with saturated aq $NaHCO_3$ solution (1×15 ml) and H_2O (2×15 ml), dried over $MgSO_4$, and evaporated. The oily residue was purified by column chromatography on silica gel using ethyl acetate/hexane (3:1) as eluent to give pure lactone **6**.

4.3.1. Diethyl 4a-methoxy-2-oxo-octahydro-2*H*-chromen-3-ylphosphonate 6. (1.79 g, 70% yield); diastereoisomer ratio 1:1; colorless oil; IR (film); 1790, 1455, 1267,

1194 cm^{-1}; ^{31}P NMR ($CDCl_3$): $\delta = 23.79, 23.66$; ^1H NMR ($CDCl_3$): $\delta = 1.36$ (t, 3H, $^3J_{HH} = 7.0$, CH_3CH_2OP), 1.39 (t, 3H, $^3J_{HH} = 7.0$, CH_3CH_2OP), 1.30–1.63 (m, 4H, $2 \times CH_2$), 1.70–1.95 (m, 2H, CH_2), 2.00–2.40 (m, 4H, $2 \times CH_2$), 3.19 (s) and 3.25 (s), (3H, CH_3O), 3.10–3.40 (m, 1H, CHP), 4.19–4.36 (m, 5H, $2 \times CH_2OP$, CHO); ^{13}C NMR ($CDCl_3$): δ 15.99 (d, $^3J_{CP} = 5.0$, CH_3CH_2OP), 16.09 (d, $^3J_{CP} = 5.0$, CH_3CH_2OP), 19.86 and 21.71 (CH_2), 22.88 and 23.31 (CH_2), 25.51 (d, $^2J_{CP} = 3.5$) and 28.45 (d, $^2J_{CP} = 3.5$), (CH_2CHP), 26.49 and 29.69 (CH_2), 30.17 and 31.44 (CH_2), 36,64 (d, $^1J_{CP} = 146.5$) and 37.80 (d, $^1J_{CP} = 145.0$), (CHP), 48.09 and 48.33 (CH_3O), 63.41 (d, $^2J_{CP} = 5.5$) and 63.52 (d, $^2J_{CP} = 5.5$), (CH_2OP), 64.48 (d, $^2J_{CP} = 6.9$) and 64.61 (d, $^2J_{CP} = 6.9$), (CH_2OP), 70.34 (d, $^3J_{CP} = 9.1$) and 72.13 (d, $^3J_{CP} = 10.0$), (C), 81.85 and 83.86 (CHO), 165.40 (d, $^2J_{CP} = 3.3$) and 165.67 (d, $^2J_{CP} = 3.3$), (COO). Anal. Calcd for $C_{14}H_{25}O_6P$: C, 52.49; H, 7.87. Found: C, 52.60; H, 7.79.

4.3.2. Ethyl 3-(diethoxyphosphoryl)-2-oxo-octahydrocyclopenta[*b*]pyran-4a-carboxylate 12. (1.95 g, 70% yield); diastereoisomer ratio 2:1; colorless oil; IR (film); 1731, 1247, 1142 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ 20.91, 21.31; ^1H NMR ($CDCl_3$): δ 1.29 (t, 3H, $^3J_{HH} = 7.2$, CH_3CH_2OC), 1.32 (t, 3H, $^3J_{HH} = 6.8$, $2 \times CH_3CH_2OP$, major), 1.36 (t, 3H, $^3J_{HH} = 7.1$, $2 \times CH_3CH_2OP$, minor), 1.70–1.80 (m, 2H, CH_2), 1.85–2.00 (m, 2H, CH_2), 2.03–2.10 (m, 3H, $CHCH_2P$, CH_2), 2.75 (dt, 1H, $^3J_{HP} = {}^3J_{HH} = 4.3$, $^2J_{HH} = 14.0$, $CHCH_2P$, major), 2.81 (ddd, 1H, $^3J_{HP} = 2.8$, $^3J_{HH} = 7.5$, $^2J_{HH} = 14.0$, CHCHP, minor), 2.98 (ddd, 1H, $^3J_{HH} = 4.3$, $^3J_{HH} = 13.6$, $^2J_{HP} = 23.3$, CHP, major), 3.09 (ddd, 1H, $^3J_{HH} = 5.8$, $^3J_{HH} = 7.5$, $^2J_{HP} = 25.5$, CHP, minor), 4.10–4.25 (m, 6H, $2 \times CH_2OP$, CH_2OC), 4.26–4.30 (m, 1H, CHO, minor), 4.96 (t, 1H, $^3J_{HH} = 4.9$, CHO, major); ^{13}C NMR ($CDCl_3$): δ 13.55 (CH_3CH_2OC, major), 13.62 (CH_3CH_2OC, minor), 16.03 (d, $^3J_{CP} = 4.7$, $2 \times CH_3CH_2OP$, major), 16.12 (d, $^3J_{CP} = 4.7$, $2 \times CH_3CH_2OP$, minor), 19.61 (CH_2, minor), 22.51 (CH_2, minor), 28.72 (d, $^2J_{CP} = 4.0$, CH_2CHP, major), 30.15 (d, $^2J_{CP} = 2.5$, CH_2CHP, minor), 33,25 (CH_2, major), 34.41 (CH_2, minor), 36.42 (CH_2, major), 36.74 (CH_2, minor), 38.55 (d, $^1J_{CP} = 151.2$, CHP, major), 39.73 (d, $^1J_{CP} = 129.2$, CHP, minor), 50.05 (d, $^3J_{CP} = 7.8$, C, minor), 51.81 (d, $^3J_{CP} = 13.2$, C, major), 60.91 (CH_2OC, minor), 61.32 (CH_2OC, major), 62.51 (d, $^2J_{CP} = 7.0$, CH_2OP, major), 62.93 (d, $^2J_{CP} = 6.9$, CH_2OP, minor), 63.21 (d, $^2J_{CP} = 7.0$, CH_2OP, major), 63.83 (d, $^2J_{CP} = 6.9$, CH_2OP, minor), 83.82 (CHO, minor), 85.02 (CHO, major), 166.93 (d, $^2J_{CP} = 3.8$, COO, major), 165.91 (d, $^2J_{CP} = 3.8$, COO, minor), 172.61 ($COOCH_2CH_3$, minor), 174.13 ($COOCH_2CH_3$, major). Anal. Calcd for $C_{15}H_{25}O_7P$: C, 51.72; H, 7.23. Found: C, 51.59; H, 7.35.

4.3.3. 6-Methyl-1,8-dioxo-2,7-dioxa-spiro[4.5]dec-9-yl-phosphonic acid diethyl ester 18a-*ul* and 18b-*lk*. (2.05 g, 80% yield); diastereoisomer ratio 2:1; colorless oil; IR (film) 1795, 1776, 1267, 1190 cm^{-1}. Anal. Calcd for $C_{13}H_{21}O_7P$: C, 48.75; H, 6.61. Found: C, 48.65; H, 6.73.

Lactones **18a**-*ul* and **18b**-*lk* were separated by column chromatography on silica gel using ethyl acetate/acetone (2:1) as eluent.

4.3.3.1. Diastereoisomer 18a-*ul*. ^{31}P NMR ($CDCl_3$): δ 21.00; ^1H NMR ($CDCl_3$): $\delta = 1.34$ (d, 3H, $^3J_{HH} = 6.5$, CH_3), 1.37 (t, 6H, $^3J_{HH} = 7.2$, $2 \times CH_3CH_2OP$), 2.00–2.33 (m, 2H, CH_2), 2.47–2.65 (m, 2H, CH_2), 3.32 (dt, 1H, $^3J_{HP} = 7.5$, $^2J_{HP} = 28.2$, CHP), 4.16–4.48 (m, 6H, $2 \times CH_2OP$, CH_2O), 4.76 (q, 1H, $^3J_{HH} = 6.5$, CHO); ^{13}C NMR ($CDCl_3$): δ 15.72 (CH_3), 15.82 (d, $^3J_{CP} = 3.5$, CH_3CH_2OP), 16.03 (d, $^3J_{CP} = 3.5$, CH_3CH_2OP), 25.43 (CH_2), 30.93 (d, $^2J_{CP} = 3.0$, CH_2), 37.15 (d, $^1J_{CP} = 137.4$, CHP), 45.62 (d, $^3J_{CP} = 8.2$, C), 63.01 (d, $^2J_{CP} = 6.9$, CH_2OP), 63.54 (d, $^2J_{CP} = 6.9$, CH_2OP), 65.42 (CH_2O), 78.25 (CHO), 164.61 (d, $^2J_{CP} = 5.1$, COO), 176.73 (COO).

4.3.3.2. Diastereoisomer 18b-*lk*. ^{31}P NMR ($CDCl_3$): δ 22.01; ^1H NMR ($CDCl_3$): δ 1.36 (t, 6H, $^3J_{HH} = 7.0$, $2 \times CH_3CH_2OP$); 1.44 (d, 3H, $^3J_{HH} = 6.5$, CH_3), 2.27–2.45 (m, 4H, $2 \times CH_2$), 3.60 (dt, 1H, $^3J_{HP} = 9.0$, $^2J_{HP} = 27.0$, CHP), 4.10–4.46 (m, 6H, $2 \times CH_2OP$, CH_2O), 4.67 (q, 1H, $^3J_{HH} = 6.5$, CHO); ^{13}C NMR ($CDCl_3$): δ 15.51 (d, $^3J_{CP} = 3.3$, CH_3CH_2OP), 15.63 (d, $^3J_{CP} = 3.3$, CH_3CH_2OP), 16.19 (CH_3), 30.10 (d, $^2J_{CP} = 3.2$, CH_2), 31,03 (CH_2), 37.12 (d, $^1J_{CP} = 137.0$, CHP), 42.52 (d, $^3J_{CP} = 6.3$, C), 62.11 (d, $^2J_{CP} = 6.8$, CH_2OP), 63.14 (d, $^2J_{CP} = 6.8$, CH_2OP), 64.91 (CH_2O), 78.85 (CHO), 164.21 (d, $^2J_{CP} = 6.3$, COO), 176.01 (COO).

4.4. General procedure for the preparation of methylene-lactones 7, 13, and 19

To a stirred solution of α-phosphonolactone **6** (1.92 g, 0.0060 mol) in diethyl ether (50 ml), potassium *tert*-butoxide (0.74 g, 0.0066 mol) was added and the resulting mixture stirred for 15 min at room temperature. Then satd NaCl solution (20 ml) was added and the mixture extracted with diethyl ether (3×10 ml). The organic layer was dried over $MgSO_4$ and evaporated. The oily residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1:5) as eluent to give lactone **7**.

4.4.1. (4a*R*,8a*R*)- and (4a*R*,8a*S*)-4a-Methoxy-3-methylene-octahydrochromen-2-one 7a and 7b. (0.88 g, 80% yield); *trans*:*cis* ratio 3:2; IR (film); 3089, 1774, 1633, 1456, 1242 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.24; H, 8.29.

4.4.1.1. Compound *trans*-7a. White crystals mp 118–120 °C; $[\alpha]_D^{25} = +80.0$ (*c* 0.65, MeOH); ^1H NMR ($CDCl_3$): δ 1.07–1.57 (m, 4H, $2 \times CH_2$), 1.80–2.06 (m, 4H, $2 \times CH_2$), 2.37 (dt, $^4J_{HH} = 2.5$, $^2J_{HH} = 16.5$, CH–C=), 2.88 (d, $^2J_{HH} = 16.5$, CH–C=), 3.13 (s, 3H, CH_3O), 4.20 (dd, 1H, $^3J_{HH} = 5.0$, $^3J_{HH} = 12.5$, CHO), 5.56 (t, 1H, $^2J_{HH} = {}^4J_{HH} = 2.5$, =CH), 6.47 (t, 1H, $^2J_{HH} = {}^4J_{HH} = 2.5$, =CH); ^{13}C NMR ($CDCl_3$): δ 19.96 (CH_2), 23.69 (CH_2), 26.68 (CH_2), 29.84 (CH_2), 36.30 (CH_2), 47.76 (CH_3O), 71.31 (C), 83.71 (CHO), 128.79 (=CH_2), 132.49 (C=), 165.11 (COO).

4.4.1.2. Compound *cis*-7b. Colorless oil; $[\alpha]_D^{25} = +4.2$ (*c* 1.12, MeOH); ^1H NMR ($CDCl_3$): δ 1.02–1.35 (m, 2H, CH_2), 1.50–1.71 (m, 4H, CH_2), 2.07–2.17 (m, 2H, CH_2), 2.60 (dt, 1H, $^4J_{HH} = 1.5$, $^2J_{HH} = 15.0$, CH–C=), 2.90 (dt, 1H, $^4J_{HH} = 2.5$, $^2J_{HH} = 15.0$, CH–C=), 3.23 (s, 3H,

CH_3), 4.34 (dd, 1H, $^3J_{HH} = 2.5$, $^3J_{HH} = 7.5$, C*H*O), 6.45 (dt, 1H, $^2J_{HH} = {}^4J_{HH} = 2.5$, $^4J_{HH} = 1.5$, =C*H*), 6.58 (dt, 1H, $^2J_{HH} = {}^4J_{HH} = 2.5$, $^4J_{HH} = 1.5$, =C*H*); ^{13}C NMR ($CDCl_3$): δ 21.15 (*C*H_2), 23.28 (*C*H_2), 26.65 (*C*H_2), 28.78 (*C*H_2), 33.68 (*C*H_2), 47.30 (*C*H_3O), 70.89 (*C*), 80.86 (*C*HO), 128.15 (=*C*H_2), 131.66 (*C*=), 164.40 (*C*OO).

4.4.2. (4a*S*,7a*S*)- and (4a*S*,7a*R*)-Ethyl 3-methylene-2-oxo-octahydrocyclopenta[*b*]pyran-4a-carboxylate 13a and 13b. (0.84 g, 75% yield); *trans*:*cis* ratio 1:2; IR (film); 3080, 1722, 1623, 1232 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_4$: C, 64.27; H, 7.19. Found: C, 64.03; H, 7.28.

4.4.3. Compound *trans*-13a. Colorless oil; $[\alpha]_D^{25} = -40.0$ (*c* 0.28, MeOH); ^{1}H NMR ($CDCl_3$); δ 1.23 (t, 3H, $^3J_{HH} = 7.2$, C*H*$_3$CH$_2$OC), 1.76–1.90 (m, 4H, 2 × C*H*$_2$), 1.95–2.16 (m, 2H, C*H*$_2$), 2.51 (dt, 1H, $^4J_{HH} = 2.7$, $^2J_{HH} = 16.5$, C*H*), 3.17 (dt, 1H, $^4J_{HH} = 1.5$, $^2J_{HH} = 16.5$, C*H*), 4.16 (q, 2H, $^3J_{HH} = 7.2$, CH$_2$OC), 4.28 (dd, 1H, $^3J_{HH} = 7.2$, $^3J_{HH} = 11.0$, C*H*O), 5.61 (dt, 1H, $^2J_{HH} = {}^4J_{HH} = 1.5$, $^4J_{HH} = 2.7$, C*H*), 6.52 (dt, 1H, $^2J_{HH} = {}^4J_{HH} = 1.5$, $^4J_{HH} = 2.7$, C*H*); ^{13}C NMR ($CDCl_3$): δ 13.68 (*C*H$_3$CH$_2$OC), 19.51 (*C*H$_2$), 26.23 (*C*H$_2$), 31.22 (*C*H$_2$), 37.05 (*C*H$_2$), 49.61 (*C*), 61.21 (*C*H$_2$O), 83.41 (*C*HO), 128.36 (*C*H$_2$), 133.25 (*C*), 166.29 (*C*OO), 172.59 (*C*OOCH$_2$CH$_3$).

4.4.3.1. Compound *cis*-13b. Colorless oil; $[\alpha]_D^{25} = -46.3$ (*c* 0.82, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, $^3J_{HH} = 7.0$, C*H*$_3$CH$_2$OC), 1.63–1.80 (m, 3H, C*H*$_2$, C*H*), 1.82–2.01 (m, 1H, C*H*), 2.10–2.24 (m, 2H, C*H*$_2$), 2.65 (d, 1H, $^2J_{HH} = 14.7$, C*H*), 3.02 (d, 1H, $^2J_{HH} = 14.7$, C*H*), 4.19 (q, 2H, $^3J_{HH} = 7.1$, CH$_2$OC), 5.12 (dd, 1H, $^3J_{HH} = 4.5$, $^3J_{HH} = 6.0$, C*H*O), 5.57 (d, 1H, $^2J_{HH} = 1.5$, C*H*), 6.30 (d, 1H, $^2J_{HH} = 1.5$, C*H*); ^{13}C NMR ($CDCl_3$): δ 13.81 (*C*H$_3$CH$_2$OC), 21.61 (*C*H$_2$), 33.55 (*C*H$_2$), 34.95 (*C*H$_2$), 51.36 (*C*), 61.21 (*C*H$_2$OC), 85.07 (*C*HO), 127.64 (*C*H$_2$), 131.96 (*C*), 165.56 (*C*OO), 173.91 (*C*OOCH$_2$CH$_3$).

4.4.4. (5*R*,6*R*)-6-Methyl-9-methylene-2,7-dioxa-spiro[4.5]-decane-1,8-dione 19b-*lk*. (1.00 g, 85% yield); white crystals mp 118–120 °C; $[\alpha]_D^{25} = 40.4$ (*c* 0.48, MeOH); IR (KBr); 3084, 1787, 1760, 1640, 1232 cm^{-1}; ^{1}H NMR ($CDCl_3$); δ 1.53 (d, 3H, $^3J_{HH} = 7.0$, C*H*$_3$), 2.22 (dt, 1H, $^3J_{HH} = 8.4$, $^2J_{HH} = 13.4$, C*H*–CH$_2$), 2.46 (ddd, 1H, $^3J_{HH} = 4.8$, $^3J_{HH} = 7.4$, $^2J_{HH} = 13.4$, C*H*–CH$_2$), 2.63 (dq, 1H, $^4J_{HH} = 1.0$, $^2J_{HH} = 16.6$, C*H*–C=), 3.17 (dt, 1H, $^4J_{HH} = 2.7$, $^2J_{HH} = 16.6$, C*H*–C=), 4.36 (ddd, 1H, $^3J_{HH} = 7.4$, $^3J_{HH} = 8.3$, $^2J_{HH} = 15.5$, C*H*O), 4.48 (ddd, 1H, $^3J_{HH} = 4.8$, $^3J_{HH} = 8.4$, $^2J_{HH} = 15.5$, C*H*O), 4.56 (dq, 1H, $^4J_{HH} = 1.0$, $^3J_{HH} = 7.0$, C*H*O), 5.69 (dt, 1H, $^4J_{HH} = 1.0$, $^4J_{HH} = {}^2J_{HH} = 2.1$, =C*H*), 6.57 (dt, 1H, $^4J_{HH} = 1.0$, $^4J_{HH} = {}^2J_{HH} = 2.1$, =C*H*); ^{13}C NMR ($CDCl_3$): δ 17.16 (*C*H$_3$), 32.51 (*C*H$_2$), 34.43 (*C*H$_2$), 44.60 (*C*), 64.75 (*C*H$_2$O), 77.81 (*C*HO), 131.96 (=*C*H$_2$, *C*), 163.62 (*C*OO), 175.63 (*C*OO). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.03; H, 6.33.

4.4.5. (5*R*,6*S*)-6-Methyl-9-methylene-2,7-dioxa-spiro[4.5]-decane-1,8-dione 19a-*ul*. (1.01 g, 85% yield); colourless oil; $[\alpha]_D^{25} = -62.7$ (*c* 0.69, MeOH); IR (KBr); 3084, 1787, 1760, 1640, 1232 cm^{-1}; ^{1}H NMR ($CDCl_3$); δ 1.36 (d, 3H, $^3J_{HH} = 6.4$, C*H*$_3$), 2.02 (dt, 1H, $^3J_{HH} = 7.0$, $^2J_{HH} = 14.0$, C*H*–CH$_2$O), 2.51 (dt, 1H, $^3J_{HH} = 7.8$, $^2J_{HH} = 14.0$, C*H*–CH$_2$O), 2.72 (dt, 1H, $^4J_{HH} = 1.0$, $^2J_{HH} = 16.0$, C*H*–C=), 3.06 (dt, 1H, $^4J_{HH} = 2.6$, $^2J_{HH} = 16.0$, C*H*–C=), 4.40 (dd, 2H, $^3J_{HH} = 7.0$, $^3J_{HH} = 7.8$, C*H*O), 4.72 (q, 1H, $^3J_{HH} = 6.4$, C*H*O), 5.74 (dt, 1H, $^4J_{HH} = 1.0$, $^4J_{HH} = {}^2J_{HH} = 2.6$, =C*H*), 6.61 (dt, 1H, $^4J_{HH} = 1.0$, $^4J_{HH} = {}^2J_{HH} = 2.6$, =C*H*); ^{13}C NMR ($CDCl_3$): δ 16.29 (*C*H$_3$), 25.98 (*C*H$_2$), 37.54 (*C*H$_2$), 46.19 (*C*), 65.51 (*C*H$_2$O), 78.19 (*C*HO), 129.94 (*C*), 131.35 (=*C*H$_2$), 163.73 (*C*OO), 176.83 (*C*OO). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.31; H, 6.13.

4.5. X-ray single crystal structure analysis for 19b-*lk*

Formula: $C_{10}H_{12}O_4$, $M_w = 196.20$, colorless crystal $0.40 \times 0.10 \times 0.05$ mm, $a = 6.3499(1)$, $b = 6.6755(1)$, $c = 22.1270(3)$ Å, $V = 937.94(2)$ Å^3, $\rho_{calcd} = 1.389$ g cm^{-3}, $\mu = 9.10$ cm^{-1}, semi-empirical absorption correction based on multiple scanned equivalent reflections[19] ($0.837 < T < 0.973$), $Z = 4$, crystal system: orthorhombic, space group: $P2_12_12_1$, $\lambda = 1.54178$ Å, $T = 293$ K, ω scans, 10,795 reflections collected ($\pm h, \pm k, \pm l$), $2\theta_{max} = 142°$, 1794 unique reflections ($R_{int} = 0.021$) and 1763 observed reflections [$I \geqslant 2\sigma(I)$], 176 refined parameters, refinement in F^2, $R_{all} = 0.029$, $wR(F^2) = 0.072$, max (min) residual electron density $\Delta\rho_{max} = 0.10\Delta\rho_{min} = -0.18$ e Å^{-3}, Flack parameter[20] with 712 Friedel pairs $\eta = 0.01(17)$, all hydrogen atoms refined with individual isotropic temperature factors. X-ray data were collected with Bruker SMART APEX CCD area detector diffractometer. Computer programs used: data collection SMART APEX,[21] data reduction SAINT-PLUS,[22] absorption correction SADABS,[23] structure solution, refinement, and molecular graphics SHELXTL.[24]

Crystallographic data (excluding structure factors) for the structure reported herein, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 294427. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Any request should be accompanied by a full literature citation.

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