Asymmetric Michael Additions via SAMP-/RAMP-Hydrazones Enantioselective Synthesis of β-Substituted δ-Oxopentanoates and δ-Lactones[1)]

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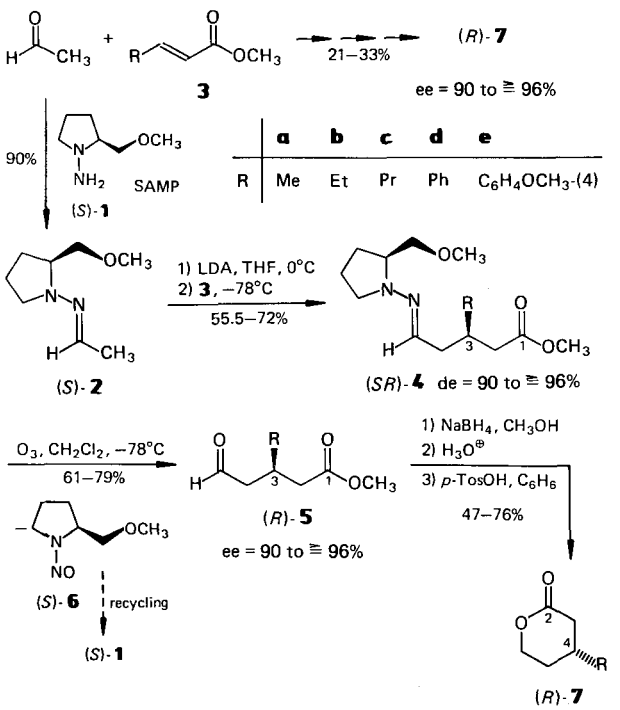
Asymmetric Michael addition of metalated acetaldehyde SAMP- or RAMP-hydrazone (*S*)- or (*R*)-**2** to α,β-unsaturated esters **3** and subsequent oxidative cleavage by ozonolysis yields the β-substituted δ-oxopentanoates (*R*)- or (*S*)-**5** with high enantiomeric excesses (ee = 90 to ≧ 96%). Racemization-free reduction and cyclization affords the corresponding optically active δ-lactones (*R*)- or (*S*)-**7**.

Asymmetrische Michael-Additionen via SAMP-/RAMP-Hydrazone. - Enantioselektive Synthese von β-substituierten δ-Oxopentansäureestern und δ-Lactonen[1)]

Asymmetrische Michael-Addition von metalliertem Acetaldehyd-SAMP- oder -RAMP-Hydrazon (*S*)- oder (*R*)-**2** an α,β-ungesättigte Carbonsäureester **3** liefert nach anschließender oxidativer Spaltung durch Ozonolyse die β-substituierten δ-Oxopentansäureester (*R*)- oder (*S*)-**5** in hohen Enantiomerenüberschüssen (ee = 90 bis ≧ 96%). Racemisierungsfreie Reduktion und Cyclisierung führt zu den entsprechenden optisch aktiven δ-Lactonen (*R*)- oder (*S*)-**7**.

Chiral δ-lactones are characteristic and crucial structural features of many biologically active and natural products and are of considerable interest as chiral building blocks in the synthesis of enantiomerically pure compounds. Thus, various enantioselective syntheses of δ-lactones have been developed recently[2-8].

Based on our SAMP-/RAMP-hydrazone methodology[9-17], we now report on an efficient and overall highly enantioselective, three-step synthesis of β-substituted δ-oxopentanoates **5** and their racemization-free transformation to the corresponding valerolactones **7**. As a key step we use the conjugate addition of acetaldehyde SAMP- or RAMP-hydrazone (*S*)- or (*R*)-**2** to enoates **3**, which occurs with high asymmetric induction. The aldehyde esters **5** thus obtained in high enantiomeric excesses (ee = 90 to ≧96%) are then reduced and cyclized to give the δ-lactones **7** with undiminished enantiomeric purities.



As is evident from the general scheme the new procedure is straightforward and based on readily available starting materials such as acetaldehyde and simple α,β-unsaturated esters **3**.

Acetaldehyde is transformed into its corresponding SAMP-hydrazone (*S*)-**2** by adding the freshly distilled carbonyl compound dropwise at 0°C to the enantiomerically pure hydrazine and stirring at room temperature over night. Workup and subsequent purification by short-path distillation affords the desired hydrazone in 90% yield. Metalation of (*S*)-**2** with lithium diisopropylamide (LDA) in tetrahydrofuran at 0°C followed by Michael addition of the so-formed chiral azaenolate to the α,β-unsaturated esters **3** at −78°C furnishes after aqueous workup and purification by kugelrohr distillation or column chromatography (silica gel; ether, *n*-pentane, 1:1) the product hydrazones (*SR*)-**4** with chemical yields ranging from 46 to 72% and high diastereoselectivities of 90 to ≧96% de. Racemization-free oxidative cleavage of the hydrazones (*SR*)-**4** by ozonolysis in dichloromethane at −78°C and separation of the nitrosamine (*S*)-**6** (recycling of the chiral auxiliary, LAH reduction) by column chromatography (silica gel; ether, *n*-pentane, 1:1) leads to the β-substituted δ-oxopentanoates (*R*)-**5** in high enantiomeric purities (ee = 90 to ≧96%) and 61–79% yield.

Reduction of the aldehyde-esters **5** with $NaBH_4$ in methanol at 0°C, hydrolysis with hydrochloric acid, and cyclization of the resulting δ-hydroxyesters by treatment with *p*-toluenesulfonic acid in refluxing benzene for two days affords the desired β-substituted δ-lactones (*R*)-**7**, which are

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Table 1. Optically active, β-substituted δ-oxopentanoates **5** prepared from acetaldehyde and enoates **3** via SAMP-/RAMP-hydrazone Michael additions

5	Overall yield (%) (3 steps)	B. p.[a] [°C/Torr]	α_D^{20} (neat)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	ee (%)[b]	Confg.
a	43	70–75/2.4[c]	−5.05°	−4.2 (0.71)[d]	≧96	(*R*)
a	37	70–75/2.3[c]	+5.1°	+4.3 (0.78)[d]	≧96	(*S*)[e]
b	37	85–95/1	+2.6°	–	90	(*R*)
c	40	90–95/2	−2.2°	−3.3 (0.65)	90	(*R*)
d	51	–[f]	−9.7°	–	≧96	(*R*)
e	30	140–160/0.02	−20.6°	−10.35 (1.45)	93	(*R*)

[a] Oven temperature of kugelrohr distillation. – [b] Determined by ^1H NMR-LIS [Eu(fod)$_3$, $CDCl_3$] on **4**. – [c] Ref.[12] b. p. 52°C/2 Torr. – [d] Ref.[13] $[\alpha]_D^{15}$ = + 4.64 (*c* = 7.56, $CHCl_3$) (*S*); ref.[14] $[\alpha]_D^{20}$ = −3.1 (*c* = 0.72, $CHCl_3$ (*R*)). – [e] RAMP was used as chiral auxiliary. – [f] Purification by column chromatography.

Table 2. Optically active, β-substituted δ-lactones **7** prepared by racemization-free reduction and cyclization of the aldehyde-esters **5**

7	Overall yield (%)	B. p.[a] [°C/Torr]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Ref. $[\alpha]_D$	ee (%)	Confg.
a	33	85–90/4[b]	+28.4 (0.89)	−23.6 (1)[3] (*S*) +27.61 (5.7)[14] (*R*)	≧96	(*R*)
a	27	80–85/3[b]	−28.2 (1.04)	−23.6 (1)[3] (*S*) +27.61 (5.7)[14] (*R*)	≧96	(*S*)
b	25	110–115/12	+24.1 (1)	−20.4 (1)[3] (*S*)	90	(*R*)
c	28	105–120/2[c]	+22.9 (8.1)	−26.0 (4.3)[6] (*S*)	90	(*R*)
d	24	130–140/0.02[d]	−4.79 (1.17)	−23.9 (8.6)[6] (*S*)	≧96	(*R*)
e	21	–[e]	−6.98 (0.96)	+3.63 (7.2)[6] (*S*) –	93	(*R*)

[a] Oven temperature of kugelrohr distillation. – [b] Ref.[3] b. p. 90°C/12 Torr. – [c] Ref.[15] b. p. 90–91°C/1.5 Torr. – [d] Ref.[2] b. p. 124–126°C/0.07 Torr. – [e] Purification by column chromatography.

purified by column chromatography (silica gel; ether, *n*-pentane, 5:1) and kugelrohr distillation. The chemical yields range from 47 to 76% and the enantiomeric excesses from 90 to ≧96%.

By using RAMP instead of SAMP as the chiral auxiliary the δ-lactones (*S*)-**7** of antipodal configuration may be obtained following the same reaction sequence. For instance, the optical antipode of **7a** starting with acetaldehyde-RAMP-hydrazone (*R*)-**2** was synthesized in this manner.

The asymmetric inductions of the Michael addition step were determined by ^1H NMR-shift experiments on the hydrazones **4** using Eu(fod)$_3$. In each case the shift experiments were also carried out with the correponding 1:1 epimeric mixtures of the hydrazones (*SS*)-/(*SR*)-**4**, which can be synthesized by Michael addition of acetaldehyde-dimethylhydrazone-cuprate[16] to the enoates **3**, followed by ozonolysis of the product hydrazones and reaction of the racemic components *rac*-**5** with SAMP. The diastereomeric excesses of the compounds **4** examined were shown to range from 90 to ≧96% de. Comparison of the values of the specific rotation with those of the known compounds **5a** and **7a–d** confirmed the high degree of enantiomeric purity and the absolute configuration of the new stereocenter formed during the C–C formation step.

In summary, the asymmetric Michael addition of acetaldehyde to enoates via lithiated SAMP-/RAMP-hydrazones allows the synthesis of β-substituted δ-oxopentanoates **5** in acceptable overall yields and with high enantiomeric purities. These compounds constitute versatile precursors to other chiral substances as was shown, for instance, by the transformation to the corresponding δ-lactones **7**. The variation of the aldehyde and enoate compounds allow the synthesis of a variety of *anti*-3,4-disubstituted 5-oxoalkanoates in excellent diastereo- and enantioselectivities[11,17]. By simply changing from SAMP to RAMP both enantiomers of the target molecules are available at will.

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Experimental

^1H-NMR and *^{13}C-NMR spectra* were recorded on Varian EM-390, Bruker WH-90 and WP-80 spectrometers. *IR spectra* were taken with a Beckman Acculab 4 instrument. *Mass spectra* were obtained on Krates MS-30 and Kratos MS-50 spectrometers at an ionization energy of 70 eV. The *elemental analysis* were carried out with a Carlo Erba type 1104 apparatus. *Optical rotation* values were measured with a Perkin Elmer P241 polarimeter. *Ozonolyses* were carried out with a Fischer ozone generator type 502. For *analytical*

TLC Merck TLC-plates silica gel 60 F_{254} were used. All reaction solvents were dried and distilled according to standard procedures. All *melting points* (Büchi apparatus; system Dr. Tottoli and *boiling points* are uncorrected. In the case of *kugelrohr distillations* (Büchi GKR 50) the oven temperatures are given.

(S)-(−)-1-(Ethylideneamino)-2-(methoxymethyl)pyrrolidine [(*S*)-**2**]: 5.5 g (125 mmol) of acetaldehyde was added dropwise at 0°C to 13.0 g (100 mmol) of SAMP and stirred at room temperature overnight. The mixture was poured into dichloromethane/water (4:1) [150 ml]. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by short-path distillation yielded 13.8 g (89%) of (*S*)-**2** as a colorless oil, b. p. 63°C/2.3 Torr (ref.[18] 43°C/0.4 Torr); $\alpha_D^{20} = -163.9°$ (neat) [ref.[18] $\alpha_D^{20} = -161.0°$ (neat)]. – The spectroscopic data are in full agreement with those given in ref.[18].

(R)-(+)-1-(Ethylideneamino)-2-(methoxymethyl)pyrrolidine [(*R*)-**2**]: Reaction of 2.2 g (50 mmol) of acetaldehyde with 5.2 g (40 mmol) of RAMP yielded after workup and short-path distillation 5.7 g (91%) of (*R*)-**2** as a colorless oil, b. p. 60°C/2 Torr; $\alpha_D^{21} = +160.3°$ (neat). The spectroscopic data were identical with those of (*S*)-**2**.

α,β-Unsaturated Esters **3**: The esters **3a** and **3d** are commercially available. The compounds **3b**, **c**, and **e** were synthesized by esterification of the corresponding acids using the method of Steglich et al.[19].

Hydrazones **4**. – *General Procedure:* A solution of *n*-butyllithium in *n*-hexane (1.1 eq., 1.6 M) was added dropwise with a syringe to a solution of diisopropylamine in terahydrofuran (1.1 eq., 0.5 to 1M) under argon at 0°C and stirred for 15 min to generate a solution of lithium diisopropylamide (1.1 eq.). After dropwise addition of **2** (1.0 eq.), the mixture was stirred at 0°C for 2h, cooled to −78°C, and the α,β-unsaturated ester **3** (1.1 eq.) was added. Stirring was continued at this temperature for 2h, after which the mixture was allowed to warm up to 0°C within 8–12h. The mixture was then poured into a saturated aqueous ammonium chloride solution and extracted three times with ether. After drying the organic layer over sodium sulfate and concentrating in vacuo, the crude oily product was purified by column chromatography on silica gel (ether, *n*-pentane, 1:1) kugelrohr distillation.

Methyl (2'S,3R)-(−)-5-[2-(Methoxymethyl)pyrrolidinoimino]-3-methylpentanoate [(*SR*)-**4a**]: Reaction of 3.12 g (20 mmol) of (*S*)-**2** with 2.2 g (22 mmol) of **3a** afforded after workup and purification by kugelrohr distillation 3.64 g (71%) of (*SR*)-**4a** as a yellow oil, b. p. 120–140°C/10^{-3} Torr; $\alpha_D^{20} = -91.3°$ (neat). – IR (film): ν = 3000–2800 cm^{-1} (CH), 1740 (C=O), 1605 (C=N). – ^1H NMR ($CDCl_3$, TMS): δ = 0.95 (m, 3H, CH_3), 1.85 [m. 4H, $(CH_2)_2$], 2.18 (m, 5H, CH_2CHCH_2), 2.7 (m, 1H, NCH_2), 3.15–3.7 (complex m, 4H, NCH_2, CH_2O, CH), 3.35 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 6.58 (t, *J*=4–5Hz, 1H, aldehydic). – ^{13}C NMR ($CDCl_3$,TMS): δ = 19.84, 22.17, 26.61, 29.49, 39.91, 40.91, 50.33, 51.43, 59.23, 63.41, 74.87, 136.37, 173.59. – MS (70 eV): *m/z* (%) = 257 (0.3, $M^+ + 1$), 256 (3, M^+), 111 (100).

$C_{13}H_{24}N_2O_3$ (256.4) Calcd. C 60.91 H 9.44 N 10.93
Found C 60.73 H 9.51 N 10.90

Methyl (2'R,3S)-(+)-5-[2-(Methoxymethyl)pyrrolidinoimino]-3-methylpentanoate [(*RS*)-**4a**]: Reaction of 2.34 g (15 mmol) of (*R*)-**2** with 1.5 g (15 mmol) of **3a** afforded after workup and purification by kugelrohr distillation 2.51 g (65%) of (*RS*)-**4a** as a yellow oil, b. p. 120–140°C/10^{-3} Torr; $\alpha_D^{21} = +89.5°$ (neat). – The spectroscopic data correspond with those of (*SR*)-**4a**.

Methyl (2'S,3R)-(−)-3-Ethyl-5-[2-(methoxymethyl)pyrrolidinoimino]pentanoate [(*SR*)-**4b**]: Reaction of 3.12 g (20 mmol) of (*S*)-**2** with 2.3 g (20 mmol) of **3b** yielded after workup and purification of the crude product by column chromatography on silica gel (ether, *n*-pentane, 1:1) 3.3 g (62%) of (*SR*)-**4b** as a light yellow oil; $\alpha_D^{20} = -87.3°$ (neat). – IR (film): ν = 3000–2800 cm^{-1} (CH), 1730 (C=O), 1605 (C=N). – ^1H NMR ($CDCl_3$, TMS): δ = 0.9 (t, *J* = 6Hz, 3H, CH_3), 1.15–1.55 (m, 2H, CH_2CH_3), 1.75–2.0 [m, 4H, $(CH_2)_2$], 2.05–2.4 (m, 5H, CH_2CHCH_2), 2.8 (m, 1H, NCH_2), 3.35 (s, 3H, OCH_3) 3.2–3.5 (m, 4H, NCH_2, OCH_2, CH), 3.65 (s, 3H, OCH_3), 6.55 (t, *J* = 5Hz, 1H, aldehydic). – ^{13}C NMR ($CDCl_3$, TMS): δ = 10.97, 22.17, 26.64, 35.60, 36.99, 38.26, 50.30, 51.43, 59.20, 63.41, 74.87, 136.46, 173.88. – MS (70 eV): *m/z* (%) = 271 (0.7, $M^+ + 1$), 270 (3, M^+), 70 (100, C_4H_8N).

$C_{14}H_{26}N_2O_3$ (270.4) Calcd. C 62.91 H 9.69 N 10.36
Found C 61.89 H 9.63 N 9.93

Methyl (2'S,3R)-(−)-5-[2-(Methoxymethyl)pyrrolidinoimino]-3-propylpentanoate [(*SR*)-**4c**]: Reaction of 2.34 g (15 mmol) of (*S*)-**2** with 1.92 g (15 mmol) of **3c** afforded after workup and purification of the crude product by column chromatography on silica gel (ether, *n*-pentane, 1:1) 2.73 g (64%) of (*SR*)-**4c** as a yellow oil; $\alpha_D^{20} = -85.3°$ (neat). – IR (film): ν = 3000–2800 cm^{-1} (CH), 1740 (C=O), 1620 (C=N). – ^1H NMR ($CDCl_3$, TMS): δ = 0.92 (m, 3H, CH_3), 1.32 [m, 4H, $(CH_2)_2CH_3$], 1.75–2.1 [m, 4H, $(CH_2)_2$], 2.1–2.4 (m, 5H, CH_2CHCH_2), 2.85 (m, 1H, NCH_2), 3.2–3.6 (m, 4H, NCH_2, OCH_3, CH), 3.35 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 6.58 (t, *J* = 4–5Hz, 1H, aldehydic). – ^{13}C NMR ($CDCl_3$, TMS): δ = 14.24, 19.78, 22.17, 26.57, 33.89, 36.35, 37.38, 38.65, 50.27, 51.43, 59.20, 63.38, 74.83, 136.43, 173.85. – MS (70 eV): *m/z* (%) = 285 (0.3, $M^+ + 1$), 284 (4, M^+), 70 (100, C_4H_8N).

$C_{15}H_{28}N_2O_3$ (284.4) Calcd. C 63.35 H 9.92 N 9.85
Found C 63.50 H 10.06 N 9.82

Methyl (2'S,3R)-(−)-5-[2-(Methoxymethyl)pyrrolidinoimino]-3-phenylpentanoate [(*SR*)-**4d**]: Reaction of 2.34 g (15 mmol) of (*S*)-**2** with 2.45 g (15 mmol) of **3d** afforded after workup and purification of the crude product by column chromatography (silica gel; ether, *n*-pentane, 1:1) 3.46 g (72%) of (*SR*)-**4d** as a yellow oil; $\alpha_D^{20} = -62.4°$ (neat). – IR (film): ν = 3070cm^{-1}, 3040, 3000–2800, 1735 (C=O), 1655, 1620 (C=N). – ^1H NMR ($CDCl_3$, TMS): δ = 1.85 [m, 4H, $(CH_2)_2$], 2.4–2.75 (m, 4H, CH_2CHCH_2), 2.85 (m, 1H, NCH_2), 3.0–3.55 (m, 5H, NCH_2, OCH_2, NCH, CH), 3.34 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 6.54 (t, *J* = 4–5Hz; 1H, aldehydic), 7.2 (m, 5H, arom.). – ^{13}C NMR ($CDCl_3$, TMS): δ = 22.14, 26.57, 39.62, 40.46, 40.75, 50.14, 51.50, 59.20, 63.34, 74.77, 126.62, 127.53, 128.53, 135.36, 143.65, 172.78. – MS (70 eV): *m/z* (%) = 319 (0.3, $M^+ + 1$), 273 (100, $M^+ - CH_2OCH_3$).

$C_{18}H_{26}N_2O_3$ (318.4) Calcd. C 67.90 H 8.23 N 8.80
Found C 67.52 H 8.21 N 9.18

Methyl (2'S,3R)-(−)-5-[2-(Methoxymethyl)pyrrolidinoimino]-3-(4-methoxyphenyl)pentanoate [(*SR*)-**4e**]: Reaction of 3.12 g (20 mmol) of (*S*)-**2** with 3.84 g (20 mmol) of **3e** afforded after workup and purification of the crude product by column chromatography on silica gel (ether, *n*-pentane, 1:1) 3.87 g (55.5%) of (*SR*)-**4e** as a yellow oil; $\alpha_D^{21} = -70.4°$ (neat). – IR (film): ν = 3040–2800 cm^{-1} (CH), 1745 (C=O), 1620 (C=N) – ^1H NMR ($CDCl_3$, TMS): δ = 1.6–2.05 [m, 4H, $(CH_2)_2$], 2.35–2.95 (m, 5H, CH_2 $CHCH_2$,CH), 3.0–3.62 (m, 5H, NCH_2, OCH_2, NCH, CH), 3.32 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 6.45 (t, *J* = 4–5Hz; 1H, aldehydic), 6.80 (d, *J* = 9Hz, arom.), 7.14 (d, *J* = 9Hz, 2H, arom.) – ^{13}C NMR ($CDCl_3$, TMS): δ = 22.11, 26.54, 39.75, 39.97, 40.69, 50.14, 51.47, 55.19, 59.20, 63.31, 74.77, 113.84, 128.40, 135.59,

158.21, 172.84. – MS (70 eV): *m/z* (%) = 349 (0.3, $M^+ + 1$), 348 (2, M^+), 303 (100, $M^+ - CH_2OCH_3$).

$C_{19}H_{28}N_2O_4$ (348.5) Calcd. C 65.49 H 8.10 N 8.04
Found C 65.42 H 8.21 N 8.33

Cleavage by Ozonolysis to Form the Aldehyde-Esters **5**. – *General Procedure:* The hydrazone **4** (10 mmol) was dissolved in dichloromethane (30 ml), and after cooling to –78°C a gentle stream of O_3 was flushed through the solution. After the reaction was complete (determined by TLC), argon was flushed through the solution as it warmed up to room temperature. The solution was concentrated in vacuo, and the aldehyde-ester was separated from the nitrosamine **6** by column chromatography on silica gel (ether, *n*-pentane, 1:1).

Methyl (3R)-(–)-3-Methyl-5-oxopentanoate [(*R*)-**5a**]: Ozonolysis of 2.56 g (10 mmol) of (*SR*)-**4a** and purification of the crude product by column chromatography (silica gel; ether, *n*-pentane, 1:1) and kugelrohr distillation afforded 0.98 g (68%) of (*R*)-**5a** as a colorless oil; b. p. 70–75°C/2.4 Torr (ref.[12] 52°C/2 Torr); α_D^{20} = –5.05° (neat); $[\alpha]_D^{20}$ = –4.2 (*c* = 0.71, $CHCl_3$) [ref.[12]] $[\alpha]_D^{15}$ = +4.64 (*c* = 7.56, $CHCl_3$) (*S*); ref.[13] $[\alpha]_D^{20}$ = –3.1 (*c* = 0.72, $CHCl_3$) (*R*)]. – The spectroscopic data were in agreement with those given in ref.[12].

Methyl (3S)-(–)-3-Methyl-5-oxopentanoate [(*S*)-**5a**]: Oxidative cleavage of 2.3 g (9 mmol) of (*RS*)-**4a** afforded after column chromatography on silica gel (ether, *n*-pentane, 1:1) and kugelrohr distillation 0.82 g (63%) of (*S*)-**5a** as a colorless oil; b. p. 70–75°C/2.3 Torr (ref.[12] 52°C/2 Torr); α_D^{19} = +5.1° (neat); $[\alpha]_D^{20}$ = +4.3 (*c* = 0.78, $CHCl_3$) [ref.[12]] $[\alpha]_D^{15}$ = +4.64 (*c* = 7.56, $CHCl_3$) (*S*); ref.[13] $[\alpha]_D^{20}$ = –3.1 (*c* = 0.72, $CHCl_3$) (*R*)]. – The spectroscopic data were identical with those of (*R*)-**5a**.

Methyl (3R)-(–)-3-Ethyl-5-oxopentanoate [(*R*)-**5b**]: Ozonolysis of 2.7 g (10 mmol) of (*SR*)-**4b** and purification of the crude product by column chromatography on silica gel (ether, *n*-pentane, 1:1) and kugelrohr distillation yielded 1.05 g (67%) of (*R*)-**5b** as a colorless oil; b. p. 85–95°C/1 Torr; α_D^{20} = +2.6° (neat). – IR (film): ν = 3000–2840 cm^{-1} (CH), 2740, 1740 (C=O). – ^1H NMR ($CDCl_3$, TMS): δ = 0.9 (t, *J* = 6 Hz, 3H, CH_3), 1.15–1.6 (m, 2H, CH_2CH_3) 2.15–2.65 (m, 5H, CH_2CHCH_2), 3.65 (s, 3H, OCH_3), 9.75 (m, 1H, aldehydic). – ^{13}C NMR ($CDCl_3$, TMS): δ = 11.04, 27.06, 31.46, 38.10, 47.84, 51.59, 173.07, 201.91. – MS (70 eV): *m/z* (%) = 159 (0.4, $M^+ + 1$), 158 (0.1, M^+), 74 (100).

$C_8H_{14}O_3$ (158.2) Calcd. C 60.74 H 8.92
Found C 60.75 H 8.98

Methyl (3R)-(–)-5-Oxo-3-propylpentanoate [(*R*)-**5c**]: Ozonolysis of 3.4 g (11.9 mmol) of (*SR*)-**4c** afforded after purification by column chromatography on silica gel (ether, *n*-pentane ,1:1) and kugelrohr distillation 1.43 g (70%) of (*R*)-**5c** as a colorless oil, b. p. 90–95°C/2 Torr; α_D^{19} = –2.2° (neat), $[\alpha]_D^{19}$ = –3.3 (*c* = 0.65; $CHCl_3$). – IR (film): ν = 2970 cm^{-1}, 2940, 2880, 2740, 1740 (C=O). – ^1H NMR ($CDCl_3$, TMS): δ = 0.9 (t, *J* = 6–7Hz, 3H, CH_3), 1.1–1.5 [m, 4H, $(CH_2)_2$], 2.2–2.62 (m, 5H, CH_2CHCH_2), 3.65 (s, 3H, OCH_3), 9.85 (t,*J* = 2Hz, 1H, aldehydic). – ^{13}C NMR ($CDCl_3$, TMS): δ = 14.05, 19.87, 29.81, 36.64, 38.49, 48.23, 51.59, 173.10,201.98. – MS (70 eV): *m/z* (%) = 173 (0.5, $M^+ + 1$), 172 (0.04, M^+), 74 (100).

$C_9H_{16}O_3$ (172.2) Calcd. C 62.77 H 9.36
Found C 62.28 H 9.56

Methyl (3R)-(–)-5-Oxo-3-phenylpentanoate [(*R*)-**5d**]: Oxidative cleavage of 1.3 g (5 mmol) of (*SR*)-**4d** yielded after column chromatography and removal of the solvent 0.81 g (79%) of (*R*)-**5d** as a colorless oil; ^{20} = –9.7° (neat). – IR (film): ν = 3090 cm^{-1}, 3070, 3030, 3010, 2960, 2840, 2735, 1735 (C=O). – ^1H NMR ($CDCl_3$ TMS): δ = 2.66 (d, *J* = 8Hz, 2H, $CH_2CO_2CH_3$), 2.80 (dd, *J* = 8Hz, *J* = 2Hz, 2H, $OHCCH_2$), 3.58 (s, 3H, OCH_3), 3.7 (quint, *J* = 8Hz, 1H, CH), 7.3 (m, 5H, arom.), 7.74 (t, *J* = 2Hz, 1H, aldehydic). – ^{13}C NMR ($CDCl_3$, TMS): δ = 36.19, 40.72, 49.39, 51.69, 127.17, 127.30, 128.89, 142.52, 127.07, 200.78. – MS (e V): *m/z* (%) = 206 (13, M^+), 118 (100).

$C_{12}H_{14}O_3$ (206.2) Calcd. C 69.89 H 6.84
Found C 69.38 H 6.88

Methyl (3R)-(–)-3-(4-Methoxyphenyl)-5-oxopentanoate [(*R*)-**5e**]: Ozonolysis of 1.88 g (5.4 mmol) of (*SR*)-**4e** afforded after column chromatography on silica gel (ether, *n*-pentane, 1:1) and kugelrohr distillation 0.77 g (61%) of (*R*)-**5e** as a colorless oil, b. p. 140–160°C/0.02 Torr; α_D^{20} = –20.6° (neat), $[\alpha]_D^{20}$ = –10.35 (*c* = 1.45, $CHCl_3$). – IR (film): ν = 3030 cm^{-1}, 2960, 2920, 2850, 2740, 1735 (C=O). – ^1H NMR ($CDCl_3$, TMS): δ = 2.64 ((d, *J* = 7.5Hz, 2H, $CH_2CO_2CH_3$), 2.78 (dd,*J* = 7.5Hz, *J* = 2Hz, 2H, $OHCCH_2$), 3.58 (s, 3H, OCH_3), 3.68 (m, 1H, CH), 3.75 (s, 3H, OCH_3), 6.82 (d, *J* = 9Hz, 2H, arom.), 7. **14** (d, *J* = 9Hz, 2H, arom.), 9.68 (t, *J* = 2Hz, 1H, aldehydic). – ^{13}C NMR ($CDCl_3$, TMS): δ = 35.51, 40.98, 49, 56, 51.69, 55.25, 114.23, 128.31, 134.46, 158.64, 172.13, 201.00. – MS (70 eV): *m/z* (%) = 237 (7, $M^+ + 1$), 236 (52, M^+), 151 (100).

$C_{13}H_{16}O_4$ (236.3) Calcd. C 66.09 H 6.83
Found C 65.90 H 6.92

Reduction of the Aldehyde-Esters **5** *and Cyclization to Form the Lactones* **7**. – *General Procedures:* The aldehyde-ester **5** (3 mmol) was dissolved in methanol (20 ml) and, after cooling the solution to 0°C, potassium hydroxide (0.1 g) in water (1 ml) and $NaBH_4$ (60 mg) was added. The mixture was stirred at this temperature for 3h and then allowed to warm up to room temperature. The solution was treated with hydrochloric acid (6N) until pH < 7 was attained. Following extraction with dichloromethane (5 × 60 ml), the organic layer was separated, washed with water, and dried over sodium sulfate. After removal of the solvent the crude reduction product was dissolved in benzene (30 ml), *p*-toluenesulfonic acid (0.3–0.5 g) was added, and the reaction mixture was refluxed for 2d. The solution was then washed with water and dried over sodium sulfate. Removal of the solvent and purification of the crude product by column chromatography on silica gel (ether, *n*-pentane, 5:1) and kugelrohr distillation or recrystallization afforded the β-substituted δ-lactones **7**.

(4R)-(+)-4-Methyltetrahydro-2H-pyran-2-one [(*R*)-**7a**]: 0.45 g (3.1 mmol) of (*R*)-**5a** was reduced with 65 mg (1.6 mmol) of $NaBH_4$, and the resulting crude product was treated with *p*-toluenesulfonic acid in refluxing benzene. Workup and purification by column chromatography and kugelrohr distillation yielded 0.27 g (76%) of (*R*)-**7a** as a colorless oil, b. p. 85–90°C/4 Torr (ref.[3] 90°C/12 Torr); $[\alpha]_D^{19}$ = +28.4 (*c* = 0.89, $CHCl_3$) [ref.[3]] $[\alpha]_D^{25}$ = –23.6 (*c* = 1, $CHCl_3$), ee = 78% (*S*); ref.[6] $[\alpha]_D^{27}$ = +27.61 (*c* = 5.716, $CHCl_3$)]. – The spectroscopic data correspond with those given in ref.[6].

(4S)-(–)-4-Methyltetrahydro-2H-pyran-2-one [(*S*)-**7a**]: Reduction of 0.5 g (3.5 mmol) of (*S*)-**5a** with 70 mg (1.85 mmol) of $NaBH_4$ and cyclization of the crude product with *p*-toluenesulfonic acid in refluxing benzene provided after workup, column chromatography (silica gel; ether, *n*-pentane, 5:1), and kugelrohr distillation 0.29 g (72%) of (*S*)-**7a** as a colorless oil, b. p. 80–85°C/3 Torr (ref.[3] 90°C/12 Torr); $[\alpha]_D^{20}$ = –28.2° (*c* = 1.04, $CHCl_3$) [ref[3]] $[\alpha]_D^{25}$ = –23.6 (*c* = 1, $CHCl_3$), ee = 78% (*S*); ref.[14] $[\alpha]_D^{27}$ = +27.61 (*c* = 5.716, $CHCl_3$)]. – The spectroscopic data correspond with those of (*R*)-**7a**.

(4R)-(+)-4-Ethyltetrahydro-2H-pyran-2-one [(*R*)-**7b**]: Reduction of 0.6 g (3.8 mmol) of (*R*)-**5b** with 65 mg (1.7 mmol) of $NaBH_4$ and cyclization of the crude product with *p*-toluenesulfonic acid in refluxing benzene afforded after workup, column chromatography, and kugelrohr distillation 0.33 g (67%) of (*R*)-**7b** as a colorless oil, b. p. 110–115°C/12 Torr; $[\alpha]_D^{21} = -24.1$ (*c* = 1.0, $CHCl_3$) [ref.[3] $[\alpha]_D^{25} = -20.4$ (*c* = 1.0, $CHCl_3$), ee = 74% (*S*); ref.[6] $[\alpha]_D^{23} = -26.0$ (*c* = 4.3, $CHCl_3$), ee = 95% (*S*)]. – The spectroscopic data correspond with those given in ref.[6].

(4R)-(+)-4-Propyltetrahydro-2H-pyran-2-one [(*R*)-**7c**]: 0.51 g (3 mmol) of (*R*)-**5c** was reduced with 65 mg (1.7 mmol) of $NaBH_4$ Cyclisation and purification by column chromatography (silica gel; ether, *n*-pentane, 5:1) and kugelrohr distillation yielded 0.33 g (70%) of (*R*)-**7c** as a colorless oil, b. p. 105–120°C/2 Torr (ref.[15] 90–91°C/1.5 Torr); $[\alpha]_D^{18} = +22.9$ (*c* = 8.1, $CHCl_3$) [ref.[6] $[\alpha]_D^{23} = -23.9$ (*c* = 8.6, $CHCl_3$), ee = 95% (*S*)]. – The spectroscopic data correspond with those given in ref.[6].

(4R)-(−)-4-Phenyltetrahydro-2H-pyran-2-one [(*R*)-**7d**]: Reduction of 0.79 g (4.85 mmol) of (*R*)-**5d** with 90 mg (2.4 mmol) of $NaBH_4$ afforded after cyclization, purification by column chromatography (silica gel; ether, pentane, 5:1), and kugelrohr distillation 0.42 g (46.5%) of (*R*)-**7d** as a colorless oil, b. p. 130–140°C/0.02 Torr (ref.[2] 124–126°C/0.07 Torr); $[\alpha]_D^{20} = -4.79$ (*c* = 1.17, $CHCl_3$) [ref.[6] $[\alpha]_D^{23} = +3.63$ (*c* = 7.2, $CHCl_3$), ee = 98% (*S*)]. – The spectroscopic data correspond with those given in ref.[6].

(4R)-(−)-4-(4-Methoxyphenyl)tetrahydro-2H-pyran-2-one [(*R*)-**7e**]: 0.68 g (2.8 mmol) of (*R*)-**5e** was reduced with 55 mg (1.4 mmol) of $NaBH_4$. Cyclization and purification by column chromatography on silica gel (ether, pentane, 5:1) afforded 0.39 g (67%) of (*R*)-**7e** as colorless crystals; m. p. 83.4–83.6°C; $[\alpha]_D^{21} = -6.98$ (*c* = 0.96, $CHCl_3$). – IR (KBr): ν = 3090 cm^{-1}, 3060, 3020, 3000, 2970, 2910, 2850, 1725. – ^1H NMR ($CDCl_3$, TMS): δ = 1.8–3.3 (complex m, 5H, CH_2 $CHCH_2$), 3.78 (s, 3H, OCH_3), 4.35 (m, 2H, OCH_2) 6.85 (d, *J* = 9Hz, 2H, arom., *meta*), 7.1 (d, *J* = 9Hz, 2H arom., *ortho*). – ^{13}C NMR ($CDCl_3$,TMS): δ = 30.56, 36.71, 37.81, 55.35, 68.65, 114.39, 127.50, 134.97, 158.76, 170.81. – MS (70 eV): *m/z* (%) = 207 (8, $M^+ + 1$), 206 (61, M^+), 147 (100).

$C_{12}H_{14}O_3$ (206.2) Calcd. C 69.89 H 6.84
Found C 70.04 H 7.01

CAS Registry Numbers

(*S*)-**1**: 59983-39-0 / (*R*)-**1**: 72748-99-3 / (*S*)-**2**: 107985-85-3 / (*R*)-**2**: 107985-86-4 / **3a**: 18707-60-3 / **3b**: 818-59-7 / **3c**: 2396-77-2 / **3d**: 103-26-4 / **3e**: 832-01-9 / (*SR*)-**4a**: 107985-87-5 / (*RS*)-**4a**: 107985-88-6 / (*SR*)-**4b**: 107985-89-7 / (*SR*)-**4c**: 107985-90-0 / (*SR*)-**4d**: 107985-91-1 / (*SR*)-**4e**: 107985-92-2 / (*R*)-**5a**: 79936-62-2 / (*S*)-**5a**: 93714-78-4 / (*R*)-**5b**: 107985-93-3 / (*R*)-**5c**: 107985-9-4- / (*R*)-**5d**: 107985-95-5 / (*R*)-**5e**: 107985-96-6 / (*R*)-**7a**: 61898-55-3 / (*S*)-**7a**: 61898-56-4 / (*R*)-**7b**: 71301-88-7 / (*R*)-**7c**: 71301-89-8 / (*R*)-**7d**: 71302-21-1 / (*R*)-**7e**: 107985-97-7 / Acetaldehyde: 75-07-0

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