Asymmetric Michael Additions via SAMP-/RAMP-Hydrazones Enantioselective 1,4-Addition of Methyl Ketones to Knoevenagel Acceptors[1)]

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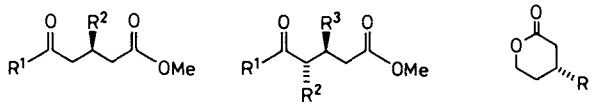
Asymmetric Michael addition of lithiated methyl ketone SAMP-hydrazones (*S*)-**2** to 2-benzylidenemalonates and -dinitriles **3** followed by oxidative cleavage of the 1,4-adducts (*SR*)-**4** by ozonolysis affords 2-substituted 4-oxo diesters and -dinitriles (*R*)-**5** in good overall yields of 50–82% and high enantiomeric excesses (ee ≧ 95%).

Asymmetrische Michael-Additionen via SAMP-/RAMP-Hydrazone. – Enantioselektive 1,4-Addition von Methylketonen an Knoevenagel-Akzeptoren[1)]

Asymmetrische Michael-Addition von lithiierten Methylketon-SAMP-Hydrazonen (*S*)-**2** an 2-Benzylidenmalonsäureester und -dinitrile **3** und anschließende oxidative Spaltung der 1,4-Addukte (*SR*)-**4** durch Ozonolyse liefert 2-substituierte 4-Oxodiester und -dinitrile (*R*)-**5** in guten Gesamtausbeuten von 50–82% und hohen Enantiomerenüberschüssen (ee ≧ 95%).

Asymmetric Michael additions have been studied extensively in the recent years[2)]. Employing our SAMP-/RAMP-hydrazone method[3)], we recently reported on the diastereo- and enantioselective synthesis of β-substituted δ-keto-[4)] and δ-aldehyde (R^1 = H) esters **A**[5)], the β,γ-disubstituted δ-oxo esters **B**[6)], and the δ-lactones **C**[5a)]. Thus, aldehydes and ketones can be added in a conjugate fashion to enoates and other Michael acceptors[7)] in very high stereoselectivities and in many cases with virtually complete asymmetric induction.

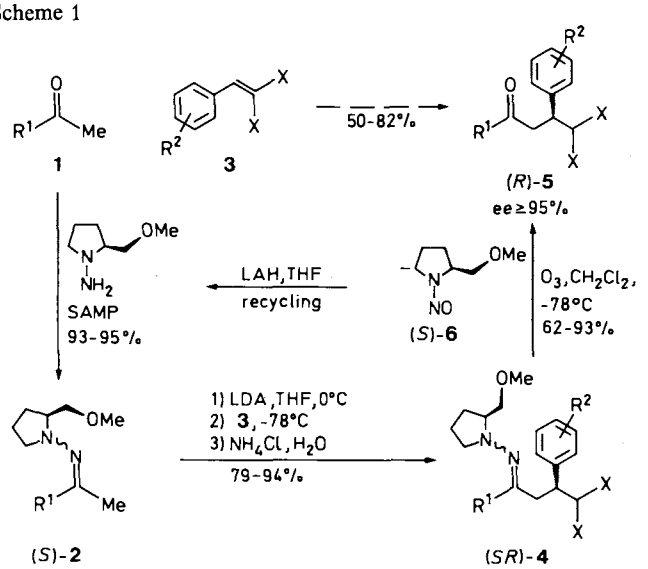


A **B** **C**

In this paper we describe overall enantioselective 1,4-additions of methyl ketones **1** to dimethyl benzylidenemalonates and -malodinitriles **3** affording the δ-keto diesters (dinitriles) (*R*)-**5** of high enantiomeric purity (ee ≧ 95%). Efficient asymmetric Michael addition of ethyl acetoacetate via its (*S*)-valine-based lithiated enamine[8)] and cyclohexanone using the corresponding SMP-enamine[9)] to Knoevenagel acceptors have recently been published. However, the SMP-enamine route did not give satisfactory results with acyclic ketones. Thus, the hydrazone technique reported here nicely fills this gap.

As is shown in Scheme 1, the methyl ketones **1** are transformed into their corresponding SAMP-hydrazones (*S*)-**2** as usual in excellent yields (93–95%), followed by metalation with lithium diisopropylamide (LDA) in tetrahydrofuran at 0°C. Trapping of the resulting chiral azaenolates with the Knoevenagel acceptors **3** at −78°C yields the 1,4-adducts (*SR*)-**4**, which are purified by column chromatography. Subsequent oxidative cleavage of the hydrazone double bond by ozonolysis in dichloromethane at −78°C and separation of the nitrosamine (*S*)-**6** (recycling of the chiral auxiliary SAMP is possible through LAH reduction) leads to the keto diesters (dinitriles) (*R*)-**5** in overall yields of 50–82% and enantiomeric excesses of ≧ 95%.

Scheme 1



1,2	R^1
a	Me
b	Et
c	Ph

3	R^2	X
a	H	CO_2Me
b	3-OMe 4-OBzl	CO_2Me
c	4-OMe	CN

4,5	R^1	R^2	X
a	Me	H	CO_2Me
b	Et	H	CO_2Me
c	Ph	H	CO_2Me
d	Et	3-OMe 4-OBzl	CO_2Me
e	Ph	3-OMe 4-OBzl	CO_2Me
f	Ph	4-OMe	CN

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The asymmetric inductions of the Michael addition step were determined by ^{1}H-NMR shift experiments at the stage of the final products (*R*)-**5** using Eu(hfc)$_3$. The results were confirmed by the synthesis of the racemic products, *rac*-**5**, using the corresponding achiral dimethylhydrazones (DMHs)[10] along the lines given in Scheme 1. For instance, conjugate addition of lithiated acetophenone-DMH to dimethyl benzylidenemalonate gave after oxidative cleavage *rac*-**5c** in 87% yield. In all cases a baseline separated 1:1-splitting of the methoxycarbonyl singlet could be achieved upon lanthanide-induced shift. In addition, in **5a** the acetyl singlet and in **5f** the 4-methoxy singlet were splitted.

Table 1. Highly enantiomerically pure 3-substituted 5-oxo diesters and -dinitriles (*R*)-**5** prepared from methyl ketones and Knoevenagel acceptors via SAMP-hydrazone Michael additions

(*R*)-**5**	Overall yield (%)	M.p. [°C]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	ee (%)[a]
a	72	64[b]	−13.2 (1.5)	≧95
b	74	47	−3.5 (1.3)	≧95
c	82	106.5−107[c]	−28.5 (1)	≧95
d	62[d]	106.5−107	−0.77 (1.3)	≧95
e	50	107−107.5	−18.2 (1)	≧95
f	53	119−120[e]	+12.2 (0.9, CH_3OH)	≧95

[a] Determined by ^{1}H NMR L.I.S. [Eu(hfc)$_3$, $CDCl_3$]. − [b] ref.[11] m.p. 64°C. − [c] ref.[12] m.p. 106−107°C. − [d] Cleavage of (*SR*)-**4d** during column chromatography (silica gel). − [e] ref.[13] m.p. 119−120°C.

The (*R*) configuration of the final products is based on a chemical correlation of (*R*)-**5a** with methyl (*R*)-5-oxo-3-phenylhexanoate[4] of known absolute configuration[19]. Needless to mention that the (*S*) enantiomers are available by simply using RAMP instead of SAMP as chiral auxiliary.

Although we recently predicted a S_E2'-front metallo-retentive mechanism for asymmetric electrophilic substitutions via lithiated SAMP-/RAMP-hydrazones under the standard deprotonation conditions[20], we hesitate to speculate on a particular transition-state picture of these Michael additions before more is known on the structure of the lithiated hydrazones. However, it is interesting to note that the relative topicity during mutual approach of the reactants nicely correlates with our previously reported 1,4-additions via SAMP-/RAMP-hydrazones[4−7] (*si*-face of the Michael acceptor is attacked). This is different to the mechanism proposed for the corresponding SMP-enamine Michael additions (*re*-face of the acceptor is attacked)[9].

In summary, the asymmetric Michael addition of methyl ketones to Knoevenagel acceptors via lithiated SAMP-/RAMP-hydrazones offers an efficient three-step entry to a variety of β-substituted δ-keto diesters and -dinitriles of high enantiomeric purity.

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Experimental

^{1}H-NMR spectra were recorded on a Varian EM-390 spectrometer. − IR spectra were taken with a Beckman Acculab 4 instrument. − Mass spectra were obtained on Kratos MS-30 and MS-50 spectrometers at an ionization energy of 70 eV. − The elemental analyses were carried out with a Carlo Erba type 1104 and a Heraeus Mikro U/D apparatus. − Optical rotation values were measured with a Perkin Elmer P 241 polarimeter. − Ozonolyses were carried out with Fischer ozone generators, type 502 and OZ II. − 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.

SAMP-Hydrazones (*S*)-2

(S)-(+)-2-Methoxymethyl-1-(1-methylethylideneamino)pyrrolidine [(*S*)-**2a**]: A mixture of 6.5 g (50 mmol) of SAMP and 4.0 g (80 mmol) of acetone (**1a**) was stirred at room temperature over night and then poured into dichloromethane/water (4:1). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by short-path distillation afforded 8.1 g (95%) of (*S*)-**2a** as a colorless oil, b.p. 46−47°C/1 Torr (ref.[14] b.p. 44°C/0.25 Torr); α_D^{20} = +307.8° (neat) [ref.[14] α_D^{22} = +307.0° (neat)]. The spectroscopic date were identical with those given in the literature[14].

(S)-(+)-2-Methoxymethyl-1-(1-methylpropylideneamino)pyrrolidine [(*S*)-**2b**]: A mixture of 6.5 g (50 mmol) of SAMP and 3.6 g (50 mmol) of butanone (**1b**) was stirred at 60°C for 4 h and then poured into dichloromethane/water (4:1). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by short-path distillation yielded 8.5 g (93%) of (*S*)-**2b** as a colorless oil, b.p. 51−53°C/0.5 Torr (ref.[14] b.p. 53°C/0.3 Torr); α_D^{20} = +289.0° (neat) [ref.[14] α_D^{20} = +289.0° (neat)]. The spectroscopic data were identical with those given in the literature[14].

(S)-(−)-2-Methoxymethyl-1-(1-phenylethylideneamino)pyrrolidine [(*S*)-**2c**]: 6.0 g (50 mmol) of acetophenone (**1c**), 6.5 g (50 mmol) of SAMP, and 0.2 g of *p*-toluenesulfonic acid were dissolved in benzene (70 ml), and the mixture was refluxed while the reaction water was removed via a Dean Stark trap. After the reaction was complete (followed by TLC), the benzene phase was concentrated in vacuo. Purification by short-path distillation yielded 10.8 g (93%) of a yellow oil, b.p. 107°C/0.01 Torr (ref.[15] b.p. 105°C/0.08 Torr); α_D^{20} = −780.4° (neat) [ref.[15] α_D^{20} = −780.0° (neat)]. The spectroscopic data were identical with those given in the literature[15].

Michael Acceptors 3

Methyl 2-Methoxycarbonyl-3-phenylacrylate (Dimethyl 2-Benzylidenemalonate; **3a**): Reaction of 18.0 g (170 mmol) of benzaldehyde with 22.5 g (170 mmol) of dimethyl malonate according to known procedures[16] yielded after purification by distillation 33.5 g (90%) of **3a** as a colorless solid, m.p. 41°C (ref.[16] m.p. 41°C); b.p. 115−116°C/0.01 Torr (ref.[16] b.p. 174−177°C/15 Torr).

Methyl 2-Methoxycarbonyl-3-(4-benzyloxy-3-methoxyphenyl)-acrylate [Dimethyl 2-(4-Benzyloxy-3-methoxybenzylidene)malonate; **3b**]: Reaction of 24.2 g (100 mmol) of 4-benzyloxy-3-methoxybenzaldehyde with 13.2 g (100 mmol) of dimethyl malonate according to the method of Sprangler et al.[17] yielded 31.3 g (88%) of **3b** as a colorless solid, m.p. 99–101°C (ether). – IR (KBr): ν = 3100–2800 cm^{-1} (CH), 1740–1700 (C=O), 1620, 1600, 1510, 1500, 1460, 1440, 1420. – ^1H NMR ($CDCl_3$): δ = 3.81, 3.83, 3.87 (3 s, 9H, $3OCH_3$), 5.15 (s, 2H, OCH_2), 6.88–7.5 (m, 8H, arom.), 7.65 (s, 1H, olef.).

$C_{20}H_{20}O_6$ (356.4) Calcd. C 67.40 H 5.65
Found C 67.61 H 5.52

2-Cyano-3-(4-methoxyphenyl)acrylonitrile [2-(4-Methoxybenzylidene)malodinitrile; **3c**]: Reaction of 20.4 g (150 mmol) of 4-methoxybenzaldehyde and 9.9 g (150 mmol) of malodinitrile according to the method of Corson et al.[18] yielded 25.0 g (91%) of **3c** as a yellow solid, m.p. 115–115.5°C (CH_3OH) [ref.[18] m.p. 114.5–115.5°C]. The spectroscopic data were identical with those given in the literature[18].

Hydrazones **4**. – *General Procedure:* A solution of *n*-butyllithium in *n*-hexane (1.1 eq, 1.6 M) was added dropwise via syringe to a solution of diisopropylamine in tetrahydrofuran (1.1 eq, 0.5–1.0 M) under argon at 0°C and stirred for 15 min to generate a solution of lithium diisopropylamide (1.1 eq). After dropwise addition of (*S*)-**2** (1.0 eq), the mixture was stirred at 0°C for 2 h, cooled to −78°C, and the acceptor **3** (1.0 eq) was added without solvent. Stirring was continued at this temperature for 2 h, after which the mixture was allowed to warm up to 0°C within 8–12 h. The mixture was then poured into a saturated aqueous ammonium chloride solution and extracted three times with ether. After drying the organic layer with sodium sulfate and concentrating in vacuo, the crude oily product was purified by column chromatography on silica gel (ether or ether/pentane, 1:1).

Dimethyl (2'S,2R)-(+)-4-[2-(Methoxymethyl)pyrrolidinoimino]-2-phenyl-1,1-pentanedicarboxylate [(*SR*)-**4a**]: Reaction of 2.55 g (15 mmol) of (*S*)-**2a** with 3.3 g (15 mmol) of **3a** afforded after workup and purification by column chromatography (silica gel, ether) 5.3 g (91%) of (*SR*)-**4a** as a yellow oil, α_D^{20} = +111.0° (neat). – IR (film): ν = 3090–2800 cm^{-1} (CH), 1760–1720 (C=O), 1640 (C=N), 1600, 1560, 1500, 1460, 1440. – ^1H NMR ($CDCl_3$): δ = 1.51–2.13 [m, 4H, $(CH_2)_2$], 2.0 (s, 3H, CH_3), 2.61–3.29 (m, 7H, NCH_2, CH, OCH_2, CH_2), 3.23 (s, 3H, OCH_3), 3.30–3.89 (m, 2H, CHCH), 3.38, 3.45, 3.63, 3.71 [4 s, 6H, $2CO_2CH_3$, (*E*)/(*Z*)], 6.95–7.38 (m, 5H, arom.). – MS (70 eV): *m/z* (%) = 390 (1, M^+), 345 (23, $M^+ - CH_2OCH_3$), 43 (100, CH_3CO).

$C_{21}H_{30}N_2O_5$ (390.5) Calcd. C 64.59 H 7.74 N 7.17
Found C 64.82 H 7.94 N 7.28

Dimethyl (2'S,2R)-(+)-4-[2-(Methoxymethyl)pyrrolidinoimino]-2-phenyl-1,1-hexanedicarboxylate [(*SR*)-**4b**]: Reaction of 1.84 g (10 mmol) of (*S*)-**2b** with 2.2 g (10 mmol) of **3a** afforded after workup and purification by column chromatography (silica gel, ether) 3.6 g (89%) of (*SR*)-**4b** as a yellow oil, $[\alpha]_D^{20}$ = +51.5 (*c* = 3, $CHCl_3$). – IR (film): ν = 3090–2790 cm^{-1} (CH), 1760–1730 (C=O), 1630 (C=N), 1600, 1580, 1500, 1460, 1430. – ^1H NMR ($CDCl_3$): δ = 0.85–1.28 (m, 3H, CH_2CH_3), 1.52–2.57 (compl. m, 8H, 2 β-ring CH_2, CH_2CH_3, CH_2), 2.97–3.45 (compl. m, 7H, NCH_2, CH, OCH_2, CHCH), 3.07, 3.22 [2 s, 3H, OCH_3, (*E*)/(*Z*)], 6.98–7.36 (m, 5H, arom.). – MS (70 eV): *m/z* (%) = 404 (3, M^+), 373 (4), 359 (100, $M^+ - CH_2OCH_3$).

$C_{22}H_{32}N_2O_5$ (404.5) Calcd. C 65.32 H 7.97 N 6.92
Found C 65.54 H 8.25 N 7.00

Dimethyl (2'S,2R)-(+)-4-[2-(Methoxymethyl)pyrrolidinoimino]-2,4-diphenyl-1,1-butanedicarboxylate [(*SR*)-**4c**]: Reaction of 2.32 g (10 mmol) of (*S*)-**2c** with 2.2 g (10 mmol) of **3a** afforded after workup and purification by column chromatography (silica gel, ether), 4.24 g (94%) of (*SR*)-**4c** as a yellow oil, $[\alpha]_D^{20}$ = +206.7 (*c* = 1.4, $CHCl_3$). – IR (film): ν = 3100–2790 cm^{-1} (CH), 1750, 1740 (C=O), 1620 (C=N, C=C), 1580, 1500, 1450. – ^1H NMR ($CDCl_3$): δ = 1.56–2.21 (m, 4H, 2 β-ring CH_2), 2.90–3.56 [m, 8H, CH_2, $CH(CO_2CH_3)_2$, NCH_2, CH, OCH_2], 3.25 (s, 3H, OCH_3), 3.35, 3.80 (2 s, 6H, $2CO_2CH_3$), 3.7 (m, 1H, CH), 6.82–7.45 (m, 10H, arom.). – MS (70 eV): *m/z* (%) = 452 (M^+, 0.5), 407 (100, $M^+ - CH_2OCH_3$).

$C_{26}H_{32}N_2O_5$ Calcd. 452.2311 Found 452.2316 (MS)

Dimethyl (2'S,2R)-2-(4-Benzyloxy-3-methoxyphenyl)-4-[2-(methoxymethyl)pyrrolidinoimino]-1,1-hexanedicarboxylate [(*SR*)-**4d**]: Reaction of 0.95 g (5 mmol) of (*S*)-**2b** with 1.8 g (5.5 mmol) of **3b** yielded after workup 2.71 g (93%) of crude (*SR*)-**4d**. Column chromatography (silica gel; ether, pentane 1:1) afforded the keto ester (*R*)-**5d**.

Dimethyl (2'S,2R)-(+)-2-(4-Benzyloxy-3-methoxyphenyl)-4-[2-(methoxymethyl)pyrrolidinoimino]-4-phenyl-1,1-butanedicarboxylate [(*SR*)-**4e**]: Reaction of 2.32 g (10 mmol) of (*S*)-**2c** with 3.6 g (10 mmol) of **3b** yielded after workup and purification by column chromatography (silica gel, ether) 5.06 g (86%) of (*SR*)-**4e** as a yellow oil, $[\alpha]_D^{20}$ = +254.6 (*c* = 0.85, $CHCl_3$). – IR (film): ν = 3100–2800 cm^{-1} (CH), 1755 (C=O), 1610 (C=N), 1600, 1520, 1455. – ^1H NMR ($CDCl_3$): δ = 1.4–2.18 (m, 4H, 2 β-ring CH_2), 2.2–3.55 (compl. m, 9H, CH_2CHCH, NCH_2, CH, OCH_2), 3.24 (s, 3H, CO_2CH_3), 3.3 (s, 3H, OCH_3), 3.6 (s, 3H, $C_6H_3OCH_3$), 3.8 (s, 3H, CO_2CH_3), 4.98 (s, 2H, $OCH_2C_6H_5$), 6.2 (s, 1H, arom.), 6.3 (d, *J* = 7.5 Hz, 1H, arom.), 6.65 (d, *J* = 7.5 Hz, 1H, arom.), 7.28 (m, 5H, arom.). – MS (70 eV): *m/z* (%) = 589 (4, $M^+ + 1$), 588 (10, M^+), 544 (35), 543 (100, $M^+ - CH_2OCH_3$), 91 (54, C_7H_7).

$C_{34}H_{40}N_2O_7$ (588.7) Calcd. C 69.37 H 6.85 N 4.76
Found C 69.59 H 7.04 N 4.64

(2'S,2R)-(+)-4-[2-(Methoxymethyl)pyrrolidinoimino]-2-(4-methoxyphenyl)-4-phenyl-1,1-dicarbonitrile [(*SR*)-**4f**]: Reaction of 2.32 g (10 mmol) of (*S*)-**2c** with 2.84 g (10 mmol) of **3c** yielded after workup and purification by column chromatography (silica gel; ether, pentane, 1:1), 3.3 g (79%) of (*SR*)-**4f** as a colorless solid, m.p. 109–110°C; $[\alpha]_D^{20}$ = +192.0 (*c* = 0.5, CH_3OH). – IR (KBr): ν = 3040–2800 cm^{-1} (CH), 2250 (CN), 1610 (C=N, C=C), 1580, 1570, 1510, 1480, 1470, 1460, 1440. – ^1H NMR ($CDCl_3$): δ = 1.55–2.23 (m, 4H, 2 β-ring CH_2), 2.50–3.62 [m, 8H, CH_2, NCH_2, CH, OCH_2, $CHCH(CN)_2$], 3.37 (s, 3H, OCH_3), 3.76 (s, 3H, $C_6H_4OCH_3$), 4.81 [m, 1H, $CH(CN)_2$], 6.68–7.72 (m, 9H, arom.). – MS (70 eV): *m/z* (%) = 416 (0.5, M^+), 391 (35), 350 (8), 305 (35), 236 (40), 187 (100).

$C_{25}H_{28}N_4O_2$ (416.5) Calcd. C 72.10 H 6.77 N 13.45
Found C 72.38 H 6.77 N 13.36

Cleavage of the Hydrazones **4** *by Ozonolysis to Form the Compounds* **5**. – *General Procedure:* The hydrazones **4** were dissolved in dichloromethane (50 ml), and after cooling to −78°C a gentle stream of O_3 was flushed through the solution until the color of the solution turned green to blue (indicating excess O_3). Argon was then flushed through the solution as it warmed up to room temperature. The solution was concentrated in vacuo, and the keto diesters or -dinitriles **5** were separated from the nitrosamine (*S*)-**6** by column chromatography (silica gel; ether or ether, pentane, 1:1).

Dimethyl (R)-(−)-4-Oxo-2-phenyl-1,1-pentanedicarboxylate [(*R*)-**5a**]: Ozonolysis of 1.95 g (5 mmol) of (*SR*)-**4a** and purification of the crude product by column chromatography on silica gel (ether)

yielded 1.15 g (83%) of (*R*)-**5a** as a colorless solid, m.p. 64°C (ref.[11] m.p. 64°C); $[\alpha]_D^{20} = -13.2$ (c = 1.5, $CHCl_3$). – IR (KBr): ν = 3090–2820 cm^{-1} (CH), 1760–1710 (C=O), 1600, 1560, 1490, 1450, 1440. – ^1H NMR ($CDCl_3$): δ = 2.05 (s, 3H, CH_3), 2.90 (d, 2H, CH_2), 3.45, 3.68 (s, 6H, $2OCH_3$), 3.60–4.05 (m, 2H, 2CH), 6.95–7.34 (m, 5H, arom.). – MS (70 eV): m/z (%) = 278 (2, M^+), 43 (100, CH_3CO).

$C_{15}H_{18}O_5$ (278.3) Calcd. C 64.73 H 6.52
Found C 64.75 H 6.69

Dimethyl (R)-(–)-4-Oxo-2-phenyl-1,1-hexanedicarboxylate [(*R*)-**5b**]: Ozonolysis of 3.0 g (7.4 mmol) of (*SR*)-**4b** and purification of the crude product by column chromatography (silica gel; ether, pentane, 1:1) yielded 1.93 g (89%) of (*R*)-**5b** as a colorless solid, m.p. 47°C; $[\alpha]_D^{20} = -3.5$ (c = 1.3, $CHCl_3$). – IR (KBr): ν = 3100–2820 cm^{-1} (CH), 1750–1720 (C=O), 1600, 1500, 1460, 1440, 1410. – ^1H NMR ($CDCl_3$): δ = 0.86 (t, J = 7 Hz, 3H, CH_2-CH_3), 2.22 (q, J = 7 Hz, 2H, CH_2CH_3), 2.83 (d, J = 7 Hz, 2H, CH_2), 3.43, 3.66 (2 s, 6H, $2OCH_3$), 3.55–4.04 (m, 2H, CHCH), 7.0–7.38 (m, 5H, arom.). – MS (70 eV): m/z (%) = 292 (2, M^+), 57 (100, C_2H_5CO).

$C_{16}H_{20}O_5$ (292.3) Calcd. C 65.74 H 6.89
Found C 65.58 H 7.00

Dimethyl (R)-(–)-4-Oxo-2,4-diphenyl-1,1-butanedicarboxylate [(*R*)-**5c**]: Ozonolysis of 3.61 g (8 mmol) of (*SR*)-**4c** and purification of the crude product by column chromatography (silica gel; ether, pentane, 1:1) yielded 2.55 g (94%) of (*R*)-**5c** as a colorless solid, m.p. 106.5–107°C; (ref.[12] m.p. 106–107°C), $[\alpha]_D^{20} = -28.5$ (c = 1.0, $CHCl_3$). – IR (KBr): ν = 3100–2820 cm^{-1} (CH), 1730 (C=O), 1680 (C=O), 1600 (C=C), 1580, 1490, 1460, 1430, 1420. – ^1H NMR ($CDCl_3$): δ = 3.34–3.57 (m, 2H, CH_2), 3.43, 3.67 (2 s, 6H, $2OCH_3$), 3.85 (d, J = 7 Hz, 1H, CH), 4.15 [m, 1H, $CH(CO_2CH_3)_2$], 7.05–7.50, 7.67–8.0 (m, 10H, arom.). – MS (70 eV): m/z (%) = 340 (1, M^+), 105 (100, C_6H_5CO).

$C_{20}H_{20}O_5$ (340.4) Calcd. C 70.57 H 5.92
Found C 70.60 H 5.80

Dimethyl (R)-(–)-2-(4-Benzyloxy-3-methoxyphenyl)-4-oxo-1,1-hexanedicarboxylate [(*R*)-**5d**]: Cleavage of the hydrazone (*SR*)-**4d** during column chromatography on silica gel (ether, pentane, 5:1) yielded 1.44 g (67%) of (*R*)-**5d** as a colorless crystalline solid, m.p. 106.5–107°C (CH_2Cl_2/pentane); $[\alpha]_D^{20} = -0.77$ (c = 1.3, $CHCl_3$). – IR (KBr): ν = 3090–2820 cm^{-1} (CH), 1755, 1710, 1610, 1590, 1520, 1470, 1460, 1430. – ^1H NMR ($CDCl_3$): δ = 0.92 (t, J = 7 HZ, 3H, CH_3), 2.28 (m, 2H, CH_2CH_3), 2.88 (d, J = 7 Hz, 2H, CH_2CO), 3.48 (s, 3H, CO_2CH_3), 3.62–4.0 (m, 2H, CHCH), 3.7 (s, 3H, $C_6H_3OCH_3$), 3.84 (s, 3H, CO_2CH_3), 5.08 (s, 2H, OCH_2), 6.74 (m, 3H, arom.), 7.33 (m, 5H, arom.). – MS (70 eV): m/z (%) = 429 (5, $M^+ + 1$), 428 (19, M^+), 91 (100, C_7H_7).

$C_{24}H_{28}O_7$ (428.5) Calcd. C 67.28 H 6.59
Found C 67.13 H 6.60

Dimethyl (R)-(–)-2-(4-Benzyloxy-3-methoxyphenyl)-4-oxo-4-phenyl-1,1-butanedicarboxylate [(*R*)-**5e**]: Ozonolysis of 1.6 g (2.7 mmol) of (*SR*)-**4e** and purification of the crude product by column chromatography (silica gel, ether) yielded 0.8 g (62%) of (*R*)-**5e** as a colorless crystalline solid, m.p. 107.0–107.5°C (CH_2Cl_2/pentane); $[\alpha]_D^{25} = -18.2$ (c = 1.0, $CHCl_3$). – IR (KBr): ν = 3080–2850 cm^{-1} (CH), 1750, 1730 (C=O), 1685 (C=O), 1595, 1580, 1520, 1470, 1460, 1450, 1440, 1430. – ^1H NMR ($CDCl_3$): δ = 3.45 (m, 2H, CH_2CO), 3.48 (s, 3H, CO_2CH_3), 3.7 (s, 3H, $C_6H_3OCH_3$), 3.82 (m, 1H, CH), 3.82 (s, 3H, CO_2CH_3), 4.12 (m, 1H, CH), 5.05 (s, 2H, OCH_2), 6.75 (m, 3H, arom.), 7.35 (m, 8H, arom.), 7.87 (m, 2H, arom.). – MS (70 eV): m/z (%) = 477 (6, $M^+ + 1$), 476 (18, M^+), 105 (100, C_6H_5CO).

$C_{28}H_{28}O_7$ (476.5) Calcd. C 70.58 H 5.92
Found C 70.82 H 6.04

(R)-(+)-2-(4-Methoxyphenyl)-4-oxo-4-phenyl-1,1-butanedicarbonitrile [(*R*)-**5f**]: Ozonolysis of 2.08 g (5 mmol) of (*SR*)-**4f** and purification of the crude product by column chromatography (siliga gel; ether, pentane, 1:1) yielded 1.1 g (72%) of (*R*)-**5f** as a colorless solid, m.p. 119–120°C (ref.[13] m.p. 119–120°C); $[\alpha]_D^{20} = +12.2$ (c = 0.9, CH_3OH). – IR (KBr): ν = 3090–2820 cm^{-1} (CH), 2250 (C≡N), 1690 (C=O), 1620 (C=C), 1600, 1590, 1520, 1460, 1450. – ^1H NMR ($CDCl_3$): δ = 3.35–3.85 (m, 3H, CH_2CH), 3.67 (s, 3H, OCH_3), 4.55 [d, J = 4 Hz, 1H, $CH(CN)_2$], 6.73–7.88 (m, 9H, arom.). – MS (70 eV): m/z (%) = 304 (0.6, M^+), 105 (100, C_6H_5CO).

$C_{19}H_{26}N_2O_2$ (304.3) Calcd. C 74.98 H 5.38 N 9.20
Found C 75.06 H 5.39 N 9.15

Synthesis of rac-5 (Typical Procedure). – *rac*-**5c**: According to the general procedure given for the hydrazones **4**, 1.62 g (10 mmol) of acetophenone dimethylhydrazone was treated with 2.2 g (10 mmol) of **3a** to afford after workup and purification by column chromatography (silica gel, ether) 3.7 g (97%) of the DMH-derivative of *rac*-**5c** as a yellow oil. – IR (film): ν = 3090–2780 cm^{-1} (CH), 1750, 1740 (CO), 1640 (CN), 1600, 1570, 1500, 1470. – ^1H NMR ($CDCl_3$): δ = 2.32 (s, 6H, NMe_2), 2.81–3.10 (m, 2H, CH_2), 3.40–3.78 (m, 2H, CH), 3.41 and 3.78 (2 s, 6H, OCH_3), 6.91–7.47 (m, 10H, C_6H_5). – MS (70 eV): m/z (%) = 382 (19, M^+), 44 (100, NMe_2).

$C_{22}H_{26}N_2O_4$ (382.2) Calcd. C 69.10 H 6.85 N 7.32
Found C 68.74 H 6.95 N 7.76

3.05 g (8 mmol) of *rac*-**5c**-DMH was cleaved by ozonolysis (see general procedure) to give after workup and column chromatography (silica gel, ether, pentane, 1:1), 2.45 g (90%) of *rac*-**5c** as a colorless solid, m.p. 107°C.

CAS Registry Numbers

(*S*)-**2a**: 65651-52-7 / (*S*)-**2b**: 65651-53-8 / (*S*)-**2c**: 89393-53-3 / **3a**: 6626-84-2 / **3b**: 109012-75-1 / **3c**: 2826-26-8 / (*SR*)-**4a**: 109012-76-2 / (*SR*)-**4b**: 109012-77-3 / (*SR*)-**4c**: 109012-78-4 / (*SR*)-**4d**: 109012-79-5 / (*SR*)-**4e**: 109033-99-0 / (*SR*)-**4f**: 109012-80-8 / (*R*)-**5a**: 109012-81-9 / (*R*)-**5b**: 109012-82-0 / (*R*)-**5c**: 109012-83-1 / (±)-**5c** (dimethylhydrazone): 109012-87-5 / **5d**: 109012-84-2 / **5e**: 109012-85-3 / **5f**: 109012-86-4 / Me_2CO: 67-64-1 / AcEt: 78-93-3 / AcPh: 98-86-2 / $CH_2(CO_2Me)_2$: 108-59-8 / PhCHO: 100-52-7 / $CH_2(CN)_2$: 109-77-3 / 4-$MeOC_6H_4CHO$: 123-11-5 / 4,3-$(PhCH_2O)$-$(MeO)C_6H_3CHO$: 2426-87-1 / $Me_2NN{=}C(Me)Ph$: 13466-32-5 / SAMP: 59983-39-0

[1] Part of the *Dissertations* of A.S.D., Univ. of Bonn, 1985, and B.E.M.R., Techn. Hochschule Aachen, 1987.

[2] Reviews: [2a] K. Tomioka, K. Koga in *Asymmetric Synthesis* (J. D. Morrison, Ed.), vol. 2, p. 201, Academic Press, Orlando 1983. – [2b] G. H. Posner in ref.[2a], p. 225. – For leading references see: [2c] S. J. Blarer, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **65** (1982) 1637.

[3] Review: [3a] D. Enders in *Asymmetric Synthesis* (J. D. Morrison, Ed.), vol. 3, p. 275, Academic Press, Orlando 1984. – [3b] D. Enders, H. Eichenauer, U. Baus, H. Schubert, *Tetrahedron* **40** (1984) 1345. – [3c] D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **65** (1987), in press. – For recent applications see: [3d] D. Enders, H. Schubert, C. Nübling, *Angew. Chem.* **98** (1986) 1118; *Angew. Chem. Int. Ed. Engl.* **25** (1986) 1109. – [3e] D. Enders, B. Bhushan Lohray, *Angew. Chem.* **99** (1987) 359; *Angew. Chem. Int. Ed. Engl.* **26** (1987), 351.

[4] D. Enders, K. Papadopoulos, *Tetrahedron Lett.* **24** (1983) 4967.
[5] [5a] D. Enders, B. E. M. Rendenbach, *Chem. Ber.* **120** (1987) 1223. – [5b] D. Enders, B. E. M. Rendenbach, Enantioselective Synthesis of Bioregulators in *Pesticide Science and Biotechnology* (R. Greengalph, T. R. Roberts, Eds.), p. 17, Blackwell Scientific Publ., Oxford 1987.
[6] [6a] D. Enders, K. Papadopoulos, B. E. M. Rendenbach, R. Appel, F. Knoch, *Tetrahedron Lett.* **27** (1986) 3491. – [6b] D. Enders, B. E. M. Rendenbach, *Tetrahedron* **42** (1986) 2235.
[7] Acrylates, methacrylates: K. Papadopoulos, *Dissertation*, Univ. of Bonn, 1985; B. E. M. Rendenbach, *Dissertation*, Technische Hochschule Aachen, 1987. α,β-Unsaturated sulfones and phosphonates: D. Enders, K. Papadopoulos, unpublished results.
[8] [8a] K. Tomioka, K. Ando, K. Yasuda, K. Koga, *Tetrahedron Lett.* **27** (1986) 715. – [8b] K. Tomioka, K. Yasuda, K. Koga, *Tetrahedron Lett.* **27** (1986) 4611.
[9] [9a] S. J. Blarer, D. Seebach, *Chem. Ber.* **116** (1983) 2250. – [9b] D. Seebach, R. Imwinkelried, T. Weber in *Modern Synthetic Methods* (R. Scheffold, Ed.), vol. 4, p. 125, Springer-Verlag, Berlin 1986.
[10] E. J. Corey, D. Enders, *Chem. Ber.* **111** (1978) 1337, 1362.
[11] E. P. Kohler, R. Allen, *J. Am. Chem. Soc.* **45** (1923) 1989.
[12] [12a] E. P. Kohler, G. Heritage, A. Macleod, *J. Am. Chem. Soc.* **46** (1911) 217. – [12b] C. A. Kingsbury, R. F. Hutton, D. Durham, *J. Org. Chem.* **43** (1978) 4452.
[13] J. L. Soto, C. Seoane, J. A. Ciller, *Ann. Chim. (Paris)* **760** (1980) 281.
[14] H. Eichenauer, *Dissertation*, Univ. of Gießen, 1980.
[15] H. Schubert, *Dissertation*, Univ. of Bonn, 1985.
[16] [16a] J. W. Baker, A. Eccles, *J. Chem. Soc.* **1927**, 2126. – [16b] C. Liebermann, *Ber. Dtsch. Chem. Ges.* **27** (1984) 289.
[17] C. F. H. Allen, F. W. Sprangler, *Org. Synth.*, Coll. Vol. III (1955) 377.
[18] B. B. Corson, R. W. Stoughton, *J. Am. Chem. Soc.* **50** (1928) 2828.
[19] A. S. Demir, *Dissertation*, Univ. of Bonn, 1985.
[20] D. Enders, *Chem. Scr.* **25** (1985) 139.

[123/87]