Pergamon

Tetrahedron, Vol. 52, No. 16, pp. 5805-5818, 1996
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0040-4020/96 $15.00 + 0.00

S0040-4020(96)00236-0

Novel Asymmetric Syntheses of (−)-Malyngolide and (+)-*epi*-Malyngolide

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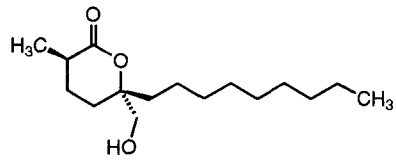
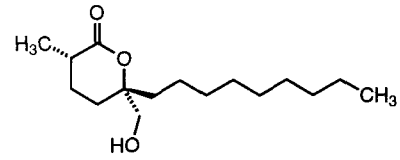
Abstract: The diastereo- and enantioselective synthesis of (−)-malyngolide [(*S,R*)-**1**], an antibiotic against *Mycobacterium smegmatis* and *Streptococcus pyogenes*, using the asymmetric Carroll rearrangement as key step is described. Furthermore, the diastereo- and enantioselective synthesis by double α,α′-alkylation using SAMP/RAMP hydrazone methodology affords the diastereomer (+)-*epi*-malyngolide [(*S,S*)-**1**]. Copyright © 1996 Elsevier Science Ltd

(−)-Malyngolide [(*S,R*)-**1**] was firstly isolated from the blue-green marine algae *Lyngbya majuscula* in 1979[1] and showed antibiotic activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes*.[2] Due to its structural simplicitiy, the combination of the two stereogenic centres of which one is quarternary and the large number of more complex natural products that possess a five substituted δ-lactone moiety, malyngolide has been a target of a large number of syntheses. The first reported synthesis was developed by *Mukaiyama et al.*.[3] Up to now, several syntheses of racemic malyngolide,[4] several "ex chiral pool"-syntheses[5] and eight asymmetric syntheses[6] to generate the optically active antibiotic have been reported.



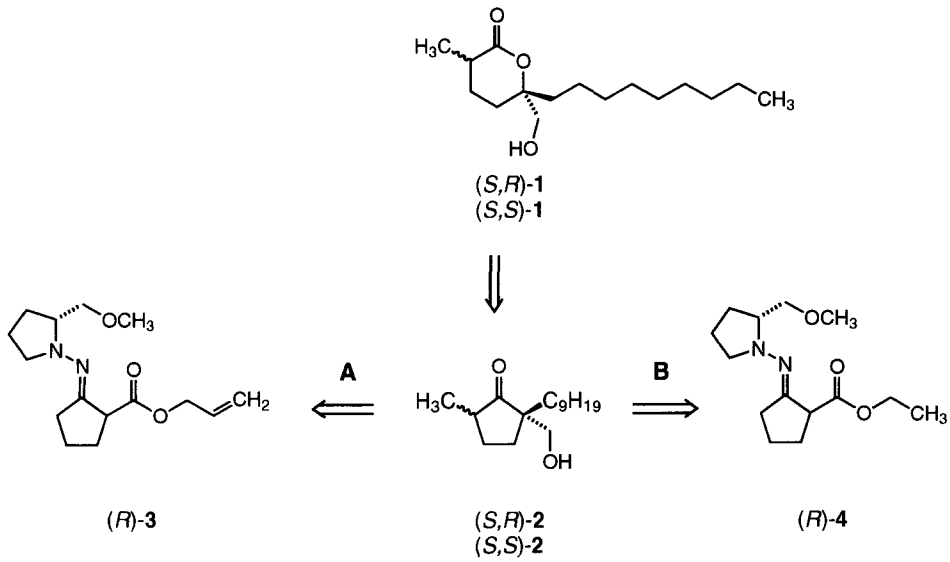
(*S,R*)-**1**



(*S,S*)-**1**

In this paper we report an efficient synthesis of (−)-malyngolide [(*S,R*)-**1**] in high enantiomeric purity (*ee* > 96%). As described in scheme 1, our retrosynthetic approaches start from the β-hydroxyketones **2** which are accessible by retro-Baeyer-Villiger oxidation. Recently, we reported the first asymmetric auxiliary-directed [3.3]-sigmatropic Carroll rearrangement of β-hydrazonoesters leading to γ,δ-unsaturated-α-quarternary-β-sub-

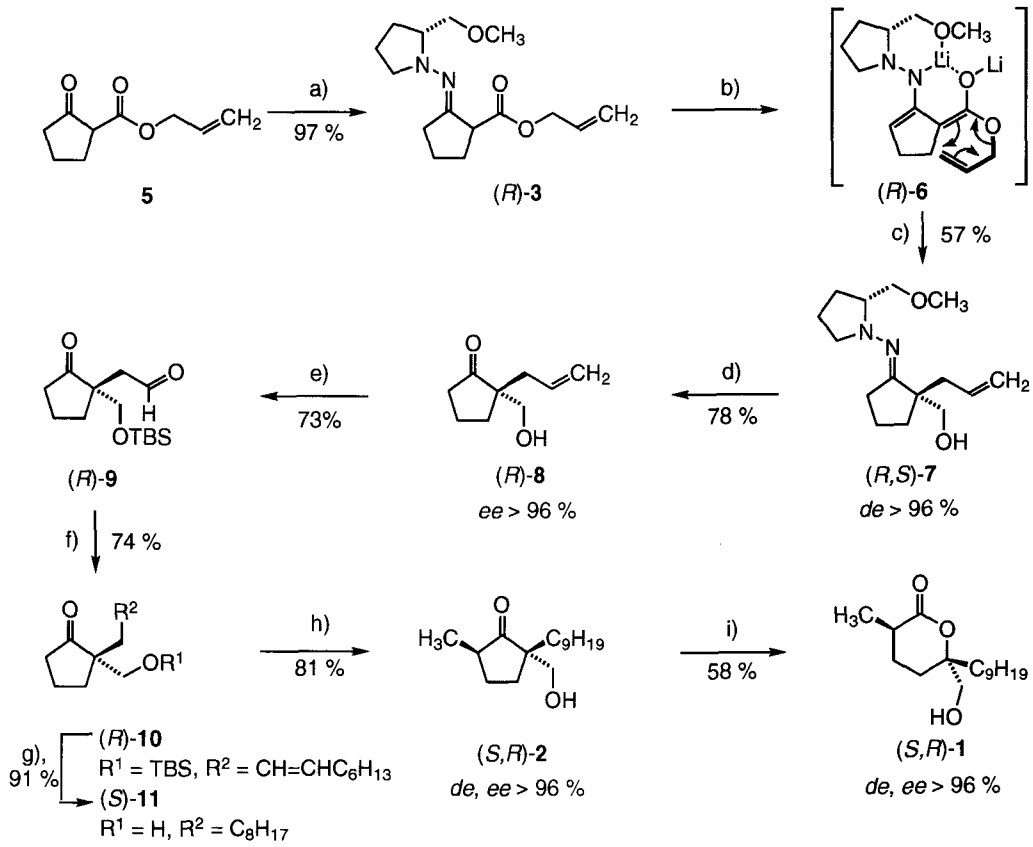
stituted ketones.[7] The first concept **A** is a synthesis using this asymmetric Carroll rearrangement. Key step in this synthesis is the diastereo- and enantioselective [3.3]-sigmatropic rearrangement of allyloxycarbonylcyclopentanone RAMP hydrazone [(*R*)-**3**] to generate the quarternary stereogenic centre. The tertiary stereogenic centre is obtained by α-alkylation. Alternatively concept **B** generates both stereogenic centres by double α,α'-alkylation of hydrazone (*R*)-**4** employing again the SAMP/RAMP hydrazone methodology leading to (+)-*epi*-malyngolide [(*S,S*)-**1**]. In both cases, the desired absolute configuration is obtained by using RAMP as chiral auxiliary.



Scheme 1. Retrosynthetic analysis of (*S,R*)-**1** and (*S,S*)-**1**

As depicted in scheme 2 the allyloxycyclopentanone **5** was converted to the corresponding RAMP hydrazone (*R*)-**3** in excellent yield. Upon double deprotonation with 2.4 equiv. lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in toluene the intermediate dianion (*R*)-**6** underwent rearrangement and was immediately reduced with 5 equiv. $LiAlH_4$ in diethyl ether to the α-quarternary hydrazone (*R,S*)-**7**. The yield over these two steps was only 57% but the diastereomeric excess was very good (*de* > 96%). The absolute configuration is assumed as (*R,S*)-**7** in accordance with earlier results of the asymmetric Carroll rearrangement of β-hydrazonoesters, which was assigned by X-ray structure determination,[7] or intermolecular electrophilic substitutions of β-hydrazonoesters.[8] We postulate an intramolecular chelation of the lithium by the methoxymethyl group of the hydrazonoester dienolate (*R*)-**6** and consequently the allylic moiety approaches from the less hindered front side (*si*-attack).[9] The chiral auxiliary was oxidatively cleaved with ozone in

excellent yield, with no epimerisation or concomitant oxidation of the C=C-double bond leading to ketone (*R*)-**8**. The enantiomeric excess (*ee* > 96%) was measured after formation of its MPA ester.[10]

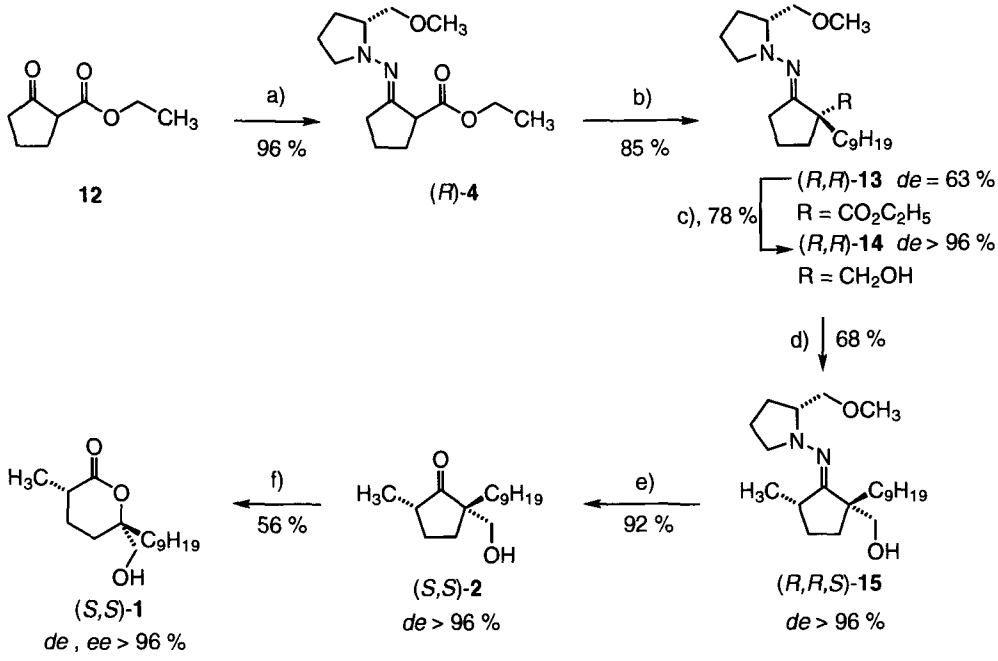


Reaction conditions.
a) RAMP, toluene, *p*TsOH, molecular sieves, b) 2.4 equiv. LiTMP, toluene, -100 °C, c) 1. rt, 2. $LiAlH_4$, diethyl ether, d) ozone, pentane, -78 °C, e) 1. TBSCl, Hünig's base, DMF, rt, 2. OsO_4, $NaIO_4$, dioxane, rt, f) $C_7H_{15}PPh_3Br$, KO*t*Bu, THF, -78 °C, g) H_2, Pd/C, h) 1. LDA, THF, CH_3I, -78 °C, 2. LDA, THF, -78 °C; NH_4Cl, i) *m*CPBA, $CHCl_3$, $NaHCO_3$, rt.

Scheme 2. Synthesis of (–)-malyngolide [(*S,R*)-**1**] *via* asymmetric Carroll rearrangement

After protection of the hydroxyl function as the *t*-butyldimethylsilyl-(TBS)-ether[11] the terminal double bond was oxidatively cleaved *via* dihydroxylation with catalytic amounts of OsO_4 in dioxane with subsequent periodate cleavage with excess $NaIO_4$ as one pot reaction.[12] The aldehyde (*R*)-**9** was obtained in a good yield. The chain-extension was achieved by Wittig reaction of the aldehyde (*R*)-**9** with heptyltriphenylphosphonium bromide in the presence of KO*t*Bu. The olefin (*R*)-**10** was yielded as *E/Z*-mixture of 1/5.7 in good yield. In the

following step the olefin (*R*)-**10** was reduced by hydrogenation with H_2 on Pd/C affording the α-quarternary ketone (*S*)-**11** in very good yield. The tertiary stereogenic centre has been introduced by alkylation with methyl iodide. The crude product was again deprotonated with excess LDA and diastereoselectively protonated at –78 °C leading to ketone (*S,R*)-**2** in good yield and very good diastereo- and enantiomeric excesses (*de* > 96%, *ee* > 96%), which were determined by comparison of the optical rotation value measured with the literature data.[6c] In the final step, the lactone was obtained by Baeyer-Villiger oxidation in moderate yield,[13] which occurred with complete retention of absolute configuration. Comparison of the optical rotation value with that of the reported known compound[1,3b,6c] confirmed the optical purity of the product (*S,R*)-**1**.



Reaction conditions.
a) RAMP, toluene, *p*TsOH, molecular sieves, b) LDA, toluene/HMPA, *n*Nonl, -100 °C, c) 1. $LiAlH_4$, diethyl ether, 2. separation by flash chromatography, d) LDA, diethyl ether, CH_3I, -100 °C, e) ozone, pentane, -78 °C, f) *m*CPBA, $CHCl_3$, $NaHCO_3$, rt.

Scheme 3. Synthesis of (+)-*epi*-malyngolide (*S,S*)-**1**

The synthesis of (+)-*epi*-malyngolide [(*S,S*)-**1**] was carried out by double α,α′-alkylation using the SAMP/RAMP hydrazone methodology (Scheme 3). Firstly, the ethoxycarbonylcyclopentanone **12** was converted to the corresponding RAMP hydrazone (*R*)-**4** in excellent yield, deprotonated with LDA in toluene

and alkylated with excess *n*-nonyl iodide in the presence of HMPA[14] at –100 °C. The α-quarternary hydrazone (*R,R*)-**13** was obtained by alkylation in very good yield and a diastereomeric excess of 63%. The absolute configuration of the α-quarternary hydrazone **13** was investigated by NMR spectroscopy using NOE measurements and was in accordance with earlier results concerning electrophilic substitutions *via* SAMP/RAMP hydrazones creating quarternary stereogenic centres.[8] We postulate again the chelation of the lithium by the methoxymethyl group of the chiral auxiliary and consequently, the alkyl iodide approaches from the less hindered front side. Enrichment by flash chromatography or HPLC proved fruitless. However, enrichment by flash chromatography was possible after reduction of the ester to the alcohol (*R,R*)-**14** with 5 equiv. $LiAlH_4$ in diethyl ether at room temperature leading to the diastereomerically pure β-hydroxyhydrazone (*R,R*)-**14**. The tertiary stereogenic centre was introduced by deprotonation with 1.4 equiv. LDA in diethyl ether and alkylation with excess methyl iodide leading to hydrazone (*R,R,S*)-**15**. Oxidative cleavage of the chiral auxiliary occurred without epimerisation to afford the ketone (*S,S*)-**2** in very good yield. The lactone (*S,S*)-**1** was obtained by Baeyer-Villiger oxidation. The final step was achieved in 56% yield with complete retention of absolute configuration leading to the enantiopure (+)-*epi*-malyngolide [(*S,S*)-**1**]. Comparison of the optical rotation value with that of the reported known compound[3a,6g] confirmed the optical purity of the product.

In conclusion, two new concise highly efficient diastereo- and enantioselective strategies to synthesise optically pure (–)-malyngolide [(*S,R*)-**1**] in 9 steps with an overall yield of 10% (variant A) and (+)-*epi*-malyngolide [(*S,S*)-**1**] in 6 steps with an overall yield of 23% (variant B) with excellent enantiomeric excesses of > 96% have been developed.

EXPERIMENTAL

General: All reactions were carried out using standard Schlenk techniques unless otherwise stated. Solvents were dried and purified by conventional methods prior to use. Tetrahydrofuran (THF) was freshly distilled from sodium, dichloromethane, pentane and DMF from CaH_2 under argon. Light petroleum refers to the fraction with b.p. 40 - 80 °C. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. *n*-Butyllithium (1.6 M in hexane) was purchased from Merck, Darmstadt. – Analytical TLC: Merck glass-backed silica 60 F254 plates. – Preparative column chromatography: Merck silica gel 60, particle size 0.040 - 0.063 mm (230 - 400 mesh) (flash). – Optical rotation: Perkin Elmer P 241 polarimeter; solvents of Merck UVASOL quality. – IR spectra: Perkin Elmer 1420 and Perkin Elmer FT/IR 1750. – ^1H NMR spectra (300 MHz), ^{13}C NMR spectra (75 MHz): Varian VXR 300 and Gemini 300 (solvent: $CDCl_3$, TMS as internal standard). – Mass spectra: Varian MAT 212 (EI 70 eV) (relative intensities in paranthesis). Elemental analyses: Heraeus CHN-O-Rapid.

2-(Prop-2'-enoxycarbonyl)cyclopentanone (**5**): Adipinic acid diallyl ester (1.11 g, 50 mmol) was added dropwise to a stirred suspension of sodium (1.2 g, 50 mmol) in refluxing toluene (200 ml) and stirring was continued for 6 h. The reaction mixture was given to a mixture of 0.2 N HCl/ice (200 g), the organic layer was

separated, the aqueous layer was extracted with diethyl ether for three times and the combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether = 10/1) afforded 4.05 g (48%) of a colourless oil. – R_f = 0.3 (petroleum ether/diethyl ether = 2/1). – keto : enol > 98 : 2. – IR (film): $\tilde{\nu}$ = 3085 (w, $=CH_2$), 2970, 2883 (m, CH), 1757 (s, $C=O_{ketone}$), 1728 (s, $C=O_{ester}$), 1620 (w, C=C), 1335 (m), 1298 (m), 1251 (m), 1186 (m), 1113 (m), 993 (m), 931 (m, $HC=CH_2$) cm^{-1}. – ^1H NMR: δ = 1.82-1.97 (m, 1H, $CHHCH_2C=O$), 2.09-2.24 (m, 1H, $CHHCH_2C=O$), 2.26-2.36 (m, 4H, $CH_2CH_2CH_2C=O$), 3.20 (t, J = 9.1 Hz, 1H, CHC=O), 4.61-4.66 (m, 2H, $CH_2CH=CH_2$), 5.23 (dt, J = 10.4/1.4 Hz, 1H, $CH=CHH_{cis}$), 5.34 (dq, J = 17.3/1.7 Hz, 1H, $CH=CHH_{trans}$), 5.85-5.95 (m, 1H, $CH=CH_2$). – ^{13}C NMR: δ = 20.98 ($CH_2CH_2C=O$), 27.45 ($CH_2CHC=O$), 38.01 ($CH_2C=O$), 54.72 (CHC=O), 65.71 ($OCH_2CH=$), 118.23 ($CH=CH_2$), 131.90 ($CH=CH_2$), 169.08 (COO), 212.06 (C=O). – MS (70 eV), *m/z* (%) = 168 (11.5, M^+), 140 (16) [M^+–$CH_2=CH_2$], 128 (6) [$C_5H_7OCOOH^+$], 111 (48) [$C_5H_6OCOH^+$], 99 (18) [$C_6H_9O^+$], 83 (34) [$C_6H_9^+$], 71 (26) [$C_5H_{11}^+$], 55 (69) [$C_4H_7^+$], 41 (100) [$C_3H_5^+$]. – $C_9H_{12}O_3$ [168.2] calcd. C: 64.27, H: 7.19; found C: 64.22, H: 7.48.

(E,2R)-(+)-1-[2'-(Prop-2''-enoxycarbonyl)cyclopentylidene]amino-2-methoxymethylpyrrolidine [(*R*)-**3**]: β-Ketoester **5** (2.52 g, 15 mmol) and RAMP (2.34 g, 18 mmol) were heated to reflux in toluene (20 ml) in the presence of *p*TsOH (0.15 g, 10 mol-%) and molecular sieves. After filtration, to remove the molecular sieves the reaction mixture was evaporated under reduced pressure, the residue was dissolved in diethyl ether, washed twice with saturated aqueous NaCl solution and dried over $MgSO_4$. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether/NEt_3 = 5/1/0.1) yielded 4.07 g (97%) of a colourless liquid. – R_f = 0.4 (petroleum ether/diethyl ether = 1/1). – $[\alpha]_D^{20}$ = + 85.3 (*c* = 1.3, $CHCl_3$). – enhydrazine : hydrazone > 98 : 2. – IR (film): $\tilde{\nu}$ = 3081 (w, $=CH_2$), 2955, 2873 (m, CH), 1664 (s, $C=O_{enhydrazine}$), 1607 (s, $C=C_{enhydrazine}$), 1459 (m), 1268 (s), 1128 (m), 1033 (m) cm^{-1}. – ^1H NMR: δ = 1.65-1.86 (m, 5H, NCH_2CH_2CHH, CH_2CH_2CN), 1.89-2.01 (m, 1H, NCH_2CH_2CHH), 2.55 (t, J = 8.2 Hz, 2H, $CH_2C=CN$), 2.57 (q, J = 9.1 Hz, 1H, NCHH), 2.69 (t, J = 7.7 Hz, 2H, CH_2CN), 2.73-2.82 (m, 1H, NCHH), 3.22 (dt, J = 9.1/4.7 Hz, 1H, NCH), 3.31 (dd, J = 9.3/6.0 Hz, 1H, CH_3OCHH), 3.33 (s, 3H, OCH_3), 3.42 (dd, J = 9.3/3.9 Hz, 1H, CH_3OCHH), 4.60 (dt, J = 5.2/1.4 Hz, 2H, $OCH_2CH=CH_2$), 5.19 (dd, J = 10.4/1.4 Hz, 1H, $CH=CHH_{cis}$), 5.30 (dd, J = 17.3/1.7 Hz, 1H, $CH=CHH_{trans}$), 5.96 (ddd, J = 17.3/10.7/5.5 Hz, 1H, $CH=CH_2$), 7.74 (s, 1H, NH). – ^{13}C NMR: δ = 21.31 (NCH_2CH_2), 21.37 (CH_2CH_2CN), 26.41 ($NCH_2CH_2CH_2$), 30.02 ($CH_2C=CN$), 33.30 (CH_2CN), 58.27 (NCH_2), 59.63 (CH_2OCH_3), 63.88 ($OCH_2CH=$), 66.69 ($NCHCH_2O$), 74.28 (CH_2OCH_3), 91.68 (C=CN), 117.18 ($CH=CH_2$), 134.17 ($CH=CH_2$), 166.85 (COO), 168.33 (C=O). – MS (70 eV), *m/z* (%) = 280 (19) [M^+], 235 (29) [M^+–CH_2OCH_3], 177 (100) [M^+–CH_2OCH_3–$C_3H_{16}O$], 163 (7) [M^+–CH_2OCH_3–C_4H_8O], 149 (22) [M^+–CH_2OCH_3–$C_5H_{10}O$], 114 (5) [$CH_3OCH_2C_4H_7N^+$], 108 (56) [$C_7H_8O^+$], 98 (3) [$C_6H_{10}O^+$], 82 (11) [$C_6H_{10}^+$], 70 (27) [$C_4H_8N^+$], 55 (10) [$C_4H_7^+$], 45 (12) [$CH_2OCH_3^+$], 41 (43) [$C_3H_7^+$]. – $C_{15}H_{24}N_2O_3$ [280.4] calcd. C: 64.26, H: 8.63, N: 9.99; found C: 64.40, H: 8.85, N: 9.98.

(2R,2'S)-(–)-[2'-Hydroxymethyl-2'-(prop-2''-enyl)cyclopentylidene]amino-2-methoxymethylpyrrolidine [(*2R,2'S*)-**7**]: A solution of RAMP hydrazone (*R*)-**5** (0.84 g, 3 mmol) in toluene (2 ml) was added dropwise to 2.4 equiv. of a LTMP solution in toluene [0.73 g (7.2 mmol) TMP/ 4.5 ml (7.2 mmol) 15% *n*BuLi solution in hexane] at −100 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 15 h. The reaction mixture was then added to a stirred suspension of $LiAlH_4$ (0.57 g, 15 mmol) in diethyl ether (50 ml) and stirring was continued until for 2 h. The hydrolysis was achieved by adding 1% HCl. After filtration from aluminum hydroxide precipitate the organic layer was washed with saturated NaCl solution and dried over $MgSO_4$. The crude product was purified by flash chromatography (silica gel, petroleum ether/diethyl ether = 2/1) to afford 0.41 g (57%) of a pale yellow oil. – R_f = 0.1 (petroleum ether/diethyl ether = 1/1). – $[\alpha]_D^{20}$ = – 229.8 (*c* = 0.3, $CHCl_3$). – *de* > 96% (determined by ^{13}C NMR). – IR (film): $\tilde{\nu}$ = 3410 (m, OH), 3075 (m, $=CH_2$), 2956, 2876 (s, CH), 1639 (m, C=N), 1451 (m), 1377 (m), 1124, 1100 (s), 914 (m, $=CH_2$) cm^{-1}. – ^1H NMR: δ = 1.45-2.02 (m, 8H, $CH_2CH_2CH_2CN$, $NCH_2CH_2CH_2$), 2.18-2.29 (m, 1H, CHHCN), 2.32 (d, *J* = 7.7 Hz, 2H, $CH_2CH{=}CH_2$), 2.47 (q, *J* = 8.7 Hz, 1H, NCHH), 2.49-2.61 (m, 1H, CHHCN), 3.26 (dt, *J* = 9.1/6.4 Hz, 1H, NCHH), 3.33 (s, 3H, CH_3O), 3.34-3.62 (m, 5H, CH_3OCH_2, CH_2OH, NCH), 4.20 (s, 1H, OH), 5.07 (d, *J* = 10.1 Hz, 1H, $CH{=}CH_{cis}H$), 5.08 (d, *J* = 16.8 Hz, 1H, $CH{=}CH_{trans}H$), 5.77 (ddt, *J* = 16.8/10.1/7.7 Hz, 1H, $CH{=}CH_2$). – ^{13}C NMR: δ = 21.66 (CH_2CH_2C=N), 22.18 (NCH_2CH_2), 26.30 ($NCH_2CH_2CH_2$), 31.33 (CH_2CC=N), 33.74 (CH_2C=N), 39.94 ($CH_2CH{=}CH_2$), 49.80 (*C*C=N), 54.16 (NCH_2), 59.09 (CH_2OCH_3), 66.11 (NCHCH$_2$O), 66.97 (CH_2OH), 76.39 (CH_2OCH_3), 117.83 ($CH{=}CH_2$), 134.55 ($CH{=}CH_2$), 173.87 (C=N). – MS (70 eV), *m/z* (%): 266 (4) [M^+], 221 (72) [M^+–CH_2OCH_3], 191 (2) [M^+–CH_2OCH_3–CH_2O], 122 (13) [$C_7H_{10}N_2^+$], 114 (11) [$CH_3OCH_2C_4H_7N^+$], 96 (13) [$C_7H_{12}^+$], 82 (1) [$C_6H_{10}^+$], 70 (100) [$C_4H_8N^+$], 55 (13) [$C_4H_7^+$], 45 (11) [$CH_2OCH_3^+$], 43 (20) [$C_3H_7^+$]. – $C_{15}H_{26}N_2O_2$ [266.4]: calcd. C: 67.63, H: 9.84, N: 10.52; found C: 67.56, H: 9.92, N: 10.59.

(2R)-(+)-2-Hydroxymethyl-2-(prop-2'-enyl)cyclopentanone [(*R*)-**8**]: The hydrazone (*2R,2'S*)-**7** (0.72 g, 3 mmol) was dissolved in pentane at −78 °C and ozone was bubbled through for 6 min. Evaporation of the solvent and purification by flash chromatography (silica gel, petroleum ether/diethyl ether = 2/1) afforded 0.36 g (78%) of a pale yellow liquid. – R_f = 0.6 (petroleum ether/diethyl ether = 1/2). – $[\alpha]_D^{20}$ = + 39.8 (*c* = 1.0, $CHCl_3$). – *ee* > 96% (determined by ^1H NMR of the MPA ester). – IR (film): $\tilde{\nu}$ = 3442 (m, br, OH), 3076 (w, $=CH_2$), 2959, 2882 (s, CH), 1734 (s, C=O), 1639 (m, C=C), 1418 (m), 1304 (s, br), 1123 (m), 1058 (m), 922 (m) cm^{-1}. – ^1H NMR: δ = 1.80-2.30 (m, 6H, $CH_2CH_2CH_2CO$), 2.66 (s, 1H, OH), 3.38 (s, 2H, $CH_2CH{=}CH_2$), 3.49 (d, *J* = 11.1 Hz, 1H, CHHOH), 3.65 (d, *J* = 11.1 Hz, 1H, CHHOH), 5.08 (dd, *J* = 11.4/1.4 Hz, 1H, CH=CHH), 5.09 (dd, *J* = 15.1/1.4 Hz, 1H, CH=CHH), 5.70 (ddt, 17.5/9.7/7.3 Hz, 1H, $CH{=}CH_2$). – ^{13}C NMR: δ = 19.05 (CH_2CH_2C=O), 30.30 (CH_2CC=O), 37.10, 38.94 (CH_2C=O, $CH_2CH{=}CH_2$), 56.18 (*C*C=O), 65.74 (CH_2OH), 118.64 ($CH{=}CH_2$), 133.24 ($CH{=}CH_2$), 223.57 (C=O). – MS (70 eV); *m/z* (%) = 154 (3) [M^+], 123 (5) [M^+–CH_2OH], 110 (14) [$C_5H_6OCO^+$], 94 (21) [M^+–C_3H_6–H_2O], 82 (16) [$C_6H_{10}^+$], 79 (45) [$C_5H_3O^+$], 67 (40) [$C_5H_7^+$], 55 (28) [$C_4H_7^+$], 41 (58) [$C_3H_5^+$]. – $C_9H_{14}O_2$ [154.2]: calcd. C: 70.10, H: 9.15; found C: 70.48, H: 9.39.

(2R)-(−)-2-tert-Butyldimethylsilyloxymethyl-2-(2'-oxoethyl)cyclopentanone [(*R*)-**9**]: I.) β-Hydroxyketone (*R*)-**8** (0.74 g, 4.8 mmol) was dissolved in DMF (4 ml) and transformed with TBSCl (1.44 g, 9.6 mmol) and imidazole (0.95 g, 14.4 mmol) and stirring was continued for 1 h (TLC control). The reaction mixture was diluted with petroleum ether (50 ml) washed with water and dried over $MgSO_4$. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether/NEt_3 = 20/1/0.5) afforded 1.24 g (96%) of a pale yellow liquid. – R_f = 0.7 (petroleum ether/diethyl ether = 4/1). – II.) The protected β-hydroxyketone (1.21 g, 4.5 mmol) was dissolved in dioxane/water (13.5 ml/4.5 ml). A 2% OsO_4 solution in dioxane (1.2 ml, 2 mol-%) was added at room temperature, giving a black solution, presumably due to the formation of the osmate ester. After 5 minutes $NaIO_4$ (2.03 g, 9.5 mmol) was added and stirring was continued for 2 h until the solution became light again. The reaction mixture was extracted three times with diethyl ether (100 ml), dried over $MgSO_4$ and purification by flash chromatography (silica gel, petroleum ether/diethyl ether/NEt_3 = 4/1/0.1) yielded 0.92 g (76%) of a colourless liquid. – R_f = 0.6 (petroleum ether/diethyl ether = 1/1). – $[\alpha]_D^{20}$ = − 21.1 (*c* = 1.2, $CHCl_3$). – *ee* > 96%. – IR (film): $\tilde{\nu}$ = 2955, 2930, 2886, 2858 (s, CH), 1739 (s, C=O), 1725 (s, C=O), 1471 (m), 1404, 1389 (m), 1255 (m), 1102 (s, SiOC), 839 (s), 779 (s) cm^{-1}. – ^1H NMR: δ = 0.03 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.88 (s, 9H, $(CH_3)_3CSi$), 1.88-2.04 (m, 3H, C*H*HCH_2CH_2CO), 2.16-2.34 (m, 2H, CH*H*CH_2C*H*HCO), 2.42-2.54 (m, 1H, CH*H*CO), 2.62 (dd, *J* = 17.2/1.1 Hz, 1H, C*H*HCHO), 2.71 (dd, *J* = 17.9/1.8 Hz, 1H, CH*H*CHO), 3.43 (d, *J* = 9.3 Hz, 1H, C*H*HOSi), 3.59 (d, *J* = 9.3 Hz, 1H, CH*H*OSi), 9.67 (s, 1H, CHO). – ^{13}C NMR: δ = –5.71 (CH_3Si), –5.65 (CH_3Si), 18.20 (($CH_3)_3$*C*Si), 19.23 (*C*H_2CH_2C=O), 25.78 (($CH_3)_3$CSi), 30.81 (*C*H_2CC=O), 38.30 (*C*H_2C=O), 48.15 (*C*H_2CHO), 51.81 (*C*C=O), 66.75 (CH_2OSi), 199.88 (CHO), 220.78 (C=O). – MS (70 eV), *m/z* (%) = 271 (2) [M^++1], 253 (2) [M^+–OH], 229 (2) [M^+–C_3H_6], 213 [M^+–C_4H_9], 183 (69) [M^+–C_6H_{15}], 169 (69), 139 (12), 121 (10), 93 (12), 75 (100), 67 (9) [$C_5H_7^+$], 61 (15), 43 (26) [$C_3H_7^+$]. – $C_{14}H_{26}O_3Si$ [270.5]: calcd. C: 62.18, H: 9.69; found C: 62.47, H: 9.78.

(E,2R)-(+)-tert-Butyldimethylsilyloxymethyl-2-(non-2'-enyl)cyclopentanone [(*E*,2*R*)-**10**]: A solution of *t*-BuLi (2.25 ml of 15% in pentane, 3.6 mmol) was added dropwise to a solution of heptyltriphenylphosphonium bromide (1.72 g, 3.9 mmol) in THF (10 ml) at –78 °C and stirring was continued for 2 h at –78 °C, the solution becoming light orange. Aldehyde (*R*)-**9** (0.81 g, 3 mmol) in THF (2 ml) was added and stirring was continued overnight causing the solution become yellow again. The reaction mixture was poured into petroleum ether (200 ml) and after filtration to remove the solid purification by flash chromatography (silica gel, petroleum ether/diethyl ether/NEt_3 = 20/1/0.5) afforded 0.78 g (74%) of a colourless liquid. – R_f = 0.8 (petroleum ether/diethyl ether = 5/1). – *E*/*Z* (C=C) 1 : 5.7 (determined by ^{13}C NMR). – $[\alpha]_D^{20}$ = + 5.8 (*c* = 1.0, $CHCl_3$). – *ee* > 96%. – IR (film): $\tilde{\nu}$ = 2956, 2927, 2856 (s, CH), 1741 (s, C=O), 1465 (s), 1405 (m), 1254 (s), 1162 (m), 1099 (s, br, SiOC), 1007 (m), 839 (s), 778 (s) cm^{-1}. – ^1H NMR: δ = 0.00 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.88 (t, *J* = 7 Hz, 3H, CH_3), 1.24-1.32 (m, 10H, $CH_3(CH_2)_5$), 1.76-2.22 (m, 8H, CH_2CH_2CH_2CO, CH_2CH=CH), 3.41 (d, *J* = 9.3 Hz, 1H, C*H*HOSi), 3.68 (d, *J* = 9.3 Hz, 1H, CH*H*OSi), 5.24 (dtt, *J* = 10.7/8.0/1.4 Hz, 1H, CCH$_2$CH=C*H*), 5.47 (dtt, *J* = 10.7/8.07/1.4 Hz, 1H, CCH$_2$C*H*=CH). – ^{13}C NMR: δ = –5.66 (CH_3Si), –5.64 (CH_3Si), 14.60 (CH_3), 18.70 (($CH_3)_3$*C*Si), 19.97

(CH_2CH_2C=O), 23.18 (CH_3CH_2), 26.33 ((CH_3)$_3$CSi), 27.80, 29.55, 30.12, 30.64, 31.43, 32.32 (CH_2CC=O, CCH_2CH=, $CH_3CH_2(CH_2)_4$), 40.04 (CH_2C=O), 54.65 (CC=O), 68.01 (CH_2OSi), 124.39 (CH_2CH=CH), 133.71 (CH_2CH=CH), 223.10 (C=O). – MS (70 eV), *m/z* (%) = 353 (1) [M^+] 339 (2) [M^+–CH_2], 297 (100) [M^+–C_4H_8], 213 (11) [M^+–$C_{10}H_{20}$], 171 (7), 142 (3), 121 (3), 105 (5), 89 (9), 75 (29), 55 (6) [$C_4H_7^+$]. – $C_{21}H_{40}O_2Si$ [352.6]: calcd. C: 71.53, H: 11.43; found C: 71.55, H: 11.69.

(2S)-(+)-2-Hydroxymethyl-2-nonylcyclopentanone [(2*S*)-**11**]: The unsaturated ketone (*R*)-**10** (0.63 g, 1.8 mmol) was dissolved in methanol (10 ml). After addition of a catalytic amount of Pd/C (10%) the reaction mixture was stirred overnight at room temperature. After filtration to remove the catalyst and evaporation of the solvent, purification by flash chromatography (silica gel, petroleum ether/diethyl ether = 5/1) afforded 0.39 g (91%) of a colourless liquid. – R_f = 0.1 (petroleum ether/diethyl ether = 5/1). – *ee* > 96%. – $[\alpha]_D^{20}$ = + 9.7 (*c* = 0.4, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3446 (m, br, OH), 2955, 2926, 2855 (s, CH), 1734 (s, C=O), 1466 (m), 1405 (m), 1163 (m), 1056 (m) cm^{-1}. – ^{1}H NMR: δ = 0.88 (t, *J* = 7.1 Hz, 3H, CH_3), 1.23-1.27 (m, 14H, $CH_3(CH_2)_7$), 1.39-1.48 (m, 2H, CH_2CH_2CO), 1.86-1.95 (m, 4H, $CH_2CH_2CCH_2$), 2.24-2.32 (m, 2H, CH_2CO), 2.39 (s, 1H, OH), 3.48 (d, *J* = 11.1 Hz, 1H, CHHOH), 3.63 (d, *J* = 11.1 Hz, 1H, CHHOH). – ^{13}C NMR: δ = 14.13 (CH_3), 19.22 (CH_2CH_2C=O), 22.71 (CH_3CH_2), 24.11 ($CH_3CH_2CH_2$), 29.34, 29.51, 29.59, 30.27, 30.62, 31.91, 32.57 (CH_2CC=O, 6CH_2), 38.91 (CH_2C=O), 53.52 (CC=O), 65.79 (CH_2OH), 224.74 (C=O). – MS (70 eV), *m/z* (%) = 240 (6) [M^+], 114 (100) [$C_6H_9OCH_2OH^+$], 97 (11) [$C_6H_9O^+$], 83 (15) [$C_6H_{11}^+$], 69 (48) [$C_5H_9^+$], 55 (28) [$C_4H_7^+$], 41 (26) [$C_3H_5^+$]. – $C_{15}H_{28}O_2$ [240.4]: calcd. C: 74.95, H: 11.74; found C: 74.63, H: 11.81.

(2S,5R)-(–)-2-Hydroxymethyl-5-methyl-2-nonylcyclopentanone [(2*S*,5*R*)-**2**]: Ketone (*S*)-**11** (0.38 g, 1.6 mmol) was added dropwise to a solution 2.5 equiv. LDA at –78 °C. After 2 h CH_3I (0.43 g, 3 mmol) was added at –100 °C and stirring was continued overnight while the reaction mixture was allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, the aqueous layer was separated, extracted twice with diethyl ether and the combined organic layers were dried over $MgSO_4$. After purification by flash chromatography (silica gel, petroleum ether/diethyl ether = 2/1) the crude product was again dissolved in 2 ml THF and added dropwise to 5 equiv. of a solution of LDA at –78 °C. After 1 h the reaction mixture was hydrolysed with NH_4Cl solution at –100 °C. The work-up was carried out as described above. Purification by flash chromatochraphy (silica gel, petroleum ether/diethyl ether = 3/1) afforded 0.33 g (81%) of a colourless liquid. – R_f = 0.3 (petroleum ether/diethyl ether = 1/1). – *de* > 96% (determined by ^{13}C NMR). – *ee* > 96% (determined by comparison of optical rotation value with that of the known compound). – $[\alpha]_D^{20}$ = – 19.3 (*c* = 0.5, $CHCl_3$). – $[\alpha]_D^{20}$ = – 19.3 (*c* = 1.5, $CHCl_3$).[6c] – IR (film): $\tilde{\nu}$ = 3449 (m, br, OH), 2957, 2927, 2871, 2855 (s, CH), 1729 (s, C=O), 1458 (m), 1375 (w), 1174 (w), 1046 (m) cm^{-1}. – ^{1}H NMR: δ = 0.88 (t, *J* = 6.7 Hz, 3H, CH_3CH_2), 1.10 (d, *J* = 6.7 Hz, 3H, CH_3CH), 1.23-1.28 (m, 14H, $CH_3(CH_2)_7$), 1.36-2.28 (m, 8H, CH_2CH_2CHCO, $CH_3(CH_2)_7CH_2$, OH), 3.45 (d, *J* = 10.7 Hz, 1H, CHHOH), 3.65 (d, *J* = 10.7 Hz, 1H, CHHOH). – ^{13}C NMR: δ = 14.13, 14.42 (2CH_3), 22.69 (CH_3CH_2), 24.29 ($CH_3CH_2CH_2$),

28.40, 29.09, 29.31, 29.49, 29.57 ($CH_2CH_2CH_2C{=}O$, $3CH_2$), 31.62, 31.89, 32.69 ($3CH_2$), 44.76 ($CH_2C{=}O$), 53.70 ($CC{=}O$), 66.42 (CH_2OH), 225.91 (C=O). – MS (70 eV); *m/z* (%) = 254 (1) [M^+], 142 (7) [M^+–C_8H_{16}], 128 (100) [$C_6H_9OCH_2OH^+$], 110 (45) [$C_6H_8OCH_2^+$], 97 (14) [$C_6H_9O^+$], 83 (14) [$C_6H_{11}^+$], 69 (51) [$C_5H_9^+$], 55 (27) [$C_4H_7^+$], 41 (23) [$C_3H_5^+$]. – $C_{16}H_{30}O_2$ [254.4]: calcd. C: 75.54, H: 11.89; found C: 75.24, H: 11.80.

(2S,5R)-(–)-Malyngolide [(2*S*,5*R*)-**1**]: β-Hydroxyketone (2*S*,5*R*)-**2** (0.28 g, 1.1 mmol) in $CHCl_3$ (3 ml) was treated with *m*CPBA (0.63 g, 2.2 mmol, 60%) and $NaHCO_3$ (0.18 g, 2.2 mmol) and stirring was continued for 3 d at room temperature with the exclusion of light. The reaction mixture was diluted with 20 ml CH_2Cl_2, washed with saturated aqueous $NaHCO_3$- and NaCl solutions and dried over $MgSO_4$. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether = 1/1) yielded 0.17 g (58%) of colourless crystals. – R_f = 0.2 (petroleum ether/diethyl ether = 1/1). – m.p. = 36 -38 °C. – *de* > 96% (determined by ^{13}C NMR). – *ee* > 96% (determined by comparison of optical rotation value with that of the known compound).– $[\alpha]_D^{20}$ = – 13.0 (*c* = 0.9, $CHCl_3$). – $[\alpha]_D^{20}$ = – 12.7,[3b] $[\alpha]_D^{20}$ = – 13.0,[6c] $[\alpha]_D^{20}$ = – 13.2.[1] – IR (KBr): $\tilde{\nu}$ = 3418 (m, br, OH), 2926, 2855 (s, CH), 1729 (s, C=O), 1462 (m), 1379 (m), 1237, 1208 (m, br), 1110, 1087 (m, br) cm^{-1}. – ^1H NMR: δ = 0.88 (t, *J* = 7.1 Hz, 3H, CH_3CH_2), 1.25-1.28 (m, 14H, $CH_3(CH_2)_7$), 1.28 (d, *J* = 6.3 Hz, 3H, CH_3CH), 1.52-2.07 (m, 6H, CH_2CH_2CHCO, $CH_3(CH_2)_7CH_2$), 2.44 (m, 1H, CH_3CHCO), 2.84 (s, 1H, OH), 3.47 (d, *J* = 11.3 Hz, 1H, CHHOH), 3.68 (d, *J* = 11.3 Hz, 1H, CHHOH). – ^{13}C NMR: δ = 14.12 (CH_3), 17.13 (CH_3), 22.67, 23.65, 25.29, 26.32, 29.32, 29.50, 29.55, 30.08, 31.90 ($CH_2CH_2CHC{=}O$, $7CH_2$), 35.56 ($CHC{=}O$), 36.73 (CCH_2), 67.70 (CH_2OH), 87.01 (CCH_2OH), 175.42 (C=O). – MS (70 eV), *m/z* (%) = 270 (2) [M^+], 239 (100) [M^+–CH_2OH], 211 (37) [M^+–CH_2CH_2–CH_2OH], 155 (31) 144 (18) [M^+–C_9H_{19}], 127 (28) [$C_9H_{19}^+$], 109 (14) [$C_8H_{13}^+$], 95 (20) [$C_7H_{11}^+$], 81 (32) [$C_6H_9^+$], 71 (29) [$C_5H_{11}^+$], 55 (38) [$C_4H_7^+$], 43 (43) [$C_3H_7^+$]. – $C_{16}H_{30}O_3$ [270.4] calcd. C: 71.07, H: 11.18, found C: 71.10, H: 10.74.

(E,2R)-(+)-1-[2'-(Ethoxycarbonyl)cyclopentylidene]amino-2-methoxymethylpyrrolidine [(*R*)-**4**]: Ethoxycarbonylcyclopentanone **12** (1.87 g, 12 mmol) and RAMP (1.89 g, 14.5 mmol) were heated to reflux in toluene (20 ml) in the presence of *p*TsOH (0.15 g, 10 mol-%) and molecular sieves. After filtration, to remove the molecular sieves the reaction mixture was evaporated under reduced pressure, the residue was dissolved in diethyl ether, washed twice with saturated aqueous NaCl solution and dried over $MgSO_4$. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether/NEt_3 = 5/1/0.1) yielded 3.09 g (96%) of a colourless liquid. – R_f = 0.2 (petroleum ether/diethyl ether = 2/1). – $[\alpha]_D^{20}$ = + 77.9 (*c* = 1.1, $CHCl_3$). – enhydrazine : hydrazone > 98:2. – IR (film): $\tilde{\nu}$ = 2957, 2929, 2872 (s, CH), 1662 (s, $C{=}O_{enhydrazine}$), 1609 (s, $C{=}C_{enhydrazine}$), 1461 (m), 1364 (m), 1271 (s), 1173 (m), 1129 (m), 1049 (m) cm^{-1}. – ^1H NMR: δ = 1.27 (t, *J* = 7.4 Hz, 3H, CH_3), 1.65-1.85 (m, 5H, CH_2CH_2CN, NCH_2CH_2CHH), 1.90-2.04 (m, 1H, NCH_2CH_2CHH), 2.52 (t, *J* = 7.4 Hz, 2H, $CH_2C{=}CN$), 2.57 (q, *J* = 8.7 Hz, 1H, NCHH), 2.68 (t, *J* = 7.7 Hz, 2H, CH_2CN), 2.73-2.82 (m, 1H, NCHH), 3.22 (dt, *J* = 9.1/5.4 Hz, 1H, NCH), 3.32 (dd, *J* = 9.4/6.0 Hz, 1H, CH_3OCHH), 3.34 (s, 3H, OCH_3), 3.43 (dd, *J* = 9.4/3.7 Hz, 1H, CH_3OCHH), 4.14 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 7.73 (s, 1H,

NH). – ^{13}C NMR: δ = 14.76 (CH_3CH_2O), 20.80 (NCH_2CH_2), 20.85 (CH_2CH_2CN), 25.92 ($NCH_2CH_2CH_2$), 29.59 (CH_2CCN), 32.79 (CH_2CN), 57.80 (NCH_2), 58.57 (CH_3CH_2O), 59.11 (CH_2OCH_3), 66.22 ($NCHCH_2O$), 73.81 (CH_2OCH_3), 91.65 (CC=N), 165.84 (C=N), 168.39 (COO). – MS (70 eV), *m/z* (%) = 268 (22) [M^+], 223 (25) [M^+–CH_2OCH_3], 177 (100) [M^+–CH_2OCH_3–C_2H_6O], 149 (17) [M^+–CH_2OCH_3–C_4H_9OH], 114 (4) [$CH_3OCH_2C_4H_7N^+$], 108 (6) [$C_8H_{12}^+$], 82 (7) [$C_6H_{10}^+$], 70 (18) [$C_4H_8N^+$], 55 (7) [$C_4H_7^+$], 45 (9) [$CH_2OCH_3^+$], 41 (12) [$C_3H_5^+$]. – $C_{14}H_{24}N_2O_3$ [268.4] calcd. C: 62.66, H: 9.01, N: 10.44, found C: 63.06, H: 9.20, N: 10.38.

(2R,2'R)-(–)-1-[2'-Ethoxycarbonyl-2'-nonylcyclopentylidene]amino-2-methoxymethylpyrrolidine [(2*R*,2'*R*)-**13**]: β-Hydrazonoester (*R*)-**4** (1.34 g, 5 mmol) was added dropwise to 1.5 equiv. of a solution of LDA in toluene (10 ml) at –78 °C. After stirring 30 min HMPA (0.69 g, 7.5 mmol) was added and after a further 30 min at –78 °C methyl iodide (2.13 g, 15 mmol) was added at –100 °C and stirring was continued overnight while the reaction mixture was allowed to warm to room temperature. The hydrolysis was carried out by adding saturated aqueous NH_4Cl solution. The organic layer was separated, the aqueous layer twice extracted with diethyl ether and the combined organic layers were dried over $MgSO_4$. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether/NEt_3 = 10/1/0.2) afforded 1.68 g (85%) of a pale yellow liquid. – R_f = 0.3 (petroleum ether/diethyl ether = 2/1). – $[\alpha]_D^{20}$ = – 157.2 (*c* = 1.0, $CHCl_3$). – *de* = 63% (determined by ^{13}C NMR). – ^{1}H NMR: δ = 0.88 (t, *J* = 7.1 Hz, 3H, $CH_3(CH_2)_8$), 1.25 (t, *J* = 7.4 Hz, 3H, CH_3CH_2O), 1.17-1.30 (m, 16H, $CH_3(CH_2)_8$), 1.50-1.76 (m, 3H, NCH_2CH_2CH, CH_2CH_2CN), 1.78-1.90 (m, 2H, NCH_2CH_2), 1.91-2.02 (m, 2H, NCH_2CH_2CH, $CHHCH_2CH_2CN$), 2.15-2.32 (m, 2H, $CHHCH_2CHHCN$), 2.47 (q, *J* = 8.4 Hz, 1H, NCHH), 2.57 (ddd, *J* = 18.8/7.4/4.7 Hz, 1H, CHHCN), 2.72-2.81 (m, 1H, NCHH), 3.21-3.30 (m, 2H, CH_3OCHH, NCH), 3.33 (s, 3H, OCH_3), 3.45 (dd, *J* = 13.1/7.4 Hz, 1H, CH_3OCHH), 4.13 (dtd, *J* = 10.4/7.1/3.4 Hz, 2H, OCH_2CH_3). – ^{13}C NMR: δ = 14.13, 14.32 (CH_3CH_2O, $CH_3CH_2CH_2$), 22.29, 22.72, 22.88, 24.96 [25.05], 26.39 [26.57] (CH_2CH_2CN, $CH_3CH_2CH_2$, $NCH_2CH_2CH_2$), 29.34, 29.55, 29.60, 30.13, 30.98, 31.98, 34.12 [34.87], 36.99 ($CH_2CH_2CH_2CN$, $7CH_2$), 53.45 [53.26] (NCH_2), 56.91 [57.24] (CC=N), 59.18 (CH_2OCH_3), 60.46 [60.53] (CH_3CH_2O), 66.33 [66.30] ($NCHCH_2O$), 75.24 [75.51] (CH_2OCH_3), 169.04 [167.73] (C=N), 174.92 [174.34] (COO).

(2R,2'R)-(–)-1-[2'-Hydroxymethyl-2'-nonylcyclopentylidene]amino-2-methoxymethylpyrrolidine [(2*R*,2'*R*)-**14**]: Hydrazone (2*R*,2'*R*)-**13** (1.50 g, 3.8 mmol) was added dropwise to a stirred slurry of $LiAlH_4$ (0.72 g, 19 mmol) in diethyl ether (50 ml) and stirring was continued for 3 h at room temperature. Hydrolysis was carried out by the addition of 15 ml 1% HCl at 0 °C. After filtration from the aluminum hydroxide precipitate, the filtrate was washed with diethyl ether and dried over $MgSO_4$. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether = 2/1) afforded 1.06 g (79%) of a pale yellow liquid. – R_f = 0.1 (petroleum ether/diethyl ether = 2/1). – $[\alpha]_D^{20}$ = – 173.7 (*c* = 1.0, $CHCl_3$). – *de* > 96% (determined by ^{13}C NMR, 63% before chromatography). – IR (film): $\tilde{\nu}$ = 3434 (m, br, NH), 2955, 2925, 2871, 2854 (s, CH), 1651 (w, C=N), 1461 (m), 1198 (w), 1101 (m), 1061 (m) cm^{-1}. – ^{1}H NMR: δ = 0.88 (t, *J* = 6.7 Hz, 3H, CH_3), 1.24-1.32 (m,

16 H, $CH_3(CH_2)_8$), 1.40-1.76 (m, 5H, $CH_2CH_2CH_2CN$, NCH_2CH_2CHH), 1.76-1.90 (m, 2H, NCH_2CH_2), 1.96-2.20 (m, 1H, NCH_2CH_2CHH), 2.26 (q, J = 8.7 Hz, 1H, CHHCN), 2.47 (q, J = 8.7 Hz, 1H, NCHH), 2.52-2.62 (m, 1H, CHHCN), 3.20-3.32 (m, 1H, NCHH), 3.33 (s, 3H, OCH_3), 3.33-3.54 (m, 4H, NCH, CH_3OCH_2, CHHOH), 3.61 (d, J = 10.8 Hz, 1H, CHHOH), 4.20 (s, 1H, OH). – ^{13}C NMR: δ = 14.10 (CH_3), 21.74, 22.12, 22.69 (CH_2CH_2CN, CH_3CH_2, NCH_2CH_2), 24.28 ($CH_3CH_2CH_2$), 26.30 ($NCH_2CH_2CH_2$), 29.33, 29.62, 30.33, 31.21, 31.92, 32.24, 35.51 ($CH_2CH_2CH_2CN$, $6CH_2$), 49.06 (CC=N), 54.06 (NCH_2), 59.05 (CH_2OCH_3), 66.07 ($NCHCH_2O$), 66.78 (CH_2OH), 76.38 (CH_2OCH_3), 175.08 (C=N). – MS (70 eV), *m/z* (%) = 352 (6) [M^+], 307 (100) [M^+–CH_2OCH_3], 208 (9), 163 (5), 114 (5) [$CH_3OCH_2C_4H_7N^+$], 96 (4) [$C_7H_{12}^+$], 83 (4) [$C_6H_{11}^+$], 70 (45) [$C_4H_8N^+$], 55 (9) [$C_4H_7^+$], 41 (10) [$C_3H_5^+$]. – $C_{21}H_{40}N_2O_2$ [352.6] calcd. C: 71.54, H: 11.55, N: 7.95, found C: 71.67, H: 11.62, N: 8.31.

(2R,2'R,5'S)-(–)-1-[2'-Hydroxymethyl-5'-methyl-2'-nonylcyclopentylidene]amino-2-methoxymethylpyrrolidine [(2*R*,2'*R*,5'*S*)-**15**]: Hydrazone (2*R*,2'*R*)-**14** (0.88 g, 2 mmol) was added dropwise to 2.8 equiv. of a solution of LDA at –78 °C. After 4 h at –78 °C, methyl iodide (1.07 g, 7.5 mmol) was added at –100 °C and stirring was continued overnight, while the reaction mixture was allowed to warm up to room temperature. The reaction mixture was quenched with NaCl solution, the organic layer was separated, washed with water and dried over $MgSO_4$. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether = 3/1) yielded 0.62 g (68%) of a pale yellow liquid. – R_f = 0.6 (petroleum ether/diethyl ether = 1/1). – *de* > 96% (determined by ^{13}C NMR). – $[\alpha]_D^{20}$ = – 130.0 (*c* = 1.0, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3424 (m, OH), 2929, 2870, 2854 (s, CH), 1655 (w, C=N), 1460 (m), 1119 (m), 1100 (m), 1060 (m) cm^{-1}. – ^{1}H NMR: δ = 0.88 (t, J = 6.7 Hz, 3H, CH_3CH_2), 1.15 (d, J = 7.4 Hz, 3H, CH_3CH), 1.24-1.29 (m, 16H, $CH_3(CH_2)_8$), 1.36-1.64 (m, 5H, CH_2CH_2CHCN, NCH_2CH_2CHH), 1.78-2.02 (m, 3H, NCH_2CH_2CHH), 2.43 (q, J = 8.4 Hz, 1H, NCHH), 2.78 (quint, J = 7.4 Hz, 1H, CH_2CHCN), 3.21 (dt, J = 8.7/5.7 Hz, 1H, NCHH), 3.30 (s, 3H, OCH_3), 3.25-3.52 (m, 4H, NCH, CH_3OCH_2, CHHOH), 3.62 (d, J = 10.4 Hz, 1H, CHHOH), 4.21 (s, 1H, OH). – ^{13}C NMR: δ = 14.14, 15.40 ($2CH_3$), 22.27, 22.74 (CH_3CH_2, NCH_2CH_2), 24.50 ($CH_3CH_2CH_2$), 26.49 ($NCH_2CH_2CH_2$), 29.39, 29.50, 29.68, 30.44, 30.65, 31.98 (CH_2CH_2CHCN, $5CH_2$), 36.17 (CCH_2), 37.08 (CHCN), 50.88 (CC=N), 53.82 (NCH_2), 58.94 (CH_2OCH_3), 66.01 ($NCHCH_2O$), 68.20 (CH_2OH), 76.71 (CH_2OCH_3), 179.44 (C=N). – MS (70 eV), *m/z* (%) = 366 (7) [M^+], 321 (76) [M^+–CH_2OCH_3], 291 (4) [M^+–CH_2OCH_3–CH_2O], 222 (10) [M^+–CH_2O–$CH_3OCH_2C_4H_7N$], 177 (6) [$C_{11}H_{17}N_2^+$], 114 (8) [$CH_3OCH_2C_4H_7N^+$], 95 (4) [$C_7H_{11}^+$], 81 (7) [$C_6H_9^+$], 70 (100) [$C_4H_8N^+$], 55 (16) [$C_4H_7^+$], 41 (14) [$C_3H_5^+$]. – $C_{22}H_{42}N_2O_2$ [366.6] calcd. C: 72.08, H: 11.55, N: 7.64, found C: 72.11, H: 11.65, N: 8.05.

(2S,5S)-(+)-2-Hydroxymethyl-5-methyl-2-nonylcyclopentanone [(2*S*,5*S*)-**2**]: Ozone was passed through a solution of hydrazone (2*R*,2'*R*,5'*S*)-**15** (0.55 g, 1.5 mmol) in pentane for 3 min at –78 °C. After evaporation of the solvent purification by flash chromatography (silica gel, petroleum ether/diethyl ether = 3/1) afforded 0.35 g (92%) of a colourless liquid. – R_f = 0.3 (petroleum ether/diethyl ether = 1/1). – *de* > 96% (determined by ^{13}C NMR). – $[\alpha]_D^{20}$ = + 35.5 (*c* = 0.3, $CHCl_3$). – ^{1}H NMR: δ = 0.88 (t, J = 6.7 Hz, 3H, CH_3CH_2), 1.09 (d,

J = 6.4 Hz, 3H, CH_3CH), 1.22-1.28 (m, 14H, $CH_3(CH_2)_7$), 1.42-2.32 (m, 7H, $CH_3(CH_2)_7CH_2$, CH_2CH_2CHCO), 2.33-2.44 (s, 1H, OH), 3.47 (d, J = 10.8 Hz, 1H, CHHOH), 3.58 (d, J = 10.8 Hz, 1H, CH*H*OH). – ^{13}C NMR: δ = 14.04, 14.12 ($2CH_3$), 22.69 (CH_3CH_2), 24.14 ($CH_3CH_2CH_2$), 28.54, 29.11, 29.32, 29.51, 29.57, 30.19 (CH_2CH_2CHC=O, $6CH_2$), 31.89, 33.62 ($2CH_2$), 44.71 (*C*HC=O), 53.28 (*C*C=O), 66.15 (CH_2OH), 225.79 (C=O). – The further analytical data are identical to (2*S*,5*R*)-**2**.

(2S,5S)-(+)-epi-malyngolide [(2*S*,5*S*)-**1**]: β-Hydroxyketone (2*S*,5*S*)-**2** (0.25 g, 1.0 mmol) in $CHCl_3$ (3 ml) was treated with *m*CPBA (0.57 g, 2.0 mmol, 60%) and $NaHCO_3$ (0.18 g, 2.0 mmol) and stirring was continued for 3 days at room temperature with the exclusion of light. The reaction mixture was diluted with 20 ml CH_2Cl_2, the organic layer was washed with saturated aqueous $NaHCO_3$- and NaCl solutions and dried over $MgSO_4$. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether = 1/1) afforded 0.15 g (56%) of a colourless liquid. – R_f = 0.2 (petroleum ether/diethyl ether = 1/1). – *de* > 96% (determined by ^{13}C NMR). – *ee* > 96% (determined by comparison of optical rotation value with that of the known compound). – $[\alpha]_D^{20}$ = + 19.1 (*c* = 0.3, $CHCl_3$). – $[\alpha]_D^{20}$ = + 19.1,[3a] $[\alpha]_D^{20}$ = + 19.5.[6g] – ^{1}H NMR: δ = 0.88 (t, J = 6.4 Hz, 3H, CH_3CH_2), 1.22-1.27 (m, 14 H, $CH_3(CH_2)_7$), 1.28 (d, J = 7.1 Hz, 3H, CH_3CH), 1.61-2.00 (m, 6H, $CH_3(CH_2)_7CH_2$, CH_2CH_2CHCO), 2.38-2.50 (m, 2H, CH_3CH, OH), 3.60 (s, 2H, CH_2OH). – ^{13}C NMR: δ = 14.11 (CH_3), 17.23 (CH_3), 22.67, 23.21, 25.45, 27.12, 29.29, 29.52, 29.96, 31.86 (CH_2CH_2CHC=O, $7CH_2$), 35.21 (*C*HC=O), 37.54 (CCH_2), 67.70 (CH_2OH), 86.36 (CCH_2OH), 175.33 (C=O). – The further analytical data are identical to (2*S*,5*R*)-**1**.

Acknowledgement: This work was supported by the Deutsche Forschungsgesellschaft (Leibniz-Prize) and by the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG, Bayer AG and Hoechst AG for donations of chemicals.

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(*Received in Germany* 6 *February* 1996; *accepted* 26 *February* 1996)