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A New Route to the Asymmetric Synthesis of (–)-Malyngolide and (–)-*epi*-Malyngolide Using *N*-Sulfonyl-1,3-oxazolidines as Chiral Auxiliaries

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Abstract: (–)-Malyngolide (**1**), an antibiotically active δ-lactone, and its epimer **10** were prepared enantioselectively using [2*R*,2(1*S*),4*R*]- and [2*R*,2(1*R*),4*R*]-4-ethyl-3-(2-nitrobenzenesulfonyl)-2-(1-nonyl-2-oxocyclopentyl)-1,3-oxazolidine (**5a** and **5b**) as key-intermediates. Furthermore, a new cleavage procedure for the chiral auxiliary is reported.

Recently, we [1] and others [2] introduced *N*-arenesulfonyl-2-methoxy-1,3-oxazolidines as reagents for the asymmetric formylation of silyl enol ethers. In particular, 1,3-oxazolidines of type **5** bearing a 1-alkyl-2-oxocycloalkyl group in 2 position [3] deserve attention as new chiral building blocks for the stereoselective construction of quaternary carbon centres. [4] In this communication we wish to report the application of the new technology for the synthesis of (–)-malyngolide (**1**) and its epimer **10** utilizing *N*-sulfonyl-1,3-oxazolidines as chiral auxiliaries. (–)-Malyngolide was firstly isolated from the blue-green marine alga *Lyngbya majuscula* Gomont in 1979, showing an antibiotic effect against *Mycobacterium smegmatis* and *Streptococcus pyogenes*.[5] The first synthesis of (±)-malyngolide was published by T. Mukaiyama [6], and up to now, several chiral pool [7] and asymmetric syntheses [8] followed. In 1988 a synthesis of **1** was reported using a baker's yeast reduction of *S*-ethyl 2-oxocyclopentanecarboxythioate.[8d] **1** was also synthesized by utilizing a $BF_3{\cdot}Et_2O$-catalyzed ring contraction of 2,3-epoxycyclohexanone leading to 2-alkyl-2-formylcyclopentanone.[8f] D. Enders and M. Knopp published the synthesis of **1**, using the asymmetric Carroll rearrangement as a key step.[8i] Furthermore, the enantioselective synthesis by double α,α'-alkylation using the SAMP/RAMP hydrazone method afforded the diastereomer (+)-*epi*-malyngolide (***ent*-10**).[8i] As shown in Scheme 1, our approach started with the condensation of the 2-methoxy-1,3-oxazolidine **3** and silyl enol ether **4**.[3] After methylation and removal of the chiral auxiliary, (–)-malyngolide (**1**) would easily be obtained by well-established Baeyer-Villiger oxidation.[8d,f,i]

The known 2-nonylcyclopentanone [9] was converted to the thermodynamically more stable silyl enol ether **4** by the standard procedure.[11] The Lewis-acid mediated condensation of **4** and the *N*-(*o*-nitrobenzenesulfonyl)-2-methoxy-1,3-oxazolidine **3** (derived from the readily available (*R*)-2-amino-1-

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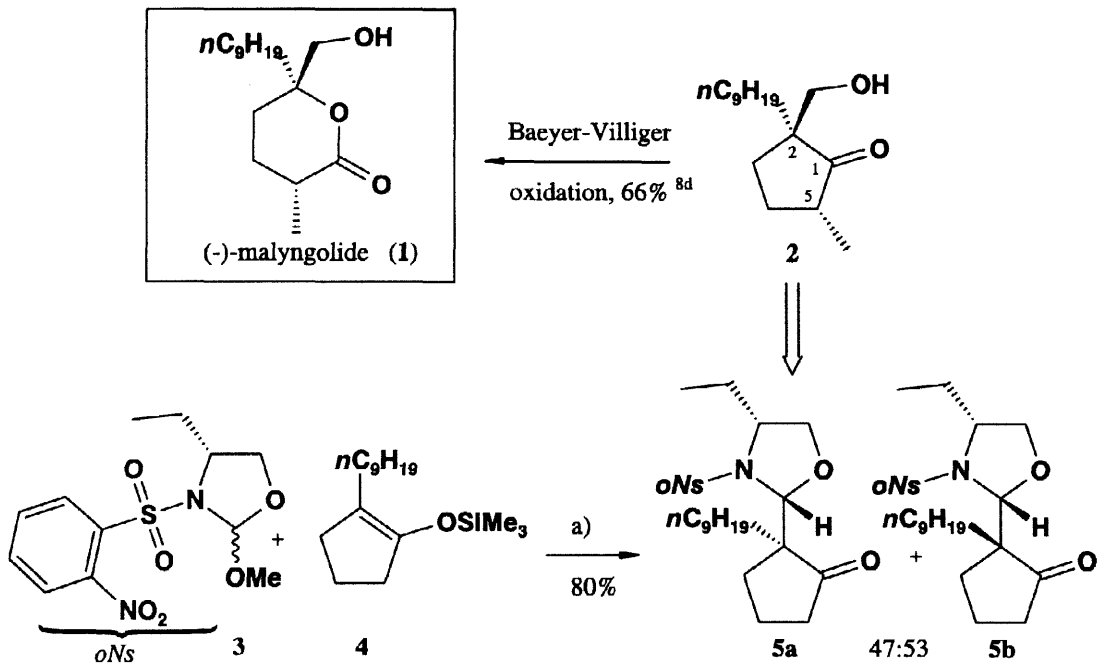
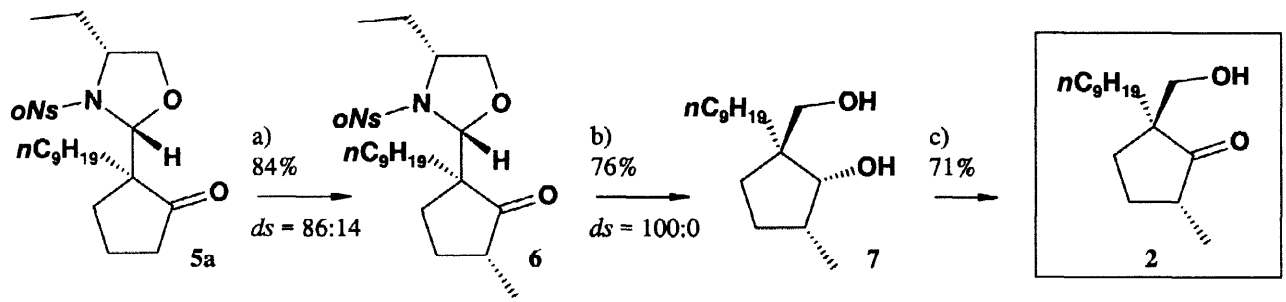
butanol) afforded only two out of the four possible diastereomers **5a** and **5b**, in a ratio of 47:53. They were separated completely by flash-chromatography on silica gel in yields of 38% (**5a**) and 42% (**5b**), respectively.



a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 2 h; LC separation

Scheme 1. Strategy of the (−)-malyngolide (**1**) synthesis

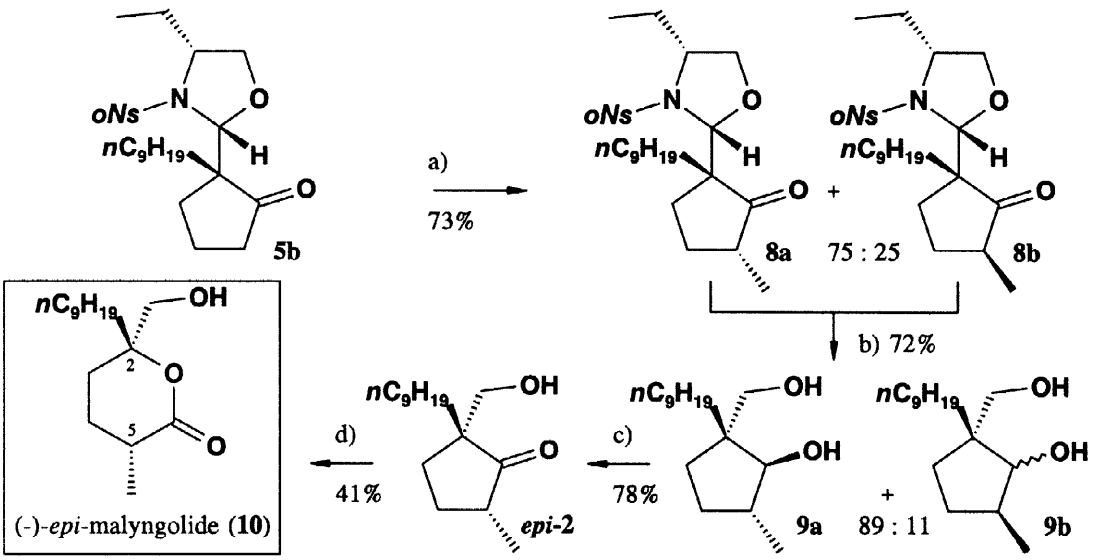
The ketone **5a** (Scheme 2) was deprotonated with KO*t*Bu at −78°C in the presence of DMPU in THF, and alkylated with methyl iodide to afford a diastereomeric mixture **6** and ***epi*-6** (*ds* = 86:14, 84%). The diastereomers were separated by silica gel column chromatography. After treatment of the pure diastereomer **6** with *p*-thiocresole and K_2CO_3 in DMF at rt, facile deprotection [12, 13] of **5a** was achieved presumably via the formation of Meisenheimer complex,[12] and the crude product was reduced immediately with $NaBH_4$ to yield diol **7**. Sodium hypochlorite in acetic acid solution oxidized the secondary carbinol group to afford ketone **2** in 71% yield.[14] Comparison of the specific optical rotation with that of the reported compound **2** confirmed the absolute configuration (2*S*,5*R*) and the high optical purity of the product.[15] The known Baeyer-Villiger reaction was not carried out in this sequence.[8f,i]



a) KO*t*Bu, 3.3 eq. DMPU, MeI, -78°C to rt, THF, 14 h; LC separation b) 1. K_2CO_3, *p*-thiocresole, DMF, rt, 30 min; 2. $NaBH_4$, MeOH, 30 min; c) NaOCl, conc. HOAc, rt, 45 min;

Scheme 2. Synthesis of key intermediate **2**, starting from **5a**

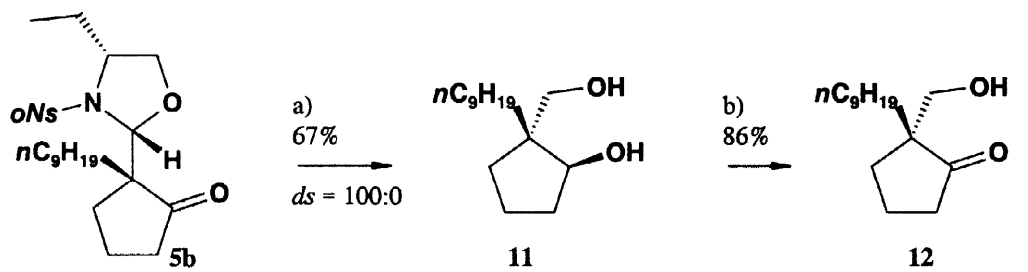
The synthesis of (−)-*epi*-malyngolide (**10**) started from the 1,3-oxazolidine **5b** (Scheme 3). For generating the enolate LDA [16] was used, the methylation gave a mixture of two diastereomers **8a** and **8b** in 73% yield. Analogously to the protocol applicated to the deprotection of **6**, the diastereomeric mixture of **8a** and **8b** was converted to the diols **9a** and **9b** [17] which were easily separated by flash chromatography on silica gel (64% yield of pure diastereomere **9a**). The chemoselective oxidation of the secondary alcohol **9a** by NaOCl in acetic acid yielded ketone ***epi*-2** in 78%. The Baeyer-Villiger oxidation of ***epi*-2** was achieved in moderate yield of 41% with complete retention of configuration leading to the enantiopure (−)-*epi*-malyngolide (**10**). Comparison of the specific optical rotation with that of the reported compound **10** confirmes the absolute configuration (2*R*,5*R*) and the high optical purity of the product.[18]



a) LDA, 3.0 eq. DMPU, MeI, -78°C to rt, THF, 14 h; b) 1. K_2CO_3, *p*-thiocresole, DMF, rt, 30 min; 2. $NaBH_4$, *i*PrOH, 30 min; LC separation c) NaOCl, conc. HOAc, rt, 45 min; d) MCPBA, $NaHCO_3$, $CHCl_3$, rt, 3 d;

Scheme 3. Synthesis of (−)-*epi*-malyngolide (**10**), starting from **5b**

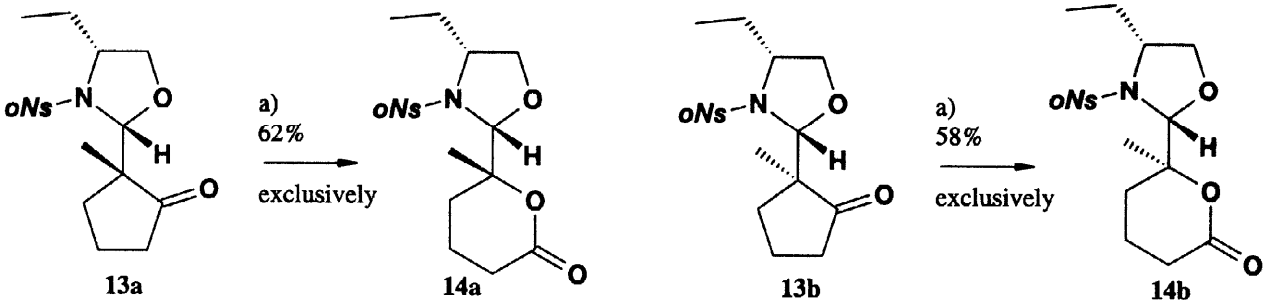
An alternative route leading to (+)-malyngolide (***ent*-1**) was also examined (Scheme 4). Cleavage of **5b** in 67% yield followed by chemoselective oxidation of **11** gave the corresponding hydroxylmethyl ketone **12**. The transformation of **12** to (+)-malyngolide (***ent*-1**) is possible by the method of M. Asaoka et al., utilizing methylation and reprotonation under kinetic conditions with excellent diastereoselectivity.[8f]



a) 1. *p*-thiocresole, K_2CO_3, DMF, rt, 2 h; 2. $NaBH_4$, MeOH, rt, 1 h; b) NaOCl, conc. HOAc, rt, 45 min;

Scheme 4. Synthesis of the key intermediate **12**

In model experiments the regioselective Baeyer-Villiger oxidation could be achieved on the stage of the oxazolidine-substituted ketones **13a** and **13b** by means of MCPBA (Scheme 5).[8f] These conditions failed when applied to the α-nonyl derivatives **5a** and **5b**.



a) MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 19 h-2 d;

Scheme 5. Baeyer-Villiger oxidation of ketones **13a** and **13b**

Thus, the 1,3-oxazolidine method provides enantiomerically pure α,α,α'-trisubstituted cycloalkanone derivatives containing a quaternary carbon centre with few steps and high efficiency. Besides of (–)-malyngolide or (–)-*epi*-malyngolide structure variants should be readily accessible in a predictable way by using this technology.

EXPERIMENTAL

Experiments involving air-sensitive intermediates were carried out under Ar atmosphere with oven dried glassware. All solvents were purified by distillation and dried, if necessary, prior use. ^1H- and ^{13}C NMR spectra were recorded on Bruker WM 300 spectrometer. IR spectra were recorded on Perkin-Elmer 298 spectrophotometer. Optical rotations were recorded on Perkin-Elmer polarimeter 241. Melting points were obtained on a Büchi melting point apparatus 510 and are uncorrected. Products were purified by distillation, flash column chromatography on silica gel (μm), and/or recrystallization.

(2S,4R)-4-Ethyl-2-methoxy-3-(4-nitrobenzenesulfonyl)-1,3-oxazolidine (**3**): To a solution of (*R*)-2-amino-1-butanol (17.8 g, 200 mmol) and triethylamine (30.5 ml, 220 mmol) in CH_2Cl_2 (500 ml) at 0°C, 2-nitrobenzenesulfonyl chloride (46.6 g, 220 mmol) in CH_2Cl_2 (300 ml) was slowly added and strirring continued for 16 h. The reaction was stopped by adding H_2O (80 ml) and the organic layer was washed with brine (100 ml) and dried over Na_2SO_4. A flash filtration (Et_2O) on silica gel (200 g) took off the polar components. The crude sulfonamide, dissolved in trimethyl orthoformate (500 ml), and methanesulfonic acid (cat. amount) were stirred 1 h at rt, and the reaction mixture was neutralized with K_2CO_3 (8 g). After filtration the solution was concentrated and the crude oxazolidine **3** (61.4 g, 97%, containing 32% of the (2*R*,4*R*)-epimer) was used without further purification.

IR (KBr): ν [cm^{-1}] = 3100 (ar-H), 2980 (alkyl-H), 1590 (C=C of ar), 1540 (NO_2), 1360, 1170 (SO_2). ^{1}H NMR (300 MHz, containing 32% of the (2*R*,4*R*)-epimer): δ = 0.88 (t, 3 H, $J_{Me,41}$ = 7.5, CH_2CH_3), 1.52-1.96 (m, 2 H, 41-H_2), 3.42 (s, 3 H, OMe), 3.86-3.94, and 4.10-4.19 (2 m, 1 H and 2 H, 4-H, and 5-H_2), 6.07 (s, 1 H, 2-H), 7.57-7.77, and 8.05-8.14 (2 m, 2 H and 2 H, *oNs*). ^{13}C NMR (75 MHz, containing 32% of the (2*R*,4*R*)-epimer): δ = 9.67 (CH_2CH_3), 26.89 (C-41), 53.55 (OMe), 59.31 (C-4), 70.46 (C-5), 108.47 (C-2), 124.14, 130.41, 131.76, and 134.05 (C-3'', -4'', -5'', and -6'' of *oNs*), 148.64 (C-2'' of *oNs*). $C_{12}H_{16}N_2O_6S$ (316.3) Calc.: C 45.56 H 5.10 N 8.86. Found: C 45.18 H 5.31 N 8.68.

[2R,2(1S),4R]- and [2R,2(1R),4R]-4-Ethyl-3-(2-nitrobenzenesulfonyl)-2-(1-nonyl-2-oxocyclopentyl)-1,3-oxazolidine (**5a** and **5b**): To a solution of (2*S*,4*R*)-4-ethyl-2-methoxy-3-(2-nitrobenzenesulfonyl)-1,3-oxazolidine [3] (**3**) (6.33 g, 20.0 mmol) and silyl enol ether **4** (6.22 g, 22.0 mmol) in CH_2Cl_2 (80 ml), BF_3·Et_2O (2.76 ml, 22.0 mmol) was added at rt and stirring was continued for 2 h. For work-up, brine (40 ml) was added and the aq. layer extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were dried with Na_2SO_4, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/Et_2O 5:1) on silica gel (600 g). The two diastereomers were separated completely and furnished 3.69 g (38%) **5a** and 4.16 g (42%) **5b** as yellow-orange viscous oils.

5a: $[\alpha]_D^{20}$ = −58.1 (*c* = 1.0, CH_2Cl_2), IR (film): ν [cm^{-1}] = 2920, 2850 (alkyl-H), 1730 (C=O), 1545 (NO_2), 1370, 1170 (SO_2). ^{1}H NMR (300 MHz): δ = 0.83-0.87 (m, 3 H, methyl of nonyl), 0.95 (t, 3 H, $J_{Me,41}$ = 7.4, CH_2CH_3), 1.22, 1.41-1.67, 1.70-1.93, 2.03-2.13, 2.20-2.30, and 2.42-2.55 (m_c and m, 15 H, 2 H, 3 H, 1 H, 1 H, and 2 H, 41-H_2, nonyl, and cyclopentyl), AB signal (δ_A = 3.71, δ_B = 3.52, 2 H, J_{AB} = 8.8, $J_{A,4}$ = 2.2, $J_{B,4}$ = 5.7, 5-H_2), 4.07 (dddd, 1 H, $J_{4,41\text{-}H(1)}$ = 7.7, $J_{4,41\text{-}H(2)}$ = $J_{4,5\text{-}H(B)}$ = 5.7, $J_{4,5\text{-}H(A)}$ = 2.0, 4-H), 5.13 (s, 1 H, 2-H), 7.52-7.55 (m, 1 H, 6''-H of *oNs*), 7.68-7.79 (m, 2 H, 4''-, and 5''-H of *oNs*), 8.06-8.09 (m, 1 H, 3''-H of *oNs*). ^{13}C NMR (75 MHz): δ = 10.62 (CH_2CH_3), 14.02 (methyl of nonyl), 19.04 (C-4'), 22.61, 23.52, 27.36, 29.22, 29.32, 29.52, 29.82, 30.26, and 31.81 (C-41, and nonyl), 35.01 (C-5'), 37.98 (C-3'), 55.64 (C-1'), 61.63 (C-4), 69.59 (C-5), 93.88 (C-2), 123.67, 131.49, 132.84, and 134.02 (C-3'', -4'', -5'', and -6'' of *oNs*), 130.14 (C-1'' of *oNs*), 148.71 (C-2'' of *oNs*), 219.68 (C-2'). $C_{25}H_{38}N_2O_6S$ (494.6) Calc.: C 60.70 H 7.74 N 5.66. Found: C 60.60 H 7.95 N 5.74.

5b: $[\alpha]_D^{20}$ = +41.8 (*c* = 1.0, CH_2Cl_2), IR (film): ν [cm^{-1}] = 2920, 2850 (alkyl-H), 1730 (C=O), 1540 (NO_2), 1365, 1170 (SO_2). ^{1}H NMR (300 MHz): δ = 0.85 (m, 6 H, CH_2CH_3, and methyl of nonyl), 1.24, 1.48-2.03, and 2.17-2.35 (m_c and m, 14 H, 7 H, and 3 H, 41-H_2, nonyl, and cyclopentyl), 3.56-3.62, and 3.80-3.87 (m, 1 H, and 2 H, 4-H, and 5-H_2), 5.46 (s, 1 H, 2-H), 7.54-7.57 (m, 1 H, 6''-H of *oNs*), 7.68-7.78 (m, 2 H, 4''-, and 5''-H of *oNs*), 7.99-8.02 (m, 1 H, 3''-H of *oNs*). ^{13}C NMR (75 MHz): δ = 10.55 (CH_2CH_3), 13.99 (methyl of nonyl), 18.94 (C-4'), 22.58, 24.30, 27.09, 29.18, 29.38, 29.45, 29.62, 30.19, and 31.78 (C-41, and nonyl), 33.83 (C-5'), 39.56 (C-3'), 56.92 (C-1'), 61.26 (C-4), 70.53 (C-5), 96.34 (C-2), 123.91, 131.15, 131.52, and 134.49 (C-3'', -4'', -5'', and -6'' of *oNs*), 130.04 (C-1'' of *oNs*), 149.42 (C-2'' of *oNs*), 220.92 (C-2'). $C_{25}H_{38}N_2O_6S$ (494.6) Calc.: C 60.70 H 7.74 N 5.66. Found: C 60.75 H 8.00 N 5.69.

[2R,2(1S,3R),4R]-4-Ethyl-2-(3-methyl-1-nonyl-2-oxocyclopentyl)-3-(2-nitrobenzenesulfonyl)-1,3-oxazolidine (**6**): To a solution of KO*t*Bu (168 mg, 1.53 mmol) in THF (3 ml) was added dropwise 1,3-oxazolidine **5a** (444 mg, 0.90 mmol) in THF (2 ml) at −78°C. The mixture was stirred for 1 h, and after addition of DMPU (0.36

ml, 2.97 mmol), MeI (0.31 ml, 5.04 mmol) was added. Stirring was continued for 17 h while the mixture was allowed to warm up to rt. The hydrolysis was carried out by adding brine (4 ml), the organic layers were separated, the aqueous layer extracted twice with Et_2O (3 x 10 ml), and the combined organic layers were dried over Na_2SO_4. Purification by flash chromatography afforded 386 mg (84%) of **6** and ***epi*-6** as a yellow-orange oil. When the diastereomeric mixture of **6** and ***epi*-6** was carefully chromatographed (petroleum ether/Et_2O 2:1) on an SiO_2 column again, pure **6** was eluted from the column first in 267 mg (58%) yield.
$[\alpha]_D^{20}$ = −62.2 (*c* = 1.0, CH_2Cl_2), IR (film): ν [cm^{-1}] = 2900 (alkyl-H), 1725 (C=O), 1540 (NO_2), 1370, 1170 (SO_2). ^1H NMR (300 MHz): δ = 0.87 (t, 3 H, $J_{Me,CH}$ = 6.8, methyl of nonyl), 0.96 (t, 3 H, $J_{Me,41}$ = 7.5, CH_2CH_3), 1.15 (d, 3 H, $J_{Me,3'}$ = 7.3, 3'-methyl), 1.09-1.33, 1.40-1.87, 2.22-2.31, and 2.40-2.54 (m, 16 H, 4 H, 1 H, and 2 H, 41-H_2, nonyl, and cyclopentyl), AB signal (δ_A = 3.70, δ_B = 3.56, 2 H, J_{AB} = 8.8, $J_{A,4}$ = 2.4, $J_{B,4}$ = 5.7, 5-H_2), 4.08 (dddd, 1 H, $J_{4,41\text{-}H(2)}$ = 8.4, $J_{4,5\text{-}H(B)} = J_{4,41\text{-}H(1)}$ = 6.0, $J_{4,5\text{-}H(A)}$ = 2.7, 4-H), 5.19 (s, 1 H, 2-H), 7.53-7.56 (m, 1 H, 6''-H of *oNs*), 7.70-7.80 (m, 2 H, 4''-, and 5''-H of *oNs*), 8.08-8.11 (m, 1 H, 3''-H of *oNs*). ^{13}C NMR (75 MHz): δ = 10.65 (CH_2CH_3), 14.02 (methyl of nonyl), 14.83 (3'-methyl), 22.61, and 23.52 (C-4', and -5'), 27.19, 28.21, 28.31, 29.22, 29.28, 29.52, 30.33, 31.81, and 34.88 (C-41, and nonyl), 43.34 (C-3'), 55.91 (C-1'), 61.80 (C-4), 69.65 (C-5), 93.92 (C-2), 123.67, 131.45, 132.94, and 134.02 (C-3'', -4'', -5'', and -6'' of *oNs*), 130.21 (C-1'' of *oNs*), 148.68 (C-2'' of *oNs*), 220.45 (C-2'). $C_{26}H_{40}N_2O_6S$ (508.7) Calc: C 61.39 H 7.93 N 5.51. Found: C 61.39 H 8.13 N 5.50.

(1R,2S,5R)-2-Hydroxymethyl-5-methyl-2-nonylcyclopentanol (**7**): A mixture of K_2CO_3 (191 mg, 1.38 mmol) and *p*-thiocresole (68 mg, 0.55 mmol) in DMF (2 ml) was stirred for 10 min at rt. Then, a solution of 1,3-oxazolidine **6** (235 mg, 0.46 mmol) in DMF (2 ml) was added dropwise and stirring was continued for 2.5 h. The reaction mixture was diluted with CH_2Cl_2 (5 ml), the solids filtered off, and the solvent was evaporated in vacuum. A flash filtration (petroleum ether/Et_2O 1:1) on silica gel (5 g) took off the polar components. To the crude product, dissolved in methanol (6 ml), $NaBH_4$ (174 mg, 4.60 mmol) was added in portions over a period of 1 h. The hydrolysis was achieved by adding 2*N* aq. HCl (4 ml) and the aq. layer was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography (petroleum ether/Et_2O 5:1) on silica gel yielded 91 mg (76%) of **7** as a cereous solid.
mp = 50°C (petroleum ether/Et_2O), $[\alpha]_D^{20}$ = +3.6 (*c* = 1.2, CH_2Cl_2), IR (KBr): ν [cm^{-1}] = 3400 (OH), 2920 (alkyl-H). ^1H NMR (300 MHz): δ = 0.87 (t, 3 H, $J_{Me,CH}$ = 6.8, methyl of nonyl), 1.01 (d, 3 H, $J_{Me,5}$ = 7.2, 5-methyl), 1.14-1.77, and 2.09-2.20 (m, 20 H, and 1 H, nonyl, and cyclopentyl), AB signal (δ_A = 3.48, δ_B = 3.35, 2 H, J_{AB} = 11.0, CH_2OH), 3.82 (d, 1 H, $J_{1,5}$ = 5.2, 1-H). ^{13}C NMR (75 MHz): δ = 14.09 (methyl of nonyl), 14.22 (5-methyl), 22.68, and 24.67 (C-3, and -4), 29.32, 29.65, 29.72, 29.86, 30.70, 30.83, 31.74, and 31.88 (nonyl), 37.61 (C-5), 51.25 (C-2), 67.16 (CH_2OH), 79.33 (C-1). $C_{16}H_{32}O_2$ (256.4) Calc.: C 74.94 H 12.58. Found: C 74.77 H 12.49.

(2S,5R)-2-Hydroxymethyl-5-methyl-2-nonylcyclopentanone (**2**): According to ref. 15, to a solution of diol **7** (54 mg, 0.21 mmol) in conc. acetic acid (0.20 ml) was added dropwise aq. NaOCl (0.13 ml, containing approx. 13% of active chlorine) at rt. The mixture was stirred for 45 min and then quenched by addition of isopropanol (2 ml). After diluting with CH_2Cl_2 (3 ml) and washing with sat. aq. $NaHCO_3$ the combined organic layers were dried over Na_2SO_4. Purification by flash chromatography (petroleum ether/Et_2O 2:1) on silica gel yielded 39 mg (71%) of **2** as an oil. $[\alpha]_D^{20}$ = −19.6 (*c* = 0.5, $CHCl_3$), ref. 8d: $[\alpha]_D^{23}$ = −10.8 (*c* = 1.0,

$CHCl_3$), ref. 8f: $[\alpha]_D^{22} = -19.3$ (c = 1.5, $CHCl_3$), ref. 8i: $[\alpha]_D^{23} = -19.3$ (c = 0.5, $CHCl_3$). The IR and NMR data were identical with those reported in ref. 8f.

[2R,2(1R,3R),4R]-4-Ethyl-2-(3-methyl-1-nonyl-2-oxocyclopentyl)-3-(2-nitrobenzenesulfonyl)-1,3-oxazolidine (**8a**): To a solution of **5b** (3.13 g, 6.33 mmol) in THF (15 ml), LDA (9.50 mmol) in THF (10 ml) was added dropwise at −78°C. The mixture was stirred for 1 h, and after addition of DMPU (2.30 ml, 19.0 mmol) and MeI (1.97 ml, 31.7 mmol) stirring was continued for 14 h while the mixture was allowed to warm up to rt. For hydrolysis brine (20 ml) was added. The organic layers were separated, the aqueous layer extracted with Et_2O (3 x 40 ml), and the combined organic layers were dried over Na_2SO_4. Purification by flash chromatography (petroleum ether/Et_2O 5:1) on silica gel afforded 2.34 g (73%, **8a**:**8b** = 75:25) of a diastereomeric mixture of **8a** and **8b** as a yellow-orange oil.

8a: IR (film): ν [cm^{-1}] = 2920, 2850 (alkyl-H), 1730 (C=O), 1545 (NO_2), 1370, 1170 (SO_2). ^1H NMR (300 MHz, containing 12% of **8b**): δ = 0.83-0.92 (m, CH_2CH_3, and CH_3 of nonyl), 1.11 (d, $J_{Me,3'}$ = 6.7, 3'-methyl), 1.23-1.34, 1.56-1.67, 1.80-1.87, and 2.12-2.24 (4 m, 41-H_2, nonyl, and cyclopentyl), 3.54-3.59 [m, 5-H(1)], 3.80-3.91 [m, 4-H, and 5-H(2)], 5.44 (s, 2-H), 7.56-7.59 (m, 6''-H of *oNs*), 7.69-7.76 (m, 4''-, and 5''-H of *oNs*), 8.00-8.04 (m, 3''-H of *oNs*). ^{13}C NMR (75 MHz, containing 12% of **8b**): δ = 10.65 (CH_2CH_3), 14.05 (methyl of nonyl, 3'-Me), 22.61, 24.40, and 24.70 (C-4', and -5'), 27.03, 27.19, 27.30, 27.46, 27. 87, 28.71, 29.22, 29.49, 30.16, 30.33, 31.81, 34.30, and 34.68 (C-41, and nonyl), 45.26 (C-3'), 57.35 (C-1'), 61.53 (C-4), 70.33 (C-5), 97.66 (C-2), 123.91, 131.25, 131.49, and 134.42 (C-3'', -4'', -5'', and -6'' of *oNs*), 130.14 (C-1'' of *oNs*), 149.48 (C-2'' of *oNs*), 222.47 (C-2'). $C_{26}H_{40}N_2O_6S$ (508.7) Calc.: C 61.39 H 7.93 N 5.51. Found: C 61.13 H 7.98 N 5.68.

(1S,2R,5R)-2-Hydroxymethyl-5-methyl-2-nonylcyclopentanol (**9a**) was prepared according to the procedure described for compound **7** starting from a diastereomeric mixture of **8a** and **8b** (254 mg). Purification by flash chromatography (petroleum ether/Et_2O 5:1) afforded 72 mg (64%) of the pure diastereomer **9a** as a cereous solid. Furthermore, the reaction product of the minor diastereomer **9b** was also isolated in 8% yield.

mp = 64°C (petroleum ether/Et_2O), IR (KBr): ν [cm^{-1}] = 3400 (OH), 2910, 2850 (alkyl-H), $[\alpha]_D^{20} = -30.5$ (c = 1.0, CH_2Cl_2). ^1H NMR (300 MHz): δ = 0.88 (t, 3 H, $J_{Me,CH}$ = 6.8, methyl of nonyl), 1.06 (d, 3 H, $J_{Me,5}$ = 6.2, 5-methyl), 1.09-1.35, and 1.45-1.90 (m, 17 H, and 4 H, nonyl, and cyclopentyl), 2.66 (br. s, 2 H, 2 OH), AB signal (δ_A = 3.46, δ_B = 3.33, 2 H, J_{AB} = 9.9, CH_2OH), 3.68 (d, 1 H, $J_{1,5}$ = 10.5, 1-H). ^{13}C NMR (75 MHz): δ = 14.05 (methyl of nonyl), 18.16 (5-methyl), 22.61, and 23.62 (C-3, and -4), 28.37, 28.78, 29.01, 29.32, 29.62, 29.72, 30.70, and 31.84 (nonyl), 39.16 (C-5), 47.45 (C-2), 69.42 (CH_2OH), 86.64 (C-1). $C_{16}H_{32}O_2$ (256.4) Calc.: C 74.94 H 12.58. Found: C 74.81 H 12.29.

(2R,5R)-2-Hydroxymethyl-5-methyl-2-nonylcyclopentanone (***epi*-2**) was prepared according to the procedure described for compound **2** starting from **9a** (127 mg). Purification by flash chromatography (petroleum ether/Et_2O 2:1) afforded 99 mg (78%) of the pure diastereomer ***epi*-2** as a colourless oil.

$[\alpha]_D^{20} = -38.2$ (c = 1.5, $CHCl_3$), IR (film): ν [cm^{-1}] = 3500 (OH), 2910, 2840 (alkyl-H), 1720 (C=O). ^1H NMR (300 MHz): δ = 0.84 (t, 3 H, $J_{Me,CH}$ = 6.7, methyl of nonyl), 1.05 (d, 3 H, $J_{Me,5}$ = 6.9, 5-methyl), 1.22, 1.41-1.54, 1.76-1.84, and 2.07-2.25 (m_c, and m, 15 H, 2 H, 2 H, and 2 H, cyclopentyl, and nonyl), 2.35 (br. s, 1 H, OH), AB signal (δ_A = 3.58, δ_B = 3.46, 2 H, J_{AB} = 11.7, CH_2 OH). ^{13}C NMR (75 MHz): δ = 13.99 (methyl of

nonyl, and 5-methyl), 22.58, and 24.06 (C-3, and -4), 28.44, 29.04, 29.22, 29.42, 29.49, 30.13, 31.78, and 33.60 (nonyl), 44.58 (C-5), 53.28 (C-2), 66.15 (CH_2OH), 225.51 (C-1). $C_{16}H_{30}O_2$ (254.4) Calc.: C 75.54 H 11.89. Found: C 75.04 H 11.47.

(−)-epi-Malyngolide (**10**) was prepared from ***epi*-2** (81 mg) according to the literature procedure [8f]. Purification by flash chromatography (petroleum ether/Et_2O 2:1) gave 34 mg (48%) of *(−)-epi-malyngolide* as an oil. $[\alpha]_D^{20} = -17.4$ (c = 1.0, $CHCl_3$), ref. 8c: $[\alpha]_D^{20} = -18.7$ (c = 2.2, $CHCl_3$), ref. 7f: $[\alpha]_D^{22} = -21.5$ (c = 0.9, $CHCl_3$), ref. 8b: $[\alpha]_D^{17} = -20.4$ (c = 1.5, $CHCl_3$), ref. 8a: $[\alpha]_D^{20} = -20.8$ (c = 2.0, $CHCl_3$). The IR and NMR data were identical with those reported in ref. 8c.

(1S,2R)-2-Hydroxymethyl-2-nonylcyclopentanol (**11**) was prepared according to the procedure described for compound **7** starting from **5b** (494 mg). Purification by flash chromatography (petroleum ether/Et_2O 1:1) afforded 162 mg (67%) of the pure diastereomer **11** as a white solid.
mp = 57°C (petroleum ether/Et_2O), $[\alpha]_D^{20} = -3.4$ (c = 1.0, CH_2Cl_2), IR (KBr): ν [cm^{-1}] = 3350 (OH), 2910, 2850 (alkyl-H). ^1H NMR (300 MHz): δ = 0.88 (t, 3 H, $J_{Me,CH}$ = 6.8, methyl of nonyl), 1.18-1.31 (m, 16 H, nonyl), 1.48-2.06 (m, 6 H, cyclopentyl), AB signal (δ_A = 3.66, δ_B = 3.35, 2 H, J_{AB} = 10.5, CH_2OH), 4.04 (t, 1 H, $J_{1,5}$ = 7.2, 1-H). ^{13}C NMR (75 MHz): δ = 14.09 (methyl of nonyl), 19.65, 22.68, and 24.03 (C-3, -4, and -5), 27.73, 29.35, 29.65, 29.76, 30.36, 30.73, 31.91, and 32.32 (nonyl), 48.53 (C-2), 68.61 (CH_2OH), 79.93 (C-1). $C_{15}H_{30}O_2$ (242.4) Calc.: C 74.33 H 12.47. Found: C 74.02 H 12.61.

(R)-2-Hydroxymethyl-2-nonylcyclopentanone (**12**) was prepared according to the procedure described for compound **2** starting from **11** (105 mg). Purification by flash chromatography (petroleum ether/Et_2O 2.5:1) afforded 89 mg (86%) of the pure diastereomer **12** as a colourless oil. $[\alpha]_D^{20} = -9.1$ (c = 2.4, $CHCl_3$), ref. 8f: $[\alpha]_D^{26} = -9.8$ (c = 1.8, $CHCl_3$). The IR and NMR data were identical with those reported in ref. 8i.

[2R,2(6R),4R]-4-Ethyl-2-(2-methyl-6-oxotetrahydropyran-2-yl)-3-(2-nitrobenzenesulfonyl)-1,3-oxazolidine (**14a**): According to ref. 8f, to a solution of [2*R*,2(*R*),4*R*]-4-ethyl-2-(1-methyl-2-oxocyclopentyl)-3-(2-nitrobenzenesulfonyl)-1,3-oxazolidine [3] (**13a**) (191 mg, 0.50 mmol) in CH_2Cl_2 (4 ml) was added $NaHCO_3$ (63 mg, 0.75 mmol) and MCPBA (208 mg, 60 proc., 0.75 mmol), and the mixture was stirred in the dark at rt for 19 h. After addition of sat. aq. $NaHCO_3$ (4 ml) the organic layer was dried over Na_2SO_4 and then concentrated. Purification by flash chromatography (petroleum ether/Et_2O 1:1) gave 124 mg (62%) of **14a** as a solidifying oil.
$[\alpha]_D^{20}$ = +61.5 (c = 1.0, CH_2Cl_2), IR (film): ν [cm^{-1}] = 1730 (OC=O), 1540 (NO_2), 1370, 1170 (SO_2). ^1H NMR (300 MHz): δ = 0.86 (t, 3 H, $J_{Me,41}$ = 7.5, CH_2CH_3), 1.47 (s, 3 H, 6'-methyl), 1.66-2.04 [m, 5 H, 41-H_2, 4'-H_2, and 5'-H(1)], 2.21 [ddd, $J_{A,B}$ = 14.1*, $J_{5',4'\text{-H}(1)}$ = 11.9*, $J_{5',4'\text{-H}(2)}$ = 4.5*, 5'-H(2)], AB signal (δ_A = 2.58, δ_B = 2.46, 2 H, J_{AB} = 18.4, $J_{A,4'\text{-H}(1)}$ = 6.2**, $J_{A,4'\text{-H}(2)}$ = 3.8**, $^4J_{A,5'\text{-H}(1)}$ = 1.4, $J_{B,4'\text{-H}(1)}$ = 10.2***, $J_{B,4'\text{-H}(2)}$ = 7.1***, 3'-H_2), 3.81 (dddd, 1 H, $J_{4,41\text{-H}(1)}$ = 10.0, $J_{4,5\text{-H(A)}} = J_{4,5\text{-H(B)}}$ = 7.3, $J_{4,41\text{-H}(2)}$ = 5.0, 4-H), AB signal (δ_A = 4.13, δ_B = 4.03, 2 H, J_{AB} = 8.1, $J_{A,4}$ = 6.9, $J_{B,4}$ = 7.8, 5-H_2), 5.30 (s, 1 H, 2-H), 7.61-7.64 (m, 1 H, 6''-H of *oNs*), 7.71-7.82 (m, 2 H, 4''-, and 5''-H of *oNs*), 8.02-8.05 (m, 1 H, 3''-H of *oNs*). *, **, *** assignments interchangeable. ^{13}C NMR (75 MHz): δ = 10.55 (CH_2CH_3), 16.01 (C-4'), 22.71 (6'-methyl), 26.66 (C-41), 28.78, and 29.55 (C-3', and -5'), 62.00 (C-4), 72.62 (C-5), 85.80 (C-6'), 95.30 (C-2),

124.14, 131.02, 131.66, and 134.52 (C-3'', -4'', -5'', and -6'' of *oNs*), 129.87 (C-1'' of *oNs*), 149.38 (C-2'' of *oNs*), 169.87 (C-2'). $C_{17}H_{22}N_2O_7S$ (398.4) Calc.: C 51.25 H 5.57 N 7.03. Found: C 51.01 H 5.58 N 6.95.

[2R,2(6S),4R]-4-Ethyl-2-(2-methyl-6-oxotetrahydropyran-2-yl)-3-(2-nitrobenzenesulfonyl)-1,3-oxazolidine (**14b**) was prepared according to the procedure described for compound **14a** starting from **13b** (191 mg). Purification by flash chromatography (petroleum ether/Et_2O 1:1) gave 116 mg (58%) of **14b** as a solidifying oil. Furthermore, 40% of the educt **13b** were recovered.
$[\alpha]_D^{20}$ = +26.8 (*c* = 1.0, CH_2Cl_2), IR (film): ν [cm^{-1}] = 2970 (alkyl-H), 1725 (OC=O), 1545 (NO_2), 1370, 1170 (SO_2). ^1H NMR (300 MHz): δ = 0.93 (t, 3 H, $J_{Me,41}$ = 7.5, CH_2CH_3), 1.48 (s, 3 H, 6'-methyl), 1.73-2.11, and 2.43-2.52 (m, 6 H, and 2 H, 41-H_2, cyclohexyl), 3.85-3.92 (m, 3 H, 4-H, and 5-H_2), 5.23 (s, 1 H, 2-H), 7.62-7.65 (m, 1 H, 6''-H of *oNs*), 7.72-7.81 (m, 2 H, 4''-, and 5''-H of *oNs*), 8.04-8.07 (m, 1 H, 3''-H of *oNs*). ^{13}C NMR (75 MHz): δ = 10.62 (CH_2CH_3), 16.48 (C-4'), 24.09 (6'-methyl), 26.86 (C-41), 29.72 (C-3', and -5'), 61.67 (C-4), 71.91 (C-5), 84.89 (C-6'), 95.40 (C-2), 124.18, 131.42, 131.69, and 134.45 (C-3'', -4'', -5''and -6'' of *oNs*), 130.24 (C-1'' of *oNs*), 149.18 (C-2'' of *oNs*), 170.38 (C-2'). $C_{17}H_{22}N_2O_7S$ (398.4) Calc.: C 51.25 H 5.57 N 7.03. Found: C 51.16 H 5.69 N 6.97.

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16. The diastereoselectivity depends on the base used: whereas the deprotonation with LDA of **5a** affords a diastereomeric mixture of **6**:***epi*-6** in a ratio of 65:35, the selectivity increased by using KO*t*Bu (**6**:***epi*-6** = 86:14). This effect is moderate for the epimer **5b** (LDA: **8a**:**8b** = 75:25; KO*t*Bu: **8a**:**8b** = 71:29).

17. The configuration on C-1 of **9b** is not certain.

18. (–)-*epi*-Malyngolide (**10**): $[\alpha]_D^{20} = -17.4$ ($c = 1.0$, $CHCl_3$), ref. 8c: $[\alpha]_D^{20} = -18.7$ ($c = 2.2$, $CHCl_3$), ref. 7f: $[\alpha]_D^{22} = -21.5$ ($c = 0.9$, $CHCl_3$), ref. 8b: $[\alpha]_D^{17} = -20.4$ ($c = 1.5$, $CHCl_3$), ref. 8a: $[\alpha]_D^{20} = -20.8$ ($c = 2.0$, $CHCl_3$).