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New Route to (–)-Frontalin and (–)-Malyngolide via Epoxyketone Rearrangement

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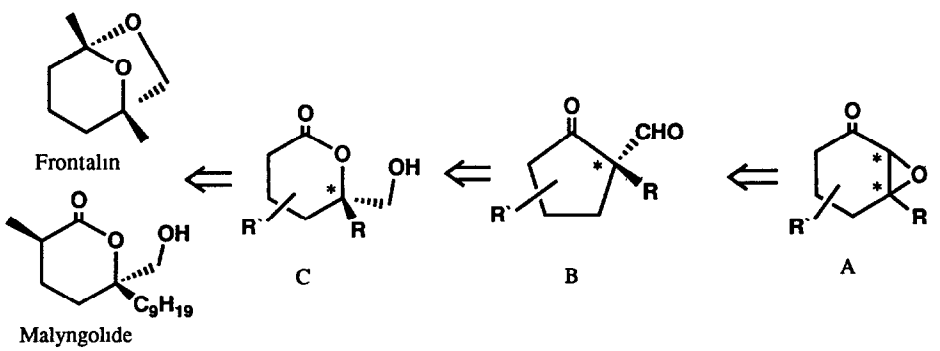
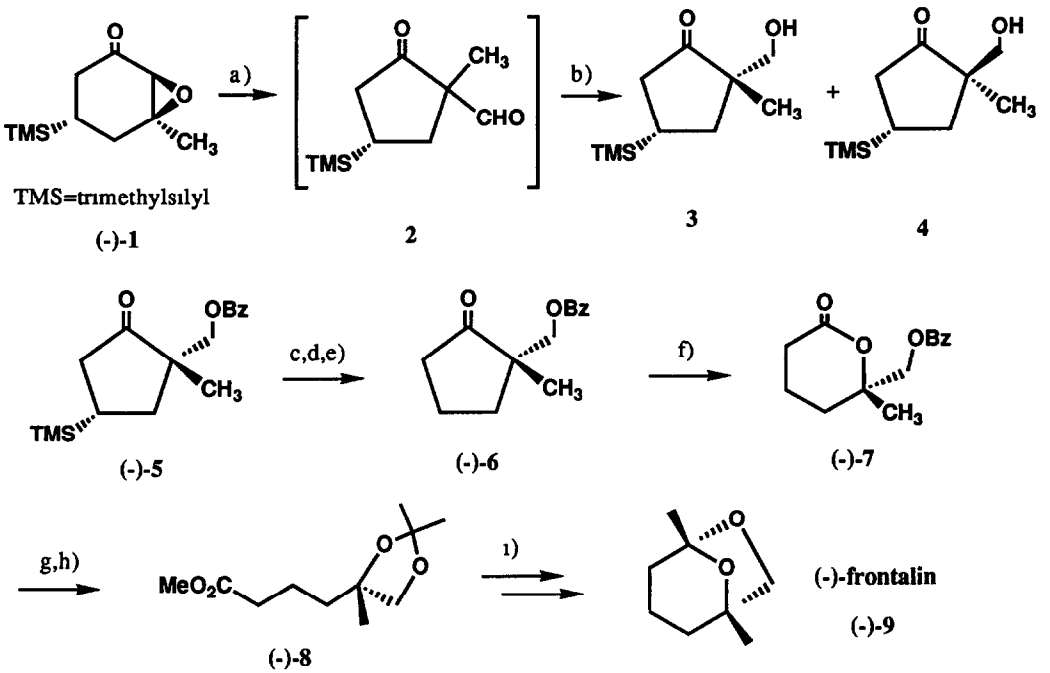
Abstract Synthesis of the title compounds by utilizing BF_3 Et_2O catalyzed ring contraction of 2,3-epoxycyclohexanones leading to 2-alkyl-2-formylcyclopentanones is described

Though the Lewis acid catalyzed rearrangement of cyclic epoxyketones is well established, only a limited extent of its utilization for the synthesis of optically active compounds is reported [1] One of the reason for the limited utilization is the rather difficult accessibility to highly optically active starting epoxyketones We have recently developed an enantioselective access to 2,3-epoxycyclohexanones[2] and our interest in using enantiomeric epoxyketones for asymmetric natural product synthesis led us to design the synthesis of (–)-frontalin[3] and (+)-malyngolide[4] via the Lewis acid catalyzed rearrangement of 2,3-epoxycyclohexanones



As shown in the above retrosynthetic analysis, γ-valerolactone derivative C is a useful intermediate for the synthesis of both frontalin and malyngolide, and the lactone would easily be obtained by the chemoselective reduction of the formyl group and subsequent Baeyer-Villiger oxidation of

formylcyclopentanone **B**, which in turn can be prepared by the Lewis acid catalyzed rearrangement of epoxyketone **A** In the above sequence, the Baeyer-Villiger oxidation is known to proceed with retention of chiral center, however, the former step (**A** $\rightarrow$ **B**) is reported to proceed with partial racemization [1b] Thus, to enhance the stereospecificity of the rearrangement and to isolate homochiral products, we started our work with the 5-trimethylsilyl group substituted epoxycyclohexanone (–)-**1** which was prepared in 81% yield by a diastereoselective (>20 1) epoxidation of (+)-(5S)-3-methyl-5-trimethylsilyl-2-cyclohexenone [2] The Lewis acid catalyzed rearrangement of (–)-**1** (BF_3 Et_2O, dichloromethane, rt, 0 5 min) followed by chemoselective reduction of aldehyde moiety with Bu_3SnH in methanol[5] gave a mixture of two ketols **3** and **4** (3 5 1) in 88% yield [6] Though the ketols themselves and their t-butyldimethylsilyl derivatives could not be separated, their benzoyl esters were chromatographically separable



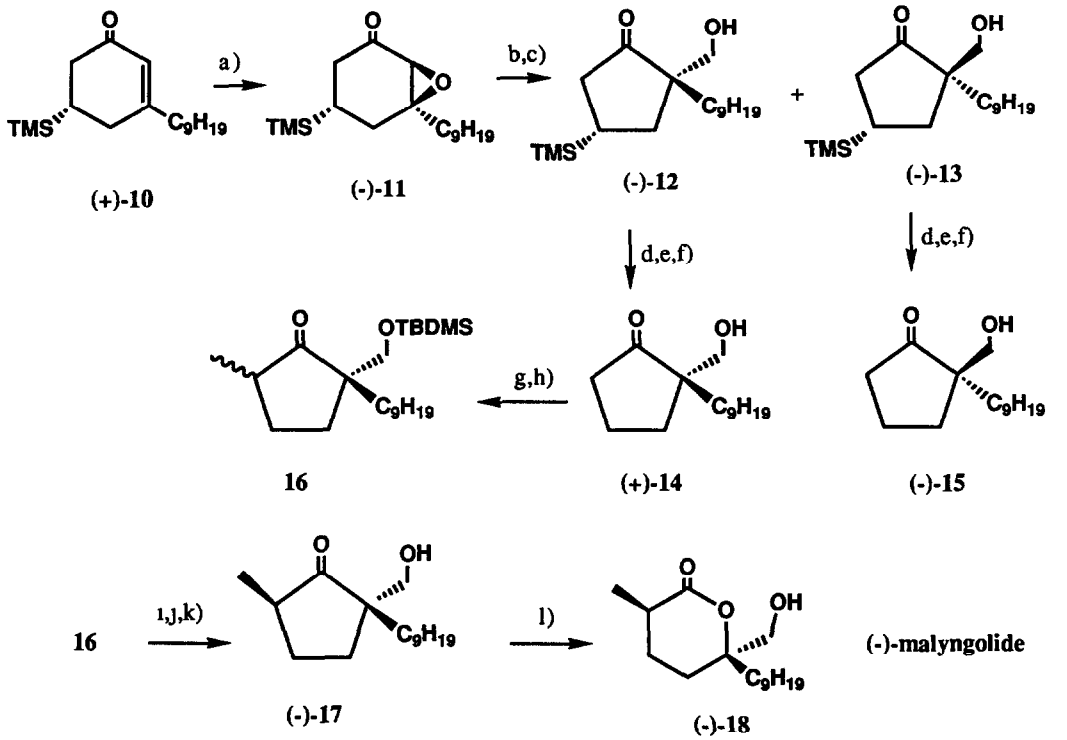
Scheme 1.

a) BF_3•Et_2O, CH_2Cl_2, b) Bu_3SnH, c) PyH•HBr_3, d) TBAF, e) H_2, Pd-C, f) m-CPBA, g) K_2CO_3, MeOH, h) $Me_2C(OMe)_2$, TsOH, i) ref 3e (2 steps)

Desilylation of the major product (–)-**5** via α-bromination of the carbonyl group with pyridinium tribromide followed by the treatment with tetrabutylammonium fluoride (TBAF) and hydrogenation of formed double bond gave (–)-**6** in 78% overall yield By the use of large excess (5 equivalents) of m-CPBA, the Baeyer-Villiger oxidation of (–)-**6** gave lactone (–)-**7** in good (84%) yield Ring opening of the

lactone by the treatment with K_2CO_3 in MeOH and subsequent diol protection as an acetonide gave known ester (–)-**8** [$[\alpha]_D^{21}$–1 37°(c 2 98, $CHCl_3$), lit [3e] $[\alpha]_D^{23}$–1 65°(c 5.44, $CHCl_3$)] in 66% overall yield The conversion of (–)-**8** to (–)-frontalin has been achieved in 2 steps by Sato et al ,[3e] and thus the above sequence constitute a formal synthesis of (–)-frontalin

On the basis of the above results, synthesis of (–)-malyngolide was started from enone (+)-**10**.[7] Epoxidation with 35% H_2O_2 in MeOH in the presence of a catalytic amount of 6M NaOH at 0°C gave (–)-**11** in 84% yield (diastereoselectivity >20 1) The Lewis acid catalyzed ring contraction (BF_3 Et_2O, dichloromethane, rt, 1 h) followed by Bu_3SnH reduction in methanol gave chromatographically separable two diastereoisomers (–)-**12** (71%) and (–)-**13** (24%) According to the same method used for the desilylation of (–)-**5**, (–)-**12** and (–)-**13** were converted to (+)-**14** [73%, $[\alpha]_D^{27}$+9 95°(c 2 15, $CHCl_3$), lit [4d] $[\alpha]_D^{25}$+8 12°(c , $CHCl_3$)] and (–)-**15** [54%, $[\alpha]_D^{26}$–9 83°(c 1 83, $CHCl_3$)] respectively



Scheme 2.

a) 35% H_2O_2, NaOH, b) BF_3•Et_2O, CH_2Cl_2, c) Bu_3SnH, d) PyH•HBr_3, e) TBAF, f) H_2, Pd-C, g) TBDMSCl, Et_3N, cat. DMAP, h) LDA, MeI, i) TBAF, j) LDA, k) H_3O^+, l) m-CPBA

While the conversion of (+)-**14** to (–)-malyngolide is possible by the method of Matsuo et al ,[8] an alternative route of higher diastereoselectivity was examined, and the following procedure was proved to be efficient Silylation of (+)-**14** with chloro-t-butyldimethylsilane (TBDMSCl) in the presence of Et_3N and a catalytic amount of 4-dimethylaminopyridine (DMAP) gave the corresponding silyl ether which was methylated with lithium diisopropylamide (LDA) and methyl iodide to give a diastereomeric mixture of methylated ketone **16** in 82% yield After removal of the TBDMS group with tetrabutylammonium fluoride (TBAF), enolate formation with LDA and subsequent protonation under kinetic conditions gave the expected diastereoisomer (–)-**17** selectively (95%) The hydroxyketone was subjected to the Baeyer-Villiger oxidation under Matsuo's conditions[8] to give (–)-malyngolide [$[\alpha]_D^{20}$–13 2°(c 0 94, $CHCl_3$), lit [3e] $[\alpha]_D$–13 1°(c 0 58, $CHCl_3$)] in 48% yield

Experimental

Specific rotation was measured on a Horiba SEPA-200 in $CHCl_3$ Ir was recorded on a Hitachi 260-50 ^{1}H- and ^{13}C-nmr are recorded on a Hitachi R-24B or JNM-FX-90Q in $CDCl_3$

(–)-(2S,3S,5S)-2,3-Epoxy-3-methyl-5-(trimethylsilyl)cyclohexanone (–)-1 To a solution of (+)-(5S)-3-methyl-5-trimethylsilyl-2-cyclohexenone (3 50 g, 19 2 mmol) dissolved in MeOH (100 ml) were added 35% H_2O_2 (3 74 ml, 38 5 mmol) and 6M NaOH (1 6 ml, 9 6 mmol) at 0°C, and the reaction mixture was stirred at that temperature for 0 5 h After the addition of 10% aq Na_2SO_3 and saturated NH_4Cl, methanol was removed under reduced pressure Extraction with ether and purification by column chromatography (hexane ether=4 1) gave (–)-**1** (3 12 g, 82%) Oil $[\alpha]_D^{26}$–121 8°(c 3 4) ^{1}H-nmr δ=0 0(9H, s), 0 8-2 6(5H, m), 1 42(3H, s), 3 00(1H, s) ppm ^{13}C-nmr δ=–3 79, 14 36, 21 78, 29 90, 36 78, 61 43, 61 60, 206 13 ppm Ir (neat) 1700 cm^{-1} (C=O) Found C, 60 24, H, 9 59% Calcd for $C_{10}H_{18}O_2Si$ C, 60 56, H, 9 15%

(–)-(2S,4S)-2-Benzoyloxymethyl-2-methyl-4-(trimethylsilyl)cyclopentanone (–)-5: To a solution of (–)-**1** (1 98 g, 10 mmol) in dry CH_2Cl_2 (50 ml) was added BF_3 Et_2O (628 μl, 5 mmol), and the resulted solution was stirred under Ar at rt for 0 5 min After diluted with CH_2Cl_2, the solution was washed with water, dried over $MgSO_4$, and concentrated The residue was dissolved in absolute methanol (50 ml). To the solution was added Bu_3SnH (5 36 ml, 20 mmol), and the reaction mixture was stirred under Ar at room temperature for 4 h The reaction was quenched by the addition of acetone (5 ml), and the solution was stirred at rt for 0 5 h After removal of volatiles under reduced pressure, chromatographical purification gave a mixture of **3** and **4** (1 76 g, 88%) To a solution of **3** and **4** in dry pyridine (1 ml) was added benzoyl chloride (1 12 ml, 9 68 mmol) , and the resulted solution was stirred for 1 h Usual work-up followed by purification by column chromatography (hexane:ether=9 1) gave (–)-**5** [1.98 g, 65% from (–)-**1**] Oil $[\alpha]_D^{25}$–64 3°(c 1 9). ^{1}H-nmr δ=0.04(9H, s), 1 14(3H, s), 0.7-2.6(5H, m), 4 27(2H, s), 7 1-7 6(3H, m), 7 7-8 1(2H, m) ppm Ir (neat) 1741 and 1724 cm^{-1} (C=O) Found C, 66 74, H, 7 80% Calcd for $C_{17}H_{24}O_3Si$ C, 67 06, H, 7 95%

(−)-(2S)-Benzoyloxymethyl-2-methylcyclopentanone (−)-6: To a solution of (−)-**5** (1 12 g, 3.68 mmol) in THF (20 ml) was added pyridinium tribromide (1.41 g, 4.42 mmol) and the reaction mixture was stirred at rt for 0.5 h Addition of aq Na_2SO_3 and saturated $NaHCO_3$ solution, and extraction with ether gave a brominated product, which was dissolved in dry THF (20 ml) and treated with 1M solution of tetrabutylammmonium fluoride in THF (3 68 ml, 3.68 mmol) at rt for 5 min to give a crude enone Hydrogenation of the crude enone in methanol (20 ml) in the presence of 10% Pd-C (394 mg) under hydrogen atmosphere for 5 h and isolation by column chromatography (hexane ether=4 1) gave (−)-**6** (663 mg, 78%). Oil: $[\alpha]_D^{25}$–50 8°(c 1.3) ^{1}H-nmr· δ=1 11(3H, s), 1.5-2 7(6H, m), 4 23(2H, s), 7.1-7 6(3H, m), 7.7-8 1(2H, m) ppm. Ir (neat): 1745 and 1727 cm^{-1} (C=O) Found. C, 72.06; H, 7.29% Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94%.

(−)-(5S)-6-Benzoyloxy-5-methyl-5-hexanolide (−)-7: To a solution of (−)-**6** (464 mg, 2 0 mmol) in dry $CHCl_3$ (20 ml) were added m-CPBA (1 72 g, 10 mmol) and anhydrous $NaHCO_3$ (840 mg, 10 mmol) The reaction mixture was stirred in the dark at rt for 1 day After addition of 10% Na_2SO_3 (5 ml), the reaction mixture was extracted with CH_2Cl_2 and the organic layer was washed with saturated $NaHCO_3$ solution. Purification of the product by column chromatography (hexane:ether=1:2) gave (−)-**7** (419 mg, 84%). Oil $[\alpha]_D^{25}$–17 3°(c 1.3) ^{1}H-nmr· δ=1 49(3H, s), 1 7-2.2(4H, m), 2.3-2 7(2H, m), 4.31(2H, s), 7.3-7.6(3H, m), 7 8-8.1(2H, m) ppm Ir (neat) 1745 and 1722 cm^{-1} (C=O). Found· C, 67 45, H, 6.72% Calcd for $C_{14}H_{16}O_4$ C, 67.73, H, 6 50%.

(−)-(5S)-5-(3′-Methoxycarbonylpropyl)-2,2,5-trimethyl-1,3-dioxolane (−)-8 To a solution of (−)-**7** (300 mg, 1.2 mmol) in MeOH (3 ml) was added K_2CO_3 (250 mg, 1.8 mmol), and the reaction mixture was stirred at rt for 0.5 h After removal of MeOH, CH_2Cl_2 and saturated NH_4Cl solution were added to the reaction mixture. The water layer was acidified with 1M HCl, and extracted 5 times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure To the residue in 2,2-dimethoxypropane (3 ml) was added p-toluenesulfonic acid (20.8 mg, 0 12 mmol), and the solution was stirred under Ar at rt for 1 h The reaction mixture was diluted with ether, and washed with water and brine Removal of solvent and purification by column chromatography (hexane.ether=4 1) gave (−)-**8** (173 mg, 66%). Oil. $[\alpha]_D^{21}$–1 37°(c 3.0) ^{1}H-nmr δ=1 27(3H, s), 1.38(6H, s), 1 3-2 0-(4H, m), 2 1-2.5(2H, m), 3 63(3H, s), 3 72(2H, s) ppm Ir (neat) 1740 cm^{-1} (C=O) Found C, 60 84, H, 9.26% Calcd for $C_{11}H_{20}O_4$ C, 61 09, H, 9.32%

(+)-(5R)-3-Nonyl-5-trimethylsilyl-2-cyclohexenone (+)-10 Oil $[\alpha]_D^{20}$+42 1°(c 3.0) ^{1}H-nmr δ=0 04(9H, s), 0 87(br t, J=4 5 Hz), 0 6-1 9(17H, m), 2 0-2 4(4H, m), 5 78(br s) ppm. Found· C, 72 98, H, 11.84%. Calcd for $C_{18}H_{34}OSi$ C, 73 40, H, 11 64%

(−)-(2S,3S,5S)-2,3-Epoxy-3-nonyl-5-(trimethylsilyl)cyclohexanone (−)-11. According to the same method described for (−)-**1**, (−)-**11** was obtained in 84% yield. Oil: $[\alpha]_D^{24}$–77.8°(c 5.8) ^{1}H-nmr: δ=0.0(9H, s), 0 87(3H, br t, J=5 0 Hz), 0.6-2 3(21H, m), 3.05(1H, br s) ppm ^{13}C-nmr: δ=–3 8, 14.1, 22 6, 24.6, 28 0, 29 3, 29 5, 29 6, 31.9, 35 6, 37 1, 60 8, 64.3, 206.3 ppm Ir (neat) 1720 cm^{-1} (C=O) Found C, 69 40, H, 11 30% Calcd for $C_{18}H_{34}O_2Si$. C, 69 62, H, 11.04%.

(–)-(2S,4S)-2-Hydroxymethyl-2-nonyl-4-(trimethylsilyl)cyclopentanone (–)-12 and (–)-(2R,4S)-2-Hydroxymethyl-2-nonyl-4-(trimethylsilyl)cyclopentanone (–)-13. To a solution of (–)-**11** (1 47 g, 4 74 mmol) in dry CH_2Cl_2 (30 ml) was added BF_3 Et_2O (298 μl, 2 37 mmol), and the solution was stirred under Ar at rt for 1 h The reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over $MgSO_4$ After removal of solvent, the residue was dissolved in absolute MeOH To the solution was added Bu_3SnH (2.25 ml, 9 48 mmol), and stirred under Ar at rt for 0 5 h Usual work-up followed by purification by column chromatography (hexane·ether=3·1) gave (–)-**12** (1 05 g, 71%) and (–)-**13** (349 mg, 24%) (–)-**12**· oil; $[\alpha]_D^{24}$–31 9°(c 2 5) ^{1}H-nmr· δ=0 03(9H, s), 0 65-2.0(19H, m), 0 87, br t, J=4 0 Hz), 2 05-2 65(3H, m), 4 42(1H, d, J=11 0 Hz), 4 62(1Hm d, J=11 0 Hz) ppm. Ir (neat)· 3450 (OH) and 1735 (C=O) cm^{-1} Found. C, 69 57, H, 11 88%. Calcd for $C_{18}H_{36}O_2Si$· C, 69 17, H, 11.61% (–)-**13** oil, $[\alpha]_D^{21}$–72 1°(c 1.1) ^{1}H-nmr· δ=0 03(9H, s), 0.87(3H, br t, J=5.0Hz), 0 6-2 7(22H, m), 3 52(1H, br s) ppm Ir (neat) 3420 (OH) and 1730 (C=O) cm^{-1} Found C, 68 88, H, 12 00%

(+)-(2S)-2-Hydroxymethyl-2-nonylcyclopentanone (+)-14· Bromination of (–)-**12** (156 mg, 0 5 mmol) with pyridinium tribromide (480 mg, 1 5 mmol) in THF (5 ml) was carried out at rt for 12 h , and the subsequent operation was carried out as described for (–)-**6** Purification by column chromatography (hexane·ether=2 1) followed by bulb to bulb distillation [bp (bath temp). 160-170°C/0 1 mmHg] gave (+)-**14** (88 mg, 73%) Oil $[\alpha]_D^{26}$+9 83°(c 1 8) ^{1}H-nmr δ=0 86(br t, J=5 0Hz), 0 7-2 6(23H, m), 3 44(1H, d, J=11 0Hz), 3 59(1H, d, J=11 0Hz) ppm Ir (neat) 3460 (OH) and 1740 (C=O) cm^{-1} Found· C, 74 59, H, 11 59% Calcd for $C_{15}H_{28}O_2$ C, 74 95, H, 11 74%

(–)-(2S)-2-t-Butyldimethylsiloxymethyl-2-nonylcyclopentanone To a solution of (+)-**14** (320 mg, 1 33 mmol) in dry CH_2Cl_2 (15 ml) were added triethylamine (307 ml, 2 2 mmol), t-butylchlorodimethylsilane (TBSCl, 301 mg, 2 0 mmol), and 4-dimethylaminopyridine (6 0 mg, 0 05 mmol), and the solution was stirred under Ar at rt for 24 h The reaction mixture was diluted with CH_2Cl_2, washed with water and brine, and dried over $MgSO_4$ Removal of solvent and purification by column chromatography (hexane·ether=50 1) gave TBS ether in 99% (466 mg) yield Oil $[\alpha]_D^{21}$–10 5°(c 2 1) ^{1}H-nmr δ=0 0 (6H, s), 0 85(9H, s), 0.6-2 3(25H, m), 3.35(1H, d, J=9.0Hz), 3 60(1H, d, 9 0Hz) ppm. Ir (neat) 1745 cm^{-1} (C=O) Found C, 70 99, H, 11 97% Calcd for $C_{21}H_{42}O_2Si$ C, 71 12, H, 11 94%

(–)-(2S,5R)-2-Hydroxymethyl-2-nonyl-5-methylcyclopentanone (–)-17 To a solution of LDA (2 mmol) in dry THF (4 ml) was added a THF (2 ml) solution of the TBS ether (354 mg, 1 0 mmol) at -78°C, and the solution was stirred at that temperature for 1 h After addition of MeI (125 ml, 2 0 mmol), the reaction mixture was stirred at -78°C for 1 h, and then allowed to warm to rt Usual work-up followed by purification by column chromatography (hexane ether=50 1) gave **16** (305 mg, 83%) To a solution of **16** (305 mg, 0 38 mmol) in dry THF (5 ml) was added a 1M solution of tetrabutylammonium fluoride (TBAF) in THF, and the reaction mixture was stirred at rt for 3 h After addition of 1M HCl (2 ml), the mixture was extracted with ether The organic layer was washed with saturated $NaHCO_3$ solution and brine, and then dried over $MgSO_4$ The solvent was removed under reduce pressure and the residue was purified by column chromatography (hexane·ether=2 1) After removal of the solvent, the product was dissolved in

dry THF (2 ml) and added to a precooled (–78°C) solution of LDA (5 mmol) in dry THF (3 ml). After 1 h, saturated NH_4Cl solution was added at once to the reaction mixture Usual work-up followed by purification by column chromatography (hexane ether=2 1) gave (–)-**17** (199 mg, 95% from **16**) Oil $[\alpha]_D^{22}$–19 3°(c 1.5) ^{1}H-nmr δ=0 87(3H, br t, J=4 0Hz), 1 07(3H, d, J=6 5Hz), 0 65-2 65(22H, m), 3 42(1H, d, J= 10 0Hz), 3 58(1H d, J=10 0Hz) ppm Ir (neat) 3480 (OH) and 1725 (C=O) cm^{-1} Found C, 75 10, H, 11 88% Calcd for $C_{16}H_{30}O_2$ C, 75 54, H, 11 89%

(–)-Malyngolide (–)-18 To a solution of (–)-**17** (70 mg, 0 276 mmol) in dry $CHCl_3$ (10 ml) were added m-CPBA (173 mg, 1 0 mmol) anhydrous $NaHCO_3$ (84 mg, 1 0 mmol), and the mixture was stirred in the dark under Ar at rt for 1 day After further addition of m-CPBA (95 5 mg, 0 552 mmol) and $NaHCO_3$ (46 4 mg, 0 552 mmol), the mixture was stirred in the dark for 2 days After addition of 10% aq Na_2SO_3 (2 ml), the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution Removal of the solvent followed by purification by column chromatography (hexane ether=1 2) gave (–)-**18** (34 mg, 48%) The ir and nmr spectral properties of this hydroxy lactone were identical with those previously reported for the (–)-malyngolide [4]

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6) Though the stereochemistry of these products was not clear at this stage, by the completion of this synthesis, the major isomer **3** was proved to have the depicted structure This result suggests that the large part of the rearrangement is not a concerted but a cationic process Detailed study and mechanistic speculation on the rearrangement step is underway and will be published elsewhere

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