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Synthesis of Spirolactone Sesquiterpenes, Curcumanolide-A and Curcumalactone[1]

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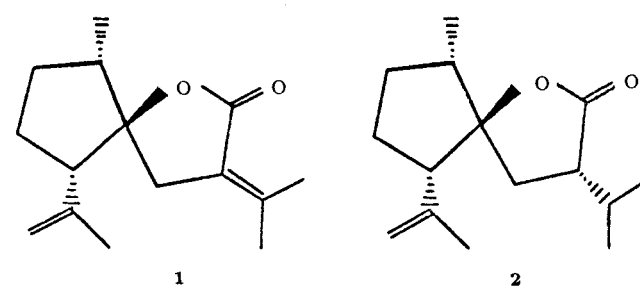
Spirocyclic γ-lactones, curcumanolide-A and curcumalactone were synthesized in a racemic form. The carbon skeleton was constructed by Br^+-induced cyclization of bishomogeranyl acetate and subsequent ring contraction. The hydroboration assisted by a remote hydroxy group was achieved for the regioselective functionalization of tetrasubstituted double bond.

INTRODUCTION

Curcumanolide-A, **1**, was isolated from the crude drug zedoary and other Curcuma species [2,3]. Although zedoary, the dried and ground rhizome of Curcuma zedoaria Roscoe, has been used medicinally for a long time, **1** had not been utilized in medical practice, probably due to the limited availability of the isolated material from natural sources. Due to its structural resemblance to curcumalactone **2**, which is reported to exhibit anti-inflammatory activity [4,5], compound **1** is highly expected to possess potential biological activity. Compound **2** is a component of the essential oil of Curcuma aromatica, utilized as a folk remedy of uterine cancer in China. For the sake of furnishment of enough materials for the medicinal experiments, a short step synthesis of these natural products possessing the unique skeleton has been explored [6]. In this article, a racemic synthesis of spirolactones, **1** and **2**, starting from geraniol, **3** is described (Scheme 1) [6].

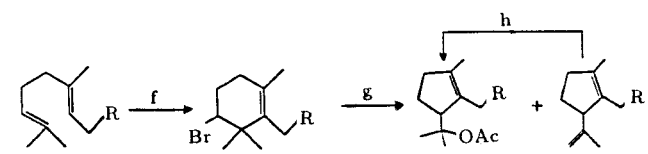


Scheme 1

RESULTS AND DISCUSSION

The homogeranyl cyanide **5** was prepared from geraniol **3** in 62% yield by literature method, i.e., conversion of **3** to the corresponding bromide **4** followed by reaction with $CuCH_2CN$ [7]. The cyanide **5** was hydrolyzed to the carboxylic acid **6**, reduced with $LiAlH_4$ and then acetylated in conventional manners to give bishomogeranyl acetate **7** in high overall yield. Cyclization of **7** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) in acetonitrile furnished the brominated product **8**, which was treated with silver acetate to give the desired ring contraction product, 3-[5-(1-acetoxy-1-methylethyl)-2-methyl-1-cyclopentenyl] propyl acetate, **9**, accompanied by diene acetate **10** [8]. The latter was converted to the former acetate **9** by application of oxymercuration demercuration reaction (Scheme 2).

The stereo- and regioselective hydration of the double bond of **9** was aimed by application of



3 R = OH
4 R = Br
5 R = CH_2CN
6 R = CH_2CO_2H
7 R = CH_2CH_2OAc
8 R = CH_2CH_2OAc
9
10
R = CH_2CH_2OAc

3 → **7**: a) PPh_3, CBr_4 b) ^nBuLi, CH_3CN, CuI 68% from **3** c) KOH d) $LiAlH_4$ e) Ac_2O, Py 87% from **5**
7 → **8**: f) 2,4,4,6-tetrabromocyclohexa-2,5-dienone, CH_3CN g) AgOAc, AcOH **9** 33% **10** 37% from **7** h) $Hg(OAc)_2$ then $NaBH_4$, NaOH 34% as diol **12**

Scheme 2

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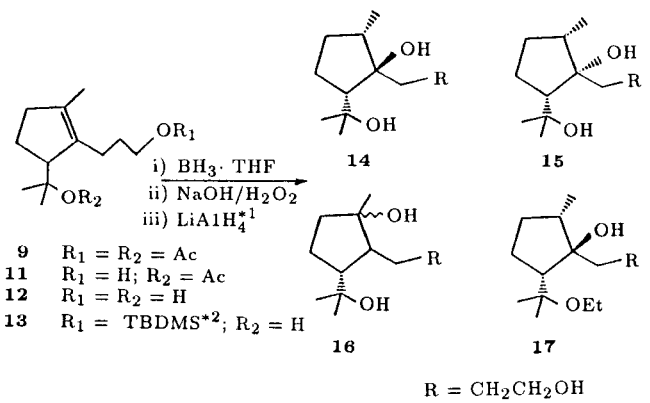
hydroboration-oxidation reaction. For this purpose, substrates **11-13** were prepared by conventional methods and submitted to the reactions with an excess of borane-tetrahydrofuran complex and subsequently alkaline hydrogen peroxide. When the substrate **12** was subjected to the reaction, the requisite triol **14**, was formed in 81% yield accompanying the stereoisomer **15** in ca 5% yield. No regioisomer corresponding to **16** was detected. On the other hand, the acetates **9** and **11** afforded **14** in 54 and 47% yields, respectively. The characterized by-products were **15** and its ethyl ether **17**, the ethoxy group of which may be reductively derived from acetyl group (R_2 = Ac) [9]. The regioselectivity of **12** is clearly caused by the participation of the primary hydroxy group of **12**, since, in the case of silyl ether **13**, detectable amounts of the triol **14** was not isolated after desilylation of the reaction products. Although the exact stereochemistry of cyclopentane ring of **14** could not be demonstrated by physical methods at this stage, the trans relation of the newly introduced hydroxy group with respect to the neighboring 2-propanol moiety is reasonably expected from consideration of the six-membered transition state of the hydroboration via BH_3-$HO(CH_2)_3R$ complex, where R corresponds to cyclopentene ring. Hydroboration may take place from the opposite site of the dimethylcarbinol group. In fact, the stereochemistry of **14** was confirmed at later stage (Scheme 3).

The triol **14** was oxidatively cyclized with pyridinium dichromate in DMF, affording hydroxy lactone **18** in 87% yield. The hydroxy lactone **18** was submitted to the dehydration reactions under several different conditions. It afforded a 7:1 mixture of isopropenyl- and 1-chloro-1-methylethyl-spirolactones, **19** and **20**, by treatment with thionyl chloride in the absence of pyridine. When the reaction was carried out in pyridine solution, the chloride **20** was formed quantitatively. When dehydration of **18** was attempted using Burgess reagent [10], $MeO_2CNSO_2NEt_3$ at 50°C, a 7:2 mixture of **19** and isomeric isopropylidene lactone, **21** was obtained quantitatively. The reaction was quite slow at 0°C, affording a 1:1 mixture of **19** and **21** in 45% yield accompanying the recovered material



9 $R_1 = R_2$ = Ac
11 R_1 = H; R_2 = Ac
12 $R_1 = R_2$ = H
13 R_1 = TBDMS*2; R_2 = H

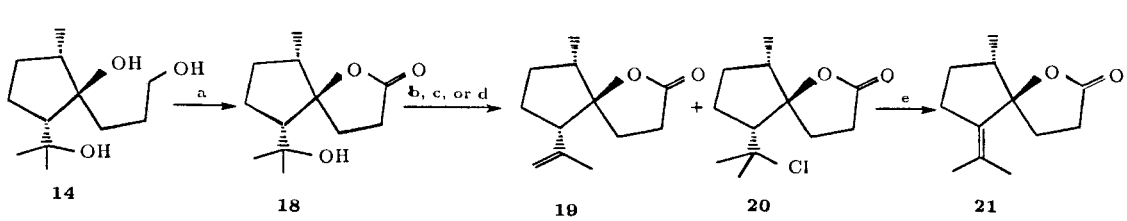
R = CH_2CH_2OH

*1 In the cases of **9** and **11**, the reaction products were treated with $LiAlH_4$.
*2 TBDMS = ^{t}Butyldimethylsilyl

Scheme 3

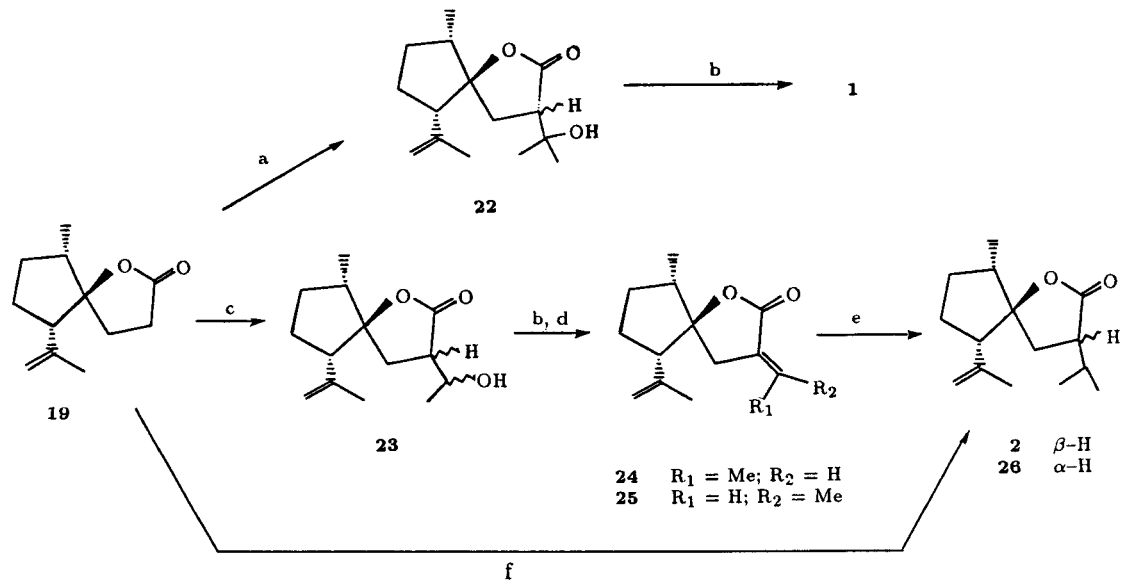
(53%). Dehydrochlorination of **20** with Li_2CO_3 and LiBr in DMF at 105°C provided **21**, exclusively. In the ^{1}H NMR spectrum of **19**, clear NOE was observed between secondary methyl at δ 0.96 (d, 7 Hz) and methyl at δ 1.77 (s) due to isopropenyl group, thus indicating the cis relation of these pendants attached to the cyclopentane ring (Scheme 4).

The synthesis of (±)-curcumanolide -A, **1**, from **19** was carried out in 59% overall yield by successive reactions of condensation of the lithium enolate of **19** with acetone to the hydroxy lactone **22**, followed by dehydration with methanesulfonyl chloride in pyridine. (±)-Curcumalactone **2** was synthesized by two different routes. One starts from condensation of lithium enolate of **19** with acetaldehyde to give a mixture of diastereoisomers **23** in 86% yield. The mixture was, without separation, successively treated with methanesulfonyl chloride and pyridine to the corresponding mesylate, followed by DBU, providing a 3:4 mixture of (E)- and (Z)-ethylidene lactones **24** and **25** in 95% yield from **23**. Reaction of the mixture **24** and **25** with lithium dimethylcuprate in the presence of BF_3-ether complex at -78°C provided a 1:8 mixture of curcumalactone **2** and its stereoisomer **26** in 77% yield. Compounds **2** and **26** were easily separated by HPLC. Another route was concerned with direct introduction



a) PDC, DMF 87% b) $SOCl_2$ **19:20** = 7:1 74% c) $SOCl_2$, Py **19:20** = 0:1 83% d) $MeO_2CNSO_2NEt_3$ **19:21** = 7:2 98% e) Li_2CO_3, LiBr, DMF 70%

Scheme 4



a) LDA then acetone 88% b) MsCl, Py, DMAP 67% c) LDA then CH_3CHO 86% d) DBU **24** 40%, **25** 54% e) CuI and MeLi then BF_3OEt_2, -78°C **2** and **26** = 1:8 77% f) LDA then $(CH_3)_2CHI$, HMPA, aq NH_4Cl, rt., **2** and **26** = 2:3 89%.

Scheme 5

of isopropyl group by the action of isopropyl iodide to the lithium enolate of **19** in the presence of HMPA. Quenching the reaction mixture at 0°C afforded a 2:3 mixture of **2** and **26** in 89% yield. When pure **2** and **26** were independently refluxed in xylene in the presence of DBU, both changed to a ca 2:3 mixture. When pure **2** or **26** were converted to lithium enolate by the action of LHMDS (lithium hexamethyldisilazide) at 0°C and quenched at -78°C, both afforded a ca 1:7 mixture of **2** and **26**. The equilibrium experiments described so far indicate that the isomer **26** predominates under the experimental conditions (Scheme 5).

Physical data, except optical rotation, of the synthesized compounds **1** and **2** were indistinguishable with those reported for natural products. The synthetic compounds were submitted for biological activity assessment and the results will be published elsewhere.

EXPERIMENTAL

Melting points (measured on Yanaco-MP) are uncorrected. Unless otherwise noted, ^1H NMR and ^{13}C NMR spectra were recorded on JEOL spectrometers, using $CDCl_3$ solutions and $SiMe_4$ as an internal standard. Chemical shifts are reported in δ-units with δ_H (^1H NMR) and δ_C(^{13}C NMR), moreover J-values are in Hz. The mass spectra were measured with Hitachi M-80 and M-80 A spectrometers. The usual work-up involved dilution of the reaction mixture with water, extraction with diethyl ether (ether) and washing of the organic extract with water and brine, followed by drying over Na_2SO_4, and evaporation at aspirator pressure. Column chromatographic purification was carried out on Kiesel gel 60, Art 7734 (70-230 mesh) and the weight of the silica gel and elution solvents is being indicated in parentheses.

Homogeranyl Cyanide 5

Into a stirred ether (100 ml) solution of geraniol **3** (10.01 g, 65.0 mmol) and tetrabromomethane (29.6 g, 89.3 mmol) was gradually added triphenylphosphine (23.4 g, 89.3 mmol) at 0°C and the stirring was continued for 1 h at room temperature. Then, hexane (100 ml) was added to the mixture which was kept in a refrigerator for 5 h afterwards. The resultant white powder was removed by filtration. The mother liquid was concentrated under reduced pressure. Hexane (150 ml) was again added to the residue and the mixture was kept in a refrigerator for several hours. The white precipitate was removed by filtration. After repeating this procedure several times, **crude geranyl bromide 4** (16.9 g) was obtained as a colorless oil. A 1.6 M hexane solution (100 ml, 0.16 mol) of ^{n}BuLi was added to a THF solution (200 ml) of dry acetonitrile (10.8 ml, 0.207 mol) at -78°C under argon atmosphere and the mixture was stirred for 40 min. The temperature was raised to -25°C, copper (I) iodide (39.2 g, 0.206 mol) was added and the stirring was continued at the same temperature for 1 h to give a brown solution. A THF solution (110 ml) of the geranyl bromide **4** (16.88 g) was

gradually added to the mixture and the stirring was continued for another 1 h under the same conditions. After addition of aqueous NH_4Cl solution, the reaction mixture was extracted with hexane and then ether. The combined organic layers were successively washed with aq $Na_2S_2O_3$ and then submitted to the usual work-up. Chromatography (400 g, hexane-AcOEt, 15:1) gave homogeranyl cyanide **5** (7.08 g, 62% from geraniol) as a colorless oil. δ_H (90 MHz) 5.13 (2H, m), 1.70 (3H, s), 1.67 (3H, s) and 1.61 (3H, s). δ_C (22.5 MHz) 138.6 (s), 131.2 (s), 123.7 (d), 120.0 (d), 119.2 (s), 39.3 (t) x 2, 26.3 (t), 25.3 (q), 23.8 (t), 17.3 (q) and 15.8 (q). HRMS found: m/z 177.1525. Calcd for $C_{12}H_{19}N$: M, 177.1517.

Bishomogeranyl Acetate 7

After refluxing a mixture of homogeranyl cyanide **5** (5.28 g, 29.8 mmol) and 20 M KOH (4 ml) in ethanol (53 ml) for 12 h, 6 M aqueous HCl solution was added in order to acidify the mixture. Then, following the usual work-up, the residue was passed through a short silica gel column using hexane-AcOEt 10:1 to give homogeranioic acid **6** (5.73 g, 98%) as a pale yellow oil. δ_H (90 MHz) 8.85 (1H, br s), 5.10 (2H, m), 1.68 (3H, s) and 1.61 (6H, s). δ_C (22.5 MHz) 180.0 (s), 137.0 (s), 131.4 (s), 124.2 (d), 122.1 (d), 39.7 (t), 34.4 (t), 26.7 (t), 25.7 (q), 23.4 (t), 17.7 (q) and 16.0 (q). LRMS found: m/z 196. Calcd for $C_{12}H_{20}O_2$: M, 196. Into a stirred ether (920 ml) solution of $LiAlH_4$ (5.2 g, 137 mmol) was added an ether (220 ml) solution of bishomogeranioic acid **6** (25 g, 128 mmol) at 0°C. Stirring was continued for 30 min at the same temperature and then the mixture was quenched by successive addition of MeOH and aqueous NH_4Cl solution. The resulting mixture was stirred for 20 min and filtered through a pad of silica gel. The pad was washed with ether and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1 kg, hexane-AcOEt 15:1) gave bishomogeraniol (21.4 g, 92%) as a pale yellow oil. δ_H (90 MHz) 5.10 (2H, m), 3.63 (2H, t, J 6.4 Hz), 1.68 (3H, s) and 1.61 (6H, s). δ_C (22.5 MHz) 135.8 (s), 131.3 (s), 124.3 (d), 123.8 (d), 62.8 (t), 39.8 (t), 32.8 (t), 26.7 (t), 25.7 (q), 24.3 (t), 17.7 (q) and 16.0 (q). LRMS found: m/z 182. Calcd for $C_{12}H_{22}O$: M, 182. After stirring a mixture of bishomogeraniol (4.44 g, 24.4 mmol), pyridine (9.0 ml) and acetic anhydride (4.63 ml) for 12 h, MeOH (1 ml) and water (300 ml) were successively added. Then, following the usual work-up, the residue was passed through a short silica gel column, using hexane-AcOEt 15:1 to afford bishomogeranyl acetate **7** (5.3 g, 97%) as a colorless oil. δ_H (90 MHz) 5.12 (2H, m), 4.05 (2H, t, 6.7 Hz), 2.05 (3H, s), 1.69 (3H, s) and 1.61 (6H, s). δ_C (22.5 MHz) 170.4 (s), 135.8 (s), 130.9 (s), 124.1 (d), 123.0 (d), 63.7 (t), 39.5 (t), 28.6 (t), 26.5 (t), 25.3 (q), 24.0 (t), 20.5 (q), 17.4 (q) and 15.6 (q). HRMS found: m/z 224.1792. Calcd for $C_{14}H_{24}O_2$: M, 224.1776.

Cyclopentene Derivatives 9 and 10 from Bishomogeranyl Acetate 7

Into a stirred acetonitrile (50 ml) solution of bishomogeranyl acetate **7** (854 mg, 3.81 mmol) was added 2,4,4,6-tetrabromocyclohexa-2,5-dienone (2.33 g, 5.69 mmol) at 0°C and the stirring was continued for 1.5 h. After acetonitrile was removed in vacuo, the residue was taken up into mixed solvent of hexane-ether 5:1 and solution was passed through an alumina column, using hexane-ether 5:1 to remove the resulting 2,4,6-tribromophenol. Evaporation of the solvent afforded crude brominative cyclization product **8** (1.31 g) containing small amounts of 2,4,6-tribromophenol. The crude **8** (1.31 g) was dissolved in AcOH (27 ml) containing silver acetate (1.19 g) and the mixture was stirred at room temperature for 12 h. Water (50 ml) was poured into the mixture and then was extracted with ether. The ether solution was carefully washed first with aq Na_2CO_3 and then with brine and was dried over Na_2SO_4. The volatile materials were removed and chromatography of residue over silica gel (100 g, hexane-AcOEt 10:1) gave diacetate **9** (350 mg, 33%) and isopropenyl acetate **10** (310 g, 37%), respectively. Diacetate **9**, as a yellow oil. δ_H (90 MHz) 4.08 (2H, t, 6.3 Hz), 3.23 (1H, m), 2.06 and 2.00 (each 3H, s), 1.65 (3H, s), 1.48 (3H, s) and 1.34 (3H, s). δ_C (22.5 MHz) 171.1 (s), 170.2 (s), 136.8 (s), 134.0 (s), 86.6 (s), 64.2 (t), 54.7 (d), 36.7 (t), 26.6 (t), 24.8 (q), 24.7 (q), 24.3 (t), 22.6 (q), 21.3 (t), 20.9 (q) and 14.0 (q). LRMS found: m/z 222. Calcd for $C_{14}H_{22}O_2$ (M-AcOH): m/z 222. Isopropenyl acetate **10** as a yellow oil. δ_H (90 MHz) 4.70 (2H, m), 4.00 (2H, t, 6.3 Hz), 3.29 (1H, m), 2.05 (3H, s), 1.67 (3H, s) and 1.57 (3H, m t, 0.8 Hz). δ_C (22.5 MHz) 171.2 (s), 148.4 (s), 134.8 (s), 134.6 (s), 110.6 (t), 64.3 (t), 55.8 (d), 37.6 (t), 27.7 (t), 26.6 (t), 22.7 (q), 21.0 (t), 18.4 (q) and 14.0 (q). HRMS found: m/z 222.1613. Calcd for $C_{14}H_{24}O_2$: M, 222.1620.

Hydrolysis of Diacetate 9 with Sodium Carbonate

Into a methanol (3.0 ml) solution of diacetate **9** (100 mg) was added a methanol (5 ml) solution saturated with Na_2CO_3 and the mixture was kept at room temperature for 6 h. After acidification with 2 M HCl, the mixture was treated by the usual work-up to give monoacetate **11** (80 mg, 95%).

Hydrolysis of Diacetate 9 with KOH

Into a methanol (9.0 ml) solution of diacetate **9** (305 mg) was added a 2 M KOH methanol (9 ml) solution and the mixture was gently refluxed for 6 h. After

acidification with 2 M HCl, the usual work-up gave diol **12** (208 mg, 97%). Monoacetate **11**, as a colorless oil. δ_H (90 MHz) 3.60 (2H, t, 6.7 Hz), 1.99 (3H, s), 1.66 (3H, s), 1.47 (3H, s) and 1.33 (3H, s). δ_C (22.5 MHz) 170.1 (s), 135.6 (s), 134.7 (s), 86.4 (s), 61.9 (t), 54.4 (d), 36.4 (t), 30.6 (t), 24.6 (q), 24.3 (q), 24.1 (t), 22.2 (q), 21.2 (t) and 13.7 (q). LRMS found: m/z 180. Calcd for $C_{12}H_{20}O$ (M-AcOH): m/z 180. Diol **12**, as a colorless oil. δ_H (90 MHz) 3.61 (2H, t, 6.0 Hz), 1.67 (3H, s), 1.22 (3H, s) and 1.11 (3H, s). δ_C (22.5 MHz) 136.1 (s), 135.1 (s), 74.7 (s), 61.8 (t), 58.1 (d), 36.6 (t), 31.1 (t), 29.8 (q), 26.1 (t), 24.1 (t), 23.9 (q) and 14.0 (q). HRMS found: m/z 198.1624. Calcd for $C_{12}H_{22}O_2$: M, 198.1620.

Diol 12 from Isopropenyl Acetate 10

Into a solution of mercury (II) acetate (113 mg) in water (2 ml) and THF (2 ml) was added isopropenyl acetate **10** (100 mg) in THF (2 ml) and the mixture was kept for 29 h at 0°C. After addition of 3 M NaOH (1 ml) and $NaBH_4$ (17 mg), the mixture was stirred for 48 h at room temperature. Then, following the usual work-up, chromatography of the residue over silica gel (14 g, CH_2Cl_2 – MeOH 20:1) afforded diol **12** (31 mg, 34%).

Hydroboration-Oxidation of Diol 12 and its Derivatives, 9, 11 and 13

A THF (0.6 ml) solution of diol **12** (28 mg, 0.14 mmol) was added to a 1.0 M THF (1.4 ml, 1.4 mmol) solution of BH_3 – THF complex at 0°C under argon atmosphere and the mixture was kept overnight at room temperature. After addition of 3 M aqueous NaOH solution (1.4 ml) and 35% aqueous H_2O_2 (1.4 ml), the mixture was stirred overnight at room temperature. The usual work-up and chromatography over silica gel (15 g, CH_2Cl_2–MeOH 35:1, 25:1 and then 15:1) afforded triol **14** (24.4 mg, 81%) and the isomer **15** (1.6 mg, 5.3%). Similarly, monoacetate **11** (105 mg, 0.44 mmol) was consecutively treated with 1 M BH_3 – THF complex in THF (3.46 ml), 3 M NaOH solution (1.0 ml) and 35% aq H_2O_2 solution (1.0 ml). Following the usual work-up, the residue was taken up in dry ether (12.0 ml) and the ether solution was added to $LiAlH_4$ (12 mg) in ether (8 ml). After stirring for 1 h, MeOH was added and the resulting mixture was filtered through a pad of silica gel. The pad was washed with ether and the filtrate was concentrated. Chromatography of the residue over silica gel (25 g, CH_2Cl_2–MeOH) gave triol **14** (51 mg, 54%), its isomer **15** (6 mg, 8.0%) and ethyl ether **17** (8.3 mg, 9.8%). The diacetate **9** (303 mg, 1.07 mmol) was successively treated with BH_3 – THF solution (8.6 ml), 3 M aq NaOH and aq 35% H_2O_2 solutions (6.5 ml each) and finally with $LiAlH_4$ (13.8 mg) to afford triol **14** (110 mg, 47%), its isomer **15** (15 mg, 6.6%) and ethyl ether **17** (15.6 mg, 6.0%). Triol **14**, as a colorless oil. δ_H (270 MHz) 3.62 (2H, t, 5.6 Hz), 3.26 (2H, br s), 2.05 (1H, dd, 12.2 and 8.9 Hz), 1.32 (3H, s), 1.26 (3H, s) and 0.97 (3H, d, 6.6 Hz). δ_C (68 MHz) 82.3 (s), 73.5 (s), 63.6 (t), 59.3 (d), 46.5 (d), 32.7 (q), 27.7 (t) x 2, 27.7 (q), 27.2 (t), 22.5 (t) and 14.1 (q). Triol isomer **15**: δ_H (270 MHz) 3.67 (2H, m), 1.36 (3H, s), 1.23 (3H, s) and 0.89 (3H, d, 7.3 Hz). δ_C (68 MHz) 85.0 (s), 74.0 (s), 63.3 (t), 52.3 (d), 45.8 (d), 34.4 (t), 30.8 (q), 30.0 (t), 28.7 (q), 26.8 (t), 25.5 (t) and 14.9 (q). LRMS of **14** and **15** found: m/z 198. Calcd for $C_{12}H_{22}O_2$ (M – H_2O): m/z 198. Ethyl ether **17**: δ_H (270 MHz) 3.63 (2H, t, 5.6 Hz), 3.48 (2H, q, 6.9 Hz), 2.12 (1H, dd, 12.9, 9.2 Hz), 1.23 (3H, s), 1.21 (3H, s), 1.17 (3H, t, 6.9 Hz) and 0.98 (3H, d, 6.6 Hz). δ_C (68 MHz) 81.5 (s), 78.9 (s), 64.3 (t), 59.7 (d), 56.0 (t), 46.1 (d), 27.9 (q), 27.8 (t) x 2, 27.7 (t), 22.5 (t), 20.4 (q), 16.0 (q) and 14.3 (q).

Oxidation of Triol 14 to Hydroxy Lactone 18

A DMF (1.0 ml) solution of triol **14** (142 mg, 0.66 mmol) was added to a stirred DMF (1.5 ml) solution of PDC (944 mg, 2.51 mmol) under argon atmosphere and the mixture was stirred for 18 h at room temperature. The usual work-up and chromatography of the resulting residue over silica gel (30 g, hexane-AcOEt 4:1) gave hydroxy lactone **18** as a colorless oil (122 mg, 87%). δ_H (270 MHz) 1.31 (3H, s), 1.22 (3H, s) and 0.92 (3H, d, 6.6 Hz). δ_C (68 MHz) 177.4 (s), 95.0 (s), 71.5 (s), 53.8 (d), 43.9 (d), 31.5 (q), 29.7 (t), 29.5 (q), 26.4 (t), 20.5 (t), 20.0 (t) and 12.7 (q). HRMS found: m/z 212.1413. Calcd for $C_{12}H_{20}O_3$: M, 212.1412.

Dehydration of Hydroxy Lactone 18 with $SOCl_2$

After stirring a mixture of hydroxy lactone **18** (72 mg, 0.30 mmol) and $SOCl_2$ (0.88 ml) in CH_2Cl_2 (6.0 ml) for 3 days at room temperature, the volatile materials were removed in vacuo. Chromatography of the residue over silica gel (6 g, hexane-AcOEt 5:1) gave a 7:1 mixture of isopropenyl lactone **19** and 1-chloro-1-methylethyl lactone **20** (50 mg, 74%). The mixture was separated by HPLC (μ-porasil SiO_2 column; hexane-AcOEt 25:1).

Dehydration of Hydroxy Lactone 18 with $SOCl_2$ in Pyridine

After addition of $SOCl_2$ (0.05 ml, 0.69 mmol) to a stirred pyridine (1 ml) solution of hydroxy lactone **18** (10.0 mg, 0.047 mmol) at 0°C, the mixture was stirred for 30 min at room temperature and poured into ice in ether. The ether solution was washed with aq $CuSO_4$ solution and treated by the usual work-up. Chromatography of the residue over silica gel (1 g, hexane-AcOEt 4:1) gave 1-chloro-1-methylethyl lactone, **20** (9 mg, 83%).

Dehydration of Hydroxy Lactone 18 with Burgess Reagent

A mixture of hydroxy lactone **18** (17.4 mg) and Burgess reagent (63 mg) in benzene (2 ml) was stirred at 50°C for 1 h. The usual work-up and chromatography of the residue over silica gel (10 g, hexane-AcOEt 10:1) gave a 7:2 mixture of isopropenyl lactone **19** and isopropylidene lactone **21** (16 mg, 98%). The mixture was separated by HPLC (μ-porasil SiO_2 column; hexane-AcOEt 25:1). Isopropenyl lactone **19**: δ_H (90 MHz) 5.01 (1H, d, 0.8 Hz), 4.83 (1H, br s), 2.86 (1H, m), 1.78 (3H, s) and 0.97 (3H, d, 6.3 Hz). δ_C (68 MHz) 176.9 (s), 143.5 (s), 113.3 (t), 94.9 (s), 53.0 (d), 42.6 (d), 29.5 (t), 27.1 (t), 23.6 (t), 23.6 (q), 21.0 (t) and 13.6 (q). HRMS found: m/z 194.1298. Calcd for $C_{12}H_{18}O_2$: M, 194.1307. 1-Chloro-1-methylethyl lactone **20**: δ_H (90 MHz) 1.66 (3H, s), 1.57 (3H, s) and 0.94 (3H, d, 6.4 Hz). δ_C (23 MHz) 176.5 (s), 94.8 (s), 71.7 (s), 55.4 (d), 44.2 (d), 35.0 (q), 31.7 (q), 29.6 (t), 26.5 (t), 22.7 (t), 19.9 (t) and 12.6 (q). HRMS found: m/z 230.1061. Calcd for $C_{12}H_{19}ClO_2$: M, 230.1074. Isopropylidene lactone **21**: δ_H (90 MHz) 1.69 (3H, s), 1.65 (3H, s) and 0.98 (3H, d, 6.4 Hz). δ_C (23 MHz) 177.1 (s), 136.0 (s), 128.4 (s), 94.2 (s), 45.2 (d), 29.8 (t), 28.8 (t), 28.5 (t), 28.0 (t), 22.6 (q), 19.5 (q) and 12.5 (q). HRMS found: m/z 194.1310. Calcd for $C_{12}H_{18}O_2$: M, 194.1307.

Dehydrochlorination of 1-Chloro-1-methylethyl lactone 20

A mixture of chloroisopropyl lactone **20** (44.4 mg), LiBr (33.5 mg) and Li_2CO_3 (28.5 mg) in DMF (4 ml) was stirred at 105°C for 24 h. After the usual work-up, chromatography of the residue over silica gel (16 g, hexane-AcOEt 5:1) afforded a crude product. HPLC purification with μ-porasil SiO_2 column using hexane-AcOEt 25:1 gave isopropylidene lactone **21** (26 mg, 70%).

Condensation of Isopropenyl Lactone 19 with Acetone

A LDA solution was freshly prepared by the addition of 1.6 M ^{n}BuLi solution in hexane (1.6 ml, 2.56 mmol) to diisopropylamine (0.36 ml) in THF (2.4 ml) at -78°C under argon atmosphere and the solution was stirred at 0°C for 1 h. Into the LDA solution was added isopropenyl lactone **19** (65 mg, 0.34 mmol) in THF (2.4 ml) at -78°C and the mixture was stirred at 0°C for 2 h. Dry acetone (0.36 ml) was then dropped to the cooled solution at -78°C and the mixture was stirred at room temperature for 2 h. After the usual work-up, chromatography of the resulting residue over silica gel (5 g, hexane-AcOEt 20:1) afforded a 1:2 mixture of stereoisomers of, **22** (75 mg, 88%). The mixture was separated by HPLC with μ-porasil SiO_2 column using hexane-AcOEt 8:1. **22a**: mp 134-135°C, δ_H (90 MHz) 5.04 (1H, d, 1 Hz), 4.96 (1H, br s), 3.80 (1H, br s), 1.82 (3H, s), 1.24 (6H, s) and 0.96 (3H, d, 7.2 Hz). δ_C (23 MHz) 178.6 (s), 143.0 (s), 113.9 (t), 93.0 (s), 71.3 (s), 53.6 (d), 51.0 (d), 41.6 (d), 27.9 (q), 26.8 (t), 25.0 (t), 24.7 (q), 23.9 (t), 23.9 (q) and 13.8 (q). **22b**: mp 70.7-71°C, δ_H (90 MHz) 5.08 (1H, d, 1.0 Hz), 4.92 (1H, br s), 3.82 (1H, br s), 2.86 (1H, dd, 11.7, 9.9 Hz), 1.76 (3H, s), 1.24 (3H, s), 1.21 (3H, s) and 0.99 (3H, d, 6.6 Hz). δ_C (23 MHz) 178.2 (s), 143.3 (s), 113.6 (t), 92.5 (s), 71.6 (s), 52.4 (d), 51.3 (d), 43.1 (d), 27.9 (q), 26.7 (t), 24.7 (t), 24.7 (q), 24.1 (q) and 14.0 (q). HRMS of **22a** and **22b** found (**22a**): m/z 252.1724. (**22b**): m/z 252.1729. Calcd for $C_{15}H_{24}O_3$: M, 252.1725.

(±)-Curcumanolide-A

A mixture of 1-hydroxy-1-methylethyl lactone **22a** and **b** (53 mg, 0.21 mmol), pyridine (0.8 ml, 9.9 mmol), DMAP (2 mg) and mesyl chloride (0.14 ml, 1.18 mmol) in CH_2Cl_2 (3.5 ml) was stirred at room temperature for 24 h. The usual work-up of the reaction mixture and subsequent chromatography of the residue over silica gel (5 g, hexane-AcOEt 20:1) provided a crude product. Purification of the product with HPLC with μ-porasil SiO_2 column using hexane-AcOEt 45:1 gave pure (±)-curcumanolide-A, **1** (33 mg, 67%). mp 78-79°C, δ_H (270 MHz) 4.95 (1H, d, 1.3 Hz), 4.76 (1H, s) 2.82 (1H, dd, 11.6, 8.9 Hz), 2.47 (2H, br s), 2.24 (3H, t, 2.1 Hz), 1.85 (3H, s), 1.74 (3H, s) and 0.87 (3H, d, 6.6 Hz). δ_C (23 MHz) 170.0 (s), 149.2 (s), 143.9 (s), 121.0 (s), 112.7 (t), 89.7 (s), 52.4 (d), 42.8 (d), 27.7 (t), 26.6 (t), 24.4 (q), 24.0 (q), 23.3 (t), 20.0 (q) and 13.2 (q). HRMS found: m/z 234.1619. Calcd for $C_{15}H_{22}O_2$: M, 234.1620.

(±)-Curcumalactone 2. Ethylidene Route

A LDA solution was freshly prepared by the addition of 1.6 M ^{n}BuLi solution in hexane (1.6 ml, 2.56 mmol) to diisopropylamine (0.15 ml, 1.1 mmol) in THF (2.0 ml) at -78°C under argon atmosphere and the mixture was stirred at 0°C for 1 h. Into the LDA solution was added isopropenyl lactone **19** (50 mg, 0.26 mmol) in THF (2.4 ml) at -78°C and the mixture was stirred at 0°C for 2 h. Dry acetaldehyde (0.15 ml, 2.7 mmol) was then combined with the cooled solution at -78°C and the stirring was continued for 2 h at room temperature. The reaction mixture was quenched with aq NH_4Cl solution. The usual work-up and chromatography of the residue over silica gel (5 g, hexane-AcOEt 5:1) gave 1-hydroxyethyl lactone **23** (53 mg, 86%) as a stereoisomeric mixture. A mixture of hydroxyethyl lactone **23** (40 mg, 0.17 mmol), pyridine (0.13 ml, 1.6 mmol), DMAP (2 mg) and mesyl chloride (0.05 ml, 0.65 mmol) in CH_2Cl_2 (2.0 ml) was stirred at room temperature for 24 h. After quenching the reaction mixture with aq $NaHCO_3$ solution, the usual work-up gave crude mesylate of lactone **23**. Without purification, the crude mesylate was stirred with DBU (0.11 ml, 0.74 mmol) in benzene (2.0 ml) at room

temperature for 1 h. Then, the reaction mixture was quenched with aq NH_4Cl solution. The usual work-up and chromatography of the residue over silica gel (5 g, hexane-AcOEt 30:1) gave (E)-ethylidene lactone **24** (15 mg, 40%) and (Z)-isomer **25** (20 mg, 54%), respectively. (E)-Ethylidene lactone **24**, as a yellow oil. δ_H (90 MHz) 6.25 (1H, m), 5.00 (1H, br s), 4.80 (1H, br s), 2.85 (1H, m), 2.58 (2H, m), 2.17 (3H, dt, 7.4, 2.3 Hz), 1.77 (3H, s) and 0.91 (3H, d, 6.2). δ_C (23 MHz) 143.6 (s), 137.9 (d), 113.2 (t), 52.4 (d), 43.0 (d), 28.9 (t), 26.7 (t), 23.9 (q), 23.3 (t), 14.2 (t) and 13.4 (q). (Z)-Ethylidene lactone **25**: mp 49°C, δ_H (90 MHz) 6.75 (1H, tq, 2.8, 7.2 Hz), 4.99 (1H, d, 1.5 Hz), 4.80 (1H, br s), 2.88 (1H, m), 2.49 (2H, dq, 2.8, 2.2 Hz), 2.29 (1H, m), 1.84 (3H, dt, 7.2, 2.2 Hz), 1.73 (3H, s) and 0.87 (3H, d, 6.7 Hz). δ_C (23 MHz) 170.1 (s), 143.3 (s), 134.5 (d), 128.8 (s), 112.9 (t), 91.3 (s), 52.2 (d), 42.7 (d), 26.4 (t), 25.0 (t), 23.7 (q), 23.1 (t), 15.5 (q) and 12.9 (q). HRMS **24** found: m/z 220.1466. **25** found: m/z 220.1466. Calcd for $C_{14}H_{20}O_2$: M, 220.1463. Into a stirred ether (0.5 ml) solution of copper (I) iodide (26 mg, 0.14 mmol) was added 1.4 M ether solution of MeLi (0.54 ml, 0.76 mmol) under argon atmosphere at -20°C and the stirring was continued for 30 min. After cooling to -78°C, a mixture of **24** and **25** (7.4 mg, 0.034 mmol) in ether (0.5 ml) was added gradually at -78°C under argon atmosphere and the mixture was stirred for 5 min. After addition of Et_2OBF_3 complex (11μ l, 0.089 mmol), the reaction mixture was stirred at room temperature for 2 h. Then aqueous NH_4Cl solution was added to the mixture and submitted to the usual work-up. Chromatography over silica gel (1 g, hexane: AcOEt 30:1) gave a mixture of curcumalactone **2** and its isomer **26** (6.1 mg, 77%). Purification of the mixture with HPLC with μ-porasil SiO_2 column using hexane-AcOEt 30:1 gave **2** and **26** with a 1:8 ratio. (±)-Curcumalactone **2**, as a yellow oil. δ_H (270 MHz) 4.99 (1H, br s), 4.91 (1H, br s), 2.75 (1H, dd, 8.9, 11.2 Hz), 2.57 (1H, m), 2.42 (1H, m), 2.19 (1H, m), 1.81 (3H, s), 0.99 (3H, d, 6.9 Hz), 0.94 (3H, d, 6.6 Hz) and 0.90 (3H, d, 6.6 Hz). δ_C (68 MHz) 178.4 (s), 143.3 (s), 113.3 (t), 92.4 (s), 53.5 (d), 46.4 (d), 41.7 (d), 28.2 (d), 26.7 (t), 24.0 (q), 23.7 (t), 22.3 (t), 20.5 (q), 18.0 (q) and 13.7 (q). The isomer **26**: δ_H (270 MHz) 5.03 (1H, br s), 4.79 (1H, br s), 2.88 (1H, dd, 8.3, 11.9 Hz), 2.64 (1H, m), 2.30 (1H, m), 2.19 (1H, m), 1.75 (3H, s), 1.25 (1H, m), 1.00 (3H, d, 6.9 Hz), 0.96 (3H, d, 6.9 Hz) and 0.88 (3H, d, 6.9 Hz). δ_C (68 MHz) 177.9 (s), 143.4 (s), 113.2 (t), 91.7 (s), 52.2 (d), 46.5 (d), 43.0 (d), 28.4 (d), 26.5 (t), 24.1 (q), 22.9 (t), 22.6 (t), 20.4 (q), 17.7 (q) and 13.9 (q). HRMS of **2** found: m/z 236.1777, **26** found: m/z 236.1790. Calcd for $C_{15}H_{24}O_2$: M, 236.1776.

Direct Isopropylation of Lactone 19

A LDA solution was freshly prepared by addition of 1.6 M ^{n}BuLi solution in hexane (0.99 ml, 1.55 mmol) to diisopropylamine (0.22 ml, 1.56 mmol) in THF (1.5 ml) at -78°C under argon atmosphere and the mixture was stirred at 0°C for 1.5 h. Into the LDA solution was added isopropenyl lactone **19** (28 mg, 0.14 mmol) in THF (1.5 ml) at -78°C and the mixture was stirred at 0°C for 2 h. After being cooled at -78°C, HMPA (0.28 ml, 1.57 mmol) and then isopropyl iodide (1.70 ml, 17.0 mmol) were added and the reaction mixture was stirred for 20 h at room temperature. Then, aqueous NH_4Cl solution was added to the reaction mixture. The usual work-up and chromatography over silica gel (7 g, hexane-AcOEt 30:1) gave a 2:3 mixture of **2** and **26** (30.0 mg, 89%).

Isomerization of 2 with LHMDS

A LHMDS solution was freshly prepared by the addition of 1.6 M ^{n}BuLi solution in hexane (0.24 ml, 0.38 mmol) to hexamethyldisilazane (HMDS) (0.08 ml, 0.38 mmol) in THF (0.7 ml) at 0°C under argon atmosphere and the mixture was stirred for 1 h. Into the LHMDS solution was added curcumalactone **2** (10 mg, 0.04 mmol) in THF (0.7 ml) at -78°C and the mixture was stirred at 0°C for 2 h. After being cooled at -78°C, the mixture was quenched by adding MeOH and aq NH_4Cl solutions. The usual work-up and chromatography over silica gel (1 g, hexane-AcOEt 30:1) gave a mixture of **2** and **26** (8.1 mg). HPLC analysis with μ-porasil SiO_2 column using hexane-AcOEt 200:1 showed a 1:6 mixture of **2** and **26**.

Isomerization of the Isomer 26 with LHMDS

The isomer **26** was treated with LHMDS under the same conditions as in the case of curcumalactone **2** to give a 1:8 mixture of **2** and **26** in 82% yield. The ratio was determined by HPLC under the same conditions.

Isomerization of 2 with DBU

After refluxing a mixture of curcumalactone **2** (11.2 mg, 0.05 mmol) and DBU (0.043 ml, 0.29 mmol) in xylene (6 ml) for 64 h, an additional DBU (0.043 ml) was added and the refluxing was further continued for 49 h. After removal of xylene, chromatography of the residue over silica gel (2 g) gave a 3:4 mixture of **2** and **26** (10.8 mg). The ratio was determined by HPLC under the same conditions.

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