Reaction of Methyl 4,5-Epoxy-(2*E*)-pentenoate with Arenes. II. Application to the Synthesis of (±)-Curcudiol, (±)-Curcuphenol, (±)-Curcuhydroquinone, and (±)-Curcuquinone[1)]

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Four bisabolane sesquiterpenes, (±)-curcudiol (2), (±)-curcuphenol (3), (±)-curcuhydroquinone (5) and (±)-curcuquinone (6), were synthesized based on the reaction of methyl 4,5-epoxy-(2*E*)-pentenoate (1) with methoxytoluenes in the presence of boron trifluoride etherate.

Key words methyl 4,5-epoxy-(2*E*)-pentenoate; bisabolane sesquiterpene; (±)-curcudiol; (±)-curcuphenol; (±)-curcuhydroquinone; (±)-curcuquinone

In the preceding paper[1,2)] we reported the reaction of methyl 4,5-epoxy-(2*E*)-pentenoate (**1**) with benzene derivatives possessing at least one methoxyl group in the presence of boron trifluoride etherate to give 4-aryl-5-hydroxy-(2*E*)-pentenoate (A) or/and 2-aryl-5-hydroxy-(3*E*)-pentenoate (B) in good yields (Chart 1). We now report the application of the pentenoate A to the synthesis of bisabolane sesquiterpenes. The simplest monocarbocyclic sesquiterpenes are the aromatic members of the bisabolane family. Pentenoates of type A possess a part of the bisabolane skeleton, while the hydroxymethyl group at the benzylic position of the type A compound can be converted into a methyl group and the ester group of A is useful for carbon–carbon bond formation.

It was reported that several bisabolane sesquiterpenes, such as α-curcumene, *ar*-turmerone and xanthorrhizol, exhibited anti-tumor activity.[3)] Further, (*R*)-(−)-curcuphenol,[4)] isolated from the Caribbean gorgonian *Pseudopterogorgia rigida*, is responsible for the antibiotic properties of *P. rigida*, while its enantioisomer, (*S*)-(+)-curcuphenol, isolated from marine organisms, has inhibitory activity against H,K-ATPase[5)] and exhibited antifungal properties.[6)]

We examined the synthesis of (±)-curcudiol (**2**) and (±)-curcuphenol (**3**) using methyl 4-(2′-methoxy-4′-methylphenyl)-5-hydroxy-(2*E*)-pentenoate (**4**)[2)] as a starting material, which was obtained as one of the products of the reaction of **1** and *m*-methoxytoluene in the presence of boron trifluoride etherate. Syntheses of (±)-curcuhydroquinone (**5**), which was isolated from marine organisms as an optically active component,[4)] and (±)-curcuquinone (**6**), formally derived from curcuhydroquinone, were achieved by using methyl 4-(2′,5′-dimethoxy-4′-methylphenyl)-5-hydroxy-(2*E*)-pentenoate (**7**)[2)] as a starting material.

Synthesis of (±)-Curcudiol (2) and (±)-Curcuphenol (3) Catalytic hydrogenation of **4** gave methyl 4-(2′-methoxy-4′-methylphenyl)-5-hydroxy-pentanoate (**8**), then without further purification, **8** was treated with tosyl chloride (TsCl) in pyridine to afford **9** in 91% yield (Chart 2). Compounds **8** and **9** could not be stored in the pure state because of gradual lactonization and partial decomposition. For a conversion of the hydroxymethyl group at the benzylic position (4-position) of **8** into a methyl group, **9** was reduced with 5 eq of sodium borohydride in dimethylsulfoxide (DMSO) at 80 °C for 3 h to give 4-

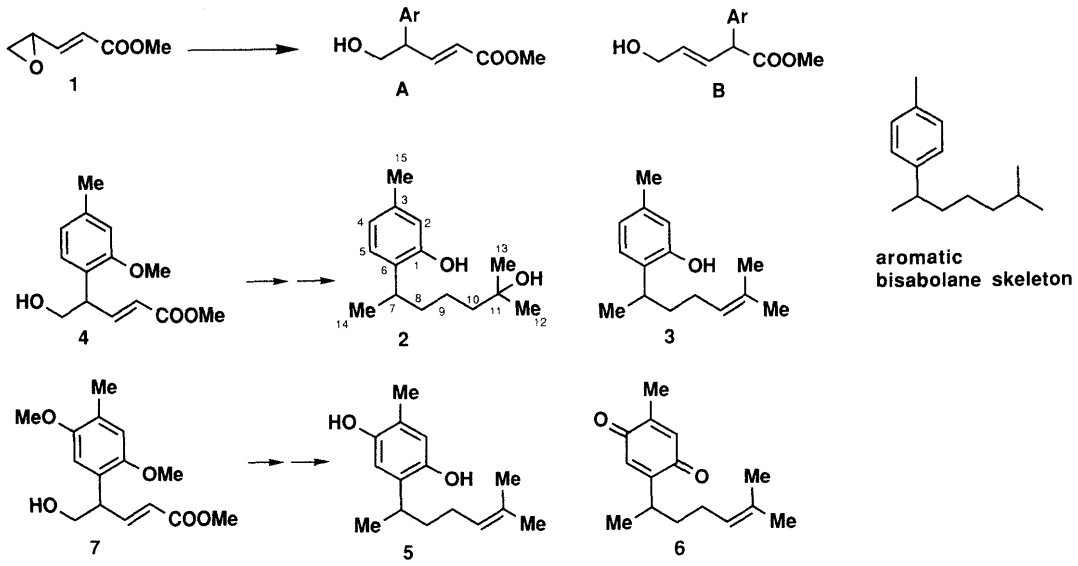

Chart 1

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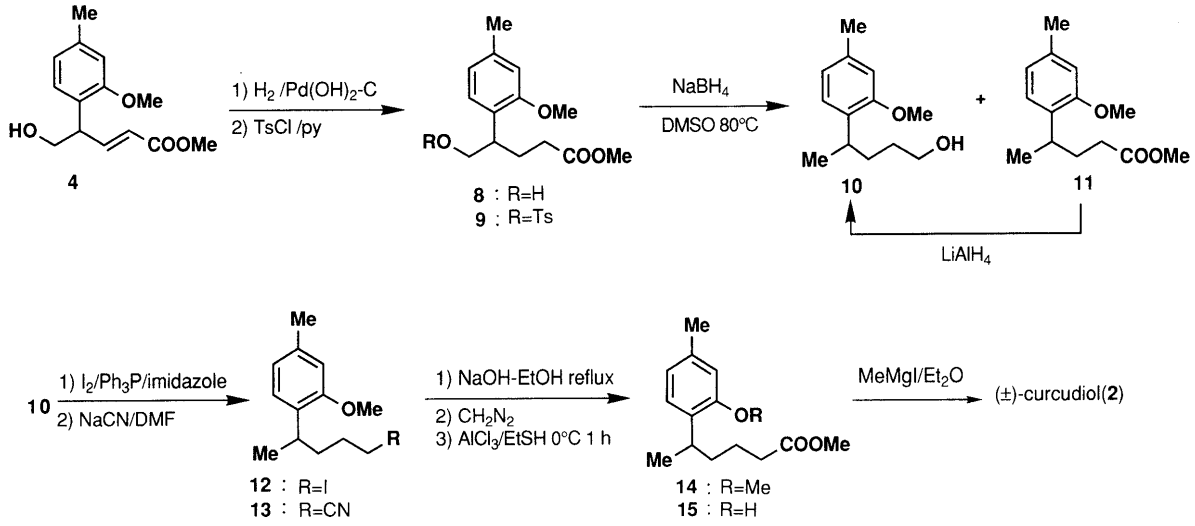

Chart 2

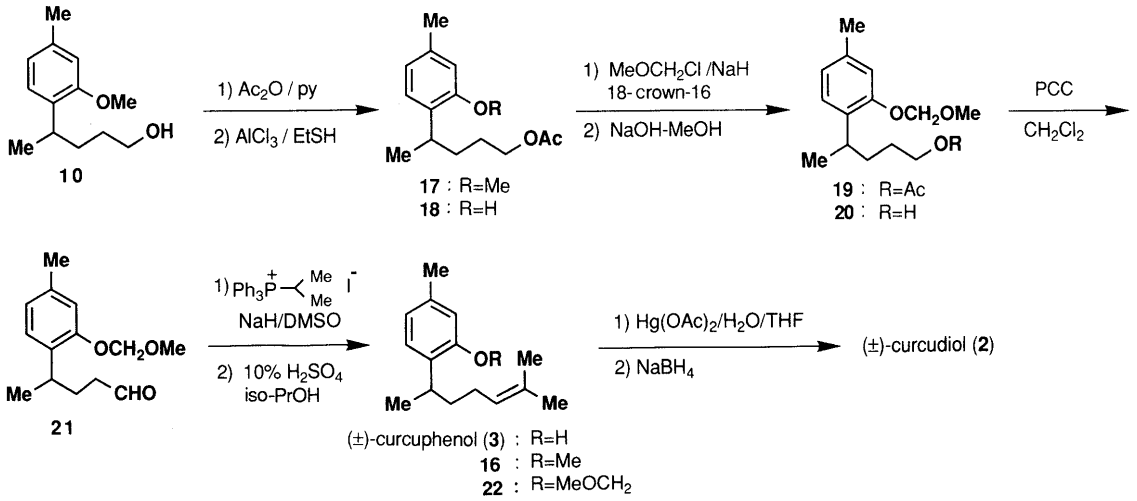

Chart 3

(2′-methoxy-4′-methylphenyl)pentanol (**10**) (63% yield) and methyl 4-(2′-methoxy-4′-methylphenyl)pentanoate (**11**) (24% yield), which was quantitatively reduced into **10** with lithium aluminum hydride. The reduction of **9** using 10 eq amounts of sodium borohydride in DMSO at 80 °C for 16 h gave **10** (74% yield) and **11** (8% yield). In order to convert **10** into the one-carbon homologue **13**, compound **10** was treated with iodine, triphenylphosphine and imidazole[7] to give 1-iodo-4-(2′-methoxy-4′-methylphenyl)pentane (**12**) (89% yield) which was treated with sodium cyanide to afford 5-(2′-methoxy-4′-methylphenyl)hexanenitrile (**13**) (98% yield). An attempt to get **13** *via* 1-bromo-4-(2′-methoxy-4′-methylphenyl)pentane was unsuccessful because the aromatic ring was brominated with the combination of *N*-bromosuccinimide (NBS) and triphenylphosphine. Alkaline hydrolysis of **13** followed by the esterification with diazomethane afforded methyl 5-(2′-methoxy-4′-methylphenyl)hexanoate (**14**), which was subjected to demethylation in the presence of excess aluminum chloride in ethanethiol[8] at 0 °C to give methyl 5-(2′-hydroxy-4′-methylphenyl)hexanoate (**15**) in 97% yield. Without protection of the phenolic hydroxyl group, **15** was treated with methylmagnesium iodide (MeMgI) to afford (±)-curcudiol (**2**) in 90% yield. The spectral data of the synthesized (±)-**2** were identical with those of the natural (+)-curcudiol.[4,5] The overall yield (64%) for six steps (**2** from **10**) was improved from that reported in the previous communication (30%).[1] For dehydration, a benzene solution of (±)-curcudiol (**2**) was warmed in the presence of camphorsulfonic acid at 50 °C for 5 h to give a mixture of the *endo*-dehydrated product, curcuphenol (**3**), and the *exo*-dehydrated product (0.77 : 0.23),[9] which could not be separated by column chromatography. Thus, the synthesis of pure (±)-curcuphenol (**3**) was carried out through a different route.

In a preliminary experiment, oxidation of **10** followed by Wittig reaction gave the methylated curcuphenol (**16**). When demethylation of **16** was examined with excess aluminum chloride in ethanethiol, an addition product of ethanethiol to the double bond was obtained. The use of boron tribromide or 47% hydrobromic acid in acetic acid also failed to give the desired **3**. So demethylation was required at an earlier stage. Acetylation of **10** gave 4-(2′-methoxy-4′-methylphenyl)pentyl acetate (**17**), which was

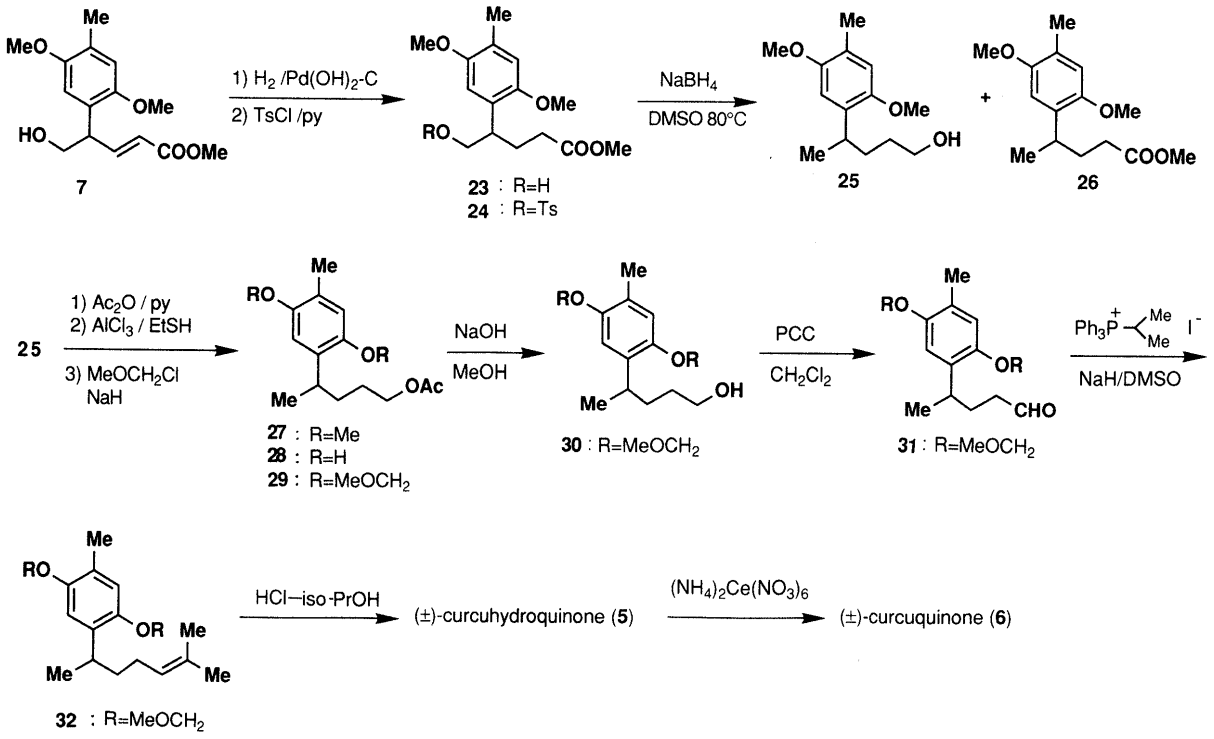

Chart 4

subjected to demethylation to afford the desired phenol **18** (Chart 3). Then treatment of **18** with methoxymethyl chloride (MOMCl) provided the MOM ether **19**, which was subjected to an alkaline hydrolysis to yield the pentanol **20**. Oxidation of **20** with pyridinium chlorochromate (PCC) afforded the aldehyde **21**, which was allowed to react with Wittig reagent to give the protected (±)-curcuphenol (**22**) (45% yield from **20**). Deprotection of **22** by acid hydrolysis gave (±)-curcuphenol (**3**) in 43% yield. The spectral data of the synthesized (±)-curcuphenol (**3**) were identical with those of the natural (+)-curcuphenol.[4,5] Oxymercuration-demercuration of (±)-**3** afforded (±)-curcudiol (**2**) in 56% yield.

Synthesis of (±)-Curcuhydroquinone (5) and (±)-Curcuquinone (6) The synthesis of (±)-curcuhydroquinone (**5**) from **7** was carried out in the same way as that of **3**. Conversion of **7** into 4-(2′,5′-dimethoxy-4′-methylphenyl)pentanol (**25**) through **24** was achieved by the same route as shown in Chart 4. Thus, after three processes (catalytic reduction, tosylation, reduction with sodium borohydride), **25** (73% yield) and methyl 4-(2′,5′-dimethoxy-4′-methylphenyl)pentanoate (**26**) (16% yield) were obtained, and then **25** was acetylated to provide **27**. Demethylation of **27** with ethanethiol in the presence of aluminum chloride gave the hydroquinone **28**, which was treated with methoxymethyl chloride to give the MOM ether **29** in 98% overall yield from **27**. Alkaline hydrolysis of **29** was performed in a usual manner to afford 4-(2′,5′-dimethoxymethyloxy-4′-methylphenyl)pentanol (**30**) (91% yield), which was oxidized with PCC to give the aldehyde **31**. Wittig reaction of **31** provided a protected curcuhydroquinone **32** in 26% yield. Deprotection of **32** by acid hydrolysis yielded (±)-curcuhydroquinone (**5**), which was oxidized with ceric ammonium nitrate (CAN) to afford (±)-curcuquinone (**6**).[10] The spectral data of the synthesized (±)-curcuhydroquinone (**5**) and (±)-curcuquinone (**6**) were identical with those of natural (−)-curcuhydroquinone and (−)-curcuquinone, respectively.[4]

In conclusion, the syntheses of (±)-curcudiol (**2**), (±)-curcuphenol (**3**), (±)-curcuhydroquinone (**5**) and (±)-curcuquinone (**6**) on the basis of the reaction of methyl 4,5-epoxy-(2*E*)-pentenoate (**1**) with *m*-methoxytoluene or 2,5-dimethoxytoluene in the presence of boron trifluoride etherate were achieved. This new synthetic methodology is useful for the preparation of this type of sesquiterpenoids. Although various synthetic methods for racemic sesquiterpenes have been reported,[11] the synthesis of an optically active form has not yet been achieved. We are investigating optical resolution based on the primary hydroxymethyl group at the 4-position of the type A compounds.

Experimental

IR spectra were recorded on a Hitachi 260-30 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL EX-400 (400 MHz) or a JEOL α-500 (500 MHz) spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), multiplet (m), broad (br). High-resolution mass spectra (HRMS) were obtained with a JEOL JMX-DX 303 spectrometer. In general, reactions were carried out in dry solvents under an argon atmosphere, unless otherwise mentioned. For column chromatography, Silica gel 60 (Merck 7734) was employed.

Methyl 4-(2′-Methoxy-4′-methylphenyl)-5-tosyloxypentanoate (9) A solution of **4** (2.50 g, 10 mmol) in AcOEt (25 ml) was hydrogenated over 20% $Pd(OH)_2$ on carbon at room temperature under atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the solvent was evaporated to give **8** as a colorless oil quantitatively. ^{1}H-NMR ($CDCl_3$) δ: 1.92, 2.09 (each 1H, m, 3-H), 2.22 (2H, m, 2-H), 2.33(3H, s, Me), 3.25 (1H, m, 4-H), 3.63 (3H, s, COOMe), 3.75 (2H, m, 5-H), 3.80 (3H, s, OMe), 6.69 (1H, br s, 3′-H), 6.76 (1H, br d, J=8.0 Hz, 5′-H), 7.02 (1H, d, J=8.0 Hz, 6′-H). Compound **8** was dissolved in pyridine (2 ml), then TsCl (2.09 g, 11 mmol) was added to the solution,

and the whole was allowed to stand overnight at room temperature. Ether and 7% $NaHCO_3$ were added to the mixture, and the organic layer was dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography to afford pure **9** (3.70 g, 91% from **4**) as a colorless oil. *Anal.* HRMS Calcd for $C_{21}H_{26}O_6S$ (M^+, *m/z*): 406.1450. Found: 406.1443. IR (CCl_4): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19, 2.07 (each 1H, m, 3-H), 2.14 (2H, m, 2-H), 2.30 (3H, s, Me), 2.44 (3H, s, Me of tosyl group), 2.99 (1H, m, 4-H), 3.59 (3H, s, COOMe), 3.68 (3H, s, OMe), 4.10 (1H, dd, J=8.0, 10.0 Hz, 5-H), 4.15 (1H, dd, J=6.0, 10.0 Hz, 5-H), 6.59 (1H, br s, 3′-H), 6.67 (1H, br d, J=8.0 Hz, 5′-H), 6.88 (1H, d, J=8.0 Hz, 6′-H), 7.27 (2H, d, J=8.0 Hz, *o*-position of tosyl Me), 7.67 (2H, d, J=8.0 Hz, *m*-position of tosyl Me).

4-(2′-Methoxy-4′-methylphenyl)pentanol (10) and Methyl 4-(2′-Methoxy-4′-methylphenyl)pentanoate (11) A solution of **9** (3.63 g, 8.9 mmol) and $NaBH_4$ (1.68 g, 45 mmol) in DMSO (20 ml) was warmed for 3.0 h at 80 °C, then allowed to cool. Small amounts of acetone, ether and 7% $NaHCO_3$ were added, and the mixture was stirred for 30 min at room temperature, then extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a crude mixture of **10** and **11**. The residue was subjected to column chromatography to afford **11** (0.50 g, 24%) from the first eluate and **10** (1.17 g, 63%) from the second eluate. Compound **10**: Colorless oil. *Anal.* HRMS Calcd for $C_{13}H_{20}O_2$ (M^+, *m/z*): 208.1463. Found: 208. 1398. IR (CCl_4): 3620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=7.0 Hz, 5-H), 1.40—1.67 (4H, m, 2- and 3-H) 2.33 (3H, s, Me), 3.16 (1H, sixtet, J=7.0 Hz, 4-H), 3.60 (2H, t, J=6.0 Hz, 1-H), 3.81 (3H, s, OMe), 6.66 (1H, br s, 3′-H), 6.74 (1H, br d, J=8.0 Hz, 5′-H), 7.05 (1H, d, J=8.0 Hz, 6′-H). Compound **11**: Colorless oil. *Anal.* HRMS Calcd for $C_{14}H_{20}O_3$. (M^+, *m/z*): 236.1412. Found 236.1406. IR (CCl_4): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=7.0 Hz, 5-H), 1.88 (2H, m, 3-H), 2.20 (2H, m, 2-H), 2.33 (3H, s, Me), 3.16 (1H, sextet, J=7.0 Hz, 4-H), 3.62 (3H, s, COOMe), 3.78 (3H, s, OMe), 6.66 (1H, br s, 3′-H), 6.74 (1H, br d, J=8.0 Hz, 5′-H), 7.03 (1H, d, J=8.0 Hz, 6′-H).

1-Iodo-4-(2′-methoxy-4′-methylphenyl)pentane (12) To a solution of **10** (0.96 g, 4.6 mmol) in MeCN (10 ml) and Et_2O (10 ml), Ph_3P (2.42 g, 9.2 mmol), imidazole (0.79 g, 11.5 mmol) and I_2 (2.93 g, 11.5 mmol) were added successively. The whole was stirred for 30 min at 0 °C, then Celite (1 g) was added, and the mixture was filtered. The filtrate was purified by column chromatography to afford **12** as a colorless oil (1.30 g, 89%). *Anal.* HRMS Calcd for $C_{13}H_{19}IO$ (M^+, *m/z*): 318.0479. Found: 318.0529. IR (CCl_4): 2920 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, J=7.0 Hz, 5-H), 1.60—1.78 (4H, m, 2- and 3-H), 2.33 (3H, s, Me), 3.14 (2H, t, J=7.0 Hz, 1-H), 3.17 (1H, quintet, J=7.0 Hz, 4-H), 3.80 (3H, s, OMe), 6.66 (1H, br s, 3′-H), 6.74 (1H, br d, J=8.0 Hz, 5′-H), 7.03 (1H, d, J=8.0 Hz, 6′-H).

4-(2′-Methoxy-4′-methylphenyl)hexanenitrile (13) A solution of **12** (1.30 g, 4.1 mmol) in *N,N*-dimethylformamide (DMF) (2 ml) was treated with NaCN (0.22 g, 4.5 mmol), and the whole was stirred overnight at room temperature. Ether and 7% $NaHCO_3$ were added, and the organic layer was separated and dried over $MgSO_4$, then evaporated. The residue was purified by column chromatography to give **13** as a colorless oil (0.87 g, 98%). *Anal.* HRMS Calcd for $C_{14}H_{19}NO$ (M^+, *m/z*): 217.1467. Found: 217.1510. IR (CCl_4): 2240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=7.0 Hz, 6-H), 1.50—1.73 (4H, m, 3- and 4-H), 2.29 (2H, t, J=7.0 Hz, 2-H), 2.33 (3H, s, Me), 3.17 (1H, sextet, J=7.0 Hz, 5-H), 3.80 (3H, s, OMe), 6.67 (1H, br s, 3′-H), 6.75 (1H, br d, J=8.0 Hz, 5′-H), 7.02 (1H, d, J=8.0 Hz, 6′-H).

Methyl 5-(2′-Methoxy-4′-methylphenyl)hexanoate (14) A solution of **13** (0.89 g, 4.1 mmol) in EtOH (20 ml) was treated with 2 N NaOH (5 ml) and the whole was refluxed for 12 h. After cooling, the reaction mixture was acidified with 2 N HCl, and extracted with ether, then treated with CH_2N_2. The ether layer was dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography to afford **14** as a colorless oil (0.85 g, 83%). *Anal.* HRMS Calcd for $C_{15}H_{22}O_3$ (M^+, *m/z*): 250.1569. Found: 250.1573. IR (CCl_4): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=7.0 Hz, 6-H), 1.48—1.62 (4-H, m, 3- and 4-H), 2.28 (2H, t, J=6.0 Hz, 2-H), 2.31 (3H, s, Me), 3.15 (1H, sextet, J=7.0 Hz, 5-H), 3.63 (3H, s, COOMe), 3.78 (3H, s, OMe), 6.65 (1H, br s, 3′-H), 6.73 (1H, br d, J=8.0 Hz, 5′-H), 7.02 (1H, d, J=8.0 Hz, 6′-H).

Methyl 5-(2′-Hydroxy-4′-methylphenyl)hexanoate (15) A mixture of **14** (0.35 g, 1.4 mmol), $AlCl_3$ (0.93 g, 7.0 mmol), and EtSH (2 ml) were stirred for 1 h at 0 °C, then ether and 2 N HCl were added. The mixture was extracted with ether and the organic layer was dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography to give **15** as a colorless oil (0.32 g, 97%). *Anal.* HRMS Calcd for $C_{14}H_{20}O_3$ (M^+, *m/z*): 236.1412. Found: 236.1418. IR (CCl_4): 3420, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=7.0 Hz, 6-H), 1.50—1.70 (4H, m, 3- and 4-H), 2.25 (3H, s, Me), 2.31 (2H, t, J=6.0 Hz, 2-H), 3.05 (1H, sextet, J=7.0 Hz, 5-H), 3.65 (3H, s, COOMe), 4.85 (1H, br s, OH), 6.56 (1H, br s, 3′-H), 6.72 (1H, br d, J=8.0 Hz, 5′-H), 7.01 (1H, d, J=8.0 Hz, 6′-H).

(±)-Curcudiol (2) A 2.0 M MeMgI ether solution (2.4 ml) was added to a solution of **15** (0.38 g, 1.6 mmol) in ether (1 ml) and the whole was stirred overnight at room temperature. Under ice-cooling 2 N HCl was added, and the mixture was extracted with ether. The organic layer was dried over $MgSO_4$, and evaporated. Crude **2** was purified by column chromatography to give **2** as a colorless oil (0.34 g, 90 %). *Anal.* FAB-MS Calcd for $C_{15}H_{24}O_2$ (M^+, *m/z*): 236. Found: 236. IR (neat): 3320, 2920 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.16, 1.18 (each 3H, s, 12- and 13-H), 1.22 (3H, d, J=7.0 Hz, 14-H), 1.28—1.36 (2H, m, 9-H), 1.40—1.55 (2H, m, 10-H), 1.50—1.55 and 1.60—1.68 (each 1H, m, 8-H), 1.83 (1H, br s, OH), 2.26 (3H, s, 15-H), 3.08 (1H, sextet, J=8.0 Hz, 7-H), 5.33 (1H, br s, phenolic OH), 6.57 (1H, br s, 2-H), 6.71 (1H, br d, J=8.0 Hz, 4-H), 7.03 (1H, d, J=8.0 Hz, 5-H). ^{13}C-NMR ($CDCl_3$, 500 MHz) δ: 20.7 (15-C), 21.0 (14-C), 22.1 (9-C), 28.4 (12 or 13-C), 29.0 (12 or 13-C), 31.0 (7-C), 37.6 (8-C), 43.4 (10-C), 71.6 (11-C), 116.2 (2-C), 120.9 (4-C), 126.9 (5-C), 131.8 (6-C), 135.8 (3-C), 153.9 (1-C).

4-(2′-Methoxy-4′-methylphenyl)pentyl Acetate (17) A mixture of **10** (0.80 g, 3.8 mmol) and Ac_2O (0.78 g, 7.5 mmol) in pyridine (2 ml) was allowed to stand overnight at room temperature. Ether and 7% $NaHCO_3$ were added and the organic layer was separated and concentrated. The residue was subjected to column chromatography to afford **17** as a colorless oil (0.92 g, 97%). *Anal.* HRMS Calcd for $C_{15}H_{22}O_3$ (M^+, *m/z*): 250.1569. Found: 250.1557. IR (neat): 2920, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, J=7.0 Hz, 5-H), 1.48—1.68 (4H, m, 2- and 3-H), 2.02 (3H, s, Me of acetyl group), 2.32 (3H, s, Me), 3.15 (1H, sextet, J=7.0 Hz, 4-H), 3.79 (3H, s, OMe), 4.02 (2H, t, J=6.0 Hz, 1-H), 6.67 (1H, br s, 3′-H), 6.74 (1H, br d, J=8.0 Hz, 5′-H), 7.03 (1H, d, J=8.0 Hz, 6′-H).

4-(2′-Hydroxy-4′-methylphenyl)pentyl Acetate (18) A mixture of **17** (0.84 g, 3.4 mmol), $AlCl_3$ (2.24 g, 17.0 mmol) and EtSH (5 ml) was stirred for 1 h at 0 °C, then ether and 2 N HCl were added. The whole was extracted and the organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography to give **18** (0.78 g, 97%). *Anal.* HRMS Calcd for $C_{14}H_{20}O_3$ (M^+, *m/z*): 236.1412. Found: 236.1428. IR (neat): 3380, 2900, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=7.0 Hz, 5-H), 1.53—1.70 (4H, m, 2- and 3-H), 2.04 (3H, s, Me of acetyl group), 2.25 (3H, s, Me), 3.09 (1H, sextet, J=7.0 Hz, 4-H), 4.05 (2H, m, 1-H), 5.79 (1H, br s, OH), 6.57 (1H, br s, 3′-H), 6.70 (1H, br d, J=8.0 Hz, 5′-H), 7.01 (1H, d, J=8.0 Hz, 6′-H).

4-(2′-Methoxymethyloxy-4′-methylphenyl)pentyl Acetate (19) To a stirred solution of **18** in MeCN (10 ml) at 0 °C, 55% NaH (0.25 g), 18-crown-6 (0.06 g), and methoxymethyl chloride (0.34 g, 5.4 mmol) were added, and the whole was stirred for 1 h at 0 °C. Ether and aqueous NH_4Cl were added. The ether layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography to give **19** as a colorless oil (0.74 g, 97%). *Anal.* HRMS Calcd for $C_{16}H_{24}O_4$ (M^+, *m/z*): 280.1675. Found: 280.1670. IR (neat): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7.0 Hz, 5-H), 1.50—1.70 (4H, m, 2- and 3-H), 2.01 (3H, s, Me of acetyl group), 2.31 (3H, s, Me), 3.18 (1H, sextet, J=7.0 Hz, 4-H), 3.48 (3H, s, $OCH_2\underline{O}Me$), 4.03 (2H, t, J=6.0 Hz, 1-H), 5.17 (2H, s, $OC\underline{H}_2OMe$), 6.79 (1H, br d, J=8.0 Hz, 5′-H), 6.89 (1H, br s, 3′-H), 7.05 (1H, d, J=8.0 Hz, 6′-H).

4-(2′-Methoxymethyloxy-4′-methylphenyl)pentanol (20) A solution of **19** (0.35 g, 1.2 mmol) in methanol (2 ml) was treated with 2 N NaOH (1 ml), and the whole was warmed for 10 min at 50 °C, then allowed to cool. Ether was added and the ether layer was dried over $MgSO_4$. After removal of the solvent the residue was subjected to column chromatography to give **20** (0.29 g, 98 %) as a colorless oil. *Anal.* HRMS Calcd for $C_{14}H_{22}O_3$ (M^+, *m/z*): 238.1569. Found: 238.1559. IR (neat): 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7.0 Hz, 5-H), 1.40—1.68 (4H, m, 2- and 3-H), 2.30 (3H, s, Me), 3.18 (1H, sextet, J=7.0 Hz, 4-H), 3.48 (3H, s, $OCH_2\underline{O}Me$), 3.59 (2H, t, J=6.0 Hz, 1-H), 5.17 (2H, s, $OC\underline{H}_2OMe$), 6.79 (1H, br d, J=8.0 Hz, 5′-H), 6.87 (1H, br s, 3′-H), 7.05 (1H, d, J=8.0 Hz, 6′-H).

Protected Curcuphenol (22) To a mixture of **20** (0.57 g, 2.4 mmol) and Celite 545 (2 g) in CH_2Cl_2 (10 ml), PCC (2.59 g) was added under ice-cooling. The reaction mixture was stirred for 1 h at room temperature and filtered. The filtrate was subjected to short column chromatography

to give the pentanal **21** (0.51 g, 90%). This was added to a solution of triphenylisopropyl-phosphonium iodide (2.08 g, 4.8 mmol) and 55% NaH (0.41 g) in DMSO (3 ml) under stirring, and the whole was allowed to stand overnight at room temperature. Ether and aqueous NH_4Cl were added. The ether layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography to give **22** as a colorless oil (0.25 g, 45%). *Anal.* HRMS Calcd for $C_{17}H_{26}O_2$ (M^+, *m/z*): 262.1933. Found: 262.1896. IR (neat): 2900 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=7.0 Hz, 14-H), 1.48—1.65 (2H, m, 8-H), 1.53, 1.67 (each 3H, s, 12- and 13-H), 1.85—1.98 (2H, m, 9-H), 2.30 (3H, s, 15-H), 3.15 (1H, sextet, J=6.0 Hz, 7-H), 3.48 (3H, s, $OCH_2O\underline{Me}$), 5.11 (1H, br t, J=7.0 Hz, 10-H), 5.17 (2H, s, $OC\underline{H}_2OMe$), 6.78 (1H, br d, J=8.0 Hz, 4-H), 6.87 (1H, br s, 2-H), 7.05 (1H, d, J=8.0 Hz, 5-H).

(±)-Curcuphenol (3) A mixture of 10% H_2SO_4 (1 ml) and isopropanol (1 ml) was added to a solution of **22** (0.10 g, 0.38 mmol) in isopropanol (0.5 ml). The whole was allowed to stand for 3 d at room temperature. Ether and aqueous NaCl were added. The ether layer was dried over $MgSO_4$ then evaporated. The residue was subjected to column chromatography to give **3** as a colorless oil (33 mg, 43%). *Anal.* HRMS Calcd for $C_{15}H_{22}O$ (M^+, *m/z*): 218.1617. Found: 218.1689. IR (neat): 3600 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.22 (3H, d, J=7.0 Hz, 14-H), 1.54 (3H, s, 13-H), 1.55—1.69 (2H, m, 8-H), 1.68 (3H, s, 12-H), 1.89—1.97 (2H, m, 9-H), 2.27 (3H, s, 15-H), 2.96 (1H, sextet, J=7.0 Hz, 7-H), 4.67 (1H, s, OH), 5.13 (1H, br t, J=7.0 Hz, 10-H), 6.59 (1H, br s, 2-H), 6.72 (1H, br d, J=8.0 Hz, 4-H), 7.03 (1H, d, J=8.0 Hz, 5-H). ^{13}C-NMR ($CDCl_3$, 500 MHz) δ: 17.7 (13-C), 20.8 (15-C), 21.2 (14-C), 25.7 (12-C), 26.2 (9-C), 31.5 (7-C), 37.4 (8-C), 116.4 (2-C), 121.8 (4-C), 124.8 (10-C), 126.9 (5-C), 130.4 (6-C), 131.6 (11-C), 136.4 (3-C), 152.8 (1-C).

(±)-Curcudiol (2) from (±)-Curcuphenol (3) A solution of **3** (25 mg, 0.12 mmol) in tetrahydrofuran (0.5 ml) was added to a solution of $Hg(OAc)_2$ (0.10 g) in H_2O (3 ml) under vigorous stirring. The whole was stirred for 20 min at room temperature. Then, 2 N NaOH (1 ml) and a solution of $NaBH_4$ (0.10 g) in 2 N NaOH (1 ml) were added successively at room temperature. After the reaction mixture was stirred for 20 min, then 7% $NaHCO_3$ and ether were added. The ether layer was dried over $MgSO_4$ and concentrated. The residue was subjected to a column chromatography to give **2** (16 mg, 56 %).

Methyl 4-(2′,5′-Dimethoxy-4′-methylphenyl)-5-tosyloxypentanoate (24) Compound **7** (5.68 g, 0.02 mol) was treated in the same manner as described for the conversion of **4** to **9** *via* **8** to give **24** (7.58 g, 86% from **7** *via* **23**). Compound **23**: Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (1H, br s, OH), 1.91, 2.09 (each 1H, m, 3-H), 2.20 (3H, s, Me), 2.24 (2H, m, 2-H), 3.25 (1H, m, 4-H), 3.63 (3H, s, COOMe), 3.75, 3.78 (each 3H, s, OMe), 3.76 (2H, m, 5-H), 6.64, 6.70 (each 1H, s, 3′- and 5-H). Compound **24**: Colorless oil. *Anal.* HRMS Calcd for $C_{22}H_{28}O_7S$ (M^+, *m/z*): 436.1556. Found: 436.1567. IR (CCl_4): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.92, 2.07 (each 1H, m, 3-H), 2.16 (2H, m, 2-H), 2.18 (3H, s, Me), 2.44 (3H, s, Me of Ts group), 3.30 (1H, m, 4-H), 3.59, 3.65, 3.72 (each 3H, s, COOMe, OMe), 4.14, 4.16(each 1H, dd, J=6.0, 9.0 Hz, 5-H), 6.47, 6.59 (each 1H, s, 3′- and 6′-H), 7.26 (2H, d, J=8.0 Hz, *o*-position to Me of the Ts group), 7.65 (2H, d, J=8.0 Hz, *m*-position to Me of the Ts group).

4-(2′,5′-Dimethoxy-4′-methylphenyl)pentanol (25) and Methyl 4-(2′,5′-Dimethoxy-4′-methylphenyl)pentanoate (26) Compound **24** (3.59 g, 9.1 mmol) was treated (reduction time; 2.0 h) in the same manner as described for **9** to give **25** as a colorless oil (1.57 g, 73%) and **26** as a colorless oil (0.39 g, 16%). Compound **25**: *Anal.* HRMS Calcd for $C_{14}H_{22}O_3$ (M^+, *m/z*): 238.1569. Found: 238.1567. IR (neat): 3360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7.0 Hz, 5-H), 1.42—1.68 (4H, m, 2- and 3-H), 2.20 (3H, s, Me), 3.17 (1H, sextet, J=7.0 Hz, 4-H), 3.62 (2H, t, J=6.5 Hz, 1-H), 3.77, 3.79 (each 3H, s, OMe), 6.66, 6.68 (each 1H, s, 3′- and 6′-H). Compound **26**: *Anal.* HRMS Calcd for $C_{15}H_{22}O_4$ (M^+, *m/z*) 266.1518. Found: 266.1499. IR (neat): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=7.0 Hz, 5-H), 1.89 (2H, m, 3-H), 2.20 (3H, s, Me), 2.22 (2H, m, 2-H), 3.17 (1H, sextet, J=7.0 Hz, 4-H), 3.62 (3H, s, COOMe), 3.76, 3.79 (each 3H, m, OMe), 6.64, 6.66 (each 1H, s, 3′- and 6′-H).

4-(2′,5′-Dimethoxy-4′-methylphenyl)pentyl Acetate (27) Compound **25** (1.50 g, 6.3 mmol) was acetylated in the same manner as described for **17** to give **27** as a colorless oil (1.70 g, 96%). *Anal.* HRMS Calcd for $C_{16}H_{24}O_4$ (M^+, *m/z*): 280.1675. Found: 280.1668. IR (neat): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7.0 Hz, 5-H), 1.50—1.64 (4H, m, 2- and 3-H), 2.02 (3H, s, Me of acetyl group), 2.20 (3H, s, Me), 3.16 (1H, sextet, J=7.0 Hz, 4-H), 3.76, 3.79 (each 3H, s, OMe), 4.02 (2H, t, J=7.0 Hz, 1-H), 6.65, 6.68 (each 1H, s, 3′- and 6′-H).

4-(2′,5′-Dimethoxymethyloxy-4′-methylphenyl)pentyl Acetate (29) Compound **27** (0.42 g, 1.5 mmol) was treated in the same manner as described for the case of **18** to give the hydroquinone **28**. Without purification, **28** was reacted with methoxymethyl chloride in the same manner as described for **18** to give **29** as a colorless oil (0.50 g, 98%). *Anal.* HRMS Calcd for $C_{18}H_{28}O_6$ (M^+, *m/z*): 340.1886. Found: 340.1886. IR (neat): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d. J=7.0 Hz, 5-H), 1.50—1.65 (4H, m, 2- and 3-H), 2.02 (3H, s, Me of acetyl group), 2.21 (3H, s, Me), 3.15 (1H, sextet, J=7.0 Hz, 4-H), 3.48, 3.50 (each 3H, s, $OCH_2O\underline{Me}$), 4.03 (2H, t, J=7.0 Hz, 1-H), 5.11, 5.12 (each 2H, s, $OC\underline{H}_2OMe$), 6.85, 6.88 (each 1H, s, 3′- and 6′-H).

4-(2′,5′-Dimethoxymethyloxy-4-methylphenyl)pentanol (30) Compound **29** (1.16 g, 3.4 mmol) was treated in the same manner as described for **19** to give **30** as a colorless oil (0.92 g, 91%). *Anal.* HRMS Calcd for $C_{16}H_{26}O_5$ (M^+, *m/z*): 298.1780. Found: 298.1774. IR (neat): 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=7.0 Hz, 5-H), 1.40—1.70 (4H, m, 2- and 3-H), 1.90 (1H, br s, OH), 2.20 (3H, s, Me), 3.16 (1H, sextet, J=7.0 Hz, 4-H), 3.48, 3.49 (each 3H, s, $OCH_2O\underline{Me}$), 3.58 (2H, t, J=6.0 Hz, 1-H), 5.10, 5.13 (each 1H, d, J=6.5 Hz, $OC\underline{H}_2OMe$), 5.11 (2H, s, $OC\underline{H}_2OMe$), 6.86, 6.87 (each 1H, s, 3′- and 6′-H).

Protected Curcuhydroquinone (32) Compound **30** (0.40 g, 1.3 mmol) was treated *via* **31** in the same manner as described for **20** to give **32** as a colorless oil (0.11 g, 26%). *Anal.* HRMS Calcd for $C_{19}H_{30}O_4$ (M^+, *m/z*): 322.2144. Found: 322.2185. IR (neat): 2900, 1495 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=7.0 Hz, 14-H), 1.53, 1.68 (each 3H, s, 12- and 13-H), 1.50—1.63 (2H, m, 8-H), 1.90 (1H, m, 9-H), 2.20 (3H, s, 15-H), 3.33 (1H, sextet, J=7.0 Hz, 7-H), 3.48, 3.49 (each 3H, s, $OCH_2O\underline{Me}$), 5.11, 5.12 (each 2H, s, $OC\underline{H}_2OMe$), 5.11 (1H, br t, J=7.0 Hz, 10-H), 6.86, 6.87 (each 1H, s, 2′- and 5′-H).

(±)-Curcuhydroquinone (5) A solution of **32** (0.13 g, 0.4 mmol) in isopropanol (2 ml) was treated with 2 N HCl (1 ml). The whole was allowed to stand for 3 d at room temperature. Ether and aqueous NaCl were added. The ether layer was dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography to give **5** as a colorless oil **5** (0.06 g, 61%). *Anal.* HRMS Calcd for $C_{15}H_{22}O_2$ (M^+, *m/z*): 234.1619. Found: 234.1610. IR (CCl_4): 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.20 (3H, d, J=7.0 Hz, 14-H), 1.53 (3H, s, 13-H), 1.50—1.63 (2H, m, 8-H), 1.68 (3H, s, 12-H), 1.92 (2H, m, 9-H), 2.17 (3H, s, 15-H), 2.94 (1H, sextet, J=7.0 Hz, 7-H), 4.54 (2H, br s, OH), 5.12 (1H, br t, J=7.0 Hz, 10-H), 6.56 (1H, br s, 2-H), 6.58 (1H, s, 5-H). ^{13}C-NMR ($CDCl_3$, 500 MHz) δ: 15.4 (15-C), 17.7 (13-C), 21.1 (14-C), 25.7 (12-C), 26.0 (9-C), 31.5 (7-C), 37.4 (8-C), 113.5 (5-C), 118.0 (2-C), 121.8 (3-C), 124.6 (10-C), 131.8 (6-C), 132.1 (11-C), 146.7 (1-C), 147.8 (4-C).

(±)-Curcuquinone (6) from (±)-Curcuhydroquinone (5) A solution of **33** (0.05 g, 0.2 mmol) in tetrahydrofuran (0.5 ml) was added to a solution of CAN (0.63 g) in H_2O (1 ml). The whole was stirred for 10 min at room temperature, then ether and aqueous NaCl were added. The ether layer was dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography to give **6** as a colorless oil (0.01 g, 23%), which could not be stored for long. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=7.0 Hz, 14-H), 1.40—1.59 (2H, m, 8-H), 1.54, 1.66 (each 3H, s, 12- and 13-H), 1.96 (2H, m, 9-H), 2.04 (3H, d, J=1.5 Hz, 15-H), 2.91 (1H, sextet, J=7.0 Hz, 14-H), 5.05 (1H, t, J=7.0 Hz, 10-H), 6.50 (1H, s, 5-H), 6.58 (1H, q, J=1.5 Hz, 2-H).

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References and Notes

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