

(2) 2-(4-Dodecylphenyl)ethanol

To a solution (50 ml) of the compound obtained above (34.5 g) in trifluoroacetic acid was added triethylsilane (22.7 ml) under ice-cooling and the mixture was stirred at room temperature for 3 hours. The solvent was distilled away and ice water was poured to the residue. A cold, saturated aqueous sodium hydrogencarbonate solution was slowly added to the mixture. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed and dried over magnesium sulfate. The solvent was distilled away and methanol (250 ml) was added to the residue to give a methanol solution. To the solution was added sodium methoxide (10.2 g) and the mixture was refluxed under heating for 4 hours. The reaction mixture was concentrated and ice water was poured to the residue. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a 5% aqueous hydrochloric acid solution and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away to give the subject compound (27.1 g) as an oily substance.

Rf : 0.21 (ethyl acetate:hexane = 1:3)

(3) 2-(4-Dodecylphenyl)ethyl iodide

To a solution (500 ml) of the compound obtained above (27.1 g) in dichloromethane was added triethylamine (14.4 ml) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into ice water and the mixture was extracted with dichloromethane. The dichloromethane layer was washed with a saturated aqueous potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and 2-butanone (500 ml) was added to the residue. Thereto was added sodium iodide (12.2 g) and the mixture was refluxed under heating for 3 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:20) to give the subject compound (18.6 g) as an oily substance.

¹H-NMR (CDCl₃) δ:

0.37 (3H, t, J = 6Hz), 0.66-0.86 (18H, m), 1.05-1.10 (2H, m), 2.06(2H, t, J = 6Hz), 2.63 (2H, t, J = 4Hz), 2.83 (2H, t, J = 4Hz), 6.60 (4H, dd, J = 4Hz, 8Hz)

IR(neat)_{max} : 2919, 1513, 1467, 1168 cm⁻¹

(4) Diethyl 2-acetamido-2-[2-(4-dodecylphenyl)ethyl]malonate

A solution (100 ml) of sodium ethoxide (6.3 g) in absolute ethanol was dropwise added to diethyl acetamidomaltonate (20.2 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 30 minutes. Then, a solution (50 ml) of the compound obtained above (18.6 g) in anhydrous tetrahydrofuran was dropwise added thereto and the mixture was stirred at 65 °C for 3 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (8.9 g).

melting point = 60-62 °C

¹H-NMR (CDCl₃) δ:

0.86 (3H, t, J = 6Hz), 1.24 (6H, t, J = 6Hz), 1.23-1.59 (18H, m), 1.54-1.59 (2H, m), 1.97 (3H, s), 2.45 (3H, t, J = 6Hz), 2.54 (3H, t, J = 6Hz), 2.67 (3H, t, J = 6Hz), 4.15-4.24 (4H, m), 6.75 (1H, br.s), 7.06 (4H, dd, J = 6Hz, 6Hz)

IR(KBr)_{max} : 3253, 2920, 2850, 1747, 1644, 1517 cm⁻¹

(5) 2-Acetamido-1,3-diacetoxy-2-[2-(4-dodecylphenyl)ethyl]propane

A solution (50 ml) of the compound obtained above (8.9 g) in anhydrous tetrahydrofuran was dropwise added to a solution (200 ml) of lithium aluminum hydride (1.38 g) in anhydrous tetrahydrofuran in a stream of nitrogen under ice-cooling, and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and the resultant aluminum hydroxide was filtered off. The resultant mixture was dried over anhydrous sodium sulfate and the solvent was distilled away. Pyridine (28.7 ml) was added to the residue. Thereto was added acetic

anhydride (18.5 ml) under ice-cooling and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice-cooled 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (2.5 g) as white crystals.

melting point = 111-113 °C

¹H-NMR (CDCl₃) δ:

0.86 (3H, t, J=6Hz), 1.24-1.31 (18H, m), 1.53-1.58 (4H, m), 1.95 (3H, s), 2.09 (6H, s), 2.56 (2H, t, J=6Hz), 2.58 (2H, t, J=6Hz), 4.35 (4H, s), 5.62 (1H, br.s), 7.09 (4H, s)

IR(KBr): 3309, 2918, 2850, 1738, 1651 cm⁻¹

(6) 2-Amino-2-[2-(4-dodecylphenyl)ethyl]-1,3-propanediol hydrochloride

An aqueous solution (25 ml) of lithium hydroxide (1.7 g) was added to a solution (25 ml) of the compound obtained above (2.5 g) in methanol and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and a 26% hydrochloric acid - ethanol solution was added thereto, followed by stirring. The solvent was distilled away and the residue was recrystallized from ethanol to give the subject compound (770 mg) as white crystals.

¹H-NMR (DMSO) δ:

0.88 (3H, t, J=6Hz), 1.25-1.30 (18H, m), 1.52-1.58 (2H, m), 1.94-2.02 (2H, m), 2.56-2.60 (2H, m), 2.64-2.68 (2H, m), 3.81 (4H, dd, J=11, 26Hz), 4.79 (2H, br.s), 7.09 (4H, dd, J=6, 26Hz), 8.07 (3H, br.s)

IR(KBr): 2921, 2852, 1738, 1686, 1240 cm⁻¹

Exmample 291 : 2-Amino-2-[2-(2-octylphenyl)ethyl]-1,3-propanediol

(1) 1-(2-Bromophenyl)octanol

Magnesium pieces (6.56 g) were added to anhydrous tetrahydrofuran (10 ml) in a stream of nitrogen and the mixture was stirred at room temperature. A solution (200 ml) of 1-bromoheptane (48.4 g) in anhydrous tetrahydrofuran was dropwise added thereto while heating gradually and the mixture was stirred at 40 °C for 1 hour. Thereto was dropwise added a solution (100 ml) of 2-bromobenzaldehyde (25 g) in anhydrous tetrahydrofuran at room temperature and the mixture was stirred for 1 hour. The reaction mixture was poured into a saturated, aqueous ammonium chloride solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:8) to give the subject compound (18.9 g) as an oily substance.

¹H-NMR (CDCl₃) δ:

0.85 (3H, t, J=6Hz), 1.24-1.58 (10H, m), 1.61-1.79 (2H, m), 5.05(1H, m, J=4Hz), 7.08-7.12 (1H, m, J=6Hz), 7.29-7.31 (1H, m, J=6Hz), 7.50-7.54 (2H, m, J=4Hz)

IR_ν (neat): 3350, 2927, 1466, 1023 cm⁻¹

(2) trans-2-(1-Octenyl)bromobenzene

Diphosphorus pentaoxide (7.1 g) was added to a solution (200 ml) of the compound obtained above (2.85 g) in benzene and the mixture was refluxed under heating for 2 hours. The diphosphorus pentaoxide was filtered off and the solvent was distilled away. Ice water was added to the residue. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:15) to give the subject compound (2.4 g) as an oily substance.

¹H-NMR (CDCl₃) δ:

0.86 (3H, t, J=7Hz), 1.18-1.45 (6H, m), 1.46-1.55 (2H, m), 2.24 (2H, m, J=1Hz, 7Hz), 6.16 (1H, m, J=7Hz), 6.72 (1H, d, J=16Hz), 7.02-7.08 (1H, m), 7.19-7.33 (1H, m), 7.46-7.55 (2H, m)

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IR_v (neat): 2957, 2855, 1466, 1023cm⁻¹

(3) trans-2-(1-Octenyl)-benzaldehyde

5 Magnesium pieces (3.74 g) were added to anhydrous tetrahydrofuran (10 ml) in a stream of nitrogen and the mixture was stirred at room temperature. A solution (100 ml) of the compound obtained above (37.4 g) in anhydrous tetrahydrofuran was dropwise added thereto while heating gradually and the reaction mixture was stirred at 60 °C for 1.5 hours. Thereto was dropwise added a solution (100 ml) of dimethylformamide (11.5 ml) in anhydrous tetrahydrofuran at room temperature and the mixture was stirred overnight.
10 The reaction mixture was poured into a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:15) to give the subject compound (26.7 g) as an oily substance.

15 ¹H-NMR (CDCl₃) δ:
0.88 (3H, t, J=6Hz), 1.22-1.38 (6H, m), 1.45-1.52 (2H, m), 2.24-2.36 (2H, m), 6.11-6.18 (1H, m), 7.15 (1H, d, J=18Hz), 7.33-7.37 (1H, m), 7.48-7.53 (2H, m), 7.58 (1H, d, J=4Hz), 10.31 (1H, s)

IR_v (neat): 2927, 2855, 1699, 1597 cm⁻¹

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(4) 2-Octylbenzaldehyde

To a solution (200 ml) of the compound obtained above (26.7 g) in methanol was added a solution (20 ml) of 10% palladium carbon (1 g) in methanol and the mixture was stirred at ordinary temperature and at atmospheric pressure in a stream of hydrogen for 14 hours for catalytic reduction.
25 The 10% palladium carbon was filtered off and the solvent was distilled away. The residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:20) to give the subject compound (22 g) as an oil.

¹H-NMR (CDCl₃) δ:
30 0.86 (3H, t, J=7Hz), 1.25-1.38 (10H, m), 1.54-1.63 (2H, m), 3.00 (2H, t, J=7Hz), 7.24-7.26 (1H, m), 7.31-7.35 (1H, m), 7.46-7.50 (1H, m), 7.80-7.83 (1H, m), 10.28 (1H, s)

IR_v (neat): 3335, 2926, 1701, 1601cm⁻¹

(5) Ethyl (2-octylphenyl)acetate

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Methyl methylsulfinylmethyl sulfide (12.4 g) and Triton B (9.16 ml) were added to a solution (100 ml) of the compound obtained above (22 g) in dioxane at room temperature and the mixture was refluxed under heating for 2 hours. The solvent was distilled away and ethyl acetate was added to the residue. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent
40 was distilled away and ethanol (200 ml) was added to the residue. Thereto was added a 26% hydrochloric acid-ethanol solution and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled away and ice water was poured to the residue. The mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:30) to give the subject compound (20.2 g) as an oily substance.

45 ¹H-NMR (CDCl₃) δ:
0.86 (3H, t, J=5Hz), 1.19-1.38 (10H, m), 1.24 (3H, t, J=5Hz), 1.49-1.62 (2H, m), 2.59 (2H, t, J=6Hz), 3.85 (2H, s), 4.13 (2H, q, J=5Hz), 7.10-7.35 (4H, m)

50 (6) 2-(2-Octylphenyl)ethyl alcohol

A solution (50 ml) of the compound obtained above (20.2 g) in anhydrous tetrahydrofuran was dropwise added to a solution (200 ml) of lithium aluminum hydride (3.04 g) in anhydrous tetrahydrofuran in stream of nitrogen under ice-cooling and the mixture was stirred at room temperature for 2 hours. A saturated
55 aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and the resultant aluminum hydroxide was filtered off. The filtrate was dried over anhydrous sodium sulfate and the solvent was distilled away. The residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:30) to give the subject compound (10.2 g) as an oily substance.

¹H-NMR (CDCl₃) δ:

0.87 (3H, t, J=6Hz), 1.21-1.46 (10H, m), 1.47-1.62 (2H, m), 2.61(2H, t, J=6Hz),
2.96 (3H, t, J=6Hz), 3.82 (2H, dd, J=6Hz, 12Hz), 7.14-7.24 (4H, m)

IR_ν (neat): 3335, 2926, 2854, 1467cm⁻¹

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(7) 2-(2-Octylphenyl)ethyl methanesulfonate

Triethylamine (7.37 ml) was added to a solution (250 ml) of the compound obtained above (10.2 g) in dichloromethane and the mixture was cooled with ice. Thereto was dropwise added methanesulfonyl chloride (6.04 g) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated aqueous potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:8) to give the subject compound (13.4 g) as an oily substance.

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¹H-NMR (CDCl₃) δ:

0.86 (3H, t, J=6Hz), 1.22-1.41 (10H, m), 1.51-1:59 (2H, m), 2.60 (2H, t, J=6Hz),
2.84 (3H, s), 3.09 (2H, t, J=6Hz), 4.38 (2H, t, J=6Hz), 7.10-7.20 (4H, m)

IR(neat): 2929, 1467, 1357, 1174 cm⁻¹

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(8) 2-(2-Octylphenyl)ethyl iodide

To a solution of the compound obtained above (13.4 g) in 2-butanone (300 ml) was added sodium iodide (7.7 g) and the mixture was refluxed under heating for 2 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:30) to give the subject compound (11.9 g).

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¹H-NMR (CDCl₃) δ:

0.87 (3H, t, J=6Hz), 1.18-1.74 (10H, m), 1.50-1.59 (2H, m), 2.57 (2H, t, J=6Hz),
3.18 (2H, t, J=6Hz), 3.28 (2H, t, J=6Hz), 7.10-7.25 (4H, m)

IR(neat): 2923, 2854, 1490, 1468 cm⁻¹

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(9) Diethyl 2-acetamido-2-[2-(2-octylphenyl)ethyl]malonate

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A solution (50 ml) of sodium ethoxide (6.39 g) in anhydrous ethanol was dropwise added to diethyl acetamidomalonate (20.4 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 1.5 hours. A solution of the compound obtained above (10.8 g) in tetrahydrofuran was dropwise added thereto and the mixture was refluxed under heating for 7 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (5.8 g) as white crystals. melting point = 37-38 °C

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¹H-NMR (CDCl₃) δ:

0.86 (3H, t, J=6Hz), 1.21-1.36 (10H, m), 1.25 (6H, t, J=6Hz), 1.46-1.57 (2H, m),
2.03 (3H, s), 2.38-2.47 (2H, m), 2.51 (2H, t, J=6Hz), 2.55-2.63 (2H, m, J=6Hz),
4.16-4.41 (4H, m), 6.82 (2H, br.s), 7.05-7.15 (4H, m)

IR(KBr): 3415, 2977, 2855, 1741, 1683, 1492 cm⁻¹

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(10) 2-Acetamido-1,3-diacetoxy-2-[2-(2-octylphenyl)ethyl]propane

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A solution (50 ml) of the compound obtained above (4.3 g) in anhydrous tetrahydrofuran was dropwise added to a solution (200 ml) of lithium aluminum hydride (0.76 g) in anhydrous tetrahydrofuran in a stream of nitrogen under ice-cooling, and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and the resultant aluminum hydroxide was filtered off. The filtrate was dried over anhydrous sodium sulfate and the solvent was distilled away. Pyridine (10 ml) was added to the residue and then, acetic anhydride (13 ml) was added thereto, and the mixture was allowed to stand at room temperature overnight. The reaction mixture was

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poured into ice-cooled 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (2.2 g) as an oily substance.

5 $^1\text{H-NMR}$ (CDCl_3) δ :
 0.86 (3H, t, J=6Hz), 1.21-1.38 (12H, m), 1.47-1.58 (2H, m), 1.97 (3H, s), 2.08 (6H, s), 2.56 (2H, t, J=6Hz), 2.58 (2H, t, J=6Hz), 4.35 (4H, s), 5.66 (1H, br.s), 7.09-7.13 (4H, m)
 IR(neat): 3295, 2927, 1747, 1660, 1256 cm^{-1}

10 (11) 2-Amino-2-[2-(2-octylphenyl)ethyl]-1,3-propanediol hydrochloride

An aqueous solution (20 ml) of lithium hydroxide (1.7 g) was added to a solution of the compound obtained above (2.2 g) in methanol (20 ml) and the mixture was refluxed under heating for 4 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and a 26% hydrochloric acid-ethanol solution was added to the residue. The solvent was distilled away and the residue was recrystallized from ethanol to give hydrochloride of the subject compound (800 mg). melting point = 168-170 °C

20 $^1\text{H-NMR}$ (DMSO) δ :
 0.85 (3H, t, J=7Hz), 1.22-1.37 (10H, m), 1.43-1.54 (2H, m), 1.68-1.78 (2H, m), 2.52-2.63 (4H, m), 3.49-3.59 (4H, m), 5.40 (2H, t, J=4Hz), 7.05-7.17 (4H, m), 7.89 (3H, br.s)
 IR ν (KBr): 3385, 3272, 2925, 1519, 1069 cm^{-1}

25 Example 292 : 2-Amino-2-(4-octylthiobenzyl)-1,3-propanediolhydrochloride 1/2 hydrate

(1) 4-(Methylthio)benzyl alcohol

30 Sodium borohydride (3.78 g) was added to isopropyl alcohol (50 ml) and the mixture was stirred under ice-cooling. Thereto was dropwise added 4-(methylthio)benzaldehyde (15 g) and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled away and water was added to the residue. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was recrystallized from hexane-ethyl acetate to give the subject compound (15 g) as white crystals.
 35 melting point = 41-43 °C

$^1\text{H-NMR}$ (CDCl_3) δ :
 2.40 (3H, s), 4.43 (2H, s), 7.10 (4H, s), 3.36 (1H, br.s)

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elemental analysis($\text{C}_8\text{H}_{10}\text{OS}$)	calculated	C 62.30,	H 6.54
	found	C 61.90,	H 6.55

MS: 154 (M^+)

45 (2) 4-(Methylsulfinyl)benzyl alcohol

m-Chloroperbenzoic acid (content 50%, 35 g) was added to a solution (100 ml) of the compound obtained above (15 g) in chloroform under ice-cooling and the mixture was stirred for 1 hour. Thereto was added calcium hydroxide (37 g) and the mixture was stirred at room temperature for 1 hour. The insoluble matters were filtered off, and the filtrate was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; chloroform:methanol = 20:1) to give the subject compound (15.56 g) as an oily substance.

55 $^1\text{H-NMR}$ (CDCl_3) δ :
 2.73 (3H, s), 3.28 (1H, br.s), 4.45 (2H, s), 7.52 (4H, s)
 IR(neat): 3364, 1409, 1303, 1148, 1031 cm^{-1}

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