Synthesis of (-)-3-Butyl-4-hydroxyphthalide

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Abstract — (-)-3-Butyl-4-hydroxyphthalide 1 was first synthesized enantioselectively by using a chiral aryllithium reagent and its absolute stereochemistry at C-3 was determined to be S-configuration. (-)-3-Butyl-4-hydroxyphthalide 1 was isolated from the rhizome of Ligusticum wallichii Franch (Japanese name 'senkyu') of which phenolic constituents was known to have the effect of increasing coronary flow'. Although the structure of this compound was shown to possess structure 1, its stereochemistry hasn't been clear yet. In this paper we wish to describe the first total synthesis of (-)-1 in a high optical yield' and the absolute stereochemistry of this phthalide.

We considered two approaches for the asymmetric synthesis of (-)-1 as shown in Scheme 1. In the first approach(A) a chiral center may be introduced by the asymmetric reduction of the ketone 2 with chiral reductant. In the second approach(B), the asymmetric induction would be performed by the reaction of chiral aryllithium reagent 4 with aldehyde, followed by oxidation.
1) RCHO
2) Oxidation

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\begin{align*}
\text{R} &= \text{Alkyl group} \\
\text{Z}^* &= \text{Chiral ortho-directing group}
\end{align*}
\]

Scheme 1

It is known that asymmetric reduction of the prochiral aryl ketone with (S)-BINAL-H \(^5\) reported by Noyori et al.\(^3\) provides an alcohol of S-configuration with high enantioselectivity. The asymmetric synthesis of \((-\rangle-1\) was examined as shown in Scheme 2.

The reduction of the ester \(6\) with (S)-BINAL-H afforded \((-\rangle-3\)-butylphthalide \(7\) containing S-configuration\(^6\) at C-3 in 83\%ee\(^7\)). On the other hand, in the case of ester \(8\) no (S)-3-butyl-4-methoxyphthalide \(9\) was obtained. This result suggested that fairly bulky (S)-BINAL-H \(^5\) couldn't approach to the acyl group by steric interference with two ortho-substituents in the ester \(8\).

Scheme 2

Previously the asymmetric synthesis of (S)-(-)-7 was accomplished via the lithiation with the halogen-metal exchange of chiral aminal obtained from o-bromobenzaldehyde with (S)-2-(anilinomethyl)pyrrolidine \(10\) by Asami and Mukaiyama\(^9\). As the regioselective directed lithiation of aromatic compounds by the chelation effect was well known\(^1\), the directed ortho lithiation of the
chiral aminal 12 containing a methoxy group at m-position was examined as shown in Scheme 3.

The chiral aminal 12 was easily obtained by condensation of m-methoxybenzaldehyde 11 with 10. Then the directed ortho lithiation of the aminal 12 with n-BuLi, followed by reaction with valeraldehyde and then hydrolysis under mild conditions afforded the optically active lactol (-)-13. The desired compound (-)-1 was obtained in 84% ee by the demethylation of (-)-9 obtained by the oxidation of the lactol 13 with Ag2O.

It was speculated that (-)-1 has S-configuration at C-3 according to the mechanism proposed by Asami and Mukaiyama. That is, the directed ortholithiation of aminal first occurred to give a rigid tricyclic five-membered ring (Figure 1) and then the aldehyde approaches from the less hindered front side in the manner shown in Figure 2 to avoid steric repulsion between the alkyl group of the aldehyde and the pyrrolidine ring illustrated with arrow in Figure 3. Further, the phthalide (-)-1 was converted to 7 via the triflate 14 to confirm the absolute configuration of (-)-1. The optical rotation of the resultant phthalide 7 was identical with that of the authentic phthalide (-)-7. Consequently, it was possible to determine the absolute stereochemistry of 1 to be S-configuration at C-3 position.
EXPERIMENTAL

Melting points were measured on a YANACO micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-300 spectro-photometer. Nuclear magnetic resonance spectra were obtained with a JEOL FX-200 spectrometer using tetramethylsilane as an internal standard. Mass spectra were determined on a JEOL DX-300 spectrometer. Optical rotations were taken on a JASCO DIP-360 using a 100mm cell.

Methyl 2-valerylbenzoate 6

The esterification of 2-valerylbenzoic acid prepared from phthalic anhydride with dibutylcadmium gave methyl 2-valerylbenzoate 6: \( \nu \) (KBr) \( \nu_{\text{max}} \) 1726, 1700 cm\(^{-1}\); \(^1\)H-nmr (CDCl\(_3\)) \( \delta \) 0.94 (3H, t, \( J=7.3\)Hz), 1.40 (2H, t, \( J=7.3\)Hz), 1.72 (2H, t, \( J=7.5\) Hz), 2.80 (2H, t, \( J=7.5\)Hz), 7.35 (1H, dd, \( J=7.3\), 1.5Hz), 7.48 (1H, ddd, \( J=7.3\), 7.3, 1.5Hz), 7.56 (1H, ddd, \( J=7.3\), 7.3, 1.5Hz), 7.89 (1H, dd, 7.3, 1.5Hz); ms m/z 220 (M\(^+\)), 163 (M-C,C\(_6\)).

Methyl 3-methoxy-2-valerylbenzoate 8

A solution of diazomethane in ether was gradually added to a stirred solution of 3-methoxy-2-valerylbenzoic acid (2.0g, 8.46mmol) in ether at 0 °C. The mixture
was continued to stir at 0 °C for 1 h, then at room temperature for 1 h and evaporated to give a residue. The residue was purified by flash column chromatography (SiO₂; eluent, AcOEt:n-hexane=1:3) to give a colorless oil of methyl 3-methoxy-2-valerylbenzoate 8 (1.65g, 78%): \( \text{IR (KBr)} \nu_{max} 1726, 1466, 1280, 1060 \text{ cm}^{-1} \); \( \text{'H-NMR (CDCl₃) } \delta 0.94 (3H, t, J=7Hz), 1.12-1.95 (4H, m), 2.81 (2H, t, J=7Hz), 3.11 (3H, s), 3.84 (3H, s), 7.09 (1H, dd, J=8, 1Hz), 7.39 (1H, dd, J=8, 8Hz), 7.57 (1H, dd, J=8, 1Hz). \) 

\( \text{MS m/z 250 (M), 193 (M-C,H₃).} \)

(S)-(−)-3-Butylphthalide 2

A solution of (S)-BINAL-H 5 (0.4M in THF) was prepared in situ from LiAlH₄ (39mg, 1.03mmol), abs EtOH (1.05mmol) and (S)-(−)-2,2'-dihydroxy-1,1'-binaphthyl 6 (300mg, 1.05mmol) under argon atmosphere. 1.0M THF solution of methyl 2-valerylbenzoate 6 (68mg, 0.31mmol) was injected into the stirred solution of (S)-BINAL-H 5 at -80 °C. The reaction mixture was stirred at this temperature for 3 h and quenched by addition of 2N HCl at -80 °C and then extracted with ether 2 times. The combined organic layer was washed with brine, dried (MgSO₄) and evaporated to a residue. After (S)-(−)-2,2'-dihydroxy-1,1'-binaphthyl was removed from the residue by recrystallization (n-hexane-CHCl₃), the residue was purified by flash column chromatography (SiO₂; eluent, AcOEt:CHCl₃=2:3) to give a colorless oil of (S)-(−)-3-butylphthalide 2 (18mg, 30% optical yield 83%ee): \( [\alpha]_D -49.3^\circ (c=0.4, \text{CHCl₃}) \); \( \text{lit.} \) \( [\alpha]_D -59.5^\circ (c=0.2, \text{CHCl₃}) \); \( \text{IR (KBr)} \nu_{max} 1764 \text{ cm}^{-1} \); \( \text{'H-NMR (CDCl₃) } \delta 0.91 (1H, t, J=7.1Hz), 1.20-2.31 (6H, m), 2.78 (IH, dd, J=7.8, 4.2Hz), 7.44 (1H, dd, J=7.4, 1.0Hz), 7.52 (1H, dd, J=7.8, 7.4Hz), 7.67 (1H, ddd, J=7.6, 7.6, 1.0Hz), 7.93 (1H, d, J=7.6Hz); \) \( \text{MS m/z 190 (M²), 133 (M-C,H₆).} \)

3-(3-Methoxyphenyl)-2-phenyl-1,5,6,7-tetrahydro-3H-pyrro[1,2-c]imidazole 12

A solution of m-methoxybenzaldehyde 11 (2.0g, 14.69mmol) and (S)-(−)-2-(anilinomethyl)pyrrolidine 10 1' (2.59g, 14.69mmol) in benzene (20ml) was refluxed for removal of water azeotropically under argon atmosphere for 3 h. The mixture was evaporated and then recrystallized from ether to give 3-(3-methoxyphenyl)-2-phenyl-1,5,6,7-tetrahydro-3H-pyrro[1,2-c]imidazole 12 (3.95g, 91%): mp 78-80°C; \( \ [\alpha]_D +38.5^\circ (c=0.3, \text{CH₃Cl}) \); \( \text{IR (KBr) } \nu_{max} 1602, 1504, 1368, 1278, 1042; \text{'H-NMR (CDCl₃) } \delta 1.70-2.20 (4H, m), 2.78 (1H, dd, J=18, 9Hz), \)
3.21 (1H, dd, J=9, 9Hz), 3.33 (1H, m), 3.72 (1H, dd, J=7, 7Hz), 3.76 (3H, s), 3.89 (1H, m), 5.28 (1H, s), 6.45 (2H, d, J=8Hz), 6.65 (1H, dd, J=7, 7Hz), 6.78 (1H, dd, J=8, 2Hz), 6.88 (1H, d, J=2Hz), 6.91 (1H, d, J=8Hz), 7.12 (1H, d, J=7Hz), 7.18 (2H, dd, J=8, 8Hz); ms m/z 294 (M+), 166.

(-)-3-Butyl-1-hydroxy-4-methoxy-2-oxaindane 13

A solution of n-BuLi (1.6M in hexane, 2.13ml) was injected into a stirred solution of (-)-3-(3-methoxyphenyl)-2-phenyl-1,5,6,7-tetrahydro-3H-pyrr0[1,2-c]imidazole 12 (1.0g, 3.40mmol) in dry ether (10ml) under argon atmosphere at room temperature. The mixture was stirred at room temperature for 4 h and then a solution of valeraldehyde (0.54ml, 5.10mmol) in dry ether (2ml) was injected at -80 °C. The mixture was stirred at -80 °C for 3 h and quenched with sat.NH4Cl at this temperature. The ethereal layer was hydrolyzed with 2%HCl at 0 °C for 1 h and then was extracted with ether 2 times. The ethereal layer was washed with water, dried (MgSO4) and evaporated to give a residue. The residue was purified by flash column chromatography (SiO2; eluent, AcOEt:benzene=1:5) to give a colorless oil of (-)-3-butyl-1-hydroxy-4-methoxy-2-oxaindane 13 (250mg, 33%, a mixture of diastereoisomers): [α]D -45.9° (c=0.1, CHCl3); ir (KBr) ν max, 3416, 1604, 1486, 1266 cm⁻¹; 'H-nmr (CDCl3) δ 0.88 and 0.90 (3H, t, J=7.3Hz and t, J=7.3Hz, respectively), 1.10-1.55 (4H, m), 1.55-1.80 (1H, m), 1.90-2.15 (1H, m), 3.52 and 3.58 (1H, d, J=8.3 and d, J=7.6Hz, respectively, D2O exchangeable), 3.82 and 3.83 (3H, s and s), 5.22 and 5.49 (1H, dd, J=7.8, 2.9Hz and m, respectively), 6.36 and 6.46 (1H, d, J=7.6Hz and m, respectively), 6.82 (1H, d, J=7.8Hz), 7.00 (1H, d, J=7.3Hz), 7.30 (1H, dd, J=7.8, 7.3Hz); ms m/z 222 (M+), 166.

(-)-3-Butyl-4-hydroxyphthalide 1

A solution of (-)-3-butyl-1-hydroxy-4-methoxy-2-oxaindane 13 (137mg, 0.61mmol) in MeOH (2.5ml) was added to a stirred solution of Ag2O (667mg, 2.88mmol) in H2O (3ml) -MeOH (0.5ml) at room temperature. The mixture was stirred for 1 h and filtered through a celite. The filtrate was evaporated to give a residue. After 2N H2SO4 (3ml) was added to the residue at 0 °C, the mixture was extracted with ether 2 times. The ether layer was washed with brine, dried (MgSO4) and evaporated to give a residue. The residue was purified by flash column
chromatography (SiO₂; eluent, AcOEt:n-hexane=1:1) to give (-)-3-butyl-4-methoxyphthalide 9 (103mg, 76%); \([\alpha]_D^-=-69.3^\circ\) (c=0.2, CHCl₃); ir (KBr) \(\nu_{max} 1770, 1492, 1274; \)'H-nmr (Acetone-d₆) \(\delta 0.88\) (3H, t, J=6.8Hz), 1.10-1.45 (4H, m), 1.57-1.83 (1H, m), 2.10-2.37 (1H, m), 3.97 (3H, s), 5.53 (1H, dd, J=7.6, 3.1Hz), 7.32 (1H, d, J=7.8Hz), 7.38 (1H, d, J=7.8Hz), 7.56 (1H, dd, J=7.8, 7.8Hz); ms m/z 220 (M⁺), 163 (M-C,H₅).

A solution of BBr₃ (0.6M in CH₂Cl₂, 0.9ml) was added to a solution of (-)-3-butyl-4-methoxyphthalide 9 (75mg, 0.34mmol) in dry CH₂Cl₂ (1ml) at -30 °C. The mixture was stirred at -30 °C for 1 h and then at room temperature for 2 h. The mixture was poured into ice-water and extracted with CHCl₃ 2 times. The combined organic layer was washed with brine, dried (MgSO₄) and evaporated to give a residue. The residue was recrystallized from benzene to give a colorless needle of 3-butyl-4-hydroxyphthalide 1 (61mg, 87%, optical yield 84%ee); mp 188-190°C; \([\alpha]_D^-=-88.7^\circ\) (c=0.38, EtOH), \([\alpha]_D^-=-105.5^\circ\) (EtOH); ir (KBr) \(\nu_{max} 3224, 1720; \)'H-nmr (Acetone-d₆) \(\delta 0.89\) (3H, t, J=7.1Hz), 1.20-1.50 (4H, m), 1.65-1.90 (1H, m), 2.15-2.40 (1H, m), 5.57 (1H, dd, J=7.6, 2.9Hz), 7.18 (1H, dd, J=7.8, 1.0Hz), 7.31 (1H, dd, J=7.6, 1.0Hz), 7.42 (1H, dd, J=7.8, 7.6Hz); ms m/z 206 (M⁺), 149 (M-C,H₅).

Conversion of (-)-1 to (-)-7

Trifluoromethanesulfonic anhydride (0.2ml, 1.20mmol) was added to a solution of (-)-3-butyl-4-hydroxyphthalide 1 (206mg, 1.00mmol) and dry pyridine (0.24ml, 3.00mmol) in dry-CH₂Cl₂ (1ml) at 0 °C. The mixture was stirred at 0 °C for 10min and then at room temperature for 1h. The mixture was poured into iced 2%HCl and extracted with ether. The organic layer was washed with water 2 times and brine, dried (Na₂SO₄) and evaporated to give a yellow oil of 3-butyl-4-trifluoromethanesulfonyloxyphthalide 14 (283mg, 84%); \(\nu_{max} \text{H-nmr (CDCl₃)} 0.91\) (3H, t, J=7.1Hz), 1.15-1.50 (4H, m), 1.65-1.90 (1H, m), 2.10-2.35 (1H, m), 5.70 (1H, dd, J=8.1, 3.0Hz), 7.58 (1H, dd, J=8.1, 1.2Hz), 7.66 (1H, dd, J=8.1, 7.3Hz), 7.95 (1H, dd, J=7.3, 1.2Hz). Without purification of 14, formic acid (0.06ml, 1.67mmol) was added to a solution of the triflate 14 (263mg, 0.84mmol), bis(triphenylphosphine)-palladium(II)chloride (30mg, 0.04mmol) and tributylamine (0.6ml, 2.51mmol) in dry DMF (1.8ml) under argon atomosphere at room temperature. The mixture was heated at 110 °C for 3h and then filtered. The filtrate was washed...
with sat. NaHCO\(_3\), 2% HCl, water and brine, dried (MgSO\(_4\)) and evaporated to give a residue. The residue was purified by flash column chromatography (SiO\(_2\); eluent, AcOEt:n-hexane=1:8) to give a colorless oil of (-)-3-butyolphthalide 7 (128mg, 81%): \([\alpha]_D -49.1^\circ (c=0.2, \text{CHCl}_3)\); the other spectral data was identical with those of the preceding (-)-7.

REFERENCES AND NOTES
1) Peking Institute of Pharmaceutical Industries, Yao Hsueh Hsueh Pao, 1979, 14, 670.
2) The optical yields (%) was calculated by the A/B ratio x100.
   A=Specific rotation of a synthesized product
   B=Specific rotation of a natural product

Received, 17th October, 1988