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

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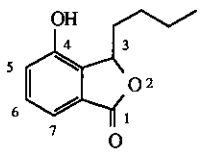
Abstract —— (-)-3-Butyl-4-hydroxyphthalide 1 was first synthesized enantioselectively by using a chiral aryllithium reagent and its absolute stereochemistry at C-3 was determined to be S-configuration.

(-)-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[1]. 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[2] and the absolute stereochemistry of this phthalide.



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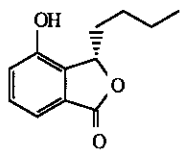
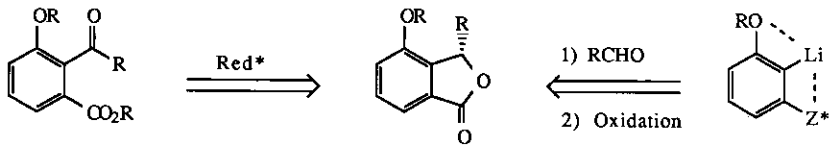


(-)-1

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.



(A) (B)

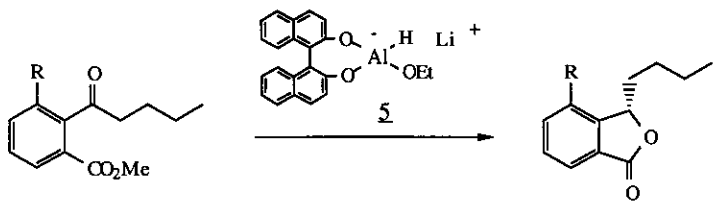
2 3 4

R=Alkyl group
Z*=Chiral ortho-directing group

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 (-)-1 was examined as shown in Scheme 2.

The reduction of the ester 6 [4] with (S)-BINAL-H afforded (-)-3-butylphtalide 7 containing S-configuration[5] at C-3 in 83%ee[2]. On the other hand, in the case of ester 8 [6] 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 .



R=H, 6
R=OMe, 8

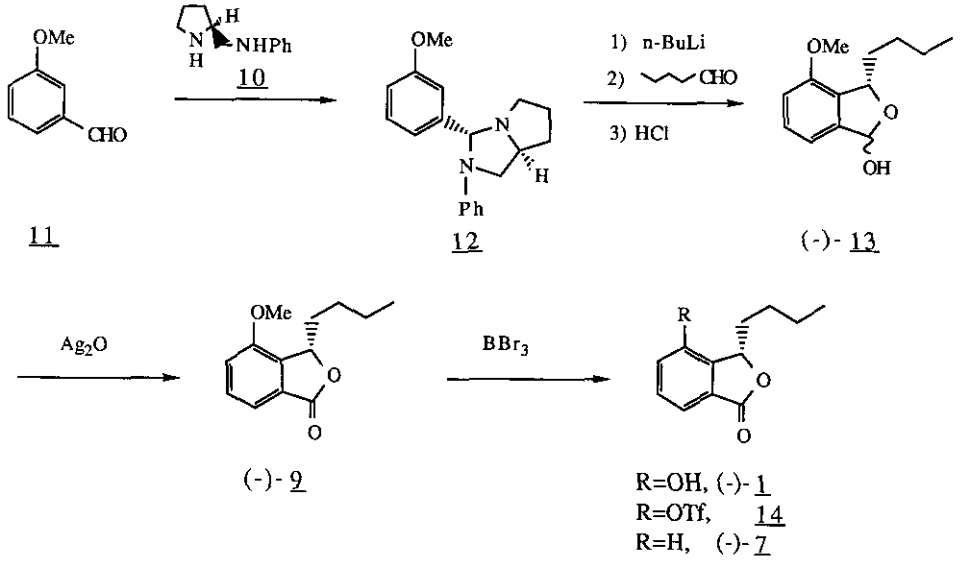
R=H, (-)-7
R=OMe, (-)-9

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[7a]. As the regioselective directed lithiation of aromatic compounds by the chelation effect was well known[8], 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[2] by the demethylation[10] of (-)-9 obtained by the oxidation of the lactol 13 with Ag_2O [9].



Scheme 3

It was speculated that (-)-1 has S-configuration at C-3 according to the mechanisum proposed by Asami and Mukaiyama[7a]. That is, the directed ortho lithiation 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 [7b] 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.

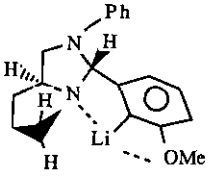


Figure 1

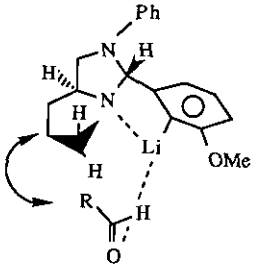


Figure 2

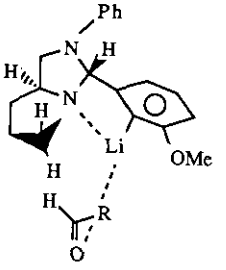


Figure 3

EXPERIMENTAL

Melting points were measured on a YANACO micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-300 spectrophotometer. 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[4b] of 2-valerylbenzoic acid[4a] prepared from phthalic anhydride with dibutylcadmium gave methyl 2-valerylbenzoate 6 : ir(KBr) ν_{max} 1726, 1700 cm^{-1} ; ^{1}H-nmr($CDCl_3$) δ 0.94 (3H, t, J=7.3Hz), 1.40 (2H, tq, J=7.3, 7.3Hz), 1.72 (2H, tt, J=7.5, 7.3Hz), 2.80 (2H, t, J=7.5Hz), 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 ($M-C_4H_9$).

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[8] (2.0g, 8.46mmol) in ether at 0 ℃. The mixture

was continued to stir at 0 ℃ for 1 h, then at room temperature for 1 h and evaporated to give a residue. The residue was purified by flash column chromathography (SiO_2 ;eluent,AcOEt:n-hexane=1:3) to give a colorless oil of methyl 3-methoxy-2-valerylbenzoate 8 (1.65g, 78%) : ir (KBr) ν_{max} 1726, 1466, 1280, 1060 cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.94 (3H, t, J=7Hz), 1.12-1.95 (4H, m), 2.81 (2H, t, J=7Hz), 3.81(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) ; ms m/z 250 (M^+), 193 ($M-C_4H_9$).

(S)-(-)-3-Butylphthalide 7

A solution of (S)-BINAL-H 5 (0.4M in THF) was prepared in situ from $LiAlH_4$ (39mg, 1.03mmol), abs.EtOH (1.05mmol) and (S)-(-)-2,2'-dihydroxy-1,1'-binaphthyl[11] (300mg, 1.05mmol) under argon atomosphere[9]. 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 ℃. The reaction mixture was stirred at this temperature for 3 h and qenched by addition of 2N HCl at -80 ℃ and then extracted with ether 2 times. The combined organic layer was washed with brine, dried ($MgSO_4$) and evaporated to a residue. After (S)-(-)-2,2'-dihydroxy-1,1'-binaphthyl was removed from the residue by recrystallisation (n-hexane-$CHCl_3$), the residue was purified by flash column chromathography (SiO_4 ; eluent, AcOEt:$CHCl_3$=2:3) to give a colorless oil of (S)-(-)-3-butylphthalide 7 (18mg, 30% , optical yield 83%ee[2]) : $[\alpha]_D$ -49.3° (c=0.4, $CHCl_3$), [lit.[12] $[\alpha]_D$ -59.5° (c=0.2, $CHCl_3$)] ; ir (KBr) ν_{max} 1764 cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.91 (1H, t, J=7.1Hz), 1.20-2.31 (6H, m), 5.48 (1H, dd, J=7.8, 4.2Hz), 7.44 (1H, dd, J=7.4, 1.0Hz), 7.52 (1H, dd, J=7.6, 7.4Hz), 7.67(1H, ddd, J=7.6, 7.6, 1.0Hz), 7.93(1H, d, J=7.6Hz) ; ms m/z 190 (M^+), 133 ($M-C_4H_9$).

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[13] (2.59g, 14.69mmol) in benzene (20ml) was refluxed for removal of water azeotropically under argon atomosphere 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℃ ; $[\alpha]_D$ +38.5° (c=0.3, CH_2Cl_2) ; ir (KBr) ν_{max} 1602, 1504, 1368, 1278, 1042 ; ^{1}H-nmr ($CDCl_3$) δ 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^+), 189.

(-)-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-pyrro[1,2-c]imidazole 12 (1.0g, 3.40mmol) in dry ether (10ml) under argon atomosphere 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 ℃. The mixture was stirred at -80 ℃ for 3 h and quenched with sat.NH_4Cl at this temperature. The ethereal layer was hydrolyzed with 2%HCl at 0 ℃ for 1 h and then was extracted with ether 2 times. The ethereal layer was washed with water, dried ($MgSO_4$) and evaporated to give a residue. The residue was purified by flash column chromathography (SiO_2 ; 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) : $[\alpha]_D$ -45.9° (c=0.1, $CHCl_3$) ; ir (KBr) ν_{max} 3416, 1604, 1486, 1266 cm^{-1} ; ^1H-nmr ($CDCl_3$) 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, D_2O 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 Ag_2O[9] (667mg, 2.88mmol) in H_2O (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 H_2SO_4 (3ml) was added to the residue at 0 ℃, the mixture was extracted with ether 2 times. The ether layer was washed with brine, dried ($MgSO_4$) and evaporated to give a residue. The residue was purified by flash column

chromathography (SiO_2 ; eluent, AcOEt:n-hexane=1:1) to give (-)-3-butyl-4-methoxyphthalide 9 (103mg, 76%) : $[\alpha]_D$ -69.3° (c=0.2, $CHCl_3$) ; ir (KBr) ν_{max} 1770, 1492, 1274 ; ^{1}H-nmr (Acetone-d_6) δ 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 ($M-C_4H_9$).

A solution of BBr_3[10] (0.8M in CH_2Cl_2, 0.9ml) was added to a solution of (-)-3-butyl-4-methoxyphthalide 9 (75mg, 0.34mmol) in dry CH_2Cl_2 (1ml) at -30 ℃. The mixture was stirred at -30 ℃ for 1 h and then at room temperature for 2 h. The mixture was poured into ice-water and extracted with $CHCl_3$ 2 times. The combined organic layer was washed with brine, dried ($MgSO_4$) 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℃ ; $[\alpha]_D$ -88.7° (c=0.38, EtOH), [lit.[1] $[\alpha]_D$ -105.5° (EtOH)] ; ir (KBr) ν_{max} 3224, 1720 ; ^{1}H-nmr (Acetone-d_6) δ 0.89 (3H, t, J=7.3Hz), 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 ($M-C_4H_9$).

Convertion of (-)-1 to (-)-7

Trifluoromethanesulfonic anhydride (0.2ml, 1.20mmol) was added to a solution of (-)-3-butyl-4-hydroxyphthalide (206mg, 1.00mmol) and dry pyridine (0.24ml, 3.00mmol) in dry-CH_2Cl_2 (1ml) at 0 ℃. The mixture was stirred at 0 ℃ 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 (Na_2SO_4) and evaporated to give a yellow oil of 3-butyl-4-trifluoromethanesulfonyloxyphthalide 14 (283mg, 84%) : ^{1}H-nmr ($CDCl_3$) δ 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 (283mg, 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[7b]. The mixture was heated at 110 ℃ 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 chromathography (SiO_2 ; eluent, AcOEt:n-hexane=1:8) to give a colorless oil of (-)-3-butylphthalide 7 (128mg, 81%) : $[\alpha]_D$ -49.1° (c=0.2, $CHCl_3$) ; the other spectral data was identical with those of the preceding (-)-7 .

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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

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