SYNTHESIS OF EGONOL AND (±)-MACHICENDIOL

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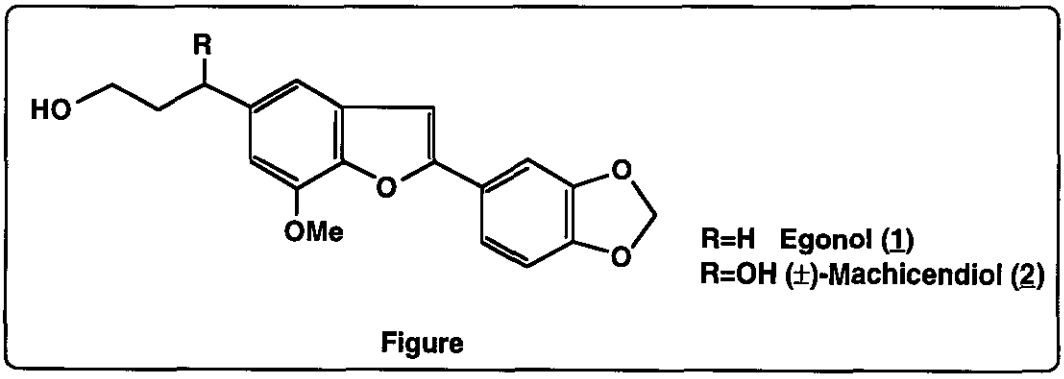
Abstract-Two norneolignans, egonol (1) and (±)-machicendiol (2), were synthesized by using the palladium-catalyzed cross-coupling reaction as a key step. This paper describes a new strategy for the preparation of norneolignans having a benzo[*b*]furan skeleton.

Lignans and neolignans, which are contained in most plants, have attracted much attention in medicinal chemistry for their various biological activities such as insecticidal, fungicidal, antimicrobial and antioxidant properties.[1] Egonol (1) was first isolated from the seed oil of *Syrax japonicum*[2] and (±)-machicendiol (2) from the leaf extracts of *Machilus glaucescens,* which are used for the treatment of asthema, rheumatism, and ulcers.[3]

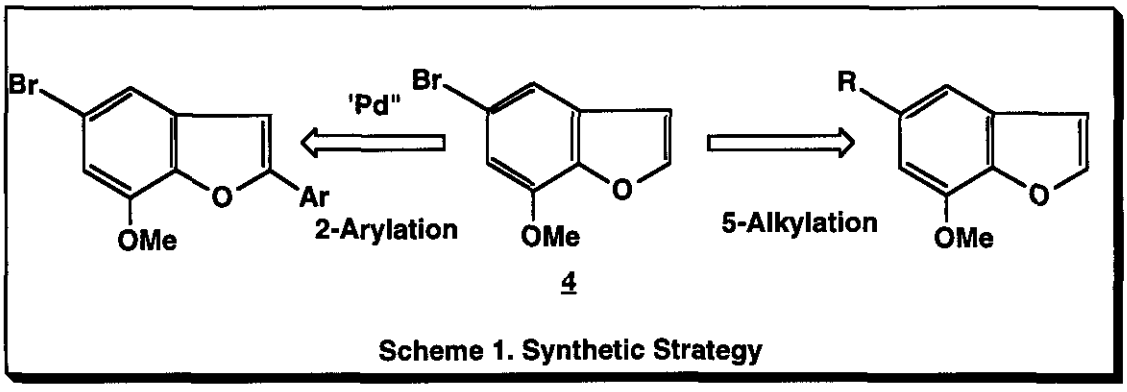


Figure

Compound (1) and (2) are norneolignans with a benzo[*b*]furan skeleton and Hirano *et al.* reported that they show cytosatic activitiy against human leukemic HL-60 cells.[4]

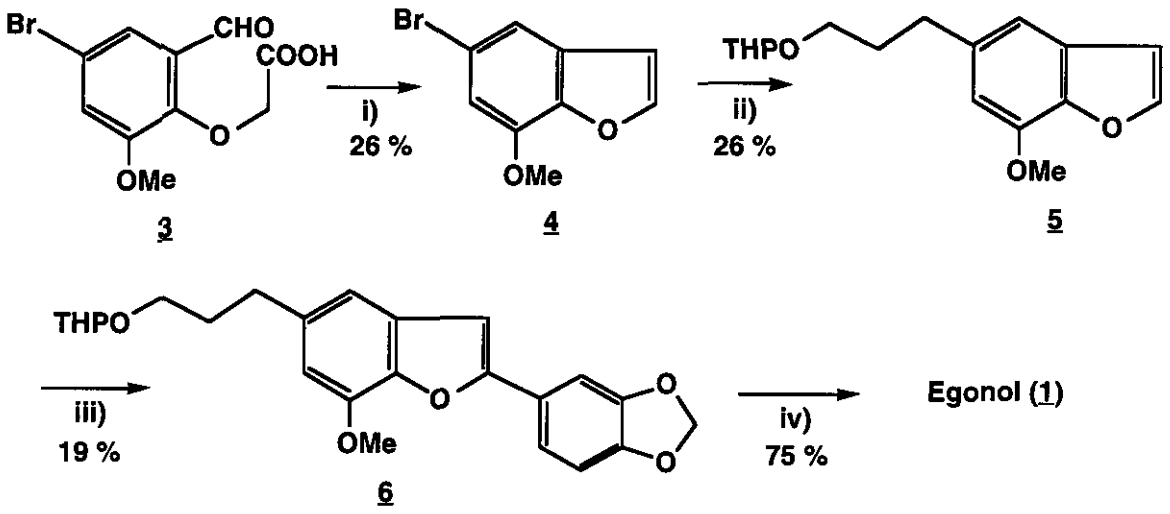
Synthesis of benzo[*b*]furans has been reported by several groups. For example, egonol (**1**)[5] and (±)-machicendiol (**2**)[6] were prepared by Castro's method,[7] *via* the coupling reaction of a cuprous acetylide with an *o*-halophenol. However, since the coupling reactions of this type often give 1,4-bisaryl-1,3-dienes as a by-product, the yield of the desired benzo[*b*]furan is generally low. Watanabe *et al.* reported a more efficient synthesis of 2-arylbenzo[*b*]furans *via* lithiation of *o*-tetramethylphosphorodiamidates.[8] Mann and co-workers describe a total synthesis of moracin M, 6-hydroxy-2-(5-resorcinyl)benzofuran[9] *via* the palladium-catalyzed coupling reactions of either 2-halobenzo[*b*]furans with 5-metalloresorcinol tricarbonyl chromium(0) complexes or 2-metallobenzo[*b*]furans with 5-haloresorcinol tricarbonyl chromium(0) complexes. We have already reported an efficient palladium-catalyzed cross-coupling reaction of benzo[*b*]furan with aryl bromides.[10]

In this paper, we describe a total synthesis of egonol (**1**) and (±)-machicendiol (**2**) from 5-bromo-7-methoxybenzo[*b*]furan (**4**) by application of our coupling reaction. The bromobenzo[b]furan (**4**) was prepared by cyclization of 4-bromo-2-formyl-6-methoxyphenylacetic acid (**3**)[11] according to the procedures for the synthesis of coumarones described by Burgstahler.[12]



Scheme 1. Synthetic Strategy

Introduction of alkyl substituents to 5-position of **4** was achieved by the treatment of a lithiated **4** with 3-bromopropyl tetrahydropyranyl ether.[13] The palladium-catalyzed cross-coupling reaction with 4-bromo-1,2-methylenedioxybenzene did not occur, when non-metallated **5** was used. When the zinc salt of **5**, prepared by treating **5** with ^{n}BuLi / $ZnCl_2$ at 0°C, was employed as a substrate, the coupling reaction proceeded to give the corresponding coupling product (**6**) in 19 % yield. The deprotection of the tetrahydropyranyl group in **6** gave egonol (**1**) in 75 % yield (Scheme 2).



i) Ac_2O, AcONa, AcOH, reflux ii) ^nBuLi, -78 °C then $Br(CH_2)_3OTHP$ iii) a) ^nBuLi, 0°C b) $ZnCl_2$ c) 4-Bromo-1,2-methylenedioxybenzene, $Pd(PPh_3)_4$, reflux iv) *p*-TsOH, MeOH

Scheme 2. Synthesis of Egonol (1)

(±)-Machicendiol (2) was also synthesized from 4 by the combination of the following reactions: introduction of an alcoholic function using 3-*t*butyldiphenylsilyloxypropan-1-al,[14] protection of the hydroxyl group of 7, palladium-catalyzed arylation of 8, and desilylation (Scheme 3).

Application of the synthetic strategy described above to other natural lignans with a benzo[*b*]furan skeleton are now in progress.

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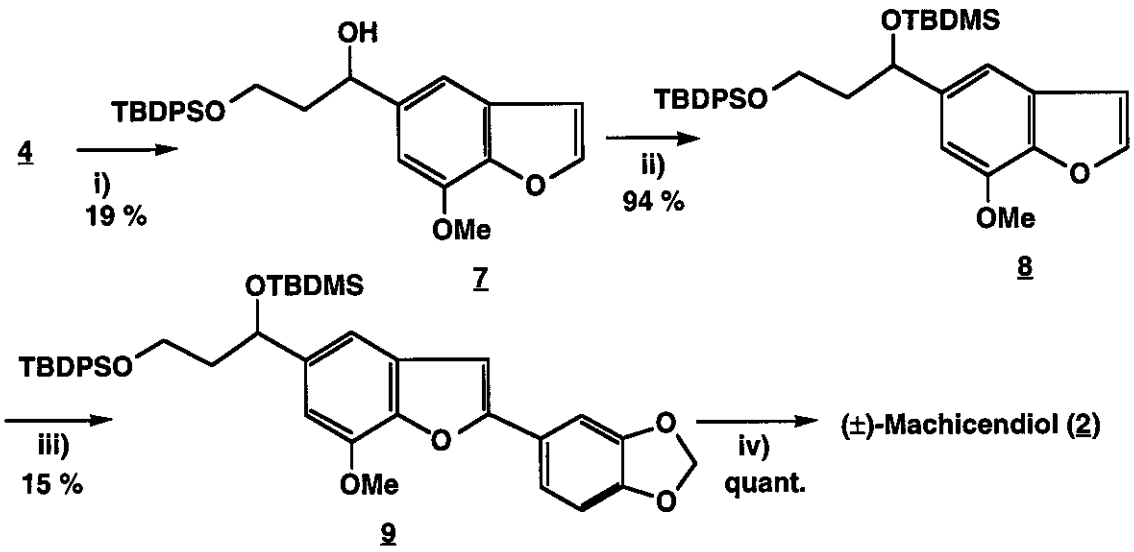

i) ^{n}BuLi, -78 °C then TBDPSO$(CH_2)_2$CHO ii) TBDMSCl, imidazole, DMF iii) a) ^{n}BuLi, 0°C b) $ZnCl_2$ c) 4-Bromo-1,2-methylenedioxybenzene, $Pd(PPh_3)_4$, reflux iv) $^{n}Bu_4NF$, THF

Scheme 3. Synthesis of (±)-Machicendiol (2)

EXPERIMENTAL

No correction was made to melting and boiling points. ^{1}H-Nmr spectral data were obtained with a Varian Gemini-300 (300 MHz) or a Brucker AM-400 (400 MHz) in $CDCl_3$ using TMS as an internal standard. Medium pressure liquid chromatography (MPLC) was conducted using a UVILOG 5III as a UV detector (Oyo Bunko Kiki Co., Ltd. Tokyo) and Kiesel gel 60 (Merck AG, Darmstadt) as the packing material. Other spectral data were obtained using the following instruments. Ir spectra: Japan Spectroscopic Co. A-100 (Nihon Bunko Kiki Co., Ltd.) ; Ms: Hitachi M-80B (Hitachi Co., Ltd.) or Auto spec spectrometer (Faisons Co., Ltd.).

Preparation of 4

A mixture of 3 (30.0 g, 104 mmol), Ac_2O (98 ml, 1.04 mol), anhydrous powdered AcONa (37.7 g, 468 mmol), and AcOH (95.0 ml, 1.66 mol) was refluxed for 8 h. After the reaction mixture was poured into ice-cooled H_2O (500 ml), the aqueous layer was extracted with Et_2O (300 ml x 3). The combined organic phase was washed with cold 5 % NaOH (300 ml x 4), H_2O (300 ml x 3), and sat. NaCl (300 ml x 3), successively. The Et_2O was removed *in vacuo* and the oily residue was distilled using a bulb to bulb distillation apparatus (180 -190 °C / 18 torr) to give 4 in 26 % yield.

5-Bromo-7-methoxybenzo[*b*]furan (4): colorless oil, bp 180-190 °C / 18 torr. Ms: m/z 226 (M^+). ^{1}H-Nmr (300 MHz): 4.00 (3H, s), 6.71 (1H, d, J = 2.1 Hz), 6.92 (1H, d, J = 1.7 Hz), 7.34 (1H, d, J = 1.7 Hz), 7.62 (1H, d, J = 2.1 Hz). *Anal.* Calcd for $C_9H_7O_2Br$: C, 47.61; H, 3.11. Found: C, 47.57; H, 3.13.

Alkylation of Compound 4: Synthesis of 5 and 7

1.6 M ^{n}BuLi in hexane (4 ml, 6.4 mmol) was added to a solution of 4 (0.66 g, 3.0 mmol) in dry THF (30 ml) at -78 °C. After the resulting mixture was stirred at this temperature for 15 min, 3-bromopropyl tetrahydropyranyl ether [13] (1.34 g, 6 mmol) or 3-^{t}butyldimetylsilyloxypropan-1-al [14] (1.87 g, 6 mmol) in dry THF (5 ml) was added dropwise. The mixture was stirred at -78°C for 1.5 h and at 0 °C for 30 min, and then poured into sat. NH_4Cl (50 ml). After the usual treatment, MPLC (hexane:Et_2O = 4:1) gave 5-alkylated benzo[*b*]furan (5 or 7).

7-Methoxy-5-(3-tetrahydropyranyloxypropyl)benzo[*b*]furan (5): Yield 26 %, colorless oil, bp 190-200 °C / 1 torr (bath temp.). Ms: m/z 290 (M^+). ^{1}H-Nmr (300 MHz): 1.51-2.02 (8H, m), 2.78 (2H, td, J = 7.8 and 3.0 Hz), 3.39-3.54 (2H, m), 3.77-3.89 (2H, m), 4.00 (3H, s), 4.40 (1H, dd, J = 4.4 and 2.9 Hz),6.66 (1H, d, J = 1.3 Hz), 6.68 (1H, d, J = 2.1 Hz), 7.01 (1H, d, J = 1.4 Hz), 7.59 (1H, d, J = 2.1 Hz). High-resolution ms Calcd for $C_{17}H_{22}O_4$: 290.151809. Found: 290.149528.

5-(1-Hydroxy-3-^{t}butyldiphenylsilyloxypropyl)-7-methoxybenzo[*b*]furan (7): Yield 19%, colorless oil. Ir (neat): 3450 cm^{-1}. CIms: m/z 461 (M^++1). ^{1}H-Nmr (300 MHz): 1.10 (9H, s), 1.91-2.15 (2H, m), 3.88

(2H, m), 4.01 (3H, s), 5.10 (1H, dd, J = 8.2 and 3.8 Hz), 6.74 (1H, d, J = 2.1 Hz), 6.89 (1H, d, J = 1.4 Hz), 7.19 (1H, d, J = 0.9 Hz), 7.35-7.47 (6H, m), 7.62 (1H, d, J = 2.1 Hz), 7.66-7.71 (4H, m). High-resolution ms Calcd for $C_{28}H_{32}O_4Si$: 460.206988. Found: 460.203930.

Silylation of 7

A DMF (5 ml) solution of **7** (0.246 g, 0.53 mmol), ^{t}butyldimethylsilyl chloride (0.121 g, 0.80 mmol), and imidazole (0.075 g, 1.1 mmol) was stirred overnight under Ar atmosphere. The mixture was poured into H_2O (30 ml) and the aqueous layer was extracted with Et_2O (30 ml x 3). The combined organic layer was washed with H_2O (20 ml x 2), and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give an oily residue, which was purified by MPLC (hexane:AcOEt= 4:1) to give **8** (0.287 g, 94 %) as a colorless oil.

5-(1-^{t}Butyldimethylsilyloxy-3-^{t}butyldiphenylsilyloxypropyl)-7-methoxybenzo[*b*]furan (**8**): Colorless oil. Ms: m/z 574 (M^+). ^{1}H-Nmr (300 MHz): 0.14 (3H, s), 0.16 (3H, s), 1.00 (9H, s), 1.21 (9H, s), 1.92-2.18 (2H, m), 3.71-3.79 (1H, m), 3.91-3.99 (1H, m), 4.11 (3H, s), 5.14 (1H, dd, J = 7.7 and 5.3 Hz), 6.85 (1H, d, J = 2.2 Hz), 6.96 (1H, d, J = 1.4 Hz), 7.19 (1H, d, J = 1.0 Hz), 7.45-7.56 (6H, m), 7.74-7.82 (5H, m). High-resolution ms Calcd for $C_{34}H_{46}O_4Si_2$: 574.293467. Found: 574.292038.

Arylation of 5 and 8

A THF (10 ml) solution of **5** (0.21 g, 0.72 mmol) was added to a THF (5 ml) solution of 1.6 M ^{n}BuLi in hexane (0.5 ml, 0.79 mmol) at 0 °C under Ar atmosphere and the mixture was stirred at 0 °C for 1 h. A 1.0 M solution of $ZnCl_2$ in Et_2O (0.8 ml, 0.8 mmol) was added dropwise and the mixture was stirred for further 20 min at this temperature. The resulting solution was added to a THF (5 ml) solution of 4-bromo-1,2-methylenedioxybenzene (0.1 ml, 0.86 mmol) and $Pd(PPh_3)_4$ (0.084 g, 0.072 mmol) at 0 °C through a double-chipped needle and the mixture was refluxed for 12 h under Ar atmosphere. After addition of sat. NH_4Cl (20 ml), the mixture was extracted with Et_2O (20 ml x 3), and the organic layer was dried over Na_2SO_4 and evaporated to give an oily residue, which was purified by MPLC (hexane:Et_2O= 9:1) to give

the corresponding coupling product (**6**) (0.057 g, 19 %) as an oil. By the same procedure, in which **8** (0.413 g, 0.72 mmol) was used in place of **5**, **9** (0.075 g, 15 %) was obtained as an oil.

7-Methoxy-2-(3,4-methylenedioxy)phenyl-5-(3-tetrahydropyranyloxypropyl)benzo[*b*]furan (**6**): Colorless oil. Ms: m/z 410 (M^+). ^{1}H-Nmr (400 MHz): 1.51-1.74 (6H, m), 1.97 (2H, t, J = 7.6 Hz), 2.77 (2H, m), 3.41-3.53 (2H, m), 3.77-3.91 (2H, m), 4.03 (3H, s), 4.59 (1H, dd, J = 4.4 and 2.9 Hz), 6.00 (2H, s), 6.64 (1H, d, J = 1.3 Hz), 6.78 (1H, s), 6.86 (1H, d, J = 8.1 Hz), 6.97 (1H, d, J = 1.4 Hz), 7.32 (1H, d, J = 1.6 Hz), 7.40 (1H, dd, J = 8.1 and 1.7 Hz). High-resolution ms Calcd for $C_{24}H_{26}O_6$: 410.172939. Found: 410.171669.

7-Methoxy-2-(3,4-methylenedioxyphenyl)-5-(1-*t*butyldimethylsilyloxy-3-*t*butyldiphenylsilyloxypropyl)-benzo[*b*]furan (**9**): Colorless oil. Ms: m/z 694 (M^+). ^{1}H-Nmr (300 MHz): 0.13 (3H, s), 0.16 (3H, s), 0.87 (9H, s), 1.26 (9H, s), 1.90-2.17 (2H, m), 3.71-3.79 (1H, m), 3.91-3.90 (1H, m), 4.12 (3H, s), 5.12 (1H, dd, J = 7.6 and 5.3 Hz), 6.14 (2H, s), 6.93 (1H, d, J = 1.2 Hz), 6.93 (1H, s), 7.00 (1H, d, J = 8.0 Hz), 7.14 (1H, s), 7.44-7.55 (8H, m), 7.76-7.82 (4H, m). High-resolution ms Calcd for $C_{41}H_{50}O_6Si_2$: 694.314597. Found: 694.316345.

Removal of the THP Group in 6: Synthesis of Egonol (1)

A mixture of **6** (0.057 g, 0.014 mmol), *p*-TsOH (0.027 g, 0.16 mmol), and MeOH (5 ml) was treated in a sonic bath at room temperature for 1 h. The solvent was evaporated under reduced pressure and sat. $NaHCO_3$ (10 ml) was added to the residue. The mixture was extracted with Et_2O (10 ml x 3) and the combined organic phase was washed with H_2O (15 ml x 3). The solvent was evaporated *in vacuo*, and the residue was purified by MPLC (hexane:AcOEt= 1:1) to give **1** (0.034 g, 75 %) as a colorless solid, whose physical data were identical with those reported previously.[2]

Desilylation of 9: Synthesis of (±)-Machicendiol (2)

A mixture of **9** (0.044 g, 0.063 mmol), 1.0 M ^{n}Bu$_4$NF in THF (0.5 ml, 0.5 mmol), and THF (5 ml) was stirred at room temperature overnight. Sat. NH_4Cl (5 ml) was added to the mixture and the aqueous layer

was extracted with Et_2O (10 ml x 3). The combined organic layer was washed with sat. NaCl (10 ml x 3) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by MPLC ($CHCl_3$:MeOH= 20:1) to give **2** (0.021 g, 100 %) as a coloress solid, whose physical data were identical with those reported previously.[3]

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