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Stereoselective Synthesis of the Neolignan, (+)-Dehydrodiconiferyl Alcohol

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A stereo controlled synthesis of the biologically active neolignan, (+)-dehydrodiconiferyl alcohol (1) was achieved. This synthetic method was also efficient for preparing its enantiomer and other derivatives with biological activity.

Key words: stereoselective synthesis; (+)-dehydrodiconiferyl alcohol; neolignan; Evans' diastereoselective aldol condensation

Dehydrodiconiferyl alcohol (**1**), which is thought to be a precursor of lignin,[1,2] and its derivatives have been reported to have such biological activities, as antioxidative[3] and cytokinin-like.[4,5] As **1** has two chiral carbons in its structure, it is necessary to stereoselectively prepare each enantiomer for examining such biological activities in detail. The absolute configuration of **1** was elucidated by Hirai *et al.*[6] in 1994: (+)-**1** has the (2*S*,3*R*) configuration and its (−)-isomer has (2*R*,3*S*) configuration. Rummakko *et al.*[7] have recently reported an enantioselective synthesis of **1** based on asymmetric bimolecular-radical coupling of Oppolzer's camphor sultam or Evans' chiral oxazolidinone derivatives of ferulic acid. Their method, however, required optical resolution of the product to obtain pure enantiomers since the optical purity of the product was not at a satisfactory level (up to 84% ee) for a detailed evaluation of the biological activity. This prompted us to develop a new and efficient synthetic method for preparing both enantiomers of **1**.

We describe in this paper the preparation of (+)-**1**, (2*S*,3*R*)-2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-5-[(*E*)-3-hydroxy-1-propenyl)-3-hydroxymethyl-7-methoxybenzofuran, *via* Evans' asymmetric aldol condensation using ferulic acid amide derived from D-phenylalanine.[8]

The bromo derivative of *o*-eugenol **3** was obtained by allylation of 4-bromoguaiacol **2**, which had been prepared from guaiacol and bromine in CH_2Cl_2,[9] and subsequent Claisen rearrangement.[10] After protecting the phenolic hydroxy group of **3** with benzyl bromide, resulting **4** was subjected to a double-bond cleavage reaction with a catalytic amount of osmium tetroxide and sodium periodate[11] and then to oxidation with sodium chlorite and hydrogen peroxide.[12] Phenylacetic acid **5** was thereby obtained in a 61% yield in 6 steps from guaiacol. After treating **5** with oxalyl chloride, the resulting acyl chloride was condensed with the lithio derivative of oxazolidinone, which had been generated by the reaction of (4*S*)-4-(phenylmethyl)-2-oxazolidinone[8] with butyllithium in THF at −78 °C, to give carboxyimide (+)-**6**.[13] The next Evans' diastereoselective aldol condensation step, first required the conditions for generating boron enolate from (+)-**6** and Bu_2BOTf[13,14] to be examined. It was found to be affected by temperature; although the enolate could not be generated below −25°C, it decomposed above −10°C. The reaction of the enolate from (+)-**6** with 4-benzyloxy-3-methoxybenzaldehyde gave 2,3-*syn*-aldol (+)-**7** in an 87% yield as a single product; in the NMR spectrum of the product, no signals other than those of protons derived from (+)-**7** were apparent. To this end, subjection of (+)-**7** to the action of lithium borohydride accomplished the reductive cleavage of the chiral oxazolidinone function, furnishing 1,3-diol (−)-**8** in a 95% yield.

Hydrogenation of (−)-**8** with palladium carbon in ethyl acetate directly produced cyclized product (+)-**9** in a 77% yield. In this reaction, the intermediary phenol produced by debenzylation of **8** itself might have acted as an acid catalyst for the subsequent dehydrative cyclization. The bromo group of **8** seemed to enhance the acidity of the *p*-phenolic group, because an analogous compound lacking the bromo group at 3′-C required the addition of a catalyst such as *p*-toluenesulfonic acid for cyclization. It should be noted that acid-catalyzed dehydrative cyclization solely gave thermodynamically preferable 2,3-*trans*-disubstituted (+)-**9** (δ 5.54 ppm,

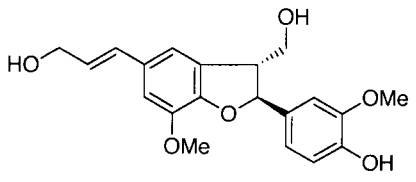

Fig. Structure of (+)-Dehydrodiconiferyl Alcohol **1**.

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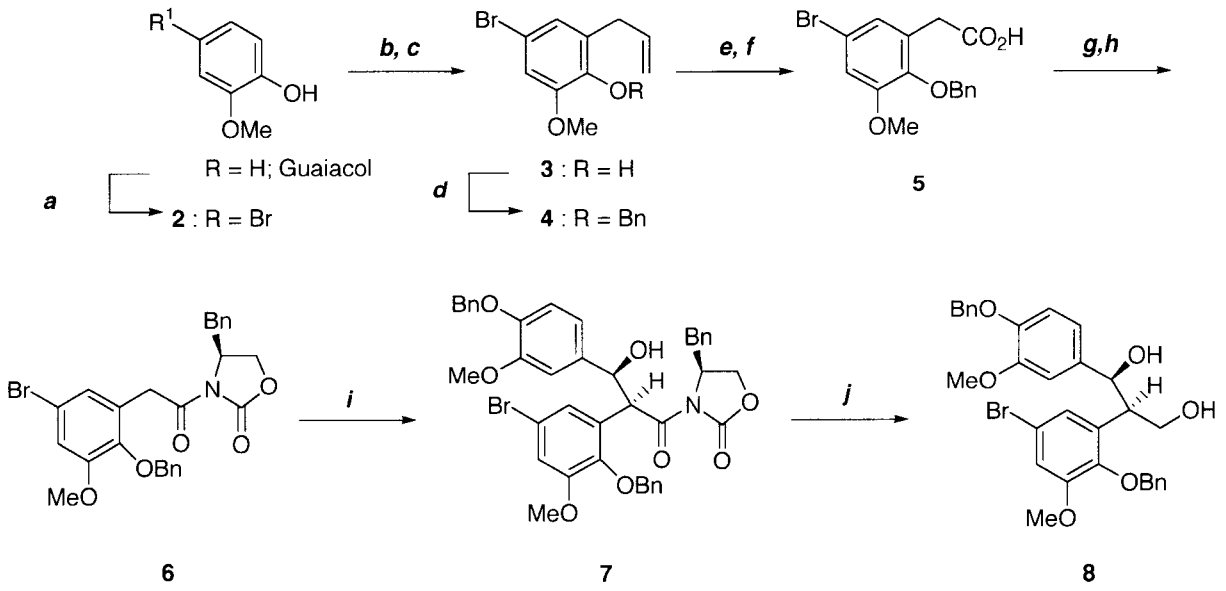
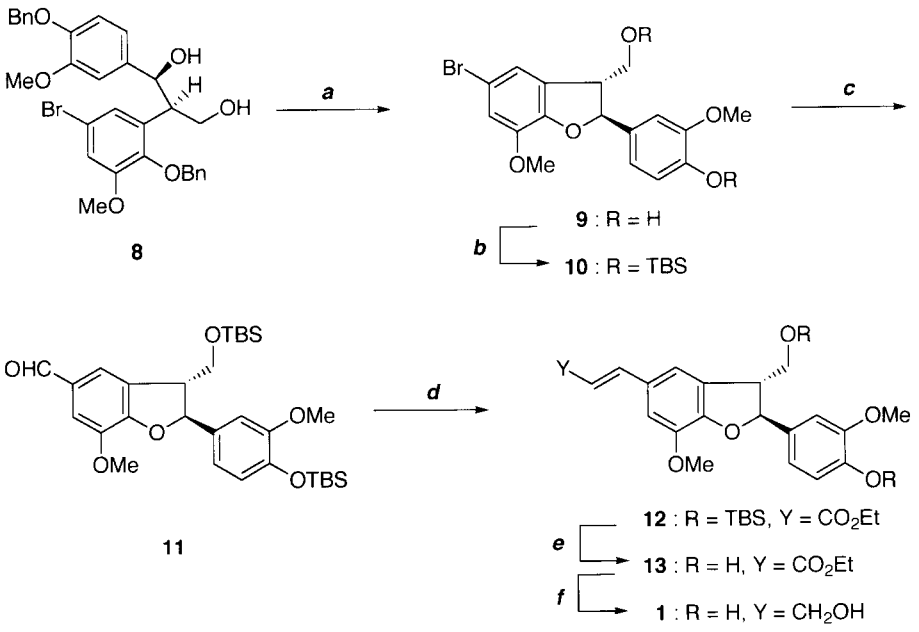


Scheme 1. Synthesis of Diol **8**.

Reagents and conditions: a) Br_2, CH_2Cl_2, −78°C to rt, 86%; b) allyl bromide, K_2CO_3, CH_3CN; c) 200°C, 94% from **2**; d) BnBr, K_2CO_3, CH_3CN, 81%; e) OsO_4, $NaIO_4$, acetone-H_2O; f) H_2O_2, $NaClO_2$, NaH_2PO_4, CH_3CN-H_2O, 87% from **4**; g) $(COCl)_2$, CH_2Cl_2; h) *n*-BuLi, THF −78°C, and then (4*R*)-4-(phenylmethyl)-2-oxazolidinone, THF, 95% from **5**; i) Bu_2BOTf, *iso*-Pr_2NEt, 4-benzyloxy-3-methoxybenzaldehyde, CH_2Cl_2, 86%; j) $LiBH_4$, Et_2O, 95%.



Scheme 2. Synthesis of (+)-Dehydrodiconiferyl Alcohol **1**.

Reagents and conditions: a) H_2, 10% Pd/C, EtOAc, 77%; b) TBS-Cl, imidazole, DMF, 97%; c) *tert*-BuLi, 1-formylpiperidine, Et_2O, −78°C. 91%; d) triethyl phosphonoacetate, *tert*-BuOK, 18-crown-6-ether, Et_2O, 81%; e) TBAF, THF, 94%; f) DIBAL-H, CH_2Cl_2, −78°C, 65%.

doublet, $J_{2,3}=7.3$ Hz for 2-*H*), irrespective of the stereochemistry at the benzylic carbon of **8**, although a compound without a bromo group on the aromatic ring of **8** required an acid treatment to give the cyclized product after deprotection. The bromo group of **8** seemed to enhance the acidity of the *p*-phenolic group, because (+)-**9** was produced directly by dehydrating cyclization without the addition of an acid.

After protecting the hydroxy groups with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) in the presence of imidazole, the bromo group on the aromatic ring was transformed to a formyl group by treating with *tert*-butyllithium in diethyl ether at −78°C and then with1-formylpiperidine,[15] giving (+)-5-formylcoumaran **11** in an 88% yield from **9**. Unsaturated ester (+)-**12** was obtained by the reaction of (+)-**11** with

triethyl phosphonoacetate in the presence of potassium *tert*-butoxide in diethyl ether. Finally, after removing the silyl group of (+)-**12** with tetrabutylammonium fluoride (TBAF) in THF, the synthesis of **1** was accomplished by reducing the ethoxycarbonyl moiety of (+)-**13** with diisobutylaluminium hydride (DIBAL-H) in CH_2Cl_2 in a 65% yield.

Product **1** obtained in this manner proved to be spectroscopically identical with the natural material by comparing its ^{1}H- and ^{13}C- NMR spectral data with those reported in the literature.[6] The optical rotation value for synthesized (+)-**1** was $[\alpha]_D^{25}$ +62.0° (*c* 1.42, acetone), this being in close agreement with the value of $[\alpha]_D^{25}$ +63.3° (*c* 2.1, acetone) that has been described by Hirai *et al.*[6] for (+)-**1** obtained by optical resolution. The enantiomeric excess of product (+)-**1** by this synthesis was evaluated to be >99.3% by an HPLC analysis which was performed with a Chiralcel OF column (4.6 i.d. × 250 mm, Daisel Chemical Industries).[6]

In summary, we accomplished the total synthesis of (+)-**1** from guaiacol with 16 steps in a 16% overall yield to high optical purity. This synthetic method could be suitable for preparing the (−)-isomer of **1** by using the chiral auxiliary oxazolidinone prepared from L-phenylalanine. It would also be useful for the synthesis of other natural products with various biological activities possessing the same phenylcoumaran framework as a component.

Experimental

All melting point (mp) and boiling point (bp) data are uncorrected. IR spectra were recorded with a Shimadzu IR-420 spectrometer, and ^{1}H- and ^{13}C-NMR spectra were measured with a JEOL JNM EX-400 spectrometer at 400 MHz and 100 MHz, respectively. The internal references were TMS (0.00 ppm for ^{1}H for a solution in $CDCl_3$), acetone (2.23 ppm for ^{1}H and 31.00 ppm for ^{13}C for a solution in acetone-d_6), and $CDCl_3$ (77.00 ppm for ^{13}C for a solution in $CDCl_3$). Optical rotation values were measured at 25°C with a Horiba SEPA-200 polarimeter. Silica gel 60 (100–210 μm) was obtained from Kanto Chemical Co. Inc. TLC and preparative TLC were respectively done by using Merck silica gel 60 F_{254} precoated plastic plates of 0.2 mm in thickness and Merck silica gel 60 F_{254} precoated glass plates of 0.5 mm in thickness.

2-Allyl-4-bromo-6-methoxyphenol (**3**). A solution of **2** (14.0 g, 69.0 mmol), allyl bromide (6.27 ml, 72.5 mmol), and anhydrous potassium carbonate (11.9 g, 86.2 mmol) in dry acetonitrile (80 ml) was refluxed for 12 h and then cooled. The mixture was filtered through a glass filter, and the resulting filtrate was concentrated under reduced pressure.

The crude product (17.3 g) was cautiously warmed at 190°C under N_2 for 6 h. After the mixture had cooled, the resulting oil was diluted with Et_2O, and the solution was extracted with 4N-NaOH (100 ml × 3 times). The combined alkaline extract was acidified with conc. HCl, and the mixture was extracted with Et_2O. The organic layer was successively washed with satd. aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. The residual oil was distilled under reduced pressure to give 15.7 g of **3** (94%) as a colorless oil, bp 150–152°C at 12 mm of Hg; NMR δ_H ($CDCl_3$): 3,36 (2H, d, J=6.3 Hz, Ar-CH_2-CH=CH_2), 3.87 (3H, s, Ar-OCH_3), 5.06 (1H, dd, J=5.9, 1.5 Hz, -CH=CH_2), 5.09 (1H, dd, J=16.6, 1.5 Hz, -CH=CH_2), 5.62 (1H, s, Ar-OH), 5.96 (1H, ddd, J = 16.6, 6.3, 5.9 Hz, -CH=CH_2), 6.85 (1H, d, J=2.4 Hz, Ar-H), 6.89 (1H, d, J=2.4 Hz, Ar-H); NMR δ_C ($CDCl_3$): 33.48, 56.24, 111.11, 112.10, 116.11, 124.85, 127.54, 135.75, 142.53, 146.94; IR ν_{max} (neat) cm^{-1}: 3517 (OH), 2940, 1769, 1613 (C=C), 1482, 1278, 1226, 1077, 914, 856. *Anal.* Found: C, 49.65; H, 4.63%. Calcd. for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56%.

1-Allyl-2-benzyloxy-5-bromo-3-methoxybenzene (**4**). A mixture of **3** (5.45 g, 22.4 mmol), benzyl bromide (2.26 ml, 22.4 mmol), and anhydrous potassium carbonate (3.56 g, 25.8 mmol) in dry acetonitrile (30 ml) was stood for 12 h at room temperature. The mixture was then filtered through a glass filter, and the resulting filtrate was concentrated under reduced pressure. The crude product was distilled under reduced pressure to give 6.05 g of **4** (81%) as a colorless oil, bp 160–162°C at 1 mm of Hg; NMR δ_H ($CDCl_3$): 3.29 (2H, d, J=6.8 Hz, Ar-CH_2-CH=CH_2), 3.84 (3H, s, Ar-OCH_3), 4.59 (2H, s, Ar-OCH_2Ar), 5.03 (1H, dd, J=8.1, 1.9 Hz, -CH=CH_2), 5.05 (1H, dd, J=13.2, 1.9 Hz, -CH=CH_2), 5.82 (1H, ddd, J=13.2, 8.1, 6.8 Hz, -CH=CH_2), 6.90 (1H, d, J=2.0 Hz, Ar-H), 6.92 (1H, d, J=2.0 Hz, Ar-H), 7.29–7.45 (5H, m, Ar-H); NMR δ_C ($CDCl_3$): 33.83, 55.97, 74.60, 111.71, 113.93, 116.30, 124.67, 127.93, 127.97, 128.15, 128.36, 125.93, 136.30, 144.86, 135.45; IR ν_{max} (neat) cm^{-1}: 2940, 1769, 1640 (C=C), 1586, 1577, 1474, 1440, 1281, 1214, 1077, 996, 919, 837, 739. *Anal.* Found: C, 60.88; H, 5.13%. Calcd. for $C_{17}H_{17}BrO_2$: C, 61.28; H, 5.14%.

(2-Benzyloxy-5-bromo-3-methoxyphenyl)acetic acid (**5**). To a solution of **4** (18.9 g, 55.5 mmol) in acetone (250 ml) was added 2% aq. osmium oxide (5 ml) and sodium periodate (25.4 g, 0.119 mol) in water (200 ml), and the mixture was vigorously stirred for 5 h. After removing the solvent under reduced pressure, the aqueous layer was extracted with Et_2O. The organic extract was washed with brine, dried (Na_2SO_4) and concentrated to give 18.8 g

of a crude aldehyde which was used for the next step without purification.

A solution of sodium chlorite (7.21 g, 63.8 mmol) in water (70 ml) was added dropwise during 2 h while stirring to a mixture of the crude aldehyde (*ca.* 55.5 mmol) in acetonitrile (50 ml), sodium dihydrogenphosphate (1.6 g) in water (5 ml), and 30% hydrogen peroxide (6.0 ml, 58.2 mmol), while the internal temperature was maintained at 10°C. After 1 h, a small amount of sodium sulfite was added, and the mixture was acidified with 2N-HCl before being extracted with Et_2O. After drying (Na_2SO_4) and concentrating the ethereal layer, the residue was recrystallized from toluene-petroleum ether (3:1) to give 17.0 g (87%) of acid **5** as white crystals, mp 117–118°C; NMR δ_H ($CDCl_3$): 3.52 (2H, s, Ar-CH_2-COOH), 3.88 (3H, s, Ar-OCH_3), 5.01 (2H, s, Ar-OCH_2Ar), 6.96 (1H, d, J=2.4 Hz, Ar-*H*), 7.00 (1H, d, J=2.4 Hz, Ar-*H*), 7.26–7.40 (5H, m, Ar-*H*); NMR δ_C ($CDCl_3$): 35.19, 56. 06, 74.78, 115.42, 116.26, 125.38, 128.17, 128.33, 128.46, 129.40, 137.14, 145.26, 153.33,176.12; IR ν_{max} ($CHCl_3$) cm^{-1}: 3288–2639 (OH), 3026, 1718 (C=O), 1581, 1483, 1466, 1414, 1278, 1226, 1214, 1090, 978, 842, 701. *Anal.* Found: C, 54.68; H, 4.38%. Calcd. for $C_{16}H_{15}BrO_4$: C, 54.72; H, 4.31%.

(4S)-4-Benzyl-3-[2-(2-benzyloxy-5-bromo-3-methoxyphenyl)acetyl]-2-oxazolidinone (**6**). To a solution of (4*S*)-4-benzyl-2-oxazolidinone (0.76 g, 4.27 mmol) in THF (8 ml) was added *n*-BuLi (3.00 ml, 1.5 M in hexane, 4.48 mmol) at −78°C under N_2. After 30 min, an acid chloride, which had been prepared from **5** (1.50 g, 4.27 mmol) and oxalyl chloride (0.37 ml, 4.27 mmol) in CH_2Cl_2 at 0°C to room temperature, in THF (5 ml) was added dropwise to the reaction mixture. After stirring for 1 h at −78°C, the mixture was worked up with 1 N HCl and extracted with Et_2O. The organic layer was successively washed with satd. aq. $NaHCO_3$ and brine. After drying (Na_2SO_4) and concentrating, the residue was chromatographed on silica gel (hexane/EtOAc, 3:1) to give 2.07 g of **6** (95%) as a colorless oil, $[\alpha]_D^{25}$ +39.5° (*c* 8.93, $CHCl_3$); NMR δ_H ($CDCl_3$): 2.46 (1H, dd, J=13.2, 10.3 Hz, Ar-CH_2-CH-N), 3.16 (1H, dd, J=13.3, 3.4 Hz, Ar-CH_2-CH-N), 3.88 (3H, s, Ar-OCH_3), 3.94 (1H, t, J=8.7 Hz, O-CH_2-CH-N), 4.03 (1H, dd, J=8.7, 2.6 Hz, O-CH_2-CH-N), 4.12 (1H, d, J=17.6 Hz, Ar-CH_2-CON), 4.23 (1H, d, J=17.6 Hz, Ar-CH_2-CON), 4.39 (1H, dddd, J=10.3, 8.7, 3.4, 2.6 Hz, Ar-CH$_2$-C*H*-N), 4.95 (1H, d, J=10.9 Hz, Ar-OCH_2Ar), 5.11 (1H, d, J=10.9 Hz, Ar-OCH_2Ar), 6.95 (1H, d, J=2.0 Hz, Ar-*H*), 7.03 (1H, d, J=2.0 Hz, Ar-*H*), 7.10 (1H, d, J=6.4 Hz, Ar-*H*), 7.23–7.41 (9H, m, Ar-*H*); NMR δ_C ($CDCl_3$): 37.21, 37.57, 55.28, 56.01, 66.22, 74.30, 115.41, 116.10, 125.74, 127.21, 127.85, 128.38, 128.87, 129.29, 130.06, 135.33, 137.80, 145.53, 153.21, 153.42, 170.44; IR ν_{max} (neat) cm^{-1}: 3029, 1782 (C=O), 1705 (C=O), 1483, 1388, 1364, 1268, 1090, 842, 696. *Anal.* Found: C, 60.16; H, 4.71; N, 2.66%. Calcd. for $C_{26}H_{24}BrNO_5$: C, 61.19; H, 4.74; N, 2.74%.

(4S)-4-Benzyl-3-[(2S,3S)-2-(2-benzyloxy-5-bromo-3-methoxyphenyl)-3-(4-benzyloxy-3-methoxyphenyl)-3-hydroxypropionyl]-2-oxazolidinone (**7**). Diisopropylethylamine (3.11 ml, 17.9 mmol) was added dropwise to a solution of acylated oxazolidinone **6** (6.15 g, 14.3 mmol) in CH_2Cl_2 (120 ml) at 0°C, before Bu_2BOTf in CH_2Cl_2 (15.7 ml, 1 M in CH_2Cl_2, 15.7 mmol) was added at −78°C. The reaction mixture was stirred for 30 min at −78°C, next allowed to warm to −15°C over 30 min and then stirred for 3 h at −15°C. The solution was recooled to −78°C, and a solution of 4-benzyloxy-3-methoxybenzaldehyde (3.46 g, 14.3 mmol) in CH_2Cl_2 (10 ml) was added dropwise to the reaction mixture. The reaction mixture was stirred for 20 min at −78°C, allowed to warm to −10°C over a period of 30 min and stirred for a further 1 h at −10°C. The reaction was quenched by adding MeOH (50 ml) and then a phosphate buffer (15 ml, pH 7). Hydrogen peroxide (15 ml, 30%) in MeOH (35 ml) was added dropwise to the solution, and the mixture was stirred and warmed to room temperature over 1 h. After the reaction mixture had been concentrated under reduced pressure, the residue was diluted with Et_2O, and the organic layer was washed with brine. The dried (Na_2SO_4) organic layer was concentrated, and the residue was chromatographed on silica gel (hexane/EtOAc, 3:1 to 2:1) to afford 8.26 g of aldol **7** (86%) as a light yellow syrup, $[\alpha]_D^{25}$ +8.0° (*c* 2.86, $CHCl_3$); NMR δ_H ($CDCl_3$): 2.34 (1H, dd, J=13.4, 10.0 Hz, Ar-CH_2-CH-N), 2.66 (1H, br, -O*H*), 3.01 (1H, dd, J=13.4, 3.1 Hz, Ar-CH_2-CH-N), 3.60 (1H, t, J=8.3 Hz, O-CH_2-CH-N), 3.75 (3H, s, Ar-OCH_3), 3.84 (1H, dd, J=8.3, 2.4 Hz, O-CH_2-CH-N), 3.88 (3H, s, Ar-OCH_3), 4.25 (1H, dddd, J=10.0, 8.3, 3.1, 2.4 Hz, Ar-CH$_2$-C*H*-N), 5.02 (1H, d, J=10.3 Hz, Ar-OCH_2Ar), 5.07 (1H, d, J=8.3 Hz, Ar-C*H*-CON), 5.08 (1H, d, J=10.3 Hz, Ar-OCH_2Ar), 5.10 (2H, s, Ar-OCH_2Ar), 6.00 (1H, d, J=8.3 Hz, Ar-C*H*-OH), 6.71 (1H, d, J=9.8 Hz, Ar-*H*), 6.74 (1H, d, J=8.3 Hz, Ar-*H*), 6.87 (1H, s, Ar-*H*), 7.04–7.72 (17H, m, Ar-*H*); NMR δ_C ($CDCl_3$): 37.43, 49.79, 55.40, 55.85, 56.09, 65.73, 70.89, 74.44, 76.11, 110.28, 113.49, 115.59, 116.55, 119.25, 123.79, 127.22, 127.27, 127.83, 127.91, 128.32, 128.48, 128.54, 128.85, 129.32, 130.94, 134.54, 135.22, 137.04, 137.66, 146.29, 147.78, 149.54, 152.48, 153.38, 171.36; IR ν_{max} ($CHCl_3$) cm^{-1}: 3603 (OH), 3033, 1791 (C=O), 1748 (C=O), 1705, 1521, 1385, 1221, 1189, 1081, 745. *Anal.* Found: C, 64.98; H, 5.09; N, 1.81%. Calcd. for

$C_{41}H_{38}BrNO_8$: C, 65.43; H, 5.09; N, 1.86%.

(1S,2R)-2-(2-Benzyloxy-5-bromo-3-methoxyphenyl)-1-(4-benzyloxy-3-methoxyphenyl)-1,3-propanediol (**8**). Lithium borohydride (0.13 g, 4.68 mmol) was added to a solution of aldol **7** (1.58 g, 2.12 mmol) in Et_2O (15 ml) at 0°C. The resulting solution was allowed to warm to room temperature and then stirred for 5 h, before being quenched with 0.5 M sodium potassium tartrate. The ethereal layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized from benzene to give 0.86 g of **8** as white crystals. The mother liquor was concentrated, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:2) to give 0.31 g of a second crop of **8**, the total yield being 95% from **7**, mp 88–89°C; $[\alpha]_D^{25}$ −48.8° (*c* 1.29, $CHCl_3$); NMR δ_H ($CDCl_3$): 1.60 (2H, br, -O*H*), 3.57 (1H, dd, *J*=11.0, 5.3 Hz, Ar-C*H*-CH_2-OH), 3.61 (1H, dd, *J*=11.0, 5.0 Hz, Ar-CH-C*H*$_2$-OH), 3.66 (1H, ddd, *J*=6.3, 5.3, 5.0 Hz, Ar-CH-CH_2-OH), 3.73 (3H, s, Ar-OC*H*$_3$), 3.85 (3H, s, Ar-OC*H*$_3$), 4.59 (1H, d, *J*=11.2 Hz, Ar-OC*H*$_2$Ar), 4.91 (1H, d, *J*=6.8 Hz, Ar-C*H*-OH), 4.92 (1H, d, *J*=11.2 Hz, Ar-OC*H*$_2$Ar), 5.11 (2H, s, Ar-OC*H*$_2$Ar), 6.65 (1H, dd, *J*=8.3, 2.0 Hz, Ar-*H*), 6.71 (1H, d, *J*=2.0 Hz, Ar-*H*), 6.77 (1H, d, *J*=7.8 Hz, Ar-*H*), 6.97 (1H, d, *J*=2.5 Hz, Ar-*H*), 7.19 (1H, d, *J*=2.0 Hz, Ar-*H*), 7.25–7.41 (10H, m, Ar-*H*); NMR δ_C ($CDCl_3$): 47.67, 55.79, 55.97, 63.97, 71.02, 74.60, 75.00, 77.20, 110.01, 113.65, 114.51, 116.65, 118.73, 123.65, 127.19, 127.80, 128.01, 128.44, 128.51, 135.09, 135.44, 137.05, 137.52, 145.99, 147.72, 149.62, 153.51; IR ν_{max} ($CHCl_3$) cm^{-1}: 3624 (OH), 3026, 2363, 1735, 1594, 1577, 1513, 1466 1269, 1218, 1141, 1030, 837. *Anal.* Found: C, 63.55; H, 5.37%. Calcd. for $C_{31}H_{31}BrO_6$: C, 64.25 H, 5.39%.

(2S,3R)-5-Bromo-2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxybenzo[b]furan (**9**). Diol **8** (1.00 g, 1.73 mmol) and 10% Pd on charcoal (0.1 g) in EtOAc (10 ml) were stirred under an atmosphere of hydrogen (1 atm) at room temperature for 45 min. The insoluble materials were filtered and then washed with EtOAc. The combined filtrate was washed with brine, before being dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (hexane/EtOAc, 1:1 to 1:2) to give 0.51 g of diol **9** (77%) as a colorless oil, $[\alpha]_D^{25}$ +24.0° (*c* 2.21, $CHCl_3$); NMR δ_H ($CDCl_3$): 1.83 (1H, br, -CH_2-O*H*), 3.61 (1H, ddd, *J*=7.3, 6.2, 2.1 Hz, Ar-CH-C*H*$_2$-OH), 3.84 (3H, s, Ar-OC*H*$_3$), 3.86 (3H, s, Ar-OC*H*$_3$), 3.87 (1H, dd, *J*=11.0, 2.1 Hz, Ar-CH-C*H*$_2$-OH), 3.92 (1H, dd, *J*=11.0, 6.2 Hz, Ar-CH-C*H*$_2$-OH), 5.54 (1H, d, *J*=7.3 Hz, Ar-C*H*-O-Ar), 5.72 (1H, br, Ar-O*H*), 6.87–6.97 (5H, m, Ar-*H*); NMR δ_C ($CDCl_3$): 53.33, 55.93, 56.17, 63.76, 88.25, 108.66, 108.69, 112.43, 114.36, 115.38, 119.36, 129.52, 132.46, 144.97, 145.74, 146.68, 147.52; IR ν_{max} ($CHCl_3$) cm^{-1}: 3560 (OH), 3026, 1735, 1620, 1517, 1487, 1466, 1273, 1218, 1038, 787, 747, 738. *Anal.* Found: C, 53.05; H, 4.50%. Calcd. for $C_{17}H_{17}BrO_5$: C, 53.56; H, 4.49%.

(2S,3R)-5-Bromo-2-(4-tert-butyldimethylsilyloxy-3-methoxyphenyl)-3-tert-butyldimethylsilyloxymethyl-2,3-dihydro-7-methoxybenzo[b]furan (**10**). A mixture of diol **9** (0.4 g, 1.05 mmol), *tert*-butyldimethylchlorosilane (0.35 g, 2.31 mmol), and imidazole (0.36 g, 5.29 mmol) in dry DMF (4 ml) was stood at 3°C for 24 h. The mixture was diluted with Et_2O and then successively washed with 4% aq. $CuSO_4$, satd. aq. $NaHCO_3$ and brine, before the organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (hexane/EtOAc, 9:1) to give 0.62 g of **10** (97%) as a colorless oil, $[\alpha]_D^{25}$ +20.4° (*c* 1.32, $CHCl_3$); NMR δ_H ($CDCl_3$): 0.03 (3H, s, -Si-C*H*$_3$), 0.04 (3H, s, -Si-C*H*$_3$), 0.13 (6H, s, -Si-C*H*$_3$), 0.88 (9H, s, -Si-C-C*H*$_3$), 0.98 (9H, s, -Si-C-C*H*$_3$), 3.60 (1H, ddd, *J*=7.5, 5.9, 5.8 Hz, Ar-C*H*-CH_2-O-), 3.77 (3H, s, Ar-OC*H*$_3$), 3.78 (1H, dd, *J*=9.2, 7.5 Hz, Ar-CH-C*H*$_2$-O-), 3.86 (1H, dd, *J*=9.2, 5.8 Hz, Ar-CHC*H*$_2$-O-), 3.88 (3H, s, Ar-OC*H*$_3$), 5.52 (1H, d, *J*=5.9 Hz, Ar-C*H*-O-Ar), 6.79–6.96 (5H, m, Ar-*H*); NMR δ_C ($CDCl_3$): −5.49, −5.41, −4.66, 18.22, 18.42, 25.71, 25.83, 53.77, 55.49, 56.20, 65.19, 88.28, 109.94, 112.07, 115.16, 116.97, 118.43, 120.02, 120.69, 120.78, 130.09, 134.56, 144.96, 151.01; IR ν_{max} ($CHCl_3$) cm^{-1}: 2962, 1739, 1521, 1496, 1478, 1470, 1286, 1261, 1110, 919, 846. *Anal.* Found: C, 58.04; H, 7.89%. Calcd. for $C_{29}H_{45}BrO_5Si_2$: C, 57.12; H, 7.44%.

(2S,3R)-2-(4-tert-Butyldimethylsilyloxy-3-methoxyphenyl)-3-tert-butyldimethylsilyloxymethyl-2,3-dihydro-5-formyl-7-methoxybenzo[b]furan (**11**). A solution of bromide **10** (0.70 g, 1.18 mmol) in dry Et_2O (2 ml) was added dropwise to a solution of *tert*-BuLi (2.35 mmol) in Et_2O (8 ml) at −78°C under N_2. After 30 min, 1-formylpiperidine (0.5 ml) in Et_2O (2 ml) was added dropwise to the reaction mixture. After stirring for 10 min at −78°C, the mixture was worked up with water and extracted with Et_2O. After washing with brine, drying (Na_2SO_4) and concentrating, the residue was chromatographed on silica gel (hexane/EtOAc, 4:1) to give 0.60 g of aldehyde **11** (91%) as a colorless oil, $[\alpha]_D^{25}$ +51.5° (*c* 1.59, $CHCl_3$); NMR δ_H ($CDCl_3$): 0.04 (3H, -Si-C*H*$_3$), 0.06 (3H, s, -Si-C*H*$_3$), 0.14 (6H, s, -Si-C*H*$_3$), 0.80 (9H, s, -Si-C-C*H*$_3$), 0.98 (9H, s, -Si-C-C*H*$_3$), 3.68 (1H, ddd, *J*=7.3, 5.9, 5.6 Hz, Ar-C*H*-CH_2-O-), 3.77 (3H, s, Ar-OC*H*$_3$), 3.84 (1H, dd, *J*=9.9, 7.3 Hz, Ar-CH-C*H*$_2$-O-), 3.94 (1H, dd, *J*=9.9, 5.6 Hz,

Ar-CH-CH_2-O-), 3.96 (3H, s, Ar-OCH_3), 5.66 (1H, d, J=5.9 Hz, Ar-C*H*-O-Ar), 6.81-6.85 (3H, m, Ar-*H*), 7.39 (2H, d, J=4.4 Hz, Ar-*H*), 9.82 (1H, s, Ar-C*H*O); NMR δ_C ($CDCl_3$): −5.61, −5.58, −5.52, −4.77, 18.08, 18.31, 25.57, 25.68, 52.88, 55.39, 55.96, 65.00, 89.47, 109.86, 111.64, 118.40, 120.76, 121.43, 129.01, 131.08, 133.87, 144.85, 145.09, 150.97, 153.93, 190.38; IR ν_{max} ($CHCl_3$) cm^{-1}: 2940, 1692 (C=O), 1598, 1521, 1495, 1470, 1332, 1141, 846. *Anal.* Found: C, 65.18; H, 8.73%. Calcd. for $C_{30}H_{46}O_6Si_2$: C, 64.48 H, 8.30%.

(2S,3R) - 2 - (4 - tert - Butyldimethylsilyloxy - 3 - methoxyphenyl)-3-tert-butyldimethylsilyloxymethyl-2,3 - dihydro - 5E - (3 - ethoxy - 3 - oxo - 1 - propenyl) - 7-methoxybenzo[b]furan (**12**). Potassium *tert*-butoxide (0.15 g, 1.34 mmol) was added to a solution of triethyl phosphonoacetate (0.27 ml, 1.43 mmol) in dry THF (4 ml) at 0°C. After stirring at room temperature for 30 min, a solution of aldehyde **11** (0.4 g, 0.716 mmol) and a catalytic amount of dibenzo-18-crown-6 (*ca.*10 mg) in dry THF (4 ml) was added to the reaction mixture at 0°C. After stirring for 30 min at room temperature, the mixture was poured into 2 N HCl (10 ml) while vigorously stirring. The aqueous layer was extracted with EtOAc, and the organic layer was successively washed with satd. aq. $NaHCO_3$ and brine. After drying (Na_2SO_4) and concentrating, the residue was chromatographed on silica gel (hexane/EtOAc, 9:1) to give 0.36 g of unsaturated ester **12** (81%) as a colorless oil, $[\alpha]_D^{25}$ +60.7° (*c* 1.41, $CHCl_3$); NMR δ_H ($CDCl_3$): 0.03 (3H, s, -Si-CH_3), 0.05 (3H, s, -S-CH_3), 0.13 (6H, s, -Si-CH_3), 0.88 (9H, s, -Si-C-CH_3), 0.98 (9H, s, -Si-C-CH_3), 1.33 (3H, t, J=6.8 Hz, -O-CH$_2$-CH_3), 3.63 (1H, ddd, J=10.3, 7.8, 2.9 Hz, Ar-C*H*-CH$_2$-O-), 3.78 (3H, s, Ar-OCH_3), 3.81 (1H, dd, J=10.3, 7.8 Hz, Ar-CH-CH_2-O-), 3.92 (3H, s, Ar-OCH_3), 3.92 (1H, dd, J=10.3, 2.9 Hz, Ar-CH-CH_2-O-), 4.25 (2H, q, J=6.8 Hz, O-CH_2-CH$_3$), 5.59 (1H, d, J=6.3 Hz, Ar-C*H*-O-Ar), 6.28 (1H, d, J=15.8 Hz, -CO-C*H*=CH-Ar), 6.79-6.86 (3H, m, Ar-*H*), 6.99 (1H, s, Ar-*H*), 7.05 (1H, d, J=1.5 Hz, Ar-*H*), 7.62 (1H, d, J=15.8 Hz, -CO-CH=C*H*-Ar); NMR δ_C ($CDCl_3$): −5.52, −5.42, −4.70, 18.18, 18.38, 25.66, 25.78, 53.45, 55.46, 55.98, 60.25, 65.20, 88.81, 111.65, 115.35, 117.76, 118.43, 120.75, 128.17, 129.14, 134.50, 144.43, 144.78, 144.96, 150.49, 150.98, 167.27; IR ν_{max} ($CHCl_3$) cm^{-1}: 2961, 1696 (C=O), 1598 (C=C), 1521, 1504, 1470, 1282, 1149, 850. *Anal.* Found: C, 65.25; H, 8.55%. Calcd. for $C_{34}H_{52}O_7Si_2$: C, 64.93; H, 8.33%.

(2S,3R) - 5 - [(E) - 2 - Ethoxycarbonylvinyl] - 2,3 - dihydro - 2 - (4 - hydroxy - 3 - methoxyphenyl) - 3 - hydroxymethyl - 7 - methoxybenzo[b]furan (**13**). To a solution of silyl ether **12** (0.40 g, 0.636 mmol) in THF (5 ml) was added tetrabutylammonium fluoride (1.50 ml, 1.0 M in THF, 1.50 mmol) at 0°C, and the mixture was stirred for 1 h at 0°C. The reaction mixture was diluted with water (10 ml) and extracted with EtOAc. The organic layer was successively washed with satd. aq. $NaHCO_3$ and brine. The dried (Na_2SO_4) organic layer was concentrated under reduced pressure, and the residue was recrystallized from toluene to give 0.18 g of diol **13** as white crystals. The mother liquor was concentrated, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give 0.06 g of a second crop of **13**, the total yield being 94% from **12**, mp 156-157°C; $[\alpha]_D^{25}$ +115.6° (*c* 1.52, $CHCl_3$); NMR δ_H ($CDCl_3$): 1.26 (3H, t, J=7.3 Hz, -O-CH$_2$-CH_3), 1.78 (1H, br, -CH$_2$-O*H*), 3.64 (1H, ddd, J=11.2, 5.9, 2.0 Hz, Ar-C*H*-CH$_2$-OH), 3.86 (3H, s, Ar-OCH_3), 3.88 (1H, dd, J=11.2, 2.0 Hz, Ar-CH-CH_2-OH), 3.91 (3H, s, Ar-OCH_3), 3.97 (1H, dd, J=11.2, 5.9 Hz, Ar-CH-CH_2-OH), 4.25 (2H, q, J=7.3 Hz, O-CH_2-CH$_3$), 5.61 (1H, d, J=7.3 Hz, Ar-C*H*-O-Ar), 5.71 (1H, br, Ar-O*H*), 6.30 (1H, d, J=15.8 Hz, -CO-C*H*=CH-Ar), 6.88-6.91 (3H, m, Ar-*H*), 7.00 (1H, s, Ar-*H*), 7.06 (1H, s, Ar-*H*), 7.63 (1H, d, J=15.8 Hz, -CO-CH=C*H*-Ar); NMR δ_C ($CDCl_3$): 14.32, 32.16, 55.97, 56.00, 60.38, 63.92, 88.70, 108.74, 111.79, 114.40, 115.66, 117.27, 119.41, 128.54, 128.66, 132.47, 144.61, 144.65, 145.84, 146.71, 150.55, 167.30; IR ν_{max} ($CHCl_3$) cm^{-1}: 3620 (O-H), 3012, 1701 (C=O), 1610 (C=C), 1521, 1504, 1470, 1282, 1149, 850. *Anal.* Found: C, 65.98; H, 6.04%. Calcd. for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04%.

(2S,3R) - 2,3 - Dihydro - 2 - (4 - hydroxy - 3 - methoxyphenyl) - 5 - [(E) - 3 - hydroxy - 1 - propenyl] - 3 - hydroxymethyl - 7 - methoxybenzo[b]furan (**1**, dehydrodiconiferyl alcohol). To a solution of unsaturated ester **13** (0.24 g, 0.599 mmol) in CH_2Cl_2 (3 ml) was added diisobutylaluminium hydride (3.00 ml, 1 M in toluene, 3.00 mmol) at −78°C, and the mixture was stirred for 2 h at −78°C. The reaction mixture was quenched with MeOH (0.5 ml), and the solvent was removed under reduced pressure. The residue was added to 2N HCl (10 ml), and then extracted with EtOAc. The organic extract was successively washed with satd. aq. $NaHCO_3$ and brine. After drying (Na_2SO_4) and concentration, the residue was chromatographed on silica gel (hexane/EtOAc, 1:2 to 100% EtOAc) to give 0.14 g of **1** (65%) as a colorless oil, $[\alpha]_D^{25}$ +62.0° (*c* 1.42, acetone); NMR δ_H (acetone-d_6): 2.85 (2H, br, -CH$_2$-O*H*), 3.53 (1H, ddd, J=6.8, 6.3, 5.5 Hz, Ar-C*H*-CH$_2$-OH), 3.82 (3H, s, Ar-OCH_3), 3.84 (1H, dd, J=11.9, 6.3Hz, Ar-CH-CH_2-OH), 3.87 (3H, s, Ar-OCH_3), 3.89 (1H, dd, J=11.9, 5.5 Hz, Ar-CH-CH_2-OH), 4.20 (2H, dt, J=5.2, 1.3 Hz, -CH=CH-CH_2-), 5.56 (1H, d, J=6.8 Hz, Ar-C*H*-O-Ar), 6.24 (1H, dt, J=16.1, 5.2 Hz, Ar-CH=C*H*-CH$_2$-), 6.53 (1H, d, J=

16.1 Hz, Ar-C*H*=CH-CH_2-), 6.80 (1H, d, J=8.3 Hz, Ar-*H*), 6.88 (1H, dd, J=8.3, 2.0 Hz, Ar-*H*), 6.95 (1H, s, Ar-*H*), 6.98 (1H, s, Ar-*H*), 7.04 (1H, d, J=2.0, Ar-*H*), 7.56 (1H, br, Ar-O*H*); NMR δ_C (acetone-d_6): 55.25, 56.75, 56.87, 63.90, 65.10, 89.01, 110.94, 112.19, 116.14, 116.56, 120.07, 128.82, 130.88, 131.02, 132.39, 34.86, 145.63, 147.76, 148.83.

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