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A facile enantioselective approach to neolignans

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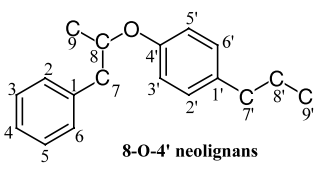
Abstract—An enantioselective and stereoselective synthesis of 8-*O*-4′ neolignans is reported in which a natural 8-*O*-4′ norneolignan is enantioselectively synthesized as a single *erythro* isomer. Furthermore the route has been adapted to allow the enantioselective synthesis of 1,4-benzodioxane neolignans.

1. Introduction

8-*O*-4′ Neolignans have a wide range of biological effects including anti-cercaria penetration, inhibition of the growth of silkworm larvae, antileukemic and antifungal activity, anti-leishmanial activity and so on.[1,2] Moreover, this type of neolignan is structurally analogous to the major interunit linkage of lignin, in which about 40% of the arylpropane units are 8-*O*-4′ linked. Some 8-*O*-4′ neolignans have often been used as models for studying reactions of lignin.[3] For these reasons, this type of natural product is of great synthetic and biological interest and several efficient racemic syntheses of 8-*O*-4′ neolignans have been reported.[4–6] However, most of the reported methods are racemic syntheses and lead to mixtures of *erythro* and *threo* isomers. An asymmetric synthesis of 8-*O*-4′ neolignans was reported in 1996, but equal amounts of two diastereoisomers were obtained.[7] Thus, stereoselectivity and enantioselectivity remain unsolved problems in the synthesis of 8-*O*-4′ neolignans.



8-O-4' neolignans

We report herein a novel asymmetric synthetic approach to *erythro* 8-*O*-4′ neolignans. Using our approach a natural 8-*O*-4′ neolignan **1**,[8] which was isolated as a mixture of *erythro* and *threo* isomers from *Larix leptolepis*, was synthesized enantioselectively. As shown in Scheme 1, the synthesis of (7*S*,8*S*)-**2** was described in our previous paper.[9] The benzylidene protection of (7*S*,8*S*)-**2** was effected in CH_2Cl_2 with benzaldehyde dimethylacetal using a catalytic amount of *p*-TSA to afford a mixture of the 1,3-benzylidene (7*S*,8*S*)-**3** and the 1,2-benzylidene (7*S*,8*S*)-**4** in a 4:1 ratio, which could not be separated by silica gel column chromatography. Fortunately we found (7*S*,8*S*)-**4** in the mixture was completely converted to the corresponding ester (7*S*,8*S*)-**5** using sterically hindered acid chlorides such as *p*-TsCl or PhCOCl while (7*S*,8*S*)-**3** in the mixture remained unreacted. (7*S*,8*S*)-**3** and (7*S*,8*S*)-**5** were readily separated by column chromatography over silica gel, and pure (7*S*,8*S*)-**3** was obtained in 67% yield. Mitsunobu reaction[10] between (7*S*,8*S*)-**3** and vanillin gave the characterized ether (7*S*,8*R*)-**6** in 70% yield. In this reaction the absolute configuration at C-8 in **3** was inverted completely by the S_N2-type nucleophilic displacement with vanillin.

Cleavage of the benzylidene group from (7*S*,8*R*)-**6** with 0.01N HCl in MeOH afforded the diol (7*S*,8*R*)-**7**. The benzyl group of (7*S*,8*R*)-**7** was removed by hydrogenolysis under atmospheric pressure of hydrogen in the presence of 5% Pd/C to afford (7*S*,8*R*)-**1** in 89% yield.

1,4-Benzodioxane neolignans are another important class of lignans which show cytotoxic and hepatoprotective activities.[11,12] The structures of 1,4-benzodioxane neolignans are analogous to those of 8-*O*-4′ neolignans,

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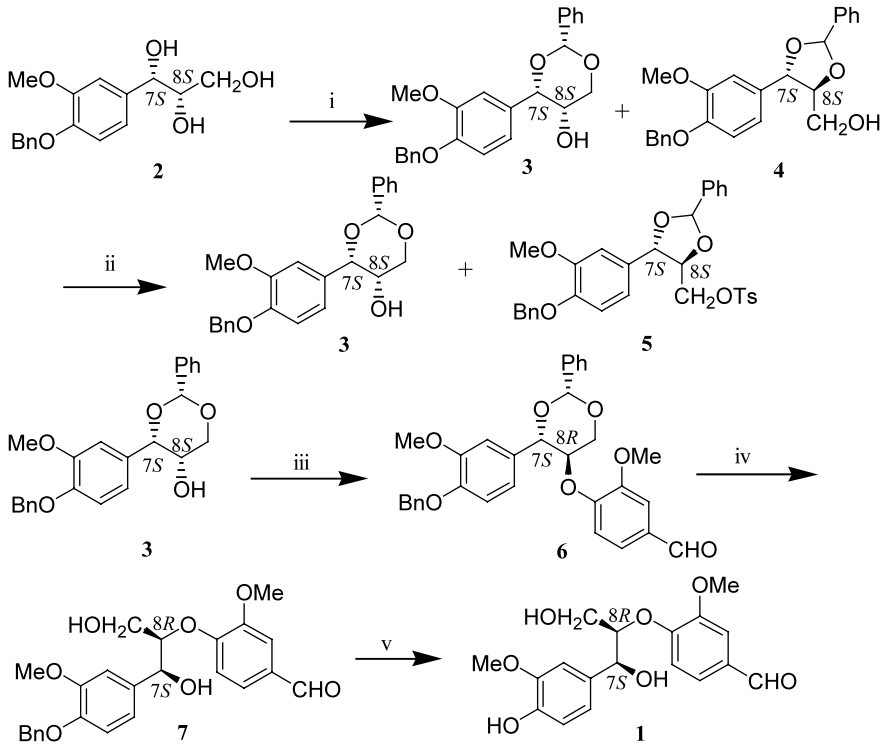
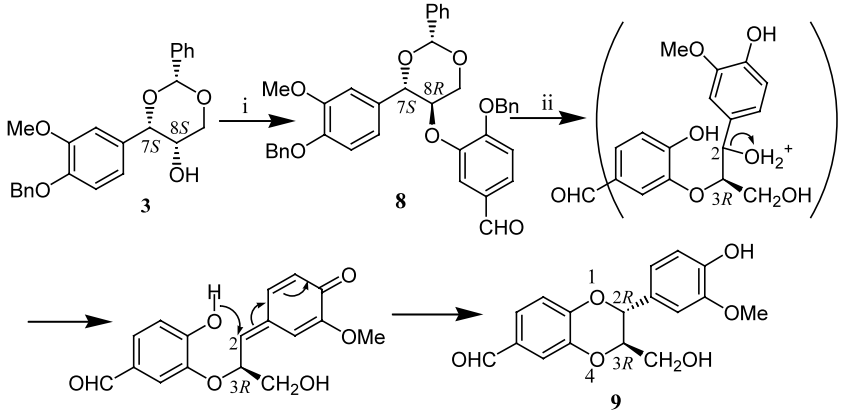


Scheme 1. *Reagents and conditions*: (i) $PhCH(OMe)_2$, TsOH, CH_2Cl_2, rt, 2.5 h; (ii) TsCl, Et_3N, CH_2Cl_2, rt, 8 h (v and vi 67%); (iii) vanillin, Ph_3P, DEAD, THF, ArOH, reflux, 24 h, 70%; (iv) HCl, MeOH, rt, 8 h, 93%; (v) 5% Pd/C, H_2, MeOH, rt, 2 h, 89%.

we completed the following investigations (Scheme 2). Mitsunobu reaction of the key intermediate (7*S*,8*S*)-**3** with 4-benzyloxy-3-hydroxybenzaldehyde in place of vanillin then provided the aryl alkyl ether (7*S*,8*R*)-**8** in 41% yield. However, because the 4-Obn group in 4-benzyloxy-3-hydroxybenzaldehyde is much bigger than the 3-OMe group in vanillin, the Mitsunobu reaction of 4-benzyloxy-3-hydroxybenzaldehyde with the rigid 1,3-benzylidene (7*S*,8*S*)-**3** was retarded by steric factors and the yield of (7*S*,8*R*)-**8** was drastically reduced in comparison with that of (7*S*,8*R*)-**6**. Finally, deprotection and cyclization of (7*S*,8*R*)-**8** upon heating in acetic acid in the presence of 36% HCl, presumably via a quinone methide intermediate,[13] afforded the 1,4-benzodioxane (2*R*,3*R*)-**9** in 53% yield. In the ^1H NMR spectrum of (2*R*,3*R*)-**9** H-2 resonated as a doublet signal at δ 5.12 with a coupling constant ($J=8.1$ Hz) typical of the *trans*-configuration and *threo*-isomer. Therefore in the cyclization to form (2*R*,3*R*)-**7**, the *R* absolute configuration at C-2 must be induced by the intact 3*R*-configuration. This is a new approach to the asymmetric synthesis of 1,4-benzodioxane neolignans. The 1,4-dioxane **9** has been used as the key intermediate in the synthesis of several important 1,4-benzodioxan lignans such as isosilybin and hydnocarpin.[14,15]

In conclusion, we have demonstrated a highly enantioselective synthesis of *erythro*-8-*O*-4′ neolignans, and



Scheme 2. *Reagents and conditions*: (i) 4-benzyloxy-3-hydroxybenzaldhyde, Ph_3P, DEAD, PhH, Ar, 70°C, 24 h, 41%; (ii) AcOH:36% HCl (1:1), 65°C, 1 h, 53%.

we have successfully adapted the route to allow the asymmetric synthesis of 1,4-benzodioxane neolignans. The route presented herein can thus be applied to the asymmetric syntheses of both neolignans.

2. Experimental

Melting point was measured on a Kofler apparatus and was uncorrected. MS were performed on a HP 5988A GC/MS instrument and a ZAB-HS instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-80 FT NMR spectrometer, a Bruker AM-200 FT NMR spectrometer and a Bruker AM-400 FT NMR spectrometer in $CDCl_3$. Chemical shifts are referred to TMS on the 'δ' scale. Chiral analysis was performed on Varian Dynamax SD-300 using Chiralcel column CDMPC (150×4.6 mm D) with hexane/isopropyl alcohol as eluent. IR spectra were recorded on a Nicolet FT-170 SX spectrometer. Microanalyses were performed on a MOD-1106 elemental analyzer. Chromatography was employed to purify the crude reaction mixture using 200–300 mesh silica gel.

2.1. (1*S*,2*S*)-1,3-*O*-Benzylidene-1-(4-benzyloxy-3-methoxyphenyl)-1,2,3-propanetriol, 3

To a solution of (1*S*,2*S*)-**2** (1.20 g, 3.9 mmol) in CH_2Cl_2 (100 mL) was added *p*-toluenesulfonic acid (20 mg) and benzaldehyde dimethylacetal (0.62 mL, 4.1 mmol), the mixture was stirred at rt for 2 h. The mixture was neutralized with sat. aq $NaHCO_3$ and the organic phase was separated, washed with H_2O, dried with Na_2SO_4 and concentrated. Column chromatography using petroleum ether:ethyl acetate (6:1, v/v) furnished a mixture of (1*S*,2*S*)-**3** and (1*S*,2*S*)-**4** (1.30 g, 4:1).

To the solution of (1*S*,2*S*)-**3** and (1*S*,2*S*)-**4** (1.30 g, 3.3 mmol) in CH_2Cl_2 (50 mL) containing Et_3N (1 mL) was added *p*-toluenesulfonyl chloride (0.63 g, 3.3 mmol) and the mixture was stirred for 8 h at rt. The excess *p*-toluenesulfonyl chloride was destroyed by the addition of MeOH (1 mL) and the solvent was concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated; chromatography over silica gel eluted with petroleum ether:ethyl acetate (6:1, v/v) gave pure (1*S*,2*S*)-**3** (1.03 g, 67%). Colorless gum, $[\alpha]_D^{25}$ +55 (*c* 0.7, acetone); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.79 (br.s, 1H, 8-H), 3.90 (s, 3H, -OMe), 4.23 (d, 11.9 Hz, 1H, 9-H), 4.36 (dd, 11.9, 1.8 Hz, 1H, 9-H), 5.02 (s, 1H, 7-H), 5.16 (s, 2H, $PhCH_2O$-), 5.77 (s, 1H, PhCH-), 6.8–7.7 (m, 13H, Ar-H); EI-MS: *m*/*z* 392[M]$^+$(0.7), 243 (9), 107 (15), 91 (100), 77 (10), 65 (10), 57 (11), 43 (18). Anal. calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16; found C, 73.47; H, 6.11%.

2.2. (1*S*,2*R*)-1,3-*O*-Benzylidene-1-(4-benzyloxy-3-methoxyphenyl)-2-(4-formyl-2-methoxyphenoxy)propane-1,3-diol, 6

A mixture of (1*S*,2*S*)-**3** (0.40 g, 1.0 mmol), vanillin (0.23 g, 1.5 mmol), triphenylphosphine (0.40 g, 1.5 mmol) and diethylazodicarboxylate (0.24 mL, 1.5 mmol) was heated to reflux in anhydrous THF (12 mL) for 24 h under argon. The mixture was concentrated under reduced pressure, and the residue was chromatographed using petroleum ether:ethyl acetate (6:1) gave (1*S*,2*R*)-**6** (0.37 g, 70%) as a colorless gum, $[\alpha]_D^{25}$ −51 (*c* 0.6, acetone); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.83 (s, 3H, -OMe), 3.85 (s, 3H, -OMe), 4.28–4.68 (m, 3H, 8-H, 9-H), 4.91 (d, 1H, 9.0 Hz, 7-H), 5.11 (s, 2H, $PhCH_2O$-), 5.77 (s, 1H, PhCH-), 6.6–7.7 (m, 16H, Ar-H), 9.79 (s, 1H, CHO); EI-MS: *m*/*z* 526[M]$^+$ (0.8), 242 (10), 178 (10), 133 (8), 105 (12), 91 (100), 77 (9). Anal. calcd for $C_{32}H_{30}O_7$: C, 72.99; H, 5.74; found C, 73.04; H, 5.73%.

2.3. (1*S*,2*R*)-1-(4-Benzyloxy-3-methoxyphenyl)-2-(4-formyl-2-methoxyphenoxy)propane-1,3-diol, 7

To a solution of HCl in MeOH (0.01N, 40 mL) was added (1*S*,2*R*)-**6** (0.2 g, 0.38 mmol), and the mixture was stirred at rt for 8 h. The solution was neutralized with sat. aq $NaHCO_3$. Subsequently the solvent was concentrated in vacuo and the residue was taken up in AcOEt. The organic phase was separated, washed with H_2O, dried with Na_2SO_4 and concentrated. Column chromatography using petroleum ether:ethyl acetate (3:1, v/v) furnished (1*S*,2*R*)-**7** (0.15 g, 93%) as a colorless gum, $[\alpha]_D^{25}$ −36 (*c* 0.4, acetone); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.75–4.10 (m, 2H, 9-H), 3.88, 3.91 (2×s, 6H, OMe), 4.42 (m, 1H, 8-H), 5.00 (d, 1H, 5.2 Hz, 7-H), 5.14 (s, 2H, $PhCH_2O$-), 6.8–7.6 (m, 11H, Ar-H), 9.85 (split s, 1H, -CHO). EI-MS: *m*/*z* 438 [M]$^+$ (0.9), 243 (17), 242 (26), 178 (6), 151 (6), 91 (100), 65 (9). Anal. calcd for $C_{25}H_{26}O_7$: C, 68.48; H, 5.98; found C, 68.47; H, 5.99%.

2.4. (1*S*,2*R*)-1-(4-Hydroxy-3-methoxyphenyl)-2-(4-formyl-2-methoxyphenoxy)propane-1,3-diol, 1

To a stirred solution of (1*S*,2*R*)-**7** (50 mg, 0.11 mmol) in methanol (7 mL) was added 10% palladized charcoal (5 mg). After stirring for 2 h at room temperature under atmospheric pressure of hydrogen, the solvent was concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluted with petroleum ether:ethyl acetate (2:1, v/v) to afford (1*S*,2*R*)-**1** (35 mg, 89%). Colorless gum, $[\alpha]_D^{25}$ −12 (*c* 0.4, acetone); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.75–4.10 (m, 2H, 9-H), 3.86, 3.90 (2×s, 6H, OMe), 4.40 (m, 1H, 8-H), 4.98 (d, 1H, 5.2 Hz, 7-H), 6.8–7.1 and 7.3–7.5 (m, 6H, Ar-H), 9.83 (split s, 1H, -CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.9, 56.0, 61.3 (9-C), 73.4 (7-C), 85.6 (8-C), 108.9, 110.2, 114.3, 117.6, 119.3, 126.6, 131.8, 145.4, 146.7, 151.4, 152.8, 190.8. EI-MS: *m*/*z* 348 [M]$^+$ (0.4), 195 (1), 178 (100), 153 (68), 152 (61), 151 (40), 137 (21), 93 (38). IR (film): 3450, 1678, 1590, 1510, 1462, 1427, 1271, 1237, 1157, 1133, 1029, 912, 864, 815, 782, 732 cm^{-1}. Anal. calcd for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79; found C, 62.10; H, 5.78%.

2.5. (1*S*,2*R*)-1,3-*O*-Benzylidene-2-(2-benzyloxy-5-formylphenoxy)-1-(4-benzyloxy-3-methoxyphenyl)-propane-1,3-diol, 8

A mixture of (1*S*,2*S*)-**3** (0.10 g, 0.26 mmol), 4-benzyloxy-3-hydroxybenzaldhyde (87 mg, 0.38 mmol), triphenylphosphine (0.10 g, 0.38 mmol) and diethylazodicarboxylate (0.06 mL, 0.38 mmol) was heated at 70°C in anhydrous PhH (8 mL) for 24 h under argon. The mixture was concentrated under reduced pressure and the residue was chromatographed using petroleum ether:ethyl acetate (6:1) gave (1*S*,2*R*)-**8** (63 mg, 41%) as a colorless gum, $[\alpha]_D^{25}$ −22 (*c* 0.5, acetone); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.86 (s, 3H, -OMe), 4.30–4.70 (m, 3H, 8-H, 9-H), 4.88 (d, 1H, 8.8 Hz, 7-H), 5.13, 5.21 (2×s, 4H, $PhCH_2O$-), 5.75 (s, 1H, PhCH-), 6.6–7.7 (m, 21H, Ar-H), 9.69 (s, 1H, -CHO); FAB-MS: 601 $[M-1]^+$. Anal. calcd for $C_{32}H_{30}O_7$: C, 75.73; H, 5.69; found C, 75.76; H, 5.60%.

2.6. (2*R*,3*R*)-3-Hydroxymethyl-2-(4-hydroxy-3-methoxyphenyl)-1,4-benzodioxan-6-carbaldehyde, 9

A solution of (1*S*,2*R*)-**8** (50 mg, 0.08 mmol) in 36% aqueous HCl (1 mL) and AcOH (1 mL) was heated at 65°C for 1 h. The mixture was poured into water and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4, and evaporated. Purification of the residue over silica gel column with petroleum ether:ethyl acetate (2:1) gave (2*R*,3*R*)-**9** (14 mg, 53%) as a white powder, mp: 114–116°C. $[\alpha]_D^{25}$ +24 (*c* 0.3, acetone). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.5–3.9 (2dd, 12.2, 4.0 Hz, 2H, 9-H), 3.88 (s, 3H, -OMe), 4.13 (m, 1H, 8-H), 5.12 (d, 1H, 8.2 Hz, 7-H), 6.8–7.4 (m, 6H, Ar-H), 9.79 (s, 1H, -CHO). EI-MS: *m*/*z* 316 $[M]^+$ (89), 298 (45), 283 (21), 180 (53), 162 (33), 138 (32), 137 (100), 124 (37), 77 (11). Anal. calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10; found C, 64.47; H, 5.11%.

Acknowledgements

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