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# A Novel Stereoselective Synthesis of 8-O-4' Neolignans

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**Abstract:** 1-(4-hydroxy-3-methoxyphenyl)-2-(4-formyl-2-methoxyphenoxy)-propane-1,3-diol, A 8-O-4' neolignan, has been stereoselectively synthesized in eight steps from ferulic acid, and the directly *cis* opening of epoxide in epoxidation and Mitsunobu reaction were used ingeniously as two key steps with high stereoselectivity.

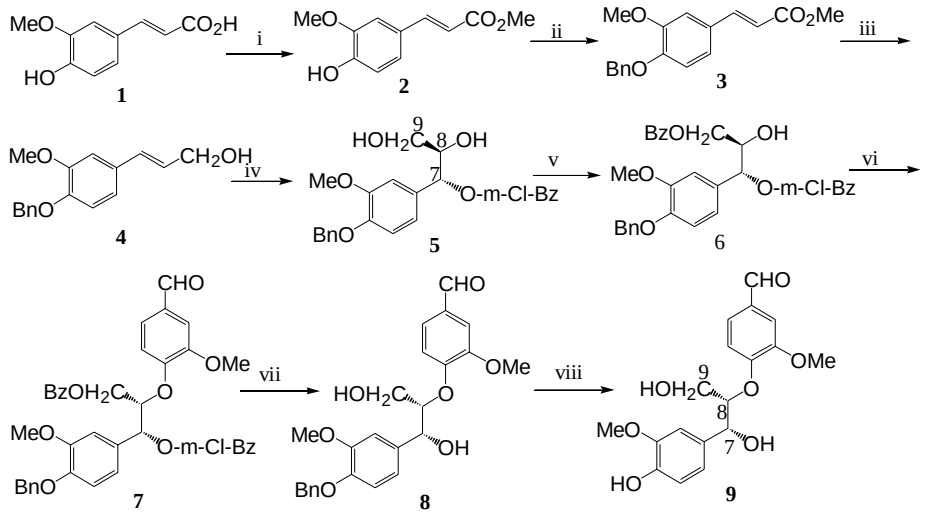
**Keywords:** 8-O-4' Neolignans, ferulic acid, addition, Mitsunobu reaction, stereoselective synthesis.

1-(4-hydroxy-3-methoxyphenyl)-2-(4-formyl-2-methoxyphenoxy)-propane-1,3-diol **9**, a natural 8-O-4' neolignan, was isolated as a mixture of *erythro* and *threo* isomers from wood of *Larix leptolesis*[1]. This kind of neolignans have shown various biological activities[2-4].

As reported previously, the synthesis of 8-O-4' neolignans was mainly achieved using oxidative coupling of monolignols[4,5] and reduction of ketones which were prepared from bromoketone and phenols in basic conditions[6], But these methods led to the mixture of *erythro* and *threo* isomers in all cases tested. A stereoselective synthesis route to directly obtain single diastereoisomer has not been reported. Herein, we developed a stereoselective synthesis approach to single *erythro* isomer of 8-O-4' neolignans, by which a 8-O-4' neolignan **9** was synthesized from ferulic acid firstly.

As shown in **Scheme**, ferulic acid **1** was converted into compound **4** through esterification and reduction with LAH in high yields. It is interesting to note that compound **4** was treated with *m*CPBA to afford directly compound **5** with *threo*-configuration[7], which was confirmed by the H-9 signal in its $^1$H-NMR spectrum[8], but not the corresponding epoxide. In fact, this reaction was a *cis* addition of *m*CPBA to double bond of **4** with high regioselectivity. Selective protection of primary hydroxy group of **5** using benzoyl chloride afford compound **6**. Mitsunobu reaction between **6** and vanillin gave aryl alkyl ether **7** with *erythro*-configuration by a $S_N2$ nucleophilic displacement. Removal of the *m*-chlorobenzoyl and benzoyl groups with $K_2CO_3$ in aqueous methanol furnished compound **8**. After hydrogenolysis of **8** under atmospheric pressure of hydrogen in the presence of 5% Pd/C, compound **9**[9] was obtained as single *erythro* isomer which was confirmed by the C-8 signal at δ85.6 in its $^{13}$CNMR spectra[10].

**Scheme**




i. MeOH, $H_2SO_4$, 85°C, 36h, 95%; ii. BnBr, $K_2CO_3$, DMF, r.t., 2h, 98%; iii. LAH, THF, -15 °C, 1h, 86%; iv. MCPBA, $CH_2Cl_2$, 0 °C, 12h, 74%; v. PhCOCl, $Et_3N$, $CH_2Cl_2$, -10 °C, 6h, 83%; vi. vanillin, $Ph_3P$, DEAD, THF, Ar, r.t., 16h, 75%; vii. $K_2CO_3$, MeOH:$H_2O$(9:1), r.t., 2h, 98%; viii. 5% Pd/C, $H_2$, MeOH, r.t., 6h, 77%.

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## References and notes

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8. Compound **5**: Pale yellow solid, mp: 61-63°C. $^1$HNMR (400MHz, $CDCl_3$) δ: 3.47 (1H, dd, J=11.5, 5.7Hz, H-9), 3.59 (1H, dd, J=11.5, 3.5Hz, H-9), 3.90 (3H, s, OMe), 4.09 (1H, m, H-8), 5.14 (2H, s, $PhCH_2O$-), 6.01 (1H, d, J=7.4Hz, H-7), 6.85-8.05 (12H, m, Ar-H). EI-MS (*m*/*z*): 442 [$M^+$](0.47), 444 [M+2$^+$](0.17), 286(4), 243(12), 156(15), 139(31), 91(100). Anal. Calcd for $C_{24}H_{23}O_6Cl$: C, 65.09; H, 5.23; Cl, 8.00. Found: C, 65.08; H, 5.24; Cl, 8.00.
9. Compound **9**: Colourless gum, $^1$HNMR (200MHz, $CDCl_3$) δ: 3.7-4.1 (2H, m, H-9), 3.86, 3.90 (6H, 2xs, OMe), 4.40 (1H, m, H-8), 4.98 (1H, d, J=5.2Hz, H-7), 6.8-7.1, 7.3-7.5 (6H, m, Ar-H), 9.83 (1H, s, CHO). EI-MS (*m*/*z*): 348 [$M^+$](0.4), 195(1), 178(100), 153(68), 152(61), 151(40), 137(21), 93(38). $^{13}$CNMR(100MHz, $CDCl_3$): 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. Anal. Calcd for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.10; H, 5.78.
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