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Asymmetric synthesis of *erythro*-8-*O*-4′-neolignan Machilin C

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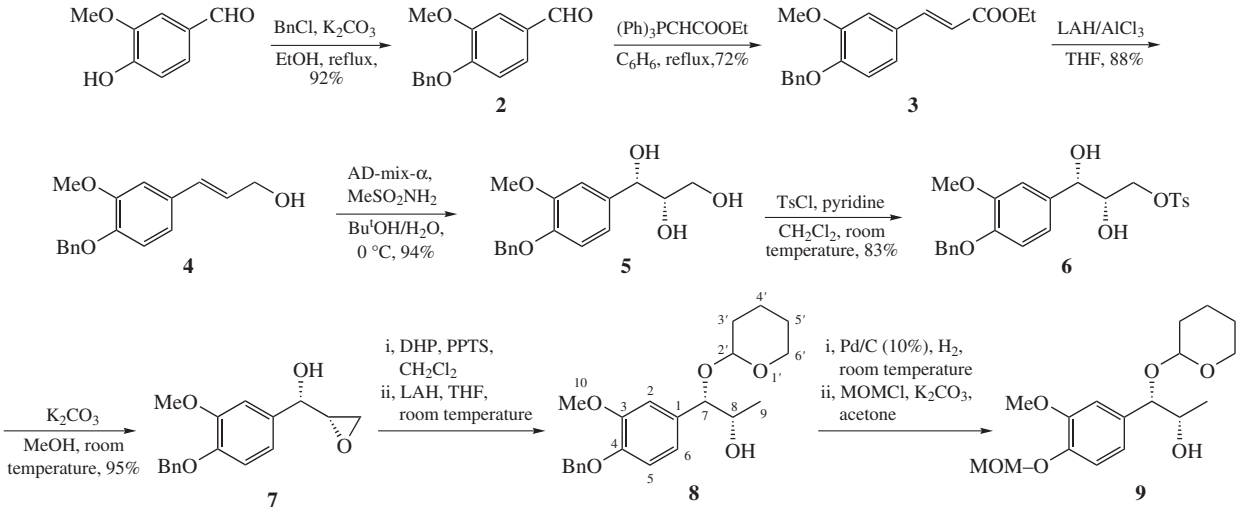
A new methodology for the synthesis of the *erythro*-8-*O*-4′-neolignan Machilin C based on the Sharpless asymmetric dihydroxylation reaction and the Mitsunobu reaction as two key steps is described.

Machilin C was first obtained from the bard of *Machilus thunbergii*, which have been used in traditional chinese medicine.[1] As a plant-derived natural product, Machilin C belongs to the class of 8-*O*-4′-neolignans, and this class comprises a large group of secondary plant metabolites, which are biochemically related to the shikimic acid pathway.[2] In nature, 8-*O*-4′-neolignans are formed by oxidative coupling of two phenyloro-panokd units, and display biological activities including an inhibitory effect on seed germination and antioxidant and antimalarial activities.[3–6]

The representatives of 8-*O*-4′-neolignans occur in nature as racemic mixtures.[7] Since the natural compounds with biological activity are usually enantiopure, the study of asymmetric synthesis will help us to find other versions of neolignan and similar types of compounds with higher activity. On the other hand, the alternative of obtaining enantiopure materials *via* synthesis has not been carefully pursued. Synthetic studies have given rise to racemic mixtures of *syn*- and *anti*-configured products, while existing enantioselective routes appear efficiency, poor enantioselective processes and some chiral syntheses give *threo*-8-*O*-4′-neolignans.[8–10] The modification of optical purity under totally achiral conditions without any external action or special environmental context was reported.[11,12]

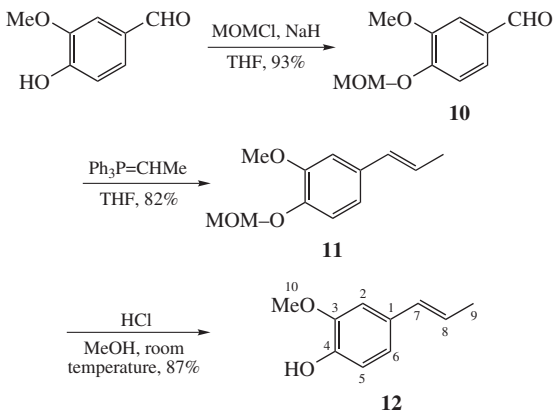
Here, we report the design and development of a new asymmetric route to *erythro*-8-*O*-4′-neolignans. The synthetic route involved two key procedures: the chiral configuration of (1*S*,2*S*)-alcohol was formed *via* the asymmetric dihydroxylation reaction and the absolute configuration was inverted from *threo*- to *erythro*-isomer *via* the Mitsunobu reaction.†

As shown in Scheme 1, the synthesis of the target compound began from vanillin. Treatment of vanillin with benzyl chloride afforded compound **2**. By the Wittig reaction between compound **2** and $(Ph)_3PCHCOOEt$, unsaturated ester (*E*)-**3** was synthesized. Reduction of (*E*)-**3** with LAH gave corresponding unsaturated alcohol (*E*)-**4** in a high yield. Note that compound **4** was treated with AD-mix-α to afford compound (1*S*,2*S*)-**5**.[13] In fact, this reaction was the Sharpless dihydroxylation, and it was used in the enantioselective preparation of 1,2-diols from prochiral olefins. At 0 °C, a good result has been achieved, and asymmetric dihydroxylation of *trans*-1,2-disubstituted olefin **4** with AD-mix-α [$(DHQ)_2PHAL$] led to (1*S*,2*S*)-**5**. Chrial analysis of (1*S*,2*S*)-**5** was performed on Varian Dynamax SD-300 using chiralcel column CDMPC with hexane–isopropanol (20:1 v/v, 0.5 ml min^{-1}, 25 °C) as an eluent and reached the 93% *ee*. Treatment of (1*S*,2*S*)-**5** with TsCl in pyridine provided (1*S*,2*S*)-**6**. Due to the steric hindrance of TsCl, this reaction only occurred in primary hydroxyl group of compound **5**. Ring closure of (1*S*,2*S*)-**6** was promoted by K_2CO_3 in methanol, generating oxirane (1*S*,2*S*)-**7**. The hydroxy group of **7** was protected by DHP, and then three-ring was opened by $LiAlH_4$ in THF to give (1*S*,2*S*)-**8** in 82% yield. The ^1H NMR spectrum of compound **8** showed two doublets, ascribable to H^9 at δ 1.00 (*J* 7.0 Hz) and H^7 at δ 4.16 (*J* 7.5 Hz). The configuration was deduced to be *threo* on the basis of the coupling constant (*J* 7.5 Hz) between H^7 and H^8.† The benzyl group of compound **8** was removed; then, it was protected with methoxymethyl chloride (MOMCl) to produce key intermediate **9** in 90% yield.



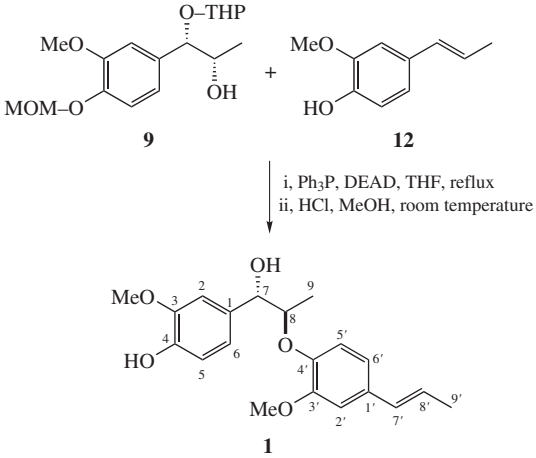
Scheme 1

Vanillin was protected with MOMCl to obtain compound **10**. The Wittig reaction carried out between compound **10** and $(Ph)_3P$=CHMe resulted in (*E*)-**11**. Then, the MOM group was cleaved by HCl to give intermediate (*E*)-isoeugenol **12** (Scheme 2).†



Scheme 2

As shown in Scheme 3, the Mitsunobu protocol involves the reaction of alcohol **9** and phenol **12** (NuH) in the presence of triphenylphosphine and diethylazodicarboxylate to afford a homologous compound containing a newly formed C–O bond. In this reaction, the C^8 stereogenic centre of compound **9** was completely inverted from *S*- to *R*-configuration.[14] Then, the MOM and THP groups were cleaved by HCl in MeOH and (1*S*,2*R*)-Machilin C **1** was obtained in 74% yield.† In the ^{1}H NMR spectrum of Machilin C, H^7 resonated as a doublet signal at δ 4.84 with the coupling constant *J* 2.9 Hz indicates *erythro*-configuration. Chiral analysis of Machilin C was in agreement with that of compound **5** and reached 92% *ee*.



Scheme 3

In summary, we have developed a chiral synthetic method of *erythro*-8-*O*-4′-neolignans to give Machilin C. With cheap materials, short experimental procedures, mild conditions and simple operations, the route can exhibit a more potential value in the future.

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† *(1S,2R)-Machilin C* **1**: amorphous powder in 92% *ee*, $[\alpha]_D^{20}$ –18.4 (*c* 0.1, $CHCl_3$). IR (KBr, ν/cm^{-1}): 3540, 2963, 2862, 1612, 1520, 1505, 1382, 1028. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.18 (d, 3H, C^9H_3, *J* 6.5 Hz), 1.87 (d, 3H, $C^{9'}H_3$, *J* 7.0 Hz), 3.87 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.35 (m, 1H, C^8H), 4.84 (d, 1H, C^7H, *J* 2.9 Hz), 6.18 (m, 1H, $C^{8'}H$), 6.35 (m, 1H, $C^{7'}H$), 6.75–7.10 (m, 6H, H_{Ar}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.4 (C^9), 18.3 ($C^{9'}$), 56.0 (2OMe), 73.6 (C^8), 82.4 (C^7), 108.9 (C^2), 109.4 ($C^{2'}$), 113.9 (C^5), 119.0 ($C^{6'}$), 119.1 ($C^{5'}$), 119.9 (C^6), 125.0 ($C^{8'}$), 130.5 ($C^{7'}$), 131.9 ($C^{1'}$), 133.7 (C^1), 144.8 (C^4), 145.6 ($C^{3'}$), 146.5 (C^3), 151.5 ($C^{4'}$). EI-MS, *m*/*z* (%): 344 (M^+, 2.6), 192 (25.7), 164 (3.8), 137 (4.6), 91 (100). HRMS, *m*/*z*: 362.1967 ($[M + NH_4]^+$, calc. for $C_{20}H_{28}NO_5$: 362.1962). The spectral data are in agreement with those reported in the literature.[1]

(1S,2S)-1-(4′-Benzyloxy-3′-methoxyphenyl)-1-(2″-oxotetrahydropyrane)-propan-2-ol **8**: amorphous powder, $[\alpha]_D^{20}$ –31.8 (*c* 0.3, $CHCl_3$). IR (KBr, ν/cm^{-1}): 3418, 2936, 2869, 1593, 1513, 1457, 1380, 1263, 1137, 1028. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00 (d, 3H, C^9H_3, *J* 7.0 Hz), 1.44–1.72 (m, 6H, $C^{3'}H_2$, $C^{4'}H_2$, $C^{5'}H_2$), 3.20 (m, 1H, $C^{6'}H$), 3.45 (m, 1H, $C^{6'}H$), 3.89 (s, 3H, $C^{10}H_3$), 3.84–4.05 (m, 1H, C^8H), 4.16 (d, 1H, C^7H, *J* 7.5 Hz), 4.84 (s, 1H, $C^{2'}H$), 5.14 (s, 2H, $phCH_2O$), 6.82–6.90 (m, 3H, C^2H, C^5H, C^6H), 7.30–7.44 (m, 5H, H_{Ar}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.2 ($C^{4'}$), 19.3 (C^9), 25.2 ($C^{5'}$), 30.5 ($C^{3'}$), 55.9 (C^{10}), 62.4 ($phCH_2O$), 71.0 ($C^{6'}$), 71.1 (C^8), 85.7 (C^7), 100.0 ($C^{2'}$), 110.8, 113.4, 119.7, 127.3, 127.3, 127.8, 128.5, 128.5, 133.3, 137.1, 147.6, 149.3 (C_{Ar}). EI-MS, *m*/*z* (%): 372 (M^+, 0.4), 328 (1.6), 288 (0.3), 271 (0.6), 243 (37), 91 (98), 85 (100). HRMS, *m*/*z*: 390.2275 ($[M + NH_4]^+$, calc. for $C_{17}H_{30}NO_6$: 390.2273).

*(*E*)-Isoeugenol* **12**: amorphous powder. IR (KBr, ν/cm^{-1}): 3450, 3017, 2962, 2850, 1696, 1675, 1513, 1427, 1267, 1207, 1034, 963. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.84 (d, 3H, C^9H_3, *J* 6.5 Hz), 3.82 (s, 3H, $C^{10}H_3$), 6.08 (m, 1H, C^8H), 6.30 (d, 1H, C^7H, *J* 15.0 Hz), 6.79–6.87 (m, 3H, C^2H, C^5H, C^6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.3 (C^9), 55.8 (C^{10}), 107.9, 114.4, 119.2, 123.2 (C^8), 130.6, 130.7 (C^7), 144.7, 146.4. EI-MS, *m*/*z* (%): 164 (M^+, 100), 149 (53), 131 (22), 103 (12), 91 (18), 55 (13).