Total Synthesis of Machilin A

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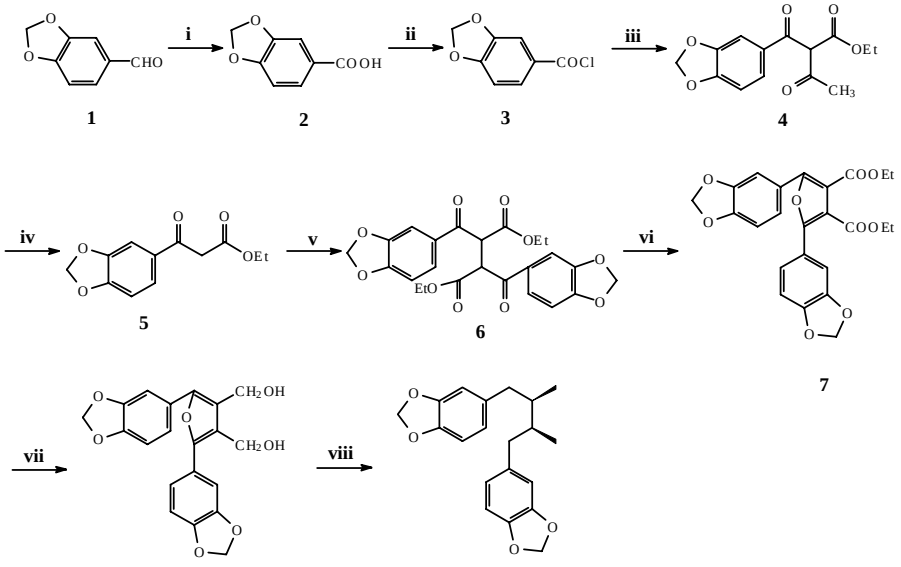
Abstract: Machilin **A**, isolated from the bark and root of *Machilus thunbergii* Sieb. *et* Zucc., was synthesized in eight steps from piperonal, with the coupling reaction as a key step.

Keywords: Machilin **A**, piperonal, reduction, synthesis.

Machilin **A 9**, a natural diarylbutane-lignan, was isolated from the bark and root of *Machilus thunbergii* Sieb. *et* Zucc., which was used in traditional Chinese madicine[1]. This kind of lignan has shown various bioactivities and attracted organic chemists a great attention[2, 3].

Scheme



i. $KMnO_4$, 70-80 ^{0}C, 1h, 88%; ii. $SOCl_2$, 95 ^{0}C; iii. CH_3COCH_2COOEt/NaOEt, THF, reflux; iv. NH_4Cl, EtOH, reflux, (ii, iii, iv overall yield 78%); v. I_2 / NaOEt, THF, 98%; vi. PTSA, Benzene, reflux, 84%; vii. LAH, THF, reflux, 95%; viii. PdO, H_2, THF / $CHCl_3$ (v : v = 10 :1), 80%.

Up to now, no synthetic route of machilin **A** has been achieved yet. Herein, we report the first total synthesis of machilin **A** using piperonal **1** as starting material and this approach could be applied to other lignans as a new and efficient synthetic route.

As shown in **Scheme**, compound **5**, which was prepared from piperonal **1** through four steps, was treated with NaOEt / I_2 to give dimer **6** quantitatively[4]. Acid catalyzed cyclization of compound **6** led to furan **7** and reduction of **7** with $LiAlH_4$ produced furan **8**, both of the reactions were easily achieved in good yield. From compound **8** to machilin **A**, it could be achieved in one step by a novel selective reductive removal of allylic hydroxy, we found that the reaction was accomplished in a mixed solvent of THF-$CHCl_3$ (v : v = 10 :1) under hydrogen (6 Mpa) using palladium oxide as a catalyst in higher yield. All of our spectral data of machilin **A 9** were in agreement with the literature report[1, 6].

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References and notes

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5 Compound **8**: mp 158~159 ^{0}C; IR (KBr): 3402, 2909, 1496, 1261cm^{-1}; ^{1}HNMR (80Mz, DMSO-d_6) δ: 3.42 (s, 2H, O**H** D_2O exchange), 4.61 (s, 4H, C**H**$_2$O), 6.05 (s, 4H, OC**H**$_2$O), 6.8-7.5 (m, 6H, Ar**H**); MS (m/z): 368 (M^+, 72), 366 (89), 350 (10), 149 (100).
6. Compound **9**: mp 49~50 ^{0}C (lit 1: 48~50 ^{0}C); IR (KBr): 2901, 1605, 1505, 1495, 1451cm^{-1}; ^{1}HNMR (80Mz, $CDCl_3$) δ: 0.85 (d, 6H, 6.6Hz, -C**H**$_3$), 1.72 (m, 2H, C**H**), 2.22-2.28 (m, 2H, ArC**H**$_2$), 2.68-2.72 (m, 2H, ArC**H**$_2$), 5.90 (s, 4H, OC**H**$_2$O), 6.55-6.73 (m, 6H, Ar**H**); MS (*m/z*): 326 (M^+, 14), 267 (8), 238 (11), 135 (100), 77 (26).

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