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An Efficient Synthetic Method of Nordihydroguaiaretic Acid (NDGA)

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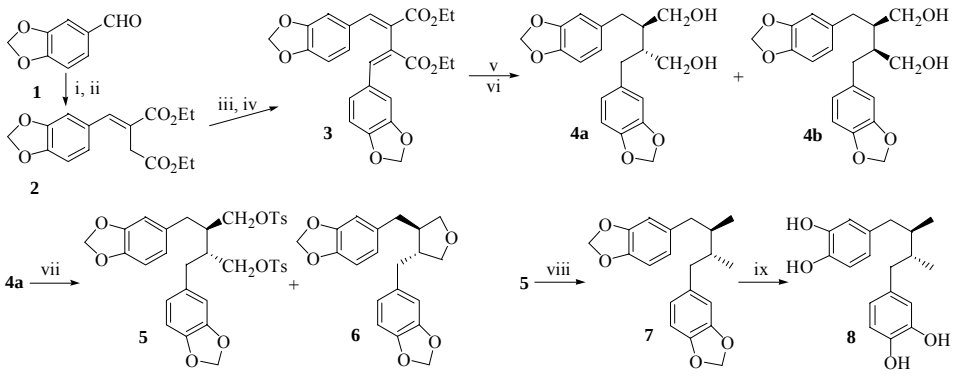
Abstract: Nordihydroguaiaretic acid (NDGA) has been synthesized in nine steps from piperonal using Stobbe condensation as the key step with high yield. By this approach, five relative natural products were obtained.

Keywords: Nordihydroguaiaretic acid, piperonal, Stobbe condensation.

Nordihydroguaiaretic acid (NDGA) is a phenolic lignan found in the resinous exudations of many plants. This lignan is associated with a wide range of pharmacological activities, including the inhibition of the herpes simplex[1], HIV[2], and the naturally occurring antioxidation[3].

Scheme 1



i) a: EtONa, diethylsuccinate, reflux, 4h; b: H_2O, NaOH, reflux, 2h, 90%; ii) EtOH, C_6H_6, reflux, 24h, 87%; iii) a: EtONa, piperonal, 0°C, 24h; b: H_2O, NaOH, reflux, 2h, 82%; iv) EtOH, C_6H_6, reflux, 36h, 87%; v) H_2, Pd/C (10%), 99%; vi) $LiAlH_4$, THF, reflux, **4a**:**4b** (2:1), 92%; vii) TsCl, pyridine, CH_2Cl_2, **5**, 56%, **6**, 40%; viii) $LiAlH_4$, THF, reflux, 90%; ix) a: PCl_5, CCl_4, reflux, 10h; b: H_2O, reflux, 16h, 73%.

Several synthetic methods of NDGA have been reported in the literatures[4, 5, 6], but all

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involve low yield reactions, expensive starting materials and reagents or produce a mixture of one and other stereoisomer. In this paper, we wish to report a simple, novel and stereoselective route to the synthesis of NDGA.

In **Scheme 1**, the approach used piperonal as the starting material, two Stobbe condensations as the key steps to give diester **3**. This diester **3** was followed by hydrogenation and reduction with $LiAlH_4$, to result a mixture of diols (±)**4a** and (±)**4b** (about 2:1). Racemate **4a** isolated by column-chromatography was converted to the corresponding toluenesulfonyl ester **5**. Simultaneously, tetrahydrofuran derivative (±)**6** was obtained. Compound **5** was reduced to (±)**7** with $LiAlH_4$ in THF, and then methylene groups of **7** were removed to provide (±)NDGA **8** as threo isomer.

This way offers many possibilities to synthesize a wide variety of derivatives of NDGA **8** and five natural products **4a**, **4b**, **6**, **7**, **8** were obtained.

Acknowledgments

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Reference and Notes

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7. **4a**[8]: mp 112-113°C. ^{1}HNMR(200MHz, $CDCl_3$, δ_{ppm}): 1.83(m, 2H), 2.69(m, 4H), 3.48(dd, 2H, *J*=3.6, 11Hz), 3.74(s, 2H), 3.76(dd, 2H, *J*=3.7, 1.2Hz), 5.91(s, 4H), 6.58-6.73(m, 6H). ^{13}CNMR(50MHz, $CDCl_3$, δ_{ppm}): 35.8, 44.2, 59.9, 100.7, 108.1, 109.2, 121.8, 134.3, 145.6, 147.5. EI-MS(*m/z*, %): 358(M^+, 2.1), 340(0.1), 204(0.3), 161(3.3), 135(100). **4b**[8]: mp 112-113°C. ^{1}HNMR(200MHz, $CDCl_3$, δ_{ppm}): 1.93(m, 2H), 2.53(m, 4H), 3.44(m, 4H), 4.09(s, 2H), 5.86(s, 4H), 6.53-6.70(m, 6H). ^{13}CNMR(50MHz, $CDCl_3$, δ_{ppm}): 33.3, 45.2, 62.7, 100.7, 108.1, 109.2, 121.8, 134.3, 145.7, 147.6. EI-MS(*m/z*, %): 358(M^+, 2.1), 340 (0.1), 204(0.3), 161(3.3), 135(100). **6**[8]: ^{1}HNMR(200MHz, $CDCl_3$, δ_{ppm}): 2.13(m, 2H), 2.53(m, 4H), 3.49(dd, 2H, *J*=6.0, 8.8Hz), 3.89(dd, 2H, *J*=6.6, 8.6Hz), 5.90(s, 4H), 6.51-6.75(m, 6H). ^{13}CNMR(50MHz, $CDCl_3$, δ_{ppm}): 39.1, 46.4, 73.2, 100.7, 107.9, 108.9, 121.4, 134.0, 145.7, 147.5. EI-MS(*m/z*, %): 340(M^+, 11.3), 204(2.2), 161(2.1), 136(100), 135(97.2). **7**[9]: mp 43-45°C. ^{1}HNMR(200MHz, $CDCl_3$, δ_{ppm}): 0.86(m, 6H), 1.74(m, 2H), 2.35(dd, 2H, *J*=8.2, 13.2Hz), 2.55(dd, 2H, *J*=6.0 and 13.2Hz), 5.92(s, 4H), 6.52-6.75(m, 6H). EI-MS(*m/z*, %): 326(M^+, 1.3), 246(40.3), 135(19.6), 123(100). **8**[6]: mp 185-186℃. ^{1}HNMR (200MHz, acetone-d_6, δ_{ppm}): 0.78 (d, 6H, *J*=6.6Hz), 1.76(m, 2H), 2.27(dd, 2H, *J*=8.2, 13.6Hz), 2.50(dd, 2H, *J*=6.0, 13.6Hz), 6.43(dd, 2H, *J*=2.0, 8.2Hz), 6.60(d, 2H, *J*=1.8Hz), 6.70((dd, 2H, *J*=4.4, 7.8Hz), 7.60(d, 4H, *J*=8.2Hz). ^{13}CNMR(50MHz, acetone-d_6, δ_{ppm}): 14.2, 39.1, 41.5, 115.8, 116.8, 121.0, 134.1, 143.8, 145.6. EI-MS(*m/z*, %): 302(M^+, 3.9), 178(0.8), 151(2.1), 137 (3.5), 123(100).
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