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First Total Synthesis of (±)-Aiphanol

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Abstract: (±)-Aiphanol was first synthesized in which coupling reaction and Horner-Wittig reaction as the key steps.

Keywords: Aiphanol, stilbenolignan, coupling reaction.

Aiphanol was isolated from the seeds of *Aiphanes aculeate* Willd. (Arecaceae) collected in Peru and was reported to exhibit significant inhibitory activities against cyclooxygenases-1 and -2. The structure of aiphanol was elucidated by spectroscopic methods as an unprecedented stilbenolignan skeleton in which a stilbene moiety is linked to a phenylpropane unit through a dioxane bridge[1].

In our previous works the synthetic approach to 1,4-benzodioxane lignans were achieved[2]. Since aiphanol represents the first example of stilbenolignan linked through a dioxane bridge[1], it arose our interest in the synthesis of this natural product. Our synthetic strategy is to construct the substituted benzodioxane ring, followed by formation of stilbene moiety by Horner-Wittig reaction.

As shown in **Scheme 1**, treatment of aldehyde **1** with monoethyl malonate[3] gave ester **2** that was reduced to afford the corresponding unsaturated alcohol **3**. In the presence of Ag_2O according to our previous procedure[2a], **3** was coupled with ester **5**, which was derived from aldehyde **4**, to give 1,4-benzodioxane intermediate **6**[4]. The ^{1}H NMR spectrum of **6** revealed a doublet signal of H-2 at δ 4.95 with a coupling constant J = 8.1 Hz which is typical of a benzylic methine substituted by an oxygen and *trans* orientation of the benzodioxane ring[1, 5]. Additionally, a multiplet signal of H-3 at δ 4.05 also implies the existence of 1,4-dioxane ring[1]. Selective protection of phenolic hydroxy group of **6** with chloromethoxymethane afforded methoxymethyl (MOM) ether **7**, which was oxidized by $NaIO_4/OsO_4$(cat.) to give the key intermediate aldehyde **8**[6]. Although exclusively preparation of *trans*-stilbene by the Horner-Wittig reaction has been reported in the literature[7], treatment of **8** with phosphonate **9**, a mixture of **10** [(*E*) and (*Z*), *ca*. 4:1 by ^{1}H NMR] was obtained and could not be separated by column chromatography. The mixture could be converted to (*E*)-isomer **10** in high yield by treatment with thiophenol in ref-

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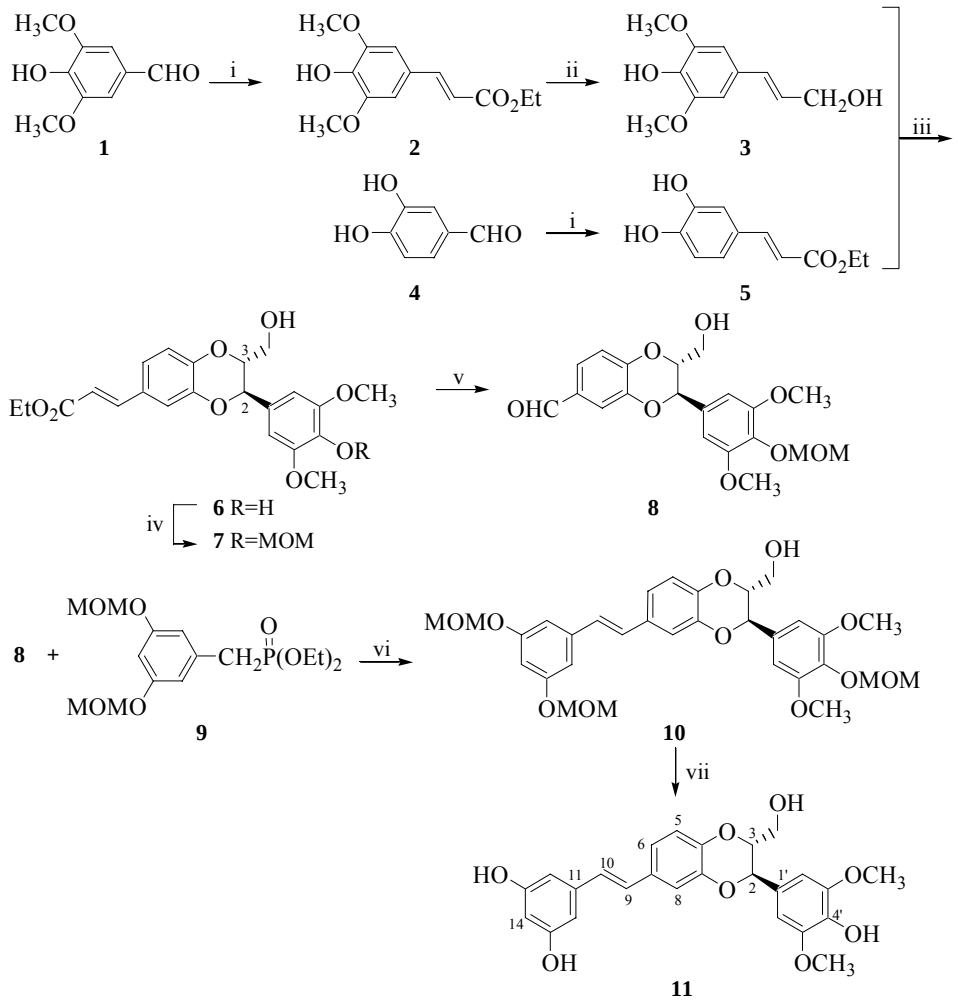
Scheme 1



i) $HO_2CCH_2CO_2Et$, pyridine, piperidine(cat.), reflux, 6 h, 94%; ii) $LiAlH_4/AlCl_3$ (3:1), THF, 0.5 h, 87%; iii) Ag_2O, benzene-acetone (2:1), reflux, 8 h, 52%; iv) MOMCl, K_2CO_3, acetone, 4 h, 93%; v) $NaIO_4$, OsO_4(cat.), dioxane-H_2O (1:1), 92%; vi) (a) NaH, THF, 90%; (b) PhSH, AIBN, benzene, reflux, 8 h, 93%; vii) 3N HCl-MeOH (1:1), 40-50 °C, 90%.

luxing benzene in the presence of azoisobutyronitrile (AIBN)[8]. Final deprotection of **10** with diluted HCl in methanol at 40-50 °C afforded the stilbenolignan (±)-aiphanol **11**[9], of which the spectral data (IR, NMR and MS) were identical with the literature report[1].

In summary, we have presented a concise approach of preparation of (±)-aiphanol **11**. The synthetic routes are facile and the yields are satisfactory. Biological evaluation and asymetric synthesis of aiphanol are in progress.

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References and Notes

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4. Intermediate **6**: a yellow solid, mp 180-181°C; IR ν (KBr), cm^{-1}: 3391, 2936, 1508, 1270, 1115, 858, 810; ^{1}HNMR(300MHz, $CDCl_3$, δ_{ppm}): 1.33 (t, 3H, *J*=7.2Hz), 3.56 (dd, 1H, *J*=12.3, 3.6Hz), 3.84 (dd, 1H, *J*=12.3, 2.1Hz), 3.91 (s, 6H), 4.06 (m, 1H), 4.25 (q, 2H, *J*=7.2Hz), 4.95 (d, 1H, *J*=8.1Hz), 6.29 (d, 1H, *J*=16.2Hz), 6.67 (s, 2H), 6.96 (d, 1H, *J*=8.1Hz), 7.09 (dd, 1H, *J*=8.1, 1.8Hz), 7.18 (d, 1H, *J*=1.8Hz), 7.59 (d, 1H, *J*=16.2Hz); ^{13}CNMR(75MHz, $CDCl_3$, δ_{ppm}): 14.3, 56.3, 60.4, 61.5, 76.4, 78.5, 104.0, 116.6, 117.3, 122.2, 126.7, 128.3, 135.4, 143.8, 144.0, 145.2, 147.3, 167.2; EI-MS(*m/z*, %): 416 (M^+, 75), 219 (20), 210 (73), 167 (96), 91 (52), 43 (100).
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6. Intermediate **8**: Colorless oil; IR ν (KBr)/cm^{-1}: 3402, 2918, 1594, 1281, 1124, 875, 826; ^{1}HNMR(300MHz, $CDCl_3$, δ_{ppm}): 3.60 (s, 3H), 3.61 (dd, 1H, *J*=12.3, 3.3Hz), 3.87 (s, 6H), 3.88 (dd, 1H, *J*=12.3, 2.4Hz), 4.09 (m, 1H), 5.00 (d, 1H, *J*=8.1Hz), 5.14 (s, 2H), 6.68 (s, 2H), 7.10 (d, 1H, *J*=8.1Hz), 7.48 (d, 1H, *J*=8.1Hz), 7.51 (s, 1H), 9.85 (s, 1H); ^{13}CNMR(75MHz, $CDCl_3$, δ_{ppm}): 56.1, 57.1, 61.7, 76.2, 78.8, 98.1, 104.3, 117.5, 118.5, 124.2, 130.7, 131.4, 135.1, 144.0, 148.8, 153.7, 190.7; EI-MS(*m/z*, %): 390 (M^+, 15), 209 (13), 181 (5), 149 (32), 45(100).
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8. R. Annunziata, M. Cinquini, F. Cozzi, *et al*., *J. Org. Chem.*, **1987**, *52*, 4674.
9. (±)-Aiphanol **11**: amorphous powder; IR ν (KBr), cm^{-1}: 3356, 2922, 1583, 1497, 1266, 1104, 827, 740; ^{1}HNMR(300MHz, acetone-d_6, δ_{ppm}): 3.52 (dd, 1H, *J*=12.3, 4.2Hz), 3.74 (dd, 1H, *J*=12.3, 2.4Hz), 3.85 (s, 6H), 4.13 (m, 1H), 4.97 (d, 1H, *J*=8.1Hz), 6.27 (t, 1H, *J*=2.1Hz), 6.55 (d, 2H, *J*=2.1Hz), 6.83 (s, 2H), 6.90 (d, 1H, *J*=8.1Hz), 6.92 (d, 1H, *J*=16.5Hz), 7.01 (d, 1H, *J*=16.5Hz), 7.08 (dd, 1H, *J*=8.1, 1.8Hz), 7.13 (d, 1H, *J*=1.8Hz); ^{13}CNMR(75MHz, acetone-d_6, δ_{ppm}): 56.7, 61.7, 77.4, 79.6, 102.7, 105.6, 106.1, 115.3, 117.7, 120.8, 128.1(overlapping), 128.6, 131.8, 137.2, 140.5, 144.4, 145.0, 148.7, 159.5; EI-MS(*m/z*, %): 452 (M^+, 1), 299 (1), 223 (3), 210 (6), 149 (44), 109 (5), 43(100).

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