SHORT PAPER

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Synthesis of neolignans from *Anaxagorea clavata*

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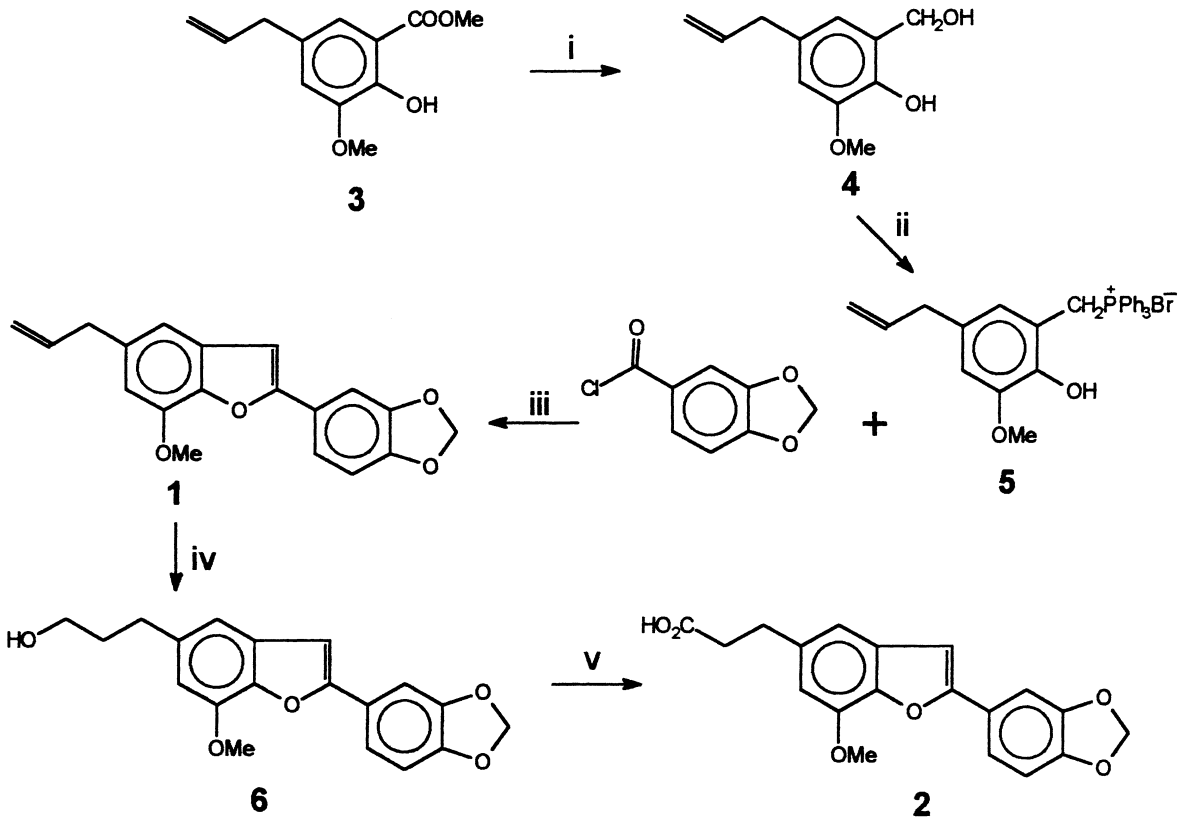
A synthesis of the neolognans (**1**) and (**2**) is described employing an intramolecular Wittig cyclisation to generate the 2-arylbenzofuran ring system.

Keywords: neolignans, intramolecular Wittig cyclisation, anti-Markovnikov hydration

Neolignans constitute a group of natural products showing wide structural variations.[1] The benzofuranoid neolignans display a varied biological activity including antibacterial, cytotoxic, antiproliferative, immunosuppressive and insecticidal activity.[2] A large number of neolignans have been isolated and characterised in recent years and novel methodologies for their synthesis have been developed.[1,3] We report here the synthesis of the neolignans,3'-methoxy-3,4-methylenedioxy-4',7-epoxy-9-nor-8,5'-neolignan-7,8'-diene (**1**) and 3'-methoxy-3,4-methylenedioxy-4',7-epoxy-9-nor-8,5'-neolignan-7-en-9'-oic acid (**2**). These neolignans have recently been isolated from the wood of *Anaxagorea clavata R.E. Fries*[4] which is widely used in carpentry. The synthesis relies on an intramolecular Wittig cyclisation[5] for generating the 2-aryl benzofuran ring system enshrined in (**1**) and (**2**).

The known allyl phenol (**3**),[6] obtained from o-allylation of methyl-0-vanillate followed by Claisen rearrangement was reduced with lithium aluminium hydride to furnish the alcohol (**4**). This was converted to the Wittig salt (**5**) through reaction with triphenylphosphine hydrobromide. Interaction of this Wittig salt with piperonyloyl chloride in presence of triethylamine resulted in o-acylation and concomitant cyclisation to afford the neolignan (**1**), whose melting point and spectral data were in accord with those reported.

The neolignan (**1**) was subjected to anti – Markovnikov hydration[7] by reaction with a mixture of titanium tetrachloride and sodium borohydride to furnish the alcohol (**6**), which on oxidation with Jones reagent afforded the neolignan carboxylic acid (**2**), whose melting point and spectral data were also in agreement with those reported.



Scheme 1 Reagents and conditions(i) LAH, ether, reflux, 4 h, HCl, 75%; (ii) PPh_3. HBr, CH_3 CN, 100°C, 2 h, 82%; (iii) Et_3N, toluene, reflux, 6 h, 46%; (iv) $TiCl_4$, $NaBH_4$, DME, rt, 83%; (v) Jones reagent, 60%

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

In summary, we have achieved a synthesis of the neolignans (**1**) and (**2**) employing an intramolecular Wittig cyclisation to generate the 2-aryl benzofuran ring system.

Experimental

Melting points are uncorrected. Solvents were reagent grade materials and were further purified by conventional methods. Petroleum ether refers to the fraction of b.p. 60 – 80° C. Preparative TLC was performed with silica gel ^{60} HF $_{254}$ plates of 1mm thickness. All organic extracts were dried over anhydrous sodium sulfate.

NMR spectra of CCl_4 or $CDCl_3$ solutions were recorded at 60 or 300 MHz and peak positions are indicated in ppm downfield from internal TMS in δ units.

5-Allyl-3-methoxy –2-hydroxybenzyl alcohol (**4**): To a magnetically stirred slurry of lithium aluminum hydride (40 mg, 1.1 mmole) in anhydrous ether (5 ml), was added dropwise, a solution of the ester (**3**) (200 mg, 1 mmole) in ether (3 ml). After the addition was over, the reaction mixture was refluxed for 4 h. It was the decomposed with saturated sodium sulfate solution. The reaction mixture was further acidified with hydrochloric acid (6N) and extracted with ether. The combined ether extracts were washed with saturated brine, dried and concentrated to afford the alcohol (**4**) (150 mg, 75%) as a colourless liquid, b.p.130 -132°C / 0.05mm, (Found C, 67.86; H, 7.45, $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.27%) ^{1}H NMR (CCl_4): δ 3.27 (d, 2H, *J* 4.2 Hz), 3.77 (s, 3H), 4.63 (s, 2H), 4.8 – 6.2 (m, 3H), 6.6 (s, 1H) 6.7 (s.1H).

3'-Methoxy-3,4-methylenedioxy-4'7-epoxy-9-nor-8,5'-neolignan-7,8'-diene (neolignan 1): A solution of triphenyl phosphonium-bromide (1.78 g, 5.2 mmol) and 5-allyl-3-methoxy – 2 - hydroxy benzyl alcohol (**4**) (1g, 5.2 mmole) in anhydrous acetonitrile (6 ml) was heated on a boiling water bath for 2h. On cooling, the precipitated phosphonium salt was filtered and dried at 150°C under vacuum. Yield, 2.2g (82%), m.p. 277–278°C, (Found: C, 67.46; H, 5.52. $C_{29}H_{28}B_rO_2P$ requires C, 67.07s H, 5.39%).

The above 5-allyl-3-methoxy-2-hydroxy benzyl triphenylphosphoniumbromide (2g, 3.9 mmole), piperonyloyl chloride (792mg, 4.3 mmole) and freshly distilled triethylamine (1.18g, 11.7 mmole) in toluene (18 ml) were heated under reflux under a nitrogen atmosphere. After 6h, the triethyammonium salt was removed by filtration and toluene evaporated. The residue was chromatographed through silica gel. Elution with petroleum ether: EtOAc (49:1) afforded the neolignan (**1**) (550 mg, 46%), as a colourless crystalline solid, m.p. 69 – 70°C (lit.[4] m.p.69 –70°C.

^{1}H NMR ($CDCl_3$): δ 3.44 (d, *J* 6.6 Hz, 2H), 4.01 (s, 3H), 5.1 (m,2H), 6.02 (m, 1H), 6.00 (s, 2H), 6.61 (d, *J* 1.2 Hz, 1H), 6.78 (s, 1H), 6.86 (d, *J* 9 Hz,1H), 6.96 (s, 1H), 7.38 (dd, J_1 9Hz, J_2 1.5Hz, 1H), 7.31 (d, *J* 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 40.92, 56.47, 100.81, 101.71, 105.96, 107.98, 109.04, 112.97, 116.03, 119.62, 125.14, 131.48, 136.13, 138.31, 143.01, 145.22, 148.39, 148.46, 156.51. Anal. Calcd. For $C_{19}H_{16}O_4$: C,74.02; H, 5.19. Found: C, 73.81; H , 5.39. $C_{19}H_{16}O_4$.: C, 74.02; H, 5.19%).

3'-Methoxy-3,4-methylenedioxy-4',7-epoxy-9-nor-8,5'-neolignan-7-en-9'oic acid (Neolignan 2):

To a magnetically stirred slurry of $TiCl_4$ – $NaBH_4$ complex (prepared by mixing $TiCl_4$ (100 mg, 0.52mmole) and $NaBH_4$ (40mg, 1.04 mmole) in 1,2-dimethoxy-ethane (2 ml) at room temperature for 1h), a solution of the neolignan (**1**) (160mg, 0.52 mmole) in 1,2-dimethoxyethane (1.5 ml) was added at room temperature and stirred for 24h. The reaction mixture was decomposed with water and extracted with ether. The combined ethereal layers were dried and concentrated. The residue was purified by preparative TLC, petroleum ether: EtOAc (70:30) to furnish the alcohol (**6**) (80mg, 49%) as a colourless oil. Based on recovered (**1**), the yield was 83%. ^{1}H NMR ($CDCl_3$): δ 1.92 (m, 2H), 2.74 (m,2H), 3.7 (t, *J* 6.3 Hz, 2H), 4.02 (s, 3H), 5.99 (s, 2H), 6.62 (s,1H), 6.77 (s, 1H), 6.96 (s, 1H), 7.39 (d, *J* 8.1Hz, 1H), 6.87 (d, *J* 8.2Hz, 1H),7.31 (s,1H). ^{13} C NMR ($CDCl_3$): δ 32.83, 35.08, 56.55, 62.98, 100.73, 101.71, 105.94, 107.83, 109.02, 112.71, 119.61, 125.11, 131.45, 138.15, 142.86, 145.19, 148.38, 148.45, 156.49. Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.94; H, 5.52. Found: C, 70.24; H, 5.91.

To a magnetically stirred solution of the above alcohol (**6**) (80mg) in acetone (5 ml), Jones reagent was added dropwise at room temperature until the colour of the Jones reagent persisted. Then the mixture was stirred for another 30 min, diluted with water and extracted with ether. The ethereal extract was further extracted with saturated sodium bicarbonate solution. This bicarbonate extract was acidified in the cold with hydrochloric acid (6N) and extracted with ether. The ethereal extract was dried and concentrated to give the acid (**2**) (50mg, 60%), crystallised from ethanol, m.p. 112 –113°C (lit.[4] m.p. 113 –114°C).

^{1}H NMR ($CDCl_3$): δ 2.74 (t, *J* 7.6Hz,2H), 3.03 (t, *J* 7.6Hz,2H), 4.02 (s, 3H), 6.05 (s, 2H), 6.63 (s, 1H), 6.79 (s,1H), 6.98 (s, 1H), 7.39 (d, *J* 8.15 Hz, 1H), 6.86 (d, *J* 8.15 Hz, 1H), 7.32 (s, 1H).

^{13} C NMR ($CDCl_3$): δ 31.03, 35.85, 56.21, 100.39, 101.11, 105.61, 107.31, 108.66, 112.97, 119.30, 120.56,124.69,131.19, 132.18, 135.95, 144.92, 148. 10, 148.19, 177.41. Anal. Calcd. for $C_{19}H_{16}O_6$: C, 67.06; H, 4.71. Found: C, 67.41; H, 4.94.

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