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SYNTHESIS OF TWO ARYLNAPHTHALENE LIGNANS[1]

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Abstract—Two natural products have been synthesized: isodiphyllin (**11**) from the condensation of 2-(3,4-methylenedioxyphenyl)-2-γ-butyrolactone-1,3-dithian (**7**) with veratrumaldehyde and 4-deoxy-isodiphyllin (**5**) by the Diels–Alder condensation of *trans*-3,4-methylenedioxycinnamyl chloride (**1**) and the sodium salt of 3,4-dimethoxyphenylpropionic acid (**2**).

In a previous paper,[2] we reported the isolation of two lignans (isodiphyllin and 4-deoxy-isodiphyllin) from the *Umbellifera Bupleurum frutiscens* L and assigned to them the structures **11** and **5** respectively. As these compounds can be useful in pharmacology, their synthesis was undertaken because the plant yields are low and the syntheses of lignans with an OH group in position 4 are inordinately long.[3-6]

The Diels–Alder[7] condensation of *trans*-3,4-methylenedioxycinnamyl chloride (**1**) and the sodium salt of 3,4-dimethoxyphenylpropionic acid (**2**) gave a crystalline solid (**3**): m.p. 245°; NMR ($CDCl_3$) with a structure compatible with **3**, —signals typical of aromatic protons at δ 6.93–6.77 (4H) and 6.54 (1H), a triplet of two protons at δ 4.70 (J = 9 Hz) and another at δ 4.00 (J = 8 Hz) partially superimposed upon the OMe singlets at δ 3.95 and 3.87. A further singlet at δ 5.96 assigned to the methylenedioxy group protons and a complex signal at δ 3.37 due to the CH_2–C$\underline{H}$–CH_2 protons were observed. Treatment of **3** with SeO_2 gave a product identical with natural 4-deoxy-isodiphyllin (**5**).

Attempts to oxidize **3** (with position 4 allylic to the aromatic nucleus) with various reagents such as MnO_2, DDQ, CAN, NBS, etc. brought about total aromatization and 4-deoxy-isodiphyllin (**5**) was formed. When **3** was hydrogenated in the presence of Pd–C, compound **4** was produced which, when treated with the same oxidizing reagents, also yielded 4-deoxy-isodiphyllin (**5**).

Synthesis of isodiphyllin (**11**). 2 - (3,4 - Methylenedioxyphenyl) - 1,3 - dithian (**6**) condensed with γ-crotonolactone to form the Michael adduct **7**, m.p. 154° (rep.,[8] 154–155°); IR revealing a band characteristic of a γ-lactone. Compound **7** condensed with 3,4-dimethoxybenzaldehyde to yield a mixture of isomers (**8**) which could not be separated by any of the usual methods. F_3CCO_2H treatment of this mixture produced the crystalline dithian derivative (**9**), m.p. 262–264°; NMR ($CDCl_3$), singlets at δ 5.90 (O–CH_2–O), 3.88 and 3.84 (two OMe's) and two multiplets at δ 2.94 (4H) and 2.19 (2H) due to the dithian group methylenes. The dithian protector group in **9** was eliminated by treatment with HgO–BF_3OEt_2, yielding the crystalline ketone (**10**) with an indefinite m.p. (176–184°) again indicating a mixture of isomers. The IR spectrum revealed an arylketone band at cm^{-1} 1690; the NMR ($CDCl_3$) showed a singlet at δ 6.01 typical of the methylenedioxy group protons. The methylene signals of the dithian group could be seen in the NMR of **9** but were missing from the spectrum of **10** and the OMe signals were further apart, appearing in **10** at δ 3.90 and 3.82.

Isodiphyllin (**11**) was obtained by refluxing the ketone **10** in AcOH with SeO_2 and was identified by comparison of its spectral data and physical constants with those of the natural lignan.

EXPERIMENTAL

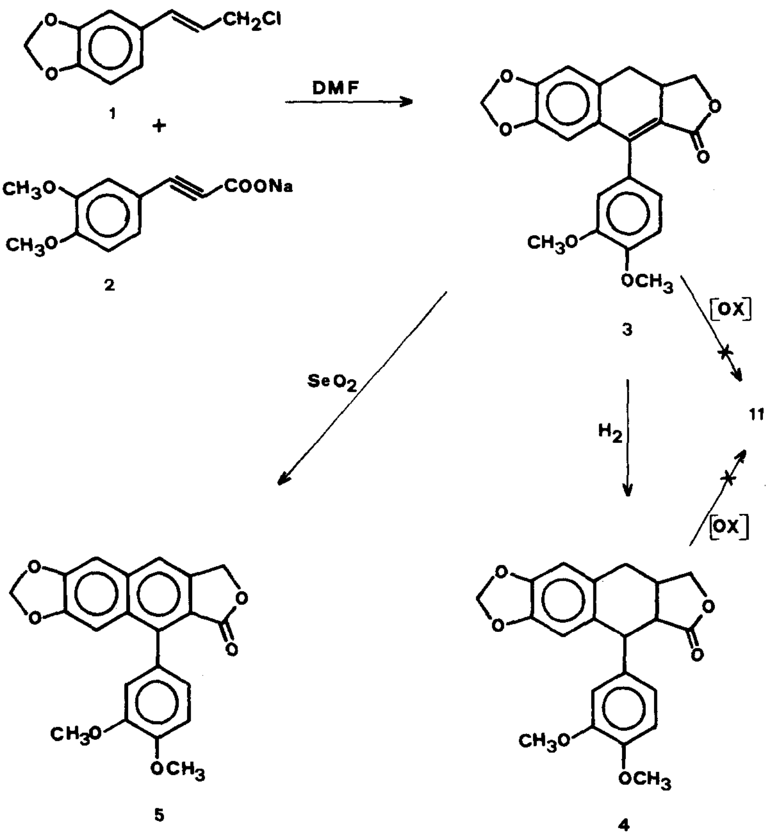
M.p.'s are uncorrected. IR spectra were taken in $CHCl_3$ or KBr on a PE 257; UV spectra were recorded on a PE 402 spectrophotometer. NMR were taken on a PE R-32 (90 MHz) with 1–10% solns of TMS as internal standard. The MS were recorded on a Hewlett-Packard 5930A and column chromatography was performed using silica gel in thicknesses of 0.2–0.5 mm.

1 - (3,4 - *Dimethoxyphenyl*) - 3 - *hydroxymethyl* - 6,7 - *methylenedioxy* - 3,4 - *dihydro* - 2 - *naphthoic acid lactone* (**3**). A mixture of the Na salt **2** (3 g) and *trans*-**1** (2.5 g) were dissolved in dry DMF (40 ml) and the soln was refluxed for 8 hr. It was then filtered through NaCl and dried. The oily residue was chromatographed on a column with Be, Be–EtOAc (5%) and Be–EtOAc (10%) as eluents. This last elution yielded 1.5 g (31%) white crystals: m.p. 245° (Me_2CO–PE); *m/e* 366 (M^+); ν_{max}^{KBr} cm^{-1} 3300, 2850, 2820, 1720, 1640, 1590, 1435 and 1405; λ_{max}^{EtOH} nm 247 (20,000), 352 (12,400); δ ($CDCl_3$) 6.93–6.77 (4H aromatic), 6.54 (s, 1H, aromatic), 5.96 (s, 2H, O–CH_2–O), 4.70 (t, 2H, J = 9 Hz, lactone CH_2), 4.00 (t, 2H, J = 8 Hz, benzilic CH_2), 3.95 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.37 (m, 1H, CH_2–C$\underline{H}$–CH_2). (Found: C, 68.92; H, 5.02. Calc. for $C_{21}H_{18}O_6$: C, 68.85; H, 4.91%).

1 - (3,4 - *Dimethoxyphenyl*) - 3 - *hydroxymethyl* - 6,7 - *methylenedioxy* - 1,2,3,4 - *tetrahydro* - 2 - *naphthoic acid lactone* (**4**). Compound **3** (260 mg) was dissolved in AcOH (50 ml) and hydrogenated with 10% Pd–C (130 mg) for 2 hr under 1.2 atmos at 85°. After filtration, the AcOH was eliminated *in vacuo*. The residue was purified using 20 g of silica gel to yield a foamy white solid which could not be crystallized (200 mg, 76%): *m/e* 368 (M^+); $\nu_{max}^{CHCl_3}$ cm^{-1} 2940, 2900, 2840, 1760, 1480 and 1465; λ_{max}^{EtOH} (ϵ_{max}) nm 211 (21,700), 235 (8400), 288 (4750); δ ($CDCl_3$) 7.00–6.63 (5H, aromatic), 5.91 (s, 2H, O–CH_2–O), 4.42–4.16 (m, 2H), 3.94–3.70 (7H), 3.54–2.64 (4H). (Found: C, 68.25; H, 5.46. Calc. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.43%).

4-*Deoxy-isodiphyllin* (**5**). Compound **3** (300 mg) was dissolved in AcOH (20 ml) and SeO_2 (200 mg) was added. The mixture was refluxed for 0.5 hr and then poured into water. After being extracted in the usual way, dried and evaporated, the residue was purified by column chromatography yielding 90 mg (30%) of a white crystalline solid, m.p. 227° (Me_2CO–PE); *m/e* 364 (M^+); $\nu_{max}^{CHCl_3}$ cm^{-1} 3000, 1760, 1620, 1460 and 1040; λ_{max}^{EtOH} (ϵ_{max}) 207 (35,900), 224 (29,100), 258 (54,350), 310 (11,640) and 353 (5820) nm; δ ($CDCl_3$) 7.67 (s, 1H, aromatic), 7.18 (s, 1H, aromatic), 7.10 (s, 1H, aromatic), 6.98–6.80 (3H, aromatic), 6.04 (s, 2H, O–CH_2–O), 5.32 (s, 2H, lactone CH_2), 3.94 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3). (Found: C, 69.55; H, 4.12. Calc. for $C_{21}H_{16}O_6$: C, 69.23; H, 4.39%).

2 - (3,4 - *Methylenedioxyphenyl*) - 1,3 - *dithian* (**6**). Dry HCl was passed for 10 min into an externally ice-chilled mixture of



1,3-propanedithiol (10 ml) and piperonal (15 g) in $CHCl_3$ (100 ml). This was stirred for 20 min then washed twice in H_2O, conc. soln of NaOH and H_2O again. After drying and evaporating, 22.25 g (92%) oil was obtained which crystallized with Me_2CO, m.p. 84° (rep.,[9] 84.5–85.5°): *m/e* 240 (M^+); δ ($CDCl_3$) 6.95–6.65 (3H, aromatic), 5.90 (s, 2H, O–CH_2–O), 5.05 (s, 1H), 3.10–2.70 (4H), 2.20–1.70 (2H). (Found: C, 55.14; H, 5.06; S, 27.00. Calc. for $C_{11}H_{12}S_2O_2$: C, 55.00; H, 5.00; S, 26.66%).

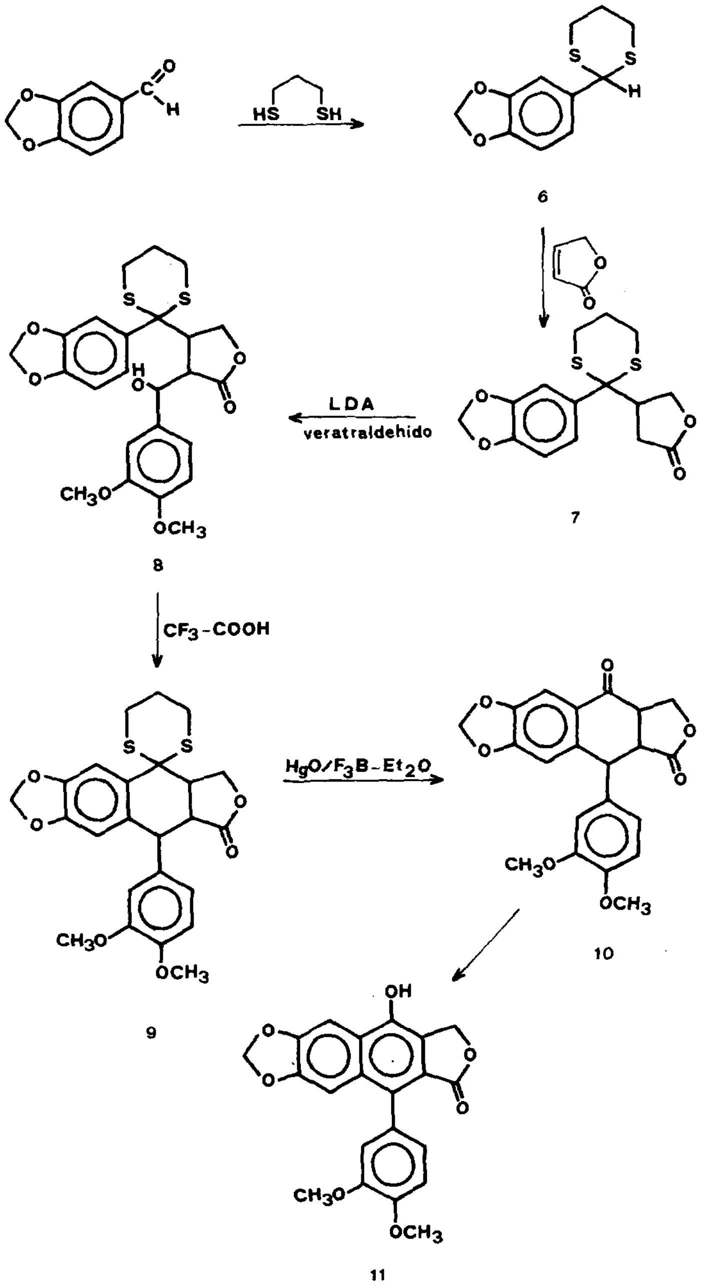
2 - (3,4 - *Methylenedioxyphenyl*) - 2γ - *butyrolactone* - 1,3 - *dithian* (**7**). Compound **6** (5.34 g) was dissolved in dry THF (250 ml) under argon. The mixture was chilled to −78°, n-BuLi (12 ml) was added and the temp. was raised to −45°, and maintained for 1 hr and then lowered again to −78°. γ-Crotonolactone[10] (1.73 g) dissolved in dry THF (77 ml) was added and the mixture left for 2 hr, 3 ml of conc. AcOH was then added and the mixture slowly warmed to r.t. It was extracted as usual, dried and evaporated leaving an oily residue which crystallized with Me_2CO– di-isopropyl ether (6 g, 90%), m.p. 154°; *m/e* 324 (M^+), base peak 239; $\nu_{max}^{CHCl_3}$ cm^{-1} 2900, 1770, 1710, 1600 and 1475; λ_{max}^{EtOH} (ϵ_{max}) nm 207 (17,000), 248 (3200), 290 (2900); δ ($CDCl_3$) 7.55–7.40 (2H, aromatic), 6.83 (d, 1H, aromatic), 6.01 (s, 2H, O–CH_2–O), 4.51–4.09 (m, 2H, lactone CH_2), 3.10–2.90 (m, 1H, CH_2–$\underline{C}H$–CH_2), 2.92–2.30 (6H), 2.05–1.80 (2H). (Found: C, 55.23; H, 5.02; S, 19.62. Calc. for $C_{15}H_{16}O_4S_2$: C, 55.55; H, 4.93; S, 19.75%).

2 - (3″,4″ - *Dimethoxybenzil*) - 6 - *hydroxy* - 5 - (1,3 - *dithian*) - 3 - (3′,4′ - *methylenedioxybenzil*) - *butyrolactone* (**8**). n-BuLi (15 ml) was added to a soln of di-isopropylamine (4.24 g) dissolved in dry THF (37.5 ml) under argon and cooled to −78°. After 20 min, **7** (7 g) dissolved in THF (100 ml), was added, and then left for a further hr. Veratrumaldehyde (3.6 g) in THF (30 ml) was next added and the mixture stirred for 1 hr. Finally, AcOH (3 ml) was added and the mixture brought slowly to r.t. The usual extraction was carried out and, after drying and evaporating, a dark yellow oil (12.83 g) was obtained which, upon chromatography, yielded 6.85 g (66%) of an isomer mixture.

1 - (3,4 - *Dimethoxyphenyl*) - 3 - *hydroxymethyl* - 4 - (2,3 - *dithian*) - 6,7 - *methylenedioxy* - 2 - *naphthoic acid lactone* (**9**). Compound **8** (2.45 g) was dissolved in Be (100 ml) and F_3CCO_2H (6.4 ml) was added while stirring. The soln was refluxed for 1 hr extracted in the normal way, dried, evaporated, yielding 2.09 g of brown residue which was purified by column chromatography. 1.5 g (62%) was separated and crystallized with Me_2CO-di-isopropyl ether: m.p. 262–264°; *m/e* 472 (M^+); $\nu_{max}^{CHCl_3}$ cm^{-1} 3000, 1775, 1500, 1478; λ_{max}^{EtOH}(ϵ_{max}) nm 210 (35,700), 285 (5100); δ ($CDCl_3$) 7.69 (s, 1H, aromatic), 6.89–6.69 (3H, aromatic), 6.26 (s, 1H, aromatic), 5.90 (s, 2H, O–CH_2–O), 4.84–4.39 (2H), 4.14–3.94 (1H), 3.88 (s, 3H, OCH_3), 3.84 (s, 2H, OCH_3), 3.44–3.24 (2H), 2.99–2.79 (4H), 2.29–1.99 (2H). (Found: C, 61.28; H, 5.33; S, 13.42. Calc. for $C_{24}H_{24}O_6S_2$: C, 61.01; H, 5.08; S, 13.56%).

1 - (3,4 - *Dimethoxyphenyl*) - 3 - *hydroxymethyl* - 4 - *keto* - 1,2,3,4 - *tetrahydro* - 6,7 - *methylenedioxy* - 2 - *naphthoic acid lactone* (**10**). Compound **9** (1 g) was dissolved in 15% THF–H_2O (50 ml) and while this was being stirred, HgO (1.4 g) and BF_3OEt_2 (0.82 ml) was added. Stirring was continued for 2 hr at r.t. Twice the total volume $CHCl_3$ was added and the mixture was washed with sat Na_2CO_3 aq and then with sat NaCl aq. After drying and evaporation, 0.64 g (80%) of **10** was obtained and crystallized from Me_2CO-di-isopropyl ether: m.p. 176–184°; *m/e* 382 (M^+); $\nu_{max}^{CHCl_3}$ cm^{-1} 3000, 1780, 1685, 1510, 1475, 1620; λ_{max}^{EtOH} (ϵ_{max}) nm 206 (35,000), 235 (24,300), 268 (9000), 320 (6250); δ ($CDCl_3$) 7.48 (s, 1H, aromatic), 6.92–6.60 (3H, aromatic), 6.40 (s, 1H, aromatic), 6.01 (s, 2H, O–CH_2–O), 4.78–4.15 (m, 4H), 3.90 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.30–3.00 (2H). (Found: C, 65.87; H, 4.66. Calc. for $C_{21}H_{18}O_7$: C, 65.96; H, 41.71%).

Isodiphyllin (**11**). Ketone **10** (400 mg) was dissolved in AcOH (50 ml) and SeO_2 (218 mg) was added. The mixture was refluxed for 2 hr and extracted as usual. After drying and evaporation, it was chromatographed and 120 mg (30%) of a crystalline product was obtained by crystallization with Me_2CO: m.p. 256° (decomp); *m/e* 380 (M^+); ν_{max}^{KBr} cm^{-1} 3500, 2900, 1740, 1635, 1460, 1340, 1235; λ_{max}^{EtOH} (ϵ_{max}) nm 207 (32,300), 230 (29,640), 267 (39,580), 313 (8230), 325 (8250), 364 (5000); δ [$(CD_3)_2CO$] 7.64 (s, 1H, aromatic), 7.10–6.75 (4H, aromatic), 6.12 (s, 2H, O–CH_2–O), 5.36 (s, 2H, lactone CH_2), 3.88 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3). (Found: C, 66.27; H, 4.25. Calc. for $C_{21}H_{16}O_7$: C, 66.31; H, 4.21%).



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