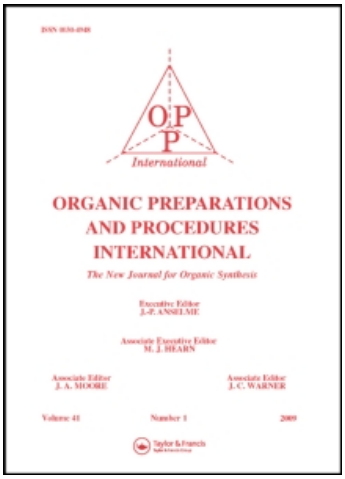

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PREPARATION OF 1,4-BIS(2,4,5-TRIMETHOXYPHENYL) BUTANE

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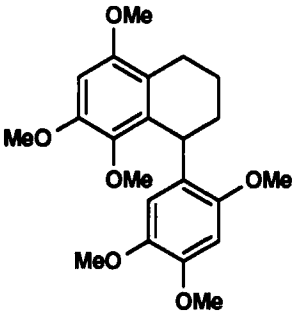
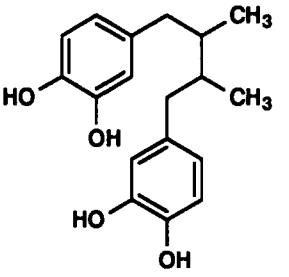
The aryltetralin pachypostaudin-A (**1**) has recently been isolated from extracts of the small tree *Pachypodanthium staudtii* Engl. & Diels, used for treatment of bronchitis, gastro-intestinal ailments, edemas and cancer.[1] Although the biogenesis of this product has not been established, the constitution presents the interesting features of having a *bisnor*-lignan structure and a 2,4,5-trimethoxyphenyl substitution pattern, rare in this class of natural products. We are presently undertaking a synthesis of **1** and report here a synthesis of the *seco* analogue, 1,4-bis(2,4,5-trimethoxyphenyl)butane (**3**) also required for biological evaluation. The parent lignan analogue, mesonordihydroguaiaretic acid (NDGA **2**) has long been of pharmacological interest[2] and recognition that it is a potent 5-lipoxygenase inhibitor led to use as an assay standard for this activity.[3,4]

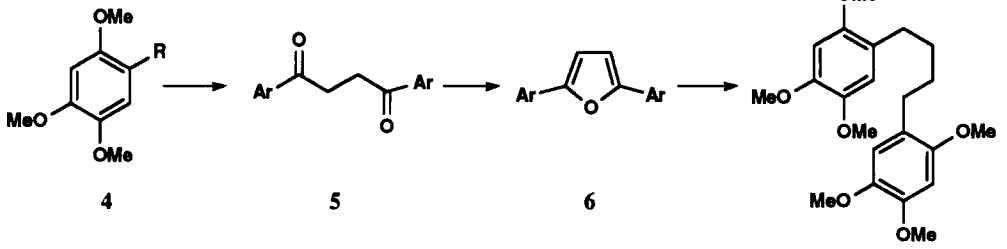


1



2

Acetylation of 1,3,4-trimethoxybenzene (**4a**) with acetic anhydride and iodine catalysis, by modification of the method recently used for the propiophenone analogue,[5] gave the methyl ketone **4b** in 88% yield, which surpasses that obtained by conventional Friedel-Crafts acetylation.[6] Conversion of **4b** to the 1,4-diketone **5**, was achieved, albeit in modest yield, by the cupric chloride promoted dimerization of the enolate of **4b** formed using lithium diisopropylamide in dimethylfor-



4 **5** **6** **3**

a) R = H b) R = COMe Ar = 2,4,5-Trimethoxyphenyl

mamide.[7] The diaryl furan **6** was formed quantitatively from **5** by cyclization with hydrogen chloride in methanol. This route was chosen additionally to provide **6** as an intermediate to the corresponding diaryltetrahydrofuran, analogues of which have been shown to be potent platelet activating factor (PAF) receptor antagonists[8-10] and which interestingly may also be regarded as *bisnor*lignans. Finally, catalytic hydrogenolysis of **6** at atmospheric pressure and ambient temperature gave the required bisarylbutane **3** cleanly.

EXPERIMENTAL SECTION

NMR measurements were carried out in $CDCl_3$ solution with a Varian XL-300 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C. Chemical shifts are given in ppm relative to TMS (0.00 ppm) for ^1H and to $CDCl_3$ (77.00 ppm) for ^{13}C.

2,4,5-Trimethoxyacetophenone (4b).- A mixture of 1,3,4-trimethoxybenzene (16.8 g, 0.1 mol), acetic anhydride (75 mL) and iodine (*ca.* 200 mg) was heated under reflux for 18 hr and the solvent then removed under reduced pressure. The residue was dissolved in benzene and filtered through a short column of alumina to effect decolorization. Concentration of the filtrate and dilution with petroleum ether gave a precipitate (18.5 g, 88%) which on crystallization from benzene yielded the ketone **4b** as colorless needles, mp. 98-98.5°, lit.[6] mp. 94-95°; ^1H NMR: δ 2.60 (s, 3H, CH_3CO), 3.88 (s, 3H, 4-OMe), 3.92(s, 3H, 5-OMe), 3.96 (s, 3H, 2-OMe), 6.50 (s, 1H, H-3), 7.43 (s, 1H, H-6). ^{13}C NMR: δ 32.42 ($COCH_3$), 56.42 (OMe), 56.46 (OMe), 56.58 (OMe), 96.68 and 112.80 (Ar*C*H), 119.45 (C-1), 143.33, 154.22 and 155.91 (Ar*C*-O) and 197.60 (*C*OCH_3).

1,2-bis(2,4,5-Trimethoxybenzoyl)ethane (5).- *n*-Butyllithium (28 mL, 1.6 M solution in hexane) was added to freshly distilled diisopropylamine (6.2 mL, 44 mmol) in dry tetrahydrofuran (16 mL) at -10°. The temperature was then lowered to -70° to -78° (acetone-CO_2 bath) and a solution of ketone **4b** (8.40 g, 40 mmol) in tetrahydrofuran (110 mL) added dropwise to the stirred mixture. A solution of cupric chloride (5.92 g, 44 mmol) in dimethylformamide (150 mL) was added dropwise after 2 hrs, and stirring was continued for 1 hr at this temperature and for an additional 16 hrs at room temperature. Addition of hydrochloric acid (1N, *ca.* 200 mL) to the reaction mixture (external ice cooling) gave a yellow-brown precipitate, which was collected and crystallized from tetrahydrofuran to yield the *diketone* **5** as colorless prisms (1.92 g, 23%), mp. 160-161.5°.

^1H NMR: δ 3.40 (s, 2H, -CH_2CO), 3.87 (s, 3H, 4-OMe), 3.95(s, 3H, 5-OMe), 3.96 (s, 3H, 2-OMe), 6.52 (s, 1H, H-3) and 7.48 (s, 1H, H-6). ^{13}CNMR: δ 38.38 ($COCH_2$-), 55.97 (OMe), 56.04 (OMe), 56.15 (OMe), 96.36 and 112.56 (Ar*C*H), 118.4 (C-1), 142.87, 154.58 and 155.36 (Ar*C*-O) and 198.53 (*C*O).

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H,6.26. Found: C, 63.10; H, 6.25

2,5-bis(2,4,5-Trimethoxyphenyl)furan (6).- To a solution of hydrogen chloride in methanol (180 mL) (prepared by bubbling HCl gas) was added the diketone **5** (400 mg) and mixture heated under reflux for 1 hr. It was then concentrated to about half bulk and allowed to cool to ambient tempera-

ture at which time a crystalline precipitate separated. Recrystallization from methanol gave the *furan* **6** as felted needles (380mg, 98%), mp. 167.5-168°.

^{1}H NMR: δ 3.93 (s, 6H, two OMe), 3.95 (s, 3H, OMe), 6.91 (s, 1H, H-3), 6.59 (s, 1H, H-3') and 7.48 (s, 1H, H-6'). ^{13}C NMR: δ 55.95 (OMe), 56.08 (OMe), 56.43 (OMe), 97.75 (C-3), 109.58 and 110.63 (ArCH), 112.19 (C-2), 142.98, 147.91, 148.57 and 150.16 (Ar*C*).

Anal. Calcd. for $C_{22}H_{24}O_7$: C, 65.99; H,6.04. Found: C, 65.59; H, 6.05

1,4-bis(2,4,5-Trimethoxyphenyl)butane (3).- A solution of the furan **6** (400 mg) in acetic acid (200 mL) was stirred under hydrogen with Pd/C (10%, 650 mg) for 16 hrs at atmospheric pressure. It was then filtered and evaporated under reduced pressure to give a residual solid which was recrystallized from methanol to yield the *diarylbutane* **3** as prisms (210 mg, 54%), mp. 128.5-129°.

^{1}H NMR: δ 1.61 (m, 2H, $ArCH_2CH_2$-), 2.58 (m, 2H, $ArCH_2$-), 3.79 (s, 3H, 4-OMe), 3.82 (s, 3H, 5-OMe), 3.87 (s, 3H, 2-OMe), 6.51 (s, 1H, H-3) and 6.69 (s, 1H, H-6). ^{13}C NMR: δ 29.38 and 30.06 ($ArCH_2CH_2$), 56.13 (OMe), 56.35 (OMe), 56.55 (OMe), 97.87 and 114.08 (ArCH), 122.74 (Ar-C-1'), 142.68, 147.36 and 151.37 (Ar*C*).

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H,7.74. Found: C, 67.59; H, 7.88

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