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Synthesis of 4-(1,5,9-Trimethyl-1-vinyl-4,8-decadienyl)catechol Dimethyl Ether

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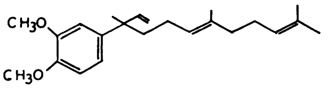
Synposis. Synthesis of 4-(1,5,9-trimethyl-1-vinyl-4,8-decadienyl)catechol dimethyl ether has been described utilizing Wittig reaction for the introduction of vinylic substituent at the quaternary carbon.

4-(1,5,9-Trimethyl-1-vinyl-4,8-decadienyl)catechol (**I**), a C_{21} terpenoid with novel structure has recently been isolated[1] from the hexane extracts of the roots and leaves of *Potomorphe umbellata (L)* Miq (Piperaceae*) by Kijjoa and coworkers. It has been assigned constitution (**I**) on the basis of spectroscopic studies.



(I) R=H
(Ia) R=CH3

In the present paper we wish to report a synthesis of 4-(1,5,9-trimetyl-1-vinyl-4,8-decadienyl)catechol dimethyl ether and thus corroborate the structure assigned to (**I**).

4-(1,5,9-Trimethyl-1-vinyl-4,8-decadienyl)catechol dimethyl ether (**Ia**) could be synthesized using 2-(3,4-dimethoxyphenyl)ethanenitrile (**II**) as the suitable starting compound and Wittig reaction for the introduction of vinylic substituent at the quaternary carbon-1. The scheme of the synthesis is given below: 2-(3,4-Dimethoxyphenyl)ethanenitrile (**II**) was subjected to alkylation with 9-bromo-2,6-dimethyl-2,6-nonadiene[2] in the presence of NaH–DME. The quaternary carbon could conveniently be generated by methylation of alkylated nitrile (**III**) with CH_3I in NaH–HMPA mixture. Grignard reaction of CH_3MgI on nitrile (**IV**) followed by acid hydrolysis of the crude product afforded a complex mixture as indicated by TLC. IR also did not show any significant absorption in the carbonyl region. However, nitrile(**IV**) could be converted into vinyl group through multi-step sequence of reactions (**IV**→**Ia**).

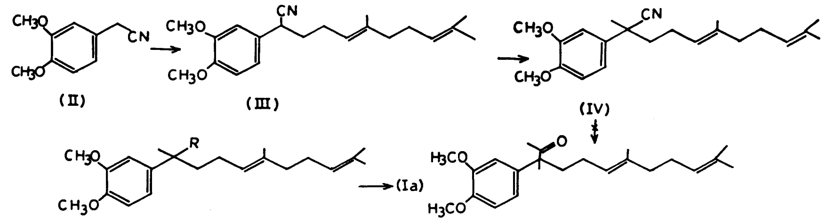
Alkaline hydrolysis of 2-(3,4-dimethoxyphenyl)-2,6,10-trimethyl-5,9-undecadienenitrile (**IV**) furnished the acid (**V**) which was esterified with CH_3I in NaH–DMF. LAH reduction of the ester (**VI**) gave the corresponding alcohol. Pyridinechlorochromate oxidation of the alcohol (**VII**) generated the aldehyde (**VIII**) which on submission to methylenetriphenylphosphorane resulted in the formation of 4-(1,5,9-trimethyl-1-vinyl-4,8-decadienyl)catechol dimethyl ether. IR and NMR of this product is in good agreement with the data reported by Kijjoa and coworkers'.

Experimental

Boiling points are uncorrected. IR spectra were recorded on Pye Unicam SP 1200 or Perkin-Elmer IR spectrophotometer. Thin liquid films were used in NaCl or KBr optics. NMR spectra were recorded in CCl_4 or $CDCl_3$ at 60 MHz Varian A60D, 90 MHz Perkin Elmer spectrometer or 100 MHz JNM-FX 100 FT-NMR spectrometer (JEOL). TMS was used as internal standard. Anhydrous Na_2SO_4 was used as drying agent. DMSO and HMPA were dried over CaH_2 and DME was dried over LAH.

2-(3,4-Dimethoxyphenyl)ethanenitrile (II). To a suspension of $SOCl_2$ (8 ml) and powdered $CaCl_2$ (0.5 g) at 35 °C was added 3,4-dimethoxybenzyl alcohol (15.0 g, 0.083 mol) in benzene (15 ml) in 1 h whereupon ether (25 ml) and $CaCO_3$ (1 g) were added. After stirring for overnight, the excess reagent was decomposed by cold water (120 ml) and then worked up in the usual manner. The solvent was distilled off and the residue was refluxed with a mixture of benzene (20 ml), NaCN (8.5 g) and water (40 ml) for 6 h. The solvent was washed with water and dried. The solvent was distilled off and the residual oil was fractionated *in vacuo* to afford nitrile (**II**, 7.7 g) in 52.7 % yield, bp 131—132 °C/2 mm, R_f 0.59 (C_6H_6 : EtOAc 9 : 1). IR: ν_{max} 2255, 1520, 1460, 1385, 1162, 1148, 1030, 810, 768, 745 cm^{-1}. NMR: δ=3.6(2H, s), 3.84 (6H, s), 6.76 (3H, s). Found: C, 68.12; H, 6.74; N, 8.1 $C_{10}H_{11}O_2N$ requires C, 67.78; H, 6.26; N, 7.9%.

2-(3,4-Dimethoxyphenyl)-6,10-dimethyl-5,9-undecadienenitrile (III). 2-(3,4-Dimethoxyphenyl)ethanenitrile (II, 2.0 g,



(V) R=COOH
(VI) R=$COOCH_3$
(VII) R=CH_2OH
(VIII) R=CHO

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* Also known as pariparoba or Caapeba and used in Brazil as popular medicine for the treatment of liver diseases or epilepsy.

0.011 mol) dissolved in DME (5 ml) was added to a stirred suspension of NaH (50 %, 0.625, 0.013 mol) in DME (8 ml) under N_2. After stirring for 1 h, a solution of 9-bromo-2,6-dimethyl-2,6-nonadiene (2.77 g, 0.012 mol) in DME (6 ml) was added to the reaction mixture. It was stirred overnight at room temperature and then heated at 50 ° for 5h. After cooling, it was poured into ice cold water (120 ml). The reaction mixture was extracted with ether (3 × 40 ml). The combined organic extracts were washed with brine and dried. The solvent was evaporated and the residue chromatographed on silica gel (120 g). The desired product (**III**, 1.4 g) was obtained from the elute with benzene in 40 % yield. R_f 0.76 (C_6H_6–EtOAc 9 : 1). IR: ν_{max} 2245, 1622, 1605, 1530, 1460, 1428, 1272, 1248, 1150, 1032, 850, 810, 765, 640 cm^{-1}. NMR: $\delta = 1.56$(6H, s), 1.68(3H, s), 1.8—2.16(8H, m), 3.64(1H, t, $J=7$ Hz), 3.84(6H, s), 5.08—5.16(2H, m), 6.76(3H, br). Found: C, 77.40; H, 9.20; N, 3.99. $C_{21}H_{29}O_2N$ requires C, 77.02; H, 8.93; N, 4.28%.

2-(3,4-Dimethoxyphenyl)-2,6,10-trimethyl-5,9-undecadienenitrile (IV). To a stirred and cooled solution of NaH(50%, 0.145 g, 3.0 mmol) in HMPA(6 ml) under N_2 atmosphere was added alkylated nitrile (**III**, 0.8 g, 2.4 mmol) dissolved in HMPA (8 ml) dropwise. It was stirred at room temperature for 1 h followed by dropwise addition of a solution of CH_3I (0.710 g, 5.0 mmol) in HMPA (4 ml) at room temperature. After stirring overnight, it was warmed to 60 °C for 2 h. Ice cold water (50 ml) was added to the reaction mixture and extracted with ether (4 × 25 ml). The combined ether extracts were washed with water (3 × 25 ml) and dried. The solvent was distilled and residual oil chromatographed on silica gel (60 g). The desired product was obtained with petroleum ether–benzene (2 : 8) as a light yellow oil (**IV**, 0.630 g) in 77% yield; R_f 0.78 (C_6H_6–EtOAc 9 : 1). IR: ν_{max} 2248, 1612, 1530, 1460, 1428, 1398, 1272, 1250, 1155, 1032, 850, 820, 730 cm^{-1}. NMR: $\delta = 1.49$(3H, s), 1.56(6H, s), 1.6—2.12(11H, m), 3.86(6H, s), 5.02—5.16(2H, m), 6.78—6.86(3H, m). Found: C, 77.82; H, 9.20; N, 4.33. $C_{22}H_{31}O_2N$ requires C, 77.37; H, 9.15; N, 4.1%.

Reaction of 2-(3,4-Dimethoxyphenyl)-2,6,10-trimethyl-5,9-undecadienenitrile (IV) with Methylmagnesium Iodide. Methylmagnesium iodide was prepared from Mg(0.1 g, 4.2 mmol) and CH_3I(0.596 g, 4.2 mmol) in ether (30 ml). To this chilled solution was added nitrile (**IV**, 0.5 g, 1.4 mmol) in ether (8 ml) with stirring. The resulting mixture was allowed to stir at room temperature overnight and then refluxed for 6 h. The reaction mixture was cooled and acidified with HCl (10%, 25 ml). After working up in the usual manner, it was dried and solvent removed. TLC of the residual oil showed it to be a complex mixture difficult to separate and IR did not show any significant absorption in carbonyl region.

2-(3,4-Dimethoxyphenyl)-2,6,10-trimethyl-5,9-undecadienoic Acid (V). To a mixture or NaOH (1.5 g) in aqueous ethanol (60%, 8 ml) was added alkylated nitrile (**IV**, 0.6 g, 1.7 mmol). The reaction mixture was heated to reflux for 26 h with stirring. After cooling the reaction mixture was poured into ice cold water (75 ml) and unreacted nitrile was extracted with ether (3 × 50 ml). Aqueous phase was acidified with dil HCl (20%, 30 ml) to pH ≈2. It was saturated with NaCl and extracted with ether (5 × 20 ml). The combined organic phase was washed with brine (3 × 25 ml) and dried. The solvent was evaporated and the residual oil was chromatographed on silica gel (50 g). The pure acid (**V**, 0.530 g) was procured through benzene–ethyl acetate (8 : 2) as the eluent in 86.6% yield; R_f 0.36 (C_6H_6–EtOAc 9 : 1). IR: ν_{max}. 3520—3080, 1710, 1630, 1598, 1520, 1462, 1452, 1278, 1140, 1030, 830, 742 cm^{-1}. NMR: $\delta = 1.34$(3H, s), 1.56(6H, s), 1.62(3H, s), 1.8—2.1(6H, m), 2.64(2H, m), 3.82(6H, s), 4.98—5.0(2H, m), 6.74—6.84(3H, m), 10.79 (1H, s). Found: C, 73.40; H, 8.88. $C_{22}H_{33}O_4$ requires C, 73.30; H, 8.95%.

Methyl 2-(3,4-Dimethoxyphenyl)-2,6,10-trimethyl-5,9-undecadienoate (VI). To a stirred suspension of NaH (50%, 0.067 g, 1.4 mmol) in DMF (4 ml) was added acid (**V**, 0.450 g, 1.2 mmol) in DMF (3 ml). After 30 min, a solution of CH_3I (0.340 g, 2.4 mmol) in DMF (4 ml) was added to the resulting solution. The reaction mixture was quenched by adding it to ice cold water(60 ml). It was extracted with ether (3 × 50 ml) and the organic layer was washed with brine (2 × 30 ml) and dried. The solvent was removed and oil left behind was purified by PLC in benzene–hexane (9 : 1) to give the ester (**VI**, 0.452 g) in 96.7% yield; R_f 0.6 (C_6H_6–EtOAc 9 : 1). IR: ν_{max} 1738, 1598, 1525, 1460, 1280, 1145, 1105, 1030, 820, 805 cm^{-1}. NMR: $\delta = 1.29$(3H, s), 1.56(6H, s), 1.64(3H, s), 1.66—1.88(6H, m), 2.56(2H, br), 3.6(3H, s), 3.78(6H, s), 4.96(2H, m), 6.64(3H, m). Found: C, 74.20; H, 9.00. $C_{23}H_{34}O_4$ requires C, 73.46; H, 9.15%.

2-(3,4-Dimethoxyphenyl)-2,6,10-trimethyl-5,9-undecadien-1-ol (VII). A solution of ester (**VI**, 0.4 g, 1.0 mmol) in ether (8 ml) was added dropwise at room temperature to a slurry of LAH (0.152 g, 4.0 mmol) in ether (15 ml). After refluxing for 6 h, it was decomposed with NaOH (2%, 20 ml), and worked up in the usual way. The solvent was evaporated and the residual oil was purified by PLC in benzene-ethyl acetate (9 : 1) to get the pure alcohol (**VII**, 0.28 g) in 80.9% yield; R_f 0.39 (C_6H_6–EtOAc 9 : 1). IR: ν_{max} 3560—3240, 1615, 1525, 1480—1460, 1422, 1270, 1165, 1038, 840, 790, 770 cm^{-1}. NMR: $\delta = 1.28$(3H, s), 1.56(6H, s), 1.64(3H, s), ≈1.94(6H, br), 2.28(2H, m), ≈3.6(2H, br), 3.8(6H, s), 4.96(2H, m), 6.64(3H, m). Found: C, 76.34; H, 9.40. $C_{22}H_{34}O_3$ requires C, 76.26; H, 9.89%.

2-(3,4-Dimethoxyphenyl)-2,6,10-trimethyl-5,9-undecadienal (VIII). PCC oxidation of alcohol (**VIII**, 0.2 g, 0.57 mmol) was carried out using PCC(0.170 g), fused NaOAc (0.015 g) in CH_2Cl_2 (30 ml) to afford the aldehyde (**VIII**, 0.172 g) in 87.7% yield; R_f 0.42(C_6H_6–EtOAc 9 : 1). IR: ν_{max} 2728, 1735, 1630, 1525, 1460, 1278, 1268, 1032, 828, 805 cm^{-1}.

3-(3,4-Dimethoxyphenyl)-3,7,11-trimethyl-1,6,10-dodecatriene (Ia). Reaction of aldehyde (**VIII**) with methylenetriphenylphosphorane was carried with NaH (50%, 0.052 g, 1.1 mmol) in DMSO (2.2 ml), methyltriphenylphosphonium iodide (0.458 g, 1.2 mmol) in DMSO(4.2 ml) under N_2 atmosphere. To this solution was added aldehyde (**VIII**, 0.160 g, 0.46 mmol) in DMSO (4 ml) at 10 °C. It was worked up in the usual manner and then chromatographed over silica gel (75 g). The desired product was obtained in petroleum ether–benzene (8 : 2). This was followed by PLC in benzene–hexane (6 : 4) to afford 4-(1,5,9-trimethyl-1-vinyl-4,8-decadienyl)catechol dimethyl ether (**Ia**, 0.066 g) in 42% yield; R_f 0.71 (C_6H_6–EtOAc 9.5 : 0.5). IR: ν_{max} 3110, 1600, 1518, 1447, 1378, 1280, 1128, 1020, 920, 850, 800, 760, 660 cm^{-1}. NMR: $\delta = 1.3$ (3H, s, $CH_2{=}CH{-}\underset{|}{C}{-}C\underline{H}_3$), 1.58[6H, s, $-CH{=}C(C\underline{H}_3)_2$], 1.67 (3H, s, $C\underline{H}_3{-}\overset{|}{C}{=}CH{-}$), 1.7—2.35 [8H, m, $-(C\underline{H}_2)_2{-}CH{=}\overset{|}{C}(C\underline{H}_2)_2{=}C(CH_3)_2$], 3.86 (6H, s, 2 × aromatic OCH_3), 5.08 [4H, br, $-CH{=}C\underline{H}_2$ plus $-\overset{|}{C}{=}C\underline{H}$–plus–$C\underline{H}{=}C(CH_3)_2$], 5.92 (1H, br, $-C\underline{H}{=}CH_2$), 6.72 (3H, m, aromatic protons). Found: C, 81.10; H, 10.24. $C_{23}H_{34}O_2$ requires C, 80.65; H, 10.01%.

References

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