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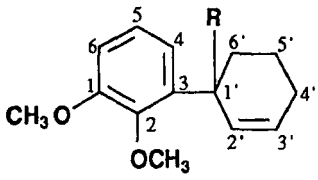
A NEW APPROACH TO 2-(1-ALKYL-CYCLOHEX-2-EN-1-YL) PHENOLS.

M. Essamkaoui[a], J. Mayrargue[a], J.-M. Vierfond[a], A. Reynet[a], H. Moskowitz[a]* et C. Thal[b]

ABSTRACT - The synthesis of 2-(1-alkylcyclohex-2-en-1-yl) phenols has been accomplished in three steps : *o*-iodination of veratrole, palladium cross-coupling with cyclohexene and angular alkylation.

The 2-(1-alkylcyclohex-2-en-1-yl) phenols **1** are useful intermediates in the synthesis of molecules with a dibenzofuranic skeleton and are related to Pummerer's ketone **2**[1], and to Amaryllidaceae alkaloids **3**[2].



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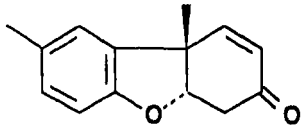

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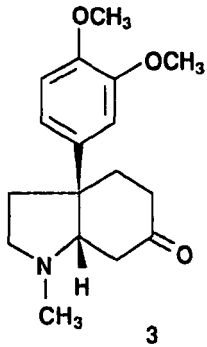

3

1a R = CH_3 (7')

1b R = D

1c R = CH_2-CH=CH_2 (7', 8', 9')

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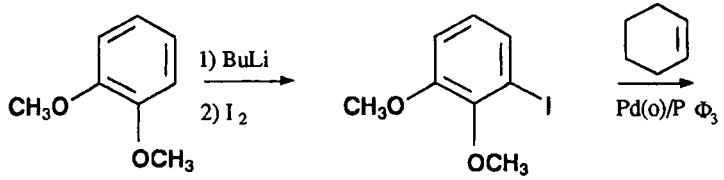
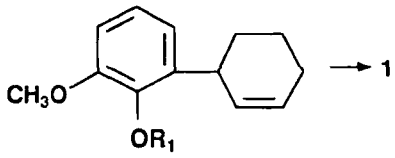
The compounds **1** are usually obtained by annelation reactions[3,4] or by Claisen-Eschenmoser rearrangements[5,6]. Searching for a new shorter solution, we looked at the preparation of arylcyclohexene **4** and its subsequent angular alkylation.





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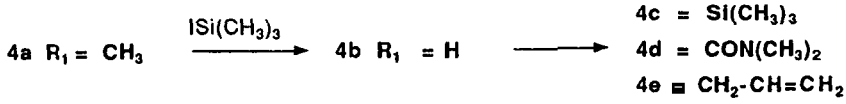

Methods for *o*-iodination of phenols or ethers are not general and often complex and unselective[7-8]. We therefore performed the iodination of *o*-lithiated veratrole with iodine, by adaptation of a procedure described for arylamides[9]. The palladium-catalysed cross-coupling[10] of iodoveratrole and cyclohexene leads, in 50% yield, to compound **4a**. We encountered difficulties in the creation of the quaternary carbon. At first, the procedures used to alkylate benzylic carbons[11-13] were tried unsuccessfully. We also failed on use of techniques previously applied, with variable results[13], to 2-arylcyclohexanones.

We have then studied carefully the metalation conditions (solvent, base, catalyst, temperature). Carbanion formation is well correlated with the appearance of a red-purpish color and this anion is only obtained under very strict conditions : use of butyllithium in anhydrous THF, without co-solvent, with an equimolar amount of TMEDA, in a temperature range between -10 °C and -15 °C. The formation of this benzylic anion was established by a deuteriation experiment, if R_1 is a methoxy group (**1b**, 60%). However, if R_1 = $OSi(CH_3)_3$ or $OCON(CH_3)_2$, the

coloration does not appear and a total or partial deprotection of the phenolic function is observed. Therefore, the assistance of metalation by adjunction of a carbamate protecting group, as described by Snieckus[14], cannot be retained. In our conditions, only very reactive alkyl halides (methyl iodide and allyl bromide) lead to alkylated products. This angular allylation reaction is nevertheless important, in view of the functional reactivity of the allylic group, leading to total synthesis previously described.

Experimental

- *o*-iodoveratrole :

A solution of 1.38 g (0.01 mole) of veratrole in 15 ml of THF under a nitrogen atmosphere was cooled to -10 °C, followed by the addition of 7 ml (1.1 equivalent) of a 1.6 M n-butyllithium solution in hexane. The mixture was allowed to warm to room temperature under two hours stirring. The solution was cooled at -45 °C, followed by the addition of 2,79 g ((0.011 mole) of iodine in 20 ml of THF. The cold bath was removed and the reaction mixture was stirred at 20 °C for two hours. The solution was concentrated *in vacuo* and the residue was extracted with diethyl ether. The organic layer was washed with a 20% solution of $NaHSO_3$ (2x20 ml), then with a saturated $NaHCO_3$ (2x20 ml) solution. After drying over anhydrous Na_2SO_4, the organic solution was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (eluent : dichloromethane/hexane 40/60) to yield 1.96 g (74%) of *o*-iodoveratrole.

Anal. calc.% : C = 36.39; H = 3.43. Found % : C = 36.27; H = 3.58.

^1H NMR ($CDCl_3$, δ ppm) : 7.3 (dd, 1H); 6.7 (m, 2H); 3.8 (2s, 2 OCH_3).

^{13}C NMR ($CDCl_3$, δ ppm) : 152.3 (s, C_1); 148.3 (s, C_2); 129.9 (d, C_5); 125.5 (d, C_4); 112.3 (d, C_6); 92.1 (s, C_3); 59.8 and 55.5 (2s, 2 OCH_3).

- 3-(cyclohex-2-en-1-yl)-1,2-dimethoxybenzene 4a :

A mixture of 132 mg (0.5 mmole) of iodoveratrole, 200 mg (2.5 mmoles) of cyclohexene, 2.5% of $Pd(OAc)_2$, 0.5 mmole of n-Bu_4NCl, 1.5 mmol of KOAc, 2.5% of $P(C_6H_5)_3$ and 1 ml of DMF was warmed at 80 °C for three days under argon. The reaction mixture was concentrated *in vacuo*; 5 ml of water was added to the residue, which was extracted with ethyl acetate (3x10 ml). After usual work-up,

the product was isolated (50%) by silica gel chromatography (eluent : 30% ethyl acetate/hexane).

Anal. Calc.% : C = 77.03 ; H = 8.31 ; found% : C = 76.84 ; H = 8.21.

^{1}H NMR ($CDCl_3$, δ ppm) : 7.1-6.7 (m, ArH); 5.9 (m, 1H); 5.6 (m, 1H); 3.9 (2s+m, 7H); 2.2-1.5 (m, 6H).

^{13}C NMR ($CDCl_3$, d ppm) : 152.5 (s, C_1); 146.6 (s, C_2); 140.0(s, C_3); 130.4 (d, $C_{2'}$); 128.0 (d, $C_{3'}$); 123.6 (d, C_5); 120.4 (d, C_4); 110.0 (d, C_6); 60.8 (q, OCH_3); 55.5 (q, OCH_3); 34.7 (d, $C_{1'}$); 31.3 (t, $C_{6'}$); 24.9 (t, $C_{4'}$); 21.4 (t, $C_{5'}$).

Typical procedure for the preparation of 1a-1c : 3-(1-alkylcyclohex-2-en-1-yl)-1,2-dimethoxybenzene :

To a stirring and cooled (-15 °C to -10 °C) solution of 0.01 mole of 3-(cyclohex-2-enyl)-1,2-dimethoxy-benzene in 15 ml of dry THF, under argon, was added dropwise n-butyllithium solution (0.012 mole of 1.6 M solution in hexane), the temperature being kept under -10 °C. After stirring for 1h30 at room temperature, the mixture was cooled at -10 °C and 0.012 mole of methyl iodide or allyl bromide in 2 ml of dry THF was added dropwise. After stirring for 12 h at room temperature, the mixture was quenched with methanol and, after normal work-up, chromatographed on silica gel (eluent : ethyl acetate/petroleum ether 5/95) to yield isolated products **1a** (30 %), **1c** (64 %).

1a.

^{1}H NMR ($CDCl_3$, δ ppm) : 7.0 and 6.85 (2m, ArH); 5.8 (s, 2H); 3.9 (2s, 6H); 2.35 (m, 1H); 2.0 (m,2H); 1.6 (m, 2H); 1.5 (s, 3H), 1.4 (m, 1H).

^{13}C NMR ($CDCl_3$, δ ppm) : 153.3 (s,C_1); 148.1 (s, C_2); 141.9 (s, C_3); 136.5 (d, C_2); 125.2 (d, $C_{3'}$); 122.5 (d, C_5); 121.4 (d, C_4); 110.6 (d, C_6); 60.2 (q, CH_3); 55.6 (q, CH_3); 39.6 (s, $C_{1'}$); 35.9 (t, $C_{2'}$); 28.4 (q, CH_3); 25.2 (t, $C_{4'}$); 19.5 (t, $C_{5'}$).

1c.

Anal. Calc.% : C = 79.03 ; H = 8.58; found% : C = 79.1; H = 8.7.

^{1}H NMR ($CDCl_3$, δ ppm) : 7 (m, ArH); 6 (dq, 1H); 5.9 (dt, 1H); 5.6 (m, 1H); 5 (m, 2H); 3.9 and 3.85 (2s, 6H); 2.95 (ddt, 1H); 2.5 (m, 2H); 2.05 (m, 2H); 1.8-1.3 (m, 3H).

^{13}C NMR ($CDCl_3$, δ ppm) : 153.2 (s, C_1); 147.8 (s, C_2); 139.5 (s, C_3); 135.9 (d, $C_{8'}$); 134.2 (d, $C_{2'}$); 126.6 (d, $C_{3'}$); 122.6 (d, C_5); 122.3 (d, C_4); 116.4 (t, $C_{9'}$); 110.8 (d, C_6); 60.0 (q, CH_3); 55.6 (q, CH_3) ; 44.9 (t, $C_{7'}$); 43.0 (s, $C_{1'}$); 34.0 (t, $C_{6'}$); 25.4 (t, $C_{4'}$); 19.2 (t, $C_{5'}$).

In the case of **1b**, after cooling at -10 °C, the mixture was quenched with some drops of deuterium oxide; the solution was evaporated and the crude residue was examined by NMR. The percentage of deuteration (60%) was estimated by disappearence of multiplet at 3.9 ppm and NMR integration.

Demethylation of 4a[15]

To a stirring solution of 218 mg (1 mmole) of **4a** in 3 ml of $CHCl_3$, was added 0.17 ml (1 mmole) of trimethylsilyl iodide, under argon. After stirring for 1hour at room temperature, 4 mmoles of methanol was added . The solvent was removes *in vacuo* and, after normal work-up, chromatographed on silica gel (eluent: ethyl acetate/ petroleum ether 5/95) to yield 132 mg of **4b** (65 %).

Anal. Calc.% : C = 76.81; H = 7.43; found% : C = 76.65; H = 7.59.

^1H NMR ($CDCl_3$, δ ppm) : 6.8 (m, ArH); 5.95 (m, 1H); 5.8 (s, OH); 5.65 (m, 1H); 3.9 (s+m, 4H); 2.1 (m, 3H); 1.8-1.5 (m, 3H).

^{13}C NMR ($CDCl_3$, δ ppm) : 146.2 (s, C_1); 143.0 (s, C_2); 131.9 (s, C_3); 130.0 (d, $C_{2'}$); 128.3 (d, $C_{3'}$); 120.8 (d, C_5); 119.0 (d, C_4); 108.3 (d, C_6); 55.9 (q, CH_3); 34.5 (d, $C_{1'}$); 29.8 (t, $C_{6'}$); 25.0 (t, $C_{4'}$); 21.0 (t, $C_{5'}$).

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