A New Method of Aromatization of Cyclohexenone Derivatives; Synthesis of Cannabichromene

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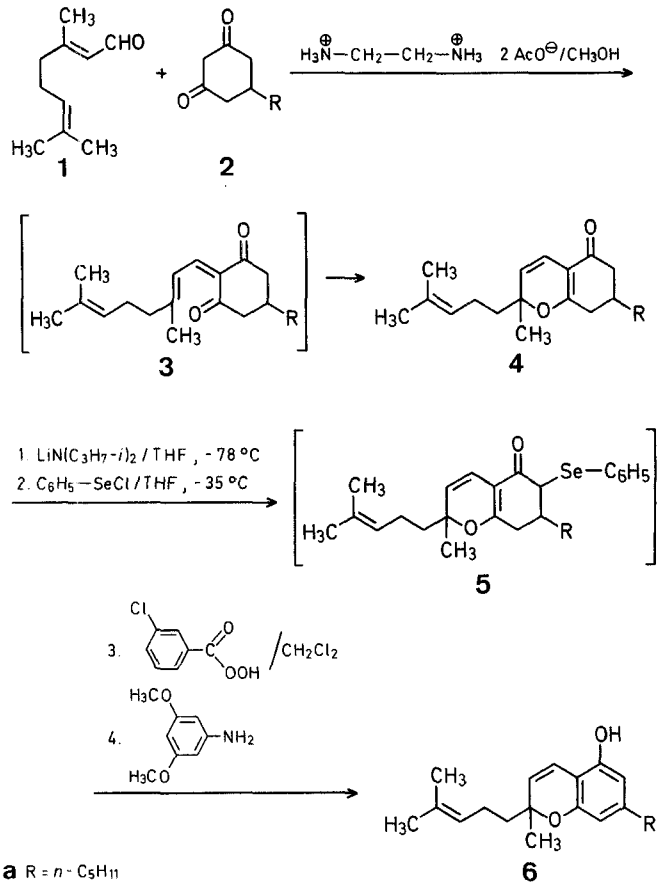
Cannabichromene **(6a)** was first isolated from extracts of *Cannabis sativa L.*[1]. It can be synthesized by base-catalyzed condensation of citral **(1)** with olivetol (5-*n*-pentylresorcinol). The yields of **6a** are quite low since the compound is sensitive and various by-products are formed which are difficult to separate[2]. In this paper, we describe a selectively proceeding synthesis of **6a** in which a hydroaromatic intermediate is aromatized by a new, mild method using a selenoorganic compound.

The reaction[3] of citral **(1)** with 5-pentyl-1,3-cyclohexanedione[4] **(2a)** in methanol in the presence of catalytic amounts of 1,2-ethanediammonium diacetate at 20 °C gives, after purification on silica, the 5,6,7,8-tetrahydrochromene derivative **4a** in 62% yield. It can be assumed that the aldol condensation product **3a** is an intermediate from which **4a** is formed by an electrocyclic process. For the transformation of **4a** into **6a** it is necessary to aromatize the cyclohexenone ring; this can be achieved without affecting the double bond in **4a** by a three-step process which may be carried out as a one-pot procedure without isolation of the intermediates.

Deprotonation of **4a** with lithium diisopropylamide followed by treatment with phenylselenenyl chloride at −35 °C leads to the formation of the selenide **5a** which is oxidized with 3-chlorobenzoperoxoic acid at −35 °C to give the corresponding selenoxide. Addition of 3,5-dimethoxyaniline and warming up to 20 °C then affords cannabichromene **(6a)** in 37% yield. By this method, no seleno-derivative of cannabichromene is obtained since the phenylselenenic acid, which is produced during the elimination process, attacks only 3,5-dimethoxyaniline as the most electron-rich aromatic system. Without the addition of 3,5-dimethoxyaniline, selenoderivatives of **6a** are formed nearly exclusively. Compound **4b**, obtained from citral **(1)** and 1,3-cyclohexanedione in 63% yield, may be analogously aromatized to **6b** in 45% yield.

Using known aromatization methods[4,5], the conversion of compounds **4a** and **4b** into **6a** and **6b**, respectively, cannot be achieved. There either is no reaction at all or the C=C double bond and the formed aromatic system are attacked; these are the most frequent side reactions. Therefore, it should be emphasized that even compounds with C=C double bonds in a side chain could be aromatized using the described procedure.



2-Methyl-2-(4-methyl-3-pentenyl)-5-oxo-7-pentyl-5,6,7,8-tetrahydro-2*H*-chromene (4a):

Citral (**1**; 0.76 g, 5 mmol) is added within 30 min to a stirred, water-cooled solution of 5-pentyl-1,3-cyclohexanedione (**2a**; 1.00 g, 5.5 mmol) and 1,2-ethanediammonium diacetate (50 mg, 0.28 mmol) in dry methanol (10 ml) at 20 °C. The mixture is stirred for 1 h, the solvent then evaporated in vacuo, and the residue dissolved in ether (25 ml). The solution is washed with water (10 ml), saturated sodium hydrogen carbonate solution (10 ml), and saturated sodium chloride solution (10 ml), dried with sodium sulfate, and evaporated in vacuo. The residual product is purified by column chromatography on silica gel using ether/petroleum ether (1/7.5) as eluent; yield: 0.97 g (62%); yellow oil, R_F: 0.10.

$C_{21}H_{32}O_2$	calc.	C 79.69	H 10.19
(316.5)	found	79.46	10.33

M.S.: m/e = 316.2400 (calc. 316.2402).

I.R. (film): ν = 2960, 2920, 2850 (C—H aliphat.); 1655 (C=O, C=C); 1600 cm^{-1} (C=C).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 0.83 (t, 3H, J = 6 Hz, CH_3); 1.0–1.4 (m, 8H, CH_2); 1.34 (s, 3H, 2-CH_3); 1.54 (s, 3H, C=C—CH_3); 1.62 (s, 3H, C=C—CH_3); 1.75–2.6 (m, 9H, CH_2—CH_2, 6-H_2, 7-H, 8-H_2); 4.80–5.15 (m, 1H, 3'-H); 5.06 (d, 1H, J = 10 Hz, 3-H); 6.31 ppm (d, 1H, J = 10 Hz, 4-H).

2-Methyl-2-(4-methyl-3-pentenyl)-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene (4b):

Citral (**1**; 15.2 g, 0.10 mol) is added within 2 h to a stirred, water-cooled solution of 1,3-cyclohexanedione (**2b**; 11.5 g, 0.21 mol) and 1,2-ethanediammonium diacetate (0.85 g, 4.7 mmol) in dry methanol (150 ml) at 20 °C. The mixture is stirred for 1 h, the solvent then evaporated in vacuo, and the residue dissolved in ether (500 ml). The solution is washed with water (100 ml), saturated sodium hydrogen carbonate solution (100 ml), and saturated sodium chloride solution (100 ml), dried with sodium sulfate, and evaporated in vacuo. The residual product is purified by Kugelrohr distillation; yield: 14.6 g (63%); b.p. 145 °C (oven)/0.1 torr (Ref.[3], b.p. 135–136 °C/0.1 torr); light yellow oil.

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^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.35 (s, 3H, 2-CH_3); 1.55 (s, 3H, C=C—CH_3); 1.65 (s, 3H, C=C—CH_3); 1.70–2.15 (m, 4H, CH_2—C—O, 7-H_2); 2.15–2.50 (m, 6H, C=C—CH_2, 6-H_2, 8-H_2); 4.9–5.2 (m, 1H, pentenyl 3-H); 5.16 (d, 1H, J = 10 Hz, 3-H); 6.43 ppm (d, 1H, J = 10 Hz, 4-H).

Cannabichromene [6a, 5-Hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-7-pentyl-2*H*-chromene]:

A solution of tetrahydrochromene **4a** (316 mg, 1.0 mmol) in tetrahydrofuran (1 ml) is added dropwise to a stirred, freshly prepared mixture of lithium diisopropylamide (2.20 mol) and dry tetrahydrofuran (5 ml) at −78 °C, followed after 15 min by the fast addition of a solution of phenylselenenyl chloride (420 mg, 2.20 mmol) in tetrahydrofuran (2 ml). The mixture is allowed to warm to −35 °C within 15 min, and excess base is neutralized with benzoic acid (146 mg, 1.20 mmol). Then, a solution of 3-chlorobenzoperoxoic acid (447 mg, 2.30 mmol) in dichloromethane (10 ml) is added dropwise, stirring is continued for 1 h, a solution of 3,5-dimethoxyaniline (306 mg, 2.0 mmol) in tetrahydrofuran (2 ml) is added, and the mixture is stirred for 15 min at 20 °C. For work-up, ether (20 ml), petroleum ether (20 ml), and 0.5 molar hydrochloric acid (20 ml) are added, the organic layer is separated, and the aqueous layer is extracted with ether/petroleum ether (1/1; 2 × 20 ml). The combined organic layers are washed with saturated sodium hydrogen carbonate solution (2 × 20 ml) and saturated sodium chloride solution (2 × 20 ml). The solution is dried with sodium sulfate and evaporated. The residual crude product **6a** is purified by column chromatography on silica gel using ether/petroleum ether (1/5) as eluent; yield: 116 mg (37%); light yellow oil which cannot be distilled because of decomposition; R_F: 0.27.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 0.88 (t, 3H, J = 7 Hz, CH_2—CH_3); 1.37 (s, 3H, 2-CH_3); 1.57 (s, 3H, C=C—CH_3); 1.65 (s, 3H, C=C—CH_3); 1.05–2.25 (m, 10H); 2.42 (t, 2H, J = 7 Hz, Ar—CH_2); 4.65 (br s, 1H, OH); 5.05 (tm, 1H, J = 7 Hz, pentenyl 3-H); 5.42 (d, 1H, J = 10 Hz, 3-H); 6.05 (d, 1H, J = 1.5 Hz, 6-H); 6.18 (d, 1H, J = 1.5 Hz, 8-H); 6.54 ppm (d, 1H, J = 10 Hz, 4-H).

5-Hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-2*H*-chromene (6b):

The compound is prepared as described for **6a** using 2-methyl-2-(4-methyl-3-pentenyl)-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene (**4b**; 247 mg, 1.00 mmol) as starting material. The crude product is purified by column chromatography on silica gel using ether/petroleum ether (1/5) as eluent; yield: 103 mg (45%); yellow oil; R_F: 0.21. Distillation is not possible because of decomposition of the product.

$C_{16}H_{20}O_2$	calc.	C 78.65	H 8.25
(244.3)	found	78.37	8.22

M.S.: m/e = 244.1462 (calc. 244.1463).

I.R. (film): ν = 3400 (OH); 3040 (CH_{arom}); 2960; 2920; 1635 (C=C); 1615 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.36 (s, 3H, 2-CH_3); 1.56 (s, 3H, C=C—CH_3); 1.64 (s, 3H, C=C—CH_3); 1.45–2.3 (m, 4H, CH_2); 4.72 (s, 1H, OH); 5.06 (m, 1H, 3′-H); 5.49 (d, J = 10 Hz, 1H, 3-H); 6.20 (d, J = 8 Hz, 1H, 6-H); 6.30 (d, J = 8 Hz, 1H, 8-H); 6.58 (d, J = 10 Hz, 1H, 4-H); 6.85 ppm (t, J = 8 Hz, 1H, 7-H).

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