A NEW SYNTHESIS OF PRECOCENE II AND PRECOCENE III BASED ON THE PHOTO-FRIES REARRANGEMENT OF A SESAMOL ESTER

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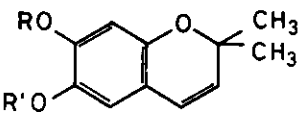
Abstract - The photo-Fries rearrangement of the sesamol ester of 3-methylcrotonic acid (**2**) in the presence of potassium carbonate affords a mixture of the o-hydroxyketones (**3c**) and (**3d**). Basic cyclization of the latter leads to the chromanones (**4c**) or (**4d**), respectively. Treatment of **4c** with alkoxide/alcohol results in the regioselective cleavage of the methylenedioxy ring, to give the corresponding 7-alkoxy derivatives (**4e**) or (**4f**). Subsequent methylation with methyl iodide gives rise to **4a** or **4b** and final reduction/dehydration by conventional methods affords the target compounds Precocene II (**1a**) or Precocene III (**1b**).

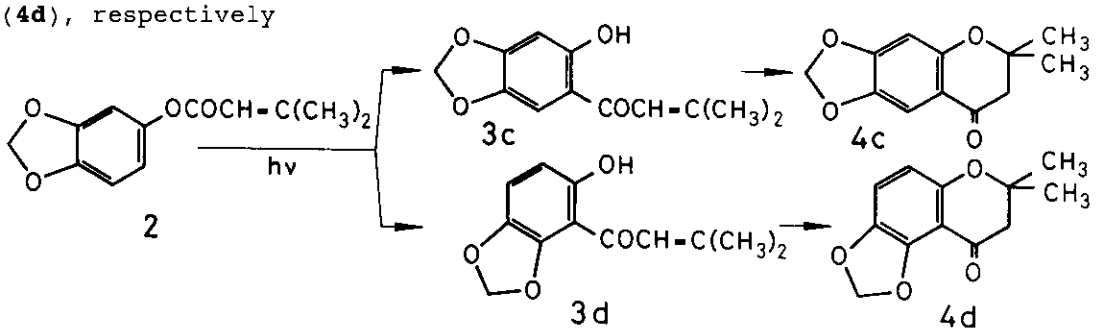
In previous communications we have reported a synthetic entry to chromene derivatives based on the photo-Fries rearrangement of phenyl esters of α,β-unsaturated carboxylic acids.[1,2] Following this approach, a number of compounds with antijuvenile hormone (AJH) activity substituted at the 6-

or 7-position have been synthesized. Precocene II and Precocene III are 6,7-disubstituted 2,2-dimethyl-2H-chromenes very well known as AJH inhibitors.[3,4]

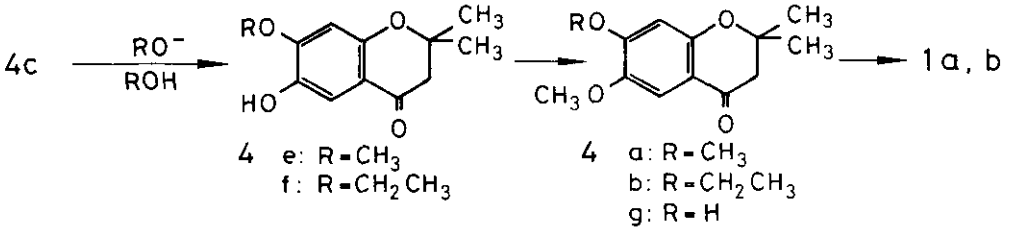


1 a: R = R' = CH_3
b: R = CH_2CH_3, R' = CH_3

Unfortunately, there is not a fully satisfactory method to obtain these compounds, specially in the case of Precocene III, where the 6- and 7-substituents are of different nature. In connection with this problem, and as the final work within our series devoted to applications of the photo-Fries rearrangement to the synthesis of 2H-chromenes, we wish now to report on the photolysis of the sesamol ester of 3-methyl-2-butenoic acid (**2**) and the subsequent chemical modifications of the resulting products, which lead to the obtention of Precocene II and Precocene III. Thus, the irradiation of **2** in hexane with a medium pressure mercury lamp in the presence of potassium carbonate gave the o-hydroxy ketone (**3c**) with 22% yield, accompanied by the other possible rearrangement product (**3d**) (8%). In the absence of potassium carbonate, as it has been reported in previous cases,[2,5] the irradiation did not produce any observable transformation after 20 h. The rearrangement products (**3c**) and (**3d**) were separated by means of preparative hplc and then cyclized to the chromanones (**4c**) or (**4d**), respectively



Cleavage of the methylenedioxy group in **4c** with sodium methoxide in methanol afforded **4e** in 60% yield. The ^{1}H-nmr spectrum of **4e** using 10% NaOH in D_2O as solvent showed a marked upfield shift of the signal corresponding to C_5-H as compared to the spectrum recorded in $CDCl_3$, indicating that this hydrogen is in the <u>orto</u>-position with respect to the phenolate anion. This fact confirms the structure of **4e**, allowing to rule out the structure of the possible 7-hydroxy-6-methoxy isomer (**4g**). Likewise, when the reaction was carried out with ethoxide/ ethanol compound (**4f**) was obtained in 60% yield. The different reactivity of the 6- and 7-positions of the chromanone (**4c**), due to the combined effect of the electron-donating oxygen atom and the electron-withdrawing carbonyl group of the heterocyclic ring, can be responsible for the regioselectivity of this reaction. The phenolic chromanones (**4e**) and (**4f**) were easily methylated with methyl iodide in basic medium under phase transfer conditions, affording **4a** and **4b**, respectively. These compounds were converted into the target molecules Precocene II and III by means of reduction/dehydration, following conventional methods



In summary, the photo-Fries rearrangement of the sesamol ester of 3-methylcrotonic acid (**2**), coupled with the regioselective opening of the methylenedioxy bridge of the chromanone (**4c**) by alkoxide, provides a new entry to chromenes with the desired substitution pattern in the 6- and 7-positions, which are not easily accessible by other methods, specially when the attached substituents are two different alkoxy groups.

EXPERIMENTAL SECTION

Melting points were determined with a Büchi 510 apparatus and are uncorrected. Ir spectra were obtained in CCl_4 solns with a Perkin-Elmer 781 spectrophotometer; max(cm^{-1}) is given only for the main bands. ^{1}H-nmr spectra were measured in CCl_4 with a 60 MHz Varian 360 EM instrument, chemical shifts are reported in δ(ppm) values, using TMS as internal standard. Mass spectra were obtained with a Hewlett-Packard 5988 A spectrometer, the ratios m/z and the relative intensities (%) are reported. The combustion analyses were performed at the Instituto de Quimica Bio-Organica of C.S.I.C. in Barcelona. Isolation and purification were done by flash column chromatography on silica gel Merck 60,70-230 mesh, using hexane as eluent, or alternatively by means of a Waters isocratic HPLC equipment provided with a semipreparative microporasil column, using hexane-ethyl acetate as eluent.

Esterification procedure

3-Methyl-2-butenoyl chloride (11.8 g, 0.1 mol) was added to a solution of sesamol (10 g, 0.072 mol) in 50 ml of benzene in the presence of Mg(2 g, 0.08 mol). The reaction mixture was refluxed for 9 h, filtered, washed with 10% NaOH, then with water, dried (Na_2SO_4), and concentrated in vacuo to afford **2**.

Irradiation

A solution of the ester (500 mg, 2.27 mmol) in hexane (400 ml) with anhydrous potassium carbonate (2 g, 0.014 mol) was irradiated for 20 h with magnetic stirring, using a 125 W medium pressure mercury lamp inside a quartz immersion well. After irradiation the potassium carbonate was filtered off and washed thoroughly with dichloromethane. The organic solutions were combined and concentrated in vacuo. The residues were submitted to chromatography, using hexane as eluent, yielding **3c,d**.

Cyclization to chromanones

A solution of the o-hydroxyaryl ketone (**3c,d**) (200 mg, 0.9 mmol) in hexane (100 ml) together with aqueous sodium hydroxide (10%, 25 ml) was stirred at room temperature for 4 h. The organic layer was washed with water, dried and evaporated to give the pure chromanone (**4c,d**).

Cleavage of the methylenedioxy ring by alkoxides

A solution of the chromanone (**4c**) (1 g, 4.5 mmol) in 50 ml of alcohol containing 20 g (methoxide 0.37 mol, ethoxide 0.3 mol) of sodium alkoxide was refluxed during 3 h. The solvent was evaporated and the crude residue was treated with 2M HCl (30 ml). The products were extracted with dichlorometane and the extracts were evaporated. The residues were submitted to chromatography, using a mixture of dichloromethane and ethyl acetate (4:1 vol/vol) as eluent, yielding **4e** or **4f**.

Methylation of 6-hydroxychromanones

To a magnetically stirred solution of **4e** or **4f** (500 mg, ca. 2.2 mmol) in 25% NaOH (5 ml, 0.03 mol) were 20% added tetraethylammonium hydroxide (1 ml, 1.3 mmol) and subsequently methyl iodide (0.6 g, 4.7 mmol). The reaction mixture was maintained at 60-65 °C for 1 h and then poured in water (25 ml) and extracted with dichloromethane. Evaporation of the solvent gave the pure chromanones (**4a**) or (**4b**).

Preparation of Precocenes II and III

To a solution containing 500 mg (0.013 mol) of lithium aluminium hydride in 25 ml of ether was added dropwise with stirring a solution containing the corresponding chromanone (**4a** :1.2 g, 0.005 mol; **4b** :1.25 g, 0.005 mol) in 30 ml of ether. The resulting mixture was heated to reflux for 1 h and then filtered. To the resulting filtrate was added acetone (20 ml) to decompose the excess lithium aluminium hydride, and then 6M hydrochloric acid (10 ml). After boiling the mixture during 10 min, 50 ml of water were added and the solvent was evaporated. The remaining aqueous phase was extracted with dichloromethane. The organic extract was dried (Na_2SO_4) and

evaporated. The residue was purified by chromatography, using dichloromethane as eluent.

Products

3,4-Methylenedioxyphenyl 3-methyl-2-butenoate (**2**)[6] (85%), mp 52-53°C, Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.48; Found: C, 65.29; H, 5.49; ir 1725; ^{1}H-nmr 6.95 (m, 3H, ArH), 5.87 (s, 2H, CH_2), 5.75 (br s, 1H, CH=), 2.15 (s, 3H, $_H\!\!>\!C = C\!<^{CH_3}_{CH_3}$), 1.90 (s, 3H, $_H\!\!>\!C = C\!<^{CH_3}_{CH_3}$); ms: 220 (8), 138 (53), 137 (19),107 (6), 83 (100), 55 (16).

1-(2-Hydroxy-4,5-methylenedioxyphenyl)-3-methyl-2-buten-1-one (**3c**)[6] (22%), mp 100°C, Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.48; Found: C, 65.30; H, 5.65; ir 1650; ^{1}H-nmr 13.40 (s, 1H, OH), 7.05 (s, 1H, 6-ArH), 6.55 (s, 1H, CH=), 6.36 (s, 1H, 3-ArH), 5.93 (s, 2H, CH_2), 2.20 (s,3H, $_H\!\!>\!C = C\!<^{CH_3}_{CH_3}$), 2.03 (s, 3H, $_H\!\!>\!C = C\!<^{CH_3}_{CH_3}$); ms: 220 (11), 205 (100), 165 (18), 164 (10), 147 (4), 136 (4), 107 (7).

1-(6-Hydroxy-4,5-methylenedioxyphenyl)-3-methyl-2-buten-1-one (**3d**) (8%), mp 105-107°C, Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.48; Found: C, 65.35; H 5.74; ir 1650; ^{1}H-nmr 12.20 (s, 1H, OH), 6.90 (s, 1H, CH=), 6.90-6.20 (AB, J=8 Hz, 2H, ArH), 5.97(s, 2H, CH_2),2.23(s, 3H, $_H\!\!>\!C = C\!<^{CH_3}_{CH_3}$), 2.03 (s, 3H, $_H\!\!>\!C = C\!<^{CH_3}_{CH_3}$); ms: 220 (23), 205 (100), 165 (32), 164 (48), 136 (13), 107 (15).

2,2-Dimethyl-6,7-methylenedioxy-4-chromanone (**4c**)[7](98%), mp 59°C (lit.[7] 59-60°C); ir 1680; ^{1}H-nmr 7.05 (s, 1H, 5-ArH), 6.20 (s, 1H, 8-ArH), 5.90 (s, 2H, OCH_2O), 2.50 (s, 2H, CH_2), 1.40 (s, 6H, CH_3).

2,2-Dimethyl-5,6-methylenedioxy-4-chromanone (**4d**) (96%), mp 133-134°C, Anal. Calcd for $C_{12}H_{12}O_4$: C,65.45; H,5.48; Found: C, 65.73; H, 5.40; ir 1690; ^{1}H-nmr 6.75 (d, J=8 Hz, 1H, 7-ArH), 6.20 (d, J=8 Hz, 1H, 8-ArH), 6.00 (s, 2H, OCH_2O), 2.54 (s, 2H, CH_2), 1.43 (s, 6H, CH_3); ms: 220 (48), 205 (81), 164 (100), 136 (25), 107 (10), 94 (9), 82 (11).

6-Hydroxy-7-methoxy-2,2-dimethyl-4-chromanone (**4e**)[7] (60%), mp 136-137°C; ir 1680; ^{1}H-nmr 7.30 (s, 1H, 5-ArH), 6.40 (s, 1H, 8-ArH), 3.93 (s, 3H, OCH_3), 2.67 (s, 2H, CH_2), 1.46 (s, 6H, CH_3); ms: 222 (36), 207 (100), 167 (69), 166 (52), 123 (51), 95 (16), 69 (22).

7-Ethoxy-6-hydroxy-2,2-dimethyl-4-chromanone (**4f**) (60%), mp 130-132°C, Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.82; Found: C, 66.11; H, 6.840; ir 1670; ^{1}H-nmr 7.36 (s, 1H, 5-ArH), 6.40 (s, 1H, 8-ArH), 4.15 (q, J=7 Hz, 2H, OCH_2CH_3), 2.66 (s, 2H, CH_2), 1.43 (t, J=7 Hz, 3H, OCH_2CH_3), 1.43 (s, 6H, CH_3); ms: 236 (43), 221 (100), 181 (54), 180 (52), 153 (50), 69 (63).

6,7-Dimethoxy-2,2-dimethyl-4-chromanone (**4a**)[8] (85%), mp 105°C (lit.[8] 106°C); ir 1675; ^{1}H-nmr 7.3 (s, 1H, 5-ArH), 6.43 (s, 1H, 8-ArH), 3.93 and 3.90 (s+s, 6H, 2 x OCH_3), 2.66 (s, 2H, CH_2), 1.46 (s, 6H, 2 x CH_3); ms: 236 (30), 221 (75), 181 (48), 180 (29), 165 (27), 137 (43), 109 (30), 69 (34).

7-Ethoxy-6-methoxy-2,2-dimethyl-4-chromanone (**4b**)[4] (85%), mp 120°C; ir 1650; ^{1}H-nmr 7.10 (s, 1H, 5-ArH), 6.20 (s, 1H, 8-ArH), 4.03 (q, J=7 Hz, 2H, OCH_2CH_3), 3.80 (s, 3H, OCH_3), 2.50 (s, 2H, CH_2), 1.46 (t, J=7 Hz, 3H, OCH_2CH_3), 1.40 (s, 6H, 2 x CH_3).

6,7-Dimethoxy-2,2-dimethyl-2H-chromene (**1a**)[4] (80%), oil; ir 1600; ^{1}H-nmr 6.43 and 6.26 (s + s, 2H, 5,8-ArH), 6.17 (d, J=9 Hz, 4-CH), 5.35 (d, J=9 Hz, 3-CH), 3.80 and 3.73 (s + s, 6H, 2 x OCH_3), 1.36 (s, 6H, 2 x CH_3).

7-Ethoxy-6-methoxy-2,2-dimethyl-2H-chromene (**1b**)[4] (75%), oil; ir 1600; ^{1}H-nmr 6.40 and 6.23 (s + s, 2H, 5,8-ArH), 6.16 (d, J=9 Hz, 4-CH), 5.37 (d, J=9 Hz, 3-CH), 3.97 (q, J=7 Hz, 2H, OCH_2CH_3), 3.70 (s, 3H, OCH_3), 1.40 (t, J=7 Hz, 3H, OCH_2CH_3), 1.33 (s, 6H, 2 x CH_3).

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