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Aromatic Ring Synthesis by 1,3-Michael-Claisen Annulation : Application to a Trolox analogue and to Precocene II

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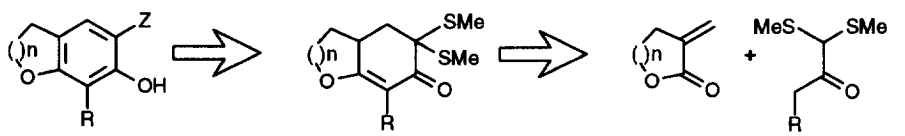
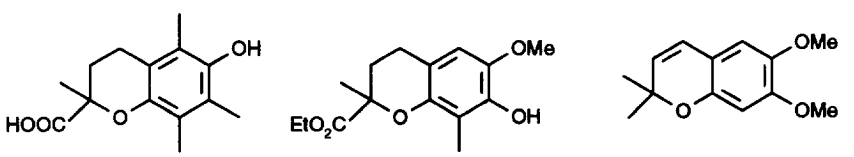
Abstract. A Trolox analogue, 3,4-dihydro-2-ethoxycarbonyl-6-methoxy-7-hydroxy-benzopyran and Precocene II, were prepared from substituted α-methylene-δ-valerolactone and 1,1-bis-(methylthio)-2-propanone or butanone, via a 1,3-Michael-Claisen annulation.

We recently described[1] our results concerning the preparation of substituted dihydrobenzofurans and tetrahydrochromans from α-methylene δ-butyrolactone and δ-valerolactone respectively via a 1,3-Michael-Claisen annulation reaction as shown in scheme I in a retrosynthetic manner.

Scheme I



We now report on the application of this methodology to the synthesis of a Trolox analogue **1** and of Precocene II, **2**.



Trolox **1** **Precocene II, 2**

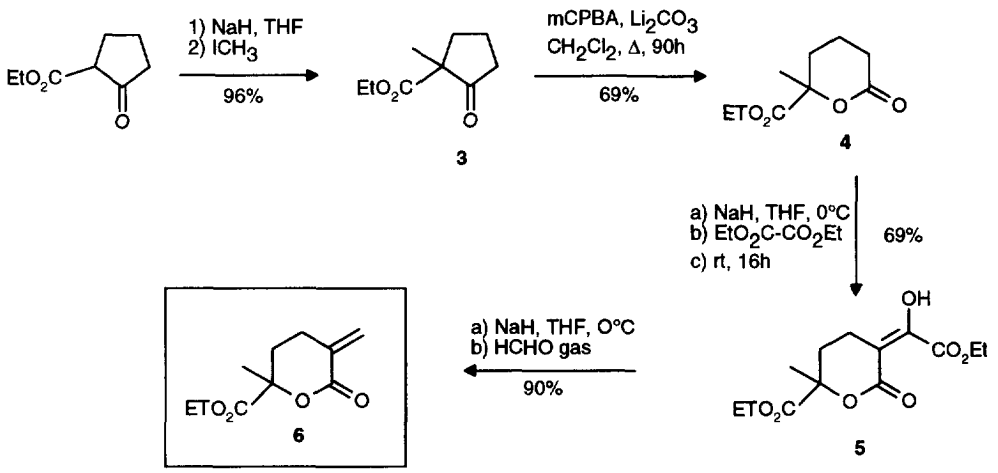
Trolox[2] is a well known anti-oxidant used in food industry in place of α-tocopherol (vitamin E) and also a synthetic precursor[3] of α-tocopherol. The compound **1** was synthesized as a part of our program concerning

the anti-oxidant properties of organic compounds. Precocene II was isolated in a plant extract[4], *Ageratum houstonianum*, and was shown[5] to be the more active natural compound inducing precocious metamorphosis in immature hemipterans and preventing ovarian development in several adult insects. That was the first discovery of a molecule showing an insect anti-juvenile activity. Due to its interest as an insect specific insecticide, many syntheses of Precocene II have been reported[6].

On the basis of the retrosynthetic scheme I, the synthesis of compound **1** requires first the preparation of the substituted α-methylene lactone **6** and of course of the parent lactone **4**, both being new compounds.

Lactone **4** was readily obtained in good yield from 2-carbethoxy-cyclopentanone via methylation and subsequent Baeyer-Villiger oxidation (scheme II). The resulting δ-methyl-δ-ethoxycarbonyl-δ-valerolactone **4** was contaminated by 5% of β-methyl-β-ethoxycarbonyl-δ-valerolactone, the minor isomer formed during the Baeyer-Villiger reaction, which was difficult to remove by chromatography. Therefore this crude product was used without further purification in the next step, α-methylenation via the method described by McMurry[7] for the preparation of α-methylene δ-valerolactone.

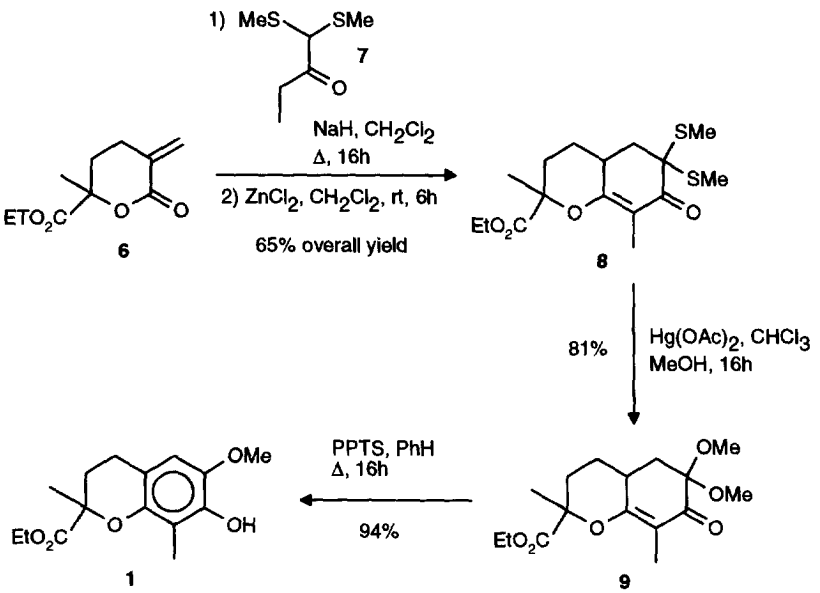
Scheme II



Condensation of lactone **4** enolate with ethyl oxalate yielded the adduct **5** which, being totally enolized, was soluble in the basic aqueous phase. Therefore the organic impurities, including the β-disubstituted δ-valerolactone, were extracted with ether and the pure lactone **5** was isolated by acidification. Condensation of the enolate **5** with formaldehyde afforded in 90% yield the α-methylene-δ-valerolactone **6**.

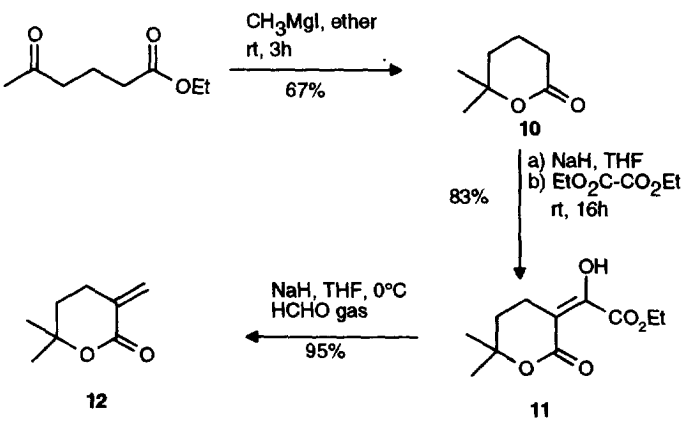
Michael addition of the thioacetal **7**[1] enolate to α-methylene lactone **6** gave the corresponding adduct with concomitant lactone opening. Ring closure was carried out in smooth conditions at room temperature with $ZnCl_2$ giving the tetrahydrochroman **8** in 65% overall yield. Trans-acetalization with methanol in presence of mercuric acetate followed by aromatisation with PPTS gave in high yield the trolox analogue **1** (Scheme III).

Scheme III



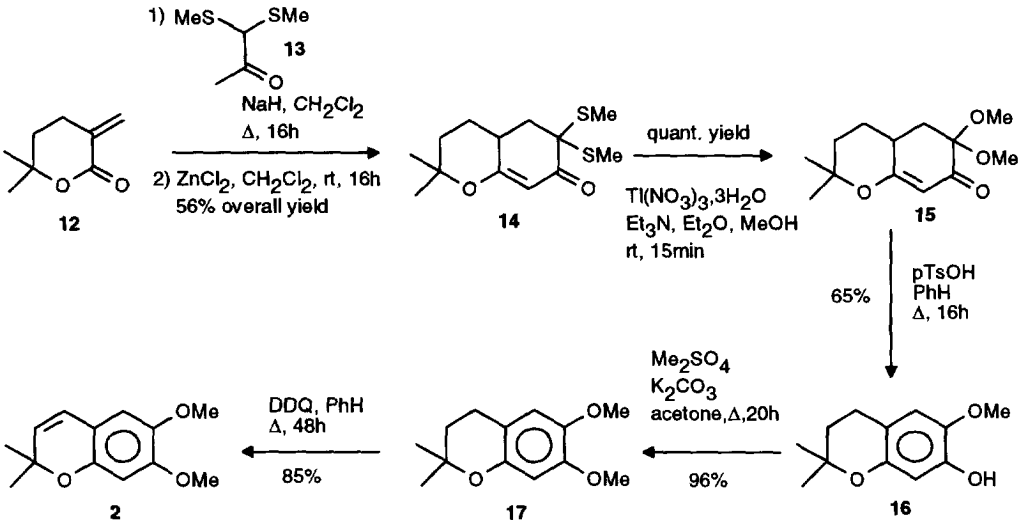
For the synthesis of Precocene II, **2**, it was necessary to prepare α-methylene-δ,δ-dimethyl-δ-valerolactone **12**. δ,δ-dimethyl-δ-valerolactone **10** was obtained by addition of 2 eq. of methylmagnesium bromide to ethyl 4-acetylbutyrate and *in situ* cyclization of the resulting alcohol (scheme IV). α-methylenation was carried out by the method used for lactone **4**. The compound **12** was obtained in high yield.

Scheme IV



Michael addition of the thioacetal **13** anion followed by cyclization of the resulting adduct with $ZnCl_2$ afforded the tetrahydrochroman **14** in 56% yield (scheme V). Trans acetalization was carried out in high yield using Fujita's conditions[8] (thallium trinitrate / Et_3N/ ether/ methanol).

Scheme V



Aromatisation with pTsOH, methylation of the resulting phenol with methylsulfate and dehydrogenation with DDQ[9] lead to Precocene II.

In conclusion, these two applications showed that the aromatic ring synthesis we developped can be a powerful synthetic method to prepare highly susbstituted chromans or dihydro-chromans such as **2** and **1**.

Acknowledgments : we thank l'Oréal for financial support and for a scholarship to one of us (DB).

Experimental Section

Ethyl 1-methyl-2-oxo-cyclopentanecarboxylate, 3.

Ethyl 2-oxo-cyclopentanecarboxylate (1 eq, 5 mL, 33.7 mmol) was added dropwise to an ice-bath cooled suspension of NaH (1.2 eq, 0.97 g, 40.5 mmol) in THF (50 mL) and the resulting solution was stirred for 10 min at 0°C. Methyl iodide (2eq, 4.2 mL, 67.4 mmol) was added slowly and the mixture was stirred for 10 min at room temperature. Workup was performed by slow addition of cold water (50 mL) and careful removal of THF under reduced pressure (15 mmHg, compound **3** being volatile) The residue was extracted with ether (5 x 100 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$. Ether was removed to yield **3** (5.59 g, 32.9 mmol, 97.5%) as a pale yellow oil which was used without further purification in the next step (R_f : 0.4, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.23 (t, 3H, J=7Hz, CH_3 ester), 1.29 (s, 3H, CH_3), 1.91 (m, 3H, H-4 , H-5), 2.41 (m, 3H, H-3 , H-5), 4.14 (q, J=7Hz, 2H, CH_2 ester). ^{13}C NMR (50 MHz, $CDCl_3$) : 13. 9 (CH_3 ester), 19.2 (CH_3), 19. 5 (C-4), 36.0 (C-5), 37.4 (C-3), 55.7 (C-1), 61.0 (CH_2 ester), 172.1 (C=O ester), 214.7 (C-2)

δ-methyl-δ-ethoxycarbonyl-δ-valerolactone, 4

MCPBA (2.5eq, 54.3 g, 0.22 mol) and lithium carbonate (0.05 eq, 0.325 g, 4.4 mmol) were added to the cyclopentanone **3** (1 eq, 15 g, 88.1 mmol) in CH_2Cl_2 (500 mL) and refluxed for 90 h. The solvent was removed and the residue dissolved in ether (500 mL) and filtrated to remove most of m-chloro-benzoic acid. The filtrate was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated. Purification of the residue by flash-chromatography (eluent, CH_2Cl_2 / MeOH : 99/1) gave **4** (11.4 g, 61.2 mmol, 69%) as a pale yellow oil (containing 5% of the other insertion isomer) which was used in the next step without further purification.

R_f : 0.13 (CH_2Cl_2). IR (CCl_4) : 1730, 1625 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.29 (t, 3H, J=7Hz, CH_3 ester), 1.61 (s, 3H, CH_3), 1.77 (m, 3H, H-3, H-4), 2.39 (m, 3H, H-2, H-4), 4.23 (AB part of ABX_3, J_{AB}=2Hz, J_{AX}=7Hz, 2H, CH_2 ester). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 13.0 (CH_3 ester), 16.3 (C-3), 24.1 (C-4), 27.5 (CH_3), 30.6 (C-2), 60.1 (CH_2 ester), 82.2 (C-5), 165.2 (C=O ester), 169.1 (C-1). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05 ; H, 7.58. Found : C, 58.09 ; H, 7.61.

α-ethoxyoxalyl-δ-methyl-δ-ethoxycarbonyl-δ-valerolactone, 5

A solution of lactone **4** (1 eq, 1.84 g, 9.38 mmol) and diethyl oxalate (1.05 eq, 1.34 mL, 9.85 mmol) in THF (20 mL) was added dropwise to an ice bath cooled suspension of NaH (1.05 eq, 0.236 g, 9.85 mmol) in THF (20 mL). After stirring for 20h at room temperature the solution became turbid and brownish. Hydrolysis was carried out by adding slowly water (20 mL) to the mixture and the resulting clear solution was extracted with ether (3 x 20 mL) to remove starting materials in excess. The aqueous layer was acidified to pH 1-2 with a 10% HCl solution, then extracted with CH_2Cl_2 (5 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield **5** (1.86g, 6.5 mmol, 69 %) as a viscous yellow oil.

IR (neat) : 3000 (OH) ; 1745, 1660, 1600 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.28 (t, 3H, J=7Hz, H-8), 1.38 (t, 3H, J=7Hz, H-12), 1.67 (s, 3H, CH_3), 1.83 (td, 1H, $J_{4a\text{-}4b}$=$J_{4a\text{-}3b}$=13Hz, $J_{4a\text{-}3a}$=5Hz, H-4a), 2.34 (ddd, 1H, $J_{4b\text{-}4a}$=13Hz, $J_{4b\text{-}3a}$=3Hz, $J_{4b\text{-}3b}$=5Hz, H-4b), 2.47 (ddd, 1H, $J_{3b\text{-}3a}$=17Hz, $J_{3b\text{-}4a}$=13Hz, $J_{3b\text{-}4b}$=5Hz, H-3b), 2.97 (ddd, 1H, $J_{3a\text{-}3b}$=17Hz, $J_{3a\text{-}4a}$=5Hz, $J_{3a\text{-}4b}$=3Hz, H-3a), 4.26 (AB part of ABX_3, 2H, J_{AB}=2Hz, J_{AX}=7Hz, H-7), 4.34 (q, 2H, J=7Hz, H-11), 13.5 (s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 13.5 (C-8), 13.5 (C-12), 19.6 (C-4), 24.0 (CH_3), 30.4 (C-3), 61.6 (C-7), 61.8 (C-11), 82.3 (C-5), 99.9 (C-2), 158.0 (C-9), 161.7 (C-6), 170.5 (C-10), 171.7 (C-1). Anal. Calcd for $C_{13}H_{18}O_7$: C, 54.54 ; H, 6.34. Found : C, 54.53 ; H, 6.33.

α-methylene-δ-methyl-δ-ethoxycarbonyl-δ-valerolactone, 6.

Enol **5** (1eq, 1.73 g , 6.05 mmol) in THF (20mL) was added dropwise to an ice-bath cooled suspension of NaH (1.4 eq , 0.200 g , 8.3 mmol) in THF (20mL). The resulting clear solution was stirred during 15 min at 0°C. Paraformaldehyde (1 g), depolymerised by heating through an argon stream, was bubbled into the solution. After 10 min stirring, the solution was filtrated on celite to remove excess paraformaldehyde. The filtrate was diluted by addition of a saturated solution of $NaHCO_3$ (50 mL) and THF was removed under reduced pressure. CH_2Cl_2 (50 mL) was added to the residue and the mixture was stirred during 30 min at room temperature. The organic layer was decanted and the aqueous layer was extracted again with CH_2Cl_2 (3 x 50 mL). The

combined organic extracts were washed with water (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield **6** (1.087g , 5.48 mmol, 90%) as a pale yellow oil.
IR (CCl_4) : 2990-2840 (C-H) ; 1730, 1625 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.27 (t, 3H, J=7Hz, CH_3 ester), 1.63 (s, 3H, CH_3), 1.90 (td, 1H, $J_{4a\text{-}4b}$=$J_{4a\text{-}3b}$=13Hz, $J_{4a\text{-}3a}$=5Hz, H-4a), 2.30 (ddd, 1H, $J_{4b\text{-}4a}$=13Hz, $J_{4b\text{-}3a}$=3Hz, $J_{4b\text{-}3b}$=5Hz, H-4b), 2.45 (dtdd, 1H, $J_{3b\text{-}3a}$=17Hz, $J_{3b\text{-}6}$=1Hz, $J_{3b\text{-}4a}$=13Hz, $J_{3b\text{-}4b}$=5Hz, H-3b), 2.65 (dtdd, 1H, $J_{3a\text{-}3b}$=17Hz, $J_{3a\text{-}6}$=1Hz, $J_{3a\text{-}4a}$=5Hz, $J_{3a\text{-}4b}$=3Hz, H-3a), 4.19 (AB part of ABX_3, 2H, J_{AB}=2Hz, J_{AX}=7Hz, CH_2 ester), 5.57 (t, 1H, $J_{6\text{-}4}$=1Hz, H-6), 6.48 (t, 1H, $J_{6\text{-}4}$=1Hz, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 13.6 (CH_3 ester), 24.4 (CH_3), 24.5 (C-4), 31.3 (C-3), 61.6 (CH_2 ester), 82.3 (C-5), 128.1(C-6), 131.7 (C-2), 163.0 (C=O ester), 171.2 (C-1). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59 ; H, 7.12. Found : C, 60.72 ; H, 7.23.

3,4,10,5-tetrahydro-2,8-dimethyl-2-ethoxycarbonyl-6,6-bis(methylthio)-benzopyran-7-one, 8

In a three-necked round bottomed flask equiped with a dropping funnel, a suspension of NaH (2 eq, 0.134 g, 5.6 mmol) in CH_2Cl_2 (10 mL) was cooled at 0°C with an ice bath. Thioacetal **7**[1] (1 eq; 0.460g, 2.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the suspension. After 10 min stirring at 0°C, lactone **6** (1 eq, 0.556 g, 2.8 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise and the ice bath was replaced by a heating bath. The suspension was refluxed during 16 h, allowed to cool and poured onto a 10% aqueous HCl solution (50 mL). The organic layer was decanted, the aqueous layer was extracted with CH_2Cl_2 (3 x 30mL) and the joined organic layers washed with brine, dried over Na_2SO_4 and concentrated to one third of their initial volume under vacuum. The solution was added to anhydrous zinc chloride (1.1 eq, 0.420 g, 3.1 mmol) and stirred during 6h at room temperature, filtrated and concentrated. Purification of the brownish residue by flash-chromatography (eluent : ether/hexane 4/6) yielded adduct **8** (0.630 g, 1.83 mmol, 65%) as a viscous yellow oil. Compound **8** was obtained as a 53/47 mixture of diastereomers after chromatography.
R_f : 0,36 (ether/hexane 4/6). IR (CCl_4) : 2990-2840 (C-H) ; 1730, 1625 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 0.81 and 0.95 (t, 3 H, J=7Hz, CH_3 ester), 1.05-1.50 (m, 3H, H-3, H-4), 1.26 and 1.35 (s, 3H, CH_3 on C-2), 1.68-2.15 (m, 3H, H-3, H-5), 1.86 and 1.89 (s, 3H, S-CH_3), 2.02 and 2.14 (d, 3H, J=2Hz, CH_3 on C- 8), 2.04 and 2.08 (s, 3H, S-CH_3), 2.59 (m, 1H, H-10), 3.80 and 3.94 (q, J=7Hz and AB part of ABX_3, J_{AB}=2Hz, J_{AX}=7Hz, 2H, CH_2 ester). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 8.1 and 8.2 (CH_3 on C-8), 11.1 and 14.2 (S-CH_3), 11.0 and 12.1 (CH_3 ester), 23.7 and 25.3 (C-3), 24.4 and 25.9 (CH_3 on C-2), 30.8 and 32.1 (C-10), 31.0 and 32.1 (C-5), 40.8 and 41.3 (C-4), 61.7 and 61.9 (CH_2 ester), 63.2 and 63.3 (C-6), 79.8 and 81.4 (C-2), 112.6 and 113.6 (C-8), 168.2 and 168.5 (C=O ester), 172.6 and 172.7 (C-9), 191.0 and 191.2 (C-7). Anal. Calcd for $C_{16}H_{24}O_4S_2$: C, 55.79 ; H, 7.02. Found : C, 55.95 ; H, 7.14.

3,4,10,5-tetrahydro-2,8-dimethyl-2-ethoxycarbonyl-6,6-bis(methoxy)-benzopyran-7-one, 9

Mercuric acetate (2.2 eq, 0.49 g, 1.54 mmol) in methanol (10 mL) was added dropwise to the dithioketal **8** (1 eq, 0.241 g, 0.7 mmol) dissolved in anhydrous chloroform (10 mL), and the resulting solution was stirred at room temperature during 16 h. Unsoluble mercury salts were formed and the solution became pink. The solvents were removed under reduced pressure and the residue was suspended in CH_2Cl_2 (5mL). The suspension was filtrated on celite to remove mercury salts. The clear filtrate was washed first with a 10% solution of sodium hydrogenosulfite, then with brine. The organic layer was decanted, dried over sodium

sulfate and the solvent was removed to give a yellow-brown wax. The crude product was purified by flash-chromatography on silica gel (eluent: ether / hexane 6/4) to yield compound **9** (0.176 g, 0.564 mmol, 81%) as a red wax. Compound **9** was obtained as a 53/47 mixture of diastereomers after chromatography.
Rf : 0,39 and 0.44 (ether). IR (neat) : 3050-2840 (C-H) ; 1745, 1670 (C=O). ^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.22 and 1.28 (t, 3 H, J=7Hz, CH_3 ester), 1.21-1.66 (m, 2H, H-4), 1.51 and 1.59 (s, 3H, CH_3 on C-2), 1.74 and 1.79 (d, 3H, J=2Hz, CH_3 on C-8), 1.77-1.97 (m; 2H, H-3), 2.29-2.46 (m, 2H, H-5), 2.69 (m, 1H, H-10), 3.13 and 3.15 (s, 3H, OCH_3), 3.31 and 3.32 (s, 3H, OCH_3), 4.16 and 4.21 (q, J=7Hz and AB part of ABX$_3$, J_{AB}=2Hz, J_{AX}=7Hz, 2H, CH_2 ester). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 7.8 and 7.9 (CH_3 on C-8), 14.1 and 14.1 (CH_3 ester), 24.1 and 25.7 (C-3), 24.4 and 25.9 (CH_3 on C-2), 30.8 and 31.9 (C-10), 31.2 and 33.2 (C-5), 36.6 and 36.9 (C-4), 48.7 and 50.6 (O-CH_3), 61.7 and 61.8 (CH_2 ester), 79.9 and 81.6 (C-2), 96.2 (C-6), 113.9 and 114.9 (C-8), 169.8 and 169.9 (C=O ester), 172.7 and 172.8 (C-9), 192.1 and 192.3 (C-7). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52 ; H, 7.74. Found : C, 61.65 ; H, 7.90.

3,4-dihydro-2,8-dimethyl-2-ethoxycarbonyl-6-methoxy-benzopyran-7-ol, 1.
A solution of dimethoxyketal **9** (0.219 g, 0.7 mmol) and a catalytic amount of pyridinium p-toluenesulfonate (5mg) in benzene (7mL) was refluxed during 16 h. After removal of the solvent under reduced pressure, water (5mL) and CH_2Cl_2 (5mL) were added to the residue. The organic layer was decanted and the aqueous layer was washed twice with 5 mL CH_2Cl_2 .The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield **1** (0.184 g, 0.66 mmol, 94%) as a yellow oil.
Rf : 0,50 (ether/hexane 1/1). IR (CCl_4) : 3560 (OH), 2990-2840 (C-H) ; 1740 (C=O). ^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.19 (t, 3 H, J=7Hz, CH_3 ester), 1.61 (s, 3H, CH_3 on C-2), 1.86 (ddd, 1H, J_{3a-3e}=13Hz, J_{3a-4a}=10Hz, J_{3a-4e}=7Hz, H-3a), 2.17 (s, 3H, CH_3 on C-8), 2.38 (ddd, 1H, J_{3e-3a}=13Hz, J_{3e-4a}=3.5Hz, J_{3e-4e}=5Hz, H-3e), 2.65 (m, 2H, H-4), 3.80 (s, 3H, OCH_3), 4.13 (q, 2H, J=7Hz, CH_2 ester), 5.61 (s, 1H, OH), 6.35 (s, 1H, H-5). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 8.1 (CH_3 on C-8), 13.9 (CH_3 ester), 22.3 (C-3), 25.1 (CH_3 on C-2), 30.5 (C-4), 56.1 (O-CH_3), 60.8 (CH_2 ester), 77.4 (C-2), 107.7 (C-5), 110.1 (C-8), 112.2 (C-10), 140.4 (C-6), 142.5 (C-7), 146.2 (C-9), 173.5 (C=O ester). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27 ; H, 7.19. Found : C, 64.36 ; H, 7.00.

δ,δ-dimethyl-δ-valerolactone, 10
A solution of methylmagnesium iodide in ether (10 mL) prepared from magnesium turnings (1.15 eq, 0.683 g, 28.1 mmol) and methyl iodide (1.15 eq, 1.75 mL, 28.1 mmol) was added dropwise to an ice-bath cooled solution of ethyl 4-acetylbutyrate (1 eq, 3.9 mL, 24.4 mmol) in ether (40 mL). The resulting white suspension was stirred at room temperature during 3 h. Workup was performed by slow addition of a 10% HCl solution (30 mL). The organic layer was decanted and the aqueous phase washed again with ether (3x2 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and ether was removed. Purification of the residue by flash-chromatography on silica (eluent, ether / hexane 1/1) yielded compound **10** (2.1 g, 16.4 mmol, 67%) as a colorless oil.
Rf : 0,17 (ether/hexane 1/1). ^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.33 (s, 6H, CH_3), 1.68 (m, 2H, H-4), 1.82 (m, 2H, H-3), 2.40 (t, 2H, J=7Hz, H-2). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 12.8 (C-3), 27.15 (CH_3), 27.6 (C-4), 32.2 (C-2), 80.2 (C-5), 169.9 (C-1).

α-ethyloxalyl-δ,δ-dimethyl-d-valerolactone, 11

Obtained from δ,δ-dimethyl-δ-valerolactone **10** by the procedure described for the preparation of compound **5**. Yield : 83%, dark yellow oil. IR (CCl_4) : 3000 (OH), 3000-2850 (C-H), 1730, 1625 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.32 (t, 3H, J=7Hz, CH_3 ester), 1.40 (s, 6H , CH_3), 1.79 (t; 2H, J=7Hz, H-4), 2.80 (t, 2H, J=7Hz, H-3), 4.32 (q, 2H, J=7Hz, CH_2 ester), 12.22 (bs, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 13.1 (CH_3 ester), 18.7 (C-4), 26.3 (CH_3), 31.6 (C-3), 60.9 (CH_2 ester), 80.9 (C-5), 99.2 (C-2), 158.2 (C-6), 161.3 (C=O ester), 171.9 (C-1). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88 ; H, 7.06. Found : C, 57.95 ; H, 7.16.

α-methylene-δ,δ-dimethyl-δ-valerolactone, 12

Compound **12** was obtained from α-ethyloxalyl-δ,δ-dimethyl-δ-valerolactone **11** using the procedure described for the preparation of compound **6**.

Yield : 95%, pale yellow viscous oil. IR (CCl_4) : 3000-2850 (C-H), 1735 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.42 (s, 6H, CH_3), 1.85 (t, 2H, J=7Hz, H-4), 2.69 (tt , 2H, J=7Hz et J=2Hz, H-3), 5.58 (t 1H, J=2Hz, H-6), 6.46 (t, 1H, J=2Hz, H-6)· ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 24.4 (C-4), 28.0 (CH_3), 33.5 (C-3), 81.4 (C-5), 128.1 (C-6), 132.8 (C-2), 165.6 (C-1). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54 ; H, 8.63. Found : C, 68.72 ; H, 8.90.

3,4,10,5-tetrahydro-2,2-dimethyl-6,6-bis(methylthio)-benzopyran-7-one, 14

Compound **14** was obtained from 1,1-bis(methylthio)-2-propanone[1] **13** and α-methylene-δ,δ-dimethyl-δ-valerolactone **12** by the procedure described for the obtention of **8**.

Yield : 56%, pale yellow solid. R_f : 0,36 (ether/hexane 4/6). IR (neat) : 2980-2850 (C-H), 1635 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.25 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.44 - 1.66 (m, 1H, H-4), 1.70 - 1.94 (m, 3H, H-3, H-4), 2.06 (s, 3H, S-CH_3), 2.07 (s, 3H, S-CH_3), 2.28 (m, 2H, H-5), 2.74 (m, 1H, H-10), 5.45 (bs, 1H, H-8)· ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 11.1 (S-CH_3), 12.0 (S-CH_3), 23.9 (C-4), 25.9 (CH_3), 30.0 (CH_3), 32.5 (C-10), 34.7 (C-3), 41.6 (C-5), 63.2 (C-6), 79.6 (C-2), 108.2 (C-8), 175.4 (C-9), 191.2 (C-7). Anal. Calcd for $C_{13}H_{20}O_2S_2$: C, 57.32 ; H, 7.40. Found : C, 57.06 ; H, 7.52.

3,4,10,5-tetrahydro-2,2-dimethyl-6,6-bis(methoxy)-benzopyran-7-one, 15

Ketal **15** was obtained from dithioketal **14** using the general trans-acetalization procedure[8] with $Tl(NO_3)_3$ but employing 1.1 eq of Et_3N instead of 2.2.

Yield : 100% (crude), viscous red oil. Purification of **15** by flash-chromatography on silica gel (eluent: ether/CH_2Cl_2 1/9) could not be performed without substential loss of product (50%). R_f : 0,39 (ether/CH_2Cl_2 1/9). IR (CCl_4) : 2980-2900 (C-H), 1665 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.24 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.46-1.93 (m, 5H, H-3, H-4, H-5b), 2.42 (A part of ABX, 1H, $J_{5a\text{-}5b}$=13Hz, $J_{5a\text{-}10}$=5Hz, H-5a), 2.67 (m, 1H, H-10), 3.20 (s, 3H, O-CH_3), 3.34 (s, 3H, O-CH_3), 5.45 (d, 1H, J=2Hz, H-8)· ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 24.4 (C-4), 26.1 (CH_3), 30.1 (CH_3), 32.7 (C-10), 34.9 (C-3), 37.2 (C-5), 48.8 (O-CH_3), 50.8 (O-CH_3), 80.1 (C-2), 96.8 (C-6), 107.3 (C-8), 177.5 (C-9), 192.5 (C-7). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98 ; H, 8.39. Found : C, 65.20 ; H, 8.40.

3,4-dihydro-2,2-dimethyl-6-methoxy-benzopyran-7-ol, 16

A solution of dimethoxyketal **15** (0.240 g, 1 mmol) and a catalytic amount of p-toluenesulfonic acid (5mg) in benzene (10 mL) was refluxed during 16 hours. After removal of the solvent under reduced pressure, purification of the residue by flash-chromatography on silica gel (eluent: CH_2Cl_2) yielded compound **16** (0.135 g, 0.65 mmol, 65%) as a pink-yellow oil.

R_f : 0,34 (CH_2Cl_2). IR (CCl_4) : 3560 (OH), 2980-2850 (C-H). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.31 (s, 6H, CH_3), 1.77 (t, 2H, J=7Hz, H-3), 2.69 (t, 2H, J=7Hz, H-4), 3.82 (s, 3H, OCH_3), 5.48 (s, 1H, OH), 6.40 (s, 1H, H-8), 6.53 (s, 1H, H-5)· ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 22.2 (C-3), 26.7 (CH_3), 33.0 (C-4), 56.5 (OCH_3), 73.7 (C-2), 103.7 (C-8), 111.2 (C-10), 111.4 (C-5), 140.4 (C-6), 144.8 (C-7), 148.3 (C-9). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21 ; H, 7.74. Found : C, 69.25 ; H, 7.68.

3,4-dihydro-2,2-dimethyl-6,7-dimethoxy-benzopyran, 17

Potassium carbonate (3 eq, 0.1g, 0.72 mmol) and dimethyl sulfate (4 eq, 0.091mL, 0.96mmol) were successively added to a solution of phenol **16** (1 eq, 0.050 g, 0.24 mmol) in anhydrous acetone (4 mL). The mixture was refluxed during 20h, allowed to cool and filtrated. After removal of the solvent under reduced pressure, purification of the residue by flash-chromatography on silica gel (eluent: CH_2Cl_2/hexane 1/1) yielded compound **17** (0.051 g, 0.23 mmol, 96%) as white cristals.

mp : 59-60°C (lit. 60°C[10]). R_f : 0.18 (CH_2Cl_2/hexane 1/1). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.32 (s, 6H, CH_3), 1.77 (t, 2H, J=7Hz, H-3), 2.69 (t, 2H, J=7Hz, H-4), 3.81 (s, 6H, OCH_3), 6.40 (s, 1H, H-8), 6.53 (s, 1H, H-5)· ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 22.2 (C-3), 26.8 (CH_3), 33.1 (C-4), 55.9 and 56.5 (OCH_3), 73.9 (C-2), 101.3 (C-8), 111.3 (C-10), 112.3 (C-5), 142.7 (C-6), 147.7 (C-7), 148.5 (C-9).

2,2-dimethyl-6,7-dimethoxychromene, (Precocene II), 2

Dehydrogenation of chromane **17** by the general procedure of Ahluwalia and Jolly[9] afforded crude Precocene II which was purified by flash-chromatography on silica gel (eluent: CH_2Cl_2).

Yield : 85%, pale yellow cristals. mp : 46-47°C (lit. 47.5°C [4]). R_f : 0.48 (CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.42 (s, 6H, CH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.48 (d, 1H, J=10Hz, H-4), 6.25 (d, 1H, J=10Hz, H-3), 6.42 (s, 1H, H-8), 6.54 (s, 1H, H-5)· ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 27.6 (CH_3), 55.9 (OCH_3), 56.5 (OCH_3), 76.0 (C-2), 101.0 (C-8), 109.7 (C-5), 113.0 (C-10), 121.9 (C-4), 128.2 (C-3), 143.0 (C-6), 147.2 (C-7), 149.6 (C-9).

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