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CYCLISATION OF 6-HYDROXY-2-YNALS AND YNOATES : A NEW PATHWAY TO SUBSTITUTED 2-METHYLENE-TETRAHYDROFURANS

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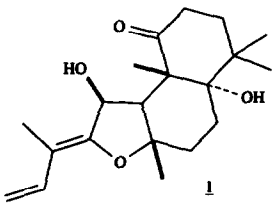
Abstract : Substitued 2-methylene-tetrahydrofurans are obtained by an efficient cyclisation of acetylenic alcohols and phenols. The presence of an electron-withdrawing group activates the triple bond and leads to high yields under weakly basic or acidic conditions. Our cyclisation products are stable against hydrolysis.

2-Methylene-tetrahydrofurans are often encountered in natural products of biological interest such as scapanine 1 [1], prostacyclin 2 [2] and bisabolangelone 3, an insect antifeedant [3].



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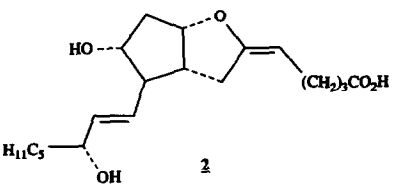

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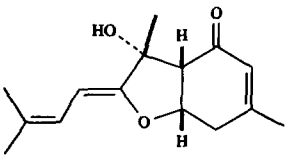

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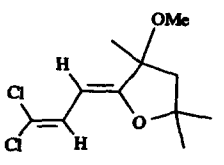
The sensitivity of the enol-ether function against hydrolysis is responsible for the unstability of these molecules. But the presence of a conjugated double-bond is sufficient to make 1 and 3 reasonably stable in the dark at room temperature. As pest control agent, we needed stable analogs of bisabolangelone 3. Our goal was to synthesize compound 4 by means of the cyclisation of a substitued 4-pentynol [4].



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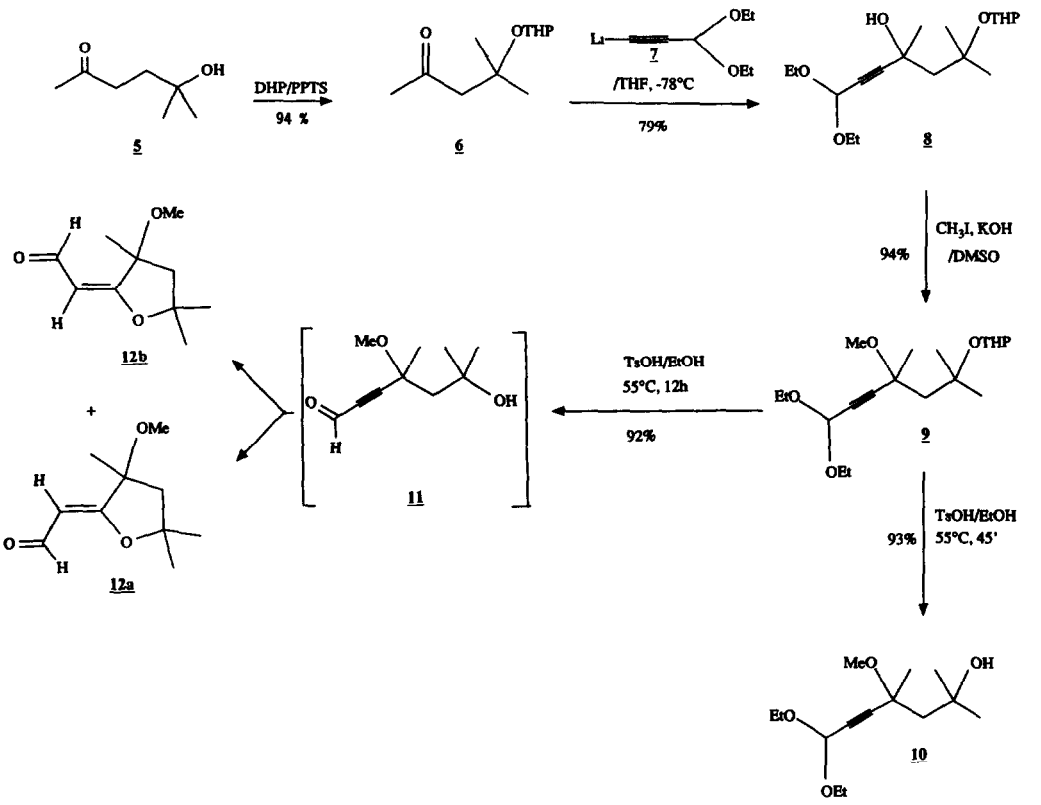
It is well known that electron-deficient substituents activate the acetylenic bond towards alkoxide addition [5], but to our knowledge this has not been applied to intramolecular addition. In fact, the following cyclisations occured with good yields generally under slightly basic conditions, without palladium or rhodium catalysts, as in the case of purely aliphatic substituents [6].

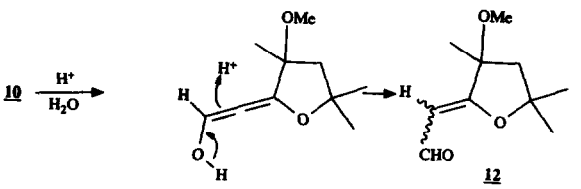
We started from diacetone alcohol 5 which was protected as a tetrahydropyranyl ether 6 [7] (scheme 1). Addition of the lithium acetylide 7 [8] gave alcohol 8. Compound 8 was converted into methyl ether 9 to avoid elimination side reactions. Thus we found that aldehyde 11, generated *in situ* by hydrolysis of the diethylacetal 10, cyclises intramoleculary in slightly acidic conditions to give the unexpected aldehydes 12 with good yields. Uncyclised aldehyde 11 could not be isolated.

Scheme 1



This result can probably be related to the formation of an allenic intermediate as shown in scheme 2.

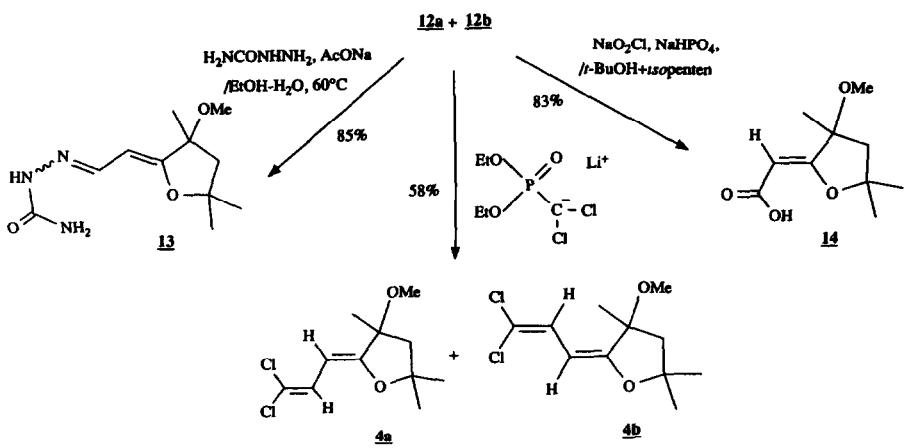
Scheme 2



Compound 12 is obtained as a mixture of *Z* and *E* isomers (*Z*/*E* = 87/13, measured by NMR and GC). These proportions are due to steric hindrance between the carbonyl function and the C-3 substituents (methyl and methoxy group). The two isomers are easily distinguishable by their ^{1}H-NMR spectra. The olefinic proton of the *Z* isomer appears as a doublet at 5.13 ppm and the *E* isomer at 5.55 ppm [9].

Aldehydes 12 were characterised by the semicarbazone 13 and oxidised [10] to acid 14. These compounds were obtained as pure *Z* isomers after recrystallisation (scheme 3). Aldehydes 12 were also converted into compounds 4 by a Wittig-Horner reaction [11].

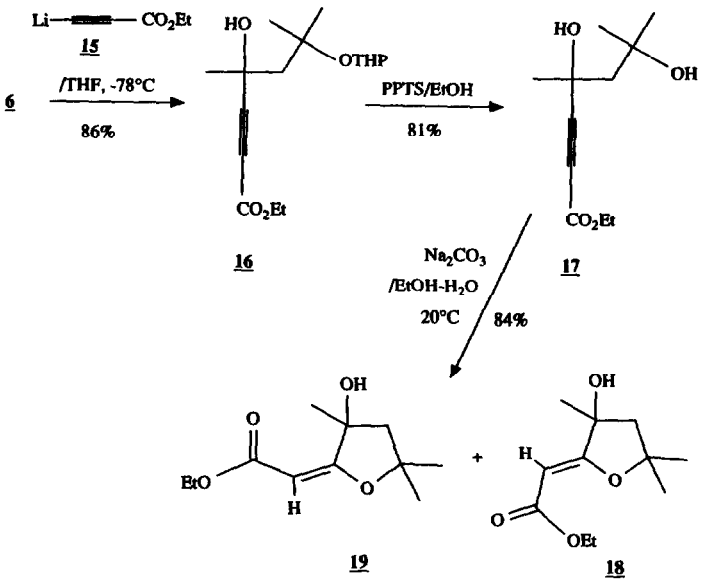
Scheme 3



Whereas the halogenated analog 4 is very sensitive to light or moisture and polymerises in a few hours even at low temperature, the compounds 12, 13 and 14 show great stability against these conditions. This result can be related to the presence of a carbonyl function on the double bond which decreases markedly the rate of hydrolysis of the enol ether group.

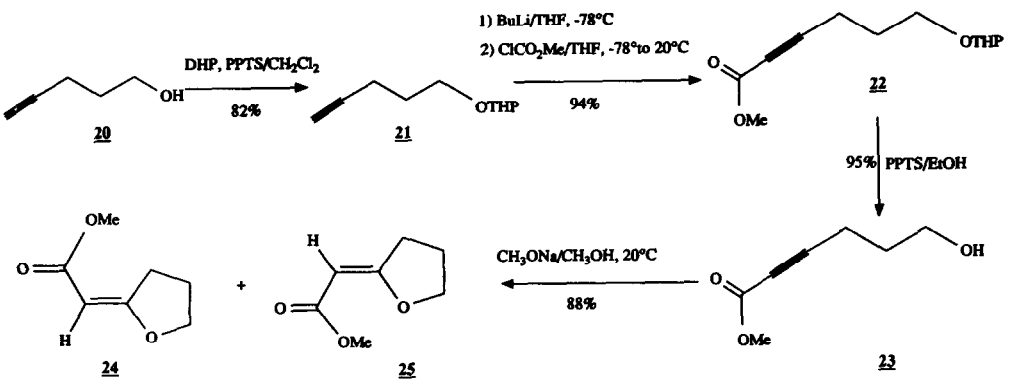
Biological studies [12] showed the importance of a free hydroxyl function in our test molecules. According to these results, we replaced the protected aldehyde on the starting molecule 8 by an ester function (scheme 4). The lithium salt of ethyl propiolate 15 [13] was added to the protected diacetone alcohol 6, giving alcohol 16 with a good yield. Deprotection of the tetrahydropyranyl ether was achieved in slightly acidic conditions but did not give the expected cyclisation products even after a few days. In fact, our mild acidic conditions are probably insufficient to activate the conjugated ester group for the intramolecular cyclisation mechanism proposed in scheme 2. The cyclisation of dihydroxy-ester 17 needed basic conditions and gave two separable isomers 18 (*Z*) and 19 (*E*) of ethyl (3-hydroxy-3,5,5-trimethyl-2-tetrahydrofurylidene)acetates without any side reactions due to the unprotected tertiary alcohol.

Scheme 4

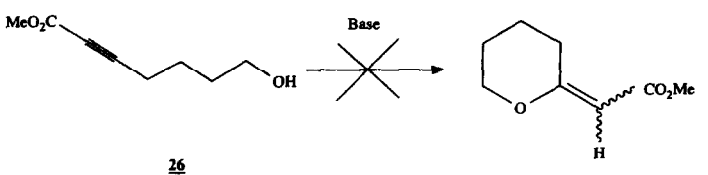


The methyl 2-tetrahydrofurylideneacetates 24 (E) and 25 (Z) have been described as interesting building blocks in organic synthesis [14]. The precursor 23, needed for our method of cyclisation was prepared in a classical way [15] according to scheme 5. 4-Pentynol 20 [16] was first protected as a tetrahydropyranyl ether 21 which was converted into methyl ester 22. After deprotection of the hydroxyl group, the cyclisation step could be performed with a catalytic amount of sodium methylate in anhydrous methanol. Other anhydrous conditions (KOH/MeOH ; KOH/DMSO ; DBU/toluene/reflux) gave similar results whereas sodium carbonate in aqueous ethanol gave only 51 % of 24 (*E*) and 25 (*Z*). The proportions of *Z* and *E* isomers *Z*/*E* = 10/90 can be related to steric hindrance between the furanic oxygen and the ester function.

Scheme 5

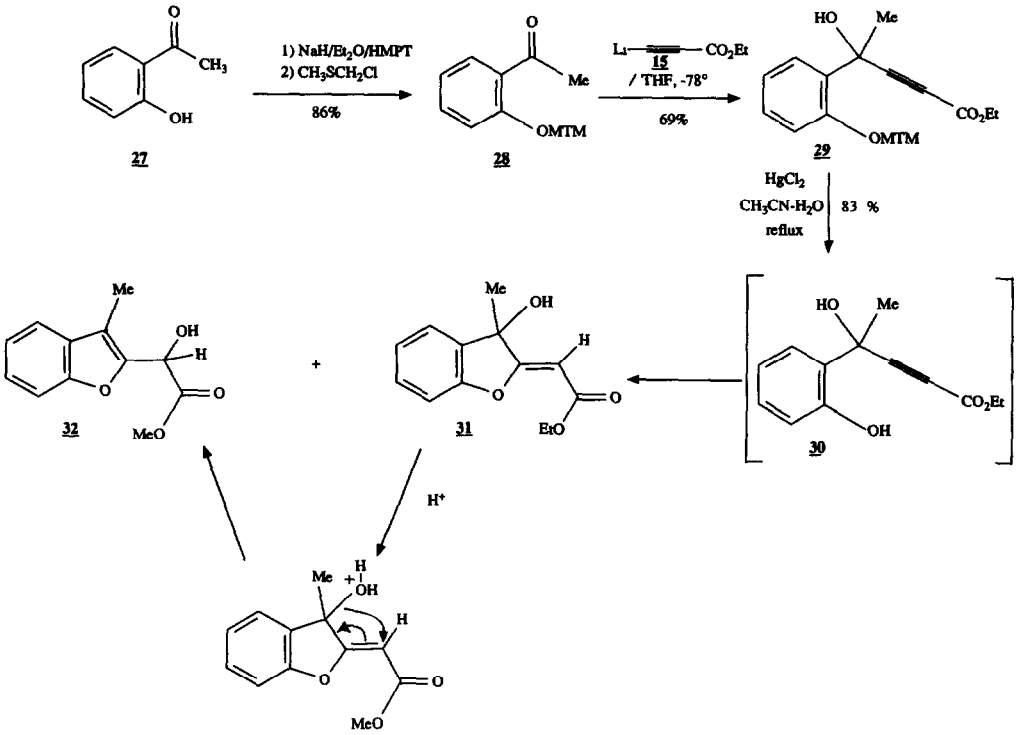


Cyclisation of hydroxy-ester 26 [15] did not give the expected results.



Finaly, we tried to cyclise an acetylenic phenol (scheme 6). Our starting molecule, commercial *ortho*-hydroxy-acetophenone 27 needed to be protected as a methylthiomethyl ether 28 [17]. In this case, cyclisation of phenol 30 takes place during deprotection of the methylthiomethyl ether 29 with mercuric chloride. The expected compound 31 was obtained with a low yield of 15 %. The cyclisation is followed by aromatisation into benzofuran 32 (68 % yield) in the acidic medium.

Scheme 6



EXPERIMENTAL

Gas chromatographic analyses were conducted on a Carlo Erba 4130 chromatograph equipped with a FID detector and a fused silica capillary column (CP Sil 5 CB, 10 m x 0.33 mm). N.M.R. spectra were recorded on the following spectrometers : Hitachi-Perkin Elmer R-24A (60 MHz) and Bruker WM 200 SY (200 MHz). Chemical shifts are reported in ppm downfield from tetramethylsilane. IR spectra were taken on a Perkin-Elmer 457 spectrophotometer, UV on a Perkin-Elmer Lambda 5 with cells of 1 cm path length. Mass spectra were recorded on LKB 9000S spectrometer. Elemental analyses were performed at the institut de chimie, Strasbourg. Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. All reactions were followed by thin layer chromatography on Merck 5715 plates (Kieselgel 60 F254). All anhydrous reactions were run under a positive pressure of dry argon. Column chromatography were carried out under pressure on silica gel Merck 7734 (Kieselgel 60 ; 0.063 - 0.200 mm). Usual work-up means partitioning the reaction mixture between brine and an organic solvent (usually ether), drying the combined organic layers with $MgSO_4$ and removing the solvent on a rotary evaporator.

4-Tetrahydropyranoxy-4,4-dimethyl-2-pentanone 6:
A solution of diacetone alcohol 5 (15 g, 129 mmoles) in 45 ml of methylene chloride is stirred at room temperature for 3 days with 3.6 g (13 mmoles) of pyridinium *para*-toluenesulfonate (PPTS) and 25 ml (260 mmoles) of dihydropyran (DHP). Usual work-up is followed by distillation under vacuo (85-90°C/0.5 mm Hg) yielding 24.3 g of 6 as a colourless liquid. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97 ; H, 10.07. Found : C, 65.7 ; H, 10.0.
^{1}H - NMR (60 MHz, $CDCl_3$) : δ = 1.3 (s, 6H, 2 x 4-CH_3) ; 1.4 - 1.8 (m, 6H) ; 2.1 (s, 3H, CH_3-1) ; 2.6 (s, 2H, CH_2-3) ; 3.1 - 4.0 (m, 2H, OCH_2) ; 4.7 (m, 1H, OCHO). IR (neat) : 2880, 1710 cm^{-1}.

6-Tetrahydropyranoxy-4-hydroxy-4,6-dimethyl-2-heptyn-al diethylacetal 8:
A solution of propargylic aldehyde diethylacetal 7 (990 mg, 7.5 mmoles) in 10 ml anhydrous THF is stirred at -78°C for 15 mn with 7 mmoles of LDA. A solution of protected diacetone-alcohol 6 (1 g, 5 mmoles) in 10 ml THF is then added and stirring is continued for 15 mn. The reaction mixture is then allowed to warm at room temperature for 30 mn and is finaly quenched with a saturated solution of NH_4Cl. After usual workup and silica gel column chromatography (eluant : hexane - ether 7/3), the alcohol 8 is distillated in a kugelrohr apparatus (160 - 180°C/0.1 mm Hg) to give 1.3 g of 8 as a colourless liquid (yield : 79 %). Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82 ; H, 9.82. Found : C, 65.9 ; H, 10.2.
^{1}H - NMR (60 MHz, $CDCl_3$) : δ = 1.2 (t, 6H, 2 x OCH_2CH_3) ; 1.4 - 1.8 (m, 15H) ; 1.95 (m, 2H, CH_2-5) ; 3.4 - 4.1 (m, 6H, 3 x OCH_2) ; 4.95 (m, 1H, OCHO) ; 5.3 (s, 1H, 1-H).
IR (neat) : 3460, 2280, 2240 cm^{-1}.

6-Tetrahydropyranoxy-4-methoxy-4,6-dimethyl-2-heptyn-al diethylacetal 9:
A solution of alcohol 8 (5 g, 15.2 mmoles) in 20 ml DMSO is stirred at 0°C with 4 equivalents (0.4 ml) of methyl iodide. Powdered potassium hydroxide (3 equivalents, 300 mg) is then added and stirring is continued for 40 mn at room temperature. After usual workup, chromatography on a silica gel column (eluant : hexane - ether 9/1) and distillation in a kugelrohr apparatus (160-180°C/0.08 mm Hg) 4.9 g of ether 9 are obtained as a colourless liquid (yield : 94 %).
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.23 (t, 6H, 2 x $OCH_2\underline{CH_3}$) ; 1.30 - 1.70 (m, 15H) ; 2.00 (m, 2H, CH_2-5) ; 3.33 (s, 3H, 4-OCH_3) ; 3.50 - 4.00 (m, 6H, 3 x OCH_2) ; 4.80 (m, 1H, OCHO) ; 5.30 (s, 1H, 1-H). IR (neat) : 2880, 2240 cm^{-1}.

6-Hydroxy-4-methoxy-4,6-dimethyl-2-heptyn-al diethylacetal 10:
A solution of ether 9 (550 mg, 1.61 mmoles) in 25 ml water and 25 ml THF is heated at 55°C for 45 mn with 0.1 equivalents (30 mg) of *para*-toluenesulfonic acid (*p*TsOH). Usual workup followed by silica gel column chromatography (eluant : hexane - ether 7/3) and distillation in a kugelrohr apparatus (150-155°C/0.5 mm Hg) gives 385 mg of 10 as a colourless liquid (yield : 93 %). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.08 ; H, 10.14 ; Found : C, 65.3 ; H, 10.4.
^{1}H - NMR (60 MHz, $CDCl_3$) : δ = 1.2 (t, 6H, 2 x $OCH_2\underline{CH_3}$) ; 1.4 (s, 3H, 4-CH_3) ; 1.5 (s, 6H, 2 x 6-CH_3) ; 1.95 (s, 2H, CH_2-5) ; 3.35 (s, 3H, 4-OCH_3) ; 3.4 - 3.9 (m, 4H, 2 x $O\underline{CH_2}CH_3$) ; 5.2 (s, 1H, 1-H). IR (neat) : 3520, 2240 cm^{-1}.

(3-Methoxy-3,5,5-trimethyl-2-tetrahydrofurylidene)acetaldehydes 12a (*Z*) and 12b (*E*):
A solution of acetal 9 (1.24 g, 3.6 mmoles) in 60 ml aqueous ethanol (50 %) with 0.1 equivalents (75 mg) of *p*TsOH is stirred at 55°C for 12 h. The reaction is then quenched with a solution of $NaHCO_3$. Usual workup followed by silica gel column chromatography (eluant : hexane - ether 7/3) and distillation in a kugelrohr apparatus (100-130°C/0.5 mm Hg) gives 615 mg of a mixture of aldehydes 12a (*Z*) and 12b (*E*) as a colourless liquid (yield : 92 % ; *Z*/*E* = 87/13). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19 ; H, 8.75. Found : C, 65.0 ; H, 9.0.
^{1}H -NMR (200 MHz, $CDCl_3$) : δ = 1.46 (s, 6H, 2 x 5-CH_3) ; 1.52 (s, 3H, 3-CH_3) ; 2.08 (syst. AB, 2H, J_{AB} = 13.6 Hz, CH_2-4) ; 3.23 (s, 3H, 3-OCH_3) ; 5.13 (d, $J_{6,7}$ = 8.4 Hz, 6-H of *Z* isomer) ; 5,55 (d, $J_{6,7}$ = 8.4 Hz, 6-H of *E* isomer) ; 9.96 (d, $J_{6,7}$ = 8.4 Hz, 7-H of *Z* isomer) ; 10.12 (d, $J_{6,7}$ = 8.4 Hz, 7-H of *E* isomer). IR (neat) : 2820, 1660, 1630 cm^{-1}. MS : 184 (M^+ ; 3 %) ; 154 (50 %) ; 152 (34 %) ; 99 (22 %) ; 43 (100 %).

Semicarbazone 13: A solution of aldehyde 12 (155 mg, 0.84 mmoles) in 2 ml ethanol is heated at 60°C with 2 ml of a solution of $H_2NNHCONH_2$.HCl (1 g/8 ml H_2O) and CH_3COONa (1.5 g/8 ml H_2O) for 5 min. Usual workup followed by recrystallisation in ethanol gives 172 mg of semicarbazone 13 (yield : 85 %) ; m.p. 183 - 185°C. Anal. Calcd for $C_{11}H_{19}O_3N_3$: C, 54.75 ; H, 7.94 ; N, 17.42. Found : C, 54.9 ; H, 8.2 ; N, 17.6.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.37 (s, 3H, 3-CH_3) ; 1.43 (s, 3H, 5-CH_3) ; 1.45 (s, 3H, 5-CH_3) ; 2.03 (syst. AB, 2H, $J_{A,B}$ = 13.5 Hz, CH_2-4) ; 3.20 (s, 3H, 3-OCH_3) ; 5.15 (d, 1H, $J_{6,7}$ = 9.6 Hz, 6-H) ; 7.65 (d, 1H, $J_{6,7}$ = 9.6 Hz, 7-H) ; 8.30 (broad s, 1H, NHCO).

(3-Methoxy-3,5,5-trimethyl-2-tetrahydrofurylidene)acetate 14:
A solution of 100 mg (0.54 mmoles) aldehyde 12 in 12 ml *t*-butanol and 3 ml 2-methyl-2-butene is stirred at room temperature. Sodium chlorite (10 equivalents, 500 mg) and sodium dihydrogenophosphate (500 mg, 4.15 mmoles) in 5 ml water are then added dropwise. The reaction is then stirred for 48 h. Usual workup followed by silica gel column chromatography (eluant : CH_2Cl_2 - ether 9/1) and recrystallisation in CCl_4 yields 90 mg (83 %) of acid 14. m.p. 140 - 141°C. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98 ; H, 8.05. Found : C, 59.8 ; H, 8.0.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.46 (s, 3H, 5-CH_3) ; 1.50 (s, 3H, 5-CH_3) ; 1.55 (s, 3H, 3-CH_3) ; 2.14 (syst. AB, 2H, $J_{A,B}$ = 13.6 Hz, CH_2-4) ; 3.23 (s, 3H, 3-OCH_3) ; 4.97 (s, 1H, 6-H). IR ($CHCl_3$) : 3400, 2880, 1720, 1645 cm^{-1}.

3-Methoxy-2-(3,3-dichloro-2-propenylidene)-3,5,5-trimethyl-tetrahydrofuran 4a (*Z*) and 4b (*E*): A suspension of LiCl (179 mg, 4.2 mmoles) in 10 ml anhydrous THF is stirred at 0°C with 2.1 mmoles of nBuLi in hexane (1.75 ml ; 1.2 M). The temperature is then lowered to -78°C after which 330 µl (2.1 mmoles) of diethyl chloromethane phosphonate in 2 ml de THF are added to the reaction mixture. Stirring is continued for 10 mn before adding 205 µl (2.1 mmoles) of CCl_4 in 2 ml THF. 260 mg (1.4 mmoles) of aldehyde 12 in 10 ml THF are finaly added 5 mn later. The reaction mixture is stirred another 30 mn at - 78°C before temperature is allowed to rise at room temperature. After usual workup, chromatography on silica gel (eluant : hexane - CH_2Cl_2 9/1) followed by distillation in a kugelrohr apparatus (110-150°C/0.1 mm Hg) gives 204 mg of 4 (yield : 58 % ; *Z*/*E* = 87/13 by GC) colourless liquid (very unstable).
^{1}H -NMR (60 MHz, $CDCl_3$) : δ = 1.3 (s, 3H, 3-CH_3) ; 1.4 (s, 6H, 2 x 5-CH_3) ; 1.95 (syst. AB, 2H, $J_{A,B}$ = 12.5 Hz, CH_2-4) ; 3.15 (s, 3H, 3-OCH_3) ; 5.05 (d, 1H, $J_{6,7}$ = 10.5 Hz, 6-H) ; 6.65 (d, 1H, $J_{6,7}$ = 10.5 Hz, 7-H). IR (neat) : 2820, 1650, 1590 cm^{-1}. MS : 252 (M^+ + 1 ; 13 %) ; 250 (M^+ - 1 ; 20 %) ; 205 (8,5 %) ; 203 (16%) ; 161 (33 %) ; 159 (100 %).

Ethyl 6-tetrahydropyranoxy-4-hydroxy-4,6-dimethyl-2-heptynoate 16:
A solution of 1.47 g (15 mmoles) ethyl propiolate 15 in 20 ml anhydrous THF is stirred at - 78°C with 15 mmoles of a solution of LDA (17 ml ; 0.9 M) in THF. The reaction is stirred for 10 mn before adding a solution of 2 g (10 mmoles) of ketone 6 in 20 ml THF. Stirring is then continued for 20 mn at - 78°C before temperature is allowed to rise at room temperature for 30 mn. The reaction is finaly quenched with an aqueous solution of NH_4Cl. Usual workup, silica gel column chromatography (eluant : hexane - ether 9/1) and distillation in a kugelrohr apparatus (150 - 175°C/0.1 mm Hg) yields 2.55 g (86 %) of alcohol 16 as a colourless liquid. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.40 ; H, 8.78. Found : C, 64.3 ; H, 8.8.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.28 (t, 3H, $OCH_2\underline{CH_3}$) ; 1.50 - 1.85 (m, 15H) ; 1.90 - 2.20 (m, 2H, CH_2-5) ; 3.55 and 3.95 (m, 2H, OCH_2) ; 4.20 (q, 2H, $O\underline{CH_2}CH_3$) ; 5.00 (m, 1H, OCHO). IR (neat) : 3440, 2870, 2240, 1710 cm^{-1}.

Ethyl 4,6-Dihydroxy-4,6-dimethyl-2-heptynoate 17:
A solution of ester 16 (750 mg, 2.5 mmoles) in 50 ml ethanol is stirred for 10 mn at 55°C with 0.2 equivalents (160 mg) of PPTS. Usual workup is followed by silica gel column chromatography (eluant : hexane - ether 7/3) and distillation in a kugelrohr apparatus (150-190°C/0.1 mm Hg) yielding 436 mg (81 %) of diol 17 as a colourless liquid. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66 ; H, 8.47. Found ; C, 61.9 ; H, 8.7.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.32 (s, 3H, 4-CH_3) ; 1.34 (t, 3H, $OCH_2\underline{CH_3}$) ; 1.57 (s, 3H, 6-CH_3) ; 1.59 (s, 3H, 6-CH_3) ; 1.97 (d, 2H, J = 1.8 Hz, CH_2-5) ; 4.23 (q, 2H, $O\underline{CH_2}CH_3$). IR (neat) : 3360, 2240, 1710 cm^{-1}.

Ethyl (3-hydroxy-3,5,5-trimethyl-2-tetrahydrofurylidene)acetates 18 (*Z*) and 19 (*E*):
A solution of ester 17 (100 mg, 0.5 mmoles) in 20 ml aqueous ethanol (50 %) is stirred for 10 mn at room temperature with 10 equivalents (500 mg) of sodium carbonate. Usual workup is followed by a silica gel column chromatography. Isomer 19 desorbs with hexane - ether 9/1 as eluant and is obtained from distillation in a kugelrohr apparatus (75-90°C/0.1 mm Hg) as a colourless liquid (37 mg ; 37 %). Isomer 18 desorbs with hexane - ether 5/5 and is obtained from distillation in a kugelrohr apparatus (150 - 205°C/0.1 mm Hg) as a white solid (47 mg ; 47 %). m.p. 62 - 65°C. Overall yield : 84 % ; *Z*/*E* = 56/44.
18 : Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66 ; H, 8.47. Found : C, 61.6 ; H, 8.5.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.28 (t, 3H, $OCH_2\underline{CH_3}$) ; 1.42 (s, 3H, 5-CH_3) ; 1.45 (s, 3H, 5-CH_3) ; 1.69 (s, 3H, 3-CH_3) ; 2.22 (syst. AB, 2H, $J_{A,B}$ = 13 Hz, CH_2-4) ; 4.15 (q, 2H, $O\underline{CH_2}CH_3$) ; 5.21 (s, 1H, 6-H). IR (neat) : 3460, 1690, 1645 cm^{-1}.
19 : Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66 ; H, 8.47. Found : C, 61.8 ; H, 8.5.
^{1}H - NMR (200 MHz, $CDCl_3$) : identical to spectral data of isomer 18. IR (neat) : 3360, 1675, 1620 cm^{-1}.

1-Tetrahydropyranoxy-4-pentyne 21:
To a mixture of 2.7 g (31,6 mmoles) of 4-pentynol 20 in 10 ml CH_2Cl_2 is added 3 equivalents (9 ml) of dihydropyran and 0.1 equivalents (800 mg) of PPTS after which the reaction is stirred overnight at room temperature. Usual workup, followed by silica gel column chromatography (eluant : hexane - ether 95/5) and distillation in a kugelrohr apparatus (75-100°C/0.08 mm Hg) gives 4.3 g (yield : 82 %) of ether 21 as a colourless liquid. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39 ; H, 9.59. Found : C, 71.3 ; H, 9.6.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.40 - 2.00 (m, 10H) ; 2.35 (m, 1H, 5-H) ; 3.50 and 3.85 (m, 4H, 2 x CH_2O) ; 4.65 (m, 1H, OCHO). IR (neat) : 3290, 2120 cm^{-1}.

Methyl 6-tetrahydropyranoxy-2-hexynoate 22:
To a stirred solution of ether 21 (3.6 g, 21.3 mmoles) in 20 ml anhydrous THF cooled to - 78°C is added 1.2 equivalents (18 ml ; 1.45 M) of *n*-butyllithium in hexane. Stirring is then continued for 30 mn, after which this solution is added by means of a canula to a solution of 4 equivalents (6.7 ml) of methyl chloroformiate in 20 ml anhydrous THF cooled to -78°C. Stirring is continued for 2 h before the temperature is allowed to rise at room temperature. Usual workup is followed by silica gel column chromatography (eluant : hexane - ether 9/1) and distillation in a kugelrohr apparatus (110-140°C/0.08 mm Hg). 4.5 g ester 22 is obtained as a colourless liquid (yield : 94 %). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70 ; H, 8.02. Found : C, 63.7 ; H, 8.0.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.55 (m, 6H) ; 1.87 (quint, 2H, CH_2-5) ; 2.48 (t, 1H, CH_2-4) ; 3.50 (m, 2H, CH_2O) ; 3.76 (s, 3H, CO_2Me) ; 3.80 (m, 2H, CH_2O) ; 4.59 (m, 1H, OCHO). IR (neat) : 2240, 1715 cm^{-1}.

Methyl 6-hydroxy-2-hexynoate 23:
A solution of 4.1 g (18.1 mmoles) ether 22 in 150 ml ethanol is refluxed over 30 mn with 0.1 equivalents (40 mg) of PPTS. Usual workup followed by silica gel column chromatography (eluant : hexane - ether 9/1) and distillation in a kugelrohr apparatus (115 - 130°/0.08 mm Hg) yields 2.5 g (95 %) of hydroxy-ester 23.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.84 (quint, 2H, CH_2-5) ; 2.49 (t, 2H, CH_2-4) ; 3.75 (t, 2H, CH_2-6) ; 3.76 (s, 3H, CO_2CH_3). IR (neat) : 3400, 2240, 1715 cm^{-1}.

Methyl 2-tetrahydrofurylideneacetates 24 (*E*) and 25 (*Z*):
A solution of 1 g (7.0 mmoles) of hydroxy - ester 23 in 20 ml anhydrous methanol is stirred at room temperature. Sodium hydride (0.1 equivalents, 20 mg of a 55-60 % dispersion in oil) is then added and stirring is continued for 30 mn. Usual workup is followed by silica gel column chromatography. Isomer 24 is eluted with hexane - ether 9/1 before being recrystallised in pentane (m.p. 41 - 43°C). Isomer 25 desorbs with hexane - ether 5/5 and is distilled in a kugelrohr apparatus (85-105°C / 0.08 mm Hg). We obtained 735 mg of 24 (yield : 74 %) and 140 mg of 25 (yield : 14 %). Overall yield : 88 % ; *Z/E* = 11/89 by GC.
24 : Anal. Calcd for $C_7H_{10}O_3$: C, 59.14 ; H, 7.09. Found : C, 59.3 ; H, 6.9.
^{1}H-NMR (200 MHz,$CDCl_3$) : δ = 2.10 (quint, 2H, $J_{3,4}$ = 7.8 Hz, $J_{4,5}$ = 7 Hz, CH_2-4) ; 3.10 (dt, 2H, $J_{3,4}$ = 7.8 Hz, $J_{3,6}$ = 1.7 Hz, CH_2-3) ; 3.67 (s, 3H, CO_2CH_3) ; 4.23 (t, 2H, $J_{4,5}$ = 7 Hz, CH_2-5) ; 5.32 (t, 1H, $J_{3,6}$ = 1.7 Hz, 6-H).
IR (nujol) : 2850, 1710, 1650 cm^{-1}. MS : 142 (M^+ ; 39 %) ; 111 (86 %) ; 69 (100 %).
25 : Anal. Calcd for $C_7H_{10}O_3$: C, 59.14 ; H, 7.09. Found : C, 58.6 ; H, 7.3.
^{1}H-NMR (200 MHz, $CDCl_3$) : δ = 2.05 (quint, 2H, $J_{3,4}$ = 7.7 Hz, $J_{4,5}$ = 6.8 Hz, CH_2-4) ; 2.71 (dt, $J_{3,4}$ = 7.7 Hz, $J_{3,6}$ = 1.2 Hz, CH_2-3) ; 3.68 (s, 3H, CO_2CH_3) ; 4.45 (t, 2H, $J_{4,5}$ = 6.8 Hz, CH_2-5) ; 4.91 (t, 1H, $J_{3,6}$ = 1.2 Hz, 6-H). IR (neat) : 2900, 1710, 1650 cm^{-1}. MS : 142 (M^+ ; 31 %) ; 111 (71 %) ; 69 (100 %).

Methylthiomethylether *of ortho* - hydroxyacetophenone 28:
A suspension of sodium hydride (1.1 g, 33 mmoles) in 50 ml of anhydrous ether is stirred at room temperature. *Ortho*-hydroxyacetophenone 27 (5.44 g, 30 mmoles) dissolved in 50 ml HMPT is then added. Stirring is continued for 30 mn before adding 1.6 equivalents (4 ml) of methylthiomethyl chloride. After 24 h, usual workup followed by distillation in a kugelrohr apparatus (130-150 °C/0.04 mm Hg) gives 5.15 g (86 %) of ether 28 as a yellow solid. m.p. 34 - 35°C. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.22 ; H, 6.12 % H. Found : C, 61.3 ; H, 5.9.
^{1}H - NMR (60 MHz, $CDCl_3$) : δ = 2.2 (s, 3H, $COCH_3$) ; 2.6 (s, 3H, SCH_3) ; 5.1 (s, 2H, OCH_2S) ; 6.7 - 7.8 (m, 4H, Ph).
IR (neat) : 1600, 1675 cm^{-1}.

Ethyl 4-(2'-methylthiomethoxy-phenyl)-4-hydroxy-2-pentynoate 29:
A solution of 2 equivalents ethyl propiolate 15 (735 mg ; 7.5 mmoles) in 15 ml anhydrous THF is stirred at -78°C. An excess of LDA (1.5 equivalents, 16.6 ml of a 0.9 M solution in THF) is then slowly added. Stirring is continued for 10 mn before adding 735 mg (3.75 mmoles) of ketone 28 in 10 ml THF. Twenty minutes later the temperature is allowed to rise at room temperature and the reaction is quenched with an aqueous solution of NH_4Cl. Usual workup is followed by silica gel column chromatography (eluant : hexane - ether 8/2) and distillation in a kugelrohr apparatus (200 - 220°C/0.1 mm Hg) yielding 884 mg (80 %) of 29 as a yellow syrup. Anal. Calcd for $C_{15}H_{18}O_4S$: C, 61.21 ; H, 6.17. Found : C, 61.5 ; H, 6.2.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.28 (t, 3H, OCH_2CH_3) ; 1.95 (s, 3H, 4-CH_3) ; 2.35 (s, 3H, SCH_3) ; 4.20 (q, 2H, OCH_2CH_3) ; 5.28 (s, 2H, OCH_2S) ; 7.05 (m, 2H, Ph) ; 7.40 (m, 2H, Ph). IR (neat) : 3500, 2240, 1710, 1600, 1590 cm^{-1}.

Ethyl (3-hydroxy-3-methyl-2,3-dihydro-2-benzo(b)furylidene)acetate 31 and ethyl (3-methyl-2-benzo(b)furyl)-2-hydroxyacetate 32:
A solution of 335 mg (1.14 mmoles) ester 29 in 15 ml acetonitrile - water 8/2 with 1.1 equivalents (340 mg) of mercuric chloride ($HgCl_2$) is refluxed for 1 h. Usual workup is followed by silica gel chromatography. Compound 32 desorbs with hexane - ether 8/2 and is distillated in a kugelrohr apparatus (150-200°C/0.1 mm Hg) yielding 180 mg (68 %) of benzofuran 32 as a white solid. m.p. 67 - 69°. The product 31 is eluted with hexane - ether 7/3 and is recrystallised in ether yielding 40 mg (15 %) of 31 as colourless plates m.p. 109 - 111°C. Overall yield : 83 %.
31 : ^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1,30 (t, 3H, OCH_2CH_3) ; 1,68 (s, 3H, 3-CH_3) ; 4,20 (m, 2H, OCH_2CH_3) ; 5,50 (s, 1H, 10-H) ; 7,10 - 7,45 (m, 4H, Ph). IR ($CHCl_3$) : 3580, 3400, 1700, 1685, 1615, 1600 cm^{-1}. SM : 234 (M^+ ; 13 %) ; 219 (35 %) ; 173 (67 %) ; 161 (100 %). UV (EtOH) : τ max : 207 nm (ϵ = 48000) ; 257 nm (ϵ = 32400) ; 280 nm (ϵ = 19800)
32 : Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65 ; H, 6.02. Found : C, 66.5 ; H, 6.1.
^{1}H - NMR (200 MHz, $CDCl_3$) : δ = 1.24 (t, 3H, OCH_2CH_3) ; 2.30 (s, 3H, 3-CH_3) ; 4.28 (q, 2H, OCH_2CH_3) ; 5,37 (d, 1H, $J_{10,OH}$ = 6,2 Hz, 10-H) ; 7.20 - 7.55 (m, 4H, Ph). IR (neat) : 3480, 1745, 1460 cm^{-1}. SM : 234 (M^+ ; 14 %) ; 161 (100 %). UV (EtOH) : τ max : 204 (ϵ = 37600) ; 252 (ϵ = 13700)

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