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A NEW BIS-ANNELATION METHOD. APPLICATION TO STEROID SYNTHESIS

Jean-Marie Poirier* and Laurent Hennequin

Laboratoire de Chimie Organique, U.A. n° 464 du C.N.R.S.,
Faculté des Sciences et des Techniques de Rouen et IRCOF
BP 118, 76134 Mont Saint Aignan Cedex, France

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Abstract : New bis-annelation reagents 1 or 2 are described. With monocyclic enolates equivalents 4, these reagents led to the formation of tricyclic compounds in few steps. The utility of the method is tested for the steroid rings synthesis.

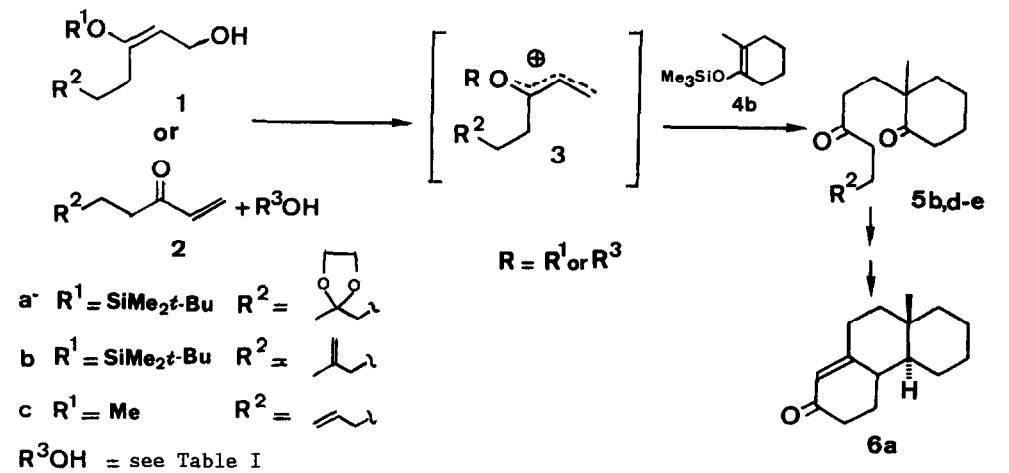
Since they were proposed as precursors of the A and B rings of steroids, bis-annelation reagents have always been important intermediates in the synthesis of polycyclic natural products.[1]

They mainly appeared as functionalized enones, β-ketoesters or aromatic rings.[2] But in spite of their utility, it appears that only the α-silylenones proposed by Stork[3] have been able to trap regiospecifically-formed enolates.

We previously reported a new preparation method for 1,5-dicarbonyl compounds by condensation of silyl enol ethers with functionalized carbocations. We showed that the carbocations could be prepared by reaction of boron trifluoride etherate with either hemiacetal vinylogs[4-7] or a mixture of an enone and a hydroxylic compound.[8,9]

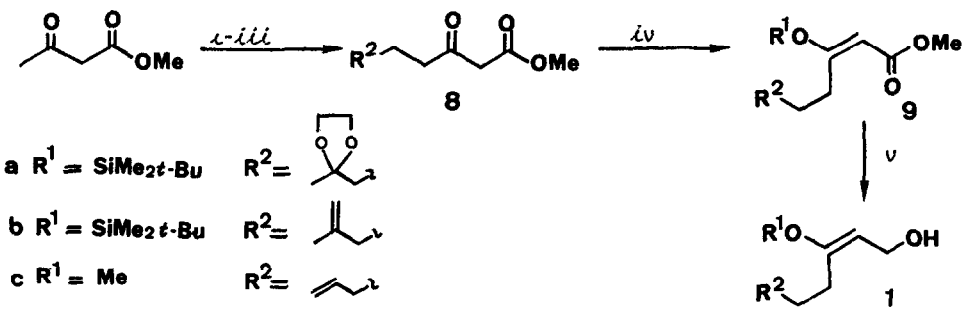
We now describe the results obtained with bisannelation reagents (scheme I) and the application of these reagents to the synthesis of steroids.

Scheme I



The hemiacetal vinylogs 1a-c were prepared as described in scheme II. The dianion of methylacetoacetate was condensed with the halogenocompounds 7a-c. The resulting β-ketoesters 8a-c were then treated either with trimethyl orthoformate in the presence of sulfuric acid (8c) to give the enemethoxyester 9c or with tert-butyldimethylsilylchloride in the presence of triethylamine (8a,b) to give the corresponding enesilyloxyesters 9a and 9b. Finally, the ene-esters 9a-c were reduced by $LiAlH_4$ following the procedure of Steglich[10] to give the hemiacetal vinylogs 1a-c.

Scheme II

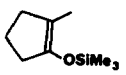
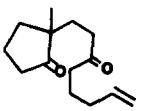
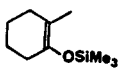
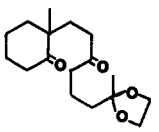
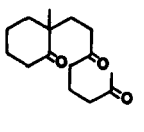
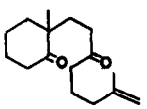
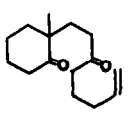
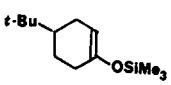
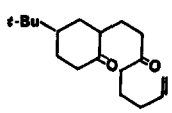


i) NaH,THF,0°C ; ii) nBuLi,THF,0°C ; iii) R^2⌒Br (7a-c) ; iv) 8a or 8b : t-$BuMe_2SiCl$,Et_3N; 8c : $HC(OCH_3)_3$, H^+ ; v) $LiAlH_4$,Et_2O

The enones of bisannelation 2a,c were prepared[11] by condensation of Grignard reagents with acrolein followed by oxidation of the resulting allylic alcohol with pyridinium chlorochromate (PCC). The enone 2b was obtained by degradation of the hemiacetal vinylog 1b over silica gel.

By condensation of the intermediate carbocations 3a-c with the silylenol ethers 4 , 1,5-dicarbonylcompounds 5 were isolated with good yields (table I). The reactions were done in similar conditions to those previously described for simple reagents either hemiacetal vinylogs[4,6] or enones[8] : they were done in nitromethane at -20°C using the silylenol ether 4 in excess (1.4 eq.) and using 0.25 eq. of boron trifluoride etherate. The results we obtained, showed that the alkoxy derivatives 1c gave higher yields than the corresponding silyloxy derivatives 1a,b. This result may be attributed to better electron donating effect of the methoxy group in carbocation 3c compared with the t-butyldimethylsilyloxy group in carbocations 3a and 3b . In the case of 1a, some of the condensation product appeared to be the triketone 5c (see Table I), the acetal being partially cleaved by the Lewis acid. As observed with monoannelating reagents[8], the results obtained from a mixture of an enone and a hydroxylic compound R^3OH, led to higher yields than those obtained from the hemiacetal vinylogs. Menthol and isopropanol were used as hydroxylic compounds, according to our previous results.[8]

Table I : 1,5-dicarbonylcompounds 5 prepared by condensation of silylenol ethers 4 with bis-annelation reagents 1 or 2.

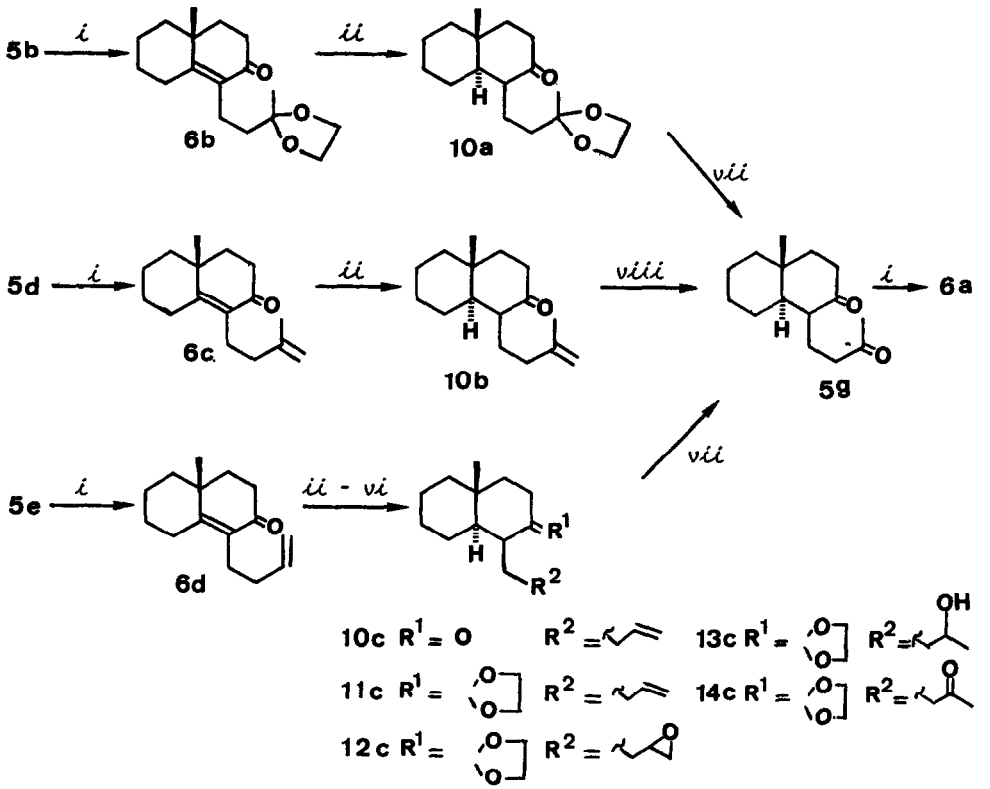
Silylenol ethers 4	Bis-annelation reagents 1 or 2	Hydroxylic compound R^3OH	1,5-dicarbonylcompounds 5	Yield % [a]
 4a	1c	——	 5a	56
	2c	iPrOH		75
 4b	1a	——	 5b  5c	17[b]
	2a	menthol		45[b]
	1b	——	 5d	42
	2b	menthol		80
	1c	——	 5e	76
	2c	iPrOH		85
 4c	1c	——	 5f	67

a) yield of product purified by flash-chromatography

b) ratio 5b/5c = 1/1

Finally, the diketones 5b,d,e were transformed into the tricyclic enone 6a as described in scheme III. After cyclization of 5b,d,e in basic medium and Birch type reduction of the resulting enones 6b,c,d , we isolated the δ-functionalized ketones 10a,b,c,.

Scheme III

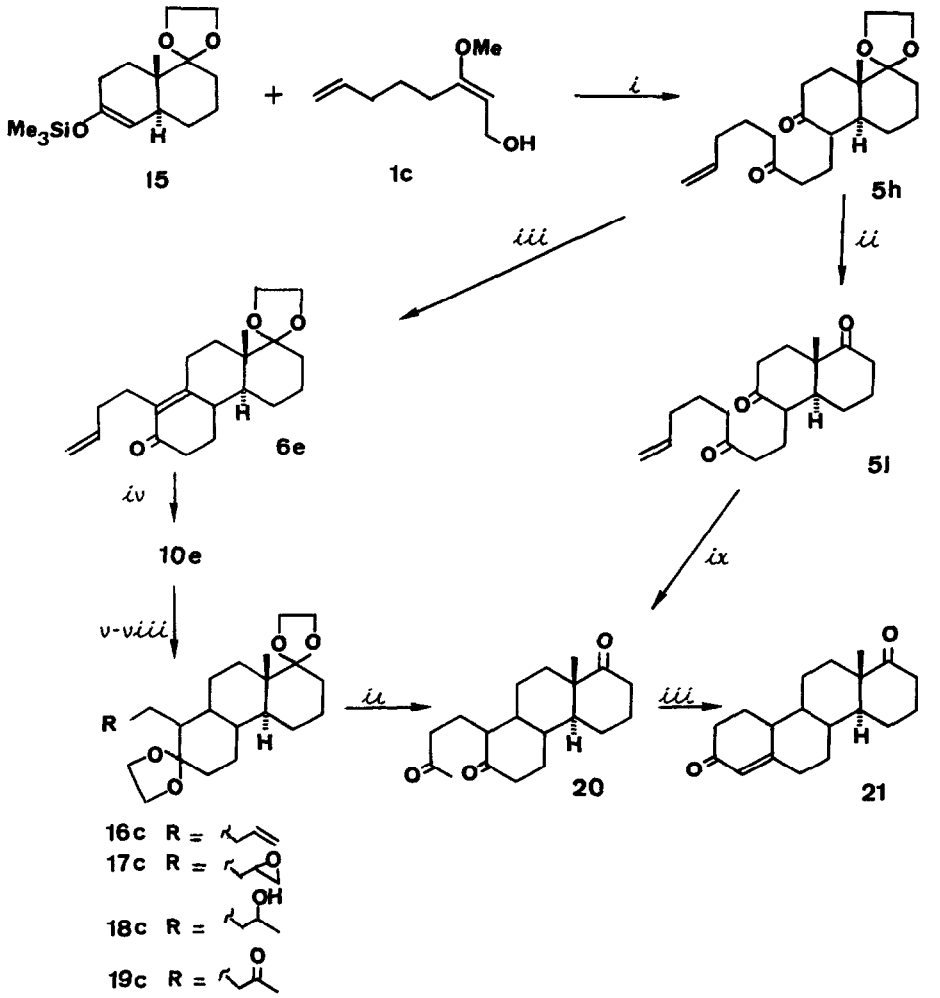


i) KOH,EtOH 3M ; ii) Li/NH_3 ; iii) $(HOCH_2)_2$, pTSA ;iv) m-CPBA ; v) $LiBH_4$,Et_2O; vi) PCC, CH_2Cl_2 ; vii) HCl 3M,THF ; viii) O_3 .

For 10a, the carbonyl group was regenerated by acidic cleavage of the acetal whereas for 10b it was generated by ozonolysis of the disubstituted double bond. In the case of 10c the direct epoxidation led mainly to Baeyer-Villiger products. In order to avoid this undesired reaction, we protected the carbonyl group of 10c as an acetal 11c. Then, the monosubstituted double bond of 11c was successfully epoxidized with meta-chloroperbenzoic acid, leading to 12c. After opening of the epoxide with lithium borohydride, the resulting alcohol 13c was oxidized with pyridinium chlorochromate to give the ketoacetal 14c. The cyclisation of 5g to 6a was achieved in basic medium.

In order to test the utility of these methods for the synthesis of steroids, we condensed the hemiacetalvinylog 1c with the functionalized bicyclic silylenol ether 15 (scheme IV)

Scheme IV



i) CH_3NO_2, -20°C, BF_3,Et_2O ii) HCl 3M,THF iii) KOH,EtOH,3M iv) Li/NH_3 ; v) $(HOCH_2)_2$, H^+ vi) m-CPBA vii) $LiBH_4$, Et_2O viii) PCC ix) Tsuji (see ref 12).

As expected, the corresponding diketoacetal 5h was isolated in a good yield (53%). Only few electrophilic reagents have been condensed successfully with regiospecifically formed enolate-equivalents such as 15 and usually these condensations required the preliminary regeneration of the metallated enolate, by treatment of the silylenol ether with methyllithium.[1,2] In order to confirm the structure of 5h, we deprotected the masked carbonyl function to generate the triketone 5i the analysis of which are in good agreement with those described by Tsuji.[12]

The cyclisation in basic medium of 5h led to the enone 6e, which was reduced by lithium in liquid ammonia to the ketone 10e. The transformation of 10e to the triketone 20 was accomplished with the same sequence as described for the acetal 11c (scheme III), and involved the intermediate epoxide 17c. It must be noted that the direct transformation of the triketone 5i to the triketone 20 has been accomplished by Tsuji,[12] the final oxidation of the double bond being done with oxygen in the presence of $PdCl_2$ and CuCl. The cyclisation of 20 and the regression of the six membered D ring of 21 has already been published by Stork[13] and Tsuji.[12] Different attempts to condense the bis annelation enone 2c with the silylenolether 15 in the presence of menthol have until now been unsuccessful. Some other experiments are in progress.

The method we describe in this paper appears to be an efficient method for the transformation , in few steps, of monocyclic compounds to tricyclic products. This reaction was applied successfully with bis annelation vinyl ketones, usually known for their poor condensation yields, resulting from their high ability to polymerise. Applied to a functionalized bicyclic silylenol ether, this new reaction led to the tetracyclic enone 21, an important intermediate[12] in the synthesis of many steroids.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on a Perkin Elmer R12 60 MHz and on a Brucker WM 300 MHz. ^{13}C NMR spectra were recorded on a Varian CFT-20 and on a Brucker WR 67.8 MHz. All chemical shifts are given in units downfield from internal tetramethylsilane in $CDCl_3$ solution unless otherwise noted. IR spectra were obtained with a Perkin Elmer Infracord 377. Flash chromatography[14] was performed on silica gel (230-400 mesh) (ether/petroleum ether). Nitromethane was dried over molecular sieves 4A and purified by distillation on P_2O_5. The reaction progress was monitored by thin layer chromatography (ether/ petroleum ether : 50/50).

Preparation of the β-ketoesters 8a-c:

To a suspension of 0.53g (22mmol) of sodium hydride (50% in oil) in 25 mL of dry tetrahydrofuran cooled to 0°C, was added 1.27g (11 mmol) of methyl acetoacetate. Stirring was continued for 10 min at 0°C. Then 4.4 mL of n-BuLi (2.5M in hexane) were added dropwise to the suspension. After stirring 10 min at 0°C, 10 mmol of halogeno compound 7 in 2 mL of tetrahydrofuran were added. Stirring was continued for 10 min at 0°C and for an additional hour at room temperature. Then the mixture was cooled to 0°C and neutralized by addition of 3N HCl. After extraction with ether, the organic phases were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography or by distillation.

7,7-Ethylenedioxy-3-oxo-methyl-octanoate (8a)
Yield : 22%; IR cm^{-1} : 1720 and 1745 (νCO); ^1H NMR : 1.3 (s,3H), 1.5-1.8 (m,4H), 2.4-2.8 (m,2H), 3.45 (s,2H), 3.75 (s,3H), 3.95 (s,4H); ^{13}C NMR (C_6D_6) : 18.2, 23.7, 38.2, 42.6, 48.8, 51.8, 64.6 (2C), 109.7, 167.8, 202.5. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.37; H, 7.88. Found : C, 57.6; H, 8.1.

7-Methyl-3-oxo-methyl-oct-7-en-oate (8b)
Yield : 70%; bp : 92°C/0.5 mmHg; IR cm^{-1} : 1650 (νC=C), 1720 and 1755 (νCO); ^1H NMR : 1.70 (s,3H), 1.5-2.2 (m,4H), 2.55 (t,2H), 3.45 (s,2H), 3.72 (s,3H), 4.7 (m,2H); ^{13}C NMR (C_6D_6): 21.4, 22.1, 37.0, 42.0, 48.9, 51.7, 110.7, 145.0, 167.6, 201.7. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found C, 65.0; H, 8.7.

3-Oxo-methyl-oct-7-en-oate (8c)
Yield : 83%; bp : 68-70°C/0.3 mmHg; IR cm^{-1}: 1645 (νC=C), 1720 and 1750 (νCO); ^1H NMR :

1.5-2.3 (m,4H), 2.5 (t,2H), 3.45 (s,2H), 3.75 (s,3H), 4.8-5.2 (m,2H), 5.4-6.1 (m,1H); ^{13}C NMR (C_6D_6) : 22.7, 33.0, 41.9, 48.9, 51.7, 115.1, 138.2, 167.6, 201.9.

Preparation of the ene-silyloxyesters 9a and 9b:

A solution of 0.1 mol of β-ketoester 8a or 8b, 12.6 g (0.125 mol) of triethylamine and 18.8 g (0.125 mol) of t-butyldimethylsilyl chloride in 130 mL of anhydrous ether was stirred at 20°C until no more starting material appeared on TLC plates. The suspension was then filtered. The solvent was evaporated and the ene-silyloxyester was purified by flash chromatography (ether/petroleum ether : 5/100).

7,7-Ethylenedioxy-3-(t-butyldimethylsilyl)oxy-ethyl-oct-2-en -oate (9a)

Yield : 76%; IR cm^{-1} : 1620 (νC=C), 1710 (νCO); ^1H NMR : 0.25 (s,6H), 0.95 (s,9H), 1.25 (t,3H), 1.3 (s,3H), 1.5-1.8 (m,2H), 2.3 -2.9 (m,2H), 3.9 (s,4H), 4.1 (q,2H), 5,1 (s,1H); ^{13}C NMR (C_6D_6) : -4.6, 14.6, 18.2, 21.9, 24.0, 25.7 (3C), 33.3, 38.9, 59.2, 64.7 (2C), 99.8, 109.9, 167.1, 172.8.

7-Methyl-3-(t-butyldimethylsilyl)oxy-methyl-oct-2en-oate (9b)

Yield : 75%; IR cm^{-1} : 1620 (νC=C), 1725 (νCO); ^1H NMR : 0.2 (s,6H), 0.9 (s,9H), 1.75 (s,3H), 1.5-2.4 (m,4H), 2.75 (t,2H), 3.65 (s,3H), 4.75 (s,2H), 5.15 (s,1H); ^{13}C NMR (C_6D_6) : -2.2 (2C), 18.2, 22.3, 24.4, 25.6 (3C), 33.1, 37.7, 50.3, 99.3, 110.6, 145.2, 167.1, 172.9.

Preparation of the enealkoxyester 9c :

A solution of 22.26g (0.21 mol) of trimethylorthoformate, 35.7g (0.21 mol) of β-ketoester 8c and 7 drops of sulfuric acid was stirred during 24 hours at 20°C. The solution was then neutralized with 13 drops of quinoleine and slowly distilled.

3-Methoxy-methyl-hepta-2,7-dienoate (9c)

Yield : 81%; bp : 105°C/13 mm Hg; ^1H NMR : 1.5-2.4 (m,4H), 2.8 (t,2H), 3.6 (s,3H), 3.65 (s,3H), 4.8-5.2 (m,2H), 5.0 (s,1H), 5.5-6.2 (m,1H); ^{13}C NMR : 26.1, 30.8, 32.8, 49.7, 54.5, 89.5, 113.9, 137.6, 166.9, 175.8.

Preparation of the hemiacetal vinylogs 1a-c :

The enesilyloxy and enealkoxy esters 9a-c were reduced according to the procedure described by Steglich[10].

7,7-Ethylenedioxy-3-(t-butyldimethylsilyl)oxy-oct-2-en-1ol (1a)

Yield : 93%; IR cm^{-1} : 1655 (νC=C), 3200-3600 (νOH); ^1H NMR (CCl_4) : 0.2 (s,6H), 0.9 (s,9H), 1.25 (s,3H), 1.4-1.7 (m,4H), 1.9-2.3 (m,2H), 3.5-4.0 (m,1H,OH), 3.85 (s,4H), 3.95 (d,2H),4.8 (t,1H).

7-Methyl-3-(t-butyldimethylsilyl)oxy-oct-2,7-dien-1ol (1b)

Yield : 81%; ^1H NMR (CCl_4) : 0.15 (s,6H), 0.9 (s,9H), 1.7 (s,3H), 1.5-2.3 (m,6H + 1H,OH), 3.95 (d,2H), 4.65 (s,2H), 4.8 (t,1H); ^{13}C NMR (C_6D_6) :-2.55 (2C), 18.3, 22.5, 25.3, 26.0 (3C), 31.2, 37.5, 58.5, 106.8, 110.6, 145.2, 155.2.

3-Methoxy-octa-2,7-dien-1-ol (1c)

Yield : 82%; IR cm^{-1} : 1645 and 1660 (νC=C), 3200-3600 (νOH); ^1H NMR (CCl_4) : 1.2-2.4 (m,6H), 3.45 (m,1H,OH), 3.5 (s,3H), 4.0 (d,2H), 4.6 (t,1H), 4.8-5.2 (m,2H), 5.5-6.1 (m,1H); ^{13}C NMR (C_6D_6) : 27.3, 29.9, 33.5, 54.0, 58.4, 96.9, 114.8, 138.7, 160.3.

Preparation of the enone 2a,c.[11]

To a solution of 50 mmol of alkylmagnesium halide in 100 mL of anhydrous ether (prepared by reaction of 50 mmol of halocompound : 1-chloro-4,4-ethylendioxy pentane for 22a or 1-bromo-4-pentene for 22c with 4.68g (0.2 mol) of magnesium at 60°C during 3 hours) cooled to -78°C, was added dropwise a solution of 2.8 g (50 mmol) of freshly distilled acrolein in 4 mL of tetrahydrofuran. The suspension was stirred for 1 hour at -78°C. Then 10 mL of an aqueous saturated solution of sodium sulfate was added. After warming up to 20°C, the mixture was extracted with ether (5x50 mL). The organic layers were dried ($MgSO_4$) and evaporated. The allylic alcohols 22a,c were purified by flash chromatography (ether/petroleum ether : 15/100). In the case of the alcohol 22c, acrolein was added at room temperature and the suspension was stirred 24 hours at room temperature. The allylic alcohol 22c was isolated as previously described for 22a.

7,7-Ethylenedioxy-oct-1-en-3-ol (22a)
Yield : 98%; IR cm^{-1} :1640 (νC=C), 3200-3600 (νOH); ^1H NMR : 1.2 (s,3H), 1.1-1.9 (m,6H), 2.3-2.7 (m,1H, OH), 3.5-3.7 (m,1H), 3.9 (s, 4H), 4.9-5.5 (m,2H), 5.5-6.2 (m,1H).
Octa-1,7-dien-3-ol (22c)
Yield : 63%; IR cm^{-1} : 1645 (νC=C), 3200-3600 (νOH); ^1H NMR 1.2-1.7 (m,4H), 1.8-2.3 (m,3H including OH), 3.9-4.2 (m,1H), 4.8-5.4 (m,4H), 5.4-6.2 (m,2H); ^{13}C NMR (C_6D_6) : 25.1, 34.0, 36.9, 72.8, 114.1, 114.7, 138.9, 142.0.

To a suspension of 0.43g (2mmol) of pyridinium chlorochromate in 5 mL of dichloromethane was added a solution of 1 mmol of allylic alcohol 22a or 22c in 1 mL of dichloromethane. Stirring was continued for 1 hour at 20°C. The suspension was then filtered over florisil (60-100 mesh) and the column was washed with 300 mL of ether. After evaporation of the solvents, the crude products were purified by flash chromatography (ether/ petroleum ether : 10/ 100).
7,7 Ethylenedioxy-oct-1-en-3-one (2a)
Yield : 63%; IR cm^{-1} : 1620 (νC=C), 1685 (νCO); ^1H NMR : 1.25 (s,3H), 1.1-2.0 (m,4H), 2.2-2.7 (m,2H), 3.85 (s,4H), 5.6-6.1 (m,1H), 6.2-6.4 (m,2H); ^{13}C NMR (C_6D_6) : 19.4, 24.5, 39.3, 40.2, 65.4 (2C), 110.5, 128.0, 137.7, 200.2. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found C, 64.7; H, 8.3.
Octa-1,7-dien-3-one (2c)
Yield : 67%; ^1H NMR : 1.5-2.3 (m,4H), 2.6 (t,2H),4.8-5.3 (m,2H), 5.5-6.2 (m, 3H), 6.2-6.4 (m,1H); ^{13}C NMR (C_6D_6) : 23.8, 33.9, 39.4, 115.8, 128.0, 137.5, 138.8, 200.2. Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found C, 77.4; H, 9.7.

Preparation of 7-methyl- octa-1,7-dien-3-one 2b:

To a solution of 1.34g (5mmol) of hemiacetal vinylog 1b in 10 mL of dichloromethane was added 4 drops of boron trifluoride etherate. Stirring was continued for 15 min at 20°C. Then 2mL of an aqueous saturated solution of sodium hydrogenocarbonate were added and stirring continued for 15 min at room temperature. The mixture was then extracted with dichloromethane (5x10 mL). The organic layers were dried ($MgSO_4$) and evaporated. The enone 2b was purified by flash chromatography (ether/ petroleum ether : 10/ 100). Yield : 95%; ^1H NMR: 1.75 (s,3H), 1.7-2.3 (m,4H), 2.6 (t,2H), 4.8 (s,2H), 5.7-6.2 (m,1H), 6.3-6.46 (m,2H); ^{13}C NMR (C_6D_6) : 21.8, 22.2, 37.3, 38.8, 110.7, 127.1, 136.9, 145.0, 199.1.

Preparation of the silylenol ethers 4a-c, 15 :

The silylenol ethers 4a-c were prepared according to a procedure we have previously described[6]. Analysis and spectral data are in good agreement with the literature[15]. The silylenol ether 15 was prepared according to the procedure described by G. Stork[16,17].
trans-4a-Methyl-5,5-ethylenedioxy-2-trimethylsilyloxy-3,4, 4a,5,6,7,8,8a-octahydronaphtalene (15):
Yield : 82%; IR cm^{-1} : 1670 (νC=C); ^1H NMR (300 MHz): 0.16 (s,9H), 0.93 (s,3H), 1.2-2.1 (m,10H), 2.4 (m,1H), 3.8-4.0 (m,4H),4.52 (s,1H); ^{13}C NMR : 0.53 (3C), 13.71, 23.46, 27.22, 27.45, 27.56, 30.91, 39.92, 41.13, 65.29, 108.34, 112.94, 149.19.

Preparation of the 1,5-dicarbonylcompounds 5a-f,h from a silylenol ether and an hemiacetal vinylog. General procedure:

To a stirred solution of 5 mmol of hemiacetal vinylog 1 and 8 mmol of silylenol ether in 10 mL of nitromethane cooled to -20°C, was added dropwise 0.2 mL of a mixture of boron trifluoride etherate and ether (ratio BF_3,Et_2O/ Et_2O = 4/1; v/v). The reaction mixture was stirred for 1 hour at -20°C and then hydrolyzed at 0°C with 5 mL of an aqueous saturated solution of sodium hydrogenocarbonate. The solution was stirred for 15 min at 20°C. The mixture was then extracted with 7x15 mL of dichloromethane. The organic layers were dried ($MgSO_4$) and evaporated. The 1,5-dicarbonylcompounds 5 were purified by flash chromatography (ether/ petroleum ether : 10/100).

Preparation of the 1,5-dicarbonylcompounds 5a-e from a silylenol ether and a mixture of an enone and a hydroxylic compound. General procedure:
1) With isopropanol
To a stirred solution of 4 mmol of silylenol ether 4 in 3 mL of nitromethane cooled to

-20°C was added a solution of 3 mmol of enone 2 in 3 mL of nitromethane. Then a solution of 0.75 mmol of boron trifluoride etherate (0.25 eq.) in 3 mmol of isopropanol was added dropwise. Stirring was continued for 1 hour at -20°C. The mixture was then warmed up to 0°C and treated with 5 mL of an aqueous saturated solution of sodium hydrogenocarbonate. Purification of dicarbonylcompounds was accomplished as described above.

2) With menthol

To a stirred solution of 4 mmol of silylenol ether in 3 mL of nitromethane cooled to -20°C was added a solution of 3 mmol of the enone 2 in 3 mL of nitromethane. Then a mixture of 0.75 mmol of boron trifluoride etherate (0.25 eq.) and a solution of 3 mmol of menthol in 1 mL of dry dichloromethane was added dropwise. Stirring was continued for 1 h at -20°C and the reaction mixture was warmed up to 0°C. Work-up and purification were accomplished as described above.

2-(3-Oxo-oct-7-enyl)-2-methyl-cyclopentanone (5a)
IR cm^{-1} : 1645 (νC=C), 1720 and 1740 (νCO); ^1H NMR : 0.95 (s,3H), 1.0-2.55 m,16H), 4.8-5.15 (m,2H), 5.4-6.1 (m,1H); ^{13}C NMR (C_6D_6) : 18.6, 21.5, 23.0, 30.4, 33.4, 36.4, 37.3, 37.5, 41.7, 47.1, 115.1, 138.5, 208.5, 220.6.

2-(7,7-Ethylenedioxy-3-oxooctyl)-2-methyl-cyclohexanone (5b)
IR cm^{-1} : 1705 (νCO); ^1H NMR : 1.08 (s,3H), 1.35 (s,3H), 1.0-2.6 (m,18H), 3.95 (s,4H); ^{13}C NMR (C_6D_6) : 18.6, 21.1, 22.6, 23.9, 27.5, 31.3, 37.4, 38.7 (2C), 39.6, 42.6, 47.8, 64.6 (2C), 109.9, 208.8, 213.5.

2-(3,7-dioxooctyl)-2-methyl-cyclohexanone (5c)
IR cm^{-1} : 1710 (νCO); ^1H NMR : 1.05 (s,3H), 1.0-2.65 (m,18H), 2.15 (s,3H); ^{13}C NMR : 17.2, 20.4, 22.0, 26.8, 29.2, 30.6, 36.8, 38.2, 38.9, 41.0, 41.9, 47.2, 207.6, 209.2, 214.7. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found : C, 70.8, H, 10.0.

2-(7-Methyl-3-oxo-oct-7-enyl)-2-methyl-cyclohexanone (5d)
IR cm^{-1} : 1710 (CO); ^1H NMR : 1.05 (s,3H), 1.5-2.6 (m,18H), 1.7 (s,3H), 4.75 (s,2H); ^{13}C NMR (C_6D_6) : 21.3, 21.7, 22.25, 22.7, 27.6, 31.3, 37.3 (2C), 38.7, 39.6, 41.9, 47.8, 110.6, 145.2, 208.7, 213.4.

2-(3-oxo-oct-7-enyl)-2-methyl-cyclohexanone (5e)
IR cm^{-1} : 1640 (νC=C), 1710 (νCO); ^1H NMR : 1.05 (s,3H), 1.3-2.6 (m,18H), 4.8-5.2 (m,2H), 5.5-6.2 (m,1H); ^{13}C NMR (C_6D_6) : 21.2, 22.7, 23.1, 27.5, 31.2, 33.3, 37.3, 38.7, 39.6, 41.8, 47.7, 115.0, 138.4, 208.8, 213.5. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found : C, 76.3; H, 10.0.

2-(3-oxo-oct-7-enyl)-4-t-butyl-cyclohexanone (5f):
^1H NMR : 0.9 (s,9H), 0.9-2.9 (m,18H), 4.9-5.4 (m,2H), 5.7-6.1 (m,1H); ^{13}C NMR (C_6D_6) : 23.1, 24.3, 27.7 (3C), 28.8, 32.3, 33.4, 35.6, 40.5, 41.7 (2C), 47.1, 48.8, 115.1, 138.4, 209.1, 211.1. Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.64; H, 10.86. Found : C, 77.8; H, 11.0.

trans-5,5-Ethylenedioxy-10-methyl-1-(3-oxo-oct-7-en-yl)-decalone (5h) :
IR cm^{-1} : 1645 (νC=C), 1715 (νCO); ^1H NMR (300 MHz): 1.18 (s,3H), 1.37-2.5 (m,22H), 3.87 (m,4H), 4.9-5.1 (m,2H), 5.6-5.85 (m,1H); ^{13}C NMR (67.8 MHz): 14.37, 19.73, 22.74, 22.90, 24.88, 29.95, 30.84, 33.22, 37.98, 39.63, 41.94, 42.46, 45.48, 49.12, 65.02, 65.23, 112.55, 115.21, 138.12, 211.01, 212.29.

Preparation of the enones 6a-e:

3.3 mL of a 3M solution of KOH in ethanol were added to 6 mmol of the diketone 5. The solution was stirred at room temperature until no more starting material appeared on TLC plates. Then 10 mL of an aqueous saturated solution of NaCl were added. The mixture was extracted with ether (7x20 mL). The organic layers were dried ($MgSO_4$) and evaporated. The enones were purified by flash chromatography (ether/ petroleum ether : 10/100).

8a-Methyl-2-oxo-2,3,4,4a,4b,5,6,7,8,8a,9,10-dodecahydrophenanthrene (6a)[18,19] :
mp :123°C; yield : 80%; IR cm^{-1} : 1615 (νC=C), 1660 (νCO); ^1H NMR : 0.95 (s,3H), 0.9-2.5 (m,18H), 5.80 (s,1H); ^{13}C NMR : 16.1, 21.3, 24.7, 26.8 (2C), 31.5, 33.8, 36.9, 38.4, 41.3, 41.5, 50.7, 124.8, 167.3, 199.7. Anal. Calcd for $C_{15}H_{22}O$: C, 82.57; H, 10.09. Found : C, 82.4; H, 10.2.

1-(3,3-Ethylenedioxy-butyl)-10-methyl-2-octalone (6b):
Yield : 85%; IR cm^{-1} : 1605 (νC=C), 1660 (νCO); ^1H NMR 1.2 (s,3H), 1.35 (s,3H), 1.1-2.7 (m,16H), 3.9 (s,4H); ^{13}C NMR (C_6D_6) : 20.4, 21.8, 22.4, 23.8, 27.4 (2C), 34.2, 36.1, 38.0, 39.3, 42.2, 64.7 (2C), 110.0, 133.4, 161.2, 196.8.

1-(3-Methyl-but-3-en-yl)-10-methyl-octal-2-one (6c)
Yield : 76%; IR cm^{-1} : 1610 (νC=C), 1670 (νCO); ^1H NMR : 1.25 (s,3H), 1.4-2.75 (m,16H), 1.8 (s,3H), 4.8 (s,2H); ^{13}C NMR : 21.1, 22.1 (2C), 22.9, 26.9, 27.1, 33.5, 35.8, 37.2, 37.3, 41.8, 109.6, 132.3, 145.1, 162.6, 197.8.
1-(But-3-enyl)-10-methyl-octal-2-one (6d):
Yield : 76%; IR cm^{-1} : 1610 (νC=C), 1670 (νCO); ^1H NMR : 1.25 (s,3H), 1.3-2.6 (m,16H), 4.7-5.2 (m,2H), 5.4-6.2 (m,1H); ^{13}C NMR (C_6D_6) : 21.7, 22.4, 24.7, 27.5 (2C), 34.2 (2C), 36.2, 38.0, 42.3, 114.6, 132.7, 138.7, 161.8, 196.9.
8,8-Ethylenedioxy-1-(but-3-en-yl)-8a-methyl-2-oxo-2,3,4,4a,4b,5,6,7,8,8a,9,10-dodecahydrophenanthrene (6e):
Yield : 80%; IR cm^{-1} : 1645 (νC=C), 1675 (νCO); ^1H NMR (300MHz) : 1.13 (s,3H), 1.4-2.5 (m,19H), 2.75 (d,1H), 3.9 (m,4H), 4.9-5.05 (m,2H), 5.7-5.9 (m,1H); ^{13}C NMR (67.8 MHz) : 14.1, 22.4, 23.4, 24.3, 25.9, 26.3, 29.7, 30.0, 33.3, 36.5, 38.4, 41.8, 47.0, 64.7 (2C), 112.3, 114.2, 132.7, 138.2, 159.5, 198.3.

Preparation of the ketones 10a-c,e :

To 15 mL of liquid ammonia cooled to -78°C, containing 38 mg of lithium, was added dropwise a solution of 1.1 mmol of enone 6 and 69 mg (0.8 eq.) of t-butanol in 4.7 mL of dry tetrahydrofuran. 30 min after completion of the addition the excess of lithium was destroyed with isoprene and ammonia was removed at room temperature. The solid enolate was then solubilized in 10 mL of tetrahydrofuran and the solution was cooled to -10°C. Then 5 mL of an aqueous saturated solution of sodium sulfate were added and the solution was warmed up to 20°C. After extraction with ether (7x20 mL), the organic layers were dried ($MgSO_4$) and evaporated. The crude ketones 10 were purified by flash chromatography (ether/petroleum ether : 10/100).
trans-1-(3,3-Ethylendioxy-butyl)-10-methyl-decal-2-one (10a):
Yield : 90%; IR cm^{-1} : 1710 (νCO); ^1H NMR : 1.25 (s,3H), 1.3 (s,3H), 1.1-2.5 (m,18H), 3.8 (s,4H).
trans-1-(3-Methyl-but-3-en-yl)-10-methyl-decal-2-one (10b):
Yield : 95%; IR cm^{-1} : 1650 (νC=C), 1720 (νCO); ^1H NMR : 1.05 (s,3H), 1.05-2.6 (m,18H), 1.65 (s,3H), 4.7 (s,2H); ^{13}C NMR (C_6D_6) : 16.2, 21.5, 22.6, 23.5, 25.9, 26.5, 33.9, 35.2, 38.6, 41.3, 41.9, 48.7, 50.0, 110.0, 146.2, 210.5.
trans-1-(But-3-en-yl)-10-methyl-decal-2-one (10c):
Yield : 95%; IR cm^{-1} : 1640 (νC=C), 1710 (νCO); ^1H NMR (300 MHz) : 1.1 (s,3H), 1.1-2.6 (m,18H), 4.8-5.2 (m,2H), 5.5-6.1 (m,1H); ^{13}C NMR (C_6D_6) : 16.2, 21.6, 24.7, 25.9, 26.4, 31.4, 33.9, 38.5, 41.3, 41.9, 48.6, 49.9, 114.3, 139.4, 209.5.
1-(But-1-ene-yl)-2-oxo-8a-methyl-8,8-ethylenedioxy tetradecahydrophenanthrene (10e):
Yield : 82%; IR cm^{-1} : 1710 (νCO); ^1H NMR : 1.01 (s,3H), 1.0-2.4 (m,22H), 3.8-4.0 (m,4H), 4.85-5.02 (m,2H), 5.7-5.9 (m,1H); ^{13}C NMR : 14.6, 22.4, 23.1, 24.0, 26.3, 29.5, 29.8, 30.8, 31.0, 34.8, 40.2, 41.5, 45.6, 47.6, 53.9, 64.8 (2C), 112.5, 114.1, 138.7, 212.1.

Preparation of the acetals 11c, 16c :

In a flask equiped with a Dean-Stark apparatus, a mixture of 2 mmol of ketone, 4 mmol of ethylene glycol, 50 mL of benzene and 200 mg of paratoluenesulfonic acid was refluxed until no more water was collected. Then the mixture was cooled to room temperature and treated with 5 mL of an aqueous saturated solution of sodium hydrogenocarbonate. After extraction with ether (5x10 mL), the organic layers were washed with water, dried ($MgSO_4$) and evaporated. The acetals were purified by flash chromatography.
2,2-Ethylenedioxy-1-(but-3-en-yl)-10-methyl-decalin (11c)
Yield : 95%; IR cm^{-1} : 1640 (νC=C); ^1H NMR : 0.85 (s,3H), 1.0-2.4 (m,18H), 3.9 (s,4H), 4.8-5.2 (m,2H), 5.45-6.1 (m,1H); ^{13}C NMR (C_6D_6) : 16.3, 21.9, 25.6, 25.7, 27.3, 31.0, 33.9, 34.3, 39.3, 41.9, 44.2, 47.3, 64.4, 64.6, 112.0, 114.0, 139.9.
1-(But-2-en-yl)-2,2,8,8-diethylenedioxy-8a-methyl-tetradecahydrophenanthrene (16c)
Yield : 75%; IR cm^{-1} :1640 (νC=C); ^1H NMR (300 MHz): 0.98 (s,3H), 1.0-2.4 (m,22H), 3.8-4.02 (m,8H), 4.85-5.05 (m,2H), 5.7-5.9 (m,1H); ^{13}C NMR (C_6D_6) : 14.7, 22.6, 23.0, 25.3, 25.8, 27.0, 29.8 (2C), 33.4, 34.3, 40.4, 42.2, 45.1, 45.6, 48.4, 64.2 (2C), 64.7, 64.9, 111.1, 112.8, 113.4, 139.6.

Preparation of the epoxides 12c and 17c :

To a stirred solution of 0.21 g (1.2 mmol) of m-chloroperbenzoic acid in 5 mL of dichloromethane was added dropwise a solution of 1 mmol of acetal in 2 mL of dichloromethane. After complete epoxidation of the starting material, a 10% aqueous solution of sodium hydrogenosulfate was added until obtention of a negative iodide test (no more coloration due to iodine). The organic layers were then washed two times with 10 mL of an aqueous saturated solution of sodium hydrogenocarbonate and then with water (2x10mL). The organic layers were dried ($MgSO_4$) and evaporated. The epoxides were purified by flash chromatography.

2,2-Ethylenedioxy-1-(3,4-epoxy-butyl)-10-methyl-decalin (12c)

Yield : 86%; ^1H NMR : 0.9 (s,3H), 1.0-1.9 (m,18H), 2.45 (dd,1H), 2.6-2.95 (m,2H), 3.95 (s,4H); ^{13}C NMR (C_6D_6) : 16.2, 21.8, 22.5, 25.4, 27.2, 31.0, 32.7, 33.9, 39.2, 41.9, 44.2, 46.3, 47.0, 52.3, 64.4, 64.6, 111.9.

1-(3,4-Epoxy-butyl)-2,2,8,8-diethylenedioxy-8a-methyl-tetradecahydrophenanthrene (17c)

Yield : 80%; ^1H NMR : 0.97 (s,3H), 1.0-1.82 (m,22H), 2.45 (m,1H), 2.72 (m,1H), 2.9 (m,1H), 3.8-4.0 (m,8H); ^{13}C NMR : 14.5, 21.8, 22.4, 22.8, 25.6, 26.7, 29.3, 29.6, 31.4, 34.1, 40.1, 42.0, 44.5, 45.4, 46.4, 48.1, 52.2, 64.0 (2C), 64.5, 64.7, 110.7, 112.5.

Preparation of the alcohols 13c and 18c:

To a suspension of 8 mg (0.36 mmol) of lithium borohydride in 5 mL of anhydrous ether cooled to 0-5°C was added dropwise a solution of 0.5 mmol of epoxyde in 1 mL of dry ether. Stirring was continued for 15 min at 0°C and 24 h at room temperature. The mixture was then cooled to 0-5°C and treated with 1 mL of an aqueous saturated solution of sodium sulfate. After being stirred for one hour at 20°C, the suspension was filtered. The organic layers were dried ($MgSO_4$) and evaporated. The alcohols were purified by flash chromatography.

2,2-Ethylenedioxy-1-(3-hydroxy butyl)-10-methyl-decalin (13c)

Yield : 83%; IR cm^{-1} : 3200-3600 (νOH); ^1H NMR (CCl_4) : 0.9 (s,3H), 1.05 (d,3H), 1.0-1.9 (m,18H), 2.2 (s,1H,OH), 3.4-3.8 (m,1H), 3.85 (s,4H); ^{13}C NMR (C_6D_6) : 16.4, 21.9, 23.7, 25.5, 27.4, 30.9, 33.9, 39.3 (2C), 41.9, 43.9, 44.8, 47.5, 64.5 (2C), 68.5, 112.2.

1-(3-Hydroxy butyl)-2,2,8,8-diethylenedioxy-8a-methyl-tetradecahydrophenanthrene (18c)

Yield : 73%; IR cm^{-1} : 3200-3600 (νOH); ^1H NMR : 0.95 (s,3H), 1.15 (d,3H), 0.9-2.1 (m,22H), 2.8-3.2 (m,1H, OH), 3.7 (m,1H), 3.8 (s,8H).

Preparation of the ketones 14c and 19c :

To a suspension of 0.153 g (0.71 mmol) of pyridinium chlorochromate in 4 mL of dichloromethane was added a solution of 0.35 mmol of alcohol in 2 mL of dichloromethane. Stirring was continued for 5 h at 20°C. The suspension was then filtered over a florisil column (60-100 mesh), the ketones being eluted with ether. The organic layers were evaporated and the ketones purified by flash chromatography.

2,2-Ethylenedioxy-1-(3oxobutyl)-10-methyl-decalin (14c)

Yield : 96%; IR cm^{-1} : 1715 (νCO); ^1H NMR : 0.9 (s,3H), 1.0-1.9 (m,16H), 2.15 (s,3H), 2.25-2.75 (m,2H), 4.05 (s,4H); ^{13}C NMR (C_6D_6) : 16.3, 19.9, 21.8, 25.3, 27.2, 29.5, 30.9, 33.8, 39.2, 41.9, 43.1, 43.6, 46.4, 64.4 (2C), 111.7, 207.0.

1-(3-Oxobutyl)-2,2,8,8-diethylenedioxy-8a-methyl-tetradecahydrophenanthrene (19c)

Yield : 78%; IR cm^{-1} : 1710 (νCO); ^1H NMR : 0.9 (s,3H), 0.85-2.6 (m,22H), 2.0 (s,3H), 3.85 (s,8H).

Preparation of the ketones 5g,5i and 20 :

1) From the ketals 10a, 14c, 5h and 19c :

To a stirred solution of 0.35 mmol of acetal in 2 mL of tetrahydrofuran were added 2 mL of a 3M solution of chlorhydric acid. Stirring was continued for 30 min at 20°C. The solution was then extracted with dichloromethane (4x10 mL). The organic layers were dried ($MgSO_4$) and evaporated. The diketones were purified by flash chromatography.

2) Preparation of diketone 5g from the ketone 10b

A solution of 1.92 g (1mmol) of ketone 10b in 10 mL of dry methanol was cooled to

-30°C. Two equivalents of ozone were bubbled through the solution during 30 min. Then oxygen and argon were bubbled during 20 min, after which the solution was cooled to -40°C. At this temperature 1g of zinc powder was added portionwise followed by 2 mL of 50% acetic acid. The mixture was then warmed to room temperature and stirred for one hour. Then the solution was poured into 2 mL of water and extracted with dichloromethane (5x 10 mL). The organic layers were washed with 5 mL of an aqueous saturated solution of sodium hydrogenocarbonate, dried ($MgSO_4$) and evaporated. The diketone was purified by flash chromatography (yield : 85%).

1-(3-Oxobutyl)-10-methyl-decalone (5g)

Yield : 98%; IR cm^{-1} : 1710 (νCO); ^1H NMR : 1.1 (s,3H), 1.1-2.7 (m,18H), 2.15 (s,3H); ^{13}C NMR : 16.1, 19.1, 21.0, 25.4, 25.9, 29.6, 33.6, 38.4, 40.6, 40.8, 41.7, 48.6, 49.5, 208.8, 212.4.

trans-5-Oxo-10-methyl-1-(3-oxo oct-7-enyl)-decalone (5i)[12]

Yield : 98%; IR cm^{-1} : 1640 (νC=C), 1705 (νCO); ^1H NMR (300 MHz) : 1.34 (s,3H), 1.5-2.7 (m,22H), 4.9-5.05 (m,2H), 5.67-5.8 (m,1H); ^{13}C NMR (67.8 MHz) : 16.56, 20.09, 22.98, 24.74, 25.82, 33.17, 33.29, 37.20, 37.81, 39.83, 42.15, 48.19, 48.88, 49.50, 115.40, 138.15, 211.08, 211.28, 214.22.

1-(3-Oxobutyl)-2,8-dioxo-tetradecahydrophenanthrene (20)

Yield : 90%; IR cm^{-1} : 1710 (νCO); ^1H NMR (300 MHz) : 1.17 (s,3H), 1.1-2.7 (m,22H), 2.12 (s,3H); ^{13}C (67.8 MHz) NMR : 17.04, 19.45, 23.46, 25.89, 26.42, 30.14, 31.52, 32.41, 37.28, 40.32, 41.02, 41.76, 48.06, 48.30, 50.26, 53.92, 209.22, 212.26, 215.88.

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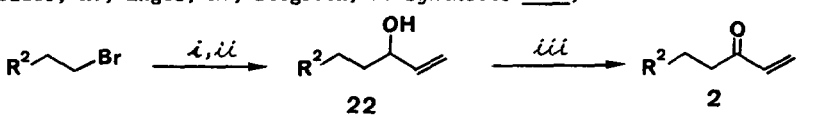

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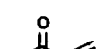
i) Mg, THF *ii*)  *iii*) PCC, CH_2Cl_2

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