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Aqueous Hetero Diels-Alder Reactions : The Carbonyl Case.

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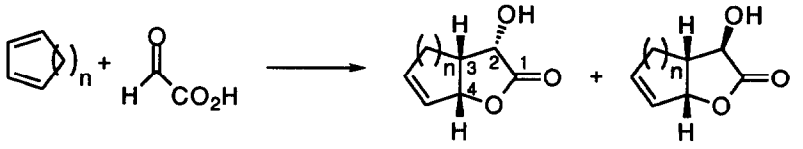
Abstract: Commercially available aqueous solution of glyoxylic acid, pyruvaldehyde and glyoxal were shown to react with cyclic or non-cyclic dienes to give the corresponding cycloadducts and/or α-hydroxy γ-lactones. Activated ketone (Pyruvic acid) was shown to react as well in the same conditions.

Introduction

Functionally substituted dihydropyran structures which are important intermediates in synthesis of natural products can be obtained through hetero Diels-Alder cycloadditions using carbonyl compounds as dienophiles. However, this reaction required Lewis acid catalysis, high pressure or high thermal conditions and preferably electron deficient aldehydes or ketones such as alkyl glyoxylates or mesoxalates.[1,2] We and others have shown that the homo Diels-Alder reactions are considerably accelerated in water[3] and we wonder if the same effect can still be used for the hetero Diels-Alder reactions. In fact, *Grieco et al*[4] have already shown that it is the case for imminium salts generated *in situ* which react smoothly in water with 1,3-dienes to give the corresponding adducts in good yields. Of course, we were aware that such a reaction in the case of carbonyl group have to compete with the very low concentration of reactive species : that is the carbonyl function in water which is for the most part in the hydrated form especially in the case of activated compounds with electron-withdrawing groups. However, if possible, these reactions will be especially useful for using directly cheap commercially available aqueous solutions of α-activated carbonyl compounds such as glyoxylic acid, pyruvaldehyde or glyoxal, the use of which avoiding for example, the tedious preparation of alkyl glyoxylates.

Results and discussion

In a preliminary note,[5] we recently shown that aqueous solution of glyoxylic acid, which curiously had never been used directly in cycloaddition, reacted with cyclopentadiene and cyclohexadiene to give good yields of α-hydroxy-γ-lactones (eq1) as a mixture of epimers at C-2.



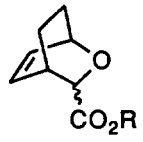
(eq 1)

n = 1 **1** **2**

n = 2 **3** **4**

The configurations at C-2 were elucidated using NOESY experiments. Correlations between H-2 and H-3, H-3 and H-4 and even H-2 and H-4 are visible in the phase sensitive NOESY spectrum for **1**, whereas for **2**, a correlation is only found between H-3 and H-4 and a very small one between H-2 and H-3 but no interaction at all could be detected between H-2 and H-4. The more acidic is the solution, the faster is the reaction. Thus, with cyclopentadiene at pH 0.9 (2.25 M glyoxylic acid in water) the reaction is complete after 90 mn at 40°C providing in 83% isolated yield, the α-hydroxy lactones **1** and **2** in a 73 : 27 ratio. We assumed that the reaction occurred through the Diels-Alder adduct which rearranged spontaneously to the lactones in the reaction conditions. This has not been proved in the case of the reaction with cyclopentadiene as it was impossible to prepare the postulated cycloadducts because cyclopentadiene only dimerizes when heated neat or in an organic solvent with an alkyl glyoxylate. At this stage, it is worth pointing out that the use of water as solvent, favors the heterocycloaddition compared to the dimerisation of cyclopentadiene.

On the other hand, in the case of cyclohexadiene, whereas the reaction in aqueous solution led only to the α-hydroxy γ-lactones **3** and **4** (85%, 60:40). The reaction in a sealed tube (120°C, 21hours) with butyl glyoxylate led to the cycloadducts **5** (57%, endo/exo, 9:1)[6] which after saponification and acidification gave the free acid **6** which were shown to rearrange spontaneously in water to α-hydroxy-γ-lactones **3** and **4** even at room temperature. Without solvent, the rearrangement required high temperature (150°C) to proceed[7].

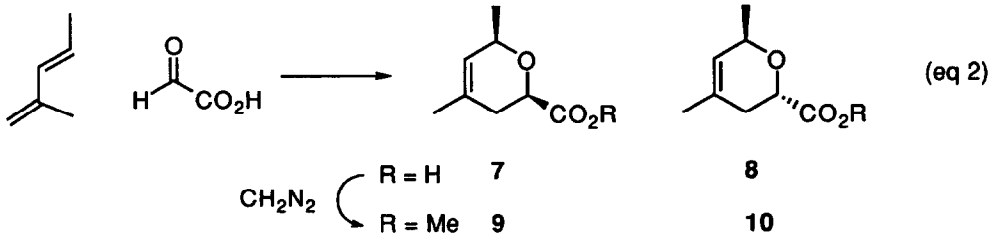


R = Bu **5**

R = H **6**

The aqueous cycloaddition is possible at higher pH *albeit* in lower yields. Thus cyclopentadiene (0.22 M) in glyoxylic acid solution (2.25M) brought to pH 2.5 by addition of sodium hydroxide gave the α-hydroxy γ-lactones (72%, **1** : **2**, 60:40) after 7.5 hrs at 60°C whereas at pH 6 the lactones are obtained in the same ratio but in only 16% yield after 24 hrs at 60°C.

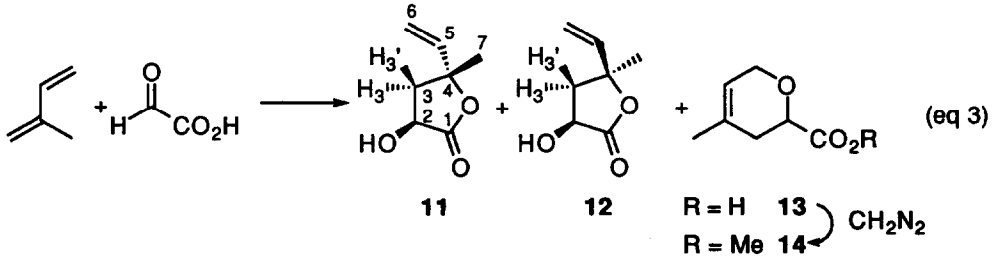
Then we wondered if the reaction was possible using less reactive non-cyclic dienes such as 2-methyl pentadiene or 2-methyl butadiene. In fact, despite the very low solubility of 2-methyl pentadiene in water and the almost complete hydration of the carbonyl function, as shown by the lack of aldehyde signal in ^{13}C NMR the reaction is quantitative after 1.5 hour at 100° C using the cheap commercially available glyoxylic acid solution (eq2).



The adducts **7** and **8** obtained in a 64:36 ratio (as shown by ^{1}H and ^{13}C NMR) were transformed (CH_2N_2, 99%) into the known[8] methyl ester **9** and **10** which were obtained in the same ratio. The 64:36 ratio reflects thermodynamic rather than kinetic conditions as each of the purified methyl ester when heated in the same acidic conditions gave the same free acid mixture with compound **7** as major stereoisomer, in which both the methyl and the carboxyl groups are in pseudo-equatorial position.

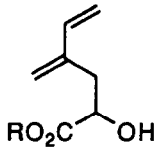
Then we looked for a possible catalysis by lanthanide trifluoromethanesulfonates known as water-tolerant Lewis acids. Actually, Kobayashi[9] have found a very efficient catalysis of the aqueous aldolisation of silyl enol ether onto aldehyde described by one of us in 1986[10] and we wondered if this carbonyl activation by ytterbium or neodynium triflates found in the aldolisation reaction could be used in these aqueous hetero Diels-Alder reactions. We were pleased to see that it is in fact the case, since the reaction (eq 2) is quantitative in 12 hours at 60°C in the presence of 0.1 eq of $Yb(OTf)_3$ or $Nd(OTf)_3$ whereas without catalyst the reaction gave only 55% yield in the same conditions. However, this catalysis which allows the reaction to proceed at lower temperature was unfortunatly not found effective at moderate pH (using sodium glyoxylate) as lanthanides salts immediatly precipitate in these reaction conditions.

The reaction of glyoxylic acid with the less reactive isoprene required more drastic conditions (100°C, 18 hours) and led to the new vinyl lactones **11** and **12** (33%,**11**/**12** = 60:40) along with the cycloadduct **13** (28%) (eq3).



The structures of lactones **11** and **12** were assigned using NOESY experiments which showed correlation signals between H-2 and H-3, and H3 with the methyl group in **12** whereas

this last correlation is lacking in compound **11**. Compound **13** was characterized after transformation to the known[8] methyl ester **14**. We first thought that, as with cyclohexadiene, these α-hydroxy-γ-lactones arose from a rearrangement of the cycloadduct **13**. In fact, in this case, purified compound **13** placed in the same reactions conditions did not give any lactone. Alternatively, the lactones could arise from the ene product **15**. This was verified by preparing the butyl ester **16** following a known procedure[11] from isoprene and butyl glyoxylate in CH_2Cl_2 in the presence of $SnCl_4$ as catalyst.

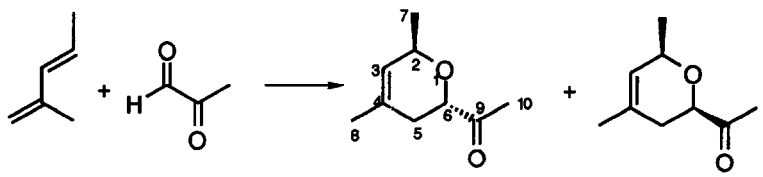


R = H **15**

R = Bu **16**

In fact, when an acidic solution of **16** (H_2SO_4, pH 1) was heated for 3 hours at 100°C, lactones **11** and **12** *and* the cycloadduct **13** as well, were found in the reaction mixture as judged by analytical reverse-phase HPLC of the mixture [Nucleosil N225 C_{18}, 1‰ HCOOH in H_2O-MeOH (65:35)]. Moreover we were able to show that each isolated lactone **11** and **12** rearranged partially in the reaction conditions into the cycloadduct **13**. So, we can not discriminate for the cycloadduct the part coming from the cycloaddition process or from the ene reaction through the formation of lactones and the subsequent rearrangement.

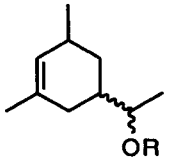
Then we turned to other heterodienophiles, commercially available as aqueous solution, such as pyruvaldehyde and glyoxal. Thus pyruvaldehyde (commercial solution, 6.15M) with 2-methyl pentadiene gave in 96% yield the cycloadducts **17** and **18** in a 47: 53 ratio after 48 hours at 100°C (eq4).



17 **18** (eq 4)

The corresponding structures were assigned using NOESY experiment showing a correlation between H-6 and H-7 for **17** and between H-7 and H-10 for **18**. Each of the cycloadduct, obtained pure in small quantity, after partial separation by preparative HPLC, gave a mixture, when heated in the same conditions, indicating that the reaction was under thermodynamic control. The mixture of ketone **17** and **18** (47:53) was reduced in 93% yield by $NaBH_4$ to a mixture of unseparable four stereoisomers **19** in which one can recognize (by ^1H and ^{13}C NMR analysis) two epimeric alcohols coming from the *cis* ketone **18** (32% and 21%) and two epimeric alcohols coming from the *trans* ketone **17** (27% and 20%) by comparison with

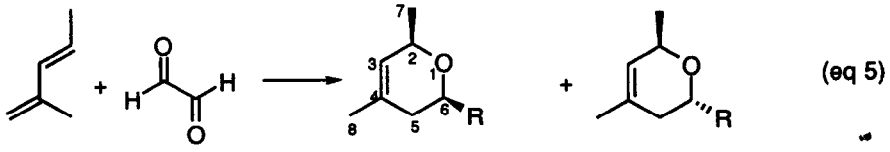
the alcohols obtained from reduction of the hardly separated, but pure, ketones **17** and **18**. The mixture was then acetylated (Ac_2O-pyridine) in 93% isolated yield to give **20** as a mixture of four stereoisomers which were found by ^1H and ^{13}C NMR in the same ratio [(cis : 53% (32:21) and *trans* : 47% (27:20)].



R = H **19** (as a mixture of four stereoisomers)

R = Ac **20** Id

Aqueous solution of glyoxal, also, were shown to react with 2-methyl pentadiene (eq 5) to give after 60 hours at 100°C the cycloadducts **25** and **26** in a 1:1 ratio, isolated after $NaBH_4$ reduction and acetylation in 36% overall yield. This result is particularly striking in view of the negligible concentration of non-hydrated glyoxal molecule in water as the cycloaddition required certainly **both** of the carbonyl groups present, one for cycloaddition and one for the activation. Compounds **25** and **26** were compared and found similar to those obtained by $LiAlH_4$ reduction of the methyl esters **9** and **10** followed by acetylation.

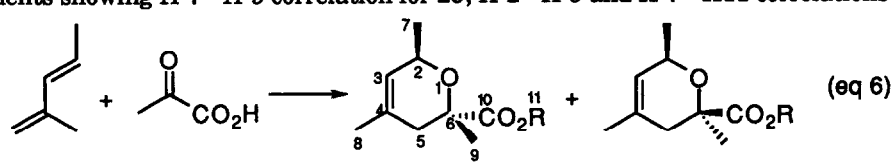


R = CHO **21** **22** $NaBH_4$

R = CH_2OH **23** **24** Ac_2O, pyr.

R = CH_2OAc **25** **26**

This aqueous hetero Diels-Alder reaction is also possible with activated ketones. Thus aqueous solution of pyruvic acid reacted with 2-methyl pentadiene (eq 6) to give after 48 hours at 100°C the corresponding cycloadducts **27** and **28** in 74% yield in a 2:1 ratio. The structures were assigned after transformation to the methyl esters **29** and **30** (MeOH, H^+) and NOESY experiments showing H-7 - H-9 correlation for **29**, H-2 - H-9 and H-7 - H11 correlations for **30**.



R = H **27** **28** MeOH, H^+

R = Me **29** **30**

Although pyruvic acid is commercially available in pure form, this reaction is of interest as the corresponding reaction conducted neat or in toluene solution gave about the same yield of cycloadducts **27** and **28** but with a reverse selectivity (1:2). This reversal of selectivity was shown to be the result of thermodynamic control in water and kinetic control in toluene as each of the purified cycloadduct gave a mixture when heated at 100°C in water whereas they stay unchanged when heated in toluene solution.

Conclusion

In conclusion , we have shown that despite the low concentration in water of the non-hydrated carbonyl group in activated aldehydes or ketones, the aqueous hetero Diels-Alder reaction is possible and that the reaction gave in good to excellent yields valuable compounds such as substituted dihydropyrans and α-hydroxy-γ-lactones[12]. Moreover, the use of the cheap commercially available, aqueous solution of glyoxylic acid, avoiding the tedious preparation of alkyl glyoxylate should find large applications in organic synthesis.

Experimental.

General procedures.

Flash chromatography were performed on silica gel 60A C.C. (6-35μ) from SDS company. Preparative HPLC were performed using the Jobin-Yvon apparatus, with a 4 x 20 cm column packed with the same silica gel. The elution solvents are indicated in brakets and are given v/v. Melting points (uncorrected) were measured on a oil-bath Büchi apparatus. IR spectra were recorded using FTIR Bruker IFS66 with OPUS IR version 1.4.4A. NMR spectra were recorded at 250 MHz for ^{1}H and 62.5 MHz for ^{13}C on a Bruker AC 250 and respectively at 200 MHz and 50 MHz on a bruker AC 200 spectrometer using TMS as internal standard. Stereochemical assignments were based on homonuclear dipolar-correlated 2D NMR in phase-sensitive NOESY experiments which were carried out with data matrices of (1k x 1k) points to digitalize spectral widths of 1460 Hz. 16 scans were used per increment with a relaxation time of 1s ; the 90° pulse width was 7.5 μs and the mixing time 2.4s.

Reaction of glyoxylic acid with cyclopentadiene. Preparation of 1 and 2.

Cyclopentadiene (freshly prepared from the dimer, 122 mg, 2 mmol) was added to an aqueous solution of 2.25M glyoxylic acid (8.8 mL, 10 equiv) in a screw-capped tube. The mixture was then heated at 40°C for 1.5 hr under vigorous stirring. After extraction with ether, the lactones were purified by flash-chromatography (hexane-ether, 2:8)

1 : 170 mg (61%) ; mp 63 - 64°C (ether-hexane, 1:1) ; IR (nujol) ν 1745 ; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.46 (dddd, 1H, J = 2.2, 9.5, 18 Hz, CH_2), 2.77 (dddd, 1H, J = 2.2, 6, 18 Hz, CH_2), 3.23 (tt, 1H, J = 6.0, 6.5, 9.5 Hz, H-3), 4.75 (d, 1H, J = 9.5 Hz, H-2), 5.35 (td, 1H, J = 2.2, 5.5 Hz, H-4), 5.94 (qd, 1H, J = 2.2, 5.5 Hz, CH=), 6.27 (td, 1H, J = 2.2, 5.5 Hz, CH=) ; ^{13}C NMR ($CDCl_3$,

62.9 MHz) δ 30.8, 40.5, 69.2, 86.6, 127.5, 141.2, 177.6. Anal. Calcd for $C_7H_8O_3$: C : 60.00, H : 5.75, O : 34.25 ; found : C : 60.22, H : 5.74, O : 34.13.

2 : 63 mg (23%), colorless oil ; IR (neat) ν 1780 ; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.58 (qd, 1H, J = 2.0, 4.5, 17.5 Hz, CH_2), 2. 77 (qd, 1H, J = 2.0, 7.5, 17.5 Hz, CH_2), 3.06 (dq, 1H, J = 2.0, 7.5 Hz, H-3), 4.17 (d, 1H, J = 7.5 Hz, H-2), 5.55 (qd, 1H, J = 2.0, 7.5 Hz, H-4), 5.91 (qd, 1H, J = 2.0, 5.5 Hz, CH=), 6.10 (tt, 1H, J = 2.0, 4.5, 5.5 Hz, CH=) ; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 36.6, 44.1, 74.4, 87.5, 129.3, 139.7, 178.1. Anal. Calcd for $C_7H_8O_3$: C : 60.00, H : 5.75, O : 34.25 ; found : C : 59.82, H : 5.78, O : 34.24.

Reaction of glyoxylic acid with cyclohexadiene. Preparation of 3 and 4.

Cyclohexadiene (160 mg, 2 mmol) was added to an aqueous solution of 2.25M glyoxylic acid (8.8 mL, 10 equiv) in a screw-capped tube. The mixture was then heated at 90°C for 2 days under vigorous stirring. After extraction with ether, the lactones were purified by flash-chromatography (hexane-ether, 2:8) :

3 : 157 mg (51%) ; mp 91-92°C (ether-hexane, 1:1) [lit[7] mp 88-90°C] ; IR (nujol) ν 1750 ; ^{1}H NMR (C_6D_6, 200 MHz) δ 0.8-1.8 (m, 4H, 2 CH_2), 2.01 (tdd, 1H, J = 4.5, 13.5 Hz, H-3), 3.97 (t, 1H, J = 3.5, 4.5 Hz, H-4), 4.15 (d, 1H, J = 7.5 Hz, H-2), 5.60 (dddd, 1H, J = 1.5, 2.45, 3.5, 10 Hz, CH=), 5.77 (tdd, 1H, J = 1, 5.5, 10 Hz, CH=). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.5, 23.2, 39.1, 71.2, 71.5, 122.14, 135.9. Anal. Calcd for $C_8H_{10}O_3$: C : 62.32, H : 6.54, O : 31.14 ; found : C : 62.30, H : 6.53, O : 30.85.

4 : 105 mg (34%) ; mp 98-101°C (ether-hexane, 1:1) [lit[7] mp 97-99°C] ; IR (nujol) ν 1747 ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.7-2.1 (m, 2H, CH_2), 2.1-2.3 (m, 2H, CH_2), 2.71 (tdd, 1H, J = 4.0, 7.5, 10 Hz, H-3), 3.25 (d, 1H, J = 3.5 Hz, OH), 4.31 (dd, 1H, J = 3.5, 10 Hz, H-2), 5.10 (dt, 1H, J = 1.5, 2.5, 10 Hz, H-4), 5.77 (dq, 1H, J = 2.5, 10 Hz, CH=), 6.10 (dt, 1H, J = 1.5, 3.5, 10 Hz, CH=). ^{13} C NMR ($CDCl_3$, 50 MHz) δ 20.1, 40.6, 68.4, 74.2, 124.3, 132.7. Anal. Calcd for $C_8H_{10}O_3$: C : 62.32, H : 6.54, O : 31.14 ; found : C : 62.22, H : 6.56, O : 31.06.

Reaction of glyoxylic acid with 2-methyl pentadiene. Preparation of 7 and 8 and their methyl esters 9 and 10.

2-methyl pentadiene (as a 3 : 7 cis-trans mixture, 4.9 mL, 30 mmol) was added to the commercially available 9 M aqueous glyoxylic acid solution (1.11 mL, 10 mmol) in a screw-capped tube. The mixture was then heated at 100°C under vigorous stirring for 1.5 h. After decantation, the aqueous phase is saturated with sodium chloride and extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography (hexane-ethyl acetate, 5:1 to 0:1) of the residue afforded 1,522 g (97%) of a mixture of compounds **7** and **8** in a 64:36 ratio. Anal. Calcd for $C_8H_{12}O_3$: C : 61.52, H : 7.74, O : 30.73 ; found : C : 60.69, H : 7.79, O : 31.51. ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ **7** : 21.1, 22.4, 31.9, 71.5, 72.2, 124.7, 130.7, 175.6. **8** : 20.3, 22.7, 31.1, 67.9, 68.8, 124.1, 129.6, 176.7.

A large excess of a freshly prepared solution of CH_2N_2 in ether was added to a solution of the above mixture of **7** and **8** (64:36) (1.0 g, 6.4 mmol) in ether (5 mL). Flash chromatography (hexane-ethyl acetate, 4:1) of the residue obtained after evaporation afforded 1.083 g (99%) of the partially separated known[8] methyl esters **9** and **10** in the same ratio than **7** and **8** (64:36). All spectroscopic data (^{13}C and ^1H NMR) are identical with those reported.[8]

Reaction of glyoxylic acid with 2-methyl butadiene. Préparation of 11, 12, 13 and its corresponding methyl ester 14.

2-Methyl butadiene (16.2 mL, 100 mmol) was added to an 5.4 M aqueous solution of glyoxylic acid (3 mL, 16.2 mmol) in a screw-capped tube. The mixture was then heated at 100°C under vigorous stirring for 18hrs. After extraction with CH_2Cl_2, the dried (Na_2SO_4) combined extracts were evaporated and the residue diluted with methanol. Large excess of freshly prepared diazomethane solution in ether was then added until the yellow color persisted. Flash chromatography (hexane-ethyl acetate, 2:1 to 2:3) of the residue obtained after evaporation afforded first, the known[8] methyl ester **14** (0.708 g, 28%) with all spectroscopic data (^{13}C and ^1H NMR) identical with those reported followed by the lactones **11** and **12** (0.758 g, 33%, **11/12**, 60:40). Preparative HPLC (hexane-ethyl acetate, 10:1) of the above mixture of lactones allowed us to obtained pure *ca* 50 mg of each of them as colorless oil.

11 : IR (neat) ν 1779 ; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.55 (s, 3H, CH_3), 2.11 (dd, 1H, J = 10.8, 12.6 Hz, H-3'), 2.67 (dd, 1H, J = 8.3, 12.6 Hz, H-3), 4.55 (dd, 1H, J = 8.2, 10.9 Hz, H-2), 5.15 (d, 1H, J = 11 Hz, H-6), 5.27 (d, 1H, J = 17.1 Hz, H-6'), 5.93 (dd, 1H, J = 10.9, 17.3 Hz, H-5). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.3, 41.6, 68.1, 82.8, 113.9, 139.3, 177.7. Anal. Calcd for $C_7H_{10}O_3$: C : 59.14, H : 7.09, O : 33.76 ; found : C : 59.35, H : 7.30, O : 33.56.

12 : IR (neat) ν 1779 ; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 3H, CH_3), 2.21 (dd, 1H, J = 10.0, 12.8 Hz, H-3'), 2.56 (dd, 1H, J = 8.6, 12.8 Hz, H-3), 4.70 (dd, 1H, J = 8.6, 9.9 Hz, H-2), 5.20 (d, 1H, J = 11.0 Hz, H-6), 5.33 (d, 1H, J = 17.4 Hz, H-6'), 6.02 (dd, 1H, J = 10.9, 17.4 Hz, H-5). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.4, 41.7, 68.2, 82.9, 114.4, 140.3, 177.4. Anal. Calcd for $C_7H_{10}O_3$: C : 59.14, H : 7.09, O : 33.76 ; found : C : 58.40, H : 7.19, O : 34.59.

Reaction of pyruvaldehyde with 2-methyl pentadiene. Preparation of 17, 18, 19 and 20.

2-methyl pentadiene (as a 3 : 7 cis-trans mixture, 32.5 mL, 200 mmol) was added to a 6.15 M aqueous solution of pyruvaldehyde (6.5 mL, 40 mmol) in a screw-capped flask. After heating at 100°C under vigorous stirring for 48 hrs, the mixture was extracted with CH_2Cl_2. The dried (Na_2SO_4) combined extracts were evaporated. Flash chromatography (hexane-ethyl acetate, 10:1) of the residue afforded 5.910 g (96%) of a mixture of **17** and **18** in a 47:53 ratio. Preparative HPLC (hexane-ethyl acetate, 10:1) of 1 g of the above mixture allowed us to obtained pure *ca* 50 mg of each of them as colorless oil, for which, however, we were enable to obtain good centesimal analysis.

17 : IR (neat) ν 2970.9, 2929, 1720.9, 1445.7, 1355.9, 1171.5, 1144.8, 1085.4,1047.1, 915.8, 841.8, 733.8. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (d, 3H, J = 6.7 Hz, 3 H-7), 1.72 (s, 3H, 3 H-8), 2.08-2.15 (m, 2H, 2 H-5), 2.24 (s, 3H, 3H-10), 4.17 (dd, 1H, J = 5.4, 7.85 Hz, H-6), 4.37-4.49 (m, 1H, H-2), 5.38 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.0, 22.9, 25.8, 30.4, 69.1, 73.9, 124.3, 130.2, 209.2.

18 : IR (neat) ν 2975.8, 2931.5, 1720.9, 1427.3, 1353.3, 1171.4, 1151.2, 1122.8, 1051.0, 857.6. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (d, 3H, J = 6.6 Hz, 3 H-7), 1.72 (s, 3H, 3 H-8), 2.02-2.10 (m, 2H, 2 H-5), 2.26 (s, 3H, 3 H-10), 4.02 (dd, 1H, J = 6.4, 8.7 Hz, H-6), 4.18-4.33 (m, 1H, H-2), 5.36 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.3, 22.6, 25.6, 31.3, 71.2, 79.3, 125.1, 130.8, 209.1.

Sodium borohydride (62 mg, 1.63 mmol) was added portionwise to a solution of a mixture as obtained in the above reaction (47:53) of **17** and **18** (0.457 g, 2.96 mmol) in ethanol - water (2 mL, 1.5:1). After stirring for 2 hrs at room temperature, the reaction mixture is made acidic by careful addition of aqueous HCl followed by extraction with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography (hexane-ethyl acetate, 10:1) of the residue afforded **19** (0.430 g, 93%) as a mixture of four stereoisomers. Then, pyridine (1 mL) and acetic anhydride (1 mL) were added successively . After 8 hrs at room temperature, the mixture was diluted with CH_2Cl_2, washed with water and coevaporated with toluene. Flash chromatography (hexane -ethyl acetate, 14:1) of the residue afforded **20** (0.510g, 93%) as a mixture of four stereoisomers in similar ratio than for **19** as shown by ^{13}C NMR. The same reaction conducted with purified **17** and **18** allowed us to confirm the assignment of the signals in ^{13}C NMR spectrum : the reduction of the cis adduct **18** gave after acetylation a 60:40 mixture (**20a,b**), whereas the reduction and acetylation of the trans adduct **17** gave a 57:43 mixture (**20c,d**).

20 : colorless oil. Anal. Calcd for $C_{11}H_{18}O_3$: C : 66.62, H : 9.16, O : 24.22 ; found : C : 65.82, H : 9.23, O : 24.01. ^{13}C NMR ($CDCl_3$, 50 MHz) δ **20a** : 15.6, 21.3, 21.4, 22.8, 31.1, 71.3, 71.7, 75.5, 125.3, 131,2, 170,8. **20b** : 15.6, 21.3, 21.5, 22.9, 31.4, 71.2, 72.5, 75.8, 125.2, 131.2, 170.5. **20c** : 16.1, 19.7, 21.3, 23.1, 31.2, 69.2, 69.3, 71.4, 124.5, 130.6, 170.8. **20d** : 15.8, 19.9, 21.3, 23.1,30.9, 69.1, 69.4, 72.0, 124.5, 130.6, 170.5.

Reaction of glyoxal with 2-methyl pentadiene. Preparation of 21 - 26.

2-methyl pentadiene (as a 3 : 7 cis-trans mixture, 32.5 mL, 200 mmol) was added to a 40% aqueous solution of glyoxal (5,8 g, 40 mmol) in a screw-capped flask. After heating at 100°C under vigorous stirring for 60 hrs, the reaction mixture was diluted with water (25 mL) and ethanol (30 mL). A solution of sodium borohydride (0.76 g, 20 mmol) in water (10 mL) was then added and the reaction mixture left overnight at room temperature. After careful addition of aqueous HCl, the reaction mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated. Flash chromatography (hexane - ethyl acetate, 5:1) of the residue afforded compounds **23** and **24** (2.065 g, 36%) in a 1:1 ratio. Then, acetic anhydride (4 mL) and pyridine (4 mL) were added, and the mixture left at room temperature for 2 hrs. The

mixture was then diluted with CH_2Cl_2, washed with water and coevaporated with toluene. Flash chromatography (hexane -ethyl acetate, 14:1) of the residue afforded compounds **25** and **26** (2.67 g, 100% from **23** and **24**, 36% overall) in a 1:1 ratio. ^1H and ^{13}C NMR spectra were identified by comparison with compounds obtained from $LiAlH_4$ reduction of the known methyl ester **9** and **10**. $LiAlH_4$ (0.38 g, 10 mmol) was added portionwise to a solution of the methyl ester **9** and **10** (64:36, 3.10g, 18.2 mmol) in THF (15 mL). The mixture was then heated under reflux for 2 hrs and treated after cooling successively with water (0.38 mL), 15% aqueous NaOH (0.38 mL) and water (3 x 0.38 mL). After filtration, and evaporation of the filtrate, flash chromatography (hexane-ethyl acetate, 5:1) of the residue afforded **23** and **24** (2.194 g, 85%) in a 64:36 ratio. Acetylation as above gave compounds **25** and **26** (2.84 g, 100%) in a 64:36 ratio).

25 : ^1H NMR ($CDCl_3$, 200 MHz) δ 1.22 (d, 3H, J = 6.8 Hz, CH_3), 1.7-1.8 (m, 4H, CH_3, H-5), 1.9-2.00 (m, 1H, H-5'), 2.10 (s, 3H, $COCH_3$), 3.72-3.87 (m, 1H, H-6), 4.00-4.12 (dd, 1H, J = 6.6, 11.7 Hz, CH_2OAc), 4.12-4.30 (m, 2H, H-2, CH_2OAc), 5.32 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.9, 21.4, 22.7, 31.6, 66.8, 70.9, 71.9, 125.2, 130.8, 171.0.

26 : ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23 (d, 3H, J = 6.7 Hz, CH_3), 1.70 (s, 3H, CH_3), 1.77-1.89 (dd, 1H, J = 4.3, 16.7 Hz, H-5), 1.89-2.03 (m, 1H, H-5'), 2.10 (s, 3H, $COCH_3$), 3.98 (m, 1H, H-6), 4.14 (d, 2H, J = 5.3 Hz, CH_2OAc), 4.32-4.43 (m, 1H, H-2), 5.40 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.1, 20.9, 23.1, 31.3, 65.8, 66.3, 68.8, 124.5, 130.2, 171,0.

25 + 26 : colorless oil. Anal. Calcd for $C_{10}H_{16}O_3$: C : 65.19, H : 8.75, O : 26.05 ; found : C : 64.31, H : 8.90, O : 26.57.

Reaction of pyruvic acid with 2-methyl pentadiene. Preparation of 27 - 30.

In water : 2-methyl pentadiene (as a 3 : 7 cis-trans mixture, 16.2 mL, 100 mmol) was added to a solution of pyruvic acid (1.761 g, 20 mmol) in water (4 mL) in a screw-capped tube. After heating at 100°C for 48 hrs under vigorous stirring, the reaction mixture was cooled and extracted with ether. The combined extracts were dried (Na_2SO_4) and evaporated. Flash chromatography (dichloromethane - ethyl acetate, 5:1) of the residue afforded **28** (0.85 g, 25%) followed by **27** (1.70 g, 50%) .

without solvent : Pyruvic acid (1.761 g, 20 mmol) was added to 2-methyl pentadiene (as a 3 : 7 cis-trans mixture, 16.2 mL, 100 mmol) in a screw-capped tube and the stirred mixture was heated at 100°C for 48 hrs. Flash chromatography (dichloromethane - ethyl acetate, 5:1) of the residue obtained after evaporation afforded in the order of elution **28** (1.90 g, 56%) followed by **27** (0.95 g, 28%).

27 : colorless oil. IR (neat) ν 1710.6. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (d, 3H, J = 6.7 Hz, CH_3), 1.51 (s, 3H, CH_3), 1.70 (m, 3H, CH_3), 2.08 (m, 1H, H-5), 2.50 (dd, 1H, J = 2.3, 16.8 Hz, H-5'), 4.40-4.58 (m, 1H, H-2), 5.29 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.9, 22.9, 26.8, 37.1, 68.4, 76.0, 123.9, 130.0, 179.6. Anal. Calcd for $C_9H_{14}O_3$: C : 63.51, H : 8.29, O : 28.20 ; found : C : 63.35, H : 8.27, O : 27.97.

28 : colorless oil. IR (neat) ν 1744.3. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (d, 3H, J = 6.4 Hz, CH_3), 1.48 (s, 3H, CH_3), 1.74 (m, 3H, CH_3), 2.03 (dd, 1H, J = 2.4, 17.1 Hz, H-5), 2.34 (m, 1H, H-5'), 4.30-4.40 (m, 1H, H-2), 5.33 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.2, 21.3, 23.0, 36.3, 67.1, 74.9, 122.9, 129.6, 175.4. Anal. Calcd for $C_9H_{14}O_3$: C : 63.51, H : 8.29, O : 28.20 ; found : C : 64.05, H : 8.60, O : 27.35.

Paratoluenesulfonic acid (10 mg) was added to a solution of compounds **27** and **28** (2:1, 1.177g, 6.9 mmol) in methanol (10 mL). After heating at 60°C for 20 hrs, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated. Flash chromatography (hexane - ethyl acetate, 10:1) of the residue afforded **29** (0.75 g, 59%) followed by **30** (0.38 g, 30%).

29 : colorless oil. IR (neat) ν 1741.5. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (d, 3H, J = 6.7 Hz, CH_3), 1.46 (s, 3H, CH_3), 1.69 (m, 3H, CH_3), 1.98-2.12 (m, 1H, H-5), 2.43-2.56 (dd, 1H, J = 2.4, 16.6 Hz, H-5), 3.72 (s, 3H, CH_3), 4.31-4.46 (m, 1H, H-2), 5.25 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.7, 22.7, 26.6, 37.3, 51.9, 68.0, 76.1, 123.7, 129.9, 174.6. Anal. Calcd for $C_{10}H_{16}O_3$: C : 65.19, H : 8.75, O : 26.05 ; found : C : 64.99, H : 8.69, O : 26.24.

30 : colorless oil. IR (neat) ν 1736.7. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (d, 3H, J = 6.6 Hz, CH_3), 1.47 (s, 3H, CH_3), 1.72 (m, 3H, CH_3), 1.86-1.98 (dd, 1H, J = 2.4, 16.8 Hz, H-5), 2.35-2.50 (m, 1H, H-5'), 3.77 (s, 3H, CH_3), 4.21-4.38 (m, 1H, H-2), 5.34 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.9, 21.2, 22.9, 36.6, 52.2, 66.3, 74.9, 123.4, 129.2, 174.8. Anal. Calcd for $C_{10}H_{16}O_3$: C : 65.19, H : 8.75, O : 26.05 ; found : C : 64.98, H : 8.65, O : 25.89.

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