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Synthetic Approaches to Pentacyclic Triterpenes of the Arborane Family

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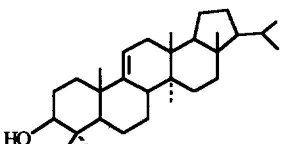
Abstract *Synthesis, from 2-methylcyclohexane-1,3-dione and 2-methylcyclopentane-1,3-dione, of optically pure bicyclic intermediates representing the A/B and D/E fragments required for an approach to isoarborinol*

Introduction:

Isoarborinol **1**[1] is a pentacyclic triterpene presenting several interesting characteristics Its structure makes it a "hybrid" of the very important hopanoids[2] such as diplopterol **2** and of the triterpenes of the lanostane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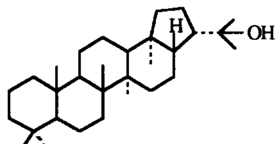
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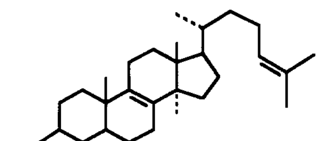
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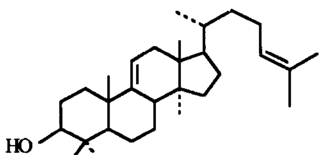
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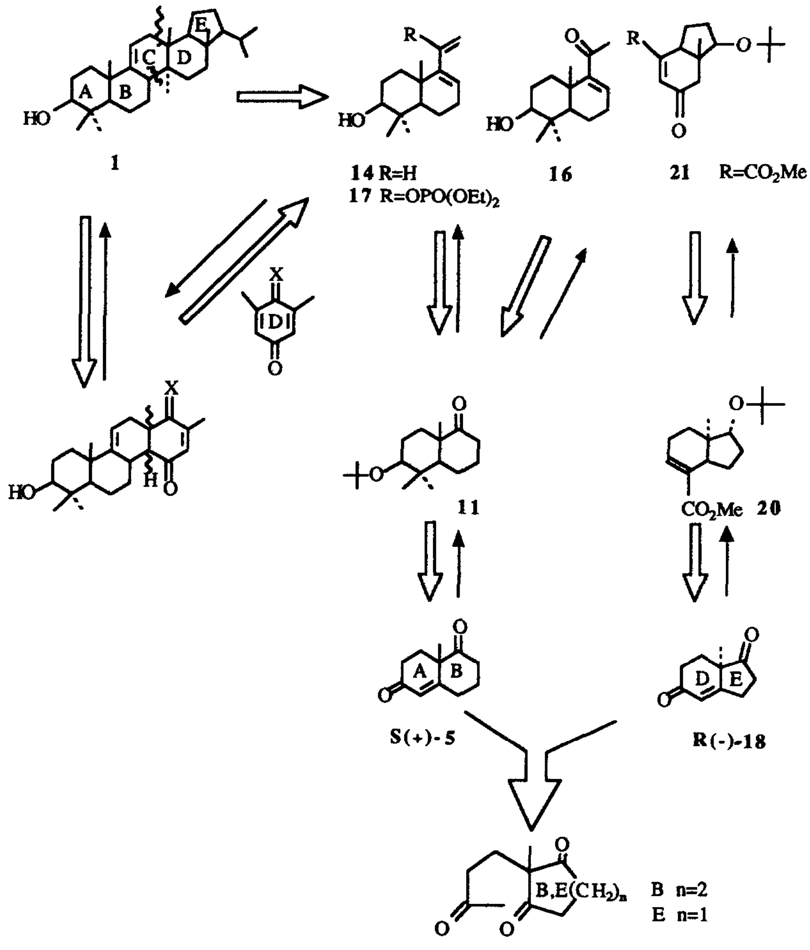
family such as lanosterol **3** or parkeol **4** Furthermore, it is so far the only 3-hydroxy triterpene to have been found intact in several sediments[3], which has led us to postulate[3b] that it may have originated there from some aerobic bacteria, not yet identified but possibly related to *Methylococcus caspsulatus*, a lanosterol-containing organism[4] Assuredly, one cannot exclude as an alternate source some *Gramineae* many of these contain isoarborinol, but it is usually accompanied by several of its epimers and isomers, and by their methyl ethers[5] We have nevertheless remarked that isoarborinol, should it really be a bacterial product, could well be another example of the many polyterpenic cholesterol surrogates involved in membrane stabilization, and that the microorganisms containing it, if existing, would be a welcome link between the hopane-containing bacteria and the Eucaryotes containing lanosterol, or cycloartenol, or sterols[6] We have therefore planned to check the effect of isoarborinol and of some of its isomers and epimers on the physicochemical properties of phospholipid bilayers[7] Experiments are in progress with isoarborinol itself[7] but extraction can give only a limited variety of these substances, and we have also initiated total syntheses

We wish to present at this stage the general scheme followed (Scheme 1), and to describe our first results with the synthesis of the intermediates required, in pure enantiomeric form, as precursors of the A/B rings (**14, 16, 17**) and of the D/E rings (**21**)

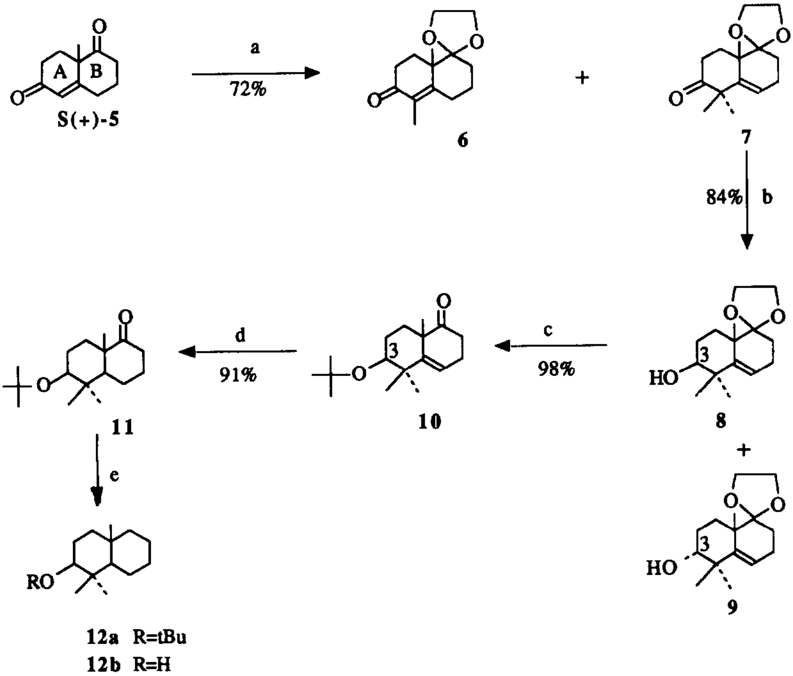


Scheme 1

The structure of isoarborinol immediately suggests a possible disconnection of ring C, and a retrosynthetic pathway making use as the key-step of a Diels-Alder, a tandem Michael or an analogous reaction to form the C-ring Two convergent synthetic schemes have been considered the A/B + D/E -> A/B/C/D/E, and the A/B + D -> A/B/C/D , A/B/C/D -> A/B/C/D/E approaches (Scheme 1). In the first one, ring C is formed by reaction between a partner AB derived from 2-methylcyclohexane-1,3-dione and one, D/E, derived from the lower homologue 2-methyl-cyclopentane-1,3-dione, both reacting with methyl-vinyl-ketone in an asymmetric Robinson annelation, catalyzed with (S)-proline for A/B[8], with (R)-proline for D/E[9] Transfer of chirality from (R)-proline to the (R)-enedione **18** and from (S)-proline to the (S)-enedione **5** would provide all the nine asymmetric centers in the desired configuration.

Results and Discussion:

Selective ketalization of the saturated carbonyl group of the Wieland-Mischer ketone S-(+)-5[10] with ethylene glycol, followed by kinetic methylation with potassium t-butoxide and methyl iodide[11] afforded ketones **6** (16%) (recycled into the synthetic scheme using Stork's reductive methylation[12]) and **7** (64%), along with 5%



a 1)-Ethylene glycol, toluene, reflux, 5h 95%, 2)- tBuOK, MeI, 10 min, RT 75% **b** $NaBH_4$, EtOH

c 1)- i-butene, BF_3 Et_2O, -78°C to RT, 98%, 2) 5% HCl -THF, 100 % **d** 1)- H_2, 1 atm , 10% Pd/C, AcOH, 2)- PDC-CH_2Cl_2

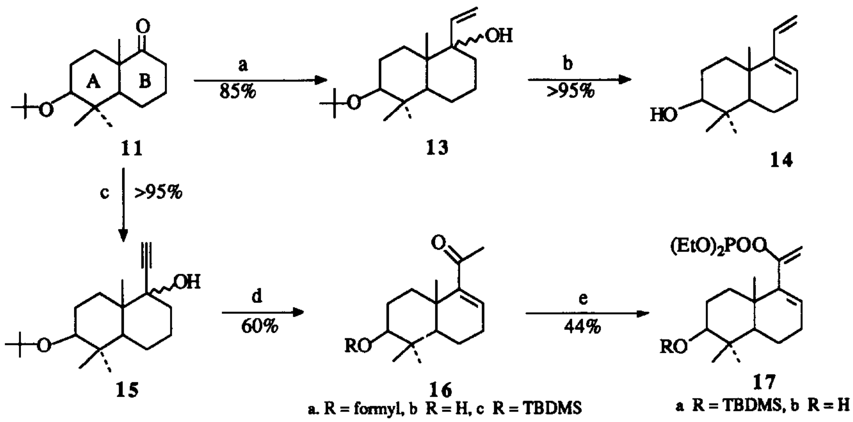
e - 1)- W K , 2)- BF_3 Et_2O, toluene, RT, or 1)- $NaBH_4$, 2)- MsCl, Py, 3)- Li/NH_3, 4)- BF_3 Et_2O, toluene or CH_2Cl_2

Scheme 2

of the corresponding 2,2,4,4-tetramethylated homologue (Scheme 2) Reduction of **7** with sodium borohydride in ethanol at room temperature afforded **8** and **9** in a 13 1 ratio and 84% yield Catalytic hydrogenation of **8** was difficult to achieve (Pd/C, PtO_2, various solvents) Attempts to reduce the 5(6) double bond in the presence of the ketal protecting group failed, the main product, the 3,9-diol, resulting unexpectedly from ketal cleavage[13] Indeed, we have observed that a rapid cleavage of the ketal **7** was achieved by simply stirring it in the presence of a small amount of Pd/C in ethyl acetate Protection of the 3β-OH group was achieved instead as its t-butyl ether **10** , this octalone was then hydrogenated in the presence of Pd/C or of PtO_2, and the partially reduced 9-

ketone was quantitatively re-oxidized with pyridinium dichromate in dichloromethane at room temperature[14] Decalone **11** is only a few trivial steps away from **12b**, a known inhibitor of cholesterol biosynthesis[15], this was prepared by a Wolff-Kishner reduction of the 9-keto group of **11** followed by deprotection of the t-Bu-protected 3β-OH group by short treatment with $BF_3.Et_2O$ (this was found to be a very convenient procedure, of the many cases we have used, one is shown on Scheme 3 We have run this deprotection in benzene, toluene or dichloromethane, with 1-4 h stirring, as established by TLC monitoring, under argon, at room temperature) Alternately, **12b** was obtained by sodium borohydride reduction, mesylation (MesCl, Py), deoxygenation (-70°C, excess of lithium metal, in liquid ammonia with THF as cosolvent, and finally ethanol as a proton donor) and again deprotection of the 3β-hydroxyl group (95% overall yield).

Addition of vinyl magnesium bromide to the decalone **11** (THF, -20°C to 0°C) gave the vinyl carbinols **13** as an epimeric mixture, in 85% yield Dehydration[16] of the mixture (BF_3 Et_2O cat, benzene-THF 4 1, 4hr



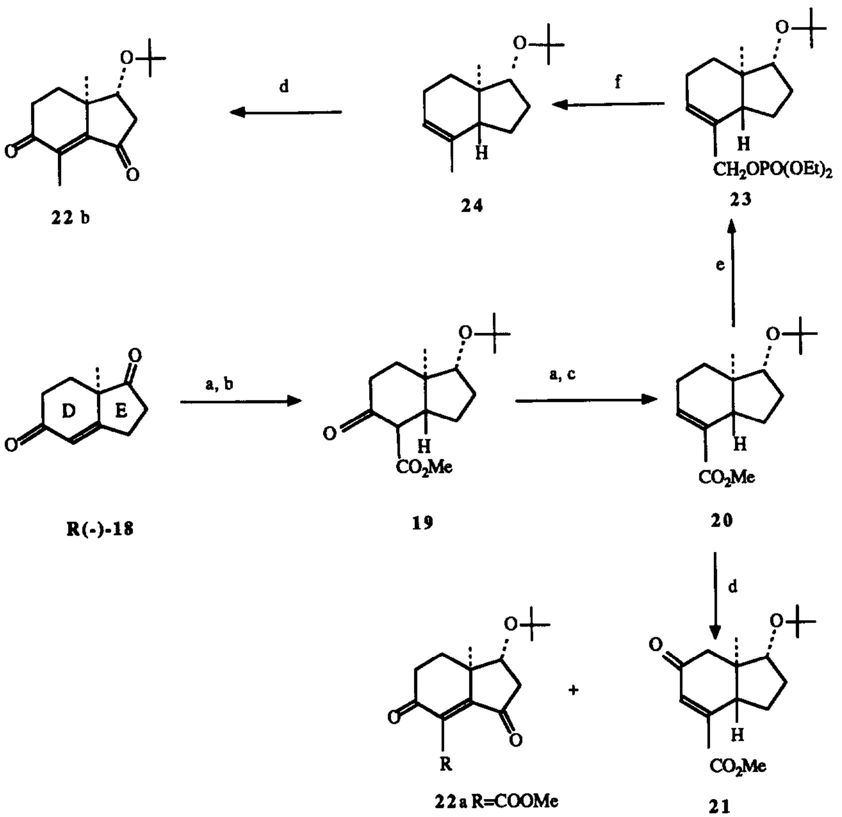
a Vinylmagnesium bromide, THF, -78°C to RT **b** BF_3 Et_2O, benzene, THF **c** lithium acetylide, liq NH_3 **d** 1) HCOOH, H_2SO_4, 5 min, 2) K_2CO_3, MeOH, H_2O, 3) TBMDS-Cl, DMF, imidazole **e** LDA, $(EtO)_2POCl$, -70°C to RT

Scheme 3

reflux) led to the A/B diene **14** in quantitative yield, provided proper precautions were taken (see Experimental Part even a trace of moisture leads to the isomeric 7, 9(11) E+Z dienes) Reaction of **11** with lithium acetylide[17] (excess metal in liquid ammonia, acetylene stream through the reaction mixture at -70°C) afforded in excellent yield the epimeric ethinyl carbinols **15**, which upon treatment with a few drops of concentrated sulfuric acid in formic acid (5 min at 90°C) led to the conjugated ketone **16** by a Rupe rearrangement[18] (60% from **11**) The resulting product **16a**, a 3-formate, was easily deformylated by treatment with potassium carbonate in methanol and water (1hr, room temperature) and the resulting 3-alcohol **16b** was quantitatively protected as the 3-TBDMS-ether **16c** with TBDMS-Cl, DMF, imidazole

We had planned to use this ether **16c** in a "tandem" Michael (or Mukaiyama-Michael[19]), approach or as the precursor of the 11-substituted dienes **17** (R = OTMS, $OPO(OEt)_2$, OAc, etc) Phosphate substituted dienes are said to have a reactivity comparable to that of the O-TMS dienes[20]; however, the dienolphosphate **17** proved totally unreactive towards dienophiles **21** or 3-methyl-2-cyclohexen-1-one, whereas diene **14** reacted very well with 2,6-dimethylbenzoquinone even at -78°C under Lewis-acid catalysis[21] (Scheme 1)

With the A/B synthetic intermediates available, we turned our attention to the D/E part of our retrosynthetic scheme Starting from the Wieland-Miescher ketone lower homologue **18**, the overall transformation required to obtain **21** amounts to a 1,2-carbonyl transposition on the D-ring moiety To ensure the trans D/E ring junction, we used the procedure of Uskokovic *et al* [22] up to the conjugated ester **20** All transformations depicted in Scheme 4 ran smoothly up to this point. We next focussed on the allylic oxidation

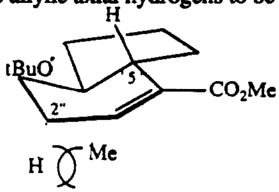


a $NaBH_4$, EtOH, CH_2Cl_2 (99%) **b** 1)- isobutene, H^+ (97%) 2)- Mg methyl carbonate (63%), 3)- H_2, Pd/$BaSO_4$ (100%) 4)- CH_2N_2 (100%) **c** 1)- MsCl, Py (98%), 2)- NaI, DMF (80%) **d** CrO_3, AcOH, Ac_2O, benzene, 5°C, 30 min (see Exp) **e** 1)- DIBAH (>95%), 2)- BuLi, then $(EtO)_2POCl$ (80%) **f** Li-$EtNH_2$/Argon, THF, t-BuOH, -70 to 0°C (80%)

Scheme 4

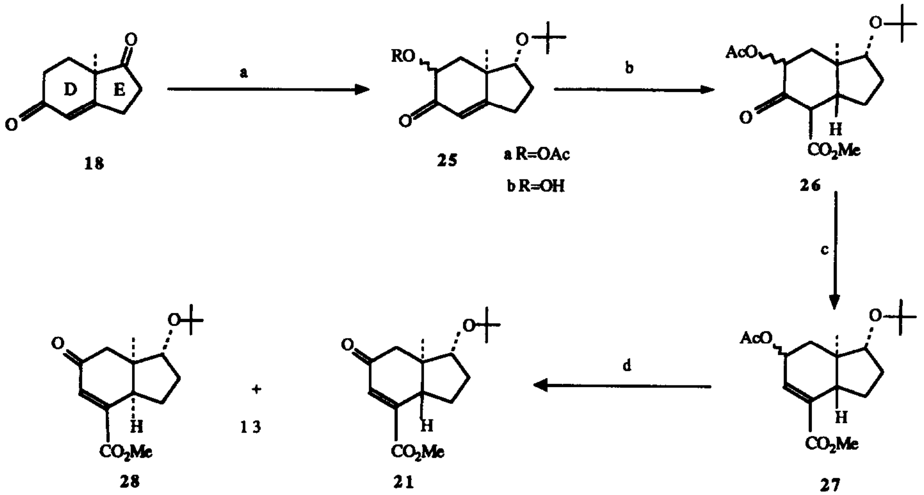
of **20**, which we hoped would lead us to the desired trans-hydrindane derivative **21** In fact, we encountered serious difficulties to carry out this apparently trivial transformation· the major oxidation product was the ene-dione **22a**, under varying oxidation conditions[23], and at best 15% of the desired **21** was obtained (with 26 % of

22a and unidentified polar products) by using $CrO_3/AcOH/Ac_2O$[24]. Furthermore, reductive dephosphorylation of the phosphate **23a**, obtained according to ref.25, at 0°C under argon, afforded **24**, which upon oxidation led similarly to the undesired enedione **22b** (24 %, plus unidentified polar products) This may be due to the different steric accessibilities of the two allylic axial hydrogens to be abstracted by the oxidant, as deduced from



Scheme 5: Steric representation of 20 *

the application of Toromanoff's "TAN" method,[26] or simply from a consideration of the steric representation of **20** (Scheme 5), based on an MM2 analysis, and showing that the secondary allylic axial hydrogen is cis to the angular methyl group (slower attack), but that the tertiary allylic axial hydrogen is not hindered This easier accessibility, and the preference for tertiary allylic hydrogen abstraction[27] would make the diketone **22** the favoured product of any allylic oxidation These considerations led to the conclusion that an alternative approach



a 1)- $NaBH_4$, EtOH, CH_2Cl_2, -78°C, 2)- i-butene, H^+, 3)- $Pb(OAc)_4$, benzene, reflux (ca 98%)

b 1)- Mg methyl carbonate (60%), 2)- H_2, $Pd/BaSO_4$ (100%), 3)- CH_2N_2 (100%)

c 1)- $NaBH_4$, EtOH, CH_2Cl_2, -78°C (>95%), 2)- MsCl, Py (>95%), 3)- NaI, DMF (45%)

d 1)- K_2CO_3, MeOH, H_2O (100%), 2)- PDC, CH_2Cl_2, or Jones, or Swern (100%)

Scheme 6

to **21** would be necessary. To overcome the undesired diketone formation, we used a slightly modified strategy for the formation of **21**, where the C-"2"/O bond was introduced at the beginning of the synthesis (Scheme 6).

* The "numbering" used in Scheme 5 and in the text below is, for convenience, steroid-like

Selective reduction of the saturated carbonyl of **18**, followed by t-butyl protection of the resulting alcohol and lead tetraacetate oxidation at C-"2"[28] (20 mmol of conjugated ketone in dry benzene, 2-fold excess of lead tetraacetate, reflux under an inert atmosphere for 3 days) afforded stereorandomly the epimeric mixture of "2"-acetoxy derivatives **25a** (ca. 98% yield) The orientation of the acetate group not being crucial, we pursued our synthesis as in Scheme 4 up to the conjugated ester **27**, all steps (carboxymethyl introduction at C-"4", hydrogenation, reduction, mesylation, elimination) proceeded in high yields, without requiring separation of the epimers temporarily produced as the epimeric centers become ultimately trigonal (we have nevertheless separated and fully characterized several of these epimers) For analytical purposes, the unseparable mixture of acetates **25a** was saponified (K_2CO_3, water-MeOH, r.t., 1h) to the corresponding alcohols **25b**, which were easily separated by silica gel column chromatography (1 2 ethyl acetate heptane) and the major alcohol was reacetylated (Ac_2O-Py, 0°C) to be fully characterized (Scheme 6) Sodium carbonate hydrolysis of the acetoxy-methyl ester **27** proceeded smoothly, but further oxidation of the "2"-hydroxy group was again fraught with difficulties Under either Corey[14], Jones[29] or Swern[30] conditions, we always obtained a 3:1 trans:cis ratio of the conjugated keto-esters **21a** and **28**, unseparable by silica gel flash column chromatography. However, HPLC separation (heptane ethyl acetate 97 3) gave pure **21a** and **28** The epimeric homogeneity of **21a** and **28** was confirmed by their ^1H and ^{13}C NMR spectra, and the *cis*-junction of **28** was established by NOEDIFF measurements[31] (400 MHz NMR) . presaturation of the signal due to the angular methyl group revealed its cis relationship with H-"5"

The use of the bicyclic intermediates described here to obtain tetracyclic adducts with benzoquinone derivatives (see Scheme 1) as well as pentacyclic structures on the way to isoarborinol, will be described later

***Acknowledgements:** We thank Dr M Uskoković (Hoffmann La Roche, Nutley, N J), for a generous gift of S(+)-Wieland-Miescher ketone, Dr E Toromanoff for useful discussions, and the Académie des Sciences and the Maxwell Foundation for post-doctoral fellowships (E C , R R and A T)*

Experimental Section :

Flash chromatographies were run on silicagel with the solvent mixture indicated IR spectra were recorded on a Nicolet 205 FTIR spectrometer. Optical rotations were recorded in $CHCl_3$ solution using a Perkin-Elmer 243 polarimeter Thin layer chromatography was performed on commercial silica gel glass plates that were developped by immersion in 5% phosphomolybdic acid in 95% ethanol Mass spectra (MS), recorded on an AEI MS-50 (electron impact spectra, EI), an AEI MS-9 (chemical ionization spectra, CI), or a Kratos MS-50 (high resolution mass spectra, HR) instruments are reported in the form· "m/z (intensity relative to base peak=100%)" ^1H NMR were recorded on Bruker AM400 or WP200 instruments in $CDCl_3$ Chemical shifts are expressed in ppm downfield from TMS (the ^1H NMR data are presented in the order· δ value of signal, integrated number of protons, peak multiplicity (s, singlet ; d, doublet , t, triplet , q, quartet ; m, multiplet) and coupling constant in Hz ^{13}C spectra were obtained either at 100 MHz (Bruker AM400 wide-bore) or at 50 2 MHz (Bruker WP200) and the chemical shifts are reported relative to $CDCl_3$ (77 00 ppm) For all compounds investigated,[13]C resonances were assigned by the SEFT technique.[32] Determinations of nuclear Overhauser effects by the NOEDIFF method were performed with the aid of Aspect 3000 microprograms which allowed direct accumulations of difference FID's. Samples were prepared as 10% (w/w) solutions in $CDCl_3$, degassed by several freeze-pump-thaw cycles, and sealed in NMR tubes

General procedure for boron trifluoride deprotection of t-Bu ethers:

The t-butyl ether (50-200 mg) in toluene (5mL; dichloromethane can also be used) is treated with 0.2-1 mL of borontrifluoride etherate. The reaction is monitored by TLC. After about 1 h at room temperature, it is usually complete. Addition of water (1mL) is followed by stirring (30 min, and addition of sodium hydrogen carbonate Work-up as usual has given in each case a nearly quantitative yield of the free alcohol, with no detectable trace of side product (TLC, NMR of the crude)

Catalytic deketalization of ketal 7:

The ketal **7**[11](300 mg) was dissolved in ethyl acetate (20 mL) and 10 % Pd/C (200 mg) was added. After 1 hr stirring at room temperature, a TLC control indicated complete deprotection Isolation as usual gave the pure diketone corresponding to **7** (245 mg)

Saturated ketone 11:

The ketone **10** (1 38 g, 5 15 mmol) and platinum oxide (80 mg) were stirred in ethyl acetate (25 mL) under 40 psi of hydrogen After 4 hrs, the solution was evaporated to dryness and afforded 1 4 g of crude product, which was oxidized with pyridinium dichromate (2 9 g, 7 75 mmol) in dry dichloromethane (25 ml), at room temperature under nitrogen After one night, the reaction mixture was diluted with ether and washed repeatedly with water and brine Flash chromatography (ethyl acetate heptane 1·4) gave 1 25 g of the decalone **11**

11 mp 80°C (ether-hexane), IR (film) 1700, 1200, 1100, 1050, ^{1}H NMR δ 0 887 (3H, s), 0 947 (3H, s), 1 159 (3H, s), 1 190 (9H, s), 1.150-1.800 (8H, m), 2 040-2 280 (2H, m), 2 580 (1H, m); 2.980 (1H, m); ^{13}C NMR δ 16 8, 18 7, 21.0, 31 4, 37.4, 39 9, 48 6, 53 4, 73 1, 77 7, 215.3, MS, EI. 266 $M^{+\bullet}$(52), 210 (60), 154 (77), 111 (78), 57 (100), $[\alpha]^{20}_D$ -18 (c=3 5), Anal Calcd for $C_{17}H_{30}O_2$ C, 76 64, H, 11 35, Fd C, 76 5, H, 11.3.

Reduction of ketone 11:

Sodium borohydride reduction of the ketone **11** was achieved according to ref 22b. The resulting 9-alcohol (320 mg, 1 2 mmol) was treated with mesyl chloride (150 mg, 1 3 mmol) in pyridine (15 mL), at 0°C under an inert atmosphere After one night, the usual work-up and flash chromatography gave the mesylate, which was treated with excess lithium in liquid ammonia (100 ml) and dry THF (5 ml), ethanol was then added at -78°C, and the usual work-up gave the t-butyl ether **12 a** in overall 95 % yield.

12a mp 115-118°C (ether-hexane) , IR (film) 2950, 1240, 1100, ^{1}H NMR . δ 0 739 (3H, s); 0 879 (3H, s), 0 919 (3H, s), 1.189 (9H, s), 0.80-1 80 (13H, m), 3 033 (1H, dd, J=10, 5), ^{13}C NMR δ 16 1, 19 4, 21 9, 22 0, 27 6, 27 7, 28.6, 29 3, 34 2, 39 0, 40 8, 45 5, 53.7, 72.8, 79 12, MS, EI . 252 $M^{+\bullet}$(12), 196 (11), 177 (8), 163 (7), 139 (69), 138 (57), 83 (84), 57 (100), $[\alpha]^{20}_D$ + 6 (c=1 15), Anal Calcd. for $C_{17}H_{32}O$ C, 80 88, H, 12.78, Fd C, 80.9; H, 12 5

Vinylation of ketone 11:

To a solution of decalone **11** (900 mg, 3 38 mmol) in dry THF, was added ot -78°C a 1M commercial solution of vinylmagnesium bromide in THF (10 mL, 10 mmol) The reaction mixture was allowed to warm up and monitored with TLC After 4 hrs at room temperature, it was cooled to 0°C and quenched with a saturated solution of ammonium chloride Flash chromatography (ethyl acetate heptane 1 6) afforded the mixture of epimers **13** in 85% yield; 90 mg of the starting material **11** was recovered

13a (faster eluting isomer) m p 62-65°C (ether-hexane); IR (film) 3500, 1200, 1060, ^{1}H NMR δ 0 793 (3H, s), 0 934 (3H, s), 0 958 (3H, s), 1 177 (9H, s), 1 250-2 000 (11H, m), 3 038 (1H, dd, J=9 9, 5), 5 094 (1H, dd, J=11, 1 3), 5 181 (1H, dd, J=17, 1 3), 6 023 (1H, dd, J=11, 1 3), ^{13}C NMR δ 16 6, 17 1, 21 3, 21 9, 26 9, 29 2, 30 5, 33 3, 40 0, 40 7, 45 6, 72 9, 77 1, 78 2, 113 4, 142 8, MS, EI 294 $M^{+\bullet}$ (1 5), 220 (93), 178 (43), 57 (100), $[\alpha]^{20}_D$ -22 (c=1 4) Anal Calcd for $C_{19}H_{34}O_2$ C, 77 49, H, 11 64, Fd C, 77 7, H, 11 5

13b (slower eluting isomer) m p 52-53°C (ether-hexane), IR (film) 3450, 1200, 1050, ^{1}H NMR δ 0 812 (3H, s), 0921 (3H, s), 1 081 (3H, s), 1 177 (9H, s), 1 30-1 95 (11H, m), 2 950 (1H, dd, J=10, 5), 5 188 (1H, dd, J=17, 11), ^{13}C NMR δ 14 5, 16 4, 21 2, 23 0, 27 0, 29 1, 29.3, 30 9, 36 1, 39 0, 41 5, 48 3, 72 8, 77 8, 78 4, 113 5, 141 9, MS, EI 294 $M^{+\bullet}$(1), 220 (93), 178 (43), 57 (100) $[\alpha]^{20}_D$ +9 (c=1 1) Anal Calcd for $C_{19}H_{34}O_2$ C, 77 49, H, 11 64, Fd C,77 6, H, 11 8

Diene 14:

Dehydration of the mixture of epimers **13** was achieved according to ref 16 N B All reagents and tools used for this reaction must be *perfectly dry* in order to avoid double-bond migration to the unwanted E+Z 7, 9(11) dienes (fully characterized but not separated and therefore not described here) The epimeric alcohols **13** (294 mg, 1 mmol) were heated at reflux under an inert atmosphere in a mixture of benzene (24 mL) and THF (6 mL), containing 0 1 mL of boron trifluoride etherate After cooling to 0°C, powdered sodium hydrogen carbonate was added, and the mixture was well stirred Dilution with ether, washings with 10% aqueous sodium hydroxide, water and brine, and drying over magnesium sulfate, afforded the diene **14** (215 mg, >95 %) after flash chromatography (ethyl acetate heptane 1 6) This diene is perfectly stable (several years) if it is fully purified immediately, and if it is kept at -18°C in the dark

14 : m p 69-72°C (hexane), ^{1}H NMR δ 0 832 (3H, s), 1 015 (3H, s), 0 85-2 31 (9H, m), 3 263 (1H, dd, J=12, 4), 4 928 (1H, dd, J=10, 2), 5 261 (1H, dd, J=17, 2), 5 677 (1H, t, J=4), 6 310 (1H, dd, J=17, 10), ^{13}C NMR δ 15 3, 18 2, 20 4, 27 1, 27 5, 27 9, 35 2, 37 0, 38 7, 50 4, 78 5, 113 4, 121 4, 135 9, 147 6, MS, EI 220 $M^{+\bullet}$(91), 202 (21), 187 (100), 159 (32), 145 (32) $[\alpha]^{20}_D$+20 (c=0 75), Anal Calcd for $C_{15}H_{24}O$ C, 81 76 , H, 10 98, Fd C, 81 5, H, 10 9

Ethinylation of decalone 11:

Excess lithium metal (>4 equ) was added in a 3-necked flask to liquid ammonia (150 mL, -78°C) and stirred After 30 min, dry acetylene was passed through the solution until the blue colour disappeared Decalone **11** (638 mg, 2 4 mmol), dissolved in anhydrous THF (10 mL), was added and stirring was continued for 4 hrs at -78°C under a constant flow of acetylene Dilution with ether, addition of ammonium chloride, and evaporation of the ammonia, were followed by the usual work-up and flash chromatography with ethyl acetate heptane 1 4 The mixture of epimeric ethinyl-carbinols **15** (665 mg, >95 %) was obtained, small amounts of the starting material were isolated.

15 (major isomer) m p 95-97°C (hexane-ether), IR (film) : 3500, 3290, 1180, 1050, ^{1}H NMR δ 0 787 (3H, s), 0 919 (3H, s), 0 997 (3H, s), 1 201 (9H, s), 1.30-1 85 (11H, m), 2 049 (1H, s), 3 022 (1H, dd, J=10 3, 4 6), ^{13}C NMR δ 13 0, 14 0, 16 1, 20 6, 23 3, 26 8, 28 7, 31 8, 35 2, 38 6, 41 7, 48 8, 72 6, 74 7, 76 6, 78 0, 87 1; MS, EI · 292 $M^{+\bullet}$(1), 274 (1), 245 (12), 235 (100), 218 (57), 189 (87), 175 (89), 57 (84) $[\alpha]^{20}_D$ - 12 (c=3 1), Anal Calcd for $C_{19}H_{32}O_2$ C,78 03, H, 11 03, Fd C, 78 05, H, 11 2.

Rupe rearrangement of carbinols 15:

The mixture of alcohols **15** (1 16 g) was dissolved in formic acid (20 mL), and 2 drops of concentrated sulfuric acid were added under stirring at room temperature After 2 hrs, the reaction mixture was heated to 90°C for 10 min, cooled to 0°C, poured into ice-cooled water, and neutralized slowly with potassium hydroxide Extraction (dichloromethane), drying (magnesium sulfate), evaporation of the solvent and flash chromatography (ethyl acetate heptane 1 4) yielded the α,β-unsaturated ketone **16**, as the 3-formate **16a**

16a m p 118-120°C (hexane-ether); IR ($CHCl_3$) 1700, 1650, 1170, ^1H NMR δ 0 931 (6H, s), 1 254 (3H, s), 2.242 (3H, s), 1 00-2 60 (9H, m), 4.641 (1H, dd, J=9 2, 7), 6 627 (1H, t, J=3 5), 8 123 (1H, s), ^{13}C NMR δ 16 5, 17.4, 20.1, 24 0, 27 4, 28 1, 33 5, 37 5, 37 7, 51 0, 80 5, 138 6, 149 9, 160 7, 199 6, MS , EI 264 $M^{+\bullet}$(30), 249 (13), 236 (21), 218 (19), 203 (20), 175 (37), 43 (100), $[\alpha]^{20}_D$ + 86 (c=0.4, $CHCl_3$), Anal Calcd. for $C_{16}H_{24}O_3$ C, 72 69, H, 9 15, Fd C, 72 6, H, 9 3

Hydrolysis of the formate 16a:

The formate **16a** (500 mg) was stirred at room temperature for 1 h in a mixture of methanol (20 mL), water (1mL) and potassium carbonate (500 mg) The reaction mixture was evaporated to dryness *in vacuo*, extracted with dichloromethane, washed with water, dried over magnesium sulfate, evaporated, and flash-chromatographed (ethyl acetate heptane 1 4), to yield 446 mg of the 3-alcohol **16 b**

16b · m p 103-104°C (hexane-iPr$_2$O), IR (nujol) 3550, 1660, 1620, ^1H NMR δ 0 837 (3H, s), 1 030 (3H, s), 1 225 (3H, s), 0 95-1 15 (2H, m); 1 40-1 85 (5H, m), 2 20-2 58 (3H, m), 3 242 (1H dd, J=10,6), 6 599 (1H, t , J=3.6), ^{13}C NMR δ 15 4, 17 6, 20 1, 27 6, 28 3, 33 9, 37 8, 38 9, 51 0, 78 8, 138 6, 150 4, 200.0, MS, EI 236 $M^{+\bullet}$(100), 218 (54), 208 (68), 203 (72), 193 (44), MS, HR, EI for $C_{15}H_{24}O_2$. Calcd 236 1776 Fd 236 1767, $[\alpha]^{20}_D$ + 93 (c=2 1), Anal Calcd for $C_{15}H_{24}O_2$ C, 76 22, H, 10 24, Fd C,75 35, H, 10 9

Enol phosphate 17·

The 3β-alcohol **16b** was protected as its t-Bu ether as described in ref 22 The resulting ether **16 c** (150 mg, 0 51 mmol) was treated with 1 1 eq of lithium diethylamide at -78°C under argon After 15 min, was added diethyl chlorophosphate (174 mg, 1 1 equ) The reaction mixture was allowed to warm up to room temperature, recooled to 0°C, quenched with water, and de-t-butylated with boron trifluoride etherate in dichloromethane The resulting alcohol **17 b** was purified by flash chromatography (84 mg, 44 %), and treated in DMF (0 2 mL) with 1 2 equ of t-butyldimethylsilyl chloride and 2 5 equ. of imidazole; after overnight stirring at room temperature under argon, isolation as usual yieded the 3-t-butyldimethylsilyl ether **17a** (109 mg, 100 %.

17a . oil, IR (film) 3425, 1630, 1360, ^1H NMR δ 0 005 (3H, s), 0 012 (3H, s), 0 770 (3H, s), 0 863 (9H, s), 0 900 (3H, s), 1 131 (3H, s), 1 00-2 25 (9H, m), 3.194 (1H, dd, J=11, 4 8), 4 136 (4H, m), 4 526 (1H, t, J=1 7), 4 864 (1H, t, J=1 7), 5 732 (1H, t, J=3 6), ^{13}C NMR δ 15 9, 16 0 18 0, 18 1, 20 8, 25 8, 26 7, 27 8, 28 4, 34 4, 36 6, 39 5, 50 4, 64 0, 79 2, 99 1, 128 9, 144 6, 155 9, MS, EI 486 $M^{+\bullet}$(4), 429 (2), 332 (7), 275 (21), 230 (18), 229 (100), 211 (26), 155 (33), $[\alpha]^{20}_D$ + 17 (c=3.5)

17b : m p 55-61°C (hexane-iPr$_2$O), IR($CHCl_3$) 3600, 3450, 1630, 1360, ^1H NMR δ 0 850 (3H, s), 1.050 (3H, s), 1 15 (3H, s); 1.35 (6H, m); 0 50-2 50 (9H, m), 3 25 1H, dd, J=10, 5 5), 4.50 (4H, m), 4 55 (1H, br s), 4 90 (1H, br s), 5 75 (1H, br s), ^{13}C NMR δ 15.5, 16 1, 16 2 18 2, 20 9, 26 8, 27 8, 28 3, 34 8, 37 1, 39.1, 50 8, 64.2, 64 3, 78.9, 99 6, 129 1, 144 8, 155 9, MS, EI 372 $M^{+\bullet}$(0 5), 218 (12), 203 (4), 200 (4), 185 (10), 157 (7), 155 (100), 127 (23), 99 (29), MS, HR, EI · Calcd. for $C_{19}H_{33}O_5P$ 372 2059, Fd . 372 2065, $[\alpha]^{20}{}_D$ + 8 (c=4 0)

For the transformations **18** to **22**, we have similarly followed the procedures described in ref 22 and in the refs cited therein

19 IR (film) 2950, 1749, 1712, 1363, 1201, 1160, 1125 , ^{1}H NMR δ 1 017 (3H, s), 1 140 (9H, s), 1 35-2 55 (9H, m) 3 352 (1H, d, J=13 5), 3 520 (1H, t, J=8), 3 733 (3H, s), ^{13}C NMR δ 10 7, 24 2, 28 4, 31 3, 34 8, 37 0, 41 8, 46 5, 51 5, 58 6, 72 4, 78 7, 169 5, 205 4, MS, EI 282 $M^{+\bullet}$ (7), 251 (9), 226 (39), 208 (27), 57 (100), $[\alpha]^{20}{}_D$ - 37 (c=1.6).

20 IR (film) · 3020, 2980, 1705, 1620, 1250, 1200, 1150, ^{1}H NMR δ 0.176 (3H, s), 1 141 (9H, s), 1 143-2 342 (9H, m), 3 454 (1H, DD, J=8, 6), 3.689 (3H, s), 6 795 (1H, q, J=2 8), ^{13}C NMR δ 11 0, 24 2, 24 8, 28 6, 31.3, 32 8, 42 6, 42 7, 50 8, 72 0,78 8, 131 8, 139 5, 167 4, MS, EI 266 $M^{+\bullet}$ (2), 235 (50), 210 (100), 192 (81), MS, CI 267 M+H (100), 211 (42), Anal Calcd for $C_{16}H_{26}O_3$ C, 72 14, H, 9 84, Fd C, 71 6 , H, 9 9, $[\alpha]_D{}^{20}$ + 18 (c=0 7)

Chromic oxidation of the unsaturated ester 20

The reagent was prepared according to ref 24, with 4 7 g (47mmol) CrO_3 The oxidation of the unsaturated ester **20** (2 5 g, 9 4 mmol) was carried out over 20 min and the temperature never exceeded 20°C Quenching was achieved by pouring into dilute aq potassium hydroxide and extraction with ethyl acetate was followed by drying (magnesium sulfate), evaporation, and flash chromatography (ethyl acetate heptane 1 6), to give the starting material (360 mg, 14 %), the unsaturated keto-ester **21** (390 mg, 15 %), and the ene-dione **22a** (680 mg, 26 %), accompanied by unidentified polar products

21 IR (film) 3040, 2984, 1722, 1689, 1620, 1244, 1191, 1118, ^{1}H NMR : δ 0.825 (3H, s), 1 149 (9H, s), 1 55-1 75 (2H, m), 2 06 (1H, m), 2 148 (1H, d, J=16 2), 2 25 (1H, m), 2 652 (1H, d, J=16 2); 2 70 (1H, m) , 3 738 (1H, t, J=7 8), 3 804 (3H, s), 6 593 (1H, d, J=3) , ^{13}C NMR δ 12 2, 23 9, 28 6, 30 9, 43 9, 46 7, 51 7, 52 1, 72 7, 78 4, 133 1, 148 2, 166 8, 200 6 , MS, CI 281 M+H (100), 225 (96), Anal Calcd for $C_{16}H_{24}O_4$ C, 68 54, H, 8 63, Fd C, 68 1, H, 8 6, $[\alpha]_D{}^{20}$ -45 (c=1 2)

22a mp (ether) 137-140° C IR 3000, 2950, 1733, 1682, 1247, 1200, 1176, 1100, 1008, ^{1}H NMR δ 1 210 (9H, s), 1 307 (3H, s), 2 008 (1H, m), 2 284 (1H, ddd, J=13, 4 6, 2 6), 2 42-2 82 (4H, m), 3 859 (3H, s), 3 939 (1H, dd, J=9 8, 7 7), ^{13}C NMR δ 16 5, 28 3, 33 2, 34 1, 43 2, 45 0, 52 4, 73 8, 74 2, 128 8, 154 6, 164 5, 195 4, 201 6, MS, EI 294 $M^{+\bullet}$ (1), 238 (73), 221 (13), 207 (53), 206 (100), 57 (2); HREIMS for $C_{16}H_{22}O_5$ calc 294 1467, Fd 294 1500, Anal Calcd for $C_{16}H_{22}O_5$ C, 65 29, H, 7 53, Fd C, 65 4, H, 7 4, $[\alpha]_D{}^{20}$ - 248 (c=0 8)

Oxidation of the olefin 24

Oxidation of the olefin **24** (125 mg, 0.56 mmol) with CrO_3 (279 mg, 2 79 mmol), under the same conditions as before with did not give the simple allylic oxidation product corresponding to **21**, but only unidentified polar material and the ene-dione **22b** (35 mg)

22b IR ($CHCl_3$) 3023, 2977, 2937, 1715, 1674, 1180, 1104, 1034, ^{1}H NMR δ 1 196 (9H, s), 1 218 (3H, s), 1 889 (1H, m), 2 082 (3H,s), 2 234 (1H, m), 2 45-2 72 (4H, m), 3 832 (1H, dd, J=9 9, 7 6), ^{13}C NMR d 10 4, 17 2, 28 7, 33 5, 34 8, 44 3, 46 1, 73 7, 74 7, 136 0, 152 1, 200 3, 205 7, MS, EI 250 $M^{+\bullet}$ (1), 195 (14), 194 (100), 150 (79), 57 (71), $[\alpha]_D{}^{20}$ -63 (c=0 5)

Preparation of the phosphate 23.

Reduction of the ester **20** with DIBAH was followed by phosphorylation according to ref. 25

23 ^{1}H NMR δ 0 713 (3H, s); 1 138 (9H, s), 1 331 (6H, t, J=7), 0.88-2 25 (9H, m), 3 482 (1H, dd, J=10, 6 5), 4 098 (4H, q, J=7), 4 412 (1H, m), 5 853 (1H, d, J=2 8), ^{13}C NMR δ 10.9, 16 0 (d, $^3J_{P-C}$=6 6), 22 1, 28 6, 31 4, 33.3, 42 3, 43 7, 63 4 (d, $^2J_{P-C}$=5 6), 69 6 (d, $^2J_{P-C}$=5 5), 72 1, 79 2, 126 1, 133 7 (d, $^3J_{P-C}$=7 3), MS, EI . 374 $M^{+\cdot}$ (0 5), 221 (2), 155 (100), 57 (24); Anal Calcd for $C_{19}H_{35}O_5P$ C, 66 64, H, 10 30, Fd . C, 67 0, H, 10 0; $[\alpha]_D^{20}$ + 3 (c=0 5).

Reduction of the phosphate 23

Reduction of the phosphate **23** was accomplished following ref 25 at 0°C under argon and gave the ether **24.**

24 ^{1}H NMR : δ 0 717 (3H, s); 1.128 (9H, s); 1 0-2.1 (9H, m); 1 61 (3H, s), 3 45 (1H, dd, J=8 9, 6 5), 5 20 (1H, br s), ^{13}C NMR δ 11 1, 20 2, 23 0, 24 2, 28 8, 31 5, 34 0, 42 4, 46 5, 72 1, 79 7, 120 0, 134 5, MS, CI 223 M+H$^+$ (100), 167 (59), 149 (100)

Lead tetracetate oxidation of 25 :

The saturated carbonyl of the ene-dione **18** was reduced using the usual procedure (sodium borohydride in ethanol, -78°C) and the resulting alcohol was protected as the t-butyl ether. This (**25**, H instead of OR), was treated using the procedure of Lansbury and Nickson[28] with a 2-fold excess of lead tetracetate in dry benzene (3-days reflux under argon) The epimeric mixture of acetates **25a** thus obtained nearly quantitatively was not separable by flash chromatography The mixture **25a** (1.17 g, 3 57 mmol) was stirred in methanol (20 mL) and water (1 mL) at room temperature in the presence of potassium carbonate (2 g, 15 mmol). After 1 hr the methanol was removed under reduced pressure and the crude product was taken up in dichloromethane, washed with water, dried and evaporated *in vacuo*, to give the mixture of epimers **25b** (986 mg, 100 %), easily separated by flash chromatography (ethyl acetate heptane 1 2). The major epimer (200 mg, 0 84 mmol) was then reacetylated (Ac_2O, Py, 0°C) to give the major acetate **25 a** (235 mg, 0.84 mol).

25a (major epimer, equatorial C-OAc) IR (film) 1748, 1691, 1638, 1377, 1237, 1207, 1095, ^{1}H NMR δ 1 178 (9H, s), 1 242 (3H, s); 1 75-2 10 (3H, m), 2 175 (3H, s), 2 22-2 47 (2H, m), 2 730 (1H, m), 3 620 (1H, t, J=8 7), 5 557 (1H, dd, J=5 3, 13 5), 5 613 (1H, br s), ^{13}C NMR δ 16 4, 20 7, 26 8, 28 5, 29 4, 40 4, 46 3, 70 6, 73 1, 79 3, 121 4, 170 0, 174 5, 193 1, MS, CI 281 M+H (100), 225 (39), 147 (15), MS, HR, EI calcd for $C_{16}H_{25}O_4$ M+H Calcd 281 1753, Fd 281 1743, $[\alpha]_D^{20}$ - 52 (c=2 2)

25b (major epimer, equatorial C-OH) IR ($CHCl_3$) 3490, 2980, 1673, 1150, 1095, 1073, ^{1}H NMR δ 1 168 (9H, s), 1 205 (3H, s), 1 638 (1H, t, J=12 7), 1 798 (1H, m), 1 981 (1H, m), 2 370 (1H, m), 2 425 (1H, m), 2 727 (1H, m), 3 596 (1H, t, J=9), 4 329 (1H, dd, J=13 2, 5 5), 5 850 (1H, s), ^{13}C NMR δ 16 2, 27 1, 28 5, 29 1, 43 0, 46 2, 69 1, 73 0, 79 2, 119 8, 176 6, 199 2, MS, EI 239 $M^{+\cdot}$ (0 7), 238 (0 5), 223 (0 6), 222 (0 5), 182 (72), 57 (100), $[\alpha]_D^{20}$ - 61 (c=0 95)

Conversion of 25a to the α,β-unsaturated ketones 21 and 28.

The steps **25a-26-27-21a+28** were carried out by the standard procedures indicated on Scheme 6, on the mixture of acetates **25a** The final mixture of cis-trans products (1 3) could only be separated by HPLC

28 IR (film) 3040, 2977, 1728, 1676, 1621, 1603, 1273, 1250, 1199, 1124, ^{1}H NMR δ 1.021 (3H, s), 1 148 (9H, s), 1 517 (1H, m), 1 736 (1H, m), 2 148 (1H, d, J=16), 2 167 (1H, m), 2 363 (1H, d, J=16), 2 415 (1H, m), 2 923 (1H, t, J=9 1), 3 536 (1H, dd, J=6 2, 3 6), 3 827 (3H, s), 6 655 (1H, s), ^{13}C NMR δ 20 4, 28 5, 29 9, 33 9, 43 8, 45 4, 47 9, 52 4, 73 2, 78 2, 130 6, 150 8, 167 1, 199 5, MS, EI 280 $M^{+\cdot}$

(1 5), 224 (79), 192 (53), 167 (97), 57 (100), MS, HR, EI for $C_{16}H_{24}O_4$ Calcd 2780 1674, Fd 280 1672, $[\alpha]^{20}_D$ - 78 (c=0 95)

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