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STEREOSELECTIVE ROUTE TO HIGHLY FUNCTIONALIZED 4a,8a-SUBSTITUTED,1,2,3,4,4a,6,8a,9,10,10a-DECAHYDROPHENANTHRENES, A NEW ENTRY TO THE QUASSINOID AND FUSIDANE FRAMEWORKS.[1]

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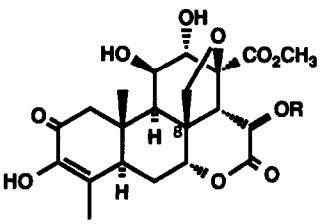
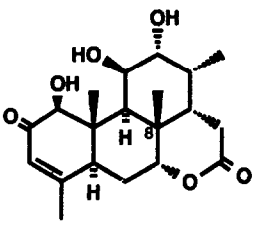
Abstract: A series of highly functionalized angularly substituted bicyclic and tricyclic ketones were obtained regio- and stereoselectively by means of the Birch reductive alkylation on the properly functionalized benzylic ketones.

Amongst of the family of natural triterpenoids, there is a huge number of compounds possessing biological activity.[2] For this reason, the synthesis of their different molecular frameworks has always been a matter of concern. In a rough manner, two kinds of 8-substituted triterpenoids can be pointed out, i.e., those bearing an angular substituent either with a β or an α orientation. In the first group we find the well-known quassinoids, like bruceantin **1** and klaineanone **2**:



1 R= -COCH=C(CH$_3$)CH(CH$_3$)$_2$



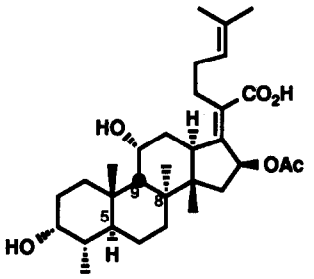
2

They possess a profuse antileukemic, antimalaric and amebicide activity.[2,3] For this reason, their syntheses have called the attention of many research groups in the past decade.[4]

On the other hand, in the 8a-substituted series we can point out the fusidane steroidal antibiotics, like fusidic acid **3** and cephalosporin P1, **4**,[3] which are powerful therapeutic agents against staphylococus.

From the chemical point of view the synthesis of the fusidane skeleton is challenging, because the construction of a trans-syn-trans configuration forces ring B to adopt a boat conformation.[5] Hence, we must avoid any possibility of isomerization upon C-5 and C-9 during the formation of the ring junction. On the other

hand, any reaction with a transition state resembling the products is inconvenient, because a boat like conformation would raise the activation energy, favoring the all trans ring junction.



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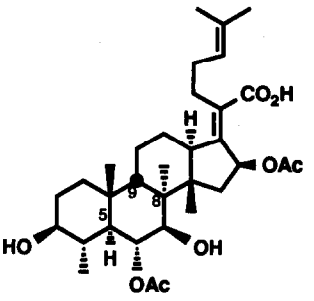

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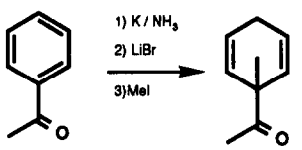
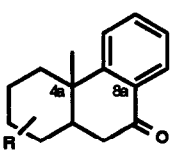
For these reasons new reactions, providing a high degree of stereoselectivity in establishing the C-8 configuration, are of continuous interest. In general, several approaches were devoted to attain the introduction of the angular substituent, either by the α- or by the β-face, using Claisen rearrangements,[6] Robinson annelations[7,8] or a biomimetic cyclization.[9] Recently, J. Sutherland et al. reported a stereocontrolled synthesis of tricyclic intermediates in which the C-8 configuration could be directed by that of C-7.[10]

Narisada and Watanabe[11] developed the appropriate reaction conditions to achieve the reductive alkylation of acetophenone without affecting the keto group. This implies using potassium instead of the usual lithium or sodium as reducing agent and the subsequent exchange of the counter ion K^+ by Li^+ in the intermediate enolate, to enhance the C/O alkylation ratio:



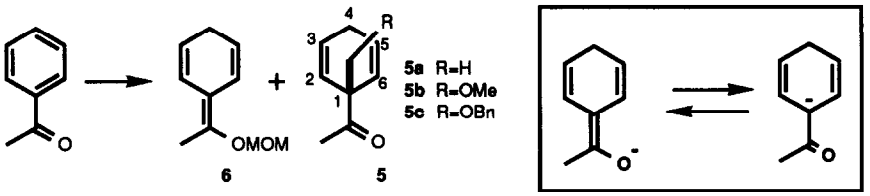
At the same time, literature precedents[12] and our previous experience[13,14] with the octahydrophenanthrenes gave us the necessary insight into a tricyclic system that could be conveniently substituted. Therefore, we envisaged 4a-methyl octahydro-phenanthren-9-ones as the adequate substrates to assay a Birch reductive alkylation in order to study their stereochemical outcome. Since we were interested also in the introduction of oxygenated angular substituents, we decided to adjust first the reaction conditions using the simpler acetophenone as a model substrate.



4a-methyl octahydrophenanthren-9-one skeleton

Of the several alternative reagents for introducing an angular oxygenated moiety: methyl ortoformate, methyl chloroformate, gaseous formaldehyde and α-haloethers, the latter being most successful. Thus, using chloromethyl methyl ether (MOMCl) the reductive alkylation took place, but a 1:1 mixture of the C- and the O-alkylated product was obtained.

As we were concerned only with the C-alkylated product, we decided to explore the reaction conditions that could favor the electrophilic attack upon carbon rather than oxygen, taking into account that the intermediate enolate exists in a tautomeric equilibrium and therefore, it behaves as an ambiphilic anion.

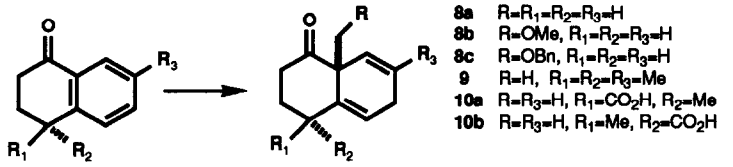


It is known that an appropriate choice of the countercation and the solvent may direct the reaction towards one of the products.[15] It has been proven that lithium is the cation which induces the best C/O alkylation ratio. In addition, in solvents with lower cation-solvating ability (i.e. benzene or toluene), even strong electrolytes are found to be associated,[16] so that the cation remains strongly attached to the atom which bears a higher electron density (i.e., the oxygen) diminishing its reactivity towards the incoming electrophile.

Therefore, in a new experiment, after generating the Li^+ enolate the organic cosolvent used in the reduction step (either ethyl ether or tetrahydrofuran) was replaced by dry benzene or toluene and the alkylation step was carried out in the nonpolar solvent. This time, the product was mainly the expected C-alkylated one.

In order to generate a weaker protecting group, we also prepared the corresponding benzylic ethers using chloromethyl benzyl ether (BOMCl) and, in this case, the change of solvent was not required to maintain the regioselectivity.

Once we had the appropriate procedure in hand, we decided to extend this study to some selected bicyclic systems. This allowed firsthand experience on handling the 1,4 diene systems.



At the same time we wanted to explore the possibility of producing potentially useful bicyclic intermediaries. Therefore, several α-tetralones, prepared through straightforward reactions,[17,18] were utilized as substrates for a series of reductive alkylations. The results obtained are listed in Table 1.

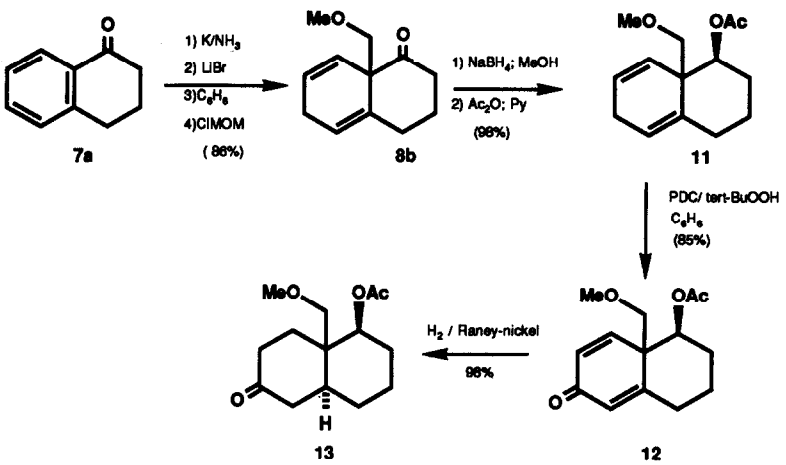
Table 1

Starting Material	Alkylating Reagent	Reaction Method	Products (% yield)[a]
acetophenone	MeI	A	**5a** (81)[b]
acetophenone	MOMCl	A	**5b** (37) + **6** (35)
acetophenone	MOMCl	B	**5b** (88)
acetophenone	BOMCl	A	**5c** (92)
7a	MeI	A	**8a** (82)[b]
7a	MOMCl	B	**8b** (86)
7a	BOMCl	A	**8c** (81)
7b	MeI	A	**9a** (86)
7c	MeI	A	**10a** (32) + **10b** (32)[b]

[a]Pure compound isolated yield; [b]Taken from reference 11

To exemplify the potential of the method, the product of the reductive alkylation of α-tetralone (**7a**), was further elaborated as shown in Scheme I.

Scheme I



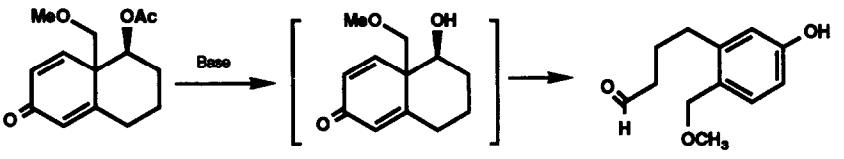
7a 8b 11 12 13

To achieve the oxidation of the sensitive diene **11**, we used the method reported by Schultz et al.[19] A remarkable fact is the high selectivity[20] in the hydrogenation step of the dienone (**12**) to produce exclusively the trans-fused decalone. This sequence could be regarded as an entry into the trans decalones with oxygenated angular substituents, alternative to the classic Robinson annelation.

The 1,4-diene system produced upon reductive alkylation proved to be somewhat unstable. The presence of the keto group near to the oxygenated angular substituent seemed to cause an extensive retro-alkylation, regenerating some of the starting aromatic compound, during the purification (column chromatography) or even on standing. The reduction of the carbonyl prior to any attempt of purification normally prevented such problem.

Nevertheless, we observed a more dramatic retro-reaction on an attempt to deprotect the hydroxyl function on compound **12** (Scheme II). Compound (**14**) was produced exclusively in better than 80% yield.

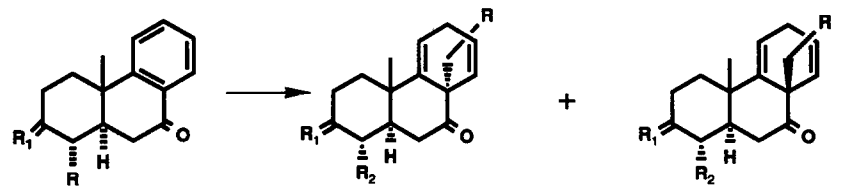
Scheme II



12 **14** (>80%)

For the assault on the tricyclic system three substrates were selected: ketones (**15a**), (**15b**) and (**15c**). The latter possessed an extra functionality in ring A, so that they may be further elaborated into the final products. The syntheses of these ketones, from known precursors found in references 13, 21 and 22 respectively, were straightforward and required the protection of the oxygenated function in ring A followed by a benzylic oxidation.[19]

The reductive methylation of ketone (**15b**), proceeded as expected, producing two stereoisomers compounds **18a** and **19a** (epimers at C-8) in a 83:5 ratio (measured by ^{1}H NMR). Unfortunately, the minor product seemed prone to undergo decomposition regenerating the starting material upon column chromatography. In turn, the major product **18a** was isolated in ca. 83% yield. The methoxymethylation was also carried out successfully, and this time only one isomer **18b** could be detected and it was isolated in 82% yield.



15a R_1=R=H
15b R_1= OCH_2CH_2O, R=H
15c R_1= OCH_2CH_2O, R=Me

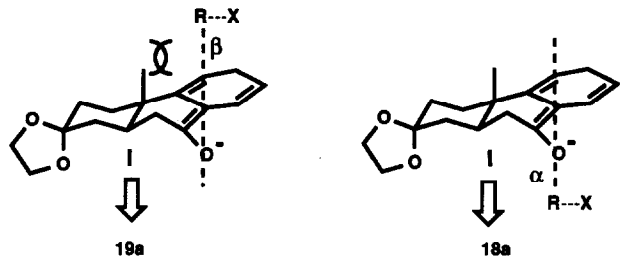
16 R_1=R_2=H, R=OMe
18a R_1=OCH_2CH_2O, R_2=R=H
18b R_1=OCH_2CH_2O, R_2=H, R=OMe
20a R_1=OCH_2CH_2O, R_2=Me, R=H
20b R_1=OCH_2CH_2O, R_2=Me, R=OMe

17 R_1=R_2=H, R=OMe
19a R_1=OCH_2CH_2O, R_2=R=H

In order to determine the relative stereochemistry of the new angular substituent, a series of nuclear Overhauser enhancement experiments (n.O.e)[23] was performed in which no enhancements were observed between the 4a-methyl and the 8a-CH_2OMe groups. Thus a β-orientation, for the newly introduced substituent, should be discarded. However, as the 1,4-diene system and the carbonyl function may impose some distortion upon rings B and C, that could drive the angular substituents far apart, the possibility of a syn relationship could not be definitively ruled out based in this evidence only.

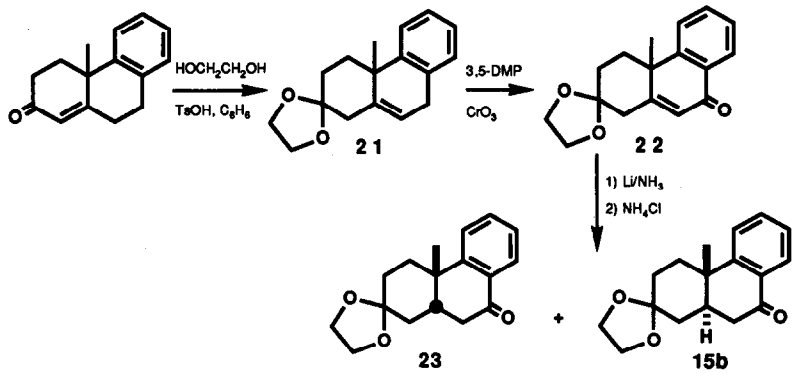
However, upon hydrogenation of the diene system, the single isomer obtained, again showed no n.O.e. also suggesting that the alkylation proceeded exclusively from the α-face. Besides, such selectivity might be explained by the preferred attack of the alkylating agent from the less hindered α-face of the enolate since from the β-face it suffers an 1,3 direct interaction with the C_{4a}-methyl group. In addition, AM1 calculations of the

energy versus reaction coordinate pathways, for the C_{8a}-C_R bond formation in both approaches, showed the expected consistently lower energy profile for the α-approach. The calculated ΔH_f for both final products are -80.9 Kcal/mol (**19a**) and -81.8 Kcal/mol (**18a**).



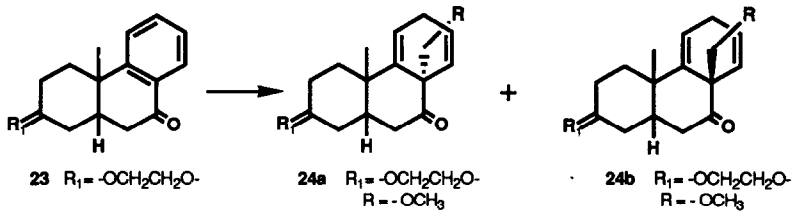
Due to our previous experience with the conformational behavior of the 4a-methyl octahydrophenanthrene system,[24,25] we decided to attempt this reaction upon the cis-fused related ketone (**23**). The synthesis of **23** was carried out as shown in Scheme III.

Scheme III



The reductive methoxymethylation of **23** took place yielding two products: **24a** and **24b** (Figure 1) in ca. 1:1 ratio. Such lack of stereoselectivity can be explained considering the flexibility of the A/B cis fused system.

Figure 1



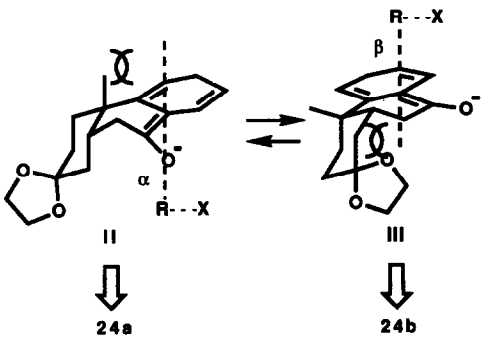
As already has been reported,[24,25] the cis-fused 4a-methyl octahydrophenanthrenes may exist in a dynamic equilibrium between two conformations each one leading to a distinct approach of the alkylating agent. In this

case, the compound exists almost in a 1:1 mixture of conformations II and III and since, in both reaction intermediates the steric hindrance is similar, the stereoselection is completely lost.

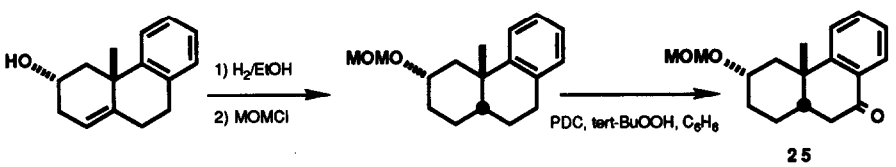
Again, AM1 calculations showed that, in conformation II, the energy for the α-approach is lower than that calculated for the β-approach, while the opposite stands for conformation III.

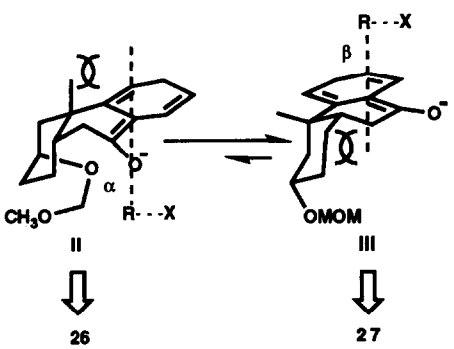
However, it has been demonstrated that, through an appropriate substitution in rings A or B, cis-4a-methyl octahydrophenanthrenes can be locked into one of the conformations (II or III) by shifting the fluxional equilibrium.[25]

In our case, as the α-face attack was predominant in the trans fused series, we were interested to achieve a good stereocontrol for the β-alkylation, which seemed to be favoured in conformation III. Therefore, with this in mind we synthesized ketone (**25**), from a known alcohol,[13] by extending a reported procedure as shown in Scheme IV. Compound (**25**) exists mainly in conformation III, since the oxygenated moiety in C-3 tends to adopt the more stable equatorial orientation:



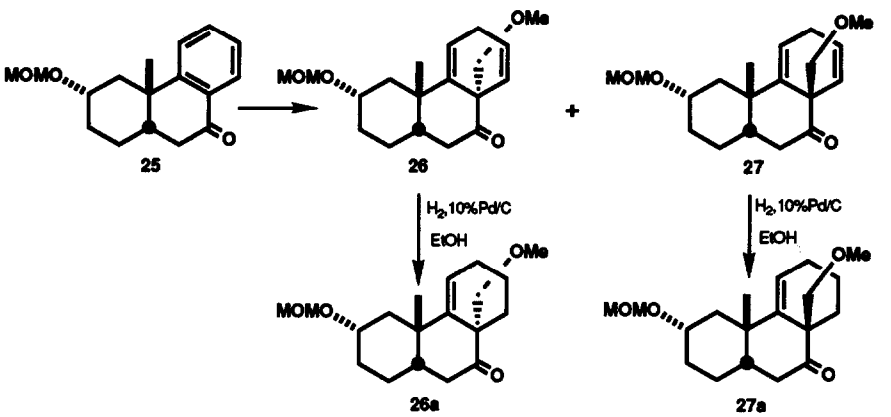
Scheme IV





The methoxymethylation of ketone (**25**) produced, in agreement with our previous assumptions, a mixture of compounds **27** and **26** (85% yield) in a 4:1 ratio (^{1}H NMR). Unfortunately, the β-alkylated product is unstable

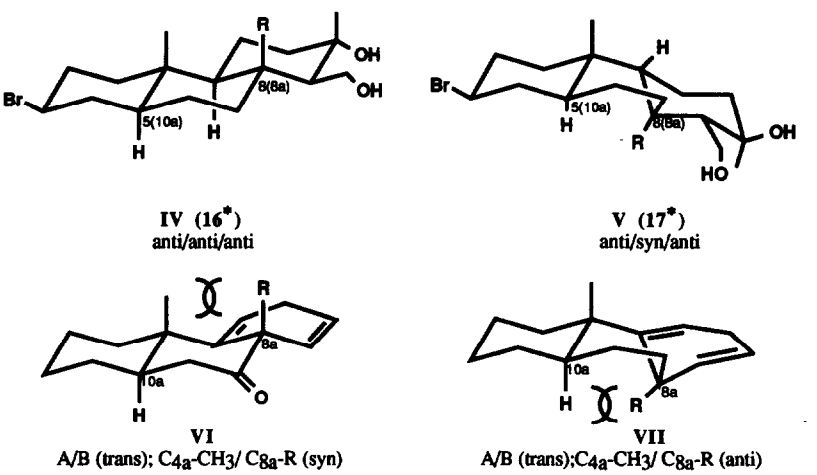
and the isolated ratio dropped, after chromatography, to 3:1 and some aromatic ketone from the retro-reaction was also recovered. The retro-reaction was somewhat prevented by partial hydrogenation of the products to compounds **26a** and **27a**.



Finally, a confirmation of the stereochemical outcome of this reactions was provided by the ^{13}C analysis of the products.[26] The ^{13}C NMR chemical shifts of the compounds studied are shown in Table 2.

Taking into consideration that the conformational preferences of a tricyclic system are determined by the different combinations of the ring juncture stereochemistry, there are several alternatives to consider. Thus, as representative members of a tricyclic all-trans saturated system, compounds **16*** (anti/anti/anti) and **17*** (anti/syn/anti) were chosen, from the literature,[9] as reference compounds.

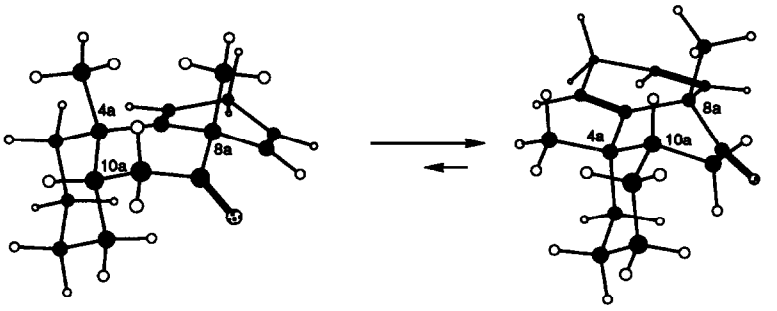
Figure 2



*Compounds and numbering taken from reference 9

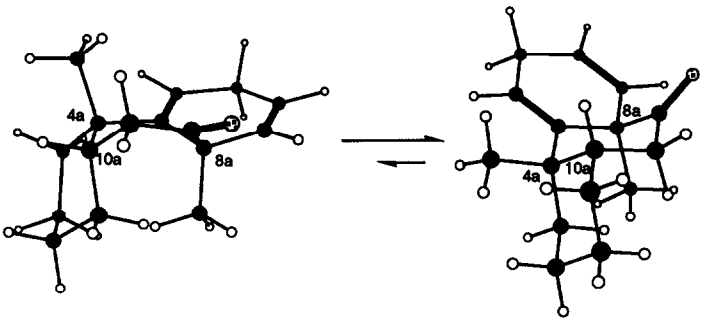
Each compound in Figure 2, due to the all-trans nature of their ring junctions, adopts a single conformation IV and V respectively. In analogy, the trans 1,4-diene series could be seen as represented for the basic structures VI and VII, which can be correlated directly to IV and V.

Figure 3



VIII IX

A/B (cis); C_{4a}-CH_3/ C_{8a}-R (syn)



X XI

A/B (cis); C_{4a}-CH_3/ C_{8a}-R (anti)

On the other hand, for the cis 1,4-diene series we have also two configurational (epimeric) isomers each one with two possible extreme conformations, giving a total of four conformers: VIII, IX, X and XI (Figure 3).

Table 3, shows some selected ^{13}C NMR chemical shifts for a series of C_{8a} epimers, including the reference compounds **16*** and **17***. The table also lists the most representative configurational characteristics and the preferred conformational extremes adopted by those compounds in solution.

It is clear, from Table 3, that whenever there is a syn relationship between the C_{10a}-H and the C_{8a}-R, an upfield shift (4.7 to 9 ppm) can be observed for the C_{10a} signal in the ^{13}C NMR spectra. This substantial shielding might be explained by the existence of a compressing stem-to-stem interaction between these groups, such as that shown in structures VII (Figure 2) and IX (Figure 3). Thus, in the A/B trans series, the shielding of the C_{10a} signal indicates an anti relationship for the angular substituents at C_{4a} and C_{8a} while, in the A/B cis series, it stands for a syn disposition of the same groups. In addition, this protection also indicates the preferred conformations VII and IX respectively.

Table 2

Cpnd/Cn	15a	15b	15c	16	18a	19a	20a	20b	24a	24b	27	26	26a	27a
1	28.2	30.8	43.3	28.3	35.5	25.5	39.7	40.4	29.0	35.3	25.3	26.7	25.0	25.3
2	25.6	107.5	108.9	21.9	108.2	108.3	109.5	109.8	109.0	108.7	27.1	27.3	27.0	26.9
3	21.8	33.8	30.3	25.8	31.1	30.9	30.7	30.9	33.4	30.9	72.6	72.7	72.9	72.9
4	36.5	36.9	33.3	42.2	37.0	37.2	39.2	40.6	39.8	37.3	42.5	41.7	42.5	42.5
4a	36.7	35.7	35.9	37.8	38.0	41.4	37.6	37.7	40.1	38.0	39.3	40.2	40.4	39.4
4b	154.4	153.0	153.2	147.6	149.2	152.1	149.7	146.8	146.1	141.1	145.7	145.8	145.9	145.8
5	123.6	123.9	123.5	120.3	119.5	119.1	118.6	120.7	125.0	124.5	123.4	124.6	126.0	126.1
6	125.8	125.9	125.5	27.8	26.7	26.8	26.5	27.3	26.8	27.3	26.8	26.7	26.2	24.9
7	127.2	127.1	126.6	125.0	123.5	123.1	123.4	124.9	126.1	125.6	125.8	124.7	16.5	17.4
8	133.3	133.2	132.9	129.0	130.8	131.6	130.4	129.0	131.8	128.3	127.9	128.1	29.5	29.0
8a	131.1	130.9	130.5	55.5	49.3	49.0	49.8	55.3	52.8	55.3	54.1	55.7	54.5	52.2
9	197.6	196.8.	196.9	210.0	211.4	208.3	211.6	209.8	209.0	210.4	211.8	210.0	213.0	213.1
10	41.6	40.8	37.9	37.9	40.8	30.1	34.7	34.5	38.0	43.2	42.2	40.8	40.5	41.4
10a	41.3	38.1	38.8	37.5	34.4	39.1	40.3	41.1	45.6	39.8	32.8	39.4	40.6	35.4
C_1-Me	-	-	9.42	-	-	-	9.94	10.1	-	-	-	-	-	-
C_{4a}-Me	20.2	19.4	20.5	20.9	20.0	15.1	21.0	21.1	20.1	28.9	27.5	26.1	26.2	28.0
C_{8a}-Me	-	-	-	-	28.2	17.8	27.5	-	-	-	-	-	-	-
C_{8a}-$\underline{CH_2}$OMe	-	-	-	79.1	-	-	-	78.8	78.1	80.2	79.8	79.9	76.9	78.1
C_{8a}-$CH_2\underline{OMe}$	-	-	-	59.3	-	-	-	59.4	57.4	59.0	58.6	59.1	59.2	59.0
-OCH_2CH_2O-	-	63.7	64.2	-	64.1	65.7	64.5	64.8	63.4	63.9	-	-	-	-
-O$\underline{M}$OM	-	-	-	-	-	-	-	-	-	-	94.2	94.5	94.6	94.5
-OMO$\underline{M}$	-	-	-	-	-	-	-	-	-	-	54.7	55.0	55.2	55.1

^{13}C NMR of the compounds studied

Finally, it is interesting to mention that the empirical rules for the conformational assignment of 4a-methyl octahydrophenanthrenes, described in reference 25, also can be applied to the corresponding decahydro system. Thus, the C_{4a}-methyl and C_{4b} chemical shift values, listed also in Table 3, were used to assign the preferred conformations for the rest of the compounds.

Table 3

Cpd	A/B	C_{4a}Me/ C_{8a}R	C_{10a}H/ C_{8a}R	δC_{10a} (ppm)	$\Delta\delta$ δ_a-δ_s	δC_{4a}Me	δC_{4a}	Pref. Conf.
16*	Trans	syn	anti	57.6		16	–	-
					– 9.0			
17*	Trans	anti	syn	47.7		22.0	–	-
18a	Trans	syn	anti	39.1		20.0	149.2	**VI**
					– 4.7			
19a	Trans	anti	syn	34.4		15.1	152.1	**VII**
24b	cis	syn	syn	39.8		28.9	145.1	**IX**
					+ 5.8			
24a	cis	anti	anti	45.6		20.1	146.1	**XI**
27	cis	syn	syn	32.8		27.5	145.7	**IX**
					+ 6.6			
26	cis	anti	anti	39.4		26.1	145.8	**XI**
27a	cis	syn	syn	35.4		28.0	145.8	**IX**
					+ 5.2			
26a	cis	anti	anti	40.6		26.2	145.9	**XI**

Conclusions: The reported novel applications of the Birch reductive alkylation, are promising to prepare intermediates for the synthesis of highly funtionalized systems.

First of all, we have described the conditions for direct introduction of an angular -CH_2OR moiety upon mono-, bi- and tricyclic benzylic ketones. Second, the starting ketones may be prepared with the desired latent functionality and third, the resulting alkylated products may be further elaborated into multifunctionalized decalins and tricyclic diterpenoids.

First of all, we have described the conditions for direct introduction of an angular -CH_2OR moiety upon mono-, bi- and tricyclic benzylic ketones. Second, the starting ketones may be prepared with the desired latent functionality and third, the resulting alkylated products may be further elaborated into multifunctionalized decalins and tricyclic diterpenoids.

We have also shown that the reaction in the 4a-methyl tricyclic systems proceeded with a high degree of stereoselectivity producing an anti disposition of the angular substituents as in the fusidanes. On the other hand, in the cis series the stereoselection can be controlled through appropriate substitution on the substrates.

Finally, the 1,4-dienes obtained may be seen as versatile intermediaries in natural product synthesis, for the construction of highly functionalized structures with stereochemically defined substituents.

Experimental

General methods:

Melting points were determined on a hot-stage microscope and are uncorrected. IR spectra were measured with a spectrophotometer as specified in each case. The ^1H and ^{13}C NMR spectra were measured in a spectrometer at 80.13 and 20.15 Mhz respectively. 2D

spectra and N.O.E. difference experiments were measured using standard Bruker software. The chemical shifts are in part per million down from TMS, and the *J* are in Hertz. All the ^{13}C NMR data are included in Tables 2 and 3, the signal assignments were normally based upon signal multiplicities, DEPT, chemical shift rules,[27] comparison with data from the literature,[28] substituent parameters,[26] and a combination of hetero- and homonuclear correlated 2D spectra.[29] All solvents were purified and dried by standard techniques. THF and ethyl ether were distilled from $LiAlH_4$ just before they were used. All reactions were performed in flame dried apparatuses under dry nitrogen. Column chromatography was performed on silica gel 60H, slurry-packed, run under a low pressure of nitrogen, with increasing amounts of ethyl acetate in hexane as eluent. The homogeneity of all intermediates prior to spectral determinations was carefully verified by t.l.c., using the following solvent systems: hexane-ethyl acetate (7:3), chloroform-methanol (9:1), and cyclohexane-ether (6:4) on Merck aluminium plates pre-coated with 0.2 mm of silicagel 60 F-254. Ether (Et_2O) refers to diethyl ether. MMP2 and AM1 calculations were performed on an PC 80486.

General Procedure for the Reductive Alkylations:

Method A: (a) Ammonia (35 mL), was condensed into a flame dried, two-necked round bottom flask equipped with a dry-ice condenser, magnetic stirrer (for volumes of ammonia larger than 100 mL is convenient to use a three-necked round bottom flask and a mechanical stirrer) and maintained at -78°C, under a slight positive pressure of dry nitrogen. (b)A solution of the benzylic ketone (8.2 mmol) and tert-butanol (0.94 mL, 9.8 mmol) in THF or ether (4 mL), was introduced via a double needle, and potassium (703 mg, 18.0.mmol) was then added in small portions and the blue resulting suspension stirred during 15 more min. (c) To this suspension, anhydrous lithium bromide (1.570 mg, 18.0 mmol) was then added and the mixture stirred vigorously for 30 min keeping the temperature at -78°C. d) Finally, methyl iodide (1.04 mL, 16.4 mmol) was added, and the mixture was stirred for 15 min. The cooling bath was removed, and the ammonia was allowed to evaporate. The residue was diluted with brine (20 mL) and ether (20 mL), the pH of the solution was adjusted to 7.5 by careful addition of 10% HCl, the aqueous layer was then separated and extracted with more ether (5x10 mL). The combined ether extract was washed with brine, dried (anhy. Na_2SO_4), filtered and evaporated.

Method B: The procedure for the reductive alkylations with MOMCl, were carried out using ether as co-solvent for the reduction step, to facilitate its elimination as it was necessary to replace the solvent during the alkylation step. The procedure for the Birch reduction followed the same procedure [steps (a), (b), (c) and (d)] as described in Method A. At this point the cooling bath was removed, the ammonia was allowed to evaporate, and the co-solvent (Et_2O) was then removed in a stream of dry nitrogen. Dry benzene or toluene (25 mL) was added and the mixture cooled 0°C, and MOMCl (16.0 mmol, freshly distilled from $CaCl_2$) was added. The mixture was allowed to stir for 15 min and then brine (20 mL) and ether (15 mL) were added. The pH was adjusted to 7.5 by addition of saturated $NaHCO_3$ followed by the usual work-up.

Ketone 5b: Starting from acetophenone, using Method B, (acetophenone, 1 mmol; K, 2.4 mmol; tert-butanol, 1.2 mmol; MOMCl, 2.2 mmol) produced dienone **5b**, 146 mg (88% yield) as a colorless oil. IR (film) ν : 2920, 2870, 2810, 1610, 1420, 1250, 1200, 1120, 1060, 990, 840, 760 cm^{-1}; ^1H NMR (Cl_3CD) δ, 2.15 (3 H, s, CH_3), 2.77 (2 H, m, $w_{1/2}$=6 Hz, C-4 CH_2), 3.32 (3 H, s, OCH_3), 3.52 (2 H, s, CH_2OCH_3), 5.67 (2 H, dt, $J_{5\text{-}6}$=10.7 Hz, $J_{4\text{-}6}$=1.7 Hz, C-2 and C-6 CH), 6.00 (2 H, dt, $J_{5\text{-}6}$=10.7 Hz, $J_{4\text{-}5}$=3.3 Hz, C-3 and C-5 CH); ^{13}C NMR (Cl_3CD) ppm: 25.9 (C-4), 26.7 (CH_3CO), 55.2 (C-1), 58.8 (CH_2OCH_3), 77.2 (CH_2OMe), 125.5 (C-3, C-5), 126.5 (C-2, C-6), 207.2 ($COCH_3$).

Ketone 5c: Starting from acetophenone, using Method A, (acetophenone, 1 mmol; K, 2.4 mmol; tert-butanol, 1.2 mmol; BOMCl, 2.2 mmol) produced dienone **5c**, 211.6 mg (92% yield) as a colorless oil. IR (film) ν: 2900, 2850, 1600, 1450, 1400, 1360, 1250, 1180, 1070, 980, 880, 760 cm^{-1}; ^1H NMR (Cl_3CD) δ, 2.15 (3 H, s, CH_3CO), 2.75 (2 H, m, $w_{1/2}$=8 Hz C-4 CH_2), 3.6 (2 H, s, CH_2OPh), 4.51 (2 H, s, $PhCH_2O$), 5.72 (2 H, dt, *J*=10 and 1Hz, C-2 and C-6 CH), 5.99 (2 H, dt, *J*=10 and 3 Hz, C-3 and C-5 CH), 7.29 (5 H, s, Ph); ^{13}C NMR (Cl_3CD) ppm: 26.2 (C-4), 27.0 (CH_3CO), 55.0 (C-1), 77.2 (CH_2OBn), 81.3 (OCH_2Ph), 125.2 (C-3, C-5), 126.4 (PhCH), 126.8 (PhCH), 126.9 (PhCH), 127.0 (C-2, C-6), 127.4 (PhCH), 127.6 (PhCH), 130.1 (PhC), 208.0 (CH_3CO).

3,4,6,8a-Tetrahydro-8a-methyl-naphthalen-1-(2H)-one (8a): Starting from α-Tetralone **7a**, using the procedure described as Method A, (**7a**, 8.2 mmol; K, 18.0 mmol; tert-butanol, 9.8 mmol; MeI, 16.4 mmol) afforded compound **8a**, 1.09 g (6.7 mmol, 82%) as an oil. IR (film) ν: 2980, 2820, 1600, 1460, 1380, 1280, 1180, 1060, 980, 780 cm^{-1}; ^1H NMR (Cl_3CD) δ, 1.37 (3 H, s, C-8a CH_3), 1.5-2.5 (6 H, m, aliphatic protons), 2.64 (2 H, m, *J*=8.3 Hz, C-6 CH_2), 5.66 (2 H, m, C-5 and C-7 CH), 5.98 (1 H, dt, *J*=10.4 and 1.2 Hz, C-8H); ^{13}C NMR (Cl_3CD) ppm: 24.7 (C-3), 26.1 (C-6), 26.6 (8a CH_3), 30.5 (C-2), 37.6 (C-4) 50.4 (C-8a), 119.6 (C-5), 122.6 (C-7), 128.3 (C-8), 130.2 (C-4a), 211.6 (C-1).

3,4,6,8a-Tetrahydro-8a-methoxymethyl-naphthalen-1-(2H)-one (8b): Starting from α-Tetralone **7a** Method B was used. (Ketone **7a**, 1040 mg 7.1 mmol; K, 694 mg, 17.8 mmol; tert-butanol 8 mL, 8.5 mmol; MOMCl 16.2 mmol) produced compound **8b**, 1.04 g (5.4 mmol, 76%) as a yellowish oil. IR (film) ν: 2950, 2870, 1630, 1450, 1250, 1210, 1120, 1060, 980, 820, 760 cm^{-1};^1H NMR (Cl_3CD) δ, 1.6-2.5 (6 H, m, aliphatics), 2.62 (2 H, m, $w_{1/2}$=8.6 Hz, C-6 CH_2), 3.30 (3 H, s, OCH_3), ABq, centered at 3.60, Δδ=0.20, J_{AB}=9.0 Hz, (2H, -$\underline{CH_2}OCH_3$), 5.7 (2 H, m, C-5, C-7CH), 6.02 (1 H, dt, *J*=10 and 2 Hz, C-8H); ^{13}C NMR (Cl_3CD) ppm: 24.9 (C-3), 26.0 (C-6), 30.9 (C-2), 38.1 (C-4), 52.3 (C-8a), 59.0 (CH_2OCH_3), 76.7 (CH_2OCH_3), 120.2 (C-5), 122.8 (C-7), 128.6 (C-8), 129.7 (C-4a), 208.0 (C-1).

1,2,3,4,6,8a-Hexahydro-8aβ-methoxymethyl-naphth-1β-ol acetate (11): To ketone **8b** (787.2 mg, 4.1 mmol) in cold methanol (20 mL) was added portionwise $NaBH_4$ (150 mg, 4.1 mmol) and the mixture was stirred until the reaction was completed

ca. 30 min. The excess of reducing agent was destroyed by addition of water (4 mL and brine 40 mL), the mixture was extracted with ether (5x15 mL), the combined ether extract was dried, filtered and evaporated, affording the crude alcohol (779 mg, 4.0 mmol, 98%) as colorless oil. IR (film) ν: 3450, 2910, 2880, 2820, 1460, 1440, 1230, 1060, 1040, 980, 710 cm^{-1}; ^1H NMR (Cl_3CD) δ, 1.4-2.0 (6 H, m, aliphatics), 2.66 (2 H, m, $w_{1/2}$=8 Hz, C-6 CH_2), 3.34 (3 H, s, OCH_3), 3.45 (1 H, m, $w_{1/2}$=15 Hz, C-1 CHOH), ABq, centered at 3.73, Δδ=0.55, J_{AB}=9.1 Hz, (2 H, -CH_2OCH_3), 5.80 (2 H, m, C-5, C-7H), 6.23 (1 H, dt, J=10 and 2 Hz, C-8H); ^{13}C NMR (Cl_3CD) ppm: 24.7 (C-6), 26.5 (C-2), 31.6 (C-4), 31.8 (C-3), 45.1 (C-8a), 59.3 (OCH_3), 76.1 (CH_2OCH_3), 77.6 (C-1), 120.7 (C-5), 123.4 (C-7), 128.9 (C-8), 136.4 (C-4a). To the dried (0.05 Torr, 3 h) alcohol (360 mg, 1.8 mmol) in pyridine (5 mL) cooled (0°C) was added Ac_2O (0.25 mL, 0.27 mg, 2.6 mmol), and DMAP catalytic amount, the reaction mixture was stirred over night, poured into cold (0°C) 10% HCl solution (25 mL), and extracted with ether (5x15 mL). The combined ether extract was washed with 10% $CuSO_4$ solution (2x20 mL) and water, dried (anhy., Na_2SO_4), filtered and evaporated affording acetate **11** (436.4 mg, 1.8 mmol, 98%) as a clear oil (solidifies in the freezer). IR (film) ν: 2950, 2880, 2820, 1740, 1450, 1390, 1250, 1210, 1120, 1060, 980, 940, 820, 760 cm^{-1}; ^1H NMR (Cl_3CD) δ, 1.6-2.1 (6 H, m, aliphatics), 2.05 (3 H, s, AcO), 2.66 (2 H, m, $w_{1/2}$=8 Hz, C-6 CH_2), 3.35 (3 H, s, OCH_3), ABq, centered at 3.64, Δδ=0.51, J_{AB}=9.0 Hz (2 H, -CH_2OCH_3), 4.72 (1 H, m, $w_{1/2}$=17 Hz, C-1H); ^{13}C NMR (Cl_3CD) ppm: 21.0 (CH_3CO_2), 24.7 (C-6), 26.7 (C-2), 27.6 (C-3), 31.5 (C-4), 44.7 (C-8a), 59.6 (CH_2OCH_3), 73.9 (CH_2OCH_3), 78.3 (C-1), 121.5 (C-5), 125.5 (C-7), 128.1 (C-8), 136.1 (C-4a), 170.1 (CH_3CO_2). Anal. calc. for $C_{14}H_{20}O_3$: H, 8.54; C, 71.14. Found H, 8.70; C, 70.96.

5β-Acetoxy-4a,5,6,7-tetrahydro-4aβ-methoxymethyl-naphthalen-2-(8H)-one (12): To a solution of acetate **11** (798 mg, 3.4 mmol) in benzene (31 mL) was added pyridinedichromate (PDC) (3.16 g, 8.4 mmol), tert-butylhydroperoxide (1.55 mL, 16.9 mmol) and Celite (2.5 g). The suspension was stirred vigorously at rt until tlc indicates that the reaction was complete ca. 6 h. The suspension was filtered, washed with ether and the filtrate evaporated affording **12** (729 mg, 2.9 mmol, 85%) as a white solid. IR (KBr) ν: 2950, 2910, 1750, 1690, 1480, 1430, 1380, 1250, 1120, 1040, 930, 890, 860 cm^{-1}; ^1H NMR (Cl_3CD) δ, 1.2-2.0 (6 H, m, aliphatics), 2.11 (3 H, s, AcO), 3.27 (3 H, s, OCH_3), ABq, centered at 3.85, Δδ=0.36, J_{AB}=9.0 Hz (2 H, -CH_2OCH_3), 4.63 (1 H, m, $W_{1/2}$=17 Hz, C-1 CHOH), 6.24 (1 H, brs, $w_{1/2}$=3 Hz, C-5H), 6.33 (1 H, dd, J=10 and 1.8 Hz, C-7H), 6.87 (1 H, d, J=10 Hz, C-8H); ^{13}C NMR (Cl_3CD) ppm: 20.5 (CH_3CO_2), 23.9 (C-3), 26.6 (C-4), 31.5 (C-2), 49.1 (C-8a), 59.2 (CH_2OCH_3), 72.0 (CH_2OCH_3), 76.5 (C-1), 127.6 (C-7), 130.0 (C-5), 149.9 (C-4a), 160.4 (C-8), 169.3 (CH_3CO_2), 185.8 (C-6).

Trans-5β-acetoxy-3,4,4a,5,6,7,8,8a-octahydro-4aβ-methoxymethyl-naphthalen-2-(1H)-one (13): To a solution of dienone acetate **12** (80 mg, 0.3 mmol) in ethanol (15 mL) was added freshly prepared Raney-nickel (two tea spoons) and the mixture was stirred under hydrogen atm. (30 Psi) overnight. The catalyst was then filtered and the solvent eliminated under reduced pressure, affording **13** (82 mg, 100%), as a colorless solid, m.p. 130.5-131°C (from isopropyl ether). IR (KBr) ν: 2940, 2900, 1750, 1610, 1460, 1380, 1200, 1120, 1080, 960, 800, 780 cm^{-1}; ^1H NMR (Cl_3CD) δ, 1.2-2.4 (13 H, m, aliphatics), 2.07 (3 H, s, AcO), 3.33 (3 H, s, OCH_3), ABq, centered at 3.55, Δδ=0.43, J_{AB}=9.0 Hz, (2 H, -CH_2OCH_3), 5.15 (1 H, m, $W_{1/2}$=16 Hz, C-1HOAc); ^{13}C NMR (Cl_3CD) ppm: 19.3 (C-3), 20.6 (CH_3COO-), 25.6 (C-7), 27.0 (C-2, C-5), 35.7 (C-4a), 36.8 (C-4), 39.7 (C-8a), 43.0 (C-8), 58.9 (-CH_2OCH_3), 71.2 (C-1), 72.8 (-CH_2OCH_3), 169.7 (CH_3COO-), 210.7 (C-6). Anal. calc. for $C_{14}H_{22}O_4$: H, 8.72; C, 66.10. Found H, 8.60; C, 66.21.

4-[(2'-Methoxymethyl-5'-hydroxy-phenyl)]-butanal (14): A solution of dienone acetate **12** (50 mg, 0.2 mmol) in methanol (2 mL) and K_2CO_3 (86 mg, 0.6 mmol) was stirred 1 h at rt. The mixture was poured into water (20 mL) and extracted with ether-ethyl acetate, washed with brine, dried (anhy. Na_2SO_4), filtered and evaporated, affording **14** (39 mg, 0.2 mmol, 94 %) as an oil. ^1H NMR (Cl_3CD) δ, 1.28 (1 H, m), 1.89 (2 H, m), 2.56 (3 H, m), 3.36 (3 H, s, -OCH_3), 4.38 (2 H, s, -CH_2OCH_3), 5.62 (1 H, brs), 6.53-6.67 (2 H, m, ArH), 7.09-7.20 (1 H, m, ArH), 9.76 (1 H, t, HCO); ^{13}C NMR (Cl_3CD) ppm: 23.09 (CH_2), 31.26 (CH_2), 43.10 (CH_2), 57.50 (OCH_3), 72.34 (-OCH_2-), 112.86 (=CH-), 116.36 (=CH-), 127.09 (=CCH_2CH_2-), 131.48 (=CH-), 142.09 (=$CHCH_2OCH_3$-), 155.99 (=COH-), 202.95 (-HCO).

2-Ethylenedioxy-1,2,3,4,4a,10aα-hexahydro-4aβ-methyl-phenanthren-9-(10H)-one (15b): Starting from protected (ethylenedioxy) 4a-methyl-hexahydro-phenanthren-2-one[21] (1.06 g, 4.1 mmol). To a solution of the protected ketone, in benzene (50 mL), PDC (9.2 g, 24.6 mmol), 66% tert-butylhydroperoxide (2.76 g, 24.6 mmol) and Celite (6.2 g) were added. The mixture was stirred vigorously at rt. for ca. 9 h. The dark suspension was then filtered, and the filtrate evaporated under vacuo producing the benzylic ketone **15b**, (846.8 mg, 3.1 mmol, 76%) as a yellowish oil. IR (film) ν: 2944, 2880, 1683, 1597, 1477, 1259, 1081, 748 cm^{-1}; ^1H NMR (Cl_3CD) δ, 1.21 (3 H, s, 4a-Me), 1.6-2.4 (7 H, m, aliphatics), 2.52 (2 H, m, C-10H), 3.97 (4 H, s, OCH_2CH_2O), 7.2-7.6 (3 H, m, ArH), 8.04 (1 H, dt, C-8H); ^{13}C NMR (Cl_3CD) ppm: 19.4 (4a-Me), 30.8 (C-1), 33.8 (C-3), 35.7 (C-4a), 36.9 (C-4), 38.1 (C-10a), 40.8 (C-10), 63.7 and 63.8 (OCH_2CH_2O), 107.5 (C-2), 123.9 (C-5), 125.9 (C-6), 127.1 (C-7), 130.9 (C-8a), 133.2 (C-8), 153.0 (C-4b), 196.8 (C-9).

1,2,3,4,4a,6,8a,10aα-Octahydro-8aα-methoxymetyl-4aβ-methyl-phenanthren-9-(10H)-one (16): According to Method B (ketone **15a**, 320 mg, 1.5 mmol; K, 128.7 mg, 3.3 mmol; NH_3, 15 mL; THF, 3 mL; tert-butanol, 0.12 mL, 1.8 mmol; LiBr, 287 mg, 3.3 mmol; benzene, 7 mL, MOMCl, 265.6 mg, 3.3 mmol) produced, after chromatography, pure **16** (253.5 mg, 0.9 mmol, 65%) ^1H NMR (Cl_3CD) δ, 0.84 (3 H, s, 4a-Me), 1.3-2.3 (m, aliphatics), 2.68 (m, C-6 CH_2), 3.25 (3 H, s, OCH_3), ABq, centered at 3.47, Δδ=0.54, J_{AB}=9.0 Hz, (2 H, -CH_2OCH_3), 5.92 (2 H, m, C-5 and C-7-CH), 6.56 (1 H, dt, J=10 and 2Hz, C-8H); ^{13}C NMR (Cl_3CD) ppm: 20.9 (4a-Me), 21.9 (C-2), 25.8 (C-3), 27.2 (C-6), 28.3 (C-1), 37.5 (C-10a), 37.8 (C-4a), 37.9 (C-10), 42.2 (C-4), 55.5 (C-8a), 59.3 (OCH_3), 79.1 (CH_2O), 120.3 (C-5), 125.0 (C-7), 129.0 (C-8), 147.6 (C-4b), 210.0 (C-9).

4aβ, 8aα- and 4aβ, 8aβ-Dimethyl-2-ethylenedioxy-1,2,3,4,4a,6,8a,10aα-octahydrophenanthren-9-(10H)-ones (18a) and **(19a)**: The reductive alkylation of **15b** according to Method A (**15b**, 540 mg, 1.9 mmol: THF, 3 mL; NH_3, 20 mL; K, 184 mg, 4.7 mmol; LiBr, 411 mg, 4.7 mmol; tert-butanol, 0.35 mL, 3.7 mmol; MeI, 0.6 mL, 10 mmol) afforded a mixture of **18a** and **19a** (525 mg, 1.7 mmol 92%). After column chromatography, pure **18a** (468 mg, 1.5 mmol 82%), was obtained as a colorless oil. IR (film) ν: 2980, 2960, 1720, 1480, 1460, 1390, 1300, 1180, 1110, 1060, 1020, 920, 740 cm^{-1}; ^1H NMR (Cl_3CD) δ, 0.89 (3 H, s, 4a-Me), 1.31 (3 H, s, 8a-Me), 1.5-2.0 (6 H, m, aliphatics), 2.08 (1 H, d, *J*=11 Hz, C-10βH), 2.3 (1 H, d, *J*=11 Hz, C-10αH), 2.66 (2 H, m, $W_{1/2}$=8 Hz, C-6 CH_2), 3.96 (4 H, s, OCH_2CH_2O), 5.74 (1 H, t, *J*=4 Hz, C-5H), 5.82 (1 H, td, *J*=10 and 4 Hz, C-7H), 6.42 (1 H, dt, *J*=10 and 1.4 Hz, C-8H); ^{13}C NMR (Cl_3CD) ppm: 20.0 (4a-Me), 26.7 (C-6), 28.2 (8a-Me), 31.1 (C-3), 34.4 (C-10a), 35.5 (C-1), 37.0 (C-4), 38.0 (C-4a), 40.8 (C-10), 49.3 (C-8a), 64.1 (OCH_2CH_2O), 108.2 (C-2), 119.5 (C-5), 123.5 (C-7), 130.8 (C-8), 149.2 (C-4b), 211.4 (C-9).

2-Ethylenedioxy-1,2,3,4,4a,6,8a,10aα-octahydro-1α,4aβ,8aα-trimethyl-phenanthren-9-(10H)-one (20a): According to the procedure described under Method A, (ketone **15c**, 540 mg, 1.9 mmol; K, 184 mg, 4.7 mmol; THF, 3 mL; NH_3, 20 mL; LiBr, 410 mg, 4.7 mmol; tert-butanol, 0.35 mL, 3.7 mmol; MeI, 0.6 mL, 10 mmol), afforded compound **20a**, (525 mg, 1.7 mmol, 92%) as an oil. ^1H NMR (Cl_3CD) δ, 0.84 (3 H, d, *J*=7 Hz, 1-Me), 0.88 (3 H, s, 4a-Me), 1.29 (3 H, s, 8a-Me), 1.5-2.4 (m, aliphatics), 2.65 (2 H, m , $W_{1/2}$=9 Hz, C-6 CH_2), 3.96 (4 H, s, OCH_2CH_2O), 5.74 (1 H, t, *J*=4.6 Hz, C-5H), 5.86 (1 H, td, *J*=10 and 3.8 Hz, C-7H), 6.42 (1 H, dt, *J*=10 and 1.8 Hz, C-8H); ^{13}C NMR (Cl_3CD) ppm: 9.94 (1-Me), 21.0 (4a-Me), 26.5 (C-6), 27.5 (8a-Me), 30.7 (C-3), 34.7 (C-10), 37.6 (C-4a), 39.2 (C-4), 39.7 (C-1), 40.3 (C-10a), 64.5 (OCH_2CH_2O), 109.5 (C-2), 118.6 (C-5), 123.4 (C-7), 130.4 (C-8), 149.7 (C-4b), 211.6 (C-9).

2-Ethylenedioxy-1,2,3,4,4a,6,8a,10aα-octahydro-8aα-methoxymethyl-1α,4aβ-dimethyl-phenanhren-9-(10H) -one (20b): Following the procedure described in Method B, (ketone **15c**, 1.58 g, 5.5 mmol; K, 540 mg, 13.8 mmol; ether, 6 mL; NH_3, 30 mL; LiBr, 1.2 g ; tert-butanol, 0.63 mL, 6.7 mmol; MOMCl, 0.7 mL, 7.8 mmol), afforded after column chromatography, pure **20b**, (1.46 g, 4.4 mmol, 80%) white crystals, m.p. 144.5-145.2°C (from isopropyl ether). IR (film) ν: 2920, 2880, 1650, 1460, 1380, 1180, 1100, 1080, 1020, 960, 780 cm^{-1}; ^1H NMR (Cl_3CD) δ, 0.86 (3 H, d, *J*=6.5 Hz, 1-Me), 0.9 (3 H, s, 4a-Me), 1.4-2.3 (m, aliphatics), 2.66 (2 H, m, $W_{1/2}$=8 Hz, C-6 CH_2), 3.24 (3 H, s, -OCH_3), ABq, centered at 3.47, Δδ=0.67, J_{AB}=9.0 Hz, (2 H, -$\underline{CH_2}OCH_3$), 3.95 (4 H, s, OCH_2CH_2O), 5.76 (1 H, t, *J*=4 Hz, C-5H), 6.00 (1 H, td, *J*=10 and 4 Hz, C-7H), 6.56 (1 H, dt, *J*=10 and 2 Hz, C-8H); ^{13}C NMR (Cl_3CD) ppm: 10.1 (1-Me), 21.1 (4a-Me), 27.3 (C-6), 30.9 (C-3), 34.5 (C-10), 37.7 (C-4a), 40.4 (C-1), 40.6 (C-4), 41.1 (C-10a), 55.3 (C-8a), 59.4 (OCH_3), 64.8 (OCH_2CH_2O), 78.8 (CH_2OCH_3), 109.8 (C-2), 120.7 (C-5), 124.9 (C-7), 129.0 (C-8), 146.8 (C-4b), 209.8 (C-9). EIMS m/z (relative intensity): (Found: M^+, 332.1978. $C_{20}H_{28}O_4$ requires M, 332.1987). Anal. calc. for: $C_{20}H_{28}O_4$: H, 8.49; C, 72.25. Found: H, 8.63; C, 72.15.

Catalytic hydrogenation of **20b**: A solution of **20b** (50 mg, 0.15 mmol) in ethanol (10 mL), and 10% Pd/C (20 mg) was stirred under an hydrogen atm. (40 Psi) overnight. The catalyst was filtered through a Celite pad and the solvent evaporated affording the saturated ketone (52 mg, 0.15 mmol, 100%). IR (film) ν: 2910, 2843, 1700, 1450, 1230, 1180, 1120, 1060, 780 cm^{-1}; ^1H NMR (Cl_3CD) δ, 0.77 (3 H, d, *J*=6 Hz, 1-Me), 0.83 (3 H, s, 4a-Me), 1.5-1.8 (16 H, m, aliphatics), 2.4 (1 H, dd, *J*=10.and 8 Hz, C-10αH), 3.24 (3 H, s, -OCH_3), ABq, centered at 3.43, Δδ=0.20, J_{AB}=9.6 Hz, (2 H,-$\underline{CH_2}OCH_3$), 3.92 (4 H, s, OCH_2CH_2O-); ^{13}C NMR (Cl_3CD) ppm: 9.9 (1-Me), 14.2 (4a-Me), 17.9 (C-6), 20.1 (C-7), 20.3 (C-8), 24.9 (C-3), 30.4 (C-5), 36.0 (C-4a), 36.2 (C-10), 40.1 (C-4a), 40.8 (C-4), 44.3 (C-1), 49.6 (C-4b), 51.2 (C-8a), 59.0 (OCH_3), 64.6 and 64.9 (OCH_2CH_2O), 77.2 (CH_2OCH_3), 109.9 (C-2), 215.8 (C-9).

2-Ethylenedioxy-1,2,3,4,4a,10aβ-hexahydro-4aβ-methyl-phenanthren-9-(10H)-one (23): Starting from 4a-methyl-4,4a,9,10-tetrahydrophenanthren-2-(3H)-one.[21] To the α,β-unsaturated ketone (3.5 g, 16.5 mmol) dissolved in benzene (150 mL), was added p-TsOH (0.35 g, 1.8 mmol) and ethylene glycol (8.0 mL) and the mixture refluxed under a Dean-stark trap until complete water separation. The reaction was then cooled, poured into cold (0°C) brine (100 mL), extracted with ether (3x70 mL). The combined ether extract was dried (anhy., Na_2SO_4), filtered and evaporated affording **21**, 4.04 g (95%) as colorless needles, m.p. 71.0-72.0°C (from methanol). ^1H NMR (Cl_3CD) δ, 1.42 (3 H, s, 4a-Me), 1.7-3.0 (6 H, m, aliphatics), 3.41 (2 H, t, benzylic), 3.95 (4 H, s, OCH_2CH_2O), 5.53 (1 H, m, vinylic), 6.9-7.3 (4 H, m, ArH). EIMS m/z (relative intensity): 256 (M^+, 0.87), 197 (1.4), 167 (1.6), 156 (2.1), 155 (5.5), 141 (9), 128 (3.8), 100 (13), 99 (100), 77 (2.9), 55 (14).

The protected ketone was oxidized using the CrO_3-3,5-DMP complex.[30] To a cooled (-20°C) suspension of CrO_3 (1.2 g, 12 mmol) in dry CH_2Cl_2 (15 mL) was added at once 3,5-DMP (1.16 g, 12 mmol). The mixture was allowed to stir 15 min. and then, ketal **21** (310 mg, 1.2 mmol) was added. After completion (t.l.c.) the solvent was evaporated under vacuum and the residue, suspended in ether (3x20 mL), was filtered and the solvent evaporated. The crude product was purified by column chromatography, yielding the α,β-unsaturated ketone **22** (240.4 mg, 0.9 mmol, 89%). ^1H NMR (Cl_3CD) δ, 1.53 (3H, s, 4a-Me), 1.7-2.5 (4 H, m, C-3H and C-4H), 2.7 (1 H, dd, *J*=16 and 2 Hz, C-1βH), 2.93 (1 H, dd, *J*=16 and 2 Hz, C-1αH), 3.99 (4 H, s, OCH_2CH_2O-), 6.29 (1 H, d, *J*= 2 Hz, C-10H), 7.3-7.6 (3 H, m, ArH), 8.18 (1 H, dt, C-8H); ^{13}C NMR (Cl_3CD) ppm: 26.1 (4a-Me), 30.8 (C-3), 35.5 (C-4), 39.7 (C-4a), 42.3 (C-1), 64.3 (OCH_2CH_2O-), 108.9 (C-2), 125.6 (C-5), 126.0 (C-7), 126.2 (C-6), 126.4 (C-8), 130.1 (C-8a), 132.2 (C-10), 150.5 (C-4b), 162.6 (C-10a), 184.1 (C-9). EIMS m/z (relative intensity): 270 (M^+, 2.8), 242 (0.5), 211 (0.3), 171 (0.8), 165 (1.7), 152 (1.6), 141 (5.4), 115 (4.4), 99 (100), 55 (8.5).

The α,β-unsaturated ketone **22** (2.0 gr, 7.4 mmol) was submitted to a Birch reduction [NH_3 (50 mL); Li (125.3 mg; 17.9 mmol); THF (15 mL); tert-butanol (0.7 mL, 7.4 mmol)] affording, after column chromatography pure **15b** (7.0%) and **23** (1.28 g, 64%). Compound **23**, white needles, m.p. 79.0-80.2°C (from isopropyl ether). IR (KBr) ν: 2926, 2867, 1686, 1475, 1365, 1143, 1094, 1044, 889, 747 cm^{-1}; ^1H NMR (Cl_3CD) δ, 1.36 (3 H, s, 4a-Me), 3.1 (1 H, dd, *J*=15 and 5 Hz, C-10αH), 3.91 (4 H, s,

OCH_2CH_2O-), 7.2-7.6 (3 H, m, ArH), 8.05 (1 H, dt, C-8H); ^{13}C NMR (Cl_3CD) ppm: 31.36 (C-1), 30.84 (4a-Me), 34.39 (C-3), 37.38 (C-4a), 37.83 (C-4), 40.38 (C-10a), 40.90 (C-10), 64.14 and 64.08 (OCH_2CH_2O-), 108.54 (C-2), 125.68 (C-5), 126.35 (C-6), 127.5 (C-7), 131.71 (C-8a), 134.13 (C-8), 147.28 (C-4b), 197.18 (C-9). Anal. calc. for: $C_{17}H_{20}O_3$: H, 7.41; C, 74.96. Found: H, 7.53; C, 74.80.

1,2,3,4,4a,10aβ-Hexahydro-3α-methoxymethoxy-4aβ-methyl-phenanthren-9-(10H)-one (25): Starting from the protected (R=MOM) 10aβ-octahydro phenanthren-3α-ol[13] (100 mg, 0.4 mmol), in benzene (7 mL), were added PDC (360 mg, 1.0 mmol), tert-butylhydroperoxide (0.17 mL, 1.9 mmol) and Celite (280 mg). The suspension was stirred at r.t. for 48 h. The resulting dark suspension was filtered, washed over the filter with ether. The filtrate was evaporated affording the ketone **23**, (90.5 mg, 0.3 mmol, 87%) as a light yellow oil. ^1H NMR (Cl_3CD) δ, 1.47 (3 H, s, 4a-Me), 1.56-2.13 (7 H, m, aliphatics), 2.60-2.92 (2 H, m, $-CH_2CO$-), 3.31 (3 H, s, $-OCH_3$), 3.96 (1 H, brm, -CHOMOM-), 4.60 (2 H, dd, $-OCH_2OCH_3$), 7.06-7.38 (3 H, m, ArH), 8.13 (1 H, dd, ArH); ^{13}C NMR (Cl_3CD) ppm: 25.25 (C-1), 26.99 (C-4a Me), 27.30 (C-2), 37.91 (C-4a), 38.28 (C-10a), 40.11 (C-10), 41.05 (C-4), 54.77 (-OMe), 94.17 ($-OCH_2O$-), 125.76 (C-6), 126.30 (C-5), 126.41 (C-7), 130.25 (C-8a), 133.43 (C-8), 198.12 (C-9). EIMS m/z (relative intensity): 274 (M^+, 1.5), 214 (15), 200(7), 199(24), 197(14), 185(10), 183(7), 172(11), 171(13), 154(8), 153(24), 152(14), 150(11.4), 145(11.6), 144(8), 143(13), 142(5.5), 141(10), 131(14), 130(5.5), 129(16), 128(14), 127(5.5) 117(10), 115(16), 91(11), 77(7), 55(8), 45(100); (Found: M^+, 274.1582. $C_{17}H_{22}O_3$ requires M, 274.1569).

8aα- and 8aβ-Methoxymethyl-1,2,3,4,4a,6,8a,10aβ-octahydro-3α-methoxymethoxy-4aβ-methyl-phenanthren-9-(10H)-ones (26) and **(27)**: The procedure described in Method B was used. (ketone **25**, 309 mg, 1.1 mmol; K, 171mg, 4.4 mmol; tert-butanol, 0.22 mL, 2.3 mmol; ether 5 mL; NH_3, 10 mL; LiBr 383 mg; benzene 6.1 mL; MOMCl 0.45 mL, 0.4 mmol), affording after column chromatography pure **27** (175.8 mg, 0.5 mmol, 51%), and pure **26** (55 mg, 0.2 mmol, 15%). Compound **27**, ^1H NMR (Cl_3CD) δ, 1.32 (3 H, s, 4a-Me), 1.40-2.40 (9 H, m, aliphatic), 2.68 (2 H, m, allylic), 3.23 (3 H, s, $-CH_2OCH_3$), 3.37 (3 H, s, $-OCH_2OCH_3$), ABq, centered at 3.34, $\Delta\delta$=0.32, J_{AB}=8.0 Hz (2 H, $-CH_2OCH_3$), 4.68 (2 H, s, $-OCH_2OCH_3$), 5.91 (3 H, brs, vinylic); ^{13}C NMR (Cl_3CD) ppm: See Table 2.

Compound **26**, ^1H NMR (Cl_3CD) δ, 1.28 (3 H, s, 4a-Me), 1.30-2.26 (9 H, m, aliphatic), 2.69 (2 H, m, allylic), 3.25 (3 H, s, $-CH_2OCH_3$), 3.37 (3 H, s, $-OCH_2OCH_3$), ABq, centered at 3.61, $\Delta\delta$=0.53, J_{AB}=9.6 Hz (2 H, $-CH_2OCH_3$), 4.68 (2 H, s, $-OCH_2OCH_3$), 5.91 (2 H, m, vinylic), 6.41 (1 H, dt, vinylic); ^{13}C NMR (Cl_3CD) ppm: See Table 2.

1,2,3,4,4a,6,7,8,8a,10aβ-Decahydro-3α-methoxymethoxy-8aα-methoxymethyl-4aβ-methyl-phenanthren-9-(10H)-one (26a): To a solution of **26** dissolved in ethyl acetate (176 mL/mmol) was added 10% Pd/C (50 mg) and the suspension was then stirred under a hydrogen atm. (30 Psi) overnight. The catalyst was filtered and the solvent evaporated under vacuo producing **26a** (72.6%) as colorless needles. ^1H NMR (Cl_3CD) δ, 1.21 (3 H, s, 4a-CH_3) 1.30-2.30 (15 H, m, aliphatic), 3.27 (3 H, s, $-CH_2OCH_3$), 3.37 (3 H, s, $-OCH_2OCH_3$), ABq, centered at 3.70, $\Delta\delta$=0.42, J_{AB}=9.1 Hz (2 H, $-CH_2OCH_3$), 4.67 (2 H, s, $-OCH_2OCH_3$), 5.75 (1 H, t, allylic); ^{13}C NMR (Cl_3CD) ppm: See Table 2. Anal. calc. for: $C_{19}H_{30}O_4$: H, 9.38; C, 70.76. Found: H, 9.50; C, 70.76.

1,2,3,4,4a,6,7,8,8a,10aβ-Decahydro-3α-methoxymethoxy-8aβ-methoxymethyl-4aβ-methyl-phenanthren-9-(10H)-one (27a): Following the same procedure **27** gave **27a** (64%). ^1H NMR (Cl_3CD) δ, 1.23 (3 H, s, 4a-CH_3), 1.30-2.33 (15 H, m, aliphatic), 3.24 (3 H, s, $-CH_2OCH_3$), 3.35 (3 H, s, $-OCH_2OCH_3$), 3.53 (2 H, s, $-CH_2OCH_3$), 4.65 (2 H, s, $-OCH_2OCH_3$), 5.79 (1 H, t, allylic); ^{13}C NMR (Cl_3CD) ppm: See Table 2.

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