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SYNTHETIC STUDIES ON *trans*-CLERODANE DITERPENOIDS AND CONGENERS : STEREOCONTROLLED TOTAL SYNTHESIS OF (±)-4-METHYLENE-9α-(3-OXOBUTYL)-5β,8β,9β-TRIMETHYL-*trans*-DECALIN AND RELATED INTERMEDIATES[1].

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Abstract: A stereocontrolled total synthesis of the title compound, a marine natural product as well as a degradation product of sigmosceptrellins and palauolide, has been accomplished by a simple route broadly applicable to certain *trans*-clerodanes and congeners. In addition, the synthesis of two key degradation products of ilimaquinone, which can serve as *trans*-clerodane precursors, and 4,4-ethylenedioxy-9α-(2-hydroxyethyl)-5β,8β,9β-trimethyl-*trans*-decalin, an intermediate employed earlier in a total synthesis of (±)-annonene, are described.

Several clerodane diterpenoids[2,3] and many of the structurally related[4] marine products like avarol (1) and its derivatives (2a/2b)[5], sigmosceptrellins (3)[6], arenarol and arenarone (4a/4b)[7], palauolide (5)[8], PR 1421 (6a) and PR 1389 (6b)[9], agelasine-A (7a) and -B (7b)[10], are known to exhibit interesting physiological properties such as insect-antifeedant, insecticidal, ichthyotoxic, antibiotic or cytotoxic activity. Because of their wide association with antifeedant property, clerodane diterpenoids have received considerable synthetic interest, resulting in a few total syntheses[11] as well as preparation of several structural analogues[12]. Earlier, we reported[13] a stereocontrolled total synthesis of 1, based on a general methodology of potential applicability for the construction of functionalized bicyclo/‾4.4.0_7decane skeleton present in several other members in this series. The present paper deals with our studies on an extension of this approach to *trans*-clerodanes[1]. A stereocontrolled total synthesis of the title compound 15 which is a marine natural product[6] as well as a degradation product of sigmosceptrellins[6]

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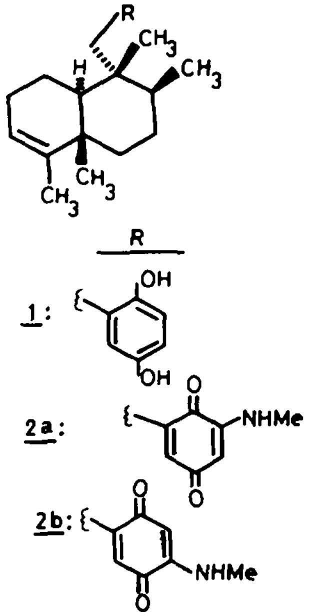
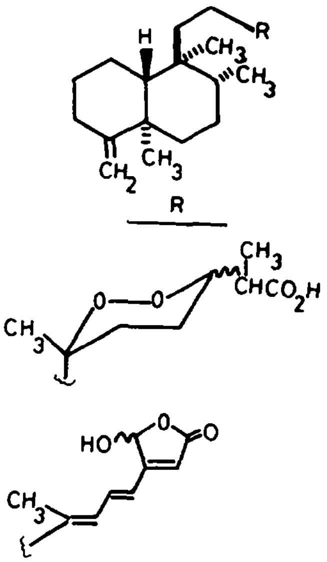
and palauolide[8], and the synthesis of a few *trans*-clerodane precursors (eg., 10e, 11c, 13b, and 14b) are described herein.



1:

2a:

2b:



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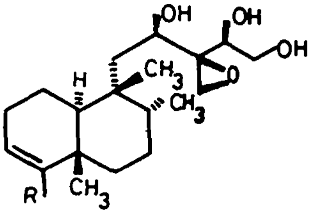
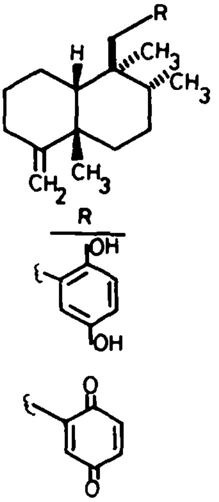


R

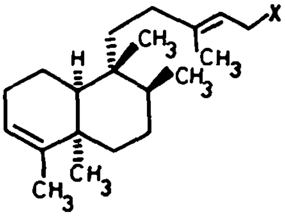
6a: CHO

6b: CH_2OH



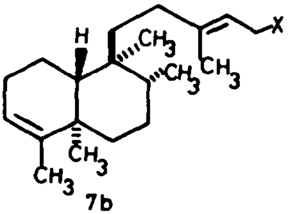
4a:

4b:



7a

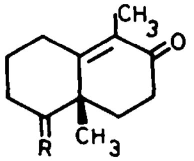
7a/7b: X = heterocyclic moiety.



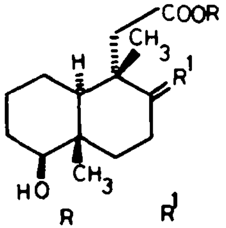
7b

Results and Discussion

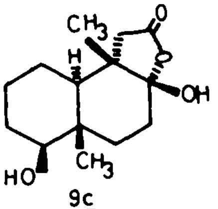
The main transformations (8a → 9a → 9d → 10a) are similar to those employed in the synthesis of avarol[13]; certain modifications in procedures were however, necessary. The product from reductive alkylation of ene-ketal (8a) with ethyl bromoacetate was purified by hydrolysis followed by esterification (CH_2N_2) of the resulting crude acid 9b, to obtain the keto-ester 9a in 50% overall yield. The compound exhibited two strong C=O bands at 1730 and 1700 cm^{-1} in the IR spectrum, indicating respectively, the presence of an ester and a six-membered ketone groups. In ^{1}H NMR (200 MHz) spectrum keto-ester 9a showed two clean Me-singlets at δ 1.04 and 1.08, and a sharp COOMe singlet at δ 3.63, thereby confirming it's structure. The assigned stereochemistry of 9a, has been confirmed through its transformation to 10f (vide infra). The purified 9b exhibited a single carbonyl IR band at 1755 cm^{-1}, indicating that it is possibly existing in γ-lactol from 9c. However, its smooth reaction with diazomethane leading to the keto-ester 9a† as the only isolable product, clearly indicated its ready equilibration with 9b in solution. It may be noted that reductive alkylation of ketal 8b with methyl bromoacetate was reported[14] to afford some intractable high-boiling products.



R
8a: β-OH, α-H
8b: -OCH$_2$CH$_2$O-



	R	R^1
9a:	CH$_3$	O
9b:	H	O
9d:	CH$_3$	CH$_2$



9c

Initial attempts on Wittig-methylenation of keto-ester 9a under different conditions were quite frustrating. It may noted that a ketone similar to 9a (with an allyl substituent at C-9, instead of acetic acid side chain) failed to undergo methylenation under usual conditions[14], and in our synthesis of 1, the corresponding reaction was effected under somewhat stronger conditions (7 moles of ylide, 80°C, 40 h) so as to overcome steric problems. Under these conditions, only a 11% yield of the desired olefin (9d) was obtained in one experiment which could not be reproduced. Even under several modified conditions, no tangible products could be isolated, although the starting material was partly recovered in some cases. Since these failures could be due to side-reactions[15] involving ester function of 9a, further attempts were made based on methods which are expected to improve normal olefination, such as the use of a milder base to generate the ylide, or an inverse-addition of ylide to substrate. However, none of these methods gave satisfactory results, although in one case, the desired product was obtained in a poor yield (see Experimental).

Next, we turned our attention to Wittig-reaction under salt-free conditions. As evident from a recent report[16], it is desirable to use a less polar solvent in such cases (particularly while using phosphonium iodides) so as to minimize the presence of dissolved inorganic salt in the reaction medium. While employing methyltriphenylphosphonium iodide as the Wittig-salt, we followed cartain modifications in our earlier procedure, including a change of solvent. In this event, the desired olefin (9d) was finally obtained in 50% yield.

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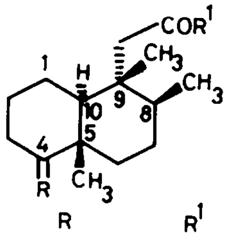
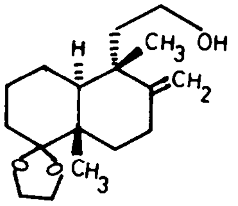
† It should be mentioned that on standing at room temperature for a few months in the presence of moisture, keto-ester 9a slowly hydrolysed to the respective γ-lactol 9c.

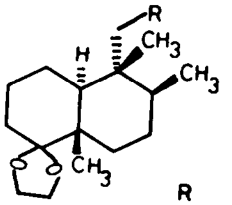
Catalytic hydrogenation of purified 9d in presence of 10% Pd-C in dry DMF, proceeded smoothly, to afford a mixture of corresponding methyl epimers in a ratio of about 4:1. These were separated by column chromatography, and the major product was identified as 10a as described below. The minor isomer was assigned the alternative stereostructure, 11a. Oxidation of 10a with pyridinium-chlorochromate furnished quantitatively the keto-ester (10b), mp 74-75°C. Wittig-methylation of 10b under salt-free conditions gave 10e in 55% yield. The corresponding acid 10f, mp 138-139°C, was found to be identical[17] in its spectral data, with one of its optical isomers, obtained[8] by degration of ilimaquinone.



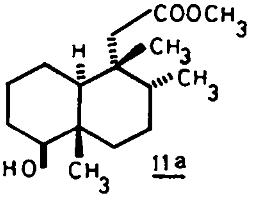
	R	R^1
10a:	β-OH,α-H	OMe
10b:	O	OMe
10c:	O	OH
10d:	O	CHN_2
10e:	CH_2	OMe
10f:	CH_2	OH



12



	R
13a:	$COOCH_3$
13b:	CH_2OH

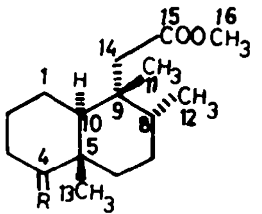


11a

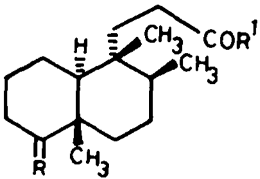
Catalytic hydrogenation of a related olefin, 12 (prepared by a non-regioselective route) was reported[11a] to give a 1:1 mixture of corresponding methyl epimers, which on further transformations through 13b and its C-8 axial methyl isomer was finally converted to (±)-annonene[11a]. We converted 10b to the corresponding ketal (13a), which was subsequently reduced with $LiAlH_4$ to afford 13b (mp 100-101°C), in an overall yield of about 60%. The ^1H NMR spectral data of this product agreed well with the chemical shifts which can be attributed to 13b in the spectrum[17] of a mixture of corresponding C-8 epimers. Thus, the preparation of 13b as above, has resulted in a formal, stereocontrolled synthesis of (±) annonene.

Another oxidation product derived[8] from ilimaquinone is the homologous ester (14b). In an effort to prepare the same, the ester 10b was hydrolyzed to 10c and the respective acid chloride was converted to diazo ketone (10d). Attempted rearrangement of 10d under photolytic conditions led to a complex mixture. However, rearrangement[18] of 10d in presence of silver benzoate in triethylamine afforded the desired product (14a) in 50% yield, which on Wittig-methylenation gave the olefin 14b, mp 85-86°C, in 50% yield. The spectral data of 14b were found to be identical[17] with those of one of its optical isomers.

Our studies were, next, extended to the synthesis of 15, which was isolated[6] earlier from a marine sponge, and also obtained as a degradation product of sigmosceptrellins[6] as well as an antimicrobial sesterterpene, palauolide[8]. Towards this end, the acid 14c, obtained by hydrolysis of 14b, was treated[19] with MeLi and Me_3SiCl to give methyl ketone (15) in ca. 50% yield. The spectral data of this compound closely agreed[17] with those of an optical isomer of 15[6].



	R
11a :	β-OH, α-H
11b :	O
11c :	CH$_2$



	R	R^1
14a :	O	OCH$_3$
14b :	CH$_2$	OCH$_3$
14c :	CH$_2$	OH
15 :	CH$_2$	CH$_3$

In connection with our studies on correlation[20] of ^{1}H and ^{13}C NMR spectral data of C-8 epimers of *trans*-clerodane derivatives, we converted the C-8 axial methyl derivative 11a to the olefin 11c. For this, 11a was oxidised with PCC to 11b (88% yield) which was then transformed to 11c (60%) by Wittig-methylenation under salt-free conditions. With the recent isolation[21] of certain *trans*-clerodanes having an axial C-8 substituent, some of which have shown physiological activity (for eg., 6), it can be envisaged that compounds such as 11c can serve as useful precursors. Their stereocontrolled synthesis, as major reaction products, would be possible based on the present methodology by suitably modifying the conditions for hydrogenation of 9d analogues[22].

EXPERIMENTAL

The compounds described are all in racemic form. All melting and boiling points are uncorrected. Spectra were obtained by using the following instruments : IR spectra, Perkin-Elmer PE 298 and Beckman IR 20A spectrophotometer; ^{1}H NMR spectra, Varian T-60A, XL-200 and JEOL FX-100 spectrometers; ^{13}C NMR spectra, JEOL FX-100 spectrometer. Chemical shifts are given as parts per million (ppm) downfield from internal Me_4Si in δ units. Gas chromatographic analyses were performed on a Hewlett-Packard Model 5730A (dual-channel flame-ionization detector) instrument, using 10% UCW 982 on 80-100-mesh WAW-DMCS packed in a stainless-steel column. Peak area measurements were obtained, in some cases, on a Hewlett-Packard Model 3380A digital integrator. The purity of most of the products was checked by GC analysis. E. Merck silica gel 60 (63-200 µm) was used for column chromatography.

Petroleum ether refers to the fraction with a boiling range of 40-60°C, and ether refers to diethyl ether. All the dry solvents and reagents were prepared from reagent grade materials by conventional methods. Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$.

The ene - ketol 8a was prepared as according to the reported procedure[13].

5β,9β-Dimethyl-4β-hydroxy-9α-[(methoxycarbonyl)methyl]-*trans*-decalin-8-one (9a).

This was prepared by reductive alkylation of 8a with ethyl bromoacetate adopting our earlier procedure[13]. As before, there was violent reaction during the rapid addition of this alkylating agent also. After work-up, the residue was distilled and crude product was collected in the range of 110-150°C at 0.1 torr. This was hydrolyzed with 5% aqueous methanolic KOH, the acidic fraction was isolated, and esterified in methanol with an Et_2O solution of diazomethane. The resulting product was chromatographed over silica gel and eluted with ethyl acetate-benzene (1:9) to obtain methyl ester (9a) as a light yellow liquid in 50% yield starting from 8a. Evaporative distillation at 125-130°C (bath temperature)/0.6 torr, afforded analytically pure 9a; IR (film) 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$ at 200 MHz) 1.04 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 3.63 (s, 3H, $COOCH_3$). Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found : C, 67.12; H, 9.20.

γ-Lactol of 5β,9β-dimethyl-4β-hydroxy-9α-[(hydroxycarbonyl)methyl-*trans*-decalin-8-one (9c). The aforementioned keto-acid 9b and/or γ-lactol 9c was twice recrystallized from ethyl acetate, to afford an analytically pure 9c (insoluble in $CHCl_3$), mp 177-178°C; IR (KBr) 1755 cm^{-1}. Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found : C, 66.01; H, 8.77.

Attempted Wittig-methylenation Reaction : Preparation of 5β,9β-Dimethyl-4β-hydroxy-9α-[(methoxycarbonyl)methyl]-8-methylene-*trans*-decalin (9d). The following experiments are representative of some of the attempts made :

Using NaH/DMSO : (A) The reaction was carried out on keto-ester 9a, according to our earlier method[13]. After work-up of the reaction mixture as before, the residue was thoroughly chromatographed twice over silica gel to obtain liquid 9d (11%) by elution with ethylacetate-benzene (1:9); IR (film) 1730, 1635 cm^{-1}; ^1H NMR (CCl_4) 0.95 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.44 (s, 2H, $C\underline{H}_2COOMe$), 3.55 (s, 3H, $COOCH_3$), 4.67 (bs, 2H, vinyl $C\underline{H}_2$). Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found : C, 72.54; H, 9.87. Repetition of this experiment failed to give 9d or the starting material.

When the above conditions were modified in which 3.1 mmol of ylide (prepared under dry N_2 as above, using 3.1 mmol of NaH and 3.4 mmol of triphenylmethylphosphonium iodide) was treated with 9a (1 mmol) at room temperature and the mixture stirred at room temperature for 17 h, a part of 9a was recovered (30%) by chromarography, as the only tangible compound.

(B) In another attempt, methylenetriphenylphosphorane (5.2 mmol), prepared as above, was added to a solution of 9a (1 mmol) in DMSO (inverse-addition) at 5°C over 1.5 h and the mixture was then stirred under dry N_2 at room temperature for 16 h. By this procedure, the desired olefin 9d was obtained in 6% yield, along with some starting material (25%). A further modification in the above conditions, in which the ylide (2.2 mmol) was added to 9a (inverse-addition) at 65°C over 3 h, and the mixture was then stirred at room temperature for 0.5 h, led to 20% recovery of 9a, and no olefin 9d was obtained.

Using *t*-BuOK in *t*-BuOH : To a stirred solution of potassium *t*-butoxide in *t*-butanol (from 100 mg potassium and 3 mL *t*-butanol) was added under nitrogen a solution of methyltriphenylphosphonium iodide (1.1 g, 2.72 mmol) in dry THF (16 mL) at 30°C. The mixture was stirred at 50°C for 1 h. To this ylide was added a solution of 9a (268 mg, 1 mmol) in dry THF (10 mL) over 0.5 h at room temperature. The mixture was stirred at 50°C for 2.5 h, cooled, treated with 3% HCl aq (50 mL) and then worked-up. The residue was subjected to column chromatography over silica gel twice to obtain 80 mg (30%) of olefin 9d by elution with ethyl acetate-benzene (1:9). However, the yield of 9d was inconsistent in a few repetition experiments.

Using 9b/9c as the substrate : To a solution of the ylide (5.3 mmol) in 10 mL DMSO (prepared from NaH/DMSO/$Ph_3\overset{+}{P}Me\ I^-$) was added dropwise under dry N_2 a solution of 9b/9c (1 mmol) in THF (5 mL), and the mixture was stirred at 60°C for 40 h. After work-up, the residue was chromatographed over silica gel to obtain only the starting material (50% recovery).

Under Salt-free conditions using 9a : Sodium hydride (56% oil dispersion, 140 mg, 5.8 mmol), taken in a dry three-neck flask, was washed a few times under nitrogen with petroleum ether to remove mineral oil. Dry THF (40 mL, freshly distilled) was added followed by the addition of powdered and well dried methyltriphenylphosphonium iodide (2.65 g, 6.5 mmol), the mixture was stirred for 16 h at room temperature and then at 50°C for 1.5 h, and finally allowed to settle at room temperature. The supernatant greenish yellow ylide solution was then transferred by means of a syringe to another dry flask, under dry N_2 (care was taken to avoid transferring the solid as far as possible) and the solvent was distilled out partly (25 mL) on a water bath at 70°C. The remaining solvent was removed under reduced pressure at room temperature. The residual ylide was dried well for 1 h at 0.05 torr, dissolved in dry benzene (40 mL) and the solution was again allowed to settle under dry N_2. A separate flask containing a solution of 9a (0.5 g, 1.86 mmol) in dry benzene (15 mL) under nitrogen was equipped with a magnetic bar and a pressure-equalising dropping funnel into which the supernatant solution of the above ylide (about 35 mL) was transferred by means of a syringe. This was added dropwise to the compound (inverse-addition) at 72-74°C over 3.5 h. The reaction mixture was stirred for further 15 min, cooled to room temperature and excess ylide was decomposed by the addition of acetone (2.5 mL). The solvents was then removed and the residual oil chromatographed over silica gel to obtain olefin 9d in a mixture of ethyl acetate-benzene (1:9) as a thick oil, along with some impurities. Rechromatography of this material afforded 260 mg of pure 9d (50%). The spectral data of this material were the same as described above.

4β-Hydroxy-9α-[(methoxycarbonyl)methyl]-5β,8β,9β-trimethyl-*trans*-decalin (10a), and the corresponding C-8α-Methyl Epimer (11a). A solution of 9d (950 mg, 3.54 mmol) in 8 mL of dry DMF was hydrogenated in the presence of 350 mg of 10% Pd-C at 30°C and atmospheric pressure. Uptake of hydrogen was slow (particularly when more solvent was used) and was complete in 15 h, at the end of which the mixture was worked-up. GC analysis of the crude residue revealed a major and a minor product (4:1 ratio), along with some impurities. The material was carefully chromatographed over silica gel. Elution with petroleum ether-benzene mixtures and then with benzene gave some undesired materials. Elution with ethyl acetate-benzene (1:19) provided 11a, contaminated with some 10a (180 mg, Fraction-1). Further elution with the same solvent gave an almost pure sample of 10a (Fraction-2, 510 mg) as a solid. The combined yield of 10a and 11a was 70%. Rechromatography of Fraction-1 afforded 130 mg of pure 11a as a solid, which was crystallized twice from petroleum ether to get an analytical sample, mp 66-68°C; IR (KBr) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) 0.93 (s, 3H, C-9 CH_3), 0.94-1.02 (partially overlapping d, 3H, C-8 CH_3), 1.12 (s, 3H, C-5 CH_3), 3.59 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$) 20.7 (t, C-1), 24.4 (t, C-2), 30.0 (t, C-3), 80.7 (d, C-4), 40.0 (s, C-5), 30.6 (t, C-6), 25.0 (t, C-7), 35.5 (d, C-8), 38.5 (s, C-9), 45.5 (d, C-10), 21.4 (q, C-11), 15.1 (q, C-12), 13.0 (q, C-13), 44.0 (t, C-14), 172.9 (s, C-15), 51.0 (q, C-16). Anal. Calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found : C,71.82; H, 10.73.

Recrystallization of Fraction-2 from petroleum ether gave an analytical sample of 10a,87.5-88.5°C; IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) 0.77 (s, 3H, C-9 CH_3), 0.89-0.95 (partially overlapping d, 3H, C-8 CH_3), 0.89 (s, 3H, C-5 CH_3), 2.33 (s, 2H, $C\underline{H}_2COOMe$), 3.64 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$) 21.3 (t, C-1), 24.4 (t, C-2), 30.1 (t, C-3), 80.8 (d, C-4), 40.4 (s, C-5), 37.3 (t, C-6), 26.9 (t, C-7), 37.8 (d, C-8), 39.7 (s, C-9), 48.4 (d, C-10), 17.2 (q, C-11), 16.3 (q, C-12), 12.6 (q, C-13), 42.7 (t, C-14), 172.2 (s, C-15), 51.0 (q, C-16). Anal. Calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found : C, 71.66; H, 10.67.

9α-[(Methoxycarbonyl)methyl]-5β,8β,9β-trimethyl-*trans*-decalin-4-one (10b). To a stirred solution of pyridiniumchlorochromate (160 mg, 0.74 mmol) in 2 mL of dry CH_2Cl_2 was rapidly added a solution of 10a (110 mg, 0.4 mmol) in dry CH_2Cl_2 (3 mL) at 30°C and the mixture was stirred further for 2 h. The black mixture was diluted with Et_2O (50 mL) and filtered through a silica gel column. Removal of solvent afforded a thick residue (100 mg, 95%) which was crystallized twice from petroleum Et_2O to obtain pure 10b, mp 74-75°C; IR (KBr) 1730, 1700 cm^{-1}; ^1H NMR (CCl_4) 0.85 (s, 3H, C-9 CH_3), 0.85-0.89 (partially submerged d, 3H, C-8 CH_3), 1.10 (s, 3H, C-5 CH_3), 3.58 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$) 21.3 (t, C-1), 25.7 (t, C-2), 37.4 (t, C-3), 215.0 (s, C-4), 49.0 (s, C-5), 32.8 (t, C-6), 26.5 (t, C-7), 37.5 (d, C-8), 41.3 (s, C-9), 49.2 (d, C-10), 17.4 (q, C-11), 16.2 (q, C-12), 19.0 (q, C-13), 42.8 (t, C-14), 171.7 (s, C-15), 51.1 (q, C-16). Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found : C, 72.15; H, 9.87. This compound was found to be identical with keto-ester 10b reported[13] by us earlier.

4,4-Ethylenedioxy-9α-[(methoxycarbonyl)methyl]-5β,8β,9β-trimethyl-*trans*-decalin (13a). The keto-ester 10b was converted to ketal 13a by the usual procedure (ethylene glycol, *p*-TsOH, H_2O and benzene; 7 h reflux). After work-up, the residue was rapidly chromatographed over neutral alumina and 13a (80% yield) was eluted with petroleum ether-benzene (1:1). Evaporative distillation of this material at 125-130°C (bath temperature) at 0.6 torr, gave an analytical sample of 13a; IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) 0.72 (s, 3H, C-9 CH_3), 0.89 (d, J=6 Hz, 3H, C-8 CH_3), 1.03 (s, 3H, C-5 CH_3), 2.33 (AB_q centered at, 2H, $C\underline{H}_2COOMe$), 3.64 (s, 3H, $COOCH_3$), 3.59-3.82 (m, 4H, OCH_2CH_2O). Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found : C, 69.68; H, 9.84.

4,4-Ethylenedioxy-9α-(2-hydroxyethyl)-5β,8β,9β-trimethyl-*trans*-decalin (13b). To a stirred suspension of $LiAlH_4$ (50 mg, 1.3 mmol) in Et_2O (35 mL) was added dropwise a solution of 13a (90 mg, 0.29 mmol) in 20 mL dry Et_2O over 15 min at room temperature. The mixture was gently refluxed for 4 h, cooled and decomposed with saturated Na_2SO_4 aq. The mixture was filtered and the solid was washed thoroughly with Et_2O. The filtrate was concentrated to afford an oily residue which was purified by rapid column chromatography over neutral alumina. Elution with ethyl acetate-benzene (1:4) afforded the desired compound (70 mg, 85%) as a semi-solid.

Recrystallization from petroleum ether afforded a pure sample of 13b, mp 100-101°C; IR (KBr) absence of carbonyl; ^{1}H NMR ($CDCl_3$) 0.71 (s, 3H, C-9 CH_3), 0.85 (d, J=5 Hz, 3H, C-8 CH_3), 1.03 (s, 3H, C-5 CH_3), 3.66 (t, 2H, $CH_2\underline{CH_2}OH$), 3.83-3.91 (m, 4H, OCH_2CH_2O). Anal. Calcd. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found : C, 72.35; H, 10.97. The ^{1}H NMR data corresponded closely[17] with some of the chemical shifts in a spectrum of a mixture of 13b and its C-8 axial methyl epimer.

9α-[(Methoxycarbonyl)methyl]-4-methylene-5β,8β,9β-trimethyl-*trans*-decalin (10e).

A solution of salt-free methylenetriphenylphosphorane (about 1.6 mmol) in dry benzene was prepared as described above, using 1.8 mmol of NaH and 2 mmol of Wittig-salt.

To a solution of keto-ester 10b (215 mg, 0.8 mmol) in dry benzene (5 mL) was added (inverse-addition) under dry N_2 the above ylide solution (25 mL) at 68°C over 1 h 45 min. The reaction mixture was stirred further for 15 min, cooled, decomposed by the addition of acetone (2 mL), and the solvents were then removed. The residual oil was chromatographed over silica gel (15 g). Elution with petroleum ether-benzene (9:1) afforded olefin 10e (110 mg, 55%) and on further elution, a small amount of 10b was recovered (40 mg, 20%). Evaporative distillation of the product at 130-135°C (bath temperature)/0.2 torr, furnished pure 10e as colorless thick liquid; IR (film) 1735, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.76 (s, 3H, C-9 CH_3), 0.89 (d, J=6 Hz, 3H, C-8 CH_3), 1.01 (s, 3H, C-5 CH_3), 3.59 (s, 3H, $COOCH_3$), 4.47 (d, J=1.5 Hz, 2H, vinyl $\underline{CH_2}$). Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found : C, 77.01; H, 10.31.

9α-[(Hydroxycarbonyl)methyl]-4-methylene-5β,8β,9β-trimethyl-*trans*-decalin (10f).

The ester 10e was hydrolyzed by refluxing for 4 h with an aqueous methanolic KOH. The acidic fraction (95% yield) obtained as a yellow solid after usual work-up, was crystallized from petroleum ether to obtain pure (10f), mp 138-139°C; IR (KBr) 3090, 1690, 1635 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) 0.79 (s, 3H, C-9 CH_3), 0.91 (d, J=6.7 Hz, 3H, C-8 CH_3), 1.04 (s, 3H, C-5 CH_3), 4.51 (s, 2H, vinyl $\underline{CH_2}$). The ^{1}H NMR spectrum was identical[17] with that of an optical isomer of 10f.

9α-[(Methoxycarbonyl)methyl]-5β,8α,9β-trimethyl-*trans*-decalin-4-one (11b).

The hydroxy ester 11a was oxidised with PCC, according to the method of preparation of 10b. The semi-solid (90% yield) product obtained after filtering through a silica gel column, was crystallized from petroleum ether to get pure 11b, mp 105-106°C; IR (KBr) 1740, 1700 cm^{-1}; ^{1}H NMR (CCl_4) 0.94 (d, J=7 Hz, 3H, C-8 CH_3), 1.17 (s, 3H, C-9 CH_3), 1.20 (s, 3H, C-5 CH_3), 3.58 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$) 20.7 (t, C-1), 24.6 (t, C-2), 37.2 (t, C-3), 214.8 (s, C-4), 49.2 (s,C-5), 26.1 (t, C-6), 25.8 (t, C-7), 35.4 (d, C-8), 39.5 (s, C-9), 46.2 (d, C-10), 21.7 (q, C-11), 14.9 (q, C-12), 19.4 (q, C-13), 43.8 (t, C-14), 172.4 (s, C-15), 51.1 (q, C-16). Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found : C, 72.40; H, 9.98.

9α-[(Methoxycarbonyl)methyl]-4-methylene-5β,8α,9β-trimethyl-*trans*-decalin (11c).

Wittig-methyleneation of 11b was carried out following the procedure as described above for the preparation of 10e from 10b; however, with a slight modification in conditions, namely, that the addition of ylide solution to 11b at 68°C was done over 1 h and the reaction mixture was further stirred at this temperature for 1 h. After work-up, the residue was purified by chromatography over silica gel to obtain olefin 11c (60% yield) as colourless oil by elution with benzene-petroleum ether (1:9); IR (film) 1735, 1635 cm^{-1}; ^1H NMR (CCl_4) 0.94 (d,J=7.5 Hz, 3H, C-8 CH_3), 1.11 (s, 3H, C-9 CH_3), 1.14 (s, 3H, C-5 CH_3), 3.56 (s, 3H, $COOCH_3$), 4.42 (bs, 2H, vinyl $C\underline{H}_2$). Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.22; H, 10.67. Found : C, 77.15; H, 10.80.

9α-[(Hydroxycarbonyl)methyl]-5β,8β,9β-trimethyl-*trans*-decalin-4-one (10c). Hydrolysis of 10b was carried out by refluxing for 4 h with aqueous methanolic KOH. The crude acidic material (90% yield), obtained after work-up, was crystallized from ethyl acetate to obtain pure 10c, mp 181-182°C; IR (KBr) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88 (s, 3H, C-9 CH_3), 0.90 (partially overlapping d, 3H, C-8 CH_3), 1.14 (s, 3H, C-5 CH_3), 2.36 (s, 2H, $C\underline{H}_2COOH$). Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found : C, 71.37; H, 9.83.

9α-[(2-Methoxycarbonyl)ethyl]-5β,8β,9β-trimethyl-*trans*-decalin-4-one (14a).

Preparation of 10d : A solution of acid 10c (230 mg, 0.91 mmol) in 15 mL methanol was neutralized with 2% sodium methoxide in methanol. After removal of methanol, the residue was treated with dry benzene and the solvent was distilled off. The sodio-salt was finally dried for 4 h at 0.1 torr, then suspended in dry benzene (20 mL) containing 0.1 mL of pyridine, cooled in ice-water and treated with oxalyl chloride (1 mL) under N_2. The reaction mixture was warmed at 60°C for 1 h, cooled, filtered quickly under N_2, the solid washed with dry benzene, the combined filtrate was concentrated, and finally dried for 2 h at 0.1 torr. A solution of this acid chloride in dry Et_2O (20 mL) was added dropwise to a well-dried, an Et_2O solution of diazomethane (5 mmol) containing 1 mL of freshly distilled triethylamine at 5°C under stirring. The mixture was left at room temperature for 6 h, then filtered through a short column of silica gel, and the filtrate was concentrated to obtain crude diazo ketone 10d as a thick pale yellow liquid; IR ($CHCl_3$) 2110, 1780, 1700, 1635 cm^{-1}; ^1H NMR (CCl_4) 5.28 (s, 1H, $CO\underline{H}N_2$).

Rearrangement of 10d using Silver benzoate: A stirred solution of above diazo-ketone 10d (250 mg) in dry methanol (10 mL) was added dropwise to a solution of freshly prepared silver benzoate (100 mg) in distilled triethylamine (20 mL) over 15 min at room temperature, and stirred further for 12 h, during which the reaction mixture became dark. The solvents were then removed under reduced pressure, the residue dissolved in ether (100 mL), washed with 2N HCl aq, then with saturated $NaHCO_3$ aq followed by water, and dried. The material obtained after evaporation of solvent, was chromatographed over silica gel. Elution with petroleum ether-benzene (1:3) afforded homologous ester 14a (in 50% overall yield from 10c) as a colorless thick liquid. Evaporative distillation of this material at 140°C (bath temperature)/0.4 torr afforded an analytical sample; IR (film) 1735, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) 0.85 (s, 3H, C-9 CH_3), 1.14 (s, 3H, C-5 CH_3), 3.63 (s, 3H, $COOCH_3$); the C-8 CH_3 doublet was submerged under the signal at 0.85. Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found : C, 72.89; H, 10.10.

9α-[(2-Methoxycarbonyl)ethyl]-4-methylene-5β,8β,9β-trimethyl-*trans*-decalin (14b) and corresponding Acid (14c). Methylenation of keto-ester 14a was carried out as according to the preparation of 10e. The crude product was chromatographed over silica gel. Elution with petroleum ether-benzene (9:1) gave the olefin 14b (50% yield) as a solid, which was further purified by crystallization, mp 85-86°C (petroleum ether); IR (KBr) 1730, 1625 cm^{-1}; ^1H NMR (360 MHz, CCl_4) 0.76 (s, 3H, C-9 CH_3), 0.83 (d, J=6.5 Hz, 3H, C-8 CH_3), 1.03 (s, 3H, C-5 CH_3), 3.58 (s, 3H, $COOCH_3$), 4.42 (s, 2H, vinyl CH_2). The ^1H NMR spectrum was identical[17] with that of an optical isomer of 14b. Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found : C, 77.86; H, 10.84.

The corresponding acid, 14c : mp 140-141°C (ethyl acetate); IR (KBr) 3080, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) 0.77 (s, 3H, C-9 CH_3), 0.90 (d, J=7.5 Hz, 3H, C-8 CH_3), 1.04 (s, 3H, C-5 CH_3), 4.47 (s, 2H, vinyl CH_2). Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found : C, 77.01; H, 10.41.

4-Methylene-9α-(3-oxobutyl)-5β,8β,9β-trimethyl-*trans*-decalin (15). The reaction was carried out according to a reported method[19]. To a stirred solution of 14c (120 mg, 0.454 mmol) in dry THF (6 mL) was added dropwise a prepared solution of MeLi (1.02 M, 5 mL) in Et_2O at 0°C under N_2 and stirred further for 2.5 h. Freshly distilled Me_3SiCl (6 mL) was then added in rapid drops at 0°C, the mixture was then treated with 1N HCl aq (25 mL), and the organic layer was separated. After work-up, the residue was chromatographed over neutral alumina and the oily methyl ketone 15 (60 mg, 50%) was eluted with benzene-petroleum ether (1:9); IR (film) 1715, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) 0.76 (s, 3H, C-9 CH_3), 1.04 (s, 3H, C-5 CH_3), 2.12 (s, 3H, $COCH_3$), 4.49 (d, J=2 Hz, 2H, vinyl CH_2), the C-8 CH_3 doublet (one shoulder at 0.79) was partially submerged under the signal at 0.76. The IR (neat) and ^1H NMR spectrum closely resembled[17] that of an optical isomer of 15.

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