

MODEL STUDIES IN THE TAXANE DITERPENE SERIES - Part. I

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(Received in France 24 March 1986)

Abstract : Photochemical [2 + 2] cycloaddition of enol acetate **10a** to cyclohexene led to a 3 : 1 mixture of the tetracyclic photoadducts **A** and **B** which, through reverse aldol reactions, under mild alkaline conditions produced two compounds : a tetracyclic ketone **13** and a tricyclic diketone **14**. Hydrolytic cleavage in methanolic hydrochloric acid of **15** and **16** resulting from irradiation of the enol ether **10b** to cyclohexene gave rise to the rearranged tricyclic diketone **14** only. The trans stereochemistry 3 α , 8 β of the fused-ring system in **14**, established by X-ray measurements, is different from the stereochemistry of the naturally occurring taxane derivatives.

*Ejus elementi compositionem quod vim habet in taxo baccata, photochimiae beneficio, quidam in exemplo simplicione reddito experti sunt .
Perincommode tamen accidit ut materiae ita quaesitae figura dissimilis sit ejus rei natura praebitae .*

This work was submitted as part of a 3^{ème} cycle D. Thesis - Humberto CERVANTES-CUEVAS, 26.01.1983 - Université PARIS XI - Centre d'ORSAY, France and a conference : H. CERVANTES, D. DO KHAC, Thierry PRANGE and M. FETIZON* : Fifth asian symposium on medicinal plants and spices - 647, August 1984 - SEOUL (S. Korea) .

INTRODUCTION

Taxus baccata had a very bad reputation in the roman world . According to PLINY the ELDER ^(*), even its shadow is fatal to mammals, including men ^{1,2,3} . Since that time, interest in taxane and its derivatives ⁴ grew up . Now it goes far beyond the structural novelty of the uncommon tricyclic carbon framework **1**, due to the rather potent antileukemic and antitumoral activity⁵ of taxol ⁶ **2**, and cephalomannine ⁷ **3**, among others (scheme 1) .

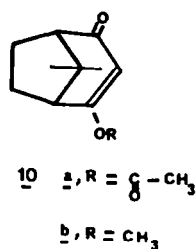
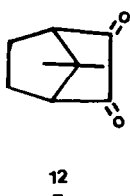
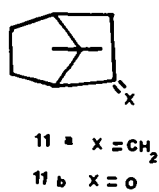
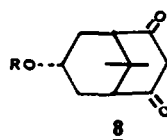
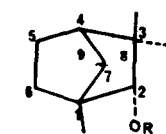
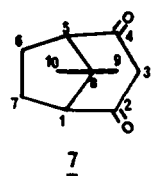
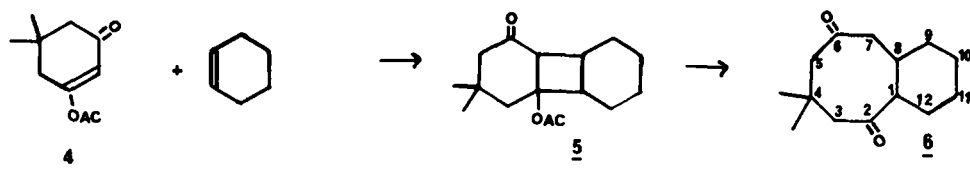
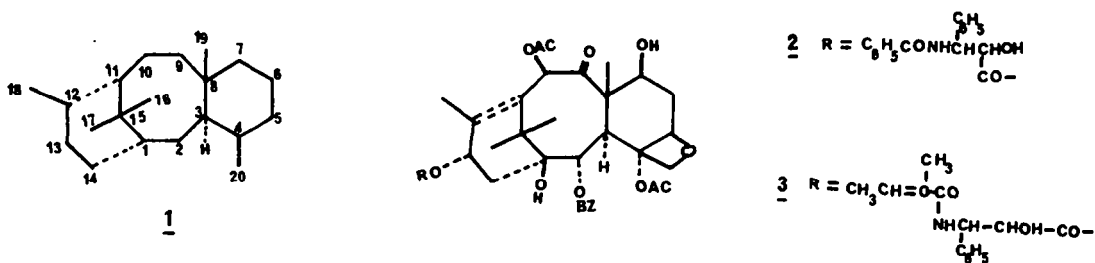
In spite of numerous investigations ^{8,9,10,11,12} no total synthesis of any taxane diterpenes has been reported yet . If the strategy consists in building first rings A and B, then introducing ring C, the major problem to settle is the construction of the latter ring with the right stereochemistry . Among the various methods which show some promise in the formation of functionalized eight membered ring systems, we selected an intermolecular de MAYO's reaction^{13(**)} :

(*) In order to underline this time-honoured observation, a short summary of our paper is also provided in latin .

(**) The stereochemistry of the trans fused ring of **6** ¹³ at C-1 and C-8 remained undetermined .

a photochemical cycloaddition of cyclohexene, or, more generally, an olefin, to an enol derivative of a cyclohexane-1,3-dione 4. The resulting adduct 5, undergoes a retroaldol reaction leading to the expected product 6 (scheme 1).

In order to overcome the problems connected to regioselectivity and to focus our attention on the stereochemistry of the final compound 6, we decided to study a model reaction, in which a fairly accessible cyclohexane-1,3-dione would have a plane of symmetry. For this purpose, symmetrical bicyclo [3.2.1] octane-2,4-dione 7 is almost ideal, since it is closely related to the compound 8, which would lead to taxane derivatives, and very easily prepared in large quantity from commercially available α -fenchol 9a (scheme 1).



However, it has been found previously that, although there is a fairly good regio and stereoselectivity in many photochemical [2 + 2] cycloadditions, the structure of the final product is difficult to predict ¹⁴ .

Our exploratory experiments have, thus, been carried out with model substances 10a and 10b (scheme 1) .

Synthesis of 8,8-dimethyl bicyclo [3.3.1] octane-2,4 dione 7 (scheme 1)

α -fenchol 9a was converted into its tosylate 9b which gave α -fenchene ¹⁵ 11a upon solvolysis . The best practical method for oxidation of α -fenchene is ozonolysis ¹⁶ . The resulting α -fenchocamphorone ¹⁷ (apocamphor) 11b is then submitted to a selenium dioxide oxidation ¹⁸ , whereby the yellow α diketone 12 (norcamphorquinone) is obtained in good yield . Diazomethane reacts with this non enolizable diketone with ring expansion and o-methylation of the intermediate diketone 7 . The latter enol ether 10b is hydrolysed into diketone 7 in the presence of diluted hydrochloric acid ¹⁹ . Acetylation of the dione 7 with acetic anhydride, in the presence of n-butyllithium, according to the method of PATTENDEN ²⁰ leads to the enol acetate 10a .

R E S U L T S a n d D I S C U S S I O N

The photocycloaddition of enol acetate 10a was investigated first . Irradiation of 10a with a large excess of cyclohexene in methylene chloride at - 50°C, using pyrex filtered light from a medium pressure Hg lamp, gave a mixture of two adducts A and B, in a combined yield of 80 % (scheme 3) . Attempts to separate these isomers met with limited success . When the mixture A + B is treated with potassium hydroxide in anhydrous ethanol, the major compound (65 %) which is highly fluorescent in U.V. light in t.l.c. (silica gel Merck PF 254) is the tetracyclic enone 13 ^{13,21} (U.V. $\frac{\text{EtOH}}{\lambda_{\text{max}}}$: 252 nm, $\epsilon = 6.900$, I.R. $\nu_{\text{C=O}} = 1678 \text{ cm}^{-1}$; no olefinic proton in ¹H n.m.r.) .

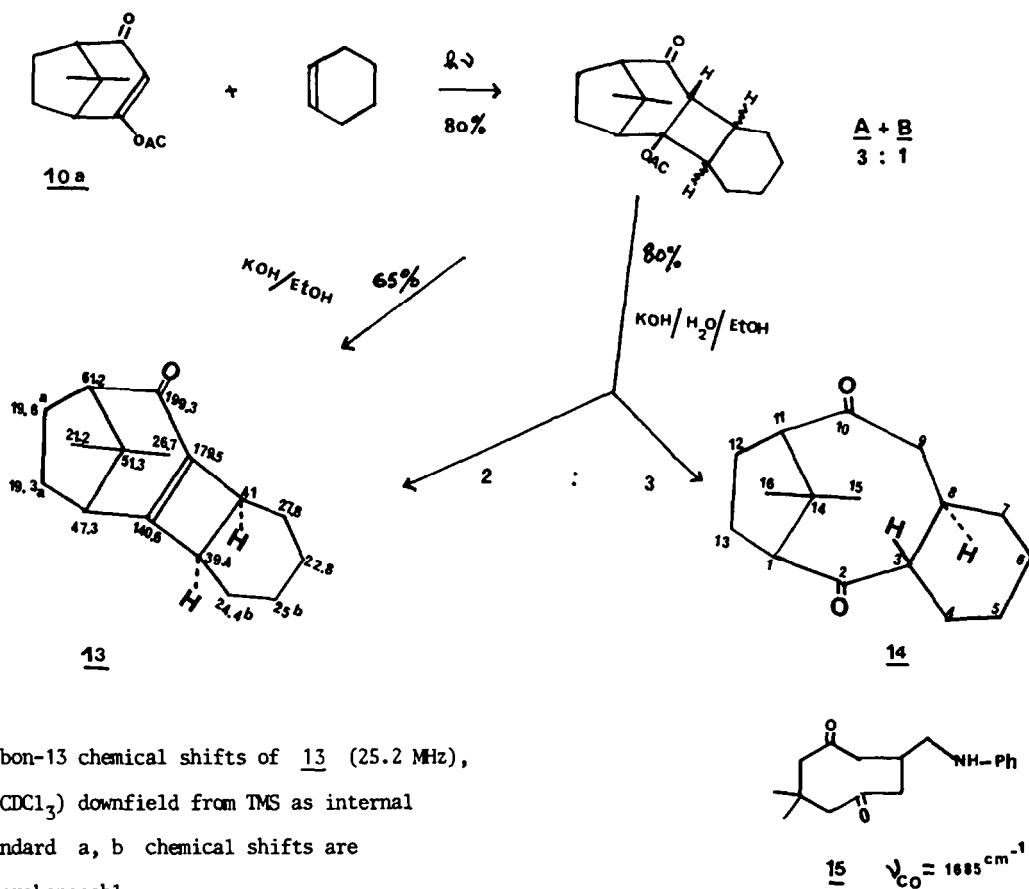
A tentative assignment of ¹³C chemical shifts of compound 13 is shown on scheme 2 . No other pure compounds could be isolated (scheme 2) .

In the presence of potassium hydroxide in aqueous ethanol at 20°C, the mixture A + B was converted into two ketones in 80 % yield (ratio 2 : 3) . The major compound which is not fluorescent in t.l.c. under the conditions described above, is a crystalline compound, m.p. 91-92°C (pentane) . There is a very weak absorption in U.V. ($\lambda_{\text{max}} = 300 \text{ nm}$ ($\epsilon = 56$), 220 nm ($\epsilon = 248$)) indicative of a non conjugated system . In the infrared spectrum, there is a very intense absorption band at 1678 cm^{-1} , which coincides with the $\nu_{\text{C=O}}$ band of 14 . Such low values have already been observed in diketones similar to the expected one 15 (scheme 3) .

Since no firm proof of the structure of our compound could be obtained from its

^1H and ^{13}C n.m.r. spectra, it was submitted to X-ray crystallography studies which gave results shown on scheme 3 .

As expected, rings B and C of 14 are transfused . However, their relative stereochemistry with respect of the bridgehead protons is opposite to taxane's one . The minor component of the mixture is the unsaturated ketone 13



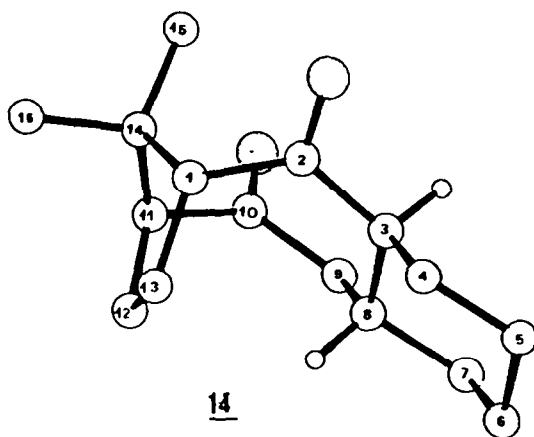
SCHEME 2

Triclinic crystals of 14 were obtained from pentane-ether solution (0,2 x 0,4 x 0,3 mm) . Crystal data : $\text{C}_{16}\text{H}_{24}\text{O}_2$, space group $P\bar{1}$ ($2 = 2$), $a = 11.006$ (4) ; $b = 10.127$ (3) ; $c = 6.897$ (3) ; A , $\alpha = 99^\circ.8$; $\beta = 101^\circ.6$ and $\gamma = 106^\circ.2$; $U = 701.26 \text{ \AA}^3$; 1300 independent reflections were measured with $I > 2\sigma(I)$ on a four circle PW 1100 automatic diffractometer using $\text{Cu-K}\alpha$ radiation . The structure was solved by direct method ²² and anisotropically refined to a final conventional R factor of 5.4% (all hydrogen atoms were located on difference Fourier synthesis) .

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, CAMBRIDGE CG₂ IEW . Any request should be accompanied by the full literature citation for this communication .

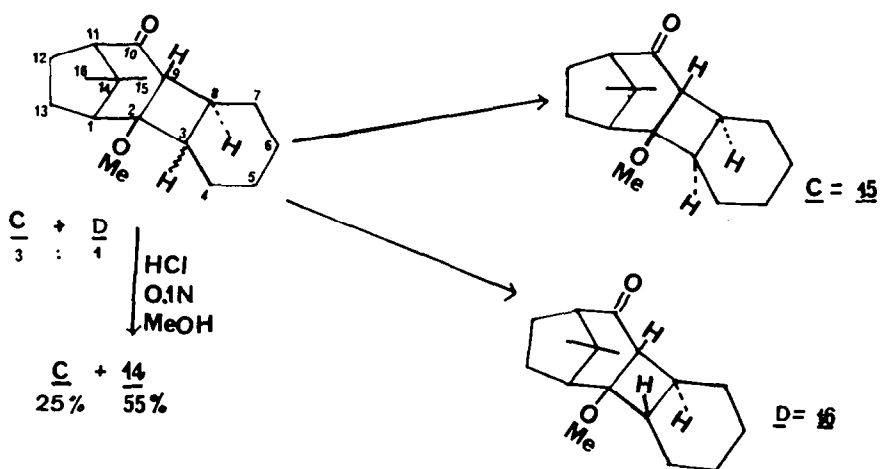
Scheme 3 : Molecular structure of 14

The figure shows one of the two independent molecules in the unit cell .



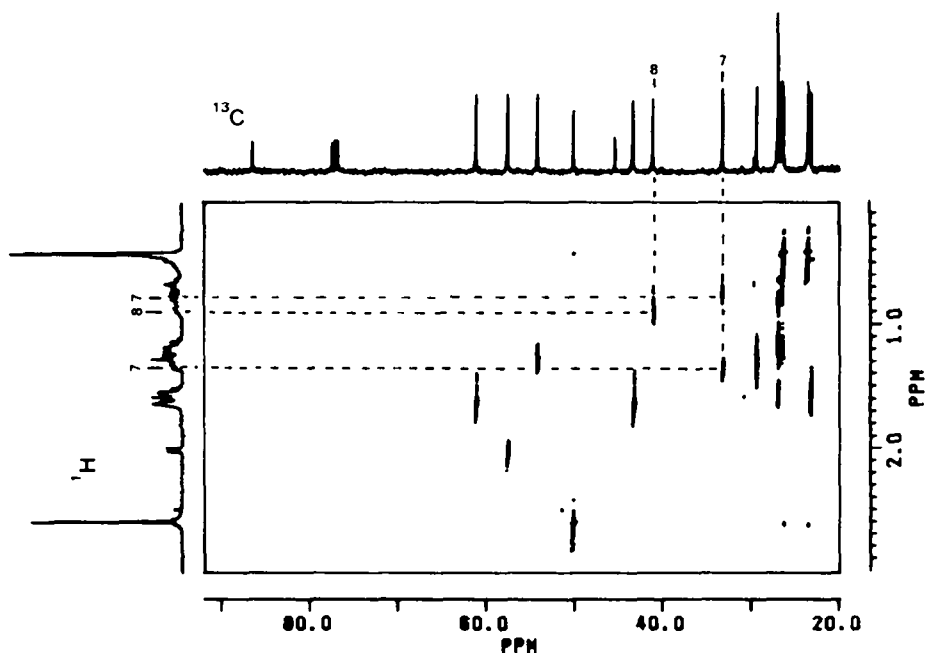
Similarly, photocycloaddition of enol ether 10b to cyclohexene led to two products C and D (ratio : 3 : 1) which could be readily separated . However the crude mixture of C and D, treated with methanolic 0,1 N hydrochloric acid, at room temperature, afforded a mixture of two easily separable compounds . The major compound (55 %) based on the starting methyl ether, is the diketone 14 . The minor compound is C (25 %) . No trace of the unsaturated ketone 13 could be detected (scheme 4) .

Since the amount of ketone 14, resulting from the rearrangement of the mixture C + D is larger than the amount of the major cycloaddition product C, we may assume that both C and D are converted into 14, very likely at different rates .



scheme 4

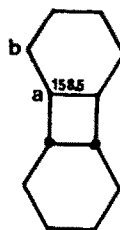
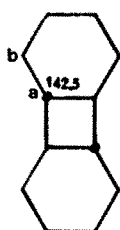
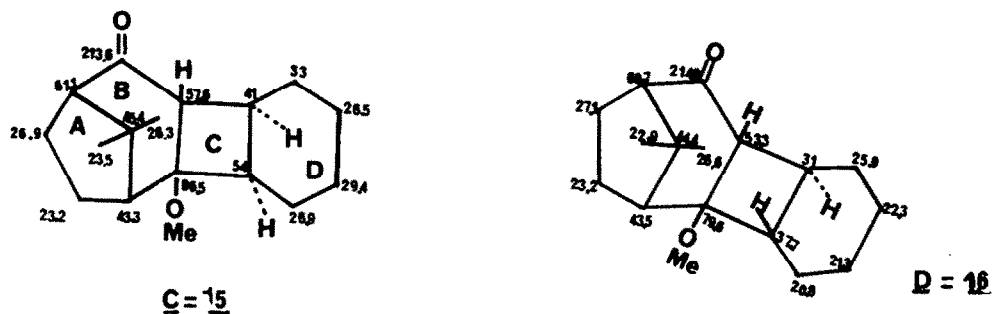
As the configuration of H_8 , either in C or in D has been confirmed by X-ray analysis of compound 14 (scheme 4), and 1H n.m.r. (400 MHz) spectra of compounds C and D show that $^3J_{H_9-H_8}$ coupling is about the same (9.75 Hz and 10.50 Hz respectively), hence proton H-9 should be β in both compounds (scheme 5) should H-9 be α , the $^3J_{H_9-H_8}$ coupling constant would be smaller (≈ 4 Hz) ²³.



Scheme 5 : 2D 1H - ^{13}C chemical shift correlation spectrum of compounds C = 15

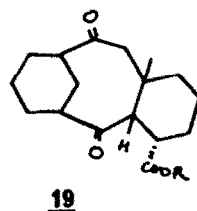
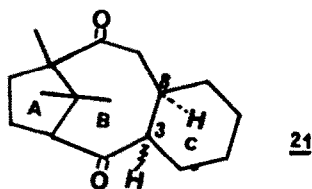
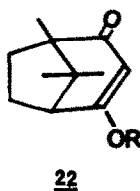
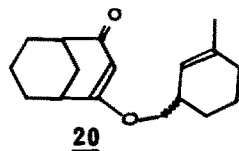
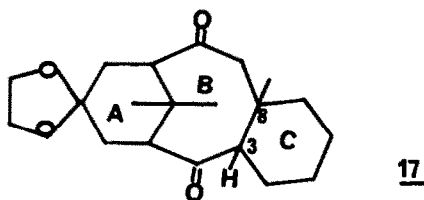
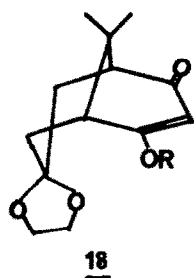
Assignment of the 1H (400 MHz) and ^{13}C (100 MHz) spectra of compound C was obtained from two dimensional n.m.r. experiments : 1H - 1H chemical shift correlation ²⁴ (COSY) and 1H - ^{13}C chemical shift correlation ²⁵ (scheme 5) . This method was very efficient, especially for the assignment of 1H and ^{13}C spectra of $-CH_2-$, 4,5,6,7,12 and 13 . The spectra of compound D were interpreted by comparison with the results discussed above for compounds C . ^{13}C n.m.r. spectra of C and D were in full agreement with their assigned structure 15 (cis-anti-cis) and 16 (cis-anti-trans) respectively . The latter was the most unstable in acidic condition using to open the cyclobutane ring (scheme 4) . In particular there is a large difference in the chemical shifts of C_2 and C_9 (5 ppm), C_8 (10 ppm) and C_3 (17 ppm) for 15 and 16, produced probably by conformational changes of C and D rings (scheme 6) . On the other hand, the cyclobutyl "a" carbon resonance of the trans-fused isomer E comes at appreciably higher field, compared to the cis-anti-cis stereoisomer F ²⁶ .

Hence, the geometry of A and B rings (with a cis($H_{9\beta}$) and $MeO_{\beta}(C_9)$ configuration) was identical in the two isomers 15 and 16 and the photocycloaddition occurred from the endo side . It seems likely that photochemical [2 + 2] cycloaddition of cyclohexene to enol-ether 10 affords a stereoselective route for B and C rings, different from the stereochemistry of the naturally occurring taxane derivatives .


scheme 6

(Carbon-13 chemical shifts of **E** and **F**, δ (CS₂) downfield from CCl₄ as internal standard)

After the completion of our studies, BLECHERT and al.²⁷ described a preparation of tricyclic compound **17**, starting from bicyclic enol-ether **18**, and INOUE and al.²⁸ presented a synthesis of **19** from enol ether **20** with a cis C₇ β , C₈ β fusion for B and C rings (scheme 6). Recently, BERKOWITZ and al.²⁹ reported a synthesis of tricyclic compounds **21**, in which the stereochemistry B/C fused ring at C₇ has remained undetermined, from a photocycloaddition of cyclohexene with homocamphorquinone derivatives **22** (scheme 7).


scheme 7

A c k n o w l e d g e m e n t s

We thank Dr S. KAN (Université PARIS XI), Dr M. BERTRANNE and Dr G. ARANDA (Ecole Polytechnique) for recording ^1H (400 MHz) and ^{13}C n.m.r. spectra . We also thank Professor R. LESUEUR for the latin summary .

E x p e r i m e n t a l S e c t i o n

General methods : All reactions were performed under argon unless otherwise specified, using standard syringe techniques for transfer of materials . Where necessary organic solutions were dried over MgSO_4 and the product was isolated by filtration and evaporation of the filtrate using rotary evaporator . Infrared spectra were measured on a PERKIN-ELMER 399 spectrophotometer . Proton nuclear magnetic resonance spectra were obtained at 400 MHz . ^{13}C n.m.r. spectra were recorded at 25.2 MHz using a VARIAN CFT.20 or a VARIAN XL.100 spectrometer operating in the FOURIER transform mode . Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard . Coupling constants (J) are given in hertz (Hz) with the following abbreviations for splitting patterns : s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet . Melting points were determined on a BUCHI melting point apparatus and are uncorrected . Preparative t.l.c. plates were prepared of about 1 mm in thickness (Merck silica gel PF - 254) . Column chromatography was performed on 230-400 mesh MERCK silica gel 60 . Tetrahydrofuran (THF) and ether were dried by distillation over sodium benzophenone . Dichloromethane was purified by washing with sulfuric acid and water, followed by distillation from phosphorus pentoxide .

Irradiations were carried out in dichloromethane as the solvent under argon by using a TW 150 W HANAU lamp and a pyrex filter ($\lambda > 295 \text{ nm}$) . The reaction was followed by U.V. absorption of the starting material .

2D spectra : All spectra were recorded on a BRUKER WM 400 (conc. 80 mg/0.6 ml), ^1H - ^1H chemical shift correlation (COSY) : the applied pulse sequence was $(\pi/2) - (t_1) - (\pi/4) - (\text{FID}, t_2)$. The spectral width in F_1 and F_2 was 1200 Hz ; the number of data points in t_2 was 2048, and 512 increments were recorded . Before FOURIER transformation, the data were multiplied with unshifted sinebell . Total acquisition time was 10 hours . The $\pi/2$ pulse was 10 μs .

^1H - ^{13}C shift correlation : The pulse sequence was $(\pi/2, ^1\text{H}) - (t_1/2) - (\pi, ^{13}\text{C}) - (t_1/2) - (t_1) - (\pi/2, ^1\text{H}; \pi/2, ^{13}\text{C}) - (t_2) - (\text{BB}, ^1\text{H}; \text{FID}, t_2)$ with $\tau_1 = 0.00357 \text{ s}$ and $\tau_2 = 0.01785 \text{ second}$. The spectral width in F_1 was 1200 Hz and in F_2 , 7246 Hz ; the number of data points in t_2 was 4096 and 256 increments were recorded . Before FOURIER transformation, the data were multiplied with unshifted sine-bell in F_2 and exponential in F_1 . Total acquisition was 20 hours . The $\pi/2$ pulse was 14 μs for ^{13}C and the decoupler $\pi/2$ pulse was 43 μs .

α -fenchene (11a) : Fenchyl alcohol (12 g, 0.078 mol) and 4-toluenesulfonyl chloride (19 g, 0.10 mol) were heated at reflux (120°C) in pyridine (120 ml) for 24 h . The reaction mixture was added to cold aqueous NaHCO_3 , and the mixture was extracted with pentane (3 x 60 ml), organic layers combined, washed with aqueous HCl (10 %), water, brine and dried (MgSO_4) . Filtration and concentration gave 10.06 g (95 %) of 11a . I.R. (film) : 3065, 1665 and 875 cm^{-1} . ^1H n.m.r. (400 MHz) δ : 0.93 (3H, s, CH_3) ; 0.95 (3H, s, CH_3) ; 1.03 (1H, m) ; 1.25 (2H, m) ; 1.65 (1H, t) ; 1.85 (1H, m, $\text{H}_{3\beta}$, $^3\text{J} = 5 \text{ Hz}$, $^2\text{J} = 18 \text{ Hz}$) ; 1.92 (1H, m) ; 2.03 (1H, d, $^3\text{J} = 5 \text{ Hz}$) ; 2.41 (1H, d, $\text{H}_{3\alpha}$, $^2\text{J} = 18 \text{ Hz}$) ; 4.61 (1H, s, H_{10}) ; 4.81 (1H, s, H_{10}) ; ^{13}C n.m.r. : 53.8 (C_1) ; 156.7 (C_2) ; 37.6 (C_3) ; 45.0 (C_4) ; 28.8 (C_5 or C_6) ; 28.7 (C_5 or C_6) ; 46.0 (C_7 , s) ; 20.8 (C_9) ; 21.8 (C_8) ; 102.9 (C_{10} , t) .

Apocamphor (11b) : A solution of 20.0 g of α -fenchene 11a in 180 ml of absolute methanol was exhaustively ozonized at - 70 to - 80°C . The ozonized solution was then added to a vigorously stirred mixture of 150 ml of absolute methanol, 40 ml of glacial acetic acid and 80 g of sodium iodide . The resulting iodine colored solution was stirred for 4 h and diluted with a liter of water . Sodium bisulfite was added until the color of the iodine disappeared ; this was followed by the addition of sodium carbonate until the solution was basic . The reaction mixture was then extracted with 800 ml of diethyl ether and the ethereal extract was dried over anhydrous magnesium sulfate . The drying agent was removed by filtration and the solvent was distilled under reduced pressure . The residu gave 12.05 g of 11b (60 %) ; m.p. = 124-125°C . I.R. (CCl_4) : 1752 cm^{-1} . ^1H n.m.r. δ : 1.04 (6H, s, 2 CH_3) ; 1.40 (3H, m) ; 1.48 (1H, m, H_2) ; 1.78 (1H, d, $\text{H}_{3\alpha}$, $^2\text{J} = 20$

H_z) ; 2.03 (3H, m, H₄ + H_{5β} + H_{6β}) ; 2.2 (1H, d, H₁) ; 2.41 (1H, d of d, ²J = 20 Hz, ³J = 4 Hz) ; ¹³C n.m.r. : 59.4 (C₁) ; 218.8 (C₂) ; 44.2 (C₃) ; 43.5 (C₄) ; 27.7 (C₅) ; 22.8 (C₆) ; 45.4 (C₇) ; 21.7 (C₈) ; 20.8 (C₉) .

Norcamphorquinone (12) : Apocamphor 11b (3.7 g) and selenium dioxide (7 g) were heated at 140°C in acetic acid (5 ml) for 15 h . After cooling the reaction mixture was treated with 2N aqueous NaOH and extracted with ether (3 x 40 ml) . The organic layers combined, washed with H₂O, then brine and dried (MgSO₄) . Filtration and concentration gave 3.6 g of 12 (90 %) . m.p. = 113-116°C ; I.R. (CCl₄) : 1780 and 1760 cm⁻¹ . ¹H n.m.r. δ : 1.11 (3H, s, Me-8) ; 1.15 (3H, s, Me-9) ; 1.7 (2H, m, H_{5α} + H_{6α}) ; 2.24 (2H, m, H_{5β} + H_{6β}) ; 2.52 (2H, d of d, H₁ + H₄) . ¹³C n.m.r. : 57.7 (C₁) ; 202.7 (C₂) ; 202.7 (C₃) ; 57.7 (C₄) ; 23.0 (C₅) ; 23.0 (C₆) ; 41.05 (C₇) ; 23.0 (C₈) ; 19.9 (C₉) .

Enol-ether (10b) : 3 g of diazomethane in ether (prepared from 21.0 g of diazald, with the diazald kit) was added dropwise with cooling at 0°C to 3.5 g of norcamphorquinone 12 in ether (100 ml), then at 25°C overnight . The reaction mixture was treated with 10 % aqueous HOAc (100 ml) . The organic layer washed with brine and dried (MgSO₄) . Filtration and concentration gave 3.82 g of 10b (100 %) : yellow liquid . I.R. (film) : 3065, 1665 and 1660 cm⁻¹ . ¹H n.m.r. δ : 0.98 (3H, s, Me-9) ; 1.1 (3H, s, Me-10) ; 1.57 (1H, m, H_{7α}) ; 1.68 (1H, m, H_{6α}) ; 2.24 (2H, m, H_{6β} + H_{7β}) ; 2.31 (1H, d, H₅, ³J = 6 Hz) ; 2.36 (1H, d, H₂, ³J = 7 Hz) ; 3.69 (3H, s, O-Me) ; 5.15 (1H, s, H₃) . ¹³C n.m.r. : 59.5 (C₁) ; 203.8 (C₂) ; 98.0 (C₃) ; 183.7 (C₄) ; 52.1 (C₅) ; 25.3 (C₆) ; 28.9 (C₇) ; 46.6 (C₈) ; 25.6 (C₉) ; 20.8 (C₁₀) ; 56.0 (O-Me) .

8,8-Dimethylbicyclo [3.3.1] octane-2,4-dione (7) : A solution of 10b (4.0 g) in ether (60 ml) was added to aqueous 4N HCl (60 ml) with stirring at 20°C overnight . The aqueous layer was extracted with CH₂Cl₂ (4 x 60 ml) . The organic layers combined washed with brine and dried (MgSO₄) . Filtration and concentration gave 3.80 g of dione 7 (97 %) . m.p. = 208-211°C (MeOH-CH₂Cl₂) . I.R. (CHCl₃) : 1726, 1704 cm⁻¹ . ¹H n.m.r. δ : 0.98 (3H, s, Me-9) ; 1.1 (3H, s, Me-10) ; 1.91 (2H, m, H_{6α} + H_{7α}) ; 2.32 (2H, m, H_{6β} + H_{7β}) ; 2.55 (2H, m, H₁ + H₂) ; 3.03 (1H, 2 t, ²J = 19 Hz, ⁴J = 2 Hz, H_{3β}) ; 3.38 (1H, d, ²J = 19 Hz, H_{3α}) . ¹³C n.m.r. : 60.0 (C₁) ; 207.6 (C₂) ; 50.9 (C₃) ; 207.6 (C₄) ; 60.0 (C₅) ; 25.2 (C₆) ; 25.2 (C₇) ; 41.9 (C₈) ; 24.76 (C₉) ; 22.1 (C₁₀) . Anal. calc. for C₁₀H₁₄O₂ : C, 72.26 ; H, 8.49 ; Found : C, 71.96 ; H, 8.48 .

Enol-Acetate (10a) : N-butyllithium (1.6 M) in hexane was added dropwise to a mixture of 7 (2 g) in THF (140 ml) and triphenylmethane (10 mg) with stirring under argon at - 30°C (until the colour turned to pink), then acetic anhydride (3 ml) was added . The reaction mixture was left to warm to room temperature, and treated with H₂O (60 ml), extracted with ether (3 x 50 ml), washed with aqueous NaHCO₃ (5 %), water, brine and dried (MgSO₄) . Filtration and concentration to dryness gave 2.3 g of 10a (80 %), yellow liquid . I.R. (film) : 1770, 1672, 1625 cm⁻¹ . ¹H n.m.r. δ : 1.02 (3H, s, Me-9) ; 1.18 (3H, s, Me-10) ; 1.59 (1H, t, H_{7α}, ²J = 10 Hz, ³J = 10 Hz) ; 1.88 (1H, t, H_{6α}, ²J = 10 Hz, ³J = 10 Hz) ; 2.25 (3H, s, O=C-CH₃) ; 2.25 (2H, m, H_{6β} + H_{7β}) ; 2.40 (1H, d, H₁, ³J = 6 Hz, ⁴J = 1.5 Hz) ; 2.45 (1H, d of d, H₅, ³J = 6 Hz & ⁴J = 1.5 Hz) ; 5.86 (1H, s, H₃) . ¹³C n.m.r. : 59.5 (C₁) ; 203.1 (C₂) ; 113.7 (C₃) ; 167.2 (C₄) ; 51.3 (C₅) ; 28.8 (C₆) ; 24.3 (C₇) ; 48.0 (C₈) ; 25.4 (C₉) ; 20.6 (C₁₀) ; 173.9 (-C-acetate) ; 21.4 (Me-C) .

Anal. calc. for C₁₂H₁₆O₃ : C, 69.21 ; H, 7.74 ; Found : C, 68.98 ; H, 7.75 .

Photocycloaddition of enol-acetate 10a to cyclohexene : A solution of 10a (2.2 g) in CH₂Cl₂ (50 ml) and cyclohexene (30 ml) was purged with argon for 0.5 h in a photoreaction vessel then irradiated with a TW.150.W HANAU medium pressure Hg lamp through a pyrex filter at - 50°C for 6 h until t.l.c. (SiO₂, EtOAc : pentane 1 : 4) indicated loss of starting material . Concentration to dryness gave 2.7 g of two photoadducts A + B / 3 : 1 (after crystallisation from pentane ; m.p. =

145-155°C); I.R. (CCl₄) δ : 1730 and 1694 cm⁻¹, major compound A : ¹H n.m.r. δ : 2.87 (1H, d, ³J = 9.75 Hz, H₁₁); 2.77 (1H, q (2t), J = 9 Hz); 2.52 (1H, d, J = 6.75 Hz, H₁); 1.95 (3H, s, C-Me); 0.93 (6H, s, Me-15 + Me-16); minor compound B : 2.67 (1H, d, J = 10.5 Hz, H₁₁); 2.40 (1H, d, J = 6 Hz, H₁); 1.93 (3H, s, -C-Me); 0.91 (6H, s, Me-15 + Me-16).

Rearrangement of photoproducts A + B : 10 % aqueous KOH (10 ml) was added dropwise to a solution of photoproducts A + B (410 mg) in EtOH (20 ml) with stirring. After 24 h at room temperature the reaction mixture was treated with 1N HCl (Ph = 7) and extracted with Et₂O (3 x 20 ml). The organic layers were combined, washed with brine, and dried (MgSO₄). Filtration and concentration to dryness gave a residue (335 mg) which was purified by flash column chromatography²⁸ using a mixture of pentane and ethylacetate (4 : 1 v/v) as eluent to give ketone 13 (117 mg); R_f = 0.5 and diketone 14 (216 mg), R_f = 0.35.

Ketone 13 (liquid) : I.R. (film) : 1678 cm⁻¹. U.V. λ_{\max} = 252.5 nm (ϵ = 6900, EtOH), MS, m/z (MH⁺) = 131 (C.I.). ¹H n.m.r. (400 MHz) 2.2H, δ 3.05 and 3.08 (2H, septuplet H₄ + H₉, ³J_{H₄-H₉} = 6 Hz, ³J = 6 Hz and ³J = 12 Hz); 2.31 (1H, d, H₁, ³J = 7.5 Hz); 2.28 (1H, d, H₁₁, ³J = 6 Hz); 2.23 (1H, m, H_{13 β}); 2.15 (1H, m, H_{12 β}); 1.75 (4H, m, 2 H₅ + 2 H₈); 1.48 (6H, m, 2 H₆ + 2 H₇ + H_{12 α} + H_{13 α}); 1.13 (3H, s, Me-16); 0.98 (3H, s, Me-15). ¹³C n.m.r. : 47.3 (C₁); 140.6 (C₂); 39.4 (C₃); 24.4 (C₄); 25.1 (C₅); 22.8 (C₆); 27.8 (C₇); 41.0 (C₈); 179.5 (C₉); 199.3 (C₁₀); 61.2 (C₁₁); 19.5 (C₁₂); 19.3 (C₁₃); 51.3 (C₁₄); 26.7 (C₁₅); 21.2 (C₁₆).

Anal. calc. for C₁₆H₁₆O : C, 85.68; H, 7.19; Found : C, 85.15; H, 7.20.

15,16-Dimethyltricyclo [9.2.1.0.^{3.8}] tetradecan-2,10-dione; diketone 14 : m.p. = 91-92°C (pentane-ether). I.R. (CCl₄) : 1678 cm⁻¹. U.V. λ_{\max} = 300 nm (ϵ = 56) and λ_{\max} = 220 nm (ϵ = 248, EtOH). ¹H n.m.r. δ : 2.65 (2H, d of d, H₁, ³J = 6 Hz and H₁₁, ³J = 7.5 Hz); 2.56 (1H, d of d, ²J = 18 Hz and ³J = 3 Hz); 2.32 (2H, m, H_{12 β} + H_{13 β}); 2.25 (1H, q, H_{9 β} , ²J = 18 Hz and ³J = 10 Hz); 2.11 (1H, t of d, H_{3 β} , ³J_{H₃-H₈} = 12 Hz, ³J_{H₃-H_{4 α}} = 12 Hz and ³J_{H₃-H_{4 β}} = 3 Hz); 1.55 (1H, q of d, H_{4 α} , ²J_{H_{4 α} -H_{4 β}} = 12 Hz, ³J_{H_{4 α} -H₃} = 12 Hz, ³J_{H_{4 α} -H_{5 β}} = 12 Hz and ³J_{H_{4 α} -H_{5 α}} = 3 Hz); 1.10 (3H, s, Me-16); 0.93 (3H, s, Me-15). ¹³C n.m.r. : 65.1 (C₁); 217.3 (C₂); 61.2 (C₃); 33.0 (C₄); 29.67 (C₅); 26.0 (C₆); 35.4 (C₇); 32.78 (C₈); 51.3 (C₉); 212.5 (C₁₀); 63.3 (C₁₁); 26.15 (C₁₂ or C₁₃); 26.7 (C₁₃ or C₁₂); 47.0 (C₁₄); 32.78 (C₁₅); 22.91 (C₁₆).

Anal. calc. for C₁₆H₁₈O₂ : C, 79.31; H, 7.49; Found : C, 79.10; H, 7.50.

Photocycloaddition of enol-ether 10b to cyclohexene : A solution of 10b (0.5 g) in CH₂Cl₂ (55 ml) and cyclohexene (16 ml) was purged with argon for 0.5 h in a photoreaction vessel then irradiated with a TQ 150 W HANAU medium pressure Hg lamp through a Heliosil ($\lambda > 245$ nm) filter at -50°C for 8 h until t.l.c. (SiO₂, EtOAc : pentane 1 : 4) indicated loss of starting material concentration to dryness gave 0.7 g of crude product. This product was purified by flash column chromatography²⁹ using silica gel (230-400 Mesh) and a mixture of petroleum-ether and ethyl-acetate (4.5/0.5 and 4/1 v/v) as eluent to give 0.49 g (70 %) of a mixture of photoadducts of 15 and 16. The material was shown to be a 3 : 1 mixture of 15 and 16 respectively by 400 MHz ¹H n.m.r. Since separation of the individual components of the photoadduct mixture was very difficult, the sequence was carried through on the mixture (0.2 g) with fractions of 20 ml. The fractions (6 to 10) isolated by the above chromatography were further purified on two 20 x 20 cm silica gel Merck (PF₂₅₄) plates (thickness 1 mm), using a mixture of petroleum-ether and ethyl-acetate (4 : 1, v/v) as eluent to give 35 mg of 16 (R_f : 0.52). Treatment of the mixture of photoadducts (15 and 16) 200 mg with HCl (0.1 N) in MeOH (25 ml) at room temperature for 48 h, the reaction mixture was neutralised by solid NaHCO₃, the solvent was removed under reduced pressure to give 190 mg of the crude product. This product was purified by t.l.c. (PF₂₅₄, Merck, silica gel 60) using a mixture of petroleum-ether and ethyl-acetate (4.1, v/v) to give 50 mg (25 %) of 15 (R_f : 0.48) and 110 mg (55 %) of 14 (R_f = 0.15).

15 : Liquid, I.R. (CCl_4) : 1695 cm^{-1} . ^1H n.m.r. δ : 3.18 (3H, s, OMe) ; 2.6 (1H, d, H_9 , $J = 9.75$ Hz) ; 2.60 + 2.25 (5H, m, $\text{H}_1 + \text{H}_{11} + \text{H}_{12} + 2\text{H}_{13}$) ; 2.05 + 1.47 (8H, m, $\text{H}_7 + 2\text{H}_4 + \text{H}_5 + \text{H}_3 + \text{H}_6 + \text{H}_8 + \text{H}_{12}$) ; 1.40 + 1.18 (3H, m, $\text{H}_7 + \text{H}_6 + \text{H}_5$) ; 1.01 and 1.0 (6H, d, Me-15 + Me-16) .

Anal. calc. for $\text{C}_{17}\text{H}_{20}\text{O}_2$: C, 79.65 ; H, 7.86 ; Found : C, 79.45 ; H, 7.95 .

16 : Liquid, I.R. : 1695 cm^{-1} . ^1H n.m.r. δ : 3.08 (3H, s, OMe) ; 2.71 (1H, d, H_9 , $J = 10.5$ Hz) ; 2.52 (1H, q) ; 1.06 (3H, s, Me-16) ; 1.03 (3H, s, Me-15) .

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