Tetrahedron, Vol. 40, No. 21, pp. 4285 to 4295, 1984.
Printed in Great Britain.

0040-4020/84 $3.00 + 00

SYNTHETIC STUDIES ON TAXANE DITERPENES
X-RAY STRUCTURE OF A KEY INTERMEDIATE

R. Z. ANDRIAMIALISOA[†], M. FETIZON[*] and I. HANNA
Laboratoire de Synthèse Organique, Ecole Polytechnique
91128 PALAISEAU Cedex, France .

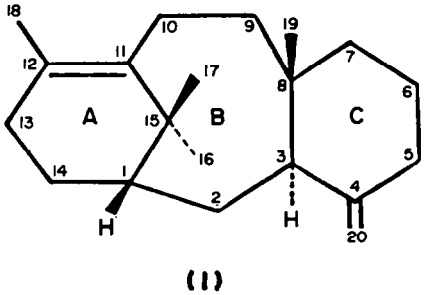
C. PASCARD and T. PRANGE
Institut de Chimie des Substances Naturelles, C.N.R.S.,
91190 GIF-sur-YVETTE, France .

(*Received in France* 16 *July* 1984)

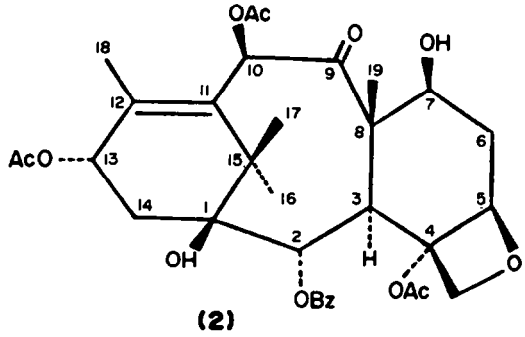
A b s t r a c t - Michael condensation of the dienone (3) with the vinyllactone (19) leads to the compound (20) . Attempts to construct the B ring of the taxane skeleton by direct cyclization of (20) are reported . The stereochemistry of (20) is established by X-ray structure determination .

The taxanes are a group of natural products isolated from various species of *Taxus* and possess a unique carbone skeleton (1) [1] . This unusual structure containing a sterically congested eight-membered B ring provides a challenging synthetic target . Moreover, some taxane derivatives, such as taxol (2) exhibit highly potent antileukemic and tumor inhibitory properties [2] .

The key step in taxane diterpenes synthesis is the construction of B ring . Several approaches have been reported involving an anionic Oxy-Cope rearrangement [3], an intramolecular Diels-Alder cyclization [4] or a fragmentation process [5] .



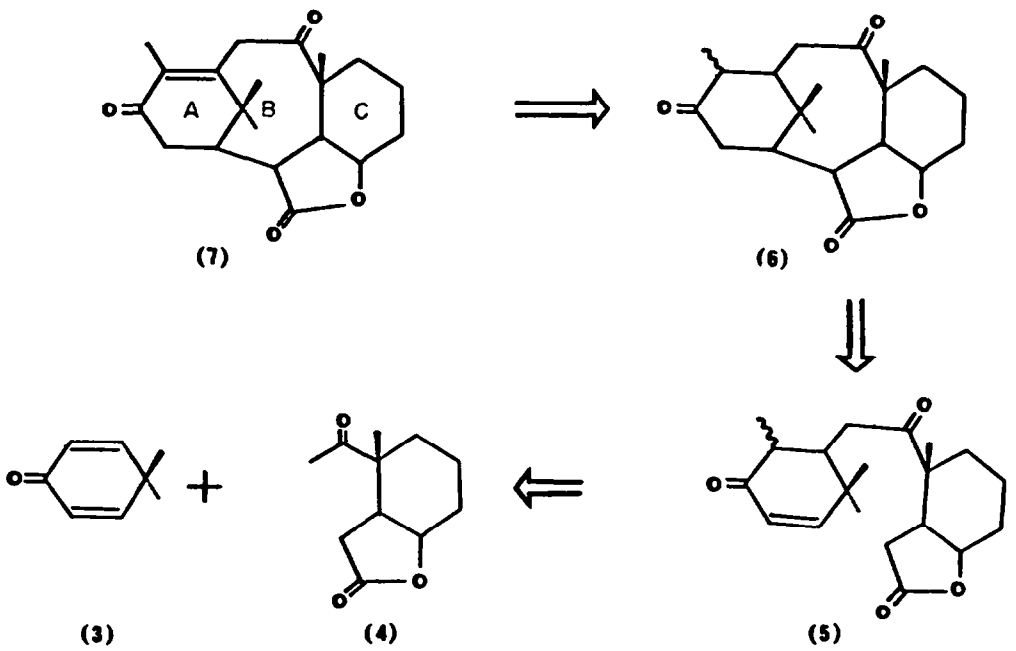
(1)



(2)

† I.C.S.N. Postdoctoral fellow 1981 . Present adress : Institut de Chimie des Substances Naturelles GIF-sur-YVETTE .

In designing a synthesis of the taxane skeleton, our first approach was to begin by coupling two units (3) and (4) which would provide the two six-membered A and C rings, followed by direct cyclization to form the B ring . A retro-synthetic analysis shown in Scheme I summarizes this approach .



Scheme I

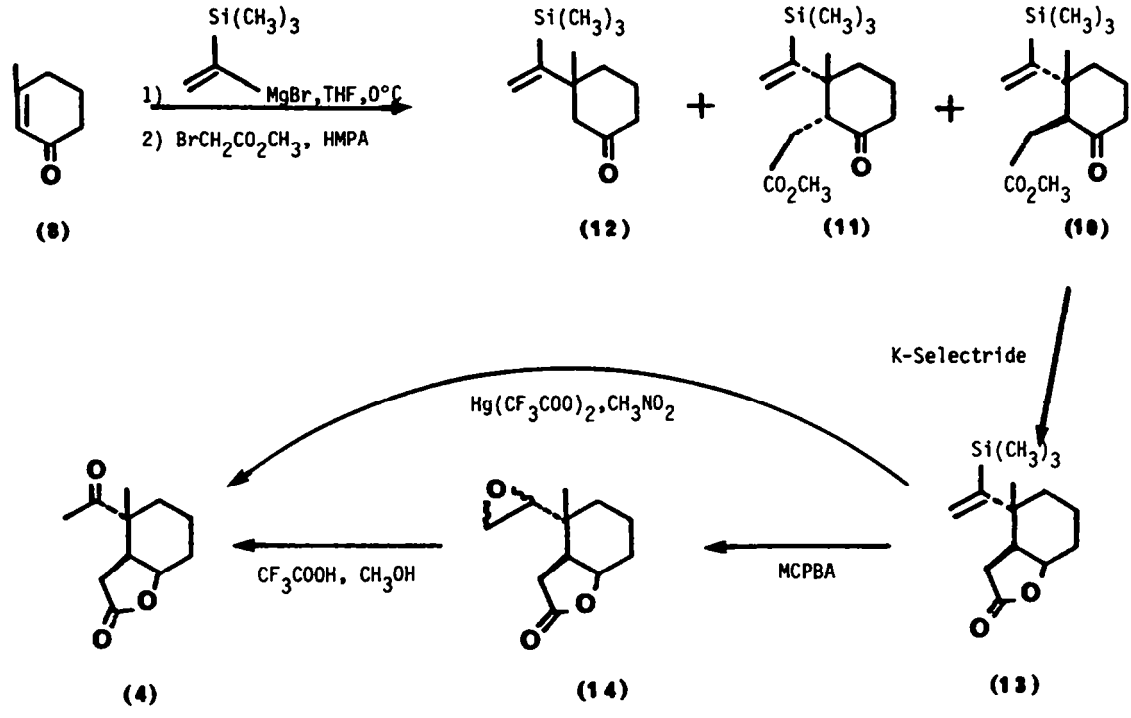
While this work was in progress, such an approach was reported but without success [6] . This paper describes the result of our investigation and reports the X-ray structure of the coupling product .

Results and Discussion

The 4,4-dimethylcyclohexadienone (3) was readily available . Thus dehydrogenation of 4,4-dimethylcyclohexenone [7] with D.D.Q. in refluxing dioxane afforded (3) in 80 % yield . The ketolactone (4) has been synthesized from the 3-methylcyclohexenone (8) according to the Scheme II . Reaction of (8) with 1-trimethylsilyl-1 vinyl magnesium bromide [8] (an acylanion equivalent) in the presence of 10 % cuprous iodide was effected in THF at 0°C . The resulting metalloenolate was trapped by inverse addition a solution of methyl bromoacetate in HMPA .

Standard workup and separation by flash chromatography on silica gel afforded the isomers (10) and (11) in 50 % yield along with the non alkylated product (12) in 30 % yield . The base-catalyzed equilibration of (11) (MeONa in MeOH) led to the thermodynamically stable ketone (10).The expected stereochemistry of (10) was based on the well documented reaction mechanism of the alkylation of an enolate ion, which should proceed from the less hindered side of the molecule, that is opposite to the bulky vinyltrimethylsilane group . Actually this has been proved by analysis of

the ^{1}H NMR spectrum . Thus, the methyl group signal at δ 0.92 is schielded relative to the analogous signal for (11) at δ 1.28, in accordance with expectation based on steric interaction . This was confirmed by ^{13}C NMR data (methyl peaks at δ 18.9 and δ 28.5 for (10) and (11) respectively) .



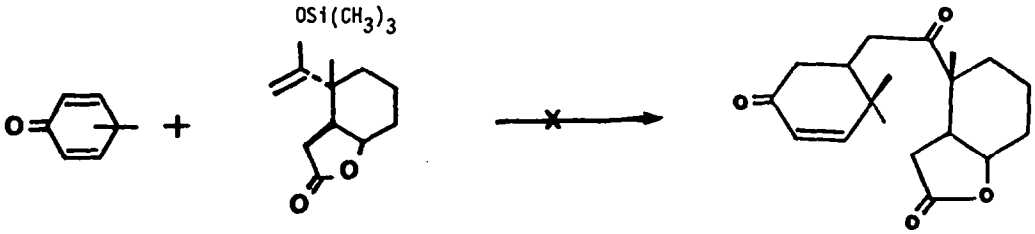
Scheme II

As expected, reduction of the ketoester (10) by potassium tri-sec-butyl borohydride (K-Selectride) in THF at - 70°C gave the lactone (13) as the sole product . Preparation of the ketolactone (4) from (13) was achieved according to Stork [9] who had shown that vinylsilane are transformable to carbonyl group by epoxidation followed by acid treatment . Thus epoxidation of (13) by m-chloroperbenzoic acid in CH_2Cl_2 gave a mixture of stereoisomers (14) . However upon attempted hydrolysis of (14) with methanolic H_2SO_4 or Lewis acid (BF_3-Et_2O) in methanol, a mixture of unseparable products were obtained . On screening different acids we found the most satisfactory one to be trifluoroacetic acid in methanol at reflux which afforded the ketolactone (4) in 37 % overall yield from (13) .

In order to improve this yield, we attempted direct (13) → (4) transformation by means of oxymercuration-demercuration (OM-DM) reaction . It was reported that vinyltrimethylsilane derivatives undergo the OM-DM to give different products depending upon the vinyl substitution [10] . Indeed, treatment of (13) with mercuric trifluoroacetate in nitromethane at room temperature followed by hydrolysis at reflux led to the desired ketolactone (4) in 41 % yield .

With the ketolactone (4) in hand, we turned our attention to the study of the condensation with the dienone (3) . In order to realize this transformation, a differentiation of the two carbonyl groups in (4) is required . The well-known difference in acidity of ketones vs. esters (4-5 pKa units) [11] did not allow a regioselective deprotonation . Selective trimethylsilylation

of the ketone moiety seemed to be the convenient solution . Thus, treatment of (4) by iodotrimethylsilane and trimethylamine in CH_2Cl_2 afforded the trimethylsilylenol ether (15) in 90 % yield . This procedure was found to be very efficient for the selective silylation of hindered ketones [12]. It is interesting to note that iodotrimethylsilane and hexamethyldisilizane (HMDS) in pentane [13] were unreactive toward such compounds .

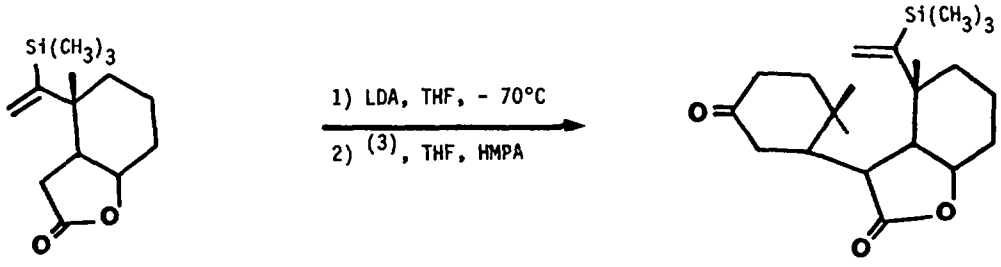


(3) (15) (16)

At this point of the synthesis it was planned that the silylenol ether (15) would undergo the Michael condensation with the dienone (3) by Mukaiyama's reaction [14] to give (16) .

All attempts to exploit this reaction using $TiCl_4$ or $TiCl_4$-$Ti(O\text{-}iPr)_4$ as Lewis acid proved fruitless . The dienone (3) and the ketolactone (4) were recovered . This failure may be explained in terms of the steric hinderance of the silylenol ether .

Having been thwarted in our initial attempt, we turned our attention to an alternative strategy . While our previous approach involved a condensation with the dienone (3) by the ketone side, there appeared to be no reason that the lactone could not be employed for the initial Michael condensation . To evaluate this possibility, we examined the condensation of (3) with the lactone (13). Indeed deprotonation of (13) by the LDA followed by reaction with the dienone (3) afforded (17) in 40 % yield .



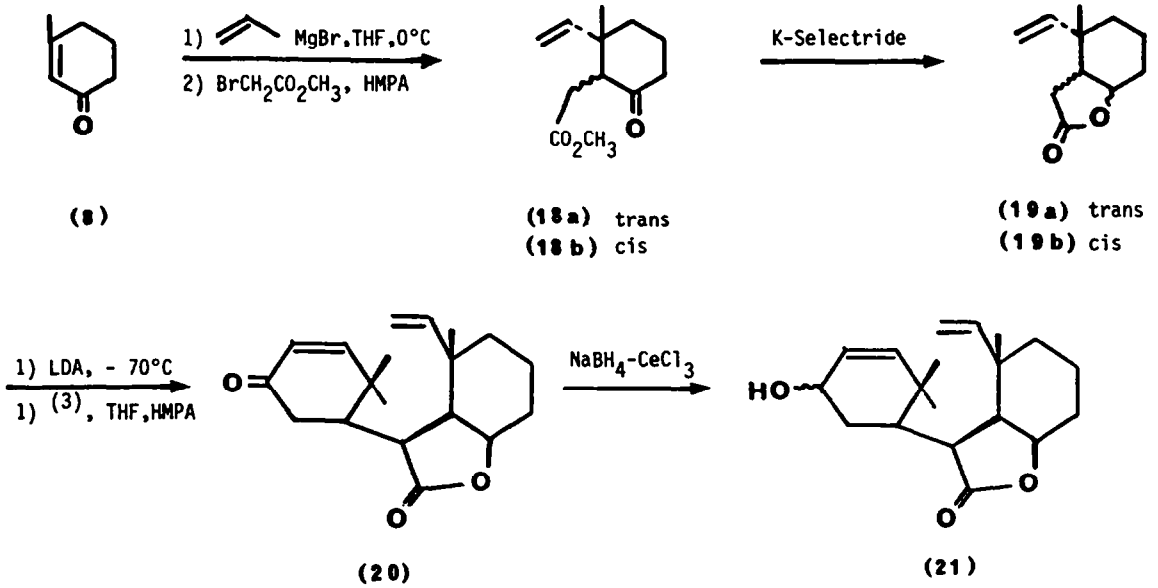
(13) (17)

This positive result suggested the construction of the taxane skeleton by condensing (3) and (18) (Scheme III) .

While the 1,4-Grignard addition of the trimethylsilylvinyl magnesium bromide gave a separable isomers (10) and (11), the reaction with the vinyl magnesium bromide led to an unseparable

mixture of isomers . The ^{1}H NMR spectrum showed two methyl singulets at δ 0.85 and 1.16 corresponding to (18a) and (18b) respectively in 1.5 : 1 ratio .This difference in chemical shifts has previously been observed for compounds (10) and (11) .Base-catalyzed equilibration did not provide the pure thermodynamic isomer but afforded a mixture of (18a) and (18b) in 3 : 1 ratio . Potassium-Selectride reduction of this mixture provided the lactones (19a) and (19b) in the same ratio .

As we were unable to separate these isomers, the Michael condensation was effected on the mixture . Thus, deprotonation of the lactone with the LDA-HMPA complex followed by inverse addition of the dienone (3) solution in THF diluted with HMPA afforded, after flash chromatography, a colorless cristalized product in 66 % yield .The I.R. spectrum showed the characteristic absorptions of γ-lactone (1780 cm^{-1}) and α,β-unsaturated ketone (1690 cm^{-1}) . ^{1}H NMR showed one methyl singlet at δ 1.13 and ^{13}C NMR spectrum confirmed the purity of the product . These spectroscopic data are in agreement with the structure (20) . The relative stereochemistry at C-3 and C-8 was deduced from the stereochemistry of its precursor : the major isomer (19a) . Moreover, since the C_1-C_2 bond should be equatorial with respect to the A ring, the relative stereochemistry at C-1 and C-2 was assumed to be trans .



Scheme III

Attention was focused on the key step of the synthesis, i.e. the cyclization of (20) . We first attempted acid-catalyzed cyclization of the enone using trifluoroacetic acid (TFA), TFA-trifluoroacetic anhydride or diethylaluminium chloride in CH_2Cl_2 . These attempts were unsuccessful and the starting material was recovered . Having in mind that allylic carbonium ions are the most flexible initiators [15], we attempted acid-catalyzed cyclization of the allylic alcohol (21) which was obtained from the enone (20) by $NaBH_4$-$CeCl_3$ reduction [16] in quantitative yield . Treatment of (21) with TFA in CH_2Cl_2 led to disappearence of the starting material . Unfortunatly, no cyclized product was formed .

After failure of other attempts, we looked for an explanation to the unreactivity of the vinyl group toward cyclization . More evidence for the stereochemistry of the enone (20) was required since inspection of molecular models suggests that this product may have different possible conformations . Therefore, it was subjected to X-ray analysis .

X - Ray Analysis

The system is monoclinic, space group $P2_1/c$, with the following parameters : a = 8.520(3) ; b = 13.063(4) ; c = 15.292(4) Å and β = 104.5(3)° for Z = 4 . The volume of the cell is 1647.8 $Å^3$. The structure has been solved by application of the multisolution technique [17] . All the atoms but the two carbons at C(15) were located on the E-map corresponding the heighest figures of merit . The missing atoms were subsequently deduced from the first Fourier synthesis based on all the structural factors . The coordinates and the individual thermal isotropic thermal parameters were refined by block-diagonal matrix least-squares .All the hydrogen atoms were located on F_o-F_c Fourier maps and introduced in the refinements with a fixed isotropic thermal factor of 5. $e\text{-}Å^{-2}$. The use of anisotropic thermal factors led the refinement to converge at a conventional agreement factor : $R = \Sigma||F_o| - |F_c|| / \Sigma|F_o| = 8.6\ \%$.

The figure shows the mean plane projection of the structure ; the numbering of the atoms is that of the taxol derivatives [1] .

The vinyl group at C(8) is in a axial disposition whereas the six-membered rings and the lactone display a cis junction (C(2) - C(3) : axial ; C(4) - O(1) : equatorial) . The second cyclohenon ring is linked via the C(1) - C(2) bond in equatorial position and situated in trans in respect to the vinyl at C(8) . *Thus leading to a unfavorable situation for cyclisation at C(11)* .

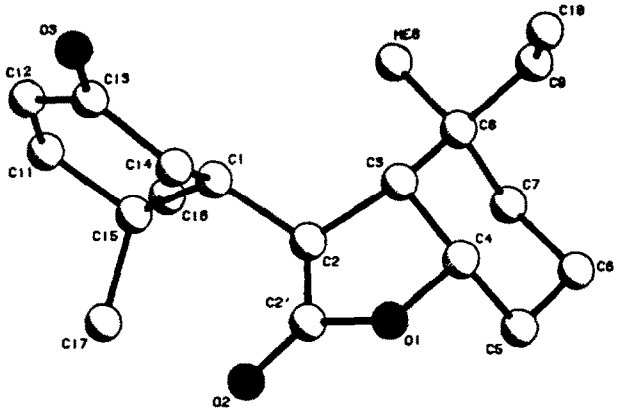


Figure - The X-Ray Structure of (20)

In summary, although this approach did not come off, the investigations confirmed the difficulty to construct the B ring by direct cyclization . Another approach is on investigation and the synthetic studies are in progress .

EXPERIMENTAL

Melting points were taken on a Reichert apparatus and are uncorrected . Infrared spectra were recorded with a Perkin-Elmer 399 spectrometer for solution in CCl_4 . ^1H NMR spectra were recorded at 60 MHz using a Varian T.60 or Jeol PMX.60, or at 400 MHz using a Bruker 400 WM instruments, for solutions in deuteriochloroform with tetramethylsilane as internal standard . ^{13}C NMR spectra were recorded on a Varian CFT.20 (20 MHz) or XL.100 (25 MHz) spectrometers .

Mass spectra were obtained using a V.G. Micromass ZAB.2F spectrometer . Solvents were dried using standard methods . Flash chromatography [18] was performed on 40-63 µm (400 - 230 mesh) silica gel 60 .

Conjugate addition of 1-(trimethylsilyl)vinylmagnesium bromide to 3-methyl-2-cyclohexenone . Synthesis of (10,) (11) and (12) .

1-(Bromovinyl)trimethylsilane (15 g, 82.5 mmol) was added dropwise with stirring to magnesium (2.0 g, 82.5 mmol) and one crystal of iodine in dry THF (75 ml) so as to keep a gentle reflux . Refluxing was continued for one hour after addition . The mixture was then cooled to - 5°C, CuI (1.5 g, 7.8 mmol) added and the resulting purplish black solution was stirred for 15 min at 0°C, and then 3-methylcyclohexenone (8) (5.0 g, 45.5 mmol) was added neat over 5 min . The solution was stirred for 1 h at 0°C and transferred by argon pressure over 10 min period to stirred and cooled (0°C) solution of methyl bromoacetate (13 ml) in HMPA (45 ml) . The cooling bath was removed and the solution was stirred for 2 h at room temperature . After quenching the solution with saturated NH_4Cl solution, the reaction mixture was diluted with ether . The organic phase was washed successively with water and brine, dried and the solvent was removed in vacuo . The resulting oil was flash chromatographed on a 5 cm column by using pentane/ethyl acetate (92 : 8, v/v) as eluant affording 2.8 g of 3-methyl-3-[1-(trimethylsilyl)-1-vinyl] cyclohexanone (12) as an oil, ν 3060, 1715 cm^{-1} ; ^1H NMR δ 5.57 (1H, d, J = 2 Hz), 5.40 (1H, d, J = 2 Hz), 1.10 (3H, s), 0.17 (9H, s) . ^{13}C NMR δ 211.5 (C=O), 156.4 (s), 124.6 (t, CH_2=), 53 (t, CH_2), 45.2 (s), 40.6 (t, CH_2), 35.9 (t, CH_2), 27.2 (q, CH_3), 21.7 (t, CH_2), 1.4 (q, CH_3) .

4.2 g of pure methyl trans-2-[3-methyl-3-(1-vinyltrimethyl-silyl)cyclohexa-1-one-2-yl] acetate (10) as an oil, ν 3100, 1740, 1715 cm^{-1} ; ^1H NMR δ 5.56 (1H, br. s), 5.41 (1H,br. s), 3.58 (3H, s), 0.92 (3H, s), 0.21 (9H, s) . ^{13}C NMR δ 210.7 (C=O), 173.3 (C=O, ester), 157.8 (s), 125.4 (t, CH_2=), 53.3 (d, CH), 51.4 (q, methoxy), 48.6 (s), 41.2 (t, CH_2), 39.1 (t, CH_2), 29.1 (t, CH_2), 22.7 (t, CH_2), 18.9 (q, CH_3), 1.6 (q, CH_3) .

0.8 g of pure methyl cis-2-[3-methyl-3-(1-vinyltrimethysily)cyclohexa-1-one-2-yl] acetate (11) as an oil, ν 3100, 1740, 1715 cm^{-1} ; ^1H NMR δ (1H, br. s), 5.18 (1H,br. s), 3.61 (3H, s), 1.28 (3H, s), 0.16 (9H, s) ; ^{13}C NMR δ 210 (C=O), 173.5 (C=O, ester), 154.4 (s), 127.4 (t, CH_2=), 57.1 (d, CH), 51.5 (q, methoxy), 49.5 (s), 39.9 (t, CH_2), 36.9 (t, CH_2), 29.4 (t, CH_2), 28.5 (q, CH_3), 20.7 (t, CH_2), 1.3 (s, CH_3) . 1.5 g mixture of (10) and (11) .

Reduction of ketoester (10), Lactone (13)

To a stirred and cooled (- 70°C) solution of ketoester (10) (2.0 g, ≃ 7.1 mmol) in dry THF (40 ml) was added K-Selectride (21 ml, 21 mmol, 1 M solution in THF) under argon . The reaction mixture was stirred at - 70°C for 7 h . After the addition of 3 N NaOH solution (20 ml), the mixture was warmed to room temperature and 30 % H_2O_2 (20 ml) was added . Following the initial exothermic reaction, the mixture was stirred and additional 30 min, then 3N HCl solution (60 ml) was added and

the mixture was stirred 15 min at room temperature . After the extraction with ether, the combined organic layers were washed with brine and dried and the solvent was removed in vacuo to afford crude (13) as a white cristalline product . m.p. 108 - 109°C (pentane); ν 3100, 1780 cm^{-1} ; ^1H NMR δ 5.68 (1H, br. s), 5.53 (1H, br. s), 4.45 (1H, m), 2.80 (1H, m), 2.40 (1H, d, J = 10 Hz), 2.30 (1H, d, J = 10 Hz), 1.03 (3H, s), 0.17 (9H, s) ; ^{13}C NMR δ 1763 (C=O), 157.4 (s), 124.5 (t; CH_2=), 77.7 (d, CH), 42.5 (d, CH), 31.8 (t, CH_2), 30.6 (t, CH_2), 28.2 (t, CH_2), 27.0 (q, CH_3), 18.5 (t, CH_2), 1.7 (q, CH_3) .

Ketolactone 4

A - *Epoxidation of (13) . Epoxylactone (14)*

A solution of m-chloroperbenzoic acid (1.8 g, 98 % purity) in CH_2Cl_2 (12 ml) was added dropwise to a stirred solution of (13) (1.65 g) in 15 ml of CH_2Cl_2 cooled to 0°C under argon . The mixture was stirred at 0°C for 30 min and at room temperature for 14 h . Washing with saturated sodium sulfite (2 X) and sodium bicarbonate (1 X) as well as brine, followed by drying and solvent evaporation, left 1.73 g of a crude mixture of two isomer epoxides (14) . This product was utilized without further purification for the next step .

Acid-Catalysed rearrangement of (14)

A solution of the above crude epoxide in methanol (10 ml) and trifluoroacetic acid (5 ml) was heated at 70°C under argon for 48 h . After being cooled, the reaction mixture was diluted with water and extracted with ether . The combined ether layers were washed with water, saturated $NaHCO_3$ solution and brine before drying . The resulting residue (0.94 g) was flash chromatographed on 4 cm column by using pentane/ethyl acetate (2 : 1, v/v) affording 470 mg of pure ketolactone (4) (37 % from (13)) .ν 1780, 1710 cm^{-1} ; ^1H NMR (400 MHz) δ 4.70 (1H, m), 3.11 (1H, m), 2.14 (3H, s), 1.16 (3H, s) ; ^{13}C NMR δ 211.5 (C=O), 176.1 (C=O, lactone), 77.7 (d, CH-O), 50.4 (s), 39.6 (d, CH), 29.9 (t, CH_2), 29.7 (t, CH_2), 28.2 (t, CH_2), 24.2 (q, CH_3), 23.4 (q, CH_3), 19.2 (t, CH_2) ; mass spectrum m/z 196 ($M^{\cdot+}$) .

B - *Oxymercuration-Demercuration of (13)*

A solution of (13) (126 mg, 0.5 mmol) in nitromethane (1.3 ml) was added to a stirred solution of mercury (II) trifluoroacetate (426 mg, 1 mmol) in nitromethane (1.5 ml). After stirring for 5 min, water (1.5 ml) was added and the mixture was stirred at 55°C for 48 h under argon . The reaction mixture was cooled, diluted with water and extracted with ether . The combined ether layers were washed with water (3 X) and brine (2 X) followed by drying and solvent evaporation . The resulting residue was flash chromatographed on a 1 cm column using pentane/ethyl acetate (3 : 1, v/v) as affording 40 mg (41 %) of (4), identical to that prepared above .

Trimethylsilyl enol ether (15)

Dry triethylamine (0.6 ml, 3.3 mmol) was added to a stirred solution of (4) (470 mg, 2.4 mmol) in dry freshly distilled CH_2Cl_2 (7 ml) under argon . The mixture was cooled to - 20°C and freshly distilled iodotrimethylsilane from copper powder (0.5 ml) was added via seringue . The reaction mixture was allowed to warm to room temperature and stirring continued for 4 h . The solvent removed in vacuo and the residue taken up in dry ether (20 ml) . The precipitated was filtered off and the solution was evaporated under reduced pressure to give (15) (580 mg, 90 %) as cristalline product . ν 1780, 1615 cm^{-1} ; ^1H NMR δ 4.66 (1H,m), 4.25 (2H, br. s), 1.02 (3H, s), 0.40 (9H, s) ; ^{13}C NMR δ 175.4 (C=O), 161.4 (s), 88.5 (t, CH_2=), 78.4 (d, CH), 41.7 (s), 41.3 (d, CH), 31.0 (t, CH_2), 30.5 (t, CH_2), 28.4 (t, CH_2), 25.1 (q, CH_3), 18.4 (t, CH_2), - 0.2 (q, CH_3) .

Michael-type reaction of (13) with 4,4-dimethylcyclohexdienone(3) . Synthesis of (17)

To a stirred solution of LDA, generated from diisopropylamine (0.2 ml) and n-BuLi (0.9 ml, 1.6 M in hexane), in THF (2 ml) at - 70°C was added dropwise a solution of (13) (252 mg, 1 mmol) in THF (1 ml) . The mixture was stirred 30 min at - 70°C and transferred dropwise by argon pressure to a stirred and cooled (- 70°C) solution of (3) (122 mg, 1 mmol) in THF (1 ml) and HMPA (1 ml) . The mixture was allowed to warm to room temperature and stirred overnight followed by addition of saturated NH_4Cl solution . Extraction with ether and usual work up yielded 388 mg of residue which was flash chromatographed to give 140 mg (40 %) . ν 3100, 1760, 1680 cm^{-1} ; ^1H NMR (400 MHz) δ 6.59 (1H, d, J = 10 Hz), 5.85 (1H, d, J = 10 Hz), 5.79 (1H, d, J = 1 Hz), 5.60 (1H, d, J = 1 Hz), 4.60 (1H, q, J = 7 Hz), 1.20 (3H, s), 1.17 (3H, s), 1.13 (3H, s), 0.17 (9H, s) .

Methyl-2-[3-methyl-3-vinylcyclohexan-1-one-2-yl]acetate (18a) and (18b)

To a solution of vinylmagnesium bromide (58 ml, 1.3 M in THF) cooled at - 5°C and stirred underargon was added CuI (1.5 g) and the dark resulting solution stirred for 30 min, then 3-methylcyclohexenone (8) (5.5 g, 50 mmol) was added neat dropwise . The mixture was stirred for 1 h and transferred by argon pressure dropwise to a stirred and cooled (- 20°C) solution of methyl bromoacetate (15.3 g) in HMPA (50 ml) . The cooling bath was removed and the solution stirred for 90 min at room temperature . After quenching with saturated NH_4Cl solution, the solution was extracted with ether . Usual work up yielded a residue which was flash chromatographed to afford a colorless liquid (3.1 g) giving a single spot by T.L.C. (R_f 0.3, pentane/ethyl acetate 9 : 1) . ν 3080, 1735, 1715 cm^{-1} ; ^1H NMR showed two singlets at δ 0.85 and 1.16 corresponding to (18a) and (18b) respectively in 1.5 : 1 ratio . Equilibration with MeONa/MeOH afforded a mixture of (18a) and (18b) in 3 : 1 ratio which was used for the next reaction .

Reduction of ketoesters (18a) and (18b) by K-Selectride . Lactones (19a) and (19b)

Reduction of a mixture of ketoesters (18a) and (18b) (900 mg) by K-Selectride was carried out as described for (13) . The crude oily product was flash chromatographed yielding a colorless

oil (580 mg, 75 %) and a single spot by T.L.C.(R_f 0.3, pentane/ethyl acetate 9 : 1) . ν 3080, 1780, 1640, 920 cm^{-1} ; ^1H NMR showed two methyl singlets at δ 1.0 and 1.1 corresponding to (19a) and (19b) respectively in 3 : 1 ratio . ^{13}C NMR showed two isomers with resonances for the major isomer, (19a), at δ 176.6 (s), 146.0 (d), 112.5 (t), 77.9 (d), 42.9 (d), 38.2 (s), 32.7 (t), 28.3 (t), 26.7 (q), 18.5 (t) and for the minor isomer (19b), at δ 176.5 (s), 145.5 (d), 112.1 (t), 77.9 (d), 44.9 (d), 37.7 (s), 32.7 (t), 25.1 (q), 17.9 (t) .

Michael-type condensation of the lactones (19a) and (19b) with (3) . Synthesis of (20)

To a stirred solution of LDA, generated from diisopropylamine (0.8 ml) and n-BuLi (4 ml, 1.6 M in hexane), in THF (14 ml) at - 70°C, was added dropwise a solution of lactones (540 mg, 3 mmol) in THF (5 ml) and HMPA (0.2 ml) over 30 min . After the addition, the mixture was stirred for 1 h at - 70°C and transferred by argon pressure to a stirred and cooled (- 70°C) solution of (3) (700 mg) in THF (4 ml) and HMPA (2 ml) . The mixture was allowed to warm to room temperature and stirred for 19 h . Quenching with saturated NH_4Cl solution, extraction with ether and usual work up afforded 1.56 g of crude material . Flash chromatography (pentane/ethyl acetate 1 : 4 as eluant) yielded 600 mg (66 %) of (20) as cristalline product . m.p. 122 - 124°C (MeOH), ν 3080, 1780, 1690, 1638, 920 cm^{-1} ; ^1H NMR (400 MHz) δ 6.62 (1H, d, J = 10 Hz), 5.86 (1H, d, J = 10 Hz), 5.68 (1H, dd, J = 16, 10 Hz), 5.16 (2H, 2d, J = 16, 10 Hz), 4.62 (1H, q, J = 7 Hz), 1.22 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H) ; ^{13}C NMR δ 198.8 (s, C-13), 177.2 (s, C'-2, lactone), 160.4 (d, C-11), 147.3 (d, C-12), 126.0 (d, C-9), 112.8 (t, C-10), 76.7 (d, C-4), 50.2 (d, C-2), 44.8 (d, C-1), 43.5 (d, C-3), 38.3 (s and t, C-15 and C-14), 37.7 (s, C-8), 35.5 and 27.4 (2t, C-5 and C-7), 21.9 and 21.3 (2q, C-16 and C-17), 16.70 (t, C-6) .

Reduction of (20) by $NaBH_4$-$CeCl_3$

To a stirred solution of the enone (20) (200 mg) in MeOH (2 ml) was added $CeCl_3$, 7 H_2O (280 mg) and then $NaBH_4$ (28 mg) . The resulting milky solution was stirred an additional 15 min (the reaction was complete within 5 min, T.L.C.) and then quenched with water . The aqueous layer was extracted with ether and the combined organic layers were washed with brine and concentrated in vacuo to yield 200 mg of (21) as pale yellow residue showing a single spot by T.L.C. . ν 3620, 1780, 1470, 1220, 930 cm^{-1} ; ^1H NMR (400 MHz) showed a mixture of two epimers (in 4 : 1 ratio) with resonances for the major isomer at δ 5.68 (1H, dd, J = 16, 10 Hz), 5.48 (1H, br. d, J = 12 Hz), 5.37 (1H, dd, J = 12, 1 Hz), 5.05 (2H, 2d, J = 10, 10 Hz), 4.62 (1H, q, J = 7 Hz), 4.23 (1H, m), 1.13 (3H, s), 1.10 (3H, s), 1.02 (3H, s) .

REFERENCES

1 R. W. Miller, *J. Nat. Prod.*, 43, 425 (1980) .

2 R. W. Miller, R. G. Powell and C. R. Smith Jr, *J. Org. Chem.*, 46, 1469 (1981) ; D. P. Della Casa de Marcano and T. G. Halsall, *J. Chem. Soc., Chem. Commun.*, 365 (1975) .

3 S. F. Martin, J. B. White and R. Wagner, *J. Org.Chem.*, 47, 3192 (1982) .

4 K. Sakan and B. M. Craven, *J. Am. Chem. Soc.*, 105, 3732 (1982); P. A. Brown, P. R. Jenkins, J. Fawcett and D. R. Russel, *J. Chem. Soc., Chem. Commun*, 253 (1984) .

5 B. M. Trost and H. Hiemstra, *J. Am. Chem. Soc.*, 104, 886 (1982) .

6 H. Shibuya, S. Tsujii, Y. Yamomoto, K. Murakawa, K. Takagi,N. Kurokawa and I. Kitagawa, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* 24 th, 1981, 340 ; *Chem. Abs.*, 96, 218050 v., (1982).

7 Y. Chan and W. W. Epstein, *Org. Syn.*, 53, 48 (1973) .

8 R. Boeckman Jr., D. M. Blum, B. Ganem and N.Halvey, *Org. Syn.*, 58, 152 (1978) .

9 G. Stork and E. Colvin, *J. Am. Chem. Soc.*, 93, 2080 (1971) ; R. K. Boeckman Jr. and K. J. Bruza, *J. Org. Chem.*, 44, 4781 (1979).

10 J. S. Soderquist and K. L. Thompson, *J. Organomet. Chem.*,159, 237 (1978) .

11 H. O. House, "*Modern Synthetic Reaction*", 2nd ed., W. A. Benjamin, 1972, p. 494 .

12 M. Fétizon and I. Hanna, *unpublished results* .

13 R. D. Miller and D. R. Mc Kean, *Synthesis*, 730 (1979) .

14 K. Narasaka, K. Soai, Y. Aikawa and T. Mukaiyama, *Bull. Chem. Soc. Jap.*, 49, 779 (1976) .

15 J. K. Sutherland, *Chem. Soc. Rev.*, 9, 265 (1980) .

16 J. L. Luche and A. L. Gemal, *J. Am. Chem. Soc.*, 103, 5454 (1981) .

17 G. Germain, P. Main, M. Woolfson, *Acta Crystallogr. Sect.* A, 27, 368-376 (1971) .

18 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 43, 2923 (1978) .