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Exploratory studies towards AB-ring system of taxanes *via* intramolecular alkylation reaction. Formation of bicyclo[2.2.2]octanones in preference to bicyclo[5.3.1]undecanes

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An intramolecular alkylation based approach has been explored for the enantiospecific construction of AB-ring system of taxanes starting from 3-allyl-4,4-dimethylcarvone, which however led only to bicyclo[2.2.2]octanones.

Keywords: Taxanes, intramolecular alkylation, bicyclo[5.3.1]undecanes, carvone, bicyclo[2.2.2]octanes

Although taxane diterpenoids have been known since 1856, and the first structure determination was reported in 1963, the field of taxoid synthesis did not begin to develop until the early 1980's. Much of the efforts towards the total synthesis of this class of compounds have been motivated by taxol® (paclitaxel)[1,2] **1**, one of the most functionally and stereochemically complex taxoids and its analogue taxotere **2**. Only very few molecules in the last two decades have stirred as much imagination and activity among the synthetic chemists as taxanes. Potent antitumour[3] and antileukemic properties of taxol **1** as well as its unique mode of action evoked tremendous interest in taxol. Taxol was isolated from the bark of the pacific yew tree in very low yield (approximately 100 mg per kilo of bark) by a method which is fatal to the tree. This has prompted world wide effort towards the total synthesis. From synthetic point of view, abundance of stereohemical detail and high level of structural complexity made the taxoids one of the most synthetically challenging classes of compounds.

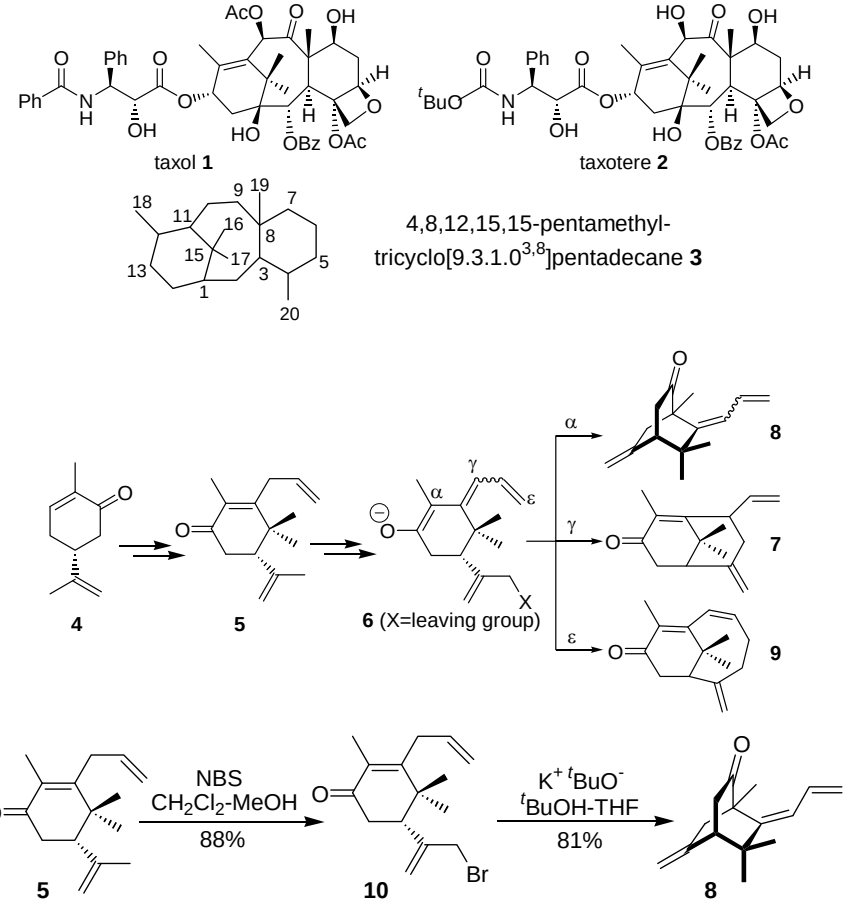
Taxane ditepenoids contain the tricyclic carbon skeleton 4,8,12,15,15-pentamethyltricyclo[9.3.1.$0^{3,8}$]-pentadecane **3**, commonly referred as taxane. The degree and location of oxygenation can vary greatly. Although the complete functionality and stereo-chemical issues must ultimately be dealt with, the development of a general and efficient method for the construction of a suitably substituted tricyclic carbon skeleton has often been recognized as the major task. In almost all the taxanes reported so far, except very few, there is a bridgehead double bond at C-11 making it an integral part of the skeleton. As target for chemical synthesis, taxol presents a plethora of potential problems. Perhaps most obvious is the challenge presented by the central B-ring, an eight-membered carbocycle. Such rings are notoriously difficult to form because of both entropic and enthalpic factors. The normally high transannular strain of an eight- membered ring is further increased in this case by the presence of the *geminal* dimethyl groups which projects into the interior of the B-ring. The A-ring includes a somewhat problematic bridgehead alkene, formally forbidden in a six-membered ring by Bredt rule. If assembling the carbon skeleton alone is not a daunting enough task, one should consider the high degree of oxygenation that must be introduced in a manner which allows a differential protection to five alkoxy groups. Over the past two decades more than 40 research groups, attracted by the molecule's challenging architecture and its potential utility in medicine, undertook the task of total synthesis of taxol and its analogues[3]. The focus of the most research groups has been the preparation of the partial structures in an effort to explore various concepts that deal with the construction of the strained tricyclo[9.3.1.$0^{3,8}$]-pentadecane skeleton equipped with suitable functionalities for further elaboration to various taxoids.

In our laboratory, utilisation of monoterpenes, in particular (*R*)-carvone **4**, for the synthesis of various natural products and their part structures is an area of active pursuit. We have initiated carvone based approach to taxanes, and developed efficient enantiospecific strategies for the synthesis of A-ring

as well as A,C- and B,C-ring systems of taxanes[4]. In continuation, we explored extension of these strategies for the enantiospecific synthesis of AB-ring system of taxanes. Herein we describe the exploratory studies, which instead of AB-ring system of taxanes, resulted in the enantiospecific generation of functionalised bicyclo[2.2.2]octanes.

For the synthesis of the AB ring system of taxanes, an intramolecular alkylation based strategy[5] for the construction of the C-3, C-8 bond of taxanes was conceived, choosing the alkylated enone **5** as the starting material, whose synthesis[4e] from (*R*)-carvone in four steps is already well established. It was contemplated that the presence of a good leaving group on the isopropenyl group (*i.e.,* at the C-3 carbon of taxanes) and generation of a thermodynamic trienolate **6** could bring about the intramolecular alkylation reaction[5]. Of the three possible modes of intramolecular alkylation, *i.e.,* from α, γ and ε positions of the trienolate **6**, the γ alkylation was ruled out as it will generate a bicyclo[3.3.1]non-1-ene system **7** with a highly strained bridgehead olefin (*anti*-Bredt)[6]. Alkylation from the α-position leads to a bicyclo[2.2.2]octane system **8**, whereas, the alkylation from the ε-position leads to a bicyclo[5.3.1]undecane skeleton **9**, *i.e.,* AB ring system of taxanes.

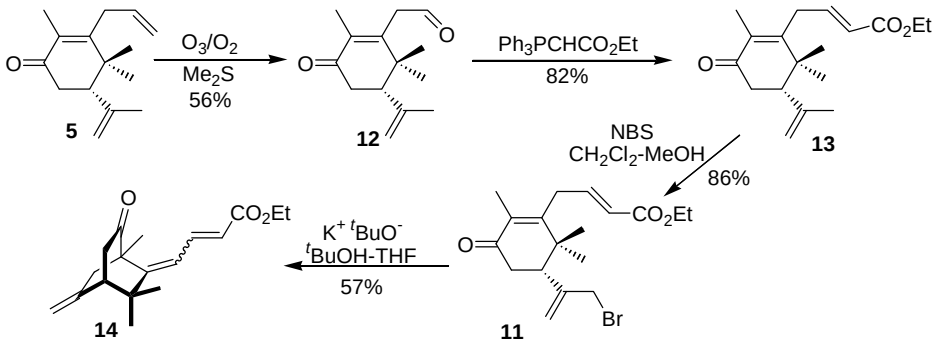
Recently, it was discovered in our laboratory that treatment of 6,6-dimethylcarvone with *N*-bromo-succinimide (NBS) in methanol and methylene chloride generates predominantly 10-bromo-6,6-dimethylcarvone[7] without formation of a bromo-etherification product. The same reaction was exploited for the generation of a suitable precursor for the intramolecular alkylation reaction. Thus, treatment of the allyl enone[4e] **5** with one equivalent of NBS in a 3:2 mixture of methylene chloride and methanol medium furnished predominantly, the bromoenone **10** in 88% yield, whose structure was established from its spectral data in comparison with that of the starting material **5**. Particularly, in the ^{1}H NMR spectrum, disappearance of a singlet due to one of the olefinic methyl groups and appearance of an AB quartet at δ 4.00 and 3.96 (J = 10.1 Hz) ppm due to CH_2-Br group established the structure of the bromo compound **10** as well as the regioselectivity of the reaction, which was further confirmed by the 15 lines ^{13}C NMR spectrum. The regioselectivity was obviously due to



the electron rich nature of the isopropenyl olefin when compared to the other two olefins in the triene **5**.

Based on the earlier studies[5], potassium *tert*-butoxide in *tert*-butanol was opted for the generation of the thermodynamic trienolate **6**. Thus, treatment of the allyl bromide **10** with 1 *M* solution of potassium *tert*-butoxide in *tert*-butanol and dry THF, however failed to generate the bicyclo[5.3.1]undecene system **9**, and generated exclusively the bicyclo[2.2.2]-octanone **8** in 81% yield *via* intramolecular alkylation from the α-carbon atom. Change of conditions, *e.g.,* sodium hydride in refluxing THF, did not change the course of the reaction. The structure of the product **8** was delineated from its spectral data. Presence of the molecular ion peak at *m/z* 216 ($C_{15}H_{20}O$) in the mass spectrum, presence of a strong absorption band at 1720 cm^{-1} due to an unconjugated carbonyl group in the IR spectrum and absence of a resonance due to CH_2-Br in the ^1H NMR spectrum indicated the formation of the α-alkylation product. In the ^1H NMR spectrum, presence of resonances, a doublet of a doublet of a doublet at δ 6.96 (*J* = 16.5, 11.4 and 10.2 Hz) and three doublets at 6.07 (*J* = 11.4 Hz), 5.11 (*J* = 16.5 Hz) and 5.09 (*J* = 10.2 Hz) due to C=CH–CH=CH_2 group, two singlets at 4.92 and 4.78 due to exomethylene, absence of a resonance due to olefinic methyl group and presence of three singlets at 1.44, 1.19 and 1.17 ppm due to three tertiary methyl groups established the structure of the bicyclo[2.2.2]octanone **8**, as well as the regioselectivity of the α-alkylation. It was further confirmed by the 15 lines ^{13}C NMR spectrum, which exhibited characteristic resonances, a singlet at δ 210.8 due to carbonyl carbon, two singlets at 145.8 and 145.3, two doublets at 132.7 and 127.8 and two triplets at 118.3 and 108.4 due to six olefinic carbons, three quartets at 31.2, 28.7 and 20.5 ppm due to three methyl groups.

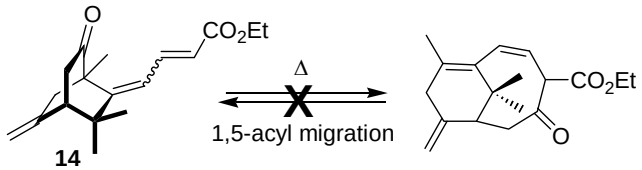
It was considered that the presence of one more electron withdrawing group at the ε-position, *e.g.,* **11**, might change the course of the alkylation reaction. The requisite starting material was obtained from the enone **5** by regioselective ozonolysis followed by a Wittig reaction. Thus, controlled ozonolysis of the allyl compound **5** followed by reductive work up with dimethyl sulfide furnished the aldehyde **12** in 56% yield in addition to starting material, which was separated by silica gel column chromatography. The regioselective Wittig reaction of the keto-aldehyde **12** using ethoxycarbonylmethylenetriphenylphosphorane in benzene furnished the ester **13** in 82% yield, whose structure was established from spectral data. Bromination of isopropenyl group in the enone ester **13** using NBS in a 3:2 mixture of the methylene chloride and methanol furnished, exclusively, the allyl bromide **11** in 86% yield, whose structure was delineated from its spectral data in comparison with the starting material **13** and the allyl bromide **10**. Treatment of the bromoenone **11** with 1 *M* solution of potassium *tert*-butoxide in *tert*-butanol, contrary to our expectation, furnished only a 1:3 *E,Z*-mixture of the bicyclo[2.2.2]octanone **14**, whose structure was established from its spectral data. The presence of molecular ion peak at m/z 288 ($C_{18}H_{24}O_3$) in the mass spectrum, absence of the resonances due to CH_2-Br and olefinic methyl groups in the ^1H NMR spectrum and the presence of strong carbonyl absorption band at 1710 cm^{-1} due to saturated ketone and conjugated ester in the IR spectrum suggested the α-alkylation. The ^1H NMR spectrum, with characteristic resonances for the major isomer, a doublet of a doublet at δ 7.80 (*J* = 15.0 and 12.1 Hz) and two doublets at 5.98 (*J* = 12.1 Hz) and 5.80 (*J* = 15.0 Hz) due to β,γ and α hydrogens, respectively, of the diene ester, two singlets at 4.97 and 4.82 due to exomethylene, a quartet at 4.21 (*J* = 7.2 Hz) and a triplet at 1.30 (*J* = 7.0 Hz) due to ethoxy group, three singlets at 1.40, 1.39 and 1.18 ppm due to three tertiary methyl groups, established the structure of the bicyclo[2.2.2]octanone **14**. The 17 lines ^{13}C NMR spectrum with characteristic resonances, two singlets

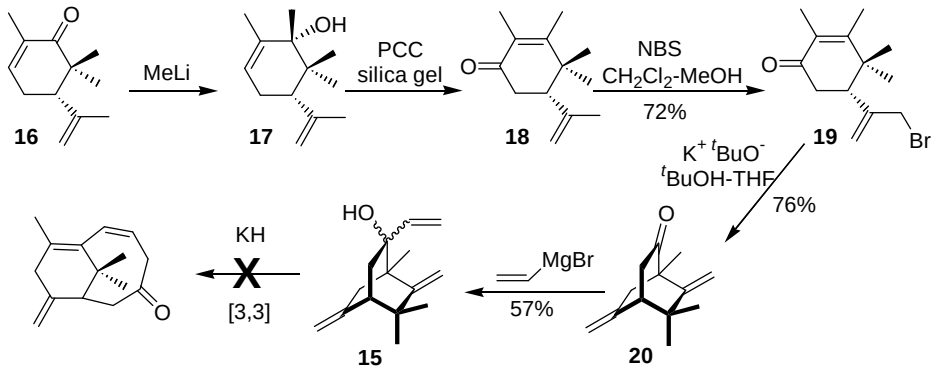


at δ 210.7 and 166.7 due to ketone and ester carbonyl carbons, respectively, two singlets at 156.8 and 144.6, three doublets at 140.2, 122.2 and 121.8 and a triplet at 109.2 due to six olefinic carbons, a triplet at 60.2 and a quartet at 14.2 due to ethoxy group, two singlets at 54.2 and 38.3 due to two quaternary carbons, two triplets at 40.4 and 38.3 due to two methylene carbons, three quartets at 29.7, 27.8 and 17.3 ppm due to the three methyl groups, further confirmed the structure of the compound **14**. Molecular mechanics calculations indicated that the *trans*-trienolate of **11** is 1.5 kcal/mol more stable than the corresponding *cis*-enolate, which might also had been responsible, besides the steric crowding and high energy of bicyclo[5.3.1]undecene system when compared to bicyclo[2.2.2]octane system, for the formation of α-alkylated product **14**. A brief unsuccessful attempt was made to bring about a thermal 1,5-acyl shift in the dienone ester **14**. Thermal activation of the ester **14** to 180°C in toluene in a sealed tube for 24 hr failed to bring about any noticeable change, whereas at higher temperature (>230°C) considerable amount of decomposition was observed.

Since the construction of a bicyclo[2.2.2]octane, *e.g.,* **8**, was found to be efficient, subsequently, an oxy-Cope rearrangement[8] of the allyl alcohol **15** for the construction of the AB ring system of taxanes was also briefly investigated. Thus, reaction of 6,6-dimethylcarvone **16** with methyllithium, followed by oxidation of the resultant tertiary alcohol **17** with PCC and silica gel furnished the trimethylcarvone **18** in 70% yield. Reaction of the trimethylcarvone **18** with NBS in methylene chloride-methanol medium furnished the allyl bromide **19** in 72% yield. Intramolecular alkylation reaction of the bromoenone **19** with potassium *tert*-butoxide in *tert*-butanol furnished the bicyclo[2.2.2]octanone **20** in 76% yield. Reaction of the bicyclic ketone **20** with vinylmagnesium bromide in THF furnished an inseparable 3:1 mixture of the allyl alcohols **15**. However, attempted anionic oxy-Cope rearrangement of the mixture of the allyl alcohols **15** with potassium hydride in THF (either at RT or reflux) failed to furnish any significant amount of the rearranged product.

In conclusion, an intramolecular alkylation based strategy was explored for the construction of the AB-ring system of taxanes. Although it failed to generate the AB-ring system of taxanes, the strategy led to an efficient enantiospecific methodology for the construction of multifunctional bicyclo[2.2.2]octanes containing two quaternary carbon atoms.





Experimental Section

Melting points were recorded using a Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H (90, 200 and 400 MHz) and ^{13}C NMR (22.5 MHz) spectra were recorded on Jeol FX-90Q, Brucker ACF-200 and AMX-400 spectrometers. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra off-resonance multiplicities, when recorded are given in parentheses. Low and high resolution mass measurements were carried out using a Jeol JMS-DX 303 GC-MS instrument using a direct inlet mode. Relative intensities of the ions are given in parentheses. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and $[\alpha]_D$ values are given in the units of 10^{-1}.deg.cm^2.g^{-1}. Ozonolysis experiments were carried out using a Penwalt Wallace

and Tierman ozonator. Analytical thin-layer chromatographies (TLC) were performed on glass plates coated with Acme's silica gel G containing 13% calcium sulphate as binder and various combinations of ethyl acetate and hexane were used as eluents. Visualisatation of spots was accomplished by exposure to iodine vapour. Acme's silica gel (100-200 mesh) was used for column chromatography appoximately 15-20 g. per 1 g. of the crude product. All small scale dry reactions were carried out using standard syringe-septum technique.

(5*R*)-3-Allyl-5-(3-bromopropen-2-yl)-2,4,4-trimethylcyclohex-2-enone 10. To a magnetically stirred solution of the enone **5** (1.065 g, 4.89 mmoles) in a 3:2 mixture of CH_2Cl_2 and methanol (13 mL) was slowly added NBS (1.31 g, 7.36 mmoles) over a period of 40 min. The reaction mixture was stirred for 8 hr, diluted with water and extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 extract was washed with 5% aq. NaOH and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:50 to 1:20) as eluent furnished the allyl bromide **10** (1.3 g, 88%) as oil. $[\alpha]_D^{24}$: +29.3° (*c* 2.46, $CHCl_3$); IR (neat): 3080, 1665, 1605, 1470, 1445, 1415, 1330, 1210, 995, 915 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.77 (1 H, ddt, J = 16.9, 10.4 and 6.5 Hz, $CH_2CH{=}CH_2$), 5.47 (1 H, s) and 5.07 (1 H, s) [$C{=}CH_2$], 5.12 (1 H, dq, J_{cis} = 10.4 and J_2 = 1.6 Hz) and 5.06 (1 H, dq, J_{trans} = 16.9 and J_2 = 1.7 Hz) [$CH{=}CH_2$], 4.00 and 3.96 (2 H, AB q, J = 10.1 Hz, CH_2-Br), 3.06 (2 H, d, J = 6.5 Hz, CH_2-$CH{=}CH_2$), 2.80 (1 H, t, J = 8.0 Hz, H-5), 2.61 (2 H, d, J = 8.0 Hz, H-6), 1.80 (3 H, s, C_2-CH_3), 1.16 (3 H, s) and 1.11 (3 H, s) [CH_3-C-CH_3]; ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 197.4 (s, C=O), 160.5 (s, C-3), 145.5 (s, $C{=}CH_2$), 133.6 (d, $CH{=}CH_2$), 131.8 (s, C-2), 118.8 (t, $CH{=}CH_2$), 116.5 (t, $C{=}CH_2$), 47.1 (d, C-5), 40.5 (t), 40.0 (s, C-4), 39.0 (t, C-6), 34.1 (t, CH_2Br), 26.2 (q), 21.2 (q), 11.2 (q) [3 × CH_3]; MS: *m/z* (%) 283 (M-Me, 8), 217 (100), 175 (27), 161 (21), 150 (20), 135 (30), 133 (39), 119 (30), 107 (68); HRMS: *m/z* for $C_{15}H_{21}O$ (M - Br), Calcd.: 217.1593; Found: 217.1587.

(1*R*,4*S*)-6-(Allylidene)-8-methylene-1,5,5-trimethylbicyclo[2.2.2]octan-2-one 8. To a cold (–5°C), magnetically stirred 1 M solution of potassium *tert*-butoxide (1.4 mmole) [prepared from potassium (55 mg, 1.4 mmole) and *tert*-butanol (1.4 mL)] in 1.6 mL of THF was added a solution of the bromoenone **10** (214 mg, 0.72 mmole) in 1.6 mL of THF. The reaction mixture was slowly warmed up to RT and stirred for 12 hr. It was then quenched with water and extracted with ether (2 × 10 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:40 to 1:20) as eluent furnished the bicyclic compound **8** (125 mg, 81%) as oil. $[\alpha]_D^{24}$: -59.2° (*c* 3.46, $CHCl_3$); IR (neat): 3060, 2960, 1720, 1650, 1630, 1460, 1405, 1385, 1210, 1080, 985, 900 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.96 (1 H, ddd, J = 16.5, 11.4 and 10.2 Hz, H-2'), 6.07 (1 H, d, J = 11.4 Hz, H-1'), 5.11 (1 H, d, J_{trans} = 16.5 Hz) and 5.09 (1 H, d, J_{cis} = 10.2 Hz) [H-3'], 4.92 (1 H, br s) and 4.78 (1 H, br s) [$C_8{=}CH_2$], 2.15-2.80 (5 H, m), 1.44 (3 H, s), 1.19 (3 H, s) and 1.17 (3 H, s) [3 × *tert*-CH_3]; ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 210.8 (s, C=O), 145.8 (s) and 145.3 (s) [C-6 and 8], 132.7 (d) and 127.8 (C-1' and 2'), 118.3 (t, C-3'), 108.4 (t, $C_8{=}CH_2$), 54.3 (s, C-1), 50.3 (d, C-4), 40.5 (t) and 39.6 (t) [C-3 and 7], 38.7 (s, C-5), 31.2 (q), 28.7 (q), 20.5 (q) [3 × CH_3]; MS: *m/z* (%) 216 (M^+, 100), 201 (40), 173 (32), 159 (90), 145 (35), 133 (35), 131 (49), 121 (32), 117 (32), 119 (34), 105 (47), 91 (45); HRMS: *m/z* for $C_{15}H_{20}O$, Calcd.: 216.1514; Found: 216.1511.

(5*S*)-3-[3-Carboethoxyallyl]-5-isopropenyl-2,4,4-trimethylcyclohex-2-enone 13. Through a cold (–90°C) solution of the compound **5** (500 mg, 2.29 mmoles) and a catalytic amount of $NaHCO_3$ in methanol (0.2 mL) and CH_2Cl_2 (12 mL) was passed a mixture of ozone in oxygen *ca* 10 min. Excess ozone was flushed off with oxygen. Dimethyl sulfide (1 mL) was added to the reaction mixture. It was then slowly warmed up to RT and magnetically stirred for 8 hr. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20 to 1:5) as eluent furnished the aldehyde **12** (280 mg, 55.7%) as oil. IR (neat): 3060, 2960, 2720, 1715, 1660, 1610, 1470, 1445, 1375, 1325, 1090, 1060, 900 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 9.67 (1 H, t, J = 1.5 Hz, H-C=O), 4.95 (1 H, s) and 4.76 (1 H, s) [$C{=}CH_2$], 3.47 (2 H, s, CH_2CHO), 2.40-2.70 (3 H, m, H-5 and 6), 1.74 (6 H, s, 2 × olefinic CH_3), 1.16 (3 H, s) and 1.06 (3 H, s) [CH_3-C-CH_3]; ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 196.9 (s, C=O), 196.4 (d, H-C=O), 154.0 (s, C-3), 144.5 (s, $C{=}CH_2$), 132.9 (s, C-2), 114.7 (t, $C{=}CH_2$), 50.8 (d and s, C-4 and 5), 45.0 (t, CH_2CHO), 38.9 (t, C-6), 26.0 (q), 22.2 (q), 20.9 (q), 11.3 (q) [4 × CH_3]. To a solution of the aldehyde **12** (220 mg, 1 mmole) in 5 mL of dry benzene was added (ethoxycarbonyl-

methylene)triphenylphosphorane (373 mg, 1.07 mmole). The reaction mixture was stirred at RT for 8 hr. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the Wittig product **13** (239 mg, 82.4%) as oil. $[\alpha]_D^{25}$: +44.0° (*c* 2.0, $CHCl_3$); IR (neat): 3060, 1710, 1660, 1600, 1360, 1305, 1260, 1155, 1035, 975, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (1 H, dt, *J* = 15.7 and 6.2 Hz, H-β), 5.84 (1 H, dt, *J* = 15.7 and 1.8 Hz, H-α), 4.99 (1 H, s) and 4.79 (1 H, s) [C=CH_2], 4.22 (2 H, q, *J* = 7.2 Hz, O-C*H*$_2$CH$_3$), 3.21 (2 H, d, *J* = 6.2 Hz, H-γ), 2.45-2.80 (3 H, m), 1.79 (3 H, s) and 1.76 (3 H, s) [2 × olefinic CH_3], 1.32 (3 H, t, *J* = 7.2 Hz, O-CH_2C*H*$_3$), 1.19 (3 H, s) and 1.1 (3 H, s) [CH_3-C-CH_3]; ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 197.9 (s, C=O), 165.7 (s, O-C=O), 158.8 (s, C-3), 144.7 (s, *C*=CH_2), 144.1 (d, C-*β*), 132.4 (s, C-2), 122.8 (d, C-α), 115.1 (t, C=*C*H_2), 60.1 (t, O-*C*H_2CH$_3$), 51.2 (d, C-5), 39.8 (s, C-4), 39.4 (t), 32.6 (t), 26.5 (q), 22.9 (q), 21.4 (q), 13.9 (q) and 11.4 (q) [5 × CH_3]; MS: *m/z* (%) 290 (M^+, 10), 275 (44), 244 (15), 233 (17), 177 (21), 159 (20), 149 (100), 135 (25), 121 (76); HRMS: *m/z* for $C_{18}H_{26}O_3$, Calcd.: 290.1882; Found: 290.1886.

(5*R*)-5-(3-Bromopropen- 2-yl)- 3-(3-carboethoxy-allyl)-2,4,4-trimethylcyclohex-2-enone 11. Reaction of the ester **13** (130 mg, 0.45 mmole) in a 3:2 mixture of methylene chloride and methanol (1.2 mL) with NBS (96 mg, 0.54 mmole) for 10 hr as described for the compound **10**, and purification of the product on a silica gel column using ethyl acetate-hexane (1:10 to 1:5) as eluent furnished the bromo compound **11** (140 mg, 86%) as oil. $[\alpha]_D^{25}$: +37.0° (*c* 7.14, $CHCl_3$); IR (neat): 1710, 1660, 1610, 1470, 1360, 1310, 1265, 1170, 1090, 1035, 980, 920 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 6.89 (1 H, dt, *J* = 15.2 and 6.3 Hz, H-β), 5.80 (1 H, dt, *J* = 15.2 and 2.0 Hz, H-α), 5.49 (1 H, s) and 5.05 (1 H, s) [C=C*H*$_2$], 4.20 (2 H, q, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 3.96 (2 H, s, CH_2-Br), 3.16 (2 H, d, *J* = 6.3 Hz, H-γ), 2.50-2.90 (3 H, m), 1.77 (3 H, s, C_2-CH_3), 1.29 (3 H, t, *J* = 7.0 Hz, OCH_2C*H*$_3$), 1.13 (3 H, s) and 1.10 (3 H, s) [CH_3-C-CH_3]; ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 197.5 (s, C=O), 165.8 (s, O–C=O), 158.6 (s, C-3), 145.3 (s, *C*=CH_2), 143.8 (d, C-β), 132.7 (s, C-2), 122.9 (d, C-α), 119.1 (t, C=*C*H_2), 60.2 (t, O*C*H_2CH$_3$), 46.9 (d, C-5), 40.5 (t, C-γ), 40.1 (s, C-4), 38.8 (t), 32.7 (t), 26.1 (q), 21.1 (q), 14.0 (q) and 11.5 (q) [4 × CH_3]; MS: *m/z* (%) 369 (M^++1, 5), 371 (M^++3, 4.5), 357 (10), 289 (100), 243 (40), 215 (22), 176 (95), 175 (40), 161 (32), 149 (100), 133 (38), 121 (89).

(1*R*, 4*S*)-6-(3-Carboethoxypropenylidene)-1, 5, 5-trimethyl-8-methylenebicyclo[2.2.2]octan-2-one 14. Intramolecular alkylation of the bromoenone **11** (200 mg, 0.543 mmole) in 1.4 mL of THF using potassium *tert*-butoxide (1.2 mmole, 1 M in ^{t}BuOH) in 1.2 mL of THF for 2 hr as described for the compound **8**, and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the ester **14** (62 mg, 39.4%) as oil. $[\alpha]_D^{25}$: -9.7° (*c* 3.2, $CHCl_3$); IR (neat): 3060, 2980, 1710, 1620, 1455, 1355, 1265, 1155, 1125, 1035, 980, 890 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 3:1 diastereomeric mixture): Peaks due to the major isomer: δ 7.80 (1 H, dd, *J* = 15.0 and 12.1 Hz, H-β), 5.98 (1 H, d, *J* = 12.1 Hz, H-γ), 5.80 (1 H, d, *J* = 15.0 Hz, H-α), 4.97 (1 H, s) and 4.82 (1 H, s) [C=CH_2], 4.21 (2 H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.72 and 2.30 (2 H, 2 × dd, *J* = 19.8 and 3.3 Hz, CH_2C=O), 2.46 (1 H, br s, H-4), 2.52 and 2.31 (2 H, AB q, *J* = 16.0 Hz, H-7), 1.40 (3 H, s), 1.39 (3 H, s) and 1.18 (3 H, s) [3 × *tert*-CH_3], 1.30 (3 H, t, *J* = 7.0 Hz, O-CH_2C*H*$_3$); Peaks due to the minor isomer: δ 7.93 (1 H, dd, *J* = 14.8 and 12.2 Hz, H-β), 6.19 (1 H, d, *J* = 12.1 Hz, H-γ), 5.77 (1 H, d, *J* = 14.9 Hz, H-α), 4.20 (2 H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 2.57 (1 H, br s, H-4), 1.29 (3 H, t, *J* = 7.0 Hz, O-CH_2C*H*$_3$), 1.29 (3 H, s) and 1.25 (3 H, s) [2 × *tert*-CH_3]; ^{13}C NMR (22.5 MHz, $CDCl_3$, 3:1 diastereomeric mixture): Peaks due to major isomer: δ 210.7 (s, C=O), 166.7 (s, O–C=O), 156.8 (s, C-6), 144.6 (s, C-8), 140.2 (d, C-β), 122.2 (d) and 121.8 (d) [C-α and γ], 109.2 (t, C=*C*H_2), 60.2 (t, O*C*H_2CH$_3$), 54.2 (s, C-1), 52.7 (d, C-4), 40.4 (t), 38.3 (2 c, s and t), 29.7 (q), 27.8 (q), 17.3 (q), 14.2 (q) [4 × CH_3]; Peaks due to minor isomer: δ 209.9 (s, C=O), 155.7 (s, C-6), 139.0 (d), 124.8 (d), 108.8 (t, C=*C*H_2), 55.3, 50.2, 39.6, 31.1, 28.5, 20.5; M S: *m/z* (%) 288 (M^+, 39), 243 (18), 215 (100), 171 (30), 157 (52), 133 (48), 105 (30), 91 (37); HRMS: *m/z* for $C_{18}H_{24}O_3$, Calcd.: 288.1725; Found: 288.1733.

The aqueous layer, from the above work up, was acidified with 3 *N* HCl, extracted with ether (2 × 10 mL). The organic phase was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and reesterification of the crude acid with an excess of diazomethane in ether furnished a 3:1 *E,Z*-mixture of the corresponding methyl ester (25 mg, 16.7%).

(5*S*)-5-Isopropenyl-2, 3, 4,4-tetramethylcyclohex-2-enone 18. To a cold (0°C), magnetically stirred solution of 6,6-dimethylcarvone **16** (1 g, 5.62 mmoles) in ether (2 mL) was slowly added a solution of methyllithium (1.1 *M* in ether, 6.1 mL, 6.7

mmoles) over a period of 20 min. The reaction mixture was slowly warmed up to room temperature and stirred for 1 hr. It was then poured into a cold saturated aqueous NH_4Cl solution and extracted with ether (2 × 10 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the tertiary alcohol **17**. A mixture of PCC (1.80 g, 8.4 mmoles) and silica gel (1.8 g) was added to a solution of the tertiary alcohol **17** in 5 mL of CH_2Cl_2 and stirred for 12 hr at RT. The reaction mixture was filtered through a small silica gel column and the column was eluted with more CH_2Cl_2. Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate-hexane (1:50 to 1:20) as eluent furnished the trimethylcarvone **18** (750 mg, 70%) as oil. $[\alpha]_D^{25}$: +76.3° (*c* 2.74, $CHCl_3$); IR (neat): 3080, 2980, 1665, 1615, 1450, 1380, 1330, 1080, 895 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 4.90 (1 H, br s) and 4.73 (1 H, br s) [C=CH_2], 2.30-2.70 (3 H, m, H-5 and 6), 1.86 (3 H, s, C_3-CH_3), 1.73 (3 H, s, C_2-CH_3), 1.67 (3 H, s, isopropenyl CH_3), 1.14 (3 H, s) and 1.03 (3 H, s) [CH_3-C-CH_3]; ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 198.2 (C=O), 161.3 (C-3), 145.4 (*C*=CH_2), 130.2 (C-2), 115.0 (C=*C*H_2), 51.7, 39.6 (2 C), 26.8, 22.9, 21.6, 16.4, 11.4; M S: *m/z* (%) 192 (M^+, 19), 177 (62), 150 (23), 135 (58), 124 (55), 109 (100), 81 (78); HRMS: *m/z* for $C_{13}H_{20}O$, Calcd.: 192.1514; Found: 192.1523.

(5*S*)-5-(3-Bromopropen-2-yl)-2,3,4,4-tetramethylcyclohex-2-enone 19. Reaction of the enone **18** (353 mg, 1.84 mmole) in 4.8 mL of a 3:2 mixture of CH_2Cl_2-methanol with NBS (393 mg, 2.21 mmole) for 6 hr at RT as described for the compound **10**, and purification of the product on a silica gel column using ethyl acetate-hexane (1:50 to 1:20) as eluent furnished the bromoenone **19** (357 mg, 71.4%). $[\alpha]_D^{24}$: +10.1° (*c* 4.86, $CHCl_3$); IR (neat): 3100, 2975, 1660, 1610, 1375, 1325, 1210, 1080, 920 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.46 (1 H, s) and 5.05 (1 H, s) [C=CH_2], 3.97 and 3.94 (2 H, AB q, *J* = 10.0 Hz, CH_2-Br), 2.78 (1 H, dd, *J* = 9.4 and 6.4 Hz, H-5), 2.50-2.60 (2 H, m, H-6), 1.91 (3 H, s) and 1.78 (3 H, s) [2 × olefinic CH_3], 1.17 (3 H, s) and 1.12 (3 H, s) [CH_3-C-CH_3]; ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 197.6 (C=O), 161.1 (C-3), 145.8 (*C*=CH_2), 130.4 (C-2), 119.1 (C=*C*H_2), 47.4, 40.6, 39.8, 39.1, 26.6, 21.3, 16.5 and 11.7 (4 × CH_3); MS: *m/z* (%) 271 (M^++1, 13), 273 (M+3, 12), 255 (11), 257 (10), 191 (100), 149 (30), 133 (26), 124 (58), 123 (48), 109 (100), 107 (77); HRMS: *m/z* for $C_{13}H_{19}O$ (M - Br), Calcd.: 191.1436. Found: 191.1433.

(1*R*,4*S*)-1,5,5-Trimethyl-6,8-bis(methylene)bicyclo[2.2.2]octan-2-one 20. Intramolecular alkylation reaction of the bromoenone **19** (280 mg, 1.04 mmole) in 2.5 mL of THF using potassium *tert*-butoxide (2.2 mmoles, 1 *M* in ^{t}BuOH) [prepared from potassium (87 mg, 2.2 mmole)] for 12 hr as described for the compound **8** and purification of the product on a silica gel column using ethyl acetate-hexane (1:50) as eluent furnished the bicyclic compound **20** (150 mg, 76.1%) as oil. $[\alpha]_D^{26}$: -4.9° (*c* 7.32, $CHCl_3$); IR (neat): 3080, 2960, 2920, 1720 1650, 1630, 1400, 1120, 1080, 890 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.00 (2 H, s, C=CH_2), 4.93 (1 H, br s) and 4.79 (1 H, br s) [C=CH_2], 2.68 (1 H, dd, *J* = 20.4 and 3.9 Hz, H-3a), 2.41 (2 H, t, *J* = 2.3 Hz, H-7), 2.31 (1 H, br s, H-4), 2.26 (1 H, dd, *J* = 20.4 and 2.9 Hz, H-3b), 1.18 (3 H, s), 1.15 (3 H, s) and 1.14 (3 H, s) [3 × *tert*-CH_3]; ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 211.3 (s, C=O), 156.4 (s, C-6), 145.4 (s, C-8), 108.6 (t) and 108.4 (t) [2 × C=*C*H_2], 52.4 (s, C-1), 50.1 (d, C-4), 40.6 (t, C-3), 38.4 (t, C-7), 37.4 (s, C-5), 31.0 (q), 28.2 (q), 16.2 (q) [3 × CH_3]; MS: *m/z* (%) 190 (M^+, 37), 175 (23), 161 (20), 149 (25), 147 (62), 133 (100), 119 (48), 105 (70); HRMS: *m/z* for $C_{13}H_{18}O$, Calcd.: 190.1358; Found: 190.1358.

(1*R*,2*S*,4*S*)- and (1*R*,2*R*,4*S*)-1,5,5-Trimethyl-6,8-bis(methylene)-2-vinylbicyclo[2.2.2]octan-2-ol 15. To a solution of vinylmagnesium bromide (4 mmoles) [prepared from magnesium (96 mg, 4 mmoles and vinyl bromide (0.5 mL) in 3 mL of dry THF] was added a solution of the bicyclic ketone **20** (30 mg, 0.16 mmoles) in 0.8 mL of THF. The reaction mixture was stirred for 1 hr at RT, followed by refluxed for 4 hr. It was then poured into a saturated aq. NH_4Cl solution and extracted with ether (3 × 5 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:40) as eluent furnished an ≈1:3 epimeric mixture of the tertiary allyl alcohol **15** (20 mg, 56.5%). IR (neat): 3550, 3070, 2960, 1630, 1455, 1410, 1005, 920, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 3:1 diastereomeric mixture): δ 5.89 (1 H, dd, *J* = 17.0 and 10.5 Hz) & 5.96 (1 H, dd, *J* = 17.3 and 10.8 Hz) (1 H C*H*=CH_2), 5.32-5.40 (2H,m 3×=CH_2 4.83 & 4.85 (1 H, q, *J* = 2.0 Hz) and 4.70 & 4.76 (1 H, q, *J* = 2.0 Hz) [C_8-methylene], 1.50-2.75 (6 H, m), 1.26 and 1.18 (3 H, s), 1.096 & 1.09 (3 H, s) and 0.96 & 0.92 (3 H, s) [3 × *tert*-CH_3]. MS: *m/z* (%) 218 (M^+, 2), 185 (10), 148 (67), 133 (100), 119 (13), 105 (17); HRMS: *m/z* for $C_{15}H_{22}O$, Calcd.: 218.1671; Found: 218.1665.

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References

1 Taxol is the registered trademark for the molecule with the generic name paclitaxel.

2 (a) Wani M C, Taylor H L, Wall M E, Coggon P & McPhail A T, *J Am Chem Soc*, 93, **1971**, 2325;
(b) Wall M E & Wani M C, *ACS Symp Ser,* 583, **1995**, 18.

3 Uttaro J-P, Audran G, Galano J-M & Monti H, *Tetrahedron Lett*, 43, **2002**, 2757 and references cited therein.

4 (a) Srikrishna A, Reddy T J & Kumar P P, *J Chem Soc, Chem Commun*, **1996**, 1369; (b) Srikrishna A, Reddy T J & Kumar P P, *J Indian Chem Soc,* 75, **1998**, 616; (c) Srikrishna A, Reddy T J & Kumar P P, *Tetrahedron Lett*, 39, **1998**, 5815; (d) Srikrishna A, Reddy T J & Kumar P P, *J Chem Soc, Perkin Trans 1*, **1998**, 3143; (e) Srikrishna A, Reddy T J, Kumar P P & Gharpure S J, *Indian J Chem*, 41B, **2001**, 905; (f) Srikrishna A, Kumar P R & Padmavathi V, *Synlett*, **2002**, 1907; (g) Srikrishna A, Dethe D H & Kumar P R, *Tetrahedron Lett*, 45, **2004**, 2939.

5 Srikrishna A & Hemamalini P, *Indian J Chem*, 29B, **1990**, 201.

6 Buchanan G L, *Chem Soc Rev,* 3, **1974**, 41.

7 Srikrishna A, Reddy T J & Kumar P P, *Synlett*, **1997**, 663.

8 (a) Evans D A & Golob A M, *J Am Chem Soc*, 97, **1975**, 4765; (b) Rao C S S, Kumar G, Rajagopalan K & Swaminathan S, *Tetrahedron*, 38, **1982**, 2195; (c) Paquette L A, Sturino C F, Wang X, Prodger J C & Koh D, *J Am Chem Soc*, 118, **1996**, 5620.