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Model Studies Directed Towards the Synthesis of Functionalised Chiral A-ring Derivatives of Taxanes[1,†]

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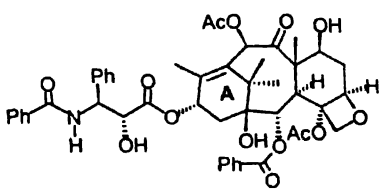
Model studies, starting from the monoterpene *R*-carvone, directed towards the synthesis of chiral A-ring derivatives of taxanes with oxygen functionalities at C-2, 9 and 13 carbon atoms as in taxol is described.

Paclitaxel **1** (Taxol®)[2] by virtue of its complex and densely functionalised structure coupled with potent antitumor activity through a novel mechanism of action has attracted the attention of synthetic chemists. During the last two decades, more than thirtyfive research groups have been actively involved in the development of convenient approaches to taxane diterpenoids[3] and so far four groups have reported the total synthesis of taxol **1**[4]. Recently, we have initiated a new approach[5] to taxanes starting from the readily available monoterpene, carvone **2**, and developed efficient routes for the construction of functionalised chiral A-ring derivatives and C-ring derivatives of taxanes[5,6]. Herein, we describe the details of our model studies directed towards the synthesis of chiral A-ring derivatives of taxanes containing oxygen functionalities at C-2, 9 and 13 carbons as in taxol.

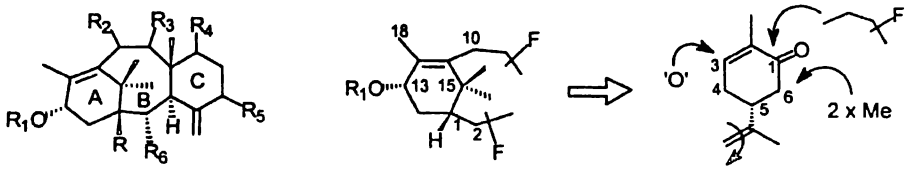


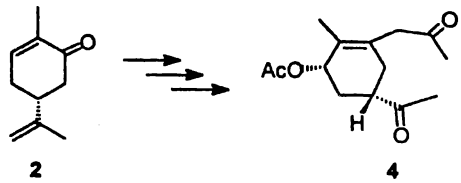
Paclitaxel (Taxol®) **1**

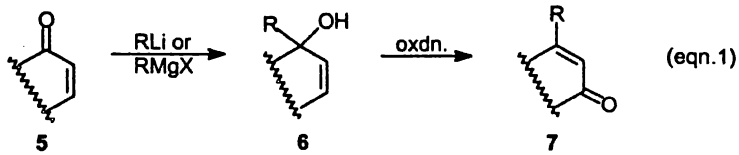
Monoterpenes are being widely used as chiral auxiliaries but their potential as chiral synthons has not been properly exploited. The overwhelming emphasis on carbohydrates as chirons[7a] in natural product synthesis, during the last two decades, has sidelined the importance of monoterpenes as chiral building blocks for the synthesis of natural pro-ducts in their chiral form[7b]. This has come about despite the fact that many terpenes are cheap, readily available (in both the enantiomeric forms in some cases, unlike carbohydrates and amino acids) and endowed with only one or two chiral centres and modest functionality, and thus do not require recourse to destruction of excess chirality or the functiona-lity present in them. The unique molecular architecture, unprecedented mechanism of its action against the ovarian and breast cancers of taxol (**1**) has generated tremendous interest in the synthesis of taxanes, and several approaches have been reported. The most efficient of these exploit a convergent strategy, constructing a functionalised A-ring derivative upon which the remaining carbon skeleton is appended. A variety of strategies have been developed for the cons truction of the A-ring of taxanes both in racemic as well as chiral forms. With this background, in continuation of the work carried out in our laboratory[8] on the use of the monoterpene *R*-carvone as chiral starting material in the asymmetric synthesis, a new approach to chiral taxanes has been initiated. The origin of the present strategy, relied on the identification of the absolute configuration at the C-5 carbon[9] of *R*-carvone as identical with that of the C-1 carbon of taxanes. This in turn, equated C-3 and C-6 carbons of carvone with the C-13 and C-15 carbons respectively, and the C-2 methyl group with the C-18 carbon of taxanes. Based on these identifications, for the conversion of *R*-carvone (**2**) into a functionalised A-ring derivative of taxanes, e.g., **3**, it can be readily visualised that four important transformations to be carried out. These are : (1) introduction of a functionalised side-chain at C-1 carbon of carvone, (2) introduction of a stereodefined oxygen functionality at C-3 carbon of carvone, (3) introduction of two methyl groups on C-6 carbon of carvone and (4) degradation of the isopropenyl moiety at C-5 carbon of carvone to a suitably functionalised side-chain. As a model study, the sequence was carried out without the *gem*-dimethyl grouping, and *R*-carvone (**2**) was converted into the diketoacetate **4**.

For bringing out the first and second transformations mentioned above, an alkylative 1,3-enone transposition strategy[10] was chosen. As depicted in equation 1, regioselective 1,2-addition of an appropriate Grignard or organolithium reagent to an enone **5** generates an allylic tertiary alcohol **6** which on oxidation with a chromium reagent isomerises the olefin and oxidises at the third position to furnish the new β-substituted enone **7**. Consequently, 1,2-addition of allylmagnesium chloride to *R*-carvone (**2**) followed by oxidation of the resultant allylic tertiary alcohol **8** with a mixture of pyridinium chlorochromate (PCC) and silica gel[11]

†Respectfully dedicated to Professor Sukh Dev.

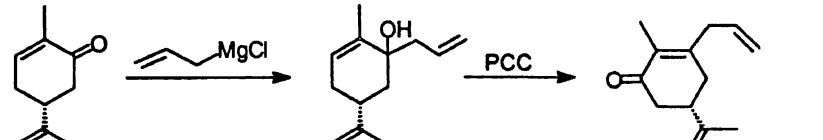


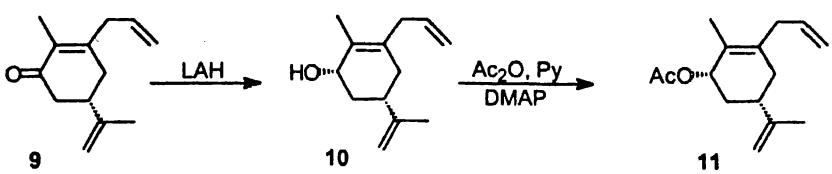


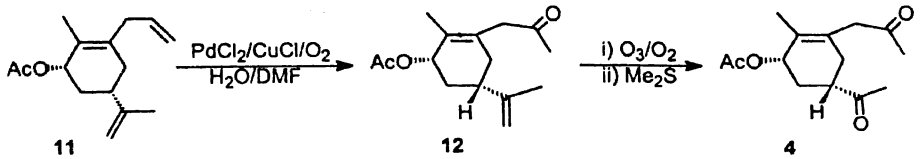


cleanly furnished the transposed product, β-allylcarvone **9**, in 70% yield, whose structure was established from its spectral data.

The well established stereo- and regioselective reduction of 5-substituted cyclohexenones[12] was exploited for the stereoselective creation of the *syn*-allylic alcohol. Thus, reduction of allylcarvone **9** with lithium aluminum hydride (LAH) in ether at low temperature furnished the *syn*-allyl alcohol **10** in a highly stereo- and regioselective manner, which was converted into its acetate **11** employing acetic anhydride, pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP). It is worth noting that the stereochemistry of the acetoxy group is identical to that present in several taxanes. For the generation of the two functionalised side-chains, regioselective oxidation of the terminal olefin of the allyl group and oxidative cleavage of the isopropenyl moieties were contemplated to transform the acetate **11** into the diketoacetate **4**. The regiospecificity of the Wacker oxidation[13] was exploited for the transformation of the allyl into an acetonyl group in the presence of the isopropenyl group. Thus, oxidation of the terminal olefin moiety of the allyl group in the acetate **11** employing Wacker conditions ($PdCl_2$, CuCl, O_2, H_2O and DMF) generated the ketoacetate **12** in 73% yield, whose spectral data were in full agreement with its formulation. Finally, regioselective ozonolysis followed by reductive workup with dimethyl sulfide of the isopropenyl moiety in the ketoacetate **12** generated the diketoacetate **4** in 69% yield, whose structure rests secured from its spectral data. Presence of strong carbonyl absorption bands at 1730 and 1705 cm^{-1} due to acetate and ketone functionalities respectively, in the ir spectrum and absence of resonances due to olefinic protons in the ^1H nmr spec-







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trum suggested the structure of the diketoacetate **4**. In the ^{1}H nmr spectrum, presence of a multiplet at δ 5.36 due to C*H*-OAc and three singlets at 2.19, 2.17 and 2.07 ppm due to two acetyl and one acetate methyl groups established the structure of the diketoacetate **4** which was further confirmed by the 14 lines ^{13}C nmr spectrum with characteristic resonances, two singlets at δ 207.9 and 204.9 due to two carbonyl carbons, a singlet at 169.6 due to acetate carbonyl carbon, two singlets at 128.2 and 127.8 due to two olefinic carbons, a doublet at 71.6 due to *C*H-OAc, a triplet at 47.7 due to CH_2COMe, a doublet at 44.3 due to C-5, four quartets at 28.6, 26.8, 20.2 and 14.1 due to four methyl groups. It is worth mentioning that the three oxygen functionalities present in the diketoacetate **4**, can be readily equated to those present at C-2, 9 and 13 carbons of taxanes, which are commonly encountered in a number of natural taxanes.

Experimental

Ir spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H (90 and 200 MHz) and ^{13}C nmr (22.5 MHz) spectra were recorded on Jeol FX-90Q and Brucker ACF-200 spectrometers. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either internal tertramethylsilane (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. All small scale dry reactions were carried out using standard syringe-septum techniques. Low temperature reactions were conducted in a bath made of alcohol and liquid nitrogen. Dry ether was obtained by distillation over sodium and stored over sodium wire.

(+)-(5S)-3-Allyl-2-methyl-5-isopropenylcyclohex-2-enone (**9**). *Step 1. Grignard reaction* : To a cold (0°), magnetically stirred solution of allylmagnesium chloride (24 mmol) [prepared from magnesium (576 mg, 24 mmol) and allyl chloride (1.9 g, 2.03 ml, 25 mmol) and a catalytic amount of iodine] in dry THF (10 ml) was added *R*-carvone (**2**; 1.5 g, 1.56 ml, 10 mmol) in dry THF over a period of 15 min. The reaction mixture was slowly warmed up to RT and stirred for 8 h. It was then poured into saturated aq. NH_4Cl solution and extracted with ether (2 × 15 ml). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the tertiary alcohol **8**, which was used as such in the next step.

Step 2. Oxidation : To a magnetically stirred solution of the tertiary alcohol **8** (2.3 g), obtained above, in dry CH_2Cl_2 (25 ml) was added a homogenous mixture of PCC (4.5 g, 20.9 mmol) and silica gel (4.5 g), and stirred vigorously for 6 h at RT. The mixture was then filtered through a small silica gel column and eluted the column with excess CH_2Cl_2. 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 allyl enone (**9**; 1.33 g, 70%) as an oil, $[\alpha]_D^{25}$ +83.2 (*c* 4.7, $CHCl_3$); ν_{max} (neat) 3070, 1660 (C=O), 1625 (C=C), 1430, 1375, 995, 915 and 890 cm^{-1} (C=CH_2); ^{1}H nmr (200 MHz, $CDCl_3$) δ 5.77 (1H, t of dd, *J* 16.8, 9.5 and 6.2 Hz, C*H*=CH_2), 5.12 (1H, d, J_{cis} 9.5 Hz) and 5.10 (1H, d, J_{trans} 16.8 Hz) [CH=CH_2], 3.09 and 2.96 (2H, d of AB q, *J* 14.7 and 6.2 Hz, doubly allylic CH_2), 2.1–2.75 (5H, m), 1.79 (3H, s) and 1.75 (3H, s) [2 × olefinic CH_3]; ^{13}C nmr (22.5 MHz, $CDCl_3$) δ 196.6 (s, C=O), 152.8 (s, C-3),145.8 (s, *C*=CH_2), 132.0 (d, *C*H=CH_2), 130.1 (s, C-2), 115.7 (t, CH=*C*H_2), 109.2 (t, C=*C*H_2), 41.3 (t), 40.4 (d, C-5), 38.2 (t), 34.6 (t), 19.3 (q) and 9.3 (q) [2 × CH_3]; *m/z* 190 (M^+, 25%), 175 (10, M–Me), 148 (38, M–C_3H_6), 133 (30), 119 (25), 107 (85), 106 (50), 91 (35), 79 (100); HRMS *m/z* for $C_{13}H_{18}O$ calcd. : 190.1358. Found : 190.1359.

(+)-(1S,5R)-3-Allyl-2-methyl-5-isopropenylcyclohex-2-enol (**10**) : To a cold (–90°), magnetically stirred solution of the enone **9** (1.3 g, 6.8 mmol) in dry ether (20 ml) was added $LiAlH_4$ (250 mg, 6.58 mmol) and stirred for 2 h. The reaction mixture was then diluted with ether (15 ml) and carefully quenched with water (5 ml). The organic layer was separated and the aqueous phase was extracted with ether (2 × 20 ml). The combined organic phase was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1 : 20 to 1 : 10) as eluent furnished the alcohol (**10**; 1.3 g, 99%), $[\alpha]_D^{25}$ +50.5 (*c* 3.7, $CHCl_3$); ν_{max} (neat) 3320 (O–H), 3080, 3920, 1640, (C=C), 1440,

1020, 1000, 910 and 890 cm^{-1} (C=CH_2); ^1H nmr (90 MHz, $CDCl_3$) δ 5.5–6.0 (1H, m, C*H*=CH_2), 5.02 (1H, br d, J_{trans} 15.0 Hz) and 5.0 (1H, br d, J_{cis} 11.0 Hz) [CH=CH_2], 4.73 (2H, s, C=CH_2), 4.18 (1H, m, C*H*–OH), 2.65–2.85 (2H, m), 1.9–2.3 (3H, m), 1.73 (6H, s, 2 × olefinic CH_3), 1.4–1.65 (2H, m); ^{13}C nmr (22.5 MHz, $CDCl_3$) δ 148.2 (s, *C*=CH_2), 134.9 (d, *C*H=CH_2), 130.4 (s) and 129.5 (s) [C-2 and 3], 114.6 (t, CH=*C*H_2), 108.6 (t, C=*C*H_2), 71.0 (d, *C*H–OH), 39.9 (t), 37.6 (2C, t and d), 35.0 (t), 20.1 (q) and 13.5 (q) [2 × olefinic CH_3]; *m/z* 192 (M^+, 2%), 174 (5, M–H_2O), 151 (58, M–C_3H_5), 133 (30), 123 (27), 109 (100, M–OH-isoprene); HRMS *m/z* for $C_{13}H_{20}O$ calcd. : 192.1514. Found : 192.1531.

*(+)-(1*S,5R*)-3-Allyl-5-isopropenyl-2-methylcyclohex-2-enyl acetate* (**11**) : To a magnetically stirred solution of the alcohol **10** (480 mg, 2.5 mmol) in CH_2Cl_2 (6 ml) was sequentially added pyridine (396 mg, 0.40 ml, 5 mmol), acetic anhydride (511 mg, 0.47 ml, 5 mmol) and a catalytic amount of DMAP, and stirred for 8 h at RT. The reaction mixture was then quenched with 1.5 *N* aq. HCl (3 ml) and extracted with CH_2Cl_2 (2 × 10 ml). The combined organic phase was washed with saturated aq. $NaHCO_3$ solution 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 : 20) as eluent furnished the acetate (**11**; 556 mg, 95%), $[\alpha]_D^{25}$ +47.8 (*c* 4.0, $CHCl_3$); ν_{max} (neat) 3070, 2910, 1730 (C=O), 1635 (C=C), 1450, 1430, 1365, 1230, 1020, 970, 890 cm^{-1} (C=CH_2); ^1H nmr (90 MHz, $CDCl_3$) δ 5.35–6.0 (2H, m, C*H*=CH_2 and C*H*-OAc), 4.9–5.1 (2H, m, CH=CH_2), 4.71 (2H, s, C=CH_2), 2.5–3.0 (2H, m, biallylic CH_2), 2.1 (3H, s, $OCOCH_3$), 1.9–2.3 (5H, m), 1.71 (3H, s) and 1.6 (3H, s) [2 × olefinic CH_3]; ^{13}C nmr (22.5 MHz, $CDCl_3$) δ 170.3 (s, O–C=O), 147.9 (s, *C*=CH_2), 134.7 (d, *C*H=CH_2), 132.8 (s) and 126.6 (s) [C-2 and 3], 115.1 (t, CH=*C*H_2), 109.2 (t, C=*C*H_2), 74.3 (d, *C*H–OAc), 39.7 (d, C-5), 37.7 (t), 35.1 (t), 34.1 (t), 20.8 (q), 20.2 (q) and 13.5 (q) [3 × CH_3]; *m/z* 234 (M^+, 5%), 192 (55, M–C_3H_6), 175 (26), 174 (30, M–AcOH), 159 (38), 151 (57), 149 (60), 131 (50), 133 (100), 117 (45), 109 (55), 105 (75); HRMS *m/z* for $C_{15}H_{22}O_2$ calcd. : 234.1620. Found : 234.1612.

*(+)-(1*S,5R*)-5-Isopropenyl-3-(2-oxopropyl)-2-methylcyclohex-2-enyl acetate* (**12**) : A suspension of palladium chloride (67 mg, 0.38 mmol) and cuprous chloride (510 mg, 5.15 mmol) in DMF (2 ml) and water (0.65 ml) was magnetically stirred in an oxygen atmosphere, created via evacuative displacement of air using an oxygen balloon, for 1 h at RT. A solution of the acetate **11** (500 mg, 2.14 mmol) in DMF (1 ml) was then added, and the reaction mixture was stirred for 24 h at RT in the oxygen atmosphere. Then aq. HCl (3 *N*, 5 ml) was added to the reaction mixture and extracted with ether (3 × 10 ml). The combined ether layer was washed with saturated aq. $NaHCO_3$ solution followed by brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1 : 5) as eluent furnished the keto acetate (**12**; 389 mg, 73%) as an oil, $[\alpha]_D^{25}$ +43.8 (*c* 2.6, $CHCl_3$); ν_{max} (neat) 1730 (C=O), 1645 (C=C), 1440, 1370, 1240, 1160, 1020, 960, 890 cm^{-1} (C=CH_2); ^1H nmr (200 MHz, $CDCl_3$) δ 5.45 (1H, t, *J* 6.6 Hz, C*H*–OAc), 4.72 (1H, s) and 4.7 (1H, s) [C=CH_2], 3.16 (2H, s, C$H_2$$COCH_3$), 2.14 (3H, s, CH_3C=O), 2.07 (3H, s, CH_3COO), 1.9–2.4 (4H, m), 1.70 (3H, s) and 1.6 (3H, s) [2 × olefinic CH_3], 1.3–1.6 (1H, m); ^{13}C nmr (22.5 MHz, $CDCl_3$) δ 205.6 (C=O), 170.5 (O–C=O), 147.4 (*C*=CH_2), 129.2 and 128.8 [C-2 and 3], 109.3 (C=*C*H_2), 73.9 (*C*H–OAc), 48.5 (*C*H_2–C=O), 39.3, 35.9, 33.7, 29.1, 20.8, 20.2 and 14.2 (3 × CH_3); *m/z* 208 (M^+–CH_2=C=O, 12%), 190 (55, M–AcOH), 175 (13), 165 (25), 147 (65), 132 (100); HRMS *m/z* for $C_{13}H_{20}O_2$ (M–CH_2=C=O) calcd. : 208.1463. Found : 208.1477.

*(+)-(1*S,5R*)-5-Acetyl-3-(2-oxopropyl)-2-methylcyclohex-2-enyl acetate* (**4**) : Through a cold (–90°) solution of the keto acetate **12** (450 mg, 1.8 mmol) and a catalytic amount of $NaHCO_3$ in methanol (0.09 ml, 2.2 mmol) and CH_2Cl_2 (10 ml) was passed a precooled (–80°) mixture of ozone in oxygen, *ca.* 5 min. The excess ozone was flushed off with oxygen. Dimethyl sulfide (0.8 ml) was added to the reaction mixture, it was then slowly warmed up to RT and magnetically stirred for 8 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate-hexane (1 : 5) as eluent first furnished the starting material keto acetate (**12**; 50.8 mg, 11.2%). Further elution of the column with ethyl acetate-hexane (1 : 2.5) furnished the diketo acetate (**4**; 317 mg, 69.4%) as an oil, $[\alpha]_D^{24}$ +16.7 (*c* 2.8, $CHCl_3$); ν_{max} (neat) 2920, 1730 (ester C=O), 1705 (C=O), 1355, 1240, 1020 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 5.36 (1H, m, C*H*–OAc), 3.25 and 3.15 (2H, AB q, *J* 15.2 Hz, C$H_2$$COCH_3$), 2.71 (1H, m, H-5), 2.0–2.35 (2H, m, H-6), 2.19 (3H, s, CH_3–C=O), 2.17 (3H, s, CH_3–C=O), 2.07 (3H, s, $OCOCH_3$), 1.5–1.8 (2H, m), 1.53 (3H, s, olefinic CH_3); ^{13}C nmr (22.5 MHz, $CDCl_3$) δ 207.9 (s, *C*OCH_3), 204.7 (s, CH_2*C*OCH_3), 169.6 (s, O–C=O), 128.2 (s) and 127.8 (s) [C-2 and 3], 71.6 (d, *C*H–OAc), 47.7 (t, *C*$H_2$$COCH_3$), 44.3 (d, *C*HCOCH), 30.9, 29.9, 28.6, 26.8, 20.2, 14.1; *m/z* 210 (M^+–CH_2=C=O, 5%), 193 (80, M–OAc), 149 (100, M–AcOH–Ac), 107 (25); HRMS *m/z* for $C_{12}H_{18}O_3$ (M–CH_2=C=O) calcd. : 210.1256. Found : 210.1255.

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