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Carvone Based Approaches to Chiral Functionalised C-Ring Derivatives of Taxanes[1]

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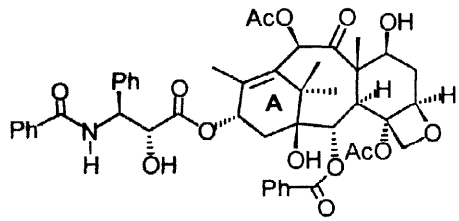
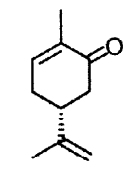
Abstract: Enantiospecific synthesis of functionalised chiral C-ring derivatives of taxanes, starting from R-carvone, is described. © 1998 Elsevier Science Ltd. All rights reserved.

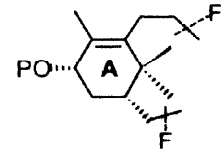
Paclitaxel **1** (Taxol®)[2a] by virtue of its complex and densely functionalised structure coupled with potent antitumor activity through a novel mechanism of action has attracted the attention of synthetic chemists. During the last two decades, more than thirty five research groups have been actively involved in the development of convenient approaches to taxane diterpenoids[2b] and so far four groups have reported the total synthesis of taxol **1**.[3] Recently, we have initiated a new approach[4] to taxanes starting from the readily available monoterpene, carvone **2**, and developed an efficient route for the construction of functionalised chiral A-ring derivatives of taxanes, *e.g.*, **3**.[4] This led us to explore the versatility of carvone for the generation of chiral C-ring[5] derivatives of taxanes, *i.e.*, to construct both left and right halves of taxanes from carvone. It was anticipated that generation of a suitably functionalised C-ring derivative comprising of C-2 to C-10 carbons of taxanes and coupling with 6,6-dimethylcarvone[6] **4** would provide a convenient approach to taxanes. Herein, we describe our results on the synthesis of chiral functionalised C-ring derivatives of taxanes.



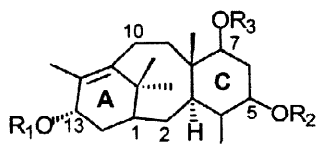
Paclitaxel (Taxol®) **1**



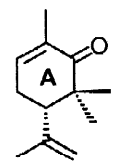
Carvone **2**



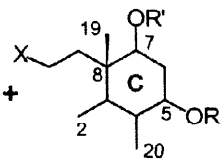
(A-Ring) **3**



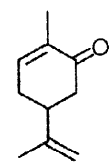
Taxanes



4



C-Ring
(X = functionality)



Carvone

The isopropenyl group of carvone was readily identified as a masked oxygen functionality at the C-5 carbon of taxanes and the C-2 methyl group of carvone as the C-19 carbon (*tert*-methyl on C-8) of taxanes.[6] First attention was focused on the generation of the C-3 to C-10 subunit of taxanes without the oxygen functionality at C-7 carbon of taxanes, Scheme 1. To begin with the C-20 carbon of taxane was introduced *via* kinetic alkylation. Thus, alkylation of R-carvone **2** with LDA-MeI furnished a 3:2 epimeric mixture of 6-

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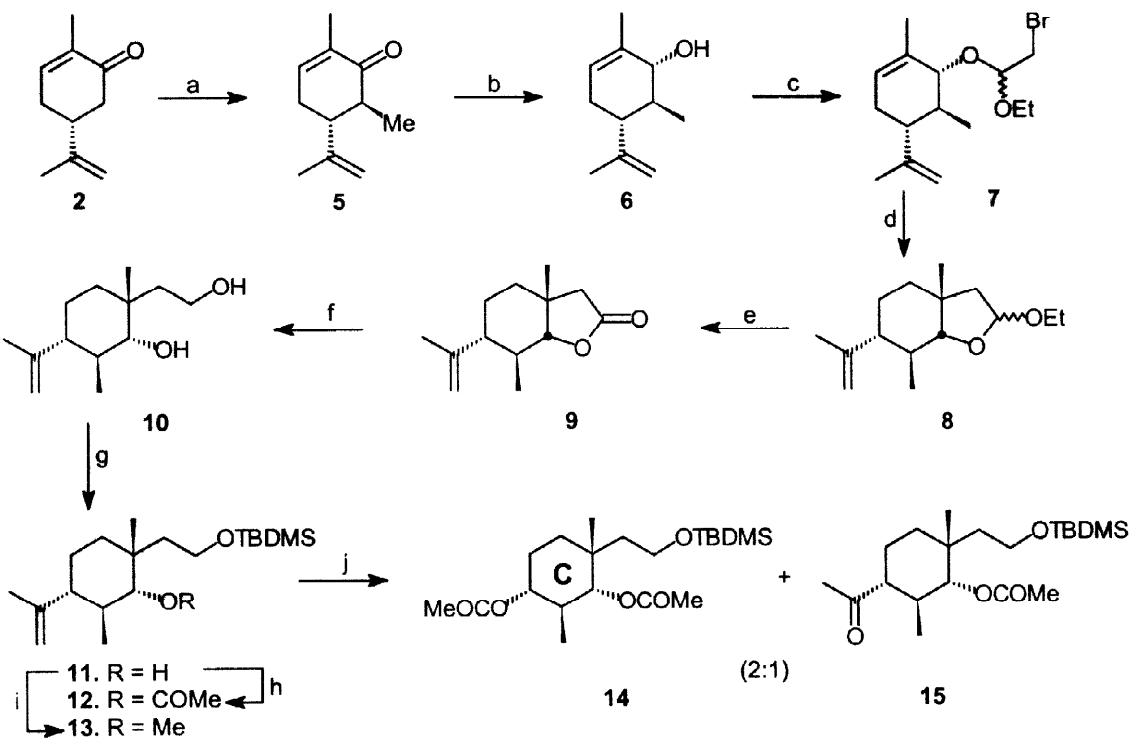
methylcarvone,[7] which on DBU catalysed equilibration followed by crystallisation furnished stereochemically pure *trans* isomer **5**. For the stereospecific introduction of the two carbon side chain (C-9 and 10 carbons of taxanes) at C-2 carbon of 6-methylcarvone, a radical cyclisation based methodology[8] was contemplated *via* the annulation of a butyrolactone moiety. Thus, reduction of 6-methylcarvone **5** with lithium aluminium hydride (LAH) furnished the allyl alcohol **6**, $\{[\alpha]_D^{27}$ –34 (c 2, $CHCl_3)\}$, in a highly stereoselective manner,[4] which on bromoacetalisation reaction[9] with N-bromosuccinimide (NBS) and ethyl vinyl ether generated the radical precursor, bromoacetal **7**. Radical cyclisation of the bromoacetal **7** employing an *in situ* generated catalytic tri-n-butyltin hydride ($^nBu_3SnCl$ and $NaCNBH_3$)[10] in the presence of a catalytic amount of azoisobutyronitrile (AIBN) in refluxing *tert*-butanol furnished the cyclic acetal **8**. Sonochemically accelerated one step hydrolysis and oxidation of the cyclic acetal **8** employing Jones reagent generated the butyrolactone **9**.[11] Prior to the degradation of the isopropenyl moiety, the lactone **9** was reduced and the two hydroxy groups were differentially protected. Thus, LAH reduction of the lactone **9** furnished the diol **10**, $\{[\alpha]_D^{27}$ –12.1 (c 1.16, $CHCl_3)\}$ which on regioselective protection of the primary alcohol employing TBDMSCl and imidazole generated the TBDMS ether **11**. The secondary alcohol in **11** was protected either as its acetate[11] **12** (Ac_2O, Py, DMAP) or its methyl ether **13** (NaH, MeI, Bu_4NI). For the conversion of the isopropenyl group into an acetoxy group, Criegee rearrangement based protocol was envisaged.[12] Thus, ozonation in 1:4 methanol-methylene chloride followed by treatment of the resulting methoxyhydroperoxide with acetic anhydride, triethylamine and DMAP in refluxing benzene transformed the compound **12** into a 2:1 mixture of the C-ring derivative of taxanes **14**[11] and the simple ozonolysis product **15**.[11]

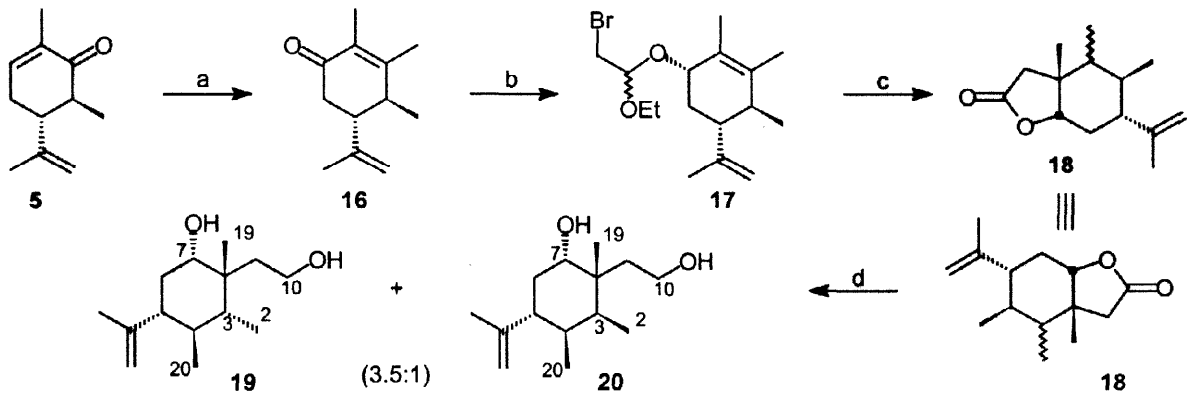
Scheme 1



Reagents, Conditions and Yields: *(a) i. LDA, THF, MeI, 99%; ii. DBU, CH_2Cl_2, rt, 24h; iii. crystallisation (hexanes); (b) LAH, Et_2O, 2h, -78 °C, 100%; (c) CH_2=CH-OEt, NBS, CH_2Cl_2, -50 °C, 2h, 80%; (d) $^nBu_3SnCl$, $NaCNBH_3$, AIBN, t-BuOH, reflux, 6h, 65%; (e) Jones reagent, Me_2CO; sonication; 4 min, 90%; (f) LAH, Et_2O, 2h, -78 °C, 98%; (g) TBDMSCl, CH_2Cl_2, imidazole, DMAP, rt, 15h, 95%; (h) Ac_2O, py, CH_2Cl_2, DMAP, rt, 6h, 90%; (i) NaH, THF, Bu_4NI, MeI, 95%; (j) i. O_3/O_2, CH_2Cl_2-MeOH (4:1), -78 °C; ii. C_6H_6, Et_3N, Ac_2O, DMAP, 6h, reflux, 70%.*

After successfully synthesising the functionalised C-3 to C-10 subunit of taxanes **14**, attention was turned towards the extension of this methodology for the synthesis of C-ring derivative of taxanes comprising of C-2 to C-10 carbons of taxanes incorporating an oxygen functionality at the C-7 carbon of taxanes, Scheme 2. For the simultaneous introduction of the C-2 carbon and an oxygen functionality at C-7 carbon of taxanes, an alkylative 1,3-enone transposition strategy[13] was chosen. Thus, regiospecific 1,2-addition of methylmagnesium iodide to methylcarvone **5** followed by oxidation of the resulting allyl alcohol with pyridinium chlorochromate (PCC)-silica gel furnished *trans*-3,4-dimethylcarvone **16**, $\{[\alpha]_D^{24}$ –7.7 (c 6, $CHCl_3)\}$. Introduction of the functionalised two carbon side chain at C-2 was accomplished employing the same methodology. Thus, regio- and stereoselective reduction of 3,4-dimethylcarvone **16** with LAH furnished the allyl alcohol, which on bromoacetalisation reaction with NBS and ethyl vinyl ether generated the radical precursor, bromoacetal **17**. Radical cyclisation of the bromoacetal **17** followed by sonochemically accelerated reaction of the resulting cyclic acetal with Jones reagent furnished a 3.5:1 epimeric mixture of the lactone **18**. Finally, reduction of the epimeric mixture of the lactone **18** with LAH followed by separation on a silica gel column furnished the C-ring derivatives of taxanes, diols **19** and **20**.[11]

Scheme 2



Reagents, Conditions and Yields: *(a) i. MeMgI, Et_2O, 6h, rt; ii. PCC, silica gel, CH_2Cl_2, 6h; 74%; (b) i. LAH, Et_2O, 2h, -78 °C, 83%; ii. CH_2=CH-OEt, NBS, CH_2Cl_2, -50 °C, 2h, 67%; (c) i. $^nBu_3SnCl$, $NaCNBH_3$, AIBN, t-BuOH, reflux, 3h, 68%; ii. Jones reagent, Me_2CO, sonication, 4 min, 75%; (d) LAH, Et_2O, 2h, -78 °C, 97%.*

In conclusion, we have demonstrated that the monoterpene, carvone **2**, can serve as a convenient chiral starting material for the construction of the A-ring[4] as well as C-ring derivatives of taxanes. Currently, we are investigating the extension of this methodology for the construction of chiral taxanes starting from S-carvone, which will generate the right absolute stereochemistry at C-8 carbon of taxanes for further elaboration.

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11. All the compounds exhibited spectral data (IR, NMR, LRMS and HRMS) consistent with their structures. IR and NMR spectra for selected compounds are as follows: For the lactone **9**: IR (neat): ν_{max} 1770, 1640, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.76 (1 H, s) and 4.72 (1 H, s) [$C=CH_2$], 3.69 (1 H, d, J=9.5 Hz, CH-O), 2.68 (1 H, d, J=16.9 Hz) and 2.00 (1H, d, J=16.9 Hz) [$CH_2C=O$], 1.20-1.90 (6 H, m), 1.62 (3 H, s, olefinic CH_3), 1.17 (3 H, s, *tert*-CH_3), 0.95 (3 H, d, J=6.3Hz, *sec*-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9 (O-C=O), 146.2 and 112.2 ($C=CH_2$), 91.8 (CH-O), 49.7, 39.1, 38.4, 33.3, 27.3, 28.9, 18.6, 16.7. For the acetate **12**: IR (neat): ν_{max} 1740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.73 (2 H, s, $C=CH_2$), 4.47 (1 H, d, J=10.4 Hz, CH-OAc), 3.60-3.80 (2 H, m, CH_2-OSi), 2.08 (3 H, s, $CH_3C=O$), 1.66 (3 H, s, olefinic CH_3), 1.10-1.80 (8 H, m), 0.91 (9 H, s, $C(CH_3)_3$), 0.85 (3 H, s, *tert*-CH_3), 0.72 (3 H, d, J=5.9 Hz, sec-CH_3), 0.07 (6 H, s, $Si(CH_3)_2$). ^{13}C NMR (50 MHz, $CHCl_3$+$(CD_3)_2C=O$): δ 170.7 (OCO), 147.2 and 111.4 ($C=CH_2$), 84.5 (*C*-OAc), 59.4 (CH_2OSi), 52.5, 37.0, 35.2, 33.9, 33.7, 26.7, 25.8 (3 C), 20.7, 18.5, 15.5, –5.5. For the diacetate **14**: IR (neat): ν_{max} 1740, 1090, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.48 (1 H, d, J=11.2 Hz, CH-OAc), 4.47 (1 H, d of triplet, J=11 and 5 Hz, CH-OAc), 3.75-3.60 (2 H, m, CH_2-OTBDMS), 2.08 (3 H, s) and 2.05 (3 H, s) [2 x $CH_3C=O$), 1.40-2.00 (6 H, m), 1.19 (1 H, d of t, J=14.2 and 3.5 Hz), 0.90 (9 H, s, $C(CH_3)_3$), 0.88 (3 H, s, *tert*-CH_3), 0.83 (3 H, d, J=6.4 Hz, *sec*-CH_3), 0.06 (6H, s, $Si(CH_3)_2$). For the keto acetate **15**: IR (neat): ν_{max} 1730, 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.47 (1 H, d, J=11.0 Hz, CH-OAc), 3.60-3.70 (2 H, m, CH_2-OSi), 2.29 (1 H, d of t, J=12.1 and 4.25 Hz, CH-Ac), 2.15 (3 H, s, $CH_3C=O$), 2.07 (3 H, s, $CH_3C=O$), 1.85-1.15 (7 H, m), 0.88 (12 H, s, *tert*-CH_3 and $C(CH_3)_3$), 0.74 (3 H, d, J=6.2 Hz, *sec*-CH_3), 0.05 (6 H, s, $Si(CH_3)_2$). For the major diol **19**: $[\alpha]_D^{24}$: -13.7 (c 4.1, $CHCl_3$). IR (neat): ν_{max} 3200, 1630, 880 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.72 (2 H, br s, $C=CH_2$), 3.65-3.75 (2 H, m, O-CH_2), 3.37 (1 H, dd, J=11.0 and 5.0 Hz, C*H*-OH), 2.00-2.50 (2 H, 2 x O-H), 1.60-2.00 (5 H, m), 1.65 (3 H, s, olefinic CH_3), 1.20-1.50 (2 H, m), 1.09 (3 H, s, *tert*-CH_3), 0.86 (3 H, d, J=6.0 Hz) and 0.74 (3 H, d, J=6.3 Hz) [2 x *sec*-CH_3]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2 ($C=CH_2$), 111.5 ($C=CH_2$), 77.8 (*C*H-OH), 59.1 (CH_2-OH), 52.5, 48.2, 41.7 (C-2), 36.2, 34.4, 31.0, 22.3, 18.8, 17.6, 12.9. For the minor diol **20**: IR (neat): ν_{max} 3200, 1635, 895 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 4.71 (2 H, s, $C=CH_2$), 3.50-3.90 (3 H, m, *CH*OH and CH_2OH), 3.16 (2 H, 2 x OH), 1.30-2.50 (7 H, m), 1.66 (3 H, s, olefinic CH_3), 1.07 (3 H, s, *tert*-CH_3), 0.85 (3 H, d, J=7.8 Hz) and 0.72 (3 H, d, J=6.0 Hz) [2 x *sec*-CH_3].
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