Synthesis of taxanes—the carvone approach; a simple, efficient stereo- and enantio-selective synthesis of the functionalised A ring

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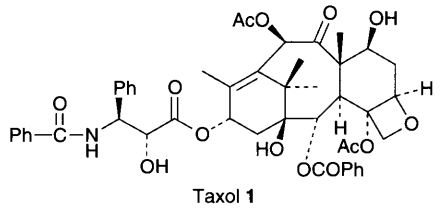
A highly stereo- and enantio-selective methodology for the construction of the chiral functionalised A-ring of taxanes, starting from (*R*)-carvone employing a short, simple and efficient sequence is described.

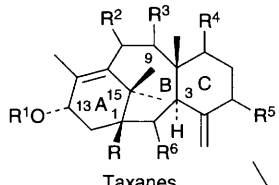
The unique molecular architecture coupled with the promising antitumor activity, in particular to ovarian and breast cancers, of taxol **1** have generated tremendous interest in the synthesis of taxanes, and several approaches have been reported.[2,3] The most efficient of these exploit a convergent strategy, constructing a functionalised A ring derivative upon which the remaining carbon skeleton is appended. A variety of strategies have been developed for the construction of the A-ring of taxanes both in racemic as well as chiral forms.[3] We have initiated a new approach to chiral taxanes starting from the readily available monoterpene (*R*)-carvone **2**, wherein the C-4 of carvone was identified as the C-1 of taxanes.† Here we describe a highly stereo- and enantio-selective synthesis of functionalised chiral derivatives of the A-ring of taxanes incorporating easily differentiable oxygen functionalities at carbon atoms 2, 9 (or 10) and 13 of the taxane framework suitable for further elaboration, employing a short, simple and efficient route.

To begin with, as a model study, the sequence was tested without the gem-dimethyl grouping, and (*R*)-carvone **2** was converted into the acetate **3** as depicted in Scheme 1. A 1,3-enone transposition methodology was adopted for the introduction of the side chain at C-2 and an oxygen at C-6 of carvone which also creates the tetrasubstituted alkene moiety as in taxanes. Thus 1,2-addition of allylmagnesium chloride to (*R*)-carvone **2** followed by oxidation of the resultant tertiary allyl alcohol **4** with pyridinium chlorochromate (PCC) cleanly furnished the transposed enone **5**. Regioselective reduction[4] of the enone **5** with lithium aluminium hydride at low temperature‡ followed by acetylation of the resultant *syn*-allyl alcohol **6** furnished the acetate **3** in 80–85% yield, creating the two chiral centres in a highly stereoselective manner as present in the A-ring† of taxanes (C-1 and -13). Regioselective oxidation of the allyl alkene moiety under Wacker conditions ($PdCl_2/CuCl/O_2/DMF/H_2O$) generated the ketoacetate **7** in 75% yield. The extra carbon atom present in the isopropenyl side chain was cleaved *via* selective ozonolysis of the ketoacetate **7** generating the diketoacetate **8**, $[\alpha]_D^{24}$ = 16.7 (*c* 2.2, $CHCl_3$), in 80% yield.

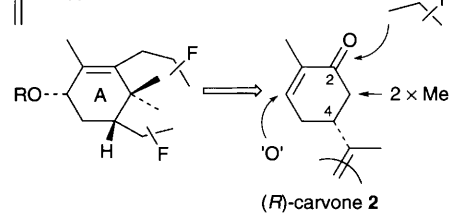
After successful synthesis of acetate **3** and diketoacetate **8**, the methodology has been extended for the synthesis of functionalised chiral derivatives of the A-ring of taxanes as depicted in Scheme 2. Scheme 1 readily equated the C-3 position of carvone with the C-15 position of taxanes for incorporating the gem dimethyl grouping. The requisite gem dimethyl groups at C-3 position of carvone were introduced *via* alkylation. Thus sequential kinetic alkylation of carvone with LDA and methyl iodide generated the dimethylcarvone **9**, $[\alpha]_D^{25}$ = 1.8 (*c* 3.8, $CHCl_3$), in 90–95% yield. Grignard reaction with allylmagnesium chloride followed by oxidation of the resultant tertiary alcohol with PCC transformed the dimethylcarvone **9** into the transposed compound **10**, $[\alpha]_D^{24}$ = 62.8 (*c* 4.7, $CHCl_3$) in 85–90% yield. In an analogous manner employing vinylmagnesium bromide generated the vinyl compound **11**, $[\alpha]_D^{24}$ = 48.6 (*c* 3.6, $CHCl_3$). In contrast, use of prop-2-enylmagnesium bromide failed to add in a 1,2-manner and gave only the 1,4-addition product **12** highlighting the steric crowding around the ketone moiety in **9**. Low temperature $LiAlH_4$ reduction of the carbonyl group‡ followed by benzoylation of the resultant *syn* allyl alcohols **13** and **14** transformed the enones **10** and **11** into the A-ring derivatives of the taxane **15**§ and **16**§ in 90–95% yield.



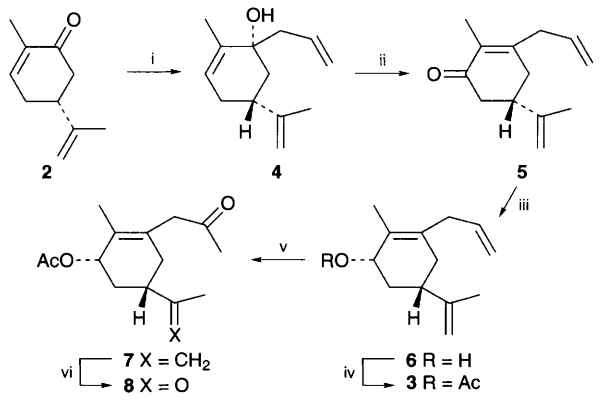
Taxol **1**



Taxanes



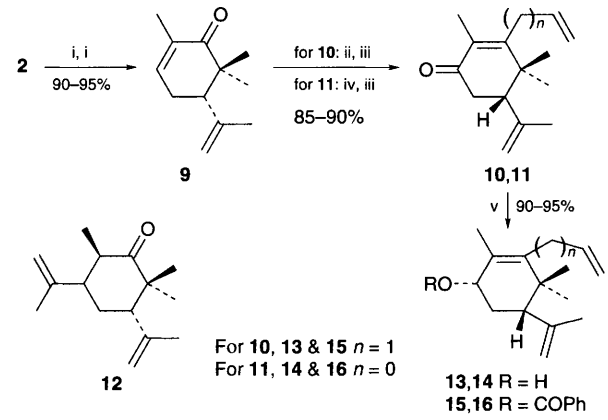
(*R*)-carvone **2**



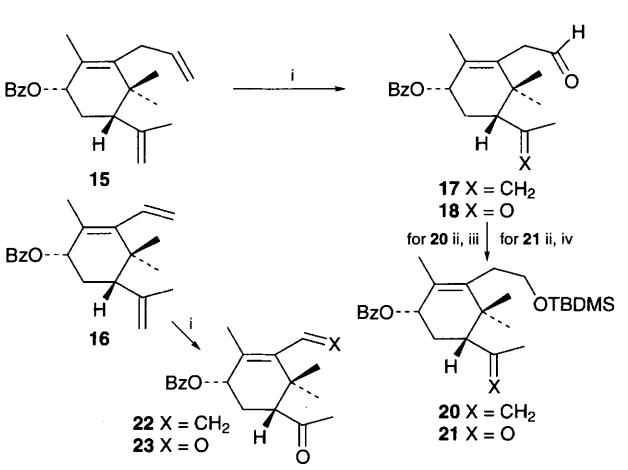
Scheme 1 *Reagents and conditions*: i, CH_2=CH–CH_2MgCl, THF, 0 °C → room temp., 8 h; ii, PCC, silica gel, CH_2Cl_2, room temp., 3 h; iii, $LiAlH_4$, Et_2O, −80 °C, 2 h; iv, Ac_2O, pyridine, CH_2Cl_2, DMAP, room temp., 3 h; v, $PdCl_2$, CuCl, O_2, DMF, H_2O, room temp., 12 h; vi, (*a*) O_3/O_2,MeOH, CH_2Cl_2, −80 °C; (*b*) Me_2S, −80 °C → room temp., 8 h

The benzoates **15** and **16** were further elaborated as depicted in Scheme 3. Controlled ozonolysis of the benzoate **15** generated first the aldehyde **17** and later the ketoaldehyde **18**¶ cleaving the extra carbon atom present in the isopropenyl side chain. Reduction of the aldehyde **17** with sodium borohydride followed by protection of the resultant primary alcohol **19** with *tert*-butyldimethylchlorosilane (TBDMS-Cl) furnished the TBDMS ether **20**, $[\alpha]_D^{24}$ = 8.5 (*c* 3.4, $CHCl_3$). Analogously reduction of the ketoaldehyde **18** with sodium borohydride followed by selective protection of the primary alcohol with TBDMS-Cl and reoxidation of the secondary alcohol with PCC furnished the TBDMS ether **21**.§ Similarly ozonolysis of the benzoate **16** followed by purification over a silica gel column furnished the ketone **22** and the ketoaldehyde **23**. The compounds ketoaldehydes **18** and **23**, and ketoether **21** containing three easily differentiable oxygen functionalities at suitable positions are ideally suited for further elaboration into taxanes.

We thank the DST and UGC for the financial support, and the departments IPC and MBU of IISc for recording the NMR spectra of some of the compounds reported here.



Scheme 2 *Reagents and conditions*: i, (*a*) LDA, THF, 0 °C, 2 h; (*b*) MeI, 0 °C → room temp., 12 h; ii, CH_2=CH–CH_2MgCl, THF, 0 °C → room temp., 12 h; iii, PCC, silica gel, CH_2Cl_2, room temp., 24 h; iv, CH_2=CH–MgBr, THF, 0 °C → room temp., 12 h; v, (*a*) $LiAlH_4$, Et_2O, −80 °C, 2 h; (*b*) PhCOCl, pyridine, CH_2Cl_2, DMAP, room temp., 10 h



Scheme 3 *Reagents and conditions*: i, (*a*) O_3/O_2, MeOH, CH_2Cl_2, −80 °C; (*b*) Me_2S, −80 °C → room temp., 8 h; 75–80%; ii, $NaBH_4$, MeOH, room temp., 2 h, 75–80%; iii, TBDMS-Cl, pyridine, DMAP, CH_2Cl_2, room temp., 8 h, 85%; iv, (*a*) TBDMS-Cl (1 equiv.), imidazole, DMAP, CH_2Cl_2, room temp., 45 min, 85%; (*b*) PCC, silica gel, CH_2Cl_2, room temp., 1 h, 75%

Footnotes

† Unlike **1** most of the taxanes do not contain a C-1 hydroxy group.

‡ Analogous to the reduction of carvone,[4] a high degree of stereoselectivity (>20:1) was observed in the reduction of the enones **5**, **10** and **11**. The resonances due to the minor isomers were not noticed in the δ_H (200 MHz) and δ_C (22.5 MHz) spectra of **13** and **14**.

§ Reactions in Scheme 2 were carried out typically on 5–10 mmol scale, whereas those in Schemes 1 and 3 were carried out on a 1–3 mmol scale. All the compounds exhibited spectral data consistent with their structures. *Selected spectral data* for the benzoate **15**: $[\alpha]_D^{25}$ = 17.8 (*c* 2.0, $CHCl_3$). ν_{max}/cm^{-1} 3070, 1710, 1630, 1600, 1260, 1110, 1090, 1070 and 710. δ_H (200 MHz, $CDCl_3$) 8.07 (2 H, dd, *J* 7.0, 1.3 Hz), 7.55 (1 H, t, *J* 7.1 Hz), 7.44 (2 H, t, *J* 7.0 Hz), 5.7–5.8 (1 H, m), 5.64 (1 H, t, *J* 8.2 Hz), 5.03 (1 H, d, *J* 12.0 Hz), 5.02 (1 H, d, *J* 16.0 Hz), 4.93 (1 H, s), 4.70 (1 H, s), 2.87 (2 H, d of AB q, *J* 16.5, 6.1 Hz), 2.29 (1 H, d, *J* 13.4 Hz), 1.8–2.2 (2 H, m), 1.76 (3 H, s), 1.62 (3 H, s), 1.05 (3 H, s) and 1.00 (3 H, s). δ_C (22.5 MHz, $CDCl_3$) 166.2 (s), 145.6 (s), 140.7 (s), 136.4 (d), 132.6 (d), 130.7 (s), 129.5 (2 C, d), 128.2 (2 C, d), 128.0 (s), 114.9 (t), 114.7 (t), 74.7 (d), 49.8 (d), 39.5 (s), 33.0 (t), 30.8 (t), 26.5 (q), 22.9 (q), 22.3 (q) and 15.0 (q). For the benzoate **16**: $[\alpha]_D^{24}$ = 23.4 (*c* 5.0, $CHCl_3$). ν_{max}/cm^{-1} 3070, 1710, 1260, 1110, 920, 890 and 710. δ_H (200 MHz, $CDCl_3$) 8.07 (2 H, d, *J* 6.1 Hz), 7.3–7.7 (3 H, m), 6.22 (1 H, dd, *J* 17.6, 11.3 Hz), 5.64 (1 H, t, *J* = *ca.* 8 Hz), 5.36 (1 H, dd, *J* 11.3, 2.5 Hz), 5.05 (1 H, dd, *J* 17.6, 2.5 Hz), 4.94 (1 H, s), 4.72 (1 H, s), 2.31 (1 H, dd, *J* 13.5, 2.4 Hz), 1.8–2.2 (2 H, m), 1.76 (3 H, s), 1.71 (3 H, s), 1.04 (3 H, s) and 1.00 (3 H, s). δ_C (22.5 MHz, $CDCl_3$) 166.3 (s), 145.6 (s), 144.3 (s), 135.0 (d), 132.8 (d), 130.7 (s), 129.6 (2 C, d), 128.3 (2 C, d), 126.8 (s), 119.8 (t), 114.8 (t), 74.8 (d), 49.7 (d), 38.3 (s), 30.7 (t), 27.0 (q), 23.0 (q), 22.5 (q) and 16.9 (q). For the TBDMS ether **20**: $[\alpha]_D^{24}$ = 8.5 (*c* 3.4, $CHCl_3$). ν_{max}/cm^{-1} 3065, 1710, 1265, 1090, 895, 830, 770 and 710. δ_H (200 MHz, $CDCl_3$) 8.06 (2 H, dd, *J* 6.85, 1.6 Hz), 7.57 (1 H, t, *J* 7.2 Hz), 7.45 (2 H, t, *J* 7.0 Hz), 5.58 (1 H, t), 4.93 (1 H, s), 4.7 (1 H, s), 3.62 (1 H, t, *J* 6.9 Hz), 1.8–2.5 (5 H, m), 1.75 (3 H, s), 1.69 (3 H, s), 1.07 (3 H, s), 0.998 (3 H, s), 0.914 (9 H, s) and 0.084 (6 H, s). For the keto ether **21**: $[\alpha]_D^{25}$ = −2.1 (*c* 4.4, $CHCl_3$). ν_{max}/cm^{-1} 1708, 1260, 1090, 830, 770 and 710. δ_H (200 MHz, $CDCl_3$) 8.04 (2 H, dd, *J* 6.8, 1.1 Hz), 7.53–7.58 (1 H, m), 7.45 (2 H, t, *J* 6.7 Hz), 5.53 (1 H, t, *J* 7.4 Hz), 3.64 (2 H, t, *J* 8.2 Hz), 2.67 (1 H, dd, *J* 12.0, 2.9 Hz), 1.9–2.5 (4 H, m), 2.18 (3 H, s), 1.69 (3 H, s), 1.18 (3 H, s), 1.11 (3 H, s), 0.913 (9 H, s) and 0.085 (6 H, s). δ_C (22.5 MHz, $CDCl_3$) 209.2 (s), 165.9 (s), 139.1 (s), 132.6 (d), 130.2 (s), 129.4 (2 C, d), 128.1 (2 C, d), 127.6 (s), 72.8 (d), 62.0 (t), 55.4 (d), 37.7 (s), 32.4 (t), 31.2 (q), 27.9 (q), 27.2 (t), 25.9 (3 C, q), 22.7 (q), 18.1 (s), 15.5 (q) and −5.4 (2 C, q).

¶ The ratio of aldehyde and ketoaldehydes vary depending on the extent of ozonation, and can be controlled by varying the time.

References

1 For part 18 of *Chiral synthons from carvone*, see A. Srikrishna, P. Hemamalini, G. V. R. Sharma and S. Danieldoss, *J. Chem. Soc., Perkin Trans. 1*, in the press.

2 D. G. I. Kingston, A. A. Molinero and J. M. Rimoldi, *Prog. Chem. Natl. Prod.*, 1993, **61**, 1; K. C. Nicolaou, W.-M. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15; A. N. Boa, P. R. Jenkins and N. J. Lawrence, *Contemp. Org. Synth.*, 1994, **1**, 47; C. S. Swindell, *Org. Prep. Proc. Int.*, 1991, **23**, 465. For the total synthesis of taxol see, R. A. Holton, C. Somaza, H.-B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile and J. H. Liu, *J. Am. Chem. Soc.*, 1994, **116**, 1597; K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan and E. J. Sorensen, *Nature*, 1994, **367**, 630; J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1723; For the other synthetic aspects of taxanes see, S. W. Elmore and L. A. Paquette, *J. Org. Chem.*, 1995, **60**, 889 and references cited therein as well as those cited in ref. 3*c*,*d*.

3 (*a*) Y. Ding and X.-R. Jiang, *J. Chem. Soc., Chem. Commun.*, 1995, 1693; (*b*) M. W. Tjepkema, P. D. Wilson, T. Wong, M. A. Romero, H. Audrain and A. G. Fallis, *Tetrahedron Lett.*, 1995, **36**, 6039; (*c*) D. F. Taber, A. Sahli, H. Yu and R. P. Meagley, *J. Org. Chem.*, 1995, **60**, 6571; (*d*) L. Alcaraz, J. J. Harnett, C. Mioskowski, T. L. Gall, D.-S. Shin and J. R. Falck, *J. Org. Chem.*, 1995, **60**, 7209 and references cited therein.

4 L. Garver, P. van Eikeren and J. E. Byrd, *J. Org. Chem.*, 1976, **41**, 2773.

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