

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

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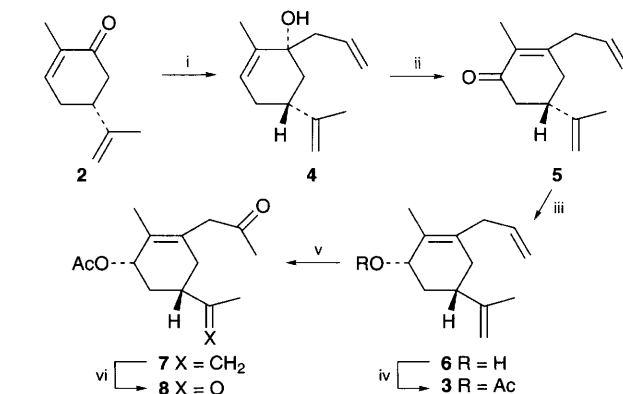
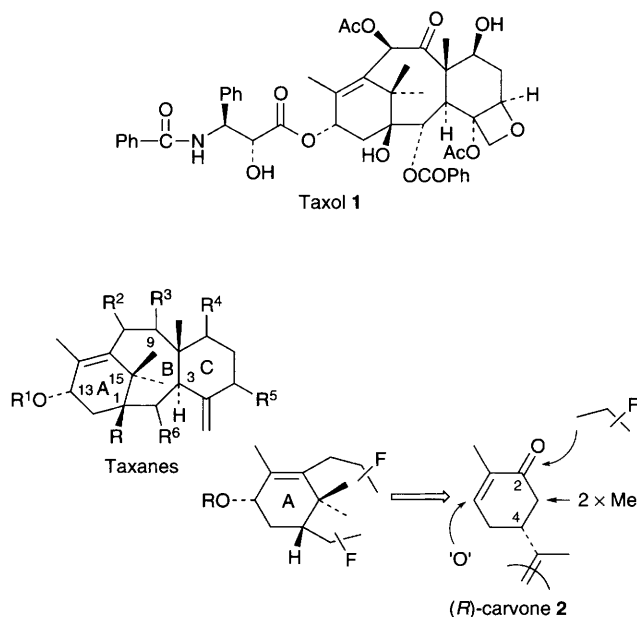
A highly stereo- and enantio-selective methodology for the construction of the chiral functionalised A-ring of taxanes, starting from (*R*)-carvone employing a short, simple and efficient sequence is described.

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 reduction⁴ 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 (PdCl₂/CuCl/O₂/DMF/H₂O) 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**, [α]_D²⁴ = 16.7 (c 2.2, CHCl₃), in 80% yield.

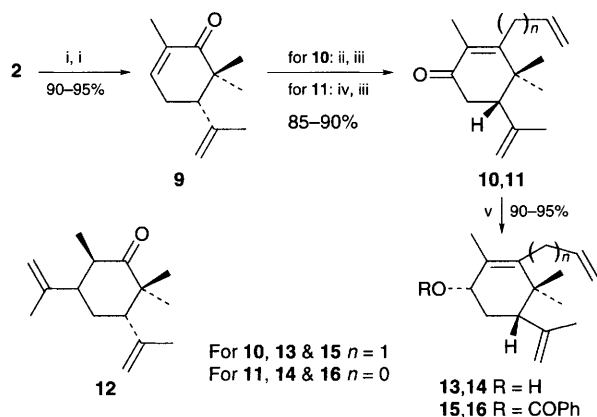
After successful synthesis of acetate **3** and diketoacetate **8**, the methodology has been extended for the synthesis of functionalised chiral derivatives of the A-ring of taxanes as depicted in Scheme 2. Scheme 1 readily equated the C-3 position of carvone with the C-15 position of taxanes for incorporating 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**, [α]_D²⁵ = 1.8 (c 3.8, CHCl₃), 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**, [α]_D²⁴ = 62.8 (c 4.7, CHCl₃) in 85–90% yield. In an analogous manner employing vinylmagnesium bromide generated the vinyl compound **11**, [α]_D²⁴ = 48.6 (c 3.6, CHCl₃). 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 LiAlH₄ 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.



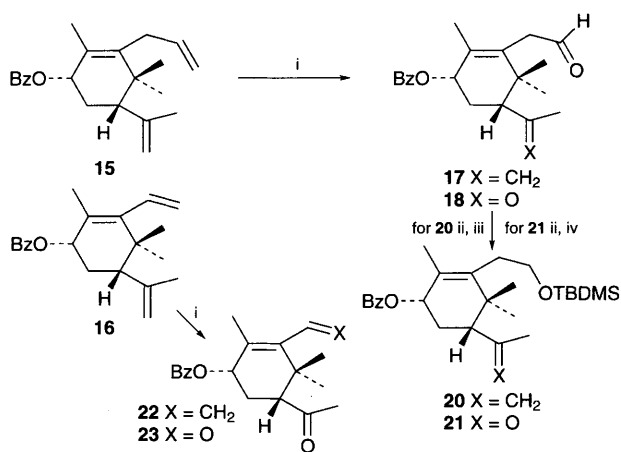
Scheme 1 Reagents and conditions: i, CH₂=CH-CH₂MgCl, THF, 0 °C → room temp., 8 h; ii, PCC, silica gel, CH₂Cl₂, room temp., 3 h; iii, LiAlH₄, Et₂O, -80 °C, 2 h; iv, Ac₂O, pyridine, CH₂Cl₂, DMAP, room temp., 3 h; v, PdCl₂, CuCl, O₂, DMF, H₂O, room temp., 12 h; vi, (a) O₃/O₂, MeOH, CH₂Cl₂, -80 °C; (b) Me₂S, -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.

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Scheme 2 Reagents and conditions: i, (a) LDA, THF, 0 °C, 2 h; (b) MeI, 0 °C \rightarrow room temp., 12 h; ii, $\text{CH}_2=\text{CH}-\text{CH}_2\text{MgCl}$, THF, 0 °C \rightarrow room temp., 12 h; iii, PCC, silica gel, CH_2Cl_2 , room temp., 24 h; iv, $\text{CH}_2=\text{CH}-\text{MgBr}$, THF, 0 °C \rightarrow 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 \rightarrow 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). $\nu_{\text{max}}/\text{cm}^{-1}$ 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). $\nu_{\text{max}}/\text{cm}^{-1}$ 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). $\nu_{\text{max}}/\text{cm}^{-1}$ 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). $\nu_{\text{max}}/\text{cm}^{-1}$ 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.

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