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COMMUNICATION

Carvone based approaches to chiral functionalised B-seco-taxanes †

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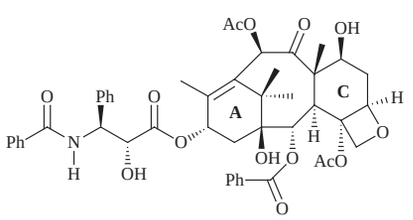
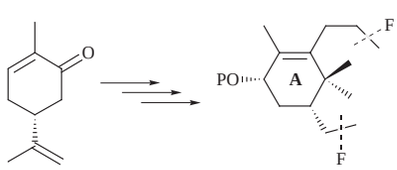
Starting from (*R*)-carvone, the synthesis of chiral, functionalised C-aromatic-B-seco-taxanes and an extension to the synthesis of a B-seco-20-nortaxane derivative have been described.

Paclitaxel **1** (Taxol),[1] by virtue of its complex and densely functionalised structure, coupled with potent antitumor activity and novel mechanism of action, has attracted the attention of many 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[2] 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** (Scheme 1).[4] It



Paclitaxel (Taxol®) **1**

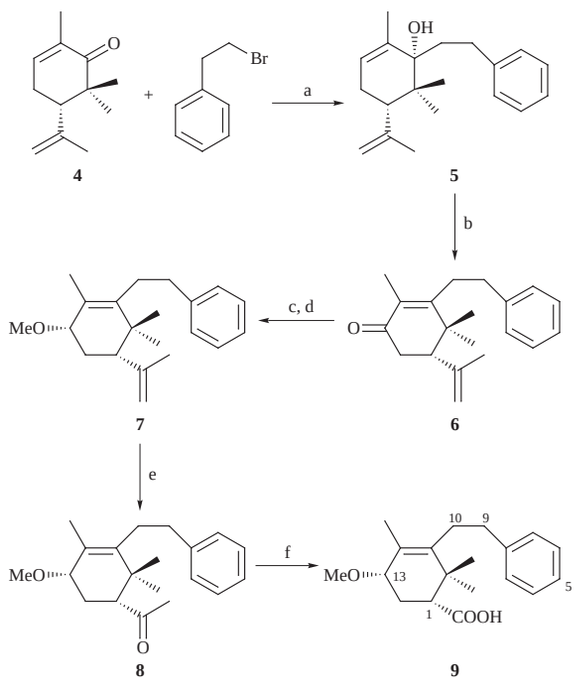


Carvone **2** (A-Ring) **3**

Scheme 1

was anticipated that incorporation of a suitable C-ring component would result in the generation of B-seco-taxane derivatives[5] *en route* to taxanes. As a model study in this direction, herein we describe the synthesis of various chiral functionalised B-seco-nortaxane derivatives.

We first contemplated an intramolecular Friedel–Crafts acylation or equivalent for the closure of the B-ring, and thus focused our attention on the synthesis of C-aromatic B-seco derivatives of taxanes employing phenethyl bromide as the starting material, Scheme 2. Thus, reaction of dimethylcarvone[4] **4** with phenethyl bromide in the presence of lithium, activated by ultrasonic irradiation, followed by oxidation of the resulting *tert*-allyl alcohol **5** furnished the enone **6**.‡ For the conversion of the enone **6** into a B-seco-taxane derivative, prior to the degradation of the isopropenyl group, the carbonyl group was masked. Consequently, stereoselective[6] reduction of the enone **6** followed by protection of the resulting allyl alcohol (mp 106–108 °C) as its methyl ether generated the ether **7**, $[a]_D^{24}$ +58 (*c* 2.1, $CHCl_3$). A two step protocol was chosen for the degradation of the isopropenyl moiety into the corresponding acid. First, regioselective ozonolysis followed by reductive work-up transformed the isopropenyl compound **7** into the acetyl compound **8**.‡ Haloform reaction of compound **8** using freshly prepared sodium hypobromide furnished the B-seco-taxane derivative, the acid **9**.



Scheme 2 *Reagents and conditions*: (a) Li, THF, sonication, 1 h; (b) PCC–silica gel, CH_2Cl_2, 36 h, 92% (2 steps); (c) LAH, Et_2O, −78 °C, 2 h, 99%; (d) NaH, THF, DMF, Bu_4NI, MeI, 8 h, 99%; (e) O_3–O_2, MeOH–CH_2Cl_2 (1:4), −70 °C; Me_2S, 8 h, 76%; (f) NaOH, Br_2, dioxane, 3 h, 0 °C–RT, 50%.

This methodology was extended to incorporate the desired oxygen functionality at the C-9 and C-10 positions present in the taxane skeleton. Thus the sequence was carried out as in Scheme 3 using the illustrated phenylacetylene compound as a 1,2-dioxygenated ethyl group equivalent. Reaction of dimethylcarvone **4** with the lithium anion of phenylacetylene followed by oxidation of the resulting allyl alcohol furnished the enynone **11**, $[a]_D^{25}$ +36 (*c* 2.39, $CHCl_3$). Analogous to the earlier series, reduction followed by protection of the resulting allyl alcohol with benzoyl chloride, pyridine and DMAP transformed the enynone **11** into the benzoate **12**, $[a]_D^{25}$ +33.3 (*c* 2.40, $CHCl_3$) which on ozonolysis furnished the acetyl compound **13** $[a]_D^{25}$ +22.7 (*c* 2.07, $CHCl_3$). In another reaction, controlled hydrogenation of the acetylene moiety in the enynone **11** using Lindlar catalyst furnished the *cis*-olefin **14**,‡ suitable for further elaboration to taxanes. In continuation, the sequence was also carried out with *p*-methoxyphenylacetylene to incorporate the oxygen functionality at the C-5 carbon of taxanes as well. Thus, employing the same sequence of reactions, dimethylcarvone **4** was converted into the oxobenzoate **15** {$[a]_D^{26}$ +3.27 (*c* 2.75, $CHCl_3$)}, *via* the enynone **16** {$[a]_D^{26}$ +35.5 (*c* 2.25, $CHCl_3$)} and the benzoate **17** {$[a]_D^{26}$ −200 (*c* 0.2, $CHCl_3$)}.

After successfully accomplishing the synthesis of C-aromatic bis-nortaxane derivatives, attention was turned towards the synthesis of a C-20 nortaxane derivative employing an appropriate aliphatic C-ring precursor containing the C-19 carbon (*tert*-methyl at C-8) of taxanes, Scheme 4. Bromide **18** was identified as a potential precursor, and was prepared in four steps starting from 3-methylcyclohex-2-enol. Coupling of the bromide **18** with dimethylcarvone **4** in the presence of lithium

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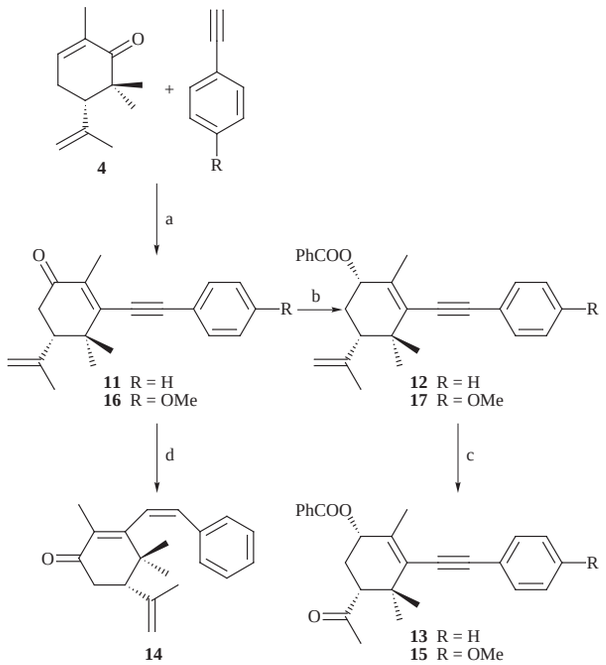
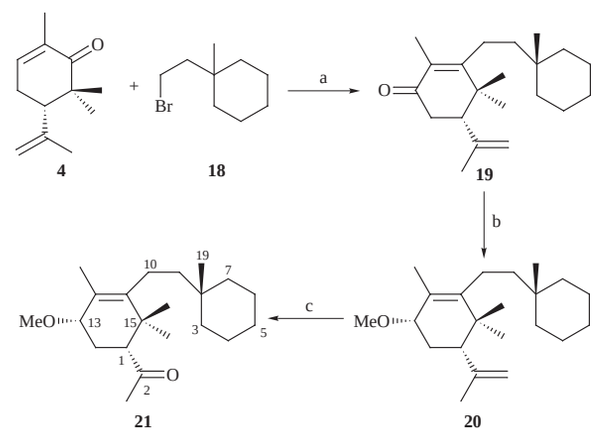


Scheme 3 *Reagents and conditions*: (a) i, *n*-BuLi, THF, 8 h, 0 °C–RT; ii, PCC–silica gel, CH_2Cl_2, 92 and 80% (2 steps); (b) i, LAH, Et_2O, −78 °C, 2 h, 99 and 90%; ii, PhCOCl, Py, DMAP, CH_2Cl_2, 95 and 85%; (c) O_3–O_2, −70 °C, MeOH–CH_2Cl_2 (1 : 4), Me_2S, 8 h, 80 and 72%; (d) Lindlar catalyst, H_2 (balloon), MeOH, 35 h, 90%.



Scheme 4 *Reagents and conditions*: (a) i, Li, THF, sonication; ii, PCC–silica gel, CH_2Cl_2, 81% (2 steps); (b) i, LAH, Et_2O, −78 °C, 2 h, 90%; ii, NaH, THF, Bu_4NI, MeI, 6 h, 91%; (c) i, O_3–O_2, MeOH–CH_2Cl_2 (1 : 4), −70 °C; ii, Me_2S, 8 h, 55%.

followed by oxidation of the resulting allyl alcohol furnished the enone[6] **19** [2-methyl-2-methylene-(20)-nor-(2,3)-secotax-11-en-13-one]. Regioselective reduction of the enone **19** and protection of the allyl alcohol generated the methyl ether **20**, $[\alpha]_D^{24}$ +58.0 (*c* 2.12, $CHCl_3$), which on ozonolysis followed by reductive work-up generated 13-methoxy-2-methyl-(2,3)-seco-20-nortax-11-en-2-one **21**.

In conclusion, we have achieved the synthesis of various functionalised B-seco-analogues of taxanes starting from the readily available monoterpene (*R*)-carvone, and currently we are investigating the extension of this methodology with functionalised chiral C-ring derivatives for the construction of B-seco analogues suitable for further elaboration to taxanes.

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Notes and references

† Chiral synthons from carvone, Part 35. For part 34 see reference 7.

‡ All the compounds exhibited spectral data (IR, ^1H and ^{13}C NMR, LRMS and HRMS) consistent with the proposed structures. Spectral data for selected compounds are as follows: For the enone **6**: mp 52–53 °C $[\alpha]_D^{26}$ +36.4 (*c* 3.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1665, 1605, 895, 750, 700; δ_H (200 MHz, $CDCl_3$) 7.15–7.40 (5 H, m), 4.95 (1 H, s), 4.8 (1 H, s), 2.40–2.85 (7 H, m), 1.90 (3 H, s), 1.74 (3 H, s), 1.29 (3 H, s), 1.15 (3 H, s); δ_C (22.5 MHz, $CDCl_3$) 198.1 (s), 162.9 (s), 145.4 (s), 141.3 (s), 130.9 (s, C-2), 128.4 (2 C, d), 127.9 (2 C, d), 126.1 (d), 114.9 (t), 51.8 (d), 39.6 (2 C, t and s), 34.5 (t), 33.1 (t), 27.1 (q), 22.9 (q), 22.0 (q), 11.4 (q); *m*/*z* 282 (M^+, 13%), 267 (39), 191 (49), 105 (37), 91 (100) (Found: C, 85.38; H, 9.5; $C_{20}H_{26}O$ requires C, 85.06; H, 9.28%). For the keto ether **8**: $[\alpha]_D^{24}$ +45.0 (*c* 2.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1700, 1600, 750, 695; δ_H (90 MHz, $CDCl_3$) 7.00–7.40 (5 H, m), 3.73 (1 H, dd, *J* 8.0 and 6.5 Hz), 3.38 (3 H, s), 2.22 (3 H, s), 1.85–2.35 (7 H, m), 1.78 (3 H, s), 1.2 (3 H, s), 1.09 (3 H, s); δ_C (22.5 MHz, $CDCl_3$) 209.6 (s), 141.7 (s), 140.1 (s), 128.5 (s), 127.7 (2 C, d), 127.3 (2 C, d), 125.2 (d), 78.0 (d), 55.1 (q), 54.8 (d), 37.6 (s), 35.3 (t), 30.7 (2 C, t), 26.6 (q), 26.2 (q), 22.0 (q), 14.5 (q); *m*/*z* 300 (M^+, 10%), 202 (52), 195 (17), 187 (23), 111 (35), 105 (47), 91 (100). For the dienone **14**: $[\alpha]_D^{27}$ +9.0 (*c* 1.33, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1660, 1590, 895, 770, 690; δ_H (200 MHz, $CDCl_3$) 7.35–7.20 (5 H, m), 6.60 (1 H, d, *J* 13.0 Hz), 6.16 (1 H, d, *J* 13.0 Hz), 5.00 (1 H, s), 4.80 (1 H, s), 2.70–2.50 (3 H, m), 1.8 (3 H, s), 1.6 (3 H, s), 1.23 (3 H, s), 1.18 (3 H, s). For 2-methyl-2-methylene-(20)-nor-(2,3)-secotax-11-en-13-one **19**: $[\alpha]_D^{25}$ +38.5 (*c* 3.9, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1660 (C=O), 1600, 890; δ_H (200 MHz, $CDCl_3$) 4.9 (1 H, s) and 4.74 (1 H, s) [C=CH_2], 2.54 (3 H, s, H-1 and 14), 2.19 (2 H, dd, *J* 11.7 and 8.3 Hz, H-10), 1.78 (3 H, s) and 1.69 (3 H, s) [2 × olefinic CH_3], 1.1–1.6 (12 H, m), 1.2 (3 H, s), 1.08 (3 H, s) and 0.94 (3 H, s) [3 × *tert*-CH_3]; δ_C (22.5 MHz, $CDCl_3$) 196.8 (C=O), 163.8 (C-11), 145.1 (*C*=CH_2), 129.9 (C-12), 114.1 (C=*C*H_2), 51.6 (C-1), 39.4 (C-15), 39.1 (2 C, C-14 and 10), 37.0 (2 C, C-3 and 7), 32.5, 26.8, 25.9, 24.1, 23.8, 22.4, 21.8, 21.5 (2 C), 10.7; *m*/*z* 302 (M^+, 43%), 287 (69), 245 (29), 234 (25), 177 (42), 137 (20), 135 (22), 123 (23), 109 (22), 97 (100) (Found: *m*/*z* 302.2599. $C_{21}H_{34}O$ requires 302.2610).

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