Enantiospecific synthesis of B-\textit{seco}-nortaxanes from two molecules of carvone†

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Enantiospecific syntheses of B-\textit{seco}-nortaxanes have been accomplished starting from the readily and abundantly available monoterpenene (R)-carvone. Carvone has been converted into both A-ring as well as C-ring derivatives of taxane and coupled with a two carbon unit.

**Keywords**: Enantiospecific syntheses, \textit{seco}-nortaxanes, carvone, monoterpene

**IPC**: Int.Cl. 7 C 07 C

Potent antitumor and antileukemic properties of taxol\textsuperscript{1} (paclitaxel) \textbf{1} as well as its unique mode of action evoked tremendous interest in taxanes\textsuperscript{2}. Only very few molecules in the last decade have stirred as much imagination and activity among the synthetic chemists as taxol \textbf{1}. Much of the efforts towards the total synthesis of this class of compounds have been motivated by taxol \textbf{1}, one of the most functionally and stereochemically complex taxoid and its analogue taxotere \textbf{2}. Taxane diterpenoids contain the tricyclic carbon skeleton 4,8,12,15,15-pentamethyltricyclo[9.3.1.0\textsubscript{3,8}]pentadecane \textbf{3}, commonly referred as taxane. In almost all the taxanes reported so far, except very few, there is a bridgehead double bond at C-11 making it an integral part of the skeleton. Although the complete functionality and stereochemical issues must ultimately be dealt with, the development of a general and efficient method for the construction of a suitably substituted tricyclic carbon skeleton has often been recognized as the major task. Over the past two decades more than 40 research groups, attracted by the molecule's challenging architecture and its potential utility in medicine, undertook the task of synthesis of taxol \textbf{1} and its analogues. Although six successful total synthesis of taxol \textbf{1} have been reported in the literature, focus of the most research groups has been the preparation of the partial structures in an effort to explore various concepts that deal with the construction of the tricyclo[9.3.1.0\textsubscript{3,8}]-pentadec-11-ene skeleton equipped with functionalization suitable for further elaboration to various taxoids\textsuperscript{3}. As a consequence, several methods were developed for the construction of A-, C-, AB-, BC-, CD- and ABC-ring systems of taxanes, both in

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{taxol 1}};
\node at (2,0) {\textbf{taxotere 2}};
\end{tikzpicture}
\end{center}

\textsuperscript{†} Chiral synthons from carvone, part 70. For part 69, see reference 9; for part 68, see reference 4g.
racemic and enantioselective manner. Earlier in our laboratory enantiospecific approaches were developed\(^4\) for the synthesis of part structures of taxanes, such as A-ring derivatives, C-ring derivative, 2,3-\textit{seco}-taxanes and 8,9-\textit{seco}-C-aromatic taxanes starting from the readily available monoterpene (\(R\))-carvone 4. In continuation of the synthesis of B-\textit{seco}-taxanes, we conceived that carvone 4 can also be exploited for the generation of suitable fragment containing C-ring of taxanes and can club with A-ring of taxanes (Scheme I), \textit{i.e.} to generate a diterpenoid (taxoid) from two molecules of a monoterpene (carvone), and developed two approaches for the generation of B-\textit{seco}-taxanes.

In the first strategy, we anticipated that carvone 4 as such can serve as C-ring of taxanes and acetylene can be used to link 6,6-dimethylcarvone 5 and carvone 4 to generate a B-\textit{seco}-bisnortaxane (c.f. 6). First a direct approach was tried. Thus, sonochemical irradiation of a mixture of (\(R\))-carvone 4 and lithium acetylide-ethylenediamine complex in dry THF generated the tertiary alcohol 7. It was anticipated that reaction of the tertiary alcohol 7 with two equivalents of \(n\)-butyllithium in dry THF and coupling with 6,6-dimethylcarvone 5 generates the tertiary alcohol 8, a direct precursor for the B-\textit{seco}-taxane derivative 6 by oxidation of both the allylic alcohols in 7 at the same time. But reaction of the allyl alcohol 7 with two equivalents of \(n\)-butyllithium and dimethylcarvone 5 was not successful, hence the sequence was carried out in a stepwise manner as depicted in Scheme II.

Sonochemical irradiation of a mixture of dimethylcarvone 5 and lithium acetylide-ethylenediamine complex in an ultrasonic bath furnished the tertiary alcohol 9. Oxidation of the tertiary alcohol 9 with PCC in methylene chloride gave the transposed enone 10 in 85\% yield, whose structure was established from its spectral data. For further elaboration, the ketone group in 10 was masked. Low temperature (-70\°C) reduction of the enone 10 using LAH in ether furnished the \textit{syn} alcohol 11. Reaction of the alcohol 11 in methylene chloride with TBDMS chloride, imidazole and a catalytic amount of DMAP at room temperature for 15 hr furnished the TBDMS ether 12 in 92\% yield (Scheme II), whose structure rests secured from its spectral data.

Next, the silyl ether 12 was coupled with carvone 4 to obtain the B-\textit{seco}-19,20-bisnortaxane system. Accordingly, treatment of the \textit{silyl} ether 12 with one equivalent of \(n\)-butyllithium and reaction of the resultant lithium alkyne with \(R\)-carvone 4 at 0 \°C furnished the tertiary alcohol 13, which on oxidation...
with PCC and molecular sieves powder in methylene chloride at room temperature furnished the enone 14 in 53% yield. Presence of the molecular ion peak at m/z 466 (C₃₀H₄₆O₂Si) in the mass spectrum and presence of a strong absorption band at 1660 cm⁻¹ due to the enone carbonyl group in the IR spectrum suggested the formation of the product 14. Presence of characteristic resonances in the ¹H NMR spectrum, in particular, four singlets at δ 4.98, 4.85, 4.81 and 4.76 due to the olefinic protons of the two isopropenyl groups, a triplet at 4.26 due to the methine proton attached to the OTBDMS group, four singlets at 2.01, 1.99, 1.88 and 1.79 due to the four olefinic methyl groups and two methyl groups at 1.22 and 1.10 due to the gem-dimethyl group and three singlets at 0.94, 0.14 and 0.13 ppm due to the TBDMS group confirmed the structure of the compound 14.

In the second strategy, an alternate C-ring derivative 15 was considered, which could be prepared from carvone 4 and coupled to A-ring (cf. 5) to generate a B-seco-20-nortaxane system 16 (Scheme III). For the synthesis of the bromide 15, Claisen rearrangement of the allyl alcohol 17 was contemplated for the generation of the ester 18 (Scheme IV). Regioselective 1,2-addition of methylmagnesium iodide to (R)-carvone 4, followed by oxidation of the resultant allylic tertiary alcohol with PCC and silica gel generated (S)-(+)β-methylcarvone 19 in 76% yield. Regioselective reduction of methylcarvone 19 in ether with LAH at -70°C furnished the syn allyl alcohol 17 in 95% yield, with a high degree of regio- and stereoselectivity. The syn relation between the hydroxy and isopropenyl groups in the allyl alcohol 17 was assigned in analogy with earlier examples of carvone². An orthoester variant of the Claisen rearrangement, developed by Johnson et al.,³ was opted for the stereospecific creation of the quaternary center. Thus, thermal activation of a solution of the allyl alcohol 17, triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube at 180 °C furnished the diene ester 18 in 80% yield. The stereochemistry of the ester side chain in 18 was assigned based on the well established stereospecificity of the Claisen rearrangement. For the coupling of C-ring with A-ring moiety, the ester 18 was converted into the bromide 15 via the alcohol 20. Thus, reduction of the ester 18 with LAH in ether furnished the primary alcohol 20 in...
90% yield, which on reaction with triphenylphosphine and carbon tetrabromide in methylene chloride furnished the bromide 15 in quantitative yield.

The bromide 15 was then coupled to dimethylcarvone 5 employing Barbier conditions. Thus, addition of a mixture of the bromide 15 and dimethylcarvone 5 to a sonically irradiated suspension of lithium in dry THF furnished the tertiary alcohol 21. Oxidation of the tertiary alcohol 21 with PCC and silica gel afforded the 1,3-enone transposition product 16 in 55% yield. The structure of 16 as 1,6-bisopropenyl-1,2-seco-taxa-3,11-dien-13-one was established from its spectral data. The presence of the molecular ion peak at m/z 354 (C_{25}H_{38}O) in the mass spectrum and the presence of strong absorption bands at 1660 and 885 cm\(^{-1}\) due to the enone and RR'C=CH\(_2\) functionalities, respectively, in the IR spectrum indicated the formation of the enone 16. Considering the two isopropenyl groups as masked hydroxy groups, the enone 16 is a B-seco-20-nortaxane derivative.

In conclusion, we have accomplished the enantiospecific synthesis of B-seco-nortaxanes. The highlight of the present strategy is the utilization of carvone for the generation of both A as well as C rings of taxanes.

**Experimental Section**

\((-\text{Ss})\)-3-Ethynyl-5-isopropenyl-2,4,4-trimethylcyclohex-2-enone 10. A solution of 6,6-dimethylcarvone 5 (356 mg, 2 mmoles) and lithiumacetylide-ethylenediamine complex (280 mg, 3 mmoles) was taken in dry THF (10 mL) and sonically irradiated in an ultrasonic cleaning bath for 45 min. The reaction was quenched with saturated aq. NH\(_4\)Cl solution and extracted with ether (2 \(\times\) 10 mL). The ether extract was washed with brine and dried (Na\(_2\)SO\(_4\)). Evaporation of the solvent furnished the
tertiary alcohol 9, which was used in the oxidation reaction without further purification; IR (neat): 3480, 3300, 2970, 2910, 1640, 1450, 1375, 1306, 975, 890 cm\(^{-1}\); \(^1\)H NMR (90 MHz, CDCl\(_3\)); \(\delta\) 5.47 (1 H, br s), 4.90 (1 H, s), 4.78 (1 H, s), 2.80–2.00 (3 H, m), 2.53 (1 H, s), 1.85 (3 H, s), 1.80 (3 H, s), 1.10 (3 H, s), 0.95 (3 H, s).

To a magnetically stirred solution of the tertiary alcohol 9 (408 mg) in 3 mL of dry CH\(_2\)Cl\(_2\) was added a homogeneous mixture of PCC (860 mg, 4 mmoles) and molecular sieves powder (860 mg), and stirred vigorously for 15 hr at RT. The mixture was then filtered through a small silica gel column and eluted the column with excess CH\(_2\)Cl\(_2\). Evaporation of the solvent furnished the enone 10 (343 mg, 85%) as an oil; [\(\alpha\)]\(_D\)\(^{27}\) –37.9 (c 0.58, CHCl\(_3\)); IR (neat): 3180, 2910, 2080, 1650, 1570, 1430, 1370, 1320, 890, 710 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta\) 4.96 (1 H, s), 4.77 (1 H, s), 3.77 (1 H, s), 2.70–2.40 (3 H, m), 1.98 (3 H, s), 1.74 (3 H, s), 1.31 (3 H, s), 1.17 (3 H, s); \(^13\)C NMR (75 MHz, CDCl\(_3\)); \(\delta\) 198.4, 145.5, 144.7, 139.1, 115.4, 92.3, 80.5, 50.9, 39.6, 38.8, 28.1, 23.0, 22.4, 14.3; Mass: m/z 202 (M\(^+\), 8%), 187 (20), 146 (58), 145 (60), 134 (50), 131 (70), 120 (82), 91 (100); HRMS (m/z): Calcd for C\(_{14}\)H\(_{18}\)O: 202.1358. Found: 202.1357.

(+)-(1S,5S)-3-Ethynyl-5-isopropenyl-2,4,4-trimethylyclohex-2-enol 11. To a cold (-90\(^\circ\)C) magnetically stirred solution of the enone 10 (300 mg, 1.5 mmoles) in 5 mL of dry ether was added LiAlH\(_4\) (0.24 mmole, 0.12 mL of a 2.0 M solution in hexane) and stirred for 2 hr. The reaction mixture was then diluted with ether (10 mL) and carefully quenched with water (2 mL). The organic layer was separated and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic phase was washed with brine and dried (Na\(_2\)SO\(_4\)). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the allyl alcohol 11 (285 mg, 95%); [\(\alpha\)]\(_D\)\(^{29}\) 13.9 (c 2.3, CHCl\(_3\)); IR (neat): 3300, 3080, 2970, 2930, 2850, 2100, 1640, 1450, 1380, 1080, 1020, 900 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)); \(\delta\) 4.94 (1 H, s), 4.72 (1 H, s), 4.18 (1 H, dd, \(J = 9.0\) and 7.0 Hz), 3.13 (1 H, s), 2.16 (1 H, dd, \(J = 13.0\) and 2.1 Hz), 1.99 (3 H, s), 1.77 (3 H, s), 2.00–1.60 (3 H, m), 1.18 (3 H, s), 1.05 (3 H, s); \(^13\)C NMR (75 MHz, CDCl\(_3\)); \(\delta\) 145.7, 143.5, 127.1, 114.7, 81.8 (2 C), 71.0, 49.3, 38.3, 34.3, 28.0, 23.0, 22.8, 17.6; Mass: m/z 204 (M\(^+\), 5%), 189 (15), 171 (46), 145 (95), 121 (60), 107 (75), 96 (100), 91 (70).

(–)-(1S,5S)-3-Ethynyl-5-isopropenyl-2,4,4-trimethylyclohex-2-enyl tert-butylmethylsilylether 12. To a magnetically stirred solution of the alcohol 11 (20 mg, 0.1 mmole) in dry CH\(_2\)Cl\(_2\) (2 mL) was added imidazole (13 mg, 0.2 mmole), TBDMSCl (30 mg, 0.2 mmole) and a catalytic amount of DMAP and stirred for 15 hr at RT. The reaction mixture was then diluted with CH\(_2\)Cl\(_2\) (3 mL), washed with brine and dried (Na\(_2\)SO\(_4\)). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the TBDMS ether 12 (29 mg, 92%); [\(\alpha\)]\(_D\)\(^{27}\) –41.0 (c 1.39, CHCl\(_3\)); IR (neat): 3320, 2960, 2860, 1640, 1460, 1250, 1100, 1080, 1050, 890, 830, 770 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)); \(\delta\) 4.93 (1 H, s), 4.72 (1 H, s), 4.18 (1 H, t, \(J = 7.8\) Hz), 3.08 (1 H, s), 2.20–2.10 (1 H, m), 1.93 (3 H, s), 1.77 (3 H, s), 1.80–1.65 (2 H, m), 1.17 (3 H, s), 1.05 (3 H, s), 0.91 (9 H, s), 0.10 (3 H, s), 0.09 (3 H, s); \(^13\)C NMR (75 MHz, CDCl\(_3\)); \(\delta\) 146.0 (C), 145.0 (C), 126.1 (C), 114.6 (CH\(_2\)), 82.3 (C), 81.2 (CH), 71.8 (CH), 49.4 (CH), 38.2 (C), 34.7 (CH\(_2\)), 28.1 (CH\(_3\)), 26.0 (3 C, CH\(_3\)), 22.9 (CH\(_3\)), 22.8 (CH\(_3\)), 18.4 (CH\(_3\)), 18.1 (C), –4.10 (CH\(_3\) ), –4.90 (CH\(_3\)); Mass: m/z 318 (M\(^+\), 1%), 303 (2), 261 (3), 145 (20), 91 (20).

(+)-(1S,6R,13S)-1,6-Bisisopropenyl-13-tert-butylmethylsilyloxy-1,2-seco-19,20-bisnor-tax-9-yne-3,8,11-dien-4-one 14. To a cold (-90\(^\circ\)C) magnetically stirred solution of the acetylene compound 12 (86 mg, 0.242 mmole) in dry THF (2 mL) was added a solution of n-ButLi (0.24 mmole, 0.12 mL of a 2.0 M solution in hexane) over a period of 5 min and the reaction mixture was stirred for 40 min at the same temperature. Carvone (4, 37 mg, 0.242 mmole) in dry THF (2 mL) was then added to the reaction mixture and slowly warmed up to RT and stirred for 8 hr. It was then quenched with saturated aq. NH\(_4\)Cl solution and extracted with ether (2 × 5 mL). The organic extract was washed with brine and dried (Na\(_2\)SO\(_4\)). Evaporation of the solvent furnished the tertiary alcohol 13.

To a magnetically stirred solution of the tertiary alcohol 13 in 2 mL of dry CH\(_2\)Cl\(_2\) was added a homogeneous mixture of PCC (80 mg, 0.37 mmole) and molecular sieves powder (80 mg) and stirred vigorously for 15 hr at RT. The mixture was then filtered through a small silica gel column and eluted the column with excess CH\(_2\)Cl\(_2\). Further purification...
on a silica gel column using ethyl acetate-hexane (1:25 to 1:5) as eluent furnished the enone 14 (60 mg, 53%) as an oil; IR (neat): 3060, 2940, 2840, 2160, 1660, 1580, 1450, 1430, 1370, 1340, 1250, 1100, 1080, 890, 840, 770 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 4.98 (1 H, s), 4.85 (1 H, s), 4.81 (1 H, s), 4.76 (1 H, d, \(J = 2.0\) Hz), 4.26 (2 H, q, \(J = 7.2\) Hz), 3.5-3.8 (2 H, m), 2.0-3.0 (2 H, br), 1.74 (3 H, s), 1.66 (3 H, t, \(J = 7.2\) Hz), 1.16 (3 H, s), 1.26 (3 H, s). Mass: m/z 466 (M\(^+\), 1%), 350 (18), 335 (22), 293 (19), 75 (100).

\(\text{–(1S,5R)-5-Isopropenyl-1,2-dimethylcyclohex-2-ene-1-acetic acid ethyl ester 18.}\) A solution of the allyl alcohol 17 (3.0 g, 18.07 mmol) in dry CH\(_2\)Cl\(_2\) (25 mL) was simultaneously added orthoacetate (16.3 mL, 88.9 mmol) and a catalytic amount of propionic acid was placed in a sealed tube for 5 days in an oil-bath. The reaction mixture was then diluted with ether (20 mL) and warmed up to RT, and stirred for 2 hr. The reaction mixture was slowly warmed up to RT and then solvent was evaporated under reduced pressure. Purification of the residue over a neutral alumina column using hexane as eluent furnished the bromide 15 (660 mg, 100%); IR (neat): 3060, 1640, 1440, 1370, 890 cm\(^{-1}\); \(^1\)H NMR (90 MHz, CDCl\(_3\)): \(\delta\) 5.46 (1 H, d, \(J = 7.2\) Hz), 4.71 (2 H, s), 3.0-3.6 (2 H, m), 1.4-2.4 (7 H, m), 1.74 (3 H, s), 1.63 (3 H, s), 1.07 (3 H, s); \(^13\)C NMR (22.5 MHz, CDCl\(_3\)): \(\delta\) 149.5 (s), 137.6 (s), 124.1 (d), 108.8 (t), 44.3 (t), 40.0 (2 C, t and s), 37.6 (d), 31.3 (t), 29.1 (t), 26.7 (q), 18.5 (q).

\(\text{–(1S,6R,8R)-1,6-Bisisopropenyl-(1,2)-seco-tax-3,11-dien-13-one 16.}\) To a suspension of lithium (42 g, 6.0 mmol) in dry THF (2 mL) in a round bottom flask placed in an ultrasonic cleaning bath was added a mixture of 6,6-dimethylcarvone 5 (178 mg, 1 mmol) and the bromide 15 (536 mg, 2.08 mmol) in dry THF (3 mL) while sonicating at 15-20 °C. The reaction mixture was further sonicated for 25 min and worked up as described for the alcohol 9. Purification of the product over a silica gel column using ethyl acetate-hexane (1:100 to 1:20) as eluent furnished the tertiary alcohol 21 (196 mg, 55%). Oxidation of the tertiary alcohol 21 in CH\(_2\)Cl\(_2\) (2 mL) using PCC (300 mg, 1.39 mmol) and silica gel (300 mg) for 30 hr as described for 10 and purification of the product over a silica gel column using ethyl acetate-hexane (1:50 to 1:40) as eluent furnished the B-seco-nortaxane 16 (104 mg, 54%); \([\alpha]_D^{29}\) +30.3 (c 3.0, CHCl\(_3\)); IR (neat): 3070, 2960, 1660, 1600, 1445, 1370, 1325, 885, 800 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.46 (1 H, d, \(J = 5.7\) Hz), 4.90 (1 H, s), 4.72 (1 H, s), 4.75 (2 H, s), 2.55 (2 H, s), 2.15-2.30 (2 H, m), 2.0-2.15 (2 H, m), 1.3-1.9 (6 H, m), 1.80 (3 H, s), 1.76 (3 H, s), 1.59 (3 H, s), 1.66 (3 H, t, \(J = 1.1\) Hz), 1.22 (3 H, s), 1.10 (3 H, s), 1.09 (3 H, s); \(^13\)C NMR (22.5 MHz, CDCl\(_3\)): \(\delta\) 198.3, 164.8, 149.7, 145.6, 138.5, 130.7, 123.1, 114.8, 108.4, 52.0 (2 C), 40.0, 39.6, 38.7, 37.8, 31.3, 27.4, 26.0, 25.3, 23.0, 22.5, 20.8, 18.3, 11.4; Mass:
m/z 354 (M+, 12%), 339 (25), 205 (30), 149 (37), 177 (27), 121 (47), 107 (100); HRMS (m/z): Calcd for C$_{25}$H$_{38}$O: 354.2923. Found: 354.2938.

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