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Enantiospecific construction of the BC-ring system of taxanes ☆

A. Srikrishna,* Dattatraya H. Dethe and P. Ravi Kumar

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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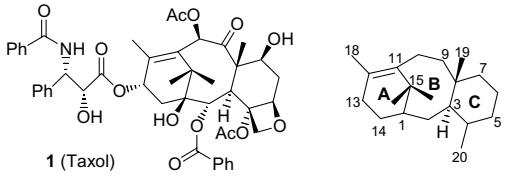
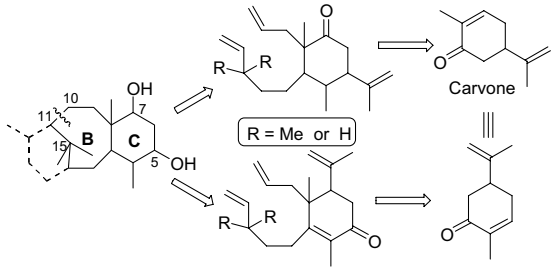
Abstract—Two alternative approaches to the BC-ring system of taxanes, suitable for generating both enantiomeric forms of taxanes, starting from the readily and abundantly available monoterpene (*R*)-carvone employing a ring-closing metathesis reaction as key step, are described.

Paclitaxel (**1**, Taxol),[1] by virtue of its complex and densely functionalised structure, coupled with its novel mechanism of action, potent antitumour activity and its clinical use as a powerful anticancer drug has attracted the attention of many synthetic chemists. Indeed, only very few molecules in the last two decades have stirred as much imagination and activity among synthetic chemists as the taxanes.[2] While a few groups have addressed the total synthesis of **1**, a larger number have confined themselves to the development of methodologies towards various segments of **1** as well as analogues of taxanes.[3] One of the most difficult tasks in the synthesis of the taxane framework is the construction of the B-ring, because of the well known[2i] complications associated with the formation of an eight-membered ring. In this context, we have developed two simple and efficient routes for the enantiospecific generation of the BC-ring system of taxanes employing (*R*)-carvone **2** as the C-ring of taxanes, and a ring-closing metathesis (RCM)[4] strategy for the formation of the C-10–C-11 bond of the eight-membered B-ring of taxanes. The present methodology also provides access to both enantiomeric forms of the BC-ring system of taxanes starting from a single enantiomer of carvone.



We envisaged two appropriate side arms, with terminal olefins suitable for forming the B-ring by a RCM reaction, could be attached to carvone **2** either at (i) C-2 and C-3 or (ii) C-3 and C-4 positions, and that the ketone and isopropenyl groups could be considered as hydroxy group equivalents at the C-5 and C-7 positions of taxanes (Scheme 1). For the construction of the B-ring via formation of the C-10–C-11 bond, in addition to the high activation energy for the formation of eight-membered ring, it would also be necessary to overcome steric crowding at the C-11 olefinic carbon in the precursor, and moreover, the product would be neopentylic in nature. Hence, to begin with, a synthesis of the BC-ring system without the *gem* dimethyl group was investigated by following the first option via 6-methylcarvone **3**. Kinetic alkylation of (*R*)-carvone **2** using lithium diisopropylamide (LDA) and methyl iodide furnished a 3:2 diastereomeric mixture of 6-methylcarvone **3**, which on low temperature crystallisation provided the major isomer *trans*-6-methylcarvone **3t** in stereochemically pure form.[5] An alkylative 1,3-enone transposition methodology[6] followed by a reductive allylation sequence was contemplated for the introduction of the five- and three-carbon side-chains at the C-3 and C-2 positions



Scheme 1.

☆ Chiral Synthons from Carvone, Part 63. For Part 62, see: Srikrishna, A.; Dethe, D. H. *Org. Lett*. **2004**, *6*, 165–168.

* Corresponding author. Tel.: +91-80-2932215; fax: +91-80-23600683/23600529; e-mail: ask@orgchem.iisc.ernet.in

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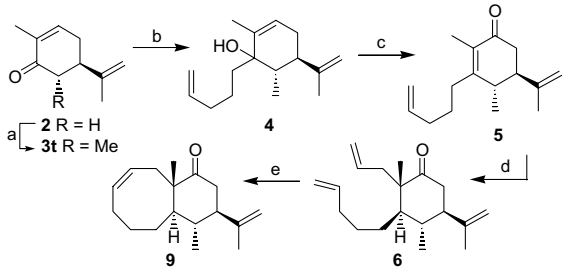
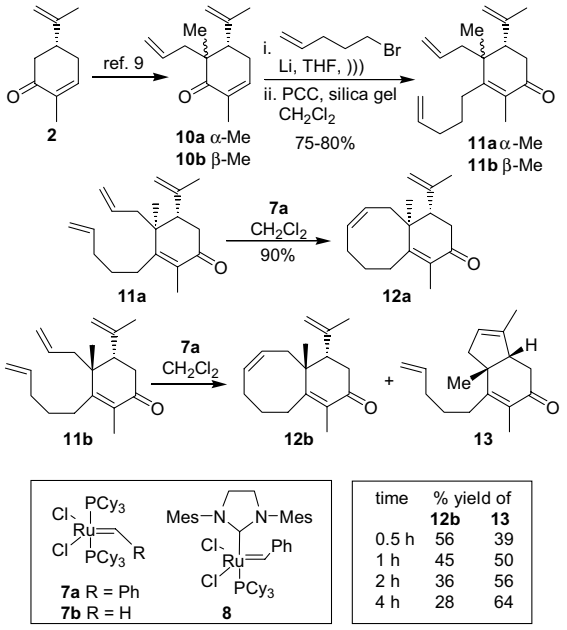
(Scheme 2). Thus, sonochemically accelerated reaction of the enone **3t** with pent-4-enyl bromide and lithium under Barbier conditions followed by oxidation of the resultant tertiary alcohol **4** with pyridinium chlorochromate (PCC) and silica gel furnished the enone **5**. Reductive allylation of the enone **5** with lithium in liquid ammonia and allyl bromide generated the RCM precursor **6**, $[\alpha]_D^{24}$ −10.0 (*c* 6.6, $CHCl_3$), in a highly stereoselective manner. The stereochemistry of **6** was established on the basis of the spectral data and literature precedents.[7] Contrary to our expectations,[8] the RCM reaction of the compound **6** was found to be very efficient even with the first generation Grubbs' catalyst **7a**. Treatment of the dienone **6** with 10 mol% of the catalyst **7a** in 0.005 M methylene chloride solution at room temperature for 2 h resulted in the efficient closure of the eight-membered ring to give the bicyclic compound† **9** in near quantitative yield. Compound **9** represents a typical BC-ring system of taxane containing both the C-19 and C-20 methyl groups, with the natural configuration at the C-3 and C-8 positions and a *trans*-BC ring junction.



Scheme 2. Reagents and conditions: (a) (i) LDA, THF, −70 °C; MeI, →rt, 12 h, 95%; (ii) crystallisation from hexane; (b) Li, $CH_2{=}CH(CH_2)_3Br$, THF,))), 15 °C → rt, 0.5 h; (c) PCC, silica gel, CH_2Cl_2, rt, 4 h; 85% from **3t**; (d) Li, liquid NH_3, THF, −33 °C, allyl bromide, 80%; (e) 10 mol% **7a**, CH_2Cl_2, rt, 2 h, >95%.

After successfully generating the BC-ring system **9** via the first option, we then investigated the second option, Scheme 3. Since the isopropenyl group is a masked ketone, it was conceived that generation of the two 6,6-dialkylated carvones **10a** and **10b** would give access to both enantiomeric forms of BC-taxanes. Generation of the kinetic enolate of 6-methylcarvone **3** with LDA and treatment with allyl bromide generated the alkylated product (4*S*,5*S*)-**10a**. Reversal of the alkylation sequence, namely first allylation of carvone followed by methylation, gave the compound (4*R*,5*S*)-**10b**.[9] Coupling of the dialkylated compounds **10a**,**b** with pent-4-

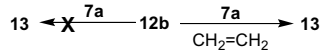
† All compounds exhibited spectral data consistent with their structures. Yields (unoptimised) refer to isolated and chromatographically pure compounds. Selected spectral data for **9**: Mp: 86–88 °C. $[\alpha]_D^{22}$ −4.5 (*c* 1.8, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1708. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.73 (1H, ddd, J = 10.5, 7.8, 7.8 Hz), 5.59 (1H, ddd, J = 10.5, 10.5, 6.6 Hz), 4.74 (2H, s), 2.64 (1H, t, J = 13.5 Hz), 2.45 (1H, dd, J = 12.9, 6.6 Hz), 2.20–1.90 (5H, m), 1.80–1.50 (5H, m), 1.67 (3H, s, olefinic-CH_3), 1.40–1.10 (1H, m), 1.14 (3H, s, *tert*-CH_3), 0.87 (3H, d, J = 5.4 Hz, *sec*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 212.6 (C, C=O), 146.1 (C, *C*=CH_2), 131.5 (CH), 129.1 (CH), 112.7 (CH_2, C=*C*H_2) 53.6 (CH), 52.7 (C, C-8), 48.8 (CH), 42.7 (CH_2), 34.8 (CH), 33.6 (2 C, CH_2), 29.0 (CH_2), 27.6 (CH_2), 21.0 (CH_3), 18.2 (CH_3), 17.2 (CH_3). Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.47; H, 10.64. For **12a**: $[\alpha]_D^{23}$ +135.4 (*c* 2.6, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1665, 1605. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.85–5.65 (2H, m, H-3 and 4), 5.02 (1H, br s) and 4.87 (1H, s) [C=CH_2], 2.86 (1H, dd, J = 14.7, 3.6 Hz), 2.64–2.46 (3H, m), 2.30–2.16 (4H, m), 2.07 (1H, dd, J = 13.8, 5.4 Hz), 2.00–1.85 (1H, m), 1.84 (3H, s), 1.74 (3H, s) [2 × olefinic-CH_3], 1.58–1.44 (1H, m), 1.09 (3H, s, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 197.9 (C, C=O), 164.5 (C, C-8), 144.9 (C, *C*=CH_2), 132.8 (C, C-9), 132.5 (CH), 128.8 (CH), 115.7 (CH_2, C=*C*H_2), 47.5 (C), 45.7 (CH), 39.3 (CH_2), 34.7 (CH_2), 31.5 (CH_2), 28.2 (CH_2), 27.8 (CH_2), 23.0 (CH_3), 20.7 (CH_3), 11.6 (CH_3). HRMS (QTOF): m/z calcd for $C_{17}H_{24}ONa$ (M+Na): 267.1725. Found: 267.1750. For **12b**: $[\alpha]_D^{23}$ +177.0 (*c* 1.3, $CHCl_3$). For **13**: $[\alpha]_D^{22}$ −83.3 (*c* 1.2, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1670, 1615. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.77 (1H, t of dd, J = 16.8, 10.2, 6.6 Hz, C*H*=CH_2), 5.19 (1H, s, H-8), 5.02 (1H, d, J = 16.8 Hz) and 4.98 (1 H, d, J = 10.2 Hz) [CH=CH_2], 2.60–2.00 (9H, m), 1.73 (3H, s) and 1.67 (3H, s) [2 × olefinic-CH_3], 1.53 (1H, quintet, J = 7.5 Hz), 1.29–1.25 (1H, m), 1.28 (3H, s, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 198.1 (C, C=O), 160.1 (C, C-5), 142.3 (C, C-9), 137.7 (CH, *C*H=CH_2), 130.9 (C, C-4), 122.0 (CH, C-8), 115.8 (CH_2, CH=*C*H_2), 52.8 (CH, C-1), 48.2 (C, C-6), 43.3 (CH_2), 37.8 (CH_2), 34.6 (CH_2), 31.5 (CH_2), 28.1 (CH_2), 26.6 (CH_3), 15.2 (CH_3), 12.2 (CH_3). HRMS (QTOF): m/z calcd for $C_{17}H_{24}ONa$ (M+Na): 267.1725. Found: 267.1723. For **16a**: $[\alpha]_D^{23}$ +5.8 (*c* 1.8, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1667, 1644, 1613. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.75 (1H, dd, J = 17.1, 10.5 Hz, C*H*=CH_2), 5.41 (1H, s, H-8), 4.98 (1H, d, J = 10.5 Hz) and 4.96 (1H, d, J = 17.1 Hz) [CH=CH_2] 2.75 (1 H, d, J = 14.8 Hz), 2.56 (1H, dd, J = 17.1, 3.6 Hz), 2.38 (1H, dd, J = 17.1, 15.0 Hz), 2.42-2.00 (5H, m), 1.71 (6H, s) [2 × olefinic-CH_3], 1.43 (1H, dd, J = 9.9, 7.5 Hz) 1.05 (6H, s), 1.00 (3H, s) [3 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 199.4 (C, C=O), 166.2 (C, C-5), 147.2 (CH, *C*H=CH_2), 140.8 (C, C-9), 130.5 (C, C-4), 123.6 (CH, C-8), 111.6 (CH_2, C=*C*H_2) 52.5 (CH, C-1), 49.6 (C, C-6), 40.8 (CH_2), 40.7 (CH_2), 37.1 (C, C-3), 36.0 (CH_2), 27.0 (CH_2), 26.6 (CH_3), 26.5 (CH_3), 22.2 (CH_3), 14.6 (CH_3), 11.5 (CH_3). HRMS (QTOF): m/z calcd for $C_{19}H_{28}ONa$ (M+Na): 295.2038. Found: 295.2050. For **16b**: $[\alpha]_D^{23}$ −83.9 (*c* 1.55, $CHCl_3$). For **19a**: Mp: 123–125 °C. $[\alpha]_D^{23}$ +41.4 (*c* 1.4, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1665, 1605. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.47 (1H, d, J = 11.7 Hz, H-4), 5.40 (1H, ddd, J = 11.7, 11.7, 7.2 Hz, H-3), 2.79, 2.63 (2H, 2 × d, J = 4.8 Hz, O-CH_2), 2.71 (1H, dd, J = 15.0, 10.5 Hz), 2.60–2.30 (4H, m), 2.26 (1H, dd, J = 15.0, 6.6 Hz), 1.98 (1H, dd, J = 10.5, 6.6 Hz), 1.75 (3H, s, olefinic-CH_3), 1.70–1.60 (1 H, m), 1.62 (1H, dd, J = 10.5, 3.3 Hz), 1.35 (3H, s), 1.25 (3H, s), 1.13 (3H, s) and 1.05 (3H, s) [4 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 197.0 (C, C=O), 165.6 (C, C-8), 142.5 (CH, C-4), 132.4 (C, C-9), 126.4 (CH, C-3), 57.2 (C, C-O), 54.2 (CH_2, CH_2-O), 47.1 (C), 44.5 (CH, C-12), 42.1 (CH_2), 36.6 (CH_2), 35.7 (CH_2), 35.4 (C), 35.3 (CH_3), 26.0 (CH_2), 25.7 (CH_3), 21.5 (CH_3), 20.5 (CH_3), 11.8 (CH_3). HRMS (QTOF): m/z for $C_{19}H_{28}O_2Na$ (M+Na), calcd: 311.1987. Found: 311.1993. For **19b**: $[\alpha]_D^{23}$ −102.0 (*c* 1.4, $CHCl_3$). Crystal data for **19a**: X-ray data were collected at 293 K on a SMART CCD-BRUKER diffractometer with graphite monochromatic Mo-Kα radiation (λ = 0.7107 Å). Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The nonhydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. $C_{19}H_{28}O_2$, MW = 288.41, colourless crystal, Crystal system: monoclinic, space group: $P2(1)$, cell parameters: a = 8.470 (4) Å, b = 10.268 (5) Å, c = 10.497 (5) Å, β = 112.44° (1), V = 843.89 Å^3, Z = 2, D_c = 1.135 gcm^{-3}, $F(0\,0\,0)$= 316.0, μ = 0.07 mm^{-1}. Total number of l.s. parameters = 195, $R1$ = 0.0581 for 1647 $Fo > 4\sigma(Fo)$ and 0.1193 for all 2828 data. WR2 = 0.2328, GOF = 0.748, restrained GOF = 0.748 for all data. Crystallographic data (without structure factors) have been deposited with the Cambridge Crystallographic Data Centre and the depository number is CCDC 226177.



time	% yield of	
	12b	13
0.5 h	56	39
1 h	45	50
2 h	36	56
4 h	28	64

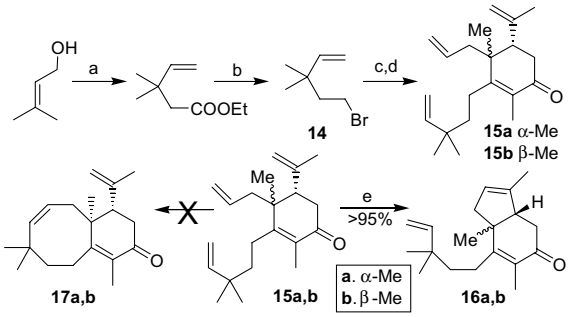
Scheme 3.

enyl bromide under Barbier conditions followed by oxidation of the resultant tertiary alcohols furnished the RCM precursors **11a**, $[\alpha]_D^{23}$ +9.7 (*c* 1.75, $CHCl_3$), and **11b**, $[\alpha]_D^{23}$ +64.5 (*c* 3.1, $CHCl_3$). The RCM reactions of both the isomers **11a**,**b** were found to be very rapid and efficient.[8] Thus, treatment of the 4*S*,5*S* isomer **11a** with 10 mol% of the catalyst **7a** in 0.005 M methylene chloride solution at room temperature for 30 min furnished **12a** in near quantitative yield. In contrast, under the same conditions, reaction of the 4*R*,5*S* isomer **11b** with 10 mol% of **7a** for 30 min gave a mixture of the desired **12b** (56%) and the hydrindane **13** (39%), which were separated on a silver nitrate impregnated silica gel column. The structures of **12a**,**b** and **13** were established from their spectral data.† As the formation of trisubstituted olefin **13** in the RCM reaction by first generation Grubbs' catalyst **7a** is unusual, the reaction was further probed to discover the origin of the hydrindane **13**. Extending the reaction time increased the yield of the hydrindane **13** at the expense of the cyclooctene product **12b** as shown in Scheme 3. This result indicated that the initial product of the RCM reaction is the cyclooctene **12b**, which isomerised to the hydrindane **13** with time, perhaps via the ring-opening metathesis (ROM) followed by RCM. The cyclooctene **12b** was resubjected to RCM conditions using the catalyst **7a**, but was found to be stable and no detectable amount of **13** was observed, probably because of the absence of the reactive RCM catalyst **7b** in the medium. On the other hand, treatment of **12b** with catalyst **7a** in methylene chloride containing ethylene (thereby generating the reactive catalyst **7b** in the medium) for 1 h furnished a ≈1:2 mixture of the hydrindane **13** and **12b**, confirming that the hydrindane **13** was formed via a RCM–ROM–RCM pathway. A similar result employing the more reactive Grubbs' second generation catalyst **8** was observed by Meng and Parker.[10]



Next, attention was turned towards the synthesis of the BC-ring system of taxanes also containing the C-15 *gem* dimethyl group, starting from the dialkylated carvones **10a**,**b** (Scheme 4). Bromide **14** was obtained in three steps from dimethylallyl alcohol. Coupling the bromide **14** with **10a**,**b** followed by oxidation resulted in the formation of the RCM precursors **15a**, $[\alpha]_D^{23}$ +2.0 (*c* 2.65, $CHCl_3$), and **15b**, $[\alpha]_D^{23}$ +50.9 (*c* 1.2, $CHCl_3$). Interestingly, RCM reaction of the compounds **15a** and **15b** with the catalyst **7a** in 0.005 M methylene chloride solution for 15 minutes furnished only the hydrindanes† *trans*-**16a** and *cis*-**16b**, respectively, in near quantitative yields. No detectable amounts of the cyclooctene compounds **17a**,**b** (BC-ring system of taxanes) were found in either of these reactions, even when the reaction was stopped after ca. 3 min, indicating that the hydrindanes **16a**,**b** were formed directly and not via cyclooctene intermediates. The reluctance of the formation of the B-ring of taxane in the compounds **15a**,**b** is clearly a reflection of the effect of the steric crowding due to the neopentylic nature of the second olefin partner.[9] The RCM of **15a**,**b** with 5 mol% of the second generation Grubbs' catalyst **8** for 15 min also produced the same result.

It seemed that in order to prevent formation of the hydrindanes, the isopropenyl group in **15a**,**b** needed to be masked. Thus, regio- and stereoselective epoxidation of **15a**,**b** with 1 equiv of *m*-chloroperbenzoic acid (MCPBA) furnished the epoxides **18a**, $[\alpha]_D^{24}$ −64.6 (*c* 1.3, $CHCl_3$), and **18b**, $[\alpha]_D^{25}$ +40.6 (*c* 1.8, $CHCl_3$). Though no reaction was observed with the catalyst **7a**, gratifyingly RCM of the trienones **18a**,**b** with Grubbs' second generation catalyst **8** in refluxing methylene chloride furnished **19a**,**b** in excellent yields.† In order to rule out the possibility of olefin isomerisation during or after RCM reaction,[8] the structures were confirmed by single crystal X-ray diffraction analysis of the epoxide **19a** (Fig. 1), which also established the stereochemistry of the epoxy carbon.



Scheme 4. Reagents and conditions: (a) $MeC(OEt)_3$, $EtCO_2H$, sealed tube, 160 °C, 2 d, 80%; (b) (i) LAH, −70 °C → rt, Et_2O, 2 h, 95%; (ii) CBr_4, PPh_3, CH_2Cl_2, rt, 10 h, 90%; (c) Li, **10a** or **10b**, THF,))), 10 °C → rt, 0.5 h; (d) PCC, silica gel, CH_2Cl_2, 4 h; 70% from **10a** or **10b**; (e) 10 mol% of **7a** or 5% mol of **8**, CH_2Cl_2, 0.25 h.

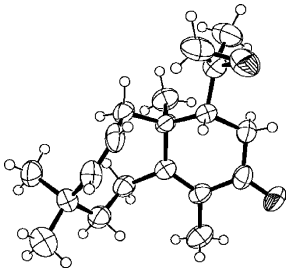
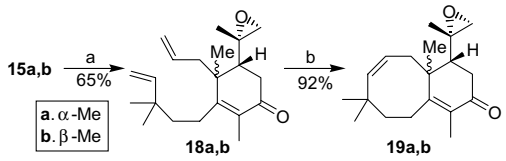


Figure 1. ORTEP diagram of **19a**.



Reagents and conditions: (a) MCPBA, CH_2Cl_2, 0 °C, 1 h; (b) 5 mol% **8**, CH_2Cl_2, reflux, 3 h.

In conclusion, we have developed two very convenient, short and efficient RCM-based enantiospecific routes for the construction of the complete BC-ring system of taxanes. Generation of either enantiomeric form further enhances the synthetic potential of this strategy. Currently, we are investigating the extension of this methodology for the enantiospecific synthesis of the ABC ring system of taxanes by incorporating suitable substituents at the C-1 and C-11 positions of the BC-ring system.

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