Cyclohexannulated [5.3.1]Propellanes as Precursors to the *ABC* Ring System of Paclitaxel (Taxol™)

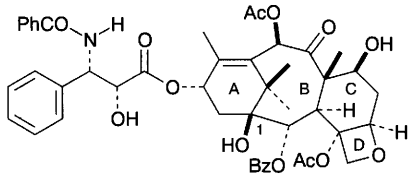
Martin G. Banwell,*[a] Robert W. Gable,[b] Steven C. Peters[b] and James R. Phyland[b]

[a] *Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia*

[b] *School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia*

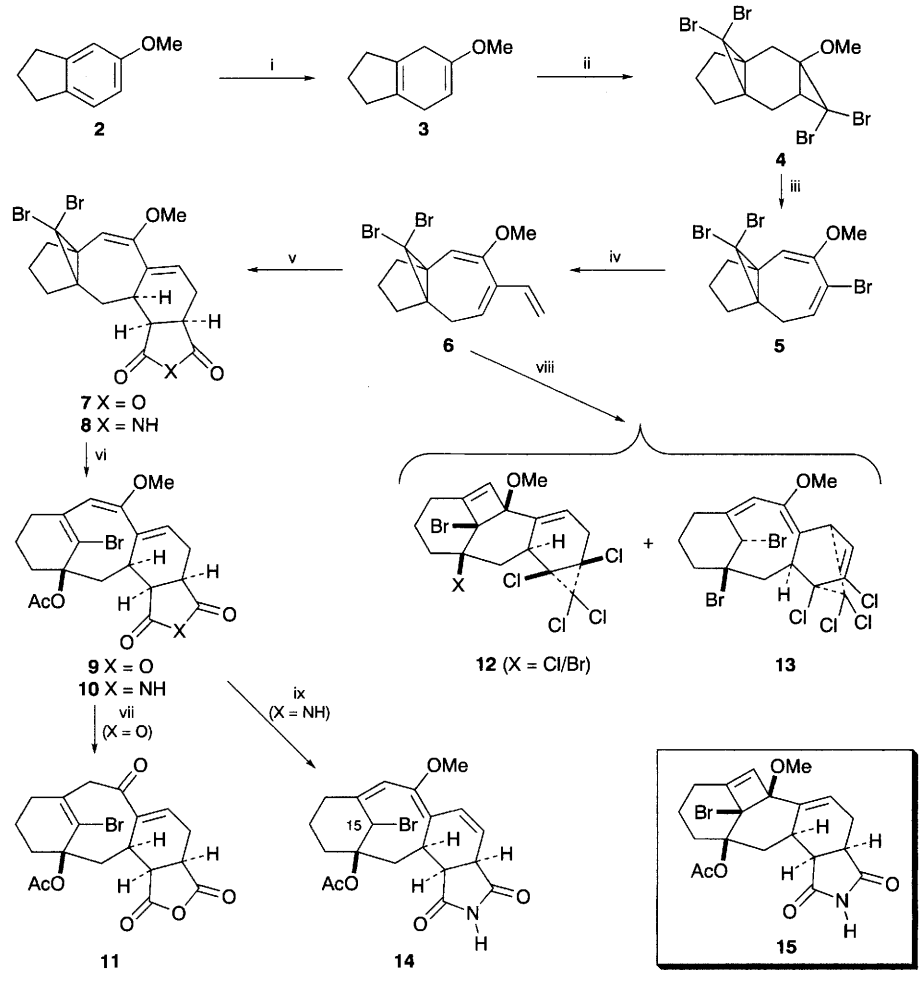
Thermal or silver-ion induced electrocyclic ring-opening of cyclohexannulated [5.3.1]propellanes such as **7** and **8** provides *ABC* ring analogues of paclitaxel (taxol) including compounds **10**, **11** and **14**.

The complex structure of the diterpene paclitaxel (taxol™, **1**) together with its powerful anti-mitotic activity and unique mode of action have inspired an unprecedented effort by chemists to construct this remarkable chemotherapeutic agent.[1] For good reason, paclitaxel has been described as 'one of the most challenging targets for synthesis chemists today'.[1f] Many approaches have been explored and two total syntheses of compound **1** have recently been reported.[2] 'Second generation' routes to taxoids are now required in order to provide workable amounts of such compounds for extended biological testing. We report herein a new, simple and efficient method for assembling the *ABC* ring system of paclitaxel which involves, as key intermediates, readily accessible cyclohexannulated [5.3.1]propellanes. The protocols described provide, in a concise fashion, usefully functionalised *ABCD* ring analogues of paclitaxel.



1

Our synthetic sequence (Scheme 1) starts with commercially available 5-methoxyindane **2** which is subjected to standard Birch reduction conditions. The resulting dihydro-compound **3**[3] is very susceptible to re-aromatisation but undergoes bis-cyclopropanation on treatment with a large excess of dibromocarbene (generated under phase transfer conditions from bromoform and sodium hydroxide). The tetracycle **4** [68%



Scheme 1 *Reagents and conditions*: i, Li, NH_3, DMF, −33 °C, 0.5 h then EtOH; ii, $CHBr_3$, NaOH, TEBAC, 18 °C, 40 h; iii, toluene/pyridine, 110 °C, 15 h; iv, $(H_2C{=}CH)SnBu_3$, $(Ph_3P)_4Pd$, 1,4-dioxane, 18 °C, 40 h; v, MA (to form **7**) or MI (to form **8**), C_6H_6, 18 °C, 15 h; vi, AgOAc (10 equiv.), CH_2Cl_2, 40 °C, 15 h; vii, MeCN, 18 °C, 10 d or C_6H_6, *p*-TsOH (cat.), 80 °C, 1 h; viii, TCCP (1 equiv.), C_6H_6, 130 °C, 15 h; ix, C_6H_6, 130 °C, 15 h. TEBAC = triethylbenzylammonium chloride, MA = maleic anhydride, MI = maleimide, TCCP = tetrachlorocyclopropene.

(from **2**), mp 120.5–121.5 °C]†‡ so-formed is presumed to possess the illustrated *anti*-relationship between the two *gem*-dibromocyclopropyl moieties on the basis that either of the two possible mono-cyclopropanated intermediates would direct attack of a second molecule of dibromocarbene to the opposite face of the remaining double bond.[4] Thermolysis of compound **4** in refluxing toluene–pyridine (9:1) resulted in smooth electrocyclic ring-opening[5] of the oxygenated (and therefore more activated) cyclopropane ring and formation of the [5.3.1]propelladiene **5** (95%, mp 103–104 °C).[6] Confirmation of the *cisoid* arrangement of the double bonds within this latter compound followed from the observation that a 1:1 Diels–Alder adduct (100%, mp 224 °C) is produced when diene **5** is reacted with 4-phenyl-1,2,4-triazoline-3,5-dione.[7] Stille cross-coupling[8] of compound **5** with vinyltrimethylstannane in the presence of tetrakis(triphenylphosphine)palladium(0) produced triene **6** (83%, mp 80–82 °C) which readily engaged in a regio- and diastereo-selective Diels–Alder reaction with maleic anhydride to give adduct **7** (100%, mp 130–140 °C). In a similar fashion, triene **6** reacted with maleimide to give compound **8** (91%, mp 142–147 °C). The preference for selective addition of dienophiles to the semi-cyclic diene moiety within triene **6** is presumably steric in origin.[9] The observed facial selectivity of these Diels–Alder reactions stems from the high degree of curvature associated with the [5.3.1]propelladiene framework which effectively precludes delivery of reagents to the concave surface of such molecules.

Electrocyclic ring-opening of the *gem*-dibromocyclopropane unit within pentacycle **7** was readily achieved[10] using silver acetate and it is presumed that the primary product of reaction is the triene **9**, but isolation of this latter compound was not possible because of its rapid hydrolysis to the corresponding ketone **11** [24% (from **7**), mp 214–216 °C]. In contrast, reaction of compound **8** under the same conditions afforded the isolable triene **10** (71%, mp 225–226 °C),§ the structure of which was determined by single crystal X-ray analysis (Fig. 1).¶ Presumably the observed regioselectivities of the ring-cleavage processes associated with the conversions **7** → **9** and **8** → **10** are determined by the electron-donating enolether moiety which is positioned adjacent to the propellane bond undergoing fission.

The interesting behaviour of cyclohexannulated [5.3.1]propellanes is further demonstrated by the reaction of triene **6** with tetrachlorocyclopropene (TCCP) in benzene at 130 °C. Under such conditions polycycles **12** (40%, mp 142–145 °C; variable mixture of cocrystallising bromo and chloro isomers) and **13** (*ca.* 1%, mp 168–170 °C) are obtained and the structures of these products have been established by single crystal X-ray analysis (Fig. 2).¶ Formation of pentacycle **12** can be rationalised in terms of an initial Diels–Alder cycloaddition reaction between triene **6** and TCCP. The resulting cyclohexannulated [5.3.1]propellane then undergoes thermally-induced electrocyclic ring opening involving cleavage of the propellane bond and formation of a bridgehead alkene similar to compounds **9** and **10** [but with bromine/chlorine at C-1‖ (paclitaxel numbering)]. Finally, thermally promoted (conrotatory) electrocyclic ring closure of the *B*-ring diene unit would produce the cyclobutene ring associated with product **12**. In an attempt to provide some support for the last step of this proposed pathway, triene **10** was heated in benzene at 130 °C but compound **14** (65%, mp 244–253 °C; stereochemistry at C-15 undefined), rather than the isomeric cyclobutene **15**, was obtained.

Formation of compound **13** presumably involves the same initial events as those leading to isomer **12** but, after

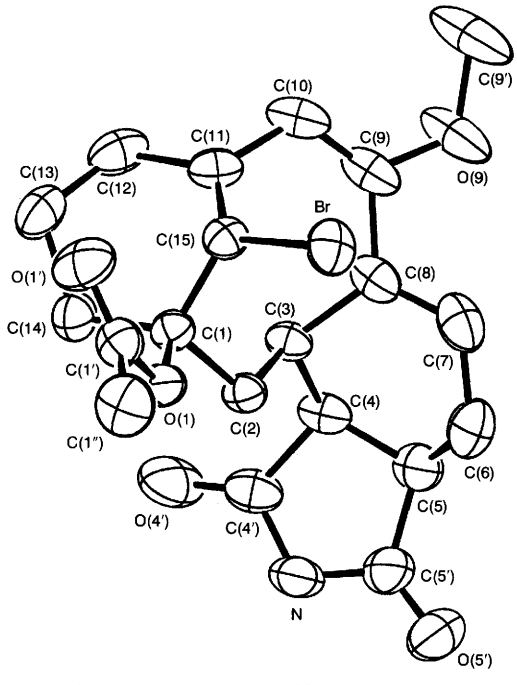


Fig. 1 ORTEP[12] drawing of compound **10** derived from X-ray crystallographic data

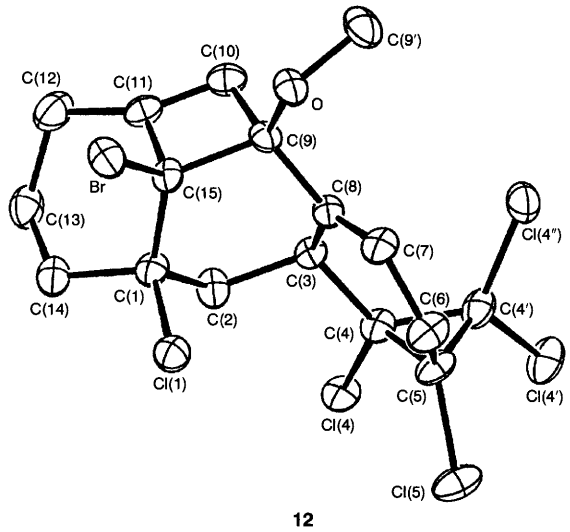


Fig. 2 ORTEP[12] drawings of compounds **12** (X=Cl) and **13** derived from X-ray crystallographic data

electrocyclic ring cleavage of the propellane σ-bond, π-bond migrations occur (*cf.* **10** → **14**) and this is followed by a vinylcyclopropane to cyclopentene rearrangement[13] of the ring-fused tetrachlorocyclopropane moiety.

The Australian Research Council is thanked for generous financial support including provision of a post-Doctoral Fellowship to S. C. P.; J. R. P. is the grateful recipient of a Melbourne University post-Graduate Scholarship.

Received, 10th March 1995; Com. 5/01507C

Footnotes

† All new compounds are racemic but, for the sake of simplicity, only one enantiomer is shown.

‡ All new compounds had spectroscopic data [IR, UV (where appropriate), NMR, mass spectrum] consistent with the assigned structure. With the exception of compounds **8** and **9**, satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives. Compound **8** was exceptionally unstable and only limited spectroscopic characterisation has been possible.

§ *Spectral data* for **10**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 177.6, 169.3, 160.2, 141.9, 140.3, 130.8(4), 130.7(6), 102.2, 83.7, 56.3, 47.0, 44.7, 40.2, 36.6, 36.3, 35.1, 22.1, 21.6 and 19.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1 H, brs, NH), 6.53 (1 H, dd, J = 3 and 8 Hz, 7-H), 5.27 (1 H, s, 10-H), 3.67 (3 H, s, OMe), 3.05 (1 H, m), 2.95 (1 H, m), 2.84 (1 H, m), 2.50 (1 H, brd, J = 14 Hz), 2.36 (1 H, m), 2.32–2.18 (3 H, cm), 2.12–1.89 (3 H, cm), 2.05 (3 H, s, Ac), 1.79 (1 H, d, J = 12 Hz) and 1.72 (1 H, m); MS *m/z* (EI, 70 eV) 437 (4%) 435 (4) [$M^{+\cdot}$], 377 (4) 375 (4) [$(M - AcOH)^{+\cdot}$], 356 (12) [$(M - Br^{\cdot})^+$] and 296 (100) [$(M - AcOH - Br^{\cdot})^+$]; ν_{max} (KBr)/cm^{-1} 3338, 2932, 1777, 1716, 1578, 1367, 1269, 1235, 1199, 1176 and 1080; λ_{max}/nm (1,4-dioxane) 280 (log ε 3.5), 224 (log ε 3.9) and 210 (sh, log ε 3.8); HRMS, $M^{+\cdot}$ 435.0679. $C_{20}H_{22}BrNO_5$ requires 435.0681.

¶ *Crystal data* for compound **10**: $C_{20}H_{22}BrNO_5$, M = 436.30, T = 293(1) K; monoclinic, space group $P2_1/n$, a = 7.4459(8), b = 18.7035(9), c = 13.3845(10) Å, β = 92.814(8)°, U = 1861.7(3) Å^3, D_c (Z = 4) = 1.557 g cm^{-3}, F(000) = 896, μ(Cu-Kα) = 32.88 cm^{-1}, analytical absorption correction; 3845 unique data ($2\theta_{max}$ = 150°), 3483 with $I > 2\sigma(I)$; conventional $R_1[I > 2\sigma(I)]$ = 0.0307, wR_2 [all data] = 0.0813, GOF [all data] = 1.109. For compound **12**: $C_{17}H_{16}Br_{1.15}Cl_{4.85}O$, M = 500.13, T = 150(1) K; monoclinic, space group $P2_1/c$, a = 7.3752(12), b = 24.522(4), c = 10.512(2) Å, β = 103.37(2)°, U = 1849.6(6) Å^3, D_m (293 K) = 1.76(1) g cm^{-3}, D_c (Z = 4, 293 K) = 1.764 g cm^{-3}, F(000) = 994.8, μ(Cu-Kα) = 98.78 cm^{-1}, analytical absorption correction; 3065 unique data ($2\theta_{max}$ = 130°), 2688 with $I > 2\sigma(I)$; conventional $R_1[I > 2\sigma(I)]$ = 0.0488, wR_2 [all data] = 0.1437, GOF [all data] = 1.052. For compound **13**: $C_{17}H_{16}Br_2Cl_4O$, M = 537.92, T = 293(1) K; monoclinic, space group $P2_1/n$, a = 7.170(2), b = 21.395(4), c = 12.373(2) Å, β = 94.18(2)°, U = 1893.0(7) Å^3, D_c (Z = 4) = 1.887 g cm^{-3}, F(000) = 1056, μ(Mo-Kα) = 48.49 cm^{-1}, analytical absorption correction; 3726 unique data ($2\theta_{max}$ = 52°), 2148 with $I > 2\sigma(I)$; conventional $R_1[1 > 2\sigma(I)]$ = 0.0801, wR_2 [all data] = 0.3582, GOF [all data] = 1.064. Data were measured on an Enraf-Nonius CAD4MachS diffractometer (nickel filter, λ = 1.54180 Å, or graphite crystal monochromator, λ = 0.71073 Å). Refinement was by full-matrix least-squares analysis on F^2 (SHELXL-93[11]) using all data, wR_2 = $[(\Sigma w(Fo^2 - Fc^2)^2/\Sigma w(Fo^2)^2]^{1/2}$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‖ Presumably the incorporation of chlorine at C-1 in compound **12** involves TCCP acting as the (organic soluble) source of chloride ion.

References

1 For some excellent reviews concerned with the chemistry and/or biology of taxoids, see: (*a*) K. C. Nicolaou, W-M. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15; (*b*) A. N. Boa, P. R. Jenkins and N. J. Lawrence, *Contemp. Org. Synth.*, 1994, **1**, 47; (*c*) D. Guénard, F. Guéritte-Voegelein and P. Potier, *Acc. Chem. Res.*, 1993, **26**, 160; (*d*) D. G. I. Kingston, A. A. Molinero and J. M. Rimoldi, *Prog. Chem. Nat. Prod.*, 1993, **61**, 1; (*e*) M. Suffness, *Annual Reports in Medicinal Chemistry*, Academic Press, New York, 1993, vol. 28, ch. 32; (*f*) C. S. Swindell, *Org. Prep. Proc. Int.*, 1991, **23**, 465.

2 (*a*) K. C. Nicolaou, H. Ueno, J.-J. Liu, P. G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan and R. Chadha, *J. Am. Chem. Soc.*, 1995, **117**, 653 and refs. cited therein; (*b*) R. A. Holton, H.-B. Kim, C. Somoza, 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**, 1599.

3 H. O. House and C. J. Blankley, *J. Org. Chem.*, 1968, **33**, 53.

4 M. G. Banwell and B. Halton, *Aust. J. Chem.*, 1979, **32**, 849.

5 E. N. Marvell, *Thermal Electrocyclic Reactions*, Academic Press, New York, 1980.

6 For alternate modes of ring cleavage of closely related systems, see: M. G. Banwell, R. W. Gable, B. Halton and J. R. Phyland, *Aust. J. Chem.*, 1994, **47**, 1879.

7 For a related Diels–Alder cycloaddition reaction involving a simpler [5.3.1]propelladiene, see M. G. Banwell, *Aust. J. Chem.*, 1988, **41**, 1037.

8 M. E. Krolski, A. F. Renaldo, D. E. Rudisill and J. K. Stille, *J. Org. Chem.*, 1988, **53**, 1170.

9 A. G. Fallis and Y-F. Lu, in *Advances in Cycloaddition*, ed. D. Curran, JAI Press, Greenwich, Connecticut, 1993, vol. 3, pp. 1–66. Similar cycloaddition reactions have recently been employed by others in the paclitaxel area, see: J. Oh and J. K. Cha, *Synlett.*, 1994, 967.

10 For related ring-cleavage reactions of [*n.m.*1]propellanes, see: (*a*) P. M. Warner, *Chem. Rev.*, 1989, **89**, 1067 and refs. cited therein; (*b*) G. W. Wijsman, W. H. de Wolf, F. Bickelhaupt, H. Kooijman and A. L. Spek, *J. Am. Chem. Soc.*, 1992, **114**, 9191.

11 G. M. Sheldrick, SHELXL-93. *Program for Crystal Structure Refinement*, University of Göttingen, Germany.

12 C. K. Johnson, ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, USA, 1976.

13 J. Salaün, *Rearrangements Involving the Cyclopropyl Group*, in *The Chemistry of the Cyclopropyl Group*, ed. Z. Rappoport, Wiley, New York, 1987.