A Stereocontrolled Route to the Tricyclo[9.3.1.$0^{3,8}$]pentadecane Ring System of Taxane

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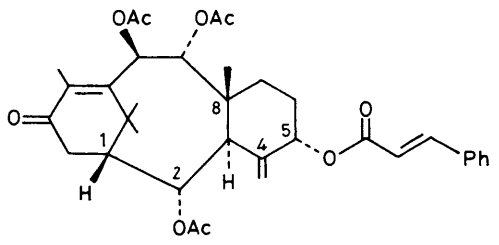
The synthesis of a tricyclo[9.3.1.$0^{3,8}$]pentadecane system which has the same relative stereochemistry about its chiral centres as the taxane natural products is reported.

The taxanes[1] are a group of natural products which have attracted considerable interest recently; they not only provide challenging synthetic targets,[2] but also show anticancer activity.[3] Taxinine (**1**) illustrates the general features of the series; its structure has been confirmed by *X*-ray analysis.[4]

In our synthetic approach to the taxane ring system we concentrated our efforts on the stereochemistry at centres C-1, -3, and -8. We now report a successful stereocontrolled route to a model system which has the correct relative stereochemistry at these centres. Our strategy involved an intramolecular Diels–Alder cyclisation[5] of a 2-substituted diene fragment[6] prepared in the latter stages of the route.

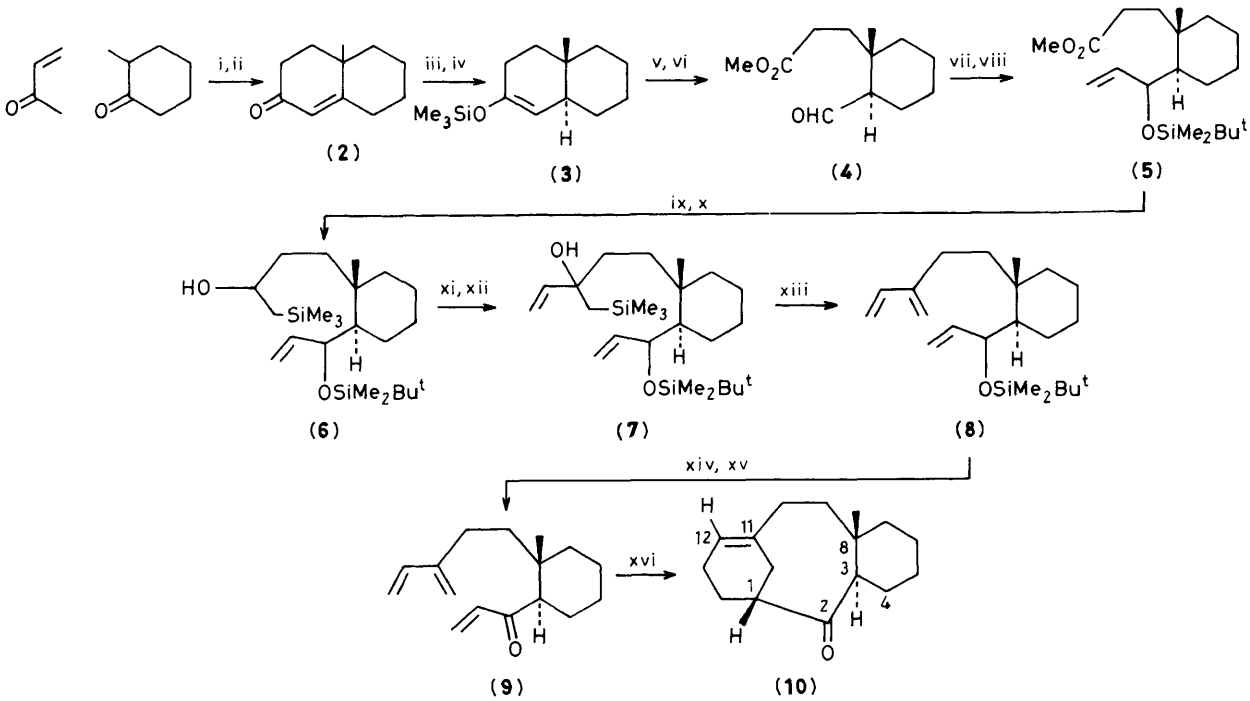
The first problem we addressed was the construction of an appropriately substituted cyclohexane derivative. Enone (**2**) was prepared by the method of Marshall and Fanta[7] and then reduced with lithium in liquid ammonia followed by enolate trapping to give the silyl enol ether (**3**) with the *trans* decalin stereochemistry.[8] Ozonolysis led to cleavage of the double bond and treatment with diazomethane gave the ester-aldehyde (**4**)† as a single diastereoisomer in 78% yield. Addition of vinylmagnesium bromide occurred with efficient 1,2-asymmetric induction to furnish (**5**) after protection, again as a single isomer. Several crystalline derivatives of both (**4**) and (**5**) were prepared; however, none was suitable for *X*-ray analysis and hence the relative stereochemistry of the new exocyclic chiral centre in (**5**) remains unknown. The structure of (**5**) is based on spectroscopic evidence [ν_{max} 1742 cm^{-1}; ^1H n.m.r. (400 MHz) δ −0.04 (3H, s), −0.02 (3H, s), 0.85 (9H, s), 0.91 (3H, s), 1.04—1.76 (11H, m), 2.24 (2H, m), 3.64 (3H, s), 4.31 (1H, br.d, *J* 7.2 Hz), 4.95 (1H, ddd, *J* 10.3, 1.5, 1.0 Hz), 5.03 (1H, ddd, *J* 17.4, 1.5, 1.3 Hz), and 5.86 (1H, ddd, *J* 17.4, 10.3, 7.2 Hz); ^{13}C n.m.r. (100 MHz) 21.21 p.p.m. (q) and other signals consistent with a single isomer].

† All new compounds gave satisfactory ^1H, ^{13}C n.m.r., i.r., and mass spectral data; compounds (**4**), (**5**), (**8**), and (**10**) gave correct microanalysis results.

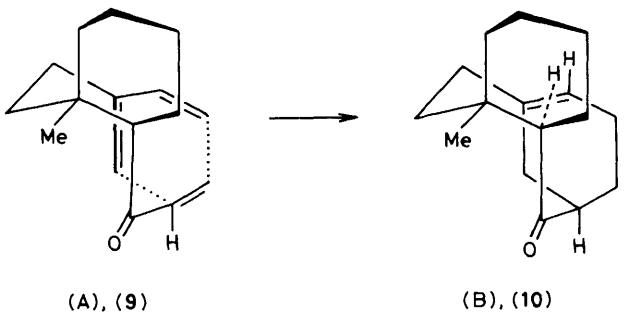


(**1**)

After several unsuccessful attempts to convert ester (**5**) into a diene using conventional methods we developed a new procedure using silicon as a control element. Di-isobutylaluminium hydride (DIBAH) reduction of ester (**5**) at −78 °C gave an aldehyde which was converted into the β-hydroxy silane (**6**) *via* reaction with trimethylsilylmethyl-magnesium chloride[9] in 67% overall yield. Rapid *in situ* Collins oxidation produced a sensitive β-keto silane which reacted with vinylmagnesium bromide at room temperature to provide the β-hydroxy silane (**7**).[10] Treatment of the crude product with acetic acid and sodium acetate[11] caused a controlled elimination to give a 51% overall yield from (**6**) of triene (**8**) [^1H n.m.r. (400 MHz) δ −0.02 (3H, s), 0.03 (3H, s), 0.97 (9H, s), 0.96 (3H, s), 1.19—1.60 (10H, m), 1.74 (2H, m), 2.15 (2H, m), 4.30 (1H, br.d, *J* 7.2 Hz), 4.96 (1H, ddd, *J* 10.1, 1.5, 1.0 Hz), 4.99 (2H, br.s), 5.03 (1H, ddd, *J* 17.6, 1.5, 1.5 Hz), 5.05 (1H, ddd, *J* 10.7, 2.0, 1.0 Hz), 5.23 (1H, dd, *J* 17.6, 1.0 Hz), 5.89 (1H, ddd, *J* 17.6, 10.1, 7.2 Hz), and 6.36 (1H, dd, *J* 17.6, 10.7 Hz)]. Deprotection, which only worked in glass apparatus,[12] was followed by Collins oxidation to give enone (**9**) in 71% yield. Diels-Alder cyclisation catalysed by diethylaluminium chloride[13] occurred smoothly at room temperature to give ketone (**10**) as a white crystalline single isomer [72%; m.p. 84–85 °C; ν_{max} 1688 cm^{-1}; ^1H n.m.r. (400 MHz) δ 0.87 (3H, s), 1.02—1.30 (5H, m), 1.43—1.70



Scheme 1. *Reagents:* i, NaOEt (catalytic), −10 °C, 12 h; ii, KOH, H_2O, steam distil; iii, Li (2.2 equiv.), NH_3(l), tetrahydrofuran (THF), 15 min; destroy excess Li, remove NH_3, add THF, cool to −10 °C; iv, Me_3SiCl (2 equiv.), Et_3N (2 equiv.); v, O_3, CH_2Cl_2, MeOH, Sudan Red III; vi, CH_2N_2; vii, CH_2=CHMgBr (1 equiv.), THF, −78 °C; viii, $Bu^tMe_2SiOSO_2CF_3$ (1.5 equiv.), 2,6-lutidine (2.0 equiv.), CH_2Cl_2, room temp.; ix, DIBAH in hexane (1 equiv.), PhMe, −78 °C; x, Me_3SiCH_2MgCl, Et_2O, reflux, 1 h; xi, CrO_3 (6 equiv.), pyridine (12 equiv.), CH_2Cl_2, room temp., 30 s; xii, CH_2=CHMgBr (1 equiv.), THF, room temp., 1 h; xiii, $MeCO_2H$, $MeCO_2Na{\cdot}3H_2O$; xiv, HF (15%), H_2O, MeCN, room temp., 1.5 h; xv, as xi, room temp., 5 min; xvi, Et_2AlCl in hexane (1 equiv.), CH_2Cl_2, room temp., 1.5 h.



(7H, m), 1.82—1.93 (3H, m), 2.15—2.26 (2H, m), 2.34 (1H, ddd, *J* 13.7, 1.8, 1.8 Hz), 2.46 (1H, td, *J* 14.36, 2.85 Hz), 2.78 (1H, m), 3.19 (1H, dd, *J* 12.3, 3.0 Hz, 3-H), and 5.77 (1H, m, 12-H), 5% nuclear Overhauser enhancement (n.O.e.) between δ 5.77 and 3.19].

Our rationalisation of these results is summarised in the three-dimensional representation [(A) → (B)] of the cyclisation (**9**)→(**10**). The eight-membered ring in (B) has the chair–boat conformation which explains the observed n.O.e. data because 3-H and 12-H are in close proximity. Calculations along with *X*-ray and n.m.r. studies[14] indicate the chair–boat to be the most stable conformation for simple cyclo-octanes. The remarkable stereochemical control shown in the cyclisation appears to arise from a preference for the chair–boat conformation of the eight-membered ring in the transition state over the alternative twist chair–boat conformation. The structure of (**10**) was confirmed by *X*-ray analysis and is shown in Figure 1.

Crystal Data: (**10**), $C_{16}H_{24}O$, M = 232.19, triclinic, space group $P\bar{1}$ No. 2, a = 8.412(8), b = 13.125(12), c = 6.645(10) Å, α = 90.5(1), β = 104.9(2), γ = 105.5(2)°, U = 681.08 Å^3, Z = 2, λ (Mo-K_α) = 0.7107 Å. The intensities of 1700 unique reflections with 2θ< 45° were measured using a Stoe STADI-2 Weissenberg diffractometer; of these 537 reflections had $|F_O|>5\sigma(|F_O|)$. The structure was solved by direct methods

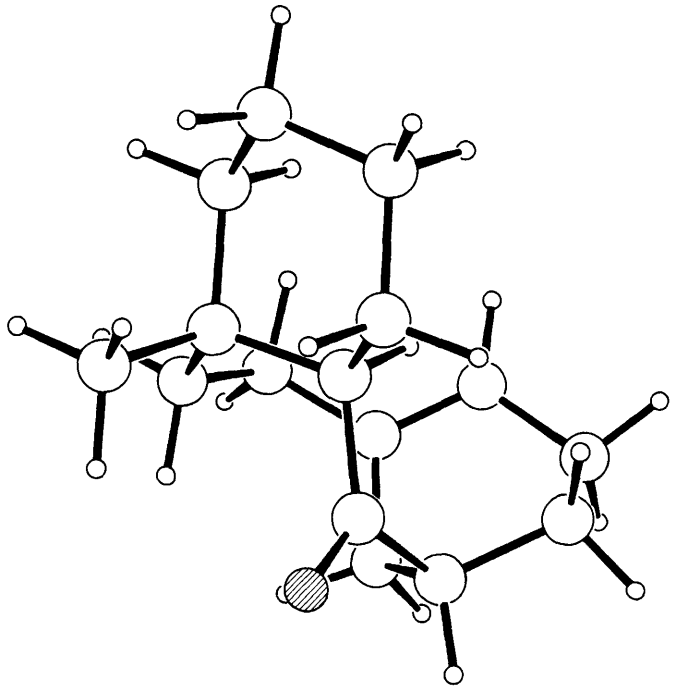


Figure 1. A view of the molecular structure of (**10**). Atoms are represented by circles of arbitrary radius. The shaded atom is oxygen and the remaining atoms carbon (large circles) or hydrogen.

and refined to $R = 0.1079$, R_w 0.0972.‡ Hydrogen atoms were included in calculated positions for structure factor calculations.

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References

1 B. Lythgoe, 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1968, vol. X, p. 597.
2 A. S. Kende, M. Benechie, D. P. Curran, and P. Fludzinski, *Tetrahedron Lett.*, 1979, 4513; B. M. Trost and H. Hiemstra, *J. Am. Chem. Soc.*, 1982, **104**, 886; S. F. Martin, J. B. White, and R. Wagner, *J. Org. Chem.*, 1982, **47**, 3192; H. Shibuya, S. Tsujii, Y. Yamamoto, K. Murakawa, K. Takagi, N. Kurukawa, and I. Kitagawa, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 24th,* 1981, 340; *Chem. Abs.*, 1982, **96**, 218050v; K. Sakan and B. M. Craven, *J. Am. Chem. Soc.*, 1983, **105**, 3732.
3 M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325; R. G. Powell, R. W. Miller, and C. R. Smith, *J. Chem. Soc., Chem. Commun.*, 1979, 102.
4 M. Shiro, T. Sato, H. Koyama, Y. Maki, K. Nakanishi, and S. Uyeo, *Chem. Commun.*, 1966, 98.
5 Recently this strategy has been used independently in a route to a C-aromatic taxane skeleton, K. J. Shea and P. D. Davis, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 419.
6 P. A. Brown and P. R. Jenkins, *Tetrahedron Lett.*, 1982, **23**, 3733.
7 J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, 1964, **29**, 2501.
8 G. Stork and J. Singh, *J. Am. Chem. Soc.*, 1974, **96**, 6181.
9 C. R. Hauser and C. R. Hance, *J. Am. Chem. Soc.*, 1952, **74**, 5091.
10 R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 1970, **35**, 4000; P. F. Hudrlik and D. Petersen, *Tetrahedron Lett.*, 1974, 1133; R. A. Ruden and B. L. Goffney, *Synth. Commun.*, 1975, **5**, 15.
11 P. F. Hudrlik and D. Petersen, *Tetrahedron Lett.*, 1972, 1785.
12 R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Lett.*, 1979, 3987. We thank Dr P. B. Kay for pointing this out to us.
13 K. J. Shea and J. W. Gilman, *Tetrahedron Lett.*, 1983, **24**, 657.
14 J. B. Hendrickson, *J. Am. Chem. Soc.*, 1967, **89**, 7036 and 7043; N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, 1972, **28**, 1173; J. D. Dunitz in 'Perspectives in Structural Chemistry,' eds. J. D. Dunitz and J. A. Ibers, Wiley, New York, 1968, Vol. 2, p. 35; F. A. L. Anet and M.St Jacques, *J. Am. Chem. Soc.*, 1966, **88**, 2585 and 2586; F. J. Weigert and J. D. Roberts, *ibid.*, 1970, **92**, 1347.

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.