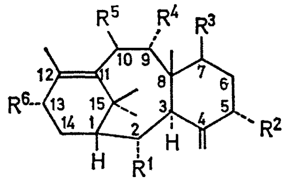
Application of the Olefin Octant Rule to some Taxane Derivatives: Assignment of Absolute Configuration using the Cotton Effect

By D. P. DELLA CASA DE MARCANO and T. G. HALSALL*
(*The Dyson Perrins Laboratory, Oxford University, Oxford* OX1 3QY)

and A. I. SCOTT and A. D. WRIXON
(*Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut* 06520)

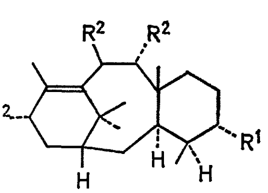
Summary The signs of the Cotton Effects associated with each of the mono-olefinic centres in taxane derivatives can be used to assign the absolute configuration of the molecule.

THE Octant Rule for chiral mono-olefins[1,2] relates the absolute configuration of a variety of endo- and exo-cyclic alkenes to the sign of the lowest energy Cotton Effect.[3] The olefinic centres in the taxane skeleton provide examples of both rigid *trans*-cyclodecene and *exo*-methylene geometry in a highly oxygenated environment. Moreover, the $\pi \rightarrow \pi^*$ olefinic u.v. absorption normally found between 190 and 200 nm is displaced to higher wavelengths (210—230 nm) in the bicyclo[5,3,1]undecane series.[4] It was therefore of interest to apply octant analysis to the o.r.d. and c.d. spectra (Table; Figures 1 and 2) of the taxanes (I)—(XII).[4-6]

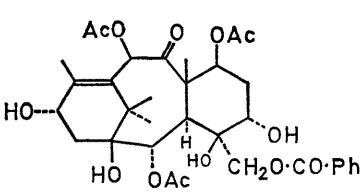


	R¹	R²	R³	R⁴	R⁵	R⁶
(I)	H	OAc	H	OAc	OAc	OAc
(II)	H	OH	H	OAc	OAc	OH
(III)	OAc	OAc	H	OAc	OAc	OAc
(IV)	H	OAc	OAc	OAc	OAc	OAc
(V)	OAc	OAc	OAc	OAc	OAc	OAc
(VI)	OMB	OAc	OAc	H	OAc	H
(VII)	OMB	OH	OAc	OAc	OAc	H
(VIII)	OMB	OAc	OAc	OAc	OAc	H
(IX)	H	OH	H	OH	OH	OH

OMB = α-methylbutyrate



(X) $R^1 = R^2 = OH$
(XI) $R^1 = H; R^2 = OAc$



(XII)

Each of the compounds (I)—(XII) exhibited very intense positive Cotton Effects ([θ] *ca.* 10^5) in the region (214—230 nm) corresponding to the $N \rightarrow V$ ($\pi \rightarrow \pi^*$) band (λ 210—230 nm, ε *ca.* 10^4). An oppositely signed transition is uncovered some 30 nm to lower wavelength and may be an optically active $\sigma \rightarrow \pi^*$ or $\pi_x \rightarrow \pi_y^*$ absorption.[7] The dominant $\pi \rightarrow \pi^*$ positive Cotton Effect is reminiscent of the high rotational strength of the 196 nm transition of *trans*-cyclo-octene[7] {$[\theta]_{196}$ — 140,800 for *R*-(—)-*trans*-cyclo-octene}, and in fact the octant projection of the configurations shown in Figure 3 corresponds to a rigid (*S*)-(+)-form of *trans*-cyclodecene. This assignment is in accord with the absolute configuration of the taxanes determined by a combination of Horeau's technique, o.r.d., c.d., n.m.r., and *X*-ray diffraction analysis.[5] The negative contribution from the second isolated 4(20) double bond can be obtained from the subtraction of the c.d. and o.r.d. curves (IX)—(X) as shown in Figure 2 and accords with a negatively signed rear octant population for an *exo*-methylene chromophore at C-4.

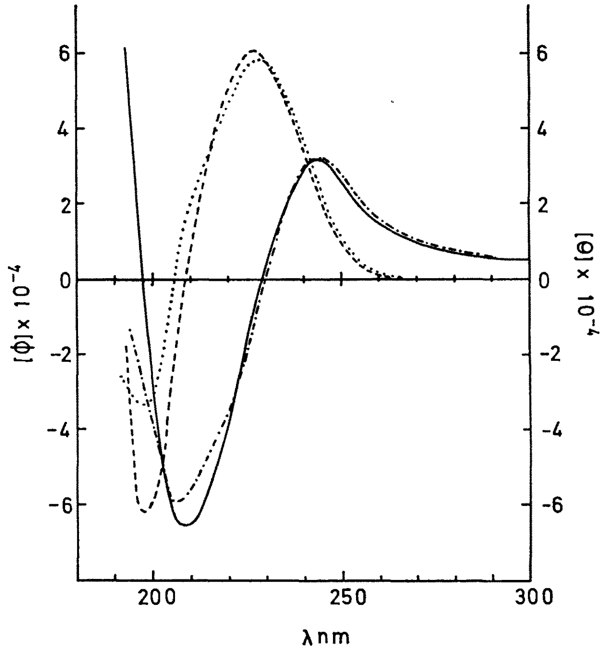


FIGURE 1. *The o.r.d.* (————) *and c.d.* (– – – – – –) *spectra of taxa*-4(20),11-*diene*-5α,9α,10β,13α-*tetraol* (IX) *and the o.r.d.* (–·–·–·–·–·) *and c.d.* (..............) *spectra of taxa*-11-*ene*-5α,9α,10β,13α-*tetraol* (X) *in methanol.*

The effects of the various substituents upon the sign and magnitude of the Cotton Effect (Table) may be assessed as follows:

(i) The allylic axial methyl group on C-15 (positive octant) enhances the positive Cotton Effect predicted above for the Δ^{11}-chromophore in the (*S*)-*trans*-cyclodecene configuration.

(ii) An α-substituent at C-13 lies very close to the nodal plane of the octant projection and is not expected to give rise to any dramatic (*e.g.* sign change) effect [*cf.* (V) and (VI)].

C.d., o.r.d., and u.v. data for some taxane derivatives in cyclohexane (unless otherwise stated)

	C.d. data		O.r.d. data		U.v. max	
No.	λ	[θ]	λ	[φ]	λ	ε
(I)	217·5	+108,200	230·5	+ 55,000	221	6900
	190	−139,000	203	−128,300		
	217·5[a]	+104,600[a]	230[a]	+53,100[a]		
			200[a]	−137,800[a]		
(II)	227	+ [b]	240	+ [b]	223	4800
			210	− [b]		
(III)	215·5	+84,300	228	+39,500	217	11,600
	187·5	−124,900	196	−123,100		
(IV)	217	+113,200	230	+54,600	211	8100
			204	−124,100		
	189·5	−140,900	185[c]	+33,600[c]		
(V)	215	+76,300	228·5	+36,800	213	11,100
	187	−106,700	195	−115,800		
(VI)	214	+94,600	227	+49,000	209	9100
	185[c]	−49,300[c]	203	−80,000		
			199	−76,400		
			190	−104,800		
(VII)	216·5	+113,300	230	+53,400	215	10,400
			202	−115,300		
	185[c]	−119,600[c]	197	−110,400		
			190	−139,100		
(VIII)	216	+112,800	228	+54,950	214	9200
	187[c]	−114,300[c]	192	−140,200		
(IX)	224·5	+ [b]	233	+ [b]	227	7000
	200	− [b]	212	+ [b]		
	227[a]	+60,600[a]	243[a]	+31,400[a]		
	198[a]	−61,900[a]	208[a]	−65,650[a]		
			193[a,c]	+61,950[a,c]		
(X)	229·5[a]	+56,800[a]	244[a]	+32,000[a]	227	7000
	198[a]	−33,800[a]	206·5[a]	−58,900[a]		
(XI)	220	+94,600	234	+50,900		
	191	−123,700	198	−143,000		
			185[c]	+18,000[c]		
	304	−24,050	321	−12,520	280	850
(XII)	230	+50,850	247	+35,390	274	1000
	190	−98,900	200	−86,050	230	13,900

[a] Values obtained in methanol.

[b] Insufficient sample or solubility for accurate measurement.

[c] Lowest recorded value, not a peak or extremum.

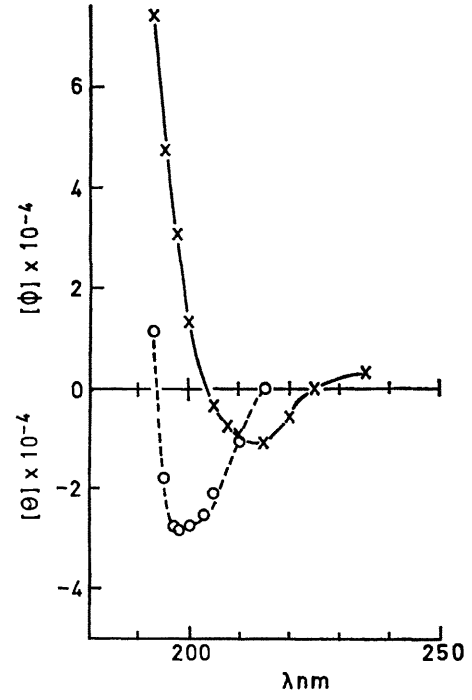


FIGURE 2. *The o.r.d. (———) and c.d. (– – – – – –) subtraction curves of compound* (IX) — *compound* (X) *showing the negative Cotton Effect contribution of the* 4(20)*olefinic chromophore.*

(iii) The ubiquitous β-oxygenated function at C-10 lies in an allylic negative octant. However, such a substituent has been found[3] in several cases so far examined to exhibit reverse octant behaviour (*cf.* Mills' Rule).[8]

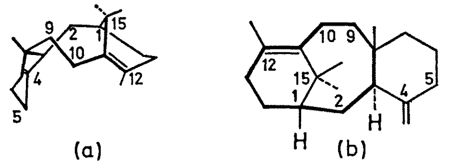


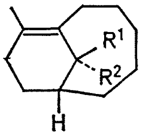
FIGURE 3. *Taxane skeleton showing* (a) *absolute configuration and probable conformation and* (b) *relationship to* S-trans-*cyclodecene.*

(iv) The additive contributions of as many as five or (in one case) six chiral ester groupings might be expected to cause some complication in interpretation. However as indicated by earlier work on the rotomers of steroidal mono- and di-acetates,[9] the maximum contribution to [φ] near 215 nm is expected to be about 3000 and the intensity of the $\pi \rightarrow \pi^*$ Cotton Effect ([θ] *ca.* 10^5] is not signally different in (IX) $[\theta]_{227}$ + 60,600 and its tetra-acetate (I) ($[\theta]_{217\cdot5}$ + 104,600) or in (X) ($[\theta]_{229\cdot5}$ + 56,800) and (XI) ($[\theta]_{220}$ + 94,600).

(v) In baccatin-III (XII)[10] carbonyl, benzoate, and olefinic chromophores are present. The $n \rightarrow \pi^*$ of the ketone at

304 nm (negative) is amenable to analysis by the carbonyl octant rule whilst the contribution of the benzoate chromophore does not appear to influence the intense olefinic Cotton Effect ($[\theta]_{230}$ + 50,850); ($[\theta]_{190}$ − 98,900).

(vi) In all of these cases the absolute stereochemistry of the Δ^{11}-olefin is predicted by the Octant Rule and the Cotton Effect is observed near the $\pi \rightarrow \pi^*$ u.v. maximum. In this regard it is interesting to note that the rather high wave-length of the mono-olefinic absorption in the taxane series is perhaps more a function of the C-15 substitution than of the strain imposed upon the chromophore and its chiral envelope.[4]



(XIII) R^1 = H, R^2 = Me λ_{max} 197 nm
(XIV) R^1 = H, R^2 = OH λ_{max} 202 nm
(XV) R^1 = Me, R^2 = OH λ_{max} 212 nm

This is illustrated by the u.v. spectra of compounds (XIII)—(XV).[11]

(vii) The chiral contribution of the $\Delta^{4(20)}$ chromophore is additive at 200 nm (Figure 2) and in turn conforms to the Octant Rule (negative Cotton Effect). Finally we note that in this and all cases so far studied[3] there is no evidence for interchange of the $\pi_x \rightarrow \pi_x^*$, $\pi_x \rightarrow \pi_y^*$, or $\sigma \rightarrow \pi^*$ energy levels.[7]

(*Received, March* 26*th*, 1970; *Com.* 434.)

---

[1] A. I. Scott and A. D. Wrixon, *Chem. Comm.*, 1969, 1182.

[2] J. A. Schellman, *J. Chem. Phys.*, 1966, **44**, 55.

[3] A. I. Scott and A. D. Wrixon, *Tetrahedron*, 1970, in the press.

[4] Review: B. Lythgoe in "The Alkaloids," ed. R. H. Manske, Academic Press, New York, 1968, vol. 10.

[5] (a) M. Kurono, Y. Maki, K. Nakanishi, M. Ohashi, K. Ueda, S. Uyeo, M. C. Woods, and Y. Yamamoto, *Tetrahedron Letters*, 1965, 1917; (b) M. Shiro, T. Sato, H. Koyama, Y. Maki, K. Nakanishi, and S. Uyeo, *Chem. Comm.*, 1966, 97; (c) W. R. Chan, T. G. Halsall, G. M. Hornby, A. W. Oxford, W. Sabel, K. Bjåmer, G. Ferguson, and J. M. Robertson, *ibid.*, p. 923; (d) M. C. Woods, H.-C. Chiang, Y. Nakadaira, and K. Nakanishi, *J. Amer. Chem. Soc.*, 1968, **90**, 522; (e) N. Harada and K. Nakanishi, *ibid.*, 1969, **91**, 3989.

[6] D. P. Della Casa de Marcano and T. G. Halsall, *Chem. Comm.*, 1969, 1282.

[7] A. I. Scott and A. D. Wrixon, *Chem. Comm.*, 1970, 43.

[8] J. A. Mills, *J. Chem. Soc.*, 1952, 4976.

[9] J. P. Jennings, W. P. Mose, and P. M. Scopes, *J. Chem. Soc.* (*C*), 1967, 1102.

[10] D. P. Della Casa de Marcano, T. G. Halsall, and G. M. Hornby, *Chem. Comm.*, 1970, 216.

[11] M. S. Hadley and T. G. Halsall, unpublished work.