Tetrahedron Letters,Vol.26,No.28,pp 3397-3400,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

INVESTIGATION OF TRANSANNULAR CYCLISATIONS OF VERTICILLANES TO THE TAXANE RING SYSTEM

Michael J. Begley, Christopher B. Jackson and Gerald Pattenden*
Department of Chemistry, The University, Nottingham NG7 2RD

Summary: Treatment of either the verticillenes (3), (6), (13) or (14) with Lewis acids fails to produce the corresponding taxane carbon framework viz (2), and instead only products, e.g.(8), (9), (16), of rearrangement of the epoxide rings in the substrates are obtained.

Taxane is the generic name applied to the group of alkaloids e.g. taxinin I (1), first isolated from the common yew Taxus baccata; they show structures based on the novel tricyclo [10.3.1.$0^{4,6}$] pentadecene carbon framework(2)[1]. A number of taxanes have recently been shown to exhibit potent anti-leukemic properties[2], and these properties in combination with their relatively complex structures have made the molecules an interesting and challenging group of compounds for total synthesis[3]. The carbon framework (2) has its origins in geranylgeranyl pyrophosphate (GGPP), and verticillene (3) is considered to be the most likely intermediate between GGPP and taxane (2)[4]. Verticillene(3) correlates with cembrene (4), a constituent of conifer wood, and also with casbene(5) produced by seedlings of Ricinus communis. In the previous Letter, we described a total synthesis of E,E-verticillene(3)[4]. In this Letter, we summarise the outcome of our attempts to effect transannulation of both verticillene (3) and the related verticillol(12) a constituent of the conifer Sciadopitys verticillata, and their derivatives, to the taxane ring system(2).

We first investigated the transannulation of verticillene(3), using BF_3-etherate under varying conditions, but to our surprise found no evidence for the formation of tricyclic products; instead the verticillene underwent extensive decomposition, even at room temperature. Suspecting that this might be due to preferential complexation between BF_3-etherate and the more nucleophilic bridgehead double bond in (3), rather than the 7,8-double bond, we then decided to prepare the corresponding 7,8-epoxide (6) of verticillol. Treatment of verticillene(3) with meta-chloroperbenzoic acid (MCPBA) in dichlormethane in the presence of disodium hydrogen phosphate, led to a mixture of 3,4- and 7,8-monoepoxides(78%) which were separated by chromatography (reverse phase h.p.l.c; 17:3 MeOH-H_2O). The 7,8-epoxide (6) showed spectral data δ1.02(CMe), 1.1(CMe), 1.29(CMe), 1.6(:CMe), 1.63(:CMe), 1.5-2.5(m,15H), 2,6(dd,J9 and 2,CHO),

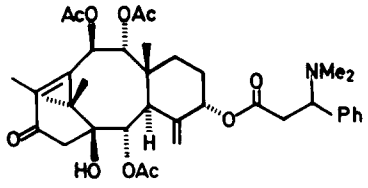
5.41(br,:CH), closely similar to those of verticillol 7,8-epoxide (13)[5], which was synthesised in a similar manner from natural verticillol (12) and whose structure and stereochemistry were rigidly established by X-ray crystallography[6].

Treatment of the vertillene 7,8-epoxide(6) with BF_3-etherate, under conditions used previously by Look and Fenical[7] to effect transannulation of the 11-membered ring epoxide(10) to (11), gave none of the hoped for tricyclic alcohol(7). Instead, the corresponding allylic alcohol(8), needles m.p. 174-175°C was isolated as the major product (52%), together with the fluorohydrin(9)(35%). These observations led us to suspect that the initial epoxide (6) had the alternative configuration at the epoxide, with epoxidation occurring from the 'inside' face of the macrocycle(3). Transannulation in a crown conformation, and through a chair like transition state would then be much less favoured, and possibly account for the formation of the allylic alcohol (8) rather than (7). An X-ray structure determination of the crystalline alcohol (8)[8] however, fully established the pseudo-equatorial orientation of the hydroxyl group, thereby confirming that the original epoxide(6) was produced from attack on the outside face of the 12-membered ring in (3).

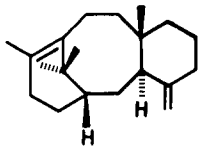
With the failure of verticillene (3) and its 7,8-epoxide(6) to undergo transannular cyclisation to the taxane ring system (2), we decided to investigate transannulation of the epoxides (13) and (14) derived from natural verticillol (12)[9]. Treatment of verticillol with MCPBA, in a similar manner to that described earlier for (3), followed by chromatogrpahy (silica; EtOAC-petrol 4:1), gave the 7,8-epoxide (13) (47%), as colourless crystals m.p. 146-9°C, accompanied by the corresponding 3,4-epoxide (23%), m.p. 139-40°C, and the known bis-epoxide (13%), m.p. 160-1°C (lit.[9],m.p. 159-60°). The structure and stereochemistry of verticillol 7,8-epoxide (13) was established rigorously by x-ray crystallography[6]. Dehydration of verticillol ($POCl_3$-C_5H_5N) produced a mixture of endo- and exo- anhydroverticillols which could be separated by chromatography[9]. The endo-isomer gave rise to a mixture of the corresponding 3,4- and 7,8-monepoxides and the bis-epoxide on treatment with MCPBA, from which the 7,8-epoxide (14) was separated by chromatography. We were unable, however, to resolve the mixture of monoepoxides resulting from epoxidation of the exo-anhydroverticillol. Interestingly, in neither case were we able to detect concurrent epoxidation of the six-ring double bonds in the anhydroverticillols.

Reactions between verticillol 7,8-epoxide(13) and BF_3-etherate, and between (13) and trimethylsilyl triflate, under a range of reaction conditions, resulted in the formation of largely the ketone (18), m.p. 130-3°C (EtOAc), ν_{max}1670cm.$^{-1}$, δ1.12(d,J7,CHMe); δ_{carbon}219.7ppm., accompanied by small amounts of the products (16) and (17) resulting from straightforward dehydration of (13). In a similar manner, treatment of the endo-anhydroverticillol epoxide (14) with BF_3-etherate led only to decomposition, and none of the hoped-for taxol (17) could be detected amongst the products.

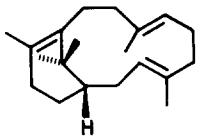
The failure of either of the verticillenes (3), (6), (13) and (14) to undergo transannular cyclisation, in vitro, to the corresponding taxane ring



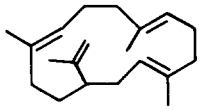
(1)



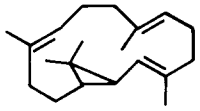
(2)



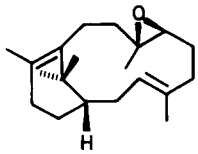
(3)



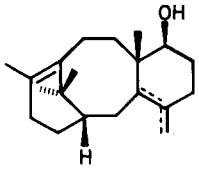
(4)



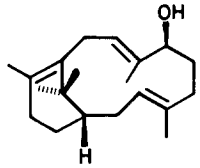
(5)



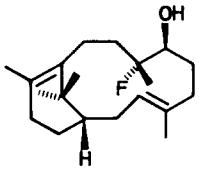
(6)



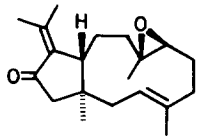
(7)



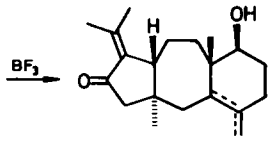
(8)



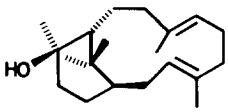
(9)



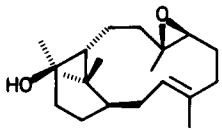
(10)



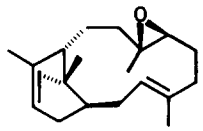
(11)



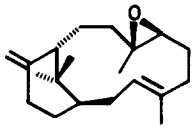
(12)



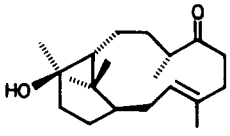
(13)



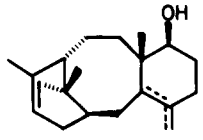
(14)



(15)



(16)



(17)

systems is both interesting and perplexing[10]. Although the observations do not disprove the involvement of verticillenes in the biosynthetic sequence leading to the taxane ring system from GGPP, they do lead us to suspect that this is a much more subtle sequence than we had hitherto imagined, and one which may involve alternative pathways for elaborating the tricycle or use different geometrical/positional isomers of GGPP for its purpose.

We thank Professors Norin (Stockholm) and Sumimoto (Fukuoko) for providing us with generous amounts of natural verticillol, and the S.E.R.C. for a studentship (to C.B.J.)

References

1. See: R.W. Miller, J. Nat. Prod., 1980, 43, 425 and references therein.
2. e.g. M.C. Wani, H.L. Taylor, M.E. Wall, P. Coggan and A.T. McPhail, J. Am. Chem. Soc., 1971, 93, 2325.
3. K.L. Shea and P.D. Davis, Agnew Chem. Int. Ed., 1983, 22, 419 K. Sakan and B.M. Craven, J. Am. Chem. Soc., 1983, 105, 3732; P.A. Brown, P.R. Jenkins, J. Fawcett, and D.R. Russell, J. Chem. Soc., Chem. Commun., 1984, 253; C.S. Swindell and S.J. deSolms, Tetrahedron Lett., 1984, 25, 3801.
4. C.B. Jackson and G. Pattenden, Tetrahedron Lett., 1985, 0000.
5. All new compounds showed satisfactory spectral data and microanalytical or mass spectral data.
6. M.J. Begley, Unpublished data.
7. S.A. Look and W. Fenical, J. Org. Chem., 1982, 47, 4129.
8. Crystals of (8) are monoclinic, space group C2/c, with a = 25.308(3), b = 16.308(2), c = 8.945(1) Å and β = 109.66(1)°. Final R value 4.48% over 1939 reflections. The atomic co-ordinates 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 paper.
9. B. Karlsson, A.-M. Pilotti, A.-C. Sonderholm, T. Norin, S. Sundin, and M. Sumimoto, Tetrahedron, 1978, 34, 2349.
10. Transannular cyclisations involving 1,5-diene systems set within 8-, 9-, 10- and 11- membered rings have been the subject of intense research; see J.K. Sutherland Tetrahedron, 1974, 30, 1651 and refs cited therein. We have recently highlighted the value of such transannulations in the 'biomimetic' syntheses of the triquinanes capnellene and pentalenene; see A.M. Birch and G. Pattenden, J. Chem. Soc., Perkin Trans I, 1983, 1913. G. Pattenden and S.J. Teague, Tetrahedron Lett., 1984, 25, 3021.

(Received in UK 29 April 1985)