Tetrahedron Letters, Vol.31, No.24, pp 3445-3448, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

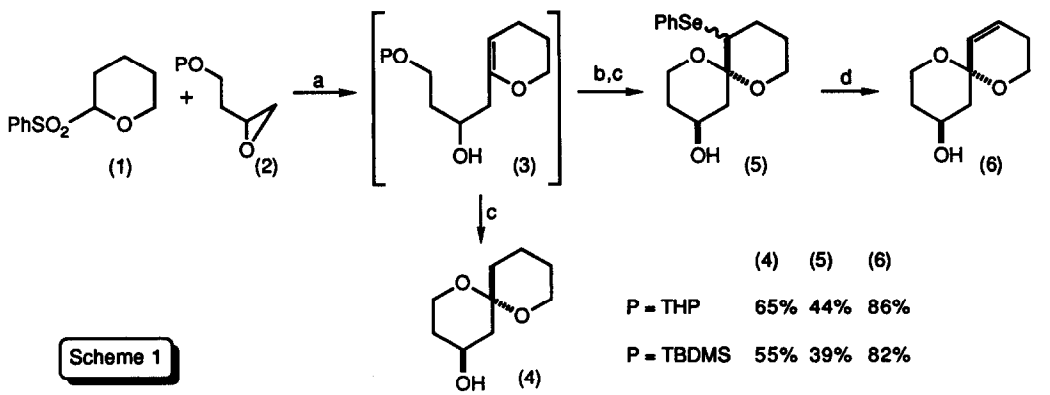
Synthesis of a C16-C28 Spiroacetal Fragment of Avermectin B_{1a} and Reassignment of Some ^{1}H and ^{13}C Resonances of Avermectin B_{1a}

David Diez-Martin, Peter Grice, Hartmuth C. Kolb, Steven V. Ley* and Andrew Madin

Department of Chemistry, Imperial College of Science Technology and Medicine, London SW7 2AY.

Abstract: A new method for the synthesis of unsaturated spiroacetals from 2-benzenesulphonyltetrahydropyrans is presented. ^{1}H and ^{13}C studies of one of these spiroacetals led to a reassignment of some ^{1}H and ^{13}C resonances of Avermectin B1a.

The spiroacetal functional group occurs in a wide variety of important natural products.[1] Whilst there are many methods for the synthesis of saturated spiroacetals,[1] unsaturated spiroacetals have received much less attention and few general methods[2] for their synthesis exist. Here we report an extension of methodology developed in these laboratories[3] to encompass the preparation of unsaturated spiroacetals. Previously, reaction of the anion of the sulphone (1) with epoxide (2) afforded an enol ether intermediate (3) which upon treatment with acid gave the saturated spiroacetal (4). We now show that the reactive enol ether (3) may be isolated and reacted with phenylselenenyl chloride, triethylamine and methanol[4] followed by treatment with acid to afford phenylselenenyl substituted spiroacetal (5) as a mixture of epimers. These upon oxidation and syn elimination[5] afford the unsaturated spiroacetal (6), Scheme 1.

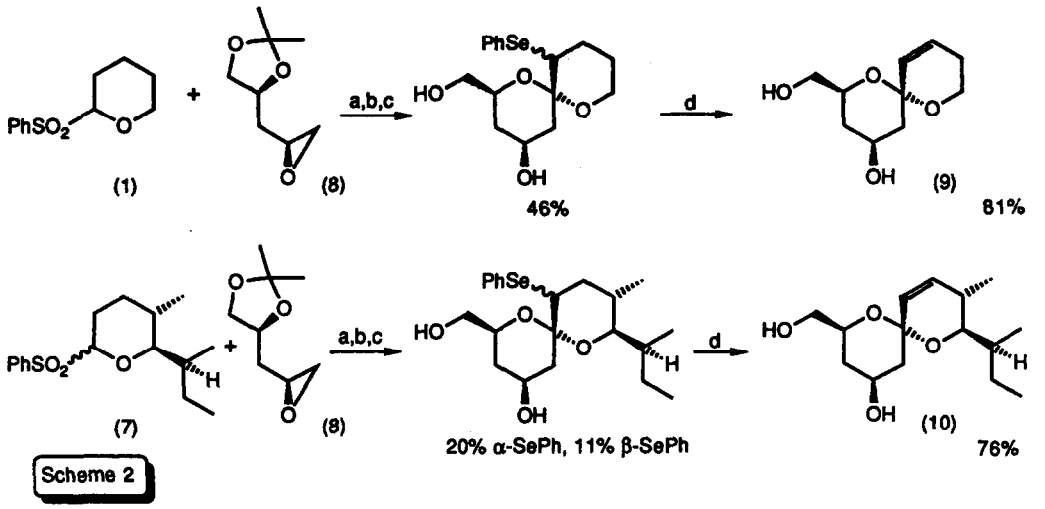


	(4)	(5)	(6)
P = THP	65%	44%	86%
P = TBDMS	55%	39%	82%

Scheme 1

a) 1. *n*-BuLi, THF, -78°C 2. epoxide b) PhSeCl, MeOH, Et_3N c) TsOH, MeOH d) *p*-nitrophenyl-N-sulphonyloxaziridine

Using this methodology sulphones (1) and (7)[6] were reacted with the protected epoxide (8) to afford the corresponding spiroacetals (9) and (10) respectively. Compound (10) is the spiroacetal portion of the potent antiparasitic agent Avermectin B1a, Scheme 2.

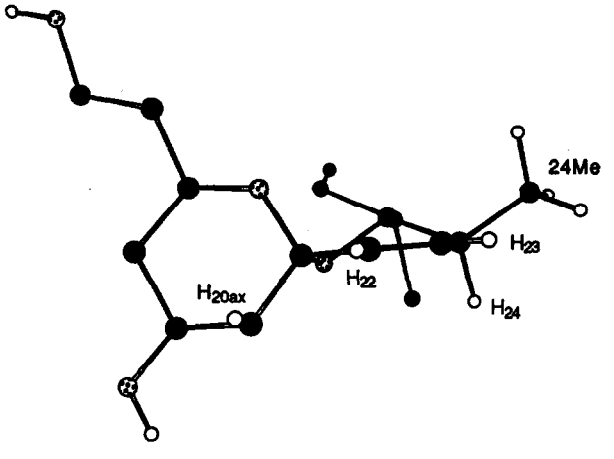


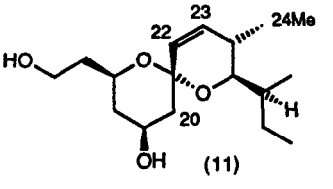
Scheme 2

a)1. *n*-BuLi, THF, -78°C 2. epoxide b) PhSeCl, MeOH, Et_3N c) TsOH, MeOH d) *p*-nitrophenyl-N-sulphonyloxaziridine

In order to prove the relative stereochemistry of the spiro carbon of (10) we undertook n.O.e. difference studies in which the olefinic resonances were irradiated. These results showed that the stereochemistry of the spiro carbon was as drawn and also allowed the olefinic resonances to be positively assigned. Comparison of these data with that published[7] for Avermectin B1a revealed that these resonances have been previously misassigned. Accordingly we have carried out an extensive ^1H and ^{13}C nmr study of spiroacetal fragment (11) and the aglycone of Avermectin B1a (12), (available in gram quantities by degradation of the natural product[8]) in addition to Avermectin B1a (13) itself. The n.O.e difference studies of (11), shown below in figure 1., revealed identical results to those on (10). Due to overlap of other olefinic signals only the signal at δ5.54 in aglycone (12) and B1a (13) could be cleanly irradiated. This gave rise to an enhancement of $H20_{ax}$, 3.0% in (12) and 3.1% in (13). This signal is thus assigned as H22.

Figure 1. Calculated structure (MM2) of (11) and result of n.O.e. difference studies.

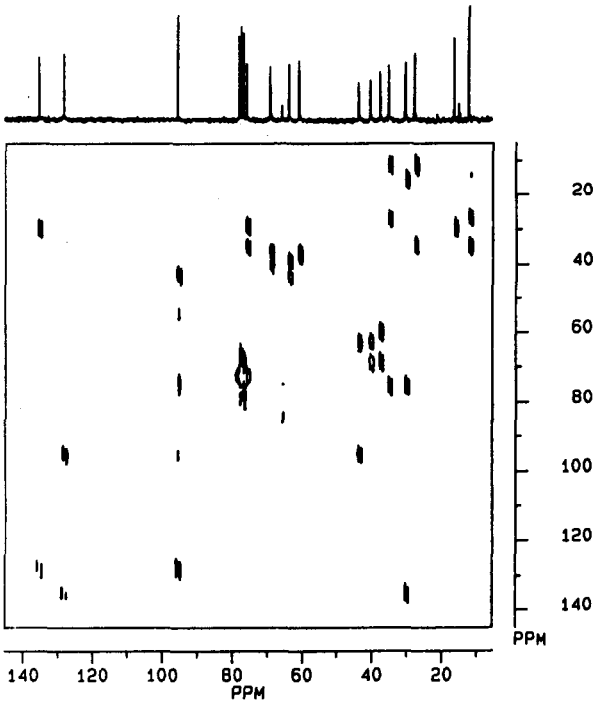


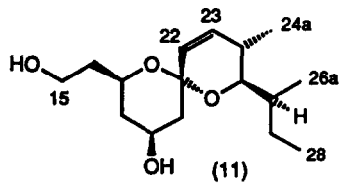


Irradiation.	Response.
H22, δ5.53 (dd, J = 9.8, 2.6Hz)	3.4% to $H20_{ax}$
H23, δ5.71 (dd, J = 9.8, 1.8Hz)	2.9% to H24 0.9% to 24Me

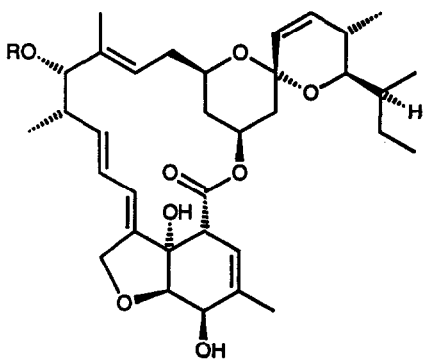
Heteronuclear correlation studies allowed complete assignment of (11) and partial assignment of aglycone (12) and B1a (13). These indicated that the published assignments[7] for C22 and C23 should be interchanged. To provide corroboration for the ^{13}C assignments of (11) and to positively assign quaternary carbons in (12) and (13) we have recorded 2D-INADEQUATE[9] spectra of (11) and (12), that for (11) is shown in figure 2. This allows unequivocal assignments of all carbons and is in agreement with results from n.O.e and heteronuclear correlation studies. The 2D-INADEQUATE of aglycone (12) confirmed the assignments of C22 and C23 derived from n.O.e and heteronuclear correlation data and also allowed positive assignment of quaternary carbons C4 and C14. A list of corrections to the published data are given in Table 1.

Figure 2. 2D-INADEQUATE and ^{13}C assignment of (11)





Carbon	shift, ppm
15	60.5
16	37.4
17	68.8
18	40.1
19	63.4
20	43.5
21	95.2
22	127.9
23	135.1
24	30.1
24a	16.2
25	75.5
26	35.0
26a	12.0
27	27.5
28	12.0



(12) R = H, Avermectin B1a aglycone

(13) R = oleandrosyl-oleandrose, Avermectin B1a

Table 1. Selected ^{1}H and ^{13}C assignments.

Resonance	Spiroacetal (10)	Fragment (11)	Aglycone (12)	B1a (13)
H22	5.56 J=9.9, 2.6 Hz	5.53 J=9.8, 2.6 Hz	5.54 J=9.8, 2.6 Hz	5.54 J=9.9, 2.6 Hz
H23	5.75 J=9.9, 1.8 Hz	5.71 J=9.8, 1.8 Hz	5.76 J=9.8, 1.6 Hz	5.75 J=9.9, 1.8 Hz
C22	128.8	127.9	127.7	127.7
C23	135.6	135.1	136.0	136.3
C4	—	—	137.4	135.1[10]
C14	—	—	138.6	137.8[10]

Molecular mechanics calculations[11] on (11) revealed a rationalisation for the observed coupling constants $J_{23,24}$ and $J_{22,24}$. A fragment derived from the x-ray structure of B1a[12] was used as starting geometry. This rapidly minimised with little change. The calculated structure is shown in figure 1. The calculated H23-C23-C24-H24 dihedral angle of 83° correlates well with the observed $J_{23,24}$ (vicinal) coupling of 1.8 Hz,[13] furthermore, the angle between the mean plane of the 22-23 double bond and the C24-H24 bond of 84° is in excellent agreement with the observed $J_{22,24}$ (allylic) coupling of 2.6 Hz.[14]

Acknowledgements.

Financial support from SERC (AM), Merck Sharp and Dohme, Synlab Organics (PG), British Council (DDM) and Schering Agrochemicals (HCK) is gratefully acknowledged. We thank Dick Sheppard for n.O.e. studies.

References and Notes.

1. Kluge, A.F. *Heterocycles*, **1986**, *26*, 1699.
2. Crimmins, M.T.; O'Mahoney, R. *Tetrahedron Lett.*, **1989**, *30*, 5993. DeShong, P.; Waltermire, R.E.; Ammon H.L. *J. Am. Chem. Soc.*, **1988**, *110*, 1901. Hirama, M.; Nakamine, T.; Itô, S. *Tetrahedron Lett.*, **1988**, *29*, 1197. Danishefsky, S.J.; Wincott F.E. *Tetrahedron Lett.*, **1987**, *28*, 4951. Whitby, R.; Kocienski, P. *Tetrahedron Lett.*, **1987**, *28*, 3619. Baker, R.; Head, J.C.; Swain, C.J. *J. Chem. Soc., Chem. Commun.*, **1985**, 309. Hanessian, S.; Ugolini, A.; Therien M. *J. Org. Chem.*, **1983**, *48*, 4427. Williams, D.R.; Barner, B.A.; Nishitani, K.; Phillips, J.G. *J. Am. Chem. Soc.*, **1982**, *104*, 4708.
3. Greck, C.; Grice, P.; Ley, S.V.; Wonnacott, A. *Tetrahedron Lett.*, **1986**, *27*, 5277.
4. Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Org. Chem.*, **1984**, *49*, 3517.
5. Davis, F.A.; Sheppard, A.S. *Tetrahedron* , **1989**, *45*, 5703.
6. The synthesis of sulphone (7) in homochiral form and the successful application of this methodology to the total synthesis of avermectin B1a will be reported elswhere.
7. Albers-Schönberg, G.; Arison, B.H.; Chabala, J.C.; Douglas, A.W.; Eskola, P.; Lusi, A.; Mrozik, H.; Smith, J.L.; Tolman R.L. *J. Am. Chem. Soc.*, **1981**, *103*, 4216.
8. Carried out by M.J. Ford using a modification of the procedure of Hanessian. S.; Ugolini, A.; Hodges, P.J.; Dubé D. *Tetrahedron Lett.*, **1986**, *27*, 2699.
9. Recorded on a Bruker AM-200 using the INADSYM.AUR micro programme to give a cosy-like symmetry representation. Turner, D.L. *J. Magn. Res.*, **1982**, *49*, 175. Mareci, T.H.; Freeman R. *J. Magn. Res.*, **1982**, *49*, 158.
10. These signals assigned by analogy with the aglycone (12) ie. C4 higher field than C14.
11. Using the programme Macromodel v2.5, W.C. Still, Columbia University, New York.
12. Springer, J.P.; Arison, B.H.; Hirshfield, J.M.; Hoogsteen K. *J. Am. Chem. Soc.*, **1981**, *103*, 4221.
13. Karplus, M. *J. Chem. Phys.*, **1960**, *33*, 1842.
14. Garbisch, E.W. *J. Am. Chem. Soc.*, **1964**, *86*, 5561.

(Received in UK 29 March 1990)