Tetrahedron Letters, Vol 32, No 32, pp 4049-4050, 1991
Printed in Great Britain

0040-4039/91 $3.00 + 0
Pergamon Press plc

HIGHLY STEREOSELECTIVE SYN-HYDROXYLATION OF SPIROKETALS

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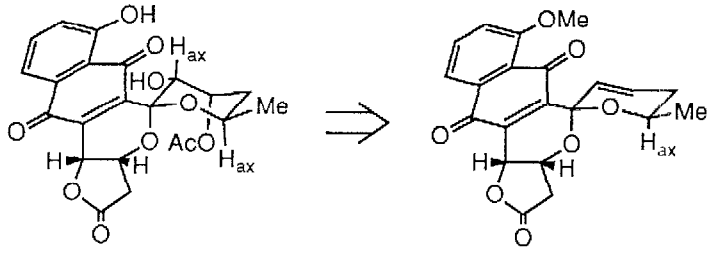
Summary: The highly stereoselective *syn*-hydroxylation of unsaturated spiroketals (**3**,**5**) is reported.

Griseusin A (**1**)[1], a pyranonaphthoquinone antibiotic, is structurally unique compared to simpler members of the family due to the presence of the highly oxygenated 1,7-dioxaspiro[5.5]undecane ring system. We envisaged a key step in our synthetic route[2] to griseusin A to involve functionalisation of an unsaturated spiroketal (**2**) (Scheme). Towards this end, we examined the stereochemical outcome of the *syn*-hydroxylation of a series of model unsaturated spiroketals (**3**,**5**) and herein report our results (Table).



Griseusin A (**1**) **Scheme** (**2**)

Using a catalytic amount of osmium tetraoxide and *N*-methylmorpholine-*N*-oxide (NMO)[3] in aqueous acetone at room temperature for 16 h., the spiroketals (**3**)[4] underwent smooth hydroxylation to the *syn*-diols (**4**)[5]. In all cases, hydroxylation occurred from the β-face giving the diols (**4**) in which the hydroxyl group at C-5 was axial and *anti* to the C-O bond of the neighouring tetrahydropyran ring.[6] Despite the fact that this was the opposite stereochemistry to that required for the synthesis of griseusin A, no evidence for formation of other diastereomeric diols was observed.[7] Whilst the addition of other electrophiles such as peracids and *t*-butyl hypochlorite to related 1,7-dioxaspiro[5 5]undec-4-enes[8] is much less stereoselective, the preferred site of attack was the same as that observed in the present case for osmylation.

Conversion of the spiroketal diols (**4**) into open chain derivatives may provide access to compounds of known relative configuration [9] Thus, osmylation of the more functionalised equatorial allylic acetates (**5**)[4] was effected providing the diols (**6**) in moderate yield. These latter examples yield highly oxygenated spiroketals with the potential to provide acyclic derivatives of predetermined relative stereochemistry for use in complex natural products synthesis

Diols (**4**) underwent selective monoacetylation on the least hindered hydroxyl group at C-4 affording acetates (**7**) in high yield. This latter reaction provides the opportunity for further manipulation of the diol functionality either before or after the ring opening reaction.

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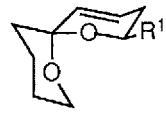
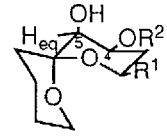
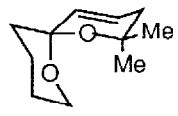
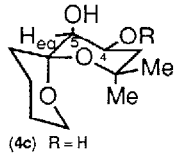
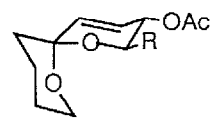
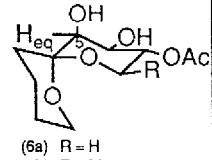
Table

Alkene	Diol	Yield (%)	M.p. (^{0}C)
 (3a) R^1 = H (3b) R^1 = Me	 (4a) R^1 = H, R^2 = H (4b) R^1 = Me, R^2 = H	(4a) 78% (4b) 80% (7a) 89% (7b) 91%	(4a) 124-125^{0}C (7a) 111-113^{0}C (R^1=H, R^2 = Ac) (4b) oil (7b) · 129-130^{0}C (R^1= Me, R^2 = Ac)
 (3c)	 (4c) R = H	(4c) 73% (7c) 88%	(4c) 94-96^{0}C (7c) oil, (R = Ac)
 (5a) R = H (5b) R = Me	 (6a) R = H (6b) R = Me	(6a) 59% (6b) 61%	(6a) 145-146^{0}C (6b) . oil

References and Notes

1. N. Tsuji, M. Kobayashi, Y. Wakisaka, Y. Kawamura, M. Mayama and K. Matsumoto, *J. Antibiot.*, 1976, **29**, 7
2. M.A. Brimble and M.R. Nairn, *J Chem Soc. Perkin Trans. I*, 1990, 169.
3. V. Van Rheenen, R C. Kelly and D Y. Cha, *Tetrahedron Lett.*, 1976, 1973.
4. M A. Brimble, M K. Edmonds and G.M. Williams, *Tetrahedron Lett*, 1990, **31**, 7509.
5. All new compounds gave satisfactory spectroscopic and analytical data.
6. This is consistent with the model proposed by Kishi for allylic alcohols see: J.K Cha, W.J Christ and Y Kishi, *Tetrahedron Lett.*, 1983, **24**, 3943.
7. Whilst no examples of *syn*-hydroxylation of spiroketals have been reported, a highly stereoselective osmylation of an unsaturated acetal was published during the course of this work see: E.A. Mash, J B Arterburn, J.A. Fryling and S.H Mitchell, *J Org Chem*, 1991, **56**, 1088.
8. R Baker, J.C. Head and C J. Swain, *J. Chem. Soc, Perkin Trans I*, 1988, 85.
9. Spiroketals have been converted to their open-chain derivatives see: F. Perron and K.F Albizati, *Chem. Rev.*,1989, **89**, 1617.

(Received in UK 10 May 1991)