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ALLYLIC OXIDATION OF UNSATURATED SPIROKETALS.

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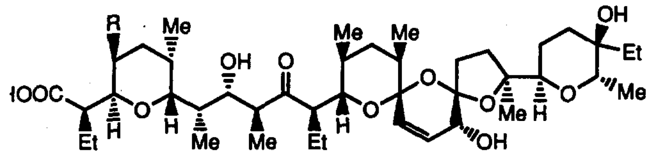
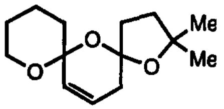
Abstract: Allylic bromination of the bicyclic spiroketals (4a-c) gave predominantly the axial bromides (6), (9) and (12) which underwent S_N2 displacement to the equatorial alcohols (7), (11) and (14) respectively using KO_2/18-crown-6 in THF/DMSO (10:1).

Numerous synthetic strategies have been reported to construct spiroketals[1] due to their presence as a structural feature in a multitude of biologically active naturally occurring metabolites. In contrast synthetic transformations on intact spiroketals has attracted less attention. As part of our program directed torward the synthesis of the bis-spiroketal containing antibiotics salinomycin (1) and narasin A (2) we have reported[2] a synthesis of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (3). In order to extend this methodology to the synthesis of these antibiotics a mild method for introduction of an hydroxyl group at the allylic position of unsaturated spiroketals was required.

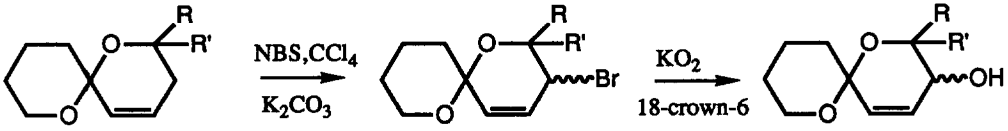


salinomycin (1) : R=H
narasin A (2) : R=Me



(3)

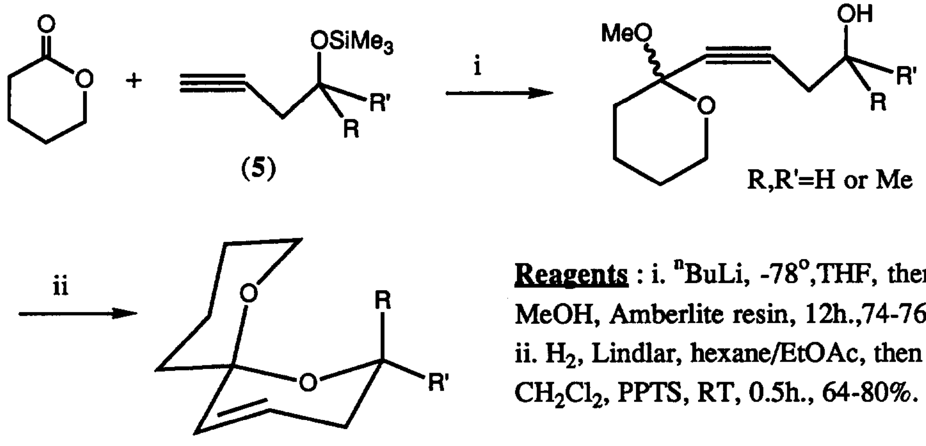
Whilst Deslongchamps *et al.*[3] have successfully used the classical reagent, selenium dioxide, to oxidise the allylic position of a bicyclic spiroketal, this reagent proved ineffective for the tricyclic compound (3) due to the lability of the bis-spiro ring. Similarly an alternative strategy[4-7] to synthesise unsaturated spiroketals bearing a carbonyl group at the allylic position utilising the oxidative rearrangement of a 2-furyl ketone gave the wrong stereochemistry upon reduction to the alcohol. In view of the numerous methods available to construct unsaturated spiroketals, a method to introduce an allylic hydroxyl substituent indirectly *via* allylic bromination was investigated (Scheme 1).



(4) R,R' = H or Me

Scheme 1

In order to investigate the feasibility of the indirect allylic oxidation, a series of bicyclic unsaturated spiroketals (4) was prepared *via* addition of the appropriate acetylene (5) to δ-valerolactone (Scheme 2)



(5)

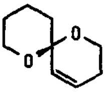
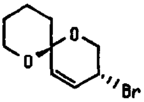
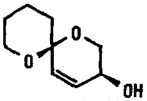
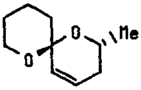
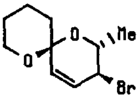
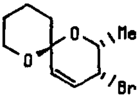
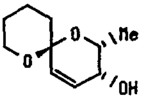
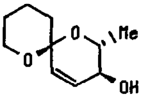
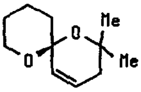
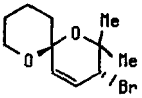
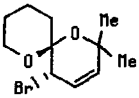
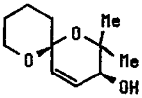
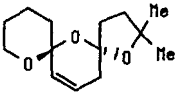
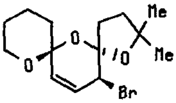
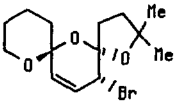
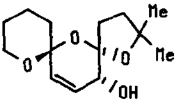
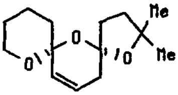
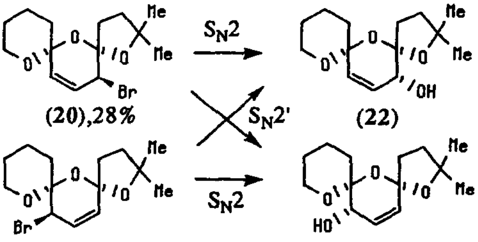
(4)

Reagents : i. ^{n}BuLi, -78°,THF, then MeOH, Amberlite resin, 12h.,74-76%; ii. H_2, Lindlar, hexane/EtOAc, then CH_2Cl_2, PPTS, RT, 0.5h., 64-80%.

Scheme 2

Treatment of the unsubstituted spiroketal (**4a**) with N-bromosuccinimide (1 equiv) in carbon tetrachloride in the presence of K_2CO_3 gave the axial bromide (**6**) (54%) after heating under reflux for 3h. A minor component of the reaction mixture was also isolated and proved to be an inseparable mixture of the equatorial bromide and the diene byproduct. The axial bromide underwent S_N2 displacement to the equatorial alcohol (**7**) upon treatment with KO_2 (4 equiv) and 18-crown-6 (1 equiv) in THF/DMSO (10:1) at room temperature for 16 h.

The monomethyl spiroketal (**4b**) similarly underwent allylic bromination to the equatorial (**8**) and axial (**9**) bromides in 25% and 51% yields respectively after purification by flash chromatography. Individual treatment of the isomeric bromides (**8**), (**9**) with KO_2/18-crown-6 gave the appropriate alcohols (**10**), (**11**) arising from S_N2 displacement.

 (4a)	 (6),54%	 (7),84%
 (4b)	 (8),25%  (9),51%	 (10),87%  (11),85%
 (4c)	 (12),48%  (13),24%	 (14),87% —
 (15)	 (17),30%  (18),28%	 (19) —
 (16)	 (20),28% (21),37% 	(22) (23)

In the case of the dimethyl spiroketal (**4c**), bromination afforded the axial bromide (**12**) (48%) together with the rearranged bromide (**13**) (24%). Whereas bromide (**12**) underwent facile displacement with KO_2 to the alcohol (**14**), the minor product (**13**) yielded only recovered starting material after 3 days.

Extension of this work to the tricyclic bis-spiroketals (**15**)[2] and (**16**) provided interesting results. The *trans* isomer (**15**) gave a 1:1 mixture of the two isomeric bromides (**17**) and (**18**) but only one isomer (**17**) underwent displacement with KO_2 to the corresponding alcohol (**19**)[8]. The *cis* isomer (**16**) afforded the minor axial bromide (**20**) (28%) along with the rearranged major bromide (**21**) (37%) upon reaction with NBS. In this case both bromides (**20**) and (**21**) when individually treated with KO_2/18-crown-6 gave a 1:1 mixture of the alcohols (**22**) and (**23**) indicating that both S_N2 and S_N2' displacement had occurred. Alcohol (**22**) has the same stereochemistry as that present in salinomycin (**1**) and narasin A (**2**).

References and Notes

1. For reviews on the chemistry of spiroketals see :
   (a) F. Perron and K.F. Albizati, *Chem. Rev.*,1989, **89**, 1617. (b) T.L.B. Boivin, *Tetrahedron*, 1987, **43**, 3309. (c) A.F. Kluge, *Heterocycles*, 1986, **24**,1699.

2. R. Baker and M.A. Brimble, *J. Chem. Soc. Perkin. Trans. I*, 1988, 125.

3. B. Bernet, P.M. Bishop, M. Caron, T. Kawamata, B. L. Roy, L. Ruest, G. Sauve, P. Soucy and P. Deslongchamps, *Can. J. Chem.*, 1985, **63**, 2810.

4. P. Deshong, R. E. Waltermire and H. L. Ammon, *J. Am. Chem. Soc.*, 1988, **110**, 1901.

5. P. Kocienski, Y. Fall and R. Whitby, *J. Chem. Soc. Perkin Trans. I*, 1989, 841.

6. F. Perron and K. F. Albizati, *J. Org. Chem.* 1989, **54**, 2044.

7. The earlier assignment by Albizati and Perron[6] of the major product of this reduction as alcohol (**22**) has now been shown to be incorrect by comparison of their nmr data with that obtained by Kocienski *et al.* and ourselves.

8. Nmr data for alcohols (**19**) and (**22**) is in agreement with that reported by Kocienski *et al.*[5] We thank Professor Kocienski for kindly providing nmr spectra for compounds (**19**) and (**22**) and their isomers.

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