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MODEL STUDIES DIRECTED TOWARD THE AVERMECTINS: A ROUTE TO THE SPIROKETAL SUBUNIT

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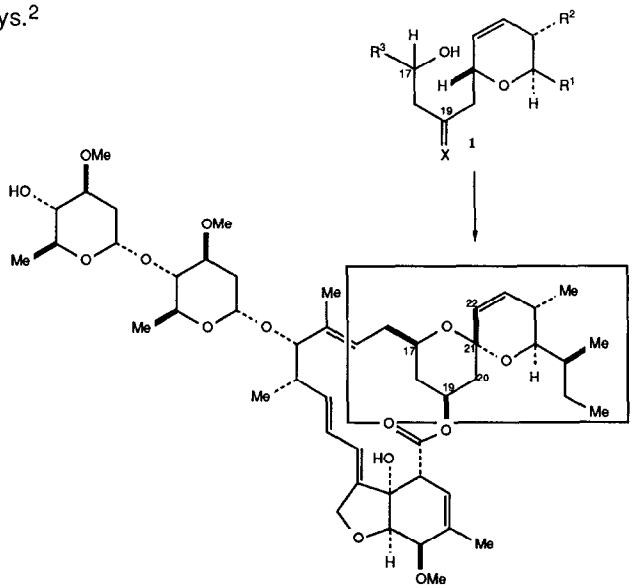
Abstract: Oxidative cyclization of a dihydropyran bearing a pendant alcohol is used to synthesize a spiroketal system of the type found in the avermectins.

The realization of a total synthesis of a naturally occurring avermectin[1] (see avermectin A_{1a}) requires coordinated solutions to several component problems. Among the regional issues to be approached is that of the spiroketal (see enclosed area). This subject has been addressed in a variety of ways.[2]

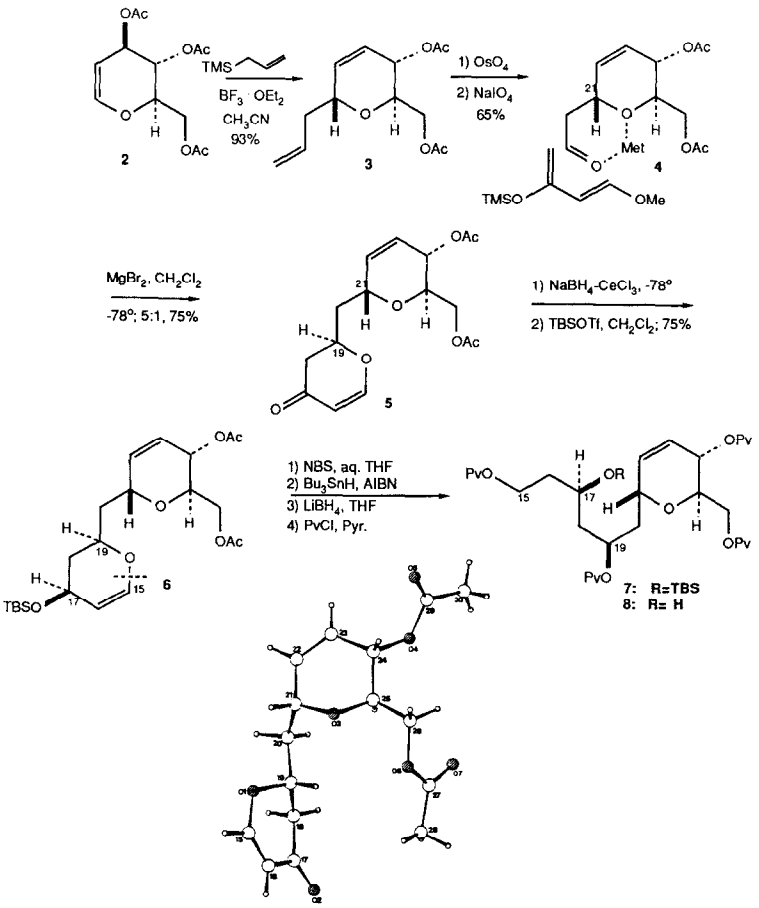


Avermectin A_{1a}

For a scheme to be useful in terms of the larger objective, the required antipode should be reached without recourse to resolution. To be well targeted toward avermectin A_{1a}, the route should make smooth provision for the C_{22}-C_{23} olefin.[3] *As a matter of esthetic preference, we sought to include in our plan the feature that the required stereochemical relationships would be established by communication from a single precursor of appropriate chirality rather than by batching of two or more coordinated chiral subunits.*[4] An emphasis on maximal stereochemical communication would tend to disfavor strategies which depend on attack by a carbon nucleophile on a C_{21} acyl (cf. lactone) moiety. Such routes would presumably entail recourse to two chiral subunits to correlate the stereochemistry at carbons 19 and 17 with that at carbons 24-26.[5] Below is presented an

approach which utilizes a single chiral precursor in the construction of the spiroketal. A precursor of the type **1** was synthesized. The stereochemistry of D-glucose was communicated to C_{19} which, in turn, dictated the outcome at C_{17}.

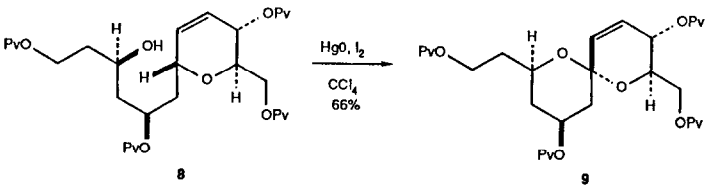
The reaction of D-glucal triacetate (**2**) with allyltrimethylsilane, as previously described,[6] afforded the C-glycoside, **3**. Osmylation followed by periodate cleavage provided an aldehyde which underwent cyclocondensation with trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene under the influence of anhydrous $MgBr_2$. A 75% yield of a 5:1 ratio of dihydropyrone **5** and its C_{19} epimer was obtained. It was hoped and expected that the major product would be the one arising from a chelation-controlled conformer (see structure **4**). Reaction of such a species with the diene, syn to the C_{21} hydrogen (i.e., anti to that face of the aldehyde which contains the dihydropyran ring), would give the desired outcome. While the rationale for the outcome can be debated, the result itself is established by an X-ray crystallographic determination of a sample (mp 93-94°C) of the major pyrone (see ORTEP of structure **5**).[7]



ORTEP of 5

Reduction under standard Luche conditions[9] cleanly afforded the equatorial alcohol, protected as its tert-butyldimethylsilyl ether, **6**. A four step sequence described above served to generate the silyl ether tetra-pivalate, **7**, and thence, by deprotection with Bu_4NF, the alcohol, **8**. The overall yield for the series of five steps is only 25%,[8] but it did allow for the opportunity to test the critical oxidative cyclization reaction.

While reactions of the type **8** → **9** were known in simple substrates,[10] the process had never been tested in the context of a proximal double bond and in the presence of potentially competing functionalities. In the event, compound **8** underwent smooth conversion to **9** under the action of mercuric oxide and iodine. Only one spirocyclization isomer is observed. Whether this is the only kinetic product produced, or is the consequence of rapid thermodynamic equilibration, has not been determined.



8 **9**

Thus the allylic character of the C_{21} methinyl carbon seems to be not only consistent with a successful ring closure, but apparently has a favorable effect. Oxidative cyclization of strategically functionalized dihydropyrans, bearing a strategically placed, pendant hydroxyl group, is a crucial element in our fully synthetic route to avermectin A_{1a}.

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2. For previous syntheses of milbemycin and avermectin spiroketals, cf. interalia (a) Smith, A.B.; Schow, S.R.; Bloom, J.D.; Thompson, A.S.; Winzenburg, K.N. *J. Am. Chem. Soc. 104*, 4015, (1982). (b) Street, D. A.; Kocienski, P.; Campbell, S.F. *J. Chem. Soc., Chem. Comm.* 1326 (1985). (c) Baker, R.; Boyes, R.H.O.; Broom, D.M.P.; Devlin, J. A.; Swain, C.J. *ibid.* 829 (1983). (d) Baker, R.; Swain, C.J.; Head, J.C. *ibid.* 309 (1985). (e) Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem. 48,* 4427 (1983). (f) Culshaw, D.; Grice, P.; Ley, S.V.; Strange, G.A. Tetrahedron Lett. 26, 5837 (1985). (g) Williams, D.R.; Barner, B.A.; Nishitani, K.; Phillips, J.G. *J. Am. Chem. Soc. 104*, 4708 (1982). (h) Ardisson, J.; Ferezou, J.P.; Julia, M.; Lenglet, L.; Pancrazi, A. *Tetrahedron Lett. 28,* 1997 (1987). (i) Attwood, S.V.; Barrett, A.G.M.; Carr, R.A.E.; Richardson, G. *J. Chem. Soc, Chem. Comm.* 479 (1986).

3. The carbon numbering system anticipates the eventual construction of avermectin A_{1a}.

4. For a discussion of this distinction see: Danishefsky, S.J. *Aldrichimica Acta 19*, 59 (1986).

5. For previous examples of this type of approach see reference 2, (a)-(g).

6. Danishefsky, S.J.; Kerwin, J.F., Jr. *J. Org Chem. 47*, 3803 (1982).

7. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated diffractometer using graphite monochromated MoKα radiation. All data processing was done on a departmental Digital Equipment Corp. VAX 11/750, using the Enraf-Nonius SDP-PLUS programs. The programs URANUS and SKK-PUB, plot and tables programs, respectively, were written by Simon Kay Kearsley, Yale University, 1985.

8. While the hydroxybromination, debromination proceeded in very good yield, the highly polar tetra-ol could not be reclaimed satisfactorily. These yields, however, were not optimized.

9. Luche, J.L. and Gemal, A.L *J. Am. Chem. Soc. 101*, 5848 (1979).

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