Tetrahedron Letters,Vol.28,No.42,pp 4955-4958,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

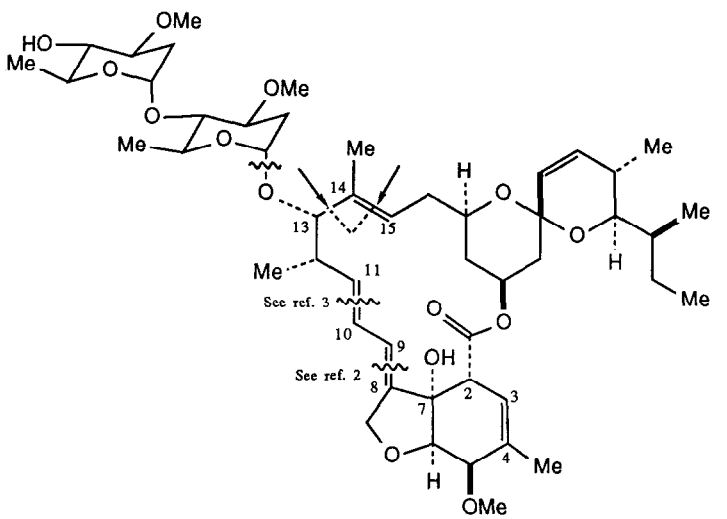
A NOVEL DEGRADATION IN THE AVERMECTIN SERIES: A STEREOSPECIFIC OSMYLATION REACTION

Harold G. Selnick and Samuel J. Danishefsky*
Department of Chemistry, Yale University, New Haven, Connecticut 06511

Abstract: The reaction of osmium tetroxide on a Δ^2 (conjugated) isomer of avermectin aglycone, bearing a free hydroxyl group at C_{13} occurs with high regio and facial selectivity.

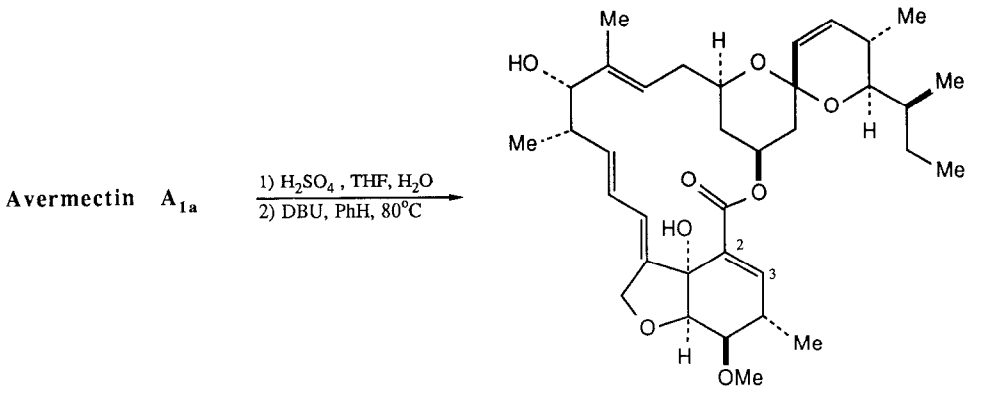
The goal of a total synthesis of a naturally occurring avermectin (cf. avermectin A_{1a}, **1**) becomes more manageable if progress at crucial stages of the program can be monitored by comparisons with degradation products.[1] Moreover, systems derived in this way can be used to test the feasibility of contemplated steps in the advanced stages of a synthesis. Furthermore, as elegantly demonstrated by Smith,[2] the sequence of degradation and synthesis can be used to construct "hybrids" which are useful in probing the effects of structural variations on biological activity.

Smith had exploited a free hydroxyl group at C_7 to direct epoxidation to the C_8-C_9 double bond, thereby achieving degradation of that linkage. In the course of studies which established the basis for a fully synthetic route to the avermectins, Hanessian demonstrated that several seco-acid derivatives, bearing conjugated (i.e., C_2-C_3) double bonds, undergo ozonolysis at C_{10}-C_{11} with good selectivity.[3] For reasons of strategy, our goal was to effect cleavage at the C_{14}-C_{15} double bond and the C_{13}-C_{14} σ-bond (see cleavage points in **1**).



1

The oleandrosyl groups of **1** were detached through acidic treatment.[1] Conjugation of the double bond was smoothly accomplished through the action of D.B.U. In this fashion the "conjugated" aglycone **2** was obtained (93%). Previous methods for conjugation[1,3] had also resulted in opening of the macrolactone.

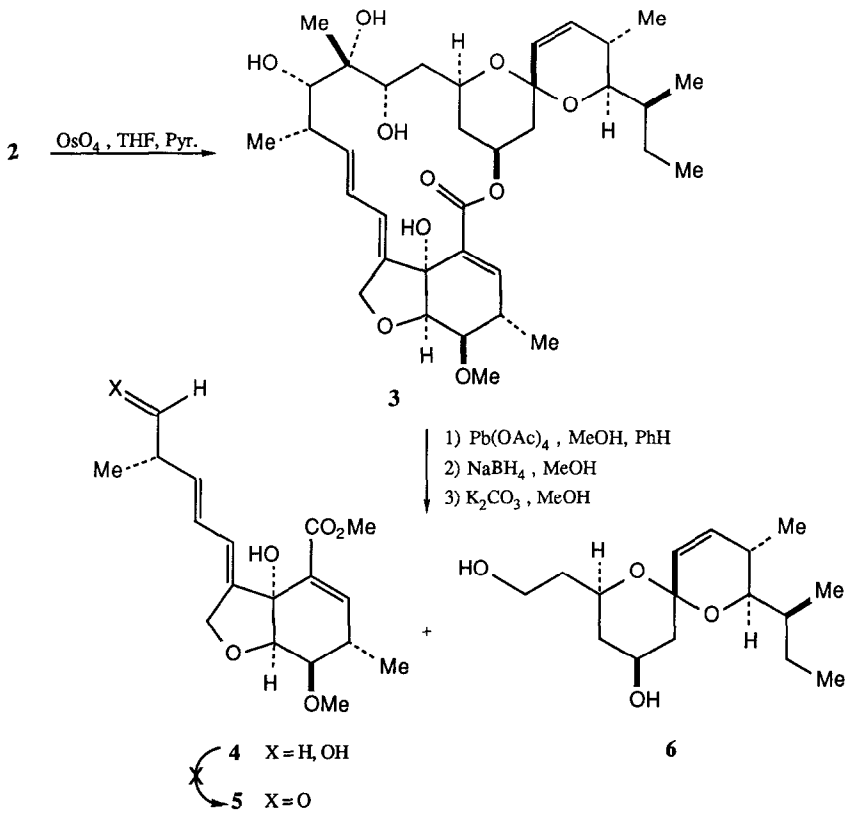


2

Reaction of **2**[4] with osmium tetroxide[5,6] followed by workup with sodium bisulfite afforded a 78% yield of the tetraol, **3**, as a single facial isomer. Examination of the stereo structure arising from a crystallographic determination[7] of avermectin B_{2a}, wherein the double bond in the cyclohexeno ring is in its natural Δ^1 position, provides a clue for this apparent stereospecificity. The conformation of the macrolactone is such that the carbon-oxygen bond of the C_{13} alcohol is s-cis to the C_{14}-C_{15} double bond. Attack on the β-face would corresond to approach of the external reagent from the inside of the macrocyclic array. Such an attack trajectory, were it to occur in the preferred ground state conformation,[7] would encounter serious interference from the C_{17}-C_{18} sector of the spiroketal lattice. Accordingly, the tetraol is formulated as shown in **3.**

Cleavage of the triol with excision of C_{14} was accomplished through the action of lead tetraacetate. The secodialdehyde thus generated could be characterized spectroscopically, but in the usual case was immediately reduced with sodium borohydride. Cleavage of the ester linkage with potassium carbonate-methanol afforded diols **4** (83%) and **6** (60%).

With a view to utilizing **4** in a projected reconstruction, we attempted the oxidation of the homoallylic alcohol to the β,γ-unsaturated aldehyde **5.** We emphasize that a variety of attempts to achieve such a transformation[8] led to complex mixtures from which the desired **5** was never obtained. Indeed, a total synthesis of **4** has been accomplished,[9] but it has, in our hands, never proven to be a useful intermediate. However, compound **6** has proven to be amenable to useful development in a total synthesis of avermectin A_{1a}.[10]



Acknowledgments: This research was supported by PHS Grant AI 16943. A PHS Postdoctoral Fellowship (Grant 5 F32 GM10576) to H. G. S. is gratefully acknowledged. NMR spectra were obtained through the auspices of The Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. In addition, we thank The Merck Company (Rahway, New Jersey) for its generous support of our efforts.

References

1. Fisher, M.H.; Mrozik, H. "Macrolide Antibiotics," Academic Press: New York, NY., **1984**; p. 553.
2. (a) Smith, A.B.; Thompson, A.S. *Tetrahedron Lett. 26*, 4279 (1985). (b) Smith, A.B.; Thompson, A.S. *ibid.*, 4283.
3. (a) Hanessian, S.; Ugolini, A.; Hodges, P.J.; Dube, D.; *Tetrahedron Lett. 27,* 2699 (1986). (b) Hanessian, S.; Ugolini, A.; Hodges, P.J.; Dube, D.; Andre, C. *J. Am. Chem. Soc. 108*, 2776 (1986). (c) Hanessian, S.; Ugolini, A.; Hodges, P.J.; Beaulieu, P.; Dube, D.; Andre, C. *Pure and Applied Chemistry 59,* 299 (1987).
4. In the reaction of OsO_4 with avermectin A_{1a} aglycon before conjugation, osmylation at C_3-C_4 became competitive with osmylation at C_{14}-C_{15}.
5. The osmylation could be carried out with either stoichiometric or catalytic[6] OsO_4.
6. Van Rheenen, V.; Kelly, R.C.; Cha, D.Y. *Tetrahedron Lett 23* , 1973 (1976).
7. Springer, J.P.; Arison, B.H.; Hirshfield, J.M.; Hoogsteen, K. *J. Am. Chem. Soc., 103*, 4221 (1981).
8. Analogous reactions on protected versions of the C_7 alcohol were equally unsuccessful.
9. D.M. Armistead, unpublished results, Yale University.
10. F.E. Wincott, unpublished results, Yale University

(Received in USA 16 June 1987)