of **31** to **33** is ca. 70–80%. The aglycon **33** is identical with an authentic sample obtained by acidic treatment of avermectin $A_{1a}$ by spectroscopic (500-MHz NMR) and chromatographic comparisons. The conversion of aglycon **33** to avermectin $A_{1a}$ itself is described in the communication which follows.

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## The Total Synthesis of Avermectin $A_{1a}$. New Protocols for the Synthesis of Novel 2-Deoxypyranose Systems and Their Axial Glycosides

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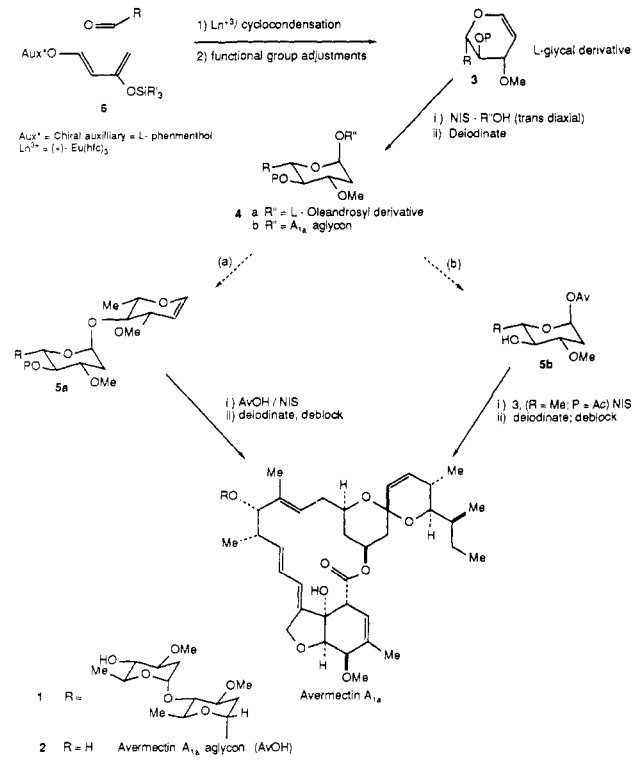
The elucidation of the structure activity of the antiparasitic avermectins and semisynthetic congeners (cf. ivermectins) presents significant challenges and opportunities for medicinal science.[1,2] Adding to the formidability of the problem is the fact that seemingly subtle structural perturbations in the aglycon (particularly in the environs of the oxahydrindene moiety or at $C_{13}$) and in the carbohydrate sectors occasion significant changes in biological activity.

Having established a fully synthetic route to aglycon **2**,[3] we undertook the total synthesis of avermectin $A_{1a}$ (**1**) itself[4] (Scheme I). Our goals in this enterprise were several. We sought to synthesize the L-oleandrose residues, required for avermectin, by chemistry developed as part of our interests in the larger field of polyoxygenated natural products.[5] In so doing we could perhaps provide straightforward routes to a variety of artificial L-sugar analgoues, the availability of such compounds could help to elucidate the structure-activity consequences of deep seated modifications in the carbohydrate area of the avermectins. Another subgoal, which would serve both total synthesis and medicinal chemistry ends, was the development of a capability to synthesize $\alpha$ (axial) glycosides of these novel L-sugars. Incuded in this objective would be disaccharides of the L-oleandrosyl-L-oleandrose types (see structures **4a** and **5a**) and "avermectinyl" glycosides (see structures **4b** and **5b**).

Below we describe the total synthesis of avermectin $A_{1a}$. This target was reached in a manner such that major progress was registered on the broader issues identified above. Two variations of the overall protocol set forth below have been reduced to practice. Through the chemistry developed in conjunction with the Lewis acid catalyzed diene–aldehyde cyclocondensation reaction, a properly chosen chiral auxiliary in conjunction with a properly chosen chiral catalyst (oxidative) can lead directly to a 2,3-dihydropyrone of the L- (or D-)pyranose series.[6] This chemistry permits wide variation in the nature of the $C_6$ substituent. Functional group adjustments of a type previously described[7] can lead to an L-glycal derivative (cf. **3**). A central element of the application described herein is that reaction of the glycal with *N*-iodosuccinimide in the presence of R″OH (including situations where R″OH corresponds to a complex alcohol) leads to the establishment of a glycosidic bond with high axial fidelity.[8] Deiodination leads to system **4**. In permutation a, the R″OH which reacted with **3** itself corresponds to an oleandrosyl residue. In this circumstance a glycal linkage must be unveiled in the pyranose of the original R″OH residue (see **4a** → **5a**). The disaccharide glycal **5a** is joined to avermectin aglycon, AvOH (**2**) via the action of *N*-iodosuccinimide, again with high trans diaxial selectivity.[8] Alternatively (permutation b), R″OH corresponds to AvOH. After reductive deiodination ($n$-$Bu_3SnH$) cf. **4b**, the protecting group P is removed, leading to **5b**. Another cycle, starting with iodoglycosylation of **5b** via **3** in a trans diaxial fashion produced shortly thereafter avermectin $A_{1a}$.

**Scheme I**




The previously described L-dihydropyrone **7**, derived from diene **6** and acetaldehyde followed by oxidation with $Mn(OAc)_3$,[7,9] was reduced with sodium borohydride in the presence of $CeCl_3$ (87%). Methylation of the resultant glycal was smoothly accomplished ($Ag_2O$–MeI, 91%) to afford **8**, which upon hydrolysis ($K_2CO_3$–MeOH, 96%) gave the hydroxy compound **9**. The L-methyl oleandrosides (2:1) anomeric mixture of $\alpha$ and $\beta$ compounds were obtained through the standard sequence of methoxybromination (NBS–methanol) followed by debromination ($n$-$Bu_3SnH$, 95% overall yield). Both anomers of methyl glycoside **10** were carried forward. The results with the axial glycoside are shown here. Reaction of **9** with NIS and **10** gave a 66% yield of **11**. The presence of the 2′ iodo linkage in this compound helped provide high regioselectivity to the Hanessian reaction ($Me_3SiSPh$;

(1) Fisher, M. H.; Mrozik, H. *Macrolide Antibiotics*; Academic Press: New York, 1984; p 553.
(2) Fisher, M. H. *Recent Advances in the Chemistry of Insect Controls*; Burlington House: London, 1985; p 53.
(3) Danishefsky, S. J.; Armistead, D. M.; Selnick, H. G.; Wincott, F. E.; Hungate, R., previous paper in this issue.
(4) For previous work on the attachment of the disaccharide unit, see: (a) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. *J. Am. Chem. Soc.* **1984**, *106*, 4189. (b) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Benlieu, P.; Dube, D.; Andre, C. *Pure Appl. Chem.* **1987**, *59*, 299.
(5) Danishefsky,S. J. *Aldrichimica Acta* **1986**, *19*, 54.
(6) Danishefsky, S. J.; Bednarski, M. D. *J. Am. Chem. Soc.* **1986**, *108*, 7060.
(7) Danishefsky, S. J.; Bednarski, M. D. *Tetrahedron Lett.* **1985**, *26*, 3411.
(8) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696.
(9) Compound **7** was obtained as the major component of a mixture (ca. 2.5:1) of acetoxyl epimers (cf. ref 7) in 60–70% yield.

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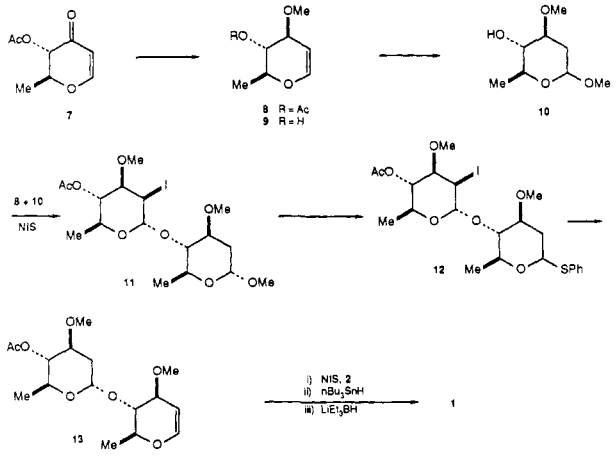
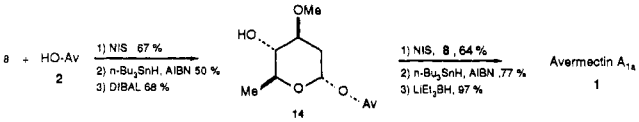


$ZnI_2$; $n$-$Bu_4I$).[10] Compound **12** was obtained in 82% yield. Oxidation (MCPBA), thermolysis (72%), and reductive deiodination led (81%) to the unsaturated disaccharide derivative, **13**. This compound was coupled (64%) to **2** through the agency of NIS. *Reductive deiodination ($n$-$Bu_3SnH$, 78%) followed by deacylation ($LiEt_3BH$, 97%) completed the total synthesis of avermectin $A_{1a}$ (**1**).* The material thus obtained was identical by spectroscopic (500 MHz)and chromatographic comparisons with an authentic sample.

In a second version of the total synthesis, compound **8** was coupled to AvOH again through the action of NIS. Deiodination followed by deacylation afforded **14**. Coupling of **14** with **8** (NIS) followed by reductive deiodination and deacylation again afforded **1** by total synthesis.



In summary, the total synthesis of avermectin $A_{1a}$ has been achieved. This has been done in a fashion which has larger implications in the avermectin series and, indeed, in broader domains of the glyconjugate synthesis.

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(10) Hanessian, S. W.; Guindon, Y. *Carbohydr. Res.* **1980**, *86*, C3.

**Chart I**

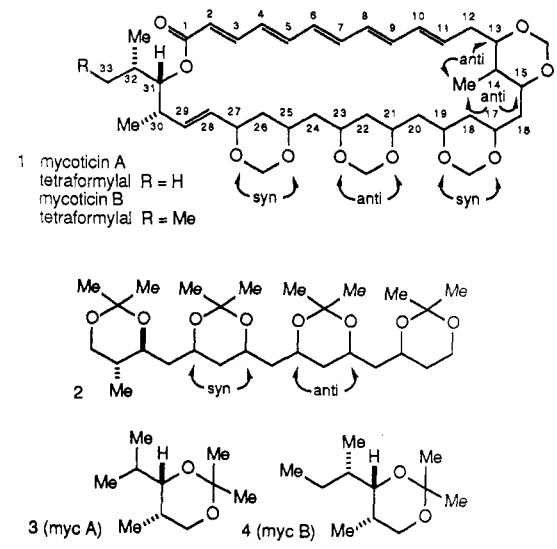
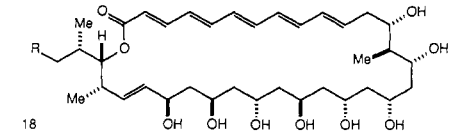


**Chart II**



of a large subclass, represented by mycoticin A and B, is the skipped-polyol chain that is synthesized in vivo from the consecutive coupling of acetate-derived components. Surprisingly, little stereochemical information is available on members of this class. Despite their prominent role in antifungal therapy and promise as antiviral agents, amphotericin B is the single member of this class of over 200 whose complete stereochemical assignment of structure has been determined.[2] Recently, we reported that speculation of the stereochemistry of members of the skipped-polyol polyene class based on structural analogies to the distant relative amphotericin B is not productive.[3]

The issue of stereochemistry is not without practical implications. For example, the antifungal properties of these compounds are associated with their ability to selectively alter the permeability of membranes that contain sterols.[4] It has been recognized that the design and synthesis of analogues with increased selectivity toward ergosterol rich membranes (characteristic of fungi), relative to cholesterol containing bilayers of mammalian cells, holds promise for antifungal agents with increased therapeutic index.[5] Lead structures are available from selectivity studies that have demonstrated, for example, that phosphatidylcholine vesicles containing ergosterol were markedly more sensitive to amphotericin B and less sensitive to the skipped-polyol macrolide filipin than corresponding preparations containing cholesterol.[6] The inter-

## Application of the Two-Directional Chain Synthesis Strategy to the First Stereochemical Assignment of Structure to Members of the Skipped-Polyol Polyene Macrolide Class: Mycoticin A and B†

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The polyene macrolide antibiotics are large-ring lactones that contain polyhydroxylated fragments.[1] A characteristic feature

† Dedicated to Professor Kenneth B. Wiberg on the occasion of his 60th birthday.

(1) Reviews: (a) Gale, E. F.; Curdliffe, E.; Reynolds, P. E.; Richmond, M. H.; Waring, M. J. In *The Molecular Basis of Antibiotic Action*; John Wiley: New York, 1981; p 201-219. (b) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic: New York, 1984; pp 351-404.

(2) Structure determination: Mechlinski, W.; Schaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873. Synthesis: Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2205. Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2208.

(3) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718. An arbitrary distinction has been made between compounds such as amphotericin B, which contains two consecutive skipped hydroxyls, and the mycoticins, which contain eight consecutive skipped hydroxyls.

(4) (a) Kinsky, S. C. *Ann. Rev.* Pharmacology **1970**, *10*, 119. (b) Hamilton-Miller, J. M. T. *Adv. Appl. Microbiol.* **1974**, *17*, 109.

(5) Floyd, D. M.; Fritz, A. W. *Tetrahedron Lett.* **1981**, *22*, 2847.

(6) (a) De Kruilff, B.; Gerritsen, W. J.; Oerlemans, F.; Van Dijck, P. W. M.; Demel, R. A.; VanDeenan, L. L. M. *Biochim. Biophys. Acta* **1974**, *339*, 44. (b) Archer, D. B. *Biochim. Biophys. Acta* **1976**, *436*, 68.

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