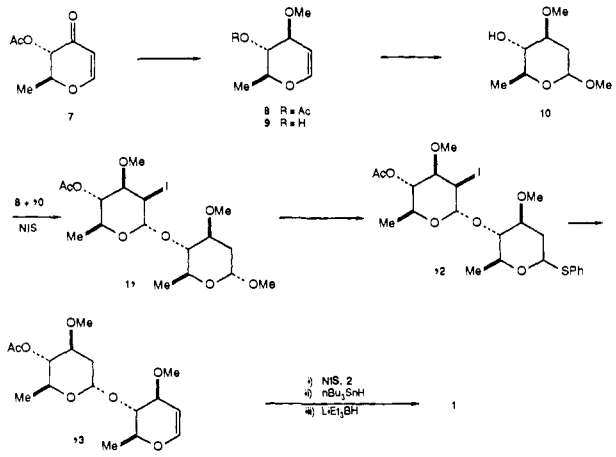
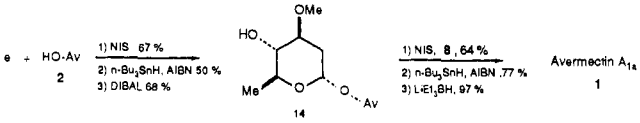


ZnI_2; n-Bu_4I).[10] Compound **12** was obtained in 82% yield. Oxidation (MCPBA), thermolysis (72%), and reductive deiodination led (81%) to the unsaturated disaccharide derivative, **13**. This compound was coupled (64%) to **2** through the agency of NIS. *Reductive deiodination (n-Bu$_3$SnH, 78%) followed by deacylation (LiEt$_3$BH, 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.

Acknowledgment. This research was supported by PHS Grant AI 16943. PHS Postdoctoral Fellowships (Grant 5 F32 GM 10576) to H.G.S. and (Grant 5 F32 GM11051) to D.M.A. are 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. We thank Drs. Helmut Mrozik and Michael Fisher of The Merck Company for furnishing samples of avermectin B_{1a} for degradations and comparisons.

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

Chart I

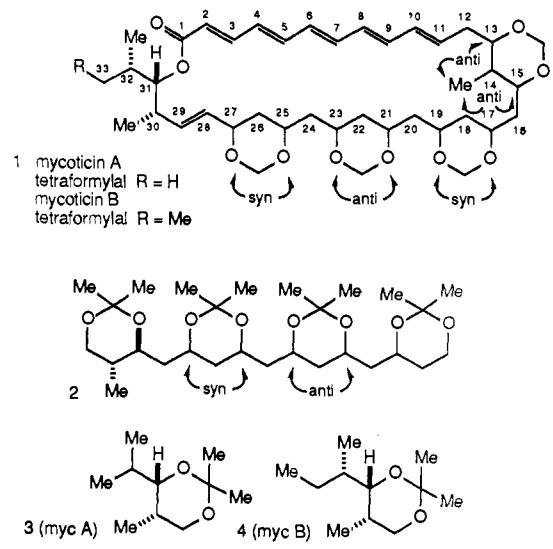
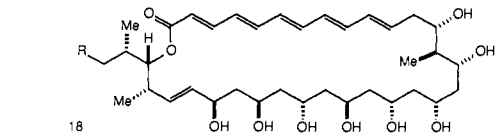


Chart II



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†

Stuart L. Schreiber* and Mark T. Goulet

Department of Chemistry, Yale University
New Haven, Connecticut 06511

Received August 24, 1987

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

† 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.

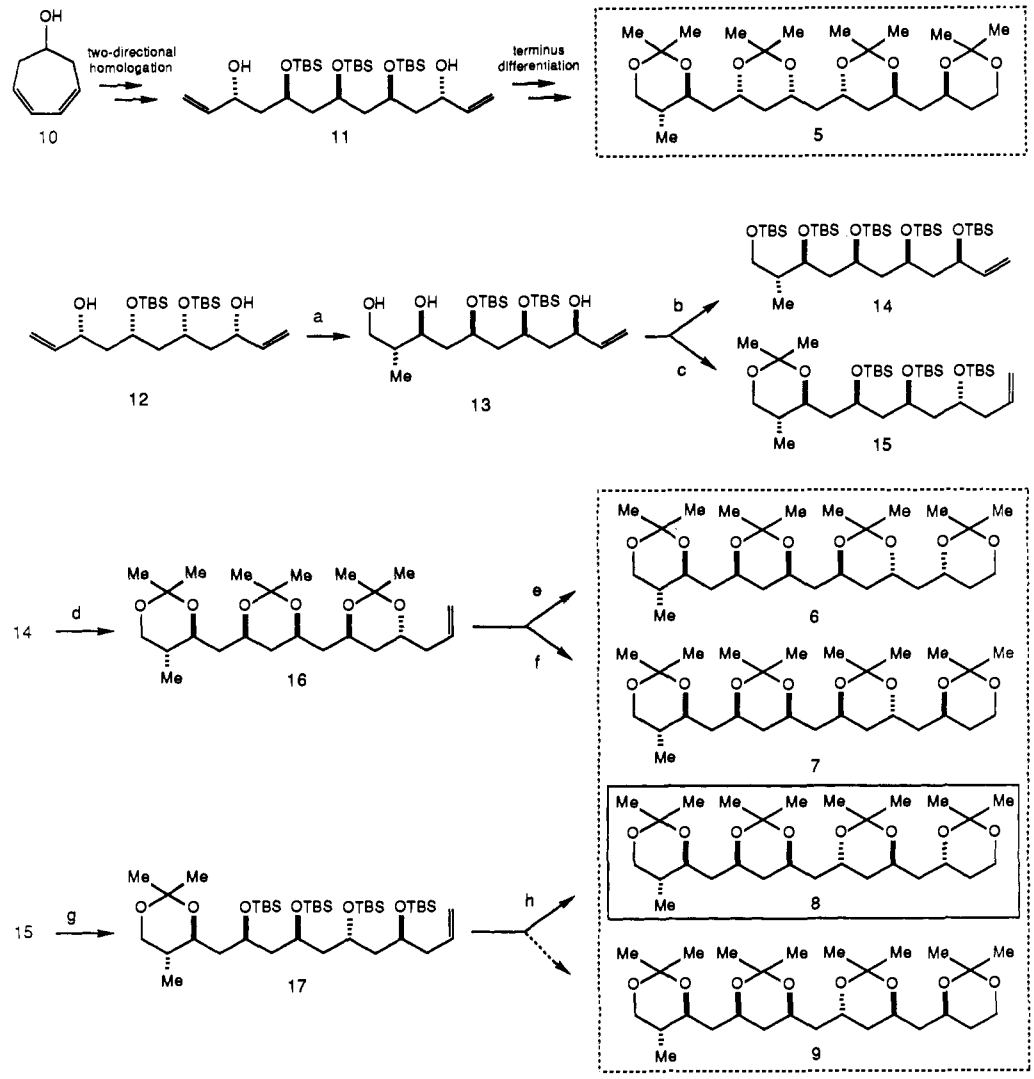
(4) (a) Kinsky, S. C. *Ann. Rev.* Pharmacology **1970**, *10*, 119. (b) Hamilton-Miller, J. M. T. *Adv. Appl. Microbiol.* **1974**, *17*, 109.

(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.

0002-7863/87/1509-8120$01.50/0

Scheme I[a]



[a](a) (1) $Ti(OiPr)_4$, L(+)DIPT, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −20 °C, 82%; (2) Na, isopropyl alcohol, 95%; (3) lithium dimethyl cuprate, Et_2O, −20 °C (6:1), 80%; (b) TBSOTf, CH_2Cl_2, 2,6-lutidene, 99%; (c) (1) acetone, *p*-TsOH (catalyst), $CuSO_4$, 84%; (2) O_3, $MeOH/CH_2Cl_2$, −78 °C, then $NaBH_4$, 0 °C, 94%; (3) $NaIO_4$, THF (aqueous); (4) (+)-Ipc_2B(allyl), Et_2O, −78 °C (>20:1), 71% overall; (5) b, 99%; (d) (1) disiamylborane, DME, 0 °C, then 10% NaOH, 30% HOOH, 90%; (2) PCC, CH_2Cl_2; (3) c-4, (14:1), 67% overall; (4) tetrabutylammonium fluoride, THF; (5) 2-methoxypropene, HCl (catalyst), THF, 80% overall; (e) (1) O_3, MeOH, −78 °C, then DMS, room temperature; (2) c-4 (15:1), 84% overall; (f) (1) e-1; (2) (−)-Ipc_2B(allyl) Et_2O, −78 °C (20:1), 68% overall; (3) c-2; (4) c-1, 78% overall; (g) (1) e-1; (2) f-2, (11:1), 60% overall; (3) b, 99%; (h) (1) e-1,2 (14:1), 68%; (2) c-2; (3) d-5, 81%, overall.

pretation of structure-function relationships is made difficult, however, due to the lack of stereochemical information on skipped-polyol macrolides such as filipin.[7] Herein, we describe the conclusion of our stereochemical investigations of mycoticin A and B[8] and report, for the first time, the absolute stereostructure of members of the skipped-polyol polyene macrolide class.

The preparation and structural analysis of mycoticin A and B derivatives **1**–**4** have been described elsewhere.[8,9] The information accrued from these studies is summarized in Chart I. The problem was reduced to identifying the natural configuration of fragment **2** from the eight remaining diastereomeric candidates. In particular, the relative stereochemistry between carbons C_{15} and C_{17}, C_{19} and C_{21}, C_{23} and C_{25} remained in question. Five of the eight diastereomers are depicted in Scheme I (**5**–**9**); four of these were eventually prepared by synthesis (vide infra).

We first turned to the asymmetric synthesis of isomer **5**, which, based on our interpretation of the NMR data on derivative **1**,[8b] was considered the most likely composition of naturally derived **2**. For the synthesis of compound **5**, we took note of a subunit which contains a mirror plane of symmetry that suggests the application of the (class A) two-directional chain synthesis strategy.[10] An enantiotopic group selective terminus differentiation of meso chain **11** according to the recently described procedure[3,11] was central to the success of our plan. Details of the synthesis of **5** from cycloheptadienol **10** are provided in the Supplementary Material. Comparison of the tetraacetonide **5** to the naturally derived fragment **2** revealed a diastereomeric relationship. Importantly, the ^1H NMR spectrum of **5** in the region of the trimethyl-substituted dioxane ring differed significantly from naturally derived **2**, unlike the previously reported all-syn isomer.[3] We concluded that the diastereomeric configuration of our degradation fragment **2** could be narrowed to four candidates, structures **6**–**9**.

(7) Dhar, M. L.; Thaller, V.; Whiting, M. C. *J. Chem. Soc.* **1964**, *842*.
(8) (a) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, in press. (b) Schreiber, S. L.; Goulet, M. T.; Sammakia, T. *Tetrahedron Lett.* **1987**, in press.
(9) Stereochemical studies of the polyene macrolide lienomycin have been reported: Pawlak, J.; Nakanishi, K.; Iwashita, T.; Borowski, E. *J. Org. Chem.* **1987**, *52*, 2896.
(10) Schreiber, S. L. *Chem. Scr.* **1987**, in press.
(11) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525.

A general strategy was devised that would permit the synthesis of each isomer **6–9** from a common and advanced intermediate. Such a target is represented by the triol **13**, which was obtained from the achiral precursor **12** by the terminus differentiation sequence employed in an earlier study. The two-directional chain synthesis of **12** proceeded according to previously described methods.[3] Although compound **14** was obtained from **13** by tris-silylation, the synthesis of **15** required degradation of the vinyl carbinol to a chain-shortened aldehyde, subsequent homologation with the Brown reagent, (+)-allyldiisopinocampheylborane,[12,13] and protection.

A stereoselective homologation was achieved by a (+)-Brown reagent addition to the aldehyde derived from hydroboration and oxidation of the vinyl group in **14**. The tris(acetonide) **16** served as a common progenitor to both **6** and **7** by a final application of the Brown method. Enantiomeric Brown reagents[12] were employed to arrive upon the two target systems.[13] With disappointment, both compounds were found to be diastereomerically related to the naturally derived fragment **2**. However, as with the all-syn isomer the similarity of the ^{1}H NMR spectra in the region of the trimethyl-substituted dioxane was striking, in support of our earlier structural analysis.

In a similar manner, compound **17** was prepared from **15** by application of the three-step iterative process. The addition of (+)-allydiisopinocampheylborane to the aldehyde derived from **17** and subsequent ozonolysis, reduction, desilylation, and acetonide formation produced **8**. Happily, this compound proved to have the same relative stereochemistry as the mycoticin A and B derived fragment **2** by comparison of their chromatographic properties (TLC) and richly detailed 500-MHz ^{1}H NMR spectra. These compounds were shown to have an enantiomeric relationship by comparison of the CD spectra of their corresponding octaacetates.

The accumulated information concerning mycoticin A and B permits the stereochemical formulation of these two prototype members of the skipped-polyol polyene macrolide class as shown in Chart II (**18**).[14] With knowledge of mycoticin structure and the reported NMR data (including NOEDS),[8b] conformational analysis of mycoticin A and B and derivatives (e.g., **1**) is now possible. These and other studies of the polyene macrolide antibiotics are underway.

Acknowledgment. These investigations were supported by the NIGMS, NSF (Presidential Investigator Award), Alfred P. Sloan Foundation (1985–1987), and The Camille and Henry Dreyfus Foundation, Inc. (Teacher/Scholar Award 1984–1989) to whom we are grateful. Matching funds for the NSF-PYI Award were generously provided by Pfizer, Inc. We thank Gayle Schulte for her efforts with several crystallographic analyses and Professor Harry H. Wasserman for his advice and encouragement.

Supplementary Material Available: Spectral data for compounds **5–17** and details of the synthesis of compound **5** from compound **10** (13 pages). Ordering information is given on any current masthead page.

(12) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

(13) Our stereochemical analysis is dependent on the reliability of the reagent controlled facial selectivity of the enantiomeric Brown reagents. Two findings are relevant to this issue. The degree of facial selectivity observed in the addition of achiral allyl reagents to β-alkoxy aldehydes lacking α-substituents is frequently modest; in other words, a minimal degree of substrate control was expected to be operative. Even more significant, we have found that in each instance the enantiomeric Brown reagents add to aldehyde substrates with stereoselectivity (>10:1) to produce diastereomeric products. Accordingly, we feel that the substantial precedent for the faithful addition of these reagents to achiral and chiral substrates can be extended to the chiral aldehydes employed in these studies and serve as a basis for stereochemical assignment.

(14) Mycoticin A and B are the first members of this class whose constitutions were determined and are apparently identical with the flavofungins. (i) Mycoticin: (a) Burke, R. C.; Swartz, J. H.; Chapman, S. S.; Huang, W. Y. *J. Invest. Dermatol.* **1954**, *23*, 163. (b) Wasserman, H. H.; VanVerth, J. E.; McCaustland, D. J.; Barowitz, I. J.; Kamber, B. *J. Am. Chem. Soc.* **1967**, *89*, 1535. (c) Wasserman, H. H.; Zoretic, P. A.; Mariano, P. S. *J. Chem. Soc., Chem. Commun.* **1970**, 1634. (ii) Flavofungin: Bognar, R.; Makleit, S.; Zsupan, K.; Brown, B. O.; Lockley, W. J. S.; Toube, T. P.; Weedon, B. C. L. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1848.