The Total Synthesis of the Aglycon of Avermectin A_{1a}†

Samuel J. Danishefsky,* David M. Armistead,
Francine E. Wincott, Harold G. Selnick, and
Randall Hungate

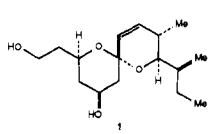
Department of Chemistry, Yale University
New Haven, Connecticut 06511

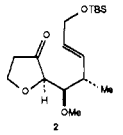
Received August 6, 1987

The avermectins are a related series of anthelmintic agents originally isolated from *Streptomyces avermitilis*. These compounds were discovered and developed by Merck scientists.[1-5] The determination of the structure–activity relationships of the avermectins and the full identification of range of potentialities of the natural series of compounds and semisynthetic congeners are important frontier areas of neurobiological as well as pharmacological research.[1,2] Not surprisingly then, the avermectins and their structurally less complex relatives, the milbemycins, have stimulated a great deal of interest in the synthesis community. Ingenious solutions to various segments of the avermectin problem have emerged. An important milestone in this pursuit was provided by Hanessian and associates who described a comprehensive strategy and extensive progress for a laboratory synthesis of the avermectins.[6-9]

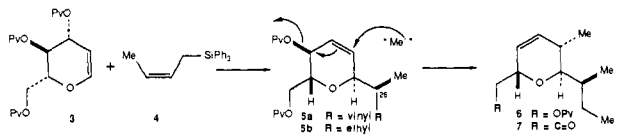
In this communication we describe the synthesis of the aglycon of avermectin A_{1a} (see compound **33**). In the following communication we describe the total synthesis of avermectin A_{1a} itself. In approaching the aglcyon we identified the subunits 1 and 2 in properly matched enantiomerically pure form as our first subgoals. Access to the particular antipodes shown here was accomplished through the use of D-glucose and D-ribose, respectively as chirons.[10]

In reaching spiroketal **1** we took advantage of our recently introduced "carbon-Ferrier" technology.[11a,b] The synthesis started with the D-glucal derivative **3**. Reaction of **3** with (*Z*)-tri-



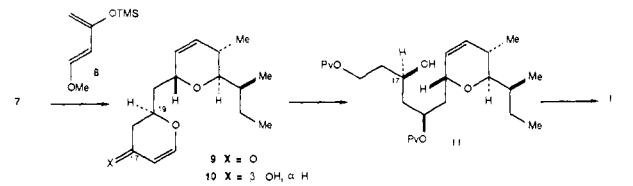


phenylcrotylsilane (**4**)[12] afforded a 90% yield of a readily separable (4.5:1) mixture of **5a** and its C_{26}[13] epi compound (not shown here). Selective hydrogenation of the monosubstituted double bond was readily achieved (90%) with H_2,Pd/C in MeOH containing 10% pyridine. The C_{24} methyl group was introduced through the action



of **5b** with lithium dimethylcuprate in ether at −30 °C,[14] giving **6** in 70% yield. *Thus through the use of the silane and cuprate reactions, the chiral imprint of the glucal had been conveyed to carbons 24, 25, and 26 of the avermectin precursor, and the double bond was installed between carbons 22 and 23.* Depivaloylation (LAH, Et_2O, 0 °C), triflylation (Tf_2O), cyanation (NaCN, DMF), reduction (DIBAH, Et_2O, 0 °C) and acidic hydrolysis provided the aldehyde **7** in 66% overall yield.

A key goal was to communicate the chirality of the tetrahydropyran ring fashioned as above to the newly emerging stereogenic centers at C_{19} and C_{17}.[13] In this way, the need for two resolved matched subunits to reach system **1** could be avoided. In the event, reaction of **7** with diene **8** in the presence of an-



hydrous magnesium bromide in CH_2Cl_2, afforded a 75% yield of the pyrone–pyran system. The major product (3.5–5.0:1) has the structure represented as **9**. It is, formally, the product arising from the chelated conformer (see **7**) undergoing cyclocondensation from its less hindered face. The minor product (not shown) is presumably the C_{19} epimer. Compound **9** was not obtained in a homogeneous state at this stage. Reduction of the mixture with $NaBH_4$–$CeCl_3$[15] followed by purification by silica gel chromatography afforded homogeneous **10**. The sequence (i) TBSOTf; (ii) NBS·H_2O–THF; (iii) Bu_3SnH, $PhCH_3$, AIBN; (iv) $LiBH_4$, THF; (v) pivaloyl chloride, pyridine, DMAP, CH_2Cl_2; (vi) HF, CH_3CN (49% overall), served to convert **10** to **11**. The critical oxidative cyclization of **11** was accomplished through the action of HgO–I_2, CCl_4, 70% yield.[16] Diol **1** [α_D = 109.9° *c* 1.60] (LiOH, MeOH, THF, H_2O, 90%) derived from **11** was identical in its spectral (500 MHz, IR) and chromatographic properties with an authentic sample derived by degradation of avermectin A_{1a}.[17]

The synthesis of subunit **2** started with the D-ribose derived aldehyde **12**.[18] Here we took advtange of chemistry which was recently developed in our laboratory in the context of reactions of allylic silanes with aldoseulose derivatives to control the stereochemistry at carbons 4 and 5.[19] Reaction of **12** with (*E*)-trimethylcrotylsilane followed by methylation (sodium hydride–methyl iodide) afforded a 78% yield of **13**.[20] This was converted to epoxide **14** by the following well-precedented sequence: (i) HCl,

† We dedicate this paper to our colleague Professor K. B. Wiberg on the occasion of his 60th birthday.

(1) Fisher, M. H.; Mrozik, H. *Macrolide Antibiotic*; Academic Press: New York, 1984; p 553.

(2) Fisher, M. H. *Recent Advances in the Chemistry of Insect Control*; Burlington House: London, 1985; p 53.

(3) Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1981**, *103*, 4221.

(4) The first commercially important product to arise from this family is marketed as IVERMECTIN by Merck and Co. For a discussion of the nomenclature of the avermectins see ref 1 and 2.

(5) Motokizawa, F.; Reuben, J. P.; Grundfest, H. *J. Gen. Physiol.* **1969**, *54*, 437.

(6) Hanessian, S.; Ugolini, A.; Dube, D.; Hodges, P. J.; Andre, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776.

(7) (a) Hanessian, S.; Beulieu, P.; Dube, D. *Tetrahedron Lett.* **1986**, *27*, 507. (b) Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1985**, *48*, 5837.

(8) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beulieu, P.; Dube, D.; Andre, C. *Pure Appl. Chem.* **1987**, *59*, 299.

(9) For a more comprehensive listing of avermectin references, see: ref 8.

(10) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1983.

(11) (a) Danishefsky, S. J.; Kerwin, J. R., Jr. *J. Org. Chem.* **1982**, *47*, 3803. (b) Danishefsky, S. J.; DeNinno, S. L.; Lartey, P. A. *J. Am. Chem. Soc.* **1987**, *109*, 2082.

(12) While higher ratios could be achieved with other crotylsilanes, invariably this increase was accompanied by lowered yields. The (*Z*)-triphenylcrotylsilane produced the best combination of ratio and yield and was prepared by the procedure of Matarasso-Tchiroukhine and Cadiot (Matarasso-Tchiroukhine, E.; Cadiot, P. *J. Org. Met. Chem.* **1976**, *121*, 155).

(13) This carbon-numbering protocol anticipates the construction of avermectin A_{1a}.

(14) Cf. Goering, H. L.; Singleton, V. D., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854.

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

(16) (a) Wincott, F. E.; Danishefsky, S. J.; Schulte, G. *Tetrahedron Lett.*, in press. (b) Kay, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915. (c) Kay, I. T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, *25*, 2035. (d) Mihailovic, M. Lj.; Gojkovic, S.; Konstantinovic, S. *Tetrahedron* **1973**, *29*, 3675.

(17) Prepared from the Δ^2 isomer of avermectin A_{1a} aglycon by the action of osmium tetroxide: Selnick, H. F., Yale University, unpublished results.

(18) Jones, G. H.; Moffatt, J. G. *Methods in Carbohydrate Chemistry*; Academic Press: New York, 1972; Vol. VI, p 315.

(19) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809.

(20) The addition of (*E*)-trimethylcrotylsilane to aldehyde **12** produces a 8.9:1.1:1.0 mixture of stereoisomers (isolated weight ratios). The chemical yield cited is for diastereomerically homogeneous **13**.

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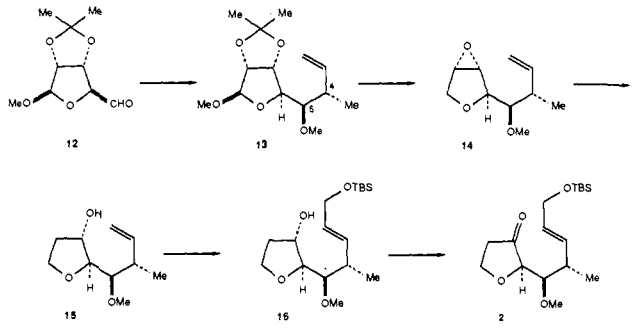
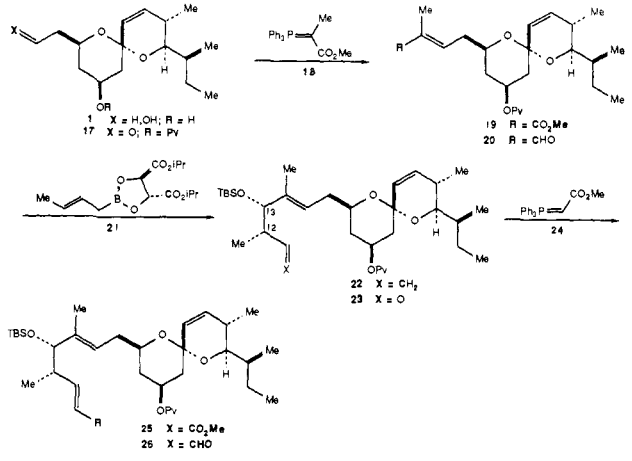


MeOH; (ii) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2;[21] (iii) $(CH_3)_2C(OAc)$-COBr, CH_2Cl_2;[22] and (iv) Amberlite IRA 400 (OH), MeOH, in 74% overall yield. Reaction of **14** with lithium triethylborohydride afforded, regioselectively, the alcohol **15**. The latter was subjected, *in seriatum*, to ozonolysis with reductive (zinc–AcOH) workup, followed by Wittig-like reaction (Ph_3P = $CHCO_2Me$), reduction (DIBAH), and selective protection (TBSCl) to afford alcohol **16**. Oxidation of **16** with PCC afforded the desired ketone **2** in 70% overall yield from **14**. The properly matched subunits were thus in hand.

In the next phase of the effort, compound **1** was to be converted to **26** in anticipation of the possibility that the latter would be coupled to ketone **2**. Selective protection of the primary alcohol

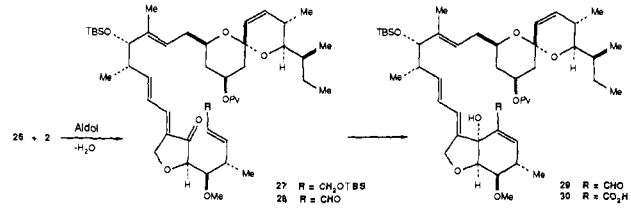


of diol **1** (t-$BuPh_2SiCl$), followed by pivaloylation of the secondary alcohol, desilylation (n-Bu_4NF, THF) and Swern oxidation[23] afforded a 67% overall yield of aldehyde **17**. Reaction of **17** with **18** afforded a 94% yield of the *E* enoate **19**. Selective reduction ($LiEt_3BH$) of **19** followed by Swern oxidation of the resultant alcohol led (79% overall yield) to aldehyde **20**.

At this juncture we made recourse to the concept of auxilliary guided diastereoselection to introduce the required stereochemistry at carbons 12 and 13.[24] Fortunately, the powerful crotyl boronate chemistry of Roush and co-workers[25,26] was available for the required "threo aldol" objective. Reaction of **20** with **21** afforded a 92% yield of a 4:1 mixture of two stereoisomers. As subsequent events proved, the major product after silylation (TBSOTf) was the 12*S*, 13*S* threo compound **22**. The minor product was shown to be the corresponding 12*R*,13*R* threo isomer.

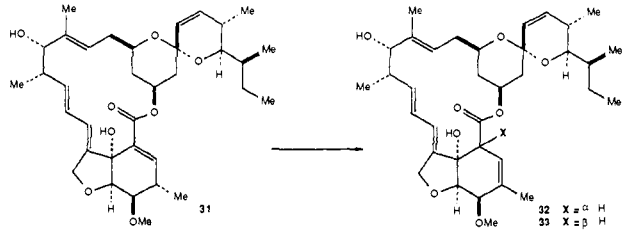
The monosubstituted double bond of **22** was selectively attacked with osmium tetroxide, and the resultant diol was cleaved with lead tetraacetate to afford aldehyde **23** in 67% yield. Wittig-like olefination with **24** gave enoate **25** (95%). Reduction (DIBAH) followed by oxidation, again under the conditions of Swern, gave enal **26** in 89% overall yield.

Fortunately, a classical crossed aldol condensation–dehydration sequence did indeed achieve the consolidation of fragments **2** and **26**. The lithium enolate of **2** (generated in THF through the action of lithium hexamethyldisylazide) reacted with **26** to give, after dehydration (MsCl; Et_3N), the enone **27** (67%). Selective cleavage of the C_1 silyl ether was accomplished through careful treatment of this compound with HF in acetonitrile, −20 °C. The resultant alcohol was oxidized to aldehyde **28** (85% overall yield). The stage was now set for the all critical intramolecular Nozaki[27] process.



Reaction of **28** with the "ate" species produced from the reaction of trimethylaluminum and lithium thiophenoxide in THF, followed by oxidation with MCPBA and thermolysis (toluene, reflux) afforded a 76% yield of the "seco" aldehyde **29**. The latter, upon oxidation ($NaClO_2$)[28] and depivaloylation (LiOH–MeOH) gave the 13 OTBS protected seco acid **30** (93% overall yield). Macrolactonization was achieved in 67% yield through the action of 2-chloro-*N*-methylpyridinium iodide and triethylamine in methylene chloride.[29,30] Liberation of the 13-alcohol group (n-Bu_4NF, 87%) afforded **31**, the conjugated Δ^2 tautomer of the aglycon of avermectin A_{1a}. The compound so obtained was identical in its spectroscopic (500 MHz NMR) and chromatographic properties with a sample obtained by conjugation and deglycosylation of avermectin A_{1a}.[31]

The last hurdle involved deconjugation of the double bond of **31** to produce the required 2βH epimer. The deconjugation step was accomplished cleanly through the action of LDA in THF at −78 °C, followed by quenching with aqueous HCl. This treatment



produced a 75% yield of the C_2 epi (i.e., αH) compound **32** plus a 21% yield of recovered **31**.[32] At this stage we benefitted from the recently developed epimerization methodology demonstrated by Hanessian[33] in related systems. Reaction of **32** with a concentrated solution of imidazole in benzene under reflux for 1.5 h afforded a mixture of **32** (33%), **31** (21%), and the long-awaited aglycon of avermectin A_{1a}, **33** (32%). Since **32** can be readily recycled and **31** can be converted to **32**, the overall conversion

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(22) Robins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. *Tetrahedron Lett.* **1984**, *24*, 367.
(23) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(24) For a review of reagent-controlled diastereoselection, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(25) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.
(26) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 953.
(27) (a) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361. (b) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274. (c) Armistead, D. M.; Danishefsky, S. J. *Tetrahedron Lett.*, in press.
(28) Bal. B. S.; Childers, W. F. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(29) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
(30) For the first macrolactonization of this skeleton, see: Hanessian, S.; Ugolini, A.; Dube, D.; Hodges, P. J.; Andre, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776.
(31) Selnick, H. G., Yale University, unpublished results.
(32) For a discussion of previous deconjugation experiments, see: (a) Hanessian, S.; Dube, D.; Hodges, P. J. *J. am. Chem. Soc.*, in press. (b) Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 933.
(33) Reference 12a. We thank Professor Hanessian for the opportunity to use these prepublication conditions in our system.

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.

Acknowledgment. This research was supported by PHS Grant AI 16943. PHS Postdoctoral Fellowships (Grant 5 F32 GM11051) to D.M.A., (Grant 5 F32 GM10576) to H.G.S., and (Grant 5 F32 CA07583) to R.H. are gratefully acknowledged. NMR spectra were obtained through the auspices of the 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 supplying samples of avermectin B_{1a}.

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

Samuel J. Danishefsky,* Harold G. Selnick,
David M. Armistead, and Francine E. Wincott

Department of Chemistry, Yale University
New Haven, Connecticut 06511

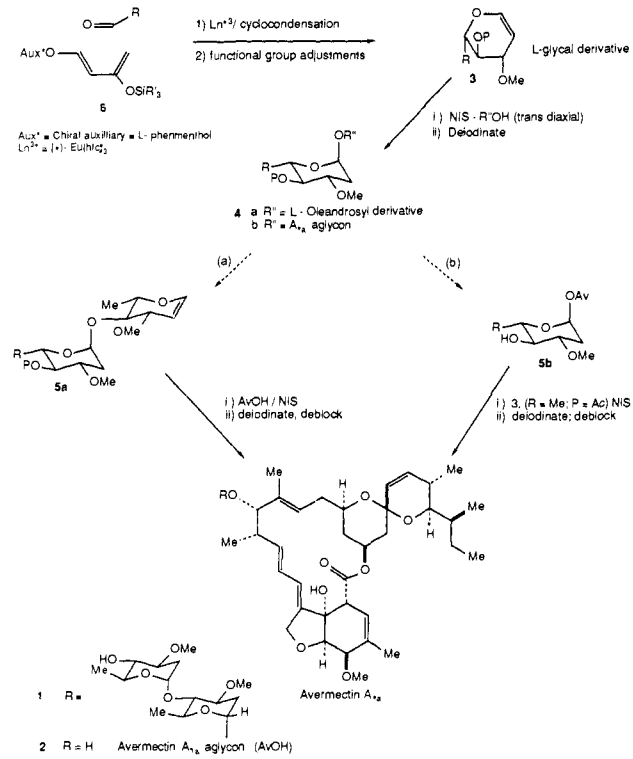
Received August 6, 1987

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 α (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 α and β 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.
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(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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