Methyl Ether of De-A,B-8α-ethynylcholestan-8β-ol (17). Alcohol **16** (6.9 mmol) and methyl iodide (0.87 mL, 14 mmol) were added to a solution of KOH (1.57 g, 28 mmol) in 14 mL of Me_2SO. The reaction mixture was stirred for 15 min at room temperature, poured in 200 mL of water, and extracted with pentane (2 × 50 mL). The organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography (hexane/AcOEt, 99/1): yield, 70% from ketone **15**; mp 51-52 °C; $[\alpha]^{21}_D$ +4.0° ($CHCl_3$, *c* 2.0); IR ($CHCl_3$) 3310, 2870 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.9 (m, 12 H, CH_3), 1-2 (m, 20 H, CH_2 + CH), 2.38 (s, 1 H, C*H*), 3.31 (s, 3 H, CH_3O); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.4, 20.9, 23.8, 26.7, 34.4, 35.9, 39.5, 40.3, 42.6, 71.8, 74.7, 76.4, 77.0, and 77.6 (8 CH_2 + 3 C) 13.3, 18.5, 22.5, 22.8, 28.0, 35.4, 51.3, 56.8, and 57.1 (5 CH_3 + 5 CH).

Coupling Reaction of Alkyne 17 with Ketones 6, 11, 13, and 14. General Procedure. *n*-BuLi (1.25 mL; 1.32 M in hexane) was added to 500 mg (1.6 mmol) of product **17** in 5 mL of anhydrous THF. After 5 min at room temperature, 1.6 mmol of ketone in 5 mL of THF was added. After 1 h at room temperature, the reaction mixture was hydrolyzed with 10 mL of saturated NH_4Cl and extracted with ether (2 × 20 mL). The organic phase was washed with saturated NaCl, dried over $MgSO_4$, and evaporated. The crude product (80% yield) was used in the next step without purification.

Hydroxy Ethers 18 and 19. The TBDMS ether of **18** or **19** (0.61 mmol) in acetonitrile (10 mL) was treated by 1 mL of 40% FH for 30 min. The solution was then washed with saturated $NaHCO_3$ and extracted with ether (3 × 10 mL). The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated: quantitative yield; ^1H NMR (60 MHz, CCl_4) δ 0.9-2.1 (m), 3.2 (s, 3 H, OCH_3), 3.6 (m, 1 H, C*H*OH).

Hydroxy Ethers 20 and 21. $ZnBr_2$ (1.1 g, 5 mmol) was added to a solution of 1.0 mmol of the MEM ether of **20** or **21** in 20 mL of dichloromethane. The dark reaction mixture was stirred for 8 h and then hydrolyzed with saturated $NaHCO_3$ (100 mL). The solution became yellow, and a white precipitate formed. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the organic layer dried over $MgSO_4$ and evaporated: quantitative yield; ^1H NMR (60 MHz, CCl_4) δ 1-2.2 (m), 3.2 (s, 3 H, OCH_3), 3:6 (m, 1 H, C*H*OH).

Reduction of Propargylic Alcohols 18-21. General Procedure. A titrated $LiAlH_4$ (2.4 mL, 1.8 mmol, 3 equiv) solution (0.77 M) in ether was added at 0 °C to a solution of 0.61 mmol of propargylic alcohol in 20 mL of ether. After 1 h at 0 °C, the reaction mixture was hydrolyzed with 2 mL of EtOAc and 20 mL of 5% HCl and extracted with ether (3 × 20 mL). The organic phase was washed with saturated NaCl (100 mL), dried over $MgSO_4$, and evaporated: quantitative yield; ^1H NMR (200 MHz, $CDCl_3$) δ 0.9-2.1 (m), 3.3 (s, 3 H, OCH_3), 3.6 (m, 1 H, C*H*OH), 4.21 (2 AB systems, 2 H, J_{AB} = 12 Hz, Δν = 28.6 Hz, vinylic H).

Low-Valent Titanium Reductive Elimination. General Procedure. A titrated solution of $LiAlH_4$ (8.3 mL, 6.4 mmol) in ether (0.77 M) was added to 1.97 g (12.8 mmol) of $TiCl_3$ in 10 mL of THF under argon. A black suspension formed. The reaction mixture was stirred at room temperature for 30 min. Then 1.6 mmol of allylic hydroxy ether in 5 mL of THF was added and the reaction mixture refluxed for 1 h, hydrolyzed with 50 mL of 2 N HCl, and extracted with chloroform (3 × 20 mL). The organic layer was washed with water several times to remove the brown color, dried over $MgSO_4$, and evaporated.

The diastereoisomer ratio was determined by NMR on the crude product from the signals of the proton α to the hydroxyl group.

The products (DHT_3 and $DHTV_3$) were then separated by preparative TLC (hexane/ether, 90/10). Yields of purified products after TLC separation are between 60% and 75%.

DHV_3 (5*Z*,7*E*,3*S*,10*R*)-**26**: ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.50 (m, 1 H, C*H*OH), 5.9 (m, 2 H, vinylic H).

DHT_3 (5*E*,7*E*,3*S*,10*R*)-**27**: $[\alpha]^{21}_D$ +0.5, $[\alpha]^{21}_{365}$ +2.4° (*c* 1.2, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ -2.5 (m), 3.89 (m, 1 H; C*H*OH), 6.0 (m, 2 H, vinylic H).

DHV_3 (5*Z*,7*E*,3*R*,10*R*)-**30**: ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.85 (m, 1 H, C*H*OH), 5.8 (m, 2 H, vinylic H).

DHT_3 (5*Z*,7*E*,3*R*,10*R*)-**31**: $[\alpha]^{21}_D$ +6.3°, $[\alpha]^{21}_{365}$ +19.4° (*c* 2.2, acetone); mp 92 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.65 (m, 1 H, C*H*OH), 6.61 (AB, J_{AB} = 11 Hz, Δν = 33 Hz, vinylic H).

DHV_3 (5*Z*,7*E*,3*R*,10*S*)-**28**: ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.66 (m, 1 H, C*H*OH), 6.16 (AB, 2 H, J_{AB} = 10 Hz, Δν = 7.5 Hz, vinylic H).

DHT_3 (5*E*,7*E*,3*R*,10*S*)-**29**: $[\alpha]^{21}_D$ +1.2°, $[\alpha]^{21}_{365}$ +4.8° (*c* 1.1, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.73 (m, 1 H, C*H*OH), 6.24 (AB, 2 H, J_{AB} = 11.5 Hz, Δν = 7 Hz).

DHV_3 (5*Z*,7*E*,3*S*,10*S*)-**32**: $[\alpha]^{21}_D$ +36.9; $[\alpha]^{21}_{365}$ +152° (*c* 0.4, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 4.00 (m, 1 H, C*H*OH), 5.9 (m, 2 H, vinylic H).

DHT_3 (5*E*,7*E*,3*S*,10*S*)-**33**: $[\alpha]^{21}_D$ +5.2°, $[\alpha]^{21}_{365}$ +14.8° (*c* 1.1, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.65 (td, 1 H, C*H*OH), 6.03 (AB, 2 H, J_{AB} = 10 Hz, Δν = 30 Hz, vinylic H).

Acknowledgment. We are indebted to CNRS for financial support and for a scholarship to J. Hutt. We expressed our gratitude and thanks to Prof. H. Walborsky (Florida State University) for helpful discussions and advice. We also thank Roussel-Uclaf for a generous gift of vitamin D_3.

Synthetic Approaches to Nogalamycin-Related Anthracyclines. An Approach to a Western Synthon[1]

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A synthetic approach to the "western" portion of nogalamycin is described. The synthesis of the 3-aminoglucose synthon **21** and its utilization in the stereocontrolled glycosidation of the D-ring synthon **9** is reported. The resulting glycoside **24** was converted to the 5′,6′-olefin **36**. The formation of the 2,5′-C-C bond was attempted via an intramolecular cation induced olefinic cyclization approach. While model intermolecular studies were successful, the intramolecular reaction failed presumably due to insufficient nucleophilicity of the aromatic moiety.

The clinical utility of the anthracycline antibiotics daunorubicin (**1**) and doxorubicin (**2**)[2] in the treatment of cancer has prompted the development of so-called second generation anthracyclines which include both natural products and their semisynthetic analogues. Therapeutic

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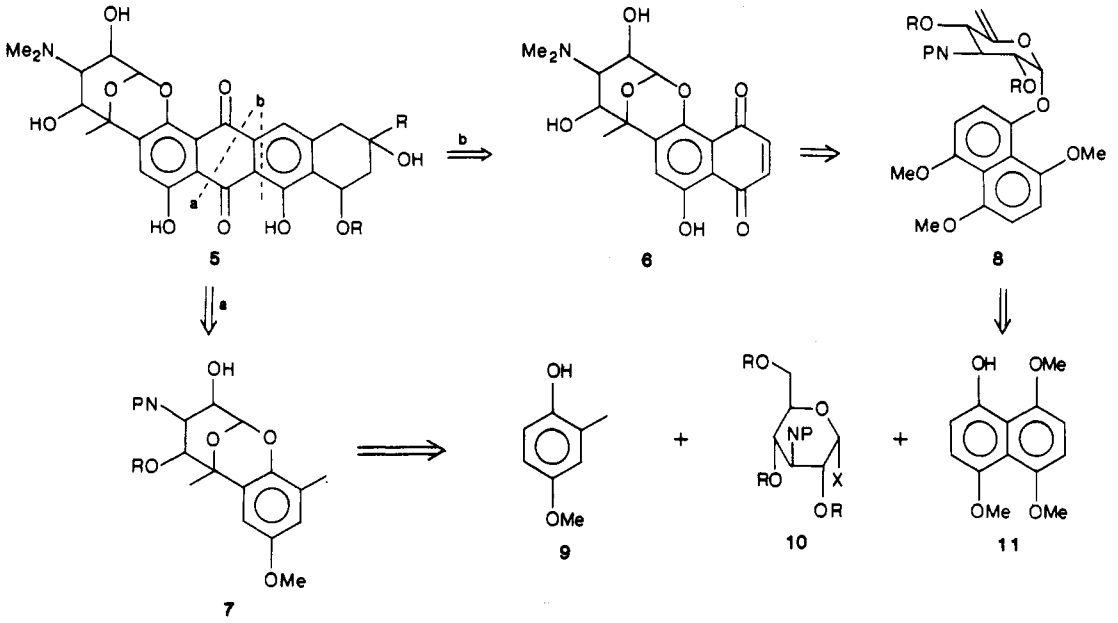
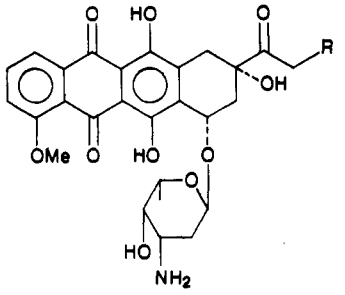
(1) A preliminary account of this work was presented by T. H. Smith and H. Y. Wu at the 185th National Meeting of the American Chemical Society, Seattle, WA, March, 1983, Abstract ORGN 14.

0022-3263/87/1952-3566$01.50/0

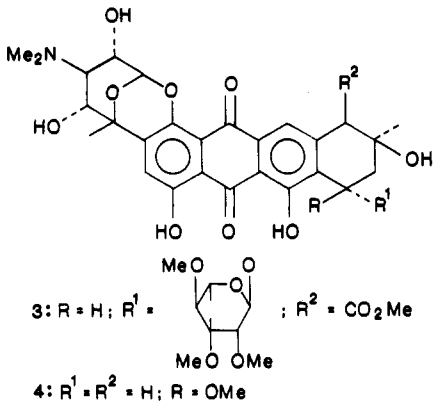
Scheme I



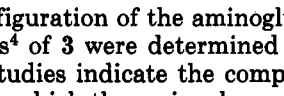
advantages over 1 and 2 in experimental tumors have been claimed for several of these agents. Nogalamycin (3) and its derivatives are examples of such second generation drugs isolated from *Streptomyces nogalater* var. nogalater sp.n. The structure,[3] except for A-ring stereochemistry



1: R = H
2: R = OH



3: R = H; R¹ = ; R² = CO_2Me



4: R¹ = R² = H; R = OMe

and configuration of the aminoglucose residue, and biosynthesis[4] of 3 were determined by Wiley et al. More recent studies indicate the complete structure to be as shown in which the aminoglucose moiety has the L-configuration and the 9-hydroxyl has a β-orientation unlike that found in other anthracyclines.[5] From a program of structure modification 4 has emerged as the most interesting analogue of 3 and appears to have potential as a clinically useful antitumor agent. Nogalamycin and its analogs are structurally different from the classical anthracyclines in that the amino sugar residue is joined to the aromatic D-ring via both glycoside and C–C bonds forming a benzoxocin ring system. Additional examples of anthracyclines containing this structural feature have recently been reported.[7] In this paper we report our efforts to prepare a synthon incorporating the "western" portion of nogalamycin including the unusually fused amino sugar residue suitable for eventual elaboration to nogalamycin related anthracyclines.

Due to the lack of appropriate synthetic methodology for the construction of the optically active aminoglucose-2,6-epoxy-2*H*-1-benzoxocin moiety at the outset of this study, we focused our initial efforts on the "western" portion of nogalamycin.[8] Our general approach is outlined retrosynthetically in Scheme I. Our plan involves (1) syntheses of a suitably functionalized aminoglucose and a CD- or D-ring synthon, (2) stereoselective glycosidation of the D-ring-containing fragment with the amino sugar reagent, and (3) adjustment of the functionality of the resulting glycoside to permit formation of the bond between C-2 and C-5′. Further elaboration of the western synthon then becomes a problem of 11-deoxyanthracycline synthesis which has been successfully addressed by several groups in recent years.[9]

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(3) Wiley, P. F.; Kelly, R. B.; Caron, E. L.; Wiley, V. H.; Johnson, J. H.; MacKellar, F. A.; Miszak, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 542.

(4) Wiley, P. F.; Elrod, D. W.; Marshall, V. P. *J. Org. Chem.* **1978**, *43*, 3457.

(5) (a) Wiley, P. F. *J. Nat. Prod.* **1979**, *42*, 569. (b) Wiley, P. F.; Elrod, D. W.; Houser, D. J.; Johnson, J. L.; Pschigoda, L. M.; Kreuger, W. C.; Moscowitz, A. *J. Org. Chem.* **1979**, *44*, 4030. (c) Eckle, E.; Stezowski, J. J.; Wiley, P. F. *Tetrahedron Lett.* **1980**, *21*, 507. (d) Wiley, P. F.; Elrod, D. W.; Richard, F. A. *J. Med. Chem.* **1982**, *25*, 560. (e) Arora, S. K. *J. Am. Chem. Soc.* **1983**, *105*, 1328.

(6) (a) Wiley, P. F.; Johnson, J. L.; Houser, D. J. *J. Antibiot.* **1977**, *30*, 628. (b) McGovren, J. P.; Nelson, K. G.; Lassus, M.; Craddock, J. C.; Plowman, J.; Christopher, J. P. *Invest. New Drugs* **1984**, *2*, 359.

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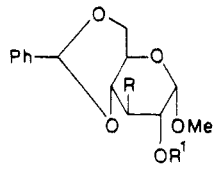
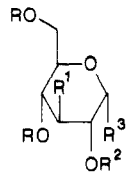
(8) Several partial solutions to this problem have recently been reported. (a) Bates, M. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1983**, 896. (b) Hauser, F. M.; Ellenberger, W. P.; Adams, T. C., Jr. *J. Org. Chem.* **1984**, *49*, 1169. (c) Hauser, F. M.; Adams, T. C., Jr. *J. Org. Chem.* **1984**, *49*, 2296. (d) Kawasaki, M.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1985**, *26*, 2693.

The partially protected 3-aminoglucose derivative **12**,[10] readily available from D-glucose, was a convenient starting material for the preparation of the amino sugar synthon.[11] The amino group was protected by conversion (*N*-carbethoxyphthalimide, 91%) to the phthalimide **13**. The 2-hydroxyl was protected via methylation (MeI, Ag_2O, CH_2Cl_2, 76%), which afforded **14**. Protection of the 4- and 6-hydroxyls to the acidic conditions required to functionalize the anomeric carbon for glycosidation was achieved by mild acid hydrolysis (50% HOAc) of the benzylidene moiety followed by *p*-nitrobenzoylation (p-$O_2NC_6H_4COCl$, DMAP, 77%) to provide **17**. Functionalization of the anomeric carbon was accomplished via acetolysis of **17** (Ac_2O, HOAc, H_2SO_4, 92%) to provide **18**. Reaction of **18** with anhydrous HCl or HBr afforded the corresponding halo sugars **19** and **20**, respectively. Acetolysis of **14** afforded **21** (74%) thus functionalizing the 1-position and affording acid-stable protection to the 4- and 6-hydroxyls in a single operation.



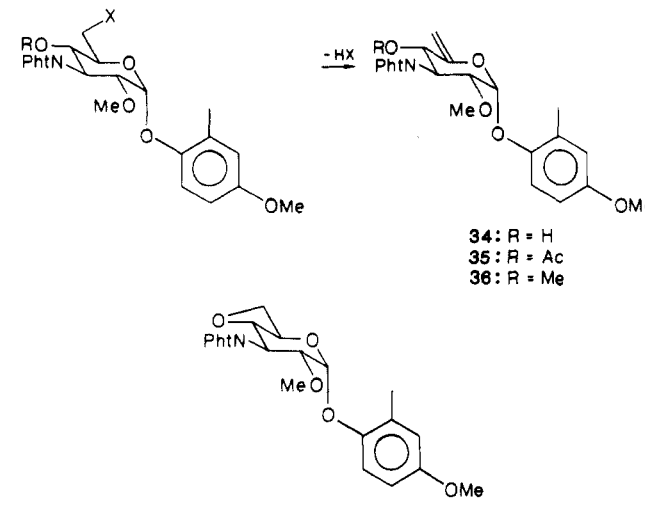
12: R = NH_2; R^1 = H
13: R = NPht; R^1 = H
14: R = NPht; R^1 = Me
15: R = NHTFA; R^1 = H
16: R = NHTFA; R^1 = Bzl



17: R = PNB; R^1 = NPht; R^2 = Me; R^3 = OMe
18: R = PNB; R^1 = NPht; R^2 = Me; R^3 = OAc
19: R = PNB; R^1 = NPht; R^2 = Me; R^3 = Cl
20: R = PNB; R^1 = NPht; R^2 = Me; R^3 = Br
21: R = Ac; R^1 = NPht; R^2 = Me; R^3 = OAc
22: R = PNB; R^1 = NHTFA; R^2 = Bzl; R^3 = OMe

The choice of protecting groups in this sequence proved to be crucial. The protected aminoglucose derivative **22**, prepared from **13** by standard methods via **15** and **16**, was unsuitable as a synthon for incorporating the amino sugar residue into the target. The main obstacle to the use of **22** was the resistance of the methyl glycoside to hydrolysis under conditions to which the 2-*O*-benzyl and 3-trifluoroacetamido groups were stable.

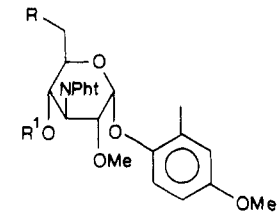
Scheme II

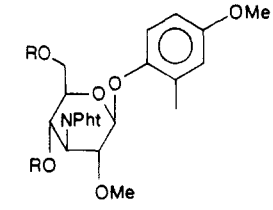


34: R = H
35: R = Ac
36: R = Me

37

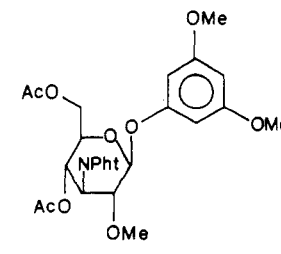
Glycosidation of **9**[12] and **11**[13] with the halo sugars **19** and **20** could not be achieved under a variety of Koenigs–Knorr conditions. An additional complication was the instability of the CD-ring synthon **11** under these conditions. This led us to concentrate on **9** as a simpler substrate upon which to work out suitable glycosidation conditions. The $SnCl_4$-catalyzed[14] reactions of **9** with **18** and **21** provided the α-glycosides **23** and **24** in reasonable yield along with the corresponding β-anomers **31** and **32** in a 5:1 ratio. The stereocontrol achieved in this process was presumed to be





31: R = PNB
32: R = OAc

23: R = R^1 = OPNB
24: R = R^1 = OAc
25: R = R^1 = OH
26: R = OMs; R^1 = OH
27: R = I; R^1 = OH
28: R = I; R^1 = OAc
29: R = OMs; R^1 = OMe
30: R = I; R^1 = OMe



33

(9) (a) Bauman, J. G.; Barber, R. B.; Gless, R. D.; Rapoport, H. *Tetrahedron Lett.* **1980**, *21*, 4777. (b) Tatsuta, K.; Takeuchi, T. *J. Antibiot.* **1980**, *33*, 1581. (c) Confalone, P. N.; Pizzalato, G. *J. Am. Chem. Soc.* **1981**, *103*, 4251. (d) Boeckman, R. K., Jr.; Seem, F.-W. *J. Am. Chem. Soc.* **1982**, *104*, 4604. (e) Mitscher, L. A.; Wu, T.-S.; Khanna, I. *Tetrahedron Lett.* **1983**, *24*, 4809. (f) Vedejs, E.; Miller, W. H.; Pribish, J. R. *J. Org. Chem.* **1983**, *48*, 3611. (g) Rama Rao, A. V.; Chanda, B. M.; Borate, H. B. *Synth. Commun.* **1984**, *14*, 257. (h) Deshpande, V. H.; Ravichandran, K.; Ramamohan Rao, B. *Synth. Commun.* **1984**, *14*, 477. (i) Uemura, M.; Minami, T.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1193. (j) Krohn, K. *Liebigs Ann. Chem.* **1983**, 2151. (k) Kelly, T. R., Ed. *Tetrahedron (Symposia-in-Print)* **1984**, *40* (17), 4537–4789. (l) Tanaka, H.; Yoshioka, T.; Shimauchi, Y.; Yoshimoto, A.; Ishikura, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *Tetrahedron Lett.* **1984**, *25*, 3355 and references cited therein. (m) Bauman, J. G.; Hawley, R. C.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1569.

(10) Guthrie, R. D.; Johnson, L. F. *J. Chem. Soc.* **1961**, 4166.

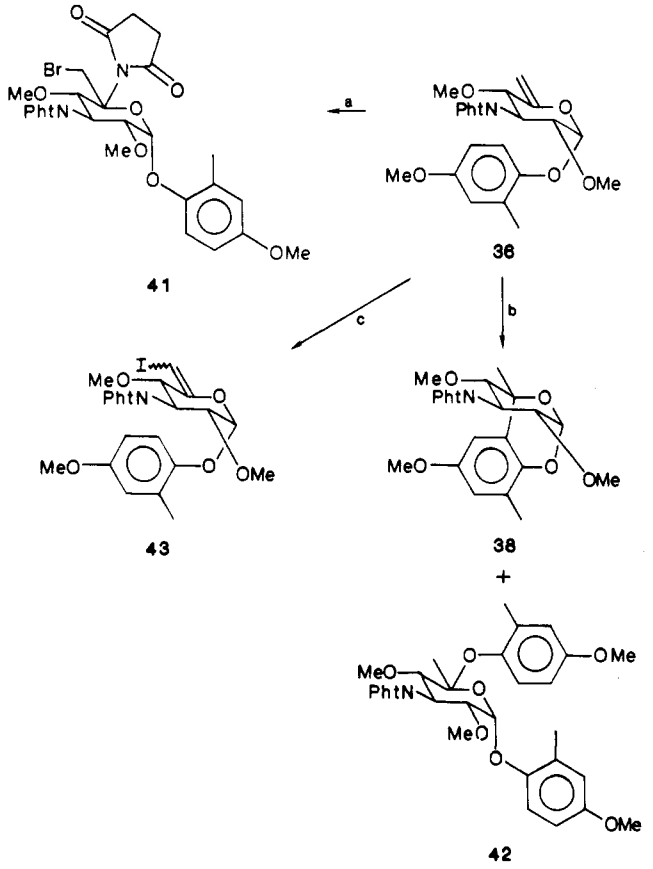
(11) When this study was initiated the configuration of the amino glucose residue had not been determined. We chose to work with the D-glucose series due to its greater accessibility and biosynthesis evidence (ref 4) that the amino sugar of **3** was of the D series. X-ray data has now been reported (ref 4e) indicating that the amino sugar has the L configuration. However, the chemistry developed for the D series should also be applicable to the corresponding compounds having the L-glucose configuration.

(12) Green, J.; McHale, D.; Mammalis, P.; Marcinkewicz, S. *J. Chem. Soc.* **1959**, 3374.

(13) Smith, T. H.; Wu, H. Y. *J. Org. Chem.* **1982**, *47*, 1974.

(14) Honma, K.; Nakazima, K.; Uematsu, T.; Hamada, A. *Chem. Pharm. Bull.* **1976**, *24*, 394.

Scheme III[a]



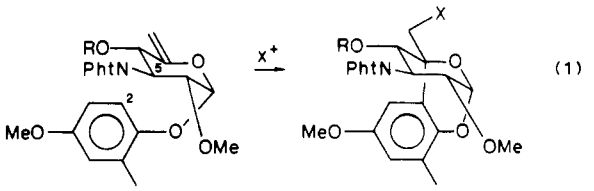
[a] (a) NBS; (b) TFA; (c) iodonium dicollidine perchlorate.

due to the influence of the phthalimido group. Steric control of a glycosidation reaction by a phthalimido moiety has previously been reported.[15] However an attempt to extend this process to the condensation of 3,5-dimethoxyphenol with **21** afforded only the β-glycoside **33**. An explanation for the dramatic difference in the stereochemical outcome of these seemingly similar reactions is not obvious.

With the α-glycoside in hand, our next objective was to generate the 5′,6′-olefin required for the projected cyclization to form the 2,5′-C–C bond (Scheme II). Quantitative removal of the *O*-acyl protecting groups of **23** and **24** was achieved with Dowex resin (OH^- form) in EtOH and Na_2CO_3 in MeOH, respectively, to provide **25**. Selective functionalization of the 6-position was best achieved via reaction of **25** with 1 equiv of methanesulfonyl chloride in pyridine to afford **26**. Reaction of **26** with NaI in acetone afforded **27** in high yield. It ultimately proved to be necessary to protect the 4′-hydroxyl. This could be achieved either by acylation (Ac_2O, DMAP, CH_2Cl_2) of **27** to provide **28** or by methylation (MeI, Ag_2O, CH_2Cl_2) of **26** to provide **29**, which is converted to **30** via reaction with NaI in 2-butanone. Attempts to generate the olefin **34** from **26** or **27** were unsuccessful, possibly due to the presence of the free hydroxyl, which in similar systems can form oxetanes such as **37** via intramolecular displacement of the leaving group.[16] Olefins **35** and **36** were readily prepared via reaction of the hydroxyl-protected intermediates **28** and **30**, respectively, with DBU in HMPA.[17]

(15) Ogawa, T.; Nakahayashi, S.; Sasajima, K. *Carbohydr. Res.* **1981**, *95*, 308.
(16) Hough, L.; Otter, B. *J. Chem. Soc., Chem. Commun.* **1966**, 173.
(17) Crugnola, A.; Lombardi, P.; Gandolfe, C.; Arcamone, F. *Gazz. Chem. Ital.* **1981**, *111*, 395.

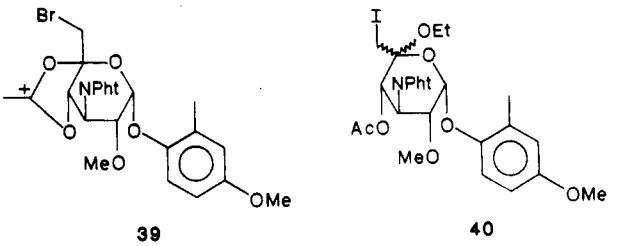
Having synthesized **35**, our next objective was the formation of the C–C bond between C-5 of the amino sugar residue and C-2 of the D-ring synthon. To achieve ring closure we proposed to develop a positive charge at C-5 of the vinyl ether which would then undergo intramolecular nucleophilic attack by the electron rich aromatic system (eq 1). Our approach was to treat the olefin with



(1)

a proton source or equivalent, such as a Lewis acid or positive halogen species, which could generate the positive charge at C-5′.

The mode of protection of the 4′-hydroxyl proved to be critical in this process. Reaction of **35** with *N*-bromosuccinimide (NBS), iodonium dicollidine perchlorate,[18] or a catalytic amount of TFA gave rise to a less polar (TLC) product which could not be isolated but decomposed on workup to an intractable mixture of polar products. NMR monitoring of the reaction between 35 and NBS revealed the rapid disappearance of the 4′-acetate signal. This is consistent with interaction of the 4′-acetate moiety with the positive center at C-5′ giving rise to a species such as **39**, which could decompose to the observed polar products.

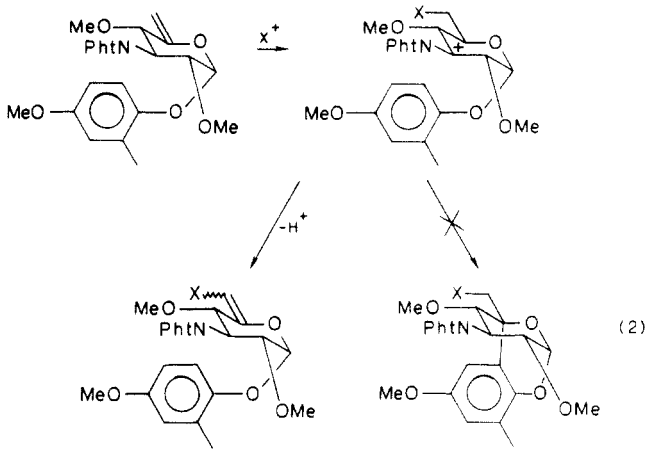


However it was possible to trap the C-5′ cation. Reaction of **35** with iodonium dicollidine perchlorate in the presence of an external nucleophile, EtOH, gave rise to **40**. Although this result supported the general feasibility of our method, it was clear that a nonparticipating protecting group for the 4′-hydroxyl was required if this approach was to be successful. This led us to investigate **36** as a cyclization substrate (Scheme III). Reaction of **36** with NBS was unsuccessful, generating an unstable, less polar product characterized as **41** by NMR. However, reaction of **36** with a catalytic amount of TFA afforded, after workup, mostly starting material along with low and erratic yields of a material tentatively characterized as the desired product **38** as well as the bisaglycone adduct **42**. Reaction of **36** with iodonium dicollidine perchlorate afforded the iodo olefin **43** as the major product.

These results indicate that the reaction of **36** at least under the conditions studied thus far, follows the pathway outlined in eq 2. Positively charged species do react with the olefin to generate a carbcation at C-5′. However, proton loss to afford an olefinic species is apparently favored over nucleophilic attack by the aromatic moiety.

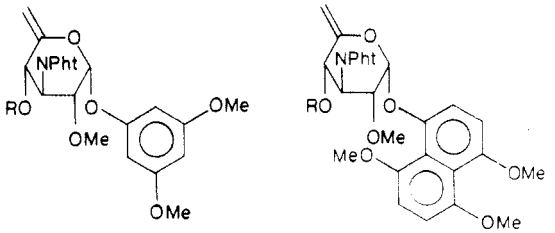
Future research in this area could explore the reaction of **36** with other Lewis acid catalysts and the cyclization of olefinic glycosides such as **44** and **45** in which the nu-

(18) (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2199. (b) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956.



(2)

cleophilicity of the C-2 position (anthracycline numbering) is enhanced relative to that of **36**. As noted earlier our



44

45

efforts to prepare **44** were frustrated when the $SnCl_4$ glycosidation of 3,5-dimethoxyphenol with **21** afforded exclusively the undesired β-anomer. We have also noted the stability problems experienced in attempting to glycosidate **11**, the aglycon of **45**.

In summary the approach described herein has not as yet provided a satisfactory route to a nogalamycin western synthon. However, the ability of the olefinic substrate **36** to trap external nucleophiles at C-5′ indicates that this approach may still be viable with the appropriate substrate. The logical extension of this work is to attempt the cyclization of a substrate bearing a more nucleophilic aromatic moiety. This, however, must await the stereocontrolled construction of such a substrate with the proper configuration at the anomeric center, a goal which has thus far been elusive.

Experimental Section

Ag_2O was freshly prepared immediately prior to use.[19] Me_2SO was distilled from CaH_2 immediately prior to use. Solvent extracts of aqueous solutions were dried over anhydrous Na_2SO_4. Solutions were concentrated under reduced pressure using a rotary evaporator. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Spectra were determined as follows: UV, Cary 11 or Cary 14 recording spectrophotometer; IR (Nujol mull), Perkin-Elmer 137; ^1H NMR ($CDCl_3$ solution unless otherwise stated, Me_4Si internal reference), Varian EM-390 or Varian XL-100 spectrometer; MS measured by Dr. D. W. Thomas with an LKB Model 9000 spectrometer. Elemental microanalyses were provided by the microanalytical laboratory of Stanford University and by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatograms (TLC) were obtained on silica gel GF 250 m plates (Analtech). All compounds reported were homogenous by TLC unless otherwise noted. Preparative layer chromatograms (PLC) were obtained on 20 × 20 × 0.2 cm silica gel 60 F-254 plates (E. Merck). Preparative liquid chromatography was performed with a Waters LC/500 system or prepacked E. Merck LOBAR silica gel 60 columns. Dry column chromatography was preformed with silica Woelm TSC.

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-phthalimido-α-D-glucopyranoside (13). A solution of **12** (4.50 g, 16.0 mmol), *N*-(ethoxycarbonyl)phthalimide (3.86 g, 17.6 mmol), and triethylamine (2.27 mL, 17.6 mmol) in Me_2SO (30 mL) was stirred at 23 °C for 16 h, diluted with H_2O, and extracted with CH_2Cl_2 (3 × 60 mL). The extracts were combined, washed with 0.5 M citric acid (2 × 50 mL), saturated $NaHCO_3$ (100 mL), and water (50 mL), dried, and evaporated. The oily residue was crystallized from CH_2Cl_2/hexane to afford 6.0 g (91%) of **13**: mp 158–159 °C: IR 2.90 (OH), 5.65, 5.85 (CO), 6.85, 6.90, 7.27, 8.95, 9.33, 9.48, 9.95, 10.38, 10.70, 10.90, 11.10, 13.18, 13.84, 14.30 μM; NMR δ 3.52 (s, 3, OMe), 3.86 (m, 2), 4.3–4.6 (m, 4), 4.90 (d, 1, *J* = 3 Hz, 1-H), 5.50 (s, 1, PhCH), 7.30 (m, 5, PhCH), 7.75 (m, 4, Pht H's); TLC (97:3 CH_2Cl_2/MeOH) R_f 0.40.

Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.22; H, 5.15; N, 3.40. Found: C, 64.11; H, 5.22; N, 3.40.

Methyl 4,6-*O*-Benzylidene-3-deoxy-2-methoxy-3-phthalimido-α-D-glucopyranoside (14). Freshly prepared Ag_2O (20 g) was added to a solution of **13** (26.0 g, 0.063 mol) and MeI (20 mL) in CH_2Cl_2 (500 mL) and the mixture refluxed with vigorous stirring for 96 h. Five further additions of MeI (20 mL) and Ag_2O (20 g) were made at 4, 8, 24, 48, and 72 h with the old Ag salts removed by filtration prior to each new addition. The reaction mixture was filtered and evaporated. The residue was chromatographed (dry column 30 mm × 5 ft, silica gel, 98.5:1.5 CH_2Cl_2/MeOH) and the product recrystallized from CH_2Cl_2/hexane to afford 20.4 g (76%) of **14**: mp 202–203 °C; IR 5.60, 5.80 (C=O), 6.85, 7.30, 8.70, 9.00, 9.29, 9.45, 10.00, 10.30, 10.40, 10.85, 11.00, 13.20, 13.80, 14.30 μm; NMR δ 3.35 (s, 3, 2-OMe), 3.52 (s, 3, 1-OMe), 3.60–4.10 (m, 3), 4.20–4.50 (m, 2), 4.81 (t, 1, 3-H), 5.02 (d, 1, *J* = 3 Hz, 1-H), 5.46 (s, 1, PhCH), 7.00–7.40 (m, 5, Ph H's), 7.60–7.90 (m, 4, Pht H's); UV (MeOH) λ_{max} 220 nm (ε 40 800), 241 (8700), 292 (2000); TLC (99:1 CH_2Cl_2/MeOH) R_f 0.26.

Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.61; H, 5.46; N, 3.18.

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-trifluoroacetamido-α-D-glucopyranoside (15). Trifluoroacetic anhydride (3.0 mL) was added to a solution of **12** (1.40 g, 4.99 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The mixture was stirred at 0 °C for 0.25 h and at 23 °C for 4 h. The solvent was evaporated. The residue was dissolved in EtOAc (36 mL) and stirred with saturated $NaHCO_3$ (30 mL) for 20 h. The mixture was filtered and the precipitate washed with EtOAc and water and dried to afford 1.87 g (99%) of **15**: mp 342–343 °C dec; IR 2.90, 3.02 (OH, NH), 5.85 (C=O), 6.36, 6.85, 7.31, 8.11, 8.24, 8.42, 8.86, 9.30, 10.06, 13.32, 14.35 μm; NMR (Me_2SO-d_6) δ 3.38 (s, 3, OMe), 3.68 (m, 4), 4.02 (m, 1), 4.20 (m, 1), 4.71 (d, 1, *J* = 3 Hz, 1-H), 5.21 (d, 1, D_2O exchangable, 2-OH), 5.52 (s, 1, PhCH), 7.37 (s, 5, Ph H's), 9.28 (d, 1, NH).

Anal. Calcd for $C_{16}H_{18}F_3NO_6$: C, 50.84; H, 4.80; N, 3.71. Found: C, 50.84; H, 4.83; N, 3.67.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-3-trifluoroacetamido-α-D-glucopyranoside (16). A solution of **15** (601.5 mg, 1.60 mmol) in Me_2SO (3.5 mL) was added under N_2 to NaH (147.8 mg of 57% dispersion, 3.51 mmol) in Me_2SO (1.2 mL), and the mixture was stirred for 0.5 h. Benzyl chloride (0.50 mL) was added and the mixture stirred at 23 °C for 3 h. The reaction mixture was poured into ice–water (50 mL) and the precipitate collected, washed with water and hexane, and dried to afford 565.7 mg (76%) of **16**: mp 272–273 °C; IR 3.02 (NH), 5.85 (C=O), 6.35, 6.81, 6.88, 7.30, 7.70, 8.25, 8.45, 8.85, 8.98, 9.12, 9.60, 10.05, 10.28, 13.20, 13.33, 13.58, 13.73 μm; NMR (Me_2SO-d_6) δ 3.38 (s, 3, OMe), 3.71 (m, 4), 4.20 (m, 2), 4.58 (d, 2, CH_2Ph), 4.95 (d, 1, *J* = 3 Hz, 1-H), 5.57 (s, 1, CHPh), 7.25 (m, 10, Ar H's), 9.48 (d, 1, NH); TLC (95:5 $CHCl_3$/MeOH) R_f 0.60.

Anal. Calcd for $C_{23}H_{24}F_3NO_6$: C, 59.09; H, 5.18; N, 3.00. Found: C, 58.66; H, 5.09; N, 2.99.

Methyl 3-Deoxy-2-methoxy-4,6-bis-*O*-(*p*-nitrobenzoyl)-3-phthalimido-α-D-glucopyranoside (17). A suspension of **14** (20.4 g, 48.0 mmol) in 50% HOAc (1.5 L) was stirred at 100 °C for 1 h with the solid gradually going into solution. The solvent was evaporated, benzene was added to the remaining syrup and evaporated, and the residue was dried under vacuum. The residue,

(19) Mellor, J. W. *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*; Longmans, Green and Co.: New York, 1922; Vol. III, pp 371–375.

p-nitrobenzoyl chloride (29.3 g, 158 mmol), triethylamine (16 mL), and 4-(dimethylamino)pyridine (6.9 g, 56.4 mmol) were placed in DMF (300 mL) and stirred at 0 °C for 15 h. The mixture was treated with water (10 mL), stirred for 0.5 h at 23 °C, diluted with water (500 mL), and extracted with CH_2Cl_2 (3 × 500 mL). The extracts were combined, washed with 1 N HCl (2 × 500 mL), saturated $NaHCO_3$ (500 mL), and saturated NaCl (200 mL), dried, and evaporated. The residue was chromatographed (dry column, silica gel, 30 mm × 5 ft, 98:2 CH_2Cl_2/MeOH) and the product recrystallized from CH_2Cl_2/hexane to afford 23.6 g (77%) of **17**: mp 202–203 °C: IR 5.60, 5.75 (C=O), 6.18, 6.51, 6.80, 7.22, 7.40, 7.76, 9.00, 9.45, 11.40, 12.00, 12.74, 13.87 μm; NMR δ 3.37 (s, 3, 2-OMe), 3.58 (s, 3, 1-OMe), 4.2–4.7 (m, 4), 4.94 (t, 1, 3-H), 5.12 (d, 1, *J* = 3 Hz, 1-H), 6.00 (t, 1, 4-H), 7.6–7.9 (m, 4, Pht H's), 7.9–8.4 (m, 8, PNB H's); UV (MeOH) λ_{max} 219 nm (ε 51 000), 234 (23 300), 242 (29 400e, 258 (27 100); TLC (1:1 hexane/EtOAc) R_f 0.50.

Anal. Calcd for $C_{30}H_{25}N_3O_{13}$: C, 56.69; H, 3.97; N, 6.61. Found: C, 56.36; H, 4.07; N, 6.53.

Acetyl 3-Deoxy-2-methoxy-4,6-bis-*O*-(*p*-nitrobenzoyl)-3-phthalimido-α-D-glucopyranoside (18). To a solution of **17** (23.0 q, 36.2 mmol) and acetic anhydride (135 mL) in glacial acetic acid (720 mL) at 10 °C was added dropwise concentrated H_2SO_4 (43.2 mL). The solution was kept at 23 °C for 48 h and then poured into ice–water (4 L). The precipitate was collected, dried, and recrystallized from CH_2Cl_2/hexane to afford 22.0 g (92%) of **18**: mp 165–166 °C; IR 5.80, 5.90, 6.25, 6.60, 6.90, 7.30, 7.50, 7.95, 8.25, 8.75, 9.10, 9.90, 10.70, 11.00, 11.50, 12.05, 12.80, 13.97 μm; NMR δ 2.28 (s, 3, 1-OAc), 3.34 (s, 3, 2-OMe), 4.3–4.7 (m, 4), 4.88 (t, 1, 3-H), 6.05 (t, 1, 4-H), 6.60 (d, 1, *J* = 3 Hz, 1-H), 7.6–7.9 (m, 4, Pht H's), 7.9–8.4 (m, 8, PNB H's); UV (MeOH) λ_{max} 258 nm (ε 27 230), 242 (25 500), 233 (23 400), 219 (52 100); TLC (2:1 hexane/EtOAc) R_f 0.2.

Anal. Calcd for $C_{31}H_{25}N_3O_{14}$: C, 56.11; H, 3.80; N, 6.33. Found: C, 55.88; H, 4.27; N, 6.07.

Bromo 3-Deoxy-2-methoxy-4,6-bis-*O*-(*p*-nitrobenzoyl)-3-phthalimido-α-D-glucopyranoside (20). Anhydrous HBr was passed into a solution of **18** (1.40 g, 2.1 mmol) and acetyl bromide (2.0 mL) in CH_2Cl_2 (25 mL) at 23 °C for 0.5 h. The solution was allowed to stand at 23 °C for 16 h and evaporated. Two 10-mL portions of benzene and CH_2Cl_2 were added to and evaporated from the residue, which was then dried under vacuum to afford 1.45 g (100%) of **20**: IR 5.65, 5.80, 5.85 (C=O), 6.25, 6.60, 6.88, 6.95, 7.25, 7.30, 7.48, 7.62, 7.90, 8.00, 8.40, 8.72, 9.10, 9.68, 9.88, 11.46, 11.65, 12.00, 12.80, 13.95, 14.65 μm; NMR δ 3.37 (s, 3, 2-OMe), 4.40–4.75 (m, 4), 4.96 (t, 1, 3-H), 6.05 (t, 1, 4-H), 6.80 (d, 1, *J* = 3 Hz, 1-H), 7.35 (s, 2, C_6H_6), 7.6–7.9 (m, 4, Pht H's), 7.9–8.4 (m, 8, PNB H's); TLC (2.1 hexane/EtOAc) R_f 0.35.

Anal. Calcd for $C_{29}H_{22}BrN_3O_{12}\cdot{}^1/_3\,C_6H_6$: C, 52.40; H, 3.40; N, 5.91. Found: C, 52.74; H, 3.58; N, 5.91.

Acetyl 4,6-Di-*O*-acetyl-3-deoxy-2-methoxy-3-phthalimido-α-D-glucopyranoside (21). To a solution of **14** (42.0 g, 98.7 mmol) and acetic anhydride (250 mL) in glacial acetic acid (1.3 L) at 10 °C was added dropwise concentrated H_2SO_4 (79 mL). The solution was stirred at 23 °C under N_2 for 72 h. The reaction mixture was poured into ice–water (4 L) and extracted with EtOAc (4 × 1 L). The extracts were combined, washed with water (500 mL) and saturated $NaHCO_3$ (2 × 1 L), dried, and evaporated. The residue was crystallized from CH_2Cl_2/hexane to afford 40 g (90%) of **21**: IR 5.72, 5.85, 6.95, 7.35, 8.00, 8.28, 8.75, 9.08, 9.30, 9.60, 9.90, 10.67, 10.90, 11.25, 12.50, 13.86 μm; NMR δ 1.87 and 2.03 (2 s, 6, 4- and 6-OAc's), 2.22 (s, 3, 1-OAc), 3.30 (s, 3, 2-OMe), 4.18 (m, 4), 4.57 (m, 1), 5.55 (t, 1, 4-H), 6.52 (d, 1, *J* = 3 Hz, 1-H), 7.80 (m, 4, Pht H's); TLC (2:1 hexane/EtOAc) R_f0.25.

Anal. Calcd for $C_{21}H_{23}NO_{10}$: C, 56.12; H, 5.16; N, 3.12. Found: C, 56.13; H, 5.08; N, 3.03.

4-Methoxy-2-methylphenyl 3-Deoxy-2-methoxy-4,6-bis-*O*-(*p*-nitrobenzoyl)-3-phthalimido-α-D-glucopyranoside (23). $SnCl_4$ (0.45 mL) was added to a solution of **9** (414 mg, 3.0 mmol) and **18** (1.0 g, 1.50 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at 23 °C for 5 h, diluted with CH_2Cl_2 (150 mL), washed with water (100 mL), dried, and evaporated. While it is more convenient to carry this material on to the next step it can be purified at this stage by chromatography (preparative HPLC, silica gel, 3:1 hexane/EtOAc) to afford 350 mg (32%) of an 86:14 mixture of **23** and the β-anomer **31**: IR 5.64, 5.80, 6.23, 6.60, 6.70, 6.90, 7.30, 7.48, 7.65, 7.90, 8.30, 9.00, 9.10, 9.75, 9.90, 10.65, 11.45, 11.55, 11.72, 12.80, 13.95 μM; NMR δ 2.39 (s, 3, ArMe), 3.37 (s, 3, 2-OMe), 3.75 (s, 3, ArOMe), 4.4–4.6 (m, 3), 4.62 (dd, 1, *J* = 10 Hz and 3 Hz, 2-H), 5.15 (t, 1, 3-H), 5.70 (d, 1, J = 3 Hz, 1-H), 6.05 (t, 1, 4-H), 6.55 (dd, 1, Ar H), 6.78 (d, 1, Ar H), 7.14 (d, 1, Ar H), 7.6–7.9 (m, 4, Pht H's), 7.9–8.4 (m, 8 PNB H's); MS, *m/e* (relative intensity) 741 [M^+] (1), 604 (8), 437 (25), 290 (48), 270 (100), 150 (100); UV (MeOH) λ_{max} 259 nm (ε 27 400), 242 (25 500), 219 (61 300); TLC (2:1 hexane/EtOAc) R_f 0.35.

Anal. Calcd for $C_{37}H_{31}N_3O_{14}$: C, 59.91; H, 4.22; N, 5.66. Found: C, 59.50; H, 4.13; N, 5.66.

4-Methoxy-2-methylphenyl 4,6-Di-*O*-acetyl-3-deoxy-2-methoxy-3-phthalimido-α-D-glucopyranoside (24). $SnCl_4$ (1.15 mL) was added to a solution of **21** (3.4 g, 7.57 mmol) and **9** (1.26 g, 9.08 mmol) in CH_2Cl_2 (35 mL) at 23 °C and the solution was stirred for 2.5 h. A second portion of **9** (105 mg, 0.76 mmol) was added and stirring was continued for an additional 0.5 h. The reaction mixture was poured into saturated $NaHCO_3$ (300 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The extracts were combined, washed with water (100 mL), dried, and evaporated. The residue was chromatographed (preparative HPLC, silica gel, 3:1 hexane/EtOAc) to afford 1.9 g (48%) of a 5:1 mixture of **24** and the β-anomer **32**: IR 5.78, 5.90 (C=O), 6.95, 7.35, 8.28, 9.64, 13.95 μm; NMR δ 1.88 (s, 3, OAc), 2.08 (s, 3, OAc), 2.32 (s, 3, ArMe), 3.30 (s, 2.5, 2-OMe of α-anomer), 3.48 (s, 0.5, 2-OMe of β-anomer), 3.76 (s, 3, ArOMe), 4.0–4.6 (m, 4), 4.86 (t, 1, 3-H), 5.52 (m, 1, 4-H), 5.59 (d, 1, *J* = 3 Hz, 1-H), 6.67 (m, 2, Ar 3- and 5-H's), 7.10 (d, 1, *J* = 8 Hz, Ar 6-H), 7.78 (m, 4, Pht H's); TLC (2:1 hexane/EtOAc) R_f 0.30.

4-Methoxy-2-methylphenyl 3-Deoxy-2-methoxy-3-phthalimido-α-D-glucopyranoside (25). To a solution of crude **23** (300 mg) in MeOH (30 mL) was added Dowex 2X8 resin (OH^- form, 300 mg). The mixture was refluxed for 0.5 h, filtered, and evaporated. The residue was recrystallized from CH_2Cl_2/hexane and chromatographed (PLC, 97:3 CH_2Cl_2/MeOH) to afford **25** as a 5:1 α/β anomeric mixture in 32% yield from **18**: IR 2.88 (OH), 5.63, 5.84 (Pht C=O), 6.22, 6.70, 7.30, 8.30, 9.05, 9.40, 9.75, 10.65, 10.95, 11.50, 12.60, 13.90 μm; NMR δ 2.26 (s, 3, ArMe), 3.28 (s, 2.5, 2-OMe of α-anomer), 3.46 (s, 0.5, 2-OMe of β-anomer), 3.76 (s, 3, ArOMe), 3.75–4.00 (m, 4), 4.30 (dd, 1, 2-H), 4.80 (t, 1, 3-H), 5.57 (d, 1, *J* = 3 Hz, 1-H), 6.6–6.8 (m, 2, Ar 3- and 5-H's), 7.06 (d, 1, Ar 6-H), 7.6–7.9 (m, 4, Pht H's); UV (MeOH) λ_{max} 285–289 nm (ε 4127), 220.5 (51 100); MS, *m/e* (relative intensity) 443 M^+ (2), 306 (38), 288 (1), 274 (5), 258 (63), 256 (18), 226 (28), 216 (26), 138 (100); TLC (97:3 CH_2Cl_2/MeOH) R_f 0.20.

Anal. Calcd for $C_{23}H_{25}NO_8\cdot 0.2H_2O$: C, 61.79; H, 5.73; N, 3.13. Found: C, 61.70; H, 5.87; N, 3.09.

Method B. To a solution of **24** (471 mg, 0.89 mmol) in MeOH (235 mL) was added saturated K_2CO_3 in MeOH (0.8 mL). The solution was stirred at 23 °C for 2 h, neutralized with HOAc in MeOH, and evaporated. The residue was triturated with $CHCl_3$ and filtered and the filtrate evaporated to afford 410 mg (100%) of **25**.

4-Methoxy-2-methylphenyl 3-Deoxy-6-[(methylsulfonyl)oxy]-2-methoxy-3-phthalimido-α-D-glucopyranoside (26). To a solution of **25** (2.22 g, 5.0 mmol) in pyridine (20 mL) at 0 °C was added methanesulfonyl chloride (0.44 mL, 5.7 mmol). The mixture was stirred at 0 °C for 48 h, poured into water (100 mL), and extracted with CH_2Cl_2 (2 × 150 mL). The extracts were combined, washed with saturated $NaHCO_3$ (50 mL) and water (50 mL), dried, and evaporated to afford 2.54 g (98%) of **26**: IR 2.86 (OH), 5.62, 5.89 (Pht C=O), 6.22, 6.70, 6.89, 7.18, 7.31, 7.45, 8.30, 8.57, 9.03, 9.18, 9.38, 9.58, 9.78, 10.10, 10.88, 11.50, 12.05, 13.50, 13.90 μm; NMR δ 2.35 (s, 3, ArMe), 3.07 (s, 3, SO_2Me), 3.29 (s, 3, 2-OMe), 3.77 (s, 3, ArOMe), 4.09 (dt, 1, 5-H), 4.35 (dd, 2), 4.45 (dd, 1), 4.60 (dd, 1), 4.80 (t, 1, 3-H), 5.60 (d, 1, *J* = 3 Hz, 1-H), 6.68 (dd, 1, Ar 5-H), 6.75 (d, 1, Ar 3-H), 7.10 (d, 1, Ar 6-H), 7.6–7.9 (m, 4, Pht H's); TLC (98:2 CH_2Cl_2/MeOH) R_f 0.30.

Anal. Calcd for $C_{24}H_{27}NO_{10}S\cdot 0.3H_2O$: C, 54.70; H, 5.28; N, 2.66. Found: C, 54.56; H, 5.36; N, 2.63.

4-Methoxy-2-methylphenyl 3,6-Dideoxy-6-iodo-2-methoxy-3-phthalimido-α-D-glucopyranoside (27). **26** (2.0 g, 3.84 mmol) was placed in 10% KI in acetone (80 mL) and stirred at 50 °C for 120 h. The mixture was filtered and the filtrate evaporated. The residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (20 mL). The organic layer was separated, dried, and evaporated to afford 2.10 g (97%) of **27**: IR 2.90 (OH), 5.60, 5.85

(C=O), 6.70, 6.88, 7.30, 8.30, 9.05, 9.40, 9.70, 10.60, 10.90, 11.50, 13.55 μm; NMR δ 2.30 (s, 3, ArMe), 3.25 (s, 3, 2-OMe), 3.3–3.7 (m, 2), 3.75 (s, 3, ArOMe), 4.1–4.4 (m, 2), 4.80 (t, 1, 3-H), 5.55 (d, 1, J = 3 Hz, 1-H), 6.6–6.8 (m, 2, Ar 3- and 5-H's), 7.20 (m, 2, Ar 6-H), 7.6–7.8 (m, 4, Pht H's); TLC (99:1 CH_2Cl_2/MeOH) R_f 0.30.

4-Methoxy-2-methylphenyl 4-*O*-Acetyl-3,6-dideoxy-6-iodo-2-methoxy-3-phthalimido-α-D-glucopyranoside (28). To a solution of **27** (2.0 g, 3.55 mmol) and 4-(dimethylamino)pyridine (80 mg, 0.65 mmol) in CH_2Cl_2 (20 mL) was added acetic anhydride (0.64 mL, 6.70 mmol). The solution was stirred at 23 °C for 2 h, diluted with CH_2Cl_2 (40 mL), washed with 1 M citric acid, saturated $NaHCO_3$, and water, dried, and evaporated. The residue was chromatographed (dry column, silica gel, 98.5:1.5 CH_2Cl_2/MeOH) to afford 1.6 g (80%) of **28**: IR 5.70, 5.80 (C=O), 6.65, 6.85, 7.25, 8.20, 9.05, 9.55, 10.45, 11.40, 11.90, 12.50, 13.85 μm; NMR δ 1.90 (s, 3, OAc), 2.30 (s, 3, ArMe), 3.25 (s, 3, 2-OMe), 3.70 (s, 3, ArOMe), 3.8–4.1 (m, 1), 4.50 (dd, 1, 2-H), 4.90 (t, 1, 3-H), 5.40 (t, 1, 4-H), 5.60 (d, 1, J = 3 Hz, 1-H), 6.6–6.8 (m, 2, Ar 3- and 5-H's), 7.30 (d, 1, Ar 6-H), 7.6–7.9 (m, 4, Pht H's): TLC (99:1 CH_2Cl_2/MeOH) R_f 0.7.

Anal. Calcd for $C_{25}H_{26}INO_8$: C, 50.43; H, 4.40; N, 2.35. Found: C, 50.94; H, 4.79; N, 2.27.

4-Methoxy-2-methylphenyl 3-Deoxy-6-[(methylsulfonyl)oxy]-2,4-dimethoxy-3-phthalimido-α-D-glucopyranoside (29). A mixture of **26** (229.9 mg, 0.44 mmol), Ag_2O (600 mg), and methyl iodide (2.0 mL) in CH_2Cl_2 (12.0 mL) was refluxed for 4 h. The reaction mixture was filtered through Celite and evaporated. The residue was crystallized from $CHCl_3$/hexane to afford 201.4 mg (85%) of **29**: IR 5.62, 5.83 (Pht C=O), 6.69, 6.86, 7.28, 7.39, 8.27, 8.50, 9.10, 9.69, 13.85 μm; NMR δ 2.35 (s, 3, ArMe), 3.09 (s, 3, SO_2Me), 3.30 and 3.35 (2 s, 6, 2- and 4-OMe's), 3.78 (s, 3, ArOMe), 4.0–4.5 (m, 5), 4.88 (t, 1, 3-H), 5.57 (d, 1, J = 3 Hz, 1-H), 6.67 (dd, 1, Ar 5-H), 6.71 (br s, 1, Ar 3-H), 7.08 (d, 1, Ar 6-H), 7.80 (m, 4, Pht H's); TLC (95:5 $CHCl_3$/MeOH) R_f 0.73.

Anal. Calcd for $C_{25}H_{29}NO_{10}S$: C, 56.07; H, 5.45; N, 2.61. Found: C, 55.81; H, 5.27; N, 2.47.

4-Methoxy-2-methylphenyl 3,6-Dideoxy-6-iodo-2,4-dimethoxy-3-phthalimido-α-D-glucopyranoside (30). A solution of **29** (52.4 mg, 0.098 mmol) and NaI (300 mg) in 2-butanone (3.0 mL) was refluxed for 6 h, filtered, and evaporated. The residue was partitioned between $CHCl_3$ (15 mL) and water (5 mL). The organic solution was separated, washed with water (5 mL) and saturated NaCl (5 mL), dried, and evaporated. The residue was taken up in 1:1 hexane/EtOAc (5 mL) and passed through a silica gel column (1 × 3 cm). The eluent was evaporated to afford 55.5 mg (100%) of **30** as a syrup: IR 5.67, 5.88 (Pht C=O), 6.25, 6.73, 6.92, 7.35, 7.86, 8.30, 8.55, 9.08, 9.25, 9.75, 10.10, 10.60, 11.50, 12.50, 13.90 μm; NMR δ 2.32 (s, 3, ArMe), 3.30 and 3.40 (2 s, 6, 2- and 4-OMe's), 3.45–3.70 (m, 3), 3.79 (s, 3, ArOMe), 4.01 (t, 1, 4-H), 4.29 (dd, 1, J = 2 Hz and 10 Hz, 2-H), 4.90 (t, 1, 3-H), 5.58 (d, 1, J = 2 Hz, 1-H), 6.68 (m, 2, Ar 3- and 5-H's), 7.08 (d, 1, Ar 6-H), 7.82 (m, 4, Pht H's); TLC (1:1 hexane/EtOAc) R_f 0.63.

3,5-Dimethoxyphenyl 4,6-Di-*O*-acetyl-3-deoxy-2-methoxy-3-phthalimido-β-D-glucopyranoside (33). $SnCl_4$ (1.7 mL) was added dropwise over 0.5 h to a solution of **21** (5.0 g, 11.14 mmol) and 3,5-dimethoxyphenol (3.4 g, 22.28 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred at 23 °C for 8 h. The reaction mixture was poured into saturated $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The extracts were combined, washed with water (150 mL), dried, and evaporated. The residue was chromatographed (preparative HPLC, silica gel, 3:1 hexane/EtOAc) to afford 1.95 g (31%) of **33**: IR 5.78, 5.88 (C=O), 6.26, 6.40, 6.90, 7.32, 7.68, 8.00, 8.18, 8.32, 8.70, 9.00, 9.15, 9.60, 9.68, 11.45, 12.35, 13.90 μm; NMR δ 1.88 (s, 3, OAc), 2.08 (s, 3, OAc), 2.81 (s, 3, 2-OMe), 3.78 (s, 6, ArOMe's), 3.91 (m, 1), 4.27 (m, 2), 4.32 (m, 2), 5.02 (d, 1, J = 8 Hz, 1-H), 5.68 (t, 1, 4-H), 6.08 (m, 2, Ar H's), 7.52 (br s, 1, Ar H), 7.6–7.9 (m, 4, Pht H's); TLC (2:1 hexane/EtOAc) R_f 0.25.

Anal. Calcd for $C_{27}H_{29}NO_{11}$: C, 59.66; H, 5.37; N, 2.58. Found: C, 59.44; H, 5.08; N, 2.43.

4-Methoxy-2-methylphenyl 4-*O*-Acetyl-3-deoxy-2-methoxy-3-phthalimido-α-D-*xylo*-hex-5-enopyranoside (35). To a solution of **28** (1.55 g, 2.61 mmol) in HMPA (8.0 mL) was added DBU (0.62 mL, 4.0 mmol). The solution was stirred at 50 °C for 60 h, diluted with ether (150 mL), and filtered. The filtrate was washed with 10% $NaHSO_4$ (50 mL), saturated $NaHCO_3$ (50 mL), and water (50 mL), dried, and evaporated. The residue was chromatographed (PLC, silica gel, 99.5:0.5 CH_2Cl_2/MeOH) to afford 860 mg (71%) of **35**: IR 5.75, 5.90 (Pht C=O), 6.70, 6.90, 7.20, 7.35, 8.30, 8.80, 9.05, 9.45, 9.65, 9.85, 10.50, 11.50, 12.05, 12.35, 13.50, 13.95 μM; NMR δ 1.90 (s, 3, OAc), 2.30 (s, 3, ArMe), 3.30 (s, 3, 2-OMe), 3.70 (s, 3, ArOMe), 4.5–4.7 (m, 3), 4.90 (t, 1, 3-H), 5.60 (d, 1, J = 3 Hz, 1-H), 6.10 (dt, 1, 4-H), 6.5–6.8 (m, 2, Ar 3- and 5-H's), 7.6–7.9 (m, 4, Pht H's); TLC (99:1 CH_2Cl_2/MeOH) R_f 0.7.

Anal. Calcd for $C_{25}H_{25}NO_8$: C, 64.23; H, 5.39; N, 2.99. Found: C, 63.76; H, 5.78; N, 3.08.

4-Methoxy-2-methylphenyl 3-Deoxy-2,4-dimethoxy-3-phthalimido-α-D-*xylo*-hex-5-enopyranoside (36). By a procedure similar to that described above **30** (79.8 mg, 0.14 mmol) was treated with DBU (42.7 mg, 0.28 mmol) in HMPA (1.0 mL). The crude product was chromatographed (PLC, silica gel, 2:1 hexane/EtOAc) to afford 35.5 mg (58%) of **36**: IR 5.61, 5.82, 5.95, 6.70, 6.90, 7.30, 7.81, 8.32, 8.74, 9.00, 9.10, 9.32, 9.55, 9.85, 10.10, 10.55, 11.58, 12.00, 12.55, 13.95 μm; NMR δ 2.30 (s, 3, ArMe), 3.32 and 3.41 (2 s, 6, 2- and 4-OMe's), 3.79 (s, 3, ArOMe), 4.3–4.9 (m, 5), 5.64 (d, 1, J = 3 Hz, 1-H), 6.69 (m, 2, Ar 3- and 5-H's), 7.17 (d, 1, Ar 6-H), 7.82 (m, 4, Pht H's); TLC (99.4:0.6 CH_2Cl_2/MeOH) R_f 0.6.

Anal. Calcd for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.15; H, 5.75; N, 3.20.

Cation-Induced Cyclization Studies. a. Reaction of 35 with Iodonium Dicollidine Perchlorate in the Presence of EtOH. Freshly prepared iodonium dicollidine perchlorate (46.7 mg, 0.1 mmol) was added to a solution of **35** (46.7 mg, 0.1 mmol) in 9:1 $CHCl_3$/EtOH (0.7 mL), and the mixture was stirred in the dark for 16 h. Additional iodonium dicollidine perchlorate (0.1 mmol) was added, and stirring was continued for 6 h. The excess reagent was precipitated by addition of ether (20 mL), and the filtrate was washed with 0.5 M $Na_2S_2O_4$ (5 mL), saturated $NaHCO_3$ (5 mL), and water (5 mL), dried, and evaporated. The residue was chromatographed (PLC, silica gel, $CHCl_3$) to afford 10 mg (16%) of **40** as the major product: NMR δ 1.22 (t, 3, OCH_2CH_3), 1.92 (s, 3, ArMe), 2.30 (s, 3, 2-OMe), 3.22 (s, 3, OAc), 3.5–3.9 (m, 7, ArOMe, OCH_2CH_3, 6-H_2), 4.63 (dd, 1, J = 8 Hz and J = 2 Hz, 2-H), 4.92 (t, 1, J = 8 Hz, 3-H), 5.68 (d, 1, J = 2 Hz, 1-H), 5.97 (d, 1, J = 8 Hz, 4-H), 6.70 (m, 2, Ar H's), 7.32 (m, 1, Ar H), 7.6–7.9 (m, 4, Pht H's).

b. Reaction of 36 with Trifluoroacetic Acid. **36** (26 mg, 0.055 mmol) and trifluoroacetic acid (1.6 μL, 0.021 mmol) were placed in $CDCl_3$ (0.4 mL) and allowed to stand at 23 °C for 16 h at which time no **36** could be detected by NMR. The reaction mixture was diluted with $CHCl_3$ (10 mL), washed with saturated $NaHCO_3$ (5 mL), dried, and evaporated to afford a complex (TLC) mixture. The residue was chromatographed (PLC, silica gel, 99.7:0.3 CH_2Cl_2/MeOH) to afford 4 mg of **36**, identical with an authentic sample by MS, NMR, and TLC, as the major product. Several experiments gave similar results with **36** always the principal product accompanied by low (0–5%) and erratic yields of aglycon **9** and materials tentatively identified (MS) as **38** and **42**.

c. Reaction of 36 with *N*-Bromosuccinimide. *N*-Bromosuccinimide (9.7 mg, 0.055 mmol) and **36** (26.0 mg, 0.055 mmol) were placed in $CDCl_3$ (0.5 mL) and allowed to stand at 23 °C for 5 min. The reaction mixture was diluted with $CHCl_3$ (10 mL), washed with water (5 mL), dried, and evaporated. The residue was chromatographed (PLC, silica gel, 99.75:0.25 CH_2Cl_2/MeOH) to afford 5 mg of **41** as the major component: MS, m/e 616 (M^+); NMR δ 2.20 (s, 3, ArMe), 2.88 (s, 4, succinimide H's), 3.22, 3.31 (2 s, 6, 2- and 4-OMe's), 3.68 (s, 3, ArOMe), 4.3–4.9 (m, 5), 5.58 (d, 1, J = 2 Hz, 1-H), 6.60 (m, 2, Ar H's), 7.03 (m, 1, Ar H), 7.6–7.9 (m, 4, Pht H's).

d. Reaction of 36 with Iodonium Dicollidine Perchlorate. Freshly prepared iodonium dicollidine perchlorate (16.8 mg, 0.036 mmol) and **36** (15.6 mg, 0.036 mmol) were placed in $CDCl_3$ (0.5 mL) and allowed to stand at 23 °C for 0.5 h. Ether (20 mL) was added to precipitate excess reagent. The filtrate was washed with 0.5 M $Na_2S_2O_4$ (5 mL), saturated $NaHCO_3$ (5 mL), and water (5 mL), dried, and evaporated. The residue was chromatographed (PLC, silica gel, $CHCl_3$, three passes) to afford 7.0 mg (34%) of **43**: NMR δ 2.23 (s, 3, ArMe), 3.28, 3.36 (2 s, 6, 2- and 4-OMe's), 3.72 (s, 3, ArOMe), 4.38 (dd, 1, J = 8 Hz and J = 2 Hz, 2-H), 4.58

(dd, 1, J = 8 Hz and J = 1 Hz, 4-H), 4.90 (t, 1, J = 8 Hz, 3-H), 5.70 (m, 2, 1- and 6-H's), 6.60 (m, 2, Ar H's), 7.25 (m, 1, Ar H), 7.6–7.9 (m, 4, Pht H's); MS, m/e 565 (M^+); TLC ($CHCl_3$, two passes) R_f 0.42.

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Registry No. **9**, 5307-05-1; **12**, 4603-89-8; **13**, 42775-84-8; **14**, 108512-22-7; **15**, 108590-49-4; **16**, 108590-50-7; **17**, 108512-23-8; **18**, 108512-24-9; **20**, 108512-25-0; **21**, 108512-26-1; **23**, 108512-27-2; **24**, 108512-29-4; **25**, 108512-31-8; **26**, 108512-32-9; **27**, 108512-33-0; **28**, 108512-34-1; **29**, 108512-35-2; **30**, 108512-36-3; **31**, 108512-28-3; **32**, 108512-30-7; **33**, 108512-37-4; **35**, 108512-38-5; **36**, 108512-39-6; **38**, 108512-41-0; **40**, 108512-40-9; **41**, 108512-43-2; **42**, 108512-42-1; **43**, 108512-44-3; *N*-(ethoxycarbonyl)phthalimide, 22509-74-6; 3,5-dimethoxyphenol, 500-99-2.

Synthesis of Bufalitoxin and Bufotoxin[1a,2]

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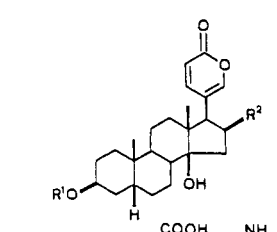
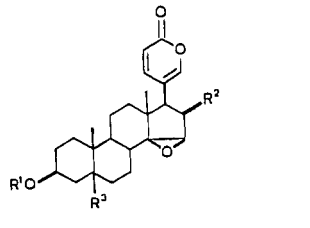
Completion of a formal total synthetic route to the toad venom constituents bufotalin (8), cinobufagin (**2a**), bufalitoxin (**3f**), and bufotoxin (**1a**) has been accomplished. Bufalin (**3a**) was employed as relay and converted to 14-dehydrobufalin 3-acetate (**4**). Selective oxidation of olefin **4** with a chromium trioxide–pyridine reagent afforded 16-ketone **5**, which we had previously transformed to bufotalin (8) and thence to cinobufagin (**2a**). Condensation of bufalin (**3a**) with suberic anhydride followed by a mixed carbonic anhydride reaction sequence using arginine monohydrochloride yielded bufalitoxin (**3f**), and an analogous route from bufotalin (8) led to bufotoxin (**1a**).

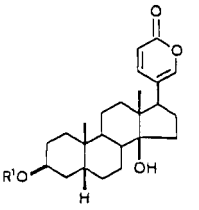
In a classic investigation of toad venom constituents, Wieland and colleagues isolated bufotoxin (**1a**) in 1922[3] from the European toad *Bufo vulgaris* (*Bufo bufo bufo* Linnê), and some 20 years later they were able to propose a tentative structure.[4] Meanwhile, Kondo and co-workers succeeded in isolating bufotoxin and the parent steroid bufotalin from the Japanese toad venom preparation Senso (the Chinese Ch'an Su).[5] The same substance was reisolated from *Bufo bufo bufo* L. and named vulgarobufotoxin.[6] In 1955 the isolation of bufotoxin from *Bufo bufo bufo* L. was reconfirmed by the Reichstein group[7] and more recently the correct structure proposed by one of us (Y.K.) and Meyer[8] was confirmed by our partial synthesis of bufotoxin from bufotalin.[2]



1a, R^1 = $CO(CH_2)_6CONHCH(CH_2)_3NHCNH_2$; R^2 = $OCOCH_3$
1b, R^1 = $CO(CH_2)_6COOH$; R^2 = $OCOCH_3$



2a, R^1,R^2 = H; R^2 = $OCOCH_3$
2b, R^1 = $CO(CH_2)_6COOH$; R^2 = $OCOCH_3$; R^3 = H
2c, R^1 = $CO(CH_2)_6CONHCH(CH_2)_3NHCNH_2$; R^2 = H; R^3 = OH



3a, R^1 = H
3b, R^1 = $COCH_3$
3c, R^1 = $CO(CH_2)_6COOH$
3d, R^1 = $CO(CH_2)_6CONHNHCOOC(CH_3)_3$
3e, R^1 = $CO(CH_2)_6CONHCH_2CH_3$
3f, R^1 = $CO(CH_2)_6CONHCH(CH_2)_3NHCNH_2$

Until 1974 the only known bufotoxin-type toad venom constituents were suberylarginine esters of a 3β-hydroxybufadienolide. Investigation of the venom from *Bufo vulgaris formosus* Boulenger has led to the isolation of bufotoxins with succinic, glutaric, pimelic, or adipic acid replacing suberic acid.[9a] From *Bufo melanosticus*

(1) (a) The present contribution is part 104 of Steroids and Related Natural Products and series number 36 of Bufadienolides; for parts 103 and 35 refer to, respectively: Pettit, G. R.; Herald, D. L.; Herald, C. L.; Kokke, W. C. M. C.; Djerassi, C. *Steroids* **1986**, *47*, 321. Green, B.; Snatzke, F.; Snatzke, G.; Pettit, G. R.; Kamano, Y.; Niven, M. L. *Croat. Chim. Acta* **1985**, *58*, 371. (b) On leave from the Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague, Czechoslovakia.

(2) A portion of the present study was summarized in a preliminary report by: Pettit, G. R.; Kamano, Y. *Chem. Commun.* **1972**, 45.

(3) Wieland, H.; Alles, R. *Chem. Ber.* **1922**, *55*, 1789.

(4) Wieland, H.; Behringer, H. *Ann.* **1941**, *549*, 209. In this remarkable study the average yield of crude bufotoxin from *Bufo vulgaris* (800 males and 400 females) was found to be 1.34 mg/toad, while the female was found to yield 1.23 mg on the average of bufotalin. The male provided only 0.55 mg of bufotalin. In the same investigation, arenobufotoxin was isolated from the South American toad *Bufo arenarum* and purified by column chromatography on aluminum oxide.

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