atmosphere at 25 °C was added BH_3 (2.00 mL, 0.97 M in THF) dropwise during 5 min. The mixture was stirred for an additional 1 h, and then 10% HCl (3 mL) was cautiously added. The solution was refluxed for 30 min, cooled to 25 °C, diluted with water (30 mL), and washed with ether (2 × 20 mL). The solution was made basic (pH 9) with 10% NaOH, and the liberated base was extracted with hexane (3 × 30 mL). The combined hexane layers were dried (Na_2SO_4) and evaporated under reduced pressure. The colorless residual gum was purified on silica gel (CH_2Cl_2:MeOH = 4:1) to afford the diamine **28** [66 mg (69%)] as a colorless oil. Conversion to the hydrochloride was accomplished by dissolving the gum in THF (5 mL) and adding concentrated HCl (0.25 mL): mp 192–195 °C dec; IR (KBr) 2600 (NH_{2+}) cm^{-1}; free-base proton NMR ($CDCl_3$) δ 7.26–7.50 (m, 5 H, $OCH_2C_6H_5$), 5.99 (s, 1 H, ArH), 4.91 (s, 2 H, $OCH_2C_6H_5$), 4.19 (br s, 1 H, ArNH), 3.81 (s, 3 H, OCH_3), 3.80 (m, 1 H, ArCHN), 3.32 (m, 3 H, $ArCH_2CHN$ and $ArNHCH_2$), 2.57–3.17 (m, 3 H, $ArCH_2CHN$), 2.00 (m, 1 H, $ArNHCH_2CH$), 1.53–1.70 (m, 1 H, $ArCH_2CH$); MS, m/e (M^+) 311 (100%), 310 (55%), 220 (18%), 219 (50%), 190 (25%). Anal. Calcd for $C_{19}H_{23}N_2O_2Cl$: C, 65.79; H, 6.68; N, 8.08; Cl, 10.22. Found: C, 66.00; H, 6.61; N, 8.19; Cl, 10.01.

Demethyloxyaaptamine (3). A mixture of the diamine **28** (125 mg, 0.403 mmol) and 5% Pd–C (50 mg) in degassed xylene under a nitrogen atmosphere was refluxed for 20 h. The mixture was allowed to cool to 25 °C; the catalyst was filtered and then washed with CH_2Cl_2 (3 × 10 mL). The filtrate was condensed under reduced pressure and the greenish brown residual gum was chromatographed on silica gel (CH_2Cl_2:MeOH = 9:1). The fast-moving yellow product was separated cleanly from the slower moving complex mixture. Demethyloxyaaptamine [**3**; 30 mg (35%)] was obtained as fine bright yellow rods. It was recrystallized from ethyl acetate: mp 210–212 °C (lit.[2b] mp 198–200 °C); IR (KBr) 1660 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.19 (d, J = 5.6 Hz, 1 H, C_3-H), 7.48 (d, J = 4.4 Hz, C_6-H), 6.72 (s, 1 H, C_7-H), 4.02 (s, 3 H, OCH_3); HRMS, m/e (M^+) 212.0631 (30%), calcd for $C_{12}H_8N_2O_2$ 212.0582, [(M+1)$^+$] 213.0596; calcd for $C_{12}DH_7N_2O_2$ 213.0647. Authentic demethyloxyaaptamine (**3**): mp 212–214 °C; IR (KBr) 1660 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.19 (d, J = 5.7 Hz, 1 H, C_3-H), 9.11 (d, J = 4.4 Hz, 1 H, C_5-H), 8.18 (d, J = 5.7 Hz, 1 H, C_3-H), 7.49 (d, J = 4.4 Hz, 1 H, C_6-H), 6.72 (s, 1 H, C_7-H), 4.02 (s, 3 H, OCH_3); HRMS (Cl, isobutane), m/e (M^+) 213.0655, calcd for $C_{12}H_8N_2O_2$ 213.0662.

Acknowledgment. We thank Professor Nakamura for providing samples of aaptamine and demethyloxyaaptamine. We also acknowledge Professor T. R. Kelly for providing a preprint of ref 6.

Registry No. 1, 96838-36-7; **1a**, 85547-22-4; **4**, 105400-80-4; **4a**, 36917-96-1; **6**, 105400-81-5; **7**, 53921-72-5; **9**, 105400-82-6; **10**, 105400-83-7; **11**, 105400-84-8; **12**, 105400-85-9; **13**, 68345-67-5; **14**, 5868-19-9; **15**, 105400-86-0; **16a**, 105400-87-1; **16b**, 105400-93-9; **17a**, 96838-34-5; **18**, 105400-88-2; **19**, 4602-73-7; **20**, 96838-32-3; **21**, 96860-72-9; **21a**, 96838-33-4; **22**, 96838-35-6; **23**, 85547-23-5; **25**, 105400-89-3; **25a**, 105400-94-0; **26**, 105400-90-6; **27**, 105400-91-7; **28**, 105400-92-8; **28**·HCl, 105400-95-1; 3,4-dihydroisoquinoline, 3230-65-7; 1,2,3,4-tetrahydroisoquinoline, 91-21-4; malonic acid, 141-82-2; 6,7-dimethoxy-3,4-dihydroisoquinoline, 3382-18-1; malonic acid methyl ester, 1071-46-1.

An Approach to the Synthesis of Bactobolin and the Total Synthesis of *N*-Acetylactinobolamine: Some Remarkably Stable Hemiacetals

David Askin, Christof Angst, and Samuel Danishefsky*

Department of Chemistry, Yale University, New Haven, Connecticut 06511

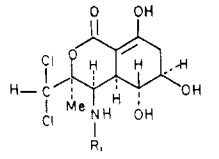
Received July 21, 1986

The key steps in the synthesis of *N*-acetylactinobolamine were the siloxy-Cope rearrangement **17** → **18** and the transformation of pseudoglycal **54**, via its glycosyl azide derivative **55**, to hemiacetal **56**. This hemiacetal, as well as closely related hemiacetals **37** and **48**, proved remarkably unreactive toward processes intended to trap open-chain tautomeric hydroxy aldehydes. In no instance could aldehydo chemistry be realized from these systems.

The Synthetic Plan

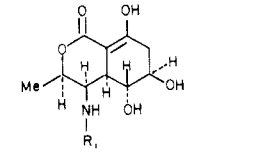
Our orienting goal at the inception of this program was that of a total synthesis of the novel antibiotic bactobolin[1,2] (**1**). Since in this exploratory phase we would be working in the racemic series, we defined as our subgoal the desalanyl derivative of **1**, i.e., bactobolamine[3] (**2**). It was assumed that the lessons learned in a synthesis of rac-**2** could be applied to the antipode of the "correct" configuration. Acylation with a suitable derivative of 1-alanine would lead, in a straightforward fashion, to **1**.

The novel structural and stereochemical features of bactobolin constitute a formidable challenge to those who would undertake its synthesis. The promising biological properties of this antibiotic (activity against Gram-positive and Gram-negative bacteria via inhibition of protein synthesis, activity against L-1210 mouse leukemia and nonsuppression of immune responses) add to this interest. At the present writing the goal of a total synthesis of bactobolin or bactobolamine has not been accomplished.[4]



1 R_1 = (bactobolin)

2 R_1 = H (bactobolamine)



3 R_1 = (actinobolin)

4 R_1 = H (actinobolamine)

5 R_1 = Ac (*N*-acetylactinobolamine)

(1) Isolation and structure determination: (a) Kondo, S.; Horiuchi, Y.; Hamada, M.; Takeuchi, T.; Umezawa, S. *J. Antibiotics* **1979**, *32*, 1069. (b) Ezaki, N.; Miyadoh, S.; Hisamatsu, T.; Kasai, T.; Yamada, Y. *J. Antibiotics* **1980**, *33*, 213. (c) Ueda, I.; Munakata, T.; Sakai, J. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1980**, *B36*, 3128.

(2) Biological activity of bactobolin: (a) Ezaki, N.; Miyadoh, S.; Hisamatsu, T.; Kasai, T.; Yamada, Y. *J. Antibiot.* **1980**, *33*, 213. (b) Ishizuka, M.; Fukasawa, S.; Masuda, T.; Sato, J.; Kanbayashi, N.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1980**, *33*, 1054. (c) Hori, M.; Suzukake, K.; Ishikawa, C.; Asakura, H.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 465.

(3) Munakata, T. *Yakugaku Zasshi* **1981**, *101*, 138.

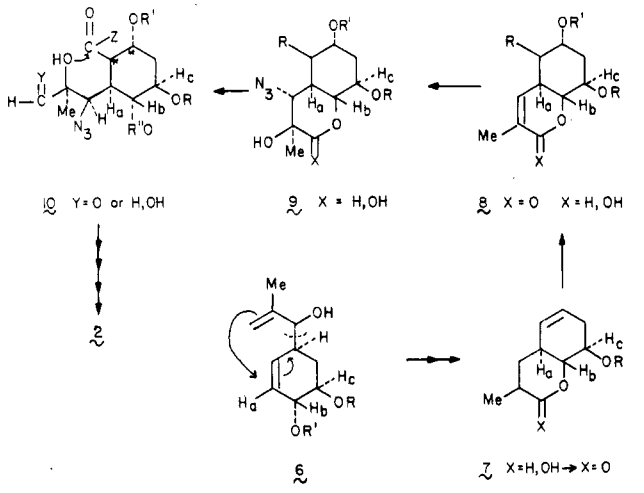
(4) A preliminary report of an attempted synthesis has appeared: Yoshioka, M.; Nakai, H.; Ohno, M. *Heterocycles* **1984**, *21*, 151.

0022-3263/87/1952-0622$01.50/0

Closely related to bactobolin is the antibiotic actinobolin[5] (3). While actinobolin obviously shares many structural features with bactobolin, its biological profile is less promising.[6] During the course of our investigations, a total synthesis of actinobolin was accomplished by Ohno[7a] and more recently, by Weinreb.[7b] The synthesis of *N*-acetylactinobolamine (5) has also recently been accomplished by Frasier-Reid.[8a]

In this report, the experiments which led to a total synthesis of racemic *N*-acetylactinobolamine are described. Since, as was noted above, the original target was bactobolin, the strategy of the synthesis was organized around this goal. It is with a brief discussion of the bactobolin-oriented strategy that we begin.

The plan contemplated the intermediacy of a system of the type 10 in which the relative configurations of the five stereogenic centers of bactobolamine would have been properly arranged. It will be noted that intermediate 10 contains two additional stereogenic carbon centers not present in the end target (see asterisks). For the purpose of achieving favorable regiochemical control (vide infra) it was deemed to be advantageous for these centers to have the indicated configurations. The key supposition was that a trans-fused hemiacetal of the type 9 would undergo re-



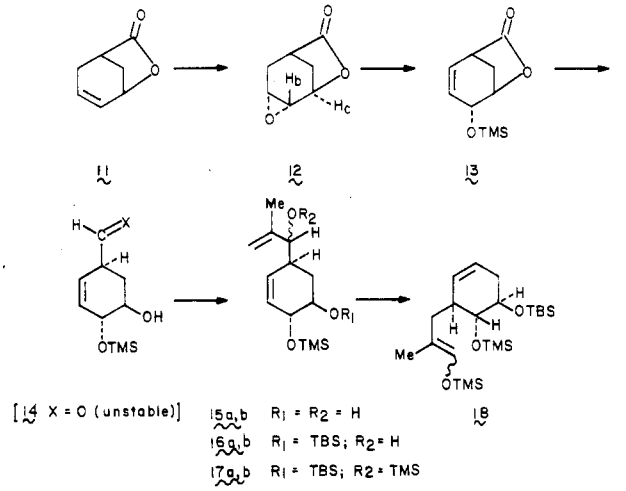
versible ring–chain tautomerism with the open chain system 10. The tertiary hydroxyl group of 10 would lactonize with a suitable acyl function (cf. C(0)Z) giving rise to a cis-fused δ-lactone. The dichloromethyl group would be fashioned from a suitable version of C(Y)H.[9] In the simplest (and most simplistic version), C(Y)H would be the aldehyde directly generated by the ring–chain tautomerism. Such a lactone could be converted to 2. Alternatively, reductive ring opening of 9 would produce a hydroxymethyl function (10; Y = H, OH) rather than an aldehyde. By such a formulation, success would depend on the conversion of 10 to a six- rather than a seven-membered lactone, possibly through appropriate differential protection.

A central element of this plan was the surmise that a pseudoglycal system (to be derived by 1,2-reduction of an unsaturated δ-lactone; cf. structure 8) would be well suited to the stereoselective introduction of the heterofunctionality (see secondary azide and tertiary hydroxyl functions) required to reach 9 and subsequently 10 and 2.

Retrosynthetically the unsaturated δ-lactone 8 (X = O) led us back to the olefinic lactone 7. It was assumed that a program could be devised which would provide for introduction of unsaturation into the lactone ring. The relatively rigid trans-fused oxadecalin system would serve as a matrix onto which the "R and OR′" groups could be mounted with proper regiochemical and stereochemical control. Continuing at the level of conjecture, it was envisioned that a system such as 6 might play a useful role. Upon some version of a suprafacial oxy-Cope transformation (see arrows), 6 would be converted eventually to an aldehyde. With OR and OR′ in system 6 properly distinguished (allowing for the unmasking of OH from OR′) the hemiacetal version of 7 might become accessible. The synthesis started with a sequence which was directed toward the oxy-Cope substrate, 6. A viable aldehydo precursor of 6 became our first focus.

Discussion of Results

Epoxidation of the known lactone[10] 11 was expected to occur on the exo face of the olefin on the basis of precedents.[11] In practice, treatment of the bridged lactone with *m*CPBA in refluxing CH_2Cl_2 in the presence of the inhibitor, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide,[12] afforded a 77% yield of epoxide 12 along with 1.5% yield



of the isomeric β-epoxide. Isolation of the major *exo*-epoxide 12 was simply achieved by fractional crystallization of the crude reaction mixture. Chromatography of the mother liquors afforded an analytical sample of the minor epoxide (see Experimental Section). Treatment of epoxide 12 with trimethylsilyl trifluoromethanesulfonate[13] in benzene followed by the addition of DBU afforded the silyl ether 13.

(5) Isolation and structural determination: (a) Haskell, T. H.; Bartz, Q. R. *Antibiot. Annu.* **1959**, 505. (b) Pitillo, R. F.; Fischer, M. W.; McAlpine R. J.; Thompson, P. E.; Ehrlich, J. *Antibiot. Annu.* **1959**, 497. (c) Antosz, F. J.; Nelson, D. B.; Herald, D. L., Jr.; Munk, M. E. *J. Amer. Chem. Soc.* **1970**, *92*, 4934 and references therein. (d) Wetherington, J. B.; Moncrief, J. W. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *B31*, 501.

(6) Biological activity of actinobolin: (a) Smithers, D.; Bennett, L. L.; Struck, R. F. *Mol. Pharmacol.* **1969**, *5*, 433. (b) Pittillo, R. F.; Schabel, F. M., Jr.; Quinnelly, B. G. *Antibiot. Chemother. (Washington, D.C.)* **1961**, *11*, 501.

(7) Total synthesis of actinobolin: (a) Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133. (b) Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790.

(8) Synthesis of *N*-acetylactinobolamine: (a) Rahman, M. A.; Frazier-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576. (b) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1985**, *50*, 5005.

(9) Conversion of an aldehyde to a dichloromethyl group: (a) Newman, M. S.; Sujeeth, P. K. *J. Org. Chem.* **1978**, *43*, 4367. (b) Findeisen, K.; Wagner, K.; Holtschmidt, H. *Synthesis* **1972**, 599.

(10) Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoshi, Y. *J. Org. Chem.* **1975**, *40*, 1932.

(11) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.

(12) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

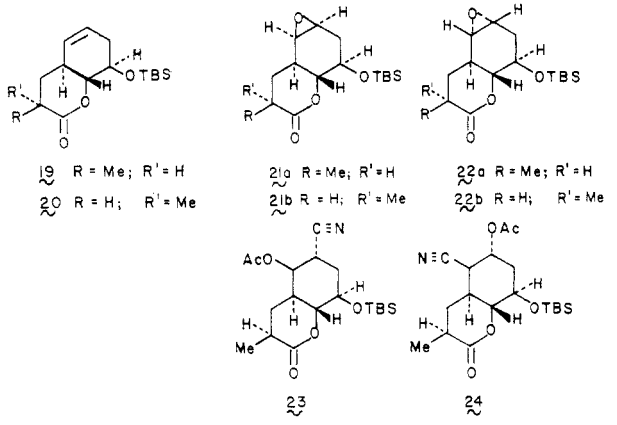
(13) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738.

Reduction of **13** with diisobutylaluminium hydride (DIBAH) followed by treatment of the product with the Grignard derivative of 2-bromopropene[14] gave, after chromatography, a 1:1 ratio of the epimers **15a,b** in 67% overall yield from **13**. Selective protection of the diols was achieved with *tert*-butyldimethylsilyl triflate[15] and lutidine in CH_2Cl_2 at −78 °C to afford the bis(silyl) ethers **16a,b** in 91% yield. Silylation was completed with trimethylsilyl triflate to afford the tris(silyl) ethers **17a,b** in 97% yield. Silyloxy-Cope rearrangement[16] took place for both isomers upon heating at 310 °C for 1 h to afford the siloxyenol ethers **18**.

Lactolization was accomplished readily via the treatment of **18** with dilute HCl in dioxane at 5–10 °C for 45 min. Under these conditions, the trimethylsilyl ether and the silyl enol ether functions were selectively cleaved. There was obtained a 3.2 to 1 mixture of lactols (45% overall yield from **17**). The individual lactols were oxidized separately using PDC in CH_2Cl_2 to afford the lactones[17] **19** and **20** in 79% and 84% yields, respectively.

Epoxidation of compound **19** occurred with *m*CPBA in refluxing in dichloroethylene in the presence of the Kishi radical inhibitor.[12] After workup of the reaction mixture, a 1.8 to 1 mixture of epoxides (**21a** and **22a**) was isolated. The stereochemistry of epoxides **21a** and **22a** was deduced from the following series of experiments.

Treatment of the major epoxide (**21a**) with Nagata's reagent,[18] Et_2AlCN, in THF, followed by acetylation afforded a single acetoxy nitrile. Decoupling studies of the proton NMR spectrum revealed its structure to be **23**,



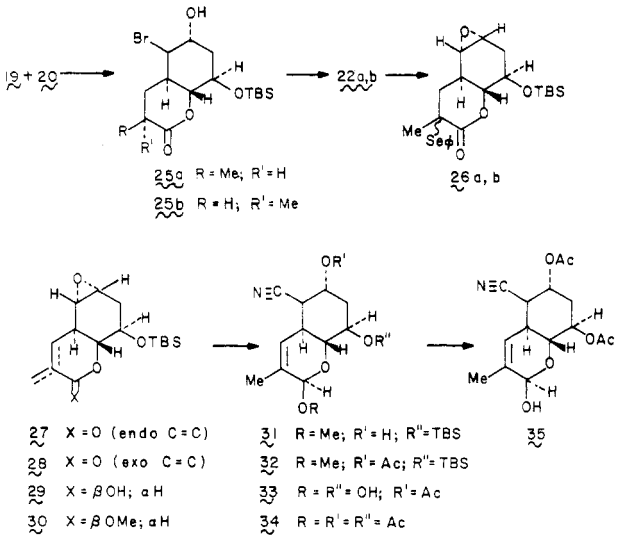
containing the undesired regiochemistry. Thus, assuming trans-diaxial epoxide opening, the progenitor of **23** is the β-epoxide (**21a**), and the minor epoxide must be the desired α-isomer (**22a**). Similar treatment of the minor epoxide (**22a**) led to a different acetoxy nitrile, which was also a trans-diaxial substituted compound as evidenced by the lack of a large coupling between the acetoxy and cyano methine protons. While a decoupling experiment was not helpful in this case, this compound was most likely the desired cyanohydrin **24**.

A stereospecific route to the α-epoxide (**22a,b**) was developed. Remarkably, treatment of lactone **19** with NBS in aqueous dioxane at room temperature led to a single bromohydrin **25a** in essentially quantitative yield. Treatment of the bromohydrin with potassium *tert*-butoxide in toluene afforded the compound **22a** in 80% overall yield from olefin **19**. Similarly, the epimeric lactone **20** afforded epoxide **22b**.

At this juncture, it seemed advisable to introduce the α,β-unsaturation into the δ-lactone ring prior to opening of the epoxide. In the event, selenylation of lactones **22a,b** in the usual way afforded a 1.4:1 mixture of selenides **26a** and **26b** in 93% yield. The components were separated by crystallization.

Oxidation of the major selenide with *m*CPBA afforded (92%) the desired endocyclic olefin isomer **27**. However, treatment of the minor selenide under the same conditions afforded a mixture of the desired olefin **27** and the exocyclic isomer **28** in a ratio of 1 to 1.4 in quantitative yield. Attempts to isomerize olefin **28** to its endocyclic isomer **27** with $PdCl_2(CH_3CN)_2$ and $RhCl_3$ were not successful.

Reduction of the α,β-unsaturated lactone **27** with DIBAH in toluene,[19] followed by protection of the pseudoglycal system **29** as the methyl acetal **30** took place in 74% overall



yield. The single anomer formed was assumed to contain the methoxyl group in the axial configuration by virtue of the anomeric effect. Having achieved protection of the lactol, we turned out attention to the crucial epoxide opening.

Treatment of epoxide **30** with Et_2AlCN in CH_2Cl_2 resulted in a smooth reaction affording cyanohydrin **31** in 97% yield. The stereo- and regiochemistry of epoxide opening were rigorously proven by a complete ^1H NMR decoupling experiment on the derived acetate **32**. With the desired cyanohydrin in hand, we could now turn our attention to the next and central problem, vicinal azidohydroxylation of the pseudoglycal olefin.

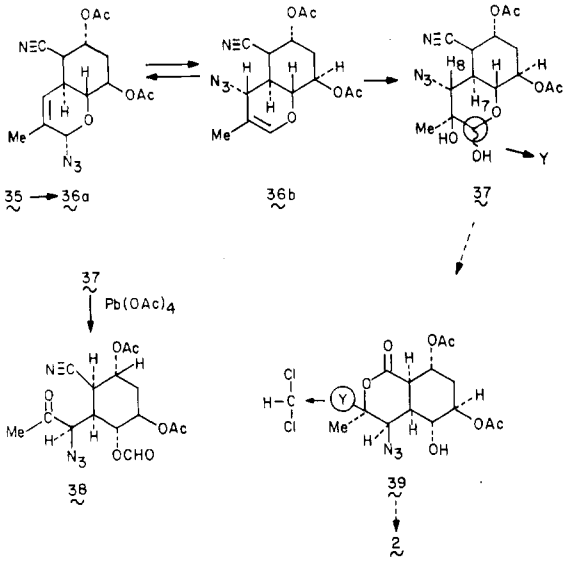
Selective exposure of the anomeric hydroxyl group was accomplished in the following way. Hydrolysis of the methyl acetal and silyl ether functions of compound **32** gave the diol **33** which was peracetylated to the triacetate **34**. Solvolysis of the anomeric acetate in wet CH_3CN with $BF_3{\cdot}OEt_2$ afforded the pseudoglycal **35** in 96% overall yield.

The program for azidohydroxylation commenced with the action of methanesulfonyl chloride on pseudoglycal **35**. The product (either anomeric mesylate or anomeric chlo-

(14) House, H. O.; Latham, R. A.; Slater, C. D. *J. Org. Chem.* **1966**, *31*, 2667.
(15) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, 3455.
(16) Thies, R. W.; Wills, M. T.; Chin, A. W.; Schick, L. E.; Walton, E. S. *J. Am. Chem. Soc.* **1973**, *95*, 5281.
(17) The methyl stereochemistry of the lactone **19** was assigned at the point of the derived epoxide (**22a**) since the assignment was ambiguous based on the ^1H NMR spectra of **19** or **20**.
(18) Nagata, W.; Yoshioka, M.; Okumura, T. *Tetrahedron Lett.* **1966**, 847.
(19) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066.

ride) was directly treated with tetrabutylammonium azide[20] to give initially at −40 °C a single product (TLC analysis). After warming the reaction mixture to room temperature, two products were present by TLC analysis. Proton NMR analysis of the purified mixture showed olefinic peaks attributable to both the glycal (δ 6.3) and pseudoglycal (δ 5.6) linkages. Separation of the isomers by HPLC gave cleanly the individual compounds, but upon standing at room temperature for several hours, each individual isomer had equilibrated to a similar mixture of isomers. These results implied that, as predicted,[21] the allylic azides **36a** and **36b** existed in equilibrium at room temperature.

Treatment of the mixture of allylic azides with *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetroxide[22] in THF led to formation of the desired azidohydrin[23,24] **37** in 93% yield. This much desired

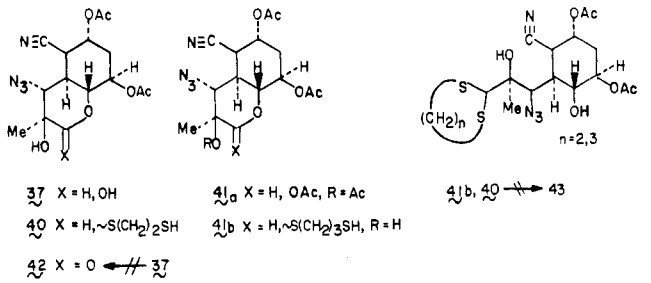


product existed as a mixture of lactol anomers which could be demonstrated by separation, followed by reequilibration. Proof of the structure of **37** was amply furnished by an NOE difference spectrum experiment wherein a positive enhancement was observed between the tertiary methyl group and the ring-junction methine proton (H_7), and no enhancement was seen between the same methyl group and the azidomethine proton (H_8). The C7–C8 proton coupling constant (J = 12 Hz) indicates that the azide substituent is equatorial. Assuming the chair–chair conformation pertains to the oxadecalin system, the configuration of the azide would be α, as desired. Reaction of diol **37** with $Pb(OAc)_4$ afforded a single keto formate **38**. This process establishes the regiochemistry of the hydroxylation.

It will be recognized that compound **37** is the equivalent of the protected system **9**, proposed earlier at the planning level. At this stage, a hydrolytic transformation of **37** to a product of type **39** would afford a clear route to bactobolamine (**2**). We turned our attention to investigation of lactol opening regimens as a route to bactobolin.

Early harbingers of difficulty in translating this scheme to practice arose from unsuccessful attempts to convert lactol **37** to the diethyl thioacetal of the corresponding hydroxy aldehyde using classical carbohydrate thioketalizing conditions[25] (ethanethiol/concentrated HCl). Starting material (**37**) was recovered and no other products could be isolated from the reaction mixture. A wide variety of other conditions were attempted.[26–29] These numerous experiments resulted in either recovered starting material or extensive decomposition. Indeed, the only conditions which led to any isolable products were those recently provided by Corey for the thioketalization of particularly sensitive substrates.[30] Treatment of lactol **37** with ethanedithiol in refluxing dichloroethane with the catalyst $Mg(OTF)_2$ gave the anomeric hemithioacetals **40**. Submission of the hemithioacetals to further treatment with various acid catalysts ($Mg(OTf)_2$, TsOH, $BF_3{\cdot}OEt_2$) led to recovery of starting material or decomposition. Thus, apparently the lactol form represents an energy minimum for this system, conceivably due to the high degree of substitution of the hemiacetal group, or to the free hydroxyl group adjacent to the anomeric center.

It was hoped that protection of the tertiary hydroxyl group might facilitate ring opening.[31] Accordingly, lactol **37** was treated with a trace of 70% perchloric acid in acetic



anhydride. This led to the formation of tetraacetate **41a** in 69% yield. Treatment of compound **41a** with propanedithiol and $Mg(OTf)_2$ in hot toluene again resulted in only partial ketalization and isolation of hemithioacetals **41b**. Attempts to convert **41b** to **43** were unsuccessful.

Another possibility for ring opening was via saponification of the lactone **42**. Attempts to achieve oxidation of lactol **37** via pyridinium dichromate and Fetizon's reagent led to carbon–carbon bond cleavage, producing keto formate **38**. Other reagents known to oxidize *vic*-glycols to ketol systems[32a–d] (dimethyl sulfide/*N*-chlorosuccinimide, Me_2SO-oxalyl chloride, Me_2SO-Ac_2O, ozone) were without effect.

Furthermore, various attempts at nitrile hydrolysis via N-alkylation and hydrolysis of the nitrilium salt were not successful, since **37** was unreactive towards Meerweins salts

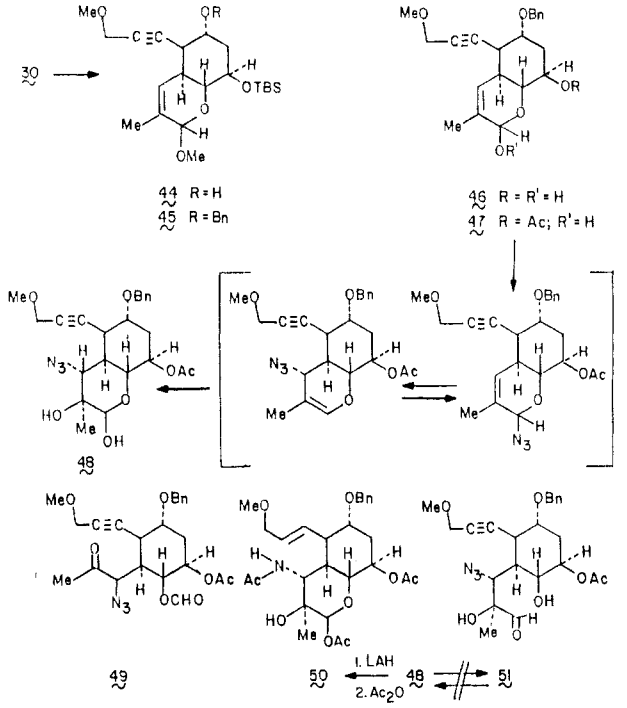
(20) Brandstrom, A.; Lamm, B.; Palmertz, I. *Acta Chem. Scand. Ser B* **1974**, *28*, 699.
(21) Heyns, K.; Feldmann, J.; Hadamczyk, D.; Schwenter, J.; Thiem, J. *Chem. Ber.* **1981**, *114*, 232.
(22) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(23) In analogy to the antiperiplanar effect of hydroxy- and alkoxy-groups in the OsO_4 mediated hydroxylation of allylic alcohols: (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, 3943. (b) Christ, W. J.; Cha, J. K.; Kishi, Y., Ibid. **1983**, 3947. (c) Stork, G.; Kahn, M. *Ibid.* **1983**, 3951.
(24) For a similar osymlation anti to the allylic substituent of a glycal, see: Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1597.
(25) Wolfrom, M. L.; Anno. K. *J. Am. Chem. Soc.* **1952**, *74*, 6150.
(26) Among the attempted methods with obvious goals in mind were reactions with the following reagents: (a) EtSH, HCl(g); (b) EtSH, cat. $BF_3{\cdot}OEt_2$; (c) 1,3-propanedithiol, concentrated HCl; (d) 1,3-propanedithiol, $BF_3{\cdot}OEt_2/CH_2Cl_2$;[27] (e) $BF_3{\cdot}OEt_2$/MeOH; (f) $NaBH_4$, ethanol or isopropanol, reflux; (g) methylenetriphenylphosphorane/THF; (h) ethylene glycol, *p*-TsOH, benzene, reflux; (i) unsym-dimethylhydrazine;[28] (j) lithium tri-*tert*-butoxyaluminumhydride/THF; (k) ethylene glycol, *p*-TsOH, toluene, reflux; (l) $BF_3{\cdot}OEt_2$/ethanedithiol;[29] (m) 2,2-dimethyl-1,3-propanediol, TsOH, toluene, heat.
(27) Ireland, R. E.; Daub, J. P. *Tetrahedron Lett.* **1982**, 3471.
(28) Danishefsky, S.; Etheredge, S. J., unpublished results.
(29) Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945.
(30) Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, 169.
(31) Grewe, R.; Nolte, E. *Justus Liebigs Ann. Chem.* **1952**, *575*, 1.
(32) (a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (c) Kuzuhara, H.; Fletcher, H. G. *J. Org. Chem.* **1967**, 2531. (d) Deslongchamps, P., Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651.

and methyl fluorosulfonate. Also unsuccessful was an attempted hydroperoxide-assisted hydrolysis[33] of the nitrile. The task of characterizing the products of these reactions was further complicated by the formation of highly polar materials due to hydrolysis of the acetate functions.

In light of these reverses, it seemed advisable to abandon the use of the nitrile function in favor of a carboxylic acid surrogate which might be more study towards projected forcing (cf. lithium aluminum hydride) lactol-opening reactions. A vinyl group was chosen as the latent carboxylic acid, since it would be stable to powerful hydride reagents, yet easily convertible to the desired carboxyl functionality by oxidation.

Toward this end, we returned to epoxide **30** and examined its viability as a substrate toward attack by various organometallic reagents. In the event, this substance was unreactive toward several versions of lithium divinyl cuprate and toward 2-lithio-1,3-dithiane.

Opening of the epoxide was cleanly achieved, however, with a Yamaguchi type reagent[34] generated from the lithium acetylide of methyl propargyl ether and $BF_3 \cdot OEt_2$. Subsequent benzylation of the resulting alcohol **44** gave the benzyl ether **45** in 90% overall yield. The regiochem-

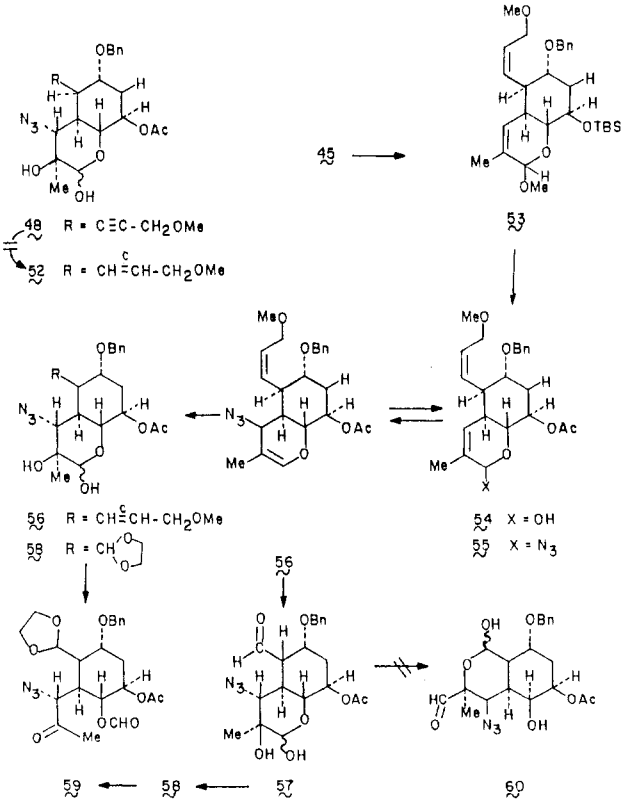


istry of the epoxide opening was again rigorously proven by a decoupling experiment. Hydrolysis of the silyl ether and acetal functions gave the diol **46** (87%), which was selectively protected in a manner similar to that employed in the nitrile series to afford the acetylenic pseudoglycal **47** in 80% overall yield. Glycosyl azide formation followed by osmylation afforded a 68% overall yield of the desired diol **48**. That lactol **48** existed as a mixture of anomers was again demonstrated by separation using HPLC followed by reequilibration to the starting mixture upon standing at room temperature. Again, the coupling constant of 12 Hz for the azidomethine (H_8) indicates the correct stereochemistry for this substituent. While an NOE experiment was not performed in this case, the fact that only one isomer is produced implies that the azide is again directing the osmylation reaction.

Similar to the situation in nitrile series, compound **48** also undergoes oxidative cleavage, in this case mediated by $NaIO_4$, to afford the keto formate **49**, assuring the correct regiochemistry in the hydroxylation reaction. Having secured compound **48**, we could now attempt to cleave the lactol with vigorous reducing conditions.

Treatment of lactol **48** with a large excess of LAH in refluxing THF for 6 h, followed by quenching the reaction with acetic anhydride gave rise to compound **50**, in which both the azide and the acetylene had undergone reduction. However, the lactol ring was still intact. Additional reductive regimens were attempted on this system without success. From the foregoing results, it can be safely assumed that there is essentially none of the open hydroxy aldehyde form in equilibrium with the closed lactols. Apparently, these lactols can undergo anomerization via an oxonium ion (cf. formation of compounds **40** and **41b**), but the free open-chain tautomer **51** does not exist to an operationally useful extent. A contributing factor may well be the high degree of substitution of the lactol ring. Ring–chain tautomerization would involve serious nonbonded interactions in the side chain of **51** which are minimized in the closed form.

We sought to convert the acetylenic group of **48** to the desired carboxylic acid functionality, in the hope that transannular lactonization would force open the obdurate lactol. Attempted preparation of olefin **52** by Lindlar reduction of compound **48** afforded a complex mixture of



polar products. Apparently, the azide functionality was more readily reduced than was the acetylene. Therefore, it was necessary to carry out the reduction at an earlier stage in the synthetic route. Accordingly, we returned to acetylene **45** from which *cis*-olefin **53** was obtained in 90% yield upon Lindlar reduction.

Protecting group processing as in the acetylenic route gave the pseudoglycal **54** in 87% overall yield from the olefin **53**. Allylic azide formation and trapping with OsO_4 under conditions previously established afforded a 71%

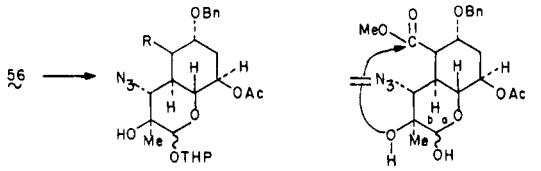
(33) Payne, G. B. *Tetrahedron* **1962**, *18*, 763.
(34) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, 391.

overall yield of diol **56** as a 3.5 to 1 mixture of lactol anomers. It will be noted that the pendant olefin did not suffer competitive osmylation.

The olefin **56** was now subjected to ozonolysis at −78 °C followed by dimethyl sulfide workup to afford the aldehyde **57** in 99% yield. The possibility that this aldehyde lactol could be in equilibrium with the desired isocoumarin type aldehyde lactol **60** now presented itself. In order to differentiate between the two possibilities, the free aldehyde was first converted to the ethylene ketal **58**. Oxidative cleavage of the diol with $NaIO_4$ gave the keto formate **59** in 73% overall yield, clearly implicating **57** as its progenitor. There was no encouraging evidence for the equilibration of undesired diol **57** to the desired series **60**.

Thus, we turned our attention to an irreversible lactonization which might force open the lactol.

Protection of the diol **56** as its THP ether **61** was accomplished under standard conditions. Ozonolysis as in the unprotected case gave the aldehyde **62**. The desired



61 R = CH=CHCH$_2$OMe
62 R = CHO
63 R = CO$_2$H
64 R = C(O)NR'-C(O)NHR' (R' = cyclohexyl)
65 R = CO$_2$Me

66

carboxylic acid **63** was obtained by oxidation of the aldehyde with RuO_4 at 0 °C in a biphasic mixture of $CCl_4/CH_3CN/H_2O$.[35] Lactonization of **63** using DCC was attempted in hot pyridine.[11] Chromatography on silica gel allowed isolation of the undesired *N*-acyl urea **64**, indicating lactonization had not taken place.

The acid **63** was converted to methyl ester **65** with diazomethane. Hydrolysis of the THF acetal then afforded the hydroxy ester **66** in 65% overall yield from olefin **56** (5 steps). Attempted lactonization of compound **66** with TsOH in refluxing toluene led to a complex mixture of products. Analysis of the crude reaction mixture by NMR spectroscopy indicated that no lactonization had occurred from the conspicuous presence of apparent methyl ester singlets in the δ 3.7–3.8 region.

Failure of all efforts to use the anomeric carbon (cf. cleavage of the "a" bond in compound **66**) of the various lactol derivatives as the stereospecifically placed progenitor of the dichloromethyl group of bactobolin now necessitated a serious reorientation of our central goal. It was decided to excise this intractable carbon and to focus at least for the moment on a synthesis of actinobolamine (**4**). The format for this painful excission was all too familiar. The "b" bond of the 1,2-diol system (see compound **66**) would be cleaved oxidatively. Needless to say, the disintegration of this "b" bond would lead to forfeiture of the carefully crafted stereochemical control which was built into the bactobolin program.

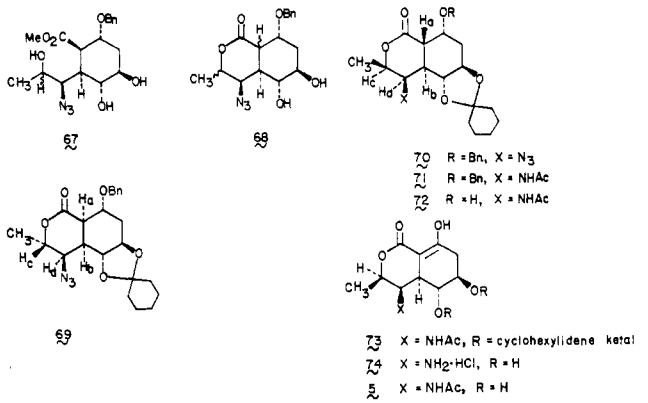
In the event, treatment of diol ester **66** with $NaIO_4$ followed immediately by reduction of the resultant ketone with $NaBH_4$ gave the triol **67**, unfortunately as a 1.25 to 1 mixture of epimers in 61% overall yield. Lactonization of **67** was achieved with TsOH in benzene at reflux to give the lactones **68** in 93% yield. Apparently the lactones emerged as a mixture of epimers at the center α to the lactone, but this was of no consequence, since this center is lost upon oxidation.

Protection of the diol as the cyclohexylidene ketal proceeded to afford the separable ketals **69** (minor isomer from reduction) and **70** (major isomer from reduction). Interestingly, the undesired isomer **69** exists as the homogeneous cis-ring-fused isomer whereas the desired isomer **70** emerges as the epimerized trans-ring-fused isomer, as judged from the coupling constant of the methine protons (compound **69**, $J_{a,b} = 0$ Hz, $J_{c,d} = 11$ Hz; compound **70**, $J_{a,b} = 8$ Hz, $J_{c,d} = 2$ Hz). A probable reason for this is a serious nonbonded 1,3-diaxial interaction of the methyl group of **70** with the axial ring residue in the cis-fused lactone form.

Reduction of the azide function of compound **70** was accomplished with Lindlar's catalyst in ethyl acetate containing acetic anhydride, thereby providing the corresponding acetamide **71** in 81% yield. The presence of the acylating agent at the reduction stage was essential for good mass recovery.

Removal of the benzyl protecting group was uneventfully effected with $H_2/Pd(OH)_2$ in ethanol to afford in essentially quantitative yield the alcohol **72**. Initial attempts at Collins' oxidation of **72** with pyridine distilled from CaH_2 and stored over KOH were not successful. However, use of pyridine distilled from BaO[36] led to a smooth reaction and isolation of the desired acetamidoketal **73** in 72% yield.

The identity of compound **73** was confirmed by comparison with a naturally derived sample from the following route. Natural actinobolin hemisulfate hydrate was subjected to an Edman degradation[37] to afford the hydrochloride salt **74** which was acetylated to the acetamide **5**.



67

68

70 R = Bn, X = N$_3$
71 R = Bn, X = NHAc
72 R = H, X = NHAc

69

73 X = NHAc, R = cyclohexylidene ketal
74 X = NH$_2$·HCl, R = H
5 X = NHAc, R = H

Cyclohexylidene ketal formation then afforded **73**, which was identical with the synthetic material by 250-MHz ^{1}H NMR, IR, and TLC mobility. Hydrolysis of the cyclohexylidene ketal in the natural series then gave (92%) *N*-acetylactinobolamine **5**, which marks the completion of this phase of our synthetic studies.

Experimental Section

General. Melting points were determined on a Thomas-Hoover Uni-Melt capillary melting point apparatus and are uncorrected. Infrared spectra were recorded using NaCl cells in chloroform on a Perkin-Elmer infrared spectrometer. Absorptions are reported with the polystyrene absorption at 1601 cm^{-1} as a reference. Low-resolution mass spectra were measured on a HP5985 system by direct insertion. High-resolution mass spectra were obtained on a Kratos/Carlo Erba system at Harvard University using either electron impact or ammonia chemical ionization. NMR spectra were recorded at 90 MHz with a Varian EM-390 spectrometer, at 250 MHz with a Bruker WM-250, at 270 MHz with a Bruker

(35) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(36) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(37) Edman, P. *Acta Chem. Scand.* **1950**, 283.

HX-270, at 490 MHz with a Bruker WM-490, and at 500 MHz with a Bruker WM-500 from the Southern New England NMR facility at Yale University. Chemical shifts are reported in ppm relative to tetramethylsilane and are followed by multiplicity, spin–spin coupling constant, and integral. Abbreviations for multiplicity are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. TLC analyses were obtained on E.M. Merck silica gel 60 F-254 plates and were developed by iodine or ammonium molybdate/cerric sulfate solution. Analyses were obtained through Galbraith Laboratories, Knoxville, TN. Flash chromatography was conducted with E.M. Merck Silica gel 60, 230–400 mesh under a positive pressure of nitrogen. All reactions were run under a positive pressure of nitrogen gas unless stated otherwise.

Glass ampules for the Cope rearrangements were treated overnight with ammonium hydroxide, then oven dried for 5 h. The ampules were sealed with a torch at high vacuum.

(1α,2β,4β,6α)-3,8-Dioxatricyclo[4.2.1.0^{2,4}]nonan-7-one (12) and (1α,2α,4α,6α)-3,8-Dioxatricyclo[4.2.1.0^{2,4}]nonan-7-one. A mechanically stirred solution containing 75 g (0.59 mol) of lactone **11**, 200 g (0.93 mol) of 80% MCPBA, and 350 mg of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide as a radical inhibitor in 1750 mL of CH_2Cl_2 was refluxed for 12 h. After cooling to room temperature the white precipitate of benzoic acid was removed by filtration and washed with methylene chloride. The filtrate was washed successively with saturated sodium carbonate (1 × 200 mL) and water (1 × 200 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to leave a viscous oil. The oil was dissolved in 300 mL of ether and placed in the freezer (−20 °C) to crystallize for 24 h. The mother liquors were decanted and the crystals washed with cold hexane and dried at high vacuum to afford 65 g (77%) of *exo*-epoxide **12**. Recrystallization from hexane/ether gave an analytical sample: mp 111–112 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.07 (dd, *J* = 3.5, 5.5 Hz, 1 H), 3.46 (t, *J* = 3.5 Hz, 1 H), 3.26 (bt, *J* = 3.5 Hz, 1 H), 2.52 (m, 1 H), 2.31–2.04 (m, 4 H); IR ($CHCl_3$) λ_{max} 3000, 1780, 1110, 980 cm^{-1}; mass spectrum, *m/z* 140 (*m*), 119, 95. Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 60.15; H, 5.99.

Chromatography of the mother liquors on 45 g of silica gel eluting with CH_2Cl_2/ether/hexane (5:4:5) gave the *endo*-epoxide. Recrystallization from CH_2Cl_2/hexane afforded 1.2 g (1.4%) as colorless plates: mp 91–93 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.00 (bt, *J* = 5 Hz, 1 H), 3.45 (~t, *J* = 4 Hz, 1 H), 3.16 (~t, *J* = 3.5 Hz, 1 H), 2.51–2.37 (m, 3 H), 2.13 (ddd, *J* = 3.5, 6, 16 Hz, 1 H), 1.94 (d, *J* = 11 Hz, 1 H); IR ($CHCl_3$) λ_{max} 3000, 1780, 1110, 980 cm^{-1}; mass spectrum, *m/z* 140 (M), 95, 83. Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 60.15; H, 5.87.

***exo*-4-[(Trimethylsilyl)oxy]-6-oxabicyclo[3.2.1]oct-2-en-7-one (13).** To a magnetically stirred solution containing 9.0 g (63.4 mmol) of *exo*-epoxide **12** and 9.0 mL (77.5 mmol) of distilled 2,6-lutidine in 120 mL of dry benzene was slowly added (1 h) a solution containing 9.0 mL (7.75 mmol) of 2,6-lutidine and 13.8 mL (75.9 mmol) of trimethylsilyl trifluoromethanesulfonate in 80 mL of dry benzene. After stirring for 2 more h at room temperature, 12.0 mL (80.6 mmol) of DBU was added dropwise (30 min) while cooling the reaction mixture to 15–20 °C. The resulting brown mixture was kept for 2 h at room temperature, poured into saturated sodium bicarbonate solution (100 mL), and extracted with benzene (3 × 200 mL), washed with water (2 × 100 mL), and dried over magnesium sulfate. Concentration of the extracts in vacuo gave an oil that was kept at high vacuum (0.1 Torr) overnight to remove most of the lutidine. The crude product was distilled twice in a Kugelrohr (0.1 Torr/100 °C oven temperature) to afford 10.2 g (75%) of the trimethylsilyl allylic ether **13** as a white solid. An analytical sample was prepared by recrystallization from ether/hexane to give **13** as white platelets: mp 59–61 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.20 (dd, *J* = 7, 8 Hz, 1 H), 5.70 (ddd, *J* = 2, 3, 9.5 Hz, 1 H), 4.56 (m, 1 H), 4.18 (t, *J* = 3 Hz, 1 H), 2.96 (dd, *J* = 4, 7 Hz, 1 H), 2.29 (m, 1 H), 2.22 (t, *J* = 11.5 Hz, 1 H), 0.18 (s, 9 H); IR ($CHCl_3$) λ_{max} 2950, 1780, 1250, 1070 cm^{-1}; mass spectrum, *m/z* 212 (M), 184, 155, 73. Anal. Calcd for $C_{10}H_{16}O_3Si$: C, 56.57; H, 7.59. Found: C, 56.72; H, 7.54.

(1α,4β,5α)-5-Hydroxy-α-(1-methylethenyl)-4-[(trimethylsilyl)oxy]-2-cyclohexene-1-methanol (15a and 15b). A solution of unsaturated lactone **13** (14.15 g, 66.7 mmol) in 1100 mL of dry toluene was cooled to −78 °C, and a solution of diisobutylaluminum hydride (57.8 mL, 1.5 M, 86.7 mmol) in toluene was added slowly dropwise over a period of 75 min. After stirring the mixture for 2 h at −78 °C, TLC of the reaction indicated that the starting material had been consumed. A solution of isopropenylmagnesium bromide (206.7 mmol) in 190 mL THF was added dropwise over a period of 45 min to the reaction. After the reaction had been stirred at −78 °C for 1 h, the temperature was allowed to rise to 0 °C for 1 h, and then the reaction was quenched at 0 °C with 24 mL of water and 26 g of ammonium chloride. The reaction was stirred for 2 h, then 25 g of celite and 52 g of magnesium sulfate were added, and the mixture was stirred for another 60 min. The precipitate was removed by filtration and washed several times with ethyl acetate. The combined filtrates were concentrated in vacuo to afford a crude epimeric mixture of **15a** and **15b**. Chromatography on 900 g of silica gel with hexane/ethyl acetate (2:1 ratio) as the eluant gave, as the initial product-containing fractions, 3.87 g of pure **15a**. The middle fractions contained 3.57 g of product as a mixture of epimers. Further elution with 50% hexane/ethyl acetate gave 4.06 g of pure **15b**, for a total yield of 11.5 g (67%). Less polar isomer **15a**: mp 90–91 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.78 (bd, *J* = 10 Hz, 1 H), 5.62 (dt, *J* = 10, 2 Hz, 1 H), 4.98 (s, 1 H), 4.95 (s, 1 H), 4.08 (m, 1 H), 3.84 (d, *J* = 6 Hz, 1 H), 3.67 (ddd, *J* = 4, 7, 11 Hz, 1 H), 2.54 (m, 1 H), 2.46 (bs, 1 H), 1.90 (m, 1 H), 1.75 (s, 3 H), 1.74 (bs, 1 H), 1.51 (q, *J* = 11 Hz, 1 H), 0.18 (s, 9 H); IR ($CHCl_3$) λ_{max} 3600, 2950, 1650, 1070 cm^{-1}; mass spectrum, *m/z* 256 (M), 168, 96. Anal. Calcd for $C_{13}H_{24}O_3Si$: C, 60.89; H, 9.43. Found: C, 61.21; H, 9.41.

More polar isomer **15b**: mp 68–70 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.64 (dt, *J* = 10, 2 Hz, 1 H), 5.56 (bd, *J* = 10 Hz, 1 H), 5.00 (s, 1 H) 4.96 (s, 1 H), 4.07 (m, 1 H), 4.01 (d, *J* = 5 Hz, 1 H), 3.65 (ddd, *J* = 4, 8, 11 Hz, 1 H), 2.57 (m, 2 H), 1.97 (m, 1 H), 1.95 (bs, 1 H), 1.72 (s, 3 H), 1.52 (~q, *J* = 11 Hz, 1 H), 0.17 (s, 9 H); IR ($CHCl_3$) λ_{max} 3600, 2950, 1650, 1450, 1070 cm^{-1}; mass spectrum, *m/z* 256 (M), 194, 168, 96. Anal. Calcd for $C_{13}H_{24}O_3Si$: C, 60.89; H, 9.43. Found: C, 60.68; H, 9.18.

(1α,4β,5α)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α-(1-methylethenyl)-4-[(trimethylsilyl)oxy]-2-cyclohexene-1-methanol (16a,b). A magnetically stirred solution containing 11.23 g (42.7 mmol) of an approximately 1:1 mixture of epimeric diols **15a,b** in 315 mL of CH_2Cl_2 was cooled to −78 °C and a solution containing 10.45 mL (89.6 mmol) of distilled 2,6-lutidine and 10.06 mL (43.7 mmol) of freshly prepared *tert*-butyldimethylsilyl trifluoromethane sulfonate in 60 mL of dry dichloromethane was added slowly dropwise over a 45-min period. The resulting mixture was stirred for 30 min at −78 °C, treated with 1.9 mL of absolute methanol and allowed to warm to room temperature. After addition of 500 mL of CH_2Cl_2, the reaction mixture was successively washed with water (1 × 200 mL) and brine (200 mL) and dried over magnesium sulfate. After removal of the volatiles in vacuo, the remaining oil was chromatographed on 900 g of SiO_2 with an eluant of hexane/ethyl acetate (10:1) to provide 14.76 g (91%) of *tert*-butyldimethylsilyl derivatives **16a,b**. High-pressure-liquid chromatography provided analytical samples of **16a** and **16b**, but separation was not necessary for the next step. Less polar isomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.63 (m, 2 H), 5.03 (bs, 1 H), 4.96 (bs, 1 H), 4.01 (m, 1 H), 3.97 (bt, *J* = 5 Hz, 1 H), 3.71 (ddd, *J* = 4, 6, 9 Hz, 1 H), 2.53 (m, 1 H), 2.33 (d, *J* = 5 Hz, 1 H), 1.91 (ddd, *J* = 4, 6, 13 Hz, 1 H), 1.72 (bs, 3 H), 1.54 (ddd, *J* = 8, 10, 14 Hz, 1 H), 0.92 (s, 9 H), 0.16 (s, 9 H), 0.11 (s, 6 H); IR ($CHCl_3$) λ_{max} 3600, 3350, 2950, 1650, 1250 cm^{-1}; mass spectrum, *m/z* 313 (M − butyl), 295, 223, 185. Anal. Calcd for $C_{19}H_{38}O_3Si_2$: C, 61.57; H, 10.33. Found: C, 61.53; H, 10.50.

More polar isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.76 (bd, *J* = 10 Hz, 1 H), 5.62 (dt, *J* = 10, 2 Hz, 1 H), 5.02 (bs, 1 H), 4.95 (bs, 1 H), 4.05 (m, 1 H), 3.84 (bt, *J* = 5 Hz, 1 H), 3.73 (ddd, *J* = 3, 6, 10 Hz, 1 H), 2.49 (m, 1 H), 2.15 (d, *J* = 4 Hz, 1 H), 1.83 (dt, *J* = 13, 4 Hz, 1 H), 1.74 (bs, 3 H), 1.58 (q, *J* = 8 Hz, 1 H), 0.92 (s, 9 H), 0.16 (s, 9 H), 0.11 (s, 6 H); IR ($CHCl_3$) λ_{max} 3600, 3400 (b), 1650, 1250 cm^{-1}; mass spectrum, *m/z* 370 (M), 368, 313 (M − butyl), 236. Anal. Calcd for $C_{19}H_{38}O_3Si_2$: C, 61.57; H, 10.33. Found: C, 61.71; H, 10.41.

(1α,4β,5α)-[[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α-(1-methylethenyl)-4-[(trimethylsilyl)oxy]-2-cyclohexen-1-yl]methoxy]trimethylsilane (17a,b). A magnetically stirred

solution of alcohols **16a** and **16b** (19.16 g, 51.78 mmol) in 450 mL of dry CH_2Cl_2 was cooled to −78 °C, and a solution containing 12.07 mL (103.5 mmol) of 2,6 lutidine and 10.37 mL (56.92 mmol) of trimethylsilyl trifluoromethanesulfonate in 80 mL of dry CH_2Cl_2 was added over a 40-min period. The reaction mixture was allowed to stir at −78 °C for 30 min, then warmed to 0 °C, and kept at that temperature for 60 min, after which time it was poured into 200 mL of H_2O. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 500 mL). The combined organic phases were washed with brine (1 × 200 mL) and dried with magnesium sulfate. Concentration in vacuo and chromatography on silica gel with hexane/ethyl acetate as the eluant gave 21.12 g (97%) of **17a** and **17b** as a colorless oil. Isomer **17a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.42 (q, J = 10 Hz, 2 H), 4.87 (bs, 1 H), 4.84 (bs, 1 H), 4.07 (m, 1 H), 3.71 (bd, J = 8 Hz, 1 H), 3.66 (ddd, J = 4, 8, 11 Hz, 1 H), 2.40 (m, 1 H), 2.02 (dt, J = 13, 4 Hz, 1 H), 1.69 (s, 3 H), 1.32 (q, J = 12 Hz, 1 H), 0.92 (s, 9 H), 0.16 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 9 H); IR ($CHCl_3$) λ_{max} 2950, 1650, 1250, 840 cm^{-1}; mass spectrum, m/z 442 (M), 385 (M − butyl), 295, 143; exact mass calcd for $C_{18}H_{37}O_3Si_3$ (M − butyl) 385.2051, found 385.2041.

Isomer **17b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77 (dt, J = 10, 2 Hz, 1 H), 5.49 (dt, J = 10, 2 Hz, 1 H), 4.86 (bs, 1 H), 4.85 (bs, 1 H), 4.06 (m, 1 H), 3.64 (m, 2 H), 2.34 (m, 1 H), 1.67 (s, 3 H), 1.55 (dt, J = 12, 3 Hz, 1 H), 1.24 (q, J = 12 Hz, 1 H), 0.90 (s, 9 H), 0.16 (s, 9 H), 0.09 (s, 15 H); IR ($CHCl_3$) λ_{max} 2950, 1650, 1250, 840 cm^{-1}; mass spectrum, m/z 442 (M), 385 (M − butyl), 143; exact mass calcd for $C_{18}H_{37}O_3Si_3$ (M − butyl) 385.2051, found 385.2041.

(1α,5α,6β)-(1,1-Dimethylethyl)dimethyl-[[5-(2-methyl-3-[(trimethylsilyl)oxy]-2-propenyl]-6-[(trimethylsilyl)oxy]-3-cyclohexen-1-yl]oxy]silane (18). The tris(silylethers) **17a,b** as a neat oil were placed in glass ampules (500-mg lots), and the ampules were sealed under high vacuum. The ampules were then placed in an oil filled autoclave and kept at 310 °C for a period of 1 h. After cooling to room temperature the ampules were opened and analyzed by ^{1}H NMR. The proton NMR spectrum showed the rearranged products **18** in addition to some minor decomposition products. As such the crude product was used directly in the next step: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.14 and 6.04 (bs, 1:4 ratio, 1 H), 4.48 (bs, 2 H), 3.77 (dt, J = 5, 7 Hz, 1 H), 3.42 (t, J = 7 Hz, 1 H), 2.45–1.93 (m, 4 H), 1.66 (dd, J = 11, 13 Hz, 1 H), 1.59 (bs, 3 H), 0.91 (s, 9 H), 0.18 (s, 9 H), 0.16 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); IR ($CHCl_3$) λ_{max} 2940, 1660, 1250, 840 cm^{-1}.

(3α,4aβ,8α,8aα)-8-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3,4,4a,7,8,8a-hexahydro-3-methyl-2*H*-1-benzopyran-2-one (19) and (3β,4aβ,8α,8aα)-8-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4,4a,7,8,8a-hexahydro-3-methyl-2*H*-1-benzopyran-2-one (20). To a solution of crude enol silyl ethers **18** (20.4 g, 46.2 mmol) in 1000 mL of dioxane at 5–10 °C was added 125 mL of 0.01 N HCl with rapid stirring. After 45 min the reaction was quenched with 300 mL of saturated $NaHCO_3$. This solution was extracted with CH_2Cl_2 (3 × 500 mL), dried with magnesium sulfate, and concentrated in vacuo. Chromatography on silica gel with hexane/ether (6:1) as the eluant gave 4.69 g of the faster eluting lactol isomer and 1.47 g of the slower eluting isomer, for a total yield of 45% from **17a,b**. The lactols were each a 1:1 ratio of anomers by HPLC analysis. To a solution of the higher R_f lactol isomer (4.636 g, 15.56 mmol) in 96 mL of CH_2Cl_2 at room temperature was added pyridinium dichromate (21.7 g, 57.68 mmol), and the mixture was stirred magnetically for 78 h. The mixture was then diluted with ether and filtered through a pad of silica gel, and the pad was washed several times with ether. The volatiles were removed in vacuo to leave a crude yellow oil that was chromatographed on 231 g of silica gel. Elution with hexane/ether (6:1) gave 3.618 g (79%) of lactone **19** as a low melting white semisolid: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.59 (m, 2 Hz, 1 H), 5.37 (bd, J = 10 Hz, 1 H), 3.95 (dt, J = 7, 10 Hz, 1 H), 3.88 (t, J = 10 Hz, 1 H), 2.68 (ddq, J = 7, 11, 7 Hz, 1 H), 2.53 (m, 1 H), 2.38 (bt, J = 10 Hz, 1 H), 2.16 (m, 3 H), 1.35 (d, J = 7 Hz, 3 H), 0.90 (s, 9 H), 0.17 (s, 3 H), 0.10 (s, 3 H); IR ($CHCl_3$) λ_{max} 2940, 1730, 1460, 1100 cm^{-1}; mass spectrum, m/z 239 (M − butyl), 221, 181, 119. Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.519. Found: C, 65.04; H, 9.80.

A solution of the lower R_f lactol isomer (81 mg, 0.27 mmol) in 3 mL of CH_2Cl_2 was treated with 382 mg (1.10 mmol) of pyridinium dichromate and was stirred at room temperature for 48 h. The reaction mixture was then diluted with ether and filtered through 10 g of silica gel with hexane/ether 5:1 to afford a crude mixture of lactone **20**. Chromatography on 35 g of silica gel (hexane/ether 5:1) afforded 68 mg (84%) of a single lactone isomer **20** epimeric to **19**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.57 (m, 1 H), 5.38 (m, 1 H), 3.99 (m, 2 H), 2.73 (ddq, J = 7, 10, 7 Hz, 1 H), 250 (m, 1 H), 2.38 1 H), 2.15 (m, 1 H), 1.89 (dt, J = 13, 10 Hz, 1 H), 1.70 (dt, J = 13, 8 Hz, 1 H), 1.23 (d, J = 7 Hz, 3 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.12 (s, 3 H); IR ($CHCl_3$) λ_{max} 2940, 1740, 1460, 1110 cm^{-1}; mass spectrum, m/z 296 (M), 239 (M − butyl), 221, 181. Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.519. Found: C, 64.82; H, 9.46.

(1aβ,3α,3aα,6α,7aβ,7bα)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-6-methyl-5*H*-oxireno[*f*][1]benzopyran-5-one (21a) and (1aα,3α,3aα,6α,7aβ,7bα)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-6-methyl-5*H*-oxireno[*f*][1]benzopyran-5-one (22a). *mCPBA* Method. To a solution of olefin **19** (11.9 mg, 0.0402 mmol) in 2 mL of $ClCH_2CH_2Cl$ was added a solution of *m*CPBA $ClCH_2CH_2Cl$ (170 μL, 0.467 M, 0.079 mmol) and 1 mg of 4,4′ thiobis-(6-*tert*-butyl-3-methyl phenol), and the resulting mixture was heated at reflux for 2.5 h. The reaction was diluted with 125 mL of CH_2Cl_2, washed with 10% $NaHSO_3$ (1 × 10 mL), saturated $NaHCO_3$ (1 × 10 mL), and brine (1 × 10 mL) and dried with sodium sulfate. Removal of the volatiles gave 13.3 mg of crude epoxides which were separated by high-pressure liquid chromatography (eluant:hexane/ether 2:1) to afford 4.1 mg of the less polar α-epoxide **22a** and 7.3 mg of the more polar β-epoxide **21a** for a total yield of 91%. The identity of the epoxides was established by the expected regiochemistry in the reaction with diethylaluminum cyanide (see compounds **23** and **24**). Major β-epoxide **21a**: ^{1}H NMR ($CDCl_3$, 490 MHz) δ 3.93 (t, J = 9 Hz, 1 H), 3.73 (dt, J = 9, 8 Hz, 1 H), 3.13 (m, 2 H), 2.68 (ddq, J = 7, 11, 7 Hz, 1 H), 2.39 (ddd, J = 5, 8, 15 Hz, 1 H), 2.19 (ddd, J = 3, 8, 13 Hz, 1 H), 2.02 (m, 2 H), 1.74 (dt, J = 11, 13 Hz, 1 H), 1.36 (d, J = 7 Hz, 3 H), 0.89 (s, 9 H), 0.14 (s, 3 H), 0.07 (s, 3 H); IR ($CHCl_3$) λ_{max} 2910, 1725, 1460, 850 cm^{-1}; mass spectrum, m/z 313 (M + 1), 255 (M − butyl), 209, 197. Minor α-epoxide **22a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.73 (dt, J = 6, 9 Hz, 1 H), 3.67 (t, J = 9 Hz, 1 H), 3.24 (m, 1 H), 2.88 (bd, J = 4 Hz, 1 H), 2.72 (ddq, J = 8, 11, 7 Hz, 1 H), 2.58 (ddd, J = 1, 5, 15 Hz, 1 H), 2.28 (ddd, J = 3, 8, 13 Hz, 1 H), 2.05 (ddd, J = 4, 10, 14 Hz, 1 H), 1.81 (ddd, J = 2, 9, 11 Hz, 1 H), 1.53 (dt, J = 11, 13 Hz, 1 H), 1.36 (d, J = 7 Hz, 3 H), 0.89 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H); IR ($CHCl_3$) λ_{max} 2925, 1735, 1460, 870 cm^{-1}; mass spectrum, m/z 313 (M + 1), 312 (M), 255 (M − butyl), 197. Anal. Calcd for $C_{16}H_{28}O_4Si$: C, 61.50; H, 9.03. Found: C, 61.73; H, 9.05.

(1aα,3α,3aα,6α,7aβ,7bα)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-6-methyl-5*H*-oxireno[*f*][1]benzopyran-5-one (22a) and (1aα,3α,3aα,6β,7aβ,7bα)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-6-methyl-5*H*-oxireno[*f*][1]benzopyran-5-one (22b). Bromohydrin Method. To a solution of olefin **19** (2.47 g, 8.35 mmol) in 450 mL of dioxane/water (1:1) at room temperature was added *N*-bromosuccinimide (1.49 g, 8.35 mmol) and the solution stirred for 12 h in the dark. The reaction was quenched with 50 mL of 10% sodium bisulfite. Extraction with CH_2Cl_2 (4 × 300 mL) gave a solution which was washed with brine (1 × 100 mL) and dried with magnesium sulfate. Removal of the volatiles in vacuo gave 3.38 g of a solid that contained a single bromohydrin **25a** and a small amount of succinimide. An analytical sample of bromohydrin **25a** could be obtained from the crude sample by high-pressure liquid chromatography (eluant:hexane/ethyl acetate 2:1): mp 193–194 °C; ^{1}H NMR ($CDCl_3$, 490 MHz) δ 4.28 (bt, J = 3 Hz, 1 H), 4.16 (dd, J = 9, 11 Hz, 1 H), 4.13 (q, J = 3 Hz, 1 H), 4.05 (ddd, J = 5, 9, 11 Hz, 1 H), 2.62 (ddq, J = 7, 11, 7 Hz, 1 H), 2.38 (bd, J = 3 Hz, 1 H), 2.32 (tt, J = 3.5, 11 Hz, 1 H), 2.22 (ddd, J = 3, 11, 14 Hz, 1 H), 2.02 (m, 1 H), 1.85 (ddd, J = 3.5, 7, 13 Hz, 1 H), 1.80 (q, J = 12 Hz, 1 H), 1.33 (d, J = 7 Hz, 3 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.11 (s, 3 H); IR ($CHCl_3$) λ_{max} 3600, 3400 (b), 2900, 1725 cm^{-1}; mass spectrum, m/z 337 and 335 (M − butyl), 319 and 317 (M − butyl − H_2O), 255, 197. Acetate derivative: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (q, J = 3 Hz, 1 H), 4.20 (bs, 1 H), 4.19 (dd, J = 9, 11 Hz, 1 H), 3.94 (ddd, J = 5, 9, 11 Hz, 1 H), 2.64 (ddq, J = 7, 11, 7 Hz, 1 H), 2.31 (ddd, J = 3, 11, 14 Hz, 1 H), 2.12

(s, 3 H), 2.05 (m, 2 H), 1.87 (ddd, J = 3, 7, 14 Hz, 1 H), 1.81 (q, J = 12 Hz, 1 H), 1.35 (d, J = 7 Hz, 3 H), 0.91 (s, 9 H), 0.18 (s, 3 H), 0.11 (s, 3 H).

The crude bromohydrin was dried at high vacuum overnight, then dissolved in 500 mL of anhydrous toluene. A solution of freshly prepared potassium *tert*-butoxide in *tert*-butyl alcohol (1.19 M, 8.2 mL, 9.76 mmol) was added slowly over a period of 20 min. The reaction was then poured into 300 mL of distilled water. Separation of the layers, followed by extraction of the aqueous phase with CH_2Cl_2 (3 × 330 mL) gave a combined organic phase which was washed with 200 mL of brine and dried with magnesium sulfate. The volatiles were removed in vacuo to give 2.49 g of a crude white solid which was chromatographed on 125 g of silica gel. Elution with hexane/ethyl acetate (3:1) gave 2.09 g (80%) of epoxide **22a**. Further elution gave 250 mg (8%) of recovered bromohydrin which had undergone epimerization of the methyl group. Similarly, treatment of the minor epimer **20** under the above conditions led to a single α-epoxide, **22b**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.76 (m, 2 H), 3.25 (m, 1 H), 2.88 (bd, J = 4 Hz, 1 H), 2.73 (m, 1 H), 2.57 (dd, J = 3, 15 Hz, 1 H), 2.08 (m, 2 H), 1.83 (m, 2 H), 1.26 (d, J = 7 Hz, 3 H), 0.88 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H); IR ($CHCl_3$) λ_{max} 2900, 1740, 1100, 860 cm^{-1}; mass spectrum, m/z 313 (M + 1), 312 (M), 255 (M - butyl), 197. Anal. Calcd for $C_{16}H_{28}O_4Si$: (mixture of methyl epimers) C, 61.50; H, 9.03. Found: C, 61.73; H, 9.05.

(3α,4aβ,5α,6β,8α,8aα)-6-Acetoxy-5-cyano-8-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2*H*-1-benzopyran-2-one (23). To a solution of β-epoxy lactone **21a** (4.9 mg, 0.0157 mmol) in 1 mL of THF was added diethylaluminum cyanide in toluene (52 μL, 1.8 M, 0.094 mmol), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with 2 mL of aqueous Na_2SO_4, extracted with CH_2Cl_2 (4 × 10 mL), washed with brine, and dried with sodium sulfate. Removal of the volatiles gave 5.2 mg (98%) of cyanohydrin which was purified by high pressure liquid chromatography (eluant: hexane/ethyl acetate 2:1): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.19 (bs, 1 H), 4.18 (dd, J = 9, 11 Hz, 1 H), 3.97 (ddd, J = 5, 9, 11 Hz, 1 H), 3.01 (m, 1 H), 2.67 (ddq, J = 7, 11, 7 Hz, 1 H), 2.10 (m, 4 H), 1.95 (ddd, J = 3, 7, 13 Hz, 1 H), 1.80 (q, J = 12 Hz, 1 H), 1.37 (d, J = 7 Hz, 3 H), 0.93 (s, 9 H), 0.21 (s, 3 H), 0.15 (s, 3 H); IR ($CHCl_3$) λ_{max} 3600, 3450, 2250, 1730 cm^{-1}. Acetate derivative **23**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.17 (bs, 1 H, collapses to d upon irradiation at δ 2.26), 4.11 (dd, J = 9, 11 Hz, 1 H, collapses to d upon irradiation at δ 2.26), 4.01 (ddd, J = 5, 9, 11 Hz, 1 H), 3.15 (m, 1 H, irradiation causes peaks at δ 2.12 and δ 1.91 to simplify), 2.66 (ddq, J = 7, 11, 7 Hz, 1 H), 2.26 (tt, J = 2, 11 Hz, 1 H), 2.14 (s, 3 H), 2.12 (m, 1 H), 1.95 (ddd, J = 3, 7, 13 Hz, 1 H), 1.91 (ddd, J = 5, 11, 13 Hz, 1 H), 1.55 (q, J = 13 Hz, 1 H), 1.34 (d, J = 7 Hz, 3 H), 0.92 (s, 9 H), 0.20 (s, 3 H), 0.16 (s, 3 H).

(3α,4aβ,5α,6β,8α,8aα)-6-Acetoxy-5-cyano-8-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2*H*-1-benzopyran-2-one (24). To a solution of α-epoxy lactone **22a** (4.1 mg, 0.0131 mmol) in 1 mL of THF was added diethylaluminum cyanide in toluene (1.8 M, 45 μL, 0.079 mmol) and the reaction was stirred for 6 h at room temperature. The reaction was quenched with 2 mL of aqueous Na_2SO_4, extracted with CH_2Cl_2 (4 × 10 mL), washed with brine, and dried with sodium sulfate. Purification by high-pressure liquid chromatography (eluant: hexane/ethyl acetate 2:1) gave 3.0 mg (68%) of a single cyanohydrin: ^{1}H NMR ($CDCl_3$, 500 MHz) 4.19 (bs, 1 H), 4.16 (dd, J = 9, 11 Hz, 1 H), 3.96 (ddd, J = 5, 9, 11 Hz, 1 H), 3.01 (m, 1 H), 2.66 (ddq, J = 7, 11, 7 Hz, 1 H), 2.10 (m, 3 H), 1.93 (ddd, J = 3, 7, 13 Hz, 1 H), 1.89 (bd, J = 4 Hz, 1 H), 1.79 (q, J = 13 Hz, 1 H), 1.36 (d, J = 7 Hz, 3 H), 0.92 (s, 9 H), 0.20 (s, 3 H), 0.15 (s, 3 H); IR ($CHCl_3$) λ_{max} 3600, 3350, 2250, 1735 cm^{-1}; mass spectrum, m/z 340 (M + 1), 282 (M - butyl), 224, 206. Acetate derivative **24**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.22 (q, J = 3 Hz, 1 H), 4.12 (dd, J = 9, 11 Hz, 1 H), 3.91 (ddd, J = 5, 9, 11 Hz, 1 H), 3.12 (quintet, J = 2 Hz, 1 H), 2.65 (ddq, J = 7, 11, 7 Hz, 1 H), 2.15 (m, 2 H), 2.12 (s, 3 H), 2.00 (m, 2 H), 1.80 (q, J = 12 Hz, 1 H), 1.37 (d, J = 7 Hz, 3 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.10 (s, 3 H).

(1aα,3aα,3aα,7aβ,7bα)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-6-methyl-6-(phenylseleno)-5*H*-oxireno[*f*][1]benzopyran-5-one (26a,b). To a solution of diisopropylamine (1.96 mL, 13.9 mmol) in 350 mL of dry THF at -10 °C was added *n*-BuLi in hexane (10.96 mL, 1.16 M, 12.7 mmol), and the solution was cooled to -78 °C, after stirring for 10 min at -10 °C. A solution of epoxides **22a,b** (3.605 g, 11.55 mmol) in 50 mL of dry THF (precooled to -78 °C) was then added dropwise via cannula to the LDA solution over a 20 min period and stirred for 30 min after the addition was complete. A solution of phenylselenenyl chloride (4.42 g, 23.1 mmol) in 26 mL of dry THF (precooled to -78 °C) was added via cannula to the enolate solution over a 10-min period. After stirring for 1 h, the reaction was quenched by pouring into a mixture of 400 mL of CH_2Cl_2 and 200 mL of water. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic phase was washed with brine (200 mL) and dried with magnesium sulfate, and the volatiles were removed in vacuo, to give a yellow semisolid mass. Crystallization from hexane/ether gave 1.29 g of the less polar A selenide, mp 135–137 °C. Chromatography of the mother liquors on 150 g silica gel (eluant: hexane/ethyl acetate 4:1) gave an additional 794 mg of selenide A, 1.54 g of the more polar selenide B and 999 mg of recovered starting material. The yield of selenides was 93% based on recovered starting material. It was not possible to distinguish the stereochemistry of the individual selenides from the ^{1}H NMR spectrum. Less polar selenide **26a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.61–7.28 (m, 5 H), 4.29 (dt, J = 2, 9 Hz, 1 H), 3.79 (dt, J = 6, 9 Hz, 1 H), 3.26 (m, 1 H), 2.80 (d, J = 3 Hz, 1 H), 2.56 (ddd, J = 1, 6, 15 Hz, 1 H), 2.33 (m, 1 H), 2.05 (ab system, J = 13 Hz, 2 H), 1.84 (ddd, J = 2, 10, 15 Hz, 1 H), 1.65 (s, 3 H), 0.93 (s, 9 H), 0.18 (s, 3 H), 0.11 (s, 3 H); IR ($CHCl_3$) δ_{max} 2900, 1725, 1120, 860, 840 cm^{-1}; mass spectrum, m/z 467 (M), 410 (M - butyl), 225, 207. More polar selenide **26b**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.64–7.31 (m, 5 H), 3.79 (dt, J = 6, 10 Hz, 1 H), 3.67 (t, J = 10 Hz, 1 H), 3.22 (m, 1 H), 2.81 (d, J = 4 Hz, 1 H), 2.56 (m, 2 H), 2.30 (dd, J = 3, 14 Hz, 1 H), 1.96 (t, J = 14 Hz, 1 H), 1.81 (ddd, J = 2, 9, 15 Hz, 1 H), 1.66 (s, 3 H), 0.89 (s, 9 H), 0.15 (s, 3 H), 0.10 (s, 3 H); IR ($CHCl_3$) λ_{max} 2930, 1730, 1110, 870, 840 cm^{-1}; mass spectrum, m/z 467 (m), 410 (M - butyl), 368, 313, 236.

(1aα,3aα,3aα,7aβ,7bα)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1a,2,3,3a,7a,7b-hexahydro-6-methyl-5*H*-oxireno[*f*][1]benzopyran-5-one (27). To a solution of the less polar selenide **26a** (1.828 g, 3.92 mmol) in 326 mL of CCl_4/CH_2Cl_2 (1:1 v/v) at -22 °C was added solid *m*CPBA (1.30 g, 6.0 mmol), and the solution was stirred at -22 °C for 90 min; 350 mg of *m*CPBA was then added, and the solution was stirred for another 2 h at -22 °C. The reaction was quenched with 100 mL of 10% $NaHSO_3$ solution and warmed to room temperature. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 500 mL). The combined organic phase was washed with saturated $NaHCO_3$ (1 × 200 mL) and brine, and dried with $MgSO_4$. Removal of the volatiles in vacuo gave 1.32 g of an off-white solid that was chromatographed on 65 g of silica gel. Elution with hexane/ethyl acetate (6:1) gave 1.11 g (92%) of **27** as a white solid: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.64 (m, 1 H), 3.80 (m, 2 H), 3.27 (m, 1 H), 3.11 (d, J = 3 Hz, 1 H), 2.77 (dt, J = 12, 3 Hz, 1 H), 2.62 (dd, J = 4, 12 Hz, 1 H), 1.96 (q, J = 1 Hz, 3 H), 1.85 (ddd, J = 2, 9, 15 Hz, 1 H), 0.91 (s, 9 H), 0.17 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.3 MHz, proton decoupled) δ 164.6, 140.5, 129.8, 81.6, 66.9, 53.0, 38.7, 34.1, 25.7, 18.1, 16.8, -4.5, -5.1; IR ($CHCl_3$) λ_{max} 2930, 1730, 1470, 1120, 840 cm^{-1}; mass spectrum, m/z 253 (M - butyl), 235, 217, 181. Anal. Calcd for $C_{16}H_{26}O_4Si$: C, 61.90; H, 8.44. Found: C, 61.68; H, 8.50.

(1aα,3aα,3aα,7aβ,7bα)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-6-methylene-5*H*-oxireno[*f*][1]benzopyran-5-one (28). To a solution of more polar selenide **26b** (1.54 g, 3.30 mmol) in 275 mL of CCl_4/CH_2Cl_2 (1:1 v/v) at -22 °C was added solid *m*CPBA (1.42 g, 80%, 6.6 mmol) and the resulting solution was stirred for 2.5 h at -22 °C. The reaction was quenched with 100 mL of 10% $NaHSO_3$ at -22 °C. After warming to room temperature, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phase was washed with saturated $NaHCO_3$ (1 × 100 mL) and brine (1 × 100 mL) and dried with magnesium sulfate. Removal of the volatiles gave 1.3 g of an oil that was chromatographed on 65 g of silica gel. Elution with hexane/ethyl acetate (6:1) gave 429 mg (42%) of the desired endocyclic isomer **27**. Further elution with hexane/ethyl acetate (4:1) gave 592 mg (58%) of the exocyclic isomer **28**, mp 79–80 °C; Exocyclic isomer **28**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.50 (m, 1 H), 5.67 (m, 1 H), 4.83 (dt,

J = 5, 10 Hz, 1 H), 3.69 (t, J = 10 Hz, 1 H), 3.28 (m, 1 H), 2.94 (ddt, J = 6, 16, 2 Hz, 1 H), 2.88 (d, J = 3 Hz, 1 H), 2.57 (m, 2 H), 2.20 (ddd, J = 5, 10, 15 Hz, 1 H), 1.83 (ddd, J = 2, 9, 15 Hz, 1 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.11 (s, 3 H); IR ($CHCl_3$) λ_{max} 2930, 1730, 1620, 1125, 860, 840 cm^{-1}; mass spectrum, m/e 253 (m – butyl), 235, 217, 193. Anal. Calcd for $C_{16}H_{26}O_4Si$: C, 61.90; H, 8.44. Found: C, 61.48; H, 8.45.

3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1a,3,3a,5,7a,7b-hexahydro-6-methyl-2*H*-oxireno[*f*][1]benzopyran-5-ol (29). To a solution of lactone **27** (1.516 g, 4.89 mmol) in 225 mL of dry toluene at −78 °C was added a solution of diisobutylaluminum hydride in hexane (1.0 M, 4.89 mL) over a 25-min period. The solution was then stirred at −78 °C for 30 min, and then it was allowed to warm to −40 °C. After stirring for 40 min at −40 °C, 0.489 mL of DIBAL was added, and 60 min later another 0.489 mL of DIBAL was added. After 30 min the reaction was quenched at −40 °C with 2 mL of methanol, and it was allowed to warm to room temperature. The reaction mixture was partitioned between CH_2Cl_2 (500 mL) and saturated Na_2SO_4 (300 mL). Separation and extraction of the aqueous phase with CH_2Cl_2 (2 × 300 mL) gave a combined organic phase that was dried with magnesium sulfate and concentrated in vacuo. Silica gel chromatography of the crude product, (80 g, eluant: hexane/ethyl acetate 4:1) gave 1.311 g (86%) of lactols **29**: ^1H NMR ($CDCl_3$, 250 MHz) δ 5.73 (bs, 1 H), 5.21 (bd, J = 4 Hz, 1 H), 3.67 (dt, J = 6, 10 Hz, 1 H), 3.45 (t, J = 10 Hz, 1 H), 3.18 (bs, 1 H), 2.97 (d, J = 4 Hz, 1 H), 2.58 (bdd, J = 6, 15 Hz, 1 H) 2.39 (d, J = 4 Hz, 1 H), 2.36 (m, 1 H), 1.82 (ddd, J = 3, 9, 15 Hz, 1 H), 1.78 (m, 3 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); IR ($CHCl_3$) λ_{max} 3600, 2940, 1680, 840 cm^{-1}; mass spectrum, m/z 313 (M + 1), 312 (M), 255 (M – butyl), 219, 109. Anal. Calcd for $C_{16}H_{28}O_4Si$: C, 61.50; H, 9.03. Found: C, 61.64; H, 9.13.

(1aα,3aα,3aα,5α,7aβ,7bα)-(1,1-Dimethylethyl)-[[1a,3,3a,5,7a,7b-hexahydro-5-methoxy-6-methyl-2*H*-oxireno[*f*][1]benzopyran-3-yl]oxy]dimethylsilane (30). To a solution of lactol **29** (547.7 mg, 1.76 mmol) in 65 mL of dry methanol at −20 °C was added a solution of $BF_3{\cdot}OEt_2$ in methanol (0.79 M, 665 μL, 0.525 mmol), and the reaction was stirred at −20 °C. After 1.5 h, another 150 μL of $BF_3{\cdot}OEt_2$/MeOH solution was added, and after another 2 h, 100 μL of the $BF_3{\cdot}OEt_2$/MeOH solution was added. The reaction was quenched 2.5 h after the last addition with 50 mL of saturated $NaHCO_3$. Extraction with CH_2Cl_2 (4 × 125 mL) gave a combined organic layer which was dried with magnesium sulfate and concentrated in vacuo. Chromatography on 28 g of silica gel (eluant: hexane/ethyl acetate 10:1) gave 487 mg (85%) of acetal **30** as one anomer: ^1H NMR ($CDCl_3$, 270 MHz) δ 5.70 (bs, 1 H), 4.67 (bs, 1 H), 3.66 (dt, J = 6, 10 Hz 1 H), 3.43 (s, 3 H), 3.35 (t, J = 10 Hz, 1 H), 3.15 (m, 1 H), 2.95 (bd, J = 4 Hz, 1 H), 2.56 (dd, J = 6, 15 Hz, 1 H), 2.35 (bd, J = 10 Hz, 1 H), 1.81 (ddd, J = 3, 10, 15 Hz, 1 H), 1.74 (bs, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); IR ($CHCl_3$) λ_{max} 2900, 1460, 1060, 820 cm^{-1}; mass spectrum, m/z 326 (M), 269 (M – butyl), 237, 219; exact mass calcd for $C_{17}H_{34}O_4SiN$ (M + NH_4) 344.22570, found 344.22585.

(2α,4aβ,5α,6β,8α,8aα)-5-Cyano-8-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4a,5,6,7,8,8a-hexahydro-2-methoxy-3-methyl-2*H*-1-benzopyran-6-ol 6-Acetate (32). A solution of epoxide **30** (131.1 mg, 0.402 mmol) in 14 mL of CH_2Cl_2 at 0 °C was treated with diethylaluminum cyanide in toluene (1.8 M, 0.466 mL, 0.839 mmol) for 3.5 h at 0 °C. The reaction was quenched with saturated sodium sulfate (20 mL), extracted with CH_2Cl_2 (4 × 50 mL), washed with brine, and dried with sodium sulfate. Concentration in vacuo gave an oil that was chromatographed on silica gel. Elution with hexane/ethyl acetate (4:1) gave 138.2 mg (97%) of the cyanohydrin **31**. The cyanohydrin could be acetylated by dissolving in 5 mL of CH_2Cl_2 and treating with acetic anhydride (0.074 mL), pyridine (0.063 mL), and a trace of dimethylaminopyridine at room temperature for 6 h. The volatiles were removed in vacuo to give an oil that was passed through a pad of silica gel (hexane/ethyl acetate 4:1) to give 150.1 mg (97%) of the acetate **32**: mp 130.5–131.5 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.39 (bs, 1 H), 5.21 (q, J = 2.5 Hz, 1 H), 4.67 (bs, 1 H), 3.91 (ddd, J = 5, 9, 10 Hz, 1 H), 3.72 (t, J = 10 Hz, 1 H), 3.46 (s, 3 H), 3.06 (~quintet, J = 2.5 Hz, 1 H), 2.53 (bd, J = 11 Hz, 1 H), 2.16 (m, 1 H), 2.09 (s, 3 H), 2.02 (ddd, J = 3, 11, 15 Hz, 1 H), 1.76 (bs, 3 H), 0.92 (s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H). Upon irradiation of triplet at δ 3.72 (homoallylic methine proton bearing oxygen), the ddd at δ 3.91 (OTBS methine proton) collapsed to dd and the bd at δ 2.53 (allylic methine proton) collapsed to a broad singlet. Upon irradiation of the quintet at δ 3.06, the quartet at δ 5.21 (acetate methine proton) collapsed to a triplet and the bd at δ 2.53 (allylic methine proton) lost a small coupling, establishing the cyano-bearing methine proton in the desired regiochemistry. Irradiation of the acetate methine proton at δ 5.21 caused the methine proton at δ 3.06 to collapse to a broad doublet (J = 4 Hz) and both methylene protons at δ 2.16 and 2.02 to lose small couplings, rigorously establishing the acetate in the correct position. IR ($CHCl_3$) λ_{max} 2940, 2210 (w), 1740, 1370, 1210 cm^{-1}; mass spectrum, m/z 395 (M), 364, 338 (M – butyl), 306, 246, 172, 136.

(2α,4aβ,5α,6β,8α,8aα)-5-Cyano-4a,5,6,7,8,8a-hexahydro-3-methyl-2*H*-1-benzopyran-2,6,8-triol 6,8-Diacetate (35). A solution of cyanohydrin acetate **32** (158.4 mg, 0.401 mmol) in 10 mL of dioxane at room temperature was treated with 10 mL 0.5 N HCl for 9 h. The reaction was quenched with 20 mL of saturated sodium bicarbonate, extracted with ethyl acetate (4 × 50 mL), dried with magnesium sulfate, and concentrated in vacuo. This was directly treated with 0.232 mL of acetic anhydride, 0.264 mL of pyridine and several mg of dimethylaminopyridine in 10 mL of CH_2Cl_2 for 7 h at room temperature. The reaction was then concentrated in vacuo, and the volatiles were removed at high vacuum. The crude triacetate **34** was then dissolved in 11 mL of acetonitrile with two drops of water and treated with borontrifluoride etherate (0.082 mL, 0.65 mmol) at 0 °C for 1.5 h. The reaction was quenched with saturated sodium bicarbonate (5 mL), extracted with ethyl acetate (3 × 50 mL) and dried with magnesium sulfate. Removal of the volatiles in vacuo gave 144 mg of crude product that was chromatographed on silica gel. Elution with hexane/ethyl acetate (1:1) gave 119 mg (96%) of pseudoglycal **35** as a colorless oil; ^1H NMR ($CDCl_3$, 490 MHz) δ 5.44 (bs, 1 H), 5.25 (q, J = 3 Hz, 1 H), 5.18 (bd, J = 5 Hz, 1 H), 5.17 (ddd, J = 5, 10, 11 Hz, 1 H), 3.96 (t, J = 10 Hz, 1 H), 3.19 (bd, J = 5 Hz, 1 H), 3.11 (m, 1 H), 2.63 (bd, J = 10 Hz, 1 H), 2.31 (bd, J = 15 Hz, 1 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.00 (ddd, J = 3, 11, 15 Hz, 1 H), 1.80 (bs, 3 H). IR ($CHCl_3$) λ_{max} 3600, 3020, 2240, 1740, 1370, 1220, 1020 cm^{-1}; mass spectrum, m/z 267, 249, 189, 171, 161.

(3α,4β,4aβ,5α,6β,8α,8aα)-4-Azido-5-cyanooctahydro-3-methyl-2*H*-1-benzopyran-2,3,6,8-tetrol 6,8-Diacetate (37). To a solution of pseudoglycal **35** (119.4 mg, 0.313 mmol) in 13 mL of CH_2Cl_2 at −40 °C were added triethylamine (0.108 mL, 0.772 mmol), mesyl chloride (0.059 mL, 0.772 mmol), and dimethylaminopyridine (2 mg) and the resulting solution stirred at −40 °C for 2 h. A solution of tetrabutylammonium azide (946 mg, 3.427 mmol) in 5 mL of CH_2Cl_2 was added and the resulting solution allowed to stir at −40 °C for 1.5 h. The reaction was quenched with saturated bicarbonate solution (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried with magnesium sulfate and concentrated to give a crude oil that was chromatographed on silica gel. Elution with hexane/ethyl acetate (4:1) gave 105 mg (81%) of the allylic azides **36a,b** which by NMR analysis existed as a (1:1) mixture of pseudoglycal and glycal forms. This mixture of compounds was directly treated with osmium tetroxide (0.39 M in THF, 0.04 mL, 0.016 mmol) and *N*-methylmorpholine oxide (44 mg, 0.376 mmol) in 17 mL of THF for 19 h at room temperature. The reaction was quenched with sodium dithionite (200 mg), Florisil (500 mg), and 250 μL of water. After 30 min, magnesium sulfate was added and the mixture was filtered through a plug of silica gel to give a crude oil that was chromatographed on silica gel. Elution with hexane/ethyl acetate (1:1) gave 107.5 mg (93%) of the lactol **37** as a colorless oil. Lactol **37** existed as a mixture of anomers (8:1) by TLC and ^1H NMR analysis; ^1H NMR ($CDCl_3$, 500 MHz) (major anomer only) δ 5.30 (q, J = 3 Hz, 1 H), 5.11 (ddd, J = 5, 10, 12 Hz, 1 H), 5.00 (s, 1 H), 4.20 (t, J = 10 Hz, 1 H), 3.99 (d, J = 12 Hz, 1 H), 3.34 (m, 1 H), 3.20 (bs, 1 H), 2.68 (bs, 1 H), 2.32 (bd, J = 14 Hz, 1 H), 2.15 (s, 3 H), 2.10 (s, 3 H), 1.94 (ddd, J = 3, 12, 14 Hz, 1 H), 1.82 (dt, J = 4, 10 Hz, 1 H), 1.37 (s, 3 H); irradiation of the azidomethine proton (δ 3.99 d) caused the resonance at δ 1.82 (dt) to collapse to a dd (J = 4, 10 Hz), establishing this resonance as the ring-junction methine proton. Irradiation of the tertiary methyl (δ 1.37, s) gave approximately a 10% enhancement

in the integrated area of the axial ring-junction methine proton at δ 1.82 by NOE-difference spectrum technqiue. No enhancement in the azide methine proton (δ 3.99) was observed. This established a 1,3 diaxial relationship between the tertiary methyl group and the tertiary junction methine proton; IR ($CHCl_3$) λ_{max} 3550, 3400–3200 (b), 2200 (w), 2110 (s), 1740, 1360, 1220 cm^{-1}; mass spectrum, m/z 368 (m), 280, 266, 159, 104.

[1α,2α(*R),3β,4α,6β]-[2-(1-Azido-2-oxopropan-1-yl)-4,6-diacetoxy-3-(formyloxy)cyclohex-1-ane]carbonitrile (38).** To a solution of lactol **37** (11.8 mg, 0.0321 mmol) in 4 mL of methanol/benzene (1:1) at 0 °C was added lead tetraacetate (29 mg, 0.0655 mmol) and the mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h, and then it was quenched with one drop of ethylene glycol. After stirring for 30 min, the mixture was partitioned between aqueous bicarbonate and ethyl acetate, and then extracted three times with ethyl acetate, washed with saturated bicarbonate, and concentrated in vacuo. Purification by high-pressure liquid chromatography (hexane/ethyl acetate 2:1) gave 8.0 mg (68%) of the keto formate **38**: ^1H NMR (270 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 5.46 (dd, J = 10, 11 Hz, 1 H), 5.26 (q, J = 3 Hz, 1 H), 5.18 (ddd, J = 5, 9, 11 Hz, 1 H), 4.12 (d, J = 6.5 Hz, 1 H), 3.25 (m, 1 H), 2.83 (ddd, J = 4, 6, 11 Hz, 1 H), 2.40 (m, 1 H), 2.36 (s, 3 H), 2.18 (s, 3 H), 2.13 (m, 1 H), 2.06 (s, 3 H); IR ($CHCl_3$) λ_{max} 3000, 2100 (s), 1740, 1370, 1220 cm^{-1}; mass spectrum, m/z 321, 295, 253, 235, 207.

(3α,4β,4aβ,5α,6β,8α,8aα)-4-Azido-5-cyano-2-[(2-mercaptoethanyl)thio]-3-methyloctahydro-2*H*-1-benzopyran-2,3,6,8-tetrol 6,8-Diacetate (40). To a solution of ethanedithiol (20 μL, 0.24 mmol) and magnesium triflate (7.4 mg, 0.023 mmol) in dichloroethylene (0.5 mL) was added a solution of lactol **37** (4.2 mg, 0.0114 mmol) in 1.0 mL of dichloroethylene, and the mixture was heated to reflux. After 2 h the mixture was cooled to room temperature, then quenched with several mL of aqueous bicarbonate, and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were washed with brine and dried with magnesium sulfate. Concentration in vacuo gave a crude product that was chromatographed on silica gel. Elution with hexane/ethyl acetate (3:1) gave the two anomeric hemithioacetals **40** in approximately a 1:1 ratio, 2.6 mg total (51%). Less polar anomer: ^1H NMR ($CDCl_3$, 270 MHz) δ 5.30 (q, J = 3 Hz, 1 H), 5.09 (ddd, J = 5, 9, 11 Hz, 1 H), 4.45 (s, 1 H), 3.75 (d, J = 12 Hz, 1 H), 3.65 (dd, J = 10, 11 Hz, 1 H), 3.33 (m, 1 H), 3.02–2.73 (complex m, 4 H), 2.32 (bd, J = 14 Hz, 1 H), 2.30 (s, 1 H), 2.11 (s, 3 H), 2.10 (s, 3 H), 1.92 (ddd, J = 3, 12, 14 Hz, 1 H), 1.80 (dt, J = 4, 11 Hz, 1 H), 1.37 (s, 3 H), 1.25 (s, 1 H); IR ($CHCl_3$) λ_{max} 3550, 2230 (w), 2110 (s), 1740, 1380, 1220 cm^{-1}. More polar anomer: ^1H NMR ($CDCl_3$, 270 MHz) δ 5.30 q, J = 3 Hz, 1 H), 5.15 (ddd, J = 5, 9, 11 Hz, 1 H), 5.12 (s, 1 H), 4.38 (t, J = 10 Hz, 1 H), 3.76 (d, J = 12 Hz, 1 H), 3.32 (m, 1 H), 3.02–2.80 (complex m, 4 H), 2.41 (s, 1 H), 2.30 (bd, J = 14 Hz, 1 H), 2.16 (s, 3 H), 2.12 (s, 3 H), 2.01 (ddd, J = 3, 12, 14 Hz, 1 H), 1.81 (dt, J = 4, 11 Hz, 1 H), 1.50 (s, 3 H), 1.25 (bs, 1 H); IR ($CHCl_3$) λ_{max} 3550, 2230 (w), 2110 (s), 1740, 1380, 1220 cm^{-1}.

(3α,4β,4aβ,5α,6β,8α,8aα)-4-Azido-5-cyanooctahydro-3-methyl-2*H*-1-benzopyran-2,3,6,8-tetrol 2,3,6,8-Tetraacetate (41a). A solution of lactol **37** (5.8 mg, 0.0158 mmol) in 1 mL of acetic anhydride was treated with one drop of 70% perchloric acid. The resulting mixture was stirred for 11 h. The reaction was then poured into 10 mL of aqueous bicarbonate solution, extracted with CH_2Cl_2 (3 × 50 mL), washed with brine, and dried with magnesium sulfate. Removal of the volatiles gave a crude product that was chromatographed on silica gel. Elution with hexane/ethyl acetate (3:1) gave 4.9 mg (69%) of the tetraacetate **41a** as a colorless oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 6.73 (s, 1 H), 5.32 (q, J = 3 Hz, 1 H), 5.11 (ddd, J = 5, 10, 12 Hz, 1 H), 4.20 (d, J = 12 Hz, 1 H), 3.91 (t, J = 10 Hz, 1 H), 3.36 (m, 1 H), 2.30 (bd, J = 14 Hz, 1 H), 2.20 (s, 3 H), 2.15 (s, 3 H), 2.08 (s, 3 H), 2.04 (s, 3 H), 1.98 (ddd, J = 3, 12, 14 Hz, 1 H), 1.92 (dt, J = 4, 11 Hz, 1 H), 1.71 (s, 3 H); IR ($CHCl_3$) λ_{max} 2110 (s), 1740, 1200 cm^{-1}.

(2α,4aβ,5α,6β,8α,8aα)-8-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4a,5,6,7,8,8a-hexahydro-2-methoxy-5-(3-methoxy-1-propynyl)-3-methyl-2*H*-1-benzopyran-6-ol (44). A solution of n-butyllithium in hexane (4.26 mL, 1.4 M, 5.97 mmol) was added to a solution of methylpropargyl ether (0.504 mL, 5.97 mmol) in 19 mL of THF at −78 °C. After 15 min boron trifluoride etherate (0.753 mL, 5.97 mmol) was added dropwise, and the reaction was allowed to stir at −78 °C for 15 min. A solution of epoxide **30** (486.8 mg, 1.49 mmol) in 6 mL of THF at −78 °C was then added to the reaction flask via cannula which was followed by a wash of 3 mL of cold THF. The reaction was stirred for 3 h at −78 °C and then quenched by addition of 20 mL of saturated $NaHCO_3$ at −78 °C. After warming to room temperature, the mixture was extracted with ethyl acetate (4 × 100 mL), washed with brine, and dried with magnesium sulfate. Concentration gave 646 mg of a crude product that was chromatographed on 32 g of silica gel. Elution with hexane/ethyl acetate (4:1) gave 565 mg (96%) of **44**: ^1H NMR ($CDCl_3$, 270 MHz) δ 5.46 (bs, 1 H), 4.65 (bs, 1 H), 4.19 (m, 1 H), 4.08 (ab system, 2 H), 3.98 (dt, J = 7, 9 Hz, 1 H), 3.70 (t, J = 9 Hz, 1 H), 3.44 (s, 3 H) 3.34 (s, 3 H), 2.80 (bs, 1 H), 2.60 (bd, J = 9 Hz, 1 H), 1.99 (m, 2 H), 1.73 (bs, 3 H), 1.62 (bs, 1 H), 0.92 (s, 9 H), 0.14 (s, 6 H); IR ($CHCl_3$) λ_{max} 3600, 3400 (b), 1100, 860, 820 cm^{-1}; mass spectrum, m/z 339 (M − butyl), 275, 149; exact mass calcd for $C_{21}H_{40}O_5SiN$ (M + NH_4) 414.26756, found: 414.26734.

(2α,4aβ,5α,6β,8α,8aα)-8-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4a,5,6,7,8,8a-hexahydro-2-methoxy-5-(3-methoxy-1-propynyl)-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran (45). To a suspension of NaH (283 mg, 60% dispersion in oil) and tetra-N-butylammonium iodide (10 mg, 0.027 mmol) in 15 mL of THF under an argon atmosphere at 0 °C was added via cannula a solution of alcohol **44** (560.7 mg, 1.416 mmol) in 10 mL of THF which was followed by a 5 mL of THF wash. Benzyl bromide (0.842 mL, 7.08 mmol) was added, and the solution was stirred at room temperature for 21 h. The reaction was quenched at 0 °C with 20 mL of saturated NH_4Cl. Extraction with CH_2Cl_2 (3 × 100 mL) gave a combined organic layer which was dried with magnesium sulfate and concentrated in vacuo. Chromatography on 50 g SiO_2 (eluant: hexane/ethyl acetate 15:1) gave 644 mg (94%) of benzyl ether **45**; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.42–7.27 (m, 5 H), 5.45 (bs, 1 H), 4.64 (bs, 1 H), 4.53 (ab quartet, 2 H), 4.07 (ab quartet, 2 H), 3.98 (ddd, J = 5, 9, 11 Hz, 1 H), 3.80 (q, J = 3 Hz, 1 H), 3.71 (t, J = 9 Hz, 1 H), 3.44 (s, 3 H), 3.33 (s, 3 H), 2.97 (m, 1 H, irradiation causes signal at δ 2.58 (allylic methine proton) to lose a small coupling and the signal at δ 2.12 (equatorial methylene proton) to lose a small "W" coupling), 2.58 (bd, J = 9 Hz, 1 H, irradiation causes the triplet at δ 3.71 (homoallylic methine proton bearing oxygen) to collapse to a doublet and the multiplet at δ 2.97 (acetylenic methine proton) to simplify to a broad singlet), 2.12 (bd, J = 14 Hz, 1 H), 1.91 (ddd, J = 3, 11, 14 Hz, 1 H), 1.70 (bs, 3 H), 0.92 (s, 9 H), 0.12 (s, 6 H); IR ($CHCl_3$) λ_{max} 2940, 1090, 850, 830 cm^{-1}; mass spectrum m/z 429 (M − butyl), 397, 307, 91; exact mass calcd for $C_{28}H_{46}O_5SiN$ (M + NH_4) 504.31450, found 504.31434.

(4aβ,5α,6β,8α,8aα)-4a,5,6,7,8,8a-Hexahydro-5-(3-methoxy-1-propynyl)-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran-2,8-diol (46). To a solution of silyl ether **45** (373 mg, 0.768 mmol) in 20 mL of dioxane at room temperature was added 0.5N HCl (20 mL) and the mixture stirred for 10 h. The reaction was quenched with 20 mL of saturated sodium bicarbonate, extracted with ethyl acetate (4 × 150 mL), and dried with magnesium sulfate, and the volatiles were removed in vacuo. Chromatography on 20 g of silica gel gave, after elution with hexane/ethyl acetate (1:2), 239.4 mg (87%) of diol **46** as a colorless oil; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.40–7.27 (m, 5 H), 5.49 (bs, 1 H), 5.18 (bd, J = 5 Hz, 1 H), 4.52 (ab system, J = 12 Hz, 2 H), 4.06 (ab system, 2 H), 4.02 (m, 1 H), 3.86 (m, 1 H), 3.82 (t, J = 10 Hz, 1 H), 3.34 (s, 3 H), 3.22 (m, 1 H), 3.01 (m, 1 H), 2.60 (bd, J = 10 Hz, 1 H), 2.30 (bd, J = 13 Hz, 1 H), 2.92 (m, 2 H), 1.77 (bs, 3 H); IR ($CHCl_3$) λ_{max} 3600, 3400 (b), 3000, 1460, 1080, 1020 cm^{-1}; mass spectrum, m/z 359 (M + 1), 358 (M), 313, 249, 91.

(4aβ,5α,6β,8α,8aα)-4a,5,6,7,8,8a-Hexahydro-5-(3-methoxy-1-propynyl)-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran-2,8-diol 8-Acetate (47). To a solution of diol **46** (153 mg, 0.42 mmol) in 5 mL of CH_2Cl_2 was added 5 drops of pyridine and 3 drops of acetic anhydride, and the resulting solution was stirred for 31 h. The reaction was quenched with 5 mL of saturated sodium bicarbonate, extracted with CH_2Cl_2 (3 × 50 mL), dried with magnesium sulfate, and concentrated in vacuo. The resulting diacetate was dissolved in 5 mL of dioxane and treated with 5 mL of 0.5 N HCl. After 1.5 h, the reaction was quenched with 10 mL of saturated sodium bicarbonate, extracted with CH_2Cl_2 (4 × 50 mL), and dried with magnesium sulfate. The volatiles

were removed to afford a crude product that was chromatographed on silica gel. Elution with hexane/ethyl acetate (1:1) gave 137.4 mg (80%) of the pseudoglycal **47**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.35–7.27 (m, 5 H), 5.50 (bs, 1 H), 5.20 (ddd, J = 5, 10, 11 Hz, 1 H), 5.18 (bs, 1 H), 4.63 (d, J = 12 Hz, 1 H), 4.50 (d, J = 12 Hz, 1 H), 4.08 (ab system, 2 H), 4.01 (t, J = 10 Hz, 1 H), 3.84 (q, J = 4 Hz, 1 H), 3.36 (s, 3 H), 3.02 (m, 1 H), 2.73 (bd, J = 9 Hz, 1 H), 2.39 (bd, J = 14 Hz, 1 H), 2.11 (s, 3 H), 1.92 (ddd, J = 2.5, 8, 14 Hz, 1 H), 1.77 (bs, 3 H), 1.60 (bs, 1 H); IR ($CHCl_3$) λ_{max} 3600, 3450 (b), 2900, 2240 (w), 1730, 1480, 1100 cm^{-1}; mass spectrum, m/z 400 (M), 385, 340, 322, 291, 216, 91.

(3α,4β,4aβ,5α,6β,8α,8aα)-4-Azidooctahydro-5-(3-methoxy-1-propynyl)-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran-2,3,8-triol 8-Acetate (48). To a solution of pseudoglycal **47** (137 mg, 0.3425 mmol) in 11 mL of dry CH_2Cl_2 at −40 °C were added triethylamine (95.5 μL, 0.685 mmol), mesyl chloride (53.0 μL, 0.685 mmol), and 4-(dimethylamino)pyridine (4 mg), the reaction was stirred for 2 h at −40 °C, and then tetra-*N*-butylammonium azide (389 mg, 1.37 mmol) in 2 mL of CH_2Cl_2 was added and the reaction stirred at −40 °C for 1 h. The reaction was quenched with 5 mL of saturated sodium bicarbonate solution, extracted with hexane/ethyl acetate (1:1) (3 × 50 mL), dried with magnesium sulfate, and concentrated in vacuo. The resulting oil was dissolved in 5 mL of THF and treated with *N*-methylmorpholine *N*-oxide (82 mg, 0.70 mmol) and osmium tetroxide (in THF, 0.39M, 40 μL, 0.016 mmol) for 23 h. The reaction was quenched with 5 mL of H_2O and excess sodium dithionite, stirred for 30 min, extracted with ethyl acetate (3 × 50 mL), dried with magnesium sulfate, and concentrated in vacuo. Chromatography on silica gel gave, after elution with hexane/ethyl acetate (1:1), 107 mg (68% for two steps) of the diol **48** as a 3:1 mixture of anomers: ^{1}H NMR ($CDCl_3$, 490 MHz) (major anomer only) δ 7.38–7.27 (m, 5 H), 5.12 (ddd, J = 5, 10, 12 Hz, 1 H), 4.92 (bd, J = 3 Hz, 1 H), 4.54 (ab system, J = 12 Hz, 2 H), 4.18 (t, J = 10 Hz, 1 H), 4.12 (ab system, 2 H), 4.00 (d, J = 12 Hz, 1 H), 3.92 (bd, J = 3 Hz, 1 H), 3.81 (q, J = 3 Hz, 1 H), 3.39 (s, 3 H), 3.22 (bs, 1 H), 2.81 (s, 1 H), 2.29 (bd, J = 13 Hz, 1 H), 2.06 (s, 3 H), 1.92 (dt, J = 4, 11 Hz, 1 H), 1.85 (m, 1 H), 1.30 (s, 3 H); IR ($CHCl_3$) λ_{max} 3540, 3500–3300 (b), 2930, 2110 (s), 1730, 1230, 1100, 1060 cm^{-1}; mass spectrum, m/z 441 (M − H_2O), 399, 279, 235, 205, 91.

[1α,2α(*R),3β,4α,6β]-1-[2-(1-Azido-2-oxopropan-1-yl)-4-acetoxy-3-(formyloxy)-6-(phenylmethoxy)cyclohex-1-yl]-3-methoxy-1-propyne (49).** To a solution of diol **48** (16.2 mg, 0.0353 mmol) in 2 mL of water/methanol (1:1) was added sodium metaperiodate (11.3 mg, 0.0528 mmol) and the mixture was stirred at room temperature for 20 h. The reaction mixture was partitioned between aqueous sodium bicarbonate and CH_2Cl_2, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried with magnesium sulfate and the volatiles were removed in vacuo to give a crude oil that was chromatographed on silica gel. Elution with hexane/ethyl acetate (2:1) gave 6.9 mg (43%) of the keto formate **49**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.89 (s, 1 H), 7.40–7.27 (m, 5 H), 5.35 (t, J = 10 Hz, 1 H), 5.16 (ddd, J = 5, 10, 12 Hz, 1 H), 4.59 (ab system, 2 H), 4.15 (ab system, 2 H), 4.06 (d, J = 9.5 Hz, 1 H), 3.88 (q, J = 3 Hz, 1 H), 3.40 (s, 3 H), 3.34 (m, 1 H), 2.68 (ddd, J = 4, 9, 11 Hz, 1 H), 2.30 (bd, J = 13 Hz, 1 H), 2.26 (s, 3 H), 2.03 (m, 1 H), 2.01 (s, 3 H); IR ($CHCl_3$) λ_{max} 3020, 2930, 2100 (s), 1740, 1360, 1220, 1160, 1100 cm^{-1}; mass spectrum, m/z 414, 340, 298, 91.

[3α,4β,4aβ,5α(*E*),6β,8α,8aα]-4-Acetamidooctahydro-5-(3-methoxy-1-propenyl)-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran-2,3,8-triol 2,8-Diacetate (50). A solution of lactol **48** (28 mg, 0.061 mmol) in 4 mL of dry THF was added to a solution of $LiAlH_4$ (21.4 mg, 0.565 mmol) in 1 mL of dry THF at room temperature and the resulting solution was heated to reflux for 12 h. The reaction was quenched with acetic anhydride (2 mL) and CH_2Cl_2 (3 mL) was added with pyridine (1 mL). The resulting solution was stirred for 6 h at room temperature. The excess acetic anhydride was quenched with 20 mL of aqueous bicarbonate. After 30 min the mixture was extracted with ethyl acetate (3 × 50 mL), dried with magnesium sulfate, and concentrated in vacuo. Chromatography of the mixture on silica gel (ethyl acetate/methanol, 10%) gave 18.4 mg of a crude oil that was a mixture of compounds by ^{1}H NMR analysis. Purification by high-pressure liquid chromatography (ethyl acetate/methanol, 5%) gave acetamide **50**, (5.0 mg, 16%): ^{1}H NMR ($CDCl_3$, 490 MHz) δ 7.40–7.30 (m, 5 H), 5.81 (s, 1 H), 5.56 (dd, J = 9, 16 Hz, 1 H), 5.50 (dt, J = 16, 5 Hz, 1 H), 5.14 (ddd, J = 5, 10, 12 Hz, 1 H), 4.92 (bd, J = 9 Hz, 1 H), 4.82 (d, J = 12 Hz, 1 H), 4.32 (d, J = 12 Hz, 1 H), 4.18 (dd, J = 9, 12 Hz, 1 H), 3.89 (dd, J = 5, 13 Hz, 1 H), 3.87 (dd, J = 5, 13 Hz, 1 H), 3.85 (t, J = 10 Hz, 1 H), 3.68 (q, J = 3 Hz, 1 H), 3.32 (s, 3 H), 2.55 (bd, J = 9 Hz, 1 H), 2.38 (bd, J = 14 Hz, 1 H), 2.16 (s, 3 H), 2.04 (s, 3 H), 2.02 (dt, J = 5, 12 Hz, 1 H), 1.94 (s, 3 H), 1.60 (ddd, J = 3, 12, 14 Hz, 1 H) 1.60 (bs, 1 H), 1.15 (s, 3 H); IR ($CHCl_3$) λ_{max} 3440, 3000, 1740, 1665, 1220 cm^{-1}; mass spectrum, m/z 460, 459, 428, 368, 186, 91.

[2α,4aβ,5α(*Z*),6β,8α,8aα]-(1,1-Dimethylethyl)-[[4a,5,6,7,8,8a-hexahydro-2-methoxy-5-(3-methoxy-1-propenyl)-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran-8-yl]oxy]dimethylsilane (53). Hydrogen gas was bubbled through a solution of acetylene **45** (880 mg, 1.81 mmol) in 50 mL of CH_2Cl_2/MeOH (9:1) containing 585 mg of Lindlar's catalyst and 75 μL of quinoline. After 1 h, 500 mg of catalyst was added, the hydrogenation was continued for 30 min, and then 500 mg of catalyst was added and the reduction continued for 4.5 h. The reaction was then filtered through celite, which was washed with CH_2Cl_2, and the filtrate was concentrated. Chromatography on 45 g of SiO_2 (eluant: hexane/ethyl acetate 9:1) gave 794 mg (90%) of the olefin **53**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.40–7.27 (m, 5 H), 5.68–5.48 (m, 2 H), 5.29 (bs, 1 H), 4.63 (s, 1 H), 4.58 (ab system, 2 H), 4.01 (ddd, J = 5, 9, 11 Hz, 1 H), 3.91 (ab system, 2 H), 3.64 (t, J = 9 Hz, 1 H), 3.48 (q, J = 3 Hz, 1 H), 3.45 (s, 3 H), 3.29 (s, 3 H), 2.93 (m, 1 H), 2.66 (m, 1 H), 2.13 (bd, J = 14 Hz, 1 H), 1.69 (bs, 3 H), 1.60 (ddd, J = 3, 11, 14 Hz, 1 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H); IR ($CHCl_3$) λ_{max} 2950, 1245, 1080, 1040 cm^{-1}; mass spectrum, m/z 488 (M), 431 (M − butyl), 91; exact mass calcd for $C_{28}H_{48}O_5SiN$ (M + NH_4) 506.33015; found 506.33001.

[4aβ,5α(*Z*),6β,8α,8aα]-4a,5,6,7,8,8a-Hexahydro-5-(3-methoxy-1-propenyl)-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran-2,8-diol 8-Acetate (54). To a solution of the acetal **53** (789 mg, 1.62 mmol) in 80 mL of dioxane at room temperature was added 80 mL of 0.5 N HCl, and the reaction was stirred for 10 h at room temperature. The reaction was quenched with 100 mL of saturated $NaHCO_3$. Extraction with ethyl acetate (5 × 200 mL) gave a combined extract that was dried with magnesium sulfate and concentrated in vacuo to give a crude diol which was dissolved in 20 mL of CH_2Cl_2 and treated with Ac_2O (0.763 mL), pyridine (0.651 mL), and 5 mg of dimethylaminopyridine for 12 h at room temperature. The reaction was quenched with 20 mL of saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 150 mL), dried with $MgSO_4$, and concentrated in vacuo to give a crude diacetate, which was dissolved in 50 mL of dioxane and treated with 50 mL of 0.25N HCl at room temperature for 1 h. The reaction was quenched with 25 mL of saturated $NaHCO_3$, and extracted with ethyl acetate (3 × 150 mL) to give a combined organic layer, which was dried with $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed on 30 g of SiO_2 (eluant: hexane/ethyl acetate 1:1) to give 567 mg (87% for 3 steps) of the lactol **54**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.40–7.27 (m, 5 H), 5.65 (m, 1 H), 5.50 (t, J = 11 Hz, 1 H), 5.35 (bs, 1 H), 5.23 (ddd, J = 5, 10, 11 Hz, 1 H), 5.18 (bd, J = 5 Hz, 1 H), 4.59 (ab system, J = 12 Hz, 2 H) 3.90 (m, 3 H), 3.52 (q, J = 3 Hz, 1 H), 3.30 (s, 3 H), 3.00 (m, 1 H), 2.79 (m, 1 H), 2.76 (d, J = 5 Hz, 1 H), 2.38 (bd, J = 14 Hz, 1 H), 2.10 (s, 3 H), 1.72 (bs, 3 H), 1.59 (ddd, J = 3, 11, 14 Hz, 1 H); IR ($CHCl_3$) λ_{max} 3600, 2925, 1730, 1680, 1640 cm^{-1}; mass spectrum, m/z 402 (M), 368, 201, 91; exact mass calcd for $C_{23}H_{34}NO_6$ (M + NH_4) 420.23859, found 420.23854.

[3α,4β,4aβ,5α(*Z*),6β,8α,8aα]-4-Azidooctahydro-5-(3-methoxy-1-propenyl)-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran-2,3,8-triol 8-Acetate (56). To a solution of pseudoglycal **54** (565 mg, 1.41 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.16 mM) in 50 mL of dry CH_2Cl_2 at −40 °C were added methanesulfonyl chloride (0.162 mL, 2.10 mmol) and triethylamine (0.312 mL, 2.24 mmol), and the resulting solution was stirred at −40 °C. After 2 h, tetra-*N*-butylammonium azide (1.2 g, 4.23 mmol) in 10 mL of CH_2Cl_2 was added dropwise. After 35 min the reaction was quenched at −40 °C with 50 mL of saturated $NaHCO_3$. Extraction with hexane/ethyl acetate (1:1) (3 × 175 mL) gave an organic layer that was dried with magnesium sulfate, and concentrated in vacuo to yield an oil containing the crude allylic azides. This was dissolved in 30 mL of THF and treated with OsO_4 (0.06 mL, 0.39 M in THF, 0.0234 mmol) and *N*-

methylmorpholine *N*-oxide (0.180 g, 1.54 mmol) for 20 h at room temperature. The reaction was quenched with 400 mg of sodium dithionite and 20 mL of water. After 30 min, the mixture was extracted with ethyl acetate (3 × 150 mL) and dried with magnesium sulfate. Concentration in vacuo gave 648 mg of a crude product that was chromatographed on 32 g of silica gel. Elution with hexane/ethyl acetate (3:5) gave 461 mg (71% for 2 steps) of diols **56** as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.40–7.26 (m, 5 H), 5.80 (dt, J = 11, 6 Hz, 1 H), 5.56 (t, J = 11 Hz, 1 H), 5.18 (ddd, J = 5, 10, 11 Hz, 1 H), 4.91 (bd, J = 3 Hz, 1 H), 4.58 (ab system, J = 12 Hz, 2 H), 4.15 (t, J = 11 Hz, 1 H), 3.99 (bd, J = 6 Hz, 2 H), 3.88 (bd, J = 3 Hz, 1 H), 3.68 (d, J = 12 Hz, 1 H), 3.49 (bq, J = 3 Hz, 1 H), 3.32 (s, 3 H), 3.16 (bd, J = 11 Hz, 1 H), 2.72 (bs, 1 H), 2.31 (m, 1 H), 2.06 (s, 3 H), 1.98 (dt, J = 4, 12 Hz, 1 H), 1.57 (bq, J = 12 Hz, 1 H), 1.33 (s, 3 H); IR ($CHCl_3$) λ_{max} 3600, 2920, 2110, 1735, 1240 cm^{-1}; mass spectrum, m/z 434 (M + 1 − N_2), 402, 326, 294; exact mass calcd for $C_{23}H_{32}O_7N$ (M + 1 − N_2) 434.21786, found 434.21646.

(3α,4β,4aβ,5α,6β,8α,8aα)-8-(Acetyloxy)-4-azidooctahydro-2,3-dihydroxy-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran-5-carboxaldehyde (57). A solution of olefin **56** (14.0 mg, 0.0304 mmol) in 2 mL of CH_2Cl_2/methanol (5:1) at −78 °C was treated with ozone until a blue color persisted, and then the excess ozone was immediately discharged with nitrogen gas at −78 °C. The solution was treated with several drops of dimethyl sulfide, warmed to room temperature, and stirred at room temperature for 2 h. The volatiles were removed in vacuo to give an oil that was chromatographed on silica gel. Elution with hexane/ethyl acetate (1:1) gave 12.8 mg (99%) of the aldehyde **57**; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.75 (s, 1 H), 7.37–7.33 (m, 5 H), 5.12 (ddd, J = 5, 10, 12 Hz, 1 H), 4.94 (bs, 1 H), 4.60 (ab system, 2 H), 4.33 (d, J = 12 Hz, 1 H), 4.22 (dd, J = 10, 11 Hz, 1 H), 4.11 (q, J = 2.5 Hz, 1 H), 3.48 (bs, 1 H), 3.22 (m, 1 H), 2.68 (bs, 1 H), 2.40 (bd, J = 14 Hz, 1 H), 2.05 (s, 3 H), 2.00 (dt, J = 5, 12 Hz, 1 H), 1.35 (ddd, J = 2.5, 12, 14 Hz, 1 H), 1.32 (s, 3 H); IR ($CHCl_3$) λ_{max} 3550, 3500–3300 (b), 2940, 2110 (s), 1730 (b), 1260 cm^{-1}; mass spectrum, m/z 401 (M − H_2O), 368, 330, 135, 91.

(3α,4β,4aβ,5α,6β,8α,8aα)-8-(Acetyloxy)-4-azidooctahydro-2,3-dihydroxy-5-[2-(1,3-dioxolo)]-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran (58). To a solution of aldehyde **57** (11.8 mg, 0.0282 mmol) in 1.5 mL of dry benzene at room temperature were added ethylene glycol (0.024 mL, 0.43 mmol) and pyridinium *p*-toluenesulfonate (2 mg), and the reaction was refluxed for 4 h. The reaction was quenched at room temperature with aqueous bicarbonate, extracted 3 times with ethyl acetate, and dried with magnesium sulfate. Evaporation of the volatiles gave an oil that was chromatographed on silica gel. Elution with ethyl acetate gave 11.4 mg (87%) of the ethylene ketal **58**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.36–7.27 (m, 5 H), 5.13 (ddd, J = 5, 10, 12 Hz, 1 H), 4.95 (d, J = 8 Hz, 1 H), 4.95 (s, 1 H), 4.53 (ab system, 2 H), 4.30 (dd, J = 10, 12 H, 1 H), 4.12 (d, J = 12 Hz, 1 H), 4.15–3.78 (complex multiplet, 5 H), 2.99 (bs, 1 H), 2.50 (m, 2 H), 2.35 (bd, J = 14 Hz, 1 H), 2.07 (s, 3 H), 2.06 (dt, J = 5, 12 Hz, 1 H, obscured by acetate), 2.62 (ddd, J = 2.5, 12, 14 Hz, 1 H), 1.30 (s, 3 H); IR ($CHCl_3$) λ_{max} 3550, 3500–3300 (b), 2880, 2110, 1735, 1220 cm^{-1}; mass spectrum, m/z 445 (M − N_2), 421, 390, 346, 145, 91.

[1α,2α(*R),3β,4α,6β]-2-[2-(1-Azido-2-oxopropan-1-yl)-4-acetoxy-3-(formyloxy)-6-(phenylmethoxy)cyclohex-1-yl]-1,3-dioxolane (59).** To a solution of lactol **58** (10.5 mg, 0.0227 mmol) in 2 mL of methanol/water (1:1) was added sodium metaperiodate (9.7 mg, 0.0454 mmol), and the reaction stirred at room temperature for 6 h. The reaction was partitioned between 10 mL of saturated bicarbonate and 15 mL of ethyl acetate, the layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was dried with magnesium sulfate and concentrated in vacuo. Chromatography on silica gel (hexane/ethyl acetate 1:1) gave 8.8 mg (84%) of the keto formate **59** as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.95 (s, 1 H), 7.36–7.28 (m, 5 H), 5.52 (dd, J = 9.5, 11.5 Hz, 1 H), 5.18 (ddd, J = 5, 9.5, 11 Hz, 1 H), 4.99 (d, J = 4 Hz, 1 H), 4.52 (ab system, J = 12 Hz, 2 H), 4.24 (d, J = 8.5 Hz, 1 H), 4.02–3.80 (complex multiplet, 5 H), 2.88 (ddd, J = 5, 8.5, 11.5 Hz, 1 H), 2.55 (bm, 1 H), 2.32 (bd, J = 14 Hz, 1 H), 2.22 (s, 3 H), 2.00 (s, 3 H), 1.86 (ddd, J = 3, 11, 14 Hz, 1 H); IR ($CHCl_3$) λ_{max} 2900, 2110 (s), 1740 (b), 1220 cm^{-1}; mass spectrum, m/z 433 (M − N_2), 390, 344, 284, 176, 91.

Methyl (3α,4β,4aβ,5α,6β,8α,8aα)-8-(Acetyloxy)-4-azidooctahydro-2,3-dihydroxy-3-methyl-6-(phenylmethoxy)-2*H*-1-benzopyran-5-carboxylate (66). To a solution of diols **56** (112 mg, 0.243 mmol) in 5 mL of dry CH_2Cl_2 were added dihydropyran (300 μL, 3.29 mmol) and pyridinium *p*-toluenesulfonate (2 mg), and the reaction was stirred for 5.5 h. The reaction was quenched with 10 mL of saturated $NaHCO_3$, and the aqueous phase extracted with ethyl acetate (3 × 40 mL). The organic phase was dried with magnesium sulfate, and the volatiles were removed in vacuo. Filtration through a pad of silica gel (hexane/ethyl acetate 1:1) gave the THP acetal of the anomeric alcohol **61** which was dissolved in 10 mL of CH_2Cl_2/MeOH (5:1) with $NaHCO_3$ buffer and treated with ozone at −78 °C for 2 min. Excess ozone was removed by bubbling N_2 gas through the reaction, then 1 mL of dimethyl sulfide was added, and the reaction was warmed to room temperature. After stirring for 4 h, the volatiles were removed, and the crude oil was passed through a pad of silica gel (hexane/ethyl acetate 1:1). The resulting aldehyde **62** was dissolved in 2 mL of (1:1) CCl_4/CH_3CN and added to a mixture containing $NaIO_4$ (78 mg, 0.365 mmol) and 3 mg RuO_2 in 1.5 mL of H_2O and 1 mL of CCl_4 at 0 °C. Additional $RuO_2/NaIO_4$ mixture (RuO_4) was added dropwise to the rapidly stirred reaction to maintain a yellow color to the solution. After 5.5 h, ethereal CH_2N_2 (0.67M, 10 mL, 6.7 mmol) was added and the reaction stirred at 0 °C for 30 min. Extraction with ethyl acetate and drying with magnesium sulfate gave a dark oil that was passed through a pad of silica gel (hexane/ethyl acetate 1:1) to give a colorless oil containing the ester **65**. This was dissolved in 5 mL of dioxane and treated with 5 mL of 0.25N HCl for 12 h. The hydrolysis was quenched with 5 mL of saturated $NaHCO_3$, extracted with ethyl acetate (4 × 50 mL), dried with magnesium sulfate, and concentrated in vacuo. Chromatography on 6 g of silica gel gave 70.6 mg (65% for 5 steps) of the methyl ester **66** which contained a small amount of the benzoate resulting from oxidation of the benzyl ether: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.42–7.27 (m, 5 H), 5.13 (ddd, J = 5, 10, 12 Hz, 1 H), 4.95 (bd, J = 3 Hz, 1 H), 4.58 (ab quartet, J = 12 Hz, 2 H), 4.45 (dd, J = 10, 11 Hz, 1 H), 4.09 (d, J = 12 Hz, 1 H), 3.98 (q, J = 3 Hz, 1 H), 3.75 (s, 3 H), 3.37 (d, J = 3 Hz, 1 H), 3.25 (m, 1 H), 2.62 (s, 1 H), 2.34 (m, 1 H), 2.08 (s, 3 H), 2.02 (dt, J = 4, 12 Hz, 1 H), 1.68 (bq, J = 12 Hz, 1 H), 1.31 and 1.28 (s, 3 H); IR ($CHCl_3$) λ_{max} 3600, 3400 (b), 3000, 2010 (s), 1735, 1360 cm^{-1}; mass spectrum, m/z 432 (M + 1 − H_2O), 403, 376, 332, 91; exact mass calcd for $C_{21}H_{26}NO_7$ (M + 1 − H_2O) 432.17706, found 432.17699.

Methyl [1α,2α(1*R),3β,4α,6β]-2-(1-Azido-2-hydroxypropyl)-3,4-dihydroxy-6-(phenylmethoxy)cyclohexanecarboxylate (67).** To a solution of diol **66** (33.5 mg, 0.0746 mmol) in 4 mL of 50% MeOH/H_2O at room temperature was added $NaIO_4$ (23.7 mg, 0.111 mmol) and the reaction stirred at room temperature for 38 h. The resulting mixture was then treated with $NaBH_4$ (17 mg in 1 mL MeOH) at room temperature. After 4 h, the reduction was quenched with 3 mL of saturated NH_4Cl, extracted with ethyl acetate (4 × 30 mL), dried with magnesium sulfate, and concentrated in vacuo. Chromatography on 5 g of silica gel, with hexane/ethyl acetate (1:2) as the eluant gave 17.1 mg (61%) of the triols **67** which cochromatographed and were not separable at this stage. The ratio of the isomers was 1.25 to 1 by ^{1}H NMR analysis; IR ($CHCl_3$) λ_{max} 3600 (s), 3500–3300 (b), 2110 (s), 1730 cm^{-1}; mass spectrum, m/z 327, 198, 162, 91.

(4α,4aβ,5β,6α,8β)-4-Azidooctahydro-5,6-dihydroxy-3-methyl-8-(phenylmethoxy)-1*H*-2-benzopyran-1-one (68). A solution of the triols **67** (17.0 mg, 0.0449 mmol) and *p*-TsOH·H_2O (2 mg) in 5 mL of dry benzene was heated to reflux for 1 h. The reaction was quenched with 2 mg of solid $NaHCO_3$ at room temperature. Concentration in vacuo and chromatography on silica gel gave 14.4 mg (93%) of the lactones **68** which were not separable by high-pressure liquid chromatography. From the ^{1}H NMR spectrum it was apparent that the lactone had undergone epimerization, by the presence of two sets of methyl doublets; IR ($CHCl_3$) λ_{max} 3600–3350, 2110 (s), 1745, 1080 cm^{-1}; mass spectrum, m/z 347 (M), 91; exact mass calcd for $C_{17}H_{21}N_3O_5$ 347.14811, found 347.14819.

[2α(1*R),3β,4α,6β]-2-[1-Azido-2-hydroxypropyl]-6-(benzyloxy)-3,4-(cyclohexylidenedioxy)cyclohexanecarboxylic Acid, δ-Lactone (69, 70).** To a solution of lactones **68** (33.0 mg, 0.095 mmol) in 3 mL of dry benzene was added cyclohexanone

(100 μL), trimethyl orthoformate (50 μL), and several crystals of *p*-TsOH. The resulting solution was stirred for 12 h at room temperature. The reaction was quenched with aqueous bicarbonate, extracted with CH_2Cl_2 (3 × 20 mL), dried with magnesium sulfate, and concentrated in vacuo. The resulting oil was chromatographed on silica gel (hexane/ethyl acetate 3:1) to afford 12.2 mg of the less polar isomer **69** and 12.8 mg of the more polar isomer **70** for a total yield of 62%. Elution with ethyl acetate gave 7.4 mg (22%) of recovered **68** which was then recycled to provide an additional 1.9 mg of **69** and 3.5 mg of **70**. Isomer **70**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5 H), 4.65 (d, *J* = 12 Hz, 1 H), 4.43 (dq, *J* = 2, 6.5 Hz, 1 H), 4.40 (d, *J* = 12 Hz, 1 H), 4.38 (bs, 1 H), 4.16 (dd, *J* = 2, 9 Hz, 1 H), 3.82 (ddd, *J* = 3.5, 9, 12.5 Hz, 1 H), 3.40 (dd, *J* = 9, 12 Hz, 1 H), 3.11 (ddd, *J* = 8, 9, 12 Hz, 1 H), 3.00 (bd, *J* = 8 Hz, 1 H), 2.52 (dt, *J* = 13, 3 Hz, 1 H), 1.80 (dt, *J* = 2.5, 13 Hz, 1 H), 1.70–1.55 (m, 10 H), 1.49 (d, *J* = 6.5 Hz, 3 H); IR ($CHCl_3$) λ_{max} 2940, 2110, 1740 cm^{-1}; mass spectrum, *m/z* 427 (M), 276, 91; exact mass calcd for $C_{23}H_{29}N_3O_5$ 427.21071; found 427.21034. Isomer **69**: ^{1}H NMR ($CDCl_3$, 490 MHz) δ 7.40–7.28 (m, 5 H), 4.63 (d, *J* = 12 Hz, 1 H), 4.56 (q, *J* = 3 Hz, 1 H), 4.49 (d, *J* = 12 Hz, 1 H), 4.43 (dq, *J* = 11, 6 Hz, 1 H), 3.87 (ddd, *J* = 4, 9, 12 Hz, 1 H), 3.54 (dd, *J* = 3.5, 11 Hz, 1 H), 3.30 (dd, *J* = 9, 11.5 Hz, 1 H), 2.99 (bs, 1 H), 2.81 (dt, *J* = 11.5, 3.5 Hz, 1 H), 2.49 (bd, *J* = 13.5 Hz, 1 H), 1.75–1.55 (m, 11 H), 1.46 (d, *J* = 6 Hz, 3 H); IR ($CHCl_3$) λ_{max} 2930, 2090, 1735 cm^{-1}; mass spectrum, *m/z* 427 (m), 384, 222, 91; exact mass calcd for $C_{23}H_{29}N_3O_5$ 427.21071, found 427.21053.

[1β,2α(1*R,2*R**),3β,4α,6β]-2-[1-Acetamido-2-hydroxypropyl]-6-(benzyloxy)-3,4-(cyclohexylidenedioxy)cyclohexanecarboxylic Acid, δ-Lactone (71).** To a solution of azide **70** (6.9 mg, 16.1 μmol) in 6 mL of ethyl acetate were added 14.5 mg of Lindlar's catalyst and 10 drops of acetic anhydride. The resulting mixture was stirred under an atmosphere of nitrogen for 7.5 h, then filtered through celite (EtOAc). Removal of the volatiles in vacuo gave an oil that was chromatographed on silica gel. Elution with ethyl acetate gave 5.8 mg (81%) of the acetamide **71** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H), 6.34 (d, *J* = 8 Hz, 1 H), 4.68 (m, 2 H), 4.62 (d, *J* = 12 Hz, 1 H), 4.46 (d, *J* = 12 Hz, 1 H), 4.41 (q, *J* = 2.5 Hz, 1 H), 3.78 (ddd, *J* = 4, 9, 12 Hz, 1 H), 3.22 (dd, *J* = 9, 12 Hz, 1 H), 3.08 (bd, *J* = 5 Hz, 1 H), 2.91 (ddd, *J* = 6, 8, 12 Hz, 1 H), 2.48 (dt, *J* = 13, 2.5 Hz, 1 H), 2.02 (s, 3 H), 1.82 (dt, *J* = 3, 13 Hz, 1 H), 1.70–1.55 (m, 10 H), 1.35 (d, *J* = 6.5 Hz, 3 H); IR ($CHCl_3$) λ_{max} 3400, 2950, 1730, 1675, 1510 cm^{-1}; mass spectrum, *m/z* 443 (M), 400 (M – Ac), 292; exact mass calcd for $C_{25}H_{33}NO_6$ 443.23077, found 443.23045.

[1β,2α(1*R,2*R**),3β,4α,6β]-2-[1-Acetamido-2-hydroxypropyl]-3,4-(cyclohexylidenedioxy)-6-hydroxycyclohexanecarboxylic Acid, δ-Lactone (72).** To a solution of the benzyl ether **71** (8.8 mg, 19.8 μmol) in 3 mL of EtOH was added $Pd(OH)_2$ (14 mg). The resulting mixture was stirred under an atmosphere of H_2 gas for 3 h. The mixture was filtered through celite (EtOH), and the volatiles were removed in vacuo to afford 6.9 mg (98%) of the alcohol **72**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.33 (d, *J* = 8 Hz, 1 H), 4.79 (q, *J* = 2.5 Hz, 1 H), 4.70 (m, 2 H), 3.82 (ddd, *J* = 5, 9, 13 Hz, 1 H), 3.20 (dd, *J* = 9, 12 Hz, 1 H), 3.01 (bd, *J* = 6 Hz, 1 H), 2.95 (dt, *J* = 8, 6 Hz, 1 H), 2.25 (dt, *J* = 13, 3.5 Hz, 1 H), 2.02 (s, 3 H), 1.98 (dt, *J* = 3, 13 Hz, 1 H), 1.80–1.50 (m, 11 Hz), 1.36 (d, *J* = 6.5 Hz, 3 H); IR ($CHCl_3$) λ_{max} 3400, 2930, 1730, 1670, 1510 cm^{-1}; mass spectrum *m/z* 353 (m), 324, 310 (M – Ac), 292; exact mass calcd for $C_{18}H_{27}NO_6$ 353.18382, found 353.18356.

(3α,4α,4aβ,5β,6α)-4-Acetamido-5,6-(cyclohexylidenedioxy)-3,4,4a,5,6,7-hexahydro-8-hydroxy-3-methylisocoumarin (73). To a solution of pyridine (13.7 μL, 170 μM, distilled from BaO) in CH_2Cl_2 (0.5 mL) at room temperature was added CrO_3 (8.5 mg, 85 μM, dried over P_2O_5 at high vacuum), and the resulting mixture was rapidly stirred for 13 min. Then a solution of alcohol **72** (2.1 mg, 5.9 μmol) in 1.5 mL of CH_2Cl_2 was added and the reaction stirred at room temperature for 75 min. The supernatant was decanted from the brown tarry residue and filtered through a short silica gel pad with ethyl acetate, and the residue was washed with ethyl acetate several times. The resulting colorless liquid was concentrated in vacuo to afford 1.5 mg (72%) of the enol lactone **73** as a colorless oil, which was identical with a sample prepared from natural actinobolin by NMR, IR, and TLC mobility; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.50 (s, 1 H), 5.40 (bd, *J* = 10 Hz, 1 H), 4.68 (ddd, *J* = 1.5, 3, 10 Hz, 1 H), 4.62 (dq, *J* = 1.5, 6.5 Hz, 1 H), 3.72 (ddd, *J* = 5, 9, 11 Hz, 1 H), 3.25 (t, *J* = 9 Hz, 1 H), 2.98 (dd, *J* = 5, 17.5 Hz, 1 H), 2.91 (dt, *J* = 9, 3 Hz, 1 H), 2.60 (ddd, *J* = 3, 11, 17.5 Hz, 1 H), 2.07 (s, 3 H), 1.75–1.50 (m, 10 H), 1.35 (d, *J* = 6.5 Hz, 3 H); IR ($CHCl_3$) λ_{max} 3430, 3320 (b), 2930, 1680, 1640, 1580, 1500 cm^{-1}; mass spectrum, *m/z* 351 (M), 308 (M – Ac), 253, 99; exact mass calcd for $C_{18}H_{25}NO_6$ 351.16817, found 351.16795.

Preparation of 73 from Natural 5. To a solution of naturally derived *N*-acetylactinobolamine (**5**) (24.4 mg, 0.090 mmol) in 2 mL of dichloroethylene at room temperature was added cyclohexanone (44 μL, 0.43 mmol), trimethyl orthoformate (47 μL, 0.43 mmol), and several crystals of *p*-TsOH. The solution was then heated at reflux for 6 h. The reaction was quenched at room temperature with aqueous bicarbonate, extracted with ethyl acetate (3 × 50 mL), and dried with magnesium sulfate. The volatiles were removed at high vacuum to give an oil that was chromatographed on silica gel. Elution with ethyl acetate/hexane (50%) followed by ethyl acetate (100%) afforded 16.4 mg (52%) of the pure ketal derivative **73**, identical with the synthetic material by NMR, IR, and MS.

(3α,4α,4aβ,5β,6α)-4-Acetamido-3,4,4a,5,6,7-hexahydro-5,6,8-trihydroxy-3-methylisocoumarin (5). To a solution of naturally derived cyclohexylidene ketal **73** (2.4 mg, 6.8 μmol) in 0.5 mL dioxane at room temperature was added 0.5 mL of 1.0 N HCl. The mixture was stirred for 15 min, and then the volatiles were removed in vacuo. Chromatography of the residual oil on silica gel (eluant: acetone) gave 1.7 mg (92%) of the diol **5**, which was identical with the material from which **73** was prepared.

Preparation of 5 from Natural Actinobolin. To a solution of natural actinobolin hemisulfate hydrate (201.7 mg, 0.485 mmol) in 2 mL of dry pyridine was added phenylisothiocyanate (75 μL, 0.627 mmol) and the resulting solution stirred for 20 h at room temperature. The volatiles were then removed in vacuo and the resulting oil was dissolved in 100 mL of $CHCl_3$. The chloroform layer was washed with 10 mL of water, dried with magnesium sulfate, and concentrated in vacuo. The resulting white solid was dissolved in 3 mL of trifluoroacetic acid and heated at 60 °C for 6 h. The reaction was concentrated in vacuo and the residue dissolved in 50 mL of 5% HCl. The aqueous phase was washed with $CHCl_3$ (2 × 10 mL) and concentrated in vacuo. The resulting hydrochloride salt **74** was dissolved in 2 mL of pyridine and treated with acetic anhydride (46 μL, 0.488 mmol) overnight. The reaction was then concentrated and the resulting oil chromatographed on silica gel. Elution with ethyl acetate followed by acetone gave 49 mg (37%) of *N*-acetylactinobolamine (**5**). Recrystallization from methanol/ethyl acetate afforded white crystals, mp 249–251 °C dec: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.20 (bs, 1 H), 6.45 (bd, *J* = 8 Hz, 1 H), 4.84 (bs, 1 H), 4.62 (dq, *J* = 1.5, 6.5 Hz, 1 H), 4.37 (ddd, *J* = 1.5, 3, 8.5 Hz, 1 H), 3.91 (dt, *J* = 7, 9.5 Hz, 1 H), 3.12 (bs, 1 H), 3.11 (t, *J* = 9.5 Hz, 1 H), 2.92 (dd, *J* = 7, 19 Hz, 1 H), 2.62 (dt, *J* = 9, 3 Hz, 1 H), 2.45 (ddd, *J* = 2.5, 9.5, 19 Hz, 1 H), 2.12 (s, 3 H), 1.42 (d, *J* = 6.5 Hz, 3 H); IR ($CHCl_3$) λ_{max} 3600, 3440, 3310 (b), 3000, 1640, 1600, 1540, 1500, 1200, 1060 cm^{-1}; mass spectrum, *m/z* 271 (M), 212, 194, 99.

Acknowledgment. This research was supported by PHS Grant AI 16943. A Swiss National Fellowship to C.A. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Region NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.