Dipyranoside Precursors for Ansamycins. Pyranosidic Homologation. 5[1,2]

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Received March 30, 1987

The process of pyranosidic homologation has been applied to the readily obtainable dianhydro sugar 1 in the context of preparation of precursors for molecules containing multiple contiguous chiral centers (e.g., the ansa chains of rifamycin S and streptovaricin A). Two approaches for construction of the lower satellites have been determined. The first involves opening of the epoxide 1 with a carbanion derived from propargyl alcohol, followed by Lindlar reduction. Treatment of the resulting allylic alcohol with trifluoroacetic acid leads to internal glycosidation; the cis-fused (i.e., α) bicyclic system **9** being highly favored. Facial selectivity in the epoxidation of the double bond can be controlled admirably by insuring that the homoallylic alcohol is free or protected, depending on the desired result. The exo epoxide **11** is opened without problem from the endo surface and the C3-OH of the resulting alcohol **13** can be inverted by oxidation, followed by reduction with lithium aluminum hydride to give **15a**, the precursor for rifamycin S. In the second route, epoxide 1 is opened by a vinylic carbon nucleophile, which already has the C2-CH_3 methyl group in place. Thus, the bicyclic alkene **21**, formed upon acid-catalyzed cyclization, needs only to be hydroborated to arrive at compound **13**, obtained in the other route. This second route is, therefore, much shorter and is, in addition, more efficient. Alkene **21** is also versatile, since epoxidation and aqueous hydrolysis lead to the lower satellite, **26**, required for streptovaricin A.

Several years ago, we suggested that of the many advantages offered by carbohydrate derivatives for organic synthesis, two of the most valuable were (a) highly stereoselective reactions as a result of conformational bias and (b) ready proof of molecular stereochemistry.[5] The validity of these criteria had hitherto been well exemplified in the carbohydrate literature, but closer inspection would have shown that the synthetic targets (e.g., branched-chain sugars) on which these statements had been based normally contained 2–4 contiguous chiral centers, requirements that can be readily accommodated by simple pyranose rings. On the other hand, higher carbon sugars (i.e., with chiral centers >4) offer formidable challenges,[6,7] as was clearly apparent in the landmark synthesis of hikizimycin by Secrist and Wu.[6] In this context, many macrolides, or segments thereof, may be regarded as higher carbon sugars,[8] and the challenges are greatly enhanced for those systems that contain multiple *contiguous* chiral centers. Thus, the requirements for creating these contiguous chiral centers, (a) stereoselectively and (b) in known (or readily knowable) configurations, are severe.

If the early promise of carbohydrate synthons is to be upheld for such complex substrates, a protocol would be needed to extent the two criteria, noted above, to systems with >4 contiguous chiral centers. We have recently outlined the concept termed " pyranosidic homologation", which seeks to fill this need.[9,10] The idea is illustrated (Scheme I) with reference to the ansa chain of rifamycin S, I, and this was seen to lead to the tripyranose II as the most appropriate precursor.[11] Thus, II posesses seven of the eight chiral centers, the missing one being the C24-CH_3, which must be introduced at C6[12] with inversion of configuration.

Similar retroanalysis, applied to the even more complex ansa chain of streptovaricin A, III, leads to the tripyranoses IVa and IVb as two of the more attractive precursors generated by the pyranosidic homologation concept. The resemblance between II and IVa is striking. Thus, the backbone pyranosidic core is the same in both, possessing the D-gluco configuration. The upper satellites are also the same. Both require S_N2 displacements with carbon nucleophiles at the "same" site. The lower satellites are different, but both possess a C2-CH_3, which suggests that a common precursor could be developed for both. Thus, IVa emerges as more attractive than IVb.

Further retroanalysis of the tripyranoses II and IVa leads to the dipyranose V and thence to the monopyranose VI. In this manuscript, we describe work leading to the lower dipyranose components of II and IVa, and in the accompanying papers,[13] studies related to the upper satellite will be outlined.

As was noted above, the central ring of V has the D-gluco configuration, but preparation of 2-alkyl-D-glucopyranoses, such as VIa, have been found to require lengthy processes, if the precursors employed possess the $^4C_1$ conformation.[14] However, the equivalent $^1C_4$ structure, VIb, is readily achieved by the opening of a dianhydropyranose, e.g., 1.[15] In this context, the extensive studies of Cerny and coworkers have made it clear that the regioselectivity of

(1) We are grateful to the National Science Foundation (Grant CHE 8304283) and the University of Maryland for financial support.

(2) For part 3, see ref 11.

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(5) Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 3870.

(6) Secrist, J. A.; Wu, S.-R. *J. Org. Chem.* **1974**, *49*, 1434. Secrist, J. A.; Barnes, K. D. *Ibid.* **1980**, *45*, 4526.

(7) For some recent developments see: Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1986**, *158*, 81. Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274 and references cited therein.

(8) Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413.

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(12) The bicyclic compounds are all numbered, as indicated in **9** (Scheme I). For an alternative system, see IUPAC-IUB Joint Commission on Biochemical Nomenclature, *Eur. J. Biochem.* **1981**, *119*, 5.

(13) (a) Fraser-Reid, B.; Molino, B. F.; Magdzinski, L.; Mootoo, D. R. *J. Org. Chem.*, accompanying paper in this issue. (b) Mootoo, D. R.; Fraser-Reid, B. *J. Org. Chem.*, accompanying paper in this issue.

(14) Stoddardt, J. F. *Stereochemistry of Carbohydrates*; Wiley-Interscience: New York, 1971.

(15) Traha, T.; Cerny, M. *Collect. Czech. Chem. Commun.* **1971**, *36*, 2216.

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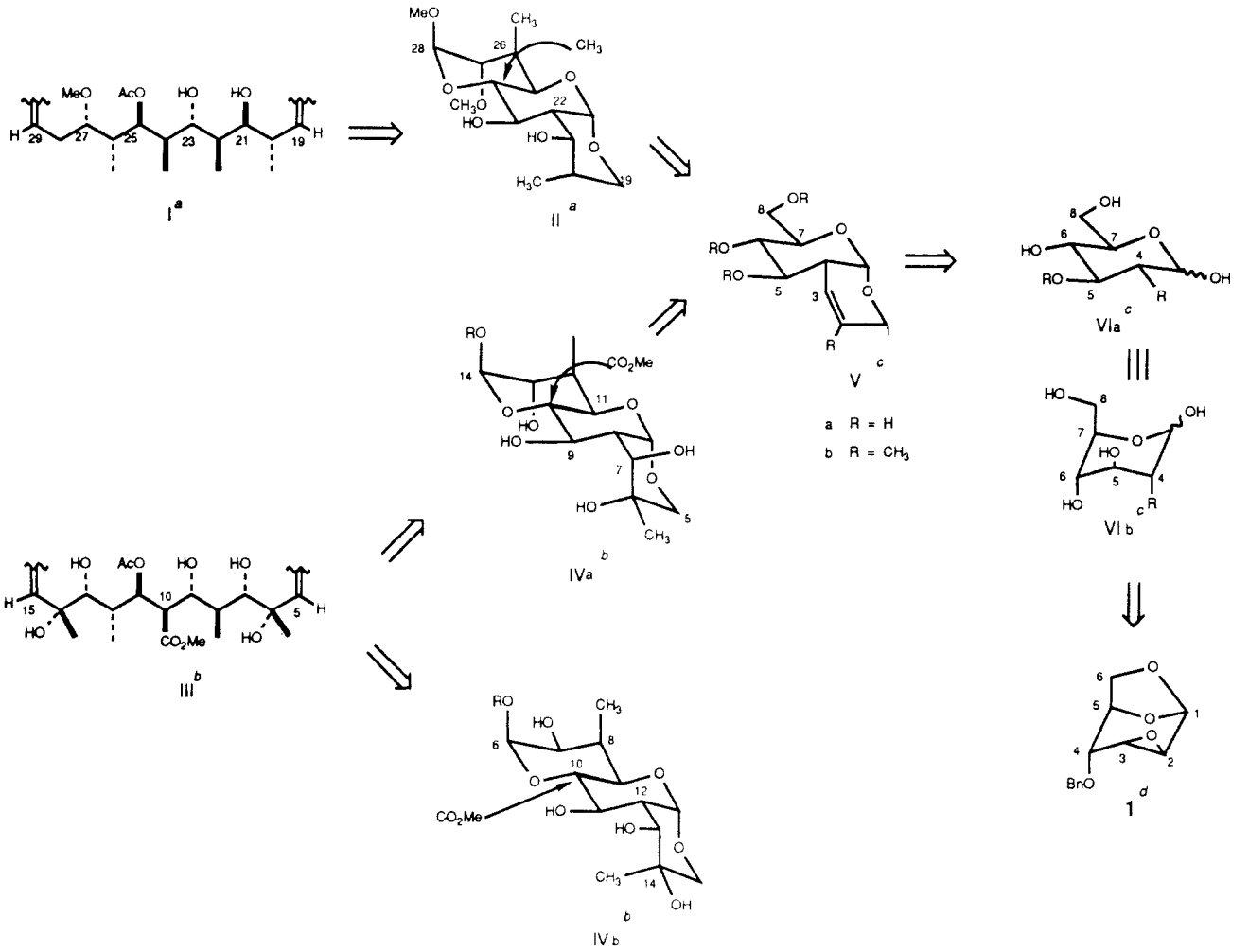
Scheme I



[a] Rifamycin numbering. [b] Streptovaricin numbering. [c] Numbering used in this paper. [d] Sugar numbering.

epoxide opening, in the sense desired by us, could be insured by the presence of a C4 oxygen, which is believed to chelate with the incoming carbon nucleophile.[16]

Approach 1 (Schemes II–IV). The epoxide **1** was prepared in four steps from levoglucosan according to the published procedure.[15] A nucleophile suitable for elaboration to the *Z*-allylic residue of Va was propargyl alcohol, and the corresponding ethynyl alane was chosen because of the ability of these derivatives to open epoxides stereospecifically[17] and regiospecifically.[17] Accordingly, the silylated propargyl ether **2** was treated with 1 equiv of *n*-butyllithium, followed by 0.75 equiv of diethyl aluminum chloride. Reaction of the reagent mixture so prepared with the epoxide **1** was complete in 30 min, giving the desired product, **3a**, quantitatively (Scheme II).

The alkynyl diol **3b**, obtained by standard desilylation, was quantitatively hydrogenated to the *Z*-alkene **4a** at atmospheric pressure over palladium on calcium carbonate poisoned with lead oxide.[19] Notably, palladium over barium sulfate poisoned with quinoline[20] did not show a sharp end point, 2 equiv of hydrogen being consumed continuously.

The preferred procedure for cleavage of 1,6-anhydro rings involves acid-catalyzed acetolysis.[21] Indeed, treatment of **4a** with trifluoroacetic acid caused the development of an intense purple color due, presumably, to the carbocation **5**, which upon quenching with acetic anhydride led to the tetraacetate **6** (α/β = 1.5) in 86% yield. However, this material decomposed on standing and could be characterized only as the dihydro derivative **7**. It was, therefore, not a very promising intermediate. Quenching of the carbocation **5** with alcohols gave low yields of glycosides, such as **8**.

The bicyclic derivatives **9b** and **10b** were always present as byproducts in the above reactions, and conditions were therefore sought for their optimization. Reaction of **4a** in neat trifluoroacetic acid at 0 °C caused complete disappearance of the starting material in 2 h (TLC after quenching with triethylamine), and pouring the reaction mixture into neat triethylamine afforded a 70% yield of **9b** and **10b** (3:1) in addition to some regenerated starting material **4a**.

Prolonging the above reaction to establish a more favorable equilibrium between **9a** and **10a** resulted in a rapid decline of total yield owing to decomposition. However, the yield of the α anomer **9a** could be optimized by dissolving the 1,6-anhydro sugar **4a** or **4c** in neat trifluoroacetic acid at 0 °C and then raising the temperature to 40

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(20) Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518.
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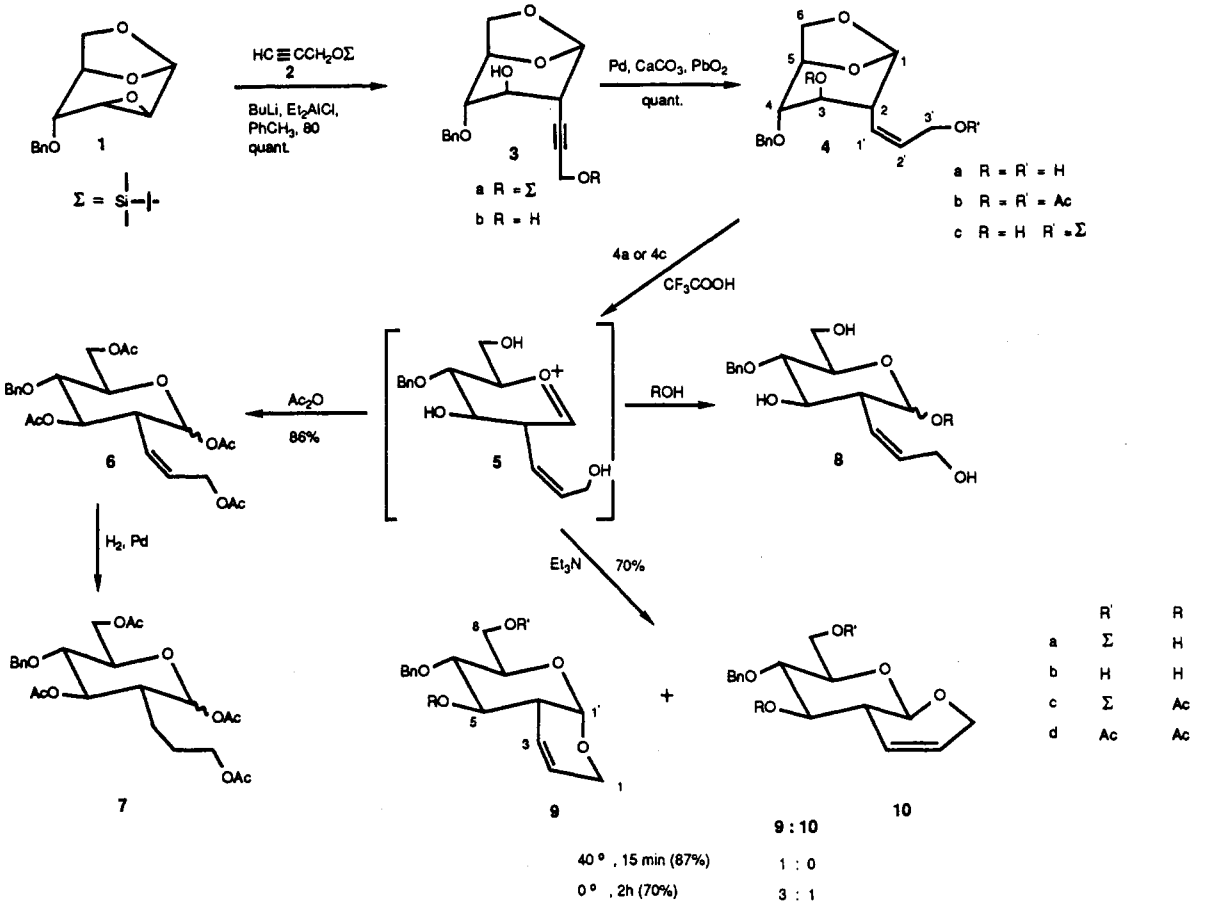
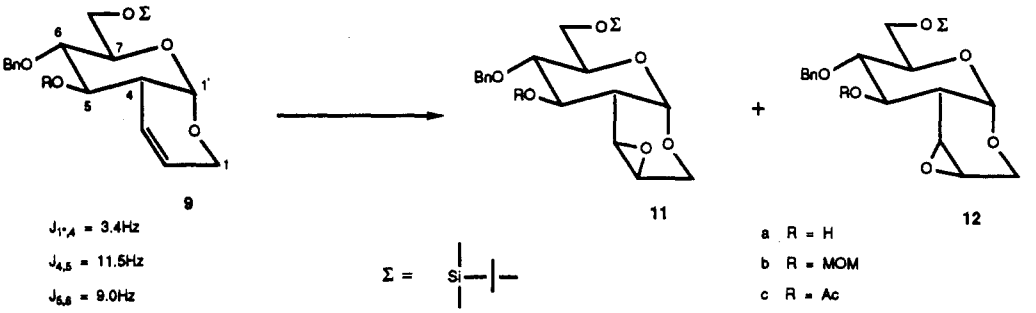
Scheme II



Scheme III



(i) 9a (R = H) tBuOOH, VO(acac)2, PhH, 48h, 25 (70%) → 11a + 12a (1 : 20)

(ii) 9a (R = H) mCPBA, CHCl3/CCl4, 18h, 25 (92%) → 11a + 12a (3 : 2)

(iii) 9c (R = MOM) mCPBA, CHCl3 / CCl4, 28h, 25 (86%) → 11b + 12b (4 : 1)

(iv) 9d (R = Ac) mCPBA, CHCl3 / CCl4, 32h, 25 (91%) → 11c + 12c (21 : 1)

°C for 15 min. Under these conditions, **9a** was obtained as the only product, isolated in 87% yield on a 200-mg scale or in 70% yield in a 5–10-g scale.

The observation of Descotes and co-workers[22] that acid-catalyzed equilibration of 1,8-dioxaoctahydronaphthalene gave cis products predominantly was attributed by them to a favorable anomeric effect.[23] Their results, therefore, provide a precedent for the formation of **9a** as the main isomer during prolonged acid treatment of **4a**. Stereoelectronic kinetic control in related systems has also been demonstrated by Deslongchamps and coworkers.[24]

The conformation of compound **9b** was clear, as shown in Scheme III, by virtue of the coupling constants listed. The C5 homoallylic hydroxyl was, therefore, well poised to direct the stereochemical course of epoxidation (Scheme III, i–iv). Indeed, application of the Sharpless and Mi-

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(23) Lemieux, R. U.; Kato, S. *Tetrahedron* **1974**, *30*, 1933. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983; (a) p 37 et. seq., (b) p 84, (c) p 39.

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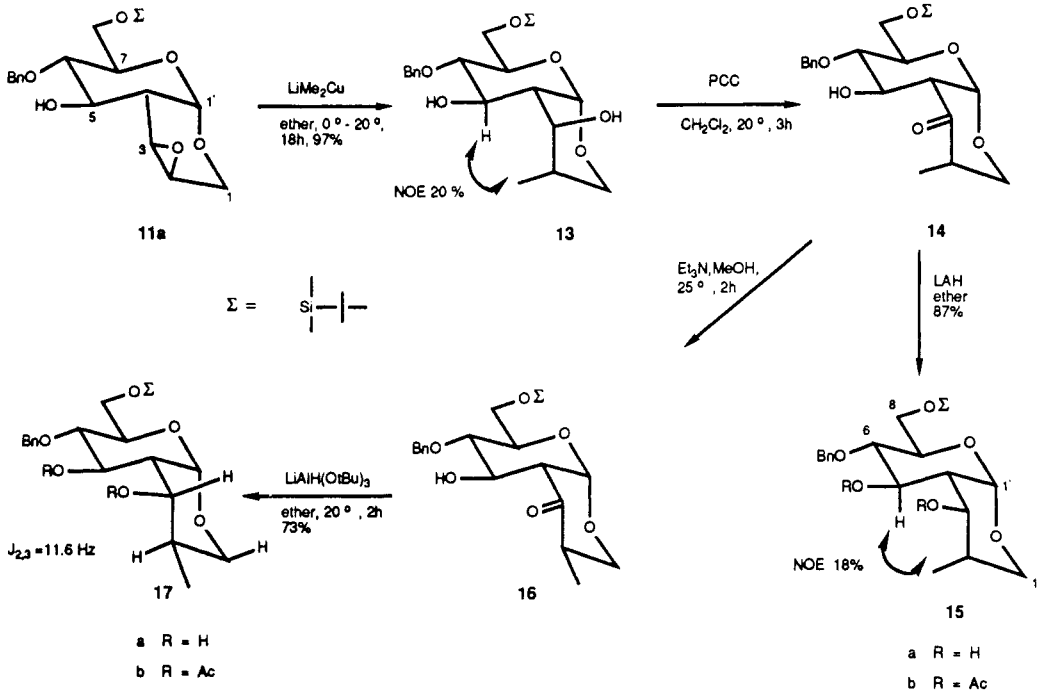
Scheme IV



chaelson[25] procedure to **9b** gave the endo epoxide **12a** predominantly, whereas with *m*-chloroperbenzoic acid, a 3:2 mixture of **11a** and **12a** was obtained.

In order to overcome the Henbest effect[26] in the peracid epoxidations, the C5-OH was protected. With the methoxymethyl ether **9c**, a 4:1 mixture of **11b** and **12b** was obtained (Scheme III, iii), but the favorable exo ratio could be further enhanced by exploiting the stereoelectronic repulsive effects, which have also been observed in peracid epoxidations.[27] Thus, the acetate **9d**, on treatment with *m*-chloroperbenzoic acid in 3:1 chloroform–carbon tetrachloride, gave virtually exclusively the exo epoxide **11c** in 91% yield (Table I, entry iv). In more polar solvents like methylene chloride, **12c** could not be detected; however, in these cases yields were lower.

Treatment of **11a** with excess lithium dimethyl cuprate[28] gave the diol **13** as the only product in 97% yield. The configuration of the product obtained was clearly demonstrated by a large NOE observed in H5 when the C2-CH_3 was irradiated.

Pyridinium chlorochromate[29] oxidized the axial hydroxyl group of **13** preferentially, a clean product, **14**, being isolated. Reduction with lithium aluminum hydride gave the diol **15a** as the sole product in 87% yield. That the C2-CH_3 had remained axial was again detected by observing a large NOE in H5. Alternatively, mild basic treatment of ketone **14** gave a new ketone, **16**, which was reduced to a different diol, **17a**, with lithium tri-*tert*-butoxyaluminum hydride. The 600-MHz ^1H NMR spectrum of the corresponding diacetate **17b** revealed parameters that confirmed the C2–C3 configuration ($J_{1a,2}$ = 11.2, $J_{2,3}$ = 11.6 Hz) and conformation ($J_{4,5}$ = 11.0, $J_{5,6}$ = $J_{6,7}$ = 9.6 Hz) shown.

The results in Scheme IV show that of the four possible 2-alkyl-3-hydroxy stereoisomers available by functionalization of alkene **9**, three of them (**13**, **15**, and **17**) *can be prepared readily in high yields and with complete stereochemical control.* Nevertheless, we considered that a precursor that already had the C2-CH_3 in place would provide for a much shorter route to these compounds. Such a precursor is **Vb** (Scheme I), and its formation would require nucleophilic attack of epoxide **1** by a vinylic organometallic derivative related to **18**.

Approach 2 (Schemes V and VI). The vinyl iodide **18a** had been prepared stereoselectivity by Duboudin and co-workers by the addition of methylmagnesium bromide to propargyl alcohol in the presence of iodine.[30] A slight modification of their procedure (See the Experimental Section) enabled us to prepare the material on a large scale in isolated yields of 50%. Normant had reported quantitative exchange between vinyl iodides and *n*-butyllithium in ether at −78 °C with complete retention of double bond geometry,[31] but the reactions of the resulting vinyllithiums with different electrophiles had been found to be erratic,[32] and this tendency was confirmed in the case at hand. After due experimentation, a procedure was adopted whereby the vinyllithium **18d** or **18e** was added to a solution of anhydrous magnesium bromide generated in situ at room temperature.[33] When the epoxide **1** was added to the resulting solution, a reaction proceeded to give a 3:1 mixture of the branched-chain sugar **19** and the bromohydrin **20** in a combined yield of 90–95% (Scheme V). Attempts to prevent bromohydrin formation by varying the reaction conditions were unavailing. (An authentic sample of **20** could be prepared by treating **1** with anhydrous magnesium bromide.) Fortunately, the bromohydrin **20** could be recycled to the starting material **1** in quantitative yield. By this procedure, it was possible to obtain 20-g amounts of the olefinic alcohol **19(a** or **b)**.

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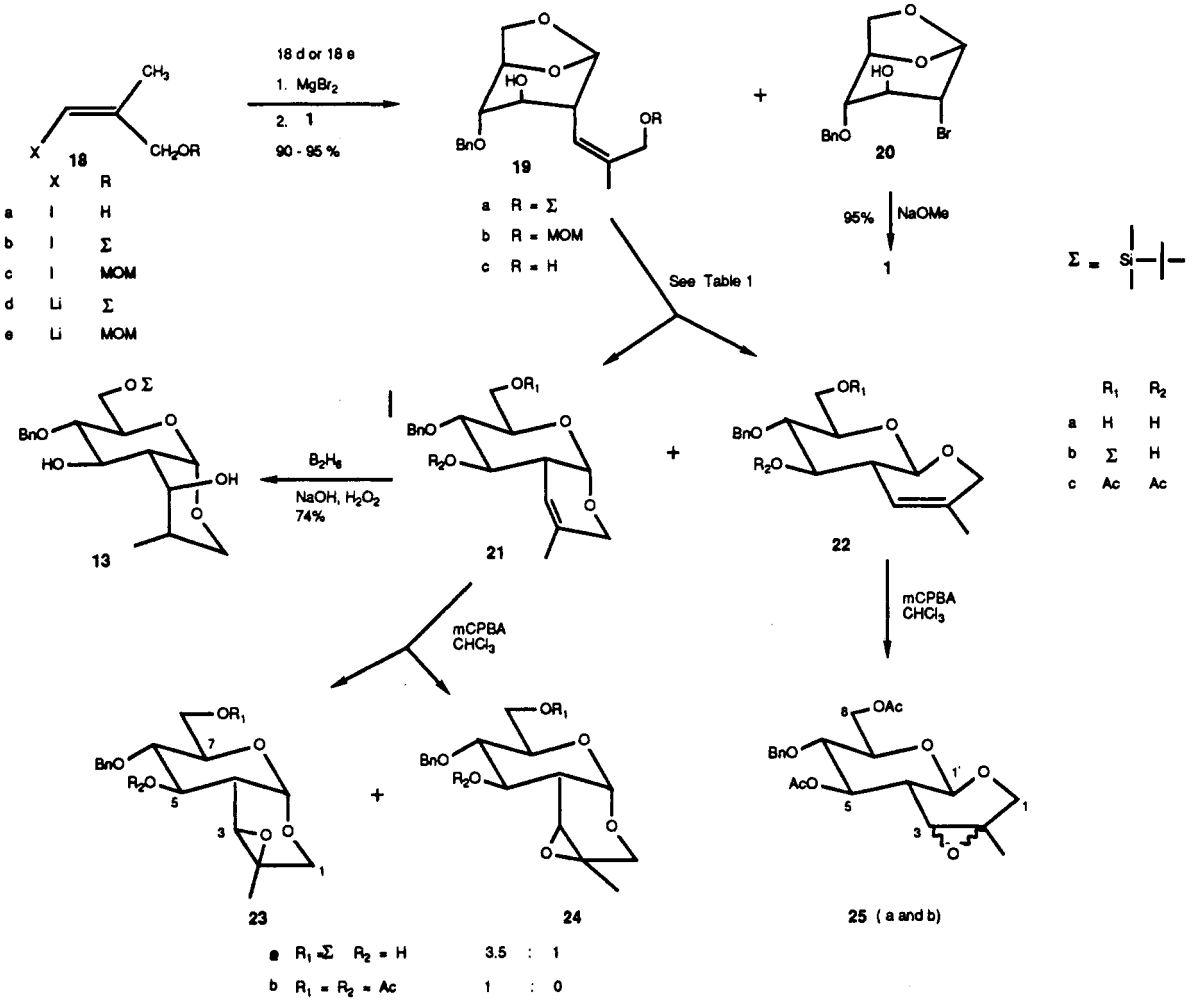
(31) Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* **1976**, 245.
(32) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
(33) Jones, R. G.; Gilman, H. *Chem. Rev.* **1954**, *54*, 835. The procedure for generating anhydrous magnesium bromide in situ was obtained by personal communication with P. Mariano, University of Maryland.

Scheme V



The next step was the cyclization. Unfortunately, application of the trifluoroacetic acid procedure that had worked so well for the formation of **9a** from the desmethyl analogue **4a** (Scheme II) gave a disappointing 34% yield of **21a** and **22a** as a 3:1 mixture. This initiated a study involving a wide variety of protic and Lewis acid catalysts on the diol **19c** and the ether **19b** (Table I). Optimum conditions favoring the α isomer **21a** (Table I, entry ix) were found to involve treating the methoxymethyl precursor **19b** with aqueous hydrochloric acid in ether at room temperature for 20 h. Under these conditions, the α/β ratio was 12:1. On the other hand, the best conditions favoring the β isomer **22a** were those in entries v and vi.

The favorable result in entry ix meant that the product could be used directly for the next step, and this was fortunate because the mixture of anomers **21** and **22** was not easily separated by fractional chromatography or crystallization. However, the monosilylated (**21b**/**22b**) or diacetylated (**21c**/**22c**) derivatives could be readily separated chromatographically.

Hydroboration of **21b** with diborane in tetrahydrofuran followed by alkaline peroxide oxidation gave exclusively the diol **13** in 74% yield. This route to **13** from the anhydro sugar **1** is two steps shorter and proceeds in better overall yield than that outlined in Schemes II–IV.

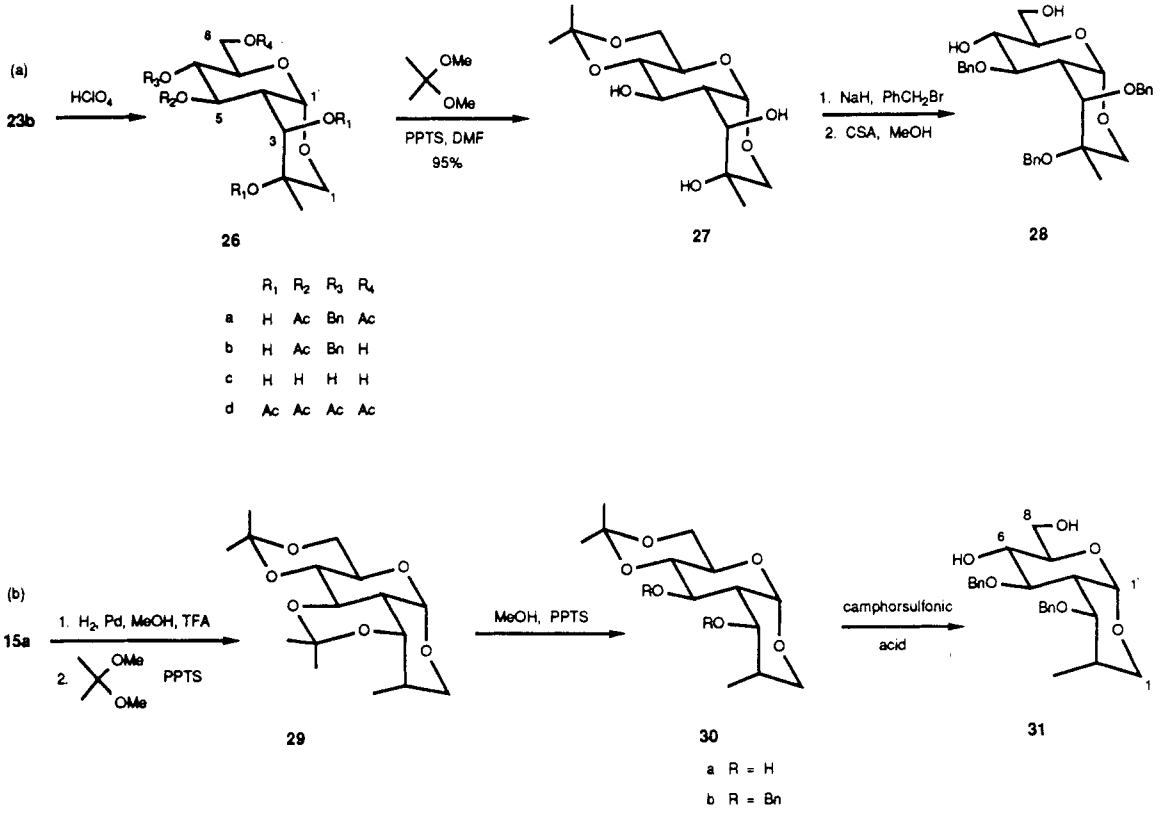
Our approach to the lower satellite of the streptovaricin A precursor (IVa, Scheme I) required preparation of the epoxide **23**. As was observed in the case of **9**, if the C5-OH was free, as in **21b**, a mixture of exo (**23a**) and endo (**24a**) epoxides was obtained in 90% yield in the ratio 3:1. However, if the C5-OH was protected, as in **21c**, the exo epoxide **23b** was obtained stereoselectivity in ~80% yield. However, for practical purposes, the epoxidation was normally carried out on the *unseparated* anomeric mixture of acetylated olefins (**21c** + **22c**) to give the desired exo epoxide **23b** in 65% yield and the diastereomeric analogues **25**(**a** and **b**) in 19% yield. This procedure proved to be the most efficient to follow because isolation of the desired material **23b** was easier than separation of the anomeric

Table I. Preparation of Bicyclic Olefins 21 and 22 from 19

entry	substrate	conditions[a]	yield, %[b]	21a/22a[c]
i	19c	CF_3CO_2H (neat), 5 min, Et_3N	34	3
ii	19c	CF_3CO_2H (0.1 equiv), CH_3Cl_2, 18 h	37[e]	3
iii	19c	$SnCl_4$ (1 equiv), CH_2Cl_2, 15 min	54	2
iv	19c	$SnCl_4$ (1 equiv), 0 °C, 25 min	40	2
v	19c	70% $HClO_4$ (1 equiv), ether, 20 min	75	1
vi	19c	$BF_3{\cdot}Et_2O$ (0.1 equiv), CH_2Cl_2, 10 min	48	1
vii	19c	CSA[d] (0.2 equiv), CH_2Cl_2, 3 h	65	3.5
viii	19c	CSA (0.2 equiv), benzene, reflux, 10 min	41	1.6[f]
ix	19b	6 M HCl, ether, 20 h	76	12

[a] Reactions conducted at ambient temperature (ca. 25 °C) unless otherwise stated. [b] Isolated yields after purification by chromatography. [c] Determined by high-field ^1H NMR; integration of H1. [d] CSA is *dl*-camphorsulfonic acid. [e] Plus 10% starting material. [f] Partial decomposition.

Scheme VI



mixture of olefinic precursors.

It was anticipated that acid-catalyzed opening of the epoxide **23b** would be regio- and stereoelectronically controlled since (a) the developing carbocation would be centered at the tertiary position and (b) the desired product would arise from trans diaxal opening. Indeed, treatment with aqueous acid gave the diol **26a** and the triol **26b**, exclusively (Scheme VI). The stereochemistry of the newly created centers could be assigned on the basis of the coupling ($J_{1,3}$ = 2.5 Hz) in the 200-MHz ^{1}H NMR spectrum of the pentaacetate **26d**, a result that indicated that there was a W arrangement between H3 and the equatorial H1 proton.

The bipyranosides **15** and **26** represent the two lower rings of the chirons II and IV (Scheme I), respectively, but in order to prepare for further pyranosidic homologation, some adjustments in the protecting groups were required. An ancillary benefit of these undertakings was the convincing demonstration that the stereochemistry, which had been assigned to **15** and **26** on the basis of ^{1}H NMR analyses, could be verified independently by chemical procedures.

Thus, acid-catalyzed hydrogenolysis of **15a** caused the removal of both protecting groups, and if the resulting tetrol was treated repeatedly with 2,2-dimethoxypropane, a diisopropylidene derivative, **29**, was obtained, a result that confirmed the relationship of the C3 and C5 hydroxyl groups. Exposure to methanol and PPTS[34] for 1 h caused removal of the "internal" isopropylidene ring, thereby paving the way for the dibenzylated derivative **30b**. More drastic acidic hydrolysis then led to diol **31**.

Similarly, treatment of **26b** with sodium in liquid ammonia gave the crude pentol **26c**, which could be characterized as the pentaacetate **26d**. Alternatively, when **26c** was treated with 2,2-dimethoxypropane and PPTS in dry dimethylformamide, the monoacetonide **27** was formed in 95% yield, and (by contrast with the results in Scheme VI(b) relating to **29**) this material showed no tendency to react further. The latter result was consistent with the orientations that had been assigned at C2 and C3 of **26** because if the hydroxyl had existed in *any other relationship*, a bisacetonide would have resulted.

The triol **27** was benzylated exhaustively, and removal of the isopropylidene ring then gave **28** in 65% overall yield.

The lower dipyranose rings of II and IVa have, therefore, been prepared unambiguously with excellent stereoselectivity and good yields. Both segments are well suited for elaboration of the third ring, and this will be described in the following paper.[13a]

Experimental Section

General Procedures. Melting points were determined in capillary tubes using a Büchi Model 510 melting point apparatus and are uncorrected. Elemental analyses were performed by Dr. F. Kasler, University of Maryland, or by M-H-W Laboratories, Phoenix, AZ. IR spectra were recorded on Perkin-Elmer Model 298 spectrometer with sodium chloride plates for thin films of liquids, syrups, or solids in Nujol mulls. Optical rotations were determined at the sodium D line with a Perkin-Elmer 241 polarimeter. ^{1}H NMR spectra were determined on the following spectrometers: Varian XL-100, Varian XL-200, or Bruker WM-250. Unless otherwise stated, the solvent used was $CDCl_3$ with internal tetramethylsilane or $CHCl_3$ as the standard. The coupling constants were verified by homonuclear decoupling experiments. For the purpose of ^{1}H NMR interpretation, compound structures have been numbered in the schemes. High-resolution mass spectra (HRMS) were performed at Herman Laboratories, Research Triangle Park, NC, with a VG7070F instrument. The progress of all reactions was monitored by thin-layer chromatography (TLC), which was performed on aluminum plates precoated with silica gel HF-254 (0.2-mm layers) containing a fluorescent indicator (Merck, 5539). The following solvent systems were used (EtOAc–petroleum ether mixtures): A, 1:9; B, 1:4; C, 3:7; D, 1:1; E, 7:3; F, 2% MeOH in CH_2Cl_2. Detection was first by UV (254 nm)

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and then by charring with sulfuric acid spray or by charring with a solution of ammonium molybdate(VI), tetrahydrate (12.5 g), and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Flash chromatography was performed with Kiesselgel 60 (230–400 mesh, E. Merck).

Standard Procedure for Acetylation. A solution of the alcohol and 4-(dimethylamino)pyridine (1.5 mmol/mmol of alcohol) in dry ethyl acetate (5 mL/mmol of alcohol) was treated with acetic anhydride (1.5 mmol/mmol of alcohol) at room temperature. For extremely hindered alcohols, the solution was warmed to 45 °C. The reaction was monitored by TLC and upon completion quenched with methanol. The volatiles were removed in vacuo, and the residue was purified by flash chromatography.

Selective Silylation of Primary Alcohols. *tert*-Butyldimethylsilyl or *tert*-butyldiphenylsilyl chloride (1.5 mmol/mmol of alcohol) was added to a solution of triethylamine (1.7 mmol/mmol of alcohol), 4-(dimethylamino)pyridine (0.05 mmol/mmol of alcohol), and the alcohol in dry methylene chloride (10 mL/mmol of alcohol). The reaction was usually completed with 16 h at room temperature, at which time the solution was diluted with methylene chloride and washed successively with saturated solutions of sodium bicarbonate and sodium chloride. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The crude residue was purified by flash chromatography.

Benzylation of Alcohols. Sodium hydride (1.5 mmol/mmol of alcohol, 50% suspension in mineral oil), which was washed with petroleum ether, was added to a solution of the alcohol in dry dimethylformamide (5 mL/mmol of alcohol) at 0 °C. After 20 min, benzyl bromide (1.2 mmol/mmol of alcohol) and tetra-*n*-butylammonium iodide (0.1 mmol/mmol of alcohol) were added, and the reaction mixture was warmed to room temperature and stirred for an additional 45 min. The mixture was then recooled to 0 °C, carefully quenched with methanol, and diluted with water. The resulting suspension was extracted with ether, and the combined organics were washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The crude residue was purified by flash chromatography.

Oxidations Using Pyridinium Chlorochromate (PCC). Pyridinium chlorochromate (5 mmol/mmol of alcohol) was added to a mixture of Celite (1 equiv wt of PCC), anhydrous sodium acetate (5 mmol/mmol of alcohol), Florisil (10% wt of PCC), and alcohol in dry methylene chloride (25 mL/mmol of alcohol). The reaction was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was diluted with ether and filtered through a short column of florisil. The column was eluted with additional ether and the filtrate concentrated in vacuo. The residue was purified by flash chromatography.

Diacetate of 1,6-Anhydro-4-*O*-benzyl-2-*C*-[3′-hydroxyprop-1′(*Z*)-enyl]-β-D-glucopyranose (4b). Propargyl ether was silylated according to the General Procedure to give **2**. To a stirred solution of the freshly distilled material (29.0 g, 170.8 mmol) in dry toluene (300 mL) at −78 °C under argon was added dropwise *n*-BuLi (1.3 M, 131 mL, 170.8 mmol). The solution was warmed to 0 °C for 1 h. After the mixture was recooled to −78 °C, Et_2AlCl (1.4 M, 76.2 mL, 106.8 mmol) was added, the dark yellow solution was stirred for 36 h at room temperature, and the resulting mixture was warmed to 80 °C. The epoxide **1**[15] (9.90 g, 42.25 mmol) was then added as a solid. After 45 min, TLC (F) showed that the reaction was complete, and the solution was cooled to 0 °C. NH_4Cl (5 M, 30 mL) was carefully added, followed by Celite (30 g) and EtOAc (400 mL). The resulting mixture was filtered through Celite, the solid was washed with EtOAc (2 × 200 mL), and the combined organic phases were evaporated and chromatographed (C) to give the alkyne **3a** as a pale yellow liquid, bp >150 °C (0.06 mm), 16.9 g (99%): $[\alpha]^{25}_D$ +38.8° (*c* 2.36, $CHCl_3$); ^1H NMR (200 MHz) δ 0.03 (s, 6 H, $SiCH_3$), 0.82 (s, 9 H, *t*-Bu), 2.49 (d, *J* = 7.0 Hz, OH, D_2O ex), 2.67 (br t, *J* = 2.5 Hz, 1 H, H2), 3.32 (ddd, *J* = 2.5, 1.5, 1.0 Hz, 1 H, H4), 3.63 (dd, *J* = 7.5, 5.5 Hz, 1 H, H6x), 3.92 (ddd, *J* = 7.0, 2.5, 2.0 Hz, 1 H, H3), 3.94 (ddd, *J* = 7.5, 0.5 Hz, H6x), 4.27 (d, *J* = 2.5 Hz, 2 H, C3′), 4.54 (br d, *J* = 5.5 Hz, 1 H, H5), 4.52 (AB q, *J* = 12.5 Hz, Δδ = 0.09 ppm, 2 H, $PhCH_2$), 5.52 (br s, 1 H, H1), 7.30 (m, 5 H, $PhCH_2$).

The silyl ether **3a** (14.4 g, 38 mmol) was dissolved in 200 mL of dry THF at 0 °C and treated with a solution of tetra-*n*-butylammonium fluoride (1 M in THF, 40 mL, 40 mmol) for 30 min (TLC, E) to give **3b**, 10.2 g (99%). A portion of the material (3.66 g, 12.6 mmol) was hydrogenated at room temperature by using 5% $Pd/CaCO_3$ poisoned with lead oxide (Lindlar's catalyst,[19] 700 mg) in 80 mL of EtOAc. Stirring was maintained such that the initial hydrogen consumption was 2 mL/min. When the rate had slowed to 0.3 mL/min (303 mL of H_2, calcd 310 mL), the hydrogenation was stopped. Filtration and evaporation provided the diol **4a** as a yellow semisolid. The material was acetylated, as described in the General Procedures, for characterization. For the diacetate **4b**: bp 110 °C (0.06 mm); R_f 0.45 (D); $[\alpha]^{25}_D$ 41.9° (*c* 3.25, $CHCl_3$); ^1H NMR (200 MHz) δ 2.10 and 2.08 (2 s, 6 H, Ac), 2.91 (br d, *J* = 10.2 Hz, H2), 3.31 (q, *J* = 1.5 Hz, 1 H, H4), 3.75 (dd, *J* = 7.4, 6.0 Hz, 1 H, H6x), 4.02 (dd, *J* = 7.4, 2.0 Hz, 1 H, H6n), 4.57 (br d, *J* = 6.0 Hz, 1 H, H5), 4.64 (d, *J* = 7.2 Hz, 2 H, H3′), 4.71 (AB q, *J* = 12.2 Hz, Δδ 0.06 ppm, 2 H, $PhCH_2$), 4.81 (t, *J* = 1.6 Hz, 1 H, H3), 5.31 (br s, 1 H, H1), 5.72 (dt, *J* = 12.0, 7.2, 7.2 Hz, 1 H, H2′), 5.88 (dd, *J* = 10.2, 12.0 Hz, 1 H, H1′), 7.34 (m, 5 H, $PhCH_2$); HRMS, $C_{20}H_{24}O_7$ calcd 376.1521, found 376.1521. Anal. Calcd for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.78; H, 6.61.

(a) Acid-Catalyzed Reactions of 4a and 4c: Formation of 9a and 10a. A deep purple solution of the (*Z*)-alkenediol **4a** (2.59 g, 8.8 mmol) in trifluoroacetic acid (50 mL) was stirred at 0 °C. TLC aliquots (0.05 mL) were periodically withdrawn, added to triethylamine (0.5 mL), and diluted with ether and saturated sodium bicarbonate solution. After 2 h, TLC indicated complete disappearance of **4a** (R_f 0.32, EtOAc) and the formation of two products (overlapping at R_f 0.55). The cold reaction solution was slowly poured onto triethylamine (150 mL) at −10 °C, and the resulting mixture was partitioned between bicarbonate solution (100 mL) and a 2:1 EtOAc–ether mixture (200 mL). The organic phase was then washed with brine, dried (Na_2SO_4), filtered, and evaporated. Further washings of the combined aqueous phase with EtOAc provided more crude materials. Column chromatography (E) provided an inseparable 3:1 mixture of **9a** and **10a** as a pale yellow syrup, 1.71 g (70%). Selective silylation of the mixture with TBDMSCl (1 g, 6.6 mmol), triethylamine (1 M, in CH_2Cl_2, 7 mL, 7 mmol), and DMAP (30 mg) in 30 mL of dry CH_2Cl_2 at 25 °C for 3 h afforded derivatives that were clearly resolved into major (R_f 0.32) and minor (R_f 0.24) components. These were separated by column chromatography (C), yielding 1.25 g of compound **9b** and 0.45 g of compound **10b**. Acetylation of the major alcohol **9b** provided compound **9c** as white needles: mp ca. 50 °C; bp 160 °C (0.1 mm); $[\alpha]^{25}_D$ +133.6° (*c*1.07, $CHCl_3$); ^1H NMR (200 MHz) δ 0.04 and 0.03 (2 s, 6 H, $SiCH_3$), 0.89 (s, 9 H, *t*-Bu), 1.90 (s, 3 H, Ac), 2.19 (m, 1 H, H4), 3.64 (t, *J* = 9.5 Hz, 1 H, H6), 3.85 (m, 3 H, H7 and H8), 4.32 (AB of ABXYY′, J_{AB} = 15.0 Hz, Δδ = 0.08 ppm, $J_{AX} = J_{AY} = J_{AY'}$ = 1.5 Hz, J_{BX} = 0 Hz, J_{BY} = 1.5 Hz, $J_{BY'}$ = 1.0 Hz, 2 H, H1e and H1a), 4.59 (AB q, J_{AB} = 11.4 Hz, Δδ = 0.12 ppm, 2 H, $PhCH_2$), 4.89 (d, *J* = 3.4 Hz, 1 H, H1′), 5.24 (dd, *J* = 10.4, 9.5 Hz, 1 H, H5), 5.65 (AB of ABXYY′, J_{AB} = 10.5 Hz, Δδ = 0.10 ppm, J_{AX} = 4.8 Hz, J_{AY} = 1.5 Hz, $J_{AY'}$ = 1.0 Hz, J_{BX} = 0 Hz, $J_{BY} = J_{BY'}$ = 1.5 Hz, 2 H, H3 and H2), 7.25 (m, 5 H, $PhCH_2$). Anal. Calcd for $C_{24}H_{36}O_6Si$: C, 64.25; H, 8.09. Found: C, 64.30; H, 8.20.

The minor product from the chromatogram was desilylated by treatment with tetra-*n*-butylammonium fluoride in THF, and the resulting diol **10a** was acetylated (see the General Procedures). The diacetate **10d** was a pale yellow semisolid: bp 160 °C (0.1 mm); $[\alpha]^{25}_D$ +57.7° (*c* 1.15, $CHCl_3$); ^1H NMR (200 MHz) δ 2.00 (s, 6 H, 2 $COCH_3$), 2.29 (m, 1 H, H4), 3.57 (dd, *J* = 10.2, 9.0 Hz, 1 H, H6), 3.79 (ddd, *J* = 9.0, 4.5, 2.4 Hz, 1 H, H7), 4.28 (AB of ABX, J_{AB} = 12.0 Hz, Δδ = 0.14 ppm, J_{AX} = 4.5 Hz, J_{BX} = 2.4 Hz, 2 H, H8), 4.37 (m, 2 H, H1), 4.38 (d, *J* = 11.0 Hz, 1 H, H1′), 4.53 (AB q, J_{AB} = 11.5, Δδ = 0.05 ppm, 2 H, $PhCH_2$), 5.00 (dd, *J* = 11.5, 10.2 Hz, 1 H, H5), 5.59 (AB of ABXYY′, J_{AB} = 10.0 Hz, Δδ = 0.19 ppm, $J_{AX} = J_{AY} = J_{AY'}$ = 2.0 Hz, $J_{BX} = J_{BY} = J_{BY'}$ = 2.5 Hz, 2 H, H2 and H3), 7.28 (m, 5 H, $PhCH_2$). HRMS calcd for $C_{20}H_{24}O_7$ 374.1365, found 374.1363.

(b) Selective Formation of 9a. Trifluoroacetic acid (100 mL) was cooled to 0 °C, and the silylated alkene **4c** (6.75 g, 16.5 mmol) was added. After 30 min, the deep purple solution was warmed to 40–50 °C for 15 min; TLC aliquots indicated complete disappearance of the intermediate alcohol **4a** (R_f 0.32, EtOAc) and formation of a new product (R_f 0.55). The hot reaction solution

was poured into cold (−10 °C) triethylamine (250 mL) with efficient stirring over 10 min. The resulting mixture was partitioned between 20% potassium hydroxide (300 mL) and a 1:1 mixture of EtOAc–ether (300 mL) and the aqueous phase was repeatedly extracted. The combined organic phases were then washed with brine, dried (Na_2SO_4), filtered, and evaporated. Column chromatography (E) provided the cis-fused bipyranosides **9a** as a pale yellow semisolid, 3.35 (70%), uncontaminated with the isomer **10a**.

Epoxidation Reactions of Alkene 9b. (a) With *m*-Chloroperbenzoic Acid. Reaction of **9b** (145.8 mg, 0.36 mmol) with *m*-chloroperbenzoic acid (0.45 mmol) in dry $CHCl_3$ (3 mL) at 25 °C for 26 h afforded major and minor products R_f 0.26 and 0.12 (B), respectively. The solution was diluted with CH_2Cl_2 (20 mL), washed successively with 10% sodium thiosulfate (3 × 5 mL) and bicarbonate solution, and then dried ($MgSO_4$). Workup afforded **11a** as a colorless syrup, 135.3 mg (86%). Preparative thin-layer chromatography (C) provided the faster moving major component **11a** as a white powder that upon acetylation in the usual way, gave **11c** as a colorless syrup: $[\alpha]^{25}_D$ +59.5° (*c* 0.83, $CHCl_3$) ^{1}H NMR (200 MHz) δ 0.04 (2 s, 6 H, $SiCH_3$), 0.90 (s, 9 H, *t*-Bu), 1.92 (s, 3 H, $COCH_3$), 2.31 (br d, J = 11.0 Hz, 1 H, H4), 3.19 (dd, J = 3.5, 3.0 Hz, 1 H, H2), 3.75 (m, 5 H), 4.18 (AB of ABX, J_{AB} = 13.0 Hz, $\Delta\delta$ = 0.30 ppm, J_{AX} = 0 Hz, J_{BX} = 3.0 Hz, 2 H, H1), 4.62 (AB q, J_{AB} = 12.0 Hz, $\Delta\delta$ = 0.10 ppm, 2 H, PhCH_2), 4.84 (d, J = 3.0 Hz, 1 H, H1′), 5.36 (dd, J = 11.0, 9.0 Hz, 1 H, H5), 7.25 (m, 5 H, *Ph*CH_2). Anal. Calcd for $C_{24}H_{36}O_7Si$: C, 62.04; H, 7.81. Found: C, 61.91; H, 7.98.

The preparative thin-layer chromatogram also provided the more polar minor component **12a** as a colorless syrup, 41.4 mg, which also gave a syrupy acetate **12c**: $[\alpha]^{25}_D$ +72.6° (*c* 0.90, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.05 (s, 6 H, $SiCH_3$), 0.91 (s, 9 H, *t*-Bu), 1.92 (s, 3 H, Ac), 2.20 (ddd, J = 10.0, 5.0, 3.5 Hz, 1 H, H4), 3.03 (d, J = 4.0 Hz, H2), 3.20 (dd, J = 5.0, 4.0 Hz, 1 H, H3), 3.75 (m, 4 H), 4.10 (AB q, J = 12.5 Hz, $\Delta\delta$ = 0.35 ppm, 2 H, H1), 4.62 (AB q, J = 12.0 Hz, $\Delta\delta$ = 0.15 ppm, 2 H, PhCH_2), 4.65 (d, J = 3.5 Hz, 1 H, H1′), 5.55 (t, J = 10.0 Hz, 1 H, H5), 7.25 (m, 5 H, *Ph*CH_2). Anal. Calcd for $C_{24}H_{36}O_7Si$: C, 62.04; H, 7.81. Found: C, 62.15; H, 7.94.

(b) Sharpless–Michaelson Epoxidation[25] of 9b. A solution of the homoallylic alcohol **9b** (71.7 mg, 0.17 mmol), *tert*-butyl hydroperoxide (0.2 mmol), and vanadyl acetylacetonate (ca. 2 mg) in dry benzene (3 mL) was stirred at 25 °C. After 40 h, the reaction was complete, and evaporation and column chromatography (C) provided **12a** as fine white needles, 53.1 mg (70%), with identical ^{1}H NMR data as the sample described above.

Stereoselective Formation of Dipyranoside 13. (a) To a stirred mixture of purified cuprous iodide[35] (2.2 g, 11.1 mol) in 50 mL of dry ether at −10 °C under argon was added dropwise methyllithium (22.2 mmol) in ether, and to the resulting colorless solution was added a solution of the epoxide **11a** (0.7582 g, 1.8 mmol) in 10 mL of dry ether. After 9 h at 0 °C, a new product (R_f 0.21, D) had formed. The reaction mixture was poured into ammonium hydroxide solution and extracted repeatedly with ether. The ether phases were dried ($MgSO_4$), filtered, and evaporated to give the title diol **13** as white plates, mp 121–123 °C, 0.7656 g (97%): $[\alpha]^{25}_D$ +19.4° (*c* 0.98, $CHCl_3$).

(b) A solution of the α-bicyclic olefin **21b** (48.2 mg, 0.115 mmol) in dry tetrahydrofuran (1 mL) was added dropwise to a borane–tetrahydrofuran (0.46 mL of 1 M stock solution) solution cooled to 0 °C under argon. The reaction mixture was stirred at this temperature for 3 h. Sodium hydroxide (0.5 mL of a 2 M aqueous solution) was then added dropwise, followed by like addition of 30% hydrogen peroxide (0.5 mL). After warming to room temperature (0.5 h), the reaction mixture was extracted with ether (3 × 5 mL). The combined organic layers were washed with 5% sodium bisulfite and saturated sodium chloride solutions. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was dissolved in 1:1 ethyl acetate–hexane, filtered through a short column of silica gel, and concentrated to give **13** (36.5 mg, 74%) as a white solid identical with that in part (a): TLC R_f 0.29 (D); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.10 (s, 6, $SiMe_2$), 0.91 (s, 9, *t*-BuSi), 1.09 (d, 3, J_{7,CH_3} = 6.5 Hz, CH_3), 1.70 (m, 1, H2), 1.80 (m, 1 H2), 2.76 (br s, 1, OH, D_2O ex), 3.10 (br s, 1, OH, D_2O ex), 3.50 (t, 1, $J_{5,6}$ = 7.2 Hz, H6), 3.65 (dd, 1, $J_{1,2}$ = 5.0 Hz, $J_{1a,1e}$ = 11.5 Hz, H1a), 3.82–4.14 (m, 6), 4.72 (AB q, 2, J = 11.5 Hz, $\Delta\delta$ = 0.14 ppm, PhCH_2), 5.20 (d, 1, $J_{1,4}$ = 3.1 Hz, H1′), 7.36 (m, 5, *Ph*CH_2). Anal. Calcd for $C_{23}H_{38}O_6Si$: C, 62.98; H, 8.73. Found: C, 62.70; H, 8.80.

Preparation of Diol 15a from Diol 13a via Ketone 14. The diol **13** (413.3 mg, 0.94 mmol) was treated with pyridinium chlorochromate[30] **29** (940 mg, 3.8 mmol) and Celite (1 g) in 20 mL of dry CH_2Cl_2 and 30 mL of dry benzene. After 1.5 h, TLC (D), indicated the presence of a new product (R_f 0.43) presumed to be **14**. The mixture was diluted with dry ether (50 mL) and filtered through a short Florisil column directly into a slurry of lithium aluminum hydride (50 mg) in dry ether (70 mL) at 20 °C. After 1 h, the excess hydride was quenched with alternating 0.5-mL portions of 20% KOH and water until the ether mixture became white, and then Celite (2 g) was added. The mixture was filtered through Celite, and the solid residue washed with EtOAc TLC (D) indicated a new product (R_f 0.39). Column chromatography (D) provided the title diol **15a** as white needles, mp 77–80 °C, 361.5 mg (87%): $[\alpha]^{25}_D$ +31.9° (*c* 0.37, $CHCl_3$); ^{1}H NMR (100 MHz) δ 0.10 and 0.07 (2 s, 6 H, $SiCH_3$), 0.92 (s, 9 H, *t*-Bu), 1.20 (d, J = 7.3 Hz, 3 H, $C2CH_3$), 1.95 (m, 1 H, H2), 2.19 (ddd, J = 3.0, 5.0 Hz, 1 H, H4), 2.80 (br s, 2 H, OH, D_2O ex), 3.50 (t, J = 9.0 Hz, 1 H, H6), 3.92 (m, 6 H), 4.31 (dd, J = 10.5, 8.5 Hz, 1 H, H5), 4.65 (d, J = 3.0 Hz, 1 H, H1′), 4.75 (AB q, J = 11.3 Hz, 2 H, PhCH_2), 7.38 (s, 5 H, *Ph*CH_2). Anal. Calcd for $C_{23}H_{38}O_6Si$: C, 62.98; H, 8.73. Found: C, 63.33; H, 9.10.

This was acetylated to the diacetate **15b**: ^{1}H NMR (200 MHz) δ 0.06 (s, 6 H, $SiCH_3$), 0.91 (s, 9 H, *t*-Bu), 1.24 (d, J = 7.5 Hz, 3 H, $C2CH_3$), 2.04 and 1.90 (2 s, 6 H, $COCH_3$), 2.46 (ddd, J = 10.4, 5.8, 3.6 Hz, 1 H, H4), 3.62 (dd, J = 9.0 8.5 Hz, 1 H, H6), 4.62 (AB q, J = 11.6 Hz, $\Delta\delta$ = 0.14 ppm, 2 H, PhCH_2), 4.80 (d, J = 3.6 Hz, 1 H, H1′), 5.12 (t, J = 5.8 Hz, 1 H, H3), 5.74 (dd, J = 10.4, 8.5 Hz, 1 H, H5), 7.36 (m, 5 H, *Ph*CH_2). Irradiation of the $C2CH_3$ signal at δ 1.24 produced an 18% NOE enhancement of the H5 signal at δ 5.74.

Preparation of 17a from 13a by Oxidation to 13 and Epimerization to 16 Followed by Reduction. In a subsequent experiment, the oxidation product from **13** was diluted with ether and filtered through Celite, and the solvents were evaporated to yield the unstable ketone **14**, IR 1722 (s) cm^{-1}. This was dissolved in dry MeOH (30 mL) containing triethylamine (1 mL). TLC (D) indicated a new product (R_f 0.51) after 2 h at 20 °C, assumed to be ketone **16**, IR 1718 (s) cm^{-1}. The material was dissolved in dry ether (30 mL) and treated with lithium tri-*tert*-butyoxyaluminohydride (600 mg). After 1 h, the reaction was worked up as described above (for **15a**) to give title diol **17a** [R_f 0.40 (D)] as a pale yellow solid. Acetylation (see the General Procedures) and column chromatography (B) provided the diacetate **17b**, 208.0 mg (73%): ^{1}H NMR (600 MHz) δ 0.10 and 0.90 (2 s, 6 H, $SiCH_3$), 0.79 (d, J = 7.5 Hz, 3 H, $C2CH_3$), 0.93 (s, 9 H, *t*-Bu), 2.03 and 1.92 (2 s, 6 H, $COCH_3$), 2.39 (m, 1 H, H2), 2.46 (ddd, J = 11.0, 4.0, 2.2 Hz, 1 H, H4), 3.13 (dd, J = 12.0, 11.6 Hz, 1 H, H1a), 3.68 (t, J = 9.6, 1 H, H6), 3.87 (AB of ABX, J_{AB} = 11.5 Hz, $\Delta\delta$ = 0.10 ppm, J_{AX} = J_{BX} = 2.5 Hz, 2 H, H8), 3.90 (dt, J = 9.6, 2.5, 2.5 Hz, 1 H, H7), 3.99 (dd, J = 12.0, 4.9 Hz, 1 H, H2e), 4.63 (AB q, J = 12.0 Hz, $\Delta\delta$ = 0.12 ppm, 2 H, PhCH_2), 4.66 (dd, J = 11.6, 4.0 Hz, 1 H, H3), 4.81 (d, J = 2.2 Hz, 1 H, H1′), 5.73 (dd, J = 11.0, 9.6 Hz, 1 H, H5), 7.30 (m, 5 H, *Ph*CH_2).

Conversion of 15a to Diacetonide 29, Thence to Monoacetonide 30a, and to Dibenzyl Ether 31. The diol **15a** (2.0609 g, 4.71 mmol) was dissolved in 200 mL of dry MeOH containing 2 drops of trifluoroacetic acid and hydrogenated with 10% palladium on carbon (200 mg) at 70 psi and 25 °C. After 24 h, TLC (acetone) indicated a homogeneous product, and the solution was filtered and evaporated to give the crude tetrol as a white solid. This material was dissolved in dry THF (100 mL) and treated with 2,2-dimethoxypropane and PPTS[34] (50 mg) at 20 °C for 25 h, when TLC indicated three products. The solvents were evaporated and fresh dry THF (100 mL) and DMP (50 mL) added, and after an additional 24 h, only one product (R_f 0.33) remained. The THF solution was diluted with ether (200 mL), washed with 5% KOH solution, dried (Na_2SO_4), filtered, and evaporated to yield the labile di-*O*-isopropylidene derivative **29** as a pale yellow syrup, TLC R_f 0.33 (D). The material was dis-

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solved in dry MeOH (150 mL) and treated with PPTS (20 mg) at 20 °C, and after 2 h, a new product (R_f 0.13) had formed. After addition of 5 drops 20% KOH, the MeOH was evaporated and the residue taken up in ether (100 mL). The ether was washed with bicarbonate solution, dried over Na_2SO_4, filtered, and evaporated to give the mono-*O*-isopropylidene derivative **30a** as a pale yellow solid, 1.0316 g (81%), TLC R_f 0.13 (D). This compound (728 mg, 2.83 mmol) was dissolved in 100 mL of dry DMF and benzylated in the standard manner. After 18 h, the reaction mixture was diluted with water and extracted with ether. The ether phase was washed with 5 M NH_4Cl solution, dried ($MgSO_4$), filtered, and evaporated to yield a syrup [TLC R_f 0.54 (D)], which was dissolved in dry MeOH (80 mL) and treated with *p*-toluenesulfonic acid monohydrate (20 mg) at 20 °C. After 20 min, a new product (TLC R_f 0.19) was observed, and the reaction was quenched by addition of solid K_2CO_3 (200 mg) and the solvent evaporated. The residue was extracted with ether (100 mL). The ether phase was washed with water, dried over $MgSO_4$, filtered, and evaporated. Column chromatography (E) provided the title compound **31** as a colorless syrup, which crystallized from benzene–hexane as white plates, mp 108–108.5 °C, 779.0 mg (69%): $[\alpha]^{25}_D$ −34.7° (*c* 0.49, $CHCl_3$); ^1H NMR (200 MHz) δ 1.35 (d, *J* = 7.4 Hz, 3 H, $C2CH_3$), 2.12 (m, 1 H, H2), 2.40 and 2.00 (2 br s, 2 H, OH, D_2O ex), 2.45 (ddd, *J* = 9.0, 5.0, 2.8 Hz, 1 H, H4), 3.56 (t, *J* = 9.0 Hz, 1 H, H6), 3.59 (dd, *J* = 12.4, 3.0 Hz, 1 H, H1a), 3.73 (t, *J* = 5.0 Hz, 1 H, H3), 3.79 (m, 2 H, H8), 3.92 (br d, *J* = 9.0 Hz, H7, and dd, *J* = 12.4, 2.0 Hz, H1e, 2 H), 3.95 (t, *J* = 9.0 Hz, 1 H, H5), 4.66 (AB q, *J* = 12.2 Hz, Δδ = 0.11 ppm, 2 H, $PhCH_2$), 4.69 (d, *J* = 2.8 Hz, 1 H, H1′), 4.75 (AB q, *J* = 11.5 Hz, Δδ = 0.40 ppm, 2 H, $PhCH_2$), 7.30 (m, 10 H, $PhCH_2$).

1,6-Anhydro-4-*O*-benzyl-2-*C*-[3′-[(*tert*-butyldimethylsilyl)oxy]-2′-methylprop-1′(*Z*)-enyl]-β-D-glucopyranose (19a) and Its Desilylated Analogue 19c. *n*-Butyllithium (1 equiv of a hexane solution) was added dropwise to a cooled solution (−78 °C) of the silylated derivative **18b** (12.0 g, 0.0384 mol), prepared as described in the General Procedures, in dry diethyl ether (75 mL), and the reaction mixture was stirred under argon for 0.5 h. This solution was added dropwise (via a double-tipped needle) to an anhydrous magnesium bromide–ether solution generated[33] in situ by adding ethylene bromide (6.74 g, 0.0359 mol) to magnesium turnings (0.871 g, 0.0359 mol) in anhydrous ether (100 mL) under argon. The reaction mixture was stirred at room temperature for 1 h. The solid benzyl epoxide **1** (6.00 g, 0.0256 mol) was added to the white slurry and stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated ammonium chloride solution (100 mL) and extracted with ether. The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (C) gave **19a** (6.46 g, 60%) as a colorless oil. The *tert*-butyldimethylsilyl protecting group was removed from compound **19a** (1.89 g, 4.49 mmol) as described above for **3a**→**3b**, and the residue was purified by flash chromatography (D), followed by (E) to give a white amorphous solid: mp 94–95 °C (recrystallized from ether–hexane); TLC R_f 0.15 (E); $[\alpha]^{25}_D$ −13.0° (*c* 1.04, $CHCl_3$); IR ($CDCl_3$) 3340, 2900, 1121, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.85 (s, 3, CH_3), 2.04 (br s, 1, OH, D_2O ex), 2.66 (dd, 1, $J_{2,3}$ = 4.3 Hz, $J_{1',2}$ = 10.5 Hz, H2), 2.85 (br s, 1, OH, D_2O ex), 3.40 (d, 1, $J_{3,4}$ = 4.0 Hz, H4), 3.60 (m, 1 H3), 3.69 (dd, 1 $J_{5,6}$ = 5.1 Hz, $J_{6,6'}$ = 7.4 Hz, H6), 3.96 (d, 1, H6′), 4.10 (AB q, 2, *J* = 12.0 Hz, Δδ = 0.24 ppm, H3′), 4.57 (d, 1, H5), 4.66 (s, 3, $PhCH_2$), 5.31 (s, 1, H1), 5.46 (d, 1, H1′), 7.28 (m, 5, $PhCH_2$). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.64; H, 7.24. Found: C, 66.76; H, 7.30.

1,6-Anhydro-4-*O*-benzyl-2-bromo-2-deoxy-β-D-glucopyranose (20). A side product in the formation of **19a** was found to be the bromohydrin **20**. An authentic sample was prepared as follows. The solid benzyl epoxide **1** (25 mg, 0.11 mmol) was added to an anhydrous magnesium bromide–ether solution generated in situ by adding ethylene bromide (41 mg, 0.22 mmol) to magnesium turnings (5.4 mg, 0.22 mmol) in anhydrous ether (2 mL) under argon.[33] The reaction was complete after stirring at room temperature for 1 h. The reaction mixture was quenched with saturated ammonium chloride solution (1 mL) and extracted with ether. The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The bromide **20** (29.5 mg, 85%) was obtained as a colorless oil: TLC R_f 0.20 (B); $[\alpha]^{18}_D$ +19.9° (*c* 1.39, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.50 (d, 1, $J_{3,OH}$ = 6.2 Hz, OH, D_2O ex), 3.41 (m, 1, H4), 3.71 (dd, 1, $J_{5,6}$ = 5.5 Hz, $J_{6,6'}$ = 7.5 Hz, H6′), 3.78 (br d, 1, $J_{2,3}$ = 3.2 Hz, H2), 3.99 (d, 1, H6), 4.16 (m, 1, H3), 4.64 (m, 1, H5), 4.71 (AB q, 2, *J* = 12.2 Hz, Δδ = 0.11 ppm, $PhCH_2$), 5.67 (s, 1 H1), 7.30–7.58 (m, 5, $PhCH_2$). Anal. Calcd for $C_{13}H_{15}BrO_4$: C, 49.54; H, 4.80. Found: C, 49.50; H, 4.86.

Conversion of Bromohydrin 20 into the Epoxide 13. A freshly made solution of sodium methoxide (1.25 g of sodium metal) in absolute methanol (50 mL) was added dropwise to a cooled solution (0 °C) of the bromohydrin **20** (3.5 g, 10.9 mmol) in chloroform (100 mL). Upon complete addition, the reaction mixture was warmed slowly to room temperature and stirred for 3 h. After this time, a single new product was observed by TLC (D). The reaction mixture was diluted with water (150 mL) and extracted with methylene chloride. The combined organic portions were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was recrystallized from ether–hexane to give the benzyl epoxide **1** (2.35 g, 92%) as a white amorphous solid. The ^1H NMR spectrum of this material was identical to that of the authentic epoxide **1**.

Acid-Catalyzed Reaction for Formation of 21 and 22 from 19. (a) Preliminary Studies. The preliminary studies for the cyclization of **19** are shown in Table I. The scale of the reactions was 75–100 mg throughout the study. All reactions were monitored by TLC (E). Upon completion, all reactions were neutralized with saturated sodium bicarbonate solution, extracted with either methylene chloride or ether and ethyl acetate, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by filtering through a short silica gel column with ethyl acetate. The mixture of the bicyclic olefins **21a** and **22a** was obtained as a crystalline solid. Separation of these anomers by chromatography or fractional recrystallization was extremely difficult at this stage. The α/β (**21a**/**22a**) ratios were determined by high-field ^1H NMR from the integration of the anomeric protons. Some of the physical properties of the α/β mixture are as follows: TLC R_f 0.34 (2:1 ethyl acetate–hexane); ^1H NMR (200 MHz, $CDCl_3$) δ 1.62 (s, 3, CH_3), 2.01–2.34 (m), 3.33–3.55 (m), 3.71–4.02 (m), 4.24 (br s, 2, H1), 4.36 (d, 1, $J_{1',4}$ = 7.4 Hz, H1[β]), 4.65–4.86 (m), 4.94 (d, 1, $J_{1',4}$ = 2.8 Hz, H1′[α]), 5.57–5.70 (m, 1, H3), 7.26–7.40 (m, 5, $PhCH_2$).

(b) Optimized Conditions for Obtaining 21a. The epoxide **1** was opened, as described above, using the Grignard reagent prepared from the vinyl iodide **18c**. (The latter was prepared from **18a** by the general conditions for obtaining methoxymethyl ethers.) The resultant alcohol **19b**, obtained in 75% yield (20.0 g, 0.057 mol), was dissolved in ether (600 mL) and stirred with 6 M hydrochloride acid (14 mL) at room temperature for 20 h. The reaction mixture was neutralized with saturated sodium bicarbonate solution (300 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The ^1H NMR spectrum of the crude oil indicated a 12:1 mixture of **21a** and **22a**, although it was homogeneous on TLC (R_f 0.4, ethyl acetate). Recrystallization from petroleum ether–ethyl acetate and flash chromatography of the mother liquor afforded a combined yield of a white solid (11.6 g, 66% from **19b**), together with the uncyclized diol **19c** (1.7 g, 10%) derived from **19b** by cleavage of the methoxymethyl ether. The diol **19c** was resubjected to the above reaction conditions and a similar ratio of **21a** and **22a** (0.9 g, 5% from **19b**) resulted. A mixture of **21a** and **22a** (319 mg, 1.04 mmol) was silylated selectively at the primary alcohol (see the General Procedures). Flash chromatography (B) gave the α anomer **21b** (286 mg, 61%) as a colorless syrup, TLC R_f 0.31 (B), $[\alpha]^{19}_D$ +154° (*c* 1.64, $CHCl_3$), and the β epimer **22b** was obtained as a colorless syrup (84.3 mg, 18%), TLC R_f 0.21 (B), $[\alpha]^{19}_D$ +18° (*c* 0.91, $CHCl_3$). Alternatively, the anomers could be separated as the diacetates. A mixture of the bicyclic olefins **21a** and **22a** (1.47 g, 4.78 mmol) was acetylated, and the diacetate mixture (1.74, 93%) was purified by flash chromatography (D). Fractional crystallization of a portion of the diacetate mixture (650 mg) from ether–petroleum ether (bp 35–60 °C) gave the α isomer **21c** (306 mg) as a white crystalline solid. A second crop of material (151 mg), which was obtained from the mother liquor, was predominantly the α isomer **21c**. For **21c**: mp 109–110 °C (from ether–petroleum ether); TLC R_f 0.23 (D); $[\alpha]^{25}_D$ +192° (*c* 1.18, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$)

δ 1.58 (s, 3, CH_3), 2.07 (s, 3, CH_3CO_2), 2.12 (s, 3, CH_3CO_2), 2.25 (m, 1, H2), 3.53 (t, 1, $J_{3,4} = J_{4,5} = 9.0$ Hz, H4), 4.05–4.42 (m, 5, H3′, H5, H6), 4.57 (AB q, 2, $J = 10$ Hz, $\Delta\delta = 0.06$ ppm, PhCH_2), 4.95 (d, 1, $J_{1,2} = 2.8$ Hz, H1), 5.25–5.40 (m, 2, H1′, H3), 7.30–7.40 (m, 5, *Ph*CH_2). Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.61; H, 6.71. Found: C, 64.49; H, 6.78.

Chromatographic fractionation (D) of the mother liquor afforded the β-diacetate **22c** as a white crystalline solid: mp 119–121 °C (from ether–petroleum ether); TLC R_f 0.19 (D); $[\alpha]^{25}_D$ +43.0° (*c* 1.04, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.62 (br s, 3, CH_3), 2.07 (s, 3, CH_3CO_2), 2.08 (s, 3, CH_3CO_2), 2.33 (m, 1, H4), 3.61 (t, 1, $J_{5,6} = 8.6$ Hz, $J_{6,7} = 9.7$ Hz, H6), 3.75 (ddd, 1, $J_{6,7} = 9.7$ Hz, $J_{7,8} = 2.2$ Hz, $J_{7,8} = 4.6$ Hz, H7), 4.25–4.41 (m, 4, H1, H8), 4.43 (d, 1, $J_{1',4} = 7.6$ Hz, H1′), 4.59 (AB q, 2, $J = 11.0$ Hz, PhCH_2), 5.04 (dd, 1, $J_{4,5} = 11.8$ Hz, $J_{5,6} = 8.6$ Hz, H5), 5.22 (m, 1, H3), 7.25–7.40 (m, 5, *Ph*CH_2). Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.61; H, 6.71. Found: C, 64.61; H, 6.78.

Preparation of Epoxide 23b. (a) From 21c. A solution containing the α-bicyclic olefin **21c** (702 mg, 1.80 mmol) and *m*-chloroperbenzoic acid (466 mg, technical grade 80–85%) in dry chloroform (40 mL) was stirred for 4 h at room temperature. After this time, the reaction mixture was diluted with methylene chloride and then washed with a 5% sodium carbonate solution and saturated sodium chloride solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The solid residue (622 mg, 85%) was sufficiently pure for subsequent reactions. An analytical sample of **23b** was obtained by recrystallization: mp 98–99 °C (from ether–hexane); TLC R_f 0.29 (E); $[\alpha]^{25}_D$ +89.5° (*c* 1.68, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.33 (s, 2, CH_3), 2.05 (s, 3, CH_3CO_2), 2.09 (s, 3, CH_3CO_2), 2.36 (m, 1, H4), 3.05 (br d, 1, $J_{3,4} = 2.1$ Hz, H3), 3.55 (t, 1, $J_{5,6} = J_{6,7} = 9.5$ Hz, H6), 3.90–4.40 (m, 5), 4.61 (s, 2, PhCH_2), 4.94 (d, 1, $J_{1',4} = 3.5$ Hz, H1′), 5.44 (dd, 1, $J_{4,5} = 10.5$ Hz, H5), 7.34 (m, 5, *Ph*CH_2). Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.59; H, 6.45. Found: C, 62.13; H, 6.45.

(b) From a Mixture of 21c and 22c. The 3.5:1 mixture of bicyclic olefins **21c** and **22c** (4.00 g, 10.20 mmol) was treated with *m*-chloroperbenzoic acid (2.64 g, technical grade 80–85%) in dry chloroform (100 mL), as described above. The solid residue was fractionated by flash chromatography (E) to give epoxide **23b** (2.696 g, 65%). Two minor products (0.800 g, 19%) were in the epoxide mixture. For **25a**: mp 143–144 °C (from ether–hexane); TLC R_f 0.15 (E); $[\alpha]^{25}_D$ +23° (*c* 0.64, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (s, 3, CH_3), 1.90–2.21 (m, 1, H3), 2.06 (s, 3, CH_3CO_2), 2.10 (s, 3, CH_3CO_2), 2.91 (s, 1), 3.55–3.73 (m, 2), 3.88 (d of AB q, 1, $J = 14.0$ Hz), 4.10–4.26 (m, 4), 4.39 (dd, 1, $J = 1.9$ Hz, $J = 12.0$ Hz), 4.61 (AB q, 2, $J = 10.5$ Hz, $\Delta\delta = 0.07$ ppm, PhCH_2), 5.20 (dd, 1, $J = 8.0$ Hz, $J = 12.5$ Hz), 7.22–7.45 (m, 5, *Ph*CH_2). Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.59; H, 6.45. Found: C, 62.27; H, 6.24.

For **25b**: mp 135–136 °C (from ether–hexane); TLC R_f 0.13 (E); $[\alpha]^{25}_D$ +64° (*c* 0.32, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (s, 3, CH_3), 1.94–2.10 (m, 1, H4), 2.05 (s, 3, CH_3CO_2), 2.07 (s, 3, CH_3CO_2), 3.10 (s, 1), 3.55–3.72 (m, 2), 4.05–4.27 (m, 3), 4.37 (br d, 1, $J = 11.5$ Hz), 4.53 (d, 1, $J = 8.0$ Hz), 4.61 (AB q, 2, $J = 11.0$ Hz, $\Delta\delta = 0.08$ ppm, PhCH_2), 5.34 (dd, 1, $J = 8.0$ Hz, $J = 11.2$ Hz), 7.20–7.40 (m, 5, *Ph*CH_2). Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.59; H, 6.45. Found: C, 61.78; H, 6.72.

Hydrolysis of Epoxide 23b To Give 26a. A solution of epoxide **23b** (2.70 g, 6.64 mmol) in acetonitrile–1% perchloric acid (2:1 v/v, 200 mL) was stirred at 35–40 °C for 48 h. The acid was neutralized with triethylamine (5 mL), and the solution was concentrated in vacuo. Carbon tetrachloride was added and evaporated off under reduced pressure to remove the water as an azetrope. The solid residue was purified by flash chromatography to give the diol **26a** [1.68 g, 60%, R_f 0.15 (E)] and the triol **26b** [0.87 g, 34%, R_f 0.05 (E)]. A mixture of the two compounds was exhaustively acetylated to give a single tetraacetate as a colorless syrup. TLC R_f 0.18 (C); $[\alpha]^{19}_D$ +69.4° (*c* 1.78, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.35 (s, 3, CH_3), 2.07 (s, 3, CH_3CO_2), 2.08 (s, 3, CH_3CO_2), 2.10 (s, 3, CH_3CO_2), 2.10 (m, 1, H4), 2.16 (s, 3, CH_3CO_2), 3.44 (t, 1, $J_{5,6} = J_{6,7} = 9.0$ Hz, H6), 3.60 (d, 1, $J_{1a,1e} = 13.3$ Hz, H1a), 4.00–4.34 (m, 3, H7, H8), 4.52 (s, 2, PhCH_2), 4.62 (dd, 1, $J_{1e,3} = 2.5$ Hz, H3), 5.01 (d, 1 $J_{1',4} = 3.4$ Hz, H1′), 5.24 (t, 1, $J_{3,4} = 3$ Hz, H3), 5.70 (dd, 1, $J_{4,5} = 11.5$ Hz, H5), 7.30 (m, 5, *Ph*CH_2). Anal. Calcd for $C_{25}H_{32}O_{11}$: C, 59.05; H, 6.34. Found: C, 58.80; H, 6.60.

Preparation of the Monoacetonide 27. An oven-dried 250-mL three-neck round-bottom flask fitted with a dry ice condenser, magnetic stirring bar, and a potassium hydroxide drying tube was charged with a mixture of **26a** (539 mg, 1.27 mmol) and **26b** (252 mg, 0.661 mmol) dissolved in dry dimethoxyethane (50 mL). The reaction mixture was cooled to −78 °C, and anhydrous ammonia (150 mL, distilled from sodium metal) was condensed into the reaction flask. Small chunks of sodium metal were added until a deep blue color persisted for at least 5 min. The reaction mixture was quenched with excess solid ammonium chloride, and the ammonia was slowly evaporated by removing the cooling bath. The reaction mixture was concentrated in vacuo, and the solid residue was dried in a vacuum desicator over potassium hydroxide for 24 h. The resulting crude residue was dissolved in freshly distilled dimethylformamide (50 mL) and treated with 2,2-dimethoxypropane (5 mL) and pyridinium *p*-toluenesulfonate[34] (~200 mg). The reaction mixture was stirred for 26–48 h under an argon atmosphere. After this time, powdered sodium carbonate (~1 g) was added to the reaction mixture and stirred for 0.5 h. After a vacuum filtration, the filtrate was concentrated in vacuo. The solid white residue was dissolved in ethyl acetate and filtered through a short silica gel column. Upon evaporation of the solvent, the acetonide **27** (535 mg, 95%) was obtained as a white amorphous solid: mp 218–219 °C (from chloroform–hexane); $[\alpha]^{19}_D$ +80° (*c* 0.69, absolute ethanol). IR ($CDCl_3$), 3455, 1264, 1026 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (s, 3, CH_3), 1.42 and 1.52 (2 s, 6, CMe_2), 1.84 (d, 1, OH, D_2O ex), 1.89 (s, 1, OH, D_2O ex), 1.97 (m, 1, H4), 2.52 (br s, 1, OH, D_2O ex), 3.47 (t, 1, $J = 9.1$ Hz), 3.64–4.11 (m, 5), 4.12 (m, 1), 4.44 (t, 1, $J = 10.2$ Hz). Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64. Found: C, 53.68; H, 7.50.

Formation of Dibenzyl Ether 28 from 27. The acetonide **27** (1.46 g, 5.03 mmol) was dissolved in dry dimethylformamide (25 mL) and benzylated, as described in the General Procedures. The reaction was complete after 18 h, and the crude residue was dissolved in absolute methanol (100 mL) and treated with *dl*-camphorsulfonic acid (100 mg) at room temperature for 3–4 h. Powdered sodium carbonate (5 g) was added, and after 0.5 h, the mixture was filtered and the filtrate concentrated in vacuo. The oily residue was purified by flash silica gel chromatography (1:1 ethyl acetate–hexane), and the diol **28** was obtained as a colorless gum. TLC R_f 0.33 (1:1 ethyl acetate–hexane); $[\alpha]^{20}_D$ +84.5° (*c* 1.01, $CHCl_3$); IR (neat) 3435, 3020, 2880, 1445, 1062, 730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (s, 3, CH_3), 1.71 (br s, 1, OH, D_2O ex), 1.87 (br s, 1, OH, D_2O ex), 2.12 (m, 1, H4), 3.44 (t, 1, $J_{6,7} = J_{5,6} = 8.9$ Hz, H6), 3.67–3.88 (m, 4), 4.16–4.70 (m, 8), 5.11 (d, 1, $J_{1',4} = 3.2$ Hz, H1′), 7.25–7.45 (m, 15, *Ph*CH_2). HRMS, *m/e* (M^+) calcd 520.2461, found 520.2464.

Acknowledgment. We thank Professor H. Paulsen of the University of Hamburg and Professor M. Cerny of Charles University for gifts of "levoglucosan".