periodically withdrawn from the reaction vessel (after a forerun was taken) into a cold vial which was immediately capped. All samples were analyzed within 24 h of collection, and control experiments established that the reaction did not proceed at a measurable rate (at 25 °C) during this time period. It was later shown that, for acetoacetylation reactions with alcohols and amines, similar kinetic data could be obtained from experiments which were run in a round-bottomed flask equipped with a reflux condenser.

Exchange of Dioxinone 1 with Hexadeuterioacetone. A solution of dioxinone **1** (2.241 g, 15.6 mmol) and acetone-d_6 (5 g, 78 mmol) was diluted to 50 mL with toluene, placed in the pressure bottle under 15 psi of N_2, and heated to 91.7 °C. The progress of the reaction was monitored as described in the general kinetic protocol, since the undeuterated and hexadeuterated materials were surprisingly easily separated by GC (t_r = 9.16 min for **1**-d_6 vs 9.24 min for protiated **1**). The rate was plotted as a function of time vs the logarithm of the percent of theoretical maximum deuterium incorporation (83.3%). The data were corrected for the slow decomposition of the dioxinone; approximately 8% of the dioxinone was lost to byproducts after 24 h at 91.7 °C. Dioxinone-**1**-d_6: MS, m/z = 148 ($M^{\bullet+}$, 22), 86 (72), 84 (51), 69 (53), 64 (37), 46 (98), 43 (100). Dioxinone **1**: MS, m/z = 142 ($M^{\bullet+}$, 16), 85 (60), 84 (28), 69 (32), 59 (19), 43 (100). Analysis of the reaction product (after concentration in vacuo) showed a reduction in the area of the integral associated with the methyl groups at C-2 (1.69 δ), confirming the incorporation of the CD_3 unit. No reduction (or D-C-H coupling) was noted for the proton resonance at C-5 or the protons on the methyl group at C-6.

Conversion of Isopropenyl Acetoacetate (8) to Dioxinone 1. In a 10-mL, round-bottomed flask was placed isopropenyl acetoacetate (0.030 g, 0.211 mmol), acetone (1.18 g, 21.1 mmol), and 3 mL of *p*-xylene. The flask, was tightly stoppered and immersed in the bath at 91.7 °C. Analysis by GC after 1 h showed complete conversion to dioxinone **1**.

Reaction of Isopropenyl Acetoacetate (8) with 1-Butanol. In a dry, 25-mL flask equipped with a condenser, a nitrogen inlet, and a stoppered sidearm was placed a solution of isopropenyl acetoacetate (62 mg, 0.436 mmol), 1-butanol (37 mg, 0.492 mmol), and *p*-dichlorobenzene (36 mg, internal standard) in 10 mL of *p*-xylene. This flask was immersed in a 91.7 °C constant temperature bath, and the reaction was monitored by GC as described above. After 1 h GC indicated complete conversion to **3b**. After correcting the data for the time the solution required to reach the elevated temperature, a rate constant of 9.2×10^{-4} s^{-1} was estimated for the process. This is in agreement with the 8.8×10^{-4} s^{-1} rate constant which was noted for a similar experiment which utilized 0.457 mmol of isopropenyl acetoacetate and 5.466 mmol 1-butanol. In a third experiment, isopropenyl acetoacetate (32 mg, 2.335 mmol), 1-butanol (208 mg, 2.870 mmol), and *p*-dichlorobenzene (284 mg) were diluted to 50 mL with *p*-xylene, placed in the pressure bottle, purged with nitrogen, and immersed in the 91.7 °C constant temperature bath. A value for k_1 was estimated from four data points to be 7.27×10^{-4} s^{-1} (standard deviation = 3.9×10^{-5}). The uncertainties associated with these rate constants are considerably greater than those for dioxinone **1** due to the faster rate of reaction and the larger experimental errors associated with the GC analysis of **8**.

Reaction of Isopropenyl Acetaoacetate (8) with Cyclohexanone. In a 10-mL, round-bottomed flask was placed 30 mg of isopropenyl acetoacetate (0.211 mmol), 200 mg of cyclohexanone (2.11 mmol), and 5 mL of xylene. The solution was immersed in the bath at 91.7 °C for 15 min. Analysis by GC showed complete conversion to the diketene-cyclohexanone adduct.

Reaction of Isopropenyl Acetoacetate (8) To Give Dehydroacetic Acid (5). In a small tube was placed 69 mg of isopropenyl acetoacetate (0.486 mmol), 52 mg of *p*-dichlorobenzene, and 0.15 mL of *p*-xylene. The solution was heated at 91.7 °C for 45 min. Analysis of the reaction mixture by GC and using response factors for **1** and **6** indicated **1** had been formed in 15% yield and **6** in 14% yield. GC/MS analysis suggested that 2,4,6-heptanetrione (**10**) and 2,6-dimethyl-4-pyrone were also present in the reaction mixture.

Reaction of 1-Butanol with 2-(4-Methoxyphenyl)-6-methyl-4*H*-1,3-dioxin-4-one (the Diketene-Anisaldehyde Adduct, 9). In a nitrogen-purged, 2-necked flask equipped with a condenser and thermocouple temperature regulator (Omega controller) was placed 25 mL of toluene. The toluene was heated to 91 °C, and a solution of the dioxinone (0.346 g, 1.57 mmol) and 1-butanol (315 mg) in 10 mL of toluene was added. Analysis by 60 MHz ^{1}H NMR spectroscopy showed ca. 50% conversion to butyl acetoacetate after 25 min and ca. 85% conversion after 50 min.

Spectroscopic Observation of Acetylketene. The apparatus consisted of a Mattson Cryolect Matrix Isolation GC-IR. This apparatus allows the effluent from an HP5890 GC to be trapped in an Ar matrix on a cold (5-12 K) gold-coated disk, from which the infrared spectrum is subsequently obtained. The GC conditions used were identical with those used in the kinetic experiments, and the transfer line between the GC and the cold disk was heated to 180-240 °C. The carrier gas contained approximately 1% Ar to provide the matrix medium. Under all conditions, acetylketene was observed. To increase the dilution of the acetylketene in the matrix, the split ratio was increased from ca. 20:1 to 100:1. This gave spectra which showed two distinct ketene absorption bands at 2142 and 2135 cm^{-1}.

Acknowledgment. We appreciate the many helpful suggestions provided by Prof. J. Peter Guthrie and Drs. John Hyatt and Dale Van Sickle. Dr. Rick Zimmerman provided expert technical assistance in isolating and observing acetylketene via GC-IR.

Registry No. 1, 5394-63-8; **2**, 691-45-2; **8**, 93304-66-6; **9**, 83559-41-5; butanol, 71-36-3; phenol, 108-95-2; dibutylamine, 111-92-2.

Supplementary Material Available: Tables that summarize the reaction conditions used in each individual experiment, the rate constants thus obtained, and an analysis of variance for each rate constant (4 pages). Ordering information is given on any current masthead page.

A Stereoselective Totally Synthetic Route to Methyl α-Peracetylhikosaminide

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Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received June 22, 1988*

Abstract: A synthesis of the title system from D-galactose has been achieved. The racemic galactose 1,2,3,4-bisacetonide is expanded to a C_7 heptulose, which is then extended to an undecose by a Lewis acid catalyzed cyclocondensation reaction. Racemic galactose was synthesized from furfural by a similar cyclocondensation reaction.

Hikizimycin (or anthelmycin **1**)[1a,b] (Figure 1) was isolated from the fermentation broths of a strain of *Streptomyces longissimus* and from *Streptomyces A-5*. While hikizimycin exhibits broad antibacterial properties, its potency is too weak to be of importance.[2] Of greater interest are its anthelmintic properties against a variety of common parasites. The synthesis of antiparasitic substances has been one of the concerns of our laboratory.[3]

(1) (a) Hamill, R. L.; Hoehn, M. H. *J. Antibiot., Ser. A* **1964**, *17*, 100. (b) Uchida, K.; Ichikawa, T.; Shimauchi, Y.; Ishikura, T.; Ozaki, A. *J. Antibiot.* **1971**, *76*, 259.

(2) Uchida, K.; Wolf, H. *J. Antibiot.* **1974**, *27*, 783. Gonzalez, A.; Vazquez, D.; Jimenez, A. *Biochem. Biophys. Acta* **1979**, *561*, 403.

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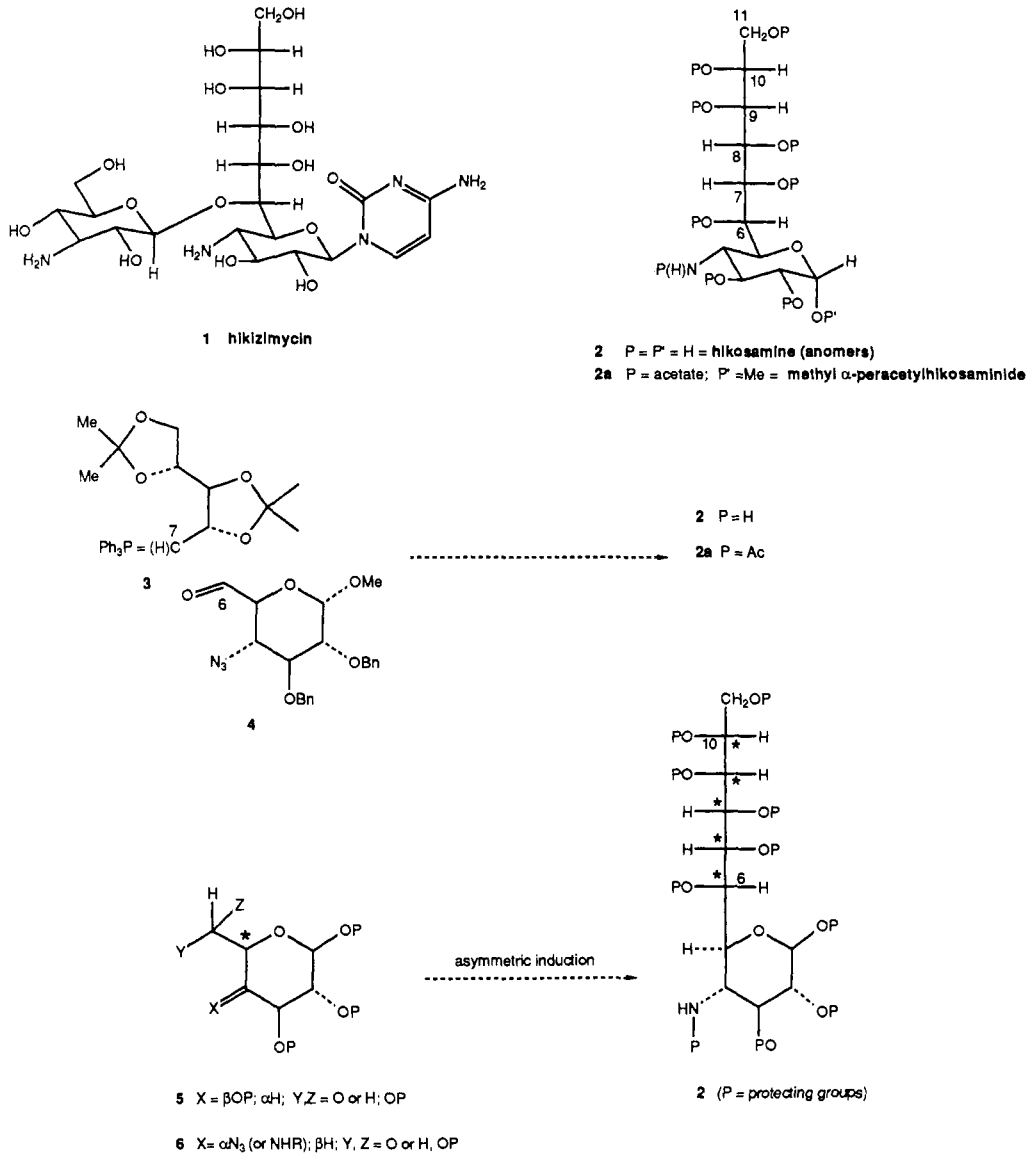

Figure 1.

However, it was the structure of hikizimycin which we found to be stimulating in terms of a total synthesis venture. In particular, the goal of a laboratory construction of the peroxygenated C_{11} long-chain hydrocarbon subunit would fall within our general program in the synthesis of complex or "higher" monosaccharides. Actually, mild degradation of **1** had resulted in the retrieval of the undecose hikosamine (**2**) which had been characterized as its peracetyl derivative (**2a**).[5a,b] The reconstitution of hikizimycin from hikosamine has never been described and, indeed, the difficulties in achieving such a reconstitution from undifferentiated **2** (or **2a**) should not be underestimated. However, it is not improbable that successes achieved in a synthesis of hikosamine could, with suitable modification, produce differentially substituted subgoal structures, which would be more suitable for reaching the natural product, **1**.

The synthesis of **2a** had been accomplished in a most interesting fashion by Secrist and Barnes.[6,7] The key feature of this effort involved the coupling of phosphorane **3**, derived from arabinose, with dialdose derivative **4**, obtained from galactose. Isomerization of the resultant *Z* 6,7 double bond to the *E* configuration was followed by cis hydroxylation, in the required sense, with osmium tetroxide.

The challenge we undertook[8] *was that of achieving control at the nine nonanomeric stereogenic centers of* **2** *by stereochemical communication.*[9] The hope was to synthesize a suitable galactose derivative generalized as **5** and to exploit its dissymmetry in the creation of the new stereogenic centers at carbons 6–10 of the hikosamine target. We preferred a galactose type **5** system relative to an aminoglucose derivative (cf. **6**). This preference arose from previous studies on chirality transmission from pyranoses to their side chains.[10,11] These investigations suggested a higher degree of stereoselectivity of the planned reactions when the 4-position of the pyranose bears an axial substituent as in galactose, rather than an equatorial function as in glucose. Indeed there were no

(3) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117. Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987**, *109*, 8119.
(4) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *21*, 15.
(5) (a) Uchida, K. *Agric. Biol. Chem.* **1976**, *40*, 395. (b) Vuilhorgne, M.; Ennifar, S.; Das, B. C.; Paschal, J. W.; Nagarajan, R.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 3289.
(6) Secrist, J. A., III; Barnes, K. D. *J. Org. Chem.* **1980**, *45*, 4526.
(7) Barnes, K. D. Ph.D. Thesis, The Ohio State University, 1980.
(8) For a preliminary account of some of this work, see: Danishefsky, S.; Maring, C. *J. Am. Chem. Soc.* **1985**, *107*, 7762.
(9) For a discussion of the concepts of stereochemical correlation and stereochemical communication in the synthesis of chiral arrays, see: Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59.
(10) Danishefsky, S.; DeNinno, M. *Tetrahedron Lett.* **1985**, *26*, 823.
(11) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809.

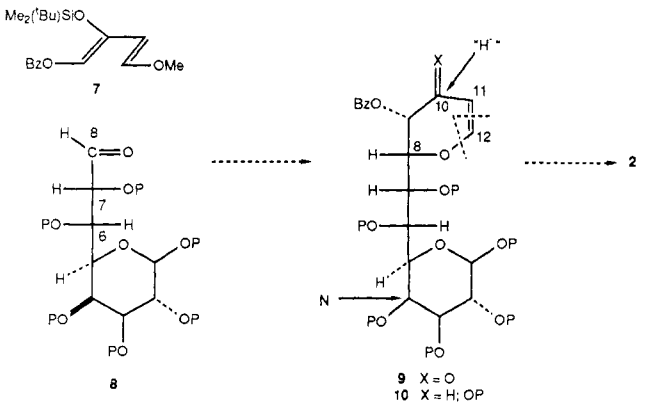

Figure 2.

data pertaining to chirality induction of structures bearing an equatorial nitrogen group at C_4 (**6**: Y = N_3; NHR).

Synthetic Planning. Two disconnection schemes were considered for extension of chirality from galactose matrices. In each instance, Lewis acid catalyzed cyclocondensation reactions of an α-oxygenated aldehyde with diene **7** would generate a new pyran ring in a defined relationship to the galactose. Further stereochemical relationships might be fashioned within the derived pyranoid matrices.[12,13] Disconnection of the pyran would serve to unveil the extensive side-chain stereochemistry of **2a**.

The first scheme involved a C_8 aldehyde, **8**. Cyclocondensation of **8** with diene **7** would afford a C_{12} ensemble, **9**. Reduction of the keto group of the dihydropyrone **9** by the method of Luche[14] would be the device for introducing the required stereochemistry at C_{10}. Oxidative cleavage between C_{11} and C_{12} would expose the former as the terminal carbon at the nonreducing end of the undecose. Installation of nitrogen at C_4 with inversion of configuration would be necessary to reach **2**. We defer for the moment consideration of the chemistry by which the C_8 aldehyde would be obtained. These general concepts are summarized under plan A (Figure 2).

Another approach contemplated the use of the C_7 aldehyde, **11**. Cycloaddition of **11** with **7** would afford a C_{11} ensemble shown as **12**. The keto group at carbon 9 would be reduced to afford the proper stereochemistry at that center in compound **13**. Syn-directed hydroxylation of **13** would provide the required configuration at carbon 10 (cf. **1**). Reductive opening of the newly fashioned pyranose *with maintenance of all the carbon atoms* would lead to **2**. Again we defer consideration of the precise route to aldehyde **11** and consider the overall scheme under plan B (Figure 3).

It is well to consider the stereochemical capabilities required of the cyclocondensation process, in each of these plans, to render them suitable for reaching hikosamine (Figure 4). We examine the two cyclocondensation reactions with respect to both the diastereofacial and topographic issues. Elsewhere we have analyzed such processes in general terms and have provided the descriptor phrases (CF, Cram Felkin; CC, chelation control) to classify the question of the diastereofacial outcome.[15] In the case

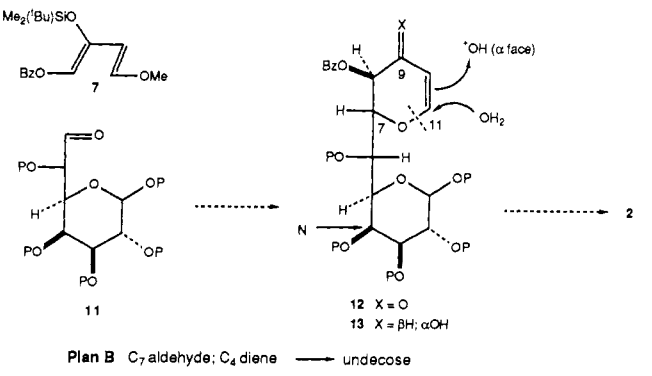

Figure 3.

at hand, the diastereofacial sense of reaction determines the connectivity between C_7 and C_8 of **9** or C_6 and C_7 in **12**. The other question is characterized as topographic (endo or exo alignment). In the case at hand, this question addresses the relationship of the side chain of the newly fashioned pyrone to its benzoyloxy group. On this outcome rests the connectivity between C_8 and C_9 of **9** or C_7 and C_8 of **12**. It is seen that plan A requires a Cram Felkin (CF) transition state in an endo topography to produce cis-disubstituted dihydropyrone **9**. Plan B could be realized via a chelation-controlled (CC) transition state in the exo fashion leading to a trans-substituted dihydropyrone. At the outset we were confident that through recourse to appropriate blocking groups and catalysts, either of these two combinations could be achieved. In each case there would also be required reduction of the keto group (C_{10} in plan A and C_9 in plan B) to an equatorial alcohol, another achievable subgoal.[14] Furthermore, in plan B it would be necessary to introduce a hydroxyl group from the β face at C_{10}, i.e., syn to the β-disposed hydroxyl at C_9. It was felt that this stereochemical requirement could be met.[16]

Below we describe our attempts to realize plan A and a most unexpected occurrence that prevented its implementation. We also report our successful attainment of plan B and describe a totally synthetic route to hikosamine by stereochemical communication.

Attempted Implementation of Plan A. A Major Surprise. Since our goal was achievement of the entire stereochemistry by communication rather than by coupling of two chiral fragments,[9] we had no hesitancy about operating in the racemic series in the exploratory phase. Our first efforts were directed toward the total synthesis of a suitable C_8 aldehyde. This phase proceeded well. Cyclocondensation of 4-(benzyloxy)crotonaldehyde[17] with diene **7** afforded a 57% yield of an 8:1 mixture of dihydropyrones (Figure 5).[18] The major product was the expected[19] cis-disubstituted isomer **14**. The minor product, not shown, was the trans system (not fully characterized). Stereoselective reduction of **14** ($NaBH_4$–$CeCl_3$) followed by silylation of **15** [$(Me_2(^tBu)SiOTf$] gave the equatorial silyloxy product, **16**. It proved to be a simple matter to distinguish the reactivities of the two centers of unsaturation. Reaction of **16** with MCPBA in methanol[20a,b] cleanly occurred at the "glycal" double bond. A 75% yield of the anomeric mixture **17** (β:α = 2:1) was obtained. Hydroxylation of the β anomer with

(12) Cf.: Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.

(13) For a review of much of the "in-matrix" methodology that we have used, see: Danishefsky, S.; Maring, C. *J. Am. Chem. Soc.* **1985**, *107*, 1269, and ref 4 above.

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

(15) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. Cram, D. J.; Knight, J. D. *Ibid.* **1952**, *74*, 5835. Cram, D. J.; Abd Elhafez, F. A.; Weingartner, H. *Ibid.* **1953**, *75*, 2293. Cram, D. J.; Greene, F. D. *Ibid.* **1953**, *75*, 6005. Cram, D. J.; Abd Elhafez, F. A.; Nyquist, H. L. *Ibid.* **1954**, *76*, 22. Cram, D. J.; Allinger, J. *Ibid.* **1954**, *76*, 4516. Cram, D. J.; McCarty, J. E. *Ibid.* **1954**, *76*, 5740. Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748. Cram, D. J.; Wilson, D. R. *Ibid.* **1963**, *85*, 1245. For the use of these terminological descriptors in our work, see: References 4 and 9.

(16) This type of transformation had been employed in our synthesis of talose; see: Reference 12.

(17) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891.

(18) For routine work, the diene mixture **24** (vide infra) was employed (see Experimental Section). Presumably only the *E*–*Z* diene is active.

(19) In reactions of diene **7** or diene mixture **14** with aldehydes wherein there are no addition sites of chelation along the chain, there is ordinarily high selectivity in favor of cis product.[13] When the aldehyde has ether functions at the α or β positions, the use of a ligatable catalyst favors an exo transition state which leads to trans product. Indeed, this principle was used subsequently in this work in the synthesis of the key pyrone **14** (vide infra and ref 27). In the (benzyloxy)crotonaldehyde case the trans compound was not characterized as a homogeneous entity, but its presence was inferred from crude spectra.

(20) (a) Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 157. (b) Frimer, A. A. *Synthesis* **1977**, 578.

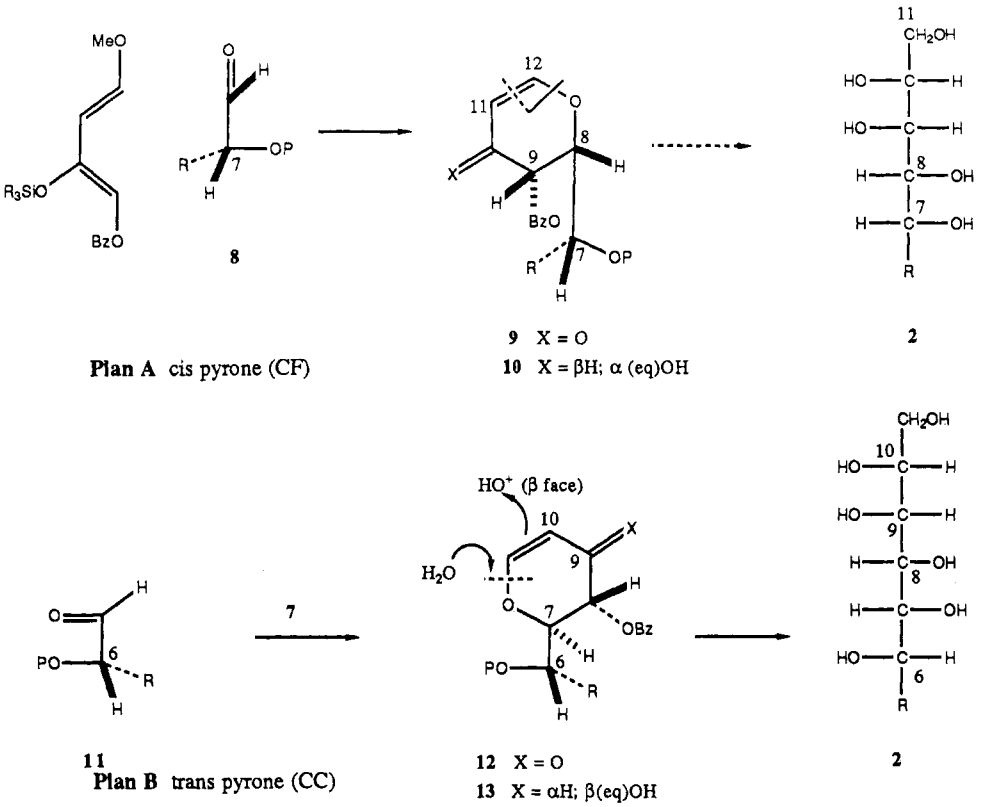

Figure 4.

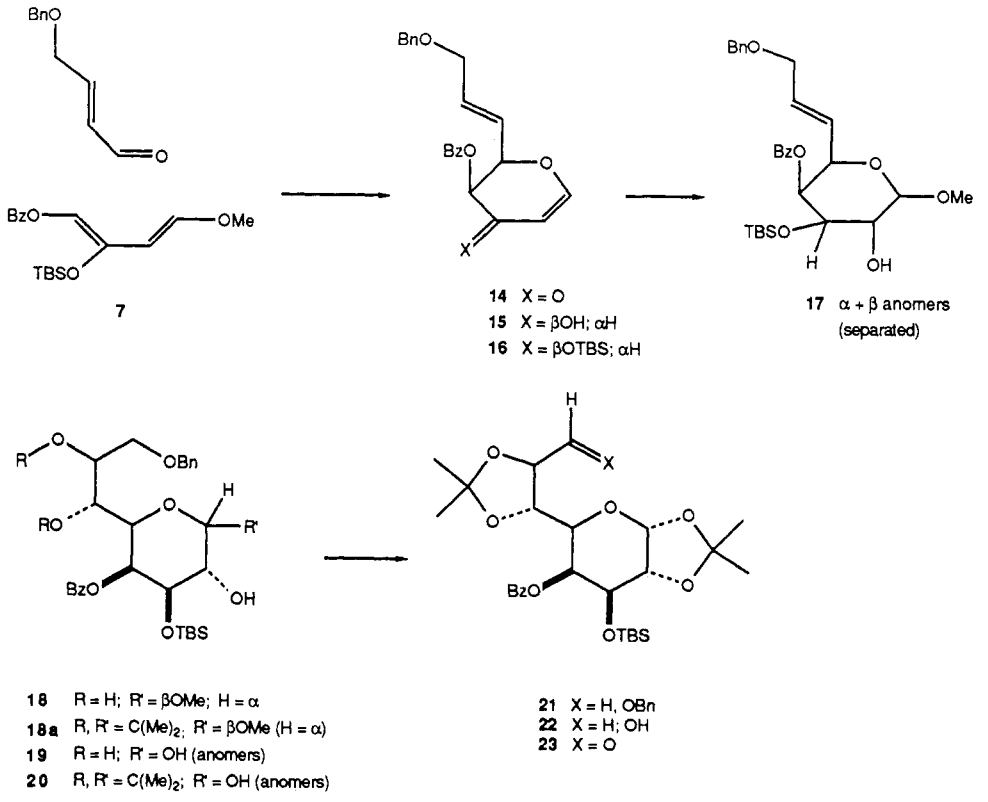

Figure 5.

catalytic osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide produced essentially a single triol which could be protected as its C_6–C_7 acetonide (**18a**).

While this chemistry did indeed nicely differentiate the ring and side-chain functionalities, it was eventually abandoned in favor of another variation in which the inconenience of the "anomeric problem" could be obviated. Treatment of **16** with catalytic osmium tetroxide[21] gave a four-component mixture of tetraols. These compounds could be grouped as an 8:1 mixture of side-chain diastereomers, each of which was a mixture of anomeric hydroxy compounds (only the major product **19** is shown). Acetalization

(21) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

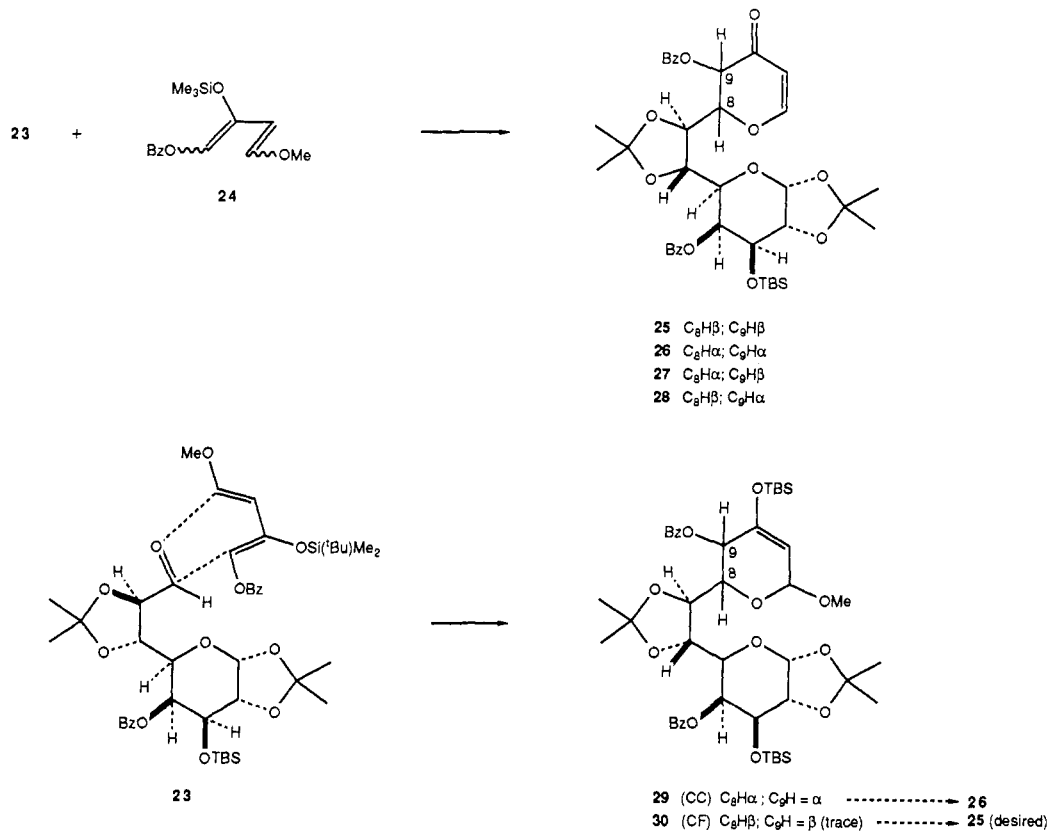

Figure 6.

with acetone in the presence of *p*-TsOH occurred exclusively at the side chain (cf. **20**). Addition of a catalytic amount of H_2SO_4 to this reaction mixture resulted in acetalization of the 1,2-diol. Purification by silica gel chromatography afforded a 73% yield of the homogeneous bisacetonide **21**.

At this point the stereochemistry at C_6 and C_7 of **21** could not be known with certainty. The assignment followed from precedents developed from earlier work in our laboratory[22] and that of Kishi and Brimacombe[23a,b] and Secrist.[6,7] Subsequent findings served to confirm the correctness of this assignment (vide infra). Cleavage of the benzyl ether followed by oxidation of the resultant alcohol **22** provided **23**, which was to function as the C_8 aldehyde contemplated in plan A.

A variety of reaction conditions were surveyed with the goal of realizing a clean CF *cis*-pyrone combination in the cyclocondensation reaction. Previous experience with homogeneous diene **7** or even with the three-component trimethylsilyl ether mixture **24** had revealed a high proclivity for *cis*-pyrone formation with aldehydes, where internal chelation was not an issue. As expected, the catalyst system BF_3 etherate had never evidenced any tendencies to produce the products of chelation control. When the reaction of **23** and **24** was carried out with BF_3 etherate in methylene chloride, a very low yield of a 2:1 ratio of *cis*-dihydropyrones now known (vide infra) to be **25** (desired) and **26**, respectively, was obtained (Figure 6). Apparently the use of BF_3 etherate was not compatible with survival of the labile acetonide blocking groups, since the starting aldehyde was substantially decomposed.

The use of the milder catalytic system zinc chloride in THF was probed. A dramatic change resulted. A 1:1 mixture of two dihydropyrone isomers **27** and **28** was obtained. However, they were each trans dihydropyrones. The ability of zinc chloride to mediate a chelation type of reacting conformation with α-oxygenated aldehydes had been previously established. Such chelation-controlled transition states are generally associated with a high preference for trans-disubstituted dihydropyrones. Thus, it was surprising to encounter a 1:1 mixture of facial isomers (CF:CC) in the trans series. In any case, as noted in the stereochemical analysis, we required a *cis*-dihydropyrone in the CF series, so the zinc chloride route was abandoned.

Instead we turned to the use of $Eu(hfc)_3$ as a mild Lewis acid catalyst,[24] which would hopefully be suitable for use in the presence of the array of labile blocking groups. Also, with aldehydes such as benzaldehyde or 2-phenylpropanal, this catalyst had afforded high CF selectivity. In the event, homogeneous diene **7** reacted with aldehyde **23** to afford a 49–55% yield of a 12.5:1 mixture of 1:1 adducts. Acidic hydrolysis of these compounds with trifluoroacetic acid afforded the previously encountered dihydropyrones **25** (desired) and **26**, wherein the latter arose from the major enol ether. At this stage, however, the stereochemistry of compounds **25** and **26** were not known with respect to their C_7–C_8 connectivity.

Fortunately, the major silyl enol ether was obtained in crystalline form, mp 169.5–171.5 °C. *X-ray diffraction studies of a single crystal revealed it to have the stereochemistry shown in* ***29***.[25] Needless to say, this was a most disheartening and unexpected result. At the diastereofacial level, $Eu(hfc)_3$ is mediating the cycloaddition via an apparent chelation-controlled mechanism. However, although this is ordinarily accompanied by formation of *trans*-pyran, in the case at hand the product was cis. These results imply that the previously formulated relationships between chelation control and exo addition are for some reason not applicable to this lanthanide-mediated process.[26]

From the standpoint of the synthesis of hikosamine, it meant that its derived dihydropyrone had the stereochemistry shown in formula **26** (formally arising from chelation control). Dihydro-

(22) Danishefsky, S. J.; DeNinno, M. P.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 3925.
(23) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. (b) Brimacombe, J. S.; Hanna, R.; Kabir, A. K. M. S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 823.
(24) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.
(25) This crystallographic determination was carried out by Dr. J. P. Springer of the Merck Co. Full data are available from the Ph.D. dissertation of Clarence Maring, Yale University, 1986.
(26) Midland, M. M.; Graham, R. S. *J. Am. Chem. Soc.* **1984**, *106*, 4294.

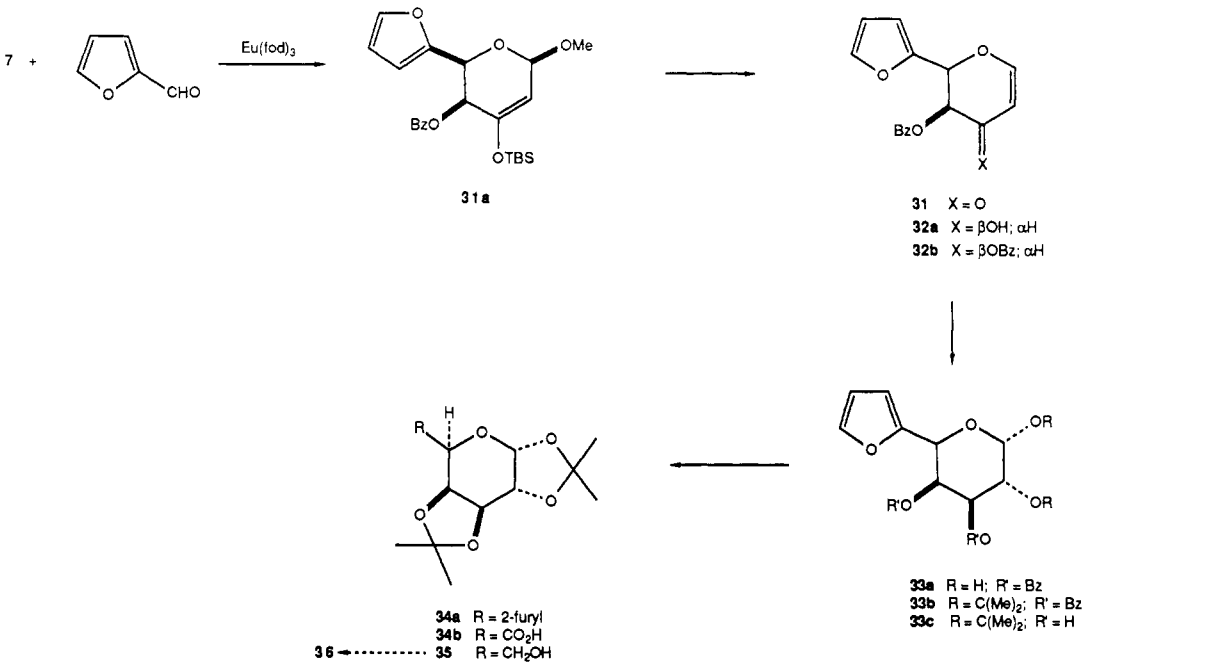

Figure 7.

pyrone **25** is now known to be the required compound. However, our only access to this compound was from the major product (2:1) of the low-yielding BF_3 etherate reaction or from the minor (1:12.5) silyl enol ether adduct via the Eu(hfc)$_3$ reaction. In light of these considerations, plan A was set aside in favor of plan B.

Implementation of Plan B. For the C_7 aldehyde type **12** the stereochemical requirement for the cyclocondensation reaction was chelation control at the diastereofacial level via an exo type transition state leading to a *trans*-dihydropyrone. As a general matter, the compatibility of these two characteristics had been demonstrated through the use of anhydrous magnesium bromide as the catalyst with α-alkoxyaldehydes.[27] Of course, the unusual stereochemical combination that was responsible for the formation of compound **29** served to underscore the fact that our understanding of the various connectivities was far from complete.

However, in the case at hand, the cyclocondensation of a highly relevant aldehyde, i.e., compound **40**, with diene **7** had indeed been demonstrated to afford dihydropyrone **41**, which contains the required configurations at carbons 7 and 8 to reach hikosamine. The stereochemistry advanced for compound **41** had been rigorously established crystallographically.[28,29]

Before describing the steps employed for conversion of **41** to the hikosamine derivative (**2a**), we describe some investigations that led to a fully synthetic route to aldehyde **36**. In our previous work, the starting material for the preparation of **36** was the differentially protected derivative **35** prepared from D-galactose. Given the availability of galactose in the proper enantiomeric form, and given the ease of its conversion to **35**,[30] from a practical standpoint D-galactose would surely be our feedstock. However, it was of interest to demonstrate, at least in principle, a totally synthetic route to hikosamine.

The first step toward this subgoal was the cyclocondensation of diene **7** with furfural under the influence of Eu(fod)$_3$ (Figure 7). The adduct, **31a**, following treatment with trifluoroacetic acid afforded virtually homogeneous **31** in 55–60% yield. Reduction of the ketone with sodium borohydride–cerium(III) chloride gave a 90% yield of equatorial alcohol **32a** which upon

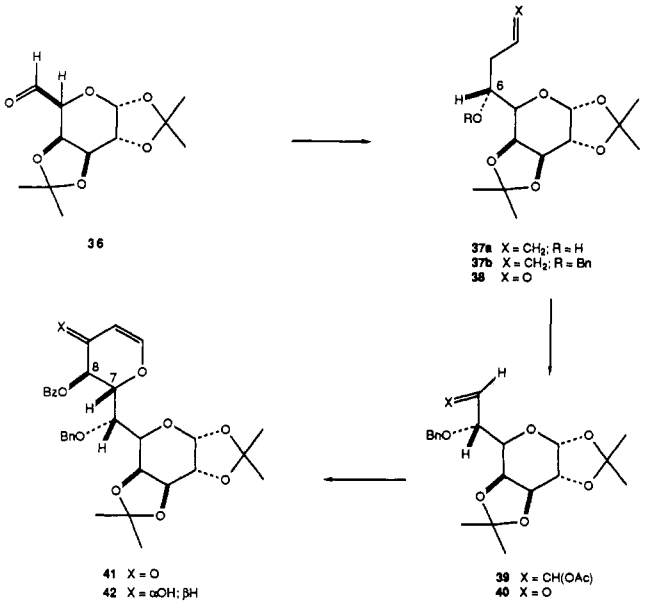

Figure 8.

benzoylation gave **32b**. Hydroxylation, via the reaction of catalytic osmium tetroxide, gave **33a**, which, upon acetalization (acetone–catalytic H_2SO_4), afforded **33b**. Double debenzoylation (K_2CO_3–methanol) led to **33c** and acetalization (acetone–catalytic H_2SO_4) to afford **34a** in 54% overall yield from **32b**.

The stage was now set for oxidation of the furan ring of **34a**.[31] This was smoothly accomplished through the action of ozone in methylene chloride–methanol at −78 °C. The resultant acid **34b**, upon reduction with borane–THF, gave rise to the racemic version of alcohol **35**. Its high-field NMR and infrared spectra were identical with the D isomer derived from D-galactose. Oxidation of the D isomer according to Horton afforded aldehyde **36**.[30]

In our earlier investigation,[28] aldehyde **40** had been derived by a sequence whose first step was the nonstereoselective addition of vinylmagnesium bromide to aldehyde **36**. Since the achievement of high levels of stereochemical induction was one of the major goals of this effort, a more selective albeit longer route was sought.

(27) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2456.
(28) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256.
(29) Full structural information is availale in the microfilm edition of ref 28.
(30) Horton, D.; Nakadate, M.; Tronchet, J. M. J. *Carbohydr. Res.* **1968**, *7*, 56.
(31) For the use of a furan as a carboxyl precursor, see: Schmid, G.; Fukuyama, T.; Akaska, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259.

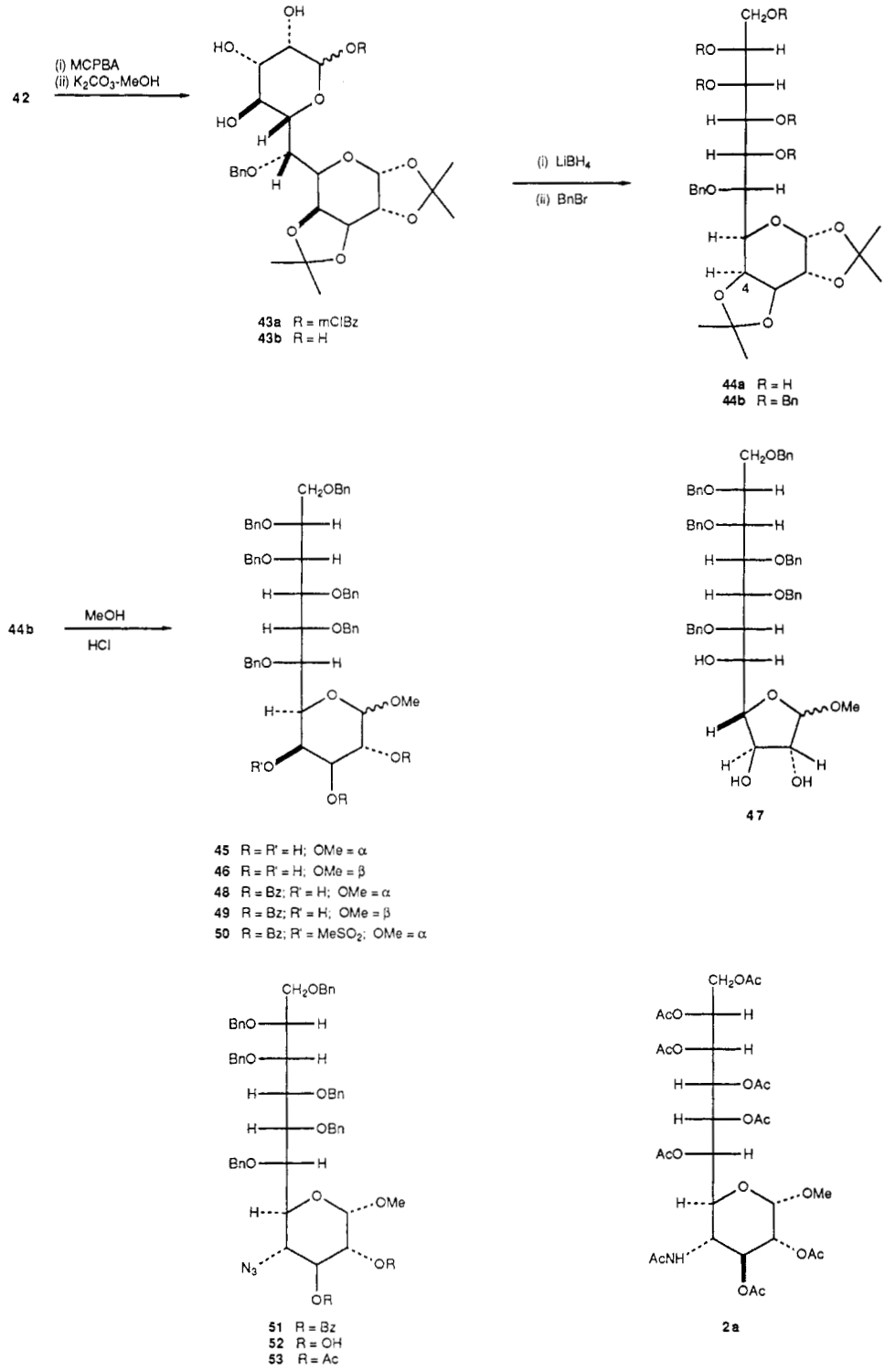

Figure 9.

In the interim it had been found[10,11] that high margins of selectivity in either diastereofacial sense could be realized in the reaction of **36** with allyltrimethylsilane under catalysis by BF_3 etherate. For the case at hand, reaction was carried under BF_3 etherate catalysis to afford a 15:1 ratio of **37a** to its C_6 epimer (not shown) (Figure 8). The alcohol was protected (NaH; BnBr; DMF) as its benzyl ether, **37b**. The double bond was cleaved by ozonolysis followed by reductive workup. The crude aldehyde **38** was converted to its enol acetate **39**, which upon ozonolysis as above afforded aldehyde **40**. *Since the cyclocondensation of* ***40*** *with 7 had already been shown to give* ***41***[28] *as virtually the sole product, a fully synthetic highly stereoselective route to the differentiated undecose system* ***41****, of proven stereochemistry, was now secured.* Reduction of **41** under the usual Luche conditions[14] afforded the equatorial alcohol **42**.

At this stage the remaining nonanomeric stereogenic center to be controlled was that of C_{10}. In the event, reaction of **42** with MCPBA (presumably under the guidance of the α-disposed C_9 hydroxyl function) gave the anomeric *m*-chlorobenzoyloxy compound **43a** (Figure 9). After deacylation with K_2CO_3–methanol, tetraol **43b** was obtained. The pyranose ring was cleaved reductively via reaction with lithium borohydride in THF under reflux. The crude pentaol **44a** was subjected to perbenzylation (BnBr; NaH–DMF) to provide the perbenzyl ether, **44b** (70% from **42**).

The last obstacle to be overcome involved the introduction of a nitrogen function at C_4 with inversion of configuration. Although in projecting a total synthesis of hikizimycin it would be advan-

tageous if this nitrogen could be distinguished from the hydroxyl groups in its protective arrangement, for the sake of simplicity in verifying our stereochemical assignments, we defined the peracetyl derivative **2a** to be our goal. The action of methanolic HCl on compound **44b** led to the cleavage of both acetonide functions and the isolation of a mixture of methyl glycoside triols. Chromatography on silica gel produced a 55% yield of a 1.5:1 mixture of the inseparable α:β methyl glycosides (cf. **45** and **46**) and a 14% yield of what is provisionally assigned as the furanoside **47** (anomeric configuration not determined). The α (axial) methyl glycoside, **45**, was of particular interest, since a direct comparison with intermediates during the Secrist synthesis[6,7] would be possible.

The **45,46** mixture was subjected to benzoylation. The hope was that the C_4 (axial) hydroxyl would be more difficultly acylable and that such a differential could be exploited synthetically. In practice this hope was realized. Treatment of the mixture of anomers with benzoyl chloride–pyridine in methylene chloride at 0 °C for 2 h did indeed produce a mixture of dibenzoates. The components (**48** and **49**) were, fortunately, chromatographically separable. The former was obtained in homogeneous form in 57% yield. Compound **49**, which could in principle be used, was isolated in 36% yield. In practice, only compound **48** was further elaborated.

The axial hydroxyl function in α methyl glycoside **48** was activated through the action of methanesulfonyl chloride to afford mesylate **50**. Treatment of this compound with tetra-*n*-butylammonium azide in toluene at 85 °C gave rise to equatorial azide **51** (70% from **48**) where all the stereochemistry of the goal system **2a** had been properly fashioned. There remained only the correlation with the Secrist specimen. This was accomplished as follows. Debenzoylation (K_2CO_3–methanol) afforded diol **52**, which upon acetylation gave rise to **53**. At this stage, the most straightforward correlation protocol involved (i) reductive cleavage of the azide (Ph_3P); (ii) perdebenzylation [H_2/$Pd(OH)_2$][32] and (iii) peracetylation to give a 35% overall yield of methyl α-peracetylhikosaminide (**2a**). *The NMR spectrum of this material was identical with that of a reference specimen provided by Professor Secrist.* While there was not enough of the reference material for other extensive comparisons, the richness of detail of the NMR spectrum, the intrinsic assignability of our synthetic intermediates in their cyclic matrices, and the crystallographic verification of compound **41** render our claim of a totally synthetic route to **2a** eminently supportable. *It will be noted that high margins of selectivity (≥10:1) were achieved in the installation of the nine nonanomeric stereogenic centers of methyl α-peracetylhikosaminide.* We also note that the availability of **44b**, in which the C_6 hydroxyl is uniquely protected, and the intermediacy of **53**, in which the C_4 nitrogen has not yet been acetylated, could in principle be exploited for a synthesis of differentially functionalized precursors to hikizimycin.

Experimental Section

***cis*-3-(Benzoyloxy)-2-[3-(benzyloxy)-1-(*E*)-propenyl]-2,3-dihydropyran-4-one (14).** A solution of the diene mixture **24** (2.65 g, 9.08 mmol) and (benzyloxy)crotonaldehyde[17] (1.92 g, 10.9 mmol) in dichloromethane (40 mL) was cooled to −78 °C, treated with BF_3·OEt_2 (1.12 mL, 9.08 mmol) for 5.5 h, and then quenched with aqueous saturated sodium bicarbonate (10 mL). The reaction was diluted with ether (350–400 mL), extracted with sodium bicarbonate solution and then brine, and dried ($MgSO_4$). Concentration in vacuo followed by treatment of the crude product with trifluoroacetic acid (0.92 mL) in carbon tetrachloride (70 mL) and chromatography (silica gel, 150 g; elution with 20% ethyl acetate–hexanes) gave **14** (1.89 g, 57%): ^{1}H NMR (250 MHz) δ 8.06–8.02 (m, 2 H), 7.61–7.55 (m, 1 H), 7.46–7.36 (m, 3 H), 7.34–7.24 (m, 6 H), 6.07 (dt, J = 15.7, 4.9 Hz), 5.95 (dd, J = 15.8, 6.0 Hz, 1 H), 5.79 (d, J = 4.6 Hz, 1 H), 5.55 (d, J = 6.1 Hz, 1 H), 5.18–5.23 (m, 1 H), 4.45 (s, 2 H), 4.05 (d, J = 4.6 Hz, 1 H); ^{13}C NMR (62.5 MHz) δ 186.3, 164.8, 162.0, 137.8, 133.5, 133.3, 129.8, 128.3, 128.2, 127.5, 122.8, 105.5, 79.9, 72.0, 70.6, 69.1; IR 1734, 1700, 1603, 1500, 1458, 1415, 1321 cm^{-1}.

Preparation of Glycal 15. A solution of the dihydropyrone **14** (1.50 g, 4.12 mmol) and $CeCl_3$·$7H_2O$[14] (1.53 g, 4.12 mmol) in methanol (60 mL) was cooled to −78 °C, and to this solution was added slowly sodium borohydride (156 mg, 4.12 mmol) in ethanol (10 mL) over approximately 1 h. The reaction mixture was quenched at −78 °C with pH 6.8 phosphate buffer (10 mL) and diluted with ether (500 mL). The organic layer was washed with water and then brine and dried ($MgSO_4$). Concentration in vacuo and chromatography (silica gel, 75 g; elution with ethyl acetate–hexanes, 20–30%) gave glycal **15** (1.3 g, 86%): ^{1}H NMR (250 MHz) δ 8.1–8.05 (m, 2 H), 7.61–7.20 (m, 8 H), 6.53 (dd, J = 6.2, 1.6 Hz, 1 H), 6.00 (dt, J = 16.6, 5.4 Hz, 1 H), 5.86 (dd, J = 15.7, 5.5 Hz, 1 H), 5.53 (d, J = 4.7 Hz, 1 H), 4.84–4.80 (m, 1 H), 4.74–4.66 (m, 2 H), 4.4 (s, 2 H), 4.00 (d, J = 5.4 Hz, 1 H).

Silylation of Glycal 15: Formation of Silyl Ether 16. A solution of glycal **15** (1.1 g, 3.00 mmol) in dichloromethane (25 mL) was cooled to −78 °C. To this solution was added 2,6-lutidine (0.422 mL, 3.75 mmol) followed by *tert*-butyldimethylsilyl triflate (0.688 mL, 3.0 mmol).[33] After 30 min, the reaction mixture was quenched with triethylamine (3 mL), diluted with ether (250 mL), washed with sodium bicarbonate solution and brine, and dried ($MgSO_4$). Concentration in vacuo and chromatography (silica gel, 75 g; elution with 20% ethyl acetate–hexanes) gave silyl ether **16** (1.25 g, 86.8%): ^{1}H NMR (90 MHz) δ 8.17–8.09 (m, 1 H), 7.61–7.30 (m, 8 H), 6.53 (br d, J = 4.2 Hz, 1 H), 6.04–5.97 (m, 2 H), 5.56–5.46 (m, 1 H), 4.84–4.67 (m, 2 H), 4.47 (s, 2 H), 4.06 (d, J = 4.5 Hz, 1 H), 0.87 (s, 9 H), 0.19 (s, 3 H), 0.113 (s, 3 H).

Tetraol Anomers 19. A solution of glycal silyl ether **16** (2.45 g, 5.10 mmol), osmium tetroxide (0.15 mmol), and *N*-methylmorpholine *N*-oxide[21] (1.49 g, 12.76 mmol) in THF (50 mL), *tert*-butyl alcohol (12 mL), and water 2.7 mL) was stirred at room temperature for 18 h. The reaction was subjected to nonaqueous workup by the addition of Florisil (6 g) and solid sodium bisulfite (2.0 g) directly to the reaction and stirred vigorously for 3 h followed by filtration through a Celite pad. The solids were washed thoroughly with chloroform. The filtrate was concentrated in vacuo and chromatographed (silica gel, 200 g). Gradient elution with methanol–chloroform (1–3%) gave the tetrol anomer mixture **19** (2.2 g, 78.8%) as the major product and a minor isomer, **21** (0.315 g, 11.2%).

Anomers 19: ^{1}H NMR (250 MHz) δ 8.10–8.05 (m, 2 H), 7.60–7.57 (1 H), 7.49–7.42 (3 H), 7.38–7.22 (m, 5 H), 5.52–5.51 (m, 1 H, H-4), 5.37 (d, J = 3.6 Hz, 1 H, H-1α), 4.72 (d, J = 7.2 Hz, 1 H, H-1β), 4.53 (d, J = 12.0 Hz, 1 H), 4.47 (d, J = 12.0 Hz, 1 H), 4.16–3.49 (m, 2 H), 2.47 (br m, 2 H), 2.29 (s, 2 H), 0.77 (s, 9 H), 0.17 (s, 3 H), 0.08 (s, 3 H); IR 3600–3150, 2960, 2940, 2865, 1725, 1700, 1605, 1585, 1455 cm^{-1}; MS *m/e* (%) 491 (M^+ − 57, 1.6), 473 (4.4), 455 (1.9), 379 (1.2), 285 (1.5), 261 (2.6), 207 (2.5), 187 (8.8), 105 (53.6).

Side-chain isomeric anomer mixture: ^{1}H NMR (250 MHz) δ 8.06–7.99 (m, 2 H), 7.55–7.37 (m, 3 H), 7.25–7.16 (m, 5 H), 5.59 (d, J = 3.2 Hz, 1 H, H-4-4α), 5.55 (d, J = 3.2 Hz, 1 H, H-4β), 5.50 (d, J = 3.7 Hz, 1 H, H-1α), 4.74 (d, J = 7.4 Hz, 1 H, H-1β), 4.47–4.41 (m, 3 H), 4.09–3.44 (m), 2.44 (br m, 2 H), 2.30 (s, 2 H), 0.75 (s, 9 H, α), 0.74 (s, 9 H, β), 0.10 (s, 3 H), 0.09 (s, 3 H); IR 3600–3150, 3020, 2980, 2940, 2870, 1725, 1601, 1451, 1385, 1360 cm^{-1}; MS *m/e* (%) 491 (M^+ − 57, 0.8), 473 (1.7), 469 (1.8), 455 (1.3), 379 (0.8), 365 (1.9), 349 (2.2), 285 (1.5), 261 (1.2), 207 (3.1), 187 (6.8), 171 (4.6), 129 (15.0), 105 (49.6).

Diacetonide 21. A solution of the tetraol anomer mixture **19** (1.5 g, 2.73 mmol) and *p*-toluenesulfonic acid (200 mg) in dry acetone (90 mL) was stirred at 50 °C with anhydrous $MgSO_4$ (12 g) for 26 h. Concentrated sulfuric acid (0.125 mL) was then added with $MgSO_4$ (5 g) to the resultant solution of **20**, and the reaction was stirred an additional 12 h. The reaction was diluted with ethyl acetate (350 mL) and filtered through Celite. The filtrate was extracted with cold saturated sodium bicarbonate solution, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (silica gel, 100 g; elution with ethyl acetate–hexanes, 20–40%) afforded **21** (0.962 g, 56%) and the side-chain monoacetonide (0.472 g). Recycling the monoacetonide **20** using the above reaction conditions afforded an additional 300 mg of **21** for an overall conversion of 73%: ^{1}H NMR (250 MHz) δ 8.04–8.00 (m, 2 H), 7.57–7.40 (m, 3 H), 7.33–7.28 (m, 5 H), 5.65–5.64 (m, 1 H), 5.61 (d, J = 4.2 Hz, 1 H), 4.58 (AB quartet, J = 12.3 Hz, 2 H), 4.27–4.22 (m, 1 H), 4.09–3.92 (m, 4 H), 3.75 (dd, J = 10.5, 2.6 Hz, 1 H), 3.59 (dd, J = 10.5, 6.0 Hz, 1 H), 1.55 (s, 3 H, 1.42 (s, 3 H), 1.39 (s, 3 H), 1.30 (s, 3 H), 0.80 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 165.0, 138.3, 132.7, 130.3, 129.5, 128.2, 128.1, 127.4, 127.2, 109.7, 108.0, 97.5, 80.0, 77.0, 73.7, 73.21, 73.16, 71.7, 70.6, 69.2, 28.0, 27.1, 27.0, 26.8, 25.5, 17.8, −4.8, −5.1.

Debenzylation of 21: Formation of 22. The benzyl ether **21** (0.962 g, 1.53 mmol) in ethanol (80 mL) was hydrogenated with Pearlman's catalyst[32] [20% $Pd(OH)_2$/C; 650 mg] under 1 atm of hydogen for 5 h. The reaction was filtered through a Celite pad and concentrated.

(32) Pearlman, W. M.; *Tetrahedron Lett.* **1967**, *17*, 1663.

(33) Emde, H.; Domsch, D.; Feger, U.; Gotz, A.; Hergoth, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

Chromatography (silica gel, 50 g; elution with 30% ethyl acetate–hexanes) afforded **22** (765 mg, 93%). Recrystallization from hexanes gave an analytical sample: mp 104.5–106 °C; ^{1}H NMR (250 MHz) δ 8.05–8.00 (m, 2 H), 7.61–7.54 (m, 1 H), 7.49–7.41 (m, 2 H), 5.68 (d, J = 4.1 Hz, 1 H), 5.65 (dd, J = 3.4, 2.0 Hz, 1 H), 4.1–3.90 (m, 5 H), 3.84 (apparent dt, J = 4.0, 11.7 Hz, 1 H), 3.72 (ddd, J = 11.6, 7.8, 4.5 Hz, 1 H), 2.11 (dd, J = 7.7, 4.6 Hz, 1 H), 1.56 (s, 3 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.29 (s, 3 H), 0.80 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 165.2, 132.7, 130.3, 129.7, 128.4, 109.6, 108.4, 97.6, 81.39, 77.6, 76.6, 74.0, 73.4, 71.6, 69.3, 62.9, 28.1, 27.1, 27.0, 26.9, 25.6, 17.9, −4.7, −5.0; IR ($CHCl_3$) 3550–3350, 2850, 1695, 1600, 1420 cm^{-1}; MS m/e (%) 523 (M^+ − 15, 5.6), 481 (M^+ − 57, 14.4), 423 (9.1), 365 (7.4), 301 (11.2), 243 (8.9), 227 (14.7), 179 (89.7), 141 (25.3), 105 (100). Anal. Calcd for $C_{27}H_{42}O_9Si$ (538.7): C, 60.20; H, 7.85. Found: C, 60.19; H, 7.98.

Oxidation of 22: Formation of 23. A solution of oxalyl chloride (0.50 mL, 5.8 mmol) in dichloromethane (20 mL) was cooled to −78 °C followed by addition of dimethyl sulfoxide (0.82 mL, 11.6 mmol) in dichloromethane (2 mL). After 10 min the alcohol **22** (624 mg, 1.16 mmol) in dichloromethane (8 mL) was added, and the reaction was stirred an additional 20 min followed by addition of triethylamine (3.23 mL, 23.2 mmol) and further stirring for 10 min. The reaction was quenched with water and diluted with dichloromethane. The organic layer was washed with water and brine and dried ($MgSO_4$). Concentration in vacuo and chromatography (silica gel, 50 g; elution with 20% ethyl acetate–hexanes) afforded the aldehyde **23** (452 mg, 73%): ^{1}H NMR (250 MHz) δ 9.72 (d, J = 0.8 Hz, 1 H), 8.04–8.00 (m, 2 H), 7.61–7.56 (m, 1 H), 7.48–7.42 (m, 2 H), 5.71 (d, J = 4.0 Hz, 1 H), 5.64 (dd, J = 3.2, 2.4 Hz, 1 H), 4.54 (dd, J = 5.7, 0.6 Hz, 1 H), 4.31 (dd, J = 8.7, 5.7 Hz, 1 H), 4.14–4.03 (m, 3 H), 1.57 (s, 3 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.27 (s, 3 H), 0.80 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); IR 2995, 2960, 2940, 2850, 1720, 1600, 1590, 1450, 1390, 1380 cm^{-1}.

Formation of Silyl Enol Ether Adducts 29 and 30. A solution of aldehyde **23** (358 mg, 0.668 mmol), diene mixture **7** (ca. 50%, 720 mg, 2.15 mmol), and Eu(hfc)$_3$[24] (440 mg, 0.386 mmol) in $CDCl_3$ (2.5 mL) was stirred at room temperature for 2.5 days and monitored by NMR. The reaction mixture was diluted with chloroform, quenched with triethylamine (5 mL), and concentrated in vacuo. Chromatography (silica gel, 125 g; elution with 10% ethyl acetate–hexanes) gave predominantly pure fractions which contained the major enol ether **29**. This compound crystallized from hexanes (mp 169.5–171.5 °C). There were also mixed fractions of enol ether **29** and the minor enol ether **30**, as well as by-products of the shift reagent catalyst. Total weight recovery of enol ether containing fractions was 441 mg and the ratio of **29**:**30** was ca. 12.5:1.

Enol ether 29: ^{1}H NMR (250 MHz) δ 8.08–8.01 (m, 4 H), 7.57–7.36 (m, 6 H), 5.60 (m, 2 H), 5.37 (d, J = 4 Hz, 1 H), 5.08 (br s, 1 H), 5.02 (d, J = 1.2 H, 1 H), 4.29 (dd, J = 6.6, 2.6 Hz, 1 H), 4.16 (dd, J = 9.0, 6.6 Hz, 1 H), 4.01–3.90 (m, 4 H), 3.34 (s, 3 H), 1.50 (s, 3 H), 1.34 (s, 3 H), 1.16 (s, 3 H), 1.04 (s, 3 H), 0.82 (s, 9 H), 0.80 (s, 9 H), 0.17 (s, 3 H), 0.09 (s, 3 H), 0.087 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 166.7, 165.1, 150.8, 132.9, 132.5, 131.1, 130.5, 130.0, 129.7, 128.4, 128.0, 110.2, 108.1, 107.9, 99.3, 97.6, 79.8, 73.2, 73.0, 72.5, 71.9, 69.5, 68.8, 54.3, 28.2, 27.2, 27.1, 26.7, 25.7, 25.4, 22.7, 17.9, −4.2, −4.6, −5.0; IR 2950, 2940, 2900, 2850, 1725, 1670, 1601, 1450 cm^{-1}.

Minor enol ether 30: ^{1}H NMR (250 MHz) δ 8.55–8.10 (m, 2 H), 8.03–7.99 (m, 2 H), 7.60–7.39 (m, 6 H), 5.77–5.73 (m, 1 H), 5.69–5.67 (m, 1 H), 5.66 (d, J = 4.5 Hz, 1 H), 5.11 (br s, 1 H), 5.02 (d, J = 1 Hz, 1 H), 3.52 (s, 3 H), 1.50 (s, 3 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 1.19 (s, 3 H), 0.09 (s, 9 H), 0.08 (s, 9 H), 0.18 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.04 (s, 3 H).

***cis*-Dihydropyrones 25 and 26.** The enol ether fractions from the above procedure (440 mg) were dissolved in carbon tetrachloride (20 mL) and treated with trifluoroacetic acid (0.1 mL) for 45 min. The solution was concentrated in vacuo and chromatographed (silica gel, 50 g; elution with 20% ethyl acetate–hexanes) to give **26** (254 mg, 51%) and **25**, mp 170–172 °C (20 mg, 4%). For **26**: ^{1}H NMR (250 MHz) δ 8.07–8.03 (m, 4 H), 7.60–7.40 (m, 7 H), 5.79 (d, J = 4 Hz, 1 H), 5.61 (dd, J = 3.1, 1.8 Hz, 1 H), 5.52–5.50 (m, 2 H), 4.79 (m, 1 H), 4.43 (dd, J = 7.1, 3.0 Hz, 1 H), 4.18 (dd, J = 9.0, 7.1 Hz, 1 H), 4.05–3.94 (m, 3 H), 1.44 (s, 3 H), 1.29 (s, 3 H), 1.25 (s, 3 H), 1.20 (s, 3 H), 0.79 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 186.0, 165.2, 162.6, 133.1, 133.0, 130.3, 130.1, 129.8, 129.7, 128.4, 128.2, 110.9, 108.0, 105.7, 97.5, 79.2, 78.9, 76.7, 73.3, 73.0, 71.5, 69.7, 28.0, 26.9, 26.6, 25.6, −4.7, −5.0; IR 2900, 2950, 1730, 1695, 1601, 1450 cm^{-1}. For **25**: ^{1}H NMR (250 MHz) δ 8.0–7.90 (m, 4 H), 7.53–7.29 (m, 7 H), 5.87 (dd, J = 3.9, 0.7 Hz, 1 H), 5.64 (m, 24), 5.49 (dd, J = 5.9, 0.7 Hz, 1 H), 4.72 (dd, J = 5.4, 3.9 Hz, 1 H), 4.62 (m, 1 H), 4.32 (dd, J = 8.7, 4.9 Hz, 1 H), 4.08 (dd, J = 8.7, 1.6 Hz, 1 H), 4.04–3.95 (m, 2 H); IR 1730, 1600, 1450, 1380 cm^{-1}; MS m/e (%) 709 (M^+ − 15, 0.4), 667 (2.3), 469 (2.4), 327 (2.0), 259 (2.5), 179 (18.8), 105 (100).

Preparation of Dihydropyran Adduct 31a. A solution of the diene **7** (0.967 g, 2.88 mmol), 2-furaldehyde (0.415 g, 4.3 mmol), and Eu(fod)$_3$[24] (171 mg, 0.1 mmol) in $CDCl_3$ (0.75 mL) was stirred for 3 days at 25 °C. The reaction was concentrated and chromatographed (silica gel 50 g; elution with 20% ethyl acetate–hexanes). The major product fractions were crystallized from hexanes to give **31a** (300 mg, first crop): mp 76–77 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.00–7.96 (m, 2 H), 7.56–7.49 (m, 1 H), 7.43–7.36 (m, 2 H), 7.25 (d, J = 0.7 Hz, 1 H), 6.33 (dd, J = 3.3, 0.6 Hz, 1 H), 6.21 (dd, J = 3.3, 1.8 Hz, 1 H), 5.72 (dd, J = 2.6, 1.4 Hz, 1 H), 5.32 (br s, 1 H), 5.11 (d, J = 1.4 Hz, 1 H), 4.96 (d, J = 2.6 Hz, 1 H), 3.57 (s, 3 H), 0.82 (s, 9 H), 0.21 (s, 3 H), 0.08 (s, 3 H); IR ($CHCl_3$) 1720, 1668, 1600, 1460, 1396 cm^{-1}; MS m/e (%) 399 (M^+ − 31, OMe, 0.6), 373 (M^+ − 15, t-Bu, 0.7), 334 (3.0), 309 (1.5), 251 (12.7), 105 (30.5).

Formation of Dihydropyrone 31. The enol ether **31a** (200 mg, 0.69 mmol) was treated with trifluoroacetic acid (0.15 mL) in dichloromethane (8 mL). Chromatography (silica gel, 25 g; elution with 20% ethyl acetate–hexanes) gave dihydropyrone **31** (195 mg, 98%). Similar treatment of the mother liquors from the crystallization of **31a** gave additional amounts of **31** and its trans isomer. Overall yield of the dihydropyrone isomers was 58% (12:1 cis to trans) based on starting diene **7**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.07–7.94 (m, 2 H), 7.61–7.37 (m, 5 H), 6.54 (d, J = 3 Hz, 1 H), 6.40 (dd, J = 3, 2 Hz, 1 H), 5.83 (d, J = 6 Hz, 1 H), 5.60 (d, J = 6 Hz, 1 H); IR ($CDCl_3$) 3020, 1734, 1696, 1601, 1500, 1455, 1410 cm^{-1}.

Formation of Alcohol 32a. A solution of the furyldihydropyrone **31** (135 mg, 0.475 mmol) and cerium(III) chloride heptahydrate (176 mg, 0.475 mmol) in methanol (5 mL) and dichloromethane (5 mL) cooled to −78 °C was treated with sodium borohydride (27 mg, 0.712 mmol) in ethanol. The reaction was quenched with pH 6.8 phosphate buffer (2 mL) and diluted with ether (100 mL). The organic layer was washed with water and brine and dried ($MgSO_4$). Concentration in vacuo and chromatography (silica gel, 12 g; elution with 20% ethyl acetate–hexanes) gave glycal **32a** (129 mg, 95%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.07–7.97 (m, 2 H), 7.6–7.22 (m, 4 H), 6.54 (dd, J = 5.5, 2 Hz, 1 H), 6.31–6.17 (m, 2 H), 5.72–5.63 (m, 1 H), 5.16 (s, 1 H), 4.75–4.65 (m, 2 H), 2.50 (br s, 1 H); IR ($CHCl_3$) 3600–3200, 3040, 1729, 1650, 1606, 1506, 1455 cm^{-1}; MS m/e (%) 286 (M^+, 0.3), 214 (19.7), 164 (7.4), 147 (2.0), 105 (100).

Benzoylation of 32b. The furylglycal **32a** (129 mg, 0.451 mmol) was treated with benzoyl chloride (0.12 mL, 1.0 mmol), pyridine (0.4 mL), and catalytic N,N-(dimethylamino)pyridine in dichloromethane (2 mL) for 12 h. The reaction was diluted with ether (100 mL), extracted with potassium hydrogen sulfate, and dried ($MgSO_4$). The crude product crystallized from 20% ethyl acetate–hexanes to give dibenzoate (132 mg), mp 132–133 °C. The mother liquors were chromatographed to give an additional 35 mg for an overall yield of 95%: ^{1}H NMR (90 MHz) 8.07–7.94 (m, 2 H), 7.83–7.73 (m, 2 H), 7.54–7.12 (m, 7 H), 6.68 (d, J = 6 Hz, 1 H), 6.37–6.22 (m, 2 H), 6.00 (br s, 2 H), 5.34 (br s, 1 H), 4.91 (apparent dt, J = 6, 2 Hz, 1 H); IR 3070, 3050, 1725, 1650, 1605, 1585, 1505, 1494, 1450 cm^{-1}. Anal. Calcd for $C_{23}H_{18}O_6$: C, 70.76; H, 4.64. Found: C, 70.68; H, 4.78.

Diol 33a. The dibenzoate **32b** (132 mg, 0.338 mmol) was treated with osmium tetroxide (0.1 mmol) and N-methylmorpholine N-oxide (100 mg, 0.85 mmol) in THF (6 mL) and water (0.2 mL) for 36 h at room temperature. The reaction was quenched with solid sodium bisulfite (60 mg), Florisil (1.2 g), and water (0.5 mL) and stirred vigorously for 2 h. The reaction was filtered through Celite and concentrated. Chromatography (silica gel, 7 g; elution with ethyl acetate) gave diol **33a** (137 mg, 95%): ^{1}H NMR (250 MHz) δ 8.08–8.02 (m, 2 H), 7.92–7.89 (m, 2 H), 7.64–7.43 (m, 4 H), 7.37–7.29 (m, 3 H), 6.32 (d, J = 3.3 Hz, 1 H), 6.26 (dd, J = 3.3, 1.5 Hz, 1 H), 5.99 (dd, J = 3.1, 1.3 Hz, 1 H), 5.71 (dd, J = 10.3, 3.2 Hz, 1 H), 5.66 (br s, 1 H), 5.55 (s, 1 H), 4.43–4.34 (m, 1 H), 2.40 (br s, 1 H), 1.57 (d, J = 6.6 Hz, 1 H); IR 3600–3200, 3040, 1730, 1605, 1452 cm^{-1}; MS m/e (%) 407 (M^+ − 17, 0.2), 347 (2.5), 284 (20.0), 223 (8.3), 163 (9.9), 105 (100).

Formation of Acetonide 33b. The diol **33a** (132 mg, 0.311 mmol) was treated with concentrated sulfuric acid (1 drop) in acetone (7 mL) in the presence of excess $MgSO_4$ at 60 °C for 8 h. The reaction was diluted with ether (100 mL), extracted with cold saturated aqueous sodium bicarbonate, and dried ($MgSO_4$). Concentration in vacuo and chromatography (silica gel, 8 g; elution with 20% ethyl acetate–hexanes) gave acetonide **33b** (108.7 mg, 75%) which could be crystallized from ethyl acetate–hexanes: mp 130–131.5 °C; ^{1}H NMR (250 MHz) δ 7.96–7.88 (m, 4 H), 7.56–7.34 (m, 6 H), 7.26 (br s, 1 H), 6.35 (d, J = 3.2, 1 H), 6.52 (dd, J = 3.2, 1.8 Hz, 1 H), 6.02–5.97 (m, 2 H), 5.60 (dd, J = 6.5, 3.3 Hz, 1 H), 5.48 (d, J = 2.6 Hz, 1 H), 4.50 (dd, J = 6.5, 4.5 Hz, 1 H), 1.67 (s, 3 H), 1.47 (s, 3 H); IR 3040, 2980, 1720, 1601, 1576, 1504, 1490, 1450 cm^{-1}. Anal. Calcd for $C_{26}H_{24}O_8$: C, 67.24; H, 5.20. Found: C, 66.99; H, 5.40.

Formation of Diol Acetonide 33c. The dibenzoate **33b** (50 mg, 0.107 mmol) was treated with potassium carbonate (15 mg) in methanol (7 mL). Concentration in vacuo and chromatography (silica gel, 5 g; elution with ethyl acetate–hexanes, 20–50%) gave **33c** (25.5 mg, 92%): ^{1}H NMR (250 MHz) δ 7.43 (dd, J = 1.7, 0.6 Hz, 1 H), 6.49 (dd, J = 3.2, 0.6 Hz, 1 H), 6.40 (dd, J = 3.2, 1.8 Hz, 1 H), 5.69 (d, J = 4.6 Hz, 1 H), 5.08 (d, J = 2.1 Hz, 1 H), 4.24–4.18 (m, 2 H), 4.04–3.98 (m, 1 H), 2.98 (d, J = 6.9 Hz, 1 H), 2.56 (d, J = 4.4 Hz, 1 H), 1.57 (s, 3 H), 1.41 (s, 3 H); IR 3600–3200, 3010, 2990, 2930, 1500, 1450, 1380, 1370 cm^{-1}; MS m/e (%) 256 (M$^+$, 3.1), 241 (1.6), 238 (5.3), 156 (12.4), 100 (100), 84 (40), 73 (63).

Bisacetonide 34a. The diol **33c** (25.5 mg, 0.010 mmol) was treated with concentrated sulfuric acid (1 drop) in acetone (4 mL) with excess $MgSO_4$ at room temperature for 2.5 h. The reaction was diluted with ether (50 mL), extracted with cold aqueous saturated sodium bicarbonate, and dried ($MgSO_4$). Concentration in vacuo and chromatography (silica gel, 5 g; elution with 20% ethyl acetate–hexanes) gave **34a** (25 mg, 84.8%) mp 117–118 °C; ^{1}H NMR (250 MHz) δ 7.40 (d, J = 1.5 Hz, 1 H), 6.52 (d, J = 3.3 Hz, 1 H), 6.36 (dd, J = 3.2, 1.8 Hz, 1 H), 5.62 (d, J = 5.0 Hz, 1 H), 4.94 (d, J = 0.8 Hz, 1 H), 4.70 (dd, J = 5.5, 2.4 Hz, 1 H), 4.50 (dd, J = 7.8, 2.8 Hz, 1 H), 4.38 (dd, J = 5.0, 2.3 Hz, 1 H), 1.60 (s, 3 H), 1.50 (s, 3 H), 1.37 (s, 6 H); IR 2985, 2910, 1500, 1450, 1375 cm^{-1}.

Ozonolysis of Furyldiacetonide 34a. Formation of 35. A solution of the furyldiacetonide **34a** (21 mg, 0.071 mmol) in dichloromethane (2 mL) and methanol (1 mL) was cooled to −78 °C. Ozone was bubbled into the solution until a saturated blue solution persisted. The reaction was immediately purged with nitrogen and then concentrated. The crude product was redissolved in THF (3 mL) and treated with BH_3·THF complex (1 M, 0.4 mL) for 24 h. The reaction was quenched with acetic acid and methanol and concentrated. Chromatography on silica gel gave the racemate **35** (9.2 mg, 50%) identical in spectral and chromatographic properties with the same compound derived from D-galactose.[31]

Formation of Benzylic Ether 37b. A solution of the previously known[11] alcohol **37a** (2.85 g, 9.53 mmol) in *N*,*N*-dimethylformamide (50 mL) was treated with sodium hydride (50% oil dispersion) (2.40 g, 50.15 mmol) followed by addition of benzyl bromide (2.5 mL, 20.9 mmol). The reaction was stirred at room temperature for 24 h, quenched carefully with water, diluted with ether (600 mL), and extracted with water and then saturated sodium bicarbonate. The ether layer was dried ($MgSO_4$) and concentrated in vacuo. Chromatography of the crude product (silica gel, 150 g; elution with 10% ethyl acetate–hexanes) afforded ether **37b** (3.54 g, 95%) as an oil which crystallized on standing. Recrystallization from methanol provided an analytical sample: mp 60.5–62.0 °C; ^{1}H NMR (250 MHz) δ 7.40–7.28 (m, 5 H), 6.01–5.90 (m, 1 H), 5.53 (d, J = 5.0 Hz, 1 H), 5.24–5.08 (m, 2 H), 4.69–4.57 (m, 2 H), 4.48 (dd, J = 8.0, 1.5 Hz, 1 H), 4.28 (dd, J = 5.0, 2.1 Hz, 1 H), 3.79–3.67 (m, 2 H), 2.66–2.55 (m, 1 H), 2.41–2.30 (m, 1 H), 1.50 (s, 3 H), 1.48 (s, 3 H), 1.38 (s, 3 H), 1.32 (s, 3 H); IR ($CHCl_3$) 2980, 2930, 1490, 1450, 1430, 1380, 1370 cm^{-1}; $[\alpha]^{23}_D$ = −87.8° (c = 2.51, $CHCl_3$). Anal. Calcd for $C_{22}H_{30}O_6$ (390.48): C, 67.67; H, 7.74. Found: C, 67.91; H, 7.88.

Ozonolysis of 37b. Formation of Aldehyde 38. A solution of the benzyl ether **37b** (1.0 g, 2.64 mmol) in dichloromethane (45 mL) at −78 °C was ozonized until a saturated blue solution persisted. The solution was then purged with nitrogen at −78 °C followed immediately by a reductive workup with zinc powder (11 g) and glacial acetic acid (2 mL). The bath was removed, and the reaction was stirred for 3 h and then filtered through a Celite pad to afford after concentration a quantitative yield of aldehyde **38** homogeneous by TLC and NMR criteria: ^{1}H NMR (250 MHz) δ 9.81 (t, J = 2.0 Hz, 1 H), 7.34 (m, 5 H), 5.51 (d, J = 5.0 Hz, 1 H), 4.67 (s, 2 H), 4.63 (dd, J = 8.0, 2.3 Hz, 1 H), 4.46 (dd, J = 8.0, 1.7 Hz, 1 H), 4.31 (dd, J = 5.0, 2.3 Hz, 1 H), 4.21 (ddd, J = 9.0, 6.6, 4.4 Hz, 1 H), 3.76 (dd, J = 9.0, 1.6 Hz, 1 H), 2.89 (ddd, J = 16.6, 4.4, 2.0 Hz, 1 H), 2.72 (ddd, J = 16.6, 6.6, 2.2 Hz, 1 H), 1.51 (s, 3 H), 1.47 (s, 3 H), 1.38 (s, 3 H), 1.32 (s, 3 H); IR 1727, 1458, 1386, 1375 cm^{-1}; $[\alpha]^{23}_D$ −56.4° (c = 1.93, $CHCl_3$); HRMS calcd for $C_{21}H_{28}O_7$ 392.1835, found 392.1833.

Formation of Enol Acetate 39. The aldehyde **38** (1.0 g, 2.55 mmol) was stirred with acetic anhydride (2.5 mL, 26.4 mmol), triethylamine (5.0 mL, 35.8 mmol), and *N*,*N*-(dimethylamino)pyridine (5 mg) in dichloromethane (10 mL) for 24 h at room temperature. The reaction was concentrated in vacuo and chromatographed (SiO_2, 25 g; elution with 10% ethyl acetate–hexanes) to give the *E* and *Z* isomers (1.09 g, 95% yield) in approximately a 6:1 ratio, respectively. Chromatography (silica gel) in 10% ether–hexanes resolved these two isomers for characterization purposes.

***E* isomer**: ^{1}H NMR (250 MHz) δ 7.40 (d, J = 12.4 Hz, 1 H), 7.37–7.25 (m, 5 H), 5.49 (d, J = 5.0 Hz, 1 H), 5.40 (dd, J = 12.6, 3.9 Hz, 1 H), 4.63–4.41 (m, 4 H), 4.29–4.26 (dd, J = 5.0, 2.2 Hz, 1 H), 4.06 (t, J = 8.8 Hz, 1 H), 3.72 (dd, J = 9.1, 1.6 Hz, 1 H), 2.14 (s, 3 H), 1.51 (s, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 167.7, 139.1, 138.2, 128.3, 128.1, 127.6, 112.5, 109.0, 108.5, 96.5, 74.6, 71.0, 70.9, 70.8, 70.4, 69.6, 26.1, 26.0, 25.0, 24.5, 20.6; IR ($CHCl_3$) 2985, 2930, 1750, 1675, 1485, 1450 cm^{-1}; $[\alpha]^{23}_D$ −48.80° (c = 2.09, $CHCl_3$); HRMS calcd for $C_{23}H_{30}O_8$ 434.1940, found 434.1906.

***Z* isomer**: ^{1}H NMR (250 MHz) δ 7.39 (d, J = 6.5 Hz, 1 H), 7.35–7.30 (m, 5 H), 5.51 (d, J = 5.0 Hz, 1 H), 4.90 (dd, J = 9.6, 6.5 Hz, 1 H), 4.71–4.45 (m, 5 H), 4.30 (dd, J = 5.0, 2.2 Hz, 1 H), 3.73 (dd, J = 9.1, 1.6 Hz, 1 H), 2.10 (s, 3 H), 1.53 (s, 3 H), 1.47 (s, 3 H), 1.39 (s, 3 H), 1.32 (s, 3 H); IR ($CHCl_3$) 2985, 2930, 1755, 1670, 1485, 1450 cm^{-1}.

Compound 40. Ozonolysis of Enol Acetates 39 (*E* and *Z* Isomers). A solution of the enol acetates **39** (*E* and *Z* isomers) (0.636 g, 1.46 mmol) in dichloromethane (14 mL) and methanol (14 mL) at −78 °C was ozonized until a saturated blue solution persisted. The solution was purged with nitrogen followed by reductive workup with dimethyl sulfide (5 mL, −78 °C to room temperature, 2 h). Concentration of the reaction mixture in vacuo gave a mixture of the desired aldehyde **40** and its dimethyl acetal by NMR analysis of the crude product. The crude product was redissolved in acetone and adsorbed onto silica gel (10 g) and the solvent removed in vacuo (high vacuum, 4 h). The dried silica gel was loaded onto a silica gel column (10 g) and eluted with 30% EtOAc–hexanes to give aldehyde **40** (0.512 g, 93%).

Reduction of Dihydropyrone 41. Formation of Glycal 42. Sodium borohydride (174 mg, 4.62 mmol) in ethanol (8 mL) was added slowly over a period of 30 min to a solution of the known dihydropyrone **41** (750 mg, 1.32 mmol) and $CeCl_3$·$7H_2O$ (490 mg, 1.32 mmol) in methanol (15 mL) and dichloromethane (12 mL) at −78 °C. The reaction was quenched with acetic acid (1.5 mL) at −78 °C and then with pH 6.5 phosphate buffer (15 mL). The reaction was diluted with ether (400 mL) and extracted with water. The aqueous layer was washed with ether (100 mL), and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (silica gel, 100 g; elution with 20% EtOAc–hexanes) gave glycal **42** (715 mg, 95%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.11–8.08 (m, 2 H), 7.63–7.60 (m, 1 H), 7.51–7.45 (m, 2 H), 7.30–7.23 (m, 5 H), 6.43 (dd, J = 6.0, 1.4 Hz, 1 H), 5.54 (d, J = 4.8 Hz, 1 H), 5.32 (dd, J = 10.7, 6.9 Hz, 1 H), 4.85 (dd, J = 6.0, 2.4 Hz, 1 H), 4.71–4.66 (m, 2 H), 4.53 (br d, J = 7.5 Hz, 1 H), 4.49 (dd, J = 8.1, 1.6 Hz, 1 H), 4.45–4.39 (m, 2 H), 4.33 (dd, J = 4.8, 2.3 Hz, 1 H), 4.24 (dd, J = 9.7, 1.3 Hz, 1 H), 4.02 (dd, 10.3, 0.5 Hz, 1 H), 3.60 (br s, 1 H), 1.5 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H); IR ($CHCl_3$) 3600–3350, 2990, 2940, 1708, 1650, 1600, 1450 cm^{-1}; $[\alpha]^{23}_D$ +90.1° (c = 3.18, $CHCl_3$); MS (EI) m/e 568 (M$^+$, 0.1), 553 (M$^+$ − 15, 7.4), 349 (22.7), 232 (39.1) 91 (79.0).

Oxidation of Glycal 42. Formation of Anomeric *m*-Chlorobenzoates 43a. A solution of glycal **42** (695 mg, 1.22 mmol) and *m*-chloroperoxybenzoic acid (85%, 296 mg, 1.46 mmol) in dichloromethane (25 mL) was stirred at 0 °C for 5 h and then allowed to warm slowly to room temperature overnight. The reaction was quenched with aqueous saturated sodium sulfite and stirred vigorously for 1 h. The reaction was then diluted with ether (400 mL) and extracted with aqueous saturated sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give the anomeric *m*-chlorobenzoates **43a** (850 mg; 94%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.14–8.06 (m, 2 H), 7.99–7.95 (m, 1 H), 7.67–7.21 (m, 1 H), 6.57 (d, J = 1.3 Hz, 1 H), 5.53 (dd, J = 10.3, 9.4 Hz, 1 H), 5.27 (d, J = 5.0 Hz, 1 H), 4.66 (d, J = 10.4 Hz, 1 H), 4.61 (dd, J = 8.2, 2.5 Hz, 1 H), 4.55 (d, J = 10.4 Hz, 1 H), 4.47–4.40 (m, 2 H), 4.19 (dd, J = 5.0, 2.3 Hz, 1 H), 4.16–4.1 (m, 3 H), 3.97 (dd, J = 9.2, 0.6 Hz, 1 H), 3.69 (d, J = 6.5 Hz, 1 H), 2.97 (br s, 1 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 1.07 (s, 3 H); IR ($CHCl_3$) 3600–3200, 3000, 2950, 1725, 1605, 1575, 1455 cm^{-1}; $[\alpha]^{23}_D$ +15.6° (c = 2.29,, $CHCl_3$).

Formation of Tetraol Anomers 43b. The *m*-chlorobenzoates **43a** were treated with anhydrous K_2CO_3 (100 mg) in methanol (40 mL) for 5 h. The solution was concentrated in vacuo, redissolved in dichloromethane (100 mL), and concentrated again to remove traces of methanol to afford the lactol **43b** which was used directly in the reduction step. A small portion of the sample was removed and chromatographed (silica gel; elution with 40% ethyl acetate–hexanes) to provide a sample of the major lactol for NMR analysis: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47–7.31 (m, 5 H), 5.53 (d, J = 4.6 Hz, 1 H), 5.21 (br s, 1 H), 4.77 (AB quartet, J = 11 Hz, 2 H), 4.67 (dd, J = 5.0, 1.9 Hz, 1 H), 4.46 (dd, J = 7.9, 1.2 Hz, 1 H), 4.33 (dd, J = 4.7, 2.0 Hz, 1 H), 4.13–3.98 (m, 4 H), 3.94 (br s, 1 H), 3.80–3.67 (m, 2 H), 3.21 (br s, 1 H), 2.85 (br s, 1 H), 2.64 (br s, 1 H), 1.57 (s, 3 H), 1.49 (s, 3 H), 1.39 (s, 3 H), 1.33 (s, 3 H).

6-*O*-Benzyl-1,2,3,4-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-D-*galacto*-undecapyranose (44a). A solution of the crude lactol anomers **43b** (1.12 mmol) and lithium borohydride (200 mg, 9.18 mmol) in THF (50 mL) was heated to 60 °C for 24 h. The reaction was quenched at room temperature with acetic acid (14 mL) and stirred for 1 h, then

methanol (25 mL) was added, and the mixture was stirred an additional hour. The reaction mixture was concentrated in vacuo, redissolved in methanol (50 mL), and concentrated again. Chromatography (silica gel; elution with EtOAc 10% MeOH–ethyl acetate) afforded **44a** (539 mg, 96%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.30 (m, 5 H), 5.51 (d, J = 5.8 Hz, 1 H), 4.76 (AB quartet, J = 11 Hz, 2 H), 4.62 (dd, J = 7.9, 2.1 Hz, 1 H), 4.42 (dd, J = 8.2, 1 Hz, 1 H), 4.28 (dd, J = 5.0, 2.1 Hz, 1 H), 4.1–3.76 (m, 12 H), 3.35 (br s, 1 H), 1.51 (s, 3 H), 1.48 (s, 3 H), 1.36 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.6, 128.4, 128.3, 127.7, 109.0, 96.3, 77.3, (76.6 overlapping), 76.1, 74.9, 72.6, 70.9, 70.8, 70.6, 69.9, 69.5, 66.1, 63.7, 26.0, 25.9, 25.0, 24.1; IR ($CHCl_3$) 3600–3150, 3000, 2940 cm^{-1}; $[\alpha]^{23}_D$ −38.4° (c = 1.63, $CHCl_3$); MS (CI isobutane) m/e (%) 501 (M^+ + 1, 2.8), 2.59 (4.8), 201 (2.3), 107 (10.6), 91 (4.8).

6,7,8,9,10,11-Hexa-*O*-benzyl-1,2,3,4-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-D-*galacto*-undecapyranose (44b). A solution of the pentaol **44a** (539 mg, 1.08 mmol) in DMF (12 mL) was treated with sodium hydride (50% oil dispersion, 1.3 g, 27 mmol). The reaction mixture was stirred for 10 min followed by addition of benzyl bromide (1.3 mL, 10.8 mmol). The reaction was stirred at room temperature for 26 h and then quenched with water. The reaction was partitioned between ether (400 mL) and water (100 mL) and then dried ($MgSO_4$). Concentration in vacuo followed by chromatography (silica gel, 75 g; elution with 10% ethyl acetate–hexanes) gave **44b** (800 mg, 78%): ^{1}H NMR (250 MHz) δ 7.38–7.2 (m, 30 H), 5.56 (d, J = 5.2 Hz, 1 H), 4.92–4.44 (m, 14 H), 4.27 (dd, J = 5.2, 2.1 Hz, 1 H), 4.20–4.13 (m, 3 H), 4.08–4.01 (m, 2 H), 3.97–3.93 (m, 1 H), 3.83 (dd, J = 10.6, 2.9 Hz, 1 H), 3.71 (dd, J = 10.6, 5.7 Hz), 1.36 (s, 3 H), 1.32 (s, 3 H), 1.26 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 139.4, 139.1, 139.0, 138.6, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 127.2, 127.1, 127.0, 126.9, 108.6, 108.2, 96.7, 80.0, 79.7, 78.4, 77.3, 76.8, 74.1, 73.9, 73.2, 73.0, 72.9, 72.2, 70.9, 70.8, 70.3, 66.8, 26.0, 25.8, 24.8, 24.3; IR ($CHCl_3$) 3000, 2940, 2920, 1500, 1455 cm^{-1}; $[\alpha]^{23}_D$ −34.8° (c = 1.76, $CHCl_3$).

Methyl 6,7,8,9,10,11-Hexa-*O*-benzyl-D-*glycero*-D-*galacto*-α(and β)-D-*galacto*-undecapyranosides (45,46 Mixture) and Methyl Furanoside 47. A solution of the diacetonide **44b** in dry methanolic HCl (3%) was heated at 75 °C for 8 h. The reaction mixture was concentrated in vacuo and chromatographed (silica gel, 35 g; elution with ethyl acetate–hexanes 50–75%) to give a mixture of the methyl pyranosides **45** and **46** (232.4 mg, 55.5%) in a 1.5:1 ratio, respectively, in addition to the furanoside **47** (60 mg, 14%). The furanoside was recycled by using the above conditions to afford essentially the same mixture of pyranosides **45** and **46** (30 mg) and the methyl furanoside **47**. A small sample of the α anomer, **45** was purified by HPLC at this stage.

Methyl α-pyranoside 45: ^{1}H NMR (250 MHz) δ 7.31–7.18 (m, 30 H), 4.80–4.40 (m, 12 H), 4.23–3.75 (m, 10 H), 3.71 (dd, J = 10.7, 4.6 Hz, 1 H), 3.58 (br d, J = 8.5 Hz, 1 H), 3.20 (s, 3 H), 3.05 (br d, J = 2.1 Hz, 1 H), 2.73 (br s, 1 H), 2.18 (br d, 1 H); ^{13}C NMR (62.5 MHz) δ 138.9, 138.7, 138.4, 136.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 99.8, 78.9, 78.8, 78.6, 78.2, 74.6, 74.2, 73.4, 73.1, 72.4, 71.9, 71.4, 69.9, 69.8, 69.5, 69.1, 68.8, 55.8; IR ($CHCl_3$) 3600–3200, 3010, 2909, 2875, 1730, 1500, 1459 cm^{-1}; $[\alpha]^{23}_D$ +37.6° (c = 1.46, $CHCl_3$;; MS FAB (thioglycerol) m/e 907 (M^+Na), 885 (M^+H), 854 (M^+ − OMe + H), 796 (M^+ − OBn + H).

Methyl furanoside 47: ^{1}H NMR (250 MHz) δ 7.30–7.14 (m, 30 H), 4.83 (s, 1 H), 4.76–3.80 (m, 33 H), 3.68–3.63 (m, 1 H), 3.32 (s, 3 H), 2.84 (d, J = 11.3 Hz, 1 H), 2.03 (br s, 2 H).

Methyl 2,3-Di-*O*-benzoyl-6,7,8,9,10,11-hexa-*O*-benzyl-D-*glycero*-D-*galacto*-α(and β)-D-*galacto*-undecapyranosides (48 and 49). To a solution of methyl pyranoside mixture **45** and **46** (200 mg, 0.226 mmol, 1.5:1) in dichloromethane (5 mL) and pyridine (4 mL) was added at 0 °C benzoyl chloride (0.4 mL, 3.42 mmol). After 2 h, the reaction was quenched with aqueous saturated sodium bicarbonate and diluted with ether (175 mL). The organic layer was washed with saturated sodium bicarbonate and potassium hydrogen sulfate and dried ($MgSO_4$). Concentration in vacuo and chromatography (silica gel, 35 g; elution with ether–hexanes, 1:4–2:1) gave **48** (140 mg, 57%) and **49** (90 mg, 36%). For **48**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05–7.97 (m, 4 H), 7.56–7.48 (m, 2 H), 7.31–7.20 (m, 34 H), 5.64 (m, 2 H), 5.14 (d, J = 2.8 Hz, 1 H), 4.81–4.37 (m, 14 H), 4.21–4.15 (m, 3 H), 4.05 (dd, J = 6.8, 3.0 Hz, 1 H), 3.93–3.86 (m, 2 H), 3.72 (dd, J = 10.6, 4.7 Hz, 1 H), 3.20 (s, 3 H), 3.03 (br d, J = 3.5 Hz, 1 H); IR ($CHCl_3$) 3015, 2940, 2370, 1725, 1605, 1495, 1455 cm^{-1}; $[\alpha]^{23}_D$ +61.1° (c = 1.93, $CHCl_3$); MS FAB (thioglycerol) m/e 1094 (M^+ + H). For **49**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97–7.94 (m, 4 H), 7.53–7.14 (m, 36 H), 5.65 (dd, J = 10.3, 7.9 Hz, 1 H), 5.17 (dd, J = 10.3, 3.1 Hz, 1 H), 4.78–4.12 (m, 17 H), 4.04 (dd, J = 6.7, 3.1, Hz, 1 H), 3.96–3.87 (m, 2 H), 3.8–3.7 (m, 2 H), 3.30 (s, 3 H), 2.4 (d, J = 5.0 Hz, 1 H); IR ($CHCl_3$) 3075, 3015, 2940, 2875, 1730, 1601, 1579, 1500, 1455 cm^{-1}; MS FAB (thioglycerol) m/e 1094 (M^+ + H).

Methyl 2,3-Di-*O*-benzoyl-6,7,8,9,10,11-hexa-*O*-benzyl-4-(methylsulfonyl)-D-*glycero*-D-*galacto*-α-D-*galacto*-undecapyranoside (50). A solution of the dibenzoate **48** (150 mg, 0.137 mmol), methanesulfonyl chloride (0.159 mL, 2.06 mmol), and *N*,*N*-(dimethylamino)pyridine (catalytic) in dry pyridine (2.5 mL) was stirred at room temperature for 5 h. The reaction was quenched with methanol (4 mL) and diluted with ether (200 mL). The organic layer was washed with aqueous saturated sodium bicarbonate (20 mL) and aqueous potassium hydrogen sulfate (20 mL) and dried ($MgSO_4$). Concentration in vacuo and chromatography (silica gel, 15 g; elution with 20% ethyl acetate–hexanes) gave mesylate **50** (154 mg, 96%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04–7.95 (m, 4 H), 7.56–7.24 (m, 36 H), 5.80 (dd, J = 10.9, 2.6 Hz, 1 H), 5.66 (br d, J = 2.6 Hz, 1 H), 5.59 (dd, J = 10.9, 3.6 Hz, H), 5.12 (d, J = 3.6 Hz, 1 H), 4.91–4.34 (m, 15 H), 4.28 (br d, J = 8.9 Hz, 1 H), 4.19 (br d, J = 6.9 Hz, 1 H), 3.98–3.88 (m, 2 H), 3.73 (dd, J = 10.5, 4.4 Hz, 1 H), 3.20 (s, 3 H), 2.80 (s, 3 H); IR ($CHCl_3$) 3100, 2940, 2870, 1730, 1605, 1500, 1455 cm^{-1}; $[\alpha]^{23}_D$ +45.4° (c = 1.95, $CHCl_3$); MS FAB (thioglycerol) m/e 1171 (M^+ + H).

Methyl 4-Azido-2,3-di-*O*-benzoyl-6,7,8,9,10,11-hexa-*O*-benzyl-4-deoxy-D-*glycero*-D-*galacto*-α-D-*gluco*-undecapyranoside (51). A solution of mesylate **50** (153 mg, 0.131 mmol) and tetrabutylammonium azide (0.93 g, 3.27 mmol) in toluene (4.5 mL) was heated at 110 °C for 32 h. The reaction was concentrated in vacuo and chromatographed (silica gel, 20 g; elution with 10% ethyl acetate–hexanes) to give **51** (109 mg, 75%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03–7.95 (m, 4 H), 7.57–7.19 (m, 36 H), 5.95 (m, 1 H), 5.04–4.98 (m, 2 H), 4.88–3.85 (m, 20 H), 3.74 (dd, J = 11.0, 5.1 Hz, 1 H), 3.1 (s, 3 H); IR ($CHCl_3$) 3040, 3020, 2940, 2875, 2115, 1730, 1615, 1500, 1455 cm^{-1}; $[\alpha]^{23}_D$ +85.8° (c = 1.14, $CHCl_3$).

Methyl 4-Azido-6,7,8,9,10,11-hexa-*O*-benzyl-4-deoxy-D-*glycero*-D-*galacto*-α-D-*gluco*-undecapyranoside (52). A solution of azide dibenzoate **51** (87 mg, 0.779 mmol) and potassium carbonate (25 mg) in methanol (10 mL) was stirred at room temperature for 12 h, concentrated in vacuo, and chromatographed (silica gel, 7 g; elution with 30% ethyl acetate–hexanes) to give diol **52** (67.2 mg, 95%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29–7.15 (m, 30 H), 4.84–4.39 (m, 13 H), 4.22–4.16 (m, 2 H), 4.04 (br s, 1 H), 3.93–3.69 (m, 6 H), 3.41–3.26 (m, 2 H), 3.06 (s, 3 H), 2.50 (br s, 1 H), 1.85 (d, J = 9.4 Hz, 1 H); IR ($CHCl_3$) 3610–3510, 3500–3300, 3020, 2975, 2940, 2880, 2120, 1500, 1460 cm^{-1}; $[\alpha]^{23}_D$ +68.4° (c = 0.79, $CHCl_3$); MS m/e (%) 881 (M^+ − N_2, 0.1), 8.50 (M^+ − N_2 − OMe, 0.1), 790 (M^+ − N_2 − Bn, 0.8).

Methyl 2,3-Di-*O*-acetyl-4-azido-6,7,8,9,10,11-hexa-*O*-benzyl-4-deoxy-D-*glycero*-D-*galacto*-α-D-*gluco*-undecapyranoside (53). A solution of the azide diol **52** (67.2 mg, 0.074 mmol) and DMAP (catalytic in acetic anhydride (0.5 mL), triethylamine (1.0 mL), and dichloromethane (5 mL) was stirred for 12 h at room temperature. The reaction was concentrated in vacuo and chromatographed (silica gel, 7 g; elution with 20% ethyl acetate–hexanes) to give diacetate **53** (73 mg, 99%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31–7.18 (m, 30 H), 5.49 (apparent t, J = 9.4 Hz, 1 H), 4.81–4.32 (m, 14 H), 4.12 (dd, J = 8.0, 3.6 Hz, 1 H)8 4.00–3.82 (m, 7 H), 3.69 (dd, J = 11.0, 4.9 Hz, 1 H), 3.08 (s, 3 H), 2.10 (s, 3 H), 2.06 (s, 3 H); IR ($CHCl_3$) 3020, 2940, 2880, 2115, 1755, 1500, 1458 cm^{-1}; $[\alpha]^{23}_D$ +76.3° (c = 0.83, $CHCl_3$).

Methyl 4-Acetamido-2,3,6,7,8,9,10,11-octa-*O*-acetyl-4-deoxy-D-*glycero*-D-*galacto*-α-D-*gluco*-undecapyranoside (2a). The azide diacetate **53** (44.8 mg, 0.451 mmol) and triphenylphosphine (55 mg, 0.21 mmol) in THF (4 mL) were heated at reflux for 6 h. The reaction was concentrated in vacuo and chromatographed to remove excess triphenylphosphine. The crude product was dissolved in methanol (15 mL) and hydrogenated at 40 lb H_2 pressure with 300 mg of palladium hydroxide on carbon for 20 h. The reaction was filtered through a Celite pad and concentrated. The crude product resulting from this process was acetylated with acetic anhydride and pyridine (1:2) with DMAP (catalytic) for 24 h. The reaction was concentrated and chromatographed (silica gel, 6 g; elution with $CHCl_3$–methanol gradient, 0–2%). Rechromatography of mixed fractions gave a total recovery of **2a** of 11 mg (35%). The NMR spectrum of this compound ($CDCl_3$, 490 MHz) was identical with that of a trace authentic sample provided by Professor Secrist.[6,7]

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Registry No. 2a, 50619-43-7; **7**, 91861-07-3; **14**, 118893-65-5; **15**, 118893-66-6; **16**, 118893-67-7; α-**19**, 118893-68-8; β-**19**, 119007-05-5; α-**20**, 118893-70-2; β-**20**, 119007-06-6; **21**, 118893-69-9; **22**, 118893-

71-3; **23**, 118893-72-4; **24**, 87461-94-7; **25**, 119007-07-7; **26**, 118893-74-6; **29**, 119008-29-6; **30**, 118893-73-5; **31**, 99166-36-6; **31a**, 118893-75-7; **32a**, 99166-37-7; **32b**, 99166-38-8; **33a**, 118920-26-6; **33b**, 118893-76-8; **33c**, 118893-77-9; **34a**, 99166-39-9; **35**, 99166-41-3; **37a**, 99166-42-4; **37b**, 99166-43-5; **38**, 99166-44-6; (*E*)-**39**, 119007-08-8; (*Z*)-**39**, 119007-09-9; **40**, 91861-00-6; **41**, 99166-46-8; **42**, 99166-47-9; α-**43a**, 119008-30-9; β-**43a**, 118893-78-0; α-**43b**, 119007-10-2; β-**43b**, 119007-11-3; **44a**, 118893-79-1; **44b**, 99212-55-2; **45**, 99212-56-3; **46**, 119007-12-4; α-**47**, 118893-80-4; β-**47**, 119007-13-5; **48**, 99212-57-4; **49**, 119007-14-6; **50**, 99212-85-8; **51**, 99212-58-5; **52**, 118920-27-7; **53**, 118893-81-5; (*E*)-$BnOCH_2CH{=}CHCHO$, 69152-87-0; 2-furaldehyde, 98-01-1.

Supplementary Material Available: NMR spectra of synthetic and authentic samples of compound **2a** (1 page). Ordering information is given on any current masthead page.

Diastereoselective Synthesis of 2,3-Disubstituted Tetrahydrofuran Synthons via the Iodoetherification Reaction. A Transition State Model Based Rationalization of the Allylic Asymmetric Induction

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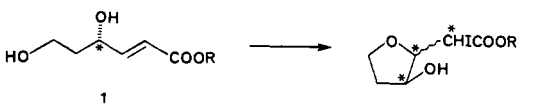
Contribution from Merck Frosst Canada, Inc., P.O. Box 1005, Pointe Claire-Dorval, Québec, Canada H9R 4P8. *Received June 29, 1988*

Abstract: The kinetically controlled iodoetherification reaction of ethyl (*S*,*E*)-4,6-dihydroxy-2-hexenoate (**1**) gives the synthetically useful synthon **2**, in which two new stereogenic centers have been generated, with selectivities up to 11:1. The mechanism of this allylic asymmetry transfer was probed by changing the allylic stereogenic substituent, and the order of efficacy for asymmetric induction was found to be F > OH ≥ OMe > Me. This result ruled out several proposed mechanisms of asymmetry transfer and led to the proposal of a transition-structure model, based on AM1 calculations. Our model rationalizes all of our results as well as those from the literature concerning selectivity and even relative rates of diastereomeric substrates.

The use of acyclic asymmetric induction has proven to be a valuable synthetic strategy, as judged by the large number of recently developed diastereoselective synthetic methods based on this mode of asymmetry transfer.[2] A reaction that is especially well-suited for this kind of asymmetry transfer is the formation of 5-membered rings by electrophilic activation of an allylic alcohol moiety.[3-12] The iodoetherification reaction (Scheme I) on which we will report here is part of this class of reactions.

Scheme I



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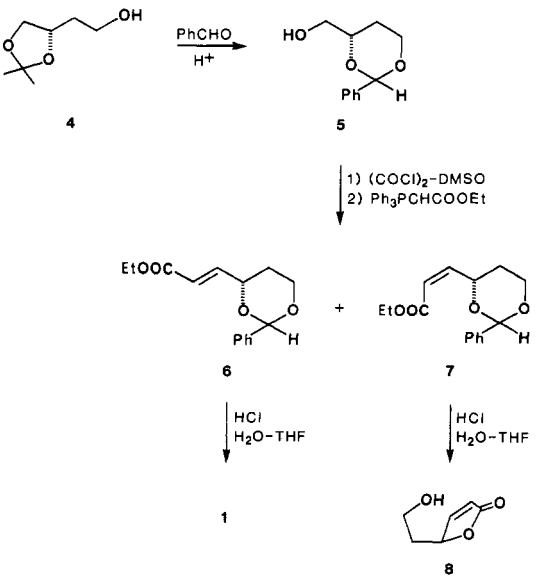
Scheme II



4 5 6 7 1 8

We became interested in allylic asymmetric induction in the formation of tetrahydrofuran derivatives after we had developed

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