periodically withdrawn from the reaction vessel (after a forerun was taken) into a cold vial which was immediately capped.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 $25^{\circ} \mathrm{C}$ ) 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 $1(2.24 \mathrm{~g}, 15.6 \mathrm{mmol})$ and acetone $-d_{6}(5 \mathrm{~g}, 78 \mathrm{mmol})$ was diluted to 50 mL with toluene, placed in the pressure bottle under 15 psi of $\mathrm{N}_{2}$, and heated to $91.7^{\circ} \mathrm{C}$. 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 ( $t_{\tau}$ $=9.16 \mathrm{~min}$ for $1-d_{6}$ vs 9.24 min for protiated $\left.\mathbf{1}\right)$. 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 $91.7^{\circ} \mathrm{C}$. Dioxinone-1- $d_{6}$ MS, $m / z=148\left(\mathrm{M}^{+}, 22\right), 86(72), 84(51), 69$ (53), 64 (37), 46 (98), 43 (100). Dioxinone 1: MS, $m / z=142\left(\mathrm{M}^{\bullet}, 16\right), 85(60), 84(28)$, 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 $\delta$ ), confirming the incorporation of the $\mathrm{CD}_{3}$ unit. No reduction (or $\mathrm{D}-\mathrm{C}-\mathrm{H}$ coupling) was noted for the proton resonance at $\mathrm{C}-5$ or the protons on the methyl group at C-6.

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

Reaction of Isopropenyl Acetoacetate (8) with 1-Butanol. In a dry, $25-\mathrm{mL}$ flask equipped with a condenser, a nitrogen inlet, and a stoppered sidearm was placed a solution of isopropenyl acetoacetate ( $62 \mathrm{mg}, 0.436$ mmol ), l-butanol ( $37 \mathrm{mg}, 0.492 \mathrm{mmol}$ ), and $p$-dichlorobenzene ( 36 mg , internal standard) in 10 mL of $p$-xylene. This flask was immersed in a $91.7^{\circ} \mathrm{C}$ 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 $9.2 \times 10^{-4} \mathrm{~s}^{-1}$ was estimated for the process. This is in agreement with the $8.8 \times 10^{-4} \mathrm{~s}^{-1}$ 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 ( $32 \mathrm{mg}, 2.335 \mathrm{mmol}$ ), I-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 $91.7^{\circ} \mathrm{C}$ constant temperature bath. A value for $k_{1}$ was estimated from four data points to be $7.27 \times 10^{-4} \mathrm{~s}^{-1}$ (standard deviation $\left.=3.9 \times 10^{-5}\right)$. The uncertainties associated with these rate constants are considerably greater than those for dioxinone $\mathbf{1}$ 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 $10-\mathrm{mL}$, 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 $91.7^{\circ} \mathrm{C}$ 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 $91.7^{\circ} \mathrm{C}$ for 45 min . Analysis of the reaction mixture by GC and using response factors for $\mathbf{1}$ and $\mathbf{6}$ indicated $\mathbf{1}$ had been formed in $15 \%$ yield and $\mathbf{6}$ 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-4H-1,3-dioxin-4-one (the Diketene-Anisaldehyde Adduct, 9). In a nitrogenpurged, 2 -necked flask equipped with a condenser and thermocouple temperature regulator (Omega controller) was placed 25 mL of toluene. The toluene was heated to $91^{\circ} \mathrm{C}$, and a solution of the dioxinone ( 0.346 $\mathrm{g}, 1.57 \mathrm{mmol}$ ) and 1 -butanol ( 315 mg ) in 10 mL of toluene was added. Analysis by $60 \mathrm{MHz}{ }^{1} \mathrm{H}$ 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 $180-240^{\circ} \mathrm{C}$. 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 $2135 \mathrm{~cm}^{-1}$.

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 $\alpha$-Peracetylhikosaminide 

Samuel J. Danishefsky* and Clarence J. Maring<br>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 $\mathbf{1}$ ) ${ }^{\text {1.b }}$ (Figure 1) was isolated from the fermentation broths of a strain of Streptomyces longissimus and from Streptomyces $A-5$. While hikizimycin exhibits broad

[^0]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]

$2 P=P=H=$ hikosamine (anamers)
2a $P=$ acetate; $\mathrm{P}^{\prime}=\mathrm{Me}=$ methyl $\alpha$-peracetylhikosaminide


4

$5 \quad X=B O P ; \alpha H ; Y, Z=O$ or $H ; O P$
$6 X=\alpha N_{3}$ (or $N H R$ ); $B H ; Y, Z=O$ or $H, O P$


2 ( $\mathrm{P}=$ = proteding groups)

## 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 $\mathrm{C}_{11}$ long-chain hydrocarbon subunit would fall within our general program in the synthesis of complex or "higher" monosaccharides. Actually, mild degradation of $\mathbf{1}$ had resulted in the retrieval of the undecose hikosamine (2) which had been characterized as its peracetyl derivative (2a). ${ }^{5 \mathrm{a}, \mathrm{b}}$ 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 $\mathbf{2 a}$ had been accomplished in a most interesting fashion by Secrist and Barnes. ${ }^{6,7}$ The key feature of this effort
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involved the coupling of phosphorane $\mathbf{3}$, 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

[^2]

Plan $A \quad C_{8}$ aldehyde $+\mathrm{C}_{4}$ diene; excision of $\mathrm{C}_{12}$
Figure 2.
data pertaining to chirality induction of structures bearing an equatorial nitrogen group at $\mathrm{C}_{4}\left(6: Y=\mathrm{N}_{3} ;\right.$ 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 $\alpha$-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 $2 \mathbf{a}$.

The first scheme involved a $\mathrm{C}_{8}$ aldehyde, 8. Cyclocondensation of 8 with diene 7 would afford a $\mathrm{C}_{12}$ 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 $\mathrm{C}_{4}$ with inversion of configuration would be necessary to reach 2 . We defer for the moment consideration of the chemistry by which the $\mathrm{C}_{8}$ aldehyde would be obtained. These general concepts are summarized under plan A (Figure 2).

Another approach contemplated the use of the $\mathrm{C}_{7}$ aldehyde, 11. Cycloaddition of $\mathbf{1 1}$ 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

[^3]

Figure 3.
at hand, the diastereofacial sense of reaction determines the connectivity between $\mathrm{C}_{7}$ and $\mathrm{C}_{8}$ of 9 or $\mathrm{C}_{6}$ and $\mathrm{C}_{7}$ 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 $\mathrm{C}_{8}$ and $\mathrm{C}_{9}$ of 9 or $\mathrm{C}_{7}$ and $\mathrm{C}_{8}$ of $\mathbf{1 2}$. 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 $\beta$ face at $\mathrm{C}_{10}$, i.e., syn to the $\beta$-disposed hydroxyl at $\mathrm{C}_{9}$. 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 $\mathrm{C}_{8}$ 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 (NaB-$\left.\mathrm{H}_{4}-\mathrm{CeCl}_{3}\right)$ followed by silylation of $\mathbf{1 5}$ [ $\left(\mathrm{Me}_{2}\left({ }^{1} \mathrm{Bu}\right) \mathrm{SiOTf}\right]$ 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 $\mathbf{1 6}$ with MCPBA in methanol ${ }^{20 a, b}$ cleanly occurred at the "glycal" double bond. A $75 \%$ yield of the anomeric mixture 17 ( $\beta: \alpha=2: 1$ ) was obtained. Hydroxylation of the $\beta$ anomer with

[^4]


8

$9 \mathrm{X}=0$
$10 \mathrm{X}=\beta \mathrm{H} ; \alpha(\mathrm{eq}) \mathrm{OH}$


11
Plan B trans pyrone (CC)

$12 \mathrm{X}=0$
$13 \mathrm{X}=\alpha \mathrm{H} ; \beta(\mathrm{eq}) \mathrm{OH}$


2


2

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 $\mathrm{C}_{6}-\mathrm{C}_{7}$ 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

[^5]

Figure 6.
with acetone in the presence of $p$ - TsOH occurred exclusively at the side chain (cf. 20). Addition of a catalytic amount of $\mathrm{H}_{2} \mathrm{SO}_{4}$ 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 ${ }^{233, b}$ 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 $\mathrm{C}_{8}$ aldehyde contemplated in plan $\mathbf{A}$.

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 $\mathbf{2 4}$ had revealed a high proclivity for cis-pyrone formation with aldehydes, where internal chelation was not an issue. As expected, the catalyst system ${B F_{3}}^{\text {etherate had never evidenced }}$ any tendencies to produce the products of chelation control. When the reaction of 23 and 24 was carried out with $\mathrm{BF}_{3}$ 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 $\mathrm{BF}_{3}$ 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 $\alpha$-oxy-

[^6]genated aldehydes had been previously established. Such che-lation-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 $\mathrm{Eu}(\mathrm{hfc})_{3}$ 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 $\mathrm{C}_{7}-\mathrm{C}_{8}$ connectivity.

Fortunately, the major silyl enol ether was obtained in crystalline form, mp $169.5-171.5^{\circ} \mathrm{C}$. 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-

[^7]

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 $\mathrm{BF}_{3}$ etherate reaction or from the minor $(1: 12,5)$ silyl enol ether adduct via the $\mathrm{Eu}(\mathrm{hfc})_{3}$ reaction. In light of these considerations, plan A was set aside in favor of plan B.

Implementation of Plan B. For the $\mathrm{C}_{7}$ aldehyde type $\mathbf{1 2}$ 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 $\alpha$-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 $\mathbf{4 1}$ to the hikosamine derivative ( $\mathbf{2 a}$ ), 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 $\mathbf{3 5}$ prepared from D-galactose. Given the availability of galactose in the proper enantiomeric form, and given the ease of its conversion to $\mathbf{3 5},{ }^{30}$ 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 $\mathrm{Eu}(\mathrm{fod})_{3}$ (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
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(30) Horton, D.; Nakadate, M.; Tronchet, J. M. J. Carbohydr. Res. 1968, 7, 56.


Figure 8.
benzoylation gave 32b. Hydroxylation, via the reaction of catalytic osmium tetroxide, gave 33a, which, upon acetalization (ace-tone-catalytic $\mathrm{H}_{2} \mathrm{SO}_{4}$ ), afforded 33b. Double debenzoylation $\left(\mathrm{K}_{2} \mathrm{CO}_{3}-\right.$ methanol) led to 33 c and acetalization (acetone-catalytic $\mathrm{H}_{2} \mathrm{SO}_{4}$ ) to afford 34 a in $54 \%$ overall yield from 32 b .

The stage was now set for oxidation of the furan ring of $34 a .{ }^{31}$ This was smoothly accomplished through the action of ozone in methylene chloride-methanol at $-78^{\circ} \mathrm{C}$. The resultant acid $\mathbf{3 4 b}$, 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.
(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.

$45 R=R^{-}=H ; O M e=\alpha$
$46 \mathrm{R}=\mathrm{R}^{\prime}=\mathrm{H} ; \mathrm{OMe}=\beta$
$48 \mathrm{R}=\mathrm{Bz} ; \mathrm{R}^{\prime}=\mathrm{H} ; \mathrm{OMe}=\alpha$
$49 \mathrm{R}=\mathrm{Bz} ; \mathrm{R}=\mathrm{H} ; \mathrm{OMe}=0$
$50 \mathrm{R}=\mathrm{Bz} ; \mathrm{R}=\mathrm{MeSO}_{2} ; \mathrm{OMe}=\alpha$

$51 R=32$ $52 R=O H$
$53 R=A C$

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 $\mathbf{3 6}$ with allyltrimethylsilane under catalysis by $\mathrm{BF}_{3}$ etherate. For the case at hand, reaction was carried under $\mathrm{BF}_{3}$ etherate catalysis to afford a $15: 1$ ratio of $\mathbf{3 7 a}$ to its $C_{6}$ epimer (not shown) (Figure 8). The alcohol was protected ( $\mathrm{NaH} ; \mathrm{BnBr}$; 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 con-
ditions ${ }^{14}$ afforded the equatorial alcohol 42.
At this stage the remaining nonanomeric stereogenic center to be controlled was that of $\mathrm{C}_{10}$. In the event, reaction of 42 with MCPBA (presumably under the guidance of the $\alpha$-disposed $C_{9}$ hydroxyl function) gave the anomeric $m$-chlorobenzoyloxy compound 43a (Figure 9). After deacylation with $\mathrm{K}_{2} \mathrm{CO}_{3}$-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 ( $\mathrm{BnBr} ; \mathrm{NaH}-\mathrm{DMF}$ ) to provide the perbenzyl ether, 44b (70\% from 42).

The last obstacle to be overcome involved the introduction of a nitrogen function at $\mathrm{C}_{4}$ 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 $\mathbf{2 a}$ to be our goal. The action of methanolic HCl on compound 44 b 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 $\alpha: \beta$ methyl glycosides (cf. 45 and 46) and a $14 \%$ yield of what is provisionally assigned as the furanoside 47 (anomeric configuration not determined). The $\alpha$ (axial) methyl glycoside, 45 , was of particular interest, since a direct comparison with intermediates during the Secrist synthesis ${ }^{6,7}$ would be possible.
The $\mathbf{4 5 , 4 6}$ mixture was subjected to benzoylation. The hope was that the $\mathrm{C}_{4}$ (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 $0^{\circ} \mathrm{C}$ 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 $\alpha$ 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 $85^{\circ} \mathrm{C}$ 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 ( $\mathrm{K}_{2} \mathrm{CO}_{3}$-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 $\left(\mathrm{Ph}_{3} \mathrm{P}\right)$; (ii) perdebenzylation $\left[\mathrm{H}_{2} / \mathrm{Pd}(\mathrm{OH})_{2}\right]^{32}$ and (iii) peracetylation to give a $35 \%$ overall yield of methyl $\alpha$-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 $\mathbf{4 1}$ render our claim of a totally synthetic route to 2 a eminently supportable. It will be noted that high margins of selectivity $(\geq 10: 1)$ were achieved in the installation of the nine nonanomeric stereogenic centers of methyl $\alpha$-peracetylhikosaminide. We also note that the availability of 44b, in which the $\mathrm{C}_{6}$ hydroxyl is uniquely protected, and the intermediacy of 53 , in which the $\mathrm{C}_{4}$ 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-dihydro-pyran-4-one (14). A solution of the diene mixture 24 ( $2.65 \mathrm{~g}, 9.08 \mathrm{mmol}$ ) and (benzyloxy)crotonaldehyde ${ }^{17}$ ( $1.92 \mathrm{~g}, 10.9 \mathrm{mmol}$ ) in dichloromethane ( 40 mL ) was cooled to $-78{ }^{\circ} \mathrm{C}$, treated with $\mathrm{BF}_{3}-\mathrm{OEt}_{2}(1.12 \mathrm{~mL}, 9.08$ 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 $\left(\mathrm{MgSO}_{4}\right)$. 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 ( $1.89 \mathrm{~g}, 57 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta$ 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 $(\mathrm{m}, 6 \mathrm{H}), 6.07(\mathrm{dt}, J=15.7,4.9 \mathrm{~Hz}), 5.95(\mathrm{dd}, J=15.8,6.0 \mathrm{~Hz}, 1 \mathrm{H})$, $5.79(\mathrm{~d}, J=4.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.55(\mathrm{~d}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.18-5.23(\mathrm{~m}, \mathrm{I}$ $\mathrm{H}), 4.45(\mathrm{~s}, 2 \mathrm{H}), 4.05(\mathrm{~d}, J=4.6 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{23} \mathrm{C}$ NMR $(62.5 \mathrm{MHz}) \delta$ 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 , $1321 \mathrm{~cm}^{-1}$.

Preparation of Glycal 15. A solution of the dihydropyrone 14 (1.50 $\mathrm{g}, 4.12 \mathrm{mmol}$ ) and $\mathrm{CeCl}_{3}-7 \mathrm{H}_{2} \mathrm{O}^{14}(1.53 \mathrm{~g}, 4.12 \mathrm{mmol}$ ) in methanol ( 60 mL ) was cooled to $-78^{\circ} \mathrm{C}$, and to this solution was added slowly sodium
borohydride ( $156 \mathrm{mg}, 4.12 \mathrm{mmol}$ ) in ethanol ( 10 mL ) over approximately 1 h . The reaction mixture was quenched at $-78^{\circ} \mathrm{C}$ 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 $\left(\mathrm{MgSO}_{4}\right)$. Concentration in vacuo and chromatography (silica gel, 75 g ; elution with ethyl acetate-hexanes, $20-30 \%$ ) gave glycal 15 ( $1.3 \mathrm{~g}, 86 \%$ ): ${ }^{1} \mathrm{H}$ NMR $(250 \mathrm{MHz}) \delta 8.1-8.05(\mathrm{~m}, 2 \mathrm{H}), 7.61-7.20(\mathrm{~m}, 8 \mathrm{H}), 6.53(\mathrm{dd}, J=6.2$, $1.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.00(\mathrm{dt}, J=16.6,5.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.86$ (dd, $J=15.7,5.5$ $\mathrm{Hz}, 1 \mathrm{H}), 5.53(\mathrm{~d}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.84-4.80(\mathrm{~m}, 1 \mathrm{H}), 4.74-4.66(\mathrm{~m}$, $2 \mathrm{H}), 4.4(\mathrm{~s}, 2 \mathrm{H}), 4.00(\mathrm{~d}, J=5.4 \mathrm{~Hz}, 1 \mathrm{H})$.
Silylation of Glycal 15: Formation of Silyl Ether 16. A solution of glycal $15(1.1 \mathrm{~g}, 3.00 \mathrm{mmol})$ in dichloromethane ( 25 mL ) was cooled to $-78^{\circ} \mathrm{C}$. To this solution was added 2,6 -lutidine ( $0.422 \mathrm{~mL}, 3.75 \mathrm{mmol}$ ) followed by tert-butyldimethylsilyl triflate $(0.688 \mathrm{~mL}, 3.0 \mathrm{mmol}) .^{33}$ 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 $\left(\mathrm{MgSO}_{4}\right)$. Concentration in vacuo and chromatography (silica gel, 75 g; elution with $20 \%$ ethyl acetate-hexanes) gave silyl ether 16 ( $1.25 \mathrm{~g}, 86.8 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( 90 MHz ) $\delta 8.17-8.09$ ( m , 1 H ), 7.61-7.30 (m, 8 H ), 6.53 (br d, $J=4.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 6.04-5.97 (m, $2 \mathrm{H}), 5.56-5.46(\mathrm{~m}, 1 \mathrm{H}), 4.84-4.67(\mathrm{~m}, 2 \mathrm{H}), 4.47(\mathrm{~s}, 2 \mathrm{H}), 4.06(\mathrm{~d}$ $J=4.5 \mathrm{~Hz}, 1 \mathrm{H}), 0.87(\mathrm{~s}, 9 \mathrm{H}), 0.19(\mathrm{~s}, 3 \mathrm{H}), 0.113(\mathrm{~s}, 3 \mathrm{H})$.
Tetraol Anomers 19. A solution of glycal silyl ether 16 ( $2.45 \mathrm{~g}, 5.10$ mmol ), osmium tetroxide ( 0.15 mmol ), and $N$-methylmorpholine $N$ oxide ${ }^{21}$ ( $1.49 \mathrm{~g}, 12.76 \mathrm{mmol}$ ) 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 $(6 \mathrm{~g})$ and solid sodium bisulfite $(2.0 \mathrm{~g})$ 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 $19(2.2 \mathrm{~g}$, $78.8 \%$ ) as the major product and a minor isomer, 21 ( $0.315 \mathrm{~g}, 11.2 \%$ ).

Anomers 19: ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 8.10-8.05$ (m, 2 H ), $7.60-7.57$ ( 1 H ), 7.49-7.42 ( 3 H ), $7.38-7.22$ ( $\mathrm{m}, 5 \mathrm{H}$ ), $5.52-5.51(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4$ ), $5.37(\mathrm{~d}, J=3.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-1 \alpha), 4.72(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-1 \beta), 4.53$ (d, $J=12.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.47 (d, $J=12.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.16-3.49(\mathrm{~m}, 2 \mathrm{H})$, 2.47 (br m, 2 H ), $2.29(\mathrm{~s}, 2 \mathrm{H}), 0.77(\mathrm{~s}, 9 \mathrm{H}), 0.17(\mathrm{~s}, 3 \mathrm{H}), 0.08(\mathrm{~s}, 3$ H); IR $3600-3150,2960,2940,2865,1725,1700,1605,1585,1455 \mathrm{~cm}^{-1}$; MS $m / e$ (\%) 491 ( $\mathrm{M}^{+}-57,1.6$ ), 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: ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta$ 8.06-7.99 (m, 2 H ), 7.55-7.37 (m, 3 H$), 7.25-7.16(\mathrm{~m}, 5 \mathrm{H}), 5.59(\mathrm{~d}$, $J=3.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-4-4 \alpha$ ), 5.55 (d, $J=3.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-4 \beta$ ), 5.50 (d, $J$ $=3.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-\mathrm{I} \alpha), 4.74(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-1 \beta), 4.47-4.41(\mathrm{~m}$, 3 H ), 4.09-3.44 (m), 2.44 (br m, 2 H ), $2.30(\mathrm{~s}, 2 \mathrm{H}), 0.75(\mathrm{~s}, 9 \mathrm{H}, \alpha)$, 0.74 (s, $9 \mathrm{H}, \beta$ ), 0.10 (s, 3 H ), 0.09 (s, 3 H ); IR 3600-3150, 3020, 2980 , 2940, 2870, 1725, 1601, 1451, 1385, $1360 \mathrm{~cm}^{-1}$; MS m/e (\%) $491\left(\mathrm{M}^{+}\right.$ $-57,0.8), 473$ (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 $50^{\circ} \mathrm{C}$ with anhydrous $\mathrm{MgSO}_{4}(12 \mathrm{~g})$ for 26 h . Concentrated sulfuric acid ( 0.125 mL ) was then added with $\mathrm{MgSO}_{4}(5 \mathrm{~g})$ 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 $\left(\mathrm{MgSO}_{4}\right)$, and concentrated in vacuo. Chromatography (silica gel, 100 g ; elution with ethyl acetate-hexanes, $20-40 \%$ ) afforded $21(0.962 \mathrm{~g}, 56 \%$ ) and the side-chain monoacetonide $(0.472 \mathrm{~g})$. Recycling the monoacetonide 20 using the above reaction conditions afforded an additional 300 mg of $\mathbf{2 1}$ for an overall conversion of $73 \%$ : ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 8.04-8.00(\mathrm{~m}, 2 \mathrm{H}), 7.57-7.40(\mathrm{~m}, 3$ H), $7.33-7.28(\mathrm{~m}, 5 \mathrm{H}), 5.65-5.64(\mathrm{~m}, 1 \mathrm{H}), 5.61(\mathrm{~d}, J=4.2 \mathrm{~Hz}, 1 \mathrm{H})$, 4.58 (AB quartet, $J=12.3 \mathrm{~Hz}, 2 \mathrm{H}$ ), 4.27-4.22 (m, I H), 4.09-3.92 (m, $4 \mathrm{H}), 3.75(\mathrm{dd}, J=10.5,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.59(\mathrm{dd}, J=10.5,6.0 \mathrm{~Hz}, 1$ H), $1.55(\mathrm{~s}, 3 \mathrm{H}, 1.42(\mathrm{~s}, 3 \mathrm{H}), 1.39(\mathrm{~s}, 3 \mathrm{H}), 1.30(\mathrm{~s}, 3 \mathrm{H}), 0.80(\mathrm{~s}, 9$ H ), $0.11(\mathrm{~s}, 3 \mathrm{H}), 0.10(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 62.5 MHz ) $\delta 165.0$, 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 $\mathrm{g}, 1.53 \mathrm{mmol}$ ) in ethanol ( 80 mL ) was hydrogenated with Pearlman's catalyst ${ }^{32}\left[20 \% \mathrm{Pd}(\mathrm{OH})_{2} / \mathrm{C} ; 650 \mathrm{mg}\right]$ under l atm of hydogen for 5 h . The reaction was filtered through a Celite pad and concentrated.
(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 ( $765 \mathrm{mg}, 93 \%$ ). Recrystallization from hexanes gave an a nalytical sample: mp $104.5-106^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta$ $8.05-8.00(\mathrm{~m}, 2 \mathrm{H}), 7.61-7.54(\mathrm{~m}, 1 \mathrm{H}), 7.49-7.41$ (m, 2 H ), 5.68 (d, $J=4.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.65(\mathrm{dd}, J=3.4,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.1-3.90(\mathrm{~m}, 5 \mathrm{H})$, 3.84 (apparent dt, $J=4.0,11.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.72 (ddd, $J=11.6,7.8,4.5$ $\mathrm{Hz}, 1 \mathrm{H}), 2.11(\mathrm{dd}, J=7.7,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.56(\mathrm{~s}, 3 \mathrm{H}), 1.41(\mathrm{~s}, 3 \mathrm{H})$, $1.39(\mathrm{~s}, 3 \mathrm{H}), 1.29(\mathrm{~s}, 3 \mathrm{H}), 0.80(\mathrm{~s}, 9 \mathrm{H}), 0.11(\mathrm{~s}, 3 \mathrm{H}), 0.10(\mathrm{~s}, 3 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( 62.5 MHz ) $\delta 165.2,132.7,130.3,129.7,128.4,109.6,108.4$, $97.6,81.39,77.6,76.6,74.0,73.4,71.6,69.3,62.9,28.1,27.1,27.0,26.9$, $25.6,17.9,-4.7,-5.0$; $1 \mathrm{R}\left(\mathrm{CHCl}_{3}\right) 3550-3350,2850,1695,1600,1420$ $\mathrm{cm}^{-1} ; \mathrm{MS} \mathrm{m} / e(\%) 523\left(\mathrm{M}^{+}-15,5.6\right), 481\left(\mathrm{M}^{+}-57,14.4\right), 423$ (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 $\mathrm{C}_{27} \mathrm{H}_{42} \mathrm{O}_{9} \mathrm{Si}$ (538.7): C, 60.20; $\mathrm{H}, 7.85$. Found: C, $60.19 ; \mathrm{H}, 7.98$.

Oxidation of 22: Formation of 23. A solution of oxalyl chloride ( 0.50 $\mathrm{mL}, 5.8 \mathrm{mmol}$ ) in dichloromethane ( 20 mL ) was cooled to $-78^{\circ} \mathrm{C}$ followed by addition of dimethyl sulfoxide ( $0.82 \mathrm{~mL}, 11.6 \mathrm{mmol}$ ) in dichloromethane ( 2 mL ). After 10 min the alcohol $22(624 \mathrm{mg}, 1.16$ mmol ) in dichloromethane ( 8 mL ) was added, and the reaction was stirred an additional 20 min followed by addition of triethylamine ( 3.23 $\mathrm{mL}, 23.2 \mathrm{mmol}$ ) 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 $\left(\mathrm{MgSO}_{4}\right)$. Concentration in vacuo and chromatography (silica gel, 50 g ; elution with $20 \%$ ethyl acetate-hexanes) afforded the aldehyde 23 ( $452 \mathrm{mg}, 73 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 9.72(\mathrm{~d}, J=0.8 \mathrm{~Hz}$, I H), $8.04-8.00(\mathrm{~m}, 2 \mathrm{H})$, $7.61-7.56(\mathrm{~m}, 1 \mathrm{H}), 7.48-7.42(\mathrm{~m}, 2 \mathrm{H}), 5.71(\mathrm{~d}, J=4.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.64$ (dd, $J=3.2,2.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.54 (dd, $J=5.7,0.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.31$ (dd, $J=8.7,5.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.14-4.03(\mathrm{~m}, 3 \mathrm{H}), 1.57(\mathrm{~s}, 3 \mathrm{H}), 1.46(\mathrm{~s}, 3 \mathrm{H})$, $1.42(\mathrm{~s}, 3 \mathrm{H}), 1.27(\mathrm{~s}, 3 \mathrm{H}), 0.80(\mathrm{~s}, 9 \mathrm{H}), 0.11(\mathrm{~s}, 3 \mathrm{H}), 0.09(\mathrm{~s}, 3 \mathrm{H})$; IR 2995, 2960, 2940, 2850, 1720, 1600, 1590, 1450, 1390, $1380 \mathrm{~cm}^{-1}$.

Formation of Silyl Enol Ether Adducts 29 and 30. A solution of aldehyde 23 ( $358 \mathrm{mg}, 0.668 \mathrm{mmol}$ ), diene mixture 7 (ca. $50 \%, 720 \mathrm{mg}$, $2.15 \mathrm{mmol})$, and $\mathrm{Eu}(\mathrm{hfc}){ }_{3}{ }^{24}(440 \mathrm{mg}, 0.386 \mathrm{mmol})$ in $\mathrm{CDCl}_{3}(2.5 \mathrm{~mL})$ 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 ( $\mathrm{mp} 169.5-171.5^{\circ} \mathrm{C}$ ). There were also mixed fractions of enol ether 29 and the minor enol ether 30, as well as byproducts of the shift reagent catalyst. Total weight recovery of enol ether containing fractions was 441 mg and the ratio of $\mathbf{2 9 : 3 0}$ was ca. 12.5:1.

Enol ether 29: ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 8.08-8.01(\mathrm{~m}, 4 \mathrm{H}), 7.57-7.36$ (m, 6 H$), 5.60(\mathrm{~m}, 2 \mathrm{H}), 5.37(\mathrm{~d}, J=4 \mathrm{~Hz}, 1 \mathrm{H}), 5.08(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.02$ (d, $J=1.2 \mathrm{H}, 1 \mathrm{H}), 4.29(\mathrm{dd}, J=6.6,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.16(\mathrm{dd}, J=9.0$, $6.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.01-3.90(\mathrm{~m}, 4 \mathrm{H}), 3.34(\mathrm{~s}, 3 \mathrm{H}), \mathrm{l} .50(\mathrm{~s}, 3 \mathrm{H}), \mathrm{I} .34(\mathrm{~s}$, $3 \mathrm{H}), 1.16(\mathrm{~s}, 3 \mathrm{H}), 1.04(\mathrm{~s}, 3 \mathrm{H}), 0.82(\mathrm{~s}, 9 \mathrm{H}), 0.80(\mathrm{~s}, 9 \mathrm{H}), 0.17$ (s, $3 \mathrm{H}), 0.09(\mathrm{~s}, 3 \mathrm{H}), 0.087(\mathrm{~s}, 3 \mathrm{H}), 0.06(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 62.5 MHz ) $\delta 166.7$, 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, $1450 \mathrm{~cm}^{-1}$.

Minor enol ether 30: ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 8.55-8.10(\mathrm{~m}, 2 \mathrm{H}$ ), 8.03-7.99 (m, 2 H), 7.60-7.39 (m, 6 H), 5.77-5.73 (m, I H), 5.69-5.67 (m, 1 H), $5.66(\mathrm{~d}, J=4.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.11(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.02(\mathrm{~d}, J=1 \mathrm{~Hz}$, $1 \mathrm{H}), 3.52(\mathrm{~s}, 3 \mathrm{H}), 1.50(\mathrm{~s}, 3 \mathrm{H}), 1.41(\mathrm{~s}, 3 \mathrm{H}), 1.33(\mathrm{~s}, 3 \mathrm{H}), 1.19(\mathrm{~s}$, $3 \mathrm{H}), 0.09(\mathrm{~s}, 9 \mathrm{H}), 0.08(\mathrm{~s}, 9 \mathrm{H}), 0.18(\mathrm{~s}, 3 \mathrm{H}), 0.12(\mathrm{~s}, 3 \mathrm{H}), 0.11(\mathrm{~s}$, 3 H ), $0.04(\mathrm{~s}, 3 \mathrm{H})$.
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 ( $254 \mathrm{mg}, 51 \%$ ) and $\mathbf{2 5}, \mathrm{mp}$ $170-172{ }^{\circ} \mathrm{C}(20 \mathrm{mg}, 4 \%)$. For 26: ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 8.07-8.03$ (m, 4 H ), $7.60-7.40(\mathrm{~m}, 7 \mathrm{H}), 5.79(\mathrm{~d}, J=4 \mathrm{~Hz}, 1 \mathrm{H}), 5.61$ (dd, $J=$ $3.1,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.52-5.50(\mathrm{~m}, 2 \mathrm{H}), 4.79(\mathrm{~m}, 1 \mathrm{H}), 4.43(\mathrm{dd}, J=7.1$, $3.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.18(\mathrm{dd}, J=9.0,7.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.05-3.94(\mathrm{~m}, 3 \mathrm{H}), 1.44$ $(\mathrm{s}, 3 \mathrm{H}), 1.29(\mathrm{~s}, 3 \mathrm{H}), 1.25(\mathrm{~s}, 3 \mathrm{H}), 1.20(\mathrm{~s}, 3 \mathrm{H}), 0.79(\mathrm{~s}, 9 \mathrm{H}), 0.09$ (s, 3 H ) , $0.08(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 62.5 MHz ) $\delta 186.0,165.2,162.6$, 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, $1450 \mathrm{~cm}^{-1}$. For 25: ${ }^{1} \mathrm{H}$ NMR $(250 \mathrm{MHz}) \delta 8.0-7.90(\mathrm{~m}, 4 \mathrm{H}), 7.53-7.29(\mathrm{~m}, 7 \mathrm{H}), 5.87(\mathrm{dd}, J=3.9$, $0.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.64(\mathrm{~m}, 24), 5.49(\mathrm{dd}, J=5.9,0.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.72(\mathrm{dd}$, $J=5.4,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.62(\mathrm{~m}, 1 \mathrm{H}), 4.32(\mathrm{dd}, J=8.7,4.9 \mathrm{~Hz}, 1 \mathrm{H})$, $4.08(\mathrm{dd}, J=8.7,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.04-3.95(\mathrm{~m}, 2 \mathrm{H})$; IR 1730,1600 , $1450,1380 \mathrm{~cm}^{-1} ;$ MS $m / e(\%) 709\left(\mathrm{M}^{+}-15,0.4\right), 667(2.3), 469(2.4)$, 327 (2.0), 259 (2.5), 179 (18.8), 105 (100).

Preparation of Dihydropyran Adduct 31a. A solution of the diene 7 $(0.967 \mathrm{~g}, 2.88 \mathrm{mmol}), 2$-furaldehyde $(0.415 \mathrm{~g}, 4.3 \mathrm{mmol})$, and $\mathrm{Eu}(\mathrm{fod}))_{3}{ }^{24}$ ( $171 \mathrm{mg}, 0.1 \mathrm{mmol}$ ) in $\mathrm{CDCl}_{3}\left(0.75 \mathrm{~mL}\right.$ ) was stirred for 3 days at $25^{\circ} \mathrm{C}$. 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 $76-77{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}$ NMR ( $250 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.00-7.96(\mathrm{~m}, 2 \mathrm{H})$, $7.56-7.49(\mathrm{~m}, 1 \mathrm{H}), 7.43-7.36(\mathrm{~m}, 2 \mathrm{H}), 7.25(\mathrm{~d}, J=0.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.33$ (dd, $J=3.3,0.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.21(\mathrm{dd}, J=3.3,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.72$ (dd, $J=2.6,1.4 \mathrm{~Hz}, \mathrm{lH}), 5.32(\mathrm{brs}, 1 \mathrm{H}), 5.11(\mathrm{~d}, J=1.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.96$ (d, $J=2.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.57(\mathrm{~s}, 3 \mathrm{H}), 0.82(\mathrm{~s}, 9 \mathrm{H}), 0.21(\mathrm{~s}, 3 \mathrm{H}), 0.08$ ( $\mathrm{s}, 3 \mathrm{H}$ ) ; IR ( $\mathrm{CHCl}_{3}$ ) 1720, 1668, 1600, 1460, $1396 \mathrm{~cm}^{-1} ; \mathrm{MS} \mathrm{m} / \mathrm{e}$ (\%) $399\left(\mathrm{M}^{+}-31, \mathrm{OMe}, 0.6\right), 373\left(\mathrm{M}^{+}-15, t-\mathrm{Bu}, 0.7\right), 334$ (3.0), 309 (1.5), 251 (12.7), 105 (30.5).

Formation of Dihydropyrone 31. The enol ether 31a ( $200 \mathrm{mg}, 0.69$ 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 ( $195 \mathrm{mg}, 98 \%$ ). 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: ${ }^{1} \mathrm{H}$ NMR ( $90 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.07-7.94(\mathrm{~m}, 2 \mathrm{H}), 7.61-7.37$ (m, 5 H), $6.54(\mathrm{~d}, J=3 \mathrm{~Hz}, 1 \mathrm{H}), 6.40(\mathrm{dd}, J=3,2 \mathrm{~Hz}, 1 \mathrm{H}), 5.83(\mathrm{~d}, J=$ $6 \mathrm{~Hz}, 1 \mathrm{H}), 5.60(\mathrm{~d}, J=6 \mathrm{~Hz}, 1 \mathrm{H})$; $\mathrm{IR}\left(\mathrm{CDCl}_{3}\right) 3020,1734,1696$, 1601, $1500,1455,1410 \mathrm{~cm}^{-1}$.

Formation of Alcohol 32a. A solution of the furyldihydropyrone 31 ( $135 \mathrm{mg}, 0.475 \mathrm{mmol}$ ) and cerium (III) chloride heptahydrate ( 176 mg , 0.475 mmol ) in methanol ( 5 mL ) and dichloromethane ( 5 mL ) cooled to $-78{ }^{\circ} \mathrm{C}$ was treated with sodium borohydride ( $27 \mathrm{mg}, 0.712 \mathrm{mmol}$ ) 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 $\left(\mathrm{MgSO}_{4}\right)$. Concentration in vacuo and chromatography (silica gel, 12 g ; elution with $20 \%$ ethyl acetate-hexanes) gave glycal 32a ( $129 \mathrm{mg}, 95 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( $90 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.07-7.97$ (m, 2 H), 7.6-7.22 (m, 4 H$), 6.54$ (dd, $J=5.5,2 \mathrm{~Hz}, 1 \mathrm{H}), 6.31-6.17$ (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, l H); IR ( $\mathrm{CHCl}_{3}$ ) 3600-3200, 3040, 1729, 1650, 1606, 1506, 1455 $\mathrm{cm}^{-1} ; \mathrm{MS} \mathrm{m} / e(\%) 286\left(\mathrm{M}^{+}, 0.3\right), 214$ (19.7), 164 (7.4), 147 (2.0), 105 (100).

Benzoylation of 32b. The furylglycal 32a ( $129 \mathrm{mg}, 0.451 \mathrm{mmol}$ ) was treated with benzoyl chloride ( $0.12 \mathrm{~mL}, 1.0 \mathrm{mmol}$ ), 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 ( $\mathrm{MgSO}_{4}$ ). The crude product crystallized from $20 \%$ ethyl acetate-hexanes to give dibenzoate ( 132 mg ), $\mathrm{mp} 132-133^{\circ} \mathrm{C}$. The mother liquors were chromatographed to give an additional 35 mg for an overall yield of $95 \%$ : ${ }^{1} \mathrm{H}$ 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, $J=6 \mathrm{~Hz}, 1 \mathrm{H}), 6.37-6.22(\mathrm{~m}, 2 \mathrm{H}), 6.00(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 5.34(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, 4.91 (apparent dt, $J=6,2 \mathrm{~Hz}, 1 \mathrm{H}$ ); IR $3070,3050,1725,1650,1605$, $1585,1505,1494,1450 \mathrm{~cm}^{-1}$. Anal. Calcd for $\mathrm{C}_{23} \mathrm{H}_{18} \mathrm{O}_{6}: \mathrm{C}, 70.76 ; \mathrm{H}$, 4.64. Found: C, 70.68 ; H, 4.78.

Diol 33a. The dibenzoate 32b ( $132 \mathrm{mg}, 0.338 \mathrm{mmol}$ ) was treated with osmium tetroxide ( 0.1 mmol ) and $N$-methylmorpholine $N$-oxide ( 100 mg , $0.85 \mathrm{mmol})$ 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 $\mathrm{mg}, 95 \%):{ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 8.08-8.02(\mathrm{~m}, 2 \mathrm{H}), 7.92-7.89(\mathrm{~m}$, $2 \mathrm{H}), 7.64-7.43(\mathrm{~m}, 4 \mathrm{H}), 7.37-7.29(\mathrm{~m}, 3 \mathrm{H}), 6.32(\mathrm{~d}, J=3.3 \mathrm{~Hz}, 1$ H), $6.26(\mathrm{dd}, J=3.3,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.99(\mathrm{dd}, J=3.1,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.71$ (dd, $J=10.3,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.66(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.55(\mathrm{~s}, 1 \mathrm{H}), 4.43-4.34$ (m, I H), $2.40(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 1.57(\mathrm{~d}, J=6.6 \mathrm{~Hz}, \mathrm{I} \mathrm{H})$; IR $3600-3200$, $3040,1730,1605,1452 \mathrm{~cm}^{-1}$; MS m/e (\%) $407\left(\mathrm{M}^{+}-17,0.2\right), 347(2.5)$, 284 (20.0), 223 (8.3), 163 (9.9), 105 (100).

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

Formation of Diol Acetonide 33c. The dibenzoate 33b ( $50 \mathrm{mg}, 0.107$ 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 ( $25.5 \mathrm{mg}, 92 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 7.43$ (dd, $J=1.7,0.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.49(\mathrm{dd}, J=3.2$, $0.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.40(\mathrm{dd}, J=3.2,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.69(\mathrm{~d}, J=4.6 \mathrm{~Hz}, 1$ H), $5.08(\mathrm{~d}, J=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.24-4.18(\mathrm{~m}, 2 \mathrm{H}), 4.04-3.98(\mathrm{~m}, 1 \mathrm{H})$, $2.98(\mathrm{~d}, J=6.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.56(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.57(\mathrm{~s}, 3 \mathrm{H}), 1.41$ ( $\mathrm{s}, 3 \mathrm{H}$ ); IR 3600-3200, 3010, 2990, 2930, 1500, 1450, 1380, $1370 \mathrm{~cm}^{-1}$; MS $m / e(\%) 256\left(\mathrm{M}^{+}, 3.1\right), 241$ (1.6), 238 (5.3), 156 (12.4), 100 (100), 84 (40), 73 (63).

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

Ozonolysis of Furyldiacetonide 34a. Formation of 35. A solution of the furyldiacetonide 34 a ( $21 \mathrm{mg}, 0.071 \mathrm{mmol}$ ) in dichloromethane ( 2 mL ) and methanol ( 1 mL ) was cooled to $-78^{\circ} \mathrm{C}$. 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 $\mathrm{BH}_{3}-\mathrm{THF}$ complex ( $1 \mathrm{M}, 0.4 \mathrm{~mL}$ ) for 24 h . The reaction was quenched with acetic acid and methanol and concentrated. Chromatography on silica gel gave the racemate $35(9.2 \mathrm{mg}, 50 \%)$ 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 $37 \mathrm{a}(2.85 \mathrm{~g}, 9.53 \mathrm{mmol}$ ) in $N, N$-dimethylformamide ( 50 mL ) was treated with sodium hydride ( $50 \%$ oil dispersion) $(2.40 \mathrm{~g}, 50.15 \mathrm{mmol}$ ) followed by addition of benzyl bromide ( $2.5 \mathrm{~mL}, 20.9 \mathrm{mmol}$ ). 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 ( $\mathrm{MgSO}_{4}$ ) and concentrated in vacuo. Chromatography of the crude product (silica gel, 150 g ; elution with $10 \%$ ethyl acetate-hexanes) afforded ether $\mathbf{3 7 b}$ ( $3.54 \mathrm{~g}, 95 \%$ ) as an oil which crystallized on standing. Recrystallization from methanol provided an analytical sample: $\mathrm{mp} 60.5-62.0{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 7.40-7.28(\mathrm{~m}, 5 \mathrm{H}), 6.01-5.90(\mathrm{~m}, 1 \mathrm{H}), 5.53(\mathrm{~d}$, $J=5.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.24-5.08(\mathrm{~m}, 2 \mathrm{H}), 4.69-4.57(\mathrm{~m}, 2 \mathrm{H}), 4.48(\mathrm{dd}, J$ $=8.0,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.28(\mathrm{dd}, J=5.0,2.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.79-3.67(\mathrm{~m}, 2$ H), 2.66-2.55 (m, 1 H), 2.41-2.30(m, 1 H), $1.50(\mathrm{~s}, 3 \mathrm{H}), 1.48(\mathrm{~s}, 3$ $\mathrm{H}), 1.38(\mathrm{~s}, 3 \mathrm{H}), 1.32(\mathrm{~s}, 3 \mathrm{H})$; IR $\left(\mathrm{CHCl}_{3}\right) 2980,2930,1490,1450$, $1430,1380,1370 \mathrm{~cm}^{-1} ;[\alpha]^{23} \mathrm{D}=-87.8^{\circ}\left(c=2.51, \mathrm{CHCl}_{3}\right)$. Anal. Calcd for $\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}_{6}$ (390.48): C, $67.67 ; \mathrm{H}, 7.74$. Found: $\mathrm{C}, 67.91 ; \mathrm{H}, 7.88$.

Ozonolysis of 37b. Formation of Aldehyde 38. A solution of the benzyl ether $37 \mathrm{~b}(1.0 \mathrm{~g}, 2.64 \mathrm{mmol})$ in dichloromethane $(45 \mathrm{~mL})$ at -78 ${ }^{\circ} \mathrm{C}$ was ozonized until a saturated blue solution persisted. The solution was then purged with nitrogen at $-78^{\circ} \mathrm{C}$ followed immediately by a reductive workup with zinc powder $(11 \mathrm{~g})$ 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: ${ }^{1} \mathrm{H}$ NMR $(250 \mathrm{MHz}) \delta 9.81(\mathrm{t}, J=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.34(\mathrm{~m}, 5 \mathrm{H}), 5.51(\mathrm{~d}, J=5.0$ $\mathrm{Hz}, 1 \mathrm{H}), 4.67(\mathrm{~s}, 2 \mathrm{H}), 4.63$ (dd, $J=8.0,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.46(\mathrm{dd}, J=$ $8.0,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.31(\mathrm{dd}, J=5.0,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.21(\mathrm{ddd}, J=9.0$, $6.6,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.76(\mathrm{dd}, J=9.0,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.89$ (ddd, $J=16.6$, $4.4,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.72$ (ddd, $J=16.6,6.6,2.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.51(\mathrm{~s}, 3 \mathrm{H})$, $1.47(\mathrm{~s}, 3 \mathrm{H}), 1.38(\mathrm{~s}, 3 \mathrm{H}), 1.32(\mathrm{~s}, 3 \mathrm{H})$; IR 1727, 1458, 1386, 1375 $\mathrm{cm}^{-1} ;[\alpha]^{23} \mathrm{D}-56.4^{\circ}\left(c=1.93, \mathrm{CHCl}_{3}\right) ;$ HRMS calcd for $\mathrm{C}_{21} \mathrm{H}_{28} \mathrm{O}_{7}$ 392.1835, found 392.1833.

Formation of Enol Acetate 39. The aldehyde 38 ( $1.0 \mathrm{~g}, 2.55 \mathrm{mmol}$ ) was stirred with acetic anhydride ( $2.5 \mathrm{~mL}, 26.4 \mathrm{mmol}$ ), triethylamine ( $5.0 \mathrm{~mL}, 35.8 \mathrm{mmol}$ ), 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 ( $\mathrm{SiO}_{2}, 25 \mathrm{~g}$; elution with $10 \%$ ethyl acetate-hexanes) to give the $E$ and $Z$ isomers ( $1.09 \mathrm{~g}, 95 \%$ yield) in approximately a 6:1 ratio, respectively. Chromatography (silica gel) in $10 \%$ ether-hexanes resolved these two isomers for characterization purposes.
$E$ isomer: ${ }^{1} \mathrm{H}$ NMR $(250 \mathrm{MHz}) \delta 7.40(\mathrm{~d}, J=12.4 \mathrm{~Hz}, 1 \mathrm{H})$, $7.37-7.25(\mathrm{~m}, 5 \mathrm{H}), 5.49(\mathrm{~d}, J=5.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.40(\mathrm{dd}, J=12.6,3.9$ $\mathrm{Hz}, 1 \mathrm{H}), 4.63-4.41(\mathrm{~m}, 4 \mathrm{H}), 4.29-4.26(\mathrm{dd}, J=5.0,2.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.06$ $(\mathrm{t}, J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.72(\mathrm{dd}, J=9.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.14(\mathrm{~s}, 3 \mathrm{H}), 1.5 \mathrm{l}$
(s, 3 H$), 1.43(\mathrm{~s}, 3 \mathrm{H}), 1.36(\mathrm{~s}, 3 \mathrm{H}), 1.31(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (62.5 $\mathrm{MHz}) \delta 167.7,139.1,138.2,128.3,128.1,127.6,112.5,109.0$, 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 $\left(\mathrm{CHCl}_{3}\right) 2985,2930,1750,1675,1485,1450 \mathrm{~cm}^{-1} ;[\alpha]^{23} \mathrm{D}-48.80^{\circ}(c=$ 2.09, $\mathrm{CHCl}_{3}$ ); HRMS calcd for $\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{O}_{8} 434.1940$, found 434.1906.
$Z$ isomer: ${ }^{1} \mathrm{H}$ NMR $(250 \mathrm{MHz}) \delta 7.39(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 1 \mathrm{H})$, $7.35-7.30(\mathrm{~m}, 5 \mathrm{H}), 5.51(\mathrm{~d}, J=5.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.90(\mathrm{dd}, J=9.6,6.5$ $\mathrm{Hz}, \mathrm{I} \mathrm{H}), 4.7 \mathrm{I}-4.45(\mathrm{~m}, 5 \mathrm{H}), 4.30(\mathrm{dd}, J=5.0,2.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.73$ (dd, $J=9.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.10(\mathrm{~s}, 3 \mathrm{H}), 1.53(\mathrm{~s}, 3 \mathrm{H}), 1.47(\mathrm{~s}, 3 \mathrm{H}), 1.39$ (s, 3 H ), 1.32 (s, 3 H ); IR $\left(\mathrm{CHCl}_{3}\right) 2985,2930,1755,1670,1485,1450$ $\mathrm{cm}^{-1}$.

Compound 40. Ozonolysis of Enol Acetates 39 ( $E$ and $Z$ Isomers). A solution of the enol acetates 39 ( $E$ and $Z$ isomers) $(0.636 \mathrm{~g}, 1.46 \mathrm{mmol})$ in dichloromethane ( 14 mL ) and methanol ( 14 mL ) at $-78^{\circ} \mathrm{C}$ was ozonized until a saturated blue solution persisted. The solution was purged with nitrogen followed by reductive workup with dimethyl sulfide ( $5 \mathrm{~mL},-78^{\circ} \mathrm{C}$ 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 $40(0.512 \mathrm{~g}, 93 \%)$.

Reduction of Dihydropyrone 41. Formation of Glycal 42. Sodium borohydride ( $174 \mathrm{mg}, 4.62 \mathrm{mmol}$ ) in ethanol ( 8 mL ) was added slowly over a period of 30 min to a solution of the known dihydropyrone 41 ( 750 $\mathrm{mg}, 1.32 \mathrm{mmol}$ ) and $\mathrm{CeCl}_{3}-7 \mathrm{H}_{2} \mathrm{O}(490 \mathrm{mg}, 1.32 \mathrm{mmol})$ in methanol ( 15 mL ) and dichloromethane ( 12 mL ) at $-78^{\circ} \mathrm{C}$. The reaction was quenched with acetic acid $(1.5 \mathrm{~mL})$ at $-78^{\circ} \mathrm{C}$ and then with pH 6.5 phosphate buffer $(15 \mathrm{~mL})$. The reaction was diluted with ether $(400 \mathrm{~mL})$ and extracted with water. The aqueous layer was washed with ether ( 100 $\mathrm{mL})$, and the combined organics were dried $\left(\mathrm{MgSO}_{4}\right)$ and concentrated in vacuo. Chromatography (silica gel, 100 g ; elution with $20 \%$ EtOAchexanes) gave glycal 42 ( $715 \mathrm{mg}, 95 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( $250 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.11-8.08(\mathrm{~m}, 2 \mathrm{H}), 7.63-7.60(\mathrm{~m}, 1 \mathrm{H}), 7.51-7.45(\mathrm{~m}, 2 \mathrm{H}), 7.30-7.23$ $(\mathrm{m}, 5 \mathrm{H}), 6.43(\mathrm{dd}, J=6.0,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.54(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 1 \mathrm{H})$, $5.32(\mathrm{dd}, J=10.7,6.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.85(\mathrm{dd}, J=6.0,2.4 \mathrm{~Hz}, 1 \mathrm{H})$, $4.71-4.66(\mathrm{~m}, 2 \mathrm{H}), 4.53(\mathrm{brd}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.49(\mathrm{dd}, J=8.1,1.6$ $\mathrm{Hz}, \mathrm{l} \mathrm{H}), 4.45-4.39(\mathrm{~m}, 2 \mathrm{H}), 4.33(\mathrm{dd}, J=4.8,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.24$ (dd, $J=9.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.02(\mathrm{dd}, 10.3,0.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.60(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 1.5$ $(\mathrm{s}, 3 \mathrm{H}), 1.39(\mathrm{~s}, 3 \mathrm{H}), 1.34(\mathrm{~s}, 3 \mathrm{H})$; IR $\left(\mathrm{CHCl}_{3}\right) 3600-3350,2990$, $2940,1708,1650,1600,1450 \mathrm{~cm}^{-1} ;[\alpha]^{23} \mathrm{D}+90.1^{\circ}\left(c=3.18, \mathrm{CHCl}_{3}\right)$; MS (EI) $m / e 568\left(\mathrm{M}^{+}, 0.1\right), 553\left(\mathrm{M}^{+}-15,7.4\right), 349$ (22.7), 232 (39.1) 91 (79.0).

Oxidation of Glycal 42. Formation of Anomeric m-Chlorobenzoates 43a. A solution of glycal 42 ( $695 \mathrm{mg}, 1.22 \mathrm{mmol}$ ) and $m$-chloroperoxybenzoic acid ( $85 \%, 296 \mathrm{mg}, 1.46 \mathrm{mmol}$ ) in dichloromethane ( 25 mL ) was stirred at $0^{\circ} \mathrm{C}$ 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 $\left(\mathrm{MgSO}_{4}\right)$ and concentrated in vacuo to give the anomeric $m$-chlorobenzoates 43 a ( 850 mg ; $94 \%):{ }^{1} \mathrm{H} \operatorname{NMR}\left(250 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.14-8.06(\mathrm{~m}, 2 \mathrm{H}), 7.99-7.95$ $(\mathrm{m}, 1 \mathrm{H}), 7.67-7.21(\mathrm{~m}, 1 \mathrm{H}), 6.57(\mathrm{~d}, J=1.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.53(\mathrm{dd}, J=$ $10.3,9.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.27(\mathrm{~d}, J=5.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.66(\mathrm{~d}, J=10.4 \mathrm{~Hz}, 1$ $\mathrm{H}), 4.61(\mathrm{dd}, J=8.2,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.55(\mathrm{~d}, J=10.4 \mathrm{~Hz}, 1 \mathrm{H})$, $4.47-4.40(\mathrm{~m}, 2 \mathrm{H}), 4.19(\mathrm{dd}, J=5.0,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.16-4.1(\mathrm{~m}, 3 \mathrm{H})$, $3.97(\mathrm{dd}, J=9.2,0.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.69(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.97(\mathrm{br} \mathrm{s}$, $1 \mathrm{H}), 1.46(\mathrm{~s}, 3 \mathrm{H}), 1.37(\mathrm{~s}, 3 \mathrm{H}), 1.34(\mathrm{~s}, 3 \mathrm{H}), 1.07(\mathrm{~s}, 3 \mathrm{H})$; IR $\left(\mathrm{CHCl}_{3}\right) 3600-3200,3000,2950,1725,1605,1575,1455 \mathrm{~cm}^{-1} ;[\alpha]^{23}{ }_{\mathrm{D}}$ $+15.6^{\circ}\left(c=2.29, \mathrm{CHCl}_{3}\right)$.

Formation of Tetraol Anomers 43b. The $m$-chlorobenzoates 43a were treated with anhydrous $\mathrm{K}_{2} \mathrm{CO}_{3}(100 \mathrm{mg})$ 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: ${ }^{1} \mathrm{H}$ NMR $\left(250 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.47-7.31$ (m, $5 \mathrm{H}), 5.53(\mathrm{~d}, J=4.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.21(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.77$ (AB quartet, $J$ $=11 \mathrm{~Hz}, 2 \mathrm{H}), 4.67(\mathrm{dd}, J=5.0,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.46(\mathrm{dd}, J=7.9,1.2$ $\mathrm{Hz}, \mathrm{l} \mathrm{H}), 4.33(\mathrm{dd}, J=4.7,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.13-3.98(\mathrm{~m}, 4 \mathrm{H}), 3.94(\mathrm{br}$ $\mathrm{s}, 1 \mathrm{H}), 3.80-3.67(\mathrm{~m}, 2 \mathrm{H}), 3.21(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.85(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.64(\mathrm{br}$ $\mathrm{s}, 1 \mathrm{H}), 1.57(\mathrm{~s}, 3 \mathrm{H}), 1.49(\mathrm{~s}, 3 \mathrm{H}), 1.39(\mathrm{~s}, 3 \mathrm{H}), 1.33$ (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 $43 \mathrm{~b}(1.12 \mathrm{mmol})$ and lithium borohydride ( $200 \mathrm{mg}, 9.18 \mathrm{mmol}$ ) in THF ( 50 mL ) was heated to $60^{\circ} \mathrm{C}$ 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 $10 \% \mathrm{MeOH}$-ethyl acetate) afforded 44 a ( 539 mg , $96 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( $250 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.35-7.30(\mathrm{~m}, 5 \mathrm{H}), 5.51(\mathrm{~d}, J$ $=5.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.76(\mathrm{AB}$ quartet, $J=11 \mathrm{~Hz}, 2 \mathrm{H}), 4.62(\mathrm{dd}, J=7.9$ $2.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.42$ (dd, $J=8.2,1 \mathrm{~Hz}, 1 \mathrm{H}), 4.28(\mathrm{dd}, J=5.0,2.1 \mathrm{~Hz}$, $1 \mathrm{H}), 4.1-3.76(\mathrm{~m}, 12 \mathrm{H}), 3.35(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 1.51(\mathrm{~s}, 3 \mathrm{H}), 1.48(\mathrm{~s}, 3 \mathrm{H})$, $1.36(\mathrm{~s}, 3 \mathrm{H}), 1.28(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $62.5 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 138.6$, 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 $\left(\mathrm{CHCl}_{3}\right)$ $3600-3150,3000,2940 \mathrm{~cm}^{-1} ;[\alpha]^{23} \mathrm{D}-38.4^{\circ}\left(c=1.63, \mathrm{CHCl}_{3}\right) ; \mathrm{MS}(\mathrm{CI}$ isobutane) $m / e(\%) 501\left(\mathrm{M}^{+}+1,2.8\right), 2.59(4.8), 201$ (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-ga/acto-D-galacto -undecapyranose (44b). A solution of the pentaol 44a $(539 \mathrm{mg}, \mathrm{I} .08 \mathrm{mmol})$ in DMF ( 12 mL ) was treated with sodium hydride ( $50 \%$ oil dispersion, $1.3 \mathrm{~g}, 27 \mathrm{mmol}$ ). The reaction mixture was stirred for 10 min followed by addition of benzyl bromide ( $1.3 \mathrm{~mL}, 10.8 \mathrm{mmol}$ ) 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 ( $\mathrm{MgSO}_{4}$ ). Concentration in vacuo fol lowed by chromatography (silica gel, 75 g ; elution with $10 \%$ ethyl ace-tate-hexanes) gave 44b ( $800 \mathrm{mg}, 78 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 7.38-7.2$ $(\mathrm{m}, 30 \mathrm{H}), 5.56(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.92-4.44(\mathrm{~m}, 14 \mathrm{H}), 4.27$ (dd, $J=5.2,2.1 \mathrm{~Hz}, \mathrm{I} \mathrm{H}), 4.20-4.13(\mathrm{~m}, 3 \mathrm{H}), 4.08-4.01(\mathrm{~m}, 2 \mathrm{H}), 3.97-3.93$ (m, 1 H), 3.83 (dd, $J=10.6,2.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.71(\mathrm{dd}, J=10.6,5.7 \mathrm{~Hz}$ ), $1.36(\mathrm{~s}, 3 \mathrm{H}), \mathrm{l} .32(\mathrm{~s}, 3 \mathrm{H}), 1.26(\mathrm{~s}, 3 \mathrm{H}), 1.24(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 62.5 $\mathrm{MHz}) \delta 139.4,139.1,139.0,138.6,128.2,128.1,128.0,127.9,127.8$ 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, $26.0,25.8,24.8,24.3$; $\mathrm{IR}\left(\mathrm{CHCl}_{3}\right) 3000,2940,2920,1500,1455 \mathrm{~cm}^{-1}$; $[\alpha]^{23} \mathrm{D}-34.8^{\circ}\left(c=1.76, \mathrm{CHCl}_{3}\right)$.

Methyl 6,7,8,9,10,11-Hexa-O-benzyl-D-glycero-D-galacto- $\alpha$ (and $\beta$ )-D-galacto-undecapyranosides ( $\mathbf{4 5 , 4 6}$ Mixture) and Methyl Furanoside 47. A solution of the diacetonide 44b in dry methanolic $\mathrm{HCl}(3 \%)$ was heated at $75^{\circ} \mathrm{C}$ 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 $\mathrm{mg}, 55.5 \%$ ) in a 1.5:1 ratio, respectively, in addition to the furanoside 47 ( $60 \mathrm{mg}, 14 \%$ ). 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 $\alpha$ anomer, 45 was purified by HPLC at this stage.

Methyl $\alpha$-pyranoside 45: ${ }^{1} \mathrm{H}$ NMR ( 250 MHz ) $\delta 7.31-7.18$ (m, 30 H), 4.80-4.40 (m, 12 H ), $4.23-3.75(\mathrm{~m}, 10 \mathrm{H}), 3.71(\mathrm{dd}, J=10.7,4.6$ $\mathrm{Hz}, 1 \mathrm{H}$ ), 3.58 (brd, $J=8.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.20(\mathrm{~s}, 3 \mathrm{H}), 3.05(\mathrm{brd}, J=$ $2.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.73 (br s, 1 H ), 2.18 (br d, 1 H ); ${ }^{13} \mathrm{C}$ NMR ( 62.5 MHz ) $\delta 138.9,138.7,138.4,136.5,128.4,128.3,128.2,127.8,127.7,127.6$, 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 $\left(\mathrm{CHCl}_{3}\right)$ $3600-3200,3010,2909,2875,1730,1500,1459 \mathrm{~cm}^{-1} ;[\alpha]^{23}{ }_{\mathrm{D}}+37.6^{\circ}(\mathrm{c}$ $=1.46, \mathrm{CHCl}_{3} ;$ MS FAB (thioglycerol) $m / e 907\left(\mathrm{M}^{+} \mathrm{Na}\right), 885\left(\mathrm{M}^{+} \mathrm{H}\right)$, $854\left(\mathrm{M}^{+}-\mathrm{OMe}+\mathrm{H}\right), 796\left(\mathrm{M}^{+}-\mathrm{OBn}+\mathrm{H}\right)$

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

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

Methyl 2,3-Di- $O$-benzoyl-6,7,8,9,10,11-hexa- $O$-benzyl-4-(methyl-sulfonyl)-D-glycero-D-galacto- $\alpha$-D-galacto-undecapyranoside (50). A solution of the dibenzoate 48 ( $150 \mathrm{mg}, 0.137 \mathrm{mmol}$ ), methanesulfonyl chloride ( $0.159 \mathrm{~mL}, 2.06 \mathrm{mmol}$ ), 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 $(20 \mathrm{~mL})$ and dried $\left(\mathrm{MgSO}_{4}\right)$. Concentration in vacuo and chromatography (silica gel, 15 g ; elution with $20 \%$ ethyl acetate-hexanes) gave mesylate 50 ( $154 \mathrm{mg}, 96 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( $250 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.04-7.95$ (m, 4 H ), $7.56-7.24$ (m, 36 H ), 5.80 (dd, $J=10.9,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.66$ (br d, $J=2.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.59$ (dd, $J=10.9,3.6 \mathrm{~Hz}, \mathrm{H}), 5.12$ (d, $J=$ $3.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.91-4.34(\mathrm{~m}, 15 \mathrm{H}), 4.28$ (br d, $J=8.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.19$ (br d, $J=6.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.98-3.88(\mathrm{~m}, 2 \mathrm{H}), 3.73(\mathrm{dd}, J=10.5,4.4 \mathrm{~Hz}$, $1 \mathrm{H}), 3.20(\mathrm{~s}, 3 \mathrm{H}), 2.80(\mathrm{~s}, 3 \mathrm{H})$; IR $\left(\mathrm{CHCl}_{3}\right) 3100,2940,2870,1730$, 1605, $1500,1455 \mathrm{~cm}^{-1} ;[\alpha]^{23} \mathrm{D}+45.4^{\circ}\left(c=1.95, \mathrm{CHCl}_{3}\right) ;$ MS FAB (thioglycerol) $m / e 1171\left(\mathrm{M}^{+}+\mathrm{H}\right)$

Methyl 4-Azido-2,3-di- $O$-benzoyl-6,7,8,9,10,11-hexa- $O$-benzyl-4-deoxy-D-glycero- D -galacto- $\alpha$ - D -gluco- undecapyranoside (51). A solution of mesylate $\mathbf{5 0}$ ( $153 \mathrm{mg}, 0.131 \mathrm{mmol}$ ) and tetrabutylammonium azide ( $0.93 \mathrm{~g}, 3.27 \mathrm{mmol}$ ) in toluene ( 4.5 mL ) was heated at $110^{\circ} \mathrm{C}$ 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 , $75 \%$ ): ${ }^{1} \mathrm{H}$ NMR ( $250 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.03-7.95(\mathrm{~m}, 4 \mathrm{H}$ ), 7.57-7.19 $(\mathrm{m}, 36 \mathrm{H}), 5.95(\mathrm{~m}, 1 \mathrm{H}), 5.04-4.98(\mathrm{~m}, 2 \mathrm{H}), 4.88-3.85(\mathrm{~m}, 20 \mathrm{H}), 3.74$ (dd, $J=11.0,5.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.1(\mathrm{~s}, 3 \mathrm{H})$; $\mathrm{IR}\left(\mathrm{CHCl}_{3}\right) 3040,3020,2940$, 2875, 2115, 1730, 1615, 1500, $1455 \mathrm{~cm}^{-1} ;[\alpha]^{23} \mathrm{D}+85.8^{\circ}(\mathrm{c}=1.14$, $\mathrm{CHCl}_{3}$ ).

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

Methyl 2,3-Di- $O$-acetyl-4-azido-6,7,8,9,10,11-hexa- $O$-benzyl-4-deoxy-D-glycero-D-galacto- $\alpha$-D-gluco-undecapyranoside (53). A solution of the azide diol 52 ( $67.2 \mathrm{mg}, 0.074 \mathrm{mmol}$ ) 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 ( $73 \mathrm{mg}, 99 \%$ ): ${ }^{1} \mathrm{H}$ NMR $\left(250 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.31-7.18(\mathrm{~m}, 30 \mathrm{H}), 5.49$ (apparent $\mathrm{t}, J=9.4 \mathrm{~Hz}$, $1 \mathrm{H}), 4.81-4.32(\mathrm{~m}, 14 \mathrm{H}), 4.12(\mathrm{dd}, J=8.0,3.6 \mathrm{~Hz}, 1 \mathrm{H}) 84.00-3.82$ (m, 7 H ), $3.69(\mathrm{dd}, J=11.0,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.08(\mathrm{~s}, 3 \mathrm{H}), 2.10(\mathrm{~s}, 3 \mathrm{H})$, 2.06 (s, 3 H ); IR ( $\mathrm{CHCl}_{3}$ ) 3020, 2940, 2880, 2115, $1755,1500,1458$ $\mathrm{cm}^{-1} ;[\alpha]^{23}{ }_{\mathrm{D}}+76.3^{\circ}\left(c=0.83, \mathrm{CHCl}_{3}\right)$.

Methyl 4-Acetamido-2,3,6,7,8,9,10,11-octa-O-acetyl-4-deoxy-D-glycero-D-galacto- $\alpha$-D-gluco-undecapyranoside (2a). The azide diacetate 53 ( $44.8 \mathrm{mg}, 0.451 \mathrm{mmol}$ ) and triphenylphosphine ( $55 \mathrm{mg}, 0.21 \mathrm{mmol}$ ) 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 $40 \mathrm{lb} \mathrm{H}_{2}$ 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 $\mathrm{CHCl}_{3}-$ methanol gradient, $0-2 \%$ ). Rechromatography of mixed fractions gave a total recovery of 2 a of $11 \mathrm{mg}(35 \%)$. The NMR spectrum of this compound ( $\mathrm{CDCl}_{3}, 490 \mathrm{MHz}$ ) was identical with that of a trace authentic sample provided by Professor Secrist. ${ }^{6.7}$

Acknowledgment. This work was supported by PHS Grant AI16943. A Heyl Fellowship to C.J.M. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF/Chemistry Division Grant CHE 7916210. We thank Dr. John Secrist for providing us with the authentic sample.

Registry No. 2a, 50619-43-7; 7, 91861-07-3; 14, $118893-65-5 ; 15$, 118893-66-6; 16, $118893-67-7 ; \alpha$-19, 118893-68-8; $\beta$-19, 119007-05-5; $\alpha$-20, 118893-70-2; $\beta$-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; $\alpha$-43a, 119008-30-9; $\beta$-43a, 118893-78-0; $\alpha$-43b, 119007-10-2; $\beta-43 \mathrm{~b}$, 119007-11-3; 44a, 118893-79-1; 44b, 99212-55-2; 45, 99212-56-3; 46,

119007-12-4; $\alpha-47$, $118893-80-4 ; \beta-47,119007-13-5 ; 48$, 99212-57-4; 49, 119007-14-6; 50, $99212-85-8$; 51, 99212-58-5; 52, 118920-27-7; 53, 118893-81-5; $(E)-\mathrm{BnOCH}_{2} \mathrm{CH}=\mathrm{CHCHO}, 69152-87-0 ; 2$-furaldehyde, 98-01-1.

Supplementary Material Available: NMR spectra of synthetic and authentic samples of compound $\mathbf{2 a}$ ( 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 

Marc Labelle* and Y. Guindon ${ }^{1}$<br>Contribution from Merck Frosst Canada, Inc., P.O. Box 1005, Pointe Claire-Dorval, Quëbec, 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 $\mathrm{F}>\mathrm{OH} \geq \mathrm{OMe}>\mathrm{Me}$. This result ruled out several proposed mechanisms of asymmetry transfer and led to the proposal of a transition-structure model, based on AMl 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.
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Scheme I


## Scheme II



5

1) $\left(\mathrm{COCl}_{2}\right.$-DMSO
2) $\mathrm{Ph}_{3} \mathrm{PCHCOOEt}$


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


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    (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 $\alpha$ or $\beta$ 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.
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