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THE PYRANOSIDIC HOMOLOGATION ROUTE TO THE NINE CONTIGUOUS CHIRAL CENTERS OF STREPTOVARICIN A1

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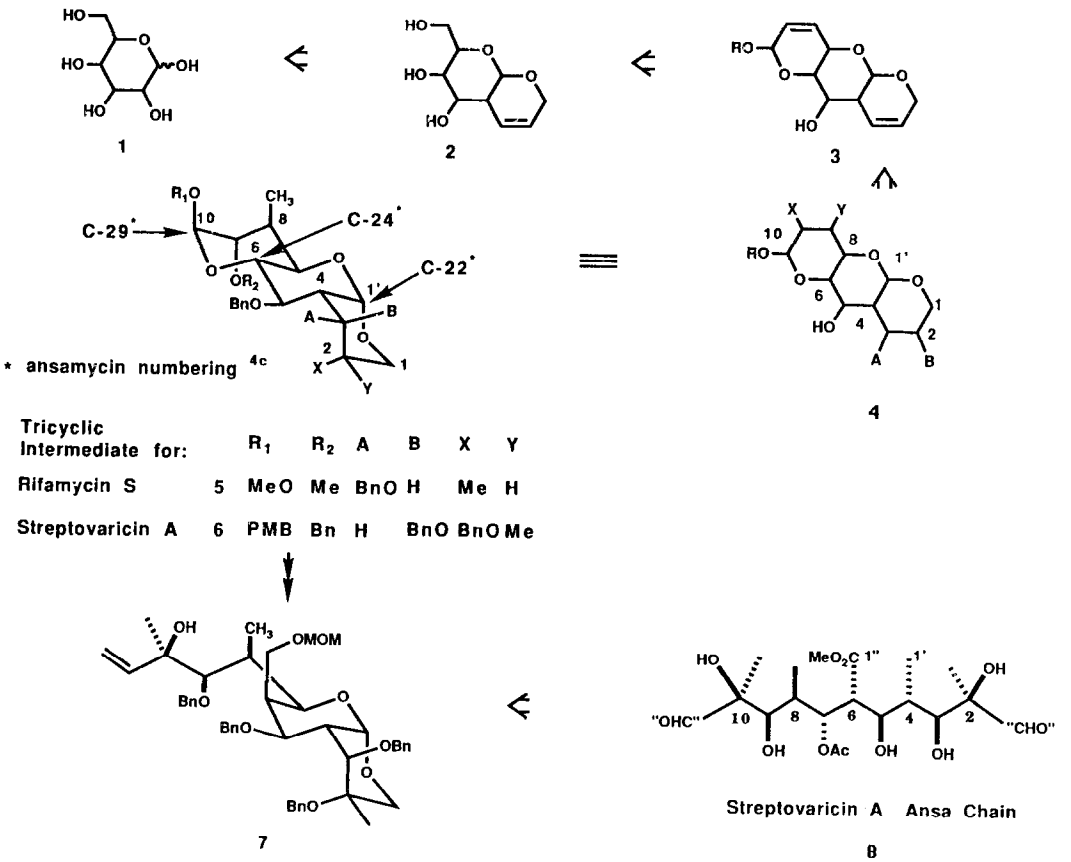
A precursor for the ansa chain of streptovaricin A has been prepared by means of the pyranosidic homologation strategy. All of the nine contiguous asymmetric centers have been assembled, their authenticity being established by simple ^1H NMR methods. The termini of the chain are suitably differentiated so as to provide for eventual attachment of the pseudo-aromatic moiety of the antibiotic. In the course of this study, a strategy for selective debenzylation by utilizing a remote electrophilic center has been developed.

Introduction

SCHEME 1



We have described a strategy for the synthesis of higher carbon sugars termed "pyranosidic homologation".[3] The protocol involves the sequential annulation of "satellite" pyranosides onto a central pyranoside to generate bicyclic,[4a] and thence tricyclic[4b] precursors **1** ---> **2** ---> **3** for the primary purpose of utilizing the predictable conformational bias of these interlocking pyranoid rings (e.g., **4**) for stereoselective introduction of the various asymmetric centers (Scheme 1). A significant advantage accruing to these systems is the ease of assigning the configurations of the newly created stereocenters by routine ^{1}H NMR analyses. Cleavage of the internal glycosidic bonds would then convert these substrates into acyclic arrays containing multiple contiguous chiral centers.

With this in mind, we embarked on a study directed towards the synthesis of the polypropionate-derived segments of the ansamycin antibiotics,[5] and in this context, we recently described[4b] the syntheses of the tripyranosides **5** and **6** as the first plateau in the preparation of the ansa chains of rifamycin S and streptovaricin A,[5] respectively.

Questions now arose regarding the C-4 and C-6 stereocenters of the targets, and additionally in the case of the streptovaricin A ansa chain **8**, concerning the "off template" chiral center at C-10. Our strategy had required construction of the tricyclic precursors before these problems were addressed, and indeed, **6** was subsequently transformed into the highly functionalized dipyranoside **7**, which contains all nine of the stereocenters required for streptovaricin A.[6] The stage was therefore set for the critical opening of the bicyclic template **7**, a process that involves cleavage of the internal acetal linkage as a prelude to reduction of the anomeric carbon to the C-4 methyl group. This manuscript describes our investigations in this area.

Results and Discussion

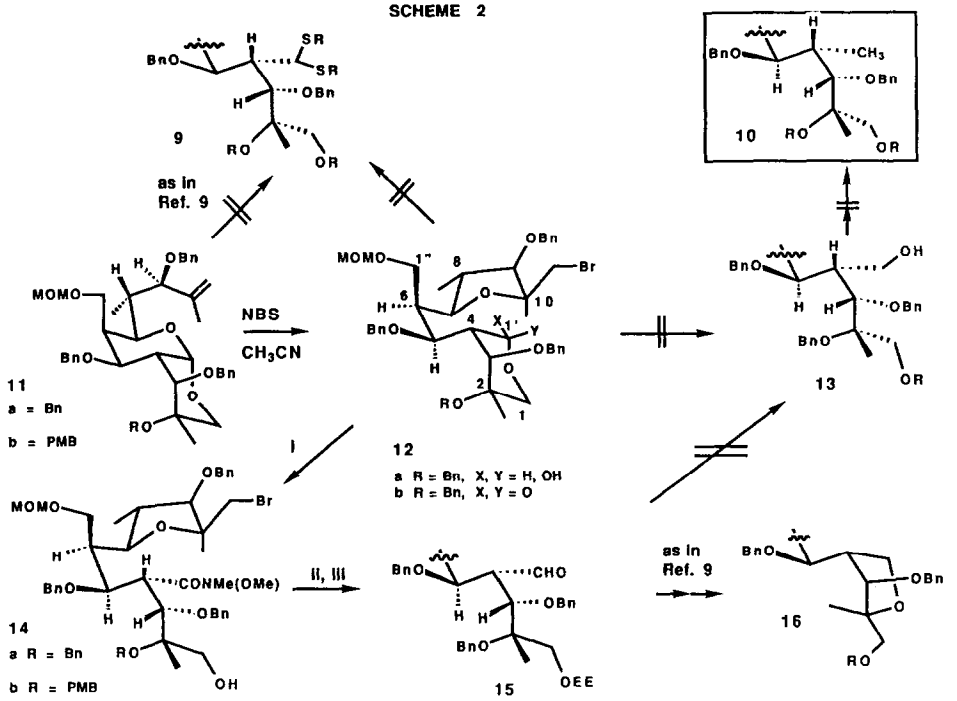
Our initial plan for opening of the dipyranoside involved mercaptolysis to give an acyclic dithioacetal[7] (e.g., **9**, Scheme 2), which would then be desulfurized to give the required methyl group in **10**.[8] However, the dipyranoside **7** proved to be highly resistant to cleavage by various acid catalyzed procedures.[9a]

The eventual solution of the problem arose from the serendipitous observation that reaction of the previously described bicyclic olefin **11a** with N-bromosuccinimide afforded the lactol **12a**.[11a] This reaction may be rationalized *via* a sequence whose essential features are detailed in Scheme 3a. Thus, bromination of the olefinic double bond in **I** sets up an electrophilic center in **II**, which undergoes 5-*exo*-tet[12] cleavage, to generate the oxonium ion **III**. The "other" oxygen of the acetal now acts as an electron donating agent whose engagement causes facile cleavage of the pyranoid ring with formation of the oxocarbenium ion **IV**, hydration of which gives the observed product **V**.[13,14]

This revised strategy dictated that generation of the C-10 stereocenter had to be deferred until after the C-4 methyl group had been obtained from the lactol carbon. However, attempts

to transform the lactol **12a** (a) into an acyclic derivative *via* standard mercaptolytic procedures, or (b) into the primary alcohol **13** were both unsuccessful.

SCHEME 2



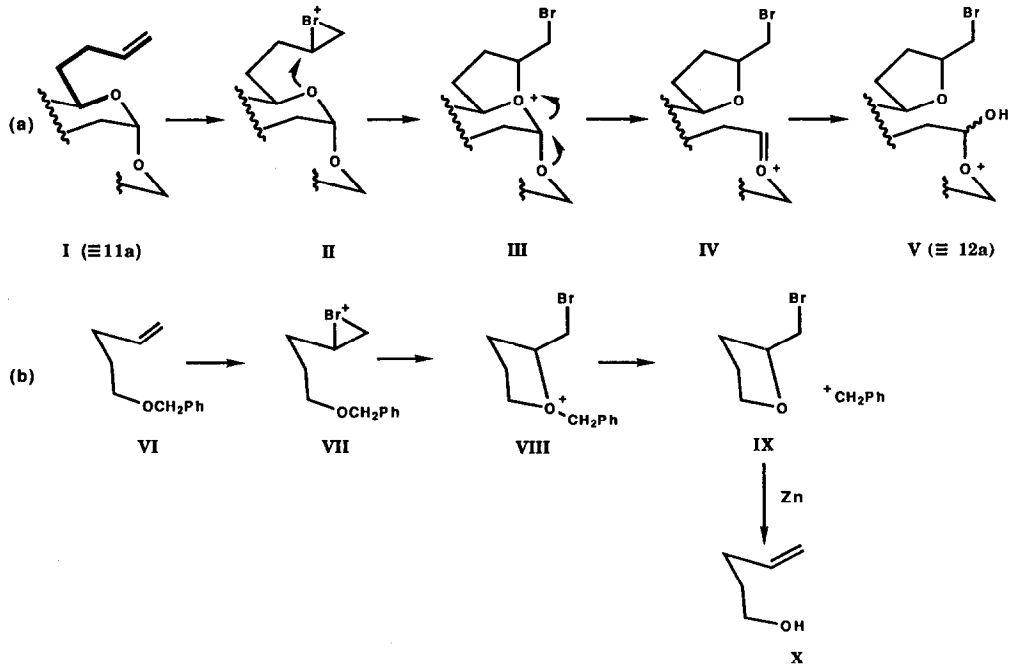
(I) $Me_2AlNMe(OMe)$, CH_2Cl_2, 84% (II) ethylvinyl ether, PPTS, CH_2Cl_2 (III) LAH, ether, steps (II), (III) 74%.

We therefore investigated a protocol in which the derived lactone **12b** would be processed to give the acyclic aldehyde **15** *via* a carboxamide, such as **14**, according to Weinreb's procedure.[10,15] However, our efforts were plagued by the easy formation of furanoid products arising from attack of the C-2 oxygen on the electrophilic center at C1. For example, reduction of the tosylhydrazone derived from **15** led to formation of furans of type **16**.[9b] One solution to this problem involved modifying the electrofugal properties of the C-2 oxygen--an adjustment which could be most easily accomplished by changing the protecting group.

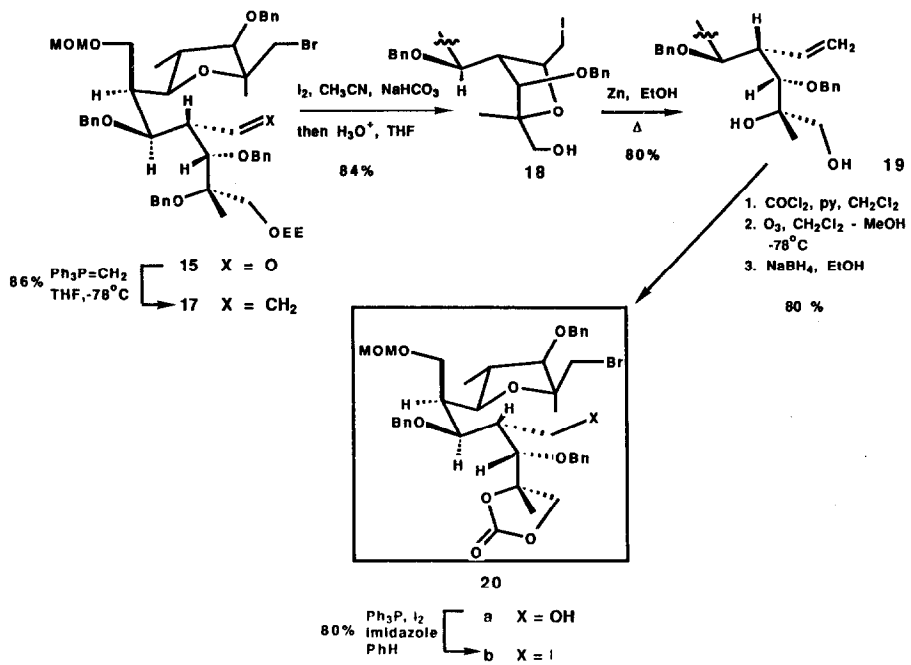
Such a change would require selective cleavage of the C-2 benzyl ether, but the standard procedures (hydrogenolysis or chemical reduction) would not be expected to give the desired selectivity.

However, a novel method for attaining the desired goal could be designed around chemospecific debenzylation by taking advantage of the very same propensity for furan formation that had led to the formation of **16**.[14] Thus, using the process detailed in Scheme 3a. as a design model, the essential components for furan formation would be (i) a pentenyl ether

SCHEME 3



SCHEME 4



(heavy lines in **I**), which upon halogenation would be attacked by the ether oxygen to give an oxonium ion (**II** ---> **III**), and (ii) a stabilized cation, such as the oxocarbenium ion in **IV**, which would trigger release the original ether oxygen.

With that model in mind, the chemospecific cleavage of benzyl ether was designed as outlined in Scheme 3b. Halogenation of the benzyl pentenyl ether **VI** would lead to eventual loss of $PhCH_2^+$ to give the halogenomethyl tetrahydrofuran **IX**. Subsequent reductive elimination would then give the alcohol **X**. Processes similar to that in equation (b) have recently been studied in the laboratories of Liotta and Maryanoff,[14a] and earlier by Bartlett.[14b]

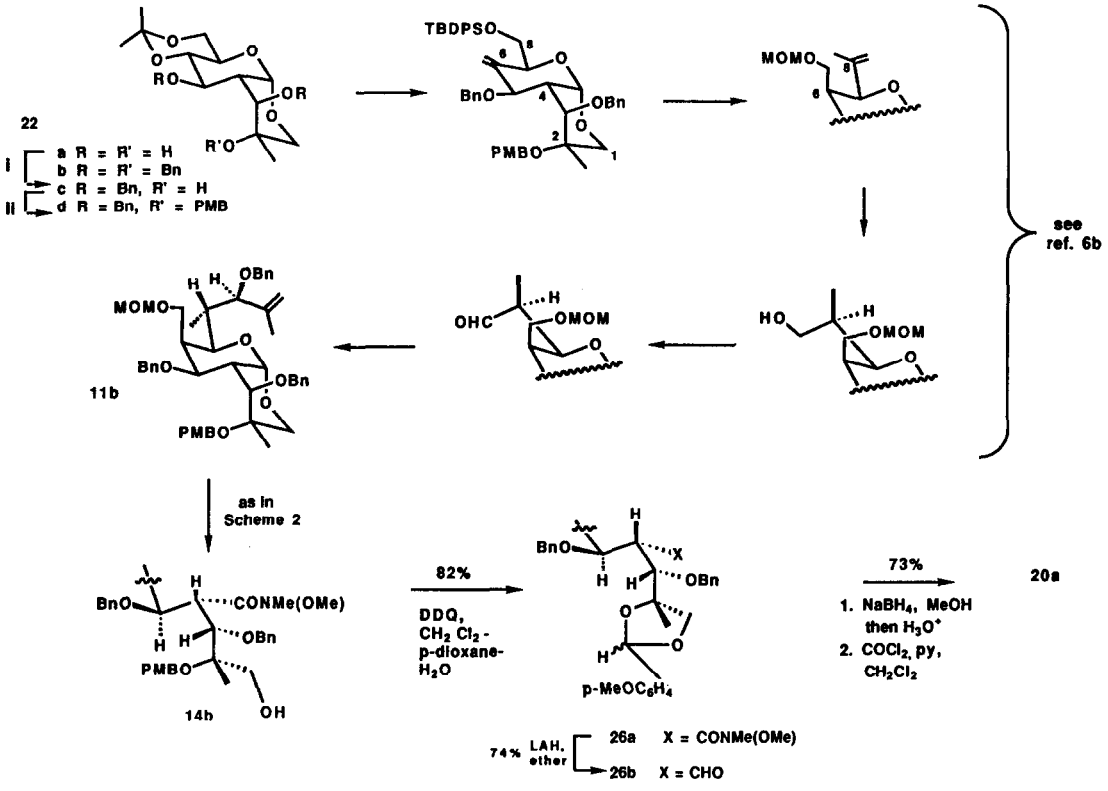
In reducing this idea to practice (Scheme 4), the aldehyde **15** was converted to olefin **17**, and the latter, after treatment with iodine in acetonitrile,[14b] afforded the compound **18**. Although **18** had two halomethylfuran residues, it was possible to effect selective reductive elimination with zinc to give the olefinic diol **19** without affecting the bromomethyl tetrahydrofuran ring. The C-2 alcohol had therefore been liberated and the resulting vicinal diol was then bridged as the cyclic carbonate. Processing of the olefinic functionality, gave the hydroxycarbonate **20a**, which was converted into the corresponding iodide **20b** without any evidence of furan formation.

Exhaustive treatment of this bis-halomethyl derivative **20b** with zinc then led to the required C-22-CH_3, as well as opening the furan ring to give **23a** (Scheme 6). Having established the importance of the protecting group on the C-2 oxygen, a more efficient route to the hydroxy carbonate **20a** was sought. The steps that were carried out in Scheme 4 for selective debenzylation at C2 (**15** ---> **17** ---> **18** ---> **19**) could be obviated by differentiating the C2 center at an earlier stage. Accordingly, benzylation of the secondary hydroxyl groups of previously prepared **22a**[4b] (Scheme 5) left the C-2-OH free in **22c**, which was then protected as its methoxybenzyl ether **22d**. This material was then converted into alkene **11b** by the procedure summarized in Scheme 5,[6b] and thence to the amide **14b** *via* the identical sequence outlined above for **11a**. Oxidation[16] of the methoxybenzyl ether of **14b** paved the way for preparation of the p-anisylidene aldehyde **26**, from which the desired hydroxy carbonate **20a** was obtained, identical to the previously described material in Scheme 4.

It should be noted that the procedure from 22a, summarized in Scheme 5,[6b] makes 20a available by 11 fewer steps than that involving tripyranoside 6.

This more efficient route to **20a** and thence to olefin **23** was a welcome development, but some uncertainty now arose regarding the possible epimerization of the C-4 center during the transformations outlined in Schemes 2 and 6. However, we had previously shown, by formation of the benzylidene derivative **28** ($J_{3,4}$=$J_{4,5}$=10.2 Hz), that these operations could be accomplished in closely related systems without loss of stereochemical integrity.[10]

SCHEME 5

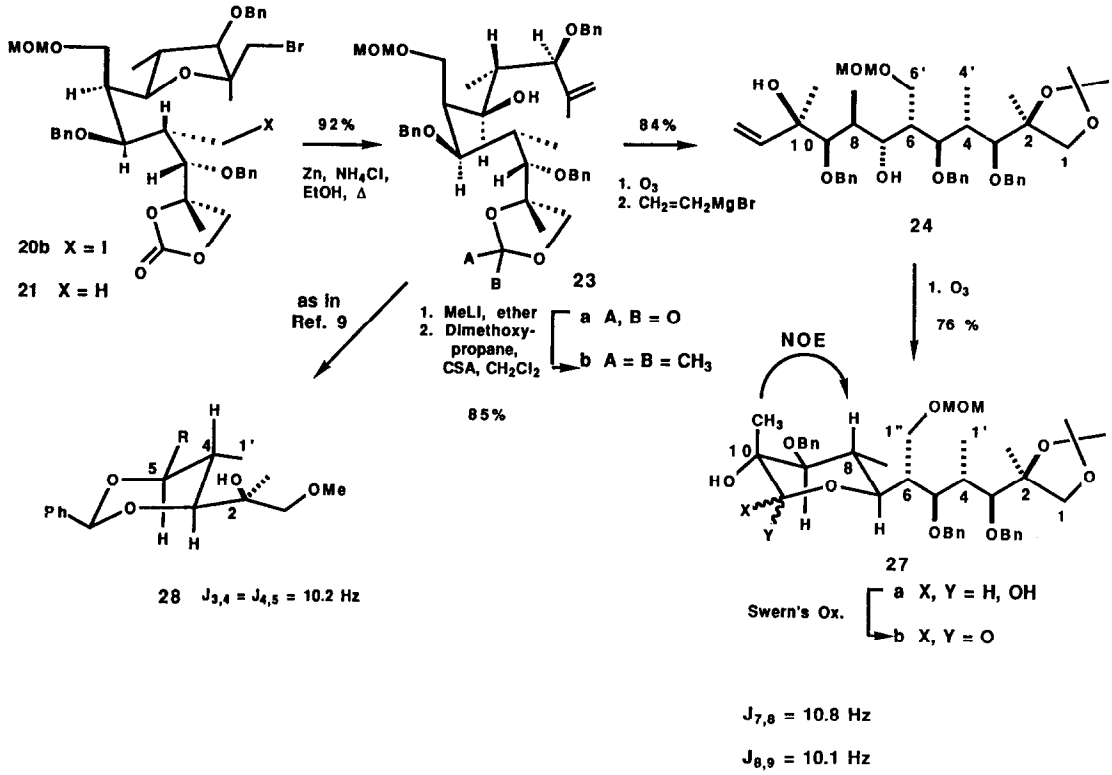


(I) NaH, BnBr, DMF-THF (1:10), 67% (II) NaH, PMBCl, DMF, nBu_4NI, 90%

The stage was therefore set for introduction of the final stereocenter at C-10 (Scheme 6). After minor adjustments in protecting groups, the isopropylidene derivative **23b** was subjected to ozonolysis and the resultant methyl ketone treated with vinylmagnesium bromide. A single Grignard adduct, **24**, was obtained and was assigned the desired configuration, in accordance with the Cram chelate model.[17,18] This assignment was verified by ^1H NMR analysis of the lactone **27** obtained by Swern's oxidation of lactol **27a**, arising from ozonolysis of olefin **24**. The conformation of the lactone ring of **27b** was established to be as shown by the parameters $J_{7,8}$ = 10.8, $J_{8,9}$ = 10.1 Hz, and a significant NOE effect between the C-10-CH_3 and H-8 proton confirmed the configuration of the newly formed tertiary alcohol.

The polyhydric olefin **24** has therefore been synthesized with high stereocontrol according to the tenets of "pyranosidic homologation", and contains all nine of the stereocenters required for streptovaricin A. Furthermore, the differentiated nature of the

SCHEME 6



termini makes **24** a convenient intermediate for connection to the pseudo aromatic nucleus of the streptovaricin A. The C7-OH, which must eventually bear an acetyl group, is also differentiated from other hydroxyl groups. In addition, the stereochemical integrity of this compound has been assured by its chiral origin and rigorous ^{1}H NMR analysis of cyclic precursors.

Final authentication by comparison with naturally derived material and the connection to the aromatic nucleus is presently under investigation.

Experimental

General Procedures. Elemental analyses were performed by M-H-W Laboratories, PO Box 15149, Phoenix, AZ, and Atlantic Microlab, Inc., PO Box 2288, Norcross, GA 30091-2288. IR spectra were recorded on a Perkin-Elmer Model 298 spectrometer with sodium chloride plates for thin films of liquids, syrups, or solids in Nujol mulls. Optical rotations were determined at the sodium D line with a Perkin-Elmer 241 polarimeter. ^{1}H NMR spectra were determined on a Varian XL-300 spectrometer. Unless otherwise stated, the solvent used was $CDCl_3$ with internal tetramethylsilane or $CHCl_3$ as the standard. The coupling constants were verified by homonuclear decoupling experiments. For the purpose of ^{1}H NMR interpretation, compound structures have been numbered in the schemes. High resolution mass spectra were obtained at the Duke University Medical Center on a VG-705 high

resolution magnetic sector instrument operating in the fast atom bombardment (FAB) mode in a glycerol or magic bullet matrix with xenon as the fast atom. The progress of all reactions was monitored by thin-layer chromatography (TLC), which was performed on aluminum plates precoated with silica gel HF-254 (0.2 mm layers) containing a fluorescent indicator (Merck, 5554). The following solvent systems were used: EtOAc-petroleum ether mixtures: A=1:9, B=1:4, C=3:7, D=1:1, E=5% acetone in chloroform. Detection was first by UV (254 nm), then charring with sulfuric acid spray, or charring with a solution of ammonium molybdate(VI), tetrahydrate (12.5 g), and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Flash chromatography was performed using Kiesselgel 60 (230-400 mesh, E. Merck).

Preparation of Dibenzyl Ether 22b.

Sodium hydride (2.60 g, 54.3 mmol of a 50% suspension in mineral oil, washed with petroleum ether), was added to a solution of triol **22a**[4b] (6.30 g, 21.7 mmol) in dry tetrahydrofuran (300 mL) and N,N-dimethylformamide (30 mL) at 0° under an argon atmosphere. The mixture was stirred at this temperature for 30 min, then benzyl bromide (5.42 mL, 45.6 mmol) was added. The reaction was warmed to room temperature and stirred for an additional 16 h, at which time methanol (1 mL) as added to the mixture. After 30 min, the mixture was diluted with water (800 mL), and extracted with ether (4x400 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Flash chromatography of the residual brown syrup afforded a less polar compound (3.0 g, 25%) which was identical (t.l.c., $[\alpha]_D$, n.m.r.) to the previously obtained tribenzyl derivative **22b**,[4b] and the more polar dibenzyl ether **22c** (6.8 g, 67%): clear gum; R_f 0.20 (B); $[\alpha]_D^{20}$ 81.0° (c 1.15, $CHCl_3$); IR (neat) 3475 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, H, CH_3-2), 1.07 (bs, 1H, OH), 1.45, 1.55 (both s, 3H(ea), $C(CH_3)_2$), 2.13 (ddd, 1H, $J_{4,1'}$=3.3, $J_{3,4}$=1.5, $J_{4,5}$=10.8 Hz, H-4), 3.53 (t, 1H, $J_{3,4}$=$J_{1(eq),3}$=1.5 Hz, H-3), 3.61 (dd, 1H, $J_{1(eq),3}$=1.5, J_{gem}=12.3 Hz, H-1(eq)), 3.73 (m, 2H, H-6, H-8a), 3.76 (d, 1H, J_{gem}=12.3 Hz, H-1(ax)), 3.92 (m, 2H, H-7, H-8b), 4.23 (dd, 1H, $J_{4,5}$=10.8, $J_{5,6}$=8.7 Hz, H-5), 4.52 (ABq, 2H, J=11.7, Δδ=0.26 ppm, PhCH$_2$), 4.78 (ABq, 2H, J=11.7 Hz, Δδ=0.20 ppm, PhCH$_2$), 5.03 (d, 1H, $J_{4,4'}$=3.3 Hz, H-1'), 7.05-7.32 (m, 10H, Phx2). Anal. Calcd. for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28. Found: C, 68.96; H, 7.28.

Preparation of 2-p-Methoxybenzyl-3,5-dibenzyl Ether 22d.

The dibenzylether **22c** (6.8 g, 14.5 mmol) in N,N-dimethylformamide (100 mL) was treated with sodium hydride (1.5 g, of a 50% suspension in mineral oil, washed with petroleum ether, 31.3 mmol) as described for the triol **22a**, together with tetra-n-butylammonium iodide (250 mg, 0.68 mmol). p-Methoxybenzyl chloride (4.00 mL, 29.5 mmol) was used as the alkylating agent, and the reaction was processed as described for the preparation of **22b**. Flash chromatography of the crude residue afforded **22d** (7.79, 90%) as a clear syrup: R_f 0.50 (B); $[\alpha]_D^{20}$ 104° (c 1.06, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 3H, CH_3-2), 1.39, 1.48 (both s, 3H(ea), $C(CH_3)_2$), 2.13 (dt, 1H, $J_{4,1'}$=$J_{3,4}$=3.3, $J_{4,5}$=9.0 Hz, H-4), 3.62 (t, 1H, $J_{5,6}$=$J_{6,7}$=9.0 Hz, H-6), 3.70 (d, 1H, J_{gem}=13.0 Hz, H-1(ax)), 3.73 (m, 2H, H-3, H-8), 3.79 (s, 3H, OCH$_3$), 3.90 (m, 2H, H-7, H-8), 4.16 (dd, 1H, $J_{1(eq),3}$=1.5, J_{gem}=13.0 Hz, H-1(eq)), 4.18 (d, 1H, J=11.4 Hz, PhCH), 4.35 (m, 3H, PhCHx2, H-5), 4.56 (d, 1H, J=10.0 Hz, PhCH), 4.58 (ABq, 2H, J=12.0 Hz, Δδ=0.10 ppm,

PhC$\underline{H}_2$), 5.09 (d, 1H, $J_{1',4}$=3.3 Hz, H-1'), 6.85, 7.05-7.40 (d, m, 2H, 12H, resp. J=12.0 Hz, Phx2, $PCH_2O_6\underline{H}_4$). Anal. Calcd. for $C_{35}H_{42}O_8$: C, 71.65; H, 7.17. Found: C, 71.42; H, 7.12.

Preparation of N,O Dimethylamide 14a.

Dimethylaluminum N,O-dimethylhydroxylamide[15] (9.0 mL of a 0.5 M solution in dichloromethane, 4.0 mmol), was added to a solution of lactone **12b**[6b] (680 mg, 0.818 mmol) in dry dichloromethane (10 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature under an argon atmosphere for 16 h, then slowly added to 1N hydrochloric acid (25 mL) at 0°. The mixture was extracted with dichloromethane (3x50 mL), and the combined organics were washed with saturated aqueous sodium bicarbonate solution (50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude residue was purified by flash chromatography to give **14a** (616 mg, 84%): clear gum; R_f 0.20 (C); $[\alpha]_D^{20}$ -42.0° (c 1.36, $CHCl_3$); IR (neat) 3420, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.43 (d, 3H, J=6.0 Hz, CH_3-8), 1.17, 1.30 (both s, 3H(ea), CH_3-2, CH_3-10), 2.09 (m, 1H, H-8), 2.28 (m, 1H, H-6), 2.79 (s, 3H, NCH_3), 3.22, 3.23 (both s, 3H(ea), OCH_3x2), 3.22 (ABq, 2H, J=10.5 Hz, Δδ=0.12 ppm, CH_2-10), 3.32 (m, 1H, OH), 3.38 (dd, 1H, $J_{6,1''}$=4.0, J_{gem}=9.0 Hz, H-1''), 3.53 (m, 2H), 3.61-3.83 (m, 6H), 4.35-4.58 (m, 9H, PhC$\underline{H}$x7, $C\underline{H}_2OCH_3$), 4.90 (d, 1H, J=12.0 Hz, PhC$\underline{H}$), 7.04-7.48 (m, 20H, Phx4). Anal. Calcd. for $C_{48}H_{62}O_{10}NBr$: C, 64.57; H, 7.00. Found: C, 64.37; H, 7.08.

Preparation of Tetra-O-benzyl Aldehyde 15.

A solution of hydroxyamide **14a** (380 mg, 0.43 mmol), ethyl vinyl ether (0.82 mL, 8.6 mmol), and pyridinium p-toluenesulfonate (10 mg, 0.40 mmol) in anhydrous dichloromethane (10 mL) was stirred at room temperature for 7 h. At this time, the reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give a pale yellow syrup.

The crude residue obtained in the previous step was dried under high vacuum and dissolved in anhydrous ether (20 mL). Lithium aluminum hydride (18 mg, 0.47 mmol) was added to the solution and the reaction mixture was stirred at room temperature under an argon atmosphere for 30 min. The mixture was then cooled to 0°, hydrated sodium sulfate (1 g) added, and stirring continued for an additional 20 min. Anhydrous sodium sulfate (5 g), celite (5 g), and wet ether was then added to the mixture and stirring continued at room temperature for 30 min. At this time, the mixture was filtered, and the filtrate concentrated *in vacuo* to give a pale yellow oil which was purified by flash chromatography to give a mixture of two diastereomeric aldehydes **15** (295 mg, 76% from **14a**): clear syrup; R_f 0.40 (B); IR (neat) 1710 cm^{-1}; selected resonances for major isomer in ^1H NMR (300 MHz, $CDCl_3$) δ 0.51 (d, J=6.5 Hz, CH_3-8), 1.10 (t, J=6.0 Hz, $C\underline{H}_3CH_2$), 1.18, 1.30 (both s, CH_3-2, CH_3-10), 1.22 (d, J=6.0 Hz, $C\underline{H}_3CHO_2$), 2.10 (m, H-8), 2.27 (m, H-6), 3.04 (m, H-4), 3.18 (ABq, J=10.0 Hz, Δδ=0.17 ppm, CH_2-10), 3.25 (s, OCH_3), 3.36 (m, H1'', $CH_3C\underline{H}_2O$), 4.20 (d, J=8.0 Hz, H-3), 9.50 (d, $J_{1',4}$=4.0 Hz, CHO). Anal. Calcd. for $C_{50}H_{65}O_{10}Br$: C, 66.29; H, 7.23. Found: C, 66.22; H, 7.39.

Preparation of p-Anisylidene Aldehyde 26b.

A mixture of hydroxyamide **14b** (93 mg, 0.10 mmol) and freshly activated, powdered molecular sieves 4Å (200 mg) in anhydrous dichloromethane (5 mL) was stirred at room temperature for 20 min. 2,3-Dichloro-5,6-dicyano-1,2-benzoquinone (28 mg, 0.12 mmol) was then added to the solution and stirring continued for an additional 15 min, at which time the reaction mixture was diluted with ether (25 mL) and filtered. The filtrate was evaporated *in vacuo*, and the residual brown oil purified by flash chromatography to give a diastereomeric mixture of acetals **26a** (76 mg, 82%): clear gum, R_f 0.40 (C); selected resonances for major isomer in ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.45 (d, J=6.5 Hz, CH_3-8), 1.21, 1.48 (both s, CH_3-2, CH_3-10), 2.12, 2.53 (both m, H-6, H-8), 2.96 (s, NCH_3), 3.28, 3.80 (both s, 2xOCH_3), 5.82 (s, $CH_3OC_6H_4C\underline{H}O_2$).

A solution of the above mixture (76 mg, 0.082 mmol) in anhydrous ether (5 mL) was treated with lithium aluminum hydride (5 mg, 0.1 mmol) and the reaction processed as described for the preparation of **15**. Flash chromatography of the crude product afforded a mixture of aldehydes **26b** (52 mg, 74%): clear gum, R_f 0.50 (C); IR (neat) 1720 cm^{-1}; selected resonances for major isomer in ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.56 (d, J=6.3 Hz, CH_3-8), 1.24, 1.46 (both s, CH_3-2, CH_3-10), 2.15, 2.46 (both m, H-6, H-8), 3.19 (m, H-4), 3.27 (ABq, J=10.5 Hz, Δδ=0.14 ppm, CH_2-10), 3.28 (s, OCH_3), 3.43 (dd, $J_{6,1"a}$=4.5, J_{gem}=9.0 Hz, H-1"a), 3.61 (m), 3.72 (dd, $J_{6,1"b}$=3.0, J_{gem}=9.0 Hz, H-1"b), 3.78 (s, $C\underline{H}_3OC_6H_4$), 3.85 (m), 4.39, 4.50, 4.53, 4.72, 4.85 (d, d, m, d, d, resp. $PhC\underline{H}_2$x3, $C\underline{H}_2OCH_3$), 5.76 (s, $CH_3OC_6H_4C\underline{H}O_2$), 6.82, 7.25 (d, m, resp. J=8.0 Hz, Phx3, $CH_3OC_6\underline{H}_4$), 9.52 (d, $J_{1',4}$=1.5 Hz, C<u>H</u>O). Anal. Calcd. for $C_{47}H_{57}O_{10}Br$: C, 65.50; H, 6.67. Found: C, 65.66; H, 6.67.

Preparation of Olefin 17.

n-Butyllithium (0.60 mL of a 2.4 M solution in hexane, 1.4 mmol) was added to a suspension of methyltriphenylphosphonium bromide (560 mg, 1.57 mmol) in dry tetrahydrofuran (10 mL) at room temperature under an argon atmosphere. The mixture was stirred at this temperature for 20 min, then cooled to -78°C, and a solution of the aldehyde **15** (275 mg, 0.304 mmol) in dry tetrahydrofuran (5.0 mg) was slowly added. The reaction mixture was allowed to warm to room temperature, then diluted with ether (50 mL) and filtered. The filtrate was concentrated *in vacuo* and the residual yellow oil purified by flash chromatography to give a mixture of diastereomeric olefins **17** (235 mg, 86%): clear oil. R_f 0.50 (B); IR (neat) 1635 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65, 0.75 (both d, 3H, J=8.0 Hz, CH_3-8), 1.04, 1.05 (both t, 3H, H=6.5 Hz, $C\underline{H}_3CH_2$), 1.16 (d, 3H, J=6.5 Hz, $C\underline{H}_3CHO_2$), 1.16, 1.24, 1.27 (all s, 6H, CH_3-2, CH_3-10), 2.08 (m, 2H, H-6, H-8), 2.68 (m, 1H, H-4), 3.18 (ABq, 2H, J=10.0 Hz, Δδ=0.13 ppm, CH_3-10), 3.18, 3.19 (both s, 3H, OCH_3), 3.32 (m, 1H, $CH_3C\underline{H}HO$), 3.38-3.50 (m, 4H), 3.62 (dd, 1H, $J_{6,1"a}$=5.0, J_{gem}=10.5 Hz, H-1"a), 2.73 (m, 3H), 3.82, 3.84 (both d, 1H, $J_{3,4}$=7.0 Hz, H-3), 4.37-4.78 (m, 11H, $PhC\underline{H}_2$x4, $OC\underline{H}_2OCH_3$, $CH_3C\underline{H}O_2$), 4.92 (m, 2H, =CH_2), 5.88 (m, 1H, $C\underline{H}$=CH_2), 7.10-7.32 (m, 20H, Phx4). Anal. Calcd. for $C_{51}H_{67}O_9Br$: C, 67.76; H, 7.47. Found: C, 67.93; H, 7.62.

Preparation of Furanoiodide 18.

Iodine (81 mg, 0.32 mmol) was added to a mixture of the olefin **17** (233 mg, 0.26 mmol)

and sodium bicarbonate (100 mg) in acetonitrile (10 mL) at 0°. The reaction mixture was stirred at this temperature for 10 min, and the reaction was then quenched by the addition of a 10% aqueous sodium thiosulfate solution (5 mL). The mixture was diluted with water (25 mL) and extracted with ether (4x25 mL). The ethereal extract was washed with brine (25 mL) and the organic phase evaporated *in vacuo*. The residue was dissolved in tetrahydrofuran (10 mL) and treated with concentrated hydrochloric acid (0.10 mL) for 20 min at room temperature, at which time sodium bicarbonate (100 mg) was added to the reaction mixture; and stirring continued for an additional 30 min. The solvent was removed *in vacuo* and the residue purified by flash chromatography to give **18** (184 mg, 84%): clear gum; R_f 0.20 (B); $[\alpha]_D^{20}$ +5.48° (c 1.26, $CHCl_3$); IR (neat) 3510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, 3H, J=8.0 Hz, CH_3-8), 1.30, 1.44 (both s, 3H(ea), CH_3-2, CH_3-10), 2.14, 2.45 (2.53 (all m, 1H(ea), H-4, H-6, H-8), 2.66 (bt, 1H, J=7.0 Hz, OH), 3.28 (m, 1H, H-1'a), 3.39 (s, 3H, OCH_3), 3.50 (m, 6H), 3.66 (dd, 1H, $J_{6,1"a}$=7.5 Hz, J_{gem}=9.0 Hz, H-1"a), 3.84 (m, 3H), 4.05 (bd, 1H, $J_{7,8}$=9.5 Hz, H-7), 4.44 (d, 1H, $J_{3,4}$=7.5 Hz, H-3), 4.58-4.76 (m, 7H, PhCHx5, CH_2OCH_3), 5.08 (d, 1H, J=11.5 Hz, PhCH), 7.35-7.54 (m, 15H, Phx3). Anal. Calcd. for $C_{40}H_{52}O_7BrI$: C, 56.42; H, 6.16. Found: C, 56.38; H, 5.96.

Preparation of Dihydroxy Olefin 19.

Freshly amalgamated zinc (250 mg) was added to a solution of furanoiodide **18** (182 mg, 0.214 mmol) in 95% ethanol (5 mL) and the temperature of the mixture raised to reflux. The reaction was maintained at the this temperature for 1 h, then filtered through a short column of florisil. The filtrate was evaporated and the residue purified by flash column chromatography to give **19** (124 mg, 80%): clear gum; R_f 0.10 (B); $[\alpha]_D^{20}$ +29.6o (c 1.04, $CHCl_3$); IR (neat) 3480, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, 3H, J=6.6 Hz, CH_3-8), 1.04, 1.18 (both d, 3H(ea), CH_3-2, CH_3-10), 2.07 (m, 2H, H-6, H-8), 2.43 (dd, 1H, $J_{1a,OH}$=5.1, $J_{1b,OH}$=8.1 Hz, 1°, OH), 2.88 (m, 1H, H-4), 3.18 (dd, 1H, $J_{1b,OH}$=8.1, J_{gem}=11.1 Hz, H-1b), 3.20 (ABq, 2H, J=10.5 Hz, Δδ=0.16 ppm, CH_2-10), 3.23 (s, 3H, OCH_3), 3.42 (dd, 1H, $J_{1a,OH}$=5.1, J_{gem}=11.1 Hz, H-1a), 3.55 (d, 1H, $J_{3,4}$=3.3 Hz, H-3), 3.62 (m, 3H, CH_2-1", H-9), 3.79 (m, 2H, H-5, H-7), 4.00 (s, 1H, 3°, OH), 4.38-4.58 (m, 6H, PhCHx4, CH_2OCH_3), 4.64 (d, 2H, J=10.8 Hz, PhCHx2), 4.98 (m, 2H, $=CH_2$), 5.78 (dt, 1H, J_{cis}=3.3, J_{cis}=J_{trans}=10.2 Hz, CH=CH_2), 7.15-7.32 (m, 15H, Phx3). Anal. Calcd. for $C_{40}H_{53}O_7Br$: C, 66.20; H, 7.36. Found: C, 65.98; H, 7.23.

Preparation of Hydroxycarbonate 20a From Dihydroxy Olefin 19.

Phosgene (0.05 mL of a 1.93 M solution in toluene, 0.10 mmol) was added at 0° to a solution of the diol **19** (17 mg, 0.023 mmol) and pyridine (0.10 mL, 1.2 mmol) in anhydrous dichloromethane (2 mL). The reaction mixture was warmed to room temperature and stirred for an additional 10 min. The solution was then diluted with dichloromethane (25 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude residue was used directly in the next step.

A saturated solution of ozone in anhydrous methanol (2 mL) was added at -78°C to a solution in dichloromethane (0.5 mL) of the crude carbonate obtained in the previous step. The reaction mixture was stirred at this temperature for 10 min, then warmed to 0°, at which time dimethylsulfide (0.5 mL) was added. Stirring was continued at this temperature for 1 h, and

the volatiles were then removed *in vacuo* to give the crude aldehydo carbonate: pale yellow gum; R_f 0.20 (B); ^1H NMR (300 MHz, $CDCl_3$) δ 0.58 (d, 3H, J=6.5 Hz, CH_3-8), 1.14, 1.32 (both s, 3H(ea), CH_3-2, CH_3-10), 2.08 (m, 1H, H-8), 2.31 (m, 1H, H-6), 3.12 (m, 1H, H-4), 3.20 (ABq, 2H, J=10.0 Hz, Δδ=0.16 ppm, CH_2-10), 3.22 (s, 3H, OCH_3), 3.44 (dd, 1H, $J_{6,1"a}$=4.5, J_{gem}=11.5 Hz, H-1"a), 3.55 (d, 1H, $J_{8,9}$=7.2 Hz, H-9), 3.65 (m, 3H, H-3, H-1"b, H-7), 4.05 (dd, 1H, $J_{4,5}$=6.5, $J_{5,6}$=2.5 Hz, H-5), 4.08 (ABq, 2H, J=10.5 Hz, Δδ=0.50 ppm, CH_2-1), 4.31 (d, 1H, J=6.5 Hz, $OCHOCH_3$), 4.37-4.50 (m, 5H, PhCHx4, $OCHOCH_3$), 4.70 (d, 1H, J=11.0 Hz, PhCH), 4.74 (d, 1H, J=10.0 Hz, PhCH), 7.10-7.30 (m, 15H, Phx3), 9.72 (bs, 1H, CHO).

Sodium borohydride (5 mg, 0.1 mmol) was added at 0° to a solution of anhydrous ethanol (2 mL), of the crude aldehyde obtained in the previous step. The reaction mixture was stirred at this temperature for 10 min, and then the solution was acidified to pH 6 by dropwise addition of a 1% solution of hydrochloric acid in methanol. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography to give **20a** (14 mg, 80% from **19**): clear gum; R_f 0.10 (D); $[\alpha]_D^{20}$ -15.2° (c 1.63, $CHCl_3$); IR (neat) 3480, 1800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, 3H, J=6.3 Hz, CH_3-8), 1.22, 1.38 (both s, 3H(ea), CH_3-2, CH_3-10), 2.06 (m, 1H, H-4), 2.19 (m, 2H, H-6, H-8), 2.35 (m, 1H, OH), 3.19 (ABq, 2H, J=10.5 Hz, Δδ=0.16 ppm, CH_3-10), 3.27 (s, 3H, OCH_3), 3.52 (dd, 1H, $J_{6,1"a}$=6.0, J_{gem}=9.0 Hz, H-1"a), 3.64 (d, 1H, $J_{8,9}$=8.4 Hz, H-9), 3.65 (m, 1H, H-1'a), 3.73 (m, 2H, H-1'b, H-1"b), 3.78 (bd, 1H, $J_{7,8}$=11.7 Hz, H-7), 3.81 (d, 1H, $J_{3,4}$=5.7 Hz, H-3), 3.87 (m, 1H, H-5), 4.21 (ABq, 2H, J=9.0 Hz, Δδ=0.71 ppm, CH_2-1), 4.41 (d, 1H, J=11.1 Hz, PhCH), 4.42 (d, 1H, J=11.1 Hz, PhCH), 4.53 (m, 4H, PhCHx2, OCH_2OCH_3), 4.64, 4.82 (both d, 1H(ea), J=11.4, 10.8 Hz resp., PhCHx2), 7.15-7.34 (m, 15H, Phx3). Anal. Calcd. for $C_{40}H_{51}O_{10}Br$: C, 62.25; H, 6.66. Found: C, 62.43; H, 6.52.

Preparation of Hydroxycarbonate 20 from p-Anisylidene Aldehyde 26b.

Sodium borohydride (25 mg, 0.6 mmol) was added at 0° to a solution of **26b** (380 mg, 0.441 mmol) in anhydrous ethanol (10 mL). The reaction mixture was stirred for 15 min at this temperature and then diluted with methanol (25 mL) and acidified to pH 3 by careful addition of a concentrated hydrochloric acid. The solution was concentrated (to ca. 10 mL) by removal of the solvent *in vacuo* at room temperature, and then diluted by addition of methanol (25 mL). The procedure was repeated (x3) until TLC (D) indicated disappearance of the baseline material, at which time the volatiles were completely removed *in vacuo*. The resultant brown syrup was triturated with ethyl acetate and filtered through a short column of silica gel. The filtrate was concentrated *in vacuo*, dried under high vacuum, and dissolved in anhydrous dichloromethane (20 mL). The solution was cooled to 0° and pyridine (0.50 mL, 5.2 mmol) and phosgene (1.0 mL of a 1.93 M solution in toluene, 1.93 mmol) added. The reaction was processed as described for the reaction of **19**, and after purification of the crude product gave hydroxy carbonate **20a** (256 mg, 73% from **26b**, t.l.c., i.r., n.m.r., and $[\alpha]_D$ identical to the previously obtained compound).

Preparation of Iodocarbonate 20b.

A mixture of triphenylphosphine (170 mg, 0.648 mmol), iodine (180 mg, 0.709 mmol), imidazole (55 mg, 0.809 mmol) in anhydrous benzene (20 mL) was stored at room temperature for 20 min under an argon atmosphere. A solution of hydroxycarbonate **20a** (240 mg, 0.311 mmol) in benzene (5 mL) was then added to the reaction mixture and stirring continued for an

additional 30 min, at which time the mixture was diluted with ether (50 mL). The resultant suspension was washed with 10% aqueous sodium thiosulfate (20 mL) and saturated aqueous sodium bicarbonate (20 mL) solutions, and brine (20 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated *in vacuo*. After flash chromatography, the residual brown oil afforded **20b** (220 mg, 80%): clear syrup; R_f 0.60 (C); $[\alpha]_D^{20}$ =16.4° (c 1.23, $CHCl_3$); IR (neat) 1802 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.58 (d, 3H, J=6.3 Hz, CH_3-8), 1.20, 1.40 (both s, 3H(ea), CH_3-2, CH2-10), 2.08 (m, 1H, H-8), 2.26 (m, 1H, H-6), 2.45 (m, 1H, H-4), 3.05 (t, 1H, $J_{4,1'a}=J_{gem}$=10.2 Hz, H-1'a), 3.26 (s, 3H, OCH_3), 3.26 (ABq, 2H, J=10.8 Hz, Δδ=0.18 ppm, CH_2-10), 3.39 (m, 2H, H-1'b, H-1"a), 3.49 (d, 1H, $J_{3,4}$=6.9 Hz, H-3), 3.61 (d, 1H, $J_{8,9}$=8.7 Hz, H-9), 3.63 (dd, 1H, $J_{6,1"b}$=3.0, J_{gem}=11.1 Hz, H-1"b), 3.79 (bd, 1H, $J_{7,8}$=10.8 Hz, H-7), 3.84 (m, 2H, H-5, H-1a), 4.50-4.60 (m, 5H, PhC<u>H</u>x3, O<u>CH_2</u>OCH_3), 4.66 (d, 1H, J=9.0 Hz, H-1b), 4.66 (ABq, 2H, J=11.1 Hz, Δδ=0.69 ppm, Ph<u>CH_2</u>), 4.77 (d, 1H, J=10.8 Hz, Ph<u>CH</u>), 7.10-7.40 (m, 15H, Phx3). Anal. Calcd. for $C_{40}H_{50}O_9BrI$: C, 54.49; H, 5.72. Found: C, 54.51; H, 5.62.

Preparation of Tri-O-benzyl-1,2-O-carbonyl-4,6,8,10,11-pentadeoxy-6-(1"-methoxymethoxymethyl)-2,4,8,10-tetra-C-methyl-L-altro-L-galacto-10-eno-undecitol 23a.

A mixture of the bishalocarbonate **20b** (217 mg, 0.246 mmol) freshly amalgamated zinc (200 mg), ammonium chloride (50 mg), and 95% ethanol (5 mL) was heated at reflux for 20 h. The reaction mixture was processed as described for the preparation of **19**. Flash chromatography of the crude product afforded **23a** (153 mg, 92%): clear gum; R_f 0.70 (B), double development; $[\alpha]_D^{20}$ +18.5° (c 1.43, $CHCl_3$); IR (neat) 3520, 1805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (d, 3H, J=6.9 Hz, CH_3-8), 1.00 (d, 3H, J=7.2 Hz, CH_3-4), 1.43 (s, 3H, CH_3-2), 1.68 (bs, 3H, CH_3-10), 1.75 (m, 1H, H-8), 2.10 (m, 1H, H-6), 2.31 (m, 1H, H-4), 3.31 (s, 3H, OCH_3), 3.45 (d, 1H, J=2.7 Hz, OH), 3.69 (dd, 1H, $J_{6,1"a}$=9.0, J_{gem}=11.2 Hz, H-1"a), 3.71 (d, 1H, $J_{3,4}$=5.4 Hz, H-3), 3.77 (dd, 1H, $J_{6,1"b}$=4.2, J_{gem}=11.2 Hz, H-1"b), 4.14 (bd, 1H, $J_{7,8}$=10.8 Hz, H-7), 4.16 (ABq, 2H, J=9.0 Hz, Δδ=0.42 ppm, CH_2-1), 4.19 (dd, 1H, $J_{4,5}$=7.9, $J_{5,6}$=3.0 Hz, H-5), 4.22 (bs 1H, H-9), 4.30 (d, 1H, J=11.7 Hz, Ph<u>CH</u>), 4.48-4.70 (m, 7H, PhC<u>H</u>x5, O<u>CH_2</u>OCH_3), 4.98, 5.03 (both d, 1Hea, $=CH_2$), 7.17-7.37 (m, 15H, Phx3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.82, 12.55, 19.76, 23.16 (CH_3x4), 37.39, 38.54, 40.70 (C-4, C-6, C-8), 55.07 (CH_3O), 64.46, 69.90, 71.15, 72.01, 72.99, 73.88 (C-1, C-3, C-5, C-6', C-7, C-9), 80.42, 81.58, 85.04 (Ph<u>C</u>H_2x3, C-2), 96.28 (CH_3O<u>C</u>H_2O), 110.48 (=CH_2), 126.73, 126.95, 127.40, 127.67, 127.91, 128.12, 137.12, 137.44, 138.85 (Phx3), 142.73 (<u>C</u>H=CH_2), 153.74 (C=O). Anal. Calcd. for $C_{40}H_{52}O_9$: C, 70.98; H, 7.74. Found: C, 70.90; H, 7.65.

When the reaction was interrupted after 30 min, the tetra C-methyl bromide **21** was obtained. For **21**: R_f 0.35 (B); ^1H NMR (300 MHz, $CDCl_3$) δ 0.76, 1.03 (both d, 3H(ea), J=6.5, 7.0 Hz, resp. CH_3-4, CH_3-8), 2.19 (m, 3H, H-4, H-6, H-8), 3.29 (ABq, 2H, J=11.0 Hz, Δδ=0.16 ppm, CH_2-10), 3.31 (s, 3H, OCH_3), 3.48 (dd, 1H, $J_{6,1"a}$=4.0, J_{gem}=10.5 Hz, H-1"a), 3.57 (dd, 1H, J=5.0, 7.0 Hz, H-5), 3.66 (dd, 1H, $J_{8,9}$=10.0 Hz, H-9), 3.72 (m, 2H, H-3, H-1"b), 3.82 (bd, 1H, $J_{7,8}$=10.0 Hz, H-7), 4.21 (ABq, 2H, J=10.0 Hz, Δδ=0.53 ppm, CH_2-1), 4.48-4.61 (m, 6H, O<u>CH_2</u>OCH_3, PhC<u>H</u>x4), 4.71, 4.87 (both d, 1H(ea), J=11.0, 12.0 Hz, resp. PhC<u>H</u>x2), 7.18-7.36 (m, 15H, Phx3).

Preparation of Tri-O-benzyl-4,6,8,11,12-pentadeoxy-1,2-O-isopropylidene-6-C-(1"-methoxymethoxymethyl-2-4-8-10-tetra-C-methyl-D-glycero-L-allo-D-gulo-11-eno-dodecitol 24.

Methyllithium (0.32 mL of a 1.4 M solution in ether, 0.44 mmol) was added to a solution of carbonate **23a** (150 mg, 0.222 mmol) in anhydrous ether (15 mL) at -78° under an argon atmosphere. The reaction mixture was warmed to -20°, and then quenched by the addition of methanol (0.1 mL). The solution was neutralized by the addition of a 1% solution of hydrochloric acid in methanol and the volatiles removed *in vacuo*. The residue was dried under high vacuum and treated with 2,2-dimethoxypropane (1 mL) and dicamphorsulfonic acid (5 mg, 0.02 mmol) in anhydrous dichloromethane (10 mL) at room temperature for 20 min. The reaction mixture was diluted with dichloromethane (25 mL), washed with saturated aqueous sodium bicarbonate (10 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The oily residue was purified by flash chromatography and gave **23b** (130 mg, 85%): clear oil, R_f 0.40 (E); ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (d, 3H, J=6.9 Hz, CH_3-8), 6.96 (d, 3H, J=7.2 Hz, CH_3-4), 1.32, 1.40 (both s, 9H $(CH_3)_2C$, CH_3-2), 1.65 (bs 3H, CH_3-10), 1.71 (m, 1H, H-8), 2.11 (m, 1H, H-6), 2.23 (m, 1H, H-4), 3.23 (s, 3H, OCH_3), 3.41 (d, 1H, J=7.5 Hz, H-3), 3.50 (d, 1H, $J_{7,OH}$=2.4 Hz, OH), 3.57 (t, 1H, $J_{6,1"a}$=J_{gem}=9.9 Hz, H-1"a), 3.71 (dd, 1H, $J_{6,1"b}$=3.9, J_{gem}=9.9 Hz, H-1"b), 3.78 (ABq, 2H, J=9.0 Hz, Δδ=0.16 ppm, CH_3-1), 4.15 (bs, 1H, $J_{7,8}$=9.0 Hz, H-7), 4.21 (bs, 1H, H-9), 4.29 (m, 1H, H-5), 4.42 (ABq, 2H, J=6.6 Hz, Δδ=0.08 ppm, $OC\underline{H}_2OCH_3$), 4.43 (ABq, 2H, J=11.4 Hz, Δδ=0.27 ppm, $PhC\underline{H}_2$), 4.54 (ABq, 2H, J=10.8 Hz, Δδ=0.18 ppm, $PhC\underline{H}_2$), 4.71 (ABq, 2H, J=11.1, Δδ=0.29 ppm, $PhC\underline{H}_2$), 4.94, 5.00 (both bs, 1H(ea), $=CH_2$), 7.14-7.35 (m, 15H, Phx3).

The solution of the olefin **23b** (75 mg, 0.11 mmol) in anhydrous dichloromethane (2 mL) was subjected to the ozonolysis procedure as described for the preparation of hydroxycarbonate **20a** from olefin **19**. The crude product was dried under high vacuum, dissolved in anhydrous tetrahydrofuran (5 mL) and added slowly over a period of 1 h to a solution of vinylmagnesium bromide (0.5 mL of a 1M solution in tetrahydrofuran, 0.5 mmol) in tetrahydrofuran (2 mL) at -30° under an argon atmosphere. The reaction mixture was then diluted with a saturated aqueous ammonium chloride solution (10 mL) and extracted with ether (3x20 mL). The combined organics were washed with brine (25 mL), dried (Na2SO4), filtered, and evaporated *in vacuo*. The residue was subjected to flash chromatography and gave **24** (66 mg, 84% from **23a**): clear gum; R_f 0.30 (E) double development; $[\alpha]_D^{20}$ -4.29° (c 1.05, $CHCl_3$); IR (neat) 3490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, 3H, J=6.6 Hz, CH_3-8), 0.94 (d, 3H, J=7.2 Hz, CH_3-4), 1.23, 1.33, 1.35, 1.41 (all s, 3Hea, CH_3-2, CH_3-10, $(CH_3)_2C$), 1.98 (m, 1H, H-8), 2.18 (m, 2H, H-4, H-6), 2.92 (bs, 1H, 3°, OH), 3.25 (s, 3H, OCH_3), 3.42 (d, 1H, J=7.5 Hz, H-3), 3.60 (bt, 1H, $J_{6,1"a}$=J_{gem}=9.6 Hz, H-1"a), 3.73 (dd, 1H, $J_{6,1"b}$=3.9, J_{gem}=9.6 Hz, H-1"b), 3.78 (ABq, 2H, J=8.7 Hz, Δδ=0.17 ppm, CH_2-1), 3.85 (bs, 1H, H-9), 3.88 (bs, 1H, 2°, OH), 3.95 (bd, 1H, $J_{7,8}$=10.5 Hz, H-7), 4.30 (dd, 1H, J=3.0, 5.4 Hz, H-5), 4.45 (ABq, 2H, J=6.3 Hz, Δδ=0.08 ppm, $OC\underline{H}_2OCH_3$), 4.57 (ABq, 2H, J=10.8 Hz, Δδ=0.19 ppm, $PhC\underline{H}_2$), 4.59 (ABq, 2H, J=11.1 Hz, Δδ=0.02 ppm, $PhC\underline{H}_2$), 4.70 (ABq, 2H, J=11.1 Hz, Δδ=0.25 ppm, $PhC\underline{H}_2$), 5.05 (dd, 1H, J_{gem}=1.5, J_{cis}=10.5 Hz, H-11*cis*)

5.30 (dd, 1H, J_{gem}=1.5, J_{trans}=17.4 Hz, H-11*trans*), 6.00 (dd, 1H, J_{cis}=10.5, Jt_{rans}=17.4 Hz, H-10); ^{13}C NMR (75 Hz, $CDCl_3$) δ 10.89, 13.68, 22.86, 24.82, 26.55, 27.65 (CH_3x5), 37.63, 37.88, 40.32 (C-4, C-6, C-8), 55.40, 65.19, 72.00, 72.41, 73.44, 74.22, 75.37, 75.48 (CH_3O, C-1, C-3, C-5, C-1", C-7, C-9, C-10), 80.73, 82.37, 84.98, 85.61 (Ph$\underline{C}H_2$x3, C-2), 96.71 (O$\underline{C}H_2OCH_3$), 108.71 ($(CH_3)_2\underline{C}O_2$), 112.31 (=CH_2), 127.30, 127.36, 127.46, 127.63, 127.82, 127.91, 128.15, 128.26, 128.52, 138.19, 138.94, 139.07 (Ph), 144.85 ($C\underline{H}$=CH_2). Anal. Calcd. for $C_{42}H_{60}O_9$: C, 71.64; H, 8.39. Found: C, 71.53; H, 8.59. M+H^+(FAB) requires 721.4316. Found: 721.4285.

Preparation of Hydroxylactone 27b.

The allylic alcohol **24** (25 mg, 0.035 mmol) was subjected to the ozonolysis procedure as described for the preparation of **20a** from **19**. Flash chromatography of the crude product afforded **27a** (19 mg, 76%): clear gum; R_f 0.10 (C); for major anomer: ^1H NMR (300 MHz, C_6D_6) δ 0.95 (d, J=6.6 Hz, CH_3-8), 1.06 (d, J=7.2 Hz, CH_3-4), 1.38, 1.44 (both s, $(CH_3)_2C$, CH_3-2, CH_3-10), 2.01 (s, 10-OH), 2.03 (m, H-8), 2.32 (m, H-4, H-OH), 2.61 (m, H-6), 3.14 (s, OCH_3), 3.32 (d, $J_{8,9}$=9.6 Hz, H-9), 3.68 (m, H-1a, H-3, H-1"a), 3.88 (bd, J5,6=6.6 Hz, H-5), 4.00 (dd, $J_{6,1"b}$=4.5, J_{gem}=10.5 Hz, H-1"b), 4.11 (d, J=9.0 Hz, H-1b), 4.33 (bd, $J_{6,7}$=10.5 Hz, H-7), 4.46 (m, O$\underline{C}H_2OCH_3$, Ph$C\underline{H}$), 4.68 (m, Ph$C\underline{H}$x2, H-11), 4.92 (ABq, J=10.5 Hz, Δδ=0.18 ppm, Ph$C\underline{H}_2$), 5.04 (d, J=10.5 Hz, Ph$C\underline{H}$), 7.05-7.50 (m, Phx3).

Dry dimethylsulfoxide (0.02 mL, 0.28 mmol) was added slowly to a solution of oxalyl chloride (0.02 mL, 0.23 mmol) in dry dichloromethane (2 mL) at -78° under an argon atmosphere. The mixture was maintained at this temperature for 20 min, and then a solution of the above lactol mixture **27a** (14 mg, 0.019 mmol) in dry dichloromethane (1 mL) was slowly added. The reaction mixture was stirred at -78° for an additional 20 min, after which anhydrous triethylamine (0.07 mL, 0.51 mmol) was slowly introduced by dropwise addition. The reaction mixture was stirred at -40° for 20 min, then warmed to 0°, diluted with saturated aqueous sodium bicarbonate (10 mL), and extracted with ether (4x10 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Flash chromatography of the crude product afforded unreacted **27a** (7 mg, 50%) and **27b** (4 mg, 29%): clear gum; R_f 0.30 (C); $[\alpha]_D^{20}$ -43° (c 0.4, $CHCl_3$); IR (neat) 3440, 1730 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 0.74 (d, 3H, J=6.6 Hz, CH_3-8), 0.98 (d, 3H, J=6.9 Hz, CH_3-4), 1.39, 1.41 (both s, 3H(ea), $C(CH_3)_2$), 1.48 (s, 3H, CH_3-2), 1.56 (s, 3H, CH_3-10), 2.21 (m, 1H, H-4), 2.44 (m, 1H, H-8), 2.73 (m, 1H, H-6), 3.12 (s, 3H, OCH_3), 3.24 (d, 1H, $J_{8,9}$=10.1 Hz, H-9), 3.30 (s, 1H, OH), 3.52 (dd, 1H, $J_{6,1"a}$=4.0, J_{gem}=11.5 Hz, H-1"a), 3.56 (d, 1H, $J_{3,4}$=8.8 Hz, H-3), 3.69 (bd, 1H, $J_{5,6}$=9.1 Hz, H-5), 3.79 (dd, 1H, $J_{6,1"b}$=6.8, J_{gem}=11.5 Hz, H-1"b), 3.84 (ABq, 2H, J_{gem}=9.4 Hz, Δδ=0.29 ppm,CH_2-1), 4.37 (ABq, 2H, J=6.7 Hz, Δδ=0.05 ppm, O$\underline{C}H_2OC\underline{H}_3$), 4.44 (bd, 1H, $J_{7,8}$=10.8 Hz, H-7), 4.68 (ABq, 2H, J=11.8 Hz, Δδ=0.34 ppm, Ph$C\underline{H}_2$), 4.86 (ABq, 2H, 10.8 Hz, Δδ=0.40 ppm, Ph$C\underline{H}_2$), 4.89 (ABq, 2H, J=10.8 Hz, Δδ=0.19 ppm, $PhCH_2$), 7.08-7.5 (m, 15H, Phx3). Irradiation of the singlet at δ 1.56 (CH_3-10), produces a strong NOE enhancement of the multiplet at δ 2.44 (H-8). ^{13}C NMR

(75 MHz, $CDCl_3$) δ 12.96, 17.52, 22.26, 22.80, 26.46, 27.75 (CH_3x6), 35.40, 37.87, 43.09 (C-4, C-6, C-8), 55.35, 64.86, 72.13, 74.63, 75.42, 76.12 (OCH_3, C-1, C-3, C-5, C-6', C-7, C-9), 82.10, 82.30, 83.04, 85.16, 86.51 ($PhCH_2$x3, C-2, C-10), 96.39 (OCH_2OCH_3), 108.63 ($(CH_3)_2CO_2$), 127.22, 127.66, 127.73, 127.97, 128.13, 128.17, 128.27, 128.38, 128.41, 138.29, 138.84, 139.28 (Ph), 177.41 (C=O), $M+H^+$(FAB) requires 721.3939. Found 721.3952.

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