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NEW APPROACHES TO SYNTHETIC RECEPTORS. STUDIES ON THE SYNTHESIS AND PROPERTIES OF MACROCYCLIC *C*-GLYCOSYL COMPOUNDS AS CHIRAL, WATER-SOLUBLE CYCLOPHANES*

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ABSTRACT

In an approach for the preparation of macrocyclic *C*-glycosyl compounds, the *C*-glycosyl residue is synthesized by acid-assisted reduction of a cyclic hemiacetal with sodium cyanoborohydride. Macrocycle formation is effected by the reaction of a symmetrical bis(*C*-glycosyl)derived diamine with a dicarboxylic acid dichloride. The product macrocycles are presented as the first examples of a new type of chiral, water-soluble cyclophane. Molecules of this type are of interest as synthetic receptors for lipophilic substrates.

INTRODUCTION

The design and preparation of model receptor–substrate systems, complementary pairs of water-soluble organic molecules, which will form stable bimolecular complexes, is an interesting contemporary challenge for synthetic organic chemists. The importance of intermolecular interactions between organic molecules and the need to understand the forces which govern such binding interactions are widely recognized. Current treatises on molecular biology and biochemistry are replete with examples of bimolecular complex-formation involving organic molecules. Ongoing efforts in many laboratories are directed toward molecular-level descriptions of how changes in drug structure lead to changes in drug–receptor interactions and response. Model receptor–substrate systems will allow detailed analyses of the solvent effects and intermolecular forces which control molecular interactions in aqueous solutions.

Our goal is to develop new synthetic approaches for preparing chiral, water-soluble molecules which have hydrophobic cavities. Such synthetic receptors (mol. wt., 650–1500) will support a rational approach to understanding the details of organic-molecular interactions in aqueous solution. These molecules are designed to form molecular complexes with benzenoid or other lipophilic substrates. The

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complexes (inclusion compounds) will be stabilized by van der Waals and solvent liberation (hydrophobic) forces, and therefore different from and complementary to the much more extensively studied crown-ether type "receptor"[1-4]. In this paper, we demonstrate that *C*-glycosyl residues may be used as structural units for the preparation of water-soluble macrocycles. The potential advantages of this approach to synthetic receptors will be described, and the preparation of two macrocyclic *C*-glycosyl derivatives will be detailed.

Designs for water-soluble macrocylic receptors. — Important observations relevant to the design of water-soluble, hydrophobic binding sites for small organic molecules have been recorded over the past 10 years[5-14]. Our approach to synthetic water-soluble receptors is founded upon these creative early investigations.

This project was begun to test the possibility that *C*-glycosyl compounds may be useful for the preparation of synthetic receptors. The essential feature of the early approaches to synthetic receptors (Fig. 1a) was the combination of the cyclophane (which defined the lipophilic cavity) with ionic groups (which rendered the cavity water-soluble). The idea presented here (Fig. 1b) is that aldose-derived structural units may be incorporated into a lipophilic macrocyclic ring. It is hypothesized that the resulting macrocyclic products will function as synthetic receptors analogous to Koga's molecules if (a) the macrocycle is water soluble (mM solutions would be adequate) and (b) the macrocycle encloses a lipophilic pocket.

This idea is a logical extension of the earlier work and has some interesting features. First, the approach allows the preparation of *chiral* receptors of known absolute configuration. No chiral and enantiomerically pure macrocyclic, water-soluble cyclophane has been reported to bind lipophilic substrates in aqueous

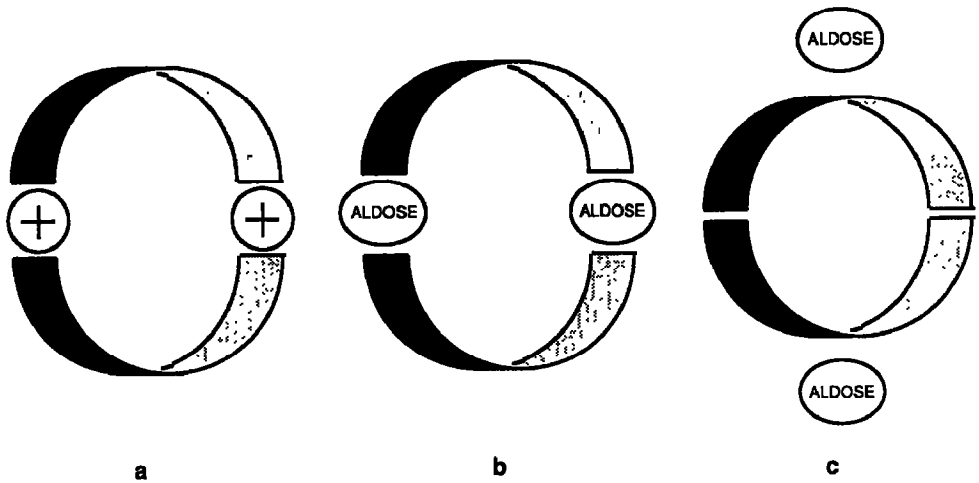
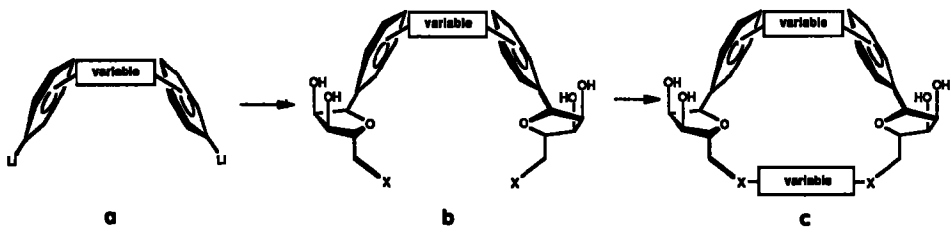


Fig. 1. Lipophilic macrocyclic binding sites may be rendered water soluble by the use of ionic functional groups (a), or by including aldose-derived polyhydroxylated substructures within the ring (b), or exterior to the ring (c).

solution. Because the chiral units are contained within the ring (rather than exterior to the ring, as shown in Fig. 1c) the receptors will provide substantially *chiral interior environments*. Such chiral cavities may allow the creation of enantioselective synthetic receptors which would be effective in aqueous media. Second, the strategy will allow the prepration of *neutral*, water-soluble cyclophanes. Neutral synthetic receptors will allow the effects of ionic charge on intermolecular forces to be systematically assessed. Finally, the hydroxyl groups carried by the aldose units will provide additional attractive interactions with some substrates, will be reactive toward other substrates, and can be used to attach additional functional groups. These functionalized synthetic receptors should be promising armatures for the construction of biomimetic systems.

The synthetic approach. — The target molecules in this project (Fig. 1b) represent a "second generation" approach to water-soluble binding sites for lipophilic substrates. Syntheses of these molecules should be short and efficient. We sought a protocol which would be modular and incorporate structural units that could be easily varied. If successful, such a strategy would allow the preparation of a number of related synthetic receptors.

The general strategy (Scheme 1) takes appropriate advantage of the fact that the targets have at least one C_2 axis of symmetry. It was envisioned that a symmetrically lithiated aryl compound (**a**) be stereospecifically ribosylated to afford a chiral bis(*C*-glycosyl) derivative (**b**) of C_2 symmetry. Model studies indicated that *C*-D-ribofuranosyl glycosides of α configuration would be suitable for preparing macrocycles which would include a lipophilic cavity. The intermediate **b** may be converted into the desired macrocyclic target **c** by any of a number of methods. For example, as shown below, macrocyclization may be effected by the reaction of a chiral diamine, derived from this bis(*C*-glycosyl) compound, with a dicarboxylic acid dichloride. The construction of the macrocycle is substantially simplified because the synthesis proceeds symmetrically outward from the axis of symmetry. The choice of the dilithio unit (**a**) and the means of cyclization (the two variable units in Scheme 1) will affect the properties of the ultimate macrocycle. A *C*-glycosyl linkage was chosen for attaching the lipophilic unit to the aldose residue because the carbon–carbon bond in the *C*-glycosyl compound will be more robust



Scheme 1. A generalized approach for preparing macrocyclic *C*-glycosyl compounds.

(less reactive) than the carbon–oxygen bond in glycosides, and the direct connection of an aryl group to C-1 of the aldosyl residue provides a more rigid structure than would result from a glycosidic linkage. The D-ribofuranose unit was chosen because it is readily available in a protected form from D-ribonic acid and because the 2,3-*O*-isopropylidene protecting group offered the possibility of controlling the stereochemical outcome of the *C*-glycosylation process.

RESULTS AND DISCUSSION

The approach outlined in Scheme 1 required a stereoselective method for forming α-D-ribofuranosylarenes. Previous work in this area indicated that nucleophilic additions of alkylmetals to activated D-ribofuranose derivatives affords mixtures of anomeric products[15]. Based on experience in a related system, we hypothesized that hydride donation to a cationic intermediate would lead more cleanly to the desired *C*-α-D-glycosyl compounds.

To test this possibility, the D-ribonolactone derivative **1** was alkylated to afford hemiacetals **2–8**. The product hemiacetals were obtained in excellent yield (Table I) as mixtures of anomeric isomers. In contrast to the other adducts, the 4-(dimethylamino)phenyl derivative **8** exists (in $CDCl_3$ or CCl_4 solution) only in the keto-hydroxy form (**8b**) and no hemiacetal was observable by ^1H- or ^{13}C-n.m.r. spectroscopy. Under similar conditions, the other products **2–7** were preponderantly in the hemiacetal form (**2a–7a**). The stability of the open form of **2g** probably

TABLE I

FORMATION AND REDUCTION OF THE CYCLIC HEMIACETALS **2–8**

Starting compound	*Hemiacetal formed*		*Reduction*				
	Residue at C-1	*Yield (%)*[a]	*Conditions*[b]	*C-Glycosyl compounds formed*			
				Compound	*Yield (%)*	*Compound*	*Yield (%)*
2	Me	97	A	**10**	0	**17**	0
			B		0		0
3	Ph	94	A	**11**	0	**18**	0
			B		68		0
4	4-(Me)C_6H_4	100	B	**12**	63	**19**	19
5	4-(MeO)C_6H_4	100	A	**13**	98	**20**	0
6	4-Biphenyl	96	B	**14**	66	**21**	17
7	2-Furyl	96	A	**15**	62	**22**	0
			B		73		24
8	4-(Me_2N)C_6H_4	31	B	**16**	0	**23**	0

[a]All yields reported for isolated products. [b]Conditions: (A) *p*-toluenesulfonic acid–methanol, room temp.; (B) dichloroacetic acid–2,2,2-trifluorethanol, room temp. See Experimental section.

Me2
OSiMe2But
R-Li
1
2a–8a
2b–8b
H+, BH3CN−
9
10–16
24
17–23
2, 10, 17 R = Me
3, 11, 18 R = Ph
4, 12, 19 R = 4-MeC6H4
5, 13, 20 R = 4-MeOC6H4
6, 14, 21 R = 4-Biphenyl
7, 15, 22 R = 2-Furyl
8, 16, 23 R = 4-(Me2N)C6H4
SiMe2But = (1,1-dimethylethyl)dimethylsilyl

contributes to the low yield observed for its formation. The major by-product was the diol formed by reaction of a second alkyllithium reagent.

Reduction of carbohydrate-derived acetals has been studied for many years and has been achieved most recently by the use of triethylsilane with Lewis acid catalysts[16,17]. In this case, the goal was a direct reduction of the hemiacetal and we chose to evaluate sodium cyanoborohydride for this purpose because it is readily available and inexpensive.

The direct reduction of hemiacetals to afford *C*-glycosyl compounds (**10–16** and **17–23**) proceeded in good to excellent yield (Table I), provided that the alkyl group at C-1 was adequately electron releasing. A limited study of solvent and proton source indicated that nitromethane or 2,2,2-trifluoroethanol are good solvents for this reaction and dichloroacetic acid is an adequate proton source. The products had preponderantly the α-D configuration and in two cases the α-D anomer was the only cyclic product obtained. The product structures could be readily determined by established spectroscopic methods including ^{13}C- and ^{1}H-n.m.r. spectroscopy[18–21].

The process just outlined afforded a completely stereoselective method for preparing (4-alkoxy)aryl derivatives of (4-alkoxyl)-α-D-ribofuranosylarenes and attention was therefore turned toward preparation of the requisite macrocyclic *C*-glycosyl compounds.

Bromination of diphenoxyethane afforded the 4,4′-dibromo derivatives **25** in 86% yield[22]. Alkylation of dilithium compound **26** in oxolane with the lactone **1** under the conditions applied in the model systems provided the bis(hemiacetals) **27**. Reduction of the bis(hemiacetal) **27** proceeded as expected based upon the model studies and provided a quantitative yield of the desired bis(*C*-glycosyl) compound **29**. The only product detected by ^{1}H- or ^{13}C-n.m.r. spectroscopy was the desired α-D anomer. After removal of the protecting group at O-5′ and chromatographic purification, the diol **30** was obtained (80% overall yield from lactone **1**). This symmetrical diol (**30**) was converted into the diamine **32** *via* the Mitsunobu–Gabriel procedure[23]. This diamine, with terephthaloyl chloride, under the high dilution conditions described by Dietrich *et al.*[24] provided the *C*-glycosyl macrocycle **34** (*m/e* calc. 686.2839; found 686.2823) in 15% yield after purification. Deprotection of this macrocycle afforded the desired tetrahydroxy macrocyclic diamide **35** in good yield. In a similar manner, diamine **32** and the dicarboxylic acid dichloride derived from 2,3-*O*-methylene-D-tartaric acid[25] afforded the macrocyclic diamide **33** in 10% overall yield.

CONCLUSION

Inevitably, water-soluble synthetic receptors more complex than the simple cyclophanes currently known must be synthesized. The results described herein establish a general approach for preparing *C*-glycosyl macrocycles of a type previously unknown. By this approach, for the first time, a cyclophane-like molecule has been rendered water soluble without the use of ionic groups.

25 R = Br
26 R = Li
27 R = H
28 R = Me
29 R = OSiMe2But
30 R = OH
31 R = NPhth
32 R = NH2
33
34
35
SiMe2But = (1,1-dimethylethyl) dimethylsilyl

For convenient n.m.r. studies of binding properties, it is necessary that monomeric synthetic receptor solutions of at least mM concentration be attainable. We found that aqueous solutions of the tartaric acid diamide macrocycle (**33**) were readily prepared. N.m.r. spectra of these solutions in D_2O showed no changes over the concentration range from 0.5 to 50mM. In contrast, the terephthalamide macrocycle (**35**) has very low solubility. Sonication of warm solutions of **35** in deuterium oxide, followed by centrifugation, provided a supernatant centrifugate which gave no usable n.m.r. signal. The limiting solubility of **35** is therefore probably below 0.5mM.

We conclude that this approach to water-soluble macrocyles, prototypes for a new generation of synthetic receptors for small organic molecules, is promising and worthy of further exploration. A more rigid dilithium unit will afford a less flexible diamine intermediate and should lead to improved yields in the macrocyclization step. Further control of conformation and additional enhancement of solubility will be obtainable by prudent selection of the dicarboxylic acid dichloride component of the cyclization reaction.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover capillary melting-point apparatus and are uncorrected. Boiling points are uncorrected. Optical rotations were measured in 1-dm cells of 1-mL capacity with a Perkin–Elmer Model 141 polarimeter. Chloroform was used as the solvent for all optical rotations and was filtered through neutral alumina immediately prior to use. ^{1}H-N.m.r. spectra were recorded with Varian EM-390, Nicolet NT-200, and Nicolet NMC-1280 spectrometers. Chemical shifts (δ) are reported relative to the signal of tetramethylsilane (δ 0.0) as an internal standard. ^{13}C-N.m.r. spectra were recorded with Varian FT80 and Nicolet NMC-1280 spectrometers. Chemical shifts (δ) are reported relative to the signal of tetramethylsilane (δ 0.0) as an internal standard, or relative to that of $CDCl_3$ (δ 77.0). I.r. spectra were determined with a Perkin–Elmer 298 spectrometer for solutions in carbon tetrachlorideunless oherwise stated. Low-resolution mass spectra were obtained with Finnigan GC/MS and Dupont (CEC) 21-491 spectrometers, and high-resolution mass spectra with a Dupont (CEC) 21-11 spectrometer. T.l.c. was conducted on 2.5 × 10 cm pre-coated t.l.c. plates, Silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany. Flash column chromatography was carried out on Silica gel 60 (E. Merck, particle size 0.040–0.063 mm, 230–400 mesh ASTM). "Dry" solvents were distilled shortly before use from the appropriate drying agent. Ether and oxolane were distilled under dry N_2 from Na metal in the presence of benzophenone. Methanol and pentane were distilled from Na metal under dry N_2. Benzene, dichloromethane, pyridine, and 1,2-dimethoxyethane were distilled from CaH_2. *N,N*-Dimethylformamide was distilled from CaH_2 at 74° and 7.2 KPa (54 mm Hg). Other reagents were purified as follows. Dimethyl sulfoxide was

fractionally distilled from CaH_2 at 50° and 0.5 KPa (4 mm Hg), and triethylamine from Na metal. 1-Chloro-2,2,3,3-tetramethyl-2-silapropane (*t*-butyldimethylsilyl chloride) was sublimed at 80° and 0.1 MPa (750 mm Hg). Ethyl acetate was stored over molecular sieves (4A, 4–8 mesh) at least 10 days prior to use. All other reagents and solvents were "Reagent Grade" unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Matheson, Coleman, and Bell. "Petroleum ether" and "Skelly B" are used interchangeably to refer to reagent grade hexanes (b.p. 60–70°), purified by stirring for 24 h over conc. H_2SO_4, stirring subsequently over anhydrous $CaCO_3$ for 24 h, and then fractionally distilling. Reactions were run under an N_2 atmosphere with a mercury bubbler arranged so that the system could be alternately evacuated and filled with N_2 and kept under a positive pressure of N_2. The temperature of reactions run without external cooling or heating ("room temperature") was 25 ±5°. Syringes, needles, and reaction flasks were dried at least 12 h in an oven (110°) and cooled in a dessicator over anhydrous $CaSO_4$ prior to use. Removal of solvents "under reduced pressure" refers to rotary evaporation at ~40° and 3 KPa (23 mm Hg), followed by evacuation under high vacuum (13 Pa, 0.1 mm Hg) to constant weight.

*1-Deoxy-6-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-3,4-*O*-(1-methylethylidene)-*D*-psicofuranose* (**2**). — To a stirred solution of 5-*O*-[1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-D-ribono-1,5-lactone (**1**; 906 mg, 3.00 mmol) in oxolane (10 mL) at −78° was added a 1.41M ethereal solution of methyllithium (2.13 mL, 3.00 mmol). After 6 h at −78°, methanol (1 mL) was added and the mixture allowed to warm to room temperature. The mixture was partitioned between ether (80 mL) and water (40 mL). The organic layer was separated, washed with water (40 mL), and dried ($MgSO_4$). Removal of solvent under reduced pressure and purification of the residue by flash chromatography (40 × 150 mm column of SiO_2, 20% ethyl acetate–petroleum ether) afforded **2** (922 mg, 97%), colorless white syrup, $[\alpha]_D^{23}$ −10° (*c* 1.5, chloroform), R_F 0.42 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 3550, 3500–3300, 3000, 2960, 2930, 2860, 1380, 1350, 1100, and 1050 cm^{-1}; ^{1}H-n.m.r. (CCl_4): δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.23 (s, 3 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 3.60 (d, 2 H, *J* 5 Hz), 4.00 (m, 1 H), 4.28 (d, 1 H, *J* 5 Hz), and 4.68 (d, 1 H, *J* 5 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.06, 21.17, 25.02, 25.60, 26.47, 64.76, 81.95, 85.67, 87.74, 106.39, and 112.16; m.s. ($M^+ - CH_3$): Calc. for $C_{14}H_{27}O_5Si$, *m/z* 303.1618; found, 303.1628.

5-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-1-C-phenyl-D-ribofuranose (**3**). — By the procedure used to prepare **2**, **1** (906 mg) in oxolane (10 mL) and a 0.95M benzene–ether solution of phenyllithium (3.16 mL) afforded, after flash chromatography (40 × 150 mm column of SiO_2, 20% ethyl acetate–petroleum ether) afforded **3** (1.072 g, 94%), colorless white syrup (mixture of anomers), $[\alpha]_D^{23}$ −20° (*c* 1.5, ethanol), R_F 0.45 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3580, 2950, 2930, 2860, 1500, 1250, 1220, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.02 (s, 6 H), 0.85 (s, 9 H), 1.06 (s, 3 H), 1.18 (s, 3 H), 3.63 (d, 2 H, *J* 6 Hz), 4.08 (m, 1 H), 4.36 (m, 1 H), 4.68 (d, 1 H, *J* 6 Hz), and 7.05–7.30

(m, 5 H); ^{13}C-n.m.r. ($CDCl_3$): δ 18.29, 24.87, 25.81, 26.39, 64.81, 81.97, 86.18, 88.65, 112.59, 125.69, 126.96, 127.42, 128.00, and 138.99; m.s. (M^+): Calc. for $C_{20}H_{32}O_5Si$, *m/z* 380.2014; found, 380.2019.

5-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-1-C-(4-methylphenyl)-D-ribofuranose (**4**). — To a stirred solution of 4-bromotoluene (1.026 g, 6.00 mmol) in oxolane at −78° was added a 1.8M solution of *tert*-butyllithium in pentane (7 mL, 12.2 mmol). The mixture was stirred at −78° for 1 h, allowed to warm to 0°, and then cooled to −78°. To this solution was added a solution of **1** (1.812 g, 6.00 mmol) in oxolane (15 mL). The mixture was stirred at −78° for 6 h, then methanol (1 mL) was added and the mixture allowed to warm to room temperature. The solution was poured into ether (200 mL) and washed twice with water (150 mL). The organic phase was dried ($MgSO_4$) and then evaporated under reduced pressure to give **4** (2.38 g, 100%), colorless white syrup, $[\alpha]_D^{23}$ −32° (*c* 1.5, chloroform), R_F 0.66 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3680, 3500–3200, 3000, 2960, 2940, 2860, 1520, 1470, 1420, 1380, 1370, 1220, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.12 (s, 6 H), 0.93 (s, 9 H), 1.20 (s, 3 H), 1.38 (s, 3 H), 2.33 (s, 3 H), 3.70 (d, 2 H, *J* 3 Hz), 4.42 (s, 1 H), 4.58 (d, 1 H, 6 Hz), 4.89 (d, 1 H, *J* 6 Hz), 7.15 (d, 2 H, 8 Hz), and 7.51 (d, 2 H, *J* 8 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ −5.83, 17.99, 20.88, 24.62, 25.59, 26.19, 64.51, 81.95, 85.84, 88.04, 106.74, 112.74, 126.74, 127.83, 136.13, and 137.07; m.s. (M^+): Calc. for $C_{21}H_{34}O_5Si$, *m/z* 394.2175; found, 394.2195.

5-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-1-C-(4-methoxyphenyl)-D-ribofuranose (**5**). — By the procedure used to prepare **4**, 4-bromoanisole (561 mg, 3.00 mmol) in oxolane (9 mL) with a 1.8M solution of *tert*-butyllithium in pentane (3.4 mL, 6.15 mmol) provided a solution of 4-lithio-1-methoxybenzene. This solution and **1** (906 mg, 3.00 mmol) in oxolane (9 mL) afforded **5** (1.230 g, 100%), colorless white syrup, $[\alpha]_D^{23}$ −45° (*c* 1.5, chloroform), R_F 0.39 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 3580, 3500–3200, 2960, 2940, 2860, 1685, 1600, 1510, 1380, 1370, 1250, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.09 (s, 6 H), 0.90 (s, 9 H), 1.15 (s, 3 H), 1.28 (s, 3 H), 3.70 (m, 5 H), 4.18 (m, 1 H), 4.45 (d, 1 H, *J* 5 Hz), 4.75 (d, 1 H), 6.76 (d, 2 H, *J* 8 Hz), and 7.40 (d, 2 H, *J* 8 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.27, 25.55, 25.79, 26.42, 55.07, 64.79, 81.90, 86.02, 88.50, 106.80, 112.53, 112.83, 128.24, 131.24, and 159.35; m.s. ($M^+ - CH_3$): Calc. for $C_{20}H_{31}O_6Si$, *m/z* 395.1881; found, 395.1890.

1-C-[1,1'-Biphenyl]-4-yl-5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-D-ribofuranose (**6**). — By the procedure used to prepare **4**, 4-bromobiphenyl (671 mg, 3.00 mmol) in oxolane (9 mL) and a 1.8M solution of *tert*-butyllithium in pentane (3.4 mL, 6.15 mmol) provided a solution of 1-lithio-4-phenylbenzene. This solution and **1** (906 mg, 3.00 mmol) in oxolane (9 mL) afforded **6** (1.314 g, 96%), a colorless white syrup, $[\alpha]_D^{23}$ −54° (*c* 1.5, chloroform); R_F 0.52 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3680, 3400–3200, 3000, 2960, 2940, 2860, 1385, 1375, 1220, and 1080 cm^{-1}; ^{1}H-n.m.r. (CCl_4): δ 0.03 (s, 6 H), 0.90 (s, 9 H), 1.18 (s, 3 H), 1.30 (s, 3 H), 3.70 (d, 2 H, *J* 5 Hz), 4.12 (t, 1 H, *J*

5 Hz), 4.77 (m, 1 H), 5.05 (d, 1 H, *J* 4 Hz), and 7.35 (m, 9 H); ^{13}C-n.m.r. ($CDCl_3$): δ −5.65, 18.32, 24.59, 25.88, 26.54, 64.87, 82.13, 86.13, 88.68, 106.97, 112.71, 126.25, 126.82, 127.16, 127.53, 128.63, 138.25, 140.84, and 141.16; m.s. ($M^+ - CH_3 - H_2O$): Calc. for $C_{25}H_{31}O_5Si$, *m/z* 439.1994; found, 439.1940.

5-O-[*(1,1-Dimethylethyl)dimethylsilyl*]-*1*-C-*(2-furanyl)-2,3*-O-*(1-methylethylidene)*-D-*ribofuranose* (**7**). — To a stirred solution of furan (309 mg, 4.5 mmol) and tetramethylethylenediamine (105 mg, 0.9 mmol) in ether (3 mL) at −20° was added butyllithium in hexane (1.90 mL, 3.00 mmol). The mixture was allowed to warm to room temperature, and after 3 h stirring the mixture was cooled to −78° and oxolane (4 mL) was added to give a clear solution of 2-lithiofuran. A solution of **1** (906 mg, 3.00 mmol) in oxolane (10 mL) was added, and after stirring for 6 h at −78° methanol (1 mL) was added. The mixture was allowed to warm to room temperature, poured into ether (250 mL), and washed twice with M ammonium chloride (50 mL) and twice with saturated $NaHCO_3$ (50 mL). The organic phase was dried ($MgSO_4$) and then evaporated under reduced pressure to give a colorless white syrup. This was purified by flash chromatography (60 × 180 mm column of SiO_2, 20% ethyl acetate–petroleum ether) to give **7** (996 mg, 96%) as a colorless white syrup; it was present as three interconverting forms, two hemiacetal anomers and the open-chain ketonic form; therefore in the ^{13}C-n.m.r. spectrum only the major characteristic peaks are reported; $[\alpha]_D^{23}$ −44° (*c* 1.5, chloroform), R_F 0.35 (SiO_2, 18% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 3580, 3500–3250, 2960, 2940, 2850, 1700, 1475, 1390, 1380, 1260, 1220, and 1090 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.16, 1.29, 1.45, 1.50 (all s, total 6 H), 3.66 (d, 2 H, *J* 5 Hz), 4.18 (t, 1 H, *J* 5 Hz), 4.51, 4.70 (both, total 1 H), 5.23 (d, 1 H, *J* 5 Hz), 6.28 (m, 2 H), and 7.32 (m, 1 H); ^{13}C-n.m.r. ($CDCl_3$): δ 18.05, 24.67, 24.92, 25.31, 25.62, 26.07, 27.00, 64.46, 78.59, 81.95, 85.78, 88.30, 104.34, 108.04, 109.85, 112.62, 142.18, 151.40, and 184.00; m.s. ($M^+ - CH_3$): Calc. for $C_{17}H_{27}O_6Si$, *m/z* 355.1571; found, 355.1577.

1-C-[*4-(Dimethylamino)phenyl*]-*5*-O-[*(1,1-dimethylethyl)dimethylsilyl*]-*2,3*-O-*(1-methylethylidene)*-D-*ribofuranose* (**8**). — By the procedure used to prepare **4**, 4-bromo-*N,N*-dimethylaniline (600 mg, 3.00 mmol) in oxolane (9 mL) and a 1.8M solution of *tert*-butyllithium in pentane (3.4 mL, 6.15 mmol) provided a solution of 4-lithio-*N,N*-dimethylaniline. This solution and **1** (906 mg, 3.00 mmol) in oxolane (9 mL) afforded, after flash chromatography (40 × 150 mm column of SiO_2, 10% ethyl acetate–dichloromethane), **8** (31%), colorless white syrup, $[\alpha]_D^{23}$ +6.8° (*c* 1.5, chloroform), R_F 0.50 (SiO_2, 10% ethyl acetate–dichloromethane); $\nu_{max}^{CHCl_3}$ 3005, 2960, 2940, 2850, 1600, 1530, 1480, 1430, 1370, and 1220 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.33 (s, 3 H), 1.48 (s, 3 H), 2.89 (s, 3 H), 2.99 (s, 3 H), 3.79 (d, 2 H, *J* 3 Hz), 4.59 (m, 1 H), 4.70 (m, 1 H), 5.20 (d, 1 H, *J* 6 Hz), 6.65 (d, 2 H, *J* 10 Hz), and 8.80 (d, 2 H, 10 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.26, 25.83, 26.86, 27.23, 39.86, 64.03, 72.63; 76.69, 78.95, 110.53, 123.58, 131.79, 153.63, and 183.53; m.s. (M^+): Calc. for $C_{22}H_{37}O_5NSi$, *m/z* 423.2446; found, 423.2441.

(R)-1,4-Anhydro-5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-1-C-phenyl-D-ribitol (**11**). — To a stirred solution of **3** (692 mg, 1.82 mmol) in 2,2,2-trifluorethanol (14 mL) at room temperature was added first sodium cyanoborohydride (349 mg, 5.46 mmol), followed by dichloroacetic acid (705 mg, 5.46 mmol). The mixture was stirred at room temperature for 10 min, sat. aq. $NaHCO_3$ (10 mL) was added, and the mixture was poured into water (120 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give a white oil. Chromatography (50 × 180 mm column of SiO_2, 15% ethyl acetate–petroleum ether) afforded **11** (448 mg, 68%), colorless white syrup, $[\alpha]_D^{23}$ −65° (*c* 1.5, chloroform), R_F 0.45 (SiO_2, 10% ethyl acetate–petroleum ether); ν_{max} 2980, 2960, 2930, 2860, 1600, 1495, 1440, 1420, 1410, 1260, 1210, and 1160 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.046 (s, 3 H), 0.894 (s, 9 H), 1.246 (s, 3 H), 1.397 (s, 3 H), 3.754 (dd, 1 H, *J* 10, *J* 3.6 Hz), 3.816 (dd, 1 H, *J* 10, *J* 3.6 Hz), 4.224 (t, 1 H, *J* 3.6 Hz), 4.776 (t, 1 H, *J* 5.4 Hz), 4.907 (d, 1 H, *J* 5.4 Hz), 5.194 (d, 1 H, *J* 4.7 Hz), and 7.18–7.38 (m, 5 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.59, 18.13, 24.79, 25.86, 26.16, 65.18, 83.23, 83.35, 84.30, 84.44, 112.37, 127.35, 127.53, 127.79, and 137.06; m.s. ($M^+ - CH_3$): Calc. for $C_{19}H_{29}O_4Si$, *m/z* 349.1835; found, 349.1841.

[R (**12**) *and* S]-*1,4-Anhydro-5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-1-C-(4-methylphenyl)-D-ribitol* (**19**). — By the procedure used to prepare **11**, **4** (624 mg, 1.584 mmol) in 2,2,2-trifluoroethanol (7 mL) at room temperature, sodium cyanoborohydride (200 mg, 4.752 mmol), and dichloroacetic acid (400 mg, 4.752 mmol) afforded, after chromatography (60 × 180 mm column of SiO_2, 10% ethyl acetate–petroleum ether), **12** and **18**.

Compound **12**. Yield 381 mg (63%), colorless white oil, $[\alpha]_D^{23}$ −85.5° (*c* 1.5, chloroform), R_F 0.51 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 2960, 2930, 2860, 1615, 1470, 1460, 1380, 1370, 1255, 1210, 1130, and 1070 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.34 (s, 3 H), 1.50 (s, 3 H), 2.38 (s, 3 H), 3.87 (d, 2 H, *J* 3 Hz), 4.32 (t, 1 H, *J* 3 Hz), 4.85 (m, 1 H), 5.04 (m, 1 H), 5.28 (d, 1 H, *J* 5 Hz), and 7.22 (d, 2 H, *J* 7.5 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.08, 21.10, 24.70, 25.80, 26.41, 65.16, 83.31, 84.21, 84.35, 112.31, 127.34, 128.57, 133.90, and 137.16; m.s. (M^+): Calc. for $C_{21}H_{34}O_4Si$, *m/z* 378.2226; found, 378.2238.

Compound **19**. Yield 112 mg (19%), colorless white syrup, $[\alpha]_D^{23}$ −41° (*c* 1.5, chloroform), R_F 0.59 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 2990, 2980, 2860, 2730, 1515, 1470, 1380, 1370, 1260, 1210, and 1080 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.115 (s, 3 H), 0.125 (s, 3 H), 0.943 (s, 9 H), 1.382 (s, 3 H), 1.647 (s, 3 H), 2.364 (s, 3 H), 3.878 (m, 2 H), 4.180 (dd, 1 H, *J* 7.2, *J* 3.6 Hz), 4.506 (dd, 1 H, *J* 6.8, *J* 5.4 Hz), 4.769 (dd, 1 H, 6.8 Hz, 3.6 Hz), 4.895 (d, 1 H, *J* 5.4 Hz), 7.170 (d, 2 H, *J* 8 Hz), and 7.326 (d, 2 H, *J* 8 Hz); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.42, 18.35, 21.07, 25.65, 25.90, 27.68, 63.42, 87.77, 84.54, 85.75, 82.25, 114.30, 125.76, 128.99, and 137.27; m.s. ($M^+ - CH_3$): Calc. for $C_{20}H_{31}O_4Si$, *m/z* 363.1992; found, 363.2009.

(R)-1,4-Anhydro-5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methyl-

ethylidene)-1-C-*(4-methoxyphenyl)*-D-*ribitol* (**13**). — To a stirred solution of **5** (511 mg, 1.25 mmol) in methanol (8 mL) at room temperature was added first 4-toluenesulfonic acid monohydrate (400 mg, 2.10 mmol), and then sodium cyanoborohydride (233 mg, 3.75 mmol). After stirring for 5 min at room temperature, no starting material was detectable (t.l.c.). Sat. aq. $NaHCO_3$ (6 mL) was added, and the mixture was poured into ether (200 mL) and washed with sat. aq. $NaHCO_3$ (50 mL), and then water (20 mL). The organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure to give **12** (479 mg, 98%), colorless white oil, $[\alpha]_D^{23}$ −32° (*c* 1.5, chloroform), R_F 0.39 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3010, 2960, 2940, 2860, 1515, 1425, 1385, 1375, and 1220 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.12 (s, 6 H), 0.93 (s, 9 H), 1.20 (s, 9 H), 1.38 (s, 3 H), 2.33 (s, 3 H), 3.70 (d, 2 H, *J* 3 Hz), 4.42 (s, 1 H), 4.58 (d, 1 H, *J* 6 Hz), 4.89 (d, 1 H, *J* 6 Hz), 7.15 (d, 2 H, *J* 8 Hz), and 7.51 (d, 2 H, *J* 8 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.3, 25.55, 25.8, 26.4, 55.1, 64.8 81.9, 86.0, 88.5, 106.8, 112.5, 112.8, 128.2, 131.2, and 159.3; m.s. ($M^+ - CH_3$): Calc. for $C_{20}H_{31}O_5Si$, *m/z* 395.1881; found, 395.1890.

*(*R (**14**) *and* S*)-1,4-Anhydro-1*-C-*(biphenyl-4-yl)-5*-O-[*(1,1-dimethylethyl)dimethylsilyl*]-*2,3*-O-*(1-methylethylidene)*-D-*ribitol* (**27**). — By the procedure used to prepare **11**, **6** (760 mg, 1.67 mmol) in 2,2,2-trifluorethanol (13 mL), sodium cyanoborohydride (315 mg, 5.00 mmol), and dichloroacetic acid afforded at room temperature (645 mg, 5.00 mmol), after flash chromatography (50 × 150 mm column of SiO_2, 10% ethyl acetate–petroleum ether), **14** and **21**.

Compound **14**. Yield 480 mg (66%), colorless white syrup, $[\alpha]_D^{23}$ −44° (*c* 1.5, chloroform), R_F 0.44 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3005, 2960, 2930, 2860, 1520, 1490, 1470, 1420, 1385, 1375, 1220, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.08 (s, 6 H), 0.91 (s, 9 H), 1.23 (s, 3 H), 1.33 (s, 3 H), 3.78 (d, 2 H, *J* 3 Hz), 4.12 (t, 1 H, *J* 3 Hz), 4.80 (m, 2 H), 5.10 (d, 1 H, *J* 3 Hz), and 7.37 (m, 9 H); ^{13}C-n.m.r. ($CDCl_3$): δ 18.14, 24.73, 25.87, 26.17, 65.26, 83.24, 83.39, 84.31, 112.43, 126.65, 127.09, 127.82, 128.63, 136.06, 140.49, and 141.46; m.s. (M^+): Calc. for $C_{26}H_{36}O_4Si$, *m/z* 440.2383; found, 440.2366.

Compound **21**. Yield 122 mg (17%), colorless white syrup, $[\alpha]_D^{23}$ −53° (*c* 1.5, chloroform), R_F 0.54 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3015, 2995, 2960, 2930, 2860, 1600, 1490, 1470, 1460, 1380, 1370, 1250, and 1080 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.107 (s, 3 H), 0.117 (s, 3 H), 0.927 (s, 9 H), 1.381 (s, 3 H), 1.649 (s, 3 H), 3.884 (ddd, 2 H, *J* 16.5, *J* 7.2, *J* 3.6 Hz), 4.217 (dd, 1 H, *J* 7.2, *J* 3.6 Hz), 4.549 (dd, 1 H, *J* 6.5, *J* 5 Hz), 4.783 (dd, 1 H, *J* 6.5, *J* 3.6 Hz), 4.960 (d, 1 H, *J* 5 Hz), 7.338 (tt, *J* 7.2, *J* 1.4 Hz), and 7.435–7.590 (m, 8 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.42, −5.32, 18.33, 25.65, 25.90, 27.69, 63.45, 81.85, 84.62, 85.69, 87.22, 114.36, 126.18, 127.09, 128.70, 139.37, 140.63, and 141.04; m.s. ($M^+ - CH_3$): Calc. for $C_{25}H_{33}O_4Si$, *m/z* 425.2148; found, 425.2156.

1,4:5,8-Dianhydro-2,3-dideoxy-9-O-[*(1,1-dimethylethyl)dimethylsilyl*]-*6,7*-O-*(1-methylethylidene)*-D-[altro- (**15**) *and* allo]-*nono-1,3-dienitol* (**22**). — To a stirred solution of **7** (896 mg, 2.42 mmol) in 2,2,2-trifluorethanol (19 mL) at room temperature was added first sodium cyanoborohydride (465 mg, 7.27 mmol), and

then dichloroacetic acid (931 mg, 7.27 mmol). The mixture was stirred at room temperature for 10 min, sat. aq. $NaHCO_3$ (10 mL) was added, and the mixture was poured into water (150 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give a white oil which was purified by flash chromatography (60 × 180 mm column of SiO_2, 10% ethyl acetate–petroleum ether) to give **15** and **22**.

Compound **15**. Yield 642 mg (73%), colorless white oil, $[\alpha]_D^{23}$ −58° (*c* 1.5, chloroform), R_F 0.45 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 2980, 2960, 2940, 2900, 2840, 1540, 1520, 1360, 1340, 1310, 1220, 1180, 1120, and 980 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.065 (s, 6 H), 0.895 (s, 9 H), 1.327 (s, 3 H), 1.475 (s, 3 H), 3.740 (dd, 2 H, *J* 3.2, *J* 10.9 Hz), 3.824 (dd, 1 H, *J* 3.2, *J* 10.9 Hz), 4.197 (t, 1 H, *J* 3.2 Hz), 4.836 (dd, 1 H, *J* 4.3, *J* 6.1 Hz), 4.907 (d, 1 H, *J* 6.1 Hz), 5.222 (d, 1 H, *J* 4.3 Hz), 6.438 (d, 1 H, *J* 3.2 Hz), 7.344 (dd, 1 H, *J* 1.8, *J* 3.2 Hz), and 7.382 (d, 1 H, *J* 1.8 Hz); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.6, 18.1, 25.08, 25.86, 26.25, 65.25, 78.86, 82.34, 83.26, 84.04, 108.76, 110.30, 112.70, 141.91, 150.59; m.s. (M^+): Calc. for $C_{18}H_{30}O_5Si$, *m/z* 354.1862; found, 354.1856.

Compound **22**. Yield 210 mg (24%), colorless white oil, $[\alpha]_D^{24}$ −44° (*c* 1.5, chloroform), R_F 0.52 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 2990, 2980, 2940, 2860, 1480, 1460, 1380, 1360, 1250, 1210, 1150, and 1080 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.01 (s, 3 H), 0.021 (s, 3 H), 0.865 (s, 9 H), 1.348 (s, 3 H), 1.557 (s, 3 H), 3.660 (dd, 1 H, *J* 11.2, *J* 4.7 Hz), 3.725 (dd, 1 H, *J* 11.2, *J* 4.7 Hz), 4.123 (dd, 1 H, *J* 6.5, *J* 4.7 Hz), 4.745 (dd, 1 H, *J* 5.0, *J* 4.7 Hz), 4.830 (dd, 1 H, *J* 6.5, *J* 5.0 Hz), 4.884 (d, 1 H, *J* 4.7 Hz), 6.308 (m, 2 H), and 7.359 (s, 1 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.38, −3.42, 18.37, 25.59, 25.90, 27.50, 63.36, 79.91, 82.30, 83.65, 85.03, 107.98, 110.23, 114.06, 142.61, and 152.24; m.s. (M^+): Calc. for $C_{18}H_{30}O_5Si$, *m/z* 354.1862; found, 354.1844.

The identity of **14** and **21** was confirmed by desilylating each to afford the known[15] compounds **9** and **24**.

1,4:5,8-Dianhydro-2,3-dideoxy-6,7-O-(1-methylethylidene)-D-altro-*nono-1,3-dienitol* (**9**). — To a stirred solution of **19** (366 mg, 0.99 mmol) in oxolane at room temperature was added tetrabutylammonium fluoride (500 mg, 1.88 mmol). After 4 h at room temperature, the mixture was poured into ether (80 mL) and washed three times with water. The organic phase was dried ($MgSO_4$) and then evaporated under reduced pressure to give **9** (263 mg, 94%), colorless white syrup, R_F 0.40 (SiO_2, 50% ethyl acetate–petroleum ether); ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 (s, 3 H), 1.47 (s, 3 H), 3.65 (d, 2 H, *J* 5 Hz), 4.22 (t, 1 H, *J* 5 Hz), 4.66–4.90 (m, 2 H), 5.10 (d, 3 Hz), 6.39 (dd, 1 H, *J* 3.5, *J* 1.5 Hz), 6.50 (d, 1 H, *J* 3.5 Hz), and 7.45 (s, 1 H); ^{13}C-n.m.r. ($CDCl_3$): δ 24.97, 26.14, 62.30, 78.43, 81.75, 82.57, 84.15, 109.32, 110.49, 113.16, 142.16, and 149.84; m.s. (M^+): Calc. for $C_{12}H_{16}O_5$, *m/z* 240.0997; found, 240.0994.

1,4:5,8-Dianhydro-2,3-dideoxy-6,7-O-(1-methylethylidene)-D-allo-*nono-1,3-dienitol* (**24**). — To a stirred solution of **22** (60 mg, 0.16 mmol) in acetonitrile (4 mL) at −5° was added 48% aqueous HF (0.10 mL, 2.4 mmol). After 15 min at −5°,

sat. aq. $NaHCO_3$ (3 mL) was added, and the mixture was poured into dichloromethane (80 mL) and washed with water (30 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give **22** (28 mg, 73%), colorless white syrup; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 1.340 (s, 3 H), 1.558 (s, 3 H), 3.619–3.685 (m, 2 H), 4.174 (dd, 1 H, *J* 7.2, *J* 5.0 Hz), 4.765 (m, 1 H), 4.861 (t, 1 H, *J* 5.0 Hz), 4.910 (d, 1 H, *J* 4.7 Hz), 6.350 (m, 2 H), and 7.394 (s, 1 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 25.430, 27.392, 62.896, 80.058, 81.915, 83.798, 85.079, 108.558, 110.395, 114.444, 143.089, and 151.773.

*1,4:5,8-Dianhydro-2,3-dideoxy-9-*O*-[(1,1-dimethylethyl)dimethylsilyl]-6,7-*O*-(1-methylethylidene)-*D*-(*altro*-)-nono-1,3-dienitol* (**15**) *by reduction of* **7** *in methanol.* — By the procedure used to prepare **13**, **7** (70 mg, 0.19 mmol) in methanol (0.5 mL) was treated at 0° with 4-toluenesulfonic acid hydrate (65 mg, 0.34 mmol) and sodium cyanoborohydride (75 mg, 1.19 mmol) at 0° for 10 s, and then the reaction quenched with sat. aq. $NaHCO_3$ (2 mL). The mixture was poured into ether (30 mL) and washed with sat. aq. $NaHCO_3$ (20 mL) and water (20 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give, after flash chromatography (20 × 140 mm column of SiO_2, 20% ethyl acetate–petroleum ether), **15** (41 mg, 62%), colorless white oil, identical with the material described earlier.

4,4′-(Ethylenedioxy)dibromobenzene (**25**). — To a stirred solution of 1,2-bis(phenoxy)ethane (15 g, 70.1 mmol) in glacial acetic acid (530 mL) at room temperature was aded Br_2 (23.5 g, 147 mmol). After stirring at room temperature for 1 h, 5% aqueous $Na_2S_2O_3$ solution was added. Dilution of the mixture with water (400 mL) afforded a crude product which was collected by filtration and recrystallized from chloroform–ethanol to give **25** (22.3 g, 86%), lustrous white plates, m.p. 125–126.5° (lit.[22] m.p. 131–132°).

*4,4′-(Ethylenedioxy)bis[5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-*D*-ribofuranosyl]benzene* (**27**). — To a vigorously stirred solution of 1.8M *tert*-butyllithium (18.2 mL, 32.8 mmol) in pentane at −78° was added dropwise a solution of dibromide **25** (2.98 g) in oxolane (70 mL). After being stirred at −78° for 1 h, the yellow solution was warmed to −15° for 10 min and then again cooled to −78°. To this solution of 4,4′-(ethylenedioxy)dilithiobenzene (**26**) was added, dropwise, over 10 min, a precooled (−70°) solution of **1** (5.074 g, 16.8 mmol) in oxolane (50 mL). The mixture was stirred at −78° for 6 h, then methanol (1 mL) was added, the mixture was allowed to warm to room temperature, and then poured into ether (500 mL) and washed three times with water (200 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated under reduced pressure to give **27** (6.55 g, 100%), white foam; $[\alpha]_D^{23}$ −51° (*c* 1.5, chloroform), R_F 0.22 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 3590, 3550–3250, 2960, 2930, 2860, 1610, 1515, 1380, 1370, 1240, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.64 (d, 2 H, *J* 8.6 Hz), 6.91 (d, 2 H, *J* 8.6 Hz), 5.15 (s, 1 H), 4.89 (d, 1 H, *J* 5.4 Hz), 4.60 (d, 1 H, *J* 5.4 Hz), 4.43 (br. s, 1 H), 4.29 (s, 2 H), 3.88 (dd, 1 H, *J* 10.8, *J* 2.5 Hz), 3.82 (dd, 1 H, *J* 10.8, *J* 2.5 Hz), 1.39 (s, 3 H), 1.24 (s, 3 H), 0.94 (s, 9 H), and 0.16

(s, 6 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.52, 131.83, 128.31, 114.22, 113.65, 112.53, 106.86, 88.49, 86.08, 82.00, 66.46, 64.82, 26.46, 25.80, 24.87, 18.24, and −5.64. For quantitative analysis, a portion of this product was converted into the corresponding methyl glycoside **28** by the action of methanolic trifluoroacetic acid. The glycoside crystallized from the solution and was recrystallized from ethyl acetate–methanol, m.p. 107–108.5°, $[\alpha]_D^{23}$ −67° (*c* 1.5, chloroform), R_F 0.64 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 2980, 2930, 2860, 1610, 1515, 1380, 1370, 1240, and 1100 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.394 (d, 2 H, *J* 8.6 Hz), 6.928 (d, 2 H, *J* 8.6 Hz), 4.805 (d, 1 H, *J* 5.8 Hz), 4.643 (d, 1 H, *J* 5.8 Hz), 4.318 (br. s, 2 H), 3.757 (appar. t, 2 H), 2.980 (s, 3 H), 1.296 (s, 3 H), 1.229 (s, 3 H), 0.918 (s, 9 H), and 0.095 (s, 6 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.53, 129.42, 128.93, 113.98, 112.37, 111.65, 87.46, 86.60, 82.79, 66.45, 63.91, 49.06, 26.48, 25.92, 25.22, 18.34, and −5.28.

Anal. Calc. for $C_{44}H_{70}O_{12}Si_2$: C, 62.38; H, 8.33. Found: C, 61.69; H, 8.41.

*4,4'-(Ethylenedioxy)bis(1*R*,1'*R*)-1,4-anhydro-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-*D*-ribit-1-yl)benzene* (29). — To a solution of **27** (6.55 g, 8.00 mmol) in methanol (54 mL) at 0° was added first 4-toluenesulfonic acid monohydrate (5.43 g, 28.5 mmol), and then sodium cyanoborohydride (3.39 g, 53.6 mmol). The mixture was stirred at 0° for 7 min, and then poured in sat. aq. $NaHCO_3$ (200 mL). Ether (500 mL) was added and the organic phase was washed with water (3 × 200 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give (**29**) (6.40 g, 100%), white foam, $[\alpha]_D^{23}$ −71° (*c* 1.5, chloroform), R_F 0.22 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 2995, 2960, 2930, 2860, 1590, 1510, 1380, 1370, 1240, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.306 (d, 2 H, *J* 8.6 Hz), 6.921 (d, 2 H, *J* 8.6 Hz), 5.179 (d, 1 H, *J* 4 Hz), 4.934 (d, 1 H, *J* 6.1 Hz), 4.758 (dd, 1 H, *J* 6.1, *J* 4 Hz), 4.289 (s, 2 H), 4.237 (t, 1 H, *J* 3.2 Hz), 3.848 (dd, 1 H, *J* 10.8, *J* 3.2 Hz), 3.789 (dd, 1 H, *J* 10.8, *J* 3.2 Hz), 1.471 (s, 3 H), 1.294 (s, 3 H), 0.935 (s, 9 H), and 0.090 (s, 6 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.25, 129.42, 128.68, 114.16, 112.26, 84.01, 83.27, 83.12, 66.54, 65.08, 26.18, 25.8, 24.70, 18.08, and −5.58; m.s.: Calc. for $C_{42}H_{66}O_{10}Si$, *m/z* 786.4194; found, 786.4170.

*4,4'-(Ethylenedioxy)bis[(1*R*,1'*R*)-1,4-anhydro-2,3-*O*-(1-methylethylidene)-*D*-ribit-1-yl]benzene* (**30**). — To a stirred solution of **29** (5.786 g, 7.36 mmol) in acetonitrile (50 mL) at 0° was added 48% aqueous HF (625 mg, 18 mmol). The mixture was stirred at 0° for 40 min, then poured into a mixture of sat. aq. $NaHCO_3$ (25 mL) and ethyl acetate (200 mL), and then washed twice with water (200 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give **30**, white powder which crystallized from ethanol–water (3.292 g, 80%), m.p. 145.5–146.5°, $[\alpha]_D^{23}$ −96.9° (*c* 1.5, chloroform),, R_F 0.22 (SiO_2, ethyl acetate); $\nu_{max}^{CHCl_3}$ 3600, 3620–3500, 3000, 2960, 2860, 1510, 1380, 1370, 1220, 1110, and 1060 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.333 (d, 2 H, *J* 8.6 Hz), 6.935 (d, 2 H, *J* 8.6 Hz), 4.954 (d, 1 H, *J* 3.6 Hz), 4.741 (dd, 1 H, *J* 6.1, *J* 3.6 Hz), 4.709 (d, 1 H, *J* 6.1 Hz), 4.323 and 4.303 (overlapping s, 5 H), 3.674 (d, 2 H, 5.8 Hz), 1.481 (s, 3 H), and 1.278 (s, 3 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.48, 128.84, 128.62, 114.30, 112.77, 84.41, 82.69, 82.46, 66.61, 62.07, 26.27, and 24.80.

Anal. Calc. for $C_{30}H_{38}O_{10}$: C, 64.50; H, 6.86. Found: C, 64.18; H, 6.77.

4,4'-(Ethylenedioxy)bis(1R,1R')-1,4-anhydro-5-deoxy-5-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-2,3-O-(1-methylethylidene)-D-ribit-1-yl]benzene (**31**). — To a stirred solution of **30** (2.02 g, 3.62 mmol) in oxolane (30 mL) at room temperature was added triphenylphosphine (1.90 g, 7.24 mmol), phthalimide (1.07 g, 7.24 mmol), and diethyl azodicarboxylate (1.26 g, 7.24 mmol). The mixture was heated at reflux for 3.5 h, cooled, and then poured into 50% ether–ethyl acetate (200 mL). The organic phase was washed with water (200 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The oily residue was purified by flash chromatography (50 × 180 mm column of SiO_2, ethyl acetate) to give a powder which crystallized from chloroform–methanol to give **31** (2.09 g, 71%), white powder, m.p. 212–214°, $[\alpha]_D^{23}$ 49° (*c* 1.5, chloroform), R_F 0.58 (SiO_2, ethyl acetate); $\nu_{max}^{CHCl_3}$ 3000, 2840, 1775, 1715, 1515, 1400, 1380, 1370, and 1220 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.820 (dd, 2 H, *J* 7.8, *J* 2.9 Hz), 7.692 (dd, 2 H, *J* 7.8, *J* 2.9 Hz), 7.346 (d, 2 H, *J* 8.6 Hz), 6.900 (d, 2 H, *J* 8.6 Hz), 5.085 (d, 1 H, *J* 3.6 Hz, 4.844 (dd, 1 H, *J* 5.8, *J* 3.6 Hz), 4.732 (d, 1 H, 5.8 Hz), 4.589 (m, 1 H), 4.276 (s, 2 H), 3.900 (dd, 1 H, *J* 13.7, *J* 9.7 Hz), 3.733 (dd, 1 H, *J* 13.7, *J* 6.1 Hz), 1.472 (s, 3 H), and 1.279 (s, 3 H); ^{13}C-n.m.r. ($CDCl_3$): δ 168.04, 158.48, 133.93, 132.12, 129.14, 128.13, 123.33, 114.24, 112.77, 83.38, 82.3, 81.65, 80.57, 66.55, 37.18, 26.12, and 24.76.

Anal. Calc. for $C_{46}H_{44}O_{12}N_2 \cdot 2\ CH_3OH$: C, 65.45; H, 5.91. Found: C, 65.36; H, 5.27.

4,4'-(Ethylenedioxy)bis(1R,1'R)-5-amino-1,4-anhydro-5-deoxy-2,3-O-(1-methylethylidene)-D-ribit-1-yl)benzene (**32**). — To a stirred solution of **31** (2.09 g, 2.56 mmol) in a mixture of benzene (5 mL) and ethanol (12 mL) at room temperature was added hydrazine hydrate (2.06 g, 41.2 mmol). The mixture was heated at reflux, after which time the initially clear white solution became a white paste. After 16 h at reflux, the mixture was poured into 50% ether–ethyl acetate (200 mL) and washed twice with M NaOH solution. The organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure to give a white oil. Flash chromatography (30 × 180 mm column of SiO_2, 2% triethylamine–methanol) afforded **32** (808 mg, 78%), clear white oil, $[\alpha]_D^{23}$ −81° (*c* 1.5, chloroform), R_F 0.22 (SiO_2, 2% triethylamine–methanol); $\nu_{max}^{C_6H_6}$ 3700, 3640, 3070, 3020, 1620, 1530, 1480, 1390, 1240, and 1180 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.348 (d, 2 H, *J* 8.6 Hz), 6.935 (d, 2 H, *J* 8.6 Hz), 4.860 (d, 1 H, *J* 3.6 Hz), 4.730 (dd, 1 H, *J* 5.8, *J* 3.6 Hz), 4.625 (d, 1 H, *J* 5.8 Hz), 4.300 (s, 2 H), 4.180 (dd, 1 H, *J* 9.0, *J* 4.7 Hz), 2.843 (dd, 1 H, *J* 13.3, *J* 4.7 Hz), 2.729 (dd, 1 H, *J* 13.3, *J* 4.7 Hz), 1.486 (s, 3 H), and 1.275 (s, 3 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.34, 128.77, 128.55, 114.46, 112.54, 85.70, 83.58, 82.49, 81.41, 66.49, 42.08, 26.16, and 24.72; m.s. ($M^+ - CH_3$): Calc. for $C_{29}H_{37}O_8N_2$, *m/z* 541.2550; found, 541.2561.

[3aS-(3aR,4S*,17S*,17aR*,20aS*,21S*,32S*,32aS*)]-3a,4,10,11,17,17a,20a,21,22,23,30,31,32,32a-Tetradecahydro-2,2,19,19-tetramethyl-4,32:17,21-diepoxy-5,8:13,16:25,28-triethenobis[1,3]dioxolo[4,5-j:4',5'-x][1,3,14,21]dioxadiaza-*

cyclotriacontine-24,29-dione (**34**). — To a solution of triethylamine (2.03 g, 20.0 mmol) in toluene (54 mL) at 26° was added, simultaneously, over a period of 13 h, a solution of **32** (1.11 g, 2.00 mmol) in oxolane (36 mL) and a solution of terephthaloyl chloride (406 mg, 2.00 mmol) in toluene (36 mL). The resulting solution was evaporated under reduced pressure to a white powder which was washed with water (100 mL) and ether (50 mL), and then dried under vacuum to give a white powder (662 mg) which was dissolved with dichloromethane (25 mL) and the solution filtered. Removal of the dichloromethane and crystallization from chloroform–methanol gave **34** (207 mg, 15%), amorphous white powder, homogeneous by t.l.c., m.p. >300° (chars), $[\alpha]_D^{23}$ 58° (*c* 1.5, chloroform), R_F 0.16 (SiO_2, dichloromethane), R_F 0.76 (SiO_2, 10% methanol–dichloromethane); $\nu_{max}^{CHCl_3}$ 3005, 2830, 1660, 1610, 1510, 1420, 1380, 1375, 1220, 1100, and 1080 cm^{-1}; ^{1}H-n.m.r. (50% Me_2SO–$CDCl_3$, 65°, 200 MHz): δ 7.732 (s, 2 H), 7.162 (d, 2 H, *J* 8.6 Hz), 6.772 (d, 2 H, *J* 8.6 Hz), 4.783 (dd, 1 H, *J* 5.8, *J* 3.4 Hz), 4.682 (d, 1 H, *J* 3.4 Hz), 4.657 (d, 1 H, *J* 5.8 Hz), 4.292 (br. s, 4 H), 4.242 (br. d, 1 H, *J* 9 Hz), 3.412 (d, 1 H, *J* 2.4 Hz), 3.395 (d, 1 H, *J* 9 Hz), 1.402 (s, 3 H), 1.248 (s, 3 Hz); ^{13}C-n.m.r. (DMSO): δ 228.52, 166.43, 156.86, 137.01, 129.09, 128.71, 126.92, 114.40, 111.17, 82.99, 81.54, 79.64, 79.42, 65.22, 38.01, 25.96, and 24.49; m.s.: Calc. for $C_{38}H_{42}O_{10}$, *m/z* 686.2839; found, 686.2823.

[*3a*S-*(3a*R*,*4*S*,*17*S*,*17a*R*,*20a*S*,*21*S*,*32*S*,*32a*S*)]-*3a,4,10,11,17,17a,20a,21,22,23,30,31,32,32a-Tetradecahydro-2,2,19,19-tetramethyl-4,32:17,21-diepoxy-5,8:13,16:25,28-triethenobis*[*1,3*]*dioxolo*[*4,5*-j:*4',5'*-x][*1,4,14,21*]*dioxadiazacyclotriacontine-24,29,dione* (**35**). — A solution of **32** (36 mg, 0.052 mmol) in 70% acetic acid (3 mL) was heated at 70° for 72 h. The mixture was cooled, and the solvent removed under reduced pressure to give a tan powder which was purified by flash chromatography (30 × 180 mm column of SiO_2, 73% dichloromethane–25% methanol–2% water) to give **33** (21 mg, 66%), amorphous white powder, $[\alpha]_D^{23}$ −1.4° (*c* 1.0, 50% methanol–chloroform), R_F 0.65 (SiO_2, 73% dichloromethane–25% methanol–2% water); $\nu_{max}^{Me_2SO}$ 3700–3150, 3000, 2915, 1655, 1440, and 1420 cm^{-1}; ^{1}H-n.m.r. [50% ($^2H_4$)methanol–(^{2}H)chloroform]: δ 7.555 (s, 2 H), 7.032 (d, 2 H, *J* 8.6 Hz), 6.637 (d, 2 H, *J* 8.6 Hz), 4.736 (d, 1 H, *J* 1.8 Hz), 4.057 (d, 1 H, *J* 9.4 Hz), 4.003 (d, 1 H, *J* 9.4 Hz), 3.901 (br. s, 2 H), 3.823 (d, 1 H, *J* 13.0 Hz), and 3.061–3.000 (m, 2 H); ^{13}C-n.m.r. [50% ($^2H_4$)methanol–(^{2}H)chloroform): δ 167.64, 157.43, 137.1, 130.12, 128.89, 126.94, 115.12, 81.82, 79.35, 75.31, 73.24, 66.00, and 42.60.

Synthesis and deprotection of [*3a*S-*(3a*R*,*4*S*,*17*S*,*17a*R*,*20a*S*,*21*S*,*24a*S*,*27a*S*,*31*S*,*31a*S*)]-*3a,4,10,11,17,17a,20a,21,22,23,24a,27a,29,30,31a-hexadecahydro-2,2,19,19-tetramethyl-4,31:17,21-diepoxy-5,8:13,16-diethenotris*[*1,3*]*dioxolo*-[*4,5*-j:*4',5'*-p:*4'',5''*-y][*1,4,14,19*]*dioxadiazacyclooctacosine-24,28-dione (methylene tartramide macrocyle)* (**33**). — To a solution of toluene (50 mL) containing triethylamine (1.30 g, 12.9 mmol) at 23° were added, simultaneously, over 18 h, a solution of **32** (1.07 g, 1.92 mmol) and triethylamine (726 mg, 7.19 mmol) in oxolane (34 mL) and a solution of 2,3-*O*-methylenetartaric acid dichloride[25] (380

mg, 1.92 mmol) in toluene (35 mL). After the addition was complete, the mixture was stirred an additional 2 h, and then water (20 mL) was added and stirring continued for 10 min. The mixture was poured into 4:1 ethyl acetate–dichloromethane (250 mL). A small amount of insoluble material was removed by filtration and the liquid organic phase was washed twice with M HCl (100 mL), and twice with sat. aq. $NaHCO_3$ (100 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (40 × 180 mm column of SiO_2, 45% ethyl acetate–45% dichloromethane–10% methanol) gave the protected macrocycle (146 mg, 11%), m.p. >260° (chars), $[\alpha]_D^{23}$ −43° (*c* 0.85, chloroform), R_F 0.51 (SiO_2, 45% ethyl acetate–45% dichloromethane–10% methanol); $\nu_{max}^{CHCl_3}$ 2980, 2930, 1690, 1610, 1515, 1380, 1370, 1220, and 1100 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.221 (d, 2 H, *J* 8.6 Hz), 6.776 (d, 2 H, *J* 8.6 Hz), 4.871 (s, 1 H), 4.800 (dd, 1 H, *J* 5.8, *J* 3.6 Hz), 4.649 (d, 1 H, *J* 3.6 Hz), 4.618 (s, 1 H), 4.582 (d, 1 H, *J* 5.8 Hz), 4.363 (s, 2 H), 4.260 (dd, 1 H, *J* 10.8, 4.7 Hz), 3.46–3.54 (m, 1 H), and 3.25–3.33 (m, 1 H); ^{13}C-n.m.r. (Me_2SO): δ 168.83, 157.23, 129.32, 128.78, 117.56, 115.04, 111.32, 95.42, 82.92, 81.49, 80.80, 79.73, 77.05, 66.49, 26.06, and 24.57.

A solution of the protected macrocycle (31 mg, 0.045 mmol) in 70% acetic acid (4 mL) was heated at 70° for 12 h. The solvent was removed under reduced pressure and the residual oil purified by chromatography on SiO_2 (5 g, 20% methanol–dichloromethane) to give **33** (25.5 mg, 93%), glass, $[\alpha]_D^{23}$ −11.3° (*c* 0.95, methanol), R_F 0.46 (SiO_2, 20% methanol–dichloroform); $\nu_{max}^{Me_2SO}$ 3700–3150, 2995, 2810, 1660, 1440, 1405, 1310, and 1080 cm^{-1}; ^{1}H-n.m.r. [D_2O, sodium 4,4-dimethyl-4-sila(2,3-$^2H_4$)pentanoate as external reference]: δ 7.171 (d, 2 H, *J* 8.6 Hz), 6.824 (d, 2 H, *J* 8.6 Hz), 5.238 (s, 2 H), 5.077 (d, 1 H, *J* 2.5 Hz), 4.610 (s, 1 H), 4.454 (br. s, 2 H), 4.229–4.287 (m, 2 H), 4.135 (td, 1 H, *J* 7.9, *J* 2.5 Hz), 3.648 (dd, 1 H, *J* 14.4, *J* 2.5 Hz), and 3.504 (dd, 1 H, *J* 14.4, *J* 7.9 Hz); ^{13}C-n.m.r. [D_2O, sodium 4,4-dimethyl-4-sila(2,3-$^2H_4$)pentanoate as external reference]: δ 173.87, 159.68, 132.94, 130.96, 119.06, 99.60, 84.62, 82.16, 80.32, 77.25, 76.07, 70.24, and 44.48.

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