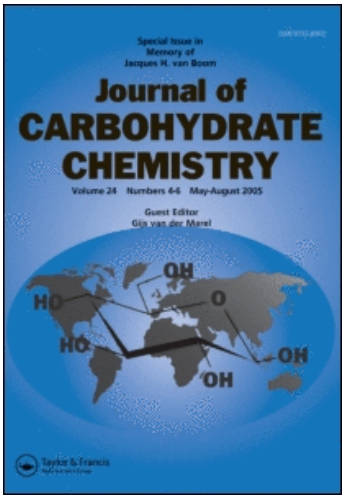

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SYNTHESIS OF DEOXY AND DEOXYHALOGENO ANALOGUES OF myo-INOSITOL

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ABSTRACT

A number of deoxy and deoxyhalogeno analogues of myo-inositol of interest in investigating the biochemical processes of the phosphoinositide pathway were synthesized. Syntheses include those deoxyinositols (cyclohexane pentols) which correspond to myo-inositol deoxygenated at positions 1, 4 and 5, as well as a set of 5-deoxyhalogeno (F, Cl, Br, I) myo- and epimeric neo-inositols. Configurational assignments are based primarily on ^{1}H NMR spectroscopy.

INTRODUCTION

Phosphoinositides have recently emerged as compounds of considerable interest on account of their relationship with sundry fundamental cellular processes.[1 - 3] Several hormones and cell growth factors mediate their effects by stimulating the hydrolysis of phosphatidylinositol-4,5-diphosphate (PIP_2). The two hydrolysis components of PIP_2, diacylglycerol (DAG) and inositol triphosphate (IP_3), act as second messengers, exerting control over processes such as calcium release and protein phosphorylation. Production of arachidonic

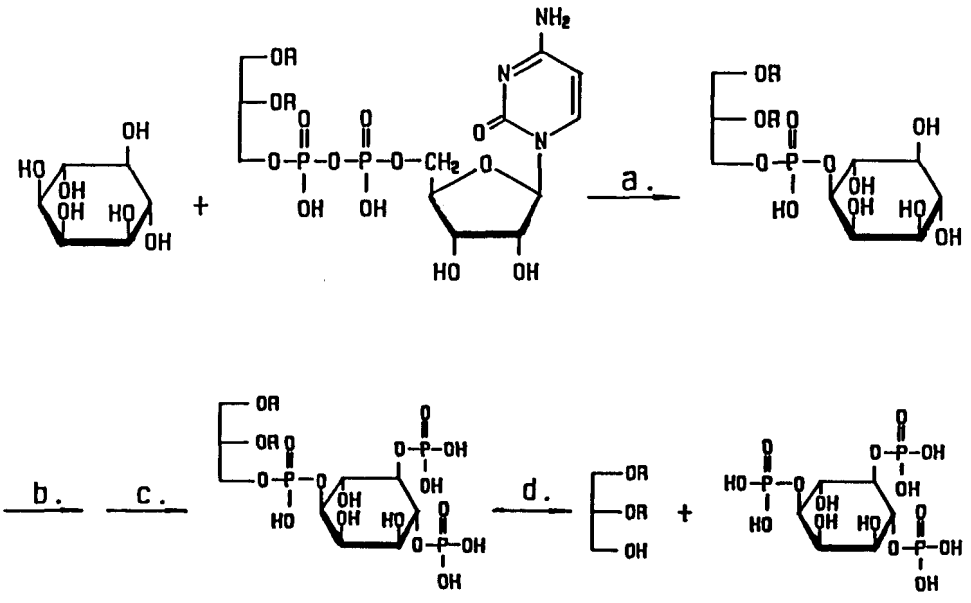


Fig. 1. Phosphoinositide Pathway

a. phosphatidylinositol synthetase (PI synthetase); b. phosphatidylinositol kinase (PI kinase); c. phosphatidylinositol-4-phosphate kinase (PIP kinase); d. phospholipase C. R = -palmitoyl or other long-chain fatty acid chain.

acid, the primary starting material in prostaglandin biosynthesis, depends in part on DAG as a carbon source. These biochemical pathways influence many physiological processes and disease conditions including arthritis, pain, inflammation, platelet aggregation, and possibly, oncogenesis. Thus inhibition of key enzymes along the phosphoinositide pathway could be of significant medicinal interest.

In considering the design of inhibitors of the enzymes involved, certain key processes come under consideration (see FIG. 1): (1) synthesis of phosphatidylinositol (PI) from inositol and cytidine monophosphate diglyceride (CMP - diglyceride) [via phosphatidylinositol (PI) synthetase], (2) phosphorylation of the resulting phosphoinositide, first at C-4 (via PI kinase), then at C-5 (via PIP kinase), and (3)

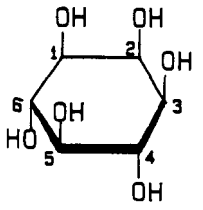


Fig. 2. myo-Inositol

hydrolysis of PIP_2 to DAG and IP_3 (via phospholipase C). All are considered important targets for drug design. These reactions involve essentially positions at C-1, C-4, and C-5 on the myo-inositol ring (FIG. 2), and these centers were therefore targeted for synthetic modification. The objectives were to produce analogues of myo-inositol that would be inhibitors of the above-cited key enzymes, either directly (i.e., for the first-encountered enzyme, P.I. synthetase) or indirectly (i.e., for PI- or PIP-kinase or phospholipase C) via the incorporation of fraudulent cyclitols into the PI pathway, a process which should affect either biosynthesis or hydrolysis at later stages. To this end, a number of deoxy- and deoxyhalogenocyclitols were synthesized with modification at the key 1 (3), 4, and 5-positions. The chemical aspects of this work are presented in this paper.

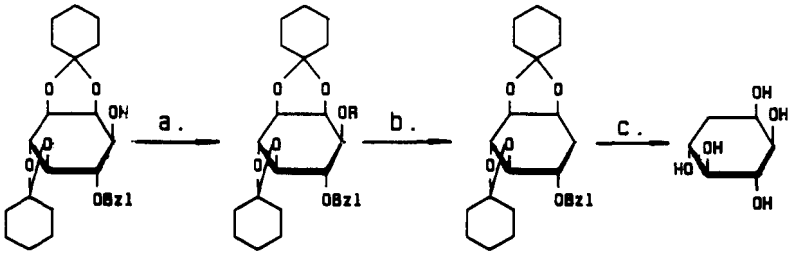
RESULTS AND DISCUSSION[4]

Deoxyinositols. Of the ten possible deoxycyclitols (cyclohexanepentols) known,[5] those considered for synthesis (See Schemes 1 and 2.), based on the stereochemistry known for the phosphatidylinositol (FIG. 1) include the 1-deoxy-D-chiro- (**4**, i.e., the "1- or 3-deoxy-myo-" or the D-124/35 isomer, (+)-viburnitol [38653-82-0]),[6,7] the 2-deoxy-L-epi- (**8**, "4-deoxy-myo-" or 1235/4 isomer [488-74-4]),[8] and 5-deoxy-myo-inositol (**12**, the 123/46 isomer [26671-58-9]).[9 - 11] As existing routes[6 - 8] to the chiral isomers **4** and **8** are lengthy and often low yielding or require special starting materials, or both, the present

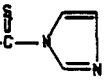
research was directed toward developing relatively straightforward routes from myo-inositol to the racemic compounds **4** and **8**, along with developing a practical synthesis of the meso compound **12**.

1-Deoxy-D,L-chiro-inositol ([81623-43-0], **4**). A direct route to this racemic compound is shown in Scheme 1. 4-O-Benzyl-1,2:5,6-di-O-cyclohexylidene-myo-inositol (**1**) was prepared by phase-transfer benzylation[12] of 1,2:5,6-di-O-cyclohexylidene-myo-inositol,[13] itself prepared by an improved cyclohexylidenation process.[14] Deoxygenation was affected by one of the methods of Barton and McCombie[15] that makes use of the intermediate 3-O-(1-imidazolthiocarbonyl) derivative **2**, derived from **1** by reaction with 1,1'-thiocarbonyldiimidazole in N,N-dimethylformamide. The resulting thionoester **2**, isolated in greater

SCHEME 1



1 2 3 4

Bzl = $-CH_2Ph$; R = 

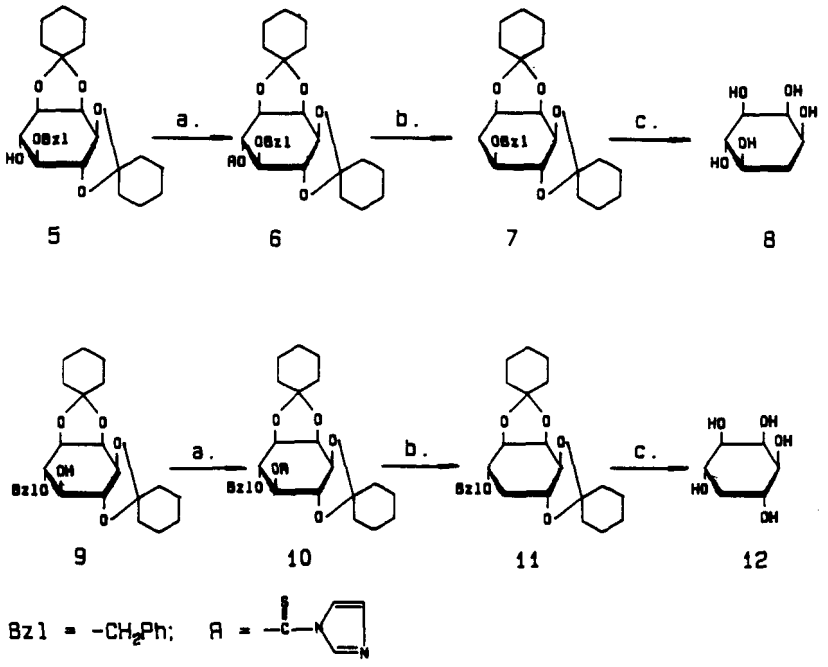
a. 1,1'-thiocarbonyldiimidazole;
b. $n\text{-}Bu_3SnH$ - AIBN; c. H_2 - $Pd(OH)_3/C$, HOAc

than 90% yield, was reacted with tri-n-butyltin hydride and 2,2-azobis-(2-methylpropionitrile) to give the deoxygenated **3** in 75% yield. This process from **1** to **3** was found superior, at least in our hands, to other methods of deoxygenation of inositols[7] which have been employed. Deprotection to **4** was cleanly effected via hydrogenolysis - acetal

hydrolysis in acetic acid. The sequence of reactions of **1** to **4** could be followed by ^{1}H NMR spectroscopy. Conversion of **1** to **2** was accompanied by a pronounced downfield shift of the H-3 resonance by 1.91 ppm which is characteristic of such derivatives.[16] Deoxygenation at C-3 in **3** was evidenced by the appearance of two high-field multiplets (δ1.83 and 2.37) typical of geminal protons coupled to two different protons. Compound **4** was identical in mp to that previously reported for "d,l-viburnitol,"[6] and the ^{1}H NMR spectrum supported the structure. The expected conformation having all OH groups equatorial, is indicated. The geminal H's at C-3 appear as characteristic AB multiplets at δ1.56 and 2.10, respectively, and the sole equatorial H at C-2 is isolated downfield at δ4.07. H-4 is a complex multiplet centered at δ3.77. While the spin-spin splittings for both H-1 and H-6 are obscured due to overlapping lines, the trans diaxial arrangement for H-5 is evidenced by the pseudotriplet at δ3.25 having $J_{4,5} = J_{5,6} = 9$ Hz.

2-Deoxy-D,L-epi-inositol ([488-74-4], **8**). This racemic compound, considered a "4-deoxy-myo-inositol," was synthesized from 5-O-benzyl-1,2:3,4-di-O-cyclohexylidene-myo-inositol (**5**)[12] as shown in Scheme 2. Thus **5** was converted to its 6-O-(1-imidazolthiocarbonyl) derivative **6** (62%), and the latter was deoxygenated to give **7** in 73% yield. As with the foregoing example, ^{1}H NMR spectroscopy supported the assigned structures, with H-6 in **6** showing a 2.17 ppm shift downfield and the site of deoxygenation in **7** showing a rather nondescript multiplet which integrated for two hydrogens. Deprotection of **7** to give **8** was effected in high yield by hydrogenolysis in acetic acid. The product **8** had mp 208 - 210 °C with considerable decomposition at ca. 190 °C. This value agrees with that of earlier workers.[17 - 20] The most striking characteristics of the ^{1}H NMR spectrum of **8** include the AB multiplets at δ1.78 and 1.97 for H-4_a and H-4_b and the equatorial H-2 resonance at δ 4.08, a multiplet reflecting an axial-equatorial spin-spin coupling. A multiplet at δ3.81 could be assigned to either H-3 or H-5. The remaining protons are contained in a complex envelope of resonances ranging from δ3.38 - 3.83.

SCHEME 2



Bzl = $-CH_2Ph$; R =

a. 1,1'-thiocarbonyldiimidazole;
b. $n\text{-}Bu_3SnH$ - AIBN; c. H_2 - $Pd(OH)_3/C$, HOAc

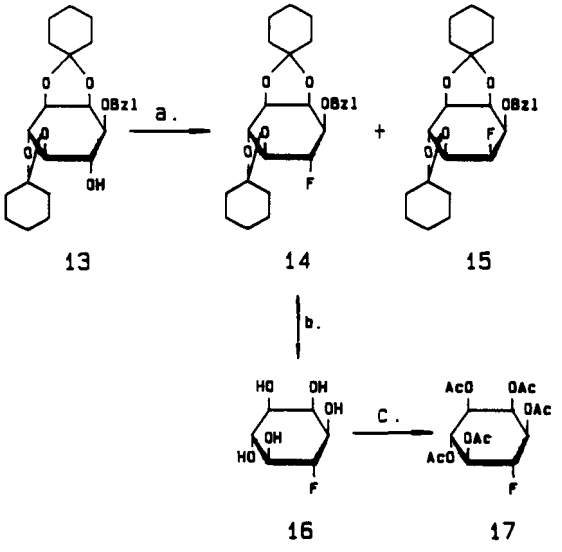
5-Deoxy-myo-inositol ([26671-58-9], 12). While this compound has been previously reported,[9 - 11] no direct route from myo-inositol, a logical precursor,[21] has been heretofore reported. Such a direct route is shown from 6-O-benzyl-1,2:3,4-di-O-cyclohexylidene-myo-inositol (9) in Scheme 2. Compound **9** was converted to the 5-O-(1-imidazolthiocarbonyl) derivative **10**, then subjected to deoxygenation with tri-n-butyltin hydride - AIBN to give the deoxycyclitol **11** in an overall yield of 78%. As with the previous examples, the conversion of **9** to **11** was clearly shown by ^1H NMR spectroscopy, with H-5 in **10** moving downfield by >2 ppm upon formation of the (1-imidazolthiocarbonyl) derivative. This wide low-field doublet (δ5.94), which showed a $J_{4,5}$ = 7.3 Hz, with no coupling to H-6, is explained upon examination of a

Dreiding model which revealed a conformation whereby H-5 and H-6 would assume a dihedral angle of approximately 90°. The conversion of **9** to **10** appears to be accompanied by a distortion of the ring to give a nearly trans-diaxial arrangement for H-3 - H-4 - H-5 as evidenced by the large couplings. The ^{1}H NMR spectrum of **11** showed one of the H-5 methylene protons at δ2.45, the other being obscured by the cyclohexylidene resonances. Deprotection of **11** by hydrogenolysis in acetic acid, as with the previous examples, afforded crystalline **12** in 86% yield. The mp of **12** was found to be some 10 °C higher than that previously published;[9] however, the ^{1}H NMR spectrum matched exactly that recently reported for **12**.[11]

Deoxyhalogenocyclitols. Cyclitols having selected hydroxy functions replaced by halogen were targeted for synthesis. Such replacements at the C-4 and C-5 positions, for example, could strategically serve to block enzymic phosphorylation at those sites on phosphatidylinositol (PI) known to be phosphorylated by PI- and PIP-kinase, respectively. The synthesis of fluorinated derivatives seemed particularly attractive, as fluorine is known to be virtually isosteric with hydrogen; however, inasmuch as little is known concerning the steric tolerances of the enzymes of the PI pathway,[22] other halogeno analogues might be of interest, particularly those which retain the natural myo configuration. Targeted for synthesis were those cyclitols with deoxyhalogeno functionality at (myo numbering) the C-4 for the myo- and epi-configurations, as well as at C-5 for the myo- and neo-configurations.

4-Deoxy-4-fluoro-myo-inositol **16**. Compound **16** was prepared via the sequence shown in Scheme 3. Of the methods available for fluoro-dehydroxylation, diethylaminosulfur trifluoride (DAST)[23] has emerged as a favored reagent for carbohydrates.[24] The reagent has advantage over traditional methods of fluoride ion displacements in that only a single step, one-flask reaction is required to convert OH to F. 3-O-Benzyl-1,2:5,6-di-O-cyclohexylidene-myo-inositol (**13**) was reacted with DAST at 20 - 65 °C to give a mixture of epimers **14** and **15** in yields of 31% and

SCHEME 3



a. Diethylaminosulfur trifluoride (DAST);
b. H_2 - $Pd(OH)_3/C$, HOAc; c. Ac_2O - pyridine

8.8%, respectively. Examination of the ^1H NMR spectra for **14** and **15** permitted a tentative assignment of configurations. The most obvious resonances were those associated with H-4: in each case wide primary H-F couplings of 51 and 45 Hz, respectively, for **14** and **15** were observed (partially obscured by the benzyl resonances in **14**). That **14** was indeed a product of retention of configuration was indicated by $J_{3,4}$ = 3.7 Hz and $J_{4,5}$ = 8.0 Hz in comparison with 3.7 and 4.4 Hz for the same couplings in **15**. Deprotection of **14** under conditions of hydrogenolysis - acid hydrolysis gave free 4-deoxy-4-fluoro-myo-inositol (**16**), isolated in 87% yield. H-4 of **16** appeared as a "doublet of pseudo triplets" representing a broad H-F coupling of 53 Hz and $J_{3,4} = J_{4,5}$ = 9.4 Hz, indicating a set of consecutive trans diaxial couplings in the H-3 - H-4 - H-5 portion of the molecule ($J_{1,2}$ = 4.1 and $J_{2,3}$ = 2.8 Hz, while overlapping resonances prevented chemical shift assignments for H-1, H-5 or H-6.) The ^1H NMR spectral assignments in **16** were further confirmed

Table 1. ^{1}H NMR Data for Compounds 1 - 44[a]

Compound	Solvent[b]	H_1 ($J_{1,2}$)	H_2 ($J_{2,3}$)	H_3 ($J_{3,4}$)	H_4 ($J_{4,5}$)	H_5 ($J_{5,6}$)	H_6 ($J_{6,1}$)	Other
1	A	4.36ψt (7.3)	4.45dd (3.6)	4.03ψt (1.7)	3.90dd (7.9)	3.56dd (10.5)	4.19dd (7.4)	1.22 - 1.84 (m, 20H, cyclohex.), 4.66, 4.81 (2d, $PhCH_2$), 722 - 7.50 (m, 5H, aryl)
2	A	4.50ψt (7.2)	4.66dd (3.7)	5.94dd (2.0)	3.94dd (7.7)	3.71dd (10.9)	4.00dd (7.2)	1.2 - 1.77 (m, 20H, cyclohex.), 4.81 (bs, 2H, $PhCH_2$), 7.22 - 7.44 (m, 5H, aryl), 7.05, 7.64, 8.37 (3s, 1H, imidazole)
3	A	4.20dd (8.0)	4.44dd (5.2)	1.83ddd (10, 5.2)[c] 2.37ddd (10, 4.4)[c]	3.39-3.61m		3.86ψt (8.0)	1.2 - 1.75 (m, 20H, cyclohex.), 4.66, 4.83 (2d, $PhCH_2$), 7.22 - 7.45 (m, 5H, aryl)
4	B	3.46-3.62m[d]	4.07m (width 8.65)	1.56ddd (10, 2.2)[c] 2.10 dψt (10, 4.4)[c]	3.77ddd (width ~26)	3.25ψt (9)	--[d]	
5	A	4.20ψt (5.6)	4.63ψt (3.1)	3.71dd (9.9)	4.07ψt (9.6)	3.52dd (7.0)	3.86ψt (5.6)	1.2 - 1.8 (m, 20H, cyclohex.), 4.6 (m, 2H, $PhCH_2$), 7.26 - 7.42 (m, 5H, aryl)

cont'd.

Table 1, cont'd.

Compound	Solvent[b]	H_1 ($J_{1,2}$)	H_2 ($J_{2,3}$)	H_3 ($J_{3,4}$)	H_4 ($J_{4,5}$)	H_5 ($J_{5,6}$)	H_6 ($J_{6,1}$)	Other
6	A	4.47dd (6.0)	4.70dd (3.1)	3.71dd (10.2)	4.27dd (9.0)	3.80dd (4.8)	6.03ψt (4.6)	1.2 - 1.95 (m, 20H, cyclohex.), 4.7 (m, 2H, $PhCH_2$), 7.2 - 7.45 (m, 5H, aryl), 7.06, 7.53, 8.22 (3s, 1H, imidazole)
7	A	4.45dd (6.4)	4.53dd (3.3)	3.36dd (10.2)	4.21dd (9.0)	3.80dd (5.4)	2.04m (width 13.5)	1.2 - 1.8 (m, 20H, cyclohex.), 4.67, 4.79 (2d, 2H, $PhCH_2$), 7.30 - 7.42 (m, 5H, aryl)
8	B	3.38-3.83m	4.08ψt (2.5)	3.81ddd[e] (2.8)	1.78m (12.0) 1.97ddd	3.38-3.83m		
9	A	4.43ψt (6.2)	4.65ψt (3.3)	3.48-3.84m	4.03ψt (9.1)	3.48-3.84m		1.2 - 1.85 (m, 20H, cyclohex.), 4.68, 4.92 (2d, $PhCH_2$), 7.29 - 7.35 (m, 5H, aryl)
10	A	4.53dd (7.0)	4.74ψt (3.3)	4.13dd (10.6)	4.45dd (7.3)	5.94d (0)	3.93d (2.9)	1.25 - 1.9 (m, 20H, cyclohex.), 4.68, 4.71 (2d, $PhCH_2$), 7.29 - 7.35 (m, 5H, aryl), 7.05, 7.62, 8.32 (3s, 1H, imidazole)
11	A	4.36ψt (5.0)	4.68ψt (3.2)	3.74-3.84m	3.98dψt (6 lines)	2.45[f] (width 19)	--[g]	1.28 - 1.8 (m, 21H, cyclohex.),[f] 4.67 (m, 2H, $PhCH_2$), 7.30 - 7.35 (m, 5H, aryl)

12	B	3.46dd (2.9)	4.04ψt (2.7)	3.46dd (9.8)	3.73-3.86m	2.19ddd (4.5, 12.0)[c] 1.30dd (4.5, 12.0)[c]	--[h]	
13	A	4.21dd (5.4)	4.41ψt (4.8)	3.57dd (7.1)	4.09ddd (10.0)	3.31ψt (9.8)	3.78dd (8.4)	1.26 - 1.82 (m, 20H, cyclohex.), 4.70, 4.80 (2d, 2H, $PhCH_2$), 7.31 - 7.42 (m, 5H, aryl)
14	A	4.31ψt (5.4)	4.38ψt (3.7)	3.84dψt (3.7, 16.5 H-F)	4.88ddd[i] (8.0, 51.1 H-F)	3.59ddd (10.7, 18.1 H-F)	4.03ψt (7.2)	1.25 - 1.82 (m, 20H, cyclohex.), 4.75 (bs, 3H, [i] $PhCH_2$) 7.29 - 7.37 (m, 5H, aryl)
15	A	4.10-4.47m		3.63ddd (3.7, 11 H-F)	4.90ddd (4.4, 45 H-F)	4.10-4.47m		1.28 - 1.84 (m, 20H, cyclohex.), 4.71, 4.92 (2d, 2H, $PhCH_2$), 7.27 - 7.39 (m, 5H, aryl)
16	B	3.51-3.80m (4.1)	4.08dd (2.8)	3.84ddd (9.4)	4.50dψt (9.4, 53.2 H-F)	3.51-3.80m		
17	A	5.09-5.49m (6.3)	5.63dd (3.1)	5.09-5.49m (9.5)	4.80dψt (9.5, 51.6 H-F)	5.09-5.49m		2.00, 2.03, 2.08, 2.10 (4s, 3H ea., acetyl)

cont'd.

Table 1, cont'd.

Compound	Solvent[b]	H_1 ($J_{1,2}$)	H_2 ($J_{2,3}$)	H_3 ($J_{3,4}$)	H_4 ($J_{4,5}$)	H_5 ($J_{5,6}$)	H_6 ($J_{6,1}$)	Other
18	A	4.39dd (5.2)	4.67dd (3.7)	4.22dψt (9.0)	3.90dd (~0, 28.2 HF)	5.10dd (1.9, 55.5 H-F)	3.45ddd (6.7, 30.5 H-F)	1.22 - 1.84 (m, 20H, cyclohex.), 4.79 (bs, 2H, $PhCH_2$), 7.28 - 7.41 (m, 5H, aryl)
19	A	4.48dd (6.6)	4.59-4.97m	3.80ddd (10.0)	4.28ddd (8.0, 18.2 H-F)	ca. 4.8 (7.7)	3.95ddd (6.7, 20.6 H-F)	1.22 - 1.82 (m, 20H, cyclohex.), 4.62, 4.74 (2d, J= 11.7, $PhCH_2$), 7.30 - 7.41 (m, 5H, aryl)
20	B	3.81-3.90m	4.11ψt (2.7)	3.78-3.90m	3.96dd (2.2)	4.91dψt (2.2, 52.8 H-F)	3.78-3.90m	
21	B	3.58dd (2.7)	4.05ψt (2.7)	3.58dd (10.1)	3.90dψt (9.2, 14.4 H-F)	4.28dψt (9.2, 51.8 H-F)	3.90dψt (9.0, 14.4 H-F)	
22	A	5.33-5.44m	5.67ψt (2.7)	5.33-5.44m	5.22dd (2.0)	5.05dψt (2.0, 54.4 H-F)	5.33-5.44m	2.02, 2.11, 2.17 (3s, 6H, 6H, 3H, respectively, -OAc's)
23	A	5.02dd (2.5)	5.54-5.71m	5.02dd (10.4)	5.54-5.71m (9.4)	4.50dψt (9.4, 50.8 H-F)	5.54-5.71m	2.01, 2.09, 2.22 (3s, 6H, 6H, 3H, respectively, -OAc's)

24	A	4.00-4.07m	4.33ψt (4.4)	3.66-3.77m	4.00-4.07m (10.1)	3.33ψt (10.1)	3.66-3.77m	1.2 - 1.78 (m, 20H, cyclohex.), 4.77 - 4.93 (m, 4H, $PhCH_2$), 7.29 - 7.44 (m, 10H, aryl)
25	A	4.10dd (4.5)	4.33ψt (4.5)	3.55m	3.95ψt (9.3)	3.37ψt (9.2)	3.55m (5.2)	1.24 - 1.82 (m, 10H, cyclohex.), 4.67, 4.97 (2d, 2H, J = 11.5 Hz, $PhCH_2$), 4.77 (s, 2H, $PhCH_2$), 7.28 - 7.39 (m, 10H, aryl)
26	A	4.10ψt (5.0)	4.31ψt (4.3)	3.66-3.85m	3.66-3.85m	3.51ψt (9.3)	3.66-3.85m	1.2 - 1.84 (m, 15H, cyclohex.), ca. 4.75 (m, 4H, $PhCH_2$), 7.25 - 7.35 (m, 10H, aryl)
27	A	4.00-4.17m (4.6)	4.32ψt (4.6)	3.56dd (9.7)	4.00-4.17m	3.28ψt (9.1)	3.70dd (6.7)	1.2 - 1.85 (m, 10H, cyclohex.), ca. 4.75 (m, 6H, $PhCH_2$), 7.23 - 7.42 (m, 15H, aryl)
28	A	4.22-4.29m		4.15dd (9.8)	3.87dd (2.9)	4.38ψt (2.9)	3.51dd (6.9)	1.2 - 1.78 (m, 10H, cyclohex.), ca. 4.75 (m, 6H, $PhCH_2$), 7.30 - 7.38 (m, 15H, aryl)
29	A	4.13-4.26m		4.13-4.26m (9.8)	3.70dd (2.9)	4.41ψt (3.0)	3.38dd (6.8)	1.22 - 1.72 (m 10H, cyclohex.), ca. 4.75 (m, 6H, $PhCH_2$), 7.30 - 7.42 (m, 15H, aryl)
30	A	4.08-4.21m		4.08-4.21m (8.5)	3.05dd (3.4)	4.45ψt (3.4)	2.81dd (6.9)	1.22 - 1.72 (m, 10H, cyclohex.), ca. 4.75 (m, 6H, $PhCH_2$), 7.30 - 7.39 (m, 15H, aryl)

cont'd.

Table 1, cont'd.

Compound	Solvent[b]	H_1 ($J_{1,2}$)	H_2 ($J_{2,3}$)	H_3 ($J_{3,4}$)	H_4 ($J_{4,5}$)	H_5 ($J_{5,6}$)	H_6 ($J_{6,1}$)	Other
31	B	3.90dd (2.9)	4.06ψt (3.6)	3.90dd (10.1)	4.06ψt (3.2)	4.58ψt (3.2)	4.06dd (9.6)	
32	B	3.82-3.98m	4.04d (1.7)	3.82-3.98m		4.65ψt (2.4)	3.82-3.98m	
33	B	3.85dd (3.1)	3.97ψt (3.1)	3.85dd (9.8)	3.19dd (3.7)	4.70ψt (3.7)	3.19dd (9.8)	
34	A	5.47dd (2.7)	5.64ψt (2.7)	5.47dd (10.6)	5.36dd (3.2)	4.81ψt (3.2)	5.36dd (10.6)	2.02, 2.11, 2.17 (3s; 6H, 6H, 3H, respectively; -OAc's)
35	A	5.47dd (3.0)	5.61ψt (3.0)	5.47dd (10. 5)	5.20dd (3.6)	4.85ψt (3.6)	5.20dd (10.5)	2.02, 2.11, 2.17 (3s; 6H, 6H, 3H, respectively; -OAc's)
36	A	5.41dd (3.0)	5.54ψt (3.0)	5.41dd (10.4)	4.58dd (4.0)	4.93ψt (4.0)	4.58 (10.4)	2.02, 2.11, 2.17 (3s; 6H, 6H, 3H, respectively; -OAc's)
37	A	4.12dd (4.8)	4.34ψt (4.8)	3.97dd (9.8)	3.82dd (2.4)	5.78ψt (2.4)	3.43dd (7.8)	1.22 - 1.70 (m, 10H, cyclohex.), 1.12 (t, 3H, Pr), 2.36 (q, 2H, Pr), ca. 4.75 (m, 6H, $PhCH_2$), 7.25 - 7.41 (m, 15H, aryl)

38	A	4.10-4.13m	4.10-4.13m	4.10-4.13m	3.79dd	4.10-4.13m	3.45dd	
				(9.2)	(2.9)	(2.4)	(6.7)	
39	A	4.09dd	4.29dd	3.66dd	3.79ψt	3.97dψt	3.79ψt	1.25 - 1.86 (m, 10H, cyclohex.), ca. 4.8 (m, 6H, $PhCH_2$), 7.28 - 7.46 (m, 15H, aryl)
		(5.3)	(3.7)	(8.3)	(8.3)	(8.3)	(ca. 8.5)	
40	A	3.92-4.11m	4.29dd	3.64dd	3.86ψt[j]	3.92-4.11m	3.86ψt[j]	1.20 - 1.84 (m, 10H, cyclohex.), ca. 4.8 (m, 6H, $PhCH_2$), 7.28 - 7.48 (m, 15H, aryl)
		(5.0)	(4.0)	(8.4)				
41	B	3.56dd	4.09ψt	3.56dd	3.79ψt	3.68ψt	3.79ψt	
		(2.6)	(2.6)	(9.8)	(9.6)	(9.6)	(9.8)	
42	B	3.56dd	4.09ψt	3.56dd	3.92m	3.67m	3.92m	
		(2.8)	(2.8)	(9.3)	(9.9)	(9.9)	(9.3)	
43	A	5.02dd	5.59ψt	5.02dd	5.55ψt	3.89ψt	5.55ψt	2.01, 2.10, 2.23 (3s; 6H, 6H, 3H, respectively; -OAc's)
		(2.7)	(2.7)	(10.3)	(10.5)	(10.5)	(10.3)	

cont'd.

Table 1, cont'd.

Compound	Solvent[b]	H_1 ($J_{1,2}$)	H_2 ($J_{2,3}$)	H_3 ($J_{3,4}$)	H_4 ($J_{4,5}$)	H_5 ($J_{5,6}$)	H_6 ($J_{6,1}$)	Other
44	A	5.00dd (2.8)	5.56-5.66m (2.8)	5.00dd (10.4)	5.56-5.66m	3.91ψt (10.8)	5.56-5.66m (10.4)	2.00, 2.10, 2.23 (3s; 6H, 6H, 3H, respectively; -OAc's)

[a] Chemical shift data are referenced to internal tetramethylsilane. Apparent, first-order values of spin-spin couplings are reported in hertz (J = Hz). Multiplicities are as follows: d = doublet; dd = doublet of doublets; s = singlet; ψt = triplet (a dd where couplings are equivalent).

[b] Solvents: A, chloroform-d; B, deuterium oxide.

[c] Couplings are typical of those of an ABX system.

[d] H-1 and H-6 are overlapping multiplets.

[e] H-5 is also a possible assignment.

[f] $H\text{-}5_B$ is obscured by the cyclohexylidene resonances.

[g] Overlaps with H-3.

[h] Overlaps with H-4. Compare assignments made in ref. 11.

[i] Upfield portion (dd) of H-4 overlaps with $PhCH_2$ resonance.

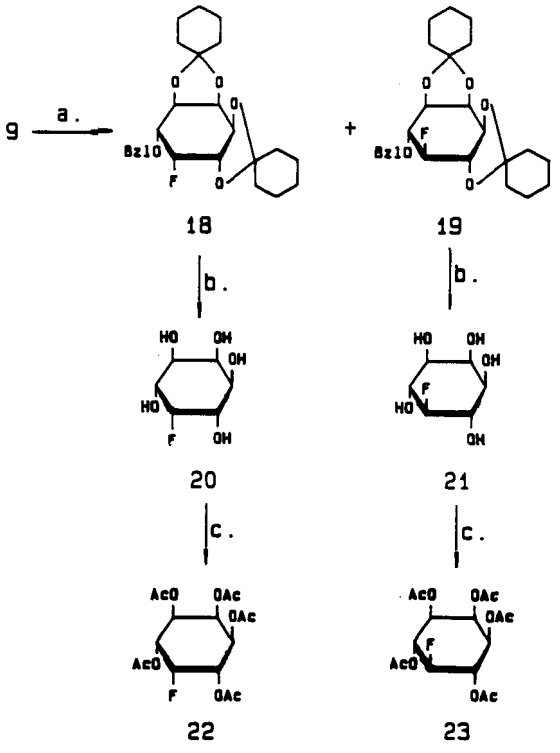
[j] Overlapping resonances prevented an accurate determination of J-values.

by converting the free hydroxy compound to the penta-O-acetyl derivative 17 in which all methine protons associated with -OAc groups shifted by >1 ppm to resonate below δ5 ppm, leaving the H-C-F proton (doublet of pseudo triplets) at δ4.8 (see Table 1). Unfortunately, attempted deprotection of 15 led to decomposition products, possibly due to a more ready trans elimination of HF, a fact which precluded a ^{1}H NMR spectral comparison between the free cyclitols.

While the majority of fluoro-de-hydroxylations with DAST have been shown to lead to products of inversion,[24] a few exceptions have been observed in the carbohydrate literature, among them a sugar that was apparently sterically hindered to backside approach.[25] Fluorination of a cyclitol that had a neighboring benzoyl group which offered anchimeric assistance resulted in retention.[26] (Compare a cyclitol example whereby inversion is observed.)[27] Thus in the fluoro-de-hydroxylation of 13, it can be argued that the 1,2-, 3-, and 5,6-substituents offer steric crowding to the backside attack of F^-, giving the product of retention.

2-Deoxy-2-fluoro-neo-inositol (20) and 5-Deoxy-5-fluoro-myo-inositol (21). Fluoro-de-hydroxylation of 6-O-benzyl-1,2:3,4-di-O-cyclohexylidene-myo-inositol (9)[14] with DAST (Scheme 4) led to a 35% yield of 6-O-benzyl-1,2:3,4-di-O-cyclohexylidene-5-deoxy-5-fluoro-neo-inositol (18), the product of inversion, and a lesser amount, 14.5%, of the product of retention, 6-O-benzyl-1,2:3,4-di-O-cyclohexylidene-myo-inositol (19). Configurational assignments for 18 and 19 were made from their ^{1}H NMR spectra. H-5 in 18 appeared as a wide doublet of doublets centered far downfield at δ5.10 reflecting a wide H-F coupling of 55.5 Hz and very small to non-existent cis couplings to H-4 and H-5 of ~0 and 1.9 Hz, respectively. Unusually large vicinal H-F couplings were observed in the resonances for H-4 (δ3.90dd: H_{H-F} = 28.2, $J_{3,4}$ = 9.0, and $J_{4,5}$ = ~0 Hz) and H-6 (δ3.45ddd: J_{H-F} = 30.5, $J_{5,6}$ = 1.9 and $J_{1,6}$ = 6.7 Hz). Thus a H-3 - H-4 trans and a H-4 - H-5 - H-6 cis geometry is indicated for 18. Although the ^{1}H NMR spectrum of 19 was far more complex due to overlapping resonances for H-4 - H-5 - H-6, a coupling of $J_{3,4}$ = 10.0, $J_{4,5}$ = 8.0 and $J_{5,6}$ = 7.7 Hz, respectively, were observed,

SCHEME 4



a. Diethylaminosulfur trifluoride (DAST);
b. H_2 - $Pd(OH)_3/C$, HOAc; c. Ac_2O - pyridine

indicating an all-trans relationship among these centers. While the geminal H-F coupling for H-5 could not be precisely determined (ca. 50 - 55 Hz) due to signal overlap, the vicinal H-F couplings were observed at both H-4 (18.2 Hz) and H-5 (20.6 Hz).

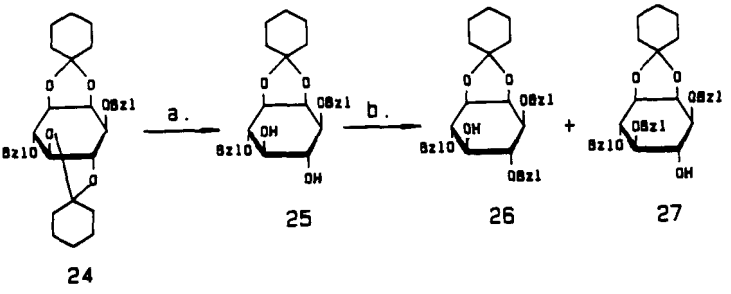
Deprotection of both **18** and **19** using hydrogenation in acetic acid smoothly furnished the free cyclitols **20** and **21**, respectively. While overlapping resonances, particularly in **20**, prevented full ^1H NMR spectral analysis, the stereochemistry at C-5 in **20** was confirmed by the doublet of "pseudo triplets" centered at δ4.91 with $J_{4,5} \sim J_{5,6}$ = 2.2 Hz and $J_{H,F}$ = 52.8 Hz. Likewise, the ^1H NMR spectrum of **21** was interpreted to reveal at δ4.28 a doublet of "pseudo triplets" for H-5 with large

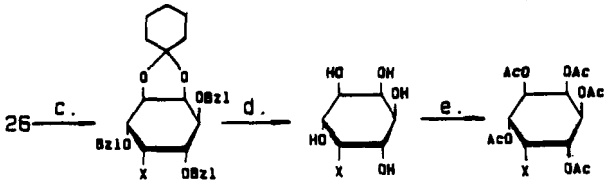
coupling constants ($J_{4,5} \sim J_{5,6}$ = 9.2 Hz and $J_{H,F}$ = 51.8 Hz), indicating the all-trans, myo configuration. Acetylation of both **20** and **21** gave their respective penta-O-acetyl derivatives **22** and **23** whose ^1H NMR spectra (Table 1) fully supported the assignments made for the free cyclitols.

2-Deoxy-2-halogeno (Cl, Br, I)-neo-inositols (**31**, **32**, **33**). For halogeno-de-hydroxylation at the C-5 position of myo-inositol, one might consider using 6-O-benzyl-1,2:3,4-di-O-cyclohexylidene-myo-inositol (**9**); however, the 3,4-cyclic acetal group was found to be exceedingly labile, making its manipulation during synthesis difficult. Moreover, 1,2:3,4-di-O-cyclohexylidene-myo-inositol, the precursor to **9**, was available in only ca. 10% yield.[13,14] A more satisfactory precursor for C-5 modification is **26** (Scheme 5), shown to be a far more stable intermediate whose precursor was available in two-fold higher yield than that for **9**. Thus 1,2:4,5-di-O-cyclohexylidene-myo-inositol was benzylated by phase-transfer methods to give the known **24**,[28] then selectively deprotected by a process advocated by Angyal and Tate[29] to give the protected 4,5-diol **25**.[30] Benzylation by phase-transfer methods then furnished 3,4,6-tri-O-benzyl-1,2-O-cyclohexylidene-myo-inositol **26** in near-equal proportion to its 3,5,6-tri-O-benzyl analogue **27**. The two isomers were separated by chromatography and crystallized to give products **26** and **27** melting at 87 - 88 °C and 96 - 98 °C, respectively. The two were also distinguishable by ^1H NMR spectroscopy (Table 1).[31]

Compound **26** was found to be the ideal intermediate for preparation of the halogenated neo-analogues **28** - **30** (Scheme 5). Compound **26**, when reacted with carbon tetrachloride - triphenylphosphine in DMF[32 - 34] at room temperature, gave a 38% yield of syrupy neo-**28** which was purified by column chromatography. The expected product of inversion (**28**) was confirmed by ^1H NMR spectroscopy whereby the low-field (δ4.38) proton appeared as a "pseudo triplet" reflecting a small $J_{4,5} \sim J_{5,6}$ = 2.9 Hz, indicating the cis geometry for H-4 - H-5 - H-6. Deprotection to give the free cyclitol was accomplished by boron tribromide-methylene chloride, followed after evaporation of the solvent by a dry methanol

SCHEME 5





28: X = -Cl	31: X = -Cl	34: X = -Cl
29: X = -Br	32: X = -Br	35: X = -Br
30: X = -I	33: X = -I	36: X = -I

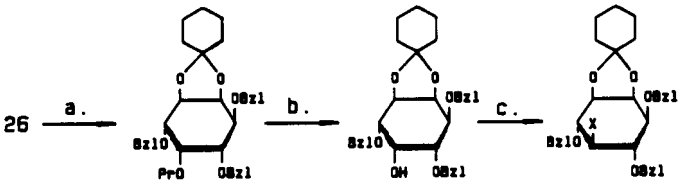
a. TsOH - $HOCH_2CH_2OH$; b. $n\text{-}Bu_4NHSO_4$ - $PhCH_2Br$; c. CCl_4 - Ph_3P - DMF for 28; Br_2 (or I_2) - Ph_3P - imidazole - toluene for 29 and 30; d. BBr_3 - CH_2Cl_2; e. Ac_2O - Pyridine

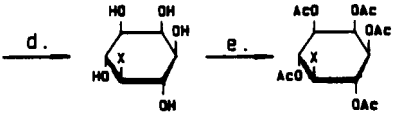
treatment (acidic due to boron tribromide methanolysis) and subsequent neutralization of the acid with ethylene oxide. The ^1H NMR spectrum of **31**, a molecule having a plane of symmetry through C-2 - C-5, confirmed its neo configuration which showed H-5 at δ4.58 as a "pseudo triplet" with $J_{4,5} = J_{5,6} = 3.2$ Hz. The spectral assignments were made via spin-spin decoupling and spectral simulation techniques which verified the assigned resonances.[35] The spectrum of the penta-O-acetyl derivative, due to better signal separation, permitted the assignment of each resonance, further confirming the neo-configuration having $J_{3,4}$ and $J_{1,6}$ = 10.6 Hz (trans), with the remainder showing small cis coupling constants (See Table 1).

Similar procedures allowed for the preparation of the bromo and iodo analogues **29** and **30**, respectively. While carbon tetrabromide failed to yield **29**, even under forcing conditions, the elemental halogens, bromine and iodine, with triphenylphosphine and imidazole under toluene reflux, both gave good yields of products.[36,37] ^{1}H NMR spectral patterns were similar to those for the chloro analogues, thus confirmining the neo configurations for the bromo and iodo compounds.

5-Deoxy-5-halogeno (Cl, Br)-myo-inositols (**41** and **42**). Entry into the 5-deoxy-5-halogeno-myo series was accomplished by inversion of the C-5 center using (a) triflation followed by (b) displacement with cesium propionate (Scheme 6).[38] Compound **26** was converted in a two-step process to give the syrupy neo-product **37** in 89% yield. ^{1}H NMR analysis

SCHEME 6





41: X = -Cl 43: X = -Cl
42: X = -Br 44: X = -Br

Pr = $-\overset{O}{\overset{\|}{C}}CH_2CH_3$

a. $(CF_3SO_2)_2O$ - Pyridine; $CsO\overset{O}{\overset{\|}{C}}CH_2CH_3$ - DMF; b. NaOH - MeOH;
c. CCl_4 - Ph_3P for **39**; Br_2 - Ph_3P for **40**; d. BBr_3 - CH_2Cl_2;
e. Ac_2O - Pyridine

of **37** showed coupling patterns (Table 1) analogous to the 5-deoxy-5-halogeno-neo-products **28** - **30**. Hydrolysis of **37** by dilute sodium hydroxide afforded the hydroxy compound **38**. Halogenation of **38** was

accomplished as for the previous examples using triphenylphosphine - carbon tetrachloride - imidazole (methylene chloride reflux) or triphenylphosphine - bromine - imidazole (toluene reflux), respectively, for the chloro and bromo derivatives.[32 - 37] Deprotection to give the free cyclitols was carried out as in the foregoing examples. Inversion of the C-5 center to yield myo-products was evident upon examination of the ^{1}H NMR spectra, especially for **41** and **42**, whereby large trans couplings of 9 - 10 Hz or greater were observed for $J_{3,4}$, $J_{4,5}$ and $J_{5,6}$ (Table 1).

CONCLUSIONS

A number of 1 (3)-, 4-, and 5-deoxy- and 4- and 5-deoxyhalogeno cyclitols (myo numbering) have been prepared from mono- and di-O-cyclohexylidene derivatives of myo-inositol. It is anticipated that many of these selectively protected compounds will serve as useful chemical intermediates in future chemical developments in this area, including the synthesis of phospholipid analogues with strategically modified structures. A detailed study of the biochemical activity of the target cyclitols will be reported elsewhere.[39]

EXPERIMENTAL

General. Solvents were evaporated under aspirator vacuum at ~40 °C. Melting points were determined using a Thomas-Hoover "Unimelt" capillary melting point apparatus equipped with a Cole-Parmer model 8520-50 Digi-Sense digital thermocouple combination that was calibrated with known standards. Infrared (IR) spectra were recorded on a Perkin-Elmer model 710B spectrophotometer.

^{1}H NMR spectra were determined at 200 MHz as ca. 0.1% solutions using a Nicolet NT-200 instrument. Chemical shifts are reported in δ-units downfield from internal tetramethylsilane (TMS) in chloroform, while those in deuterium oxide are reported relative to internal 2,2-dimethyl-2-silapentane-5-sulfonate (DSS). Multiplicities are first-order values (in Hz) and are indicated as: d, doublet; dd, doublet of

doublets; m, multiplet; q, quartet; s, singlet; ψt, triplet (a dd where J-values are approximately equal). Gas chromatography - mass spectrometry (GC/MS) was caried out on a Hewlett-Packard 5985A system using a CP-Sil 5 CB (CHROMPACK), fused silica wall-coated open tubular capillary column (10 m x 0.32 mm) operating at 40 mL min^{-1} nitrogen carrier gas, under a temperature program of 60 to 210 °C, heating at 8 °C min^{-1}. Retention times of the per(trimethylsilyl) ethers of the free cyclitols[40] are expressed in absolute terms (T_R, min). Adsorption chromatography was carried out using E. Merck Silica Gel-60 products: (a) TLC on 0.2 mm aluminum-backed plates (catalog no. 5760); (b) open-column chromatography using either 10 - 200 μm and 230 - 400 μm silica gel (catalog nos. 7734 and 9385, respectively). Solvents include: A, 3:7 ethyl acetate - hexane; B, 1:9 benzene - dichloromethane; C, 3:7 ethyl acetate - petroleum ether; D, 5:95 ethanol - chloroform; E, 2:8 ethyl acetate - petroleum ether; F, 2:8 benzene - dichloromethane. All solvents and reagents were "reagent grade" unless otherwise noted. N,N-dimethylformamide (DMF) and pyridine were distilled from calcium hydride under vacuum and at atmospheric pressure, respectively, and stored over 4-A molecular sieves.

Preparation of 4-O-Benzyl-1,2:5,6-di-O-cyclohexylidene-myo-inositol (1), 5-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-myo-inositol (5), 6-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-myo-inositol (9), and 3-O-Benzyl-1,2:5,6-di-O-cyclohexylidene-myo-inositol (13). These were prepared from their respective di-O-cyclohexylidene-myo-inositols[13,14] according to known methods.[12] For ^1H NMR data, see Table 1.

4-O-Benzyl-1,2:5,6-di-O-cyclohexylidene-3-O-(1-imidazolthiocarbonyl)-myo-inositol (2). To 1.50 g (3.48 mmol) of 1 in 25 mL of N,N-dimethylformamide, 1.68 g (9.43 mmol) of 1,1'-thiocarbonyldiimidazole (Fluka) was added. The mixture was stirred at 60 °C under nitrogen for 12 h, at the end of which time the DMF was evaporated to give a yellow syrup to which 50 mL of ethyl acetate was added. The solution was washed with 3 x 30 mL of saturated aqueous sodium chloride, the organic layer was separated and dried over magnesium sulfate, and the solvent was evaporated to yield a yellow syrup that was purified by column

chromatography over 130 g of silica gel using solvent A to give 1.75 g (90.6%) of pure **2** as a white glass after drying under high vacuum: mp 76 - 78 °C; R_f 0.45 (A); IR (KBr) 738 (m), 910 (m), 980 (m), 1080 (s), 1235 (s), 1290 (s), 3120 (s), 1390 (s), 1445 (m), 2825 (m), 2868 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{29}H_{36}N_2O_6S$: C, 64.42; H, 6.71; N, 5.18. Found: C, 64.45; H, 6.74; N, 5.15.

4-O-Benzyl-1,2:5,6-di-O-cyclohexylidene-3-deoxy-myo-inositol (3). To 1.6 g (2.9 mmol) of **2** in 30 mL of toluene, 2.3 g (7.8 mmol) of tri-n-butyltin hydride and 0.83 g (5.0 mmol) of 2,2-azobis-(2-methylpropionitrile) were added. The mixture was heated under reflux under a nitrogen atmosphere for 3 h, at the end of which time the toluene was evaporated to yield a colorless syrup. This syrup was purified by column chromatography over 100 g of silica gel using solvent F to yield 0.9 g (75%) of pure **3** as a syrup: R_f 0.29 (B); IR (chloroform) 850 (m), 918 (m), 1100 (s), 1162 (m), 1280 (m), 1362 (m), 1450 (m), 2825 (m), 2865 (s), 2895 (m) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.44; H, 8.27. Found: C, 72.38; H, 8.53.

Preparation of 1-Deoxy-D,L-chiro-inositol (4). To 600 mg (1.45 mmol) of **3** in 20 mL of 80% aqueous acetic acid, 120 mg of 20% palladium hydroxide on charcoal (Aldrich) was added. The mixture was shaken under 65 psi hydrogen pressure at room temperature for 72 h, at the end of which time the catalyst was filtered through Celite™, and the filter cake was washed with 20 mL of 1:1 ethanol - water. The colorless, clear filtrate was evaporated to give a white solid. Two, 30-mL portions of absolute ethanol were added to the flask and were evaporated to remove traces of acetic acid. The resulting white solid was crystallized from 95% aqueous ethanol to yield 210 mg (88%) of **4** as white crystals: mp 155 - 157 °C. Recrystallization from 95% ethanol gave 170 mg of analytically pure compound as colorless crystals: mp 161 - 162 °C [Lit.[6] 161 - 163 °C]. For ^1H NMR data, see Table 1.

5-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-6-O-(1-imidazolthiocarbonyl)-myo-inositol (6). By the same procedure used for preparation of **2**, 0.50 g (1.16 mmol) of **5** was converted to 0.40 g (62%) of **6**, isolated as

a syrup: R_f 0.31 (A); IR (chloroform) 740 (m), 910 (m), 1083 (s), 1240 (s), 1295 (s), 1330 (s), 1395 (s), 1450 (s), 2825 (m), 2870 (s). For ^1H NMR data, see Table 1. Anal. Calcd for $C_{29}H_{36}N_2O_6S$: C, 64.39; H, 6.74; N, 5.18. Found: C, 64.42; H, 6.71; N, 5.16.

5-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-6-deoxy-myo-inositol (7). By the same procedure used for preparation of **3**, 0.26 g (0.47 mmol) of **6** was converted to 0.14 g (73%) of **7**, isolated as a syrup: R_f 0.27 (B); IR (chloroform) 920 (m), 1105 (s), 1170 (m), 1285 (m), 1370 (m), 1455 (m), 2825 (m), 2870 (s), 2900 (m) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.44; H, 8.27. Found: C, 72.30; H, 8.29.

2-Deoxy-D,L-epi-inositol (8). By the same procedure used for preparation of **4**, 120 mg (0.29 mmol) of **7** was deprotected to give 40 mg (85%) of **8**, isolated as colorless crystals: mp 208 - 210 °C (darkens at ca. 190 °C) [Lit.[17] - [20] mp 205 °C,[17] mp 207 - 9 °C,[18] mp 205 - 215 °C[19]]. For ^1H NMR data, see Table 1.

6-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-5-O-(1-imidazolthiocarbonyl)-myo-inositol (10). By the same procedure used for preparation of **2**, 0.60 g (1.39 mmol) of **9** was converted to 0.73 g (94%) of **10**: mp 80 - 82 °C; R_f 0.40 (A); IR (KBr) 738 (m), 820 (m), 900 (m), 990 (m), 1090 (s), 1223 (s), 1280 (s), 1325 (m), 1385 (s), 1440 (m), 2820 (m), 2860 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{29}H_{36}N_2O_6S$: C, 64.42; H, 6.71; N, 5.18. Found: C, 64.30; H, 6.75; N, 5.17.

6-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-5-deoxy-myo-inositol (11). By the same procedure used for preparation of **3**, 0.40 g (0.73 mmol) of **10** was converted to 0.25 g (83%) of **11**, isolated as a syrup: R_f 0.23 (B); IR (chloroform) 850 (m), 910 (m), 1110 (s), 1161 (m), 1278 (m), 1362 (m), 1445 (m), 2825 (m), 2865 (s), 2895 (m) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.45; H, 8.27. Found: C, 72.33; H, 8.31.

Preparation of 5-deoxy-myo-inositol (12). By the same procedure used for preparation of **4**, 300 mg (0.73 mmol) of **11** was deprotected to give 102 mg (86%) of white crystals of **12**: mp 230 - 232 °C (dec). Recrystallization twice from aqueous ethanol gave 50 mg of pure **12** as

colorless crystals: mp 248 - 249 °C (dec) [Lit.[9] 238 - 239 °C (dec)]. T_R [per(trimethylsilyl)-5-deoxy-myo-inositol] 2 min. For ^1H NMR data, see Table 1. The ^1H NMR data match those reported.[11]

3-O-Benzyl-1,2,5,6-di-O-cyclohexylidene-4-deoxy-4-fluoro-myo-inositol (14) and 3-O-Benzyl-1,2,5,6-di-O-cyclohexylidene-4-deoxy-4-fluoro-epi-inositol (15). By essentially the same procedure used for the synthesis of **18** and **19** (vide infra), 1.7 g (4.0 mmol) of **13** was converted to 530 mg (31%) of **14** and 150 mg (8.8%) of **15**. The products were separated by silica gel column chromatography using solvent F. Physical data for **14**: R_f 0.45 (B); IR ($CHCl_3$) 850 (m), 905 (m), 1100 (s), 1280 (m), 1360 (m), 1441 (m), 2845 (m), 2920 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{25}H_{33}FO_5$: C, 69.42; H, 7.69. Found: C, 69.43; H, 7.71. Physical data for **15**: R_f 0.53 (B); IR ($CHCl_3$) 850 (m), 920 (m), 1080 (s), 1105 (s), 1280 (m), 1360 (m), 1445 (m), 2850 (m), 2930 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{25}H_{33}FO_5$: C, 69.42; H, 7.69. Found: C, 69.29; H, 7.69.

4-Deoxy-4-fluoro-myo-inositol (16). By the same procedure used for **20** (vide infra), 300 mg (0.69 mmol) of **14** was deprotected to give 110 mg (87.6%) of **16** which was recrystallized twice from ethanol - water to give 5 mg of analytically pure **16** as colorless crystals: mp 209 - 210 °C; IR (KBr) 890 (m), 930 (m), 1000 (s), 1050 (s), 1130 (s), 1450 (m), 3400 (bs) cm^{-1}. For ^1H NMR data, see Table 1. T_R [per(trimethylsilyl) derivative of **16**] 2.96 min. Anal. Calcd for $C_6H_{11}FO_5$: C, 39.57; H, 6.09; F, 10.43. Found: C, 39.35; H, 6.03; F, 10.24.

1,2,3,5,6-Penta-O-acetyl-4-deoxy-4-fluoro-myo-inositol (17). By the same procedure used for the preparation of **22** (vide infra), 10 mg of **16** was acetylated to give the acetate **17**. For ^1H NMR data, see Table 1. MS m/z (%) 350 (0.7, M - CH_2=C=O), 333 (1.4, M - OAc), 43 (93.7, Ac).

6-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-5-deoxy-5-fluoro-neo-inositol (18) and 6-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-5-deoxy-5-fluoro-myo-inositol (19). To 2.0 g (4.7 mmol) of **9** in 50 mL of toluene was added 0.75 g (4.7 mmol) of diethylaminosulfur trifluoride (DAST, Aldrich) under nitrogen atmosphere, and the mixture was stirred at room

temperature for one h. The temperature was then raised to 65 °C for 4 h, at the end of which time the mixture was cooled to room temperature, and 40 mL of saturated aqueous sodium bicarbonate was added. The mixture was extracted with 100 mL of ethyl acetate, and the extract was washed with 2 x 50 mL of saturated aqueous sodium chloride. The organic layer was dried over potassium carbonate and magnesium sulfate, and the solvent was evaporated to provide a yellow syrup which was purified by column chromatography over 80 g of silica gel using solvent F as eluent to give first 0.29 g (14.5%) of **19**, followed by 0.70 g (35%) of **18**, both as syrups. Physical data for **18**: R_f 0.34 (B); IR ($CHCl_3$) 825 (m), 855 (m), 1080 (s), 1160 (s), 1280 (m), 1360 (m), 1450 (m), 2850 (m), 2940 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{25}H_{33}FO_5$: C, 69.42; H, 7.69. Found: C, 69.43; H, 7.71. Physical data for **19**: R_f 0.47 (B); IR ($CHCl_3$) 860 (m), 940 (m), 1105 (s), 1285 (m), 1370 (m), 1450 (m), 2855 (m), 2950 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{25}H_{33}FO_5$: C, 69.42; H, 7.69. Found: C, 69.52; H, 7.71.

2-Deoxy-2-fluoro-neo-inositol (20). To 400 mg (0.92 mmol) of **18** in 20 mL of 80% aqueous acetic acid was added 140 mg of 20% palladium-on-charcoal. The mixture was shaken under hydrogen at 65 psi at room temperature for 48 h, at the end of which time the catalyst was removed by filtration through a Celite pad, the filter cake being washed with 20 mL of ethanol and then 20 mL of water. The solvent from the colorless, clear filtrate was evaporated to give a white solid to which two, 30-mL portions of absolute ethanol were added and evaporated to remove traces of acetic acid. The resulting white solid was crystallized from 90% aqueous ethanol to give 151 mg (90%) of **20** as colorless crystals which were recrystallized from ethanol - water to give 72 mg of analytically pure **20**: mp 280 - 281 °C (dec); IR (KBr) 910 (m), 1050 (s), 1130 (s), 1280 (m), 1380 (m), 3300 (bs) cm^{-1}. For ^1H NMR data, see Table 1; T_R [per(trimethylsilyl) derivative of **20**]: 2.83 min. Anal. Calcd for $C_6H_{11}FO_5 \cdot 0.25\ H_2O$: C, 38.61; H, 6.21; F, 10.18. Found: C, 38.75; H, 6.05; F, 9.91.

1,2,3,4,6-Penta-O-acetyl-2-deoxy-2-fluoro-neo-inositol (22). To 15 mg of **20** in 1 mL of dry pyridine was added 0.4 mL of acetic anhydride,

and the mixture was stirred at 60 °C under a dry nitrogen atmosphere for 5 h, at which time all the solid had dissolved. The solvent was evaporated, and three, 20-mL portions of ethanol were added to the residue and evaporated to give a light yellow solid which was crystallized from ethanol to give colorless crystals of pure **22**: mp 218 - 220 °C. For ^{1}H NMR data, see Table 1. MS: *m/z* (%): 350 (0.4, M - CH_2=C=O); 333 (1.6, M - AcO); 43 (100, Ac).

5-Deoxy-5-fluoro-*myo*-inositol (21). By the same procedure used for **20**, 280 mg (0.64 mmol) of **19** was deprotected to give 100 mg (85.3%) of crude **21** (mp 210 - 212 °C) which was recrystallized from ethanol - water three times to give 30 mg of analytically pure **21** as colorless crystals: mp 222 - 224 °C; IR (KBr) 870 (m), 980 (m), 1040 (s), 1135 (m), 1380 (m), 3300 (bs) cm^{-1}. For ^{1}H NMR data, see Table 1; T_R [per(trimethylsilyl) derivative of **21**]: 2.61 min. Anal. Calcd for $C_6H_{11}FO_5$: C, 39.56; H, 6.09; F, 10.43. Found: C, 39.79; H, 6.07; F, 10.16.

1,2,3,4,6-Penta-*O*-acetyl-5-deoxy-5-fluoro-*myo*-inositol (23). By the same procedure used for **22**, **21** was acetylated to give **23**: mp 180 - 181 °C. For ^{1}H NMR data, see Table 1. MS: *m/z* (%): 350 (0.5, M - CH_2=C=O), 333 (1.2, M - OAc), 43 (100, Ac).

Preparation of 3,6-Di-*O*-benzyl-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (24). To 15 g (43.3 mmol) of 1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol[13,14] and 15 g (43.3 mmol) of tetra-*n*-butylammonium hydrogen sulfate in 600 mL of dichloromethane was added 15 mL (130 mmol) of benzyl bromide over a period of 5 min, followed by 500 mL of 5% aqueous sodium hydroxide. The mixture was heated under reflux for 12 h, at the end of which time an additional 2.5 mL of benzyl bromide was added. After a further 16 h under reflux, TLC showed the absence of starting material. After cooling the mixture to room temperature, the organic layer was separated, washed with 2 x 300 mL of saturated aqueous sodium chloride, and then with water. The extract was dried over magnesium sulfate, and the solvent was evaporated to provide a yellow syrup which, when applied to high vacuum to remove benzyl bromide, gave a semisolid

that was crystallized from ether - petroleum ether to give 17.5 g of colorless crystals. The mother liquor was collected and applied to a 150-g column of silica gel. Using chloroform as the eluent, an additional amount of syrupy product was isolated and crystallized as before to give 3.0 g of pure **24**; total yield 20.5 g (92.8%) of **24**: mp 147 - 148 °C; [Lit.[28] mp 148 - 149 °C]; R_f 0.57 (C); For ^{1}H NMR data, see Table 1.

Preparation of 3,6-Di-O-benzyl-1,2-O-cyclohexylidene-myo-inositol (25). Compound **25** was prepared by a modified method reported by Angyal and coworkers.[29] To 17.0 g (31.7 mmol) of **24** in 250 mL of chloroform, 2.1 g (31.7 mmol) of ethylene glycol, 100 mg of p-toluenesulfonic acid was added. The mixture was stirred at room temperature for 1.5 h, at the end of which time it was poured into 150 mL of saturated aqueous sodium bicarbonate. The organic layer was separated and washed with two, 100-mL portions of saturated aqueous sodium chloride and dried over magnesium sulfate. The solvent was evaporated to give a syrup which was crystallized from acetone - petroleum ether to provide 12.2 g (85%) of colorless crystals of pure **25**: mp 146 - 147 °C [Lit.[30] 147.6 - 148 °C]. For ^{1}H NMR data, see Table 1.

3,4,6-Tri-O-benzyl-1,2-O-cyclohexylidene-myo-inositol (26) and 3,5,6-Tri-O-benzyl-1,2-O-cyclohexylidene-myo-inositol (27). The synthesis was carried out by a modification of the method reported by Garegg et al.[12] To 10.0 g (2.2 mmol) of **25** and 8.0 g (2.2 mmol) of tetrabutylammonium hydrogen sulfate in 500 mL of dichloromethane were added 3.4 mL (2.9 mmol) of benzyl bromide and 500 mL of 5% aqueous sodium hydroxide. The mixture was heated under reflux for 18 h, at the end of which time the organic layer was separated, washed with two, 200-mL portions of water and dried over magnesium sulfate. The dichloromethane was evaporated to give a syrup which was purified by column chromatography over 400 g of silica gel using solvent E as eluent to give two major products, **26** and **27**, as syrups. Crystallization of **26** from 10:90 ethyl acetate - petroleum ether provided 4.5 g (37.5%) of analytically pure **26**: mp 87 - 88 °C; R_f 0.44 (C); IR (KBr) 690 (m), 720

(m), 920 (m), 1100 (s), 1350 (m), 1440 (m), 2900 (s), 3500 (sb) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{33}H_{38}O_6$: C, 74.69; H, 7.22. Found: C, 74.76; H, 7.25.

In a similar fashion syrupy **27** was crystallized to give 4.3 g (36.2%) of the pure compound as colorless crystals: mp 96 - 98 °C; R_f 0.33 (C); IR (KBr) 690 (m), 920 (m), 1060 (s), 1100 (s), 1360 (m), 1440 (m), 2920 (s), 3550 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{33}H_{38}O_6$: C, 74.69; H, 7.22. Found: C, 74.69; H, 7.27.

3,4,6-Tri-O-benzyl-5-chloro-1,2-O-cyclohexylidene-5-deoxy-neo-inositol (28). To 1.0 g (1.9 mmol) of **26** and 1.44 g (5.5 mmol) of triphenylphosphine in 20 mL of DMF was added 0.54 mL (5.6 mmol) of carbon tetrachloride. The mixture was stirred at room temperature under nitrogen for 48 h, at the end of which time the solvents were removed to give a syrup that was dissolved in 100 mL of dichloromethane and washed with 70 mL of saturated aqueous sodium chloride. The organic extract was dried over magnesium sulfate, and the solvent was evaporated to provide a semisolid to which 30 mL of ethyl acetate was added. A brown solid which formed was removed by filtration, and the solvent was evaporated to give a syrup that was purified by column chromatography over 80 g of silica gel using solvent G to give 0.4 g (38.3%) of **28** as a syrup: R_f 0.38 (E); IR (CCl_4) 690 (m), 910 (m), 1020 (m), 1100 (s), 1200 (m), 1260 (m), 1350 (m), 1440 (m), 2900 (s), 3000 (m) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{33}H_{37}ClO_5$: C, 72.18; H, 6.79; Cl 6.46. Found: C, 72.09; H, 6.84; Cl, 6.45.

3,4,6-Tri-O-benzyl-5-bromo-1,2-O-cyclohexylidene-5-deoxy-neo-inositol (29). To 709 mg (1.3 mmol) of **26**, 1.36 g (5.2 mmol) of triphenylphosphine, and 354 mg (5.2 mmol) of imidazole in 40 mL of toluene stirred under an atmosphere of nitrogen was added 0.2 mL (3.9 mmol) of bromine. The mixture was heated under reflux overnight, at the end of which time it was cooled to room temperature, and 50 mL of ethyl acetate was added. The organic layer was separated, washed with 50 mL of saturated aqueous sodium bicarbonate and with 50 mL of water. The extract was dried over magnesium sulfate and potassium carbonate, and

the solvent was evaporated to provide a syrup. Purification of the crude product by column chromatography over 80 g of silica gel using solvent E gave a syrup which was crystallized from diethyl ether - petroleum ether to provide 0.62 g (80.3%) of **29** as colorless crystals: mp 129 - 130 °C; R_f 0.49 (E); IR (KBr) 690 (m), 730 (m), 920 (m), 1100 (s), 1200 (m), 1270 (m), 1350 (m), 1440 (m), 2900 (s), 3000 (m) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{33}H_{37}BrO_5$: C, 66.78; H, 6.28; Br, 13.46. Found: C, 66.83; H, 6.31; Br, 13.47.

3,4,6-Tri-O-benzyl-1,2-O-cyclohexylidene-5-deoxy-5-iodo-neo-inositol (30). By the same procedure used for **29**, except using iodine (990 mg, 3.9 mmol) instead of bromine, 709 mg (1.3 mmol) of **26** was converted to 600 mg (72.1%) of **30**: mp 131 - 133 °C; R_f 0.47 (E); IR (KBr) 690 (m), 730 (m), 840 (m), 910 (m), 1100 (s), 1200 (m), 1260 (m), 1350 (m), 1440 (m), 2900 (s), 3000 (m) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{33}H_{37}IO_5$: C, 61.88; H, 5.82; I, 19.81. Found: C, 61.84; H, 5.84; I, 19.87.

2-Chloro-2-deoxy-neo-inositol (31). To an ice-cold solution of 350 mg (0.64 mmol) of **28** in 6 mL of dry dichloromethane maintained under a nitrogen atmosphere was added 2.7 mL (2.7 mmol) of a 1 M solution of boron tribromide in dichloromethane (Aldrich), and the mixture was stirred for 30 min at 0 °C, then at room temperature for 4 h. The solvent was then evaporated at 20 °C to give a brown syrup to which three, 20-mL portions of dry methanol were added and successively evaporated. To the residue, dissolved in 10 mL of dry methanol, was added 10 mL of a cold, saturated solution of ethylene oxide in ether, which effectively neutralized the solution. The solvent was evaporated at 20 °C to give a light brown solid to which 20 mL of a mixture of ethyl acetate and dichloromethane was added, and a light gray solid was obtained by filtration. Recrystallization of the crude product from ethanol - water gave 95 mg (75%) of pure **31**: mp 268 - 270 °C; IR (KBr) 700 (m), 880 (m), 1050 (m), 1080 (m), 1120 (m), 1250 (m), 1360 (m), 1400 (m), 3300 (sb) cm^{-1}. For ^1H NMR data, see Table 1. T_R [per(trimethylsilyl) derivative]: 2.52 min. Anal. Calcd for $C_6H_{11}ClO_5$: C, 36.29; H, 5.58; Cl, 17.85. Found: C, 36.21; H, 5.57; Cl, 17.89.

2-Bromo-2-deoxy-neo-inositol (32). By the same procedure used for **31**, 560 mg (0.94 mmol) of **29** was deprotected to give 185 mg (81%) of **32**: mp 228 - 230 °C; IR (KBr) 1040 (s), 1080 (m), 1240 (m), 3300 (sb). For ^{1}H NMR data, see Table 1. T_R [per(trimethylsilyl) derivative]: 2.95 min. Anal. Calcd for $C_6H_{11}BrO_5$: C, 29.65; H, 4.56; Br, 32.88. Found: C, 29.65; H, 4.59; Br, 32.83.

2-Deoxy-2-iodo-neo-inositol (33). By the same procedure used for **31**, 525 mg (0.82 mmol) of **30** was deprotected to give 198 mg (83.2%) of **33**: mp 200 - 202 °C (dec.); IR (KBr) 1040 (m), 1080 (m), 1240 (m), 3350 (sb) cm^{-1}. For ^{1}H NMR data, see Table 1. T_R [per(trimethylsilyl) derivative]: 3.34 min. Anal. Calcd for $C_6H_{11}IO_5$: C, 24.85; H, 3.82; I, 43.75. Found: C, 24.91; H, 3.86; I, 43.85.

1,3,4,5,6-O-Penta-O-acetyl-2-chloro-2-deoxy-neo-inositol (34). By the same procedure used for **22**, **31** was converted to the peracetate **34**: mp 178 - 180 °C. For ^{1}H NMR data, see Table 1. MS: m/z (%) 373 (0.3 M - Cl), 271 (7.6, M - Cl - OAc - Ac), 169 (46.9, M - Cl - 2OAc - 2Ac), 43.1 (91.7, Ac).

1,3,4,5,6-Penta-O-acetyl-2-bromo-2-deoxy-neo-inositol (35). By the same procedure used for **22**, **32** was converted to the peracetate **35**: mp 196 - 198 °C. For ^{1}H NMR data, see Table 1. MS: m/z (%), 395 (0.3, M - AcO), 393 (0.3, M - AcO), 293 (1.6, M - 2OAc - Ac), 291 (1.4, M - 2OAc - Ac), 232 (21.0, M - OAc - 2AcOH - Ac), 230 (19.1, M - OAc - 2AcOH - Ac), 43 (100, Ac).

1,3,4,5,6-Penta-O-acetyl-2-deoxy-2-iodo-neo-inositol (36). By the same procedure used for **22**, **33** was acetylated to give 3[illegible] mp 222 - 223 °C. For ^{1}H NMR data, see Table 1. MS: m/z (%) 500 (0.3, M), 373 (6.2, M - I), 313 (42.5, M - I - AcOH), 271 (49.5, M - I - OAc - Ac), 43 (72.3, Ac).

3,4,6-Tri-O-benzyl-1,2-O-cyclohexylidene-5-O-propionyl-neo-inositol (37). To an ice-cold solution of 2.42 g (4.6 mmol) of **26** and 0.47 g (6.0 mmol) of pyridine in 40 mL of dry dichloromethane maintained under a nitrogen atmosphere, was added dropwise over a period of 10 min 10 mL of a solution containing 1.55 g (5.5 mmol) of trifluoromethanesulfonic

acid anhydride in dry dichloromethane. The mixture was stirred for 3 h at 0 °C, at which time TLC indicated incomplete reaction. An additional 0.1 mL of pyridine was added, followed by 0.2 mL of trifluoromethanesulfonic acid anhydride. The mixture was stirred at 0 °C for an additional 30 min and then at room temperature for 4 h, at which time TLC (R_f 0.20 for **26**; 0.42 for triflate intermediate, E) indicated complete conversion of **26** to the triflate derivative. The solvent was then evaporated at 20 °C to give a yellow syrup to which 40 mL of DMF and 1.41 g (6.9 mmol) of cesium propionate[38] was added. The mixture was stirred at room temperature for 3 h, at the end of which time TLC (E) showed that the reaction was complete as evidenced by a new zone at R_f 0.32 (E). The DMF was evaporated to give a syrup to which 200 mL of ethyl acetate was added, and the solution was washed with two, 100-mL portions of saturated aqueous sodium chloride. The organic extract was dried over magnesium sulfate. The solvent was evaporated to provide 2.4 g (89%) of **37** as a yellow syrup. An analytical sample (200 mg) was purified by column chromatography over 20 g of silica gel using solvent E: R_f 0.26 (E); IR (CCl_4) 690 (m), 930 (m), 1020 (m), 1100 (s), 1160 (s), 1350 (m), 1440 (m), 1725 (s), 2910 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{36}H_{42}O_7 \cdot 0.5\ H_2O$: C, 72.58; H, 7.28. Found: C, 72.46; H, 6.97.

3,4,6-Tri-O-benzyl-1,2-O-cyclohexylidene-neo-inositol (38). To a solution of 2.2 g (3.8 mmol) of **37** in 50 mL of methanol was added 6 mL of 1 M aqueous sodium hydroxide. The mixture was stirred at room temperature for 5 h, at the end of which time TLC (E) showed that hydrolysis was complete. The methanol was evaporated to give a yellow syrup to which 250 mL of dichloromethane was added, and the solution was washed with two, 100-mL portions of water and dried over magnesium sulfate. The solvent was evaporated to give a syrup which was purified by column chromatography over 80 g of silica gel using solvent E to give a homogenous, syrupy product that was crystallized from ether - petroleum ether to provide 1.8 g (89%) of colorless crystals of pure **38**: mp 87 - 89 °C; R_f 0.63 (D); IR (KBr) 700 (m), 780 (m), 1020 (s), 1090

(s), 1120 (s), 1255 (m), 1355 (m), 1390 (m), 2900 (m), 3300 (sb) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{33}H_{38}O_6$: C, 74.69; H, 7.22. Found: C, 74.74; H, 7.22.

3,4,6-Tri-O-benzyl-5-chloro-1,2-O-cyclohexylidene-5-deoxy-myo-inositol (39). To a solution of 700 mg (1.3 mmol) of **38** in 50 mL of dry carbon tetrachloride was added 1.35 g (5.1 mmol) of triphenylphosphine. The mixture was heated under reflux for 24 h under dry conditions, at the end of which time 350 mg (5.1 mmol) of imidazole was added. The mixture was refluxed for an additional 12 h at which time TLC (F) showed that the reaction was complete. Evaporation of the solvent gave a syrup to which 100 mL of ethyl acetate was added. Some triphenylphosphine oxide precipitated as a white solid and was removed by filtration. The solution was washed with two, 50-mL portions of saturated aqueous sodium chloride and dried over magnesium sulfate. The solvent was evaporated to give a syrup which was purified by column chromatography over 80 g of silica gel using solvent F to provide 620 mg (86.7%) of pure **39** as a syrup: R_f 0.37 (F); IR (CCl_4) 690 (m), 910 (m), 925 (m), 1100 (s), 1200 (m), 1350 (m), 1450 (m), 2850 (m), 2920 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{33}H_{37}ClO_5$: C, 72.18; H, 6.79; Cl, 6.46. Found: C, 72.13; H, 6.82; Cl, 6.56.

3,4,6-Tri-O-benzyl-5-bromo-1,2-O-cyclohexylidene-5-deoxy-myo-inositol (40). By the same procedure used for **29**, 450 mg (0.85 mmol) of **38** was brominated using 0.13 mL (2.6 mmol) of bromine to give 400 mg (79.3%) of **40** as homogeneous syrup: R_f 0.49 (F); IR (CCl_4) 690 (m), 930 (m), 1100 (s), 1350 (m), 1450 (m), 2850 (m), 2930 (s) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_{33}H_{37}BrO_5$: C, 66.78; H, 6.28; Br, 13.46. Found: C, 66.92; H, 6.32; Br, 13.39.

5-Chloro-5-deoxy-myo-inositol (41). By the same procedure used for **31**, 550 mg (1.0 mmol) of **39** was deprotected to give 170 mg (85.4%) of **41** as a colorless crystalline solid: mp 230 - 232 °C; IR (KBr) 700 (m), 770 (m), 1030 (s), 1120 (s), 1260 (m), 1350 (m), 2900 (m), 3300 (sb) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_6H_{11}ClO_5$: C, 36.29; H, 5.58; Cl, 17.85. Found: C, 36.36; H, 5.58; Cl, 17.79.

5-Bromo-5-deoxy-myo-inositol (42). By the same procedure used for **31**, 350 mg (0.59 mmol) of **40** was deprotected to give 115 mg (80.4%) of **42** as colorless crystals: mp 228 - 230 °C; IR (KBr) 710 (m), 1030 (s), 1090 (m), 1120 (m), 1170 (m), 1260 (m), 1350 (m), 2900 (m), 3340 (sb) cm^{-1}. For ^1H NMR data, see Table 1. Anal. Calcd for $C_6H_{11}BrO_5$: C, 29.65; H, 4.56; Br, 32.88. Found: C, 29.60; H, 4.59; Br, 32.78.

1,2,3,4,6-Penta-O-acetyl-5-chloro-5-deoxy-myo-inositol (43). By the same procedure used for **22**, **41** was converted to the peracetate derivative **43**: mp 208 - 210 °C. For ^1H NMR data, see Table 1. MS: m/z (%) 374 (0.1, M - Cl), 373 (0.4, M - Cl), 168 (55.1, M - HCl - 2OAc - 2Ac), 43.1 (91.7, Ac).

1,2,3,4,6-Penta-O-acetyl-5-bromo-5-deoxy-myo-inositol (44). By the same procedure used for **22**, **42** was converted to the peracetate derivative **44**: mp 196 - 198 °C. For ^1H NMR data see Table 1. MS: m/z (%) 395 (0.1, M - OAc), 393 (0.1, M - OAc), 293 (0.5, M - 2OAc - Ac), 291 (0.5, M - 2OAc - Ac), 43 (42, Ac).

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