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GLYCOSYL-INOSITOL DERIVATIVES I. SYNTHESIS OF 1-SUBSTITUTED *CHIRO*-INOSITOL DERIVATIVES

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Abstract: A series of 1,2;4,5-di-O-isopropylidene and 1,2;4,5-di-O-cyclohexylidene *myo*-inositols were mono-triflated with trifluoromethanesulfonic anhydride. These compounds were subsequently inverted with a number of nucleophiles to provide the appropriate *chiro*-inositols.

A novel class of glycosyl phosphatidylinositol has recently been identified as membrane anchors for a variety of cell surface proteins.[1,2] Similar structures, or fragments released therefrom by the action of specific phospholipase, have been proposed for a group of putative insulin mediators (PIM).[3,4] To facilitate the elucidation of the structure-activity relationship of PIM, we have investigated synthetic approaches to glycosyl inositol derivatives.

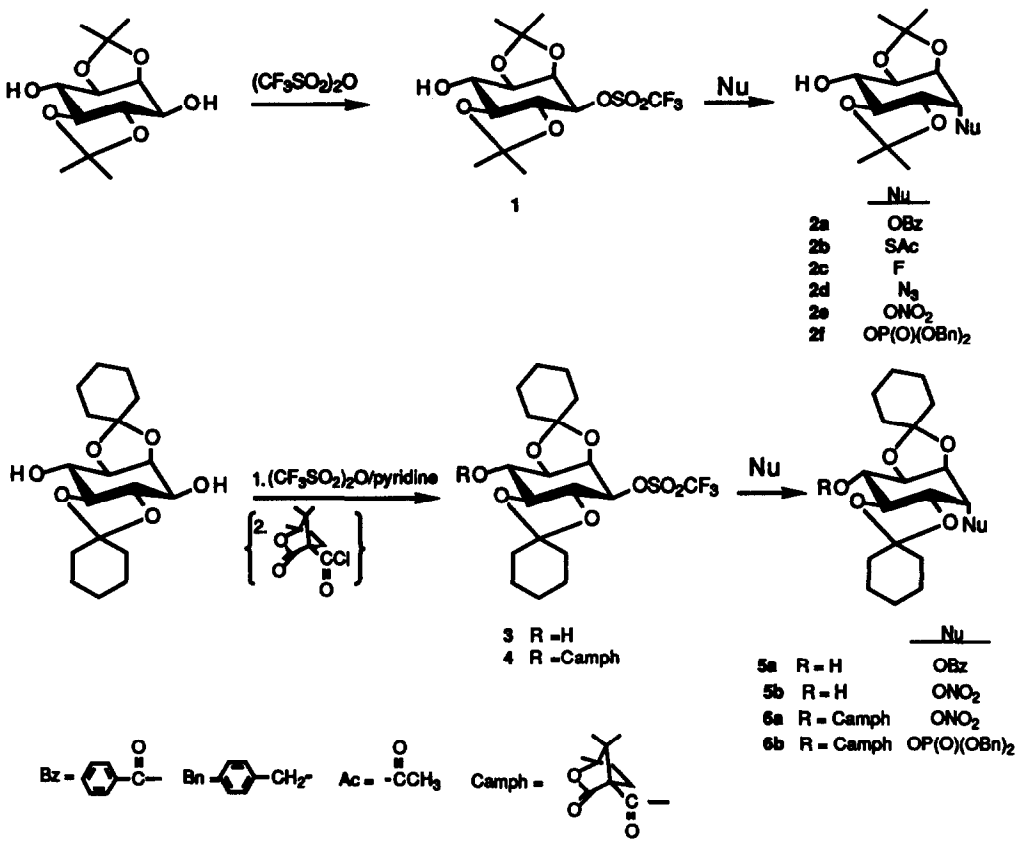
Most PIMs contain myo-inositol as a key component.[3,4] The identification of D-*chiro*-inositol as a constituent of a PIM from rat liver[5] has led us to investigate improved methods for the preparation of this rare inositol and its derivatives for incorporation into oligosaccharides related to PIM. Our primary goal is a selectively protected D-*chiro*-inositol with the 1 and 4 positions available for subsequent coupling reactions.† Since no convenient routes to such structures could be practically implemented starting from *chiro*-inositol or the naturally occurring pinitol, the nucleophilic inversion of suitably protected *myo*-inositol triflates was undertaken.

Cyclitol sulfonate inversions have been studied earlier,[6] but the use of *myo*-inositol triflates has yet to be thoroughly exploited. The fairly recent developments by Gigg[7] and Garegg[8] for the direct preparation of crystalline acetals of *myo*-inositol has allowed this triflate inversion chemistry to be applied to the synthesis of useful *chiro*-inositol intermediates. Of special interest to our work are the convenenient routes to acetals of *myo*-inositol with the 3 and 6 positions free. The greater reactivity of the 3 over the 6 position allowed us to selectively triflate and invert the 3 position without implementing elaborate blocking schemes.

† The 3 position of *myo*-inositol, when inverted, becomes the 1 position in the *chiro*-inositol numbering system.

Thus, the treatment of 1,2;4,5-di-O-isopropylidene *myo*-inositol with triflic anhydride and pyridine in methylene chloride at -40°C for 30 min. provided mono-

Schemes:



triflation on the 3 position in good yield (1). Longer reaction times and/or elevated temperatures produced significant amounts of the di-substituted product. The 1,2;4,5-di-O-cyclohexylidene *myo*-inositol could be similarily treated to also provide the mono-triflate in good yield (3).

These mono-triflates were reacted with a variety of nucleophiles in N,N-dimethylforamide (DMF) or benzene (PhH) to invert the 3 position of *myo*-inositol to

give the 1-substituted *chiro*-inositol derivative. Alkali metal and tetrabutylammonium salts were employed and provided very clean inversion products in good to excellent yields†† (Table 1).

An analogous series of reactions was carried out with the cyclohexylidene protected *myo*-inositols. Inversion with nitrate, however, proceded in very low yield with difficult product purification. Acylation of the 4-position of 3 with (1S)-(-)-camphanic acid chloride provided fully protected triflate (4) which gave clean inversion products in higher yield and in pure form. This methodology also gives ready access to resolved *chiro*-inositol derivatives.[9]

Table 1. Reaction of *myo*-inositol triflates with nucleophiles (RNu)[10].

Inositol	RNu	Solvent	Conditions	Product	m.p.	Yield
1	LiOBz	DMF	80°C/24h	2a	177-178°C	82%
1	KSAc	DMF	60°C/24h	2b	189-190°C	68%
1	$[CH_3(CH_2)_3]_4NF$	PhH	80°C/5h	2c	128-130°C	91%
1	NaN_3	DMF	50°C/7h	2d	119-120°C	80%
1	$[CH_3(CH_2)_3]_4NNO_3$	DMF	100°C/24h	2e	---	40%
1	$LiOP(O)(OBn)_2$	DMF	80°C/36h	2f	146-148°C	35%
3	LiOBz	DMF	80°C/24h	5a	176-177°C	87%
3	$[CH_3(CH_2)_3]_4NNO_3$	DMF	100°C/24h	5b	---	15%
4	$LiOP(O)(OBn)_2$	DMF	100°C/16h	6a	---	30%
4	$[CH_3(CH_2)_3]_4NNO_3$	DMF	100°C/24h	6b	---	70%

The C1 hydroxyl group of D-*chiro*-inositol in membrane anchors carries a phosphate linkage. In view of the biological importance of inositol phophates in general, the direct preparation of *chiro*-inositol phosphate from the *myo*-inositol 3-O-triflate was also investigated. A variety of reagents, including n-butyl-lithium, lithium wire and triethyamine, were employed for the generating the anion of dibenzyl phosphate as a nucleophile. The expected inversion was achieved, but in all cases the yields were no greater than 35%.

In summary, a convenenient method for the synthesis of various 1-substituted *chiro*-inositol derivatives has been developed. The incorporation of these partially protected *chiro*-inositols into structures related to PIM will be reported in subsequent communications.

†† All new compounds were characterized by ^1H NMR, mass spectrometry and elemental analysis.

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10. 300MHz ^{1}H NMR data for compounds 1-2f (chemical shifts in ppm, coupling constants in Hz):
1: 5.07, dd, 1H, (H-3, J_{32}=5.6, J_{34}=10.6), 3.93, m, 1H, (H-6, J_{16}=7.1, J_{56}=10.6).
2a: 5.94, bs, 1H, (H-1, J_{16}=.5), 4.13-3.93, m, 3H, (H-4, H-5, H-6).
2b: 4.55, dd, 1H, (H-1, J_{16}=1.5, J_{12}=4.6), 3.87, m, 1H, (H-4, J_{43}=10.1, J_{45}=6.6).
2c: 5.20, dt, 1H, (H-1, J_{HF}=49.4, J_{12}=2.0).
2d: 4.44, t, 1H, (H-1, J_{12}=1.8), 3.83, m,1H, (H-4, J_{43}=5.6).
2e: 5.79, bs, 1H, (H-1).
2f: 5.18-5.05, m, 5H, (H-1, 4 benzylic protons), 3.84-3.78, m, 3H, (H-4, H-5, H-6).

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