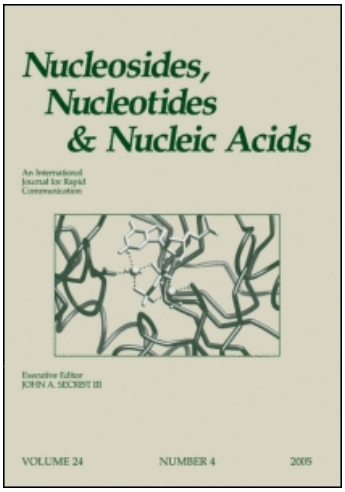

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Nucleocyclitols. Coupling of Heterocyclic Bases to Cyclitol Oxiranes

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NUCLEOCYCLITOLS. COUPLING OF HETEROCYCLIC BASES TO CYCLITOL OXIRANES.

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Abstract. Several nucleocyclitols were synthesized in good yield from an inositol epoxide and some activated purine derivatives (adenine, 6-methylmercaptopurine). The reaction was also carried out with other more basic, nitrogen heterocycles such as imidazole and piperidine, although side reactions can then became significant.

INTRODUCTION

The general term nucleocyclitol was suggested[1] for compounds obtained by condensation of a purine with an inositol, which structurally differ from nucleosides by the absence of a glycosilic bond in the molecule. This term could be applied to carbocyclic nucleoside analogs possessing a heterocyclic base linked to a cyclitol, a type of structure which shows greater stability to hydrolytic agents than nucleosides. Carbocyclic structures with cyclopentane- or cyclopentenediol rings attached to purines and pyrimidines have shown antitumor,[2,4b] antimicrobial,[3,4a] and antiviral[4a,b] properties, giving incentives to the search of new perspectives in this field.

Previously[1] we described the synthesis of 3-(adenin-9-yl)-3-deoxy-1,5,6-tri-O-(methanesulfonyl)-muco-inositol (2), a nucleocyclitol that showed cytokinin-like activity on vegetal cells[5] and immunosupressive action on animal cells.[6] This synthesis was achieved by nucleophilic attack and concomitant mesyl group displacement by sodium adenylate upon 2,3-di-O-acetyl-1,4,5,6-tetra-O-(methanesulfonyl)-myo-

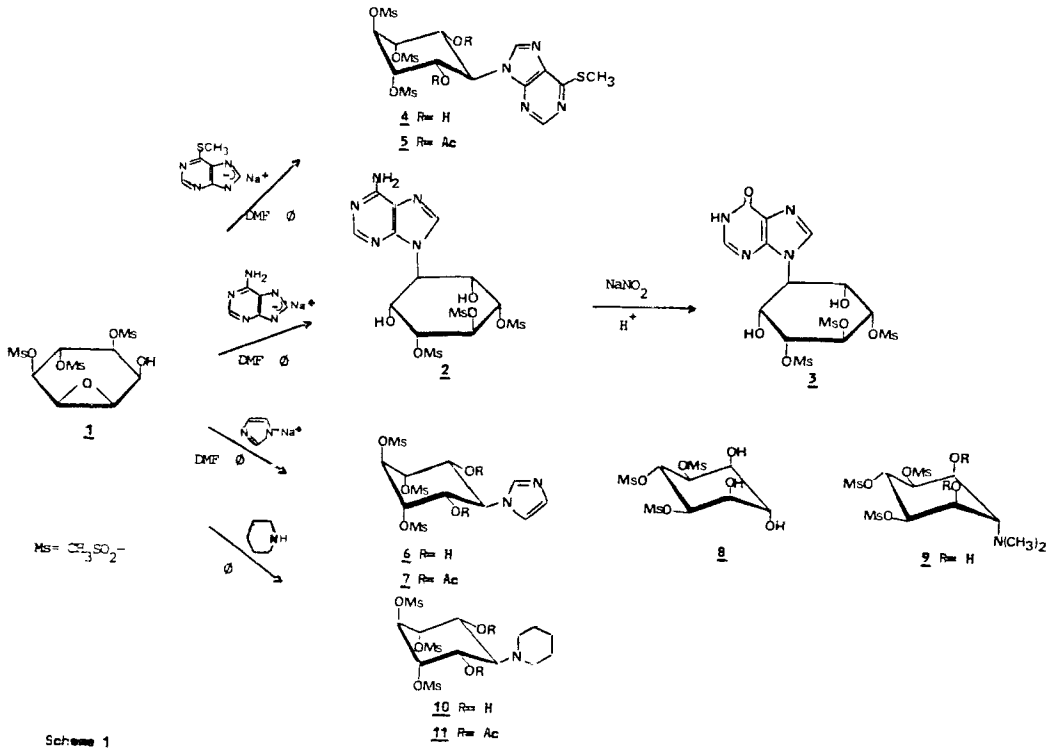
inositol. This reaction was explained through the anchimeric assistance of an acetoxy group neighboring a trans mesyloxy group. Here we describe a procedure to synthesize nucleocyclitols starting from an inositol possessing an oxirane structure, which is opened by a heterocyclic, activated base leading to coupled product. In general, this reaction can be conducted under milder conditions than that mesylate displacement[1] and the products are usually readily isolable.

RESULTS AND DISCUSSION

The coupling of 6-methylmercaptopurine with a sugar epoxide and with cyclohexene oxide have been reported to give low yields,[7a] and recently, the linking of some cyclopentene oxide derivatives with pyrimidine and purine compounds has been briefly reported.[7b] In the particular case of employing 1,2-anhydro sugars the synthesis of pyrimidine nucleosides was achieved in good yields.[8]

We reacted sodium adenylate with 2,3-anhydro-1,5,6-tri-O-(methanesulfonyl)-epi-inositol[9] (1, Scheme 1), and 2 was isolated in good yield (61%) requiring shorter reaction time and lower temperature of reaction than that required in the previously reported synthesis of 2.[1] Nitrous acid converted compound 2 into 3-(hypoxantin-9-yl)-3-deoxy-1,5,6-tri-O-(methanesulfonyl)-muco-inositol (3) in 80% yield.

The same reaction when performed with 6-mercaptopurine was very complex and lead to a dark, intractable residue. The reaction with 6-methylmercaptopurine was much cleaner and gave the corresponding nucleocyclitol 4 in 69% yield. The structure and conformation of this compound were supported by the following data: the ^{1}H NMR spectrum showed the protons of the purine nucleus (δ 8.60 and 8.64 for C-2, C-8, and 2.62 for the CH_3S group); the inositol moiety showed three mesyl groups (δ 3.54), a multiplet (δ 5.60-6.08) for five protons of the ring, and an isolated triplet at δ 5.43 for H-3' on the carbon atom linked to the base, with $J_{2',3'}=J_{3',4'}=$ 11 Hz. This value indicates the trans-diaxial relationship of that proton with its neighbors and, consequently, the equatorial orientation of the purine ring as depicted for 4 in Scheme 1. These conformational features were supported by the spectrum of its diacetate 5 which showed the signals



Scheme 1

for the C-1' and C-5' acetyl-groups at δ 1.95, a value in agreement with the resonance observed in many compounds[10,1] for equatorial acetyl groups. The coupling of the base to C-3' and not to C-4' in 4 is confirmed by the appearance of the resonances for the acetyl-groups in the diacetate 5 superimposed as a six-proton singlet and the resonances for H-1' and H-5' also superimposed as a double doublet (δ 7.02); likewise, two mesyl groups appeared as a six-proton singlet at δ 3.65 and the third at δ 3.57. These features are consistent with the proposed, symmetrical structure.

The point of attachment of C-3' to the purine ring in 4 cannot be ascertained on the basis of the UV spectrum, since the data observed (λ_{max} 282 and 289) are outside the ranges that allow an unambiguous assignment.[11] On the other hand, a ^{13}C NMR method has been developed to assign the glycosylation site in nitrogenated heterocycles.[12] According to this method, when the free electron pair on N^9 or N^7 of the anionic form of the heterocycle is glycosylated, an upfield shift for the

carbon atom α to the glycosylated nitrogen occurs and a downfield shift for the β- and γ-carbon atoms is observed, when compared with the base anion.

These "substitution parameters" found for N-glycosides[12] were previously investigated[1] for the inositol base attachment in 2 and found consistent with the results observed in nucleosides. To ascertain the type of substitution in 4, the chemical shifts of the purine nucleus in this compound were compared with those of the anion of 6-methylmercaptopurine obtained by treatment of this substance with lithium hydroxide in Me_2SO-d_6 (see Table 1). Working on the assumption of attachment at N^9, C-4 and C-8 are α to the presumably substitued nitrogen atom (N^9) whereas C-5 and C-6 are β- and γ-disposed, respectively. Large upfield shifts are observed for C-4 (+9.88 ppm) and C-8 (+6.18 ppm), and a downfield shift is observed for C-6 (-11.8 ppm), confirming the postulated attachment. The small upfield shift for C-5 constitutes an exception to the rule when a bridgehead carbon atom is under consideration.[12]

The structural aspects discussed above on the basis of ^1H NMR data for the inositol ring appear confirmed by ^{13}C NMR data for this moiety (Table 1). The two symmetrically mesylated carbon atoms (C-1' and C-5') and the two hydroxylated ones (C-2' and C-4') resonate as two separated, double intensity singlets at δ 77.3 and 64.3 ppm, respectively. The known, upfield shift provoked by a nitrogenated substituent allow the two remaining resonances to be assigned to C-6' and C-3'. The resonances of the purine nucleus showed an identical pattern to that of related compounds.[13]

The mass spectrum of 5 showed only structural changes produced by elimination of sulfonic- and acetyl-groups. The parent ion (m/z 646) appeared in 100% intensity, and the second peak in importance was that of m/z 413, attributable to the loss of methanesulfonic anhydride and one acetoxyl group. The rupture between the inositol and the base was accompanied by transfer of hydrogen to the base, giving the sequence m/z 165 (21.5%, ion 6-methylmercaptopurynyl), m/z 166 (28.0%, base + H), and m/z 167 (32.6%, base + 2 H).[14]

The simplicity of procedure of the above synthesis seems dependent, however, on the nature of the heterocyclic base.

Table I

^{13}C NMR chemical shifts for 6-methylmercaptopurinyl anion and for compounds 4, 6, and 10

Compound	Chemical shifts[a]										
	C-2	C-4	C-5	C-6	C-8	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
6-Methylmercapto-purinyl anion (I)	147.6	157.9	132.5	147.6	152.7						
4	150.7	148.3	131.1	159.4	145.5	77.3	64.3	57.9	64.3	77.3	73.7
$\Delta\delta$ I-4	-3.1	+9.6	+1.3	-11.8	+7.2						
6	128.2	121.8	138.3			77.9	66.7	58.2	66.7	77.9	73.7
10[b]	50.7	24.5				78.5	67.2	64.0	67.2	78.5	74.8

[a] Shifts given in ppm downfield from Me_4Si, for solutions in Me_2SO-d_6

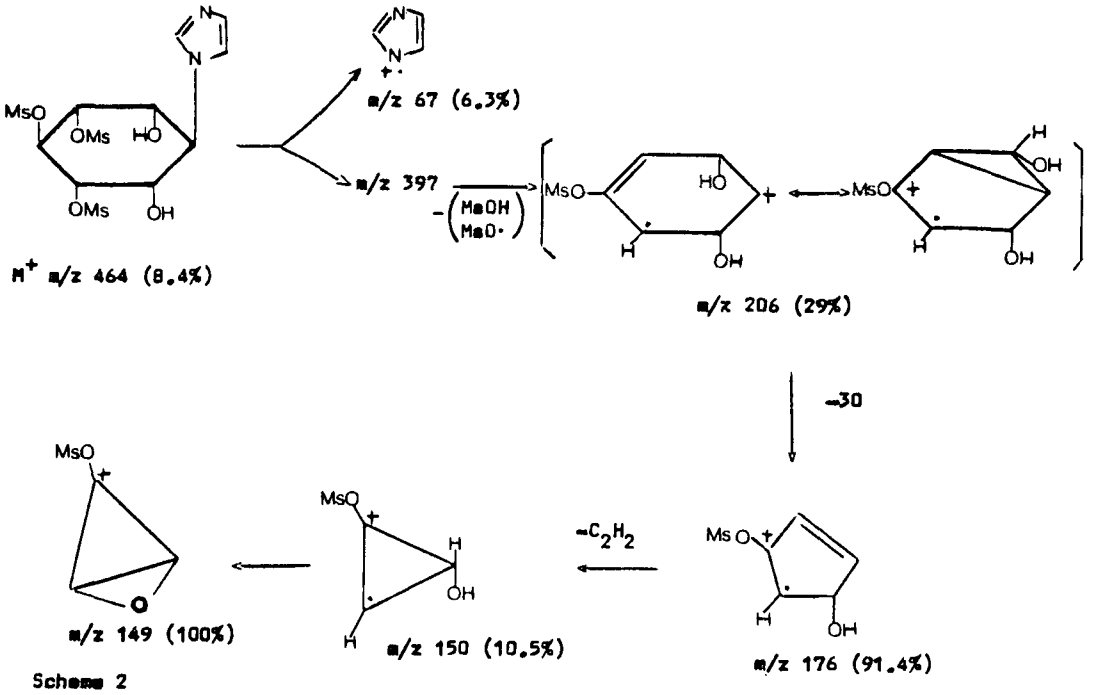
[b] δ 26.2 for C-3.

When this reaction was conducted with imidazole a complex reaction mixture with extensive darkening, from which three products could be isolated after chromatographic separation, was obtained. 3-(Imidazo-1-yl)-3-deoxy-1,5,6-tri-O-(methanesulfonyl)-muco-inositol (6) was obtained in a modest yield (19%), and, in spite of the mild conditions of the reaction, the hydrolytic opening of the oxirane ring also occurred to give 1,5,6-tri-O-(methylsulfonyl)-muco-inositol (8, 30% yield). Attack of imidazole on DMF liberated small amounts of dimethyl amine which acted as a nucleophile against 1 to give 3-dimethylamino-3-deoxy-1,5,6-tri-O-(methanesulfonyl)-muco-inositol (9, 13% yield), as a byproduct. Compounds 8[1,15] and 9[16] have been previously obtained and their structures and conformations determined.

The structure and conformation of imidazole derivative 6 could be ascertained from the ^{1}H NMR spectrum of its diacetate (7), which showed two acetyl groups superimposed as a six-proton singlet at δ 1.88. This value corresponded[10] to two acetyl-groups equatorially oriented in a symmetrical environment, as shown in the conformation depicted for 6 (Scheme 1) with the bulky imidazole ring in an equatorial orientation. Correspondingly, the high-field inositol proton at the insertion point of this base (H-6', δ 4.74) showed a triplet $J_{1',6'}=J_{5',6'}=12$ Hz indicating its transdiaxial relationship with the neighboring H-1' and H-5'. These two protons, in turn, appeared superimposed as a pair of doublets with spacings of 12 Hz and 3 Hz, indicating their symmetrical environment and its gauche relationship with H-2' and H-4'.

The ^{13}C NMR spectrum of 6 showed a similar pattern as 4 in the inositol portion, with two double-intensity peaks corresponding to C-1', C-5' (δ 77.9 ppm) and C-2', C-4' (66.7 ppm), and two single intensity peaks for C-6' (73.7 ppm) and C-3' (58.2 ppm), which support the insertion of the base at the C-3 of the inositol epoxide 1.

The mass spectrum of 6 showed important peaks corresponding to the splitting of CH_3-SO_3H (57.5%), and $CH_3SO_2^+$ (81.9%). Cleavage of the C-N inositol-base bond is accompanied by transfer of hydrogen, to yield base + H (m/z 68, 15.1%) and base + 2 H (m/z 69, 61.1%).[14] The main pathway of fragmentation of the inositol ring can be interpreted as depicted in Scheme 2.



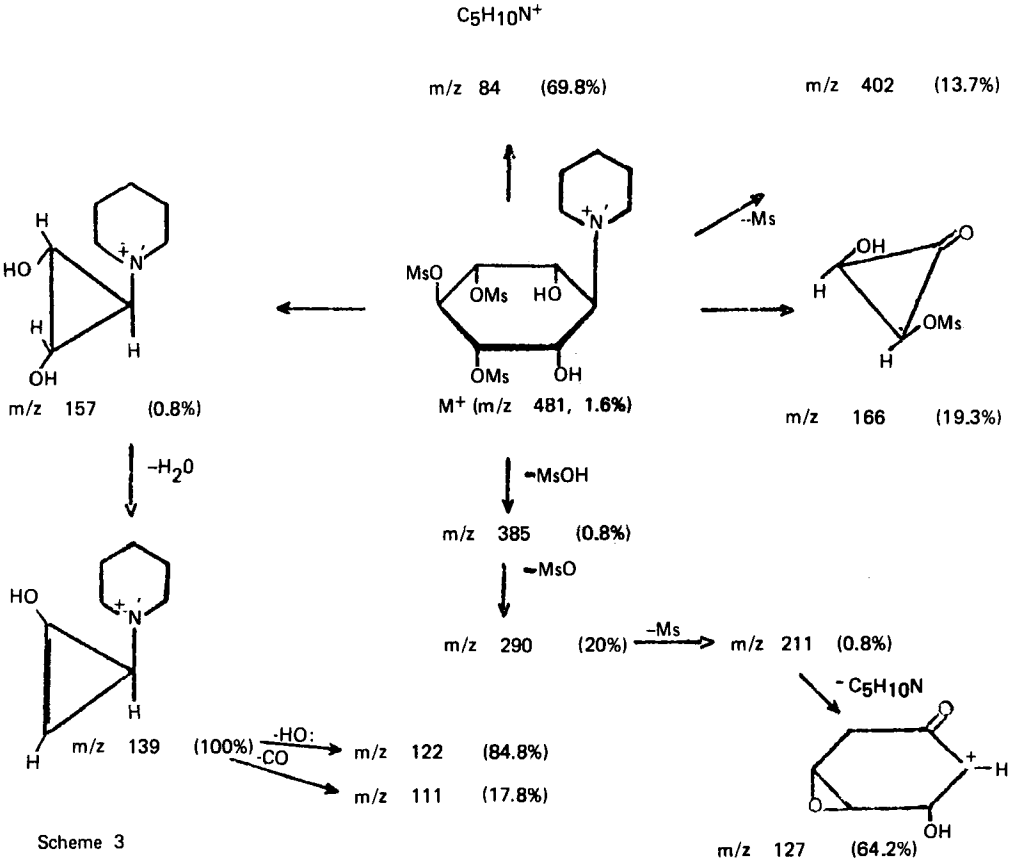
Scheme 2

A coupling, analogous to that conducted for the compounds described above was performed employing piperidine as both the nucleophile and solvent. In this case, this molecule was active enough for coupling, its prior conversion to the sodium salt being unnecessary. After refluxing for 4 h the piperidinyl derivative 10 was obtained in 67% yield. Other products of reaction could not be separated after column chromatography of the dark residue of the reaction.

Compound 10 showed similar structure and conformation as the nucleocyclitols already described, which was evidenced by the general features of the ^{1}H NMR spectrum of its diacetate 11. The two acetyl substituents resonate as a singlet at δ 2.08, which indicate[10] their equatorial orientation in a symmetrical environment. This is supported by the splitting of the H-3' resonance at high field (δ 3.00 ppm) with $J_{2',3'}=J_{3',4'}=8$ Hz, showing the trans-diaxial relationship of the corresponding protons and the equatorial disposition of the piperidinyl group. Two mesyl groups superimposed

as a singlet (O-1' and O-5' mesyl groups) and the third as an isolated singlet, showed its symmetrical arrangement. ^{13}C NMR data of 10 also support this view (see Table 1).

The mass spectrum of 10 showed the molecular ion (m/z 481, 1.6%) and a group of ions of high intensity as depicted in Scheme 3, which show the particular tendence of inositols to afford three-carbon fragments on electron impact.[17]



Scheme 3

EXPERIMENTAL

Melting points (Koffler hot-stage) are uncorrected. TLC was conducted on silica gel G (Merck) plates (0.25 mm layer thickness) with the following solvents: A) 1:4 (v/v) absolute ethanol-benzene, B) 3:7 (v/v) absolute ethanol-benzene, and

C) 1:9 (v/v) absolute ethanol-benzene. The spots were detected with 1) iodine vapor, 2) sodium iodide-1-butanol for epoxides.[18] NMR spectra were recorded at 20-25°C with a Varian XL-100 spectrophotometer at 100 (^{1}H) and 25.2 (^{13}C) MHz with Me_4Si as the internal reference standard. Mass spectra were recorded with a Varian-Mat data system 166 computer at in ionizing potential of 70 eV; (the temperature of the direct-insertion probe was 170°C).

3-(Adenin-9-yl)-3-deoxy-1,5,6-tri-O-(methanesulfonyl)-muco-inositol (2).- Sodium hydride (from a 50% oil dispersion) was rinsed with light petroleum and dried under diminished pressure. This powder (555 mg, 23 mmol) was suspended in dried $HCONMe_2$ (160 mL) and adenine (2.64 g, 19.5 mmol) was added. The suspension was stirred for 1 h at 50°C and compound 1 (4 g, 10 mmol) was added, and the mixture was stirred for 2.5 h at 70°C. The dark mixture finally obtained was cooled and filtered, and the filtrate was poured into ice-water. The solid obtained (3.25 g, 60.6% yield), recrystallized from water gave mp 248-250°C. Lit.[1] 248-250°C.

3-(Hypoxanthin-9-yl)-3-deoxy-1,5,6-tri-O-(methanesulfonyl)-muco-inositol (3).- Compound 2 (268 mg, 0.5 mmol) was suspended in water (10 mL) containing acetic acid (2 mL); sodium nitrite (138 mg, 2 mmol) was added in portions, and the suspension, shaken occasionaly, was kept at room temperature for 60 h. As only partial dissolution was observed the suspension was gently warmed and a further amount of sodium nitrite (100 mg, (1.4 mmol) was added. This was followed by evolution of nitrogen oxide vapours and total dissolution. By cooling, compound 3 was obtained (216 mg, 80.6%) as plates of mp 250-251°C, λ_{max} 259 nm (ε_{mM} 12.1); ν_{max}^{nujol} 3340 (OH), 1675 (CO), 1320 and 1140 cm^{-1} (sulfonyl group); ^{1}H NMR data (Me_2SO-d_6): δ 3.30, 3.36, 3.45 (s, 9H, CH_3SO_2), 4.54-4.74 (m, H-3'), 5.00-5.22 (m, 3H, H-1', H-5', H-6'), 5.70-6.00 (m, 2H, H-2', H-4'), 8.08 and 8.20 (s, purine ring protons), 12.11 (NH). Anal. Calc. for $C_{14}H_{20}N_4O_{12}S_3$: C, 31.57; H, 3.79; N, 10.52; S, 18.06. Found: C, 31.54; H, 4.00; N, 10.25; S, 17.92.

3-(6-Methylmercaptopurin-9-yl)-3-deoxy-1,5,6-tri-O-(methanesulfonyl)-muco-inositol (4).- Sodium hydride, prepared as described for the synthesis of compound 2 (70 mg, 2.9 mmol), was suspended in $HCONMe_2$ (8 mL), and 6-methylmer-

captopurine[19] (419 mg, 2.5 mmol) was added. The suspension was stirred for 1 h at 52°C and the epoxide 1 (500 mg, 1.2 mmol) was added. This suspension was stirred for 9 h at 100-110°C until compound 1 was not detected on TLC (solvent B, reagent 2). Then the solvent was evaporated and the residue was dried and extracted with hot ethyl acetate. An insoluble residue (292 mg) was discarded, and the ethyl acetate solution gave several crops (488 mg, 68.9% yield) of 4 as an amorphous solid R_F 0.27 (solvent B, reagent 1), mp 249-251 °C; λ_{max}^{EtOH} 282 (ε_{mM} 16.6), 289 (ε_{mM} 13.9); ^{1}H NMR data (C_5D_5N): δ 2.62 (s, CH_3S), 3.54 (s, 9H, CH_3SO_2), 5.43 (1H, H-3', $J_{2',3'}=J_{3',4'}=11$ Hz), 5.60-6.08 (5H, ring protons), 8.60, 8.64 (2H, purine protons); ^{13}C NMR data (Me_2SO-d_6): see Table 1. Anal. Calc. for $C_{15}H_{22}N_4O_{11}S_4$: C, 32.02; H, 3.94; N, 9.96; S, 22.79. Found: C, 32.25; H, 3.74; N, 9.96; S, 22.88.

1,5-Di-O-acetyl-6-(6-methylmercaptopurin-9-yl)-6-deoxy-2,3,4-tri-O-(methanesulfonyl)-muco-inositol (5).- Compound 4 (100 mg, 0.18 mmol) was dissolved in a 1:1 mixture of acetic anhydride-pyridine (3 mL) and kept at room temperature for four days. The solution was evaporated, and the dried residue (109 mg, 94.5% yield), was recrystallized from methanol to give mp 246-248°C; TLC R_F 0.26 (solvent C, reagent 1). ^{1}H NMR data (C_5D_5N): δ 1.95 (s, 6H, acetyl groups), 2.71 (s, 3H, SCH_3), 3.52 (s, 3H, CH_3SO_2), 3.65 (s, 6H, CH_3SO_2), 6.02 (t, H-6', $J_{1',6'}=J_{5',6'}=12$ Hz), 6.10-6.32 (m, 3H, H-2', H-3', H-4'), 7.02 (dd, 2H, H-1', H-5'), 8.84 and 8.91 (s, 2H, H-2, H-8); ^{13}C NMR data (Me_2SO-d_6): see Table 1; m/z (intensity, as per cent of base peak, and then assignments): 646 (100, M^+), 567 (5.0, $M^+ - CH_3SO_2$), 472 (1.2, $M^+ - (CH_3SO_2)_2O$), 413 (26.4, $M^+ - (CH_3SO_2)_2 - CH_3CO_2$), 167 (32.6, 6-methylmercaptopurinyl group + 2H).[14] Anal. Calc. for $C_{19}H_{26}N_4O_{13}S_4$: C, 35.29; H, 4.05; N, 8.66; S, 19.83. Found: C, 35.36; H, 4.17; N, 8.79; S, 19.45.

Reaction of imidazolyl-sodium with epoxide 1.- A mixture of dried sodium hydride (180 mg, 1 mmol), imidazole (600 mg, 1.2 mmol) in $HCONMe_2$ (60 mL) was heated at 55°C for 1 h with magnetic stirring. Then the epoxide 1 (3 g, 1 mmol) was added, and the mixture was heated at 70°C; for 2.5 h. The dark sol-

ution was evaporated to dryness, and the residue was chromatographed on a column on silica gel (500 x 27 mm). Elution from the column was conducted with increasing concentrations of absolute ethanol in benzene. Using 5-6% of ethanol compound 9 was isolated (428 mg, 12.8% yield): mp and mixed mp with an synthetic sample[16] gave 176-178°C; TLC R_F 0.53 (solvent A, reagent 1); ^{1}H NMR data (C_5D_5N): δ 6.05 (t, H-6', $J_{5',6'}=J_{6',1'}=9$ Hz), 5.39 (dd, H-1', H-5'), 5.05 (H-2', H-4'), 3.55 (9H, CH_3SO_2), 2.97 (t, H-3', $J_{2',3'}=J_{3',4'}=3$ Hz), 2.25 (6H, Me_2N-).

Elution from 7 to 45% of absolute ethanol afforded compound 8 (993 mg, 30% yield): mp and mixed mp[1,15] 182-184°C, TLC R_F 0.44 (solvent A, reagent 1). Finally, elution with 60-70% of absolute ethanol afforded 3-(imidazol-1-yl)-3-deoxy-1,5,6-tri-O-(methanesulfonyl)-muco-inositol 6, which recrystallized from water to give mp 224-225°C (548 mg, 18.5% yield); TLC R_F 0.22 (solvent B, reagent 1); ^{1}H NMR data (Me_2SO-d_6): δ 7.92 (s, H-2), 7.50 (s, H-5), 7.05 (s, H-4), 5.82 (H-2', H-4'), 5.16-5.04 (H-1', H-5', H-6'), 4.22 (H-3', $2HO^-$), 3.45 (s, 3H, CH_3SO_2), 3.32 (s, 6H, 2 CH_3SO_2); ^{13}C NMR data (Me_2SO-d_6): δ 138.3 (C-5), 128.2 (C-2), 118.1 (C-1), 77.9 (C-1', C-5'), 73.7 (C-6'), 66.7 (C-2', C-4'), 58.2 (C-3'). Mass spectrum: see Scheme 2. Anal. Calc. $C_{12}H_{20}N_2O_{11}S_3$: C, 31.03; H, 4.34; N, 6.03; S, 20.71. Found: C, 30.62; H, 4.64; N, 5.98; S, 20.30.

1,5-Di-O-acetyl-6-(imidazol-1-yl)-6-deoxy-2,3,4-tri-O-(methanesulfonyl)-muco-inositol (7).- Compound 6 (105 mg, 0.22 mmol) was dissolved in pyridine-acetic anhydride (1:1, 2 mL), then kept at room temperature 24 h, and evaporated to dryness. The residue, crystallized from acetone-water, gave mp 122-124°C; TLC R_F 0.53 (solvent B); ^{1}H NMR data (Me_2SO-d_6): δ 7.88 (s, H-2), 7.48 (s, H-5), 6.90 (s, H-4), 5.68 (dd, H-1', H-5'), 5.30 (m, H-2', H-3', H-4'), 4.74 (t, H-6', $J_{5',6'}=J_{6',1'}=12$ Hz), 3.52-3.40 (9H, 3 CH_3SO_2), 1.88 (s, 6H, 2 CH_3CO). Anal. Calc. for $C_{16}H_{24}N_2O_{13}S_3$: C, 35.03; H, 4.41; N, 5.11; S, 17.54. Found: C, 34.76; H, 4.64; N, 5.52; S, 17.15.

3-(Piperidin-1-yl)-3-deoxy-1,5,6-tri-O-(methanesulfonyl)-muco-inositol (10).- The epoxide 1 (500 mg, 1.26 mmol) was dissolved in distilled piperidine (10 mL), the solution was

refluxed 4 h, and then evaporated to dryness. The dried residue was dissolved in benzene, and precipitation with light petroleum (bp 60-80°C) gave crude 10 (356 mg). Concentration of the filtrate and further precipitation with light petroleum gave a second crop (53 mg). Recrystallization from ethanol gave mp 193-195°C (yield 67%); TLC R_F 0.32 (solvent C); ^1H NMR data (C_5D_5N): δ 6.02 (t, H-6', $J_{1',6'}=J_{5',6'}=7$ Hz), 5.52 (H-1', H-5'), 4.94 (H-2', H-4'), 3.20 (t, H-3', $J_{2',3'}=J_{3',4'}=$ 5 Hz), 3.52 (9H, 3 CH_3SO_2), 2.65 (4H, 2 CH_2), 1.40 (6H, 3 CH_2); ^{13}C NMR data (Me_2SO-d_6): δ 78.5 (C-1', C-5'), 67.2 (C-2', C-4'), 74.8 (C-6'), 64.0 (C-3'), 50.7 (C-2), 26.2 (C-3), 24.5 (C-4). Anal. Calc. for $C_{14}H_{27}NO_{11}S_3$: C, 34.92; H, 5.65; N, 2.91; S, 19.98. Found: C, 35.22; H, 5.54; N, 3.03; S, 19.71.

1,5-Di-O-acetyl-6-(piperidin-1-yl)-6-deoxy-2,3,4-tri-O-(methanesulfonyl)-muco-inositol (11).- Complete acetylation only could be achieved under drastic conditions. A mixture of compound 10 (70 mg, 0.15 mmol), anhydrous sodium acetate (40 mg, 0.61 mmol), and acetic anhydride (4 mL) was refluxed for 1 h and then poured into ice-water. The solid obtained (54 mg), when recrystallized from ethanol-acetone gave mp 183-185°C; TLC R_F 0.59 (solvent C, reagent 1); ^1H NMR data (Me_2SO-d_6): δ 5.26-5.11 (m, 5H, inositol ring), 3.40 (3H, CH_3SO_2), 3.30 (6H, 2 CH_3SO_2), 3.00 (t, H-6'), 2.60 (4H, 2 CH_2), 2.08 (s, 6H, 2 CH_3CO), 1.35 (s, 6H, 3 CH_2). Anal.Calc. for $C_{18}H_{31}NO_{13}S_3$: C, 38.22; H, 5.52; N, 2.48; S, 17.01. Found: C, 38.47; H, 5.25; N, 2.35; S, 16.69.

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