A General Synthesis of Cyclitols and Aminocyclitols from Carbohydrates

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In connection with our research program on mutasynthesis and total chemical synthesis[1] in the aminoglycoside field, we required a variety of chiral cyclitols and aminocyclitols. Among the numerous methods reported for the conversion of carbohydrates into cyclitols[2], the transformation of 6-deoxy-hex-5-enopyranosides into 2-deoxy-inososes[3], induced by mercury(II) salts in aqueous media, appeared the most appropriate. This ring opening-ring closure process, which mimics the D-glucose transformation proposed for the biosynthetic pathway of 2-deoxy-streptamine[4], leads to a highly reactive β-ketol system with the formation of only one new *chiral* center.

For our purpose, methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-*xylo*-hex-5-enopyranoside **(2a)** was selected as the ideal carbohydrate precursor. Thus, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **(1a)**[5] was transformed according to Garegg's method[6] into the corresponding iodo-derivative **1b** which, on treatment with silver fluoride in pyridine, gave the required olefin **2a.** Having in hand the alkene **2a,** we examined its behaviour towards mercury(II) chloride in aqueous acetone. In contrast to a very recent literature report[7], the Ferrier's carbocyclic ring closure[3] of the perbenzylated hex-5-enopyranoside **2a,** was not stereospecific: a 3:1 mixture of two epimeric cyclohexanones **3a** and **4a** was formed in 80% yield. These latter two intermediates and their readily derived α,β-unsaturated derivative **5** can be considered as versatile synthons for our present purpose and also, as *chiral* precursors for a variety of natural product syntheses. We therefore, looked for a new alternative scheme better adapted to large-scale preparation.

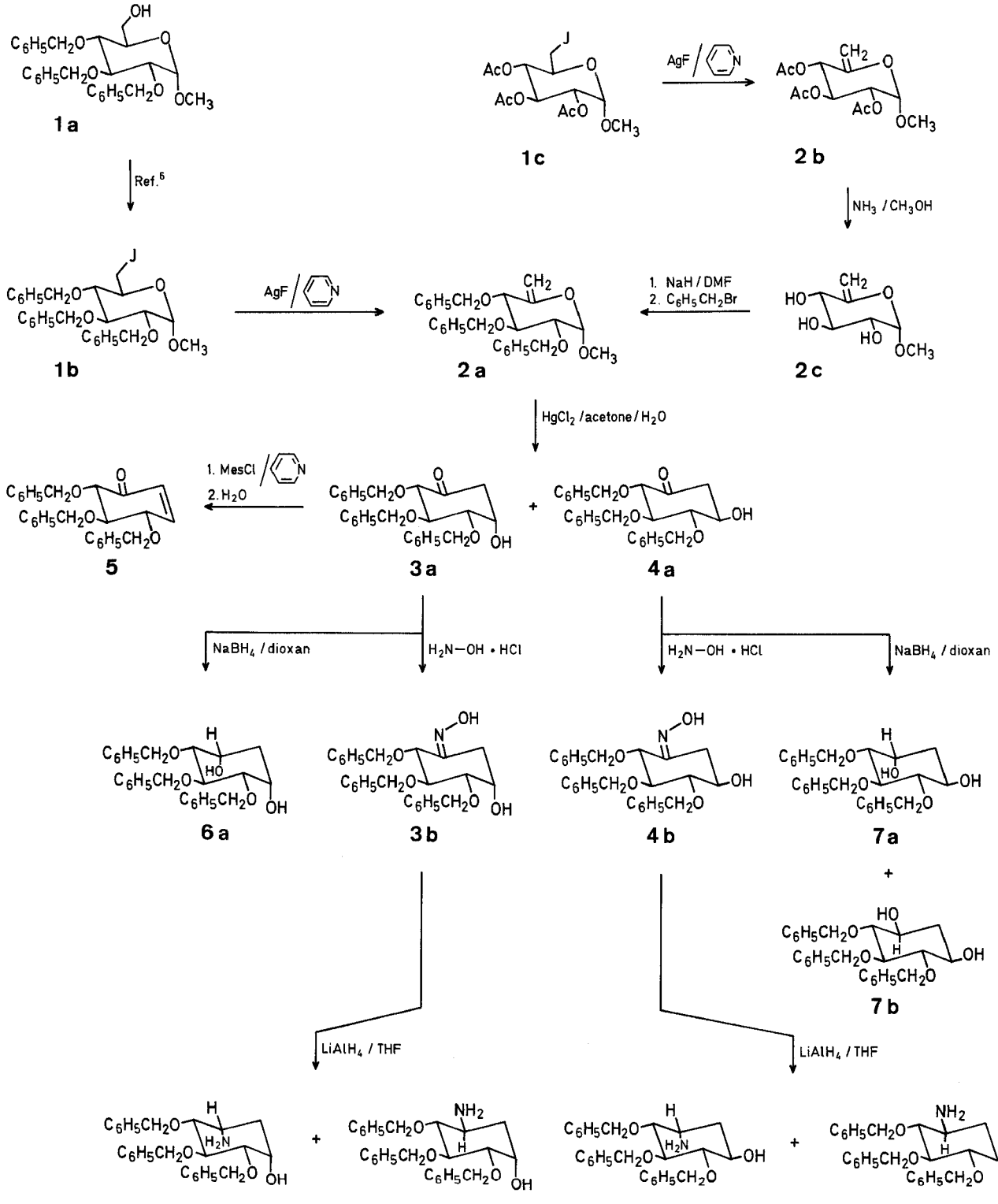
The second approach uses methyl α-D-glucopyranoside as starting material. The latter was converted in 80% yield into its crystalline iodo-peracetate **1c,** using a slightly modified version of Garegg's procedure[6]. The elimination of hydroiodic acid was realized as described previously, providing **2b**[8]. Deacetylation followed by perbenzylation led to the target **2a.** This straightforward method, described here, was achieved in 46% overall yield.

Having at our disposal, the ketols **3a** and **4a** as well as their readily accessible oximes **3b** and **4b,** the stage was thus set for their transformation into cyclitols and aminocyclitols. Reduction of **3a** with sodium borohydride in dioxan, gave almost exclusively the *meso*-cyclohexane-pentol **6a,** whereas the treatment of **4a** under identical conditions led to a 1:1 mixture of cyclohexane-pentols **7a** and **7b.** In like fashion, the reduction of both oximes **3b** and **4b** with lithium aluminium hydride in tetrahydrofuran affords a mixture of two epimeric inosamines [**3b**→**6c**+**6d** (2:1); **4b**→**7c**+**7d** (3:2)]. The structure of all these crystalline compounds were established by ^{1}H- and ^{13}C-N.M.R. analysis (Table).

We would like to emphasize that some of the cyclitols and aminocyclitols reported here are potential progenitors[9], not only for the well-known 2-deoxystreptamine but also, for the 1,4-diaminocyclitols (sporamine, istamine), aglycones of a new type of aminoglycoside[10]. In addition, rational planning of the sequences described here, might provide labelled precursors otherwise difficult to obtain.

Methyl 2,3,4-Tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside (1b): This compound was prepared according to Ref.[6]; yield: 85%; $[\alpha]_D^{20}$: +61° (*c* 1.7, ethyl acetate).

$C_{28}H_{31}JO_5$	calc.	C 58.54	H 5.44	O 13.92
(574.4)	found	58.61	5.38	13.94



Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (1c):
To a suspension of methyl α-D-glucopyranoside (50 g, 257 mmol) in toluene (60 ml) are added under vigorous stirring, imidazole (35 g, 514 mmol), triphenylphosphine (170 g, 643 mmol), and iodine (72 g, 283 mmol). The mixture is heated either for 50 min at 110 °C or for 1.5 h at 80 °C and the work-up is realized according to Ref.[6]. Acetylation is performed in pyridine (500 ml) with acetic anhydride (200 ml). The precipitate formed was filtered off and washed twice with cold ethanol to give 66.4 g of **1c**. A second crop (22.2 g) is obtained by evaporation of the filtrate to dryness followed by crystallization from ethanol: total yield: 88.6 g (80%); m.p. 149–150 °C (Ref.[6], m.p. 148–149 °C).

Methyl 2,3,4-Tri-*O*-acetyl-α-D-*xylo*-hex-5-enopyranoside (2b):
The iodo-compound **1c** (88.6 g, 206 mmol) is dissolved in dry pyridine (500 ml) and treated with silver fluoride (39.3 g, 309 mmol) at room temperature overnight. Then, the mixture is poured into vigorously stirred ethyl acetate (500 ml). The organic layer is decanted and the dark residue is digested twice with ethyl acetate (150 ml). Combined solutions are concentrated under reduced pressure, and the residue passed through a short silica gel column [ethyl acetate/hexane (8:2)] to give **2b** which is crystallized from ethanol; yield: 49.8 g (80%); m.p. 100 °C (Ref.[8], m.p. 100–101 °C).

Methyl 2,3,4-Tri-*O*-benzyl-α-D-*xylo*-hex-5-enopyranoside (2a):
From **1b**: treatment of **1b** with silver fluoride in pyridine as described above; yield (85%).

From **2b**: the peracetylated alkene **2b** (20 g, 66.2 mmol) is dissolved in methanol (400 ml) and ammonia is bubbled through over 4 h. The solution is evaporated to dryness to give the crude **2c** which is used without further purification for the next step.

A solution of **2c** in dimethylformamide (400 ml) is added dropwise over 1.5 h, at 0 °C under argon, to a vigorously stirred suspension of sodium hydride (14.3 g, 357.5 mmol) in the same solvent (180 ml). After 1 h, benzyl bromide (43.7 ml, 357.5 mmol) is added over a period of 1.5 h at 0 °C and the mixture is stirred overnight at room temperature. Then, to the cooled mixture methanol (50 ml) is added. The residue obtained after evaporation to dryness is purified by silica gel column chromatography [hexane/ethyl acetate (85:15)] to give **2a**; yield: 20.7 g (70%); m.p. 48–50 °C (dichloromethane/ethanol); $[\alpha]_{578}^{20}$: +2° (*c* 1, dichloromethane).

$C_{28}H_{30}O_5$	calc.	C 75.31	H 6.77
(446.6)	found	75.49	6.79

(2*S*,3*R*,4*S*,5*S*)-2,3,4-Tribenzyloxy-5-hydroxy-cyclohexanone (3a) and (2*S*,3*R*,4*S*,5*R*)-2,3,4-Tribenzyloxy-5-hydroxy-cyclohexanone (4a):
A solution of alkene **2a** (9.2 g, 20.6 mmol) in aqueous acetone (250 ml, 1:2) containing mercury(II) chloride (6.2 g, 22.7 mmol) is heated under reflux for 8 h. Sodium hydrogen carbonate is then added to adjust the pH to 4. Acetone is removed under reduced pressure and the mixture is extracted with dichloromethane (3 × 20 ml). Evaporation of the dried (sodium sulfate) organic solution leaves a residue which is chromatographed on a silica gel column [hexane/ethyl acetate (6:4)] to furnish first, compound **4a**; yield: 1.8 g (20%), m.p. 130–132 °C (hexane/ethyl acetate); $[\alpha]_D^{20}$: −50° (*c* 1, dichloromethane).

$C_{27}H_{28}O_5$	calc.	C 74.98	H 6.52
(432.5)	found	74.51	6.49

and then **3a**; yield: 5.35 g (60%); m.p. 122–124 °C hexane/ethyl acetate); $[\alpha]_D^{20}$: −52° (*c* 1, dichloromethane).

$C_{27}H_{28}O_5 \cdot \frac{1}{4}H_2O$	calc.	C 73.45	H 6.53
(450.5)	found	73.18	6.50

Oximes 3b and 4b:
To a solution of ketone **3a** (2.4 g, 5.6 mmol) in methanol (20 ml) containing pyridine (2.5 ml) is added hydroxylamine hydrochloride (425 mg, 6.1 mmol) and the mixture is stirred at room temperature for 2 h. After concentration in vacuo, the residue is extracted with dichloromethane to give **3b**; yield: 2.2 g (90%); m.p. 77–82 °C (hexane/ether); $[\alpha]_D^{20}$: −42° (*c* 0.98, dichloromethane).

$C_{27}H_{29}NO_5$	calc.	C 72.46	H 6.63	N 3.13
(447.5)	found	72.25	6.57	3.20

Oxime **4b**: m.p. 40–42 °C (hexane/ether); $[\alpha]_D^{20}$: −41° (*c* 1.05, dichloromethane).

$C_{27}H_{29}NO_5$	calc.	C 72.46	H 6.53	N 3.13
(447.5)	found	72.24	6.64	3.19

(2*S*,3*R*,4*S*)-2,3,4-Tribenzyloxycyclohex-5-enone (5):
To a stirred solution of ketone **3a** (800 mg, 1.83 mmol) in pyridine (30 ml) are added mesyl chloride (2.1 ml, 27.5 mmol) and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine. After 5 h, the mixture is poured into ice/water (50 ml) and extracted with ethyl acetate (3 × 50 ml). After purification on a silica gel column [hexane/ethyl acetate (8:2)], compound **5** is crystallized from hexane/ethyl acetate; yield: 690 mg (90%); m.p. 61–62 °C; $[\alpha]_D^{20}$: +64° (*c* 1, dichloromethane).

$C_{27}H_{26}O_4$	calc.	C 78.24	H 6.32
(414.5)	found	78.19	6.37

Sodium Borohydride Reduction of 3a and 4a:
To a stirred solution of **3a** (1 g, 2.3 mmol) in dioxan (15 ml) is added sodium borohydride (263 mg, 6.9 mmol). After 2 h, the mixture is neutralized with 1 molar acetic acid and evaporated to dryness. The residue is dissolved in ethyl acetate and then water (50 ml) is added. The organic layer is dried with sodium sulfate and evaporated to afford (1*R*,2*R*,3*r*,4*S*,5*S*)-2,3,4-tri-*O*-benzylcyclohexane-1,2,3,4,5-pentol **(6a)** which is crystallized from hexane/ethyl acetate; yield 850 mg (85%); m.p. 107–108 °C.

$C_{27}H_{30}O_5$	calc.	C 74.63	H 6.95
(434.54)	found	74.53	7.05

Reduction of **4a** is performed as described above for **3a** and affords a 1:1 mixture of **7a** and **7b** which are separated by column chromatography on silica gel [dichloromethane/ethyl acetate (1:1)] to give (1*R*,2*R*,3*R*,4*S*,5*R*)-2,3,4-tri-*O*-benzylcyclohexane-1,2,3,4,5-pentol **(7a)**; yield: 45%; m.p. 115–118 °C (hexane/ethyl acetate); $[\alpha]_D^{20}$: −31° (*c* 1.15, chloroform).

$C_{27}H_{30}O_5 \cdot \frac{1}{4}H_2O$	calc.	C 73.82	H 7.00
(439.0)	found	73.92	6.93

and then (1*S*,2*R*,3*r*,4*S*,5*R*)-2,3,4-tri-*O*-benzylcyclohexane-1,2,3,4,5-pentol **(7b)**; yield: 45%; m.p. 114–116° (hexane/ethyl acetate).

$C_{27}H_{30}O_5 \cdot \frac{1}{4}H_2O$	calc.	C 73.82	H 7.00
(439.0)	found	74.04	6.88

Lithium Aluminium Hydride Reduction of 3b and 4b:
To a cold suspension of lithium aluminium hydride (680 mg, 17.9 mmol) in dry tetrahydrofuran (80 ml) under an argon atmosphere is added dropwise a solution of **3b** (2 g, 4.5 mmol) in tetrahydrofuran (50 ml). The mixture is refluxed for 6 h. To the cooled mixture, water (20 ml) is slowly added, the mixture is filtered through a silica gel cake, and the filtrate is evaporated under reduced pressure. The residue is chromatographed on a silica gel column [dichloromethane/methanol/ammoniac (15:2:0.07)] to yield (1*S*,2*S*,3*S*,4*R*,5*R*)-5-amino-2,3,4-tri-*O*-benzylcyclohexane-1,2,3,4-tetrol **(6c)**; yield: 350 mg (49%); m.p. 152–154 °C (dichloromethane/ether); $[\alpha]_D^{20}$: −15° (*c* 0.94, chloroform).

$C_{27}H_{31}NO_4$	calc.	C 74.80	H 7.21	N 3.23
(433.6)	found	74.54	7.24	3.41

and then (1*S*,2*S*,3*S*,4*R*,5*S*)-5-amino-2,3,4-tri-*O*-benzylcyclohexane-1,2,3,4-tetrol **(6d)**; yield: 310 mg (16%); m.p. 142–143 °C (dichloromethane/ether); $[\alpha]_D^{20}$: +27° (*c* 1, dichloromethane).

$C_{27}H_{31}NO_4$	calc.	C 74.80	H 7.21	N 3.23
(433.6)	found	74.81	7.25	3.27

Reduction of **4b** is performed as described above for **3b** and gives a mixture which is chromatographed on silica gel [dichloromethane/methanol/ammonia (15:1:0.05)] to afford (1*R*,2*S*,3*S*,4*R*,5*R*)-5-amino-2,3,4-tri-*O*-benzylcyclohexane-1,2,3,4-tetrol **(7c)**; yield: 36%; m.p. 146–148 °C (dichloromethane/ether); $[\alpha]_D^{20}$: −31° (*c* 0.95, dichloromethane).

$C_{27}H_{31}NO_4$	calc.	C 74.80	H 7.21	N 3.23
(433.6)	found	74.59	7.20	3.21

and then (1*R*,2*S*,3*S*,4*R*,5*S*)-5-amino-2,3,4-tri-*O*-benzylcyclohexane-1,2,3,4-tetrol **(7d)**; yield: 24%; m.p. 153–154 °C (dichloromethane/ether); $[\alpha]_D^{20}$: −10° (*c* 1.01, dichloromethane).

$C_{27}H_{31}NO_4$	calc.	C 74.80	H 7.21	N 3.23
(433.6)	found	74.60	7.18	3.13

Table. N.M.R. Data for Compounds **2-7**

Compound	^{1}H-N.M.R. data[a]															^{13}C-N.M.R. data[b]					
	Chemical shifts [δ ppm], (TMS int.)							Coupling Constants [Hz]								Chemical shifts [δ ppm] (TMS int.)					
	H-1	H-2	H-3	H-4	H-5	H-6b	H-6a	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{1,6a}$	$J_{1,6b}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	C-1	C-2	C-3	C-4	C-5	C-6
2a	4.63	3.6	3.98	3.92	—	4.9	4.72	3.5	9	9							96.9	81.2[c]	79.6[c]	79.6	153.9	99.1
3a	—	4.00	4.00	3.75	4.20	2.67	2.42							2.5	3.5	15	204.2	85.5	81.7[c]	81.8[c]	66.6	42.8
4a	—	4.15	3.65	3.65	3.65	2.75	2.48		9					11	4	14	203.5	84.8	82.1	86.1	68.2	44.2
3b	—	4.00	4.00	3.60	4.10	3.08	2.46			5.5	3			4	6.5	15	154.2	79.4[c]	79.6[c]	80.5	66.6	26.8
4b	—	4.10	3.80	3.50	3.90	3.16	2.36		5	6	7			10	5.5	15.5	153.6	78.6	82.3	84.3	67.8	28.2
5	—	4.03	3.95	4.33	6.02	6.78			11	8	3			10	$J_{4,6}=2$ Hz		197.4	84.7[c]	83.8[c]	79.0	148.1	128.1
6a	4.08	3.35	4.04	3.35	4.08	2.27	1.42	3	9	9	3	2	3	2	3	15	68.6	82.7	78.9	82.7	68.6	31.5
7a	4.10	3.50	3.83	3.27	3.97	2.23	1.37	3	9	9	9	3	4.5	14	4.5	13.5	66.1	83.4	81.7	86.4	68.0	33.8
7b	3.55	3.37	3.49	3.37	3.55	2.20	1.45	9	9	9	9	12	4.5	12	4.5	12	68.9	86.5	83.6	86.5	68.9	35.9
6c	4.13	3.48	4.13	3.37	3.62	2.18	1.38	4	9	9	3	2.5	3	2.5	3	15	68.7	82.8[c]	78.9	83.3[c]	48.9	31.9
6d	4.09	3.47	3.80	3.09	3.20	2.10	1.24	3	9.5	9.5	9.5	2.5	4	12	4	14.5	66.1	83.6[c]	82.4[c]	87.2	48.3	35.1
7c	4.01	3.26	3.92	3.46	3.46	1.98	1.40	9	9	9	3	11	4.5	3	3.5	13.5	68.0	86.3	81.1	83.1	46.7	34.5
7d	3.58	3.34	3.52	3.20	2.76	2.06	1.26	9.5	9.5	9.5	9.5	12	4.5	10.5	4	12.5	69.9	86.9	84.8	87.5	50.3	36.9

[a] ^{1}H-N.M.R. spectra were measured with a Cameca TSN 250 (250 MHz) or a Bruker WM 400 (400 MHz) spectrometers.
[b] ^{13}C-N.M.R. spectra were obtained on a Bruker WP 60 (15.08 MHz).
[c] Assignments may be reversed.

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