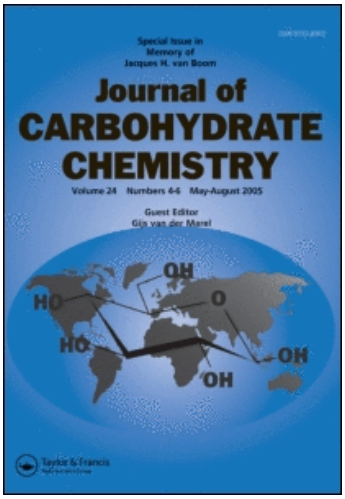

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CARBOCYCLIC RING CLOSURE OF AN AMINODEOXY HEX-5-ENOPYRANOSIDE

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ABSTRACT

Ferrier's intramolecular carbocyclic ring closure reaction of methyl 3,4-di-O-acetyl-2-benzoylamino-2,6-dideoxy-α-D-*xylo*-hex-5-enopyranoside (2) led to 2L-2,4,5/3-2,3-di-O-acetyl-4-benzoylamino-5-hydroxycyclohexanone (4). Upon acetylation compound 4 underwent β-elimination to give the conjugated enone 5. The convenient preparation of these highly functionalized aminocyclohexanones offers an efficient route to monoamino- or 1,4-diaminocyclitol-type aminoglycoside antibiotic aglycones, starting from 2-amino-2-deoxy-D-glucose.

INTRODUCTION

The recent discovery of numerous pseudodisaccharide-type aminoglycoside antibiotics[1] with relatively simple chemical structures involving 1-amino-

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or 1,4-diaminocyclitol aglycones, has stimulated interest in the synthesis of such antibiotic analogues. Several routes, starting from carbohydrates, have been developed for the preparation of the aminocyclitol parts of these molecules.

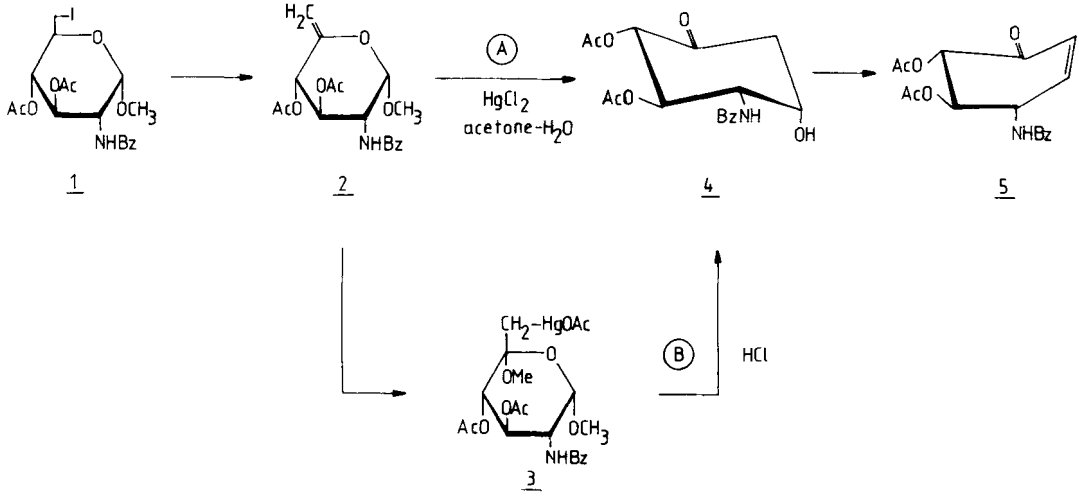
The Ferrier method[2] represents a convenient and effective way to obtain highly functionalized cyclohexanones, and has been extended by several authors[3-6] to hex-5-enopyranosides derived from various neutral carbohydrates, and most recently, from a 3-aminodeoxy sugar[7].

In contrast to previous approaches our synthetic strategy[8] involves the Ferrier-transformation of protected azido-[9] and aminodeoxy-hex-5-enopyranosides into cyclohexanones already containing one of the nitrogen functions of the desired diaminocyclitol compound in the form of an azido- or amino group. The present paper describes the first example for the conversion of a 2-aminodeoxy sugar into an aminocyclohexanone by means of the Ferrier reaction.

RESULTS AND DISCUSSION

Methyl 3,4-di-O-acetyl-2-benzoylamino-2,6-dideoxy--α-D-xylo-hex-5-enopyranoside (2) was obtained in six steps from 2-amino-2-deoxy-D-glucose by the methods of Inouye et al.,[10] Gibbs et al.[11] and Khan and Hough.[12] It is to be mentioned that upon the conversion of methyl 3,4-di-O-acetyl-2-benzoylamino-6-iodo-2,6-dideoxy-α-D-glucopyranoside (1) into exo-methylene compound 2 by treatment with dry silver fluoride, the reported[12] 40 % yield could be doubled by means of continuous extraction of the reaction mixture with warm ether.

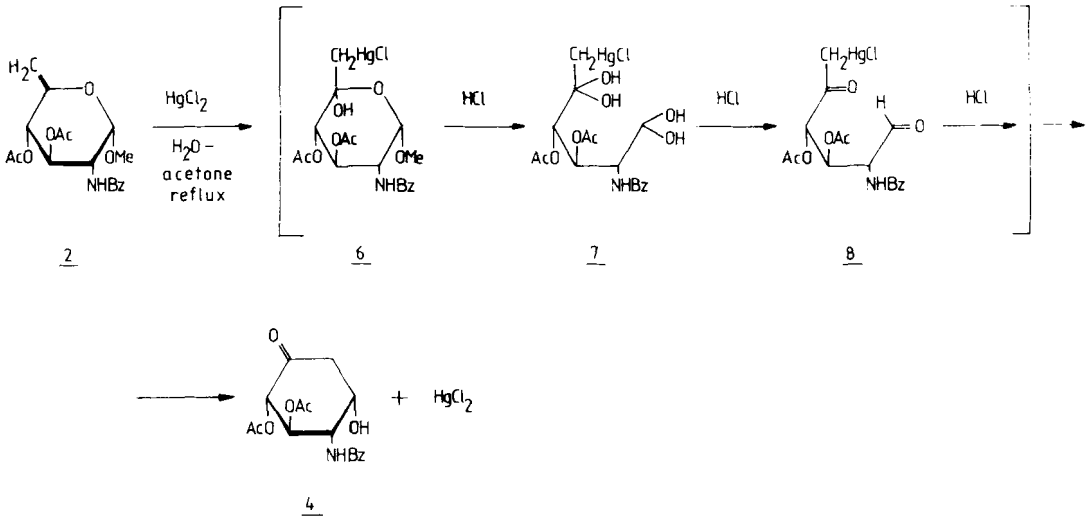
A solution of 2 and mercury(II)chloride in aqueous acetone was refluxed for 3.5 hours (Scheme 1, route A), as described by Ferrier[2], to afford 2L-2,4,5/3-2,3-di-



Scheme 1

O-acetyl-4-benzoylamino-5-hydroxycyclohexanone (4). The values of the ^{1}H-NMR coupling constants ($J_{2,3}=J_{3,4}=$ =10 Hz; $J_{4,5}=J_{5,6}=2$ Hz; $J_{5,6'}=3.5$ Hz) clearly showed that cyclohexanone 4 was present, in chloroform solution, in the form of the $^{2}C_{5}$(L) conformer bearing an axial hydroxyl group at C-5. In the ^{13}C-NMR spectrum, carbons C-1 and C-6 appeared (δ=199.95 and 45.05 ppm) in the ranges characteristic of a ketone carbonyl, and a methylene group adjacent to a carbonyl function, respectively. The additional ^{13}C-NMR data (see Experimental) were also consistent with structure 4.

Cyclohexanone 4 is formed from 2 presumably via a five-step sequence (Scheme 2), involving oxymercuration, hydrolysis, α-elimination, demercuration and acid-catalyzed intramolecular carbonyl addition. Thus, the initial step of the Ferrier reaction is a highly regioselective addition of mercury(II)chloride on the double bond of 2 to produce a 5-hydroxy-6-deoxy-6-chloromercuri intermediate (6). Although only a small portion of the positive charge resides on carbon in the chloromercuri-substituted carbocation, it is large enough to account for the



2 6 7 8 4

Scheme 2

Markovnikov-type hydration and too small to allow the usual rapid carbon-skeleton rearrangement proceeding with fully developed carbocations. In the hot solution hydrochloric acid, generated in the oxymercuration process causes rapid hemiacetal ring opening and the cleavage of the methyl glycoside. Dehydration of the developed geminal diols at C-1 and C-5 (7) results in the open-chain 1,5-dioxo intermediate 8 which is demercurated under acid condition, and then the acid-catalyzed nucleophilic addition of C-6 on the carbon-oxygen double bond of C-1 completes the reaction sequence to afford the product 4. The steric position of the C-5 hydroxyl group in 4 is presumably determined by the conformational properties of one of the open-chain intermediates of the process.

This mechanism is experimentally substantiated by the ready conversion of methyl 6-acetoxymercuri-2,3-di-O-acetyl-2-benzoylamino-2,6-dideoxy-6-methoxy-α-D-glucopyranoside (3), obtained from 2 by methoxymercu-

ration[13], into cyclohexanone 4 upon heating in dilute hydrochloric acid (Scheme 1, route B).

In accordance with Ferrier's finding[2] compound 4, as a β-hydroxyketone, underwent β-elimination upon treatment with acetic anhydride in pyridine to give the heteroconjugated 2L-2,4/3-2,3-di-O-acetyl-4-benzoylamino-cyclohex-5-enone (5). In the ^{1}H-NMR spectrum of 5 the protons attached to unsaturated carbons (H-5 and H-6) resonated at δ=6.95 and 6.24 ppm, respectively, with coupling constants $J_{4,5} \approx J_{4,6} \approx 2.0$ Hz and $J_{5,6}$=10.8 Hz.

The above simple route to aminocyclohexanones 4 and 5 provides a convenient method for the preparation of intermediates applicable for the synthesis of 1-amino- or 1,4-diaminocyclitol-type aglycones of pseudodisaccharide aminocyclitol antibiotics from the readily available 2-amino-2-deoxy-D-glucose.

EXPERIMENTAL

General methods. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. ^{1}H- and ^{13}C-NMR spectra (200 and 50.3 MHz) were obtained with a Bruker WP 200 SY spectrometer, tetramethylsilane being the internal standard. Mass spectra were recorded with a VG-7035 instrument. TLC and column chromatography were performed on DC-Alurolle Kieselgel 60 F_{254} (Merck) and Silica gel 60 (Merck) adsorbents.

Methyl 3,4-di-O-acetyl-2-benzoylamino-2,6-dideoxy-α-D-xylo-hex-5-enopyranoside (2)

A mixture of methyl 3,4-di-O-acetyl-2-benzoylamino-2,6-dideoxy-6-iodo-α-D-glucopyranoside (1) (4.9 g), silver fluoride (4.9 g, dried in vacuo at 75°C) and abs. pyridine (42 mL) was stirred with a magnetic stirrer in the dark for 20 h. The reaction mixture was continuously

extracted with ether, the extract was filtered through a pad of Hyflo Supercel adsorbent and then concentrated. The residue was dissolved in ether and purified by means of adsorptive filtration through a small column packed with Silica gel 60. Upon evaporation of the eluate the residue started to crystallize to give 3.35 g (81%) of crude 2 which was recrystallized from ether-petroleum ether, mp 118°C, lit.[12] mp 118-119°C, $[\alpha]_D^{25}$ +115° (c 1.5, chloroform), lit.[12] $[\alpha]_D^{25}$+118° (c 1.65, chloroform).

Anal. Calcd for $C_{18}H_{21}O_7N$ (363.35): N, 3.86 %.
Found : N, 4.03 %.

^{1}H-NMR data ($CDCl_3$, ppm): δ 2.0 and 2.20 (2s,6H, 2 OAc), 3.48 (s,3H,OCH_3), 4.65 and 4.72 (2d,2H,H-6 and H-6', $J_{6,6'}$=12Hz), 4.82 (d,1H,H-2), 4.95 (d,1H,$J_{1,2}$=3 Hz), 5.50 (q,1H,H-3), $J_{2,3}$=10.0 Hz), 5.62 (dd,1H,H-4, $J_{3,4}$= =9.0 Hz), 6.45 (d,1H,NH, $J_{2,NH}$=8.0 Hz), 7.80-7.30 (m, 5H,aromatic).

It is to be noted that the dehydrohalogenation of 1 into 2 failed when the reaction was performed with 1,8-diazabicyclo-(5.4.0)-undec-7-ene (DBU) in dry toluene under nitrogen atmosphere.

Methyl 3,4-di-O-acetyl-6-acetoxymercuri-2-benzoylamino--2,6-dideoxy-5-methoxy-α-D-glucopyranoside (3)

To a solution of 2 (0.56 g) in abs. methanol (1.5 mL) a solution of mercury(II)acetate (0.5 g) in abs. methanol (2.7 mL) was added and the mixture was kept at room temperature for 2 h. Solvent was then evaporated and the residue dried over P_2O_5 to obtain 3 (0.94 g, 93.2 %) mp 87°C, $[\alpha]_D^{25}$+ 45.3°(c 1.17, chloroform).

Anal. Calcd for $C_{21}H_{27}O_{10}NHg$ (654.05): C, 38.56, H, 4.16, N, 2.14 %. Found: C, 38.68, H, 4.24, N, 2.21 %.

Mass spectrum: m/e 363 (M-OCH_3-HgOAc).

^{1}H-NMR data ($CDCl_3$, ppm): δ 1.95, 2.05 and 2.15 (3s,9H,3 OAc), 2.12-2.30 (m,2H,H-6 and H-6'), 3.38 and 3.48 (2s,6H,2 OCH_3), 4.65 (bs,1H,NH), 4.90 (dd,1H,H-2,

$J_{1,2}$=4 Hz, $J_{2,3}$=11.0 Hz), 5.26 (d,1H,H-1), 5.36-5.50 (m,1H,H-4), $J_{3,4}$=10.0 Hz), 5.60 (t,1H,H-3), 6.80-7.90 (m,5H,aromatic).

2L-2,4,5/3-2,3-Di-O-acetyl-4-benzoylamino-5-hydroxycyclohexanone (4)

A. A mixture of 2 (1.5 g) and equimolar amount of mercury(II)chloride (1.1 g) in 1:2 water-acetone (45 mL) was refluxed for 3.5 h when TLC (chloroform containing 0.5 % of methanol) indicated that all of the starting 2 had disappeared. The reaction mixture was evaporated, the residue was dissolved in chloroform and then washed with small portions of water. The organic layer was dried ($MgSO_4$) and concentrated. Crystallization of the residue from chloroform-petroleum ether yielded 4 (0.985 g, 68.4%), mp 205°C (dec.), $[\alpha]_D^{25}$ +9° (c 0.1, chloroform), $[\alpha]_D^{25}$ + 24° (c 1, pyridine).

Anal. Calcd for $C_{17}H_{19}O_7N$ (349.32): C, 58.45, H, 5.44, N, 4.00 %. Found: C, 58.39, H, 5.39, N, 3.96 %.

Mass spectrum: m/e 331 ($M-H_2O$).

^{1}H-NMR data (DMSO-d_6, ppm): δ 1.90 and 2.05 (2s, 6H, 2 OAc), 2.48-3.20 (m,2H,H-6 and H-6', $J_{5,6}$=2 Hz, $J_{5,6}$=3.5 Hz , $J_{5,6}$=16 Hz), 4.18 (bs,1H,H-5, $J_{4,5}$=2 Hz), 4.92 (m,1H,H-4, $J_{3,4}$=10.0 Hz), 5.50 (t,1H,H-3, $J_{2,3}$=10 Hz), 5.62 (d,1H,OH), 5.70 (d,1H,H-2), 7.30-7.85 (m,5H, aromatic).

^{13}C-NMR data (DMSO-d_6, ppm): δ 20.21 and 20.38 (2 CH_3), 45.05 (C-6), 53.37 (C-4), 67.49 (C-5), 71.20 (C-3), 77.12 (C-2), 127.24, 128.33, 131.41 and 134.32 (aromatic carbons), 166.61 (amide C=O), 169.23 and 169.88 (2 ester C=O), 199.95 (C-1).

B. The methoxymercuri compound 3 (0.85 g) was dissolved in a mixture of acetone (9.4 mL) and water (3.4 mL) and one molar equivalent of 1 n hydrochloric acid (1.3 mL, 0.0472 g of HCl) was added. The mixture was boiled under reflux for 4.5 h and then worked up as

described in method A to obtain cyclohexanone 4 (0.34 g, 75.2 %), mp 205°C (dec.), $[\alpha]_D^{25}$ +24° (c 0.99, pyridine), the spectral data of which were in good accordance with those of the sample prepared by the Ferrier reaction of 2.

2L-2,4/3-2,3-Di-O-acetyl-4-benzoylamino-cyclohex-5-enone (5)

A mixture of 4 (0.38 g) in abs. pyridine (7.6 mL) and acetic anhydride (2 mL) was kept at room temperature for 20 h and then poured onto ice and water. The solid precipitate was filtered off, washed with cold water and dried in vacuo over P_2O_5 and KOH. The crude product (0.22 g, 61.3 %) was recrystallized from methanol to yield pure 5, mp 223°C (dec.), $[\alpha]_D^{22}$ +14.6° (c 1, chloroform).

Anal. Calcd for $C_{17}H_{17}O_6N$ (331.31): C, 61.62, H, 5.18, N, 4.23 %. Found: C, 61.57, H, 5.12, N, 4.16 %.

Mass spectrum: m/e 331 (M^+).

^{1}H-NMR data ($CDCl_3$, ppm): δ 2.25 and 2.10 (2s,6H, 2 OAc), 5.30 (m,1H,H-4, $J_{3,4}$=8.6 Hz), 5.55 (m,2H,H-2 and H-3, $J_{2,3}$=11.0 Hz), 6.24 (dd,1H,H-6, $J_{4,6}$=2.0 Hz), 6.75 (dd,1H,NH), 6.95 (dd,1H,H-5, $J_{4,5}$=2 Hz, $J_{5,6}$=10.8 Hz), 7.80-7.43 (m,5H,aromatic).

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