Aminosugars. XXVIII. A Facile Synthesis of Benzyl α- and β-Kasugaminides via the Corresponding Abequosides

Author(s)
吉村 寿次; YOSHIMURA, Juji; 佐藤 憲一; SATO, Kenichi; 橋本 弘信; HASHIMOTO, Hironobu; SHIMIZU, Kuniaki

Citation
Bulletin of the Chemical Society of Japan, 50(12): 3305-3309

Date
1977-12

Type
Journal Article

Rights
publisher
Aminosugars. XXVIII. A Facile Synthesis of Benzyl α- and β-Kasugaminides via the Corresponding Abequosides

Juji Yoshimura, Ken-ichi Sato, Hironobu Hashimoto, and Kuniaki Shimizu

Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Meguro-ku, Tokyo 152

(Received April 19, 1977)

Synthesis of benzyl α- and β-kasugaminides (benzyl 2,4-diamino-2,3,4,6-tetraoexy-α- and β-β-arabinohexopyranosides) was carried out by the simultaneous substitution at 2,4-positions of 2,4-di-O-mesy-abequosides (3,6-dideoxy-2,4-di-O-mesy-α- and β-β-d-xyl-hexopyranosides) with sodium azide followed by hydrogenation. The substitution in H, N-dimeethylformamide at higher temperature gave the elimination products (4-azido-2,3-unsaturated derivatives) and the subsequently rearranged products (3,4-unsaturated 2-azido derivatives), but, that in hexameth-yolphosphoric triamide at lower temperature gave the desired compounds in fairly good yields.

In connection with synthetic studies on kasugamycin and optically active methyl α-kasugaminide (methyl 2,4-diamino-2,3,4,6-tetraoexy-α-arabinohexopyranoside) have been published. The necessity of the resolution of a racemate is a shortcoming in the former synthesis, whereas the stepwise conversion in the latter takes longer steps, and consequently gives a lower overall yield.

In order to study the relationship between the configuration of aminosugar moiety in kasugamycin and the biological activity, we intended to develop a better pathway for synthesis of optically active kasugaminide and its diastereomers. In this paper, a facile synthesis of benzyl α- and β-kasugaminides via the simultaneous S2-substitution at 2,4-positions of the corresponding aequoses (benzyl 3,6-dideoxy-α- and β-β-d-xyl-hexopyranosides) is described. As methyl α-abequoside is known to be synthesized by the simultaneous deoxygenation of 3,6-positions of methyl 3,4-anhydro-6-0-p-tolylsulfonyl-α-d-galactopyranoside obtainable from D-glucose, the pathway offered here is advantageous.

Results and Discussion

According to the method of Siewert and Westphal, benzyl α- and β-abequosides were newly prepared. Benzoylation of benzyl 4,6-O-benzyldiene-α10 and β-β-glucopyranosides in the usual manner gave the 2,3-di-O-benzoates (1x and 1β) in good yields, respectively. Partial hydrolysis of the 4,6-O-benzyldiene group in 1x and 1β proceeded quantitatively in 70% acetic acid at 90-95°C to give 2x and 2β, respectively. Mesylation of 2x and 2β in the usual manner gave the corresponding 4,6-di-O-mesyates (3x and 3β) in good yields, respectively. Benzyl 2,3-di-O-benzyol-4,6-di-O-p-tolylsulfonyl-β-β-d-glucopyranoside (4) was also prepared from 2β in a similar manner.

Examination of the conversion of 3β in dichloromethane or chloroform into the corresponding epoxide (7β) by treatment with sodium methoxide in methanol indicated that 3β was once changed into an intermediate (5) within 6 h and then gradually converted into 7β.

In fact, 5 deposited from the reaction mixture, when the amount of solvents (especially methanol) was not enough. This conversion proceeded slower than that of the corresponding methyl glucoside and the use of a little excess (1.3-1.4 mol) sodium methoxide gave a better result. Thus, 7α and 7β were obtained in 64 and 75% yields, respectively. In a similar way, tosylated intermediate (6) and tosylated epoxide (8) were obtained from 4. It was characteristic that NMR spectra of these epoxides showed a coupling between OH and H₂, and a AB-quartet of H₃ and H₄. Reduction of 7α, 7β, and 8 in tetrahydrofuran (THF) with 3 mol of lithium aluminium hydride (LAH) gave sirupy benzyl aequoses (9α and 9β), respectively. When 1.5 mol of LAH were used in one instance, crystalline benzyl 3-deoxy-β-β-d-xyl-hexopyranoside (10) was separated from a silica gel column in 22% yield, indicating that the epoxide ring was more reducible than the 6-O-sulfonate group. Excepting the last step in the synthesis of 9α and 9β, the purification of the product in each reaction was not always necessary, and both α- and β-abequosides could be actually obtained in ca. 20% overall yield from D-glucose. Mesylation of 9α or 9β and 10 gave the corresponding 2,4-di-O-mesyates (11α or 11β) and 2,4,6-tri-O-mesylate (12) in good yields, respectively.
The simultaneous substitution at 2,4-positions of mesylates mentioned above with sodium azide was unexpectedly accompanied with the formation of unsaturated products. Reaction of 11β in N,N-dimethylformamide (DMF) with 3 mol of sodium azide at 120 °C overnight was incomplete, and two spots other than a small amount of the starting material were detected on TLC. Separation of the products on a silica gel column gave one monoazide (14β) in pure state, but the NMR spectrum of another fraction indicated the presence of unsaturated compounds. Reaction of 12 under the same condition gave also the corresponding 4,6-diazide (15) in a low yield. Even after the reaction of 11β was continued at 160-165 °C until 14β disappeared, the mixture of products could not be separated by repeating column chromatography. Therefore, the separation was tried after hydrogenation of the products with LAH in THF followed by N-acetylation. Thus, benzyl N,N'-diacetyl-β-kasugamimide (16β) and benzyl 4-acetamido-2,3,4,6-tetraideoxy-β-D-erythro-hex-2-enopyranoside (17) could be isolated in 12 and 19% yields, respectively. When the hydrogenation was carried out in the presence of Raney nickel, the corresponding saturated amino derivatives could be separated by column chromatography into three sirupy products (19, 20, and 18) in 8, 19, and 42% yields, respectively. These compounds were characterized after quantitative conversion into N-acetyl derivatives (21, 22, and 16β). The first-order analysis of the NMR spectrum of 16β (cf. Experimental) completely proved the allocated structure, and J1,2 values of 21 (J1,2=2.4, J1,3=8.0) and 22 (J1,2=8.2) supported them. It will be noteworthy that 19 is a glycoside of the enantiomer of natural L-tolypos-

amine.12,13)

The results mentioned above suggest that the second substitution at C-2 of the initial product (14β) gives 2,4-diazide (13β), but the substitution is followed by the elimination of axial C2-azido group to give benzyl 4-azido-2,3,4,6-tetraideoxy-β-D-erythro-hex-2-enopyranoside (23), which subsequently rearranges to the corresponding 2-azido-3-enopyranoside (24). Recently, several papers have been published on the thermal rearrangement of 2,3-unsaturated 4-azido- and 4-thiocyanatoglycopyranosides to 3,4-unsaturated sugars having nitrogen function at C-2.14-18) These conversions were explained on a [3,3]-sigmatropic rearrangement of cyclic allylic systems in which the asymmetry at the initial allylic centre is transmitted to the new centre by the suprafacial migration.14 Although the formation of a small amount of unsaturated product in the substitution of equatorial C2-sulfonofylox group attached to 3-deoxy-hexopyranose-ring with sodium azide in DMF has been reported,19 the question whether the formation of 23 is initiated from the equatorial C2-sulfonofylox group of 14β or from axial C2-azido group of 13β was remained ambiguous.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>14</th>
<th>13</th>
<th>Unsat. products</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>20</td>
<td>86</td>
<td>-</td>
<td>—</td>
</tr>
<tr>
<td>120</td>
<td>42</td>
<td>69</td>
<td>12</td>
<td>—</td>
</tr>
<tr>
<td>80</td>
<td>20</td>
<td>81</td>
<td>-</td>
<td>—</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
<td>78</td>
<td>-</td>
<td>—</td>
</tr>
<tr>
<td>120</td>
<td>18</td>
<td>55</td>
<td>31</td>
<td>—</td>
</tr>
</tbody>
</table>

a) Yields were estimated from the weight of crude products and the intensity ratio of olefinic proton and others in NMR spectra.

In order to prevent the formation of unsaturated compounds, the same substitution of 11α and 11β was examined at a lower temperature, using hexamethylenephosphoric triamide (HMPA) as a solvent. As shown in Table 1, the reaction at 80 °C gave exclusively monosubstituted 14 in good yields. The continuation of the reaction at 120 °C until 14 disappeared also resulted in the formation of unsaturated compounds, but the yields of the desired diazides (13) were improved. Actually, 16α and 16β were obtained from the crude products in 60 and 46% yields, respectively, by subsequent hydrogenation and N-acetylation. The structure of 16α and 16β was further confirmed by respective hydrogenation into known N,N'-diacetyl-β-kasugamimide (25).15 It has been reported that the substitution of methyl 4,6-O-isopropylidene-3-O-methyl-2-O-sulfonyl-β-D-glucos- and β-mannopyranosides with potassium benzoate in DMF proceeded smoothly, whereas that of α-anomers did not occur.19 Slower but steady substitution of the α-anomer in this experiment will be attributed to the absence of substituent at C-3 and to the flexibility of 11α.
A Facile Synthesis of Kasugaminides via Abequosides
Benzyl 3,4-di-O-methylsulfonyl-a- and -l-ribo-hexopyranoside (11a and 11b).

Mesitylation of 9a in the usual manner, and crystallization of the product from ethanol gave 11a in 77% yield. Mp 104–105 °C; [α]D = 12.7 (c 1.0, CHCl3).

Benzyl 3,6-di-O-methylsulfonyl-a- and -l-xylo-hexopyranoside (11c and 11d).

Mesitylation of 9b in pyridine with methane-sulfonyl chloride gave the tri-O-mesylate in 76% yield. Mp 78–79 °C; [α]D = 2.5° (c 0.6, CHCl3).

11p: Reaction in hexamethylphosphoric triamide (17). A suspension of 11 (100 mg, 0.2 mmol), and sodium azide (700 mg, 10.8 mmol) in DMF (15 ml) was stirred at 120 °C overnight, filtered, and the filtrate was evaporated. A usual extraction gave a sirup which showed two spots other than 12 on TLC. Separation of the sirup on a silica gel column (benzene: ethanol = 10: 1) gave two main fractions of which the first fraction (230 mg, 35%) showed no absorption of a sulfonyleoxy group, but the second fraction (110 mg, 14.3%) showed the mesyl signal in the NMR spectrum. The former was chromatographed, but it could not be purified. The latter fraction crystallized on standing, and recrystallized from benzene–petroleum ether. Mp 78–80 °C; [α]D = -25.2° (c 0.6, CHCl3); IR: 2100 (N–O), 1360 and 1180 (sulfate); NMR: 7.38 (Ph, s), 4.88 and 4.58 (CH2: Abq, J5,6 = 1.5), 4.51 (CH2: CH3, 2 × J5,6 = 3.5), 3.41 (H2: H2, H3, and H4: broad): 2.90 (OSO2CH3), 2.67 (H3: dt, J3,4 = 2.1), 1.81 (H3: broad q, Jgen = J5,6 = 11.0). Found: C, 44.26; H, 4.65; N, 22.33; S, 7.99%. Calcd for C15H11N3O9S: C, 43.97; H, 4.74; N, 21.98; S, 8.39%.

11q: Reaction in hexamethylphosphoric triamide (17). A suspension of 11 (900 mg, 2 mmol) and sodium azide (700 mg, 10.8 mmol) in DMF (15 ml) was stirred at 120 °C overnight, and then treated with water containing ethyl acetate which was added to decompose excess LAH, and then filtered. After neutralization of the filtrate, it was evaporated. The residue was dried, then acetylated in the usual manner to give a sirup which contained two main components. The two products were isolated in pure state by column chromatography repeated twice. Thus, the first fraction 16i) and the second 17 were obtained in 50 mg (12%) and 80 mg (19.4%) yields, respectively.

16i: Mp 146–147.5 °C; [α]D = -45.2° (c 1.0, CHCl3); IR: 3270 (NH); 1650 and 1530 (amide); NMR: 7.29 (Ph, s), 4.80 and 4.55 (CH2: Abq, J5,6 = 12.0), 4.54 (H2: d, J4,5 = 2.5), 4.14 (H3: broad s), 3.83 (H4: m), 3.43 (H3: d, J4,5 = 8.2), 2.18 (H4: d, J3,4 = 2.0, Jgen = 15.3), 1.93 and 1.96 (2 × Na+), 1.55 (H2: oet, J5,6 = 10.0, J3,4 = 4.0), 1.29 (CH3: d, Jgen = 7.0). Found: C, 64.03; H, 7.02; N, 8.79%.
A Facile Synthesis of Kasugaminides via Aboqueosides

December, 1977

Calcd for $C_{16}H_{21}NO_5$: C, 68.41; H, 8.04; N, 5.32%.

$\Delta$-4-Amino-2,3,4,6-tetrahydroxy-β-D-erythro-hexopyranoside (19), $\Delta$-4-Amino-2,3,4,6-tetrahydroxy-β-D-erythro-hexopyranoside (20), and Their Conversion into the Corresponding N-Acetates (16β, 19, and 20).

In the same manner mentioned above, the reaction of 11β (7.5 g) with sodium azide was carried out, and the crude product was hydrogenated in the presence of Raney nickel at 50 °C for 5 h under 50 atm hydrogen gas to give a sirup which showed three spots on TLC. The sirup on a silica gel column chromatography to give crystals which were recrystallized from ethanol-hexane. Yield, 1.17 g (60%); mp 95-98 °C; $\delta_{H}^1H NMR$: 8.2, 3.82-3.40 (H$_{11}$ and H$_6$: m), 2.3-1.3 (CH$_3$). Found: C, 68.82; H, 8.20; N, 5.37%.

Calcd for $C_{17}H_{21}NO_5$: C, 69.95; H, 8.02; N, 12.17%.

The same compound was also obtained from 16α by hydrogenolysis in 80% yield.

The authors are indebted to the members of the Laboratory of Organic Analysis for microanalysis and to Mr. H. Matsumoto for NMR measurements.

References


