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Preparation of 2-deoxystreptamine derivatives with all-axial substituents for desymmetrization

Yue-Lei Chen,[a,b] Jutta Pyplo-Schnieders,[a] Hartmut Redlich,[a,*] Heinrich Luftmann[a,†] and Roland Fröhlich[a,‡]

[a]*Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, D-48149 Münster, Germany*
[b]*NRW Graduate School of Chemistry, Corrensstraße 36, D-48149 Münster, Germany*

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Dedicated to Professor Qi-Zhuo Wang on the occasion of his 85th birthday

Abstract—2-Deoxystreptamine derivatives with all-axial substituents were prepared with new methods. They are potential compounds for desymmetrization.
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Being asymmetrically connected with various carbohydrate moieties, 2-deoxystreptamine acts as the central scaffold of many aminoglycoside antibiotics.[1] The synthesis of aminoglycoside structure from 2-deoxystreptamine has been investigated extensively.[1b] Because 2-deoxystreptamine is a *meso* compound, one focus of those researches involves desymmetrization. Chemical desymmetrization of 2-deoxystreptamine is a challenging task. Efficient and practical methods are under strong demand. However, Wong et al. have demonstrated a successful enzymatic deprotection desymmetrization of azide derivatives of 2-deoxystreptamine.[2]

In another aspect, desymmetrization by protection manipulation on polyhydroxylated cyclohexane rings has been applied by different research groups.[3] A successful strategy for that is to turn the equatorial hydroxyls on the ring to axial positions by constructing a short bridge to connect certain hydroxyls.[3a] In such an all-axial substitution conformation, higher energy difference can be expected when the substrate is protected from different faces, and thus a desymmetrization effect is achieved. Vasella et al. have demonstrated that on an inositol system, with all-axial hydroxyls, interesting desymmetrizing glycosidation reactions can be realized.[3b] In this context, a recent work[4] showed, furthermore, a nice possibility of asymmetrical modification on one of the two amide functional groups on a 2-deoxystreptamine ring. An all-axial substituted 2-deoxy streptamine reaction intermediate was suggested to support the result.

Given a short bridge connecting the two amino groups on 2-deoxystrepamine, all the remaining hydroxyls will be forced to take the axial positions. The simplest model for this is compound **1** (Fig. 1), which has been discovered during the preparation of new 2-deoxystreptamine derivatives.[5] The NMR research from compounds of

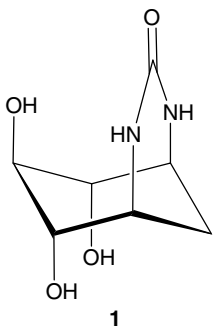

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Figure 1.

Keywords: 2-Deoxystreptamine; Urea; Regioselective deprotection; Desymmetrization; Aminoglycosides.
* Corresponding author. E-mail addresses: redlich@uni-muenster.de; chenyl@uni-muenster.de
† Dr. Heinrich Luftmann for mass analysis.
‡ Dr. Roland Fröhlich for X-ray analysis.

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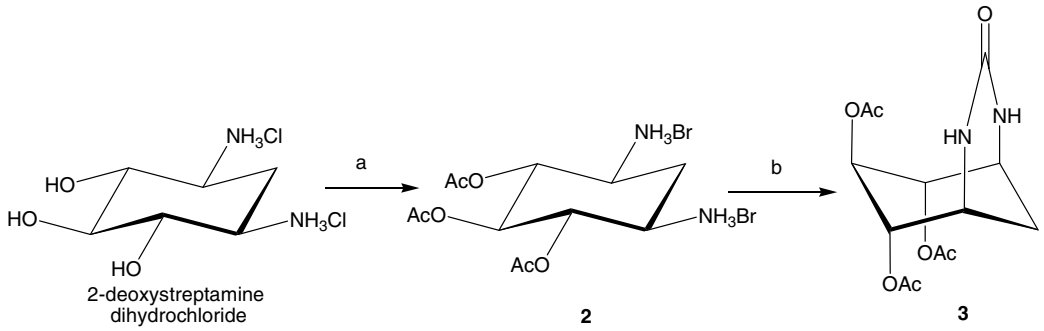


Scheme 1. Reaction conditions and yield: (a) AcOH, AcBr, reflux, 5 h; (b) 1,1-carbonyldiimidazole, triethylamine, DMF, 53% for 2 steps.

this type suggests that the 5-OH is shielded by the *N*,*N*′-carbonyl group. It results in a deactivation effect of the 5-OH, while the remaining two axial hydroxyls are still available for a direct desymmetrizing modification according to the above-mentioned strategy. Besides, considering the chemistry after a successful desymmetrization, the deprotection of the *N*,*N*′-carbonyl has been reported in several cases on aminoglycosids.[6] Hence, this compound can be a good substrate for desymmetrization.

As mentioned above, compound **1** was obtained only once according to the literature sources.[5] In our case, repetition and modification of the reported procedures gave extremely poor yield of compound **1**. Therefore, it is necessary to design a new synthetic route toward this compound or even more promising substrates with similar structures.

As a part of our ongoing project, we realized new synthetic methods for compound **1** type structures. The results are reported herein.

We found experimentally that for efficient construction of an *N*,*N*′-carbonyl group on 2-deoxystreptamine, it is necessary to follow a four-step sequence including N-protection, O-protection, N-deprotection, and then N,N′-carbonylation. For the first step, instead of standard N-acylating protection, the readily available dihydrochloride salt[5,7] of 2-deoxystreptamine already serves as a protection for the amine by reducing its electron density. However, properly using this special N-protection for a direct O-acylation as the second step requires careful manipulation of the reaction condition. In this case, we discovered that 2-deoxystreptamine dihydrochloride can be O-acetylated with AcBr in refluxed AcOH (which is a crucial solvent for this successful acetylation) to complete the second step and yield compound **2**. Since the amines are now 'protected' with protons, the third step for deprotecting nitrogen was combined directly into the fourth N,N′-carbonylation step, where the two amino groups on compound **2** were released by triethylamine in situ and again protected by carbonyl group with 1,1-carbonyldiimidazole in DMF, which is experimentally determined as an ideal solvent for this reaction, to yield compound **3** (Scheme 1). Compound **3** could be regarded as a potential substrate for enzymatic desymmetrization.

The crystal structure[8] of the resulting compound **3** is illustrated in Figure 2. The large deviation of C1–N, C3–N, and C5–O bonds from a standard axial position indicates a considerable repulsion between the urea structure and the 5-*O*-Ac.

From compound **3**, de-O-acetylation with methanolic ammonia produced compound **1** in 69% yield. Furthermore, de-O-acetylation can be performed regioselectively by taking advantage of the particular interaction between the 5-*O*-Ac and the *N*,*N*′-carbonyl group. When compound **3** was reacted with a bulky reducing reagent such as lithium tri-*sec*-butylborohydride (L-Selectride®) at low temperature, compound **4** was formed in 78% yield without any deprotection of 5-*O*-Ac being detected. The protection pattern on compound **1**, and especially on compound **4** endows them as ideal substrates for desymmetrization (Scheme 2).

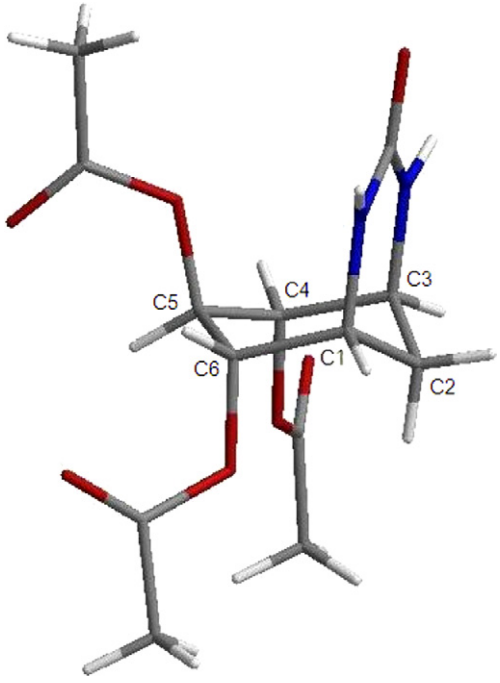
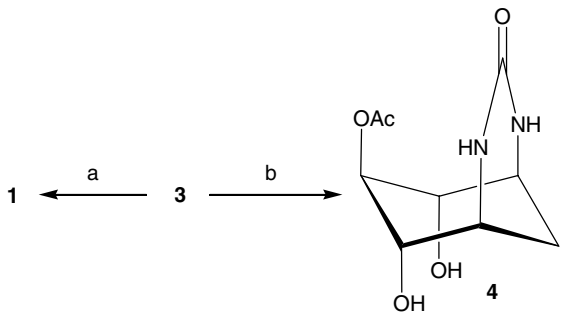


Figure 2. Crystal structure of compound **3** (with 1/2 acetone, not shown here).[8]



Scheme 2. Reaction conditions and yields: (a) methanolic ammonia, overnight, 69%; (b) L-Selectride®, THF, −80 °C to −20 °C, 78%.

In conclusion, from 2-deoxystreptamine dihydrochloride, we developed new methods for rapid and efficient syntheses of compounds **1**, **3**, and **4**,[9] which are potential precursors for direct desymmetrization reactions according to the established strategy. Desymmetrization of those compounds is under active investigation in our group.

Acknowledgments

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8. X-ray crystal structure analysis for compound **3**: formula $C_{13}H_{18}N_2O_7 \cdot 1/2C_3H_6O$, $M = 343.33$, colorless crystal $0.45 \times 0.25 \times 0.20$ mm, $a = 22.251(2)$, $b = 12.162(3)$, $c = 13.995(2)$ Å, $\beta = 112.57(1)°$, $V = 3497.2(10)$ Å^3, $\rho_{calc} = 1.304$ g cm^{-3}, $\mu = 0.902$ mm^{-1}, empirical absorption correction ($0.687 \leqslant T \leqslant 0.840$), $Z = 8$, monoclinic, space group $C2/c$ (No. 15), $\lambda = 1.54178$ Å, $T = 253$ K, $\omega/2\theta$ scans, 3717 reflections collected ($\pm h$, $-k$, $+l$), $[(\sin\theta)/\lambda] = 0.62$ Å^{-1}, 3563 independent ($R_{int} = 0.034$) and 2419 observed reflections [$I \geqslant 2\sigma(I)$], 223 refined parameters, $R = 0.065$, $wR^2 = 0.213$, max. residual electron density 0.55 (−0.35) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.
Data set were collected with an Enraf Nonius CAD4 diffractometer. Programs used: data collection EXPRESS (Nonius B.V., 1994), data reduction MolEN (K. Fair, Enraf-Nonius B.V., 1990), structure solution SHELXS-97 (Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473), structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, 1997), graphics SCHAKAL (Keller, E. Universität Freiburg, 1997).
CCDC 654638 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336–033, e-mail: deposit@ccdc.cam.ac.uk].
9. *Experimental procedures*: Nuclear magnetic resonance spectra were recorded on a Bruker AMX 400 spectrometer or a Varian Unity Plus 600. The chemical shift is specified as δ in ppm and the signal of the solvent was used as the internal standard. Electrospray ionization mass spectra (MS-ESI) were recorded on a Quattro LCZ or a MicroTof. Medium pressure liquid chromatography (MPLC) was performed on Silica Gel 60 (230– 400 mesh, Merck). Melting points were measured on an uncorrected Buchi B-540 apparatus.
4,5,6-Tri-O-acetyl-2-deoxystreptamine dihydrobromide (**2**): 20.0 g (85 mmol) of 2-deoxystreptamine dihydrochloride[5,7] and 2.0 g of DMAP (16 mmol) were suspended in 150 mL of acetic acid and 150 mL of acetyl bromide. The mixture was refluxed for 5 h before all volatile components being removed by evaporation. The remaining solid was dried by coevaporation with toluene to yield 33.4 g of crude compound **2**, which was used directly for the next step; HRMS-ESI(+): m/z $[M+H]^+$ 446.9815 as the basic peak; $C_{12}H_{21}N_2O_6Br_2$ requires 446.9761 as the basic peak; the isotopic peak pattern matches as well; ^{1}H NMR (D_2O, 600 MHz): δ 5.04 (pseudo-t, $J = 10.07$ Hz, 2H, H4,6), 3.77 (m, 1H, H5), 3.58–3.65 (m, 2H, H1,3), 2.58–2.49 (m, 2H, H2a,b), 2.12 (s, 6H, Ac × 2), 2.06 (s, 3H, Ac); ^{13}C NMR (D_2O, 150 MHz): δ 173.2 (s, 2C, Me*C*=O × 2), 172.7 (s, Me*C*=O), 73.0 (s, 2C, C4,6), 71.0 (C5), 47.9 (s, 2C, C1,3), 28.4 (C2), 20.4 (s, 2C, *C*H$_3$–Ac × 2), 20.2 (*C*H$_3$–Ac).
N,N′-Carbonyl-4,5,6-tri-O-acetyl-2-deoxystreptamine (**3**): 33.4 g of crude product **2** from last step and 13.6 g (85 mmol) of 1,1-carbonyldiimidazole was added into 400 mL of DMF. To this suspension, a solution of 50.0 mL TEA in 250 mL DMF was added dropwise at rt. Then all volatile components were removed under vacuum. The residue was distributed in dichloromethane and 1 N aqueous HCl. The water phase was separated and washed with dichloromethane for several times. Combined organic phases were washed with saturated aqueous sodium bicarbonate, evaporated to dryness and purified by MPLC (acetone/cyclohexane, 3:1 to 7:1) to yield 14.0 g of (53% based on compound **2**) compound **3** as a white powder; mp 230–231 °C (lit.[5] 240 °C decomp.); Compound **3** can also be crystallized from a mixture of acetone and cyclohexane to yield single crystals;[8] HRMS-ESI(+) m/z $[M+Na]^+$ 337.1015; $C_{13}H_{18}N_2O_7Na$ requires 337.1006; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz) δ 6.23 (br s, 2H, NH × 2), 4.81 (m, 3H, H4, 5, 6), 3.58 (s, 2H, H1, 3), 2.26

(d, $J = 13.42$ Hz, 1H, H2a), 2.03 (s, 6H, Ac × 2), 1.99 (s, 3H, Ac), 1.74 (m, 1H, H2b); HNMR results are parallel with the reported data;[5] ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 100 MHz) δ 169.0 (s, 3C, Me*C*=O × 3), 156.2 (–HN-*C*ONH–), 70.4 (s, 2C, C4,6), 68.3 (C5), 45.8 (s, 2C, C1,3), 20.7 (s, 2C, *C*H$_3$–Ac × 2), 20.5 (*C*H$_3$–Ac), 18.6 (C2).

N,*N*′-*Carbonyl-2-deoxystreptamine* (**1**): 825 mg of (2.62 mmol) compound **3** was dissolved in a mixture of 14 mL of 7 N methanolic ammonia and 60 mL of methanol. The mixture was stirred at rt overnight. Then all volatile components were removed under vacuum and the residue was purified by MPLC (ethanol/ethyl acetate, 2:1) to yield 340 mg of compound **1** (69%) as an off-white powder; mp 223–225 °C (decomp.); HRMS-ESI(+) *m*/*z* $[M+Na]^+$ 211.0677; $C_7H_{12}N_2O_4Na$ requires 211.0689; ^{1}H NMR (D_2O, 400 MHz) δ 3.76 (s, 2H, H4,6), 3.73 (s, 1H, H5), 3.49 (s, 2H, H1,3), 2.33–2.30 (m, 1H, H2a), 1.58–1.52 (m, 1H, H2b); ^{13}C NMR (D_2O, 100 MHz) δ 158.5 (–HN*C*ONH–), 72.0 (C5), 71.6 (s, 2C, C4,6), 47.9 (s, 2C, C1,3), 16.4 (C2).

N,*N*′-*Carbonyl-5-O-acetyl-2-deoxystreptamine* (**4**): 1.0 g of (3.2 mmol) compound **3** was dissolved in 20 mL THF and cooled to −80 °C followed by the addition of 25 mL (1 M in THF, 25 mmol) of L-Selectride® solution (commercially available from Aldrich). The reaction mixture was then warmed to −20 °C in 3 h and neutralized with AcOH. All volatile components were removed under vacuum and the residue was purified by MPLC (ethanol/toluene, 1:1) to yield 575 mg (78%) compound **4** as a white powder; mp 135–139 °C; HRMS-ESI(+) *m*/*z* $[M+Na]^+$ 253.0744; $C_9H_{14}N_2O_5Na$ requires 253.0795; For obtaining a better resolution, the NMR was recorded on the 4,6-di-*O*-TBS derivative of compound **4**, which was prepared by reacting compound **4** with TBSOTf, 2,6-lutidine, and imidazole in DMF at rt, extractive working up and MPLC purification. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.44–5.47 (br d, 2H, NH × 2), 4.65 (s, 1H, H5), 3.70 (s, 2H, H4, 6), 3.32 (s, 2H, H1, 3), 2.58 (d, $J = 13.12$ Hz, 1H, H2a), 2.01 (s, 3H, Ac), 1.59 (m, 1H, H2b), 0.85 (s, 18H, *t*-Bu–TBS × 2), 0.08 (s, 6H, MeSi × 2), 0.04 (s, 6H, MeSi × 2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.8 (Me*C*=O), 156.5 (–HN*C*ONH–), 73.9 (C5), 71.6 (s, 2C, C4,6), 49.8 (s, 2C, C1,3), 25.8 (*C*H$_3$–*t*-Bu–TBS), 20.9 (s, *C*H$_3$–Ac), 18.0 (s, Me$_3$*C*–*t*-Bu–TBS), −4.6 (s, 2C, CH$_3$–Si × 2), −5.4 (s, 2C, CH$_3$–Si × 2).