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Efficient Preparation of a 1,3-Diazidocyclitol as a Versatile 2-Deoxystreptamine Precursor

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A synthesis route toward 2-deoxystreptamine, a common structure in many of the clinically important aminoglycosides, is presented. Starting from *p*-benzoquinone and cyclopentadiene, 2-deoxystreptamine is synthesized with key steps involving Pd(0)-catalyzed rearrangement, a retro-Diels−Alder by flash vacuum thermolysis, and Yb(III)-directed regioselective epoxide opening. The obtained diazidocyclitol **17** is a suitable 2-deoxystreptamine precursor, conveniently protected for incorporation in new aminoglycoside entities.

Introduction

Since the discovery of the aminoglycoside antibiotic streptomycin in 1944,[1] the family of aminoglycosides has steadily grown into a powerful class of antibiotics with a broad antibacterial spectrum and proven efficacy particularly against aerobic Gram-negative bacteria. Nevertheless, extensive clinical use of the aminoglycosides is limited, due mostly to the associated nephro- and ototoxicities.[2] Another disadvantage is the global development of microbial resistance as the result of structural modification by bacterial enzymes: aminoglycoside phosphotransferases (APH), adenyltransferases (AAD or ANT), and acetyltransferases (AAC).[3,4] These circumstances validate research into novel aminoglycoside analogues which do not display the undesirable features but maintain a strong bactericidal effect. This notion has already awakened the chemical community and the number of papers along this line is rapidly increasing.[5] Surprisingly, however, none of these recent reports describes an efficient way to prepare the core diaminocyclohexanetriol 2-deoxystreptamine common to (nearly) all of the known aminoglycoside antibiotics (Figure 1).[5]

Synthetic routes toward 2-deoxystreptamine that have appeared in the literature require numerous synthetic steps and offer minimal flexibility in protective groups[6−8] or require expensive starting material. As a result, to date the most practical method to synthesize 2-deoxystreptamine (derivatives) is via degradation of natural neomycin.[9−11] However, the initially obtained "naked" *meso*-compound still demands desymmetrization as well as extensive protective group manipulations before incorporation in aminoglycoside entities can be ensured. On the basis of this reasoning we set out to investigate a practical synthetic route toward a 2-deoxystreptamine precursor that is suitable to serve as a scaffold for either 4,5- or 4,6-linked aminoglycoside antibiotics.

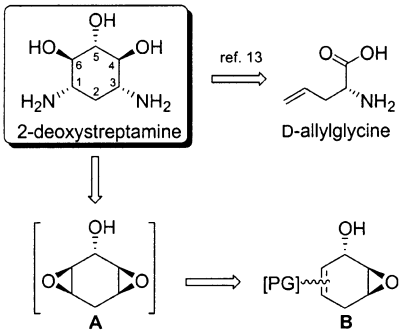

FIGURE 1. Retrosynthetic analysis of 2-deoxystreptamine.

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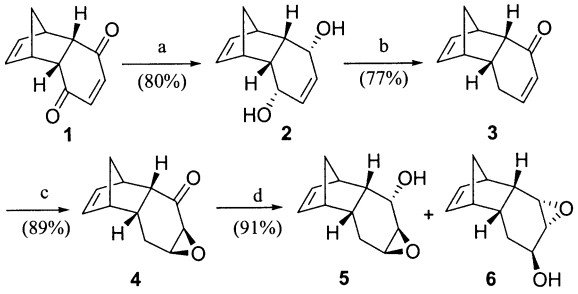
SCHEME 1[a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0−5 °C, 1 h; (b) $PdCl_2$(dppf), HCO_2NH_4, MeCN, Δ, 45 min; (c) H_2O_2, NaOH, CH_2Cl_2/MeOH, 1/1, rt, 30 min; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C, 30 min.

Results and Discussion

As becomes clear from Figure 1, the target molecule 2-deoxystreptamine shows a remarkable structural simplicity particularly due to the internal plane of symmetry. An obvious retrosynthetic approach therefore suggests introduction of both the amino functionalities by double nucleophilic opening of the bisepoxide **A**. This bisepoxide has been described in the literature, but is unstable, and the synthetic route leading to it is by no means straightforward.[6,12] Unfortunately, obtention of **A** by epoxidation of cyclohexane-2,5-dien-1-ol (not drawn) does not seem feasible since the latter molecule has not been reported presumably due to its inherent instability. We have earlier circumvented the use of unstable intermediates in a synthesis of enantiopure and fully orthogonally protected 2-deoxystreptamine by using a stepwise approach starting from D-allylglycine.[13] The latter route provides a highly useful 2-deoxystreptamine scaffold for the preparation new aminoglycoside antibiotics but we anticipated a shorter route toward a versatile 2-deoxystreptamine precursor would be of additional value to the field. As the present paper shows, a more straightforward route can be achieved via temporary "protection" of a cyclohexene double bond as schematically represented in **B**.

Our synthesis starts from the readily accessible Diels−Alder condensation product **1** of cyclopentadiene and *p*-benzoquinone (Scheme 1). Reduction under Luche conditions according to a known protocol[14,15] led to diol **2**, which was converted into the enone **3** via a 1,4-hydrogen migration catalyzed by in situ formed Pd(0), according to Takano et al.[16,17] In our hands, however, it was not possible to reproduce the reported yield under the described conditions ($PdCl_2(PPh_3)_2$ in MeCN), since an appreciable amount (16%) of starting material remained (Table 1, entry 1).

TABLE 1. Optimization of the Palladium(0)-Catalyzed 1,4-Hydrogen Migration Reaction[a]

entry	solvent	catalyst	**2** yield,[b] %	**3** yield,[b] %
1	MeCN	$PdCl_2(PPh_3)_2$	16	71 (49)
2	MeCN	$PdCl_2(MeCN)_2$	—[c]	—[c]
3	MeCN	$PdCl_2$(dppf)	9	89 (77)
4	MeCN	$Pd(OAc)_2$(dppe)	100	−
5	DMF	$PdCl_2(PPh_3)_2$	100	−
6	DMF	$PdCl_2$(dppf)	69	29 (n.d.)[e]

[a] Standard procedure is used, with given catalyst, and solvent. [b] GC yield (isolated yield). [c] Decomposition. [e] n.d.= not determined.

We therefore further investigated the optimal reaction conditions for this transformation. In DMF we saw minor amounts of **3** or no product formed (entries 5 and 6), which also applied to the use of other sources of palladium in MeCN (entries 2 and 4). On the contrary, with $PdCl_2$(dppf) as catalyst we found only traces of starting material and a much improved yield of **3** (entry 3). In the subsequent step, nucleophilic epoxidation of **3** afforded epoxide **4** in 89% yield. Reduction of the ketone to alcohol **5** proved troublesome and was inevitably accompanied by varying amounts of the Payne-rearranged product (**6**). Optimal conditions to keep this side reaction to a minimum involved a reduction under Luche conditions[15] at −78 °C to afford alcohol **5** and **6** in a favorable 7:1 ratio of isomers, which could be easily separated by column chromatography.[18−20] In this respect, it is important to note that compound **5** required additional caution due to its high acid sensitivity; purification on silica gel led to the formation of two new products. Separation by selective crystallization of the *p*-nitrobenzoate derivatives, followed by X-ray analysis revealed that the tetracycles **9** and **12** had been formed (Scheme 2).[21]

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(17) It should be noted that enzymatic resolution of compound **2** may serve as a starting point for the preparation of an enantiopure derivative of 2-deoxystreptamine: Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. *Synthesis* **1993**, 948−950.

(18) To establish whether the Payne rearrangement is in equilibrium the 2,3-epoxycyclohexanols were individually treated with sodium hydride. It turned out that only the *trans*-epoxy alcohol (**5**) rearranged to the regioisomeric 1,2-*cis*-epoxy alcohol **6**, whereas the reverse reaction did not take place.

(19) AM1 and quantum mechanics show that there is little energy difference between Payne-rearranged product **6** and unrearranged product **5**. Structures were minimized with MOPAC/AM1 and B3LYP 6-31G* predicting $\Delta E = 1.8$ and 0.75 kcal/mol, respectively.

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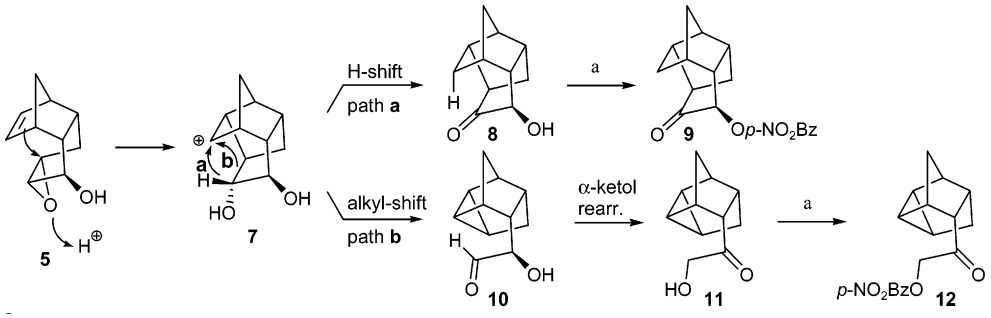
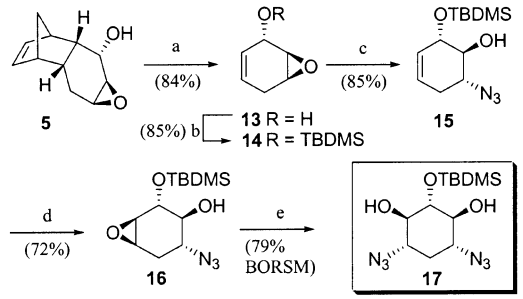
SCHEME 2. Supposed Mechanism for the Formation of Products 9 and 12[a]



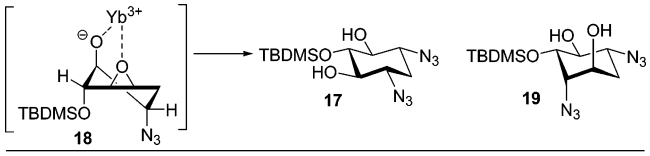
[a] Reagents and conditions: (a) *p*-NO_2-BzCl, Et_3N, DMAP, CH_2Cl_2.

SCHEME 3. Synthesis of 1,3-Diazidocyclitol as 2-Deoxystreptamine Precursor[a]



[a] Reagents and conditions: (a) 80 °C, 600 °C, 0.04 mbar, 2 h; (b) TBDMSCl, DIPEA, DMAP, CH_2Cl_2, rt, 5 h; (c) NaN_3, NH_4Cl, MeOH, Δ, 40 h; (d) *m*-CPBA, CH_2Cl_2, rt, 24 h; (e) $Yb(OTf)_3$, Et_3N, NaN_3, toluene, 80 °C, 4 d.

TABLE 2. Optimization of the Epoxide Opening of 16



entry	conditions	solvent	**17**:**19**[a]	yield of **17**, %
1	NaN_3, NH_4Cl, 80 °C	MeOH	1:2	10
2	NaN_3, $Yb(OTf)_3$, Et_3N, 80 °C	toluene	>95:5	49
3	NaN_3, $Yb(OTf)_3$, 60 °C	MeOH	—[b]	—
4	NaN_3, $Yb(OTf)_3$, Et_3N, 280 W, 135 °C	toluene	>95:5	70
5	NaN_3, $Yb(OTf)_3$, Et_3N, 80 °C, 4 Å MS	toluene	>95:5	79

[a] Regioisomeric ratio determined by ^1H NMR. [b] Major compound **19**.

We suggest that the mechanism leading to **9** and **12** involves acid activation (silica gel in this case) of the epoxide of **5**, which has the double bond π-electrons optimally aligned for nucleophilic attack. The resulting intermediate carbocation **7** undergoes one of two possible rearrangements, involving either an H-shift (path a) or alkyl-shift (path b). Although the α-hydroxy aldehyde **10** as such could not be identified, it seems likely that formation of the nitrobenzoate **12** can be explained via α-ketol rearrangement of **10** to the more stable ketone **11**. Gratifyingly, rearrangement could be completely suppressed by eluting the column with 1% Et_3N to give **5** in a final isolated yield of 80%.

Having the tricyclic system **5** in hand, the desired retro-Diels−Alder reaction could be investigated. Such reactions, typically executed in high-boiling ethereal solvents, are often accompanied by side products and the solvent is difficult to remove. These disadvantages can be elegantly circumvented by making use of flash vacuum thermolysis (FVT).[22] Optimization of the FVT conditions in our case shows that the best result was obtained with sublimation at 80 °C, thermolysis at 600 °C, and a pressure around 0.04 mbar to afford compound **13** cleanly in 84% yield (Scheme 3). In the following steps the hydroxyl was protected with a *tert*-butyldimethylsilyl group and the epoxide was converted to azido alcohol **15**. The remaining double bond was now also epoxidized, but this time with *m*-CPBA, leading to the *trans*-epoxide **16** stereoselectively (72%) although formation of the *cis*-isomer could not be suppressed completely (ratio 4:1). The final step, involving another regioselective epoxide opening, proved to be more troublesome (Table 2). Our first attempt to open epoxide **16** with NaN_3 in MeOH predominantly led to the formation of azido alcohol **19** and only to a lesser extent to the preferred regioisomer **17** (entry 1), presumably due to a favored trans-diaxial opening of the epoxide as dictated by the Fürst−Plattner rule.[23]

After some unsuccessful variation of reaction conditions a paper by Delgado et al. stimulated us to investigate chelation-controlled $Yb(OTf)_3$-catalyzed azidolysis of epoxides.[24] Much to our satisfaction, under the suggested conditions with sodium azide, ytterbium(III) triflate, and triethylamine the 1,3-diazidocyclitol **17** was formed as the only regioisomer (entry 2), most likely from nucleophilic attack at the all-axial conformer **18**, formed by chelation of ytterbium(III) with both the free (deprotonated) hydroxyl and the epoxide. Unfortunately, after 4 days of refluxing substantial amounts of starting material remained and only 49% of the product could be isolated. Replacement of toluene by MeOH was not a fortuitous choice, but by carrying out the reaction in a microwave at 280 W and at 135 °C (entry 4) product **17** was obtained in a yield of 70%. Finally, the optimal result was achieved by addition of molecular sieves to the reaction mixture, to give a yield of 79%. The structural

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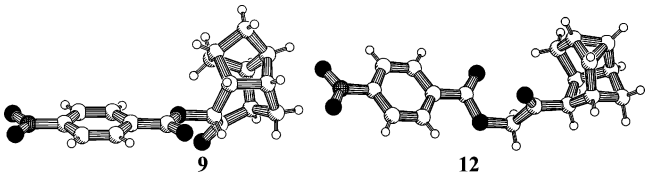


FIGURE 2. Platon visualization[25] of the X-ray structures of **9** and **12**.

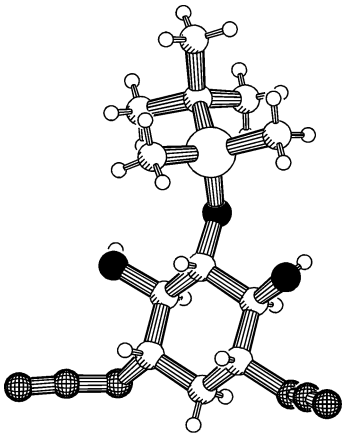
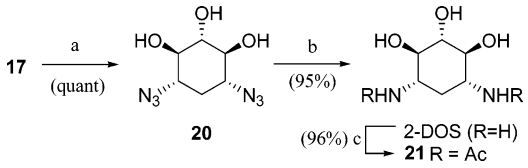


FIGURE 3. Platon visualization[25] of the X-ray structure of **17**.

SCHEME 4. Conversion of 17 into 2-Deoxystreptamine[a]



[a] Reagents and conditions: (a) 1 N HCl, MeOH, rt, 16 h; (b) Pd/C, H_2, MeOH, 16 h; (c) Ac_2O, Et_3N, MeOH/H_2O, 1/1.

identity of **17** was unequivocally established by X-ray analysis (Figure 3).[21]

The convenience of the diazido derivative **17** above carbamate-protected 2-deoxystreptamines is reflected in its excellent solubility in organic solvents and straightforward spectral analysis. Finally, the applicability of **17** as a versatile scaffold for the preparation of new 4,6-linked aminoglycoside type compounds[6e,7] was established by its smooth conversion into 2-deoxystreptamine, i.e. by desilylation and hydrogenation, in 95% yield for the two steps (Scheme 4). Comparison of spectral data of the diacetate derivative **21** provided further evidence of the structural identity of **17**.

In conclusion, the synthetic route described above is a versatile means to obtain the 1,3-diazidocyclitol as a 2-deoxystreptamine precursor in 10 steps and an overall yield of 15%. The route is suitable for gram-scale synthesis and we are currently using **17** as the key scaffold for the synthesis of new RNA-targeted ligands. We believe that the obtained diazidocyclitol **17** is a suitable 2-deoxystreptamine precursor and moreover conveniently protected for incorporation in new aminoglycoside entities.

Experimental Section

(±)-(1*R*,2*R*,7*R*,8*S*)-Tricyclo[6.2.1.0^{2,7}]undeca-4,9-dien-3-one (3). To a solution of **2** (5.1 g, 29 mmol) and HCO_2NH_4 (2.7 g, 42 mmol) in degassed MeCN (280 mL) was added 1 mol % of $PdCl_2$(dppf) (230 mg, 0.282 mmol). The solution was refluxed for 45−90 min. The reaction was diluted with Et_2O, washed with brine, and dried (Na_2SO_4). After evaporation of the solvent the crude product was purified by flash chromatography (EtOAc/*n*-heptane, 1/5) to give **3** (3.5 g, 77%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 6.66 (dt, J = 4.0, 10.3 Hz, 1H, CH), 6.12 (ddd, J = 15.8, 5.6, 2.9 Hz, 2H, CH), 5.86 (dt, J = 10.4, 2.4 Hz, 1H, CH), 3.38 (br s, 1H, CH), 3.03 (br s, 1H, CH), 2.91 (dd, J = 10.1, 3.9 Hz, 1H, CH), 2.76 (dt, J = 10.1, 3.5 Hz, 1H, CH), 2.60 (dddd, J = 20.6, 10.2, 3.9, 2.4 Hz, 1H, CH), 2.02 (ddd, J = 20.5, 6.0, 3.4 Hz, 1H, CH), 1.42 (dt, J = 8.4, 1.8 Hz, 1H, CH), 1.34 (d, J = 8.4 Hz, 1H, CH); in agreement with literature.[26]

(±)-(1*R*,2*R*,3*S*,4*R*,5*S*,7*R*,8*S*)-4,5-Epoxytricyclo[6.2.1.0^{2,7}]-undec-9-en-3-ol (5). To a cold solution (−78 °C) of **4** (3.21 g, 18.2 mmol) in MeOH (46 mL) was added $NaBH_4$ (689 mg, 18.2 mmol) and $CeCl_3{\cdot}7H_2O$ (6.77 g, 18.2 mmol). The reaction was stirred until conversion was completed. The mixture was quenched with ammonium chloride, extracted with Et_2O, washed with brine, and dried (Na_2SO_4). The crude mixture was purified by means of flash chromatography (EtOAc/*n*-heptane, 1/5 and 1% Et_3N) to yield 2.59 g (80%) of compound **5** as a colorless oil. R_f 0.4 (EtOAc/*n*-heptane, 1/3). IR υ_{max} film: 3442, 2958, 1439, 1338, 1255, 816, 729 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 6.40 (dd, J = 5.7, 3.1 Hz, 1H, H_{10}), 6.06 (dd, J = 5.7, 3.1 Hz, 1H, H_9), 4.46 (m, 1H, H_3), 3.12 (m, 2H, H_4, and H_5), 2.93 (br s, 1H, H_1), 2.77 (br s, 1H, H_8), 2.46−2.38 (m, 1H, H_7), 2.30−2.24 (m, 2H, H_2, and H_{6exo}), 1.45 (dt, J = 8.1, 1.9 Hz, 1H, H_{11}), 1.34 (dd, J = 14.4, 11.7 Hz, 2H, H_{6endo}, and H_{11}), 1.11 (br d, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 137.8, 134.0, 68.9, 51.8, 50.9, 50.7, 46.1, 45.7, 40.8, 36.1, 26.9. HRMS (CI) *m*/*z* calcd for $C_{11}H_{15}O_2$ (M + H)$^+$ 179.1072, found 179.1068.

(±)-(1*R*,2*R*,3*S*,4*R*,5*S*,7*R*,8*S*)-5,6-Epoxytricyclo[6.2.1.0^{2,7}]-undec-9-en-4-ol (6). To a solution of **5** (20 mg, 0.11 mmol) in Et_2O (1.5 mL) was added NaH (2.7 mg, 0.11 mmol) at room temperature. The reaction was followed with TLC (EtOAc/*n*-heptane, 2/3). After the mixture was stirred for 3 days water was added and the product was extracted with Et_2O and dried ($MgSO_4$). Analysis with TLC and NMR showed 100% conversion to **6**. R_f 0.30 (EtOAc/*n*-heptane, 1/3). IR υ_{max} film: 3406, 2960, 1437, 1342, 1049, 735 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm): δ 6.23 (dd, J = 5.7, 2.9 Hz, 1H, H_{10}), 6.06 (dd, J = 5.7, 3.2 Hz, 1H, H_9), 4.23 (m, 1H, H_5), 3.25 (m, 1H, H_3), 3.00 (m, 2H, H_1 and H_4), 2.70 (br s, 1H, H_8), 2.47 (dt, J = 9.8, 2.6 Hz, 1H, H_2), 2.35−2.19 (m, 1H, H_7), 1.72−1.61 (m, 2H, H_{6exo} and OH), 1.42 (m, 1H, H_{11}), 1.29−1.21 (m, 2H, H_{11} and H_{6endo}). HRMS (CI) *m*/*z* calcd for $C_{11}H_{15}O_2$ (M + H)$^+$ 179.1072, found 179.1071.

(±)-(1*S*,5*S*,6*R*)-5,6-Epoxycyclohex-2-en-1-ol (13). The thermolysis oven was preheated to 600 °C. A solution of **5** (430, 2.41 mmol) in Et_2O was brought into the sublimation flask, and Et_2O was evaporated. The vacuum gauge was carefully opened until vacuum was (0.04 mbar) reached, after which the collecting cooler was charged with CO_2/acetone (−78 °C). The sublimation oven was heated to 80 °C. The reaction was finished when no starting material remained in the sublimation flask. The crude mixture was purified by flash chromatography (diethyl ether/*n*-pentane, 1/2). Compound **13** (226 mg, 84%) was obtained as a colorless liquid. R_f 0.3 (EtOAc/*n*-heptane, 2/1). IR υ_{max} film: 3390, 1419, 1011, 929, 986, 798, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 5.7−5.66 (m, 1H, CH), 5.6−5.57 (m, 1H, CH), 4.48 (br s, 1H, CH), 3.31 (br s, 1H, CH), 3.25 (br s, 1H, CH), 2.63−2.48 (m, 2H, CH), 1.84

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(br s, 1H, OH). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 124.8, 124.7, 63.0, 53.06, 50.2, and 25.1.

(±)-(3*S*,4*S*,5*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4,5-epoxycyclohex-1-ene (14). To a solution of **13** (655 mg, 5.84 mmol) in CH_2Cl_2 (30 mL) was added DIPEA (1.43 mL, 8.17 mmol), TBDMSCl (1.06 g, 7.59 mmol), and DMAP (71.0 mg, 0.584 mmol) at 0 °C. The solution was stirred for 5 h at room temperature. Water was added, and the product was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/*n*-heptane, 1/10) to yield **14** (1.12 g, 85%) as a colorless oil. R_f 0.6 (EtOAc/*n*-heptane, 1/3). IR υ_{max} film: 2952, 2927, 2856, 1254, 1068, 837 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 5.58−5.49 (m, 2H, 2CH), 4.49 (br s, 1H, CH), 3.30 (br s, 1H, CH), 3.15 (br s, 1H, CH), 2.54 (br s, 2H, CH_2), 0.92 (s, 9H, *t*-Bu), 0.14 (s, 3H, Me), 0.12 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 125.1, 123.2, 63.7, 54.1, 50.7, 25.9, 24.9, 18.3, −4.5, −4.6. HRMS (EI) *m*/*z* calcd for $C_{12}H_{22}O_2Si$ $(M)^+$ 226.1389, found 226.1381.HRMS (EI) *m*/*z* calcd for $C_{11}H_{19}O_2Si$ (M − Me) 211.1154, found 211.1152.

(±)-(1*S*,2*S*,6*R*)-6-Azido-2-[(*tert*-butyldimethylsilyl)oxy]-cyclohex-3-en-1-ol (15). To a solution of **14** (3.05 g, 13.5 mmol) in MeOH (50 mL) was added NaN_3 (1.75 g, 26.9 mmol) and NH_4Cl (1.29 g, 24.1 mmol). The reaction was stirred under reflux for 40 h. MeOH was evaporated, CH_2Cl_2 was added, and the solution was washed with brine and dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by flash chromatography (EtOAc/*n*-heptane, 1/10) to obtain **15** as a colorless oil (4.2 g, 85%). IR υ_{max} film: 2109, 1253, 1088, 837, 779 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 5.59−5.55 (m, 1H, CH), 5.50 (d, J = 10.1 Hz, 1H, CH), 4.22−4.20 (m, 1H, CH), 3.60−3.57 (m, 2H, 2CH), 2.50−2.44 (m, 1H, CH), 2.46 (s, 1H, OH, disappears with a drop of D_2O), 2.14−2.07 (m, 1H, CH), 0.91 (s, 9H, *t*-Bu), 0.13 (s, 3H, MeSi), 0.12 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 130.0, 124.1, 76.9, 73.9, 60.7, 31.0, 25.8, 18.1, −4.5. MS(CI): 270 (M + H). HRMS (EI) *m*/*z* calcd for $C_{12}H_{23}O_2SiN_3$ $(M)^+$ 269.1559, found 269.1551.

(±)-(1*S*,2*R*,3*R*,4*R*,6*R*)-6-Azido-2-[(*tert*-butyldimethylsilyl)oxy]-3,4-epoxycyclohexan-1-ol (16). To a solution of **15** (3.61 g, 13.4 mmol) in CH_2Cl_2 (180 mL) at room temperature was added *m*-CPBA (5.76 g, 33.4 mmol). After being stirred overnight the suspension was diluted with CH_2Cl_2, filtered, and washed with water and twice with a phosphate buffer (pH 7.5) to get rid of the excess benzoic acid. The crude product was dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (EtOAc/*n*-heptane, 1/5) to give 2.74 g (72%) of compound **16** as a colorless crystalline solid. R_f 0.4 (EtOAc/*n*-heptane, 1/5). IR υ_{max} film: 2956, 2927, 2860, 2110, 1709, 841 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 3.82 (d, 1H, 3, J = 7.16 Hz, CH), 3.42−3.32 (m, 3H, CH), 3.01 (d, 1H, J = 3.66 Hz, CH), 2.53 (ddd, J = 1.9, 3.1, 6.9 Hz, 1H, CH_2), 2.40 (d, J = 2.64 Hz, 1H, OH), 1.79 (ddd, J = 1.32, 10.41, 11.87 Hz, 1H, CH_2), 0.93 (s, 9H, *t*-Bu), 0.18 (s, 3H, MeSi), 0.16 (s, 1H, MeSi). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 73.2, 57.4, 56.4, 53.1, 28.9, 25.9, 18.2, −4.5, −4.6. HRMS (CI) *m*/*z* calcd for $C_{12}H_{24}O_3SiN_3$ $(M + H)^+$ 286.1587, found 286.1577.

(1*R*,2*r*,3*S*,4*R*,6*S*)-4,6-Diazido-2-[(*tert*-butyldimethylsilyl)oxy]cyclohexane-1,3-diol (17). A solution of the starting epoxide (**16**) (448 mg, 1.66 mmol) in 22 mL of toluene is added dropwise under argon over $Yb(OTf)_3$ (515 mg, 0.83 mmol) and MS 4 Å (500 mg) at room temperature. NaN_3 (1.08 g, 16.6 mmol) and Et_3N (3.47 mL, 24.9 mmol) were added and the reaction was then stirred at 80 °C for 4 days. The reaction mixture was cooled, filtered, and evaporated. The crude product was purified by flash chromatography (EtOAc/*n*-heptane, 1/10) to give compound **17** as white crystals (321 mg, 82% based on 114 mg of recovered starting material). R_f 0.2 (EtOAc/*n*-heptane, 1/10). Mp: 104 °C. IR υ_{max} film: 2932, 2098, 1247, 1130, 841 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 3.35 (s, 5H, CH), 2.41 (s, 2H, OH), 2.18 (m, 1H, CH_2), 1.38 (m 1H, CH_2), 0.92 (s, 9H, *t*-Bu), 0.16 (s, 6H, Me_2Si). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 76.2, 59.7, 31.7, 25.7, 18.1, −4.5. HRMS (CI) *m*/*z* calcd for $C_{12}H_{25}O_3SiN_6$ $(M + H)^+$ 329.1758, found 329.1754. Anal. Calcd for $C_{12}H_{24}O_3N_6Si$: C, 43.88; H, 7.37; N, 25.59. Found: C, 43.84; H, 7.04; N, 25.11. Crystal structure data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 226046.

(1*R*,2*r*,3*S*,4*R*,6*S*)-4,6-Diazidocyclohexanetriol (20). Compound **17** (30 mg, 0.093 mmol) was dissolved in a 1 N HCl solution in MeOH (1 mL). The reaction mixture was stirred at room temperature overnight. EtOAc was added and the reaction mixture was washed with $NaHCO_3$ and dried (Na_2SO_4), to give after flash chromatography (EtOAc) the 4,6-diazidocyclohexanetriol (quant.). R_f 0.4 (EtOAc). IR υ_{max} film: 3369, 2923, 2100, 1359, 1260, 1113, 1080, 1023, 668, 616, 556 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz, ppm): δ 3.38 (m, 2H, CH), 3.18−3.27 (m, 3H, CH), 2.09 (dt, J = 4.4 Hz, 1H, CH_2), 1.25 (q, J = 12.6 Hz, 1H, CH_2); in agreement with literature.[27]

2-Deoxystreptamine. To a solution of 4,6-diazidocyclohexanetriol **20** (20 mg, 0.093 mmol) in MeOH was added Pd/C (spatula). After the mixture had been stirred for 14 h under 3 bar of H_2, Pd/C was filtered off and the filtrate was concentrated to yield 2-deoxystreptamine (14 mg, 95%). IR υ_{max} film: 3345, 2917, 2362, 2094, 1559, 1541, 1095, 988 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz, ppm): δ 3.13 (m, 1H, CH), 3.02 (t, J = 9.5 Hz, 2H, CH), 2.68−2.54 (m, 2H, 2CH), 1.98 (dt, J = 4.3, 4.1 Hz, 1H, CH_2) 1.16 (q, J = 12.1 Hz, 1H, CH_2).[28]

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Supporting Information Available: Experimental procedures, characterization, and X-ray analysis data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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