

# 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,<sup>1</sup> 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.<sup>2</sup> Another disadvantage is the global development of microbial resistance as the result of structural modification by bacterial enzymes: aminoglycoside phosphotransferases (APH), adenylyltransferases (AAD or ANT), and acetyltransferases (AAC).<sup>3,4</sup> 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.<sup>5</sup> 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).<sup>5</sup>

Synthetic routes toward 2-deoxystreptamine that have appeared in the literature require numerous synthetic steps and offer minimal flexibility in protective groups<sup>6–8</sup> 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.<sup>9–11</sup> However, the initially obtained “naked” *meso*-compound still demands desymmetrization as well

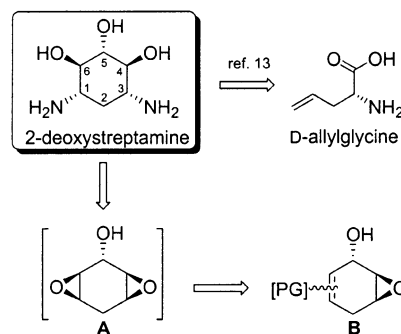


FIGURE 1. Retrosynthetic analysis of 2-deoxystreptamine.

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.

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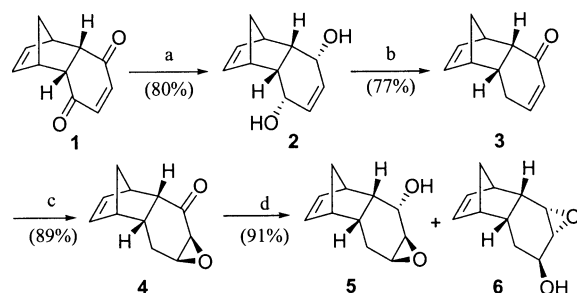
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SCHEME 1<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, 0–5 °C, 1 h; (b) PdCl<sub>2</sub>(dppf), HCO<sub>2</sub>NH<sub>4</sub>, MeCN, Δ, 45 min; (c) H<sub>2</sub>O<sub>2</sub>, NaOH, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 1/1, rt, 30 min; (d) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, 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.<sup>6,12</sup> 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.<sup>13</sup> 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

TABLE 1. Optimization of the Palladium(0)-Catalyzed 1,4-Hydrogen Migration Reaction<sup>a</sup>

| entry | solvent | catalyst   | <b>2</b> yield, <sup>b</sup> % | <b>3</b> yield, <sup>b</sup> % |
|-------|---------|--|--------------------------------|--------------------------------|
| 1     | MeCN    | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | 16                             | 71 (49)                        |
| 2     | MeCN    | PdCl <sub>2</sub> (MeCN) <sub>2</sub>              | — <sup>c</sup>                 | — <sup>c</sup>                 |
| 3     | MeCN    | PdCl <sub>2</sub> (dppf)                           | 9                              | 89 (77)                        |
| 4     | MeCN    | Pd(OAc) <sub>2</sub> (dppe)                        | 100                            | —                              |
| 5     | DMF     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | 100                            | —                              |
| 6     | DMF     | PdCl <sub>2</sub> (dppf)                           | 69                             | 29 (n.d.) <sup>e</sup>         |

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

conditions according to a known protocol<sup>14,15</sup> 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.<sup>16,17</sup> In our hands, however, it was not possible to reproduce the reported yield under the described conditions (PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> in MeCN), since an appreciable amount (16%) of starting material remained (Table 1, entry 1).

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<sub>2</sub>(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<sup>15</sup> 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.<sup>18–20</sup> 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).<sup>21</sup>

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(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 Δ*E* = 1.8 and 0.75 kcal/mol, respectively.

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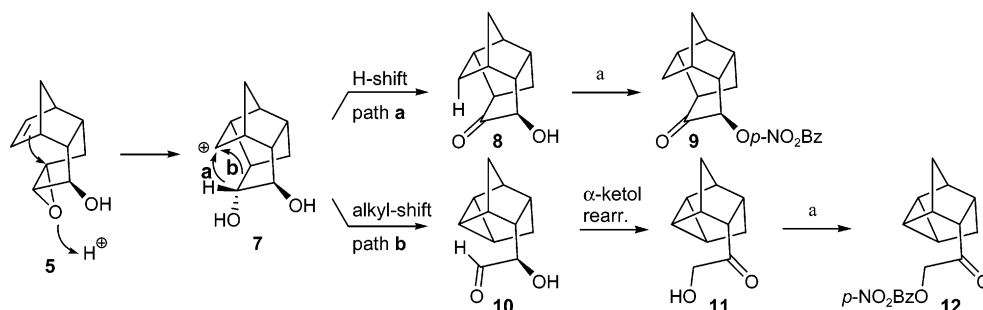
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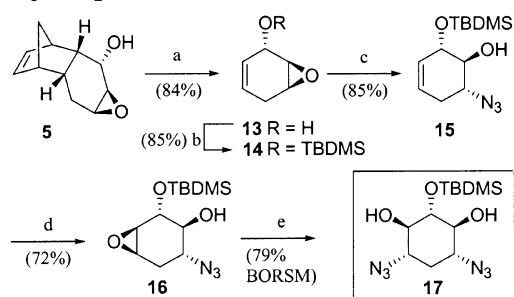
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SCHEME 2. Supposed Mechanism for the Formation of Products **9** and **12**<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) *p*-NO<sub>2</sub>-BzCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>.

SCHEME 3. Synthesis of 1,3-Diazidocyclitol as 2-Deoxystreptamine Precursor<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) 80 °C, 600 °C, 0.04 mbar, 2 h; (b) TBDMSCl, DIPEA, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 5 h; (c) NaN<sub>3</sub>, NH<sub>4</sub>Cl, MeOH, Δ, 40 h; (d) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 24 h; (e) Yb(OTf)<sub>3</sub>, Et<sub>3</sub>N, NaN<sub>3</sub>, toluene, 80 °C, 4 d.

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  $\pi$ -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  $\alpha$ -hydroxy aldehyde **10** as such could not be identified, it seems likely that formation of the nitrobenzoate **12** can be explained via  $\alpha$ -ketol rearrangement of **10** to the more stable ketone **11**. Gratifyingly, rearrangement could be completely suppressed by eluting the column with 1% Et<sub>3</sub>N 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).<sup>22</sup> 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*-

TABLE 2. Optimization of the Epoxide Opening of **16**

| entry | conditions   | solvent | 17:19 <sup>a</sup> | yield of 17, % |
|-------|--|---------|--------------------|----------------|
| 1     | NaN <sub>3</sub> , NH <sub>4</sub> Cl, 80 °C                               | MeOH    | 1:2                | 10             |
| 2     | NaN <sub>3</sub> , Yb(OTf) <sub>3</sub> , Et <sub>3</sub> N, 80 °C         | toluene | >95:5              | 49             |
| 3     | NaN <sub>3</sub> , Yb(OTf) <sub>3</sub> , 60 °C                            | MeOH    | — <sup>b</sup>     | —              |
| 4     | NaN <sub>3</sub> , Yb(OTf) <sub>3</sub> , Et <sub>3</sub> N, 280 W, 135 °C | toluene | >95:5              | 70             |
| 5     | NaN <sub>3</sub> , Yb(OTf) <sub>3</sub> , Et <sub>3</sub> N, 80 °C, 4 Å MS | toluene | >95:5              | 79             |

<sup>a</sup> Regioisomeric ratio determined by <sup>1</sup>H NMR. <sup>b</sup> Major compound **19**.

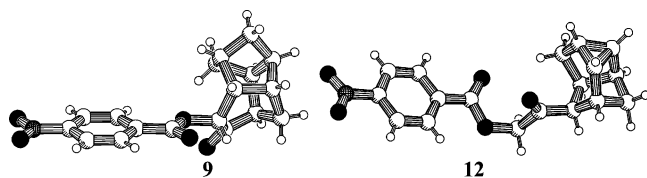
isomer could not be suppressed completely (ratio 4:1). The final step, involving another regioselective epoxide opening, proved to be more troublesome (Table 2). Our first attempt to open epoxide **16** with NaN<sub>3</sub> in MeOH predominantly led to the formation of azido alcohol **19** and only to 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.<sup>23</sup>

After some unsuccessful variation of reaction conditions a paper by Delgado et al. stimulated us to investigate chelation-controlled Yb(OTf)<sub>3</sub>-catalyzed azidolysis of epoxides.<sup>24</sup> 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

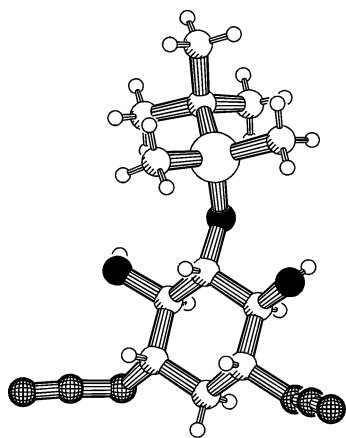
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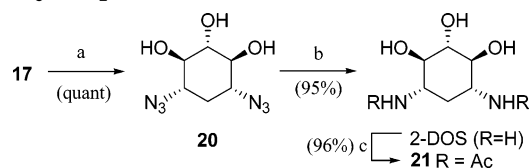


**FIGURE 2.** Platon visualization<sup>25</sup> of the X-ray structures of **9** and **12**.



**FIGURE 3.** Platon visualization<sup>25</sup> of the X-ray structure of **17**.

**SCHEME 4. Conversion of 17 into 2-Deoxystreptamine<sup>a</sup>**



<sup>a</sup> Reagents and conditions: (a) 1 N HCl, MeOH, rt, 16 h; (b) Pd/C, H<sub>2</sub>, MeOH, 16 h; (c) Ac<sub>2</sub>O, Et<sub>3</sub>N, MeOH/H<sub>2</sub>O, 1/1.

identity of **17** was unequivocally established by X-ray analysis (Figure 3).<sup>21</sup>

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<sup>6e,7</sup> 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<sup>2,7</sup>]undeca-4,9-dien-3-one (**3**). To a solution of **2** (5.1 g, 29 mmol) and HCO<sub>2</sub>NH<sub>4</sub> (2.7 g, 42 mmol) in degassed MeCN (280 mL) was added 1 mol % of PdCl<sub>2</sub>(dppf) (230 mg, 0.282 mmol). The solution was refluxed for 45–90 min. The reaction was diluted with Et<sub>2</sub>O, washed with brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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.<sup>26</sup>

(±)-(1*R*,2*R*,3*S*,4*R*,5*S*,7*R*,8*S*)-4,5-Epoxytricyclo[6.2.1.0<sup>2,7</sup>]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<sub>4</sub> (689 mg, 18.2 mmol) and CeCl<sub>3</sub>·7H<sub>2</sub>O (6.77 g, 18.2 mmol). The reaction was stirred until conversion was completed. The mixture was quenched with ammonium chloride, extracted with Et<sub>2</sub>O, washed with brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude mixture was purified by means of flash chromatography (EtOAc/*n*-heptane, 1/5 and 1% Et<sub>3</sub>N) to yield 2.59 g (80%) of compound **5** as a colorless oil. *R<sub>f</sub>* 0.4 (EtOAc/*n*-heptane, 1/3). IR *v*<sub>max</sub> film: 3442, 2958, 1439, 1338, 1255, 816, 729 cm<sup>−1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, ppm): δ 6.40 (dd, *J* = 5.7, 3.1 Hz, 1H, H<sub>10</sub>), 6.06 (dd, *J* = 5.7, 3.1 Hz, 1H, H<sub>9</sub>), 4.46 (m, 1H, H<sub>3</sub>), 3.12 (m, 2H, H<sub>4</sub>, and H<sub>5</sub>), 2.93 (br s, 1H, H<sub>1</sub>), 2.77 (br s, 1H, H<sub>8</sub>), 2.46–2.38 (m, 1H, H<sub>7</sub>), 2.30–2.24 (m, 2H, H<sub>2</sub>, and H<sub>6exo</sub>), 1.45 (dt, *J* = 8.1, 1.9 Hz, 1H, H<sub>11</sub>), 1.34 (dd, *J* = 14.4, 11.7 Hz, 2H, H<sub>6endo</sub>, and H<sub>11</sub>), 1.11 (br d, 1H, OH). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sub>11</sub>H<sub>15</sub>O<sub>2</sub> (M + H)<sup>+</sup> 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<sup>2,7</sup>]undec-9-en-4-ol (**6**). To a solution of **5** (20 mg, 0.11 mmol) in Et<sub>2</sub>O (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<sub>2</sub>O and dried (MgSO<sub>4</sub>). Analysis with TLC and NMR showed 100% conversion to **6**. *R<sub>f</sub>* 0.30 (EtOAc/*n*-heptane, 1/3). IR *v*<sub>max</sub> film: 3406, 2960, 1437, 1342, 1049, 735 cm<sup>−1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz, ppm): δ 6.23 (dd, *J* = 5.7, 2.9 Hz, 1H, H<sub>10</sub>), 6.06 (dd, *J* = 5.7, 3.2 Hz, 1H, H<sub>9</sub>), 4.23 (m, 1H, H<sub>3</sub>), 3.25 (m, 1H, H<sub>3</sub>), 3.00 (m, 2H, H<sub>1</sub> and H<sub>4</sub>), 2.70 (br s, 1H, H<sub>8</sub>), 2.47 (dt, *J* = 9.8, 2.6 Hz, 1H, H<sub>2</sub>), 2.35–2.19 (m, 1H, H<sub>7</sub>), 1.72–1.61 (m, 2H, H<sub>6exo</sub> and OH), 1.42 (m, 1H, H<sub>11</sub>), 1.29–1.21 (m, 2H, H<sub>11</sub> and H<sub>6endo</sub>). HRMS (CI) *m/z* calcd for C<sub>11</sub>H<sub>15</sub>O<sub>2</sub> (M + H)<sup>+</sup> 179.1072, found 179.1071.

(±)-(1*S*,5*S*,6*R*)-5,6-Epoxytricyclohex-2-en-1-ol (**13**). The thermolysis oven was preheated to 600 °C. A solution of **5** (430, 2.41 mmol) in Et<sub>2</sub>O was brought into the sublimation flask, and Et<sub>2</sub>O was evaporated. The vacuum gauge was carefully opened until vacuum was (0.04 mbar) reached, after which the collecting cooler was charged with CO<sub>2</sub>/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<sub>f</sub>* 0.3 (EtOAc/*n*-heptane, 2/1). IR *v*<sub>max</sub> film: 3390, 1419, 1011, 929, 986, 798, 710 cm<sup>−1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, ppm):  $\delta$  124.8, 124.7, 63.0, 53.06, 50.2, and 25.1.

**( $\pm$ )-(3S,4S,5S)-3-[(*tert*-Butyldimethylsilyl)oxy]-4,5-epoxycyclohex-1-ene (14).** To a solution of **13** (655 mg, 5.84 mmol) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$ , dried ( $\text{Na}_2\text{SO}_4$ ), 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  $\nu_{\text{max}}$  film: 2952, 2927, 2856, 1254, 1068, 837  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, ppm):  $\delta$  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,  $\text{CH}_2$ ), 0.92 (s, 9H, *t*-Bu), 0.14 (s, 3H, Me), 0.12 (s, 3H, Me).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, ppm):  $\delta$  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  $\text{C}_{12}\text{H}_{22}\text{O}_2\text{Si}$  ( $\text{M}^+$ ) 226.1389, found 226.1381. HRMS (EI)  $m/z$  calcd for  $\text{C}_{11}\text{H}_{19}\text{O}_2\text{Si}$  ( $\text{M} - \text{Me}$ ) 211.1154, found 211.1152.

**( $\pm$ )-(1S,2S,6R)-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  $\text{NaN}_3$  (1.75 g, 26.9 mmol) and  $\text{NH}_4\text{Cl}$  (1.29 g, 24.1 mmol). The reaction was stirred under reflux for 40 h. MeOH was evaporated,  $\text{CH}_2\text{Cl}_2$  was added, and the solution was washed with brine and dried ( $\text{Na}_2\text{SO}_4$ ). 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  $\nu_{\text{max}}$  film: 2109, 1253, 1088, 837, 779  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, ppm):  $\delta$  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  $\text{D}_2\text{O}$ ), 2.14–2.07 (m, 1H, CH), 0.91 (s, 9H, *t*-Bu), 0.13 (s, 3H, MeSi), 0.12 (s, 3H, MeSi).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, ppm):  $\delta$  130.0, 124.1, 76.9, 73.9, 60.7, 31.0, 25.8, 18.1, –4.5. MS (CI): 270 ( $\text{M} + \text{H}$ ). HRMS (EI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{23}\text{O}_3\text{SiN}_3$  ( $\text{M}^+$ ) 269.1559, found 269.1551.

**( $\pm$ )-(1S,2R,3R,4R,6R)-6-Azido-2-[(*tert*-butyldimethylsilyl)oxy]-3,4-epoxycyclohexan-1-ol (16).** To a solution of **15** (3.61 g, 13.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (180 mL) at room temperature was added *m*-CPBA (5.76 g, 33.4 mmol). After being stirred overnight the suspension was diluted with  $\text{CH}_2\text{Cl}_2$ , 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 ( $\text{Na}_2\text{SO}_4$ ), 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  $\nu_{\text{max}}$  film: 2956, 2927, 2860, 2110, 1709, 841  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, ppm):  $\delta$  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,  $\text{CH}_2$ ), 2.40 (d,  $J = 2.64$  Hz, 1H, OH), 1.79 (ddd,  $J = 1.32, 10.41, 11.87$  Hz, 1H,  $\text{CH}_2$ ), 0.93 (s, 9H, *t*-Bu), 0.18 (s, 3H, MeSi), 0.16 (s, 1H, MeSi).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, ppm):  $\delta$  73.2, 57.4, 56.4, 53.1, 28.9, 25.9, 18.2, –4.5, –4.6. HRMS (CI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{24}\text{O}_3\text{SiN}_3$  ( $\text{M} + \text{H}$ ) $^+$  286.1587, found 286.1577.

**(1R,2r,3S,4R,6S)-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  $\text{Yb}(\text{OTf})_3$  (515 mg, 0.83 mmol) and MS 4 Å (500 mg) at room temperature.  $\text{NaN}_3$  (1.08 g, 16.6 mmol) and  $\text{Et}_3\text{N}$  (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  $\nu_{\text{max}}$  film: 2932, 2098, 1247, 1130, 841  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, ppm):  $\delta$  3.35 (s, 5H, CH), 2.41 (s, 2H, OH), 2.18 (m, 1H,  $\text{CH}_2$ ), 1.38 (m 1H,  $\text{CH}_2$ ), 0.92 (s, 9H, *t*-Bu), 0.16 (s, 6H,  $\text{Me}_2\text{Si}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz, ppm):  $\delta$  76.2, 59.7, 31.7, 25.7, 18.1, –4.5. HRMS (CI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{25}\text{O}_3\text{SiN}_6$  ( $\text{M} + \text{H}$ ) $^+$  329.1758, found 329.1754. Anal. Calcd for  $\text{C}_{12}\text{H}_{24}\text{O}_3\text{N}_6\text{Si}$ : 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.

**(1R,2r,3S,4R,6S)-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  $\text{NaHCO}_3$  and dried ( $\text{Na}_2\text{SO}_4$ ), to give after flash chromatography (EtOAc) the 4,6-diazidocyclohexanetriol (quant.).  $R_f$  0.4 (EtOAc). IR  $\nu_{\text{max}}$  film: 3369, 2923, 2100, 1359, 1260, 1113, 1080, 1023, 668, 616, 556  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz, ppm):  $\delta$  3.38 (m, 2H, CH), 3.18–3.27 (m, 3H, CH), 2.09 (dt,  $J = 4.4$  Hz, 1H,  $\text{CH}_2$ ), 1.25 (q,  $J = 12.6$  Hz, 1H,  $\text{CH}_2$ ); in agreement with literature.<sup>27</sup>

**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  $\text{H}_2$ , Pd/C was filtered off and the filtrate was concentrated to yield 2-deoxystreptamine (14 mg, 95%). IR  $\nu_{\text{max}}$  film: 3345, 2917, 2362, 2094, 1559, 1541, 1095, 988  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz, ppm):  $\delta$  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,  $\text{CH}_2$ ) 1.16 (q,  $J = 12.1$  Hz, 1H,  $\text{CH}_2$ ).<sup>28</sup>

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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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