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Synthetic Methods

Asymmetric Stereodivergent Strategy Towards Aminocyclitols

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Abstract: A concise asymmetric synthesis of aminocyclitols, such as diastereomeric 2-deoxystreptamine analogues and conduramine A, is described. The Pd-catalyzed asymmetric desymmetrization of *meso* 1,4-dibenzolate enables the synthesis of highly oxidized cyclohexane architectures. These scaffolds can potentially be used to access new aminoglycoside antibiotics and enantiomerically pure α-glucosidase inhibitors.

Aminocyclitols, such as 2-deoxystreptamine (DOS; **1**) and conduramine A (**2**) are important structural motifs found in several aminoglycoside antibiotics and α-glucosidase inhibitors (Figure 1).[1] Although the synthesis of 2-deoxystreptamine has received significant attention,[2] the need for structural replacements continues to be an essential area of research.[3] Toxicity was observed when natural 2-deoxystreptamine containing aminoglycosides, such as kanamycin (**3**) and tobramycin (**4**), are employed in treating bacterial infections.[4] In addition, the continual emergence of resistant bacterial strains against such aminoglycosides justifies the further exploration of new antibiotics that are less susceptible to enzymatic inactivation.[5]

A majority of the strategies towards the synthesis of new analogues of **3** and **4** have focused on modifying one or more of the aminosugars (rings I and III in Figure 1). A strategy that has received less attention involves the modification of DOS itself (ring II). The ubiquity, the central location of DOS, and the hydrogen bonds that it forms with 16S RNA may suggest its significance. Further, recent studies on the modification of ring II have resulted in several potent aminoglycosides.[6,7,8]

One strategy for modifying ring II that has received virtually no attention, involves the replacement of DOS with its diastereomer.[9] This modification would have a minimal influence on the overall positive-charge density and conformational flexibility of the aminoglycoside, yet, it would significantly modify the three dimensional structure of the molecule. This altered structure may present new opportunities for differential binding to RNA and accessibility to scaffolds that may be less prone to enzymatic modification.

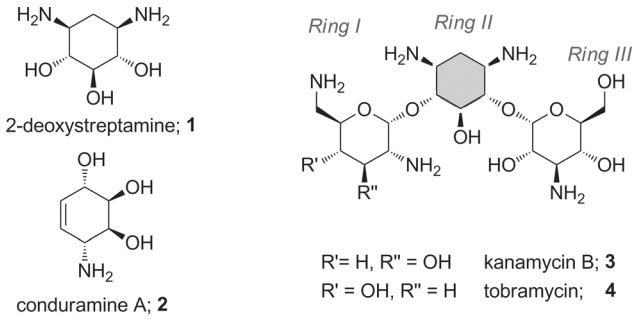

Figure 1. Clinically relevant aminoglycoside antibiotics.

We chose 2-deoxy-4,5,6-tris-*epi*- (**5a**) and 2-deoxy-3,4-bis-*epi*-streptamine (**6a**), the former because it retains the symmetry, and the latter because it does not (Figure 2). Similar to 2-DOS, diamine **5a** possesses a plane of symmetry; however, when incorporated into an aminoglycoside, it becomes a chiral motif. Thus, a synthetic equivalent must possess a differentiation element that allows for the asymmetric incorporation as envisioned in **5b** (Figure 3).

To efficiently access and investigate the biological properties of aminoglycosides that are diastereomeric at ring II, differen-

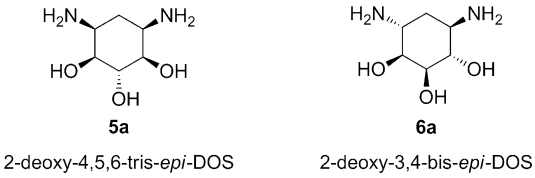

Figure 2. Diastereomeric 2-deoxystreptamine targets.

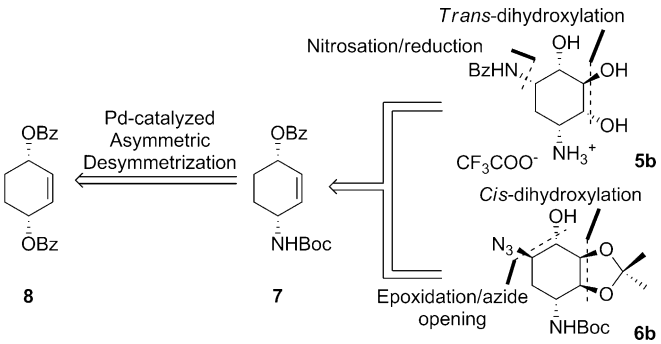

Figure 3. Stereodivergent strategy towards **5b** and **6b**.

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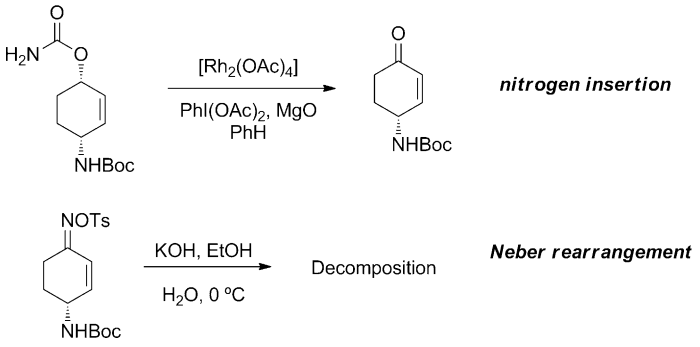
tially protected diastereomeric DOS analogues must be readily accessible. The challenge associated with a selective synthesis of such analogues lies in the presence of five highly oxidized contiguous stereocenters. Although, several racemic syntheses of diastereomeric DOS exist,[10] current methods to access enantiomerically pure diastereomeric DOS analogues require multistep sequences that employ the use of chiral pool starting materials (sugars).[11] Herein, we describe an efficient synthesis of differentially protected diastereomeric deoxystreptamines **5b** and **6b** by using asymmetric catalysis, in which both enantiomers of the desired products can be obtained.

To access DOS analogues **5b** and **6b**, our goal (Figure 3) was to maximize efficiency by: 1) designing a flexible route that allows the synthesis of either enantiomer of several aminocyclitols; and 2) employing diastereoselective transformations to fully utilize stereochemical information embedded in the molecule. We have previously described a palladium-catalyzed asymmetric allylic azidization reaction for the desymmetrization of *meso* dibenzoate **8** as a method for preparing enantiomerically pure amino alcohols (Scheme 1).[12] We envisioned that employing such a strategy would provide an efficient entry into various aminocyclitols that could be later functionalized.

Retrosynthetically, diastereomeric DOS **5b** and **6b** can be obtained by the *trans*- and *cis*-dihydroxylation of a common intermediate **7**, respectively (Figure 3). Initially, two strategies were examined to incorporate the second nitrogen in analogy with **5b** as outlined in Scheme 2. First, the depicted primary carbamate was subjected to the Rh-catalyzed intramolecular nitrogen insertion;[13] however, this resulted in the exclusive formation of the corresponding ketone. Second, when the tosyloxime was subjected to base, instead of the α-aminoketone (Neber rearrangement), aromatized products were obtained.



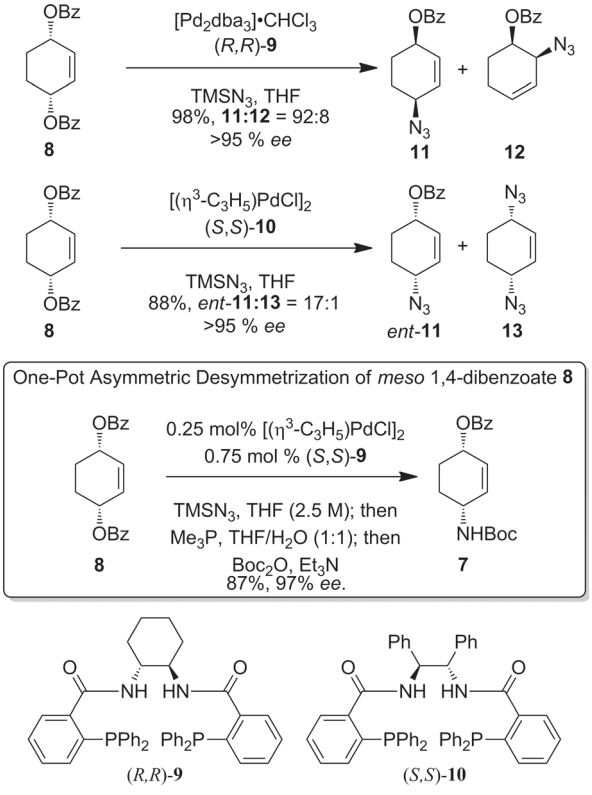
Scheme 2. Initial strategies for second nitrogen incorporation. Ts = tosyl.

In an alternative strategy, we envisioned that the second nitrogen of analogue **5** could be installed by a nitrosation. Analogously, the second nitrogen of analogue **6b** would be installed through the regioselective opening of an epoxide. Carbamate **7** could be obtained by the Pd-catalyzed asymmetric desymmetrization of *meso* dibenzoate **8**.

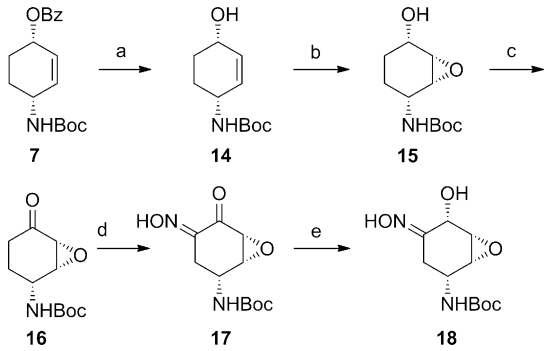
Previous work has shown that a catalyst derived from π-allylpalladium chloride dimer and ligand **9** gave a mixture of the desired product **11** and the regioisomeric azide **12**, whereas a catalyst derived from ligand **10** gave a mixture of azide *ent*-**11** and diazide **13** (Scheme 1).[12c] Gratifyingly, the desired carbamate **7** was obtained as the sole product in 87% yield and 97% enantiomeric excess (*ee*) through a one-pot protocol by using ligand **9**.[14] The low catalyst loadings and low-temperature manipulation of the reactive azide for the desymmetrization process and the Staudinger reduction contributed to the exclusive formation of carbamate **7** (Scheme 1).

With a reliable method to obtain intermediate **7** in hand, we proceeded with the hydrolysis of the benzoate group to provide allylic alcohol **14** (Scheme 3). Directed epoxidation of this alcohol **14** gave epoxide **15** as a single diastereomer, further oxidation of which provided epoxyketone **16**. Enolization of epoxyketone **16** with potassium *tert*-butoxide, followed by quenching with *iso*-amyl nitrite, gave oxime **17** as a single isomer of undetermined geometry. Reduction of the carbonyl carbon from the least hindered face by using sodium borohydride gave alcohol **18** as a single diastereoisomer.

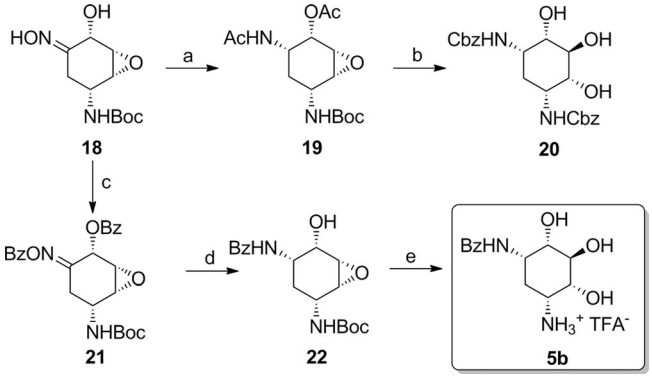
The selective reduction of oxime **18** proved to be challenging. Ultimately, we determined that a nickel boride-mediated reduction followed by acylation with acetic anhydride gave diacetate **19** as a single diastereomer (Scheme 4). The opening of epoxide **19** was attempted with several Lewis and Brønsted acids. Clean *trans* diaxial opening of epoxide **19** with aqueous trifluoroacetic acid provided an intermediate triol that was im-



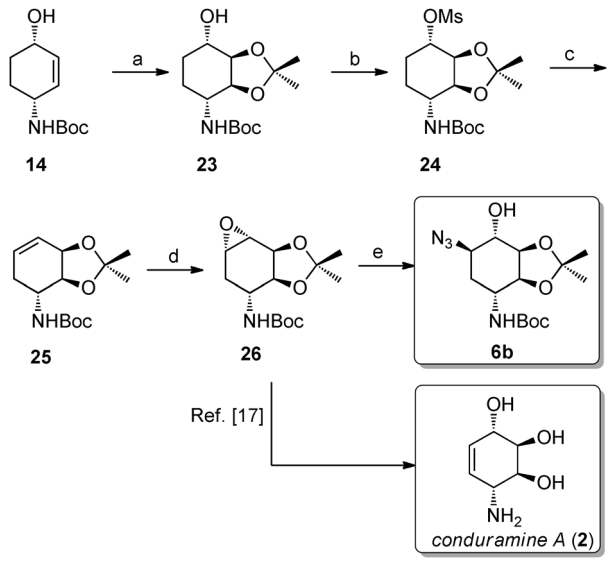
Scheme 1. Desymmetrization of dibenzoate **8**. TMS = trimethylsilyl; Bz = benzyl; Boc = *tert*-butyloxycarbonyl; $[Pd_2dba_3]$ = tris(dibenzylideneacetone)dipalladium(0).



Scheme 3. Synthesis of oxime **18**. Reaction conditions: a) K_2CO_3, MeOH, 93%; b) *meta*-chloroperoxybenzoic acid (*m*-CPBA), $CHCl_3$, 99%; c) tetrapropylammonium perruthenate (TPAP), *N*-methylmorpholine *N*-oxide (NMO), CH_2Cl_2, 86%; d) KO*t*Bu, *i*-amyl nitrite, THF, −78 °C; e) $NaBH_4$, MeOH, 56% over two steps.



Scheme 4. Synthesis of diastereomers **5b** and **20**. Reaction conditions: a) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, −78 °C; then Ac_2O, 52%; b) trifluoroacetic acid (TFA), H_2O (1:1), 110 °C; then BnOCOCl, K_2CO_3, MeOH:H_2O (3:1), 50%; c) BzCl, Et_3N, THF, 70%; d) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, −78 °C to RT, 88%; e) TFA, H_2O (1:1), 75 °C, 55% (d.r. 5:1).



Scheme 5. Synthesis of diastereomer **6b**. Reaction conditions: a) OsO_4, NMO, acetone; then 2,2-dimethoxypropane, PPTS, 62% over two steps; b) MsCl, DIPEA, 95%, CH_2Cl_2; c) DBU, microwave, 150 °C, 55%; d) *m*-CPBA, $CHCl_3$, 83%; e) NaN_3, NH_4Cl, *n*-propanol, reflux; then Boc_2O, 82%.

mediately trapped with benzyl choloroformate. NMR spectroscopic analyses, which were later corroborated by optical rotation and X-ray studies, showed that under these conditions we had not only opened the epoxide but also unexpectedly deprotected both nitrogens, destroying chirality by forming *meso* triol **20**, which also establishes the stereoselectivity of the oxime reduction.

The solution to this problem lay in the installation of a more robust differentiating group with the dibenzoylation of oxime **18**. Gratifyingly, the reduction of the resulting oxime **21** was greatly facilitated by the incorporation of an electron-withdrawing group (Scheme 3). The reduction of oxime **21** progressed with the in situ migration of the benzoyl group from O to N to give epoxide **22** (structure confirmed by NMR and X-ray analyses).[15] When conditions similar to those attempted for the opening of epoxide **19** were attempted, we were pleased to find that the opening of the epoxide proceeded with 5:1 regioselectivity and that the benzoyl group was stable to the reaction conditions. This completed the synthesis of our first diastereomeric DOS core **5b**.

To evaluate synthetic flexibility enabled by the Pd-catalyzed desymmetrization, we pursued the synthesis of diastereomer **6b** through an alternative route (Scheme 5). To this end, a diastereoselective osmium tetroxide-catalyzed *cis*-dihydroxylation of allylic alcohol **14** gave an intermediate triol that was immediately protected to generate acetonide **23** (Scheme 5). The treatment of alcohol **23** with methanesulfonyl chloride gave mesylate **24**. Elimination of mesylate **24** initially proved to be problematic. Ultimately, high-temperature microwave conditions gave olefin **25**. Epoxidation of olefin **25** gave epoxide **26** as a single diastereomer (structure confirmed by NMR and X-ray analyses).[15] The stereoselectivity of this reaction is controlled by both the steric bulk of the proximal acetonide and, to a larger extent, by the ability of the carbamate in **26** to direct the epoxidation.[16] Racemic epoxide **26** has been previously converted to conduramine A (**2**); therefore, our synthetic approach constitutes an asymmetric formal synthesis of this essential building block used in the synthesis of α-glycosidase inhibitors (Scheme 5).[17,18]

To complete the synthesis of diastereomeric DOS **6b**, the opening of epoxide **26** was attempted. Due to the electron-deficient nature of the ring, forcing conditions were required. By heating at reflux epoxide **26** with sodium azide in *n*-propanol, the expected *trans* diaxal addition product was formed, but with the concomitant loss of the *tert*-butoxycarbonyl group. Trapping the amine by the addition of di-*tert*-butyldicarbonate gave the final diastereomer **6b**.

In conclusion, we have developed a concise, asymmetric synthesis of two diastereomers of 2-deoxystreptamine and an asymmetric formal synthesis of conduramine A. Our approach demonstrates the utility of a one-pot catalytic asymmetric desymmetrization in the synthesis of epimers of ring II in aminoglycosides. The two synthetic strategies presented are concise and display a range of highly diastereoselective transforma-

tions that provide several intermediates that can potentially be of value in the design of a range of unnatural aminocyclitols, such as 2-deoxystreptamine analogues and other conduramines.

Experimental Section

1 *S*,4 *R*- Benzoic acid 4-*tert*-butoxycarbonylamino-cyclohex-2-enyl ester

To a flame-dried round-bottomed flask was added $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (29.0 mg, 0.079 mmol), (*S*,*S*)-**9** (164 mg, 0.2376 mmol), and dibenzoate **8** (12.5 g, 39.62 mmol). The flask was the placed under reduced pressure (vacuum pump) for ten seconds and refilled with Ar; this purging procedure was repeated three times to ensure that no oxygen remained in the reaction vessel. After being placed in an Ar atmosphere, degassed THF (17 mL) was added, and the mixture was stirred for 10 min at RT. Freshly distilled azidotrimethylsilane (6.31 mL, 47.54 mmol) was added dropwise at 0 °C, and the reaction was stirred at this temperature for 1.5 h. Water (30 mL) was added to the reaction mixture followed by a dropwise addition of solution of trimethyl phosphine (100 mL of a 1 M solution in THF) over 2 h. Upon complete disappearance of the intermediate allylic azide, triethylamine (13.0 mL) and di-*tert*-butyl-dicarbonate (13.3 g, 66.66 mmol) were added, and the reaction was stirred for 12 h at RT. The reaction was diluted with diethyl ether (300 mL) and washed with saturated sodium bicarbonate, brine, dried ($MgSO_4$), and concentrated. Silica-gel chromatography by using 10% ethyl acetate/hexanes gave 10.69 g (87%) of the title compound as oil. A clear $R_f = 0.5$ in 20% ethyl acetate/hexanes; $[\alpha]_D^{24} = -75.84$ (c 0.18, CH_2Cl_2); ^{1}H (400 MHz, $CDCl_3$): $\delta = 8.03$ (dd, $J = 8.0$, 1.6 Hz, 2H), 7.54 (dd, $J = 8.0$, 8.0 Hz, 1H), 7.42 (dd, $J = 8.0$ Hz, 2H), 5.93 (ddd, $J = 10.1$, 3.4, 1.0 Hz, 1H), 5.89 (dd, $J = 10.1$, 2.4 Hz, 1H), 5.42 (m, 1H), 4.60 (bd, $J = 7.9$ Hz, 1H), 4.19 (m, 1H), 2.01–1.89 (m, 3H), 1.72 (m, 1H), 1.4 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.1$, 155.2, 133.8, 133.0, 130.4, 129.6, 128.4, 128.1, 79.6, 67.4, 46.0, 28.4, 26.0 ppm; IR (thin film): $\tilde{\nu}_{max} = 3411$, 3315, 3065, 3027, 2943, 2867, 1702, 1530, 1246, 1064 cm^{-1}; HRMS (EI, $[MC_{18}H_{23}NO_4-(C_4H_9)]^+$) calcd for $C_{14}H_{15}NO_4$: 261.1001; found: 261.1010.

1 *S*,4 *R*-(5-Hydroxy-7-oxa-bicyclo[4.1.0]hept-2-yl)-carbamic acid *tert*-butyl ester

To a solution of alcohol **14** (56 mg, 0.26 mmol) in anhydrous chloroform (20 mL) was added *m*-chloroperoxybenzoic acid (50 mg, 0.29 mmol). The reaction was stirred at RT for 24 h (consumption of starting material was monitored by GC). Upon completion, the reaction mixture was washed with saturated sodium hydrogen carbonate, brine, dried ($MgSO_4$), and concentrated to afford 60 mg (99%) of title compound as a clear oil that slowly crystallized to solid. A white $R_f = 0.7$ in 100% ethyl acetate; $[\alpha]_D^{26} = +22.12$ (c 2.2, CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]DMSO) : $\delta = 6.72$ (d, $J = 8.0$ Hz), 4.82 (d, $J = 5.3$ Hz, 1H), 3.82 (m, 1H), 3.74 (m, 1H), 3.24 (dd, $J = 4.0$ Hz, 1H), 3.17 (dd, $J = 4.0$, 2.6 Hz, 1H), 1.48–1.27 ppm (m, 4H), 1.38 (s,1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 155.1$, 77.7, 64.6, 56.1, 54.7, 44.7, 28.2, 26.4, 24.7 ppm; IR (thin film) $\tilde{\nu}_{max} = 3348$, 2977, 2938, 2871, 1702, 1506, 1456, 1392, 1367, 1326, 1249, 1170, 1068, 1003, 929, 895, 848, 776 cm^{-1}; HRMS (EI, $[M]^+$) calcd for $C_{11}H_{19}NO_4$: 229.1314; found: 229.1315. The stereochemistry of the desired product was initially based on hydrogen-bond-directed epoxidation and later assigned by X-ray analysis of a downstream intermediate.[15]

1 *S*,4 *R*-(5-Oxo-7-oxa-bicyclo[4.1.0]hept-2-yl)-carbamic acid *tert*-butyl ester

Tetra-*n*-propylammonium perruthenate (0.66 g, 1.88 mmol) and activated 4 Å molecular sieves (19 g) were added to a solution of **15** (8.62 g, 37.62 mmol) in dichloromethane (268 mL). Solid 4-methylmorpholine *N*-oxide (6.61 g, 56.43 mmol) was added, and the slurry was stirred at RT for 8 h. The reaction was poured onto a bed of silica gel and eluted with dichloromethane. The eluent was concentrated, and the crude product was purified by using silica-gel flash chromatography (30% ethyl acetate/hexanes) to afford 7.36 g (86%) of the title compound as solid. A white $R_f = 0.25$ in 20% ethyl acetate/hexanes; m.p. 86–88 °C; $[\alpha]_D^{23} = +178.0$ (c 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.86$ (d, $J = 9$ Hz, 1H), 4.25 (q, $J = 9$ Hz, 1H), 3.65 (d, $J = 4$ Hz, 1H), 3.29 (d, $J = 4$ Hz, 1H), 2.53 (ddd, $J = 18.0$, 4.0, 4.0 Hz, 1H), 2.18 (ddd, $J = 18.0$, 4.0, 4.0 Hz, 1H), 1.85 (m, 1H), 1.46 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 203.2$, 155.1, 80.2, 57.5, 55.9, 46.3, 34.9, 28.3, 22.9 ppm; IR (thin film): $\tilde{\nu}_{max} = 3331$, 2976, 1693, 1524, 1455, 1391, 1365, 1306, 1249, 1167, 1056, 1007, 957, 876 cm^{-1}; HRMS (EI, $[MC_{11}H_{17}NO_4-(C_4H_9)]^+$) calcd for $C_7H_9NO_4$: 171.0532; found: 171.0539; elemental analysis calcd (%) for $C_7H_9NO_4$: C 58.14, H 7.54, N 6.16; found C 57.96, H 7.54, N 6.04.

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Keywords: aminoglycoside · azidization · conduramines · palladium · synthetic methods

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[14] Reaction could be conducted on a 20 g scale by using this protocol, in which the stepwise procedure, when conducted on smaller scales, resulted in the formation of undesired products.

[15] See the Supporting Information.

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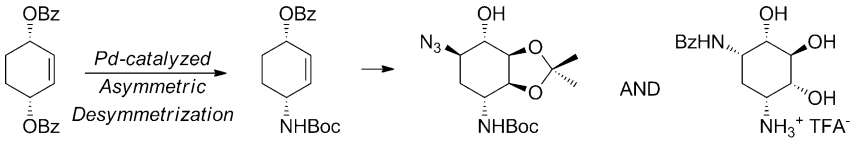
Asymmetric Stereodivergent Strategy Towards Aminocyclitols



2-Deoxystreptamine diastereoisomers

Very synthetic! Pd-catalyzed asymmetric desymmetrization enables a concise synthesis of aminocyclitols, such as diastereomeric 2-deoxystreptamine analogues and conduramine A (see scheme).