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An 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 novel aminoglycoside antibiotics and enantiomerically pure α -glucosidase inhibitors.

Keywords

Palladium; Azidization; 2-deoxystreptamine; aminoglycoside; conduramine

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 attention², the need for structural replacements continues to be an essential area of research.³ Toxicity is 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 novel antibiotics that are less susceptible to enzymatic inactivation.⁵

A majority of the strategies towards the synthesis of novel 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

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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.

We chose 2-deoxy-4,5,6-tris-*epi*- (**5a**) and 2-deoxy-3,4-bis-*epi*-streptamine (**6a**), the former since 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, differentially protected diastereomeric DOS analogues must be readily accessible. The challenge associated with a selective synthesis of such analogs 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 multi-step 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** using asymmetric catalysis where 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 for 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 via the *trans*- and *cis*-dihydroxylation of a common intermediate **7**, respectively (Figure 3). Initially two strategies were examined to incorporate the second nitrogen in analog **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), we obtained aromatized products.

In an alternative strategy, we envisioned that the second nitrogen of analog **5** could be installed via a nitrosation. Analogously, the second nitrogen of analog **6b** would be installed via the regioselective opening of an epoxide. Carbamate **7** could be obtained via 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**, while 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% ee via a one-pot protocol 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** afforded epoxide **15** as a single diastereomer whose further oxidation provided epoxyketone **16**. Enolization of epoxyketone **16** with potassium *tert*-butoxide, followed by quenching with *iso*-amyl nitrite, afforded oxime **17** as a single isomer of undetermined geometry. Reduction of the carbonyl carbon from the least hindered face using sodium borohydride afforded 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 afforded 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 immediately trapped with benzyl chloroformate. 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).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**.

In order to evaluate synthetic flexibility enabled by the Pd-catalyzed desymmetrization we pursued the synthesis of diastereomer **6b** via an alternative route (Scheme 5). To this end, a diastereoselective osmium tetroxide-catalyzed *cis*-dihydroxylation of allylic alcohol **14** afforded 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 problematic. Ultimately, high temperature microwave conditions yielded olefin **25**. Epoxidation of olefin **25** afforded epoxide **26** as a single diastereomer (structure confirmed by NMR and x-ray).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 refluxing epoxide **26** with sodium azide in *n*-propanol, the expected trans diaxial addition product was formed, but with the concomitant loss of the *tert*-butoxycarbonyl group. Trapping the amine by the addition of di-*tert*-butyldicarbonate afforded 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 transformations that provide several intermediates that can potentially be of value in the design of a range of unnatural aminocyclitols, such as 2-deoxystreptamine analogs 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 $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ (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 placed under reduced pressure (vacuum pump) for 10 seconds and refilled with Ar; this purging procedure was repeated three times to ensure 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 minutes at room temperature. 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 hours. Water (30 mL) was added to the reaction mixture followed by a dropwise addition of solution of trimethyl phosphine (100 mL of a 1M solution in THF) over 2 hours. 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 hours at room temperature. The reaction was diluted with diethyl ether (300 mL) and washed with saturated sodium bicarbonate, brine, dried (MgSO_4) and concentrated. Silica gel chromatography using 10% ethyl acetate/hexanes afforded 10.69 g (87%) of the title compound as a clear oil. $R_f = 0.5$ in 20% ethyl acetate/hexanes; $[\alpha]_{\text{D}_{24}} = -75.84$ (c 0.18, CH_2Cl_2); ^1H (400 MHz, CDCl_3): δ 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 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 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) ν_{max} 3411, 3315, 3065, 3027, 2943, 2867, 1702, 1530, 1246, 1064 cm^{-1} ; HRMS (EI, $[\text{MC}_{18}\text{H}_{23}\text{NO}_4 - (\text{C}_4\text{H}_9)]^+$) Calc'd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: 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 room temperature for 24 hours (consumption of starting material was monitored by GC). Upon completion, the reaction mixture was washed with saturated sodium hydrogen carbonate, brine, dried (MgSO₄), and concentrated to afford 60 mg (99%) of title compound as a clear oil that slowly crystallized to a white solid. *R*_f = 0.7 in 100% ethyl acetate; [^α]_D₂₆ = +22.12 (c 2.2, CH₂Cl₂); ¹H NMR (400 MHz, DMSO-*d*₆): δ 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 (m, 4H), 1.38 (s, 1H) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆): δ 155.1, 77.7, 64.6, 56.1, 54.7, 44.7, 28.2, 26.4, 24.7 ppm; IR (thin film) *v*_{max} 3348, 2977, 2938, 2871, 1702, 1506, 1456, 1392, 1367, 1326, 1249, 1170, 1068, 1003, 929, 895, 848, 776 cm⁻¹; HRMS (EI, [M]⁺) Calc'd for C₁₁H₁₉NO₄: 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°A 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 room temperature for 8 hours. The reaction was poured onto a bed of silica gel and eluted with dichloromethane. The eluent was concentrated and the crude product was purified using silica gel flash chromatography (30% ethyl acetate/hexanes) to afford 7.36 g (86%) of the title compound as a white solid. *R*_f = 0.25 in 20% ethyl acetate/hexanes; melting point: 86 – 88 °C; [^α]_D₂₃ = +178.0 (c 0.2, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ 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 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 203.2, 155.1, 80.2, 57.5, 55.9, 46.3, 34.9, 28.3, 22.9 ppm; IR (thin film) *v*_{max} 3331, 2976, 1693, 1524, 1455, 1391, 1365, 1306, 1249, 1167, 1056, 1007, 957, 876 cm⁻¹; HRMS (EI, [MC₁₁H₁₇NO₄-(C₄H₉)]⁺) Calc'd for C₇H₉NO₄: 171.0532 Found: 171.0539; Elemental analysis Theoretical C58.14, H7.54, N6.16 Found C57.96, H7.54, N6.04.

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References

1. Mahmud T, Flatt PM, Wu X. J Nat Prod. 2007; 70:1384. [PubMed: 17661520]
2. Busscher GF, Rutjes FPJT, Van Delft FL. Chem Rev. 2005; 105:775. [PubMed: 15755076]
3. (a) Hanessian S, Pachamuthu K, Szychowski J, Giguere A, Swayze EE, Migawa MT, Francois B, Kondo J, Westhof E. Bioorg Med Chem Lett. 2010; 20:7097. [PubMed: 20970332] (b) Hanessian S, Adhikari S, Szychowski J, Pachamuthu K, Wang X, Migawa MT, Griffey RH, Swayze EE.

- Tetrahedron. 2007; 63:827.(c) Kawaguchi H, Nakagawa S, Fijistawa K. J Antibiot. 1972; 25:695. [PubMed: 4568692]
4. (a) Vakulenko SB, Mobashery S. Clinical Microbiology Reviews. 2003; 16:430. [PubMed: 12857776] (b) Mingeot-Leclercq MP, Tulkens PM. Antimicrob Agents Chemother. 1999; 43:1003. [PubMed: 10223907] (c) Kotra LP, Haddad J, Mobashery S. Antimicrob Agents Chemother. 2000; 44:3249. [PubMed: 11083623]
5. Magnet S, Blanchard JS. Chem Rev. 2005; 105:477. [PubMed: 15700953]
6. (a) Sucheck SJ, Greenberg WA, Tobert TJ, Wong CH. Angew Chem Int Ed. 2000; 39:1080.(b) Haddad J, Kotra LP, Llano-Sotelo B, Kim C, Azucena EF Jr, Liu M, Vakulenko SB, Chow CS, Mobashery S. J Am Chem Soc. 2002; 124:3229. [PubMed: 11916405] (c) Greenberg WA, Priestley ES, Sears PS, Alper PB, Rosenbohm C, Hendrix M, Hung SC, Wong CH. J Am Chem Soc. 1999; 121:6527.
7. (a) Busscher GF, van den Broek SAMW, Rutjes FPJT, van Delft FL. Tetrahedron. 2007; 63:3183. (b) Barluenga S, Simonsen KB, Littlefield ES, Ayida BK, Vourloumis D, Winters GC, Takahashi M, Shandrick S, Zhao Q, Han Q, Hermann T. Bioorg Med Chem Lett. 2004; 14:713. [PubMed: 14741274]
8. Vourloumis D, Winters Geoffrey C, Takahashi M, Simonsen Klaus B, Ayida Benjamin K, Shandrick S, Zhao Q, Hermann T. Chembiochem. 2003; 4:879. [PubMed: 12964163]
9. (a) Igarashi K, Sugawara T, Honma T, Tada Y, Miyazaki H, Nagata H, Mayama M, Kubota T. Carbohydr Res. 1982; 109:73.(b) Boxler DL, Brambilla R, Davies DH, Mallams AK, McCombie SW, Morton JB, Reichert P, Vernay HF. J Chem Soc; Perkin Trans. 1981; 1:2168.
10. (a) Dijkstra D. Recl Trav Chim Pays-Bas. 1968; 87:161.(b) Beier B, Schuerrle K, Werbitzky O, Piepersberg W. J Chem Soc, Perkin Trans. 1990; 1:2255.(c) Baer HH, Yu RJ. Tetrahedron Lett. 1967:807.
11. (a) Verhelst SHL, Wennekes T, van der Marel GA, Overkleeft HS, van Boeckel CAA, van Boom JH. Tetrahedron. 2004; 60:2813.(b) Schuerrle K, Beier B, Pipersberg W. J Chem Soc, Perkin Trans. 1991; 1:2407.(c) De Almeida MV, Da Silva ET, Le Hyaric M, Machado AS, De Souza MVN, Santiago RM. J Carbohydr Chem. 2003; 22:733.
12. (a) Trost BM, Pulley S. Tetrahedron Lett. 1995; 36:8737.(b) Trost BM, Pulley SR. J Am Chem Soc. 1995; 117:10143.(c) Trost BM, Cook GR. Tetrahedron Lett. 1996; 37:7485.
13. Espino CG, Fiori KW, Kim M, Du Bois J. J Am Chem Soc. 2006; 62:2733.
14. Reaction could be conducted on a 20 gram scale using this protocol, where the stepwise procedure, when conducted on smaller scales, resulted in the formation of undesired products.
15. See Supporting Information
16. (a) Wipf P, Wang X. Tetrahedron Lett. 2000; 41:8747.(b) Rotella DP. Tetrahedron Lett. 1989; 30:1913.(c) Masesane IB, Steel PG. Tetrahedron Lett. 2004; 45:5007.(d) Kiss L, Forro E, Fueleop F. Tetrahedron Lett. 2006; 47:2855.
17. Leung-Toung R, Liu Y, Muchowski JM, Wu YL. J Org Chem. 1998; 63:3235.
18. For a recent synthesis of conduramine A see: Lu PH, Yang CS, Devendar B, Liao CC. Org Lett. 2010; 12:2642. [PubMed: 20450183]

Figure 1.
Clinically relevant aminoglycoside antibiotics.

Figure 2.
Diastereomeric 2-deoxystreptamine targets.

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

Scheme 1.
Desymmetrization of dibenzoate 8.

Scheme 2.

Initial strategies for second nitrogen incorporation

Scheme 3. Synthesis of oxime **18**.

Reaction Conditions: a) K_2CO_3 , MeOH, 93%; b) *m*-CPBA, $CHCl_3$, 99%; c) TPAP, NMO, CH_2Cl_2 , 86%; d) KO*t*-Bu, *i*-amyl nitrite, THF, $-78\text{ }^\circ\text{C}$; e) $NaBH_4$, MeOH, 56% over 2 steps.

Scheme 4.

Synthesis of diastereomers **5b** and **20**.

Reaction Conditions: a) NaBH_4 , $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, MeOH, -78°C ; then Ac_2O , 52%; b) TFA, H_2O (1:1), 110°C ; then $\text{BnOCOC}_2\text{H}_5$, K_2CO_3 , MeOH: H_2O (3:1), 50%; c) BzCl , Et_3N , THF, 70% d) NaBH_4 , $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, MeOH, -78°C to rt, 88% (e) TFA, H_2O (1:1), 75°C , 55% (5:1 dr).

Scheme 5. Synthesis of diastereomer **6b**.

Reaction Conditions: a) OsO₄, NMO, acetone; then 2,2-dimethoxypropane, PPTS, 62% over 2 steps; b) MsCl, DIPEA, 95%, CH₂Cl₂; c) DBU, microwave, 150 °C, 55%; d) *m*-CPBA, CHCl₃, 83%; e) NaN₃, NH₄Cl, *n*-propanol, reflux; then Boc₂O, 82%.