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Enzymatic desymmetrization of 2,5-dideoxystreptamine precursors

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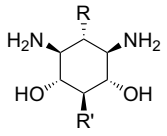
Abstract—The stereoselective enzymatic acylation of *meso*-6,7-diazabicyclo[3.2.1]oct-6-ene-2,4-diol **4** and *meso*-4,6-diazidocyclohexane-1,3-diol **5** in organic media gave the corresponding monoesters in high enantiomeric excess. The hydrolysis of the corresponding diacetate derivatives in the presence of a different set of enzymes provided the same monoesters. The products are precursors of dideoxystreptamine, an aminocyclitol found in synthetic aminoglycoside antibiotics.

1. Introduction

Aminoglycosides form a large class of antibiotics with a broad antibacterial spectrum particularly against Gram-negative bacteria. They exert their antibacterial activity by binding to specific sites in ribosomal RNA of bacteria and affecting the fidelity of protein biosynthesis.[1–3] The clinical usefulness of aminoglycoside antibiotics is hampered by their adverse side effects and by the emergence of bacterial resistance.[3,4] More recently, aminoglycosides have been shown to target a variety of other RNA structures (ribozymes, regulatory domains of HIV mRNA, group I intron, oncogenic Bcr-Abl mRNA sequence) and have, therefore, become lead models for the study of RNA-ligand recognition.[5–10] RNA molecules are involved in essential cellular processes and they are central targets for drug design.[11,12] Accordingly, there has been considerable interest in the synthesis of aminoglycosides analogues with improved biological activities.[13–23]

Their general structure consists of an aminocyclitol central core linked to one or more aminosugars by glycosidic bonds. The most common aminocyclitols are either natural streptamine and 2-deoxystreptamine or synthetic 2,5-dideoxystreptamine (Fig. 1). Although these aminocyclitols are *meso* compounds, the preparation of desymmetrized enantiopure derivatives is a prerequisite for the synthesis of aminoglycoside analogues. Herein, we report the enzymatic desymmetrization of 2,5-dideoxystreptamine precursors.



streptamine : R = OH R' = OH
2-deoxystreptamine : R = H R' = OH
2,5-dideoxystreptamine : R = H R' = H

Figure 1.

2. Results and discussion

2.1. Substrate preparation

Diepoxide **1** was prepared by epoxidation of 1,4-cyclohexadiene with *m*-chloroperbenzoic acid according to a known procedure.[24] Two pathways were used to obtain diol **5** from diepoxide **1** (Scheme 1). One route involves the reaction of **1** with hydrazine[24] to form **2**, followed by hydrogenolysis and azide transfer.[25] However, compound **2** is unstable and is decomposed gradually by air oxidation. Azo compound **4** was obtained from **2** by oxidation with hydrogen peroxide.[26] In an alternative route, regioselective ring opening of diepoxide **1** with benzylamine[27] (nucleophile and solvent) at 150 °C provided **3** in excellent yield (94%) after recrystallization; hydrogenolysis and azide transfer gave **5**. Corresponding diacetates **6** and **7** were prepared by the acetylation of **4** and **5** with acetic anhydride in pyridine.

2.2. Enzymatic desymmetrizations

We first completed some screening experiments in order to find hydrolases with the ability to distinguish the enantiotopic groups of *meso*-substrates **4**–**7**. Diol **4** (Scheme 2)

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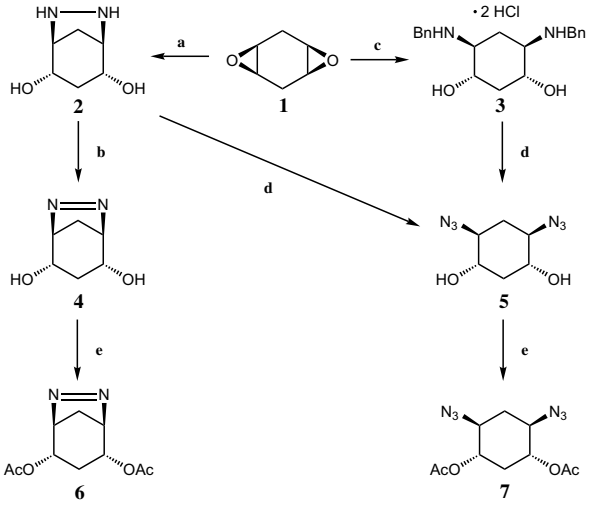
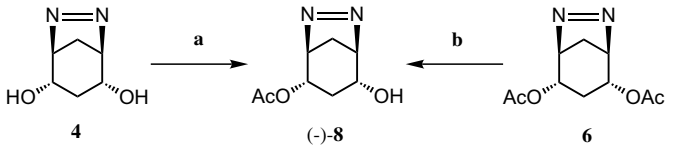


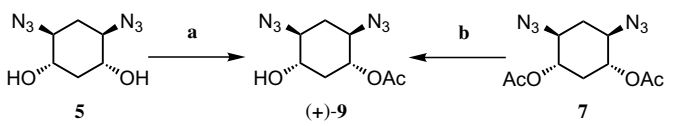
Scheme 1. Reagents and conditions: (a) NH_2NH_2, EtOH; (b) H_2O_2, H_2O; (c) $BnNH_2$; (d) (i) Pd/C, AcOH/H_2O; (ii) TfN_3, $ZnCl_2$, Et_3N, CH_2Cl_2/MeOH/H_2O; (e) Ac_2O, pyridine.

was subjected to the enzyme-catalyzed esterification by treatment with *Candida rugosa* lipase (CRL) in vinyl acetate at 21 °C for 3 days to give optically active ester (−)-**8** in moderate yield (63%) and good enantiomeric excess (ee = 92%). The reaction is very sensitive to experimental conditions and any change (temperature, solvent, and time) will have a negative effect. Also, the formation of the corresponding diacetate **6** lowers the enantiomeric purity of product **8**. In general, the esterification (transesterification) of *meso*-diols and the hydrolysis of the corresponding *meso*-diesters are complementary and give opposite enantiomers. Unexpectedly, CRL showed very little hydrolytic activity in the presence of diester **6**. However, hydrolysis of diester **6** (Scheme 2) by pig liver esterase (PLE) in a phosphate buffer provided the same monoester (−)-**8** (92% yield) in good enantiomeric excess (ee = 90%).



Scheme 2. Reagents and conditions: (a) *Candida rugosa* lipase, vinyl acetate; (b) pig liver esterase, phosphate buffer, pH 7.7.

Following the procedure reported by Wong et al.[23] for the enzymatic desymmetrization of a deoxystreptamine precursor, the hydrolysis of diacetate **7** (Scheme 3) in the presence

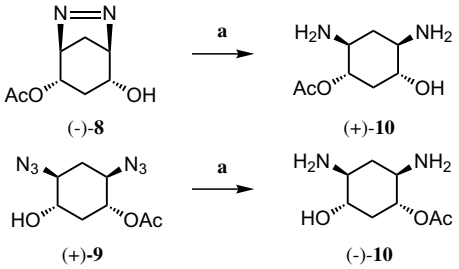


Scheme 3. Reagents and conditions: (a) *Candida rugosa* lipase, vinyl acetate; (b) *Candida antarctica* lipase B, phosphate buffer, pH 6.2/toluene (1:1).

of CAL-B provided monoester (+)-**9** in high ee (⩾99%) but low yield (32%). In the meantime, Vourloumis et al.[28] reported the same reaction under similar conditions (Novozym 435 is CAL-B immobilized on a macroporous acrylic resin, yield = 21%). Acylation of diol **5** by treatment with CRL in vinyl acetate gave (+)-**9** in high enantiomeric excess (ee ⩾99%) and higher yield (85%).

2.3. Determination of absolute configuration

The absolute configuration of compound **8** was determined by chemical correlation (Scheme 4) with compound (+)-**9** of known absolute configuration (1*R*,2*R*,4*S*,5*S*).[28] Hydrogenation of (+)-**9** in methanol in the presence of 10% Pd/C gave dideoxystreptamine monoester (−)-**10** {$[\alpha]_D^{22}$ = −10.8 (*c* 0.6, MeOH)}, while hydrogenation of (−)-**8** under the same conditions gave the opposite enantiomer (+)-**10** {$[\alpha]_D^{22}$ = +9.7 (*c* 1.0, MeOH)}.



Scheme 4. Reagents and conditions: (a) H_2, Pd/C, MeOH.

3. Experimental

3.1. General

NMR spectra were recorded on a Varian Inova AS400 spectrometer (400 MHz). Infrared spectra were recorded on a Bomem MB-100 spectrometer. Optical rotations were measured using a JASCO DIP-360 digital polarimeter (*c* as gram of compound per 100 mL). Flash column chromatography was carried out using 40–63 μm (230–400 mesh) silica gel. The enantiomeric excesses (ee) were determined by chiral HPLC analysis on a CHIRALCEL OD-H (4.6 mm × 250 mm) using racemic compounds as references. *Candida antarctica* lipase B (Chirazyme L-2) was obtained from Boehringer Mannheim. PLE (porcine liver esterase) and CRL (*C. rugosa* lipase) were from Aldrich.

3.2. (1*R*,2*R*,4*S*,5*S*)-6,7-Diazabicyclo[3.2.1]octane-2,4-diol *meso*-2

To a solution of *cis*-epoxide **1** (3.08 g, 27.5 mmol) in anhydrous EtOH (20 mL) was added anhydrous hydrazine (1.16 mL, 1.3 equiv). The solution was then refluxed for 20 h under nitrogen. The reaction mixture was cooled on ice and after 2 h, the crystalline product was collected, washed with cold ether, and dried to give **2** (3.24 g, 82%) as a white solid: mp 190–194 °C; lit.[24] mp 185–190 °C (dec.); IR (KBr) 3240, 1641, 1438, 1110, 1050 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.42 (td, J = 11.9, 6.4 Hz,

1H), 1.55 (d, $J = 15.8$ Hz, 1H), 2.01 (dt, $J = 15.8$, 5.3 Hz, 1H), 2.85 (d, $J = 11.9$ Hz, 1H), 3.38 (m, 2H), 3.74 (m, 2H), 4.87 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 26.5, 32.7, 58.8, 68.6.

3.3. (1*R*,3*S*,4*S*,6*R*)-4,6-Bis(benzylamino)cyclohexane-1,3-diol dihydrochloride *meso*-3

Diepoxide **1** (2.40 g, 21.4 mmol) was dissolved in benzylamine (4 equiv) and the solution was heated at 150 °C for 24 h. The solution was diluted with HCl 1 N (30 mL), followed by addition of EtOAc (30 mL), and the mixture was stirred at 0 °C for 30 min. The organic phase was discarded and the aqueous phase evaporated. The yellow residue was recrystallized in MeOH/dioxane/EtOAc to give **3**[27,29] (8.01 g, 94%) as white needles: mp 269–271 °C (dec.); lit.[29] mp 267–270 °C (dec.); IR (KBr) 3439, 2966, 1647, 1499, 1360, 1234 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 1.46 (m, 2H), 2.31 (m, 2H), 3.03 (m, 2H), 3.69 (m, 2H), 4.18 (m, 4H), 7.31 (m, 10H); ^{13}C NMR (100 MHz, D_2O): δ 24.7, 39.2, 48.7, 58.3, 66.6, 129.6, 129.8, 130.0, 130.2.

3.4. (1*R*,2*R*,4*S*,5*S*)-6,7-Diazabicyclo[3.2.1]oct-6-ene-2,4-diol *meso*-4

To a solution of **2** (2.40 g, 16.7 mmol) in water (15 mL) was added a fresh 30% H_2O_2 solution (5.2 mL, 3 equiv) and the solution was vigorously stirred for 3 days at room temperature. Raney Nickel was added and the stirring maintained for a few minutes. The mixture was filtered, washed with water and evaporated. The crude product was purified by flash chromatography (acetone/CH_2Cl_2, 1:2) to yield **4** (1.23 g, 52%) as a white solid: mp 142–145 °C; lit.[26] mp 140–145 °C; IR (KBr) 2926, 1728, 1518, 910, 876 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 1.33 (m, 1H), 1.43 (m, 1H), 1.69 (m, 1H), 2.47 (dd, $J = 1.4$, 12.3 Hz, 1H), 3.74 (m, 2H), 4.82 (m, 2H), 4.94 (dd, $J = 5.5$, 3.1 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 22.5, 35.9, 59.9, 84.2.

3.5. (1*R*,3*S*,4*S*,6*R*)-4,6-Diazidocyclohexane-1,3-diol *meso*-5

A solution of *meso*-diol **2** or **3** (13.9 mmol) in AcOH/H_2O (1:1, 30 mL) was stirred at 60 °C with 10% Pd-on-carbon (200 mg) under hydrogen (55 psi) for 3 days. The catalyst was removed by filtration and the solvent evaporated to give a white residue. The solid was dispersed in EtOH, filtered, and dried to afford 2,5-dideoxystreptamine (2,5-dDOS) (90% from **2** and 100% from **3**) as a white solid. 2,5-dDOS (1.80 g, 12.3 mmol) was dissolved in H_2O (12 mL), then $ZnCl_2$ (2 mol %) and Et_3N (6 mol %) were added followed by the slow addition of MeOH (36 mL). In another flask, NaN_3 (12 equiv) was dissolved in H_2O (15 mL), CH_2Cl_2 (15 mL) was added and the temperature was reduced to 0 °C. Tf_2O (5.5 equiv) was carefully added (dropwise) under nitrogen. The solution was stirred for 2 h at 0 °C. A solution of $NaHCO_3$ (satd) was slowly added until the production of CO_2 stopped. This mixture was then transferred in a separatory funnel followed by extraction with CH_2Cl_2 (2×10 mL). The organic phase was washed with $NaHCO_3$ (satd) (1×8 mL) and this solution was finally added to the first solution containing the 2,5-dDOS. The mixture was stirred overnight, evaporated and the crude product was purified by flash chromatography (hexanes/EtOAc, 1:1) to give **5** (1.46 g, 53% from **2** and 1.68 g, 61% from **3**) as a white solid: mp 80–81 °C; lit.[30] mp 80–81 °C; IR (KBr) 3256, 2923, 2098, 1448, 1257, 1016 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 1.16 (m, 1H), 1.43 (m, 1H), 2.11 (m, 2H), 3.26 (m, 2H), 3.40 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 32.4, 40.1, 64.2, 71.2.

3.6. Preparation of diacetates 6 and 7: general procedure

To a stirred solution of alcohol **4** or **5** (12.1 mmol) in pyridine (10 mL) was added acetic anhydride (3 equiv) and the solution stirred overnight at rt under nitrogen. The solution was diluted with ether, washed with brine, dried over $MgSO_4$, and evaporated. Crude diacetate **6** was recrystallized from a hot solution of ethanol to give 1.64 g (60%) as white needles. Crude diacetate **7** was purified by flash chromatography (hexanes/EtOAc, 6:1) to give 2.77 g (81%) as a white solid.

3.6.1. (1*R*,2*R*,4*S*,5*S*)-4-(Acetyloxy)-6,7-diazabicyclo-[3.2.1]oct-6-en-2-yl acetate *meso*-6. White needles: mp 101–103 °C; lit.[26] mp 103–104 °C; IR (KBr) 3445, 2958, 1727, 1361, 1242, 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36–1.72 (m, 3H), 2.05 (s, 6H), 2.34 (d, $J = 12.5$ Hz, 1H), 4.98 (sextuplet, $J = 1.4$ Hz, 1H), 5.24 (t, $J = 4.7$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 19.8, 23.8, 29.5, 62.5, 81.1, 170.5.

3.6.2. (1*R*,2*R*,4*S*,5*S*)-5-(Acetyloxy)-2,4-diazidocyclohexyl acetate *meso*-7. White solid: mp 77–79 °C; lit.[30] mp 78 °C; IR (KBr) 2920, 2101, 1735, 1368, 1246, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (m, 2H), 2.03 (s, 6H), 2.20 (m, 1H), 2.40 (m, 1H), 3.45 (m, 2H), 4.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 32.5, 33.8, 60.5, 72.1, 169.8.

3.7. (1*S*,2*S*,4*R*,5*R*)-4-(Hydroxy)-6,7-diazabicyclo[3.2.1]oct-6-en-2-yl acetate 8

3.7.1. Enzymatic acylation of diol 4. To a suspension of diol **4** (80 mg, 0.56 mmol) in vinyl acetate (6 mL) was added *C. rugosa* lipase (80 mg) and the mixture stirred at room temperature. The reaction was monitored by TLC and stopped when the formation of the diacetate was detected (~3 days). The mixture was filtered and the solvent evaporated. The crude product was purified by flash chromatography with CH_2Cl_2/acetone (3:1) to give (−)-**8** (65 mg, 63%, ee = 92%) as a colorless oil. $[\alpha]_D^{22} = -63.3$ (*c* 1.90, $CHCl_3$); IR (NaCl) 3433, 2964, 2252, 1738, 1247, 910 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 1.25–1.67 (m, 4H), 2.04 (s, 3H), 2.46 (d, $J = 12.3$ Hz, 1H), 3.88 (dd, $J = 2.9$, 6.1 Hz, 1H), 4.83 (s, 1H), 5.09 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 19.9, 23.2, 32.4, 59.5, 63.1, 81.0, 84.5, 170.7; HRMS (CI, NH_3) calcd for $C_8H_{13}N_2O_3$ $(M+H)^+$: 185.0926. Found: 185.0929.

3.7.2. Enzymatic hydrolysis of diacetate 6. Diacetate **6** (270 mg, 1.19 mmol) was suspended in a buffered aqueous solution (10 mL phosphate, pH 7.7). Porcine liver esterase

was added and the pH maintained at its initial value by addition of 0.25 M aqueous NaOH. After 2 h, the solution became clear and the aqueous mixture was filtered using 0.22 μm membrane filter, and the retained enzyme was washed with H_2O. The aqueous solution was extracted with CH_2Cl_2 (10×20 mL), and the organic layer was dried over $MgSO_4$ and concentrated. Flash chromatography of the residue with Et_2O gave monoacetate (−)-**8** (202 mg, 92%, ee = 90%) as a colorless oil. $[\alpha]_D^{22} = -61.9$ (*c* 1.44, $CHCl_3$), spectral data as above.

3.8. (1*R*,2*R*,4*S*,5*S*)-2,4-Diazido-5-hydroxycyclohexyl acetate 9

3.8.1. Enzymatic acylation of diol 5. To a solution of diol **5** (250 mg, 1.26 mmol) in vinyl acetate (5 mL) was added *C. rugosa* lipase (100 mg) and the mixture stirred at rt for 2 days. The enzyme was filtered, washed with CH_2Cl_2 and the solvent evaporated. Flash chromatography of the crude product with hexanes/EtOAc (3:1) provided monoacetate (+)-**9** (258 mg, 85%, ee ⩾99%) as a colorless oil. $[\alpha]_D^{22} = +22$ (*c* 0.6, $CHCl_3$); IR (NaCl) 3440, 2919, 2101, 1732, 1374, 1235, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 1H), 1.36 (m, 1H), 1.46 (m, 1H), 2.08 (s, 3H), 2.25 (m, 1H), 2.36 (m, 1H), 3.30 (m, 2H), 3.52 (m, 1H), 4.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 32.2, 36.1, 60.7, 63.9, 70.9, 72.7, 170.2; HRMS (CI, NH_3) calcd for $C_8H_{13}N_6O_3$ $(M+H)^+$: 241.1049. Found: 241.1044.

3.8.2. Enzymatic hydrolysis of diacetate 7. Diacetate **7** (524 mg, 1.86 mmol) was suspended in a mixture of buffered aqueous solution (10 mL, 0.1 M sodium phosphate, pH 6.2) and toluene (10 mL) at room temperature. CAL-B (500 mg) was added and the pH was maintained at its initial value by addition of 0.25 M aqueous NaOH. The reaction was monitored by TLC and stopped when the diacetate had disappeared (~3 days). The mixture was filtered using 0.22 μm membrane filter and the retained enzyme washed with CH_2Cl_2. The organic layer was separated and aqueous phase extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue with hexanes/EtOAc (3:1) gave monoacetate (+)-**9** (144 mg, 32%, ee ⩾99%) as a colorless oil. $[\alpha]_D^{22} = +21.6$ (*c* 1.0, $CHCl_3$), spectral data as above.

3.9. Determination of absolute configurations by chemical correlation and preparation of both enantiomers of dideoxystreptamine monoacetate 10

A solution of (−)-**8** (21 mg, 0.11 mmol; from PLE hydrolysis) in methanol (10 mL) was stirred at rt with 10% Pd-on-carbon (50 mg) under hydrogen (55 psi) for 5 h. The catalyst was then removed by filtration, washed with methanol, and the solvent evaporated to give (+)-**10** (20 mg, 93%) as a colorless oil: $[\alpha]_D^{22} = +9.7$ (*c* 1.0, CH_3OH); IR (NaCl) 3441, 2525, 1721, 1444, 1260 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.25 (s, 1H), 1.35 (m, 1H), 1.93 (s, 3H), 2.10 (m, 1H), 2.55 (m, 1H), 3.20 (m, 2H), 3.40 (m, 1H), 3.60 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 22.0, 29.9, 41.6, 54.6, 55.9, 71.4, 73.2, 171.3; HRMS (CI, NH_3) calcd for $C_8H_{17}O_3N_2$ $(M+H)^+$: 189.1239. Found: 189.1237. The same protocol was applied to the reduction of (+)-**9** (16 mg, 0.067 mmol; from CRL acylation) to yield (−)-**10** (12 mg, 96%) as a colorless oil: $[\alpha]_D^{22} = -10.8$ (*c* 0.6, CH_3OH); spectral data as above.

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