A novel and stereospecific synthesis of aminocyclitol: *N*-tosyldihydroconduramine E2

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A stereospecific synthesis of *N*-tosyldihydroconduramine E2, a new aminocyclitol, has been synthesised starting from cyclohexa-1,3-diene. The photooxygenation of cyclohexa-1,3-diene afforded the bicyclic endoperoxide. Reduction of the endoperoxide with thiourea and then reaction of the *bis*-carbamate with *p*-TsNCO followed by a palladium-catalysed ionisation/cyclisation reaction, gave a vinyl oxazolidin-2-one. Oxidation of the double bond in the oxazolidin-2-one with $KMnO_4$ followed by acetylation, gave the oxazolidinone-diacetates. Hydrolysis of the oxazolidinone ring and removal of the acetate groups gave the desired aminocyclitol, *N*-tosyldihydroconduramine E2.

Keywords: *N*-tosyldihydroconduramine E2, conduramine, aminocyclitol, endoperoxide

Aminocyclitols are mainly structural elements of naturally occurring some biological active compounds. Aminocyclitols such as validamine **1** have gained considerable importance because of their glycosidase inhibitory properties and antibacterial properties.[1,2] Moreover, aminoglycoside antibiotics remain important drugs for the treatment of infections.[3] Because aminocyclitols form the aglycons in many aminoglycoside antibiotics, SAR studies have established the importance of the aminocyclitol part for antibacterial activities.[4–6]

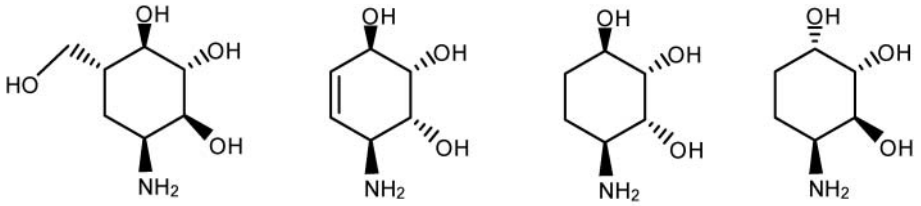
On the other hand, aminocyclitols such as **2**, exhibit remarkably similar properties as glicosidase inhibitors because of their similar framework.[7] Different approaches and methods have been used for the synthesis of aminocyclitols.[8–12] One of the promising methods was based on the cycloaddition approach with a hetero Diels–Alder reaction of nitroso dienophiles to 1,3-dienes for synthesis of compounds such as dihydroconduramine A2 **3**.[13–17] Nitrosyl cycloaddition provides the introduction of substituents at the 1,4-position of dienes. Apart from these methods, Trost *et al.* designed the synthesis of vinyl oxazolidin-2-ones *via* Pd(0) catalysed ionisation reactions.[18] Pd(0) catalysed reactions provide selective entry to amino alcohols of varying regio- and stereoselectivity. The regio- and stereoselectivity was assured by covalent tethering of the nitrogen nucleophile to the substrate. The feasibility of the regio-stereoselective synthesis of vinyl oxazolidin-2-ones via organopalladium reactions provides the opportunity for a general and flexible strategy for the synthesis of aminocyclitols.[19–22] Pandey *et al*. reported the synthesis of dihydroconduramine E1 **4** using enantiopure 7-azabicyclo[2.2.1] heptane-2-ol.[23] We report here the synthesis of *N*-tosyldihydroconduramine E2 using the Pd(0) catalysed cyclisation reaction of an allylic cis-diol in the presence of triisopropyl phosphite.

Results and discussion

The starting material, endoperoxide **5** was synthesised using tetraphenylporphyrin-sensitised photooxygenation of cyclohexa-1,3-diene in carbon tetrachloride at room temperature.[24,25] The endoperoxides with thiourea undergoes stereoselective ring-opening to give allylic *cis*-diols. Therefore, endoperoxides are the key-intermediates for stereoselective synthesis of some cyclitol and their derivatives.[26–28] Reduction of the endoperoxide linkage was performed with thiourea under mild conditions to give diol **6** in 85% yield.[24,25] Since only the oxygen–oxygen bond is cleaved in this reaction, the configuration of the carbon atoms is preserved.

Pd(0)-catalysed reactions provide the selective entry to amino alcohols with various regio- and stereoselectivity. Therefore, for the introduction of the amino alcohol functionality, a regio- and stereoselective Pd(0) catalysed reaction of diol **6** in the presence of TsNCO was employed. The diol **6** was treated with *p*-toluenesulfonylisocyanate (*p*-TsNCO) in THF to give the corresponding *bis*-carbamate **7** and then warmed to 65 °C. The resulting solution was added to a solution of the catalyst prepared from 5 mol % *tris*(dibenzylideneacetone) dipalladium chloroform complex $[(dba)_3Pd_2CHCl_3]$ and 15 mol % triisopropyl phosphite $(iPrO)_3P$ at the same temperature. The mixture was purified by chromatographed on a silica gel column with hexane/ethylacetate as an eluent to give oxazolidinone **8** in 51% yield (Scheme 1).[29]

The oxazolidinone **8** was dihydroxylated with $KMnO_4$ to furnish oxazolidinone-*cis*-diol **9**. During the synthesis of polyhydroxylated compounds, we often use acetyl chloride for acetylation of the *cis*-diols.[30–33] For further structural proof of the product, **9** was converted to oxazolidin-2-one diacetates **10** by acetyl chloride in CH_2Cl_2 (Scheme 1). The spectral data confirmed the hydroxylation of double bond and as a sole



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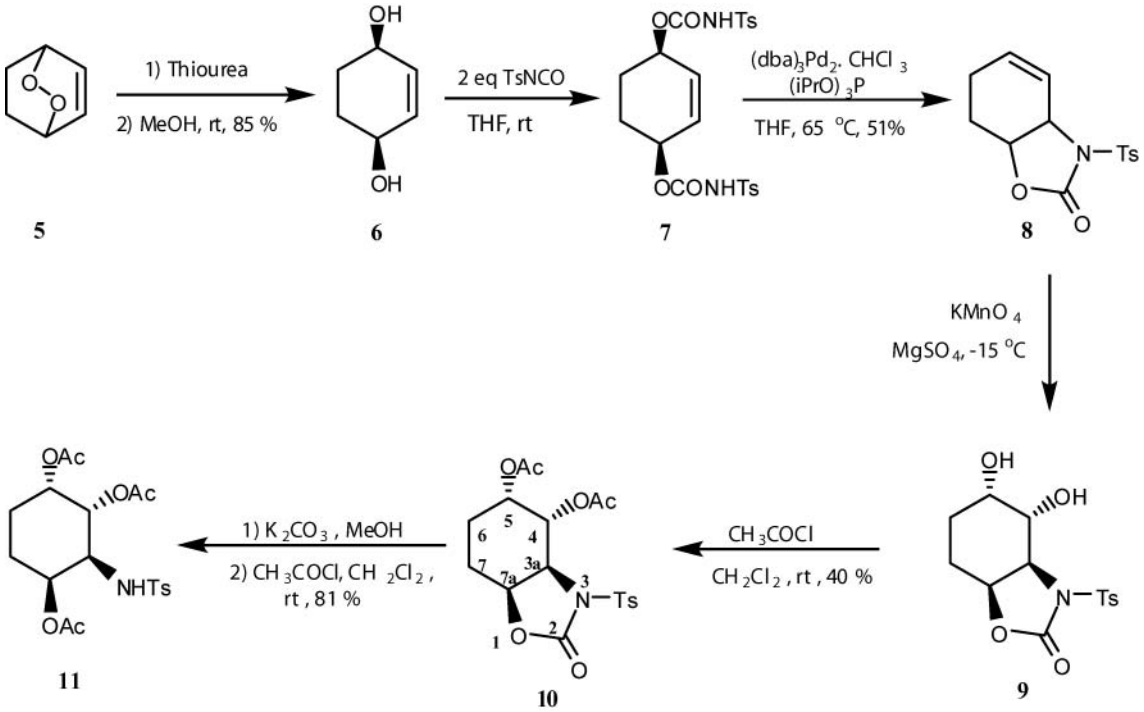


Scheme 1

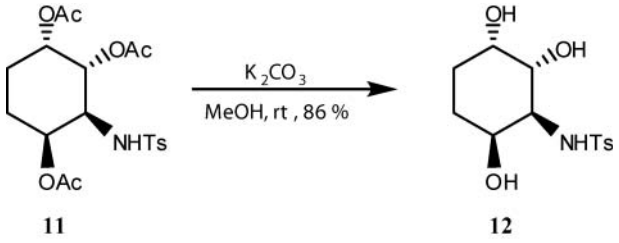
product. However, the stereochemical course of the hydroxylation can be *syn* and *anti*. Therefore, careful NMR studies did not reveal the formation of any trace of the other diastereomer. Indeed, since the *syn*-face of the molecule **8** is blocked by the oxazolidin-ring, $KMnO_4$ approaches the double bond exclusively from the *anti*-face (from less-hindered side) to give **9**.

The structure of oxazolidin-2-one diacetates **10** was elucidated on the basis of ^1H and ^{13}C NMR spectroscopic data. The 200 MHz ^1H NMR spectrum revealed a quartet at δ 5.33, a doublet of doublet at δ 4.94, and a triplet of doublet at δ 4.78, which was assigned to the acetoxy protons and CH–O (H_{7a}) in the oxazolidin-2-one ring, respectively. CH–N (H_{3a}) in the oxazolidin-2-one ring resonate as a double doublet at δ 4.60. First, while H-4 of **10** is a double doublet ($J_{4,3a}$ = 8.2, $J_{4,5}$ = 2.9 Hz), H-3a is a double doublet ($J_{3a,4}$ = 8.2, $J_{3a,7a}$ = 5.9 Hz) and H-7a is a triplet of doublet ($J_{7a,3a}$ = 5.9, $J_{7,7a}$ = 3.1 Hz). These observation clearly indicate that H-4 with H-3a have a *trans* configuration because of $J_{3a,4}$ = 8.2 Hz whereas H-3a with H-7a have a *cis* configuration because of $J_{7a,3a}$ = 5.9 Hz. These results indicate that H-3a and H-4 have a *trans* configuration while H-4 with H-5 and H-3a with H-7a exhibit a *cis* configurations with each other.

Oxazolidin-2-one diacetates **10** was hydrolysed with potassium carbonate in MeOH at room temperature and then converted to triacetates **11** which include free triacetates functionalities. Compound **11** was fully characterised by spectroscopic methods and analytical methods. Especially, a 17-line ^{13}C NMR spectrum of **11** confirms the proposed structure according to the asymmetry in the molecule. Hence, the oxazole ring was not only opened in this reaction, but also acetates groups were hydrolysed. In addition to this, the configuration of all the substituents in ring were determined by means of NMR spectrum.

Removal of the acetate groups with K_2CO_3 in methanol obtained *N*-tosyldihydroconduramine E2 **12** in high yield (Scheme 2).

In summary, *N*-tosyldihydroconduramine E2 was synthesised from the key intermediate, the diol **6**, which was



Scheme 2

efficiently obtained from the singlet oxygen and cyclohexa-1,3-diene. Thus, we now describe how different stereocontrolled aminocyclitols may be synthesised using Pd(0) source apart from hetero Diels–Alder addition reaction.

Experimental

General

Melting points were determined on a Buchi 539 capillary melting apparatus and are uncorrected. IR spectra were obtained from KBr or film on a Mattson 1000 FT-IR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on 200 (50) MHz Varian spectrometer and are reported in δ units with $SiMe_4$ as internal standard. TLC was performed on E. Merck Silica Gel 60 F_{254} plate (0.2 mm). All column chromatography was performed on silica gel (60 mesh, Merck). Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyser.

(1R,4S)-Cyclohex-2-ene-1,4-diol (**6**): The title compound was prepared in 85% yield as described in the literature. [24,25]

(3aRS,7aSR)-3-Tosyl-3a,6,7,7a-tetrahydro-1,3-benzooxazol-2(3H)-one (**8**): To a stirred solution of diol **6** (1.5 g, 13.38 mmol) in anhydrous THF (20 mL) under nitrogen at room temperature was added *p*-toluensulfonyl isocyanate (5.0 g, 3.9 mL, 25.4 mmol) dropwise. The reaction was stirred at room temperature for 6 h and then at 65 °C for 60 min. To a flask containing *tris*(dibenzylideneacetone)dip alladium chloroform complex (0.38 g, 361 μmol) in anhydrous THF (20 mL) under nitrogen was added triisopropyl phosphite (0.40 g, 1.94 mmol). The mixture was stirred at room temperature for 30 min until a clear yellow solution and then the catalyst solution was added to the reaction flask that at 65 °C. The reaction mixture was stirred at

the same temperature for 24 hours. After removal of the solvent under reduced pressure (50 °C, 20 mmHg), the mixture was chromatographed on silica gel (60 g) by eluting with 35% ethyl acetate/hexane to afford the vinyl oxazolidone **8** (1.90 g, 51%). White crystals, m.p. 125 °C (lit[29]; 122 °C). (recrystallised from ethyl acetate/hexane); IR ($CHCl_3$, cm^{-1}): 3939, 2950, 2846, 1781, 1600, 1500, 1438, 1365, 1307, 1245, 1207, 1168, 1130, 1091, 1056, 1025, 844, 817, 759, 698, 671, 586; ^{1}H NMR (200 MHz $CDCl_3$ ppm) δ 7.94 (d, A part of AA'BB' system, J = 8.3 Hz, 2H, aromatic), 7.34 (d, B part of AA'BB' system, J = 8.3 Hz, 2H, aromatic), 6.02 (m, 1H, –CH=CH) 5.94 (m, 1H, –CH=CH), 4.82 (m, 2H, –CH–O and –CH–N), 2.43 (s, 3H, arom–CH_3), 2.3–2.0 (m, 4H, –CH_2–CH_2); ^{13}C NMR (50 MHz $CDCl_3$ ppm) δ 153.9 (C=O), 147.4 (arom–ipso–C), 137.4 (arom–ipso–C), 131.7, 130.4 (aromatic), 135.2 (–C=C), 124.2 (–C=C), 75.9 (–C–O), 56.8 (–C–N), 26.2 (–CH_2), 20.7 (–CH_2), 23.7 (arom-CH_3).

*(3aSR,4RS,5SR,7aSR)-2-Oxo-3-tosyloctahydro-1,3-benzooxazole-4,5-diyl diacetate (***10**): To a stirred solution of vinyl oxazolidon **8** (0.60 g, 2.06 mmol) in ethanol (50 mL) was added a solution of $KMnO_4$ (0.33 g, 2.06 mmol) and $MgSO_4$ (0.25 g, 1.48 mmol) in water (30 mL) at –15 °C for 4 h. After the addition was completed, the reaction mixture was stirred for an additional 12 h at 10 °C and then filtered. The precipitate was washed several times with hot water. The combined filtrates were concentrated to 15 mL by evaporation. The aqueous solution was extracted with ethyl acetate (3 × 50 mL) and the extracts were dried over anhydrous sodium sulfate. After removal of the solvent, the crude mixture that was dissolved in acetyl chloride (10 mL) was magnetically stirred at room temperature for 6 h. Removal of the excess of unreacted acetyl chloride under reduced pressure (50 °C, 20 mmHg) gave **10** (0.16 g, 40%). White crystals, m.p. 98–100 °C (from CH_2Cl_2); IR(KBr, cm^{-1}) 3031, 2942, 1785, 1742, 1600, 1538, 1369, 1245, 1168, 1130, 1099, 1022, 763, 667, 578; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.91 (d, A part of AA'BB' system, J = 8.3 Hz, aromatic, 2H), 7.32 (d, B part of AA'BB' system, J = 8.3 Hz, aromatic, 2H), 5.33 (q, $J_{4,6}$ = 2.9 Hz, 1H, H_5), 4.94 (dd, $J_{4,3a}$ = 8.2, $J_{4,5}$ = 2.9 Hz, 1H, H_4), 4.78 (dt, $J_{7a,3a}$ = 5.9, $J_{7,7a}$ = 3.1 Hz, 1H, H_{7a}), 4.60 (dd, $J_{3a,4}$ = 8.2, $J_{3a,7a}$ = 5.9 Hz, 1H, H_{3a}), 2.42 (s, 3H, arom-CH_3), 2.08 (s, 3H, –CH_3), 2.02 (s, 3H, –CH_3),1.89–1.30 (m, 4H, –CH_2–CH_2); ^{13}C NMR (50 MHz $CDCl_3$) δ 171.7 (x2, C=O), 153.5 (C=O), 147.5 (arom-ipso-C), 137.5 (arom-ipso-C), 131.7 (C=C), 130.2 C=C), 78.4 (C–O), 74.8 (C–O), 69.6 (C–O), 60.7 (C–N), 24.2 (–CH_2), 23.6 (–CH_2), 22.9 (–CH_3), 22.8 (x2, –CH_3); Anal. Calcd for $C_{18}H_{21}NO_8S$: C, 52.55; H, 5.14; N, 3.40; S, 7.79; Found: C, 52.81; H, 5.34; N, 3.48; S, 7.67 %.

(1SR,2RS,3SR,4SR)-3-(4-methylphenylsulfonamido)cyclohexane-1,2,4-triyl triacetate (**11**): To a solution of oxazolidone-diacetate **10** (0.35 g, 0.83 mmol) in methanol (20 mL) was added K_2CO_3 (0.11 g, 0.72 mmol) and stirred at room temperature for 6 h. The residue filtered and then the solvent removed. The crude mixture that was dissolved in acetyl chloride (10 mL) was magnetically stirred at room temperature for 6 h. Removal of the excess of unreacted acetyl chloride under reduced pressure (50 °C, 20 mmHg) gave triacetate **11** (0.29 g, 81%). White crystals, m.p. 70–72 °C (from $CHCl_3$); IR (KBr, cm^{-1}) 3272, 2929, 2864, 1739, 1597, 1443, 1374, 1335, 1231, 1170, 1093, 1046, 1027, 950, 923, 819, 731; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, A part of AA'BB' system, J = 8.3 Hz, 2H, aromatic), 7.25 (d, B part of AA'BB' system, J = 8.3 Hz, 2H, aromatic), 5.69 (d, J = 9.0 Hz, 1H, H_3), 5.26 (m, 1H, H_4), 5.01 (d, J = 2.8 Hz, 1H, -N-H), 4.96 (d, J = 2.6 Hz, 1H, H_1), 3.77 (m, 1H, H_2), 2.36 (s, 3H, arom-CH_3), 2.02 (s, 3H, –CH_3), 1.97 (s, 3H, -CH_3), 1.71(s, 3H, –CH_3), 1.95–1.63 (m, 4H, –CH_2–CH_2); ^{13}C NMR (50 MHz $CDCl_3$) δ 172.7 (C=O), 172.0 (C=O), 171.9 (C=O), 145.3 (arom-ipso-C), 140.4 (arom-ipso-C), 131.6 (C=C), 128.8 (C=C), 74.3 (C–O), 71.9 (C–O), 71.0 (C–O), 55.2 (C–N), 25.4 (–CH_2), 25.2 (–CH_2), 23.4 (–CH_3), 22.9 (x2, –CH_3), 22.5 (–CH_3); Anal. Calcd for $C_{19}H_{25}NO_8S$: C, 53.38; H, 5.89; N, 3.28; S, 7.50; Found: C, 53.41; H, 5.86; N, 3.45; S, 7.63 %.

(1SR,2RS,3SR,4SR)-3-(4-Methylphenylsulfonamido)cyclohexane-1,2,4-triol: N-tosyldihydroconduramine E2 (**12**): To a solution of triacetate **11** (60 mg, 0.14 mmol) in methanol (15 mL) was added K_2CO_3 (110 mg, 0.80 mmol) and stirred at room temperature for 4 h. The residue filtered and then the solvent removed under reduced pressure (70 °C, 20 mmHg) to give 2-(4-methylphenylsulfonamido)cyclohexane-1,2,4-triol (*N*-tosyldihydroconduramine E2) **12** (36 mg, 86%). White crystals, m.p. 184–185 °C (from CH_3COCH_3); IR ($CHCl_3$, cm^{-1}): 3383, 3041, 2959, 2511, 1231, 1207, 1171, 1078, 1061, 1028, 1002, 885, 853, 783, 593, 582; ^{1}H NMR (200 MHz CD_3COCD_3 ppm) δ 7.80 (d, A part of AA'BB' system, J = 8.3 Hz, 2H, aromatic), 7.36 (d, B part of AA'BB' system, J = 8.3 Hz, 2H, aromatic), 3.93 (m, 1H, H_4), 3.80 (m, 1H, H_1), 3.71 (dd, J = 9.5, 2.9 Hz, 1H, H_3), 3.34 (dd, J = 9.4, 3.0 Hz, 1H, H_2), 3.30–3.00 (m, 3H, –OH), 2.41 (s, 3H, arom-CH_3), 1.80–1.54 (m, 4H, –CH_2–CH_2); ^{13}C NMR (50 MHz CD_3COCD_3 ppm) δ 145.4 (arom-ipso-C), 141.9 (arom-ipso-C), 132.0 (–C=C), 128.8 (–C=C), 72.7 (–C–O), 71.5 (–C–O), 71.7 (–C–O), 60.3 (–C–N), 28.6 (–CH_2), 27.5 (–CH_2), 23.2 (arom-CH_3). Anal. Calcd for $C_{13}H_{19}NO_5S$: C, 51.81; H, 6.35; N, 4.65; S, 10.64; Found: C, 51.73; H, 6.28; N, 4.81; S, 10.71%.

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