Stereospecific synthesis of N-tosyl derivatives of dihydroconduramine E-2 and ent-F-2

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Abstract
Conduramines, dihydroconduramines and structurally related compounds belong to an important class of glycosidase inhibitors which are essential elements of many biologically active compounds. The synthesis and characterization of N-tosyl dihydroconduramine derivatives 9a and 10a starting from cyclohexadiene were carried out in the current study. The oxazolidinone 15 was prepared by the palladium-catalyzed reaction of bis-carbamate 14, synthesized from cyclohexenediol, derived in two steps from cyclohexadiene. Hydrolysis of 15 was achieved with methanolic potassium carbonate to afford 18 and the ketalization gave 21 in good yield. Osmylation of the double bond and acid-mediated acetonide removal of 21 gave 4-methyl-N-((1S,2R,3S,6S)-2,3,6-trihydroxycyclohexyl)benzenesulfonamide 9a. The epoxidation of 21 followed by acid-mediated epoxide ring opening and subsequent acetonide removal produced 4-methyl-N-((1S,2R,3R,6S)-2,3,6-trihydroxycyclohexyl)benzenesulfonamide 10a. The molecules may be evaluated for biological activity.

Keywords: Aminocyclitols, conduramines, dihydroconduramines, glycosidase inhibitors

Introduction
Glycosidases are involved in a wide range of anabolic and catabolic processes such as intestinal digestion, lysosomal catabolism of glycoconjugates and post-translational processing of glycoproteins.1-4 The possibility of modifying or blocking these processes using glycosidase-inhibiting sugar mimics for biological and therapeutic applications has attracted much attention,5,6 especially in relation to cancer,7,8 viral infection,9,10 genetic disorders,11-13 diabetes14 and obesity.15 The biomedical and biotechnological applications of glycosidase-inhibiting sugar mimics have been reviewed.16 Inhibitors of glycoside-processing enzymes share structural homology with the natural
enzymatic substrates that are often aminohydroxy-substituted five or six-membered heterocyclic rings.\textsuperscript{17,18}

Conduramines, dihydroconduramines and structurally related compounds belong to an important class of glycosidase inhibitors which are essential elements of many biologically active compounds.\textsuperscript{19-27} In particular, conduramines 1-3 and dihydroconduramines 4-6 apart from their use as probes for biological functions of oligosaccharides have also served as important synthetic precursors of amino- and diaminocyclitols and many other biologically active compounds (Figure 1).\textsuperscript{28-30}

These features contribute to the importance of conduramines and have motivated the efforts made towards the development of new and efficient synthetic routes. Synthesis of conduramines 7 and 8, their dihydroconduramines analogues 9 and 10, and N-tosyl derivatives 9\textsuperscript{a} and 10\textsuperscript{a} have not yet been described (Figure 2).\textsuperscript{31}

Consequently in the current study we report the synthesis and characterization of N-tosyl dihydroconduramine derivatives (±)9\textsuperscript{a} and (±)10\textsuperscript{a} starting from cyclohexadiene. The compounds 9\textsuperscript{a} and 10\textsuperscript{a} are likely to have similar biological activities with their analogues and may be used as intermediates for the synthesis of new biologically active substances.
Results and Discussion

The oxazolidinone 15 was first prepared by the palladium-catalyzed reaction of bis-carbamate 14, that was available from cyclohexadiene in three steps (Scheme 1).

Scheme 1. (i) $^1$O$_2$, TPP, hv, CHCl$_3$, rt, 10 h, 80%; (ii) Thiourea, MeOH, rt.; (iii) 2eq. Ts-N=C=O, THF, rt.; (iv) (dba)$_2$Pd$_2$ CHCl$_3$, P(O i Pr)$_3$, THF, (-5 to 25 ºC), 24 h, 40%.
The starting material cyclohexene endoperoxide 12 was synthesized from the photooxygenation reaction of 1,3-cyclohexadiene 11 as reported by Balci. The endoperoxide 12 was performed with thiourea under mild conditions to give diol 13 in quantitative yield. In this reaction, since only the oxygen-oxygen bond in 12 was cleaved, the configurations of carbon atoms were preserved. The reaction of diol 13 with 2 equivalents of toluenesulfonyl isocyanate formed bis-carbamate 14. The palladium-catalyzed desymmetrization of bis-carbamate 14 was confirmed to give the monosubstitution product oxazolidin-2-one 15. The mechanism of this desymmetrization reaction has been reported by Trost (Scheme 2).

Scheme 2

The bis-carbamate 14 was treated with 2.5 mol% of palladium catalyst solution that was prepared with tris (dibenzylideneacetone)-dipalladium chloroform complex and 7.5 mol % of the ligand triisopropylphosphine. The mixture was purified by chromatography on a silica gel column with CH$_2$Cl$_2$/hexane (30:70) as eluent to give oxazolidinone 15 in 40% yield. The structure of 15 was confirmed by $^1$H and $^{13}$C NMR spectroscopy.

Initially, for the synthesis of N-tosyl derivatives of dihydroconduramine E-2 and ent-F-2, direct epoxidation and cis-dihydroxylation of the double bound in 15 was attempted with m-CPBA and catalytic osmium tetroxide at various temperatures and durations, however both reactions were unsuccessful.

As a second strategy, cis-aminoalcohol 18 was prepared by the hydrolysis of 15 with methanolic potassium carbonate. The compound 18 was converted into acetate 19 by the treatment with AcCl in methylene chloride. The dihydroxylation of 19 was obtained as a mixture of 9a and 9b isomers, and the epoxidation of 19 also formed a mixture of 20a and 20b isomers. The results of $^1$H and $^{13}$C
NMR showed that 9a was the main product of the first reaction and 20a was the main product of the second reaction (Scheme 3).

![Chemical structure diagram]

Scheme 3. (i) OsO₄/NMO, THF-H₂O, 2:1, (0 °C-rt), 48 h, 85%; (ii) m-CPBA, CHCl₃, Na₂HPO₄, 48 h, reflux, 95%; (iii) K₂CO₃, MeOH, rt., 18 h, 90%; (iv) AcCl, CH₂Cl₂, rt., 6 h, 100%.

Since the aim of this study was the stereospecific synthesis of N-tosylhydroconduramine derivatives 9a and 10a, we followed the third strategy for their synthesis (Scheme 4).

![Chemical structure diagram]

Scheme 4. (i) Me₂C(OMe)₂, p-TsOH, benzene, 4 h, reflux, 90%; (ii) OsO₄/NMO, THF-H₂O, 2:1, (0 °C-rt), 48h, 70%; (iii) 10% AcOH-THF, 1:1, 2 h, reflux, 90%; (iv) m – CPBA, CHCl₃, Na₂HPO₄, 60 h, reflux, 90%; (v) 10% AcOH-THF, 1:1, 72 h, reflux, 90%.
In order to decrease the conformational flexibility of the cyclohexene skeleton and to influence the further stereoselective transformations, the ketalization of 18 was conducted. The bicyclic ring is cis-fused and the methyl groups of the oxazolidine 21 that point above the plane of the olefin may also force the electrophile to approach anti, thus reinforcing the anti directing effect of the allylic amino moiety. Such a directing effect may also rationalize the stereochemical outcome of both the osmylation of 21 followed by acid-mediated acetonide removal, which provides (±)9a as a single isomer and the epoxidation of 21, which provides 22 as a single isomer. In addition, the steric and conformational effects of the bicyclic ring system influenced stereoselectivity of the epoxide opening reaction. Thus, acid-mediated epoxide ring opening and subsequent acetonide removal of 22 obtained (±)10a as a single isomer. Compounds (±)9a and (±)10a were characterized by 2D spectroscopy, namely COSY, NOESY as well as by the 13C NMR data. Careful examination of all these reaction mixtures did not reveal the formation of any other diastereoisomer.

In conclusion, we have described syntheses of N-tosyl derivatives of dihydroconduramine E-2 and ent-F-2 that can be used for various biological studies.

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Experimental Section

General. Solvents were purified and dried by the standard procedures before use. Melting points were determined on Electrotermal BI-9100 capillary melting apparatus and uncorrected. The ¹H and ¹³C NMR spectra were recorded on a 300 (75) MHz Varian spectrometer. Infrared spectra were obtained from Shimatzu Fourier Transform Infrared Spectrophotometer (IR Prestige-21, 200VCE). Column chromatography was performed on silica gel 60 (70-230 mesh). Thin layer chromatography was carried out on Merck 0.2 mm silica gel, 60 F₂₅₄ analytical aluminum plates.

(1R,4S)-2,3-Dioxabicyclo[2.2.2]oct-5-ene (12). The endoperoxide 12 was synthesized by the photooxygenation reaction of cyclohexadiene as reported by Balci.32

(1R, 4S)-Cyclohex-2-ene-1,4-diol (13). The cyclohexenediol 13 was synthesized by the reduction of the endoperoxide with thiourea under mild conditions in quantitative yield.32

Meso-2-ene-1,4-diol diester (14). Bis-carbamate 14 was prepared with ene-diol as described by Trost and his co-workers.33

(3aR,7aS)-3-Tosyl-3,3a,7,7a-tetrahydrobenzo[d]ox- azol-2(6H)-one (15). The oxazolidin-2-one 15 was prepared with bis-carbamate according to the procedure reported by Trost and Patterson.34,35

(3aR,7aS)-2,2-Dimethyl-3-tosyl-2,3,3a,6,7,7a-hexa- hydrobenzo[d]oxazole (21). A mixture of carbamate 15 (2 g, 6.83 mmol) and potassium carbonate (1.7 g, 12.3 mmol) in methanol/ water
(47:3 mL) was stirred at room temperature for 18 h, when TLC (silica gel, 80% ethyl acetate/hexane) indicated complete reaction. The reaction mixture was made acidic with glacial acetic acid, and the solvent was removed in vacuo. The mixture was loaded onto a short column of silica gel and eluted with 80% ethyl acetate/hexane + 1% acetic acid to afford, upon removal of solvent in vacuo, 1.8 g of the cis-aminoalcohol 18, as a white solid, 90% (white solid from chloroform solution). The cis-aminoalcohol 18 (1.8 g, 6.82 mmol) was dissolved in dry benzene (60 mL), and dimethoxypropane (40 mL) and then p-TsOH (100 mg, 0.52 mmol) were added. The reaction mixture was heated under reflux for 4 h, cooled to room temperature, and washed with the saturated solution of Na₂CO₃. The organic layer was decanted and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over MgSO₄, and the solvents were evaporated in vacuo. The crude product was purified by chromatography through silica gel (CH₂Cl₂-hexane 2:8), to afford the acetonide 21 (1.86 g, 90%) as a white solid (ether-hexane), mp: 109-110 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.96 (A part of AA'BB' system, d, 2H, J = 8.5 Hz, aromatic), 7.38 (B part of AA'BB' system, d, 2H, J₂AB = 8.3 Hz, aromatic), 5.82-5.75 (dt, 1H, J = 10.2 Hz, J = 9.9 Hz), 5.63-5.57 (d, 1H, J = 10.2 Hz), 4.16 (s, 2H, O-CH and N-CH), 2.60 (s, 3H, -CH₃), 2.22-1.65 (m, 4H, 2x-CH₂), 1.62-1.56 (s, 6H, 2x-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 143.46, 139.12, 129.81 (2C), 129.28, 127.52 (2C), 125.55, 97.01, 72.11, 56.50, 30.15, 26.03, 24.58, 21.76, 18.94. IR (ART) 3020, 2929, 1598, 1494, 1375, 1330, 1236, 1213, 1143 cm⁻¹. Anal. calcd for C₁₉H₂₁NO₅S: C, 62.30; H, 7.06; N, 4.67; S, 10.56. Found: C, 62.30; H, 7.06; N, 4.67; S, 10.56.

4-Methyl-N-((1S,2R,3S,6S)-2,3,6-trihydroxycyclohexyl)benzenesulfonamide (9a). The acetonide 21 (1.9 g, 6.13 mmol) was dissolved in acetone-H₂O (15:7.5 mL), and then NMO:H₂O (0.9 g, 6.72 mmol) and a 0.5 M solution of OsO₄ in acetone (6.2 mL, 0.3 mmol) were successively added. The reaction mixture was rapidly stirred 48 h at room temperature and was quenched with a 10% solution of Na₂SO₃. Following removal of solvent in vacuo, the mixture was chromatographed on a column of silica gel with 5% methanol/ethyl acetate, and the solvents were evaporated in vacuo to give the crude diol. The crude diol was dissolved in 1:1 mixture of 10% AcOH (10 mL) and THF (10 mL) and then was heated under reflux for 2 h. Removal of the solvent gave the crude product, which was crystallized from MeOH-acetonitrile (4:1) to give 9a as a white solid (1.18g, 90%), mp.: 190-192 °C. ¹H NMR (300 MHz, CD₃OD) δ 7.80 (A part of AA'BB' system, d, 2H, J = 8.5 Hz, aromatic), 7.34 (B part of AA'BB' system, d, 2H, J₂AB = 8.2 Hz, aromatic), 4.60 (s, 3H, -OH), 3.94-3.91 (q, 1H, J = 4.9, J = 2.6 Hz), 3.67-3.63 (dd, 1H, J = 9.3 Hz, J = 4.9 Hz), 3.40-3.36 (m, 1H, -NH), 3.37-3.30 (dd, 1H, J = 3.2 Hz, J = 9.3 Hz), 3.29-3.14 (q, 1H, J = 4.6 Hz, J = 3.2 Hz), 2.4 (s, 3H, -CH₃), 1.77-1.69 (m, 2H), 1.59-1.46 (m, 2H); ¹³C NMR (75 MHz, CD₃OD) δ 143.41, 138.50, 129.46 (2C), 127.05 (2C), 69.86, 57.27, 48.72, 47.02, 25.87, 24.95, 20.35. IR (ART) 3485, 3300, 3290, 3219, 2990, 2927,1598, 1435, 1336, 1303, 1151, 1091, 1037, 1016, 956, 846, 815, 657 cm⁻¹. Anal. calcd for C₁₃H₁₉NO₅S (301.36): C, 51.81; H, 6.35; N, 4.65; S, 10.43. Found: C, 51.68; H, 6.47; N, 4.77; S, 11.04.

Epoxide (22). The oxazolidine 21 (2 g, 6.5 mmol) was dissolved in CHCl₃ (40 mL), m-CPBA (3.5 g, 13 mmol) and Na₂HPO₄ (2.5 g, 17.4 mmol) were added and the resulting white suspension was heated under reflux for 60 h. After addition of the saturated solution of Na₂S₂O₃, the aqueous layer
was extracted with CH₂Cl₂. The combined extracts were washed with the saturated solution of Na₂CO₃ and dried over MgSO₄. The solvent was evaporated in vacuum and the crude product was purified by chromatography through silica gel (CH₂Cl₂/hexane 3:7), to afford the epoxide 22 (1.9 g, 90%) as a white solid (ether-hexane), mp.: 115-117 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.82 (A part of AA′BB′ system, d, 2H, J = 8.2 Hz.), 7.30 (B part of AA′BB′ system, d, 2H, JAB = 7.9 Hz, aromatic), 3.90 (s, 2H), 3.23-3.19 (d, 1H, J = 3.8 Hz), 3.19-3.18 (dd, 1H, J = 3.8, J = 14.0 Hz), 2.40 (s, 3H, -CH₃), 2.06-1.89 (dt, 2H, J = 14.0 Hz, J = 7.9 Hz), 1.69 (s, 3H, -CH₃), 1.65-1.60 (t, 2H, J = 7.9 Hz), 1.52 (s, 3H, -CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 143.85, 137.94, 129.75 (2C), 127.66 (2C), 97.27, 70.12, 55.23, 52.53, 52.40, 30.37, 25.05, 21.69, 18.11, 17.76. IR (ART) 3010, 2937, 1597, 1430, 1371, 1244, 1143, 1103, 1031, 989, 871, 815, 790, 740, 659 cm⁻¹. Anal. calcd for C₁₆H₂₁NO₄S (323.41): C, 59.42; H, 6.54; N, 4.33; S, 9.91; Found: C, 58.79; H, 6.60; N, 4.23; S, 9.62.

4-Methyl-N-((1S,2R,3R,6S)-2,3,6-trihydroxycyclohexyl)benzenesulfonamide (10a). Magnetically stirred solution of epoxide 22 (2 g, 6.18 mmol) in a 1:1 mixture of 10% AcOH (15 mL) and THF (15 mL) was heated under reflux for 72 h. Removal of the solvent gave the crude product, which was crystallized from MeOH-ether (4:1) to give 10a as a white solid (1.68 g, 90%), mp.: 224-226 °C. ¹H NMR (300 MHz, DMSO) δ 7.80 (A part of AA′BB′ system, d, 2H, J = 8.5 Hz, aromatic), 7.34 (B part of AA′BB′ system, d, 2H, JAB = 8.2 Hz, aromatic), 4.90 (s, 3H, -OH), 3.76-3.62 (dt, 1H, J = 11.4, J = 10.8 Hz), 3.36-3.42 (m, 1H, -NH), 3.31-3.30 (dt, 1H, J = 2.6 Hz, J = 9.0 Hz), 3.31-3.29 (dd, 1H, J = 2.9 Hz, J = 11.4 Hz), 2.94-2.93 (dd, 1H, J = 2.6 Hz, J = 2.9 Hz), 2.4 (s, 3H, -CH₃), 1.67-1.61 (m, 2H), 1.45-1.36 (m, 2H); ¹³C NMR (75 MHz, DMSO) δ 142.64, 139.87, 129.85 (2C), 127.34 (2C), 73.45, 72.96, 68.14, 61.14, 28.78, 27.20, 21.64. IR (ART) 3473, 3396, 3329, 3280, 3010, 2933, 1600, 1433, 1375, 1298, 1269, 1145, 1128, 1091, 1051, 999, 945, 848, 808, 667 cm⁻¹. Anal. calcd for C₁₅H₁₉NO₅S (301.36): C, 51.81; H, 6.35; N, 4.65; S, 10.64; Found: C, 51.54; H, 6.20; N, 4.80; S, 11.46.

References

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