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Synthesis of eight-membered aminocyclitol analogues

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ABSTRACT

The first syntheses of four stereoisomeric diaminocyclooctane diols, as well as a chlorocyclooctane aminodiol, are reported. In the first part, photooxygenation of *cis,cis*-1,3-cyclooctadiene gave a bicyclic endoperoxide, which was reduced with zinc followed by mesylation of the hydroxyl groups. Treatment with sodium azide afforded 1,4- and 1,2-cyclooctene diazides. Oxidation of the double bonds in the isomeric diazides with OsO_4, followed by hydrogenation of the azide groups, led to 3,8-diaminocyclooctane-1,2-diol and 3,4-diaminocyclooctane-1,2-diols. In the second part, *cis*-3,8-diazidocyclooctene was converted into the corresponding epoxide. Stereospecific hydrolysis of the epoxide ring with $HCl_{(g)}$ in methanol, and hydrogenation of the azide groups gave 3,8-diamino-2-chloro-cyclooctan-1-ol. Bromination of the double bond in cyclooctene diacetate, followed by acetate deprotection, azidolysis of the bromides, and hydrogenation of the azide groups resulted in the formation of 2,3-diaminocyclooctane-1,4-diol.

Introduction

The term cyclitol has been used to describe polyhydroxylated cycloalkanes as well as their amino or halogen derivatives. Aminocyclitols are formally derived from cyclitols in, which one of the hydroxyl groups is exchanged with an amino group. The aminocyclitol moiety has stimulated widespread synthetic interest owing to their diverse biological activities, especially glycosidase inhibition,[1] and has been utilised by medicinal chemists as a versatile scaffold in drug design.[1i] The central core of various aminoglycoside antibiotics, 2-deoxystreptamine **2** represents a good starting point for aminoglycoside analogue synthesis.[2] C6-Cyclitols such as conduritol derivatives **3** and **4** are also important structural motifs,[3] acting as glycosidase inhibitors[4] and potent inhibitors of the human immunodeficiency virus (HIV).[5] Finally, conduramine F-1 **4** and valienamine **5** possess aminoglycoside antibiotic[6] activities (Fig. 1).

Various methods have been reported for the synthesis of aminocyclitols containing six-membered rings,[6,7] however, only a few are available for the synthesis of seven-,[8] eight-,[9] and nine-membered[10] aminocyclitols. Eight-membered[11] cyclitols and their derivatives are important not only because of their glycosidase inhibitory effects, which are derived from their structural features, but also for the synthesis of amino- and diamino-C8 cyclitols.

Recently, we accomplished the first stereospecific synthesis of cyclooctanetetraols,[11a] as well as a stereoisomer of 3-aminocyclooctanetriol[9a] and its halogen derivative, which is an analogue of cyclooctanetetraol,[11a] from *cis,cis*-1,3-cyclooctadiene. 1,2-, 1,3- and 2,3-Diaminocyclooctanediol (**6**, **7**, and **8**, respectively) have not been previously reported in the literature (Fig. 2), however, the synthesis of the *meso* isomer **10** of 1,4-diaminocyclooctanediol **9** in six steps from *cis,cis*-1,3-cyclooctadiene has been reported by Grabowski and co-workers.[9d]

Motivated by the important biological activities of cyclitol derivatives, in this work we report a strategy for the synthesis of novel diaminocyclitols, namely 3,8-diaminocyclooctane-1,2-diol **11**, 3,4-diaminocyclooctane-1,2-diols **12** and **13**, 2,3-diaminocyclooctane-1,4-diol **14**, and 3,8-diamino-2-chloro-cyclooctan-1-ol **15** (Fig. 3).

Results and discussion

For the synthesis of 1,4- and 1,2-diaminocyclooctanediols **11**–**15**, the starting endoperoxide **16** was prepared using a literature procedure[11a] (Scheme 1).

Initially, we focused on the synthesis of dimesylate **18**. For this purpose, reduction of cyclooctene endoperoxide **16**, obtained from the photooxygenation of *cis,cis*-1,3-cyclooctadiene, with zinc followed by mesylation of the hydroxyl groups yielded dimesylate **18** and monomesylate **19** in a 19:1 ratio (^{1}H NMR), respectively (Scheme 1). The most extensively utilized precursors for the

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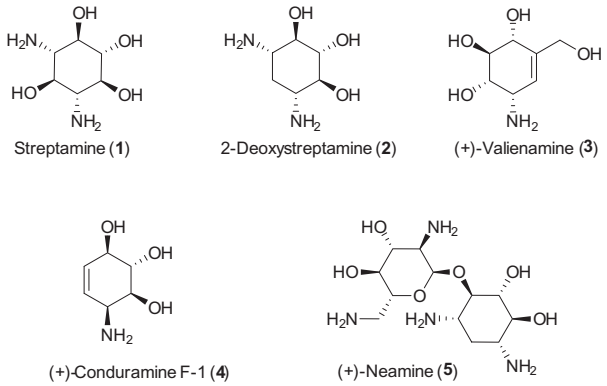

Fig. 1. Selected bioactive aminocyclitols.

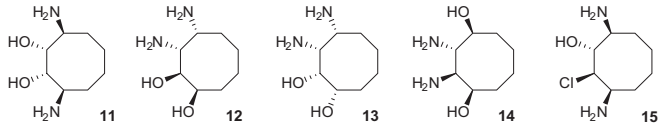

Fig. 3. Novel diaminocyclitols **11**–**15**.

syntheses of amine compounds in carbohydrate chemistry involve azido compounds. For the synthesis of diaminocyclooctanediol **11** from diazide **20**,[12c] dimesylate **18** was treated with sodium azide in DMF. The formation of the mixture of compounds **20**[12c] and **21**[12b] in a 9:1 ratio (^{1}H NMR) was observed, however all attempts at purification were unsuccessful (Scheme 1).

In order to develop a method for the synthesis of diazide **21**, 1,2-azidomesylate **24** was obtained in 96% yield from the literature compound azido alcohol **23**,[9a] which was prepared by azidolysis of cyclooctene epoxide **22** (Scheme 2). The reaction of 1,2-azidomesylate **24** with sodium azide in acetone was carried out at both rt and 80 °C in a pressure tube. However, the expected 1,2-diazide **21** was not obtained; instead 1,4-diazide **20** was formed as the sole product in 85% yield.

of **28** was determined using coupling constants between the relevant protons and 2D NMR spectroscopic data (COSY, NOESY).

The acetyl groups in diazidodiacetates **26**–**28** were removed using HCl(g)-MeOH to give diazidocyclooctanediols **25**, **29**, and **30** (97%, 98% and 97% yields, respectively), which after hydrogenation in MeOH gave diaminocyclooctanediols **11**, **12**, and **13**, respectively, each in 95% yield (Scheme 4). The NMR spectroscopic data were in agreement with the proposed structures.

For the synthesis of aminohydroxylated cyclooctanes **14**, reduction of endoperoxide **16** using Zn-AcOH and subsequent acetylation resulted in the formation of *cis*-diacetate **31**[11a] (Scheme 5). The addition of bromine to cyclooctene-1,4-diacetate **31** gave dibromodiacetate **32** as a single product in quantitative yield. Next, hydrolysis of **32** with acetyl chloride in MeOH gave dibromodiol **33** in 92% yield. To introduce the two azido groups in a *trans*-configuration, dibromodiol **33** was treated with sodium azide in DMF to afford diazide diol **34** as the major product (92%) along with the *cis*-HBr elimination product **35** (4%) after column chromatography (Scheme 5). Subsequent, hydrogenation of **34** gave diaminocyclooctanediol **14** in 95% yield (Scheme 5). The structures of **34** and **35** were assigned on the basis of NMR spectroscopy. In compound **35**, the olefinic proton H-3 resonates as a doublet with a coupling constant of $J = 6.9$ Hz, thus indicating the formation of a vinylic bromide.

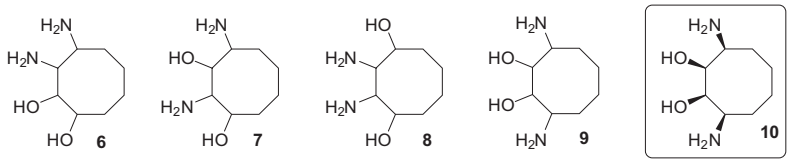

Fig. 2. Constitutional isomers of 1,2-, 1,3-, 2,3-, and 1,4-diaminocyclooctanediols **6**–**9**.

For the synthesis of diazide **21**, 1,2-azidomesylate **24** was reacted with NaN_3 in DMF at 55 °C, a mixture of compounds **20** and **21** was formed in a 35:65 ratio (^{1}H NMR) in 89% combined yield (Scheme 2).

Recognising that cyclooctene diazide **20** represented a promising substrate for the synthesis of symmetrical 1,4-diaminocyclooctanediol **11**, diazide **20** was submitted to a *cis*-dihydroxylation reaction with OsO_4-NMO, followed by hydrogenation to give diaminodiol **11** as the sole isomer in 95% yield (Scheme 3). The four resonances in the ^{13}C NMR spectrum as well as the ^{1}H NMR spectrum were in agreement with the proposed symmetric structure.

For the synthesis of diaminocyclooctanediols **11**–**13**, the mixture of diazides **20** and **21** (35:65 ratio) was reacted with OsO_4-NMO followed by acetylation with AcCl in CH_2Cl_2 to give a mixture of isomeric diacetate diazides **26**, **27**, and **28** which were isolated by column chromatography in 29%, 54% and 7% yields, respectively (Scheme 4). The structures and configurations of these compounds were assigned using ^{1}H NMR and 2D NMR spectroscopic data (COSY, NOESY). The six resonances in the ^{13}C NMR spectrum as well as the ^{1}H NMR spectrum of **26** were in agreement with the proposed symmetric structure. Similarly, the twelve resonances in the ^{13}C NMR spectrum as well as the ^{1}H NMR spectrum of **27** were in agreement with the proposed structure. The configuration

Finally, we turned our attention to the synthesis of halodiaminocyclooctanol **15** from diazide **20**[12] (Scheme 6). The reaction of diazide **20**[12] with *m*-CPBA gave the corresponding epoxide **36** as a single product in 92% yield. Ring-opening of epoxide **36** with HCl(g) in MeOH resulted in the formation of chlorodiazide **37a** in 98% yield. For structural proof, chlorodiazide **37a** was converted into the corresponding acetate **37b** using AcCl in CH_2Cl_2 (90%). The H-1 proton resonated as a triplet with a large coupling constant ($J_{1,8} = J_{1,2} = 8.8$ Hz) which clearly supports the *trans* relationship H-1 with both H-2 and H-8. The small coupling constant ($J_{2,3} = 2.2$ Hz) between H-2 and H-3 clearly confirmed the *cis* relationship of these protons.

Hydrogenation of **37a** gave 3,8-diamino-2-chlorocyclooctanol **15** in 90% yield (Scheme 6). ^{1}H and ^{13}C NMR spectroscopic data were in agreement with the proposed structure. The H-2 proton resonates as a doublet of doublets with coupling constants of $J =$ 8.7 and 2.5 Hz, clearly indicating that H-2 and H-1 with a large coupling constant ($J_{1,2} = 8.7$ Hz) are *trans* to each other. The smaller coupling constant ($J_{2,3} = 2.5$ Hz) between H-2 and H-3 shows the *cis* relationship between those protons. The H-1 proton also resonates as a triplet with a coupling constant of $J = 8.9$ Hz, which clearly supports the *trans* relationship of H-1 with both H-2 and H-8.