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Stereospecific synthesis of a new *N*-tosyl bromo-aminocyclitol

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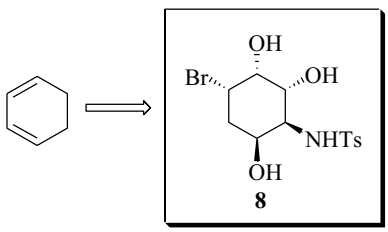
Abstract Aminocyclitols are cyclic polyhydroxylated amines formally derived from cyclitols, and they constitute an important class of biologically active compounds. In the current research, the synthesis and characterization of a new *N*-tosyl bromo-aminocyclitol **8** starting from cyclohexadiene were carried out. In accordance with this purpose, the oxazolidinone **13** was prepared by the palladium-catalyzed reaction of bis-carbamate **12**, synthesized from cyclohexenediol, derived in two steps from cyclohexadiene. Hydrolysis of **13** was achieved with methanolic potassium carbonate to afford **14** and ketalization gave **18** with good yield. Allylic bromination of **18** gave compound **19**. Bromination was conducted with *N*-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide. Osmylation of the double bond and acid-mediated acetonide removal of **19** gave *N*-((1*S*,2*R*,3*R*,4*S*,6*S*)-4-bromo-2,3,6-trihydroxycyclohexyl)-4-methylbenzenesulfonamide **8**. This molecule may also be evaluated for its biological activity.

Graphical abstract



Keywords Aminocyclitols · Bromo-aminocyclitols · Cyclitols · Dihydroconduramines

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Introduction

The cyclitols (**1**, **3**) are polyhydroxy cyclic compounds [1–5], and the biological activity of these compounds, as well as their role in intracellular communication, has been extensively studied and summarized [6]. Aminocyclitols (**2**, **4**) are cyclic polyhydroxylated amines formally derived from cyclitols, in which one of the hydroxyl groups is exchanged with an amino group. They constitute a continuing and growing class of important compounds with often interesting biological activities [7–14]. Moreover, some aminocyclitols have significant glycosidase inhibitory effects [15]. There are also applications of these compounds as substrates for mutasynthesis of new antibiotics [16]. The development of synthesis methods and the synthesis of these compounds contribute significantly to the biological and pharmaceutical industries (Fig. 1).

Numerous research groups [1–36] have reported fascinating syntheses of cyclitols, aminocyclitols, and their derivatives. In recent years, new synthetic methodologies for various polyhydroxylated aminocyclitol compounds and their analogues have also been developed [9–14, 37–39].

In our early studies, were reported the first synthesis and characterization of some aminocyclitol derivatives, such as *N*-tosyl derivatives of dihydroconduramine E-2 **5** and *ent*-dihydroconduramine F-2 **6** [40], and the *gala*-aminocyclitol **7** [5] starting from 1,3-cyclohexadine and 1,4-cyclohexadine, respectively (Fig. 2).

To the best of our knowledge, there is no previous report on the synthesis and characterization of *N*-tosyl bromo-aminocyclitol **8**, although the synthesis of the cyclitols (**1**, **3**) and related structures (**2**, **4–7**) has been reported. Therefore, in the current research, starting from 1,3-cyclohexadine, a

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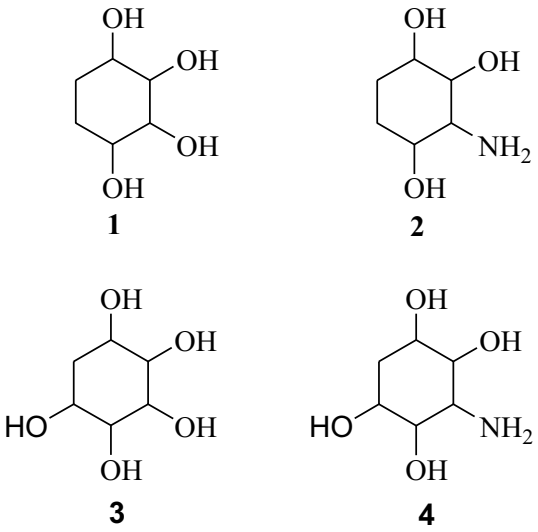


Fig. 1 Various types of cyclitols, aminocyclitols

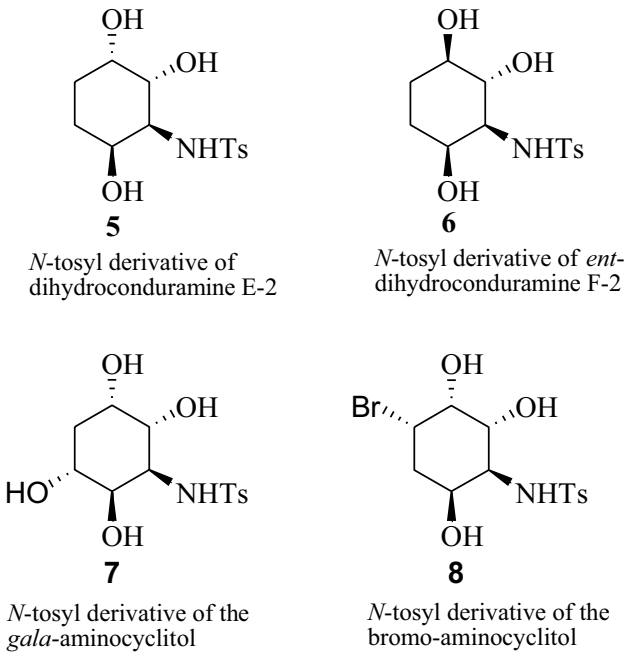


Fig. 2 *N*-tosyl derivatives of aminocyclitols

new *N*-tosyl bromo-aminocyclitol [*N*-((1*S*,2*R*,3*R*,4*S*,6*S*)-4-bromo-2,3,6-trihydroxycyclohexyl)-4-methylbenzenesulfonamide] **8** was synthesized by following the procedure described below. Cyclitols, aminocyclitols, and structurally related compounds belong to an important class of glycosidase inhibitors which are essential elements of many biologically active compounds [1–40]. Compound **8** may also be evaluated for biological activity.

Experimental

General procedures

Solvents were purified and dried by the standard procedures before used. Melting points were determined on Electrothermal BI-9100 capillary melting apparatus and uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 300 (75) MHz Varian spectrometer. Infrared spectra were obtained from Shimadzu Fourier transform infrared spectrophotometer (IR Prestige-21, 200 VCE). 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 F_{254} analytical aluminum plates.

The endoperoxide (10) and the cyclohexenediol (11)

These compounds were synthesized by the photooxygenation reaction of cyclohexadiene and subsequent the reduction of the endoperoxide with thiourea under mild conditions in quantitative yield as reported by Balci [41].

Meso-2-ene-1,4-diol diester (12)

Bis-carbamate **12** was prepared with ene-diol as described by Trost et al. [42].

(3aR,7aS)-3-Tosyl-3,3a,7,7a-tetrahydrobenzo[*d*]oxazol-2(6H)-one (13)

The oxazolidin-2-one **13** was prepared with bis-carbamate according to the procedure reported by Trost and Patterson [43, 44].

(3aR,7aS)-2,2-Dimethyl-3-tosyl-2,3,3a,6,7,7a-hexahydrobenzo[d]oxazole (18)

Hydrolysis of carbamate **13** was achieved with methanolic potassium carbonate to afford **14**, and subsequent the ketalization gave **18** with good yield as reported by Kurbanoglu et al. [40].

(3a*R*,6*S*,7a*S*)-6-Bromo-2, 2-dimethyl-3-tosyl-2,3,3a,6,7,7a-hexa-hydrobenzo[*d*]oxazole (19)

A mixture of oxazolidine **18** (2 g, 6.5 mmol) and *N*-bromosuccinimide (NBS) (1.4 g, 7.8 mmol) in the presence of catalytic amounts of benzoyl peroxide (1.5 g, 6.2 mmol) in methylene chloride (40 mL) was stirred under argon atmosphere. The allylic bromination reaction was carried out at 85 °C for 4 h. After the completion of the reaction (4 h), the

hot reaction mixture was filtered, water (100 mL) was added and the organic layer was extracted with CH_2Cl_2. The phases were separated and the organic layer was dried with $MgSO_4$. After removal of CH_2Cl_2 by using a rotary evaporator was obtained the crude product, which was separated by crystallization from reaction mixture (CCl_4-hexane) to give **19** as a single-isomer solid (0.70 g, 35 %), mp.: 127–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 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, J_{AB} = 8.3 Hz, aromatic), 6.01–5.97 (dd, 1H, J = 10.60, 10.55 Hz), 5.64-5.60 (dd, 1H, J = 10.8 Hz), 4.64–4.62 (m, 1H, J = 10.55, 10.25 Hz), 4.21–4.18 (m, 1H, N–CH, J = 4.10 Hz), 4.17–4.13 (m, 1H, O–CH, J = 6.40 Hz), 2.44–2.27 (m, 2H, J = 10.25 Hz), 2.40 (s, 3H, –CH_3), 1.62–1.56 (s, 6H, 2x–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.86, 138.53, 13.62, 129.97, 127.55, 127.42, 97.58, 72.70, 55.24, 41.85, 36.34, 30.11, 25.85, 21.79.

N-((1*S*,2*R*,3*R*,4*S*,6*S*)-4-bromo-2,3,6-trihydroxycyclohexyl)-4-methylbenzenesulfonamide (8)

The compound **19** (0.52 g, 1.34 mmol) was dissolved in THF–H_2O (10:5 mL), and then, NMO: H_2O (0.197 g, 1.47 mmol) and a 0.5 M solution of OsO_4 in THF (2 mL, 0.1 mmol) was successively added. The reaction mixture was rapidly stirred for 36 h at room temperature and was quenched with a 10 % solution of Na_2SO_3. 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 osmylation of **19** and for purification of the product was carried out the ketalization of reaction mixture. Thus, the crude diol was dissolved in dry benzene (30 mL) and dimethoxypropane (20 mL), and then, *p*-TsOH (50 mg, 0.26 mmol) were added. The reaction mixture was heated under reflux for 4 h, cooled to room temperature, and washed with the saturated solution of Na_2CO_3. The organic layer was decanted and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over $MgSO_4$, and the solvents were evaporated in vacuum. The crude product was purified by chromatography through silica gel (CH_2Cl_2-hexane, 3:7). Removal of the solvent gave the crude product, which was crystallized from CH_2Cl_2-hexane (3:2) to give **20** as a white solid (0.245 g, 40 %), mp.: 183–185 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (A part of AA′ BB′ system, d, 2H, J = 8.5 Hz, aromatic), 7.30 (B part of AA′ BB′ system, d, 2H, J_{AB} = 8.3 Hz, aromatic), 4.40–4.38 (m, 1H, J = 6.45 Hz, J = 6.15 Hz), 4.37–4.35 (dt, 1H), 4.23–4.20 (dd, 1H, J = 7.03 Hz), 4.19–4.17 (dd, 1H, J = 6.7 Hz), 3.67–3.64 (dt, 1H, J = 9.6 Hz), 2.40–2.10 (m, 2H, J = 8.8 Hz), 2.42 (s, 3H, –CH_3), 1.80–1.30 (s, 12H, 4x–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.12, 137.20, 129.78, 128.14, 109.01, 97.98, 78.36, 75.76, 73.95, 59.48, 42.56, 31.39, 29.27, 27.07, 25.23, 24.88, 21.80. IR (ART) 3501, 3232, 2980, 2924, 2302, 1597, 1490, 1454, 1373, 1342, 1236, 1213, 1154, 1092, 878, 811, 744, 676, 594 cm^{-1}. Anal. calcd for $C_{19}H_{26}BrNO_5S$ (460.38): C, 49.57; H, 5.69; N, 3.04; S, 6.96; Found: C, 49.40; H, 5.48; N, 3.31; S, 7.03.

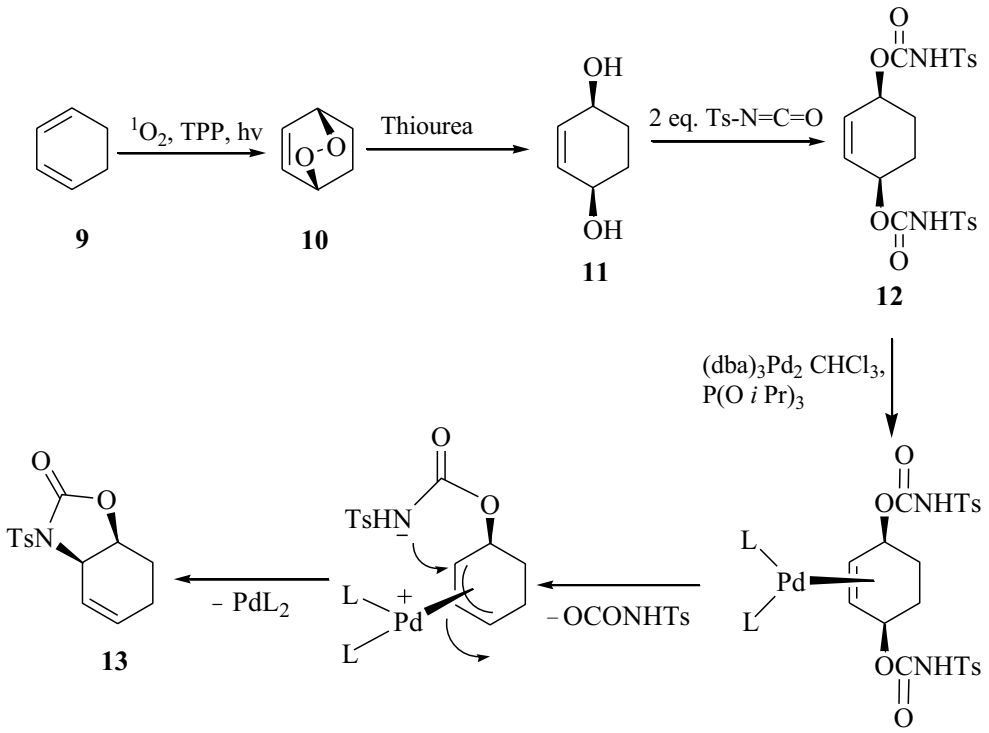
The following magnetically stirred solution of compound **20** (0.245 g, 0.54 mmol) in a 1:1 mixture of 10 % AcOH (15 mL) and THF (15 mL) was heated under reflux for 7 h. Removal of the solvent gave *N*-((1*S*,2*R*,3*R*,4*S*,6*S*)-4-bromo-2,3,6-trihydroxycyclohexyl)-4-methylbenzenesulfonamide **8** (0.18 g, 90 %), which was crystallized from MeOH-hexane (4:1) as a white solid, mp.: 217–219 °C. 1H NMR (300 MHz, CD_3OD) δ 7.80 (A part of AA′ BB′ system, d, 2H, J = 8.5 Hz, aromatic), 7.33 (B part of AA′ BB′ system, d, 2H, J_{AB} = 8.3 Hz, aromatic), 3.72–3.68 (d, 1H, –NH), 3.67 (s, 3H, –OH), 3.15–3.08 (dt, 1H, J = 12.88 Hz, J = 2.30 Hz), 2.78 (m, 1H, J = 4.40 Hz), 2.43–2.42 (dd, 1H, J = 2.90 Hz), 2.40–2.39 (t, 1H, J = 10.55 Hz), 2.13–2.08 (dd, 1H, J = 12.30 Hz), 2.02 (s, 3H, –CH_3), 0.92–0.87 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 143.30, 138.86, 129.43, 126.97, 73.93, 69.06, 55.94, 48.70, 47.00, 37.12, 20.32. IR (ART) 3551, 3333, 2922, 2624, 2522, 2479,1598, 1496, 1439, 1383, 1321, 1152, 1090, 1064, 949, 859, 819, 779, 665, 634 cm^{-1}.

Results and discussion

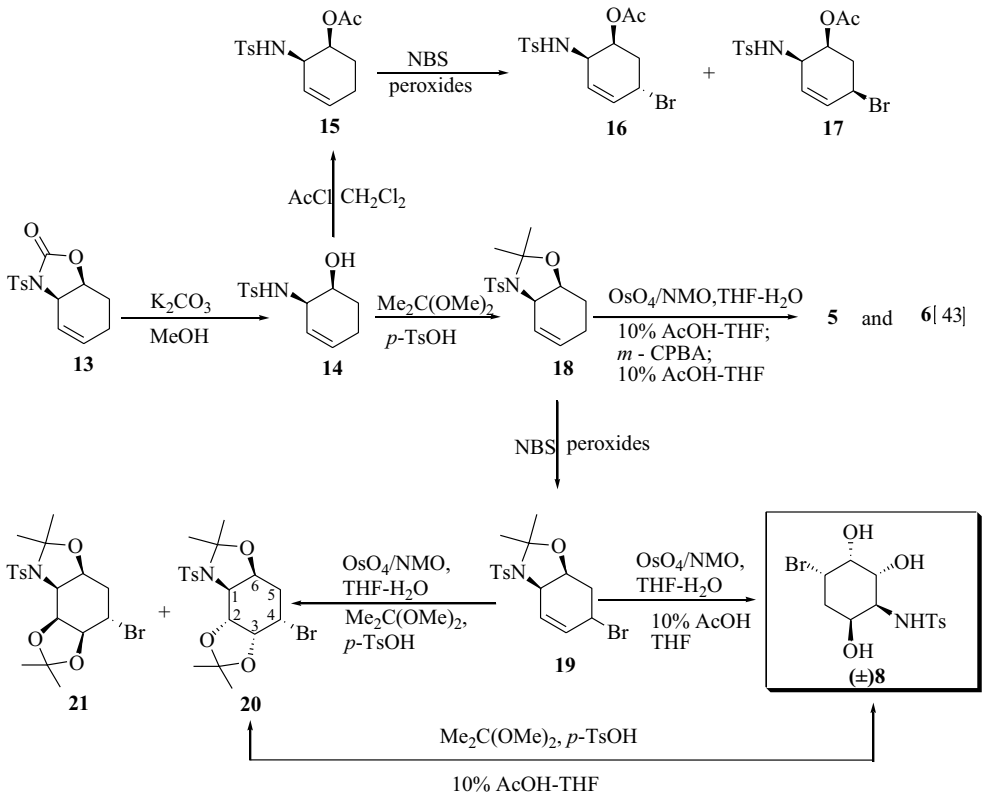
For the synthesis of oxazolidinone **13**, the starting material cyclohexene endoperoxide **10** was first prepared from the photooxygenation reaction of 1,3-cyclohexadiene **9** as reported by Balci [41]. The endoperoxide **10** was reacted with thiourea under mild conditions to give diol **11** in quantitative yield. The reaction of diol **11** with 2 equivalents of toluenesulfonyl isocyanate yielded bis-carbamate **12** [42]. The palladium-catalyzed desymmetrization of bis-carbamate **12** was confirmed to give the monosubstitution product oxazolidin-2-one **13** (Scheme 1) [40, 43, 44].

As a first strategy, cis-aminoalcohol **14** was prepared by the hydrolysis of **13** with methanolic potassium carbonate. Compound **14** was converted into acetate **15** by treatment with AcCl in methylene chloride. The allylic bromination of **15** was achieved with a mixture of **16** and **17** isomers (Scheme 2). The results of ^{1}H and ^{13}C NMR showed that **16** was the main product of the first reaction.

Since the aim of this research was the stereospecific synthesis of the *N*-tosyl derivative of bromo-aminocyclitol **8**, we followed the second strategy for the synthesis of **8**. In order to decrease the conformational flexibility of the cyclohexene skeleton and to influence the further stereoselective transformations, the ketalization of **14** was conducted. The bicyclic



Scheme 1 Synthesis of oxazolidinone **13**



Scheme 2 Synthesis of a new *N*-tosyl bromo-aminocyclitol **8**

ring is cis-fused, and the methyl groups of the oxazolidine **18** 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 [45]. Such a directing effect may also rationalize the stereochemical outcome of both the allylic bromination of **18** and the osmylation of **19** were afforded just **20** as single isomer, however **21** was not occurred, followed by acid-mediated acetonide removal, which provides (±) **8**. The allylic bromination of **18** was carried out in methylene chloride using *N*-bromosuccinimide (NBS) as a brominating agent in the presence of a catalytic amount of benzoyl peroxide $[(C_6H_5CO)_2O_2]$ under heat [46]. It is interesting to note that a single isomer **19** was obtained in the reaction, which was separated by column chromatography but the stereochemistry wasn't determined. The stereochemistry was determined when was obtained the **20.** The structure of single product **20** was established for this product on the grounds of ^{1}H and ^{13}C NMR spectroscopy (Scheme 2). The coupling constant between the proton closed to bromine atom (H-4) with H-3 is measured to be $J_{3,4} = 6.15$ Hz. This value is consistent with a typical axial/equatorial coupling constant in the cyclohexene ring, indicating the cis-configuration as well as the equatorial/axial position of the bromine atom. Furthermore, the coupling constant between protons H-1 and H-2 is measured to be $J_{1,2} = 7.03$ Hz, and this value confirms the trans-configuration as well as the axial/axial position. Moreover, the steric and conformational effects of the bicyclic ring system influenced the stereoselectivity of the osmylation reaction. Thus, the osmylation of **19** and for purification of the product the ketalization of the reaction mixture were conducted. Subsequent acetonide removal of **20** yielded (±) **8**. Compound (±) **8** was characterized by 2D spectroscopy, namely COSY and NOESY, as well as by the ^{13}C NMR data. Careful examination of all these reaction mixtures did not reveal the formation of any other diastereoisomer.

In conclusion, we have reported the synthesis of a new *N*-tosyl bromo-aminocyclitol that can be used for various biological studies.

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