# Stereocontrolled Synthesis of (1*R*,3*R*,4*S*)- and (1*S*,3*R*,4*S*)-3,4-diaminocyclopentanols

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**Abstract:** *Cis-syn* and *cis-anti*-3,4-diaminocyclopentanols have been synthesized from cyclopentadiene in eight steps. The key transformations involved construction of benzyl ether protected *cis*-diazidocyclopentanols, and sequential reduction and hydrogenolysis to the unprotected diaminocyclopentanols.

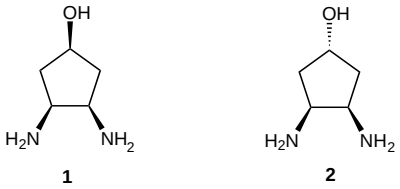
**Key words:** stereocontrolled synthesis, vicinal diamine, diaminocyclopentanol, diazide reduction, debenzylation

Despite the development of numerous methods to construct vicinal cyclic diamines and their widespread applications,[1-2] the stereospecific synthesis of *cis*-1,2-cyclopentanediamines is surprisingly uncommon. Among a few examples are the stereoselective *trans* addition of either *N*,*N*-dichlorourethane or *N*,*N*-dichloro-*t*-butylcarbamate to cyclic alkenes, followed by nucleophilic displacement of chloride with azide, and then reduction and hydrolysis to give *cis*-1,2-diamines.[3] Fraenkel *et al*. has described the synthesis of *cis*-cyclopentanediamines by two methods,[4-5] however both methods were limited to the synthesis of cyclopentanediamines containing other alkyl substituents on the amino groups. Bruncko, Khuong, and Sharpless reported the synthesis of *cis*-1,2-diamino-3-cyclopentene *via* diimidoselenium-mediated allylic amination.[6] Knapp and Levorse utilized iodolactams, prepared from cyclization of *N*,*O*-bis(trimethylsilyl)amide derivatives, as intermediates for the preparation of *cis*-diamines.[7]

We required (1*R*,3*R*,4*S*)-3,4-diaminocyclopentanol (**1**) and its stereoisomer **2** as scaffoldings for the construction of geometrically defined metal complexes. Despite the simplicity (molecular formula $C_5H_{12}N_2O$) of this compound, neither it nor its diastereomers has been described in the literature.

In order to achieve the most direct high yield synthesis of these diamines, it was necessary to devise a new route that would provide control of the stereochemistry of the hydroxyl substituent as well as the two amino groups. The synthetic route that we developed is both high yield and efficient.

Crandall *et al*.,[8] have described a synthesis of 3-cyclopentanol from cyclopentadiene. Conversion of the latter to its benzyl ether and epoxidation according to Eaton's paper afforded a 1:1 mixture of *cis* and *trans*-3,4-epoxycyclopentanol benzyl ether in 94 % yield.[9] They were separated by silica gel column chromatography with hexanes and ethyl acetate. The *trans* isomer **3** was refluxed with sodium azide and ammonium chloride to give the azido alcohol **4** and its enantiomer. Mesylation of the alcohol **4** generated the azido mesylate, which was then refluxed with sodium azide and pyridine in DMF to afford *cis-syn*-3,4-diazidocyclopentanol benzyl ether **5**. The overall yield of these three steps was 75%. Thin layer chromato-graphy indicated that it was one spot, while the $^1H$ and $^{13}C$ NMR proved it was functionalized exclusively on one face of the cyclopentane ring (Scheme).




**1** **2**

**Figure**

Reduction of vicinal diazides proved to be difficult.[10] Staudinger reduction, palladium-on-carbon, and platinum oxide at low hydrogen pressure did not lead to the corresponding vicinal diamines. However, the diamines were obtained when diazide **5** was hydrogenated at 800 psi in the presence of platinum oxide.[11] It is noteworthy that attempted debenzylation of the diazide **5** by hydrogenolysis, using palladium-on-carbon (Degussa type) or palladium hydroxide-on-carbon (Pearlman's Catalyst) at 80 psi hydrogen, led to reduction of the diazide **5** to diamine **6a** in almost quantitative yield. The stereo configuration of **6a** was proved by an NOE experiment.

Debenzylation of benzyl ethers in the presence of an amino group is very slow.[12] A combination of ammonium formate, formic acid and Pearlman's catalyst has been used for *N*-debenzylation in peptide synthesis,[13] however, this process did not work in attempting to remove the benzyl group in compound **6a**. The vicinal diamino unit is an excellent ligand for metal chelation, so it may poison the catalyst during the reactions. Conversion of the diamine to the bis-trifluoroacetamide should reduce the chelating ability dramatically. Diamide **6b** was synthesized by reaction with trifluoroacetic anhydride and then refluxed with

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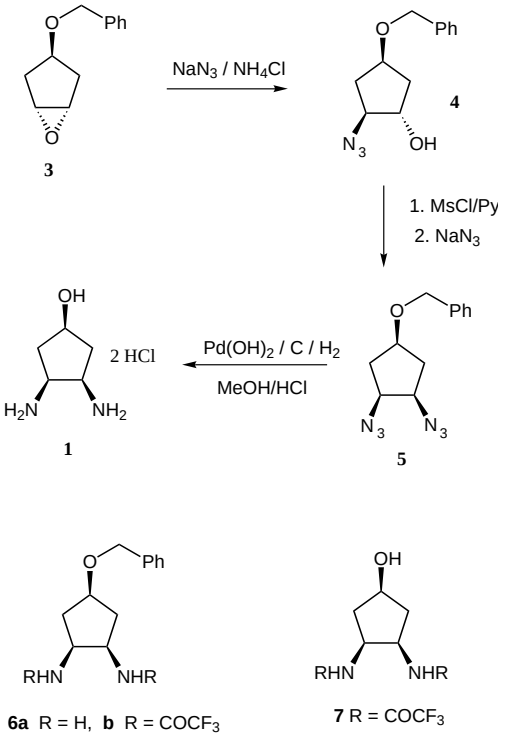
ammonium formate, formic acid and methanol in the presence of Pearlman's catalyst. The alcohol **7** was recovered and then heated with ammonia in methanol to afford the product **1**. The last two steps suffered low yield because of isolation problems. On the other hand, the hydrochloric salt of product **1** was obtained in 93% yield when **6a** was hydrogenated in methanol and hydrochloric acid (pH~2) in the presence of Pearlman's catalyst. Under the latter condition, salt **1** can be obtained directly from diazide **5** in 98% yield. The overall yield from cyclopentadiene to **1** is about 30%. It is noteworthy that the overall yield of *cis-syn* diamine **1** from trans-3,4-epoxycyclopentanol benzyl ether is 74% and can be done within a week on a gram scale. The *cis-anti* diamine **2** has also been synthesized by the same procedure. The structures of **1** and **2** have been confirmed by X-ray crystallography of their platinum complexes.[14]

**Experimental Procedure:** A solution of **3** (816 mg, 4.3 mmol), 40 ml ethanol, 8 ml water, 836 mg sodium azide and 690 mg ammonium chloride was refluxed for 12 hours. The mixture was cooled to room temperature. Additional water (20 ml) was added and the residue extracted with ether (4x20 ml). The ether layer was washed with 20 ml brine and dried by sodium sulfate. The solvent was removed by reduced pressure and the residue purified by silica gel chromatography to give compound **4** (957 mg, 4.1 mmol, 96%) as a colorless liquid (8:1=hexanes: ethyl acetate). IR ($cm^{-1}$): 3500, 2200; $^1H$ NMR ($CDCl_3$): 7.38 (m, 5H), 4.45 (s, 2H), 4.21 (dd, 13.0, 7.0, 1H), 4.06 (m, 1H), 3.60 (dd, 13.0, 7.3, 1H), 2.43 (m, 1H), 2.14 (ddd, 14.3, 7.3, 4.0, 1H), 1.79 (m, 1H); $^{13}C$ NMR ($CDCl_3$): 137.9, 128.3, 127.6, 76.0, 75.6, 70.9, 66.8, 39.1, 35.7; LC-MS (CI): calcd. for $C_{12}H_{15}N_3O_2$: 233, found 234 (M+H).

A solution of 0.29 ml mesyl chloride (3.7 mmol) and 2 ml dichloromethane was introduced into a mixture of **4** (761 mg, 3.3 mmol), 30 ml dichloromethane and 0.33 ml dry pyridine at room temperature under nitrogen. The above solution was stirred for 6 hours, then 5 % aqueous sodium bicarbonate solution (10 ml) added, and the mixture extracted with dichloromethane (3x20 ml). The organic layer was washed with 20 ml brine and dried with sodium sulfate. Removal of the solvent left a semisolid residue, which was used for next reaction without further purification. $^1H$ NMR ($CDCl_3$) confirmed formation of mesylate: 7.30 (m, 5H), 4.95 (dd, 12.3, 7.0, 1H), 4.23 (s, 2H), 4.10 (m, 1H), 3.96 (m, 1H), 3.04 (s, 3H), 2.42 (m, 2H), 2.10 (m, 1H), 1.82 (m, 1H). The mixture of mesylate residue, 30 ml DMF, 1 ml pyridine and 6 ml water was heated with 424 mg sodium azide at 130 °C for 12 hours. The reaction was quenched with 20 ml cold water and extracted with ether (4x20 ml). The crude product was purified by column chromatography to yield compound **5** (632 mg, 2.4 mmol, 76% of two steps) as a colorless liquid (5:1=hexanes: ethyl acetate). IR ($cm^{-1}$): 2200; $^1H$ NMR ($CDCl_3$): 7.32 (m, 5H), 4.50 (s, 2H), 4.01 (m, 1H), 3.77 (m, 2H), 2.27 (m, 2H), 2.02 (m, 2H); $^{13}C$ NMR ($CDCl_3$): 137.7, 128.3, 127.6, 75.0, 71.2, 62.5, 35.5; LR-MS (CI): calcd. for $C_{12}H_{14}N_6O$: 258, found: 259 (M+H).




**Scheme**

A mixture of **5** (567 mg, 2.2 mmol), 30 ml methanol, 200 mg of 20% palladium hydroxide on carbon (Pearlman's catalyst) and 3 ml 2N hydrochloric acid was stirred at 60 psi hydrogen for 6 hours. Removal of the methanol from the filtrate and lyophilization of the aqueous residue gave compound **1** as a white amorphous solid (405 mg, 2.1 mmol, 98%). mp 140-145 °C(color change to black); $^1H$ NMR ($D_2O$): 4.37 (m, 1H), 3.87 (m, 2H), 2.36 (m, 2H), 1.84 (m, 2H); $^{13}C$ NMR ($D_2O$): 72.1, 54.5, 39.6; LR-MS (CI): calcd. for $C_5H_{12}N_2O$ 116, found 117 (M+H).

Salt **2** was obtained by same reaction conditions as a white amorphous solid. mp 130-135 °C(color change to black); $^1H$ NMR ($D_2O$): 4.44 (m, 1H), 3.98 (m, 2H), 2.10 (m, 4H); $^{13}C$ NMR: 70.3, 53.9, 40.0; LR-MS (CI): calcd. for $C_5H_{12}N_2O$ 116, found 117 (M+H).

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