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Stereospecific Synthesis of Aminocyclitols via Cycloadditions of Unsymmetrical, Optically Pure Dienes: Conduramine A-1 and Dihydroconduramine A-1

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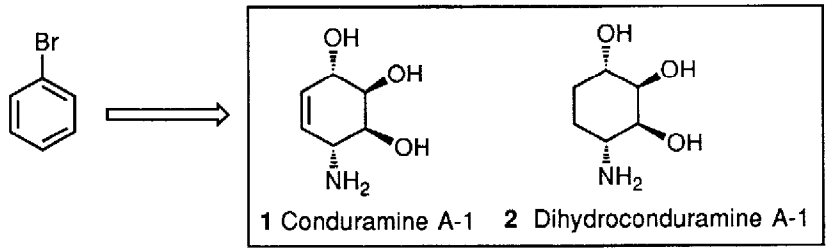
Abstract: Stereospecific synthesis of Conduramine A-1 and Dihydroconduramine A-1 has been achieved by a fully regio- and stereospecific hetero Diels-Alder cycloaddition of a nitrosyl derivative and homochiral 1-halocyclohexadiene diols obtained by microbial oxidation of halobenzenes.

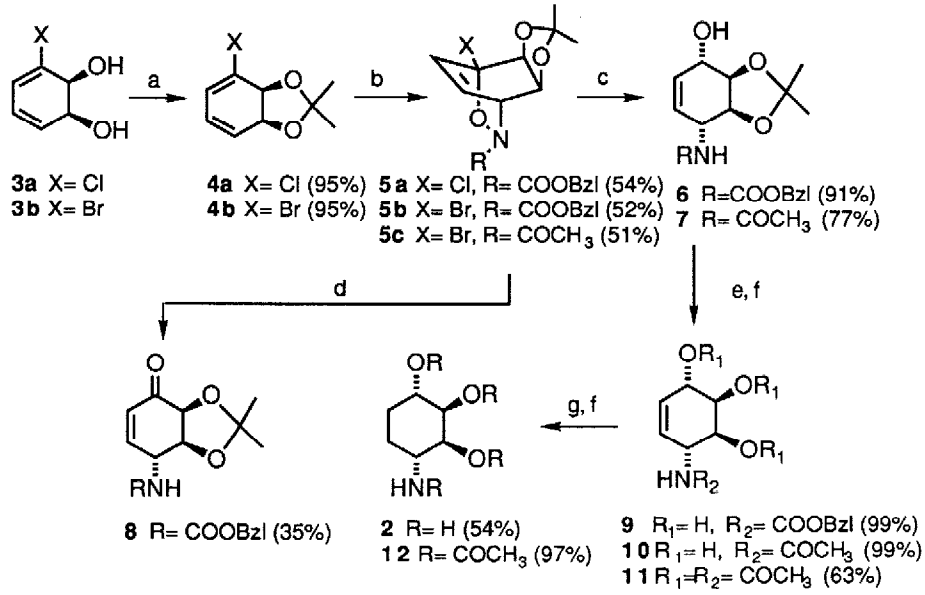
Aminocyclitols have shown interesting inhibition activity of some glycosidases[1] and are important intermediates in the synthesis of aminoinositols.[2] A recent review of the chemistry of these compounds has been published by Balci.[3]



1 Conduramine A-1 **2** Dihydroconduramine A-1

The ready availability through biocatalytic means, as well as the documented use of homochiral cyclohexadiene diols of type **3**[4], Scheme 1, prompted our investigation of an approach to aminocyclitol derivatives such as the conduramines **1**[5] and **2**. Such an approach would rely on face-selective functionalization of cyclohexadiene **4** via stereoselective [4+2] cycloaddition of an appropriate nitrosyl dienophile. Inspection of the literature confirmed wide use of nitrosyl compounds as dienophiles in many synthetic endeavors[6] as well as in recent total syntheses, such as Keck's heliotridine and retronecine,[7] Fuchs' cephalotaxine,[8] Watanabe's gephyrotoxin 223AB,[9] Kresze's Conduramine F-1 synthesis,[10] and Viehe's aminoconduritol preparations.[11] The cycloadditions of nitrosyl groups to cyclohexadiene diols derived from benzene are also known for both the cis and the trans derivatives through the efforts of Kresze[12] and Roberts.[13] All of the aforementioned syntheses are either racemic or require a chiral auxiliary group for introduction of chirality which usually lengthens the preparation of target compounds. The cycloaddition-based approaches of Vogel[14] and Viehe[11] to various carbohydrate and cyclitol synthons have recently been published. Herein we report an efficient synthesis of two aminocyclitols by taking advantage of the stereoelectronic disposition of bromo- and chloro-cyclohexadiene acetonides **4a** and **4b**, obtained by a quantitative protection of bromo- and chlorocyclohexadienediol. Diols **3a** and **3b** are available in multigram quantities by microbial oxidation of bromo- and chlorobenzene using a mutant

strain of *Pseudomonas putida*, Pp 39D.[15] Examination of the literature failed to produce an example of nitrosyl group addition to a halodiene.



Reagents: a. DMP, acetone, p-TsOH; b. Bu_4NIO_4 and BzlOCONHOH or $CH_3CONHOH$; c. Al/Hg, THF/H_2O; d. Bu_3SnH, AIBN, toluene; e. $AcOH/THF/H_2O$ f. Ac_2O, Pyr.; g. H_2(Pd), MeOH.

Scheme 1. Synthesis of Conduramines.

The Diels-Alder reaction of **4** with a nitrosyl dienophile, generated in situ from acetohydroxamic acid[16a] and benzyl-N-hydroxycarbamate,[16b] led to single enantiomers **5** with the concomitant establishment of all four contiguous asymmetric centers in the title compounds, Scheme 1. The addition of the nitrosyl dienophile occurred from the less-hindered side of the bicyclic system **4** with no evidence of either diastereomeric or regioisomeric contamination. AM1 calculations performed on **4a** and **4b** indicated a possible charge density reversal between C-1 and C-4.[17] We initially expected that the two halodienes would furnish adducts of different regiochemistry with highly polarized dienophiles such as a nitrosyl group.

Reductive cleavage of the N-O bond using Na/Hg[18] occurred with attendant dehalogenation, thereby preserving the syn relationship of the hydroxyl and the amine established during the cycloaddition. Hydroxyamine **6** was obtained from reduction of chloro-oxazine **5a** and bromo-oxazine **5b**, with identical spectroscopic and optical properties. Interestingly, the alternate method of cleavage using Bu_3SnH[19] led to the aminoketone **8** which could be used in generating C-1 diastereomers of **1** or **2** by hydride reduction, in analogy with the reduction of similar hydroxy enones.[17a,20] Acid treatment followed by hydrogenation led directly to dihydroconduramine **2**. Reduction of oxazine **5c**, acid treatment of acetamide **7** and

acetylation of the free hydroxy groups led to protected Conduramine A-1 **11** (vide NMR and α_D data in the literature[21]).

In summary, a short (four steps from bromobenzene) and fully stereocontrolled synthesis of an important aminocyclitol was accomplished in an overall yield of 24.2% (Conduramine A-1 tetraacetate) and 46.4% (Dihydroconduramine). Interestingly cycloaddition of the nitrosyl group proceeded with regiochemistry inconsistent with AM1 calculations reported for the acetonide system **4**.[17] The incorporation of an amine functionality directly into an optically pure arene cis diol bodes well for the development of an exhaustive and general synthetic protocol for this important class of compounds.

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