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Synthesis of Conduritol, Conduramine, and Validoxylamine Analogs from Tetrahydronaphthalene-*cis*-Diol.

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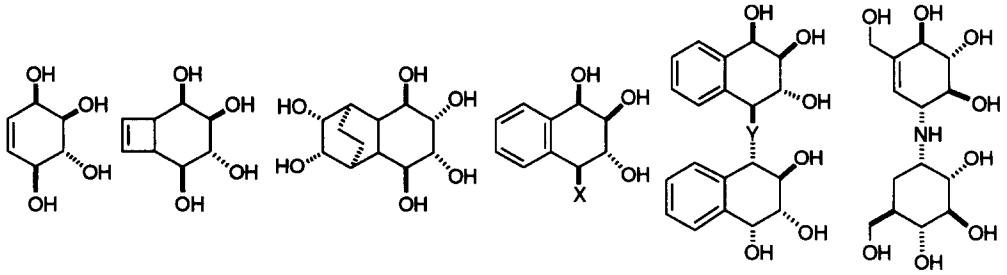
Abstract: A range of polycyclic analogs of conduritols and conduramines was prepared concisely, starting from *cis*-(1*R*,2*S*)-1,2-dihydronaphthalenediol. This methodology could be extended to the syntheses of validoxylamine A analogs. © 1997 Elsevier Science Ltd.

(-)-Conduritol F (**1**), belongs to a class of 5-cyclohexene-1,2,3,4-tetrols, and several of the ten possible isomers have proven to be glycosidase enzyme inhibitors.[1] A number of conduritols and their derivatives[2] have been found to possess antibiotic, antileukemic, and tumor-inhibitory properties.[3] Bicyclic derivatives of conduritols, in which the double bond was incorporated into additional structural motif, as in the recently reported bis-homoconduritol F (**2**), have been synthesized.[4] Tricyclic derivatives of type **3** that possess a [2.2.2] motif, have been found to inhibit insulin release at low glucose concentration *in vitro*.[5] Furthermore, it has also been shown that the conduritol F epoxide inhibited β-mannosidase B isolated from goat liver.[6] Because of the biological activities of cyclic conduritol derivatives, we undertook the synthesis of tetrol analogs **4**, which contain the stereochemistry of both (-)-conduritol F (**1**) and its cyclobutene derivative **2**, in order to ascertain if biological activity would be retained with the olefinic site contained within a hydrophobic aromatic moiety.

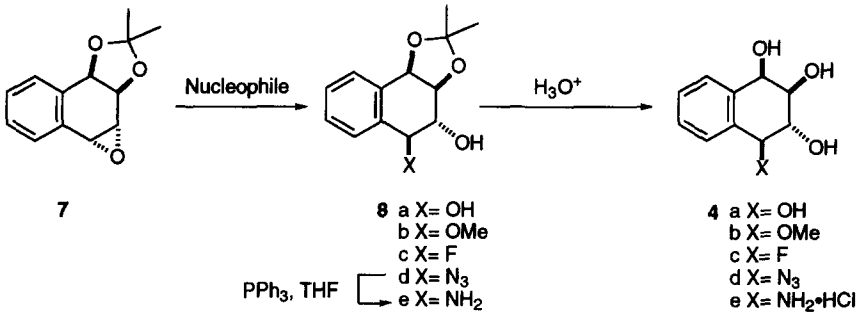
An obvious extrapolation of this work would be an attempt to connect units such as **4** to create polyhydroxylated tetrahydronaphthalene derivatives **5b** in various diastereomeric forms and to compare their activity to that of validoxylamine A (**6**). The latter was isolated from the fermentation broth of *Streptomyces hygroscopius* var. *limoneus*.[7] The synthesis of **6** and others validoxylamines has been extensively studied by Ogawa et *al.* [8]



1 **2** **3** **4** a X= OH, b X= OMe, c X= F, d X= NH_2, e X= NH_2•HCl **5** a Y= O, b Y= NH **6**

Recently, we reported the synthesis of polyhydroxylated tetrahydronaphthalene ethers of type **5a** that possess the extended features of conduritols and were shown to form aggregates in solid phase.[9] Herein, we report the preparation of new conduritol analogs, **4a-e**, *via* the nucleophilic opening of epoxide **7**[10a] and the application of a coupling methodology to produce ethers and amines of type **5b**, the latter containing some of primary structural features of validoxylamine A (**6**).

Several nucleophiles were employed to open epoxide **7**, prepared from *cis*-(1*R*,2*S*)-1,2-dihydronaphthalenediol,[10b] as shown in Scheme 1. Epoxide opening in acidic conditions led to two diastereoisomers presumably through a carbocation intermediate, with the *trans*-compound as the major product (25:1). In the case of methanolysis of **7** in the presence of a catalytic amount of camphorsulfonic acid, the ratio of *trans*- to *cis*-isomers was improved by carrying out the reaction at lower temperature (0 °C) but the *cis*-stereoisomer was still detected (ratio of *trans* to *cis* is 50:1). However, a single stereoisomer of **8a-d** was attained under basic or neutral conditions. Opening of **7** with KOH in wet DMSO afforded **8a** in 84% yield, whereas sodium methoxide in methanol at reflux gave **8b** in 94% yield. The fluoro derivative **8c** was obtained by nucleophilic opening of **7** with tetrabutylphosphonium fluoride dihydrofluoride (TBPF-DF) in a sealed tube.[11] The use of TBPF-DF proved advantageous in the facile purification of the crude mixture by column chromatography. Compounds **8a-d** were converted to **4a-d** in high yield (70-90%) by acid catalyzed hydrolysis (TFA/H_2O/THF).

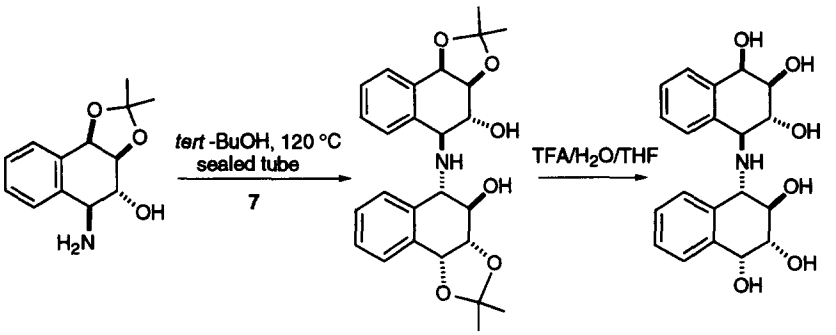


Scheme 1

The synthesis of conduramine analog **4e** was accomplished as shown in Scheme 1. Epoxide opening of **7** was accomplished by sodium azide in dimethoxyethane and water (1/1), followed by reduction of the azide functionality with triphenylphosphine[12] to afford **8e**. Compound **8e** was immediately hydrolyzed under acidic condition (HCl/MeOH) to give **4e** as the hydrochloride salt.

Conduritol F derivative **4a** was screened against β-mannosidase (isolated from snails) that accepts *p*-nitrophenylmannoside as a substrate. Compound **4a** was tested under standard conditions[13] up to a maximum concentration of 10 mM and has shown no inhibitory activity. A broader biological screening of all polyols reported in this manuscript against several common glycosidase enzymes (amylosidase, α-glucosidase, β-glucosidase, α-galactosidase, β-galactosidase and α-mannosidase) is currently under investigation.

To provide the features of validoxylamine A (**6**), we extended the above methodology to the synthesis of the amino-bridged conduritol **10** using **8e** as the key intermediate in this strategy (Scheme 2).



Scheme 2

The coupling reaction was performed by heating the mixture of **8e** and **7** in *tert*-butanol in a sealed tube at 120 °C, to generate the bridged amine **9** in 50% yield. The stereochemistry of **9** was confirmed by ^{1}H and ^{13}C NMR spectra, which indicated the presence of a C-2 symmetry axis. Removal of the acetonides from **9** using a mixture of TFA/H_2O/THF (1/1/4) gave **10** in a 90% yield.

In summary we described a short and efficient synthesis of highly oxygenated conduritol and conduramine analogs containing a fused benzene ring in place of the usual olefin. Coupling of two units of conduritol derivatives provided a new class of compounds, mimicking key structural elements of validoxylamine A. The synthetic route will be extended to the synthesis of other conduritol analogs. Systematic biological evaluation of all compounds including compound **10** is currently in progress.[14]

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11. Illustrative Experimental Procedure for opening of epoxide **7**.
    In a dry sealed tube containing **7** (1.1 g, 4.9 mmol) was added $Bu_4PH_2F_3$ (3.1 g, 9.9 mmol). The mixture was stirred for 48 hours at 100 °C and cooled to room temperature. The crude residue was purified by flash column chromatography (silica gel, ethyl acetate/hexane, 1/3) to afford **8c** (0.84 g, 71%) as a white solid. $[\alpha]_D^{25}$ -21 (*c* 1, $CHCl_3$); mp 123-124 °C (recrystalized from CH_2Cl_2/hexane); IR (KBr): 3439, 2997, 1375, 1251, 1217, 1070 cm^{-1}; ^{19}F NMR ($CDCl_3/CFCl_3$): -196.0 (dd, *J* = 51.3, 14.5 Hz); ^1H NMR (300 MHz, $CDCl_3$) δ 7.3-7.5 (m, 4H), 5.35 (dd, *J* = 52.8, 9.1 Hz, 1H), 5.21 (d, *J* = 6.6 Hz, 1H), 4.34 (dd, *J* = 8.5, 6.9 Hz, 1H), 4.00 (m, 1H), 3.33 (d, *J* = 2.2 Hz, 1H), 1.49 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 133.5 (d, *J* = 19 Hz), 130.4 (d, *J* = 5 Hz), 129.0, 128.9, 128.8, 125.0 (d, *J* = 10 Hz), 110.6, 91.2 (d, *J* = 179 Hz), 77.3 (d, *J* = 11 Hz), 74.2, 73.0 (d, *J* = 17 Hz), 27.9, 25.7; HRMS (FAB) calcd for ($C_{13}H_{15}FO_3$+H) 239.1083, Found 239.1073; Anal. calcd for $C_{13}H_{15}FO_3$: C 65.54; H 6.35, Found: C 65.68, H 6.37
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14 All new compounds exhibited satisfactory 1H and 13C NMR and IR spectral data as well as satisfactory combustion analysis or exact mass data.

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