Synthesis and biological evaluation of conduritol and conduramine analogs

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A number of dimeric conduritol and conduramine analogs have been synthesized from naphthalene *via* a combination of enzymatic and chemical methods to give oxygenated derivatives with high stereo- and regiocontrol in few steps. These compounds have been tested for enzymatic inhibition against common glycosidases.

Introduction

Conduritols (**1**) have recently become fashionable synthetic

A : 1α, 2β, 3β, 4α
B : 1α, 2β, 3α, 4β
C : 1α, 2α, 3α, 4β
D : 1α, 2α, 3α, 4α
**E** : 1α, 2α, 3β, 4β
F : 1α, 2α, 3β, 4α
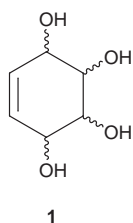
targets.[1] Theoretically, ten stereoisomers of conduritol are possible. To avoid ambiguity, the six diastereoisomers are designated by suffixed capital A to F, assigned in the order of their discovery. Conduritols A and D are symmetrical; the others exist as four enantiomeric pairs. In nature, the occurrence of only conduritols A and F has been established. Conduritol A was isolated from the bark of the vine *Marsdenia condurango* by Kübler in 1908.[2] The structure and configuration of this compound were established 30 years later by Dangschat and Fischer.[3] In 1962, Plouvier[4] isolated another conduritol from *Crysanthemum leucanthemitol*, which was named L-leucanthemitol or conduritol F. The latter is found in small quantities in almost all green plants as the L-isomer, while the abundance of conduritol A is limited to specific subfamilies of tropical plants.[5]

The synthesis of conduritol isomers has been the focal point of considerable synthetic effort. The first successful non-stereospecific synthesis of conduritol A and F was carried out by Nakajima and co-workers in 1957[6] and the non-natural conduritols B,[6,7] C,[8] D,[9] and E[10] have been synthesized by many different synthetic sequences. In addition, the ability of the prokaryotic dioxygenases to convert benzene and monosubstituted aromatic compounds to *meso*- and homochiral diols, respectively, has been recognized by several groups[11] in numerous chemoenzymatic syntheses of inositols[12] and conduritols.[13]

Conduritol A is present with numerous other complex natural products in the leaves of *Gymnema sylvestre*, a shrub which as been used as a folk remedy for diabetes.[14] It has also been shown to suppress blood glucose level, which can reduce the need for insulin.[15] Conduramine and conduritol derivatives have shown promising features such as inhibitory activity for glycosidases.[16] In addition, a number of conduritol derivatives have been found to possess antifeedant, antibiotic, anti-

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leukemic, and growth regulating activity.[1] Because of the importance of those compounds, the synthesis of conduritols and related compounds has been comprehensively reviewed.[1,17]

Many unnatural analogs possessing the basic features of conduritols have been made. For example, Billington and co-workers[18] synthesized unnatural bicyclic and tricyclic conduritol derivatives such as **2**. Those compounds have been shown to
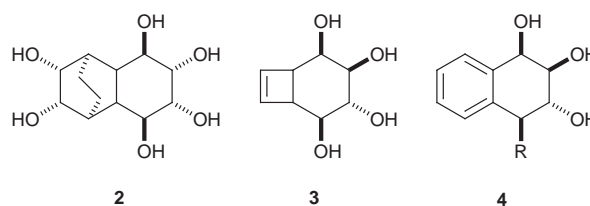
modulate the release of insulin *in vitro* from isolated pancreatic islet cells in the presence of varying concentrations of glucose, in both stimulatory and inhibitory sense. Balci and co-workers[19] achieved the synthesis of conduritol analog **3** obtained from bicyclooctatriene. The interesting properties of such compounds led us to investigate other bicyclic mimics such as **4**[20] (where R is a nucleophile), which retain the pattern of conduritol **1**, with the added feature of having the conduritol olefin as a part of an aromatic system. Such features, we reasoned, might lead to interesting stacking properties and enhanced lipophilicity of the outside band of the β-turn in higher oligomers.

Results and discussion

Synthesis of conduritol analogs

A synthetic strategy has been devised to afford tetrahydronaphthalene analogs **4** by opening of epoxide **7**, obtained from the chiral *cis*-tetrahydronaphthalene-1,2-diol **6** (Scheme 1). Diol **6** is prepared by microbial oxidation of naphthalene (**5**).[21] The combination of chemical synthesis and enzymatic biotransformation offers a unique opportunity to shorten routes to chiral compounds in an environmentally conscious process.

The biooxidation of naphthalene (**5**) was achieved with toluene dioxygenase expressed in *Escherichia coli* JM109-(pDTG601), a recombinant microorganism developed by Gibson.[22] This particular biotransformation afforded **6** in a yield of 7.5 g L⁻¹ of broth. The diol **6** was protected as its isopropylidene derivative in quantitative yield using 2,2-dimethoxypropane in acetone with a catalytic amount of toluene-*p*-sulfonic acid followed by epoxidation of the double bond with *m*-chloroperoxybenzoic acid in methylene chloride at 0 °C to yield **7** in 80% for both steps. Steric hindrance of
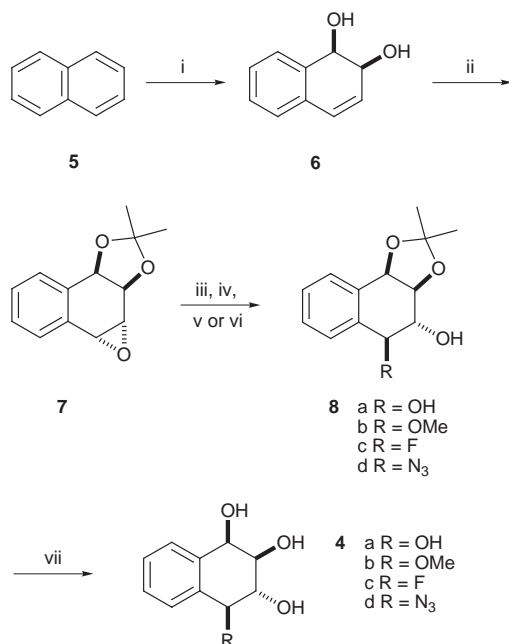
Scheme 1 *Reagents and conditions*: i, *E. coli* JM109(pDTG601); ii, a) 2,2-dimethoxypropane, acetone, *p*-TsOH, b) MCPBA, CH$_2$Cl$_2$, 0 °C; iii, KOH, wet DMSO, 75 °C; iv, MeONa, MeOH, reflux; v, TBPF-DF, 100 °C; vi, NaN$_3$, DME, H$_2$O, reflux; vii, THF–H$_2$O–TFA.

8 a R = OH
b R = OMe
c R = F
d R = N$_3$

4 a R = OH
b R = OMe
c R = F
d R = N$_3$

the ketal ring directed the peroxy acid attack to its opposing face in a stereospecific manner. (Another synthesis of **7** was recently published by Orsini and Pelizzoni,[23] using a modified strain of *Pseudomonas fluorescens* for the dihydroxylation of naphthalene).

First attempts at the epoxide ring opening of **7** were performed under acidic conditions (camphorsulfonic acid–MeOH–CH$_2$Cl$_2$) giving two diastereomers in a 25:1 ratio. This result suggests the opening of the epoxide *via* a stabilized carbocation intermediate at the benzylic position. Carrying out the reaction at low temperature gave a higher ratio (50:1) of the *trans* diastereoisomer. Recrystallization afforded diastereomerically pure *trans* compound **8b**. The regioselectivity of the nucleophilic attack was confirmed by the conversion of diastereomeric mixture of **8b** to (2*R*,3*R*)-tetrahydronaphthalene-2,3-diol, by acidic hydrogenolysis and by comparison of its optical rotation and spectroscopic data with those reported in the literature.[23]

To control the selectivity of the reaction better, the epoxide opening was carried out under basic conditions (Scheme 1). Stereospecific ring opening of **7** at the benzylic position was accomplished with sodium methoxide in methanol at reflux and afforded the alcohol **8b** (only one diastereoisomer) in 95% yield. Based on this selectivity, we have synthesized a range of polycyclic conduritol analogs using several nucleophiles. Thus treatment of **7** with KOH in wet dimethyl sulfoxide at 75 °C, afforded the diol **8a** in 84% yield. The synthesis of fluoroconduritol analog **8c** was accomplished in 71% yield by epoxide opening with tetrabutylphosphonium fluoride dihydrofluoride (TBPF-DF) used as reagent and solvent, simplifying the work-up procedure. The synthesis of **8d** proceeded *via* the nucleophilic attack of **7** with sodium azide in a mixture of DME–H$_2$O and was obtained in 89% yield. Compounds **8a–d** were deprotected upon treatment with a mixture of 4:1:1 THF–H$_2$O–TFA in excellent yield (80–90%).

**Synthesis of polyhydroxylated dimeric ethers**

Recently, an iterative procedure used for the synthesis of inositol and aminocyclitol conjugates **9** and **10** was published.[24] These compounds were tested for inhibition of enzymes against glycosidase-catalyzed hydrolysis. Thus, with the aim of synthesizing new dimeric conduritol analogs and in the hope that several of these molecules described above appeared to be reasonable candidates for testing as enzyme inhibitors, we undertook the synthesis of **11**, **12**, and **13**.
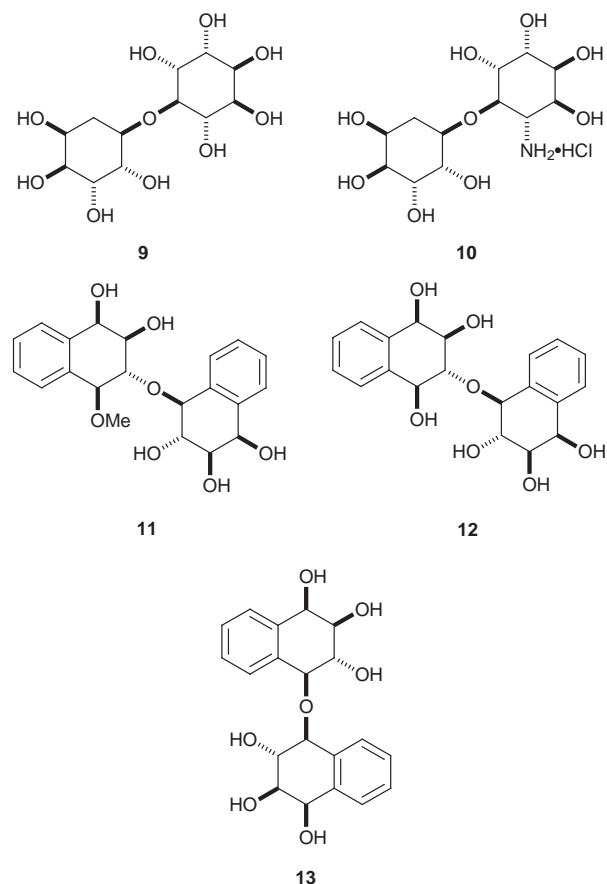
The coupling strategy in the case of **9** and **10** was based on an epoxide opening in the presence of a Lewis acid catalyst. This same strategy was used to prepare new conduritol derivatives. Thus, the ring opening of **7** with **8a** was performed in the presence of boron trifluoride–diethyl ether complex in methylene chloride at −20 °C, to give the ethers **14a** and **15** in a 3:1 ratio in 50% yield (Scheme 2). Under these conditions, complete benzylic attack was observed, but with two chemically different hydroxy groups leading to two different products. These regioisomers were readily separated by column chromatography on silica gel. The ^{1}H and ^{13}C NMR spectra of **15**, which indicated the presence of a C_2 axis of symmetry by the appearance of only half of the signals for each functionality, confirmed the structure of this isomer. In order to selectively prepare one of the two possible ethers, we decided to block the benzylic hydroxy of **8a** as a methyl ether. Better control of the coupling reaction materialized by employing a one-step procedure which provided **14b** from epoxide **7** in the presence of 0.5 equivalent of methanol and boron trifluoride–diethyl ether complex in methylene chloride at −20 °C. Compounds **11**, **12**, and **13** were obtained by deprotection of the acetonides in a mixture of THF–H$_2$O–TFA (4:1:1) in excellent yield (>90%). The stereochemistry of **11** was confirmed by single crystal X-ray diffraction analysis (see Table 1 and Fig. 1)‡ and served also to confirm the regioselectivity of the epoxide opening at
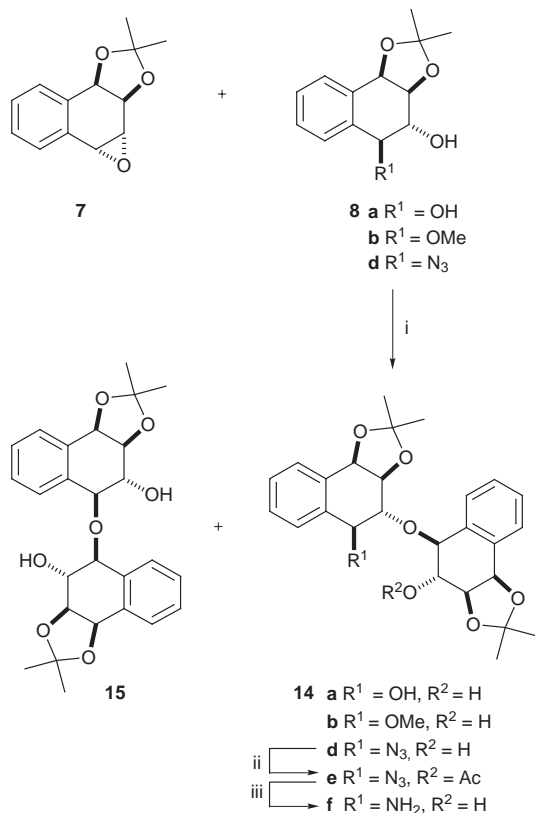
Scheme 2 *Reagents and conditions*: i, BF$_3$·OEt$_2$, CH$_2$Cl$_2$; ii, Ac$_2$O, pyridine; iii, LiAlH$_4$, Et$_2$O.

Table 1 Crystal data and structure refinement for compound **11**

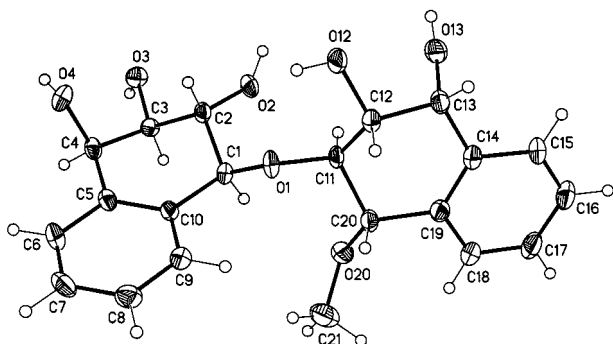|	
Empirical formula	C$_{21}$H$_{28}$O$_9$
Formula weight	424.43
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*P*2(1)
Unit cell dimensions	
a	4.8929(1) Å
b	13.8092(3) Å
c	14.8591(3) Å
α	90°
β	93.953(1)°
γ	90°
Volume	1001.60(4) Å^3
Z	2
Density (calculated)	1.407 Mg m^{-3}
Absorption coefficient	0.110 mm^{-1}
F(000)	452
Crystal size	0.42 × 0.28 × 0.02 mm^3
Theta range for data collection	2.02 to 27.49°
Index ranges	$-6 \leqslant h \leqslant 6$, $-15 \leqslant k \leqslant 17$, $-17 \leqslant l \leqslant 19$
Reflections collected	7059
Independent reflection	3742 [R(int) = 0.0294]
Completeness to $\theta = 27.49°$	99.1%
Absorption correction	Empirical
Max. and min. transmission	0.998 and 0.965
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3742/1/292
Goodness-of-fit on F^2	1.057
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0460$, $wR_2 = 0.1089$ [3103]
R indices (all data)	$R_1 = 0.0622$, $wR_2 = 0.1191$
Absolute structure parameter	0.8(11)
Extinction coefficient	0.013(4)
Largest diff. peak and hole	0.284 and -0.245 e Å^{-3}

Fig. 1 Molecular drawing of **11** (50% probability ellipsoids) with the numbering scheme.
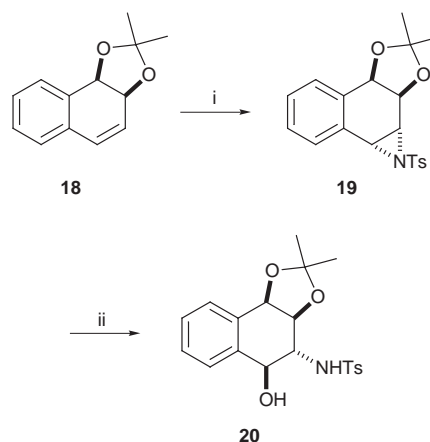
the benzylic position only in the reaction of **7** with **8a** (albeit, in this case, by two chemically different hydroxy groups).[20]
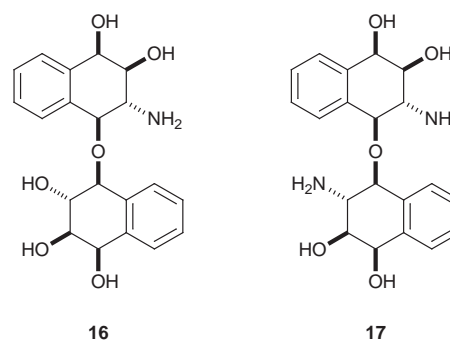
Synthesis of aminohydroxylated dimeric ether

A simple method has been developed to synthesize dimeric ethers of tetrahydronaphthalene tetrols. It has been demonstrated that the amino-derivative **10** has shown a better inhibition activity against glycosidases, inhibiting β-glucosidase by 12% at 3.5 mmol concentration.[24] Encouraged by this result, we extended this strategy to the preparation of oxygen-linked aminoconduritol dimer analogs **16** and **17**. Such strategy called for the use of **20** as the nucleophile for the opening of either epoxide **7** or aziridine **19**. The synthesis of **20** was achieved by employing the aziridination procedure developed by Jacobsen[25] and Evans,[26] by reacting acetonide **18** with a nitrene precursor and a copper catalyst to afford the aziridine **19** in 30% yield (Scheme 3). However, attempts were made to improve the yield by using longer reaction times and higher temperatures, but the decomposition of the iodonium ylide derivative into toluene-*p*-sulfonamide was observed.[27]


Scheme 3 *Reagents and conditions*: i, PhI=NTs, Cu(acac)$_2$, CH$_3$CN; ii, KOH, DMSO, 75 °C.

Opening of **19** was performed in acidic and basic media. Under acidic conditions, **19** was treated with strongly acidic Amberlyst 15 resin in acetone to give a mixture of both diastereoisomers in 72% yield. Aziridine **19** was also

opened under basic conditions with potassium hydroxide in wet dimethyl sulfoxide at 75 °C. Performing the reaction in this medium eliminated, as in the epoxide case, the formation of a benzylic carbocation and afforded **20** as only one diastereoisomer in 70% yield.

Unfortunately, the attempts for the coupling reaction of naphthalene epoxide **7** with protected amino alcohol **20** in the presence of boron trifluoride–diethyl ether in methylene chloride at −78 °C or higher temperature did not afford the expected dimer but resulted in the formation of *cis*-fluorohydrin **21** as a side product along with the recovery of most of the starting material. We observed a similar result when we tried to open the aziridine **19** with **20** and isolated only the fluoro-derivative **22**.

**21**   **22**   **23**

24
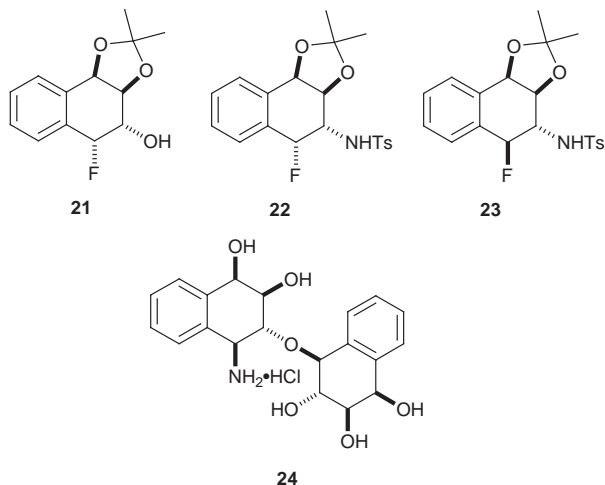
The failure of the coupling reaction was surprising, but can be explained by the hindrance of the tosyl group in compound **20**, which allowed the opening of **7** or **19** only by a fluoride ion. These results suggested a stepwise reaction, where the initial step would consist of a Lewis acid supported cleavage of the carbon–oxygen bond at the favored benzylic position to produce a carbocation, followed by internal transfer of a fluoride ion from the catalyst *via* a *syn* delivery. The total recovery of alcohol **20** supposed that the latter did not have a good nucleophilic character which could be due to the hindrance of both the tosyl group and the ketal ring. In the literature, a related type of epoxycyclopropane opening has been previously reported,[28] supporting our observations. The stereochemistry of compounds **21** and **22** was confirmed by comparison of the ^{1}H NMR spectra with their diastereoisomers **8c** and **23**, obtained from epoxide or aziridine opening with tetrabutylphosphonium fluoride dihydrofluoride (TBPF-DF) respectively. In the ^{1}H NMR spectrum of **21**, a doublet of doublets at 5.64 ppm was observed for the proton on the same carbon as the fluoride with coupling constants of 2.5 and 50.8 Hz which confirmed a *trans* relationship between the two protons (geminal to fluoride and in α-position). Concerning **8c**, the doublet of doublets is at 5.35 ppm with coupling constants of 9.3 and 52.8 Hz which confirmed a *cis* relationship between the same two protons. Because of the presence of the doublet of doublets signal, the regioselectivity of the epoxide or aziridine opening and the presence of *cis* and *trans* diastereoisomers were confirmed. To remedy this failure, another synthetic pathway was studied for the introduction of an amino group in the dimeric structure.

A coupling reaction was performed by reacting **7** and **8d** with a catalytic amount of boron trifluoride–diethyl ether at −78 °C in methylene chloride (Scheme 2). The resulting dimer **14d** could not be separated from unreacted starting material **8d**. Acetylation with acetic anhydride in pyridine was necessary to facilitate the separation and afford the O-linked conjugate **14e** in 27% yield for two steps. The Lewis acid catalyzed coupling

reactions were low yielding. Thus, coupling reactions were attempted under basic conditions with, for example, sodium hydride. The deprotonation of **8d** and reaction with **7** were unsuccessful, permitting only the recovery of starting materials. The reduction of the azide functionality of **14e** as well as the cleavage of the acetyl group were done with lithium aluminium hydride to afford the amine **14f**. Deprotection of the hydroxy groups in acidic condition (HCl, MeOH) gave **24** as its hydrochloride salt.

Biological evaluation

In order to verify if some the deprotected compounds previously described possess biological activities, compounds **4a–d**, **11**, **12**, **13**, and **24** were screened against three common glycosidases (β-mannosidase, α-galactosidase and β-galactosidase) that accept *p*- or *o*-nitrophenyl glycosides as substrate.[29] The compounds were tested up to a maximum concentration of 10 mM. The β-mannosidase was first selected because of the similarity between our compounds and mannose, especially with its transition state **25** as substrate in the enzyme active site.

4a   **25**
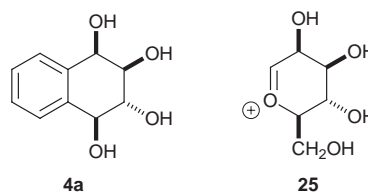
Unfortunately, compounds **4a–d** did not show any inhibition for this enzyme. Thus, the compounds were tested against α-galactosidase and none of them was active. However, derivative **4b** exhibited an inhibitory activity for β-galactosidase, extracted from *E. coli*. At the concentration of 10 mM, we observed 85% inhibition. To explain this result, we can suggest that the enzyme might recognize the ether linkage as a glycosidic bond; because of the stereochemistry of the hydroxy groups of **4b**, which corresponds to that of galactose, it is accepted as a substrate.

This interesting result led us to investigate the dimers **11**, **12**, **13** and **24**. However, because of their low solubility in water, compounds **11**, **12** and **13** were not good candidates for enzymatic assays. Dimer **24**, on which the presence of an amino group overcame the solubility problem (in its hydrochloride form), did not show any activity against the glycosidases discussed above.

Conclusion

The combination of chemical and enzymatic methodologies is emerging as a practical route to the synthesis of chiral and biologically active molecules. An efficient method for the preparation of new conduritol analogs has been developed. We extended this methodology to prepare a new class of compounds. Encouraging biological data has been reported for the compound **4b**, providing impetus for further studies in this area. Exhaustive study of the new inhibitor **4b** (IC_{50}, K_i) and the synthesis of additional amino derivatives are currently being pursued and will be published in due course.

Experimental

All non-aqueous reactions were carried out under argon using stardard techniques for the exclusion of air and moisture. Analytical thin layer chromatography was performed on Whatman K6F silica gel 60 Å plates. Flash chromatography was performed on chromatographic silica gel, 230–400 mesh (Fisher Chemical). Infrared spectra were recorded on a Perkin-Elmer FT-IR. Proton and carbon NMR spectra were obtained on a Varian 300 MHz spectrometer using TMS as reference

unless otherwise indicated in the experimental section. J Values are expressed in Hz. Optical rotations were recorded on a Perkin-Elmer 241 digital polarimeter. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. High resolution mass spectra and elemental analyses were performed at the University of Florida.

(3aS,4R,5S,9bR)-2,2-Dimethyl-3a,4,5,9b-tetrahydronaphtho-[1,2-d][1,3]dioxole-4,5-diol 8a

To a dimethyl sulfoxide (100 mL) solution of **7** (10.0 g, 45.9 mmol) was added dropwise at room temperature an aqueous solution of KOH 10% (100 mL). The resulting mixture was stirred and heated at 75 °C for 1.5 h. The reaction was diluted with brine, and extracted with ethyl acetate (4 × 80 mL). The combined organic portions were washed with water, brine, dried over MgSO$_4$ and concentrated under reduced pressure. The resulting yellow solid was chromatographed (hexane–ethyl acetate 1 : 1) to afford **8a** (9.1 g, 84%) as a white solid. Mp 146–148 °C [Found: C, 65.80 ; H, 7.11%; M + H (FAB) 235.0970. C$_{13}$H$_{16}$O$_4$ requires C, 66.08; H, 6.82%; M + H, 235.0970]; $[a]_D^{26}$ −18.7 (c 1.0, CHCl$_3$); v_{max}(KBr)/cm^{-1} 3460 (broad), 1455, 1379, 1220, 1161, 1102, 1061, 1008; δ_H(300 MHz, CDCl$_3$) 7.63 (1H, d, J 7.4), 7.5–7.3 (m, 3H), 5.23 (1H, d, J 6.9), 4.53 (1H, d, J 9.3), 4.33 (1H, dd, J 8.2, 6.9), 3.74 (1H, dd, J 9.3, 8.2), 3.32 (1H, br s, OH), 3.20 (1H, br s, OH), 1.47 (3H, s), 1.46 (3H, s); δ_C(75 MHz, CDCl$_3$) 136.8 (C), 131.0 (C), 128.8 (CH), 128.7 (CH), 127.9 (CH), 125.4 (CH), 110.1 (C), 78.1 (CH), 75.0 (CH), 74.5 (CH), 70.9 (CH), 28.0 (CH$_3$), 25.7 (CH$_3$).

(3aS,4R,5S,9bR)-5-Methoxy-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]dioxol-4-ol 8b

Epoxide **7** (588 mg, 2.69 mmol) was added to a solution of sodium methoxide (prepared from 0.44 g of Na) in dry methanol (25 mL) at 0 °C. The solution was stirred for 30 minutes at 0 °C and then refluxed for 24 hours. The methanol was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with a solution of 1 M HCl, brine, dried over MgSO$_4$ and evaporated to yield **8b** (662 mg, 98%) as a white solid. Mp 126–127 °C (from CH$_2$Cl$_2$–hexane) [Found: C, 67.02 ; H, 7.23%; M + H (CI) 251.1283. C$_{14}$H$_{18}$O$_4$ requires C, 67.18; H, 7.25%; M + H, 251.1283]; $[a]_D^{25}$ +31.5 (c 1.2, CHCl$_3$); v_{max}(KBr)/cm^{-1} 3484 (broad), 1458, 1376, 1252, 1215, 1165, 1137, 1103, 1077, 1033, 876, 744; δ_H(300 MHz, CDCl$_3$) 7.33–7.49 (4H, m), 5.21 (1H, d, J 6.9), 4.36 (1H, dd, J 8.0, 6.9), 4.18 (1H, d, J 9.9), 3.78 (1H, dd, J 9.9, 8.0), 3.70 (3H, s), 2.95 (1H, br s, OH), 1.50 (6H, s); δ_C(75.5 MHz, CDCl$_3$) 135.55 (C), 132.09 (C), 128.70 (CH), 128.51 (CH), 127.9 (CH), 124.85 (CH), 110.14 (C), 80.40 (CH), 78.59 (CH), 74.13 (CH), 73.42 (CH), 59.28 (CH$_3$), 27.88 (CH$_3$), 25.71 (CH$_3$).

(3aS,4S,5S,9bR)-5-Fluoro-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]dioxol-4-ol 8c

In a dry sealed tube containing **7** (1.1 g, 4.9 mmol) was added Bu$_4$PH$_2$F$_3$ (3.1 g, 9.9 mmol). The mixture was stirred for 48 hours at 100 °C and then, cooled to room temperature. The crude residue was purified by flash chromatography (ethyl acetate–hexane, 1 : 3) to afford **8c** (0.84 g, 71%) as a white solid. Mp 123–124 °C (from CH$_2$Cl$_2$–hexane) [Found: C, 65.68 ; H, 6.37%; M + H (FAB) 239.1073. C$_{13}$H$_{15}$FO$_3$ requires C, 65.54; H, 6.35%; M + H, 239.1083]; $[a]_D^{25}$ −21 (c 1.0, CHCl$_3$); v_{max}(KBr)/cm^{-1} 3439, 2997, 1375, 1251, 1217, 1070; δ_H(300 MHz, CDCl$_3$) 7.3–7.5 (4H, m), 5.35 (1H, dd, J 52.8, 9.1), 5.21 (1H, d, J 6.9), 4.34 (1H, dd, J 8.5, 6.9), 4.00 (1H, m), 3.33 (1H, d, J 2.2), 1.49 (3H, s), 1.48 (3H, s); δ_F(300 MHz, CDCl$_3$; CFCl$_3$) −196.0 (1F, dd, J 51.3, 14.5); δ_C(75.5 MHz, CDCl$_3$) 133.5 (C, d, J 19), 130.4 (C, d, J 5), 129.0 (CH), 128.9 (CH), 128.8 (CH), 125.0 (CH, d, J 10), 110.6 (C), 91.2 (CH, d, J 179), 77.3 (CH, d, J 11), 74.2 (CH), 73.0 (CH, d, J 17), 27.9 (CH$_3$), 25.7 (CH$_3$).

(3aS,4R,5S,9bR)-5-Azido-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]dioxol-4-ol 8d

Epoxide **7** (2.30 g, 10.5 mmol) was dissolved in a mixture of DME and water (50 mL, 3 : 2) and NaN$_3$ was added (2.00 g, 30.8 mmol). The mixture was refluxed for 6 hours. Most of the DME was evaporated and the aqueous phase was extracted three times with EtOAc. The organic portions were washed with brine, dried over MgSO$_4$ and concentrated under vacuum to give **8d** (2.25 g, 82%) as a white solid. Mp 115–116 °C (from CH$_2$Cl$_2$–hexane) [Found: C, 59.62; H, 5.77; N, 15.91%; M + H (FAB) 262.1193. C$_{13}$H$_{15}$N$_3$O$_3$ requires C, 59.76; H, 5.78; N, 16.08%; M + H, 262.1192]; $[a]_D^{26}$ −46.8 (c 1.0, CH$_2$Cl$_2$); v_{max}(KBr)/cm^{-1} 3456 (broad), 2907, 2104, 1491, 1459, 1259, 1215, 1157, 1064; δ_H(300 MHz, CDCl$_3$) 7.34–7.56 (4H, m), 5.23 (1H, d, J 8.4), 4.42 (1H, d, J 9.9), 4.34 (1H, dd, J 8.4, 6.6), 3.86 (1H, t, J 9.2), 3.17 (1H, br s, OH), 1.51 (6H, s); δ_C(75.5 MHz, CDCl$_3$) 133.27 (C) 131.34 (C), 129.54 (CH), 129.07 (CH), 128.55 (CH), 126.58 (CH), 110.34 (C), 78.50 (CH), 74.34 (CH), 74.11 (CH), 63.48 (CH), 28.04 (CH$_3$), 25.81 (CH$_3$).

Coupling procedure for 14a and 15

To a solution of epoxide **7** (300 mg, 1.4 mmol) in dry CH$_2$Cl$_2$ (10 ml), was added a solution of diol **8a** (811 mg, 3.4 mmol) in dry CH$_2$Cl$_2$ under an argon atmosphere. The solution was cooled to −20 °C. At this temperature, a solution of boron trifluoride–diethyl ether (20 µL, 0.16 mmol) was added to the mixture. After 30 minutes, a saturated solution of NaHCO$_3$ was added. The two phases were separated and the aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic extracts were washed with brine and dried over MgSO$_4$. Removal of the solvent and chromatography (hexane–ethyl acetate, 1 : 1) of the residue afforded **14a** (170 mg, 38%) and **15** (50 mg, 12%) as white solids.

(3aS,4S,5S,9bR)-4-{[(3aS,4S,5R,9bR)-4-Hydroxy-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]dioxol-5-yl]-oxy}-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]-dioxol-5-ol 14a.

Mp 233–234 °C (decomp.) [Found: C, 68.49 ; H, 6.69%; M − H (FAB), 453. C$_{26}$H$_{30}$O$_7$ requires C, 68.70; H, 6.65%; M − H, 453]; $[a]_D^{20}$ +96.3 (c 1.0, CHCl$_3$); v_{max}(KBr)/cm^{-1} 3449, 1461, 1379, 1267, 1215, 1149, 1056, 1015; δ_H(300 MHz, CDCl$_3$) 7.7–7.3 (8H, m), 5.34 (1H, d, J 7.4), 5.24 (1H, d, J 7.2), 4.81 (1H, dd, J 5.8, 9.1), 4.70 (1H, d, J 9.1), 4.62 (1H, t, J 7.4), 4.38 (1H, t, J 7.2), 4.27 (1H, d, J 1.9), 3.97 (1H, t, J 8.8), 3.87 (1H, m), 2.74 (1H, d, J 6.8), 1.54 (3H, s), 1.52 (3H, s), 1.50 (3H, s), 1.49 (3H, s); δ_C(75 MHz, CDCl$_3$) 136.5 (C), 135.9 (C), 132.5 (C), 131.1 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.78 (CH), 125.2 (CH), 125.1(CH), 110.4 (C), 110.0 (C), 84.0 (CH), 81.0 (CH), 78.2 (CH), 77.5 (CH), 75.2 (CH), 74.4 (CH), 74.0 (CH), 71.5 (CH), 27.4 (CH$_3$), 25.9 (CH$_3$), 25.3 (CH$_3$).

(3aS,4S,5S,9bR)-5-{[(3aS,4S,5R,9bR)-4-Hydroxy-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]dioxol-5-yl]-oxy}-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]-dioxol-4-ol 15.

Mp 224–225 °C (decomp.) [Found: C, 68.41; H, 6.88%; M + H (FAB) 455.2067. C$_{26}$H$_{30}$O$_7$ requires C, 68.70; H, 6.65%; M + H, 455.2069]; $[a]_D^{25}$ +76 (c 0.5, CHCl$_3$); v_{max}(KBr)/cm^{-1} 3500, 3100, 1458, 1372, 1216, 1157, 1104; δ_H(300 MHz, CDCl$_3$) 7.7–7.3 (8H, m), 5.26 (2H, d, J 6.9), 4.85 (2H, d, J 8.5), 4.32 (2H, m), 4.1–4.0 (2H, m), 2.66 (2H, d, J 3), 1.50 (6H, s), 1.48 (6H, s); δ_C(75.5 MHz, CDCl$_3$) 136.1 (C), 131.7 (C), 129.4 (CH), 128.7 (CH), 128.4 (CH), 126.9 (CH), 109.9 (C), 78.6 (CH), 74.5 (CH), 74.3 (CH), 27.5 (CH$_3$), 25.4 (CH$_3$).

(3aS,4S,5R,9bR)-5-{[(3aS,4S,5S,9bR)-5-Methoxy-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]dioxol-4-yl]-oxy}-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]-dioxol-4-ol 14b

Boron trifluoride–diethyl ether (20 µL, 0.16 mmol) was added

to a stirred solution of the epoxide **7** (3.80 g, 17.4 mmol) and dry methanol (300 µL, 7.4 mmol) in dry dichloromethane (60 mL) at −20 °C. After 20 minutes at −20 °C, the reaction mixture was warmed to room temperature. After 2 hours at room temperature, the solution was poured into a saturated aqueous solution of sodium bicarbonate. The organic and aqueous layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic extracts were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. Flash chromatography (4:1 hexane–ethyl acetate) of the residue gave **14b** (2.00 g, 57%) as a white solid. Mp 175–177 °C (from CH$_2$Cl$_2$–hexane) [Found: C, 69.13; H, 6.84%; M − H (FAB) 467.2074. C$_{27}$H$_{32}$O$_7$ requires C, 69.21; H, 6.88%; M − H, 467.2070]; [a]$_D^{25}$ +133.5 (c 1.04, CHCl$_3$); ν_{max}(KBr)/cm^{-1} 3464, 2984, 2936, 1456, 1260, 1214, 1164, 1110, 1079, 872, 746; δ_H(300 MHz, CDCl$_3$) 7.81 (1H, m), 7.31–7.50 (7H, m), 5.34 (1H, d, J 7.7), 5.23 (1H, d, J 7.4), 4.69 (1H, br s, OH), 4.66 (2H, m), 4.41 (1H, d, J 9.3), 4.36 (1H, d, J 7.4), 4.11 (1H, dd, J 9.9, 8.2), 3.77 (1H, t, J 9.1), 3.30 (3H, s), 1.54 (3H, s), 1.52 (3H, s), 1.49 (3H, s), 1.48 (3H, s); δ_C(75.5 MHz, CDCl$_3$) 136.1 (C), 135.6 (C), 132.7 (C), 132.2 (C), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 124.9 (CH), 124.4 (CH), 110.5 (C), 110.0 (C), 82.5 (CH), 81.7 (CH), 80.9 (CH), 78.3 (CH), 78.1 (CH), 76.0 (CH), 74.1 (CH), 73.9 (CH), 60.2 (CH$_3$), 27.7 (CH$_3$), 27.1 (CH$_3$), 25.5 (CH$_3$), 25.1 (CH$_3$).

General procedure of the deprotection of 8a–d, 14a–b and 15

The acetonide (0.5–1.0 mmol) was dissolved in a mixture of THF, water and trifluoroacetic acid (4:1:1, 8 mL mmol^{-1}). The mixture was stirred at room temperature for 24 hours. The solvents were evaporated under reduced pressure. The residue was purified by flash chromatography to afford the polyol.

(1R,2R,3S,4S)-1,2,3,4-Tetrahydronaphthalene-1,2,3,4-tetraol 4a. Mp 186–188 °C (from MeOH) [Found: C, 56.98; H, 5.87%; M + H (FAB) 197.0806. C$_{10}$H$_{12}$O$_4$·H$_2$O requires C, 56.60; H, 5.69%; M + H, 197.0813]; [a]$_D^{27}$ −82.5 (c 1.0, pyridine); ν_{max}-(KBr)/cm^{-1} 3637–2966, 2996, 1649, 1455, 1408, 1192; δ_H(300 MHz, CD$_3$OD) 7.4–7.1 (4H, m), 4.60 (1H, d, J 3.7), 4.27 (1H, d, J 8.0), 3.76 (1H, dd, J 9.9, 8.0), 3.50 (1H, dd, J 9.9, 3.7); δ_C(75 MHz, CD$_3$OD) 139.1 (C), 136.6 (C), 130.7(CH), 129.5 (CH), 128.8 (CH), 128.2 (CH), 81.0 (CH), 74.8 (CH), 74.3 (CH), 72.0 (CH).

(1R,2R,3R,4S)-4-Methoxy-1,2,3,4-tetrahydronaphthalene-1,2,3-triol 4b. Mp 95–96 °C (from ethyl acetate) (Found: M + H (FAB), 211.0983. C$_{11}$H$_{14}$O$_4$ requires M + H, 211.0970); [a]$_D^{27}$ −74.8 (c 1.1, MeOH); ν_{max}(KBr)/cm^{-1} 3318, 1670, 1458, 1344, 1195, 936; δ_H(300 MHz, CD$_3$OD) 7.4–7.2 (4H, m), 4.65 (1H, d, J 3.6), 4.25 (1H, d, J 8.1), 4.06 (1H, dd, J 9.6, 8.1), 3.55 (1H, dd, J 9.6, 3.6), 3.47 (3H, s); δ_C(75.5 MHz, CD$_3$OD) 137.5 (C), 136.8 (C), 130.8 (CH), 129.6 (CH), 129.1 (CH), 128.4 (CH), 83.7 (CH), 73.5 (CH), 72.1 (CH), 71.7 (CH), 57.3 (CH$_3$).

(1R,2R,3R,4S)-4-Fluoro-1,2,3,4-tetrahydronaphthalene-1,2,3-triol 4c. Mp 148–150 °C (from ethyl acetate) (Found: M − H$_2$O (EI) 181.0617. C$_{10}$H$_{11}$FO$_3$ requires M − H$_2$O, 181.0665); [a]$_D^{27}$ −82.2 (c 1.2, MeOH); ν_{max}(KBr)/cm^{-1} 3354 (broad), 1637, 1458, 1406, 1185, 1090; δ_H(300 MHz, CD$_3$OD) 7.42 (4H, m), 5.32 (1H, dd, J 52.7, 7.6), 4.76 (1H, d, J 3.4), 4.18 (1H, m), 3.65 (1H, dd, J 10.3, 2.9); δ_C(75.5 MHz, CD$_3$OD) 136.9 (C), 135.0 (C), 130.9 (CH), 130.0 (CH), 129.9 (d, J 15, CH), 128.2 (d, J 6.8, CH).

(1R,2R,3S,4S)-4-Azido-1,2,3,4-tetrahydronaphthalene-1,2,3-triol 4d. Mp 136–137 °C (from ethyl acetate) (Found: M + H (CI) 222.0851. C$_{10}$H$_{11}$N$_3$O$_3$ requires M + H, 222.0879); [a]$_D^{27}$ −81.8 (c 1.2, MeOH); ν_{max}(KBr)/cm^{-1} 3308, 2093, 1257, 1095, 1026, 918; δ_H(300 MHz, CD$_3$OD) 7.4–7.2 (4H, m), 4.68 (1H, d,

J 3.6), 4.31 (1H, d, J 8.5), 4.03 (1H, dd, J 9.9, 8.5), 3.62 (1H, dd, J 9.9, 3.6); δ_C(75.5 MHz, CD$_3$OD) 137.4 (C), 134.7 (C), 131.2 (CH), 129.7 (CH), 129.3 (CH), 128.8 (CH), 73.3 (CH), 73.1 (CH), 71.8 (CH), 67.5 (CH).

(1R,2R,3R,4S)-4-{[(1S,2R,3R,4R)-3,4-Dihydroxy-1-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl]oxy}-1,2,3,4-tetrahydro-naphthalene-1,2,3-triol 11. Mp 197 °C (decomp.) [Found: C, 59.71; H, 6.63%; M + H (FAB) 389.1589. C$_{21}$H$_{24}$O$_7$·2H$_2$O requires C, 59.43; H, 6.65%; M + H, 389.1600]; [a]$_D^{26}$ −72.1 (c 1.1, pyridine); ν_{max}(KBr)/cm^{-1} 3386, 1676, 1190, 1085, 768, 741; δ_H(300 MHz, DMSO) 7.97 (1H, m), 7.43 (1H, m), 7.4–7.2 (6H, m), 4.7 (5H, m), 4.13 (1H, dd, J 9.9, 8.0), 3.76 (1H, dd, J 9.3, 3.3), 3.68 (1H, dd, J 4.6, 3.8) 3.30 (3H, s); δ_C(75.5 MHz, DMSO) 137.78 (C), 136.93 (C), 136.37 (C), 135.09 (C), 129.16 (CH), 128.26 (CH), 127.96 (CH), 127.61 (CH), 127.26 (CH), 127.06 (CH), 126.79 (CH), 82.02 (CH), 81.64 (CH), 79.15 (CH), 72.87 (CH), 71.76 (CH), 70.32 (CH), 69.26 (CH), 54.72 (CH$_3$).

(1R,2R,3S,4S)-3-{[(1S,2R,3R,4R)-2,3,4-Trihydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]oxy}-1,2,3,4-tetrahydronaphthalene-1,2,4-triol 12. Mp 219–220 °C (decomp.) [Found: C, 64.10; H, 5.99%; M + H (FAB) 375.1420. C$_{20}$H$_{22}$O$_7$ requires C, 64.16; H, 5.92%; M + H, 375.1443]; [a]$_D^{27}$ −39.8 (c 1.0, pyridine); ν_{max}(KBr)/cm^{-1} 3600–3000, 2901, 1649, 1490, 1190; δ_H(300 MHz, DMSO) 8.01 (1H, m), 7.54 (1H, d, J 7.4), 7.4–7.2 (6H, m), 5.4–5.0 (6H, br s, OH), 4.7–4.5 (4H, m), 4.22 (1H, t, J 9), 4.00 (1H, t, J 7.4), 3.72 (1H, dd, J 9.5, 3.4), 3.66 (1H, d, J 7.7, 3.8); δ_C(75.5 MHz, DMSO) 139.9 (C), 137.7 (C), 136.5 (C), 136.2 (C), 130.7 (CH), 130.4 (CH), 129.7 (CH), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 85.0 (CH), 84.5 (CH), 75.3 (CH), 74.3 (CH), 73.1 (CH), 72.8 (CH), 72.6 (CH), 71.7 (CH).

(1R,2R,3R,4S)-4-{[(1R,2R,3R,4R)-2,3,4-Trihydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]oxy}-1,2,3,4-tetrahydronaphthalene-1,2,3-triol 13. Mp 218–220 °C (decomp.) [Found: C, 63.90; H, 6.03%; M + H (FAB) 375.1442. C$_{20}$H$_{22}$O$_7$ requires C, 64.16; H, 5.92%; M + H, 375.1443]; [a]$_D^{27}$ −31.2 (c 1.0, pyridine); ν_{max}(KBr)/cm^{-1} 3613–3002, 2996, 1678, 1496, 1378, 1296, 1190, 1090; δ_H(300 MHz, CD$_3$OD) 7.92 (2H, d, J 6.9), 7.2–7.4 (6H, m), 5.25 (2H, d, J 7.8), 4.76 (2H, d, J 3.9), 4.37 (2H, dd, J 9.9, 7.8), 3.67 (2H, dd, J 9.9, 3.9); δ_C(75.5 MHz, DMSO) 137.04 (C), 135.06 (C), 128.8 (CH), 128.1 (CH), 127.2 (CH), 127.0 (CH), 81.0 (CH), 73.8 (CH), 71.9 (CH), 69.9 (CH).

3,3-Dimethyl-1-(4-methylphenylsulfonyl)[1,3]dioxolo-[4′,5′,3,4]naphtho[1,2-b]azirene 19

Acetonide **18** (2.0 g, 9.9 mmol) was dissolved in dry acetonitrile. A catalytic amount of cupric acetylacetonate (10%) was added, followed by PhI=NTs (17.8 g, 49.5 mmol). The mixture was stirred at room temperature overnight. An additional equivalent of PhI=NTs was added to the reaction mixture. The suspension was stirred for 24 h. The solution was filtered through Celite. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane–ethyl acetate 9:1) to afford aziridine **19** (1.1 g, 30%). Mp 131–132 °C [Found: M + H (FAB) 372.1270. C$_{20}$H$_{21}$NO$_4$S requires M + H, 372.1269]; [a]$_D^{25}$ 136.4 (c 0.5, CH$_2$Cl$_2$); ν_{max}(KBr)/cm^{-1} 3422, 1684, 1653, 1637, 1559, 1492, 1410, 1368, 1325, 1299, 1233, 1164, 1067, 1018; δ_H(300 MHz, CDCl$_3$) 7.53 (8H, m), 4.91 (1H, d, J 5.7), 4.65 (1H, dd, J 2.1, 1.8), 3.92 (1H, d, J 6.3), 3.64 (1H, dd, J 2.1, 1.8), 2.44 (3H, s), 1.41 (3H, s), 1.31 (3H, s); δ_C(75.5 MHz, CDCl$_3$) 144.81 (C), 134.73 (C), 134.63 (C), 129.84 (C), 129.28 (CH), 129.10 (CH), 128.79 (CH), 128.36 (CH), 127.96 (CH), 127.84 (CH), 111.02 (C), 72.02 (CH), 70.53 (CH), 41.39 (CH), 38.20 (CH), 27.71 (CH$_3$), 26.45 (CH$_3$), 21.64 (CH$_3$); m/z 372 ((M + H)$^+$, 75%), 314 (100), 286 (7), 216 (10),159 (34).

(3a*R*,9b*R*)-4-(4-Methylphenylsulfonylamino)-2,2-dimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-*d*][1,3]dioxolo-5-ol 20

Aziridine **19** (400 mg, 1.08 mmol) was dissolved in DMSO (10 mL). A aqueous solution of KOH 10% (10 mL) was added dropwise. The mixture was stirred at 75 °C for 24 hours. The solution was cooled and poured in brine, extracted with ethyl acetate, dried over MgSO$_4$, and concentrated. The product was recrystallized to afford alcohol **20** (294 mg, 70%). Mp 183–184 °C [Found: M + H (FAB) 390.1345. C$_{20}$H$_{23}$NO$_5$S requires M + H, 390.1375]; $[a]_D^{25}$ −99.2 (*c* 0.4, CH$_2$Cl$_2$); v_{max}(KBr)/cm^{-1} 3374, 3160, 2989, 2904, 1599, 1471, 1408, 1373, 1315, 1225, 1148, 1097; δ_H(300 MHz, CDCl$_3$) 7.55 (8H, m), 5.33 (1H, d, *J* 6.9), 5.17 (1H, d, *J* 6.3), 4.49 (1H, d, *J* 8.1), 4.29 (1H, t, *J* 7.8), 3.81 (1H, s), 3.45 (1H, dd, *J* 7.5, 8.1), 2.41 (3H, s), 1.35 (3H, s), 0.97 (3H, s); δ_C(75.5 MHz, CDCl$_3$) 143.85 (C), 136.87 (C), 136.40 (C), 130.39 (C), 129.66 (CH), 129.26 (CH), 129.17 (CH), 128.46 (CH), 127.67 (CH), 127.22 (CH), 110.08 (C), 75.45 (CH), 74.14 (CH), 70.40 (CH), 58.48 (CH), 26.98 (CH$_3$), 25.46 (CH$_3$), 21.49 (CH$_3$); *m/z* 390 ((M + H)$^+$, 6%), 332 (25), 314 (100), 155 (47), 91 (38).

5-Azido-4-(2,2-dimethyl-4-acetoxy-3a,4,5,9a-tetrahydronaphtho[1,2-*d*][1,3]dioxol-5-yloxy)-2,2-dimethyl-3a,4,5,9a-tetrahydronaphtho[1,2-*d*][1,3]dioxole 14e

The alcohol **8d** (1.56 g, 5.96 mmol) and the epoxide **7** (1.41 g, 6.46 mmol) were dissolved in dry dichloromethane (60 mL) under an argon atmosphere. The solution was cooled to 0 °C and BF$_3$·OEt$_2$ (50 µL, 0.4 mmol) was added. The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The mixture was diluted with ethyl acetate and the solution was washed with a saturated solution of sodium bicarbonate, brine, dried over MgSO$_4$ and concentrated under reduced pressure. The residue was dissolved in pyridine (25 mL) and acetic anhydride (5 mL) was added, followed by DMAP (cat. amount). The solution was stirred at room temperature overnight. The mixture was diluted with ethyl acetate and the solution was washed several time with 1 M HCl, a saturated solution of sodium bicarbonate and brine, dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (ether–hexane 3:7) to yield **14e** (0.83 g, 27%). Mp 175–176 °C [Found: M + H (FAB) 522.2272. C$_{28}$H$_{31}$N$_3$O$_7$ requires M + H, 522.2240]; $[a]_D^{25}$ +58.9 (*c* 0.86, CHCl$_3$); v_{max}(KBr)/cm^{-1} 2993, 2100, 1742, 1375, 1221, 1072, 1039; δ_H(300 MHz, CDCl$_3$) 7.13–7.58 (8H, m), 5.36 (1H, m), 5.25 (2H, m), 4.76 (1H, d, *J* 8.8), 4.63 (1H, d, *J* 5.8), 4.58 (1H, dd, *J* 6.9, 3.6), 4.42 (1H, m), 4.20 (1H, dd, *J* 5.5, 3.6), 2.21 (3H, s), 1.47 (3H, s), 1.46 (3H, s), 1.45 (3H, s), 1.43 (3H, s); δ_C(CDCl$_3$, 75.5 MHz) 170.04 (C), 135.27 (C), 133.94 (C), 131.25 (C), 130.98 (CH), 129.49 (CH), 129.28 (CH), 128.84 (CH), 128.43 (CH), 125.71 (CH), 110.45 (C), 80.71 (CH), 77.43 (CH), 77.09 (CH), 76.30 (CH), 74.51 (CH), 74.28 (CH), 73.57 (CH), 60.87 (CH), 27.42 (CH$_3$), 26.89 (CH$_3$), 26.01 (CH$_3$), 24.92 (CH$_3$), 21.28 (CH$_3$).

4-(3,4-Dihydroxy-1-amino-1,2,3,4-tetrahydronaphthalen-2-yloxy)-1,2,3,4-tetrahydronaphthalene-1,2,3-triol 24

A solution of azide **14e** (0.99 g, 1.9 mmol) in dry ether (10 mL) was added slowly to a suspension of LiAlH$_4$ (0.29 g, 7.6 mmol) in ether (20 mL) at 0 °C. The mixture was then stirred under argon at room temperature for 2 hours. After destruction of the excess of LiAlH$_4$ with water, the white precipitate was removed by filtration. The organic phase was washed with brine and dried over K$_2$CO$_3$. Evaporation of the solvent was done in a cold bath to avoid decomposition of the amine. The yellow residue (**14f**) was immediately hydrolyzed in ethanol (25 mL) and HCl (1 mL) overnight. The solvent were removed under reduced pressure and the residue was recrystallized to give **24** as a white solid [Found: M + H (FAB) 374.1582. C$_{20}$H$_{23}$NO$_6$ requires M + H, 374.1603].

Inhibition analysis

β-Mannosidase (EC 3.2.1.25) from snail acetone powder, α-galactosidase (EC 3.2.1.22) from green coffee beans, and β-galactosidase (EC 3.2.1.23) from *Escherichia coli* were purchased from Sigma. The tests were done according to the Sigma quality control test procedure and using K_m as sugar concentrations (respectively *p*-nitrophenyl β-D-mannopyranoside 1.5 mM, *p*-nitrophenyl α-D-galactopyranoside 0.4 mM and *o*-nitrophenyl β-D-galactopyranoside 1.0 mM). Assays were respectively done in a 45 mM citrate buffer, in a 82 mM potassium phosphate buffer and in a 93 mM potassium phosphate buffer at 27 °C.

References

1 M. Balci, Y. Sütbeyaz and H. Seçen, *Tetrahedron*, 1990, **46**, 3715.
2 K. Kübler, *Arch. Pharm.*, 1908, **246**, 620.
3 G. Dangschat and H. Fischer, *Naturwissenschaften*, 1939, **27**, 756.
4 V. Plouvier, *C. R. Seances Acad. Sci.*, 1962, **255**, 360.
5 H. Kindl and O. Hoffmann-Ostenhof, *Fortschr. Chem. Org. Naturst.*, 1966, **24**, 149.
6 M. Nakajima, I. Tomida and S. Takei, *Chem. Ber.*, 1957, **90**, 246.
7 (*a*) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, 1953, **75**, 4020; (*b*) T. L. Nagabhushan, *Can. J. Chem.*, 1970, **48**, 383; (*c*) H. Paulsen, W. Röben and F. R. Heiker, *Chem. Ber.*, 1981, **114**, 3242; (*d*) R. A. Aleksejczyk and G. A. Berchtold, *J. Am. Chem. Soc.*, 1985, **107**, 2554; (*e*) C. Le Drian, E. Vieira and P. Vogel, *Helv. Chim. Acta*, 1989, **72**, 338; (*f*) H. Seçen, A. Maras, Y. Sütbeyaz and M. Balci, *Synth. Commun.*, 1992, **22**, 2613; (*g*) T. Akiyama, H. Shima, M. Ohnari, T. Okazaki and S. Osaki, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 3760.
8 (*a*) G. E. McCasland and J. M. Reeves, *J. Am. Chem. Soc.*, 1955, **77**, 1812; (*b*) C. R. Johnson, P. A. Plé and J. P. Adams, *J. Chem. Soc., Chem. Commun.*, 1991, 1006; (*c*) H. Seçen, A. Maras, Y. Sütbeyaz and M. Balci, *Synth. Commun.*, 1992, **22**, 2613; (*d*) S. Takano, M. Moriya, Y. Higashi and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1993, 177.
9 (*a*) S. Angyal and P. Gilham, *J. Chem. Soc.*, 1955, 375; (*b*) R. Criegee and P. Becher, *Chem. Ber.*, 1957, **90**, 2516.
10 (*a*) R. Angelaud and Y. Landais, *J. Org. Chem.*, 1996, **61**, 5202; (*b*) S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 1958, 375; (*c*) M. Nakajima, I. Tomida and S. Takei, *Chem. Ber.*, 1957, **90**, 246.
11 (*a*) D. R. Boyd and G. N. Sheldrake, *Nat. Prod. Rep*, 1998, **15**, 309; (*b*) T. Hudlicky, *Chem. Rev.*, 1996, **96**, 3; (*c*) T. Hudlicky and A. J. Thorpe, *Chem. Commun.*, 1996, 1993; (*d*) T. Hudlicky, in *Green Chemistry: Designing Chemistry for the Environment*, ed. P. T. Anastas and T. C. Williamson, American Chemical Society, Washington, 1996, p. 180; (*e*) T. Hudlicky and J. W. Reed, in *Advances in Asymmetric Synthesis*, ed. A. Hassner, JAI Press, Greenwich, CT, 1995, Vol. 1, p. 271; (*f*) A. D. Grund, *SIM News* 1995, **45**, 59; (*g*) S. M. Brown and T. Hudlicky, in *Organic Synthesis: Theory and Application*, ed. T. Hudlicky, JAI Press, London, 1993, Vol. 2, p. 113; (*h*) H. A. J. Carless, *Tetrahedron: Asymmetry*, 1992, **3**, 795; (*i*) G. N. Sheldrake, in *Chirality in Industry*, ed. A. N Collins, G. N Sheldrake and J. Crosby, Wiley, Chichester, 1992, p. 127; (*j*) D. A. Widdowson, D. A. Ribbons and S. D. Thomas, *Janssen Chim. Acta*, 1990, **8**, 3.
12 (*a*) L. E. Brammer, Jr. and T. Hudlicky, *Tetrahedron: Asymmetry*, 1998, **9**, 2011; (*b*) M. Desjardins, L. E. Brammer, Jr. and T. Hudlicky, *Carbohydr. Res.*, 1997, **304**, 39; (*c*) M. Mandel and T. Hudlicky, *J. Org. Chem.*, 1993, **58**, 2331; (*d*) M. Mandel and T. Hudlicky, *J. Chem. Soc., Perkin Trans. 1*, 1993, 741; (*e*) H. A. J. Carless and K. Busia, *Carbohydr. Res.*, 1992, **234**, 207; (*f*) H. A. J. Carless and S. S. Malik, *Tetrahedron: Asymmetry*, 1992, **3**, 1135; (*g*) H. A. J. Carless and O. Z. Oak, *Tetrahedron Lett.*, 1991, **32**, 1671; (*h*) H. A. J. Carless and K. Busia, *Tetrahedron Lett.*, 1990, **31**, 3449; (*i*) H. A. J. Carless and K. Busia, *Tetrahedron Lett.*, 1990, **31**, 1617;

(*j*) H. A. J. Carless, J. R. Billinge and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 3113.

13 (*a*) C. Sanfilippo, A. Patti, M. Piattelli and G. Nicolosi, *Tetrahedron: Asymmetry*, 1997, **8**, 1569; (*b*) H. A. J. Carless, K. Busia, Y. Dove and S. S. Malik, *J. Chem. Soc.*, *Perkin Trans. 1*, 1993, 2505; (*c*) H. A. J. Carless, *Tetrahedron Lett.*, 1992, **33**, 6379; (*d*) H. A. J. Carless, *J. Chem. Soc.*, *Chem. Commun.*, 1992, 234; (*e*) H. A. J. Carless and O. Z. Oak, *J. Chem. Soc.*, *Chem. Commun.*, 1991, 61; (*f*) T. Hudlicky, H. Luna, H. F. Olivo, C. Andersen, T. Nugent and J. D. Price, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 2907; (*g*) T. Hudlicky, J. D. Price and H. F. Olivo, *Synlett*, 1991, 645; (*h*) T. Hudlicky, F. Rulin, T. Tsunoda, H. Luna, C. Andersen and J. D. Price, *Isr. J. Chem.*, 1991, **31**, 229; (*i*) S. V. Ley and A. J. Redgrave, *Synlett*, 1990, 393; (*j*) H. A. J. Carless and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 1719.

14 (*a*) K. R. Shanmugasundaram, C. Panneerselvan, P. Samudram and E. R. B. Shanmugasundaram, *J. Ethnopharmacol.*, 1983, **7**, 205. (*b*) K. R. Shanmugasundaram, C. Panneerselvan, P. Samudram and E. R. B. Shanmugasundaram, *Pharmacol. Res. Commun.*, 1981, **13**, 475. (*c*) C. Day, in *New Antidiabetic Drugs*, ed. C. J. Bailey and P. R. Flatt, Smith-Gordon, London, 1990, p. 267.

15 K. Miyatake, S. Takenaka, T. Fujimoto, G. Kensho, S. P. Upadhaya, M. Kirihata, I. Ichimoto and Y. Nakano, *Biosci. Biotechnol. Biochem.*, 1993, **57**, 2184.

16 (*a*) S. Atsumi, K. Umezawa, H. Iinuma, H. Naganawa, H. Nakamura, Y. Iitaka and *J. Antibiot.*, 1990, **43**, 49; (*b*) G. Legler, in *Methods in Enzymology*, ed. W. B. Jakoby and M. Wilchek, Academic Press, New York, 1977, vol. XLVI, p. 368–381; (*c*) G. Legler and E. Bause, *Carbohydr. Res.*, 1973, **28**, 45; (*d*) G. Legler, *Mol. Cell. Biochem.*, 1973, **2**, 31; (*e*) K. T. Cavanagh, R. A. Fisher, G. Legler, M. Herrchen, M. Z. Jones, E. Julich, R. P. Sewell-Alger, M. L. Sinnott and F. E. Wilkinson, *Enzyme*, 1985, **34**, 75; (*f*) G. Legler and W. Lotz, *Hoppe-Seyler's Z. Physiol. Chem.*, 1973, **354**, 243.

17 (*a*) M. Balci, *Pure Appl. Chem.*, 1997, **69**, 97; (*b*) T. Hudlicky and M. Cebulak, *Cyclitols and their Derivatives*, VCH, 1993.

18 D. C. Billington, F. Perron-Sierra, I. Picard, S. Beaubras, J. Duhault, J. Espinal and S. Challal, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2307.

19 Y. Kara, M. Balci, S. A. Bourne and W. H. Watson, *Tetrahedron Lett.*, 1994, **35**, 3349.

20 (*a*) M. Desjardins, M. C. Lallemand, T. Hudlicky and K. A. Abboud, *Synlett*, 1997, 728; (*b*) M. C. Lallemand, M. Desjardins, S. Freeman and T. Hudlicky, *Tetrahedron Lett.*, 1997, **38**, 7693.

21 (*a*) A. M. Jeffrey, H. J. Yeh, D. M. Jerina, T. R. Patel, J. F. Davey and D. T. Gibson, *Biochemistry*, 1975, **14**, 575; (*b*) F. A. Catterall, K. Murray and P. A. Williams, *Biochem. Biophys. Acta*, 1971, **237**, 361; (*c*) C. E. Cerniglia, D. T. Gibson and C. van Baalen, *J. Gen. Microbiol.*, 1980, **116**, 495; (*d*) C. E. Cerniglia, C. van Baalen and D. T. Gibson, *J. Gen. Microbiol.*, 1980, **116**, 485; (*e*) C. E. Cerniglia, D. T. Gibson and C. van Baalen, *Biochem. Biophys. Res. Commun.*, 1979, **88**, 50; (*f*) M. A. Heitkamp, J. P. Freeman and C. E. Cerniglia, *App. Environ. Microbiol.*, 1987, **53**, 129.

22 G. J. Zylstra and D. T. Gibson, *J. Biol. Chem.*, 1989, **264**, 14940.

23 F. Orsini and F. Pelizzoni, *Tetrahedron: Asymmetry*, 1996, **7**, 1033.

24 (*a*) T. Hudlicky, K. A. Abboud, J. Bolonick, R. Maurya, M. L. Stanton and A. J. Thorpe, *Chem. Commun.* 1996, 1717; (*b*) T. Hudlicky and A. J. Thorpe, *Synlett*, 1994, 899; (*c*) T. Hudlicky, K. A. Abboud, D. A. Entwistle, R. Fan, R. Maurya, A. J. Thorpe, J. Bolonick and B. Myers, *Synthesis*, 1996, 897.

25 Z. Li, R. W. Quan and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5889.

26 D. A. Evans, M. M. Faul and M. T. Bilodeau, *J. Org. Chem.*, 1991, **56**, 6744.

27 Improved yields for this reaction were obtained using a modified nitrene precursor, see: M. J. Sodergren, D. A. Alonso, A. V. Bedekar and P. G. Anderson, *Tetrahedron Lett.*, 1997, **38**, 6897.

28 C. M. G. Löfström, A. M. Ericsson, L. Bourrinet, S. K. Juntunen and J. E. Backvall, *J. Org. Chem.*, 1995, **60**, 3586.

29 (*a*) K. Sugahara and I. Yamashina, in *Methods in Enzymology*, ed. V. Ginsburg, Academic Press, New York, 1972, vol. XXVIII, Part B, pp. 769–772; (*b*) A. L. Tarentino and F. Maley, in *Methods in Enzymology*, ed. V. Ginsburg, Academic Press, New York, 1972, vol. XXVIII, Part B, pp. 772–776; (*c*) F. Petek, E. Villarroya and J. E. Courtois, *Eur. J. Biochem.*, 1969, **8**, 395; (*d*) G. R. Craven, E. Jr. Steers and C. B. Anfinsen, *J. Biol. Chem.*, 1965, **240**, 2468.