Regio- and stereospecific synthesis of a new benzoconduritol-C derivative

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A stereospecific synthesis of 3-(2-bromophenoxy)-1,2,3,4-tetrahydronaphthalen-1,2,4-triol (benzoconduritol-C derivative) has been achieved by a fully regio- and stereospecific rhodium catalysed reaction of oxabenzonorbornadiene in the presence of 2-bromophenol.

Keywords: naphthalen-1,2,4-triol, benzoconduritol C, conduritol C, cyclitol, Rh catalysis

Conduritol C (**1**) belongs to a class of cyclohex-5-ene-1,2,3,4-tetrols – an important class of cyclitols named conduritols. Some of the 10 possible isomers have proved to be glycosidase enzyme inhibitor.[1-4] All of the stereoisomers of conduritols have been prepared by multi-step chemical syntheses. A number of conduritol and its derivatives have shown antibiotic, antileukaemic and growth regulating activity due to their biological activities.[1-4] In view of their promising therapeutic potential in the management of disorders like diabetes, viral infections (including HIV) and cancer, many analogues and structural variants of conduritols have been synthesised, including nonnatural bicyclic **2** and tricyclic mimics **4** and their biological activities evaluated, in particular glycosidase inhibition which plays a fundamental role in the development of new drugs.[5-19] Billington and co-workers have reported the ability of conduritols A and B to modify insulin release from isolated pancreatic islets.[18-19] More recently, Baran and co-workers have investigated the interaction of the oxovanadium (IV) cation, VO^{2+}, with myoinositol and conduritol C and investigated the bioactivity of the generated complexes.[20] According to their study, the interaction of VO^{2+} with conduritols is of special interest from the pharmacological point of view. For this reason, attention has been directed towards the bicyclic derivatives of conduritol. Bicyclic-cyclitols has a central non-planar cyclobutane **2,** benzene **3**, and polyaromatic ring which is fused to a cyclohexane moiety.

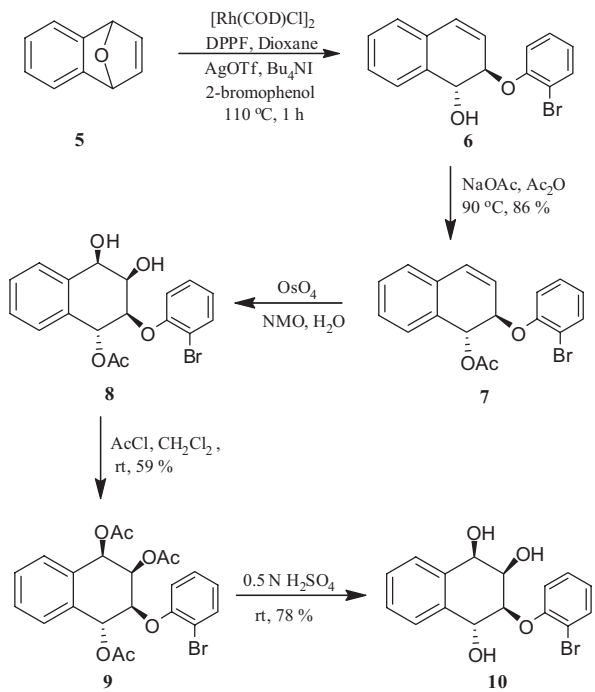
To date, there are just a few synthetic procedures for the preparation of bicyclic-conduritol C **3**.[21-23] Generally, there are two synthetic route for the synthesis of *trans*-1,2-dihydrodiol: (a) the naphthalene 1,2-oxide;[24-26] (b) oxabenzo-norbornadienes and their related derivatives which has an internal-ethers derivatives.[27-31] Both methods have generated useful intermediates for the synthesis of *trans*-1,2-dihydrodiol. The products formed by the ring-opening reaction are of particular interest since the hydronaphthalene skeleton is found in a wide range of compounds possessing diverse biological activities.[32-36] Recently, Lautens and co-workers designed the first synthesis of *trans*-l,2-dihydroxy-l,2,-dihydronaphthalene by the rhodium-catalysed ring opening reaction of oxabenzonorbornadienes.[27-31] *trans*-l,2-Dihydroxy-l,2-dihydronaphthalene has been synthesised with microbial oxidation of naphthalene or by the rhodium-catalysed ring opening reaction of oxabicyclic alkenes using various alcohol functionalised groups, respectively.

These results stimulated the study of bicyclic compounds of general formula **3**, where the double bond of conduritols is formally replaced by an aromatic ring.

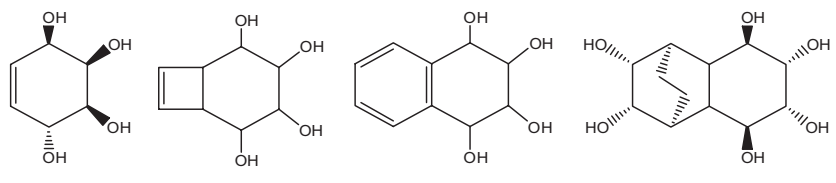
Results and discussion

Oxabenzonorbornadiene **5** was prepared using benzene-diazonium-2-carboxylate hydrochloride and furan.[37,38] This compound was used to synthesise 3-(2-bromo-phenoxy)-1,2,3,4-tetrahydronaphthalene-1,2,4-triol **10**. This synthesis was inspired from the key compound.

In this reaction, the etheric bond was cleaved stereospecifically to give benzoconduritol C configuration **10** (Scheme 1). Rhodium-catalysed ring opening has been successfully used to cleave internal-ethers fused benzene for seven years. Thus, 2-(2-bromophenoxy)-1,2-dihydro-naphthalen-1-ol **6** was obtained as the sole isomer (in 94%) according to the procedure.[27-31] **6** was subjected to



Scheme 1



1 **2** **3** **4**

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an acetylation reaction using acetyl chloride, but it did not give the expected acetylation product **7**. This problem was overcome with acetic anhydride/CH_3COONa system.

The mixture was purified by chromatography on a silica gel column with hexane/ethyl acetate (7:3) as eluant to give 1-acetoxy-2-(2-bromo-phenoxy)-1,2-dihydronaphthalene **7** in 86% yield. The structure of **7** was assigned from ^1H and ^{13}C NMR spectra. Dihydroxylation of the olefin in **7** gives access to **8**. Generally, *cis*-dihydroxlation is effected with *N*-methylmorpholine *N*-oxide (NMO) and catalytic quantities of osmium tetroxide in polar solvent. To investigate introducing two hydroxyl groups in a *cis* configuration to the double bond in 1-acetoxy-2-(2-bromophenoxy)-1,2-dihydronaphthalene **7,** the product **7** was treated with catalytic amounts of OsO_4 and *N*-methylmorpholine *N*-oxide. After the reaction was complete, for further structural proof, the crude product **8** was converted into the corresponding triacetate derivatives (benzoconduritol C, triacetate) **9** with acetyl chloride which was fully characterised. The stereochemical course of the hydroxylation may be *syn* or *anti* with respect to 2-bromophenoxy group. Thus, the observed regio- and stereoselectivity for this reaction was remarkable since 2-bromophenyl ring in the phenoxy group has been blocked approaching from *anti* position of the *N*-methylmorpholine *N*-oxide (NMO). Therefore, this position leads to a regioselectivity in this reaction. Deacetylation of **9** was achieved by employing in acid medium to give the desired benzoconduritol C derivative **10** as a white powder. It looks like the configuration of conduritol C which has *cis* stereochemistry of the two hydroxy and a 2-bromophenoxy besides a *trans* hydroxy group. The structure of benzoconduritol C derivative **10** have been elucidated on the basis of ^1H and ^{13}C NMR data and extensive double resonance experiments.

First while H-3 of **10** is a doublet of doublets ($J_{3,4}$ = 5.0 Hz, $J_{3,2}$ = 1.8 Hz), H-4 is a doublet ($J_{4,3}$ = 5.0 Hz). These observation clearly indicate that H-2 with H-3 have a *cis* configuration because of $J_{3,2}$ = 1.8 Hz whereas H-3 with H-4 have *a trans* configuration because of $J_{3,4}$ = 5.0 Hz. Irradiation of H-2 at δ = 4.48, H-1 is seen as a clear doublet ($J_{1\text{-OH}}$ = 11.0 Hz) from –OH on its own C and H-3 is seen as a doublet ($J_{3\text{-}4}$ = 5.0 Hz) and H-4 is no change, and –OH at C-2 is seen as a broad singlet. The positions of the groups in **10** were also confirmed by means of irradiation. Irradiation of –OH of C-2 at δ = 3.24, H-1, H-2 and H-3 have $J_{1,2}$ = 2.0 Hz and $J_{2,3}$ = 1.8 Hz. These results, indicate that H-1, H-2 and H-3 have a *cis* configurations with each other.

This report describes an effective and concise strategy for a new synthesis of benzoconduritol C derivative which has the same configuration as conduritol-C via a rhodium-catalysed ring opening reaction of oxabenzonorbornadienes.

Experimental

General

Melting points were determined on a Buchi 539 capillary melting apparatus and are uncorrected. IR spectra were obtained from KBr or film on a Mattson 1000 FT-IR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on 400 (100), 200 (50) MHz Varian spectrometer and are reported in δ units with $SiMe_4$ as internal standard. TLC was performed on E. Merck Silica Gel 60 F_{254} plate (0.2 mm). All column chromatography was performed on silica gel (60 mesh, Merck). Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyser.

2-(2-bromophenoxy)-1,2-dihydronaphthalen-1-ol (**6**):[27-31] To a flame-dried round-bottomed flask was added $[Rh(COD)Cl]_2$ (0.0032 g, 0.00065 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) (0.0072 g, 0.0129 mmol), which was dissolved in 1.5 ml dioxane and stirred at room temperature for 15 min. Silver triflate (AgOTf) (0.0066 g, 0.0258 mmol) was added to produce an orange heterogeneous solution. Bu_4NI (0.0143 g, 0.0387 mmol) was added followed by stirring for another 15 min to give a dark-red solution of the [Rh(COD)I] catalyst. To this catalyst solution was added oxabenzonorbornadiene **5** (0.100 g, 0.529 mmol) and 2-bromophenol (0.240 g, 1.38 mmol), which was heated to 110°C for 1 h. the mixture was poured into NaOH solution (1 M, 40 ml) and extracted with Et_2O (3×100 ml). The combined organic phase was washed with NaOH (1 M, 25 ml), brine (40 ml) and dried over Na_2SO_4. After most solvent was removed under vacuum this gave a mixture of products (crude products 0.140 g). The brown residue was purified by chromatography (9 : 1 hexane: EtOAc). (total yield; 97 mg) Rf = 0.44 on silica (206 mg, 94%). M.p. 120°C (Lit:[27-31] 120–122°C) White crystals (from hexane/Et_2O). ^1H NMR (200 MHz $CDCl_3$ ppm): δ 7.63 (m, 2H, aromatic), 7.27 (m, 3H, aromatic), 7.13 (m, 1H, aromatic), 6.88 (m, 2H, aromatic), 6.53 (dd, A part of AB-system, 1H, *J* = 9.9 and 2.1 Hz, –CH=CH), 6.06 (dd, B part of AB-system, 1H, *J* = 9.9 and 2.1 Hz, –CH=CH), 5.33 (dd, A part of AB-system, 1H, *J* = 10.8 and 2.2 Hz, –CHO or –CHOPhBr), 5.11 (dt, B part of AB-system, 1H, *J* = 10.8 and 2.1 Hz, –CHO or –CHOPhBr), 2.92 (br s, 1H, –OH); ^{13}C NMR (50 MHz $CDCl_3$ ppm): δ 156.4, 137.5, 135.7, 133.9, 131.2, 130.6, 130.3, 130.0, 128.4, 128.0, 127.1, 125.0, 117.8, 115.6, 84.2, 74.6.

1-acetoxy-2-(2-bromophenoxy)-1,2-dihydronaphthalene **(7)**: 110 mg (0.31 mmol) 2-(2-bromophenoxy)-1,2-dihydronaphthalen-1-ol **6** was dissolved in 2 ml of acetic anhydride and to this magnetically stirred solution was added excess of dry CH_3COONa. The reaction mixture was stirred at 90°C for 24 h. The mixture was cooled to 0°C and was poured to ice-water mixture (40 ml of 1 M HCl). The aqueous solution was extracted with ether (3×75 ml). The combined organic extracts were washed with Na_2CO_3 solution (20 ml) and water (50 ml) then dried (Na_2SO_4). After removal of the solvent under reduced pressure (40°C, 20 mmHg), and chromatography of the residue on a silica gel column (10 g) eluting with hexane/CH_2Cl_2 (9:1) gave 1-acetoxy-2-(2-bromophenoxy)-1,2-dihydronaphthalene **7** as liquid (107 mg, 86%); Found: C, 60.82; H, 4.38. $C_{18}H_{15}BrO_3$ requires: C, 60.18; H, 4.21%; υ_{max} (KBr) 3070, 2924, 2864, 2257, 1748, 1584, 1478, 1445, 1377, 1279, 1233, 1127, 1040, 1007, 922, 914, 830, 783, 729 cm^{-1}. ^1H NMR (200 MHz $CDCl_3$ ppm): δ 7.57 (dd, 1H, *J* = 7.9, 1.6 Hz, aromatic), 7.30 (m, 4H, aromatic), 7.20 (td, 1H, *J* = 7.0, 1.6 Hz, aromatic), 7.02 (dd, 1H, *J* = 8.3, 1.4 Hz, aromatic), 6.89 (td, 1H, *J* = 7.7, 1.4 Hz, aromatic), 6.63 (dd, A part of AB-system, 1H, *J* = 9.9, 1.6 Hz, –CH=CH), 6.54 (d, 1H, *J* = 8.4 Hz, –CHO), 6.13 (dd, B part of AB-system, 1H, *J* = 9.9, 3.0 Hz, –CH=CH), 5.19 (ddd, 1H, *J* = 10.4, 3.0, 1.6 Hz, –CHOPhBr), 2.14 (s, 3H, $–OCOCH_3$); ^{13}C NMR (50 MHz $CDCl_3$ ppm): δ 172.4, 156.5, 135.8, 134.3, 134.0, 132.0, 130.9, 130.6, 130.3, 129.1, 128.7, 127.2, 125.1, 118.3, 115.8, 79.2, 74.8, 23.1.

1,2,4-triacetoxy-3-(2-bromophenoxy)-1,2,3,4-tetrahydronaphthalene **(9)**: A 100 ml two-necked, round-bottomed flask, equipped with a magnetic stirrer and a nitrogen inlet, was charged with 43 mg (0.37 mmol) of NMO, 1 ml of water, and 2 ml of acetone. To this solution were added *ca* 10 mg of OsO4 (0.08 mmol) and 132 mg (0.37 mmol) of acetate **7**. The resulting mixture was stirred vigorously under nitrogen at 0°C. During the overnight stirring, the reaction mixture became homogeneous. After stirring for 18 h, sodium bisulfite (50 mg) and 1 g of Florisil slurried in 1 ml of water were added, the slurry was stirred for 1 h, and the mixture was filtered through a short pad 2 g of Celite in a 30 ml sintered glass funnel. The Celite cake was washed with acetone (3 × 10 ml). The filtrates were combined and solvent was removed to give the crude diol-acetate **8** (127 mg). The crude diol-acetate **8** (127 mg) was dissolved in 10 ml of acetyl chloride and the resulting solution was stirred at room temperature during overnight. The excess unreacted acetyl chloride was evaporated (60°C, 20 mmHg). The residue was dissolved in CH_2Cl_2 and filtered over silica gel. Evaporation of solvent gave 1,2,4-triacetoxy-3-(2-bromophenoxy)-1,2,3,4-tetrahydronaphthalene **9** (91 mg, 59%). M.p. 187–188°C (recrystallised from CH_2Cl_2/Et_2O); Found: C, 55.12; H, 4.51 $C_{22}H_{21}BrO_7$ requires: C, 55.36; H, 4.43%; υ_{max} (KBr) 3065, 2925, 2853, 1751, 1583, 1476, 1372, 1224, 1046, 1033, 754 cm^{-1}; NMR (400 MHz $CDCl_3$ ppm): δ 7.53 (m, 2H, aromatic), 7.41 (m, 2H, aromatic), 7.24 (m, 2H, aromatic), 6.93 (m, 2H, aromatic), 5.71 (dd, 1H, *J* = 6.6, 2.1 Hz, H-2, –CHO), 5.50 (d, 1H, *J* = 6.6 Hz, H-1, –CHO), 5.10 (dd, 1H, *J* = 5.8, 2.2 Hz, H-2, –CHO), 4.78 (dd, 1H, *J* = 8.2, 1.9 Hz, H-3, –CHOPhBr), 2.16 (s, 3H, –OAc), 2.12 (s, 3H, –OAc), 2.11 (s, 3H, –OAc); ^{13}C NMR (100 MHz $CDCl_3$ ppm): δ 172.4 (×2), 172.3, 156.1, 135.9, 135.7, 133.7, 131.8, 130.9, 130.7, 130.6, 130.4 (×2), 125.4, 117.9, 82.2, 79.3, 78.5, 77.5, 22.9, 22.7 (×2).

3-(2-bromophenoxy)-1,2,3,4-tetrahydronaphthalene-1,2,4-triol: *benzoconduritol C derivative* **(10)**: 91 mg (1.9 mmol) of triacetate **9** was dissolved in 5 ml of 0.5 N H_2SO_4. The resulting mixture was stirred at room temperature for 8 h. The acid was neutralised with

$BaCO_3$. The solid material was filtered and the filtrate was concentrated under reduced pressure to yield 3-(2-bromophenoxy)-1,2,3,4-tetrahydronaphthalene-1,2,4-triol **10**. The mixture was separated with TLC (ethyl acetate/hexane 1:4) (52 mg, 78%). M.p. 162–164°C (recrystallised from CH_3CH_2OH); Found: C, 54.83; H, 4.35 $C_{16}H_{15}BrO_4$ requires: C, 54.72; H, 4.31%; υ_{max} (KBr) 2955, 2923, 1729, 1474, 1280, 1243, 1047, 747 cm^{-1}; NMR (400 MHz $CDCl_3$ ppm): δ 7.62 (d, 1H, *J* = 7.3 Hz, aromatic), 7.52 (dd, 1H, *J* = 8.0, 1.5 Hz, aromatic), 7.36 (m, 4H, aromatic), 7.18 (br d, 1H, *J* = 8.8 Hz, aromatic), 6.92 (t, 1H, *J* = 7.7 Hz, aromatic), 5.14 (d, 1H, *J* = 5.0 Hz, H-4,–CHO), 4.80 (m, 1H, H-1,–CHO), 4.76 (dd, 1H, *J* = 5.0, 1.8 Hz, H-3, –CHOPhBr), 4.48 (m, 1H, H-2, –CHO), 3.24 (d, 1H, *J* = 7.3 Hz, C-2,–OH), 3.04 (d, 1H, *J* = 11.7 Hz, C-1, –OH), 2.33 (br s, 1H, C-4,–OH); ^{13}C NMR (100 MHz $CDCl_3$ ppm): δ 154.1, 136.2, 134.3, 133.7, 132.6, 129.8, 129.4, 129.1, 129.0, 128.9, 123.7, 116.2, 83.2, 69.6, 69.1, 67.9.

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