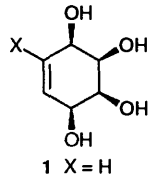
Syntheses of Conduritol D Derivatives from Aromatic Compounds

Howard A. J. Carless,* Kofi Busia, Yvonne Dove and Shahnaz S. Malik
Department of Chemistry, Birkbeck College, Gordon House, 29 Gordon Square, London WC1H 0PP, UK

cis-Cyclohexa-3,5-diene-1,2-diols **3**, which are available by microbial oxidation of aromatic compounds, have been converted into 5-substituted conduritols D **5** by catalytic osmylation: application of the method to the preparation of homochiral 5-deuteriated conduritol D **2** is described.

The conduritols A–F (cyclohex-5-ene-1,2,3,4-tetraol stereoisomers)[1,2] are useful intermediates in organic synthesis, and their epoxides can act as irreversible glycosidase inhibitors.[3] The least accessible of the conduritol isomers has been conduritol D **1**, having the all *cis* stereochemistry. Conduritol D



1 X = H
2 X = D

itself has been synthesised by a high pressure and temperature Diels–Alder reaction,[5] from an inaccessible *epi*-inositol derivative[6] or as a minor product from photo-oxidation of *cis*-cyclohexa-3,5-diene-1,2-diol.[7] We now describe brief syntheses of a number of conduritol D derivatives, by a route based on microbial oxidation of aromatic compounds and catalytic osmylation of the resulting cyclohexadienediols. We have applied the method to give the first synthesis of homochiral 5-deuteriated conduritol D **2**.

The cyclohexadienediols **3** are available by oxidation of aromatic compounds using the dioxygenase enzymes of *Pseudomonas putida* mutants.[8] Mono-osmylation of conjugated dienes has not been successfully applied in many instances. Sharpless,[9] for example, has reported *syn*, *anti*, *syn* tetraols as the major products from treatment of conjugated dienes with one equivalent of *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetraoxide, accompanied by only traces of the diol arising from mono-osmylation of the diene. Furthermore, the direction of approach by osmium tetraoxide on the double bonds of molecules such as **3** might be expected to be governed by Kishi's rule,[10] which for cyclohex-2-enol and its derivatives favours approach *anti* to the adjacent allylic C–O bonds.[11]

We were surprised to find that this *anti* preference is not the controlling factor in osmylation of the cyclohexadienediols **3**. The results for the *cis*-dienediols derived from benzene, toluene, chlorobenzene and bromobenzene are shown in Table 1 and Scheme 1. In all cases, reaction gave a reasonable quantity of the conduritol D isomers **5** arising from *syn* attack, along with the expected *anti* product, the conduritol E isomers **4**.[12] With increasing size of the substituent X in dienediol **3**, the ratio of *syn*:*anti* attack became close to 1:1. Moreover, in the present series of conjugated dienes including the symmetrical isomer **3a**, osmylation was easily controllable to afford conduritols (the products of mono-osmylation) rather than inositol products (representing di-osmylation).

The conduritols **4** and **5** were easily separated by conversion into their corresponding di-*O*-isopropylidene derivatives **6** and **7**, followed by column chromatography on silica gel. The individual conduritol D **5** isomers were then prepared in high yield by acidic hydrolysis of the acetals **7**.

Table 1

Entry	Reactant **3**	Overall yield (%)	Product ratio **4**:**5**
1	**a** X = H	64	71:29
2	**b** X = Me	57[a]	67:33
3	**c** X = Cl	88	55:45
4	**d** X = Br	84	53:47

[a] There is an additional 25% of products resulting from hydroxylation at the trisubstituted double bond.

The above method can be used to make available isotopically labelled and chiral conduritol D, for studies of glycosidase enzyme inhibition.[3] Thus, photochemically-initiated reduction[13] of bromo acetal **7d** using tributyltin deuteride in benzene gave the di-*O*-isopropylidene derivative of 5-deuterioconduritol D **8** (Scheme 2). Subsequent acid hydrolysis led to 5-deuterioconduritol D **2** itself, having the absolute configuration shown.

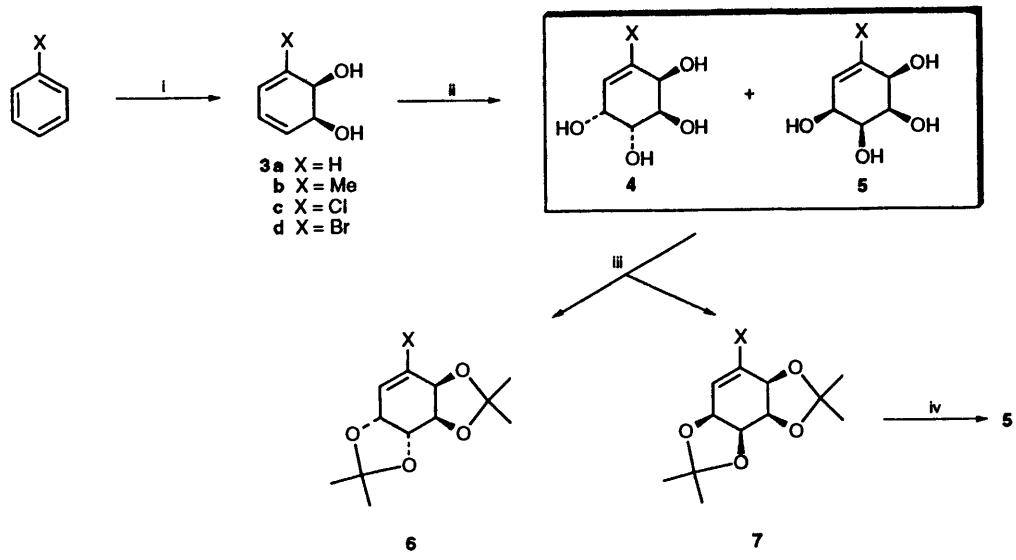
Experimental

Osmylation of 3-*Bromocyclohexa*-3,5-*diene*-1,2-*diol* **3d**.—A stirred solution of **3d** (224 mg, 1.17 mmol) in a mixture of acetone (6 cm^3) and water (1 cm^3) was treated with *N*-methylmorpholine *N*-oxide (178 mg, 1.52 mmol) and a catalytic amount of osmium tetraoxide (4 mg). After 2 days at 20 °C, the solution was filtered and evaporated; ^1H and ^{13}C NMR spectra of the crude product showed **4d**:**5d** in a 53:47 ratio. Column chromatography (10% methanol–90% ethyl acetate) on silica gel gave a 1:1 mixture of bromo conduritols **4d** and **5d** (222 mg, 0.99 mmol, 84%).

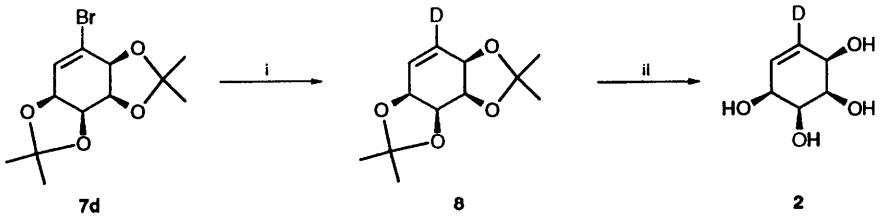
The **4d**–**5d** mixture (210 mg, 0.93 mmol) was dissolved in acetone (20 cm^3) and 2,2-dimethoxypropane (4 cm^3), cooled to 0 °C, and trifluoroacetic acid (70 mg) added. After being left to stand at 4 °C overnight, the product was neutralised with triethylamine (150 mg), concentrated by evaporation at 20 °C and then chromatographed [eluting with 20% diethyl ether–80% light petroleum (b.p. 40–60 °C)] on silica gel, to afford: (i) 1,2:3,4-di-*O*-isopropylidene-5-bromoconduritol E **6d** (124 mg, 0.41 mmol, 44%); $[\alpha]_D^{26}$ +82.2† (*c* 1.25, MeOH); δ_H(270 MHz; $CDCl_3$‡) 6.08 (1 H, m, 6-H), 4.64 (1 H, dd, *J* 2.5 and 5.3), 4.61–4.54 (3 H, m) (1-H, 2-H, 3-H and 4-H), 1.41 (6 H, s, 2 × Me) and 1.38 (6 H, s, 2 × Me); δ_C(68 MHz; $CDCl_3$) 129.20 (C-6), 124.38 (C-5), 110.07 and 109.85 (2 × CMe_2), 74.44, 74.10, 72.69 and 72.32 (C-1, C-2, C-3 and C-4), 27.84, 27.55, 26.48 and 26.36 (4 × Me).

(ii) 1,2:3,4-Di-*O*-isopropylidene-5-bromoconduritol D **7d** (120 mg, 0.39 mmol, 42%); m.p. 130–132 °C; $[\alpha]_D^{26}$ −3.8 (*c* 0.5, MeOH); δ_H(270 MHz; $CDCl_3$) 6.23 (1 H, dd, *J* 0.7 and 3.7, 6-H), 4.60–4.54 (2 H, m, 1-H and 4-H), 4.46 (1 H, t, *J ca.* 4.5, 2-H), 4.42

† $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.
‡ *J* Values are given in Hz.



Scheme 1 i, *Pseudomonas putida*; ii, *N*-methylmorpholine *N*-oxide (1.2 equiv.), Me_2CO–H_2O, OsO_4; iii, Me_2CO, $(MeO)_2CMe_2$, CF_3CO_2H; iv, HOAc–H_2O (1:9), 80 °C, 1 h



Scheme 2 i, Bu_3SnD, *hv*, benzene, 20 °C (67%); ii, HOAc–H_2O (1:9), 80 °C, 1 h (95%)

(1 H, dd, *J* 4.2 and 5.7, 3-H), 1.53 (3 H, q, *J* 0.8, Me), 1.50 (3 H, q, *J* 0.8, Me), 1.42 (3 H, q, *J* 0.8, Me) and 1.39 (3 H, q, *J* 0.8, Me); δ_C(68 MHz; $CDCl_3$) 128.45 (C-6), 124.31 (C-5), 111.16 (2 × CMe_2), 75.56, 73.91, 72.75 and 72.00 (C-1, C-2, C-3 and C-4), 26.91 (Me), 26.87 (Me) and 26.41 (2 × Me).

Hydrolysis of **7d**.—The acetal **7d** (50 mg, 0.16 mmol) was dissolved with stirring in a mixture of acetic acid (0.3 cm^3) and water (2.7 cm^3), which was heated at 80 °C for 1 h. Evaporation gave (1*S*,2*S*,3*S*,4*S*)-5-*bromocyclohex*-5-*ene*-1,2,3,4-*tetraol* **5d** (5-bromoconduritol D) (36 mg, 0.16 mmol, 98%); $[\alpha]_D^{24}$ +4.4 (*c* 0.3, MeOH); δ_H(270 MHz; D_2O) 6.24 (1 H, d, *J* 2.9, 6-H), 4.24 (2 H, m, 1-H and 4-H), 4.02 (1 H, br d, *J ca.* 3, 2-H) and 3.95 (1 H, dd, *J* 1.9 and 5.1, 3-H); δ_C(68 MHz; D_2O) 133.96 (C-6), 127.85 (C-5), 74.21, 72.38, 72.09 and 71.20 (C-1, C-2, C-3 and C-4).

References

1 M. Balci, Y. Sütbeyaz and H. Seçen, *Tetrahedron*, 1990, **46**, 3715.

2 For more recent conduritol syntheses, see C. Le Drian, E. Vieira and P. Vogel, *Helv. Chim. Acta*, 1989, **72**, 338; S. V. Ley and A. J. Redgrave, *Synlett*, 1990, 393; C. Le Drian, J.-P. Vionnet and P. Vogel, *Helv. Chim. Acta*, 1990, **73**, 161; H. A. J. Carless and O. Z. Oak, *J. Chem. Soc., Chem. Commun.*, 1991, 61; T. Hudlicky, F. Rulin, T. Tsunoda, H. Luna, C. Andersen and J. D. Price, *Isr. J. Chem.*, 1991, **31**, 229; T. Hudlicky, J. D. Price and H. F. Olivo, *Synlett*, 1991, 645; C. R. Johnson, P. A. Plé and J. P. Adams, *J. Chem. Soc., Chem. Commun.*, 1991, 1006; D. H. R. Barton, P. Dalko and S. D. Gero, *Tetrahedron Lett.*, 1991, **32**, 2471; T. Hudlicky, H. Luna, H. F. Olivo, C. Andersen, T. Nugent and J. D. Price, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2907; M. C. McIntosh and S. M. Weinreb, *J. Org. Chem.*, 1991, **56**, 5010; T. Akiyama, H. Shima and S. Ozaki, *Tetrahedron Lett.*, 1991, **32**, 5593; H. A. J. Carless, *J. Chem. Soc., Chem. Commun.*, 1992, 234; L. Dumortier, P. Liu, S. Dobbelaere, J. Van der Eycken and M. Vanderwalle, *Synlett*, 1992, 243.

3 G. Legler, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 319.

4 For the synthesis and importance of all *cis*-alkylcyclopentanetetraols, see M. J. Begley, J. P. Madeley, G. Pattenden and G. F. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1992, 57.

5 R. Criegee and P. Becher, *Chem. Ber.*, 1957, **90**, 2516.

6 S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 1958, 375.

7 H. A. J. Carless and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 1719.

8 Reviews: D. A. Widdowson, D. W. Ribbons and S. D. Thomas, *Janssen Chim. Acta*, 1990, **8**, 3; H. A. J. Carless, *Tetrahedron: Asymmetry*, 1992, **3**, 795; G. N. Sheldrake, in *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds*, eds. A. N. Collins, G. N. Sheldrake and J. Crosby, Wiley-Interscience, New York, 1992, p. 127.

9 C. Y. Park, B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.*, 1991, **32**, 1003.

10 J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron Lett.*, 1983, **24**, 3943; W. J. Christ, J. K. Cha and Y. Kishi, *Tetrahedron Lett.*, 1983, **24**, 3947; J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron*, 1984, **40**, 2247.

11 A very recent example of *cis*-hydroxylation of a conduritol B derivative provides a selective approach to *myo*-inositols in which osmylation occurs *anti* to the more electron-donating group: see O. Arjona, A. Candilejo, A. de Dios, R. Fernández de la Pradilla and J. Plumet, *J. Org. Chem.*, 1992, **57**, 6097. Other current work has emphasised the importance of (Cieplak) stereoelectronic effects in explaining product distributions: M. Burdisso, R. Gandolfi and A. Rastelli, *Tetrahedron Lett.*, 1991, **32**, 2659; R. L. Halterman and M. A. McEvoy, *J. Am. Chem. Soc.*, 1992, **114**, 980. Notable cases of a directing effect in catalytic osmylation are cited by J. S. Panek and J. Zhang, *J. Org. Chem.*, 1993, **58**, 294.

12 In contrast, osmylation of the *O*-isopropylidene derivatives of **3c** and **3d** has been shown to lead exclusively to the products of *anti* attack: T. Hudlicky, J. D. Price, F. Rulin and T. Tsunoda, *J. Am. Chem. Soc.*, 1990, **112**, 9439.

13 H. A. J. Carless, *Tetrahedron Lett.*, 1992, **33**, 6379.

Paper 3/05387C
Received 8*th September* 1993
Accepted 13*th September* 1993