Enantiospecific and Stereoselective Synthesis of (−)-Conduritol C from Chlorobenzene *via* Microbial Oxidation and Epoxidation

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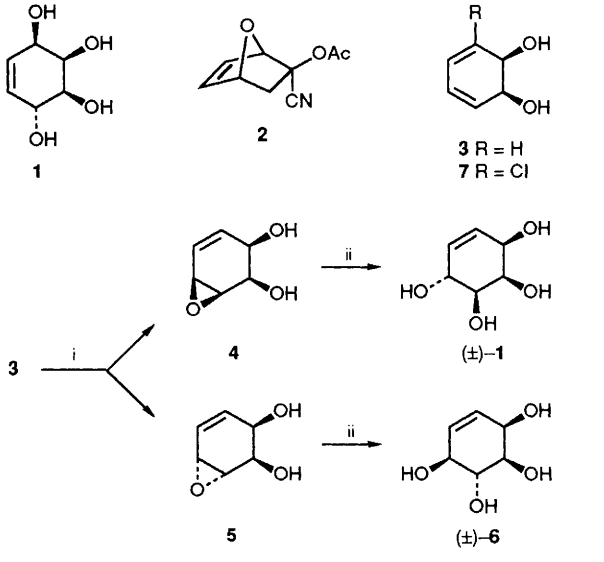
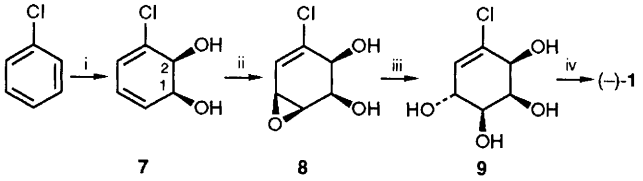
A four-step route to (−)-conduritol C **1** is described, *via* the enantiospecific conversion of chlorobenzene to the diene *cis*-diol **7** and subsequent *cis*-epoxidation to yield **8**.

There is vigorous activity in the synthesis of conduritols (cyclohex-5-ene-1,2,3,4-tetrol isomers),[1] because of the ability of various hydroxylated cyclohexene epoxides to act as glycosidase inhibitors.[2,3] Six stereoisomers of conduritol, designated A to F, are possible. Recent synthetic emphasis has been on enantiospecific routes to these molecules.[4] Vogel and coworkers[5] have published the first synthesis of (−)-conduritol C, (−)-**1**, in nine steps (28% overall) from **2**, the product of an asymmetric Diels–Alder reaction. Very recently, Johnson *et al.*[6] have prepared (−)-**1** in seven stages from benzene *via* the symmetrical cyclohexadienediol **3** and exploiting a lipase for chiral acetylation. Described herein is a concise four-step synthesis of (−)-conduritol C, (−)-**1**, starting from chlorobenzene.

The present route relies on the stereoselective *cis*-epoxidation of allylic alcohols by peroxyacids.[7] Thus, epoxidation of cyclohexadienediol **3** by *m*-chloroperoxybenzoic acid (MCPBA) in dichloromethane gave a *cis* : *trans* mixture of the sensitive benzene diol epoxides **4** and **5** (85 : 15) (Scheme 1).[8] The major epoxide **4** was isolated by column chromatography and easily converted in a regiospecific acid-catalysed reaction with water to (±)-conduritol C **1**. It was more convenient to carry out the peracid epoxidation in aqueous acetone (1 : 50 v/v) over three days, yielding (±)-conduritol C **1** and (±)-conduritol F **6** in an 88 : 12 ratio and 70% overall yield.



Scheme 1 *Reagents and conditions*: i, MCPBA (1 equiv.), CH_2Cl_2, 0 °C, 4 h, 75% combined yield, ii, THF, H_2O (4 : 1 v/v), CF_3CO_2H (0.1 equiv.), 20 °C, 48 h, 88%



Scheme 2 *Reagents and conditions*: i, *Pseudomonas putida*, ii, MCPBA (1 equiv.), acetone, 20 °C, 2 h, 61%; iii, H_2O (10 equiv.), CF_3CO_2H (0.1 equiv.), 48 h, 90%; iv, Na/NH_3, 70%

For the enantiospecific synthesis of (−)-conduritol C **1**, the key first stage is the conversion of chlorobenzene to the chiral *cis*-diol **7** by mutant strains of *Pseudomonas putida*, giving material of >98% e.e. with configuration (1*S*,2*S*),[9] as shown in Scheme 2. Treatment of **7** with MCPBA led to regioselective attack at the unchlorinated double bond[10] and *cis*-stereoselectivity (>95%) to give the vinylic epoxide **8**{$[\alpha]_D^{25}$ −127 (*c* 0.3, Et_2O)} in 61% yield. Acid-catalysed addition of water to **8**, or epoxidation of **7** in aqueous acetone, led to chloroconduritol **9**{$[\alpha]_D^{25}$ −107 (*c* 1.0, MeOH)} (crystallised from acetone, 66% from **7**). The final reductive step of dechlorination without reduction of the double bond of **9** was easily achieved by the use of sodium in liquid ammonia.[11] Column chromatography gave (−)-conduritol C **1** (70%) having ^1H and ^{13}C NMR spectra in agreement with literature data,[5] m.p. 128–130 °C, $[\alpha]_D^{25}$ −202 (*c* 0.1, H_2O) {lit.[6] m.p. 127–128 °C, $[\alpha]_D^{25}$ −207 (*c* 0.5, H_2O).

The present synthesis uses a combination of microbial oxidation and conventional chemical reactions to achieve a short route to a specific, chiral conduritol isomer, without the need for protecting groups.

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