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Enantiospecific Synthesis of (4*S*,5*S*,6*S*)-4,5,6-Trihydroxycyclohex-2-enone and (+)-Conduritol C from Fluorobenzene *via* Microbial Oxidation

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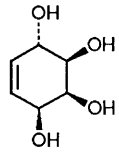
Epoxidation of the chiral diene **5**, produced by *Pseudomonas putida* oxidation of fluorobenzene, gave fluoroconduritol **9** and cyclohexenone **11**; the latter was used in a short synthesis of (+)-conduritol C **1**.

Chiral cyclohexenones are convenient intermediates in the synthesis of inositols and inosamines, and have often been prepared from carbohydrates by the Ferrier reaction.[1] Routes to conduritol (cyclohex-5-ene-1,2,3,4-tetrol) isomers[2] are currently of interest, in view of the ability of conduritol epoxides to act as glycosidase inhibitors.[3] Vogel and coworkers[4,5] have recently completed a synthesis of (−)-conduritol C, derived from an asymmetric Diels–Alder reaction of furan to a chiral cyanoalkenol ester. We now describe the first route to the enantiomer (+)-conduritol C **1**, based on microbial oxidation of fluorobenzene and occurring *via* a novel α-fluoroepoxide.

There is intense activity in the use of *Pseudomonas putida* strains in the conversion of benzene to *cis*-cyclohexa-3,5-diene-1,2-diol **2** and thence to inositols[6] or conduritols.[7] The ability of the microbial enzymes to convert monosubstituted aromatic compounds to chiral diols (*e.g.* **3** and **4** from toluene and chlorobenzene, respectively) has been used by several groups[8–11] in the synthesis of diverse products such as cyclopentenones from **3**,[8] and most recently, (−)-dihydroconduritol C[9] or pyrrolizidine alkaloids[10] from **4**.

Epoxidation of the homochiral fluorodiol **5**[12] by *m*-chloroperoxybenzoic acid (1 equiv.) in dichloromethane solution at 0 °C led to the rapid formation (<0.5 h) of two unstable intermediates, formed in the ratio 2:1 and subsequently assigned the structures **6** and **7** respectively. Their build-up was followed by ^{1}H and ^{13}C NMR spectra of reactions conducted in [$^2H_6$]acetone solution,† but these sensitive compounds evaded purification by chromatography of the reaction mixture.[13] During conventional peracid epoxidation, the allylic epoxide **6** was in turn converted over 2–4 h to the novel 6-fluoroconduritol C *m*-chlorobenzoate **8** or (in the presence of water) to the 6-fluoroconduritol **9** itself; both were easily isolated by column chromatography (30–50%). When peracid epoxidation was carried out using buffered (Na_2CO_3, stirring) conditions in dichloromethane, compound **7** could be isolated by silica gel chromatography (20%). We were unable to detect the expected α-fluoroepoxide **10**[14] and believe that it must undergo rapid rearrangement to **7** under the reaction conditions.[15] The cyclic haloether **7** also proved to be reactive towards water, especially in the presence of traces of acid. Treatment of pure **7** dissolved in aqueous acetone (1:100 v/v) with trifluoroacetic acid (0.01 mol dm^{-3}) led to crystallisation from the mixture of (4*S*,5*S*,6*S*)-4,5,6-trihydroxycyclohex-2-enone **11** (50%) $[\alpha]_D^{22}$ +212° (*c* 2, H_2O), easily identified by comparison of its ^{1}H and ^{13}C NMR spectra with those of a racemic sample of dehydroconduritol D.[7a] In fact, it proved to be much more convenient to carry out the epoxidation of **5** at 0 °C in water–acetone (1:5 v/v) containing a trace of tri-



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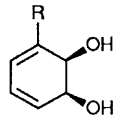
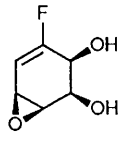


2 R = H
3 R = Me
4 R = Cl
5 R = F



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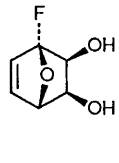

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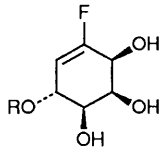
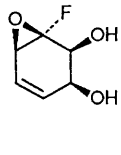


8 R = *m*-ClC$_6$H$_4$CO
9 R = H



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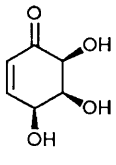

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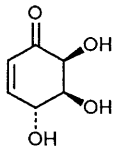
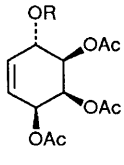
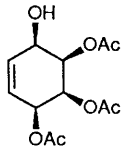


12



13 R = H
15 R = Ac



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† Compound **6**: δ_H (CD_3COCD_3, 270 MHz) 5.75 (1H, ddd, *J* 1, 4.5 and 11 Hz), 4.20 (2H, m) and 3.57 (2H, m); δ_C 165.6 (J_{CF} 270 Hz), 103.5 (J_{CF} 18 Hz), 69.3 (J_{CF} 11 Hz), 68.4 (J_{CF} 26 Hz), 57.7 and 48.5 (J_{CF} 14 Hz); compound **7**: δ_H (CD_3COCD_3) 6.32 (1H, dd, *J* 3.5 and 10.1 Hz), 6.25 (1H, m) 4.14 (1H, br t, *J* 5.5 Hz), 4.00 (1H, dd, *J* 1.2 and 5 Hz), 3.94 (1H, m) and 2.90 (2H, br s, OH); δ_C 135.8 (J_{CF} 13 Hz), 126.0 (J_{CF} 40 Hz), 93.9 (J_{CF} 261 Hz), 67.5 (J_{CF} 2 Hz), 66.2 and 63.7 (J_{CF} 16 Hz).

fluoroacetic acid, which led reliably over 1–2 days to the direct crystallisation of **11** in 20–25% yield. Although **11** is only isolated by this method in low yield, the directness of such an approach to a chiral enone from a simple aromatic compound is attractive.‡

Acetylation of the triol **11** (pyridine–acetic anhydride, 0 °C, 18 h) gave the corresponding triacetate in good yield (80%). Subsequent reduction ($NaBH_4$–$CeCl_3$, methanol)[17] of the enone functionality produced the conduritol C and D stereoisomers **13** and **14** respectively (ratio 1:2, total yield 98%) which were subjected to a final acetylation (95% yield) before separation by column chromatography; this gave the (+)-conduritol C tetraacetate **15**, $[\alpha]_D^{24}$ +194° (*c* 1.1, $CHCl_3$), besides the symmetrical conduritol D tetraacetate. Deacetylation of **15** proceeded smoothly (K_2CO_3, methanol) to afford (+)-conduritol C **1** (88%), $[\alpha]_D^{24}$ +213° (*c* 0.4, H_2O) [*cf.* (−)-conduritol C, $[\alpha]_D^{25}$ −209° (*c* 2, H_2O)],[4] thus prepared in six steps from fluorobenzene.

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‡ Conducting the epoxidation of **5** in D_2O–CD_3COCD_3 with NMR monitoring showed that **11** was the major enone produced, with no evidence for the stereoisomer **12**. Non-conjugated enones or α-fluoroketones, which might have arisen by S_N2 attack or rearrangement of **10**,[16] were not detected.