Enantioselective Syntheses of (+)- and (−)-Conduritol C from Benzene *via* Microbial Oxidation and Enzymatic Asymmetrization

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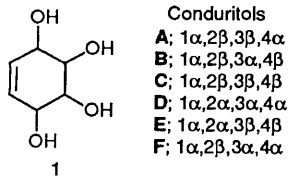
The title compounds have been prepared by a route involving the elaboration of *meso*-cyclohexa-3,5-diene-1,2-diol **4**, a product of microbial oxidation of benzene, to *meso*-diol **6** and asymmetrization of the latter by use of a lipase in organic media to the enantiometrically pure monoacetate **7**.

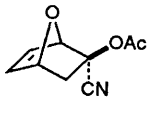
Conduritols (cyclohex-5-ene-1,2,3,4-tetraols **1**) are currently of interest due to the ability of various derivatives to inhibit glycosidases.[1] The several stereoisomers are designated by the letters **A–F** and all have been synthesized.[1] Conduritols **A** and **F** occur in nature. Only recently have routes to both enantiomers of conduritol **C** been developed. Vogel has elaborated the (−)-enantiomer from **2** using his 'naked sugar' approach.[2] The (+)-enantiomer has been prepared from **3**, the product of oxidation of fluorobenzene by *Pseudomonas putida*.[3]

We are engaged in a programme of synthesis of bioactive molecules by routes involving, as a key feature, the enzymatic asymmetrization of densely functionalized, cyclic *meso* compounds.[4] It appeared to us that *meso*-cyclohexa-3,5-diene-1,2-diol **4**, available by oxidation of benzene by mutants of *P. putida*,[5a] would provide an ideal starting material for efforts in this area.[5b] The diol **4** was protected as its acetonide **5** and the latter converted to the *meso*-2,3-diprotected conduritol **A 6** by addition of singlet oxygen and thiourea reduction.[6] The *meso* diol **6** was treated with crude lipase from *P. cepacia* (Amano



1

Conduritols
A; 1α,2β,3β,4α
B; 1α,2β,3α,4β
C; 1α,2β,3β,4β
D; 1α,2α,3α,4α
E; 1α,2α,3β,4β
F; 1α,2β,3α,4α



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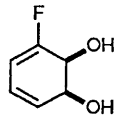

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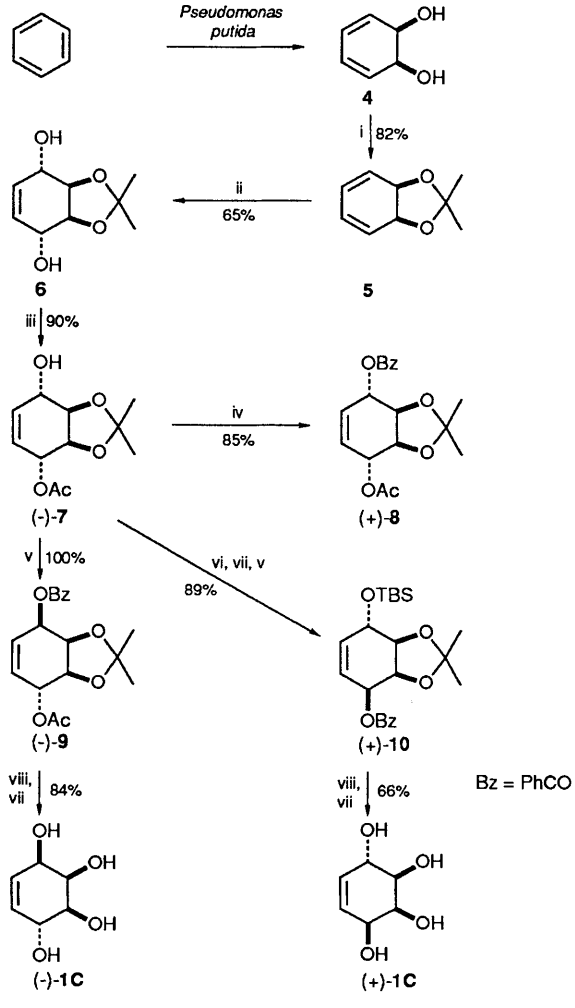

Scheme 1 *Reagents and conditions*: i, $Me_2C(OMe)_2$, CH_2Cl_2, *p*-$TolSO_3H$; ii, O_2, *meso*-tetraphenylporphin, CH_2Cl_2, MeOH, 0 °C, *hv* (4–6 h) then thiourea (12 h); iii, Amano P-30 lipase, isopropenyl acetate, 55 °C, 2 days; iv, PhCOCl, Et_3N, CH_2Cl_2; v, $PhCO_2H$, DEAD, Ph_3P, THF, 0 °C, *ca.* 30 min; vi, TBSCl, imidazole, DMF; vii, K_2CO_3, MeOH; viii *p*-$TolSO_3H$, MeOH; (TBS = *tert*-butyldimethylsilyl; DEAD = diethyl azodiformate; THF = tetrahydrofuran; DMF = dimethylformamide)

P-30 lipase) (*ca.* 1 : 1 substrate to crude lipase) in isopropenyl acetate[7] at 55 °C for 2 days to yield the monoacetate **7**, $[\alpha]_D^{25}$ −34° (*c* 3, $CHCl_3$) (90% yield, >95% e.e. as determined by NMR spectroscopy studies on the Mosher ester[8]). The absolute configuration about C-1 was determined from the benzoate **8**, $[\alpha]_D^{25}$ +47° (*c* 0.5, MeOH), m.p. 103–105 °C (Et_2O–hexane). The circular dichroism (CD) of the latter exhibited a positive Cotton effect and in the context of the Nakanishi benzoate sector rule[9] can be assigned to have the (*S*)-configuration at the stereogenic centre bearing the benzoyloxy.

Treatment of monacetate **7** with benzoic acid under Mitsunobu conditions[10] gave the fully protected (−)-**9** which upon deprotection under acidic followed by basic conditions resulted in (−)-conduritol **C** [(−)-**1C**], $[\alpha]_D^{25}$ −207° (*c* 0.5, water), m.p. 127–128 °C (from MeOH–Et_2O) {lit.[2] $[\alpha]_D^{25}$ −209° (*c* 2, water), m.p. 129–130 °C}. Elementary functional group manipulations prior to the Mitsunobu reaction followed by the same deprotection sequence resulted in the enantiomer, (+)-conduritol **C** [(+)-**1C**], $[\alpha]_D^{25}$ +212° (*c* 0.47, water), m.p. 128–129 °C {lit.[3] $[\alpha]_D^{25}$ +213° (*c* 0.4, water)} (Scheme 1).

Acetonide **5** has been prepared from benzene by a strictly chemical route.[11] In our hands, treatment of cyclohexa-1,4-diene, the product of Birch reduction of benzene, sequentially with bromine (1 equiv.), *N*-methylmorpholine *N*-oxide–OsO_4,[12] dimethoxypropane–H^+ and 1,8-diazabicyclo[5.4.0]-undec-7-ene results in the production of **5** in 87% overall yield.

In conclusion, by use of lipase-catalysed acyl transfer in organic media we have developed an exceptionally effective route to optically pure cyclohexenetetraol derivatives which should prove useful in the synthesis of numerous polyols of biological interest.

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