Tetrahedron Letters, Vol. 33, No. 42, pp. 6379-6382, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

COMPLEMENTARY ENANTIOSPECIFIC SYNTHESES OF CONDURITOL E EPOXIDES FROM HALOBENZENES

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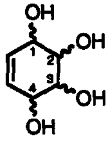
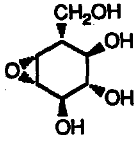
Abstract: Microbial oxidation of chlorobenzene or bromobenzene gave diols (3), which were converted in stereoselective and chemoselective sequences involving epoxidation/osmylation steps and reduction to the enantiomers of (-)- or (+)-conduritol E epoxide (4).

Conduritols (1) have recently become fashionable synthetic targets.[1] There are six geometric isomers of conduritols possible: the symmetrical A and D isomers[2] and four enantiomeric pairs (conduritols B, C, E and F). Within the last four years, enantiospecific syntheses have appeared of the (-)-B[3] and (+)-B[4], (-)-C[5-8] and (+)-C[9], (-)-E[8,10], (-)-F[4,8,10,11] and (+)-F[3,11] conduritol isomers. In early pioneering work, Angyal and Gilham synthesised (+)-conduritol E from the naturally-occurring L-quebrachitol by a multi-step route.[12] The conduritols, apart from their use as synthetic intermediates, are of interest because their epoxides act as glycosidase inhibitors.[13] The related molecule cyclophellitol (2) has been found to be a potent inhibitor of infection by human immunodeficiency virus.[14]



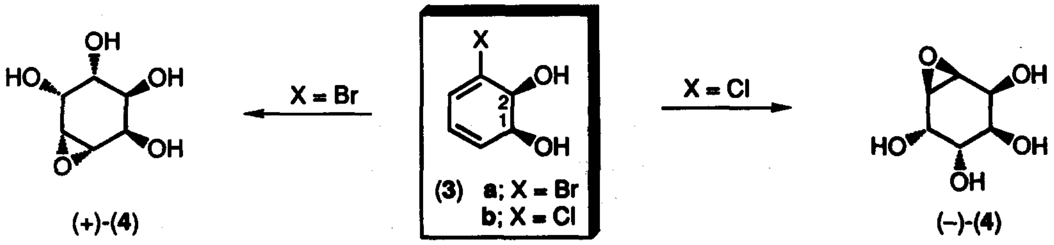
(1)

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



(2)

Other recent developments have included the use of chiral conduritol epoxides for the preparation of pseudo-sugars,[15] such as pseudo-α-D-mannopyranose[16] and pseudo-α-D-glucopyranose.[17] In this paper are described six-step routes from the halobenzenes *via* the key cyclohexadienediol intermediates (3) to the individual enantiomers of (+)- and (-)-conduritol E epoxide (4) (Scheme 1).



(+)-(4)

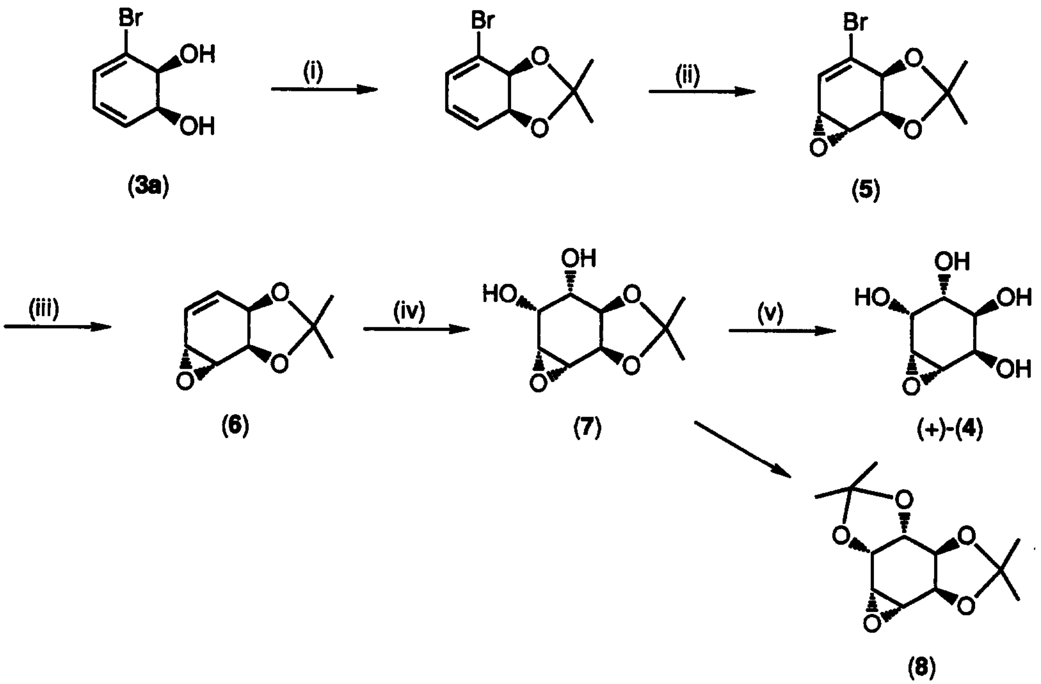
(3) a; X = Br
b; X = Cl

(–)-(4)

Scheme 1

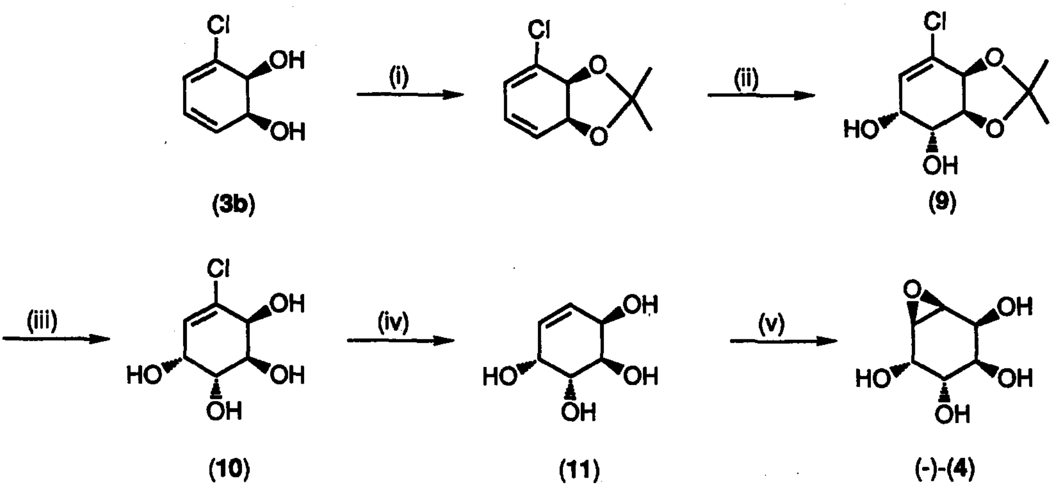
The microbial oxidation of chlorobenzene and bromobenzene to the corresponding chiral *cis*-dihydrodiols (3) by *Pseudomonas putida* mutants is now well established as a synthetic method.[18] The absolute configuration of the diols, formed in ≥98% *e.e.*, has been shown to be (1*S*,2*S*) for (3, X = Cl or Br).[19] Consideration of the target structures of the tetrol epoxides (4) shows that the required functionality can be introduced by consecutive steps of hydroxylation and epoxidation, provided that these are totally stereoselective and chemoselective.

The synthesis of (+)-conduritol E epoxide (4) from the bromodiol (3a) shown in Scheme 2 involved isopropylidene protection of the diol, followed by stereospecific epoxidation *anti* to the protecting group, to give the chiral epoxyacetal (5).[20] This vinylic epoxide is sensitive to both electrophilic[20] and nucleophilic ring opening,[21] and it could not be successfully reduced to the vinyl epoxide (6) by the use of lithium aluminium hydride, or by free radical reduction[22] under normal (Bu_3SnH, AIBN, C_6H_6, reflux) conditions. However, it is pleasing to report that clean reduction of the vinylic bromide (5)→(6) was achieved using photochemical activation at 25°C in benzene in the presence of pyridine (Hanovia 450 W mercury UV arc, 2 equiv. Bu_3SnH, 1 equiv. AIBN, N_2, 0.01 *M* pyridine in benzene). Osmylation of (6) also occurred stereospecifically *anti* to the isopropylidene group to afford diol (7), which was purified by column chromatography in good yield and converted to the 1,2:3,4-di-*O*-isopropylidene epoxide (8)[23] or deprotected by hydrolysis without epoxide ring opening to give (+)-conduritol E epoxide (4).[25]



Scheme 2: i, 2,2-dimethoxypropane, TsOH (88%); ii, *m*-CPBA, $CHCl_3$, 24 h (95%); iii, Bu_3SnH, AIBN, C_6H_6, pyridine, hv (55%); iv, OsO_4, NMMO, acetone-water (4:1) (92%); v, AcOH-water (1:9), 80°C, 1 h (94%).

To extend the range of precursors in these syntheses, the route to the enantiomeric isomer (-)-(**4**) was carried out from the chlorobenzene diol (**3b**). Isopropylidenation of the diol (**3b**) was followed by catalytic osmylation of the diene, which occurred selectively *anti* to the protecting group and at the non-chlorinated double bond to give chiral diol (**9**), isolated in 65% yield (Scheme 3). Acid catalysed hydrolysis of (**9**) yielded tetrol (**10**) in quantitative yield, which was reductively dechlorinated with retention of the double bond by using sodium in liquid ammonia.[27] The resultant (-)-conduritol E (**11**), $[\alpha]_D^{25}$ -320 (*c* 0.5, H_2O), had identical ^1H and ^{13}C NMR properties to those of authentic racemic material. It is worth noting that Hudlicky and co-workers[10] have recently published a similar synthesis of a chiral conduritol E, starting from bromobenzene, in which they repeatedly refer to the product as (+)-conduritol E, $[\alpha]_D^{20}$ +330. However, it is likely from the known absolute configuration of (**3a**)[18a] and from a later paper[21] that the synthesised isomer was (-)-conduritol E. In the present synthesis, a final peracid epoxidation of (**11**) gave (-)-conduritol E epoxide (-)-(**4**) in good yield.[28]



Scheme 3: **i**, acetone, 2,2-dimethoxypropane, TsOH (97%); **ii**, OsO_4, NMMO, acetone-water (9:1) (65%); **iii**, AcOH-water (1:9), 85°C, 2 h (100%); **iv**, Na, NH_3, THF (60%); **v**, *m*-CPBA, AcOH-water (7:1), 20°C, 5 days (68%).

In conclusion, the present work shows the possibility of using the chirality of a single cyclohexadienediol isomer (**3**), derived by microbial oxidation of an aromatic compound, to synthesise both enantiomers of conduritol E epoxide. It is intended to extend these methods to the preparation of other interesting chiral inositols and aminocyclitols.

ACKNOWLEDGEMENT

I wish to thank ICI Fine Chemicals for a supply of diols (3), and Pramila Rajani and Don Shipp for most helpful technical support in running NMR spectra.

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23. Compound (8): $[\alpha]_D^{25}$ +13.5 (*c* 0.5, MeOH) {lit.[24] $[\alpha]_D^{15}$ +13.5 (*c* 1.6, MeOH)}; n.m.r. (Me_2CO-d_6): ^1H (270 MHz) δ 4.54 (1H, dd, *J* 2.1, 6.4 Hz), 4.48 (2H, s), 4.29 (1H, d, *J* 6 Hz), 3.27 (2H, m), 1.42, 1.37, 1.33 and 1.31 (each 3H, s); ^{13}C δ 109.42, 75.42, 73.35, 72.36, 70.76, 55.59, 52.85, 27.71, 26.87, 26.05 and 25.28.
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25. Compound (+)-(4): $[\alpha]_D^{25}$ +149 (*c* 0.15, H_2O) {lit.[26] $[\alpha]_D^{25}$ +153 (*c* 0.5, H_2O)}; n.m.r. (D_2O): ^1H (270 MHz) δ 4.36 (1H, dd, *J* 2, 3.3 Hz), 4.33 (1H, t, *J* 4.5 Hz), 3.78 (1H, dd, *J* 4.7, 9.8 Hz), 3.73 (1H, dd, *J* 3.3, 9.8 Hz), 3.48 (1H, t, *J* 4 Hz) and 3.42 (1H, dd, *J* 2, 3.7 Hz); ^{13}C δ 70.14, 69.72, 69.33, 67.92, 58.85 and 56.96.
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28. Compound (-)-(4): $[\alpha]_D^{25}$ -147 (*c* 0.2, H_2O).

(Received in UK 23 June 1992)