Enzymatic and Chemical Syntheses of *cis*-Dihydrodiol Derivatives of Monocyclic Arenes

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Metabolism of bromobenzene and iodobenzene by growing cultures of *Pseudomonas putida* UV4 gave the corresponding *cis*-dihydrodiol products **1** and **2** in high yields; subsequent direct chemical substitution of the halogen atoms in these metabolites provided a new range of enantiomerically pure *cis*-dihydrodiols of known absolute configuration.

The *cis*-dihydrodiols resulting from the metabolism of benzene[1–6] and monosubstituted benzenes (*e.g.* fluorobenzene,[7] chlorobenzene[8–11] and bromobenzene[12]) by mutant strains of the bacterium *Pseudomonas putida* have recently proved to be of value in natural product synthesis. Although the *cis*-dihydrodiols of benzene and derivatives have been known for many years,[13–15] uncertainty about optical purity and absolute configuration of the chiral diols, coupled with the unavailability of significant quantities of these chiral synthons, has restricted their use in synthesis. However, improved yields of homochiral *cis*-dihydrodiols of monocyclic arenes, *e.g.* toluene,[16] bromobenzene and iodobenzene have been produced in these laboratories using a mutant strain of *P. putida* UV4 which lacks the dehydrogenase enzyme responsible for the conversion of *cis*-dihydrodiols to their respective catechols. We have also reported in a previous study[17] how both optical purity and absolute configuration of a range of *cis*-dihydrodiols can be determined *via* formation of 4-phenyl-1,2,4-

Table 1 Reactant and reaction conditions, product, yield (%), optical rotation ($[\alpha]_D$) and absolute configuration of *cis*-dihydrodiols[a] **1–10**

Reactant and reaction conditions	Product	Yield (%)	$[\alpha]_D$[b]	Absolute configuration
Bromobenzene, *P. putida*, O_2, 24 h	**1**	77	+20	1*S*,2*S*
Iodobenzene, *P. putida*, O_2, 24 h	**2**	85	+41	1*S*,2*S*
2(**1**), Me_2CuLi, Et_2O, 0 °C	**3**	38[c] (32)[d]	+72[e] +72[e,g]	1*S*,2*R*[f]
2(**1**), Bu_3SnOMe, $Pd(OAc)_2$, Ph_3P, THF, 16 h	**4**	11[b](—)[g]	+77	1*S*,2*R*[f]
2(**1**), $Bu_3SnCH{=}CH_2$, $Pd(OAc)_2$, Ph_3P, THF, 16 h	**5**	26[c](23)[d,i]	+126 +115[g]	1*S*,2*R*[f]
2(**1**), $Bu_3SnCH_2CH{=}CH_2$, $Pd(Ph_3P)_4$, THF, 0.45 h, 35 °C	**6**	31[c](—)[h,d]	+16	1*S*,2*R*[f]
2(**1**), $HC{\equiv}CSiMe_3$, $Pd(OAc)_2$, Ph_3P, Et_3N, 3h, 40 °C	**7**	39[c](53)[d]	+156[e]	1*S*,2*R*[f]
7, K_2CO_3, MeOH, 4 h	**8**	46	+216 +194[g,j]	1*S*,2*R*[f]
2(**1**), Bu_3SnCN, $Pd(Ph_3P)_4$, THF, 4 h, 50 °C	**9**	52[c](—)[h,d]	+188	1*S*,2*R*[f]
2(**1**), MeSNa, HMPA, 60 h, room temp.	**10**	10[c](14)[d,i]	+39	1*S*,2*S*

[a] *cis*-Dihydrodiols **1–10** were essentially homochiral (≥98% e.e.). [b] Degrees in MeOH solvent unless otherwise stated; [c] X = I; [d] X = Br; [e] $CHCl_3$ solvent. [f] The apparent reversal of configuration at C-2 is due to a change in the sequence rule priority. [g] Values for *cis*-dihydrodiols obtained from the arene metabolism by *P. putida*. Since these dihydrodiols were purified by preparative TLC only, their $[\alpha]_D$ values were sometimes slightly lower than their synthetic analogues, which were crystallized. [h] No detectable yield. [i] Yield corrected for recovered starting material. [j] Found to be optically pure by the diMTPA method.

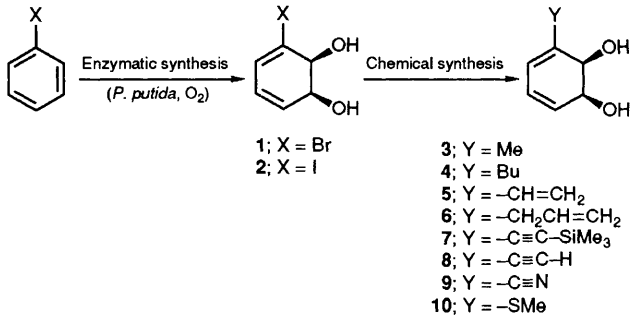
triazoline-3,5-dione cycloadducts and subsequent diesterification using both (+) and (−) forms of α-methoxytrifluoromethylphenylacetic acid (MTPA).

The present communication reports (*i*) an alternative method for the determination of optical purity and absolute configuration of *cis*-dihydrodiols bearing substituents for which the diMTPA method[17] would not be applicable (*e.g.* vinyl), (*ii*) a combination of enzymatic and chemical methods for the synthesis of *cis*-dihydrodiols which are available only in low yield (*e.g. cis*-diols **8** and **10**) by the direct biotransformation route from the corresponding arene using *P. putida* UV4.

Bromo- and iodo-benzene were found to be totally metabolised to give an isolated yield of 77–85% of the corresponding *cis*-dihydrodiols **1** and **2** based on substrate added to growing cultures of *P. putida* UV4 (see Scheme 1). The resulting *cis*-dihydrodiols were purified by column chromatography [silica gel using ethylacetate : hexane (1 : 1) as eluent] prior to determination of their yields and $[\alpha]_D$ values (see Table 1). Preparation of the 4-phenyl-1,2,4-triazoline-3,5-dione cycloadducts and the corresponding diMTPA esters to determine the optical purity and absolute configuration was carried out in a manner similar to that previously reported.[17] Diols **1** and **2** were found to be essentially optically pure [>98% enantiomeric excess (e.e.)] and of 1*S*,2*S* absolute configuration.

The substitution of vinyl halides by palladium-catalysed coupling reactions with organotin reagents provides a very mild synthetic route which has now been shown to be applicable to the unprotected *cis*-diols, **1** and **2**. Using this method a series of *cis*-dihydrodiol metabolites (**4–6, 8, 9**) have been obtained in homochiral form (see Scheme 1†). A major advantage of this synthetic strategy is that the latter *cis*-diols are formed in a single step without recourse to protection–deprotection procedures.

Substitution of the halogen atoms in *cis*-diols **1** and **2** by a methyl group (methylation) involved protection of the diol groups as *tert*-butyldimethylsilyl (TBDMS) derivatives. Treatment of the diTBDMS derivatives of **1** and **2** with dimethyllithium cuprate,[18] followed by deprotection furnished toluene *cis*-dihydrodiol **3**. Since the absolute configuration of *cis*-dihydrodiol **3** had previously been unequivocally established



Scheme 1

by X-ray crystallographic[17,19] methods, both *cis*-dihydrodiols **1** and **2** are therefore also stereochemically assigned by their respective methylations. This provides confirmation of the absolute stereochemical assignments to diols **1** and **2** based upon the diMTPA method.

Reaction of the *cis*-dihydrodiol of iodobenzene **2** with tributyltin methoxide in the presence of a palladium catalyst resulted in the formation of n-butylbenzene *cis*-dihydrodiol **4**, presumably *via* the unusual transfer of a butyl group from the organotin reagent. It is noteworthy that this substitution reaction did not occur with the corresponding bromo *cis*-dihydrodiol, **1**.

Replacement of either the bromo- or iodo-substituents in *cis*-dihydrodiols **1** and **2** by a vinyl group[20] to yield styrene *cis*-dihydrodiol **5** and the iodo-substituent in **2** by an allyl group[21] forming allylbenzene *cis*-dihydrodiol **6** occurred readily with the respective tributyltin reagents in the presence of a palladium catalyst.

Reaction of both *cis*-dihydrodiols **1** and **2** with trimethylsilylacetylene,[22] in the presence of palladium(II) acetate, triphenylphosphine and triethylamine gave the trimethylsilyl derivative **7** which was readily converted to phenylacetylene *cis*-dihydrodiol **8**.† The latter *cis*-dihydrodiol has been reported[23] to be of commercial interest as a potential source of 3-hydroxyphenylacetylene, an end-capping agent for acetylene-terminated resins used in thermosetting high-temperature polymers and adhesives. Attempts to obtain satisfactory yields of *cis*-dihydrodiol **8** by direct biotransformation using *P. putida* UV4 were disappointing. Yields of < 5% were

† We have recently synthesised *cis*-dihydrodiol **8** by direct replacement of the iodo-substituent in diol **2** [$Bu_3SnC{\equiv}CH$, $Pd(OAc)_2$, Ph_3P, THF, 25 °C, 16 h].

normally obtained. In this context the present enzymatic–chemical route from *cis*-dihydrodiols **1** and **2** is clearly more attractive. A further advantage of this route to *cis*-diol **8** is that treatment of the trimethylsilyl derivative **7** with K_2CO_3–MeOH for a short period (4 h) gave total conversion to the required *cis*-diol product **8**, whereas treatment for an extended period (12 h) resulted in the exclusive formation of the industrially important 3-hydroxyphenylacetylene. Reaction of *cis*-dihydrodiol **2** with tributyltin cyanide in the presence of tetrakis(triphenylphosphine)palladium(0)[24] formed the *cis*-dihydrodiol derivative of benzonitrile **9**.

The thiomethoxide anion proved to be a sufficiently strong nucleophile for the displacement of the halogens in *cis*-diols **1** and **2** leading to the synthesis of *cis*-dihydrodiol **10** when hexamethylphosphoramide (HMPA) was used as solvent (Scheme 1). These conditions have previously[25] been found to effect nucleophilic substitutions of unactivated vinyl halides.

Since the optical purity and absolute configuration of the metabolites **1** and **2** have been determined, and confirmed by stereochemical correlation with *cis*-dihydrodiol **3**, the synthetic *cis*-dihydrodiols **4–10** derived from **1** and **2** will necessarily be homochiral and of the same absolute configuration.

Replacement of the iodine atom in *cis*-dihydrodiol **2** occurred in all of the examples mentioned in Table 1, whereas substitution of the bromine atom in *cis*-dihydrodiol **1** (under identical conditions) was found to be possible in the synthesis of *cis*-dihydrodiols **3, 5, 7** and **10** only. The yields of synthetic *cis*-dihydrodiols have not been optimized, however, preliminary comparative studies indicate that the *cis*-dihydrodiol of bromobenzene **1** can sometimes be an equally effective (*e.g.* diol **10**) or better (*e.g.* diol **7**) precursor for substitution (Table 1).

The present study demonstrates the synthetic utility of the *cis*-dihydrodiols of bromo- and iodo-benzene as homochiral synthons which can undergo a range of functional group transformations in an unprotected form. It also represents an alternative method whereby the optical purity and absolute configuration of *cis*-dihydrodiols may be determined by stereochemical correlation.

Studies are currently under way in order to investigate further examples of halogen replacement reactions on protected and unprotected *cis*-dihydrodiols and subsequent modification of the substituent groupings.

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References

1 S. V. Ley, F. Sternfeld and S. Taylor, *Tetrahedron Lett.*, 1987, **25**, 225.
2 S. V. Ley and F. Sternfeld, *Tetrahedron Lett.*, 1988, **29**, 5305.
3 H. A. J. Carless and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 1719.
4 H. A. J. Carless, J. R. Billinge and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 3113.
5 S. V. Ley and F. Sternfeld, *Tetrahedron*, 1989, **45**, 3463.
6 H. A. J. Carless and K. Busia, *Tetrahedron Lett.*, 1990, **31**, 3449.
7 H. A. J. Carless and O. Z. Oak, *J. Chem. Soc., Chem. Commun.*, 1991, 61.
8 T. Hudlicky, H. Luna, J. D. Price and F. Rulin, *Tetrahedron Lett.*, 1989, **30**, 4053.
9 T. Hudlicky, H. Luna, J. D. Price and F. Rulin, *J. Org. Chem.*, 1990, **55**, 4683.
10 T. Hudlicky and J. D. Price, *Synlett*, 1990, 159.
11 T. Hudlicky, J. D. Price, H. Luna and C. M. Andersen, *Synlett*, 1990, 309.
12 T. Hudlicky, J. D. Price, F. Rulin and T. Tsunoda, *J. Am. Chem. Soc.*, 1990, **112**, 9439.
13 D. T. Gibson, J. R. Koch and R. E. Kallio, *Biochemistry*, 1968, **7**, 2653.
14 D. T. Gibson, M. Hensley, M. Yoshioka and T. J. Mabry, *Biochemistry*, 1970, **9**, 1626.
15 D. T. Gibson, B. Gschwendt, W. K. Yeh and V. M. Kobal, *Biochemistry*, 1973, **12**, 1520.
16 R. O. Jenkins, G. M. Stephens and H. Dalton, *Biotechnol. Bioeng.*, 1987, **29**, 873.
17 D. R. Boyd, M. R. J. Dorrity, M. V. Hand, J. F. Malone, N. D. Sharma, H. Dalton, D. J. Gray and G. N. Sheldrake, *J. Am. Chem. Soc.*, 1991, **113**, 666.
18 E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, 1967, **89**, 3911.
19 V. M. Kobal, D. T. Gibson, R. E. Davies and A. Garza, *J. Am. Chem. Soc.*, 1973, **95**, 4420.
20 J. K. Stille and B. L. Groh, *J. Am. Chem. Soc.*, 1987, **109**, 813.
21 M. Kosugi, K. Sasazawa, I. Shimizu and T. Migita, *Chem. Lett.*, 1977, 301.
22 W. B. Austin, N. Bilow, W. J. Kelleghan and K. S. Y. Lau, *J. Org. Chem.*, 1981, **46**, 2280.
23 M. G. Williams, P. E. Olson, K. J. Tautvydas, R. M. Bitner, R. A. Mader and L. P. Wackett, *Appl. Microbiol. Biotechnol.*, 1990, **34**, 316.
24 V. Nair and G. S. Buenger, *J. Am. Chem. Soc.*, 1989, **111**, 8502.
25 M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli and M. Montanucci, *J. Org. Chem.*, 1983, **48**, 4795.