syn-Benzene dioxides: chemoenzymatic synthesis from 2,3-*cis*-dihydrodiol derivatives of monosubstituted benzenes and their application in the synthesis of regioisomeric 1,2- and 3,4-*cis*-dihydrodiols and 1,4-dioxocins†

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cis-2,3-Dihydrodiol metabolites of monosubstituted halobenzenes and toluene have been used as synthetic precursors of the corresponding 3,4-*cis*-dihydrodiols. Enantiopure *syn*-benzene dioxide intermediates were reduced to the 3,4-*cis*-dihydrodiols and thermally racemised *via* the corresponding 1,4-dioxocins. The *syn*-benzene dioxide–1,4-dioxocin valence tautomeric equilibrium ratio was found to be dependent on the substituent position. The methodology has also been applied to the synthesis of both enantiomers of the 1,2-(*ipso*)- and 3,4-*cis*-dihydrodiols of toluene. This chemoenzymatic approach thus makes available, for the first time, all three possible *cis*-dihydrodiol regioisomers of a monosubstituted benzene.

Introduction

Toluene **1e**, the most abundant anthropogenic hydrocarbon in the environment, is typical of many substituted benzene compounds that are readily biodegraded by wild-type soil bacteria *e.g. Pseudomonas putida*. The initial steps in the oxidative metabolism of toluene **1e** by whole cells of *P. putida* involve (i) toluene dioxygenase (TDO)-catalysed production of the corresponding *cis*-dihydrodiol **2e**$_S$ and (ii) toluene diol dehydrogenase (TDD)-catalysed dehydrogenation of the *cis*-dihydrodiol to yield catechol **3e**, prior to mineralization (Scheme 1). Both TDO and TDD enzymes are extremely versatile in their substrate range and are therefore also capable of catalysing the dihydroxylation and dehydrogenation of other monosubstituted benzenes (*e.g.* **1a–d**) to give the corresponding *cis*-dihydrodiols (**2a**$_S$**–d**$_S$) and catechols (**3a–d**) respectively.

TDO-catalysed oxidation at the 2,3-bond of the aromatic ring of toluene **1e** (X = Me), in common with many other monosubstituted benzene substrates *e.g.* **1b–d**, was found to yield the enantiopure *cis*-dihydrodiol metabolite **2e**$_S$ having an (*S*) configuration at the chiral centre further from the substituent (X). Relatively high yields of the accumulated *cis*-dihydrodiols **2a–e** (>10 g L^{-1}) can be obtained when mutant strains of *P. putida*, *e.g.* 39D or UV4 (with TDD enzyme activity blocked)[1–5] or when *E. coli* recombinant strains with TDO enzyme incorporated, *e.g.* JM109(pDTG601),[6] JM109(pKST11)[7] or DH5α(pDTG927)[8]

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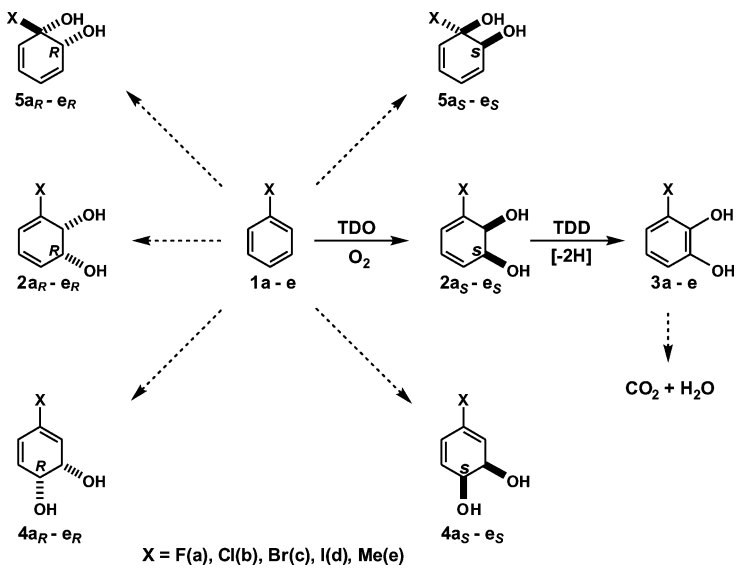


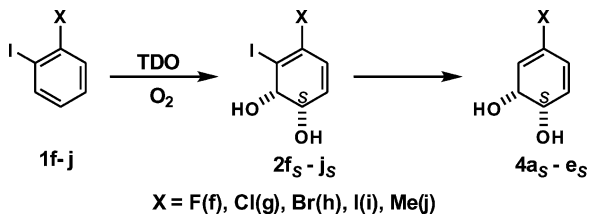
Scheme 1

(with TDD activity absent) are used. The toluene metabolite **2e**$_S$ was the first member of the chiral *cis*-dihydrodiol family to be isolated and identified,[1] and to date more than 300 other examples have been found as a result of dioxygenase-catalysed *cis*-dihydroxylation of both mono- and poly-cyclic arenes.[9–13]

The TDO enzyme has also been, by far, the most widely used biocatalyst for the formation of substituted benzene *cis*-dihydrodiol bioproducts. Despite TDO being involved in biotransformations of a diverse range of monosubstituted benzene substrates **1** (>70), a remarkable degree of regioselectivity (*cis*-dihydroxylation of the 2,3-bond of the arene substrate **1**) and stereoselectivity (*cis*-dihydroxylation from the *Si–Si* face to yield the 1*S* diol enantiomer) has been observed. Only in the case of fluorobenzene **1a**, a detectable proportion (*ca.* 20%) of the *unnatural* 1*R* *cis*-dihydrodiol enantiomer **2a**$_R$ was observed.[4] Differing proportions of the minor 1*R* enantiomer have also been observed, when using chlorobenzene dioxygenase as biocatalyst with several monosubstituted benzene substrates including cinnamonitrile (3%, 1*R*), benzonitrile (6%, 1*R*), benzylcyanide (22%, 1*R*).[14] To date, no example of the TDO-catalysed *cis*-dihydroxylation of either the 3,4-bond (to yield diols **4**) or the 1,2-bond of arene **1** (to yield diols **5**) has been found and thus these *unnatural cis*-dihydrodiol regioisomers and enantiomers (**2**$_R$, **4**$_R$, **4**$_S$, **5**$_R$, **5**$_S$) are not generally available by direct biotransformation.

One example of a *cis*-dihydrodiol of type **4**, resulting from *cis*-dihydroxylation at the 3,4-bond of a monosubstituted benzene, was found using biphenyl as substrate **1** (X = Ph) and a naphthalene dioxygenase enzyme (NDO). Compound **4** (X = Ph) was isolated as a minor metabolite in the presence of the more abundant bioproduct **2** (X = Ph).[15,16] The use of site-directed mutants of NDO caused a major change in regioselectivity and yielded *cis*-dihydrodiol **4** (X = Ph) as the major bioproduct but in reduced yield.[15,16] Recent studies of the biotransformation of toluene have provided tentative GC-MS evidence of the formation of both 2,3- and 3,4-*cis*-dihydrodiol metabolites of toluene using an *ortho*-xylene dioxygenase present in a *Rhodococcus* strain.[17,18] While the 4-catechol metabolite of toluene was isolated, no direct NMR or stereochemical data was reported for the elusive 3,4-*cis*-dihydrodiol precursor **4e**.

Biotransformations of *ortho* substituted iodobenzene derivatives as substrates **1f–j** have been carried out in these laboratories, using *P. putida* UV4 cultures. These studies revealed an exclusive preference for TDO-catalysed *cis*-dihydroxylation of the unsubstituted C=C bond proximate to the iodine atom to yield the corresponding *cis*-dihydrodiols **2f**$_S$**–j**$_S$.[19] Hydrogenolysis (H_2, Pd/C in MeOH) of *cis*-dihydrodiols **2f**$_S$**–j**$_S$ gave the *unnatural* 3,4-*cis*-dihydrodiol regioisomers **4a**$_S$**–e**$_S$ (Scheme 2). While this earlier indirect approach to 3,4-*cis*-dihydrodiols **4a**$_S$**–e**$_S$ was successful, the yields obtained after biotransformation of the more expensive



Scheme 2

ortho substituted iodobenzene substrates, and after removal of the iodine atom, were much lower than those obtained using monosubstituted benzenes. The development of an alternative method, based on monosubstituted benzene substrates, was therefore considered a worthwhile objective.

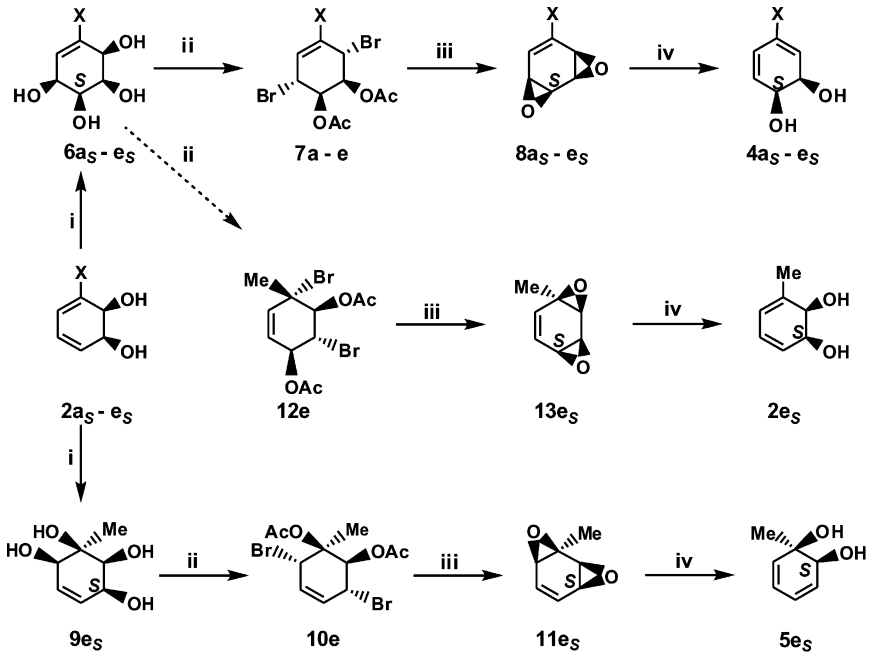
Using other dioxygenase types, enzyme-catalysed *cis*-dihydroxylation at the 1,2-*ipso* bond of monosubstituted benzene substrates **1**, to yield *cis*-dihydrodiols **5**, has been reported (Scheme 1). Thus, when benzoic acid **1** (X = CO_2H) was used as a substrate for a benzoate dioxygenase enzyme,[20,21] it yielded a stable *cis*-dihydrodiol **5** (X = CO_2H) while it was postulated that nitrobenzene **1** (X = NO_2) gave a transient *cis*-dihydrodiol intermediate **5** (X = NO_2) using a nitrobenzene dioxygenase.[22,23] Other types of 1,2-*cis*-dihydrodiols *e.g.* **5a–d**, that could in principle be derived from dioxygenase-catalysed *cis*-dihydroxylation of monohalogenated benzene substrates, will also be too unstable to isolate using either enzyme-catalysed or chemical synthesis methodology. The previously unreported 1,2-*cis*-dihydrodiol derivatives of monoalkylated benzene substrates (*e.g. cis*-dihydrodiol **5e**$_S$ and **5e**$_R$), were expected to be much more stable.

In view of the proven value of the *natural* arene *cis*-dihydrodiols (**2a**$_S$**–e**$_S$) in the synthesis of many natural products,[9–13] and our continued interest in finding new dioxygenase enzymes capable of producing the *unnatural cis*-dihydrodiol regioisomers (*e.g.* **4a**$_S$**–e**$_S$, **5e**$_S$) by direct biotransformation of the corresponding arene precursors, a generally applicable chemoenzymatic approach to their synthesis has been developed and is presented herein (Scheme 2).

Results and discussion

The 2,3-*cis*-dihydrodiols of fluorobenzene **2a**, chlorobenzene **2b**, bromobenzene **2c**, iodobenzene **2d** and toluene **2e** were available from earlier biotransformations of the corresponding monosubstituted benzenes (**1a–e**) using *P. putida* UV4.[5] Catalytic osmylation of *cis*-dihydrodiols **2a**$_S$**–d**$_S$ using the Donohoe conditions[24] (OsO_4, CH_2Cl_2, Me_3NO), resulted in the exclusive *cis*-dihydroxylation of the unsubstituted alkene bonds to yield mainly the *syn*-tetraols **6a**$_S$**–d**$_S$ (71–80% yield). The minor amount (*ca*: 15%) of the late eluting corresponding *anti*-tetraols formed was separated from the early eluting *syn*-tetraols **6a**$_S$**–d**$_S$ by charcoal–celite (1 : 1, w/w) column chromatography (H_2O → 10% EtOH in H_2O). It was assumed that the existing *cis*-diol group played a stereodirecting role through intermolecular H-bonding with an oxo ligand on OsO_4. Under similar conditions, *cis*-dihydroxylation of the toluene *cis*-dihydrodiol **2e**$_S$ resulted in the concomitant *cis*-dihydroxylation of two alkene bonds (C_3=C_4 and C_5= C_6) to yield a mixture of *syn*-tetraols **6e**$_S$ and **9e**$_S$. The mixture of *syn*-tetraols was again separated by charcoal–celite column chromatography to give the pure late eluting isomer **6e**$_S$ (50% yield) and early eluting isomer **9e**$_S$ (40% yield, Scheme 3).

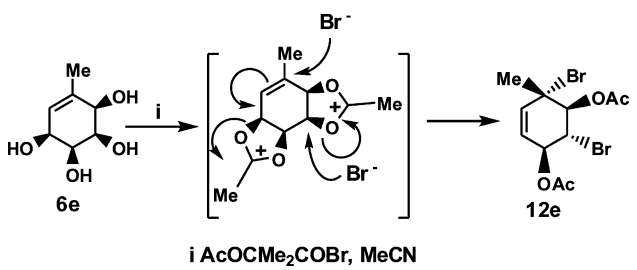
Treatment of *syn*-tetraols **6a**$_S$**–d**$_S$ with 2-acetoxyisobutyryl bromide gave the anticipated *bis*-bromoacetates **7a–d** in relatively high yields (80–87%) due to S_N2 nucleophilic attack of bromide anion at the allylic positions of the dioxolane intermediates. When this procedure was applied to the *syn*-tetraol **6e**$_S$, the desired product **7e** was found to be contaminated with a minor *bis*-bromoacetate isomer **12e** (20% by ^{1}H-NMR analysis). Since the



Scheme 3

bis-bromoacetates rapidly decompose on chromatography, only a small pure sample of the major *bis*-bromoacetate **7e** could be isolated by PLC for characterization. The major portion of the mixture of *bis*-bromoacetates **7e** and **12e** (total yield 82%) was, therefore used without separation in the next stage of the synthesis. The isolation of a pure sample *cis*-diol $\mathbf{2e}_S$, obtained from reduction of the mixture of *syn*-toluene-dioxides $\mathbf{8e}_S$ and $\mathbf{13e}_S$, is consistent with the intermediacy of the dibromoacetate **12e**. This *bis*-bromoacetate intermediate **12e** may have resulted from an initial nucleophilic (S_N2') attack of the bromide anion at the alkene bond of the transient intermediate shown in Scheme 4. While the mechanism is shown as a concerted process, involving a *bis*-dioxolanium intermediate, a stepwise process *via* a mono-dioxolanium intermediates is also possible. Similar treatment of tetraol $\mathbf{9e}_S$ yielded *bis*-bromoacetate **10e** (85% yield) as the sole product (Scheme 3).

Base-catalysed cyclisation of the *bis*-bromoacetates **7a–e** and **10e** (NaOMe, Et_2O) at ambient temperature, gave the corresponding *syn*-benzene dioxides $\mathbf{8a}_S$–$\mathbf{e}_S$ and $\mathbf{11e}_S$ (70–82% yield, Scheme 3) with all being enantiopure (>98% ee) except $\mathbf{8a}_S$ (60% ee). Under these conditions, the residual mixture of dibromodiacetates **7e** and **12e** was converted directly into a corresponding inseparable mixture of *syn*-benzene-dioxides ($\mathbf{8e}_S$ and $\mathbf{13e}_S$, 80 : 20).



Scheme 4

In earlier studies[25,26] of the reactivity of the *anti*-benzene dioxide analogues of *syn*-dioxides $\mathbf{8b}_S$–$\mathbf{d}_S$, under conditions normally associated with the carbonylation of aryl iodides [$Pd(OAc)_2$, CO, K_2CO_3, THF–H_2O], reduction to the corresponding *trans*-dihydrodiols (>85% yield) was observed. Further study has now shown that this unusual benzene dioxide reduction reaction can also be applied to *syn*-dioxides $\mathbf{8a}_S$–$\mathbf{e}_S$ and $\mathbf{11e}_S$ (and $\mathbf{11e}_R$) to give the corresponding 3,4-*cis*-dihydrodiols $\mathbf{4a}_S$–$\mathbf{e}_S$ and 1,2-*cis*-dihydrodiols $\mathbf{5e}_S$ (and $\mathbf{5e}_R$) in acceptable yields (64–77%). Similarly, the mixture of *syn*-benzene-dioxides ($\mathbf{8e}_S$ and $\mathbf{13e}_S$) gave a separable mixture of the corresponding 3,4- and 2,3-*cis*-dihydrodiols of toluene ($\mathbf{4e}_S$ and $\mathbf{2e}_S$). The isolated sample of *cis*-dihydrodiol $\mathbf{2e}_S$ proved to be indistinguishable from the starting compound, thus providing confirmation of the stereochemical integrity of the steps shown in Scheme 3. It was assumed that the mechanism of the reaction of *syn*-benzene dioxides $\mathbf{8a}_S$–$\mathbf{e}_S$, $\mathbf{11e}_S$ and $\mathbf{13e}_S$ to give the corresponding *cis*-dihydrodiols $\mathbf{4a}_S$–$\mathbf{e}_S$, $\mathbf{5e}_S$ and $\mathbf{2e}_S$, involved reduction of the Pd(II) diacetate to Pd(0) with concomitant oxidation of CO to CO_2. This assumption was supported by the observation that both *syn*- and *anti*-benzene dioxides were reduced in similar or lower yields to the corresponding *cis*- and *trans*-dihydrodiols when Pd $(PPh_3)_4$ and K_2CO_3 were used with THF–H_2O as the solvent without CO being present.

The *syn*-dioxides $\mathbf{8a}_S$–$\mathbf{e}_S$, $\mathbf{11e}_S$ and $\mathbf{13e}_S$ all proved to be relatively stable under neutral conditions below 60 °C. However, upon

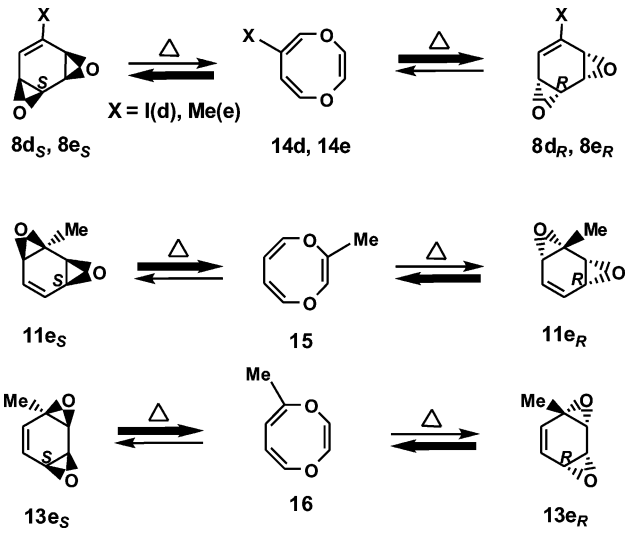
heating at higher temperatures (>70 °C), a retro-Diels–Alder cycloaddition (electrocyclic rearrangement) was expected to occur to form equilibrium mixtures with the corresponding achiral 1,4-dioxocin valence tautomers. This expectation was based on the earlier work by Vogel *et al.* on *syn*-benzene dioxide **8** (X = H) and racemic monosubstituted *syn*-benzene dioxides **8** (X = Br, CO_2H, CHO, COCl). These dioxides were synthesisied by a different route and their thermal equilibration with the corresponding 1,4-dioxocins was also reported.[27–32]

The thermal valence tautomerisation of the *syn*-toluene dioxides $\mathbf{8d}_S$ and $\mathbf{11e}_S$ (*ca.* 77 °C in CCl_4) to the corresponding 1,4-dioxocins **14d** and **15** was followed by ^{1}H-NMR spectroscopy. The proportion of 1,4-dioxocin valence tautomer **15** (>98%) present at equilibrium was higher than that observed for compound **14d** (88%), consistent with a link between substituent position and equilibrium ratio. Similarly, when the mixture of *syn*-toluene dioxides $\mathbf{8e}_S$ and $\mathbf{13e}_S$ was heated under these conditions, NMR analysis of the product mixture indicated that these dioxides were also isomerised to an inseparable mixture of the corresponding 1,4-dioxocins **14e** (40%) and **16** (>98%). Thus, the 1,4-dioxocin tautomers **15** and **16** were formed exclusively (>98%) after electrocyclic rearrangement of corresponding *syn*-toluene dioxides $\mathbf{11e}_S$ and $\mathbf{13e}_S$. The *syn*-toluene dioxide $\mathbf{8e}_S$ was found to have a lower proportion of the corresponding 1,4-dioxocin tautomer **14e** (40%) present at equilibrium. A similar link between substitution patterns and benzene oxide–oxepin valence tautomeric ratios was found earlier and rationalised in terms of the maximum number of low energy valence-bond structures that can be drawn and this was supported by MINDO/3 calculations.[33] The variation in arene dioxide–1,4-dioxocin valence tautomer ratios after thermal equilibration could also be explained on a similar basis.

The thermal equilibration of *syn*-toluene dioxides, *e.g.* $\mathbf{8e}_S$, $\mathbf{11e}_S$ and $\mathbf{13e}_S$ with the corresponding 1,4-dioxocins, *e.g.* **14e**, **15** and **16**, was assumed to involve a novel concomitant racemisation at four chiral centres. In order to provide confirmation of this rare phenomenon, the thermal racemisation–valence tautomerisation process (*ca.* 85 °C in toluene), for a typical *syn*-benzene dioxide (*e.g.* $\mathbf{8d}_S$), was followed by polarimetry, ^{1}H-NMR, and chiral stationary phase HPLC analyses. Thus, *syn*-benzene dioxide $\mathbf{8d}_S$ was heated at 85 °C in toluene until equilibrium between $\mathbf{8d}_S$ and **14d** (12 : 88) was established (*ca.* 2 h) (Scheme 5). The sample of the *syn*-benzene dioxide $\mathbf{8d}_S$ present, after complete equilibration had occurred, was isolated by PLC and was found to be racemic. When a pure sample of the 1,4-dioxocin **14d** was heated under similar conditions, an identical equilibrium ratio for compounds $\mathbf{8d}_S$ and **14d** was observed.

In principle, the 1,4-dioxocins **14d**, **14e**, **15** and **16** could be considered aromatic compounds as each contains 10π electrons and may thus adopt a planar conformation. Earlier X-ray crystallographic studies of similar 1,4-dioxocins **14** (X = COCl and a γ-pyrone)[29] indicated that while in one case the ring was essentially planar, in the second example the ring was non-planar, having a twist-boat–chair conformation in the crystalline phase. The preferred conformation of the 1,4-dioxocin ring system in the solution phase remains to be investigated.

The availability of the 2,3-*cis*-dihydrodiol of toluene with an excess of the abnormal (1*R*)-enantiomer ($\mathbf{2e}_R$ and $\mathbf{2e}_S$, 80 : 20), from an earlier biotransformation of 4-iodotoluene followed by



Scheme 5

hydrogenolysis,[34,35] allowed the corresponding 1,2-*cis*-dihydrodiol $\mathbf{5e}_R$ and 3,4-*cis*-dihydrodiol $\mathbf{4e}_R$ of toluene (*ca.* 60% ee) to be synthesised, using the methods shown in Scheme 3. It was also possible to increase the enantiopurity of this abnormal 2,3-*cis*-dihydrodiol enantiomer $\mathbf{2e}_R$ from 60% ee up to >95% by fractional crystallisation or by a *cis*-diol dehydrogenase-catalysed kinetic resolution process. When a small sample of *cis*-dihydrodiols $\mathbf{4e}_R$ (*ca.* 60% ee) was biotransformed, using naphthalene *cis*-diol dehydrogenase enzyme, present in the recombinant strain, *E. coli* narB by the reported method,[36] the recovered *cis*-dihydrodiol $\mathbf{4e}_R$ from the culture medium was found to be enantiopure (>98% ee).

Conclusion

A generally applicable synthetic route to a series of unnatural 3,4-*cis*-dihydrodiols $\mathbf{4}_S$, from the corresponding natural 2,3-*cis*-dihydrodiols $\mathbf{2}_S$, has been developed. This method has also been applied to obtain enantiomers, $\mathbf{5e}_S$ and $\mathbf{5e}_R$, of the unnatural toluene 1,2-*cis*-dihydrodiol from the 2,3-isomers, $\mathbf{2e}_S$ and $\mathbf{2e}_R$. The racemisation and isomerisation studies of the *syn*-benzene dioxide intermediates $\mathbf{8d}_S$, $\mathbf{8e}_S$, $\mathbf{11e}_S$ and $\mathbf{13e}_S$ to give 1,4-dioxocins **14d**, **14e**, **15** and **16** have also been carried out.

Experimental

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Avance DPX-300 and DPX-500 instruments and mass spectra were run at 70 eV, on a VG Autospec Mass Spectrometer, using a heated inlet system. Accurate molecular weights were determined, by the peak matching method, with perfluorokerosene as standard. Elemental microanalyses were carried out on a Perkin-Elmer 2400 CHN microanalyser. For optical rotation ($[\alpha]_D$) measurements (*ca.* 20 °C, 10^{-1} deg cm^2 g^{-1}), a Perkin-Elmer 214 polarimeter was used. Flash column chromatography and PLC were performed on Merck Kieselgel type 60 (250–400 mesh) and $PF_{254/366}$ respectively. Merck Kieselgel type $60F_{254}$ analytical plates were used for TLC. Samples of *cis*-dihydrodiols $\mathbf{2a}_S$–$\mathbf{e}_S$ and the *cis*-dihydrodiol derivative from 4-iodotoluene were available from earlier studies.[24,35]

Catalytic *cis*-dihydroxylation of *cis*-dihydrodiols 2a$_S$–d$_S$

To a solution of the diols **2a**$_S$ (*ca.* 60% ee), **2b**$_S$–**d**$_S$ (>98% ee, 8 mmol), in CH_2Cl_2 (160 cm^3), was added trimethylamine-*N*-oxide dihydrate (11 mmol) and a catalytic amount of osmium tetroxide (*ca.* 0.002 g). The reaction mixture was left stirring at room temperature until the dihydroxylation was completed (3 days, TLC analysis). A saturated solution of sodium metabisulfite (5 cm^3) was added and the reaction mixture stirred (0.5 h) at room temperature. The solvents were removed *in vacuo*, and the residual crude product purified by charcoal–celite (1 : 1, w/w) column chromatography (H_2O → 10% EtOH in H_2O). The pure tetraols **6a**$_S$–**d**$_S$ were obtained in the early eluting fractions. Catalytic *cis*-dihydroxylation (OsO_4) of *cis*-diol **2e**$_S$ (>98% ee) gave a mixture of diastereoisomeric tetraols **6e** and **9e**. This was also separated by charcoal–celite column, tetraol **9e** eluted before tetraol **6e**. An enantioenriched (*ca.* 60% ee) sample of *cis*-dihydrodiol **2e**$_R$, available from earlier studies, was treated in a similar manner to *cis*-diol **2e**$_S$.[34,35] Compound **6c**$_S$ had been reported earlier.[37]

(1*S*,2*S*,3*S*,4*S*)-5-Fluoro-5-cyclohexene-1,2,3,4-tetraol 6a$_S$

Colourless oil (1.05 g, 80%); $[\alpha]_D$ −3.0 (*c* 0.80, MeOH); *ca.* 60% ee, (found: M$^+$ − H_2O, 146.0378. $C_6H_7FO_3$ requires 146.0379); δ_H(500 MHz, CD_3OD) 3.92–3.94 (2 H, m, 2-H and 3-H), 4.32–4.34 (2 H, m, 1-H and 4-H), 5.43 (1 H, dd, $J_{6,F}$ 15.3, $J_{6,1}$ 3.7, 6-H); δ_C(125 MHz, CD_3OD) 66.66, 66.75, 68.23, 69.91, 69.99, 106.20, 160.08; *m*/*z* (EI) 146 (M$^+$ − H_2O, 91%), 128 (80), 1117 (82), 104 (100), 75 (82), 60 (29), 55 (31), 51 (18), 41 (48), 31 (18).

(1*S*,2*S*,3*R*,4*R*)-5-Methyl-5-cyclohexene-1,2,3,4-tetraol 6e$_S$

Colourless oil (0.64 g, 50%); $[\alpha]_D$ −1.0 (*c* 0.94, MeOH); (found: M$^+$, 160.0729. $C_7H_{12}O_4$ requires 160.0736); δ_H(500 MHz, D_2O) 1.62 (3 H, s, Me), 4.12 (1 H, ddd, $J_{1,6}$ 3.2, $J_{1,2}$ 4.5, $J_{1,3}$ 1.8, 1-H), 4.22 (1 H, ddd, $J_{1,4}$ 0.6, $J_{3,2}$ 3.3, $J_{3,1}$ 1.5, 3-H), 4.32 (1 H, dd, $J_{4,6}$ 0.7, $J_{4,3}$ 1.7, 4-H), 4.47 (1 H, ddd, $J_{2,1}$ 4.4, $J_{2,3}$ 3.0, $J_{2,6}$ 1.6, 2-H), 5.80 (1 H, ddd, $J_{6,1}$ 3.2, $J_{6,2}$ 1.5, $J_{6,4}$ 0.7, 6-H); δ_C(125 MHz, D_2O) 19.56, 68.22, 70.19, 70.73, 71.62, 123.96, 137.17. *m*/*z* 160 (M$^+$, 6%), 142 (33), 124 (89), 118 (90), 113 (87), 111 (84), 109 (42), 98 (89), 87 (60), 82 (87), 77 (91), 73 (99), 71 (85), 65 (87), 59 (92), 55 (90), 50 (96), 45 (93), 40 (91), 38 (100).

(1*R*,2*R*,3*S*,4*S*)-5-Methyl-5-cyclohexene-1,2,3,4-tetraol 6e$_R$

$[\alpha]_D$ +0.7 (*c* 0.44, MeOH); *ca.* 60% ee.

(1*R*,2*R*,3*S*,4*S*)-2-Methyl-5-cyclohexene-1,2,3,4-tetraol 9e$_S$

Colourless viscous oil (0.515 g, 40%); $[\alpha]_D$ +6 (*c* 0.82, MeOH); (found: M$^+$, 160.0726. $C_7H_{12}O_4$ requires 160.0736); δ_H(500 MHz, D_2O) 1.11 (3 H, s, Me), 3.53 (1 H, d, $J_{3,4}$ 4.5, 3-H), 3.82 (1 H, d, $J_{1,6}$ 3.0, 1-H), 4.09 (1 H, dd, $J_{4,3}$ 4.5, $J_{4,5}$ 2.5, 4-H), 5.77 (1 H, dd, $J_{5,6}$ 10.2, $J_{5,4}$ 2.5, 6-H); δ_C(125 MHz, D_2O) 21.5, 67.39, 71.98, 72.80, 73.96, 128.19, 130.46; *m*/*z* (EI) 160 (M$^+$, 4%), 142 (32), 124 (82), 87 (87), 81 (79), 71 (80), 69 (85), 58 (87), 56 (82), 45 (93), 42 (88), 40 (81), 53 (44), 45 (25), 43 (83), 41 (71), 39 (66), 21 (50), 29 (100).

(1*S*,2*S*,3*R*,4*R*)-2-Methyl-5-cyclohexene-1,2,3,4-tetraol 9e$_R$

$[\alpha]_D$ −4.0 (*c* 0.67, MeOH); *ca.* 60% ee.

Syntheses of bis-bromoacetates 7a–e and 10e

To a stirred suspension of the tetraol (3 mmol), in dry acetonitrile (10 cm^3) at 0 °C under a nitrogen atmosphere, 1-bromocarbonyl-1-methylethylacetate (2.5 mol equiv.) was added drop-wise. The reaction mixture was kept stirring at 0 °C for 15 min and then at room temperature for another 2 h. The solvent was removed under reduced pressure and the residue thoroughly partitioned by shaking with a mixture of diethyl ether (50 cm^3) and 3% aqueous $NaHCO_3$ (40 cm^3). The ether extract was washed with water, dried (Na_2SO_4), and concentrated to afford a crude sample of bis-bromoacetate which was purified by PLC (15% EtOAc in hexane) or by recrystallisation.

(1*R*,2*R*,5*R*,6*S*)-6-(Acetyloxy)-2,5-dibromo-3-fluoro-3-cyclohexenyl acetate 7a

Colourless oil (0.756 g, 80%); R_f 0.40; $[\alpha]_D$ +32 (*c* 0.78, $CHCl_3$); (found: M$^+$ − OAc, 314.9883. $C_8H_8Br_2FO_2$ requires 314.9875); δ_H(500 MHz, $CDCl_3$) 2.11 (3 H, s, OCOMe), 2.13 (3 H, s, OCOMe), 4.52 (1 H, br s, 5-H), 4.76 (1 H, dd, $J_{2,F}$ 9.9, $J_{2,1}$ 6.3, 2-H), 5.62 (2 H, m, 1-H and 6-H), 5.68 (1 H, dd, $J_{4,F}$ 11.9, $J_{4,5}$ 3.4, 4-H); δ_C(125 MHz, $CDCl_3$) 20.64, 20.66, 39.40, 41.19, 71.08, 71.96, 108.00, 154.57, 169.28, 169.42; *m*/*z* (EI) 315 (M$^+$ − OAc, 57%), 297 (11), 295 (12), 235 (18), 233 (19), 193 (43), 129 (52), 112 (49), 101 (81), 70 (33), 59 (72), 43 (100).

(1*S*,2*S*,5*R*,6*R*)-6-(Acetyloxy)-2,5-dibromo-3-methyl-3-cyclohexenyl acetate 7e

A small portion of the diastereoisomeric mixture **7e** and **12e** (0.87 g, 82%), on separation by PLC (15% EtOAc in hexane), gave a pure sample of bis-bromoacetate **7e** as a light yellow oil, R_f 0.35; $[\alpha]_D$ −17 (*c* 0.86, $CHCl_3$); (found: M$^+$ − Me, 354.8991. $C_{10}H_{11}Br_2O_4$ requires 354.9003); δ_H(500 MHz, $CDCl_3$) 1.96 (3 H, s, Me), 2.10 (6 H, s, 2 × OCOMe), 4.41 (1 H, d, $J_{2,1}$ 4.0, 2-H), 4.75 (1 H, dd, $J_{5,6}$ 7.7, $J_{5,4}$ 3.1, 5-H), 5.55 (1 H, dd, $J_{1,2}$ 4.1, $J_{1,6}$ 2.5, 1-H), 5.67 (1 H, dd, $J_{6,5}$ 7.7, $J_{6,1}$ 2.5, 6-H), 5.77 (1 H, d, $J_{4,5}$ 3.1, 4-H); δ_C(125 MHz, $CDCl_3$) 20.74, 20.75, 21.60, 44.62, 47.30, 71.50, 72.43, 127.15, 133.98, 169.58, 169.74; *m*/*z* (EI) 355 (M$^+$ − Me, 70%), 311 (78), 253 (84), 231 (80), 229 (81) 185 (19), 187 (20), 108 (61), 57 (16), 43 (100).

(1*R*,2*R*,5*S*,6*S*)-6-(Acetyloxy)-2,5-dibromo-3-methyl-3-cyclohexenyl acetate 7e′

$[\alpha]_D$ +11.0 (*c* 0.3, $CHCl_3$); *ca.* 60% ee.

(1*R*,2*R*,5*S*,6*S*)-6-(Acetyloxy)-2,5-dibromo-6-methyl-3-cyclohexenyl acetate 10e

Colourless oil (0.85 g, 80%); $[\alpha]_D$ −123 (*c* 0.56, $CHCl_3$); (found: M$^+$, 369.9254. $C_{11}H_{14}Br_2O_4$ requires 369.9238); δ_H(500 MHz, $CDCl_3$) 1.45 (3 H, s, Me), 1.97 (3 H, s, OCOMe), 2.16 (3 H, s, OCOMe), 4.57 (1 H, dd, $J_{2,1}$ 8.1, $J_{2,3}$ 3.2, 2-H), 5.79 (1 H, dd, $J_{3,4}$ 12.5, $J_{3,2}$ 3.2, 3-H), 5.86 (1 H, dd, $J_{4,3}$ 12.5, $J_{4,5}$ 5.2, 4-H), 6.09 (1 H, d, $J_{1,2}$ 8.1, 1-H), 6.26 (1 H, m, $J_{5,4}$ 5.2, 5-H); *m*/*z* (EI) 370 (M$^+$, 100%),

311 (42), 252 (53), 231 (13), 229 (14), 191 (50), 189 (51), 167 (99), 125 (87), 108 (85), 83 (21), 43 (91).

(1*S*,2*S*,5*R*,6*R*)-6-(Acetyloxy)-2,5-dibromo-6-methyl-3-cyclohexenyl acetate 10e′

$[\alpha]_D$ +76.0 (*c* 0.61, $CHCl_3$); *ca.* 60% ee.

Syntheses of *syn*-benzene dioxides $8a_S$–e_S, $11e_S$ and $11e_R$

To a solution of bis-bromoacetate (1.5 mmol) in dry ether (25 cm^3) at 0 °C, was added sodium methoxide (4 mol equiv.) and the mixture stirred at 0 °C for 15 min and then at room temperature (3 h). The reaction mixture was filtered through a pad of celite, the solid residue trapped on the pad washed with ether, and the combined filtrate concentrated at atmospheric pressure to yield the crude dioxide.

(1*S*,2*S*,4*S*,7*S*)-5-Fluoro-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene $8a_S$

Colourless crystals (0.135 g, 70%); mp 40–45 °C; $[\alpha]_D$ −37 (*c* 0.59, $CHCl_3$); (found: M^+, 128.0270. $C_6H_5FO_2$ requires 128.0273); δ_H(500 MHz, $CDCl_3$) 3.54 (1 H, dd, $J_{2,4}$ 4.0, $J_{2,1}$ 3.6, 2-H), 3.62 (1 H, dd, $J_{4,F}$ 8.2, $J_{4,2}$ 4.0, 4-H), 3.69 (1 H, dd, $J_{7,1}$ 3.2, $J_{7,6}$ 3.7, 7-H), 3.85 (1 H, dd, $J_{1,2}$ 3.6, $J_{1,7}$ 3.2, 1-H), 5.89 (1 H, dd, $J_{6,F}$ 13.2, $J_{6,7}$ 3.7, 6-H); *m*/*z* (EI) 128 (M^+, 14%), 110 (17), 97 (38), 83 (44), 73 (23), 69 (37), 43 (100), 39 (25).

(1*S*,2*S*,4*S*,7*S*)-5-Methyl-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene $8e_S$

Colourless oil, $[\alpha]_D$ +78 (*c* 0.76, $CHCl_3$); (found: M^+, 124.0527, $C_7H_8O_2$ requires 124.0524); δ_H(500 MHz, $CDCl_3$) 2.05 (3 H, s, Me), 3.24 (1 H, d, $J_{4,2}$ 3.2, 4-H), 3.39 (1 H, dd, $J_{7,1}$ 3.2, $J_{7,6}$ 3.6, 7-H), 3.67 (1 H, dd, $J_{1,2} = J_{1,7}$ 3.3, 1-H), 3.69 (1 H, dd, $J_{2,4} = J_{2,1}$ 3.3, 2-H), 6.12 (1 H, d, $J_{6,7}$ 3.6, 6-H); δ_C(125 MHz, $CDCl_3$) 22.60, 47.00, 47.47, 47.89, 49.22, 123.43, 139.85; *m*/*z* (EI) 124 (M^+, 2%), 106 (57), 85 (55), 81 (61), 51 (100), 43 (78), 37 (22).

(1*R*,2*R*,4*R*,7*R*)-5-Methyl-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene $8e_R$

$[\alpha]_D$ −50 (*c* 0.55, $CHCl_3$); *ca.* 60% ee.

(1*R*,2*S*,4*S*,7*R*)-1-Methyl-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene $11e_S$

Colourless oil (0.13 g, 70%); $[\alpha]_D$ −67 (*c* 0.56, $CHCl_3$); (found: M^+, 124.0593, $C_7H_8O_2$ requires 124.0524); δ_H(500 MHz, $CDCl_3$) 1.57 (3 H, s, Me), 2.93 (1 H, dd, $J_{4,2}$ 4.1, $J_{4,5}$ 2.6, 4-H), 3.13 (1 H, d, $J_{7,6}$ 2.6, 7-H), 3.60 (1 H, d, $J_{2,4}$ 4.1, 2-H), 6.06 (2 H, m, 6-H, 5-H); δ_C(125 MHz, $CDCl_3$) 20.43, 48.00, 53.27, 58.03, 60.17, 129.31, 130.63; *m*/*z* (EI) 124 (M^+, 5%), 106 (72), 95 (41), 77 (36), 57 (28), 43 (100), 29 (20).

(1*S*,2*R*,4*R*,7*S*)-1-Methyl-3,8-dioxa-tricyclo[5.1.0.0^{2,4}]oct-5-ene $11e_R$

$[\alpha]_D$ +44 (*c* 0.33, $CHCl_3$); *ca.* 60% ee.

Synthesis of *cis*-dihydrodiols $4a_S$–e_S, $5e_S$ and $5e_R$

A mixture of each of the dioxides $8a_S$–e_S, $11e_S$, $11e_R$ (0.6 mmol), THF (1 cm^3), water (0.4 cm^3) and K_2CO_3 (4 mol equiv.) was stirred in the presence of a catalytic amount of palladium(II) acetate (*ca.* 0.01 g) under an atmosphere of CO until the starting material had reacted completely (*ca.* 12 h). The catalyst was filtered off and saturated NaCl solution (6 cm^3) was added to the filtrate. The reaction mixture was extracted with EtOAc (3 × 10 cm^3), the extract dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude product (from the reactions of dioxides $8a_S$–d_S, $11e_S$ and $11e_R$) by PLC (50% EtOAc in hexane), yielded the corresponding *cis*-dihydrodiols $4a_S$–d_S, $5e_S$ and $5e_R$. The product, from the reaction of a crude mixture of dioxides $8e_S$ and $13e_S$ on multiple elution PLC (30% EtOAc in hexane) yielded pure samples of *cis*-dihydrodiols $4e_S$ and $2e_S$.

(1*S*,2*R*)-4-Fluoro-3,5-cyclohexadiene-1,2-diol $4a_S$

Colourless crystals (0.05 g, 64%); R_f 0.38 (50% EtOAc in hexane); mp 70–74 °C (from CH_2Cl_2–hexane); $[\alpha]_D$ −80 (*c* 0.50, MeOH); *ca.* 60% ee, (found: M^+, 130.0428. $C_6H_7FO_2$ requires 130.0430); δ_H(500 MHz, $CDCl_3$) 1.56 (1 H, br s, OH), 4.29 (1 H, m, 2-H), 4.44 (1 H, m, 1-H), 5.48 (1 H, m, 6-H), 5.88 (1 H, m, 5-H), 6.00 (1 H, m, 3-H); δ_C(125 MHz, $CDCl_3$) 66.57, 68.85, 119.98, 120.26, 135.65, 135.73, 160.00; *m*/*z* (EI) 130 (M^+, 65%), 112 (16), 101 (57), 95 (13), 84 (100), 73 (32), 64 (24), 57 (55), 53 (94), 51 (37), 43 (41), 39 (44).

(1*S*,2*R*)-4-Methyl-3,5-cyclohexadiene-1,2-diol $4e_S$

Colourless crystals (0.04 g, 53%); mp 78–80 °C (from EtOAc–hexane); $[\alpha]_D$ −16 (*c* 0.36, MeOH); >98% ee, (found: M^+, 126.0056. $C_7H_{10}O_2$ requires 126.0681); δ_H(500 MHz, $CDCl_3$) 1.79 (3 H, s, Me), 4.13 (2 H, dd, $J_{2,3}$ 4.8, $J_{2,1}$ 4.8, 2-H), 4.25 (1 H, m, 1-H), 5.68 (1 H, d, $J_{3,2}$ 4.8, 3-H), 5.82 (1 H, ddd, $J_{5,6}$ 9.7, $J_{5,3} = J_{5,1}$ 1.6, 5-H), 5.90 (1 H, dd, $J_{6,5}$ 9.7, $J_{6,1}$ 3.2, 6-H); δ_C(125 MHz, $CDCl_3$) 21.25, 67.32, 68.23, 123.13, 126.16, 130.44, 133.69; *m*/*z* (EI) 126 (M^+, 55%), 111 (34), 108 (10), 93 (29), 80 (100), 77 (42), 66 (6), 57 (10), 55 (45), 43 (35).

(1*R*,2*S*)-4-Methyl-3,5-cyclohexadiene-1,2-diol $4e_R$

$[\alpha]_D$ + 11 (*c* 0.30, MeOH); *ca.* 60% ee.

(1*S*,2*R*)-3-Methyl-3,5-cyclohexadiene-1,2-diol $2e_S$

White crystalline solid (0.01 g, 13%); mp 56–58 °C (EtOAc–hexane); $[\alpha]_D$ +26 (*c* 1.76, MeOH); >98% ee. The isolated product was identical to *cis*-dihydrodiol $2e_S$ used as a synthetic precursor.

(1*R*,2*S*)-1-Methyl-3,5-cyclohexadiene-1,2-diol $5e_S$

Colourless oil (0.048 g, 65%); $[\alpha]_D$ −19 (*c* 0.57, MeOH); >98% ee, R_f 0.35 (50% EtOAc in hexane); (found: M^+, 126.0677. $C_7H_{10}O_2$ requires 126.0681); δ_H(500 MHz, $CDCl_3$) 1.27 (3 H, s, Me), 4.46 (1 H, br s, 2-H), 5.71–5.80 (4 H, m, 3-H, 4-H, 5-H, 6-H); δ_C(125 MHz, $CDCl_3$) 17.88, 74.35, 75.53, 122.02, 122.54, 130.63, 134.85; *m*/*z* (EI) 126 (M^+, 13%), 108 (14), 107 (9), 97 (17), 81 (13), 77 (17), 65 (13), 55 (25), 43 (100), 39 (24).

(1*S*,2*R*)-1-Methyl-3,5-cyclohexadiene-1,2-diol 5e$_R$

$[a]_D$ +12 (*c* 0.77, MeOH); *ca.* 60% ee.

Synthesis of 1,4-dioxocins 14d and 15

syn-Benzene dioxides **8d**$_S$ and **11e**$_S$ (0.25 mmol) were each dissolved in dry CCl_4 (10 cm^3). The solution was heated at 77 °C for 10 h and samples removed periodically for analysis. The mixture was then cooled and the solvent removed under reduced pressure to yield mixtures of 1,4-dioxocin **14d** and *syn*-dioxide **8d**$_S$ (or **15** and **11e**$_S$). Purification by chromatography on silica gel (10% Et_2O–hexane) gave the pure 1,4-dioxocins (**14d** and **15**) and the residual *syn*-dioxides (**8d**$_S$ and **11e**$_S$).

6-Iodo-1,4-dioxocin 14d

Colourless low mp solid (0.036 g, 61%); R_f 0.76 (25% Et_2O in hexane); (found: C 30.7; H 2.2. $C_6H_5IO_2$ requires C 30.54; H 2.1%); δ_H(500 MHz, $CDCl_3$) 5.55 (1 H, d, $J_{7,8}$ 6.9, 7-H), 5.83 (1 H, d, $J_{2,3}$ 4.3, 2-H), 5.87 (1 H, d, $J_{3,2}$ 4.3, 3-H), 6.16 (1 H, d, $J_{8,7}$ 6.9, 8-H), 6.86 (1 H, s, 5-H); δ_C(75 MHz, $CDCl_3$) 114.34, 127.80, 127.84, 141.35, 145.74.

2-Methyl-1,4-dioxocin 15

Off-white low mp solid (0.02 g, 65%); R_f 0.74 (25% Et_2O in hexane); (found: M^+, 124.0531. $C_7H_8O_2$ requires 124.0524); δ_H(500 MHz, $CDCl_3$) 2.21 (3 H, s, CH_3), 4.93 (2 H, m, 6-H, 7-H), 6.12 (1 H, s, 3-H), 6.36 (1 H, d, $J_{8,7}$ 3.9, 8-H), 6.40 (1 H, d, $J_{5,6}$ 3.9, 5-H); δ_C(75 MHz, $CDCl_3$) 17.65, 106.54, 107.62, 112.74, 130.69, 145.38, 146.90.

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