Accessing the antipodal series in microbial arene oxidation: a novel diene rearrangement induced by tricarbonyliron(0) complexation†

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A cyclohexadiene ligand prepared by microbial arene 1,2-dihydroxylation undergoes spontaneous rearrangement upon complexation to tricarbonyliron(0). Subsequent iron removal affords a novel route to formal arene 2,3-dihydroxylation products enantiomeric to those obtainable by direct microbial arene oxidation.

Since the first report in 1968, enzymatic dihydroxylation of aromatic substrates to afford enantiopure building blocks for synthesis has become established methodology. In excess of 400 arene cis-diol products have been reported. The vast majority of these are produced by organisms expressing toluene dioxygenase (TDO), naphthalene dioxygenase (NDO) and biphenyl dioxygenase (BPDO) enzymes. These metabolise substituted arene substrates in a regio- and stereoselective fashion. A reliable predictive model has been reported for such transformations and the sense of enantioinduction is conserved across organisms and substrates (Scheme 1a). In contrast, organisms expressing benzoate dioxygenase (BZDO) enzymes oxidise benzoic acids in a process that exhibits not only different regioselectivity, but also the opposite sense of enantioinduction. For example, R. eutrophus B9, P. putida U103 and P. putida KTSY01 (pSYM01) oxidise benzoic acid to benzoate 1,2-cis-dihydrodiol (Scheme 1b). Diol 4 has proved to be a versatile chiron for synthesis, having seen several applications, most notably in the synthesis of tetracycline antibiotics.

Scheme 1. Regio- and stereoselectivity of dioxygenases.

Dienes such as 2 and 4 may be derivatised as the corresponding tricarbonyliron(0) complexes and we have recently shown that the methyl ester of 4 coordinates to iron with complete facial selectivity. The sole isomer obtained is that in which the diol is endo (6, Scheme 2a), which is noteworthy since the diene presents Lewis basic functionality on both faces. Coordination to iron permits stereoselective ligand modification at the carbons adjacent to the diene, by means of cationic $\eta^2$-dienyl intermediates. In this context we sought to access a complex in which the diol was exo, by protecting the diol as an acetonide (Scheme 2b). We reasoned that additional steric bulk on the lower face would disfavour the precoordination of the iron to a Lewis basic diol oxygen lone pair, which has been proposed to rationalise the facial selectivity observed previously.

In the event, treatment of acetonide 7 with Fe$_2$(CO)$_9$ in THF gave 9, in which the acetonide was indeed exo, but an isomerisation had occurred such that the ester was now conjugated to the diene (Scheme 3). The structure of 9 was determined by X-ray crystallography (Figure 1).

Scheme 2. Lewis basic functionality directs iron coordination.

Scheme 3. Diene rearrangement upon complexation.

Fig. 1. X-Ray structure of 9. (50% Thermal ellipsoids for all non-hydrogen atoms).

Isomerised complex 9 underwent facile oxidative
demetallation with trimethylamine N-oxide to afford uncomplexed diene (2S,3R)-11 (Scheme 4). The enantiopurity of (2S,3R)-11 was determined to be >95% e.e. by means of ester reduction and subsequent formation of Mosher’s ester derivatives.\(^\text{13}\) Attempted removal of the acetonide in (2S,3R)-11 upon exposure to BnBr and acid proved unsuccessful due to facile dehydroylation/rearomatization. However, in preliminary experiments, iodine in methanol\(^\text{13}\) has been observed by NMR to afford 12 from (2S,3R)-11, albeit with a degree of concomitant rearomatization.

![Scheme 4. Deprotection of 9.](image)

Direct microbial oxidation of methyl benzoate to afford a 2,3-diol and subsequent acetonide formation has been reported.\(^\text{14,15}\) However, in this instance, the opposite enantiomer, (2R,3S)-11 was obtained. Indeed, the enantiomer reported here, (2S,3R)-11, has not been described to date; this iron-mediated diene rearrangement represents a new route to an arene 2,3-cis diol derivative antipodal to that obtained by direct biooxidation. Thus far, the synthetic utility of arene 2,3-cis-diols has been constrained by the comparative difficulty in accessing the non-natural enantiomeric series. We anticipate that the transformation reported here will be of great synthetic utility, for example in allowing the synthesis of D-configured carbasugars (many L-carbasugars have been synthesised from diols of type 2; the synthesis of (2S,3R)-11 reported here constitutes formal syntheses of carba-β-D-galactopyranoside, carba-β-D-talopyranoside and carba-α-D-talopyranoside\(^\text{15}\). In addition, elaboration of the ester will permit access to numerous antipodal arene 2,3-cis diols not accessible by other means.

![Scheme 5. Isotopic labelling of substrate confirms acetonide migration.](image)

As regards the mechanism of formation of 9, isotopic labelling studies were undertaken to ascertain the identity of the migrating group. Biooxidation of para-deuterobenzoic acid afforded 13, which then permitted the preparation of 15 (Scheme 5). Regioisomer 14 was not formed, confirming that 9 arises through migration of the acetonide and not the carboxymethyl group.

![Scheme 6. Possible formation of 9 via cationic η5-dienyln intermediate.](image)
by this method for numerous tricarbonyliron(0)diene complexes. The calculated value of $\Delta G^{\circ}_{\text{298}}$ for 9 is comparable to that for the analogous tropone complex ($\Delta G^{\circ}_{\text{298}} = 53.1 \pm 2.1 \text{ kJ mol}^{-1}$). In summary, we have defined a rearrangement route to arene 2,3-cis diol derivatives of non-natural configuration. The complex through which this rearrangement is realised exhibits hindered ligand rotation, for which thermodynamic data are presented. Our approach is complementary to other strategies reported previously for achieving this “enantionic switch”. For example, substituted isobenzofenes can undergo 2,3-dihydroxylation followed by reductive iodine removal, but this can preclude the use of diol derivatives possessing reductively labile functionality. The conceptually distinct approach of enantiodivergent synthesis has also been employed, requiring that two different synthetic routes be established. In contrast, the approach we describe utilises only oxidative conditions and will permit access to both enantiomers of a given target by the same synthetic pathway. Investigations to elucidate further the mechanism of formation of 9 and to demonstrate the scope of this transformation are underway in our laboratory and will be reported in due course.

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### Notes and references

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### References

12. Crystal data for 9: $M_{\text{r}}$Fe$_2$, $M = 350.10$, monoclinic, $a = 10.1710(4)$Å $b = 7.2170(4)$Å $c = 10.6320(6)$Å $\alpha = 110.4263(3)^\circ$ $V = 731.36(6)$Å$^3$ $T = 150(2)$ K, space group $P2_1$, $Z = 2$, $\mu$(MoK$\alpha$) = 1.063 mm$^{-1}$, 6905 reflections measured, 3715 independent reflections (20 = 8.57-30.45°, $R_{int} = 0.0685$) against 203 parameters gave $R_1 = 0.0385$ and $wR_2 = 0.1056$ [$R_1(>2\sigma(I))$ and $R_2 = 0.0404$ and $wR_2 = 0.1107$ (for all data). The goodness of fit on $F^2$ was 1.054. Flack parameter = -0.003(16). W. Yang and M. Koreeda, *J. Org. Chem.*, 1992, 57, 3836; W. A. Szarek, A. Zamojski, K. N. Tiwari and E. R. Ison, *Tetrahedron Lett.*, 1986, 27, 3827.