**Benzoate dioxygenase from *Ralstonia eutropha* B9 — unusual regiochemistry of dihydroxylation permits rapid access to novel chirons†**

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Oxidation of benzoic acid by a microorganism expressing benzoate dioxygenase leads to the formation of an unusual *ipso, ortho* arene *cis*-diol in sufficient quantities to be useful for synthesis. This homochiral diol possesses an array of differentiated functionality which can be exploited to access diverse highly oxygenated structures by concise synthetic sequences.

**Introduction**

Of the various oxygenases that have found use in biocatalysis, it is arguably the arene dioxygenases which add the most value in terms of the synthetic versatility of the products they produce.1 The direct transformation of an aromatic ring into a dearomatised cyclohexadiene diol (Scheme 1) is a reaction that has very little precedent in organic chemistry2 and is therefore appealing to access rapidly uncharted chemical space. In wild-type organisms, these arene *cis*-diols are usually fleeting metabolic intermediates.3 However, mutants in which the subsequent enzyme in the metabolic pathway is blocked are able to accumulate these diols and they can be isolated in synthetically useful quantities.

The densely-packed, diverse functionality in these chirons finds ready application in different areas such as synthesis of natural products,4 pharmaceuticals,5 carbohydrates,6 polymers7 and dyes.8 To date, in excess of 400 arene *cis*-diol products have been reported. The majority of these are produced by organisms expressing toluene dioxygenase (TDO), naphthalene dioxygenase (NDO) and biphenyl dioxygenase (BPDO) enzymes, which are Rieske type non-heme iron oxygenases.9 These metabolise substituted aromatic substrates in a regio- and stereoselective fashion. A robust predictive model has been developed for such transformations,10 with the sense of enantioinduction being consistent across organisms and substrates (Scheme 1a, *ortho*,*meta* oxygenation). However, organisms expressing benzoate dioxygenase (BZDO) enzymes dihydroxylate benzoic acids in a process that proceeds with both differentiated regioselectivity and also the opposite absolute sense of enantioinduction. For example, *Ralstonia eutropha* B9 (formerly known as *Alcaligenes eutrophus* B9), *Pseudomonas putida* U10312 and *Pseudomonas putida* KTSY01 (pSYM01)13 oxidise benzoic acid to benzoate 1,2-*cis* dihydrodiol 4 (Scheme 1b, *ipso, ortho* oxygenation).

Diol acid 4 is a highly versatile chiral pool starting material and many transformations of this building block can be envisaged (Fig. 1). Despite this, 4 has been comparatively underutilised to date in synthesis, in comparison with arene *cis*-diols of

**Scheme 1** Regio- and stereoselectivity of dioxygenases.

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†Electronic supplementary information (ESI) available: 1H and 13C NMR spectra for all novel compounds, as well as selected 2D NMR spectra. See DOI: 10.1039/c3qo00057e
In the current work, we describe the synthesis of a library of cyclohexyl chiron from 4, both minimally and more extensively functionalised. This serves to showcase further the versatility of 4 and we anticipate these new building blocks will find diverse applications in synthesis and catalysis. With regards to handling and storage, it should be noted that although 4 is prone to exothermic decomposition by rearomatisation, as are all arene cis-diols, it may be stored in pure form in excess of a year at −78 °C without appreciable decomposition occurring. Additionally, storage of 4 as its mixed sodium/potassium salt has been described and reportedly leads to enhanced stability.16 Production of 4 on a multihundred gram scale is possible without recourse to specialised equipment.15 The absolute configuration and enantiopurity of 4 have been demonstrated through chemical correlation and by X-ray crystallographic analysis of a derivative.14,15

Results and discussion

Ring-saturated derivatives

The diene in 4 readily undergoes hydrogenation over palladium on carbon to give saturated cyclohexane diol acid 5 (Scheme 2). Perhaps surprisingly, this compound has not been reported previously, although the diastereoisomeric trans-diol is known.18 Saturation of ortho,meta arene cis-diols of type 2 to give 3-substituted cyclohexane-1,2-diols and applications of these in catalysis have been reported;19 the analogous approach has not previously been applied to ipso,ortho- arene cis-diols of type 4, however. We wished to target derivatives of 5 with the diol protected, but direct acetonide introduction was surprisingly unsuccessful. To circumvent this, esterification of 5 was carried out prior to ketalisation. Acetonide protection of 6 was successful, albeit with traces of 8 being formed through competing transesterification. Subsequent hydrolysis of ester 7 did indeed give desired acetonide acid 9, but appreciable acetonide migration and deprotection were also observed.

The structure of 10 was assigned on the basis of its polarity and of the 13C resonance for the ketal carbon (δ = 110.1 ppm, consistent with a five-membered cyclic ketal as opposed to six-membered), as well as 2D NMR spectroscopic data. In view of the difficulties associated with accessing 9 by means of base-mediated ester cleavage, we instead implemented an approach employing a benzyl ester (Scheme 3). It was found that reliable production of 9 in good yield was best achieved through purification of the final product by dry column chromatography.15

Other chiral acid building blocks were also targeted; to this end, the diol in benzyl ester 11 was protected as dioxasilole 13 prior to hydrogenation to give 14 (Scheme 4). This last step proved capricious, however, with undesired desilylation also occurring to a varying extent. A bis(ether) derivative was also accessed by permethylation of 5. With a slight excess of alkylating agent incomplete ether formation led to an inseparable mixture of bis(ether) 15 and monoether 16, which required silylation to allow separation to be effected. However, a greater excess of alkylating agent led to clean formation of 15 in good yield and hydrolysis gave bis(ether) acid 18.

Diol protection as a benzyldiene acetal was explored and a moderate (3 : 2) diastereoselectivity was observed for formation of 19 over 20. Structures were assigned on the basis of NOESY correlations (see ESI†); careful chromatography allowed for isolation of both diastereoisomers in pure form. We next sought to access novel ketones bearing an adjacent quaternary centre. One such target, 21, was available simply by oxidation of...
byproduct 10. A second such ketone was accessed by a multi-step procedure involving silyl protection of the secondary alcohol in 4. Thus, ester 6 was silylated and reduced to give monoprotected triol 23. Choice of reductant proved crucial, since with LiAlH₄, yields of 23 were low, with appreciable silyl migration observed, giving rise to 24. In contrast, NaBH₄ cleanly effected reduction to 23 only, in good yield. Ketalisation, desilylation and oxidation then gave target ketone 27, a reduced analogue of 21 (Scheme 5).

These comparatively minimally functionalised cyclohexyl chirons that all bear a quaternary stereocentre are synthetically valuable insofar as it is difficult to conceive of other means of accessing them as easily, in enantiopure form. We anticipate their finding diverse uses in synthesis and catalysis.

**Highly oxygenated derivatives**

The structures of arene cis-diols such as 2 and 4 are highly suggestive of applications in the synthesis of cyclitols such as inositols. A particular advantage of their use for synthesis of novel inositol derivatives is that they provide ready access to C-substituted derivatives. In contrast, use of natural inositols or other carbohydrates as starting materials lends itself to synthesis of O-substituted derivatives, but C-substituted derivatives are accessible only by means of more involved synthetic sequences.

The ortho/meta diols of type 2 have been extensively exploited in this context but no inositol derivatives have been synthesised to date from 4. To access rapidly such a species from 4, we opted to introduce oxygenation into the diene by means of a singlet oxygen photocycloaddition. Use of singlet oxygen to access novel cyclitols from starting materials other than arene cis-diols has previously proven to be a very successful strategy. Thus, known silyl ether 28 was transformed to endoperoxide 29 and reduced to protected pentao
Alugram® SIL G/UV 254 nm. Visualization was performed using aluminium backed plates precoated with injected after the sample. The observed mass and isotope

We have described synthetic sequences which allow for the functionalization of every position on the cyclohexadiene ring of 4. As the stereocentres in 4 are in close proximity to the diene, it has proven possible to introduce additional stereocentres in a highly selective fashion under substrate control. We anticipate that the novel chirons described here may find use in the synthesis of more complex targets.

Conclusions

We have described synthetic sequences which allow for the functionalization of every position on the cyclohexadiene ring of 4. As the stereocentres in 4 are in close proximity to the diene, it has proven possible to introduce additional stereocentres in a highly selective fashion under substrate control. We anticipate that the novel chirons described here may find use in the synthesis of more complex targets.

Experimental

General procedures

Reactions were carried out under an atmosphere of nitrogen. In most cases, solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. All other solvents were purchased as “anhydrous” grade from Fisher Scientific. “Petrol” refers to petroleum spirit b.pt 40–60 °C. TLC was performed using aluminium backed plates precoated with Alugram® SIL G/UV 254 nm. Visualization was accomplished by UV light and/or KMnO₄ followed by gentle warming. Organic layers were routinely dried with anhydrous MgSO₄ and evaporated using a Büchi rotary evaporator. When necessary, further drying was facilitated by high vacuum. Flash column chromatography was carried out using Davisil LC 60 Å silica gel (35–70 micron) purchased from Fisher Scientific. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectroscopy. 

Synthesis of methyl (1S,2R)-1,2-dihydroxycyclohexane-1-carboxylate (6). To a stirred solution of 5 (47 mg, 0.29 mmol) dissolved in MeOH–C₆H₆ (6 mL, 1:1), was added dropwise TMS-CHN₂ (0.200 mL, 2.0 M solution in THF, 0.400 mmol, 1.4 equiv.) until gas evolution ceased and a yellow colour persisted. The reaction mixture was concentrated under reduced pressure (caution: TMS-CHN₂ toxic by inhalation). Pure 6 was obtained as a yellow oil (52 mg, 100%). Rₚ = 0.05 (30% EtOAc–petrol); [α]D −10.0 (c 0.3, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ = 3.82–3.74 (1H, CH(OH)); 3.77 (3H, s, CH₃); 2.86 (2H, br s, OH); 1.83–1.22 (8H, m, CH); ¹C NMR (75 MHz, CDCl₃) δ = 176.6 (C=O), 76.8 (C(OH)(CO₂CH₃)), 72.2 (CH(OH)), 52.9 (OCH₃), 34.2, 30.1, 24.0, 19.8; νmax (film) 3453, 2938, 2858, 1736, 1439, 1199, 1318, 1023, 948, 821 cm⁻¹; HRMS (ESI−) m/z calculated for (C₇H₁₄O₄)⁻, 159.0663; found 159.0672.

Synthesis of (3aS,7aR)-2,2-dimethyltetrahydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate (7) and (1R,2S)-2-hydroxy-2-(methoxy carbonyl)cyclohexyl (3aS,7aR)-2,2-dimethyltetrahydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate (8). To a stirred solution of 6 (504 mg, 2.89 mmol) dissolved in acetone (20 mL, freshly distilled), was added 2,2-dimethoxypropane (10 mL) and p-toluenesulfonic acid (25 mg, 0.145 mmol, 5 mol%). The solution was stirred at room temperature for 20 h, then diluted with EtOAc (10 mL) followed by the addition of NaHCO₃(aq) (1.0 M, 20 mL). The biphasic system was extracted with EtOAc (504 mg, 2.89 mmol) and the organic layers combined and washed with saturated brine, dried over MgSO₄ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (0 → 20% EtOAc–petrol) to give 7 as a colourless oil (392 mg, 63%) and 8 as a colourless oil (20 mg, 2%). Data for 7: Rₚ = 0.70 (30% EtOAc–petrol); [α]D = −37.8 (c 0.65, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 4.35 (1H, t, J = 3.5 Hz, CH(OCH₃)), 3.76 (3H, s, OCH₃), 2.06–1.93 (2H, m, CH), 1.85–1.23 (6H, m, CH); ¹C NMR (75 MHz, CDCl₃) δ = 173.2
7. Dimethyl-1,3-dioxaspiro[4.5]decan-4-one (10) from ester dioxol-3-carboxylic acid (9) and (5 S; m 1.95 7.60 mmol, 1.1 equiv.) was dissolved in CH₂Cl₂ (50 mL) containing which was added dropwise a suspension of diol acid (50% EtOAc). Resulting oil was purified via flash column chromatography (50% EtOAc–petrol) to give desired acid 9 (20 mg, 8%), acetone-nitride migration product 10 (30 mg, 13%) and deprotected diol 5 (40 mg, 21%). Data for 9: R₁ = 0.40 (50% EtOAc–petrol); [α]D₂⁰ = −40.0 (c 0.70, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 4.31 (1H, t, J = 3.5 Hz, C(1)(OC(CH₃)₂)), 2.12–1.97 (2H, m, CH), 1.90–1.78 (1H, m, CH), 1.71–1.51 (4H, m, CH), 1.54 (3H, s, CH₃), 1.43 (3H, s, CH₃), 1.28–1.21 (1H, m, CH); ¹³C NMR (75 MHz, CDCl₃) δ = 175.6 (C=O), 109.6 (C(OC(CH₃)₂)), 80.7 (C(OC(CH₃)₂)CO₂H); 74.9 (C(OC(CH₃)₂)), 32.2, 28.0, 26.0, 25.7, 20.7, 18.5; v_max = 2934, 2939, 2873, 2714, 1450, 1371, 1383, 1217, 1174, 905, 725 cm⁻¹; HRMS (ESI+) m/z calculated for [C₄H₁₀NaO₄]⁺, 259.088; 259.079. Data for 10: R₁ = 0.83 (50% EtOAc–petrol); [α]D₂⁰ = +2.0 (c 1.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ = 3.75 (1H, dd, J = 11.5, 4.6 Hz, CH(OH)), 1.95–1.93 (1H, m, CH), 1.92–1.89 (1H, m, CH), 1.88 (1H, br s, OH), 1.77–1.80 (1H, m, CH), 1.73 (1H, td, J = 14.0, 4.5 Hz, CH), 1.66 (1H, s, CH₃), 1.63 (3H, s, CH₂), 1.49–1.55 (1H, m, CH), 1.44–1.48 (1H, m, CH), 1.38 (1H, t, J = 13.0, 3.5 Hz, CH); ¹³C NMR (125 MHz, CDCl₃) δ = 174.0 (C=O), 110.1 (C(OC₃)), 83.2 (C(O))=C=O), 71.0 (C(OH)), 33.7 (CH₂), 30.6 (CH), 29.1 (CH₂), 27.9 (C(OC₃)), 23.6 (CH₂), 20.1 (CH); v_max (film) 3484, 2991, 2939, 2863, 2774, 1448, 1385, 1291, 1262, 1060, 1036, 908, 860, 626 cm⁻¹; HRMS (ESI+) m/z calculated for [C₄H₁₀O₄]⁺, 201.1121; found 201.1113. Synthesis of benzyl (15,6 R, 1,6-dihydroxy-cyclohexa-2,4-diene-1-carboxylate (11). Benzyl bromide (0.92 mL, 7.60 mmol, 1.1 equiv.) was dissolved in CH₂Cl₂ (50 mL) containing triethylamine (1.12 mL, 8.29 mmol, 1.2 equiv.) to which was added dropwise a suspension of diol acid 4 (1.08 g, 6.91 mmol, 1.0 equiv.) in CH₂Cl₂ (50 mL). The resulting solution was stirred for 20 h at room temperature, then diluted with H₂O (50 mL), and extracted with EtOAc (4 × 50 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography (10 → 80% EtOAc–petrol) gave 11 as a colourless oil. R₁ = 0.29 (40% EtOAc–petrol); [α]D₂⁰ = −135.6 (c 1.6, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 7.36 (5H, br s, Bn), 6.13 (1H, dddd, J = 9.5, 4.0, 1.0, 0.5 Hz, C=CH), 5.94 (1H, dddd, J = 9.5, 5.0, 2.5, 0.5 Hz, C=CH), 5.82 (1H, ddd, J = 9.5, 2.0, 1.0 Hz, C=CH), 5.76 (1H, ddd, J = 9.5, 2.0, 1.0 Hz, C=CH), 5.29 (2H, s, CO₂-C₂), 4.87 (1H, m, C(OH)); ¹³C NMR (75.5 MHz, CDCl₃) δ = 175.2 (C=O), 135.1, 132.1, 128.8, 128.7, 128.0, 124.8, 122.4, 74.1 (C(OH)-H), 68.5 (O-CH₃); v_max (film) 3451, 3038, 1731, 1660, 1455, 1378, 1234, 1168, 1077, 1020, 909, 753, 695 cm⁻¹; HRMS (ESI+) m/z calculated for [C₁₄H₁₄NaO₄]⁺, 269.0784; found 269.0863.

Synthesis of benzyl (3a,7a R, 2,2-dimethyl-benzo[d]1,3-dioxol-3a-carboxylate (12). To a stirred solution of 11 (335 mg, 1.37 mmol) dissolved in acetone (10 mL, freshly distilled), was added, 2,2-dimethoxypropene (2.0 mL, 16.46 mmol, 12 equiv.) and para-toluene sulfonylic acid (26 mg, 0.03 mmol, 10 mol%). The solution was stirred at room temperature for 20 h, then diluted with EtOAc (10 mL) followed by the addition of water (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over MgSO₄ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10 → 20% EtOAc–petrol) to give 12 a colourless oil (358 mg, 92%). R₁ = 0.60 (30% EtOAc–petrol); ¹H NMR (250 MHz, CDCl₃) δ = 7.31 (5H, br s, Bn), 6.08–5.94 (3H, m, C=CH), 5.86–5.79 (1H, m, C=CH), 5.18 (2H, s, CH₂), 4.97 (1H, d, J = 4.0 Hz, CH(O)), 1.38 (3H, s, CH₃), 1.37 (3H, s, CH₃). Data in agreement with those previously reported.⁶

The resulting oil was purified via flash column chromatography (10 → 50% EtOAc–petrol) to yield pure 9 (14 mg, 63%) as a colourless oil, data as above.

Synthesis of benzyl (3a,7a R, 2,2-dimethoxydibenzo[d]1,3-dioxol-3a-carboxylic acid (9) from ester 12. A stirred solution of benzyl ester 12 (32 mg, 0.11 mmol) and Pd/C (10 mg, matrix activated carbon support) in MeOH (20 mL) was exposed to a hydrogen atmosphere (balloon) at room temperature. After 24 h the solution was filtered through a plug of celite and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (0 → 50% EtOAc–petrol) to yield pure 9 (14 mg, 63%) as a colourless oil, data as above.

Synthesis of benzyl (3a,7a R, 2,2-di-tert-butylbenzo[d]1,3-dioxol-3a-carboxylate (13). To a stirred solution of 11 (48 mg, 0.195 mmol) dissolved in CH₂Cl₂ (2 mL) was added triethylamine (65 µL, 0.468 mmol, 2.4 equiv.) and di-tert-butylsilanediyl bis(trifluoromethanesulfonate) (70 µL, 0.215 mmol, 1.1 equiv.). The solution was stirred at room temperature for 9 h. The resulting solution was diluted with EtOAc (10 mL) followed by the addition of water (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over MgSO₄ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (0 → 5%...
EtOAc–petrol) to give 13 as a colourless oil (61 mg, 81%). \( R_t = 0.65 \) (10% EtOAc–petrol); \([\alpha]_D^{25} = -327.0 \) (c 3.31, CHCl₃); ¹H NMR (300 MHz, CDCl₃) \( \delta = 7.35-7.31 \) (5H, Ar-H), 6.03-5.94 (3H, m, C=CH), 5.75-5.71 (1H, m, C=CH), 5.25 (1H, d, J = 12.0 Hz, -CH=H), 5.18 (1H, d, J = 12.0 Hz, -CH=H), 4.97 (1H, d, J = 1.8 Hz, CH(OH)), 0.99 (9H, s, CH₃) 0.98 (9H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃) \( \delta = 172.2 \) (C=O), 135.6, 128.6, 128.4, 128.3, 126.3, 125.8, 123.9, 122.3, 78.6 (C(OSi)(C)=O), 71.5 (CH(OH)), 67.4 (CH), 27.0 (CH₂), 26.9 (CH₃), 21.2 (C(CH₃)₂), 20.2 (C(CH₃)₃); νmax (film) 3045, 2966, 2934, 2891, 2859, 1733, 1473, 1229, 1091, 1031, 1012, 1000, 875, 825, 696 cm⁻¹; HRMS (ESI+) m/z calc for \( \text{C}_{12}\text{H}_{25}\text{O}_{4}\text{Si} \) 387.1986; found 387.1993.

Synthesis of (3aS,7aR)-2,2-di-tert-butyldimethyloxane-1-carboxylic acid (14). A stirred solution of 13 (61 mg, 0.16 mmol) and Pd/C (10 mg, 50% in mineral oil) in DMF (2.00 mL) at 22 °C. Iodomethane (0.170 mL, 2.83 mmol, 3.4 equiv.) was added dropwise over 24 h the solution was filtered through a plug of celite and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10 : 70 EtOAc–petrol) to give pure 14 (25 mg, 53%) as a colourless oil. \( R_t = 0.30 \) (30% EtOAc–petrol); \([\alpha]_D^{25} = -17.0 \) (c 0.18, CHCl₃); ¹H NMR (300 MHz, CDCl₃) \( \delta = 4.36 \) (1H, dd, J = 11.0, 4.5 Hz, CH(OSi)), 1.99–1.20 (8H, m, CH), 1.02 (9H, s, CH₃) 0.98 (9H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃) \( \delta = 179.1 \) (C=O), 77.9 (C(OSi)(C)=O), 73.9 (CH(OSi)), 33.0, 30.1, 27.7 (CH₃), 27.5 (CH₃), 23.7, 20.5, 20.3, 19.6; νmax (film) 3070, 2935, 2894, 2859, 1717, 1448, 1472, 1094, 827 cm⁻¹; HRMS (ESI+) m/z calc for \( \text{C}_{12}\text{H}_{25}\text{O}_{4}\text{Si} \), 301.1830; found 301.1830.

Synthesis of methyl (1S,2R)-1,2-dimethoxycyclohexane-1-carboxylate (15) and methyl (1S,2R)-2-methoxy-1-(trimethylsilyl)oxy-cyclohexane-1-carboxylate (17). Diol acid (133 mg, 0.27 mmol) was dissolved in toluene (15 mL) and extracted with EtOAc (3 × 20 mL). Combined organic layers were washed with saturated brine and dried over MgSO₄, then concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (50 : 45 : 2.5 : 2.5 EtOAc–petrol–AcOH–H₂O) to give 18 as a colourless oil (108 mg, 75%). \( R_t = 0.25 \) (50 : 45 : 2.5 : 2.5 EtOAc–petrol–AcOH–H₂O); \([\alpha]_D^{25} = -20.5 \) (c 0.73, CHCl₃); ¹H NMR (500 MHz, CDCl₃) \( \delta = 3.40-3.37 \) (1H, m, CH(OSi)), 3.38 (3H, s, CH₃), 3.35 (3H, s, CH₃), 2.18 (1H, dd, J = 15.0, 2.0 Hz, CH), 1.96 (1H, m, CH), 1.82–1.81 (1H, m, CH), 1.68–1.53 (3H, m, CH), 1.37–1.25 (2H, m, CH); ¹³C NMR (125 MHz, CDCl₃) \( \delta = 175.3 \) (C=O), 82.7, 81.2, 57.1, 52.0, 28.1, 24.8, 23.7, 20.0; νmax (film) 3143, 2940, 2860, 2838, 1721, 1464, 1448, 1308, 1196, 1099, 1077, 973, 939 cm⁻¹; HRMS (ESI+) m/z calc for \( \text{C}_{12}\text{H}_{25}\text{O}_{4}\text{Si} \), 187.0976; found 187.0972.

Synthesis of (2R,3aS,7aR)-2-phenyltetrahydrobenzo[d][1,3]dioxolane-3-carboxylic acid (19) and methyl (2S,3aS,7aR)-2-phenyltetrahydrobenzo[d][1,3]dioxole-3-carboxylate (20). Diol 6 (30 mg, 0.27 mmol) was dissolved in toluene (15 mL). Benzaldehyde (0.030 mL, 0.34 mmol, 2.0 equiv.) and para-toluenesulfonic acid (4.0 mg, 0.02 mmol) were added. The resulting solution was refluxed for 24 h. After cooling, the reaction mixture was diluted with NaHCO₃ (15 mL) and extracted with EtOAc (3 × 10 mL). Combined organic layers were dried over MgSO₄, then concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (5 : 10% EtOAc–petrol) to yield 19 (15 mg, 35%) and 20 (10 mg, 24%). In addition a further 17 mg (40%) of material was isolated, shown to be a 1 : 1 mixture of 19 and 20 by NMR. Data for 19: \( R_t = 0.49 \) (10% EtOAc–petrol); \([\alpha]_D^{25} = -31 \) (c 0.7, CHCl₃); ¹H NMR (300 MHz, CDCl₃) \( \delta = 7.56-7.52 \) (2H, m, Ar-H), 7.40–7.37 (3H, m, Ar-H), 5.97 (1H, s, CH(O)(O)), 4.42 (1H, t, J = 4.0 Hz, CH(O)), 3.82 (3H, s, OCH₃), 2.13–1.81 (4H, m, CH), 1.76–1.45 (4H, m, CH); ¹³C NMR (75 MHz, CDCl₃) \( \delta = 173.4 \) (C=O), 137.2, 129.3, 128.3,
126.7 (Ar–C), 103.3 (CH(O)(O)(Ar)), 81.5 (C(O)(C=O)), 77.3 (C(O)H), 52.5 (OCH3), 31.1, 26.1, 19.4, 18.5; v_{max} (film) 2951, 2869, 1734, 1451, 1247, 1163, 1084, 697 cm⁻¹; HRMS (ESI+) m/z calcd for (C15H19O4)⁺, 263.1278; found 263.1267.

Data for 20: \( R_t = 0.53 \) (10% ETOAc–petrol); \([\alpha]_{D}^{20} = -1.6 \) (c 0.08, CHCl3); \(^{1}H\) NMR (300 MHz, CDCl3) \( \delta = 7.50-7.46 \) (2H, m, Ar–H), 7.39–7.32 (3H, m, Ar–H), 6.21 (1H, s, CH(O)(O)), 4.53 (1H, t, \( J = 5.5 \) Hz, CH(O)), 3.70 (3H, s, OCH3), 2.03–1.89 (4H, m, CH), 1.75–1.39 (4H, m, CH); \(^{13}C\) NMR (75 MHz, CDCl3) \( \delta = 173.0 \) (C=O), 138.9, 129.0, 128.3, 126.4 (Ar–C), 102.8 (CH(O)(O)(Ar)), 81.9 (C(O)(C=O)), 75.9 (C(OH), 52.3 (OCH3), 30.7, 26.2, 20.9, 20.4; v_{max} (film) 2938, 2863, 1735, 1451, 1214, 1162, 1093, 698 cm⁻¹; HRMS (ESI+) m/z calcd for (C15H19O4)⁺, 263.1278; found 263.1268.

### Alternative procedure.
To a stirred solution of 22 (465 mg, 1.6 mmol) in THF at \(-78 °C\) was added dropwise LiAlH4 (0.54 mL, 2.4 M in THF, 1.3 mmol, 1.0 equiv.) over 20 min. The resulting solution was left to warm to room temperature for 12 h. The solution was quenched with addition of H2O (0.05 mL) followed by NaOH (10% aq. sol., 0.09 mL) followed by H2O (0.14 mL). The solution was filtered through MgSO4 and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (5–20% ETOAc–petrol) to give 23 (45 mg, 13%) as a colourless oil and 24 (19 mg, 5%) as a colourless oil.

### Synthesis of (\( 1R,2R \))-2-((\( tert\)-butyldimethylsilyl)oxy)-1-hydroxycyclohexane-1-carboxylate (22).
Diol ester 6 (370 mg, 2.12 mmol, 1.0 equiv.) was dissolved in CH2Cl2 (20 mL) and cooled to \(-78 °C\). Triethylamine (355 \( \mu \)L, 257 mg, 2.54 mmol, 1.2 equiv.) was added, then \( tert\)-butyldimethylsilyl trifluoromethanesulfonate (487 \( \mu \)L, 560 mg, 2.12 mmol, 1.0 equiv.) was added. The mixture was stirred at \(-78 °C\) for 1 h, then quenched by addition of H2O (20 mL). Phases were separated and the organic layer was washed further with NaCl(aq) (satd, 20 mL). The organic phase was dried over MgSO4 and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10% ETOAc–petrol) to yield 21 (205 mg, 62%, 25% yield) as a colourless oil.

### Synthesis of methyl (1S,2R)-2-((\( tert\)-butyldimethylsilyl)oxy)-1-hydroxycyclohexane-1-carboxylate (22). Diol ester 6 (370 mg, 2.12 mmol, 1.0 equiv.) was dissolved in CH2Cl2 (20 mL) and cooled to \(-78 °C\). Triethylamine (355 \( \mu \)L, 257 mg, 2.54 mmol, 1.2 equiv.) was added, then \( tert\)-butyldimethylsilyl trifluoromethanesulfonate (487 \( \mu \)L, 560 mg, 2.12 mmol, 1.0 equiv.) was added. The mixture was stirred at \(-78 °C\) for 1 h, then quenched by addition of H2O (20 mL). Phases were separated and the organic layer was washed further with NaCl(aq) (satd, 20 mL). The organic phase was dried over MgSO4 and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10% ETOAc–petrol) to yield 21 (205 mg, 62%, 25% yield) as a colourless oil.

### Synthesis of (\( 1R,2R \))-1-((\( tert\)-butyldimethylsilyl)oxy)-2-(\( hydroxymethyl\))cyclohexane-1-ol (23) and (\( 1R,2R \))-2-((\( tert\)-butyldimethylsilyl)oxy)methyl)cyclohexane-1,2-diol (24).
To a stirred solution of 22 (375 mg, 1.3 mmol) in THF at \(-78 °C\) was added dropwise LiAlH4 (0.54 mL, 2.4 M in THF, 1.3 mmol, 1.0 equiv.) over 20 min. The resulting solution was left to warm to room temperature for 12 h. The solution was quenched with addition of H2O (0.05 mL) followed by NaOH (10% aq. sol., 0.09 mL) followed by H2O (0.14 mL). The solution was filtered through MgSO4 and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (5–20% ETOAc–petrol) to give 23 (45 mg, 13%) as a colourless oil and 24 (19 mg, 5%) as a colourless oil.
petrol); $[\alpha]^2_{D} = 20$ (c 0.3, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 3.88$ (1H, $d$, $J = 8.0$ Hz), 3.70 (1H, $d$, $J = 8.0$ Hz), 3.53 (1H, dd, $J = 7.0$, 3.0 Hz), 1.95–1.86 (1H, m), 1.75–1.56 (3H, m), 1.51–1.18 (4H, m) 1.39 [6H, s, O-C(CH$_3$)$_2$], 0.90 (9H, s Si(CH$_3$)$_3$), 0.07 (3H, s, SiCH$_3$), 0.05 (3H, s, SiCH$_3$); $^1$C NMR (75 MHz, CDCl$_3$) $\delta = 109.2,$ 83.4, 72.9, 70.9, 34.0, 32.2, 27.7, 26.9, 25.9, 22.6, 21.6, 18.2, –4.5, –4.6; $\nu_{\text{max}}$ (film) 2988, 2933, 2894, 2856, 1472, 1462, 1377, 1368, 1251, 1212, 1141, 1094, 1056, 988, 989, 773 cm$^{-1}$; HRMS (ESI+)+ m/z calecd for ([C$_9$H$_{12}$NaO$_3$Si])$^+$, 323.2013; found 323.2013.

**Synthesis of ([5R,6R]-2,2-dimethyl-1,3-dioxaspiro[4,5]decan-6-one (26).** To a stirred solution of 25 (1.72 g, 5.72 mmol) in THF (50 mL) at $-78$ °C, was added dropwise tetrabutylammonium fluoride (1.0 M solution in THF, 5.72 mL, 2.0 equiv.) over 5 min. The resulting solution was allowed to warm to room temperature over 16 h, then was quenched with Et$_3$O (10 mL) and NaH$_2$CO$_3$ (10 mL). The reaction mixture was then extracted with EtOAc (4 × 10 mL) and the organic layers were combined and left to stir at room temperature for 16 h. The reaction mixture was then extracted with EtOAc (3 × 30 mL) and left to stir at room temperature for 16 h. The reaction mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with water (30 mL) and brine (30 mL). The resulting solution was dried over MgSO$_4$. Removal of the solvent under reduced pressure and purification by flash column chromatography (5 → 30% EtOAc–petrol) gave 31 as a colourless oil (254 mg, 66% yield), $R_f = 0.64$ (20% EtOAc–petrol); $[\alpha]^2_{D} = -22.2$ (c 0.09, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 5.74$ (2H, s, C–CH$_3$), 4.86 (1H, $d$, $J = 6.5$ Hz, OCH$_2$O), 4.85 (1H, $d$, $J = 6.5$ Hz, OCH$_2$O), 4.70 (1H, $d$, $J = 6.5$ Hz, OCH$_2$O), 4.40 (1H, $d$, $J = 3.0$ Hz, CHO), 4.29 (1H, br s, CHOMOM), 4.22 (1H, br s, CHOMOM); 3.96 (1H, $d$, $J = 11.0$ Hz, CHOTBDMS), 3.49 (1H, $d$, $J = 11.0$ Hz, CHOTBDMS), 3.41 (3H, s, CH$_3$OCH$_3$), 3.39 (3H, s, CH$_2$OCH$_3$), 1.47 (3H, s, O–C–CH$_3$), 1.43 (3H, s, O–C–CH$_3$), 0.89 (9H, s, Si(CH$_3$)$_3$), 0.04 (6H, s, Si(CH$_3$)$_3$); $^1$C NMR (75 MHz, CDCl$_3$) $\delta = 130.3$ (HC=CH), 127.9 (HC=CH), 108.9 (C(CH$_3$)$_2$), 96.3 (OCH$_2$O), 95.5 (OCH$_2$O), 85.3 (4’C(CH$_3$)$_3$), 78.4 (CHO), 76.8 (CHO), 75.0 (CHO), 61.9 (CH$_2$OBTBDMS), 55.5 (OCH$_3$), 55.4 (OCH$_3$), 28.4 (CCH$_3$), 27.0 (CCH$_3$), 25.9 (Si(CH$_3$)$_3$), 18.3 (Si(CH$_3$)$_3$), –5.3 (SiCH$_3$), –5.7 (SiCH$_3$); $\nu_{\text{max}}$ (film) 2954, 1252, 1043, 907, 837, 732, 649 cm$^{-1}$; HRMS (ESI+)+ m/z calecd for ([C$_2$H$_9$O$_3$NaSi])$^+$, 441.2279; found 441.2285.

**Synthesis of (3aS,4R,5S,6R,7S,7aR)-3a-((tert-butyldimethyl-silyl)oxy)methyl-4,7-bis(methoxymethylene)-2,2-dimethylhexahydrobenzo[d][1,3]dioxole-5,6-diol (32).** To a solution of 31 (75.0 mg, 0.185 mmol, 1.0 equiv.) in acetone–H$_2$O (4 : 1, 8.0 mL) was added NMO (43.4 mg, 0.370 mmol, 2.0 equiv.) followed dropwise with OsO$_4$ (40 μL, 2.5% w/v in tert-BuOH, 3.7 μmol). The resulting solution was stirred at room temperature for 72 h. The reaction mixture was diluted with EtOAc (30 mL) and extracted with saturated Na$_2$SO$_4$(aq) (2 × 30 mL). The organic phase was washed with brine (30 mL) and dried over MgSO$_4$. Removal of the solvent under reduced pressure and purification by flash column chromatography (50% EtOAc–petrol) gave 32 as a colourless oil (56 mg, 67%). $R_f = 0.43$ (50% EtOAc–petrol); $[\alpha]^2_{D} = -10.0$ (c 0.1, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 4.82$ (2H, s, OCH$_2$O), 4.74 (1H, $d$, $J = 6.5$ Hz, OCH$_2$O), 4.67 (1H, $d$, $J = 6.5$ Hz, OCH$_2$O), 4.47 (1H, $d$, $J = 2.5$ Hz, CHO), 4.18 (1H, m, CHO), 4.06 (1H, br s, CHO), 3.93 (1H, $d$, $J = 11.0$ Hz, CHOTBDMS), 3.94–3.89 (1H, m, CHO), 3.79 (1H, dd, $J = 10.0$, 4.0 Hz), 3.64 (1H, $d$, $J = 11.0$ Hz, CHOTBDMS), 3.45 (3H, s, CH$_3$OCH$_3$), 3.40 (3H, s, CH$_3$OCH$_3$), 3.05 (1H, br s, OH), 1.51 (3H, s, C(CH$_3$)$_2$), 1.37 (3H, s, C(CH$_3$)$_2$), 0.89 (9H, s, Si(CH$_3$)$_3$), 0.07 (3H, s, SiCH$_3$), 0.06 (3H, s, SiCH$_3$); $^1$C NMR (75 MHz, CDCl$_3$) $\delta = 108.6$ (C(CH$_3$)$_2$), 98.1 (OCH$_2$OCH$_3$), 95.9 (OCH$_2$OCH$_3$), 85.3 (4’C(CH$_3$)$_3$), 83.0 (CHO), 76.4 (CHO), 73.4 (CHO), 70.9 (CHO), 69.5 (CHO), 61.2 (CH$_2$OBTBDMS), 55.9 (CH$_3$OCH$_3$), 55.8 (CH$_3$OCH$_3$), 28.2 (C(CH$_3$)$_2$), 26.3 (C(CH$_3$)$_2$), 25.9 (Si(CH$_3$)$_3$), 18.3 (Si(CH$_3$)$_3$), –5.4 (SiCH$_3$), –5.7 (SiCH$_3$); $\nu_{\text{max}}$ (film) 3455, 2930, 2857, 1463, 1370, 1252, 1217, 1152, 1101, 1033, 999, 948, 919, 859, 837, 814, 777, 675 cm$^{-1}$; HRMS (ESI+)+ m/z calecd for ([C$_{19}$H$_{30}$NaO$_4$Si])$^+$, 475.2334; found 475.2334.

**Synthesis of (1R,2S,3R,4S)-6-(acetoxyethyl)-6-hydroxy-cyclohexane-1,2,3,4,5-pentyl pentaacetate (33).** To a solution of 32 (53.0 mg, 0.17 mmol) in Et$_2$O (5 mL) was added...
HCl (aq) (1.0 M, 5 mL). The solution was stirred vigorously at room temperature for 24 h, then diluted with EtO (10 mL) and extracted with H2O (3 × 10 mL). The combined aqueous layers were concentrated under reduced pressure to give heptao 34. 1H NMR showed this to be impure, so crude 34 was dissolved in pyridine (0.7 mL), to which was added acetic anhydride (1.0 mL). The reaction mixture was stirred at room temperature for a further 24 h, then diluted with EtOAc (10 mL). HCl (1.0 M, 10 mL) was added dropwise and the reaction mixture transferred to a separating funnel. The organic phase was washed with NaHCO3 (aq) (satd, 3 × 10 mL) and H2O (3 × 10 mL), then dried over Na2SO4 and concentrated under reduced pressure. Purification via flash column chromatography (50% EtOAc–petrol) gave 33 as a colourless oil (22 mg, 37%). Rf = 0.29 (50% EtOAc–petrol); [α]D25 = −5.5 (c 0.36, CH2Cl2).

1H NMR (300 MHz, CDCl3) δ = 5.66 (1H, t, J = 10.0 Hz), 5.34 (1H, t, J = 3.5 Hz), 5.29 (1H, dd, J = 9.5 Hz), 5.25 (1H, dd, J = 10.0, 3.5 Hz), 5.24 (1H, d, J = 3.5 Hz), 4.21 (1H, d, J = 12.0 Hz, −CH2OAc), 3.95 (1H, d, J = 12.0 Hz, −CH2OAc), 2.15 (3H, s, −OAc), 1.24 (3H, s, −OAc), 2.11 (3H, s, −OAc), 2.05 (3H, s, −OAc), 2.02 (3H, s, −OAc), 1.98 (3H, s, −OAc); 13C NMR (75 MHz, CDCl3) δ = 170.7 (C=O), 169.7 (2 × C=O), 169.6 (C=O), 169.0 (C=O), 168.3 (C=O), 75.0, 71.4, 68.9, 68.8, 68.1, 68.0, 65.0, 20.8 (CH3), 20.7 (CH3), 20.6 (CH3), 20.5 (CH3); v max (film) 3479, 2965, 1741, 1431, 1369, 1218, 1039, 899, 821, 731 cm−1; HRMS (ESI+) m/z calcd for [C15H23NaO12]+, 485.1266; found 485.1318.

Synthesis of (1S,2R,3S,4R,5S,6R)-1-(hydroxymethyl)cyclohexane-1,2,3,4,5,6-hexanol (34). Hexaacetate 33 (22 mg, 0.0476 mmol) was dissolved in MeOH (5 mL) at room temperature. NH3(g) was slowly bubbled through the reaction mixture for 3 d, then the reaction mixture was concentrated under reduced pressure. The crude product was then dried over high vacuum (flash heated to 60 °C to drive off acetamide) to give pure 34 (9 mg, 99%) as a colourless gum. [α]D25 +2.78 (c 3.3, H2O).

1H NMR (500 MHz, D2O) δ = 4.07 (2H, d, J = 1.3 Hz), 3.88 (1H, t, J = 9.8 Hz), 3.81–3.78 (1H, m), 3.76 (2H, d, J = 0.8 Hz, 3.56 (1H, t, J = 9.5 Hz); 13C NMR (75 MHz, D2O) δ = 77.8, 73.6, 72.5, 71.5, 71.2, 69.3, 63.8; v max (film) 3331, 2956, 2922, 2854, 1667, 1540, 1455, 1205, 1151, 1020, 742 cm−1; HRMS (ESI+) m/z calcd for [C16H29NaO13]+, 330.1803; found 330.1804.

Synthesis of (3aR,4R,7aR)-2,2-dimethylbenzol[d][1,3]dioxol-3a(7Hf)-yl)methyl acetate (36). To a stirred solution of known a alcohol 35 (637 mg, 3.50 mmol, 1 equiv.) in CH2Cl2 (20 mL) was added triethylamine (0.48 mL, 3.49 mmol, 1 equiv.), DMAP (42 mg, 0.35 mmol, 10 mol%) and Ac2O (0.33 mL, 3.50 mmol, 1 equiv.). The reaction mixture was stirred for 30 min, then H2O (20 mL) was added. The reaction mixture was then extracted with EtOAc (4 × 20 mL). The organic layers were combined and dried over MgSO4 and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (15% EtOAc–petrol) to give 36 (600 mg, 77%) as a yellow oil. Rf = 0.45 (15% EtOAc–petrol); [α]D25 = −81.6 (c 1.20, CH2Cl2); 1H NMR (300 MHz, CDCl3) δ = 6.13–6.08 (1H, m, C=CH), 6.03–5.98 (2H, m, C=CH), 5.72 (1H, d, J = 10.0 Hz, C=CH), 4.41 (1H, d, J = 4.5 Hz, CHOCH3), 4.15 (1H, d, J = 11.5 Hz, −CH2−), 3.94 (1H, d, J = 11.5 Hz −CHF−), 2.07 (3H, s, OAc), 1.44 (3H, s, CH3), 1.37 (3H, s, CH3); 13C NMR (75 MHz, CDCl3) δ = 170.6 (C=O), 128.1, 125.4, 124.3, 123.1 (C=CH2), 106.6 (C(CH3)2), 78.3 (CO(CH3)), 71.8 (CHOOC(CH3)2), 66.1 (CH3), 27.1, 26.4 (C(CH3)2), 20.8 (COCH3); v max (film) 3291, 2937, 1745, 1417, 1395, 1289, 1043, 906, 728, 648 cm−1; HRMS (ESI+) m/z calcd for [C15H18NaO4]+, 247.0941; found 247.0931.
Synthesis of \((1\alpha R,1\beta R,2\alpha R,2\beta S,5aR,5bS)-4,4\text{-dimethyltetrahydrobis(oxireno)}\)\(\left[2\right]^{13}J_{\text{C,H}}=3.5, 2.0\text{ Hz, C(H)O}\), 3.04 (1H, \(d, J = 3.5\text{ Hz}\)), 2.11 (3H, s, CO\(_2\)CH\(_3\)), 1.43 (3H, s, CH\(_3\)), 1.42 (3H, s, CH\(_3\)); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta = 170.4\) (C=O), 110.4 (C(CH\(_3\))), 78.2 (CO(CH\(_2\))COAc), 71.9 (S(CH\(_3\))OC(CH\(_2\))), 65.3 (CH\(_3\)), 51.5 (C(H)(O)), 50.9 (C(H)(O)), 47.6 (C(H)(O)), 47.6 (C(H)(O)), 28.0 (C(CH\(_3\))), 26.2 (C(CH\(_3\))), 20.8 (CO\(_2\)CH\(_3\)); \(v\text{max}\) (film) 2991, 2938, 1742, 1455, 1380, 1231, 1175, 1063, 943, 992, 963, 803, 630 cm\(^{-1}\); HRMS (ESI+) \(m/z\) calc for \((C_{12}H_{12}NaO_{5})^+\); 279.0839; found 279.0861.

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