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# 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.

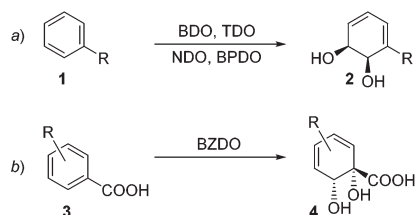
## Introduction

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.<sup>1</sup> The direct transformation of an aromatic ring into a dearomatised cyclohexadiene diol (Scheme 1) is a reaction that has very little precedent in organic chemistry<sup>2</sup> and is therefore appealing to access rapidly uncharted chemical space. In wild-type organisms, these arene *cis*-diols are usually fleeting metabolic intermediates.<sup>3</sup> 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,<sup>4</sup> pharmaceuticals,<sup>5</sup> carbohydrates,<sup>6</sup> polymers<sup>7</sup> and dyes.<sup>8</sup> 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.<sup>1e,9</sup> These metabolise substituted aromatic substrates in a regio- and stereoselective fashion. A robust predictive model has been developed for such transformations,<sup>10</sup> 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 different regioselectivity and also the opposite absolute sense of enantioinduction. For example, *Ralstonia eutropha* B9<sup>11</sup> (formerly known as *Alcaligenes eutrophus* B9), *Pseudomonas putida* U103<sup>12</sup> and *Pseudomonas putida* KTSY01 (pSYM01)<sup>13</sup> 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: <sup>1</sup>H and <sup>13</sup>C NMR spectra for all novel compounds, as well as selected 2D NMR spectra. See DOI: 10.1039/c3qo00057e

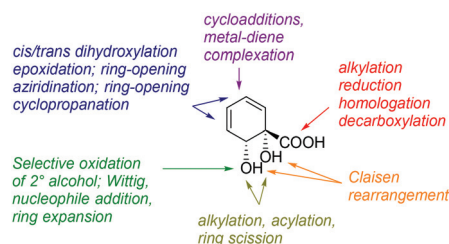


Fig. 1 Possible transformations of diol acid **4**.

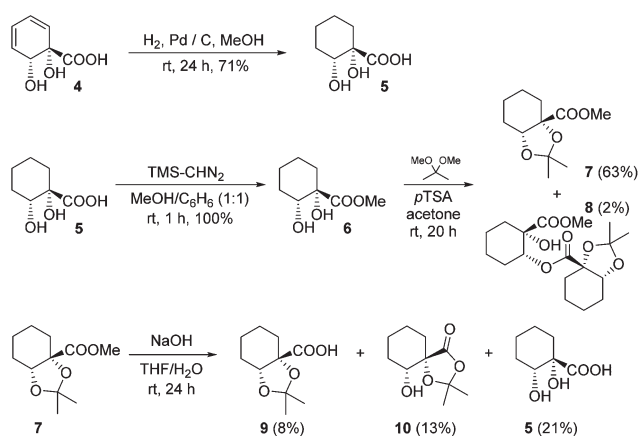


type 2.<sup>4i,g,t,5h,i,6a,e,o,14–17</sup> In the current work, we describe the synthesis of a library of cyclohexyl chiron from **4**, both minimally and more extensively functionalised. This serves to showcase further the versatility of **4** and we anticipate these new building blocks will find diverse 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  $-78\text{ }^{\circ}\text{C}$  without appreciable decomposition occurring. Additionally, storage of **4** as its mixed sodium/potassium salt has been described and reportedly leads to enhanced stability.<sup>16b</sup> Production of **4** on a multihundred gram scale is possible without recourse to specialised equipment.<sup>15</sup> The absolute configuration and enantiopurity of **4** have been demonstrated through chemical correlation and by X-ray crystallographic analysis of a derivative.<sup>14,15</sup>

## 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.<sup>18</sup> 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;<sup>19</sup> 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.

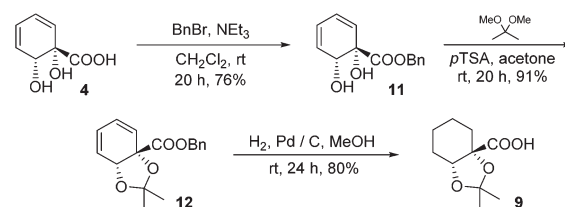


Scheme 2 Acetonide acid derivatives of **4**.

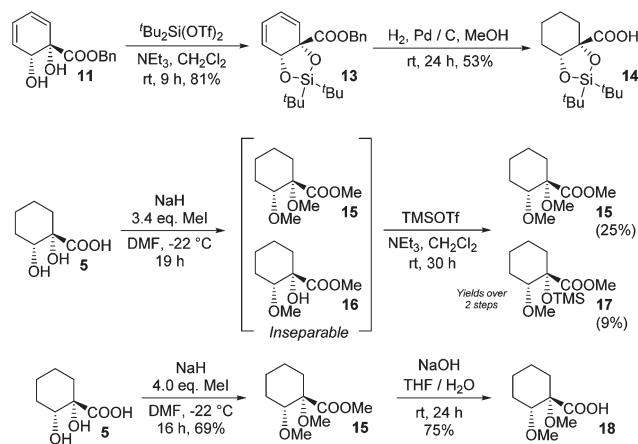
The structure of **10** was assigned on the basis of its polarity and of the  $^{13}\text{C}$  resonance for the ketal carbon ( $\delta = 110.1\text{ ppm}$ , consistent with a five-membered cyclic ketal as opposed to six-membered<sup>20</sup>), as well as 2D NMR spectroscopic data. In view of the difficulties 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.<sup>21</sup>

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 benzylidene 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<sup>†</sup>); 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

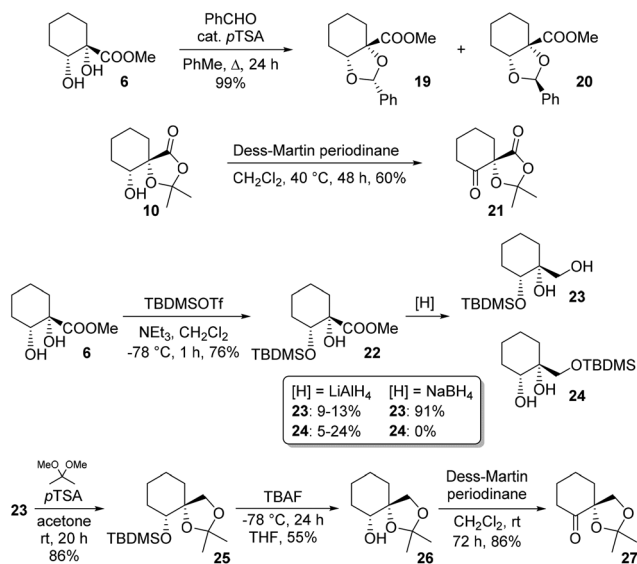


Scheme 3 Benzyl ester route to **9**.



Scheme 4 Other protected acid building blocks.





Scheme 5 Additional cyclohexyl chiral intermediates accessible from 5.

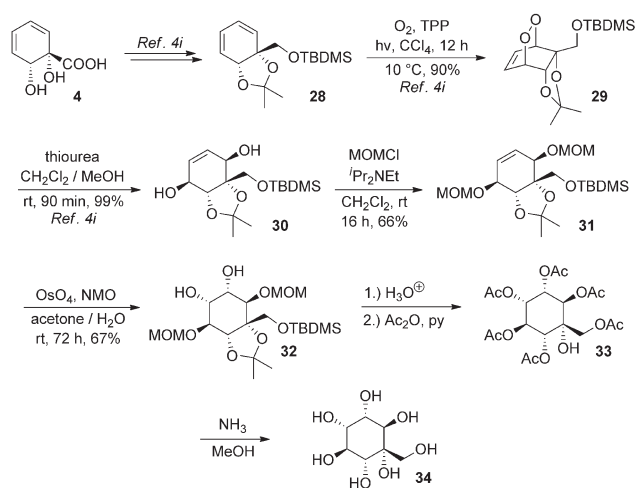
byproduct **10**. A second such ketone was accessed by a multi-step procedure involving silyl protection of the secondary alcohol in **4**. Thus, ester **6** was silylated and reduced to give monoprotected triol **23**. Choice of reductant proved crucial, since with  $\text{LiAlH}_4$ , yields of **23** were low, with appreciable silyl migration observed, giving rise to **24**. In contrast,  $\text{NaBH}_4$  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 chiral intermediates 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.<sup>22</sup> A particular advantage of their use for synthesis of novel inositol derivatives is that they provide ready access to *C*-substituted derivatives.<sup>6d,23</sup> 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.

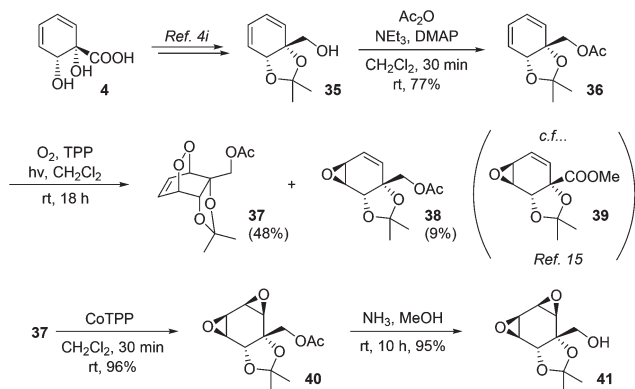
The *ortho,meta* diols of type **2** have been extensively exploited in this context<sup>6i,j,p,r,7a,24-27</sup> but no inositol derivatives have been synthesised to date from **4**. To access rapidly such a species from **4**, we opted to introduce oxygenation into the diene by means of a singlet oxygen 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.<sup>28</sup> Thus, known silyl ether **28** was transformed to endoperoxide **29** and reduced to protected pentaol

Scheme 6 Synthesis of a *C*-hydroxymethyl inositol.

**30** by our reported procedure.<sup>4i</sup> Protection of free hydroxyl groups as methoxymethyl ethers gave **31**, which underwent osmium-catalysed dihydroxylation to afford **32** as a single isomer; regiochemistry of osmylation in such systems is well precedented.<sup>6y,24d,f,l,25c,l,27d,29</sup> Global deprotection with aqueous acid (and an organic wash to remove silanol) furnished the desired product, but in impure form; attempts using acidic resins also gave impure product. Its purification necessitated exhaustive acetylation to **33**, chromatography and ammonolysis to give **34**, a *C*-hydroxymethyl-*muco*-inositol. *C*-Hydroxymethyl derivatives of other isomeric inositols are extremely rare<sup>30</sup> and those of *muco*-inositol are wholly unknown (Scheme 6).

Endoperoxides derived from diene- $^1\text{O}_2$  photocycloaddition are versatile intermediates and in addition to reductive cleavage, they are capable of undergoing several other synthetically useful transformations. For example, they undergo base-mediated Kornblum-DeLaMare fragmentation to afford  $\gamma$ -hydroxyenones; we have previously demonstrated such transformations for endoperoxides derived from **4**.<sup>4i</sup> In addition, they may be isomerised to the corresponding bis(epoxides) upon treatment with cobalt-tetraphenylporphine complex.<sup>31</sup> This latter transformation has not previously been applied to an endoperoxide derived from **4**. To this end, known alcohol **35** was acetylated and subjected to the photocycloaddition. In addition to the expected endoperoxide **37**, epoxide **38** was also isolated in small amounts. The structure of **38** was assigned on the basis of its spectroscopic data in comparison with those for the previously reported **39**.<sup>15</sup> As regards the mechanism of formation of **38**, analogous epoxide byproducts of singlet oxygen photocycloaddition have been described previously for other substrates and are believed to arise *via* a radical pathway.<sup>32</sup> Upon treatment with CoTPP, **37** underwent facile isomerisation to bis(epoxide) **40**. These epoxides proved resistant to opening with ammonia, with ammonolysis instead cleanly removing the acetate to give **41** (Scheme 7).





Scheme 7 Synthesis of a bis(epoxide).

## 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 KMnO<sub>4</sub> followed by gentle warming. Organic layers were routinely dried with anhydrous MgSO<sub>4</sub> 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 spectrometer with only selected absorbances quoted as  $\nu$  in cm<sup>-1</sup>. NMR spectra were run on Bruker Avance 250, 300, 400 or 500 MHz instruments at 298 K. A microTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10  $\mu$ L of sample was injected into a 30 : 70 flow of water–acetonitrile at 0.6 mL min<sup>-1</sup> to the mass spectrometer. For each acquisition 10  $\mu$ L of calibrant of 5 mM sodium formate was injected after the sample. The observed mass and isotope

pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

**Synthesis of (1S,2R)-1,2-dihydroxycyclohexane-1-carboxylic acid (5).** A stirred solution of **4** (857 mg, 5.48 mmol) and Pd/C (50 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 (60 : 35 : 2.5 : 2.5 EtOAc–petrol–H<sub>2</sub>O–AcOH) to yield pure **5** (625 mg, 71%) as a white crystalline solid. m.pt = 112–115 °C;  $R_f$  = 0.10 (60 : 35 : 2.5 : 2.5 EtOAc–petrol–H<sub>2</sub>O–AcOH);  $[\alpha]_D^{25} +13.3$  (c 0.3, H<sub>2</sub>O); <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O)  $\delta$  = 3.77 (1H, dd,  $J$  = 11.5, 3.5 Hz, CH(OH)), 1.60–1.56 (4H, m, CH), 1.40–1.08 (4H, m, CH); <sup>13</sup>C NMR (125 MHz, MeOH-*d*<sub>4</sub>)  $\delta$  = 180.1 (C=O), 79.5 (C(OH)CO<sub>2</sub>H), 73.7 (CH(OH)), 35.0, 30.8, 25.3, 21.1;  $\nu_{\max}$  (film) 3445, 3086, 2924, 2858, 1736, 1439, 1199, 1138, 1023, 948, 821 cm<sup>-1</sup>; HRMS (ESI<sup>-</sup>)  $m/z$  calcd for (C<sub>7</sub>H<sub>11</sub>O<sub>4</sub>)<sup>-</sup>, 159.0663; found 159.0672.

**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–C<sub>6</sub>H<sub>6</sub> (6 mL, 1 : 1), was added dropwise TMS-CHN<sub>2</sub> (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-CHN<sub>2</sub> toxic by inhalation). Pure **6** was obtained as a yellow oil (52 mg, 100%).  $R_f$  = 0.05 (30% EtOAc–petrol);  $[\alpha]_D -10.0$  (c 0.3, CHCl<sub>3</sub>); <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.82–3.74 (1H, m, CH(OH)), 3.77 (3H, s, CH<sub>3</sub>), 2.86 (2H, br s, OH), 1.83–1.22 (8H, m, CH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 176.6 (C=O), 76.8 (C(OH)(CO<sub>2</sub>CH<sub>3</sub>)), 72.2 (CH(OH)), 52.9 (OCH<sub>3</sub>), 34.2, 30.1, 24.0, 19.8;  $\nu_{\max}$  (film) 3453, 2938, 2861, 1729, 1438, 1272, 1238, 1207, 1149, 1079, 998, 923 cm<sup>-1</sup>; HRMS (ESI<sup>+</sup>)  $m/z$  calcd for (C<sub>8</sub>H<sub>15</sub>O<sub>4</sub>)<sup>+</sup>, 175.0965; found 175.0981. NMR Data are in agreement with those previously reported.<sup>33</sup>

**Synthesis of methyl (3aS,7aR)-2,2-dimethyltetrahydrobenzo-[d][1,3]dioxole-3a(4H)-carboxylate (7) and (1R,2S)-2-hydroxy-2-(methoxycarbonyl)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 NaHCO<sub>3(aq)</sub> (1.0 M, 20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over MgSO<sub>4</sub> 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**:  $R_f$  = 0.70 (30% EtOAc–petrol);  $[\alpha]_D^{25} -37.8$  (c 0.65, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.35 (1H, t,  $J$  = 3.5 Hz, CH(OC(CH<sub>3</sub>)<sub>2</sub>)), 3.76 (3H, s, OCH<sub>3</sub>), 2.06–1.93 (2H, m, CH), 1.85–1.23 (6H, m, CH); 1.50 (3H, d,  $J$  = 0.5 Hz, CH<sub>3</sub>) 1.35 (3H, d,  $J$  = 0.5 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.2



(C=O), 109.0 (C(CH<sub>3</sub>)<sub>2</sub>), 81.0 (C(OC(CH<sub>3</sub>)<sub>2</sub>)(CO<sub>2</sub>CH<sub>3</sub>)), 75.0 (CH(OC(CH<sub>3</sub>)<sub>2</sub>)), 52.5 (OCH<sub>3</sub>), 32.3, 28.0, 26.0, 25.9, 20.5, 18.7;  $\nu_{\max}$  (film) 2997, 2941, 2873, 1733, 1450, 1383, 1217, 1160, 1054, 1025, 905, 725 cm<sup>-1</sup>; HRMS (ESI+)  $m/z$  calcd for (C<sub>11</sub>H<sub>18</sub>NaO<sub>4</sub>)<sup>+</sup>, 237.1097; found 237.1079. Data for **8**:  $R_f$  = 0.85 (50% EtOAc–petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –21 ( $c$  1.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 5.08 (1H, dd,  $J$  = 10.0, 6.0 Hz, CH(OC=O)), 4.26 (1H, t,  $J$  = 3.2 Hz, CH(O)), 3.73 (3H, s, OCH<sub>3</sub>), 3.24 (1H, s, OH), 2.06–1.24 (16H, m, CH), 1.50 (3H, s, CH<sub>3</sub>), 1.35 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  = 175.3 (C=O), 171.8 (C=O), 108.9 (C(CH<sub>3</sub>)<sub>3</sub>), 80.7, 75.6, 75.2, 74.9, 53.0 (OCH<sub>3</sub>), 34.1, 32.2, 27.8, 26.2, 25.7, 25.6, 23.6, 20.2, 19.7, 18.3;  $\nu_{\max}$  (film) 3523, 2987, 2938, 2865, 1733, 1449, 1381, 1370, 1243, 1216, 1152, 1124, 1046, 1003, 874, 735 cm<sup>-1</sup>; HRMS (ESI+)  $m/z$  calcd for (C<sub>18</sub>H<sub>29</sub>O<sub>7</sub>)<sup>+</sup>, 357.1908; found 357.1929.

**Synthesis of (3aS,7aR)-2,2-dimethylhexahydrobenzo[d][1,3]-dioxole-3a-carboxylic acid (9) and (5S,6R)-6-hydroxy-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-4-one (10) from ester 7.** Ester **7** (253 mg, 1.18 mmol) was dissolved in THF (10 mL) and NaOH (6.0 mL, 2.0 M in H<sub>2</sub>O, 12 mmol, 10 equiv.) and refluxed for 14 h. The resulting solution was washed with EtOAc (3 × 10 mL) to remove any unreacted starting material. The aqueous layer was acidified to pH 2.0 with HCl and extracted with EtOAc (3 × 10 mL) and combined organic layers were washed with saturated brine and dried over MgSO<sub>4</sub>. The resulting oil was purified *via* flash column chromatography (50% EtOAc–petrol) to give desired acid **9** (20 mg, 8%), acetone migration product **10** (30 mg, 13%) and deprotected diol acid **5** (40 mg, 21%). Data for **9**:  $R_f$  = 0.40 (50% EtOAc–petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –40.0 ( $c$  0.70, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.31 (1H, t,  $J$  = 3.5 Hz, CH(OC(CH<sub>3</sub>)<sub>2</sub>)), 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, CH<sub>3</sub>), 1.43 (3H, s, CH<sub>3</sub>), 1.28–1.21 (1H, m, CH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 175.6 (C=O), 109.6 (C(CH<sub>3</sub>)<sub>2</sub>), 80.7 (C(OC(CH<sub>3</sub>)<sub>2</sub>)(CO<sub>2</sub>H)), 74.9 (CH(OC(CH<sub>3</sub>)<sub>2</sub>)), 32.2, 28.0, 26.0, 25.7, 20.7, 18.5;  $\nu_{\max}$  (film) 2994, 2939, 2873, 2714, 1450, 1371, 1383, 1217, 1174, 905, 725 cm<sup>-1</sup>; HRMS (ESI–)  $m/z$  calcd for (C<sub>10</sub>H<sub>15</sub>O<sub>4</sub>)<sup>–</sup>, 199.0976; found 199.0975. Data for **10**:  $R_f$  = 0.83 (50% EtOAc–petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +2.0 ( $c$  1.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 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 (3H, s, CH<sub>3</sub>), 1.63 (3H, s, CH<sub>3</sub>), 1.49–1.55 (1H, m, CH), 1.44–1.48 (1H, m, CH), 1.38 (1H, tt,  $J$  = 13.0, 3.5 Hz, CH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.0 (C=O), 110.1 (C(CH<sub>3</sub>)<sub>2</sub>), 83.2 (C(O)(C=O)), 71.0 (C(OH)H), 33.7 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 29.1 (C(CH<sub>3</sub>)<sub>2</sub>), 27.9 (C(CH<sub>3</sub>)<sub>2</sub>), 23.6 (CH<sub>2</sub>), 20.1 (CH<sub>2</sub>);  $\nu_{\max}$  (film) 3484, 2991, 2939, 2863, 2774, 1448, 1385, 1291, 1262, 1060, 1036, 908, 860, 626 cm<sup>-1</sup>; HRMS (ESI+)  $m/z$  calcd for (C<sub>10</sub>H<sub>17</sub>O<sub>4</sub>)<sup>+</sup>, 201.1121; found 201.1113.

**Synthesis of benzyl (1S,6R)-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate (11).** Benzyl bromide (0.92 mL, 7.60 mmol, 1.1 equiv.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (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 CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The resulting

solution was stirred for 20 h at room temperature, then diluted with H<sub>2</sub>O (50 mL), and extracted with EtOAc (4 × 50 mL). The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (10 → 80% EtOAc–petrol) gave **11** as a colourless oil. (1.30 g, 76%).  $R_f$  = 0.29 (40% EtOAc–petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –135.6 ( $c$  1.6, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 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, CO<sub>2</sub>–CH<sub>2</sub>–Ar), 4.87 (1H, m, C(O)H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  = 175.2 (C=O), 135.1, 132.1, 128.8, 128.7, 128.2, 127.0, 124.8, 122.9, 74.1 (C(OH)C=O), 71.1 (C(OH)–H), 68.5 (O–CH<sub>2</sub>);  $\nu_{\max}$  (film) 3451, 3038, 1731, 1660, 1455, 1378, 1234, 1168, 1077, 1020, 909, 753, 695 cm<sup>-1</sup>; HRMS (+ve ESI-TOF)  $m/z$  calculated for (C<sub>14</sub>H<sub>14</sub>NaO<sub>4</sub>)<sup>+</sup>, 269.0784; found 269.0863.

**Synthesis of benzyl (3aS,7aR)-2,2-dimethylbenzo[d][1,3]-dioxole-3a(7aH)-carboxylate (12).** To a stirred solution of **11** (335 mg, 1.37 mmol) dissolved in acetone (10 mL, freshly distilled), was added 2,2-dimethoxypropane (2.0 mL, 16.46 mmol, 12 equiv.) and *para*-toluenesulfonic 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 MgSO<sub>4</sub> 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%).  $R_f$  = 0.60 (30% EtOAc–petrol); <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  = 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, CH<sub>2</sub>), 4.97 (1H, d,  $J$  = 4.0 Hz, CH(O)), 1.38 (3H, s, CH<sub>3</sub>), 1.37 (3H, s, CH<sub>3</sub>). Data in agreement with those previously reported.<sup>6e</sup>

**Synthesis of (3aS,7aR)-2,2-dimethylhexahydrobenzo[d][1,3]-dioxole-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 (3aS,7aR)-2,2-di-*tert*-butylbenzo[d][1,3,2]-dioxasilole-3a(7aH)-carboxylate (13).** To a stirred solution of **11** (48 mg, 0.195 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added triethylamine (65  $\mu$ L, 0.468 mmol, 2.4 equiv.) and di-*tert*-butylsilyl diethyl bis(trifluoromethanesulfonate) (70  $\mu$ L, 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 MgSO<sub>4</sub> 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%).  $R_f = 0.65$  (10% EtOAc–petrol);  $[\alpha]_D^{25} -327.0$  ( $c$  3.31,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta = 7.35\text{--}7.31$  (5H, m, 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, –CHH–), 5.18 (1H, d,  $J = 12.0$  Hz, –CHH–), 4.97 (1H, d,  $J = 1.8$  Hz, CH(OSi)), 0.99 (9H, s,  $\text{CH}_3$ ), 0.98 (9H, s,  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 172.2$  (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(OSi)), 67.4 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_3$ ), 26.9 ( $\text{CH}_3$ ), 21.2 ( $\text{C}(\text{CH}_3)_3$ ), 20.2 ( $\text{C}(\text{CH}_3)_3$ );  $\nu_{\text{max}}$  (film) 3045, 2966, 2934, 2891, 2859, 1733, 1473, 1229, 1091, 1031, 1012, 1000, 875, 825, 696  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{22}\text{H}_{31}\text{O}_4\text{Si})^+$ , 387.1986; found 387.1993.

**Synthesis of (3*S*,7*aR*)-2,2-di-*tert*-butyltetrahydrobenzo[*d*]-[1,3,2]dioxasilole-3*a*(4*H*)-carboxylic acid (**14**).** A stirred solution of **13** (61 mg, 0.16 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 (10 → 70% EtOAc–petrol) to give pure **14** (25 mg, 53%) as a colourless oil.  $R_f = 0.30$  (30% EtOAc–petrol);  $[\alpha]_D^{25} -17.0$  ( $c$  0.18,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta = 4.36$  (1H, dd,  $J = 11.0, 4.5$  Hz, CH(OSi)), 1.99–1.20 (8H, m, CH), 1.02 (9H, s,  $\text{CH}_3$ ), 0.98 (9H, s,  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 179.1$  (C=O), 77.9 (C(OSi)(C=O)), 73.9 (CH(OSi)), 33.0, 30.1, 27.7 ( $\text{CH}_3$ ), 27.5 ( $\text{CH}_3$ ), 23.7, 20.5, 20.3, 19.6;  $\nu_{\text{max}}$  (film) 3070, 2935, 2894, 2859, 1717, 1448, 1472, 1094, 827  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{15}\text{H}_{29}\text{O}_4\text{Si})^+$ , 301.1830; found 301.1830.

**Synthesis of methyl (1*S*,2*R*)-1,2-dimethoxycyclohexane-1-carboxylate (**15**) and methyl (1*S*,2*R*)-2-methoxy-1-((trimethylsilyloxy)cyclohexane-1-carboxylate (**17**).** Diol acid **5** (133 mg, 0.83 mmol) in DMF (1.00 mL), was added dropwise to a suspension of NaH (109 mg, 2.74 mmol, 3.3 equiv., 60% 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 5 min. The resulting solution was stirred at  $-22$  °C and allowed to warm to room temperature over 19 h. The solution was cooled to  $-22$  °C,  $\text{NH}_4\text{Cl}_{(\text{aq})}$  (10 mL) was added to the solution dropwise, then the reaction mixture was transferred into a separating funnel. EtOAc (20 mL) was added to the solution and the organic layers were washed with  $\text{LiCl}_{(\text{aq})}$  (3 × 10 mL), dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (5 → 20% EtOAc–petrol) to yield an inseparable mixture of **15** and **16** as a colourless oil (99 mg). The inseparable mixture was dissolved in  $\text{CH}_2\text{Cl}_2$  (3.00 mL), to which was added triethylamine (40  $\mu\text{L}$ , 0.32 mmol) followed by trimethylsilyl trifluoromethanesulfonate (50  $\mu\text{L}$ , 0.29 mmol). The reaction mixture was stirred at room temperature for 30 h, then diluted with EtOAc (20 mL), washed with saturated brine (20 mL), dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (1 → 20% EtOAc–petrol) to give **15** (48 mg, 25%) and **17** (20 mg, 9%) as colourless oils. Data for **15**:  $R_f = 0.20$  (20% EtOAc–petrol);  $[\alpha]_D^{25} -26.9$  ( $c$  2.23,  $\text{CHCl}_3$ );  $^1\text{H NMR}$

(250 MHz,  $\text{CDCl}_3$ )  $\delta = 3.73$  (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.44 (1H, dd,  $J = 11.0, 4.0$  Hz, CH(OCH<sub>3</sub>)), 3.36 (3H, s, OCH<sub>3</sub>), 3.26 (3H, s, OCH<sub>3</sub>), 2.04–0.80 (8H, m, CH);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 174.1$  (C=O), 82.9, 81.7, 57.0, 52.1, 51.8, 29.7, 24.8, 23.5, 20.3;  $\nu_{\text{max}}$  (film) 2938, 2861, 1730, 1446, 1373, 1275, 1227, 1099, 1061, 997  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{10}\text{H}_{19}\text{O}_4)^+$ , 203.1278; found 203.1289. Data for **17**:  $R_f = 0.85$  (20% EtOAc–petrol);  $[\alpha]_D^{25} -1.4$  ( $c$  0.73,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta = 3.73$  (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.47 (1H, dd,  $J = 11.0, 4.5$  Hz, CH(OCH<sub>3</sub>)), 3.29 (3H, s, OCH<sub>3</sub>), 1.85–0.84 (8H, m, CH), 0.15 (9H, s, Si(CH<sub>3</sub>)<sub>3</sub>);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 175.6$  (C=O), 82.2, 76.1, 56.8, 51.8, 36.2, 25.1, 24.0, 20.3, 2.2;  $\nu_{\text{max}}$  (film) 2949, 2860, 1753, 1446, 1366, 1279, 1244, 1156, 1062, 1041, 837, 760, 734  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{12}\text{H}_{25}\text{O}_4\text{Si})^+$ , 261.1517; found 261.1515.

**Synthesis of (1*S*,2*R*)-1,2-dimethoxycyclohexane-1-carboxylic acid (**18**).** Ester **15** (155 mg, 0.76 mmol) was dissolved in THF (1.00 mL) and NaOH (4.00 mL, 2.0 M in H<sub>2</sub>O, 0.020 mol, 60 equiv.) and refluxed for 24 h. The resulting solution was extracted with EtOAc (3 × 20 mL) to remove any unreacted starting material. The remaining aqueous layer was acidified to pH 2.0 and extracted with EtOAc (3 × 20 mL). Combined organic layers were washed with saturated brine and dried over  $\text{MgSO}_4$ , then concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (50 : 45 : 2.5 : 2.5 EtOAc–petrol–AcOH–H<sub>2</sub>O) to give **18** as a colourless oil (108 mg, 75%).  $R_f = 0.25$  (50 : 45 : 2.5 : 2.5 EtOAc–petrol–AcOH–H<sub>2</sub>O);  $[\alpha]_D^{25} -20.5$  ( $c$  0.73,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta = 3.40\text{--}3.37$  (1H, m, CH(OCH<sub>3</sub>)), 3.38 (3H, s, OCH<sub>3</sub>), 3.35 (3H, s, OCH<sub>3</sub>), 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);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta = 175.3$  (C=O), 82.7, 81.2, 57.1, 52.0, 28.1, 24.8, 23.7, 20.0;  $\nu_{\text{max}}$  (film) 3143, 2940, 2860, 2838, 1721, 1464, 1448, 1308, 1196, 1099, 1077, 973, 939  $\text{cm}^{-1}$ ; HRMS (ESI–)  $m/z$  calcd for  $(\text{C}_9\text{H}_{15}\text{O}_4)^-$ , 187.0976; found 187.0972.

**Synthesis of methyl (2*R*,3*S*,7*aR*)-2-phenyltetrahydrobenzo[*d*][1,3]dioxole-3*a*(4*H*)-carboxylate (**19**) and methyl (2*S*,3*aS*,7*aR*)-2-phenyltetrahydrobenzo[*d*][1,3]dioxole-3*a*(4*H*)-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, 10 mol%) were added. The resulting solution was refluxed for 24 h. After cooling, the reaction mixture was diluted with  $\text{NaHCO}_3$  (15 mL) and extracted with EtOAc (3 × 10 mL). Combined organic layers were dried over  $\text{MgSO}_4$ , 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**:  $R_f = 0.49$  (10% EtOAc–petrol);  $[\alpha]_D^{25} -31$  ( $c$  0.7,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta = 7.56\text{--}7.52$  (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, OCH<sub>3</sub>), 2.13–1.81 (4H, m, CH), 1.76–1.45 (4H, m, CH);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 173.4$  (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 (OCH<sub>3</sub>), 31.1, 26.1, 19.4, 18.5;  $\nu_{\max}$  (film) 2951, 2869, 1734, 1451, 1247, 1163, 1088, 1024, 697 cm<sup>-1</sup>; HRMS (ESI+)  $m/z$  calcd for (C<sub>15</sub>H<sub>19</sub>O<sub>4</sub>)<sup>+</sup>, 263.1278; found 263.1267. Data for **20**:  $R_f$  = 0.53 (10% EtOAc-petrol);  $[\alpha]_D^{25}$  -1.6 (c 0.08, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 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, OCH<sub>3</sub>), 2.03–1.89 (4H, m, CH), 1.75–1.39 (4H, m, CH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 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(O)H), 52.3 (OCH<sub>3</sub>), 30.7, 26.2, 20.9, 20.4;  $\nu_{\max}$  (film) 2938, 2863, 1735, 1451, 1247, 1162, 1093, 698 cm<sup>-1</sup>; HRMS (ESI+)  $m/z$  calcd for (C<sub>15</sub>H<sub>19</sub>O<sub>4</sub>)<sup>+</sup>, 263.1278; found 263.1268.

**Synthesis of (S)-2,2-dimethyl-1,3-dioxaspiro[4.5]decane-4,6-dione (21).** To a stirred solution of **10** (25 mg, 0.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added Dess–Martin periodinane (131 mg, 0.31 mmol, 2.5 equiv.). The resulting solution was heated to reflux for 24 h. To the cooled solution was added NaHCO<sub>3(aq)</sub> (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (0 → 20% EtOAc-petrol) to yield **21** as a colourless oil (15 mg, 60%).  $R_f$  = 0.25 (10% EtOAc-petrol);  $[\alpha]_D^{25}$  -50.0 (c 2.2, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 2.81 (1H, ddd,  $J$  = 13.9, 10.9, 5.5 Hz), 2.63 (1H, dt,  $J$  = 13.9, 5.5 Hz), 2.32–2.17 (2H, m), 2.08–1.97 (2H, m), 1.86–1.73 (2H, m), 1.62 (3H, s, CH<sub>3</sub>), 1.57 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  = 203.1 (C=O), 169.3 (C=O), 111.4 (C(CH<sub>3</sub>)<sub>2</sub>), 85.2, 39.5, 38.7, 28.4, 27.5, 26.6, 21.0;  $\nu_{\max}$  (film) 2996, 2941, 2921, 2872, 2851, 1784, 1732, 1394, 1380, 1283, 1254, 1130, 1077, 1045, 930 cm<sup>-1</sup>; HRMS (ESI+)  $m/z$  calcd for (C<sub>10</sub>H<sub>14</sub>NaO<sub>4</sub>)<sup>+</sup>, 221.0784; found 221.0787.

**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 CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and cooled to -78 °C. Triethylamine (355  $\mu$ L, 257 mg, 2.54 mmol, 1.2 equiv.) was added dropwise, then *tert*-butyldimethylsilyl trifluoromethanesulfonate (487  $\mu$ L, 560 mg, 2.12 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h, then quenched by addition of H<sub>2</sub>O (20 mL). Phases were separated and the organic phase was washed further with NaCl<sub>(aq)</sub> (satd, 20 mL). The organic phase was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (10% EtOAc-petrol) to give **22** (465 mg, 76%) as a colourless oil.  $R_f$  = 0.60 (20% EtOAc-petrol);  $[\alpha]_D^{25}$  -7.0 (c 1.3, CHCl<sub>3</sub>); <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.94 (1H, dd,  $J$  = 10.5, 5.0 Hz), 3.72 (3H, s), 3.05 (1H, d,  $J$  = 1.5 Hz), 1.91–1.14 (8H, m), 0.83 (9H, s), 0.04 (3H, s), -0.02 (3H, s); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 176.1 (C=O), 77.5 (C(OH)), 73.8 (CH(OSi)), 52.2, 33.1, 30.1 (CH), 25.6 (SiC(CH<sub>3</sub>)<sub>3</sub>), 23.8, 19.6, 17.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), -4.1, -5.2;  $\nu_{\max}$  (film) 3555, 3027, 2928, 1705, 1494, 1453, 1281, 908, 732, 699 cm<sup>-1</sup>; HRMS (ESI+)  $m/z$  calcd for (C<sub>14</sub>H<sub>29</sub>O<sub>4</sub>Si)<sup>+</sup>, 289.1830; found 289.1831.

**Synthesis of (1R,2R)-2-((tert-butyldimethylsilyl)oxy)-1-(hydroxymethyl)cyclohexane-1-ol (23) and (1R,2R)-1-(((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 LiAlH<sub>4</sub> (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 reaction was quenched with addition of H<sub>2</sub>O (0.05 mL) followed by NaOH (10% aq. sol., 0.09 mL) followed by H<sub>2</sub>O (0.14 mL). The solution was filtered through MgSO<sub>4</sub> 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.

**Alternative procedure.** To a stirred solution of **22** (465 mg, 1.6 mmol) in THF at -78 °C was added dropwise LiBH<sub>4</sub> (0.80 mL, 4.0 M in THF, 3.22 mmol, 2.0 equiv.) over 20 min. The resulting solution was left to warm to room temperature for 12 h. The solution was quenched with addition of Et<sub>2</sub>O (10 mL) followed by H<sub>2</sub>O (10 mL). The mixture was separated, and the aqueous layer extracted with EtOAc (4 × 10 mL); the organic layers were combined, dried with MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (5 → 20% EtOAc-petrol) to yield **23** (400 mg, 91%) as a colourless oil. Data for **23**:  $R_f$  = 0.45 (20% EtOAc-petrol);  $[\alpha]_D^{25}$  -18 (c 0.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.65 (1H, br s), 3.56 (1H, d,  $J$  = 10.0 Hz), 3.37 (1H, d,  $J$  = 10.0 Hz), 2.51 (2H, br s, OH), 1.82 (1H, d,  $J$  = 13.0 Hz), 1.63 (3H, m), 1.52 (1H, m), 1.40 (1H, m), 1.29 (1H, m), 1.19–1.14 (1H, m), 0.89 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.08 (6H, s, SiCH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 73.2, 72.9, 68.3 (OCH<sub>2</sub>), 31.7, 30.7, 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 23.2, 20.7, 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), -4.0 (SiCH<sub>3</sub>), -5.0 (SiCH<sub>3</sub>);  $\nu_{\max}$  (film) 3443, 2930, 2857, 1463, 1389, 1261, 1252, 1079, 835, 777 cm<sup>-1</sup>; HRMS (ESI+)  $m/z$  calcd for (C<sub>13</sub>H<sub>29</sub>O<sub>3</sub>Si)<sup>+</sup>, 261.1881; found 261.1886. Data for **24**:  $R_f$  = 0.55 (20% EtOAc-petrol);  $[\alpha]_D^{25}$  +10 (c 0.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 3.66 (1H, d,  $J$  = 10.0 Hz), 3.64 (1H, dd,  $J$  = 10.0, 4.5 Hz), 3.52 (1H, d,  $J$  = 10.0 Hz), 1.73–1.63 (3H, m), 1.60–1.50 (2H, m), 1.45–1.39 (1H, m), 1.22–1.08 (2H, m), 0.90 (9H, s), 0.09 (3H, s), 0.08 (3H, s); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  = 73.8, 71.9, 71.8, 31.8, 29.5, 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 23.5, 20.3, 18.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), -5.5 (SiCH<sub>3</sub>), -5.6 (SiCH<sub>3</sub>);  $\nu_{\max}$  (film) 3555, 3027, 2929, 1494, 1453, 1218, 908, 732, 699 cm<sup>-1</sup>; HRMS (ESI+)  $m/z$  calcd for (C<sub>13</sub>H<sub>29</sub>O<sub>3</sub>Si)<sup>+</sup>, 261.1881; found 261.1858.

**Synthesis of tert-butyl(((5R,6R)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-yl)oxy)dimethylsilane (25).** To a stirred solution of **23** (1.81 g, 6.59 mmol) dissolved in acetone (10 mL, freshly distilled), was added 2,2-dimethoxypropane (12 mL, 100 mmol) and *para*-toluenesulfonic acid (13 mg, 0.06 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 were combined and washed with saturated brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (10 → 20% EtOAc-petrol) to give **25** as a colourless oil (1.72 g, 86%).  $R_f$  = 0.80 (10% EtOAc-



petrol);  $[\alpha]_D^{25} -20$  ( $c$  0.3,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta = 3.88$  (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,  $\text{O-C}(\text{CH}_3)_2$ ), 0.90 (9H, s  $\text{SiC}(\text{CH}_3)_3$ ), 0.07 (3H, s,  $\text{SiCH}_3$ ), 0.05 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 109.2, 83.4, 72.9, 70.9, 34.0, 32.2, 27.7, 26.9, 25.9, 22.6, 21.6, 18.2, -4.5, -4.6$ ;  $\nu_{\text{max}}$  (film) 2988, 2933, 2894, 2856, 1472, 1462, 1377, 1368, 1251, 1212, 1141, 1094, 1056, 988, 898, 773  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{16}\text{H}_{32}\text{NaO}_3\text{Si})^+$ , 323.2013; found 323.2015.

**Synthesis of (5*R*,6*R*)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-ol (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  $\text{Et}_2\text{O}$  (10 mL) and  $\text{NH}_4\text{Cl}_{(\text{aq})}$  (10 mL). The reaction mixture was extracted with EtOAc (4  $\times$  10 mL) and the organic layers were combined and washed with saturated brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (5% EtOAc–petrol) to yield 26 as a colourless oil (591 mg, 55%).  $R_f = 0.30$  (20% EtOAc–petrol);  $[\alpha]_D^{25} -4.0$  ( $c$  0.9,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta = 3.99$  (1H, d,  $J = 8.5$  Hz), 3.71 (1H, d,  $J = 8.5$  Hz), 3.49 (1H, m), 2.11 (1H, br s, OH), 1.99–1.23 (8H, m), 1.40 (3H, s), 1.39 (3H, s);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta = 109.4, 83.2, 71.5, 71.3, 33.7, 31.2, 29.7, 27.2, 27.1, 22.6$ ;  $\nu_{\text{max}}$  (film) 3204, 2930, 2855, 1563, 1406, 1371, 1184, 903, 729  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{10}\text{H}_{18}\text{NaO}_3)^+$ , 209.1148; found 209.1104.

**Synthesis of (R)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-one (27).** To alcohol 26 (591 mg, 3.17 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added Dess–Martin periodinane (2.69 g, 6.3 mmol, 2.0 equiv.) and left to stir at room temperature for 72 h. The reaction was quenched with the addition of water (20 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (5  $\times$  10 mL) and the organic layers were combined and washed with saturated brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (10% EtOAc–petrol) to yield 27 as a colourless oil (517 mg, 86%).  $R_f = 0.50$  (20% EtOAc–petrol);  $[\alpha]_D^{25} -6.0$  ( $c$  1.6,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta = 4.42$  (1H, d,  $J = 8.5$  Hz), 3.65 (1H, d,  $J = 8.5$  Hz), 2.78 (1H, ddd,  $J = 15.0, 9.0, 5.0$  Hz), 2.34–2.27 (1H, m), 2.04–1.86 (3H, m), 1.80–1.59 (3H, m), 1.40 (3H, s), 1.33 (3H, s);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta = 209.1, 110.5, 85.5, 69.1, 39.7, 38.5, 27.4, 26.9, 26.1, 22.3$ ;  $\nu_{\text{max}}$  (film) 2986, 2937, 2865, 1723, 1452, 1431, 1380, 1371, 1050, 858, 811  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{10}\text{H}_{16}\text{NaO}_3)^+$ , 207.0992; found 207.0995.

**Synthesis of (((3*aR*,4*S*,7*R*,7*aS*)-3*a*,4,7,7*a*-tetrahydro-4,7-bis-(methoxymethoxy)-2,2-dimethylbenzo[*d*][1,3]dioxole-7*a*-yl)methoxy)-(tert-butyl)dimethylsilane (31).** To a solution of known<sup>4i</sup> diol 30 (304 mg, 0.92 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added *N*-ethyl-diisopropylamine (1.61 mL, 9.20 mmol, 10.0 equiv.), followed dropwise by methoxymethyl chloride (0.42 mL, 5.52 mmol, 6.0 equiv.). The resulting solution was left to stir at room temperature for 16 h. The reaction mixture

was extracted with EtOAc (3  $\times$  30 mL) and the combined organic layers were washed with water (30 mL) and brine (30 mL). The resulting solution was dried over  $\text{MgSO}_4$ . Removal of the solvent under reduced pressure and purification by flash column chromatography (5  $\rightarrow$  30% EtOAc–petrol) gave 31 as a colourless oil (254 mg, 66% yield).  $R_f = 0.64$  (20% EtOAc–petrol);  $[\alpha]_D^{25} -22.2$  ( $c$  0.09,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta = 5.74$  (2H, s,  $\text{C}=\text{CH}$ ), 4.86 (1H, d,  $J = 6.5$  Hz,  $\text{OCH}_2\text{O}$ ), 4.85 (1H, d,  $J = 6.5$  Hz,  $\text{OCH}_2\text{O}$ ), 4.72 (1H, d,  $J = 6.5$  Hz,  $\text{OCH}_2\text{O}$ ), 4.70 (1H, d,  $J = 6.5$  Hz,  $\text{OCH}_2\text{O}$ ), 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,  $\text{CHHOTBDMS}$ ), 3.49 (1H, d,  $J = 11.0$  Hz,  $\text{CHHOTBDMS}$ ), 3.41 (3H, s,  $\text{CH}_2\text{OCH}_3$ ), 3.39 (3H, s,  $\text{CH}_2\text{OCH}_3$ ), 1.47 (3H, s,  $\text{O-C-CH}_3$ ), 1.43 (3H, s,  $\text{O-C-CH}_3$ ), 0.89 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 0.04 (6H, s,  $\text{Si}(\text{CH}_3)_2$ );  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 130.3$  ( $\text{HC}=\text{CH}$ ), 127.9 ( $\text{HC}=\text{CH}$ ), 108.9 ( $\text{C}(\text{CH}_3)_2$ ), 96.3 ( $\text{OCH}_2\text{O}$ ), 95.5 ( $\text{OCH}_2\text{O}$ ), 85.3 ( $4^\circ\text{CCH}_2\text{O}$ ), 78.4 (CHO), 76.8 (CHO), 75.0 (CHO), 61.9 ( $\text{CH}_2\text{OTBDMS}$ ), 55.5 ( $\text{OCH}_3$ ), 55.4 ( $\text{OCH}_3$ ), 28.4 ( $\text{CCH}_3$ ), 27.0 ( $\text{CCH}_3$ ), 25.9 ( $\text{SiC}(\text{CH}_3)_3$ ), 18.3 ( $\text{SiC}(\text{CH}_3)_3$ ),  $-5.3$  ( $\text{SiCH}_3$ ),  $-5.7$  ( $\text{SiCH}_3$ );  $\nu_{\text{max}}$  (film) 2954, 1252, 1043, 907, 837, 732, 649  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{20}\text{H}_{38}\text{NaO}_7\text{Si})^+$ , 441.2279; found 441.2285.

**Synthesis of (3*aS*,4*R*,5*S*,6*R*,7*S*,7*aR*)-3*a*-((tert-butyl)dimethylsilyloxy)methyl-4,7-bis(methoxymethoxy)-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– $\text{H}_2\text{O}$  (4:1, 8.0 mL) was added NMO (43.4 mg, 0.370 mmol, 2.0 equiv.) followed dropwise by  $\text{OsO}_4$  (40  $\mu\text{L}$ , 2.5% w/v in *tert*-BuOH, 3.7  $\mu\text{mol}$ ). The resulting solution was stirred at room temperature for 72 h. The reaction mixture was diluted with EtOAc (30 mL) and extracted with saturated  $\text{Na}_2\text{S}_2\text{O}_3_{(\text{aq})}$  (2  $\times$  30 mL). The organic phase was washed with brine (30 mL) and dried over  $\text{MgSO}_4$ . 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);  $[\alpha]_D^{25} -10.0$  ( $c$  0.1,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta = 4.82$  (2H, s,  $\text{OCH}_2\text{O}$ ), 4.74 (1H, d,  $J = 6.5$  Hz,  $\text{OCHHO}$ ), 4.67 (1H, d,  $J = 6.5$  Hz,  $\text{OCHHO}$ ), 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,  $\text{CHHOTBDMS}$ ), 3.94–3.89 (1H, m, CHO) 3.79 (1H, dd,  $J = 10.0, 4.0$  Hz, CHO) 3.64 (1H, d,  $J = 11.0$  Hz,  $\text{CHHOTBDMS}$ ), 3.45 (3H, s,  $\text{CH}_2\text{OCH}_3$ ), 3.40 (3H, s,  $\text{CH}_2\text{OCH}_3$ ), 3.05 (1H, br s, OH), 1.51 (3H, s,  $\text{C}(\text{CH}_3)_2$ ), 1.37 (3H, s,  $\text{C}(\text{CH}_3)_2$ ), 0.89 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 0.07 (3H, s,  $\text{SiCH}_3$ ), 0.06 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 108.6$  ( $\text{C}(\text{CH}_3)_2$ ), 98.1 ( $\text{OCH}_2\text{OCH}_3$ ), 95.9 ( $\text{OCH}_2\text{OCH}_3$ ), 85.3 ( $4^\circ\text{CCH}_2\text{O}$ ), 83.0 (CHO), 76.4 (CHO), 73.4 (CHO), 70.9 (CHO), 69.5 (CHO), 61.2 ( $\text{CH}_2\text{OTBDMS}$ ), 55.9 ( $\text{CH}_2\text{OCH}_3$ ), 55.8 ( $\text{CH}_2\text{OCH}_3$ ), 28.2 ( $\text{C}(\text{CH}_3)_2$ ), 26.3 ( $\text{C}(\text{CH}_3)_2$ ), 25.9 ( $\text{SiC}(\text{CH}_3)_3$ ), 18.3 ( $\text{SiC}(\text{CH}_3)_3$ ),  $-5.4$  ( $\text{SiCH}_3$ ),  $-5.7$  ( $\text{SiCH}_3$ );  $\nu_{\text{max}}$  (film) 3455, 2930, 2857, 1463, 1370, 1252, 1217, 1152, 1101, 1033, 999, 948, 919, 859, 837, 814, 777, 675  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{20}\text{H}_{40}\text{NaO}_9\text{Si})^+$ , 475.2334; found 475.2344.

**Synthesis of (1*R*,2*S*,3*R*,4*S*,5*R*,6*S*)-6-(acetoxymethyl)-6-hydroxycyclohexane-1,2,3,4,5-pentayl pentaacetate (33).** To a solution of 32 (53.0 mg, 0.17 mmol) in  $\text{Et}_2\text{O}$  (5 mL) was added





HCl<sub>(aq)</sub> (1.0 M, 5 mL). The solution was stirred vigorously at room temperature for 24 h, then diluted with Et<sub>2</sub>O (10 mL) and extracted with H<sub>2</sub>O (3 × 10 mL). The combined aqueous layers were concentrated under reduced pressure to give heptaol **34**. <sup>1</sup>H 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 NaHCO<sub>3(aq)</sub> (satd, 3 × 10 mL) and H<sub>2</sub>O (3 × 10 mL), then dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification *via* flash column chromatography (50% EtOAc–petrol) gave **33** as a colourless oil (22 mg, 37%). *R*<sub>f</sub> = 0.29 (50% EtOAc–petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –5.5 (*c* 0.36, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 5.66 (1H, t, *J* = 10.0 Hz), 5.34 (1H, t, *J* = 3.5 Hz), 5.29 (1H, d, *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, –CHHOAc), 3.95 (1H, d, *J* = 12.0 Hz, –CHHOAc), 2.15 (3H, s, –OAc), 2.14 (3H, s, –OAc), 2.11 (3H, s, –OAc), 2.05 (3H, s, –OAc), 2.02 (3H, s, –OAc), 1.98 (3H, s, –OAc); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 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 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 20.6 (CH<sub>3</sub>), 20.5 (CH<sub>3</sub>), 20.5 (CH<sub>3</sub>);  $\nu_{\max}$  (film) 3479, 2965, 1745, 1431, 1369, 1218, 1039, 899, 821, 731 cm<sup>–1</sup>; HRMS (ESI+) *m/z* calcd for (C<sub>19</sub>H<sub>26</sub>NaO<sub>13</sub>)<sup>+</sup>, 485.1266; found 485.1318.

**Synthesis of (1S,2R,3S,4R,5S,6R)-1-(hydroxymethyl)cyclohexane-1,2,3,4,5,6-hexaol (34).** Hexaacetate **33** (22 mg, 0.0476 mmol) was dissolved in MeOH (5 mL) at room temperature. NH<sub>3(g)</sub> 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 under high vacuum (flask heated to 60 °C to drive off acetamide) to give pure **34** (9 mg, 99%) as a colourless gum. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +2.78 (*c* 3.3, H<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O)  $\delta$  = 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, d, *J* = 9.5 Hz); <sup>13</sup>C NMR (75 MHz, D<sub>2</sub>O)  $\delta$  = 77.8, 73.6, 72.5, 71.5, 71.2, 69.3, 63.8;  $\nu_{\max}$  (film) 3331, 2956, 2922, 2854, 1667, 1540, 1455, 1205, 1151, 1020, 742 cm<sup>–1</sup>; HRMS (ESI+) *m/z* calcd for (C<sub>7</sub>H<sub>14</sub>NaO<sub>7</sub>)<sup>+</sup>, 233.0632; found 233.0620.

**Synthesis of ((3aR,7aR)-2,2-dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methyl acetate (36).** To a stirred solution of known<sup>4i</sup> alcohol **35** (637 mg, 3.50 mmol, 1 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added triethylamine (0.48 mL, 3.49 mmol, 1 equiv.), DMAP (42 mg, 0.35 mmol, 10 mol%) and Ac<sub>2</sub>O (0.33 mL, 3.50 mmol, 1 equiv.). The reaction mixture was stirred for 30 min, then H<sub>2</sub>O (20 mL) was added. The reaction mixture was then extracted with EtOAc (4 × 20 mL). The organic layers were combined and dried over MgSO<sub>4</sub> 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. *R*<sub>f</sub> = 0.45 (15% EtOAc–petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –81.6 (*c* 1.20, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 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, CHOC-

(CH<sub>3</sub>)<sub>2</sub>), 4.15 (1H, d, *J* = 11.5 Hz, –CHH–), 3.94 (1H, d, *J* = 11.5 Hz –CHH–), 2.07 (3H, s, OAc), 1.44 (3H, s, CH<sub>3</sub>), 1.37 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 170.6 (C=O), 128.1, 125.4, 124.3, 123.1 (C=C), 106.6 (C(CH<sub>3</sub>)<sub>2</sub>), 78.3 (CO(CH<sub>2</sub>)), 71.8 (C(H)OC(CH<sub>3</sub>)<sub>2</sub>), 66.1 (CH<sub>2</sub>), 27.1, 26.4 (C(CH<sub>3</sub>)<sub>2</sub>), 20.8 (COCH<sub>3</sub>);  $\nu_{\max}$  (film) 2991, 2937, 1741, 1415, 1372, 1239, 1172, 1043, 906, 728, 648 cm<sup>–1</sup>; HRMS (ESI+) *m/z* calcd for (C<sub>12</sub>H<sub>16</sub>NaO<sub>4</sub>)<sup>+</sup>, 247.0941; found 247.0931.

**Synthesis of ((3aR,4R,7S,7aR)-2,2-dimethyl-7,7a-dihydro-4,7-epidioxibenzo[d][1,3]dioxol-3a(4H)-yl)methyl acetate (37) and ((3aR,5aS,6aS,6bR)-2,2-dimethyl-6a,6b-dihydrooxireno[2',3':3,4]-benzo[1,2-d][1,3]dioxol-3a(5aH)-yl)methyl acetate (38).** To a stirred solution of **36** (94 mg, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added a solution of 5,10,15,20-tetraphenyl-21H,23H-porphine (10 mg, 0.016 mmol, 4 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) dropwise over a period of 18 h, while the solution was irradiated with 150 W halogen lamps, and simultaneously sparged with oxygen. After 18 h no more conversion was taking place; the solution was concentrated under reduced pressure and purified *via* flash column chromatography (15% EtOAc–petrol) to give **37** (52 mg, 48%) as a colourless oil, byproduct **38** as a pale pink oil (10 mg, 9%) and recovered starting material **36** (11 mg, 12%). Data for **37**: *R*<sub>f</sub> = 0.35 (15% EtOAc–petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –16.9 (*c* 0.83, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.65 (1H, t, *J* = 8.0 Hz, C=CH), 6.55 (1H, t, *J* = 8.0 Hz, C=CH), 4.88–4.91 (2H, m, C(H)O), 4.55 (1H, d, *J* = 12.0 Hz –CHH–), 4.31 (1H, d, *J* = 12.0 Hz –CHH–), 4.25 (1H, d, *J* = 4.8 Hz, C(H)OC(CH<sub>2</sub>)<sub>3</sub>), 2.13 (3H, s, COCH<sub>3</sub>), 1.39 (3H, s, CH<sub>3</sub>), 1.30 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 170.4 (C=O), 131.5 (C=C), 130.3 (C=C), 112.3 (C(CH<sub>3</sub>)<sub>2</sub>), 79.9 (CO(CH<sub>2</sub>)), 74.6 (C(H)OC(CH<sub>3</sub>)<sub>2</sub>), 72.1 (CHO–O), 71.8 (CHO–O), 65.9 (CH<sub>2</sub>), 27.8 (C(CH<sub>3</sub>)<sub>2</sub>), 26.9 (C(CH<sub>3</sub>)<sub>2</sub>), 20.8 (COCH<sub>3</sub>);  $\nu_{\max}$  (film) 2995, 2988, 2928, 1736, 1348, 1372, 1450, 1244, 1204, 1144, 1039, 919, 743, 712, 644 cm<sup>–1</sup>; HRMS (ESI+) *m/z* calcd for (C<sub>12</sub>H<sub>16</sub>NaO<sub>6</sub>)<sup>+</sup>, 279.0839; found 279.0829. Data for **38**: *R*<sub>f</sub> = 0.40 (15% EtOAc–petrol); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –14.3 (*c* 0.28, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.09 (1H, dd, *J* = 10.0, 4.0 Hz, HC=CHCO), 5.70 (1H, dt, *J* = 10.0, 1.5 Hz, HC=CHCO), 4.65 (1H, t, *J* = 1.0 Hz, CHOC(CH<sub>3</sub>)<sub>2</sub>), 4.33 (1H, *J* = 11.0 Hz, –CHH–), 3.83 (1H, *J* = 11.0 Hz, –CHH–), 3.64 (1H, dd, *J* = 3.5, 2.5 Hz, CH(O)), 3.37 (1H, m, CH(O)), 2.09 (3H, s), 1.41 (3H, s), 1.37 (3H, s); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 170.4 (C=O), 132.5 (C=CC(O)CH<sub>2</sub>), 124.1 (C=CCH(O)), 110.5 (C(CH<sub>3</sub>)<sub>2</sub>), 79.0 (CO(CH<sub>2</sub>)), 71.3 (C(H)OC(CH<sub>3</sub>)<sub>2</sub>), 66.9 (CH<sub>2</sub>), 50.3 (CH(O<sub>epox</sub>)CH(O)), 46.5 (CH(O<sub>epox</sub>)CH=CH), 27.8 (C–CH<sub>3</sub>), 26.6 (C–CH<sub>3</sub>), 20.9 (COCH<sub>3</sub>);  $\nu_{\max}$  (film) 2989, 2943, 1745, 1455, 1379, 1236, 1181, 1162, 1089, 1060, 1042, 989, 829, 721 cm<sup>–1</sup>; HRMS (ESI+) *m/z* calcd for (C<sub>12</sub>H<sub>16</sub>NaO<sub>5</sub>)<sup>+</sup>, 263.0890; found 263.0903.

**Synthesis of ((1aR,1bR,2aR,2bS,5aR,5bS)-4,4-dimethyltetrahydrobis(oxireno)[2',3':3,4;2'',3''':5,6]benzo[1,2-d][1,3]dioxol-2b-(1aH)-yl)methyl acetate (40).** To a stirred solution of **37** (755 mg, 2.94 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added 5,10,15,20-tetraphenyl-21H,23H-porphine cobalt(II) (11 mg, 0.01 mmol, 6 mol%). The solution was stirred for 30 min at room temperature, then concentrated under reduced pressure and purified *via* flash column chromatography (15% EtOAc–petrol) to give



**40** (724 mg, 96%) as a colourless oil.  $R_f = 0.15$  (15% EtOAc-petrol);  $[\alpha]_D^{25} -33.8$  ( $c$  0.80,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta = 4.35$  (1H, d,  $J = 11.0$  Hz,  $-\text{CHH}-$ ), 4.32 (1H, d,  $J = 2.0$  Hz,  $\text{C(H)OC}(\text{CH}_2)_3$ ), 4.02 (1H, d,  $J = 11.0$  Hz,  $-\text{CHH}-$ ), 3.58 (1H, t,  $J = 3.0$  Hz), 3.52 (1H, t,  $J = 3.0$  Hz), 3.39 (1H, dd,  $J = 2.0$ , 3.0 Hz), 3.04 (1H, d,  $J = 3.5$  Hz), 2.11 (3H, s,  $\text{COCH}_3$ ), 1.43 (3H, s,  $\text{CH}_3$ ), 1.42 (3H, s,  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 170.4$  ( $\text{C}=\text{O}$ ), 110.4 ( $\text{C}(\text{CH}_3)_2$ ), 78.2 ( $\text{C}(\text{O})\text{CH}_2\text{OAc}$ ), 71.9 ( $\text{C(H)OC}(\text{CH}_3)_2$ ), 65.5 ( $\text{CH}_2$ ), 51.5 ( $\text{C(H)O}$ ), 50.9 ( $\text{C(H)O}$ ), 47.6 ( $\text{C(H)O}$ ), 47.6 ( $\text{C(H)O}$ ), 28.0 ( $\text{C}(\text{CH}_3)_2$ ), 26.2 ( $\text{C}(\text{CH}_3)_2$ ), 20.8 ( $\text{COCH}_3$ );  $\nu_{\text{max}}$  (film) 2991, 2938, 1742, 1455, 1435, 1380, 1231, 1175, 1063, 1043, 992, 964, 803, 630  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{12}\text{H}_{16}\text{NaO}_6)^+$ , 279.0839; found 279.0861.

**Synthesis of ((1aR,1bR,2aR,2bS,5aR,5bS)-4,4-dimethyltetrahydrobis(oxireno)[2',3':3,4;2'',3'':5,6]benzo[1,2-d][1,3]dioxol-2b-(1aH)-yl)methanol (41).** Acetate **40** (23 mg, 0.089 mmol) was dissolved in MeOH (10 mL) at room temperature,  $\text{NH}_3(\text{g})$  was slowly bubbled through the reaction mixture for 10 h, then the reaction mixture was concentrated under reduced pressure and purified *via* flash column chromatography (50% EtOAc-petrol) to give **41** (18 mg, 95%) as a colourless oil.  $R_f = 0.20$  (50% EtOAc-petrol);  $[\alpha]_D^{25} -46$  ( $c$  1.02,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta = 4.41$  (1H, d,  $J = 2.0$  Hz,  $\text{C(H)OC}(\text{CH}_2)_3$ ), 3.77 (1H, d,  $J = 11.0$  Hz,  $-\text{CHH}-$ ), 3.61 (1H, d,  $J = 11.0$  Hz,  $-\text{CHH}-$ ), 3.57 (1H, t,  $J = 3.0$  Hz  $\text{C(H)O}$ ), 3.53 (1H, t,  $J = 3.5$  Hz,  $\text{C(H)O}$ ), 3.41 (1H, dd,  $J = 3.5$ , 2.0 Hz,  $\text{C(H)O}$ ), 3.04 (1H, dd,  $J = 3.5$ , 2.0 Hz,  $\text{C(H)O}$ ), 2.09 (3H, br s, OH), 1.44 (6H, s,  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ) 110.0 ( $\text{C}(\text{CH}_3)_2$ ), 79.4 ( $\text{CO}(\text{CH}_2)$ ), 71.5 ( $\text{C(H)OC}(\text{CH}_3)_2$ ), 64.4 ( $\text{CH}_2$ ), 51.7 ( $\text{C(H)O}$ ), 51.4 ( $\text{C(H)O}$ ), 47.6 ( $\text{C(H)O}$ ), 47.5 ( $\text{C(H)O}$ ), 28.1 ( $\text{CH}_3$ ), 26.5 ( $\text{CH}_3$ );  $\nu_{\text{max}}$  (film) 3491, 2982, 2253, 1457, 1383, 1247, 1219, 1080, 1063, 907, 726, 647  $\text{cm}^{-1}$ ; HRMS (ESI+)  $m/z$  calcd for  $(\text{C}_{10}\text{H}_{14}\text{NaO}_5)^+$ , 237.0733; found 237.0792.

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## Notes and references

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