

RESEARCH ARTICLE

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.

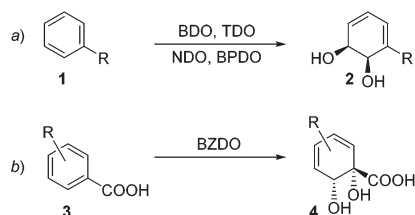
Introduction

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.^{16,9} 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 different regioselectivity and also the opposite absolute sense of enantioinduction. For example, *Ralstonia eutropha* B9¹¹ (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 under-utilised to date in synthesis, in comparison with arene *cis*-diols of type **2**.^{4*i,q,t,5h,i,6a,e,o,14-17*} In the current work, we



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

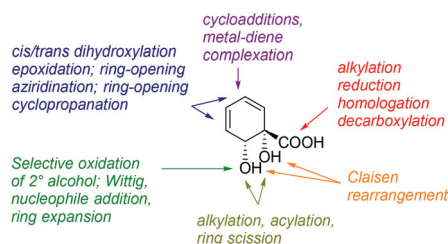


Fig. 1 Possible transformations of diol acid **4**.

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.^{16b} 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

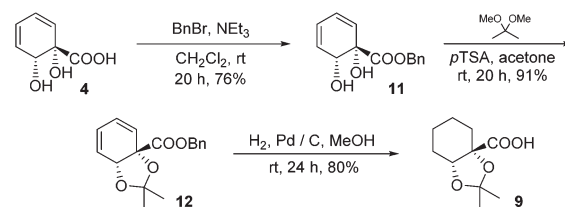
The diene in **4** readily undergoes hydrogenation over palladium on carbon to give saturated cyclohexane diol acid **5** (Scheme 2). Perhaps surprisingly, this compound has not been reported previously, although the diastereoisomeric *trans*-diol is known.¹⁸ Saturation of *ortho,meta* arene *cis*-diols of type **2** to give 3-substituted cyclohexane-1,2-diols and application 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 ^{13}C resonance for the ketal carbon ($\delta = 110.1\text{ ppm}$,

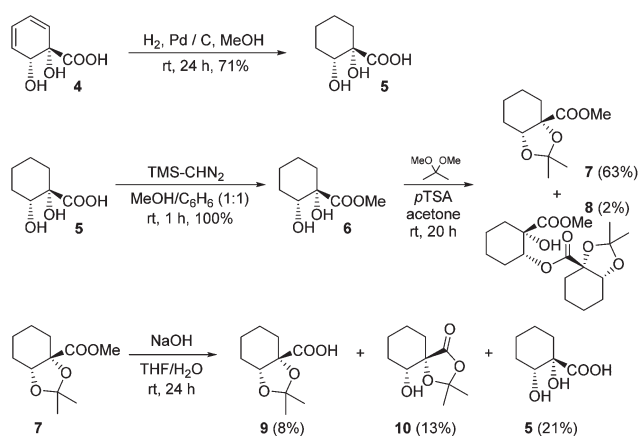
consistent with a five-membered cyclic ketal as opposed to six-membered²⁰), as well as 2D NMR spectroscopic data. In view of the difficulties associated with accessing **9** by means of base-mediated ester cleavage, we instead implemented an approach employing a benzyl ester (Scheme 3). It was found that reliable production of **9** in good yield was best achieved through purification of the final product by dry column chromatography.²¹

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**.

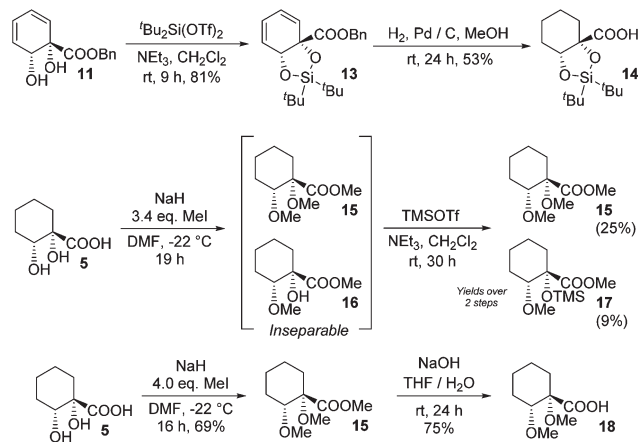
Diol protection as a benzylidene acetal was explored and a moderate (3 : 2) diastereoselectivity was observed for formation of **19** over **20**. Structures were assigned on the basis of NOESY correlations (see ESI[†]); careful chromatography allowed for isolation of both diastereoisomers in pure form. 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



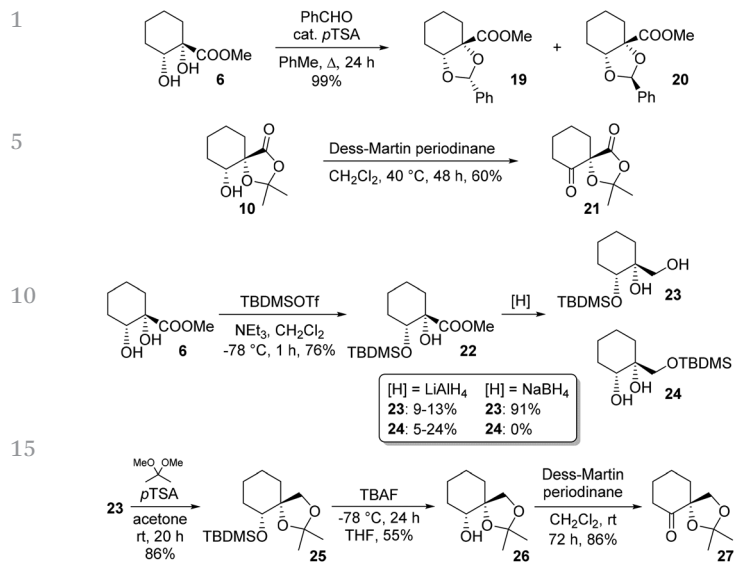
Scheme 3 Benzyl ester route to **9**.



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



Scheme 4 Other protected acid building blocks.



Scheme 5 Additional cyclohexyl chiral auxiliaries accessible from 5.

monoprotected triol **23**. Choice of reductant proved crucial, since with LiAlH_4 , yields of **23** were low, with appreciable silyl migration observed, giving rise to **24**. In contrast, 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).

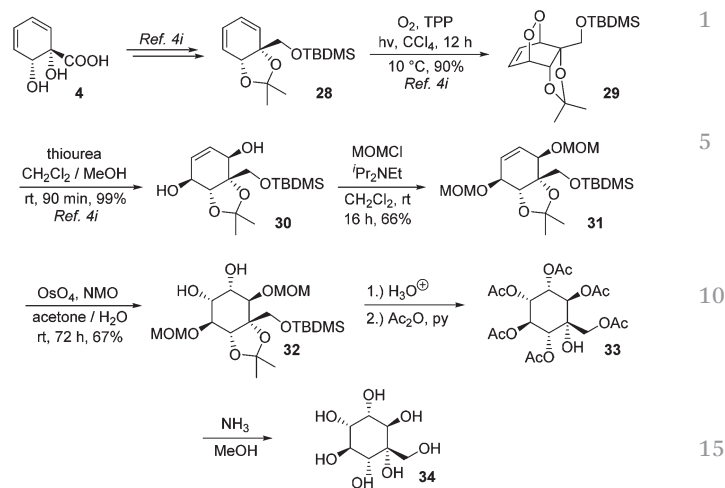
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These comparatively minimally functionalised cyclohexyl chiral auxiliaries that all bear a quaternary stereocentre are synthetically valuable insofar as it is difficult to conceive of other means of accessing them as easily, in enantiopure form. We 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.²² A particular advantage of their use for synthesis of novel inositol derivatives is that they provide ready access to *C*-substituted derivatives.^{6d,23} 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^{6i,j,p,r,7a,24–27} 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.²⁸ Thus, known silyl ether **28** was transformed to endoperoxide **29** and reduced to protected pentaol **30** by our reported procedure.⁴ⁱ 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

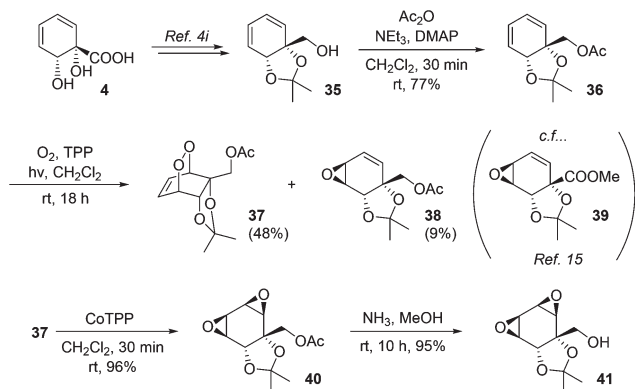
Scheme 6 Synthesis of a *C*-hydroxymethyl inositol.

precedented.^{6y,24d,f,i,25c,l,27d,29} 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 rare³⁰ and those of *muco*-inositol are wholly unknown (Scheme 6).

Endoperoxides derived from diene-¹O₂ 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 γ -hydroxyenones; we have previously demonstrated such transformations for endoperoxides derived from **4**.⁴ⁱ In addition, they may be isomerised to the corresponding bis(epoxides) upon treatment with cobalt–tetraphenylporphyrin complex.³¹ 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**.¹⁵ 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.³² 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).

Conclusions

We have described synthetic sequences which allow for the functionalization of every position on the cyclohexadiene ring



Scheme 7 Synthesis of a bis(epoxide).

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 Perkin-Elmer 1600 FT IR spectrometer with only selected absorbances quoted as ν in cm⁻¹. 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 μ L of sample was injected into a 30 : 70 flow of water-acetonitrile at 0.6 mL min⁻¹ to the mass spectrometer. For each acquisition 10 μ 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-H₂O-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-H₂O-AcOH); $[\alpha]_D^{25} +13.3$ (c 0.3, H₂O); ¹H NMR (300 MHz, D₂O) δ = 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); ¹³C NMR (125 MHz, MeOH-*d*₄) δ = 180.1 (C=O), 79.5 (C(OH)CO₂H), 73.7 (CH(OH)), 35.0, 30.8, 25.3, 21.1; ν_{\max} (film) 3445, 3086, 2924, 2858, 1736, 1439, 1199, 1138, 1023, 948, 821 cm⁻¹; HRMS (ESI⁻) m/z calcd for (C₇H₁₁O₄)⁻, 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-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%). R_f = 0.05 (30% EtOAc-petrol); $[\alpha]_D -10.0$ (c 0.3, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ = 3.82–3.74 (1H, m, CH(OH)), 3.77 (3H, s, CH₃), 2.86 (2H, br s, OH), 1.83–1.22 (8H, m, CH); ¹³C 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; ν_{\max} (film) 3453, 2938, 2861, 1729, 1438, 1272, 1238, 1207, 1149, 1079, 998, 923 cm⁻¹; HRMS (ESI⁺) m/z calcd for (C₈H₁₅O₄)⁺, 175.0965; found 175.0981. NMR Data are in agreement with those previously reported.³³

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_{3(aq)} (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 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**: R_f = 0.70 (30% EtOAc-petrol); $[\alpha]_D^{25} -37.8$ (c 0.65, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 4.35 (1H, t, J = 3.5 Hz, CH(OC(CH₃)₂)), 3.76 (3H, s, OCH₃), 2.06–1.93 (2H, m, CH), 1.85–1.23 (6H, m, CH); 1.50 (3H, d, J = 0.5 Hz, CH₃) 1.35 (3H, d, J = 0.5 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ = 173.2 (C=O), 109.0 (C(CH₃)₂), 81.0 (C(OC(CH₃)₂)(CO₂CH₃)), 75.0 (CH(OC(CH₃)₂)), 52.5 (OCH₃), 32.3, 28.0, 26.0, 25.9, 20.5, 18.7; ν_{\max} (film) 2997, 2941, 2873, 1733, 1450, 1383, 1217, 1160, 1054, 1025, 905, 725 cm⁻¹; HRMS (ESI⁺) m/z calcd for

(C₁₁H₁₈NaO₄)⁺, 237.1097; found 237.1079. Data for **8**: R_f = 0.85 (50% EtOAc–petrol); [α]_D²⁵ –21 (c 1.6, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ = 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, OCH₃), 3.24 (1H, s, OH), 2.06–1.24 (16H, m, CH), 1.50 (3H, s, CH₃), 1.35 (3H, s, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ = 175.3 (C=O), 171.8 (C=O), 108.9 (C(CH₃)₃), 80.7, 75.6, 75.2, 74.9, 53.0 (OCH₃), 34.1, 32.2, 27.8, 26.2, 25.7, 25.6, 23.6, 20.2, 19.7, 18.3; ν_{max} (film) 3523, 2987, 2938, 2865, 1733, 1449, 1381, 1370, 1243, 1216, 1152, 1124, 1046, 1003, 874, 735 cm⁻¹; HRMS (ESI+) *m/z* calcd for (C₁₈H₂₉O₇)⁺, 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 H₂O, 12 mmol, 10 equiv.) and refluxed for 14 h. The resulting solution 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 MgSO₄. The resulting oil was purified *via* flash column chromatography (50% EtOAc–petrol) to give desired acid **9** (20 mg, 8%) acetonide migration product **10** (30 mg, 13%) and deprotected diol acid **5** (40 mg, 21%). Data for **9**: R_f = 0.40 (50% EtOAc–petrol); [α]_D²⁵ –40.0 (c 0.70, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 4.31 (1H, t, J = 3.5 Hz, CH(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(CH₃)₂), 80.7 (C(OC(CH₃)₂)(CO₂H)), 74.9 (CH(OC(CH₃)₂)), 32.2, 28.0, 26.0, 25.7, 20.7, 18.5; ν_{max} (film) 2994, 2939, 2873, 2714, 1450, 1371, 1383, 1217, 1174, 905, 725 cm⁻¹; HRMS (ESI–) *m/z* calcd for (C₁₀H₁₅O₄)[–], 199.0976; found 199.0975. Data for **10**: R_f = 0.83 (50% EtOAc–petrol); [α]_D²⁵ +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 (3H, s, CH₃), 1.63 (3H, s, CH₃), 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); ¹³C NMR (125 MHz, CDCl₃) δ = 174.0 (C=O), 110.1 (C(CH₃)₂), 83.2 (C(O)(C=O)), 71.0 (C(OH)H), 33.7 (CH₂), 30.6 (CH₂), 29.1 (C(CH₃)₂), 27.9 (C(CH₃)₂), 23.6 (CH₂), 20.1 (CH₂); ν_{max} (film) 3484, 2991, 2939, 2863, 2774, 1448, 1385, 1291, 1262, 1060, 1036, 908, 860, 626 cm⁻¹; HRMS (ESI+) *m/z* calcd for (C₁₀H₁₇O₄)⁺, 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 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. (1.30 g, 76%). R_f = 0.29 (40% EtOAc–petrol); [α]_D²⁵ –135.6 (c 1.6, CH₂Cl₂); 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–CH₂–Ar), 4.87 (1H, m, C(O)H); ¹³C NMR (75.5 MHz, CDCl₃) δ = 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–CH₂); ν_{max} (film) 3451, 3038, 1731, 1660, 1455, 1378, 1234, 1168, 1077, 1020, 909, 753, 695 cm⁻¹; HRMS (+ve ESI-TOF) *m/z* calculated for (C₁₄H₁₄NaO₄)⁺, 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 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%). R_f = 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.^{6e}

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]-dioxasilole-3a(7aH)-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*-butylsilylanediyl 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_f = 0.65 (10% EtOAc–petrol); [α]_D²⁵ –327.0 (c 3.31, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 7.35–7.31 (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, 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(OSi)), 67.4 (CH₂), 27.0 (CH₃), 26.9 (CH₃), 21.2 (C(CH₃)₃), 20.2 (C(CH₃)₃); ν_{\max} (film) 3045, 2966, 2934, 2891, 2859, 1733, 1473, 1229, 1091, 1031, 1012, 1000, 875, 825, 696 cm⁻¹; HRMS (ESI+) m/z calcd for (C₂₂H₃₁O₄Si)⁺, 387.1986; found 387.1993.

Synthesis of (3*a*S,7*a*R)-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, 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; ν_{\max} (film) 3070, 2935, 2894, 2859, 1717, 1448, 1472, 1094, 827 cm⁻¹; HRMS (ESI+) m/z calcd for (C₁₅H₂₉O₄Si)⁺, 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, NH₄Cl_(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 LiCl_(aq) (3 × 10 mL), dried over MgSO₄ 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 CH₂Cl₂ (3.00 mL), to which was added triethylamine (40 μ L, 0.32 mmol) followed by Trimethylsilyl trifluoromethanesulfonate (50 μ 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 MgSO₄ 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, CHCl₃); ¹H NMR (250 MHz, CDCl₃) $\delta = 3.73$ (3H, s, CO₂CH₃), 3.44 (1H, dd, $J = 11.0, 4.0$ Hz, CH(OCH₃)), 3.36 (3H, s, OCH₃), 3.26 (3H, s, OCH₃), 2.04–0.80 (8H, m, CH); ¹³C NMR (75 MHz, CDCl₃) $\delta = 174.1$ (C=O), 82.9, 81.7, 57.0, 52.1, 51.8, 29.7, 24.8, 23.5, 20.3;

ν_{\max} (film) 2938, 2861, 1730, 1446, 1373, 1275, 1227, 1099, 1061, 997 cm⁻¹; HRMS (ESI+) m/z calcd for (C₁₀H₁₉O₄)⁺, 203.1278; found 203.1289. Data for **17**: $R_f = 0.85$ (20% EtOAc-petrol); $[\alpha]_D^{25} -1.4$ (c 0.73, CHCl₃); ¹H NMR (250 MHz, CDCl₃) $\delta = 3.73$ (3H, s, CO₂CH₃), 3.47 (1H, dd, $J = 11.0, 4.5$ Hz, CH(OCH₃)), 3.29 (3H, s, OCH₃), 1.85–0.84 (8H, m, CH), 0.15 (9H, s, Si(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) $\delta = 175.6$ (C=O), 82.2, 76.1, 56.8, 51.8, 36.2, 25.1, 24.0, 20.3, 2.2; ν_{\max} (film) 2949, 2860, 1753, 1446, 1366, 1279, 1244, 1156, 1062, 1041, 837, 760, 734 cm⁻¹; HRMS (ESI+) m/z calcd for (C₁₂H₂₅O₄Si)⁺, 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 H₂O, 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 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%). $R_f = 0.25$ (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(OCH₃)), 3.38 (3H, s, OCH₃), 3.35 (3H, s, OCH₃), 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; ν_{\max} (film) 3143, 2940, 2860, 2838, 1721, 1464, 1448, 1308, 1196, 1099, 1077, 973, 939 cm⁻¹; HRMS (ESI-) m/z calcd for (C₉H₁₅O₄)⁻, 187.0976; found 187.0972.

Synthesis of methyl (2*R*,3*a*S,7*a*R)-2-phenyltetrahydrobenzo[*d*][1,3]dioxole-3*a*(4*H*)-carboxylate (19) and methyl (2*S*,3*a*S,7*a*R)-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 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**: $R_f = 0.49$ (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; ν_{\max} (film) 2951, 2869, 1734, 1451, 1247, 1163, 1088, 1024, 697 cm⁻¹; HRMS (ESI+) m/z calcd for (C₁₅H₁₉O₄)⁺, 263.1278; found

263.1267. Data for **20**: $R_f = 0.53$ (10% EtOAc–petrol); $[\alpha]_D^{25} -1.6$ (c 0.08, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) $\delta = 7.50\text{--}7.46$ (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_3), 2.03–1.89 (4H, m, CH), 1.75–1.39 (4H, m, CH); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) $\delta = 173.0$ (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_3), 30.7, 26.2, 20.9, 20.4; ν_{max} (film) 2938, 2863, 1735, 1451, 1247, 1162, 1093, 698 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_{15}\text{H}_{19}\text{O}_4)^+$, 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_2Cl_2 (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 $\text{NaHCO}_3(\text{aq})$ (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_4 and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (0 \rightarrow 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_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) $\delta = 2.81$ (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_3), 1.57 (3H, s, CH_3); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) $\delta = 203.1$ (C=O), 169.3 (C=O), 111.4 ($\text{C}(\text{CH}_3)_2$), 85.2, 39.5, 38.7, 28.4, 27.5, 26.6, 21.0; ν_{max} (film) 2996, 2941, 2921, 2872, 2851, 1784, 1732, 1394, 1380, 1283, 1254, 1130, 1077, 1045, 930 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_{10}\text{H}_{14}\text{NaO}_4)^+$, 221.0784; found 221.0787.

Synthesis of methyl (1S,2R)-2-((tert-butyl dimethylsilyl)oxy)-1-hydroxycyclohexane-1-carboxylate (22). Diol ester **6** (370 mg, 2.12 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (20 mL) and cooled to -78 °C. Triethylamine (355 μL , 257 mg, 2.54 mmol, 1.2 equiv.) was added dropwise, then *tert*-butyl dimethylsilyl trifluoromethanesulfonate (487 μL , 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_2O (20 mL). Phases were separated and the organic phase was washed further with $\text{NaCl}(\text{aq})$ (satd, 20 mL). The organic phase was dried over MgSO_4 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_3); $^1\text{H NMR}$ (250 MHz, CDCl_3) $\delta = 3.94$ (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); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) $\delta = 176.1$ (C=O), 77.5 (C(OH)), 73.8 (CH(OSi)), 52.2, 33.1, 30.1 (CH), 25.6 ($\text{SiC}(\text{CH}_3)_3$), 23.8, 19.6, 17.8 ($\text{SiC}(\text{CH}_3)_3$), $-4.1, -5.2$; ν_{max} (film) 3555, 3027, 2928, 1705, 1494, 1453, 1281, 908, 732, 699 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_{14}\text{H}_{29}\text{O}_4\text{Si})^+$, 289.1830; found 289.1831.

Synthesis of (1R,2R)-2-((tert-butyl dimethylsilyl)oxy)-1-(hydroxymethyl)cyclohexane-1-ol (23) and (1R,2R)-1-(((tert-butyl dimethylsilyl)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_4 (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_2O (0.05 mL) followed by NaOH (10% aq. sol., 0.09 mL) followed by H_2O (0.14 mL). The solution was filtered through MgSO_4 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_4 (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. Solution was quenched with addition of Et_2O (10 mL) followed by H_2O (10 mL). The mixture was separated, and the aqueous layer extracted with EtOAc (4×10 mL); the organic layers were combined, dried with MgSO_4 and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (5 \rightarrow 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_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) $\delta = 3.65$ (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, $\text{C}(\text{CH}_3)_3$), 0.08 (6H, s, SiCH_3); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) 73.2, 72.9, 68.3 (OCH_2), 31.7, 30.7, 25.8 ($\text{SiC}(\text{CH}_3)_3$), 23.2, 20.7, 18.0 ($\text{SiC}(\text{CH}_3)_3$), -4.0 (SiCH_3), -5.0 (SiCH_3); ν_{max} (film) 3443, 2930, 2857, 1463, 1389, 1261, 1252, 1079, 835, 777 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_{13}\text{H}_{29}\text{O}_3\text{Si})^+$, 261.1881; found 261.1886. Data for **24**: $R_f = 0.55$ (20% EtOAc–petrol); $[\alpha]_D^{25} +10$ (c 0.5, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) 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); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) $\delta = 73.8, 71.9, 71.8, 31.8, 29.5, 25.8$ ($\text{SiC}(\text{CH}_3)_3$), 23.5, 20.3, 18.1 ($\text{SiC}(\text{CH}_3)_3$), -5.5 (SiCH_3), -5.6 (SiCH_3); ν_{max} (film) 3555, 3027, 2929, 1494, 1453, 1218, 908, 732, 699 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_{13}\text{H}_{29}\text{O}_3\text{Si})^+$, 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_4 and concentrated under reduced pressure. The resulting oil was purified *via* flash column chromatography (10 \rightarrow 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, CHCl_3); $^1\text{H NMR}$ (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, $\text{O-C}(\text{CH}_3)_2$), 0.90 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.07

(3H, s, SiCH₃), 0.05 (3H, s, SiCH₃); ¹³C NMR (75 MHz, CDCl₃) δ = 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; ν_{max} (film) 2988, 2933, 2894, 2856, 1472, 1462, 1377, 1368, 1251, 1212, 1141, 1094, 1056, 988, 898, 773 cm⁻¹; HRMS (ESI+) *m/z* calcd for (C₁₆H₃₂NaO₃Si)⁺, 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 Et₂O (10 mL) and NH₄Cl_(aq) (10 mL). The reaction mixture was extracted with EtOAc (4 × 10 mL) and the organic layers were combined and washed with saturated brine, dried over MgSO₄ 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); [α]_D²⁵ -4.0 (*c* 0.9, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ = 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); ¹³C NMR (100 MHz, CDCl₃) δ = 109.4, 83.2, 71.5, 71.3, 33.7, 31.2, 29.7, 27.2, 27.1, 22.6; ν_{max} (film) 3204, 2930, 2855, 1563, 1406, 1371, 1184, 903, 729 cm⁻¹; HRMS (ESI+) *m/z* calcd for (C₁₀H₁₈NaO₃)⁺, 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 CH₂Cl₂ (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 × 10 mL) and the organic layers were combined and washed with saturated brine, dried over MgSO₄ 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); [α]_D²⁵ -6.0 (*c* 1.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ = 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); ¹³C NMR (100 MHz, CDCl₃) δ = 209.1, 110.5, 85.5, 69.1, 39.7, 38.5, 27.4, 26.9, 26.1, 22.3; ν_{max} (film) 2986, 2937, 2865, 1723, 1452, 1431, 1380, 1371, 1050, 858, 811 cm⁻¹; HRMS (ESI+) *m/z* calcd for (C₁₀H₁₆NaO₃)⁺, 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 known⁴ⁱ diol 30 (304 mg, 0.92 mmol, 1.0 equiv.) in CH₂Cl₂ (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 × 30 mL) and the combined organic layers were washed with water (30 mL) and brine (30 mL). The resulting solution was dried over MgSO₄. 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); [α]_D²⁵ -22.2 (*c* 0.09, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 5.74 (2H, s, C=CH), 4.86 (1H, d, *J* = 6.5 Hz, OCH₂O), 4.85 (1H, d, *J* = 6.5 Hz, OCH₂O), 4.72 (1H, d, *J* = 6.5 Hz, OCH₂O), 4.70 (1H, d, *J* = 6.5 Hz, OCH₂O), 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, CHHOTBDMS), 3.49 (1H, d, *J* = 11.0 Hz, CHHOTBDMS), 3.41 (3H, s, CH₂OCH₃), 3.39 (3H, s, CH₂OCH₃), 1.47 (3H, s, O-C-CH₃), 1.43 (3H, s, O-C-CH₃), 0.89 (9H, s, SiC(CH₃)₃), 0.04 (6H, s, Si(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ = 130.3 (HC=CH), 127.9 (HC=CH), 108.9 (C(CH₃)₂), 96.3 (OCH₂O), 95.5 (OCH₂O), 85.3 (4°CCH₂O), 78.4 (CHO), 76.8 (CHO), 75.0 (CHO), 61.9 (CH₂OTBDMS), 55.5 (OCH₃), 55.4 (OCH₃), 28.4 (CCH₃), 27.0 (CCH₃), 25.9 (SiC(CH₃)₃), 18.3 (SiC(CH₃)₃), -5.3 (SiCH₃), -5.7 (SiCH₃); ν_{max} (film) 2954, 1252, 1043, 907, 837, 732, 649 cm⁻¹; HRMS (ESI+) *m/z* calcd for (C₂₀H₃₈NaO₉Si)⁺, 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-H₂O (4:1, 8.0 mL) was added NMO (43.4 mg, 0.370 mmol, 2.0 equiv.) followed dropwise by OsO₄ (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 Na₂S₂O_{3(aq)} (2 × 30 mL). The organic phase was washed with brine (30 mL) and dried over MgSO₄. 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); [α]_D²⁵ -10.0 (*c* 0.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 4.82 (2H, s, OCH₂O), 4.74 (1H, d, *J* = 6.5 Hz, OCHHO), 4.67 (1H, d, *J* = 6.5 Hz, 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, 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, CHHOTBDMS), 3.45 (3H, s, CH₂OCH₃), 3.40 (3H, s, CH₂OCH₃), 3.05 (1H, br s, OH), 1.51 (3H, s, C(CH₃)₂), 1.37 (3H, s, C(CH₃)₂), 0.89 (9H, s, SiC(CH₃)₃), 0.07 (3H, s, SiCH₃), 0.06 (3H, s, SiCH₃); ¹³C NMR (75 MHz, CDCl₃) δ = 108.6 (C(CH₃)₂), 98.1 (OCH₂OCH₃), 95.9 (OCH₂OCH₃), 85.3 (4°CCH₂O), 83.0 (CHO), 76.4 (CHO), 73.4 (CHO), 70.9 (CHO), 69.5 (CHO), 61.2 (CH₂OTBDMS), 55.9 (CH₂OCH₃), 55.8 (CH₂OCH₃), 28.2 (C(CH₃)₂), 26.3 (C(CH₃)₂), 25.9 (SiC(CH₃)₃), 18.3 (SiC(CH₃)₃), -5.4 (SiCH₃), -5.7 (SiCH₃); ν_{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* calcd for (C₂₀H₄₀NaO₉Si)⁺, 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 Et₂O (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 Et₂O (10 mL) and extracted with H₂O (3 × 10 mL). The combined aqueous layers were concentrated under reduced pressure to give

heptaol **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 $\text{NaHCO}_3(\text{aq})$ (satd, 3×10 mL) and H_2O (3×10 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* flash column chromatography (50% EtOAc–petrol) gave **33** as a colourless oil (22 mg, 37%). $R_f = 0.29$ (50% EtOAc–petrol); $[\alpha]_{\text{D}}^{25} -5.5$ (c 0.36, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) $\delta = 5.66$ (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, $-\text{CHHOAc}$), 3.95 (1H, d, $J = 12.0$ Hz, $-\text{CHHOAc}$), 2.15 (3H, s, $-\text{OAc}$), 2.14 (3H, s, $-\text{OAc}$), 2.11 (3H, s, $-\text{OAc}$), 2.05 (3H, s, $-\text{OAc}$), 2.02 (3H, s, $-\text{OAc}$), 1.98 (3H, s, $-\text{OAc}$); ^{13}C NMR (75 MHz, CDCl_3) $\delta = 170.7$ (C=O), 169.7 ($2 \times$ 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_3), 20.7 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 20.5 (CH_3), 20.5 (CH_3); ν_{max} (film) 3479, 2965, 1745, 1431, 1369, 1218, 1039, 899, 821, 731 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_{19}\text{H}_{26}\text{NaO}_{13})^+$, 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. $\text{NH}_3(\text{g})$ 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 under high vacuum (flask heated to 60 °C to drive off acetamide) to give pure **34** (9 mg, 99%) as a colourless gum. $[\alpha]_{\text{D}}^{25} +2.78$ (c 3.3, H_2O); ^1H NMR (500 MHz, D_2O) $\delta = 4.07$ (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); ^{13}C NMR (75 MHz, D_2O) $\delta = 77.8, 73.6, 72.5, 71.5, 71.2, 69.3, 63.8$; ν_{max} (film) 3331, 2956, 2922, 2854, 1667, 1540, 1455, 1205, 1151, 1020, 742 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_7\text{H}_{14}\text{NaO}_7)^+$, 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 known⁴¹ alcohol **35** (637 mg, 3.50 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) was added triethylamine (0.48 mL, 3.49 mmol, 1 equiv.), DMAP (42 mg, 0.35 mmol, 10 mol%) and Ac_2O (0.33 mL, 3.50 mmol, 1 equiv.). The reaction mixture was stirred for 30 min, then H_2O (20 mL) was added. The reaction mixture was then extracted with EtOAc (4×20 mL). The organic layers were combined and dried over MgSO_4 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. $R_f = 0.45$ (15% EtOAc–petrol); $[\alpha]_{\text{D}}^{25} -81.6$ (c 1.20, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) $\delta = 6.13$ – 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, $\text{CHOC}(\text{CH}_3)_2$), 4.15 (1H, d, $J = 11.5$ Hz, $-\text{CHH}-$), 3.94 (1H, d, $J = 11.5$ Hz $-\text{CHH}-$), 2.07 (3H, s, OAc), 1.44 (3H, s, CH_3), 1.37 (3H, s, CH_3); ^{13}C NMR (75 MHz, CDCl_3) $\delta = 170.6$ (C=O), 128.1, 125.4, 124.3, 123.1 (C=C), 106.6 ($\text{C}(\text{CH}_3)_2$), 78.3 ($\text{CO}(\text{CH}_2)$), 71.8

($\text{C}(\text{H})\text{OC}(\text{CH}_3)_2$), 66.1 (CH_2), 27.1, 26.4 ($\text{C}(\text{CH}_3)_2$), 20.8 (COCH_3); ν_{max} (film) 2991, 2937, 1741, 1415, 1372, 1239, 1172, 1043, 906, 728, 648 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_{12}\text{H}_{16}\text{NaO}_4)^+$, 247.0941; found 247.0931.

Synthesis of ((3aR,4R,7S,7aR)-2,2-dimethyl-7,7a-dihydro-4,7-epidioxybenzo[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_2Cl_2 (20 mL) was added a solution of 5,10,15,20-tetraphenyl-21H,23H-porphine (10 mg, 0.016 mmol, 4 mol%) in CH_2Cl_2 (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**: $R_f = 0.35$ (15% EtOAc–petrol); $[\alpha]_{\text{D}}^{25} -16.9$ (c 0.83, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) $\delta = 6.65$ (1H, t, $J = 8.0$ Hz, C=CH), 6.55 (1H, t, $J = 8.0$ Hz, C=CH), 4.88–4.91 (2H, m, $\text{C}(\text{H})\text{O}$), 4.55 (1H, d, $J = 12.0$ Hz $-\text{CHH}-$), 4.31 (1H, d, $J = 12.0$ Hz $-\text{CHH}-$), 4.25 (1H, d, $J = 4.8$ Hz, $\text{C}(\text{H})\text{OC}(\text{CH}_2)_3$), 2.13 (3H, s, COCH_3), 1.39 (3H, s, CH_3), 1.30 (3H, s, CH_3); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 170.4$ (C=O), 131.5 (C=C), 130.3 (C=C), 112.3 ($\text{C}(\text{CH}_3)_2$), 79.9 ($\text{CO}(\text{CH}_2)$), 74.6 ($\text{C}(\text{H})\text{OC}(\text{CH}_3)_2$), 72.1 ($\text{CHO}-\text{O}$), 71.8 ($\text{CHO}-\text{O}$), 65.9 (CH_2), 27.8 ($\text{C}(\text{CH}_3)_2$), 26.9 ($\text{C}(\text{CH}_3)_2$), 20.8 (COCH_3); ν_{max} (film) 2995, 2988, 2928, 1736, 1348, 1372, 1450, 1244, 1204, 1144, 1039, 919, 743, 712, 644 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_{12}\text{H}_{16}\text{NaO}_6)^+$, 279.0839; found 279.0829. Data for **38**: $R_f = 0.40$ (15% EtOAc–petrol); $[\alpha]_{\text{D}}^{25} -14.3$ (c 0.28, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) $\delta = 6.09$ (1H, dd, $J = 10.0, 4.0$ Hz, $\text{HC}=\text{CHCO}$), 5.70 (1H, dt, $J = 10.0, 1.5$ Hz, $\text{HC}=\text{CHCO}$), 4.65 (1H, t, $J = 1.0$ Hz, $\text{CHOC}(\text{CH}_3)_2$), 4.33 (1H, $J = 11.0$ Hz, $-\text{CHH}-$), 3.83 (1H, $J = 11.0$ Hz, $-\text{CHH}-$), 3.64 (1H, dd, $J = 3.5, 2.5$ Hz, $\text{CH}(\text{O})$), 3.37 (1H, m, $\text{CH}(\text{O})$), 2.09 (3H, s), 1.41 (3H, s), 1.37 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) 170.4 (C=O), 132.5 (C=C-C(O)CH₂), 124.1 (C=CCH(O)), 110.5 ($\text{C}(\text{CH}_3)_2$), 79.0 ($\text{CO}(\text{CH}_2)$), 71.3 ($\text{C}(\text{H})\text{OC}(\text{CH}_3)_2$), 66.9 (CH_2), 50.3 ($\text{CH}(\text{O}_{\text{epox}})\text{CH}(\text{O})$), 46.5 ($\text{CH}(\text{O}_{\text{epox}})\text{CH}=\text{CH}$), 27.8 (C-CH₃), 26.6 (C-CH₃), 20.9 (COCH_3); ν_{max} (film) 2989, 2943, 1745, 1455, 1379, 1236, 1181, 1162, 1089, 1060, 1042, 989, 829, 721 cm^{-1} ; HRMS (ESI+) m/z calcd for $(\text{C}_{12}\text{H}_{16}\text{NaO}_5)^+$, 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_2Cl_2 (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); $[\alpha]_{\text{D}}^{25} -33.8$ (c 0.80, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) $\delta = 4.35$ (1H, d, $J = 11.0$ Hz, $-\text{CHH}-$), 4.32 (1H, d, $J = 2.0$ Hz, $\text{C}(\text{H})\text{OC}(\text{CH}_2)_3$), 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, COCH₃), 1.43 (3H, s, CH₃), 1.42 (3H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃) $\delta = 170.4$ (C=O), 110.4 (C(CH₃)₂), 78.2 (C(O)CH₂OAc), 71.9 (C(H)O-C(CH₃)₂), 65.5 (CH₂), 51.5 (C(H)O), 50.9 (C(H)O), 47.6 (C(H)O), 47.6 (C(H)O), 28.0 (C(CH₃)₂), 26.2 (C(CH₃)₂), 20.8 (COCH₃); ν_{\max} (film) 2991, 2938, 1742, 1455, 1435, 1380, 1231, 1175, 1063, 1043, 992, 964, 803, 630 cm⁻¹; HRMS (ESI+) m/z calcd for (C₁₂H₁₆NaO₆)⁺, 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, NH_{3(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); [α]_D²⁵ -46 (c 1.02, CH₂Cl₂); ¹H NMR (250 MHz, CDCl₃) $\delta = 4.41$ (1H, d, $J = 2.0$ Hz, C(H)OC(CH₂)₃), 3.77 (1H, d, $J = 11.0$ Hz, -CHH-), 3.61 (1H, d, $J = 11.0$ Hz, -CHH-), 3.57 (1H, t, $J = 3.0$ Hz C(H)O), 3.53 (1H, t, $J = 3.5$ Hz, C(H)O), 3.41 (1H, dd, $J = 3.5$, 2.0 Hz, C(H)O), 3.04 (1H, dd, $J = 3.5$, 2.0 Hz, C(H)O), 2.09 (3H, br s, OH), 1.44 (6H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) 110.0 (C(CH₃)₂), 79.4 (CO(CH₂)), 71.5 (C(H)OC(CH₃)₂), 64.4 (CH₂), 51.7 (C(H)O), 51.4 (C(H)O), 47.6 (C(H)O), 47.5 (C(H)O), 28.1 (CH₃), 26.5 (CH₃); ν_{\max} (film) 3491, 2982, 2253, 1457, 1383, 1247, 1219, 1080, 1063, 907, 726, 647 cm⁻¹; HRMS (ESI+) m/z calcd for (C₁₀H₁₄NaO₅)⁺, 237.0733; found 237.0792.

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Notes and references

- For reviews, see: (a) D. J.-Y. D. Bon, B. Lee, M. G. Banwell and I. A. Cade, *Chim. Oggi*, 2012, **30**, 22; (b) T. Hudlický, *Pure Appl. Chem.*, 2010, **82**, 1785; (c) T. Hudlický and J. W. Reed, *Synlett*, 2009, 685; (d) K. A. B. Austin, M. Matveenko, T. A. Reekie and M. G. Banwell, *Chem. Aust.*, 2008, **75**, 3; (e) D. R. Boyd and T. D. H. Bugg, *Org. Biomol. Chem.*, 2006, **4**, 181; (f) R. A. Johnson, *Org. React.*, 2004, **63**, 117; (g) M. G. Banwell, A. J. Edwards, G. J. Harfoot, K. A. Jolliffe, M. D. McLeod, K. J. McRae, S. G. Stewart and M. Vögtle, *Pure Appl. Chem.*, 2003, **75**, 223; (h) T. Hudlický, D. Gonzales and D. T. Gibson, *Aldrichimica Acta*, 1999, **32**, 35; (i) D. A. Widdowson, D. W. Ribbons and S. D. Thomas, *Janssen Chim. Acta*, 1990, **8**, 3.
- (a) J. M. Wallis and J. K. Kochi, *J. Am. Chem. Soc.*, 1988, **110**, 8207; (b) W. B. Motherwell and A. S. Williams, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2031; (c) P. M. J. Jung, W. B. Motherwell and A. S. Williams, *Chem. Commun.*,

- 1997, 1283; (d) Y. Feng, C.-Y. Ke, G. Xue and L. Que Jr., *Chem. Commun.*, 2009, 50.
- D. T. Gibson, J. R. Koch, C. L. Schuld and R. E. Kallio, *Biochem.*, 1968, **7**, 3795.
- For recent (2011 onwards) examples, see: (a) D. K. Winter, M. A. Endoma-Arias, T. Hudlický, J. A. Beutler and J. A. Porco Jr., *J. Org. Chem.*, 2013, **78**, 7617; (b) V. Varghese and T. Hudlický, *Synlett*, 2013, 369; (c) X. Ma, M. G. Banwell and A. C. Willis, *J. Nat. Prod.*, 2013, **76**, 1514; (d) B. D. Schwartz, E. Matoušová, R. White, M. G. Banwell and A. C. Willis, *Org. Lett.*, 2013, **15**, 1934; (e) D. J.-Y. D. Bon, M. G. Banwell, J. S. Ward and A. C. Willis, *Tetrahedron*, 2013, **69**, 1363; (f) D. R. Boyd, N. D. Sharma, J. G. Carroll, P. L. Loke, C. R. O'Dowd and C. C. R. Allen, *RSC Adv.*, 2013, **3**, 10944; (g) J. C. Ramos, M. Brovotto and G. A. Seoane, *Org. Lett.*, 2013, **15**, 1982; (h) M. G. Banwell, N. Y. Gao, X. Ma, L. Petit, L. V. White, B. D. Schwartz, A. C. Willis and I. A. Cade, *Pure Appl. Chem.*, 2012, **84**, 1329; (i) M. J. Palframan, G. Kociok-Köhn and S. E. Lewis, *Chem.-Eur. J.*, 2012, **18**, 4766; (j) D. R. Boyd, N. D. Sharma, M. Kaik, P. B. A. McIntyre, P. J. Stevenson and C. C. R. Allen, *Org. Biomol. Chem.*, 2012, **10**, 2774; (k) M. K. Sharma, M. G. Banwell, A. C. Willis and A. D. Rae, *Chem. Asian J.*, 2012, **7**, 676; (l) M. G. Banwell, N. Y. Gao, B. D. Schwartz and L. V. White, *Top. Curr. Chem.*, 2012, **309**, 163; (m) D. J.-Y. D. Bon, M. G. Banwell, I. A. Cade and A. C. Willis, *Tetrahedron*, 2011, **67**, 8348; (n) M. A. A. Endoma-Arias and T. Hudlický, *Tetrahedron Lett.*, 2011, **52**, 6632; (o) B. D. Schwartz, M. G. Banwell and I. A. Cade, *Tetrahedron Lett.*, 2011, **52**, 4526; (p) L. V. White, B. D. Schwartz, M. G. Banwell and A. C. Willis, *J. Org. Chem.*, 2011, **76**, 6250; (q) M. J. Palframan, G. Kociok-Köhn and S. E. Lewis, *Org. Lett.*, 2011, **13**, 3150; (r) J. Duchek, T. G. Piercy, J. Gilmet and T. Hudlický, *Can. J. Chem.*, 2011, **89**, 709; (s) M. G. Banwell, A. L. Lehmann, R. S. Menon and A. C. Willis, *Pure Appl. Chem.*, 2011, **83**, 411; (t) D. R. Adams, C. Aichinger, J. Collins, U. Rinner and T. Hudlický, *Synlett*, 2011, 725; (u) M. Labora, V. Schapiro and E. Pandolfi, *Tetrahedron: Asymmetry*, 2011, **22**, 1705; (v) X. Ma, J. C. Jury and M. G. Banwell, *Tetrahedron Lett.*, 2011, **52**, 2192.
- For selected examples, see: (a) L. Werner, A. Machara, B. Sullivan, I. Carrera, M. Moser, D. R. Adams and T. Hudlický, *J. Org. Chem.*, 2011, **76**, 10050; (b) L. Werner, A. Machara and T. Hudlický, *Adv. Synth. Catal.*, 2010, **352**, 195; (c) F. Fabris, J. Collins, B. Sullivan, H. Leisch and T. Hudlický, *Org. Biomol. Chem.*, 2009, **7**, 2619; (d) B. Sullivan, I. Carrera, M. Drouin and T. Hudlický, *Angew. Chem., Int. Ed.*, 2009, **48**, 4229; (e) M. Matveenko, A. C. Willis and M. G. Banwell, *Tetrahedron Lett.*, 2008, **49**, 7018; erratum, 2009, **50**, 2982; (f) J.-J. Shie, J.-M. Fang and C.-H. Wong, *Angew. Chem., Int. Ed.*, 2008, **47**, 5788; (g) A. T. Omori, K. J. Finn, H. Leisch, R. J. Carroll and T. Hudlický, *Synlett*, 2007, 2859; (h) M. G. Charest, C. D. Lerner, J. D. Brubaker, D. R. Siegel and A. G. Myers, *Science*, 2005, **308**, 395; (i) M. G. Charest, D. R. Siegel and

- 1 A. G. Myers, *J. Am. Chem. Soc.*, 2005, **127**, 8292;
(j) I. W. Davies and P. J. Reider, *Chem. Ind.*, 1996, **11**, 412;
(k) I. W. Davies, C. H. Senanayake, L. Castonguay,
R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron*
5 *Let.*, 1995, **36**, 7619.
- 6 For selected examples, see: (a) J. A. Griffen, J. C. White,
G. Kociok-Köhn, M. D. Lloyd, A. Wells, T. C. Arnot and
S. E. Lewis, *Tetrahedron*, 2013, **69**, 5989;
(b) R. M. B. Carrilho, V. Heguaburu, V. Schapiro,
E. Pandolfi, L. Kollár and M. M. Pereira, *Tetrahedron*, 2012,
10 **68**, 6935; (c) V. de la Sovera, A. Bellomo, J. M. Pena,
D. Gonzalez and H. A. Stefani, *Mol. Diversity*, 2011, **15**, 163;
(d) J. Duchek, D. R. Adams and T. Hudlický, *Chem. Rev.*,
2011, **111**, 4223; (e) S. Pilgrim, G. Kociok-Köhn, M. D. Lloyd
15 and S. E. Lewis, *Chem. Commun.*, 2011, **47**, 4799;
(f) J. C. Ramos, P. Bracco, M. Mazzini, J. R. Fernández,
D. Gamenara and G. A. Seoane, *Tetrahedron: Asymmetry*,
2010, **21**, 969; (g) D. R. Boyd, N. D. Sharma, N. I. Bowers,
G. B. Coen, J. F. Malone, C. R. O'Dowd, P. J. Stevenson and
20 C. C. R. Allen, *Org. Biomol. Chem.*, 2010, **8**, 1415;
(h) A. Bellomo, A. Bertucci, H. Stefanic, Á. Vázquez and
D. Gonzalez, *Tetrahedron: Asymmetry*, 2009, **20**, 2673;
(i) A. Bellomo, J. B. Bonilla, J. López-Prados, M. Martín-
Lomas and D. Gonzalez, *Tetrahedron: Asymmetry*, 2009, **20**,
25 2061; (j) A. Bellomo, S. Camarano, C. Rossini and
D. Gonzalez, *Carbohydr. Res.*, 2009, **344**, 44; (k) A. Bellomo,
D. Gonzalez and H. A. Stefani, *J. Organomet. Chem.*, 2008,
693, 1136; (l) A. Bellomo and D. Gonzalez, *Tetrahedron*
Let., 2007, **48**, 3047; (m) G. Fonseca and G. A. Seoane,
Tetrahedron: Asymmetry, 2005, **16**, 1393; (n) D. R. Boyd,
N. D. Sharma, N. M. Llamas, J. F. Malone, C. R. O'Dowd
30 and C. C. R. Allen, *Org. Biomol. Chem.*, 2005, **3**, 1953;
(o) M. H. Parker, B. E. Maryanoff and A. B. Reitz, *Synlett*,
2004, 2095; (p) C. Vitelio, A. Bellomo, M. Brovotto,
G. Seoane and D. Gonzalez, *Carbohydr. Res.*, 2004, **339**,
1773; (q) M. G. Banwell, X. Ma, N. Asano, K. Ikeda and
35 J. N. Lambert, *Org. Biomol. Chem.*, 2003, **1**, 2035;
(r) B. J. Paul, J. Willis, T. Martinot, I. Ghiviriga,
K. A. Abboud and T. Hudlický, *J. Am. Chem. Soc.*, 2002, **124**,
10416; (s) M. G. Banwell, A. M. Bray and D. J. Wong, *New*
J. Chem., 2001, **25**, 1351; (t) S. H. Lee and C. S. Cheong,
Bull. Korean Chem. Soc., 2000, **21**, 1061; (u) M. G. Banwell,
45 C. DeSavi, D. C. R. Hockless, S. Pallich and K. G. Watson,
Synlett, 1999, **S1**, 885–888; (v) M. Banwell, C. DeSavi and
K. Watson, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2251;
(w) M. Banwell, C. DeSavi and K. Watson, *Chem. Commun.*,
1998, 1189; (x) M. Desjardins, L. E. Brammer Jr. and
50 T. Hudlický, *Carbohydr. Res.*, 1997, **304**, 39; (y) T. Hudlický,
K. A. Abboud, D. A. Entwistle, R. Fan, R. Maurya,
A. J. Thorpe, J. Bolonick and B. Myers, *Synthesis*, 1996, 897.
- 7 (a) V. P. Bui and T. Hudlický, *Tetrahedron*, 2004, **60**, 641;
(b) M. G. Williams, P. E. Olson, K. J. Tautvydas,
R. M. Bitner, R. A. Mader and L. P. Wackett, *Appl. Micro-*
biol. Biotechnol., 1990, **34**, 316; (c) D. G. H. Ballard,
A. Curtis, I. M. Shirley and S. C. Taylor, *Macromolecules*,
1988, **21**, 294; (d) D. G. H. Ballard, A. Curtis,
I. M. Shirley and S. C. Taylor, *J. Chem. Soc., Chem.* 1
Commun., 1983, 954.
- 8 (a) J. L. Royo, E. Moreno-Ruiz, A. Cebolla and E. Santero,
J. Biotechnol., 2005, **116**, 113; (b) J. Y. Kim, K. Lee, Y. Kim,
C.-K. Kim and K. Lee, *Let. Appl. Microbiol.*, 2003, **36**, 343;
5 (c) A. Berry, T. C. Dodge, M. Pepsin and W. Weyler, *J. Ind.*
Microbiol. Biotechnol., 2002, **28**, 127; (d) B. D. Ensley,
B. J. Ratzkin, T. D. Osslund, M. J. Simon, L. P. Wackett and
D. T. Gibson, *Science*, 1983, **222**, 167.
- 9 (a) T. D. H. Bugg, *Tetrahedron*, 2003, **59**, 7075;
10 (b) D. T. Gibson and R. E. Parales, *Curr. Opin. Biotechnol.*,
2000, **11**, 236.
- 10 D. R. Boyd, N. D. Sharma, M. V. Hand, M. R. Grocock,
N. A. Kerley, H. Dalton, J. Chima and G. N. Sheldrake,
J. Chem. Soc., Chem. Commun., 1993, 974.
- 11 A. M. Reiner and G. D. Hegeman, *Biochemistry*, 1971, **10**,
2530.
- 12 A. E. G. Cass, D. W. Ribbons, J. T. Rossiter and
S. R. Williams, *Biochem. Soc. Trans.*, 1986, **14**, 1268.
- 13 S.-Y. Sun, X. Zhang, Q. Zhou, J.-C. Chen and G.-Q. Chen,
Appl. Microbiol. Biotechnol., 2008, **80**, 977.
- 14 G. N. Jenkins, D. W. Ribbons, D. A. Widdowson,
A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Perkin*
Trans. 1, 1995, 2647.
- 15 A. G. Myers, D. R. Siegel, D. J. Buzard and M. G. Charest,
Org. Lett., 2001, **3**, 2923.
- 16 (a) M. D. Mihovilovic, H. G. Leisch and K. Mereiter, *Tetra-*
hedron Lett., 2004, **45**, 7087; (b) T. C. M. Fischer,
H. G. Leisch and M. D. Mihovilovic, *Monatsh. Chem.*, 2010,
30 **141**, 699.
- 17 (a) M. Ali Khan, M. F. Mahon, J. P. Lowe, A. J. W. Stewart
and S. E. Lewis, *Chem.–Eur. J.*, 2012, **18**, 13480; (b) D. van
der Waals, T. Pugh, M. Ali Khan, A. J. W. Stewart,
A. L. Johnson and S. E. Lewis, *Chem. Central J.*, 2011, **5**, 80;
35 (c) J. A. Griffen, A. M. Le Coz, G. Kociok-Köhn, M. Ali Khan,
A. J. W. Stewart and S. E. Lewis, *Org. Biomol. Chem.*, 2011,
9, 3920; (d) M. Ali Khan, J. P. Lowe, A. L. Johnson,
A. J. W. Stewart and S. E. Lewis, *Chem. Commun.*, 2011, **47**,
40 215; (e) M. Ali Khan, M. F. Mahon, A. J. W. Stewart and
S. E. Lewis, *Organometallics*, 2010, **29**, 199.
- 18 (a) J. P. Guthrie, J. Cossar and J. Lu, *Can. J. Chem.*, 1991, **69**,
1904; (b) G. Hesse and G. Krehbiel, *Liebigs Ann.*, 1955, **593**,
45 42.
- 19 D. R. Boyd, N. D. Sharma, M. V. Berberian, K. S. Dunne,
C. Hardacre, M. Kaik, B. Kelly, J. F. Malone, S. T. McGregor
and P. J. Stevenson, *Adv. Synth. Catal.*, 2010, **352**, 855.
- 20 J. G. Buchanan, A. R. Edgar, D. I. Rawson, P. Shahidi and
R. H. Wightman, *Carbohydr. Res.*, 1982, **100**, 75.
- 21 (a) J. T. Sharp, I. Gosney and A. G. Rowley, in *Practical*
Organic Chemistry, Chapman and Hall, New York, 1989;
(b) J. M. Bohem, M. M. Joullié, F. A. Kaplan and B. Loev,
J. Chem. Educ., 1973, **50**, 367.
- 22 For reviews on inositols, see: (a) B. Kilbas and M. Balci,
Tetrahedron, 2011, **67**, 2355; (b) S. J. Conway and
55 G. J. Miller, *Nat. Prod. Rep.*, 2007, **24**, 687; (c) B. V. L. Potter
and D. Lampe, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1933.

- 1 23 T. Hudlický, D. A. Entwistle, K. K. Pitzer and A. J. Thorpe, *Chem. Rev.*, 1996, **96**, 1195.
- 24 (a) H. A. J. Carless and Y. Dove, *Tetrahedron: Asymmetry*, 1996, **7**, 649; (b) H. A. J. Carless and S. S. Malik, *J. Chem. Soc., Chem. Commun.*, 1995, 2447; (c) H. A. J. Carless, K. Busia, Y. Dove and S. S. Malik, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2505; (d) H. A. J. Carless and K. Busia, *Carbohydr. Res.*, 1992, **234**, 207; (e) H. A. J. Carless, *Tetrahedron Lett.*, 1992, **33**, 6379; (f) H. A. J. Carless, K. Busia and O. Z. Oak, *Synlett*, 1993, 672; (g) H. A. J. Carless and S. S. Malik, *Tetrahedron: Asymmetry*, 1992, **3**, 1135; (h) H. A. J. Carless, *J. Chem. Soc., Chem. Commun.*, 1992, 234; (i) H. A. J. Carless and O. Z. Oak, *Tetrahedron Lett.*, 1991, **32**, 1671; (j) H. A. J. Carless and O. Z. Oak, *J. Chem. Soc., Chem. Commun.*, 1991, 61; (k) H. A. J. Carless and K. Busia, *Tetrahedron Lett.*, 1990, **31**, 3449; (l) H. A. J. Carless and K. Busia, *Tetrahedron Lett.*, 1990, **31**, 1617; (m) H. A. J. Carless, J. A. Billinge and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 3113; (n) H. A. J. Carless and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 1719.
- 25 (a) S. Freeman and T. Hudlický, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1209; (b) B. J. Paul, E. Hobbs, P. Buccino and T. Hudlický, *Tetrahedron Lett.*, 2001, **42**, 6433; (c) B. J. Paul, T. A. Martinot, J. Willis and T. Hudlický, *Synthesis*, 2001, 952; (d) T. Hudlický, N. Restrepo-Sanchez, P. D. Kary and L. M. Jaramillo-Gomez, *Carbohydr. Res.*, 2000, **324**, 200; (e) T. Hudlický, C. D. Claeboe, L. E. Brammer Jr., L. Koroniak, G. Butora and I. Ghiviriga, *J. Org. Chem.*, 1999, **64**, 4909; (f) K. A. Oppong, T. Hudlický, F. Yan, C. York and B. V. Nguyen, *Tetrahedron*, 1999, **55**, 2875; (g) L. E. Brammer Jr. and T. Hudlický, *Tetrahedron: Asymmetry*, 1998, **9**, 2011; (h) M. Desjardins, L. E. Brammer Jr. and T. Hudlický, *Carbohydr. Res.*, 1997, **304**, 39; (i) B. V. Nguyen, C. York and T. Hudlický, *Tetrahedron*, 1997, **53**, 8807; (j) T. Hudlický, K. A. Abboud, J. Bolonick, R. Maurya, M. L. Stanton and A. J. Thorpe, *Chem. Commun.*, 1996, 1717; (k) T. Hudlický, K. A. Abboud, D. A. Entwistle, R. Fan, R. Maurya, A. J. Thorpe, J. Bolonick and B. Myers, *Synthesis*, 1996, 897; (l) T. Hudlický and A. J. Thorpe, *Synlett*, 1994, 899; (m) T. Hudlický, M. Mandel, J. Rouden, R. S. Lee, B. Bachmann, T. Dudding, K. J. Yost and J. S. Merola, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1553; (n) M. Mandel and T. Hudlický, *J. Chem. Soc., Perkin Trans. 1*, 1993, 741; erratum, p. 1537; (o) M. Mandel, T. Hudlický, L. D. Kwart and G. M. Whited, *J. Org. Chem.*, 1993, **58**, 2331.
- 26 T. Tschamber, F. Backenstrass, H. Fritz and J. Streith, *Helv. Chim. Acta*, 1992, **75**, 1052.
- 27 (a) S. V. Ley, A. J. Redgrave and L. L. Yeung, *ACS Symp. Ser.*, 1991, **463**, 132; (b) S. V. Ley, *Pure Appl. Chem.*, 1990, **62**, 2031; (c) S. V. Ley, M. Parra, A. J. Redgrave and F. Sternfeld, *Tetrahedron*, 1990, **46**, 4995; (d) S. V. Ley and F. Sternfeld, *Tetrahedron*, 1989, **45**, 3463; (e) S. V. Ley, M. Parra, A. J. Redgrave, F. Sternfeld and A. Vidal, *Tetrahedron Lett.*, 1989, **30**, 3557; (f) S. V. Ley and F. Sternfeld, *Tetrahedron Lett.*, 1988, **29**, 5305; (g) S. V. Ley, F. Sternfeld and S. Taylor, *Tetrahedron Lett.*, 1987, **28**, 225.
- 28 For examples, see: (a) A. Baran, G. Aydin, T. Savran, E. Sahin and M. Balci, *Org. Lett.*, 2013, **15**, 4350; (b) Z. Ekmekci and M. Balci, *Eur. J. Org. Chem.*, 2012, 4988; (c) A. Baran, S. Çambul, M. Nebioglu and M. Balci, *J. Org. Chem.*, 2012, **77**, 5086; (d) N. I. Kurbanoglu, M. Çelik, H. Kilic, C. Alp, E. Şahin and M. Balci, *Tetrahedron*, 2010, **66**, 3485; (e) S. Cantekin, A. Baran, R. Çalışkan and M. Balci, *Carbohydr. Res.*, 2009, **344**, 426; (f) A. Baran and M. Balci, *J. Org. Chem.*, 2009, **74**, 88; (g) A. Coşkun, M. Güney, A. Daştan and M. Balci, *Tetrahedron*, 2007, **63**, 4944; (h) M. Çelik and M. Balci, *ARKIVOC*, 2007, 150; (i) E. Salamci, B. Bayram and M. Balci, *Turk. J. Chem.*, 2006, **30**, 441; (j) Ş. D. Yardımcı, N. Kaya and M. Balci, *Tetrahedron*, 2006, **62**, 10633; (k) L. Kelebekli, M. Çelik, E. Şahin, Y. Kara and M. Balci, *Tetrahedron Lett.*, 2006, **47**, 7031; (l) L. Kelebekli, Y. Kara and M. Balci, *Carbohydr. Res.*, 2005, **340**, 1940; (m) M. S. Gültekin, M. Çelik, E. Turkut, C. Tanyeli and M. Balci, *Tetrahedron: Asymmetry*, 2004, **15**, 453; erratum, p. 1959; (n) M. S. Gültekin, E. Salamci and M. Balci, *Carbohydr. Res.*, 2003, **338**, 1615; (o) Y. Kara and M. Balci, *Tetrahedron*, 2003, **59**, 2063.
- 29 (a) G. Mehta and S. Sen, *Tetrahedron Lett.*, 2010, **51**, 503; (b) G. Luchetti, K. Ding, M. d'Alarcao and A. Kornienko, *Synthesis*, 2008, 3142; (c) Y. J. Lee, K. Lee, S. I. Jung, H. B. Jeon and K. S. Kim, *Tetrahedron*, 2005, **61**, 1987; (d) G. Mehta, R. S. Senaiar and S. Sen, *Proc. Indian Acad. Sci. A*, 2005, **71**, 121; (e) G. Mehta, R. S. Senaiar and M. K. Bera, *Chem.-Eur. J.*, 2003, **9**, 2264; (f) A. Kornienko and M. d'Alarcao, *Tetrahedron: Asymmetry*, 1999, **10**, 827; (g) K. K. Reddy, J. R. Falck and J. Capdevila, *Tetrahedron Lett.*, 1993, **34**, 7869.
- 30 (a) H. Paulsen and F. R. Heiker, *Liebigs Ann.*, 1981, 2180; (b) H. Paulsen and F. R. Heiker, *Angew. Chem.*, 1980, **92**, 930; (c) S. J. Angyal, J. E. Klavins and J. A. Mills, *Aust. J. Chem.*, 1974, **27**, 1075; (d) T. Posternak, D. Janjic, E. A. C. Lucken and A. Szente, *Helv. Chim. Acta*, 1967, **50**, 1027; (e) T. Posternak, *Proc. 2nd Meet. Fed. Eur. Biochem. Soc.*, 1966, p. 31; (f) T. Posternak and J.-G. Falbriard, *Helv. Chim. Acta*, 1960, **43**, 2142; (g) T. Posternak and D. Reymond, *Helv. Chim. Acta*, 1953, **36**, 1370; (h) T. Posternak, *Helv. Chim. Acta*, 1950, **33**, 1594; (i) T. Posternak, *Helv. Chim. Acta*, 1944, **27**, 457.
- 31 (a) J. D. Boyd, C. S. Foote and D. K. Imagawa, *J. Am. Chem. Soc.*, 1980, **102**, 3641; (b) Y. Sütbeyaz, H. Seçen and M. Balci, *J. Org. Chem.*, 1988, **53**, 2312; (c) M. Balci and Y. Sütbeyaz, *Tetrahedron Lett.*, 1983, **24**, 311.
- 32 (a) C. W. Jefford, *Chem. Soc. Rev.*, 1993, **22**, 59; (b) A. A. Frimer, *Chem. Rev.*, 1979, **79**, 359; (c) C. W. Jefford and C. G. Rimbault, *J. Org. Chem.*, 1978, **43**, 1908.
- 33 (a) T. Nagasawa, N. Shimada, M. Torihata and S. Kuwahara, *Tetrahedron*, 2010, **66**, 4965; (b) J. Huang and E. J. Corey, *Org. Lett.*, 2003, **5**, 3455.