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PAPER

Expanding the chiral pool: oxidation of *meta*-bromobenzoic acid by *R. eutrophus* B9 allows access to new reaction manifolds†

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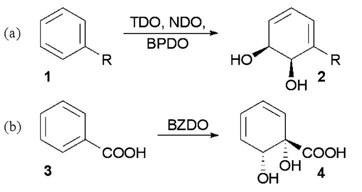
Metabolism of *meta*-bromobenzoic acid by the blocked mutant *Ralstonia eutrophus* B9 affords an enantiopure dearomatised halodiene-diol which we demonstrate is a versatile chiron for organic synthesis. The presence of the halogen leads to reactivity that is distinct to that observed for the non-halogenated analogue and also serves as a synthetic handle for further functionalisation.

Introduction

The dearomatising dihydroxylation of an aromatic substrate by a microorganism was first reported by Gibson over 40 years ago.[1] It was subsequently recognised that the resultant diene diols were useful starting materials for synthesis owing to their densely-packed, differentiated functionality. Indeed, their synthetic value is enhanced further by the fact that substituted arenes give rise to enantiopure diols in most instances. The production and utilisation of these arene-derived diols has become established methodology and the field has been the subject of several excellent reviews.[2]

Thus far, over 400 arene *cis*-diol products have been reported. The vast majority of these are produced by organisms expressing toluene dioxygenase (TDO), naphthalene dioxygenase (NDO) and biphenyl dioxygenase (BPDO) enzymes. These metabolise substituted arene substrates in a regio- and stereoselective fashion. A reliable predictive model has been reported for such transformations[3] and the sense of enantioinduction is conserved across organisms and substrates (Scheme 1a, *ortho-meta* oxygenation). In contrast, organisms expressing benzoate dioxygenase (BZDO) enzymes oxidise benzoic acids in a process that exhibits not only different regioselectivity, but also the opposite sense of enantioinduction. For example, *R. eutrophus* B9,[4] *P. putida* U103[5] and *P. putida* KTSY01 (pSYM01)[6] oxidise benzoic acid to benzoate 1,2-*cis* dihydrodiol **4** (Scheme 1b, *ipso-ortho* oxygenation).



Scheme 1 Regio- and stereoselectivity of dioxygenases.

Diol acid **4** has seen several diverse applications in organic synthesis to date. In 1995, Widdowson *et al.* reported the production of **4** with *P. putida* U103.[7] The absolute stereochemistry of **4** was determined by means of X-ray crystallographic analysis of a *para*-bromobenzoyl derivative. The ability of derivatives of **4** to participate in [4 + 2] cycloadditions with various dienophiles was also demonstrated. In 2001, Myers *et al.* described multiple approaches for elaborating **4**, demonstrating that each position on the ring could be functionalised in a selective fashion through judicious choice of reaction sequence.[8] They also described in detail a large-scale preparation of **4**. That the derivatives described therein are of synthetic utility was first shown by the report in 2004 of the synthesis of carbocyclic analogues of topiramate.[9] In this work, Parker *et al.* described a route to analogues of this anticonvulsant agent, requiring between 3 and 4 steps from one of Myers' chirons; the authors also described the first use of **4** to access a carbohydrate target, carba-β-L-fructopyranose. Also in 2004, Mihovilovic *et al.* reported intramolecular Diels–Alder reactions of derivatives of **4** bearing tethered dienophiles.[10] In 2005, Myers *et al.* disclosed the total synthesis of natural and unnatural tetracycline antibiotics[11] *via* a synthetic sequence commencing from a derivative of **4** they had described four years previously.[8] It is worth noting that whilst the first stereocentre in the target tetracyclines was set in the arene dihydroxylation step, all subsequent stereocentres were installed under substrate control; all stereochemical information in the final products is thus of ultimate enzymatic origin. In 2010, the Mihovilovic group published a full paper[12] on intramolecular Diels–Alder reactions with **4** and, most recently, the chemistry of **4** has been augmented by our

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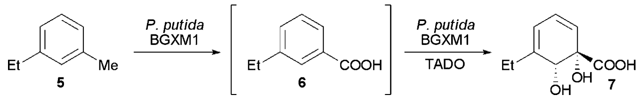
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all novel compounds. 2D NMR spectra for selected compounds. Crystallographic data for **13** and **21**. CCDC reference numbers 808270 and 808269. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05131h

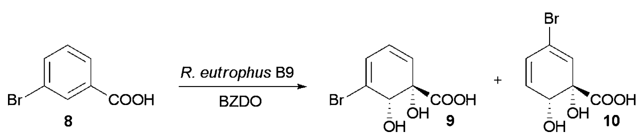
report that simple derivatives of **4** are amenable to complexation to form tricarbonyliron(0)diene complexes.[13] We have been able to demonstrate that such complexation permits the synthesis of otherwise inaccessible moieties. Most notably a diene possessing the *ortho-meta* pattern of oxygenation found in **2** but *antipodal* to **2** may be accessed from **4** by means of such organoiron complexes.[14]

The unique synthetic versatility of **4** has thus been demonstrated. However, we sought to enhance further the utility of the BZDO-mediated benzoate dihydroxylation by use of substituted benzoate substrates. The viability of metabolising substituted benzoates by this approach has been established previously. Studies on *Ralstonia eutrophus* B9‡ have shown that a variety of mono- and disubstituted benzoates are acceptable substrates. It was noted that turnover rates decreased in accordance with the steric demand of a substituent, with the *ortho* position being least tolerant of substitution (only *ortho*-fluorobenzoate underwent dioxygenation) and the *meta* position being the most tolerant.[4,15] Many other organisms expressing BZDOs have been evaluated for their ability to process substituted benzoates,[16] as have organisms expressing TADO[17] (toluate dioxygenase), TERDOS[18] (terephthalate dioxygenase) and IPADO[19] (isophthalate dioxygenase). To our knowledge, however, there is just one example to date of the use in synthesis of an arene dihydrodiol derived from a substituted benzoate: Banwell's use of a metabolite derived from *meta*-ethyltoluene in an approach to vinblastine[20] (Scheme 2).



Scheme 2 Banwell's access to arene diol **7** *via meta*-ethylbenzoic acid.

In the present study, we opted to exploit arene diols derived from the metabolism of *meta*-bromobenzoic acid by *R. eutrophus* B9 (Scheme 3). We anticipated a twofold effect due to incorporation of a bromine in the products. Firstly, this halide would modulate the electron density of the diene such that it would exhibit reactivities distinct from those of the parent system **4**. Secondly, a bromodiene would be amenable to diverse cross-coupling reactions to permit further functionalisation in a manner that would not be possible for unsubstituted diene **4**.



Scheme 3 Arene diol metabolites of *meta*-bromobenzoic acid.

As is the case for any *meta*-substituted benzoate, metabolism of **8** may give rise to two regioisomeric diols, **9** and **10**, reflecting the possibility of the substrate being accommodated in two possible orientations in the BZDO active site. In the specific case of substrate **8**, literature precedent was ambiguous. In their original report on *R. eutrophus* B9,[4] Reiner and Hegeman describe the isolation of both 3- and 5-substituted arene diols from the metabolism of *meta*-substituted benzoates, but product ratios were not quantified. Subsequently, Knackmuss and Reineke quantified product formation and found that 5-substituted diols analogous to **10** were formed more rapidly than the corresponding 3-substituted regioisomers analogous to **9**.[15a] In both of the above studies, however, only *meta*-chloro- and *meta*-methyl benzoate were employed as substrates, not *meta*-bromobenzoate **8**. Reineke and co-workers' subsequent study[15c] has been the only one thus far to specifically address the metabolism of *meta*-bromobenzoate **8** by *R. eutrophus* B9. Whilst the production of both **9** and **10** is described, the product ratio was not determined. In this same study, it is stated that when using *meta*-methylbenzoate, the 5-methyl analogue of **10** is "accessible only with difficulty", whereas the 3-methyl analogue of **9** is "isolable in good yield"; such statements seem to contradict the earlier study.[15a] Thus, it was unclear at the outset what the regiochemical outcome of metabolism of **8** by *R. eutrophus* B9 would be.

Results and discussion

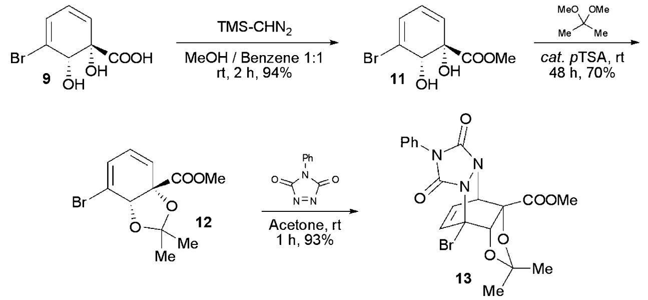
We undertook the bio-oxidation of **8** in accordance with the procedure of Myers *et al.*,[8] but on a 15 L scale. *R. eutrophus* B9 cells were induced with a small quantity of benzoate before addition of sodium *meta*-bromobenzoate solution portionwise over 48 h; disodium succinate solution was added as a sole carbon source. The fermentation broth was then centrifuged to remove cellular material and the supernatant was concentrated under reduced pressure. The concentrate was acidified to pH 3.0 and extracted numerous times with ethyl acetate. Organic washings were dried, then concentrated under reduced pressure to give a crude mixture of **8**, **9** and **10**. NMR analysis indicated that unreacted **8** was the major constituent of the crude mixture. *meta*-Bromobenzoate **8** had been introduced to the fermentation vessel at a rate comparable to that used previously[8] in the non-halogenated case, but *R. eutrophus* B9 metabolised the brominated substrate much more slowly, as expected, leading to accumulation of unreacted **8**. Formation of 3-bromo product **9** was found to have predominated (>10 : 1) over the 5-bromo isomer **10**.

Purification of this crude material was effected by repeated trituration with dichloromethane; this served to remove both the starting material **8** and also the traces of 5-bromo product **10**. After 7 triturations, NMR analysis showed the residual quantity of **8** to be negligible. By this means, pure 3-bromo product **9** was obtained in a yield of 65 mg per litre of fermentation broth, approximately two orders of magnitude lower than that reported for the unsubstituted benzoate.[8]

With access to **9** secured we sought to verify the absolute stereochemistry through X-ray analysis of a crystalline derivative. The configuration of **4** was originally determined by Widdowson *et al.* through formation of the corresponding *para*-bromobenzoylmethyl ester and subsequent X-ray analysis;[7] the same approach was adopted to determine the configuration of **7**.[20] However, as **9** already incorporates a heavy atom, we opted instead to target a crystalline cycloadduct. Esterification of **9** by means of (trimethylsilyl)diazomethane to give **11** was followed by diol protection as acetonide **12**. Upon treatment with 4-phenyl-1,2,4-triazoline-3,5-dione, **12** underwent [4 + 2] cycloaddition to afford crystalline adduct **13** (Scheme 4).[21]

Single crystals of **13** suitable for X-ray structure determination were obtained from diffusion of petroleum ether into a solution of **13** in ethyl acetate. The structure of **13** is depicted in Fig. 1 and

‡ Previously known as *Alcaligenes eutrophus* B9.



Scheme 4 Formation of crystalline derivative.

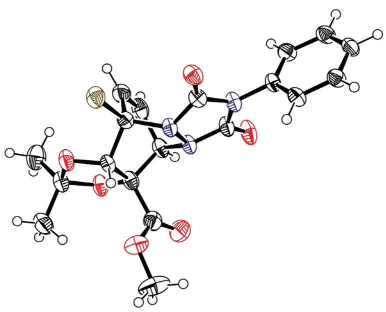


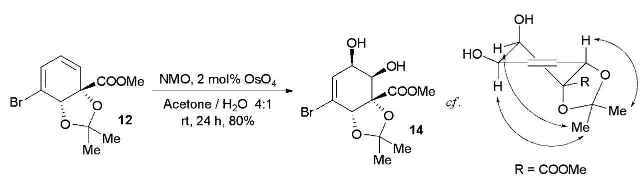
Fig. 1 Solid state structure of **13**. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius.

confirms the absolute stereochemistry as (1*S*,2*S*). Thus, the sense of enantioinduction in the formation of **9** is the same as in the formation of **4** and **7**, as expected.

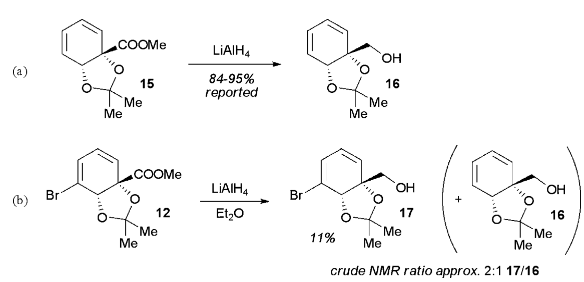
That the sole cycloadduct formed (**13**) is that in which the dienophile approaches *anti* to the acetonide is in keeping with Widdowson's precedent.[7] Aside from that report, all literature examples of heterodienophile cycloadditions with arene diol derived acetonides involve substrates with the *ortho-meta* pattern of oxygenation (*cf.* **2**). Here also, every report describes dienophile addition *anti* to the acetonide.[22,23] In such substrates the original arene substituent is attached to the diene. In contrast, in **12** (which has the *ipso-ortho* pattern of oxygenation, *cf.* **4**), the original arene substituent is attached to an sp^3 centre and will not be coplanar with the diene. If the substituent is of sufficient steric bulk, approach of the dienophile to *both* diene faces may be hindered. Exclusive formation of **13** in this instance is indicative of the steric bulk of the acetonide being the controlling factor in determining regioselectivity of cycloaddition, not steric bulk of the ester.

The above considerations are also relevant in the context of Diels–Alder dimerisation. Arene diol derived acetonides with the *ortho-meta* pattern of oxygenation (*cf.* **2**) are known to undergo spontaneous dimerisation in many instances; this has been reported with halodienes, *e.g.* R = Br,[23j,24a–c] Cl[23j,24b,c] and also with many other substituents on the diene (R = CF_3,[23b,j,24c] R = C_2H_3,[23j,24c,d] R = CN,[24e] R = COOMe,[24f] R = COOEt,[23w] R = $COOCH_2CCH$,[23w] R = $SiMe_2H$,[24g,h] R = $SiMe_2C_2H_3$[24g,h] and R = Me[24i]). In each instance, the dimerisation is reportedly totally selective for formation of the adduct which is *anti* both with respect to the diene and also the dienophile. (The only reported exception to this trend is dimerisation of the acetonide of the parent unsubstituted diene **2**, R = H[25] – a minor cycloadduct deriving from *syn* diene addition and *anti* dienophile addition has also been reported[22,26]). The behaviour of the bromodiene acetonide **12** reported here is in marked contrast to the above cases, in that we have observed *no dimerisation* of **12** upon prolonged storage at room temperature or below. Dimerisation of the non-brominated analogue of **12** has also not been reported. We ascribe this inertness to dimerisation to the fact that such acetonides with the *ipso-ortho* pattern of oxygenation (*cf.* **4**) present sterically demanding substituents on both sides of the diene, hence retarding the formation of all possible isomeric dimers.

We next examined the susceptibility of the bromodiene to oxidative elaboration. Neither **11** nor **12** gave tractable products upon attempted epoxidation with *m*CPBA, in contrast to the corresponding non-halogenated dienes.[8] However, osmium tetroxide-mediated dihydroxylation of **12** proceeded smoothly to afford diol **14** as the sole regio- and diastereoisomer (Scheme 5). Such selectivity is also in contrast to the non-halogenated series, wherein the corresponding diene **15** undergoes dihydroxylation to afford a 5 : 1 mixture of regioisomers favouring the other olefin.[8] The installation of the free diol functionality in **14** on the β-face was confirmed by NOESY NMR experiments.† Reductive elaboration of bromodiene **12** also proceeded in a markedly different fashion to the non-halogenated analogue **15**. Whereas $LiAlH_4$-mediated reduction of the ester in **15** to give **16** is reportedly[7,10,12] high-yielding (Scheme 6a), the corresponding reduction of bromodiene **12** affords the primary alcohol **17** in only 11% yield. We ascribe this low yield partly to the concomitant formation of appreciable amounts of debrominated product **16**, which we have isolated (Scheme 6b).

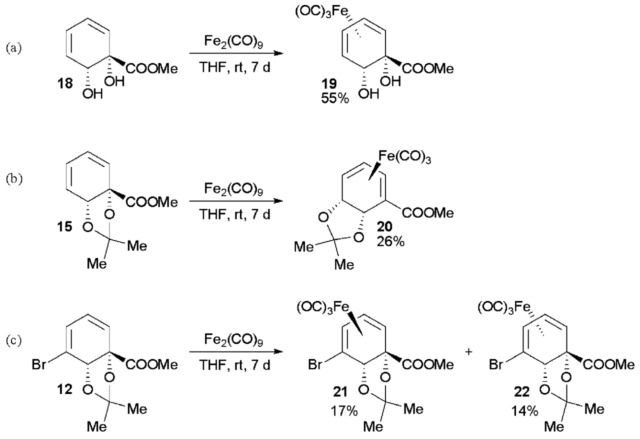


Scheme 5 Dihydroxylation on the β-face. Selected NOESY correlations in **14** shown with double-headed arrows.



Scheme 6 Reductive transformations.

The complexation of arene diols of type **2** with a tricarbonyliron fragment has been extensively studied.[27] We have reported previously[13] on the complexation of **18** (the methyl ester of **4**) to afford **19** as the sole product, with iron complexed to the α-face (Scheme 7a). A later attempt[14] to reverse the facial selectivity in this complexation by use of an acetonide **15** to block the α-face did indeed result in complexation of iron to the diene β-face, but the isolated product (**20**) was that in which acetonide migration had occurred (Scheme 7b). We were therefore keen to determine the



Scheme 7 Iron complex formation for various related dienes.

outcome of complexation of bromodiene acetonide **12** as an iron carbonyl in order to shed light on the mechanism of formation of **20**. In the event, treatment of **12** with nonacarbonyldiiron in THF afforded isomeric complexes **21** and **22**, in which **21** was the major isomer (Scheme 7c). The structure of **21** was determined unambiguously by X-ray crystallography (Fig. 2). (The minor isomer **22**, which was appreciably less stable than **21**, could not be crystallised successfully; its structure was assigned by 2D NMR experiments† and by comparison with **21**.) In this instance, the sole products are those in which acetonide migration has not occurred. This may be explained by the fact that in **12**, the carbon to which an acetonide oxygen would be bonded upon rearrangement already bears the bromine substituent. We had previously concluded that the formation of **20** arose *via* "clockwise" migration of the acetonide, rather than "anticlockwise" migration of the ester.[14] The absence of any such rearrangement in the case of bromodiene **12** is in keeping with this conclusion. The presence of the bromine in **12** also retards the rate of complexation with respect to unsubstituted analogue **15**–identical reaction conditions result in consumption of all of **15**, but recovery of 60% unreacted **12** (Scheme 7).

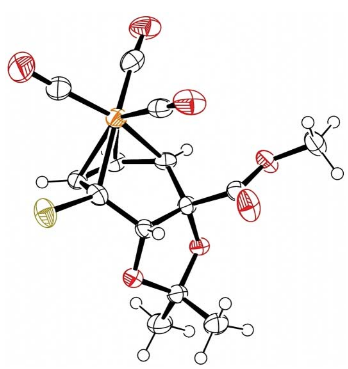
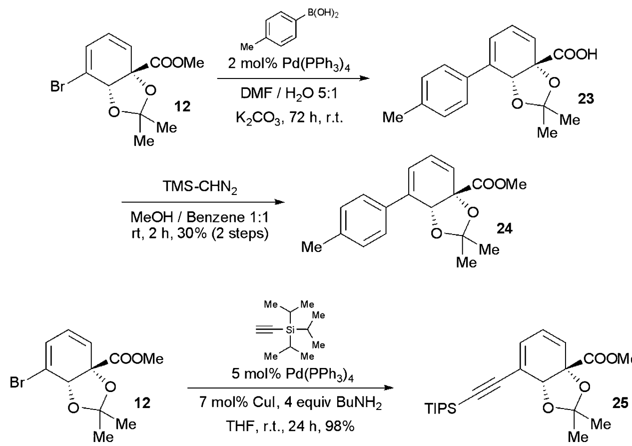


Fig. 2 Solid state structure of **21**. Of two independent molecules in the unit cell, only one is shown for clarity. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius.

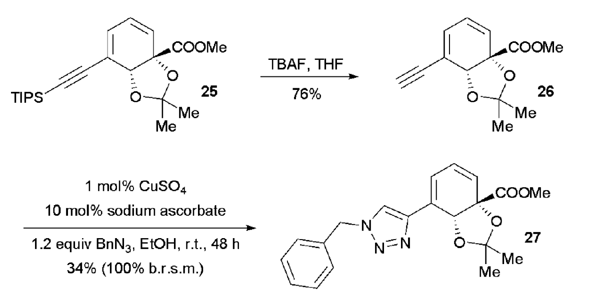
The above transformations of bromodiene **12** represent cases in which the presence of the halogen modulates the reactivity of the system with respect to the unsubstituted diene case. However, we wished to exploit further the value inherent in the bromine substituent by using transformations that would not be possible for the unsubstituted case. A dienyl bromide is suggestive of applications in cross-coupling chemistry and in the more common *ortho-meta* arene dihydrodiol series, both **2** (R = Br)[24a,28] and **2** (R = I)[28a,h,n,29] have indeed been exploited in this context. To date, such cross-couplings have not been reported for derivatives of **4**.

We first examined a Suzuki-Miyaura coupling[30] of protected bromodiene **12** with *para*-tolylboronic acid. Union of these fragments under palladium catalysis was indeed achieved, although it was found that the reaction conditions also effected ester hydrolysis. The free acid **23**, recovered from the aqueous phase, was re-subjected to esterification with (trimethylsilyl)diazomethane to afford the originally targeted methyl ester **24**, albeit in moderate yield (Scheme 8). A much more straightforward cross-coupling was the Sonogashira[31] reaction of **12** with (tri*iso*propylsilyl)acetylene, which afforded the dienyne **25** in near-quantitative yield (Scheme 8).



Scheme 8 Cross-couplings of the bromodiene.

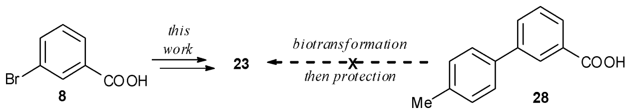
Dienyne **25** is a useful intermediate for further functionalisation. Desilylation with TBAF affords terminal acetylene **26**, which is amenable to the Huisgen[32] copper-catalysed azide-alkyne cycloaddition protocol. We have demonstrated this through the reaction of **26** with benzyl azide to afford triazole **27** (Scheme 9).



Scheme 9 Azide-alkyne "click" cycloaddition.

Conclusions

We have demonstrated the versatility of a halobenzoate-derived *ipso*,*ortho*-oxygenated arene dihydrodiol in various synthetic contexts and shown that the presence of the halogen fundamentally alters the course of the reaction in many instances. The formation of cross-coupling products **23–27** is especially significant, as these structures are arene dihydrodiol derivatives that would not be accessible by direct metabolism of the corresponding arene precursors. Thus, for example, accessing **23** by biotransformation of biaryl carboxylic acid **28** would not be expected to succeed as the steric bulk of the tolyl substituent would likely preclude docking of **28** in the *R. eutrophus* B9 BZDO active site. Compound **23** is nevertheless accessible, by means of the indirect route described in this work (Scheme 10).



Scheme 10

Current efforts in our laboratory are focused on optimising the production process for **9** and incorporating this versatile chiron in the synthesis of more complex targets, including appropriate natural products. The results of these endeavours will be reported subsequently.

Experimental

General

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen. Nonacarbonyldiiron was dispensed in a glovebox. Solvents were dried and degassed by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to petroleum ether, bp 40–60 °C. TLCs were performed using aluminium-backed plates precoated with Alugram®SIL G/UV and visualized by UV light (254 nm) and/or $KMnO_4$ followed by gentle warming. 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 absorbances quoted as ν in cm^{-1}. NMR spectra were run in $CDCl_3$ (unless otherwise specified) on Brüker Avance 250, 300. 400 or 500 MHz instruments at 298 K. Mass spectra were recorded with a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Brüker Daltonik).

Biotransformation of *meta*-bromobenzoic acid

This was performed in accordance with a literature procedure,[8] substituting *meta*-bromobenzoate for benzoate in the biotransformation step. A sterile pipette tip was streaked across the surface of a frozen glycerol stock solution of *R. eutrophus* B9 cells to produce small shards (approx. 10 mg). The frozen shards were added to a sterile 250 mL Erlenmeyer flask containing 100 mL of Hutner's mineral base medium[8,33] and aqueous sodium succinate solution (500 μL of a 1.5 M solution). The flask was shaken at 250 rpm for 48 h at 30 °C. The culture was then transferred to a 20 L plastic carboy and additional medium was added to give a total volume of 15 L. Air was continuously sparged through the culture. Sodium succinate solution (50 mL) was added and the culture was incubated for 48 h. The temperature was maintained at 30 °C by means of immersed Nalgene® 380 food grade tubing, through which was passed heated water. Subsequently, sodium benzoate solution (5 mL of a 1.0 M solution) was added to initiate BZDO expression. After 3 h, sodium *meta*-bromobenzoate (50 mL of a 1.0 M solution) and sodium succinate (25 mL of a 1.5 M solution) were added. Over the next 48 h, sodium *meta*-bromobenzoate solution (1.0 M) and sodium succinate solution (1.5 M) were added portionwise. In total 60.3 g (270 mmol) sodium *meta*-bromobenzoate and 48.6 g (300 mmol) sodium succinate were introduced. The culture was incubated for a further 72 h, then the fermentation broth was centrifuged at 6000 rpm for 25 min and the supernatant liquid decanted. The supernatant was concentrated under reduced pressure (rotary evaporator bath temperature <40 °C) to a total volume of 1.5 L. The concentrated supernatant was then carefully acidified to pH 3.0 with concentrated hydrochloric acid. The acidified solution was then extracted with ethyl acetate (20 × 1 L). After each two extractions, the aqueous phase was re-acidified to pH 3.0. Each organic extract was dried over $MgSO_4$ and filtered. Combined filtrates were concentrated under reduced pressure to give 51.4 g of crude material, of which unreacted *meta*-bromobenzoic acid was the major constituent. This material was repeatedly triturated with copious quantities of dichloromethane, resulting in the dissolution of most of the material. (Toluene was also determined to be a suitable triturant.) After 7 such triturations and drying under vacuum, the residual solid material was shown by NMR to be pure (1*S*,6*S*)-5-bromo-1,6-dihydroxycyclohexa-2,4-dienecarboxylic acid **9**, a brown powder; 979 mg (4.17 mmol), 1.5%, 65 mg dm^{-3}. $[\alpha]_D^{25}$ −0.16 (*c* 0.1, $CHCl_3$); δ_H (300 MHz, CD_3OD)[15c] 6.30 (1H, dd, *J* = 6.0, 1.0 Hz, CBr═CH), 5.89 (1H, dd, *J* = 9.5, 6.0 Hz, CBr═CH–C*H*), 5.75 (1H, d, *J* = 9.5 Hz, CBr═CH–CH═C*H*), 4.69 (1H, d, *J* = 1.0 Hz, HO–C*H*); δ_C (75 MHz, CD_3OD) 177.3 (C═O), 130.6 (CBr), 128.5 (CBr═CH–CH═*C*H), 127.0 (CBr═CH–CH), 126.7 (CBr═*C*H), 77.6 (*C*–COOH), 74.6 (HO–CH); ν_{max}(film) 3220, 1698, 1417, 1358, 1229, 1091, 1028, 992, 671 cm^{-1}; HRMS (ESI–) *m*/*z* calcd for $(C_7H_8BrO_4–CO_2–H_2O–H)^-$, 170.9446, 172.9425; found 170.9446, 172.9422.

(1*S*,6*S*)-Methyl 5-bromo-1,6-dihydroxycyclohexa-2,4-diene-carboxylate (11)

To a stirred solution of **9** (61 mg, 0.260 mmol, 1 eq.) in MeOH–benzene (1 : 1, 32 mL) at room temperature was added dropwise (trimethylsilyl)diazomethane (1.5 mL, 2.0 M in hexane) until the yellow colour persisted and effervescence ceased. The solution was stirred for 2 h then concentrated under reduced pressure to give crude (1*S*,6*S*)-methyl 5-bromo-1,6 dihydroxycyclohexa-2,4-diene carboxylate **11** (61 mg, 94%) as a brown oil, sufficiently pure to be used without further purification: R_f 0.73 (50% EtOAc–petrol); $[\alpha]_D^{25}$ −40 (*c* 0.175, CH_2Cl_2); δ_H (250 MHz) 6.38 (1H, ddd, *J* = 6.0, 2.5, 0.5 Hz, CBr═CH), 5.99 (1H, dd, *J* = 9.5, 6.0 Hz, CBr═CH–C*H*), 5.76 (1H, d, *J* = 9.5 Hz, CBr═CH–CH═C*H*), 4.79 (1H, brs, C(OH)*H*), 3.89 (3H, s, CH_3); δ_C (75 MHz, CD_3OD) 175.5 (C═O), 130.3 (CBr), 127.9, 127.3, 126.8, 78.0 (*C*-COOMe), 74.6 (C(OH)H), 53.9 (O–CH_3); ν_{max} (film) 3451, 2953, 1734, 1643, 1572, 1255, 1105, 1034, 940, 809, 695 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_8H_9BrO_4+Na)^+$, 270.9582, 272.9561; found 270.9576, 272.9559.

(3a*S*,7a*S*)-Methyl 7-bromo-2,2-dimethyl-3a,7a-dihydrobenzo-[d][1,3]dioxole-3a-carboxylate (12)

To diol **11** (84 mg, 0.337 mmol, 1 eq.) and *para*-toluenesulfonic acid (2.0 mg, 0.01 mmol, 0.03 eq.) in acetone (30 mL) was added 2,2-dimethoxypropane (600 μL, 4.88 mmol, 14.5 eq.). The reaction mixture was stirred at room temperature for 48 h, transferred to a separating funnel, washed with saturated $NaCl_{(aq)}$ then extracted with EtOAc. The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give (3a*S*,7a*S*)-methyl 7-bromo-2,2-dimethyl-3a,7a-dihydrobenzo-[d][1,3]dioxole-3a-carboxylate **12** (68 mg, 70%) a brown oil, sufficiently pure to be used without further purification: R_f 0.82 (25% EtOAc–petrol); $[\alpha]_D^{25}$ −192 (*c* 0.65, CH_2Cl_2); δ_H (250 MHz) 6.45 (1H, d, *J* = 6.0 Hz, CBr=CH), 5.97 (1H, dd, *J* = 9.0, 6.0 Hz, CBr=CH–C*H*), 5.90 (1H, d, *J* = 9.0 Hz, CBr=CH–CH=C*H*), 5.08 (1H, s, CH–O–), 3.81 (3H, s, O–CH_3), 1.47 (3H, s, C–CH_3), 1.43 (3H, s, C–CH_3); δ_C (75 MHz) 171.3 (C=O), 125.9 (CBr), 124.2, 124.1, 123.3, 108.5 (–O–C–O–), 81.8 (*C*–C–O), 78.5 (*C*H–O), 53.2 (–OCH_3), 26.9 (–C–*C*H_3), 25.5 (–C–*C*H_3); ν_{max} (film) 2971, 1775, 1706, 1602, 1358, 1240, 1211, 1159, 1009, 957, 758, 723, 687 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{11}H_{13}BrO_4+Na)^+$, 310.9895, 312.9874; found 310.9886, 312.9873.

(3a*S*,4*R*,10*R*,10a*S*)-Methyl 10-bromo-2,2-dimethyl-6,8-dioxo-7-phenyl-4,6,7,8,10,10a-hexahydro-3aH-4,10-etheno[1,3]-dioxolo-[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-3a-carboxylate (13)

To a solution of diene **12** (49 mg, 0.17 mmol, 1 eq.) in acetone (4.0 mL) at room temperature was added in a dropwise fashion a solution of 4-phenyl-1,2,4-triazoline-3,5-dione in acetone, until a faint red colour of the dione persisted. After 1 h, the reaction mixture was concentrated under reduced pressure to give (3a*S*,4*R*,10*R*,10a*S*)-methyl 10-bromo-2,2-dimethyl-6,8-dioxo-7-phenyl-4,6,7,8,10,10a-hexahydro-3aH-4,10-etheno[1,3]dioxolo-[4,5-d][1,2,4]-triazolo[1,2-a]pyridazine-3a-carboxylate **13** (86 mg, 93% yield) as a white crystalline solid: mp 172–174 °C (EtOAc : petrol); R_f 0.54 (50% EtOAc–petrol); $[\alpha]_D^{25}$ −11.5 (*c* 0.78, CH_2Cl_2); δ_H (300 MHz) 7.44–7.37 (5H, m, Ar–H), 6.62 (1H, dt, *J* = 10.0, 1.5 Hz, CBr–C*H*–CH), 6.37 (1H, dd, *J* = 10.0, 7.0 Hz, CBr–CH=C*H*), 5.39 (1H, dd, *J* = 7.0, 1.5 Hz, N–CH–C–COO–), 5.33 (1H, d, *J* = 1.5 Hz, CBr–CH–O), 3.93 (3H, s, –OCH_3), 1.42 (3H, s, C–CH_3), 1.36 (3H, s, C–CH_3); δ_C (75 MHz) 169.7 (O–C=O), 154.3 (N–C=O), 154.0 (N–C=O), 135.4, 130.7, 129.2, 128.8, 127.6, 125.8, 114.3 (–O–C–O–), 84.2, 82.9, 67.7, 53.9, 53.8, 26.2, 26.1; ν_{max} (film) 2993, 1786, 1721, 1559, 1501, 1457, 1400, 1260, 1214, 1149, 1088, 974, 880, 754 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{19}H_{18}BrN_3O_6+H)^+$, 464.0457, 466.0437; found 464.0449, 466.0429.

(3a*S*,4*R*,5*R*,7a*S*)-Methyl 7-bromo-4,5-dihydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxole-3a-carboxylate (14)

To a solution of **12** (14.0 mg, 0.048 mmol, 1 eq.) and NMO (6.6 mg, 0.048 mmol, 1 eq.) in acetone/H_2O 4 : 1 (3 mL) was added OsO_4 (10 μL, 2.5 wt% in *t*BuOH, 2 mol%). The reaction mixture was stirred at room temperature for 24 h, then diluted with $Na_2S_2O_{3(aq)}$ and extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (40% EtOAc–petrol) to give (3a*S*,4*R*,5*R*,7a*S*)-methyl 7-bromo-4,5-dihydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxole-3a-carboxylate **14** (11 mg, 80%) as a colourless oil: R_f 0.32 (40% EtOAc–petrol); $[\alpha]_D^{25}$ −5.5 (*c* 0.55, CH_2Cl_2); δ_H (500 MHz) 6.23 (1H, d, *J* = 2.5 Hz, CBr=CH), 5.08 (1H, d, *J* = 0.5 Hz, CBr–CH–O), 4.42 (1H, br s, CHC*H*(OH)CH(OH)), 4.32 (1H, br s, CHCH(OH)C*H*(OH)), 3.87 (3H, s, –OCH_3), 2.80 (1H, br s, –OH), 2.76 (1H, br s, –OH), 1.46 (3H, s, C–CH_3), 1.41 (3H, s, C–CH_3); δ_C (75 MHz) 170.8 (C=O), 130.9 (CBr=*C*H), 121.2 (CBr), 111.3 (–O–C–O–), 83.5 (*C*–$COOCH_3$), 77.1 (CBr–*C*H–O–C), 69.9 (C–OH), 66.2 (C–OH), 52.2 (O–CH_3), 26.4 (C–*C*H_3), 25.8 (C–*C*H_3); ν_{max} (film) 3405, 1734, 1647, 1373, 1236, 1098, 1062, 620 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{11}H_{15}BrO_5+Na)^+$, 344.9950, 346.9929; found 344.9948, 346.9935.

((3a*R*,7a*S*)-7-Bromo-2,2-dimethyl-3a,7a-dihydrobenzo-[d][1,3]dioxol-3a-yl)methanol (17)

To ester **12** (68.9 mg, 0.235 mmol, 1 eq.) was added lithium aluminium hydride (9.0 mg, 0.237 mmol, 1 eq.) as a solution in diethyl ether (25 mL). The reaction mixture was stirred at room temperature for 1 h, then cooled to 0 °C. Excess EtOAc was added dropwise by syringe to quench unreacted reductant, then the reaction mixture was cautiously added to a saturated aqueous solution of sodium potassium tartrate (Rochelle's salt). The reaction mixture was stirred vigorously for 1 h, then the phases were separated. The organic phase was dried over $MgSO_4$ then filtered. The filtrate was concentrated under reduced pressure and purified by chromatography (30% EtOAc–petrol) to afford ((3a*R*,7a*S*)-7-bromo-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxol-3a-yl)methanol (**17**) (7.0 mg 11%) as a colourless oil. Debrominated product ((3a*R*,7a*S*)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxol-3a-yl)methanol (**16**) was also isolated. Alcohol **17**: R_f 0.45; (30% EtOAc–petrol); $[\alpha]_D^{25}$ −10 (*c* 0.2, CH_2Cl_2); δ_H (300 MHz) 6.42 (1H, dd, *J* = 6.0, 0.5 Hz, BrC=CH), 5.90 (1H, dd, *J* = 9.5, 6.0 Hz, BrC=CH–C*H*), 5.78 (1H, dd, *J* = 9.5, 0.5 Hz, BrC=CH–CH=C*H*), 4.91 (1H, s, CH–O–), 3.61 (1H, d, *J* = 11.5 Hz, –C*H*H–OH), 3.44 (1H, dd, *J* = 11.5, 7.0 Hz, –CH*H*–OH), 1.85 (1H, br s, –OH), 1.49 (3H, s, CH_3), 1.39 (3H, s, CH_3); δ_C (75 MHz) 127.9, 126.4, 123.4, 123.3, 107.9 (–O–C–O–), 82.9 (*C*–CH_2OH), 77.7 (*C*H–O–C), 64.7 (–CH_2OH), 27.0 (CH_3), 26.9 (CH_3); ν_{max} (film) 3413, 2918, 2956, 2852, 1465, 1383, 1222, 1943, 750 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{10}H_{11}BrO_3+Na)^+$, 282.9946: 284.9925; found 282.9932, 284.9922.

(4*S*)-Tricarbonyl(η^4-(3a*S*,7a*S*)-methyl 7-bromo-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate)iron(0) (21) and (4*R*)-Tricarbonyl(η^4-(3a*S*,7a*S*)-methyl 7-bromo-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate)-iron(0) (22)

To a flask containing **12** (185 mg, 0.59 mmol, 1 eq.) in a glovebox was added nonacarbonyldiiron (440 mg, 1.21 mmol, 2 eq.). THF (40 mL) was added and the reaction mixture was stirred at room temperature for 7 d. The reaction mixture was then concentrated under reduced pressure (***Care! Toxic pentacarbonyliron distilled over at this point***) and purified by column chromatography (10% EtOAc–petrol) to give (4*S*)-tricarbonyl(η^4-(3a*S*,7a*S*)-methyl 7-bromo-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate)iron(0) **21** as fine brown needles (43 mg, 17%)

and (4*R*)-tricarbonyl(η^4-(3a*S*,7a*S*)-methyl 7-bromo-2,2-dimethyl-3a,7a-dihydrobenzo-[d][1,3]dioxole-3a-carboxylate)iron(0) **22** as a brown oil (36 mg, 14%). Unreacted **12** (100 mg, 60%) was also isolated. Complex **21**: mp 95-97 °C (EtOAc : petrol); R_f 0.32 (10% EtOAc–petrol); $[\alpha]_D^{25}$ −10 (*c* 0.2, CH_2Cl_2); δ_H (300 MHz) 5.95 (1H, dt, *J* = 4.5, 1.5 Hz, CBr=CH), 5.47 (1H, dd, *J* = 6.5, 4.5 Hz,CBr=CH–C*H*=), 5.36 (1H, d, *J* = 1.5 Hz, CH–O–), 3.88 (3H, s, O–CH_3), 3.06 (1H, dd, *J* = 6.5, 1.0 Hz, CBr=CH–CH=C*H*), 1.45 (3H, s, C–CH_3), 1.23 (3H, s, C–CH_3); δ_C (75 MHz) 171.3 (–*C*OOMe), 117.8 (–O–C–O–), 89.9 (CBr=*C*H), 87.0 (*C*–COOMe), 86.7 (CH–O–), 83.6 (CBr=CH-*C*H=), 70.2 (CBr), 54.0 (CBr=CH–CH=*C*H), 53.3 (O–CH_3), 28.1 (C–*C*H_3), 27.3 (*C*–CH_3); ν_{max} (film) 2981, 2068, 2003, 1730, 1437, 1375, 1261, 1214, 1162, 1062, 1027, 978, 865, 752, 687, 636 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{14}H_{13}BrFeO_7+Na)^+$, 450.9092, 452.9071; found 450.9106, 452.9164. Complex **22**: R_f 0.26 (10% EtOAc–petrol); $[\alpha]_D^{25}$ −90 (*c* 0.6, CH_2Cl_2); δ_H (500 MHz) 5.76 (1H, d, *J* = 3.5 Hz, CBr=CH), 5.15 (1H, dd, *J* = 6.0, 4.5 Hz, CBr=CH–C*H*=), 4.60 (1H, s, CH–O–), 3.75 (3H, s, O–CH_3), 2.97 (1H, d, *J* = 6.5 Hz, CBr=CH–CH=C*H*), 1.71 (3H, s, C–CH_3), 1.20 (3H, s, C–CH_3); δ_C (75 MHz) 207.1 (Fe C=O), 173.3 (–COOMe), 109.7 (–O–C–O–), 89.3 (CBr=*C*H), 85.4 (*C*–COOMe), 84.8 (CH–O–), 80.5 (CBr=CH-*C*H=), 73.6 (CBr), 61.2 (CBr=CH–CH=*C*H), 53.1 (O–CH_3), 25.0 (C–*C*H_3), 24.2 (C–*C*H_3); ν_{max} (film) 2980, 2061, 1995, 1729, 1460, 1380, 1252, 1207, 1168, 1070, 1030 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{14}H_{13}BrFeO_7+Na)^+$, 450.9092, 452.9071; found 450.9091, 452.9073.

(3a*S*,7a*R*)-Methyl 2,2-dimethyl-7-(*para*-tolyl)-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate (24)

Bromodiene **12** (25.0 mg, 0.096 mmol, 1 eq.), tetrakis(triphenylphosphine)palladium (2.0 mg, 0.002 mmol, 2 mol%), *para*-tolylboronic acid (105 mg, 0.78 mmol, 8 eq.) and potassium carbonate (238 mg, 1.73 mmol, 18 eq.) were dissolved in DMF–H_2O 5 : 1 (30 mL) and stirred at room temperature for 72 h. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was devoid of product; thus, the aqueous layer was concentrated under reduced pressure to afford crude free acid cross-coupling product **23**. The crude acid **23** was then dissolved in MeOH–benzene 1 : 1 (35 mL) and (trimethylsilyl)diazomethane (1.5 mL, 2.0 M in hexane) was added dropwise with stirring until the yellow colour persisted and effervescence ceased. The solution was stirred for 2 h then concentrated under reduced pressure. Purification by column chromatography (10% EtOAc–petrol) gave (3a*S*,7a*R*)-methyl 2,2-dimethyl-7-(*para*-tolyl)-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate (**24**) (8 mg, 30% over two steps) as a colourless oil: R_f 0.36 (5% EtOAc–petrol); $[\alpha]_D^{25}$ −156 (*c* 0.3, CH_2Cl_2); δ_H (250 MHz) 7.50 (2H, d, *J* = 8.0 Hz, Ar–H), 7.18 (2H, d, *J* = 8.0 Hz, Ar–H) 6.48 (1H, d, *J* = 6.0 Hz, Ar–C=CH), 6.23 (1H, dd, *J* = 9.5, 6.0 Hz, Ar–C=CH–C*H*), 5.83 (1H, d, *J* = 9.5 Hz, Ar–C=CH–CH=C*H*), 5.26 (1H, s, CH–O–C), 3.77 (3H, s, O–CH_3), 2.36 (3H, s, Ar–CH_3), 1.53 (3H, s, C–CH_3), 1.42 (3H, s, C–CH_3); δ_C (75 MHz) 171.8 (C=O), 138.2 (4°), 135.3 (4°), 134.6 (4°), 129.4 (3° Ar), 125.8 (3° Ar), 124.8 (Ar–C=CH–*C*H), 124.5 (Ar–C=CH–CH=*C*H), 119.7 (Ar–C=*C*H), 107.6 (–O–C–O–), 81.2 (*C*–COOMe), 74.6 (CH–O–), 53.1 (O–CH_3), 27.1 (C–*C*H_3), 25.4 (C–*C*H_3), 21.4 (Ar–CH_3); ν_{max} (film) 2973, 2937, 2888, 1741, 1469, 1381, 1308, 1163, 1131, 1105, 951, 821 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{18}H_{20}O_4+Na)^+$, 323.1259; found 323.1258.

(3a*S*,7a*R*)-Methyl 2,2-dimethyl-7-((triisopropylsilyl)ethynyl)-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate (25)

To a solution of bromodiene **12** (81 mg, 0.28 mmol, 1 eq.), tetrakis(triphenylphosphine)palladium (16 mg, 0.014 mmol, 5 mol%), copper(I) iodide (3.7 mg, 0.0196 mmol, 7 mol%) dissolved in THF (20 mL), was added by syringe *n*-butylamine (110 μL, 1.12 mmol, 4 eq.) and (tri*iso*-propyl)acetylene (100 μL, 0.45 mmol, 1.6 eq.). The reaction mixture was stirred at room temperature for 24 h, then diluted with EtOAc and washed with $NH_4Cl_{(aq)}$ and $NaCl_{(aq)}$. The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% EtOAc–petrol) to give (3a*S*,7a*R*)-methyl 2,2-dimethyl-7-((tri*iso*propylsilyl)ethynyl)-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate (**25**) (108 mg, 98%) as a yellow oil: R_f 0.45 (10% EtOAc–petrol); $[\alpha]_D^{25}$ −176 (*c* 0.89, CH_2Cl_2); δ_H (250 MHz) 6.37 (1H, d, *J* = 6.0 Hz, SiC≡C–C=C*H*), 6.12 (1H, dd, *J* = 9.5, 6.0 Hz, SiC≡C–C=CH–C*H*), 5.85 (1H, dd, *J* = 9.5, 0.5 Hz, SiC≡C–C=CH–CH=C*H*), 4.91 (1H, d, *J* = 0.5 Hz, CH–O–), 3.78 (3H, s, O–CH_3), 1.45 (3H, s, C–CH_3), 1.39 (3H, s, C–CH_3), 1.08 (21H, br s, Si–CH and Si–CH–C*H*$_3$); δ_C (75 MHz) 171.7 (C=O), 129.0 (alkene C), 125.0 (alkene C), 124.4 (alkene C), 120.7 (alkene C), 108.2 (–O–C–O–), 105.5 (alkyne C), 96.7 (alkyne C), 80.0 (*C*–COOMe), 75.6 (CH–O–), 53.0 (O–CH_3), 26.9 (C–*C*H_3), 25.6 (C–*C*H_3), 18.6 (Si–C–*C*H_3), 11.3 (Si–*C*–CH_3); ν_{max} (film) 2943, 2865, 2158, 2032, 1741, 1462, 1381, 1243, 1039, 883, 677 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{22}H_{34}O_4Si+Na)^+$, 413.2124; found 413.2127.

(3a*S*,7a*R*)-Methyl 7-ethynyl-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate (26)

To a stirred solution of silylacetylene **25** (9.6 mg, 0.03 mmol, 1 eq.) in THF (30 mL) at room temperature was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 0.05 mL, 0.05 mmol, 1.1 equiv). The reaction mixture was stirred for 24 h, then diluted with EtOAc and washed with $NaCl_{(aq)}$. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (15% EtOAc–petrol) to give (3a*S*,7a*R*)-methyl 7-ethynyl-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate (**26**) (4.4 mg, 0.015 mmol, 76%) as a pale white gum: R_f 0.24 (15% EtOAc–petrol); $[\alpha]_D^{25}$ −184 (*c* 0.32, CH_2Cl_2); δ_H (400 MHz) 6.46 (1H, d, *J* = 6.0 Hz, HC≡C–C=C*H*), 6.14 (1H, dd, *J* = 9.5, 6.0 Hz, HC≡C–C=CH–C*H*), 5.90 (1H, d, *J* = 9.5 Hz, HC≡C–C=CH–CH=C*H*), 4.92 (1H, s, CH–O–), 3.80 (3H, s, O–CH_3), 3.23 (1H, s, C≡CH), 1.48 (3H, s, C–CH_3), 1.43 (3H, s, C–CH_3); δ_C (75 MHz) 171.5 (C=O), 130.6 (HC≡C–C=*C*H), 126.1 (HC≡C–C=CH–CH=*C*H), 123.8 (HC≡C–C=CH–*C*H), 118.8 (HC≡C–*C*=), 108.1 (–O–C–O–), 82.6 (HC≡*C*), 81.8 (H*C*≡C), 80.1 (*C*–COOMe), 75.0 (CH–O), 53.3 (O–CH_3), 27.0 (C–*C*H_3), 25.4 (C–*C*H_3); ν_{max} (film) 2981, 2889, 1737, 1462, 1382, 1251, 1152, 954, 807 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{13}H_{14}O_4+Na)^+$, 257.0784; found 257.0751.

(3a*S*,7a*R*)-Methyl 7-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate (27)

To a stirred solution of terminal alkyne **26** (13.0 mg, 0.05 mmol, 1 eq.) in EtOH–H_2O 5 : 1 (25 mL) were added benzyl azide (7.9 mg, 0.06 mmol, 1.2 eq.), $CuSO_4$ (1.1 mg, 1 mol%) and ascorbic acid (5.9 mg, 10 mol%). The solution was stirred at room temperature for 48 h, then diluted with $NaCl_{(aq)}$ and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% to 50% EtOAc–petrol) to give unreacted **26** (7.8 mg, 66%) and (3a*S*,7a*R*)-methyl 7-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate (**27**) (6.3 mg, 34%) as a pale brown oil: R_f 0.48 (50% EtOAc–petrol); $[\alpha]_D^{25}$ –40 (*c* 0.18, CH_2Cl_2); δ_H (300 MHz) 7.62 (1H, s, HetAr–H), 7.37–7.29 (5H, m, Ph–H) 6.94 (1H, d, J = 6.0 Hz, HetAr–C=CH), 6.28 (1H, dd, J = 9.0, 6.0 Hz, HetAr–C=CH–C*H*=), 5.92 (1H, d, J = 9.0 Hz, HetAr–C=CH–CH=C*H*), 5.61 (1H, d, J = 15.0 Hz, Ph–C*H*H–), 5.49 (1H, d, J = 15.0 Hz, Ph–CH*H*–) 5.27 (1H, s, CH–O–), 3.78 (3H, s, O–CH_3), 1.48 (3H, s, C–CH_3), 1.34 (3H, s, C–CH_3); δ_C (75 MHz) 172.0 (C=O), 134.8, 129.3, 128.8, 128.1, 127.8, 126.1, 124.9, 124.5, 121.0 (3° HetAr), 119.7 (HetAr–C=*C*H–), 108.7 (–O–C–O–), 80.6 (*C*–COOMe), 74.2 (CH–O–), 54.3 (Ph–CH_2–), 53.2 (O–CH_3), 27.1 (C-*C*H_3), 25.8 (C-*C*H_3); ν_{max} (film) 2995, 2917, 1857, 1739, 1496, 1457, 1258, 1066, 887, 799, 727 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{20}H_{21}N_3O_4+Na)^+$, 390.1429; found 390.1440.

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