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Rational Design, Synthesis, and Evaluation of Nanomolar Type II Dehydroquinase Inhibitors

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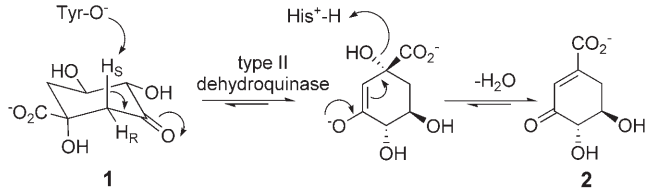
The in silico design, synthesis, and biological evaluation of ten potent type II dehydroquinase inhibitors are described. These compounds contain an anhydroquinate core, incorporated as a mimic of the enolate reaction intermediate. This substructure is attached by a variety of linking units to a terminal phenyl group that binds in an adjacent pocket. Inhibitors were synthesised from (−)-quinic acid using palladium-catalysed Stille and carboamidation chemistry. Several inhibitors exhibited nanomolar inhibition constants against type II dehydroquinases from Streptomyces coelicolor and Mycobacterium tuberculosis. These are among the most potent inhibitors of these enzymes reported to date.

Introduction

The shikimate pathway is the biosynthetic route to the aromatic amino acids and other important aromatic metabolites in plants, bacteria, fungi, and apicomplexan parasites.[1–3] The pathway is absent in mammals, making the corresponding enzymes attractive targets for the development of new herbicides and antimicrobial agents.[1] Dehydroquinase (3-dehydroquinate dehydratase, EC 4.2.1.10), the third enzyme of the pathway, catalyses the conversion of 3-dehydroquinate (**1**) to 3-dehydroshikimate (**2**). There are two forms of dehydroquinase, type I and type II, which appear to have arisen by convergent evolution. These enzymes are structurally distinct and catalyse the same overall transformation by very different mechanisms.[4] The type I dehydroquinases (for example, from *Escherichia coli*) are dimeric proteins that catalyse the *syn* dehydration of **1** through the initial formation of a Schiff base with a conserved lysine residue.[5] In contrast, type II enzymes (for example, from *Streptomyces coelicolor*) are dodecamers that catalyse the *anti* elimination of water via an enolate intermediate (Scheme 1).[6]

The type II enzymes are found in several pathogenic bacteria including *Mycobacterium tuberculosis* (TB)[7] and *Helicobacter pylori* (gastritis, stomach ulcer)[8] which cause enormous mortality and economic loss. Potent and selective inhibitors of type II dehydroquinases could consequently have potential as broad-spectrum antimicrobials.



Scheme 1. Mechanism for the conversion of 3-dehydroquinate (**1**) into 3-dehydroshikimate (**2**) catalysed by type II dehydroquinases.

The first generation of selective type II inhibitors were designed to mimic the flattened enolate intermediate in the enzyme's reaction mechanism.[9] Anhydroquinate analogue **3**, incorporating sp^2 hybridisation at C2 and C3 was 20-fold more potent ($K_i = 30$ μM) than the reduced quinate analogue **4** ($K_i = 600$ μM) (Figure 1) against the *S. coelicolor* type II dehydroquinase—which has a K_m of 120 μM.[10] Co-crystallisation of **3** with *S. coelicolor* type II dehydroquinase revealed a second binding pocket adjacent to the active site (PDB code: 1GU1, Figure 2a)[6d] which was adventitiously occupied by a glycerol mol-

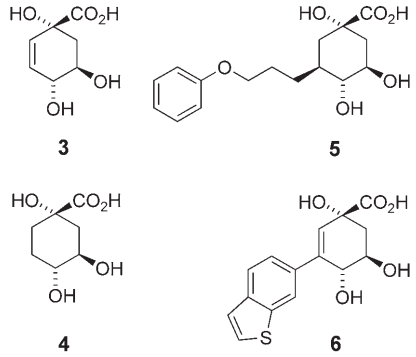


Figure 1. Previously reported type II dehydroquinase inhibitors.[9,10,13,14b]

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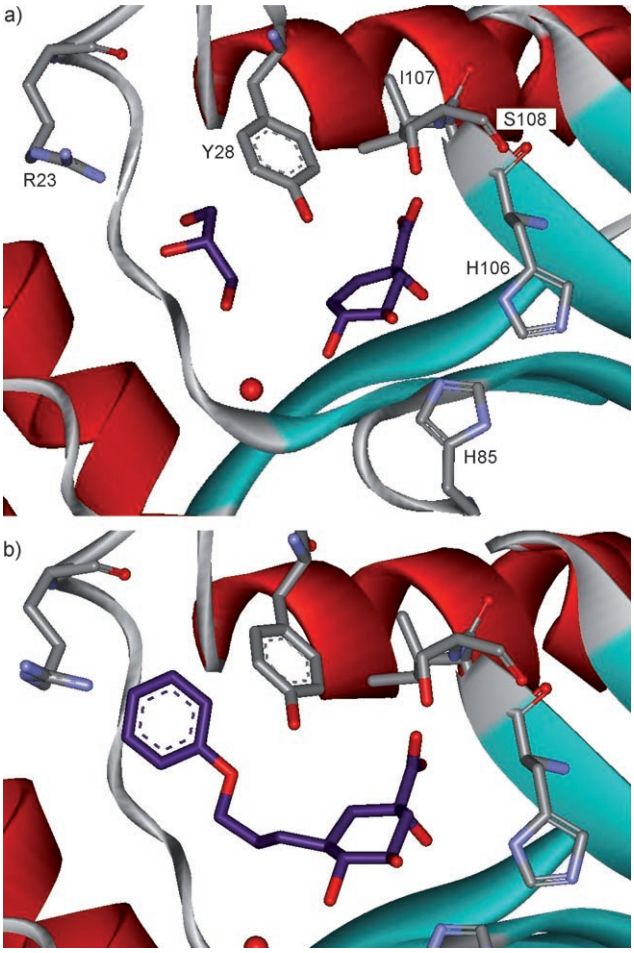


Figure 2. Crystal structure of a) **3** and glycerol[6d] and b) **5** bound in the active site of *S. coelicolor* type II dehydroquinase.[13]

ecule from the enzyme storage buffer. This binding pocket is located underneath a flexible loop, containing the catalytically important tyrosine and arginine residues. The arginine is thought to modulate the pK_a of the tyrosine, which is the base responsible for removing the C2 proton.

The identification of this second binding pocket inspired the design of several series of inhibitors. The first series had different side chains at C3 and C4 appended onto the saturated core of quinate.[11–13] Compound **5** with a phenyloxypropyl substituent attached to the C3 position had an inhibition constant of 33 μM against *S. coelicolor* type II dehydroquinase (Figure 1). A crystal structure of **5** bound in the active site of *S. coelicolor* type II dehydroquinase suggested that the increase in potency (when compared to **4**) was due to a π-stacking interaction of the terminal phenyl ring with Tyr 28 (PDB code: 2BT4, Figure 2b).[13] Two recent reports described potent inhibitors containing a variety of aryl substituents directly attached to the C3 position of the anhydroquinate ring.[14] Of particular note was the 6-benzothiophenyl derivative **6** which has a K_i of 4 nM against *S. coelicolor* type II dehydroquinase. This is the most potent inhibitor of a type II dehydroquinase reported to date.

In this paper, we describe the design and synthesis of a new series of type II dehydroquinase inhibitors. These feature side chains of different length and rigidity attached to the 3-position of the anhydroquinate core. The side chains serve to orientate a phenyl substituent in the glycerol-binding pocket. Analogues **7**–**9** contain terminal phenyloxy, 4-fluorophenyloxy, and 4-trifluoromethylphenyloxy moieties respectively (Figure 3). The electron withdrawing *para*-trifluoromethyl substituent was incorporated into analogue **9** to gauge the effect

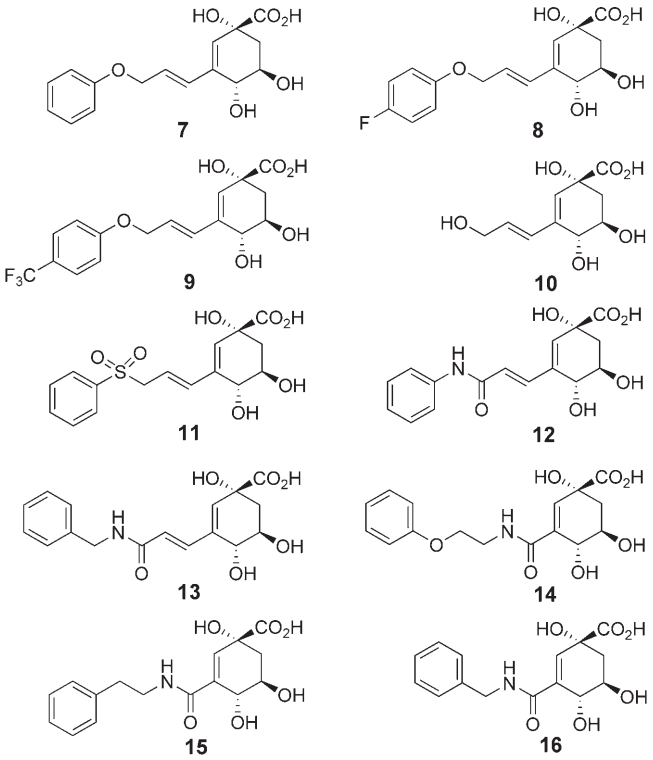


Figure 3. New series of bifunctional type II dehydroquinase inhibitors.

of reduced π-electron density on inhibitor potency. The allylic alcohol **10** was made as a control to help assess the contribution to binding of the π-stacking interaction in **7**–**9**. Analogue **11** contains a terminal phenylsulfone moiety as an alternative to the phenylether group of **7**–**9**. Analogues **12** and **13** incorporate an olefinic amide linker at C3 to further rigidify the side chain. Compound **12** contains a linker with significantly reduced conformational flexibility, whereas **13** incorporates an additional methylene unit to enable rotation of the pendant phenyl group. Compounds **14**–**16** were designed with a rigid amide link adjacent to the C3 ring carbon in place of the olefin linker in **7**–**13**. It was hoped that this amide linker would pick up additional hydrogen-bonding interactions. Compound **14** was designed with a phenoxyethyl moiety, whereas **15** and **16** contain phenylethyl and benzyl groups respectively.

Results and Discussion

Molecular modelling

Molecular docking was used to predict the binding modes of **7**–**16** and hence their suitability as type II dehydroquinase in-

hibitors. Preparation of the proposed inhibitors and receptor were conducted using SYBYL7.1[15] and the ligands were docked into the *S. coelicolor* type II dehydroquinase structure (1GU1) using GOLD (version 3.0).[16] Most inhibitors docked in a similar conformation, with the anhydroquinate core in a similar position to that adopted by the original anhydroquinate inhibitor **3** (see Supporting Information for docking solutions). A representative docking of **7** is shown in Figure 4. The C1 ring carboxylate is held in place by two backbone amide NHs from Ile 107 and Ser 108, whereas the C1 hydroxyl interacts with the side chain of His 106. There is also a possible H-bond interaction between the C5 hydroxyl group and His 106. The key binding interactions for these series of inhibitors are considered to be the edge-on stacking interaction of the terminal phenyl ring with Tyr 28, and a possible cation-π interaction with Arg 23.

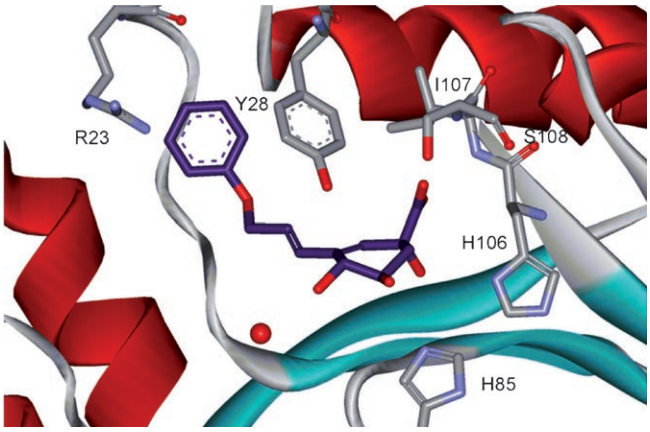


Figure 4. Molecular docking of **7** in the active site of *S. coelicolor* type II dehydroquinase.

Synthesis of 7–16

The overall synthetic strategy involved using palladium cross-coupling chemistry to introduce the various side chains at C3 via the previously reported enol-triflate intermediate **17** (Figure 5).[17]

Introduction of the C3 side chains of **7**–**13** was envisaged by Stille cross-coupling chemistry, and first required the preparation of stannyl side chain fragments. Preparation of the phenoxy-propargyl (*E*)-stannane was achieved by heating phenyl propargyl ether with tributyltin hydride and AIBN, and gave, predominantly, the desired (*E*)-stannane **18** in 45% yield (10:1 *E*:*Z*, Scheme 2).[18]

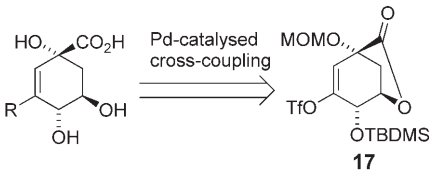
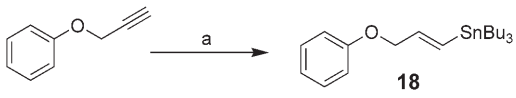
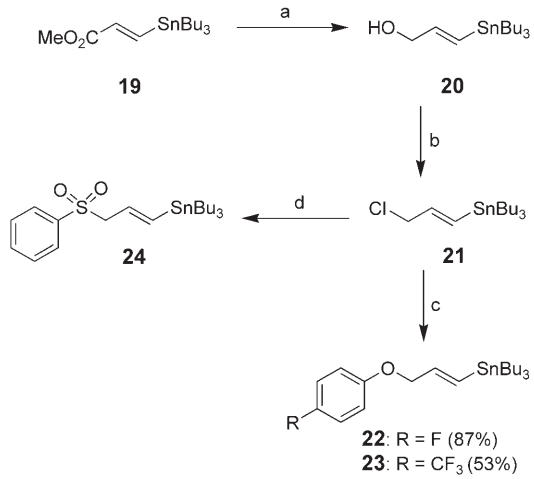


Figure 5. Retrosynthesis of inhibitors **7**–**16** from enol-triflate **17**.

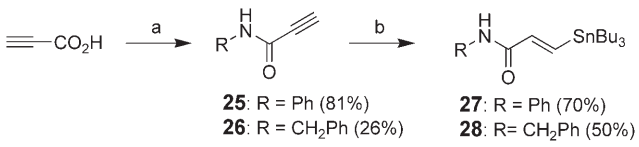


Scheme 2. Synthesis of phenoxy-propargyl (*E*)-stannane. a) Bu_3SnH, AIBN, 45%. AIBN = 2,2′-azobis(2-methylpropionitrile).

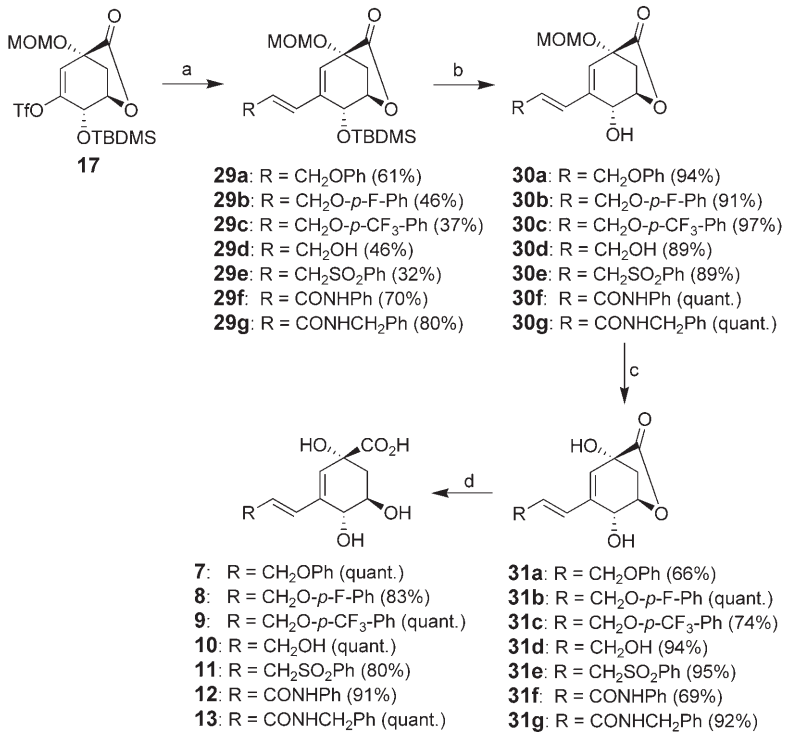
The radical-based approach was unsatisfactory for the synthesis of the remaining stannane fragments **20**, **22**–**24**, **27**, and **28** as reactions produced inseparable isomeric mixtures. The remainder of the (*E*)-stannanes were therefore synthesised by treating alkynes with the trimetallic complex [Bu_3SnCu]LiBr.DMS, generated in situ from *n*-butyllithium, *bis* tributyltin, and copper bromide dimethylsulfide complex (Piers hydrostannylation).[19] Synthesis of (*E*)-tributylstannyl alkenoate **19** was carried out using the Piers hydrostannylation as previously described.[17] Subsequent reduction of the methyl ester gave the corresponding stannyl alcohol **20** in 76% yield (Scheme 3). Organostannanes **22** and **23** were synthesised by conversion of the stannyl alcohol to the corresponding chloride (**21**) using *N*-chlorosuccinimide followed by alkylation with 4-fluorophenol and α,α,α-trifluoro-*p*-cresol, respectively. Stannyl sulfone **24** was also synthesised from **21** by treatment with sodium phenylsulfinate dihydrate. Tributyltin amides **27** and **28** were prepared by initial alkynyl amide formation followed by Piers hydrostannylation as described for **19** (Scheme 4).



Scheme 3. Synthesis of stannanes **20**, **22**, **23** and **24** by Piers hydrostannylation. a) DIBAH, THF, −78 °C—RT, 76%; b) NCS, DMS, CH_2Cl_2, 75%; c) *p*-fluorophenol or *p*-trifluoromethylphenol, K_2CO_3, acetone, 70 °C; d) Sodium phenylsulfinate dihydrate, DMF, 72%. DIBAH = diisopropylbutyl aluminium hydride , NCS = *N*-chlorosuccinimide, DMS = dimethylsulfide.



Scheme 4. Synthesis of stannyl amides **27** and **28** by Piers hydrostannylation. a) DCC, CH_2Cl_2, aniline or benzylamine; b) *n*BuLi, $(Bu_3Sn)_2$, CuBr·DMS, THF, MeOH. DCC = dicyclohexyl carbodiimide, *n*BuLi = *n*-butyllithium.



Scheme 5. Synthesis of inhibitors **7**-**13**. a) stannanes **18**, **20**, **22**–**24**, **27** or **28**, $Pd_2(dba)_3$, $AsPh_3$, NMP, 40 °C; b) TBAF, THF, 0 °C; c) 90% TFA, 0 °C; d) i. NaOH, THF/H_2O, ii. Amberlite IR120H$^+$. NMP = *N*-methyl-2-pyrrolidinone, TBAF = tetrabutylammonium fluoride.

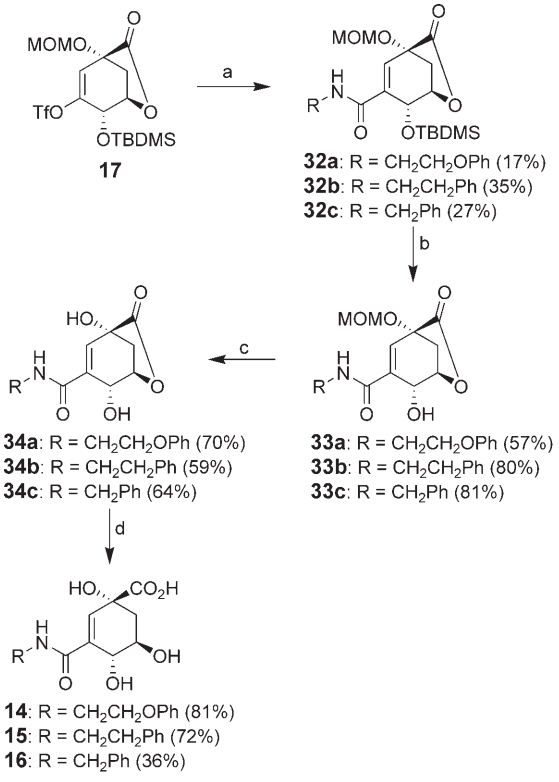
Stannanes **18**, **20**, **22**–**24**, **27**, and **28** (Scheme 5) reacted smoothly with triflate **17** under the Farina-modified Stille cross-coupling conditions [Pd_2dba_3 (2.5 mol% + $AsPh_3$ (20 mol%)] to afford the corresponding dienes **29a**–**g** (Scheme 5).[20] Treatment of **29a**–**g** with tetrabutylammonium fluoride to remove the silyl protecting group, followed by trifluoroacetic acid to cleave the methoxy methyl ether gave the corresponding lactones **31a**–**g**, which were subsequently opened to the desired acids **7**–**13** by treatment with aqueous sodium hydroxide.

Palladium-catalysed carboamidation chemistry was proposed for the introduction of the side chains of amides **14**–**16**. Palladium-catalysed carboamidation of enol-triflate **17** was carried out with 2-phenoxyethylamine, phenethylamine, and benzylamine in the presence of carbon monoxide to give the amides **32a**–**c** (Scheme 6). Unfortunately, yields of these reactions were poor because of a facile competition reaction, whereby the amine attacked the C1 lactone to form the corresponding C1 amide derivatives before the carboamidation could take place. Deprotection of the anhydroquinate core was achieved in a similar fashion as described for **7**–**13** to give the desired acids **14**–**16**.

Biological Results

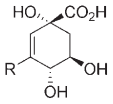
The ten inhibitors (**7**–**16**) were assayed for their inhibitory properties against *S. coelicolor* and *M. tuberculosis* type II dehydroquinases. A UV spectrophotometric assay was used to measure the initial rate of product (3-dehydroshikimate, **2**) formation, detecting the enone-carboxylate chromophore at 234 nm.[6c] The K_i values were obtained using the kinetics software Grafit[21] and the inhibition data are summarised in Table 1. All compounds were shown to be competitive reversible inhibitors of the two enzymes.

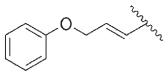
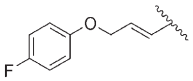
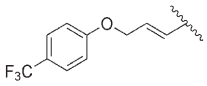
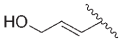
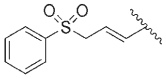
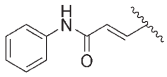
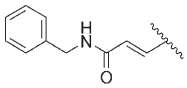
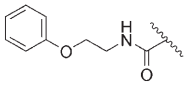
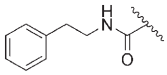
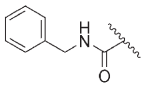
Compounds **7** and **8** proved to be very potent inhibitors of the type II dehydroquinases (Table 1), with inhibition constants of 10 nM against the *S. coelicolor* enzyme and 140 nM and 120 nM, respectively, against the *M. tuberculosis* enzyme. These compounds represent some of the most potent inhibitors of any type II dehydroquinase enzyme synthesised to date. Both analogues are 3000-fold more potent than anhydroquinate inhibitor **3** (K_i = 30 μM) against the *S. coelicolor* enzyme, suggesting that the introduction of a but-2-enyloxybenzene side chain at C3 has a



Scheme 6. Synthesis of inhibitors **14**–**16**. a) RNH_2, $Pd(OAc)_2$, PPh_3, Et_3N, CO, DMF, 60 °C, b) TBAF, THF, 0 °C; c) 90% TFA, 0 °C; d) 1. NaOH, THF/H_2O, 2. Amberlite IR120H$^+$.

Table 1. Inhibition constants of **7**–**16** against type II dehydroquinase from *S. coelicolor* and *M. tuberculosis*.[a]



Inhibitor	R	K_i *S. coelicolor* [μM]	K_i *M. tuberculosis* [μM]
7		0.01 ± 0.001	0.14 ± 0.01
8		0.01 ± 0.001	0.12 ± 0.01
9		0.77 ± 0.07	4.3 ± 0.4
10		9.2 ± 0.8	17 ± 1.7
11		11 ± 1.1	> 100
12		2.1 ± 0.2	2.3 ± 0.2
13		2.0 ± 0.2	20 ± 1.7
14		4.4 ± 0.6	49 ± 7.2
15		2.4 ± 0.3	8.7 ± 1.1
16		0.08 ± 0.01	0.91 ± 0.09

[a] *S. coelicolor* (K_m = 129 ± 20 μM, k_{cat} = 136 s^{-1}) and *M. tuberculosis* (K_m = 25 ± 5 μM, k_{cat} = 3.6 s^{-1}).

positive effect on binding. The contribution of the terminal phenyl moiety to the potency of these compounds is evident on comparison with the inhibition constant of alcohol **10**. Addition of the terminating aromatic group brings an almost 1000-fold increase in potency for **7** and **8** against the *S. coelicolor* enzyme. The positive binding effect of the terminal phenyl ring may be attributed to a combination of an edge-on ring stacking interaction between the phenyl ring and the side chain of Tyr 28, a cation-π interaction of the terminal phenyl ring with Arg 23, and a positive entropic effect due to release of water molecules from the glycerol-binding pocket into the bulk solvent. Compounds **7** and **8** were also 3000-fold more potent than the saturated quinate analogue **5**, re-emphasising the importance of the flattened anhydroquinate core and possibly the incorporation of a rigid olefin linker in the C3 side chain for potent inhibition of the type II enzymes.[13]

Introduction of a 4-trifluoromethyl functionality on the terminal phenyl ring in **9** had a detrimental effect on potency with inhibition constants of 770 nM and 4.3 μM against *S. coelicolor* and *M. tuberculosis* type II dehydroquinases, respectively. It may be that the trifluoromethyl group clashes with residues in the glycerol-binding pocket leading to an alternative binding mode not observed in the docking studies. This would reduce the efficiency of the π-stacking interaction and hence the binding affinity. Replacement of the ether linkage in the side chain of **7** with the sulfone linkage in **11** led to a significant reduction in potency, with inhibition constants over 10 μM. To explain this dramatic reduction in potency of **11**, a detailed study of the dockings was conducted. This suggested that, in order for the terminal phenyl ring to form a π-stacking interaction with Tyr 28, there would be two unfavourable interactions in the glycerol-binding pocket (Figure 6). The first is a lone pair–lone pair repulsion of one of the sulfone oxygens with the main chain carbonyl of Asn 16 (2.64 Å), whereas the other is an unfavourable hydrophobic interaction of the sulfone with the side chain of Leu 17 (2.90 Å). Crystallographic studies with these inhibitors are in progress to provide further insight to the observed structure–activity relationships.

Rigidifying the C3 side chain further by the introduction of an amide linkage, as in **12** and **13**, also lowered the potency of these compounds compared to **7** and **8**. Docking studies suggest that the terminal phenyl ring in **12** is now unable to form a π-stacking interaction with

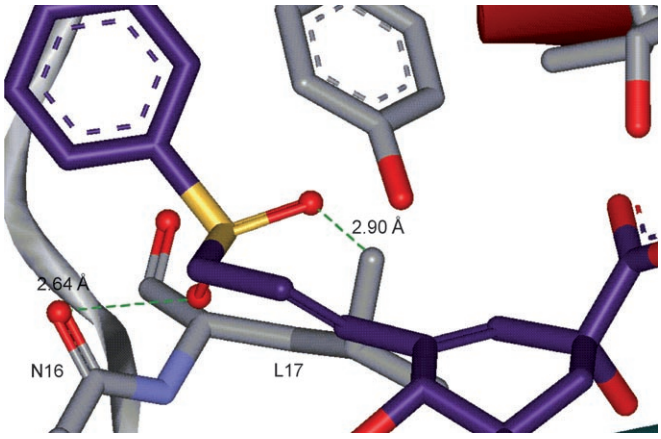


Figure 6. Docking of **11** into the active site of *S. coelicolor* type II dehydroquinase, showing the interactions of the sulfone moiety with Asn 16 and Leu 17.

Tyr 28 (Supporting Information). The increase in rigidity of the side chain may also degrade other interactions in the glycerol-binding pocket. Extension of the side chain with an additional methylene unit in **13** did not affect the potency of the compound against the *S. coelicolor* enzyme ($K_i = 2\ \mu M$), however the compound exhibited reduced potency ($K_i = 20\ \mu M$) against *M. tuberculosis* dehydroquinase. This further reduction in potency against the *M. tuberculosis* enzyme may be due to a more compact second binding pocket in this enzyme, making it more sensitive to the size of the side chain incorporated at C3. However, the disordered nature of the glycerol-binding pocket in structures of this enzyme reported to date (PDB code: 1H0R and 1H0S, unpublished)[22] make it difficult to confirm this. Future research will aim to co-crystallise these inhibitors with the *M. tuberculosis* enzyme.

Compounds **14**–**16** incorporating an amide linker were also less potent than **7** and **8**, however, **16** containing a shorter benzylamide side chain still exhibited nanomolar activity against both enzymes ($K_i = 80$ nM and 910 nM against *S. coelicolor* and *M. tuberculosis*, respectively). Docking studies suggest that the side chain can bend to orientate the phenyl ring for a π-stacking interaction with the tyrosine residue on the flexible loop (Supporting Information). The increase in potency may be due to a hydrogen bonding interaction between the amide NH and Tyr 28. Extending the length of the side chain in **14** and **15** had a detrimental effect on potency, probably due to less effective π-stacking interactions in the glycerol-binding pocket.

Conclusions

Ten potent inhibitors of type II dehydroquinase were designed using docking studies and synthesised using palladium-catalysed cross-coupling chemistry. These compounds all contained an anhydroquinate core bridged, by a variety of linkers, to a terminal phenyl ring. Compounds **7** and **8** containing phenyloxypropene substituents at C3 exhibited nanomolar inhibition of both *S. coelicolor* and *M. tuberculosis* type II dehydroquinase and are among the most potent inhibitors of these enzymes reported to date. The significant drop in potency of allylic alcohol **10** (lacking the terminal phenyl substituent) against both enzymes confirmed the importance of the phenyl ring for potent inhibition of the enzyme, presumably by an edge-on π-stacking interaction with the tyrosine residue on the flexible loop. Modification of the olefin linker (in **7**–**11**) to an amide (in **12**–**16**) had a detrimental effect on potency. Compounds **7** and **8** have shown in vivo activity in preliminary screens against *M. aurum*, a model system for *M. tuberculosis*.[23] Future studies will explore the in vivo activity of these compounds against *M. tuberculosis* and hence their potential as antimicrobial agents.

Experimental Section

Inhibitor Docking. The crystal structure of *S. coelicolor* type II dehydroquinase (PDB code: 1GU1) was downloaded from the Brookhaven Protein Databank.[22] Hydrogens were added to the protein using SYBYL7.1 and anhydroquinate inhibitor **3** and glycerol were abstracted from the active site of the complexed protein PDB files. Crystallographic water molecules were removed from the structures, except for H_2O-1221 as this is conserved in crystal structures of all type II dehydroquinases. Inhibitors were built in SYBYL7.1 and used as MOL2 files.[15] Each molecule had hydrogens added. Structures were minimised to relax bond lengths and fix angles using a Tripos force field and Gasteiger-Hückel charges calculated. Ligands were docked into the active site of the enzyme prepared above using GOLD 3.0.[16] For each independent genetic algorithm (GA) run, a maximum of 100 000 operations were performed on a population of 5 islands, each of 100 individuals. Operator weights for crossover, mutation, and migration were set to 95, 95, and 10, respectively, as well as the hydrogen bonding (4.0 Å) and van der Waals (2.5 Å) parameters. To allow for development of close contacts and poor hydrogen bonds occurring at the beginning of each GA run, the initial external van der Waals (vdw) energies were cut off at $2.5\,k_{ij}$, where k_{ij} is the depth of the vdw well between atoms *i* and *j*, and the maximum distance between a donor atom and a fitting point was set to 4 Å. Ring flipping and internal hydrogen bonds were allowed. The dockings were terminated after 25 runs for each of the inhibitors.

General Methods. All nonaqueous reactions were carried out in predried glassware under an inert atmosphere (N_2 or Ar). Organic solvents were freshly distilled prior to use and milli-Q deionised water was used for all biochemical work. Analytical thin layer chromatography was carried out on commercial silica gel 60 0.25 mm plates using either UV absorption or potassium permanganate stain (3 g potassium permanganate, 20 g potassium carbonate, 5 mL of 5% sodium hydroxide, 300 mL water) for visualisation. R_F values are quoted with respect to the solvent system used to develop the plate. Column chromatography was carried out using 230–400 mesh silica gel 60. Unless otherwise stated petroleum ether refers to the fraction collected between 40–60 °C. ^{1}H NMR spectra were recorded on a Bruker AM-400 spectrometer or a Bruker Avance 500 spectrometer in deuterated solvents, as indicated. ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer or a Bruker Avance 500 spectrometer linked to a Bruker 5 mm dual Cryoprobe (operating at 100 MHz and 125 MHz, respectively). All chemical shifts are quoted in parts per million (ppm) δ. Coupling constants for ^{1}H NMR spectroscopy are assigned where possible and are given in Hz. Infrared spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer using attenuated transmittance reflectance (ATR). Liquid-chromatography mass-spectrometry (LC–MS) was carried out using an Alliance HT Waters 2795 Separations Module coupled to a Waters Micromass ZQ Quadrapole Mass Analyzer. Samples were detected using a photomultiplier detection system. Samples were run on a gradient from 10 mM ammonium acetate containing 0.1% formic acid to 95% acetonitrile over a period of 8 min.

3-Tributylstannanyl-prop-2(*E*)-en-1-ol (20): A solution of DIBAH (2.56 mL of a 1 M solution in hexanes, 2.56 mmol) was added dropwise to a solution of (*E*)-tributylstannyl alkenoate **19**[17] (0.32 g, 0.85 mmol) in THF (5 mL) at −78 °C. After stirring for 1 h at −78 °C and 3 h at 22 °C, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous potassium sodium tartrate solution (10 mL). The reaction was diluted with diethyl ether (100 mL) and water (100 mL) and the aqueous phase extracted with diethyl ether (2×60 mL). The combined ethereal fractions were washed with brine (200 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The product was purified by column chromatography (eluent: 9:1 *v/v* hexane/diethyl ether) to afford the desired stannyl-alcohol **20** as a colourless oil (0.22 g, 76%). R_F [9:1 *v/v* hexane/diethyl ether] = 0.15; $\nu_{max.}$ (ATR): $\tilde{\nu} = 3321$ (O-H, br str), 2956, 2923, 2871, 2851 (=C-H + C-H alkane), 1603 cm^{-1} (C=C); ^{1}H NMR (400 MHz,

[D_6]benzene): $\delta = 0.97$ (15H, m, $3\times CH_3 + 3\times CH_2$), 1.41 (6H, m, $3\times CH_2$), 1.62 (6H, m, $3\times CH_2$), 3.97 (1H, dd, $J = 1.5$, 4.2 Hz, C*H*H), 3.99 (1H, dd, $J = 1.5$, 4.2 Hz, CH*H*), 6.18 (1H, dt, $J = 4.2$, 19.1 Hz, $HOCH_2CH{=}CH$), 6.32 ppm (1H, dt, $J = 1.5$, 19.1 Hz, $HOCH_2CH{=}CH$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.9$, 13.1, 26.7, 28.5, 65.8, 126.8, 146.5 ppm; HRMS calcd for $C_{15}H_{33}O^{120}Sn$: MH^+, 349.1548. Found: MH^+, 349.1545.

Tributyl-(3-chloro-propenyl)-stannane (21): Dimethylsulfide (0.12 mL, 1.61 mmol) was added dropwise to a solution of *N*-chlorosuccinimide (0.12 g, 0.89 mmol) in dichloromethane (4 mL) at $-40\,^\circ$C. After warming to $0\,^\circ$C for 5 min, the mixture was again cooled to $-40\,^\circ$C and a solution of stannyl alcohol **20** (0.28 g, 0.81 mmol) in dichloromethane (3 mL) was added dropwise. The resulting reaction mixture was allowed to warm to $0\,^\circ$C over 1 h and then stirred at this temperature for a further 1 h. The reaction mixture was diluted with diethyl ether (20 mL), before washing with ice-cold brine (2×30 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The product was purified by column chromatography (eluent: 9:1 *v/v* hexane/diethyl ether) to give the desired stannyl-chloride **21** as a colourless liquid (0.22 g, 75%). $\nu_{max.}$ (ATR): $\tilde{\nu} = 2956$, 2922, 2872, 2851 (=C-H + C-H alkane), 1597 cm^{-1} (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (15H, m, $3\times CH_3 + 3\times CH_2$), 1.30 (6H, m, $3\times CH_2$), 1.49 (6H, m, $3\times CH_2$), 4.05 (2H, dd, $J = 1.2$, 6.1 Hz, CH_2), 6.05 (1H, dt, $J = 6.1$, 18.7 Hz, $ClCH_2CH{=}CH$), 6.29 ppm (1H, dt, $J = 1.2$, 18.7 Hz, $ClCH_2CH{=}CH$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.8$, 13.9, 27.5, 29.3, 48.2, 134.2, 143.1 ppm.

Tributyl-[3-(4-fluoro-phenoxy)-propenyl]-stannane (22): 4-Fluorophenol (480 mg, 4.28 mmol) and anhydrous potassium carbonate (1.18 g, 8.56 mmol) in acetone (10 mL) were heated at $70\,^\circ$C. Stannyl-chloride **21** (308 mg, 0.84 mmol) in acetone (8 mL) was added dropwise and stirring was continued at $70\,^\circ$C for 24 h. The reaction was allowed to cool to $22\,^\circ$C before diluting with diethyl ether (30 mL). The reaction was washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), and the solvent removed in vacuo. Purification by column chromatography (eluent: 100% petroleum ether - 9:1 *v/v* petroleum ether/diethyl ether) gave the desired stannyl-fluoride **22** as a colourless liquid (0.34 g, 87%). R_F [petroleum ether] = 0.25; $\nu_{max.}$ (ATR): $\tilde{\nu} = 2922$ (=C-H + C-H alkane), 1674 cm^{-1} (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (15H, m, $3\times CH_3 + 3\times CH_2$), 1.30 (6H, m, $3\times CH_2$), 1.47 (6H, m, $3\times CH_2$), 4.51 (2H, dd, $J = 1.5$, 4.8 Hz, CH_2), 6.14 (1H, dt, $J = 4.8$, 19.2 Hz, $ROCH_2CH{=}CH$), 6.33 (1H, dt, $J = 1.5$, 19.2 Hz, $ROCH_2CH{=}CH$), 6.84 (2H, m, 2×ArH), 6.95 (2H, m, 2×ArH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 8.1$, 13.7, 27.2, 29.0, 72.0, 115.6 ($J_{C\text{-}F}$ 23 Hz, *o*-ArC), 115.8 ($J_{C\text{-}F}$ 8 Hz, *m*-ArC), 132.2, 142.6, 154.8 ($J_{C\text{-}F}$ 3 Hz, *p*-ArC), 157.1 ppm ($J_{C\text{-}F}$ 239 Hz, *i*-ArC); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -124.5$ ppm.

Tributyl-[3-(4-trifluoromethyl-phenoxy)-propenyl]-stannane (23): Anhydrous potassium carbonate (1.18 g, 8.56 mmol) and α, α, α - trifluoro-*p*-cresol (0.69 g, 4.28 mmol) in acetone (10 mL) were heated at $70\,^\circ$C. Stannyl-chloride **21** (308 mg, 0.84 mmol) in acetone (8 mL) was added dropwise and stirring was continued at $70\,^\circ$C for 24 h. The reaction was allowed to cool to $22\,^\circ$C before diluting with diethyl ether (30 mL). The reaction was washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), and the solvent removed in vacuo. Purification by column chromatography (eluent: petroleum ether) gave the desired trifluoromethyl-stannane **23** as a colourless liquid (0.22 g, 53%). R_F [petroleum ether] = 0.61; $\nu_{max.}$ (ATR): $\tilde{\nu} = 2957$, 2924, 2853 (=C-H + C-H alkane), 1615 cm^{-1} (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (15H, m, $3\times CH_3 + 3\times CH_2$), 1.30 (6H, m, $3\times CH_2$), 1.49 (6H, m, $3\times CH_2$), 4.60 (2H, dd, $J = 1.5$, 4.8 Hz, CH_2), 6.15 (1H, dt, $J = 4.8$, 19.2 Hz, $ROCH_2CH{=}CH$), 6.38 (1H, dt, $J = 1.5$, 19.2 Hz, $ROCH_2CH{=}CH$), 6.96 (2H, d, $J = 8.6$ Hz, 2×ArH), 7.52 ppm (2H, d, $J = 8.6$ Hz, 2×ArH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 8.1$, 13.6, 27.3, 29.0, 71.5, 114.8, 122.7 (q, $J_{C\text{-}F}$ 33 Hz, *i*-ArC), 124.4 (q, $J_{C\text{-}F}$ 271 Hz, CF_3), 126.7 (q, $J_{C\text{-}F}$ 3.6 Hz, *o*-ArC), 132.9, 141.8, 161.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -62.0$ ppm; HRMS calcd for $C_{22}H_{34}OF_3{}^{120}Sn$: $[M-H]^+$, 491.1578. Found: $[M-H]^+$, 491.1582.

(3-Benzenesulfonyl-propenyl)-tributyl-stannane (24): Sodium phenylsulfinate dihydrate (0.82 g, 4.11 mmol) was added to a solution of stannyl-chloride **21** (300 mg, 0.82 mmol) in DMF (2.5 mL) and the reaction was heated to $50\,^\circ$C for 3 h. The reaction was allowed to cool to $22\,^\circ$C before diluting with diethyl ether (10 mL) and water (10 mL). The organic fraction was washed with water (3×10 mL) and brine (10 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The product was purified by column chromatography (eluent: 3:1 *v/v* petroleum ether/diethyl ether) to afford the desired stannyl-sulfone **24** as a colourless liquid (280 mg, 72%). R_F [3:1 *v/v* petroleum ether/diethyl ether] = 0.50; $\nu_{max.}$ (ATR): $\tilde{\nu} = 2956$, 2920, 2851 (=C-H + C-H alkane), 1580 cm^{-1} (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.84$ (15H, m, $3\times CH_3 + 3\times CH_2$), 1.24 (6H, m, $3\times CH_2$), 1.40 (6H, m, $3\times CH_2$), 3.86 (2H, dd, $J = 1.1$, 6.8 Hz, CH_2), 5.86 (1H, dt, $J = 6.8$, 18.9 Hz, $SCH_2CH{=}CH$), 6.07 (1H, dt, $J = 1.1$, 18.9 Hz, $SCH_2CH{=}CH$), 7.50 (2H, m, 2×ArH), 7.60 (1H, m, ArH), 7.83 ppm (2H, m, 2×ArH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 9.5$, 13.6, 27.2, 28.9, 64.1, 128.6, 128.8, 133.0, 133.5, 138.2, 142.8 ppm; HRMS calcd for $C_{21}H_{40}O_2NS^{120}Sn$: $[M+NH_4]^+$, 490.1796. Found: $[M+NH_4]^+$, 490.1790.

Propynoic acid phenylamide (25): Aniline (3.65 mL, 0.04 mol) was added dropwise to a solution of propiolic acid (2.50 g, 0.04 mol) in dichloromethane (40 mL) at $0\,^\circ$C. A solution of dicyclohexyl carbodiimide (9.39 g, 0.05 mol) in dichloromethane (40 mL) was added dropwise and the reaction stirred at $0\,^\circ$C for 30 min and for a further 3 h at $22\,^\circ$C. The reaction was cooled in ice and filtered over Celite and the Celite washed with dichloromethane (50 mL). The filtrate was washed with 3 M hydrochloric acid (3×70 mL), saturated aqueous sodium bicarbonate solution (3×70 mL) and water (3×70 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The product was purified by column chromatography (eluent: 3:1 *v/v* hexane/ethyl acetate) to afford amide **25** as a yellow solid (4.10 g, 81%). R_F [3:1 *v/v* hexane/ethyl acetate] = 0.48; $\nu_{max.}$ (ATR): $\tilde{\nu} = 3269$, 3227 (N-H, str), 3129, 3060, 3020 (=C-H + C-H alkane), 2110 (C≡C), 1638 (C=O), 1593 cm^{-1} (C=C, Ar); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 2.90 (1H, s, CH), 7.12 (1H, m, ArH), 7.30 (2H, m, 2×ArH), 7.54 (2H, m, 2×ArH), 8.27 ppm (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 74.2, 77.4, 120.0, 125.0, 128.9, 136.8, 150.0 ppm; LC-MS $[M+H]^+$ 146.0, $R_t = 2.82$ min; HRMS calcd for C_9H_8NO: MH^+, 146.0600. Found: MH^+, 146.0599.

***N*-Phenyl-3-tributylstannanyl-acrylamide (27)**: A solution of *n*-butyllithium (4.30 mL of a 1.6 M solution in hexanes, 6.87 mmol) was added dropwise to a $0\,^\circ$C solution of *bis*(tributyltin) (3.47 mL, 6.87 mmol) in THF (4.85 mL). Stirring was continued at $0\,^\circ$C for 20 min before the solution was transferred by cannula to a pre-cooled solution of copper bromide dimethylsulfide complex (1.42 g, 6.89 mmol) in THF (3.25 mL) at $-50\,^\circ$C. The resulting black mixture was stirred at $-50\,^\circ$C for 25 min before cooling to $-78\,^\circ$C. Amide **25** (0.33 g, 2.29 mmol) in THF (2.15 mL) was added dropwise and the reaction was stirred at $-78\,^\circ$C for 4 h. Methanol (6.9 mL) was added and the reaction was warmed to $22\,^\circ$C. The reaction mixture was partitioned between diethyl ether (100 mL) and water (100 mL) and the whole solution filtered through Celite® to remove the dark colouration. The phases were separated and the aqueous fraction extracted with diethyl ether (50 mL). The combined ethereal fractions were washed with brine (150 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The product was purified by column chromatography (eluent: 9:1 *v/v* petroleum ether/diethyl ether) to afford the desired stannyl-amide **27** as a colourless oil (0.70 g, 70%). R_F [9:1 *v/v* petroleum ether/diethyl ether] = 0.15; $\nu_{max.}$ (ATR): $\tilde{\nu} = 3247$, 3134 (N-H, str), 2956, 2923, 2871, 2852

(=C-H + C-H alkane), 1652 (C=O), 1620, 1601 cm^{-1} (C=C + C=C Ar); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (9H, m, $3\times CH_3$), 0.97 (6H, m, $3\times CH_2$), 1.30 (6H, m, $3\times CH_2$), 1.50 (6H, m, $3\times CH_2$), 6.39 (1H, d, $J = 19.0$ Hz, C*H*=CH), 7.10 (1H, t, $J = 7.4$ Hz, ArH), 7.31 (2H, td, $J = 7.4$, 7.8 Hz, 2×ArH), 7.39 (1H, br s, NH), 7.59 (2H, d, $J = 7.8$ Hz, 2× ArH), 7.67 ppm (1H, d, $J = 19.0$ Hz, CH=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.5$, 13.5, 27.1, 28.8, 119.6, 124.1, 128.8, 137.8, 139.2, 147.7, 162.3 ppm; LC-MS $[M+H]^+$ 438.2, $[M-H]^-$ 436.1, $R_t = 5.97$ min; HRMS calcd for $C_{21}H_{36}NO^{120}Sn$: MH^+, 438.1813. Found: MH^+, 438.1817.

Propynoic acid benzylamide (26): Dicyclohexyl carbodiimide (9.10 g, 0.04 mol) in dimethoxyethane (50 mL) was added dropwise to a solution of *N*-hydroxysuccinimide (5.00 g, 0.04 mol) and propiolic acid (3.10 g, 0.04 mol) in dimethoxyethane (60 mL) and the reaction stirred at 22 °C for 18 h. The resulting precipitate was filtered over Celite and the Celite washed with dichloromethane (50 mL). The solvent was removed in vacuo and used without further purification in the next step. Benzylamine (3.50 mL, 0.03 mol) was added dropwise to a solution of the activated succinimidyl-ester synthesised above (5.4 g, 0.04 mol) in dichloromethane (80 mL) at 5 °C. The reaction was allowed to warm to 22 °C and stirred at this temperature for 24 h. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution (80 mL), 1 M HCl solution (80 mL), dried (Na_2SO_4), and the solvent removed in vacuo. Purification by column chromatography (eluent: 3:1 *v/v* hexane/ethyl acetate—2:1 *v/v* hexane/ethyl acetate) gave amide **26** as a white solid (0.90 g, 26%). R_F [3:1 *v/v* hexane/ethyl acetate] = 0.18; $\nu_{max.}$ (ATR): $\tilde{\nu} = 3203$, 3062 (N-H, str), 2969, 2937, 2852(=C-H + C-H alkane), 2106 (C≡C), 1617 (C=O), 1556 cm^{-1} (C=C, Ar); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.78$ (1H, s, CH), 4.42 (2H, d, $J = 6.0$ Hz, CH_2), 6.57 (1H, br s, NH), 7.29 ppm (5H, m, 5×ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 44.4$, 74.3, 77.7, 127.8, 128.5, 129.5, 137.6, 152.7 ppm; LC-MS $[M+H]^+$ 160.1, $R_t = 2.72$ min; HRMS calcd for $C_{10}H_{10}NO$: MH^+, 160.0757. Found: MH^+, 160.0755.

***N*-Benzyl-3-tributylstannanyl-acrylamide (28)**: A solution of *n*-butyllithium (4.30 mL of a 1.6 M solution in hexanes, 6.87 mmol) was added dropwise to a 0 °C solution of bistributyltin (3.47 mL, 6.87 mmol) in THF (4.85 mL). Stirring was continued at 0 °C for 20 min before the solution was transferred by cannula to a precooled solution of copper bromide dimethylsulfide complex (1.42 g, 6.89 mmol) in THF (3.25 mL) at −50 °C. The resulting black mixture was stirred at −50 °C for 25 min before cooling to −78 °C. Amide **26** (0.36 g, 2.29 mmol) in THF (2.15 mL) was added dropwise and the reaction was stirred at −78 °C for 4 h. Methanol (6.9 mL) was added and the reaction was warmed to 22 °C. The reaction mixture was partitioned between diethyl ether (100 mL) and water (100 mL) and the whole solution filtered through Celite to remove the dark colouration. The phases were separated and the aqueous fraction extracted with diethyl ether (50 mL). The combined ethereal fractions were washed with brine (150 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by column chromatography (eluent: 3:1 *v/v* petroleum ether/diethyl ether) to afford the desired stannyl-amide **28** as a colourless oil (0.51 g, 50%). R_F [3:1 *v/v* petroleum ether/diethyl ether] = 0.24; $\nu_{max.}$ (ATR): $\tilde{\nu} = 3265$ (N-H, str), 2956, 2922, 2851, 2871 (=C-H + C-H alkane), 1641 (C=O), 1588, 1544 cm^{-1} (C=C + C=C Ar); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (9H, m, $3\times CH_3$), 0.92 (6H, m, $3\times CH_2$), 1.29 (6H, m, $3\times CH_2$), 1.48 (6H, m, $3\times CH_2$), 4.50 (2H, d, $J = 5.7$ Hz, $PhCH_2$), 5.89 (1H, br t, $J = 5.7$ Hz, NH), 6.27 (1H, d, $J = 19.1$ Hz, C*H*=CH), 7.30 (5H, m, 5×ArH), 7.52 ppm (1H, d, $J = 19.1$ Hz, CH=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.5$, 13.6, 27.2, 28.9, 43.7, 127.5, 127.9, 128.6, 138.2, 138.8, 146.1, 164.5 ppm; LC-MS $[M+H]^+$ 452.1, $R_t = 5.77$ min; HRMS calcd for $C_{22}H_{38}NO^{120}Sn$: MH^+, 452.1970. Found: MH^+, 452.1968.

General Procedure for Stille Coupling : (1*R*, 4*R*, 5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methoxymethoxy-3-(3-phenoxy-prop-(*E*)-enyl)-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (29a): A solution of $Pd_2(dba)_3$ (14.5 mg, 0.02 mmol) in NMP (5 mL) was treated with triphenyl arsine (41 mg, 0.13 mmol). After 5 min stirring at 22 °C, a solution of triflate **17** (310 mg, 0.66 mmol) in NMP (2 mL) was added dropwise. After the solution was stirred for a further 10 min, a solution of stannane **18** (310 mg, 0.73 mmol) in NMP (1 mL) was added and the reaction stirred at 40 °C for 4 h. The reaction was allowed to cool to 22 °C before quenching by addition of saturated aqueous potassium fluoride solution (5 mL). The reaction was diluted with diethyl ether (10 mL). The ethereal layer was washed with saturated aqueous potassium fluoride solution (10 mL), water (10 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The product was purified by column chromatography (eluent: 3:1 *v/v* hexane/diethyl ether) to give **29a** as a colourless oil (180 mg, 61%). R_F [3:1 *v/v* hexane/diethyl ether] = 0.13; $\nu_{max.}$ (ATR): $\tilde{\nu} = 2953$, 2929, 2896, 2857 (=C-H + C-H alkane), 1799 (C=O), 1599, 1586 cm^{-1} (C=C); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.15$ (6H, s, $2\times CH_3$), 0.87 (9H, s, *t*Bu), 2.51 (1H, d, $J = 9.0$ Hz, H-6_{ax}), 2.57 (1H, ddd, $J = 1.5$, 6.0, 9.0 Hz, H-6_{eq}), 3.44 (3H, s, CH_3), 4.37 (1H, d, $J = 3.3$ Hz, H-4), 4.57 (2H, dd, $J = 1.3$, 5.4 Hz, $PhOCH_2$), 4.60 (1H, dd, $J = 3.3$, 6.0 Hz, H-5), 4.82 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 4.92 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 6.06 (1H, dt, $J = 16.0$, 5.4 Hz, OCH_2CH=CH), 6.08 (1H, d, $J = 1.5$ Hz, H-2), 6.18 (1H, dt, $J = 16.0$, 1.3 Hz, OCH_2CH=C*H*), 6.88 (2H, m, 2×ArH), 6.93 (1H, m, ArH), 7.26 ppm (2H, m, 2×ArH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = -4.6$, −4.1, 18.0, 25.7, 34.2, 56.1, 66.2, 67.7, 76.2, 77.7, 93.4, 114.6, 120.9, 127.2, 129.5, 129.7, 130.5, 137.0, 158.4, 174.0 ppm; LC-MS $[M+H]^+$ 447.2, $R_t = 5.26$ min; HRMS calcd for $C_{24}H_{35}O_6Si$: MH^+, 447.2197. Found: MH^+, 447.2195.

(1*R*,4*R*,5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-3-[3-(4-fluoro-phenoxy)-propenyl]-1-methoxymethoxy-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (29b): Triflate **17** (310 mg, 0.66 mmol) and stannane **22** (322 mg, 0.73 mmol) were reacted at 40 °C for 14 h under the general Stille coupling procedure described for **29a**. The product was purified by column chromatography (eluent: 3:1 *v/v* hexane/diethyl ether) to give fluorophenyl ether **29b** as a pale yellow oil (140 mg, 46%). R_F [3:1 *v/v* hexane/diethyl ether] = 0.14; $\nu_{max.}$ (ATR): $\tilde{\nu} = 2954$, 2930, 2897, 2858 (=C-H + C-H alkane), 1798 (C=O), 1505 cm^{-1} (C=C); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.14$ (3H, s, CH_3), 0.16 (3H, s, CH_3), 0.88 (9H, s, *t*Bu), 2.50 (1H, d, $J = 11.0$ Hz, H-6_{ax}), 2.57 (1H, ddd, $J = 1.9$, 6.0, 11.0 Hz, H-6_{eq}), 3.42 (3H, s, CH_3), 4.38 (1H, d, $J = 3.3$ Hz, H-4), 4.53 (2H, dd, $J = 1.2$, 5.5 Hz, $ArOCH_2$), 4.60 (1H, dd, $J = 3.3$, 6.0 Hz, H-5), 4.83 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 4.91 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 6.03 (1H, dt, $J = 16.0$, 5.5 Hz, OCH_2CH=CH), 6.09 (1H, d, $J = 1.9$ Hz, H-2), 6.17 (1H, dt, $J = 16.0$, 1.2 Hz OCH_2CH=C*H*), 6.81 (2H, m, 2×ArH), 6.95 ppm (2H, m, 2× ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -3.6$, −3.0, 19.0, 26.7, 35.3, 57.2, 67.3, 69.6, 77.2, 78.7, 94.5, 116.7 (d, $J_{C\text{-}F}$ 17 Hz, *o*-ArC), 116.7, 128.1, 131.0, 131.7, 138.0, 155.6, 158.5 (d, $J_{C\text{-}F}$ 296 Hz, *i*-ArC), 175.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -124.0$ ppm; LC-MS $[M-H]^-$ 463.3, $[M+H]^+$ 465.3, $R_t = 5.22$ min; HRMS calcd for $C_{24}H_{34}O_6FSi$: MH^+, 465.2103. Found: MH^+, 465.2105.

(1*R*,4*R*,5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methoxymethoxy-3-[3-(4-trifluoromethyl-phenoxy)-propenyl]-6-oxa-bicyclo-[3.2.1]oct-2-en-7-one (29c): Triflate **17** (159 mg, 0.34 mmol) and stannane **23** (186 mg, 0.38 mmol) were reacted at 40 °C for 14 h under the standard Stille coupling procedure described for **29a**. The product was purified by column chromatography (eluent: 2:1 *v/v* hexane/diethyl ether) to give trifluoromethylphenyl ether **29c** as a colourless oil (65 mg, 37%). R_F [2:1 *v/v* hexane/diethyl ether] = 0.24; $\nu_{max.}$ (ATR): $\tilde{\nu} = 2954$, 2931, 2895, 2858 (=C-H + C-H alkane), 1797 (C=O), 1615, 1590 cm^{-1} (C=C); ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 0.13 (3H, s, CH_3), 0.15 (3H, s, CH_3), 0.86 (9H, s, *t*Bu), 2.50 (1H, d, $J =$

11.0 Hz, H-6_{ax}), 2.57 (1H, ddd, J=1.9, 6.0, 11.0 Hz, H-6_{eq}), 3.44 (3H, s, CH_3), 4.35 (1H, d, J=3.3 Hz, H-4), 4.63 (2H, d, J=5.4 Hz, ROCH_2), 4.63 (1H, dd, J=3.3, 6.0 Hz, H-5), 4.82 (1H, d, J=7.5 Hz, CH_3OC*H*H), 4.89 (1H, d, J=7.5 Hz, CH_3OCH*H*), 6.05 (1H, dt, J=16.0, 5.4 Hz, OCH_2CH=CH), 6.08 (1H, d, J=1.9 Hz, H-2), 6.19 (1H, d, J=16.0 Hz, OCH_2CH=C*H*), 6.93 (2H, d, J=8.6 Hz, 2×ArH), 7.52 ppm (2H, d, J=8.6 Hz, 2×ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−4.7, −4.1, 17.9, 25.6, 34.2, 56.1, 66.1, 68.0, 76.1, 77.7, 93.4, 114.6, 123.1 (q, $J_{C\text{-}F}$ 33 Hz, *i*-ArC), 124.4 (q, $J_{C\text{-}F}$ 271 Hz, CF_3), 126.2, 126.9 (q, $J_{C\text{-}F}$ 4 Hz, *o*-ArC), 130.3, 131.0, 136.8, 160.8, 174.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−61.8 ppm; LC-MS $[M-H]^-$ 513.3, $[M+H]^+$ 515.4, R_t=5.38 min; HRMS calcd for $C_{25}H_{34}O_6F_3Si$: MH^+, 515.2071. Found: MH^+, 515.2072.

(1*R*,4*R*,5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-3-(3-hydroxy-prop-(*E*)-enyl)-1-methoxymethoxy-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (29d): Triflate **17** (170 mg, 0.37 mmol) and stannane **20** (140 mg, 0.40 mmol) were reacted at 40 °C for 3 h under the standard Stille coupling procedure described for **29a**. The product was purified by column chromatography (eluent: 2:1 *v/v* diethyl ether/hexane - 3:1 *v/v* diethyl ether/hexane) to give alcohol **29d** as a pale yellow oil (63 mg, 46%). R_F [2:1 *v/v* diethyl ether/hexane]=0.15; $[\alpha]_D^{25}$=−143 (c=1.1, $CHCl_3$); $\nu_{max.}$ (ATR): $\tilde{\nu}$=3435 (O-H, br str), 2954, 2930, 2895, 2857 (=C-H + C-H alkane), 1796 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.14 (3H, s, CH_3), 0.15 (3H, s, CH_3), 0.87 (9H, s, *t*Bu group), 1.60 (1H, br s, OH), 2.48 (1H, d, J=10.9 Hz, H-6_{ax}), 2.56 (1H, ddd, J=1.9, 6.0, 10.9 Hz, H-6_{eq}), 3.42 (3H, s, CH_3), 4.19 (2H, d, J=5.0 Hz, CH_2), 4.35 (1H, d, J=3.4 Hz, H-4), 4.59 (1H, dd, J=3.4, 5.9 Hz, H-5), 4.80 (1H, d, J=7.5 Hz, CH_3OC*H*H), 4.89 (1H, d, J=7.5 Hz, CH_3OCH*H*), 5.98 (1H, dt, J=15.9, 5.0 Hz, $HOCH_2CH$=CH), 6.03 (1H, d, J=1.9 Hz, H-2), 6.07 ppm (1H, d, J=15.9 Hz, $HOCH_2CH$=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−9.6, −8.9, 16.4, 24.1, 32.6, 54.5, 61.5, 64.6, 74.6, 76.1, 91.8, 126.7, 128.5, 129.7, 135.6, 171.1 ppm; LC-MS $[M+H]^+$ 371.2, R_t=4.41 min; HRMS calcd for $C_{18}H_{31}O_6Si$: MH^+, 371.1884. Found: MH^+, 371.1884.

(1*R*,4*R*,5*R*)-3-(3-Benzenesulfonyl-propenyl)-4-(*tert*-butyl-dimethyl-silanyloxy)-1-methoxymethoxy-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (29e): Triflate **17** (205 mg, 0.44 mmol) and stannane **24** (209 mg, 0.44 mmol) were reacted at 40 °C for 14 h under the standard Stille coupling procedure described for **29a.** The product was purified by column chromatography (eluent: 3:2 *v/v* diethyl ether/hexane) to give sulfone **29e** as a colourless oil (80 mg, 37%). R_F [3:2 *v/v* diethyl ether/hexane]=0.24; $[\alpha]_D^{25}$=−139 (c=0.45, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}$=2954, 2933, 2854 (=C-H + C-H alkane), 1799 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.13 (3H, s, CH_3), 0.16 (3H, s, CH_3), 0.87 (9H, s, *t*Bu group), 2.43 (1H, d, J=11.0 Hz, H-6_{ax}), 2.56 (1H, ddd, J=1.9, 6.1, 11.0 Hz, H-6_{eq}), 3.41 (3H, s, CH_3), 3.80 (2H, dd, J=3.7, 7.0 Hz, ROCH_2), 4.27 (1H, d, J=3.3 Hz, H-4), 4.57 (1H, dd, J=3.3, 6.1 Hz, H-5), 4.79 (1H, d, J=7.5 Hz, CH_3OC*H*H), 4.87 (1H, d, J=7.5 Hz, CH_3OCH*H*), 5.76 (1H, dt, J=16.0, 7.0 Hz, OCH_2CH=CH), 5.84 (1H, d, J=16.0 Hz, OCH_2CH=C*H*), 5.98 (1H, d, J=1.9 Hz, H-2), 7.53 (2H, m, 2×ArH), 7.63 (1H, m, ArH), 7.82 ppm (2H, m, 2×ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−5.3, −4.7, 13.2, 17.2, 25.3, 33.7, 55.8, 59.9, 65.7, 75.6, 77.7, 93.1, 117.5, 128.0, 128.9, 132.0, 133.6, 136.2, 138.0, 173.3 ppm; LC-MS $[M-H]^-$ 493.4, $[M+H]^+$ 495.4, R_t=4.82 min; HRMS calcd for $C_{24}H_{34}O_7SNaSi$: MNa^+, 517.1687. Found: MNa^+, 517.1687.

(1*R*,4*R*,5*R*)-3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methoxymethoxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-en-3-yl]-*N*-phenyl-acrylamide (29f): Triflate **17** (620 mg, 1.32 mmol) and stannane **27** (650 mg, 1.45 mmol) were reacted at 40 °C for 3 h under the standard Stille coupling procedure described for **29a**. The product was purified by column chromatography (eluent: 1:1 *v/v* hexane/diethyl ether—1:2 *v/v* hexane/diethyl ether) to give the amide **29f** as a yellow oil (430 mg, 70%). R_F [1:1 hexane/diethyl ether]=0.10; $[\alpha]_D^{25}$=−127 (c=1.2, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}$=3295 (N-H, str), 2954, 2931, 2898, 2857 (=C-H + C-H alkane), 1794 (C=O), 1664, 1600 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.17 (3H, s, CH_3), 0.21 (3H, s, CH_3), 0.89 (9H, s, *t*Bu), 2.51 (1H, d, J=11.1 Hz, H-6_{ax}), 2.63 (1H, ddd, J=1.8, 6.1, 11.1 Hz, H-6_{eq}), 3.43 (3H, s, CH_3), 4.38 (1H, d, J=3.0 Hz, H-4), 4.63 (1H, dd, J=3.0, 6.1 Hz, H-5), 4.82 (1H, d, J=7.6 Hz, CH_3OC*H*H), 4.90 (1H, d, J=7.6 Hz, CH_3OCH*H*), 6.16 (1H, d, J=15.5 Hz, C(O)C*H*=CH), 6.37 (1H, d, J=1.8 Hz, H-2), 7.11 (1H, m, ArH), 7.15 (1H, d, J=15.5 Hz, C(O)CH=C*H*), 7.32 (2H, t, J=7.7 Hz, 2×ArH), 7.45 (1H, br s, NH), 7.58 ppm (2H, d, J=6.6 Hz, 2×ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−4.9, −4.6, 17.5, 25.1, 33.4, 55.8, 65.7, 75.7, 77.4, 93.1, 119.5, 123.1, 124.1, 128.6, 134.7, 135.7, 137.3, 138.6, 162.6, 173.3 ppm; LC-MS $[M+H]^+$ 460.2, $[M-H]^-$ 458.1, R_t=4.85 min; HRMS calcd for $C_{24}H_{34}NO_6Si$: MH^+, 460.2150. Found: MH^+, 460.2151.

(1*R*,4*R*,5*R*)-*N*-Benzyl-3-[4-(*tert*-butyl-dimethyl-silanyloxy)-1-methoxymethoxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-en-3-yl]-acrylamide (29g): Triflate **17** (440 mg, 0.94 mmol) and stannane **28** (475 mg, 1.03 mmol) were reacted at 40 °C for 3 h under the standard Stille coupling procedure described for **29a**. The product was purified by column chromatography (eluent: 2:1 *v/v* diethyl ether/hexane) to give **29g** as a white solid (360 mg, 80%). R_F [1:2 hexane/diethyl ether]=0.22; $[\alpha]_D^{25}$=−191 (c=1.85, $CHCl_3$); $\nu_{max.}$ (ATR): $\tilde{\nu}$=3276 (N-H, str), 2954, 2930, 2896, 2858 (=C-H + C-H alkane), 1795 (C=O), 1658, 1622 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.15 (3H, s, CH_3), 0.18 (3H, s, CH_3), 0.87 (9H, s, *t*Bu), 2.49 (1H, d, J=11.0 Hz, H-6_{ax}), 2.60 (1H, ddd, J=1.6, 6.1, 11.0 Hz, H-6_{eq}), 3.43 (3H, s, CH_3), 4.35 (1H, d, J=3.3 Hz, H-4), 4.51 (2H, d, J=5.8 Hz, PhCH_2), 4.61 (1H, dd, J=3.3, 6.1 Hz, H-5), 4.81 (1H, d, J=7.6 Hz, CH_3OC*H*H), 4.89 (1H, d, J=7.6 Hz, CH_3OCH*H*), 5.91 (1H, t, J=5.8 Hz, NH), 6.02 (1H, d, J=15.6 Hz, C(O)C*H*=CH), 6.31 (1H, d, J=1.6 Hz, H-2), 7.08 (1H, d, J=15.6 Hz, C(O)CH=C*H*), 7.28 ppm (5H, m, 5×ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−4.9, −4.5, 17.5, 25.1, 33.4, 43.2, 55.7, 65.6, 75.5, 77.3, 93.0, 122.4, 127.1, 127.2, 128.2, 134.7, 135.7, 137.5, 138.0, 164.5, 173.0 ppm; LC-MS $[M+H]^+$ 474.2, R_t=4.70 min; HRMS calcd for $C_{25}H_{36}NO_6Si$: MH^+, 474.2306. Found: MH^+, 474.2301.

General Procedure for TBDMS removal: (1*R*,4*R*,5*R*)-4-Hydroxy-1-methoxymethoxy-3-(3-phenoxy-propenyl)-6-oxa-bicyclo-[3.2.1]oct-2-en-7-one (30a): TBAF (0.22 mL of a 1 M solution in THF, 0.22 mmol) was added dropwise to a solution of **29a** (100 mg, 0.22 mmol) in THF (2 mL) at 0 °C and the reaction was stirred for 1 h. The reaction was diluted with ethyl acetate (10 mL) and washed with saturated aqueous ammonium chloride solution (10 mL), brine (10 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The product was purified by column chromatography (eluent: 1:1 *v/v* petroleum ether/ethyl acetate) to afford the desired alcohol **30a** as a colourless oil (70 mg, 94%). $\nu_{max.}$ (ATR): $\tilde{\nu}$=3450 (O-H, br str), 2935, 2899 (=C-H + C-H alkane), 1789 (C=O), 1599, 1585 cm^{-1} (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.48 (1H, d, J=9.0 Hz, H-6_{ax}), 2.57 (1H, ddd, J=1.8, 6.0, 9.0 Hz, H-6_{eq}), 2.67 (1H, br s, OH), 3.42 (3H, s, CH_3), 4.49 (1H, d, J=3.3 Hz, H-4), 4.58 (2H, d, J=3.5 Hz, PhOCH_2), 4.74 (1H, dd, J=3.3, 6.0 Hz, H-5), 4.81 (1H, d, J=7.5 Hz, CH_3OC*H*H), 4.89 (1H, d, J=7.5 Hz, CH_3OCH*H*), 6.09 (1H, d, J=1.8 Hz, H-2), 6.24 (2H, m, OCH_2CH=C*H*), 6.88 (2H, m, 2×ArH), 6.95 (1H, m, ArH), 7.27 ppm (2H, m, 2×ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=34.5, 55.9, 64.7, 67.7, 75.9, 77.6, 93.3, 114.5, 121.0, 127.6, 129.4, 129.8, 132.5, 136.0, 158.2, 173.7 ppm; LC-MS $[M+H]^+$ 333.1, R_t=3.91 min; HRMS calcd for $C_{18}H_{21}O_6$: MH^+, 333.1333. Found: MH^+, 333.1337.

(1*R*,4*R*,5*R*)-3-[3-(4-Fluoro-phenoxy)-propenyl]-4-hydroxy-1-methoxymethoxy-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (30b) : TBDMS deprotection of **29b** (120 mg, 0.26 mmol) was achieved using the standard procedure described for **30a**. The product was purified

by column chromatography (eluent: 1:1 *v/v* petroleum ether/ethyl acetate) to afford the desired alcohol **30b** as a colourless oil (83 mg, 91%). R_F [1:1 *v/v* petroleum ether/ethyl acetate] = 0.33; $[\alpha]_D^{25} = -176$ ($c = 1.6$, $CHCl_3$); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3457$ (O-H, br str), 2902 (=C-H + C-H alkane), 1781 (C=O), 1600, 1504 cm^{-1} (C=C); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.47$ (1H, d, $J = 11.2$ Hz, H-6_{ax}), 2.60 (1H, ddd, $J = 1.9$, 6.0, 11.2 Hz, H-6_{eq}), 3.42 (3H, s, CH_3), 4.48 (1H, d, $J = 3.0$ Hz, H-4), 4.52 (2H, d, $J = 3.9$ Hz, ArOCH_2), 4.73 (1H, dd, $J = 3.0$, 6.0 Hz, H-5), 4.78 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 4.87 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 6.09 (1H, d, $J = 1.9$ Hz, H-2), 6.20 (2H, m, $OCH_2CH{=}CH$), 6.81 (2H, m, 2×ArH), 6.93 ppm (2H, m, 2×ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.2$, 55.8, 64.5, 68.3, 75.9, 77.5, 93.1, 115.4, 115.5 (d, $J_{C\text{-}F}$ 28 Hz, *o*-ArC), 127.2, 129.7, 132.4, 135.8, 154.8 (d, $J_{C\text{-}F}$ 220 Hz, *i*-ArC), 158.2, 173.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -124.0$ ppm; LC-MS $[M-H]^-$ 349.2, $[M+H]^+$ 351.2, $R_t = 3.97$ min; HRMS calcd for $C_{18}H_{20}O_6F$: MH^+, 351.1238. Found: MH^+, 351.1237.

(1*R*,4*R*,5*R*)-4-Hydroxy-1-methoxymethoxy-3-[3-(4-trifluoromethyl-phenoxy)-propenyl]-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (30c) : TBDMS deprotection of **29c** (53 mg, 0.10 mmol) was achieved using the standard procedure described for **30a**. The product was purified by column chromatography (eluent: 3:1 *v/v* ethyl acetate/petroleum ether) to afford the desired alcohol **30c** as a colourless oil (37 mg, 97%). R_F [3:1 *v/v* ethyl acetate/petroleum ether] = 0.63; $\nu_{max.}$ (ATR): $\tilde{\nu} = 3435$ (O-H, br str), 2953 (=C-H + C-H alkane), 1788 (C=O), 1615, 1590 cm^{-1} (C=C); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.47$ (1H, d, $J = 11.1$ Hz, H-6_{ax}), 2.63 (1H, ddd, $J = 1.9$, 6.1, 11.1 Hz, H-6_{eq}), 3.40 (3H, s, CH_3), 4.37 (1H, d, $J = 3.3$ Hz, H-4), 4.69 (3H, m, $ROCH_2$+ H-5), 4.73 (1H, dd, $J = 3.0$, 6.0 Hz, H-5), 4.79 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 4.88 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 6.10 (1H, d, $J = 1.9$ Hz, H-2), 6.30 (2H, m, $OCH_2CH{=}CH$), 7.06 (2H, d, $J = 8.6$ Hz, 2× ArH), 7.55 ppm (2H, d, $J = 8.6$ Hz, 2×ArH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 35.2$, 56.3, 65.7, 69.5, 78.2, 79.2, 94.4, 116.0, 123.8 (q, $J_{C\text{-}F}$ 32 Hz, *i*-ArC), 126.0 (q, $J_{C\text{-}F}$ 270 Hz, CF_3), 127.9 (q, $J_{C\text{-}F}$ 4 Hz, *o*-ArC), 128.3, 131.7, 133.4, 138.2, 162.7, 176.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -61.8$ ppm; LC-MS $[M-H]^-$ 399.2, $R_t = 4.27$ min; HRMS calcd for $C_{19}H_{20}O_6F_3$: MH^+, 401.1206. Found: MH^+, 401.1208.

(1*R*,4*R*,5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-3-(3-hydroxy-propenyl)-1-methoxymethoxy-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (30d): TBDMS deprotection of **29d** (47 mg, 0.13 mmol) was achieved using the standard procedure described for **30a**. The product was purified by column chromatography (eluent: 7:1 *v/v* ethyl acetate/petroleum ether) to afford the desired diol **30d** as a yellow oil (29 mg, 89%). R_F [7:1 *v/v* ethyl acetate/petroleum ether] = 0.21; $[\alpha]_D^{25} = -132$ ($c = 0.37$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3386$ (O-H, br str), 2925 (=C-H + C-H alkane), 1781 (C=O), 1630 cm^{-1} (C=C); ^1H NMR (400 MHz, [D_6]acetone): $\delta = 2.47$ (1H, d, $J = 11.1$ Hz, H-6 $_{ax}$), 2.60 (1H, ddd, $J = 1.7$, 6.1, 11.1 Hz, H-6 $_{eq}$), 3.37 (3H, s, CH_3), 3.80 (1H, br s, OH), 4.12 (2H, d, $J = 4.6$ Hz, CH_2), 4.38 (1H, d, $J = 3.3$ Hz, H-4), 4.69 (1H, dd, $J = 3.3$, 6.1 Hz, H-5), 4.78 (1H, d, $J = 7.4$ Hz, CH_3OCHH), 4.83 (1H, br s, OH), 4.86 (1H, d, $J = 7.4$ Hz, CH_3OCHH), 6.00 (1H, d, $J = 1.7$ Hz, H-2), 6.15 (1H, d, $J = 16.1$ Hz, $HOCH_2CH{=}CH$), 6.22 ppm (1H, dt, $J = 16.1$, 4.6 Hz, $HOCH_2CH{=}CH$); ^{13}C NMR (100 MHz, [D_6]acetone): $\delta = 34.5$, 55.5, 62.5, 65.3, 76.8, 78.2, 93.4, 127.6, 131.0, 132.9, 137.8, 173.9 ppm; LC-MS $[M+H]^+$ 257.2, $R_t = 2.71$ min; HRMS calcd for $C_{12}H_{17}O_6$: MH^+, 257.1020. Found: MH^+, 257.1021.

(1*R*,4*R*,5*R*)-3-(3-Benzenesulfonyl-propenyl)-4-hydroxy-1-methoxy-methoxy-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (30e): TBDMS deprotection of **29e** (70 mg, 0.14 mmol) was achieved using the standard procedure described for **30a**. The product was purified by column chromatography (eluent: 3:1 *v/v* ethyl acetate/petroleum ether) to afford the desired alcohol **30e** as a colourless oil (48 mg, 89%). R_F [3:1 *v/v* ethyl acetate/petroleum ether] = 0.10; $[\alpha]_D^{25} = -66.0$ ($c = 0.10$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3433$ (O-H, br str), 2933, 2923 (=C-H + C-H alkane), 1788 cm^{-1} (C=O); ^1H NMR (400 MHz, CD_3OD): $\delta = 2.44$ (1H, d, $J = 11.2$ Hz, H-6_{ax}), 2.61 (1H, ddd, $J = 1.8$, 6.1, 11.2 Hz, H-6_{eq}), 3.39 (3H, s, CH_3), 3.99 (2H, d, $J = 6.7$ Hz, $ROCH_2$), 4.27 (1H, d, $J = 3.2$ Hz, H-4), 4.67 (1H, dd, $J = 3.2$, 6.1 Hz, H-5), 4.77 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 4.85 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 5.94 (1H, dt, $J = 15.8$, 6.7 Hz, $OCH_2CH{=}CH$), 5.98 (1H, d, $J = 1.8$ Hz, H-2), 6.01 (1H, d, $J = 15.8$ Hz, $OCH_2CH{=}CH$), 7.58 (2H, m, 2×ArH), 7.68 (1H, m, ArH), 7.85 ppm (2H, m, 2×ArH); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 35.9$, 57.2, 61.8, 66.4, 79.0, 80.0, 95.3, 120.6, 130.4, 131.2, 135.5, 136.0, 138.8, 139.0, 140.6, 176.7 ppm; HRMS calcd for $C_{18}H_{20}O_7SNa$: MNa^+, 403.0822. Found: MNa^+, 403.0838.

(1*R*,4*R*,5*R*)-3-(4-Hydroxy-1-methoxymethoxy-7-oxo-6-oxa-bicyclo-[3.2.1]oct-2-en-3-yl)-*N*-phenyl-acrylamide (30f): TBDMS deprotection of **29f** (200 mg, 0.44 mmol) was achieved using the standard procedure described for **30a**. The product was purified by column chromatography (eluent: 3:1 *v/v* ethyl acetate/petroleum ether) to afford the desired alcohol **30f** as a colourless oil (150 mg, quant.). R_F [3:1 ethyl acetate/petroleum ether] = 0.27; $[\alpha]_D^{25} = -224$ ($c = 0.24$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3325$ (N-H + O-H, str), 1783 (C=O), 1663, 1601, 1599 cm^{-1} (C=C + C=C Ar); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.51$ (1H, d, $J = 11.3$ Hz, H-6_{ax}), 2.63 (1H, ddd, $J = 6.1$, 11.3 Hz, H-6_{eq}), 3.33 (3H, s, CH_3), 4.34 (1H, d, $J = 2.5$ Hz, H-4), 4.62 (1H, dd, $J = 2.5$, 6.1 Hz, H-5), 4.69 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 4.77 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 6.24 (1H, s, H-2), 6.38 (1H, d, $J = 15.7$ Hz, C(O)$CH{=}CH$), 7.02 (1H, m, ArH), 7.03 (1H, d, $J = 15.7$ Hz, C(O)$CH{=}CH$), 7.20 (2H, t, $J = 7.8$ Hz, 2×ArH), 7.46 (2H, d, $J = 7.9$ Hz, 2×ArH), 8.62 ppm (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.5$, 56.6, 65.0, 77.0, 78.5, 93.9, 120.9, 124.4, 125.4, 129.4, 136.0, 138.0, 138.8, 139.5, 165.0, 174.5 ppm; LC-MS $[M+H]^+$ 346.2, $[M-H]^-$ 344.1, $R_t = 3.48$ min; HRMS calcd for $C_{18}H_{20}NO_6$: MH^+, 346.1285. Found: MH^+, 346.1282.

(1*R*,4*R*,5*R*)-*N*-Benzyl-3-(4-hydroxy-1-methoxymethoxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-en-3-yl)-acrylamide (30g): TBDMS deprotection of **29g** (130 mg, 0.28 mmol) was achieved using the standard procedure described for **30a**. The product was purified by column chromatography (eluent: 3:1 *v/v* ethyl acetate/petroleum ether) to afford the desired alcohol **30g** as a colourless oil (100 mg, quant.). R_F [3:1 ethyl acetate/petroleum ether] = 0.24; $[\alpha]_D^{25} = -220$ ($c = 0.25$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3384$, 3309 (N-H + O-H, str), 2948, 2899, 2824 (=C-H + C-H alkane), 1776 (C=O), 1658, 1620, 1605 cm^{-1} (C=C + C=C Ar); ^1H NMR (400 MHz, [D_6]acetone): $\delta = 2.52$ (1H, d, $J = 11.2$ Hz, H-6_{ax}), 2.64 (1H, ddd, $J = 1.7$, 6.0, 11.2 Hz, H-6_{eq}), 3.38 (3H, s, CH_3), 4.38 (1H, dd, $J = 3.2$, 6.6 Hz, H-4), 4.45 (2H, d, $J = 5.8$ Hz, RCH_2), 4.73 (1H, dd, $J = 3.2$, 6.0 Hz, H-5), 4.80 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 4.88 (1H, d, $J = 7.5$ Hz, CH_3OCHH), 5.06 (1H, d, $J = 6.6$ Hz, OH), 6.40 (1H, d, $J = 1.7$ Hz, H-2), 6.52 (1H, d, $J = 15.6$ Hz, C(O)$CH{=}CH$), 7.10 (1H, d, $J = 15.6$ Hz, C(O)$CH{=}CH$), 7.21 (1H, m, ArH), 7.28 (4H, m, 4×ArH), 7.81 ppm (1H, br t, $J = 5.8$ Hz, NH); ^{13}C NMR (100 MHz, [D_6]acetone): $\delta = 35.0$, 44.1, 55.7, 66.1, 77.6, 79.3, 94.4, 125.5, 128.2, 128.8, 129.6, 137.7, 138.3, 139.0, 140.7, 166.5, 174.2 ppm; LC-MS $[M+H]^+$ 360.1, $R_t = 3.39$ min; HRMS calcd for $C_{19}H_{22}NO_6$: MH^+, 360.1442. Found: MH^+, 360.1445.

General Procedure for MOM ether deprotection: (1*R*,4*R*,5*R*)-1,4-Dihydroxy-3-(3-phenoxy-propenyl)-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (31a): Alcohol **30a** (70 mg, 0.21 mmol) was dissolved in aqueous 90% trifluoroacetic acid solution (6 mL). The reaction was stirred at 0 °C for 30 min before the solvent was removed in vacuo. The residue was dissolved in water (5 mL) and the solvent was removed in vacuo once more. The product was purified by column chromatography (eluent: 2:1 *v/v* ethyl acetate/petroleum ether) to afford the desired diol **31a** as a white solid (40 mg, 66%). R_F [2:1 *v/v* ethyl acetate/petroleum ether] = 0.35; $\nu_{max.}$ (ATR): $\tilde{\nu} = 3508$, 3265 (O-H, br str), 2908 (=C-H + C-H alkane), 1784 (C=O), 1601, 1586 cm^{-1} (C=C); ^1H NMR (400 MHz, [D_6]acetone): $\delta = 2.39$ (1H, ddd, $J = 1.8$, 5.5, 9.5 Hz, H-6_{eq}), 2.57 (1H, d, $J = 9.5$ Hz, H-6_{ax}), 4.43

(1H, dd, $J=3.3$, 7.0 Hz, H-4), 4.62 (2H, d, $J=2.5$ Hz, PhOCH_2), 4.67 (1H, dd, $J=3.3$, 5.5 Hz, H-5), 4.87 (1H, d, $J=7.0$ Hz, OH), 5.29 (1H, s, OH), 6.05 (1H, d, $J=1.8$ Hz, H-2), 6.34 (2H, m, $OCH_2CH{=}CH$), 6.93 (3H, m, 3×ArH), 7.26 ppm (2H, m, 2×ArH); ^{13}C NMR (125 MHz, [D_6]acetone): $\delta=37.7$, 66.1, 69.2, 74.4, 77.4, 115.8, 121.9, 128.6, 130.6, 131.8, 135.6, 137.5, 160.0, 177.0 ppm; LRMS (ESI+) MH^+ 289.2, MNH_4^+ 306.2; HRMS calcd for $C_{16}H_{20}NO_5$: MNH_4^+, 306.1336. Found: MNH_4^+, 306.1337.

(1*R*,4*R*,5*R*)-3-[3-(4-Fluoro-phenoxy)-propenyl]-1,4-dihydroxy-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (31b): MOM deprotection of **30b** (42 mg, 0.12 mmol) was achieved using the general procedure described for **31a**. The product was purified by column chromatography (eluent: 2:1 *v/v* ethyl acetate/petroleum ether) to afford the desired diol **31b** as a colourless oil (37 mg, quant.). R_F [2:1 *v/v* ethyl acetate/petroleum ether] = 0.17; $[\alpha]_D^{25}=-138$ ($c=0.74$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}=3393$ (O-H, br str), 1769 (C=O), 1601, 1504 cm^{-1} (C=C); ^{1}H NMR (400 MHz, CD_3OD): $\delta=2.39$ (1H, ddd, $J=$ 1.8, 5.5, 9.5 Hz, H-6_{eq}), 2.57 (1H, d, $J=9.5$ Hz, H-6_{ax}), 4.43 (1H, dd, $J=3.3$, 7.0 Hz, H-4), 4.62 (2H, d, $J=2.5$ Hz, ArOCH_2), 4.67 (1H, dd, $J=3.3$, 5.5 Hz, H-5), 4.87 (1H, d, $J=7.0$ Hz, OH), 5.29 (1H, s, OH), 6.05 (1H, d, $J=1.8$ Hz, H-2), 6.34 (2H, m, $OCH_2CH{=}CH$), 6.93 (2H, m, 2×ArH), 7.26 ppm (2H, m, 2×ArH); ^{13}C NMR (125 MHz, CD_3OD): $\delta=36.2$, 64.4, 68.5, 72.9, 76.6, 115.1 (d, $J_{C\text{-}F}$ 23 Hz, *o*-ArC), 115.5 (d, $J_{C\text{-}F}$ 8 Hz, *m*-ArC), 127.3, 130.0, 133.6, 136.1, 154.8 (d, $J_{C\text{-}F}$ 2 Hz, *p*-ArC), 157.5 (d, $J_{C\text{-}F}$ 237 Hz, *i*-ArC), 176.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta=-122.5$ ppm.

(1*R*,4*R*,5*R*)-1,4-Dihydroxy-3-[3-(4-trifluoromethyl-phenoxy)-propenyl]-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (31c): MOM deprotection of **30c** (38 mg, 0.10 mmol) was achieved using the general procedure described for **31a**. The product was purified by column chromatography (eluent: 7:2 *v/v* ethyl acetate/petroleum ether) to afford the diol **31c** as a colourless oil (25 mg, 74%). R_F [7:2 *v/v* ethyl acetate/petroleum ether] = 0.10; $[\alpha]_D^{25}=-105$ ($c=0.56$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}=3389$ (O-H, br str), 1733 (C=O), 1615, 1586 cm^{-1} (C=C); ^{1}H NMR (400 MHz, CD_3OD): $\delta=2.37$ (2H, m, 2× H-6), 4.37 (1H, d, $J=3.3$ Hz, H-4), 4.63 (1H, dd, $J=3.3$, 5.9 Hz, H-5), 4.69 (2H, d, $J=4.1$ Hz, $ROCH_2$), 6.01 (1H, s, H-2), 6.29 (2H, m, $OCH_2CH{=}CH$), 7.07 (2H, d, $J=8.6$ Hz, 2×ArH), 7.55 ppm (2H, d, $J=$ 8.6 Hz, 2×ArH); ^{13}C NMR (125 MHz, CD_3OD): $\delta=37.5$, 65.8, 69.5, 74.3, 77.9, 116.0, 123.9 (q, $J_{C\text{-}F}$ 32 Hz, *i*-ArC), 126.0 (q, $J_{C\text{-}F}$ 270 Hz, CF_3), 127.9 (q, $J_{C\text{-}F}$ 4 Hz, *o*-ArC), 128.0, 131.9, 135.4, 137.5, 162.8, 178.3 ppm; ^{19}F NMR (376 MHz, CD_3OD): $\delta=-59.3$ ppm; LC-MS $[M-H]^-$ 355.2, $R_t=3.91$ min; HRMS calcd for $C_{17}H_{14}O_5F_3$: $[M-H]^-$, 355.0799. Found: $[M-H]^-$, 355.0798.

(1*R*, 4*R*, 5*R*)-1,4-Dihydroxy-3-(3-hydroxy-propenyl)-6-oxa-bicyclo-[3.2.1]oct-2-en-7-one (31d): MOM deprotection of **30d** (22 mg, 0.09 mmol) was achieved using the general procedure described for **31a**. The product was purified by column chromatography (eluent: 19:1 *v/v* dichloromethane/methanol - 9:1 dichloromethane/methanol) to afford the desired triol **31d** as a colourless oil (17 mg, 94%). R_F [19:1 *v/v* dichloromethane/methanol] = 0.26; $[\alpha]_D^{25}=-129$ ($c=1.1$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}=3293$ (O-H, br str), 2917, 2872 (=C-H + C-H alkane), 1770 (C=O), 1654 cm^{-1} (C=C); ^{1}H NMR (500 MHz, [D_6]acetone): $\delta=2.37$ (1H, ddd, $J=1.9$, 5.6, 10.8 Hz, H-6_{eq}), 2.42 (1H, d, $J=10.8$ Hz, H-6_{ax}), 3.82 (1H, t, $J=$ 5.6 Hz, OH), 4.13 (2H, br t, $J=4.7$ Hz, $HOCH_2$), 4.38 (1H, dd, $J=3.3$, 6.9 Hz, H-4), 4.65 (1H, dd, $J=3.3$, 5.5 Hz, H-5), 4.79 (1H, d, $J=$ 6.9 Hz, OH), 5.27 (1H, s, OH), 5.96 (1H, d, $J=1.9$ Hz, H-2), 6.14 (1H, d, $J=16.0$ Hz, $HOCH_2CH{=}CH$), 6.22 ppm (1H, dt, $J=16.0$, 4.7 Hz, $HOCH_2CH{=}CH$); ^{13}C NMR (125 MHz, [D_6]acetone): $\delta=37.7$, 63.3, 66.2, 74.3, 77.4, 128.6, 133.7, 134.0, 137.8, 177.1; LRMS (ESI+) MNa^+, 235.0; HRMS calcd for $C_{10}H_{12}O_5Na$: MNa^+, 235.0577. Found: MNa^+, 235.0575.

(1*R*,4*R*,5*R*)-3-(3-Benzenesulfonyl-propenyl)-1,4-dihydroxy-6-oxa-bicyclo[3.2.1]oct-2-en-7-one (31e): MOM deprotection of **30e** (37 mg, 0.10 mmol) was achieved using the general procedure described for **31a**. The product was purified by column chromatography (eluent: 9:1 *v/v* dichloromethane/methanol) to afford the desired diol **31e** as a pale yellow oil (31 mg, 95%). R_F [9:1 *v/v* dichloromethane/methanol] = 0.64; $\nu_{max.}$ (ATR): $\tilde{\nu}=3420$ (O-H, br str), 2935, 2875 (=C-H + C-H alkane), 1787 (C=O), 1630 cm^{-1} (C=C); ^{1}H NMR (500 MHz, CD_3OD): $\delta=2.30$ (2H, m, 2 × H-6), 3.99 (2H, d, $J=6.1$ Hz, $ROCH_2$), 4.27 (1H, d, $J=3.3$ Hz, H-4), 4.63 (1H, dd, $J=3.3$, 5.8 Hz, H-5), 5.90 (1H, s, H-2), 5.94 (1H, dt, $J=16.0$, 6.1 Hz, $OCH_2CH{=}CH$), 5.99 (1H, d, $J=16.0$ Hz, $OCH_2CH{=}CH$), 7.60 (2H, m, 2×ArH), 7.69 (1H, m, ArH), 7.86 ppm (2H, m, 2×ArH); ^{13}C NMR (125 MHz, CD_3OD): $\delta=37.4$, 60.9, 65.6, 74.3, 77.9, 119.5, 129.6, 130.3, 135.1, 136.5, 137.2, 138.3, 139.6, 178.1 ppm; LC-MS $[M-H]^-$ 335.3, $R_t=3.15$ min; HRMS calcd for $C_{16}H_{16}O_6SNa$: MNa^+, 359.0560. Found: MNa^+, 359.0569.

(1*R*,4*R*,5*R*)-3-(1,4-Dihydroxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-en-3-yl)-*N*-phenyl-acrylamide (31f): MOM deprotection of **30f** (150 mg, 0.43 mmol) was achieved using the general procedure described for **31a**. The product purified by column chromatography (eluent: 95:5 *v/v* dichloromethane/methanol) to afford the desired diol **31f** as a colourless oil (90 mg, 69%). R_F [95:5 *v/v* dichloromethane/methanol] = 0.38; $[\alpha]_D^{25}=-71.6$ ($c=1.3$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}=3492$, 3261 (N-H + O-H, str), 2950, 2898 (=C-H + C-H alkane), 1786, 1760 (C=O), 1655, 1601 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (500 MHz, CD_3OD): $\delta=2.41$ (2H, m, 2 × H-6), 4.42 (1H, d, $J=$ 3.2 Hz, H-4), 4.71 (1H, br t, $J=3.2$ Hz, H-5), 6.36 (1H, s, H-2), 6.60 (1H, d, $J=15.6$ Hz, C(O)CH=CH), 7.08 (1H, t, $J=7.4$ Hz, ArH), 7.17 (1H, d, $J=15.6$ Hz, C(O)CH=CH), 7.29 (2H, td, $J=7.4$, 7.7 Hz, 2× ArH), 7.62 ppm (2H, d, $J=7.7$ Hz, 2×ArH); ^{13}C NMR (125 MHz, CD_3OD): $\delta=37.2$, 66.0, 74.6, 77.8, 121.3, 124.9, 125.4, 129.8, 137.0, 139.9, 140.4, 141.0, 166.4, 177.7 ppm; LC-MS $[M+H]^+$ 302.2, $R_t=$ 3.14 min; HRMS calcd for $C_{16}H_{16}NO_5$: MH^+, 302.1023. Found: MH^+, 302.1023.

(1*R*,4*R*,5*R*)-*N*-Benzyl-3-(1,4-dihydroxy-7-oxo-6-oxa-bicyclo-[3.2.1]oct-2-en-3-yl)-acrylamide (31g): MOM deprotection of **30g** (100 mg, 0.28 mmol) was achieved using the general procedure described for **31a**. The product purified by column chromatography (eluent: 95:5 *v/v* dichloromethane/methanol) to afford the diol **31g** as a white solid (80 mg, 92%). R_F [95:5 *v/v* dichloromethane/methanol] = 0.50; $[\alpha]_D^{25}=-104$ ($c=0.30$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}=$ 3282 (N-H + O-H, str), 2977, 2874 (=C-H + C-H alkane), 1781 (C=O), 1655, 1614 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (400 MHz, CD_3OD): $\delta=2.38$ (2H, m, 2 × H-6), 4.36 (1H, d, $J=3.2$ Hz, H-4), 4.42 (2H, s, RCH_2), 4.67 (1H, m, H-5), 6.31 (1H, d, $J=1.7$ Hz, H-2), 6.43 (1H, d, $J=15.7$ Hz, C(O)CH=CH), 7.07 (1H, d, $J=15.7$ Hz, C(O)CH=CH), 7.22–7.30 ppm (5H, m, 5×ArH); ^{13}C NMR (100 MHz, CD_3OD): $\delta=$ 37.7, 44.7, 66.2, 75.0, 78.2, 124.8, 128.7, 129.1, 130.0, 137.3, 140.1, 140.2, 141.1, 168.7, 178.2 ppm; LC-MS $[M+H]^+$ 316.2, $R_t=3.09$ min; HRMS calcd for $C_{17}H_{18}NO_5$: MH^+, 316.1179. Found: MH^+, 316.1179.

General procedure for lactone hydrolysis: (1*R*,4*R*,5*R*)-1,4,5-Trihydroxy-3-(3-phenoxy-prop-(*E*)-enyl)-cyclohex-2-enecarboxylic acid (7): Aqueous sodium hydroxide (0.05 mL of a 0.1 g mL^{-1} solution) was added dropwise to a solution of diol **31a** (20 mg, 0.07 mmol) in THF (1 mL) and milliQ water (1 mL) at 22 °C. After stirring for 1 h, the aqueous phase was washed with ethyl acetate (2 mL) before Amberlite IR-120 (H^+) was added and the mixture stirred for 5 min to neutralise the aqueous fraction. The resin was removed by filtration and the filtrate lyophilised to give the desired acid **7** as an off-white solid (0.07 mmol, quant.). $[\alpha]_D^{25}=-18.2$ ($c=0.46$, H_2O); $\nu_{max.}$ (ATR): $\tilde{\nu}=3278$ (O-H, br str), 2915 (=C-H + C-H alkane), 1716 (C=O), 1599, 1587 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (400 MHz, D_2O): $\delta=$ 2.00 (1H, dd, $J=3.4$, 13.6 Hz, H-6_{ax}), 2.11 (1H, dd, $J=9.4$, 13.6 Hz,

H-6 $_{eq}$), 3.91 (1H, ddd, J=3.4, 5.5, 9.4 Hz, H-5), 4.17 (1H, d, J=5.5 Hz, H-4), 4.58 (2H, d, J=5.5 Hz, PhOCH_2), 5.72 (1H, s, H-2), 6.14 (1H, dt, J=16.0, 5.5 Hz, OCH$_2$CH=CH), 6.28 (1H, d, J=16.0 Hz, OCH$_2$CH=CH), 6.94 (3H, m, 3×ArH), 7.27 ppm (2H, m, 2×ArH); ^{13}C NMR (100 MHz, D_2O): δ=35.2, 66.9, 67.8, 68.2, 71.1, 113.4, 119.9, 125.4, 125.9, 128.1, 129.8, 137.5, 155.9, 176.5 ppm; LRMS (ESI-) [M−H]$^-$ 305.3; HRMS calcd for $C_{16}H_{18}O_6Na$: MNa$^+$, 329.0996. Found: MNa$^+$, 329.0994.

(1*R*,4*R*,5*R*)-3-[3-(4-Fluoro-phenoxy)-propenyl]-1,4,5-trihydroxy-cyclohex-2-enecarboxylic acid (8): Lactone hydrolysis of **31b** (18 mg, 0.06 mmol) was achieved using the general procedure described for **7** to give the desired acid **8** as an off-white solid (0.05 mmol, 83%). $[\alpha]_D^{25}=-59.2$ (c=0.28, H_2O); $\nu_{max.}$ (ATR): $\tilde{\nu}$=3303 (O-H and O-H acid, br str), 2929 (=C-H + C-H alkane), 1716 (C=O), 1601, 1505 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (500 MHz, D_2O): δ=2.00 (1H, dd, J=3.4, 13.4 Hz, H-6$_{ax}$), 2.11 (1H, dd, J=9.9, 13.6 Hz, H-6$_{eq}$), 3.91 (1H, ddd, J=3.4, 6.5, 9.9 Hz, H-5), 4.13 (1H, d, J=6.5 Hz, H-4), 4.42 (2H, d, J=5.3 Hz, ArOCH$_2$), 5.70 (1H, s, H-2), 6.07 (1H, dt, J=16.1, 5.3 Hz, OCH$_2$CH=CH), 6.20 (1H, d, J=16.1 Hz, OCH$_2$CH=CH), 6.77 (2H, m, 2×ArH), 6.87 ppm (2H, m, 2×ArH); ^{13}C NMR (125 MHz, D_2O): δ=37.0, 69.2, 69.4, 70.1, 72.6, 115.7 (d, $J_{C\text{-}F}$ 23 Hz, o-ArC), 116.1 (d, $J_{C\text{-}F}$ 8 Hz, m-ArC), 126.9, 127.2, 131.2, 139.4, 153.8 (d, $J_{C\text{-}F}$ 2 Hz, p-ArC), 157.4 (d, $J_{C\text{-}F}$ 237 Hz, i-ArC), 177.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−124.0 ppm; LC-MS [M−H]$^-$ 323.2, R_t=2.97 min; HRMS calcd for $C_{16}H_{16}O_6F$: [M−H]$^-$, 323.0936. Found: [M−H]$^-$, 323.0940.

(1*R*,4*R*,5*R*)-1,4,5-Trihydroxy-3-[3-(4-trifluoromethyl-phenoxy)-propenyl]-cyclohex-2-enecarboxylic acid (9): Lactone hydrolysis of **31c** (12 mg, 0.04 mmol) was achieved using the general procedure described for **7** to give the desired acid **9** as a white solid (0.04 mmol, quant.). $\nu_{max.}$ (ATR): $\tilde{\nu}$=3342 (O-H and O-H acid, br str), 1715 (C=O), 1615, 1592 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (500 MHz, D_2O): δ=2.02 (1H, dd, J=3.5, 13.4 Hz, H-6$_{ax}$), 2.13 (1H, dd, J=9.8, 13.4 Hz, H-6$_{eq}$), 3.92 (1H, ddd, J=3.5, 6.5, 9.8 Hz, H-5), 4.17 (1H, d, J=6.5 Hz, H-4), 4.59 (2H, d, J=5.0 Hz, ROCH$_2$), 5.75 (1H, s, H-2), 6.15 (1H, td, J=5.0, 16.1 Hz, OCH$_2$CH=CH), 6.28 (1H, d, J=16.1 Hz, OCH$_2$CH=CH), 6.96 (2H, d, J=8.6 Hz, 2×ArH), 7.50 ppm (2H, d, J=8.6 Hz, 2×ArH); ^{13}C NMR (125 MHz, D_2O): δ=37.0, 68.5, 69.4, 70.0, 72.6, 114.9, 122.6 (q, $J_{C\text{-}F}$ 32 Hz, i-ArC), 124.3 (q, $J_{C\text{-}F}$ 271 Hz, CF_3), 126.8, 126.9 (q, $J_{C\text{-}F}$ 4 Hz, o-ArC), 127.0, 131.4, 139.3, 160.3, 177.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−61.7 ppm; LRMS (ESI-) [M−H]$^-$ 373.2; HRMS calcd for $C_{17}H_{16}O_6F_3$: [M−H]$^-$, 373.0904. Found: [M−H]$^-$, 373.0908.

(1*R*,4*R*,5*R*)-1,4,5-Trihydroxy-3-(3-hydroxy-prop-(*E*)-enyl)-cyclohex-2-enecarboxylic acid (10): Lactone hydrolysis of **31d** (9 mg, 0.04 mmol) was achieved using the general procedure described for **7** to give the desired acid **10** as a colourless oil (0.04 mmol, quant.). $[\alpha]_D^{25}=-62.8$ (c=0.14, H_2O); $\nu_{max.}$ (ATR): $\tilde{\nu}$=3262 (O-H br str), 2926 (=C-H + C-H alkane), 2501 (O-H carboxylate br str) 1711 (C=O), 1607 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (400 MHz, D_2O): δ=2.01 (1H, dd, J=3.4, 13.7 Hz, H-6 $_{ax}$), 2.13 (1H, dd, J=9.3, 13.7 Hz, H-6 $_{eq}$), 3.92 (1H, ddd, J=3.4, 6.2, 9.3 Hz, H-5), 4.10 (2H, d, J=5.3 Hz, HOCH$_2$), 4.19 (1H, d, J=6.2 Hz, H-4), 5.75 (1H, s, H-2), 6.09 (1H, dt, J=16.1, 5.3 Hz, HOCH$_2$CH=CH), 6.18 ppm (1H, d, J=16.1 Hz, HOCH$_2$CH=CH); ^{13}C NMR (125 MHz, D_2O): δ=36.8, 62.0, 69.5, 69.7, 72.8, 126.8, 129.1, 130.7, 139.3, 178.3 ppm; LRMS (ESI+) [M−H+2Na]$^+$, 275.1; HRMS calcd for $C_{10}H_{14}O_6Na$: MNa$^+$, 253.0683. Found: MNa$^+$, 253.0685.

(1*R*,4*R*,5*R*)-3-(3-Benzenesulfonyl-propenyl)-1,4,5-trihydroxy-cyclohex-2-enecarboxylic acid (11): Lactone hydrolysis of **31e** (16 mg, 0.05 mmol) was achieved using the general procedure described for **7** to give the desired acid **11** as a pale orange solid (0.04 mmol, 80%). $[\alpha]_D^{25}=-68.8$ (c=0.13, H_2O); $\nu_{max.}$ (ATR): $\tilde{\nu}$=3299 (O-H and O-H acid, br str), 1715 (C=O), 1613, 1583 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (500 MHz, D_2O): δ=1.97 (1H, dd, J=3.0, 13.5 Hz, H-6$_{ax}$), 2.07 (1H, dd, J=9.8, 13.5 Hz, H-6$_{eq}$), 3.86 (1H, ddd, J=3.0, 6.4, 9.8 Hz, H-5), 4.06 (1H, d, J=6.4 Hz, H-4), 4.07 (2H, d, J=7.6 Hz, ROCH$_2$), 5.62 (1H, s, H-2), 5.77 (1H, dt, J=15.8, 7.6 Hz, OCH$_2$CH=CH), 5.95 (1H, d, J=15.8 Hz, OCH$_2$CH=CH), 7.56 (2H, m, 2×ArH), 7.70 (1H, m, ArH), 7.77 ppm (2H, m, 2×ArH); ^{13}C NMR (125 MHz, D_2O): δ=36.9, 59.3, 69.4, 69.7, 72.6, 117.4, 128.2, 129.1, 129.4, 134.7, 135.9, 138.3, 138.8, 177.7 ppm; LC–MS [M−H]$^-$ 353.3, R_t=2.65 min; HRMS calcd for $C_{16}H_{18}O_7SNa$: MNa$^+$, 377.0665. Found: MNa$^+$, 377.0672.

(1*R*,4*R*,5*R*)-1,4,5-Trihydroxy-3-(2-phenylcarbamoyl-vinyl)-cyclohex-2-enecarboxylic acid (12): Lactone hydrolysis of **31f** (33 mg, 0.11 mmol) was achieved using the general procedure described for **7** to give the desired acid **12** as a white solid (0.10 mmol, 91%). $[\alpha]_D^{25}=-41.4$ (c=0.18, H_2O); $\nu_{max.}$ (ATR): $\tilde{\nu}$=3270 (N-H + O-H + O-H carboxylate br str), 2981 (=C-H + C-H alkane), 1690, 1660 (C=O), 1597, 1543 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (500 MHz, D_2O): δ=2.02 (1H, dd, J=3.5, 13.8 Hz, H-6$_{ax}$), 2.21 (1H, dd, J=9.3, 13.8 Hz, H-6$_{eq}$), 3.92 (1H, ddd, J=3.5, 6.2, 9.3 Hz, H-5), 4.19 (1H, br t, J=6.2 Hz, H-4), 6.02 (1H, s, H-2), 6.34 (1H, d, J=15.8 Hz, C(O)CH=CH), 7.04 (1H, d, J=15.8 Hz, C(O)CH=CH), 7.08 (1H, t, J=7.3 Hz, ArH), 7.27 (2H, br t, J=7.5 Hz, 2×ArH), 7.35 ppm (2H, d, J=7.6 Hz, 2×ArH); ^{13}C NMR (125 MHz, D_2O): δ=36.7, 69.6×2, 73.0, 121.3, 123.0, 125.4, 129.1, 134.3, 136.8, 137.7, 140.6, 166.6, 180.3 ppm; LRMS [M+Na]$^+$ 342.2. HRMS calcd for $C_{16}H_{17}NO_6Na$: MNa$^+$, 342.0948. Found: MNa$^+$, 342.0955.

(1*R*,4*R*,5*R*)-3-(2-Benzylcarbamoyl-vinyl)-1,4,5-trihydroxy-cyclohex-2-enecarboxylic acid (13): Lactone hydrolysis of **31g** (25 mg, 0.08 mmol) was achieved using the general procedure described for **7** to give the desired acid **13** as a white solid (0.08 mmol, quant.). $[\alpha]_D^{25}=-47.0$ (c=2.1, H_2O); $\nu_{max.}$ (ATR): $\tilde{\nu}$=3274 (N-H + O-H + O-H carboxylate br str), 2916 (=C-H + C-H alkane), 1724, 1655 (C=O), 1603, 1546 cm^{-1} (C=C + C=C Ar); ^{1}H NMR (400 MHz, D_2O): δ=1.93 (1H, dd, J=3.9, 13.9 Hz, H-6$_{ax}$), 2.01 (1H, dd, J=8.5, 13.9 Hz, H-6$_{eq}$), 3.83 (1H, ddd, J=3.9, 6.0, 8.5 Hz, H-5), 4.13 (1H, d, J=6.0, H-4), 4.28 (2H, d, J=1.4 Hz, RCH_2), 5.89 (1H, s, H-2), 6.24 (1H, d, J=15.8 Hz, C(O)CH=CH), 6.94 (1H, d, J=15.8 Hz, C(O)CH=CH), 7.15–7.22 ppm (5H, m, 5×ArH); ^{13}C NMR (100 MHz, D_2O): δ=36.1, 42.7, 68.9, 69.3, 72.8, 121.8, 126.8, 127.0, 128.3, 134.7, 136.8, 137.3, 139.7, 168.0, 179.0 ppm; LC-MS [M+H]$^+$ 334.2, [M−H]$^-$ 332.2, R_t=2.75 min; HRMS calcd for $C_{17}H_{20}NO_6$: MH$^+$, 334.1285. Found: MH$^+$, 334.1284.

General Procedure for Carboamidation Chemistry: (1*R*, 4*R*, 5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methoxymethoxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-ene-3-carboxylic acid (2-phenoxy-ethyl)-amide (32a): Vinyl triflate **17** (0.23 g, 0.50 mmol) in DMF (10 mL) was added dropwise to palladium (II) diacetate (5.5 mg, 0.03 mmol) and triphenylphosphine (13 mg, 0.05 mmol). The reaction vessel was purged with carbon monoxide and heated to 60 °C. Triethylamine (0.25 mL, 1.80 mmol) was added dropwise followed by 2-phenoxyethylamine (130 μL, 1 mmol) over a 30 min period. The solution was stirred for 1.5 h at 60 °C under a carbon monoxide atmosphere. After cooling, the reaction mixture was diluted with ethyl acetate (50 mL), and washed with brine (4× 50 mL), dried (Na_2SO_4), and the solvent was removed in vacuo. The product was purified by column chromatography (eluent: 2:1 *v/v* hexane/ethyl acetate) to afford the desired amide **32a** as a yellow oil (42 mg, 17%). R_F (2:1 *v/v* hexane/ethyl acetate)=0.36; $[\alpha]_D^{25}=-122.4$ (c=0.21, $CHCl_3$); $\nu_{max.}$ (ATR): $\tilde{\nu}$=3352 (N-H, br. str.), 2953, 2931, 2898, 2857 (m, satd. C-H str.), 1798 (s, C=O), 1663 (m, amide), 1627, 1599, 1588, 1529, 1497 cm^{-1} (m, amide + conjugated C=C + C=C ar); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.13 (3H, s, SiCH$_3$), 0.26 (3H, s, SiCH$_3$), 0.85 (9H, s, *t*Bu), 2.45 (1H, d, J=11.1 Hz, H-6$_{ax}$), 2.62 (1H, ddd, J=1.9, 6.0, 11.1 Hz, H-6$_{eq}$), 3.44 (3H, s, OCH$_3$), 3.61–3.78

(2H, m, CH_2N), 4.03–4.08 (2H, m, CH_2CH_2N), 4.59 (1H, dd, $J=3.3$, 6.0 Hz, H-5), 4.65 (1H, d, $J=3.3$ Hz, H-4), 4.84 (1H, d, $J=7.6$ Hz, CHOMe), 4.90 (1H, d, $J=7.6$ Hz, CHOMe), 6.37 (1H, br. t, $J=5.5$ Hz, NH), 6.61 (1H, d, $J=1.9$ Hz, H-2), 6.85–6.91 (2H, m, ArH), 6.93–6.99 (1H, m, ArH), 7.24–7.31 ppm (3H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.9$ ($SiCH_3$), -4.8 ($SiCH_3$), 17.9 ($SiC(CH_3)_3$), 25.5 ($SiC(CH_3)_3$), 33.6 (C-6), 39.2 (CH_2N), 56.3 (OCH_3), 65.2 (C-4), 66.4 (OCH_2CH_2N), 75.8 (C-5), 77.4 (C-1), 93.6 (OCH_2O), 114.4 (Ar), 121.3 (Ar), 129.6 (Ar), 135.5 (C-2), 136.2 (C-3), 158.3 (Ar), 165.5 (C=O), 172.8 ppm (C=O); LC-MS $[M+H]^+=478$, $R_t=4.89$ min; HRMS calcd for $C_{24}H_{36}NO_7Si$: MH^+, 478.2261. Found MH^+, 478.2259.

(1*R*,4*R*,5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methoxymethoxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-ene-3-carboxylic acid phenethyl-amide (32b): Vinyl triflate **17** (0.23 g, 0.50 mmol) and phenethylamine (126 μL, 1 mmol) were reacted for 1.5 h at 60 °C under a carbon monoxide atmosphere using the standard procedure described for **32a**. The product was purified by column chromatography (eluent: 4:1 *v/v* petroleum ether/ethyl acetate) to afford the desired amide **32b** as a yellow oil (80 mg, 35%). R_F (4:1 *v/v* petroleum ether/ethyl acetate) = 0.16; $[\alpha]_D^{25}=-100.7$ ($c=4.27$, $CHCl_3$); $\nu_{max.}$ (ATR): $\tilde{\nu}=3336$ (N-H, br. str.), 2952, 2929, 2856 (satd. C-H str.), 1798 (C=O), 1659 (amide), 1624 (conjugated C=C), 1532 cm^{-1} (br., amide + C=C ar); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.06$ (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$), 0.84 (9H, s, *t*Bu), 2.42 (1H, d, $J=11.0$ Hz, H-6_{ax}), 2.59 (1H, ddd, $J=1.9$, 6.0, 11.0 Hz, H-6_{eq}), 2.83 (2H, m, CH_2CH_2N), 3.42 (3H, s, OCH_3), 3.62–3.47 (2H, m, CH_2N), 4.57 (1H, dd, $J=3.3$, 6.0 Hz, H-5), 4.63 (1H, d, $J=3.3$ Hz, H-4), 4.82 (1H, d, $J=7.6$ Hz, CH_3OCHH), 4.87 (1H, d, $J=7.6$ Hz, CH_3OCHH), 5.90 (1H, t br., $J=5.4$ Hz, NH), 6.47 (1H, d, $J=1.9$ Hz, H-2), 7.15–7.26 (3H, m, ArH), 7.28–7.33 ppm (2H, m, ArH); ^{13}C NMR (125 MHz; $CDCl_3$): $\delta=-5.0$, -4.9, 17.9, 25.6, 33.6, 35.6, 40.8, 56.3, 65.1, 75.8, 77.4, 93.6, 126.6, 128.7, 128.8, 134.7, 136.7, 138.6, 165.3, 172.9 ppm; LC-MS $[M-H]^-$ 460, $[M+H]^+$ 462, $R_t=4.84$ min; HRMS calcd for $C_{24}H_{36}NO_6Si$: MH^+, 462.2306. Found: MH^+, 462.2303.

(1*R*,4*R*,5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methoxymethoxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-ene-3-carboxylic acid benzyl-amide (32c): Vinyl triflate **17** (0.23 g, 0.50 mmol) and benzylamine (109 μL, 1 mmol) were reacted for 1.5 h at 60 °C under a carbon monoxide atmosphere using the standard procedure described for **32a**. The product was purified by column chromatography (eluent: 3:1 *v/v* hexane/ethyl acetate) to afford the desired amide **32c** as a yellow oil (60 mg, 27%). R_F (3:1 *v/v* hexane/ethyl acetate) = 0.26; $[\alpha]_D^{25}=-116.9$ ($c=1.50$, $CHCl_3$); $\nu_{max.}$ (ATR): $\tilde{\nu}=3283$ (N-H, br. str.) (w, N-H), 2954, 2930, 2856, 1798 (s, C=O), 1655 (s, amide), 1626, 1528, 1454 cm^{-1} (m, amide + conjugated C=C + C=C ar); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.06$ (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.83 (9H, s, *t*Bu), 2.43 (1H, d, $J=11.1$ Hz, H-6_{ax}), 2.62 (1H, ddd, $J=1.9$, 6.1, 11.1 Hz, H-6_{eq}), 3.43 (3H, s, OCH_3), 4.47 (2H, dd, $J=1.2$, 5.7 Hz, CH_2N), 4.60 (1H, dd, $J=3.2$, 6.1 Hz, H-5), 4.67 (1H, d, $J=3.2$ Hz, H-4), 4.83 (1H, d, $J=7.6$ Hz, OCHHO), 4.88 (1H, d, $J=7.6$ Hz, OCHHO), 6.21 (1H, br. t, $J=5.7$ Hz, NH), 6.63 (1H, d, $J=1.9$ Hz, H-2), 7.23–7.36 ppm (5H, m, ArH); ^{13}C NMR (125 MHz; $CDCl_3$): $\delta=-4.8$, -4.6, 18.0, 25.8, 33.8, 43.9, 56.4, 65.4, 75.9, 77.6, 93.8, 127.9, 128.2, 129.0, 135.5, 136.5, 137.7, 165.3, 173.0 ppm; LC-MS $[M-H]^-$ 446, $[M+H]^+$ 448, $R_t=4.87$ min; HRMS calcd for $C_{23}H_{34}NO_6Si$: MH^+, 448.2150. Found: MH^+, 448.2154.

(1*R*,4*R*,5*R*)-4-Hydroxy-1-methoxymethoxy-7-oxo-6-oxa-bicyclo-[3.2.1]oct-2-ene-3-carboxylic acid (2-phenoxy-ethyl)-amide (33a): TBDMS deprotection of **32a** (37 mg, 78 μmol) was achieved using the standard procedure described for **30a**. The product was purified by column chromatography (eluent: 390:15 *v/v* dichloromethane/methanol) to give the desired alcohol **33a** as a colourless oil (24 mg, 80%). R_F (390:15 *v/v* dichloromethane/methanol) = 0.40; $[\alpha]_D^{25}=-119.0$ ($c=0.22$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}=3332$ (N-H and O-H, br. str.), 2919 (m, satd. C-H str.), 1793 (s, C=O), 1655 (m, amide), 1619, 1599, 1587, 1537, 1496 cm^{-1} (m, amide + conjugated C=C + C=C ar); ^{1}H NMR (500 MHz; [D_6]acetone): $\delta=2.44$ (1H, d, $J=11.2$ Hz, H-6_{ax}), 2.68 (1H, ddd, $J=2.0$, 6.1, 11.2 Hz, H-6_{eq}), 3.39 (3H, s, OCH_3), 3.67 (2H, ddd, $J=2.3$, 5.7, 11.4 Hz, CH_2N), 4.11 (2H, dd, $J=5.7$, 11.4 Hz, OCH_2CH_2N), 4.54 (1H, d, $J=3.2$ Hz, H-4), 4.76 (1H, dd, $J=3.2$, 6.1 Hz, H-5), 4.82 (1H, d, $J=7.5$ Hz, CH_3OCHH), 4.90 (1H, d, $J=7.5$ Hz, CH_3OCHH), 6.87 (1H, d, $J=2.0$ Hz, H-2), 6.90–6.96 (3H, m, ArH), 7.25–7.30 (2H, m, ArH), 7.85 ppm (1H, br. s, NH); ^{13}C NMR (125 MHz; [D_6]acetone): $\delta=34.1$, 39.7, 56.1, 65.7, 67.0, 76.7, 78.5, 94.1, 115.4, 121.6, 130.3, 135.3, 138.1, 159.7, 166.3, 173.5 ppm; LC-MS $[M-H]^-$ 362, $[M+H]^+$ 364, $R_t=3.50$ min; HRMS calcd for $C_{18}H_{22}NO_7$: MH^+, 364.1391. Found: MH^+, 364.1391.

(1*R*,4*R*,5*R*)-4-Hydroxy-1-methoxymethoxy-7-oxo-6-oxa-bicyclo-[3.2.1]oct-2-ene-3-carboxylic acid phenethyl-amide (33b): TBDMS deprotection of **32b** (40 mg, 87 μmol) was achieved using the standard procedure described for **30a**. The product was purified by column chromatography (eluent: 39:1 *v/v* dichloromethane/methanol) to afford the desired alcohol **33b** as a colourless oil (24 mg, 80%). R_F (39:1 *v/v* dichloromethane/methanol) = 0.29; $[\alpha]_D^{25}=-182.9$ ($c=0.25$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}=3334$ (N-H and O-H, br. str.), 2940–2700 (w, satd. C-H str.) 1792 (s, C=O), 1653 (s, amide), 1617 (s, conjugated C=C), 1537 cm^{-1} (br., s, amide + C=C ar); ^{1}H NMR (400 MHz, [D_6]acetone): $\delta=2.41$ (1H, d, $J=11.2$ Hz, H-6_{ax}), 2.66 (1H, ddd, $J=1.7$, 6.0, 11.2 Hz, H-6_{eq}), 2.83 (2H, t, $J=7.3$ Hz, CH_2CH_2N), 3.38 (3H, s, OCH_3), 3.49 (2H, dt, $J=6.3$, 7.3 Hz, CH_2N), 4.48 (1H, d, $J=3.2$ Hz, H-4), 4.73 (1H, dd, $J=3.2$, 6.0 Hz, H-5), 4.79 (1H, d, $J=7.4$ Hz, CH_3OCHH), 4.88 (1H, d, $J=7.4$ Hz, CH_3OCHH), 5.20 (1H, br., OH), 6.77 (1H, d, $J=1.7$ Hz, H-2), 7.15–7.30 (5H, m, ArH), 7.59 ppm (1H, br., NH); ^{13}C NMR (100 MHz, [D_6]acetone): $\delta=$ 34.2, 36.2, 41.7, 56.1, 65.8, 76.7, 78.5, 94.1, 127.1, 129.3, 129.6, 135.6, 137.6, 140.3, 166.2, 173.6 ppm; LC-MS $[M-H]^-$ 346, $[M+H]^+$ 348, $R_t=3.48$ min; HRMS calcd for $C_{18}H_{22}NO_6$: MH^+, 348.1442. Found: MH^+, 348.1440.

(1*R*,4*R*,5*R*)-4-Hydroxy-1-methoxymethoxy-7-oxo-6-oxa-bicyclo-[3.2.1]oct-2-ene-3-carboxylic acid benzylamide (33c): TBDMS deprotection of **32c** (37.9 mg, 84.7 μmol) was achieved using the standard procedure described for **30a**. The product was purified by column chromatography (eluent 39:1 *v/v* dichloromethane/methanol) to afford the desired alcohol **33c** as a colourless oil (23 mg, 81%). R_F (390:10 *v/v* dichloromethane/methanol) = 0.31; $[\alpha]_D^{25}=-230.2$ ($c=0.13$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}=3337$ (N-H and O-H, br. str.), 2921, 2851 (w, satd. C-H), 1790 (s, C=O), 1654 (m, amide), 1618, 1537, 1497, 1454 cm^{-1} (m, amide + conjugated C=C + C=C ar); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.48$ (1H, d, $J=11.3$ Hz, H-6_{ax}), 2.65 (1H, ddd, $J=1.8$, 6.0, 11.3 Hz, H-6_{eq}), 3.40 (3H, s, OCH_3), 4.45 (1H, dd, $J=3.2$, 5.6 Hz, H-4), 4.51 (2H, br., CH_2N), 4.74 (1H, dd, $J=3.2$, 6.0 Hz, H-5), 4.79 (1H, d, $J=7.5$ Hz, OCHHO), 4.86 (1H, d, $J=7.5$ Hz, OCHHO), 6.72 (1H, d, $J=1.8$ Hz, H-2), 6.74 (1H, br., NH), 7.21–7.36 ppm (5H, m, ArH); ^{13}C NMR (125 MHz; $CDCl_3$): $\delta=33.9$, 43.9, 56.4, 65.9, 75.7, 77.7, 93.7, 127.9, 128.0, 129.0, 134.0, 136.8, 137.4, 166.7, 173.5 ppm; LC-MS $[M-H]^-$ 332, $[M+H]^+$ 334, $R_t=$ 3.42 min; HRMS calcd for $C_{17}H_{20}NO_6$: MH^+, 334.1285. Found: MH^+, 334.1279.

(1*R*,4*R*,5*R*)-1,4-Dihydroxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-ene-3-carboxylic acid (2-phenoxy-ethyl)-amide (34a): MOM deprotection of **33a** (13 mg, 0.04 mmol) was achieved using the general procedure described for **31a**. The product was purified by column chromatography (eluent: 390:15 *v/v* dichloromethane/methanol) to afford the desired diol **34a** as a colourless oil (8 mg, 70%). R_F (390:15 *v/v* dichloromethane/methanol) = 0.26; $[\alpha]_D^{25}=-166.3$ ($c=$ 0.04, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu}=3330$ (N-H and O-H, br. str.), 2933 (w, satd. C-H), 1784 (s, C=O), 1653 (m, amide), 1615, 1598, 1537, 1493 cm^{-1} (m, amide + conjugated C=C + C=C ar); ^{1}H NMR

(500 MHz; [D$_6$]acetone): $\delta = 2.35$ (1H, d, $J = 11.1$ Hz, H-6$_{ax}$), 2.43 (1H, ddd, $J = 1.8$, 5.8, 11.1 Hz, H-6$_{eq}$), 3.66 (2H, ddd, $J = 1.9$, 5.7, 11.4 Hz, CH_2N), 4.10 (2H, dd, $J = 5.7$, 11.4 Hz, OCH_2CH_2N), 4.52 (1H, dd, $J = 3.2$, 5.4 Hz, H-4), 4.70 (1H, dd, $J = 3.2$, 5.8 Hz, H-5), 5.24 (1H, d, $J = 5.4$ Hz, OH), 5.47 (1H, s, OH), 6.83 (1H, d, $J = 1.8$ Hz, H-2), 6.89–6.95 (3H, m, ArH), 7.24–7.29 (2H, m, ArH), 7.81 ppm (1H, br., NH); ^{13}C NMR (125 MHz; [D$_6$]acetone): $\delta = 36.6$, 39.7, 65.8, 67.0, 74.0, 76.5, 115.4, 121.6, 130.3, 134.6, 140.2, 159.8, 166.5, 175.9 ppm; LC-MS $[M-H]^-$ 318, $[M+H]^+$ 320, $R_t = 3.16$ min; HRMS calcd for $C_{16}H_{18}NO_6$: MH^+, 320.1129. Found: MH^+, 320.1128.

(1*R*,4*R*,5*R*)-1,4-Dihydroxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-ene-3-carboxylic acid phenethyl-amide (34b): MOM deprotection of **33b** (17.6 mg, 0.05 mmol) was achieved using the general procedure described for **31a**. The product was purified by column chromatography (eluent: 390:15 *v/v* dichloromethane/methanol) to afford the desired diol **34b** as a colourless oil (9 mg, 59%). R_F (390:15 *v/v* dichloromethane/methanol) = 0.23; $[\alpha]_D^{25} = -184.5$ ($c = 0.12$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3316$ (N-H and O-H, br. str.), 2950–2800 (w, satd. C-H str.), 1781 (s, C=O), 1652 (s, amide), 1614 (s, conjugated C=C), 1538 cm^{-1} (br., s, amide + C=C ar); ^{1}H NMR (500 MHz; [D$_6$]acetone): $\delta = 2.34$ (1H, d, $J = 11.0$ Hz, H-6$_{ax}$), 2.42 (1H, ddd, $J = 1.8$, 5.7, 11.0 Hz, H-6$_{eq}$), 2.84 (2H, t, $J = 7.3$ Hz, CH_2CH_2N), 3.50 (2H, dt, $J = 6.0$, 7.3 Hz, CH_2N), 4.48 (1H, d, $J = 3.2$ Hz, H-4), 4.69 (1H, dd, $J = 3.2$, 5.7 Hz, H-5), 5.21 (1H, br., OH), 5.47 (1H, br., OH), 6.76 (1H, d, $J = 1.8$ Hz, H-2), 7.16–7.20 (1H, m, ArH), 7.22–7.30 (4H, m, ArH), 7.61 ppm (1H, br., NH); ^{13}C NMR (125 MHz; [D$_6$]acetone): $\delta = 36.6$, 37.0, 42.0, 66.2, 74.3, 76.9, 127.4, 129.6, 130.0, 135.2, 140.0, 140.7, 166.7, 176.3 ppm; LC-MS $[M-H]^-$ 302, $[M+H]^+$ 304, $R_t = 3.13$ min; HRMS calcd for $C_{16}H_{18}NO_5$: MH^+, 304.1179. Found: MH^+, 304.1180.

(1*R*,4*R*,5*R*)-1,4-Dihydroxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-ene-3-carboxylic acid benzylamide (34c): MOM deprotection of **33c** (18 mg, 0.05 mmol) was achieved using the general procedure described for **31a**. The product was purified by column chromatography (eluent 19:1 *v/v* dichloromethane/methanol) to afford the desired diol **34c** as a colourless oil (11 mg, 64%). R_F (19:1 *v/v* dichloromethane/methanol) = 0.34; $[\alpha]_D^{25} = -174.9$ ($c = 0.20$, MeOH); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3332$ (N-H and O-H, br. str.), 2921 (w, satd. C-H), 1782 (s, C=O), 1651 (s, amide), 1616 (s), 1536 (s), 1497 (w), 1454 cm^{-1} (amide + conjugated C=C + C=C ar); ^{1}H NMR (500 MHz; [D$_6$]acetone): $\delta = 2.37$ (1H, d, $J = 11.0$ Hz, H-6$_{ax}$), 2.44 (1H, ddd, $J = 1.8$, 5.7, 11.0 Hz, H-6$_{eq}$), 4.46 (1H, dd, $J = 5.9$, 15.0 Hz, CH*H*N), 4.51 (1H, dd, $J = 6.2$, 15.0 Hz, C*H*HN), 4.57 (1H, dd, $J = 3.2$, 5.4 Hz, H-4), 4.72 (1H, dd, $J = 3.2$, 5.7 Hz, H-5), 5.23 (1H, d, $J = 5.4$ Hz, 4-OH), 5.50 (1H, s, 1-OH), 6.85 (1H, d, $J = 1.8$ Hz, H-2), 7.21–7.26 (1H, m, ArH), 7.28–7.34 (4H, m, ArH), 7.97 ppm (1H, br., NH); ^{13}C NMR (125 MHz; [D$_6$]acetone): $\delta = 36.6$, 43.6, 65.8, 74.0, 76.6, 127.8, 128.4, 129.2, 134.8, 140.0, 140.2, 166.2, 176.0 ppm; LC-MS $[M-H]^-$ 288, $[M+H]^+$ 290, $R_t = 3.10$ min; HRMS calcd for $C_{15}H_{16}NO_5$: MH^+, 290.1023. Found: MH^+, 290.1027.

(1*R*,4*R*,5*R*)-1,4,5-Trihydroxy-3-(2-phenoxy-ethylcarbamoyl)-cyclohex-2-enecarboxylic acid (14): Lactone hydrolysis of **34a** (4 mg, 13 μmol) was achieved using the general procedure described for **7** to give the desired acid **14** as a white solid (10.1 μmol, 81%). $[\alpha]_D^{25} = -41.7$ ($c = 0.09$, H_2O); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3289$ (N-H, O-H and O-H acid, br. str), 2928 (w, satd. C-H), 1723 (m, C=O acid), 1662 (m, amide), 1598, 1541, 1494 cm^{-1} (m, amide + conjugated C=C + C=C ar); ^{1}H NMR (500 MHz; D_2O): $\delta = 1.89$ (1H, dd, $J = 4.5$, 13.6 Hz, H-6$_{eq}$), 1.94 (1H, dd, $J = 11.0$, 13.6 Hz, H-6$_{ax}$), 3.42 (1H, ddd, $J = 4.7$, 5.6, 14.4 Hz, CH*H*N), 3.57 (1H, ddd, $J = 4.5$, 5.6, 14.4 Hz, C*H*HN), 3.75 (1H, ddd, $J = 4.5$, 7.6, 11.0 Hz, H-5), 4.04–4.11 (2H, m, OCH_2), 4.17 (1H, dd, $J = 1.2$, 7.6 Hz, H-4), 5.79 (1H, d, $J = 1.2$ Hz, H-2), 6.64–6.90 (3H, m, ArH), 7.19 ppm (2H, t, $J = 8.0$ Hz, ArH); ^{13}C NMR (125 MHz; D_2O): $\delta = 38.1$, 39.1, 66.2, 69.0, 70.5, 72.8, 114.9, 121.6, 129.7, 131.3, 138.2, 157.9, 169.6, 177.8 ppm; LC-MS $[M+H]^+$ 338, $R_t = 2.73$ min; HRMS calcd for $C_{16}H_{20}NO_7$: MH^+, 338.1234. Found: MH^+, 338.1228.

(1*R*,4*R*,5*R*)-1,4,5-Trihydroxy-3-phenethylcarbamoyl-cyclohex-2-enecarboxylic acid (15): Lactone hydrolysis of **34b** (6.0 mg, 19.8 μmol) was achieved using the general procedure described for **7** to give the desired acid **15** as a white solid (14.2 μmol, 72%). $[\alpha]_D^{25} = -112.9$ ($c = 0.04$, H_2O); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3298$ (N-H, O-H and O-H acid, br. str.), 1716 (C=O acid), 1661 (amide), 1603, 1539, 1497, 1455 cm^{-1} (amide + conjugated C=C + C=C ar); ^{1}H NMR (500 MHz; D_2O): $\delta = 1.99$ (1H, ddd, $J = 1.2$, 4.9, 13.6 Hz, H-6$_{eq}$), 2.03 (1H, dd, $J = 10.5$, 13.6 Hz, H-6$_{ax}$), 2.74–2.85 (2H, m, CH_2CH_2N), 3.37–3.55 (2H, m, CH_2CH_2N), 3.83 (1H, ddd, $J = 4.9$, 7.7, 10.5 Hz, H-5), 4.21 (1H, dd, $J = 1.6$, 7.7 Hz, H-4), 5.89 (1H, dd, $J = 1.2$, 1.6 Hz, H-2), 7.17–7.22 (3H, m, ArH), 7.25–7.29 ppm (2H, m, ArH); ^{13}C NMR (125 MHz; D_2O): $\delta = 34.3$, 38.0, 40.3, 68.8, 70.5, 72.5, 126.5, 128.5, 129.0, 130.3, 139.0, 139.1, 169.2, 176.8 ppm; HRMS calcd for $C_{16}H_{19}NO_6Na$: MNa^+, 344.1105. Found: MNa^+, 344.1108.

(1*R*, 4*R*, 5*R*)-3-Benzylcarbamoyl-1,4,5-trihydroxy-cyclohex-2-enecarboxylic acid (16): Lactone hydrolysis of **34c** (7.0 mg, 24 μmol) was achieved using the general procedure described for **7** to give the desired acid **16** as a white solid (8.8 μmol, 36%). $[\alpha]_D^{25} = -172.8$ ($c = 0.02$, H_2O); $\nu_{max.}$ (ATR): $\tilde{\nu} = 3310$ (N-H, O-H and O-H acid, br. str.), 2926 (w, satd. C-H), 1721 (m, C=O acid), 1662 (m, amide), 1608, 1539, 1497, 1454 cm^{-1} (amide + conjugated C=C + C=C ar); ^{1}H NMR (500 MHz; D_2O): $\delta = 2.03$ (1H, ddd, $J = 1.2$, 4.4, 13.6 Hz, H-6$_{eq}$), 2.08 (1H, dd, $J = 10.9$, 13.6 Hz, H-6$_{ax}$), 3.90 (1H, ddd, $J = 4.4$, 7.5, 10.9 Hz, H-5), 4.33 (1H, dd, $J = 1.7$, 7.5 Hz, H-4), 4.40 (2H, $J = 4.2$ Hz, CH_2N), 6.23 (1H, dd, $J = 1.2$, 1.7 Hz, H-2), 7.23–7.30 (3H, m, ArH), 7.30–7.35 ppm (2H, m, ArH); ^{13}C NMR (125 MHz; D_2O): $\delta = 38.1$, 43.0, 69.0, 70.6, 72.7, 127.0, 127.4, 128.7, 131.0, 137.7, 138.7, 169.4, 177.3 ppm; LC-MS $[M-H]^-$ 306, $[M+H]^+$ 308, $R_t = 2.69$ min; HRMS calcd for $C_{15}H_{17}NO_6Na$: MNa^+, 330.0948. Found: MNa^+, 330.0940.

Synthesis of 3-Dehydroquinate. 3-Dehydroquinate was synthesised (as the potassium salt) from (−)-quinic acid using the method described by Le Sann et al.[24] Calibration of 3-dehydroquinate solutions (in water) were determined from the absorbance difference at 234 nm resulting from the total conversion of an aliquot of 3-dehydroquinate to 3-dehydroshikimate by 1 μL of *S. coelicolor* type II dehydroquinase (5.1 mg mL^{-1}) using the kinetic assay described below.

Kinetic assay for type II dehydroquinases. *S. coelicolor* and *M. tuberculosis* type II dehydroquinases were purified as described previously.[10,7] The enzyme stocks were diluted to 5.1 μg mL^{-1} (*S. coelicolor* type II dehydroquinase) and 160 μg mL^{-1} (*M. tuberculosis* type II dehydroquinase). The enzymes were assayed by monitoring the increase in absorbance at 234 nm due to the enone-carboxylate chromophore of 3-dehydroshikimate (**2**: $\varepsilon = 1.2 \times 10^4$ M^{-1} cm^{-1}). The assays were performed at 25 °C in Tris-HCl buffer (0.05 M, pH 7.0). The assay was initiated by the addition of x μL of substrate (3-dehydroquinate, potassium salt) solution in water to a solution containing 100 μL of buffer (0.5 M, pH 7), enzyme solution (10 μL), y μL of inhibitor solution in water, $(890-x-y)$ μL of water. Kinetic parameters (K_m and k_{cat}) for the type II dehydroquinase enzymes were obtained by measuring the initial rates of reaction over a range of substrate concentrations (typically $0.25K_m - 10K_m$). The data was fitted to the Michaelis-Menton equation using the software GraFit by least-squares fitting (supporting information).[21] The values of K_m and V_{max} were also determined using this software and the catalytic constant, k_{cat} was calculated from the latter value and the total enzyme concentration in the assay.

Kinetic data for inhibition studies were obtained by measuring the initial rates of reaction over a range of inhibitor concentrations (4–5 different concentrations) at 4–5 different substrate concentra-

tions ($0.5\,K_m - 5\,K_m$). The inhibition constants (K_i) and the standard deviations associated with these values were determined using a least-squares fitting by the software GraFit.[21] GraFit was also used to carry out a F-test statistical analysis on the data, used to confirm that the data satisfied a competitive inhibition model.[21]

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