The global population is anticipated to increase substantially in the next few decades, reaching 9–10 billion by 2050. This population expansion will place further demands on already polarized global food production. To meet these demands, effective crop protection strategies will become increasingly essential to maintain and improve yield from arable land; however, agrochemical effectiveness is being compromised by resistance. Over 60% of current herbicidal agents involve modes of action (MoAs) that are already associated with serious resistance issues. Combined with loss of arable land, urgent innovation is needed in the development of crop protection agents to meet the needs of future food security. Specifically, in order to bypass developing resistance, there is a critical requirement for new agrochemicals that operate via novel MoAs.

The most prominent approaches for lead generation in agrochemical discovery are designed libraries based on a novel target hypothesis, scaffold hopping from competitor assets, and natural-product-based leads. De novo target identification can lead to a new MoA but carries substantial risk and is both time consuming and costly. Scaffold hopping builds upon a large web of biological knowledge, but target and MoA novelty is low. However, the molecular complexity and rich diversity of natural products offers an attractive strategy for the discovery of a novel MoA. This strategy has seen notable success with several important herbicides originating from natural phytotoxins, such as the highly successful 4-hydroxyphenyl pyruvate dioxygenase (HPPD) inhibitor mesotrione (1, Fig. 1a) and the highly successful 4-hydroxyphenyl pyruvate dioxygenase (HPPD) inhibitor mesotrione (1, Fig. 1a).

Alternaric acid (2, Fig. 1b), first isolated in 1949 by Brian and co-workers, is a phytotoxin produced by the phytopathogenic fungus *Alternaria solani*, which is the causal fungus of early blight disease in potato and tomato crops. Early biological assessment identified 2 as possessing herbicidal and fungicidal activity. The first total synthesis and stereochemical determination of alternaric acid was achieved in 1994 by Ichihara and co-workers in 29 steps (0.001% yield), giving 16 mg of 2 (refs. 16,17). The same year, Ichihara and co-workers reported that 2 exhibited phytotoxic activity against tomato seedlings. The first total synthesis and stereochemical determination of alternaric acid was achieved in 1994 by Ichihara and co-workers in 29 steps (0.001% yield), giving 16 mg of 2 (refs. 16,17). The same year, Ichihara and co-workers reported that 2 exhibited phytotoxic activity against tomato seedlings. However, the MoA remains unknown and a limited structure–activity relationship (SAR) has been reported: the only data relate to an observed loss of activity when the C10 methylene or C15 hydroxyl motifs are removed (Fig. 1b). The principal issue preventing systematic analysis of 2 as a herbicidal lead has been the lack of synthetic access to the natural product and the lack of an approach to systematic editing of the structure to fully explore the SAR.
Here we report a practical, scalable synthesis of alternaric acid (2) via a key intermediate from which crucial structural modifications can be achieved in only two steps. This has allowed extensive exploration of molecular space to establish the SAR and enabled the design and synthesis of analogues. In turn, this has led to the discovery of a new class of structurally less complex and more developable lead compounds that dispays superior herbicidal activity and with a broader spectrum profile operating via an unidentified MoA (Fig. 1b).

### Results and discussion

#### Objectives

The primary objective of this synthetic campaign was to produce sufficient quantities of 2 to enable broad biological evaluation and establish a meaningful SAR for this elusive target. This is an early-stage project with the key aim of establishing the viability of the alternaric-acid-mediated phenotypic response as a target for further development. A cursory analysis of 2 immediately highlights the triketone motif, which is reminiscent of similar warheads in other herbicides, such as 1 (ref. 1). We therefore anticipated that this unit could have a major impact on activity. Consequently, our strategy was to build 2 from the union of the ‘head group’ 4 with the larger carboxylic acid ‘tail’ component 3 (Fig. 2a). This would allow rational analysis of the impact of each fragment and their constituent functional groups.

#### Synthesis of alternaric acid

Our optimized synthetic route, built on previous work by Trost and co-workers16, is described in Fig. 2b (see Supplementary Information for full details). Beginning with commercially available alcohol 5, one-pot Swern oxidation–Wittig olefination afforded the unsaturated ester 6 in 93% yield. A one-pot debromination–dehydrobromination then provided the vinyl bromide 7, which was used in an sp2–sp3 Suzuki–Miyaura2 coupling with alkyl borane 9 (accessed via hydroboration of 8) to yield 10 in 96%. The use of xantphos25 as a ligand was found to be critical for the success of the coupling (Supplementary Table 1). Sharpless dihydroxylation26 of 10 yielded the corresponding diol 11 in 93% yield as a single diastereoisomer. Diol 11 was temporarily protected as the acetoneide in a one-pot procedure during tert-butylimidethylsilyl removal to give 12, which underwent Grieco elimination27 of the primary alcohol to deliver alkene 13. Acetonide protection afforded the free diol 14. All yields in this sequence were >90% per step. From 13, our initial plan was for temporary diol protection as a carbonate at this stage, which would be removed during ester saponification in the last step in the route; however, the Grieco elimination failed in the presence of the carbonate, and the free diol was also incompatible with the elimination, necessitating this protecting group switch28.

Using 14, we employed Trost’s Alder–ene-type reaction22,27,28 using catalytic CpRu(MeCN)3PF6 (Cp = cyclopentadienyl) with alkylne 15, which was prepared in one step from the corresponding commercially available carboxylic acid. This provided skipped diene 16 in 63% yield. Protection of diol 16 as the carbonate through triphosphene was accomplished in 92% yield and selective hydrolysis of the Fmoc ester gave key intermediate 18.

Head group tricarbonyl 4 was prepared in two steps from commercially available enantiopure starting material and coupled with acid 18 in an esterification/Fries-type rearrangement sequence29 to give compound 19. Final hydrolysis of both the carbonate and the methyl ester successfully afforded alternaric acid (2) in only 12 steps with 21% overall yield. The structure and absolute stereochemistry was unambiguously confirmed by obtaining an X-ray structure of this natural product.

#### Biological screening of alternaric acid

The herbicidal activity of alternaric acid was first reported in 194912–14 but very limited progress has been made with this asset due to the difficulties in obtaining material. However, the above route enabled production of sufficient quantities of pure 2 that allowed evaluation of its biological activity using phenotypic assays at 1,000 g ha⁻¹ against a range of weed species (Fig. 3). At the 1,000 g ha⁻¹ rate, 2 demonstrated good levels of herbicidal activity with almost complete control of the target for dicot weeds (Amaranthus retroflexus and Stellaria media) both post- and pre-emergence. A high level of phytotoxicity was also observed against the monocot weed Digitaria sanguinalis pre-emergence with necrosis and stunting symptomology dominant. Interestingly, despite the head group 2 having similarities to mesotrione (1) and related herbicides, bleaching, a symptom characteristic of HPPD inhibition, was not observed. These observations were further supported by computational modelling using the Arabidopsis HPPD crystal structure model, which indicated low likelihood of activity via this signalling axis (Fig. 4). Control processes confirmed that tail group 3 and head group 4 were inactive, indicating that 2 was not acting as a pro-cide (a labile precursor to a biologically active herbicide) and that both units were essential for phytotoxicity. Further assessment through a proprietary MoA phenotypic screening platform against a broad series of defined targets could not identify the mode of action of 2. Collectively, these data suggested that 2 was potentially exhibiting its herbicidal effects via an unknown MoA.

#### Development of an herbicidal lead compound from alternaric acid

Despite promising activity and the potential for unknown MoA, an herbicidal solution is only useful if a tractable lead can be identified for development. The structural complexity of 2 is incompatible with the requirements for production on a large scale and at acceptable cost30. The synthetic strategy outlined above was therefore expanded into a bifurcated SAR and discovery campaign (Fig. 5a). The complexity of the tail structure 3 was the target of focused libraries designed to extract information about the SAR chemical space. The purpose of this was to establish the essential contributors to potency and the minimum structural requirements to maintain activity without crossover to other signalling axes, such as HPPD. The selection of carboxylic acids was guided by pre-screening to align with modern concepts of agrichemical design,
Fig. 2 | Synthetic strategy and total synthesis of alternaric acid. a. The main disconnections underpinning the synthetic strategy indicating the main components for SAR analysis. b. Practical and scalable synthesis of alternaric acid (2). Transformations from compounds 5–18 performed on the gram scale. 9-BBN, 9-borabicyclo[3.3.1]nonane; Cp, cyclopentadienyl; CSA, camphorsulfonic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP, 4-dimethylaminopyridine; (DHQD)2PHAL, hydroquinidine 1,4-phthalazinediyl diether; DMSO, dimethylsulfoxide; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; DMAP, 4-dimethylaminopyridine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP, 4-dimethylaminopyridine; (DHQD)2PHAL, hydroquinidine 1,4-phthalazinediyl diether; DMSO, dimethylsulfoxide; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; TBDMS, tert-butylimethylsilyl; TFA, trifluoroacetic acid.

including application of standard physicochemical filters (molecular weight, lipophilicity) as well as commercial availability of the chosen fragments. The head group 4, while lacking potency as described above, was simple enough for development if suitable modifications could be made to re-establish potency. Accordingly, 4 was the subject of structural elaboration via parallel synthesis to re-establish activity via the new MoA, again avoiding target crossover. The combined ‘bottom-up, top-down’ approach was envisioned to allow the combination of datasets and enable the identification of developable lead series for this unknown MoA.

The libraries of compounds (see Supplementary Information for full details) were again assessed for pre- and post-emergence phytotoxicity in phenotypic screens at 1,000 g ha⁻¹ against four weed species, with 2 and commercial herbicides used as controls for comparison. Illustrative excerpts from this analysis are provided in Fig. 5b.

All analogues showed higher levels of weed control when applied post-emergence. Inverting the stereochemistry of the methyl group had little impact (22 versus 2), while deletion (21) or homologation (22) had a slightly negative impact. A more pronounced loss of activity was observed with ketone (23) and lactam (24) analogues of 21. This suggests that the presence of the methyl substituent in the head group plays an important mechanistic role, with very little room for modification of this motif away from that found in the natural product.

Interestingly, the diversity screen revealed several compounds with attractive structural simplicity, which exhibited good phytotoxicity, despite being slightly less active than the head group series (see
Supplementary Information for full details). In general, compounds bearing a heterocycle (41, 42, 43) showed good herbicidal activity, especially when applied post-emergence. Sulfonamide 47 also demonstrated high herbicidal activity. Notably, the simple amide derivative 48 exhibited excellent phytotoxic activity both pre- and post-emergence, demonstrating increased potency compared with the natural product progenitor 2 and very similar to the commercial standards included in the test. The summarized key learnings from this campaign were twofold: (1) the head group is essential for activity and editing of this is not tolerated; and (2) the tail component can be edited to generate considerably fewer complex analogues, which exhibit similar or greater activity as compared to the natural product.

Based on these findings, we undertook a second-round amide-focused library synthesis based on 48 (see Supplementary Information, Scheme 3). Overall, all compounds demonstrated good activity, especially post-emergence (Supplementary Table 6). Several compounds in the amide variation subset (Fig. 6) were particularly promising. Specifically, cyclic amides such as the morpholine amide 55 (not shown; see Supplementary Information and Supplementary Tables 6 and 8), azetidine amide 59 and indoline amide 62 reached >90% control of at least two weed species in these phenotypic screens; however, compound 48 remained the most active of all compounds assessed.

Compounds 48, 59, and 62 were selected for progression to higher-tier profiling phenotypic screening with larger plants—the data are compared to those of alternaric acid 2 (Fig. 6 and Supplementary Table 7). In this assay, the phytotoxicity was assessed visually against six weed species at different rates. Compound 48 retained notable post-emergence activity even at 500 g ha⁻¹ against both broad-leaf and grass weeds, compared with the natural product starting point (2), which showed good levels of control only against Amaranthus spp. Additionally, compound 59 performed well in this assay with high phytotoxicity post- and pre-emergence and activity being maintained at 500 g ha⁻¹. Compounds 48 and 59 both resulted in bleaching and chlorosis symptoms when tested in the higher-tier assay. Since bleaching is a characteristic symptom associated with HPPD inhibition, this observation prompted us to evaluate in vitro activity of these compounds against the HPPD plant enzyme (Supplementary Table 8); however, low binding affinity was observed in this assay for most of the synthetic analogues tested. This suggests that other factors could contribute to the observed biological efficacy, in addition to HPPD inhibition. Furthermore, compound 62, which exhibited very encouraging weed control, especially at the 1,000 g ha⁻¹ rate (Fig. 6), did not induce bleaching, with stunting and necrosis observed instead, like the natural product 2 (Supplementary Table 7). Compounds 48, 59, and 62 also displayed a lack of HPPD activity in biochemical in vitro assays against plant HPPD enzyme (Supplementary Table 8). Collectively, these results led us to hypothesize that the amide derivatives 48, 59, and 62 may be operating via a different MoA or perhaps a combination of HPPD activity coupled to an unknown MoA, as observed for alternaric acid 2. Binding to HPPD was again evaluated via modelling (Fig. 7), which suggested a poor interaction, offering support for the as yet unidentified MoA. Lastly, a preliminary comparative analysis of the data also indicated some potential crop injury to Zea mays (Fig. 6 and Supplementary Table 7), which could potentially be a useful signal for development of a burndown concept.

In summary, an extensive synthetic study around the natural product and phytotoxin alternaric acid has been accomplished. The development of a robust 12-step gram-scale synthesis to produce quantities of the natural product allowed extensive biological profiling in vivo. This confirmed a narrow spectrum regarding biological
efficacy, coupled with structural complexity owing to the presence of several polar groups that could impact bioavailability and in planta stability. Through the gram-scale synthesis of a key intermediate, the preparation of natural product derivatives was carried out efficiently, enabling SAR investigations of the head group moiety. With the methyl-substituted dihydro-pyran-dione identified as a key constituent for herbicidal activity, a range of analogues were designed and synthesized with a view to simplify the alkyl chain moiety of alternaric acid whilst retaining good phytotoxicity. Gratifyingly, three new structurally simpler amide derivatives were found to exhibit excellent herbicidal activity, as shown in Fig. 5. Further studies are ongoing to optimize these leads for commercial application.

Fig. 5 | Lead development strategy and biological screening data of selected examples from the lead library. a, Bifurcated ‘bottom-up, top-down’ approach to lead generation. b, Phytotoxicity evaluation of selected analogues. Compounds are tested for pre- and post-emergence activity against four weed species at 1,000 g ha$^{-1}$. Negative controls were untreated checks where no phytotoxicity (0%) was observed. Test species: Amaranthus retroflexus (AMARE), Lolium perenne (LOLPE), Stellaria media (STEME), Digitaria sanguinalis (DIGSA).
properties and broader spectrum than the original natural product. These promising compounds represent a class of lead compounds for herbicidal discovery with an unknown mode of action related to that of alternaric acid. The very early-stage data invite further investigation of the molecular basis for phenotypic response before crop selectivity or specificity can be established.

**Methods**

**General procedure for esterification/Fries-type rearrangement**

A mixture of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI; 1.1 equiv), the appropriate head group (1.1 equiv), 4-dimethylaminopyridine (DMAP; 1.1 equiv) and the appropriate carboxylic acid (1.0 equiv) was dissolved in anhydrous MeCN or CH$_2$Cl$_2$ (0.20 M) and the resulting mixture was stirred at r.t. for 24 h. The reaction mixture was diluted with H$_2$O, acidified with 2 M aqueous HCl and extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel) to afford the desired product.

**Compound 6**

Dimethylsulfoxide (9.70 ml, 136 mmol, 3.0 equiv) was added dropwise to a solution of (COCl)$_2$ (5.80 ml, 68.1 mmol, 1.5 equiv.) in anhydrous CH$_2$Cl$_2$ (100 ml) at −78 °C and the resulting mixture stirred for 30 min. A solution of (S)-2-Methylbutan-1-ol (5) (4.90 ml, 45.4 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (10 ml) was added dropwise and the mixture stirred at −78 °C for 1 h. Et$_3$N (31.6 ml, 227 mmol, 5.0 equiv.) was added and the reaction mixture allowed to warm to r.t. with stirring for 1.5 h. A solution of methyl (triphenylphosphoranylidene)acetate (15.2 g, 45.4 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (40 ml) was added and the resulting mixture stirred at r.t. for 24 h. The reaction mixture was acidified with 10% aqueous HCl and extracted with CH$_2$Cl$_2$. The organic extracts were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 5% Et$_2$O in petroleum ether) to afford the desired product as a colourless oil (5.99 g, 93%).

**Compound 7**

Bromine (86 µl, 0.70 mmol, 1.0 equiv.) was added dropwise to a solution of 6 (100 mg, 0.70 mmol, 1.0 equiv.) in anhydrous CH$_2$Cl$_2$ (4.7 ml) at 0 °C and stirred. The mixture was allowed to warm to r.t. After 2 h, the mixture was cooled to 0 °C and Et$_3$N (0.49 ml, 3.52 mmol, 5.0 equiv.) was added. The resulting mixture was stirred at r.t. for 14 h. The heterogeneous mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 5% Et$_2$O in petroleum ether) to afford the desired product as a colourless oil (112 mg, 72%).

**Compound 10**

To a solution of 9-borabicyclo[3.3.1]nonane (2.0 M in THF, 88.4 ml, 44.2 mmol, 2.0 equiv.) in anhydrous THF at 0 °C was added (allyloxy) (tert-butyldimethylsilyl)dimethylsilane (9.66 ml, 44.2 mmol, 2.0 equiv.) and the mixture was stirred at r.t. After 2 h, H$_2$O (2.0 ml, 111 mmol, 5.0 equiv.) was added and the mixture transferred to a flask containing a solution...
of vinyl bromide (4.89 g, 22.1 mmol, 1.0 equiv.), Pd(OAc)₂ (247 mg, 1.10 mmol, 0.05 equiv.), zanphors (1.27 g, 2.20 mmol, 0.1 equiv.) and K₂PO₄ (14.1 g, 66.3 mmol, 3.0 equiv.) in THF (100 ml). The resulting mixture was heated to reflux for 14 h. The mixture was allowed to cool to r.t., then diluted with H₂O and extracted with Et₂O. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–5% Et₂O in petroleum ether) to afford the desired product as a colourless oil (6.67 g, 96%).

**Compound 11**
A mixture of potassium carbonate (8.76 g, 63.4 mmol, 3.0 equiv.), potassium ferricyanide (20.9 g, 63.4 mmol, 3.0 equiv.), hydroquinidine 1,4-phthalazinediyl diether (823 mg, 1.06 mmol, 0.05 equiv.), osmium tetroxide (5.60 ml, 0.85 mmol, 0.04 equiv.) in H₂O, methanesulfonamide (2.11 g, 21.1 mmol, 1.0 equiv.) and compound 10 (6.65 g, 21.1 mmol, 1.0 equiv) in BuOH/H₂O (1:1, 200 ml, 0.11 M) was stirred for 24 h at 0 °C. The mixture was diluted with saturated aqueous sodium dithionite and stirred until the mixture became homogeneous, then extracted with Et₂O. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 40% Et₂O in petroleum ether) to afford the desired product as a colourless oil (6.69 g, 93%).

**Compound 12**
Camphorsulfonic acid (173 mg, 0.75 mmol, 0.2 equiv.) was added to a solution of compound 11 (1.30 g, 3.73 mmol, 1.0 equiv.) and 2,2-dimethoxypropane (4.6 ml, 37.3 mmol, 10 equiv.) in acetonitrile (20 ml) at r.t. The mixture was stirred for 24 h at r.t. before cooling to 0 °C and addition of pyridine hydrofluoride (1.9 ml, 22.4 mmol, 6.0 equiv) and stirring for 1 h. The mixture was diluted with H₂O and extracted with Et₂O. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 20–50% Et₂O in petroleum ether) to afford the desired product as a colourless oil (919 mg, 90%).

**Compound 13**
Tri-n-butylphosphine (2.84 ml, 11.4 mmol, 2.0 equiv.) was added to a solution of compound 12 (1.56 g, 5.69 mmol, 1.0 equiv.) and o-nitrophenylselenocyanate (2.58 g, 11.4 mmol, 2.0 equiv.) in anhydrous THF (30 ml). The mixture was stirred for 12 h at r.t. before addition of NaHCO₃ (955 mg, 11.4 mmol, 2.0 equiv.) followed by the addition of H₂O₂ in H₂O (30% w/w, 5.91 ml, 56.9 mmol, 10 equiv.). The mixture was stirred for 2 h then treated with 10% aqueous HCl and extracted with Et₂O. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–10% Et₂O in petroleum ether) to afford the desired product as a colourless oil (1.32 g, 91%).

**Compound 14**
Compound 13 (1.32 g, 5.15 mmol, 1.0 equiv.) was dissolved in anhydrous CH₂Cl₂ (15 ml), trifluoroacetic acid (8.0 ml) and H₂O (0.6 ml) at r.t. The mixture was stirred for 12 h at r.t., then concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 25% Et₂O in petroleum ether) to afford the desired product as a colourless oil (1.09 g, 99%).

**Compound 15**
A solution of 4-pentyenoic acid (1.13 g, 11.5 mmol, 1.0 equiv.), 9-fluorenylmethanol (2.48 g, 12.7 mmol, 1.1 equiv.), DCC (3.56 g, 17.3 mmol, 1.5 equiv.) and DMAP (141 mg, 1.15 mmol, 0.1 equiv.) in anhydrous CH₂Cl₂ (50 ml) was stirred at r.t. for 15 h. The mixture was filtered, then concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 10% Et₂O in petroleum ether) to afford the desired product as a beige solid (2.64 g, 83%).

**Compound 16**
Compounds 14 (500 mg, 2.33 mmol, 1.0 equiv.), 15 (773 mg, 2.80 mmol, 1.2 equiv.) and CpRu(MeCN)₃PF₆ (101 mg, 0.23 mmol, 0.1 equiv.) were dissolved in anhydrous MeOH (8.0 ml) and the mixture stirred at r.t. for 12 h. The mixture was filtered through Celite then concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 30–50% Et₂O in petroleum ether) to afford the desired product as a yellow oil (724 mg, 63%).

**Compound 17**
A solution of triphosgene (795 mg, 2.68 mmol, 1.0 equiv.) in anhydrous CH₂Cl₂ (3.0 ml) was added to a solution of compound 16 (1.32 g, 2.68 mmol, 1.0 equiv.) and pyridine (1.3 ml, 16.1 mmol, 6.0 equiv.) in anhydrous CH₂Cl₂ (10 ml) at –78 °C. The resulting mixture was stirred for 3 h at 0 °C then 2 h at r.t. The mixture was quenched with aqueous NH₄Cl and extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 30–50% Et₂O in petroleum ether) to afford the desired product as a yellow oil (1.38 g, 99%).

**Compound 18**
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.14 ml, 0.94 mmol, 1.1 equiv) was added to a solution of compound 17 (443 mg, 0.85 mmol, 1.0 equiv) in anhydrous CH₂Cl₂ (13 ml) and the mixture stirred at r.t. for 3 h. The mixture was diluted with H₂O, acidified with 1 M aqueous HCl and extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 20% EtOAc in CH₂Cl₂) to afford the desired product as a yellow oil (282 mg, 97%).

**Compound 19**
A mixture of EDCI (88.9 mg, 0.71 mmol, 1.1 equiv.), compound 4 (88.9 mg, 0.71 mmol, 1.1 equiv.) and DMAP (200 mg, 1.59 mmol, 1.0 equiv.) was dissolved in anhydrous CH₂Cl₂ (4.0 ml) and the resulting mixture was stirred at r.t. for 48 h. The reaction mixture was diluted with H₂O, acidified with 2 M aqueous HCl, and extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄, filtered and
concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 10–20% EtOAc in CH₂Cl₂) to afford the desired product as a yellow oil (210 mg, 79%).

**Compound 4**

To a solution of freshly distilled diisopropylamine (2.08 ml, 14.8 mmol, 3.5 equiv.) in anhydrous THF at 0 °C was added dropwise n-BuLi (2.5 M in hexane, 5.92 ml, 14.8 mmol, 3.5 equiv.). The resulting LDA solution was stirred at 0 °C for 20 min. The mixture was cooled to −78 °C and n-BuOAc (1.70 ml, 12.7 mmol, 3.0 eq) was added dropwise. The resulting mixture was stirred for 40 min at −78 °C. A solution of methyl (10)-3-hydroxybutanoate (500 mg, 4.23 mmol, 1.0 equiv.) in anhydrous THF (20 ml) was added dropwise to the mixture at −78 °C. The reaction was allowed to warm to −30 °C and stirred for 2 h then allowed to warm to −15 °C and stirred for 1 h. The reaction mixture was slowly quenched with H₂O, acidified with 1 M aqueous HCl and extracted with Et₂O. The organic extracts were dried over Na₂SO₄, filtered and concentrated with H₂O. The resulting mixture was extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was dissolved in anhydrous CH₂Cl₂ (20 ml) and the solution cooled to 0 °C. Trifluoroacetic acid (0.33 ml, 4.23 mmol, 1.1 equiv.) was added dropwise, the mixture was allowed to warm to r.t. and stirred for 4 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by column chromatography (silica gel, 0–5% methanol in CH₂Cl₂) to afford the desired product as a beige solid (472 mg, 89%).

**Compound 2**

Compound 19 (30 mg, 0.067 mmol, 1.0 equiv.) was dissolved in 2 M aqueous LiOH/MeOH/THF (11:2; 2 ml) and the mixture stirred at r.t. for 15 min. The mixture was neutralized with 1 M aqueous HCl and the organic solvents were removed under reduced pressure. The resulting mixture was extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The desired product was obtained without further purification as a white solid (25.0 mg, 91%).

**Data availability**

All data generated during this study are included in this published article (and its Supplementary Information files). Analytical data generated during the current study are also available in the University of St Andrews repository. [https://doi.org/10.17630/c41bc9f9-57cc-4f2-94cf-c9f7559554c5](https://doi.org/10.17630/c41bc9f9-57cc-4f2-94cf-c9f7559554c5). Crystallographic data for compound 2 are available from the Cambridge Crystallographic Data Centre (CCDC) under deposition number 2169366.

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Author contributions
E.M.I. conceived and conducted the synthetic chemistry. J.C.-B. guided compound design and coordinated the biological screening. A.M.Z.S performed and analysed X-ray crystallography. E.M.I, J.C-B. and A.J.B.W. wrote the manuscript. A.J.B.W. conceived the chemistry and directed the project.

Competing interests
The authors declare no competing interests.

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