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Total Synthesis of Potent Antifungal Marine Bisoxazole Natural Products Bengazoles A and B

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Abstract: The bengazoles are a family of marine natural products that display potent antifungal activity and a unique structure, containing two oxazole rings flanking a single carbon atom. Total syntheses of bengazole A and B are described, which contain a sensitive stereogenic centre at this position between the two oxazoles. Additionally, the synthesis of 10-*epi*-bengazole A is reported. Two parallel synthetic routes were investigated, relying on construction of the 2,4-disubstituted oxazole under mild conditions and a diastereoselective 1,3-dipolar cycloaddition. Our successful route is high yielding, provides rapid access to single stereoisomers of the complex natural products and allows the synthesis of analogues for biological evaluation.

Keywords: antifungal agents · cycloaddition · heterocycles · natural products · total synthesis

Introduction

The synthesis of oxazole containing natural products has been driven by their fascinating structures and biological activities.[1,2] However, the synthesis of oxazole rings in complex structures remains a challenge, in particular their construction adjacent to stereogenic centres, which are prone to racemisation. For example, in the synthesis of the calyculins the C30 stereogenic centre is readily racemised during formation of the oxazole ring (Figure 1).[3]

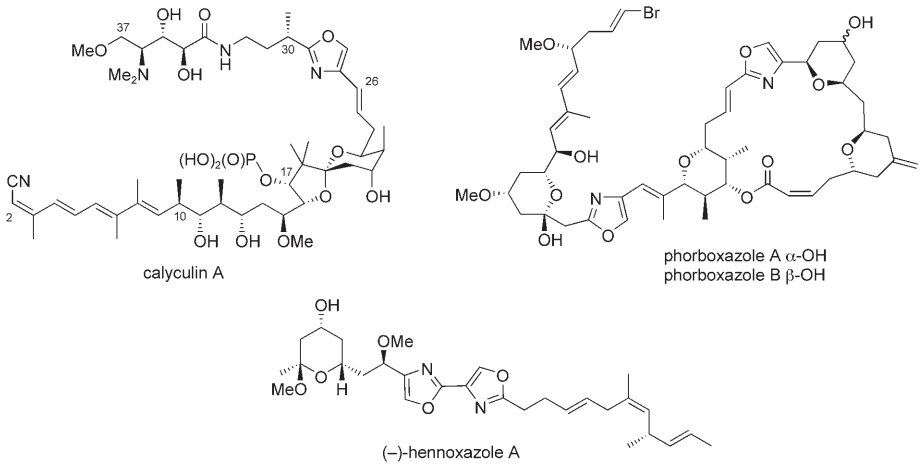

Figure 1. Oxazole natural products.

These challenging structural motifs have stimulated the discovery of milder reagents for oxazole synthesis, particularly from peptide precursors. Extensive work by Wipf and others into the use of Burgess reagent and DAST to cyclise serine and threonine amides, followed by oxazoline oxidation, have enabled the formation of oxazoles under mild conditions tolerant of complex functionality and sensitive stereochemical features.[4,5] In addition, Wipf has reported a Robinson–Gabriel oxazole synthesis under mild conditions using a Dess–Martin periodinane (DMP) oxidation I_2/PPh_3 protocol for 5-substituted oxazoles, which has also been modified for 5-unsubstituted examples.[6] These approaches have found extensive use in complex molecule synthesis.[2,7]

Bisoxazoles make up a significant subsection of oxazole natural products, with the oxazole rings either well separat-

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ed (for example in the phorboxazoles)[8] or directly linked (as found in the hennoxazoles,[9] Figure 1). The bengazoles are a unique family of bisoxazoles in that the two oxazole rings flank a single carbon atom. In bengazole A (**1**), this C10 position carries a myristate ester unit creating an isolated stereogenic centre adjacent to two oxazole rings suggesting it could be particularly prone to racemisation (Figure 2). Furthermore, the left hand oxazole is a biogenically unusual 5-monosubstituted oxazole while the central 2,4-disubstituted oxazole links to a stereochemically dense tetraol sidechain.

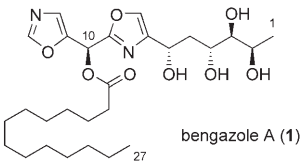


Figure 2. Bengazole A.

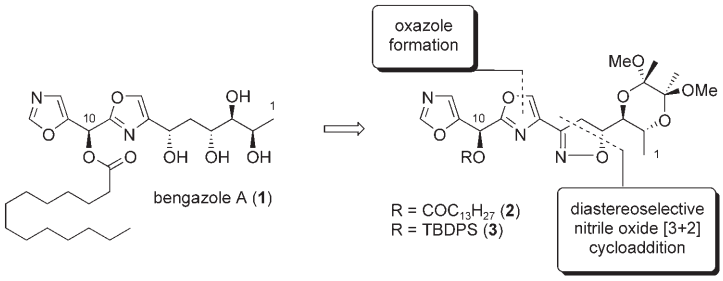
To date the bengazole family consists of 22 members from several isolation sources.[10–12] The parent molecule, bengazole A was originally isolated in 1988 and displays potent ergosterol dependant antifungal activity against *Candida albicans*, comparable to that of amphotericin B,[13,14] and is active against fluconazole-resistant *Candida* strains.[15] Furthermore, bengazole A shows full anthelminthic activity against nematode *Nippostrongylus braziliensis* at just 50 $\mu g\,mL^{-1}$.[10] The structure and absolute stereochemistry of this highly functionalised molecule was determined by NMR studies, analysis of degradation products and circular dichroism.[10,12] Other members of the bengazole family differ in the nature of the fatty acid side chain (bengazoles A to G) or lack the C10 oxygenation entirely and carry a fatty acid on one of the tetraol hydroxyl groups.

A previous synthesis of bengazole A by Molinski and co-workers used a regioselective metallation/addition strategy to graft the side chains on to the central oxazole.[15–17] However, this resulted in a 1:1 mixture of C10 epimers and once the resulting bisoxazole unit was in place the C10 epimers could not be separated at any stage during the synthesis. In addition, Shioiri and co-workers achieved a synthesis of deacylbengazole[18] that was stereochemically enriched at the C10 position by an enantioselective reduction of a bisoxazole ketone, resulting in *ee* values up to 68%.[19] We recently published a total synthesis of bengazole A, which provided a single stereoisomer of the natural product.[20] Here we report our full investigations into the synthesis of bengazole A and also 10-*epi*-bengazole A, both as single stereoisomers. Furthermore, the first total synthesis of bengazole B is also described.

Synthesis plan: Our major objective was the synthesis of bengazole A as a single stereoisomer and hence to examine methods of oxazole synthesis adjacent to the activated C10 stereogenic centre. With the challenging structural components and interesting biological profile, a synthetic route to bengazole A was devised that would both provide a single stereoisomer of the natural product and also allow for analogues to be prepared for further biological evaluation.

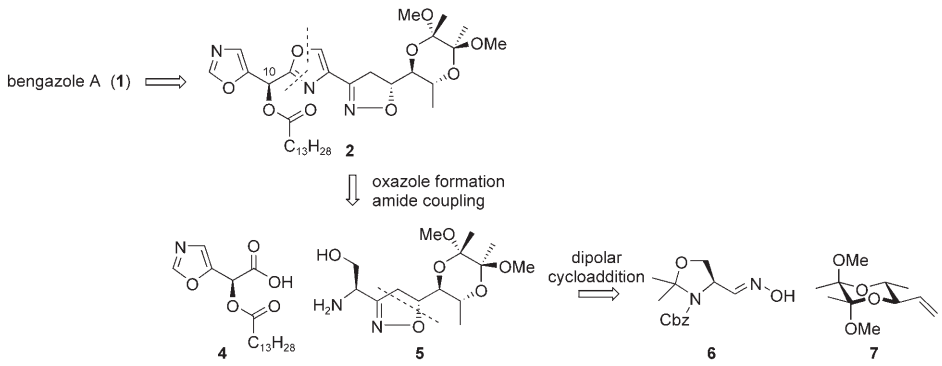
Our somewhat risky strategy was to install the sensitive C10 stereogenic centre *prior* to construction of the bisoxazole unit. This would require retention of stereochemical integrity at the C10 centre through formation of the central oxazole and on to the end of the synthesis. However, Molinski and Shioiri had found separation of the C10 epimers to be impossible once both oxazoles were in place and introduction of the stereochemistry after this point to be relatively poor, which dictated our approach towards the natural product that was ultimately successful.

It was expected that bengazole A could be synthesised from either advanced intermediate **2** with the myristate ester already in place, or **3** carrying a TBDPS protecting group (Scheme 1). The key strategic disconnections from this intermediate were then logically across the central oxazole ring and across the tetraol side chain, masked as an isoxazoline. These operations could be performed in either order imparting a degree of flexibility to the synthesis. The resultant three fragments would then be assembled by an oxazole formation under mild conditions and a diastereoselective 1,3-dipolar cycloaddition. This disconnection route was designed to avoid the use of strong bases and forcing conditions due to the propensity of the C10 position to racemise.



Scheme 1. Strategic disconnections of bengazole A.

Route A—Initial strategy: The initial approach was to perform the 1,3-dipolar cycloaddition to construct the tetraol side chain in advance of formation of the central oxazole, as this allowed the introduction of the C10 stereocentre later in the synthesis (Scheme 2). Intermediate **2** could then be constructed from carboxylic acid **4** and isoxazoline-containing amine **5** via amide coupling and oxazole formation. Amine **5** could be formed by a diastereoselective 1,3-dipolar cycloaddition between Butane-2,3-diacetal (BDA)-protected allylic diol **7** and the nitrile oxide derived from Cbz-protected Garner aldehyde oxime **6**, followed by amine deprotection.



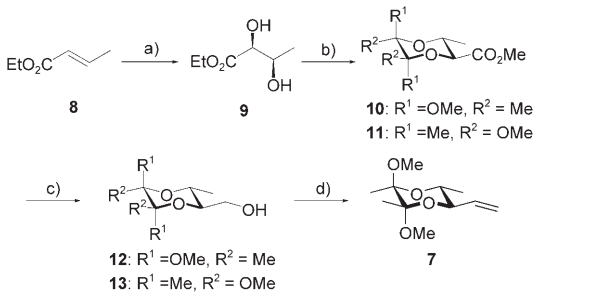
Scheme 2. Initial disconnection route.

Results and Discussion

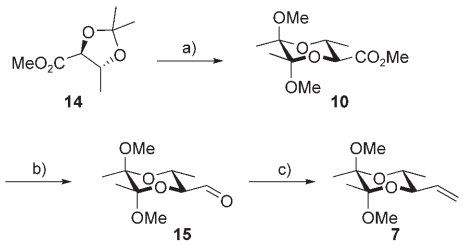
Alkene fragment 7: BDA-protected diols have been used extensively in our group as stable chiral building blocks.[21] The BDA group offers greater stability and lower volatility compared to traditional acetonides and its structural rigidity often leads to high levels of stereoinduction during addition reactions and confers crystallinity on many of the products.

In the synthesis of alkene **7**, the stereochemistry was initially introduced by Sharpless dihydroxylation of ethyl crotonate **8** to give diol **9** with >95% *ee* (Scheme 3).[22–25] Treatment of **9** with camphorsulfonic acid and 2,3-butanedione in methanol under reflux introduced the BDA-protecting group as a 6:1 mixture of anomerically (**10**) and non-anomerically (**11**) stabilised products. Reduction of the mixture to the corresponding alcohols allowed them to be separated by flash chromatography and NOE analysis gave proof of structure.[26] Alcohol **12** was then converted to alkene **7** via a sequential TPAP oxidation–Wittig methylenation without purification or isolation of the intermediate aldehyde, which gave higher yields than the stepwise process (67% vs 49%).[27,28]

However, with acetonide **14** commercially available, it was deemed more cost-effective to start with the C2 and C3 stereochemistry already in place. Therefore, acetonide **14** was transformed to the same mixture of the BDA esters **10**/**11** under the previously developed conditions (Scheme 4). This mixture could be converted to exclusively the desired diastereoisomer using catalytic BF_3·THF in CH_2Cl_2 in good yield.[29] To form alkene **7** from ester **10** it was most convenient to reduce the ester directly to aldehyde **15** with DIBAL followed by Wittig methylenation, which proceeded in 86% yield over the two steps. This route was readily scaled to rapidly provide large quantities of alkene **7**.



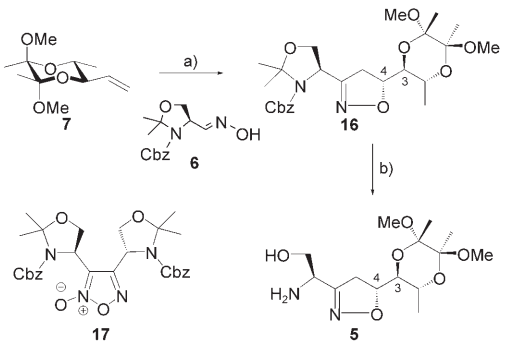
Scheme 3. Synthesis of alkene **7**. a) AD-mix-β, $MeSO_2NH_2$, H_2O/*t*BuOH, 0°C, 96% >95% *ee*; b) 2,3-butanedione, CSA, trimethylorthoformate, MeOH, reflux, 89% (dr 6:1 **10**/**11**); c) $LiAlH_4$, Et_2O, 0°C, 79% (of clean major isomer **12**); d) from **12**: TPAP, NMO, 4 Å MS, CH_2Cl_2 then addition of Ph_3PCH_3Br, KHMDS, THF, −78°C to RT, 67%. CSA = camphorsulphonic acid, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorphonline-*N*-oxide, KHMDS = potassium hexamethyldisilazide, THF = tetrahydrofuran.



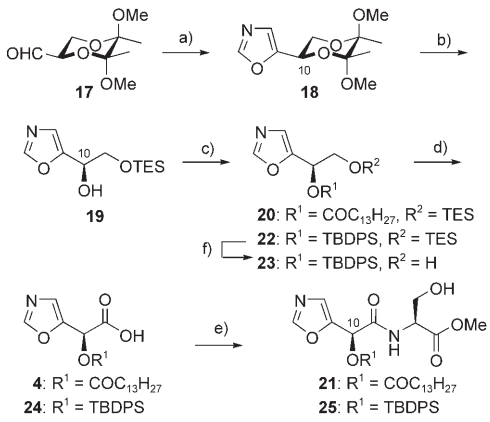
Scheme 4. Synthesis of alkene **7**. a) 1) 2,3-butanedione, CSA, trimethylorthoformate, MeOH, reflux; 2) BF_3·THF, CH_2Cl_2, RT, 83% over two steps; b) DIBAL-H, CH_2Cl_2, −78°C, 86%; c) Ph_3PCH_3Br, KHMDS, THF, −78°C to RT, quant. DIBAL-H = diisobutylaluminium hydride.

Aldehyde **15** was initially isolated as the hydrate, which dehydrated during flash chromatography to provide a crystalline solid. Following recrystallisation, this material could be stored at ambient temperature under an inert atmosphere for over 12 months with minimal (<5%) degradation. This is in stark contrast to the equivalent acetonide-protected compound which is an unstable volatile oil.[30]

Cycloaddition and synthesis of amine fragment: The nitrile oxide precursor, Garner aldehyde-derived oxime **6**, had been previously reported and was prepared according to the literature procedure.[31] A diastereoselective 1,3-dipolar cycloaddition was then required to couple the nitrile oxide derived from oxime **6** with BDA-alkene **7** and to install the C4 stereochemistry (Scheme 5). The slow addition of oxime **6** to three equivalents of alkene **7** and three equivalents of NaOCl, in the presence of NEt_3, gave cycloadduct **16** with 4.1:1 diastereoselectivity in favour of the desired *anti* isomer. These conditions were important to minimise the formation of the nitrile oxide dimer **17**[32] and of the excess alkene employed in the reaction, 98% could be recovered. The major cycloadduct was readily separated by flash chromatography and deprotection under hydrogenolysis condi-



Scheme 5. Synthesis of amine **5**. a) NaOCl aq., NEt_3, CH_2Cl_2, slow addition of oxime **6**, 0 °C, 86 % (dr 4.1:1); b) H_2, $Pd(OH)_2$/C, AcOH, MeOH, RT, 77 %.



Scheme 6. Synthesis of carboxylic acids **4** and **24**. a) TosMIC, K_2CO_3, MeOH, reflux, 82 %; b) 1) TFA, H_2O, RT; 2) TESCl, *i*Pr_2NEt, CH_2Cl_2, −78 °C, 94 % over two steps; For $R^1 = COC_{13}H_{27}$: c) myristic acid, DCC, DMAP, CH_2Cl_2, 0 °C to RT, 97 %; d) Jones′ reagent, KF, acetone, 0 °C, 76 %; e) TBTU, H-L-Ser-OMe·HCl, *i*Pr_2NEt, DMSO, RT (13:1 dr); For R^1 = TBDPS: c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, RT; f) PPTS MeOH, RT, 96 % over two steps; d) From **23**: Jones reagent, acetone, 0 °C, 49 %; e) TBTU, H-L-Ser-OMe·HCl, *i*Pr_2NEt, DMSO, RT, 64 %, single diastereoisomer. TosMIC = tosylmethylisocyanide, TFA = trifluoroacetic acid, TES = triethylsilyl, PPTS = pyridinium *para*-toluenesulfonate, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, TBTU = 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, DMSO = dimethylsulfoxide.

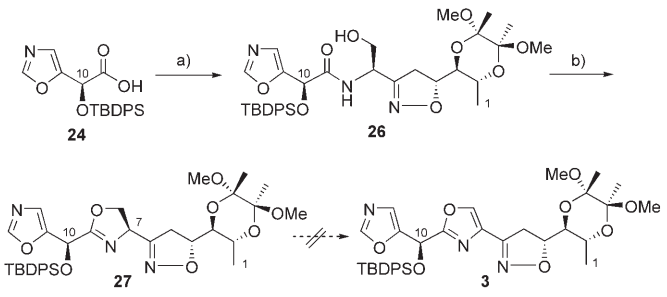
tions in the presence of mild acid smoothly afforded amine **5** ready for coupling with the carboxylic acid fragment.

The configuration of the newly formed stereocentres at C4 in the cycloadduct diastereoisomers were assigned by correlating ^{1}H NMR data with literature examples whereby the *anti* isomer has a larger coupling constant between protons at the allylic ether stereocentre and the newly-formed isoxazoline stereocentre.[33] The *anti* disposition of the major diastereoisomer is supported by comparison of the $^3J_{H3,H4}$ coupling constants with those predicted by Macromodel MMFF calculations (major: J(observed) = 4.5 Hz, J(calculated) = 5.4 Hz; minor: J(observed) = 2.0 Hz, J(calculated) = 3.0 Hz)[34] and is consistent with that predicted by the "inside-alkoxy" model reported by Houk et al.[35] Final proof of the stereochemistry came from an X-ray crystal structure of the minor isomer.[36]

Synthesis of acid fragment—Part 1: The synthesis of acid fragment **4** relied upon stereocontrol derived from our BDA-protected glyceraldehyde derivative **17**[21d] as a substrate for a Schöllkopf-type oxazole synthesis.[37] The desired 5-substituted oxazole **18** was obtained in excellent yield by treatment of aldehyde **17** with tosylmethylisocyanide (TosMIC) and potassium carbonate (Scheme 6). Oxazole **18** was isolated exclusively as the equatorially substituted diastereoisomer hence efficiently setting the desired C10 stereochemistry for the natural product. The BDA group was then removed using TFA/water, the primary alcohol was protected as TES-ether **19** and esterification with myristic acid and DCC gave **20** in excellent yield.[38] Removal of the TES group from **20** gave a primary alcohol that was prone to ester migration, which occurred on standing. However, all attempts to oxidise the silyl ether directly, or in a one-pot deprotection–oxidation, resulted in no reaction or ester migration. The only exception was Jones′ reagent, which gave acid **4** in yields ranging from 27 to 76 %. To test the conditions for the amide coupling, acid **4** was coupled with serine methyl ester. However, using coupling reagent 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) in CH_2Cl_2 caused epimerisation at C10 (dr 5.5:1 to 1:1). More polar chelating solvents appeared to suppress the racemisation; using TBTU in DMSO gave the best diastereomeric ratio, but epimerisation still occurred (dr 13:1). Subsequent attempts to couple carboxylic acid **4** with isoxazoline containing amine **5** under these optimised conditions gave variable yields and levels of racemisation.

We therefore decided to exchange the myristic ester for a bulky TBDPS group on the C10 hydroxyl in an attempt to protect the sensitive stereochemistry at this position (Scheme 6). The primary alcohol **23** was synthesised in two steps from alcohol **19**, without the previously observed migration problems, however, oxidation of this substrate also proved to be extremely difficult and was only achieved using Jones′ reagent. Subsequent amide coupling performed in dimethylsulfoxide with serine methyl ester gave the desired amide **25** as a single diastereomer showing there was no loss of stereochemical integrity during the preceding steps.

Attempted synthesis of the central oxazole ring: Gratifyingly, under these conditions the coupling between acid **24** and amine **5** proceeded smoothly, providing amide **26** in 65 % yield as a single diastereomer (Scheme 7). We envisaged that this substrate would be a suitable precursor for formation of the central 2,4-substituted oxazole. Cyclisation of amide **26** to oxazoline **27** was achieved in excellent yield by treatment with DAST at −78 °C. Oxazoline oxidation is known to be most efficient when the oxazoline is 4-substituted with an amide or ester group and it was believed that the oxime-like functionality at this centre would provide the requisite activation. However, despite investigating a variety of conditions ($BrCCl_3$, DBU; $CuBr_2$, HMTA, DBU or



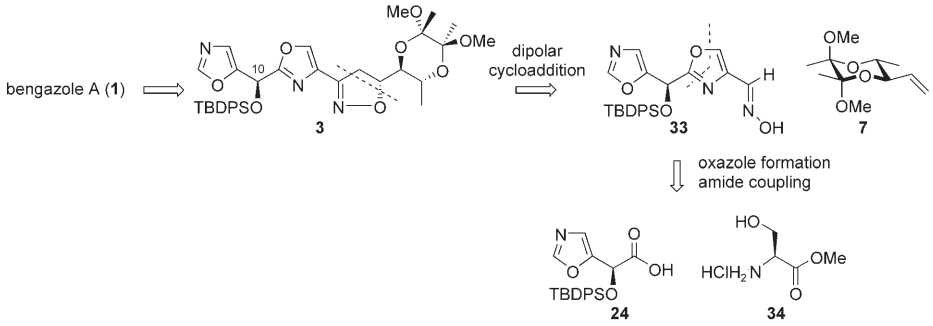
Scheme 7. Synthesis of oxazoline **27** and attempted oxidation. a) TBTU, amine **5**, DMSO, RT, 65%; b) DAST, CH_2Cl_2, −78°C, 91%.

IBX)[5] oxidation of oxazoline **27** to oxazole **3** could not be achieved.

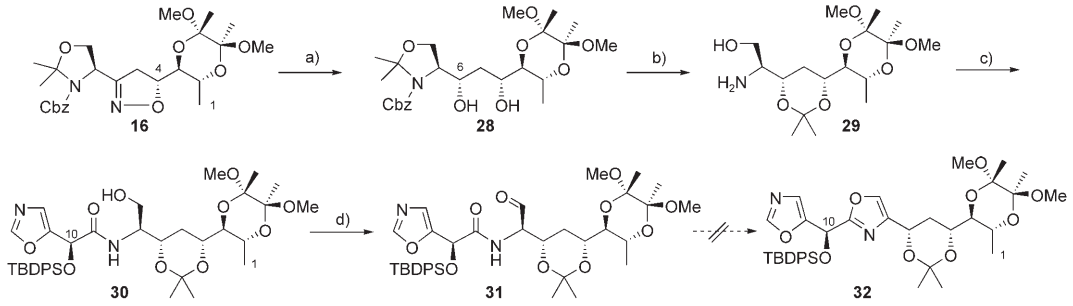
To attempt a Robinson–Gabriel oxazole synthesis, the product from the nitrile oxide cycloaddition (**16**) had to be further elaborated before deprotection and amide coupling (Scheme 8). Isoxazoline cleavage could be achieved using molybdenum hexacarbonyl in wet acetonitrile under reflux to give the β-hydroxyketone in 64% yield,[39] or with tris-acetonitrile molybdenum tricarbonyl (believed to be the active species in the reaction) at room temperature in an improved 78% yield. The secondary alcohol proved to be very difficult to protect with a MOM or TBS group and so the ketone was reduced to give 1,3-diol **28** using sodium borohydride to give a 9:1 ratio of 1,3-diols, which were then be separated by flash chromatography.[40]

After protection of diol **28** as the acetonide, the stereochemistry of the major product was confirmed using Rychnovsky's [^{13}C] acetonide method.[41] Removal of the amino alcohol protecting groups under hydrogenation conditions gave amine **29** which could be coupled with acid **24** under the previously identified conditions to give the desired amide **30** as a single diastereoisomer. Oxidation to the unstable aldehyde **31** under Swern[42] or Dess–Martin[43] conditions gave the precursor for the Robinson–Gabriel synthesis. However, when the crude aldehyde was subjected to a variety of cyclisation conditions (I_2, Ph_3P, Et_3N, CH_3CN, CH_2Cl_2; C_2Cl_6, Ph_3P, Et_3N, CH_3CN or $BrCl_2CCCl_2Br$, Ph_3Ph, CH_2Cl_2 then DBU, CH_3CN),[6,44] none of the attempts provided desired oxazole **32**. Clearly, the formation of the central 2,4-disubstituted oxazole would be a critical step in the synthesis and we therefore decided to investigate an alternative strategy whereby this oxazole could be introduced at an earlier stage.

Route B—Revised strategy: Our original disconnection strategy offered the potential for the building blocks to be assembled in the reverse order, forming the 2,4-disubstituted oxazole prior to the dipolar cycloaddition with alkene **7** (Scheme 9). This now provided a more appealing route to the bisoxazole unit but the C10 stereochemistry would need to be retained through a larger number of steps to the natural product. Bisoxazole-oxime **33** would be formed by coupling carboxylic acid **24** with serine ester **34** followed by oxazole formation. This would allow formation of the oxazole ring on a less functionalised substrate and a cyclisation/oxazoline oxidation process could be facilitated by the presence of an ester in the 4-position. The dipolar cycloaddition between alkene **7** and the nitrile oxide derived from oxime **33** would then provide isoxazoline **3**, which could be elaborated to bengazole A.

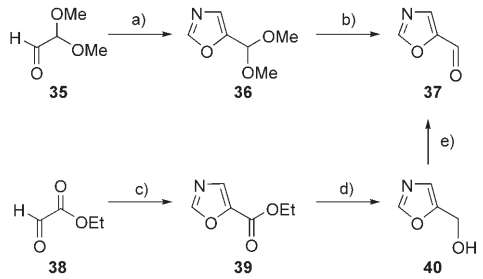


Scheme 9. Revised retrosynthesis through bisoxazole oxime **33**.



Scheme 8. Attempted Robinson-Gabriel oxazole formation. a) 1) $[Mo(MeCN)_3(CO)_3]$, H_2O, MeCN, RT, 78%; 2) $NaBH_4$, MeOH, −78°C, quant. (dr 9:1); b) 1) 2,2-dimethoxypropane, acetone, TsOH, 88%; 2) H_2, Pd/C, EtOH, RT, 83%; c) TBTU, acid **24**, DMSO, RT, 47%; d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0°C.

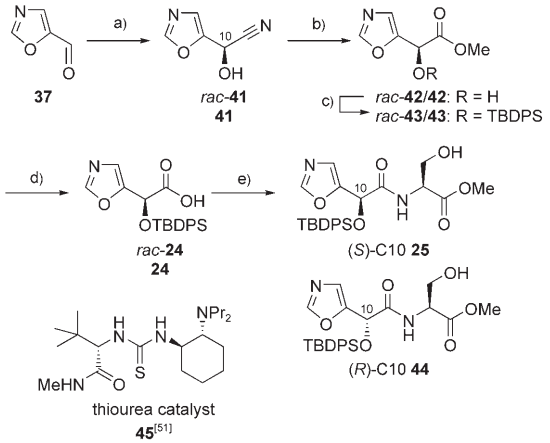
Synthesis of acid fragment—Part 2: This revised strategy required much larger amounts of acid **24** than could be provided by the BDA route described above (Scheme 6) due to the low-yielding Jones oxidation step. Therefore, alternative routes to this important fragment were investigated starting from pre-formed oxazole-5-carboxaldehyde **37** with the addition of a suitable masked carboxylic acid group. This aldehyde is known and was used in the syntheses of both Molinski and Shioiri,[15a,19,45] but was previously prepared in two steps from methyl isocyanide which is highly toxic and not commercially available. However, the reaction of TosMIC and potassium carbonate with glyoxal-1,1-dimethyl acetal **35** (available as a 45% solution in *tert*-butyl methyl ether) gave oxazole **36** in 58% yield using up to 100 grams (500 mmol) of TosMIC (Scheme 10) and hydrolysis of the resultant acetal provided oxazole-5-carboxaldehyde **37** in quantitative yield.[46,25]



Scheme 10. Synthesis of oxazole-5-carbaldehyde. a) TosMIC, K_2CO_3, MeOH, reflux, 58%; b) Amberlyst-15, acetone, H_2O, RT, quant; c) TosMIC, DBU, CH_2Cl_2, 0°C, 80%; d) $NaBH_4$, LiCl, THF, MeOH, 0°C to RT, 65%; e) $(COCl_2)$, DMSO, NEt_3, CH_2Cl_2, −78 to 0°C, 56%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Unfortunately, during the course of these studies glyoxal dimethyl acetal became unavailable commercially so we decided to develop an alternative route to the aldehyde. By the slow addition of ethyl glyoxylate **38** and DBU to a solution of TosMIC in CH_2Cl_2 at 0°C, known oxazole **39**[25,47,48] was obtained in good yields, on scales up to 250 mmol. Ester **39** was then converted into aldehyde **37** via a reduction–oxidation sequence. The best results for the reduction of ester **39** were obtained using $NaBH_4$ and LiCl which gave alcohol **40** in 65% yield on a 50 mmol scale.[25] Several oxidation conditions were attempted with Swern giving the best results, providing aldehyde **37** in moderate yields (56%), also on a 24 mmol scale. [During the course of this work a similar route to 5-oxazole compounds from ethyl glyoxylate and TosMIC was reported by Taylor.[48]]

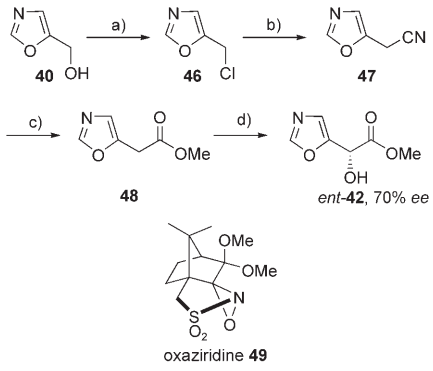
It was envisaged that the addition of cyanide to aldehyde **37**, followed by hydrolysis would provide a facile route to the desired acid. This was initially investigated under racemic conditions with the addition of trimethylsilylcyanide under Lewis basic catalysis,[49] to afford cyanohydrin *rac*-**41** in 92% yield (Scheme 11). Treating the cyanohydrin with anhydrous HCl in methanol gave β-hydroxy ketone *rac*-**42**, followed by TBDPS protection provided methyl ester *rac*-**43** in good yield. Hydrolysis of *rac*-**43** using LiOH gave the unstable carboxylic acid *rac*-**24**, which was immediately coupled with serine methyl ester to give amides **25** and **44** as a 1:1 mixture, in 66% yield over the two steps. The two amide diastereoisomers were stable to storage could be readily separated by flash chromatography hence providing a cheap and efficient resolution of the racemic acid and allowing access to large quantities of diastereomerically pure material with which to continue the synthesis.



Scheme 11. Synthesis of amide **25**. Racemic synthesis a) TMSCN, Et_3N, CH_2Cl_2, 0°C, then 2M HCl aq, 92%; b) 2M HCl in MeOH, reflux, 89%; c) TBDPSCl, Et_3N, DMAP, DMF, RT, 85%; d) LiOH, H_2O, THF, 0°C to RT; e) TBTU, H-L-Ser-OMe•HCl, iPr_2NEt, DMF, RT, 66% over two steps. Enantioselective synthesis: a) TMSCN, thiourea catalyst **45** (5 mol%), CF_3CH_2OH, CH_2Cl_2, −78°C, then 2M HCl aq, 90%, 71% *ee*; b) 1.25M HCl in MeOH, RT, 70%, 66% *ee*; c) TBDPSCl, Et_3N, DMAP, DMF, RT, 67%; d) LiOH, H_2O, THF, 0°C to RT; e) TBTU, H-L-Ser-OMe•HCl, iPr_2NEt, DMSO, RT, 42% over two steps, de 58%. TMS = trimethylsilyl, DMF = *N*,*N*-dimethylformamide.

This approach had the potential to be rendered asymmetric by using an enantioselective cyanide addition. A range of catalysts were screened for the addition of TMSCN to aldehyde **37**, however, initially the heterocyclic nature of the aldehyde led to poor *ee* values in all cases.[50] Careful re-optimisation of the reported reaction conditions using Jacobsen's thiourea catalyst **45**,[51] involving the slow addition of a solution of the TMSCN in CH_2Cl_2 to aldehyde **37** in presence of catalyst **45** over five minutes, gave (*S*)-cyanohydrin **41** with up to 78% *ee* in 89% yield.[52,53] Enantioenriched cyanohydrin **41** (71% *ee*) was converted into amide **25** with minimal racemisation (58% *de*, Scheme 11). Conditions for acidic methanolysis to form ester **42** had to be modified (room temperature, 20 equivalents of HCl) to minimise the loss of *ee* because heating the reaction to reflux or using a higher concentration of acid resulted in completely racemic material.[52] Protection as TBDPS-ether **43** and ester hydrolysis under the conditions used above followed by amide coupling in DMSO provided the desired amide **25** and the minor diastereomer **44** was easily removed by flash chromatography.

Additionally, the C10-hydroxyl functionality was introduced asymmetrically by an enantioselective oxidation of α-unfunctionalised ester **47** (Scheme 12). The required substrate was prepared by reacting alcohol **40** with thionyl chloride to provide oxazolyl methyl chloride **46** in good yield[54]

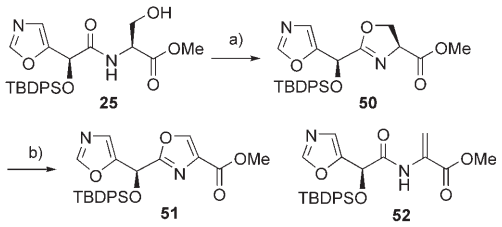


Scheme 12. Approach to α-hydroxy ester **48** via an enantioselective oxidation. a) $SOCl_2$, hexane/CH_2Cl_2, reflux; b) NaCN, DMF, 70 °C, 75%, over two steps; c) 2 M HCl in MeOH, reflux, 73%; d) LHMDS, THF, oxaziridine **49**, 64%.[56]

and reaction of the crude chloride with sodium cyanide in DMF gave nitrile **47** which was converted to the required ester **48** by methanolysis. It was envisaged that the stereochemistry could then be introduced by oxidation with a chiral oxidant, such as Davis′ chiral oxaziridines.[55] Deprotonation of ester **48** with LiHMDS and exposure of the enolate to oxaziridine **49** gave hydroxy ester *ent*-**42** in moderate yield (64%) with a selectivity of 70% *ee*.[56] Variation of the oxaziridine and base resulted in poorer selectivities, however, enhancement of the stereoinduction (82% *ee*, 33% yield) was achieved when four equivalents of anhydrous LiCl were added to the reaction mixture, possibly due to improved control of the enolate geometry.[57,58]

Successful synthesis of central oxazole ring: With large quantities of amide **25** in hand, the key challenge in this synthesis was the mild construction of the central 2,4-substituted oxazole ring in the presence of the sensitive C10 stereogenic centre, and initial attempts involved cyclisation to oxazoline **50** followed by oxidation (Scheme 13).

Synthesis of oxazoline **50** was originally attempted with DAST, which was successful in the more functionalised system. However, despite performing the cyclisation under a variety of reaction conditions, only poor yields (up to 50%) were obtained. Using Burgess reagent also resulted in poor yields of oxazoline **50**, with the dehydration product enamide **52** being preferred. Furthermore, Mitsunobu conditions resulted in epimerisation at the C10 position and heating with molybdenum(IV) oxide gave no reaction.[59] Despite extensive investigation, a scalable route to oxazoline **50** was not established, however, the isolated oxazolines were subjected to oxidation using the mild conditions reported by



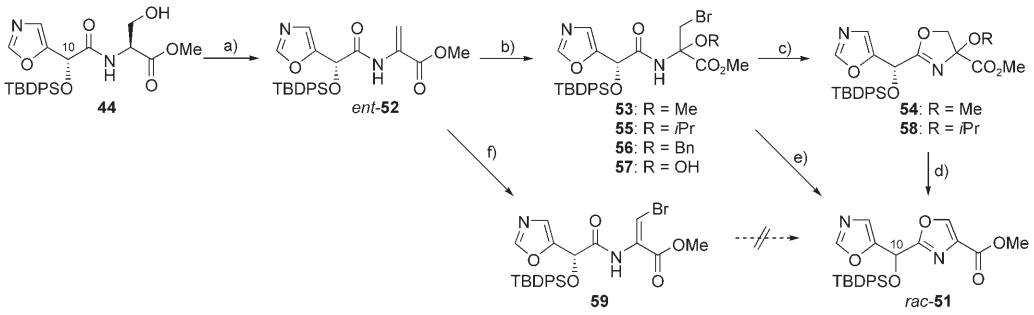
Scheme 13. Synthesis of bisoxazole **51** by oxazoline oxidation. a) DAST, CH_2Cl_2, −78 °C; b) DBU, $BrCCl_3$, CH_2Cl_2, −15 to 0 °C, 22% over two steps, 59% *ee*.

Williams to give oxazole **51**.[5a] The yields for this oxidation were low, up to 40%, and in some cases the only isolated product was TBDPS-OH. In addition, analysis of the isolated bisoxazole by chiral HPLC revealed a loss of enantiopurity during this oxidation procedure (*ee* 80–86%).[60] Applying a sequential DAST cyclisation/oxidation from **25** gave the desired bisoxazole **51** but in only 22% yield and 59% *ee*.

A synthetic route to bisoxazole **51** that proceeded via enamide **52** would exploit the propensity of amide **25** to eliminate water. Conditions to convert enamides to oxazole rings have been reported by Shin,[61] involving NBS activation and addition of methanol followed by cyclisation to the methoxy-substituted oxazoline and elimination of methanol. With this aim in mind, amide **44** was treated with mesyl chloride, which, in the presence of triethylamine, rapidly formed enamide *ent*-**52** cleanly as a single enantiomer in excellent yield (Scheme 14).[60,62] Following Shin's procedures, treatment of enamide *ent*-**52** with *N*-bromosuccinimide and methanol, gave the desired bromide **53** in good yield. Cyclisation to give methoxy-substituted oxazoline **54** was performed using caesium carbonate, however attempts to eliminate methanol by heating *ent*-**54** with CSA in toluene as reported by Shin resulted only in decomposition. A range of other conditions were investigated and methanol could be successfully eliminated using DBU/TMSOTf, however, disappointingly the resultant bisoxazole was found to be racemic.[60]

The advantage to the cyclisation in having the C7 position fully substituted encouraged further investigation into this route. Alternative hydroxyl nucleophiles were added in the NBS step (*i*PrOH, BnOH, H_2O).[63] Surprisingly, warming bromide **56** (R = Bn) with caesium carbonate to perform the cyclisation, resulted in the formation of the bisoxazole directly, in a one-pot cyclisation and elimination. However, the isolated bisoxazole was again racemic *rac*-**51**; hence, less harsh cyclisation/elimination conditions were required.

Given that racemisation was observed following heating **56** with caesium carbonate the cyclisation of methanol and isopropanol derivatives was attempted under novel non-basic conditions using silver oxide in DMF. Pleasingly, this gave excellent yields of the cyclised products for both examples (**53**/**55**) at room temperature. Water was also added directly to give **57** in 57% yield, but the attempted cyclisation in this case gave multiple by-products. Elimination occurred



Scheme 14. Attempts to form bisoxazole *ent*-**51** from enamide *ent*-**52**. a) MsCl, NEt_3, CH_2Cl_2, 0°C, 95%; b) NBS, ROH, THF, RT, R = Me, 89%; R = *i*Pr, 51%; R = Bn, 36%; R = H, 57%; c) Ag_2O, DMF, RT, R = Me, 97%; R = *i*Pr, 95%; d) For R = Me, DBU, TMSOTf, 2,6-lutidine, CH_2Cl_2, RT, 42%; for R = *i*Pr, Cs_2CO_3, dioxane, 60°C, 57% e) For R = Bn, Cs_2CO_3, dioxane, 60°C, 47%; f) Br_2, CH_2Cl_2, −78°C, then NEt_3, 75%. Ms = methanesulfonyl, NBS = *N*-bromosuccinimide.

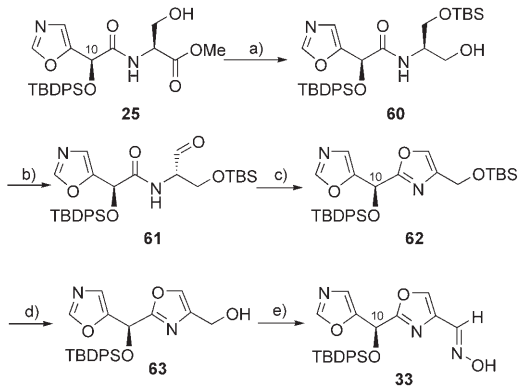
under the TMSOTf/DBU conditions for the methanol derivative but for the isopropanol example elimination could only be achieved with Cs_2CO_3. However, in both cases the bisoxazole product was again racemic!

In an attempt to form the bisbromide, which could result in a one pot cyclisation and easier elimination, enamide *ent*-**52** was reacted with bromine (Scheme 14).[64] However, following the addition of triethylamine no cyclisation was observed, instead, (*E*)-vinyl bromide **59** was formed in good yield. Unfortunately, no cyclisation was observed on heating vinyl bromide **59** with caesium carbonate, or silver oxide and therefore another change of strategy was required to obtain the bisoxazole unit as a single enantiomer.

Therefore, although a Robinson–Gabriel approach failed on the more advanced amide **30**, it was attempted on this revised disconnection route (Scheme 15). Serine amide **25** was converted to primary alcohol **60** in two steps and oxidation using buffered Dess–Martin periodinane provided aldehyde **61** which was subjected to Robinson–Gabriel-type oxazole formation under conditions reported by Panek and Beresis,[65] similar to those described previously by Wipf et al.[6b] Treating crude aldehyde **61** with triphenylphosphine, 2,6-di-*tert*-butylpyridine and dibromotetrachloroethane in CH_2Cl_2 formed the intermediate bromooxazoline, from which HBr was eliminated by the addition of DBU. This process provided the desired 2,4-disubstituted oxazole **62** in 72% yield over the two steps. However, the product still displayed significant racemisation (33–66% *ee*) at the crucial C10 centre.[60] With quantities of non-racemic material now available, the stability of the C10 stereochemistry could be tested to the conditions employed in the oxazole formation. The cause of the racemisation was identified as DBU, used to eliminate the proposed bromooxazoline intermediate. However, it was found that treating bisoxazole **62** with triethylamine did not result in any degradation of the stereochemistry.

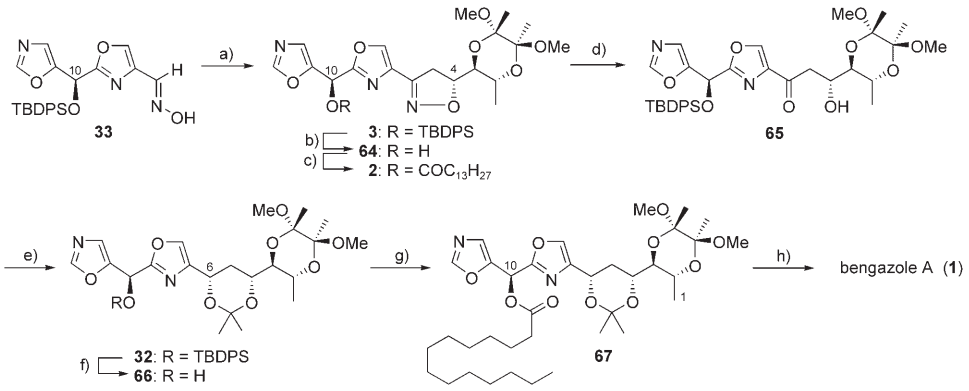
Replacing DBU with triethylamine for the second stage of the oxazole formation therefore completely prevented this racemisation and in addition improved the yield over the two steps from alcohol **60** to an excellent 89%. Bisoxazole **62** was thus obtained with >98% *ee* and the process was amenable to scale-up.[66] We believe this to be a potentially useful general modification for oxazole formation adjacent to highly epimerisable stereogenic centres. Interestingly, using NEt_3 from the start of the reaction in place of 2,6-di-*tert*-butylpyridine again provided bisoxazole **62** as a single enantiomer. However, these conditions gave a yield of only 47%, which together with a reduced reaction time and the fact that the bromooxazoline intermediate could not be observed by TLC, suggests a different reaction pathway could be operating.

In readiness for the 1,3-dipolar cycloaddition with alkene **7**, enantiopure bisoxazole **62** was converted to oxime **33** as a suitable precursor from which to generate a nitrile oxide (Scheme 15). Following TBS deprotection, treating alcohol **63** with Dess–Martin periodinane gave the aldehyde, which was used crude to prevent any racemisation of the activated system on silica gel. Oxime formation then gave the desired bisoxazole-oxime **33** in excellent yield over the two steps as a single enantiomer.[67]



Scheme 15. Synthesis of bisoxazole-oxime **33**. a) 1) TBSCl, imidazole, DMAP, DMF, RT, 90%; 2) $NaBH_4$, LiCl, THF, MeOH, 0°C to RT, 80%; b) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0°C; c) PPh_3, $C_2Br_2Cl_4$, CH_2Cl_2, 2,6-di-*tert*-butylpyridine, 0°C, then Et_3N, MeCN, 0°C to RT, 89% over two steps, >98% *ee*; d) PPTS, MeOH, RT, 93%; e) 1) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0°C; 2) $NH_2OH{\cdot}HCl$, K_2CO_3, MeOH, H_2O, RT, 93% over two steps; TBS = *tert*-butyldimethylsilyl.

Nitrile oxide cycloaddition and synthesis of bengazole A: Attempts to couple bisoxazole oxime **33** to alkene **7** using the previously optimised conditions (using sodium hypochlorite as the oxidant), resulted in a complex mixture of diastereoisomers and by-products. Instead, the required nitrile oxide was generated from oxime **33** in two stages to allow for easier optimisation of the reaction conditions (Scheme 16). Firstly, the oxime was chlorinated using *N*-chlorosuccinimide with a catalytic amount of pyridine to form the chlorooxamic acid, which could then be converted to the nitrile oxide in a separate step in the presence of alkene **7**.[68] The best results were obtained by adding caesium carbonate to a solution of the chlorooxamic acid in dimethoxyethane in the presence of 10 equivalents of alkene **7**. The resulting 1,3-dipolar cycloaddition provided isoxazoline **3** in a 60% yield of the major diastereoisomer. The minor diastereoisomer (isolated in 17%) was easily separated by column chromatography and could be used in analogue studies.[69]



Scheme 16. Synthesis of isoxazoline **3** and completion of the synthesis of bengazole A (**1**). a) 1) NCS, CH_2Cl_2, pyridine, RT; 2) alkene **7**, Cs_2CO_3, DME, RT, 77% over two steps (dr 7:2); b) TBAF, THF, 0°C, 78%; c) myristoyl chloride, NEt_3, CH_2Cl_2, 0°C, 73%; d) from **3**: Raney Nickel, H_2, $B(OH)_3$, EtOH, H_2O, 61%; e) 1) Et_2BOMe, $NaBH_4$, THF, −78°C (dr 14:1); 2) 2,2-dimethoxypropane, TsOH, 89% over two steps; f) TBAF, THF, 0°C, quant; g) From **66**: myristoyl chloride, NEt_3, CH_2Cl_2, 0°C, 85%; h) TFA, H_2O, RT, 95%. NCS = *N*-chlorosuccinimide, DME = 1,2-dimethoxyethane, TsOH = toluene-4-sulfonic acid, TBAF = tetrabutylammonium fluoride.

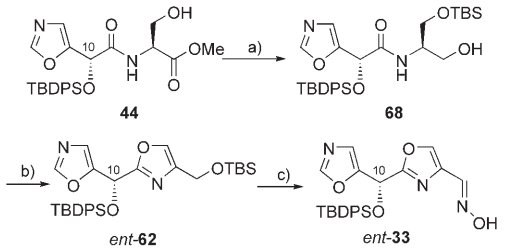
From isoxazoline **3**, the most rapid route to the natural product would have involved installation of the myristate ester to give **2**, followed by unmasking of the tetraol side chain (Scheme 16). Indeed, treatment of TBDPS-ether **3** with TBAF gave alcohol **64**, which was acylated with myristoyl chloride to provide myristate ester **2** as a single stereoisomer but the cleavage of the isoxazoline was unsuccessful at this stage. Several conditions were therefore tested for the reductive cleavage of isoxazoline **3** with the TBDPS protecting group still in place. All attempts to cleave isoxazoline **3** using molybdenum complexes or SmI_2[70] led to decomposition of the substrate, however, reductive cleavage using Raney-nickel and boric acid in ethanol/water gave β-hydroxy ketone **65**. The yield was strongly dependent on the concentration of boric acid,[71] but using a solution saturated with boric acid (about 1 M) gave β-hydroxy ketone **65** with reproducible yields in the range 53–61%.

To form the protected tetraol side chain, β-hydroxy ketone **65** was reduced to the *syn*-diol using diethylmethoxyborane and sodium borohydride (dr 14:1 by ^1H NMR).[72] Protection as isopropylidene acetal **32** gave an 89% yield of the major diastereomer over the two steps and TBDPS deprotection using TBAF in THF at 0°C gave secondary alcohol **66** in quantitative yield. Subsequent acylation using myristoyl chloride with triethylamine afforded acetal-protected bengazole A **67** in good yield. The removal of residual myristic acid (formed by an aqueous quench of the excess acid chloride) from the desired product was extremely difficult, therefore, the reaction was quenched with methanol before an aqueous work-up and the resulting ester was easily separated by flash chromatography.

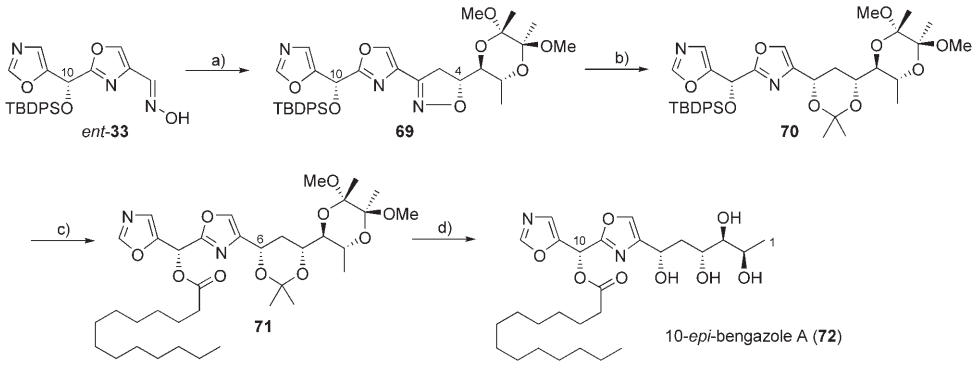
To complete the total synthesis the BDA and acetonide protecting groups were removed simultaneously by treating **67** with TFA/water 2:1 for 10 minutes then adding extra water to give a 1:1 TFA/water mixture. Within one hour, complete conversion had occurred and bengazole A **1** could be isolated cleanly and in excellent yield by an aqueous workup followed by flash chromatography. The data for our synthetic material was consistent with those reported for the natural product and NMR analysis confirmed our product to be a single C10 epimer.[10,15]

Synthesis of 10-*epi*-bengazole A: The ability to synthesise a single stereoisomer of bengazole A will allow the importance of the C10 stereochemistry to the antifungal activity to be investigated. To this end, amide **44**, which contains unnatural 10*R* stereochemistry and was available in large quantities, was used as the starting point for the synthesis of 10-*epi*-bengazole A (Scheme 17). Amide **44** was converted to alcohol **68** and the oxidation/Robinson–Gabriel procedure provided bisoxazole *ent*-**62** as a single stereoisomer, which was then elaborated to the required oxime *ent*-**33** under similar conditions to those employed for the natural diastereomer.

To form isoxazoline **69**, the previously developed conditions were again found to be optimal (Scheme 18). Using oxime *ent*-**33** a mixture of C4 epimers was obtained in good yield (72%, dr 2.5:1), which were separated using flash chromatography.[73] Performing the reductive cleavage of isoxazoline **69** using Raney nickel gave yields of the β-hy-



Scheme 17. Synthesis of bisoxazole oxime *ent*-**33**. a) 1) TBSCl, imidazole, DMAP, DMF, RT, 95%; 2) $NaBH_4$, LiCl, THF, MeOH, 0°C to RT, 77%; b) 1) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0°C; 2) PPh_3, $C_2Br_2Cl_4$, CH_2Cl_2, 2,6-di-*tert*-butylpyridine, 0°C, then Et_3N, MeCN, 0°C to RT, 75% over two steps, >98% *ee*; c) 1) PPTS, MeOH, RT, 96%; 2) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0°C; 3) $NH_2OH{\cdot}HCl$, K_2CO_3, MeOH, H_2O, RT, 87% over two steps.



Scheme 18. Synthesis of 10-*epi*-bengazole A (**72**). a) 1) NCS, CH_2Cl_2, pyridine, RT; 2) alkene **7**, Cs_2CO_3, DME, RT, 72% over two steps (dr 2.4:1); b) 1) Raney Nickel, H_2, $B(OH)_3$, EtOH, H_2O, 49–61%; 2) Et_2BOMe, $NaBH_4$, THF, −78°C, 93% (dr 17:1); 3) 2,2-dimethoxypropane, TsOH, 97%; c) 1) TBAF, THF, 0°C, 96%; 2) myristoyl chloride, NEt_3, CH_2Cl_2, 0°C, 90%; d) TFA, H_2O, RT, 85%.

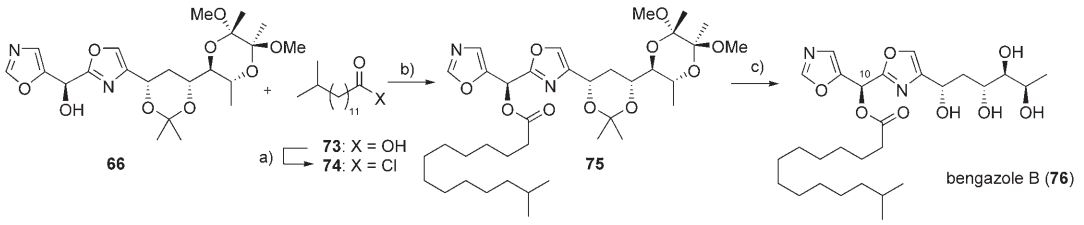
droxy ketone in the range 49–61% and *syn*-reduction to the diol proceeded with good yield and diastereoselectivity. The diol was protected as acetonide **70** in excellent yield, but the minor C6 diastereoisomer could not be fully separated at this stage. However, this minor product could be completely removed over the subsequent two steps. Removal of the TBPDS protecting group from **70** using TBAF gave the secondary alcohol and installation of the myristate ester gave **71**. Removal of the BDA and acetonide protecting groups using TFA/water afforded 10-*epi*-bengazole A **72** in excellent yield and as a single stereoisomer.

The NMR spectra of bengazole A and 10-*epi*-bengazole A are remarkably similar, as reported by Molinski.[15a] Indeed the most significant difference was the C1 protons, which were marginally different for the two diastereoisomers (δ_H 1.13/1.14 natural/10-*epi*). Molinski also reported a difference for the C15 protons ($\delta_H = 2.43/2.25$ natural/10-*epi*).[74] However, we observed that this signal in 10-*epi*-bengazole A overlayed perfectly with that from bengazole A ($\delta_H = 2.43$) and we propose that the signal at 2.25 ppm could be due to excess myristic acid inseparable from the bengazole products. This would fit with the apparent peak sizes in Molinski's spectra. It is also worth noting that when bengazole A and 10-*epi*-bengazole A were both characterised by NMR in CD_3OD, a spontaneous loss of the myristate ester was observed. Extra peaks that corresponded to deacylbengazole appeared,[18] as did a peak at 2.31 ppm, presumably due to the methanolysis of the ester to give methyl myristate.

Synthesis of bengazole B: We are also interested in the synthesis of analogues containing variations of the fatty acid at the C10 position and the related natural product, bengazole B (**76**) was prepared (Scheme 19).[10] The required acid chloride **74** was synthesised from known fatty acid **73**,[75] with quantitative conversion (by ^1H NMR) and used as a stock solution in CH_2Cl_2. Treatment of secondary alcohol **66** with the acid chloride solution gave acetal-protected bengazole B **75** in good yield. The first synthesis of bengazole B **76** was completed in excellent yield by treatment of **75** with TFA/water under the previously optimised conditions. Thus, it was demonstrated that from alcohol **66** alternative side chains could be readily introduced and that this synthetic route could potentially be used to synthesise bengazoles A to G or as a starting point for analogue synthesis.

Conclusion

Stereocontrolled total syntheses of bengazole A, 10-*epi*-bengazole A and bengazole B have been successfully complet-



Scheme 19. Synthesis of bengazole B **76**. a) $(COCl)_2$, CH_2Cl_2, DMF, RT, quant; b) acid chloride **74** in CH_2Cl_2, NEt_3, CH_2Cl_2, 0°C, 85%; c) TFA, H_2O, RT, 98%.

ed. Our route was the first to provide to single stereoisomers of the natural products whereby the sensitive C10 stereochemistry was formed early in the synthesis and was preserved through formation of the central oxazole ring and on to the natural product. Moreover our route reports a useful modification for the Robinson–Gabriel oxazole synthesis and features extensive use of the butane-2,3-diacetal (BDA) to control various oxidation patterns within the natural product. Biological testing of the natural products and relevant intermediates is underway and will be reported in due course.

Experimental Section

General methods: Solvents were freshly distilled before use. All non-aqueous reactions were performed under an atmosphere of argon and carried out using oven-dried glassware. PE = petroleum ether (PE) b.p. 40–60 °C.

Optical rotations were measured using a Perkin–Elmer Polarimeter 343 over a path length of 10 cm with the sample temperature maintained at 25 °C in the solvent indicated. Infrared spectra were recorded as thin films on a Perkin–Elmer Spectrum One FT-IR spectrometer. ^{1}H NMR spectra were recorded at 27 °C (unless stated otherwise) on Bruker DPX-400, Bruker DRX-500 (VT or Cryoprobe) and Bruker DPX-600 spectrometers. Residual protic solvent was used as the internal reference ($CHCl_3$ $\delta_H = 7.27$ ppm). ^{13}C NMR spectra were recorded at 100 MHz, 125 MHz and 150 MHz on Bruker DPX-400, Bruker DRX-500 Cryoprobe and Bruker DPX-600 spectrometers respectively. The resonance $CDCl_3$ ($\delta_c = 77.0$ ppm, t) was used as the internal reference. Assignments were made using a range of NMR experiments and these assignments are made according to the natural product numbering of bengazole A.[10] Mass spectra were recorded on Waters LCT Premier, Bruker Daltronics Bioapex II or Kratos Concept spectrometers. Melting points were performed on a Reichert hot stage apparatus and are uncorrected. Flash column chromatography was carried out using silica gel [Merck or Breckland (230–400 mesh)] under pressure. Biotage flash chromatography refers to the use of an automated Biotage SP1 system. Collection was monitored by UV absorption at 220 and 254 nm. All intermediates and final compounds were stored under argon at −20 °C.

BDA-ester 10: A solution of methyl-(4*S*)-*trans*-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate (**14**; 10.0 g, 57.4 mmol), trimethyl orthoformate (18.8 mL, 172 mmol), 2,3-butanedione (6 mL, 69 mmol) and camphorsulfonic acid (1.3 g, 5.7 mmol) in methanol (220 mL) was heated under reflux for 21 h. On cooling to RT solid $NaHCO_3$ (10 g, 120 mmol) was added and the mixture stirred for 2 h then filtered. The filtrate was concentrated in vacuo, adsorbed onto silica gel (≈150 mL) then loaded onto a plug of silica gel and the crude product was eluted with ethyl acetate. The solvent was removed in vacuo to leave an orange oil, as a 6:1 ratio of fully anomerically stabilised to non-anomerically stabilised isomers **10**/**11**.

The crude product was dissolved in CH_2Cl_2 (125 mL) and BF_3·THF (1.26 mL, 11.4 mmol) was added dropwise at RT. The brown solution was stirred for a total of 10 d adding further aliquots of BF_3·THF (1.26 mL, 11.4 mmol) after 2 and 6 d. The reaction was quenched by the dropwise addition of triethylamine (8 mL) and the mixture was concentrated under reduced pressure. The residue was filtered through a plug of silica gel (50% Et_2O/PE) and the solvent removed in vacuo. Purification by flash chromatography (35% Et_2O/PE) afforded ester **10** as an orange oil (11.77 g, 83%). R_f = 0.34 (30% ethyl acetate/PE); $[\alpha]_D^{25} = +140.7$ (c = 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.10$ (d, $J = 9.8$ Hz, 1H; 3-H), 3.99 (dq, $J = 9.8$, 6.3 Hz, 1H; 2-H), 3.77 (s, 3H; OCH_3), 3.29, 3.26, 1.35, 1.29 (4s, 4×3H; 4×BDA CH_3), 1.18 (d, $J = 6.3$ Hz, 3H; 1-H_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.4$ (C4), 98.9, 98.7 (BDA C_q), 73.8 (C3), 64.9 (C2), 52.2 (OCH_3), 48.2, 47.9 (BDA OCH_3), 17.7, 17.3 (BDA CH_3), 16.7 (C1); IR (film): ν_{max} = 2952, 1747, 1115 s, 1036 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{11}H_{20}O_6Na$: 271.1158; found: 271.1151 $[M+Na]^+$; elemental analysis calcd (%) for $C_{11}H_{20}O_6$ (248.3): C 53.21, H 8.12; found: C 53.08, H 7.99.

BDA-aldehyde 15: DIBAL (1 M in hexanes, 60 mL, 60 mmol) was added dropwise to a solution of ester **10** (10.54 g, 42.09 mmol) in CH_2Cl_2 (350 mL) at −78 °C, via syringe pump over 2.5 h. The mixture was stirred for a further 1.5 h, then methanol (10 mL) was added dropwise at −78 °C. The reaction mixture was warmed to RT then saturated aqueous Rochelle's salt (100 mL) and Et_2O (80 mL) were added and the mixture stirred overnight. Water (100 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (2×150 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (10 → 20 → 40% ethyl acetate/PE) afforded aldehyde **15** as a white crystalline solid (7.89 g, 86%). R_f = 0.63 (50% ethyl acetate/PE); m.p. 72–74 °C; $[\alpha]_D^{25} = +107.2$ (c = 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.64$ (s, 1H; 4-H), 3.87 (m, 2H; 2-H, 3-H), 3.29, 3.27 (2s, 2×3H; 2×OCH_3), 1.38, 1.30 (2s, 2×3H; 2× BDA CH_3), 1.26 (d, $J = 5.8$ Hz, 3H; 1-H_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.8$ (C4), 98.9, 98.6 (BDA C_q), 77.7 (C3), 63.1 (C2), 48.2, 48.1 (OCH_3), 17.7, 17.3 (BDA CH_3), 16.4 (C1); IR (film): ν_{max} = 2951, 1738, 1120 s, 1036, 908 s, 727 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{10}H_{18}O_5Na$: 241.1046; found: 241.1048 $[M+Na]^+$; elemental analysis calcd (%) for $C_{10}H_{18}O_5$ (218.3): C 55.03, H 8.31; found: C 54.89, H 8.24.

BDA-alkene 7: KHMDS (0.5 M in toluene, 65 mL, 33.3 mmol) was added to a suspension of methyl triphenylphosphonium bromide (12.4 g, 34.5 mmol) in Et_2O (200 mL) at RT. The solution was stirred at RT for 1.5 h then cooled to −78 °C. A solution of aldehyde **15** (4.70 g, 21.6 mmol) in Et_2O (30 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 2.5 h then allowed to warm to RT and stirred for 3 h. The reaction mixture was filtered through a plug of silica gel, eluting with Et_2O (300 mL) and concentrated in vacuo. Purification by flash chromatography (PE → 10% Et_2O/PE) afforded alkene **7** as a colourless oil (4.66 g, quant.). R_f = 0.59 (50% Et_2O/PE); $[\alpha]_D^{25} = +197.0$ (c = 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.78$ (ddd, J = 17.3, 10.3, 7.4 Hz, 1H; 4-H), 5.38 (d, J = 17.3 Hz, 1H; 5-H^{trans}), 5.26 (d, J = 10.3 Hz, 1H; 5-H^{cis}), 3.90 (dd, J = 9.5, 7.4 Hz, 1H; 3-H), 3.69 (dq, J = 9.5, 6.4 Hz, 1H; 2-H), 3.28, 3.27 (2s, 2×3H; 2×OCH_3), 1.32, 1.31 (2s, 2×3H; 2×BDA CH_3), 1.11 (d, $J = 6.4$ Hz, 3H; 1-H_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 134.4$ (C4), 119.3 (C5), 98.8 (2×BDA C_q), 75.4 (C3), 67.0 (C2), 47.88, 47.84 (OCH_3), 17.8, 17.7 (BDA CH_3), 16.7 (C1); IR (film): ν_{max} = 2951, 1376, 1122 s, 1039 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{11}H_{20}O_4Na$: 239.1259; found: 239.1258 $[M+Na]^+$; elemental analysis calcd (%) for $C_{11}H_{20}O_4$ (216.3): C 61.09, H 9.32; found: C 61.01, H 9.28.

Cycloadduct 16: A solution of oxime **6** (37 mg, 0.133 mmol) in CH_2Cl_2 (3 mL) was added over 6 h to a mixture of alkene **7** (86 mg, 0.398 mmol), triethylamine (2 μL, 0.013 mmol), and aqueous NaOCl (0.48 mL, 0.398 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C. After the addition was complete, the reaction mixture was stirred at 0 °C for 45 min before warming to RT. The suspension was poured into a mixture of water (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10 → 15 → 20% ethyl acetate/PE) to afford the major cycloadduct **16** (45 mg, 69%) and minor cycloadduct **16a** (11 mg, 17%). *Major isomer* **16**: $[\alpha]_D^{25} = -62.4$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, [D_8]toluene, 60 °C): $\delta = 7.18$–6.95 (m, Cbz Ph-H, 5H; buried under toluene peaks), 5.08 (d, $J = 12.2$, 1H; Cbz $PhCH_2$), 4.89 (d, $J = 12.4$ Hz, 1H; Cbz $PhCH_2$), 4.62 (dd, J = 2.3, 6.5 Hz, 1H; 7-H), 4.16 (ddd, J = 4.5, 6.3, 9.0 Hz, 1H; 4-H), 3.77 (m, 1H; 8-H), 3.67 (dd, J = 6.7, 9.1 Hz, 1H; 8-H), 3.58 (dd, J = 4.5, 9.7 Hz, 1H; 3-H), 3.48 (dq, J = 6.3, 9.7 Hz, 1H; 2-H), 3.06 (s, 3H; BDA OCH_3), 3.06–2.98 (m, 1H; 5-H), 2.98 (s, 3H; BDA OCH_3), 2.51 (m, 1H; 5-H), 1.60, 1.39 (2s, 2×3H; 2×acetal CH_3), 1.18, 1.16 (2s, 2×3H; 2×BDA CH_3), 1.04 (d, $J = 6.3$ Hz, 3H; 1-H_3); ^{13}C NMR (100 MHz, [D_8]toluene, 60 °C): $\delta = 157.1$ (Cbz C=O), 151.9 (C6), 136.7 (Ph C_q), Ph-H obscured by toluene peaks, 98.5, 98.4 (BDA C_q), 94.6 (acetal C_q), 79.5 (C4), 73.5 (C3), 66.6 (C8), 66.5 ($PhCH_2$), 65.5 (C2), 54.7 (C7), 47.2, 47.0 (BDA OCH_3), 34.7 (C5), 25.7, 23.3 (acetal CH_3), 17.2,

17.1 (BDA CH_3), 16.6 (C1); IR (film): ν_{max} = 2942, 1708 s, 1125 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{25}H_{36}N_2O_8Na$: 515.2369; found: 515.2346 $[M+Na]^+$.

Amine 5: $Pd(OH)_2/C$ (5 mg of 20% by wt Pd, 9 μmol) was added to a solution of isoxazoline **16** (24.0 mg, 49 μmol) in methanol (1 mL) and acetic acid (1 drop). The mixture was stirred at RT under a hydrogen atmosphere for 15 min then filtered through Celite, eluting with methanol and the solvent removed in vacuo. Purification by flash chromatography ($CHCl_3$/methanol/aq. NH_4OH 30:1:0.1) afforded amine **5** (12 mg, 77%) as a colourless oil. $[\alpha]_D^{25}=+17.5$ ($c=0.6$, $CHCl_3$); ^1H NMR (400 MHz, $CHCl_3$): $\delta=4.54$ (ddd, $J=4.5$, 6.9, 10.7 Hz, 1H; 4-H), 3.78–3.58 (m, 5H; 2-H, 3-H, 7-H, 8-H_2), 3.25 (s, 3H; BDA OCH_3), 3.23 (s, 3H; OCH_3), 3.23 (dd, $J=6.9$, 17.0 Hz, 1H; 5-H), 2.97 (dd, $J=10.8$, 17.0 Hz, 1H; 5-H), 1.27, 1.25 (2s, 2×3H; 2×BDA CH_3), 1.21 (d, $J=5.8$, 3H; 1-H_3); ^{13}C NMR (100 MHz, $CHCl_3$): $\delta=160.3$ (C6), 98.6, 98.6 (BDA C_q), 94.6 (acetal C_q), 79.5 (C4), 73.4 (C3), 65.8 (C2), 65.2 (C8), 51.3 (C7), 48.0, 47.9 (BDA OCH_3), 35.8 (C5), 17.6, 17.4 (BDA CH_3), 17.0 (C1); IR (film): ν_{max} =3361 w br, 2948, 1123 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{14}H_{26}N_2O_6Na$: 341.1689; found: 341.1689 $[M+Na]^+$.

Compound 18: K_2CO_3 (7.60 g, 55.1 mmol) and tosylmethyl isocyanide (3.79 g, 19.4 mmol) were added portionwise to a solution of BDA-protected glyderaldehyde **17** (3.30 g, 16.2 mmol) in anhydrous methanol (30 mL). The suspension was heated to reflux for 2 h then cooled to RT and water (150 mL) was added. The mixture was extracted with CH_2Cl_2 (3×100 mL) and the combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica (5% acetone in CH_2Cl_2) to give the oxazole **18** (3.94 g, 82%) as a white solid. $[\alpha]_D^{25}=-155.0$ ($c=1.2$, $CHCl_3$); m.p. 92 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.85$ (s, 1H; 13-H), 7.08 (s, 1H; 12-H), 5.06 (dd, $J=3.2$, 11.3 Hz, 1H; 10-H), 4.03 (dd, $J=11.3$, 11.3 Hz, 1H; 9-H^{ax}), 3.61 (dd, $J=3.3$, 11.2 Hz, 1H; 9-H^{eq}), 3.35, 3.32, 1.35, 1.33 (4s, 4×3H; 4× BDA OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=151.2$ (C11), 148.4 (C13), 124.6 (C12), 99.7, 98.1 (BDA C_q), 62.0 (C10), 60.9 (C9), 48.3, 48.2 (BDA OCH_3), 17.7, 17.5 (BDA CH_3); IR (film): ν_{max} = 2950, 1375, 1142 s, 1119 s, 1037 cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{11}H_{17}NO_5Na$: 266.1004; found: 266.1001 $[M+Na]^+$.

Compound 19: A solution of oxazole **18** (160 mg, 0.66 mmol) in TFA/water 4:1 (16 mL) was stirred at room temperature for 20 min. The solvent was removed in vacuo and the residue redissolved in methanol. To this solution was added triethylamine dropwise until the solution reached basic pH, and the solvent was removed in vacuo. The residue was dissolved in anhydrous CH_2Cl_2 (10 mL) and placed under an atmosphere of argon. To this solution was added Hünig's base (228 μL, 1.32 mmol) and DMAP (5 mg, cat.). The reaction mixture was cooled to −78 °C and chlorotriethylsilane (110 μL, 0.66 mmol) was added dropwise. After 15 minutes, another 10 μL of chlorotriethylsilane was added. The reaction mixture was quenched at −78 °C with saturated aqueous ammoniom chloride (15 mL) and was warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography on silica (5 → 10% acetone in CH_2Cl_2) to give TES-ether **19** (151 mg, 94%) as a colourless oil. $[\alpha]_D^{25}=+16.0$ ($c=1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CHCl_3$): $\delta=7.82$ (s, 1H; 13-H), 7.05 (s, 1H; 12-H), 4.85–4.81 (m, 1H; 10-H), 3.89 (dd, $J=4.1$, 10.1 Hz, 1H; 9-H), 3.83 (dd, $J=4.1$, 10.1 Hz, 1H; 9-H), 3.03 (br s, 1H; OH), 0.95 (t, $J=7.9$ Hz, 9H, TES CH_3), 0.35 (q, $J=$ 7.8 Hz, 6H; TES CH_2); ^{13}C NMR (100 MHz, $CHCl_3$): $\delta=151.2$ (C11), 150.6 (C13), 123.8 (C12), 66.7 (C10), 64.9 (C9), 6.6 (TES CH_3), 4.3 (TES CH_2); IR (film): ν_{max} = 3311 br, 2876, 1113 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{11}H_{21}NO_3Na$: 266.1188; found: 266.1177 $[M+Na]^+$.

Ester 20: DCC (1.64 mL of a 1 M solution in CH_2Cl_2, 1.64 mmol), DMAP (5 mg, cat.) and myristic acid (375 mg, 1.64 mmol) were added to a solution of alcohol **19** (363 mg, 1.49 mmol) in anhydrous CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 3 h. To precipitate out DCC residue, hexanes (50 mL) was added and the reaction mixture was filtered. The filtrate was extracted with saturated aqueous ammonium chloride (50 mL), and the aqueous layer was back extracted with ethyl acetate (2×50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica (10% ethyl acetate in hexanes) to give ester **20** (653 mg, 97%) as a colourless oil. $[\alpha]_D^{25}=+40.7$ ($c=1.6$, $CHCl_3$); ^1H NMR (400 MHz, $CHCl_3$): $\delta=7.83$ (s, 1H; 13-H), 7.11 (s, 1H; 12-H), 5.98 (dd, $J=6.0$, 6.0 Hz, 1H; 10-H), 3.99 (dd, $J=6.5$, 10.8 Hz, 1H; 9-H), 3.95 (dd, $J=5.6$, 10.8 Hz, 1H; 9-H), 2.33 (t, $J=7.5$, 2H; 15-H_2), 1.63–1.60 (m, 2H; 16-H_2), 1.25 (m, 20H; 17-H to 26-H), 0.93 (t, $J=7.9$ Hz, 9H, TES CH_3), 0.88 (t, $J=7.0$, 3H; 27-H), 0.59 (q, $J=7.9$ Hz, 6H; TES CH_2); ^{13}C NMR (100 MHz, $CHCl_3$): $\delta=173.1$ (C14), 151.3 (C11), 148.7 (C13), 126.1 (C12), 67.5 (C10), 63.0 (C9), 34.5, 32.3, 30.5–25.2, 23.1 (myristoyl C14 to C26), 14.5 (C27), 7.0 (TES CH_3), 4.7 (TES CH_2); IR (film): ν_{max} = 2923, 1744 s, 1108 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{25}H_{47}NO_4Na$: 476.3172; found: 476.3160 $[M+Na]^+$.

Acid 4: KF (13 mg, 0.225 mmol) and 8 N Jones' reagent (78 μL, 700 μL per mmol alcohol) were added at 0 °C to a solution of TES-ether **20** (51 mg, 0.112 mmol) in acetone (0.8 mL). The reaction mixture was stirred at 0 °C for 4 h. The crude mixture was purified by loading the neat reaction mixture onto a silica gel column and chromatographing (ethyl acetate/methanol/acetone/water 17:1:1:1 → 12:1:1:1) to give the unstable acid **4** (30 mg, 76%) as a waxy white solid. $[\alpha]_D^{25}=+30$ ($c=0.6$, $CHCl_3$); ^1H NMR (400 MHz, [D_6]DMSO): $\delta=8.26$ (s, 1H; 13-H), 7.09 (s, 1H; 12-H), 5.80 (s, 1H; 10-H), 2.23 (t, $J=7.3$, 2H; 15-H_2), 1.52–1.47 (m, 2H; 16-H_2), 1.22 (m, 20H; 17-H to 26-H), 0.84 (t, $J=6.4$, 3H; 27-H); ^{13}C NMR (100 MHz, [D_6]DMSO): $\delta=172.3$ (C14), 167.0 (C9), 158.3 (C11), 152.2 (C13), 125.6 (C12), 67.7 (C10), 31.7, 29.5, 30.5, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 28.9, 25.2, 23.1 (C15 to C26), 14.4 (C27); IR (film): ν_{max} = 3443 s br, 2923, 1684 s, 1640 s, 1209 s, 1140 s cm^{-1}.

Compound 23: Triethylamine (0.78 mL, 5.6 mmol), TBDPSCl (1.3 mL, 5.15 mmol) and DMAP (630 mg, 5.15 mmol) were added under argon to a solution of alcohol **19** (1.14 g, 4.68 mmol) in anhydrous DMF (15 mL). The reaction mixture was stirred at RT for 24 h. Water (5 mL) was added to quench, and the crude mixture was poured into water (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3× 50 mL. The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was filtered through a plug of silica (10% ethyl acetate/hexanes) to give the crude silylated-diol **22**.

PPTS (590 mg, 2.34 mmol) was added under argon to a solution of **22** in anhydrous methanol (20 mL). The reaction mixture was stirred at RT for 15 minutes and quenched by pouring into water (100 mL). This was extracted with CH_2Cl_2 (3×100 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica (40 → 50% ethyl acetate/PE) to give alcohol **23** (1.66 g, 97% over 2 steps) as a colourless oil. $[\alpha]_D^{25}=+$ 73.6 ($c=0.5$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.69$ (s, 1H; 13-H), 7.69–7.67 (m, 2H; Ph-H), 7.54–7.52 (m, 2H; Ph-H), 7.48–7.30 (m, 6H; Ph-H), 6.78 (s, 1H; 12-H), 4.86 (dd, $J=5.2$, 5.2 Hz, 1H; 10-H), 3.85 (ddd, $J=6.1$, 6.1, 11.4 Hz, 1H; 9-H), 3.74 (ddd, $J=4.7$, 6.7, 11.3 Hz, 1H; 9-H), 1.99 (dd, $J=6.6$, 6.6 Hz, 1H; OH), 1.07 (s, 9H, TBDPS CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=151.0$ (C11), 150.5 (C13), 135.7, 135.6 (Ph-C), 130.1 (Ph-H C), 130.9 (Ph C_q), 127.9, 127.7 (Ph-C), 124.4 (C12), 68.1 (C10), 65.4 (C9), 26.8 (TBDPS CH_3), 19.3 (TBDPS *t*Bu C_q); IR (film): ν_{max} = 3339 br, 2858, 1104 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{21}H_{25}NO_3SiNa$; 390.1501; found: 390.1494.

Acid 24: 8 N Jones' reagent (0.61 mL, 0.7 mL per mmol) was added at 0 °C under argon to a solution of alcohol **23** (320 mg, 0.872 mmol) in reagent-grade acetone (5 mL). The resulting bright red solution was stirred at 0 °C for 1 h then warmed to RT and stirred for another 2 h. The crude reaction mixture was then filtered through a pad of Celite, rinsing with acetone (100 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (ethyl acetate/acetone/methanol/water 97:1:1:1 → 47:1:1:1 → 17:1:1:1) to give unstable acid **24** (163 mg, 49%) as a colourless oil. ^1H NMR (400 MHz, CD_3OD): $\delta=8.02$ (s, 1H; 13-H), 7.75–7.73 (m, 2H; Ph-H), 7.57–7.55 (m, 2H; Ph-H), 7.43–7.29 (m, 6H; Ph-H), 6.70 (s, 1H; 12-H), 5.11 (s, 1H; 10-H), 1.06 (s, 9H, TBDPS *t*Bu CH_3); ^{13}C NMR (125 MHz, CD_3OD): $\delta=175.2$ (C9), 152.2 (C11), 151.1 (C13), 135.6, 135.4 (Ph-C), 133.1, 132.9 (Ph C_q), 129.6, 129.5, 127.3 and 127.2 (Ph-C), 123.0 (C12), 68.6 (C10), 25.9 (TBDPS CH_3), 18.8 (TBDPS C_q); IR (film): ν_{max} =2932, 1744 s, 1112 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{21}H_{23}NO_4SiNa$: 404.1294; found: 404.1286 $[M+Na]^+$.

Isoxazoline-containing amide 26: Amine **5** (12 mg, 0.038 mmol) as a solution in DMSO (1 mL) was added under argon to a solution of acid **24** (13 mg, 0.034 mmol) in anhydrous DMSO (1 mL). To this solution was added TBTU (12 mg, 0.038 mmol), and the reaction mixture was stirred at RT for 4 h. Another portion of TBTU (2 mg, 0.006 mmol) was added, and the reaction mixture was stirred for an additional 12 h. Water (1 mL) was added to the reaction mixture to quench, and the resulting suspension was poured into ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (60% ethyl acetate/PE → 100% ethyl acetate) to afford amide **26** (15 mg, 65%) as a colourless oil. $[\alpha]_D^{25}=+7.9$ ($c=0.8$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=8.02$ (d, $J=7.5$ Hz, 1H; amide NH), 7.70 (s, 1H; 13-H), 7.64–7.63 (m, 2H; Ph-H), 7.49–7.40 (m, 6H; Ph-H), 7.31 (dd, $J=7.7$, 7.3 Hz, 2H, Ph-H), 6.61 (s, 1H; 12-H), 5.20 (s, 1H; 10-H), 4.81 (ddd, 3.5, 3.5, 7.6 Hz, 1H; 7-H), 4.57 (ddd, $J=4.3$, 7.7, 10.8 Hz, 1H; 4-H), 4.02 (ddd, $J=3.4$, 4.9, 11.7 Hz, 1H; 8-H), 3.90 (ddd, $J=3.6$, 8.4, 11.7 Hz, 1H; 8-H), 3.68–3.62 (m, 1H; 2-H), 3.68–3.62 (m, 1H; 3-H), 3.25, 3.22 (2s, 2×3H; 2×BDA OCH_3), 3.14 (dd, $J=7.2$, 17.0 Hz, 1H; 5-H), 2.93 (dd, $J=10.7$, 17.1 Hz, 1H; 5-H), 2.67 (dd, $J=5.0$, 8.4 Hz, 1H; OH), 1.29, 1.26 (2s, 2×3H; 2×BDA CH_3), 1.23 (d, $J=5.9$ Hz, 3H; 1-H_3), 1.09 (s, 9H, TBDPS CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=169.0$ (C9), 157.1 (C6), 150.9 (C13), 148.5 (C11), 135.6, 135.4 (Ph-C), 131.5, 131.4 (Ph C_q), 130.5, 130.3, 128.1 and 127.8 (Ph-C), 126.0 (C12), 98.7, 98.6 (BDA C_q), 80.0 (C4), 73.3 (C2), 68.1 (C10), 65.7 (C3), 64.1 (C8), 49.9 (C7), 48.0, 47.9 (BDA OCH_3), 36.5 (C5), 26.7 (TBDPS CH_3), 19.2 (TBDPS *t*Bu C_q), 17.6, 17.4 (BDA CH_3), 17.0 (C1); IR (film): ν_{max} = 3486, 2947, 1691, 1507, 1122 s cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{35}H_{47}N_3O_9SiNa$: 704.2979; found: 704.2988 $[M+Na]^+$.

Oxazoline 27: DAST (2 μL, 11 μmol) was added at −78°C under argon to a solution of amide **26** (6.7 mg, 9.8 μmol) in anhydrous CH_2Cl_2 (1 mL). The reaction mixture was stirred at −78°C for 30 min. Anhydrous K_2CO_3 (2 mg) was added to quench, and the mixture was allowed to warm to RT with stirring. The reaction mixture was poured into aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (40 → 50% ethyl acetate/PE) to give oxazoline **27** (5.9 mg, 91%) as a colourless oil. $[\alpha]_D^{25}=+29.0$ ($c=0.1$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.80$ (s, 1H; 13-H), 7.68 (d, $J=6.8$ Hz, 2H; Ph-H), 7.56 (d, $J=7.0$ Hz, 2H; Ph-H), 7.49–7.38 (m, 4H; Ph-H), 7.35 (dd, $J=7.4$, 7.5 Hz, 2H; Ph-H), 6.93 (s, 1H; 12-H), 5.50 (s, 1H; 10-H), 4.95 (dd, $J=9.4$, 9.4 Hz, 1H; 7-H), 4.53 (ddd, $J=5.4$, 7.8, 10.8 Hz, 1H; 4-H), 4.40 (d, $J=9.4$ Hz, 1H; 8-H), 4.40 (d, $J=9.4$ Hz, 1H; 8-H), 3.64 (dq, $J=6.1$, 9.7 Hz, 1H; 2-H), 3.55 (dd, $J=5.3$, 9.7 Hz, 1H; 3-H), 3.24, 3.17 (2s, 2×3H; 2×BDA OCH_3), 3.10 (dd, $J=7.7$, 17.2 Hz, 1H; 5-H), 2.81 (dd, $J=10.8$, 17.3 Hz, 1H; 5-H), 1.29 (s, 3H; BDA CH_3), 1.24 (d, $J=6.5$ Hz, 3H; 1-H_3), 1.22 (s, 3H; BDA CH_3), 1.07 (s, 9H; TBDPS CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=166.6$ (C9), 157.7 (C6), 151.1 (C13), 149.0 (C11), 135.5 (Ph-C), 135.6 (TBPDS Ph-H), 132.127, 132.0 (Ph C_q), 130.2, 130.1, 127.8 and 127.8 (Ph-C), 125.0 (C12), 98.6, 98.6 (BDA C_q), 80.2 (C4), 73.1 (C3), 70.0 (C8), 66.1 (C2), 63.7 (C10), 63.5 (C7), 48.0, 47.9 (BDA OCH_3), 35.4 (C5), 26.6 (TBDPS CH_3), 19.3 (TBDPS *t*Bu C_q), 17.6, 17.4 (BDA CH_3), 17.0 (C1); IR (film): ν_{max} = 2931 s, 1120 s cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{35}H_{45}N_3O_8SiNa$: 686.2874; found: 686.2870 $[M+Na]^+$.

Diol 28: $[Mo(CO)_3(MeCN)_3]$ (443 mg, 1.46 mmol) was added to a solution of isoxazoline **16** (360 mg, 0.73 mmol) in acetonitrile/water 3:1 (20 mL) and the resulting orange/brown slurry stirred for 1 h. Silica gel (ca. 30 mL) was added and the solvent removed in vacuo. The residue was loaded onto a pad of silica and eluted with EtOAc (500 mL). The solvent was removed under reduced pressure to give a brown gum which was purified by flash chromatography on silica gel (Biotage, 40M cartridge, PhMe/EtOAc 9:1 → 4:6) to afford the β-hydroxy ketone as a colourless gum (272 mg, 0.55 mmol, 75%). $[\alpha]_D^{25}=+64.0$ ($c=0.2$, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3NO_2, 80°C): $\delta=7.44$–7.32 (m, 5H; Cbz Ph-H), 5.15 (m, 2H; Cbz $PhCH_2$), 4.60 (dd, $J=2.8$, 7.5 Hz, 1H; 7-H), 4.25 (dd, $J=9.1$, 8.2 Hz, 1H; 8-H), 4.09–4.02 (m, 1H; 4-H), 4.06 (dd, $J=2.8$, 9.1 Hz, 1H; 8-H), 3.69–3.61 (m, 1H; 2-H), 3.49 (dd, $J=4.4$, 9.8 Hz, 1H; 3-H), 3.25, 3.23 (2s, 2×3H; 2×BDA OCH_3), 2.87–2.77 (m, 2H; 5-H_2), 1.69, 1.55 (2s, 2×3H; 2×acetal CH_3), 1.27, 1.24 (2s, 2×3H; 2×BDA CH_3), 1.15 (d, $J=6.0$ Hz, 3H; 1-H_3); ^{13}C NMR (125 MHz, CD_3NO_2, 80°C): $\delta=207.7$ (C6), 152.5 (Cbz C=O), 136.9 (Ph C_q), 128.4, 127.9 (Cbz Ph-H), 127.7 (Ph-C), 98.8, 98.6 (BDA C_q), 95.2 (acetal C_q), 75.8 (C3), 67.3 (C4), 66.8 ($PhCH_2$), 65.7 (C2), 65.7 (C7), 65.1 (C8), 46.9, 46.8 (BDA OCH_3), 41.5 (C5), 24.7, 23.3 (acetal CH_3), 16.8, 16.6 (BDA CH_3), 16.3 (C1); IR (film): ν_{max} = 3526 w br, 2941, 1711 s, 1127 s cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{25}H_{37}NO_9Na$: 518.2366; found: 518.2339 $[M+Na]^+$.

$NaBH_4$ (13 mg, 0.345 mmol) was added under argon at 0°C to a solution of the β-hydroxy ketone (34 mg, 0.069 mmol) in methanol (2 mL). The reaction mixture was stirred at 0°C for 1 h before quenching with saturated aqueous NH_4Cl (1 mL). This suspension was warmed to RT, poured into water (10 mL), and then extracted with Et_2O (3×10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (40% ethyl acetate/PE) to afford diol **28** (29.5 mg, 88%), the major diastereomer, as a colourless oil. $[\alpha]_D^{25}=+55.5$ ($c=1.4$, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3NO_2, 80°C): $\delta=7.46$–7.32 (m, 5H; Cbz Ph-H), 5.19 (m, 2H; Cbz $PhCH_2$), 4.21–4.15 (m, 1H; 6-H), 4.12–4.08 (m, 1H; 8-H), 4.12–4.06 (m, 1H; 7-H), 4.02 (dd, $J=6.3$, 9.1 Hz, 1H; 8-H), 3.86–3.80 (m, 1H; 4-H), 3.75 (dq, $J=6.6$, 10.5 Hz, 1H; 2-H), 3.49 (dd, $J=4.1$, 9.5 Hz, 1H; 3-H), 3.26, 3.23 (2s, 2×3H; 2×BDA OCH_3), 2.00–1.94 (m, 1H; 5-H), 1.65–1.60 (m, 1H; 5-H), 1.63, 1.52 (2s, 2×3H; 2×acetal CH_3), 1.27, 1.23 (2s, 2×3H; 2×BDA CH_3), 1.14 (d, $J=6.6$ Hz, 3H; 1-H_3); ^{13}C NMR (125 MHz, CD_3NO_2, 80°C): $\delta=153.8$ (Cbz C=O), 137.2 (Ph C_q), 128.4 (Cbz Ph-H), 127.8 (Cbz Ph-H), 127.7 (Ph-C), 98.8, 98.6 (BDA C_q), 94.5 (acetal C_q), 76.2 (C3), 71.8 (C4), 71.6 (C6), 70.3 ($PhCH_2$), 66.6 (C2), 65.6 (C8), 59.8 (C7), 46.9, 46.7 (BDA OCH_3), 33.5 (C5), 25.6, 22.6 (acetal CH_3), 16.7, 16.6 (BDA CH_3), 16.2 (C1); IR (film): ν_{max} = 3424 w br, 2938, 1704 s, 1128 s cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{25}H_{39}NO_9Na$: 520.2523; found: 520.2536 $[M+Na]^+$.

Amine 29: 2,2-Dimethoxypropane (57 μL, 0.46 mmol) and a catalytic amount of *p*-toluenesulfonic acid (<1 mg) was added under argon at RT to a solution of diol **28** (23 mg, 0.046 mmol) in acetone (0.5 mL). The reaction mixture was stirred at RT for 15 min before quenching with saturated aqueous $NaHCO_3$ (1 mL). This mixture was diluted with Et_2O (10 mL) and poured into saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with Et_2O (2×10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10% ethyl acetate/hexanes) to afford acetonide protected diol (21.7 mg, 88%) as a colourless oil. $[\alpha]_D^{25}=+30.8$ ($c=1.3$, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3NO_2, 80°C): $\delta=7.44$–7.33 (m, 5H; Cbz Ph-H), 5.19 (d, $J=12.5$ Hz, 1H; Cbz $PhCH_2$), 5.12 (d, $J=12.5$ Hz, 1H; Cbz $PhCH_2$), 4.35 (m, 1H; 6-H), 4.13 (dd, $J=1.2$, 9.4 Hz, 1H; 8-H), 4.06–4.04 (m, 1H; 7-H), 3.96 (dd, $J=6.5$, 9.3 Hz, 1H; 8-H), 3.85–3.82 (m, 1H; 4-H), 3.72 (dq, $J=6.4$, 9.4 Hz, 1H; 2-H), 3.32 (dd, $J=6.4$, 9.5 Hz, 1H; 3-H), 3.24, 3.23 (2s, 2×3H; 2×BDA OCH_3), 1.72 (ddd, $J=2.5$, 2.5, 13.1 Hz, 1H, 5-H^{eq}), 1.61, 1.49 (2s, 2×3H; 2×NO acetal CH_3), 1.44–1.40 (m, 1H; 5-H^{ax}), 1.42 (s, 3H; acetonide CH_3), 1.33 (s, 3H; acetonide CH_3), 1.24, 1.22 (2s, 2×3H; 2×BDA CH_3), 1.16 (d, $J=6.4$ Hz, 3H; 1-H_3); ^{13}C NMR (125 MHz, CD_3NO_2, 80°C): $\delta=153.8$ (Cbz C=O), 137.3 (Ph C_q), 128.4, 127.6 (Cbz Ph-H), 127.7 (Ph-C), 98.6, 98.5 (BDA C_q), 98.4 (acetonide C_q), 94.3 (NO acetal C_q), 75.0 (C3), 69.9 (C4), 68.2 (C6), 67.2 (C2), 66.4 ($PhCH_2$), 63.4 (C8), 59.6 (C7), 46.8, 46.6 (BDA OCH_3), 29.0 (acetonide CH_3), 27.3 (C5), 25.1, 22.4 (NO acetal CH_3), 18.8 (acetonide CH_3), 16.8, 16.7 (BDA CH_3), 16.6 (C1); IR (film): ν_{max} = 2990, 1707 s, 1123 s cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{28}H_{43}NO_9Na$: 560.2836; found: 560.2822 $[M+Na]^+$.

Pd/C (1.0 mg of 10% by wt Pd, 1 μmol) was added under an argon atmosphere to a solution of the acetonide (7.0 mg, 13 μmol) in ethanol (0.5 mL). This mixture was then stirred under an atmosphere of hydrogen vigorously for 15 min, then filtered through a pad of Celite, rinsing with ethanol (15 mL). Concentration in vacuo and purification of the residue by flash chromatography on silica gel ($CHCl_3$/methanol/aq. NH_4OH 30:1:0.1) afforded amine **29** (12 mg, 77%) as a colourless oil. $[\alpha]_D^{25}=+108$ ($c=0.5$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=3.91$–3.86 (m, 1H; 4-H), 3.79–3.77 (m, 1H; 6-H), 3.70 (dq, $J=6.3$, 9.4 Hz, 1H; 2-H), 3.59 (dd,

J=4.2, 10.6 Hz, 1H; 8-H), 3.49 (dd, J=6.5, 10.7 Hz, 1H; 8-H), 3.31 (dd, J=7.5, 9.3 Hz, 1H; 3-H), 3.25, 3.25 (2s, 2×3H; 2×BDA OCH_3), 2.78–2.73 (m, 1H; 7-H), 1.79 (m, 1H; 5-H), 1.41 (s, 3H; acetonide CH_3), 1.37–1.35 (m, 1H; 5-H), 1.35 (s, 3H; acetonide CH_3), 1.28, 1.28 (2s, 2×3H; 2×BDA CH_3), 1.20 (d, J=6.4 Hz, 3H; 1-H_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ=98.4 (acetonide C_q), 98.4, 98.3 (BDA C_q), 74.6 (C3), 70.6 (C6), 69.5 (C4), 67.7 (C2), 63.5 (C8), 56.5 (C7), 47.9, 47.8 (BDA OCH_3), 29.9 (acetonide CH_3), 29.4 (C5), 19.9 (acetonide CH_3), 17.8 (C1), 17.6, 17.5 (BDA CH_3); IR (film): ν_{max} = 3360 w br, 2933, 1123 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{17}H_{33}NO_7Na$: 386.2155; found: 386.2152 $[M+Na]^+$.

Amide 30: TBTU (10 mg, 31 μmol) was added under argon to a solution of acid **24** (11 mg, 29 μmol) and amine **29** (4 mg, 11 μmol) in DMSO (0.25 mL). The reaction mixture was stirred at RT for 16 h. Water (1 mL) was added to quench, and the crude reaction mixture was poured into water (10 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organics were washed once with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (70 → 80% ethyl acetate/hexanes) to afford amide **30** (3.7 mg, 47%) as a colourless oil. R_f = 0.11 (20% ethyl acetate/2% methanol/CH_2Cl_2); $[\alpha]_D^{25}$=+104.0 (c=0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.85 (d, J=8.5 Hz, 1H; N-H), 7.67 (s, 1H; 13-H), 7.64 (d, J=7.4 Hz, 2H; Ph-H), 7.50–7.40 (m, 6H; Ph-H), 7.31 (t, J=7.3 Hz, 2H; Ph-H), 6.52 (s, 1H; 12-H), 5.19 (s, 1H; 10-H), 4.28 (d, J=11.6 Hz, 1H; 6-H), 4.00–3.97 (m, 2H; 4-H, 7-H), 3.86 (dd, J=11.1, 4.3 Hz, 1H; 8-H), 3.78 (dd, J=11.1, 6.0, 5.1 Hz, 1H; 8-H′), 3.73 (dq, J=9.7, 6.3 Hz, 1H; 2-H), 3.37 (dd, J=9.7, 7.0 Hz, 1H; 3-H), 3.27, 3.18 (2s, 2×3H; 2×OCH_3), 2.05 (br, 1H; OH), 1.91 (d, J=13.2 Hz, 1H; 5-H^{eq}), 1.91 (ddd, J=13.2, 12.5, 11.6 Hz, 1H; 5-H^{ax}), 1.48, 1.36 (2s, 2×3H; 2×acetal CH_3), 1.30 (2s, 2×3H; 2×BDA CH_3), 1.25 (d, J=6.3 Hz, 3H; 1-H_3), 1.12 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ=169.5 (C9), 150.7 (C13), 148.1 (C11), 135.7, 135.4 (Ph-C), 132.7, 131.2 (Ph C_q), 130.6, 130.2, 128.2 and 127.7 (Ph-C), 125.9 (C12), 99.0 (acetonide C_q), 98.4, 98.3 (BDA C_q), 74.5 (C3), 70.0 (C6), 69.8 (C4), 67.9 (C2), 67.9 (C10), 64.2 (C8), 54.1 (C7), 44.1, 47.9 (BDA OCH_3), 30.1 (C5), 29.7 (acetal CH_3), 27.0 ($C(CH_3)_3$), 19.9 (acetal CH_3), 19.4 ($C(CH_3)_3$), 18.1 (C1), 17.4, 17.7 (BDA CH_3); IR (film): ν_{max} = 3420 br, 3418, 2933, 2859, 1683 s, 1512 s, 1125 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{38}H_{54}N_2O_{10}SiNa$: 749.3445; found: 749.3437 $[M+Na]^+$.

5-Dimethoxymethyloxazole 36: TosMIC (100 g, 0.513 mol) and anhydrous K_2CO_3 (208 g, 1.53 mol) were suspended in methanol (750 mL) at RT. Glyoxal-1,1-dimethyl acetal (45% solution in *t*BuOMe, 145 mL, 0.564 mol) was added slowly to the stirred suspension at RT. The reaction mixture was stirred at RT for 1 h 30 min then heated under reflux for 3 h before cooling to RT. The volume of the reaction mixture was reduced by about half under reduced pressure. Water (600 mL) was added, and the resulting aqueous solution was extracted with CH_2Cl_2 (6×200 mL). The combined organics were dried ($MgSO_4$) and the solvent was removed in vacuo and the residue purified by flash chromatography (50% Et_2O/PE) to afford oxazole **36** as a colourless oil (42.6 g, 58%). R_f = 0.22 (50% Et_2O/PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.89 (s, 1H; 13-H), 7.14 (s, 1H; 12-H), 5.51 (s, 1H; 10-H), 3.36 (s, 6H; 2×OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.4 (C13), 148.6 (C11), 125.7 (C12), 97.1 (C10), 53.3 (OCH_3); IR (film): ν_{max} = 3133 w, 2940, 2834, 1506, 1446, 1103 s, 1052 s cm^{-1}; HRMS (EI+): m/z: calcd for $C_6H_9NO_3$: 143.0582; found: 143.0575 $[M]^+$.

Cyanohydrin *rac*-41/(*R*)-41: *Racemic route:* Triethylamine (1.41 mL, 10.1 mmol) was added to a solution of aldehyde **37** (9.78 g, 100.8 mmol) in CH_2Cl_2 (400 mL) at 0°C. Trimethylsilyl cyanide (10 g, 100.8 mmol) was added and the reaction mixture was stirred at 0°C for 2.5 h. Aqueous 2 M HCl (100 mL) was added dropwise to the vented flask with vigorous stirring. After 30 min further aqueous 2 M HCl (100 mL) was added, stirred for 30 min and the layers separated. The organic layer was washed with aqueous 2 M HCl (100 mL) and the combined aqueous layers extracted with ethyl acetate (7×200 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to give cyanohydrin *rac*-**41** as a yellow solid (11.54 g, 92%). R_f = 0.40 (80% ethyl acetate/PE).

Enantioselective route: Aldehyde **37** (36 mg, 0.37 mmol), thiourea catalyst **45** (7.2 mg, 18.5 μmol) and 2,2,2-trifluoroethanol (27 μL, 0.37 mmol) were dissolved in dry CH_2Cl_2 (2.0 mL) under an argon atmosphere. At −78°C, a solution of trimethylsilyl cyanide (99 μL, 0.74 mmol) in 1.5 mL dry CH_2Cl_2 was added over a period of 5 min and the solution allowed to stir for 2.5 h. It was warmed to RT and quenched with aqueous 3 N HCl (2 mL). After stirring for further 30 min, the mixture was partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (4×10 mL), the combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude material (78% *ee* by Mosher ester analysis) is purified by flash chromatography (PE/ethyl acetate 1:1) to give (*S*)-**41** (41 mg, 0.33 mmol, 89%) as a white solid. M.p. 106–107°C; $[\alpha]_D^{25}$=−15.5 (c=0.9, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ=8.30 (s, 1H; 13-H), 7.31 (s, 1H; 12-H), 5.87 (s, 1H; 10-H); ^{13}C NMR (100 MHz, CD_3OD): δ=154.8 (C13), 149.4 (C11), 126.1 (C12), 118.6 (CN), 56.2 (C10); IR (film): ν_{max} = 3134, 3043 br, 2839, 2716, 1507, 1123 s, 1056 s, 971 s cm^{-1}; HRMS (EI+): m/z: calcd for $C_5H_4N_2O_2$: 124.0273; found: 124.0271 $[M]^+$.

Preparation of 2 M HCl in MeOH: Anhydrous methanol (400 mL) was cooled to 0°C under argon. Acetyl chloride (62.8 mL, 800 mmol) was added dropwise (dropping funnel) to the rapidly stirring MeOH. After complete addition, the solution was warmed to RT and used immediately.

Hydroxy-ester *rac*-42: *Racemic route:* Cyanohydrin *rac*-**41** (11.4 g, 91.9 mmol) was dissolved in 2 M HCl/methanol (400 mL, prepared as above) and heated under reflux for 15 h. After cooling to RT, water (300 mL) was added and stirred for 1 h before the solution was neutralised to pH 7–8 by the slow addition of saturated aqueous $NaHCO_3$. Methanol (approx 250 mL) was removed under reduced pressure and the aqueous solution was extracted with $CHCl_3$ (3×100 mL) and then $CHCl_3$/*i*PrOH 3:1 (8×150 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to give methyl ester *rac*-**42** as a brown oil (12.85 g, 89%).

*Methanolysis of enantiomerically enriched (*R*)-41:* (*S*)-Cyanohydrin **41** (116 mg, 0.93 mmol, 71% *ee*) was treated with 1.25 M HCl in MeOH (18.6 mmol, 14.8 mL). The mixture was allowed to stir for 48 h at RT. It was then hydrolysed with H_2O (10 mL), the pH adjusted to 8 with sat. aqueous $NaHCO_3$ and the mixture extracted with ethyl acetate (5×20 mL). The combined organic extracts were dried with $MgSO_4$ and the solvent was removed under reduced pressure. After drying in vacuo, (*S*)-configured ester **42** (102 mg, 70%, 66% *ee* by Moshers ester analysis) was obtained as yellow oil which could be directly used in the next step without further purification.

Enantioselective α-oxidation of ester 48: Under an argon atmosphere, LiHMDS (275 μL, 0.275 mmol, 1 M in THF) is diluted with dry THF (1.5 mL). To this, a solution of ester **48** (35.3 mg, 0.25 mmol) in dry THF (1.5 mL) was added dropwise at −78°C. Stirring was continued for 30 min at −78°C and a solution of oxaziridine **49** (79.6 mg, 0.275 mmol) in dry THF (2.0 mL) was added over 2 min. The mixture was allowed to stir for further 30 min at −78°C, then quenched with sat. aqueous NH_4Cl (3.0 mL) and partitioned between water (15 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL), the combined organic extracts were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography (PE/ethyl acetate 2:1 → 1:1; → ethyl acetate) to give the (*R*)-configured α-hydroxy ester *ent*-**42** (25.0 mg, 0.159 mmol, 64%, 70% *ee* by Moshers ester analysis) as a yellow oil. The reduced camphor precursor of **49** can be recovered (57 mg, 83%). R_f = 0.31 (80% ethyl acetate/PE); ^{1}H NMR (400 MHz, CD_3OD): δ=8.21 (s, 1H; 13-H), 7.19 (s, 1H; 12-H), 5.42 (s, 1H; 10-H), 3.80 (s, 3H; OCH_3); ^{13}C NMR (100 MHz, CD_3OD): δ=172.3 (C9), 153.9 (C13), 151.6 (C11), 125.7 (C12), 66.6 (C10), 53.6 (OCH_3); IR (film): ν_{max} = 3255 br, 3136, 1746 s, 1646, 1507, 1439 cm^{-1}; HRMS (EI+): m/z: calcd for $C_6H_7NO_4$: 157.0375; found: 157.0376 $[M]^+$.

Compound 43: Imidazole (10.8 g, 159 mmol) was added to a solution of methyl ester *rac*-**42** (12.5 g, 79.6 mmol) in DMF (67 mL) at RT, followed by the addition of TBDPSCl (26 mL, 100 mmol) and DMAP (122 mg, 1 mmol) at RT. After 1 h 45 min, water (400 mL) was added to the stirred solution and the aqueous mixture extracted with Et_2O (3×300 mL). The

combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (25% Et_2O/PE) afforded silyl-protected **43** as a colourless oil (27.0 g, 85%). R_f = 0.58 (50% ethyl acetate/PE); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1H; 13-H), 7.71 (d, J = 7.2 Hz, 2H; Ph-H), 7.65 (d, J = 6.8 Hz, 2H; Ph-H), 7.47–7.33 (m, 6H; Ph-H), 6.88 (s, 1H; 12-H), 5.25 (s, 1H; 10-H), 3.63 (s, 3H; OCH_3), 1.10 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2 (C9), 151.0 (C13), 148.8 (C11), 135.9, 135.6 (Ph-C), 132.3, 132.2 (Ph C_q), 130.13, 130.06, 127.75 and 127.72 (Ph-C), 125.1 (C12), 67.0 (C10), 52.4 (OCH_3), 26.6 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$); IR (film): ν_{max} = 2955, 2859, 1764 s, 1112 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{22}H_{26}NO_4Si$: 396.1624; found: 396.1624 $[M+H]^+$. Identical conditions were used when enantioenriched **42** was employed.

Amide 25 and amide 44: Ice cooled aqueous LiOH (0.5 M, 53 mL, 26.4 mmol) was added dropwise to a rapidly stirred solution of methyl ester **43** (5.98 g, 15.1 mmol) in THF (60 mL) at 0°C. The reaction mixture was stirred at 0°C for 5 min then warmed to RT. The loss of starting material was monitored by TLC (80% ethyl acetate/PE) and when all starting material was consumed (30 min) the solution was cooled to 0°C and ice cooled aqueous HCl (0.5 M, 20 mL) was added dropwise to the rapidly stirred solution causing the solution to become cloudy. The reaction mixture was partitioned between brine (175 mL) and ethyl acetate (200 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2×150 mL) and the combined organic extracts were dried ($MgSO_4$), and the solvent removed in vacuo to give carboxylic acid *rac*-**24** as a white foam which was used immediately.

Crude carboxylic acid *rac*-**24** was dissolved in DMF (50 mL) then TBTU (7.29 g, 22.7 mmol) was added and stirred for 10 min at RT. Serine methyl ester hydrochloride (3.77 g, 24.2 mmol) was suspended in DMF (40 mL) and Hünigs base (3.95 mL, 22.7 mmol) was added to the stirred mixture. The amine solution was transferred to the activated acid by cannula and the mixture stirred overnight. The reaction mixture was partitioned between 10% w/v aqueous LiCl solution (400 mL) and ethyl acetate (300 mL) and the layers separated. The organic layer was washed with 1 M aqueous HCl (3×100 mL) and the combined HCl washings extracted with ethyl acetate (150 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (150 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (1% MeOH/10% ethyl acetate/89% CH_2Cl_2 → 1% MeOH/20% ethyl acetate/79% CH_2Cl_2) afforded amide **44** as a colourless gum (2.47 g, 34%) followed by amide **25** as a colourless gum (2.31 g, 32%). Identical conditions were used when enantioenriched **24** was employed.

Amide ***25***: R_f = 0.20 (40% ethyl acetate/2% methanol/CH_2Cl_2); $[\alpha]_D^{25}$ = +54.6 (c = 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.3 Hz, 1H; N-H), 7.70 (s, 1H; 13-H), 7.67 (d, J = 7.3 Hz, 2H; Ph-H), 7.50–7.40 (m, 6H; Ph-H), 7.32 (t, J = 7.3 Hz, 2H; Ph-H), 6.60 (s, 1H; 12-H), 5.21 (s, 1H; 10-H), 4.67 (ddd, J = 7.3, 3.7, 3.5 Hz, 1H; 7-*H*), 4.06 (ddd, J = 11.2, 6.0, 3.7 Hz, 1H; 8-*H*), 4.00 (ddd, J = 11.2, 6.0, 3.5 Hz, 1H; 8-*H*′), 3.98 (s, 3H; OCH_3), 2.26 (t, J = 6.0 Hz, 1H; O*H*), 1.13 (s, 9H; C-$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (C6), 169.3 (C9), 151.3 (C13), 149.1 (C11), 136.2, 135.9, 132.1 and 131.7 (Ph-C), 130.9, 130.7 (Ph C_q), 128.5, 128.2 (Ph-C), 126.3 (C12), 68.5 (C10), 63.5 (C8), 55.0 (C7), 53.2 (OCH_3), 27.2 ($C(CH_3)_3$), 19.6 ($C(CH_3)_3$); IR (film: ν_{max} = 3423, 3410 br, 2933, 2859, 1748 s, 1680 s, 1517 s, 1428 s, 1106 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{25}H_{31}N_2O_6Si$: 483.1946; found: 483.1950 $[M+H]^+$.

Amide ***44***: R_f = 0.31 (40% ethyl acetate/2% methanol/CH_2Cl_2); $[\alpha]_D^{25}$ = −35.4 (c = 1.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.3 Hz, 1H; N-H), 7.75 (s, 1H; 13-H), 7.68 (d, J = 7.3 Hz, 2H; Ph-H), 7.48 (d, J = 7.3 Hz, 3H; Ph-H), 7.42 (t, J = 7.3 Hz, 3H; Ph-H), 7.33 (t, J = 7.3 Hz, 2H; Ph-H), 6.75 (s, 1H; 12-H), 5.26 (s, 1H; 10-H), 4.63 (ddd, J = 7.3, 3.7, 3.4 Hz, 1H; 7-H), 3.99 (dd, J = 11.2, 3.7 Hz, 1H; 8-H), 3.86 (dd, J = 11.2, 3.4 Hz, 1H; 8-H′), 3.82 (s, 3H; OCH_3), 2.68 (br s, 1H; OH), 1.13 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (C6), 168.9 (C9), 151.0 (C13), 148.8 (C11), 135.7, 135.5 (Ph-C), 131.6, 131.5 (Ph C_q), 130.5, 130.3, 128.1 and 127.8 (Ph-C), 125.6 (C12), 68.1 (C10), 63.1 (C8), 54.7 (C7), 52.8 (OCH_3), 26.7 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$); IR (film): ν_{max} = 3415, 3400 br, 2934, 2859, 1747, 1678, 1518, 1105 s, 1083 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{25}H_{30}N_2O_6SiNa$: 505.1771; found: 505.1786 $[M+Na]^+$.

5-Oxazolylmethyl cyanide (47): Alcohol **40** (3.80 g, 38.3 mmol) was dissolved in a mixture of CH_2Cl_2 (12 mL) and *n*-hexane (12 mL). At 0°C, thionyl chloride (4.20 mL, 57.2 mmol) was added dropwise. Subsequently, the mixture was refluxed for 2.5 h whilst bubbling the exhaust gas (HCl, SO_2) through sat. aqueous $NaHCO_3$. After cooling to RT, the mixture was quenched with ice-cold water (30 mL), neutralised with sat. aqueous $NaHCO_3$ (20 mL) and extracted into Et_2O (3×30 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure (T < 35°C, p > 300 mbar) to give crude chloride **46** (4.9 g), which was directly used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 4.62 (s, 2H, CH_2).

Chloride **46** (550 mg, 4.68 mmol) was dissolved in dry DMF (4.0 mL) under an argon atmosphere. Sodium cyanide (783 mg, 16.0 mmol) was added and the suspension heated to 70°C for 2.5 h. After cooling to RT, the mixture was diluted with brine (10 mL) and water (15 mL) and extracted with Et_2O (4×15 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure (T < 30°C, p > 550 mbar). The crude material was purified by flash chromatography (PE(30–40°C)/Et_2O 1:1) to provide cyanide **47** (380 mg, 75% over two steps) as a brown liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H; Ar-H), 7.09 (s, 1H; Ar-H), 3.83 (s, 2H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 141.5, 125.5, 114.6, 15.7; IR (film): ν_{max} = 2260, 1607, 1509, 1408, 1099, 971, 919, 837 cm^{-1}.

Methyl ester 48: A solution of cyanide **27** (188 mg, 1.74 mmol) in 2 M HCl in MeOH heated under reflux for 13 h. After cooling to RT, water was added and stirring continued for further 75 min. Saturated aqueous Na_2CO_3 (20 mL) was added to give pH 8 and the aqueous layer was extracted with Et_2O (5×10 mL). The combined organic extracts were dried with $MgSO_4$ and the solvent evaporated under reduced pressure (T < 30°C, p < 550 mbar). The crude material (178 mg, 1.26 mmol, 73%) was sufficiently clean by NMR but can be further purified by flash chromatography (PE(30–40°C)/Et_2O 2:1) to give a brown liquid which slowly solidifies in the freezer. M.p. 35–37°C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1H, Ar-H), 7.00 (s, 1H, Ar-H), 3.75 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 151.3, 145.5, 125. 2, 52.9, 31.7; IR (film): ν_{max} = 1737, 1509, 1230, 1102, 970 cm^{-1}.

Oxazoline 50: DAST (41 μL, 0.34 mmol) was added dropwise to a stirred solution of amide **25** (150 mg, 0.311 mmol) in CH_2Cl_2 (2.5 mL) at −78°C. After 1 h, K_2CO_3 (65 mg, 0.467 mmol) was added and the mixture was warmed to 0°C and poured into saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to afford crude oxazoline **50**. A sample was purified by flash chromatography (50% Et_2O/PE) afforded oxazoline **50** as a colourless oil (212 mg, 57%). R_f = 0.50 (100% ethyl acetate); $[\alpha]_D^{25}$ = +45 (c = 0.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1H; 13-H), 7.68 (d, J = 7.2 Hz, 2H; Ph-H), 7.58 (d, J = 7.3 Hz, 2H; Ph-H), 7.49–7.33 (m, 6H; Ph-H), 6.96 (s, 1H; 12-H), 5.56 (s, 1H; 10-H), 4.70 (dd, J = 10.6, 8.3 Hz, 1H; 7-H), 4.50 (dd, J = 8.8, 8.3 Hz, 1H; 8-H), 4.39 (dd, J = 10.6, 8.8 Hz, 1H; 8-H′), 3.76 (s, 3H; OCH_3), 1.08 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (C6), 166.9 (C9), 151.1 (C13), 149.0 (C11), 135.8, 135.7 (Ph-C), 132.2, 132.1 (Ph C_q), 130.1, 130.1, 127.7 and 127.7 (Ph-C), 125.1 (C12), 69.9 (C8), 68.0 (C7), 63.8 (C10), 52.6 (OCH_3), 26.7 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$); IR (film): ν_{max} = 2954, 2859, 1744 s, 1666, 1112 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{25}H_{29}N_2O_5Si$: 465.1846; found: 465.1852 $[M+H]^+$.

Bisoxazole 51: DBU (93 μL, 0.622 mmol) was added to a solution of crude oxazoline **50** in CH_2Cl_2 (3 mL) at −15°C, followed by the addition of $BrCCl_3$ (46 μL, 0.467 mmol). The reaction mixture was warmed to 0°C over 30 min then stirred for 1 h. Further DBU (46 μL, 0.311 mmol) was added and the mixture stirred at RT for 3 h. The reaction mixture was then diluted with CH_2Cl_2 and washed with saturated aqueous ammonium chloride (2×15 mL). The combined aqueous layers were extracted with ethyl acetate (20 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (20 → 30% ethyl acetate/PE) afforded bisoxazole **51** as a col-

ourless oil (30 mg, 22% over two steps, 59% *ee* by chiral HPLC); R_f = 0.40 (50% ethyl acetate/PE); $[\alpha]_D^{25} = -15.0$ ($c = 0.15$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.17$ (s, 1H; 8-H), 7.78 (s, 1H; 13-H), 7.57 (m, 4H; Ph-H), 7.45–7.40 (m, 2H; Ph-H), 7.38–7.32 (m, 4H; Ph-H), 6.92 (s, 1H; 12-H), 6.01 (s, 1H; 10-H), 3.90 (s, 3H; OCH_3), 1.07 (s, 9H, C-$(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.5$ (C9), 161.2 (C6), 151.2 (C13), 148.7 (C11), 144.4 (C8), 135.62, 135.56 (Ph-C), 133.3 (C7), 131.76, 131.72 (Ph C_q), 130.20, 130.16, 127.83 and 127.83 (Ph-C), 125.1 (C12), 63.6 (C10), 52.2 (OCH_3), 26.6 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$); IR (film): ν_{max} = 2932, 2859, 1747, 1723, 1581, 1428, 1105 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{25}H_{27}N_2O_5Si$: 463.1689; found: 463.1683 $[M+H]^+$. HPLC on chiral stationary phase: Agilent 1100 series, Chiralcel AS column, hexane/2-propanol 95:5, flow rate = 1.0 mL min^{-1}, 24 °C, $\lambda = 215$ nm, retention times: (*S*)-C10 isomer 17.60 min, (*R*)-C10 isomer 21.62 min.

Enamide *ent*-52: Serine amide **44** (537 mg, 1.114 mmol) in dry CH_2Cl_2 (11 mL) was cooled to 0 °C and triethylamine (777 μL, 5.57 mmol) was added. Mesylchloride (173 μL, 2.23 mmol) was added dropwise and the solution was stirred for 20 min before quenching with saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with CH_2Cl_2 (2×30 mL) and the combined organic extracts were washed with saturated aqueous ammonium chloride (50 mL) and brine (40 mL), then dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (50% Et_2O/PE) afforded enamide *ent*-**52** as a colourless oil (490 mg, 95%, single enantiomer). R_f = 0.35 (90% Et_2O/PE); $[\alpha]_D^{25} = -40.9$ (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.54$ (br s, 1H; N-H), 7.68 (s, 1H; 13-H), 7.64 (d, $J = 7.3$ Hz, 2H; Ph-H), 7.48 (d, $J = 7.4$ Hz, 3H; Ph-H), 7.42 (t, $J = 7.3$ Hz, 3H; Ph-H), 7.32 (t, $J = 7.4$ Hz, 2H; Ph-H), 6.65 (s, 1H; 8-H), 6.58 (s, 1H; 12-H), 6.00 (s, 1H; 8-H′), 5.23 (s, 1H; 10-H), 3.90 (s, 3H; OCH_3), 1.15 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2 (C9), 163.9 (C6), 150.8 (C13), 148.3 (C11), 135.7, 135.4, 131.5, 131.1, 130.52 (Ph-C), 130.50 (C7), 130.2, 128.1, 127.7 (Ph-C), 126.1 (C12), 109.7 (C8), 68.3 (C10), 52.9 (OCH_3), 26.7 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$); IR (film): ν_{max} = 3375, 2933, 2859, 1741, 1696, 1504, 1106 cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{25}H_{28}N_2O_5SiNa$: 487.1660; found: 487.1641 $[M+Na]^+$; HPLC on chiral stationary phase: Agilent 1100 series, Chiralcel AS column, hexane/2-propanol 95:5, flow rate = 1.0 mL min^{-1}, 24 °C, $\lambda = 215$ nm, retention times: (*S*)-C10 isomer 11.38 min, (*R*)-C10 isomer 21.88 min.

Methoxy-bromide *ent*-53: *N*-Bromosuccinimide (94 mg, 0.528 mmol) was added to a solution of enamide *ent*-**52** (245 mg, 0.528 mmol) in methanol (1 mL) and THF (0.5 mL) at RT. The mixture was stirred for 30 min, then quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL) and extracted with Et_2O (2×25 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and the combined aqueous layers extracted with Et_2O (25 mL). Combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo to afford bromide *ent*-**53** as a colourless oil (270 mg, 89%, dr 1:1). The absolute stereochemistry at C7 was unassigned and the diastereomers are denoted a or b (assignment as a or b determined by partial separation). R_f = 0.29/0.41 (90% Et_2O/PE); $[\alpha]_D^{25} = -52.4$ (c = 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.76$ (s, 1H^b; N-H^b), 8.56 (s, 1H^a; N-H^a), 7.70–7.67 (m, 2H; Ph-H), 7.68 (s, 1H; 13-H), 7.51–7.40 (m, 6H; Ph-H), 7.34–7.29 (m, 2H; Ph-H), 6.73 (s, 1H^a; 12-H^a), 6.46 (s, 1H^b; 12-H^b), 5.21 (s, 1H^a; 10-H^a), 5.19 (s, 1H^b; 10-H^b), 4.64 (d, $J = 10.2$ Hz, 1H^b; 8-H^b), 4.48 (d, J = 10.3 Hz, 1H^a; 8-H^a), 3.94 (s, 3H^b, $CO_2CH_3{}^b$), 3.92 (s, 3H^a, $CO_2CH_3{}^a$), 3.81 (d, $J = 10.2$ Hz, 1H^b; 8-H′^{b}), 3.77 (d, $J = 10.3$ Hz, 1H^a; 8-H′^{a}), 3.32 (s, 3H^b; $OCH_3{}^b$), 3.24 (s, 3H^a; $OCH_3{}^a$), 1.15 (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.72 (C6^b), 168.69 (C9^b), 168.6 (C6^a), 168.4 (C9^a), 151.2 (C13^a), 151.1 (C13^b), 148.94 (C11^b), 148.85 (C11^a), 136.2, 136.1, and 135.9 (Ph-C$^{a/b}$), 132.1, 131.9, 131.83 and 131.43 (Ph $C_q{}^{a/b}$), 130.94, 130.90, 130.69, 128.5, 128.2 and 128.1 (Ph-C$^{a/b}$), 126.5 (C12^a), 126.4 (C12^b), 88.2 (C7^a), 87.7 (C7^b), 68.8 (C10^a), 68.6 (C10^b), 54.2 ($CO_2CH_3{}^b$), 54.1 ($CO_2CH_3{}^a$), 53.3 ($OCH_3{}^b$), 53.2 ($OCH_3{}^a$), 32.0 (C8), 27.1 ($C(CH_3)_3$), 19.6 ($C(CH_3)_3$); IR (film): ν_{max} = 3386, 2934, 2860, 1746 s, 1706 s, 1500 s, 1105 s, 1077 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{26}H_{32}BrN_2O_6Si$: 575.1213; found: 575.1211 $[M+H]^+$.

Methoxy-oxazoline 54: Silver oxide (121 mg, 0.522) was added to a solution of bromides *ent*-**53** (200 mg, 0.348 mmol, dr = 1:1) in DMF (2 mL) at RT. The mixture was stirred in the dark for 22 h then filtered through Celite eluting with Et_2O (150 mL). The filtrate was washed with 10% w/v aqueous LiCl solution (3×70 mL) and the combined aqueous washings were extracted with Et_2O (2×100 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (80% Et_2O/PE) oxazoline *ent*-**54** as a yellow oil (166 mg, 97%, dr 1:1). The absolute stereochemistry at C7 was unassigned and the diastereomers are denoted a or b. R_f = 0.27 (90% Et_2O/PE); $[\alpha]_D^{25} = +5.0$ (c = 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.80$ (s, 1H; 13-H), 7.71–7.68 (m, 2H; Ph-H), 7.61–7.57 (m, 2H; Ph-H), 7.45–7.33 (m, 6H; Ph-H), 6.98 (s, 1H^a; 12-H^a), 6.97 (s, 1H^b; 12-H^b), 5.60 (s, 1H; 10-H), 4.49 (d, $J = 10.3$ Hz, 1H^b; 8-H^b), 4.43 (d, $J = 10.4$ Hz, 1H^a; 8-H^a), 4.28 (d, $J = 10.4$ Hz, 1H^a; 8-H′^{a}), 4.27 (d, $J = 10.3$ Hz, 1H^b; 8-H′^{b}), 3.80 (s, 3H^b; $CO_2CH_3{}^b$), 3.79 (s, 3H^a, $CO_2CH_3{}^a$), 3.32 (s, 3H^a; $OCH_3{}^a$), 3.29 (s, 3H^b; $OCH_3{}^b$), 1.09 (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6 (C9^a), 169.4 (C6^b), 168.24 (C9^b), 169.21 (C6^a), 151.18 (C13^a), 151.16 (C13^b), 148.9 (C11^a), 148.7 (C11^b), 135.83, 135.81, 135.67 and 135.65 (Ph-C$^{a/b}$), 132.07 and 132.04 (Ph $C_q{}^{a/b}$), 130.2, 130.1, 127.78 and 127.76 (Ph-C$^{a/b}$), 125.2 (C12), 101.6 (C7), 75.1 (C10), 63.9 (C8), 52.9 (CO_2CH_3), 51.9 ($OCH_3{}^b$), 51.8 ($OCH_3{}^a$), 26.7 ($C(CH_3)_3$), 19.4 ($C(CH_3)_3$); IR (film): ν_{max} = 2954, 2859, 1754 s, 1662, 1105 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{26}H_{30}N_2O_6SiNa$: 517.1771; found: 517.1779 $[M+Na]^+$.

Benzoxy-bromide 56: Benzyl alcohol (20 μL, 0.194) was added to a solution of enamide *ent*-**52** (45 mg, 0.097 mmol) in THF (0.2 mL), followed by the addition of *N*-bromosuccinimide (17 mg, 0.97 mmol) at RT. The mixture was stirred for 3 h quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (4% Et_2O/CH_2Cl_2) afforded bromide **56** as a colourless oil (23 mg, 36%, dr 1:1), followed by 3° alcohol **57** (19 mg, 41%). The absolute stereochemistry at C7 was unassigned and the diastereomers are denoted a or b. R_f = 0.63 (15% Et_2O/CH_2Cl_2); $[\alpha]_D^{25} = -45.0$ (c = 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.91$ (s, 1H^b; N-H^b), 8.70 (s, 1H^a; N-H^a), 7.71–7.67 (m, 2H; TBDPS Ph-H), 7.68 (s, 1H^a; 13-H^a), 7.59 (s, 1H^b; 13-H^b), 7.51–7.39 (m, 6H; TBDPS Ph-H), 7.38–7.27 (m, 7H; 2×TBDPS Ph-H and 5× Bn Ph-H), 6.73 (s, 1H^a; 12-H^a), 6.44 (s, 1H^b; 12-H^b), 5.24 (s, 1H^a; 10-H^a), 5.22 (s, 1H^b; 10-H^b), 4.75 (d, $J = 10.2$ Hz, 1H^b; 8-H^b), 4.71 (d, $J = 11.0$ Hz, 1H^b; PhCHH′^{b}), 4.57 (d, $J = 10.3$ Hz, 1H^a; 8-H^a), 4.53 (d, $J = 11.1$ Hz, 1H^a; PhCHH′^{a}), 4.40 (d, $J = 11.0$ Hz, 1H^b; PhCHH′^{b}), 4.35 (d, J = 11.1 Hz, 1H; PhCH′H^a), 3.87 (d, $J = 10.2$ Hz, 1H^b; 8-H′^{b}), 3.85 (s, 3H; CO_2CH_3), 3.82 (d, $J = 10.3$ Hz, 1H^a; 8-H′^{a}), 1.16 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4 (C6^a), 168.3 (C9^b), 168.2 (C9^a), 168.3 (C6^b), 150.8 (C13^a), 150.6 (C13^b), 148.5 (C11^a), 148.4 (C11^b), 136.5 and 136.3 (Bn Ph-C$^{a/b}$), 135.8, 135.6, 135.50 and 135.49 (TBDPS Ph-C$^{a/b}$), 131.7, 131.5, 131.4 and 131.0 (TBDPS Ph C_q), 130.5, 130.5, 130.3 and 130.3 (TBDPS Ph-C$^{a/b}$), 128.39 and 128.37 (Bn Ph-C$^{a/b}$), 128.17, 128.14, 128.13 and 128.12 (TBDPS Ph-C$^{a/b}$), 127.88, 127.75, 127.74 and 127.65 (Bn Ph-C$^{a/b}$), 126.2 (C12^a), 126.0 (C12^b), 87.1 (C7^b), 86.7 (C7^a), 68.5 (C10^a), 68.2 (C10^b), 67.7 ($PhCH_2{}^a$), 67.6 ($PhCH_2{}^b$), 53.7 (CO_2CH_3), 31.9 (C8), 26.7 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$); IR (film): ν_{max} = 3387, 2931, 2859, 1746 s, 1707 s, 1499 s, 1428, 1309, 1205, 1106 s, 1069 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{32}H_{36}N_2O_6SiBr$: 651.1526; found: 651.1544 $[M+H]^+$. The data for 3° alcohol **57** is detailed later.

Isopropoxy-bromide 55: *N*-Bromosuccinimide (94 mg, 0.528 mmol) was added to a solution of enamide *ent*-**52** (245 mg, 0.528 mmol) in *i*PrOH (0.5 mL) and THF (0.5 mL) at RT. The mixture was stirred for 3 h then further *i*PrOH (1 mL) was added and the mixture stirred for 1 h. Saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (4% Et_2O/CH_2Cl_2) afforded bromide **55** as a colourless oil (162 mg, 51%, dr 1.3:1). The absolute stereochemistry at C7 was unassigned and the diastereomers are denoted maj or min. R_f = 0.39 (90% Et_2O/PE); $[\alpha]_D^{25} = -43.0$ (c = 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.86$ (s, 1H^{maj}; N-H^{maj}), 8.71 (s, 1H^{min}; N-H^{min}), 7.70–7.66 (m, 2H; Ph-H), 7.66 (s, 1H; 13-H), 7.50–7.39 (m, 6H; Ph-H), 7.33–7.28 (m, 2H; Ph-H), 6.70 (s, 1H^{min}; 12-H^{min}), 6.47 (s, 1H^{maj}; 12-H^{maj}), 5.18 (s, 1H; 10-H), 4.69 (d, $J = 10.0$ Hz, 1H^{maj}; 8-H^{maj}), 4.53 (d, $J = 10.2$ Hz, 1H^{min}; 8-

H^{min}), 3.97 (septet, $J=6.2$ Hz, $1H^{maj}$; O*i*Pr CH^{maj}), 3.92 (s, $3H^{maj}$; $CO_2CH_3{}^{maj}$), 3.91 (s, $3H^{min}$; $CO_2CH_3{}^{min}$), 3.88 (septet, $J=6.2$ Hz, $1H^{min}$; O*i*Pr CH^{min}), 3.79 (d, $J=10.0$ Hz, $1H^{maj}$; 8-H′^{maj}), 3.74 (d, $J=10.2$ Hz, $1H^{min}$; 8-H′^{min}), 1.16 (s, 9H, $C(CH_3)_3$), 1.11 (d, $J=6.2$ Hz, $6H^{maj}$, O*i*Pr $(CH_3)_2{}^{maj}$), 1.04 (d, $J=6.2$ Hz, $6H^{min}$, O*i*Pr $(CH_3)_2{}^{min}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=169.3$ (C6), 168.2 ($C9^{min}$), 168.1 ($C9^{maj}$), 150.7 ($C13^{min}$), 150.5 ($C13^{maj}$), 148.6 ($C11^{min}$), 148.5 ($C11^{maj}$), 135.8, 135.7, 135.5 and 135.4 (Ph-$C^{maj/min}$), 131.7, 131.5, 131.4 and 131.0 (Ph $C_q{}^{maj/min}$), 130.5, 130.4, 130.24, 130.22, 128.10, 128.08, 127.71 and 127.69 (Ph-$C^{maj/min}$), 126.0 ($C12^{min}$), 125.9 ($C12^{maj}$), 86.7 ($C7^{maj}$), 86.3 ($C7^{min}$), 69.13 (O*i*Pr CH^{maj}), 69.06 (O*i*Pr CH^{min}), 68.46 ($C10^{maj}$), 68.43 ($C10^{min}$), 53.5 (CO_2CH_3), 32.10 ($C8^{min}$), 32.09 ($C8^{maj}$), 26.7 ($C(CH_3)_3$), 23.7 (O*i*Pr $CH_3{}^{min}$), 23.4 (O*i*Pr $CH_3{}^{maj}$), 22.60 (O*i*Pr $CH_3{}'^{maj}$), 22.59 (O*i*Pr $CH_3{}'^{min}$), 19.23 ($C(CH_3)_3{}^{min}$), 19.22 ($C(CH_3)_3{}^{maj}$); IR (film): ν_{max} = 3385, 2933, 2861, 1744 s, 1706 s, 1501 s, 1106 s, 1063 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{28}H_{36}N_2O_6SiBr$: 603.1526; found: 603.1526 $[M+H]^+$.

Isopropoxy-oxazoline 58: Silver oxide (76 mg, 0.326 mmol) was added to a solution of bromide **55** (131 mg, 0.217 mmol, dr 1.3:1) in DMF (1.3 mL) at RT. The mixture was stirred in the dark for 20 h, then filtered through Celite eluting with Et_2O (120 mL). The filtrate was washed with 10% w/v aqueous LiCl solution (3×50 mL) and the combined aqueous washings were extracted with Et_2O (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (70% Et_2O/PE) afforded oxazoline **58** as a yellow oil (108 mg, 95%, dr 1.3:1). The absolute stereochemistry at C7 was unassigned and the diastereomers are denoted maj or min. R_f = 0.39 (90% Et_2O/PE); $[\alpha]_D^{25}=+4.2$ ($c=0.65$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.78$ (s, 1H; 13-H), 7.71–7.66 (m, 2H; Ph-H), 7.60–7.56 (m, 2H; Ph-H), 7.48–7.33 (m, 6H; Ph-H), 6.96 (s, $1H^{min}$; 12-H^{min}), 6.95 (s, $1H^{maj}$; 12-H^{maj}), 5.64 (s, $1H^{min}$; 10-H^{min}), 5.58 (s, $1H^{maj}$; 10-H^{maj}), 4.46 (d, $J=10.1$ Hz, $1H^{maj}$; 8-H^{maj}), 4.38 (d, $J=10.2$ Hz, $1H^{min}$; 8-H^{min}), 4.25 (d, $J=10.2$ Hz, $1H^{min}$; 8-H′^{min}), 4.23 (d, $J=10.1$ Hz, $1H^{maj}$; 8-H′^{maj}), 4.00 (septet, $J=6.2$ Hz, 1H; O*i*Pr CH), 3.78 (s, 3H; CO_2CH_3), 1.17 (d, $J=6.2$ Hz, $3H^{maj}$; O*i*Pr $CH_3{}^{maj}$), 1.12 (d, $J=6.2$ Hz, $3H^{min}$; O*i*Pr $CH_3{}^{min}$), 1.09 (d, $J=6.2$ Hz, $3H^{maj}$; O*i*Pr $CH_3{}'^{maj}$), 1.09 (s, 9H, $C(CH_3)_3$), 1.03 (d, $J=6.2$ Hz, $3H^{min}$; O*i*Pr $CH_3{}'^{min}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.3$ ($C6^{maj}$), 170.0 ($C6^{min}$), 169.0 ($C9^{min}$), 168.6 ($C9^{maj}$), 151.1 (C13), 148.9 ($C11^{min}$), 148.8 ($C11^{maj}$), 135.8, 135.7 and 135.6 (Ph-$C^{maj/min}$), 132.1 (Ph $C_q{}^{maj/min}$), 130.10, 130.09, 127.8 and 127.7 (Ph-$C^{maj/min}$), 125.1 (C12), 101.7 ($C7^{maj}$), 101.5 ($C7^{min}$), 76.6 (C10), 69.1 ($C8^{maj}$), 68.9 ($C8^{min}$), 64.1 (*i*Pr CH^{min}), 63.9 (*i*Pr CH^{maj}), 52.7 (CO_2CH_3), 26.6 ($C(CH_3)_3$), 24.5 (*i*Pr CH_3), 23.6 (*i*Pr $CH_3{}'$), 19.3 ($C(CH_3)_3$); IR (film): ν_{max} = 2933, 2860, 1754 s, 1661, 1106 s, 1087 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{28}H_{35}N_2O_6Si$: 523.2264; found: 523.2276 $[M+H]^+$.

Alcohol 57: *N*-Bromosuccinimide (8 mg, 0.045 mmol) was added to a solution of enamide *ent*-**52** (20 mg, 0.043 mmol) in THF (0.5 mL) and water (0.2 mL) at RT. The mixture was stirred for 1 h, then saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture was extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (90% Et_2O/PE) afforded bromide **57** as a colourless oil (13 mg, 57%, dr 1:1). The absolute stereochemistry at C7 was unassigned and the diastereomers are denoted a or b. R_f = 0.14 (90% Et_2O/PE); $[\alpha]_D^{25}=-32$ ($c=0.2$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 8.58 (s, $1H^a$, N-H^a), 8.49 (s, $1H^b$, N-H^b), 7.71 (s, $1H^b$, 13-H^b), 7.69 (s, $1H^a$, 13-H^a), 7.67 (m, 2H; Ph-H), 7.52–7.40 (m, 6H; Ph-H), 7.36–7.29 (m, 2H; Ph-H), 6.65 (s, $1H^b$, 12-H^b), 6.60 (s, $1H^a$, 12-H^a), 5.16 (s, 1H; 10-H), 3.93 (d, $J=10.2$ Hz, $1H^a$, 8-H^a), 3.83 (d, $J=10.4$ Hz, $1H^b$, 8-H^b), 3.79 (d, $J=10.2$ Hz, $1H^a$, 8-H′^{a}), 3.74 (d, $J=10.4$ Hz, $1H^b$, 8-H′^{b}), 3.90 (s, $3H^b$, $OCH_3{}^b$), 3.89 (s, $3H^a$, $OCH_3{}^a$), 1.13 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.2$ ($C6^a$), 170.25 ($C9^a$), 170.19 ($C6^b$), 170.0 ($C9^b$), 151.1 ($C13^b$), 150.9 ($C13^a$), 148.4 ($C11^a$), 148.0 ($C11^b$), 135.75, 135.69, 135.48 and 135.47 (Ph-$C^{a/b}$), 131.46, 131.35, 131.26 and 131.20 (Ph $C_q{}^{a/b}$), 130.60, 130.58, 130.39, 128.20, 128.18 and 127.83 (Ph-$C^{a/b}$), 126.1 (C12), 82.1 ($C7^a$), 81.8 ($C7^b$), 67.9 ($C10^b$), 67.8 ($C10^a$), 54.0 ($OCH_3{}^b$), 54.1 ($OCH_3{}^a$), 30.3 ($C8^b$), 29.56 ($C8^a$), 26.7 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$); IR (film): ν_{max} = 3388, 3300, 2957, 2860, 1751, 1704 s, 1504, 1112 s, 702 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{25}H_{30}BrN_2O_6Si$: 561.1057; found: 561.1066 $[M+H]^+$.

Vinyl bromide 59: Bromine (3 μL, 0.059 mmol) was added to a solution of enamide *ent*-**52** (25 mg, 0.054 mmol) in CH_2Cl_2 (0.25 mL) at −78 °C. The solution was stirred for 10 min then triethylamine (23 μL, 0.647 mmol) was added and after 15 min quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was warmed to RT, then extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (50% Et_2O/PE) afforded *E*-vinyl bromide **59** as a colourless oil (22 mg, 75%). R_f = 0.58 (70% ethyl acetate/PE); $[\alpha]_D^{25}=-20.5$ ($c=1.1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.63$ (br s, 1H; N-H), 7.69 (s, 1H; 13-H), 7.69 (m, 2H; Ph-H), 7.50 (t, $J=7.3$ Hz, 3H; Ph-H), 7.43 (t, $J=7.3$ Hz, 3H; Ph-H), 7.33 (t, $J=7.3$ Hz, 2H; Ph-H), 7.26 (s, 1H; 8-H), 6.68 (s, 1H; 12-H), 5.29 (s, 1H; 10-H), 3.82 (s, 3H; OCH_3), 1.14 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.3$ (C9), 162.0 (C6), 150.9 (C13), 148.1 (C11), 135.7, 135.5 (Ph-C), 131.4 (Ph C_q), 131.22 (C7), 131.18 (Ph C_q), 130.6, 130.4, 128.2 and 127.8 (Ph-C), 126.2 (C12), 114.0 (C8), 68.3 (C10), 52.9 (OCH_3), 26.8, 19.3 ($C(CH_3)_3$); IR (film): ν_{max} = 3391, 2955, 1715 s br, 1473 s, 1112 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{25}H_{27}BrN_2O_5SiNa$: 565.0770; found: 565.0790 $[M+Na]^+$.

Alcohol 60: Imidazole (0.86 g, 12.57 mmol) was added to a solution of serine amide **25** (3.03 g, 6.28 mmol) in DMF (18 mL), followed by the addition of TBSCl (1.14 g, 7.54 mmol) and a catalytic amount of DMAP (20 mg) at RT. The mixture was stirred for 45 min and then quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL) and water (25 mL). The aqueous solution was extracted with Et_2O (2×75 mL) and the combined organic extracts washed with 10% w/v aqueous LiCl (50 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (40 → 50% ethyl acetate/PE) afforded the TBS ether as a colourless gum (4.0 g, 90%). R_f = 0.30 (50% ethyl acetate/PE); $[\alpha]_D^{25}=+63.7$ ($c=1.3$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.06$ (d, $J=8.8$ Hz, 1H; N-H), 7.69 (d, $J=7.3$ Hz, 2H; Ph-H), 7.65 (s, 1H; 13-H), 7.48 (m, 3H; Ph-H), 7.41 (t, $J=7.4$ Hz, 3H; Ph-H), 7.30 (t, $J=7.4$ Hz, 2H; Ph-H), 6.53 (s, 1H; 12-H), 5.21 (s, 1H; 10-H), 4.76 (ddd, $J=8.8$, 2.8, 2.4 Hz, 1H; 7-H), 4.17 (dd, $J=10.1$, 2.4 Hz, 1H; 8-H), 3.89 (dd, $J=10.1$, 2.8 Hz, 1H; 8-H′), 3.80 (s, 3H; OCH_3), 1.13 (s, 9H, TBDPS $C(CH_3)_3$), 0.91 (s, 9H, TBS $C(CH_3)_3$), 0.10 (s, 3H; TBS CH_3), 0.07 (s, 3H; TBS CH_3); ^{13}C NMR (100 MHz, $CDCl_3$: $\delta=170.2$ (C6), 168.2 (C9), 150.6 (C13), 148.8 (C11), 135.8, 135.4 (Ph-C), 131.8, 131.8 (Ph C_q), 131.2, 130.4, 128.1 and 127.7 (Ph-C), 125.8 (C12), 68.1 (C10), 63.8 (C8), 54.2 (C7), 52.4 (OCH_3), 26.8 (TBDPS $C(CH_3)_3$), 25.7 (TBS $C(CH_3)_3$), 19.2 (TBDPS $C(CH_3)_3$), 18.2 (TBS $C(CH_3)_3$), −5.6, −5.7 (TBS CH_3); IR (film): ν_{max} = 3430, 2955, 2859, 1751, 1694 s, 1509, 1107 s, 837 s, 702 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{31}H_{45}N_2O_6Si_2$: 597.2814; found: 597.2816 $[M+H]^+$.

LiCl (1.04 g, 24.5 mmol) was added portionwise to a stirred solution of the TBS-ether methyl ester (5.84 g, 9.79 mmol) in dry MeOH (36 mL) and THF (20 mL) at 0 °C, followed by the portionwise addition of $NaBH_4$ (0.926 g, 24.5 mmol). The mixture was allowed to warm slowly to RT and after 19 h, the suspension was quenched with saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (4×100 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo. Purification by flash chromatography (40% ethyl acetate/PE) afforded primary alcohol **60** as colourless oil (4.46 g, 80%). R_f = 0.22 (60% ethyl acetate/PE); $[\alpha]_D^{25}=+61.7$ ($c=1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.79$ (d, $J=8.1$ Hz, 1H; N-H), 7.70 (s, 1H; 13-H), 7.65 (d, $J=6.8$ Hz, 2H; Ph-H), 7.47 (d, $J=6.8$ Hz, 3H; Ph-H), 7.41 (m, 3H; Ph-H), 7.31 (t, $J=7.4$ Hz, 2H; Ph-H), 6.62 (s, 1H; 12-H), 5.21 (s, 1H; 10-H), 4.02 (m, 1H; 7-H), 3.92–3.80 (m, 3H; 6-H_2, 8-H), 3.69 (dd, $J=11.1$, 4.8 Hz, 1H; 8-H′), 2.59 (br s, 1H; OH), 1.11 (s, 9H, TBDPS $C(CH_3)_3$), 0.94 (s, 9H, TBS $C(CH_3)_3$), 0.13 (s, 3H; TBS CH_3), 0.12 (s, 3H; TBS CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 168.6 (C9), 150.7 (C13), 149.0 (C11), 135.7, 135.4 (Ph-C), 131.6, 131.4 (Ph C_q), 130.5, 130.2, 128.1 and 127.7 (Ph-C), 125.6 (C12), 68.2 (C10), 64.1 (C8), 63.5 (C6), 51.4 (C7), 26.8 (TBDPS $C(CH_3)_3$), 25.8 (TBS $C(CH_3)_3$), 19.2 (TBDPS $C(CH_3)_3$), 18.2 (TBS $C(CH_3)_3$), −5.58 (TBS CH_3), −5.61 (TBS CH_3); IR (film): ν_{max} = 3419, 3400 br, 2954, 2858, 683 s, 1516, 1106 s, 835 s, 702 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{30}H_{45}N_2O_5Si_2$: 569.2867; found: 569.2883 $[M+H]^+$.

Bisoxazole 62: $NaHCO_3$ (2.24 g, 26.6 mmol) was suspended in CH_2Cl_2 (8.5 mL) and Dess–Martin periodinane (1.13 g, 2.66 mmol) was added at RT. The mixture was stirred for 5 min, cooled to 0 °C and then a solution of alcohol **60** (1.01 g, 1.78 mmol) in CH_2Cl_2 (11.0 mL) was added dropwise to the DMP suspension. The reaction mixture was stirred at 0 °C for 2 h before adding a 1:1 mixture of saturated aqueous $NaHCO_3$ and sodium thiosulphate solutions (80 mL). This was stirred for 10 min then partitioned between water (100 mL) and ethyl acetate (100 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2× 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give crude aldehyde **61**.

Crude aldehyde **61** was dissolved in CH_2Cl_2 (80 mL) and cooled to 0 °C. 2,6-Di-*tert*-butylpyridine (9.73 mL, 44.5 mmol) was added, followed by PPh_3 (2.33 g, 8.9 mmol), then dibromotetrachloroethane (2.90 g, 8.90 mmol) was added portionwise to the stirred solution. The reaction mixture was stirred at 0 °C for 3 h. Triethylamine (6.19 mL, 44.5 mmol) in MeCN (20 mL) was added and the mixture was allowed to warm to RT, then stirred for a further 36 h before filtering through a pad of silica eluting with CH_2Cl_2. The solvent was removed in vacuo and purification by flash chromatography (20 → 40% Et_2O/PE) afforded a single enantiomer of bisoxazole **62** as a yellow oil (870 mg, 89% over 2 steps). R_f = 0.29 (50% Et_2O/PE); $[\alpha]_D^{25} = -24.0$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (s, 1H; 13-H), 7.61 (d, $J = 7.2$ Hz, 2H; Ph-H), 7.58 (d, $J = 7.2$ Hz, 2H; Ph-H), 7.49 (s, 1H; 8-H), 7.45–7.33 (m, 6H; Ph-H), 6.93 (s, 1H; 12-H), 5.90 (s, 1H; 10-H), 4.61 (d, $J = 14.2$ Hz, 1H; 6-H), 4.58 (d, $J = 14.2$ Hz, 1H; 6-H′), 1.07 (s, 9H, TBDPS $C(CH_3)_3$), 0.93 (s, 9H, TBS $C(CH_3)_3$), 0.11 (s, 6H; TBS $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 160.6 (C9), 151.1 (C13), 149.5 (C11), 141.7 (C7), 135.7, 135.63 (Ph-C), 135.58 (C8), 132.2, 132.1 (Ph C_q), 130.0, 130.0, 127.7 and 127.7 (Ph-C), 124.8 (C12), 63.7 (C10), 58.6 (C6), 26.6 (TBDPS $C(CH_3)_3$), 25.8 (TBS $C(CH_3)_3$), 19.3 (TBDPS $C(CH_3)_3$), 18.3 (TBS $C(CH_3)_3$), −5.4, −5.4 (TBS CH_3); IR (film): ν_{max} = 2954, 2858, 1472, 1428, 1105 s, 873 s, 701 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{30}H_{41}N_2O_4Si_2$: 549.2605; found: 549.2595 $[M+H]^+$; HPLC on chiral stationary phase: Agilent 1100 series, Chiralcel AS column, hexane/2-propanol 99:1, flow rate = 0.5 mL min^{-1}, 24 °C, $l =$ 215 nm, retention times: (*S*)-C10 isomer 10.35 min, (*R*)-C10 isomer 11.85 min.

Bisoxazole alcohol 63: PPTS (0.73 g, 2.90 mmol) was added to a solution of TBS-ether **62** (2.27 g, 4.13 mmol) in methanol (32 mL) at RT. The solution was stirred for 4 h, then quenched by the addition of saturated aqueous $NaHCO_3$ (150 mL) and water (50 mL). The mixture was extracted with ethyl acetate (3×150 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (50 → 70% ethyl acetate/PE) afforded primary alcohol **63** as a pale yellow oil (1.67 g, 93%, >98% *ee* by chiral SFC). R_f = 0.33 (80% ethyl acetate/PE); $[\alpha]_D^{25} = -10.0$ ($c = 0.55$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.80$ (s, 1H; 13-H), 7.60 (d, $J = 7.1$ Hz, 2H; Ph-H), 7.57 (d, $J = 7.1$ Hz, 2H; Ph-H), 7.52 (s, 1H; 8-H), 7.45–7.40 (m, 2H; Ph-H), 7.38–7.33 (m, 4H; Ph-H), 6.94 (s, 1H; 12-H), 5.92 (s, 1H; 10-H), 4.50 (s, 2H; 6-H), 2.13 (br s, 1H; OH), 1.07 (s, 9H, TBDPS $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.1$ (C9), 151.2 (C13), 149.3 (C11), 140.6 (C7), 135.7, 135.64 (Ph-C), 135.57 (C8), 132.1, 132.0 (Ph C_q), 130.1, 130.0, 127.8 and 127.7 (Ph-C), 124.8 (C12), 63.7 (C10), 56.8 (C6), 26.7 (TBDPS $C(CH_3)_3$), 19.3 (TBDPS $C(CH_3)_3$); IR (film): ν_{max} = 3349 br, 2932, 2859, 1448, 1107 s, 703 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{24}H_{27}N_2O_4Si$: 435.1740; found: 435.1745 $[M+H]^+$. HPLC on chiral stationary phase: Agilent 1100 series, Chiralcel AS column, hexane/2-propanol 97:3, flow rate = 1 mL min^{-1}, 24 °C, $\lambda =$ 215 nm, retention times: (*S*)-C10 isomer 40.85 min, (*R*)-C10 isomer 44.69 min; Chiral SFC (supercritical fluid chromatography): (Berger Minigram, Chiralcel AS column with 7% MeOH/CO_2, flow rate = 3 mL min^{-1} at 100 bar, 35 °C, $\lambda = 210$ nm, retention times: (*S*)-C10 isomer 8.66 min, (*R*)-C10 isomer 9.08 min).

Oxime 33: Dess–Martin periodinane (1.81 g, 4.26 mmol) and $NaHCO_3$ (3.58 g, 42.6 mmol) were suspended in CH_2Cl_2 (10 mL) and cooled to 0 °C. A solution of primary alcohol **63** (1.24 g, 2.84 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the mixture was stirred at 0 °C for 2 h 30 min before adding a 1:1 mixture of saturated aqueous $NaHCO_3$ and sodium thiosulphate solutions (100 mL). This was stirred for 10 min then partitioned between water (50 mL) and ethyl acetate (50 mL) and separated. The aqueous layer was extracted with ethyl acetate (2×50 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent removed in vacuo to give the crude aldehyde, which was used without purification.

A solution of hydroxylamine hydrochloride (391 mg, 5.68 mmol) and Na_2CO_3 (300 mg, 2.84 mmol) in water (2 mL) was added to a solution of the crude aldehyde in methanol (25 mL) at 0 °C. After 1 h the solution was poured into brine (50 mL) and water (50 mL). The mixture was extracted with ethyl acetate (3×50 mL) and the combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (35% ethyl acetate/PE) afforded oxime **33** as a white foam (1.18 g, 93% over 2 steps, *cis*/*trans* 1:5). R_f = 0.25 (50% ethyl acetate/PE); $[\alpha]_D^{25} = -34.3$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.56$ (br s, 1H^{trans}; OH^{trans}), 8.52 (br s, 1H^{cis}; OH^{cis}), 8.39 (s, 1H^{trans}; 8-H^{trans}), 7.99 (s, 1H^{cis}; 8-H^{cis}), 7.82 (s, 1H^{cis}; 13-H^{cis}), 7.81 (s, 1H^{trans}; 13-H^{trans}), 7.79 (s, 1H^{trans}; 6-H^{trans}), 7.61–7.57 (m, 4H; Ph-H), 7.46 (s, 1H^{cis}; 6-H^{cis}), 7.45–7.32 (m, 6H; Ph-H), 6.97 (s, 1H^{cis}; 12-H^{cis}), 6.95 (s, 1H^{trans}; 12-H^{trans}), 5.99 (s, 1H^{trans}; 10-H^{trans}), 5.96 (s, 1H^{cis}; 10-H^{cis}), 1.09 (s, 9H^{cis}; TBDPS $C(CH_3)_3^{cis}$), 1.08 (s, 9H^{trans}; TBDPS $C(CH_3)_3^{trans}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.6$ (C9^{trans}), 160.2 (C9^{cis}), 151.30 (C13^{cis}), 151.27 (C13^{trans}), 149.1 (C11^{cis}), 149.0 (C11^{trans}), 143.7 (C8^{cis}), 141.1 (C8^{trans}), 139.8 (C6^{cis}), 137.9 (C6^{trans}), 135.65 (Ph-C), 135.60 (Ph-C), 134.7 (C7^{trans}), 131.9, 131.8 (Ph C_q), 130.8 (C7^{cis}), 130.2, 130.1, 127.81 and 127.79 (Ph-C), 124.92 (C12^{trans}), 124.89 (C12^{cis}), 63.59 (C10^{trans}), 63.54 (C10^{cis}), 26.7 (TBDPS $C(CH_3)_3$), 19.3 (TBDPS $C(CH_3)_3$); IR (film): ν_{max} = 3189 br, 2933, 2859, 1563, 1428, 1105 s, 701 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{24}H_{26}N_3O_4Si$: 448.1693; found: 448.1699 $[M+H]^+$.

Isoxazoline 3: *N*-Chlorosuccinimide (52 mg, 0.388 mmol) was added in one portion to a solution of oxime **33** (158 mg, 0.353 mmol) and pyridine (2 μL) in CH_2Cl_2 (5 mL) at RT. The reaction mixture was stirred in the dark for 1 h and the solvent was removed in vacuo to provide the crude chlorooxamic acid.

A solution of alkene **7** (764 mg, 3.53 mmol) in DME (16 mL) was added to the crude chlorooxamic acid and cooled to 0 °C, then Cs_2CO_3 (126 mg, 0.388 mmol) was added in one portion and the mixture was stirred vigorously for 18 h at 0 °C. Saturated aqueous $NaHCO_3$ (50 mL) and water (20 mL) were added, then the mixture was extracted with ethyl acetate (4×50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by Biotage flash chromatography (gradient from 10% Et_2O/PE → 90% Et_2O/PE in 3 stages) afforded the nitrile-oxide dimer **3b** as a yellow oil (10 mg, 6%), major cycloadduct **3** as a white foam (141 mg, 60%), followed by minor cycloadduct **3a** as a white foam (40 mg, 17%).

Major cycloadduct isoxazoline **3**: R_f = 0.38 (50% ethyl acetate/PE); $[\alpha]_D^{25} = -36.0$ ($c = 1.6$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.93$ (s, 1H; 8-H), 7.80 (s, 1H; 13-H), 7.58 (t, $J = 7.4$ Hz, 4H; Ph-H), 7.47–7.30 (m, 6H; Ph-H), 6.97 (s, 1H; 12-H), 5.98 (s, 1H; 10-H), 4.63 (ddd, $J =$ 11.0, 8.8, 5.1 Hz, 1H; 4-H), 3.74–3.65 (m, 2H; 2-H and 3-H), 3.41 (dd, $J =$ 17.2, 8.9 Hz, 1H; 5-H), 3.27, 3.25 (2s, 2×3H; 2×OCH_3), 3.19 (dd, $J =$ 17.2, 11.0 Hz, 1H; 5-H′), 1.30, 1.28 (2s, 2×3H; 2×BDA CH_3), 1.26 (d, $J = 5.9$ Hz, 3H; 1-H_3), 1.08 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.3$ (C9), 151.2 (C13), 150.1 (C6), 149.0 (C11), 137.5 (C8), 135.64, 135.58 (Ph-C), 132.0 (C7), 131.9, 131.9 (Ph C_q), 130.2, 130.1, 127.8 and 127.7 (Ph-C), 125.0 (C12), 98.7, 98.6 (BDA C_q), 80.3 (C4), 72.7 (C3), 66.4 (C2), 63.6 (C10), 48.0 (OCH_3), 47.9 (OCH_3), 36.3 (C5), 26.6 (C-$(CH_3)_3$), 19.3 ($C(CH_3)_3$), 17.6, 17.4 (BDA CH_3), 17.0 (C1); IR (film): ν_{max} = 2935, 2859, 1428, 1116 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{35}H_{43}N_3O_8SiNa$: 684.2717; found: 684.2718 $[M+Na]^+$. Biotage conditions: Cartridge FLASH 40M, flow rate 40 mL min^{-1}, monitor by UV (254 nm), Et_2O/PE (5% Et_2O 100 mL, 5 → 70% Et_2O 400 mL, 70% Et_2O 300 mL, 70 → 90% Et_2O 400 mL, 90% Et_2O 450 mL), 33×50 mL fractions (fractions: 7–10 recovered **7**, 16–19 **3b**, 21–25 **3**, 26–30 **3a**).

Compound 64: TBAF (1 M in THF, 0.15 mL, 0.15 mmol) was added to a solution of TBDPS-ether **3** (67 mg, 0.10 mmol) in THF (3 mL) at 0 °C. After 10 min saturated aqueous ammonium chloride (20 mL) was added and the mixture was extracted with ethyl acetate (3×20 mL). The com-

bined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (100% Et_2O) afforded bisoxazole alcohol **64** as a colourless oil (33 mg, 78%). R_f = 0.20 (80% ethyl acetate/PE); $[\alpha]_D^{25} = +3.2$ ($c = 1.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (s, 1H; 8-H), 7.89 (s, 1H; 13-H), 7.16 (s, 1H; 12-H), 6.10 (s, 1H; 10-H), 4.63 (ddd, $J = 10.7$, 8.8, 4.8 Hz, 1H; 4-H), 3.74–3.65 (m, 2H; 2-H, 3-H), 3.48 (dd, $J = 17.0$, 8.6 Hz, 1H; 5-H), 3.25 (s, 3H; OCH_3), 3.24 (s, 3H; OCH_3), 3.24 (dd, $J = 17.0$, 10.7 Hz, 1H; 5-H′), 1.29, 1.27 (2s, 2×3H; 2×BDA CH_3), 1.26 (d, $J = 5.9$ Hz, 3H; 1-H_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.2$ (C9), 151.6 (C13), 149.7 (C6), 148.8 (C11), 138.2 (C8), 132.2 (C7), 125.1 (C12), 98.72, 98.67 (BDA C_q), 80.6 (C4), 72.7 (C3), 66.3 (C2), 62.1 (C10), 48.0, 47.9 (OCH_3), 36.0 (C5), 17.6, 17.4 (BDA CH_3), 17.0 (C1); IR (film): ν_{max} = 3200br, 3134, 2951, 1432, 1375, 1121s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{19}H_{26}N_3O_8$: 424.1720; found: 424.1711 $[M+H]^+$.

Compound 2: Triethylamine (434 μL, 3.12 mmol) was added to a solution of **64** (33 mg, 0.078 mmol) in CH_2Cl_2 (3 mL) at 0°C. Myristoyl chloride (39 μL, 0.156 mmol) was added dropwise to the stirred solution and after 10 min at 0°C, saturated aqueous ammonium chloride (10 mL) was added. The mixture was extracted with ethyl acetate (3×20 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (20% to 40% ethyl acetate/PE) afforded myristate ester **2** as a colourless oil (36 mg, 73%). R_f = 0.28 (50% ethyl acetate/PE); $[\alpha]_D^{25} = -1.9$ ($c = 0.8$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.05$ (s, 1H; 8-H), 7.91 (s, 1H; 13-H), 7.27 (s, 1H; 12-H), 7.11 (s, 1H; 10-H), 4.63 (ddd, $J = 10.5$, 9.0, 5.1 Hz, 1H; 4-H), 3.75–3.65 (m, 2H; 2-H, 3-H), 3.50 (dd, $J = 17.3$, 9.0 Hz, 1H; 5-H), 3.27 (dd, $J = 17.3$, 9.0 Hz, 1H; 5-H′), 3.26, 3.25 (2s, 2×3H; 2×OCH_3), 2.43 (t, $J = 7.5$ Hz, 2H; 15-H_2), 1.66 (m, 2H; 16-H_2), 1.29, 1.27 (2s, 2×3H; 2×BDA CH_3), 1.26 (m, 20H; 17-H_2 to 26-H_2), 1.26 (d, $J = 5.9$ Hz, 3H; 1-H_3), 0.88 (t, $J = 7.0$ Hz, 3H; 27-H_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.0$ (C14), 158.5 (C9), 151.9 (C13), 150.0 (C6), 145.5 (C11), 138.1 (C8), 132.7 (C7), 127.2 (C12), 98.73, 98.67 (BDA C_q), 80.6 (C4), 72.7 (C3), 66.8 (C2), 61.3 (C10), 48.1, 47.9 (OCH_3), 36.3 (C5), 33.8 (C15), 31.9, 29.65, 29.62, 29.61, 29.55, 29.40, 29.32, 29.15, 29.0 (C17 to C25), 24.7 (C16), 22.7 (C26), 17.6, 17.4 (BDA CH_3), 17.0 (C1), 14.1 (C27); IR (film): ν_{max} = 2925s, 2854, 1752, 1464, 1375, 1122 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{33}H_{52}N_3O_9$: 634.3704; found: 634.3728 $[M+H]^+$.

β-Hydroxy ketone 65: Boric acid (240 mg, 3.87 mmol) was added to a solution of isoxazoline **3** (50 mg, 0.076 mmol) in ethanol (5 mL) and water (0.5 mL) at RT. Raney nickel (≈1 mL as an aqueous slurry) was added and the mixture stirred under an atmosphere of hydrogen. After 3 h the mixture was filtered through a plug of Celite and the solvent removed in vacuo, azetroping with toluene. The crude product was purified by flash chromatography (stepped gradient from 20 → 80% ethyl acetate/PE) to afford β-hydroxy ketone **65** as a colourless oil (31 mg, 61%). R_f = 0.26 (60% ethyl acetate/PE); $[\alpha]_D^{25} = +56.6$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.14$ (s, 1H; 8-H), 7.80 (s, 1H; 13-H), 7.59 (t, $J = 7.8$ Hz, 4H; Ph-H), 7.48–7.41 (m, 2H; Ph-H), 7.39–7.32 (m, 4H; Ph-H), 6.97 (s, 1H; 12-H), 5.97 (s, 1H; 10-H), 4.19 (m, 1H; 4-H), 3.70 (m, 1H; 2-H), 3.62 (dd, $J = 9.6$, 4.6 Hz, 1H; 3-H), 3.23 (s, 3H; OCH_3), 3.23 (s, 3H; OCH_3), 3.10 (m, 2H; 5-H_2), 1.28, 1.26 (2s, 2×3H; 2×BDA CH_3), 1.22 (d, $J = 6.2$ Hz, 3H; 1-H_3), 1.08 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8 (C6), 161.0 (C9), 151.3 (C13), 148.7 (C11), 142.7 (C8), 140.6 (C7), 135.67, 135.61 (Ph-C), 131.8, 131.8 (Ph C_q), 130.25, 130.23, 127.86 and 127.82 (Ph-C), 125.2 (C12), 98.8, 98.6 (BDA C_q), 75.1 (C3), 68.0 (C4), 65.9 (C2), 63.7 (C10), 47.9, 47.8 (OCH_3), 42.1 (C5), 26.6 (C-(CH_3)$_3$), 19.3 ($C(CH_3)_3$), 17.7, 17.4 (BDA CH_3), 17.1 (C1); IR (film): ν_{max} = 3420br, 2935, 2860, 1691, 1127s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{35}H_{44}N_2O_9SiNa$: 687.2714; found: 687.2710 $[M+Na]^+$.

Compound 32: Diethylmethoxyborane (1M in THF, 0.51 mL, 0.505 mmol) was added to a stirred solution of β-hydroxy ketone **65** (112 mg, 0.168 mmol) in THF (3 mL) at −78°C. After 2 h $NaBH_4$ (22 mg, 0.57 mmol) was added and the mixture stirred at −78°C for 16 h. Water (2 mL) was added and the reaction was warmed to RT, partitioned between water (20 mL) and ethyl acetate (30 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2×20 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was dissolved in methanol and stirred at RT for 10 min then evaporated (repeated×5) to provide the crude diol. Purification by flash chromatography (80% ethyl acetate/PE) afforded the *syn*-diol as a colourless oil (112 mg, quant., dr 14:1). R_f = 0.22 (80% ethyl acetate/PE); $[\alpha]_D^{25} = +66.0$ ($c = 1.15$, $CHCl_3$); only peaks for the major diastereoisomer are quoted: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.79$ (s, 1H; 13-H), 7.60–7.54 (m, 4H; Ph-H), 7.53 (s, 1H; 8-H), 7.45–7.31 (m, 6H; Ph-H), 6.94 (s, 1H; 12-H), 5.91 (s, 1H; 10-H), 4.87 (dd, $J = 9.0$, 3.0 Hz, 1H; 6-H), 3.88 (m, 1H; 4-H), 3.78 (dq, $J = 9.9$, 6.4 Hz, 1H; 2-H), 3.60 (dd, $J = 9.8$, 3.5 Hz, 1H; 3-H), 3.25 (s, 3H; OCH_3), 3.23 (s, 3H; OCH_3), 2.02 (m, 1H; 5-H), 1.88 (m, 1H; 5-H′), 1.30, 1.28 (2s, 2×3H; 2×BDA CH_3), 1.13 (d, $J = 6.4$ Hz, 3H; 1-H_3), 1.06 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.6$ (C9), 151.1 (C13), 149.4 (C11), 143.9 (C7), 135.58, 135.57 (Ph-C), 135.1 (C8), 132.0, 132.0 (Ph C_q), 130.1, 130.0, 127.72 and 127.66 (Ph-C), 124.6 (C12), 98.9, 98.7 (BDA C_q), 75.5 (C3), 70.9 (C4), 67.0 (C6), 64.9 (C2), 63.7 (C10), 47.87, 47.82 (OCH_3), 38.0 (C5), 26.6 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$), 17.6 (C1), 17.4, 16.9 (BDA CH_3); IR (film): ν_{max} = 3385br, 2933, 1429, 1376, 1113s, 1038s, 824s, 754s, 702s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{35}H_{47}N_2O_9Si$: 667.3051; found: 667.3065 $[M+H]^+$.

para-Toluenesulfonic acid (3 mg) was added to a solution of the diol (100 mg, 0.15 mmol) in 2,2-dimethoxypropane (2 mL) and stirred at RT for 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL) and extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (30% ethyl acetate/PE) afforded acetonide **32** as a colourless oil (94 mg, 89%). R_f = 0.41 (60% ethyl acetate/PE); $[\alpha]_D^{25} = +38.3$ ($c = 0.85$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.78$ (s, 1H; 13-H), 7.60–7.54 (m, 4H; Ph-H), 7.53 (s, 1H; 8-H), 7.45–7.40 (m, 2H; Ph-H), 7.37–7.32 (m, 4H; Ph-H), 6.93 (s, 1H; 12-H), 5.92 (s, 1H; 10-H), 4.84 (dd, $J = 11.8$, 1.9 Hz, 1H; 6-H), 3.98 (ddd, $J = 11.4$, 7.0, 2.1 Hz, 1H; 4-H), 3.75 (dq, $J = 9.4$, 6.4 Hz, 1H; 2-H), 3.41 (dd, $J = 9.4$, 7.0 Hz, 1H; 3-H), 3.27 (s, 3H; OCH_3), 3.24 (s, 3H; OCH_3), 2.11 (ddd, $J = 13.1$, 2.1, 1.9 Hz, 1H; 5-H^{eq}), 1.54 (ddd, $J = 13.1$, 11.8, 11.4 Hz, 1H; 5-H^{ax}), 1.49 (s, 3H; acetonide CH_3^{eq}), 1.43 (s, 3H; acetonide CH_3^{ax}), 1.30 (s, 6H; 2×BDA CH_3), 1.23 (d, $J = 6.4$ Hz, 3H; 1-H_3), 1.06 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 160.5$ (C9), 151.1 (C13), 149.4 (C11), 142.5 (C7), 135.68, 135.64 (Ph-C), 135.5 (C8), 132.2, 132.1 (Ph C_q), 130.1, 130.0, 127.75 and 127.69 (Ph-C), 124.8 (C12), 98.9 (acetonide C_q), 98.5, 98.4 (BDA C_q), 74.7 (C3), 69.5 (C4), 67.5 (C2), 65.7 (C6), 63.7 (C10), 47.9, 47.9 (OCH_3), 32.7 (C5), 29.9 (acetonide CH_3^{ax}), 26.7 ($C(CH_3)_3$), 19.7 (acetonide CH_3^{eq}), 19.4 ($C(CH_3)_3$), 17.9 (C1), 17.7, 17.5 (BDA CH_3); IR (film): ν_{max} = 2939, 1428, 1380, 1105s, 730s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{38}H_{50}N_2O_9SiNa$: 729.3183; found: 729.3188 $[M+Na]^+$.

Alcohol 66: TBAF (1M in THF, 0.16 mL, 0.16 mmol) was added to a solution of TBDPS-ether **32** (73 mg, 0.103 mmol) in THF (2 mL) at 0°C. After 15 min water (30 mL) was added and the mixture was extracted with ethyl acetate (5×20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (40 → 60% ethyl acetate/PE) afforded the bisoxazole alcohol **66** (48 mg, quant.) as a colourless oil. R_f = 0.14 (60% ethyl acetate/PE); $[\alpha]_D^{25} = +79.9$ ($c = 0.55$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.89$ (s, 1H; 13-H), 7.62 (s, 1H; 8-H), 7.14 (s, 1H; 12-H), 5.99 (d, $J = 6.3$ Hz, 1H; 10-H), 4.95 (dd, $J = 11.8$, 1.4 Hz, 1H; 6-H), 4.03 (ddd, $J = 11.4$, 7.6, 1.8 Hz, 1H; 4-H), 3.75 (dq, $J = 9.4$, 6.4 Hz, 1H; 2-H), 3.55 (d, $J = 6.3$ Hz, 1H; OH), 3.43 (dd, $J = 9.4$, 7.6 Hz, 1H; 3-H), 3.27 (s, 3H; OCH_3), 3.24 (s, 3H; OCH_3), 2.19 (ddd, $J = 13.0$, 1.8, 1.4 Hz, 1H; 5-H^{eq}), 1.66 (ddd, $J = 13.0$, 11.8, 11.4 Hz, 1H; 5-H^{ax}), 1.53 (s, 3H; acetonide CH_3^{eq}), 1.44 (s, 3H; acetonide CH_3^{ax}), 1.29, 1.28 (2s, 2×3H; 2×BDA CH_3), 1.24 (d, $J = 6.4$ Hz, 3H; 1-H_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 161.0$ (C9), 151.5 (C13), 148.9 (C11), 142.4 (C7), 136.2 (C8), 125.1 (C12), 99.0 (acetonide C_q), 98.5, 98.4 (BDA C_q), 74.6 (C3), 69.5 (C4), 67.6 (C2), 65.4 (C6), 62.3 (C10), 48.0, 47.9 (OCH_3), 32.4 (C5), 29.9 (acetonide CH_3^{eq}), 19.7 (acetonide CH_3^{ax}), 17.9 (C1), 17.7, 17.5 (BDA CH_3); IR (film): ν_{max} = 3240br, 2993, 2936, 1381, 1125s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{22}H_{32}N_2O_9Na$: 491.2006; found: 491.2022 $[M+Na]^+$.

Ester 67: Triethylamine (196 μL, 1.41 mmol) was added to a solution of the bisoxazole alcohol **66** (22 mg, 0.047 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. Myristoyl chloride (19 μL, 0.07 mmol) was added dropwise to the stirred solution and after 20 min methanol (0.05 mL) was added and the mixture stirred for a further 5 min. Saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture extracted with Et_2O (5×20 mL). The combined organic extracts were washed with saturated aqueous ammonium chloride (20 mL), then dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (20 → 40% ethyl acetate/PE) afforded acetal-protected bengazole A **67** as a colourless oil (27 mg, 85%). R_f = 0.13 (60% Et_2O/PE); $[\alpha]_D^{25}$ = +47.7 (c = 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (s, 1H; 13-H), 7.63 (s, 1H; 8-H), 7.24 (s, 1H; 12-H), 7.10 (s, 1H; 10-H), 4.94 (dd, J = 11.9, 1.9 Hz, 1H; 6-H), 4.03 (ddd, J = 11.4, 7.3, 2.3 Hz, 1H; 4-H), 3.74 (dq, J = 9.5, 6.4 Hz, 1H; 2-H), 3.42 (dd, J = 9.5, 7.3 Hz, 1H; 3-H), 3.26, 3.24 (2s, 2×3H; 2×OCH_3), 2.41 (t, 7.5 Hz, 2H; 15-H_2), 2.19 (ddd, J = 13.2, 2.3, 1.9 Hz, 1H; 5-H^{eq}), 1.63 (m, 3H; 16-H_2, 5-H^{ax}), 1.51 (s, 3H; acetonide CH_3^{eq}), 1.43 (s, 3H; acetonide CH_3^{ax}), 1.29, 1.28 (2s, 2×3H; 2×BDA CH_3), 1.26 (m, 20H; 17-H_2 to 26-H_2), 1.23 (d, J = 6.4 Hz, 3H; 1-H_3), 0.89 (t, J = 7.2 Hz, 3H; 27-H_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (C14), 157.5 (C9), 151.8 (C13), 146.0 (C11), 142.9 (C7), 136.2 (C8), 127.1 (C12), 99.0 (acetonide C_q), 98.4, 98.3 (BDA C_q), 74.6 (C3), 69.6 (C4), 67.5 (C2), 65.6 (C6), 61.3 (C10), 47.95, 47.89 (OCH_3), 33.8 (C15), 32.6 (C5), 31.9 (C17), 29.9 (acetonide CH_3^{eq}), 29.7, 29.63, 29.62, 29.56, 29.41, 29.33, 29.16, 28.97 (C18 to C25), 24.7 (C16), 22.7 (C26), 19.7 (acetonide CH_3^{ax}), 17.9 (C1), 17.7, 17.5 (BDA CH_3), 14.1 (C27); IR (film): ν_{max} = 2925 s, 2854, 1753, 1464, 1380, 1126 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{36}H_{58}N_2O_{10}Na$: 701.3989; found: 701.3992 $[M+Na]^+$.

Bengazole A (1): Acetal protected bengazole A **67** (22 mg, 0.032 mmol) was dissolved in TFA/water 1:1 (1 mL) and stirred for 10 min at RT, then water was added (0.5 mL, to give a 1:2 TFA/water mixture). The reaction mixture was stirred for 30 min at RT then stirred under reduced pressure for 15 min (reducing the reaction volume by about half). Saturated aqueous $NaHCO_3$ (25 mL) was added dropwise and the mixture extracted with ethyl acetate (4×25 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (5% methanol/CH_2Cl_2) afforded bengazole A **1** as a colourless oil (16 mg, 95%). R_f = 0.24 (10% methanol/ CH_2Cl_2); $[\alpha]_D^{25}$ = +6 (c = 0.18, MeOH); ^{1}H NMR (600 MHz, CD_3OD): δ = 8.25 (s, 1H; 13-H), 7.85 (s, 1H; 8-H), 7.31 (s, 1H; 12-H), 7.11 (s, 1H; 10-H), 4.91 (dd, J = 7.1, 6.9 Hz, 1H; 6-H), 3.92 (dq, J = 6.4, 3.4 Hz, 1H; 2-H), 3.67 (ddd, J = 9.2, 6.8, 2.5 Hz, 1H; 4-H), 3.18 (dd, J = 6.8, 3.4 Hz, 1H; 3-H), 2.43 (t, J = 7.3 Hz, 2H; 15-H_2), 2.23 (ddd, J = 14.1, 6.9, 2.5 Hz, 1H; 5-H), 1.90 (ddd, J = 14.1, 9.2, 7.1 Hz, 1H; 5-H′), 1.63 (t, J = 7.0 Hz, 2H; 16-H_2), 1.28 (br m, 20H; 17-H_2 to 26-H_2), 1.15 (d, J = 6.4 Hz, 3H; 1-H_3), 0.89 (t, J = 7.4 Hz, 3H; 27-H_3); ^{13}C NMR (150 MHz, CD_3OD): δ = 173.4 (C14), 159.7 (C9), 154.4 (C13), 147.7 (C11), 145.7 (C7), 138.0 (C8), 127.5 (C12), 78.8 (C3), 71.2 (C4), 67.8 (C2), 66.3 (C6), 62.9 (C10), 40.5 (C5), 34.5 (C15), 33.1, 30.77, 30.73, 30.73, 30.67, 30.55, 30.45, 30.3, 30.0 (C17 to C25), 25.8 (C16), 23.7 (C26), 19.9 (C1), 14.4 (C27); IR (film): ν_{max} = 3360 br, 2923, 2854, 1751 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{27}H_{45}N_2O_8$: 525.3176; found: 525.3163 $[M+H]^+$.

Alcohol 68: Imidazole (1.65 g, 2.08 mmol) and DMAP (15 mg) were added to a solution of serine-amide **44** (5.84 g, 12.1 mmol) in DMF (35 mL), followed by the addition of TBSCl (2.19 g, 14.5 mmol) at RT. The mixture was stirred for 90 min, then quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL) and water (50 mL). The aqueous solution was extracted with Et_2O (2×75 mL) and the combined organic extracts were washed with 10% w/v aqueous LiCl (10 mL). The combined aqueous washes were extracted with Et_2O (75 mL) and the combined organic extracts dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (30 → 40 → 50% ethyl acetate/PE) afforded the TBS ether as a colourless gum (6.85 g, 95%). R_f = 0.54 (80% ethyl acetate/PE); $[\alpha]_D^{25}$ = −26.4 (c = 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.2 Hz, 1H; N-H), 7.66 (s, 1H; 13-H), 7.65 (d, J = 6.7 Hz, 2H; Ph-H), 7.47 (d, J = 6.7 Hz, 3H; Ph-H), 7.40 (t, J = 7.5 Hz, 3H; Ph-H), 7.30 (t, J = 7.5 Hz, 2H; Ph-H), 6.69 (s, 1H; 12-H), 5.24 (s, 1H; 10-H), 4.68 (ddd, J = 8.2, 2.7, 2.4 Hz, 1H; 7-H), 4.18 (dd, J = 10.2, 2.4 Hz, 1H; 8-H), 3.91 (dd, J = 10.2, 2.7 Hz, 1H; 8-H′), 3.79 (s, 3H; OCH_3), 1.12 (s, 9H, TBDPS $C(CH_3)_3$), 0.87 (s, 9H, TBS $C(CH_3)_3$), 0.06, 0.05 (2s, 2×3H; 2×TBS CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (C6), 168.5 (C9), 150.7 (C13), 148.8 (C11), 135.7, 135.3 (Ph-C), 131.7, 131.3 (Ph C_q), 130.4, 130.1, 128.0 and 127.6 (Ph-C), 125.9 (C12), 68.0 (C10), 63.4 (C8), 54.3 (C7), 52.4 (OCH_3), 26.8 (TBDPS $C(CH_3)_3$), 25.7 (TBS $C(CH_3)_3$), 19.2 (TBDPS $C(CH_3)_3$), 18.1 (TBS $C(CH_3)_3$), −5.5, −5.8 (TBS CH_3); IR (film): ν_{max} = 3427, 2954, 2858, 1750, 1691, 1507, 1104 s, 832 s, 701 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{31}H_{45}N_2O_6Si_2$: 597.2816; found: 597.2809 $[M+H]^+$.

LiCl (1.20 g, 28.2 mmol) was added portionwise to a stirred solution of the TBS-ether methyl ester (6.73 g, 11.3 mmol) in dry MeOH (40 mL) and THF (25 mL) at 0 °C, followed by the portionwise addition of $NaBH_4$ (1.07 g, 28.2 mmol). The mixture was allowed to warm slowly to RT and after 14 h the suspension was quenched with saturated aqueous $NaHCO_3$ (100 mL) and water (100 mL). The aqueous layer was extracted with ethyl acetate (3×75 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo. Purification by flash chromatography (50% ethyl acetate/PE) afforded primary alcohol **68** as colourless oil (4.96 g, 77%). R_f = 0.28 (60% ethyl acetate/PE); $[\alpha]_D^{25}$ = −27.7 (c = 1.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (d, J = 7.8 Hz, 1H; N-H), 7.69 (s, 1H; 13-H), 7.63 (d, J = 7.1 Hz, 2H; Ph-H), 7.47 (m, 3H; Ph-H), 7.41 (m, 3H; Ph-H), 7.31 (t, J = 7.5 Hz, 2H; Ph-H), 6.60 (s, 1H; 12-H), 5.20 (s, 1H; 10-H), 4.00 (m, 1H; 7-H), 3.93 (dd, J = 11.1, 4.0 Hz, 1H; 8-H CHH′OH), 3.99 (dd, J = 10.3, 3.3 Hz, 1H; 6-H CHH′OTBS), 3.81 (dd, J = 10.3, 4.2 Hz, 1H; 6-H′ CHH′OTBS), 3.77 (dd, J = 11.1, 4.7 Hz, 1H; 8-H′ CHH′OH), 2.66 (br s, 1H; OH), 1.09 (s, 9H, TBDPS $C(CH_3)_3$), 0.91 (s, 9H, TBS $C(CH_3)_3$), 0.11, 0.09 (2s, 2×3H; 2×TBS CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.9 (C9), 150.8 (C13), 148.9 (C11), 135.7, 135.4 (Ph-C), 131.7, 131.4 (Ph C_q), 130.5, 130.2, 128.1 and 127.7 (Ph-C), 125.9 (C12), 68.2 (C10), 63.6 (C8), 63.2 (C6), 52.0 (C7), 26.8 (TBDPS $C(CH_3)_3$), 25.9 (TBS $C(CH_3)_3$), 19.3 (TBDPS $C(CH_3)_3$), 18.3 (TBS $C(CH_3)_3$), −5.5, −5.6 (TBS CH_3); IR (film): ν_{max} = 3419, 3400 br, 2954, 2859, 1677 s, 1514, 1105 s, 834 s, 701 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{30}H_{45}N_2O_5Si_2$: 569.2867; found: 569.2874 $[M+H]^+$.

Bisoxazole *ent*-62: $NaHCO_3$ (6.78 g, 80.7 mmol) was suspended in CH_2Cl_2 (22 mL) and Dess–Martin periodinane (2.97 g, 6.99 mmol) was added at RT. The mixture was stirred for 5 min, cooled to 0 °C and then a solution of alcohol **68** (3.06 g, 5.38 mmol) in CH_2Cl_2 (30 mL) was added dropwise to the DMP suspension. The reaction mixture was stirred at 0 °C for 2 h before adding a 1:1 mixture of saturated aqueous $NaHCO_3$ and sodium thiosulphate solutions (120 mL). This was stirred for 5 min then partitioned between water (100 mL) and ethyl acetate (100 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo to give the crude aldehyde. The crude aldehyde was dissolved in CH_2Cl_2 (240 mL) and cooled to 0 °C. Di-*tert*-butylpyridine (20.6 g, 107.6 mmol) was added, followed by PPh_3 (7.06 g, 26.9 mmol) then dibromotetrachloroethane (20.6 g, 107.6 mmol) was added portionwise to the stirred solution. The reaction mixture was stirred at 0 °C for 3 h 30 min. Triethylamine (6.19 mL, 44.5 mmol) in MeCN (20 mL) was added and the mixture was allowed to warm to RT, then stirred for a further 42 h before filtering through a pad of silica gel eluting with CH_2Cl_2. The solvent was removed in vacuo and purification by flash chromatography (20 → 40% Et_2O/PE) afforded a single enantiomer of bisoxazole *ent*-**62** as a yellow oil (2.21 g, 75% over 2 steps). $[\alpha]_D^{25}$ = +13.4 (c = 0.65, $CHCl_3$); R_f, IR and NMR data identical to **62** above; chiral HPLC retention times as quoted above; HRMS (ESI+): m/z: calcd for $C_{30}H_{41}N_2O_4Si_2$: 549.2605; found: 549.2592 $[M+H]^+$.

Alcohol *ent*-63: PPTS (680 mg, 2.70 mmol) was added to a solution of TBS-ether *ent*-**62** (2.12 g, 3.86 mmol) in methanol (30 mL) at RT. The solution was stirred for 3 h, then extra PPTS (340 mg, 1.35 mmol) was added. After a total of 8 h the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (150 mL) and water (50 mL). The mixture was extracted with ethyl acetate (3×150 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (50 → 70% ethyl acetate/PE) afforded primary alcohol *ent*-**63** as a pale yellow oil (1.47 g, 96%, >98% *ee* by chiral SFC). $[\alpha]_D^{25}$ = +10.6 (c = 0.65, $CHCl_3$); R_f, IR and NMR data identical to

63 above; HPLC and SFC retention times as quoted above; HRMS (ESI+): *m/z*: calcd for $C_{24}H_{27}N_2O_4Si$: 435.1740; found: 435.1741 $[M+H]^+$.

Oxime *ent*-33: Dess–Martin periodinane (2.11 g, 4.97 mmol) and $NaHCO_3$ (4.17 g, 49.7 mmol) were suspended in CH_2Cl_2 (10 mL) and cooled to 0 °C. A solution of primary alcohol *ent*-**63** (1.44 g, 3.31 mmol) in CH_2Cl_2 (12 mL) was added dropwise and the mixture was stirred at 0 °C for 2 h. Further $NaHCO_3$ (2.1 g, 25 mmol) and Dess–Martin periodinane (1.05 g, 2.5 mmol) were added and the mixture was stirred for a further 2 h; before adding a 1:1 mixture of saturated aqueous $NaHCO_3$ and sodium thiosulphate solutions (150 mL). The mixture was stirred for 10 min then partitioned between water (100 mL) and ethyl acetate (150 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2×50 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent removed in vacuo to give the crude aldehyde, which was used without purification.

A solution of hydroxylamine hydrochloride (457 mg, 6.62 mmol) and Na_2CO_3 (350 mg, 3.31 mmol) in water (2 mL) was added to a solution of the crude aldehyde in methanol (25 mL) at 0 °C. After 1 h the solution was poured into brine (60 mL) and water was added (60 mL). The aqueous mixture was extracted with ethyl acetate (3×150 mL) and the combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (35% ethyl acetate/PE) afforded oxime *ent*-**33** as a white foam (1.29 g, 87% over 2 steps, *cis*/*trans* 4:5). $[\alpha]_D^{25}=+37.7$ ($c=1.0$, $CHCl_3$); R_f, IR and NMR data identical to **33** above. HRMS (ESI+): *m/z*: calcd for $C_{24}H_{25}N_3O_4SiNa$: 470.1512; found: 470.1505 $[M+Na]^+$.

Isoxazoline 69: *N*-Chlorosuccinimide (95 mg, 0.713 mmol) was added in one portion to a solution of oxime *ent*-**33** (290 mg, 0.648 mmol) in CH_2Cl_2 (9 mL) and pyridine (3 μL) at RT. The reaction mixture was stirred in the dark for 1 h and the solvent removed in vacuo to provide the crude chlorooxamic acid.

A solution of alkene **7** (1.40 g, 6.48 mmol) in DME (29 mL) was added to the crude chlorooxamic acid and cooled to 0 °C. Cs_2CO_3 (232 mg, 0.713 mmol) was added in one portion and the mixture was stirred vigorously for 15 h warming slowly to RT. Saturated aqueous $NaHCO_3$ (60 mL) and water (20 mL) were added and the mixture was extracted with ethyl acetate (4×50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo and purification by Biotage flash chromatography (gradient from 10% Et_2O/PE → 90% Et_2O/PE in 3 stages) provided major cycloadduct **69** as a white foam (218 mg, 51%), followed by minor cycloadduct **69a** as a white foam (90 mg, 21%).

Major cycloadduct isoxazoline **69**: R_f = 0.42 (60% ethyl acetate/PE); $[\alpha]_D^{25}=+27.0$ ($c=1.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.93$ (s, 1H; 8-H), 7.80 (s, 1H; 13-H), 7.58 (t, $J=7.4$ Hz, 4H; Ph-H), 7.46–7.31 (m, 6H; Ph-H), 6.97 (s, 1H; 12-H), 5.98 (s, 1H; 10-H), 4.63 (ddd, $J=$ 10.8, 8.8, 5.5 Hz, 1H; 4-H), 3.70 (dq, $J=9.7$, 6.1 Hz, 2H; 2-H), 3.64 (dd, $J=9.7$, 5.5 Hz, 1H; 3-H), 3.43 (dd, $J=17.2$, 8.8 Hz, 1H; 5-H), 3.26, 3.23 (2s, 2×3H; 2×OCH_3), 3.18 (dd, $J=17.2$, 10.8 Hz, 1H; 5-H′), 1.29, 1.26 (2s, 2×3H; 2×BDA CH_3), 1.27 (d, $J=6.1$ Hz, 3H; 1-H_3), 1.07 (s, 9H, C-$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=161.3$ (C9), 151.2 (C13), 150.2 (C6), 149.0 (C11), 137.5 (C8), 135.64, 135.59 (Ph-C), 132.0 (C7), 131.9, 131.9 (Ph C_q), 130.1, 130.0, 127.8 and 127.7 (Ph-C), 125.0 (C12), 98.7, 98.6 (BDA C_q), 80.4 (C4), 72.7 (C3), 66.5 (C2), 63.6 (C10), 48.0, 47.9 (OCH_3), 36.4 (C5), 26.6 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$), 17.6, 17.4 (BDA CH_3), 17.0 (C1); IR (film): ν_{max} = 2935, 2859, 1429, 1115 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{35}H_{43}N_3O_8SiNa$: 684.2717; found: 684.2718 $[M+Na]^+$.

Compound 70: Boric acid (1.48 g, 24 mmol) was added to a solution of isoxazoline **69** (215 mg, 0.32 mmol) in ethanol (20 mL) and water (4 mL) at RT. Raney nickel (≈1 mL as an aqueous slurry) was added and the mixture was stirred under an atmosphere of hydrogen. After 22 h the mixture was filtered through a plug of Celite eluting with methanol and evaporated, and azetroped from toluene. Purification by flash chromatography (35 → 45% ethyl acetate/PE) afforded the β-hydroxy ketone as a colourless oil (104 mg, 49%). R_f = 0.30 (60% ethyl acetate/PE); $[\alpha]_D^{25}=+76.0$ ($c=0.75$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.14$ (s, 1H; 8-H), 7.80 (s, 1H; 13-H), 7.61–7.56 (m, 4H; Ph-H), 7.46–7.32 (m, 6H; Ph-H), 6.97 (s, 1H; 12-H), 5.96 (s, 1H; 10-H), 4.15 (m, 1H; 4-H), 3.70 (dq, $J=9.6$, 6.3 Hz, 1H; 2-H), 3.62 (dd, $J=9.6$, 4.5 Hz, 1H; 3-H), 3.23, 3.22 (2s, 2×3H; 2×OCH_3), 3.09 (m, 2H; 5-H_2), 1.28, 1.25 (2s, 2×3H; 2× BDA CH_3), 1.21 (d, $J=6.3$ Hz, 3H; 1-H_3), 1.08 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=194.9$ (C6), 161.0 (C9), 151.3 (C13), 148.8 (C11), 142.7 (C8), 140.6 (C7), 135.65, 135.62 (Ph-C), 131.84, 131.78 (Ph C_q), 130.3, 130.2, 127.87 and 127.81 (Ph-C), 125.2 (C12), 98.8, 98.6 (BDA C_q), 75.2 (C3), 68.0 (C4), 65.9 (C2), 63.6 (C10), 47.9, 47.8 (OCH_3), 42.0 (C5), 26.6 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$), 17.7, 17.4 (BDA CH_3), 17.1 (C1); IR (film): ν_{max} = 3440 br, 2933, 2859, 1692, 1126 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{35}H_{44}N_2O_9SiNa$: 687.2714; found: 687.2690 $[M+Na]^+$.

Diethylmethoxyborane (1 M in THF, 0.43 mL, 0.43 mmol) was added to a solution of the β-hydroxy ketone (96 mg, 0.144 mmol) in THF (2.5 mL) at −78 °C. After 2 h, $NaBH_4$ (20 mg, 0.50 mmol) was added and the mixture stirred at −78 °C for 15 h. Water (2 mL) was added and the reaction was warmed to RT, partitioned between water (30 mL) and ethyl acetate (30 mL) then the layers were separated. The aqueous layer was extracted with ethyl acetate (2×20 mL) then the combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was dissolved in methanol and stirred at RT for 10 min then evaporated (repeated×5), to provide the crude diol. Purification by flash chromatography (30% ethyl acetate/PE) afforded the *syn*-diol as a colourless oil (89 mg, 93%, C6 dr 17:1 by ^{1}H NMR). R_f = 0.22 (80% ethyl acetate/PE); $[\alpha]_D^{25}=+120.6$ ($c=1.1$, $CHCl_3$); only NMR peaks for the major diastereoisomer are quoted; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.79$ (s, 1H; 13-H), 7.61–7.54 (m, 4H; Ph-H), 7.52 (s, 1H; 8-H), 7.45–7.31 (m, 6H; Ph-H), 6.93 (s, 1H; 12-H), 5.90 (s, 1H; 10-H), 4.89 (dd, $J=8.8$, 3.0 Hz, 1H; 6-H), 3.90 (m, 1H; 4-H), 3.77 (dq, $J=9.6$, 6.3 Hz, 1H; 2-H), 3.61 (dd, $J=9.7$, 3.5 Hz, 1H; 3-H), 3.26, 3.20 (2s, 2×3H; 2×OCH_3), 2.03 (m, 1H; 5-H), 1.94 (m, 1H; 5-H′), 1.30, 1.28 (2s, 2×3H; 2×BDA CH_3), 1.13 (d, $J=6.3$ Hz, 3H; 1-H_3), 1.06 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=160.7$ (C9), 151.1 (C13), 149.4 (C11), 143.9 (C7), 135.6, 135.6 (Ph-C), 135.0 (C8), 132.0, 132.0 (Ph C_q), 130.1, 130.0, 127.74 and 127.68 (Ph-C), 124.7 (C12), 98.9, 98.6 (BDA C_q), 75.4 (C3), 70.9 (C4), 66.9 (C6), 64.9 (C2), 63.6 (C10), 47.9, 47.8 (OCH_3), 37.9 (C5), 26.6 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$), 17.6, 17.4 (BDA CH_3), 16.9 (C1); IR (film): ν_{max} = 3386 br, 2934, 1429, 1377, 1113 s, 1038 s, 824 s, 754 s cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{35}H_{47}N_2O_9Si$: 667.3051; found: 667.3049 $[M+H]^+$.

para-Toluenesulfonic acid (3 mg) was added to a solution of the diol in 2,2-dimethoxypropane (2 mL) and stirred at RT for 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL) and extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (30% ethyl acetate/PE) afforded acetonide **70** as a colourless oil (82 mg, 97%, C6 dr 19.5:1 by ^{1}H NMR); R_f = 0.20 (30% ethyl acetate/PE); $[\alpha]_D^{25}=+69.5$ ($c=0.85$, $CHCl_3$); only NMR peaks for the major diastereoisomer are quoted; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.79$ (s, 1H; 13-H), 7.60–7.53 (m, 4H; Ph-H), 7.51 (s, 1H; 8-H), 7.46–7.40 (m, 2H; Ph-H), 7.38–7.30 (m, 4H; Ph-H), 6.93 (s, 1H; 12-H), 5.92 (s, 1H; 10-H), 4.84 (dd, $J=11.7$, 1.9 Hz, 1H; 6-H), 3.99 (ddd, $J=11.3$, 7.1, 2.1 Hz, 1H; 4-H), 3.74 (dq, $J=9.4$, 6.4 Hz, 1H; 2-H), 3.41 (dd, $J=9.4$, 7.1 Hz, 1H; 3-H), 3.26, 3.22 (2s, 2×3H; 2×OCH_3), 2.11 (ddd, $J=13.5$, 2.1, 1.9 Hz, 1H; 5-H^{eq}), 1.59 (ddd, $J=13.5$, 11.7, 11.3 Hz, 1H; 5-H^{ax}), 1.50 (s, 3H; acetonide CH_3^{eq}), 1.42 (s, 3H; acetonide CH_3^{ax}), 1.28 (s, 6H; 2×BDA CH_3), 1.23 (d, $J=6.4$ Hz, 3H; 1-H_3), 1.06 (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=160.6$ (C9), 151.1 (C13), 149.4 (C11), 142.3 (C7), 135.67, 135.66 (Ph-C), 135.4 (C8), 132.1, 132.1 (Ph C_q), 130.1, 129.9, 127.8 and 127.7 (Ph-C), 124.9 (C12), 98.9 (acetonide C_q), 98.5, 98.4 (BDA C_q), 74.7 (C3), 69.6 (C4), 67.5 (C2), 65.5 (C6), 63.7 (C10), 47.9, 47.9 (OCH_3), 32.6 (C5), 29.9 (acetonide CH_3^{ax}), 26.7 ($C(CH_3)_3$), 19.7 (acetonide CH_3^{eq}), 19.4 ($C(CH_3)_3$), 17.9 (C1), 17.7, 17.5 (BDA CH_3); IR (film): ν_{max} = 2933, 1428, 1380, 1124 s, 1040 cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{38}H_{50}N_2O_9SiNa$: 729.3183; found: 729.3192 $[M+Na]^+$.

Ester 71: TBAF (1 M in THF, 0.21 mL, 0.21 mmol) was added to a solution of TBDPS-ether **70** (99 mg, 0.14 mmol) in THF (2.5 mL) at 0 °C. After 15 min, water (20 mL) was added and the mixture was extracted with ethyl acetate (5×20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (40 → 60% ethyl acetate/PE) afforded bisoxazole secondary al-

cohol as a colourless oil (63 mg, 96%). R_f= 0.12 (60% ethyl acetate/PE); $[\alpha]_D^{25}$ = +66.3 (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H; 13-H), 7.58 (s, 1H; 8-H), 7.11 (s, 1H; 12-H), 6.02 (d, J = 6.3 Hz, 1H; 10-H), 4.89 (dd, J = 11.7, 1.8 Hz, 1H; 6-H), 3.89 (ddd, J = 11.2, 7.3, 2.0 Hz, 1H; 4-H), 3.73 (dq, J = 9.5, 6.3 Hz, 1H; 2-H), 3.39 (dd, J = 9.5, 7.3 Hz, 1H; 3-H), 3.24, 3.21 (2s, 2×3H; 2×OCH_3), 2.14 (ddd, J = 13.2, 2.0, 1.8 Hz, 1H; 5-H^{eq}), 1.63 (ddd, J = 13.2, 11.7, 11.2 Hz, 1H; 5-H^{ax}), 1.49 (s, 3H; acetonide CH_3^{eq}), 1.41 (s, 3H; acetonide CH_3^{ax}), 1.26, 1.25 (2s, 2×3H; 2×BDA CH_3), 1.21 (d, J = 6.3 Hz, 3H; 1-H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5 (C9), 151.5 (C13), 149.2 (C11), 142.2 (C7), 136.0 (C8), 124.9 (C12), 99.0 (acetonide C_q), 98.5, 98.4 (BDA C_q), 74.5 (C3), 69.6 (C4), 67.6 (C2), 65.4 (C6), 62.1 (C10), 47.9, 47.8 (OCH_3), 32.4 (C5), 29.9 (acetonide CH_3^{eq}), 19.7 (acetonide CH_3^{ax}), 17.8 (C1), 17.6, 17.4 (BDA CH_3); IR (film): ν_{max} = 3240 br, 2993, 1381, 1124 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{22}H_{32}N_2O_9Na$: 491.2006; found: 491.2020 $[M+Na]^+$.

Triethylamine (180 μL, 1.28 mmol) was added to a solution of the bisoxazole secondary alcohol (20 mg, 0.043 mmol) in CH_2Cl_2 (2 mL) at 0°C. Myristoyl chloride (18 μL, 0.64 mmol) was added dropwise to the stirred solution and after 20 min methanol (0.05 mL) was added and the mixture stirred for a further 5 min. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and Et_2O (20 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic extracts were washed with saturated aqueous ammonium chloride (20 mL) then dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (20 → 30 → 40 → 50% Et_2O/PE) afforded acetal-protected 10-*epi*-bengazole A **71** as a colourless oil (21 mg, 90%). R_f = 0.13 (60% Et_2O/PE); $[\alpha]_D^{25}$ = +56.4 (c = 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (s, 1H; 13-H), 7.63 (s, 1H; 8-H), 7.24 (s, 1H; 12-H), 7.09 (s, 1H; 10-H), 4.94 (dd, J = 11.9, 2.2 Hz, 1H; 6-H), 4.01 (ddd, J = 11.4, 7.2, 2.3 Hz, 1H; 4-H), 3.74 (dq, J = 9.5, 6.4 Hz, 1H; 2-H), 3.41 (dd, J = 9.5, 7.2 Hz, 1H; 3-H), 3.25, 3.23 (2s, 2×3H; 2×OCH_3), 2.40 (t, 7.8 Hz, 2H; 15-H_2), 2.19 (ddd, J = 13.2, 2.3, 2.2 Hz, 1H; 5-H^{eq}), 1.64 (m, 2H; 16-H_2), 1.61 (ddd, J = 13.2, 11.9, 11.4 Hz, 1H; 5-H^{eq}), 1.51 (s, 3H; acetonide CH_3^{eq}), 1.43 (s, 3H; acetonide CH_3^{ax}), 1.28, 1.27 (2s, 2×3H; 2×BDA CH_3), 1.26 (m, 20H; 17-H_2 to 26-H_2), 1.23 (d, J = 6.4 Hz, 3H; 1-H_3), 0.89 (t, J = 7.2 Hz, 3H; 27-H_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (C14), 157.5 (C9), 151.8 (C13), 145.9 (C11), 142.9 (C7), 136.5 (C8), 127.0 (C12), 99.0 (acetonide C_q), 98.4, 98.3 (BDA C_q), 74.5 (C3), 69.6 (C4), 67.5 (C2), 65.6 (C6), 61.3 (C10), 47.94, 47.89 (OCH_3), 33.8 (C15), 32.6 (C5), 31.9 (C17), 29.9 (acetonide CH_3^{eq}), 29.64, 29.61, 29.60, 29.54, 29.38, 29.32, 29.14, 28.94 (C18 to C25), 24.7 (C16), 22.7 (C26), 19.7 (acetonide CH_3^{ax}), 17.9 (C1), 17.7, 17.5 (BDA CH_3), 14.1 (C27); IR (film): ν_{max} = 2925 s, 2854, 1753, 1463 w, 1380, 1125 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{36}H_{58}N_2O_{10}Na$: 701.3989; found: 701.4001 $[M+Na]^+$.

10-*epi*-Bengazole A 72: Acetal protected 10-*epi*-bengazole A **71** (20 mg, 0.029 mmol) was dissolved in TFA/water 1:1 (1 mL) and stirred at RT for 5 min, then extra water (0.5 mL, to give a 1:2 mixture) was added. The mixture was stirred for at RT 30 min, then stirred under reduced pressure for 10 min, (reducing the reaction volume by about half). Saturated aqueous $NaHCO_3$ (15 mL) was added dropwise and the mixture extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (5% methanol/CH_2Cl_2) afforded 10-*epi*-bengazole A **72** as a colourless oil (13 mg, 85%). R_f = 0.24 (10% methanol/CH_2Cl_2); $[\alpha]_D^{25}$ = −1.6 (c = 0.65, MeOH); ^{1}H NMR (600 MHz, CD_3OD): δ = 8.26 (s, 1H; 13-H), 7.86 (s, 1H; 8-H), 7.31 (s, 1H; 12-H), 7.11 (s, 1H; 10-H), 4.91 (dd, J = 7.1, 6.9 Hz, 1H; 6-H), 3.93 (dq, J = 6.4, 3.4 Hz, 1H; 2-H), 3.68 (ddd, J = 9.2, 6.8, 2.5 Hz, 1H; 4-H), 3.19 (dd, J = 6.8, 3.4 Hz, 1H; 3-H), 2.43 (t, J = 7.3 Hz, 2H; 15-H_2), 2.24 (ddd, J = 14.1, 6.9, 2.5 Hz, 1H; 5-H), 1.90 (ddd, J = 14.1, 9.2, 7.1 Hz, 1H; 5-H′), 1.63 (t, J = 7.0 Hz, 2H; 16-H_2), 1.28 (br m, 20H; 17-H_2 to 26-H_2), 1.16 (d, J = 6.4 Hz, 3H; 1-H_3), 0.89 (t, J = 7.4 Hz, 3H; 27-H_3); ^{13}C NMR (150 MHz, CD_3OD): δ = 173.4 (C14), 159.7 (C9), 154.4 (C13), 147.7 (C11), 145.6 (C7), 138.0 (C8), 127.5 (C12), 78.7 (C3), 71.2 (C4), 67.7 (C2), 66.3 (C6), 62.8 (C10), 40.4 (C5), 34.5 (C15), 33.1, 30.8–30.0 (C17 to C25), 25.8 (C16), 23.7 (C26), 19.9 (C1), 14.4 (C27); IR (film): ν_{max} = 3350 br, 2923, 2854, 1751 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{27}H_{45}N_2O_8$: 525.3176; found: 525.3179 $[M+H]^+$.

Acid chloride 74: Oxalyl chloride (44 μL, 0.51 mmol) was added to a solution of acid **73** in CH_2Cl_2 (1 mL) followed by one drop of DMF. The mixture was stirred at RT for 1 h and the solvent was removed in vacuo to leave a yellow oil. NMR analysis showed complete conversion. The oil was dissolved in dry CH_2Cl_2 (1 mL) to give a stock solution of the acid chloride **74** (0.17 M). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (t, J = 7.3 Hz, 2H; 15-H_2), 1.72 (m, 2H; 16-H_2), 1.53 (m, 2H; CH_2), 1.27 (br m, 17H; 8×CH_2, 26-H), 1.16 (m, 2H; CH_2), 0.86 (d, J = 6.6 Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8 (C14), 47.1 (C15), 39.1 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.4 (CH_2), 28.0 (C26), 27.4 (CH_2), 25.1 (CH_2), 22.6 (2×CH_3); IR (film): ν_{max} = 2926 s, 2855, 1803 cm^{-1}.

Compound 75: Triethylamine (107 μL, 0.767 mmol) was added to a solution of the bisoxazole alcohol **66** (12 mg, 0.026 mmol) in CH_2Cl_2 (1 mL) at 0°C. Acid chloride **74** (0.17 M in CH_2Cl_2, 0.23 mL, 0.038 mmol) was added dropwise to the stirred solution and after 25 min methanol (0.05 mL) was added and the mixture stirred for a further 5 min. Saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture extracted with Et_2O (4×20 mL). The combined organic extracts were washed with saturated aqueous ammonium chloride (20 mL) then dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (20 → 40% ethyl acetate/PE) afforded acetal-protected bengazole B **75** as a colourless oil (15 mg, 85%). R_f = 0.13 (60% Et_2O/PE); $[\alpha]_D^{25}$ = +73.2 (c = 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (s, 1H; 13-H), 7.63 (s, 1H; 8-H), 7.24 (s, 1H; 12-H), 7.10 (s, 1H; 10-H), 4.94 (dd, J = 11.8, 2.2 Hz, 1H; 6-H), 4.01 (ddd, J = 11.4, 7.3, 2.3 Hz, 1H; 4-H), 3.74 (dq, J = 9.4, 6.4 Hz, 1H; 2-H), 3.41 (dd, J = 9.4, 7.3 Hz, 1H; 3-H), 3.26, 3.23 (2s, 2×3H; 2×OCH_3), 2.40 (t, 7.5 Hz, 2H; 15-H_2), 2.19 (ddd, J = 13.2, 2.3, 2.2 Hz, 1H; 5-H^{eq}), 1.64 (m, 2H; 16-H_2), 1.61 (ddd, J = 13.2, 11.8, 11.4 Hz, 1H; 5-H^{ax}), 1.51 (s, 4H; acetonide CH_3^{eq}), 1.51 (m, 1H; 26-H), 1.43 (s, 3H; acetonide CH_3^{ax}), 1.28, 1.27 (2s, 2×3H; 2×BDA CH_3), 1.25 (m, 16H; 8×CH_2), 1.23 (d, J = 6.4 Hz, 3H; 1-H_3), 1.15 (m, 2H; CH_2), 0.86 (d, J = 7.2 Hz, 6H; 27-H_3 and 28-H_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (C14), 157.5 (C9), 151.8 (C13), 145.9 (C11), 142.9 (C7), 136.2 (C8), 127.0 (C12), 99.0 (acetonide C_q), 98.4, 98.3 (BDA C_q), 74.5 (C3), 69.6 (C4), 67.5 (C2), 65.6 (C6), 61.3 (C10), 47.93 (OCH_3), 47.89 (OCH_3), 39.0 (CH_2), 33.8 (C15), 32.6 (C5), 29.90 (CH_2), 29.88 (acetonide CH_3^{eq}), 29.67, 29.61, 29.55, 29.42, 29.39, 29.14, 28.94 (7×CH_2), 28.0 (C26), 27.4 (CH_2), 24.7 (C16), 22.6 (C27, C28), 19.7 (acetonide CH_3^{ax}), 17.9 (C1), 17.7, 17.5 (BDA CH_3); IR (film): ν_{max} = 2926 s, 2855, 1753, 1464, 1380, 1126 s cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{37}H_{61}N_2O_{10}$: 693.4326; found: 693.4296 $[M+Na]^+$.

Bengazole B (76): Acetal protected bengazole B **75** (13 mg, 0.0188 mmol) was dissolved in TFA/water 1:1 (1 mL) and stirred for 15 min, then extra water was added (0.5 mL, to give a 1:2 mixture). The mixture was stirred for 40 min at RT then stirred under reduced pressure for 15 min, (reducing the reaction volume by about half). Saturated aqueous $NaHCO_3$ (25 mL) was added dropwise and the mixture extracted with ethyl acetate (4×25 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (5% methanol/CH_2Cl_2) afforded **76** as a colourless oil (10 mg, 98%). R_f = 0.24 (10% methanol/CH_2Cl_2); $[\alpha]_D^{25}$ = +11 (c = 0.045, MeOH); ^{1}H NMR (600 MHz, CD_3OD): δ = 8.26 (s, 1H; 13-H), 7.86 (s, 1H; 8-H), 7.31 (s, 1H; 12-H), 7.11 (s, 1H; 10-H), 4.91 (dd, J = 7.1, 6.9 Hz, 1H; 6-H), 3.92 (dq, J = 6.4, 3.3 Hz, 1H; 2-H), 3.67 (ddd, J = 9.3, 6.8, 2.5 Hz, 1H; 4-H), 3.18 (dd, J = 6.8, 3.3 Hz, 1H; 3-H), 2.43 (t, J = 7.3 Hz, 2H; 15-H_2), 2.23 (ddd, J = 14.1, 6.9, 2.5 Hz, 1H; 5-H), 1.90 (ddd, J = 14.1, 9.3, 7.1 Hz, 1H; 5-H′), 1.63 (m, 2H; 16-H_2), 1.52 (m, 1H; 26-H), 1.28 (br m, 16H; 8×CH_2), 1.16 (m, 2H; CH_2), 1.15 (d, J = 6.4 Hz, 3H; 1-H_3), 0.88 (d, J = 6.6 Hz, 6H; 27-H_3, 28-H_3); ^{13}C NMR (150 MHz, CD_3OD): δ = 171.9 (C14), 158.2 (C9), 153.0 (C13), 146.3 (C11), 144.2 (C7), 136.6 (C8), 126.1 (C12), 77.3 (C3), 69.8 (C4), 66.3 (C2), 64.8 (C6), 61.4 (C10), 39.0 (C5), 38.8 (C15), 33.1, 29.6, 29.4, 29.3, 29.2, 29.1, 28.9, 28.6, 27.7 (C17 to C25), 27.1 (C26), 24.4 (C16), 21.6 (C27, C28), 18.4 (C1); ^{13}C NMR (600 MHz, $CDCl_3$): δ = 7.92 (s, 1H; 13-H), 7.65 (s, 1H; 8-H), 7.24 (s, 1H; 12-H), 7.06 (s, 1H; 10-H), 5.00 (br d, J = 9.3 Hz, 1H; 6-H), 4.08 (br s, 2H; 2-H, 4-H), 4.00 (br s, 2H; 2×OH), 3.33 (br s, 1H; 3-H), 3.00 (br s, 2H; 2×OH), 2.42 (t, J = 7.2 Hz, 2H; 15-H_2), 2.13 (br d, J = 14.3 Hz, 1H; 5-H), 1.98 (m, 1H; 5-H′), 1.65 (m, 2H; 16-H_2), 1.52 (m, 1H; 26-H), 1.28 (br m,

18H, 17-H_2 to 25-H_2), 1.15 (d, $J=6.3$ Hz, 3H; 1-H_3), 0.87 (d, $J=6.6$ Hz, 6H; 27-H_3, 28-H_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=172.1$ (C14), 158.0 (C9), 152.0 (C13), 145.7 (C11), 144.1 (C7), 135.7 (C8), 127.0 (C12), 76.4 (C3), 73.7 (C4), 67.5 (C2), 66.9 (C6), 61.3 (C10), 39.0 (C15), 38.4 (C5), 33.8, 29.9, 29.7, 29.6, 29.5, 29.4, 29.1, 29.0, 27.9, 27.4 (C17 to C26), 24.7 (C16), 22.6 (C27, C28), 19.6 (C1); IR (film): ν_{max} = 3350br, 2924, 2854, 1751 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{28}H_{47}N_2O_8$: 539.3332; found: 539.3344 $[M+H]^+$.

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