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Asymmetric total synthesis of the myxobacteria metabolites crocacins A–D

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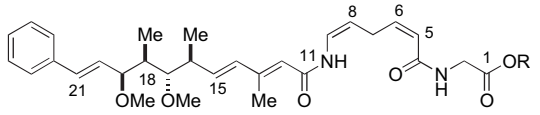
Abstract

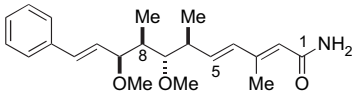
The total syntheses of crocacins A–D are described. The key steps were a *syn*-aldol reaction followed by *anti*-reduction to secure the stereotetrad and acylation of an ene- or dienecarbamate to form the enamide.

1. Introduction

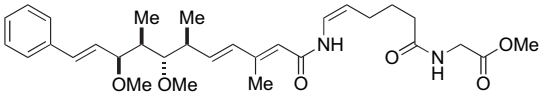
Myxobacteria are a life form at the interface between single and multicellular organisms. They live in places that are rich in organic matter and are otherwise known as gliding bacteria owing to the fact that they move by gliding over a solid surface.[1] These organisms have astonishing life cycles culminating in fruiting body formation upon starvation and are a rich source of potentially useful secondary metabolites with about 80 novel compounds characterized so far.[1] It is particularly remarkable that myxobacteria specialize in the production of molecules with mechanisms of action that are rare such as electron transport inhibition. Chemical investigation of several species of myxobacteria by Höfle and co-workers has resulted in the isolation of a number of interesting compounds, which possess both antibiotic and cytotoxic activities. In 1994, extracts from two different strains of myxobacteria, *Chondromyces crocatus* and *Chondromyces pediculatus*, were found to contain compounds possessing high activity against fungi, yeast and animal cell cultures.[2] Further work on these extracts led to the isolation of the crocacins A (**1**), B (**2**), C (**3**) and D (**4**).[3] Crocacins A (**1**), B (**2**) and C (**3**) were present in varying amounts in the extracts of several strains of *C. crocatus*, most notably in strain Cm c3 while crocacin D (**4**) was found to be present in the extracts of *C. pediculatus* strain Cm p17.



1 Crocacin A; R = Me
2 Crocacin B; R = H



3 Crocacin C



4 Crocacin D

Crocacins A (**1**) and B (**2**) are unusual linear dipeptides of glycine and 6-aminohexadienoic acid possessing a complex *N*-acylpolyketide, which is a substituted phenylundecatriene with an *anti*,*anti*,*syn* stereotetrad. This polyketide is also present as its primary amide crocacin C (**3**). Crocacin D (**4**) is a dipeptide of glycine and 6-aminohexenoic acid with the same *N*-acylpolyketide fragment. The relative configurations depicted for

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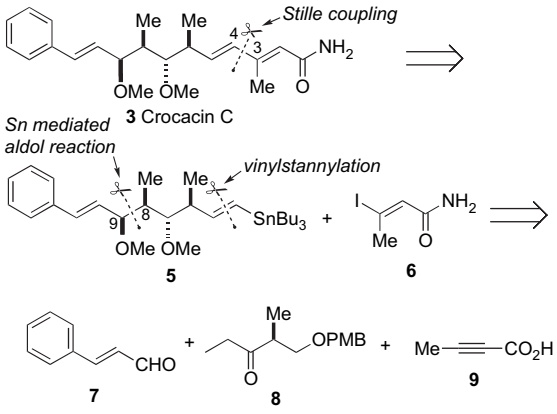
crocacins A–D were proposed by Jansen and co-workers using a combination of MM^{+} calculations and NOE experiments. Initial biological testing indicated that the crocacins possessed antibiotic activity against a few species of Gram-positive bacteria. Further testing showed that the crocacins inhibit the growth of several species of yeast and fungi, and that they are potent inhibitors of animal cell culture. In all cases crocacin D (**4**) was seen to be the most active member of the family (IC_{50} 60 ng L^{-1} against L929 mouse fibroblast). Crocacin A (**1**) inhibits NADH oxidation in beef heart submitochondrial particles by 50% at a concentration of 7.5 ng mL^{-1}.[3]

We communicated the first total synthesis of (+)-crocacin C, which allowed for the assignment of the relative and absolute configuration as shown in **3**.[4] This was closely followed by several other syntheses, which confirmed our initial assignment.[5–7] In addition, the total syntheses of crocacins A (**1**)[8,9] and D (**4**)[10–12] have also been reported as well as several formal[13,14] and fragment syntheses.[15,16] In this paper, we describe the full details of our total syntheses of the crocacins A (**1**), C (**3**) and D (**4**)[4,8,10] including the first total synthesis of crocacin B (**2**).

2. Results and discussion

2.1. Total synthesis of (+)-crocacin C

Our first target was the primary amide (+)-crocacin C (**3**). We reasoned that an asymmetric synthesis of this compound would serve to confirm the stereochemistry of the polyketide fragment and provide a common intermediate chiral fragment for the synthesis of the other members of this family. A retrosynthetic analysis of this target is shown in Scheme 1.

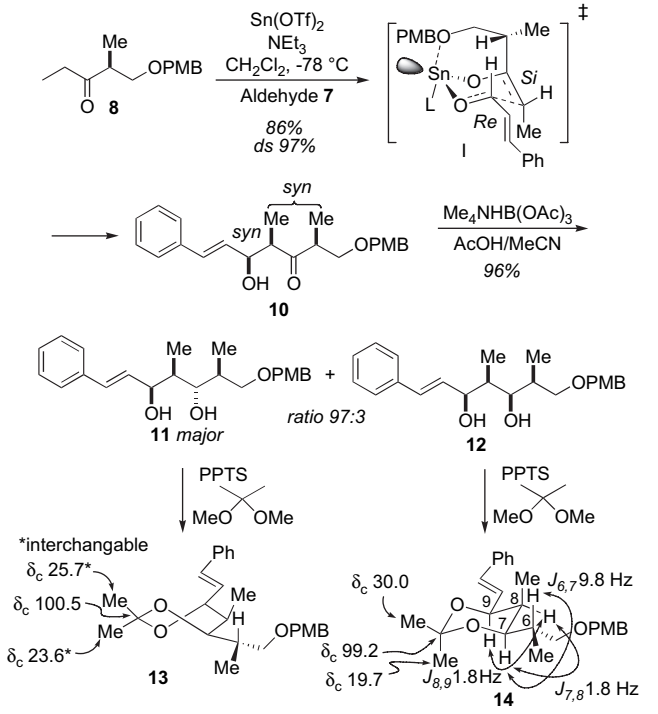


Scheme 1. Retrosynthetic analysis of crocacin C (**3**).

It was envisaged that crocacin C (**3**) could be synthesized by a Stille cross-coupling reaction[17,18] between stannane **5** and amide **6**. In this way, C3–C4 bond would be formed in a highly efficient manner to afford crocacin C directly. Compound **5** could be secured by a vinylstannation whilst the C8–C9 bond would be formed by a Paterson crossed aldol reaction[19,20] between the tin enolate derived from ketone **8** and cinnamaldehyde (**7**). The 6,7-*anti*-7,8-*anti*-8,9-*syn*-stereotetrad could then be formed by a selective *anti*-reduction[21] of the β-hydroxyketone aldol adduct. The vinyl iodide **6** coupling partner could be obtained from 2-butynoic acid (**9**).

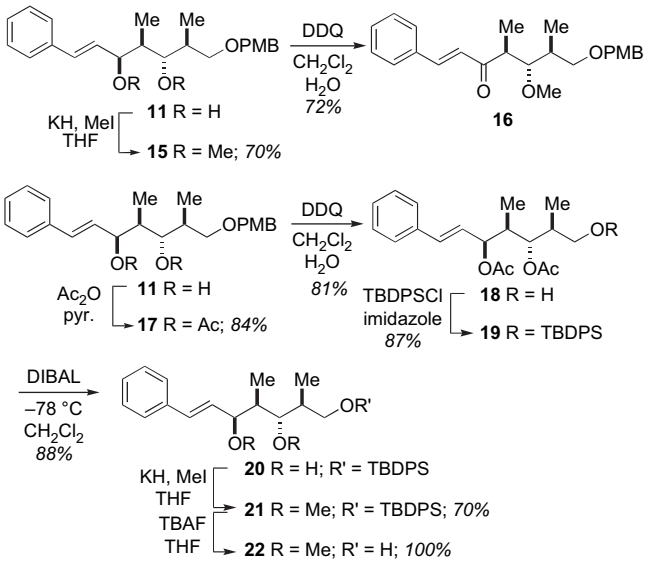
2.1.1. First generation stereotetrad synthesis

The synthesis of the stereotetrad diol **11** is outlined in Scheme 2. The tin enolate derived from the known chiral ketone **8**[4,22,23] was allowed to react with cinnamaldehyde (**7**) to afford the *syn*,*syn*-adduct **10** in good yield and high stereoselectivity. The major adduct was isolated pure after flash chromatography while two minor isomers were obtained as a mixture. This reaction presumably proceeds via the Zimmerman–Traxler[24] transition state **I** in which the OPMB group is chelated to ψ-tbp coordinated tin atom resulting in *si*-face attack of the enolate on the *re*-face of the aldehyde.[20] Subsequent *anti*-reduction proceeded smoothly to give the desired diol **11** along with a small amount of the all-*syn*-isomer. The stereochemistry of **11** followed from NMR analysis of the derived dimethylacetonide **13** and the acetonide **14** derived from the minor *syn*-isomer. The ^{13}C NMR chemical shifts measured for the acetonide **13** revealed an *anti*-diol relationship while the isomeric acetal **14** had shifts for the corresponding carbon atoms corresponding to a *syn*-diol acetonide.[25,26] In addition, the coupling constants for H6–H9 as shown in Scheme 2 supported the assignment of *syn*,*syn*,*syn*-stereochemistry for the minor diol **12**.

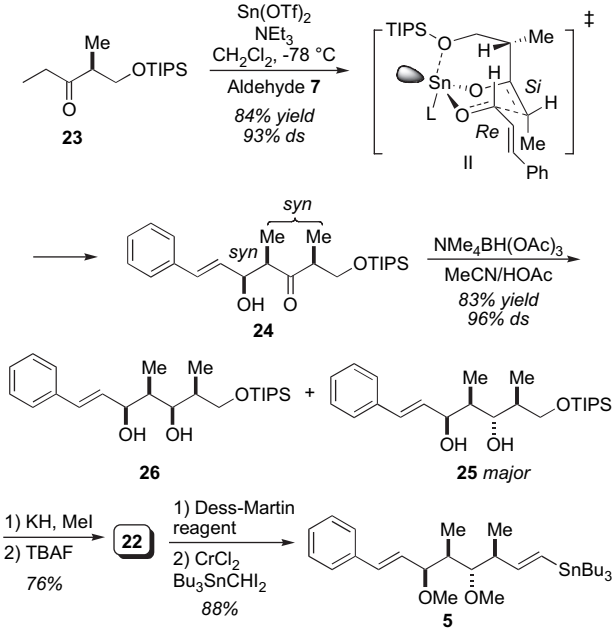


Scheme 2. Synthesis of the stereotetrad **11**.

With the desired diol **11** in hand, we then investigated the conversion of this into the stannane **5** required for Stille coupling. Methylation of the diol proceeded well using KH as base to give dimethyl ether **15** (Scheme 3). Unfortunately,



Scheme 3. Synthesis of intermediate alcohol **22**.



Scheme 4. Synthesis of vinyl stannane **5**.

attempted removal of the PMB group using 1.1 equiv of DDQ afforded the α,β-unsaturated ketone **16** with little PMB group deprotection. This result indicated that hydride removal from C9 to give a highly stabilized cinnamyl cation was preferred over hydride abstraction from the benzylic position in the PMB ether. Quenching of the cation with water then gives the ketone **16**. We reasoned that the undesired hydride abstraction could be circumvented by reducing the electron density at this position and so the diacetate **17** was synthesized from diol **11**. Treatment of this substrate with DDQ now effected removal of the PMB ether to give the desired primary alcohol **18**. Reprotection gave the TBDPS ether **19** and reductive removal of the acetates yielded diol **20**. Finally, methylation to give dimethyl ether **21** and subsequent silyl group removal afforded the key intermediate alcohol **22**. This sequence was efficient but lengthy so we elected to utilize an alternative protecting group earlier in the route to avoid these extra synthetic manipulations and shorten the synthesis of alcohol **22**.

2.1.2. Second generation stereotetrad synthesis

The second and more efficient synthesis of alcohol **22** and its conversion into the vinyl stannane **5** is depicted in Scheme 4. In this case, we began with the chiral ketone **23**, which possesses a TIPS protecting group.[19,27] The aldol reaction between the tin enolate derived from **23** and aldehyde **7** proceeded with good stereoselectivity to afford adduct **24** in high yield. The selectivity of this aldol reaction can be again rationalized by considering the transition state **II** where chelation of the silyl ether oxygen to the tin group induces *si*-face attack on the enolate. The slightly lower diastereoselectivity observed in this case could be due to the reduced chelation ability of the hindered silylated oxygen.[28] Selective *anti*-reduction[21] again proceeded with excellent stereocontrol to afford the major desired isomer **25** along with a small amount of diol **26**. In this case the minor diol **26** was crystalline and a single crystal X-ray structure was determined (Fig. 1), which

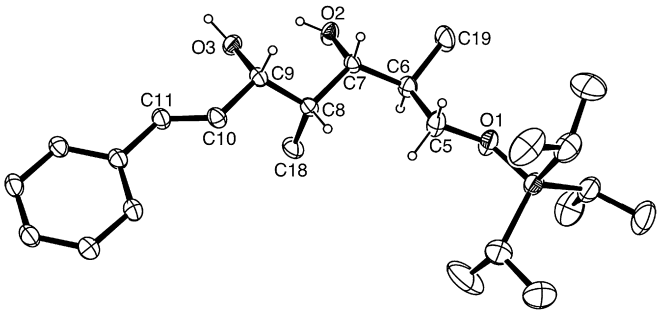
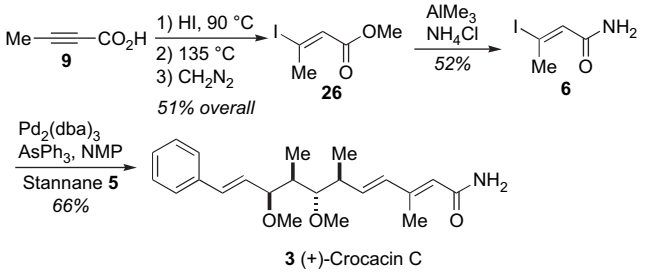


Figure 1. X-ray structure of diol **26** (some H atoms omitted for clarity).

confirmed the stereochemistry as all-*syn* and thus the stereochemistry of the major adduct **25** as *anti*,*anti*,*syn*. Methylation of compound **25** followed by desilylation then gave **22** in good yield. In this manner, the protecting group shuffle detailed in Scheme 3 is avoided providing the alcohol **22** in 56% overall yield from ketone **23**. Oxidation of the alcohol **22** followed by chromium-mediated vinylstannylation as described by Hodgson[29,30] then afforded vinyl stannane in good yield.

2.1.3. Completion of the total synthesis of (+)-crocacin C

The final steps of the synthesis of crocacin C are shown in Scheme 5. The requisite vinyl iodide coupling partner **6** was prepared from 2-butynoic acid (**9**). Addition of HI followed by isomerization and methyl ester formation gave the *E*-ester **26** along with the minor *Z*-isomer in a ratio of 7:3.[31,32] These were easily separated by flash chromatography. Ester–amide exchange[33] then afforded vinyl iodide **6**. Stille coupling between stannane **5** and iodide **6** proceeded smoothly using $AsPh_3$ as added ligand[34] to afford (+)-crocacin C (**3**), which was purified by flash chromatography. The synthetic material was identical in all respects to the natural product. In addition, the sign and absolute value of the optical rotation for the



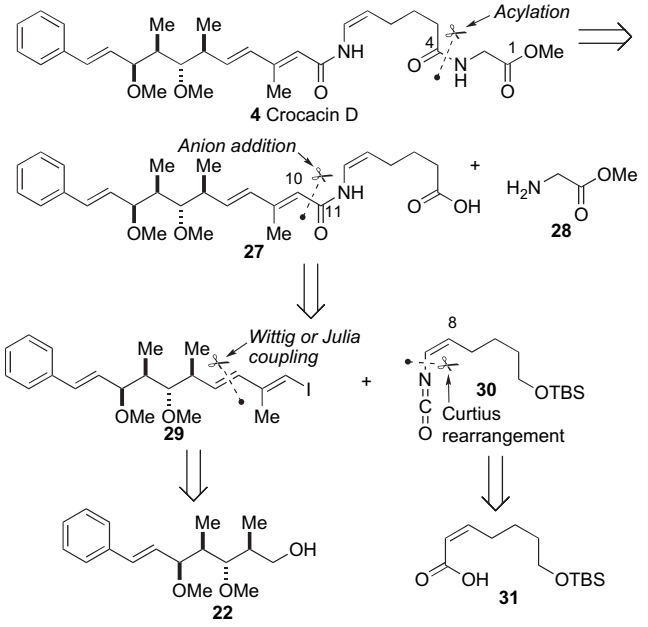
Scheme 5. Total synthesis of (+)-crocacin C (**3**).

synthetic material, $[\alpha]_D^{18}$ +61.3 (*c* 0.3, MeOH), matched that of the natural product; lit.[3] $[\alpha]_D^{22}$ +52.2 (*c* 0.3, MeOH). This confirmed the absolute configuration of **3** as that depicted.

2.2. Total synthesis of (+)-crocacin D (**4**)

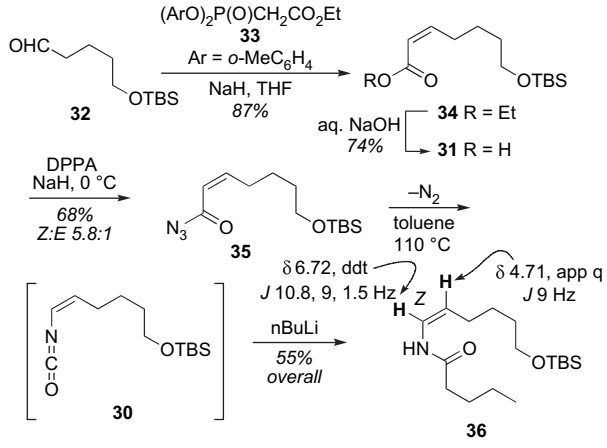
2.2.1. Initial retrosynthetic analysis

Our initial approach to crocacin D (**4**) is outlined in Scheme 6. This approach involves a late stage introduction of the glycine residue **28** by a peptide coupling with the acid **27**. A particular synthetic challenge is the introduction of the labile *Z*-enamide or *N*-acylenamine functionality. In our first approach, we envisioned the formation of the C10–C11 bond and the *Z*-enamide in one step via a rather ambitious addition of the lithium anion derived from vinyl iodide **29** to the *Z*-vinylisocyanate **30**.[35–38] Iodide **29** could arise from the common intermediate alcohol **22** by a Wittig or Julia extension whilst the vinylisocyanate could be secured from the acid **31** by stereoselective formation of the *N*-acylazide and subsequent Curtius rearrangement.



Scheme 6. Initial retrosynthetic analysis of crocacin D (**4**).

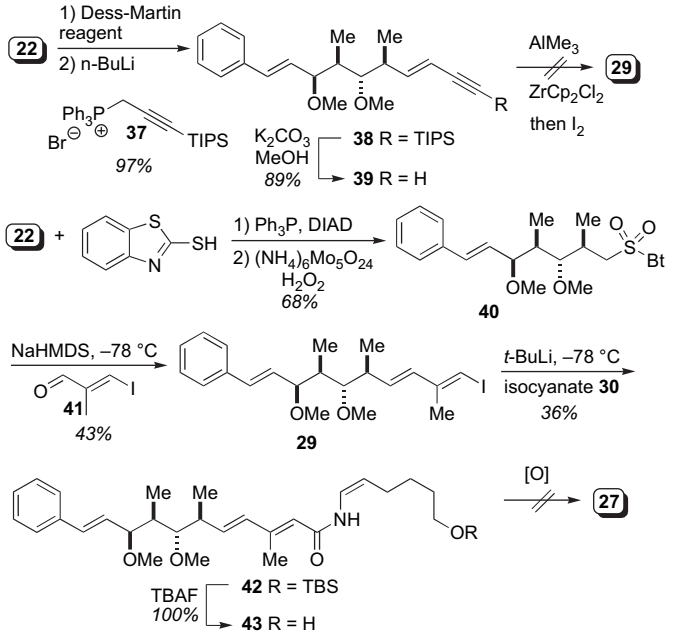
Another concern with this approach was the synthesis of the *Z*-vinylisocyanate. Taylor[35] found that during an attempted synthesis of a *Z*-enamide from a vinylisocyanate, isomerization of the alkene was observed. This appeared to have occurred during the formation of the *N*-acylazide possibly by conjugate addition/elimination of azide anion with the α,β-unsaturated system. However, a solution to this problem has been reported by Kitahara whereby use of NaH and phosphoryl azide provides *Z*-azides with minimal isomeriation.[36] To test this proposal we embarked on a synthesis of the *Z*-vinylisocyanate and addition of a simple anion to provide a model system as shown in Scheme 7. Aldehyde **32** was subjected to an Ando modified WEH reaction with the phosphonate **33**[39] to give the *Z*-α,β-unsaturated ester **34** as the only product. Saponification afforded crude acid **31**, which was immediately treated with DPPA and NaH[36] to give the *N*-acylazide with minimal isomerization of *Z*-alkene. Heating **35** in toluene induced Curtius rearrangement[40] and the crude vinylisocyanate was exposed to *n*BuLi to give the *Z*-enamide **36**. Compound **36** displayed characteristic ^{1}H NMR signals for the *Z*-enamide protons as shown in Scheme 7.



Scheme 7. Synthesis of the *Z*-vinylisocyanate **30**.

The success of the above model approach led to an investigation into the synthesis of the requisite iodide **29** for the crocacin D system (Scheme 8). We first examined a Wittig extension followed by carboalumination[41] and iodine exchange. Oxidation of alcohol **22** followed by condensation with the ylide derived from phosphonium salt **37**[42] generated the enyne **38** in excellent yield. Alkyne deprotection then gave the free enyne **39**. Unfortunately, attempts to carboaluminate this substrate resulted in decomposition, presumably due to the labile allylic methoxy group. During our investigation, Evans had encountered a similar problem in the synthesis of a related diene iodide and reported a solution, which we adopted.[43] Thus, conversion of the alcohol **22** to the sulfone **40** via Mitsunobu reaction with 2-mercaptobenzothiazole and Mo mediated oxidation[44] followed by Julia coupling with aldehyde **41**[45] afforded the vinyl iodide **29** in reasonable yield. This reaction was however capricious and difficult to optimize. Lithium–halogen exchange[46] and treatment of the resultant anion with freshly prepared vinylisocyanate **30** gave the enamide system **42** of crocacin D (**4**) in a low yield. Removal of the TBS group

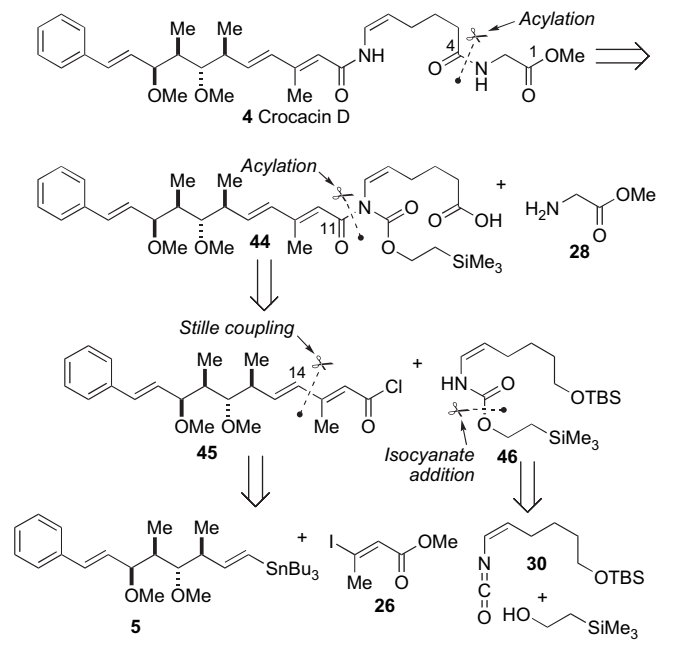
was efficient but several attempts at oxidation of the alcohol **43** to the acid **27** only resulted in degradation of the sensitive enamide system.[11]



Scheme 8. Synthesis of iodide **29** and anion coupling.

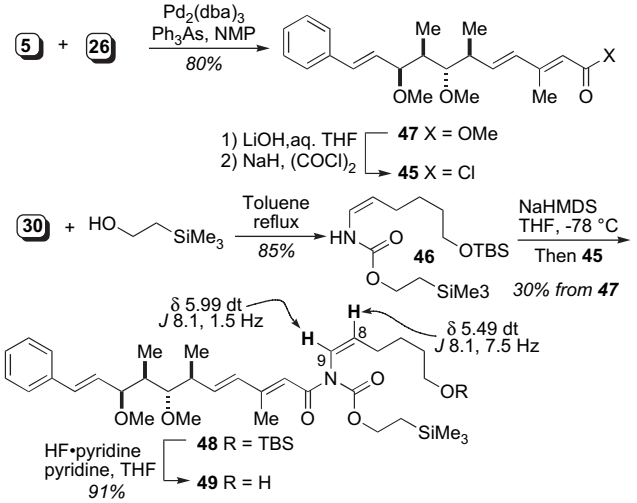
2.2.2. Alternative route to (+)-crocacin D (*4*)

At this stage, we abandoned this route to crocacin D (**4**) in favour of an alternative approach as detailed in Scheme 9. In this new route, the C11–N bond would be constructed by an acylation of the enecarbamate anion, obtained by deprotonation of **46**, with acid chloride **45**. This approach is based on the work of Brettle who described the acylation of enecarbamates as a method for the stereoselective synthesis of enamides.[47] More recently, this method was applied by Smith for the synthesis of the *E*-enamide moiety found in the salicylihalamides.[48,49] Compound **45** could arise from the ester formed by a Stille coupling between compounds **5** and **26** whilst the enecarbamate **46** could be secured by addition of 2-trimethylsilylethanol to *Z*-vinylisocyanate **30**. One of the salient features of this new route is the formation of the enamide by an operationally simpler N-acylation reaction. This results in the formation of a trimethylsilylethoxycarbamate (teoc)[48,49] protected enamide in which the electron withdrawing ability of the teoc group should impart extra stability to the enamide system allowing for adjustment of the oxidation level and subsequent peptide bond formation. This would provide teoc protected crocacin D, which upon fluoride mediated removal of the teoc group would afford crocacin D (**4**). In addition, this new route utilizes intermediates prepared earlier for the synthesis of crocacin C (**3**) and the failed approach to crocacin D (**4**).



Scheme 9. Alternative approach to crocacin D (**4**).

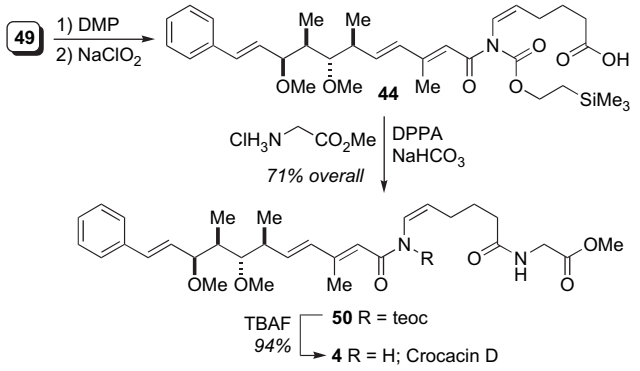
Stille coupling between stannane **5** and iodide **26** using $AsPh_3$ as added ligand[34] afforded ester **47** (Scheme 10). Hydrolysis followed by formation of the acid chloride via the sodium salt of the acid then gave **45**. The required enecarbamate **46** was synthesized in high yield by treatment of freshly prepared isocyanate **30** with trimethylsilylethanol in boiling toluene. Treatment of **46** with base produced the anion, which was allowed to react with acid chloride **45** to give the protected enamide **48** in 30% yield starting from ester **47**. In this instance, the ^{1}H NMR chemical shifts for H8 and H9 are indicative of a non-polar alkene demonstrating that the teoc group has reduced the electron density of the enamide system. Removal of the TBS group in the presence of the teoc protecting group was achieved with HF·pyridine buffered with pyridine[50] to afford the alcohol **49** in excellent yield.



Scheme 10. Acylation of enecarbamate **46** with acid chloride **45**.

The final steps in the total synthesis of crocacin D (**4**) are shown in Scheme 11. Two-step oxidation of alcohol **49** proceeded well to give crude acid **44**, which was immediately subjected to DPPA mediated peptide coupling[51,52] with

glycine methyl ester **28** (HCl salt used). The protected crocacin D was then treated with TBAF in THF at rt to give crocacin D (**4**) in excellent yield. The synthetic material was identical to a natural sample of (+)-crocacin D, $[\alpha]_D^{20}$ +102.7 (*c* 0.22, MeOH), lit.[3] $[\alpha]_D^{22}$ +109.6 (*c* 0.56, MeOH).

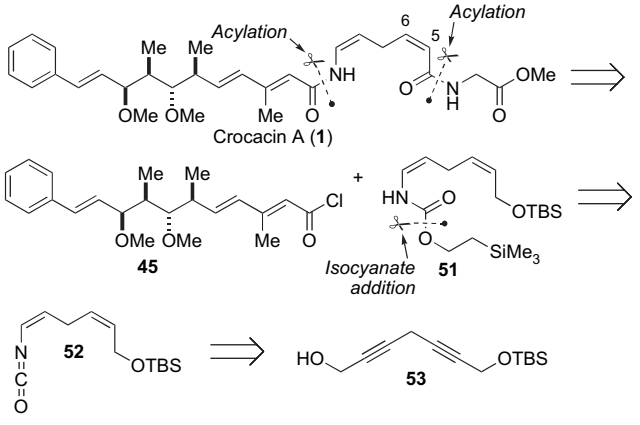


Scheme 11. Total synthesis of crocacin D (**4**).

2.3. Total synthesis of (+)-crocacins A (*1*) and B (*2*)

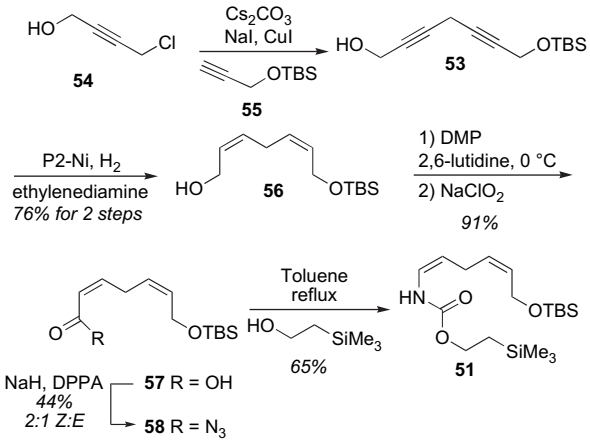
2.3.1. Total synthesis of (+)-crocacin A (*1*)

The retrosynthetic analysis of crocacin A (**1**) is depicted in Scheme 12 and is based on the successful approach to crocacin D (**4**) detailed above. The extra degree of C5–C6 unsaturation and the skipped diene added another challenge to the synthesis. However, we reasoned that the enamide system could again be formed by simple acylation of the anion derived from dienecarbamate **51** with the acid chloride **45**. Dienecarbamate **51** could be produced from addition of trimethylsilylethanol to the isocyanate **52**. We envisaged that the skipped *Z*,*Z*-diene in **52** could be secured by partial reduction of skipped diyne **53**. Compound **53** in turn would be synthesized by a copper catalyzed coupling methodology.



Scheme 12. Retrosynthetic analysis of crocacin A (**1**).

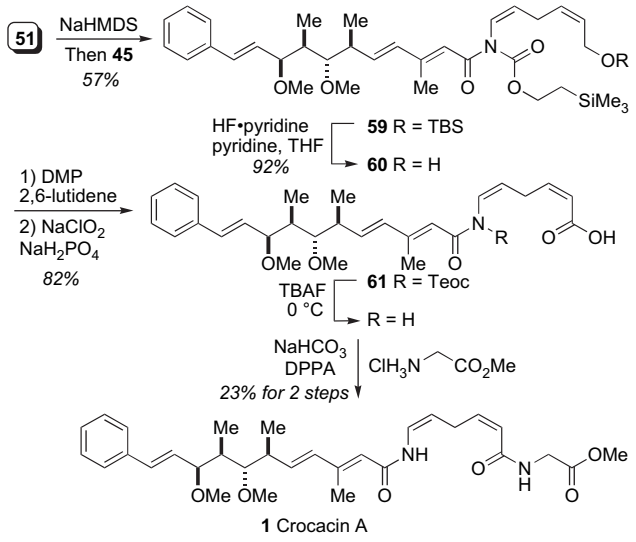
The route to dienecarbamate **51** began with the copper catalyzed coupling[53,54] of chloride **54**[55] and protected propargyl alcohol **55** to give labile diyne **53** in good yield (Scheme 13). Initially,[8] we utilized the propargylic mesylate rather than compound **54** but the chloride proved more effective. Attempted purification of **53** on silica resulted in considerable loss of material so the crude product was immediately subjected to partial reduction. Several attempts using hydrogen gas in the presence of Lindlar catalyst failed to give the diene in reasonable yield. We therefore turned to the method reported by Brown, which utilizes P2–Ni[56] as a hydrogenation catalyst in the presence of ethylenediamine.[57] Partial hydrogenation of diyne **53** with P2–Ni, generated in situ from $Ni(OAc)_2$ and $NaBH_4$ under a H_2 atmosphere, gave the diene **56** in good yield as a single geometric *Z*,*Z*-isomer. Two-step oxidation of **56** gave acid **57** in high yield and this was treated with NaH and DPPA[36] to afford the azide **58**. In this case, a greater amount of the undesired *E*,*Z*-azide was formed. Heating the azide **58** in toluene induced Curtius rearrangement to form isocyanate **52**, which upon treatment with 2-trimethylsilylethanol gave dienecarbamate **51**.



Scheme 13. Synthesis of dienecarbamate **51**.

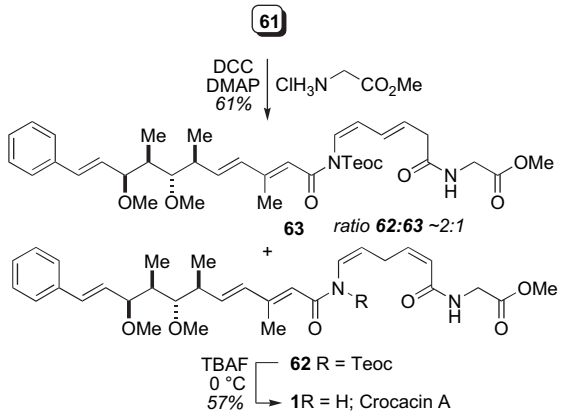
The completion of the total synthesis of crocacin A (**1**) is shown in Scheme 14. Deprotonation of dienecarbamate **51** with NaHMDS followed by addition of the acid chloride **45** gave the enamide **59** in reasonable yield. Desilylation mediated by HF·pyridine afforded alcohol **60**, which was oxidized to the acid **61** in two steps. At this stage, we elected to remove the teoc protecting group prior to the peptide coupling to ascertain whether the free enamide acid could be coupled with glycine methyl ester to afford crocacin A (**1**) directly. Unfortunately, the reaction proceeded in low yield and only a small amount of crocacin A (**1**) was isolated along with a byproduct tentatively identified as the 6,7-alkene isomer. A small amount of this compound was obtained and it could not be isolated in pure form so was not fully characterized. The low yield of this coupling prompted us to examine peptide coupling prior to removal of the teoc protecting group. We anticipated that alkene isomerization might be further suppressed by different coupling conditions and after some experimentation in model systems we found DCC/DMAP to be superior.

The alternative approach to crocacin A (**1**) is outlined in Scheme 15. Coupling of *N*-protected acid **61** with glycine methyl ester proceeded in higher yield than for the free enamide



Scheme 14. Total synthesis of crocacin A (**1**).

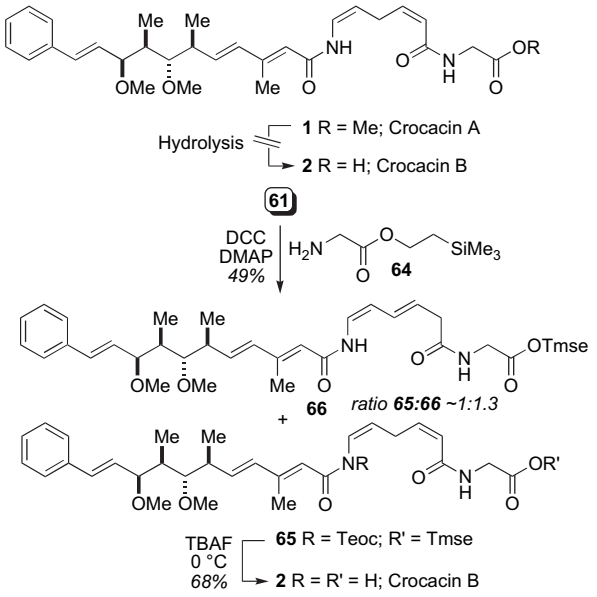
case to give the desired product **62** along with the isomerized diene **63** in a 2:1 ratio favouring **62**. The isomerization could not be suppressed and the products were contaminated with a small amount of the urea byproduct that was difficult to remove. This isomerization probably results from γ-deprotonation of the α,β-unsaturated amide followed by amide enolate protonation to give the conjugated diene system found in isomer **63**. Treatment of **62** with TBAF followed by RP-HPLC purification of the crude product then afforded crocacin A (**1**), $[\alpha]_D^{19}$ +126.8 (*c* 0.077, MeOH); lit.[3] $[\alpha]_D^{22}$ +109.6 (*c* 1.0, MeOH).



Scheme 15. Alternative synthesis of crocacin A (**1**).

2.3.2. Total synthesis of (+)-crocacin B (2)

The total synthesis of the final target crocacin B (**2**) is shown in Scheme 16. Initially, we attempted a direct synthesis of **2** from the ester crocacin A (**1**) by base hydrolysis, however, we were not able to produce any crocacin B (**2**) by this approach and only extensive degradation of **1** occurred on exposure to base. We therefore adopted a protecting strategy utilizing a trimethylsilylethyl ester (tmse) group on the glycine residue. In this way, a final deprotection of both the teoc and tmse groups would be achieved on treatment with TBAF.



Scheme 16. Total synthesis of crocacin B (**2**).

Therefore, acid **61** was coupled with the tmse ester of glycine **64**[58] to afford the enamide **65** along with the isomerized diene **66**. In this case, the isomerized diene **66** was the slightly favoured product. The coupling was also conducted with EDC·HCl and although the desired isomer was favoured (1.3:1 ratio) the yield was lower (32%). Treatment of the enamide **65** with TBAF effected full deprotection to give crocacin B (**2**). In our hands, attempts at chromatographic purification of this compound on RP-HPLC resulted in extensive decomposition, however, the crude product obtained from the deprotection reaction was pure enough to fully characterize and the synthetic material was identical to the natural product, $[\alpha]_D^{18}$ +75.0 (*c* 0.1, MeOH); lit.[3] $[\alpha]_D^{22}$ +99.0 (*c* 0.5, MeOH).

3. Conclusion

In conclusion, we have completed the total synthesis of all four crocacins A–D (**1**–**4**) from the common intermediate alcohol **22**. The key transformations included: (1) an asymmetric Sn-mediated *syn*-aldol followed by a stereoselective *anti*-reduction to secure the stereotetrad; (2) acylation of an ene- or dienecarbamate anion to install a teoc protected *Z*-enamide system. A final peptide coupling introduced the glycine methyl ester or tmse protected glycine, which in the latter case was deprotected to give crocacin B (**2**) for the first time.

4. Experimental

4.1. General

Unless otherwise stated, ^{1}H NMR (300 or 400 MHz) and proton decoupled ^{13}C NMR spectra (75.5 or 100 MHz) were recorded for deuterochloroform solutions with residual chloroform as internal standard. Optical rotations were recorded in a 10 cm microcell. Infrared spectra were recorded using

a Bio-Rad FTS165 FT-IR spectrometer. Ultraviolet spectra were recorded using a Shimadzu UV-2401PC spectrophotometer. HRMS (ESI) mass spectra were run on a Bruker 4.7T BiOAPEX FTMS mass spectrometer at Monash University, Clayton, Victoria. Flash chromatography was carried out on Merck silica gel 60. Anhydrous THF was distilled from sodium metal/benzophenone under a nitrogen atmosphere. All other anhydrous solvents were purified according to standard methods. Petrol refers to petroleum ether boiling between 40 and 60 °C.

4.2. (*S*)-Ketone **23**

To a solution of *N*,*O*-dimethyl hydroxylamine hydrochloride (9.69 g, 68 mmol) in toluene (53 mL) under argon at 0 °C was added dropwise trimethyl aluminium (2.0 M in toluene, 34.5 mL, 69 mmol). The resultant pale yellow solution was stirred a further 15 min at rt then recooled to 0 °C, and a solution of methyl (*S*)-2-methyl-3-(triisopropylsiloxy)propionate[59] (6.28 g, 22.9 mmol) in toluene (18 mL) was added by cannula. The reaction was heated to 60 °C and stirred for 3 h, then cooled to rt and quenched by the addition of ether and water. The biphasic solution was cooled to 0 °C and acidified to pH 6 using 10% v/v HCl. The aqueous phase was extracted twice further with ether and the combined organic fractions washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resultant yellow oil was purified by flash chromatography with 15% EtOAc/petrol as eluant to afford the Weinreb amide as a pale yellow oil (6.6 g, 95%). $[\alpha]_D^{16}$ +17.9 (*c* 1.18, CH_2Cl_2); IR ν_{max} (thin film) 2944, 2868, 1668, 1465, 1107, 998, 883 cm^{-1}; ^1H NMR (300 MHz) δ 1.04−1.06 (m, 21H), 1.08 (d, *J*=6.9 Hz, 3H), 3.10−3.20 (m, 1H), 3.18 (s, 3H), 3.60 (dd, *J*=9.3, 6.3 Hz, 1H), 3.70 (s, 3H), 3.92 (dd, *J*=9.3, 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 11.6, 13.5, 17.6, 31.7, 38.0, 61.1, 65.8, 175.8; HRMS (ESI) calculated for $C_{15}H_{33}NNaO_3Si$ $[M+Na]^+$ 326.2122, found 326.2125. To a solution of the Weinreb amide (3.52 g, 11.6 mmol) in THF (44 mL) under argon at 0 °C was added dropwise a solution of ethylmagnesiumbromide (1 M in THF, 23 mL, 23 mmol). The reaction was stirred at rt for 1.5 h, then quenched by the addition of ether and saturated aqueous NH_4Cl. The aqueous phase was extracted twice with ether and the combined organic fractions washed with water and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography (2.5% EtOAc/petrol eluant) to afford the ketone **23** as a colourless oil (3.161 g, 100%). $[\alpha]_D^{16}$ +46.6 (*c* 0.99, CH_2Cl_2); IR ν_{max} (thin film) 2994, 2868, 1719, 1463, 1118, 1096, 883 cm^{-1}; ^1H NMR (300 MHz) δ 0.97−1.06 (m, 27H), 2.50 (m, 2H), 2.76 (m, 1H), 3.71 (dd, *J*=9.6, 5.4 Hz, 1H), 3.78 (dd, *J*=9.6, 7.8 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 7.3, 11.8, 13.0, 17.8, 35.9, 48.4, 62.2, 214.3; HRMS (ESI) calculated for $C_{15}H_{32}NaO_2Si$ $[M+Na]^+$ 295.2064, found 295.2063.

4.3. Aldol adduct **24**

To a suspension of tin(II) triflate (5.94 g, 14.3 mmol) in CH_2Cl_2 (115 mL) at rt was added triethylamine (2.45 mL, 17.6 mmol). The resultant solution was cooled to −78 °C and a solution of ketone **23** (2.65 g, 9.7 mmol) in CH_2Cl_2 (25 mL) added dropwise via cannula. The reaction was stirred for 2 h at −78 °C, then a solution of cinnamaldehyde (1.7 g, 1.66 mL, 13 mmol) in CH_2Cl_2 (13 mL) cooled to −78 °C was added dropwise. The reaction was stirred a further 1.5 h and then quenched at −78 °C by the addition of pH 7 buffer. The resultant biphasic suspension was filtered through Celite and the filter pad washed with CH_2Cl_2 and water. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic fractions washed with water and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the crude product as a dark yellow oil. Flash chromatography with 5% EtOAc/petrol as eluant gave the desired adduct **24** as a pale yellow oil (3.3 g, 84%, 93% ds). $[\alpha]_D^{20}$ +22.1 (*c* 1.86, CH_2Cl_2); IR ν_{max} (thin film) 2943, 2867, 1703, 1462, 1101, 996, 883 cm^{-1}; ^1H NMR (300 MHz) δ 1.01−1.10 (m, 24H), 1.17 (d, *J*=7.5 Hz, 3H), 2.95 (dd, *J*=7.5, 2.7 Hz, 1H), 3.09 (m, 1H), 3.71 (dd, *J*=9, 5.1 Hz, 1H), 3.86 (dd, *J*=9, 9 Hz, 1H), 4.76 (m, 1H), 6.13 (dd, *J*=15.9, 5.4 Hz, 1H), 6.64 (dd, *J*=15.9, 1.5 Hz, 1H), 7.22 (dd, *J*=7.2, 7.2 Hz, 1H), 7.31 (dd, *J*=7.2, 7.2 Hz, 2H), 7.37 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 9.5, 11.8, 13.1, 17.9, 47.4, 51.2, 66.9, 71.2, 126.3, 127.4, 128.4, 128.9, 130.6, 136.8, 219.1; HRMS (ESI) calculated for $C_{24}H_{40}NaO_3$ $[M+Na]^+$ 427.2639, found 427.2646. Further elution provided a mixture of isomers (254 mg, 0.6 mmol, 6%).

4.4. Diols **25** and **26**

To a suspension of tetramethylammonium triacetoxyborohydride[21] (6.25 g, 24 mmol) in acetonitrile (25 mL) under argon was added acetic acid (17 mL). The suspension was stirred for 30 min by which time tetrabutylammonium triacetoxyborohydride dissolved. The reaction was cooled to −40 °C and a solution of the ketone **24** (2.4 g, 5.95 mmol) in acetonitrile (25 mL) at −40 °C added dropwise via cannula. The reaction was stirred at −40 °C for 3 h, then kept at −25 °C overnight. The reaction was then quenched by addition of CH_2Cl_2 and 1.5 M sodium tartrate. After stirring for 1 h the aqueous layer was extracted twice with CH_2Cl_2 and the combined organic fractions washed with water, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the crude diol. Flash column chromatography (10% EtOAc/petrol) gave the diol **25** as a colourless oil (2.0 g, 4.9 mmol, 83%, 96% ds). $[\alpha]_D^{16}$ +8.6 (*c* 0.93, CH_2Cl_2); IR ν_{max} (thin film) 3411, 2943, 2867, 1463, 1098, 1067, 968, 882 cm^{-1}; ^1H NMR (300 MHz) δ 0.91 (d, *J*=7.2 Hz, 3H), 1.02−1.20 (m, 24H), 1.93 (m, 1H, H4), 2.08 (m, 1H), 3.75−3.67 (m, 2H), 4.00 (dd, *J*=9.9, 3.6 Hz, 1H), 4.69 (br d, *J*=5.4 Hz, 1H), 6.25 (dd, *J*=15.9, 5.4 Hz, 1H), 6.65 (d, *J*=15.9 Hz, 1H), 7.21 (dd, *J*=7.2, 7.2 Hz, 1H), 7.30 (dd, *J*=7.2, 7.2 Hz, 2H), 7.40 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 11.6, 13.7, 17.9, 36.6, 39.7, 69.5, 72.7, 82.5, 126.3, 127.1, 128.4, 129.5, 131.0, 137.2; HRMS (ESI) calculated for $C_{24}H_{42}NaO_3Si$ $[M+Na]^+$ 429.2795, found 429.2798. Further elution then

provided the minor *syn*-diol **26** (74.6 mg, 3%), which was obtained as a colourless crystalline solid. Recrystallization from petrol afforded fine colourless needles, mp 86–87 °C; $[\alpha]_D^{20}$ +6.5 (*c* 0.24, CH_2Cl_2); IR ν_{max} (KBr disc) 3299, 2956, 2925, 2864, 1461, 1066, 967, 686 cm^{-1}; ^1H NMR (300 MHz) δ 1.02 (d, *J*=7.2 Hz, 3H), 1.05–1.1 (m, 24H), 1.86–1.96 (m, 2H), 3.72 (dd, *J*=9.9, 4.5 Hz, 1H), 3.78 (dd, *J*=9.9, 4.2 Hz, 1H), 3.95 (m, 1H), 4.55 (br d, *J*=3.3 Hz, 1H), 6.23 (dd, *J*=15.9, 5.4 Hz, 1H), 6.61 (d, *J*=15.9 Hz, 1H), 7.23 (dd, *J*=7.2, 7.2 Hz, 1H), 7.31 (dd, *J*=7.2, 7.2 Hz, 2H), 7.38 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 6.7, 11.8, 12.8, 18.0, 38.4, 40.4, 67.7, 78.5, 126.3, 127.4, 128.5, 129.8, 131.2, 136.8; HRMS (ESI) calculated for $C_{24}H_{42}NaO_3Si$ $[M+Na]^+$ 429.2754, found 429.2797.

4.5. Alcohol **22**

To a suspension of pentane washed potassium hydride (35% in mineral oil, 71 mg, 1.76 mmol) in THF (3 mL) under argon at 0 °C was added a solution of diol (143 mg, 0.35 mmol) in THF (3 mL) dropwise by cannula. The reaction was stirred for 30 min, then methyl iodide (250 mg, 1.76 mmol, 110 μL) added dropwise. The reaction was then warmed to rt and stirred a further 1.25 h. After recooling to 0 °C, ether and water were added to quench the reaction. The aqueous layer was extracted twice with ether and the combined organic fractions washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material obtained was then purified by flash chromatography (2% EtOAc/petrol eluant) to afford the dimethyl ether as a pale yellow oil (115 mg, 76%). $[\alpha]_D^{20}$ −2.9 (*c* 1.13, CH_2Cl_2); IR ν_{max} (thin film) 2962, 2942, 2867, 1464, 1091, 1070, 969, 882 cm^{-1}; ^1H NMR (300 MHz) δ 0.96 (d, *J*=6.9 Hz, 3H), 1.04–1.09 (m, 21H), 1.11 (d, *J*=7.2 Hz, 3H), 1.86 (m, 1H), 2.01 (m, 1H), 3.22 (dd, *J*=9.3, 3.0 Hz, 1H), 3.34 (s, 3H), 3.50 (s, 3H), 3.54 (m, 1H), 3.80 (dd, *J*=9.6, 5.4 Hz, 1H), 4.06 (dd, *J*=7.2, 2.4 Hz, 1H), 6.19 (dd, *J*=16.2, 7.2 Hz, 1H), 6.58 (d, *J*=16.2 Hz, 1H), 7.25 (m, 1H), 7.34 (m, 2H), 7.41 (d, *J*=7.2 Hz, 2H, H9); ^{13}C NMR (75.5 MHz) δ 10.4, 11.9, 15.8, 18.0, 38.2, 41.7, 56.4, 61.1, 64.1, 81.4, 85.4, 126.3, 127.4, 128.5, 129.6, 131.8, 136.8; HRMS (ESI) calculated for $[M+Na]^+$ 457.3108, found 457.3106. To a solution of the dimethyl ether (115 g, 0.26 mmol) in THF (2 mL) under argon was added TBAF (167 mg, 0.52 mmol). The reaction was allowed to stir overnight at rt, then quenched by the addition of ether and water. The aqueous layer was extracted twice with ether and the combined organic fractions washed with water and brine, dried ($MgSO_4$), filtered and evaporated. The crude material was purified by flash chromatography with 15% EtOAc/petrol as eluant to afford the alcohol **22** as a low melting colourless solid (73 mg, 100%). Mp 42–43 °C; $[\alpha]_D^{20}$ −4.15 (*c* 1.87, CH_2Cl_2); IR ν_{max} (thin film) 3438, 2972, 2936, 2828, 1450, 1094, 971 cm^{-1}; ^1H NMR (300 MHz) δ 0.91 (d, *J*=6.9 Hz, 3H), 1.20 (d, *J*=7.2 Hz, 3H), 1.80–1.95 (m, 2H, H2), 3.29 (dd, *J*=9.3, 2.4 Hz, 1H), 3.22 (s, 3H), 3.53 (s, 3H), 3.55 (m, 1H) 3.84 (br d, *J*=8.4 Hz, 1H), 4.07 (dd, *J*=7.2, 2.4 Hz, 1H), 6.19 (dd, *J*=15.9, 7.2 Hz, 1H), 6.58 (d, *J*=16.2 Hz, 1H), 7.24 (m, 1H), 7.33 (dd, *J*=7.5, 7.2 Hz, 2H), 7.41 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 10.2, 16.0, 35.7, 42.1, 56.2, 61.5, 64.3, 81.0, 88.2, 126.3, 127.5, 128.5, 129.2, 132.1, 136.6; HRMS (ESI) calculated for $C_{17}H_{26}NaO_3$ $[M+Na]^+$ 301.1779, found 301.1767.

4.6. Stannane **5**

To a solution of alcohol **22** (200 mg, 0.72 mmol) in CH_2Cl_2 (5 mL) under argon was added Dess–Martin reagent (457 mg, 1.08 mmol). The suspension was allowed to stir at rt for 1 h, then ether and a 1:1 mixture of saturated aqueous $NaHCO_3$ and 1.5 M sodium thiosulfate added. The solution was stirred at rt until two clear layers formed. The aqueous layer was extracted twice with ether and the combined organic fractions washed with water and brine, dried (Na_2SO_4), filtered and concentrated to afford the aldehyde as a yellow oil. Chromium(II) chloride (883 mg, 7.19 mmol) was flame dried under vacuum and then suspended in degassed DMF (12 mL) at 0 °C. The suspension was warmed to rt and a solution of tributyltindiiodomethane[30] (800 mg, 1.44 mmol) and the previously prepared aldehyde (0.72 mmol) in degassed DMF (8 mL) added dropwise. The reaction was protected from the light and allowed to stir 1.5 h. Ether and water were then added and the aqueous layer extracted twice further with ether. The combined organic fractions were then washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude vinyl stannane was purified by flash column chromatography using NEt_3 deactivated silica with 5% EtOAc/1% NEt_3/petrol as eluant to afford the stannane **5** as a colourless oil (360 mg, 89%). $[\alpha]_D^{19}$ +19.4 (*c* 1.165, CH_2Cl_2); IR ν_{max} (thin film) 2958, 2927, 1463, 1377, 1095, 998, 967, 748, 692 cm^{-1}; ^1H NMR (300 MHz) δ 0.82–0.87 (m, 12H, H–Me), 1.15 (d, *J*=6.6 Hz, 3H), 1.28 (m, 12H), 1.46 (m, 6H), 1.64 (m, 1H), 2.46 (m, 1H), 3.14 (dd, *J*=9.9, 2.4 Hz, 1H), 3.34 (s, 3H), 3.53 (s, 3H), 4.11 (br d, *J*=6.9 Hz, 1H), 5.86 (d, *J*=19.2 Hz, 1H), 5.96 (dd, *J*=19.2, 7.2 Hz, 1H), 6.17 (dd, *J*=16.2, 6.9 Hz, 1H), 6.57 (d, *J*=16.2 Hz, 1H), 7.28 (m, 1H), 7.32 (dd, *J*=7.2, 7.2 Hz, 2H), 7.39 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 9.4, 9.6, 13.6, 18.3, 27.1, 29.0, 42.5, 44.8, 56.4, 61.1, 81.2, 86.2, 126.3, 127.3, 127.8, 128.4, 129.5, 131.6, 136.9, 150.2; HRMS (ESI) calculated for $C_{30}H_{52}NaO_2Sn$ $[M+Na]^+$ 587.2881, found ^{118}Sn 585.2910, ^{120}Sn 587.2902.

4.7. (*E*)-3-Iodo-2-butenamide **6**

To a suspension of NH_4Cl (196.2 mg, 3.7 mmol) in toluene (1.5 mL) under argon at 0 °C was added dropwise a solution of $AlMe_3$ in toluene (2.0 M, 1.85 mL, 3.7 mmol). The resulting solution was allowed to warm to rt, then recooled to 0 °C and a solution of methyl *E*-3-iodo-2-butenoate **26**[33] in toluene (3 mL) added. The mixture was heated to 50 °C for 16 h, then cooled to 0 °C and partitioned between EtOAc (15 mL) and 10% v/v HCl in brine. The aqueous phase was extracted twice further with EtOAc and the combined organic layers washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was recrystallized from CH_2Cl_2/hexane to afford the iodide **6**

(136 mg, 52%) as colourless prisms; mp 124–125 °C; IR ν_{max} (KBr disc) 3365, 3188, 1662, 1598, 1399, 1066, 864 cm^{-1}; ^1H NMR (300 MHz) δ 2.97 (d, J=1.2 Hz, 3H, H4), 5.44 (br s, 1H, H–NH_2), 5.69 (br s, 1H, H–NH_2), 6.58 (d, J=1.2 Hz, 1H, H2); ^{13}C NMR (75.5 MHz) δ 30.6, 117.3, 132.5, 166.0; HRMS (ESI) calculated for C_4H_6INNaO $[M+Na]^+$ 233.9391, found 233.9384. Calculated for C_4H_6INO: C, 22.77; H, 2.87; N, 6.64; I, 60.14. Found: C, 23.06; H, 2.70; N, 6.45; I, 60.26.

4.8. (+)-Crocacin C (*3*)

Dipalladiumtrisdibenzylideneacetone (4 mg, 0.004 mmol) and triphenylarsine (11 mg, 0.035 mmol) were dissolved in degassed NMP (1 mL) under argon. A solution of iodide **6** (48.7 mg, 0.23 mmol) in degassed NMP (1.5 mL) was added and the solution stirred for 10 min at rt. A solution of stannane **5** (100 mg, 0.17 mmol) in degassed NMP (1.5 mL) was then added and the reaction heated at 60 °C overnight. The reaction was cooled to rt and poured into EtOAc and water. The aqueous layer was extracted twice with EtOAc and the combined organic fractions washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude natural product. Purification by flash chromatography with 30% EtOAc/petrol followed by 50% EtOAc/petrol as eluant afforded partly purified material, further chromatography (40% EtOAc/1% NEt_3/petrol eluant) on NEt_3 deactivated silica then afforded crocacin C (**3**) (40 mg, 66%); $[\alpha]_D^{19}$ +61.3 (*c* 0.30, MeOH), lit.[3] $[\alpha]_D^{22}$ +52.2 (*c* 0.3, MeOH); IR ν_{max} (thin film) 3477, 3398, 3341, 3189, 2976, 2933, 1663, 1602, 1449, 1369, 1266, 1089, 973 cm^{-1}; UV λ_{max} (MeOH) 253 nm (ε 3.50×10^4 L mol^{-1} cm^{-1}); ^1H NMR (400 MHz, acetone-d_6) δ 0.83 (d, J=6.8 Hz, 3H), 1.15 (d, J=7.2 Hz, 3H), 1.54 (m, 1H), 2.20 (d, J=1.2 Hz, 3H), 2.57 (m, 1H), 3.15 (dd, J=1.5, 9.6 Hz, 1H), 3.28 (s, 3H), 3.51 (s, 3H), 4.06–4.08 (m, 1H), 5.79 (s, 1H), 6.02–6.12 (m, 2H), 6.12 (br s, 1H), 6.24 (dd, J=7.2, 16.0 Hz, 1H), 6.57 (d, J=16.0 Hz, 1H), 6.70 (br s, 1H), 7.20–7.24 (m, 1H), 7.29–7.33 (m, 2H), 7.45–7.47 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 10.1, 13.4, 19.3, 40.8, 43.4, 56.4, 61.5, 81.7, 87.1, 122.0, 127.2, 128.2, 129.4, 130.4, 132.5, 135.0, 137.0, 137.8, 148.1, 169.0; HRMS (ESI) calculated for $C_{22}H_{31}NNaO_3$ $[M+Na]^+$ 380.2202, found 380.2201.

4.9. Ester *34*

To a solution of alcohol (1.93 g, 8.8 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added Dess–Martin reagent (5.6 g, 13.2 mmol). The suspension was allowed to stir at rt for 2 h, then ether and a 1:1 mixture of saturated aqueous $NaHCO_3$ and 1.5 M sodium thiosulfate added. The solution was stirred at rt until two clear layers formed. The aqueous layer was extracted twice with ether and the combined organic fractions washed with water and brine, then dried ($MgSO_4$), filtered and concentrated to afford the aldehyde **32** as a yellow oil. To a suspension of sodium hydride washed with dry pentane (60% in mineral oil, 275 mg, 11.4 mmol) in THF (10 mL) under argon at 0 °C was added a solution of ethyl(di-*o*-tolylphosphono)acetate[39] (3.37 g, 9.7 mmol) in THF (20 mL) at 0 °C. The solution was stirred at 0 °C for 15 min, then cooled to −78 °C and a solution of the previously prepared aldehyde **32** in THF (10 mL) added dropwise via cannula. The reaction was stirred at −78 °C for 30 min, then allowed to warm to rt for 2 h. Ether and water were then added and the phases separated. The aqueous phase was extracted twice further with ether and the combined organic fractions washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude material obtained was then purified by flash chromatography with 5% EtOAc/petrol as eluant to afford the desired ester **34** as a colourless oil (2.19 g, 87%). IR ν_{max} (thin film) 2859, 1721, 1645, 1473, 1416, 1388, 1255, 1167 cm^{-1}; ^1H NMR (300 MHz) δ 0.01 (s, 6H), 0.85 (s, 9H), 1.25 (t, J=6.9 Hz, 3H), 1.40–1.60 (m, 4H), 2.64 (dtd, J=7.5, 7.2, 1.5 Hz), 3.58 (t, J=5.7 Hz), 4.12 (q, J=6.9 Hz, 2H), 5.72 (dt, J=11.7, 1.5 Hz, 1H), 6.17 (dt, J=11.7, 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.3, 14.2, 18.2, 25.2, 25.8, 28.5, 32.3, 59.6, 62.7, 119.7, 150.2, 166.3; HRMS (ESI) calculated for $C_{15}H_{30}$ NaO_3Si $[M+Na]^+$ 309.1856, found 309.1861.

4.10. Ester *47*

Dipalladiumtrisdibenzylideneacetone (23 mg, 0.025 mmol) and triphenylarsine (61.6 mg, 0.2 mmol) were dissolved in degassed NMP (10 mL) under argon. A solution of iodide **26** (295 mg, 1.3 mmol) in degassed NMP (2.5 mL) was added and the solution stirred for 10 min at rt. A solution of stannane **5** (567 mg, 1.0 mmol) in degassed NMP (2.5 mL) was then added and the reaction heated at 60 °C for 5 h. The reaction was cooled to rt and poured into ether and water. The aqueous layer was extracted twice further with ether and the combined organic fractions washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude ester. Purification by flash chromatography on NEt_3 deactivated silica gel with 10% EtOAc/1% NEt_3/petrol as eluant afforded the ester **47** as a pale yellow gum (295 mg, 79%). $[\alpha]_D^{20}$ +58.0 (*c* 1.05, CH_2Cl_2); IR ν_{max} (thin film) 2974, 1717, 1635, 1612, 1486, 1358 cm^{-1}; ^1H NMR (300 MHz) δ 0.84 (d, J=7.2 Hz, 3H), 1.19 (d, J=7.2 Hz, 3H), 1.51 (ddq, J=9.6, 7.2, 2.4 Hz, 1H), 2.26 (d, J=1.0 Hz, 3H), 2.56 (ddq, J=9.0, 7.2, 2.1 Hz, 1H), 3.19 (dd, J=9.6, 2.1 Hz, 1H), 3.32 (s, 3H), 3.54 (s, 3H), 3.67 (s, 3H), 4.08 (dd, J=8.1, 2.4 Hz, 1H), 5.68 (br s, 1H), 6.07 (d, J=15.9 Hz, 1H), 6.15 (dd, J=15.9, 7.2 Hz, 1H), 6.16 (dd, J=16.2, 8.1 Hz, 1H), 6.56 (d, J=16.2 Hz, 1H), 7.22 (dd, J=7.2, 7.2 Hz, 1H), 7.31 (dd, J=7.8, 7.8 Hz, 2H), 7.39 (d, J=7.8 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 9.7, 13.9, 18.7, 40.1, 42.6, 50.9, 56.3, 61.4, 81.0, 86.3, 117.5, 126.3, 127.5, 128.5, 129.1, 132.0, 133.8, 136.7, 138.2, 152.8, 167.5; HRMS (ESI) calculated for $C_{23}H_{32}NaO_4$ $[M+Na]^+$ 395.2198, found 395.2190.

4.11. Enecarbamate *46*

To a solution of ester (500 mg, 1.7 mmol) in THF (9 mL) was added MeOH (9 mL) and aqueous NaOH (1 M, 9 mL,

9 mmol). The solution was stirred at rt overnight, then diluted with ether and cooled to 0 °C. The aqueous layer of the biphasic solution was carefully acidified to pH 2 with 10% aqueous HCl, then the phases separated. The aqueous phase was extracted twice further with ether and the combined organic fractions washed with water and brine, dried ($MgSO_4$), filtered and evaporated to yield the crude acid as a yellow oil. The crude acid was dissolved in THF (10 mL), cooled to 0 °C and added to a suspension of sodium hydride (60% in mineral oil, 38 mg, 1.57 mmol) (freshly washed with dry pentane) in THF (5 mL) at 0 °C. The reaction was stirred for 30 min at 0 °C, then diphenylphosphoryl azide (373 μL, 1.73 mmol) added dropwise. After stirring at 0 °C for further 2 h the reaction was diluted with ether and water and the phases separated. The aqueous layer was extracted twice further with ether and the combined organic fractions washed with water and brine, dried ($MgSO_4$), filtered and evaporated to yield a mixture of crude azides. Chromatography using 4% ether/petrol as eluant then afforded the pure *Z*-azide **35** (258 g, 58%); ^{1}H NMR (300 MHz) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.53 (m, 4H), 2.71 (m, 2H), 3.62 (t, J=6.0 Hz, 2H), 5.73 (dt, J=11.4, 1.8 Hz, 1H), 6.35 (dt, J=11.7, 7.8 Hz, 1H). Further elution with 4% ether/petrol then afforded the *E*-azide (45 mg, 0.1 mmol, 10%). ^{1}H NMR (300 MHz) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.53 (m, 4H), 2.25 (m, 2H), 3.61 (t, J=6 Hz, 2H), 5.83 (dt, J=15.6, 1.5 Hz, 1H), 7.06 (dt, J=15.6, 6.9 Hz, 1H). A solution of azide (158.4 mg, 0.56 mmol) in toluene under argon was heated at 110 °C for 1 h. The reaction was then cooled to 0 °C and trimethylsilylethanol (160 μL, 1.1 mmol) added dropwise. The reaction was heated again to 110 °C and stirred at this temperature for 4.5 h. The reaction was then cooled to rt and concentrated. Purification by flash chromatography using 2% EtOAc/petrol as eluant then afforded the pure enecarbamate **46** as a colourless oil (177 mg, 85%). IR ν_{max} (thin film) 3327, 2955, 1710, 1674, 1514, 1251, 1100, 837 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.04 (s, 9H), 0.05 (s, 6H), 0.89 (s, 9H), 1.00 (br m, 2H), 1.40–1.55 (m, 4H), 1.96 (br dt, J=7.5, 6.6 Hz, 2H), 3.62 (t, J=6.0 Hz, 2H), 4.19 (br m, 2H), 4.59 (br dt, J=7.8, 7.5 Hz, 1H), 6.29 (br d, J=11.1 Hz, 1H), 6.44 (br dd, J=11.1, 7.8 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.3, −1.5, 17.8, 18.4, 25.2, 25.8, 26.0, 32.1, 63.0, 63.6, 108.6, 122.3, 153.9; HRMS (ESI) calculated for $C_{18}H_{39}NNaO_3Si_2$ $[M+Na]^+$ 396.2366, found 396.2367.

4.12. Enamide *48*

To a solution of the ester **47** (100 mg, 0.3 mmol) in THF (3 mL) was added MeOH (1 mL) and water (1 mL). Lithium hydroxide (37 mg, 0.9 mmol) was added and the solution heated to 40 °C and stirred overnight. The reaction mixture was then diluted with EtOAc and water and cooled to 0 °C. The aqueous layer was acidified to pH 1 with 10% aqueous HCl and the phases separated. The aqueous phase was extracted twice further with EtOAc and the combined organic fractions washed with brine, dried ($MgSO_4$), filtered and evaporated to yield the crude acid as a yellow oil. To a suspension of sodium hydride (freshly washed with dry pentane) (60% in mineral oil, 5.8 mg, 0.24 mmol) in benzene (1 mL) at 2 °C was added a solution of acid (43.2 mg, 0.12 mmol) in benzene (1.5 mL). The reaction was stirred for 5 min at 2 °C, then warmed to rt and stirred for further 10 min. After recooling to 2 °C oxalylchloride (53 μL, 0.6 mmol) was added dropwise and the reaction stirred for 5 min. The reaction was then warmed to rt and stirred for further 45 min. Concentration then afforded the crude acid chloride **45**. To a solution of enecarbamate **46** (90 mg, 0.24 mmol) in THF (1 mL) at 0 °C under argon was added a solution of sodium bistrimethylsilylamide (1 M THF, 240 μL, 0.24 mmol). The reaction was stirred for 10 min, then cooled to −78 °C and a solution of acid chloride **45** (0.12 mmol) in THF (1 mL) at −78 °C added via cannula. The reaction was stirred for a further 1 h at −78 °C, then was quenched by the addition of ether and saturated aqueous NH_4Cl. The phases were separated and the organic phase extracted twice further with ether. The combined organic fractions were then washed with water and brine, dried (Na_2SO_4), filtered and evaporated to afford the crude product. Purification by flash chromatography using 2% EtOAc/petrol as eluant then allowed the recovery of the unreacted enecarbamate **46** (71.7 mg, 0.19 mmol), further elution (5% EtOAc/petrol) then allowed isolation of the pure protected enamide **49** as a colourless oil (25.4 mg, 30%). $[\alpha]_D^{20}$ +41.6 (*c* 1.28, CH_2Cl_2); IR ν_{max} (thin film) 2955, 1730, 1683, 1598, 1251, 1094 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.01 (s, 6H), 0.03 (s, 9H), 0.87 (s, 9H), 0.89 (d, J=6.9 Hz, 3H), 1.03 (m, 2H), 1.19 (d, J=6.9 Hz, 3H), 1.36–1.49 (m, 5H), 1.88 (ddt, J=7.5, 7.2, 1.5 Hz, 2H), 2.19 (br s, 3H), 2.56 (m, 1H), 3.19 (dd, J=9.9, 2.1 Hz, 1H), 3.32 (s, 3H), 3.54 (s, 3H), 3.55 (t, J=6.3 Hz, 2H), 4.08 (dd, J=7.2, 1.8 Hz, 1H), 4.25 (m, 2H), 5.49 (dt, J=8.1, 7.5 Hz, 1H), 5.99 (dt, J=8.1, 1.5 Hz, 1H), 6.11–6.18 (m, 3H), 6.42 (d, J=1 Hz, 1H), 6.56 (d, J=16.2 Hz, 1H), 7.22 (dd, J=7.2, 7.2 Hz, 1H), 7.31 (dd, J=7.5, 7.2 Hz, 2H), 7.39 (d, J=7.2 Hz, 2H); ^{13}C NMR (75.5 MHz) δ −5.3, −1.6, 9.8, 14.7, 17.5, 18.3, 18.7, 24.6, 25.9, 26.5, 32.4, 40.2, 42.6, 56.4, 61.4, 62.8, 65.3, 81.0, 86.3, 121.2, 123.6, 126.4, 127.5, 128.5, 129.2, 130.4, 132.0, 134.3, 136.7, 138.1, 151.5, 154.0, 167.7; HRMS (ESI) calculated for $C_{40}H_{67}NNaO_6Si_2$ $[M+Na]^+$ 736.4405, found 736.4402.

4.13. Alcohol *49*

A solution of HF·pyridine complex (52 mg, 1.78 mmol) and pyridine (104 μL, 1.28 mmol) in THF (2 mL) at 0 °C under argon was added to a solution of protected alcohol **48** (25.4 mg, 0.035 mmol) in THF (0.5 mL). The reaction was stirred at 0 °C for 8 h before being diluted with ether. Aqueous $NaHCO_3$ was then added dropwise and the layers of the biphasic solution separated. The aqueous layer was extracted twice further with ether and the combined organic fractions washed with water, saturated aqueous $CuSO_4$, water and brine, dried ($MgSO_4$), filtered and evaporated to afford the crude alcohol. Purification by flash chromatography with 30% EtOAc/petrol as eluant gave alcohol **49** (19.4 mg, 91%) as a colourless oil. $[\alpha]_D^{20}$ +43.8 (*c* 1.03, CH_2Cl_2); IR ν_{max} (thin film) 3464,

1930, 1730, 1684, 1597, 1252, 1090 cm^{-1}; ^1H NMR (300 MHz) δ 0.03 (s, 9H), 0.84 (d, J=6.6 Hz, 3H), 1.03 (m, 2H), 1.19 (d, J=7.2 Hz, 3H), 1.93–1.59 (m, 6H), 1.91 (ddt, J=7.8, 7.2, 1.2 Hz, 2H), 2.20 (s, 3H), 2.57 (m, 1H), 3.19 (dd, J=10.0, 2.1 Hz, 1H), 3.21 (s, 3H), 3.54 (s, 3H), 3.58 (t, J=6.1 Hz, 2H), 4.08 (dd, J=7.2, 1.5 Hz, 1H), 4.26 (m, 2H), 5.50 (dt, J=7.8, 7.5 Hz, 1H), 6.01 (dt, J=7.8, 1.5 Hz, 1H), 6.02–6.19 (m, 3H), 6.41 (d, J=1.0 Hz, 1H), 6.56 (d, J=15.9 Hz, 1H), 7.22 (dd, J=7.5, 6.9 Hz, 1H), 7.31 (dd, J=7.5, 6.9 Hz, 2H), 7.39 (d, J=6.9 Hz, 2H); ^{13}C NMR (100 MHz) δ −1.5, 9.7, 14.7, 17.5, 18.7, 24.4, 26.3, 32.1, 40.2, 42.6, 56.4, 61.4, 62.5, 65.4, 81.0, 86.3, 121.1, 123.8, 126.4, 127.5, 128.5, 129.2, 130.2, 132.0, 134.3, 136.7, 138.3, 151.7, 153.9, 167.8; HRMS (ESI) calculated for $C_{34}H_{53}NNaO_6Si$ $[M+Na]^+$ 622.3540, found 622.3544.

4.14. Teoc protected crocacin D (**50**)

To a solution of alcohol **49** (9.2 mg, 0.015 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C were added pyridine (6.25 μL, 0.07 mmol) and Dess–Martin reagent (13.1 mg, 0.031 mmol). The suspension was allowed to stir at 0 °C for 4 h, then ether and a 1:1 mixture of saturated aqueous $NaHCO_3$ and 1.5 M sodium thiosulfate added. The solution was stirred at rt until two clear layers formed. The aqueous layer was extracted twice with ether and the combined organic fractions washed with water, saturated aqueous $CuSO_4$, water and brine, then dried (Na_2SO_4), filtered and concentrated to afford the aldehyde as a yellow oil. To a solution of the aldehyde in 2-methyl-2-propanol (1 mL) and 2-methyl-2-butene (0.5 mL) was added dropwise a solution of sodium phosphate monobasic (8.5 mg, 0.062 mmol) and sodium chlorite (11.2 mg, 0.123 mmol) in water (0.5 mL). The solution was stirred for 1.25 h at rt, then ether and water added. The aqueous layer was extracted twice with ether and the combined organic layers washed with water and brine, dried ($MgSO_4$) and concentrated to afford the carboxylic acid **44**. To a solution of the acid **44** (0.015 mmol) in DMF (1 mL) were added sodium bicarbonate (65 mg, 0.77 mmol) and glycine methyl ester hydrochloride (19.4 mg, 0.15 mmol). The reaction was cooled to 0 °C and diphenylphosphoryl azide (34 μL, 0.15 mmol) added dropwise. The reaction was then stirred overnight at 0 °C. The resultant suspension was poured into ether and water and the phases separated. The aqueous phase was extracted twice further with ether and the combined organic fractions washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography with 40% EtOAc/petrol as eluant then afforded protected crocacin D **50** as a colourless oil (7.5 mg, 71%). $[\alpha]_D^{20}$ +43.7 (c 0.73, CH_2Cl_2); IR ν_{max} (thin film) 3347, 2955, 1734, 1676, 1597, 1252, 1192, 1087 cm^{-1}; ^1H NMR (300 MHz) δ 0.03 (s, 9H), 0.84 (d, J=7.2 Hz, 3H), 1.02 (m, 2H), 1.19 (d, J=6.9 Hz, 3H), 1.54 (ddq, J=9.6, 7.2, 2.4 Hz, 1H), 1.74 (tt, J=7.2, 6.6 Hz, 2H), 1.95 (ddt, J=7.2, 6.6, 1.5 Hz, 2H), 2.18 (br s, 3H), 2.19 (t, J=7.2 Hz, 2H), 2.57 (m, 1H), 3.19 (dd, J=9.6, 2.1 Hz, 1H), 3.32 (s, 3H), 3.54 (s, 3H), 3.72 (s, 3H), 3.98 (d, J=5.4 Hz, 2H), 4.07 (dd, J=7.2, 1.5 Hz, 1H), 4.25 (m, 2H), 5.48 (dt, J=8.1, 7.2 Hz, 1H), 6.02 (dt, J=8.1, 1.5 Hz, 1H), 6.09–6.15 (m, 4H), 6.44 (d, J=1.0 Hz, 1H), 6.56 (d, J=16.2 Hz, 1H), 7.22 (dd, J=7.2, 6.9 Hz, 1H), 7.31 (dd, J=7.2, 6.9 Hz, 2H), 7.39 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz) δ −1.6, 9.7, 14.7, 17.5, 18.7, 24.1, 26.0, 35.4, 40.2, 41.1, 42.6, 52.2, 56.4, 61.4, 65.5, 81.0, 86.3, 121.1, 124.6, 126.4, 127.5, 128.5, 129.1, 129.8, 132.0, 134.2, 136.7, 138.4, 151.8, 153.9, 168.0, 170.4, 172.8; HRMS (ESI) calculated for $C_{37}H_{56}N_2NaO_8Si$ $[M+Na]^+$ 707.3704, found 707.3706.

4.15. (+)-Crocacin D (**4**)

To a solution of the teoc protected natural product **50** (14 mg, 0.02 mmol) in THF (2 mL) at 0 °C under argon was added TBAF (13 mg, 0.04 mmol). The reaction was stirred at 0 °C for 1.75 h, then EtOAc and water were added. The phases were separated and the aqueous phase extracted twice further with EtOAc. The combined organic fractions were then washed with water and brine, dried (Na_2SO_4), filtered and evaporated to afford the crude natural product. Purification by flash chromatography on NEt_3 deactivated silica gel with 60% EtOAc/1% NEt_3/petrol as eluant then afforded crocacin D (**4**) (10.4 mg, 94%). $[\alpha]_D^{20}$ +102.7 (c 0.22, MeOH); lit. $[\alpha]_D^{20}$ +109.6 (c 0.56, MeOH); UV (MeOH) λ_{max} (log ε) 255 (4.51), 264 (4.47), 276 (4.40), 282 (4.40), 292 sh (4.36); IR ν_{max} (thin film) 3302, 2931, 1748, 1653, 1610, 1507, 1265, 1092, 974 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 0.84 (d, J=7.2 Hz, 3H), 1.17 (d, J=6.8 Hz, 3H), 1.55 (ddq, J=9.6, 7.2, 2.4 Hz, 1H), 1.67 (tt, J=7.2, 6.8 Hz, 2H), 2.11 (dt, J=7.2, 6.8 Hz, 2H), 2.25 (t, J=7.2 Hz, 2H), 2.27 (br s, 3H), 2.60 (m, 1H), 3.17 (dd, J=9.6, 2.4 Hz, 1H), 3.29 (s, 3H), 3.51 (s, 3H), 3.66 (s, 3H), 3.95 (d, J=6.0 Hz, 2H), 4.08 (dd, J=7.2, 1.6 Hz, 1H), 4.66 (dt, J=9.0, 7.2 Hz, 1H), 5.91 (d, J=1.2 Hz, 1H), 6.12 (m, 2H), 6.24 (dd, J=16, 7.2 Hz, 1H), 6.58 (d, J=16 Hz, 1H), 6.78 (dd, J=10.4, 9.0 Hz, 1H), 7.22 (dd, J=7.2, 7.2 Hz, 1H), 7.30 (dd, J=7.2, 7.2 Hz, 2H), 7.46 (d, J=7.2 Hz, 2H), 7.58 (br m, 1H), 9.13 (br d, J=10.4 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 10.0, 13.7, 19.2, 25.3, 26.1, 34.4, 40.8, 41.4, 43.4, 52.1, 56.4, 61.4, 81.7, 87.0, 109.6, 121.7, 123.8, 127.2, 128.2, 129.3, 130.3, 132.5, 135.0, 137.7, 149.6, 164.5, 171.2, 174.4; HRMS (ESI) calculated for $C_{31}H_{44}N_2NaO_6$ $[M+Na]^+$ 563.3097, found 563.3083.

4.16. Diene **56**

To a mixture of cesium carbonate (9.46 g, 29 mmol), sodium iodide (4.35 g, 29 mmol) and copper(I) iodide (2.76 g, 14.5 mmol) were added a solution of 4-chloro-2-butyn-1-ol[55] **54** (1.51 g, 14.5 mmol) in DMF (14 mL) and a solution of TBS protected propargyl alcohol **55** (2.47 g, 14.5 mmol) in DMF (14 mL). The suspension was stirred at rt for 5 h, then cooled to 0 °C and diluted with ether and saturated aqueous NH_4Cl. The solution was filtered through a Celite pad and the layers separated. The aqueous layer was then extracted twice with ether and the combined organic layers washed with water and brine, dried ($MgSO_4$), filtered and evaporated

to yield the crude diyne **53** as a yellow oil (3.311 g, 95%). The crude material proved unstable to silica gel chromatography so it was used crude in the next step. ^{1}H NMR (300 MHz) δ 0.11 (s, 6H), 0.90 (s, 9H), 3.24 (m, 2H), 4.26 (t, J=1.8 Hz, 2H), 4.30 (t, J=1.8 Hz, 2H); ^{13}C NMR (75.5 MHz) δ −5.2, 9.9, 18.2, 25.7, 51.0, 51.7, 78.4, 78.8, 79.1, 79.5. To a solution of nickel(II) acetate (3.46 g, 13.8 mmol) in ethanol (195 mL) under a hydrogen atmosphere were added a 1 M solution of sodium borohydride in ethanol (13.75 mL) and aqueous sodium hydroxide (2 M, 0.75 mL). Once hydrogen evolution had ceased, ethylene diamine (3.72 mL, 55 mmol) was added followed immediately by addition of a solution of diyne (3.311 g, 13.8 mmol) in ethanol (36 mL). The reaction mixture was once again put under a hydrogen atmosphere and allowed to stir at rt for 1 h. Water and sufficient ether to form two separate layers were then added, and the resultant suspension filtered through Celite. The aqueous layer was extracted twice with ether and the combined organic fractions washed with water and brine, dried (Na_2SO_4) and concentrated to afford the crude diene. The diene **56** was purified by silica gel chromatography on NEt_3 deactivated silica gel and elution with 15% EtOAc/1% NEt_3/petrol afforded the diene **56** as a pale yellow oil (2.54 g, 76%). IR ν_{max} (thin film) 3348, 2957, 2931, 2858, 1472, 1464, 1255, 1091 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.07 (s, 6H), 0.90 (s, 9H), 2.85 (dd, J=7.2, 7.2 Hz, 2H), 4.21 (d, J=7.2 Hz, 2H), 4.24 (d, J=6.9 Hz, 2H), 5.35−5.70 (m, 4H); ^{13}C NMR (75.5 MHz) δ −5.1, 18.3, 25.9, 26.0, 58.3, 59.2, 128.4, 128.9, 130.0, 130.3; HRMS (ESI) calculated for $C_{13}H_{26}NaO_2Si$ $[M+Na]^+$ 265.1599, found 265.1595.

4.17. Dienecarbamate *51*

To a solution of alcohol **56** (200 mg, 0.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added 2,6-lutidine (468 μL, 4.1 mmol) and Dess−Martin reagent (525 mg, 1.2 mmol). The suspension was allowed to stir at 0 °C for 2 h, then ether and a 1:1 mixture of saturated aqueous $NaHCO_3$ and 1.5 M sodium thiosulfate added. The solution was stirred at rt until two clear layers formed. The aqueous layer was extracted twice with ether and the combined organic fractions washed with water, aqueous $CuSO_4$, water and brine, then dried (Na_2SO_4), filtered and concentrated to afford the aldehyde as a yellow oil. To a solution of the aldehyde in 2-methyl-2-propanol (3 mL) and 2-methyl-2-butene (1.5 mL) was added dropwise a solution of sodium phosphate monobasic (455 mg, 3.3 mmol) and sodium chlorite (597 mg, 6.6 mmol) in water (1.5 mL). The solution was stirred for 1 h at rt, then ethylacetate and water added. The aqueous layer was extracted twice with EtOAc and the combined organic layers washed with water and brine, dried (Na_2SO_4), filtered and concentrated to afford the crude acid **57**. To a stirred suspension of sodium hydride (60% in mineral oil, 19.8 mg, 0.8 mmol) (washed three times with dry pentane) in THF (4 mL) under an argon atmosphere at 0 °C was added a solution of acid **57** in THF (4 mL). The reaction was stirred for 30 min at 0 °C, then diphenylphosphoryl azide (178 μL, 0.8 mmol) added dropwise. After stirring at 0 °C for further 2 h the reaction was diluted with ether and water and the phases separated. The aqueous layer was extracted twice further with ether and the combined organic fractions washed with water and brine, dried (Na_2SO_4), filtered and evaporated to yield a mixture of crude azides. Purification by flash chromatography with 2% ether/petrol as eluant afforded the pure *Z*-azide **58** (50.4 mg, 22%). ^{1}H NMR (300 MHz) δ 0.06 (s, 6H), 0.89 (s, 9H), 3.48 (dd, J=7.5, 7.5 Hz, 2H), 4.25 (d, J=6 Hz, 2H), 5.44 (m, 1H), 5.65 (m, 1H), 5.73 (m, 1H), 6.27 (dt, J=11.4, 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.2, 18.3, 25.9, 28.2, 59.3, 120.3, 125.8, 132.0, 151.1, 171.4. Further elution (2% ether/petrol) then provided a 1:1 mixture of *Z* and *E* azides (16.7 mg, 0.06 mmol, 7%). Further elution with 4% ether/petrol then gave pure *E*-azide (25.4 mg, 11%). ^{1}H NMR (300 MHz) δ 0.06 (s, 6H), 0.89 (s, 9H), 3.00 (dd, J=6.9, 6.9 Hz, 2H), 4.20 (d, J=6.3 Hz, 2H), 5.43 (m, 1H), 5.70 (m, 1H), 5.83 (dt, J=15.6, 1.8 Hz, 1H), 7.03 (dt, J=15.6, 6.9 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.2, 18.3, 25.8, 30.4, 59.2, 122.9, 124.4, 132.7, 149.3, 171.7. A solution of azide **58** (80.5 mg, 0.28 mmol) in toluene (3 mL) under argon was heated at 110 °C for 1 h. The reaction was then cooled to 0 °C and trimethylsilylethanol (82 μL, 0.57 mmol) added dropwise. The reaction was heated again to 110 °C and stirred at this temperature for 1 h. The reaction was then cooled to rt and concentrated in vacuo. Purification by flash chromatography with 2% EtOAc/petrol as eluant afforded the pure enecarbamate **51** as a colourless oil (85.9 mg, 81%). IR ν_{max} (thin film) 3302, 2956, 293, 2858, 1709, 1674, 1513, 1251 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.04 (s, 9H), 0.08 (s, 6H), 0.09 (s, 9H), 0.99 (m, 2H), 2.75 (dd, J=7.2, 7.2 Hz, 2H), 4.18 (m, 2H), 4.25 (d, J=6.0 Hz, 2H), 4.62 (dt, J=8.1, 7.5 Hz, 1H), 5.44 (dt, J=10.8, 7.2 Hz, 1H), 5.58 (dt, J=10.8, 6.0 Hz, 1H), 6.47 (dd, J=10.5, 9.9 Hz, 1H), 6.64 (br d, J=11.1 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.2, −1.5, 17.7, 18.4, 24.0, 25.9, 59.4, 63.6, 105.6, 123.4, 128.7, 129.6, 153.9; HRMS (ESI) calculated for $C_{18}H_{37}NNaO_3Si_2$ $[M+Na]^+$ 394.2209, found 394.2215.

4.18. Enamide *59*

To a solution of enecarbamate **51** (148 mg, 0.39 mmol) in THF (3 mL) at 0 °C under argon was added a solution of sodium bistrimethylsilylamide (1 M THF, 390 μL, 0.39 mmol). The reaction was stirred for 10 min, then cooled to −78 °C and added via cannula to a solution of the acid chloride **45** (from acid 95.3 mg, 0.27 mmol) in THF (2.5 mL) at −78 °C. The reaction was stirred for a further 1 h at −78 °C, then quenched by the addition of ether and saturated aqueous NH_4Cl. The phases were separated and the aqueous phase extracted twice further with ether. The combined organic fractions were then washed with water and brine, dried (Na_2SO_4), filtered and evaporated to afford the crude product. Purification by flash chromatography with 2% EtOAc/petrol as eluant afforded the unreacted enecarbamate (70.7 mg, 0.19 mmol) and further elution with 5% EtOAc/petrol then gave enamide **59** as a colourless oil (108.1 mg, 57%). $[\alpha]_D^{16}$ +46.5 (c 0.41, CH_2Cl_2); IR ν_{max} (thin

film) 2956, 2930, 2858, 1732, 1596, 1253, 1174, 1091 cm^{-1}; ^1H NMR (300 MHz) δ 0.03 (s, 15H), 0.84 (d, J=7.2 Hz, 3H), 0.86 (s, 9H), 1.03 (m, 2H), 1.18 (d, J=6.9 Hz, 3H), 1.53 (m, 1H), 2.20 (s, 3H), 2.56 (m, 1H), 2.62 (dd, J=7.2, 7.2 Hz, 2H), 3.19 (dd, J=9.9, 1.8 Hz, 1H), 3.32 (s, 3H), 3.54 (s, 3H), 4.08 (br d, J=5.7 Hz, 1H), 4.15 (d, J=6.0 Hz, 2H), 4.24 (m, 2H), 5.35 (dt, J=10.8, 7.2 Hz, 1H), 5.46 (dt, J=7.8, 7.2 Hz, 1H), 5.56, (dt, J=10.8, 6.0 Hz, 1H), 6.03 (d, J=7.8 Hz, 1H), 6.08–6.20 (m, 3H, H4, H5), 6.45 (s, 1H), 6.57 (d, J=15.9 Hz, 1H), 7.24 (m, 1H), 7.32 (m, 2H), 7.40 (m, 2H); ^{13}C NMR (75.5 MHz) δ −5.2, −1.6, 9.7, 14.7, 17.5, 18.3, 18.7, 25.4, 25.9, 40.2, 42.6, 56.4, 59.2, 61.5, 65.4, 80.9, 86.2, 121.0, 126.3, 126.5, 127.5, 127.9, 128.5, 129.0, 131.1, 131.9, 134.3, 136.7, 138.3, 151.9, 153.8, 167.6; HRMS (ESI) calculated for $C_{40}H_{65}NNaO_6Si_2$ $[M+Na]^+$ 734.4248, found 734.4248.

4.19. Alcohol **60**

To a solution of HF·pyridine complex (106 mg, 3.6 mmol) and pyridine (214 μL, 2.6 mmol) in THF (2.5 mL) at 0 °C under an argon atmosphere was added a solution of protected alcohol **59** (52.3 mg, 0.073 mmol) in THF (0.5 mL). The reaction was stirred at 0 °C for 5 h before being diluted with ether. Aqueous $NaHCO_3$ was then added dropwise and the layers of the biphasic solution separated. The aqueous layer was extracted twice further with ether and the combined organic fractions washed with water, saturated aqueous $CuSO_4$, water and brine, dried ($MgSO_4$), filtered and evaporated to afford the crude alcohol. Purification by flash chromatography on triethylamine deactivated silica gel using 20% EtOAc/petrol/1% NEt_3 as eluant afforded the alcohol **60** (40.5 mg, 92%). $[\alpha]_D^{17}$ +41.4 (*c* 0.59, CH_2Cl_2); IR ν_{max} (thin film) 3454, 2956, 1732, 1683, 1596, 1252, 1173, 1089 cm^{-1}; ^1H NMR (300 MHz) δ 0.03 (s, 9H), 0.84 (d, J=6.9 Hz, 3H, H–Me), 1.03 (m, 2H), 1.19 (d, J=6.9 Hz, 3H), 1.54 (m, 1H), 2.20 (s, 3H), 2.57 (m, 1H), 2.67 (dd, J=7.2, 7.2 Hz, 2H), 3.19 (dd, J=9.1, 1.8 Hz, 1H), 3.32 (s, 3H), 3.54 (s, 3H), 4.04–4.12 (m, 3H, H9), 4.26 (m, 2H), 5.46 (dt, J=10.5, 7.2 Hz, 1H), 5.51 (dt, J=7.8, 7.2 Hz, 1H), 5.63 (dt, J=11.1, 6.6 Hz, 1H), 6.02 (d, J=8.1 Hz, 1H), 6.10–6.19 (m, 3H), 6.43 (s, 1H), 6.56 (d, J=15.9 Hz, 1H), 7.22 (m, 1H), 7.31 (m, 2H), 7.39 (m, 2H); ^{13}C NMR (75.5 MHz) δ −1.5, 9.7, 14.7, 17.4, 18.6, 25.2, 40.1, 42.6, 56.4, 58.1, 61.4, 65.5, 80.9, 86.2, 120.8, 124.1, 126.3, 127.4, 127.9, 128.2, 128.5, 129.1, 129.9, 131.9, 134.2, 135.6, 138.5, 152.2, 153.8; HRMS (ESI) calculated for $C_{34}H_{51}NNaO_6Si$ $[M+Na]^+$ 620.3383, found 620.3382.

4.20. Enamide **62**

To a solution of alcohol **60** (48.6 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) at 0 °C were added 2,6-lutidine (46 μL, 0.41 mmol) and Dess–Martin reagent (51.7 mg, 0.122 mmol). The suspension was allowed to stir at 0 °C for 1.5 h, then ether and a 1:1 mixture of saturated aqueous $NaHCO_3$ and 1.5 M sodium thiosulfate added. The solution was stirred at rt until two clear layers formed. The aqueous layer was extracted twice with ether and the combined organic fractions washed with water, aqueous $CuSO_4$, water and brine, then dried (Na_2SO_4), filtered and concentrated to afford the aldehyde as a yellow oil. To a solution of the aldehyde in 2-methyl-2-propanol (2 mL) and 2-methyl-2-butene (1 mL) was added dropwise a solution of sodium phosphate monobasic (45 mg, 0.33 mmol) and sodium chlorite (59 mg, 0.65 mmol) in water (1 mL). The solution was stirred for 1.5 h at rt, then ethylacetate and water added. The aqueous layer was extracted twice with EtOAc and the combined organic layers washed with water and brine, dried (Na_2SO_4) and concentrated to afford the carboxylic acid **61**. To a solution of the crude acid **61** (20 mg, 0.033 mmol) in CH_2Cl_2 (0.3 mL) and triethylamine (5.5 μL, 0.039 mmol) was added glycine methyl ester hydrochloride (4.5 mg, 0.36 mmol). The reaction was stirred for 5 min at 0 °C, then DMAP (0.4 mg, 0.003 mmol) and DCC (7.4 mg, 0.036 mmol) were added. The reaction was stirred for 1 h at 0 °C, then warmed to rt and stirred for a further 1 h. Ether and a saturated solution of $NaHCO_3$ were then added and the phases separated. The aqueous phase was extracted twice further with ether and the combined organic fractions washed with water and brine, dried (Na_2SO_4), filtered and evaporated to afford the crude product. Purification by flash chromatography (20% EtOAc/petrol then 30% EtOAc/petrol) then afforded the enamide **62** as a colourless oil (11.3 mg, 40%); IR ν_{max} (thin film) 3337, 2955, 2930, 2857, 1747, 1664, 1535, 1252 cm^{-1}; ^1H NMR (300 MHz) δ 0.02 (s, 9H), 0.84 (d, J=6.6 Hz, 3H), 1.02 (m, 2H), 1.18 (d, J=7.2 Hz, 3H), 1.50–1.60 (m, 1H), 2.17 (s, 3H), 2.57 (m, 1H), 3.19 (br d, J=9.9 Hz, 1H), 3.29 (m, 2H), 3.32 (s, 3H), 3.54 (s, 3H), 3.74 (s, 3H), 4.03 (d, J=5.1 Hz, 2H), 4.07 (br d, J=7.5 Hz, 1H), 4.24 (m, 2H), 5.55 (dt, J=7.8, 7.8 Hz, 1H), 5.75 (d, J=11.1 Hz, 1H), 5.96 (dt, J=11.1, 7.2 Hz, 1H), 6.05 (br d, J=8.1 Hz, 1H), 6.10–6.19 (m, 3H), 6.45 (s, 1H), 6.55 (d, J=16.2 Hz, 1H), 7.22 (m, 1H), 7.31 (m, 2H), 7.39 (m, 2H); ^{13}C NMR (100 MHz) δ −1.5, 9.7, 14.7, 17.5, 18.7, 29.7, 40.2, 40.9, 42.6, 52.3, 56.4, 61.4, 65.5, 81.0, 86.4, 121.2, 122.3, 124.7, 126.4, 127.4, 127.5, 128.5, 129.1, 131.9, 134.3, 136.7, 138.2, 142.0, 151.7, 153.7, 165.8, 167.9, 170.3; HRMS (ESI) calculated for $C_{37}H_{54}N_2NaO_8Si$ $[M+Na]^+$ 705.3547, found 705.3561. Further elution with 40% EtOAc/petrol then afforded the diene isomer **63**, which was contaminated with a small amount of urea byproduct (4.7 mg, 21%); IR ν_{max} (thin film) 3331, 2955, 1738, 1732, 1439, 1251, 1089 cm^{-1}; ^1H NMR (400 MHz) δ 0.02 (s, 9H), 0.84 (d, J=7.2 Hz, 3H), 1.02 (m, 2H), 1.19 (d, J=6.8 Hz, 3H), 1.54 (m, 1H), 2.20 (s, 3H), 2.57 (m, 1H), 3.06 (d, J=7.2 Hz, 2H), 3.19 (dd, J=10, 2 Hz, 1H), 3.32 (s, 3H), 3.54 (s, 3H), 3.73 (s, 3H), 4.00 (d, J=5.2 Hz, 2H) 4.07 (br d, J=6.8 Hz, 1H), 4.25 (m, 2H), 5.89 (dt, J=14.8 Hz, 1H), 5.97–6.20 (m, 4H), 6.07 (d, J=10.8 Hz, 1H), 6.15 (dd, J=14.8, 6.8 Hz, 1H), 6.44 (s, 1H), 6.56 (d, J=16 Hz, 1H), 7.22 (m, 1H), 7.31 (m, 2H), 7.39 (m, 2H); ^{13}C NMR (100 MHz) δ −1.5, 9.7, 14.7, 17.5, 18.6, 29.6, 40.2, 41.2, 42.6, 52.3, 56.4, 61.4, 65.6, 81.0, 86.3, 120.8, 123.8, 126.4, 126.9, 127.5, 128.0, 128.5, 128.8, 129.1, 132.0, 134.2, 136.7, 138.7, 152.5, 153.8, 167.7, 170.1, 170.2; HRMS (ESI) calculated for $C_{37}H_{54}N_2NaO_8Si$ $[M+Na]^+$ 705.3547, found 705.3543.

4.21. Crocacin A (**1**)

A solution of TBAF (5.4 mg, 0.017 mmol) in THF (0.8 mL) at 0 °C was added to the protected natural product **62** (5.8 mg, 0.009 mmol) and the resultant solution allowed to stir at 0 °C for 30 min. EtOAc and pH 7 buffer were then added and the phases separated. The aqueous phase was extracted twice further with EtOAc and the combined organic fractions washed with brine, dried (Na_2SO_4), filtered and evaporated to afford the crude natural product. Column chromatography on NEt_3 deactivated silica gel with 40% EtOAc/petrol/1% NEt_3 as eluant followed by further purification by RP-HPLC (10% H_2O/MeOH) afforded crocacin A (**1**) (2.6 mg, 57%). $[\alpha]_D^{19}$ +126.8 (*c* 0.077, MeOH); lit.[3] $[\alpha]_D^{22}$ +109.6 (*c* 1.0, MeOH); IR ν_{max} (thin film) 3359, 2955, 2361, 2341, 1732, 1675, 1251, 1175 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 0.86 (d, *J*=7.2 Hz, 3H), 1.18 (d, *J*=6.8 Hz, 3H), 1.56 (m, 1H), 2.26 (s, 3H), 2.61 (m, 1H), 3.18 (dd, *J*=9.6, 2.0 Hz, 1H), 3.29 (s, 3H), 3.31 (dd, *J*=8.6, 8.6 Hz, 2H), 3.52 (s, 3H), 3.68 (s, 3H), 4.08 (m, 3H), 4.77 (dt, *J*=8.4, 8.4 Hz, 1H), 5.81 (br s, 1H), 5.95 (d, *J*=11.2 Hz, 1H), 6.05 (dt, *J*=11.2, 8.8 Hz, 1H), 6.14 (dd, *J*=15.4, 8.0 Hz, 1H), 6.19 (d, *J*=15.6 Hz, 1H), 6.24 (dd, *J*=16.0, 7.2 Hz, 1H), 6.58 (d, *J*=16.0 Hz, 1H), 6.82 (dd, *J*=10.6, 8.4 Hz, 1H), 7.21 (dd, *J*=7.6, 7.2 Hz, 1H), 7.30 (dd, *J*=8.0, 7.6 Hz, 2H), 7.46 (d, *J*=7.2 Hz, 2H), 7.98 (br m, 1H), 10.05 (br d, *J*=10.4 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 10.1, 13.6, 19.2, 26.2, 40.8, 41.6, 43.4, 52.3, 56.4, 61.4, 81.7, 87.0, 104.3, 120.9, 121.7, 125.8, 127.2, 128.2, 129.3, 130.3, 132.5, 135.1, 137.7, 137.8, 143.4, 149.8, 164.4, 168.9, 170.6; HRMS (ESI) calculated for $[M+Na]^+$ 791.4093, found 791.4088.

4.22. Enamide **65**

To a solution of the crude acid **61** and tmse protected glycine **64**[58] (11.7 mg, 0.07 mmol) in CH_2Cl_2 (0.25 mL) at 0 °C were added DCC (13.8 mg, 0.066 mmol) and a solution of DMAP (0.04 mg, 0.3 μmol) in CH_2Cl_2 (50 μL). The reaction was stirred for 2.5 h at 0 °C, then petroleum spirit added and the reaction filtered through Celite. Concentration then afforded the crude material, which was purified by flash chromatography (20% EtOAc/petrol) to afford the enamide **65** as a colourless oil (5.4 mg, 21%). $[\alpha]_D^{16}$ +43.3 (*c* 0.27, CH_2Cl_2); IR ν_{max} (thin film) 3359, 2955, 2361, 2341, 1732, 1675, 1251, 1175 cm^{-1}; ^1H NMR (400 MHz) δ 0.02 (s, 9H), 0.04 (s, 9H), 0.84 (d, *J*=6.9 Hz, 3H), 0.96–1.07 (m, 4H), 1.18 (d, *J*=6.8,Hz, 3H), 1.55 (m, 1H), 2.18 (s, 3H), 2.57 (m, 1H), 3.18 (dd, *J*=8.4, 3.0 Hz, 1H), 3.24–3.36 (m, 5H), 3.54 (s, 3H), 4.00 (d, *J*=5.1 Hz, 2H), 4.08 (br d, *J*=5.1 Hz, 1H), 4.20–4.28 (m, 4H), 5.56 (dt, *J*=7.8, 7.8 Hz, 1H), 5.74 (d, *J*=11.4 Hz, 1H), 5.95 (dt, *J*=11.4, 7.2 Hz, 1H), 6.05 (d, *J*=7.8 Hz, 1H), 6.10–6.20 (m, 3H), 6.45 (s, 1H), 6.55 (d, *J*=16.2 Hz, 1H), 7.22 (m, 1H), 7.31 (m, 2H), 7.39 (d, *J*=7.2 Hz); ^{13}C NMR (100 MHz) δ −1.55, −1.52, 9.8, 14.7, 17.3, 17.5, 18.7, 29.7, 40.2, 41.2, 42.6, 56.4, 61.4, 63.9, 65.5, 81.0, 86.4, 121.2, 122.4, 124.7, 126.4, 127.4, 127.5, 128.5, 129.2, 131.9, 134.4, 136.7, 138.2, 142.0, 151.7, 153.7, 165.8, 167.9, 170.0; HRMS (ESI) calculated for $C_{41}H_{64}N_2NaO_8Si_2$ $[M+Na]^+$ 791.4093, found 791.4088. Further elution with 30% EtOAc/petrol then afforded the enamide isomer **66** (7.2 mg, 28%). $[\alpha]_D^{18}$ +46.0 (*c* 0.19, CH_2Cl_2); IR ν_{max} (thin film) 2955, 2929, 1732, 1681, 1596, 1251, 1178, 1091 cm^{-1}; ^1H NMR (400 MHz) δ 0.02 (s, 9H), 0.04 (s, 9H), 0.84 (d, *J*=6.8 Hz, 3H), 0.98–1.04 (m, 4H), 1.19 (d, *J*=7.2 Hz, 3H), 1.54 (m, 1H), 2.20 (s, 3H), 2.57 (m, 1H), 3.06 (d, *J*=6.8 Hz, 1H), 3.19 (dd, *J*=10.0, 2.0 Hz, 2H), 3.32 (s, 3H), 3.54 (s, 3H), 3.96 (d, *J*=5.6 Hz, 2H), 4.07 (br d, *J*=8.0 Hz, 1H), 4.20–4.28 (m, 4H), 5.90 (dt, *J*=14.4, 9.6 Hz, 1H), 5.95–6.20 (m, 4H), 6.07 (d, *J*=10.0 Hz, 1H), 6.07 (d, *J*=10.0 Hz, 1H), 6.15 (dd, *J*=14.4, 7.6 Hz, 1H), 6.44 (d, *J*=0.8 Hz, 1H), 6.56 (d, *J*=16.0 Hz, 1H), 7.22 (m, 1H), 7.29 (m, 2H), 7.39 (m, 2H); ^{13}C NMR (100 MHz) δ −1.56, −1.52, 9.8, 14.7, 17.3, 17.5, 18.6, 29.7, 40.2, 41.5, 42.6, 56.4, 61.4, 63.9, 65.6, 81.0, 86.3, 120.8, 123.8, 126.4, 126.9, 127.5, 127.9, 128.5, 128.9, 129.1, 132.0, 134.2, 136.7, 138.7, 152.5, 153.8, 167.7, 169.8, 170.4; HRMS (ESI) calculated for $C_{41}H_{64}N_2NaO_8Si_2$ $[M+Na]^+$ 791.4093, found 791.4084.

4.23. Crocacin B (**2**)

A solution of TBAF (6.6 mg, 0.02 mmol) in THF (1.5 mL) cooled to 0 °C was added to the teoc ester **65** (5.4 mg, 0.007 mmol). The reaction was allowed to stir for 2.5 h at 0 °C, then ethylacetate and pH 7 buffer were added and the phases separated. The aqueous phase was extracted twice further with ethylacetate and the combined organic fractions washed with brine, dried (Na_2SO_4), filtered and evaporated to yield crocacin B (**2**) (2.5 mg, 68%). Attempted purification of this material (RP-HPLC) resulted only in extensive decomposition so the data reported is for crude material. $[\alpha]_D^{18}$ +75.0 (*c* 0.1, MeOH); lit.[3] $[\alpha]_D^{22}$ +99.0 (*c* 0.5, MeOH); IR ν_{max} (thin film) 3322, 2928, 2852, 1732, 1622, 1402, 1090 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 0.86 (d, *J*=6.8 Hz, 3H), 1.17 (d, *J*=6.8 Hz, 3H), 1.57 (m, 1H), 2.26 (d, *J*=0.8 Hz, 3H), 2.61 (m, 1H), 3.18 (dd, *J*=9.6, 2.4 Hz, 1H), 3.28 (s, 3H), 3.32 (dd, *J*=8.4, 8.4 Hz, 2H), 3.51 (s, 3H), 4.00–4.10 (m, 3H), 4.77 (dt, *J*=8.4, 8.4 Hz, 1H), 5.86 (s, 1H), 5.97 (d, *J*=11.6 Hz, 1H), 6.05 (dt, *J*=11.6, 8.4 Hz, 1H), 6.10 (dd, *J*=15.6, 8.4 Hz, 1H), 6.19 (d, *J*=16.0 Hz, 1H), 6.24 (dd, *J*=16.0, 7.2 Hz, 1H), 6.58 (d, *J*=16.0 Hz, 1H), 6.82 (dd, *J*=10.8, 8.8 Hz, 1H), 7.22 (d, *J*=7.6, 7.2 Hz, 1H), 7.31 (dd, *J*=8.0, 7.4 Hz, 2H), 7.45 (br d, *J*=8.4 Hz, 2H), 7.91 (br t, *J*=8.4 Hz), 10.11 (d, *J*=10.8 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 10.1, 13.7, 19.1, 26.2, 40.7, 41.4, 43.3, 56.4, 61.4, 81.8, 87.2, 104.3, 121.0, 121.8, 125.8, 127.2, 128.2, 129.3, 130.4, 132.5, 135.2, 137.5, 137.8, 143.2, 149.7, 164.4, 168.8, 170.9; HRMS (ESI) calculated for $[M+Na]^+$ 547.2778, found 547.2773.

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Supplementary data

It includes experimental conditions and characterization data for compounds **10**–**21**, **29**, **38**–**40** and **42** as well as NMR data comparison tables of natural and synthetic crocacins and the X-ray data as a CIF. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.01.139.

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