# Enantioselective total synthesis of pyrinodemin A†‡

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Pyrinodemin A **1**, a cytotoxic marine alkaloid, was synthesized in a convergent and enantioselective fashion. The key steps are an asymmetric intramolecular dipolar cycloaddition of an oxazoline *N*-oxide to introduce the bicyclic ring system of the molecule, a cuprate coupling for the extension of the saturated chain and a *B*-alkyl Suzuki coupling for the introduction of a 3-pyridyl moiety. Reductive amination allowed the coupling of the second side-chain onto the nitrogen atom to give **1**. Additionally, attempts to prepare **1** from a trienic precursor by a double *B*-alkyl Suzuki reaction are described.

## Introduction

In 1999, Kobayashi and co-workers reported the isolation of a new marine alkaloid, pyrinodemin A **1**, extracted from the Okinawan marine sponge *Amphimedon* sp..[1] Later, the same authors reported the isolation of three other pyrinodemins, B, C, and D **2–4**.[2] All the members of the pyrinodemin family share a common structural feature based on a *cis*-cyclopent[*c*]isoxazolidine ring system substituted with two hydrocarbon chains terminating with a 3-pyridine ring (Fig. 1). Differences between the four pyrinodemins occur in the length in the side chain on the nitrogen atom and in the presence of (*Z*)-double bonds. The exact structure and absolute configuration of pyrinomedin A **1** have been the subject of several reassignments, most of them made *via* total syntheses.[3] Since the structure originally proposed possessing the double bond at the 16′–17′ position did not correspond to **1** on the basis of $^{13}C$ NMR data, new structures with the double bond at the 14′–15′ or the 15′–16′ position were proposed by Baldwin *et al.* and Snider and Shi.[3] Finally, the correct structure was ascertained by Kobayashi and co-workers who established the position of the double bond at $C_{15'}$–$C_{16'}$ by total synthesis and degradation of natural pyrinodemin A **1**.[4]

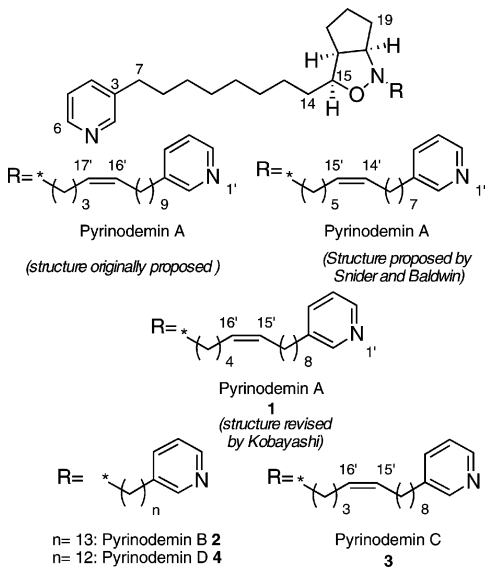


**Fig. 1** Structure of pyrinodemins A-D **1–4** (relative configuration shown).

Each pyrinodemin contains three stereogenic centers, all located on the isoxazolidine ring. The absolute configuration of **1** was originally unknown, an optical rotation of −9 (*c* 1 in $CHCl_3$) being provided. Asymmetric synthesis of **1** by Baldwin *et al.*[5] and Morimoto *et al.*[6] established the absolute configuration of **1** to be (15*S*, 16*S*, 20*R*) by comparison of the optical rotation with literature data. However, these results were called into question by more recent work:[4] HPLC analysis on a chiral column and comparison with racemic and enantiomerically pure synthetic samples revealed that natural pyrinodemin **1** was indeed a racemic mixture. Despite this intriguing feature, stereoselective elaboration of the bicyclic core of pyrinodemins remains an attractive challenge.

A biogenetic hypothesis for the pyrinodemin family has been provided by Kobayashi,[1] in which the final step involves an intramolecular dipolar cycloaddition between a nitrone and a (*Z*)-alkene for the construction of the bicyclic isoxazolidine ring system (Fig. 2). This biogenetic scheme has been the starting point for the total synthesis of pyrinodemin A **1** and B **2** in racemic form by Snider and Shi and Baldwin *et al.*,[3] and in enantioselective fashion by Baldwin *et al.*[5] and Morimoto *et al.*.[6] In the latter case, an additional function (protected hydroxyl group) was used for the asymmetric induction before removal at the end of the synthesis.

All pyrinodemins possess cytotoxic activity against murine leukemia L1210 and KB epidermoid carcinoma cells, pyrinodemin A **1** being the most active ($IC_{50}$ 0.058 μg $mL^{-1}$ and 0.5 μg $mL^{-1}$ respectively). They also possess weak activity against several bacterial strains and weak antifungal activity.

Owing to their unusual chemical structures and their biological activities, pyrinodemins have been the subject of several synthetic studies.[3–6] In the present article, we wish to report the first enantioselective synthesis of pyrinodemin A **1** under its revised structure, as proposed as Kobayashi and co-workers.[4]

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† This paper is dedicated to the memory of Dr Charles Mioskowski

‡ Electronic supplementary information (ESI) available: NMR spectra ($^1H$, $^{13}C$ NMR and HSQC) for synthetic pyrinodemin **1**. See DOI: 10.1039/b800840j

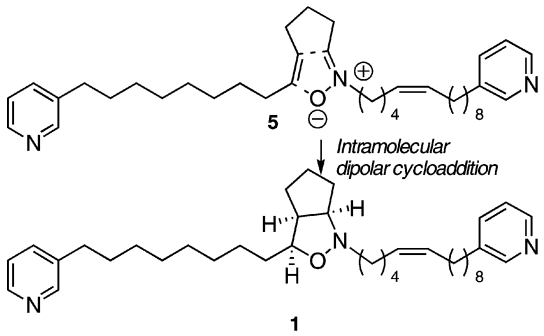



**Fig. 2** Proposed biogenetic scheme for pyrinodemin A**1**.

## Results and discussion

### Synthetic strategy

Given the controversy concerning the exact structure of pyrinodemin, it appeared important to us to design a synthetic strategy in which the side chain on the nitrogen atom ($C_{7'}$–$C_{20'}$) could be introduced at a later stage in the synthesis. Our approach to the total synthesis of **1** relies on a convergent and flexible route, suitable for analogue synthesis: it involves the enantioselective synthesis of the *cis*-cyclopent[*c*]isoxazolidine ring, followed by side-chain appendage and introduction of pyridine rings. This strategy could also allow the synthesis of all members of the pyrinodemin family from a common precursor **6** (Fig. 3).

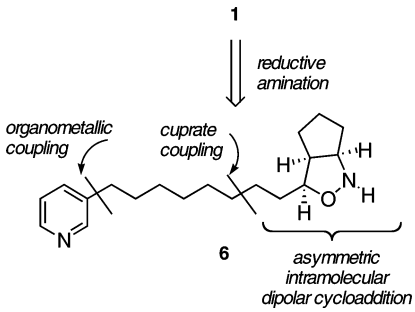



**Fig. 3** General strategy for the synthesis of pyrinodemins.

We have already reported the enantioselective synthesis of the bicyclic system of pyrinodemins[7] *via* the asymmetric intramolecular dipolar cycloaddition of a chiral, phenylglycinol-derived oxazoline *N*-oxide, according to a methodology developed in our laboratory.[8] This dipole is prepared *in situ* by condensation of an orthoester onto a hydroxylaminoalcohol hydrochloride (Fig. 4).[9] The subsequent oxazoline *N*-oxide undergoes intramolecular dipolar cycloadditions with high stereoselectivity.[10]

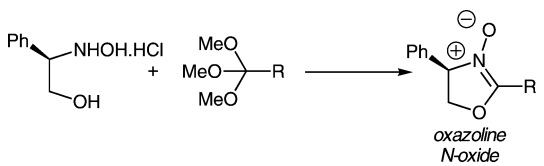



**Fig. 4** Synthesis of oxazoline *N*-oxides.

We anticipated that the intramolecular version of this cycloaddition could lead in a stereoselective fashion to the bicyclic core of pyridodemins, after removal of the chiral auxiliary. This required the preparation of an orthoester bearing a (*Z*)-alkene. Initial attempts revealed that the chain length of the orthoester had a dramatic effect on the yield in the cycloaddition steps: although good yields were obtained with short chains, the presence of a long chain completely inhibited the cycloaddition reaction (Fig. 5).

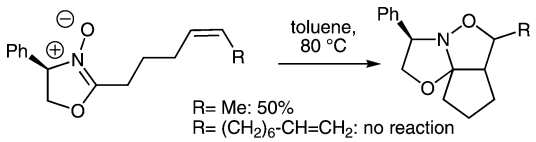
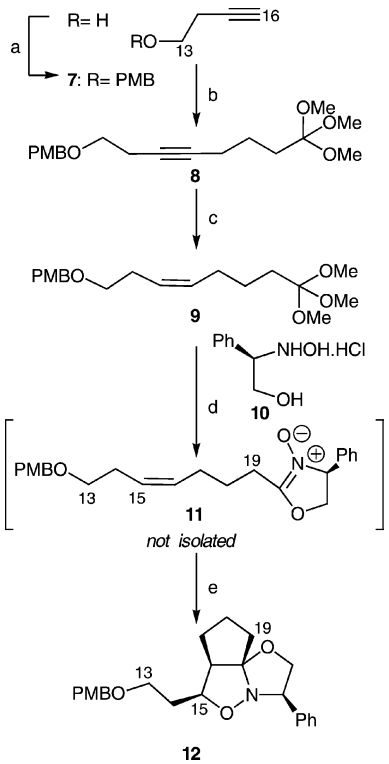



**Fig. 5** Model studies for intramolecular cycloadditions.

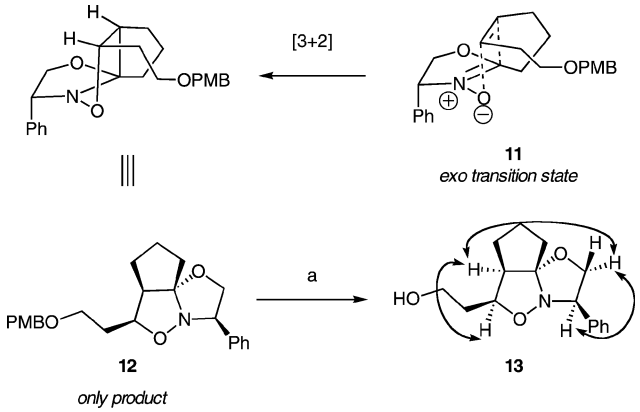
### Synthesis of a common precursor to pyrinodemins

These results led us to select orthoester **9** as the cycloaddition partner and to add the saturated $C_7$–$C_{13}$ chain at a later stage. Thus, orthoester **9** was prepared in three steps from 3-butyn-1-ol. Hydroxyl group protection as its PMB ether gave alkyne **7** which was metallated and reacted with commercially available trimethyl 4-bromoorthobutyrate[11] to give the highly acid-labile orthoester **8**. The crude product was submitted to partial hydrogenation over Lindlar catalyst in the presence of pyridine[12] to give the (*Z*)-alkene **9**. Condensation of *N*-hydroxyphenylglycinol hydrochloride **10** with **9** in the presence of triethylamine gave the intermediate oxazoline *N*-oxide **11** which underwent intramolecular dipolar cycloaddition to give the tricyclic compound **12** in good overall yield and complete stereoselectivity, as a single isomer (Scheme 1).



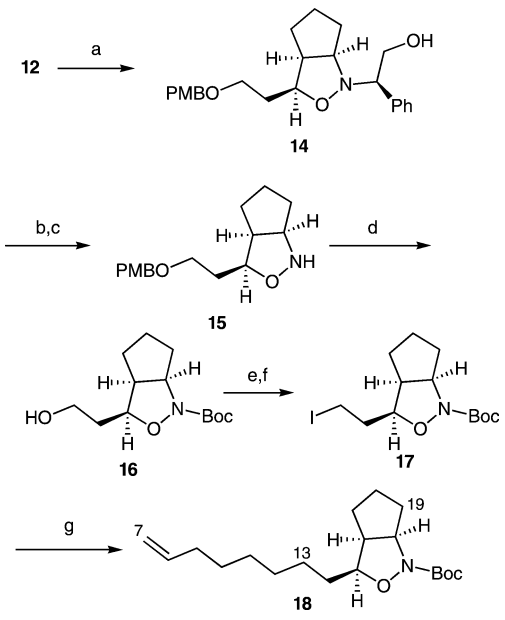

**Scheme 1** Synthesis of tricyclic compound **12**. a: NaH, PMBBr, THF, DMF, 0 °C to rt, 91%; b: BuLi, THF, DMPU, −78 °C then trimethyl 4-bromoorthobutyrate, −78 °C to rt, 99% (crude); c: $H_2$, Lindlar catalyst, pyridine, MeOH, rt; d: **10**, toluene, 4 Å MS, 45 °C, 2 h, then $Et_3N$; e: 75 °C, 16 h, 54% (over two steps).

The relative configurations in compound **12** were determined on alcohol **13** using $^1$H NMR NOESY experiments after removal of the PMB protecting group, and were assumed to arise from an *exo* transition state, in which the dipole is attacked on the *Si* face (opposite to the phenyl substituent, Scheme 2). This highly stereoselective cycloaddition secured the 15*S*,16*S* configuration required for pyrinodemins.




**Scheme 2** Relative configuration and transition state in the cycloaddition reaction; a: DDQ, $H_2O$, $CH_2Cl_2$, 84%.

Removal of the phenylglycinol-derived chiral auxiliary requires reductive cleavage of the oxazolidine C–O bond, followed by *N*-debenzylation. The first step was achieved using zinc borohydride,[13] giving alcohol **14** as a single diastereomer (Scheme 3). The cleavage of the C–N bond could not be performed under hydrogenolytic conditions, due to competitive hydrogenolysis of the N–O bond. Therefore, a slight modification of the Agami–Couty procedure for *N*-debenzylation,[14] which involves

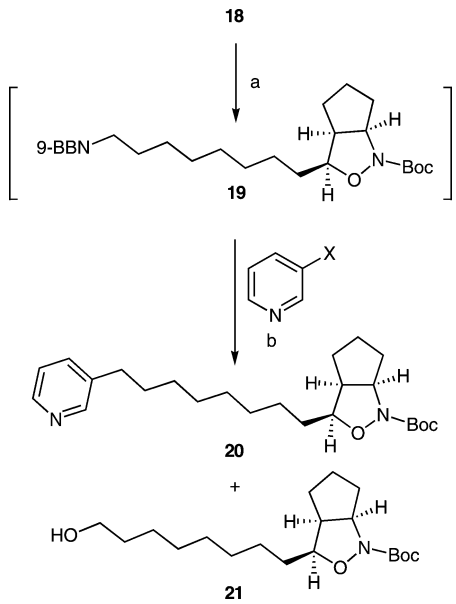



**Scheme 3** Synthesis of compound **18**: a: $Zn(BH_4)_2$, $Et_2O$, −10 °C, 84%; b: MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C; c: KCN, DMSO, 100 °C, 50% (over two steps); d: EtSH, $BF_3{\cdot}OEt_2$, then $Boc_2O$, $NaHCO_3$, $H_2O$, $CH_2Cl_2$, 93%; e: MsCl, $Et_3N$, $CH_2Cl_2$, rt; f: NaI, acetone, reflux, 99% (over two steps); g: $CH_2$=CH–$(CH_2)_4$–MgBr, CuI, THF, −20 °C, 59%.

cyanide-mediated β-elimination was applied: the primary hydroxyl group was converted into its mesylate, which was treated with potassium cyanide in DMSO to give the target bicyclic oxazoline **15** in good overall yield. This step could be performed using either conventional or microwave heating with comparable yields; the latter procedure occurred in shorter reaction times but was less reproducible.

The following step in the synthesis was the introduction of the $C_8$–$C_{13}$ chain, which was performed by cuprate coupling. Thus, *N*-protection of **15** as its Boc carbamate, followed by removal of the PMB protecting group, gave the primary alcohol **16** which was converted to the corresponding iodide **17**. Copper(I)-mediated coupling of this iodide with the Grignard reagent derived from 6-bromo-1-hexene gave the alkene **18** which contained all the carbons of the saturated side-chain of pyrinodemins.

Compound **18** was chosen as the precursor for introduction of the 3-pyridyl moiety using a *B*-alkyl Suzuki reaction.[15] This coupling reaction has been developed as a very powerful method for the alkylation of vinyl, aryl and heteroaryl derivatives, and has found many applications in total synthesis, owing to its efficiency and its high functional group tolerance, including basic nitrogen atoms.[16] Thus, we anticipated that hydroboration of **18**, followed by palladium-catalyzed coupling with a 3-halopyridine,[17] would lead to compound **20** in a highly convergent route (Scheme 4), despite the lower reactivity of 3-halopyridine derivatives compared to other isomers. Moreover, this route would be suitable for the introduction of other aryl substituents in the synthesis of analogues.




**Scheme 4** *B*-Alkyl Suzuki coupling of compound **18**. a: 9-BBN dimer, THF, rt; b: see Table 1.

Results for the *B*-alkyl Suzuki coupling reaction of **18** are reported in Table 1. Low reactivity, side reactions and difficulties in purification led to moderate yields. We observed that using 9-BBN dimer instead of 9-BBN-H in solution gave better results, due probably to higher concentration. The best results for the coupling reactions were observed using 3-bromopyridine, $Pd(PPh_3)_4$ as the catalyst and potassium carbonate as the base. Using

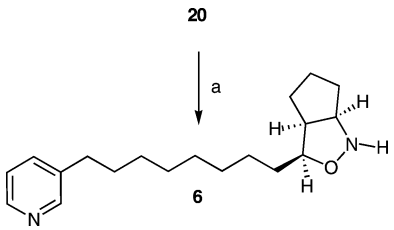
**Table 1** *B*-Alkyl Suzuki coupling of **18** with 3-halopyridine derivatives

| X | Catalyst[a] | Base | Conditions | Yield **20** |
|---|---|---|---|---|
| Br | $Pd(PPh_3)_4$ | $K_2CO_3$ | THF–DMF–$H_2O$, 80 °C | 42% |
| Br | $Pd(PPh_3)_4$ | $K_3PO_4$ | THF–DMF–$H_2O$, 80 °C | trace[b] |
| Br | $Pd(dppf)Cl_2$ | $K_2CO_3$ | THF–DMF–$H_2O$, 80 °C | trace |
| I | $Pd(PPh_3)_4$ | $K_2CO_3$ | THF–DMF–$H_2O$, 80 °C | trace |
| I | $Pd(dppf)Cl_2$ | $Cs_2CO_3$ | THF–DMF–$H_2O$, 80 °C | trace |

[a] 10% of catalyst was used. [b] 62% of compound **21** was obtained.

3-iodopyridine did not lead to the expected product. Using other catalysts or bases resulted mainly in the formation of oxidation product **21**. Under optimized conditions, a moderate yield of 42% was obtained.

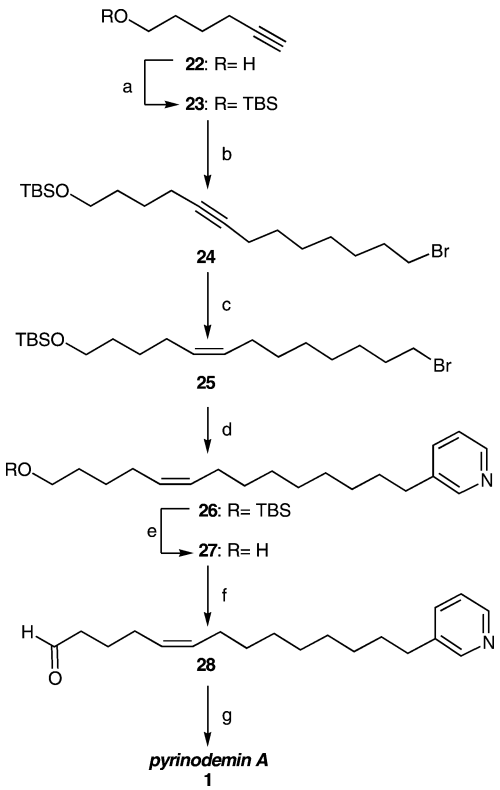
Finally, *N*-deprotection of compound **20** gave the bicyclic hydroxylamine **6**, which can be used as precursor for the synthesis of each pyrinodemin (Scheme 5).




**Scheme 5** a: $CF_3CO_2H$, $CH_2Cl_2$, rt, 86%.

### Synthesis of pyrinodemin A (1) by reductive amination

Having achieved the synthesis of precursor **6**, we turned our attention to the introduction of the second side-chain on the nitrogen atom. Reductive amination of the hydroxylamine was chosen as the key step for this *N*-alkylation. Thus, aldehyde **28** was prepared in six steps from 5-hexyn-1ol **22** (Scheme 6):[18] protection as its TBS ether, followed by metallation and alkylation with 1,7-dibromoheptane gave the alkyne **24** which was reduced to the (*Z*)-alkene **25** by hydrogenation over Lindlar catalyst. The primary bromide **25** was used for the alkylation of 3-picoline, which installed the pyridine ring on the alkyl chain. Finally, deprotection of **26** and oxidation with 2-iodoxybenzoic acid (IBX) gave the target aldehyde **28**. The final step in the synthesis of pyrinodemin A **1** was the reductive amination: condensation of hydroxylamine **6** with aldehyde **28** in the presence of sodium borohydride gave **1** in unoptimized 30% yield. Once again, some difficulties in purification lowered the yield. Spectroscopic data for synthetic pyrinodemin **1** were identical in all respects ($^1H$ and $^{13}C$ NMR, mass, HRMS) to those reported in the literature,[19] and provide further confirmation concerning the structure of **1**. Especially, the chemical shifts for olefinic carbons in the $^{13}C$ NMR spectrum are consistent with those reported by Kobayashi and co-workers (129.6 and 130.0 ppm).[4] Optical rotation (−5, *c* 0.46 in $CHCl_3$) was very close to that reported by Morimoto and co-workers[6] for a slightly different structure (−6, *c* 0.94 in $CHCl_3$), thus confirming the absolute configuration established throughout the synthesis.



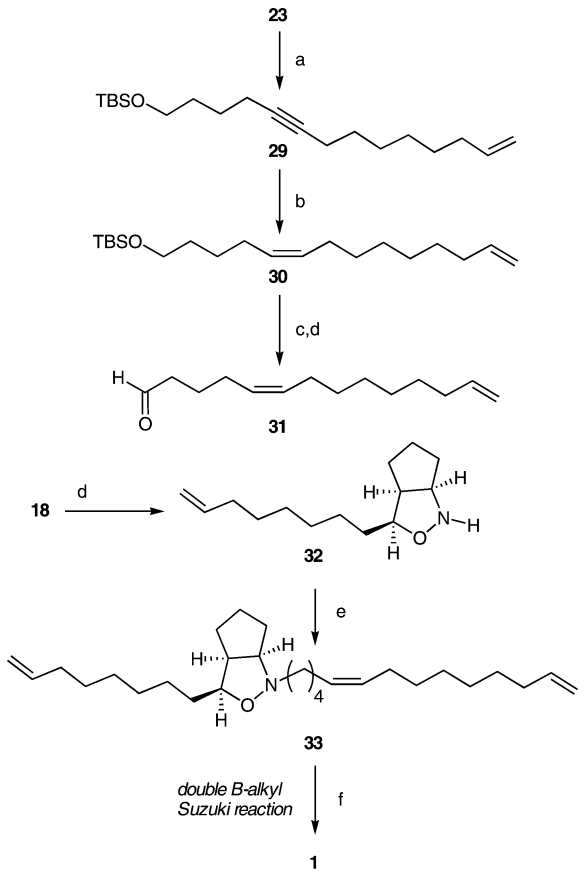

**Scheme 6** Total synthesis of pyrinodemin **1**; a: TBSCl, imidazole, DMF, 80%; b: BuLi, THF, DMPU, −78 °C, then 1,7-dibromoheptane, −78 °C to rt, 63%; c: $H_2$, Lindlar catalyst, quinoline, benzene, 94%; d: 3-picoline, BuLi, THF, DMPU, −78 °C, then **25**, −78 °C to rt, 57%; e: TBAF, THF, 0 °C to rt, 90%; f: IBX, DMSO, rt, 40%; g: **6**, $NaBH_3CN$, HCl, MeOH, rt, 30%.

### Synthesis of 1 by double *B*-alkyl Suzuki reaction

Despite the fact that the introduction of the pyridine ring onto compound **21** occurred in moderate yield, and considering that the presence of pyridine rings complicated purification steps, it was tempting to introduce *both* pyridine rings in the last steps of the synthesis using a double *B*-alkyl Suzuki coupling reaction.[20] Thus, the synthesis of a pyrinodemin precursor containing two terminal alkenes was achieved (Scheme 7): metallation of alkyne **23** and alkylation with 1-bromo-7-octene gave the enyne **29** which was partially hydrogenated as usual. Diene **30** was deprotected and oxidized to give aldehyde **31**. Meanwhile, alkene **18** was deprotected and the resulting bicyclic hydroxylamine **32** underwent reductive amination with aldehyde **31** to give the triene **33**, substrate for the double *B*-alkyl Suzuki reaction. This reaction was performed according to the conditions developed for the synthesis of **20** (9-BBN dimer, then $Pd(PPh_3)_4$, $K_2CO_3$, THF, DMF, $H_2O$, 80 °C). We observed the formation of pyrinodemin A **1**, albeit as a mixture with several by-products. Purification of the crude mixture by preparative TLC gave a disappointing 7% yield. Obviously, this strategy necessitates further optimisation in order to provide an easy access to pyrinodemins and analogues thereof.

## Conclusions

The enantioselective total synthesis of pyrinodemin A **1** has been accomplished in a highly convergent manner, in 14 steps in the




**Scheme 7** Synthesis of pyrinodemin A by double *B*-alkyl Suzuki reaction; a: BuLi, THF, DMPU, −78 °C, then 1-bromo-7-octene, −78 °C to rt, 67%; b: $H_2$, Lindlar catalyst, quinoline, benzene, 83%; c: TBAF, THF, 0 °C to rt, 74%; d: IBX, DMSO, rt, 63%; e: **31**, $NaBH_3CN$, HCl, MeOH; f: 9-BBN dimer, THF, rt, then, 3-bromopyridine, $Pd(PPh_3)_4$, $K_2CO_3$, THF, $H_2O$, DMF, 80 °C, 7%.

longest linear scheme. The key steps are the highly diastereoselective intramolecular dipolar cycloaddition for the construction of the bicyclic core and the application of organometallic coupling in the elaboration of side-chains. On this latter point, although the introduction of pyridines by Suzuki coupling increased the convergent aspect of this synthesis, it also proved that organometallic couplings in the presence of basic nitrogens induce difficulties in purifications and result in lower yields. Obviously, it would be necessary to further investigate this coupling for its application in the synthesis of pyridine-containing alkaloids.

## Experimental section

### General methods

Unless otherwise stated, all reactions were performed under argon atmosphere with oven-dried glassware. All commercially available reagents were used without further purification. Methanol was distilled from Mg turnings. Triethylamine, diisopropylamine, pyridine and dichloromethane were distilled from $CaH_2$ under argon. *N*,*N*′-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), hexamethylphosphoramide (HMPA) and quinoline were distilled from $CaH_2$ under vacuum. THF and diethyl ether were distilled from benzophenone ketyl under argon prior to use. Benzene and toluene were distilled from sodium. Reagent grade acetone was used from a freshly opened bottle. Column chromatography was perfomed using silica gel (230–400 mesh) using the indicated solvent system. NMR spectra were recorded on 200 MHz, 250 MHz, 360 MHz or 400 MHz spectrometers. Chemical shifts ($\delta$) are reported in ppm downfield from tetramethylsilane. Coupling constants (*J* values) are reported in Hertz. IR spectra were recorded on a FT-IR spectrometer. MS and HRMS experiments were performed on a high/low resolution magnetic sector mass spectrometer. Optical rotations were performed on a precision automated polarimeter.

**4-[4-Methoxyphenylmethyloxy]-1-butyne (7).** A solution of 3-butyn-1-ol (1.0 eq., 6.2 mL, 82.9 mmol) in THF (40 $cm^3$) was added at 0 °C to a suspension of sodium hydride (1.2 eq., 3.98 g of a 60% suspension in oil, 99.5 mmol) in THF–DMF (40 $cm^3$ each). After 10 min, 4-methoxybenzyl bromide (1.2 eq., 20 g, 99.5 mmol) was added dropwise and the mixture was stirred for 15 hours at room temperature, then poured on cold water (100 $cm^3$). After extraction with diethyl ether (3 × 100 $cm^3$), the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane–diethyl ether 85 : 15) gave the protected alcohol **7** (14.4 g, 91% yield) as a colourless oil. $\nu_{max}$(film)/$cm^{-1}$: 3292, 3001–2837, 2120, 1613, 1513, 1248; $\delta_H$ (360 MHz, $CDCl_3$): 7.25 (2H, d, *J* 8.0), 6.85 (2H, d, *J* 8.0), 4.50 (2H, s), 3.80 (3H, s), 3.55 (2H, t, *J* 7.0), 2.45 (2H, td, *J* 7.0 and 2.6), 1.95 (1H, t, *J* 2.6); $\delta_C$ (90 MHz, $CDCl_3$): 158.9 (s), 129.9 (s), 129.2 (d), 113.4 (d), 81.1 (s), 72.2 (t), 67.5 (t), 66.6 (d), 54.8 (q), 19.5 (t).

**8-[4-Methoxyphenylmethyloxy]-1,1,1-trimethoxy-5-octyne (8).** A solution of *n*-butyllithium (2.5 M in hexanes, 1.2 eq., 11.5 $cm^3$, 28.8 mmol) was added dropwise to a solution of alkyne **7** (1.0 eq., 4.64 g, 24.4 mmol) in dry THF (24 $cm^3$) at −78 °C. After 30 min, DMPU (1.2 eq., 3.5 $cm^3$, 28.8 mmol) was added, and the mixture was stirred for 10 min. After addition of trimethyl 4-bromoorthobutyrate (0.9 eq., 5.0 g, 22.0 mmol), the mixture was warmed to room temperature, then stirred overnight at 45 °C. After cooling to room temperature, a 10% sodium carbonate solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with saturated sodium hydrogencarbonate, dried over sodium sulfate and filtered through basic alumina. Concentration under reduced pressure afforded the crude orthoester (7.4 g, quantitative yield), which was used without further purification. $\nu_{max}$(film)/$cm^{-1}$: 3514, 2948–2836, 1513, 1459, 1248–1182, 1103–1037; $\delta_H$ (250 MHz, $CDCl_3$): 7.25 (2H, d, *J* 8), 6.85 (2H, d, *J* 8), 4.45 (2H, s), 3.80 (3H, s), 3.50 (2H, t, *J* 7), 3.25 (9H, s), 2.45 (2H, m), 2.19 (2H, m), 1.85 (2H, m), 1.55 (2H, m); $\delta_C$ (62.5 MHz, $CDCl_3$): 158.9 (s), 129.9 (s), 128.9 (d), 115.4 (s), 113.4 (d), 80.5 (s), 77.0 (s), 72.2 (t), 54.9 (q), 49.0 (q), 29.0 (t), 22.1 (t), 19.8 (t), 18.1 (t).

**5-(*Z*)-8-[4-Methoxyphenylmethyloxy]-1,1,1-trimethoxy-5-octene (9).** Lindlar catalyst (5 mol%, 0.53 g) was added to a solution of alkyne **8** (1 eq., 7.4 g, 24.4 mmol) in dry methanol (85 $cm^3$) and pyridine (3.3 $cm^3$) at room temperature under argon. The flask was purged three times with hydrogen, and the mixture was

stirred overnight under a hydrogen atmosphere. Filtration through Celite®, then through basic alumina, followed by concentration under reduced pressure gave the alkene **9** (7.4 g, 99%) as a colourless oil, which was used without further purification. $\nu_{max}$(film)/cm$^{-1}$: 3515, 3001–2836, 1513, 1463, 1247, 1173, 1091–1038; $\delta_H$ (250 MHz, $CDCl_3$): 7.25 (2H, d, *J* 8), 6.85 (2H, d, *J* 8), 5.40 (2H, m), 4.45 (2H, s), 3.80 (3H, s), 3.45 (2H, t, *J* 7), 3.20 (9H, s), 2.35 (2H, m), 2.05 (2H, m), 1.70 (2H, m), 1.40 (2H, m); $\delta_C$ (62.5 MHz, $CDCl_3$): 158.8 (s), 130.9 (d), 130.2 (s), 128.8 (d), 126.0 (d), 115.4 (s), 113.3 (d), 72.1 (t), 69.2 (t), 54.8 (q), 49.0 (q), 29.4 (t), 27.7 (t), 26.5 (t), 22.4 (t).

**(3*R*,5*S*,5a*R*,8a*S*)-5-[2-(4-Methoxyphenylmethyloxy)ethyl]-3-phenylhexahydro-1,4-dioxa-3a-azacyclopenta[*c*]pentalene (12).** A mixture of orthoester **9** (1.5 eq., 7.4 g, 22.0 mmol), hydroxylaminophenylglycinol hydrochloride **10** (1.0 eq., 2.8 g, 14.7 mmol) and 4 Å molecular sieves (2.8 g) in dry toluene (147 cm$^3$) was vigorously stirred for 2 hours at 45 °C under argon. Triethylamine (1.1 eq., 2.2 cm$^3$, 16.2 mmol) was added and the mixture was further stirred at 75 °C overnight. After cooling to rt, the reaction mixture was filtered through Celite® and concentrated under reduced pressure. Analysis of the crude mixture by $^1$H NMR revealed the presence of a single cycloadduct isomer, together with some degradation products arising from the orthoester **9**. Purification by flash chromatography (heptane–ethyl acetate 85 : 15 to 7 : 3) gave the cycloadduct **12** (3,2 g, 54% yield) as a pale yellow oil. $[\alpha]_D^{20}$ −132.6 (*c* 1.2 in $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$: 3455, 3062, 2954–2857, 2381, 1736, 1612, 1513, 1464, 1248, 1097, 1036; $\delta_H$ (360 MHz, $CDCl_3$): 7.45–7.25 (7H, m), 6.85 (2H, d, *J* 8), 4.51 (1H, dd, *J* 7 and 6), 4.45 (3H, m), 4.25 (1H, dd, *J* 9 and 7), 3.80 (3H, s), 3.70 (1H, dd, *J* 9 and 7), 3.50 (2H, t, *J* 6), 2.65 (1H, m), 2.20 (1H, m), 1.93 (1H, m), 1.85–1.65 (4H, m), 1.63 (2H, m); $\delta_C$ (100 MHz, $CDCl_3$): 159.2 (s), 139.0 (s), 130.5 (s), 129.2 (d), 128.5 (s), 127.5 (s), 127.2 (s), 116.2 (s), 113.8 (d), 76.5 (d), 72.7 (t), 72.0 (t), 69.7 (d), 67.2 (t), 56.1 (d), 55.3 (q), 37.3 (t), 29.4 (t), 25.4 (t), 24.6 (t); *m*/*z* (ES): 418.2 [M + Na]; HRMS: found: 418.200; calcd for $C_{24}H_{29}NaNO_4$ [M + Na]: 418.1994.

**(2*R*,3*S*,3a*S*,6a*R*)-2-{3-[2-(4-Methoxyphenylmethyloxy)ethyl]-hexahydrocyclopenta[*c*]isoxazol-1-yl}-2-phenyl-ethanol (14).** A freshly prepared 0.1 M zinc borohydride solution in diethyl ether (2.5 eq., 12.5 mmol, 125 cm$^3$) was added dropwise over 30 min to a cooled (−10 °C) solution of the cycloadduct **12** (1.0 eq., 1.97 g, 5.0 mmol) in anhydrous diethyl ether (50 cm$^3$). The mixture was stirred at −10 °C overnight, then neutralized with 2 N hydrochloric acid solution and extracted with diethyl ether (2 × 30 cm$^3$). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (heptane–ethyl acetate 8 : 2 to 5 : 5) gave the desired product **14** (1.66 g, 84% yield) as a white solid (mp 65 °C); $[\alpha]_D^{20}$ −35.2 (*c* 0.6 in $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$: 3455, 3064, 2954–2857, 2381, 1736, 1612, 1513, 1464, 1248, 1097, 1036; $\delta_H$ (400 MHz, $CDCl_3$): 7.35–7.15 (7H, m), 6.85 (2H, d, *J* 9), 4.30 (2H, s), 3.95 (1H, m), 3.85 (2H, m), 3.70 (3H, s), 3.65 (2H, m), 3.50–3.30 (2H, m), 2.90 (1H, br s), 2.75 (1H, m), 1.70 (4H, m), 1.60–1.31 (4H, m); $\delta_C$ (100 MHz, $CDCl_3$): 159.1 (s), 137.1 (s), 130.4 (s), 129.2 (d), 129.0 (d), 128.2 (d), 127.8 (d), 113.7 (d), 77.1 (d), 72.6 (t), 68.8 (d), 67.7 (t), 67.1 (d), 67.0 (t), 55.2 (q), 50.1 (d), 29.7 (t), 26.3 (t), 26.2 (t), 26.1 (t); *m*/*z* (ES): 420.2 ([M + Na], 100), 398.2 ([M + H], 14); HRMS found: 420.2151; calcd for $C_{24}H_{31}NaNO_4$ [M + Na]: 420.2151.

**(3*S*,3a*S*,6a*R*)-3-[2-(4-Methoxybenzyloxy)ethyl]hexahydrocyclopenta[*c*]isoxazole (15).** Triethylamine (2.0 eq., 2.0 cm$^3$, 14.6 mmol) was added to a solution of alcohol **14** (1.0 eq., 2.9 g, 7.3 mmol) in dry dichloromethane (90 cm$^3$) at 0 °C. The mixture was stirred for 10 min at 0 °C, and methanesulfonyl chloride (2.0 eq., 1.2 cm$^3$, 14.6 mmol) was added. After 1.5 h at 0 °C, an additional aliquot of triethylamine and methanesulfonyl chloride (1.0 eq. of each) was added and the mixture was stirred for 30 min before concentration under reduced pressure. The residue was dissolved in dichloromethane, and the organic layer was washed with 2 N hydrochloric acid solution then brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the mesylate (3.5 g, quantitative yield), which was used without further purification.

Potassium cyanide (10 eq., 4.88 g, 73.7 mmol) was added to a solution of the above mesylate (1.0 eq., 3.5 g, 7.37 mmol) in dry DMSO (74 cm$^3$). The solution was stirred for 1.5 h at 100 °C. After cooling to rt, a 10% sodium carbonate solution was added, and the mixture was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (heptane–ethyl acetate 6 : 4 to 0 : 10) gave **15** (1 g, 50% yield) as a pale yellow oil. $[\alpha]_D^{20}$ + 36.4 (*c* 1.04 in $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$: 3428, 2955, 2863, 1613, 1513, 1464, 1361, 1301, 1247, 1174, 1091, 1033, 819; $\delta_H$ (400 MHz, $CDCl_3$): 7.25 (2H, d, *J* 8.6), 6.80 (2H, d, *J* 8.6), 4.37 (2H, s), 3.90 (1H, m), 3.78 (3H, s), 3.68 (1H, m), 3.55 (2H, m), 2.75 (1H, m), 1.85 (3H, m), 1.65–1.42 (4H, m), 1.35 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$): 159.1 (s), 130.4 (s), 129.2 (d), 113.7 (d), 83.6 (d), 72.6 (t), 67.6 (t), 66.5 (d), 55.2 (q), 50.1 (d), 34.9 (t), 29.0 (t), 26.9 (t), 26.5 (t); *m*/*z* (ES): 300.2 ([M + Na], 100), 278.2 ([M + H], 16); HRMS: found: 300.1573; calcd for $C_{16}H_{23}NaNO_3$ [M + Na]: 300.1576.

**(3*S*,3a*S*,6a*R*)-3-(2-Hydroxyethyl)hexahydrocyclopenta[*c*]isoxazole-1-carboxylic acid *tert*-butyl ester (16).** Ethanethiol (**CAUTION**: very unpleasant odour) (4.0 eq., 1.1 cm$^3$, 14.4 mmol) and boron trifluoride (0.11 cm$^3$) were added at room temperature to a solution of **15** (1.0 eq., 1 g, 3.61 mmol) in dichloromethane (40 cm$^3$). After 20 min, most of the thiol was evaporated through argon flow. After addition of sodium carbonate (1 g), *tert*-butoxycarbonyl anhydride (1.1 eq., 870 mg, 3.97 mmol) and water (15 cm$^3$), the mixture was stirred overnight at rt. Sodium hydrogencarbonate solution was added and the mixture was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (heptane–ethyl acetate 6 : 4 to 4 : 6) gave the *N*-protected alcohol **16** (860 mg, 93% yield) as a brown oil. $[\alpha]_D^{20}$ −70 (*c* 0.63 in $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$: 3415, 2960, 2871, 1705, 1455, 1393, 1368, 1342, 1254, 1165, 1103, 1063; $\delta_H$ (360 MHz, $CDCl_3$): 4.58 (1H, ddd, *J* 7.4, 7.4 and 3.5), 3.88 (1H, ddd, *J* 10.1, 6.1 and 3.9), 3.77 (2H, t, *J* 6.6), 2.83 (1H, m), 2.72 (1H, br s), 2.00–1.80 (3H, m), 1.76–1.64 (3H, m), 1.46 (9H, s), 0.87 (2H, m); $\delta_C$ (90 MHz, $CDCl_3$): 157.2 (s), 82.4 (d), 81.6 (s), 65.6 (d), 60.3 (t), 49.9 (d), 34.4 (t), 31.1 (t), 28.1 (q), 26.3 (t), 26.1 (t); *m*/*z* (ES): 280.2 ([M + Na], 10), 224.1 (100); HRMS: found: 280.1523; calcd for $C_{13}H_{23}NaNO_4$ [M + Na]: 280.1530.

**(3*S*,3a*S*,6a*R*)-3-(2-Iodoethyl)hexahydrocyclopenta[*c*]isoxazole-1-carboxylic acid *tert*-butyl ester (17).** Triethylamine (2.0 eq., 0.9 cm$^3$, 6.46 mmol) was added to a solution of alcohol **16** (1.0 eq., 830 mg, 3.23 mmol) in dry dichloromethane (32 cm$^3$). After 15 min, methanesulfonyl chloride (2.0 eq., 0.5 cm$^3$, 6.46 mmol) was added and the solution was stirred for 1 hour at rt. After addition of sodium hydrogencarbonate and extraction with dichloromethane, the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the corresponding mesylate (1.08 g, 99%) as a brown oil, which was used without further purification. Sodium iodide (4.0 eq., 2.04 g, 12.9 mmol) was added to a solution of the mesylate (1.0 eq., 1.08 g, 3.23 mmol) in acetone (25 cm$^3$). The mixture was stirred for 2 hours at reflux. After cooling to rt and concentration of the solvent under reduced pressure, the residue was partitioned between dichloromethane and saturated sodium hydrogencarbonate. The aqueous phase was extracted with dichloromethane, and the combined organic layers were washed with sodium thiosulfate solution then brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Filtration through a pad of silica gel (heptane–ethyl acetate 1 : 1) afforded the desired iodide **17** (1.18 g, 99%) as a brown oil. $[\alpha]_D^{20}$ −63 (*c* 1.1 in $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$: 2960, 2932, 2870, 1709, 1455, 1392, 1367, 1330, 1252, 1164, 1064; $\delta_H$ (360 MHz, $CDCl_3$): 4.66 (1H, ddd, *J* 7.6, 7.6 and 3.5), 3.84 (1H, ddd, *J* 9, 5.9 and 3.5), 3.33 (1H, ddd, *J* 10.1, 7.4 and 5.2), 3.26 (1H, ddd, *J* 10.1, 8.3 and 6.8), 2.85 (1H, m), 2.22–1.89 (3H, m), 1.75–1.52 (5H, m), 1.50 (9H, s); $\delta_C$ (90 MHz, $CDCl_3$): 157.3 (s), 83.6 (d), 81.5 (s), 65.7 (d), 49.2 (d), 34.4 (t), 32.3 (t), 28.2 (q), 26.4 (t), 26.3 (t), 1.8 (t); *m*/*z* (ES): 390.0 ([M + Na], 30), 333 (100). HRMS: found: 390.0540; calcd for $C_{13}H_{22}INaNO_3$ [M + Na]: 390.0548.

**(3*S*,3a*S*,6a*R*)-3-Oct-7-enylhexahydrocyclopenta[*c*]isoxazole-1-carboxylic acid *tert*-butyl ester (18).** A suspension of magnesium turnings (10.0 eq., 442 mg, 18.4 mmol) in dry tetrahydrofuran (10 cm$^3$) was cooled to 0 °C, and a few drops of 6-bromo-1-hexene were added, followed by a solution of the above bromide (5.0 eq., 1.2 cm$^3$, 9.2 mmol) in dry tetrahydrofuran (2 cm$^3$). The mixture was stirred for 3 hours at room temperature, then added dropwise to a cold (−20 °C) solution of iodide **17** (1.0 eq., 675 mg, 1.84 mmol) and copper(I) iodide (1.3 eq., 454 mg, 2.39 mmol) in dry tetrahydrofuran (20 cm$^3$). The solution was stirred overnight at room temperature. After addition of saturated ammonium chloride and extraction with dichloromethane, the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (heptane–ethyl acetate 9 : 1) gave the alkene **18** (349 mg, 59% yield) as a pale yellow oil. $[\alpha]_D^{20}$ −40 (*c* 1.1 in $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$: 2932, 2857, 1732, 1708, 1641, 1455, 1392, 1367, 1331, 1253, 1165, 1064; $\delta_H$ (360 MHz, $CDCl_3$): 5.79 (1H, ddt, *J* 16.8, 10.0 and 6.9 Hz), 4.98 (1H, m), 4.92 (1H, m), 4.60 (1H, ddd, *J* 7.5 and 3.4 Hz), 3.72 (1H, m), 2.78 (1H, m), 2.03 (2H, m), 1.91 (1H, m), 1.68 (5H, m), 1.48 (9H, s), 1.36 (10H, m); $\delta_C$ (62.5 MHz, $CDCl_3$): 157.1 (s), 139.0 (d), 114.1 (t), 84.2 (d), 81.1 (s), 65.5 (d), 49.4 (d), 34.5 (t), 33.7 (t), 29.3 (t), 28.9 (t), 28.8 (t), 28.2 (q), 27.9 (t), 26.5 (t), 26.3 (t), 25.8 (t); *m*/*z* (ES): 346 ([M + Na], 30), 333 (100); HRMS: found: 346.2364; calcd. for $C_{19}H_{33}NaNO_3$ [M + Na]: 346.2364.

**(3*S*,3a*S*,6a*R*)-3-(8-Pyridin-3-yloctyl)hexahydrocyclopenta[*c*]-isoxazole-1-carboxylic acid *tert*-butyl ester (20).** A solution of alkene **18** (1.0 eq., 99 mg, 0.31 mmol) in dry, degassed tetrahydrofuran (3 cm$^3$) was added to solid 9-borabicyclo[3.3.1]nonane (9-BBN) dimer (1.9 eq., 143 mg, 0.59 mmol) and the solution was stirred overnight at room temperature. This solution was added *via* cannula to a solution of palladium tetrakis(triphenylphosphine) (0.1 eq., 72 mg, 0.062 mmol), potassium carbonate (3.0 eq., 128 mg, 0.93 mmol) and 3-bromopyridine (2.0 eq., 60 µL, 0.62 mmol) in DMF (3 cm$^3$) and water (1 cm$^3$) and the mixture was stirred for 2 hours at 80 °C, then cooled to rt. Water was added and the solution was extracted with diethyl ether. The combined organic layers were washed with water (5 × 1 cm$^3$) and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (heptane–ethyl acetate 8 : 2 to 6 : 4) gave the coupling product **20** (53 mg, 42% yield) as a pale yellow oil. $[\alpha]_D^{20}$ + 27.5 (*c* 0.75 in $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$: 2925, 2857, 1699, 1647, 1456, 1422, 1393, 1368, 1254, 1166, 1065; $\delta_H$ (250 MHz, $CDCl_3$): 8.44 (1H, m), 8.42 (1H, m), 7.50 (1H, ddd, *J* 7.9, 2 and 1.8), 7.21 (1H, dd, *J* 7.9 and 5), 4.58 (1H, ddd, *J* 7.6, 7.6 and 3.2), 3.72 (1H, ddd, *J* 7.6, 7.6 and 5.7), 2.78 (1H, m), 2.60 (2H, t, *J* 7.6), 1.91 (1H, m), 1.75–1.57 (6H, m), 1.50 (9H, s), 1.47 (13H, m); $\delta_C$ (75 MHz, $CDCl_3$):157.0 (s), 149.2 (d), 146.4 (d), 138.1 (s), 136.2 (d), 123.3 (d), 84.2 (d), 81.1 (s), 65.5 (d), 49.4 (d), 34.5 (t), 32.9 (t), 31.0 (t), 29.5 (t), 29.3 (t), 29.2 (t), 29.0 (t), 28.2 (q), 27.9 (t), 26.5 (t), 26.3 (t), 25.8 (t); *m*/*z* (ES): 425.3 ([M + Na], 94), 364 (15), 325 (100), 303 (38); HRMS: found: 425.2780; calcd for $C_{24}H_{38}NaN_2O_3$ [M + Na]: 425.2775.

**(3*S*,3a*S*,6a*R*)-3-(8-Pyridin-3-yloctyl)hexahydrocyclopenta[*c*]-isoxazole (6).** A solution of the *N*-Boc isoxazolidine **20** (1.0 eq., 56 mg, 0.14 mmol) and trifluoroacetic acid (10.0 eq., 0.15 cm$^3$, 1.4 mmol) in dry dichloromethane (2 cm$^3$) was stirred for 25 min at room temperature. After addition of a 10% sodium carbonate solution and extraction with dichloromethane, the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the deprotected isoxazolidine **6** (36 mg, 86% yield) as a colorless oil. $[\alpha]_D^{20}$ + 27.5 (*c* 0.65, $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$: 3400, 2929, 2855, 1647, 1422, 1092; $\delta_H$ (300 MHz, $CDCl_3$): 8.43 (1H, m), 8.42 (1H, m), 7.50 (1H, ddd, *J* 7.7, 1.9 and 1.8), 7.20 (1H, ddd, *J* 7.8, 4.7 and 0.7), 3.94 (1H, td, *J* 8.4 and 4.3), 3.56 (1H, m), 3.44 (1H, br s), 2.75 (1H, m), 2.60 (2H, t, *J* 7.5), 1.91 (1H, m), 1.67–1.44 (8H, m), 1.42–1.24 (10H, m); $\delta_C$ (75 MHz, $CDCl_3$): 149.7 (d), 147.0 (d), 138.0 (s), 136.0 (d), 123.3 (d), 87.0 (d), 66.4 (d), 49.9 (d), 35.0 (t), 33.0 (t), 31.1 (t), 29.7 (t), 29.3 (t), 29.3 (t), 29.0 (t), 28.3 (t), 26.9 (t), 26.7 (t), 26.5 (t); *m*/*z* (ES): 325.2 ([M + Na], 100), 303 (28); HRMS: found: 325.2254; calcd for $C_{19}H_{30}NaN_2O$ [M + Na]: 325.2250.

### Pyrinodemin A (1) by reductive amination

Aldehyde **28**[3] (2.0 eq., 46 mg, 0.16 mmol) was added to a solution of isoxazolidine **6** (1.0 eq., 23 mg, 0.076 mmol) in dry methanol (1 cm$^3$) at 55 °C. After 3 hours, 3 drops of helianthine were added and the pH was adjusted with 2 N hydrochloric acid solution until the solution turned red. Sodium cyanoborohydride (2.0 eq., 10 mg, 0.16 mmol) was added and the solution was stirred for 2.5 hours at room temperature. After evaporation of methanol under reduced pressure, addition of a 10% sodium carbonate solution, and

extraction with dichloromethane, the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by preparative thin layer chromatography (heptane–ethyl acetate 7 : 3 with ammonia vapor) gave pyrinodemin A **1** (12 mg, 27% yield). $[\alpha]_D^{20}$ −5 (*c* 0.46, $CHCl_3$); $\delta_H$ (300 MHz, $CDCl_3$): 8.46 (4H, br s), 7.51 (2H, m), 7.23 (2H, m), 5.35 (2H, m), 4.07 (1H, m), 3.51 (1H, m), 2.88 (2H, m), 2.64 (5H, m), 2.04 (4H, m), 1.75 (1H, m), 1.66 (6H, m), 1.48 (3H, m), 1.30 (26H, br s); $\delta_C$ (90 MHz, $CDCl_3$): 149.9 (s), 147.1 (s), 138.1 (q), 135.9 (s), 130.0 (s), 129.6 (s), 123.3 (s), 77.7 (s), 72.6 (d), 57.3 (s), 49.9 (s), 33.0 (d), 32.0 (d), 31.9 (d), 31.2 (d), 29.7 (d), 29.5 (d), 29.4 (d), 29.3 (d), 29.3 (d), 29.2 (d), 28.8 (d), 27.8 (d), 27.5 (d), 27.2 (d), 27.2 (d), 27.1 (d), 26.5 (d); *m*/*z* (ES): 612.3 ([M + K], 5), 596.3 ([M + Na], 100), 574.4 ([M + H], 25); HRMS: found: 596.4556; calcd for $C_{38}H_{59}NaN_3O$ [M + Na]: 596.4550.

**1-*tert*-Butyldimethylsilyloxy-13-tetradecene-5-yne (29).** This compound was obtained from alkyne **23** according to the same procedure as that for the preparation of **24**, using 1-bromo-7-octene. Yield: 67%. $\delta_H$ (360 MHz, $CDCl_3$): 5.88–5.73 (1H, m), 4.98 (2H, m), 3.63 (2H, t, *J* 7), 2.29–2.0 (6H, m), 1.63–1.18 (12H, m), 0.97 (9H, s), 0.04 (6H, s).

**(5*Z*)-1-*tert*-Butyldimethylsilyloxy-5,13-tetradecadiene (30).** This compound was prepared from **29** according to the same procedure as that for the preparation of **25**. Yield: 83%. $\delta_H$ (360 MHz, $CDCl_3$): 5.89–5.23 (1H, m), 5.48–5.28 (2H, m), 5.00 (2H, m), 3.63 (2H, t, *J* 7), 2.12–1.97 (6H, m), 1.61–1.48 (2H, m), 1.47–1.27 (10H, m), 0.92 (9H, s), 0.05 (6H, s); $\delta_C$ (90 MHz, $CDCl_3$): 183.8 (d), 129.9 (d), 129.6 (d), 114.1 (t), 63.0 (t), 33.8–25.1 (9t), 25.9 (q), −0.5 (q).

**(5*Z*)-5,13-Tetradecadien-1-ol.** This compound was prepared according to the same procedure as that for the preparation of **27**. Yield: 74%. $\delta_H$ (360 MHz, $CDCl_3$): 5.90 (2H, m), 5.85–5.68 (1H, m), 4.93 (2H, m), 3.62 (2H, t, *J* 10), 2.08–1.88 (6H, m), 1.72 (1H, br s), 1.54 (2H, m), 1.42–1.18 (10H, m).

**(5*Z*)-5,13-Tetradecadienal (31).** This compound was prepared according to the same procedure as that for the preparation of **28**. Yield 63%. $\delta_H$ (250 MHz, $CDCl_3$): 9.80 (1H, t, *J* 9), 5.82 (1H, m), 5.52–5.23 (2H, m), 4.96 (2H, m), 2.44 (dt, *J* 9), 2.18–1.95 (6H, m), 1.70 (2H, m), 1.46–1.20 (8H, m).

**(3*S*,3a*S*,6a*R*,5′*Z*)-3-(7-octen-1-yl)-1-[(5′,13′)-tetradecadien-1-yl]hexahydrocyclopenta[*c*]isoxazole (33).** A solution of aldehyde **31** (2.0 eq., 43 mg, 0.21 mmol) in dry methanol (1 $cm^3$) was added to a solution of deprotected amine **32** (1.0 eq., 23 mg, 0.10 mmol) in dry methanol (1 $cm^3$). After 3 hours at room temperature, 3 drops of helianthine were added and the pH was adjusted with 2 N hydrochloric acid solution until the solution turned red. Sodium cyanoborohydride (2.0 eq., 13 mg, 0.21 mmol) was added and the solution was stirred for 2 hours at room temperature. After evaporation of methanol, addition of a 10% solution of sodium carbonate and extraction with dichloromethane, the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and the solvents were evaporated under reduced pressure. Purification by preparative thin layer chromatography (heptane–ethyl acetate 8 : 2) gave the desired triene **33** (21.6 mg, 50% yield) as a pale yellow oil. $[\alpha]_D^{20}$ −9 (*c* 0.62 in $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$: 2928, 2856, 1639, 1455, 1258, 1171, 1036; $\delta_H$ (300 MHz, $CDCl_3$): 5.78 (2H, m), 5.35 (2H, m), 4.90 (4H, m), 4.05 (1H, m), 3.44 (1H, m), 2.84 (2H, m), 2.60 (1H, m), 2.05 (8H, m), 1.75–1.40 (8H, m), 1.30 (20H, m); $\delta_C$ (75 MHz, $CDCl_3$): 139.1 (d, 2C), 130.0 (d), 129.5 (d), 114.1 (t, 2C), 77.6 (s), 72.5 (s), 56.8 (d), 49.9 (s), 36.3 (d), 33.7 (d), 32.6 (d), 31.8 (d), 29.7 (d), 29.6 (d), 29.5 (d), 29.3 (d), 29.1 (d), 29.0 (d), 28.8 (d), 27.8 (d), 27.5 (d), 27.2 (d), 27.1 (d), 27.0 (d), 26.4 (d), 26.3 (d); *m*/*z* (ES): 438.3 ([M + Na], 99), 416.3 ([M + H], 100); HRMS: found: 416.3894; calcd for $C_{28}H_{50}NO$ [M + H]: 416.3887.

**Pyrinodemin A (1) by double *B*-alkyl Suzuki reaction.** A solution of triene **33** (11 mg, 0.026 mmol) in dry, degassed THF (0.8 $cm^3$) was added to solid 9-BBN dimer (3.3 eq., 21 mg, 0.086 mmol). The solution was stirred at room temperature overnight then transferred *via* cannula to a solution of palladium tetrakis(triphenylphosphine) (1.6 eq., 49 mg, 0.042 mmol), potassium carbonate (6.0 eq., 21 mg, 0.156 mmol) and 3-bromopyridine (4.0 eq., 10 µL, 0.104 mmol) in DMF (0.7 $cm^3$) and water (0.3 $cm^3$). The solution was stirred for 2 hours at 80 °C, then cooled to rt. After addition of water and extraction with ethyl acetate, the combined organic layers were washed five times with water, dried over anhydrous sodium sulfate and the solvents were evaporated under reduced pressure. Purification by preparative thin layer chromatography (heptane–ethyl acetate 7 : 3 with ammonia vapor) afforded pyrinodemin A **1** (1 mg, 7% yield).

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