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A cationic cyclisation route to prenylated indole alkaloids: synthesis of malbrancheamide B and brevianamide B, and progress towards stephacidin A

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Dedicated to Professor Steve Ley, with best wishes, affection and thanks to an inspirational chemist

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ABSTRACT

The synthesis of the prenylated indole alkaloids, malbrancheamide B and brevianamide B have been accomplished, starting with a prenylated proline derivative created using the Seebach 'self-reproduction of chirality' method, and using a cationic cascade sequence as the key step to form late-stage bridged diketopiperazine intermediates.

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1. Introduction

The numbers of fascinating structures belonging to the prenylated indole alkaloid family have been growing steadily over the years.[1] These compounds possess a bicyclo[2.2.2]diazaoctane core structure in the form of a bridged diketopiperazine (DKP) (or in some cases a partly reduced variant) fused to an indole, oxindole, indoxyl or similar grouping. The first members of this intriguing class of mycotoxins, brevianamides A–F, e.g., brevianamide B (**1**), were isolated in low yield from *Penicillium brevicompactum* by Birch and Wright in 1969.[2] Much more recent additions, such as the stephacidin family, include stephacidin A (**2**), aspergamide B (**3**), avrainvillamide (**4**) and its immensely complex dimer stephacidin B (**5**).[3–5]

These compounds, isolated by fermentation of *Aspergillus ochraceus* WC76466, display potent in vitro cytotoxic activity against a number of human tumour cell lines. Stephacidin B shows particularly potent and selective activity, for example, against testosterone-dependent prostate LNCaP cell line with an IC_{50} value of 0.06 μM. Myers has demonstrated that this activity is in fact due to dissociation of stephacidin B into avrainvillamide in solution.[6] The antiproliferative effects of this compound were traced to binding with the nuclear chaperone nucleophosmin, which regulates the tumour suppressor protein p53.[7]

The malbrancheamides, **6** and **7**, are a pair of compounds very recently isolated from *Malbranchea aurantiaca*, a fungus found on bat detritus in a Mexican cave.[8] They are unique amongst this class of alkaloid in having a chlorinated indole nucleus, and have been shown to exhibit significant, and structure-dependent, calmodulin (CaM) inhibitory activity.[9]

The combination of challenging structures, intriguing biosynthetic origins and, in many cases, potent biological activities, displayed by these compounds makes them attractive targets for synthesis. The most notable contributions, by far, in this arena have been made by the Williams group, who have achieved numerous total syntheses of key natural products (including all but **3**, shown above), and have also provided much detailed evidence for the biosynthesis.[1,10]

The most concise existing routes to these compounds have been described by Williams, and employ a bio-mimetic Diels-Alder cycloaddition as the key step to construct the bridged DKP core. This approach, whilst concise at around 11–14 steps (including brevianamide B, malbrancheamides and stephacidin A), suffers the drawback of providing racemic product.[11] Alternative enantioselective approaches, including those by Williams, Baran, Myers and Trost have involved significantly longer overall sequences.[12–14]

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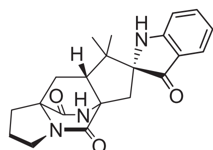
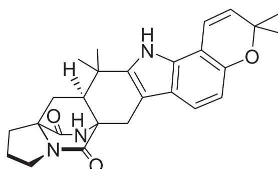
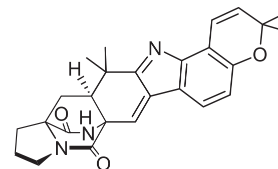
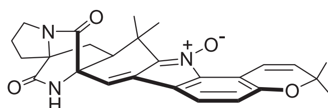
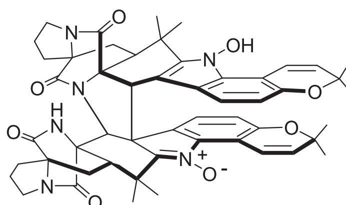
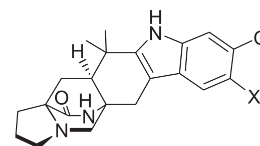












Our interest in the selective substitution of DKP structures via either metal enolate or *N*-acyliminium type reactive intermediates led us to explore a new entry to this type of alkaloid, involving a cationic cascade process to set up the core structure.[15] We recently demonstrated the utility of this new approach with a concise synthesis of ent-malbrancheamide B,[16] and here we describe this work in full, including the genesis of the new route, a previously unreported synthesis of brevianamide B, and progress towards the stephacidins.

2. Results and discussion

2.1. Synthesis and cationic cyclisation of a proline-derived DKP

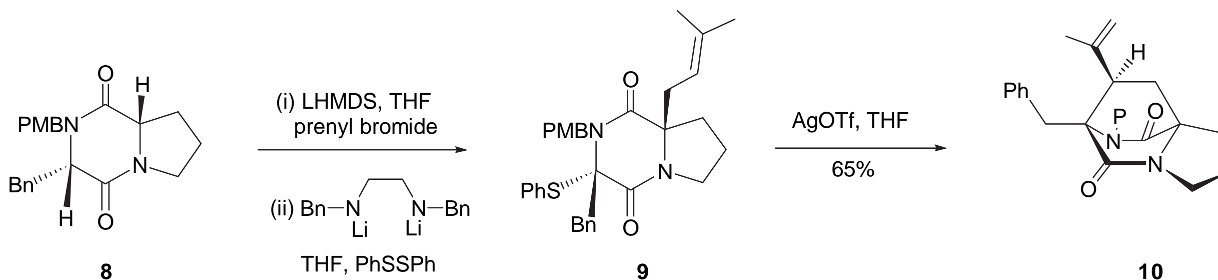
Our interest in the chemistry of DKPs originated in a study of the regio- and stereoselective substitution of mixed proline-containing systems, e.g., DKP **8**, via enolates.[15] Such systems were found to undergo initial alkylation with retention of configuration at the proline residue, and with one so-formed product we carried out a subsequent sulfenylation to give fully substituted DKP **9**. Bearing in mind the known ability to effect substitutions on DKP scaffolds via cationic-type intermediates, demonstrated by several groups, including those of Liebscher,[17] Davies[18] and Williams,[19] we reacted DKP **9** with AgOTf, and were delighted to observe selective and reasonably efficient formation of bridged DKP product **10**, Scheme 1.

This product was formed stereoselectively at the position of the new alkenyl substituent, and the relative configuration at this carbon centre augured well for syntheses of the stephacidins or malbrancheamides. At this point it is worth clarifying, that all of our synthetic work has been done in the (cheaper) L-proline series, and so product **10** is enantiomeric to the natural product drawings of **1**–**7**. It is also worth noting that some of these natural products have been obtained in either enantiomeric form, depending upon the source (e.g., stephacidin A),[20] some others are of the same series as **10**,[21] and that Williams' studies have demonstrated that either enantiomeric series of compounds may possess potent biological activity.[9] Needless to say, the chemistry described herein should apply equally well to the proline D-series.

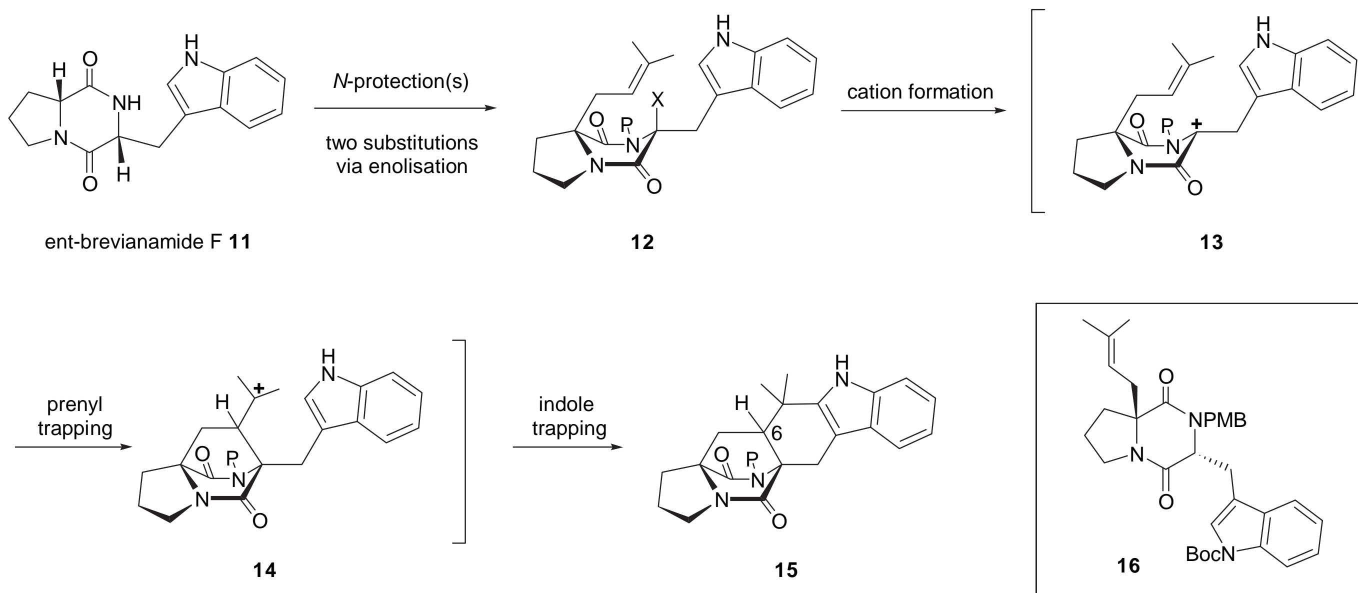
Having achieved the cyclisation of **9** to give **10**, it became clear to us that a cascade process might be productively engaged if a mixed proline/tryptophan system were employed, i.e., Scheme 2 (shown in same series as **1**–**7**).

Formation of an appropriately substituted system **12**, e.g., X=SPh, ready for cation formation appeared plausible using the chemistry outlined above. We presumed that suitable protecting groups would be required on the ring amide (P in **12**) and possibly on the indole nitrogen. The second cyclisation in the sequence, involving indole participation was well precedented by the work of Williams.[22]

Unfortunately, our first efforts to realise this concept by following the DKP substitution route proved highly problematic, due to the extreme reluctance of prenylated DKP **16** to undergo useful enolate substitution chemistry. Although we are now re-examining this tactic using alternative free radical methods, at the time we chose to adopt a modified approach.



Scheme 1. An initial cationic DKP cyclisation.

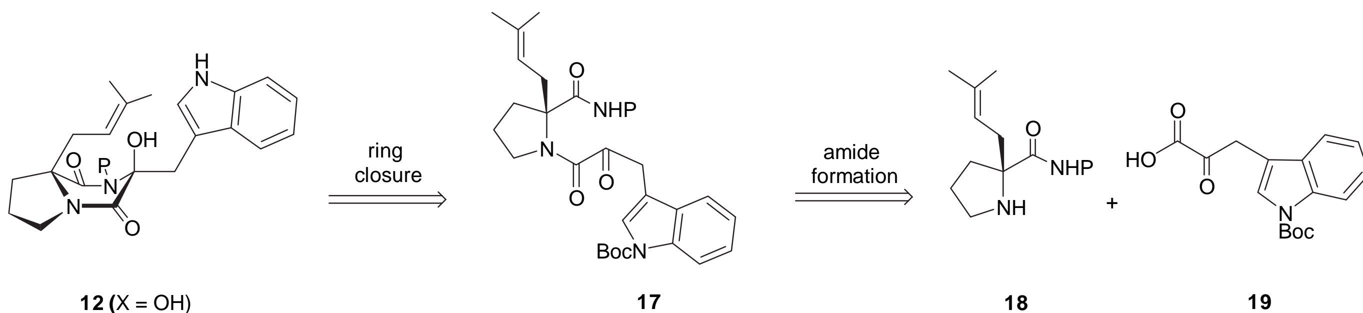


Scheme 2. Planned double cyclisation to give natural product frameworks.

It occurred to us that if the group X in **12** was simply a hydroxyl function, then cation initiation should be possible by treatment with acids, or perhaps, after derivatisation (e.g., acetylation or methylation), with Lewis acids. Further inspection reveals that this DKP would be expected to form spontaneously from a corresponding open chain keto-amide **17**, which itself should be available via a standard peptide coupling, Scheme 3.

2.2. Initial explorations of a cationic cascade

Our preliminary synthesis exploration began with the well-known Seebach proline 'acetal' **20**, which was prenylated under standard conditions to give **21**.[23] Opening of the oxazolone system with lithiated *para*-methoxybenzylamine ($PMBNH_2$) then gave proline amide **22** in practically quantitative yield, Scheme 4.[24]

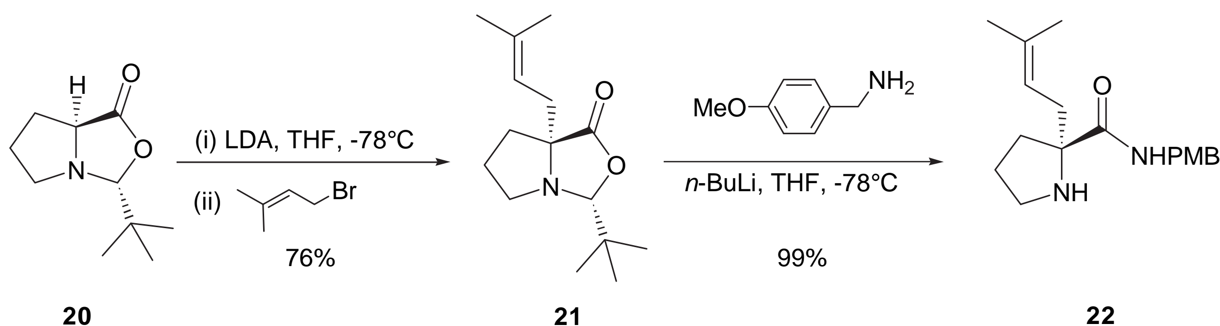


Scheme 3. Revised disconnection for cation precursor.

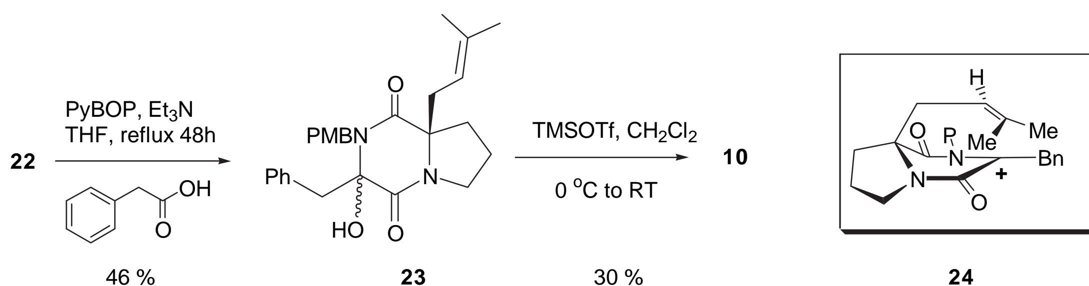
This approach immediately appeared very attractive in terms of convergency, and it was clear that the required prenylated proline derivative **18**, in the L-series, would be easily available using Seebach's 'self-reproduction of chirality' method. To facilitate peptide coupling between the two partners, as shown, we envisaged using indole pyruvic acid derivatives (with or without indole nitrogen protection), such as **19**.

Coupling of the pyrrolidine of amide **22** with the carboxyl function of commercially available phenylpyruvic acid, using PyBOP reagent according to Czarnocki and co-workers,[25] gave hydroxy-DKP **23** directly, as a 3:1 mixture of diastereoisomers, Scheme 5.

Treatment of this compound with acids (e.g., HCl, PTSA, or TFA) in THF proved insufficient to initiate cationic chemistry.[26] However, addition of TMSOTf to DKP **23**, initially at 0 °C and then at room



Scheme 4. Synthesis of quaternary proline amide.



Scheme 5. TMSOTf initiated cyclisation of a hydroxy-DKP.

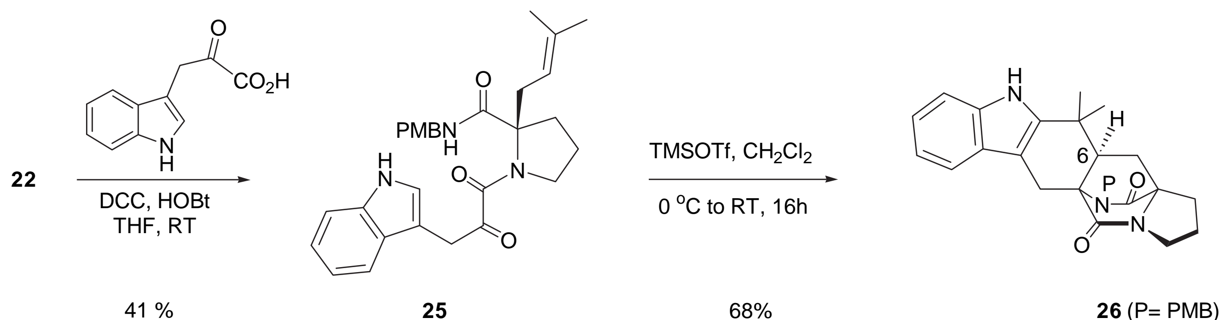
temperature overnight, led to the formation of bridged DKP **10**, identical to that observed from the silver triflate reaction. Again, we observed only one diastereomeric product, and the outcome is consistent with a conformation of the reactive intermediate that places the bulk of the prenyl group over the 'front' C=O function, as shown in **24**, and away from the relatively bulky N-PMB group.

Although at this stage the chemical yields for the peptide coupling and the key cyclisation were somewhat modest, we decided to test our double cyclisation strategy by incorporating indole pyruvic acid into the sequence. In this case, coupling with **22** proved problematic using the PyBOP reagent, and only by employing standard, base-free, DCC/HOBt conditions did we achieve workable, albeit modest, yields of product, Scheme 6.

block for our new synthetic approach we required a replacement for the troublesome PMB protection. After considering the virtues of a range of groups we decided to explore the use of an OBn group on the DKP nitrogen, since this would enable eventual lactam deprotection (i.e., N–O cleavage) under reductive conditions (SmI_2) that had previously been shown to be compatible with rather highly functionalised and sensitive intermediates.[29]

2.3. Synthesis of brevianamide B using a modified cascade

The synthetic route using the modified nitrogen substituent proceeded largely as we required, although with a few significant differences to the N-PMB series, Scheme 7.



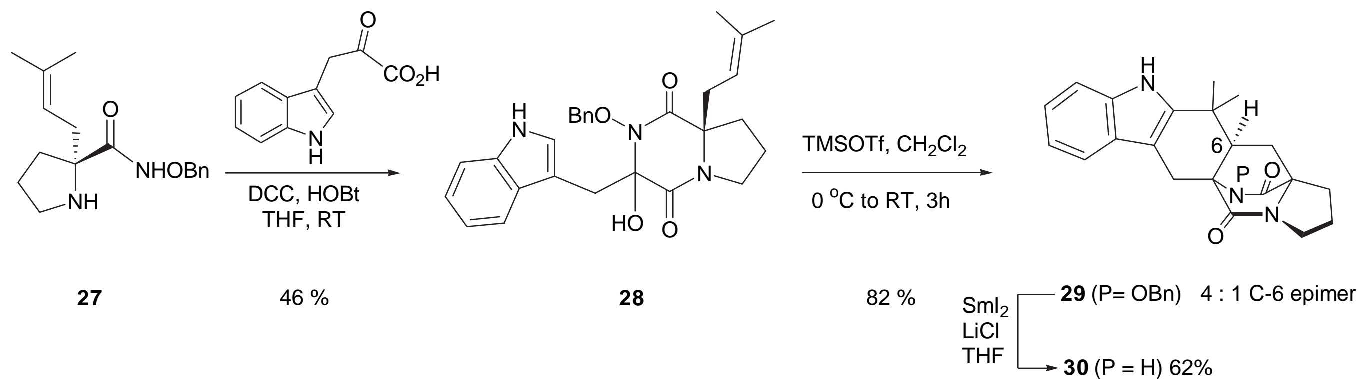
Scheme 6. TMSOTf cascade to give a known intermediate for brevianamide B.

The coupling product was isolated as the linear keto-amide **25**, rather than the corresponding cyclised hydroxy-DKP, presumably due to the milder, base-free conditions, and lower temperatures employed. To our delight, treatment of this compound with TMSOTf, as before, resulted in clean formation of the doubly cyclised product **26**, as a single diastereomer. The yield and high stereoselectivity of this process were especially pleasing, as was the realisation that the seemingly complex polycyclic framework of **26** had been prepared in only five steps from proline!

Since both C-6 epimers of DKP **26** had been prepared previously by Williams, in his pioneering synthesis of brevianamide B,[24] we were able to confirm our stereochemical assignment, and to match our spectroscopic data to those measured previously. Unfortunately, Williams had also established that removal of the PMB protecting group from the DKP lactam function could be problematic, and we were destined to re-discover this problem.[27] Despite attempts in which material was tested to destruction, we were unable to identify either reductive (hydrogenolysis with Pd/C, $PdCl_2$ or $Pd(OH)_2$ as catalyst in various solvents) or oxidative (DDQ, CAN, TFA/anisole, PTSA in toluene) conditions that provided even modest yields for this deprotection.[28] As this problem presented a major stumbling

The required *O*-benzyl proline hydroxamic acid **27** was prepared straightforwardly along the same lines as **22**, and coupling to indole pyruvic acid proceeded in similar moderate yield, but in this case gave the product in the closed, hydroxy-DKP, form **28**. We ascribe this difference to the combination of diminished steric encumbrance, and increased nucleophilic properties, of the hydroxamic acid nitrogen, compared to the corresponding amide in **25**. Cyclisation of **28** using TMSOTf proceeded smoothly, but resulted in the formation of the desired product **29**, along with the corresponding C-6 epimer in a 4:1 ratio. This slightly disappointing erosion of selectivity in the cyclisation may be due to reduced effective steric screening by N–OBn compared to N–PMB, according to the model represented by **24**, although we have not probed this effect further to date.

As shown, with the separated diastereomer **29**, we were pleased to establish that N–O bond cleavage could be effected using samarium iodide.[30] This reaction was ineffective with SmI_2 alone, and reasonable yields of the desired DKP **30** could only be obtained using the activation method involving addition of LiCl, as described by Flowers and co-workers.[31] This compound had been prepared by both the Williams and Liebscher research groups, and our data corresponded well with those published earlier.[32]

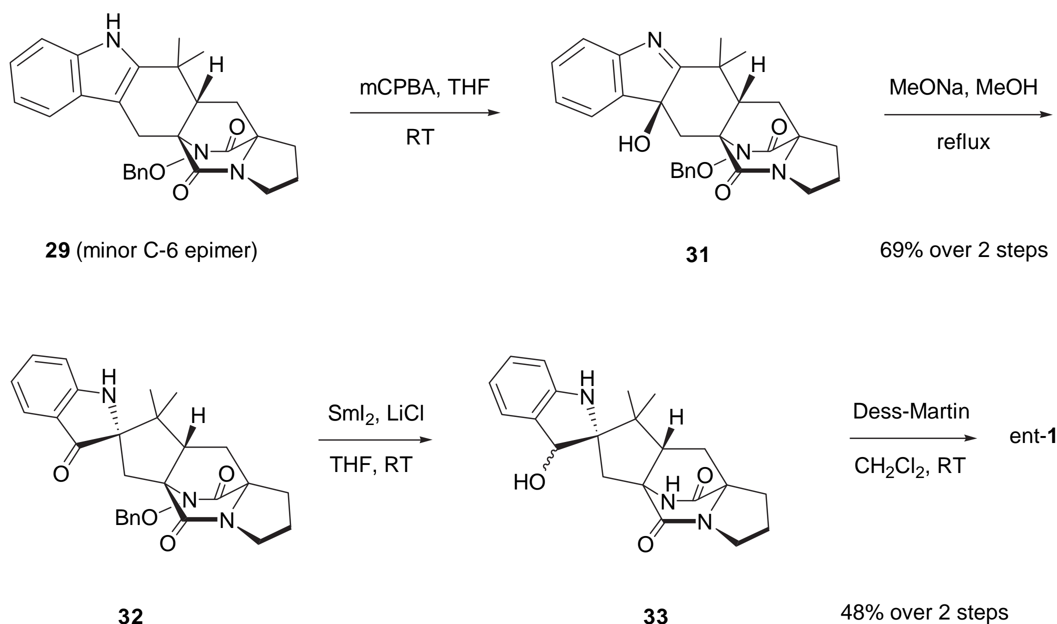


Scheme 7. Modified cascade using N–OBn DKP protection.

Bridged DKP **30** is clearly a very close relative to stephacidin A and to the malbrancheamides, and incorporation of additional indole substitution into our synthetic scheme, so as to provide access to these natural products, appeared viable. However, as an additional test of our tactic of employing the N–OBn DKP protection, we first decided to progress the minor diastereomeric cyclisation product from Scheme 7 (i.e., the C-6 epimer of **29**) towards brevianamide B, Scheme 8.

2.4. Synthesis of malbrancheamide B

Our new diastereoselective access to polycyclic bridged indoles related to structure **29** prompted us to focus on the synthesis of stephacidin A (**2**) and the malbrancheamides (**6** and **7**). A complete natural product synthesis in the major C-6 epimeric series available from our chemistry would both underline the utility of our cascade strategy and would also enable us to test its compatibility with additional indole substitution required in these natural products (and others such as paraherquamides).



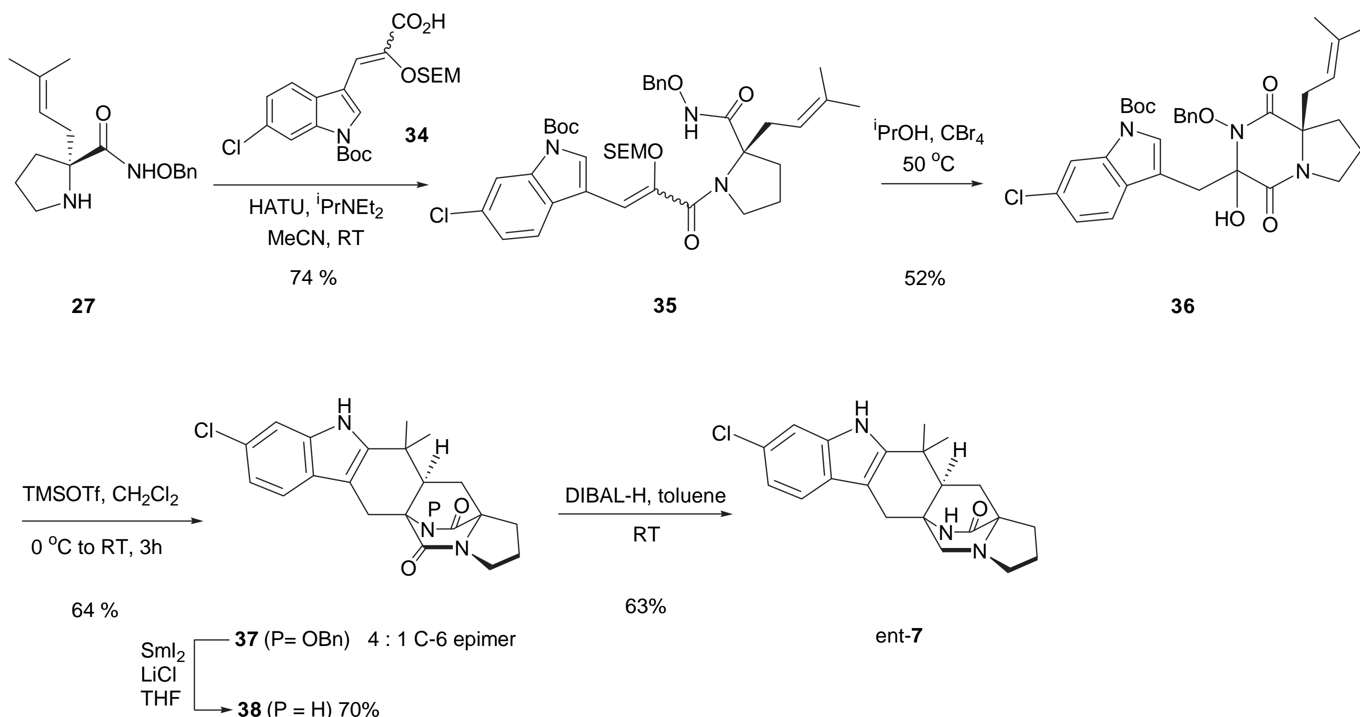
Scheme 8. Synthesis of ent-brevianamide B.

The overall transformation of linearly fused indoles, like **29**, into the corresponding spiro-indoxyls found in brevianamides, followed closely the ample precedent set by the Williams group.[1,28] Peracid oxidation of the minor C-6 epimer of **29**, followed by base treatment effected the key oxidation–rearrangement to give yellow spiro-indoxyl **32**. Although, to our chagrin, reductive cleavage of the N–OBn bond, using SmI_2/LiCl as before, resulted in concomitant indoxyl reduction, giving **33**, we were able to complete a synthesis of ent-brevianamide B (**1**) by Dess-Martin oxidation.

Despite the unwanted intervention of indoxyl reduction, and notwithstanding the fact that we employed only a minor diastereomeric intermediate in our synthesis, the brevity of this route to brevianamide B, at only nine steps from proline, highlights the power of this approach.

As described in our previous communication, a synthesis of ent-malbrancheamide B (**7**) emerged, based on the preliminary studies described above, and as summarised in Scheme 9.

The synthesis required coupling of 6-chloroindole pyruvic acid (or a derivative) to the proline hydroxamic acid component **27**. Throughout this project, we had experienced consistently low yields in the couplings of indole pyruvic acids, and preliminary experiments with synthesized samples of pyruvic acids (i.e., non-commercial samples) gave extremely poor results. Such compounds were found to exist exclusively in the enol form, rather than the keto-acid form depicted in Schemes 5–7. As a means of circumventing this problem it was decided to prepare O-alkylated



Scheme 9. Synthesis of ent-malbrancheamide B (**7**).

enol derivatives that might better participate in peptide couplings but could subsequently be unmasked to give the α-ketoamide (and thus the hydroxy-DKP) required for the cationic cascade. Several alkylated enol pyruvates (OMe, *O*-allyl, OPMB) proved surprisingly robust, and the most suitable was found to be *O*-SEM derivative **34**, which was prepared by a short and straightforward route, starting with commercial 6-chloroindole (the approach is exemplified for an analogous system below).

Coupling of **27** and **34** gave amide **35** in an acceptable yield of 74%. Unfortunately, even this compound, which we anticipated would be prone to hydrolysis to the desired ketoamide by reaction with fluoride, proved remarkably stable to reagents such as TBAF, TBAT and HF/pyridine. Exposure of **35** to the conditions described by Chen and Lee for SEM deprotections,[33] involving treatment with CBr_4 in warm isopropanol, gave a moderate yield of DKP **36**, which we have not optimised further to date.

Pleasingly, DKP **36** underwent the key double cyclisation sequence on treatment with TMSOTf, as before, giving **37** as a 4:1 mixture with the corresponding C-6 epimer, which was easily separated by chromatography. Subsequent N–O bond cleavage using SmI_2 was followed by regioselective lactam reduction, following the method of Williams, to provide the unnatural antipode of malbrancheamide B (ent-**7**) as shown. The structure of our final product was secured by comparison of our ^{1}H NMR and ^{13}C NMR data with those of Williams, which provided an exact match.[34]

Our synthesis of malbrancheamide B requires 10 synthetic steps from 6-chloroindole, and proceeds in around 4.4% overall yield. Although this already ranks as one of the most concise entries to such natural products there is clearly room for further streamlining and improvement, particularly in the low-yielding enol ether deprotection.

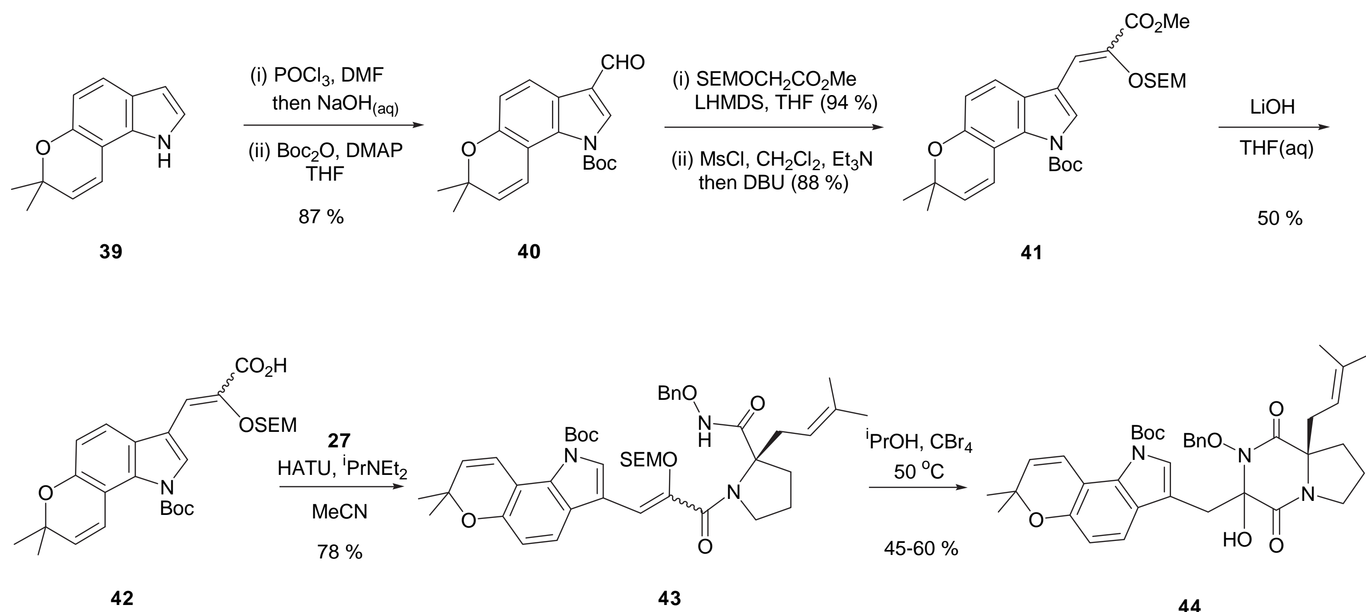
2.5. Advances towards stephacidins

Having already effected the successful cationic cascade syntheses of intermediates **29** and **37**, incorporating either a simple indole, or a chlorinated indole, respectively, we considered that stephacidin A (**2**) should also be available by this method, by the simple expedient of starting with an indole pyruvate incorporating a fused pyrano ring. Synthesis of the appropriate hydroxy-DKP precursor, following the same strategy as before, proved quite straightforward, starting from known indole **39**,[35] Scheme 10.

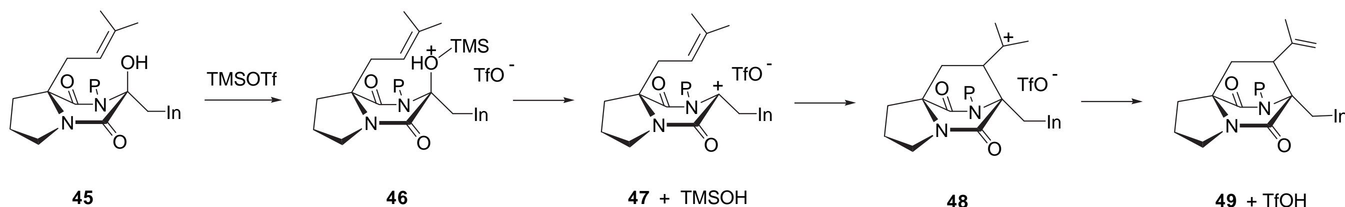
The scheme illustrates our preferred method for accessing the SEM enol ethers of indole pyruvic acids, which involves an aldol–dehydration sequence with the intermediate indole carboxaldehydes, such as **40**, to give, in this case, ester **41**. Since ester hydrolysis of **41** was accompanied by slow removal of the indole Boc protecting group, we chose not to carry hydrolysis to completion, and the 50% yield of product **42** was accompanied by ca. 5% of the corresponding indole NH carboxylic acid and 36% of starting ester **41**. Peptide coupling to give **43**, and subsequent enol ether hydrolysis proceeded very much as before, to give DKP **44** ready for cyclisation. Interestingly, these mild acidic conditions, although effective for SEM group removal, did not provoke any sign of useful cyclisation chemistry.

Much to our disappointment, all of our efforts to effect cyclisation reactions of DKP **44** were destined to meet with failure. Reaction with TMSOTf, under the conditions used previously, resulted in rapid decomposition of the starting material. Attempts using this same reagent at lower temperatures effected only the removal of the Boc protection, and no clean cyclisation products were observed. Alternative procedures, involving acetylation of the DKP tertiary hydroxyl function, followed by treatment with BF_3–OEt_2 did not provide useful products. Likewise, removal of the indole *N*-Boc protection, in an attempt to enhance indole nucleophilicity, followed by treatment with protic acids (TFA or HCl) or Lewis acids ($TiCl_4$) resulted only in complete destruction of the starting DKP **44**.

In retrospect, this problem was predictable, based on analysis of the mechanism of the TMSOTf initiated reaction, our observations of the 'cascade' process, and previous observations of the Williams and Baran groups concerning the sensitivity of stephacidin A to acids.[12,13] We envisage that the double cyclisation of our DKP systems proceeds as outlined in Scheme 11.



Scheme 10. Synthesis of an advanced intermediate towards stephacidin A.



Scheme 11. Proposed sequence in TMSOTf initiated DKP cyclisations.

Initial silylation of DKP **45** (In=indole) on oxygen forms a good leaving group, leading to the unusual *N*-acyliminium type intermediate **46**, which can then cyclise to give the tertiary cation **48**. In principle, this intermediate could directly alkylate the pendant indole, leading to the observed products. However, in a number of our earlier reactions, we observed intermediates by TLC, which correspond to the mono-cyclised DKP structure **49**, and which are then consumed in the (usually) slow conversion to doubly cyclised product. This seems to point to the initial formation of alkenyl intermediates like **49**, which then undergo cyclisation due to (probably reversible) alkene protonation by the by-product, triflic acid.

In the case of our successful syntheses the presence of strong acid is of no consequence, but in the case of stephacidin A the pyrano ring is known to be rather acid labile, and Baran demonstrated that acid-mediated cyclisation of intermediates corresponding to alkene **49** was very problematic and low-yielding at best.[13c] In our case it seems the intermediates are destroyed by the extremely strong acid liberated in the early steps of the reaction. Addition of base from the outset stops productive cyclisation chemistry, presumably due to rapid deprotonation of silylated intermediate **46**.

At present, we have not been able to find a direct way around this synthetic impasse, which casts some doubt over the applicability of this approach for systems with sensitive oxygenated rings fused to the indole system. However, this situation can be rescued if the desired sensitive rings can be incorporated post-cyclisation, using intermediates carrying more robust oxygen functions (maybe OAc or similar), or perhaps reactive halogens (Br, I) capable of conversion into ethers. Efforts to establish these possibilities are underway.

3. Conclusion

A new strategy has been demonstrated for the synthesis of members of the prenylated indole family of alkaloids that employs a double cationic cyclisation to build the key bridged DKP structure present in these natural products. Non-racemic brevianamide B and malbrancheamide B were prepared by very concise sequences using this approach. A present deficiency in the method is the presence of strong acid in the key cyclisation step. Present work is aimed at by-passing this issue, as well as extending the scope of the cation-termination step and application to other targets.

4. Experimental part

4.1. General methods

All glassware were flame dried under a steady flow of nitrogen before use; all reactions were performed under an atmosphere of nitrogen or argon unless otherwise stated. THF was distilled immediately prior to use from sodium and benzophenone. CH_2Cl_2 was distilled from calcium hydride. Prenylbromide and pyridine were distilled before use. All other solvents and reagents were used as received from commercial suppliers unless otherwise stated. Solution infra-red spectra were recorded using a Perkin–Elmer 1600 series FTIR spectrometer using chloroform as solvent. Neat infrared spectra were recorded using a Nicolet AVATAR 370 DTGS spectrometer. Wavelengths (ν) are reported in cm^{-1}. Optical rotations were recorded as dilute solutions of the indicated solvent in a 50 mm glass cell using a JASCO DIP370 digital polarimeter at

294 nm. Mass spectra were obtained using a VG Micromass 70E or VG Micron Autospec spectrometer, using electrospray ionization (ESI) with *meta*-nitrobenzyl alcohol as matrix. All ^{1}H NMR and ^{13}C NMR experiments were recorded using Bruker 300, AV400, AMX400 and DRX500 spectrometers. Chemical shifts (δ) are quoted in parts per million and coupling constants (J) are quoted in hertz. The 7.27 ppm resonance of residual $CHCl_3$ for proton spectra and 77.16 ppm resonance of $CDCl_3$ for carbon spectra were used as internal references. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with keiselgel F_{254} with 0.2 mm thickness. Visualisation was achieved by a combination of ultraviolet light (254 nm) and acidic potassium permanganate or anisaldehyde. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck and co.).

Experimental conditions and full spectral data were published previously for compounds **10**, and for ent-**7** (malbrancheamide B), **21**, **27** and **34**–**38**.[16]

*4.1.1. Preparation of (R)-N-(4-methoxybenzyl)-2-(3-methylbut-2-enyl)pyrrolidine-2-carboxamide (**22**).* To a stirred solution of 4-methoxybenzylamine (4.3 mL, 33.4 mmol, 2.0 equiv) in THF (70 mL), *n*-BuLi (22.3 mL, 1.6 M in hexane, 33.4 mmol, 2.0 equiv) was added at −78 °C and the resulting mixture was stirred for 30 min. In another flask, a solution of prenylated oxazolidinone **21** (4.21 g, 16.7 mmol) in THF (15 mL) was prepared and cooled to −78 °C. The substrate was added to the base via cannula at −78 °C. After stirring for 1.5 h at the same temperature, the solution was quenched by a saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. The solution was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Excess 4-methoxybenzylamine was removed by Kugelrhor distillation and the residue afforded amine **22** (5.02 g, 99%). This material was directly used in the next step without further purification. An analytical sample was obtained by flash column chromatography on silica gel (pet. ether/EtOAc, 1:1 to 1:4) to give amine **22** as a colourless oil. $[\alpha]_D^{20}$ −14.7 (*c* 1.0, $CHCl_3$); FTIR ($CHCl_3$) ν_{max} 3330, 2930, 2875, 1651, 1613, 1461, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 1H, NH), 7.17 (d, *J* 8.8, 2H, Ar, CH), 6.84 (d, *J* 8.8, 2H, Ar, CH), 5.05 (m, 1H, CH=C), 4.38 (dd, *J* 14.6, 6.2, 1H, NHC*H*HAr), 4.29 (dd, *J* 14.6, 5.6, 1H, NHCH*H*Ar), 3.78 (s, 3H, OCH_3), 3.00 (ddd, *J* 10.4, 6.8, 6.8, 1H, NHC*H*HCH_2), 2.82 (ddd, *J* 10.4, 6.4, 6.4, 1H, NHCH*H*CH_2), 2.68 (dd, *J* 14.6, 6.6, 1H, C*H*HCH=C), 2.33 (dd, *J* 14.6, 8.4, 1H, CH*H*CH=C), 2.18 (ddd, *J* 12.8, 6.8, 6.8, 1H, CC*H*HCH_2), 1.79–1.67 (m, 4H, CCHH*C*H$_2$, NH), 1.68 (s, 3H, CH_3), 1.62 (s, 3H, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.6 (C=O), 158.8 (Ar, C), 135.8 (CH=C), 131.1 (Ar, C), 128.9 (2×Ar, CH), 119.1 (CH=C), 114.0 (2×Ar, CH), 69.6 (C-2), 55.3 (OCH_3), 47.1 (CH_2), 42.6 (NHCH_2Ar), 36.8 (CH_2), 36.1 (CH_2), 26.3 (CH_2), 26.1 (CH_3), 18.0 (CH_3); HRMS (ESI) calculated for $C_{18}H_{27}N_2O_2$ $[M+H]^+$ 303.2073, found 303.2061.

*4.1.2. Preparation of (8aR)-3-benzyl-3-hydroxy-2-(4-methoxybenzyl)-8a-(3-methylbut-2-enyl)-hexahydro pyrrolo[1,2-a]pyrazine-1,4-dione (**23**).* To a stirred solution of phenylpyruvic acid (740 mg, 4.5 mmol, 3.0 equiv) in THF (20 mL) was added triethylamine (1.05 mL, 7.5 mmol, 5.0 equiv) and PyBOP (2.35 g, 4.5 mmol, 3.0 equiv) at room temperature under N_2. The resulting mixture was stirred at room temperature for 1 h before addition of a solution of proline derivative **22** (461 mg, 1.5 mmol) in THF (6 mL). The resulting mixture was heated to reflux for 48 h and after cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 (30 mL) and water (30 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×20 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (pet. ether/EtOAc, 2:1) to give hydroxy-DKP **23** (308 mg, 46%) as a yellow oil. The less polar diastereoisomer, which is the major one, was isolated in the first fractions of the column chromatography and was fully characterised. $[\alpha]_D^{20}$ +59.2 (*c* 1.2, $CHCl_3$); FTIR ($CHCl_3$) ν_{max} 3546, 2934, 1659, 1454, 1352, 1108, 1080, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* 8.6, 2H, Ar, CH), 7.32–7.22 (m, 3H, Ar, CH), 7.09–7.06 (m, 2H, Ar, CH), 6.85 (d, *J* 8.6, 2H, Ar, CH), 4.94 (d, *J* 13.6, 1H, NC*H*HAr), 4.51 (d, *J* 13.6, 1H, NCH*H*Ar), 4.42 (m, 1H, C*H*=C), 4.06 (br s, 1H, OH), 3.79 (s, 3H, OCH_3), 3.53 (ddd, *J* 12.4, 9.6, 5.6, 1H, NC*H*HCH_2), 3.39 (d, *J* 13.4, 1H, CC*H*HPh), 3.32 (d, *J* 13.4, 1H, CCH*H*Ph), 3.22 (ddd, *J* 12.4, 9.2, 4.4, 1H, NCH*H*CH_2), 2.14–2.08 (m, 2H, C*H*$_2$CH=C), 1.69–1.60 (m, 2H), 1.49 (s, 3H, CH_3), 1.33 (m, 1H), 1.30 (s, 3H, CH_3), 0.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9 (C=O), 164.6 (C=O), 158.7 (Ar, C), 137.3 (CH=*C*), 134.2 (Ar, C), 131.7 (2×Ar, CH), 130.0 (2×Ar, CH), 129.3 (Ar, C), 128.5 (2×Ar, CH), 127.5 (Ar, CH), 116.9 (*C*H=C), 113.3 (2×Ar, CH), 88.5 (C-3), 67.7 (C-8a), 55.2 (OCH_3), 46.3 (CCH_2Ph), 45.7 (NCH_2Ar), 43.7 (N$CH_2$$CH_2$), 36.7 ($CH_2$CH=C), 33.5 (C$CH_2$$CH_2$), 25.6 ($CH_3$), 19.1 ($CH_2$$CH_2$$CH_2$), 17.6 ($CH_3$); HRMS (ESI) calculated for $C_{27}H_{32}N_2O_4Na$ $[M+Na]^+$ 471.2260, found 471.2250.

*4.1.3. Preparation of (1R,7R,10R)-1-benzyl-2,8-diketo-9-(4-methoxybenzyl)-10-(1-methyl-ethenyl)-3,9-diazatricyclo[4.4.3.0]-undecane **10**. 4.1.3.1. General procedure for TMSOTf-mediated cationic cyclisation.* To a stirred solution of hydroxy-DKP **23** (72 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) was added TMSOTf (32 μL, 0.17 mmol, 1.1 equiv) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 16 h before addition of triethylamine (24 μL, 0.17 mmol, 1.1 equiv). The resulting mixture was diluted with CH_2Cl_2 (5 mL), washed with water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether/EtOAc, 2:1) to afford tricyclic compound **10** (20 mg, 30%) as a white solid. Mp 161–163 °C, with spectroscopic data as described previously.[15]

*4.1.4. Preparation of (R)-1-(3-(1H-indol-3-yl)-2-oxopropanoyl)-N-(4-methoxybenzyl)-2-(3-methyl-but-2-enyl)pyrrolidine-2-carboxamide (**25**).* To a stirred solution of commercially available indole pyruvic acid (382 mg, 1.88 mmol, 1.1 equiv) and amine **22** (517 mg, 1.71 mmol) in THF (40 mL) was added HOBt (254 mg, 1.88 mmol, 1.1 equiv) and then DCC (1.88 mL, 1.0 M in DCM, 1.88 mmol, 1.1 equiv) at room temperature. The resulting mixture was stirred for 16 h and the resulting urea was removed by filtration through a pad of Celite®. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (pet. ether/EtOAc, 7:3) to afford pyruvic amide **25** (338 mg, 41%) as an orange oil. $[\alpha]_D^{18}$ −27.7 (*c* 0.65, $CHCl_3$); FTIR (neat) ν_{max} 3297, 2931, 1639, 1511, 1242, 743; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H, NH), 7.56 (d, *J* 8.0, 1H, Ar, CH), 7.31 (d, *J* 8.0, 1H, Ar, CH), 7.22–7.10 (m, 5H, NH, Ar, CH), 6.95 (d, *J* 2.4, 1H, Ar, CH), 6.90 (d, *J* 8.8, 2H, Ar, CH), 4.81 (m, 1H, C*H*=C), 4.29 (dd, *J* 15.0, 6.4, 1H, NHC*H*HAr), 4.28 (d, *J* 15.2, 1H, CC*H*HAr), 4.25 (dd, *J* 15.0, 6.0, 1H, NHCH*H*Ar), 4.02 (d, *J* 15.2, 1H, CCH*H*Ar), 3.82 (s, 3H, OCH_3), 3.24 (ddd, *J* 10.4, 10.4, 6.6, 1H, NC*H*HCH_2), 3.13 (ddd, *J* 10.4, 7.6, 2.8, 1H, NCH*H*CH_2), 2.89 (dd, *J* 14.8, 8.4, 1H, C*H*HCH=C), 2.78 (dd, *J* 14.8, 6.4, 1H, CH*H*CH=C), 2.40 (ddd, *J* 10.0, 6.6, 3.0, 1H, CC*H*HCH_2), 1.69 (m, 1H, CCH*H*CH_2), 1.58 (m, 1H, CH_2C*H*HCH_2), 1.66 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.45 (m, 1H, CH_2CH*H*CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0 (C=O), 172.5 (C=O), 165.6 (C=O), 158.9 (Ar, C), 136.0 (CH=*C*, Ar, C), 130.7 (Ar, C), 128.8 (2×Ar, CH), 127.1 (Ar, C), 124.3 (Ar, CH), 122.6 (Ar, CH), 120.1 (Ar, CH), 118.5 (Ar, CH), 117.6 (*C*H=C), 114.0 (2×Ar, CH), 111.4 (Ar, CH), 104.9 (Ar, C), 72.8 (C-2), 55.3 (OCH_3), 49.8

(NCH_2), 43.1 ($NHCH_2Ar$), 36.1 (CCH_2Ar), 34.4 (CCH_2CH_2), 32.1 ($CH_2CH{=}C$), 26.0 (CH_3), 23.4 ($CH_2CH_2CH_2$), 18.2 (CH_3); HRMS (ESI) calculated for $C_{29}H_{33}N_3O_4Na$ $[M+Na]^+$ 510.2369, found 510.2374.

*4.1.5. Double cyclisation of amide **25** to give bridged DKP **26**.* The general procedure for TMSOTf-mediated cationic cyclisation was followed starting from pyruvic amide **25** (54 mg, 0.11 mmol), TMSOTf (24 μL, 0.13 mmol, 1.1 equiv), Et_3N (76 μL, 0.55 mmol, 5.0 equiv) and CH_2Cl_2 (1.5 mL). The residue was purified by flash column chromatography on silica gel (EtOAc/pet. ether, 3:2) to give DKP **26** (35 mg, 68%) as a white solid. Mp 292–294 °C; $[\alpha]_D^{22}$ −40 (*c* 0.81, $CHCl_3$), lit.[24] $[\alpha]_D^{25}$ −49.6 (*c* 0.80, $CHCl_3$); FTIR (KBr) ν_{max} 3323, 2959, 1675, 1512, 1395, 1246, 746; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (br s, 1H, NH), 7.50 (d, *J* 7.5, 1H, Ar, CH), 7.24 (d, *J* 8.0, 1H, Ar, CH), 7.15 (d, *J* 8.0, 2H, Ar, CH), 7.13–7.08 (m, 2H, Ar, CH), 6.82 (d, *J* 8.5, 2H, Ar, CH), 5.03 (d, *J* 16.0, 1H, NC*H*HAr), 4.41 (d, *J* 16.0, 1H, NCH*H*Ar), 3.76 (s, 3H, OCH_3), 3.72 (d, *J* 14.8, 1H, CC*H*HAr), 3.57 (ddd, *J* 13.4, 6.8, 6.8, 1H, NC*H*HCH_2), 3.41 (ddd, *J* 13.4, 6.8, 6.8, 1H, NCH*H*CH_2), 3.17 (d, *J* 14.8, 1H, CCH*H*Ar), 2.96 (ddd, *J* 12.8, 6.8, 6.8, 1H, CC*H*HCH_2), 2.46 (dd, *J* 10.2, 4.0, 1H, C*H*HCH), 2.25 (dd, *J* 13.5, 10.2, 1H, CH_2CH), 2.09–1.94 (m, 4H, CH*H*CH, CCH*H*CH_2, $CH_2CH_2CH_2$), 1.24 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (C=O), 168.1 (C=O), 158.8 (Ar, C), 138.5 (Ar, C), 136.4 (Ar, C), 130.4 (Ar, C), 127.9 (2×Ar, CH), 126.9 (Ar, C), 121.9 (Ar, CH), 119.4 (Ar, CH), 118.4 (Ar, CH), 114.3 (2×Ar, CH), 110.5 (Ar, CH), 105.0 (Ar, C), 65.9 (C-4), 65.0 (C-18), 55.2 (OCH_3), 48.5 (CH_2CH), 44.6 (NCH_2Ar), 44.2 (NCH_2CH_2), 35.2 ($C(CH_3)_2$), 30.9 (CCH_2CH_2), 30.2 (CH_2CH), 28.6 (CH_3), 24.4 ($CH_2CH_2CH_2$), 22.8 (CH_3), 22.3 (CCH_2Ar); HRMS (ESI) calculated for $C_{29}H_{32}N_3O_3$ $[M+H]^+$ 470.2444, found 470.2452.

*4.1.6. (8aR)-3-((1H-Indol-3-yl)methyl)-2-(benzyloxy)-3-hydroxy-8a-(3-methylbut-2-enyl)hexa-hydropyrrolo[1,2-a]pyrazine-1,4-dione (**28**).* To a stirred solution of indole pyruvic acid (337 mg, 1.66 mmol, 1.2 equiv) and proline derivative **27** (400 mg, 1.38 mmol) in THF (32 mL) was added successively HOBt (224 mg, 1.66 mmol, 1.2 equiv) and DCC (1.66 mL, 1.0 M in DCM, 1.66 mmol, 1.2 equiv) at room temperature. The mixture was stirred at room temperature for 24 h and the resulting urea was filtered though a pad of Celite®. The volatile organics were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (pet. ether/EtOAc, 7:3) to afford hydroxy-DKP **28** (284 mg, 46%) as a pale yellow solid. Mp 184–186 °C; $[\alpha]_D^{20}$ +84 (*c* 0.98, $CHCl_3$); FTIR (KBr) ν_{max} 3317, 2928, 1645, 1406, 1109, 1067; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (br s, 1H, NH), 7.65–7.61 (m, 3H, Ar, CH), 7.40–7.37 (m, 3H, Ar, CH), 7.26 (t, *J* 7.8, 1H, Ar, CH), 7.10 (t, *J* 7.8, 1H, Ar, CH), 7.07–7.02 (m, 2H, Ar, CH), 5.15 (d, *J* 9.4, 1H, OC*H*HAr), 5.11 (d, *J* 9.4, 1H, OC*H*HAr), 5.00 (m, 1H, CH=C), 4.29 (br s, 1H, OH), 3.73 (d, *J* 14.2, 1H, CC*H*HAr), 3.56 (d, *J* 14.2, 1H, CCH*H*Ar), 3.27 (ddd, *J* 12.4, 9.6, 5.2, 1H, NC*H*H), 3.04 (ddd, *J* 12.4, 10.4, 5.2, 1H, NCH*H*), 2.39 (dd, *J* 14.2, 8.2, 1H, C*H*HCH=C), 2.13 (dd, *J* 14.2, 7.4, 1H, CH*H*CH=C), 1.74 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.55 (m, 1H, CC*H*HCH_2), 1.40 (m, 1H, CH_2C*H*HCH_2), 0.60 (m, 1H, CH_2CH*H*CH_2), 0.25 (m, 1H, CCH*H*CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (C=O), 164.7 (C=O), 137.2 (Ar, C), 135.5 (CH=*C*), 135.3 (Ar, C), 129.5 (2×Ar, CH), 128.7 (Ar, CH), 128.4 (2×Ar, CH), 127.1 (Ar, C), 126.2 (Ar, CH), 121.9 (Ar, CH), 119.3 (Ar, CH), 119.2 (Ar, CH), 117.1 (*C*H=C), 110.9 (Ar, CH), 107.4 (Ar, C), 91.1 (C-3), 78.8 (OCH_2Ar), 67.7 (C-8a), 44.2 (NCH_2), 36.2 ($CH_2CH{=}C$), 34.5 (CCH_2Ar), 33.0 (CCH_2CH_2), 25.9 (CH_3), 18.5 ($CH_2CH_2CH_2$), 18.0 (CH_3); HRMS (ESI) calculated for $C_{28}H_{31}N_3O_4Na$ $[M+Na]^+$ 496.2212, found 496.2215.

*4.1.7. Cyclisation of **28** to give bridged DKP **29**, along with a minor C-6 epimer.* The general procedure for TMSOTf-mediated cationic cyclisation was followed starting from hydroxy-DKP **28** (600 mg, 1.27 mmol), TMSOTf (0.25 mL, 1.40 mmol, 1.1 equiv), Et_3N (0.88 mL, 6.35 mmol, 5.0 equiv) and CH_2Cl_2 (20 mL). The residue was purified by flash column chromatography on silica gel (pet. ether/EtOAc, 1:1) to afford the major diastereoisomeric product **29** (see Scheme 7, 384 mg, 66%) as a white solid followed by the minor C-6 epimer (95 mg, 16%) as a white solid.

Data for major epimer of **29**: mp 246–248 °C; $[\alpha]_D^{21}$ −45 (*c* 0.94, $CHCl_3$); FTIR (KBr) ν_{max} 3332, 2927, 1708, 1684, 1437, 1362; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H, NH), 7.55 (m, 1H, Ar, CH), 7.51–7.49 (m, 2H, Ar, CH), 7.43–7.37 (m, 3H, Ar, CH), 7.27 (m, 1H, Ar, CH), 7.18–7.10 (m, 2H, Ar, CH), 5.10 (d, *J* 9.6, 1H, OC*H*HAr), 5.01 (d, *J* 9.6, 1H, OCH*H*Ar), 3.66 (d, *J* 15.6, 1H, CC*H*HAr), 3.56 (ddd, *J* 11.2, 6.6, 6.6, 1H, NC*H*H), 3.42 (ddd, *J* 11.2, 7.2, 7.2, 1H, NCH*H*), 3.37 (d, *J* 15.6, 1H, CCH*H*Ar), 2.88 (ddd, *J* 13.2, 6.6, 6.6, 1H, CC*H*HCH_2), 2.60 (dd, *J* 10.4, 4.4, 1H, CH_2CH), 2.19 (dd, *J* 13.6, 10.4, 1H, C*H*HCH), 2.07–2.01 (m, 2H, $CH_2CH_2CH_2$), 1.98–1.89 (m, 2H, CCH*H*CH_2, CH*H*CH), 1.24 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C=O), 167.1 (C=O), 138.7 (Ar, C), 136.5 (Ar, C), 134.3 (Ar, C), 129.8 (2×Ar, CH), 129.2 (Ar, CH), 128.6 (2×Ar, CH), 127.2 (Ar, C), 121.8 (Ar, CH), 119.3 (Ar, CH), 118.4 (Ar, CH), 110.6 (Ar, CH), 104.8 (Ar, C), 79.7 (OCH_2Ar), 68.9 (C-18), 66.1 (C-4), 47.8 (CH_2CH), 44.2 (NCH_2), 34.8 ($C(CH_3)_2$), 31.3 (CH_2CH), 29.7 (CCH_2CH_2), 28.2 (CH_3), 24.3 ($CH_2CH_2CH_2$), 22.4 (CH_3), 20.2 (CCH_2Ar); HRMS (ESI) calculated for $C_{28}H_{29}N_3O_3Na$ $[M+Na]^+$ 478.2107, found 478.2101.

Data for minor C-6 epimer: mp 210–212 °C; $[\alpha]_D^{21}$ +61 (*c* 1.02, $CHCl_3$); FTIR (KBr) ν_{max} 3266, 2955, 1679, 1460, 1310; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H, NH), 7.54 (d, *J* 6.8, 1H, Ar, CH), 7.33–7.29 (m, 2H, Ar, CH), 7.25–7.21 (m, 2H, Ar, CH), 7.19–7.13 (m, 4H, Ar, CH), 4.93 (d, *J* 10.0, 1H, OC*H*HAr), 4.83 (d, *J* 10.0, 1H, OCH*H*Ar), 3.69 (d, *J* 18.0, 1H, CC*H*HAr), 3.57–3.53 (m, 2H, NCH_2), 3.21 (d, *J* 18.0, 1H, CCH*H*Ar), 2.90 (ddd, *J* 13.2, 6.6, 6.6, 1H, CC*H*HCH_2), 2.40 (dd, *J* 9.6, 4.8, 1H, CH_2CH), 2.19–2.05 (m, 4H, $CH_2CH_2CH_2$, CH_2CH), 1.93 (m, 1H, CCH*H*CH_2), 1.33 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (C=O), 167.9 (C=O), 139.2 (Ar, C), 136.3 (Ar, C), 134.0 (Ar, C), 129.5 (2×Ar, CH), 128.9 (Ar, CH), 128.4 (2×Ar, CH), 126.9 (Ar, C), 121.6 (Ar, CH), 119.3 (Ar, CH), 118.3 (Ar, CH), 110.6 (Ar, CH), 104.7 (Ar, C), 79.0 (OCH_2Ar), 68.8 (C-18), 67.1 (C-4), 46.3 (CH_2CH), 44.1 (NCH_2), 34.3 ($C(CH_3)_2$), 32.4 (CH_2CH), 29.4 (CCH_2CH_2), 28.6 (CH_3), 24.3 ($CH_2CH_2CH_2$), 23.2 (CH_3), 20.2 (CCH_2Ar); HRMS (ESI) calculated for $C_{28}H_{29}N_3O_3Na$ $[M+Na]^+$ 478.2107, found 478.2111.

*4.1.8. Synthesis of **30** via N–O cleavage. 4.1.8.1. General procedure for SmI_2 mediated cleavage of OBn protecting group.* A solution of LiCl (2.9 mL, 0.90 M in THF, 2.64 mmol, 12.0 equiv) was added to a stirred solution of freshly prepared SmI_2 (3.6 mL, 0.24 M in THF, 0.88 mmol, 4.0 equiv) at room temperature. After 30 min, a solution of DKP **29** (major epimer) (100 mg, 0.22 mmol) in THF (2.0 mL) was added and the resulting mixture was stirred at room temperature for 24 h. Low boiling organics were removed under reduced pressure and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with a 10% aqueous sodium thiosulfate solution (10 mL) and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/acetone, 7:1) to afford N–H DKP **30** as a white solid (47 mg, 62%). Mp 318–320 °C; $[\alpha]_D^{19}$ −14.2 (*c* 0.90, MeOH); FTIR (KBr) ν_{max} 3296, 2965, 1678, 1459, 1395, 1238, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (br s, 1H, NH), 7.53 (d, *J* 7.4, 1H, Ar, CH), 7.30 (d, *J* 7.4, 1H, Ar, CH), 7.19–7.10 (m, 2H, Ar, CH), 6.09 (br s, 1H, NH), 3.91 (d, *J* 15.2, 1H, CC*H*HAr), 3.58 (ddd, *J* 11.8, 6.4, 6.4, 1H, NC*H*H), 3.42 (ddd, *J* 11.8, 7.6, 7.6, 1H, NCH*H*), 2.83 (ddd, *J* 13.2, 6.8, 6.8, 1H, CC*H*HCH_2), 2.67 (d, *J* 15.2, 1H, CCH*H*Ar), 2.62 (dd, *J* 10.4, 5.0, 1H, CH_2CH), 2.26 (dd, *J* 13.2, 10.4, 1H, C*H*HCH), 2.08–2.01 (m, 2H, $CH_2CH_2CH_2$), 1.98 (dd, *J* 13.2, 5.0, 1H, CH*H*CH), 1.96 (ddd, *J* 13.2, 7.6, 7.6, 1H, CCH*H*CH_2), 1.33 (s, 3H, CH_3), 1.14 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 173.0 (C=O), 168.5 (C=O), 140.7 (Ar, C), 136.4 (Ar, C), 126.4 (Ar, C), 120.6 (Ar, CH), 118.1 (Ar, CH), 117.5 (Ar, CH), 110.7

(Ar, CH), 103.3 (Ar, C), 65.9 (C-18), 59.6 (C-4), 49.1 (CH_2CH), 43.5 (NCH_2), 34.5 ($C(CH_3)_2$), 30.1 (CH_2CH), 28.6 (CCH_2CH_2), 27.9 (CH_3), 24.0 ($CH_2CH_2CH_2$), 23.8 (CH_3), 21.6 (CCH_2Ar); HRMS (ESI) calculated for $C_{21}H_{23}N_3O_2Na$ $[M+Na]^+$ 372.1688, found 372.1696.

*4.1.9. Synthesis of spiro-indoxyl **32** via **31**.* To a stirred solution of indole **29** (minor epimer) (95 mg, 0.208 mmol) in THF (10 mL) was added *m*-CPBA (67 mg, 70% in water, 0.271 mmol, 1.3 equiv) at room temperature and the resulting mixture was stirred for 1.5 h. Excess *m*-CPBA was quenched with two drops of dimethyl sulfide and the solvent was evaporated under reduced pressure. The residue was dissolved in a 1 M solution of sodium methoxide in methanol (16 mL) and the resulting mixture was heated to 85 °C for 1.5 h. The resulting yellow solution was cooled to room temperature and 3 M aqueous HCl (14 mL) was slowly added. Low boiling organics were removed in vacuo and the cloudy solution was diluted in water (10 mL). The solution was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried ($MgSO_4$). After concentration in vacuo, the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/acetone, 95:5) to afford spiro-indoxyl **32** (68 mg, 69% over two steps) as a fluorescent yellow oil. $[\alpha]_D^{21}$ −114 (*c* 0.90, $CHCl_3$); FTIR (film) ν_{max} 3351, 2952, 2877, 1693, 1618, 1469, 1325, 752; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* 7.0, 1H, Ar, CH), 7.42–7.35 (m, 6H, Ar, CH), 6.78–6.75 (m, 2H, Ar, CH), 4.91 (d, *J* 9.5, 1H, OC*H*HAr), 4.82 (br s, 1H, NH), 4.70 (d, *J* 9.5, 1H, OCH*H*Ar), 3.49–3.45 (m, 2H, NCH_2), 3.31 (dd, *J* 10.5, 7.0, 1H, C*H*CH_2), 3.05 (d, *J* 15.4, 1H, CC*H*HC), 2.77 (ddd, *J* 13.2, 6.8, 6.8, 1H, CC*H*HCH_2), 2.46 (d, *J* 15.4, 1H, CCH*H*C), 2.05–1.83 (m, 4H, $CH_2CH_2CH_2$, C*H*HCH, CCH*H*CH_2), 1.78 (dd, *J* 12.8, 7.0, 1H, CH*H*CH), 0.99 (s, 3H, CH_3), 0.81 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0 (C=O), 168.1 (C=O), 167.2 (C=O), 160.2 (Ar, C), 137.2 (Ar, CH), 133.4 (Ar, C), 130.0 (2×Ar, CH), 129.3 (Ar, CH), 128.6 (2×Ar, CH), 124.9 (Ar, CH), 119.5 (Ar, C), 118.6 (Ar, CH), 111.1 (Ar, CH), 78.3 (OCH_2Ph), 77.6 (C-2), 73.2 (C-9), 68.6 (C-12), 50.7 (CH_2CH), 46.2 ($C(CH_3)_2$), 43.8 (NCH_2), 31.5 (CCH_2C), 29.4 (CCH_2CH_2), 28.4 (CH_2CH), 24.8 ($CH_2CH_2CH_2$), 22.4 (CH_3), 19.0 (CH_3); HRMS (ESI) calculated for $C_{28}H_{29}N_3O_4Na$ $[M+Na]^+$ 494.2056, found 494.2062.

*4.1.10. Synthesis of (−)-brevianamide B (ent-**1**) via **33**.* The general procedure for cleavage of OBn protecting group was followed starting from **32** (16 mg, 0.034 mmol), LiCl (0.45 mL, 0.90 M in THF, 0.408 mmol, 12.0 equiv), SmI_2 (0.84 mL, 0.24 M in THF, 0.204 mmol, 6.0 equiv) and THF (1.0 mL). The crude residue from the N–O cleavage process was dissolved in CH_2Cl_2 (1.5 mL) and commercially available Dess/Martin periodinane (0.14 mL, 15% in CH_2Cl_2, 0.068 mmol, 2.0 equiv) was added at 0 °C. The resulting mixture was stirred at the same temperature for 2 h before a saturated aqueous sodium thiosulfate solution (2 mL) was added. CH_2Cl_2 (3 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×5 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 30:1) to give ent-**1** (6.0 mg, 48% over two steps) as a fluorescent yellow oil. $[\alpha]_D^{22}$ −147 (*c* 0.23, 2.5% HCO_2H in CH_2Cl_2), lit.[24] $[\alpha]_D^{25}$ −124 (*c* 0.81, 2.5% HCO_2H in CH_2Cl_2); FTIR (film) ν_{max} 3261, 2924, 2853, 1693, 1619, 1466, 1390, 1326, 1260, 753; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* 7.2, 1H, Ar, CH), 7.41 (m, 1H, Ar, CH), 6.84 (br s, 1H, NH), 6.83 (d, *J* 8.4, 1H, Ar, CH), 6.78 (t, *J* 7.2, 1H, Ar, CH), 5.08 (br s, 1H, NH), 3.50–3.44 (m, 2H, NCH_2), 3.27 (dd, *J* 9.6, 8.0, 1H, C*H*CH_2), 3.21 (d, *J* 15.4, 1H, CC*H*HAr), 2.73 (ddd, *J* 12.8, 6.8, 6.8, 1H, CC*H*HCH_2), 2.04–1.94 (m, 3H, $CH_2CH_2CH_2$, C*H*HCH), 1.85 (d, *J* 15.4, 1H, CCH*H*Ar), 1.87–1.76 (m, 2H, CH*H*CH, CCH*H*CH_2), 1.14 (s, 3H, CH_3), 0.84 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3 (C=O), 173.7 (C=O), 169.3 (C=O), 160.4 (Ar, C), 137.3 (Ar, CH), 125.0 (Ar, CH), 119.7 (Ar, C), 118.8 (Ar, CH), 111.4 (Ar, CH), 77.2 (C-2), 68.8 (C-12), 66.5 (C-9), 49.7 (CH_2CH), 46.5 ($C(CH_3)_2$), 43.9 (NCH_2), 36.1 (CCH_2C), 29.1 (CCH_2CH_2), 28.6 (CH_2CH), 24.9 ($CH_2CH_2CH_2$), 22.6 (CH_3), 20.3 (CH_3); HRMS (ESI) calculated for $C_{21}H_{23}N_3O_3Na$ $[M+Na]^+$ 388.1637, found 388.1626.

*4.1.11. Indole formylation to give **40**.* To a stirred solution of $POCl_3$ (0.28 mL, 3.06 mmol, 1.1 equiv) in dry DMF (4 mL) at 0 °C was added a solution of pyranoindole **39** (553 mg, 2.78 mmol) in dry DMF (3 mL). The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was then cooled to 0 °C and a solution of sodium hydroxide (1.11 g, 27.8 mmol, 10 equiv) in water (4 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for another 1.5 h. The solution was diluted with water (20 mL) and extracted with EtOAc (3×25 mL). The combined organic extracts were washed with brine (3×25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. This material was *directly* used in the next step without additional purification. An analytical sample was obtained by flash column chromatography (pet. ether/Et_2O, 9:1) affording the formylated indole intermediate as a pale brown oil. FTIR (film) ν_{max} 3238, 2977, 1636, 1446, 1135, 758; ^1H NMR (300 MHz, $CDCl_3$) δ 10.02 (br s, 1H, NH), 9.96 (s, 1H, CHO), 8.03 (d, *J* 8.4, 1H, Ar, CH), 7.76 (d, *J* 3.3, 1H, Ar, CH), 6.85 (d, *J* 8.4, 1H, Ar, CH), 6.71 (d, *J* 9.7, 1H, C*H*=CH), 5.68 (d, *J* 9.7, 1H, CH=C*H*), 1.46 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.6 (HC=O), 150.2 (Ar, C), 136.0 (Ar, C), 133.6 (Ar, C), 130.7 (*C*H=CH), 121.8 (Ar, CH), 119.8 (Ar, C), 118.7 (Ar, C), 116.4 (CH=*C*H), 113.6 (Ar, CH), 105.8 (Ar, C), 76.1 ($C(CH_3)_2$), 27.4 ($C(CH_3)_2$); HRMS (ESI) calculated for $C_{14}H_{13}NO_2Na$ $[M+Na]^+$ 250.0844, found 250.0847.

To a stirred solution of the crude indole-3-carboxaldehyde obtained above (27.8 mmol) in THF (13 mL) was added successively Boc_2O (668 mg, 3.06 mmol, 1.1 equiv) and DMAP (34 mg, 0.28 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred at room temperature for 1.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (pet. ether/EtOAc, 9:1) to give *N*-Boc formyl indole **40** (793 mg, 87% over two steps) as a white solid. Mp 158–160 °C; FTIR (KBr) ν_{max} 2978, 2931, 1753, 1672, 1259, 1137, 982; ^1H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H, CHO), 8.06 (s, 1H, Ar, CH), 8.05 (d, *J* 8.8, 1H, Ar, CH), 6.95–6.92 (m, 2H, Ar, CH, C*H*=CH), 5.64 (d, *J* 10.4, 1H, CH=C*H*), 1.67 (s, 9H, $C(CH_3)_3$), 1.46 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.6 (HC=O), 152.7 (Ar, C), 148.9 (C=O), 137.7 (Ar, CH), 132.6 (Ar, C), 127.5 (*C*H=CH), 122.3 (Ar, CH), 121.6 (Ar, C), 121.0 (Ar, C), 120.9 (CH=*C*H), 115.5 (Ar, CH), 109.5 (Ar, C), 87.5 ($C(CH_3)_3$), 75.0 ($C(CH_3)_2$), 27.9 ($C(CH_3)_3$), 27.1 ($C(CH_3)_2$); HRMS (ESI) calculated for $C_{19}H_{21}NO_4Na$ $[M+Na]^+$ 350.1368, found 350.1376.

*4.1.12. Aldol addition and elimination to give ester **41**.* To a stirred solution of *O*-SEM ester (1.52 g, 6.90 mmol, 3.0 equiv), in THF (40 mL) was added LHMDS (7.13 mL, 1.0 M in THF, 7.13 mmol, 3.1 equiv) at −78 °C. The resulting mixture was stirred at the same temperature for 30 min before a solution of formyl indole **40** (755 mg, 2.30 mmol), in THF (5 mL) was added. The solution was stirred at −78 °C for an additional 2 h and then quenched with a saturated aqueous ammonium chloride solution (10 mL). The solution was allowed to warm to room temperature and then concentrated in vacuo. The residue was partitioned between EtOAc (50 mL) and water (50 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (2×50 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford an intermediate β-hydroxy ester as a light brown oil. This material was directly used in the next step without additional purification.

To a solution of the aldol adduct obtained above (1.19 g, 2.17 mmol) in CH_2Cl_2 (30 mL) was added MsCl (0.34 mL, 4.34 mmol, 2.0 equiv)

and Et_3N (0.90 mL, 6.51 mmol, 3.0 equiv). After 1 h, DBU (1.62 mL, 10.8 mmol, 5.0 equiv) was added and the mixture was stirred at room temperature for 16 h. The mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and water (40 mL) was then added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

The residue was purified by flash column chromatography (pet. ether/Et_2O, 9:1) to yield (*Z*)-**41** and (*E*)-**41*** as an inseparable 1.3:1 mixture of stereoisomers (1.01 g, 88%), as a yellow oil. FTIR (film) ν_{max} 2977, 2953, 1721, 1370, 1250, 1153, 1075, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H, Ar, CH), 7.93 (d, J 1.0, 1H, Ar, CH*), 7.47 (d, J 8.4, 1H, Ar, CH), 7.26 (d, J 8.8, 1H, Ar, CH*), 7.21 (s, 1H, CH=C), 7.03 (d, J 10.0, 1H, CH=CHC-7*), 6.99 (d, J 10.0, 1H, CH=CHC-7), 6.88 (d, J 8.4, 1H, Ar, CH), 6.85 (d, J 8.4, 1H, Ar, CH*), 6.69 (d, J 1.0, 1H, CH=C*), 5.63 (d, J 10.0, 1H, CHC-7), 5.62 (d, J 10.0, 1H, CHC-7*), 5.26 (s, 2H, OCH_2O), 5.18 (s, 2H OCH_2O^*), 3.86 (s, 3H, OCH_3), 3.85–3.81 (m, 2H, $CH_2CH_2Si^*$), 3.78 (s, 3H, OCH_3^*), 3.71–3.67 (m, 2H, CH_2CH_2Si), 1.65 (s, 18H, $C(CH_3)_3$, $C(CH_3)_3^*$), 1.49 (s, 6H, C-7$(CH_3)_2$), 1.48 (s, 6H, C-7$(CH_3)_2^*$), 1.04–0.99 (m, 2H, CH_2Si^*), 0.87–0.83 (m, 2H, CH_2Si), 0.05 ($Si(CH_3)_3^*$), −0.12 ($Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (C=O), 164.1 (C=O*), 151.9 (Ar, C), 151.7 (Ar, C*), 149.8 (C=O*), 149.6 (C=O), 143.8 (CH=C*), 141.5 (CH=C), 131.6 (Ar, C*, Ar, C), 128.8 (Ar, CH), 126.9 (CH=CHC-7, CH=CHC-7*, Ar, CH*), 125.6 (Ar, C*), 124.7 (Ar, C), 121.6 (CHC-7*), 121.5 (CHC-7), 119.0 (Ar, CH), 118.7 (Ar, CH*), 115.1 (CH=C), 114.0 (Ar, CH), 113.7 (Ar, CH*), 113.5 (Ar, C), 113.3 (Ar, C*), 109.7 (Ar, C, Ar, C*), 109.6 (CH=C*), 95.1 (OCH_2O), 94.7 (OCH_2O^*), 84.2 ($C(CH_3)_3$), 83.8 ($C(CH_3)_3^*$), 74.9 (C-7), 74.8 (C-7*), 67.5 (CH_2CH_2Si), 66.6 ($CH_2CH_2Si^*$), 52.0 (OCH_3^*, OCH_3), 28.0 ($C(CH_3)_3$, $C(CH_3)_3^*$), 27.1 (C-7$(CH_3)_2$, C-7$(CH_3)_2^*$), 18.1 (CH_2Si^*), 18.0 (CH_2Si), −1.4 ($Si(CH_3)_3^*$), −1.7 ($Si(CH_3)_3$); HRMS (ESI) calculated for $C_{28}H_{39}NO_7SiNa$ [M+Na]$^+$ 552.2393, found 552.2389.

*4.1.13. Hydrolysis of ester **41** to give acid **42**.* To a stirred solution of enol ester **41** (1.17 g, 2.21 mmol) in a mixture THF/H_2O (42 mL, 2:1) was added LiOH/H_2O (464 mg, 11.0 mmol, 5.0 equiv) at room temperature under N_2 and the resulting mixture was stirred for 8 h. The volatile organics were then removed under reduced pressure and the residue was diluted with water (40 mL). The solution was acidified by slow addition of a 1 M aqueous potassium hydrogen sulfate solution to reach pH≈2. The resulting cloudy and oily solution was extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo.

The residue was purified by flash column chromatography (pet. ether/Et_2O, 95:5 to 1:1) to give (*Z*)-**42** and (*E*)-**42*** as an inseparable 1.3:1 mixture of stereoisomers (552 mg, 50%), as a yellow oil, along with recovered starting ester **41** (419 mg, 36%). FTIR (film) ν_{max} 2977, 2253, 1738, 1694, 1633, 1371, 1277, 985, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H, Ar, CH*), 8.26 (s, 1H, Ar, CH*), 7.48 (d, J 8.8, Ar, CH), 7.40 (s, 1H, CH=C), 7.32 (d, J 8.8, 1H, Ar, CH*), 7.05 (d, J 10.4, CH=CHC-7*), 6.99 (d, J 9.6, CH=CHC-7), 6.92 (s, 1H, CH=C*), 6.90 (d, J 8.8, 1H, Ar, CH), 6.88 (d, J 8.8, 1H, Ar, CH*), 5.64 (d, J 10.4, CHC-7), 5.64 (d, J 9.6, CHC-7*), 5.30 (s, 2H, OCH_2O), 5.22 (s, 2H OCH_2O^*), 3.88–3.84 (m, 2H, $CH_2CH_2Si^*$), 3.75–3.71 (m, 2H, CH_2CH_2Si), 1.66 (s, 9H, $C(CH_3)_3$), 1.65 (s, 9H, $C(CH_3)_3^*$), 1.50 (s, 6H, C-7$(CH_3)_2$), 1.49 (s, 6H, C-7$(CH_3)_2^*$), 1.06–1.02 (m, 2H, CH_2Si^*), 0.91–0.87 (m, 2H, CH_2Si), 0.06 ($Si(CH_3)_3^*$), −0.10 ($Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C=O), 167.1 (C=O*), 152.0 (Ar, C), 151.7 (Ar, C*), 149.7 (C=O*), 149.5 (C=O), 141.8 (CH=C*), 140.7 (CH=C), 131.5 (Ar, C*, Ar, C), 129.4 (Ar, CH), 128.9 (Ar, CH*), 127.0 (CH=CHC-7, CH=CHC-7*), 125.6 (Ar, C*), 124.5 (Ar, C), 121.4 (CHC-7*), 121.3 (CHC-7), 118.9 (Ar, CH), 118.4 (Ar, CH*), 117.4 (CH=C), 114.1 (Ar, CH), 113.9 (CH=C*), 113.8 (Ar, CH*), 113.4 (Ar, C), 112.4 (Ar, C*), 109.7 (Ar, CH, Ar, CH*), 95.3 (OCH_2O), 95.1 (OCH_2O^*), 84.3 ($C(CH_3)_3$), 84.0 ($C(CH_3)_3^*$), 74.8 (C-7, C-7*), 67.7 (CH_2CH_2Si), 66.8 (CH_2CH_2Si), 28.0 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3^*$), 27.1 (C-7$(CH_3)_2^*$), 27.0 (C-7$(CH_3)_2$), 18.0 (CH_2Si^*), 17.9 (CH_2Si), −1.4 ($Si(CH_3)_3^*$), −1.7 ($Si(CH_3)_3$); HRMS (ESI) calculated for $C_{27}H_{37}NO_7SiNa$ [M+Na]$^+$ 538.2237, found 538.2214.

*4.1.14. Peptide coupling to give **43**.* To a stirred solution of proline derivative **27** (407 mg, 1.41 mmol) and acid **42** (727 mg, 1.41 mmol), in dry MeCN (30 mL) was sequentially added DIPEA (0.37 mL, 2.11 mmol, 1.5 equiv) and HATU (590 mg, 1.55 mmol, 1.1 equiv), at room temperature. The resulting mixture was stirred at room temperature for 16 h. After concentration under reduced pressure, the resulting crude oil was dissolved in EtOAc (25 mL) and washed successively with a 1 N aqueous potassium hydrogen sulfate solution (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo.

The residue was purified by flash column chromatography (pet. ether/EtOAc, 4:1) to afford (*E*)-**43** (377 mg, 34%) as a light yellow oil followed by (*Z*)-**43** (483 mg, 44%) as a light yellow oil.

Data for (*E*)-**43**; $[\alpha]_D^{22}$ −33.0 (c 0.96, $CHCl_3$); FTIR (film) ν_{max} 3284, 3013, 2978, 1742, 1687, 1633, 1370, 1217, 1154, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.50 (s, 1H, NH), 7.48 (d, J 1.0, 1H, Ar, CH), 7.42–7.40 (m, 2H, Ar, CH), 7.35–7.30 (m, 3H, Ar, CH), 7.26 (d, J 8.0, 1H, Ar, CH), 7.05 (d, J 10.0, 1H, CH=CHC-7), 6.84 (d, J 8.5, 1H, Ar, CH), 6.09 (d, J 1.0, 1H, CH=C(OSEM), 5.62 (d, J 10.0, 1H, CHC-7), 5.16 (d, J 6.8, 1H, OCHHO), 5.07 (d, J 6.8, 1H, OCHHO), 4.93 (d, J 11.2, 1H, OCHHPh), 4.83 (d, J 11.2, 1H, OCHHPh), 4.67 (m, 1H, CH=$C(CH_3)_2$), 3.85–3.73 (m, 2H, OCH_2CH_2Si), 3.60 (m, 1H, $NCHHCH_2$), 3.11–3.06 (m, 2H, $NCHHCH_2$, CHHCH=C), 2.57 (dd, J 14.5, 6.0, 1H, CHHCH=C), 2.49 (m, 1H, $CCHHCH_2$),), 1.68–1.57 (m, 3H, $CCHHCH_2$, $CH_2CH_2CH_2$), 1.55 (s, 12H, $C(CH_3)_3$, CH_3), 1.53 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.02–0.98 (m, 2H, CH_2Si), −0.06 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C=O), 165.6 (C=O), 152.0 (Ar, C), 149.5 (CH=C(OSEM)), 149.3 (C=O), 135.6 (CH=$C(CH_3)_2$), 135.4 (Ar, C), 131.9 (Ar, C), 129.2 (2×Ar, CH), 128.4 (Ar, CH), 128.3 (2×Ar, CH), 127.0 (CHC-7), 125.3 (Ar, CH), 124.6 (Ar, C), 121.5 (CH=CHC-7), 118.8 (Ar, CH), 117.8 (CH=$C(CH_3)_2$), 113.8 (Ar, CH), 113.4 (Ar, C), 109.9 (Ar, C), 97.2 (CH=C(OSEM)), 93.2 (OCH_2O), 83.8 ($C(CH_3)_3$), 77.8 (OCH_2Ph), 74.8 (C-7), 70.5 (C-2), 67.2 (CH_2CH_2Si), 50.4 (NCH_2CH_2), 34.8 (CCH_2CH_2), 32.3 (CH_2CH=C), 27.8 ($C(CH_3)_3$), 27.4 (CH_3), 26.9 (CH_3), 25.9 (CH_3), 22.9 ($CH_2CH_2CH_2$), 18.1 (CH_3), 18.0 (CH_2Si), −1.4 ($Si(CH_3)_3$); HRMS (ESI) calculated for $C_{44}H_{59}N_3O_8SiNa$ [M+Na]$^+$ 808.3969, found 808.3979.

Data for (*Z*)-**43**; $[\alpha]_D^{22}$ −45.0 (c 1.1, $CHCl_3$); FTIR (film) ν_{max} 3310, 3016, 2979, 1736, 1682, 1630, 1370, 1216, 1154, 754; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H, NH), 7.94 (s, 1H, Ar, CH), 7.45 (d, J 7.0, 2H, Ar, CH), 7.37–7.32 (m, 3H, Ar, CH), 7.29 (d, J 8.0, 1H, Ar, CH), 6.98 (d, J 10.0, 1H, CH=CHC-7), 6.86 (d, J 8.5, 1H, Ar, CH), 5.87 (s, 1H, CH=C(OSEM)), 5.63 (d, J 10.0, 1H, CHC-7), 5.12 (d, J 6.8, 1H, OCHHO), 5.09 (m, 1H, CH=$C(CH_3)_2$), 4.99 (d, J 11.2, 1H, OCHHPh), 4.88 (d, J 11.2, 1H, OCHHPh), 4.87 (d, J 6.8, 1H, OCHHO), 3.78–3.68 (m, 2H, $CHHCH_2Si$, $NCHHCH_2$), 3.60–3.51 (m, 2H, $CHHCH_2Si$, $NCHHCH_2$), 3.14 (dd, J 15.0, 7.5, 1H, CHHCH=C), 2.79 (dd, J 15.0, 7.5, 1H, CHHCH=C), 2.50 (dd, J 13.0, 6.0, 1H, $CCHHCH_2$), 2.03 (td, J 13.0, 7.0, 1H, $CCHHCH_2$), 1.81–1.72 (m, 2H, $CH_2CH_2CH_2$), 1.79 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.64 (s, 9H, $C(CH_3)_3$), 1.49 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 0.95 (m, 1H, CHHSi), 0.82 (m, 1H, CHHSi), −0.05 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (C=O), 164.7 (C=O), 151.8 (Ar, C), 149.9 (C=O), 145.3 (CH=C(OSEM)), 136.6 (CH=$C(CH_3)_2$), 135.8 (Ar, C), 131.5 (Ar, C), 129.2 (2×Ar, CH), 128.4 (Ar, CH), 128.3 (2×Ar, CH), 126.9 (CHC-7), 126.7 (Ar, CH), 124.8 (Ar, C), 121.7 (CH=CHC-7), 118.4 (Ar, CH), 117.4 (CH=$C(CH_3)_2$), 113.7 (Ar, CH), 113.3 (Ar, C), 109.9 (Ar, C), 103.2 (CH=C(OSEM)), 92.2 (OCH_2O), 84.0 ($C(CH_3)_3$), 77.7 (OCH_2Ph), 74.8 (C-7), 70.5 (C-2), 67.4 (CH_2CH_2Si), 52.2 (NCH_2CH_2), 35.0 (CCH_2CH_2), 31.5 (CH_2CH=C), 28.1 ($C(CH_3)_3$), 27.2 (CH_3), 26.9 (CH_3), 26.3 (CH_3), 23.1 ($CH_2CH_2CH_2$), 18.2 (CH_3), 17.8 (CH_2Si), −1.6 ($Si(CH_3)_3$); HRMS (ESI) calculated for $C_{44}H_{59}N_3O_8SiNa$ [M+Na]$^+$ 808.3969, found 808.3951.

*4.1.15. SEM removal to give DKP **44**.* To a stirred solution of SEM enol ether **43** (200 mg, 0.255 mmol), in dry isopropanol (5.0 mL) was added CBr_4 (17.0 mg, 0.051 mmol, 0.2 equiv) at room temperature, and the resulting mixture was then heated to 50 °C for 24 h. The mixture was cooled and the solvent removed under reduced pressure.

The residue was purified by flash column chromatography (pet. ether/EtOAc, 4:1) to afford hydroxy-DKP **44** (100 mg, 60%) as a pale brown solid. Mp 80–81 °C; $[\alpha]_D^{21}$ +39 (*c* 1.6, $CHCl_3$); FTIR (film) ν_{max} 3330, 2978, 2930, 1740, 1647, 1371, 1155, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.64 (m, 2H, Ar, CH), 7.45–7.39 (m, 3H, Ar, CH), 7.30 (t, *J* 4.0, 2H, Ar, CH), 6.98 (d, J 10.0, 1H, CHC-7), 6.77 (d, *J* 8.4, 1H, Ar, CH), 5.60 (d, *J* 10.0, 1H, C*H*=CHC-7), 5.19 (d, *J* 9.2, 1H, OC*H*HPh), 5.07 (d, *J* 9.2, 1H, OCH*H*Ph), 5.03 (m, 1H, C*H*=C(CH_3)$_2$), 3.87 (br s, 1H, OH), 3.61 (d, *J* 14.0, 1H, CC*H*HAr), 3.35 (d, *J* 14.0, 1H, CCH*H*Ar), 3.28 (m, 1H, NC*H*HCH$_2$), 3.12 (m, 1H, NCH*H*CH$_2$), 2.41 (dd, *J* 14.0, 8.4, 1H, C*H*HCH=C), 2.19 (dd, *J* 14.0, 7.2, 1H, CH*H*CH=C), 1.76 (m, 1H, CC*H*HCH$_2$), 1.74 (s, 3H, CH_3), 1.63 (s, 9H, C(CH_3)$_3$), 1.57 (m, 1H, CH$_2$C*H*HCH$_2$), 1.55 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.00 (m, 1H, CH$_2$CH*H*CH$_2$), 0.73 (m, 1H, CCH*H*CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5 (C=O), 164.3 (C=O), 151.6 (Ar, C), 149.7 (C=O), 137.5 (CH=*C*(CH_3)$_2$), 135.5 (Ar, C), 131.6 (Ar, C), 129.4 (2×Ar, CH), 128.7 (Ar, CH), 128.4 (2×Ar, CH), 128.1 (Ar, CH), 127.0 (*C*H=CHC-7), 125.3 (Ar, C), 121.4 (CHC-7), 119.8 (Ar, CH), 117.1 (*C*H=C(CH_3)$_2$), 113.4 (Ar, CH), 112.7 (Ar, C), 109.4 (Ar, C), 90.6 (C-3), 83.7 (*C*(CH_3)$_3$), 78.6 (OCH$_2$Ph), 74.8 (C-7), 67.8 (C-8a), 44.2 (N*C*H$_2$CH$_2$), 36.3 (*C*H$_2$CH=C), 33.6 (C*C*H$_2$CH$_2$), 33.5 (C*C*H$_2$C-4), 27.9 (C(*C*H$_3$)$_3$), 27.3 (CH_3), 26.8 (CH_3), 25.9 (CH_3), 18.9 (CH$_2$*C*H$_2$CH$_2$), 18.0 (CH_3); HRMS (ESI) calculated for $C_{38}H_{45}N_3O_7Na$ $[M+Na]^+$ 678.3155, found 678.3146.

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34. Although all of our NMR data matched those of the synthetic sample described by Williams, we found an apparent discrepancy between our ^{13}C NMR data and those originally reported by the Mata group in Ref. 8. Although the original paper indicates NMR spectra were recorded in DMSO-d_6, it later transpired that MeOH-d_4 was actually used. This accounts for minor differences in chemical shift throughout the spectrum. Also there is an apparent misprint for a signal at δ=125.6, which appears at δ=118.6 in our spectrum, and at δ=118.7 in that of Williams. We are grateful to both Professor Williams and Professor Mata for clarfying these issues. Full comparison tables can be found as ESI to our initial communication.
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