Rhodium catalysed conjugate addition of a chiral alkenyltrifluoroborate salt: the enantioselective synthesis of hermitamides A and B

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The concise enantioselective synthesis of hermitamides A and B is presented utilising a rhodium catalysed conjugate addition reaction to introduce the side chain and chiral information in a single step *via* an alkenyltrifluoroborate salt.

Introduction

Marine natural products from *Lyngbya mujuscula* cyanobacteria have provided a diverse set of natural products including lyngbic acid and the malyngamide family, a range of nitrogen containing lipopeptides derived from amino acid metabolism (Fig. 1).[1] The amide portion of the malyngamide family contains varied functionality such as amino acids, lactone, amide, alkaloid or pyrrole affording a number of further subclasses including the hermitamide and isomalyngamide series.[2] It is important to note that the 7-methoxytetradec-4-enoic acid unit is usually present in these materials and the (7*S*)-stereoisomer (lyngbic acid) has been the focus of most synthetic interest.[3] Apart from lyngbic acid, a small range of malyngamide natural products have been prepared, including the synthesis of serinol-derived malyngamides by Chen *et al.*[4] and the enantioselective synthesis of malyngamide U by Li *et al.*[5] The illustrated malyngamide X contains the first isolated (7*R*)-lyngbic acid side chain and is also connected to a novel tripeptide backbone.[6] The total synthesis of malyngamide X has recently been reported by Isobe *et al.*[7] The synthesis of hermitamides A and B as racemic mixtures was reported by Virolleaud *et al.* in 2006.[8] The group employ a ruthenium catalysed cross-metathesis reaction in the key step to install the alkene fragment. In this paper a concise, enantioselective synthesis of the hermitamide natural product family is presented that utilises a unique rhodium catalysed conjugate addition of a chiral organometallic donor to an acrylamide acceptor to assemble the required functionalised carbon chain in a single step.

The concept involves the retrosynthesis of hermitamide A (**1**) and B (**2**) to synthons that could be accessed *via* catalytic conjugate addition methodology. The transition-metal catalysed conjugate addition of organometallics to activated alkenes is an important tool for organic synthesis.[9] For the addition of aryl and alkenyl groups, the elegant rhodium-catalysed addition of organoboron reagents to α,β-unsaturated carbonyl acceptors, pioneered by Hayashi and Miyaura offers significant advantages in terms of accessibility of reagents, efficiency and operational simplicity.[10] As illustrated in Fig. 2, a simple disconnection of hermitamide A

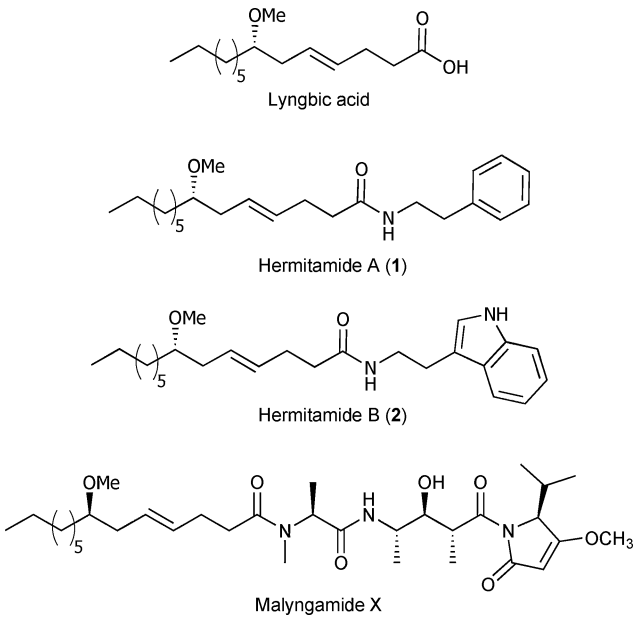

Fig. 1 Natural products from *L. mujuscula* cyanobacteria.

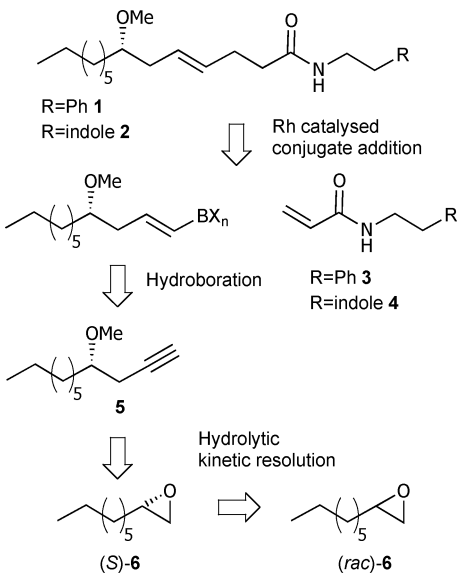

Fig. 2 Synthetic strategy.

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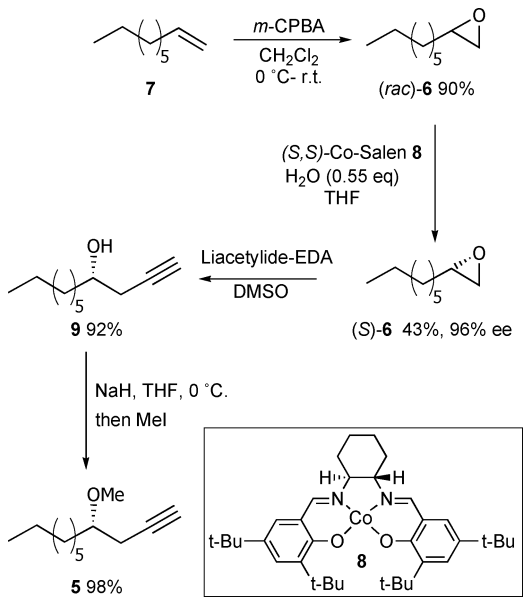
or B reveals an alkenylboron donor and an acrylamide acceptor (**3** or **4**). The chiral alkenylboron fragment required for the key conjugate addition was envisioned to arise from the (*E*)-selective hydroboration of alkyne **5**. Access to enantioenriched **5** will be addressed using the elegant hydrolytic kinetic resolution strategy developed by Jacobsen to provide enantiopure epoxide **6**, followed by a regioselective ring opening with a suitable metal acetylide and subsequent methylation.[11]

Results and discussion

The racemic epoxide **6** required for the hydrolytic kinetic resolution step was prepared in high yield by the *m*-CPBA epoxidation of 1-nonene **7**. As monosubstituted aliphatic epoxides are excellent substrates for the hydrolytic kinetic resolution process, the standard experimental procedure was followed.[12] Thus, the chiral cobalt-salen ligand complex was formed by stirring the commercial cobalt(II) complex **8** in air with acetic acid for one hour. The dark brown solid remaining after removal of solvent was resuspended in neat epoxide (*rac*)-**6** and cooled to 0 °C. Finally water was added dropwise and the solution stirred for 72 h at ambient temperature. The crude reaction mixture was then distilled to afford the chiral epoxide (*S*)-**6** as a colourless oil in 43% yield. The enantioselectivity was confirmed as being greater than 96% e.e. by comparison with the literature optical rotation as well as chiral HPLC analysis of the product from ring opening with 2-naphthalene thiol.[13] Addition of lithium acetylide complexed with ethylene diamine led to the isolation of the homopropargylic alcohol **9** in 92% yield. The alcohol was methylated in 98% yield by treatment with sodium hydride and then methyl iodide to set the stage for the key hydroboration-conjugate addition sequence (Scheme 1).

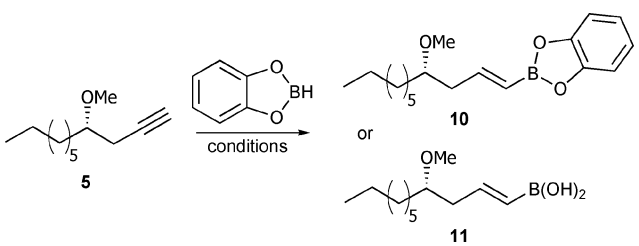


Scheme 1 Hydrolytic kinetic resolution strategy.

A method for the tandem rhodium catalysed hydroboration-conjugate addition has been reported by Hayashi *et al.*[14] However, this method was not transferable to the alkyne substrate **5**. A range of conditions were screened with no product being isolated. Further attempts at hydroboration with catecholborane (to prepare **10**) or $BHBr_2.SMe_2$ followed by hydrolysis (to prepare **11**) were also unsuccessful (Table 1). All NMR traces contained a complex mixture of products with no observed peak in the ^{11}B decoupled NMR spectra. It is plausible that the methoxy group could undergo elimination under the reaction conditions to give an enyne side product previously observed on treatment with strong bases.[15]

With a view to developing a mild protocol for preparing an isolatable chiral alkenylboron species, a route of trapping an organometallic species with pinacolborane was considered. Knochel has shown previously that pinacolborane can be used as an improved hydroboration reagent, which affords air and moisture stable boronic esters with good yields and selectivity.[16] One potential route to the sensitive alkenylpinacol boronic ester entails the trapping of the appropriate alkenylzirconium species with pinacolborane. This is an attractive method as the alkenylzirconium intermediate can be formed *in-situ* by reaction of a terminal

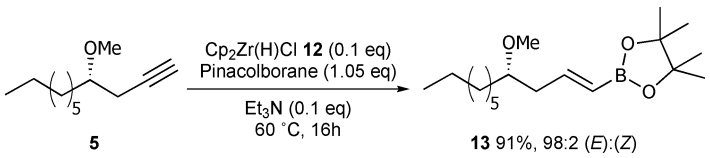
Table 1 Attempts at hydroboration



Entry	Borane source	Temperature/°C	Time	% Conv.[a]
1[b]	Catecholborane (Neat)	25	48 h	0
2[b]	Catecholborane (Neat)	80	3 h	0
3[b]	Catecholborane (0.5 M in THF)	25	72 h	0
4[b]	Catecholborane (0.5 M in THF)	70	24 h	<5%
5[b]	Catecholborane (0.5 M in THF)	100 microwave	20 min	<5%
6[c]	$BHBr_2{\cdot}SMe_2$	0	3 h	0

[a] Conversion by ^1H NMR. [b] Typical reaction conditions: terminal alkyne (0.5 mmol), catecholborane source (2 eq.), temp °C. [c] Reaction conditions: alkyne (1.0 mmol), $BHBr_2{\cdot}SMe_2$ 1 M in CH_2Cl_2 (1.05 eq.) 0 °C, 3 h, followed by diethyl ether/H_2O (10/1), 0 °C, 30 min.

alkyne with chloridobis(η^5-cyclopentadienyl)hydridozirconium (Schwartz Reagent) **12**.[17] Early studies of this type of reaction were undertaken by Srebnik *et al* and high yields of product were noted with a useful range of substrates.[18] Wang *et al* determined that with bulky silyl protected propargylic ethers an undesirable Zr–O bond could form leading to problems with catalyst turnover and resulting in more of the undesired (*Z*)-isomer.[19] This could be rectified by heating the reaction mixture to 60 °C, and adding an amine base such as DMAP or triethylamine to remove this interaction giving the (*E*)-zirconiate species. Trapping this compound with pinacolborane provides optimum yields and excellent selectivity for the (*E*)-pinacolboronate isomer. Following this protocol, alkyne **5** was treated with 0.1 equivalents of Schwartz reagent and 0.1 equivalents of anhydrous triethylamine in neat pinacolborane and heated to 60 °C for 16 h. The reaction flask was covered to reduce exposure to light as the Schwartz reagent is sensitive to decomposition (Scheme 2). The reaction occurred with complete conversion to the chiral alkenylpinacol boronic ester **13**. After purification by stirring with hexane to precipitate excess pinacol and filtering through a short silica column eluting with hexanes, a 91% yield of **13** with high (*E*) : (*Z*)-selectivity was obtained. Using this route the reaction was reproducible on a multigram scale.

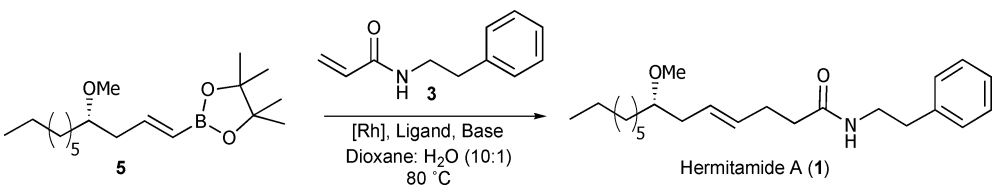


Scheme 2 Synthesis of chiral alkenylboron derivative.

With the desired alkenylboron species in hand, rhodium-catalysed conjugate additions could now be investigated. Both phenylethylamine and tryptamine acrylamide (**3** and **4**) were prepared by direct reaction of the appropriate amine with acryloyl chloride and a suitable base.[20] There are a number of reported examples in which pinacolboronate reagents are used successfully in rhodium-catalysed conjugate addition processes.[21] Using a range of established conditions the addition of chiral alkenylpinacol boronic ester **13** to phenylethylacrylamide **3** in the presence of various rhodium sources gave no conversion to hermitamide A (Table 2, entries 1–4). The addition of a range of bases such as Na_2CO_3, LiOH and NaF and triethylamine in order to form the more reactive boronate species gave no discernible improvement in the reaction (Table 2, entries 5–10). A further attempt at activating the alkenylboron derivative by treatment with methyl lithium prior to reaction gave a trace of product formation, although the predominant species by NMR were still the pinacolboronic ester and acrylamide starting materials (Table 2, entry 11).[22]

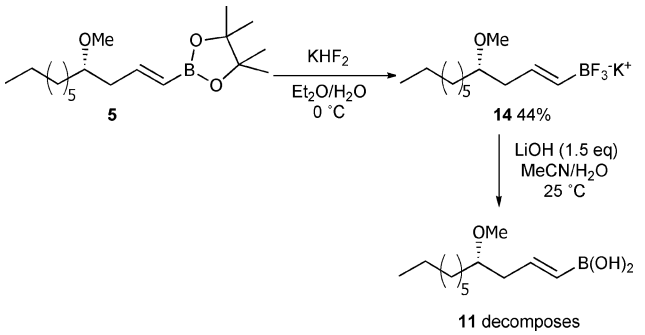
It was clear that a more reactive and stable boronate species would need to be employed. Removal of the diol protecting group in boronic esters is difficult with methods generally involving oxidative cleavage of the diol or harsh hydrolytic protocols.[23] In general all deprotection reactions suffer from incomplete conversions or problems in separating the desired boronic acid from a large excess of transesterification partner.[24] In contrast there is significant literature precedent for the conversion of pinacolboronic esters to the corresponding potassium trifluoro(organo)borate salts and these are commonly air-stable, crystalline solids.[25] Subjecting the chiral alkenylpinacol boronic ester **5** to potassium hydrogen difluoride resulted in a modest yield of the chiral alkenyltrifluoroborate salt **14** as shown in Scheme 3. The precipitated salts were washed successively with chilled or room temperature acetone, rather than hot solvent as previously described. Upon chilling in a freezer for three days multigram quantities of product could be collected as a crystalline solid and stored until required. NMR studies showed a single component by multinuclear analysis and no pinacol was observed after recrystallisation. For completeness we attempted to prepare the corresponding alkenylboronic acid **11** using the hydrolysis

Table 2 Rhodium catalysed conjugate addition of pinacolboronate

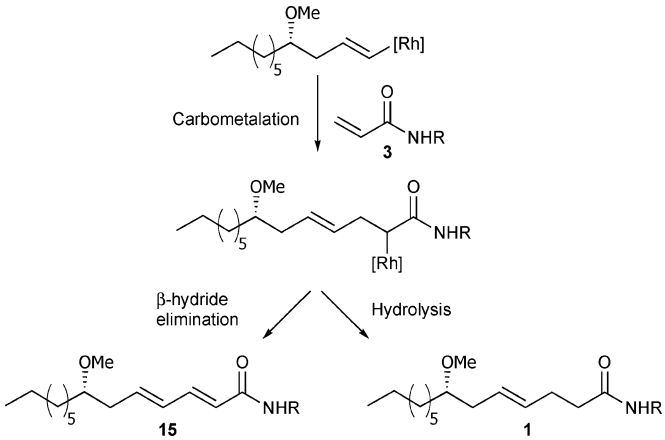


Entry[a]	[Rh]	Ligand	Base	% Conversion[b]
1	$[Rh(acac)(eth)_2]$	cod 10 mol%	—	0
2	$[Rh(cod)_2][BF_4]$	—	—	0
3	$[Rh(nbd)_2][BF_4]$	—	—	0
4	$[Rh(cod)Cl]_2$	—	—	0
5	$[Rh(cod)Cl]_2$	cod 10 mol%	Na_2CO_3 1 eq.	0
6	$[Rh(cod)Cl]_2$	cod 10 mol%	NaOH 1 eq.	0
7	$[Rh(cod)Cl]_2$	cod 10 mol%	LiOH 1 eq.	0
8	$[Rh(cod)Cl]_2$	cod 10 mol%	NaF 1 eq.	0
9	$[Rh(cod)Cl]_2$	cod 10 mol%	TEA	0
10	$[Rh(cod)OH]_2$	cod 10 mol%	Na_2CO_3 1 eq.	0
11[c]	$Rh(cod)OH]_2$	cod 10 mol%	MeLi	5%

[a] Typical reaction conditions: N-phenylethyl acrylamide (0.25 mmol), (*S,E*)-2-(4-methoxyundec-1-enyl)-pinacolboronic ester (2 eq.), followed by rhodium catalyst (5 mol%), ligand, dioxane/H_2O (10/1), 80 °C, 16 h. [b] Conversion by ^{1}H NMR spectroscopy. [c] MeLi (2 eq.) added to boronic ester at 0 °C prior to reaction.



Scheme 3 Synthesis of potassium trifluoroborate salt.



Scheme 5 Competition between β-hydride elimination and hydrolysis.

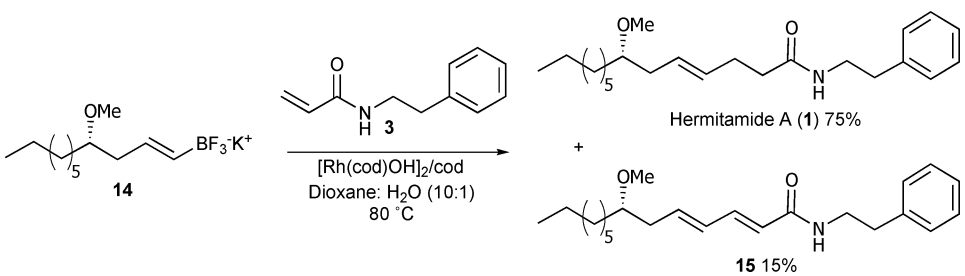
protocol reported by Yuen *et al.*[26] Thus, the chiral alkenyltrifluoroborate salt **14** was treated with a solution of lithium hydroxide in acetonitrile. Following the reported procedure afforded an intractable white gum that darkened on standing. The material could not be successfully purified and was unsuitable for further transformations.

It has been reported that potassium trifluoro(organo)borate salts offer practical advantages in terms of reactivity and stability for rhodium catalysed conjugate addition reactions.[27] Pleasingly, the reaction of phenylethylacrylamide **3** with two equivalents of chiral alkenyltrifluoroborate salt **14** in the presence of $[Rh(cod)(OH)_2]$ and 10 mol% cyclooctadiene as the ligand resulted in complete conversion to two new products (Scheme 4). Upon purification by column chromatography, hermitamide A (**1**) was isolated as a colourless oil in 75% yield. The spectral data and optical rotation of synthetic hermitamide A were in agreement with those of the natural product.[2] The minor product from the reaction was isolated in 15% yield and identified by ^{1}H NMR and 2D correlation experiments as the diene **15**. This side-product results from a β-hydride elimination of the α-rhodium carbonyl intermediate formed at the carbometalation step and is in competition with the favoured hydrolysis pathway (Scheme 5).[28]

The β-hydride elimination of the α-rhodium carbonyl intermediates arising from the conjugate addition of aryl boronic acids has been investigated in detail by Zou *et al.*[29] The systematic study revealed a number of factors that affected the product distribution including; the supporting ligand on rhodium, the ratio of aryl boronic acid to α,β-unsaturated carbonyl and the pH value of the aqueous phase. We examined other catalyst-ligand systems and reaction conditions in an attempt to eliminate the β-hydride elimination pathway and improve the yield of conjugate addition product. Using other neutral catalysts such as $[Rh(acac)(C_2H_4)_2]$ and $[Rh(nbd)Cl]_2$ gave no improvement in selectivity (Table 3, entries 2–4). Other rhodium complexes using achiral bidentate phosphine ligands such as dppb, and dppf led to a lower conversion to product, suggesting that diene ligands are superior to phosphine based systems for this particular reaction (Table 3, entries 5–7). Using 1.5 equivalents of trifluoroalkenylborate salt **14** with optimal ligand catalyst permutation $[Rh(cod)OH]_2$ with 10 mol% cod afforded a 60 : 40 mixture of hermitamide A (**1**) to β-hydride elimination product **15**. The only effective method of suppressing formation of **15** was by using at least four equivalents of the chiral trifluoroalkenylborate salt (Table 3, entry 10). Under these conditions hermitamide A (**1**) was isolated in 81% yield after column chromatography.

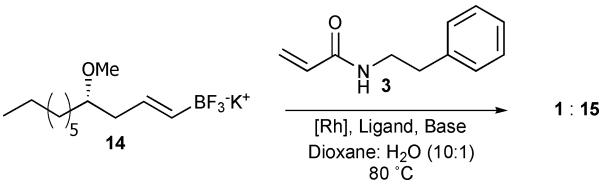
With a successful approach to hermitamide A (**1**) demonstrated, we turned our attention to the synthesis of hermitamide B (**2**). The same chiral trifluoroalkenylborate salt **14** is employed, the synthesis necessitates only a variation in acceptor to the tryptamine acrylamide derivative **4**. Using the original conditions for synthesis of hermitamide A; 2 mol% rhodium catalyst, 10 mol% cod, dioxane : water 10 : 1 gave a low conversion to product with a number of unidentified side-products that could not be successfully removed by column chromatography. Upon changing the conditions to use a higher catalyst loading, 5 mol% rhodium and four equivalents of trifluoroalkenylborate salt **14**, hermitamide B (**2**) was isolated in 36% yield after column chromatography. The spectral data and optical rotation of synthetic hermitamide B (**2**) were identical with those of the natural product (Scheme 6).[2]

In conclusion, a unique approach to the hermitamide natural product family has been successfully developed using a rhodium catalysed conjugate addition of a chiral potassium trifluoroalkenylborate donor to introduce the side chain and



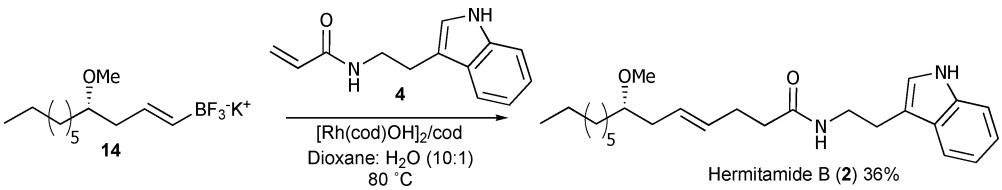
Scheme 4 Rhodium catalysed conjugate addition of chiral organotrifluoroborate salt.

Table 3 Reaction optimisation



Entry[a]	[Rh]	Ligand	Base	% Conv **1**[b,c]
1	$[Rh(acac)(eth)_2]$	cod 10 mol%	—	12
2	$[Rh(cod)_2][BF_4]$	—	—	62
3	$[Rh(nbd)Cl]_2$	—	—	0
4	$[Rh(nbd)_2][BF_4]$	—	—	22
5	$[Rh(cod)OH]_2$	cod 10 mol%	—	83 (72%)
6	$[Rh(cod)OH]_2$	dppb 5 mol%	—	40
7	$Rh(cod)OH]_2$	dppf 5 mol%	—	37
8	$Rh(cod)OH]_2$	cod 10 mol%	NaF 1 eq.	53
9	$Rh(cod)OH]_2$	cod 10 mol%	LiOH 1 eq.	15
10[d]	$Rh(cod)OH]_2$	cod 10 mol%	—	91 (81%)

[a] Typical reaction conditions: N-phenylethyl acrylamide **3** (0.25 mmol), **14** (2 eq.), followed by rhodium catalyst (2 mol%), ligand, dioxane/H_2O (10/1), 80 °C, 16 h. [b] Conversion by ^1H NMR spectroscopy. [c] Isolated yields in parentheses. [d] Using four equivalents of **14.**



Scheme 6 Synthesis of hermitamide B by rhodium catalysed conjugate addition.

chiral information in a single step. The application of chiral organometallic donors in rhodium catalysed conjugate addition offers opportunities for chemists to consider new synthetic strategies and access unique intermediates. This research is ongoing in our laboratory and further applications of chiral organoboron donors in catalytic conjugate addition reactions will be reported in due course.

Experimental

N-Phenethyl-acrylamide (3)

Phenethylamine (2.42 g, 20 mmol) was charged to a 50 mL round bottomed flask and dissolved in anhydrous dichloromethane (25 mL). The resulting solution was cooled to 0 °C (ice/water). To the cooled flask was added anhydrous triethylamine (2.12 g, 21 mmol) followed by dropwise addition of acryloyl chloride (1.90 g, 21 mmol in 5 mL dichloromethane) with vigorous stirring. The mixture was stirred for a further 3 h at 4 °C. Upon warming to room temperature reaction was quenched with 1 M HCl solution (30 mL) and the organic phase extracted, washed with 1 M NaOH (30 mL) then brine (30 mL), dried ($NaSO_4$) and concentrated to give orange oils. The crude mixture was eluted through a short pad of silica gel (6 : 1 Petrol : EtOAc) gave the title product as a light yellow oil (Yield 3.26 g, 93%); R_f (petrol : ethyl acetate, 3 : 1) 0.15; ν_{max} (neat)/cm^{-1}; 3279 (N–H), 3028,1657 (C=O), 1625, 985, 958 (C=CH_2); δ_H (300 MHz; $CDCl_3$), 7.22–7.10 (5H, m, Ph); 6.16 (1H, dd, *J* 17.0, 1.5 Hz, CHCH_2); 6.0 (1H, dd, *J* 17.0, 10.0 Hz, C*H*CH_2); 5.52 (1H, br s, N*H*); 5.52 (1H, dd, *J* 10.2, 1.1 Hz, CHCH_2); 3.49 (2H, q, *J* 7.2 Hz, CH_2); 0.87 (3H, t, *J* 6.8 Hz, CH_2). δ_C (75.5 MHz; $CDCl_3$); 138.7, 165.5, 130.8, 128.6, 128.5, 126.4, 126.1, 40.6, 35.4. All data in correspondence with literature values.[30]

N-[2-(1*H*-Indol-3-yl)-ethyl]-acrylamide (4)

Tryptamine (2.40 g, 15 mmol) was charged to a 100 mL round bottomed flask and dissolved in anhydrous dichloromethane (40 mL). The resulting solution was cooled to 0 °C (ice/water). To the cooled flask anhydrous triethylamine (1.62 g, 16 mmol) was added followed by dropwise addition of acryloyl chloride (1.44 g, 16 mmol in 5 mL dichloromethane) with vigorous stirring. The mixture was stirred for a further 3 h at 4 °C. Upon warming to room temperature reaction was quenched with 1 M HCl solution (50 mL) and the organic phase extracted, washed with 1 M NaOH (50 mL) then brine (50 mL), dried ($NaSO_4$) and concentrated to give orange oils. The crude mixture was eluted through a short pad of silica gel (2 : 1 Petrol : EtOAc) to give the title product as a yellow oil (Yield 2.06 g, 64%); R_f (petrol : ethyl acetate, 1 : 1) 0.1; ν_{max} (neat)/cm^{-1}; 3439 3309 (N–H), 3022,1667 (C=O), 1628, 976, 911 (C=CH_2); δ_H (300 MHz; $CDCl_3$), 8.20 (1H, br s, N*H* indole); 7.61 (1H, d, *J* 7.9 Hz, C*H* indole); 7.38 (1H, d, *J* 7.9 Hz, C*H* indole); 7.22 (1H, t, *J* 7.9 Hz, C*H* indole); 7.13 (1H, t, *J* 7.9 Hz, C*H* indole); 7.03 (1H, s, C*H* indole); 6.25 (1H, dd, *J* 17.0, 1.5 Hz, CHCH_2); 6.0 (1H, dd, *J* 17.0, 10.0 Hz, C*H*CH_2); 5.68 (1H, br s, N*H*); 5.60 (1H, dd, *J* 10.0, 1.5 Hz, CHCH_2); 3.69 (2H, q, *J* 6.8, CH_2); 3.02 (2H, t, *J* 6.8 Hz, CH_2); δ_C (75.5 MHz; $CDCl_3$); 165.5, 136.4, 130.9, 127.3, 126.2, 122.2, 122.0, 119.5, 118.6, 112.8, 111.2, 39.7, 25.2; HRMS (ESI^-) *calcd* for $C_{13}H_{14}N_2O_1$ [M + H^+] *m/z*

213.1028 found: *m/z* 213.1036. All data in correspondence with literature values.[31]

2-Heptyloxirane (*rac*-6)

1-Nonene **7** (25.0 g, 0.20 mol) was charged to a 500 mL 3-necked round bottomed flask equipped with nitrogen inlet and pressure equalising dropping funnel, and dissolved in anhydrous dichloromethane (150 mL). The resulting solution was cooled to 0 °C (ice/water). The dropping funnel was charged with a filtered solution of 75% *meta*-chloroperoxybenzoic acid (62.0 g, 0.35 mol) in dichloromethane (200 mL). The solution was added dropwise over 45 min at 4 °C. The mixture was stirred for a further 3 h at 4 °C and 1 h at room temperature. The reaction was quenched with 10% potassium thiosulfate (300 mL) and extracted with saturated sodium bicarbonate solution (2 × 250 mL) and brine (250 mL), dried ($MgSO_4$) and concentrated to give crude product. The epoxide was distilled under high vacuum (55 °C, 5 mmHg) to give the title product as a colourless oil (Yield 25.6 g, 90%); R_f (petrol : ethyl acetate, 20 : 1) 0.6; ν_{max} (neat)/cm^{-1}; 2958, 2930, 2858 (C–H), 916, 838 (C–O epoxide); δ_H (300 MHz; $CDCl_3$), 2.90–2.80 (1H, m, C*H*OCH_2); 2.68 (1H, dd, *J* 4.9, 4.1 Hz, CHOCH_2); 2.4 (1H, dd, *J* 4.9, 3.0 Hz, CHOCH_2); 1.60–1.19 (12H, m, CH_2); 0.83 (3H, t, *J* 6.6 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$); 52.1, 46.8, 32.3, 31.6, 29.2, 29.0, 25.8, 22.4, 13.8. All data in correspondence with literature values.[32]

(*S*)-(−)-Heptyloxirane ((*S*)-6)

(*S,S*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) **8** (0.30 g, 0.50 mmol) was charged to a 25 mL round bottomed flask. Dichloromethane (2 mL) and acetic acid (300 μL) were added and the red solution stirred in air for 30 min. The resulting brown solution was concentrated *in vacuo* to give a brown residue. The active catalyst was dissolved in neat 2-heptyloxirane (*rac*-**6**) (14.2 g, 100 mmol) with anhydrous THF (2 mL) and the flask cooled to 0 °C (ice/water). Water (1.0 mL, 55 mmol, 0.55 eq.) was added dropwise. The mixture was capped with a greased glass stopper and stirred for 48 h at 23 °C. After this time the reaction flask was attached to a short path distillation head and the volatiles distilled under high vacuum (55 °C, 5 mmHg). The recovered epoxide was passed through a short silica pad to removed residual water and THF to give the title product as a colourless oil (Yield 6.12 g, 43%, 86% theoretical maximum); R_f (petrol : ethyl acetate, 20 : 1) 0.6; $[\alpha]^{20}_D = -8.7°$ (*c* = 1.15, $CHCl_3$); ν_{max} (neat)/cm^{-1}; 2958, 2930, 2858 (C–H), 916, 838 (C–O epoxide); δ_H (300 MHz; $CDCl_3$), 2.90–2.80 (1H, m, C*H*OCH_2); 2.68 (1H, dd, *J* 4.9, 4.1 Hz, CHOCH_2); 2.4 (1H, dd, *J* 4.9, 3.0 Hz, CHOCH_2); 1.60–1.19 (12H, m, CH_2); 0.83 (3H, t, *J* 6.6 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$); 52.1, 46.8, 32.3, 31.6, 29.2, 29.0, 25.8, 22.4, 13.8. All data in correspondence with literature values.[32]

(*S*)-1-(Naphthalen-2-ylthio)nonan-2-ol

2-Naphthalene thiol (0.336 g, 2.1 mmol) was charged to a 25 mL round bottomed flask and dissolved in anhydrous methanol (10 mL). The resulting solution was cooled to 0 °C (ice/water). To the cooled flask, anhydrous triethylamine (0.253 g, 2.5 mmol) was added followed by (*S*)-2-heptyloxirane ((*S*)-**6**) (0.280 g, 2.0 mmol) with vigorous stirring. The mixture was stirred for a further 16 h at 4 °C. Upon warming to room temperature silica was added (0.50 g) and the mixture was concentrated. Elution by column chromatography (40 : 1–20 : 1 gradient petrol: diethyl ether) gave the title product as a white solid (Yield 0.206 g, 34%); R_f (petrol : ethyl acetate, 40 : 1) 0.10; mp (hexane) 65–67 °C; $[\alpha]^{20}_D = -27°$ (*c* = 1.50, $CHCl_3$); ν_{max} (KBr)/cm^{-1}; 3426 (O–H), 2927 (C–H); 2856 (C–S–Ar); δ_H (300 MHz; $CDCl_3$), 7.86–7.70 (4H, m, naphthalene); 7.54–7.41 (3H, m, naphthalene); 3.78–3.66 (1H, m, C*H*OH); 3.26 (1H, dd, *J* 14.0, 3.9 Hz, C*H*S); 2.94 (1H, dd, *J* 14.0, 8.7 Hz, C*H*S); 2.34 (1H, br s, O*H*); 1.63–1.39 (3H, m, CH_2), 1.39–1.17 (9H, m, CH_2); 0.87 (3H, t, *J* 6.8 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$); 134.1, 133.15, 132.4, 128.6, 128.1, 127.8, 127.6, 127.1, 126.6, 125.9, 69.4, 42.1, 36.1, 31.7, 29.5, 29.1, 25.6, 22.6, 14.0; HRMS (ESI^+) *calcd* for $C_{19}H_{26}O_1S_1Na_1$ [M + Na^+] *m/z* 325.1602 found: *m/z* 325.1594; Daicel Chiralcel OD-H, hexane/propan-2-ol (99.9 : 0.01), 1 mL min^{-1}, t_R = 37.95 (*S*) and 53.3 (*R*) (96% e.e.).

(*S*)-Undec-1-yn-4-ol (9)

Lithium acetylide EDA complex (8.38 g, 91 mmol) was charged to a 250 mL round bottomed flask and suspended in anhydrous dimethysulfoxide (45 mL). The resulting reaction mixture was immersed in a room temperature water bath. To the brown-black suspension was added (*S*)-2-heptyloxirane ((*S*)-**6**) (4.98 g, 35.0 mmol) in one portion with vigorous stirring. The mixture was stirred for a further 2 h at 23 °C. Upon completion the suspension was poured into 4 °C water (150 mL) and stirred for 30 min to quench excess acetylide. This was then filtered through a pad of Celite® washing with diethyl ether (3 × 100 mL). The combined washings were then extracted with water (2 × 100 mL), brine (2 × 150 mL), dried ($NaSO_4$) and concentrated. Final traces of DMSO and water were removed through a short silica pad to give the title product as a golden yellow oil (yield 5.420 g, 92%); R_f (petrol : ethyl acetate, 9 : 1) 0.2; $[\alpha]^{20}_D = -23.0°$ (*c* = 1.23, $CHCl_3$); ν_{max} (KBr)/cm^{-1}; 3401 (O–H), 3300 (C–H alkyne); 2120 (C≡C); δ_H (300 MHz; $CDCl_3$), 3.69 (1H, quint, *J* = 5.5, C*H*OH); 2.33–2.30 (2H, m, CHOCH_2); 1.99 (1H, t, *J* 2.6 Hz, CH_2CC*H*); 1.58–1.64 (12H, m, CH_2); 0.81 (3H, t, *J* 6.6 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$); 80.9, 70.6, 69.8, 36.1, 31.7, 29.4, 29.1, 27.2, 25.5 (2C), 22.5, 14.0; HRMS (ESI^+) *calcd* for $C_{11}H_{19}O_1Na_1$ [M + Na^+] *m/z* 190.2577 found: *m/z* 190.2583. All data in correspondence with literature values.

(*S*)-4-Methoxy-undec-1-yne (5)

A 60% sodium hydride suspension in mineral oil (1.06 g, 44.1 mmol) was charged to a 250 mL round bottomed flask and suspended in anhydrous tetrahydrofuran (80 mL). The resulting mixture was cooled to 0 °C (ice/water) and to this was added (*S*)-undec-1-yn-4-ol (**9**) (5.05 g, 30.0 mmol) in one portion, followed by methyl iodide (5.12 g, 36 mmol). The mixture was allowed to warm to room temperature over 1 h and then refluxed for a further 16 h. Upon completion the suspension was concentrated *in vacuo*, and then resuspended in diethyl ether (100 mL). The organic phase was extracted with water (2 × 100 mL), brine (2 × 150 mL), dried ($MgSO_4$) and concentrated. Product was isolated by column chromatography (40 : 1 petrol : diethyl ether) to give the title compound as a colourless oil (yield 5.360 g, 98%); R_f (petrol: ethyl acetate, 20 : 1) 0.7; $[\alpha]^{20}_D = -33°$ (*c* = 1.2, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 3306 (C–H alkyne); 2857 (C≡C); 2830 (C–O); δ_H (300 MHz; $CDCl_3$), 3.37 (3H, s, OCH_3); 3.29 (1H, quint, *J* 5.7 Hz, $CHOCH_3$); 2.20–2.24 (2H, m, $CHCH_2CCH$); 1.97 (1H, t, *J* 2.6 Hz, $CHCH_2CCH$); 1.66–1.49 (2H, m, CH_2); 1.48–1.19 (10H, m, CH_2); 0.87 (3H, t, *J* 6.60 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$); 81.1, 79.2, 69.7, 56.9, 33.5, 31.7, 29.2, 25.1, 23.0, 22.5, 14.0; HRMS (ESI$^+$) *calcd* for $C_{12}H_{22}NaO$ [M + Na$^+$] *m*/*z* 182.3025 found: *m*/*z* 182.3021. All data in correspondence with literature values.

2-((*E*)-(*S*)-4-Methoxy-undec-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (13)

(*S*)-4-Methoxy-undec-1-yne (**5**) (4.56 g, 25.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.36 g, 26.3 mmol) were charged to a 25 mL Schlenk tube under a positive pressure of dry argon. To the resulting solution was added sequentially bis(cyclopentadienyl)zirconium(IV) chloride hydride (0.65 g, 2.50 mmol) followed by triethylamine (0.25 g, 2.50 mmol) the mixture was capped then heated at 60 °C for 16 h protected from light. Upon completion hexane (5 mL) was added and mixture stirred for 10 min. The material was isolated through a short silica pad (elution: hexanes) to give the title product as a colourless oil (yield 7.06 g, 91%); R_f (petrol: diethyl ether, 20 : 1) 0.3; $[\alpha]^{20}_D = -8.9°$ (*c* = 0.95, $CHCl_3$); ν_{max} (neat)/cm^{-1}; 1714 (C–O), 1675 (C=C), 1620 (C=C), 1358 (B–O); δ_H (300 MHz; $CDCl_3$), 6.57 (1H, dt, *J* 17.0, 7.0 Hz C*H* alkene); 5.42 (1H, dt, *J* 17.0, 1.3 Hz C*H* alkene); 3.26 (3H, s, OCH_3); 3.18 (1H, quint, *J* 5.6 Hz, $CHOCH_3$); 2.56–2.19 (2H, m, $CHCH_2CHCH$); 1.33–1.26 (2H, m, CH_2); 1.04–1.25 (22H, m, CH_2, CH_3); 0.88 (3H, t, *J* 6.6 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$); 151.0, 83.4, 80.5, 56.8, 40.3, 34.0, 32.2, 30.1, 29.7, 25.7, 25.17, 25.15, 24.9, 23.0, 14.5. C–B peak not observed; δ_B (96.3 MHz; $CDCl_3$); 31.1; HRMS (ESI$^+$) *calcd* for $C_{18}H_{35}B_1NaO_3$ [M + Na$^+$] *m*/*z* 333.2577 found: *m*/*z* 333.2589.

Potassium 2-((*E*)-(*S*)-4-methoxy-undec-1-enyl)-trifluoroborate (14)

2-((*E*)-(*S*)-4-Methoxy-undec-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (**5**) (1.55 g, 5.0 mmol) in acetonitrile (10 mL), was charged to a 25 mL round bottom flask under an atmosphere of nitrogen. The flask was cooled to 0 °C (ice/salt) and to the resulting solution was added sequentially potassium hydrogen difluoride (1.56 g, 20 mmol) followed by water (4 mL). The mixture was capped, warmed to room temperature and stirred for 3 h until a heavy white precipitate formed. Upon completion the reaction mixture was concentrated *in vacuo* and thoroughly dried under high vacuum (0.01 mmHg). The solids were then washed with copious 4 °C acetone (250 mL) and filtered to remove inorganic salts. The solvent was concentrated to approximately 20 mL and diethyl ether (100 mL) was added and the flask triturated to precipitate the product. Storage overnight in a –20 °C freezer gave the product as a white solid (yield 0.62 g, 44%); Mp (Acetone) = 170 °C (dec.); $[\alpha]^{20}_D = -8.4°$ (*c* = 0.65, MeOH); ν_{max} (KBr)/cm^{-1}; 1652 (C–O), 1673 (C=C), 1621 (C=C), 1378, 1299, 1103, 970 (B–F); δ_H (300 MHz; CD_3OD), 6.81 (1H, dt, *J* 18.0, 6.8 Hz, C*H* alkene); 6.48 (1H, dt, *J* 18.0, 3.8 Hz, C*H* alkene); 4.35 (3H, s, OCH_3); 4.24 (1H, quint, *J* 5.8 Hz, $CHOCH_3$); 2.01–1.97 (2H, m, $CHCH_2CHCH$); 2.62–2.40 (2H, m, CH_2); 2.40–2.22 (10H, m, CH_2); 1.92 (3H, t, *J* 6.6 Hz, CH_3); δ_C (75.5 MHz; CD_3OD); 133.8, 82.9, 82.8, 56.6, 40.8, 34.5, 33.0, 30.9, 26.4, 23.7, 14.4, C–B peak not observed; δ_B (96.3 MHz; CD_3OD); –4.2; HRMS (ESI$^+$) *calcd* for $C_{14}H_{24}B_1F_3O_1$ [M + H$^+$] *m*/*z* 251.1794 found: *m*/*z* 251.1784.

Hermitamide A (1)

A 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.002 g, 0.004 mmol) and potassium 2-((*E*)-(*S*)-4-methoxy-undec-1-enyl)-trifluoroborate (**14**) (0.116 g, 0.40 mmol). 1,5-Cyclooctadiene (0.025 g, 0.040 mmol), dioxane (2 mL) and water (0.2 mL) were added by sequentially by syringe and the vessel was purged with argon. The red solution was stirred for 15 min before the addition of *N*-phenethyl-acrylamide (**3**) (0.04 g, 0.20 mmol) in dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 24 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo.* The crude residue was purified by flash column chromatography on silica gel (petrol : ethyl acetate 4 : 1) to give the title compound as a light yellow oil (yield 0.052 g, 72%); R_f (petrol : ethyl acetate, 4 : 1) 0.2; $[\alpha]^{20}_D = -9.1°$ (*c* = 1.05, $CHCl_3$); lit = –9.3° ($CHCl_3$); ν_{max} (KBr)/cm^{-1}; 3302 (N–H), 1675 (C=C), 1658 (C=C), 1527 (C=O amide) 1134, 1093; δ_H (500 MHz; C_6D_6), 7.24 (2H, t, *J* 7.3 Hz, Ph); 7.16 (1H, t, *J* 7.3 Hz Ph); 7.10 (2H, d, *J* 7.3 Hz Ph); 5.68 (1H, dt, *J* 15.0, 7.3 Hz C*H* alkene); 5.51 (1H, dt, *J* 15.0, 7.0 Hz C*H* alkene); 5.37 (1H, br s, N*H*); 3.42 (2H, dd, *J* 13.0, 6.6, $NHCH_2CH_2$); 3.21 (3H, s, OCH_3); 3.19–3.15 (1H, m); 2.94 (2H, dd, *J* 13.0, 6.8, Hz, $NHCH_2CH_2$); 2.68 (2H, t, *J* 7.0 Hz, CH_2); 2.20–2.11 (2H, m); 1.63–1.53 (2H, m); 1.52–1.33 (12H, m); 1.01 (3H, t, *J* 7.0 Hz, CH_3); δ_C (125.8 MHz; $CDCl_3$); 169.7, 139.44, 133.16, 128.9, 128.5, 126.3, 123.1, 79.7, 55.4, 40.7, 35.8, 35.3, 33.3, 32.0, 30.1, 29.6, 28.5, 25.6, 25.4, 23.2, 22.9, 14.1; HRMS (ESI$^+$) *calcd* for $C_{23}H_{38}N_1O_2$ [M + H$^+$] *m*/*z* 360.2903 found: *m*/*z* 360.2897. All data in accordance with literature values.[2]

(*S*,2*E*,4*E*)-7-methoxy-N-phenethyltetradeca-2,4-dienamide (15)

A 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.002 g, 0.004 mmol) and potassium 2-((*E*)-(*S*)-4-methoxy-undec-1-enyl)-trifluoroborate (**14**) (0.116 g, 0.40 mmol). 1,5-cyclooctadiene (0.025 g, 0.040 mmol), dioxane (2 mL) and water (0.2 mL) were added by sequentially by syringe and the vessel was purged with argon. The red solution was stirred for 15 min before the addition of *N*-phenethyl-acrylamide (**3**) (0.04 g, 0.20 mmol) in dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 24 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo.* The crude residue was purified by flash column chromatography on silica gel (petrol : ethyl acetate 4 : 1) to give the title product as light yellow semisolid (yield 0.012 g, 16%); Mp (petrol) = 32–34 °C; R_f (petrol : ethyl acetate, 4 : 1) 0.23; $[\alpha]^{20}_D = -8.4°$ (*c* = 0.70, $CHCl_3$); ν_{max} (KBr)/cm^{-1}; 3307 (N–H), 1660 (C=C), 1652 (C=C), 1525 (C=O amide) 1128, 1096; δ_H (500 MHz; C_6D_6), 7.63 (1H, dd, *J* 15.0 7.7 Hz, C*H* alkene); 7.23 (2H, t, *J* 7.3 Hz, Ph); 7.16 (1H, t, *J* 7.3 Hz, Ph); 7.08 (2H, d, *J* 7.3 Hz Ph); 6.20 (1H, dd, *J* 15.0 11.0 Hz, C*H* alkene); 5.96 (1H, dt, *J* 15.0, 7.6 Hz C*H* alkene); 5.43

(1H, d, *J* 15.0 Hz, C*H* alkene); 4.83–4.76 (1H, m, N*H*); 3.48 (2H, dd, *J* 13.0, 6.9 Hz, NHCH_2CH$_2$); 3.21 (3H, s, OCH$_3$); 3.11 (1H, quint, *J* 6.0 Hz, C*H*OCH$_3$); 2.62 (2H, t, *J* 7.3, Hz, NHCH$_2$CH_2); 2.68 (2H, t, *J* 7.0 Hz, CH_2); 2.20–2.11 (2H, m, CH_2); 1.61–1.47 (2H, m, CH_2); 1.44–1.32 (8H, m, CH_2); 1.01 (3H, t, *J* 6.8 Hz, CH_3); δ_C (125.8 MHz; CDCl$_3$); 165.2, 140.7, 139.5, 138.4, 130.5, 128.9, 128.2, 127.6, 122.9, 80.0, 72.2, 70.1, 56.3, 40.8, 37.3, 35.85, 33.9, 32.0, 29.6, 29.5, 25.44, 22.8, 14.1; HRMS (ESI$^+$) *calcd* for $C_{23}H_{35}N_1O_2$ [M + H$^+$] *m/z* 358.2746 found: *m/z* 358.2732.

Hermitamide B (2)

A 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.003 g, 0.006 mmol) and potassium 2-((*E*)-(*S*)-4-methoxy-undec-1-enyl)-trifluoroborate (**14**) (0.116 g, 0.40 mmol). 1,5-cyclooctadiene (0.013 g, 0.012 mmol), dioxane (2 mL) and water (0.2 mL) were added by sequentially by syringe and the vessel was purged with argon. The red solution was stirred for 15 min before the addition of *N*-[2-(1*H*-indol-3-yl)-ethyl]-acrylamide (**4**) (0.04 g, 0.20 mmol) in dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 36 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo.* The crude residue was purified by flash column chromatography on silica gel (petrol : ethyl acetate 3 : 1) to give the title product as a colourless oil (yield 0.029 g, 36%); R_f (petrol: ethyl acetate, 3 : 1) 0.1; $[\alpha]^{20}_D = -5.2°$ (*c* = 0.55, CHCl$_3$); Lit = –4.9° (c 0.15, CHCl$_3$); ν_{max} (KBr)/cm^{-1}; 3309 (N–H), 3022, 2930 (C=C), 1658 (C=C), 1642 (C=C), 1527 (C=O) 976, 911 (CH=CH); δ_H (300 MHz; CDCl$_3$), 8.24 (1H, br s, N*H*); 7.52 (1H, d, *J* 7.9 Hz, indole); 7.37 (1H, d, *J* 7.9 Hz, indole); 7.20 (1H, td, *J* 7.9, 1.1 Hz, C*H* indole); 7.12 (1H, td, *J* 7.9, 1.1 Hz, C*H* indole); 7.02 (1H, br d, *J* 7.2 Hz C*H* indole); 5.78 (1H, br s, N*H*); 5.60–5.40 (2H, m, alkene); 3.56 (2H, dd, *J* 13.0, 7.2 Hz, NHCH_2CH$_2$), 3.27 (3H, s, CHOCH_3); 3.13 (1H, quint, *J* 5.7 Hz, C*H*OCH$_3$); 2.97 (2H, t, *J* 6.8 Hz, NHCH$_2$CH_2); 1.33–1.38 (3H, m, CH_2); 2.23–1.95 (3H, m, CH_2); 1.35–1.20 (12H, m, CH_2); 0.88 (3H, t, *J* 6.6 Hz, CH_3); δ_C (75.5 MHz; CDCl$_3$); 171.4, 136.1, 130.8, 127.6, 127.1, 122.3, 122.1, 119.7, 118.8, 79.7, 55.4, 40.7, 35.8, 35.3, 33.3, 32.0, 30.1, 29.6, 28.5, 25.6, 25.4, 23.2, 22.9, 14.1; HRMS (ESI$^-$) *calcd* for $C_{25}H_{38}N_2O_2$ [M – H$^+$] *m/z* 397.2855 found: *m/z* 397.2860. All data in accordance with literature values.[2]

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