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Aust. J. Chem. **2015**, *68*, 1821–1828
http://dx.doi.org/10.1071/CH15407

Full Paper

Studies Towards a Concise Enantioselective Synthesis of Roseophilins

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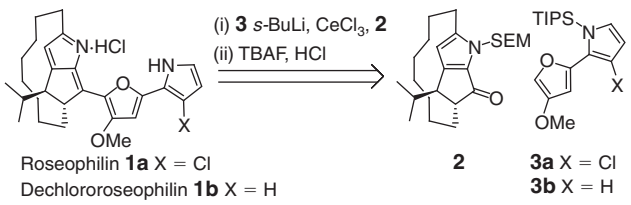
An oxazolidone auxiliary-controlled asymmetric Nazarov reaction has been applied to the synthesis of the cyclopentyl-fused pyrrole core of roseophilins. Additionally, a concise synthetic route to the pyrrole-furan biaryl fragment required in the synthesis of the recently isolated dechlororoseophilin is described. It is anticipated that these two syntheses can be combined in future efforts to provide efficient, convergent access to (+)-dechlororoseophilin.

Manuscript received: 7 July 2015.
Manuscript accepted: 24 August 2015.
Published online: 16 September 2015.

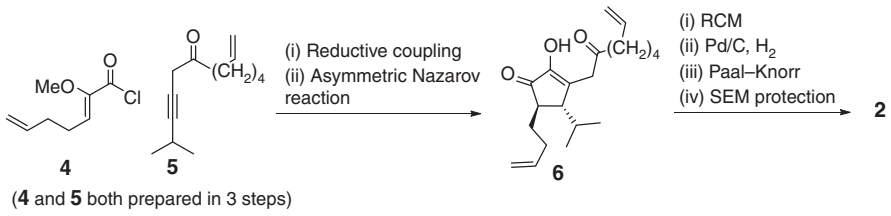
Introduction

Roseophilin (**1a**, Scheme 1) was isolated in 1992 from *Streptomyces griseoviridis* and, more recently (in 2009), dechlororoseophilin (**1b**, Scheme 1) was isolated from the same species.[1] Both compounds show anticancer activity, which has been linked to the inhibition of phosphatases, including Cdc25a, VHR, and PTP1B, all of which are important for cancer cell growth and survival.[1,2] Also, analogues of its pyrrole-furan substructure have been shown to be effective inhibitors of Mcl-1, a key protein in regulating cell apoptosis.[3]

In a landmark study, Weintritt and Fürstner described the first total synthesis of roseophilin in 1998.[4] The synthesis involved a late-stage coupling of the ansa-bridged cyclopentyl-pyrrole fragment **2** to the pyrrole-furan fragment **3a**. Nearly all subsequent approaches to preparing **1a** have focussed on alternative syntheses of fragment **2**, including some enantioselective syntheses.[5–7] We recently described an eight-step enantioselective synthesis of **2**, which represents to date, the most concise and efficient route to prepare **(+)-1a** (11 steps, 10.2 % yield, 95 % ee), albeit at this stage as a formal synthesis (Scheme 2).[6f] Key to this approach was our convergent, two-step cyclopentanoid synthesis **4** + **5** → **6**. This involves reductive coupling of an α,β-unsaturated acid chloride **4** and alkyne **5** to give a divinyl ketone (not shown), which is then subjected to enantioselective Nazarov cyclization using a chiral Brønsted acid (not shown) to afford the hydroxycyclopentenone **6**. Cyclopentenone **6** is converted to **3a** in a four-step sequence: ring-closing metathesis (RCM), hydrogenation, Paal–Knorr reaction, and 2-(trimethylsilyl)ethoxymethyl (SEM) protection.[6f] As a complement to this synthesis, we have initiated efforts to provide enantioselective access from a pyrrolyl substrate using our auxiliary-controlled asymmetric Nazarov reaction (Scheme 3).[8] We previously reported the use of oxazolidinone auxiliaries **A** and **B** in the cyclization of aryl and heteroaryl substrates **7** → **8**.[8] The use of auxiliaries is beneficial in these circumstances as the cyclization of aryl vinyl ketones usually requires high acid concentrations and are not conducive to asymmetric catalysis. Our intention was to use this chemistry to access pyrrolocyclopentanone **9** enantioselectively and convert the latter into macrocycle **2** using RCM (Scheme 4). During the planning of this synthesis, we were aware of the

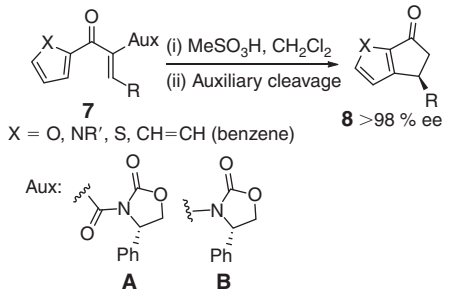


Scheme 1. Roseophilins **1a** and **1b** and the late-stage substrates **2** and **3a** and **3b** required for their synthesis.

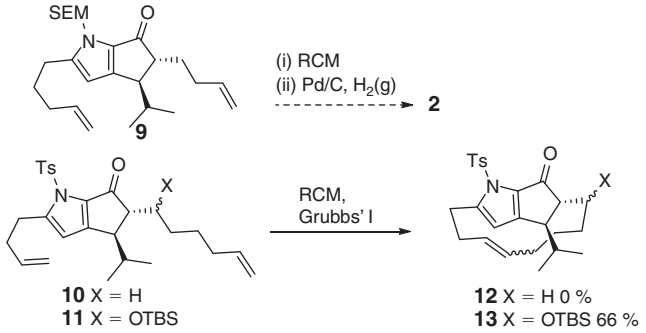


Scheme 2. Key steps in what is the currently the most efficient route to prepare **3a**.[6f]

potential issues associated with the RCM of **9** to give a moderately strained macrocycle. In fact, Fuchs and coworkers had previously attempted a similar ring closure using the first-generation Grubbs catalyst **10** → **12** (racemic), but failed.[6g] However, they were successful in cyclizing the *tert*-butyldimethylsilyl (TBS)-ether **11** (accessed from an aldol reaction) to **13** (66 %). This success was attributed to a steric-directing effect of the OTBS groups, forcing the two terminal alkenes into close proximity to favour RCM over polymerization. However, this required additional steps in order to remove the oxygen substituent: i.e. removal of TBS, conversion to a xanthate ester, and radical deoxygenation. Thus, we considered that a subtle variation in the relative tether lengths (cf. **9** and **10**) and/or a shift to the second-generation Grubbs catalyst (not used by Fuchs) may be sufficient to enable cyclization of **9** to **2**. Alternatively, we could reconfigure the synthesis to provide a concise enantioselective synthesis of Fuchs's substrate **11**. Herein, we describe our efforts to provide enantioselective access to suitably substituted pyrroles to progress through to either **9** or **10** and to ascertain the utility of **9** as a suitable substrate in RCM (initially in the racemic form). We also describe a very simple preparation of the pyrrole-furan fragment **3b** for use in a future synthesis of dechlororosephilin (**1b**).



Scheme 3. Auxiliary- (**A** and **B**) controlled Nazarov cyclization of aryl vinyl ketones.

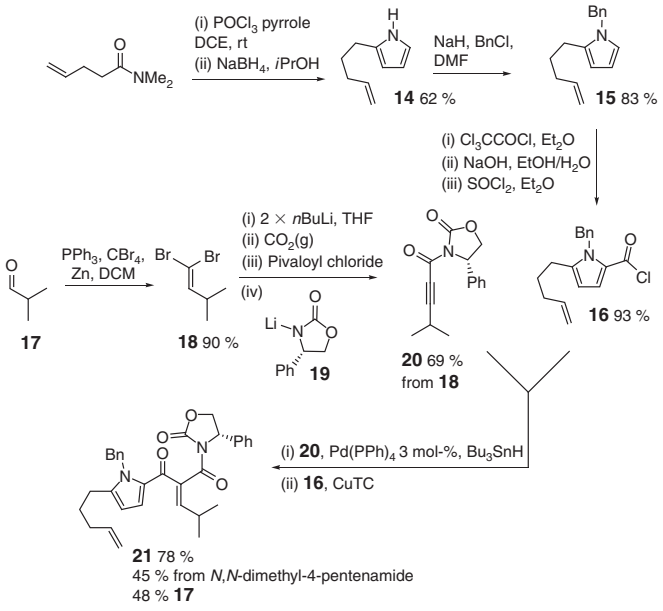


Scheme 4. RCM of cyclopentyl-fused pyrrole intermediates.

Results and Discussion

Our studies commenced with the preparation of the oxazolidinone-bearing pyrrole **21** (Scheme 5). First, the Vilsmeier–Haack reagent generated from reaction of *N*,*N*-dimethyl-4-pentenamide with $POCl_3$ was reacted with pyrrole to give a ketone (not shown), which was reduced with $NaBH_4$ in *i*PrOH to give 1-(4-pentyl)-pyrrole (**14**) in 62 % yield over two steps. Pyrrole **14** was *N*-protected with a benzyl group (**15**, 96 % yield) and converted into the acid chloride **16** in a three-step sequence without intermediate purification: (i) Friedel–Crafts acylation with trichloroacetylchloride; (ii) hydrolysis; and (iii) reaction with thionyl chloride, giving **16** in 93 % yield from **15**. Our use of the *N*-benzyl protecting group in this work was to enable the greatest range of reaction conditions to be explored in subsequent steps. Also, in their original racemic synthesis of **1a**, Fürstner and Weintritt also used a benzyl protecting group and exchanged the latter for SEM in the final steps leading to **2**.[4] In our ultimate synthesis of **1a** and **1b**, we expect to incorporate the SEM group early in the synthesis (SEM equivalent of **15**).

The alkynyl unit **20** was prepared from isopropanal **17** as previously described for its enantiomer (Scheme 5).[7] Isopropanal **17** is converted into the *gem*-dibromoalkene **18**,[9] which is reacted sequentially with 2 equivalents of *n*BuLi



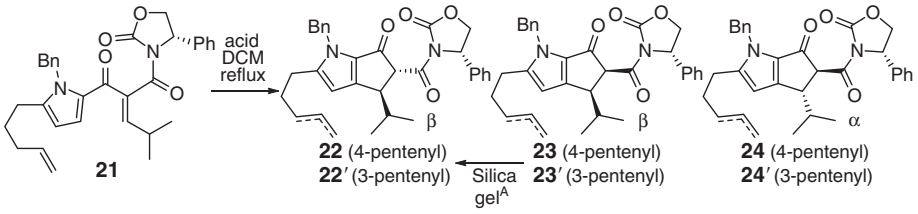
Scheme 5. Synthesis of Nazarov precursor **21**. CuTC = copper(I) thiophene-2-carboxylate; rt = room temperature.

(Corey–Fuchs), CO_2(g), pivaloyl chloride, and the lithium oxazolidonone **19** to give **20** in overall 69 % yield from **18**. Reductive coupling of **16** and **20** involves a one-pot Pd-mediated *syn*-hydrostannylation of **20** followed by Cu^{I}-co-catalyzed cross-coupling with **16** to afford the Nazarov precursor **21** in good yield (78 %) (Scheme 5).

Nazarov cyclization studies on the pyrrole-vinyl ketone **21** involved three acids: Brønsted acid methanesulfonic acid ($MeSO_3H$) and Lewis acids copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) and $FeCl_3$ (Table 1). In these studies, three different diastereomeric cyclopentanoids **22**, **23**, and **24** were observed in the ^{1}H NMR analysis of the crude reaction mixtures. In most cases, these products were also accompanied by some 3-pentenyl isomer **22′**–**24′**. Diastereomers **22** and **23** result from the same sense of induction (β-*i*Pr) in the Nazarov cyclization but are differentiated from each other based on *cis*- or *trans*-orientation of the carbonyl-linked oxazolidinone. As with other examples involving this auxiliary system, *cis*-to-*trans* isomerism to thermodynamically favoured **22** occurs rapidly upon chromatography, such that **22** is the only β-diastereomer isolated. The alternate (α-*i*Pr) stereoismer **24** was only ever observed in the *trans*-orientation. Though diastereomers **22** and **24** were readily separated by chromatography, each diastereomer was obtained as a mixture of inseparable double-bond isomers: the desired 4-pentenyl and the isomerized 3-pentenyl isomers. All diastereomers gave similar levels of double-bond isomerism; however, only the ratio of **22** and **22′** is given in Table 1. Our usual acid of choice for oxazolidinone-controlled asymmetric Nazarov cyclization (i.e. $MeSO_3H$) gave a low sense of induction (α : β = 1.3 : 1) and a significant level of double-bond isomerism (**22** : **22′** = 8 : 1). The Lewis acid Cu$(OTf)_2$ gave a higher level of induction, favouring the β-isomer (α : β = 1 : 3), but gave a much higher level of double-bond isomerism, favouring **22′** (**22** : **22′** = 1 : 4). $FeCl_3$ proved superior, giving a similar level of induction to $Cu(OTf)_2$ (α : β = 1 : 4) but a lower level of double-bond isomerism (**22** : **22′** = 4 : 1). By performing the reaction at high dilution (0.006 M), the reaction efficiency and diastereoselectivity could be maintained and double-bond isomerism could be suppressed to negligible levels (**22** : **22′** = 50 : 1), giving the major stereoisomer **22** in 70 % yield.

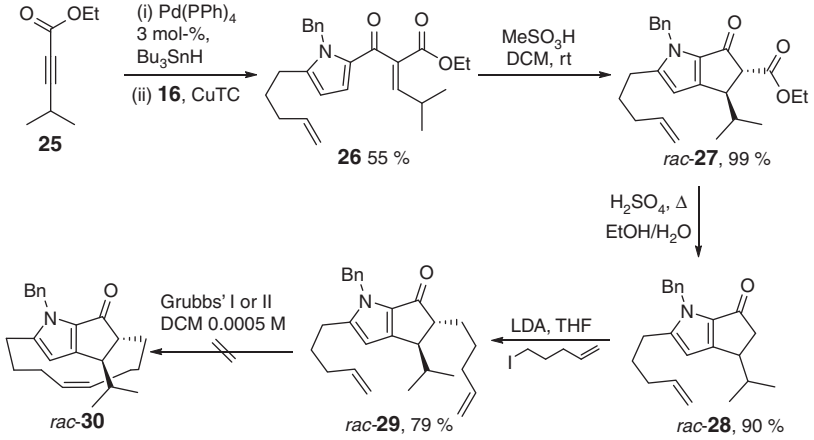
In parallel with these investigations, we also prepared the racemic *N*-benzyl-protected version of **9**, *rac*-**29** (Scheme 6). Reductive coupling of ester **25** with acid chloride **16** gave **26** (55 % yield), which underwent facile Nazarov cyclization with $MeSO_3H$ in dichloromethane (DCM), giving pyrrolocyclopentanone *rac*-**27** in near quantitative yield (99 %), without any double-bond isomerism.[10] Hydrolytic decarboxylation of

Table 1. Nazarov cyclization of 21

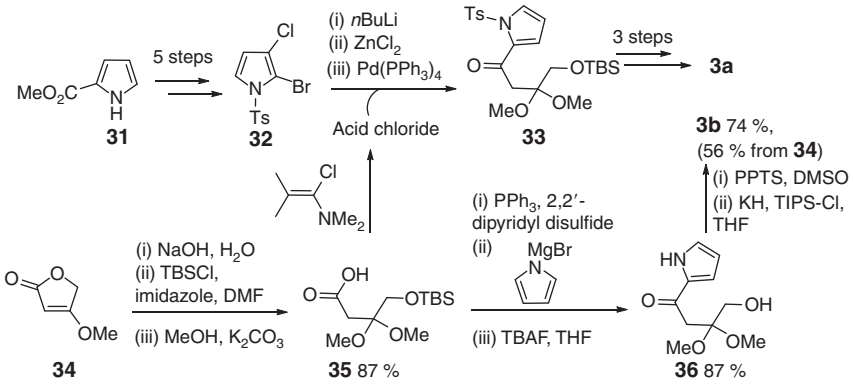


Entry	Acid	Products[A,B]				
		22+**22′** [%]	**23**+**23′** [%]	**24**+**24′** [%]	α : β	**22**: **22′**
1	10 equiv. $MeSO_3H$ (1 M)	20	22	58	1.3 : 1	8 : 1
2	1.0 equiv. $Cu(OTf)_2$ (0.1 M)	58	15	27	1 : 3	1 : 4
3	1.0 equiv. $FeCl_3$ (0.1 M)	71	8	21	1 : 4	4 : 1
4	1.0 equiv. $FeCl_3$ (0.006 M)	67 (70)	10	23 (22)	1 : 4	~50 : 1

[A]Chromatography on silica gel promotes epimerization to the thermodynamically favoured *trans*-isomer **22** and **22′**.
[B]The relative amount of each product is based on the integration of selected peaks in the ^{1}H NMR spectrum of the crude reaction mixture before chromatography. Isolated yields after chromatography are given in parentheses.



Scheme 6. Racemic access to **29** and attempted RCM to form **30**.



Scheme 7. Concise synthesis of the pyrrole-furan fragment **3b**.

rac-**27** using H_2SO_4 in ethanol (EtOH)/H_2O gave *rac*-**28** in good yield (81 %), again without double-bond isomerism. Alkylation of *rac*-**28** using lithium diisopropylamide (LDA) and 1-iodopent-4-ene gave the *rac*-**29** (79 %). Unfortunately, all attempts to cyclize *rac*-**29** to *rac*-**30**, with both first- and second-generation Grubbs catalyst, including at high dilutions, were unsuccessful, returning only undefined polymeric mixtures. At this stage, no other metathesis catalysts have been evaluated, but it is likely that in the absence of a steric directing group, as in the Fuchs example **11** → **13**, cross-metathesis leading to polymerization will dominate over RCM for this substrate.

As a part of our investigations, we also prepared the pyrrole-furan fragment **3b** (Scheme 7), suitable for late-stage attachment to **2** to give dechlororoseophilin (**1b**). This synthesis is much more straightforward than that described by Fürstner and Wentritt for the chloro-equivalent **3a**,[4] though it uses some similar chemistry. In the synthesis procedure reported by Fürstner and Wentritt, **3a** was prepared in eight steps (longest linear sequence) from commercially available methyl 4-chloro-1*H*-pyrrole-2-carboxylate (**31**) in overall 13 % yield.[4,11] This involved Negishi coupling of **32** and the acid chloride derived from **35** to give the ketone **33**, which was then cyclized to form the methoxyfuran ring, followed by exchange of the tosyl (Ts) protecting group for a triisopropysilyl (TIPS) group to complete the synthesis of **3a**. We used a similar approach to prepare dechloro-equivalent **3b**, but took advantage of the lower level of substitution in the pyrrole unit to simplify the synthesis. We used the same carboxylic acid **35**, which is readily accessible from methyl tetronate in a one-pot procedure in 87 % yield. In another one-pot procedure, we converted **35** into the corresponding 2-pyridyl thioester (PPh_3 and 2,2′-dipyridyl disulfide), reacted the latter with pyrrolylmagnesium bromide (obtained from the reaction between pyrrole and MeMgBr), and treated the crude ketone with tetrabutylammonium fluoride (TBAF) in THF to cleave the TBS, giving **36** in 87 % yield (from **34**) after flash chromatography. This material was cyclized to the methoxy furan (*para*-toluenesulfonic acid (PPTS) in DMSO) and the crude product TIPS-protected to give **3b** in 74 % yield after chromatography. This sequence provides **3b** in overall 56 % yield and is conveniently performed on a multi-gram scale (see Experimental).

Conclusion

We have demonstrated the utility of the oxazolidinone-controlled asymmetric Nazarov reaction in providing access to pyrrole **22** (Scheme 5). However, our initially intended and most concise route for converting **22** into **1a** and **1b** has failed due to the inability to achieve RCM of **29** to form **30** (Scheme 4). Nonetheless, the chemistry developed in these studies has excellent potential in gaining concise convergent asymmetric access to the roseophilins **1a** and **1b** through a modified approach that incorporates the successful steric-directed RCM strategy developed by Fuchs **11** → **13** (Scheme 4). Furthermore, our direct, high-yielding access to **3b** (Scheme 7) should facilitate convenient asymmetric synthesis of **1b**, including when combined with our existing approach to **2** (Scheme 2) and Weintritt and Fürstner's convergent coupling of **2** and **3** to give **1** (Scheme 1).

Experimental

General

All experiments were performed under an anhydrous atmosphere of nitrogen except as indicated. Melting points were recorded on an Electrothermal melting point apparatus. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded at 300 MHz for proton and 75 MHz for carbon nuclei. All NMR spectra were recorded in [D]chloroform ($CDCl_3$) at 30°C. Multiplets are recorded as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), hex (hextet) sept (septet), octet, m (multiplet), and m_c (centred multiplet). The term 'app.' (apparent) refers to combined multiplets with equal coupling constants that appear as higher multiplets (e.g. dd = app. q). The protonicities of the carbon atoms observed in the carbon NMR were determined using J-modulated spin-echo (JMOD) experiments or APT. Infrared (IR) spectra were obtained on a Fourier transform infrared spectrometer. Low-resolution mass spectra were recorded on a quadrupole spectrometer using electrospray ionization (ESI). High-resolution mass spectroscopy (HRMS) patterns were recorded on a time-of-flight mass spectrometer fitted with an ESI ion source. THF and diethyl ether (Et_2O) were distilled under nitrogen from sodium benzophenone ketyl. DCM and 1,2-dichloroethane (DCE) were distilled from calcium hydride under nitrogen. Analytical thin layer chromatography was conducted on aluminium sheets coated with silica gel 60 GF_{254}. Flash chromatography was performed on flash grade silica gel.

2-(Pent-4-enyl)-1H-pyrrole (**14**)

Phosphorus oxychloride (3.07 mL, 32.7 mmol) was added to a stirred solution of *N*,*N*-dimethyl-4-pentenamide (3.78 g, 29.7 mmol) in DCE (2 mL), and this mixture was stirred for 8 h. A solution of pyrrole (2.22 mL, 31.2 mmol) in DCE (11 mL) was added, and the reaction mixture was stirred for 8 h. The reaction

was quenched by the addition of saturated NaOAc(aq) solution (30 mL). This biphasic mixture was stirred for 1 h before being partitioned between Et_2O (50 mL) and H_2O (50 mL). The organic phase was washed with H_2O (20 mL), and the combined aqueous phases were re-extracted with Et_2O (30 mL). The extract was washed with H_2O (20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (silica gel, 9 : 1 hexane/ethyl acetate) gave 1-(1*H*-pyrrole-2-yl)pent-4-en-1-one as a clear oil (3.17 g, 72 %). δ_H ($CDCl_3$, 300 MHz) 9.32 (1H, br s), 7.02 (1H, m_c), 6.92 (1H, m_c), 6.29 (1H, m_c), 5.89 (1H, m_c), 5.13–4.96 (2H, m), 2.88 (2H, t, *J* 7.5), 2.48 (2H, m_c). This spectrum is identical to that previously reported.[12]

Sodium borohydride (3.40 g, 86 mmol) was added to a stirred solution of the above ketone (3.17 g, 21.2 mmol) in isopropanol (180 mL), and the resultant mixture was refluxed for 18 h. The reaction mixture was then concentrated to 30 mL under reduced pressure and taken up in Et_2O (60 mL) and H_2O (60 mL). The phases were separated, and the organic phase was washed with additional H_2O (60 mL). The organic phase was concentrated under reduced pressure, and the oil residue was subjected to flash chromatography (silica gel, 9 : 1 hexane/Et_2O) to give the title compound as a clear oil (2.45 g, 86 % from the ketone). δ_H ($CDCl_3$, 300 MHz) 7.90 (1H, br s), 6.67 (1H, d, *J* 1.5), 6.14 (1H, m_c), 5.93 (1H, br s), 5.83 (1H, m_c), 5.10–4.95 (2H, m), 2.63 (2H, t, *J* 7.7), 2.13 (2H, app. q, J_{app} 7.1), 1.74 (2H, app. quin, J_{app} 7.5). This spectrum is identical to that previously reported.[12]

*1-Benzyl-2-(pent-4-enyl)-1*H*-pyrrole (**15**)*

Sodium hydride (60 % in paraffin oil, 0.94 g, 24 mmol) was added gradually to a stirred solution of pyrrole **14** (2.45 g, 18.1 mmol) in DMF (22 mL) at 0°C. To the resultant mixture was added benzyl chloride (2.8 mL, 24 mmol), and this solution was stirred at 0°C for 1 h. After this time, the solution was taken up in Et_2O (60 mL) and washed with H_2O (2 × 40 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography (silica gel, 98.5 : 1.5 hexane/Et_2O) to give the title compound as a clear oil (3.94 g, 96 %). ν_{max} (neat)/cm^{-1} 3066, 2931, 1640, 1453, 1296, 1074, 911, 698. δ_H ($CDCl_3$, 300 MHz) 7.35–7.21 (3H, m), 6.99 (2H, d, *J* 7.2), 6.62 (1H, br s), 6.14 (1H, d, *J* 3.3), 5.97 (1H, d, *J* 3.3), 5.76 (1H, m_c), 5.04 (2H, s), 5.03–4.90 (2H, m), 2.47 (2H, t, *J* 7.8), 2.08 (2H, app. q, J_{app} 7.1), 1.66 (2H, app. quin, J_{app} 7.6). δ_C ($CDCl_3$, 75 MHz; JMOD) 138.7 (C), 138.5 (CH), 133.2 (C), 128.8 (CH), 127.4 (CH), 126.4 (CH), 120.9 (CH), 114.9 (CH_2), 107.3 (CH), 106.2 (CH), 50.3 (CH_2), 33.4 (CH_2), 28.1 (CH_2), 25.7 (CH_2). HRMS *m/z* 226.1597; calcd for $C_{16}H_{20}N^+$ 226.1596.

*1-Benzyl-5-(pent-4-enyl)-1*H*-pyrrole-2-carbonyl Chloride (**16**)*

Trichloroacetyl chloride (2.4 mL, 21 mmol) was added slowly to a stirred solution of pyrrole **15** (3.41 g, 17.5 mmol) in dry Et_2O (44 mL). The reaction was allowed to stir for 24 h before being concentrated under reduced pressure. The solid residue was dissolved in ethanol (95 %, 88 mL) and aqueous NaOH (4.0 M in H_2O, 23 mL, 92 mmol) was added. This solution was refluxed for 5 h before being reduced in volume to 40 mL under reduced pressure. Et_2O (60 mL) and H_2O (50 mL) were added, and the aqueous phase was collected. The organic phase was extracted with H_2O (25 mL), and the combined aqueous extracts were acidified to pH 2 with 5 M HCl(aq). This mixture was extracted with Et_2O (2 × 30 mL), and the organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude acid.

Thionyl chloride (13 mL, 175 mmol) was added to the above material in dry Et_2O (88 mL), and the resultant solution was stirred for 4 h. After this time, the solution was concentrated under reduced pressure to give the title compound as a dark oil (4.67 g, 93 %). ν_{max} (neat)/cm^{-1} 3066, 2935, 1722, 1481, 1377, 1230, 1050, 804. δ_H ($CDCl_3$, 300 MHz) 7.38 (1H, d, *J* 4.2), 7.34–7.20 (3H, m), 6.91 (2H, d, *J* 7.5), 6.15 (1H, d, *J* 4.2), 5.73 (1H, m_c), 5.48 (2H, s), 5.04–4.95 (2H, m), 2.54 (2H, t, *J* 7.7), 2.08 (2H, app. q, J_{app} 7.1), 1.69 (2H, app. quin, J_{app} 7.5). δ_C ($CDCl_3$, 75 MHz; JMOD) 156.4 (C), 147.2 (C), 137.4 (CH), 136.9 (C), 128.6 (CH), 127.3 (CH), 127.2 (CH), 125.7 (CH), 124.1 (C), 115.4 (CH_2), 109.6 (CH), 48.5 (CH_2), 33.0 (CH_2), 27.0 (CH_2), 25.8 (CH_2).

*(S,Z)-1-[1-Benzyl-5-(pent-4-enyl)-1*H*-pyrrole-2-yl]-2-(2-methylpropylidene)-3-(2-oxo-4-phenyloxazolidin-3-yl) propane-1,3-dione (**21**)*

Bis(dibenzylideneacetone)palladium(0) (90 mg, 0.157 mmol) was added to a stirred solution of triphenylphosphine (170 mg, 0.646 mmol) in THF (40 mL) and left to stir for 0.5 h at room temperature. After this time, alkyne **20**[8b] (1.45 g, 5.65 mmol) was added, followed by dropwise addition tributyltin hydride (Bu_3SnH; 1.57 mL, 5.65 mmol), and the resultant mixture was stirred for 0.5 h. Acid chloride **16** (1.63 g, 5.66 mmol) and Cu^ICl (450 mg, 4.5 mmol) were then added, and the reaction was stirred at room temperature for 24 h. After this time, potassium fluoride (30 % w/v in H_2O, 30 mL) was added, and the triphasic mixture was stirred for 2 h. To this mixture was added H_2O (60 mL) and Et_2O (80 mL). After separation, the aqueous phase was re-extracted with Et_2O (60 mL), and the combined organic fractions were dried over $MgSO_4$ and concentrated onto silica gel (10 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, 82 : 18 hexane/ethyl acetate) giving the title compound as a discoloured oil (2.23 g, 78 %). ν_{max} (neat)/cm^{-1} 3032, 2961, 1784, 1694, 1606, 1320, 1200, 761, 698. δ_H ($CDCl_3$, 300 MHz) 7.42–7.16 (8H, m), 6.98–6.88 (3H, m), 6.55 (1H, d, *J* 10.5), 6.04 (1H, d, *J* 3.9), 5.74 (1H, m_c), 5.63–5.44 (3H, m), 5.03–4.92 (2H, m), 4.67 (1H, app. t, J_{app} 8.9), 4.21 (1H, dd, *J* 8.9, 4.1), 2.53–2.37 (3H, m), 2.07 (2H, app. q, J_{app} 7.0), 1.66 (2H, app. quin, J_{app} 7.5), 1.06 (3H, d, *J* 6.6), 1.00 (3H, d, *J* 6.6). δ_C ($CDCl_3$, 75 MHz; JMOD) 181.5 (C), 165.8 (C), 153.4 (CH), 152.9 (C), 143.4 (C), 138.7 (C), 138.5 (C), 137.8 (CH), 136.3 (C), 129.3 (C), 129.0 (CH), 128.5 (CH), 128.4 (CH), 126.8 (CH), 126.01 (CH), 125.98 (CH), 122.4 (CH), 115.1 (CH_2), 107.7 (CH), 70.2 (CH_2), 57.5 (CH), 48.1 (CH_2), 33.1 (CH_2), 29.7 (CH), 27.3 (CH_2), 25.8 (CH_2), 21.8 (CH_3, 2 carbons). *m/z* (ESI) 1038.5 (5 %, 2 × $[M + NH_4]^+$), 528.6 (10 %, $[M + NH_4]^+$), 511.3 (100 %, $[MH]^+$). HRMS *m/z* 511.2613; calcd for $C_{32}H_{35}N_2O_4^+$ 511.2597.

*(S)-3-{(4*R*,5*R*)-1-Benzyl-4-isopropyl-6-oxo-2-(pent-4-enyl)-1,4,5,6-tetrahydrocyclopenta[*b*]-pyrrole-5-carbonyl}-4-phenyloxazolidin-2-one (**22**)*

$FeCl_3$ (50 mg, 0.305 mmol) was added to a stirred solution of **21** (156 mg, 0.305 mmol) in dry DCM (50 mL) at room temperature, this mixture was then refluxed for 24 h. After cooling to room temperature, the reaction was quenched by gradual addition of saturated $NaHCO_3$(aq) (30 mL). The phases were separated, and the aqueous phase was re-extracted with DCM

(20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated onto silica gel (2 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, sequential elution 78 : 22 → 7 : 3 hexane/ethyl acetate) giving the title compound as a thick gum (109 mg, 70 %). ν_{max} (neat)/cm^{-1} 3065, 2958, 1777, 1673, 1475, 1386, 1200, 910, 727. δ_H ($CDCl_3$, 300 MHz) 7.42 (2H, dd, *J* 8.0, 1.7), 7.35–7.22 (6H, m), 7.02 (2H, dd, *J* 7.2, 2.1), 5.93 (1H, s), 5.71 (1H, m_c), 5.50 (1H, dd, *J* 9.2, 6.4), 5.43 (1H, br s), 5.24 (2H, s), 5.02–4.92 (2H, m), 4.72 (1H, app. t, J_{app} 9.0), 4.21 (1H, dd, *J* 9.0, 6.4), 3.51 (1H, dd, *J* 6.8, 2.9), 2.48–2.40 (2H, m), 2.03 (2H, app. q, J_{app} 7.1), 1.96 (1H, app. octet, J_{app} 6.7), 1.59 (2H, app. quin, J_{app} 7.7), 1.01 (3H, d, *J* 6.9), 0.97 (3H, d, *J* 6.9). δ_C ($CDCl_3$, 75 MHz; JMOD) 181.8 (C), 169.6 (C), 153.9 (C), 153.8 (C), 149.3 (C), 138.3 (C), 137.7 (CH), 137.3 (C), 131.3 (C), 129.1 (CH), 128.8 (CH), 128.4 (CH), 127.5 (CH), 126.9 (CH), 126.1 (CH), 115.4 (CH_2), 105.3 (CH), 69.7 (CH_2), 61.3 (CH), 58.7 (CH), 47.7 (CH_2), 43.7 (CH), 33.2 (CH_2), 31.7 (CH), 27.4 (CH_2), 25.9 (CH_2), 20.5 (CH_3), 20.1 (CH_3). *m/z* (ESI) 1038.7 (5 %, 2 × $[M + NH_4]^+$), 533.4 (10 %, $[M + Na]^+$), 511.4 (100 %, $[MH]^+$). HRMS *m/z* 533.2409; calcd for $C_{32}H_{34}N_2NaO_4^+$ 533.2416.

Minor isomer **24** was obtained as a thick gum (34 mg, 22 %). ν_{max} (neat)/cm^{-1} 3032, 2957, 1777, 1698, 1672, 1474, 1385, 1194, 911, 712. δ_H ($CDCl_3$, 300 MHz) 7.44–20 (8H, m), 7.05 (2H, d, *J* 6.9), 5.96 (1H, s), 5.71 (1H, m_c), 5.47 (1H, dd, *J* 8.3, 2.6), 5.43 (1H, d, *J* 3.0), 5.33–5.20 (2H, m), 5.02–4.93 (2H, m), 4.76 (1H, app. t, J_{app} 8.6), 4.29 (1H, dd, *J* 8.9, 2.6), 3.39 (1H, dd, *J* 6.6, 3.0), 2.46 (2H, t, *J* 7.7), 2.05 (2H, app. q, J_{app} 7.1), 1.95 (1H, app. octet, J_{app} 6.7), 1.62 (2H, app. quin, J_{app} 7.7), 0.98 (3H, d, *J* 6.9), 0.93 (3H, d, *J* 6.6). δ_C ($CDCl_3$, 75 MHz; JMOD) 183.0 (C), 169.8 (C), 154.2 (C), 154.0 (C), 149.6 (C), 139.5 (C), 137.7 (CH), 137.3 (C), 131.6 (C), 129.2 (CH), 128.8 (CH), 128.6 (CH), 127.6 (CH), 126.8 (CH), 125.7 (CH), 115.4 (CH_2), 105.4 (CH), 69.9 (CH_2), 60.6 (CH), 58.2 (CH), 47.7 (CH_2), 44.9 (CH), 33.2 (CH_2), 31.6 (CH), 27.4 (CH_2), 25.9 (CH_2), 20.3 (CH_3), 20.1 (CH_3). *m/z* (ESI) 1021.7 (5 %, 2 × $[M + H]^+$), 533.4 (10 %, $[M + Na]^+$), 511.5 (100 %, $[MH]^+$). HRMS *m/z* 533.2404; calcd for $C_{32}H_{34}N_2NaO_4^+$ 533.2416.

*(Z)-Ethyl 2-[1-benzyl-5-(pent-4-enyl)-1*H*-pyrrole-2-carbonyl]-4-methylpent-2-enoate (**26**)*

Bis(dibenzylideneacetone)palladium(0) (82 mg, 0.143 mmol) was added to a stirred solution of triphenylphosphine (150 mg, 0.570 mmol) in THF (35 mL) and left to stir for 0.5 h at room temperature. After this time, alkyne **25**[9] (0.701 g, 5.00 mmol) was added, followed by dropwise addition of Bu_3SnH (1.40 mL, 5.0 mmol), and the mixture was then stirred for 0.5 h. Acid chloride **16** (1.44 g, 5.0 mmol) and Cu^ICl (350 mg, 3.5 mmol) were then added, and the reaction stirred at room temperature for 24 h. After this time, potassium fluoride (10 % w/v in H_2O, 30 mL) was added, and the triphasic mixture was stirred for 5 h. To this mixture, H_2O (20 mL) and Et_2O (60 mL) were added. After separation, the aqueous phase was re-extracted with Et_2O (30 mL), and the combined organic fractions were dried over $MgSO_4$ and concentrated onto silica gel (5 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, sequential elution 94 : 6 → 87 : 13 hexane/Et_2O) giving the title compound as a discoloured oil (1.09 g, 55 %). ν_{max} (neat)/cm^{-1} 3066, 2961, 1719, 1638, 1623, 1478, 1215, 1183, 1032, 727. δ_H ($CDCl_3$, 300 MHz) 7.30–7.20 (3H, m), 6.95 (2H, d, *J* 7.5), 6.82 (1H, d, *J* 4.2), 6.27 (1H, d, *J* 9.9), 6.03 (1H, d, *J* 4.2), 5.74 (1H, m_c), 5.68 (2H, s), 5.02–4.94 (2H, m), 4.20 (2H, q, *J* 7.1), 3.21 (1H, dsept, *J* 9.9, 6.6), 2.51 (2H, t, *J* 7.8), 2.07 (2H, app. q, J_{app} 7.1), 1.67 (2H, app. quin, J_{app} 7.5), 1.21 (3H, t, *J* 7.1), 1.09 (6H, d, *J* 6.6). δ_C ($CDCl_3$, 75 MHz; JMOD) 182.2 (C), 165.8 (C), 153.8 (CH), 144.3 (C), 138.3 (C), 137.7 (CH), 133.3 (C), 129.9 (C), 128.4 (CH), 126.9 (CH), 126.0 (CH), 122.4 (CH), 115.2 (CH_2), 107.9 (CH), 60.6 (CH_2), 48.2 (CH_2), 33.1 (CH_2), 28.5 (CH), 27.3 (CH_2), 25.6 (CH_2), 22.1 (CH_3), 14.0 (CH_3). *m/z* (ESI) 804.7 (25 %, 2 × $[M + NH_4]^+$), 394.5 (100 %, $[MH]^+$). HRMS *m/z* 394.2376; calcd for $C_{25}H_{32}NO_3^+$ 394.2382.

trans-*Ethyl 1-Benzyl-4-isopropyl-6-oxo-2-(pent-4-enyl)-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-5-carboxylate (*rac*-**27**)*

$MeSO_3H$ (0.70 mL, 10.5 mmol) was added dropwise to a stirred solution of **26** (825 mg, 2.10 mmol) in DCM (11 mL) at room temperature, and the mixture was stirred for 0.5 h. After this time, the acid was quenched by gradual addition of $NaHCO_3$ (5 % w/v aqueous, 60 mL). After stirring for 1 h, the mixture was taken up in DCM (40 mL), and the organic phase was separated. The aqueous phase was then re-extracted with DCM (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to give the title compound as a thick oil (817 mg, 99 %). ν_{max} (neat)/cm^{-1} 2958, 1732, 1677, 1473, 1247, 1153, 1029, 725. δ_H ($CDCl_3$, 300 MHz) 7.32–7.18 (3H, m), 7.08 (2H, d, *J* 7.5), 5.97 (1H, s), 5.73 (1H, m_c), 5.35–5.22 (2H, m), 5.03–4.94 (2H, m), 4.23 (2H, q, *J* 7.1), 3.56 (1H, d, *J* 2.7), 3.31 (1H, dd, *J* 6.3, 2.7), 2.49 (2H, t, *J* 7.8), 2.06 (2H, app. q, J_{app} 7.1), 1.94 (1H, app. octet, J_{app} 6.7), 1.64 (2H, app. quin, J_{app} 7.5), 1.29 (3H, t, *J* 7.1), 1.00 (3H, d, *J* 6.6), 0.99 (3H, d, *J* 6.6). δ_C ($CDCl_3$, 75 MHz; JMOD) 183.2 (C), 170.7 (C), 153.6 (C), 149.4 (C), 137.6 (CH), 137.2 (C), 132.2 (C), 128.6 (CH), 127.4 (CH), 126.8 (CH), 115.3 (CH_2), 105.1 (CH), 62.7 (CH), 61.1 (CH_2), 47.6 (CH_2), 45.4 (CH), 33.1 (CH_2), 31.8 (CH), 27.2 (CH_2), 25.8 (CH_2), 20.1 (CH_3), 19.7 (CH_3), 14.1 (CH_3). *m/z* (ESI) 804.6 (20 %, 2 × $[M + NH_4]^+$), 394.5 (100 %, $[MH]^+$). HRMS *m/z* 394.2367; calcd for $C_{25}H_{32}NO_3^+$ 394.2382.

*1-Benzyl-4-isopropyl-2-(pent-4-enyl)-4,5-dihydrocyclopenta[*b*]pyrrole-6(1*H*)-one (*rac*-**28**)*

Sulfuric acid (680 μL, 12.9 mmol) was added dropwise to a stirred mixture of ester *rac*-**27** (817 mg, 2.08 mmol) and H_2O (1.2 mL) in ethanol (95 %, 8 mL). This solution was then refluxed for 8 h. After this time, the reaction was cooled to room temperature and quenched with aqueous $NaHCO_3$ (5 % v/w aqueous, 100 mL) before addition of DCM (30 mL) and separation of the organic phase. The aqueous phase was re-extracted with DCM (2 × 20 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated onto silica (3 g). Flash chromatography (silica gel, sequential elution 9 : 1 → 88 : 12 hexane/ethyl acetate) gave the title compound as a discoloured oil (601 mg, 90 %). ν_{max} (neat)/cm^{-1} 3065, 2956, 1668, 1470, 1389, 1259, 911, 721. δ_H ($CDCl_3$, 300 MHz) 7.32–7.20 (3H, m), 7.08 (2H, d, *J* 7.5), 5.94 (1H, s), 5.73 (1H, m_c), 5.31 (2H, s), 5.02–4.94 (2H, m), 2.99 (1H, ddd, *J* ~6.6, 6.3, 1.6), 2.90 (1H, dd, *J* 17.8, 6.3), 2.54 (1H, dd, *J* 17.8, 1.6), 2.48 (2H, t, *J* 7.8), 2.06 (2H, app. q, J_{app} 7.1), 1.84 (1H, app. octet, J_{app} 6.6), 1.64 (2H, app. quin, J_{app} 7.5), 0.96 (6H, d, *J* 6.9). δ_C ($CDCl_3$, 75 MHz; JMOD) 190.1 (C), 154.2 (C), 147.9 (C), 137.7 (CH), 137.6 (C), 133.6 (C), 128.6 (CH), 127.3 (CH), 126.7 (CH), 115.2 (CH_2), 104.8 (CH), 47.4 (CH_2), 46.1 (CH_2), 40.3 (CH), 33.1 (CH_2), 32.1 (CH), 27.4 (CH_2), 25.7 (CH_2), 20.2 (CH_3), 19.6 (CH_3). *m/z* (ESI)

643.5 (50 %, 2 × $[M + H]^+$), 322.2 (100 %, $[MH]^+$). HRMS *m/z* 322.2168; calcd for $C_{22}H_{28}NO^+$ 322.2171.

trans-*1-Benzyl-4-isopropyl-2,5-di(pent-4-enyl)-4,5-dihydrocyclopenta[b]pyrrole-6(1H)-one* (rac-***29***)

n-Butyllithium (1.92 M in cyclohexane, 1.07 mL, 2.05 mmol) was added dropwise to a stirred solution of diisopropylamine (269 μL, 2.05 mmol) in THF (2 mL) at −78°C. This solution was then stirred for 10 min. Ketone *rac*-**28** (507 mg, 1.58 mmol) in THF (4 mL) was added, and the reaction mixture was allowed to warm to room temperature before being cooled to −78°C. 5-Iodopentene (341 mg, 1.74 mmol) was added, and the reaction mixture was warmed to room temperature and was stirred for 4 h. After this time, the reaction was taken up in Et_2O (20 mL) and H_2O (40 mL). The organic phase was separated, and the aqueous phase was re-extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated onto silica (3 g). Flash chromatography (silica gel, 92 : 8 hexane/ethyl acetate) gave the title compound as a viscous oil (488 mg, 79 %). ν_{max} (neat)/cm^{-1} 3072, 2929, 1668, 1472, 1389, 909, 725. δ_H ($CDCl_3$, 300 MHz) 7.31–7.20 (3H, m), 7.05 (2H, d, *J* 7.5), 5.91 (1H, s), 5.88–5.66 (2H, m), 5.31 (2H, s), 5.04–4.91 (4H, m), 2.69 (1H, dd, *J* 5.3, 1.7), 2.54 (1H, ddd, *J* 7.7, 4.8, 1.7), 2.48 (2H, t, *J* 7.8), 2.12–2.02 (4H, m), 1.94–1.73 (2H, m), 1.72–1.58 (3H, m), 1.56–1.43 (2H, m), 1.02 (3H, d, *J* 6.9), 0.88 (3H, d, *J* 6.6). δ_C ($CDCl_3$, 75 MHz; JMOD) 192.3 (C), 152.1 (C), 147.9 (C), 138.4 (CH), 137.7 (C), 137.6 (CH), 133.2 (C), 128.5 (CH), 127.2 (CH), 126.6 (CH), 115.1 (CH_2), 114.4 (CH_2), 104.8 (CH), 56.7 (CH), 47.3 (CH_2), 46.9 (CH), 34.0 (CH_2), 33.1 (CH_2), 32.0 (CH_2), 31.9 (CH), 27.3 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 20.9 (CH_3), 19.0 (CH_3). *m/z* (ESI) 779.7 (20 %, 2 × $[M + H]^+$), 390.5 (100 %, $[MH]^+$). HRMS *m/z* 390.2795; calcd for $C_{27}H_{36}NO^+$ 390.2797.

*4-[(*tert*-Butyldimethylsilyl)oxy]-3,3-dimethoxybutanoic Acid (**35**)*

Methyl tetronate (8.0 g, 70.1 mmol) and NaOH (3.34 g, 83.6 mmol) were refluxed for 16 h in methanol (80 mL) with stirring. After this time, the reaction was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in DMF (80 mL) and TBSCl (31.7 g, 210 mmol) and imidazole (28.6 g, 421 mmol) were added. The reaction was stirred at room temperature for 3 days before being poured into water and extracted with Et_2O. The organic phase was then concentrated under reduced pressure. The residue was dissolved in methanol (MeOH)/THF/H_2O (3 : 1 : 1, 1100 mL) and stirred with K_2CO_3 (33.9 g, 245 mmol) at room temperature for 0.5 h. The reaction mixture was then concentrated to 200 mL under reduced pressure and extracted with Et_2O (200 mL) to remove silyl impurities. The aqueous phase was diluted with brine (650 mL), acidified to pH 4 with 1 M $KHSO_4$, and extracted with Et_2O. This organic extract was dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound as a low-melting white solid (16.9 g, 87 %). δ_H ($CDCl_3$, 400 MHz) 10.15 (1H, br s), 3.70 (2H, s), 3.31 (6H, s), 2.80 (2H, s), 0.91 (9H, s), 0.10 (6H, s). This spectrum was identical to that previously reported.[4]

*4-Hydroxy-3,3-dimethoxy-1-(1H-pyrrole-2-yl)butan-1-one (**36**)*

2,2′-Dipyridyl disulfide (6.45 g, 29.3 mmol) and triphenylphosphine (PPh_3; 7.69 g, 29.3 mmol) were added to a stirred solution of acid **35** (7.10 g, 25.5 mmol) in toluene (26 mL) at room temperature. After stirring at room temperature for 16 h, the reaction was cooled to −78°C. A cooled (−40°C) solution of pyrrolylmagnesiumbromide [formed from slow addition of MeMgBr (2.47 M in ether, 41.3 mL, 102 mmol) to pyrrole (7.4 mL, 107 mmol) in toluene (90 mL) at −40°C] was added via a cannula. After stirring at −78°C for 2 h, the reaction was quenched with saturated aqueous NH_4Cl and warmed to room temperature. The phases were separated, and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were washed sequentially with 5 % K_2CO_3, H_2O, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was dissolved in THF (82 mL) and cooled to 0°C with stirring. TBAF (1.0 M in THF, 28.1 mL, 28.1 mmol) was added slowly, and the reaction was allowed to warm to room temperature over 1 h. The reaction was quenched with aqueous NH_4Cl and extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated onto silica gel (35 g) under reduced pressure. Flash chromatography (silica gel, 1 : 1 ethyl acetate (EtOAc)/hexanes) gave the title compound as a yellow oil (4.74 g, 87 %). δ_H ($CDCl_3$, 400 MHz) 10.15 (1H, br s), 7.07 (1H, m_c), 7.04 (1H, m_c), 6.27 (1H, m_c), 3.75 (2H, s), 3.45 (1H, br s), 3.28 (6H, s), 3.21 (2H, s). δ_C ($CDCl_3$, 100 MHz) 187.2 (C), 132.6 (C), 126.2 (CH), 118.4 (CH), 111.0 (CH), 101.4 (C), 63.1 (CH_2), 48.5 (CH_3), 41.0 (CH_2). HRMS *m/z* 214.1077; calcd for $C_{10}H_{16}NO_4^+$ 214.1079.

*2-(4-Methoxyfuran-2-yl)-1-(triisopropylsilyl)-1H-pyrrole (**3b**)*

PPTS (1.49 g, 5.93 mmol) was added to a solution of keto-alcohol **36** (4.74 g, 22.2 mmol) in DMSO (740 mL) at room temperature, and the solution was then stirred for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (250 mL; an external water bath used to limit warming), followed by addition of H_2O (700 mL) until homogeneity. The aqueous mixture was extracted with Et_2O (4 × 400 mL). The combined organic extracts were concentrated to 200 mL, washed sequentially with $NaHCO_3$(aq) and brine, dried over $MgSO_4$, filtered into a flask for the next reaction, and concentrated to give 2-(4-methoxyfuran-2-yl)-1*H*-pyrrole. [δ_H ($CDCl_3$, 400 MHz) 8.52 (1H, br s), 7.02 (1H, d, *J* 1.0), 6.80 (1H, m_c), 6.40 (1H, m_c), 6.24 (1H, m_c), 6.18 (1H, d, *J* 1.0), 3.74 (3H, s)]. This material was dissolved in THF (220 mL), cooled to 0°C, and KH (1.31 g, 32.6 mmol) was carefully added, followed by triisopropylsilyl chloride (7.0 mL, 32.7 mmol). The reaction was warmed to room temperature and stirred for 3 h. Flash chromatography (silica gel, 15 % toluene in hexanes) gave the title compound as a sensitive low-melting white solid (5.25 g 74 %). δ_H NMR ($CDCl_3$, 400 MHz) 7.06 (1H, d, *J* 1.1), 6.93 (1H, dd, *J* 2.8, 1.5), 6.42 (1H, dd, *J* 3.2, 1.5), 6.28 (1H, t, *J* 3.0), 6.18 (1H, d, *J* 1.1), 3.74 (3H, s), 1.34 (3H, septet, *J* 7.5), 1.07 (18H, d, *J* 7.5). δ_C ($CDCl_3$, 100 MHz) 151.0 (C), 148.1 (C), 127.8 (C), 127.4 (CH), 121.2 (CH), 114.7 (CH), 109.8 (CH), 102.1 (CH), 57.6 (CH_3), 18.2 (CH_3), 12.8 (CH). HRMS *m/z* 320.2033; calcd for $C_{18}H_{30}NO_2Si^+$ 320.2040.

Supplementary Material

Copies of ^1H and ^{13}C NMR spectra of all key compounds synthesised in this study are available on the Journal's website.

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