Total synthesis of siphonazole and its *O*-methyl derivative, structurally unusual bis-oxazole natural products†

Jörg Linder, Alexander J. Blake and Christopher J. Moody*

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The details of the first syntheses of the unusual bis-oxazole natural products siphonazole and its *O*-methyl derivative are reported. The cinnamyl substituted oxazole was constructed using diazocarbonyl chemistry, whereby the cinnamamide was reacted with the rhodium carbene derived from methyl 2-diazo-3-oxobutanoate to give a β-ketoamide that was cyclodehydrated to the corresponding oxazole-4-ester. Reduction to the corresponding aldehyde was followed by coupling with a zinc reagent derived from methyl 2-iodomethyl-5-methyloxazole-4-carboxylate, also prepared using rhodium carbene chemistry, to give, after oxidation of the resulting secondary alcohol, the desired bis-oxazole ketone. The syntheses were completed by hydrolysis of the ester and coupling of the 2,4-pentadienylamine side chain.

Introduction

Although once considered unusual, naturally occurring oxazoles have attracted increasing attention over the last two decades. The interest has been heightened by the isolation of a range of structurally diverse and synthetically challenging oxazoles, particularly from the marine environment.[1–7] In addition to a number of complex molecules containing a single oxazole, many of these natural products contain two or more oxazole rings that are either directly linked (2,4′-bis-oxazoles) or separated by at least three atoms.[8] Thus, for example, directly linked bis-oxazoles occur in muscoride A,[9–12] diazonamide A,[13–17] and the hennoxazoles,[18–22] tris-oxazoles in ulapualide A[23–25] whilst the telomerase inhibitor telomestatin contains a remarkable array of seven 2,4′-linked oxazoles.[26,27] Bis-oxazoles in which the 2,4′-link is part of a peptide chain occur in, for example, leucamide A,[28,29] whilst polyene units link the two oxazole rings in the disorazoles[30,31] and the antitumor phorboxazoles (Fig. 1).[32–44]

Bis-oxazoles that are linked by just one or two carbon atoms are very unusual as natural products, and the antifungal bengazoles are unique with their two oxazole rings being linked (2,5′) by a single carbon (Fig. 1).[45–47] Recently König and co-workers reported a further example of this rare class of natural products, a bis-oxazole in which the two heterocyclic rings are linked by two carbon atoms.[48] Siphonazole **1** was isolated, along with its *O*-methyl derivative **2** (Fig. 2), from a gliding bacterium of the *Herpetosiphon* genus, and its structure assigned on the basis of detailed spectroscopic studies.[48] As well as the aforementioned, unusual C_2 link between the two oxazoles, siphonazole contains an unprecedented *N*-penta-2,4-dienyl amide side chain, as well as a cinnamate residue, also rare in bacterial natural products. Feeding studies using ^{13}C-labeled precursors confirmed mixed biosynthetic pathways with the incorporation of five acetate units, both oxazole rings originating from threonine, and, unusually, benzoate (as opposed to phenylalanine) being postulated as the precursor to the cinnamate moiety.[48] We now report the details of the first synthesis of this new structural class of natural products.[49]

Results and discussion

Our synthetic strategy, shown by the disconnections indicated in Fig. 2, involved the installation of the pentadienylamino side-chain as the last step, that would be preceded by the union of the two oxazole fragments using acylation of a 2-methyloxazole derivative. The two oxazole rings themselves would be constructed using the methodology previously developed in our laboratory, whereby reactive rhodium carbenes, formed upon treatment of diazocarbonyl compounds with catalytic amounts of dirhodium(II) carboxylates, led to oxazoles upon reaction with nitriles, or with carboxamides followed by cyclodehydration.[50–56]

The synthesis was initiated from 3-hydroxy-4-methoxycinnamic acid **3a** that was protected as its *tert*-butyldimethylsilyl ether, and converted into the carboxamide **4a** in good yield. Subsequent dirhodium tetraacetate catalyzed reaction with methyl 2-diazo-3-oxobutanoate resulted in chemoselective N–H insertion of the metal carbene into the amide N–H bond in high yield to give the ketoamide **5a**. No products formed by competing cyclopropanation of the double bond were observed illustrating the highly selective nature of the N–H insertion process. Cyclodehydration of the ketoamide **5a** using the Ph_3P–I_2–Et_3N protocol introduced by Wipf and co-workers[57] gave the desired oxazole **6a** (Scheme 1). In a similar manner, 3,4-dimethoxycinnamamide **4b** was converted into the oxazole **6b** in 80% yield over the two steps.

The above sequence involving carbene addition to carboxamides followed by dehydration can, of course, be reversed, since nitriles are known to react with diazocarbonyl compounds to give oxazoles.[50,52,58–61] Hence dehydration of the cinnamamide **4a** with ethyl dichlorophosphate gave the corresponding nitrile **9a**,

School of Chemistry, University of Nottingham, University Park, Nottingham, UK NG7 2RD

† Electronic supplementary information (ESI) available: Experimental details for compounds **4**, **5**, **9–14**, **20**, **21** and 2,4-pentadienylamine; X-ray crystal structure of compound **8b**; copies of ^1H and ^{13}C NMR spectra; and HPLC data for natural and synthetic siphonazole. CCDC reference number 693019. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b810855b

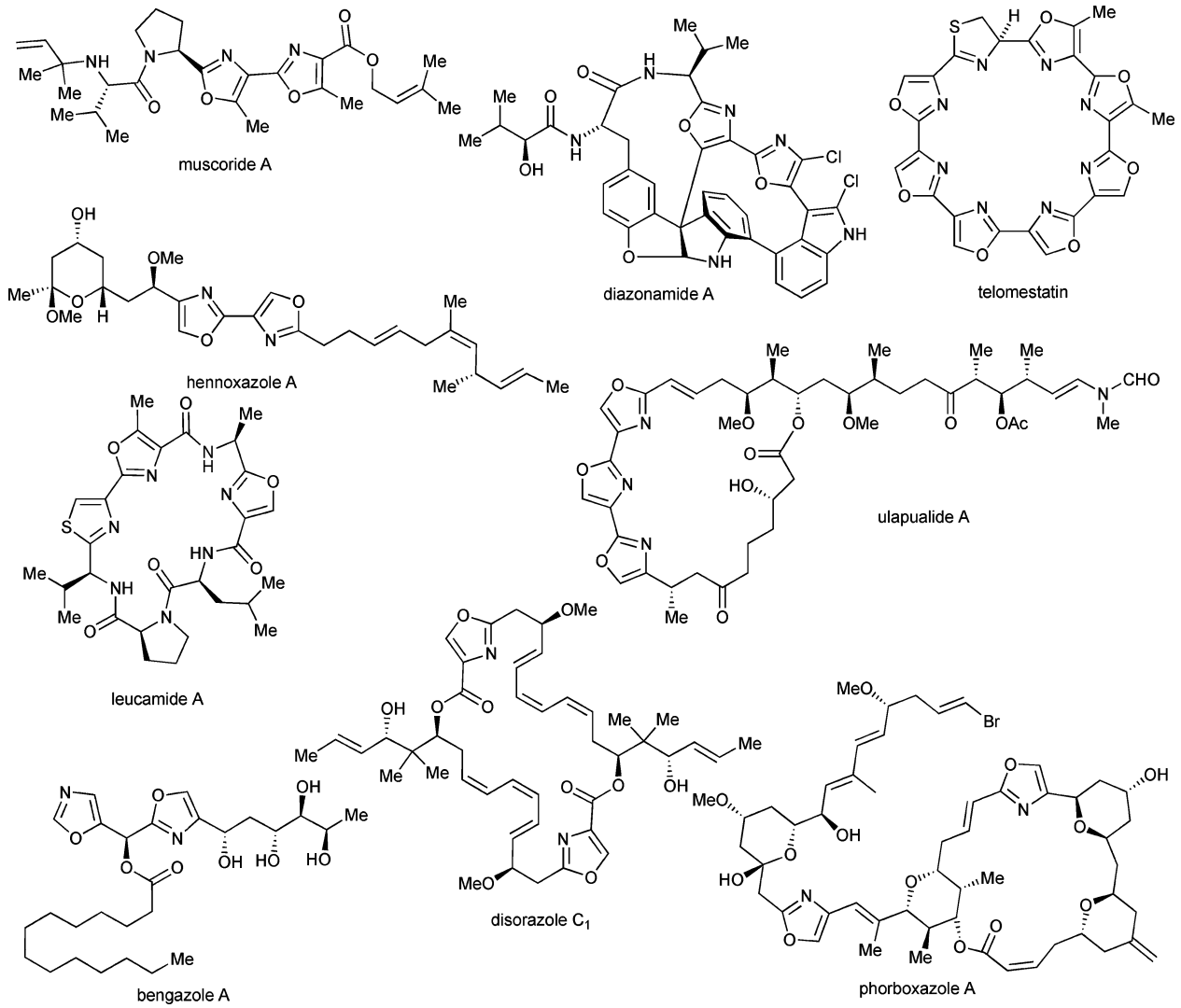


Fig. 1 Some naturally occurring oxazoles.

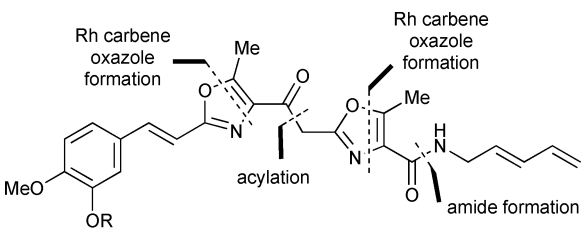
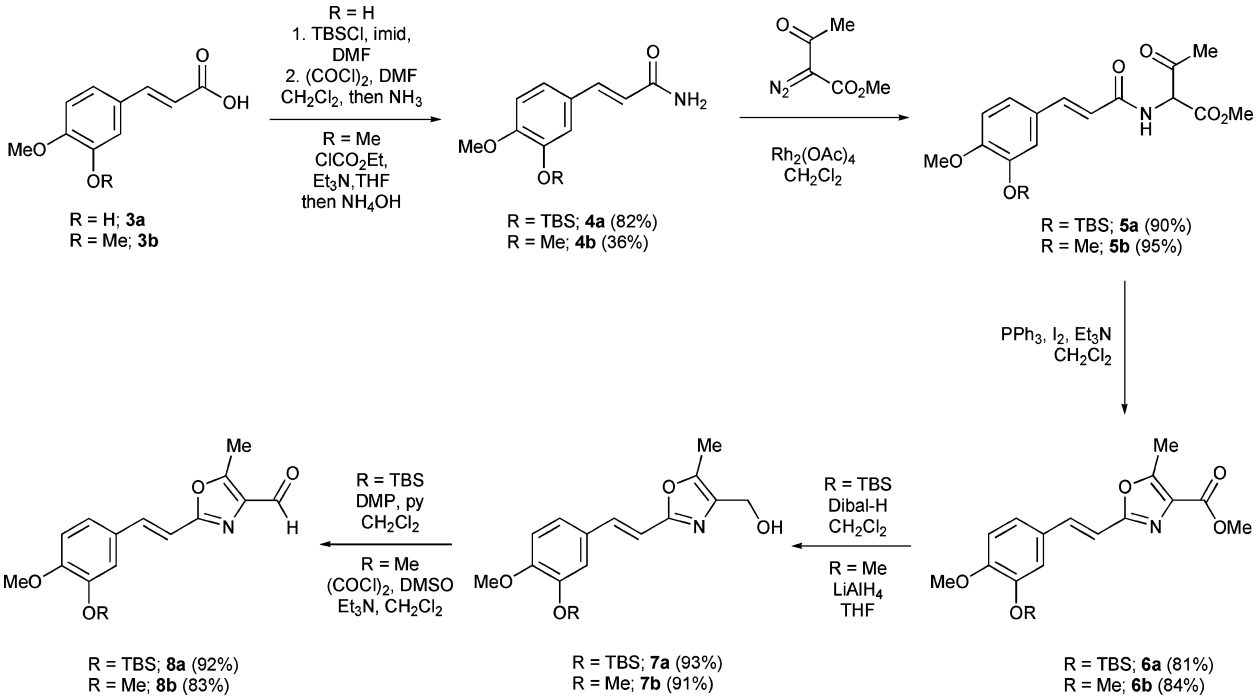


Fig. 2 Retrosynthetic analysis of siphonazole.

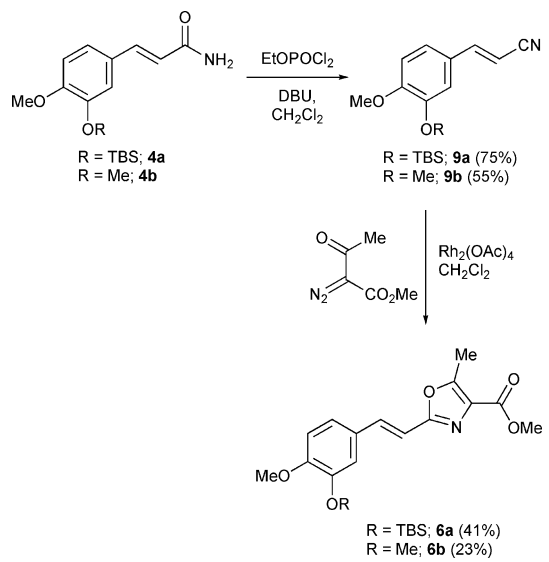
reaction of which with methyl 2-diazo-3-oxobutanoate gave the same oxazole **6a** although in poorer overall yield (Scheme 2). Likewise, the 3,4-dimethoxy derivative **4b** was converted into the corresponding nitrile **9b**, and hence the oxazole **6b**, although the yield was again poor.

Methyl 2-diazo-3-oxobutanoate also served as precursor to the second oxazole ring of siphonazole, although in this case reactions with nitriles proceeded well. Thus, dirhodium tetraacetate catalyzed reaction with iodoacetonitrile or acetonitrile gave the oxazoles **10** and **11** in good yield. The 2,5-dimethyloxazole **11** was converted into other potential nucleophilic coupling partners, namely the acid **12**, the *N*-ethyl carboxamide **13**, and the *tert*-butyl ester **14** by standard methods (Scheme 3).

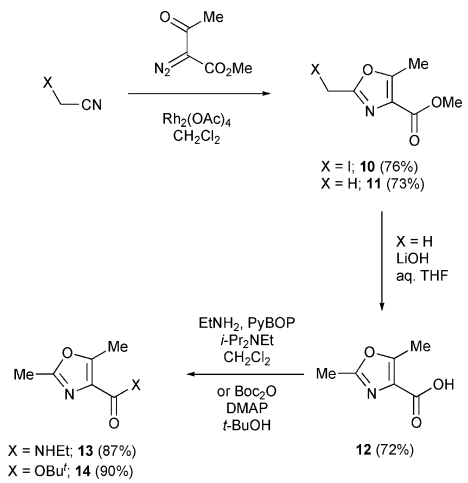
Since Grignard reagents derived from 2-halomethyloxazoles are known to be acylated by ester type electrophiles,[36] and oxazole-4-esters are known to function as acylating agents,[62] initial attempts to forge the link between the two oxazole rings required for siphonazole focused on the reaction between the oxazole-4-ester **6a** and the Grignard reagent formed by treatment of 2-iodomethyloxazole **10** with isopropylmagnesium chloride. Unfortunately, despite some spectroscopic evidence for its formation, the required ketone **15** (Scheme 4) could never be isolated from the reaction mixture. Likewise, reaction of the same Grignard reagent with the Weinreb amide derived from oxazole **6b** was also unsatisfactory (not shown). Next, we attempted to acylate the dianion formed by treatment of 2,5-dimethyloxazole-4-carboxylic acid **12** with LDA with oxazole ester **6b**. Again, very small



Scheme 1



Scheme 2

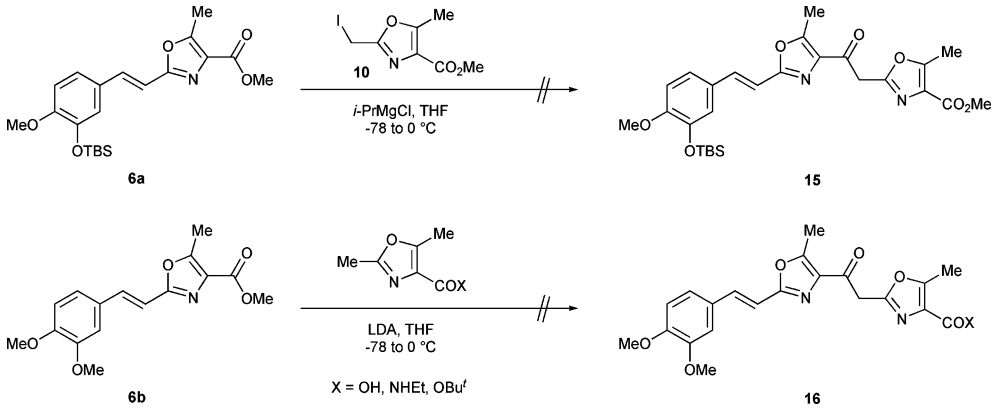


Scheme 3

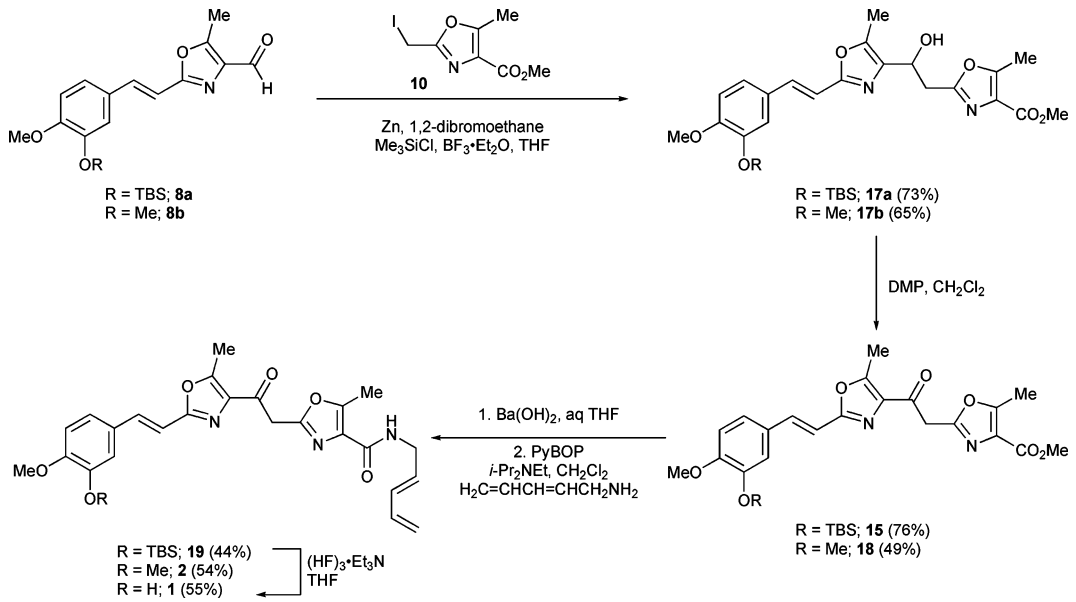
amounts of the desired ketone **16** were formed, but in common with previous reactions of the 2,5-dimethyloxazole-4-carboxylic acid dianion,[63] deprotonation and acylation of the 5-methyl group was also observed. Attempts to use the dianion from oxazole-4-carboxamide **13** were similarly disappointing, as were all efforts employing the anion from the 2,5-dimethyloxazole *tert*-butyl ester **14**, even under conditions ($LiNEt_2$ as base) developed by Evans and co-workers that are known to favour deprotonation of the oxazole-2-methyl group.[64]

In light of the failure to engage the oxazole-4-carboxylate ester **6a** in acylation reactions, we elected to convert it into the corresponding aldehyde **8a** in preparation for a potentially easier coupling to an organometallic derivative of the second oxazole ring. Hence reduction of ester **6a** with Dibal-H followed by reoxidation of the alcohol **7a** with the Dess–Martin periodinane delivered the required aldehyde **8a** in 81% yield over the two steps (Scheme 1), direct conversion of the ester to the aldehyde being unsatisfactory. In a similar manner, the dimethoxy derivative **6b** was converted into the oxazole-4-carboxaldehyde **8b** in 76% yield over the two steps. The structure of aldehyde **8b** was confirmed by X-ray crystallography (Figure in the ESI†).

The key coupling reaction was effected by formation of the zinc reagent from the 2-iodomethyloxazole **10** using activated zinc,[65] followed by reaction with the aldehyde **8a** in the presence of boron trifluoride etherate.[66] Although 2-bromomethyloxazoles have previously been successfully converted into zinc reagents,[67] in the present case, the use of the iodide was essential. The addition



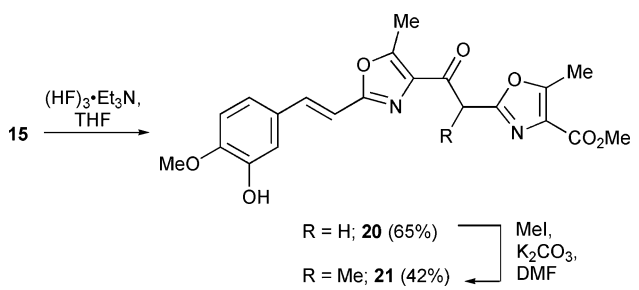
Scheme 4



Scheme 5

proceeded in good yield (73%), and the resulting secondary alcohol **17a** was oxidized with the Dess–Martin periodinane to give the desired bis-oxazole ketone **15** (Scheme 5). Hydrolysis of the ester with barium hydroxide, and coupling to 2,4-pentadienylamine,[68] prepared from methyl 2,4-pentadienoate by reduction to the alcohol and conversion to the amine by way of the bromide and azide (see ESI†), using PyBOP (benzotriazol-1-yloxy-tris-pyrrolidino-phosphonium hexafluorophosphate) and Hünig's base gave protected siphonazole **19** in 44% yield over the two steps. Finally, treatment with triethylamine trihydrofluoride resulted in removal of the silicon protecting group to give siphonazole **1** (Scheme 5). The ^{1}H and ^{13}C NMR spectroscopic data of our synthetic siphonazole were identical to those reported for the natural product,[48] and the material was identical to an authentic sample by HPLC and NMR spectroscopy.

With supplies of siphonazole **1** in hand, we attempted to convert it directly into the naturally occurring *O*-methyl derivative **2** by treatment with diazomethane, but without success. In a related manner, we also attempted to react phenol **20**, obtained by desilylation of bis-oxazole **15**, with diazomethane to give the corresponding *O*-methyl compound, but again without success. Reaction of phenol **20** with iodomethane and potassium carbonate in DMF somewhat surprisingly resulted in the formation of the *C*-methylated product **21** in modest yield with no sign of the desired *O*-methyl compound (Scheme 6). In view of the disappointing failure to effect a late stage methylation, we returned to the dimethoxycinnamyl oxazole aldehyde **8b** prepared from 3,4-dimethoxycinnamic acid **3b** as previously described in



Scheme 6

Scheme 1. Coupling with the zinc derivative formed from 2-iodomethyloxazole **10** proceeded smoothly to give bis-oxazole **17b**, oxidation of which gave the bis-oxazole ketone **18** (Scheme 5). Ester hydrolysis and coupling with 2,4-pentadienylamine then gave *O*-methylsiphonazole **2** in 54% yield over the two steps. Our synthetic material showed identical ^{1}H and ^{13}C NMR spectroscopic data to those reported for the natural product.[48]

The syntheses of siphonazole **1** and its *O*-methyl derivative **2** not only illustrates the versatility of rhodium carbene chemistry but also confirm unambiguously the structures of these unusual natural products.

Experimental section

General

Commercially available reagents were used throughout without purification unless otherwise stated. Light petroleum refers to the fraction with bp 40–60 °C. Ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Analytical thin layer chromatography was carried out on aluminium backed plates coated with silica gel, and visualized under UV light at 254 and/or 360 nm. R_f values refer to these TLC plates developed in the solvents indicated. Chromatography was carried out on silica gel unless otherwise stated. Fully characterized compounds are chromatographically homogeneous. Infrared spectra were recorded in the range 4000–600 cm^{-1}. NMR spectra were recorded at 400 and 500 MHz (^{1}H frequencies, corresponding ^{13}C frequencies 100 and 125 MHz). Chemical shifts are quoted in ppm and are referenced to residual H in the deuterated solvent as the internal standard. *J* values are recorded in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from DEPT. High and low resolution mass spectra were recorded on a time-of-flight mass spectrometer.

Methyl 2-(3-*tert*-butyldimethylsiloxy-4-methoxystyryl)-5-methyloxazole-4-carboxylate 6a

A solution of the ketoamide **5a** (2.40 g, 5.70 mmol) and triethylamine (3.10 mL, 22.8 mmol) in dry dichloromethane (10 mL) was added dropwise over a period of 1 h to a solution of triphenylphosphine (3.0 g, 11.4 mmol) and iodine (2.90 g, 11.4 mmol) in dry dichloromethane (20 mL) at room temperature. After the addition was complete the reaction mixture was stirred for a further 1 h at which point no starting material could be observed. The mixture was quenched with water. The organic layer was washed with water (30 mL) and brine (30 mL), then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude material was purified by chromatography (eluting with ethyl acetate–light petroleum 1 : 1 + 0.5% triethylamine) to give the *title compound* **6a** as a light yellow solid (1.86 g, 81%); R_f = 0.82 (light petroleum–ethyl acetate 3 : 1); mp 97–99 °C; (Found: C, 62.3; H, 7.2; N, 3.3. $C_{21}H_{29}NO_5Si$ requires C, 62.5; H, 7.2; N, 3.5%); (Found: MH^+, 404.1907. $C_{21}H_{30}NO_5Si$ requires 404.1888); ν_{max} ($CHCl_3$)/cm^{-1} 2951, 2858, 1719, 1616, 1443, 1352, 1305, 1140, 1103, 957; δ_H (400 MHz; $CDCl_3$) 7.40 (1H, d, *J* 16.4, ArC*H*=CH), 7.06 (1H, dd, *J* 8.3, 2.1, ArH-6), 7.03 (1H, d, *J* 2.1, ArH-2), 6.83 (1H, d, *J* 8.3, ArH-5), 6.70 (1H, d, *J* 16.4, ArCH=C*H*), 3.91 (3H, s, OMe), 3.82 (3H, s, OMe), 2.65 (3H, s, Me), 1.0 (9H, s, CMe_3), 0.16 (6H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 162.7 (C), 159.6 (C), 155.7 (C), 152.4 (C), 145.2 (C), 136.7 (CH), 128.3 (C), 128.2 (C), 121.9 (CH), 118.8 (CH), 111.8 (CH), 110.8 (CH), 55.4 (Me), 51.8 (Me), 25.6 (Me), 18.4 (Me), 12.0 (Me), –4.7 (Me); *m*/*z* (ESI^+) 404 (MH^+, 100%).

[2-(3-*tert*-Butyldimethylsiloxy-4-methoxystyryl)-5-methyloxazol-4-yl)]methanol 7a

Ester **6a** (200 mg, 0.50 mmol) was dissolved in dichloromethane (5 mL) and cooled to 0 °C. Dibal-H (1 M in dichloromethane; 1.5 mL) was added dropwise over a period of 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 1 h until the reaction was complete. The mixture was cooled to 0 °C again and hydrochloric acid (2 M) was added dropwise until no further gas formation could be observed. After filtering through a pad of Celite, the mixture was diluted with ethyl acetate (20 mL), the organic layer washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the *title compound* **7a** (175 mg, 93%) as a colourless solid which was used without further purification for the next step; mp 113–116 °C; (Found: MH^+, 376.1948. $C_{20}H_{30}NO_4Si$ requires 376.1939); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 2857, 1694, 1595, 1463, 1274, 1137, 968; δ_H (400 MHz; $CDCl_3$) 7.32 (1H, d, *J* 16.3, ArC*H*=CH), 7.08 (1H, dd, *J* 8.3, 2.0, ArH-6), 7.05 (1H, d, *J* 2.0, ArH-2), 6.83 (1H, d, *J* 8.3, ArH-5), 6.68 (1H, d, *J* 16.3, ArCH=C*H*), 4.54 (2H, d, *J* 4.7, CH_2OH), 3.83 (3H, s, OMe), 2.36 (3H, s, Me), 1.01 (9H, s, CMe_3), 0.17 (6H, s, $SiMe_2$); OH not observed; δ_C (100 MHz; $CDCl_3$) 160.2 (C), 152.0 (C), 145.2 (C), 144.5 (C), 135.4 (C), 135.2 (CH), 128.6 (C), 121.6 (CH), 119.0 (CH), 111.8 (CH), 111.5 (CH), 55.9 (Me), 55.4 (Me), 25.7 (Me), 18.4 (C), 10.2 (Me), –4.7 (Me); *m*/*z* (ESI^+) 376 (MH^+, 100%).

2-(3-*tert*-Butyldimethylsiloxy-4-methoxystyryl)-5-methyloxazole-4-carbaldehyde 8a

Pyridine (0.19 mL, 2.44 mmol) and Dess–Martin periodinane (1.05 g, 2.44 mmol) were added to a solution of alcohol **7a** (460 mg, 1.22 mmol) in dichloromethane (15 mL), and the mixture stirred at room temperature for 2 h. The mixture was diluted with ether (60 mL), aqueous saturated sodium hydrogen carbonate (15 mL) and aqueous sodium metabisulfite (10%; 15 mL) and stirred until two clear layers were formed. The organic layer was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the *title compound* **8a** (420 mg, 92%) as a pale yellow solid which was used without further purification for the next step; mp 112–115 °C; (Found: MH^+, 374.1780. $C_{20}H_{28}NO_4Si$ requires 374.1788); ν_{max} ($CHCl_3$)/cm^{-1} 3612, 2930, 2858, 1640, 1577, 1463, 1304, 1273, 1154, 996; δ_H (400 MHz; $CDCl_3$) 9.97 (1H, s, CHO), 7.43 (1H, d, *J* 16.4, ArC*H*=CH), 7.11 (1H, dd, *J* 8.3, 2.1, ArH-6), 7.05 (1H, d, *J* 2.1, ArH-2), 6.85 (1H, d, *J* 8.3, ArH-5), 6.71 (1H, d, *J* 16.3, ArCH=C*H*), 3.84 (3H, s, OMe), 2.67 (3H, s, Me), 1.01 (9H, s, CMe_3), 0.18 (6H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 185.2 (CH), 160.5 (C), 155.8 (C), 152.5 (C), 145.2 (C), 137.4 (CH), 135.8 (C), 128.0 (C), 122.0 (CH), 119.0 (CH), 111.8 (CH), 110.5 (CH), 55.4 (Me), 25.6 (Me), 18.4 (C), 11.7 (Me), –4.7 (Me); *m*/*z* (ESI^+) 374 (MH^+, 100%).

Methyl 2-(2-(2-(3-*tert*-butyldimethylsiloxy-4-methoxystyryl)-5-methyloxazol-4-yl)-2-hydroxyethyl)-5-methyloxazole-4-carboxylate 17a

Zinc dust (294 mg, 4.50 mmol) was placed in a Schlenk tube under an argon atmosphere and suspended in dry THF (6 mL), 1,2-dibromoethane (37.0 μL, 0.45 mmol) added and the mixture heated up to 60 °C for 5 min. After cooling down to room temperature, trimethylsilyl chloride (10.3 μL, 0.08 mmol) was added and stirring continued for further 15 min. At 0 °C aldehyde **8a** (280 mg, 0.75 mmol) and boron trifluoride-etherate (0.19 mL, 1.50 mmol) were added. Iodo-oxazole **10** (419 mg, 1.50 mmol) in THF (4 mL) was added dropwise over a period of 3 h. The zinc residues were filtered off, the solvent removed under reduced pressure and the residue purified by chromatography (eluent ethyl acetate–light petroleum 2 : 1 + 0.5% triethylamine) to give the *title compound* **17a** as a light yellow solid (290 mg, 73%); $R_f = 0.27$ (light petroleum–ethyl acetate 1 : 2); mp 142–144 °C; (Found: MH^+, 529.2361. $C_{27}H_{37}N_2O_7Si$ requires 529.2292); ν_{max} ($CHCl_3$)/cm^{-1} 3416, 2930, 2858, 1722, 1625, 1462, 1354, 1101, 986; δ_H (400 MHz; $CDCl_3$) 7.27 (1H, d, *J* 16.3, ArC*H*=CH), 7.03 (1H, dd, *J* 8.3, 2.1, ArH-6), 7.01 (1H, d, *J* 2.1, ArH-2), 6.81 (1H, d, *J* 8.3, ArH-5), 6.64 (1H, d, *J* 16.3, ArCH=C*H*), 5.17 (1H, dd, *J* 8.7, 4.7, C*H*OH), 3.86 (3H, s, OMe), 3.80 (3H, s, OMe), 3.36 (1H, dd, *J* 15.6, 8.7, C*H*H), 3.16 (1H, dd, *J* 15.6, 4.7, CH*H*), 2.55 (3H, s, Me), 2.32 (3H, s, Me), 0.97 (9H, s, CMe_3), 0.15 (6H, s, $SiMe_2$); OH not observed; δ_C (100 MHz; $CDCl_3$) 162.6 (C), 160.2 (C), 160.1 (C), 156.3 (C), 152.1 (C), 145.2 (C), 144.2 (C), 136.1 (C), 135.2 (CH), 128.6 (C), 127.2 (C), 121.7 (CH), 118.7 (CH), 111.8 (CH), 111.5 (CH), 64.3 (CH), 55.4 (Me), 51.8 (Me), 35.4 (CH_2), 25.7 (Me), 18.4 (C), 11.9 (Me), 10.4 (Me), –4.2 (Me); *m*/*z* (ESI^+) 551 (MNa^+, 100%), 529 (MH^+, 79%).

Methyl 2-(2-(2-(3-*tert*-butyldimethylsiloxy-4-methoxystyryl)-5-methyloxazol-4-yl)-2-oxoethyl)-5-methyloxazole-4-carboxylate 15

Dess–Martin periodinane (52.0 mg, 0.12 mmol) was added to a solution of alcohol **17a** (60.0 mg, 0.11 mmol) dissolved in dichloromethane (3 mL) and the mixture stirred at room temperature for 20 min. The mixture was diluted with ether (12 mL), aqueous saturated sodium hydrogen carbonate (3 mL) and aqueous sodium metabisulfite (10%; 3 mL) and stirred until two clear layers were formed. The organic layer was washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by chromatography (eluting with ethyl acetate–light petroleum 1 : 3 + 0.5% triethylamine) to give the *title compound* **15** as a light yellow solid (44.0 mg, 76%); $R_f = 0.73$ (light petroleum–ethyl acetate 1 : 2); mp 116–120 °C; (Found: MH^+, 527.2226. $C_{27}H_{35}N_2O_7Si$ requires 527.2214); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 2857, 1624, 1593, 1354, 1274, 1102, 968; δ_H (400 MHz; $CDCl_3$) 7.37 (1H, d, *J* 16.3, ArC*H*=CH), 7.07 (1H, dd, *J* 8.3, 1.8, ArH-6), 7.05 (1H, d, *J* 1.8, ArH-2), 6.84 (1H, d, *J* 8.2, ArH-5), 6.67 (1H, d, *J* 16.3, ArCH=C*H*), 4.47 (2H, s, CH_2), 3.88 (3H, s, OMe), 3.83 (3H, s, OMe), 2.64 (3H, s, Me), 2.62 (3H, s, Me), 1.00 (9H, s, CMe_3), 0.16 (6H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 189.3 (C), 162.6 (C), 159.2 (C), 157.0 (C), 156.5 (C), 155.4 (C), 152.5 (C), 145.2 (C), 137.1 (CH), 134.3 (C), 128.1 (C), 127.6 (C), 122.1 (CH), 118.9 (CH), 111.8 (CH), 110.6 (CH), 55.4 (Me), 51.8 (Me), 39.5 (CH_2), 25.6 (Me), 18.4 (C), 12.3 (Me), 11.9 (Me), –4.7 (Me); *m*/*z* (ESI^+) 527 (MH^+, 100%).

TBDMS-protected siphonazole 19

Ester **15** (23.0 mg, 43.7 μmol) was dissolved in THF (4 mL) and barium hydroxide (15.0 mg, 87.4 μmol) in water (1 mL) added and the mixture stirred for 16 h. The solvent was removed in *vacuo*, the residue dissolved in ethyl acetate (15 mL) and aqueous citric acid (10%; 10 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (15 mL), the combined organic layers washed with brine (15 mL) and dried ($MgSO_4$). After removal of the solvent the crude carboxylic acid (18.0 mg, 35.0 μmol, 80%) was directly used for the next step. The carboxylic acid was dissolved in dichloromethane (4 mL), diisopropylethylamine (26.0 μL, 175 μmol) and PyBOP (20.0 mg, 42.0 μmol) were added and the reaction stirred at room temperature for 20 min before (*E*)-2,4-pentadienylamine was added and stirring continued for 12 h. The mixture was diluted with dichloromethane (15 mL) and subsequently washed with hydrochloric acid (1 M; 8 mL), saturated aqueous sodium hydrogen carbonate (8 mL) and brine (10 mL). After drying ($MgSO_4$) and removal of the solvent under reduced pressure, purification by chromatography (eluent: ethyl acetate–light petroleum 1 : 3) gave the *title compound* **19** as light yellow solid (11 mg, 55%), $R_f = 0.63$ (light petroleum–ethyl acetate 1 : 1); mp 45–48 °C; (Found: MH^+, 578.2673. $C_{31}H_{40}N_3O_6Si$ requires 578.2681); ν_{max} ($CHCl_3$)/cm^{-1} 2929, 1657, 1274, 968, 908; δ_H (400 MHz; $CDCl_3$) 7.39 (1H, d, *J* 16.3, ArC*H*=CH), 7.09 (1H, dd, *J* 8.3; 2.0, ArH-6), 7.06 (1H, d, *J* 2.0, ArH-2), 7.03–7.01 (1H, m, NH), 6.85 (1H, d, *J* 8.3, ArH-5), 6.70 (1H, d, *J* 16.3, ArCH=C*H*), 6.36–6.28 (1H, m, CH_2=C*H*), 6.27–6.18 (1H, m, CH_2=CH=C*H*), 5.73 (1H, dt, *J* 15.0, 6.2, C*H*=CH_2NH), 5.20–5.16 (1H, m, C*H*H=CH), 5.07–5.05 (1H, m, CH*H*=CH), 4.41 (2H, s, CH_2CO), 4.04–4.02 (2H, m, CH_2NH), 3.83 (3H, s, OMe), 2.66 (3H, s, Me), 2.64 (3H, s, Me), 1.01 (9H, s, CMe_3), 0.17 (6H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 189.4 (C), 161.7 (C), 159.2 (C), 155.6 (C), 155.3 (C), 153.8 (C), 152.6 (C), 145.3 (C), 139.9 (CH), 137.3 (CH), 136.1 (CH), 134.4 (C), 132.8 (CH), 129.5 (C), 128.1 (C), 122.1 (CH), 119.0 (CH), 117.4 (CH_2), 111.9 (CH), 110.6 (CH), 55.4 (Me), 40.3 (CH_2), 39.4 (CH_2), 25.7 (Me), 18.4 (C), 12.4 (Me), 11.7 (Me), –4.6 (Me); *m*/*z* (ESI^+) 600 (MNa^+, 65%), 578 (MH^+, 32%), 549 (100%).

Siphonazole 1

Protected siphonazole **19** (20.0 mg, 35.5 μmol) was dissolved in THF (1.5 mL) and cooled to 0 °C. Triethylamine trihydrofluoride (6.30 mg, 39.0 μmol) was added and stirring continued for 48 h. The mixture was quenched with saturated aqueous ammonium chloride (5 mL), diluted with ethyl acetate (10 mL) and the organic phase washed with water (8 mL) and brine (8 mL). After drying with $MgSO_4$ and removal of the solvent under reduced pressure, a yellow solid was obtained. Further purification by reversed phase preparative HPLC (Varian Polaris, C_{18}, 250 × 21.2 mm; eluent: acetonitrile–water 65 : 35, flow rate 18 mL min^{-1}; retention time 6.0 min) gave *siphonazole* **1** as a colourless solid (10.0 mg, 55%); mp 62–65 °C (lit.,[48] mp not given); (Found: M^+, 463.1763. $C_{25}H_{25}N_3O_6$ requires 463.1743); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2928, 1731, 1658, 1593, 1461, 1374, 1281, 1130, 1046, 967; δ_H (400 MHz; $CDCl_3$)

7.81 (1H, br, OH or NH), 7.55 (1H, br, NH or OH), 7.47 (1H, d, *J* 16.4, ArC*H*=CH), 7.23 (1H, d, *J* 2.1, ArH-2), 7.15 (1H, dd, *J* 8.3, 2.1, ArH-6), 7.01 (1H, d, *J* 8.3, ArH-5), 6.86 (1H, d, *J* 16.4, ArCH=C*H*), 6.42–6.33 (1H, m, CH_2=C*H*), 6.23–6.20 (1H, m, CH_2=CH=C*H*), 5.81 (1H, dt, *J* 14.9, 5.9, C*H*=CH_2NH), 5.20–5.15 (1H, m, CH_2=CH), 5.04–5.02 (1H, m, CH_2=CH), 4.44 (2H, s, CH_2CO), 4.02–4.00 (2H, m, CH_2NH), 3.91 (3H, s, OMe), 2.65 (3H, s, Me), 2.60 (3H, s, Me); δ_C (125 MHz; $CDCl_3$) 190.1 (C), 161.9 (C), 160.0 (C), 156.8 (C), 155.9 (C), 153.8 (C), 150.1 (C), 147.9 (C), 138.2 (CH), 137.6 (CH), 135.3 (C), 132.7 (CH), 131.9 (CH), 130.5 (C), 129.5 (C), 121.4 (CH), 117.0 (CH_2), 113.9 (CH), 112.4 (CH), 111.5 (CH), 56.3 (Me), 40.7 (CH_2), 40.0 (CH_2), 12.2 (Me), 11.5 (Me); *m*/*z* (EI^+) 463 (M^+, 100%).

(*E*)-Methyl 2-(3,4-dimethoxystyryl)-5-methyloxazole-4-carboxylate 6b

A solution of the ketoamide **5b** (100 mg, 0.31 mmol) and triethylamine (125 µl, 1.24 mmol), in dry dichloromethane (2 mL) was added dropwise over a period of 1 h to a solution of triphenylphosphine (163 mg, 0.62 mmol) and iodine (157 mg, 0.62 mmol) in dry dichloromethane (4 mL) at room temperature. After the addition was complete the reaction mixture was stirred for a further 1 h at which point no starting material could be observed. The mixture was quenched with water. The organic layer was washed with water and brine, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude material was purified by chromatography (eluting with ethyl acetate–light petroleum 1 : 1 + 0.5% triethylamine) to give the *title compound* **6b** as a colourless solid (79.0 mg, 84%); R_f = 0.45 (light petroleum–ethyl acetate 1 : 2); mp 142–143 °C; (Found: C, 63.4; H, 5.6; N, 4.5. $C_{16}H_{17}NO_5$ requires C, 63.4; H, 5.7; N, 4.6%); (Found: MH^+, 304.1175. $C_{16}H_{18}NO_5$ requires 304.1179); ν_{max} ($CHCl_3$)/cm^{-1} 2955, 1719, 1616, 1464, 1352, 1268, 1140, 1103, 1025; δ_H (400 MHz; $CDCl_3$) 7.42 (1H, d, *J* 16.4, ArC*H*=CH), 7.03 (1H, dd, *J* 8.3, 1.9, ArH-6), 6.99 (1H, d, *J* 1.9, ArH-2), 6.82 (1H, d, *J* 8.3, ArH-5), 6.71 (1H, d, *J* 16.4, ArCH=C*H*), 3.88 (3H, s, OMe), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 2.62 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 162.6 (C), 159.5 (C), 155.7 (C), 150.3 (C), 149.1 (C), 136.7 (CH), 128.2 (C), 128.1 (C), 121.1 (CH), 111.0 (CH), 110.9 (CH), 108.9 (CH), 55.8 (Me), 55.7 (Me), 51.8 (Me), 11.9 (Me); *m*/*z* (ESI^+) 304 (MH^+, 100%).

2-((3,4-Dimethoxystyryl)-5-methyloxazol-4-yl)methanol 7b

Lithium aluminium hydride (12.1 mg, 0.32 mmol) was suspended in THF (3 mL) and cooled to 0 °C. Ester **6b** (100 mg, 0.33 mmol) was dissolved in THF (3 mL) and added dropwise over a period of 1 h at 0 °C. Water (12.1 µL), followed by aqueous sodium hydroxide (2 M; 12.1 µL) and again water (24.2 µL) were added and the mixture allowed to stir at room temperature for 1 h. After filtering the mixture through a short pad of Celite the solvent was removed *in vacuo* to give the *title compound* **7b** (80.0 mg, 91%) that could be used in the next step without any further purification; mp 136–138 °C; (Found: C, 65.3; H, 6.2; N, 5.0. $C_{15}H_{17}NO_4$ requires C, 65.4; H, 6.2; N, 5.1%); (Found: MH^+ 276.1229. $C_{15}H_{18}NO_4$ requires 276.1236); ν_{max} ($CHCl_3$)/cm^{-1} 3613, 2936, 1640, 1601, 1509, 1464, 1268, 1140, 1025; δ_H (400 MHz; $CDCl_3$) 7.32 (1H, d, *J* 16.3, ArC*H*=CH), 7.06 (1H, dd, *J* 8.3, 1.8, ArH-6), 7.04 (1H, d, *J* 1.8, ArH-2), 6.86 (1H, d, *J* 8.3, ArH-5), 6.72 (1H, d, *J* 16.3, ArCH=C*H*), 4.54 (2H, d, *J* 6.0, CH_2OH), 4.42 (1H, t, *J* 6.0, CH_2O*H*), 3.92 (3H, s, OMe), 3.90 (3H, s, OMe), 2.36 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 160.0 (C), 150.0 (C), 149.1 (C), 144.6 (C), 135.5 (CH), 135.3 (C), 128.5 (C), 121.0 (CH), 111.6 (CH), 111.1 (CH), 109.0 (CH), 55.9 (Me), 55.8 (Me), 55.6 (CH_2), 10.2 (Me); *m*/*z* (ESI^+) 276 (MH^+, 100%).

2-(3,4-Dimethoxystyryl)-5-methyloxazole-4-carbaldehyde 8b

To a stirred solution of oxalyl chloride (0.65 g, 5.10 mmol) in dichloromethane (30 mL) under nitrogen at −78 °C was added dropwise DMSO (0.79 g, 0.79 mmol) with the evolution of gas. After 15 min, alcohol **7b** (1.16 g, 4.20 mmol) in dichloromethane (10 ml) was added dropwise *via* cannula and the cloudy solution stirred for 30 min. Triethylamine (1.66 g, 16.4 mmol) was then added dropwise to give a light yellow suspension. The mixture was stirred at −78 °C for 75 min, warmed to 0 °C and stirred for a further 5 min. The reaction mixture was quenched at 0 °C with saturated aqueous sodium hydrogen carbonate (30 mL) and stirred until two clear layers could be seen. The aqueous layer was extracted with dichloromethane (30 mL), the organic layers combined, washed with water (30 mL) and brine (30 mL) and dried with $MgSO_4$. After evaporation to dryness, chromatography (light petroleum–ethyl acetate 3 : 1) gave the *title compound* **8b** as a light yellow solid (0.95 g, 83%); R_f = 0.61 (light petroleum–ethyl acetate 3 : 1); mp 99–101 °C; (Found: MH^+, 274.1087. $C_{15}H_{16}NO_4$ requires 274.1074); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1694, 1596, 1513, 1267, 1140, 1025; δ_H (400 MHz; $CDCl_3$) 9.96 (1H, s, CHO), 7.48 (1H, d, *J* 16.3, ArC*H*=CH), 7.09 (1H, dd, *J* 8.3, 1.8, ArH-6), 7.05 (1H, d, *J* 1.8, ArH-2), 6.88 (1H, d, *J* 8.3, ArH-5), 6.75 (1H, d, *J* 16.3, ArCH=C*H*), 3.92 (3H, s, OMe), 3.91 (3H, s, OMe), 2.66 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 185.2 (CH), 160.4 (C), 155.9 (C), 150.5 (C), 149.2 (C), 137.4 (CH), 135.9 (C), 128.0 (CH), 121.4 (CH), 111.1 (CH), 110.7 (CH), 109.0 (CH), 55.9 (Me), 55.8 (Me), 11.7 (Me); *m*/*z* (ESI^+) 279 (100%), 274 (MH^+, 66%).

Methyl 2-(2-(2-(3,4-dimethoxystyryl)-5-methyloxazol-4-yl)-2-hydroxyethyl)-5-methyloxazole-4-carboxylate 17b

Zinc dust (144 mg, 2.20 mmol) was placed in a Schlenk tube under an argon atmosphere and suspended in dry THF (2 mL), 1,2-dibromoethane (19.0 µL, 0.22 mmol) was added and the mixture heated up to 60 °C for 5 min. After cooling down to room temperature, trimethylsilyl chloride (5.10 µL, 0.04 mmol) was added and stirring continued for a further 15 min. At 0 °C aldehyde **8b** (100 mg, 0.37 mmol) and boron trifluoride-etherate (93.0 µL, 0.73 mmol) were added. Iodo-oxazole **10** (204 mg, 0.73 mmol) in THF (1 mL) was added dropwise over a period of 3 h. The zinc dust was filtered off, the solvent removed under reduced pressure and the residue purified by chromatography (eluent: ethyl acetate–light petroleum 2 : 1 + 1% triethylamine) to give the *title compound* **17b** as a colourless solid (103 mg, 65%); R_f = 0.31 (light petroleum–ethyl acetate 1 : 5); mp 164–165 °C; (Found: MH^+, 429.1645. $C_{22}H_{25}N_2O_7$ requires 429.1656); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 1719, 1586, 1511, 1441, 1354, 1266, 1101; δ_H (400 MHz; $CDCl_3$) 7.35 (1H, d, *J* 16.3, ArC*H*=CH), 7.07 (1H, dd, *J* 8.4, 1.9, ArH-6), 7.05 (1H, d, *J* 1.9, ArH-2), 6.87 (1H, d, *J* 8.4, ArH-5), 6.80 (1H, d, *J* 16.3, ArCH=C*H*), 5.19 (1H, dd, *J* 8.8, 4.6, C*H*OH), 3.92 (3H, s,

OMe), 3.91 (3H, s, OMe), 3.90 (3H, s, OMe), 3.48 (1H, dd, *J* 15.7, 8.8, C*H*H), 3.18 (1H, dd, *J* 15.7, 4.6, CH*H*), 2.60 (3H, s, Me), 2.36 (3H, s, Me); OH not observed; δ_C (100 MHz; $CDCl_3$) 162.7 (C), 160.2 (C), 160.0 (C), 156.4 (C), 150.0 (C), 149.2 (C), 144.3 (C), 136.1 (C), 135.3 (CH), 128.5 (C), 127.2 (C), 121.1 (CH), 111.8 (CH), 111.1 (CH), 108.8 (CH), 64.3 (CH), 55.9 (Me), 55.8 (Me), 51.9 (Me), 35.4 (CH_2), 11.9 (Me), 10.4 (Me); *m*/*z* (ESI^+) 451 (MNa^+, 100%); 429 (MH^+, 33%).

Methyl 2-(2-(2-(3,4-dimethoxystyryl)-5-methyloxazol-4-yl)-2-oxoethyl)-5-methyloxazole-4-carboxylate 18

Dess–Martin periodinane (174 mg, 0.41 mmol) was added to a solution of alcohol **17b** (160 mg, 0.37 mmol) dissolved in dichloromethane (10 mL) at 0 °C and the mixture stirred at room temperature for 20 min until the reaction was complete. The mixture was diluted with ether (30 mL), aqueous saturated sodium hydrogen carbonate (10 mL) and aqueous sodium metabisulfite (10%; 10 mL) and stirred until two clear layers were formed. The organic layer was washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by chromatography (eluting with ethyl acetate–light petroleum 1 : 3 + 0.5% triethylamine) to give the *title compound* **18** as a colourless solid (77 mg, 49%); $R_f = 0.73$ (light petroleum–ethyl acetate 1 : 5); mp 138–140 °C; (Found: C, 61.7; H, 5.1; N, 6.5. $C_{22}H_{22}N_2O_7$ requires C, 62.0; H, 5.2; N, 6.6%); (Found: MH^+, 427.1504. $C_{22}H_{23}N_2O_7$ requires 427.1500); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1719, 1594, 1513, 1423, 1266, 1102; δ_H (400 MHz; $CDCl_3$) 7.43 (1H, d, *J* 16.3, ArC*H*=CH), 7.09 (1H, dd, *J* 8.3, 1.9, ArH-6), 7.06 (1H, d, *J* 1.9, ArH-2), 6.87 (1H, d, *J* 8.3, ArH-5), 6.74 (1H, d, *J* 16.3, ArCH=C*H*), 4.47 (2H, s, CH_2), 3.92 (3H, s, OMe), 3.91 (3H, s, OMe), 3.88 (3H, s, OMe), 2.64 (3H, s, Me), 2.62 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 189.3 (C), 162.7 (C), 159.1 (C), 157.3 (C), 156.5 (C), 155.5 (C), 150.5 (C), 149.3 (C), 137.2 (CH), 134.4 (C), 128.1 (C), 127.7 (C), 121.5 (CH), 111.1 (CH), 110.8 (CH), 108.9 (CH), 56.0 (Me), 55.9 (Me), 51.9 (Me), 39.6 (CH_2), 12.4 (Me), 12.0 (Me); *m*/*z* (ESI^+) 449 (MNa^+, 100%), 427 (MH^+, 44%).

O-Methyl siphonazole 2

The ester **18** (40.0 mg, 93.0 μmol) was dissolved in THF (4 mL) and barium hydroxide (59.0 mg, 190 μmol) in water (1 mL) added and the mixture stirred for 16 h. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (20 mL) and hydrochloric acid (1 M; 10 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (15 mL), the combined organics washed with brine (15 mL) and dried ($MgSO_4$). After removal of the solvent, the crude carboxylic acid (38.5 mg, 100%) was obtained and used without further purification.

Crude carboxylic acid (24 mg, 58.0 μmol) was dissolved in dichloromethane (1.5 mL), diisopropylethylamine (38 mg, 290 μmol) and PyBOP (36.4 mg, 70 μmol) were added and the mixture stirred at room temperature for 20 min, (*E*)-2,4-pentadienylamine (5.80 mg, 70 μmol) added and stirring continued for 12 h. The mixture was diluted with dichloromethane (15 mL) and subsequently washed with hydrochloric acid (1 M; 8 mL), saturated aqueous sodium hydrogen carbonate (8 mL) and brine (8 mL). After drying ($MgSO_4$) and evaporation of the solvent under reduced pressure, purification by chromatography (eluent: ethyl acetate–light petroleum 1 : 2) gave the *title compound* **2** as light yellow solid (15 mg, 54%); $R_f = 0.76$ (light petroleum–ethyl acetate 1 : 1); mp 107–108 °C (lit.,[48] mp not given); (Found: M^+, 477.1883. $C_{26}H_{27}N_3O_6$ requires 477.1900); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2935, 1691, 1656, 1594, 1513, 1465, 1386, 1267, 1140, 1102, 1025; δ_H (400 MHz; acetone-d_6) 7.55 (1H, br t, *J* 5.6, N*H*CH_2), 7.49 (1H, d, *J* 16.4, ArC*H*=CH), 7.37 (1H, d, *J* 2.0, ArH-2), 7.21 (1H, dd, *J* 8.3; 2.0, ArH-6), 7.00 (1H, d, *J* 8.3, ArH-5), 6.94 (1H, d, *J* 16.4, ArCH=C*H*), 6.43–6.30 (1H, m, CH_2=C*H*), 6.26–6.20 (1H, m, CH_2=CH=C*H*), 5.81 (1H, dt, *J* 15.2, 5.9, C*H*=CH_2NH), 5.19–5.14 (1H, m, CH_2=CH), 5.03–5.01 (1H, m, CH_2=CH), 4.42 (2H, s, CH_2CO), 4.05–4.00 (2H, m, NHCH_2), 3.91 (3H, s, OMe), 3.86 (3H, s, OMe), 2.64 (3H, s, Me), 2.60 (3H, s, Me); δ_C (100 MHz; acetone-d_6) 190.0 (C), 161.9 (C), 160.0 (C), 156.7 (C), 155.9 (C), 153.7 (C), 151.9 (C), 150.6 (C), 138.1 (CH), 137.6 (CH), 135.2 (C), 132.6 (CH), 131.9 (CH), 130.5 (C), 129.0 (C), 122.6 (CH), 116.9 (CH_2), 112.4 (CH_2), 111.5 (CH), 110.4 (CH), 56.1 (Me), 56.0 (Me), 40.6 (CH_2), 40.0 (CH_2), 12.2 (Me), 11.5 (Me); *m*/*z* (EI^+) 478 (MH^+, 17%), 426 (100%).

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References

1 J. R. Lewis, *Nat. Prod. Rep.*, 2001, **18**, 95.
2 Z. Jin, Z. G. Li and R. Q. Huang, *Nat. Prod. Rep.*, 2002, **19**, 454.
3 J. R. Lewis, *Nat. Prod. Rep.*, 2002, **19**, 223.
4 Z. Jin, *Nat. Prod. Rep.*, 2003, **20**, 584.
5 V. S. C. Yeh, *Tetrahedron*, 2004, **60**, 11995.
6 Z. Jin, *Nat. Prod. Rep.*, 2005, **22**, 196.
7 Z. Jin, *Nat. Prod. Rep.*, 2006, **23**, 464.
8 E. Riego, D. Hernandez, F. Albericio and M. Alvarez, *Synthesis*, 2005, 1907.
9 Isolation: A. Nagatsu, H. Kajitani and J. Sakakibara, *Tetrahedron Lett.*, 1995, **36**, 4097.
10 Synthesis (and ref. 11,12): P. Wipf and S. Venkatraman, *J. Org. Chem.*, 1996, **61**, 6517.
11 J. C. Muir, G. Pattenden and R. M. Thomas, *Synthesis*, 1998, 613.
12 P. Y. Coqueron, C. Didier and M. A. Ciufolini, *Angew. Chem., Int. Ed.*, 2003, **42**, 1411.
13 Isolation: N. Lindquist, W. Fenical, G. D. VanDuyne and J. Clardy, *J. Am. Chem. Soc.*, 1991, **113**, 2303.
14 Synthesis (and ref. 15–17): K. C. Nicolaou, M. Bella, D. Y. K. Chen, X. H. Huang, T. T. Ling and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2002, **41**, 3495.
15 A. W. G. Burgett, Q. Y. Li, Q. Wei and P. G. Harran, *Angew. Chem., Int. Ed.*, 2003, **42**, 4961.
16 K. C. Nicolaou, P. B. Rao, J. L. Hao, M. V. Reddy, G. Rassias, X. H. Huang, D. Y. K. Chen and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2003, **42**, 1753.
17 C.-M. Cheung, F. W. Goldberg, P. Magnus, C. J. Russell, R. Turnbull and V. Lynch, *J. Am. Chem. Soc.*, 2007, **129**, 12320.
18 Isolation: T. Ichiba, W. Y. Yoshida, P. J. Scheuer, I. Higa and D. G. Gravalos, *J. Am. Chem. Soc.*, 1991, **113**, 3173.
19 Synthesis (and ref. 20–22): P. Wipf and S. Lim, *J. Am. Chem. Soc.*, 1995, **117**, 558.
20 D. R. Williams, D. A. Brooks and M. A. Berliner, *J. Am. Chem. Soc.*, 1999, **121**, 4924.
21 F. Yokokawa, T. Asano and T. Shioiri, *Tetrahedron*, 2001, **57**, 6311.
22 T. E. Smith, W. H. Kuo, V. D. Bock, J. L. Roizen, E. P. Balskus and A. B. Theberge, *Org. Lett.*, 2007, **9**, 1153.
23 Isolation: J. A. Roesener and P. J. Scheuer, *J. Am. Chem. Soc.*, 1986, **108**, 846.

24 Synthesis (and ref. 25): S. K. Chattopadhyay and G. Pattenden, *Tetrahedron Lett.*, 1998, **39**, 6095.
25 S. K. Chattopadhyay and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2429.
26 Isolation: K. Shin-ya, K. Wierzba, K. Matsuo, T. Ohtani, Y. Yamada, K. Furihata, Y. Hayakawa and H. Seto, *J. Am. Chem. Soc.*, 2001, **123**, 1262.
27 Synthesis: T. Doi, M. Yoshida, K. Shin-ya and T. Takahashi, *Org. Lett.*, 2006, **8**, 4165.
28 Isolation: S. Kehraus, G. M. König, A. D. Wright and G. Woerheide, *J. Org. Chem.*, 2002, **67**, 4989.
29 Synthesis: W. L. Wang and F. J. Nan, *J. Org. Chem.*, 2002, **68**, 1636.
30 Isolation: R. Jansen, H. Irschik, H. Reichenbach, V. Wray and G. Hofle, *Liebigs Ann.*, 1994, 759.
31 Synthesis: P. Wipf and T. H. Graham, *J. Am. Chem. Soc.*, 2004, **126**, 15346.
32 Isolation: P. A. Searle and T. F. Molinski, *J. Am. Chem. Soc.*, 1995, **117**, 8126.
33 Synthesis (and ref. 34–44): D. A. Evans and D. M. Fitch, *Angew. Chem., Int. Ed.*, 2000, **39**, 2536.
34 D. A. Evans, D. M. Fitch, T. E. Smith and V. J. Cee, *J. Am. Chem. Soc.*, 2000, **122**, 10033.
35 A. B. Smith, P. R. Verhoest, K. P. Minbiole and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 4834.
36 A. B. Smith, K. P. Minbiole, P. R. Verhoest and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 10942.
37 M. A. Gonzalez and G. Pattenden, *Angew. Chem., Int. Ed.*, 2003, **42**, 1255.
38 D. R. Williams, A. A. Kiryanov, U. Emde, M. P. Clark, M. A. Berliner and J. T. Reeves, *Angew. Chem., Int. Ed.*, 2003, **42**, 1258.
39 L. O. Haustedt, I. V. Hartung and H. M. R. Hofftmann, *Angew. Chem., Int. Ed.*, 2003, **42**, 2711.
40 G. Pattenden, M. A. Gonzalez, P. B. Little, D. S. Millan, A. T. Plowright, J. A. Tornos and T. Ye, *Org. Biomol. Chem.*, 2003, **1**, 4173.
41 A. B. Smith, T. M. Razler, J. P. Ciavarri, T. Hirose and T. Ishikawa, *Org. Lett.*, 2005, **7**, 4399.
42 D. R. Li, D. H. Zhang, C. Y. Sun, J. W. Zhang, L. Yang, J. Chen, B. Liu, C. Su, W. S. Zhou and G. Q. Lin, *Chem.–Eur. J.*, 2006, **12**, 1185.
43 J. D. White, T. H. Lee and P. Kuntiyong, *Org. Lett.*, 2006, **8**, 6043.
44 B. S. Lucas, V. Gopalsamuthiram and S. D. Burke, *Angew. Chem., Int. Ed.*, 2007, **46**, 769.
45 Isolation: J. Rodriguez, R. M. Nieto and P. Crews, *J. Nat. Prod.*, 1993, **56**, 2034.
46 Synthesis (and ref. 47): R. J. Mulder, C. M. Shafer and T. F. Molinski, *J. Org. Chem.*, 1999, **64**, 4995.
47 J. A. Bull, E. P. Balskus, R. A. J. Horan, M. Langner and S. V. Ley, *Angew. Chem., Int. Ed.*, 2006, **45**, 6714.
48 M. Nett, O. Erol, S. Kehraus, M. Kock, A. Krick, E. Eguereva, E. Neu and G. M. König, *Angew. Chem., Int. Ed.*, 2006, **45**, 3863.
49 J. Linder and C. J. Moody, *Chem. Commun.*, 2007, 1508.
50 K. J. Doyle and C. J. Moody, *Tetrahedron*, 1994, **50**, 3761.
51 K. J. Doyle and C. J. Moody, *Synthesis*, 1994, 1021.
52 C. J. Moody and K. J. Doyle, *Prog. Heterocycl. Chem.*, 1997, **9**, 1.
53 M. C. Bagley, R. T. Buck, S. L. Hind and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1998, 591.
54 J. R. Davies, P. D. Kane and C. J. Moody, *Tetrahedron*, 2004, **60**, 3967.
55 J. R. Davies, P. D. Kane, C. J. Moody and A. M. Z. Slawin, *J. Org. Chem.*, 2005, **70**, 5840.
56 J. R. Davies, P. D. Kane and C. J. Moody, *J. Org. Chem.*, 2005, **70**, 7305.
57 P. Wipf and C. P. Miller, *J. Org. Chem.*, 1993, **58**, 3604.
58 M. P. Doyle, W. E. Buhro, J. G. Davidson, R. C. Elliott, J. W. Hoekstra and M. Oppenhuizen, *J. Org. Chem.*, 1980, **45**, 3657.
59 R. Connell, F. Scavo, P. Helquist and B. Åkermark, *Tetrahedron Lett.*, 1986, **27**, 5559.
60 R. D. Connell, M. Tebbe, P. Helquist and B. Åkermark, *Tetrahedron Lett.*, 1991, **32**, 17.
61 J. S. Tullis and P. Helquist, *Org. Synth.*, 1996, **74**, 229.
62 A. I. Meyers and D. G. Walker, *J. Org. Chem.*, 1982, **47**, 2999.
63 P. Cornwall, C. P. Dell and D. W. Knight, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2417.
64 D. A. Evans, V. J. Cee, T. E. Smith and K. J. Santiago, *Org. Lett.*, 1999, **1**, 87.
65 P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390.
66 M. C. P. Yeh, P. Knochel and L. E. Santa, *Tetrahedron Lett.*, 1988, **29**, 3887.
67 A. R. Gangloff, B. Åkermark and P. Helquist, *J. Org. Chem.*, 1992, **57**, 4797.
68 P. A. Grieco, P. Galatsis and R. F. Spohn, *Tetrahedron*, 1986, **42**, 2847.

