The total synthesis of siphonazole, a structurally unusual bis-oxazole natural product†

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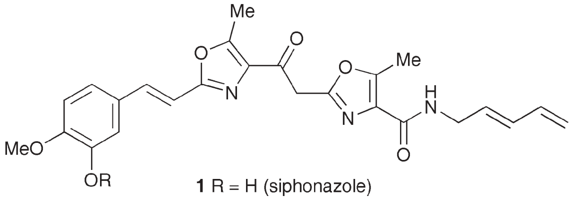
The first synthesis of the unusual bis-oxazole natural product siphonazole is reported, both oxazole rings being constructed using rhodium carbene chemistry.

Naturally occurring oxazoles, once considered a rarity, have assumed increasing importance over the last two decades. This interest has been fuelled by the isolation of a number of structurally complex and synthetically challenging oxazoles, mainly from marine sources.[1] 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.[2] Thus, for example, directly linked bis-oxazoles occur in diazonamide A[3] and the hennoxazoles,[4] tris-oxazoles in ulapualide A[5] and in YM-216391,[6] whilst telomestatin contains a remarkable array of seven 2,4′-linked oxazoles.[7] Bis-oxazoles in which the 2,4′-link is part of a peptide chain (–CHRNHCO–) occur in, for example, leucamide A,[8] whilst polyene units link the two oxazole rings in the disorazoles.[9]

Bis-oxazoles that are linked by just one or two carbon atoms are very unusual as natural products. The bengazoles are unique with the two oxazoles being linked (2,5′) by single carbon.[10] Very recently König and co-workers have reported another example of this extremely rare class of natural bis-oxazoles, in which the two oxazole rings are linked by two carbons.[11] Siphonazole **1** was isolated, along with its *O*-methyl derivative **2**, from the genus *Herpetosiphon* and its structure assigned on the basis of detailed NMR studies.[11] As well as the unusual C_2 link between the two oxazoles, siphonazole contains an unprecedented *N*-penta-2,4-dienyl amide side chain, as well as a cinnamic residue, also rare in bacterial natural products. We now report the first synthesis of this new structural class of natural products.

Our synthetic strategy involved the preparation of both oxazole rings using rhodium carbenes, reactive intermediates formed upon treatment of diazocarbonyl compounds with catalytic amounts of dirhodium(II) carboxylates,[12] followed by followed by installation of the pentdienylamino side-chain. The synthesis started with the known 3-hydroxy-4-methoxycinnamamide **2**[13] which was protected as its *tert*-butyldimethylsilyl ether **3**. Dirhodium tetraacetate catalysed 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 **4**. No products formed by competing cyclopropanation of the double bond were observed, illustrating the selective nature of the carbene N–H insertion process. Cyclodehydration of the ketoamide **4** using $Ph_3P/I_2/Et_3N$[14] gave the oxazole **5** (Scheme 1). Although in principle, the oxazole ester **5** could function in an acylation reaction of an appropriate nucleophile, given the presence of an ester in the coupling partner **7**, we elected to convert it into the corresponding aldehyde **6** in preparation for coupling to a zinc derivative of the second oxazole ring. The second oxazole **7** was also prepared from methyl 2-diazo-3-oxobutanoate in a single step by dirhodium tetraacetate catalysed reaction with iodoacetonitrile.[15] The key coupling reaction was effected by formation of the zinc reagent from the iodomethyloxazole **7** using activated zinc,[16] followed by reaction with the aldehyde **6** in the presence of boron trifluoride etherate.[17] Oxidation of the resulting secondary alcohol with the Dess–Martin periodinane gave the bis-oxazole **8**. Finally, hydrolysis of the ester with barium hydroxide, coupling to 2,4-pentadienylamine[18] using PyBOP (benzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate) and Hünig's base, followed by removal of the silicon protecting group gave siphonazole **1**. The ^{1}H and ^{13}C NMR spectroscopic data of our synthetic siphonazole were identical to those reported for the natural product,[11] and the material proved identical to an authentic sample by HPLC and NMR spectroscopy.



1 R = H (siphonazole)
2 R = Me

The first synthesis of siphonazole not only illustrates the versatility of rhodium carbene chemistry but also confirms unambiguously the structure of this unusual natural product.

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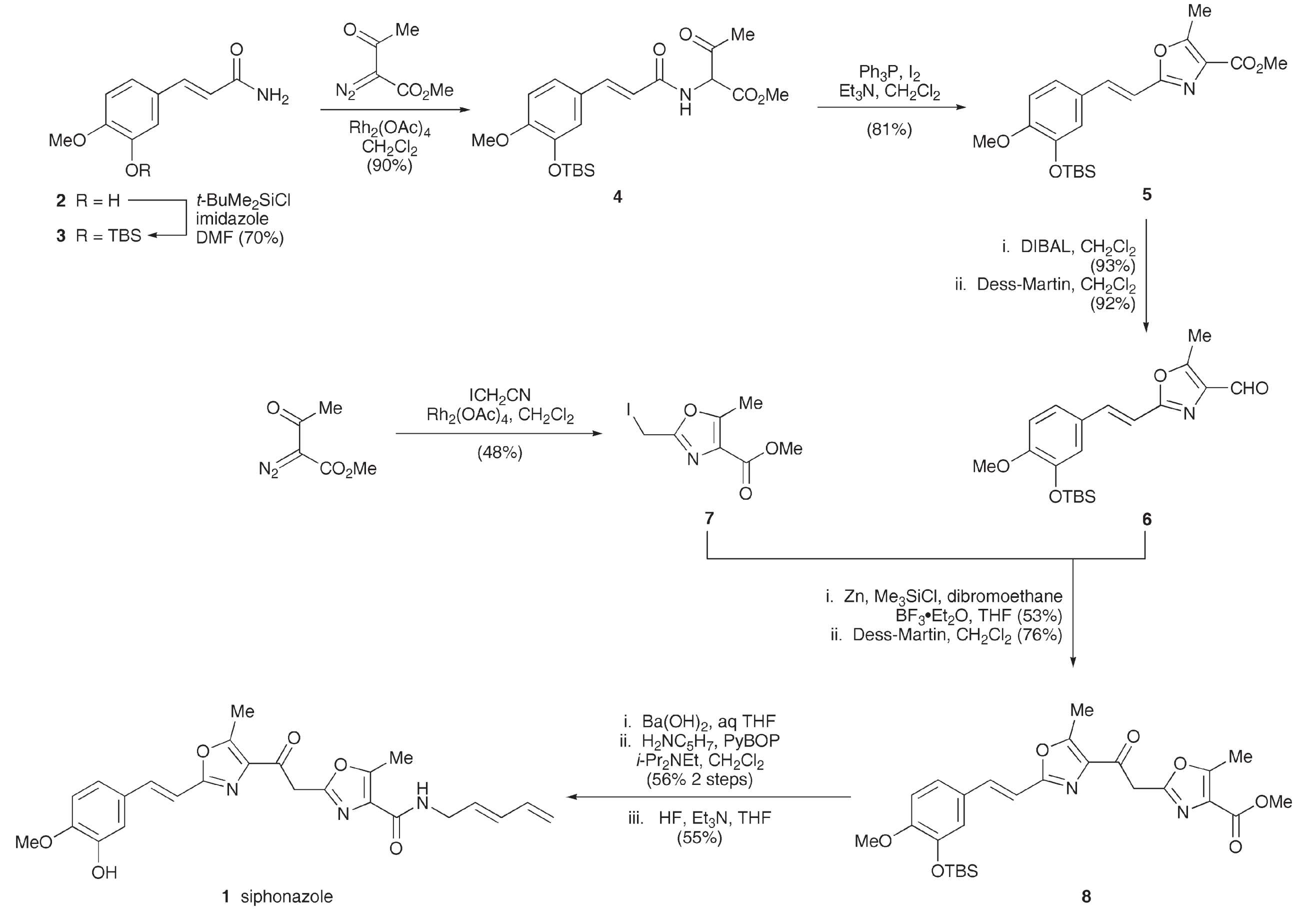
† Electronic supplementary information (ESI) available: Experimental details for compounds **4**, **5**, **7** and **8**; HPLC comparison of natural and synthetic material; ^{1}H NMR spectra of synthetic and natural siphonazole, and ^{13}C NMR spectrum of synthetic siphonazole. See DOI: 10.1039/b618160k



Scheme 1

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