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A Synthetic Approach towards the Aromatic Macrocyclic Core of Diazonamide A based on sp^2-sp^2 Coupling Protocols

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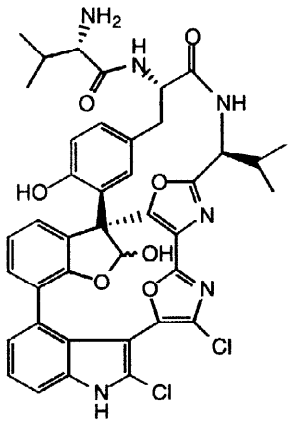
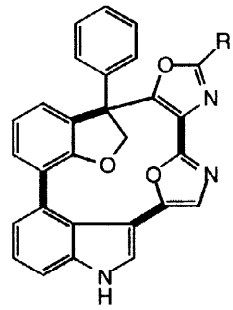
Abstract: The scope for a range of sp^2-sp^2 coupling protocols to elaborate the phenyl-indole, indole-oxazole, oxazole-oxazole, and quaternary carbon units in the marine natural product diazonamide A **1** are described, leading to the synthesis of the benzofuran oxazoles **11a** and **18**, the benzofuran/biphenyl/indole **16**, and the indole-*bis*-oxazole **25**.

Diazonamide A **1** is a highly unusual natural product which has been isolated from the colonial ascidian *Diazona chinensis*.[1] The secondary metabolite has a structure based on a complex aromatic macrocyclic core made up of conjugated (bi)phenyl/indole/(bis)oxazole units linked *via* a chiral quaternary carbon centre and existing as a single atropisomer. The macrocyclic core is further linked to a cyclopeptide residue composed of tyrosine and valine residues. Diazonamide A has significant cytotoxicity towards HCT-116 human colon carcinoma and B-16 murine melanoma cancer cell lines. The combination of novel and unusual structural features and biological activity make diazonamide A an attractive target for total synthesis studies.[2] In addition to other strategies we have explored the scope for a range of sp^2-sp^2 coupling protocols, *i.e.* Stille, Suzuki, Heck, to elaborate the phenyl-indole, indole-oxazole, oxazole-oxazole and quaternary carbon units in diazonamide A (see structure **2**).[3] These studies, which complement our related synthetic work with other poly-oxazole[4] and polyene macrolide[5] based marine natural products, are now presented here.



1



2

Perhaps one of the most striking and synthetically demanding structural features in diazonamide A **1** is the chiral quaternary carbon centre linking the oxazole, tyrosine and biphenyl units, and adjacent to the cyclic hemi-acetal centre in the natural product (see structure **2**). Early on in our studies we decided that the best approach to this particular system would be based on a transition metal-mediated intramolecular aryl-olefin coupling reaction involving a suitably substituted iodoaryl ether system.[6] To our satisfaction we found that the ubiquitous intramolecular Heck reaction[7] with the substrate **3** in the presence of $Pd(PPh_3)_4$, Ag_2CO_3, DMF at 80°C, produced the corresponding benzofuran **4**, in an excellent 95% preparative yield.[8] After unsuccessful attempts to carry out a satisfactory asymmetric Heck reaction[9] with the substrate **3**, we found that we could resolve the *R*- and *S*- centres in the product by oxidative cleavage of the alkene bond in **4** followed by fractional crystallisation of the amides (*cf* **6**) derived from the corresponding carboxylic acid **5** and (*S*)-α-methylbenzylamine.[10] With the carboxylic acid **5** in hand, it then became a straightforward matter to elaborate the adjacent oxazole ring, *i.e.* **11a**, *via* the corresponding β-keto ester **8**, the amine **9**, the amide **10**, and finally an *in situ* Hantzch cyclisation[11] according to Scheme 1.

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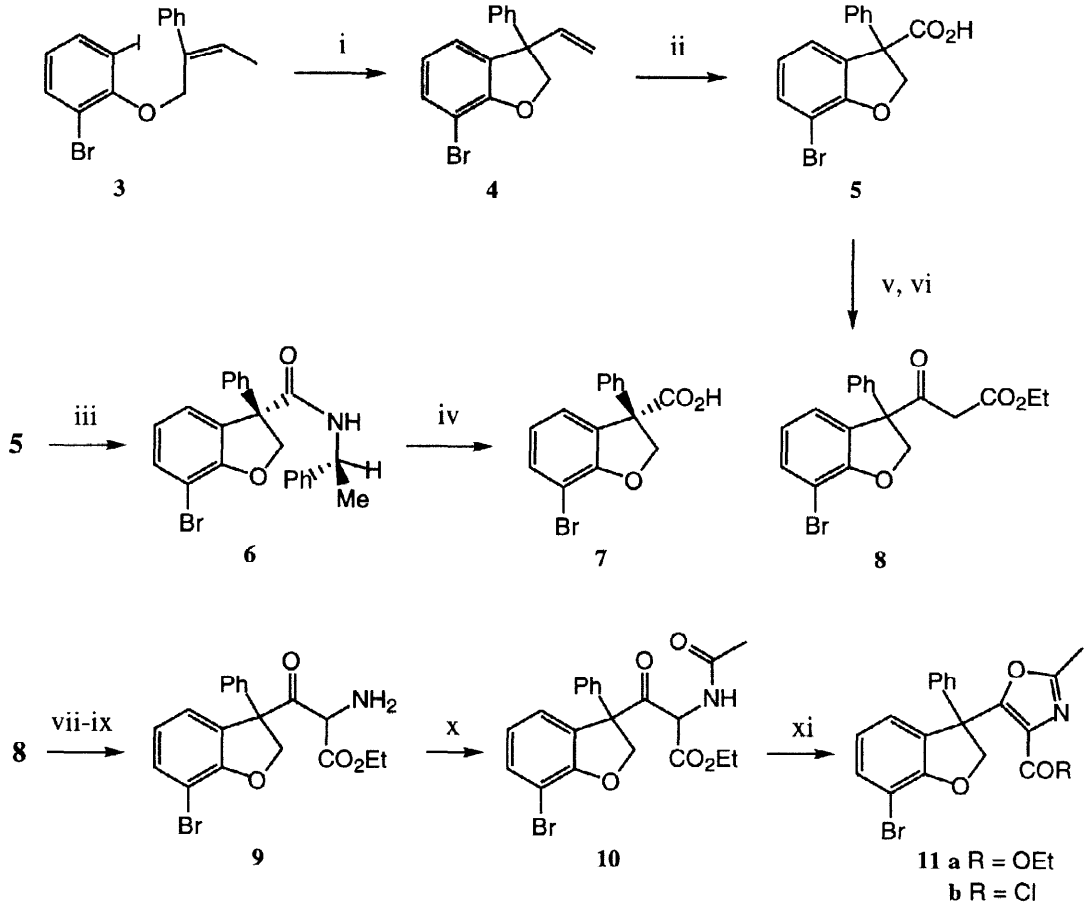
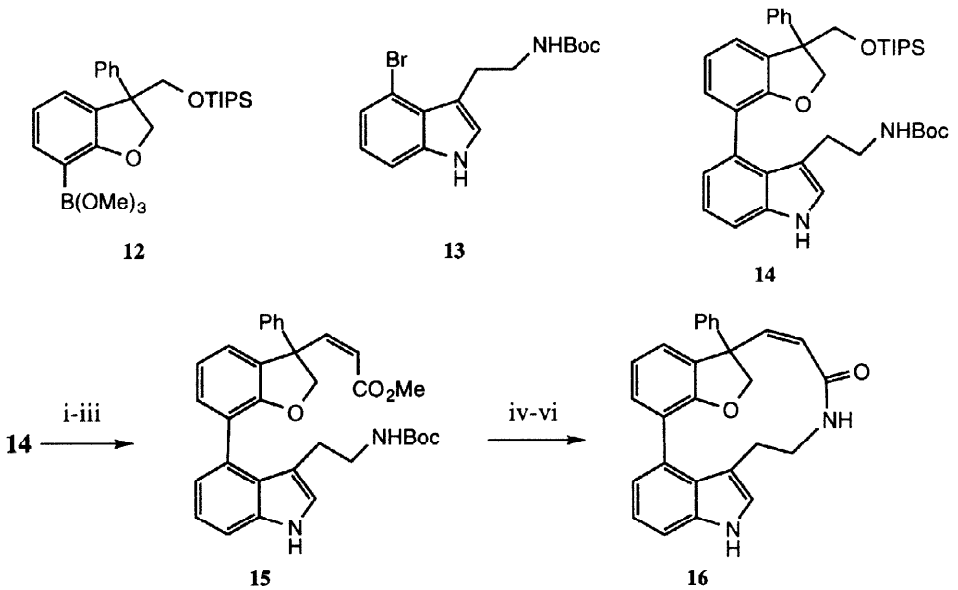


Reagents: i, $Pd(PPh_3)_4$, Ag_2CO_3, DMF, 80°C, 95%; ii, O_3, PPh_3, 85%; then $NaClO_4$, KH_2PO_4, ^tBuOH, H_2O, butene, 97%; iii, $SOCl_2$, (*S*)-2-methylbenzylamine, 92%; iv, *p*TSA, then NaOH, 78%; v, $(Im)_2CO$, THF, 100%; vi, $EtO_2CCH_2CO_2H$, $(CH_3)_2CHMgBr$, THF, Δ, 60%; vii, NaH, Br_2, THF, 99%; viii, NaN_3, DMF, 99%; ix, PPh_3, THF, H_2O, 100%; x, AcCl, Et_3N, CH_2Cl_2 ; xi, *in situ*, 44% overall.

Scheme 1

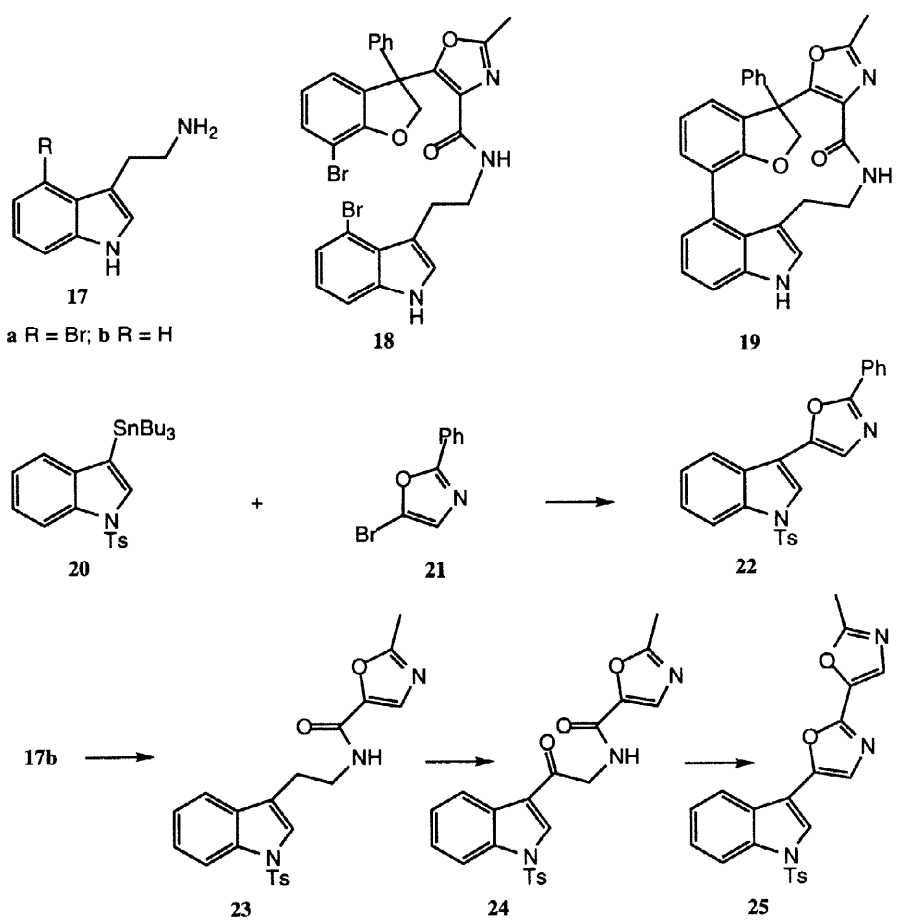
A huge range of cocktails for carrying out subtle variations of the Ullmann reaction leading to biaryls have been described in recent years.[12] In the case of coupling reactions to the C-4 position of indoles we would extol the virtues of using 4-thalliumtrifluoroacetate indoles[13] and arylstannanes ($Pd(PPh_3)_4$, DME, 80°C, 55%) or 4-triflate indoles and arylboronic acids ($Pd(PPh_3)_4$, LiCl, DME, 80°C, 60%).[14] Similarly we found that the Pd(0) coupling between the 4-bromoindole **13** and the boronate **12** could be smoothly accomplished in 58% yield providing the useful precursor **14** to **15** and hence the macrolactam **16** (Scheme 2). By contrast, we have been unable to effect the intramolecular Ullmann coupling of the dibromide **18** produced from 4-bromotryptamine **17a**[15] and the acid chloride **11b** as a route to the analogous macrolactam **19** *en route* to the aromatic macrocyclic core **2** of diazonamide A.

Finally in alternative approaches to the indole-oxazole connection in diazonamide A we have established that i, the palladium(0) catalysed coupling between the 3-stannyl substituted indole **20** and the 3-bromooxazole **21** provides a particularly expeditious route to the ring system **22**,[16] and ii, that the related indole-*bis*-oxazole unit **25** is easily accessible from tryptamine *via* the corresponding oxazole amide **23** and the keto-amide **24** produced from **23** by oxidation with DDQ[17] followed by a conventional Hantzch oxazole ring forming cyclisation.[11,3] The present studies have laid the foundation for an approach to the aromatic macrocyclic core in diazonamide A based on Heck, Stille and Suzuki sp^2-sp^2 coupling reactions. The development of these studies, alongside others, towards a total synthesis of diazonamide A are presently in progress in our laboratories.



Reagents: i, TBAF, THF, 79%; ii, py·SO_3, CH_2Cl_2, DMSO, 82%; iii, KHMDS, 18-crown-6, $(F_3CH_2CO)_2POCH_2CO_2Me$, 79%; iv, LiOH, DME, H_2O; v, TFA, CH_2Cl_2; vi, $^iPr_2NEt$, DPPA, CH_2Cl_2, 49% over 3 steps.

Scheme 2



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