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A Synthetic Approach towards the Aromatic Macrocyclic Core of Diazonamide A based on sp²-sp² Coupling Protocols

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Department of Chemistry, Nottingham University, Nottingham NG7 2RD, England Received 7 July 1998; accepted 28 August 1998 Abstract: The scope for a range of sp²-sp² coupling protocols to elaborate the phenyl-indole, indole-

Abstract: The scope for a range of sp^2-sp^2 coupling protocols to elaborate the phenyl-indole, indoleoxazole, 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. © 1998 Elsevier Science Ltd. All rights reserved.

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 sp²-sp² 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-oxazole⁴ and polyene macrolide⁵ based marine natural products, are now presented here.



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 reaction⁷ with the substrate 3 in the presence of Pd(PPh₃)₄, Ag₂CO₃, 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 reaction⁹ 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 cyclisation¹¹ according to Scheme 1.

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Reagents: i, Pd(PPh₃)₄, Ag₂CO₃, DMF, 80°C, 95%; ii, O₃, PPh₃, 85%; then NaClO₄, KH₂PO₄, 'BuOH, H₂O, butene, 97%; iii, SOCl₂, (S)-2-methylbenzylamine, 92%; iv, *p*TSA, then NaOH, 78%; v, (Im)₂CO, THF, 100%; vi, EtO₂CCH₂CO₂H, (CH₃)₂CHMgBr, THF, Δ , 60%; vii, NaH, Br₂, THF, 99%; viii, NaN₃, DMF, 99%; ix, PPh₃, THF, H₂O, 100%; x, AcCl, Et₃N, CH₂Cl₂; 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 indoles¹³ and arylstannanes (Pd(PPh₃)₄, DME, 80°C, 55%) or 4-triflate indoles and arylboronic acids (Pd(PPh₃)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 DDQ¹⁷ 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 sp²-sp² 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·SO₃, CH₂Cl₂, DMSO, 82%; iii, KHMDS, 18-crown-6, (F₃CH₂CO)₂POCH₂CO₂Me, 79%; iv, LiOH, DME, H₂O; v, TFA, CH₂Cl₂; vi, ⁱPr₂NEt, DPPA, CH₂Cl₂, 49% over 3 steps.



Scheme 2

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