

Tetrahedron Letters 39 (1998) 8167-8170

TETRAHEDRON LETTERS

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

Alicia Boto, Matthew Ling, Graham Meek and Gerald Pattenden*

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.

0040-4039/98/\$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved. PII: S0040-4039(98)01819-X



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

Acknowledgements: We thank the Spanish Ministry of Education (Fellowship to A.B.) and the EPSRC (Fellowship to G.M.). We also thank Dr A J Blake for the X-ray crystal structure determination of compound 6.

References

- 1. N. Lindquist, W. Fenical, G. D. Van Duyne and J. Clardy, J. Am. Chem. Soc., 1991, 113, 2303.
- 2. For other synthetic approaches towards diazonamide A see: K. J. Doyle, M. C. Elliot, T. J. Mowlem and C. J. Moody, J. Chem. Soc., Perkin Trans. 1, 1997, 2413, and earlier references cited therein.
- 3. For recent and related complementary synthetic work see: P. Wipf and F. Yokokawa, *Tetrahedron Lett.*, 1998, **39**, 2223.
- 4. see: S. K. Chattopadhyay and G. Pattenden, Synlett, 1997, 1345; S. K. Chattopadhyay and G. Pattenden, Synlett, 1997, 1342; J. C. Muir, G. Pattenden and R. M. Thomas, Synthesis, 1998, 613.
- D. J. Critcher and G. Pattenden, Tetrahedron Lett., 1996, 37, 9107; D. A. Entwistle, S. I. Jordan, J. Montgomery and G. Pattenden, J. Chem. Soc., Perkin Trans. 1, 1996, 1315; R. J. Boyce and G. Pattenden, Tetrahedron Lett., 1996, 37, 3501; G. Pattenden and S. M. Thom, Synlett, 1993, 215.
- 6. A. Ali, G. B. Gill, G. Pattenden, G. A. Roan and T.-S. Kam, J. Chem. Soc., Perkin Trans. 1, 1996, 11, 1081.
- A. de Meijere and F. E. Meyer, Angew. Chem. Int. Ed. Engl., 1994, 33, 2379; S. E. Gibson and R. J. Middleton, Contemporary Org. Syn., 1996, 3, 447; R. C. Larock and D. E. Stinn, Tetrahedron Lett., 1988, 29, 4687; E. Negishi, T. Nguyen and B. O'Connor, Heterocycles, 1989, 28, 55; A. Madin and L. E. Overman, Tetrahedron Lett., 1992, 33, 4859; A. Ashimori and L. E. Overman, J. Org. Chem., 1992, 57, 4571; R. Grigg, V. Sridharan, P. Stevenson and T. Worakun, J. Chem. Soc., Chem. Commun., 1986, 1697.
- 8. All new compounds showed satisfactory spectroscopic data together with mass spectrometry or microanalytical data.
- M. Shibasaki, C. D. J. Boden and A. Kojima, *Tetrahedron*, 1997, 53, 7371; Y. Sato, S. Watanabe and M. Shibasaki, *Tetrahedron Lett.*, 1992, 33, 2589; Y. Sato, T. Honda and M. Shibasaki, *Tetrahedron Lett.*, 1992, 33, 2593; S. Nukui, M. Sodeoka, H. Sasai and M. Shibasaki, *J. Org. Chem.*, 1995, 60, 398; L. F. Tietze and T. Raschke, *Synlett*, 1995, 597.
- 10. The stereochemistry of **6** was established by X-ray crystallography analysis. Details will be published later in a full paper.
- 11. G. Theilig, Chem. Ber., 1953, 86, 96.
- M. Sainsbury, *Tetrahedron*, 1980, 36, 3327; R. C. Fuson and E. A. Cleveland, Org. Synth. Coll. Vol. 3, 339; M. F. Semmelhack, P. Helquist, L. D. Jones, L. Keller, L. Mendelson, L. Speltz Ryono, J. Gorzynski Smith and R. D. Stauffer, J. Am. Chem. Soc., 1981, 103, 6460; W. Carruthers, P. Coggins and J. B. Weston, J. Chem. Soc., Perkin Trans. 1, 1991, 611.
- 13. J. P. Konopelski, J. M. Hottenroth, H. Monzó Oltra, E. A. Véliz and Z.-C. Yang, Synlett, 1996, 609; M. Somei, F. Yamada and K. Naka, Chem. Pharm. Bull., 1987, 35, 1322.
- A. Suzuki, Pure and Appl. Chem., 1994, 66, 213; V. Upender, D. J. Pollart, J. Liu, P. D. Hobbs, C. Olsen, W. Chao, B. Bowden, J. L. Crase, D. W. Thomas, A. Pandey, J. A. Lawson and M. I. Dawson, J. Heterocyclic Chem., 1996, 33, 1371.
- 15. Ullmann coupling reactions were also attempted on component aryl bromides 4 and 13 but no homocoupled products were obtained.
- cf A. G. M. Barrett and J. T. Kohrt, Synlett, 1995, 415; A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici and P. Pedrini, Synthesis, 1987, 693; T. Ross Kelly and F. Lang, J. Org. Chem., 1996, 61, 4623.
- 17. Y. Oikawa and O. Yonemitsu, J. Org. Chem., 1977, 42, 1213.