Pergamon

Tetrahedron Letters 41 (2000) 6897–6900

TETRAHEDRON LETTERS

Studies towards the synthesis of diazonamide A. Synthesis of the indole bis-oxazole fragment

Mark C. Bagley, S. Lucy Hind and Christopher J. Moody*

School of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK

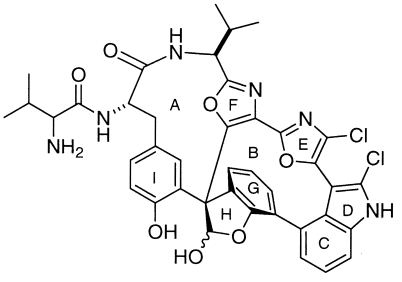
Received 24 May 2000; accepted 29 June 2000

Abstract

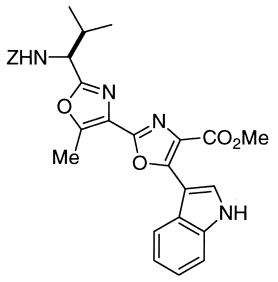
The indole bis-oxazole **2**, a potential intermediate for the synthesis of the marine natural product diazonamide A **1**, has been synthesised, and attempts to construct the model macrocycle (ring B) **3** are also described; in both approaches rhodium carbenoid N–H insertion reactions are used in key steps.

Keywords: rhodium carbenoid insertion; indoles; oxazoles.

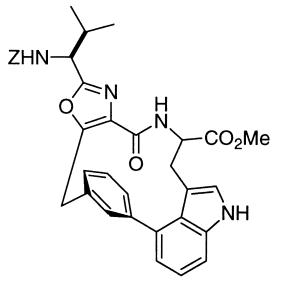
In the preceding letter we described the synthesis of a tyrosine-derived benzofuranone,[1] a key intermediate (rings G–H–I) in our projected synthesis of diazonamide A **1**, a structurally unique marine metabolite with potent antitumour properties.[2,3] We now report our approach to the tryptophan-derived indole fragment of diazonamide A **1**, and describe the synthesis of the model indole bis-oxazole **2**,[4] together with our attempts to construct the right hand macrocycle (ring B) **3** of the natural product by intramolecular biaryl bond formation.



diazonamide A **1**



2



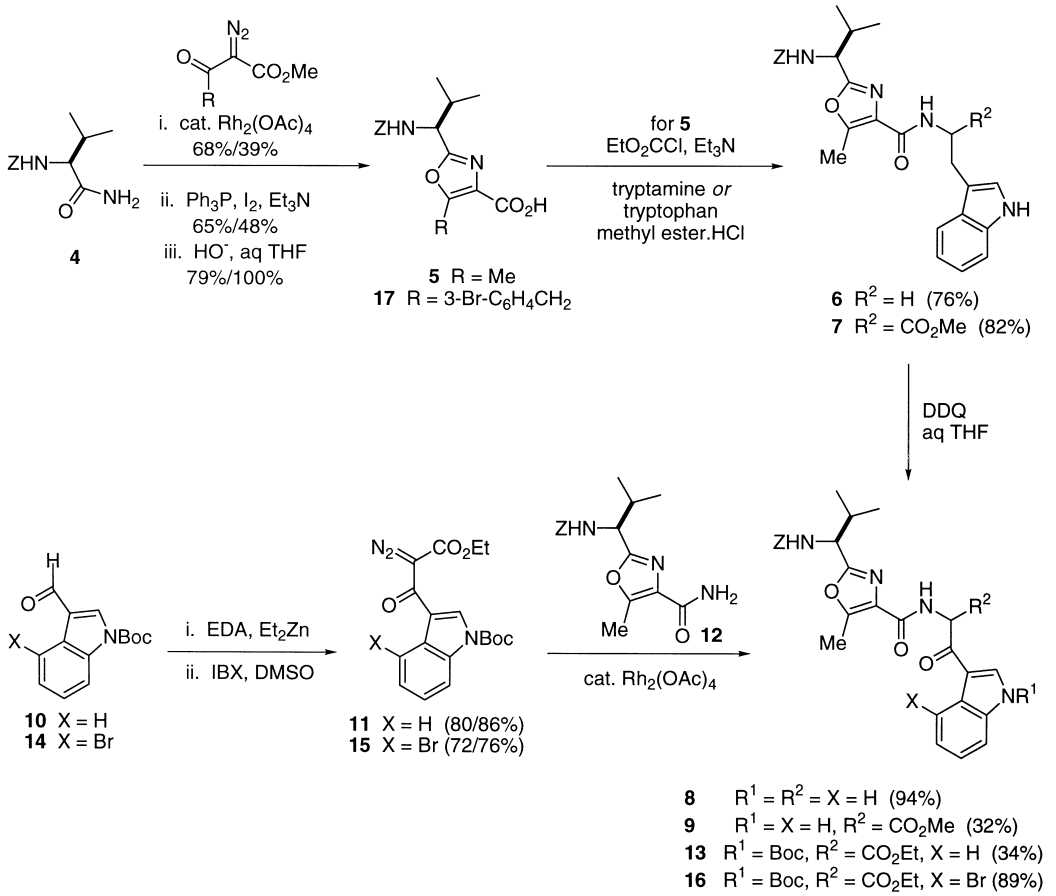
3

With the relatively strained nature of the ring B macrocycle in mind, our synthesis was planned so that one of the oxazole rings (ring E) was formed at a late stage by cyclodehydration of an

* Corresponding author. E-mail: c.j.moody@ex.ac.uk

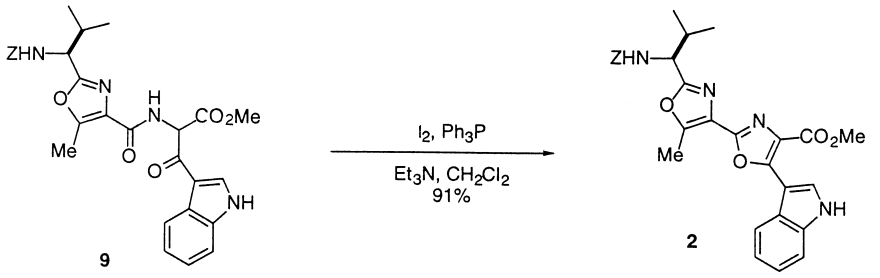
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01120-5

appropriate 1,4-dicarbonyl compound. Therefore, our initial model studies sought to demonstrate the viability of this approach. The starting material was the valine-derived oxazole-4-carboxylic acid **5**, prepared by our previously developed route based on rhodium carbenoid N–H insertion reactions.[5] Thus, dirhodium(II) acetate-catalysed reaction of methyl 2-diazo-3-oxobutanoate with (S)-*N*-benzyloxycarbonylvalinamide **4** resulted in carbenoid insertion into the primary amide N–H bond; cyclodehydration of the intermediate 1,4-dicarbonyl compound using Wipf's protocol[6] gave the corresponding oxazole-4-ester, alkaline hydrolysis of which gave the required oxazole carboxylic acid **5** (Scheme 1). Activation of the acid by mixed anhydride formation followed by coupling with tryptamine (76%) or tryptophan methyl ester (82%) gave the indoles **6** and **7**. Oxidation of **6** and **7** with DDQ[7] gave the keto amides **8** and **9**, the required 1,4-dicarbonyl precursors of the second oxazole ring (Scheme 1). The closely related ketoamide **13** was also prepared by an alternative method. Addition of ethyl diazoacetate (EDA) to the indole-3-carboxaldehyde **10** in the presence of diethylzinc[8] gave the corresponding α-diazo-β-hydroxyester, oxidation of which with *o*-iodoxybenzoic acid (IBX)[9] gave the α-diazo-β-ketoester **11**. Dirhodium-(II)-catalysed reaction in the presence of the oxazole-4-carboxamide **12**, prepared from the carboxylic acid **5**, resulted in carbenoid N–H insertion and formation of the desired ketoamide **13**. The sequence was repeated with the 4-bromoindole **14** to give the corresponding ketoamide **16**, the 4-bromo substituent being incorporated to allow subsequent sp^2–sp^2 coupling at this position.



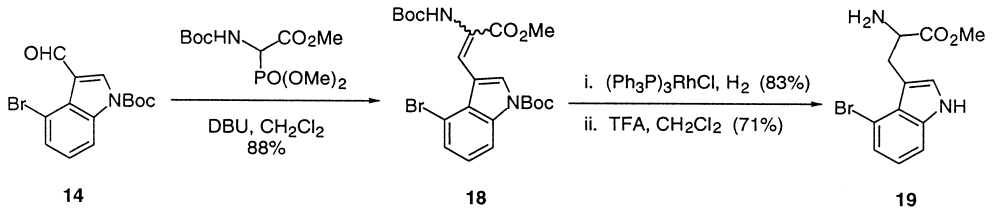
Scheme 1.

With two routes to the indole–oxazole 1,4-dicarbonyl compounds available, the subsequent cyclodehydration to form the second oxazole ring was readily demonstrated. Thus, treatment of **9** with triphenylphosphine/iodine/triethylamine gave the model indole bis-oxazole **2**, comprising the C–D–E–F rings of diazonamide A, in excellent yield (Scheme 2).



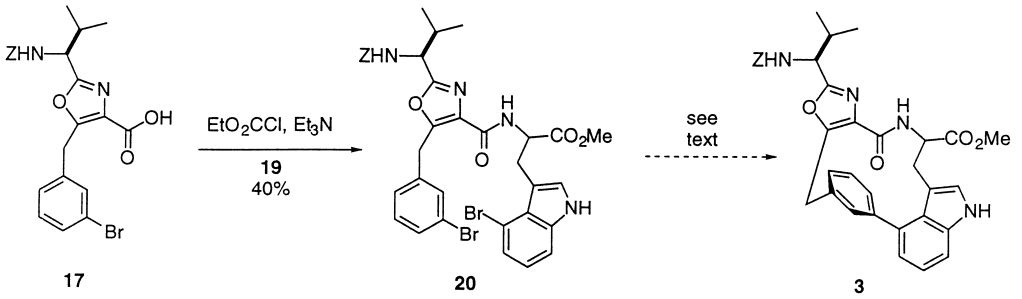
Scheme 2.

In order to adapt the above methodology to the synthesis of the indole bis-oxazole containing ring B macrocycle of the natural product we required a route to the model macrocycle **3**, and our initial attempts focused on an intramolecular biaryl coupling. In order to construct the dibromo-precursor **20** by amide bond formation, the relevant acid (5-(3-bromobenzyl)oxazole-4-carboxylic acid **17**) and amine (4-bromotryptophan methyl ester **19**) components were required. The oxazole **17** was obtained from the valinamide **4** by another carbenoid N–H insertion, followed by cyclo-dehydration and ester hydrolysis as shown in Scheme 1. 4-Bromotryptophan methyl ester **19** was prepared as shown in Scheme 3. Thus, Wadsworth Emmons reaction of *N*-Boc-4-bromoindole-3-carboxaldehyde **14** with trimethyl 2-[*N*-(*tert*-butoxycarbonyl)amino]phosphonoacetate (itself prepared in 93% yield by a rhodium carbenoid N–H insertion reaction of trimethyl diazophos-phonoacetate with *tert*-butyl carbamate[10]) gave the dehydrotryptophan derivative **18** in good yield. Hydrogenation followed by removal of the two Boc groups then gave the required 4-bromo tryptophan derivative **19** (Scheme 3).



Scheme 3.

The oxazole acid **17** was activated using mixed anhydride methodology, and coupled with the tryptophan **19** to give the required dibromo compound **20**, the precursor for the intramolecular biaryl coupling reaction. However, all attempts to effect the intramolecular biaryl coupling of dibromide **20** using various conditions [e.g. $NiCl_2$, PPh_3, NaI, Zn[11] or $Pd(PPh_3)_4$, Me_6Sn[12]] failed to give any of the desired macrocycle **3** (Scheme 4).[13]



Scheme 4.

With the failure to effect the desired *intra*-molecular biaryl coupling, efforts were concentrated on carrying out an *inter*-molecular coupling at an earlier stage in the synthesis; the results of this approach are described in the following letter.[14]

Acknowledgements

We thank the Association for International Cancer Research for a studentship (to S.L.H.), the Leverhulme Trust for financial support, and the EPSRC Mass Spectrometry Service at Swansea for mass spectra.

References

1. Lach, F.; Moody, C. J. *Tetrahedron Lett*. **2000**, *41*, 6893–6896.
2. Lindquist, N.; Fenical, W.; Duyne, G. D. V.; Clardy, J. *J. Am. Chem. Soc*. **1991**, *113*, 2303–2304.
3. For a compilation of references to other approaches to the synthesis of diazonamide A, see Ref. 1.
4. For other syntheses of indole bis-oxazoles related to diazonamide A, see: (a) Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett*. **1998**, *39*, 8167–8170; (b) Magnus, P.; McIver, E. G. *Tetrahedron Lett*. **2000**, *41*, 831–834.
5. Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 591–600.
6. Wipf, P.; Miller, C. P. *J. Org. Chem*. **1993**, *58*, 3604–3606.
7. Oikawa, Y.; Yonemitsu, O. *J. Org. Chem*. **1977**, *42*, 1213–1216; Oikawa, Y.; Yoshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457–1462.
8. Moody, C. J.; Morfitt, C. N. *Synthesis* **1998**, 1039–1042.
9. Frigerio, M.; Santagostino, M. *Tetrahedron Lett*. **1994**, *35*, 8019–8022.
10. Ferris, L.; Haigh, D.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2885–2888.
11. Kageyama, H.; Miyazaki, T.; Kimura, Y. *Synlett* **1994**, 371–372.
12. Kelly, T. R.; Li, Q.; Bhushan, V. *Tetrahedron Lett*. **1990**, *31*, 161–164.
13. Others have also reported a failure to construct the 4-arylindole by intramolecular biaryl bond formation; see Ref. 4a.
14. Bagley, M. C.; Moody, C. J.; Pepper, A. G. *Tetrahedron Lett*. **2000**, *41*, 6901–6904.