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Studies towards the synthesis of diazonamide A. Synthesis of the 4-(oxazol-5-ylmethyl) aryltryptamine fragment

Mark C. Bagley, Christopher J. Moody* and Adrian G. Pepper

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

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Abstract

The oxazole substituted 4-aryltryptamine **5**, a potential intermediate for the synthesis of the marine natural product diazonamide A **1**, has been synthesised.

Keywords: indoles; Claisen rearrangement; Suzuki reaction; rhodium carbenoid insertion; oxazoles.

In the preceding two letters we described the synthesis of the tyrosine-derived benzofuranone **2**,[1] and the indole bis-oxazole **3**,[2] key intermediates (rings G–H–I and rings C–D–E–F) in our projected synthesis of diazonamide A **1**, a structurally unique marine metabolite with potent antitumour properties.[3,4] We also described our attempts to construct the right hand macrocycle (ring B) of the natural product by intramolecular biaryl bond formation using the dibromide **4** as substrate.[2] With the failure to effect the key biaryl bond formation at the indole-4-position by an *intra*-molecular coupling reaction, we turned our attention to an *inter*-molecular coupling at an earlier stage in the synthesis, and the results of this approach are described herein.

The target of our studies was the highly substituted 4-aryltryptamine **5**, which not only contains the C–D–F–G ring system of the natural product, but also the functionality to form the macrocyclic B-ring by a macrolactamisation reaction. In addition, oxidation of the CH_2-group α-to the indole ring with DDQ will provide the required 1,4-dicarbonyl compound for cyclodehydration to form the second oxazole (ring E).[2] The indole component for the synthesis of the 4-aryltryptamine **5** was the di-Boc-protected 4-bromotryptamine **10**, and this was prepared from 4-bromoindole **6** as shown in Scheme 1. Thus, Vilsmeier formylation of 4-bromoindole **6** gave the known[5] 4-bromoindole-3-carboxaldehyde **7** in good yield. Henry reaction of the aldehyde with nitromethane gave the nitroalkene **8**, reduction of which with lithium aluminium hydride gave 4-bromotryptamine **9**. Finally, protection of both the primary amine and the indole nitrogen as their Boc derivatives gave the required 4-bromotryptamine derivative **10** (Scheme 1).

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

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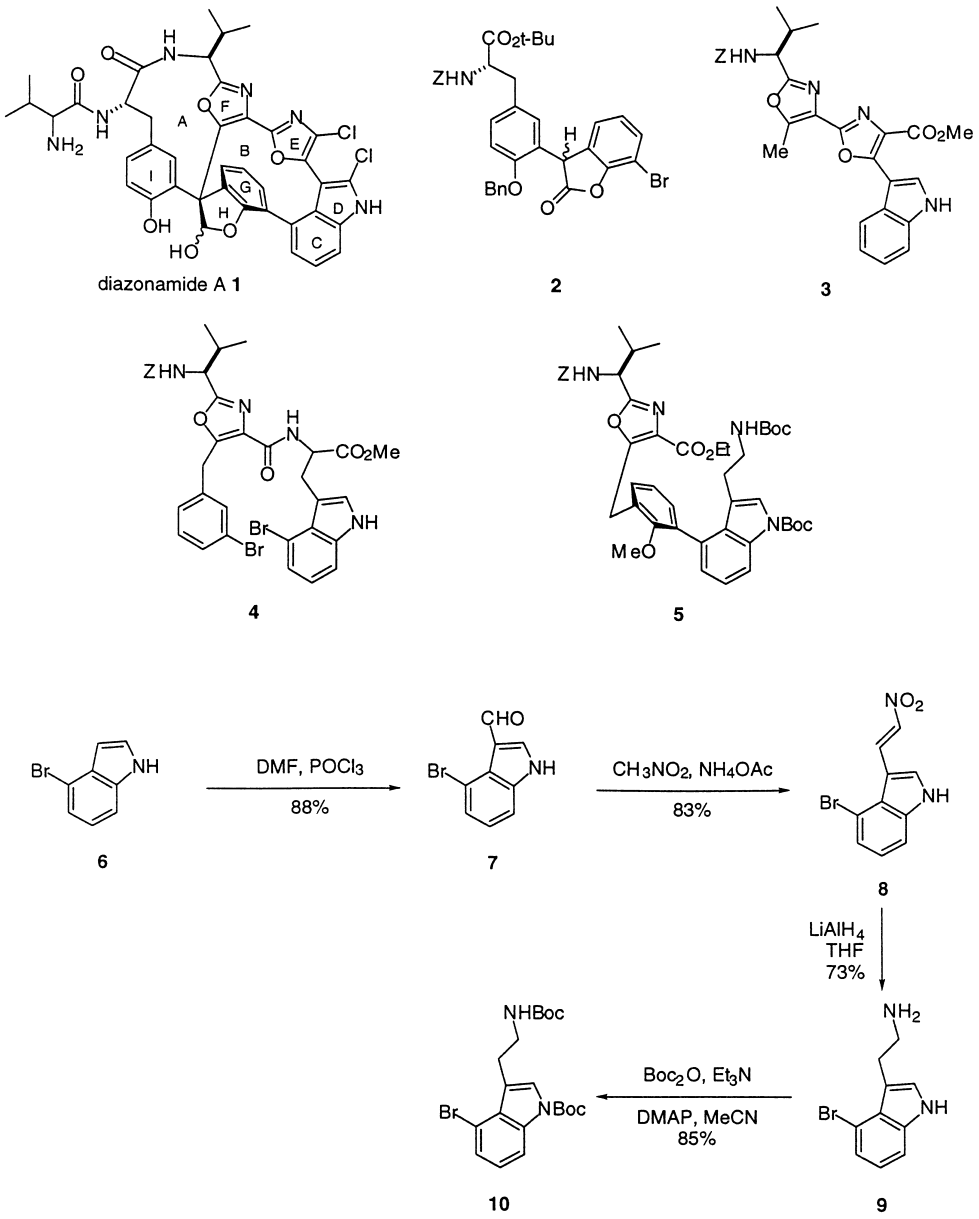
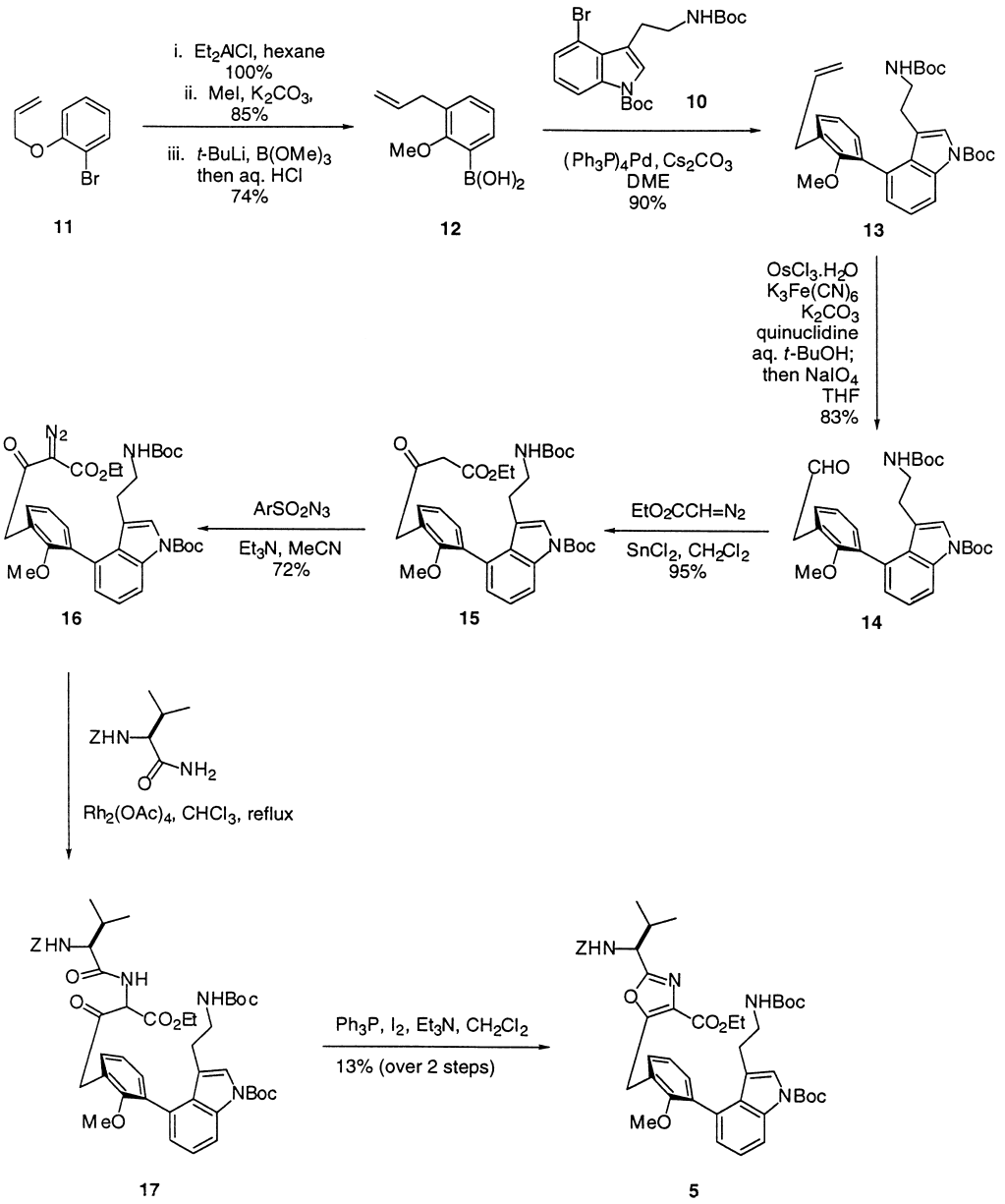


Scheme 1.

The second component for the formation of the biaryl bond in **5** was the boronic acid **12**, readily prepared from 2-allyloxybromobenzene **11** by Lewis acid-catalysed Claisen rearrangement (100%), *O*-methylation (85%) and treatment with *t*-butyllithium followed by trimethyl borate (74%) (Scheme 2). The Suzuki coupling of **10** and **12** proceeded smoothly in the presence of $Pd(PPh_3)_4$ and caesium carbonate to give the 4-aryltryptamine **13** in excellent yield (90%).[6] The oxazole ring was constructed using our rhodium carbenoid N–H insertion methodology,[7] and hence required the conversion of the allyl side chain into an α-diazo-β-ketoester. Oxidative cleavage of the allyl group in a two-step process by dihydroxylation,[8] followed by periodate gave



Scheme 2.

the aldehyde **14** in good yield. Attempts to form the required α-diazo-β-ketoester **16** by addition of ethyl diazoacetate in the presence of diethylzinc,[9] followed by oxidation of the resulting α-diazo-β-hydroxyester were unsatisfactory, and therefore an alternative procedure was adopted. Addition of ethyl diazoacetate in the presence of tin(II) chloride[10] gave the β-ketoester **15** in excellent yield; the diazo group was reintroduced by standard diazo transfer methodology using 4-acetamidobenzenesulfonyl azide,[11] and gave the required α-diazo-β-ketoester **16** setting the stage for the key rhodium carbenoid N–H insertion reaction (Scheme 2). Dirhodium(II) acetate-catalysed reaction of the α-diazo-β-ketoester **16** in the presence of (S)-*N*-benzyloxy-

carbonylvalinamide resulted in selective carbenoid insertion into the primary amide N–H bond; finally, cyclodehydration of the intermediate 1,4-dicarbonyl compound **17** using Wipf's protocol[12] gave the oxazole-4-ester **5**, albeit in poor yield over the two steps, comprising the highly functionalised 4-aryltryptamine fragment of diazonamide A **1**.

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