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Studies towards the synthesis of diazonamide A. Synthesis of a tyrosine-derived benzofuranone

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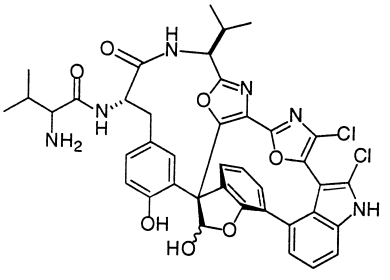
Abstract

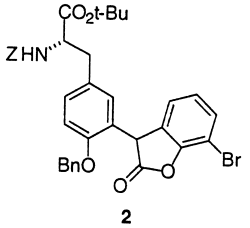
The benzofuranone **2**, a potential intermediate for the synthesis of the marine natural product diazonamide A **1**, has been synthesised in eight steps from the *N*-protected tyrosine ester **3**.

Keywords: Stille reaction; Claisen rearrangement; lactones.

Diazonamide A **1**, a structurally unique secondary metabolite isolated from the colonial ascidian *Diazona chinensis*, is reported to have potent in vitro cytotoxic activity against human and murine tumour cell lines.[1] The structure of the natural product, which was assigned on the basis of an X-ray crystal structure of a closely related derivative,[1] comprises a complex arrangement of aromatic and heteroaromatic rings linked either directly as biaryls or via an intermediate quaternary centre or peptide bonds, in a macrocyclic array. These unusual structural features and the interesting biological activity have combined to make diazonamide A an extremely attractive target for synthesis, and several groups, including our own, have reported a range of approaches to various structural subunits of the natural product.[2–14] We now report the synthesis of the tyrosine-derived benzofuranone **2** by a route which involves a Claisen rearrangement as a key step.



diazonamide A **1**



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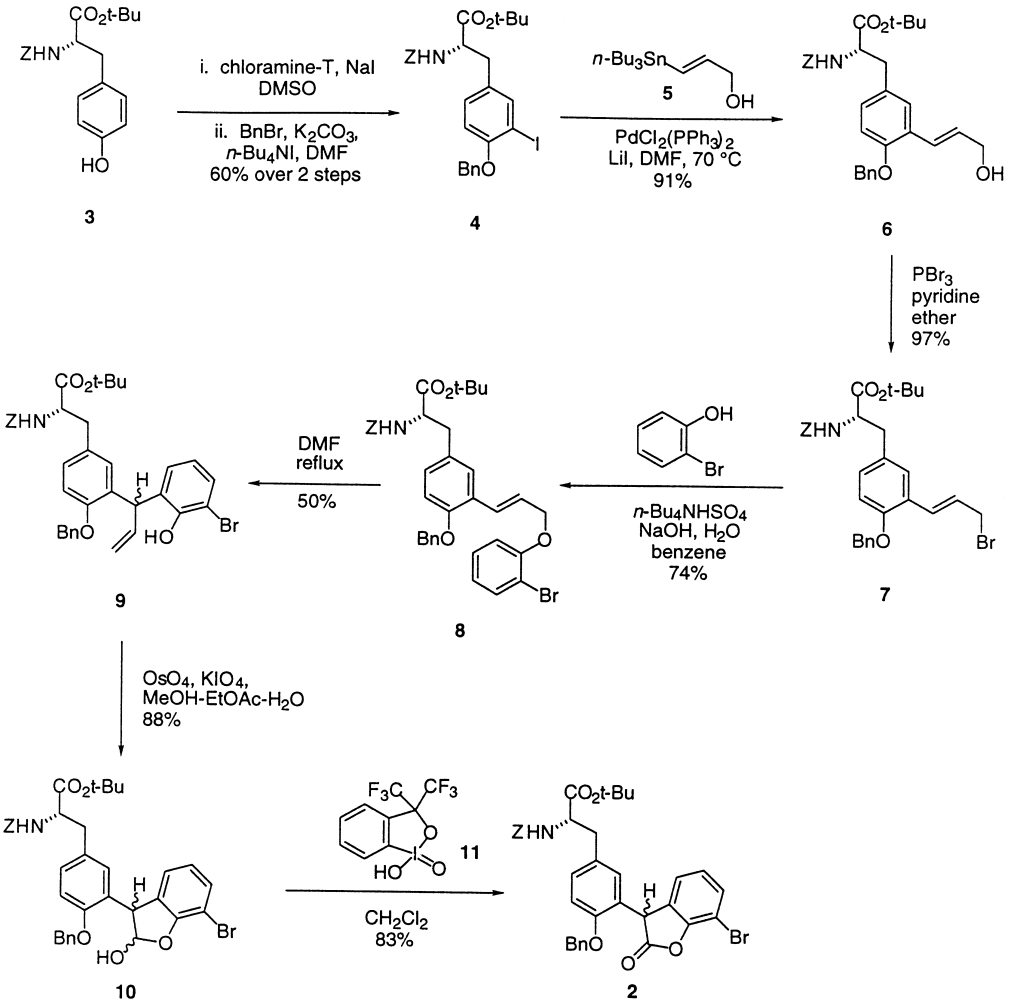
Benzofuranone **2** was selected as a potential precursor to diazonamide A **1** on the basis that it not only contains the required tyrosine unit (in protected form), but also a bromine at C-7 (benzofuran numbering) which will allow transition-metal catalysed sp^2–sp^2 coupling to form the biaryl bond to the 4-position of an appropriate indole at a later stage in the synthesis. Additionally, the use of Black's *C*-acylation procedure,[15] should allow the introduction of an additional carbon substituent at the 3-position of the benzofuran, the eventual C-10 quaternary centre in diazonamide A. This *C*-acylation procedure was used in a simple benzofuranone in our early preliminary studies,[2,4] and also very recently by Vedejs in his approach to a fragment of diazonamide A.[12]

The starting material for the synthesis of the benzofuranone **2** was the known *N*-benzyloxycarbonyl tyrosine *tert*-butyl ester **3**.[16] *ortho*-Iodination of the phenol was achieved under neutral conditions using chloramine-T/sodium iodide.[17] The *ortho*-iodophenol was not purified, but immediately *O*-alkylated under conditions known to minimise racemisation[18] to give the benzyl ether **4** in 60% yield over the two steps (Scheme 1). After considerable experimentation, it was



Scheme 1.

found that the palladium-catalysed coupling of the iodotyrosine derivative **4** with allyl alcohol, under the conditions developed by Jeffery to prevent subsequent isomerisation of the double bond,[19] gave the required cinnamyl alcohol derivative **6** but in modest yield (30–35%). Therefore, we resorted to a Stille coupling of the iodide **4** with the tri-*n*-butylstannyl allyl alcohol **5**, prepared from propargyl alcohol,[20–22] and this gave the cinnamyl alcohol **6** in excellent yield (91%). Conversion into the allylic bromide **7** without any isomerisation of the double bond, was followed by reaction with 2-bromophenol using sodium hydroxide as base under phase transfer conditions to give the cinnamyl aryl ether **8**. This substrate underwent Claisen rearrangement on heating under reflux in DMF to give the phenol **9** as a mixture of diastereomers. Reaction of alkene **9** with catalytic osmium tetroxide with potassium periodate as co-oxidant resulted in oxidative cleavage of the double bond, and cyclisation of the intermediate aldehyde to the lactol **10**. Oxidation of the lactol **10** to the desired lactone **2** proved surprisingly difficult, and a number of commonly used reagents (PCC, PDC, Fetizon's reagent, Swern conditions) failed to effect this transformation. Eventually it was found that the iodinane oxide **11**,[23] a reagent reported by Grieco et al. to be useful for similar oxidations,[24] converted the lactol **10** into the required lactone **2** in 83% yield (Scheme 1).

Thus the benzofuranone **2**, a potential intermediate in the synthesis of diazonamide A, has been prepared in eight steps from the *N*-protected tyrosine ester **3**. Although obtained as a mixture of diastereomers, the introduction of the additional carbon substituent at C-3 (benzofuran numbering) and hence generation of the C-10 quaternary centre in diazonamide will involve *C*-acylation and an sp^2-hybridised intermediate at this centre (cf. Ref. 2, 4 and 12); experiments along these lines are in progress.

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