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The diazo route to diazonamide A: studies on the tyrosine-derived fragment†‡

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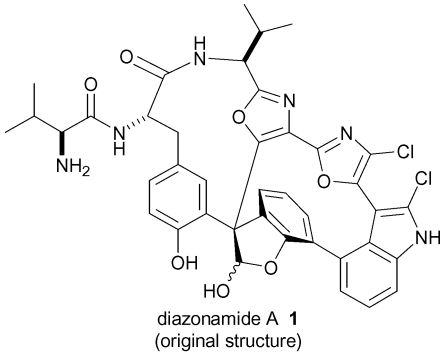
Various approaches to the tyrosine-derived fragment of the marine secondary metabolite diazonamide A are described. Initial efforts were focused on the originally proposed structure of the natural product, and a feasibility study established that a model 4-aryltryptamine could be readily prepared. Protected 4-bromotryptamine underwent Pd(0)-catalyzed coupling with the boronic acid derived from 2-bromophenyl allyl ether by Claisen rearrangement, *O*-methylation and lithiation–boration. The resulting biaryl was elaborated into an α-diazo-β-ketoester, dirhodium(II)-catalyzed reaction of which with *N*-*Z*-valinamide gave the desired tryptamine-oxazole following cyclodehydration of the intermediate ketoamide. A potential precursor to the benzofuran ring of the original structure of diazonamide A was prepared in eight steps from *N*-*Z*-tyrosine *tert*-butyl ester. Iodination, *O*-protection and Stille coupling gave the cinnamyl alcohol **25**, converted *via* the bromide into the allyl aryl ether **27**. Subsequent Claisen rearrangement and oxidative cleavage of the alkene gave the lactol **29**, converted into the desired benzofuranone **31**. The revision in the structure of diazonamide A to **2** resulted in the targeting of an alternative tyrosine-derived model benzofuranone **41** synthesized in four steps from *N*-*Z*-tyrosine methyl ester **36** by a route involving Claisen rearrangement of cinnamyl ether **37**. Poor yields in this sequence prompted an investigation into the intramolecular Heck reaction as a route to benzofuranone **50**. Coupling of 3-iodotyrosine **44** with 2-phenylbutenoic acid **48** gave ester **49** that readily underwent intramolecular Heck reaction to give benzofuranone **50**, albeit with poor stereocontrol.

Introduction

The marine secondary metabolite diazonamide A, isolated from the colonial ascidian *Diazona chinensis*, was assigned as structure **1** on the basis of an X-ray crystallographic study of a derivative.[2] This unique and complex strained structure, together with the reported nanomolar *in vitro* cytotoxicity against human tumor cell lines,[2,3] ensured that diazonamide A immediately attracted the attention of synthetic organic chemists. Hence in the 15 years since the structure of diazonamide A was reported in 1991, more than 10 research groups have published approaches to this fascinating natural product.[4–31] The story acquired a new dimension in 2001 when Harran and co-workers completed a total synthesis of structure **1** only to discover that it was different from the natural product.[32,33] On the basis of a re-examination of the original X-ray data, Harran proposed the alternative structure **2** for diazonamide A (Fig. 1). Not only did this subsequently prove to be correct, but it also better fits a biosynthetic route in which the bicyclic core derives from modification of a Tyr-Val-Trp-Trp tetrapeptide. Final proof that the revised structure **2** was indeed that of diazonamide A came in 2002 when Nicolaou and co-workers published the first total synthesis of the natural product.[34,35] Subsequently, the Nicolaou group reported a second route to diazonamide A,[36,37] whilst Harran and co-workers completed their own total synthesis of the correct structure.[38] Despite the fact that Nicolaou's and Harran's endeavours in total synthesis have now solved the structural problem of diazonamide A, such is its attraction as a target molecule that it continues to hold the attention of a number of research groups.



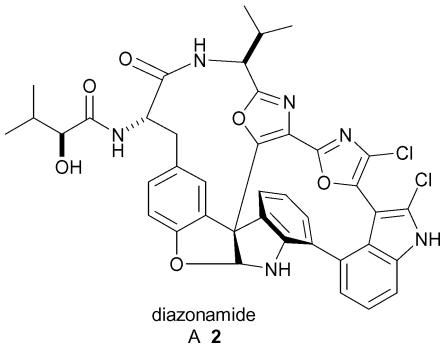


Fig. 1 The original and revised structures for the marine secondary metabolite diazonamide A.

Our own interest in diazonamide A started over a decade ago when we reported an approach to a benzofuranone related to the original structure using the DMAP-induced *C*-acylation reaction, and an approach to 5-(3-indolyl)oxazoles

† The diazo route to diazonamide A. Part 2.[1]

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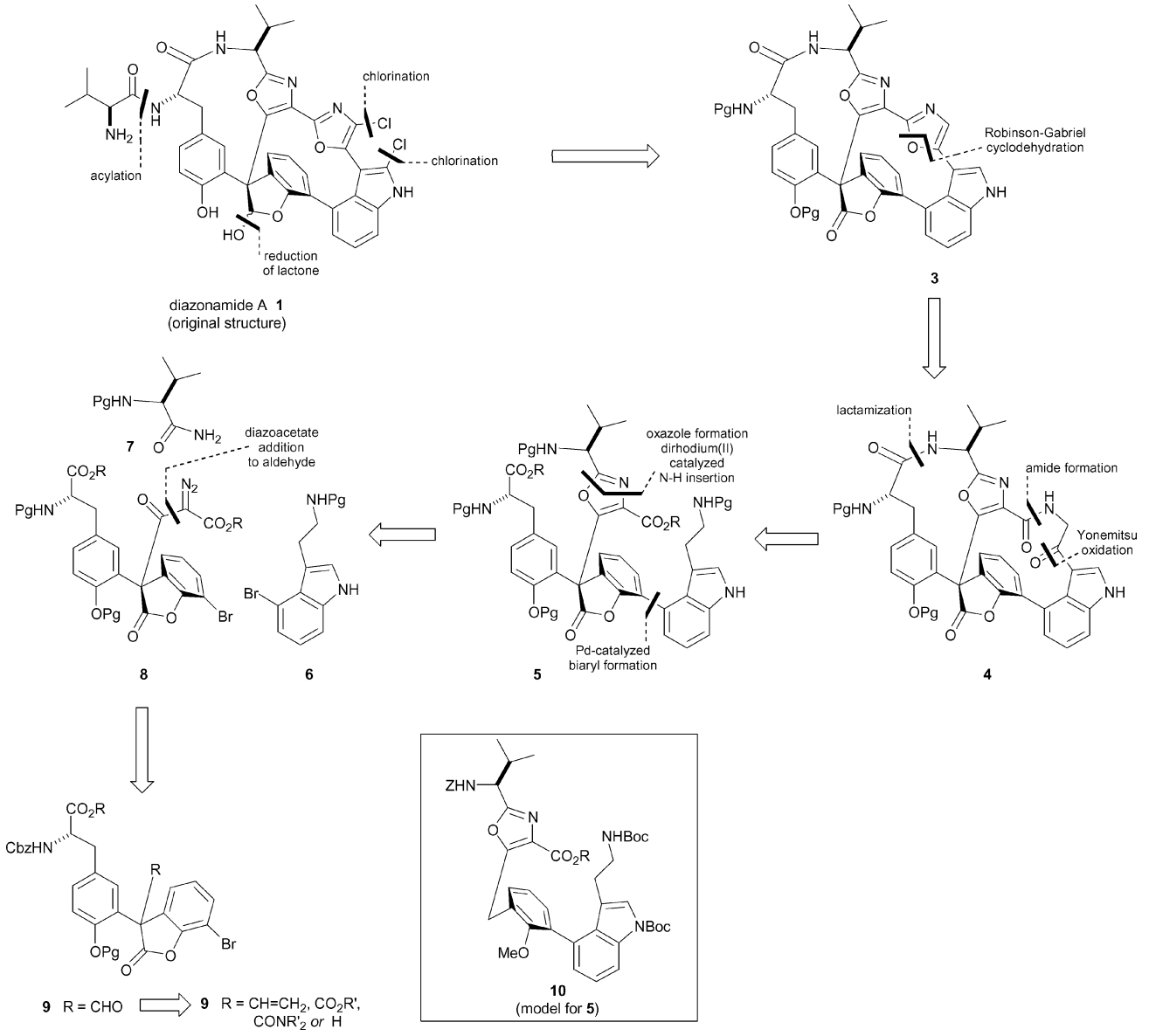
using dirhodium(II) catalyzed reactions of diazocarbonyl compounds.[39,40] We have also reported preliminary results on a second approach to the tyrosine-derived benzofuran unit of the original structure using the Claisen rearrangement,[41] and further studies on the indole fragments.[42,43] The first paper in this series described our efforts towards the indole bis-oxazole fragment of diazonamide A,[1] whilst the present paper describes the full details of our various approaches to the tyrosine-derived fragment of the natural product. Some of the work reported here has appeared in the preliminary publications referred to above.[41,43]

Results and discussion

Retrosynthetic analysis

Although devised some years ago, our retrosynthetic analysis of diazonamide A remains largely unaltered in its overall strategy, notwithstanding the fact that it was designed for the original structure **1** of the natural product. Thus, in common with most other reported strategies, our initial simplification was to disconnect the valine side-chain (or α-hydroxy isocaproic acid as in the correct structure) and the two chlorine atoms. It was established early on in the diazonamide saga that both these chlorines could be introduced by a late stage electrophilic chlorination reaction.[6,13] This initial analysis of the "old" diazonamide A **1**, together with the assumption that the γ-lactol could derive simply from the corresponding lactone, leads back to the bicycle **3**. Formation of the oxazole would result from a Robinson–Gabriel cyclodehydration of a 1,4-dicarbonyl compound **4** that in turn could be accessed *via* a Yonemitsu DDQ-oxidation of the indole-CH_2-group;[44,45] breaking of the two amide bonds in the retrosynthetic sense leads to compound **5**. Oxazole formation using the N-H insertion reaction of a rhodium carbene intermediate, a reaction extensively developed in our laboratory,[46–50] and a palladium-catalyzed biaryl formation then reveals three fragments: the 4-bromotryptamine **6**, the carboxamide **7**, and α-diazo-β-ketoester **8**, the precursor of the rhodium carbene intermediate (Scheme 1). Finally, it was envisaged that the diazocarbonyl compound **8** would derive from the corresponding aldehyde **9** (R = CHO) by either our previously developed diethylzinc mediated reactions of ethyl diazoacetate,[51] or the Roskamp protocol,[52] followed by diazo-transfer. This reveals the 3-formylbenzofuranone **9** (R = CHO), which in turn could be formed from the corresponding ester, amide, vinyl or unsubstituted compounds **9** (R = CO_2R', $CONR'_2$, vinyl or H) (Scheme 1).

This paper focuses on our approaches to benzofuranones **9** of the original diazonamide A structure and our attempts to adapt the methodology to the corresponding oxindoles of the correct structure. However, the paper is introduced by an early

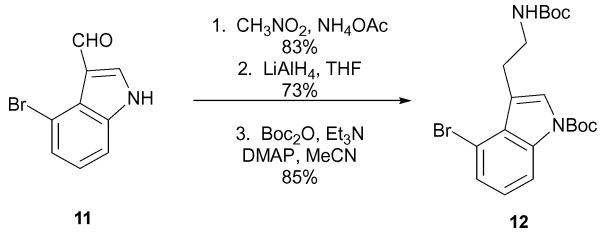


Scheme 1 Retrosynthetic analysis of the original structure of diazonamide A **1** [Pg = protecting group].

feasibility study in which a very simple model for aldehyde **9** (R = CHO) was investigated to confirm that elaboration at both the aldehyde and bromide functional groups to incorporate both oxazole and tryptamine fragments was indeed possible to give model structure **10**, a simpler version of one of our proposed key intermediates **5** (Scheme 1).

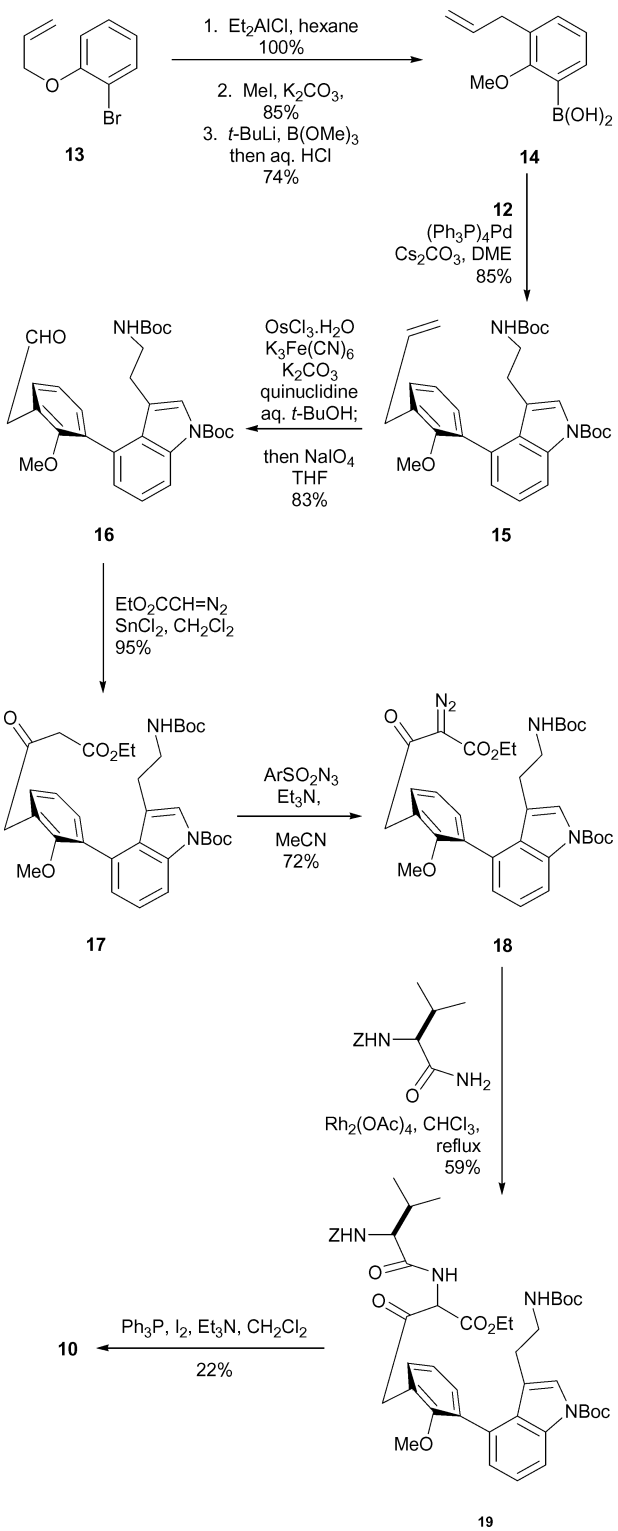
Synthesis of model 4-aryltryptamine 10

The synthesis of the model compound **10** started with the known 4-bromoindole-3-carboxaldehyde **11**[53] that was converted into the corresponding tryptamine by conventional means involving Henry reaction with nitromethane, and reduction of the resulting nitroalkene with lithium aluminium hydride. The 4-bromotryptamine was not purified, but was protected on both indole and side-chain nitrogens as the di-Boc-derivative **12** ready for Pd-catalyzed coupling at the indole 4-position (Scheme 2).



Scheme 2

The synthesis of the coupling partner **14** for 4-bromoindole **12** started with the allyl ether **13** of 2-bromophenol. Lewis acid-catalyzed Claisen rearrangement, methylation of the resulting phenol,[54] and lithium–halogen exchange followed by quenching with trimethyl borate gave the boronic acid **14**. Suzuki coupling of bromide **12** and boronic acid **14** using caesium carbonate as base gave the biaryl **15** in excellent yield. Oxidative cleavage of the allyl side-chain to the key aldehyde **16** was achieved in a two-step procedure by osmium tetroxide dihydroxylation followed by periodate cleavage. Reaction of the aldehyde **16** with ethyl diazoacetate in the presence of tin(II) chloride,[52] gave the β-ketoester **17**, that underwent smooth diazo-transfer with 4-acetamidobenzenesulfonyl azide[55] to give the required α-diazo-β-ketoester **18**. The stage was now set for the key rhodium carbene N-H insertion reaction, and this proceeded as planned, though in modest yield, to give the 1,4-dicarbonyl ketoamide **19**. Final Robinson–Gabriel cyclodehydration using the Wipf Ph_3P–I_2–Et_3N protocol[56] gave the model tryptamine-biaryl-oxazole **10**, albeit in poor yield (Scheme 3). Although some of the above (unoptimized) reactions only proceed in modest yield, the feasibility study has established that given an appropriate aromatic precursor containing a bromide and an aldehyde, then both bromine and aldehyde groups can be elaborated into tryptamine and oxazole units respectively as required in our proposed route to diazonamide A.

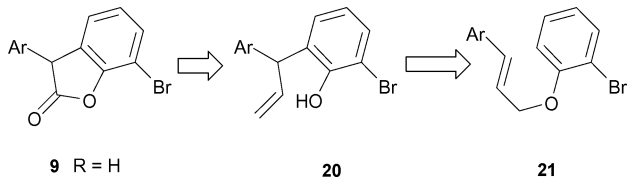


Scheme 3 Ar = 4-$AcNHC_6H_4$.

Synthesis of benzofuranone 9 (R = H), a potential precursor to the original structure of diazonamide A

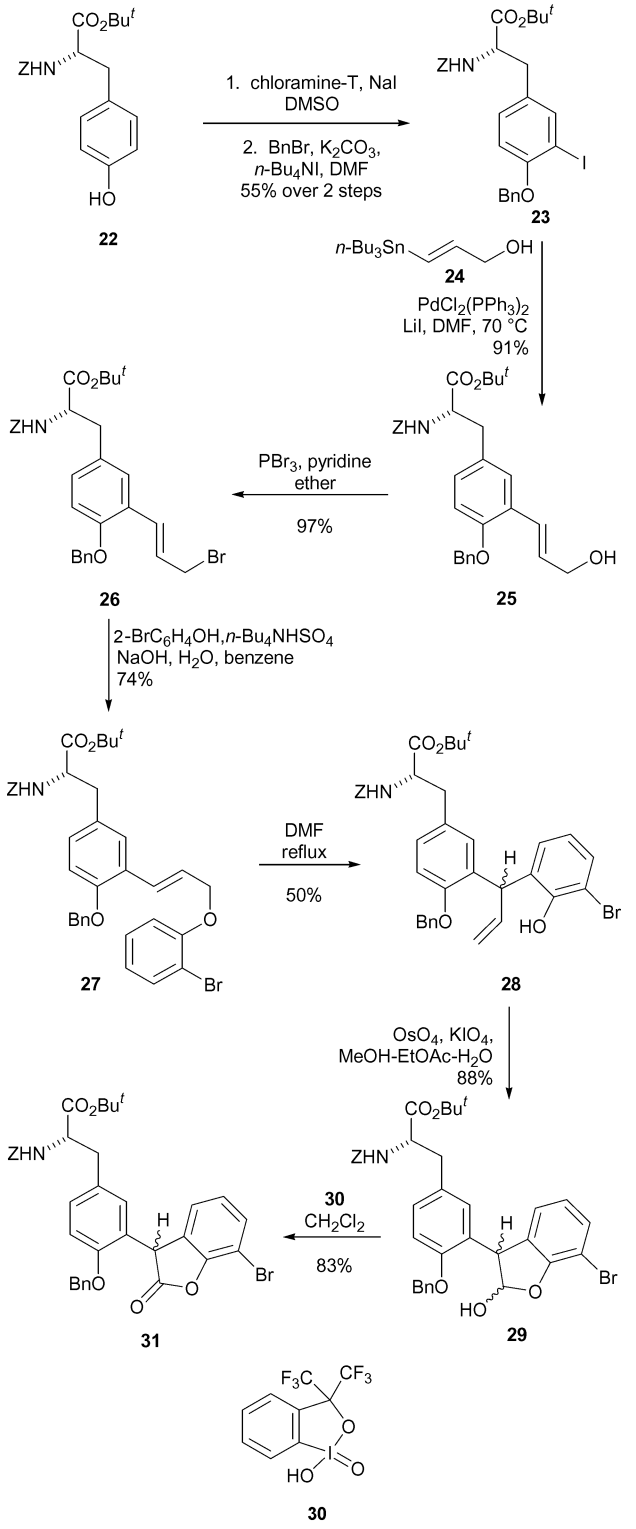
As outlined above, a benzofuranone **9** (R = H) was identified as a possible precursor to the tyrosine-derived benzofuran fragment of the original structure of diazonamide A **1** on the basis that it not only contains the required tyrosine unit (in protected form), but also a bromine at C-7 (benzofuran numbering) that will allow transition-metal catalyzed 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, *cf.* the feasibility study described above. Additionally, the use of Black's *C*-acylation procedure based on Steglich's original observations,[57] should allow the introduction of an additional carbon substituent that will become the aldehyde at the 3-position of the benzofuran—the C-10 quaternary centre in diazonamide A—for further elaboration to an oxazole as also described in the model study above. This *C*-acylation procedure was used in a simple benzofuranone in our early preliminary studies,[39,40] and also recently by Vedejs in his approach to a fragment of diazonamide A.[19] It was anticipated that a benzofuranone **9** (R = H) would be accessible by lactonization of an appropriate phenol and side-chain carboxylate, that in turn could be derived by oxidative cleavage of an allyl group double bond. The requirement for an *ortho*-allyl phenol immediately suggests a strategy involving a Claisen rearrangement as outlined in Scheme 4.

The starting material for the synthesis of the required benzofuranone **31** was the known *N*-benzyloxycarbonyl tyrosine *tert*-butyl ester **22**.[58] *ortho*-Iodination of the phenol was achieved



Scheme 4 Ar = protected 3-tyrosinyl residue.

under neutral conditions using chloramine-T–sodium iodide.[59,60] The *ortho*-iodophenol was not purified, but immediately *O*-alkylated under conditions known to minimize racemization[61] to give the benzyl ether **23** in 55% yield over the two steps (Scheme 5). After considerable experimentation, it was found that the palladium catalyzed coupling of the iodotyrosine derivative **23** with allyl alcohol, under the conditions [$Pd(OAc)_2$, Ph_3P, AgOAc, DMF] developed by Jeffery to prevent subsequent isomerization of the double bond,[62] gave the required cinnamyl alcohol derivative **25** but in modest yield (30–35%). Therefore we resorted to a Stille coupling of the iodide **23** with the tri-*n*-butylstannyl allyl alcohol **24**, prepared from propargyl alcohol by stannylcupration methodology,[63] and this gave the cinnamyl alcohol **25** in excellent yield (91%). Conversion into the allylic bromide **26** without any isomerization 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 **27**. This substrate underwent Claisen rearrangement on heating under reflux in DMF to give the phenol **28** as a mixture of diastereomers. Reaction of alkene **28** with catalytic osmium tetroxide with potassium periodate as co-oxidant resulted in oxidative cleavage of the double bond, and cyclization of the intermediate aldehyde to the lactol **29**. Oxidation of the lactol **29** to the desired lactone **31** 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 **30**,[64] a reagent reported by Grieco *et al.* to be useful for similar oxidations,[65] converted the lactol **29** into the required lactone **31** in 83% yield (Scheme 5). Thus the required benzofuranone **31** has been prepared in eight steps from the *N*-protected tyrosine ester **22**. Although we did initiate some preliminary experiments to establish a quaternary centre at the benzofuranone 3-position (C-10 in diazonamide),[66] these were curtailed when the revised structure of diazonamide A was revealed.

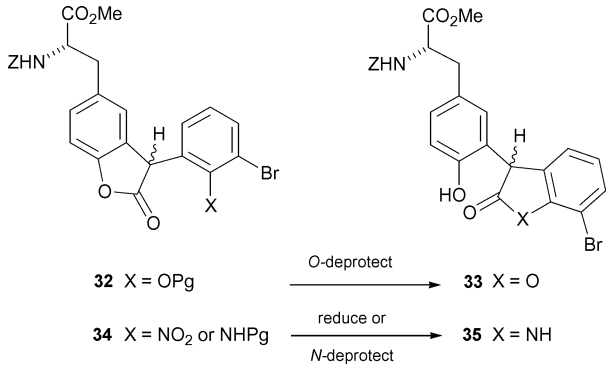


Scheme 5

Synthesis of alternative benzofuranone precursors to "both" structures of diazonamide A

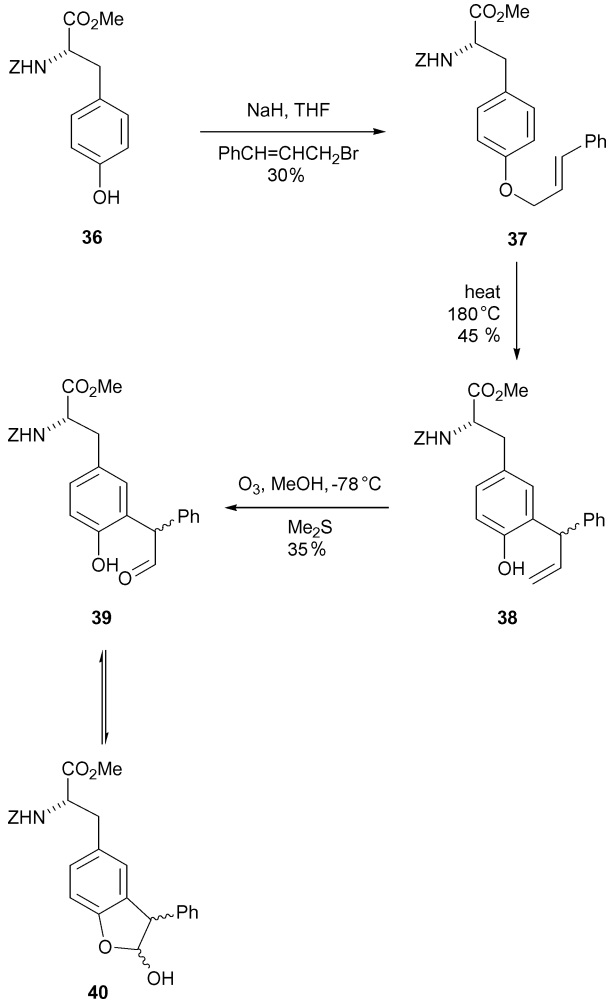
The publication of the revised and correct structure **2** for diazonamide A in 2001[32,33] caused us to reconsider our strategy. Although on the face of it, the required O to N switch in the heterocyclic core of the natural product, *i.e.* replacement of a benzofuranone precursor by the corresponding oxindole, seemed simple enough, the strategies described above both rely on a Claisen rearrangement of an allyl ether of 2-bromophenol. A few unsuccessful experiments with *N*-allyl derivatives of 2-bromoaniline quickly confirmed that an analogous strategy based on the aza-Claisen rearrangement[67] was unlikely to be successful, and therefore an alternative approach was adopted. This approach targets different tyrosine-derived benzofuranone precursors **32** and **34** on the basis that deprotection of the phenol in **32** or the aniline in **34** (X = NHPg) should result in cyclization to give the benzofuranone **33** or oxindole **35** rings of the original and revised structures of diazonamide A respectively. Likewise, reduction of a nitro-group in **34** ($X = NO_2$) would also result in cyclization to the oxoindole **35** (Scheme 6). Although it was not obvious which of the two benzofuranone structures, **32** (X = OH) or **33**, would be favoured under equilibrating conditions, we were confident that in the "correct" nitrogen series, the desired oxindole **35** would be favoured over its benzofuranone precursor **34** ($X = NH_2$).

Our first route to such benzofuranones did involve a Claisen rearrangement. Thus *N*-benzyloxycarbonyltyrosine methyl ester **36** was converted into the cinnamyl ether **37** by reaction with cinnamyl bromide. The Claisen rearrangement was investigated under a variety of conditions, none of which were entirely satisfactory, the best being prolonged heating in boiling 1,2-dichlorobenzene (bp 178–180 °C). The rearrangement proceeded in 45% yield to give the 3-allyl tyrosine derivative **38** as a mixture of diastereomers; ozonolysis of the alkene followed by reductive work-up with dimethyl sulfide gave a hemiacetal



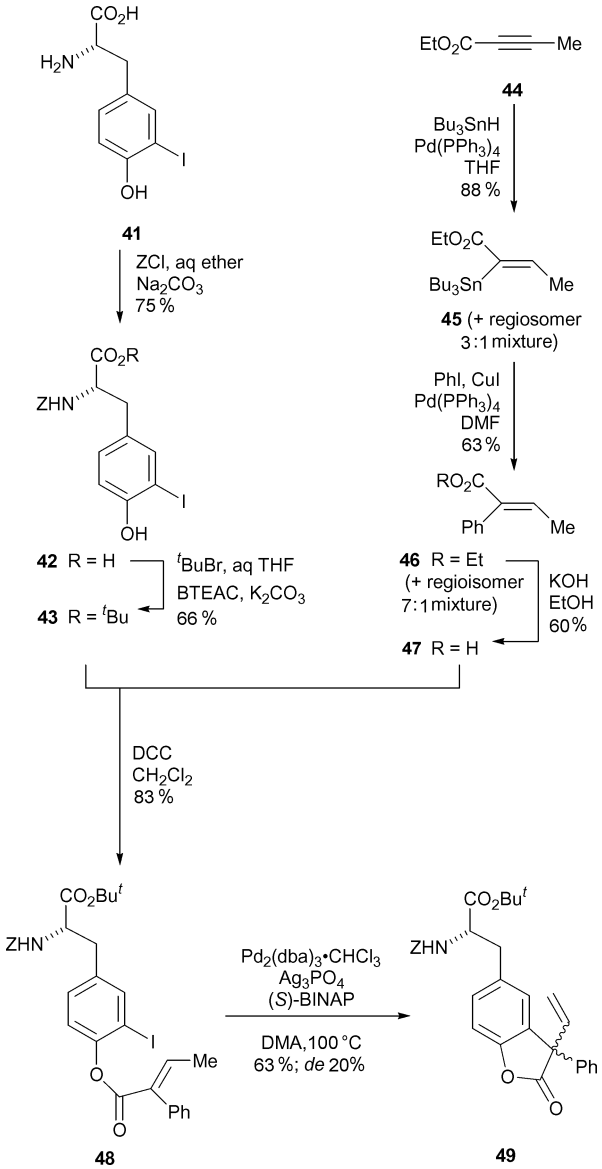
Scheme 6

directly, the lactol **40**, as a complex mixture of isomers, with no evidence for the intermediate aldehyde **39**. Although lactol **39** could, in principle, be readily oxidized to the corresponding lactone, a benzofuranone, all of the reactions described in Scheme 7 are unsatisfactory in terms of yield, and therefore no attempt was made to repeat the sequence with the appropriate substituents in the aromatic ring of the cinnamyl group.



Scheme 7

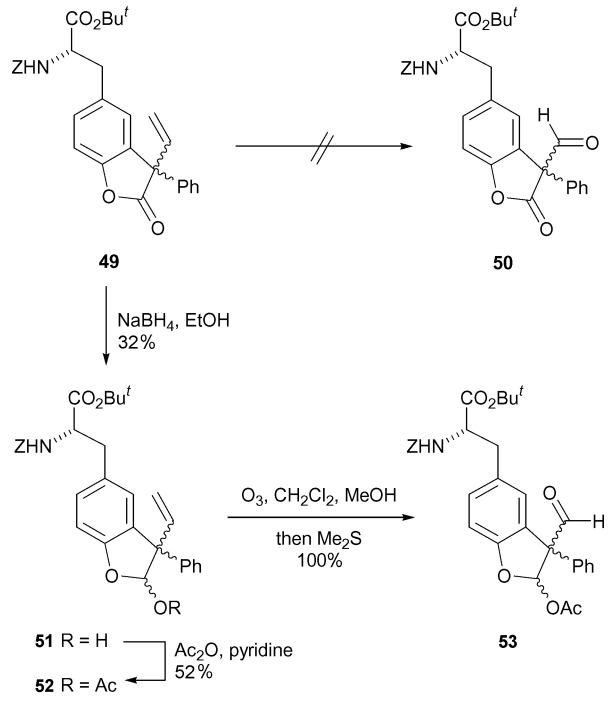
In view of the poor yields in the above Claisen rearrangement-based approach to benzofuranones, an alternative strategy based on the intramolecular (and asymmetric) Heck reaction was adopted.[68,69] Related uses of the intramolecular reaction in the synthesis of diazonamide A fragments have been reported by both Wipf and Pattenden and co-workers.[6,8] The substrate for the model intramolecular Heck reaction was the iodotyrosine derivative **48**. Although the related iodotyrosine **23** had been successfully prepared by iodination of a tyrosine derivative (Scheme 5), in this case it proved easier to start from commercially available 3-iodotyrosine itself. Thus 3-iodotyrosine **41** was *N*-protected as its benzyl carbamate **42**, although this process was always complicated by over-reaction at the phenolic oxygen, and the resulting di-benzyloxycarbonyl derivative had to be removed after the next step. Esterification was achieved using phase-transfer catalyzed alkylation with *tert*-butyl bromide[58] to give the iodotyrosine derivative **43**. The alkene required for the Heck reaction was incorporated from 2-phenylbutenoic acid **47**, itself prepared by an adaptation of a literature method for the analogous heptenoic acid derivative.[70] Ethyl tetrolate **44** underwent Pd-catalyzed hydrostannylation in high yield to give ethyl 2-tri-*n*-butylstannnylbut-2-enoate **45**, presumed at this stage to result from *trans*-addition. The reaction was not regioselective and the major (*ca.* 3 : 1) vinylstannane **45** was accompanied by its regioisomer, ethyl 3-tri-*n*-butylstannnylbut-2-enoate, inseparable at this stage, but readily removed later. Stille reaction of the vinylstannane(s) with iodobenzene gave ethyl 2-phenylbutenoate **46** (now a 7 : 1 mixture with its regioisomer ethyl 3-phenylbutenoate), hydrolyzed to the corresponding acid **47** (Scheme 8). The acid **47** was readily purified by crystallization and by comparison of melting points with literature data, the



Scheme 8 BTEAC = benzyltriethylammonium chloride; DMA = dimethylacetamide; $Pd_2(dba)_3{\cdot}CHCl_3$ = tris(dibenzylideneacetone)-dipalladium(0) chloroform adduct.

(*E*)-geometry of the alkene was confirmed. Coupling of the phenol **43** with the acid **47** using standard carbodiimide methodology gave the substrate **48** for the intramolecular Heck reaction in good yield (Scheme 8). Our first attempt at the intramolecular Heck used literature conditions [$Pd(OAc)_2$, PPh_3, Ag_2CO_3, THF],[71] but these proved unsuccessful, and we eventually settled on the conditions employed by Wipf in his diazonamide A work,[6] namely $Pd_2(dba)_3{\cdot}CHCl_3$ as catalyst, (*S*)-BINAP as the phosphine, in the presence of silver phosphate in dimethylacetamide (DMA). This gave the desired product **49** in 63% yield as a 3 : 2 mixture of diastereomers (Scheme 8). Hence the intramolecular reaction has given the desired benzofuranone, with the C-10 (diazonamide numbering) quaternary centre installed, albeit as a mixture of stereoisomers; the stereochemistry of the major diastereomer remains unknown. A number of attempts were made to improve the stereochemical outcome of the Heck reaction employing other chiral phosphines (Tol-BINAP, DIOP, *etc.*) but with little improvement in either yield or selectivity. Similar poor levels of stereoselectivity were also observed by Wipf in his work.[6]

With the 3,3-disubstituted benzofuranone **49** in hand, it remained only to cleave the vinyl group oxidatively to give the aldehyde **50** that could be elaborated using diazocarbonyl chemistry (*cf.* Scheme 3) into the required oxazole. This transformation proved surprisingly difficult, and could not be achieved directly using a wide range of conditions (ozone, OsO_4–$NaIO_4$, $RuCl_3$–$NaIO_4$, $KMnO_4$). Given that a related 2,3-dihydrobenzofuran is reported to undergo clean oxidative cleavage,[8] we speculated that the lactone **49** was somehow too strained, and therefore it was reduced to the corresponding lactol **51** using sodium borohydride in poor yield (Scheme 9). Protection of the lactol as its acetate **52** was followed by smooth ozonolysis of the alkene to give aldehyde **53** in essentially quantitative yield, as a complex mixture of isomers that could not be completely characterized. Although it was satisfying that the desired oxidative cleavage had finally been achieved in the lactol derivative **52**, the lack of reactivity of the corresponding lactone **49** remains a mystery.



Scheme 9

Finally an intramolecular Heck reaction was attempted with a substrate bearing an additional nitro-group in order to access a 3,3-disubstituted benzofuranone **58** that should be readily converted into the oxindole of the natural product upon reduction of the nitro group (*cf.* Scheme 6). The 2-arylbutenoic acid **56** was easily obtained by condensation of the anion of methyl (2-nitro)phenylacetate[72] **54** with acetaldehyde to give ester **55**, followed by hydrolysis. X-Ray crystallography confirmed the (*E*)-geometry of the alkene (Fig. 2). The acid **56** was coupled to iodotyrosine **43** in good yield to give the desired substrate **57** (Scheme 10). However, compound **57** failed to undergo intramolecular Heck reaction under a variety of conditions, the presence of the nitro-group apparently having a major adverse effect on this reaction.

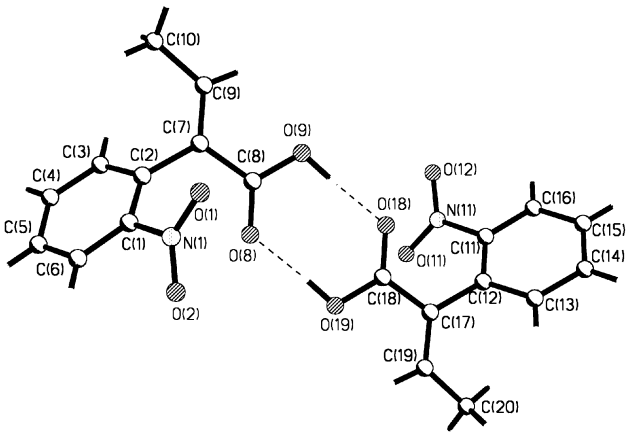
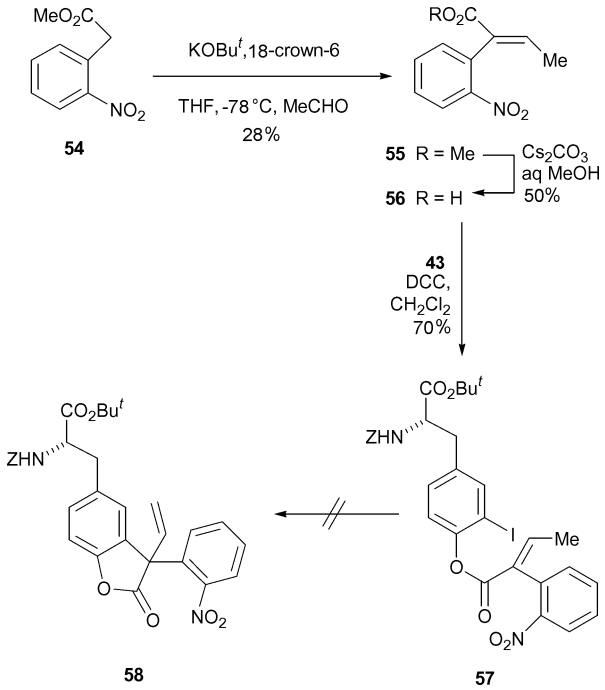


Fig. 2 X-Ray crystal structure of (*E*)-2-(2-nitrophenyl)but-2-enoic acid **56**.§



Scheme 10

Conclusions

This paper has described a number of routes to potentially useful intermediates for the synthesis of the tyrosine-derived fragment

§ **Crystal data**: $C_{10}H_9NO_4$; $M = 207.18$; $a = 10.244(2)$ Å; $b = 13.920(3)$ Å; $c = 13.155(3)$ Å; $\alpha = 90°$; $\beta = 92.4243(17)°$; $\gamma = 90°$; temp. = 93(2) K; $P2(1)/n$; $Z = 8$; $\mu = 0.115$ mm^{-1}; reflections collected = 11668; independent reflections 3344 [R(int) = 0.0314]; Final R indices [$I > 2\sigma(I)$] $R1 = 0.0367$, w$R2 = 0.0886$; R indices (all data) $R1 = 0.0471$, w$R2 = 0.0937$. CCDC reference numbers 279634. See http://dx.doi.org/10.1039/b510653b for crystallographic data in CIF or other electronic format.

of the marine natural product diazonamide A. Although a number of problems remain, in particular, unsatisfactory yields in key steps, and lack of stereochemical control leading to mixtures of diastereoisomers, that must be addressed before a synthesis can be completed, the above routes have successfully delivered appropriately functionalized benzofuranones that, with subsequent improvement, might be incorporated into a total synthesis of diazonamide A by linking with the successful diazocarbonyl-based approach to the model 4-aryltryptamine.

Experimental

Full experimental details are given in the Electronic Supplementary Information.‡

Acknowledgements

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