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Formal Total Synthesis of Diazonamide A by Indole Oxidative Rearrangement

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Abstract: A short formal total synthesis of the marine natural product diazonamide A is described. The route is based on indole oxidative rearrangement, and a number of options were investigated involving migration of tyrosine or oxazole fragments upon oxidation of open chain or macrocyclic precursors. The final route proceeds from 7-bromoindole by sequential palladium-catalysed couplings of an oxazole fragment at C-2, followed by a tyrosine fragment at C-3. With the key 2,3-disubstituted indole readily in hand, formation of a macrocyclic lactam set the stage for the crucial oxidative rearrangement to a 3,3-disubstituted oxindole. Notwithstanding the concomitant formation of the unwanted indoxyl isomer, the synthesis successfully delivered, after deprotection, the key oxindole intermediate, thereby completing a formal total synthesis of diazonamide A.

Introduction

In 1991, Fenical, Clardy and co-workers reported the composition and stereochemistry of two unusual marine toxins possessing potent cytotoxic activities. These toxins were extracted from tissues of the sea squirt *Diazona angulata* (originally misidentified as *Diazona chinensis*), collected from caves along the northwest coast of Siquijor Island (Philippines).[1] The structure of the major isolate, diazonamide B (**4**) was determined by X-ray crystallographic studies of a derivative, whilst the minor metabolite, diazonamide A was subsequently assigned structure **1** by analogy (Figure 1). The scarcity of diazonamide A, its biological activity (see below), and its challenging structure soon attracted the attention of the synthetic chemistry community. Much to our chagrin, since we, like many others,[2] had entered the race to synthesize the core dihydrobenzofuran structure,[3] this structure **1** proved to be incorrect some 10 years later with the completion of its synthesis.[4] Not only did Harran complete the synthesis of the originally assigned diazonamide A **1**, he also proposed an alternative structure **2**, that was more in accord with a possible biosynthesis from four amino acids, tyrosine, valine and two tryptophans. This structure was proven to be correct with Nicolaou's first synthesis of the natural product.[5]

It was observed that diazonamide A blocks cell division during mitosis with an efficacy comparable to current anti-tubulin drugs, such as vinblastine, vincristine and paclitaxel.[6] Moreover, treatment with diazonamide A showed no evidence of the side effects observed with taxanes and vinca alkaloids at doses sufficient to regress human tumor xenografts in mice.[7] However, it has been shown that the compound does not act by binding directly to tubulin like other antimitotic agents.[6] Further studies identified a unique mechanism of action for diazonamide A,[8] with its antimitotic effects mediated through ornithine δ-aminotransferase (OAT), previously known as a mitochondrial enzyme that regulates flux through the urea cycle and indirectly promotes L-proline biosynthesis.[9] Although OAT may not be essential for normal development, it appears to be critical for cell division in human tumor cells that are sensitive to diazonamide A. Recently, a number of diazonamide analogues have been patented as antimitotic agents.[10]

Notwithstanding the confusion over the true structure of diazonamide A, its unique and complex structure has continued to serve as a challenge to organic chemists,[2] fuelled by the interest in its biological properties, and by the isolation of three new diazonamide compounds (C (**3**), D (**5**), E (**6**)) (Figure 1).[11] Nicolaou's first synthesis was quickly followed by a second synthesis from the same group,[12] and, in the same year, a synthesis inspired by the possible biogenesis from the Harran group.[13] The most recent total synthesis was achieved by MacMillan and co-workers in 2011,[14] whilst both the Magnus and Sammakia groups have completed a formal synthesis,[15] by converging on the key intermediate **7** (or its protected version) in Nicolaou's first synthesis. In addition to the total and formal syntheses, a wide range of different approaches to this fascinating molecule has been published.[2,16]

The key to any synthesis of diazonamide A **2** is the construction of the all-carbon quaternary centre at C-10, and the successful approaches differ in their tactics towards this crucial element. Essentially, the six syntheses (four total, two formal) divide into two groups—those that form a bond from C-10 to

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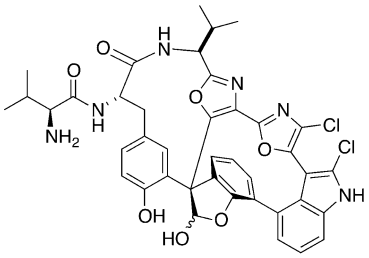
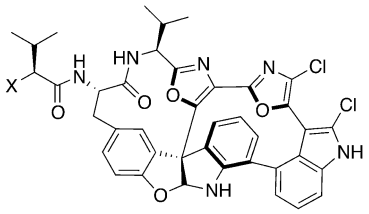
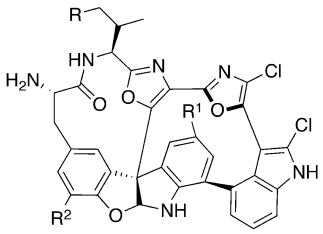


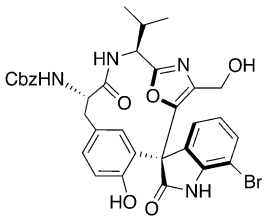
1 diazonamide A
(original structure)



2 diazonamide A : X = OH
3 diazonamide C: X = NH_2



4 diazonamide B: R = R^1 = H, R^2 = Br
5 diazonamide D: R = Me, R^1 = Cl, R^2 = H
6 diazonamide E: R = Me, R^1 = R^2 = H



7 Nicolaou intermediate

Figure 1. Structures of the diazonamides.

the tyrosine residue to generate the quaternary centre, or those that form the oxazole (or oxazole precursor) bond to C-10 (Figure 2). Thus both Nicolaou and Magnus generate an electrophile at C-3 (indole numbering) of an oxindole intermediate, employing the nucleophilicity of the tyrosine benzene ring to form the key bond,[5,15a] whereas Harran exploits the natural nucleophilicity of indoles at C-3 to react with an electrophile generated by a biomimetic oxidation of the tyrosine moiety.[13] On the other hand, in Nicolaou's second synthesis,[12] and in MacMillan's route,[14] the quaternary centre is assembled from an oxindole or indole that already bears the tyrosine group by addition of an electrophilic residue (formaldehyde or propargyl aldehyde, respectively) that can subsequently be converted into the desired oxazole ring. Sammakia's route differs in that the complete oxazole unit is added to an oxindole anion by an intramolecular S_NAr reaction on a bromooxazole (Figure 2 A).[15b] We now report the details of a formal

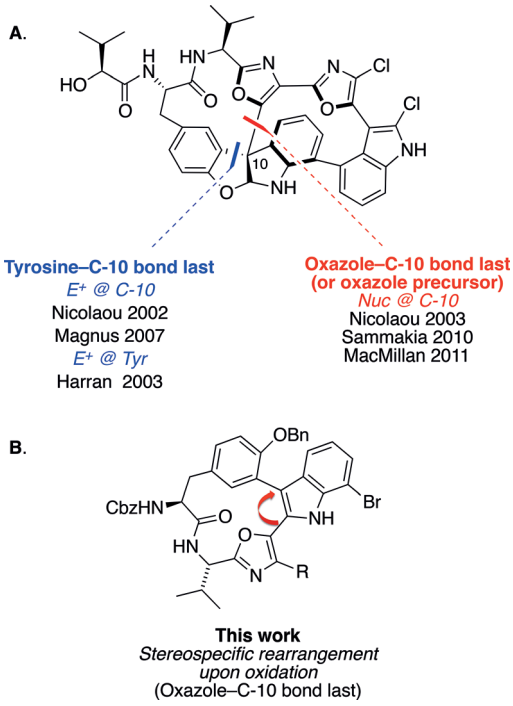


Figure 2. A) Summary of key disconnections at the C-10 quaternary centre in the four total and two formal syntheses of diazonamide A. B) Proposed route to key intermediate **7** by oxidative rearrangement.

synthesis of diazonamide A **2** by a different strategy based on the oxidative rearrangement of a 2,3-disubstituted indole during which the oxazole migrates stereospecifically to generate the new C-10 centre (Figure 2 B).[17]

Results and Discussion

As noted above, a key strategic intermediate towards diazonamide A is a suitable 3,3-disubstituted oxindole, and hence we sought to explore the oxidative rearrangement of indoles as a potential route. The oxidative rearrangement of 2,3-disubstituted indoles to 3,3-disubstituted oxindoles upon treatment with electrophiles such as halogenating agents or oxidants has been known for about 50 years. The reaction was originally investigated in simple indoles,[18] but it has also been applied to indole alkaloids,[19] and has been used in a biosynthesis-inspired formation of the *Strychnos* alkaloid skeleton by rearrangement of the *Corynanthe* system.[20] Our own work started with an extension of the seminal work of Walser et al.[18d] into more complex indole systems. Thus the 2,3-disubstituted indole **8**, assembled by a selective palladium-catalysed coupling of a 7-bromo-3-iodoindole with a tyrosine-derived boronate, was treated under Walser's conditions (*tert*-butyl hypochlorite, followed by acid), and gave the desired 3,3-disubstituted oxindole **9** by rearrangement of the chloroindolenine intermediate, in good yield, but as a 1:1 mixture of diastereoisomers (Scheme 1).[21] In an attempt to introduce some stereoselectivity into the rearrangement, we employed the (*S*)-methoxymethylpyrrolidine-containing indole **10**, and were pleased to observe significant asymmetric induction in the for-

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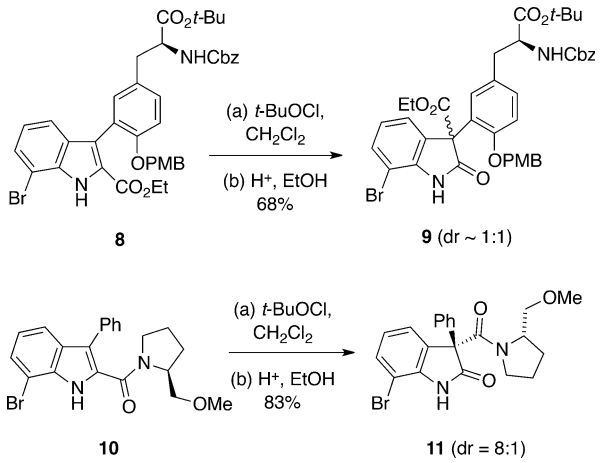


Scheme 1. Oxidative rearrangements of 2,3-disubstituted indoles to 3,3-disubstituted oxindoles.[21,22]

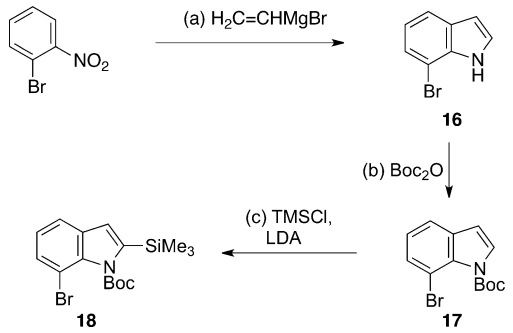
mation of the oxindole **11**, which could be obtained optically pure after a single recrystallization (Scheme 1).[22] This pleasure was, however, short lived when it proved impossible to elaborate the 3-carboxamido substituent into the required oxazole ring, and therefore we turned our attention to 2,3-disubstituted indoles that already contained a preformed oxazole.

Hence we focused on indoles that contained both tyrosine- and valine-derived oxazole fragments, reasoning that these should be easily available by successive palladium-catalysed sp^2–sp^2 coupling reactions. On this basis, we identified four possible precursors to the pivotal intermediate **7** in the form of the indoles **12**–**15**. These were classified according to whether the tyrosine or oxazole group migrates from C-2 to C-3 in the rearrangement step, and whether the rearrangement occurs in the non-cyclized form or in a preformed macrocycle (Routes A–D, Scheme 2), and we embarked on an investigation of all four possibilities.

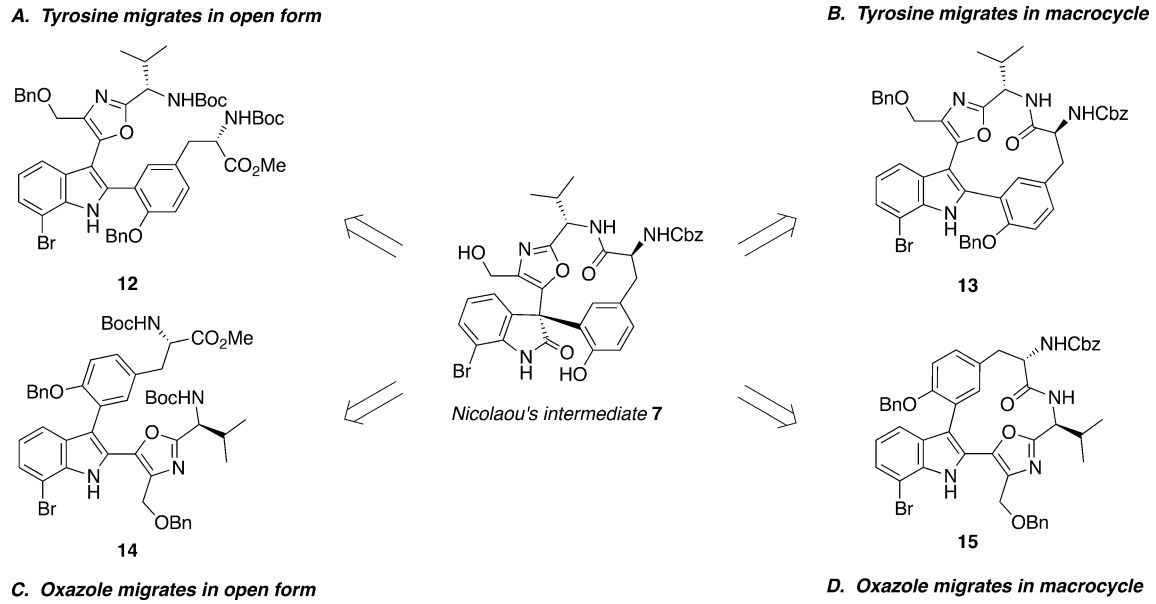
Preparation of indole, oxazole and tyrosine building blocks

All of our putative diazonamide A precursors **12**–**15** should be accessible from relatively simple indole, oxazole and tyrosine fragments. After a considerable number of preliminary experiments towards indole **12** entailing C-2 iodination, and subsequent Pd-catalysed coupling reactions, we reverted to a strategy adopted by Snieckus and co-workers involving *ipso*-borodesilylation with boron trichloride, followed by Suzuki reaction of the chloroborane intermediate carried out in situ.[23] Thus our target building block became the *N*-Boc-protected 7-bromo-2-trimethylsilylindole (**18**). This was readily prepared by a Bartoli synthesis of 7-bromoindole (**16**),[24] followed by introduction of the Boc-group, and lithiation/silylation of the resulting N-protected indole **17** to give the desired building block **18** (Scheme 3).

The oxazole building blocks were the complementary boronic acid **24** and iodide **25** (Scheme 4). These were obtained from the known methyl oxazole-4-carboxylate **21**, prepared as



Scheme 3. Synthesis of indole building block **18**. Reagents and conditions: a) vinylmagnesium bromide (3.0 equiv), THF, −40 °C, 1 h, 55%; b) Et_3N (1.5 equiv), DMAP (0.3 equiv), Boc_2O (2.3 equiv), CH_2Cl_2, 0 °C, 40 min, 90%; c) TMSCl (1.5 equiv), THF, 0 °C, then LDA (1.5 equiv), 0 °C, 30 min, 100%.



Scheme 2. Possible precursors to a key diazonamide A intermediate **7** by oxidative rearrangement of 2,3-disubstituted indoles. Although specific protecting groups are shown in compounds **12**–**15**, the optimum choice of such groups was unknown at the outset.

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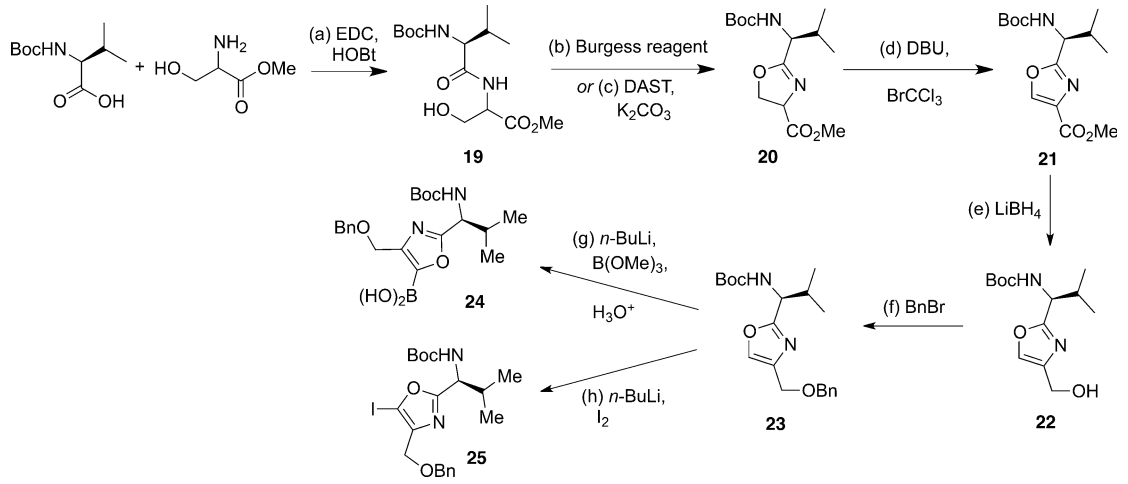


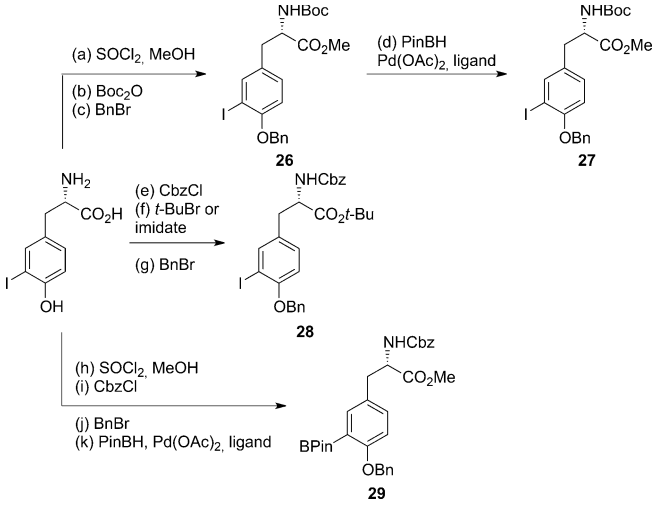
Scheme 4. Synthesis of oxazole building blocks **24** and **25**. Reagents and conditions: a) EDC (1.05 equiv), HOBt (1.05 equiv), THF, 25 °C, 5 min, then Et_3N (2.0 equiv), 25 °C, 15 h, 96%; b) Burgess reagent (1.5 equiv), THF, 65 °C, 4 h, 61%; *or* c) DAST (1.1 equiv), CH_2Cl_2, −78 °C, 1.5 h, then K_2CO_3 (1.5 equiv), −78 °C→25 °C, 1.5 h, 100%; d) $BrCCl_3$ (1.1 equiv), DBU (1.1 equiv), CH_2Cl_2, 0 °C→25 °C, 18 h, 91%; e) $LiBH_4$ (2.0 M in THF, 3.0 equiv), EtOH (5.0 equiv), THF, 0 °C→25 °C, 3 h, 95%; f) NaHMDS (1.0 M in THF, 2.1 equiv), THF, −78 °C, 10 min, then *n*Bu_4NI (0.1 equiv), BnBr (0.8 equiv), −78 °C→25 °C, 24 h, 61%; g) *n*BuLi (2.5 equiv), THF, −78 °C, 1 h, then $B(OMe)_3$ (7.0 equiv), −78 °C, 1 h, then 25 °C, 2 h, HCl, 80% crude; h) *n*BuLi (2.5 equiv), THF, −78 °C, 1 h, then I_2 (2.0 equiv), −78 °C, 1 h, 74%.

previously described.[5] Lithium borohydride reduction of ester **21** was followed by benzylation of the primary alcohol **22** to give oxazole **23**. Subsequent lithiation at the 5-position was followed by quenching with trimethyl borate to give, after acid hydrolysis, the boronic acid **24**, or with iodine to give iodide **25** (Scheme 4).

Finally a number of tyrosine derivatives containing different protecting groups were prepared as coupling partners. These were obtained from iodotyrosine using standard methods as outlined in Scheme 5. For the formation of compound **29**, some problems were encountered with the palladium-catalysed borylation reaction, since the boronate was difficult to purify by flash chromatography over silica gel due its tendency to remain adsorbed on the column. Indeed, only a small amount of compound **29** could be isolated in this manner, and elution with more polar solvents resulted in contamination with polar byproducts. To address this problem, the purification process was performed using freshly prepared silica gel impregnated with boric acid, which is reported to help in the purification of pinacolboronates and boronic acids by column chromatography.[25]

Oxidative rearrangement model studies

A crucial question for our oxidative strategy as set out in Scheme 2 is the relative propensity of tyrosine-derived fragments versus oxazole moieties to migrate from C-2 to C-3 in the key rearrangement step. To this end we investigated two simpler model systems **32** and **35** as substitutes for the real systems **12** and **14**, wherein a phenyl group replaces the tyrosine fragment, not only as model substrates, but also as a chance to develop and optimize the critical sp^2–sp^2 coupling methodology. Both compounds **32** and **35** were synthesized by the initial coupling of either iodobenzene or iodooxazole moiety **25** with the indole derivative **18**. The coupling steps were conducted using the aforementioned *ipso*-borodesilylation with boron trichloride followed by Suzuki reaction carried out in situ.[23] The optimized Suzuki conditions employed



Scheme 5. Synthesis of tyrosine building blocks **27**–**29** [PinB = 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]: Reagents and conditions: a) $SOCl_2$ (1.1 equiv), MeOH, 25 °C, 20 h, 100%; b) Boc_2O (1.2 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 25 °C, 3.5 h, 72%; c) BnBr (1.3 equiv), K_2CO_3 (1.4 equiv), *n*Bu_4NI (0.15 equiv), acetone, 56 °C, 16 h, 89%; d) pinacolborane (3.0 equiv), $Pd(OAc)_2$ (0.1 equiv), *i*Pr_2NEt (5.0 equiv), 2-(biphenyl)dicyclohexylphosphine (0.4 equiv), 1,4-dioxane, 85 °C, 3 h, 73%; e) CbzCl (1.0 equiv), Na_2CO_3 (3.0 equiv), Et_2O/H_2O (1:1), 25 °C, 16 h, 100%; f) BTEAC (2.4 equiv), *tert*-BuBr (46 equiv), K_2CO_3 (25 equiv), H_2O, THF, 60 °C, 48 h, 57%; or *tert*-butyl 2,2,2-trichloroacetimidate (3.5 equiv), CH_2Cl_2/THF (4:1), 25 °C, 16 h, 100%; g) BnBr (1.3 equiv), K_2CO_3 (1.4 equiv), *n*Bu_4NI (0.15 equiv), acetone, 56 °C, 16 h, 88%; h) $SOCl_2$ (1.1 equiv), MeOH, 0 °C to reflux, 100%; i) CbzCl (1.1 equiv), Na_2CO_3 (1.0 equiv), acetone/H_2O (1:1), 25 °C, 2 h, 100%; j) BnBr (1.2 equiv), K_2CO_3 (2.4 equiv), *n*Bu_4NI (0.10 equiv), acetone, reflux, 18 h, 97%; k) pinacolborane (3 equiv), Et_3N (4 equiv), $Pd(OAc)_2$ (0.05 equiv), 2-(biphenyl)dicyclohexylphosphine (0.4 equiv), 1,4-dioxane, 50 °C, 1 h, 84% (Purification by flash column chromatography over boric acid-impregnated silica gel).

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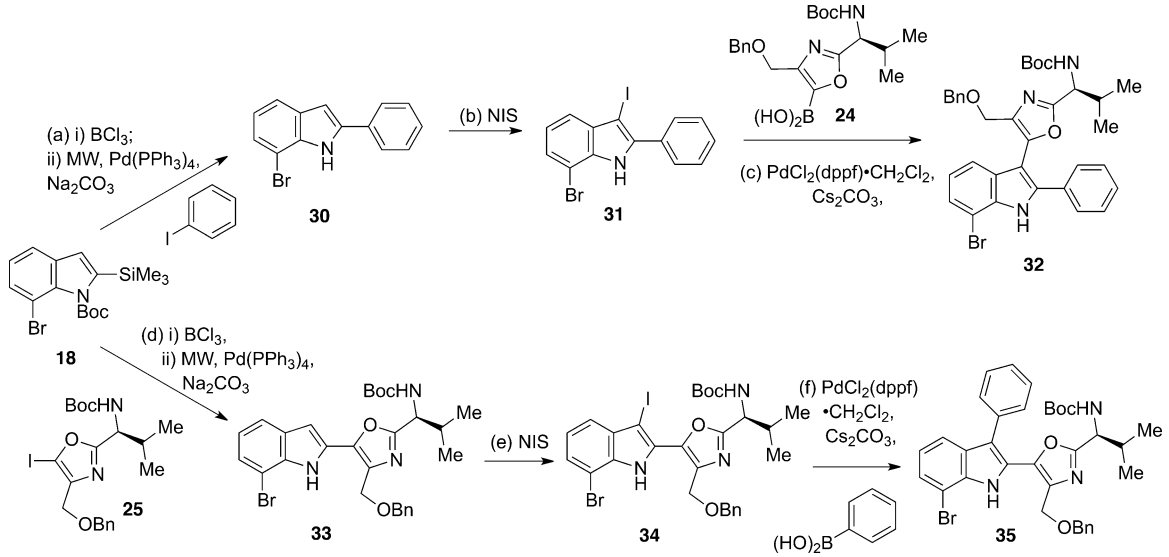
sodium carbonate as base in 1,2-dimethoxyethane (DME) with the reaction carried out under microwave irradiation. The Boc protecting group on the indole was removed during the coupling, probably due to the formation of hydrochloric acid in the reaction mixture at the time of the addition of boron trichloride, but this was of little consequence, since it had to be cleaved at some stage. The coupled products were then iodinated at C-3 in very good yield using *N*-iodosuccinimide. Further functionalization at C-3 with either oxazole boronic acid **24** or phenylboronic acid using similar Suzuki conditions in the microwave afforded compounds **32** in 37% yield and **35** in 65% yield (Scheme 6). To form compound **35**, it was necessary to decrease the amount of boronic acid from 1.5 to 0.9 equivalents, lower the temperature from 105 °C to 70 °C and reduce the reaction time from 45 min to 10 min. This avoided the formation of the undesired double coupling of benzeneboronic acid with both the 3-iodo and the 7-bromo substituents.

With both model precursors in hand, we were able to investigate the pivotal oxidative rearrangement steps. However, it quickly became clear that whilst acyl groups migrated from C-2 to C-3 upon formation of a 3-chloroindolenine intermediate under Walser's conditions (Scheme 1), aromatic groups did not. However, application of a Lewis acid mediated rearrangement of 3-hydroxyindolenines reported by Movassaghi and co-workers,[26] looked more promising. Accordingly, both precursors were treated with dimethyldioxirane (DMDO) generated in situ from acetone and Oxone® (Scheme 7). This gave hydroxyindolenines **36** and **38** in good yields, which without separation of the diastereoisomers, were subjected to the rearrangement conditions. When treated with scandium triflate in toluene under reflux, precursor **36** was converted into the desired oxindole **37**, in good yield as a mixture of diastereoisomers, after reprotection of the amino group, which underwent cleavage of the Boc-group under the reaction conditions, with di-*tert*-butyl dicarbonate. However, when precursor **38** was rearranged, it only resulted in the formation of the undesired indoxyl product **39**, again after reprotection of the amino group (Scheme 7). The structures were readily differentiated from their ^{13}C NMR spectra: the oxindole C-2 amide signal appears in the region of 180 ppm, whilst the indoxyl ketonic carbonyl signal C-3 appears at about 200 ppm. Additionally, the oxindole quaternary carbon C-3 is observed at about 55 ppm, whilst the indoxyl quaternary carbon C-2 comes around 70 ppm.

The competing formation of indoxyls upon rearrangement of 3-hydroxyindolenines had been previously noted by Movassaghi and co-workers,[26] although in their case, the indoxyls could be isomerized to oxindoles by further heating with scandium triflate. Unfortunately subjecting indoxyl **39** to these conditions resulted in its degradation. These preliminary model studies led us to the initial conclusion that Routes A and B (Scheme 2) in which the tyrosine fragment migrates upon oxidative activation were more likely to result in the formation of the desired oxindole in the real system and avoid the formation of the undesired indoxyl.

Route A: rearrangement of the tyrosine fragment in non-cyclized precursor

The precursor for our initial approach was the 2,3-disubstituted indole **12**. After a number of preliminary experiments, it was established that the tyrosine phenol had to be protected in order to carry out the subsequent macrocyclization step. Therefore a benzyl group was preferred, since it would be re-



Scheme 6. Synthesis of model systems **32** and **35** for oxidative rearrangement. Reagents and conditions: a) **18** (1.2 equiv), BCl_3 (1.35 equiv), CH_2Cl_2, 35 °C, 2.5 h, then evaporation of solvent and addition of iodobenzene (1.0 equiv), $[Pd(PPh_3)_4]$ (0.15 equiv), aq. Na_2CO_3 (5.0 equiv), DME, MW (300 W), 100 °C, 20 min, 51%; b) NIS (1.2 equiv), DMF, 25 °C, 2 h, 84%; c) **24** (1.5 equiv), $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (0.2 equiv), Cs_2CO_3 (5.0 equiv), 1,4-dioxane/H_2O (8:2), MW (300 W), 105 °C, 45 min, 37%; d) **18** (1.25 equiv), BCl_3 (3.75 equiv), CH_2Cl_2, 35 °C, 3 h, then evaporation of solvent and addition of **25** (1.0 equiv), $[Pd(PPh_3)_4]$ (0.10 equiv), aq. Na_2CO_3 (2 M, 4.00 equiv), DME, MW (300 W), 100 °C, 30 min, 75%; e) NIS (1.2 equiv then extra 0.5 equiv), DMF, 0 °C→rt, 16 h, 95%; f) benzeneboronic acid (0.9 equiv), $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (0.2 equiv), Cs_2CO_3 (5.0 equiv), 1,4-dioxane/H_2O (8:2), MW (300 W), 70 °C, 10 min, 65%.

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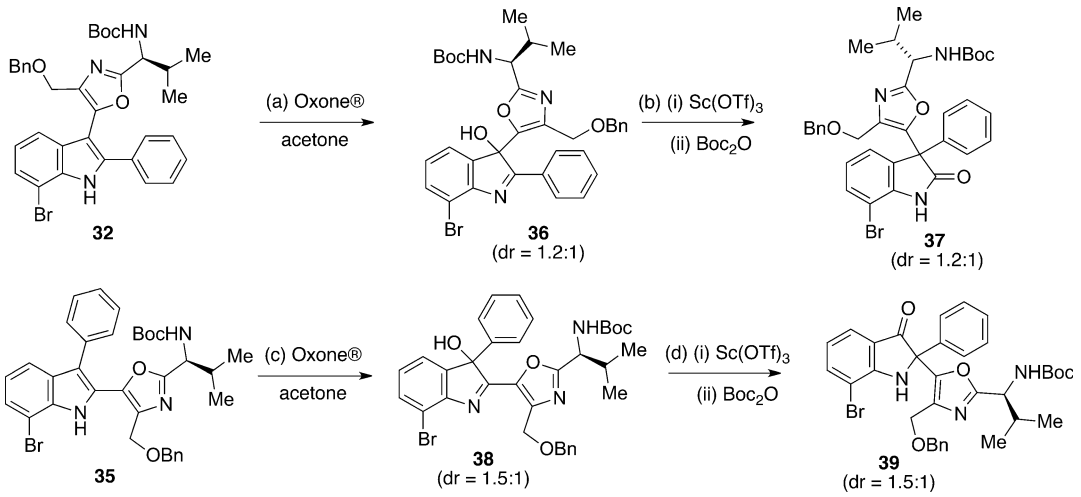

Scheme 7. Application of the oxidative rearrangement on model systems. Reagents and conditions: a) Oxone® (3.0 equiv), sat. aq. $NaHCO_3$, acetone, 0 °C, 1 h, 68%; b) i) $Sc(OTf)_3$ (1.0 equiv), toluene, 110 °C, 6 h, ii) Boc_2O (1.2 equiv), $NaHCO_3$ (5.0 equiv) THF, rt, 16 h, 58% (2 steps); c) Oxone® (5.0 equiv), sat. aq. $NaHCO_3$, acetone, 25 °C, 1 h, 70%; d) i) $Sc(OTf)_3$ (1.0 equiv), toluene, 110 °C, 6 h, ii) Boc_2O (1.2 equiv), $NaHCO_3$ (5.0 equiv) THF, rt, 16 h, 58% (2 steps).

sistant to a range of conditions and could be removed at the same time as the benzyl group on the primary alcohol on the oxazole ring at the end of the synthesis. A Boc group was chosen for protection of the tyrosine amino group to complement that present on the oxazole moiety, which had already been employed in the model rearrangement studies (Scheme 7). The 2,3-disubstituted indole **12** was synthesized by coupling the indole derivative **18** with iodotyrosine derivative **26** using the presumed dichloroborane indole generated in situ, and further palladium-catalysed cross-coupling under microwave irradiation. After iodination at C-3, the indole **41** was coupled with oxazole boronic acid **24** to give the key precursor indole **12** in 47% yield. This was treated with DMDO to give 3-hydroxyindolenine **42** in 80% yield as a mixture of diastereoisomers (Scheme 8). Unfortunately, when treated with scandium triflate in toluene under reflux, only indoxyl **43** was formed in poor yield. Thus, in comparison with the results obtained from the model compound **32** (Scheme 7), it appears that the introduction of the tyrosine side chain, as opposed to a simple phenyl substituent, surprisingly prevents the rearrangement to the desired oxindole.

Route B: rearrangement of the tyrosine fragment in macrocyclic precursor

Undeterred by the above set back, we next investigated the macrocyclic precursor **13**. To this end, indole **18** was coupled with tyrosine fragment **28** as described above, again with concomitant removal of the Boc-protecting group to give indole **44**. Iodination and coupling to oxazole boronic acid **24** gave the macrocycle precursor **46**. Next, treatment with trifluoroacetic acid in dichloromethane afforded the deprotected intermediate, which underwent macrocyclization using *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU) and Hünig's base in dichloromethane at high dilution to give the desired product **13** in 75% yield. In addition, the alcohol-deprotected product **47** was formed in 18% yield. Monitoring of these last two steps by mass spectrometry suggests that the partial loss of the benzyl-protecting group on the primary alcohol occurs during the macrocyclization step. A similar phenomenon was observed by Nicolaou in his first total synthesis, with partial loss of the methoxymethyl ether (MOM)-protecting group on the phenol during the macrocyclization.[5] Oxidation of macrocycle **13** with DMDO proved to be very slow and only traces of product were generated. In contrast, the free alcohol **47** was readily oxidized under the same conditions, although the resulting 3-hydroxyindolenine failed to undergo the desired rearrangement. Nevertheless, upon changing the oxidant to the Davis oxaziridine, the desired 3-hydroxyindolenine **48** was obtained in 63% yield, although the reaction mixture did require heating in 1,2-dichloroethane under reflux. Interestingly, 3-hydroxyindolenine **48** was obtained as a single diastereoisomer, although we were unable to determine the stereochemistry at the indole C-3 position. On treatment with scandium triflate, 3-hydroxyindolenine **48** underwent rearrangement to give, after reaction with benzyl chloroformate to reprotect the tyrosine-derived amino group, only the undesired indoxyl **49** in 56% yield (Scheme 9), as a single diastereoisomer of unknown configuration at the indoxyl C-2 position. Further treatment of indoxyl **49** with scandium triflate in toluene did not result in the rearrangement to the desired oxindole, and attempts to effect the rearrangement under alternative conditions, such as copper triflate or formic acid in toluene[27] or in different solvents, were also ineffective. The failure of the oxidative rearrangement to deliver any of the required oxindole was a puzzle. It is possible that the stereoselective oxidation with the Davis oxaziridine gives a 3-hydroxyindolenine that cannot rearrange by migration of the tyrosine fragment due to the constraints of the macrocycle.

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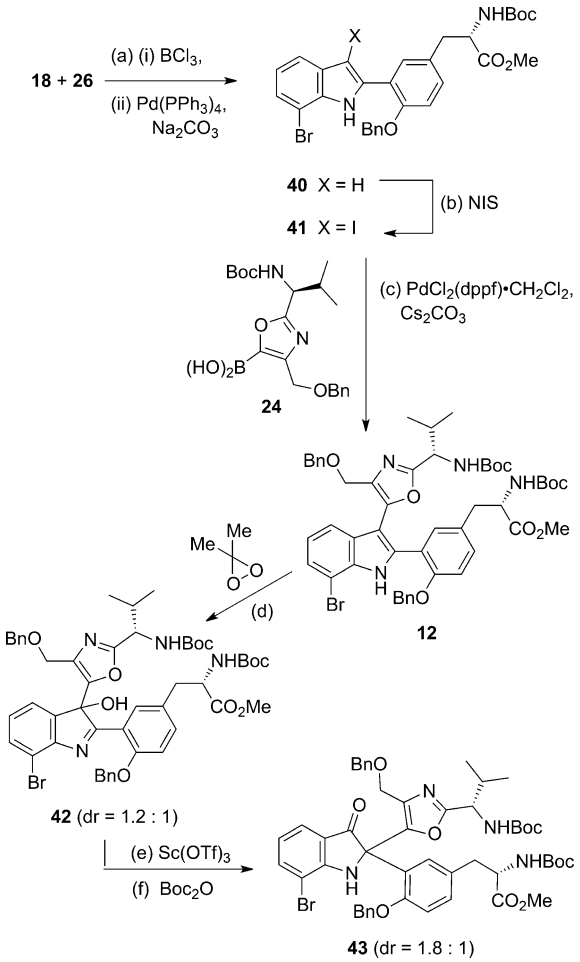

Scheme 8. Synthesis and oxidative rearrangement of 2,3-disubstituted indole **12**. Reagents and conditions: a) **18** (1.2 equiv), BCl_3 (3.5 equiv), CH_2Cl_2, 35 °C, 2.5 h, then evaporation of solvent and addition of **27** (1.0 equiv), $[Pd(PPh_3)_4]$ (0.15 equiv), aq. Na_2CO_3 (5.0 equiv), DME, MW (300 W), 100 °C, 20 min, 45%; b) NIS (1.2 equiv), DMF, 25 °C, 1.5 h, 100%; c) **24** (1.5 equiv), $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (0.2 equiv), Cs_2CO_3 (5.0 equiv), 1,4-dioxane/H_2O (8:2), MW (300 W), 105 °C, 45 min, 47%; d) Oxone® (3.0 equiv), sat. aq. $NaHCO_3$, acetone, 0 °C→25 °C, 1.5 h, then Oxone® (3 equiv), 25 °C, 1 h, 80%; e) $Sc(OTf)_3$ (.01 equiv), anhydrous toluene, 110 °C, 6 h; (f) Boc_2O (3.0 equiv), $NaHCO_3$ (5.0 equiv), THF, 25 °C, 15 h, 19% (2 steps).

Route C: rearrangement of the oxazole fragment in non-cyclized precursor

Therefore despite the inauspicious precedent set by our model studies (Scheme 7), we were compelled to consider Routes C and D in which the oxazole moiety rearranges from C-2 to C-3 in the indole precursors **14** and/or **15** (Scheme 2), as opposed to from C-3 to C-2 as it does to give the indoxyls above. Indeed, in Routes A and B we never observed migration of the tyrosine fragment from C-2 to C-3, in contrast to the facile migration of the phenyl ring in the model studies (Scheme 7). Although we initially concluded that the oxazole ring at C-3, as in model compound **36**, would favour the formation of the oxindole, our investigations with the real substrates in Routes A and B strongly suggested that the tyrosine group was less likely to migrate from C-2 than the oxazole.

The key substrate **14** was obtained from 3-iodoindole **34** and tyrosine-derived boronate **27**, which were successfully coupled under our usual Suzuki conditions. Lowering the temperature from 105 to 85 °C improved the yield from 30 to 47%. Next, the indole **14** was successfully oxidized to 3-hydroxyindolenine **50** in 67% yield using DMDO. Fortunately, under treatment with scandium triflate, hydroxy compound **50** rearranged to the desired oxindole **51** in 10% yield, together with 20% of the undesired indoxyl **43** (Scheme 10), after reprotection of the amino group. This result seems to confirm our hypothesis that the oxazole ring does indeed migrate more easily than the tyrosine, although indoxyl **43**, the same compound as prepared in Route B, was still formed alongside the required oxindole **51**. Further treatment of indoxyl **43** with scandium triflate did not cause its conversion into the desired oxindole **51**. At this stage, rather than attempt to optimize this reaction sequence, we chose to investigate the rearrangement in the macrocyclic system **15**.

Route D: rearrangement of the oxazole fragment in macrocyclic precursor—a formal total synthesis of diazonamide A

Encouraged by the successful formation of oxindole **51** (Scheme 10), we embarked upon the synthesis and oxidative rearrangement of the macrocyclic indole **15** (Scheme 2). With the indole, oxazole and tyrosine building blocks already to hand, the macrocycle **15** was readily accessible. However, the coupling of 3-iodo-2-oxazolylindole **34**, prepared during our initial model studies (Scheme 6), with tyrosine-derived boronate **29** under our standard microwave Suzuki conditions, was highly capricious because the deiodo indole and protodeboronated tyrosine were often obtained, especially at high temperatures. Following considerable investigation into the choice of catalyst, ligand, base and solvent, we were pleased to find that the use of potassium carbonate as the base, a 9:1 mixture of acetonitrile and water as the solvent and the introduction of a slight excess of boronate **29** (1.2 equiv) led to the formation of the desired 2,3-disubstituted indole **52** in 70% yield at 60 °C with thermal heating (Scheme 11). Hydrolysis of the methyl ester, acid cleavage of the *N*-Boc group and HATU-mediated macrolactamization gave the desired macrocyclic indole **15** in good yield. Unlike the isomeric macrocycle **13** (Scheme 9), compound **15** was readily oxidized in good yield with DMDO to give the diastereomeric 3-hydroxyindolenines **53** and **54** in a ratio of 2.5:1. At this stage, we were unable to assign the configuration of the new stereocentre in compounds **53** and **54**, and therefore in common with other syntheses of diazonamide A,[5,12] we were obliged to continue the synthesis with both compounds in parallel. The stereochemistry shown for the 3-hydroxyindolenines **53** and **54** in Scheme 11 was assigned post facto upon completion of the formal synthesis, with isomer **54** having the desired stereochemistry. At this point, we devoted considerable effort to addressing the selectivity of the oxidation procedure to deliver the desired hydroxyindolenine **54**. Armed with the knowledge that we required the minor diastereomer, we attempted to override the apparent substrate control through reagent con-

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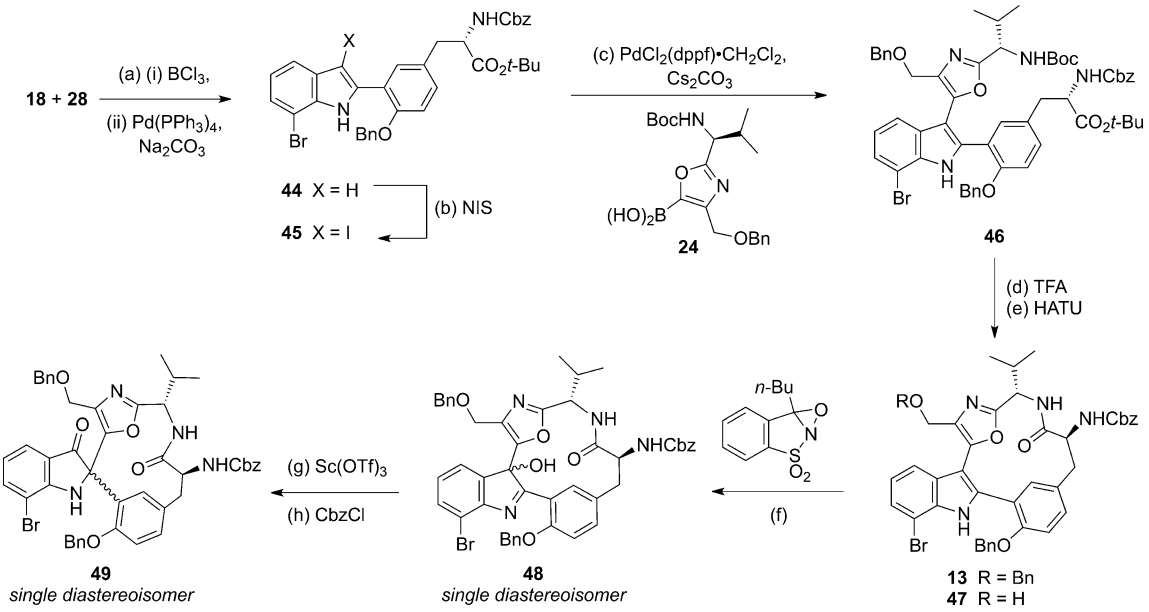
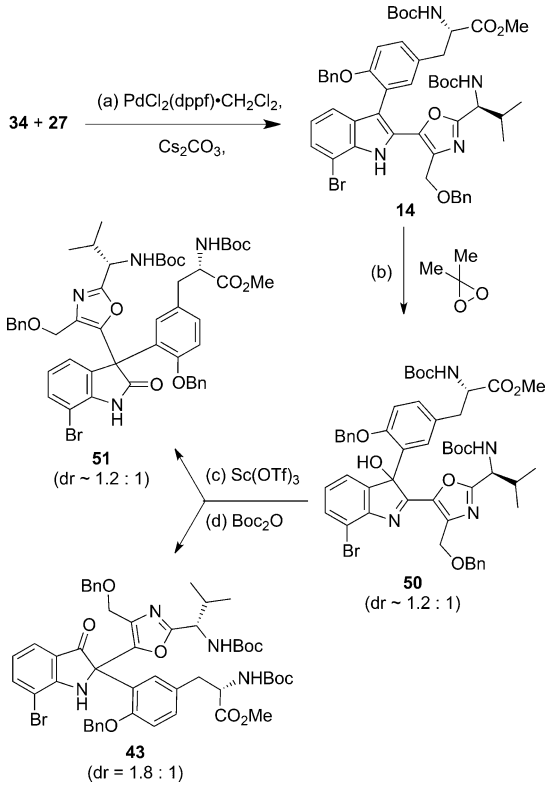
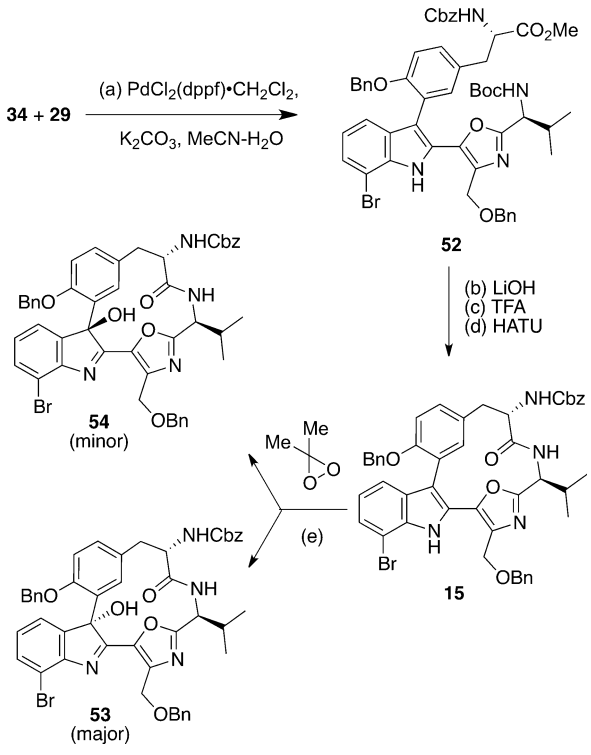


Scheme 9. Synthesis and oxidative rearrangement of macrocyclic indole **13**. Reagents and conditions: a) **18** (1.14 equiv), BCl_3 (3.0 equiv), CH_2Cl_2, 35 °C, 2.5 h, then evaporation of solvent and addition of **28** (1.0 equiv), $[Pd(PPh_3)_4]$ (0.15 equiv), aq. Na_2CO_3 (5.0 equiv), DME, MW (300 W), 100 °C, 20 min, 50%; b) NIS (1.2 equiv), DMF, 25 °C, 1 h, 90%; c) **24** (1.5 equiv), $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (0.2 equiv), Cs_2CO_3 (5.0 equiv), 1,4-dioxane/H_2O (8:2), MW (300 W), 105 °C, 45 min, 50%; d) TFA/CH_2Cl_2 (1:1), 25 °C, 2.5 h, 100% crude; e) HATU (1.3 equiv), *i*Pr_2NEt (6.0 equiv), CH_2Cl_2, 4×10^{-4} M, 25 °C, 15 h, 75% of **13** and 18% of **47**; f) Davis oxaziridine (4.0 equiv), 1,2-dichloroethane, 83 °C, 30 h, 63%; g) $Sc(OTf)_3$ (1.2 equiv), anhydrous toluene, 110 °C, 2 h; h) CbzCl (0.9 equiv), Na_2CO_3 (3.0 equiv), ether/water (1:1), 25 °C, 16 h, 56% for 2 steps.



Scheme 10. Synthesis and oxidative rearrangement of 2,3-disubstituted indole **14**. Reagents and conditions: a) **34**, **27** (1.2 equiv), $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (0.2 equiv), Cs_2CO_3 (5.0 equiv), 1,4-dioxane/H_2O (8:2), MW (300 W), 85 °C, 45 min, 47%; b) Oxone® (3.0 equiv), sat. aq. $NaHCO_3$, acetone, 0 °C 25 °C, 2.5 h, 67%; c) $Sc(OTf)_3$ (1.0 equiv), toluene, 110 °C, 6 h; d) Boc_2O (5.0 equiv), $NaHCO_3$ (5.0 equiv), THF, 25 °C, 15 h, 10% oxindole **51** and 20% indoxyl **43**, both yields over two steps.



Scheme 11. Synthesis and oxidation of macrocyclic indole **15**. Reagents and conditions: a) **34**, **29** (1.2. equiv), $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (0.1 equiv), K_2CO_3 (10.0 equiv), acetonitrile/H_2O (9:1), 60 °C, 15 h, 70%; b) LiOH (20 equiv), THF/MeOH/H_2O (10:2:1), reflux, 10 min; c) TFA/CH_2Cl_2 (1:1), 25 °C, 1 h; d) HATU (1.2 equiv), *i*Pr_2NEt, CH_2Cl_2, 25 °C, 15 h, 75% over 3 steps; e) Oxone® (3.0 equiv), sat. aq. $NaHCO_3$, acetone, 0 °C to rt, 6 h, 75% (d.r. 2.5:1), 54% **53** and 21% **54**.

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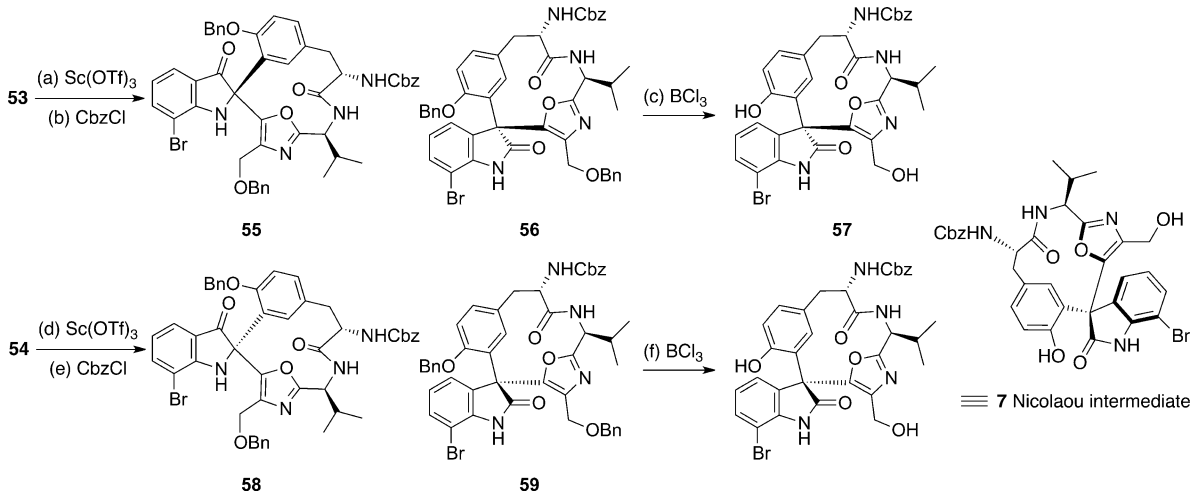

Scheme 12. Rearrangement of macrocyclic 3-hydroxyindolenines **53** and **54**: completion of formal synthesis of diazonamide A. Reagents and conditions: a) $Sc(OTf)_3$ (1.0 equiv), toluene, 110 °C, 6 h; b) CbzCl (1.1 equiv), $NaHCO_3$ (5.0 equiv), THF, 25 °C, 16 h, 20% indoxyl **55**, 8.4% oxindole **56**; c) BCl_3 (20 equiv), CH_2Cl_2, −78 °C, 2.5 h, 65%; d) $Sc(OTf)_3$ (1.1 equiv), toluene, 110 °C, 6 h; e) CbzCl (1.0 equiv), $NaHCO_3$ (4.0 equiv), THF, 25 °C, 16 h, 22% indoxyl **58**, 10% oxindole **59**; f) BCl_3 (20 equiv), CH_2Cl_2, −78 °C, 2.5 h, 63%.

trol with chiral oxidants (Davis' oxaziridine and Oppolzer's sultam-derived oxaziridines, Shi dioxiranes and vanadium catalysts in combination with *tert*-butyl hydroperoxide). Unfortunately, in all cases it appeared that the substrate was too hindered, with no oxidation being observed under mild conditions and with significant decomposition upon more forcing reaction conditions. Finally, we resorted to using trifluoroacetone to form a more reactive dioxirane in situ in an attempt to achieve a less diastereoselective oxidation. Although this protocol significantly increased the amount of the wanted diasteromer **54** on a small scale, attempts to scale up the reaction were less successful.

With both 3-hydroxyindolenines **53** and **54** now readily available in significant quantities (> 100 mg), we were able to address the crucial rearrangement step. Treatment of the major diastereomer **53** with scandium triflate in toluene at reflux, followed by reprotection of the tyrosine-derived amino group with benzyl chloroformate, gave a separable mixture of indoxyl **55** and oxindole **56** in a ratio of about 2:1 in very modest yield (Scheme 12). Removal of the benzyl groups using boron trichloride gave oxindole **57** in good yield. At this stage we were able to compare the spectroscopic data with those reported by Nicolaou.[5] and Sammakia[15b] for the key intermediate **7**. We were immediately suspicious that oxindole **57** possessed the wrong stereochemistry at the quaternary centre, because it proved rather insoluble in deuteroacetonitrile, the NMR solvent used by both the Nicolaou and Sammakia groups. Unfortunately this proved to be the case—the NMR spectroscopic data for oxindole **57** are clearly at odds with the previously reported data. The fact that oxindole **57** (and **56**) had the wrong configuration at the quaternary centre allowed us to assign the stereochemistry of the 3-hydroxyindolenine **53** on the basis that the group (the oxazole in this case) that migrates from C-2 (indole numbering) does so from the opposite side to the hydroxyl group as established by Movassaghi and colleagues.[26] Repeating the rearrangement-protection sequence with the diastereomeric hydroxyindolenine **54** produced a separable mixture of indoxyl **58** and oxindole **59**, again in a ratio of about 2:1 in favor of the unwanted indoxyl. Deprotection of oxindole **59** with boron trichloride produced an oxindole that showed identical NMR spectroscopic properties to the Nicolaou intermediate **7**, thereby completing a formal total synthesis of diazonamide A (Scheme 12).

Conclusions

A formal total synthesis of the complex marine metabolite diazonamide A has been completed. The route is different to previous approaches in that it is based on oxidative rearrangement of indoles, a strategy that not only ensures that the key precursors are readily available from simple indole, oxazole and tyrosine building blocks using uncomplicated, scaleable chemistry, but also that the overall route to the key oxindole **7** is relatively short (13 steps in longest linear sequence from commercially available Boc-L-valine and DL-serine methyl ester hydrochloride).

Experimental Section

For full details of all experiments, see the Supporting Information.

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Keywords: oxindoles · natural products · total synthesis

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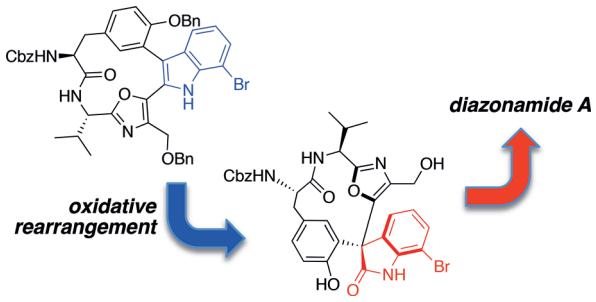

Totally indole darling! A formal total synthesis of the complex marine metabolite diazonamide A has been completed. The route is different to previous approaches in that it is based on oxidative rearrangement of indoles

Total Synthesis

*N. David, R. Pasceri, R. R. A. Kitson, A. Pradal, C. J. Moody**

■■ – ■■

Formal Total Synthesis of Diazonamide A by Indole Oxidative Rearrangement

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