Biomimetic approaches to diazonamide A. Direct synthesis of the indole bis-oxazole fragment by oxidation of a TyrValTrpTrp tetrapeptide

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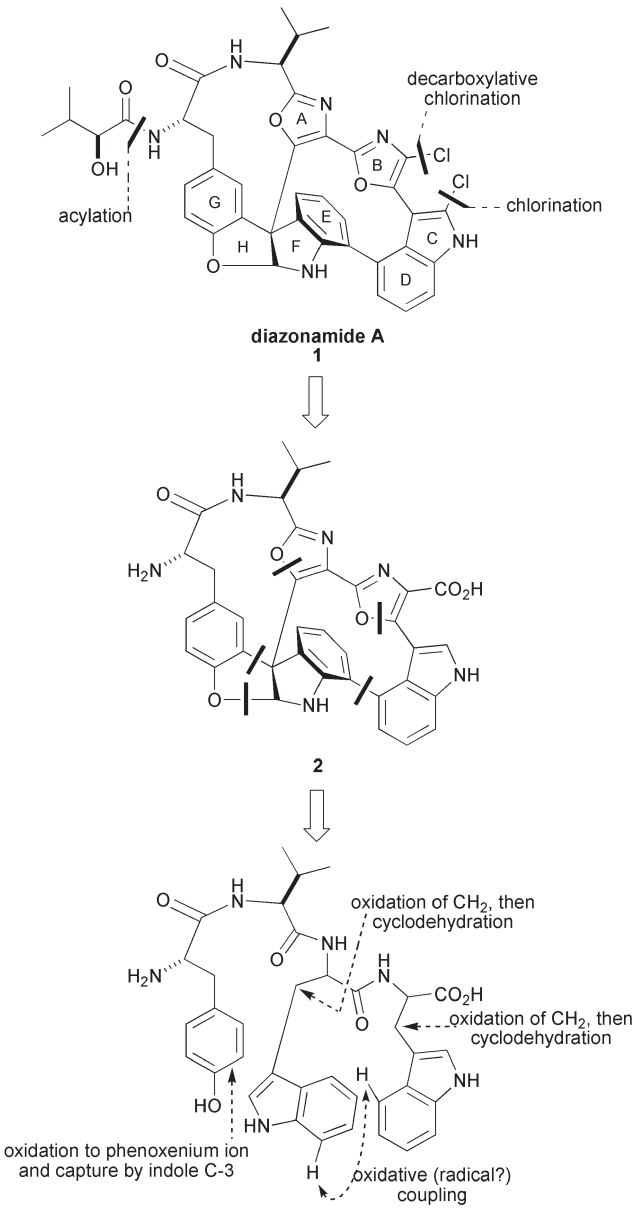
Oxidation of a protected TyrValTrpTrp tetrapeptide results in direct formation of the indole bis-oxazole core of diazonamide A.

The marine secondary metabolite diazonamide A, isolated from the colonial ascidian *Diazona chinensis*, was reported to have potent *in vitro* cytoxicity against human tumor cell lines.[1] This biological activity,[2] together with its unique and complex structure, assigned on the basis of an X-ray crystallographic study of a derivative,[1] ensured that diazonamide A immediately captured the imagination of synthetic organic chemists. Therefore in the 15 years since the structure of diazonamide A was reported in 1991, some 10 research groups have published approaches to this fascinating natural product.[3–12] The story acquired a new dimension in 2001 when Harran and co-workers completed a total synthesis of the reported structure only to discover that not only was it rather unstable, but it was also different from the natural product.[13,14] On the basis of his own studies and a re-examination of the original X-ray data, Harran proposed an alternative structure **1** for diazonamide A. Unequivocal proof that the revised structure **1** was indeed that of diazonamide A came when Nicolaou and co-workers published the first total synthesis of the natural product.[15] Subsequently, the Nicolaou group reported a second route to diazonamide A,[16] whilst Harran and co-workers completed their own total synthesis of the correct structure.[17] Despite the fact that Nicolaou's and Harran's efforts in total synthesis have laid to rest 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.

Importantly, the revised structure of diazonamide A **1** better fits a biosynthetic route in which the bicyclic core derives from modification of a TyrValTrpTrp tetrapeptide,[14] and Harran's own synthesis of the natural product involves the formation of the G-H-F-E aminal by an oxidative cyclisation of a tyrosine derivative that likely mimics the biosynthesis.[17] In continuation of our own longstanding interest in diazonamide A **1**,[18–24] which primarily involves the use of diazocarbonyl chemistry to construct strategic C–N bonds by rhodium carbene N–H insertion reactions, we were intrigued by the possibility of a biomimetic route that started from the putative biosynthetic precursor, the TyrValTrpTrp tetrapeptide itself. We now report the first results from this study.

Our retrosynthetic analysis of diazonamide A **1** (Scheme 1) involves an initial simplification and disconnection of the α-hydroxy isovaleric acid side chain and the two chlorine atoms.



Scheme 1

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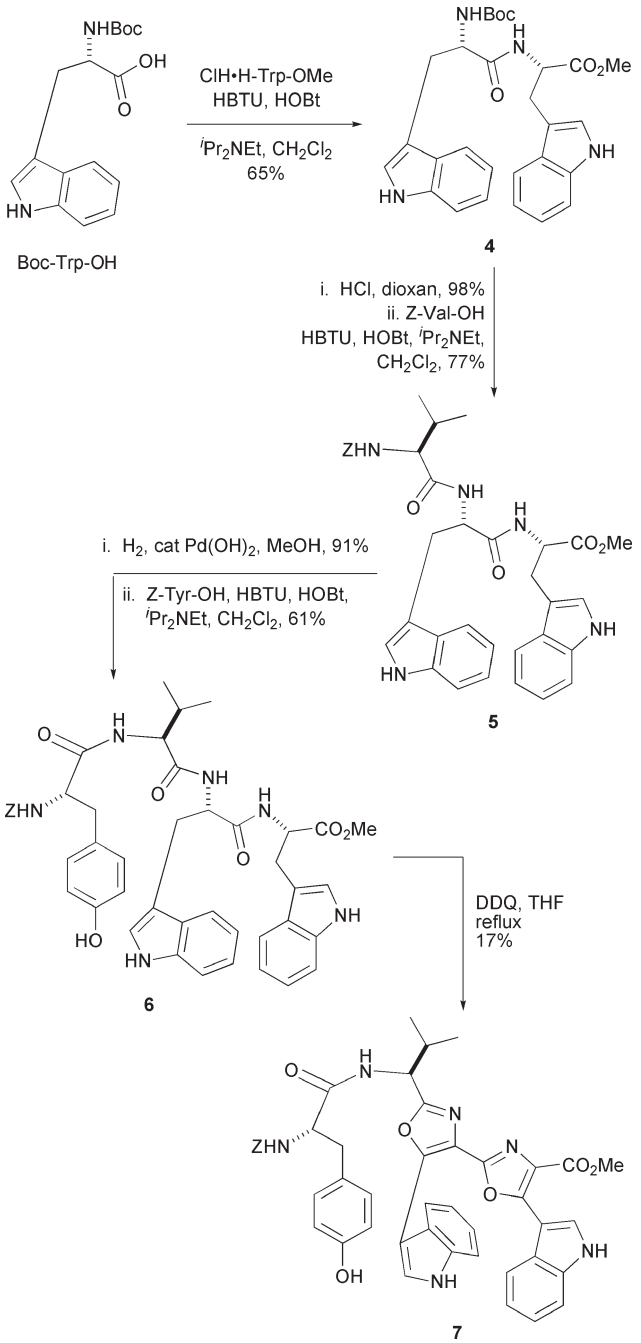
It was established early on that both these chlorines could be introduced by a late stage electrophilic chlorination reaction.[25,26] However, as did Magnus and co-workers,[26] we recognised an additional possibility that the 4-chlorooxazole might derive by a decarboxylative chlorination of the corresponding oxazole-4-carboxylic acid. This again relates to the putative biosynthetic precursor to diazonamide A in that C-4 of the ring-B oxazole derives from the α-carbon of tryptophan and therefore would originally bear a carboxylic acid. Hence the initial target is the macrocyclic core **2** that can be envisaged to result from a series of oxidative cyclisations of the tetrapeptide **3** as depicted in Scheme 1. Of these, the oxidation of the tyrosine ring followed by capture by the nucleophilic indole 3-position has precedent in the aforementioned Harran synthesis,[17] and 3-indolyl oxazoles are known to result from the so-called Yonemitsu oxidation of tryptamine derivatives.[27,28]



Scheme 2

The synthesis of the substrate tetrapeptide started with the formation of the known Boc-TrpTrp-OMe dipeptide **4**[29] by reaction of Boc-Trp-OH with H-Trp-OMe using HBTU in the presence of 1-hydroxybenzotriazole (HOBt) and Hünigs base as the peptide coupling agent.[30] Removal of the *N*-Boc protecting group under acidic conditions was followed by a second HBTU-mediated coupling with Z-Val-OH to give the tripeptide **5**. Finally, hydrogenolysis of the *N*-Z protecting group and a further HBTU-coupling to Z-Tyr-OH gave the protected TyrValTrpTrp tetrapeptide **6** in an overall yield of 27.2% from Boc-Trp-OH (Scheme 2).

The stage was now set for oxidative cyclisation of the tetrapeptide, and after initial experimentation with simpler model systems (not shown) it was discovered that the Yonemitsu oxidation conditions were the most appropriate. Therefore, treatment of the tetrapeptide **6** with DDQ in anhydrous THF gave the indole bis-oxazole **7** directly, albeit in poor yield (17%).† This result establishes the possibility that such an (enzymatic) oxidation of the indole-3-carbinyl position in tryptophan residues, followed by cyclodehydration, could form the basis of the biosynthesis of the heterocyclic core of diazonamide A **1**. Notwithstanding the poor yield in the final step, the advanced intermediate **7** is available in just six steps from Boc-Trp-OH.

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Notes and references

† Compound **7**, mp 146–148 °C (from ethyl acetate); $[\alpha]_D^{25}$ + 40.0 (*c* 0.1, THF); (Found: MH^+, 793.2980. $C_{45}H_{40}N_6O_8$ + H requires 793.2986); ν_{max} (KBr)/cm^{-1} 3411, 2960, 2915, 1704, 1668, 1617, 1589, 1516, 1457, 1375, 1337, 1244, 1218, 1130, 1086, 1052, 745; δ_H (400 MHz; d_6-DMSO) 12.00 (2 H, br s, 2 NH), 9.21 (1 H, d, *J* 2.9, ArH), 9.11 (1 H, s, OH), 8.82 (1 H, d, *J* 8.7, NH), 8.72 (1 H, d, *J* 2.9, ArH), 8.18 (1 H, d, *J* 7.8, ArH), 8.13 (1 H, d, *J* 7.7, ArH), 7.40–7.38 (2 H, m, ArH), 7.73–7.05 (12 H, m, 11 ArH and NH), 6.58–6.56 (2 H, m, ArH), 5.08–5.01 (1 H, m, CH), 4.93 (2 H, s, CH_2), 4.39 (1 H, m, CH), 3.91 (3 H, s, OMe), 2.95 (1 H, m, CH of CH_2), 2.70 (1 H, m, CH of CH_2), 2.46 (1 H, m, C*H*Me$_2$), 1.11 (3 H, d, *J* 6.6, CH*Me*$_2$), 1.03 (3 H, d, *J* 6.6, CH*Me*$_2$); δ_C (100 MHz; d_6-DMSO) 172.6, 163.1, 160.9, 156.4, 156.2, 153.9, 152.7, 149.1, 137.5, 136.6, 136.5, 130.7 (CH), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.5, 128.14 (CH), 128.09 (CH), 128.0 (CH), 127.9 (CH), 125.2, 125.0, 123.4, 123.1 (CH), 121.6 (CH), 121.4 (CH), 119.8, 115.5 (CH), 115.2 (CH), 112.8 (CH), 112.7 (CH), 103.2, 102.7, 65.6 (CH_2), 56.8 (Me), 53.0 (CH), 52.3 (CH), 31.7 (CH), 19.6 (Me), 19.1 (Me), 1 CH_2 not observed; *m*/*z* (ES+) 793 (3%, MH^+), 698 (3), 687 (12), 685 (39), 684 (95), 669 (11), 651 (10), 641 (10), 638 (17), 637 (31), 579 (9), 494 (9), 420 (11), 394 (10), 365 (9), 337 (9), 310 (9), 309 (10), 280 (19), 266 (23), 239 (21), 223 (29), 219 (52), 205 (50), 170 (53), 169 (80), 168 (100), 144 (20), 117 (15), 108 (58), 107 (63), 91 (30), 79 (99), 77 (98), 53 (28), 52 (81), 46 (70).

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