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Synthesis of the dichlorobisoxazole-indole portion of the antitumor agent diazonamide by a putative biogenetic strategy

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Abstract

Chlorination of the bis-oxazole-indole **16** using *N*-chlorosuccinimide gave the dichloride **13** (86%) and the trichloride **12** (5%) thus completing the synthesis of the CDEF rings of diazonamide.

In 1991 Fenical and Clardy reported the structure of diazonamide A, **1** and diazonamide B, **2**, Scheme 1.[1] The diazonamides were isolated from the colonial ascidian *Diazona chinensis*, collected from the ceilings of caves along the northwest coast of Siquijor Island in the Philippines. It was reported that **1** has potent in vitro activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cells (IC_{50} <15 ng/mL). The structures of **1** and **2** were inferred from the X-ray structure of the derivative **3**. The diazonamides have generated some synthetic interest,[2] and the synthesis of oxazoles and bis-oxazoles has undergone renewed interest.[3–5] There is a growing number of oxazole natural products with interesting biological properties, but the diazonamides are manifestly unique in their structural features.[6]

The footnoted report by Wipf and Yokokawa that chlorination of a CDE-ring model compound with *N*-chlorosuccinimide (NCS)/dibenzoylperoxide/CCl_4/70°C resulted in the direct introduction of the required chlorine atoms into the 2- and 4-positions of the indole and oxazole, respectively, prompted this letter.[7] We speculate that the tryptophan derived bisoxazole **4** can undergo chlorodecarboxylation via **5** to give **6**, and this forms the basis of the subsequent experiments.

The known[8] valine-derived oxazole **7** was treated with Et_3N and isobutyl chloroformate in THF at 0 to 25°C, followed by methyl tryptophan·HCl to give **8** in 95% yield (Scheme 2). Dehydrogenation of **8** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[9] in dry THF gave the bis-oxazole **9** (64%). It should be noted that this dehydrogenation reaction does not work well (if at all) on the corresponding tryptamine derived substrates. While oxazoles are normally quite resistant to electrophilic substitution reactions,[10] the presence of the indole was expected to increase the reactivity of the oxazole. It was found that treatment of **10** with *N*-chlorosuccinimide (NCS) (2.0 equiv.)/CCl_4 at 40°C for 48 h gave

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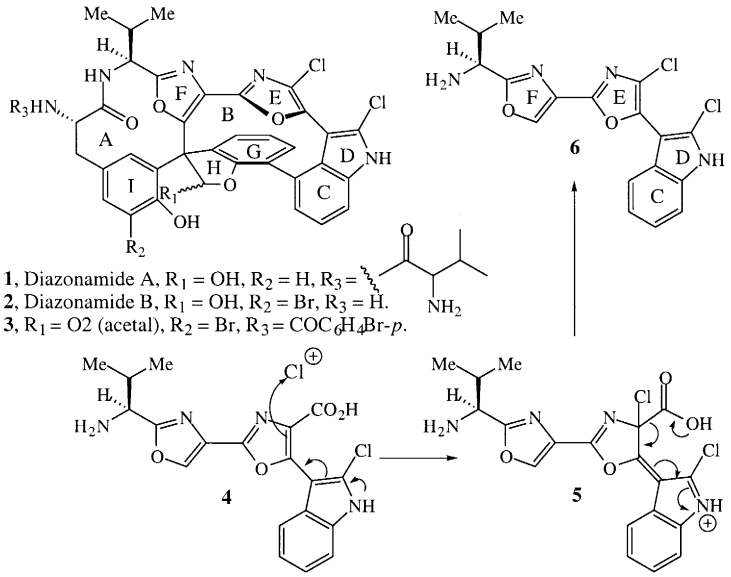
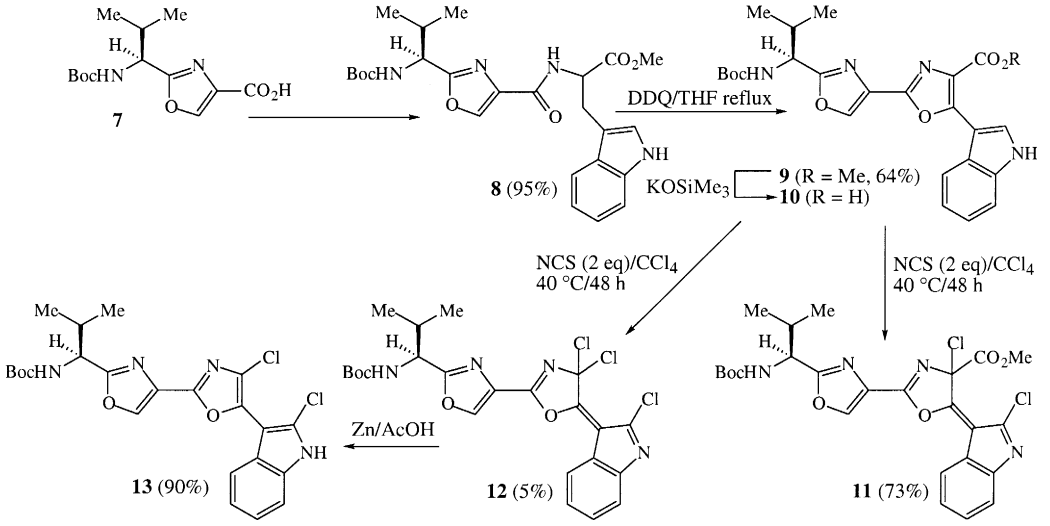


Scheme 1.

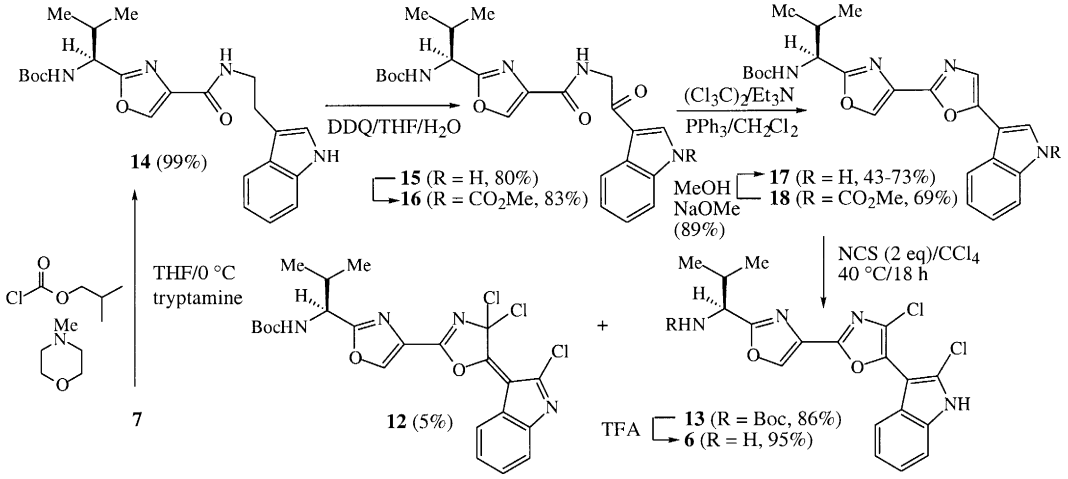
11 (73%). Attempted hydrolysis of the methyl ester **11** (LiOH/THF/H_2O, $KOSiMe_3$/THF) with the reasonable expectation that decarboxylation would ensue and result in the direct formation of **13** was not successful. Only numerous intractable decomposition products were formed. As a consequence it was decided to hydrolyze the ester **9** to the acid **10** prior to chlorination. Treatment of **9** with a variety of hydroxide bases (LiOH/THF/H_2O) resulted in extensive decomposition and only very low yields of the acid **10** were isolated. Treatment of **9** with $KOSiMe_3$/THF/20 h gave after work-up **10** (crude) which was immediately chlorinated as before [(NCS) (2.0 equiv.)/CCl_4 at 40°C for 48 h] to give the trichloro-adduct **12** in poor yield. The structure of **12** was partially confirmed by treatment with Zn/AcOH to give the desired dichlorobisoxazole-indole portion of diazonamide, namely **13** in excellent yield.[11] Clearly, the low yield in the chlorodecarboxylation step (**10**→**12**) does not make this a practical route to **13**, and therefore we examined the same type of sequence of reactions as depicted in Scheme 2 except that the decarboxylation is avoided by using tryptamine instead of tryptophan (Scheme 3).

Coupling **7** to tryptamine using the chloroformate procedure gave **14** (99%) (Scheme 3). The direct DDQ oxidation of **14** to give **17** does not work (alluded to before), and therefore a two-step sequence was used. Treatment of **14** with DDQ in aqueous THF gave the ketone **15** (80%). Dehydration of **15** to give **17** proved to be difficult (Burgess reagent gave 35% yield of **17**) but using the Wipf[7] procedure gave **17** in 43% yield.[12] In one instance we obtained a 73% yield of **17**, although this was not reproducible. Chlorination of **17** proceeded cleanly to give a mixture of **12** and **13** in 5% and 86% yield, respectively. The trichloro-adduct **12** was converted into **13** by treatment with Zn/AcOH.[13] In an effort to improve the yield of the keto-amide dehydration to form the oxazole (**15**→**17**) we protected the indole **15** as the carbamate **16**. Treatment of **16** with $(Cl_3C)_2$/PPh_3/Et_3N gave **18** (69%), which on deprotection gave **17** (89%). The dehydration step was considerably improved and more reproducible; the overall yield from **15** to **17** via **16** and **18** was significantly improved to 51% (over three steps) to make the protection/deprotection steps worthwhile.

Finally, treatment of the Boc-protected amine **13** with trifluoroacetic acid (TFA)/CH_2Cl_2 cleanly removed the Boc group to give **6** (Scheme 1) in almost quantitative yield. This relatively short route for



Scheme 2.



Scheme 3.

the synthesis of the CDEF rings of diazonamide is currently being examined for substrates that contain the G ring where the possibility of atropisomerism could manifest itself.

Acknowledgements

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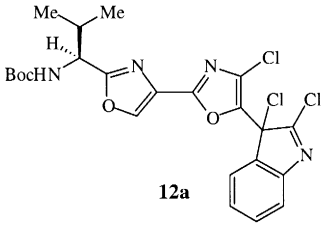
11. The isomeric structure **12a** is also a possibility, and would be readily reduced by Zn/AcOH to give **13**.



12a

12. Spectral data for **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, d, *J*=6.0 Hz), 0.97 (3H, d, *J*=6.0 Hz), 1.45 (9H, s), 2.25 (1H, m), 4.86 (1H, dd, *J*=9.0, 6.0 Hz), 5.40 (1H, bd, *J*=9.0 Hz), 7.23–7.32 (2H, m), 7.37 (1H, s), 7.46 (1H, dd, *J*=6.0, 3.0 Hz), 7.63 (1H, d, *J*=3.0 Hz), 7.64 (1H, dd, *J*=6.0, 3.0 Hz), 8.18 (1H, s), 8.83 (1H, b s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.0, 18.7, 28.3, 33.0, 54.4, 80.0, 105.2, 111.7, 119.8, 121.0, 121.1, 122.5, 123.1, 124.0, 130.6, 136.3, 137.6, 148.0, 152.8, 155.5, 165.2. HRMS (CI) calcd for $C_{23}H_{26}N_4O_4$ (M^+): 422.1954. Found: 422.1958.
13. Spectral data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, d, *J*=6.0 Hz), 0.96 (3H, d, *J*=6.0 Hz), 1.45 (9H, s), 2.25 (1H, m), 4.86 (1H, dd, *J*=6.0, 9.0 Hz), 5.39 (1H, bd, *J*=9.0 Hz), 7.18 (1H, t, *J*=6.0 Hz), 7.24 (1H, t, *J*=6.0 Hz), 7.35 (1H, d, *J*=6.0 Hz), 7.59 (1H, d, *J*=6.0 Hz), 8.18 (1H, s), 9.22 (1H, b s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.9, 18.6, 28.2, 32.9, 54.3, 80.1, 99.4, 110.8, 119.3, 121.4, 123.2, 124.2, 126.1, 128.0, 130.0, 134.3, 138.5, 139.4, 153.8, 155.5, 165.5. HRMS (CI) calcd for $C_{23}H_{24}N_4O_4Cl_2$ (M^+): 490.1175. Found: 490.1164.