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Synthesis of novel pentacyclic pyrrolothiazolobenzoquinolinones, analogs of natural marine alkaloids

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Abstract—Multistep synthesis (12 steps) of new pentacyclic compounds, which are structurally very close to natural marine alkaloids, was performed via a Diels–Alder reaction between 4-methylene-5-(bromomethylene)-4,5-dihydrothiazole and a protected dioxotryptamine, itself obtained from the commercially available 2,5-dimethoxybenzaldehyde.

For the last two decades, marine natural products have constituted an important source of inspiration for chemists and have received increasing attention as a source of new and useful anticancer drugs.[1] Recently we described the synthesis and the antiproliferative evaluation of original 7-aminosubstituted pyrroloiminoquinone derivatives and showed that, by itself, the pyrroloiminoquinone core can induce good cytotoxicity despite its lack of interaction with the cellular cycle (L1210 cells).[2] In search of new polyheterocyclic systems with potential pharmacological values, we planned to prepare new pentacyclic compounds by fusing the pyrroloiminoquinone and the benzothiazole rings. The original structure **1** (Fig. 1), described in this paper, is structurally close to natural alkaloids such as the pyridoacridines (e.g. Kuanoniamine A) and the pyrroloiminoquinones (e.g. Wakayin),[3] which have shown interesting antitumour activities.[4,5]

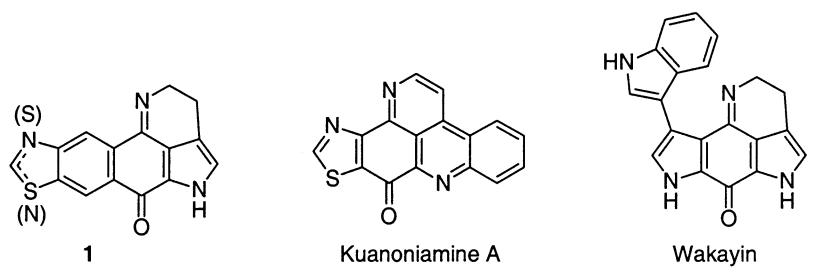
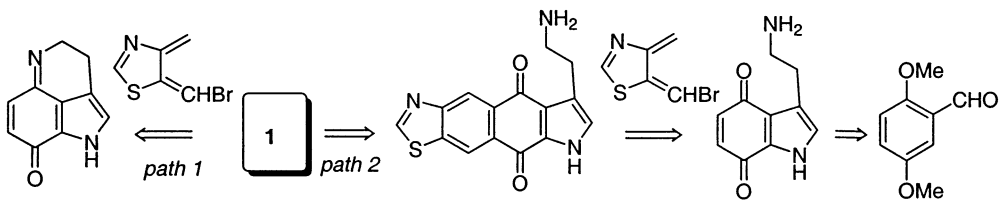


Figure 1.



Scheme 1.

Keywords: large ring heterocycles; pyrroloiminoquinones; thiazoles; marine alkaloids.

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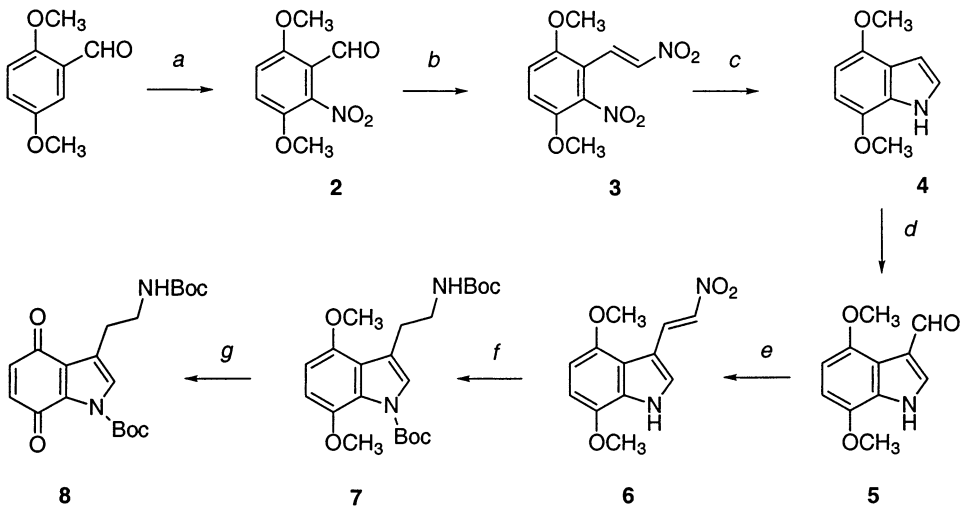
The retrosynthetic pathway described in Scheme 1 was inspired by recent works on generation and trapping of analogues of *o*-quinodimethane with dienophiles.[6] Path 1 was rapidly judged unfeasible[7] to the profit of path 2 in which the intermediate quinone may be expected by Diels–Alder reaction between 4-methylene-(5-bromomethylene)-4,5-dihydrothiazole (generated from 4-(bromomethyl)-5-dibromomethylthiazole)[6] and a protected dioxotryptamine, itself obtained from the commercially available 2,5-dimethoxybenzaldehyde.

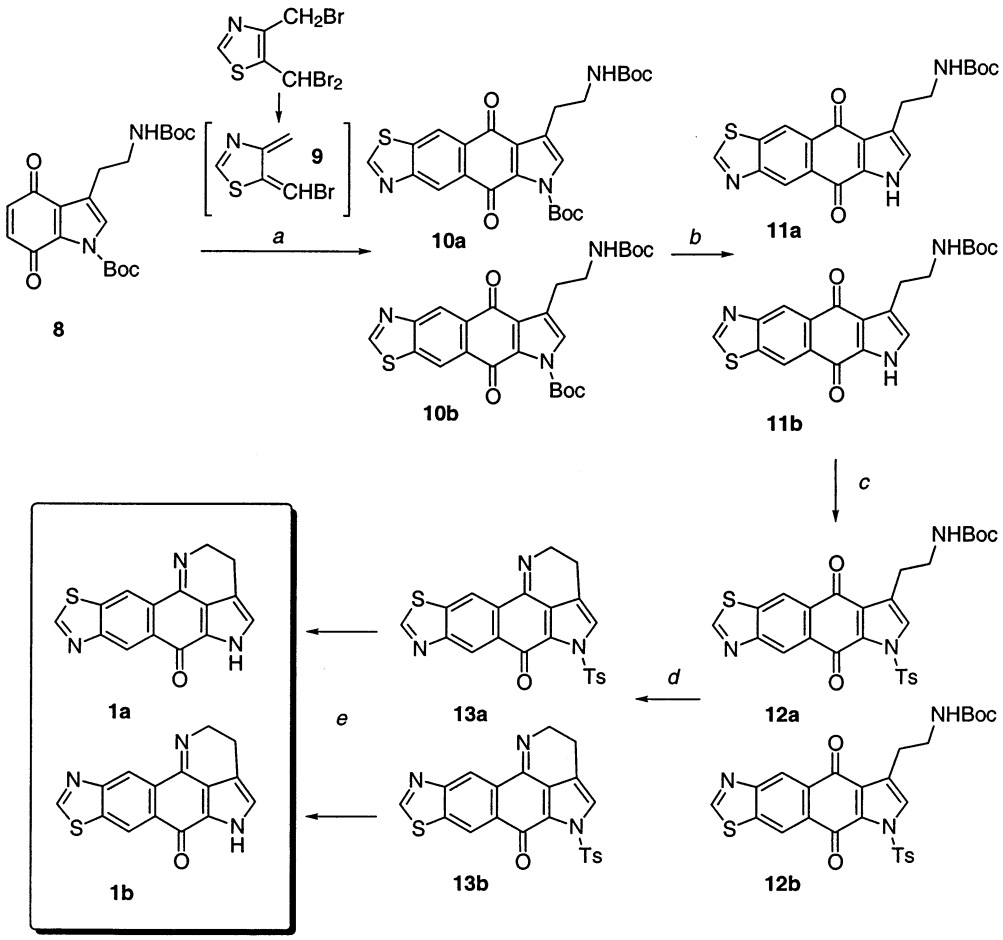
(a) Synthesis of the 4,7-dioxotryptamine **8** (Scheme 2). Nitration of 2,5-dimethoxybenzaldehyde with nitric acid in dichloromethane at 0°C led to the 2-nitro derivative **2**,[8] which was transformed in good yield (70%) into the intermediate *o*,β-dinitrostyrene **3** by a classical Henry reaction with nitromethane. Reductive cyclization of **3** in the presence of ammonium formate in ethanol[8,9] provided the attempted indole **4** (yield: 84%), which was quantitatively formylated according to Vilsmeier–Haack conditions to give the 4,7-dimethoxy-3-formylindole **5** in very good yield (96%). At this step of the synthesis, our first intention was to protect (by tosyl group) or to alkylate (methyl or benzyl groups) the nitrogen atom of the indole ring. Unfortunately, preliminary experiments performed by our group[7] have shown that whatever solutions were chosen the following steps were unsuccessful. The best alternative was to condense nitromethane on **5** as described in step (**3→4**) to give **6** in 76% yield. The side chain of the 3-(2-nitrovinyl)indole **6** was then completely reduced at room temperature, using lithium aluminum hydride, and the intermediate amine was subsequently treated with di-*t*-butoxycarbonyl oxide (BOC_2O), in the presence of 4-dimethylaminopyridine, to give **7** in 50% yield. The protected tryptamine **7** was oxidized into the expected quinone **8** by treatment with ceric ammonium nitrate (CAN)[10] in the presence of 2,6-dicarboxypyridinium oxide in aqueous acetonitrile.

(b) Preparation of the pentacyclic compound **1** (Scheme 3). Fusion of the benzothiazole and the quinone skeletons suggested the use of 4-methylene-(5-bromomethylene)-4,5-dihydrothiazole **9**, which have been proved to undergo highly regioselective Diels–Alder reactions.[6] Treatment of the tribrominated precursor, with sodium iodide in DMF,[6] allowed the *o*-quinodimethane **9** which was trapped in situ with the dienophile **8** with a weak regioselectivity, leading to **10**, a mixture of two isomers **10a** and **10b** (ratio **10a**/**10b**: 2:1), which were not separated whatever conditions were used. At this part of our work, we decided to continue the synthesis from the mixture **10** with the hope of separating the two isomers a and b in a further step. Because recent works have demonstrated that the final cyclization of similar *N*-protected indoles can occur when there is a strong electron-withdrawing group linked to the indolic nitrogen,[7] selective deprotection of **10** was performed. Tosylation of the intermediate quinone **11** gave **12** in a yield of 50%; the ratio of isomers a and b remained unchanged. The primary amine was quantitatively deprotected by treatment of **12** with trifluoroacetic acid and the cyclic imine **13** was formed, in a very good yield (85%), by heating in ethyl acetate in the presence of molecular sieves. Then, the two isomers **13a** (major) and **13b** (minor) were easily separated by column chromatography with dichloromethane/ethyl acetate (7:3, v/v) as solvent. After various experiments, difficult deprotection of the indolic nitrogen of the iminoquinones **13a** and **13b** was finally realized at room temperature in the presence of tetrabutylammonium fluoride in tetrahydrofuran to give **1a** and **1b**,[11–13] respectively (yields: 20% for **1a** and 5% for **1b**).

In conclusion, we have described the synthesis of new pentacyclic systems, which are structurally very close to natural marine alkaloids such as Kuanoniamines and pyrroloiminoquinones. Unfortunately, the low solubil-



Scheme 2. Reagents and conditions: (a) HNO_3 69%, CH_2Cl_2, 0°C, 1 h, 79%; (b) NH_4OAc, CH_3NO_2, reflux, 1 h, 70%; (c) Pd/C, EtOH, HCO_2NH_4, reflux, 1 h, 84%; (d) $POCl_3$, DMF, 0°C, 1.5 h, 96%; (e) NH_4OAc, CH_3NO_2, reflux, 1 h, 76%; (f) i. LAH, CH_2Cl_2/Et_2O (4/1), rt, 1 h; ii. BOC_2O, CH_2Cl_2, TEA, DMAP, 0°C, 4.5 h, 50%; (g) CAN/pyridine-2,6-dicarboxylic acid *N*-oxide, CH_3CN/H_2O, 0°C, 30 min, 65%.



Scheme 3. Reagents and conditions: (a) NaI, DMF, 60°C, 4 h, 44%; (b) trifluoroacetic acid, CH_2Cl_2, rt, 1 h, 60%; (c) *p*-toluenesulfonyl chloride, Bu_4NHSO_4, NaOH, CH_2Cl_2, rt, 3 h, 90%; (d) i. trifluoroacetic acid, CH_2Cl_2, rt, 4 h; ii. EtOH, molecular sieves, reflux, 8 h, 85%; (e) Bu_4NF, tetrahydrofuran, rt, 1 h, 20% (for **1a**); 5% (for **1b**).

ity of compounds **1** into usual solvents is a limitation of a correct estimation of their biological activity. Preparation of various substituted derivatives that may exhibit a better solubility (and will then allow their biological evaluation) is under way and will be described later.

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8. In our experiments, the 4-nitro isomer was also obtained in poor yield (10%) and was easily separated by column chromatography. The nitration of the starting benzaldehyde was previously described in: Hollis Showalter, H. D.; Pohlmann, G. *Org. Proc. Int.* **1992**, *24*, 484–488 (3,6-dimethoxy derivatives) and Knölker, H. J.; Hartmann, K. *Synlett* **1993**, 755–757 (3,6-dibenzyloxy derivatives).
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11. The low yields observed might be explained, in part, by the very difficult purification of the final products.
12. All compounds were fully characterized by spectroscopy and elemental analysis. The structural assignments of regioisomers **1a** and **1b** were made by 2D ^{1}H–^{13}C NMR HMBC correlation performed on compounds **13a** and **13b**.
13. IUPAC name and selected data for compounds **1a** and **1b**: 8,9 - Dihydro - 6*H* - 1 - thia - 3,6,10 - triaza - benzo[*h*]dicyclopenta[*b*,*g*]naphtalen-5-one **1a**: pale yellow needles, mp> 220°C (dec.) (found M^+, 279.0459. $C_{15}H_9N_3OS$ requires 279.0466); δ_H (400 MHz, DMSO-d_6+D_2O) 2.81 (t, 2H, *J* 7.8 Hz, CH_2), 4.17 (t, 2H, *J* 7.8 Hz, CH_2N), 7.19 (s, 1H, H_{indol}), 8.72 (s, 1H, H_{ar}), 8.99 (s, 1H, H_{ar}), 9.57 (s, 1H, H_{thiaz}); δ_C (100 MHz, DMSO-d_6) 117.1, 117.9, 121.2, 122.5, 124.1, 125.1, 126.3, 129.4, 130.7, 133.1, 137.6, 154.1, 154.4, 159.8, 172.5; *m*/*z* 279 (M^+, 100%).
8,9 - Dihydro - 6*H* - 3 - thia - 1,6,10 - triaza - benzo[*h*]dicyclopenta[*b*,*g*]naphtalen-5-one **1b**: pale yellow needles, mp> 220°C (dec.) (found M^+, 279.0458. $C_{15}H_9N_3OS$ requires 279.0466); δ_H (400 MHz, DMSO-d_6+D_2O) 2.80 (t, 2H, *J* 7.5 Hz, CH_2), 4.18 (t, 2H, *J* 7.5 Hz, CH_2N), 7.18 (s, 1H, H_{indol}), 8.77 (s, 1H, H_{ar}), 8.97 (s, 1H, H_{ar}), 9.60 (s, 1H, H_{thiaz}); δ_C (100 MHz, DMSO-d_6) 117.1, 117.9, 121.2, 122.5, 124.1, 125.1, 126.4, 129.3, 130.8, 133.1, 137.6, 154.1, 154.4, 159.8, 172.6; *m*/*z* 279 (M^+, 100%).