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Total synthesis of the marine pyridoacridine alkaloid sebastianine A

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Abstract—The synthesis of the marine alkaloid sebastianine A and of a regioisomer has been accomplished via hetero-Diels–Alder reaction of indole-4,7-dione or *N*-tosylindole-4,7-dione with trifluoroacetamidocinnamaldehyde dimethylhydrazone, and subsequent cyclisation in alkaline conditions.

Pyrido[4,3,2-*mn*]acridine alkaloids represent a group of natural products isolated from marine source, many of which exhibit significant biological properties including tumor toxicity and fungal growth inhibition.[1] In 1998, Plubrukarn and Davidson[2] reported the isolation and structure elucidation of arnoamines A (**1**) and B (**2**), the first members of the pyridoacridine family that possess a pyrrole ring fused to the pyridoacridine ring system, and for which we proposed an original synthesis.[3] Recently, two other pyridoacridine alkaloids, sebastianine A (**3**) and B (**4**) presenting the same structural features were described by Torres et al., from the ascidian *Cystodytes delle Chiaijei*[4] (Fig. 1).

We report herein, the first total synthesis of sebastianine A and of its regioisomer **5** using hetero-Diels–Alder reaction.

Two hetero-Diels–Alder cycloaddition involving *N*-tosylindole-4,7-dione **9** or indole-4,7-dione **11** as dienophile, and *o*-trifluoroacetamidocinnamaldehyde dimethylhydrazone as diene were investigated (Scheme 1).

The two dienophiles **9** and **11** were obtained starting from 4,7-dimethoxyindole **6**, itself prepared from 2,5-dimethoxybenzaldehyde according to the three-step procedure previously described by Beneteau and Besson.[5] Two protective groups: tosyl and BOC were introduced to compound **6**, and the protected indoles **7** and **8** were oxidised by CAN into the indole-4,7-diones **9** and **10**, respectively.[6] The protective group of **10** was cleaved to give indole-4,7-dione **11**.[7]

The hetero-Diels–Alder reactions with both dienophiles **9** and **11** in refluxing toluene afforded in low yield after aromatisation by MnO_2 (8 and 6%, respectively) a mixture of the two regioisomers **12a**/**12b** and **13a**/**13b**. The tosylindoloquinone **9** gave compound **12b** as the major isomer (**12a**/**12b** being 5/95) whereas with indole-4,7-dione, isomer **13a** predominated (**13a**/**13b** being 60/40). This reversal of regioselectivity when changing the

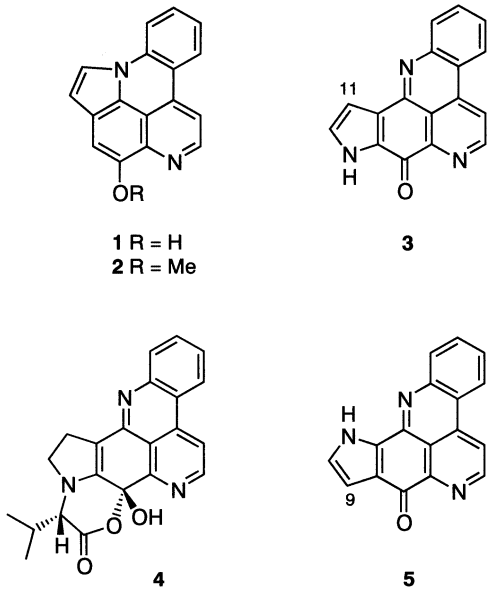

Figure 1.

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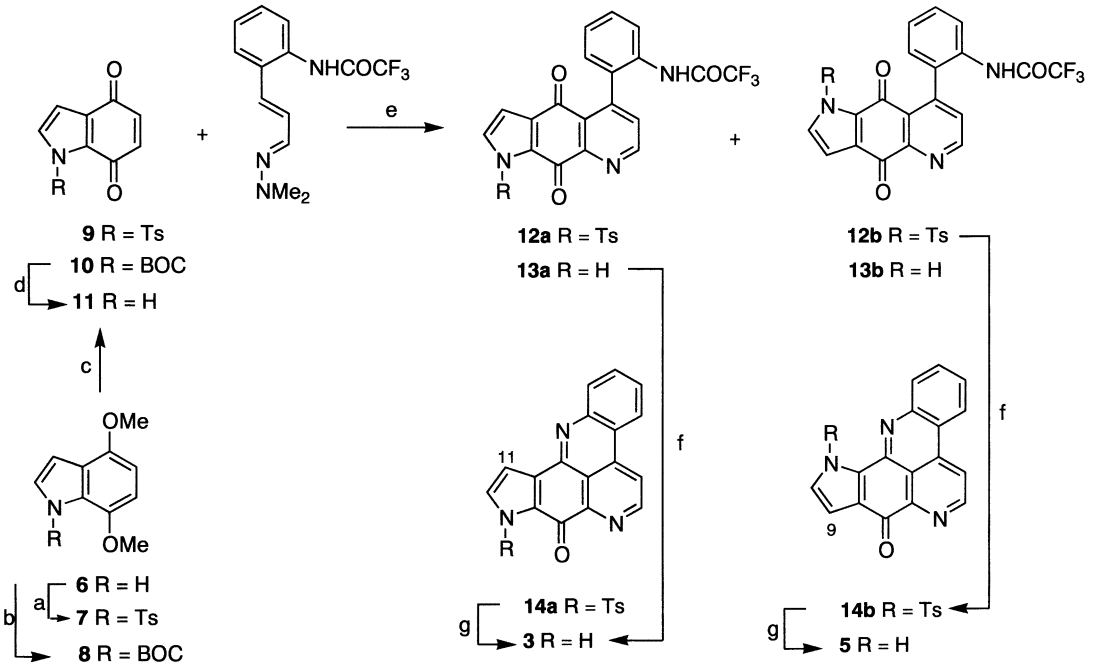

Scheme 1. *Reagents and conditions*: (a) KOH, *p*TsCl, THF, 1 h, (67%); (b) NaH, BOC_2O, THF, rt, 30 min (95%); (c) CAN, CH_3CN/H_2O (4:1), rt, 30 min (R = Ts, 100%, R = BOC, 90%); (d) TFA, CH_2Cl_2, rt, 2 h (100%); (e) toluene, reflux, 12 h (R = Ts, 8%, R = H, 6%); (f) 1N NaOH, CH_2Cl_2, 2 h (**13a**, 85%, **12b**, 92%); (g) 1N NaOH, CH_2Cl_2, 12 h (**14a**, 95%, **14b**, 98%).

nature of the substituent on the indolic nitrogen was previously reported by Barret et al. in hetero-Diels–Alder reactions involving indoloquinones and crotonaldehyde dimethylhydrazone as the diene.[8] They studied the structure assignement of each isomer in 2D-NMR experiments (HMQC and HMBC) concluding that the unsubstituted quinones afforded **a** regioisomers whereas **b** isomers were obtained with quinones bearing an electronwithdrawing substituent on the nitrogen. Based on the same regioselectivity for the cycloaddition of *o*-trifluoroacetamidocinnamaldehyde dimethylhydrazone, we propose structure **a** to be the major isomer in the reaction involving dienophile **11** whereas structure **b** is the major isomer in the reaction with dienophile **9**. The Diels–Alder adducts **13a** and **12b** were subsequently cyclised in alkaline conditions to give the corresponding pentacyclic compounds **3** and **5**[9] in 85 and 92% yield, respectively. It has to be noted that in the case of the tosyl-derivative **12b**, the tosyl pentacyclic derivative **14b** was intermediately obtained by shortening the time of the reaction. As we have previously reported in the case of quinolinic or isoquinolinic derivatives.[10] the proton close to the iminoquinone function in isomer **5** (H_{11}) shows a deshielding effect related to the same proton in isomer **3** (H_9) which confirms the structure assignement established for the Diels–Alder adducts.

The spectroscopic data of **3** and **5**, obtained in the same solvent conditions, were compared with the values reported for the natural product sebastianine A. The values of the natural product were similar with those of compound **3** proving the structure of sebastianine A. The synthesis of sebastianine B is currently in progress.

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9. 11*H* - 7,11,12 - Triazabenzo[*de*]cyclopenta[*a*]anthracen - 8-one, **3**: yellow solid, mp >260°C. MS *m*/*z* (%): 271 (100); 243 (37); 215 (21); 188 (14). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.00 (d, 1H, J=2.6 Hz); 7.48 (d, 1H, J=2.6 Hz); 7.79 (t, 1H, J=8.0 Hz); 7.94 (t, 1H, J=8.0 Hz); 8.18 (d, 1H, J=8.1 Hz); 8.88 (d, 1H, J=8.1 Hz); 8.96 (d, 1H, J=5.2 Hz); 9.19 (d, 1H, J=5.2 Hz); 12.83 (s, 1H). ^{13}C

NMR (100 MHz, DMSO-d_6) 106.95; 117.72; 120.28; 121.90; 124.63; 128.63; 129.53; 130.17; 130.41; 131.54; 132.19; 137.67; 145.84; 149.05 (2C); 149.76; 172.58.

9*H*-7,9,12-Triazabenzo[*de*]cyclopenta[*a*]anthracen-8-one, **5**: orange solid, mp >260°C. MS *m*/*z* (%): 271 (100); 243 (51); 215 (16); 188 (15). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.76 (d, 1H, $J=2.8$ Hz); 7.27 (d, 1H, $J=2.8$ Hz); 7.82 (td, 1H, $J=7.0$ and 1.1 Hz); 7.96 (td, 1H, $J=7.0$ and 1.1 Hz); 8.18 (dd, 1H, $J=7.0$ and 1.1 Hz); 8.89 (dd, 1H, $J=7.0$ and 1.1 Hz); 8.95 (d, 1H, $J=5.6$ Hz); 9.18 (d, 1H, $J=5.6$ Hz); 12.88 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 108.44; 117.32; 120.11; 122.12; 124.79; 125.24; 126.17; 128.72; 130.07; 132.35; 135.28; 137.59; 145.22; 145.55; 149.09; 149.88; 178.38.

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