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Total synthesis of fuligocandines A and B

Birgitta Pettersson, Vedran Hasimbegovic, Jan Bergman *

Karolinska Institute, Department of Biosciences at Novum, Unit of Organic Chemistry, SE-141 57 Huddinge, Sweden

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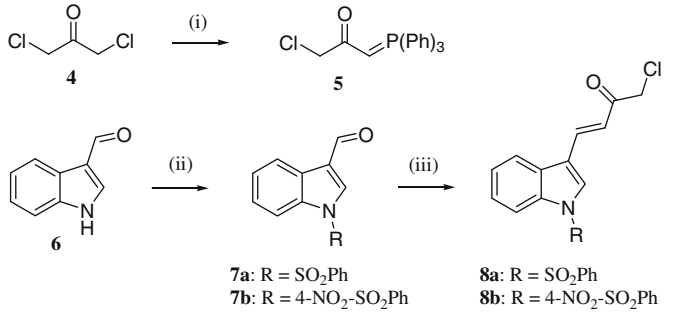
ABSTRACT

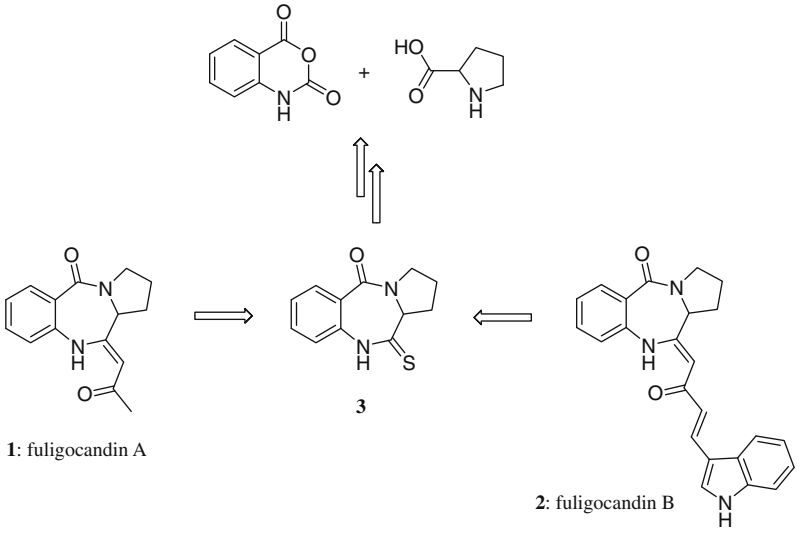
A practical synthesis of the biologically active cycloanthranilylproline derivatives fuligocandines A and B is described, starting from L-proline and isatoic anhydride, employing an Eschenmoser episulfide contraction as the key step.

Fuligocandines A (**1**) and B (**2**) (Scheme 1) are two cycloanthranilylproline derivatives isolated in 2004 from the myxomycete *Fuligo candida* by Nakatani et al. who also established their structures, largely by extensive NMR and MS studies.[1] A recent study has shown that fuligocandin B (**2**) sensitizes leukaemia cells to apoptosis caused by a tumour necrosis factor-related apoptosis-inducing ligand (TRAIL).[2] Intrigued by the interesting biological activity and our ongoing interest in cycloanthranilylproline-derived natural products we have developed practical syntheses of both these alkaloids.

Herein, we report the synthesis of fuligocandines A and B using an Eschenmoser episulfide contraction as the key step. This transformation represents a versatile and efficient method to prepare vinylogous amides by alkylation of thioamides with an appropriate electrophilic reactant followed by extrusion of sulfur.[3] Although



Scheme 2. Synthesis of the indole fragment of fuligocandin B. Reagents and conditions: (i) (a) PPh_3, THF, reflux, 24 h, (98%); (b) Na_2CO_3, H_2O/MeOH, rt, ~1 h (90%); (ii) For **7a**: NaOH, TBAHS (tetrabutylammonium hydrogen sulfate), $PhSO_2Cl$, CH_2Cl_2, rt, 2 h (80%), for **7b**: NsCl, Et_3N, DMAP, CH_2Cl_2, rt, 12 h (90%); (iii) compound **5**, MeOH, reflux, 48 h (**8a**: 60%, **8b**: 80%).



Scheme 1. Retrosynthetic analysis of fuligocandines A and B.

* Corresponding author.
E-mail address: jan.bergman@ki.se (J. Bergman).

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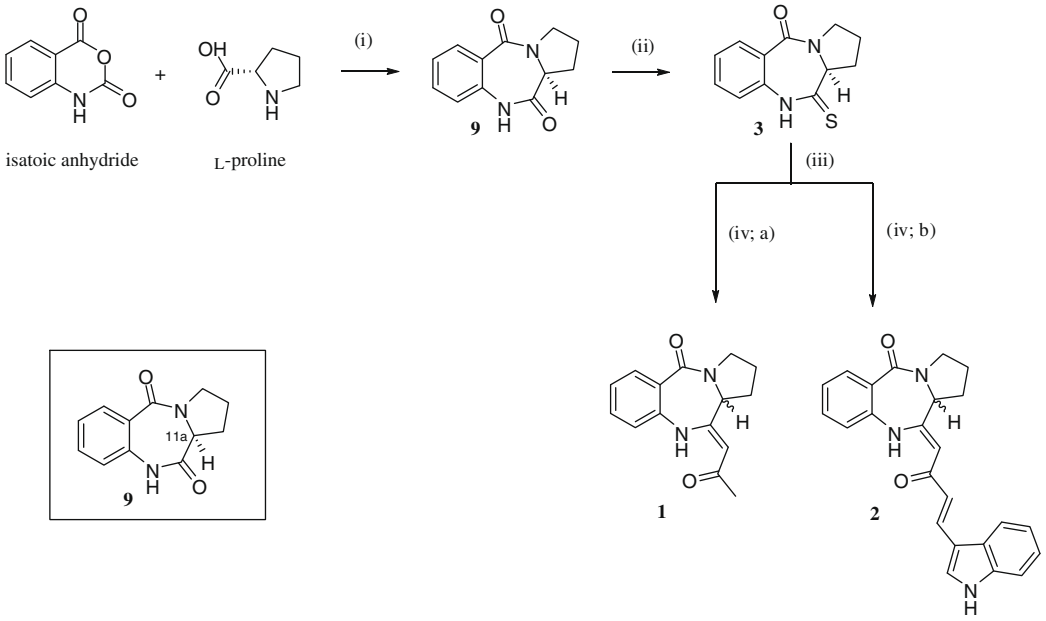

Scheme 3. Synthesis of fuligocandines A and B. Reagents and conditions: (i) L-proline, DMSO, 100 °C, 4 h (95%); (ii) P_2S_5–Py_2, ~60 °C, MeCN, 4 h, (75%); (iii) NaH, DMSO, rt, 30 min, (quant.); (iv) (a) chloroacetone, rt, 40 min then $P(OMe)_3$, DABCO, 100 °C, 24 h (60%, unoptimized); (b) **8a** or **8b**, rt, 40 min then $P(OMe)_3$, DABCO, 100 °C, ~30 h (20%, for both, unoptimized).

the episulfide contraction was first studied by Knott,[4] it has gained widespread use ever since the Eschenmoser–Woodward collaboration on vitamin B_{12}.[5]

As outlined in Scheme 2 (en route to **2** via **8**), 1,3-dichloroacetone **4** was selectively combined with triphenylphosphine and the resulting intermediate phosphonium salt was neutralized with a base to give the desired mono ylide **5**.[6] The aldehyde **6** was protected with benzenesulfonyl chloride to give **7a** and with *p*-nitrobenzenesulfonyl chloride (NsCl) to give **7b**. Both aldehydes **7a** and **7b** underwent a smooth Wittig reaction with the phosphorus ylide **5** when the reaction was conducted in refluxing methanol; other solvents gave no reaction or poor yields of the required indole derivatives **8**. Attempts to obtain this molecule by halogenation of the readily available[7] 3-(3-oxo-1-butenyl)indole failed.

Next, the pyrrolo-1,4-benzodiazepine derivative **9** was readily prepared by heating isatoic anhydride and L-proline in DMSO.[8] This diamide was selectively thionated to give the known monothione[9a,b] **3**, using the P_2S_5–Py_2 complex (Scheme 3).

Finally, one-pot alkylation of the thione **3** and subsequent sulfur extrusion gave fuligocandin A (as the required *Z*-isomer).[10] The racemate of this compound has recently been synthesized in six steps starting from azide derivatives.[11] Employing our Eschenmoser coupling strategy we also obtained fuligocandin B (as the required *Z*- and *E*-isomer) using the convergent route outlined in Scheme 3.[12] As a bonus, under the conditions employed, the indole N-protecting group was also removed. Determination of the optical purities of compounds **1**–**3**, somewhat surprisingly showed that the chirality at C-11a (Scheme 3) was lost in the last step, probably due to tautomerization brought on by the basic reaction conditions. We are currently optimizing this final step and are studying the general applicability of this one-pot alkylation-sulfur extrusion protocol. Previously used standard conditions (such as *t*-butoxide or triethylamine and triphenylphosphine in benzene or xylene at high temperature) failed in these cases. The use of DBU or DBN as a base also gave the desired product, but in inferior yields as compared with DABCO.

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10. Fuligocandin A gave the following ^{1}H NMR data (300 MHz, $CDCl_3$) δ ppm: 2.00–2.10 (m, 2H), 2.11–2.29 (m, 4H), 2.34–2.46 (m, 1H), 3.64–3.70 (m, 1H), 3.80–3.85 (m, 1H), 4.30 (dd, 1H, J = 7.9, 1.6 Hz), 5.30 (s, 1H), 7.02–7.05 (m, 1H), 7.19–7.24 (m, 1H), 7.43–7.48 (m, 1H), 7.96–7.98 (m, 1H), 12.6 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 23.6 (t), 27.2 (t), 30.0 (q), 47.2 (t), 55.6 (d), 91.4 (d), 122.4 (d), 124.8 (d), 127.3 (s), 131.4 (d), 132.8 (d), 137.2 (s), 159.3 (s), 165.9 (s), 198.4 (s).These NMR data are in agreement with data previously reported by Nakatani et al.[1]
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12. Fuligocandin B gave the following ^{1}H NMR (300 MHz, acetone-d_6) δ ppm: 2.06–2.17 (m, 2H), 2.27–2.30 (m, 1H), 2.57–2.62 (m, 1H), 3.55–3.65 (m, 2H), 4.46 (dd, 1H, J = 8.0, 1.6 Hz), 5.82 (s, 1H), 7.02 (d, 1H, J = 15.1 Hz), 7.13–7.16 (m, 1H), 7.19–7.23 (m, 3H), 7.50–7.62 (m, 2H), 7.82–7.85 (m, 1H), 7.87–7.91 (m, 1H), 7.93 (d, 1H, J = 15.1 Hz), 8.02–8.05 (m, 1H), 10.9 (br s, 1H), 13.4 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 24.1 (t), 29.0 (t), 47.6 (t), 56.2 (d), 93.6 (d), 113.0 (d), 114.1(s), 121.4 (d), 121.7 (d), 122.7 (d), 123.6 (d), 124.0 (d), 124.5 (d), 126.5 (s), 128.3 (s), 131.5 (d), 131.6 (d), 133.2 (d), 135.0 (d), 138.6 (s), 138.7 (s), 160.6 (s), 165.9 (s), 190.4 (s). These NMR data are in agreement with the data previously reported by Nakatani et al.[1]