An Efficient Synthetic Route to Homocarbonyltopsentine

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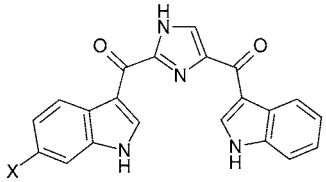
Abstract: Efficient synthesis of homocarbonyltopsentine **Ia**, starting from readily available triiodoimidazole **9** and 3-formylindoles **2** and **18** is described. The key steps of the synthesis are selective halogen-metal exchanges at the imidazole nucleus and subsequent addition to formylated indoles.

Key words: indoles, metalation, regioselectivity, addition reactions, alkaloids

Homocarbonyltopsentines **I** are known to exhibit anti-inflammatory activity in vivo (Figure 1).[1] The structure of these compounds is closely related to well known families of naturally occurring bis-indole alkaloids extracted from marine organisms, such as hamacanthins, topsentins, and rhopaladins.[2] The latter display a wide spectrum of pharmacological properties such as antiviral, cytotoxic, anti-inflammatory and anti-fungal activities[3] and represent new targets for synthetic and medicinal chemists. Several groups have already reported total syntheses of these compounds using different strategies.[4]

Herein, we wish to report our synthetic efforts to access the homocarbonyltopsentine skeleton in order to prepare new derivatives and then evaluate more deeply their biological activities.

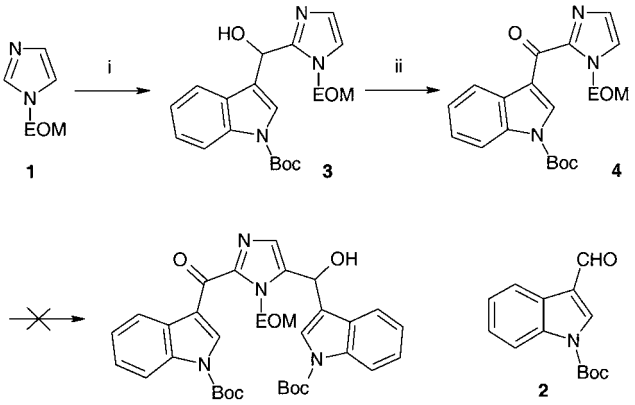


Ia, X = OH : Homocarbonyltopsentine
Ib, X = $OCOCH_3$: Homocarbonyltopsentine monoacetate

Figure 1

Our first strategy was to start from properly *N*-protected imidazole and perform selective metalations followed by additions to formylated indoles and subsequent oxidation of the alcohols formed (Scheme 1).[5] Ethoxymethyl (EOM) was preferred as protective group for the imidazole NH because of its stability under basic/nucleophilic conditions and its ability to stabilise imidazolium derivatives.[6]

Imidazole **1** was deprotonated at –78 °C using 1 equivalent of BuLi and reacted with the aldehyde **2** to give the expected alcohol **3** in 79% yield.[7] The latter was then quantitatively oxidised using manganese oxide (MnO_2) in dichloromethane at room temperature to lead to the ketone **4**.[8] Unfortunately, it has not been possible to perform efficiently the second deprotonation/addition process using BuLi or LDA as base.



Scheme 1 i) BuLi (1 equiv), THF, –78 °C, 30 min then **2** (1.1 equiv), –78 °C, 45 min, 79%; ii) MnO_2, CH_2Cl_2, r.t., 15 h, quantitative.

According to the methodology described by Achab[9] for the synthesis of topsentin, selective iodine/lithium exchange at position-5 of 4,5-diiodoimidazole **5** was carried out in the presence of BuLi. The 5-lithio-4-iodoimidazole was equilibrated within 45 min at –78 °C into the 2-lithio-4-iodoimidazole **6** and added to aldehyde **2** (1.1 equiv) to give **7** in 42% yield (not optimised). The corresponding ketone **8** was readily prepared by oxidation in 92% yield. In our hands, a second exchange at position-4[10] of the imidazole ring with BuLi or EtMgBr was much more problematic and the expected alcohol was not obtained (Scheme 2). Similarly, deprotonation at position-5 using LDA as base failed.

Finally, the protected triiodoimidazole **9** was used as starting material, as the second exchange reaction should be easier in position-5 than in position-4, due to the stabilisation of the lithium by the oxygen of the ethoxymethyl group; the last iodine being removed before final deprotections.

Selective exchange at position-2 of triiodoimidazole derivative **9** using 1 equivalent of BuLi occurred at –78 °C in 5 minutes. Subsequent trapping of the anion formed by

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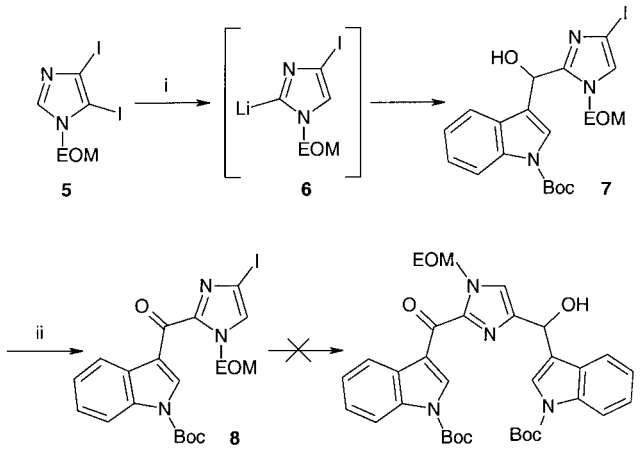
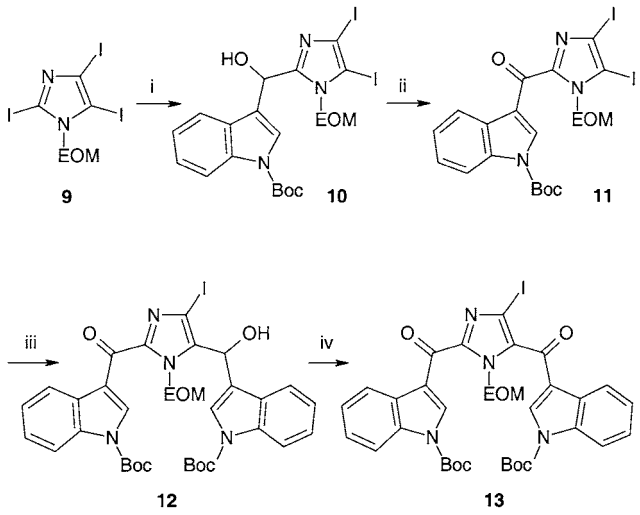


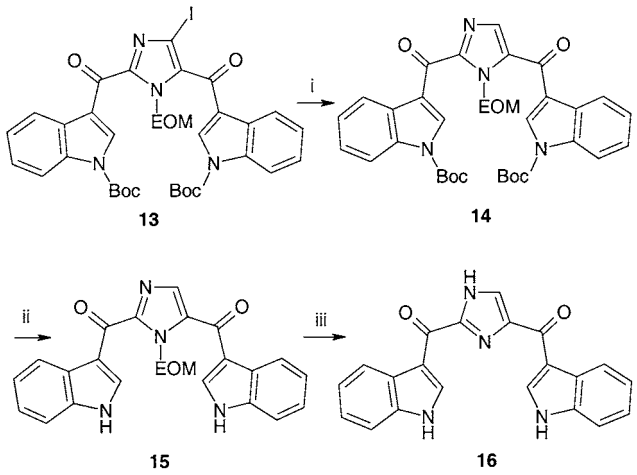
Scheme 2 i) BuLi (1 equiv), THF, –78 °C, 45 min then **2** (1.1 equiv), –78 °C, 45 min, 42%; ii) MnO_2, CH_2Cl_2, r.t., 15 h, 92%.

the appropriate aldehyde **2** produced the expected alcohol **10** in fair yield. The latter was then oxidised using MnO_2 to give the ketone **11** in good yield. The second exchange reaction, at position-5, was performed under the conditions used for the first one, and we were pleased to observe that it occurred cleanly, giving after reaction with **2**, the alcohol **12**. Subsequent oxidation produced the expected diketone **13** in good yield (Scheme 3).



Scheme 3 i) BuLi (1 equiv), THF, –78 °C, 5 min then **2** (1.1 equiv), 45 min, 73%; ii) MnO_2, CH_2Cl_2, r.t., 4 h, 90%; iii) BuLi (1 equiv), THF, –78 °C, 5 min then **2** (1.1 equiv), 45 min, 71%; iv) MnO_2, CH_2Cl_2, r.t., 5 h, 84%.

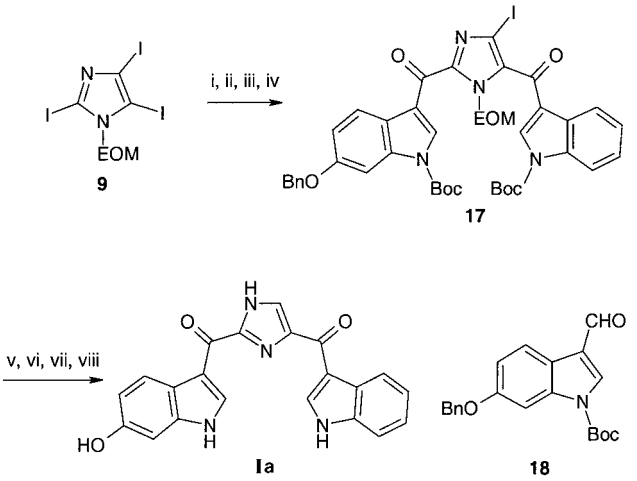
Removal of the iodine atom of the imidazole was then investigated. Exchange with BuLi and subsequent hydrolysis gave unsatisfactory results confirming the difficulty to realise exchange at position-4, of our substrates. Cleavage under homolytic conditions using *n*-Bu_3SnH proved to be inefficient even with an excess of reagent and heating, the expected compound being obtained only in 57% yield (not shown). Finally, hydrogenolysis of **13** using palladium on charcoal 10% as catalyst in the presence of potassium carbonate afforded the reduced bis-indole **14** in 85% yield. The protective groups were then sequentially removed first under basic conditions and then under acidic conditions to give the final compound **16**[11] in good yield (Scheme 4).



Scheme 4 i) H_2 (15 bar), Pd/C 10%, K_2CO_3, EtOH/CH_2Cl_2, 15 h, 85%; ii) NaOH aq, 1,4-dioxane, 70 °C, 30 min, 89%; iii) HCl aq, 1,4-dioxane, 70 °C, 30 min, 90%.

After having set up the conditions for the preparation of the simplest member of the family, we carried out the 8 steps synthesis of homocarbonyltopsentine **Ia** (Scheme 5) from starting materials **9** and *tert*-butyl 6-benzyloxy-3-formyl-1*H*-indole-1-carboxylate **18**[12] in 20% overall yield.

In summary, we have developed an efficient synthesis of homocarbonyltopsentine **Ia** using selective metal-halogen exchange reactions with the protected triiodoimidazole **9**.



Scheme 5 i) BuLi (1 equiv), THF, –78 °C, 5 min then **18** (1 equiv), 45 min, 75%; ii) MnO_2, CH_2Cl_2, r.t., 4 h, 91%; iii) BuLi (1 equiv), THF, –78 °C, 5 min then **2** (1.1 equiv), 45 min, 61%; iv) MnO_2, CH_2Cl_2, r.t., 5 h, 84%; v) H_2 (15 bar), Pd/C 10%, K_2CO_3, EtOH/CH_2Cl_2, 15 h, 89%; vi) NaOH aq, 1,4-dioxane, 70 °C, 30 min, 85%; vii) HCl aq, 1,4-dioxane, 70 °C, 30 min, 83%; viii) $HCOONH_4$, Pd/C 10%, EtOH, reflux, 2 h, 91%.

Preparation of derivatives taking advantage of the presence of iodine on the imidazole ring is currently under way in our laboratory.

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(11) All new compounds gave satisfactory spectroscopic and analytical data. Selected spectroscopic data: **16**: white solid, mp >210 °C; IR (KBr): 3198, 1609, 1590, 1512, 1415, 1110, 859 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.22–7.30 (m, 4 H, H_{Ar}), 7.53–7.59 (m, 2 H, H_{Ar}), 8.02 (s, 1 H, H_{Ar}), 8.37–8.40 (m, 2 H, H_{Ar}), 8.97 (s, 1 H, H_{Ar}), 9.14 (s, 1 H, H_{Ar}), 12.00 (s, 1 H, NH), 12.21 (s, 1 H, NH), 13.70 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.2 (CH), 112.5 (CH), 113.4 (C), 114.9 (C), 121.6 (CH), 121.7 (2 CH), 122.3 (CH), 122.9 (CH), 123.2 (CH), 124.3 (CH), 126.5 (C), 126.7 (C), 135.7 (CH), 136.2 (C), 136.3 (C), 137.1 (CH), 143.3 (C), 145.5 (C), 176.5 (CO), 181.6 (CO); MS (ESI): *m/z* 355 ($M + H^+$); HRMS (LSIMS) for $C_{21}H_{15}N_4O_2$: calculated: 355.1195, found: 355.1195. **Ia**: yellow solid, mp >210 °C; IR (KBr): 3380, 3200, 1592, 1572, 1525, 1430, 1120, 868 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 6.78 (dd, 1 H, J = 1.7 Hz, 8.6 Hz, H_{Ar}), 6.92 (br s, 1 H, H_{Ar}), 7.20–7.28 (m, 2 H, H_{Ar}), 7.53–7.56 (m, 1 H, H_{Ar}) 8.01 (s, 1 H, H_{Ar}), 8.15 (d, 1 H, J = 8.6 Hz, H_{Ar}), 8.38–8.41 (m, 1 H, H_{Ar}), 8.96 (br s, 2 H, H_{Ar}), 9.33 (s, 1 H, OH), 11.84 (s, 1 H, NH), 11.99 (s, 1 H, NH), 13.63 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 97.6 (CH), 112.2 (CH), 112.3 (CH), 113.6 (C), 114.9 (C), 119.4 (C), 121.7 (CH), 121.8 (CH), 122.1 (CH), 122.9 (CH), 124.2 (CH), 126.8 (C), 135.7 (CH), 135.9 (CH), 136.2 (C), 137.6 (C), 143.3 (C), 145.6 (C), 154.4 (C), 176.3 (CO), 181.6 (CO); MS (ESI): *m/z* 371 ($M + H^+$); HRMS (LSIMS) for $C_{21}H_{15}N_4O_3$: calculated: 371.1144, found: 371.1143.
(12) Synthesised by formylation ($POCl_3$, DMF)[9] and protection (Boc_2O, DMAP, acetonitrile) of 6-benzyloxyindole prepared according to; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1333.