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Synthesis of 2,3′-biindolyls and indolo[3,2-*a*]carbazoles

Niklas Wahlström[a,b] and Jan Bergman[a,b,*]

[a]*Unit for Organic Chemistry, CNT, Department of Biosciences at NOVUM, Karolinska Institutet, Novum Research Park, SE-141 57 Huddinge, Sweden*
[b]*Södertörn University College, SE-141 04 Huddinge, Sweden*

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Abstract—Several highly activated 2,3′-biindolyls were prepared from methyl 5,6-dimethoxyindole-2-carboxylate and oxindoles. The 2,3′-biindolyls were further transformed into a hydroxy indolo[3,2-*a*]carbazole and a bisindole amide.

1. Introduction

Several mono and bisindoles (**1**–**2**) have recently been isolated from a marine sponge of the *Ancorina* species.[1] Interestingly the indoles **1a** and **1d** showed weak HIV-inhibitory activity. Although several indolo[2,3-*a*]carbazoles, such as 6-cyano-5-methoxy-12-methylindolo-[2,3-*a*]carbazole[2] **3** and the tjipanazoles,[3] here exemplified by tjipanazole F1[4] **4** (Fig. 1) have been obtained from algae, the bisindole ancorinazole **2** is the first indolo[3,2-*a*]carbazole[5] isolated from natural sources. In connection with our studies of sulfates and sulfamates of some secondary metabolites of the potent aryl hydrocarbon receptor ligand 6-formylindolo[3,2-*b*]-carbazole,[6–8] the hydroxylated and sulfated indolocarbazole **2** became of interest as a synthetic target and also for further biological evaluation. We describe herein a short synthesis of activated 2,3′-bisindoles that can serve as precursors towards a synthesis of **2**.

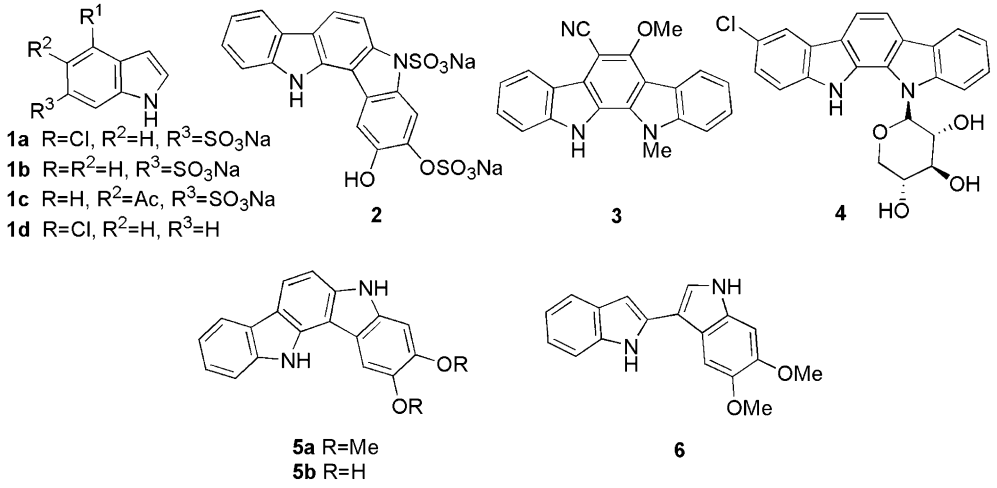

Figure 1.

Keywords: Indole; 2,3′-Biindolyls; Indolocarbazole; Vilsmeier reaction; Triflic anhydride.
* Corresponding author. Tel.: +46 8 6089206; fax: +46 8 6081501; e-mail: jabe@biosci.ki.se

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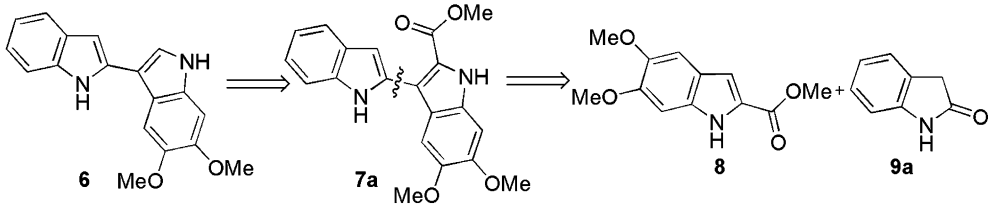
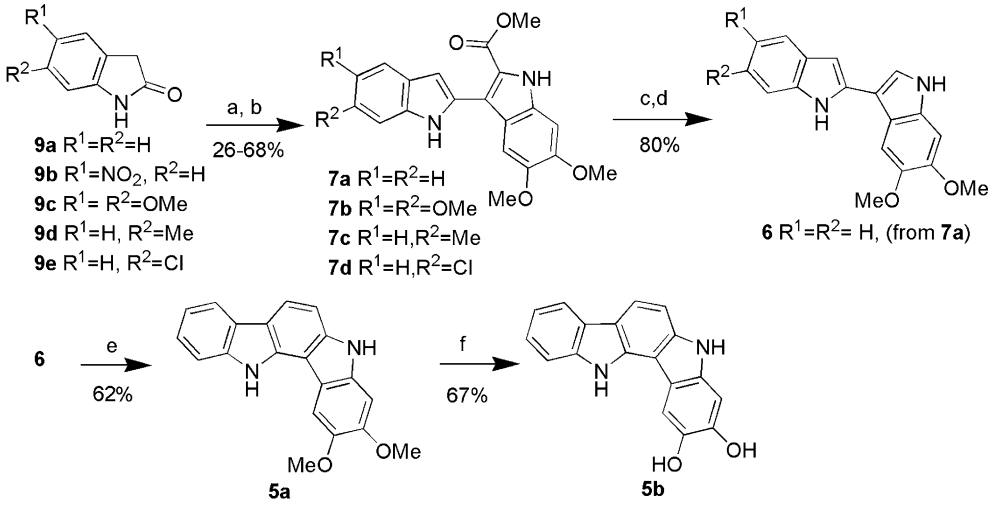
2. Results and discussion

An efficient synthesis of unsubstituted indolo[3,2-*a*]carbazole starting from 2,3′-biindolyl has been described recently by Janosik and Bergman.[9] In the key step, 2,3′-biindolyl was reacted with dimethylaminoacetaldehyde diethyl acetal in acetic acid to give the corresponding indolo[3,2-*a*]carbazole. Several synthetic approaches have been applied for the synthesis of 2,3′-biindolyls, however, none of the existing major synthetic routes,[10–15] has been applied for the required sensitive 2,3′-biindolyl precursor **6**. A retrosynthetic analysis of this molecule leads to ester **7a**, which in turn might be formed from scission of the bond between the two indole units (Scheme 1). In practice, methyl 5,6-dimethoxyindole-2-carboxylate[16] **8** and oxindole **9a** act as the two starting materials (Scheme 2). The oxindole **9a** was treated with triflic anhydride in dichloromethane, to give an intermediate with an excellent leaving group,[17] and then reacted with the indole **8**. After gentle heating, the product **7a** was isolated in 68% yield. This type of modified Vilsmeier reaction has previously been applied by Bergman and Eklund[18] and by Black and co-workers.[19–21]

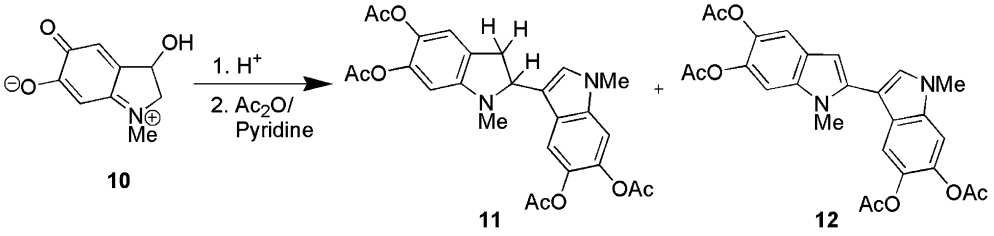
When methyl 5,6-dimethoxyindole-2-carboxylate **8** was reacted with the deactivated oxindole **9b**[22] no reaction took place. The less deactivated oxindole **9e**,[23] however, afforded the desired 2,3′-bindolyl **7d** in a moderate 41% yield. Activated oxindoles like 5,6-dimethoxyoxindole[24] **9c** and 6-methyloxindole[25] **9d** on the other hand reacted faster and in a more complex fashion than **9a** with **8** to produce **7b–c** in 26% and 32% yields. Other indoles with no activating substituent (e.g., ethyl 5-nitroindole-2-carboxylate[26] and ethyl indole-2-carboxylate) did not react satisfactorily even at elevated temperatures. When methyl 5-methoxyindole-2-carboxylate, oxindole **9a** and triflic anhydride were allowed to interact some of the desired product was formed. This substance, however, could not be obtained in an analytically pure state as an unidentified isomeric substance co-eluted and co-crystallized with the 2,3′-biindolyl obtained. The ester functionality in the biindolyl **7a** was hydrolyzed with sodium hydroxide in ethanol and the acid subsequently decarboxylated with copper in quinoline to give the sensitive 2,3′-biindolyl **6** in 80% yield after chromatography on neutral aluminium oxide. The product **6** was then cyclized with dimethylaminoacetaldehyde diethyl acetal in acetic acid.[9] Some polymerization occurred in this step, but in spite of this the yield of the indolocarbazole **5a** was 62%. In order to produce the deprotected dihydroxyindolocarbazole **5b**, compound **5a** was first demethylated using boron tribromide in dichloromethane to give crude **5b**, which was protected with *tert*-butyldimethylsilyl chloride (TBSCl) using imidazole in DMF followed by purification on neutral aluminium oxide. Deprotection of TBS-protected indolocarbazole with tetrabutylammonium fluoride (TBAF) in THF produced 2,3-dihydroxyindolo[3,2-*a*]carbazole **5b**. This molecule is highly sensitive towards oxidation under these conditions and the reaction mixture turns black within 20–30 s. Formation of molecular complexes of the



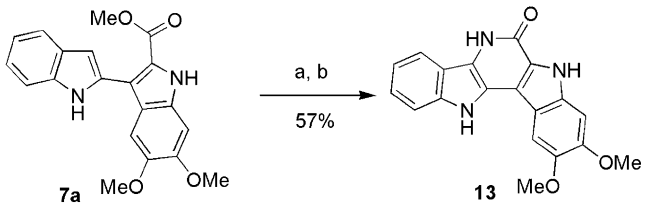
Scheme 1. Retrosynthetic analysis of 2,3′-biindolyl **6**.



Scheme 2. Reagents and conditions: (a) triflic anhydride, CH_2Cl_2, 0–21 °C; (b) compound **8**; (c) NaOH, EtOH, 78–21 °C; (d) copper, quinoline, reflux; (e) dimethylaminoacetaldehyde diethyl acetal, AcOH, reflux; (f) pyridine hydrochloride, 220 °C.



Scheme 3.



Scheme 4. Reagents and conditions: (a) $NaNO_2$, AcOH, 50–70 °C; (b) zinc, AcOH, 50–115 °C.

quinhydrone type can possibly explain the precipitation of this black coloured material. Several other conditions used for demethylation were tested on **5a** and it was found that the Prey demethylation (pyridinium hydrochloride at high temperature) gave **5b** in 67% yield.

Interestingly, Prota and co-workers isolated both trimeric and dimeric compounds during acidic transformations of the adrenochrome **10** the first isolable intermediate in the oxidation of adrenalin (Scheme 3).[27,28] The dimeric structures **11** and particularly compound **12** can potentially be prepared from the biindolyl **7b**.

In an alternative cyclization, Scheme 4, the ester **7a** was first treated with sodium nitrite in acetic acid at 50–70 °C until the starting material was consumed. In the second consecutive step the intermediate product was reduced by adding zinc powder. An aza derivative of **5a**, the bisindoleamide **13**, could be prepared in 57% yield over two steps. Interestingly, several pyridodiindole molecules related to **13** have been prepared by Cook and co-workers,[29] and these substances have been found to be high affinity ligands for the benzodiazepine receptor.[30]

In summary, we have prepared several activated 2,3′-biindolyls via a modified Vilsmeier reaction. These biindolyls may serve as precursors to indolo[3,2-*a*]carbazoles and other pentacyclic ring systems. In this study, a precursor to the marine sulfamate ancorinazole has been prepared, which will enable further chemical and biological evaluations.

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