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A Three-Component Coupling Approach to the Marine bis-Indole Alkaloids: Topsentin, Deoxytopsentin and Bromotopsentin.

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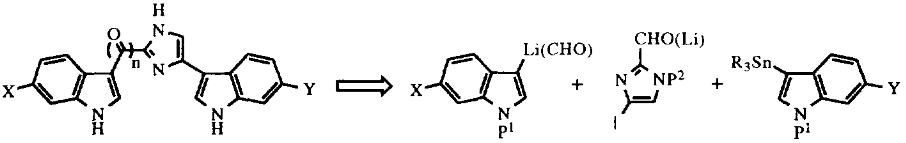
Abstract: The total syntheses of three marine bis-indole alkaloids (**1**, **2**, **4**) of the topsentin family together with the synthesis of the unnatural deoxybromotopsentin (**33**) are described. Key elements include, a 1,2-addition–oxidation sequence to construct the bis-heteroarylketones (**18**, **19**, **29**, **30**) and a Pd-catalyzed heteroarylation involving the 3-stannylindoles (**12**, **26**)

During the recent years the transition metals catalyzed cross-coupling methodology has provided versatile new routes in heterocyclic chemistry that have led to remarkable achievements in areas ranging from natural products synthesis to newly designed materials preparation.[1] In the course of synthetic studies we[2a] and others[2b] have recently reported a short route to the rare 3-(5-imidazolyl)indole derivatives based on such a methodology. With a view to extending the synthetic utility of this approach we contemplated its incorporation into a reaction sequence aimed at the total synthesis of the topsentins (**1**-**4**, Scheme1), a small group of closely related and biologically active bis-indolylimidazoles recently isolated from sponges.[3] Structurally these compounds feature a 2-acylimidazole inserted between two indole units substituted or not on the benzene rings (Scheme 1).



1 Deoxytopsentin X = Y = H, n = 1
2 Topsentin X = OH, Y = H, n = 1
3 Hydroxytopsentin X = Y = OH, n = 1
4 Bromotopsentin X = OH, Y = Br, n = 1
5 Nortopsentin D X = Y = H, n = 0

6 **7** **8**

P^1, P^2 = protecting groups

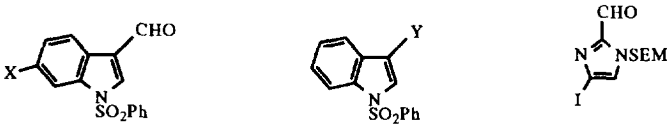
Scheme 1

Two strategically related syntheses[3b,4] of compounds **1** and **2** featuring an elegant condensation of two 3-glyoxylylindole derivatives with ammonia[3b] as the key step were recently carried out as part of the structural elucidation of these natural products.

We wish to report herein on a totally different route to these compounds which, according to obvious disconnections, relies on successive indole introduction onto a functionalized imidazole derivative (Scheme 1).

Thus, alkylation involving indole derivatives **6** and imidazoles **7** followed by oxidation of the resulting alcohol was expected to provide the required iodo-bis-heteroarylketone suitably disposed for the attachment of the second indolyl group at the site of iodine substitution through Pd-catalyzed coupling with 3-stannylindole derivatives **8**. Recently a conceptually similar approach has been used in the total synthesis of nortopsentin D[5] **5** (Scheme 1), the simplest member of this family of natural products.

The synthesis of deoxytopsentin **1** and topsentin **2** that share a common unsubstituted indolyl moiety was first attempted. To this end, the requisite 3-formylindole derivatives **9**[6] and **10**[7] as well as iodoindole **11**[8] and stannane **12**[9] (Fig. 1) were readily prepared through well-established procedures.



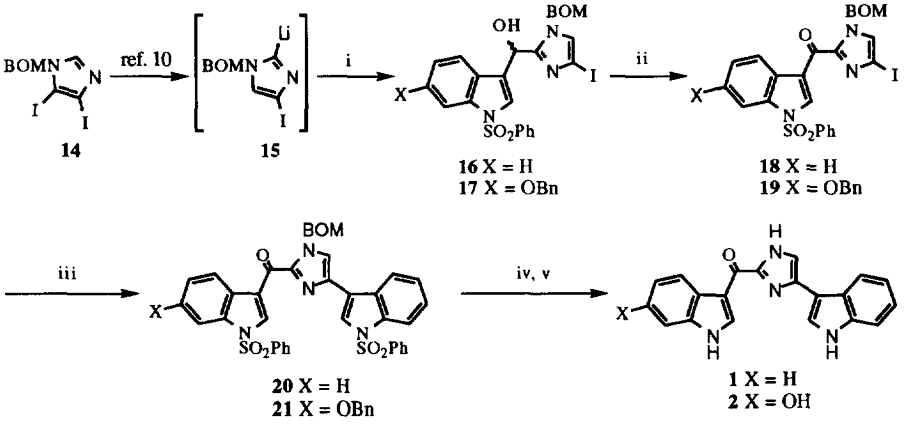
9 X = H
10 X = OBn

11 Y = I
12 Y = $SnBu_3$

13

Fig. 1

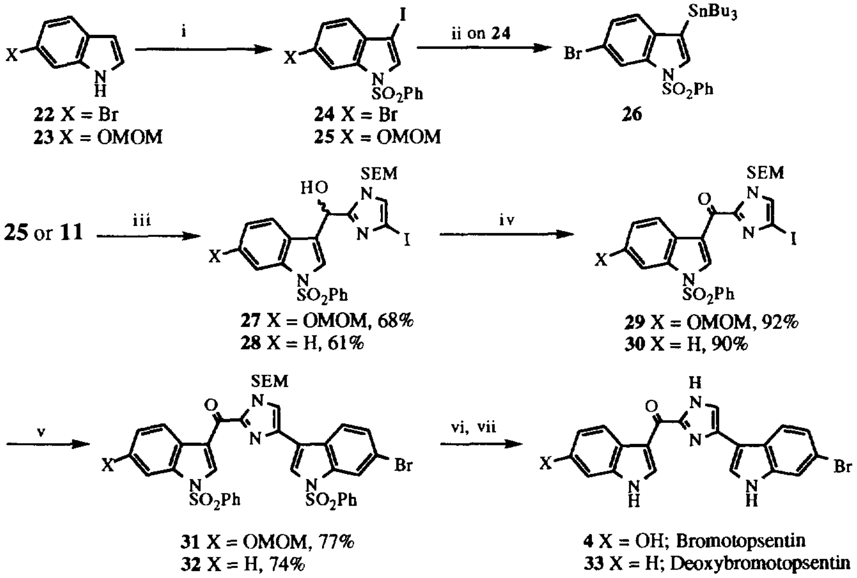
Compounds **9** and **10** were then reacted with 2-lithioimidazole **15**[10] to provide alcohols **16** and **17**, respectively.[11] Subsequent oxidation with MnO_2 in dichloromethane gave the corresponding ketones **18** and **19** in good yields. The iodides **18** and **19** were then independently subjected to cross-coupling reaction with stannane **12** in the presence of $PdCl_2(PPh_3)_2$ and CuI[12] as co-catalyst to furnish the protected topsentins **20** and **21**, in fairly good yields. Finally, compounds **20** and **21** underwent facile saponification and hydrogenolysis under standard conditions to give deoxytopsentin **1** and topsentin **2**, respectively (Scheme 2).



Scheme 2. *reagents and conditions*i) **15** (2 eq.) on **9** or **10**, THF,-78° C to 0° C, 63-84%; ii) MnO_2, CH_2Cl_2, rt, 5h, 95%; iii)**18** or **19**, $PdCl_2(PPh_3)_2$, CuI, **11**, DMF, 100° C, 2h, 76-81%; iv) 10%KOH, EtOH-THF, reflux, 2h, 86-97%; v) EtOH, $HCO_2^-NH_4^+$, 10% Pd-C, reflux, 4h, 88-96%.

Next, we addressed the synthesis of the somewhat more complex bromotopsentin **4**, which required prior formation of stannane **26**. To this end, the known 6-bromoindole **22**[13] was transformed into the bis-haloindole

24 in high yield upon iodination[14] and *N*-phenylsulfonylation. Treatment of **24** with hexabutylditin in the presence of $Pd(PPh_3)_2Cl_2$ as catalyst then furnished the required stannane **26** in good overall yield (Scheme 3). With compound **26** in hand we turned our attention to the preparation of its coupling partner, *i.e.* imidazoloindole **29**. This was readily achieved by a three step-process: metalation of the protected 6-hydroxy-3-iodoindole **25**, addition of the resulting 3-lithioindole to 2-formylimidazole **13**[15] and oxidation (Scheme 3). Indole **23**, precursor of **25**, was obtained in a straightforward manner from the methoxymethylether of 4-hydroxybenzaldehyde following Moody's procedure.[7] Cross-coupling between stannane **26** and imidazoloindole **29** under the conditions used previously provided the bis-indole derivative **30** whose deprotection proceeded efficiently to afford the natural bromotopsentin **4**. Similarly, when the coupling reaction was carried out with imidazoloindole **30**, under otherwise identical conditions, the unnatural deoxybromotopsentin **33** was obtained *via* bis-indole **32** (Scheme 3). In both cases the chemoselectivity of the cross-coupling reaction was remarkable, in agreement with the established order of reactivity.[16]



Scheme 3. *reagents and conditions*: i) KOH, I_2, DMF, rt ; workup then NaH, DMF-THF, $PhSO_2Cl$, 2h, 95%; ii) $PdCl_2(PPh_3)_2$, $(Bu_3Sn)_2$, DMF, 100° C, 30 mn, 65-71%; iii) t-BuLi/ THF/ –90°C/ 30 mn, then add **13**, warm to 0° C over 4h; iv) MnO_2, CH_2Cl_2, rt, 4h; v) **26**, $PdCl_2(PPh_3)_2$, CuI, DMF, 120° C, 2h; vi) KOH, EtOH-THF, reflux, 2h, 92-95%; vii) 5M HCl, ETOH, reflux, 3h, 68%.

In summary, a unified strategy leading to the synthesis of three topsentins[17] (*i.e.* **1**, **2** and **4**), including the first total synthesis of bromotopsentin **4**, has been developed. Noteworthy here is the target-oriented nature of our approach which avoids the random product distribution inherent in Rinehart's route[3b] toward the unsymmetrically substituted topsentin **2**. Furthermore, the versatility of the palladium-catalyzed reactions together with the high convergency of the above strategy should allow for the preparation of a range of potentially bioactive analogs.

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16. For a related example of such a selectivity, see: Yang, Y.; Martin, A. R. *Synth. Commun.* **1992**, *22*, 1757-1762.
17. Selected data: **(1)** ^1H NMR (300 MHz, 1% TFA in Me_2SO-d_6) δ 12.38 (1H, bs, NH), 11.56 (1H, bs, NH), 9.05 (1H, d, 2.5Hz), 8.37 (1H, dd, 5.2Hz, 3.5Hz), 8.08 (1H, d, 1.8Hz), 8.04 (1H, bd, 7.6Hz), 7.92 (1H, s), 7.61-7.58 (1H, m, 4.8Hz, 3.5Hz), 7.52 (1H, d, 7.4Hz), 7.33-7.30 (2H, m, 5.5Hz, 2.5Hz), 7.23 (1H, t, 7.2Hz), 7.18 (1H, t, 7.1Hz); ^{13}C NMR (75 MHz, 1% TFA in Me_2SO-d_6) δ 174.4, 143.51, 137.82, 136.66, 136.66, 133.14, 126.57, 124.66, 124.62, 123.58, 122.52, 122.10, 121.66, 120.15, 119.61, 118.83, 113.68, 112.71, 112.21, 105.46; EIHRMS calc for $C_{20}H_{14}N_4O$ ($M^{+\cdot}$) 326.1167 found 326.1169. **(2)** ^1H NMR (300 MHz, 1% TFA in Me_2SO-d_6) δ 12.14 (1H, NH, d, 2.6Hz), 11.65 (1H, NH, d, 2.4Hz), 8.85 (1H, d, 2.9Hz), 8.18 (1H, d, 8.6 Hz), 8.11 (1H, d, 2.6Hz), 8.05 (1H, d, 7.5Hz), 7.95 (1H, s), 7.53 (1H, d, 7.2Hz), 7.24 (1H, dt, 7.1Hz, 0.9Hz), 7.19 (1H, dt, 7.1Hz, 0.9Hz), 7.0 (1H, d, 1.9Hz), 6.86 (1H, dd, 8.5Hz, 2.0Hz); ^{13}C NMR (75 MHz, 1% TFA in Me_2SO-d_6) δ 174.62, 154.64, 144.05, 137.8, 136.63, 136.38, 133.36, 124.70, 124.25, 122.21, 121.97, 120.00, 119.84, 119.47, 118.07, 114.18, 112.45, 112.11, 106.07, 97.75; EIHRMS calc for $C_{20}H_{14}N_4O_2$ ($M^{+\cdot}$) 342.1110 found 342.1116. **(4)** ^1H NMR (300 MHz, 1% TFA in Me_2SO-d_6) δ 12.21 (1H, bd, NH, 3.0Hz), 11.29 (1H, bd, NH, 2.6Hz), 8.62 (1H, d, 3.1Hz), 8.12 (1H, d, 2.6Hz), 8.10 (1H, d, 8.2Hz), 8.09 (1H, s), 8.0 (1H, d, 8.5Hz), 7.73 (1H, d, 1.5Hz), 7.32 (1H, dd, 8.6Hz, 1.5Hz), 6.96 (1H, d, 1.9Hz), 6.84 (1H, dd, 8.4Hz, 2.0Hz); ^{13}C NMR (75 MHz, 1% TFA in Me_2SO-d_6) δ 172.67, 155.52, 142.41, 138.33, 137.60, 137.51, 131.5, 126.3, 123.61, 123.25, 122.22, 121.52, 119.05, 117.22, 115.13, 115.04, 114.15, 113.05, 104.45, 98.11; EIHRMS calc for $C_{20}H_{13}N_4O_2$ Br, (^{79}Br, $M^{+\cdot}$) 420.0208 found 420.0221, (^{81}Br, $M^{+\cdot}$) 422.0185 found 422.0201.

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