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A new approach to N-protected staurosporinones

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Abstract—A completely regioselective synthesis of two advanced precursors to glycosidic indolopyrrolo[2,3-*a*]carbazole alkaloids is described.

One of the major difficulties associated with the synthesis[1] of structurally interesting and biological active[2] alkaloids such as K252a (**1**) is the regiocontrol required in the glycosidation step of an advanced precursor such as **2** (Fig. 1).

Left undiscriminated to the last, the attachment of a chiral sugar moiety to a specific indolic nitrogen of **2** ($R_1 = R_2 = H$) occurs nonselectively producing regioisomers.[3,4]

Our interest in the synthesis of alkaloids such as staurosporine (**3**),[5] K252a (**1**),[6] K252d (**4**)[7] and holyrine A (**5**)[8] prompted us to examine an approach leading to a structure of type **2** (wherein the N_{12} and N_{13} are differentiated), that could serve as an appropriate precursor to the substances mentioned above (Fig. 1).

Accordingly the known urea **6**[9] derived from 2,2′-bisindole, was treated with an equivalent of potassium *tert*-butoxide in anhydrous benzene in the presence of 18-crown-6-ether to yield the *N*-Boc derivative **7a** (Scheme 1).[10] Selective iodination in the more nucleophilic indole ring was achieved from the derived indolyl anion and I_2 in DMF. Owing to its slight instability the resulting iodo bis-indole **7b** was isolated as the *N*-acetyl derivative **7c** in an overall yield of ca. 81% from **6**.

The other partner **8d**, required for a Stille reaction with **7c**, was secured from the known tetramic acid **8a**[11] by conversion first into the mesylate **8b**, followed by I^- ion exchange. The resulting iodide **8c** on reaction with Me_6Sn_2 and $Pd_2(dba)_3$[12] furnished the stannylated α,β-unsaturated imide **8d** (ca. 65% overall yield from **8a**) (Scheme 2).

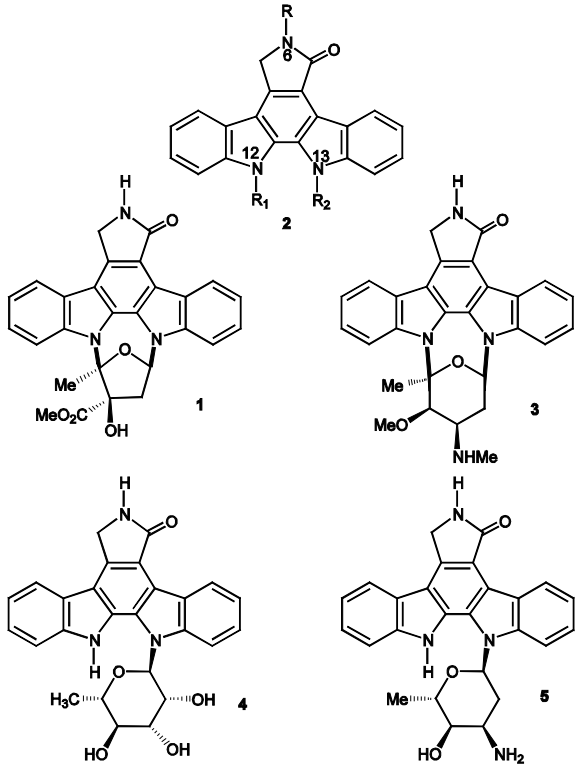

Figure 1.

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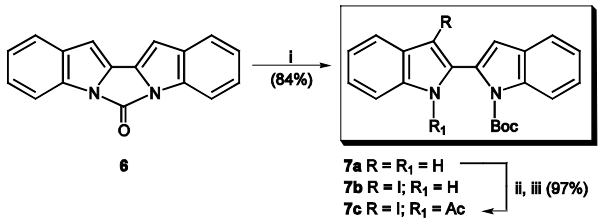
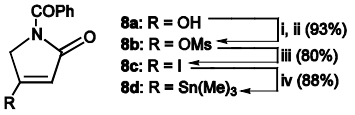


Scheme 1. Reagents and conditions: (i) *t*-BuOK, C_6H_6, crown ether, 45 min, rt; (ii) NaH, I_2, DMF, 20 min, rt; (iii) KH, Ac_2O, 4-DMAP, DMF, 20 min, rt.



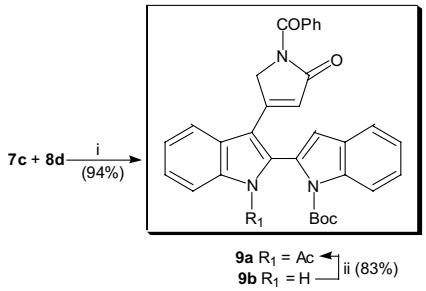
Scheme 2. Reagents and conditions: (i) NEt_3, 4-DMAP, CH_2Cl_2, t.a.; (ii) $ClSO_2Me$, 1 h, 0 °C; (iii) $BzNEt_3I$, $BF_3(OEt)_2$, CH_2Cl_2, 22 h reflux; (iv) $(Me_3Sn)_2$, Pd_2dba_3, AcOEt, 40 min, rt.

The coupling between **7c** and **8d** promoted by $Pd(PPh_3)_4$/CuCl/LiCl in degassed DMSO[13] occurred smoothly to afford an excellent yield of a mixture of **9a** and **b** (94%; 1:2 ratio as determined by ^1H NMR). Since separation into pure components proved to be difficult the mixture was reacetylated and the resulting product purified by chromatography to provide the fully protected triacyl compound **9a** (overall 78%) (Scheme 3).

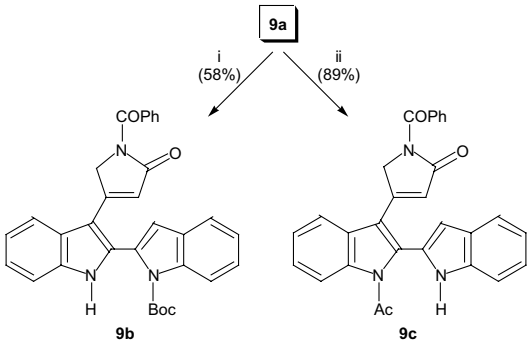
This key intermediate can be chemoselectively manipulated so as to furnish either the N_{12}-deacetyl or the N_{13}-H compounds, **9b** and **c**, respectively. Thus, whilst exposure of **9a** to KH in DMF, generated the former, ultrasonic irradiation[14] of an intimate mixture of the same with silica gel afforded the latter **9c** (Scheme 4).

All the three compounds **9a**, **b**[15] and **c**,[15] incorporating a trienic system, underwent photocyclisations to furnish the corresponding indolocarbazoles **10a**,[16,17] **b**[18] and **c** in 65%, 48% and 69% yield, respectively (Scheme 5).

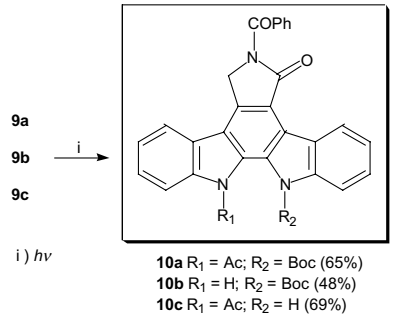
Thus the N_6,N_{13}-diacyl substituted (**10b**) or the N_6,N_{12}-protected (**10c**) staurosporinones, secured in 22 and 48% overall yields (from **9a**), respectively, are both of value in the stereocontrolled synthesis of indolocarbazole alkaloids containing either a single N-glycosidic bond or



Scheme 3. Reagents and conditions: (i) LiCl, $Pd(PPh_3)_4$, CuCl, DMSO, 19 h, rt; (ii) KH, Ac_2O, 4-DMAP, DMF, 1 h, 0 °C.



Scheme 4. Reagents and conditions: (i) KH, DMF, 1.5 h, 0 °C; (ii)))))/ SiO_2.



Scheme 5.

two such linkages. Further progress in this area will be reported elsewhere.

Acknowledgements

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10. A suspension of 1,1′-carbonyl-2,2′-bi-indole (1.5 g, 5.81 mmol, 1.0 equiv) and 18-crown-6 ether (205.0 mg), in benzene (13 mL), under argon atmosphere was stirred at rt (10 min) after which time potassium *tert*-butoxide (814.0 mg, 7.25 mmol, 1.2 equiv), was introduced. On completion of the reaction (45 min, TLC control) aq acetic acid (25 mL; 1 M) and water were added and the resulting mixture extracted with ether. The residue obtained on evaporation of the dried organic phase was chromatographed to give **7a** (1.6 g; 84%) as a colourless solid, mp 137–138 °C (ether/*n*-hexane); IR (KBr): 3377, 2980, 1708 cm^{-1}; ^1H NMR δ ($CDCl_3$): 9.08 (1H, br s, exchangeable with D_2O), 8.15 (1H, d, $J = 8.2$ Hz), 7.65 (1H, d, $J = 7.8$ Hz), 7.58 (1H, d, $J = 7.6$ Hz), 7.42 (1H, d, $J = 8.0$ Hz), 7.36 (1H, t, $J = 7.5$ Hz), 7.28 (1H, t, $J = 7.5$ Hz), 7.23 (1H, t, $J = 7.7$ Hz), 7.14 (1H, t, $J = 7.3$ Hz), 6.90 (1H, s), 6.80 (1H, s), 1.53 (9H, s) ppm. Found: C, 75.81; H, 5.91; N, 8.57 ($C_{21}H_{20}N_2O_2$ requires C, 75.88; H, 6.06; N, 8.43).
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