A rapid stereocontrolled synthesis of the 3a-hydroxy-pyrrolo-[2,3-b]indole skeleton, a building block for 10b-hydroxy-pyrazino[1′,2′:1,5]pyrrolo[2,3-b]indole-1,4-diones

Steven V. Ley,* Ed Cleator and Peter R. Hewitt

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: svl1000@cam.ac.uk; Fax: +44 (0)1223 336442; Tel: +44 (0)1223 336398

A two-step selenocyclisation–oxidative deselenation sequence was used to establish the 3a-hydroxy-pyrrolo-[2,3-b]indole core; these tricycles were used as effective precursors to 10b-hydroxy-pyrazino[1′,2′:1,5]pyrrolo-[2,3-b]indole-1,4-diones.

The 10b-hydroxy-pyrazino[1′,2′:1,5]pyrrolo[2,3-b]indole-1,4-dione core (Fig. 1) is of pharmaceutical interest. Many biologically active natural products are also based on this structure, such as the sporidesmins[1] and certain members of the brevianamide[2] and okaramine[3] families.
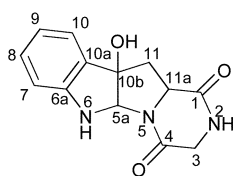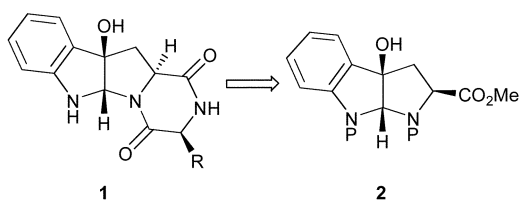

Fig. 1 The 10b-hydroxy-2,3,6,10b,11,11a-hexahydro-5aH-pyrazino-[1′,2′:1,5]-pyrrolo[2,3-b]indole-1,4-dione core.

It was envisaged that compounds such as **1** could be most efficiently prepared from tricyclic pyrroloindoles **2** (Scheme 1).

Scheme 1 Retrosynthetic approach. P = Protecting group.

Existing methods for generating compounds with the core structures of **1** or **2** have suffered from problems with poor yield and stereocontrol.[4] One notable exception was Danishefsky's dimethyldioxirane (DMDO) oxidation of tryptophan derivatives. Using this procedure, the 3a-hydroxy-pyrroloindole was produced as a single diastereomer in 42% yield over four steps from L-tryptophan (Scheme 2), following extensive substrate screening of tryptophan-derived congeners to identify the derivative most amenable to the desired oxidative cyclisation.[5]
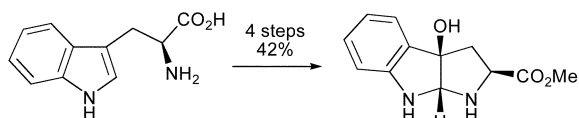

Scheme 2 Danishefsky's cyclisation using DMDO.

It was proposed that 3a-hydroxy-pyrroloindoles such as **2** should be available *via* oxidative deselenation of the corresponding 3a-phenylseleno-pyrroloindoles, which were to be obtained *via* selenocyclisation of a protected tryptophan derivative.[6] Orthogonal *N*-protecting groups were desired so that selective deprotection of the aliphatic amine could be achieved, allowing for the desired subsequent peptide coupling without participation of the indole nitrogen.

Accordingly, starting from commercially available *N*-α-Z-tryptophan **3**, esterification using thionyl chloride in methanol and subsequent indole *N*-protection with di-*tert*-butyldicarbonate (Boc₂O) proceeded uneventfully to provide the diprotected tryptophan methyl ester **4** (Scheme 3). This was subject to selenocyclisation. The success of this selenocyclisation reaction in terms of yield and stereocontrol (*exo vs. endo* products) has been found to be dependent on the particular *N*-protecting groups employed.[7] Yields up to 83% have been reported as an 11 : 1 mixture of diastereomers, with the observed kinetic bias in favour of the *exo* product; alternatively, the product can be obtained diastereopure but in a modest 40% yield. We found, however, that the present case was optimal in terms of both yield and stereocontrol, producing *exo* selenide **5** in 93% yield as a single diastereomer.

Oxidative deselenation could then be achieved. Pleasingly, treatment of **5** with an excess of wet *m*CPBA afforded the corresponding tertiary benzylic alcohol **6** in quantitative yield, presumably *via* oxidation to the selenone, elimination of benzeneseleninic acid[8] and attack of water on the carbocation thus formed. The stereochemistry of the alcohol is constrained to be the same as that of the parent selenide, owing to the necessarily *syn* [5,5] ring junction.

Removal of the Z protecting group in **6** *via* catalytic hydrogenolysis was found to proceed smoothly to afford the monoprotected diamine **7**. Attention was then turned to effecting coupling of the amine **7** with an *N*-protected amino acid. A range of coupling procedures was attempted, including the use of acid chlorides, 1-hydroxy-7-azabenzotriazole based reagents[9] and *in situ* activation of the acid to the pentafluorophenol ester; all such attempts, however, were unsuccessful. Similar problems were observed by Overman and Paone in the course of their synthesis of ditryptophenaline,[10] and it is thought that the steric environment in the neighbourhood of the free amine is too hindered for coupling to take place. However, it did prove possible to obtain an X-ray diffraction crystal structure of **7**, from which the absolute stereochemistry was proven unambiguously. †

In order to reduce the steric crowding and facilitate the necessary amide coupling, the Boc group had to be removed. Owing to the acid-sensitivity of the aminal functionality in the absence of electron-withdrawing groups, it was decided to remove the Boc group before hydrogenolysis of the Z group. Rapid protolysis with trifluoroacetic acid (TFA) gave
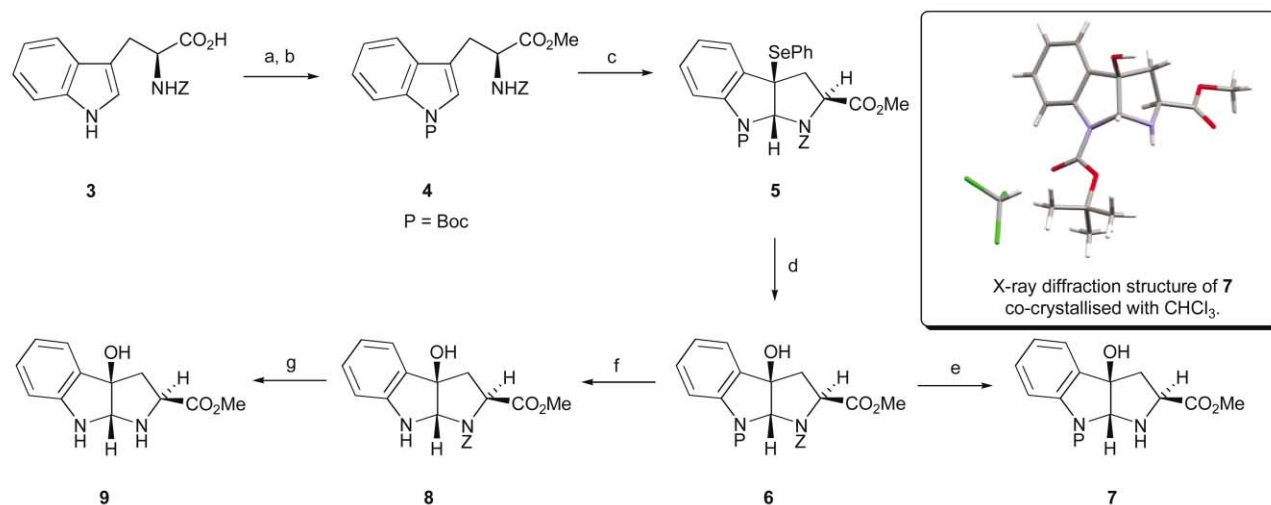
Scheme 3 *Reagents and conditions*: a) $SOCl_2$, MeOH, 100%; b) Boc_2O, NaOH, DCM, Bu_4NHSO_4, 93%; c) *N*-PSP, DCM, PPTS, Na_2SO_4, 93%; d) wet *m*CPBA 5 eq., K_2CO_3, DCM, 0–25 °C, 100%; e) H_2, Pd/C, MeOH, 79%; f) TFA/DCM, 5 minutes, 97%; g) H_2, Pd/C, MeOH, 88%.

X-ray diffraction structure of **7** co-crystallised with $CHCl_3$.

monoprotected diamine **8**, the ease of the deprotection presumably reflecting the release of steric strain. Catalytic hydrogenolysis then proceeded uneventfully affording fully deprotected diamine **9**.

Amide coupling with **9** proved to be still surprisingly problematic, presumably reflecting the steric crowding which remains at the amino position. After unsuccessful attempts with a range of standard peptide coupling conditions it was found that using the uronium salt *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) gave satisfactory results with *N*-Z-amino acids (Scheme 4).[9]
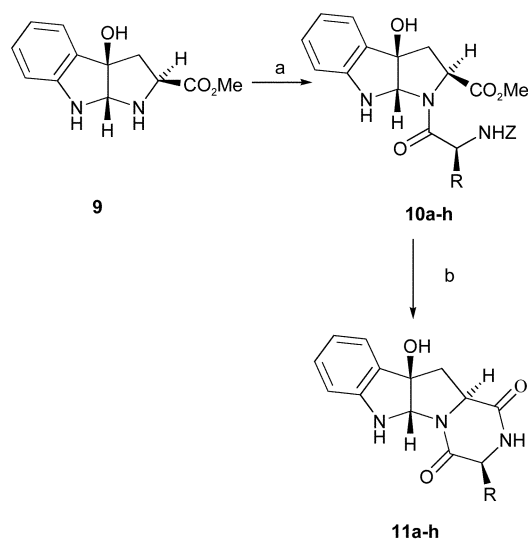
Scheme 4 *Reagents and conditions*: a) HATU 1.2 eq., NEt_3, DMF, *N*-Z-amino acid; b) H_2, Pd/C, MeOH.

The coupled products **10a–h** were purified but not characterised due to severe NMR line broadening even at elevated temperatures, with rotameric effects arising from the carbamate *N*-protecting groups and the peptide bond. Hydrogenolytic deprotection of the coupled amino acids, followed by direct cyclisation, gave the corresponding diketopiperazines **11a–h** in good to excellent yield for the three step sequence (coupling, deprotection and cyclisation, Table 1).

While *N*-Z amino acids were successfully used in preparing diketopiperazines **11**, similar attempts using *N*-Boc amino acids were unsuccessful. This is thought to be due to the incompatibility of the acid-sensitive aminal centre with the acidic conditions used for Boc deprotection. Alternative deprotection

Table 1 Diketopiperazines **11a–h** and yields over three steps

Entry	Amino acid	Yield (%)
A	Ala	56
B	Phe	75
C	Pro	51
D	Ser	63
E	*O*-TBS Ser	40
F	*O*-Bn Thr	56[a]
G	Trp	45
H	Val	66

[a] The hydrogenolysis procedure was modified by addition of ammonium acetate to suppress cleavage of the *O*-benzyl group, and the yield quoted is as an approximately 7 : 1 mixture of benzylated : debenzylated products.

conditions such as trimethylsilyl iodide in acetonitrile have, however, been used in the preparation of similar compounds.[11]

Our investigations are continuing into further functionalisation of the pyrazino-pyrroloindoles and application of this methodology to the synthesis of natural products, and will be reported in due course.

Notes and references

† Single crystals of **7** incorporating one molar equivalent of solvent were recrystallised from chloroform. *Crystal data*: $C_{18}H_{23}Cl_3N_2O_5$, $M = 453.73$, monoclinic, $a = 12.2184(6)$, $b = 6.3844(3)$, $c = 14.8429(9)$ Å, $U = 1100.68(10)$ Å^3, $T = 180(2)$ K, space group $P2(1)$, $Z = 2$, $\mu(0.71073$ Å$)$ 0.4346 mm^{-1}, 5544 reflections measured, 3372 unique ($R_{int} = 0.0389$). The final $wR(F^2)$ was 0.1757 (all data), and the absolute structure parameter was 0.04(13). CCDC reference number 215821. See http://www.rsc.org/suppdata/ob/b3/b308288a/ for crystallographic data in CIF or other electronic format.

1 E. Francis, R. Rahman, S. Safe and A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1972, 470 and other papers in the same series.
2 A. J. Birch and J. J. Wright, *Chem. Commun.*, 1969, 644.
3 K. Furutsuka, H. Hayashi and Y. Shiono, *J. Nat. Prod.*, 1999, **62**, 315; J. M. Roe, R. A. B. Webster and A. Ganesan, *Org. Lett.*, 2003, **5**, 2825.
4 Y. Fukui and M. Somei, *Heterocycles*, 2001, **55**, 2055; U. Anthoni, C. Christophersen, P. H. Nielsen, M. W. Christoffersen and

D. Sørensen, *Acta Chem. Scand.*, 1998, **52**, 958; A. Sakai, H. Tani, T. Aoyama and T. Shioiri, *Synlett*, 1998, 257.

5 T. M. Kamenecka and S. J. Danishefsky, *Chem. Eur. J.*, 2001, **7**, 41.

6 S. P Marsden, K. M. Depew and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1994, **116**, 11143.

7 D. Crich and X. Huang, *J. Org. Chem.*, 1999, **64**, 7218.

8 S. Uemura, S. Fukuzawa and A. Toshimitsu, *J. Chem. Soc., Chem. Commun.*, 1983, 1501.

9 L. A. Carpino, *J. Am. Chem. Soc.*, 1993, **115**, 4397.

10 L. E. Overman and D. V. Paone, *J. Am. Chem. Soc.*, 2001, **123**, 9465.

11 K. M. Depew, S. P. Marsden, D. Zatorska, A. Zatorski, W. G. Bornmann and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1999, **121**, 11953.