

SIMPLE SYNTHESIS OF 1,3,4,5a,6,10b,11,11a-OCTAHYDRO-2H-PYRAZINO[1',2':1,5]PYRROLO[2,3-*b*]INDOLE DERIVATIVES BASED ON 1-HYDROXYINDOLE CHEMISTRY¹

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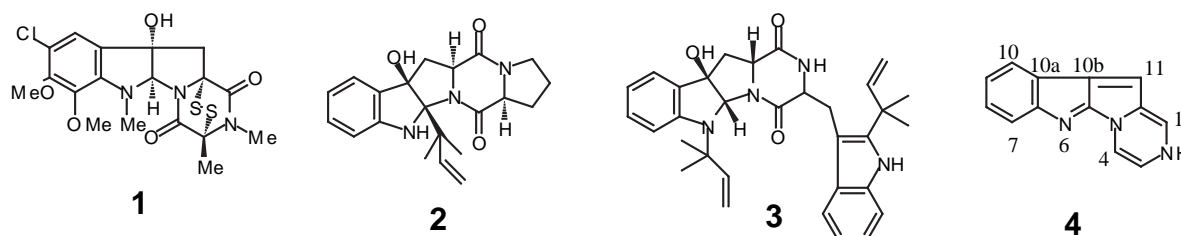
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Abstract — 3-Substituted (3*S*,6*S*)-6-(1-hydroxyindol-3-ylmethyl)-2,5-piperazine-diones are prepared for the first time. They are shown to be suitable intermediates for the synthesis of 3,10*b*-disubstituted (3*S*,5*aR*,10*bS*,11*aS*)-1,3,4,5*a*,6,10*b*,11,11*a*-octahydro-2*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4-dione derivatives.

We have been much interested in indole alkaloids such as sporidesmin B³ (**1**, Figure 1), brevianamide E⁴ (**2**), okaramine C⁵ (**3**), etc., which have 2*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole (**4**) as a common skeleton. In our hypotheses,⁶ we have speculated that biosyntheses of these indole alkaloids might occur through 1-hydroxytryptophan derivatives.

In the previous paper,⁷ we have established that pyrrolo[2,3-*b*]indoles (**7**) can be prepared in one step from the 1-acyloxy- or 1-aryloxyindoles (**5**) in accord with the speculation (Scheme 1). The mechanism is believed to proceed through initial rearrangement of the 1-acyloxy- or 1-aryloxy group to the 3-position of indole nucleus, followed by the nucleophilic addition of the *Nb*-side chain to the resultant imine carbon atom of **6**. In order to explore the scope of these findings, we have attempted in this communication a model reaction for the synthesis of core structure of **1–3**.

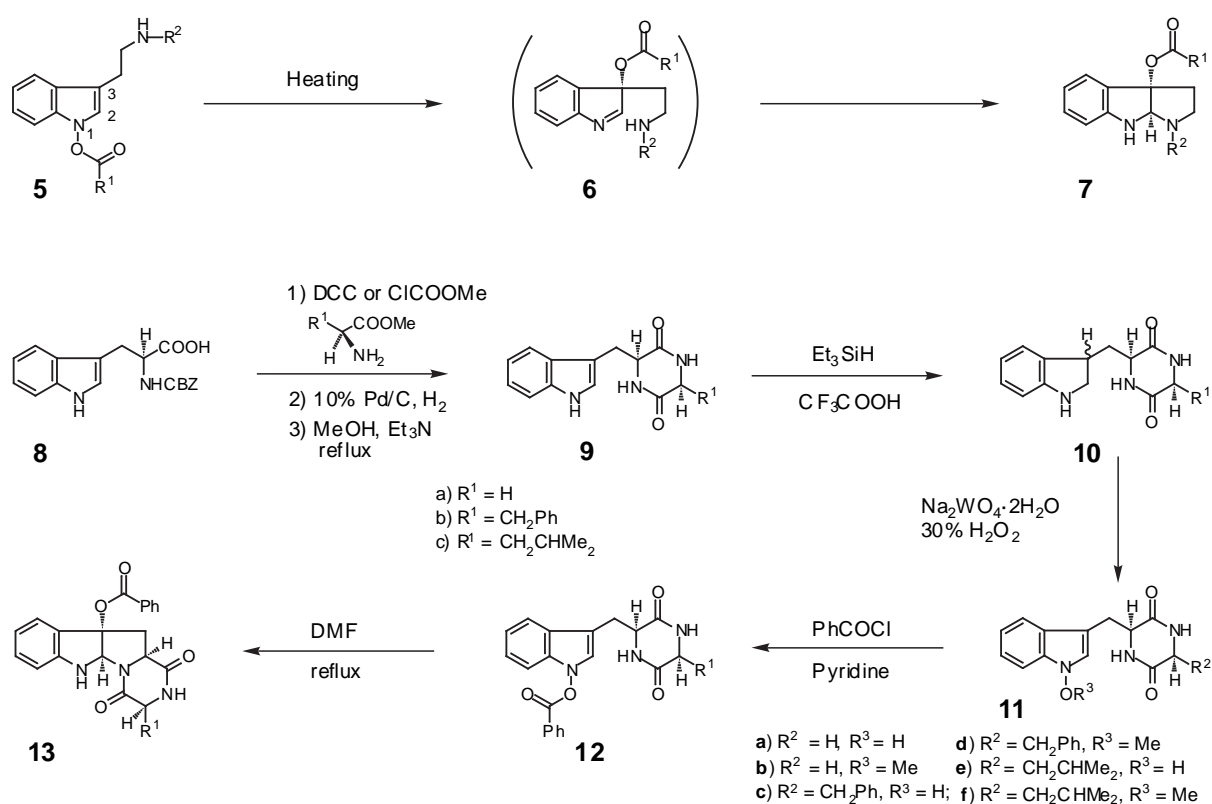
Figure 1



First of all, 2,5-piperazinedione derivatives (**9a–c**) were prepared from (+)-*N*-benzyloxycarbonyl-L-tryptophan [(+)-**8**] according to the reported procedures.⁸ The compound [(+)-**9a**]^{8a} was prepared by the following sequence of reactions; 1) condensation of (+)-**8** with glycine methyl ester in the presence of DCC, 2) catalytic hydrogenation of the resultant amide to remove the protecting benzyl group,^{8b} 3) cyclization of the resultant dipeptide to 2,5-piperazinedione by heating in MeOH-Et₃N at reflux. The condensations of (+)-**8** with L-phenylalanine methyl ester^{8c} and L-leucine methyl ester^{8d} were conducted by mixed anhydride method with methyl chloroformate. Catalytic hydrogenation of both products over 10% Pd/C, followed by

cyclization in refluxing MeOH afforded (–)-**9b**^{8c} and (+)-**9c**^{8d,e} in 86 and 46% yields, respectively. Reduction of (+)-**9a**, (–)-**9b**, and (+)-**9c** with Et₃SiH in TFA⁹ afforded 1:1 mixtures of diastereomers (**10a**), (**10b**), and (**10c**) in 74, 96, and 83% yields, respectively. Application of our 1-hydroxyindole synthetic method to **10a** encountered with a solubility problem. To overcome the problem, a mixed solvent, DMF-MeOH-H₂O, was chosen. Consequently, oxidation of **10a** with Na₂WO₄·2H₂O and 30% H₂O₂,⁶ followed by methylation with CH₂N₂ produced 1-methoxyindole derivative [(+)-**11b**] in 53% yield. However, attempts to isolate **11a** after oxidation process were unsuccessful mainly because of its insolubility to almost all organic solvents.

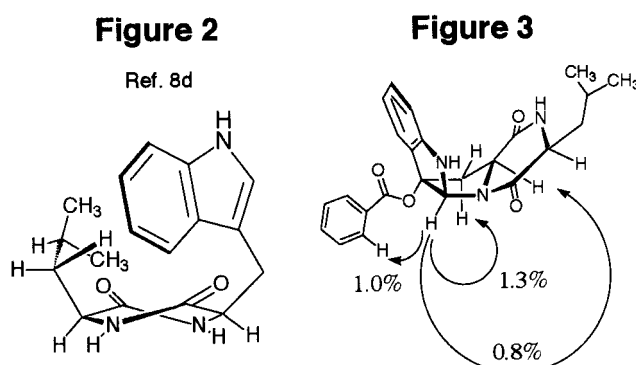
Scheme 1



In contrast to the case of **11a**, the desired (3*S*,6*S*)-(–)-6-(1-hydroxyindol-3-ylmethyl)-3-benzyl- [(–)-**11c**] and -3-isobutyl-2,5-piperazinedione [(–)-**11e**] were isolated smoothly in 78 and 63% yields, respectively, by the oxidation of **10b** and **10c** with Na₂WO₄·2H₂O and 30% H₂O₂ in CH₂Cl₂-MeOH-H₂O. The structures were proved by converting them to the corresponding 1-methoxyindoles [(–)-**11d**] and [(–)-**11f**] in 78 and 93% yields, respectively, by the reaction with CH₂N₂.

Subsequent benzylation of 1-hydroxy group of (–)-**11c** and (–)-**11e** with benzoyl chloride provided (–)-**12b** and (–)-**12c** in 77 and 96% yields, respectively. Compound [(+)-**9c**] is concluded to take the conformation as shown in Figure 2 in solution.^{8d} Therefore, the rearrangement of 1-benzoyloxy group was expected to proceed stereoselectively. In fact, heating (–)-**12c** in DMF at reflux produced (3*S*,5*aR*,10*bS*,11*aS*)-(–)-10*b*-benzoyloxy-3-isobutyl-1,3,4,5*a*,6,10*b*,11,11*a*-octahydro-2*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4-dione [(–)-**13c**] as a sole product in 37% yield. The structure of (–)-**13c** was determined by spectral data, and its stereochemistry was confirmed by the nOe experimental results in ¹H-NMR

spectroscopy as shown in Figure 3. Under similar reaction conditions, (-)-**12b** afforded two products, which are considered to be stereoisomers at the 5a- and 10b-positions. Their structural determinations are now in progress. With the success in the above model experiment in hand, further efforts towards synthesis of the related alkaloids are under investigation.



REFERENCES AND NOTES

1. a) This is Part 110 of a series entitled "The Chemistry of Indoles". b) Part 109: F. Yamada, M. Tamura, A. Hasegawa, and M. Somei, *Chem. Pharm. Bull.*, submitted. c) All new compounds gave satisfactory spectral and elemental analysis data. **11b**, mp 213—214°C, $[\alpha]_D^{20} +4.2^\circ$ ($c=0.30$, DMF); **11c**, mp 248—251°C (decomp), $[\alpha]_D^{29} -153^\circ$ ($c=0.30$, DMF); **11d**, mp 273—278°C (decomp), $[\alpha]_D^{26} -154^\circ$ ($c=0.30$, DMF); **11e**, oil, $[\alpha]_D^{29} -46.6^\circ$ ($c=0.30$, DMF); **11f**, mp 200—202°C, $[\alpha]_D^{26} -47.5^\circ$ ($c=0.30$, DMF); **12b**, oil, $[\alpha]_D^{21} -95.1^\circ$ ($c=0.30$, DMF); **12c**, oil, $[\alpha]_D^{26} -8.2^\circ$ ($c=0.29$, MeOH); **13c**, oil, $[\alpha]_D^{22} -438^\circ$ ($c=0.20$, MeOH).
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