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

Yoshikazu Fukui[2] and Masanori Somei*

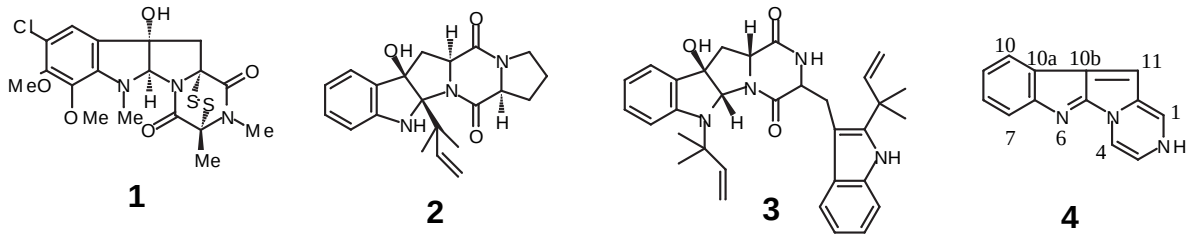
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract — 3-Substituted (3*S*,6*S*)-6-(1-hydroxyindol-3-ylmethyl)-2,5-piperazinediones are prepared for the first time. They are shown to be suitable intermediates for the synthesis of 3,10b-disubstituted (3*S*,5a*R*,10b*S*,11a*S*)-1,3,4,5a,6,10b,11,11a-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 B[3] (**1**, Figure 1), brevianamide E[4] (**2**), okaramine C[5] (**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 *N*b-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 synthsesis of core structure of **1**–**3**.

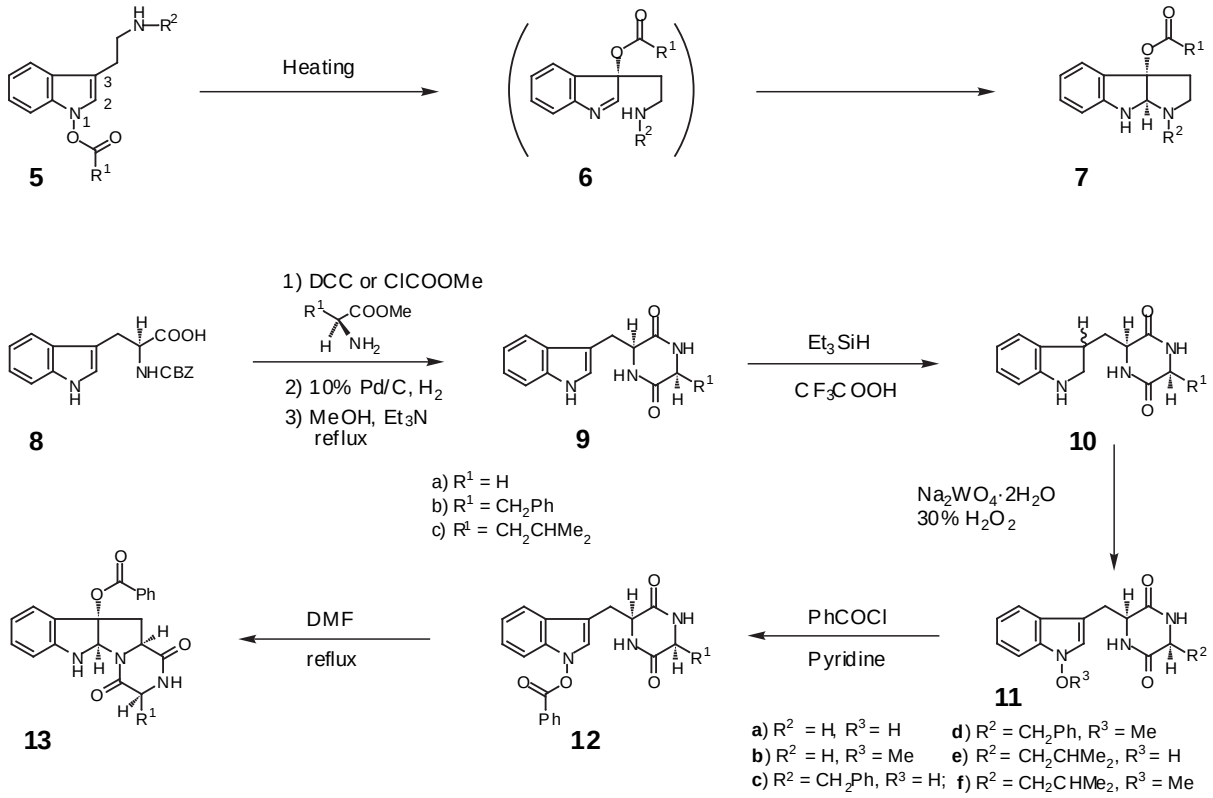
Figure 1



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-Et_3N 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 Et_3SiH in TFA[9] 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-H_2O, was chosen. Consequently, oxidation of **10a** with $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2,[6] followed by methylation with CH_2N_2 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 $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2 in CH_2Cl_2-MeOH-H_2O. 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 CH_2N_2.

Subsequent benzoylation 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*,5a*R*,10b*S*, 11a*S*)-(–)-10b-benzoyloxy-3-isobutyl-1,3,4,5a,6,10b,11,11a-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 ^{1}H-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.

Figure 2

Ref. 8d

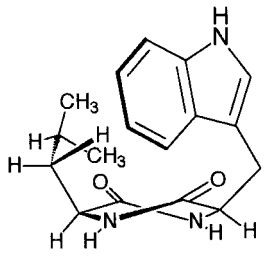
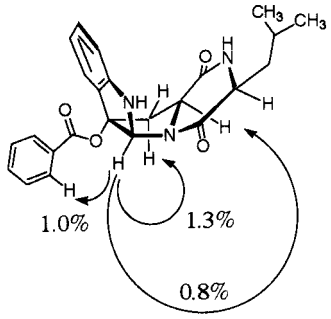


Figure 3



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° (*c*=0.30, DMF); **11c**, mp 248—251°C (decomp), [α] &$_D^{29}$–153° (*c*=0.30, DMF); **11d**, mp 273—278°C (decomp), $[\alpha]_D^{26}$ –154° (*c*=0.30, DMF); **11e**, oil, $[\alpha]_D^{29}$ –46.6° (*c*=0.30, DMF); **11f**, mp 200—202°C, $[\alpha]_D^{26}$ –47.5° (*c*=0.30, DMF); **12b**, oil, $[\alpha]_D^{21}$ –95.1° (*c*=0.30, DMF); **12c**, oil, $[\alpha]_D^{26}$ –8.2° (*c*=0.29, MeOH); **13c**, oil, $[\alpha]_D^{22}$ –438° (*c*=0.20, MeOH).
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