

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 chemistry

メタデータ	言語: eng 出版者: 公開日: 2017-10-03 キーワード (Ja): キーワード (En): 作成者: メールアドレス: 所属:
URL	http://hdl.handle.net/2297/4364

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 CHEMISTRY¹

Yoshikazu Fukui² and Masanori Somei*

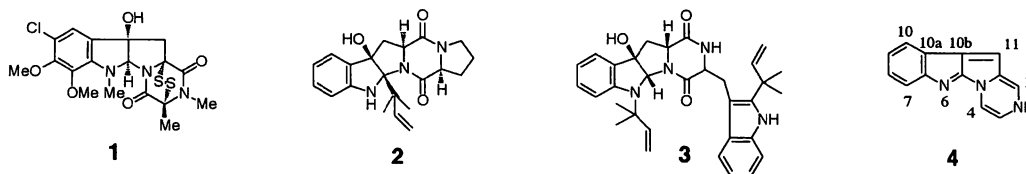
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract — 3-Substituted (3*S*,6*S*)-6-(1-hydroxyindol-3-ylmethyl)-2,5-piperazine-diones 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 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**.

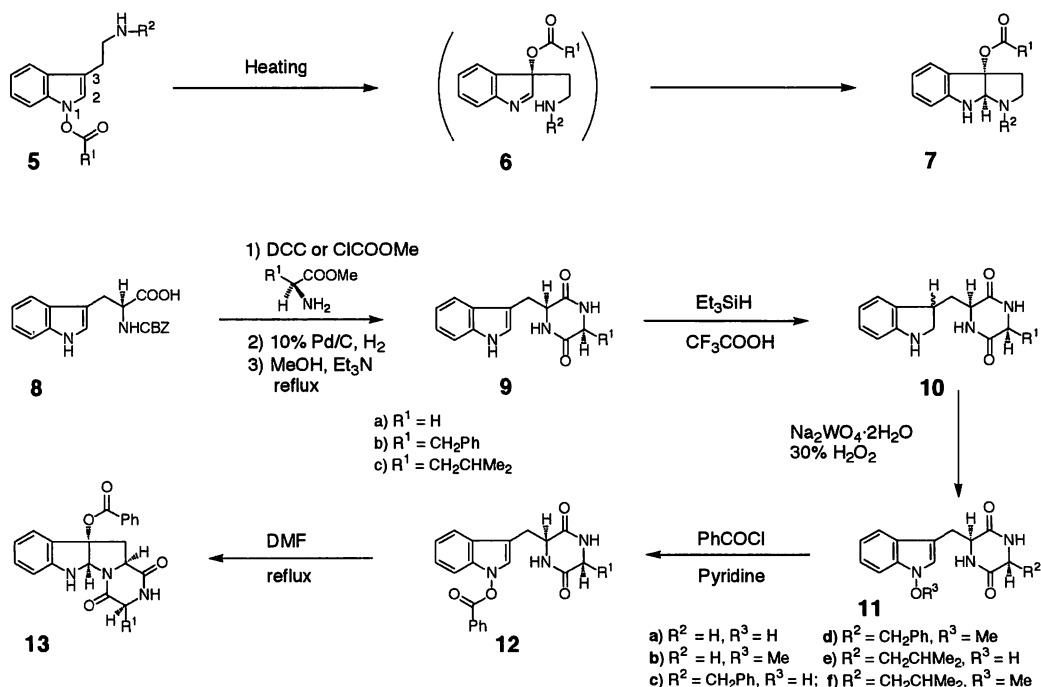
Figure 1



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 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*,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.

Figure 2

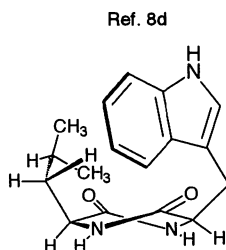
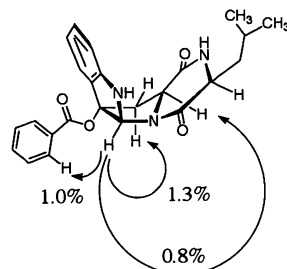


Figure 3



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, $[\alpha]_D^{20} +4.2^\circ$ ($c=0.30$, 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).
2. Present address: Discovery Research Laboratories, Shionogi & Co., Ltd., 12-4 Sagisu 5-chome, Fukushima-ku, Osaka 553-0002, Japan
3. S. Safe and A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1972, 427.
4. A. J. Birch and J. J. Wright, *Tetrahedron*, 1970, **26**, 2329.
5. H. Hayashi, T. Fujiwara, S. Murao, and M. Arai, *Agric. Biol. Chem.*, 1991, **55**, 3143.
6. Review; M. Somei, *J. Synth. Org. Chem. Jpn.*, 1991, **49**, 205; F. Yamada, Y. Fukui, D. Shinmyo, and M. Somei, *Heterocycles*, 1993, **36**, 99; M. Somei and Y. Fukui, *ibid.*, 1993, **36**, 1859; F. Yamada, D. Shinmyo, and M. Somei, *ibid.*, 1994, **38**, 273; M. Hasegawa, M. Tabata, K. Satoh, F. Yamada, and M. Somei, *ibid.*, 1996, **43**, 2333; Review: M. Somei, *ibid.*, 1999, **50**, 1157. See also reference 7.
7. M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles*, 1992, **34**, 1877.
8. a) K. Hoffmann, M. E. Woolner, G. Spühler, and E. T. Schwartz, *J. Am. Chem. Soc.*, 1958, **80**, 1486; b) catalytic reduction over Pd/C: G. P. Slater, *Chem. Ind.*, 1969, (32), 1092; c) H. Zahn and D. Brandenburg, *Ann. Chem.*, 1966, **692**, 220; d) T. Shiba and K. Nunami, *Tetrahedron Lett.*, 1974, 509; e) D. E. Nitecki, B. Halpern, and J. W. Westley, *J. Org. Chem.*, 1968, **33**, 864.
9. A. E. Lanzilotti, R. Littell, W. J. Fanshawe, T. C. McKenzie, and F. M. Lovell, *J. Org. Chem.*, 1979, **44**, 4809.

Received, 3rd September, 2001