

HETEROCYCLES, Vol. 67, No. 1, 2006, pp. 129 - 134. © The Japan Institute of Heterocyclic Chemistry
Received, 1st August, 2005, Accepted, 9th September, 2005, Published online, 13th September, 2005. COM-05-S(T)57

SYNTHESIS OF OPTICALLY ACTIVE METHYL 1,2,3,3a,8,8a-HEXAHYDROPYRROLO[2,3-*b*]INDOLE-2-CARBOXYLATES HAVING A HALOGEN OR AN OXYGEN FUNCTIONAL GROUP AT THE 3a-POSITION¹

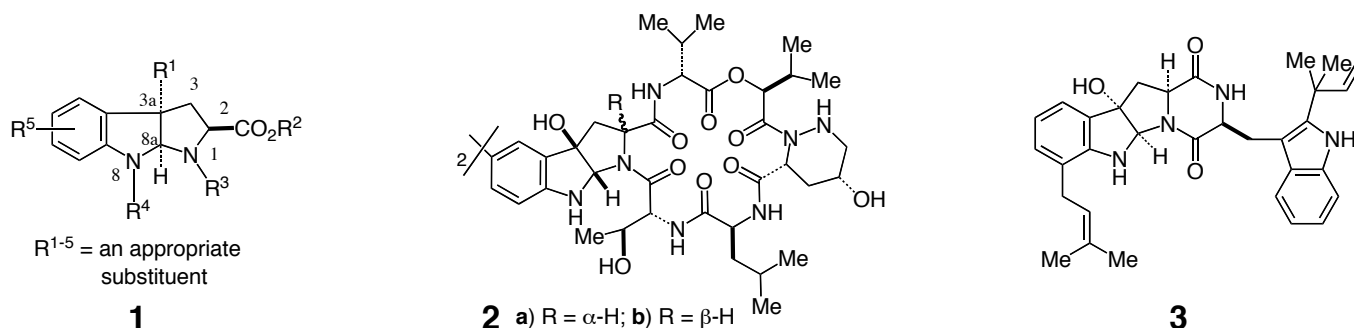
Fumio Yamada, Yoshikazu Fukui, Takako Iwaki, Sachiko Ogasawara,
Masaki Okigawa, Satomi Tanaka, and Masanori Somei*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and
Technology, Kanazawa University, Kakuma-machi, Kanazawa, 920-1192, Japan
e-mail address: somei@mail.p.kanazawa-u.ac.jp

Abstract – A simple and new method for the preparation of optically active methyl 3a-chloro-, 3a-bromo-, 3a-hydroxy-, and 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates has been developed.

We have been engaged in finding a simple method for the preparation of optically active methyl 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates having an oxygen functional group at the 3a-position as shown in general formula (**1**, Figure 1). Once the compounds (**1**) became available, creation of our original biologically active lead compounds² would be possible.

Figure 1



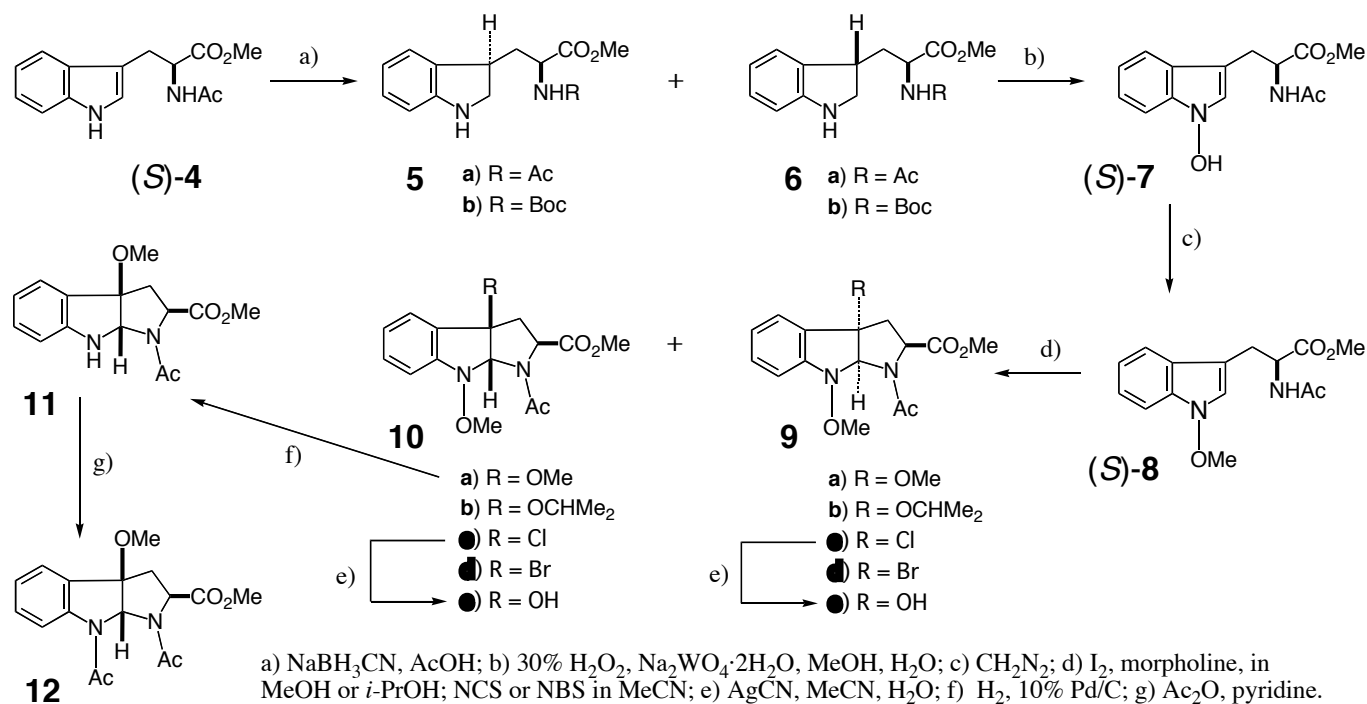
In the previous communication,^{1c} we reported the discovery of a simple synthetic method for 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles directly from 1-methoxy-*N*b-methoxycarbonyltryptamine by the reaction with iodine-morpholine in alcoholic solvent. Based on the results and further examinations of reaction conditions, we have now succeeded in the first preparation of optically active,

methyl 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates having a halogen or an oxygen functional group at the 3a-position, which would be useful synthetic intermediates for the total synthesis of 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole alkaloids such as himastatin³ (**2a**), *iso*-himastatin³ (**2b**), (+)-okaramine J⁴ (**3**), and so on.⁵

Reduction of *N*b-acetyl-L-tryptophan methyl ester (**4**, Scheme 1) with NaBH₃CN in AcOH gave *N*b-acetyl-2,3-dihydro-L-tryptophan methyl esters (**5a** and **6a**) in 68% yield as a mixture of diastereomers in a ratio of 1.4:1. These diastereomers (**5a** and **6a**) were easily separated with high performance liquid chromatography (HPLC). Their stereochemistries were determined as shown in Scheme 1 comparing each ¹H-NMR spectrum with the known set of diastereomers of *N*b-*tert*-butoxycarbonyl-2,3-dihydro-L-tryptophan methyl ester (**5b** and **6b**) determined by Van Vranken's group.⁶

Oxidation of **5a** and **6a** was successfully carried out with 30% H₂O₂ in the presence of a catalytic amount of Na₂WO₄·2H₂O⁷ producing *N*b-acetyl-1-hydroxy-L-tryptophan methyl ester ((*S*)-**7**) in 69 and 67% yields, respectively. Similar oxidation of the mixture of diastereomers (**5a** and **6a**) without separation gave (*S*)-**7** in 69% yield as reported previously.⁸ Subsequent treatment of (*S*)-**7** with an excess ethereal CH₂N₂ yielded *N*b-acetyl-1-methoxy-L-tryptophan methyl ester ((*S*)-**8**) in 94% yield.⁸ Optical purity of (*S*)-**8** was established to be more than 99% ee by its analysis using chiral column chromatography.

Scheme 1



With (*S*)-**8** in hand, various reaction conditions for converting it into optically active methyl 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates (**9** and **10**) were thoroughly examined. As a

result, treatment of (*S*)-**8** with iodine-morpholine in an alcoholic solvent was found to give the best results among the examined reagent systems such as bromine, bromine-NaOAc, 4-dimethylaminopyridinium tribromide, NIS, iodine-triethylamine, iodine-K₂CO₃, iodine-NaHCO₃, iodine-pyridine, iodine-NaI, iodine-NH₄Cl, and iodine only. Based on these results, (*S*)-**8** was treated with iodine (10 mol eq.) and morpholine (3 mol eq.) in MeOH at room temperature for 2 h resulting in the formations of (2*S*,3*aS*,8*aS*)-(**9a**) and (2*S*,3*aR*,8*aR*)-methyl 1-acetyl-1,2,3,3*a*,8,8*a*-hexahydro-3*a*,8-dimethoxypyrrolo[2,3-*b*]indole-2-carboxylates (**10a**) in 6 and 48% yields, respectively.^{1c} When isopropyl alcohol was employed as a solvent, corresponding **9b** and **10b** were obtained in 6 and 34% yields, respectively.

On the other hand, treatment of (*S*)-**8** with NCS (1 mol eq.) in MeCN at room temperature provided (2*S*,3*aS*,8*aS*)- (**9c**) and (2*S*,3*aR*,8*aR*)-methyl 1-acetyl-3*a*-chloro-1,2,3,3*a*,8,8*a*-hexahydro-8-methoxypyrrolo[2,3-*b*]indole-2-carboxylates (**10c**) in 42 and 42% yields, respectively. When NBS (1 mol eq.) was employed in MeCN, (2*S*,3*aS*,8*aS*)- (**9d**) and (2*S*,3*aR*,8*aR*)-methyl 1-acetyl-3*a*-bromo-8-methoxy-1,2,3,3*a*,8,8*a*-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates (**10d**) were produced in 8 and 81% yields, respectively.

We next tried to obtain optically active 3*a*-hydroxy compounds (**9e** and **10e**) from **9c** and **10c** and found the treatment with AgCN in MeCN-H₂O was superior to AgNO₃ in MeCN-H₂O producing (2*S*,3*aS*,8*aS*)-(**9e**) and (2*S*,3*aR*,8*aR*)-methyl 1-acetyl-3*a*-hydroxy-8-methoxy-1,2,3,3*a*,8,8*a*-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates (**10e**) in 52 and 51% yields, respectively.

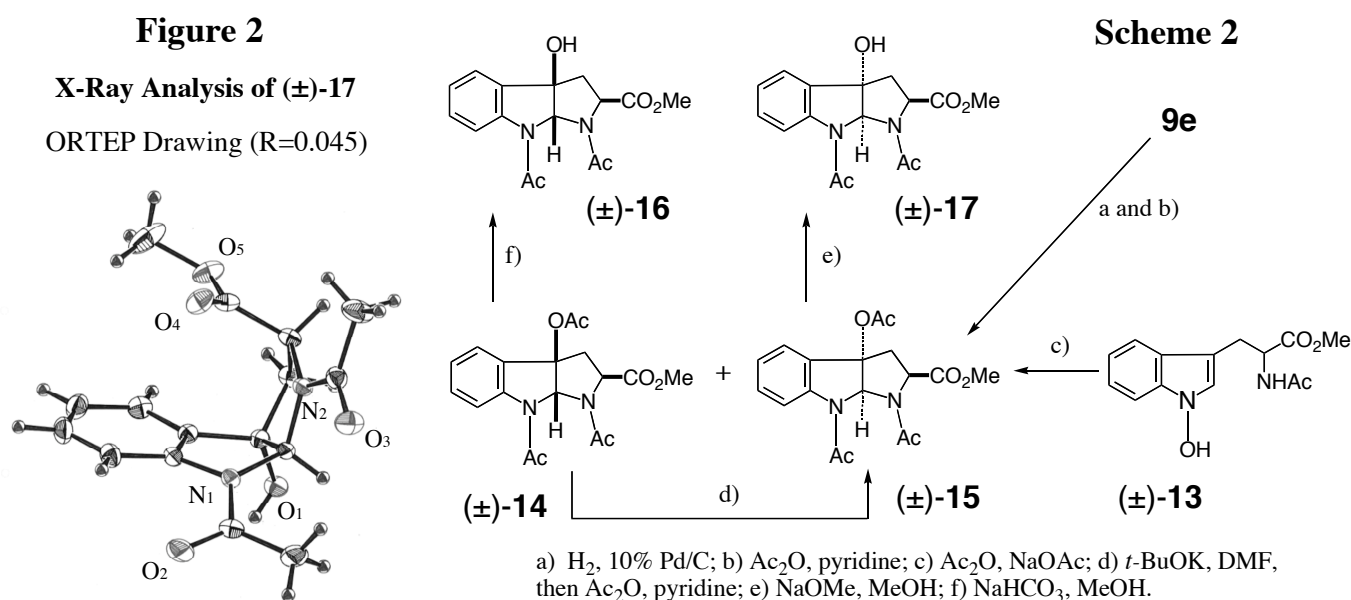
The stereochemistries of **9a—e** and **10a—e** were deduced based on the ¹H-NMR spectral data. Thus, the methyl proton in the 2-methoxycarbonyl group of **9a—e** appeared at higher magnetic field by ca. 0.20—0.24 ppm than that of **10a—e** showing the methyl group is located above the benzene ring and the protons feel the shielding effect of π -electron ring currents.

In order to obtain unequivocal proof for the above structures, the following sequence of reactions were carried out. First, **9e** was hydrogenated with 1 atm hydrogen in the presence of 10% Pd/C at room temperature, and subsequent treatment of the product with acetic anhydride provided 78% overall yield of (2*S*,3*aS*,8*aS*)-**15** (Scheme 2). Similarly, **10a** was hydrogenated with 1 atm hydrogen to (2*S*,3*aR*,8*aR*)-**11** in 97% yield in the presence of 10% Pd/C at room temperature, and subsequent acetylation of (2*S*,3*aR*,8*aR*)-**11** with acetic anhydride provided 78% yield of (2*S*,3*aR*,8*aR*)-**12**.

On the other hand, ($\pm$)-*Nb*-acetyltryptophan methyl ester⁸ (($\pm$)-**13**) was converted to ($\pm$)-methyl 3*a*-acetoxy-1,8-diacetyl-1,2,3,3*a*,8,8*a*-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates (($\pm$)-**14** and ($\pm$)-**15**) in 21 and 23% yields, respectively, by the reaction with Ac₂O at 120°C in the presence of NaOAc. Isomerization of ($\pm$)-**14** to thermodynamically stable ($\pm$)-**15** occurred easily in 51% yield by the treatment with *t*-BuOK in DMF, followed by acetylation with Ac₂O. Subsequent hydrolysis of the 3*a*-acetoxy group of ($\pm$)-**14** and ($\pm$)-**15** with either NaHCO₃ or NaOMe in MeOH provided ($\pm$)-methyl 1,8-diacetyl-3*a*-

hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates (($\pm$)-**16** and ($\pm$)-**17**) in 84 and 96% yields, respectively. Luckily, ($\pm$)-**17** became suitable prisms for X-Ray single crystallographic analysis.⁹ The results shown in Figure 2 clearly proved the structure and the presence of the methyl moiety in the 2-methoxycarbonyl group above the benzene ring, which is responsible for the appearance of the methyl proton at higher magnetic field by ca. 0.2 ppm than that of ($\pm$)-**16** in their ¹H-NMR spectra. Consequently, stereochemistry of the 8a-proton and the 2-methoxycarbonyl group in ($\pm$)-**16** and ($\pm$)-**17** are proved to be *cis* and *trans*, respectively.

The ¹H-NMR spectrum and TLC behavior of ($\pm$)-**15** were identical with those of optically active (2*S*,3*aS*,8*aS*)-**15** derived from (2*S*,3*aS*,8*aS*)-**9e**.



In conclusion, we have established simple synthetic method for optically active methyl 3a-halogeno-, 3a-hydroxy-, and 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates. Evaluations of their biological activity and potential as synthetic intermediates for natural products are now in progress.

ACKNOWLEDGMENT

This work is supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, which is gratefully acknowledged.

REFERENCES AND NOTES

- a) Dedicated to the 65th birthday of Prof. Barry M. Trost; b) This report is Part 126 of a series entitled "The Chemistry of Indoles"; c) Part 125: T. Iwaki, F. Yamada, S. Funaki, and M. Somei,

Heterocycles, 2005, **65**, 1811; d) All new compounds gave satisfactory spectral and elemental analysis or high-resolution MS spectral data for crystals or oils, respectively. **5a**) oil; $[\alpha]_D^{28} +79.1^\circ$ ($c=0.261$, CHCl_3); **6a**) oil; $[\alpha]_D^{27} -20.3^\circ$ ($c=0.209$, CHCl_3); **7**) mp $115-117^\circ\text{C}$; $[\alpha]_D^{24} +11.8^\circ$ ($c=0.102$, MeOH);⁸ **8**) oil; $[\alpha]_D^{20} +16.8^\circ$ ($c=0.107$, MeOH);⁸ **9a**) mp $129-130^\circ\text{C}$; $[\alpha]_D^{29} +45.5^\circ$ ($c=0.302$, CHCl_3); **9b**) oil; $[\alpha]_D^{30} +15.2^\circ$ ($c=0.211$, CHCl_3); **9c**) mp $113-114^\circ\text{C}$; $[\alpha]_D^{29} +5.9^\circ$ ($c=0.314$, CHCl_3); **9d**) oil; $[\alpha]_D^{28} +1.2^\circ$ ($c=0.174$, CHCl_3); **9e**) oil; $[\alpha]_D^{29} +37.6^\circ$ ($c=0.344$, CHCl_3); **10a**) mp $123-124^\circ\text{C}$; $[\alpha]_D^{30} -167.2^\circ$ ($c=0.301$, CHCl_3); **10b**) oil; $[\alpha]_D^{28} -131.3^\circ$ ($c=0.166$, CHCl_3); **10c**) mp $114-115^\circ\text{C}$; $[\alpha]_D^{30} -105.3^\circ$ ($c=0.314$, CHCl_3); **10d**) oil; $[\alpha]_D^{29} -66.9^\circ$ ($c=0.331$, CHCl_3); **10e**) oil; $[\alpha]_D^{28} -110.7^\circ$ ($c=0.317$, CHCl_3); **11**) mp $192-193^\circ\text{C}$; $[\alpha]_D^{27} -261.9^\circ$ ($c=0.320$, CHCl_3); **12**) oil; $[\alpha]_D^{30} -36.1^\circ$ ($c=0.329$, CHCl_3); **14**) mp $156-157^\circ\text{C}$; **15**) mp $130-132^\circ\text{C}$; (2*S*,3*aS*,8*aS*)-**15**) oil; $[\alpha]_D^{30} +112.5^\circ$ ($c=0.275$, CHCl_3); **16**) mp $239-240^\circ\text{C}$; **17**) mp $274-275^\circ\text{C}$; e) Enantiomer excess (ee) of compounds **9a—e** and **10a—e** were determined to be more than 99% based on their $^1\text{H-NMR}$ (500 MHz) spectra using shift reagent ((+)-Eu-DPPM) comparing with the corresponding ($\pm$)-compounds.

- Our new lead compounds for cerebral infarction and myocardial infarction: JP Patent 157475 (1996) [*Chem. Abstr.*, 1996, **125**, 195426y]; JP Patent 31257 (1991) [*Chem. Abstr.*, 1991, **114**, 247138a]. New compounds for osteoporosis: JP Patent 2004-64408, applied March, 2004; JP Patent 2005-209753, applied July, 2005. New compounds for ED (erectile dysfunction): JP Patent 2004-280104, applied Sept. 2004; JP Patent 2002-255963 (2001) [*Chem. Abstr.*, 2002, **137**, 217126c].
- K. S. Lam, G. A. Hesler, J. M. Mattel, S. W. Mamber, and S. Forenza, *J. Antibiot.*, 1990, **43**, 956; J. E. Leet, D. R. Schroeder, B. S. Krishnan, and J. A. Matson, *ibid.*, 1990, **43**, 961.
- Y. Shiono, K. Akiyama, and H. Hayashi, *Biosci. Biotechnol. Biochem.*, 2000, **64**, 103.
- Our attempt to synthesize the related alkaloid applying 1-hydroxyindole chemistry: Y. Fukui and M. Somei, *Heterocycles*, 2001, **55**, 2055.
- T. D. Dinh and D. L. Van Vranken, *J. Peptide Res.*, 1999, **53**, 465.
- M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251; M. Somei, *J. Synth. Org. Chem.*, 1991, **49**, 205; M. Somei, *Heterocycles*, 1999, **50**, 1157; M. Somei, *Advances in Heterocyclic Chemistry*, Vol. 82, ed. by A. R. Katritzky, Elsevier Science, USA, 2002, pp. 101—155.
- M. Somei, T. Kawasaki, K. Shimizu, Y. Fukui, and T. Ohta, *Chem. Pharm. Bull.*, 1991, **39**, 1905.
- The reflection data were collected on a Rigaku AFC5R diffractometer over the range of $7.48^\circ < 2\theta < 15.08^\circ$ using $\text{CuK}\alpha$ radiation ($\lambda=1.54178 \text{ \AA}$) and the ω - 2θ scan method at a 2θ scan speed of $6^\circ/\text{min}$. The structure of ($\pm$)-**17** was solved by the direct method using MITHRIL¹⁰ and refined by the full-matrix least-squares method with anisotropic thermal factors for non-hydrogen

atoms and with isotropic ones for hydrogen atoms. The final R - and R_w -factors were 0.045 and 0.050 for 1830 observed reflections [$I > 3.00\sigma(I)$], respectively. Crystal data for ($\pm$)-**17**: $C_{16}H_{18}N_2O_5$, $M=318.33$; monoclinic, space group $P2_1/a$ (#14); $a=8.230$ (5) Å, $b=20.75$ (1) Å, $c=9.607$ (6) Å; $\beta=112.86$ (5)°; $V=1512$ (2) Å³, $Z=4$, $D_{\text{calc}}=1.398$ g/cm³.

10. C. J. Gilmore, *J. Appl. Cryst.*, 1984, **17**, 42.