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-position

HETEROCYCLES, Vol. , No. , , pp. -,
Received, , Accepted, , Published online, (Please do not delete.)

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-POSITION[1]

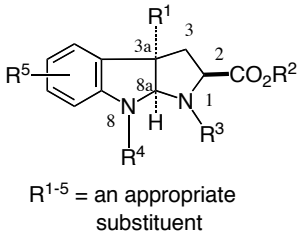
Fumio Yamada, Yoshikazu Fukui, Takako Iwaki, Sachiko Ogasawara, Masaki Okigawa, Satomi Tanaka, and Masanori Somei*

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.

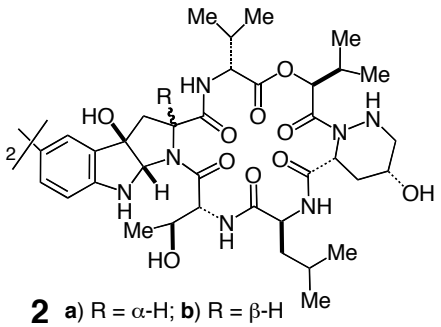
We have been engaged in finding a simple method for the preparation of optically active methyl 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates having an oxygen functional group at the 3a-position as shown in general formula (**1**, Figure 1). Once the compounds (**1**) became available,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

Figure 1

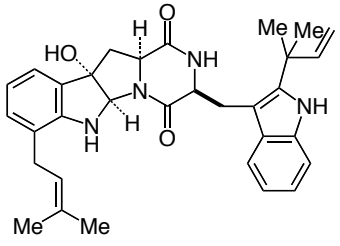


R1-5 = an appropriate substituent

1



2 **a**) R = α-H; **b**) R = β-H



3

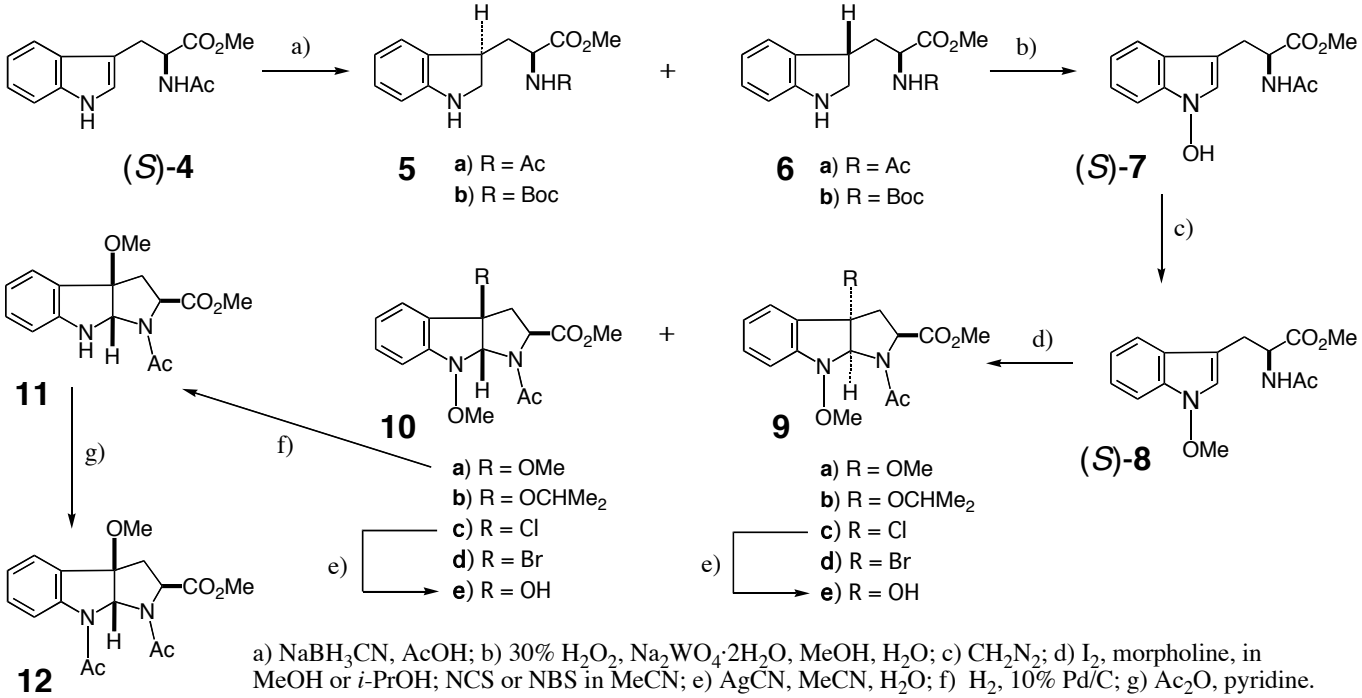
In the previous communication,[1c] we reported the discovery of a simple synthetic method for 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles directly from 1-methoxy-*N*b-methoxycarbonyltryptamine by the reaction with iodine-morpholine in alcoholic solvent. Based on the results and further examinations 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 himastatin[3] (**2a**), *iso*-himastatin[3] (**2b**), (+)-okaramine J[4] (**3**), and so on.[5]

Reduction of *N*b-acetyl-L-tryptophan methyl ester (**4**, Scheme 1) with $NaBH_3CN$ in AcOH gave *N*b-acetyl-2,3-dihydro-L-tryptophan methyl esters (**5a** and **6a**) in 68% yield as a mixture of diasteromers 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 ^{1}H-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' group.[6]

Oxidation of **5a** and **6a** was successfully carried out with 30% H_2O_2 in the presence of a catalytic amount of $Na_2WO_4 \cdot 2H_2O$[7] 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 CH_2N_2 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



a) $NaBH_3CN$, AcOH; b) 30% H_2O_2, $Na_2WO_4 \cdot 2H_2O$, MeOH, H_2O; c) CH_2N_2; d) I_2, morpholine, in MeOH or *i*-PrOH; NCS or NBS in MeCN; e) AgCN, MeCN, H_2O; f) H_2, 10% Pd/C; g) Ac_2O, pyridine.

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-K_2CO_3, iodine-$NaHCO_3$, iodine-pyridine, iodine-NaI, iodine-NH_4Cl, 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*,3a*S*,8a*S*)-(**9a**) and (2*S*,3a*R*,8a*R*)-methyl 1-acetyl-1,2,3,3a,8,8a-hexahydro-3a,8-dimethoxypyrrolo[2,3-*b*]indole-2-carboxylates (**10a**) in 6 and 48% yields, respectively.[1e] 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*,3a*S*,8a*S*)- (**9c**) and (2*S*,3a*R*,8a*R*)-methyl 1-acetyl-3a-chloro-1,2,3,3a,8,8a-hexahydro-8-methoxy-pyrrolo[2,3-*b*]indole-2-carboxylates (**10c**) in 42 and 42% yields, respectively. When NBS (1 mol eq.) was employed in MeCN, (2*S*,3a*S*,8a*S*)- (**9d**) and (2*S*,3a*R*,8a*R*)-methyl 1-acetyl-3a-bromo-8-methoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates (**10d**) were produced in 8 and 81% yields, respectively.

We next tried to obtain optically active 3a-hydroxy compounds (**9e** and **10e**) from **9c** and **10c** and found the treatment with AgCN in MeCN-H_2O was superior to $AgNO_3$ in MeCN-H_2O producing (2*S*,3a*S*,8a*S*)-(**9e**) and (2*S*,3a*R*,8a*R*)-methyl 1-acetyl-3a-hydroxy-8-methoxy-1,2,3,3a,8,8a-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 ^{1}H-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*,3a*S*,8a*S*)-**15** (Scheme 2). Similarly, **10a** was hydrogenated with 1 atm hydrogen to (2*S*,3a*R*,8a*R*)-**11** in 97% yield in the presence of 10% Pd/C at room temperature, and subsequent acetylation of (2*S*,3a*R*,8a*R*)-**11** with acetic anhydride provided 78% yield of (2*S*,3a*R*,8a*R*)-**12**.

On the other hand, (±)-*N*b-acetyltryptophan methyl ester[8] ((±)-**13**) was converted to (±)-methyl 3a-acetoxy-1,8-diacetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates ((±)-**14** and (±)-**15**) in 21 and 23% yields, respectively, by the reaction with Ac_2O at 120°C in the presence of NaOAc. Isomerization of (±)-**14** to thermodynamically stable (±)-**15** occurred easily in 51% yield by the treatment with *t*-BuOK in DMF, followed by acetylation with Ac_2O. Subsequent hydrolysis of the 3a-acetoxy group of (±)-**14** and (±)-**15** with either $NaHCO_3$ or NaOMe in MeOH provided (±)-methyl 1,8-diacetyl-3a-

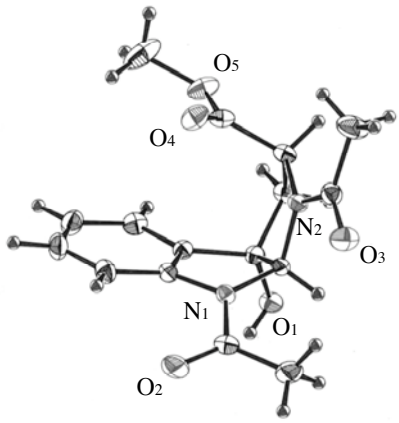
hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates ((±)-**16** and (±)-**17**) in 84 and 96% yields, respectively. Luckily, (±)-**17** became suitable prisms for X-Ray single crystallographic analysis.[9] The results shown in Figure 2 clearly proved the structure and the presence of 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 (±)-**16** in their ^{1}H-NMR spectra. Consequently, stereochemistry of the 8a-proton and the 2-methoxycarbonyl group in (±)-**16** and (±)-**17** are proved to be *cis* and *trans*, respectively.

The ^{1}H-NMR spectrum and TLC behavior of (±)-**15** were identical with those of optically active (2*S*,3a*S*,8a*S*)-**15** derived from (2*S*,3a*S*,8a*S*)-**9e**.

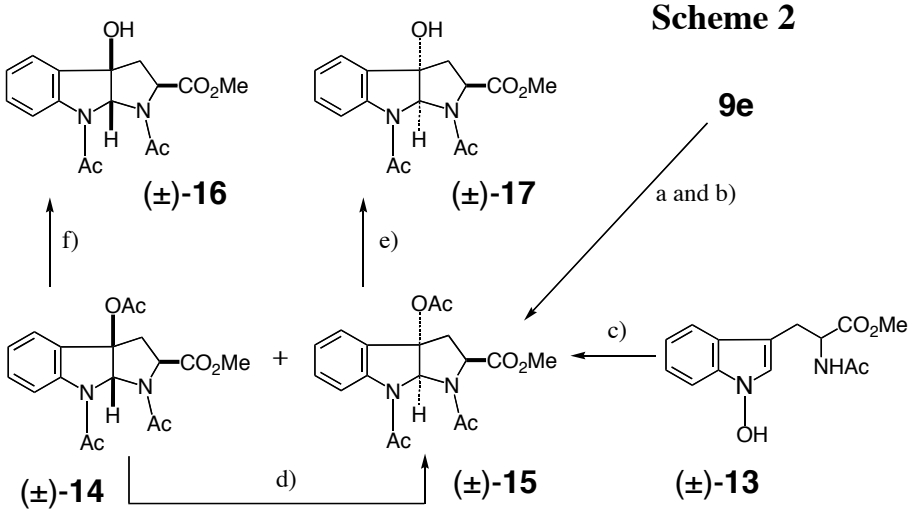
Figure 2

X-Ray Analysis of (±)-17

ORTEP Drawing (R=0.045)



Scheme 2



a) H_2, 10% Pd/C; b) Ac_2O, pyridine; c) Ac_2O, NaOAc; d) *t*-BuOK, DMF, then Ac_2O, pyridine; e) NaOMe, MeOH; f) $NaHCO_3$, MeOH.

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

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

2. 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].
3. 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.
4. Y. Shiono, K. Akiyama, and H. Hayashi, *Biosci. Biotechnol. Biochem.*, 2000, **64**, 103.
5. Our attempt to synthesize the related alkaloid applying 1-hydroxyindole chemistry: Y. Fukui and M. Somei, *Heterocycles*, 2001, **55**, 2055.
6. T. D. Dinh and D. L. Van Vranken, *J. Peptide Res.*, 1999, **53**, 465.
7. 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.
8. M. Somei, T. Kawasaki, K, Shimizu, Y. Fukui, and T. Ohta, *Chem. Pharm. Bull.*, 1991, **39**, 1905.
9. The reflection data were collected on a Rigaku AFC5R diffractometer over the range of $7.48°<2\theta<15.08°$ using Cu$K\alpha$ radiation (λ=1.54178 Å) and the ω–2θ scan method at a 2θ scan speed of 6°/min. The structure of (±)-**17** was solved by the direct method using MITHRIL[10] 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 (±)-**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; β=112.86 (5)°; V=1512 (2) Å^3, Z=4, D_{calc}=1.398 g/cm^3.

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