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## 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<sup>1</sup>

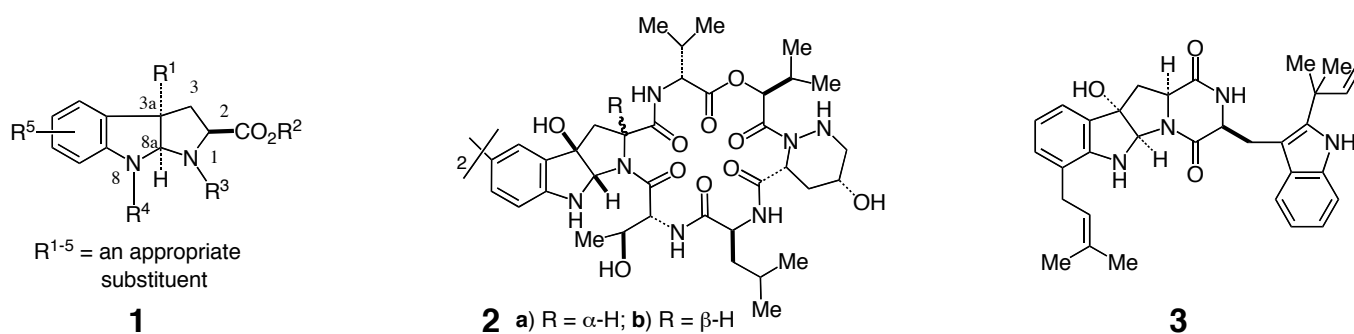
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**Abstract** – A simple and new method for the preparation of optically active methyl 3a-chloro-, 3a-bromo-, 3a-hydroxy-, and 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates has been developed.

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<sup>2</sup> would be possible.

**Figure 1**



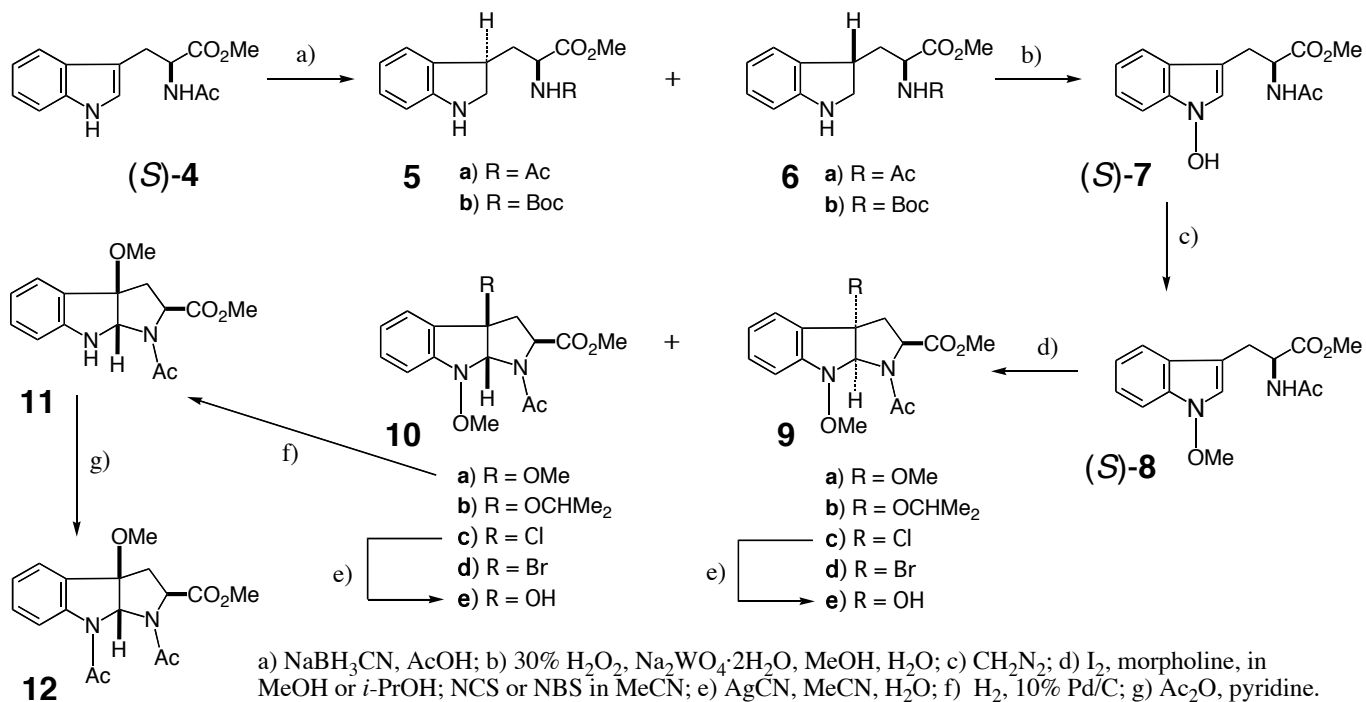
In the previous communication,<sup>1c</sup> we reported the discovery of a simple synthetic method for 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles directly from 1-methoxy-*Nb*-methoxycarbonyltryptamine by the reaction with iodine-morpholine in alcoholic solvent. Based on the results and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

Reduction of *Nb*-acetyl-L-tryptophan methyl ester (**4**, Scheme 1) with NaBH<sub>3</sub>CN in AcOH gave *Nb*-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 <sup>1</sup>H-NMR spectrum with the known set of diastereomers of *Nb*-*tert*-butoxycarbonyl-2,3-dihydro-L-tryptophan methyl ester (**5b** and **6b**) determined by Van Vranken's group.<sup>6</sup>

Oxidation of **5a** and **6a** was successfully carried out with 30% H<sub>2</sub>O<sub>2</sub> in the presence of a catalytic amount of Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O<sup>7</sup> producing *Nb*-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.<sup>8</sup> Subsequent treatment of (*S*)-**7** with an excess ethereal CH<sub>2</sub>N<sub>2</sub> yielded *Nb*-acetyl-1-methoxy-L-tryptophan methyl ester ((*S*)-**8**) in 94% yield.<sup>8</sup> 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-K<sub>2</sub>CO<sub>3</sub>, iodine-NaHCO<sub>3</sub>, iodine-pyridine, iodine-NaI, iodine-NH<sub>4</sub>Cl, 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.<sup>1c</sup> 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-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*,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-H<sub>2</sub>O was superior to AgNO<sub>3</sub> in MeCN-H<sub>2</sub>O 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.

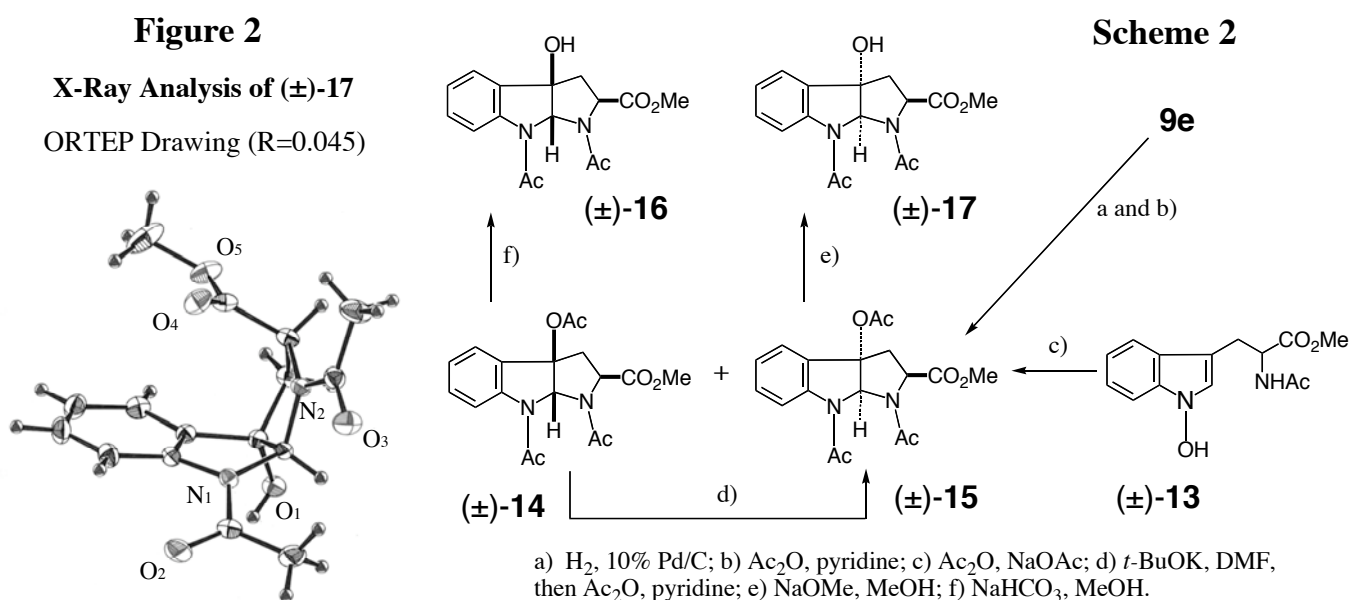
The stereochemistries of **9a–e** and **10a–e** were deduced based on the <sup>1</sup>H-NMR spectral data. Thus, the methyl proton in the 2-methoxycarbonyl group of **9a–e** appeared at higher magnetic field by ca. 0.20–0.24 ppm than that of **10a–e** showing the methyl group is located above the benzene 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*,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, (±)-*Nb*-acetyltryptophan methyl ester<sup>8</sup> ((±)-**13**) was converted to (±)-methyl 3*a*-acetoxy-1,8-diacetyl-1,2,3,3*a*,8,8*a*-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates ((±)-**14** and (±)-**15**) in 21 and 23% yields, respectively, by the reaction with Ac<sub>2</sub>O 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<sub>2</sub>O. Subsequent hydrolysis of the 3*a*-acetoxy group of (±)-**14** and (±)-**15** with either NaHCO<sub>3</sub> or NaOMe in MeOH provided (±)-methyl 1,8-diacetyl-3*a*-

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.<sup>9</sup> 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 <sup>1</sup>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 <sup>1</sup>H-NMR spectrum and TLC behavior of (±)-**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.

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*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<sub>3</sub>); **6a**) oil;  $[\alpha]_D^{27} -20.3^\circ$  (c=0.209, CHCl<sub>3</sub>); **7**) mp 115–117°C;  $[\alpha]_D^{24} +11.8^\circ$  (c=0.102, MeOH);<sup>8</sup> **8**) oil;  $[\alpha]_D^{20} +16.8^\circ$  (c=0.107, MeOH);<sup>8</sup> **9a**) mp 129–130°C;  $[\alpha]_D^{29} +45.5^\circ$  (c=0.302, CHCl<sub>3</sub>); **9b**) oil;  $[\alpha]_D^{30} +15.2^\circ$  (c=0.211, CHCl<sub>3</sub>); **9c**) mp 113–114°C;  $[\alpha]_D^{29} +5.9^\circ$  (c=0.314, CHCl<sub>3</sub>); **9d**) oil;  $[\alpha]_D^{28} +1.2^\circ$  (c=0.174, CHCl<sub>3</sub>); **9e**) oil;  $[\alpha]_D^{29} +37.6^\circ$  (c=0.344, CHCl<sub>3</sub>); **10a**) mp 123–124°C;  $[\alpha]_D^{30} -167.2^\circ$  (c=0.301, CHCl<sub>3</sub>); **10b**) oil;  $[\alpha]_D^{28} -131.3^\circ$  (c=0.166, CHCl<sub>3</sub>); **10c**) mp 114–115°C;  $[\alpha]_D^{30} -105.3^\circ$  (c=0.314, CHCl<sub>3</sub>); **10d**) oil;  $[\alpha]_D^{29} -66.9^\circ$  (c=0.331, CHCl<sub>3</sub>); **10e**) oil;  $[\alpha]_D^{28} -110.7^\circ$  (c=0.317, CHCl<sub>3</sub>); **11**) mp 192–193°C;  $[\alpha]_D^{27} -261.9^\circ$  (c=0.320, CHCl<sub>3</sub>); **12**) oil;  $[\alpha]_D^{30} -36.1^\circ$  (c=0.329, CHCl<sub>3</sub>); **14**) mp 156–157°C; **15**) mp 130–132°C; (2*S*,3*aS*,8*aS*)-**15**) oil;  $[\alpha]_D^{30} +112.5^\circ$  (c=0.275, CHCl<sub>3</sub>); **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 <sup>1</sup>H-NMR (500 MHz) spectra using shift reagent ((+)-Eu-DPPM) comparing with the corresponding (±)-compounds.

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- The reflection data were collected on a Rigaku AFC5R diffractometer over the range of 7.48° < 2θ < 15.08° using CuKα 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<sup>10</sup> 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) Å<sup>3</sup>,  $Z=4$ ,  $D_{\text{calc}}=1.398$  g/cm<sup>3</sup>.

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