Syntheses 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

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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[1]

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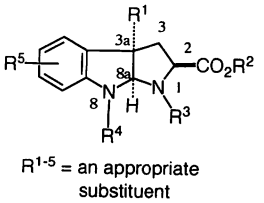
Abstract – A simple and new method for the preparation of optically active methyl 3a-chloro-, 3a-bromo-, 3a-hydroxy-, and 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates has been developed.

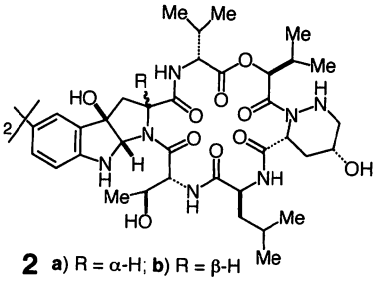
We have been engaged in finding a simple method for the preparation of optically active methyl 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates having an oxygen functional group at the 3a-position as shown in general formula (**1**, Figure 1). Once the compounds (**1**) became available,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

Figure 1

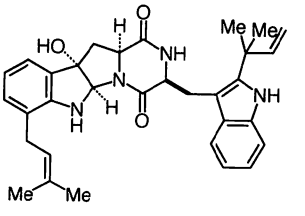


R1-5 = an appropriate substituent

1



2 **a**) R = α-H; **b**) R = β-H



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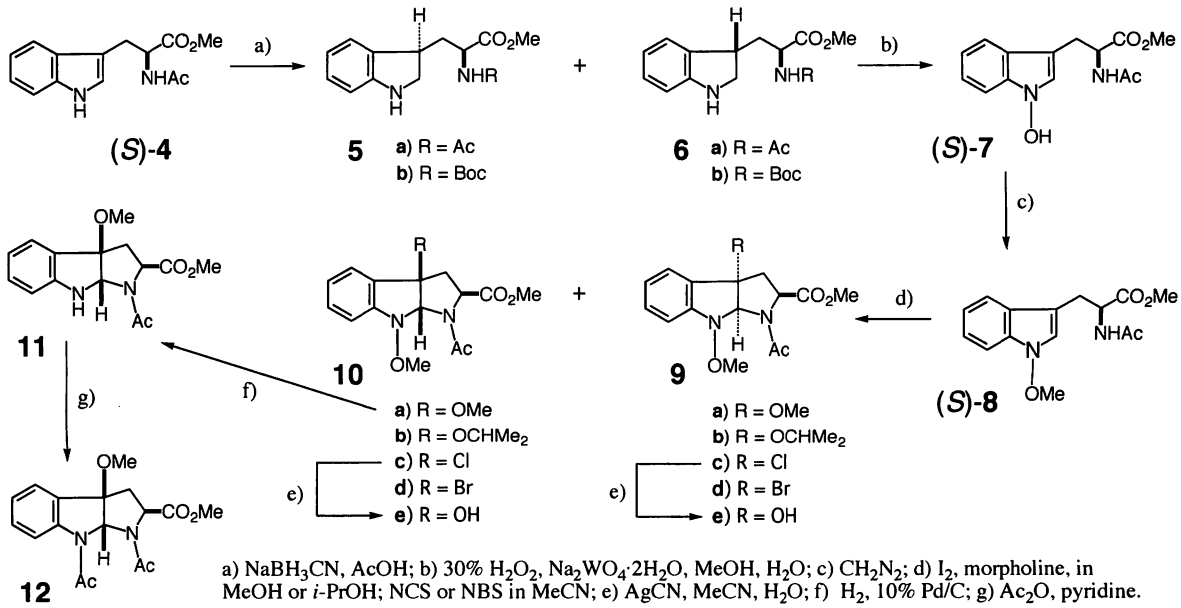
In the previous communication,[1c] we reported the discovery of a simple synthetic method for 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles directly from 1-methoxy-*N*b-methoxycarbonyltryptamine by the reaction with iodine-morpholine in alcoholic solvent. Based on the results and further examinations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



(*S*)-**4** **5** **6** (*S*)-**7** **11** **10** **9** (*S*)-**8** **12**

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-

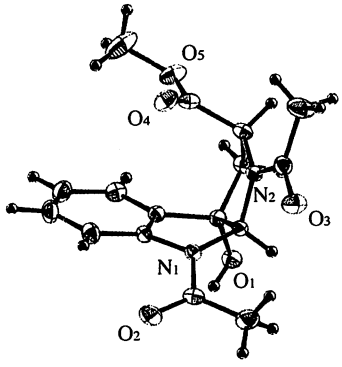
hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylates ((±)-**16** and (±)-**17**) in 84 and 96% yields, respectively. Luckily, (±)-**17** became suitable prisms for X-Ray single crystallographic analysis.[9] The results shown in Figure 2 clearly proved the structure and the presence of 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**.

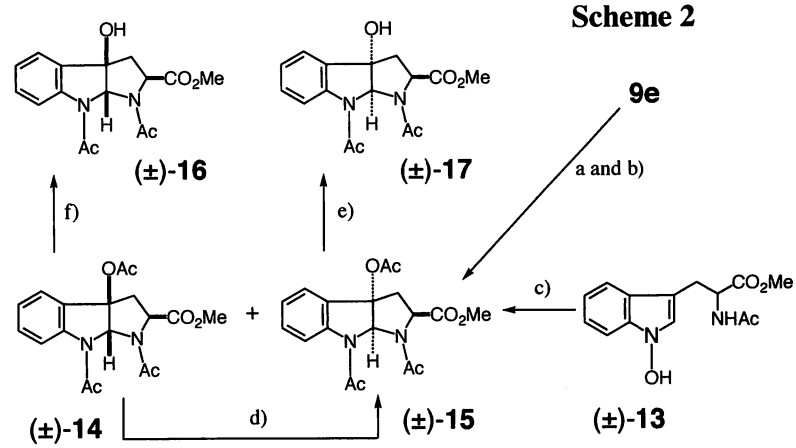
Figure 2

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.

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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° (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.

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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.

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