Three new synthetic methods for the 1,2,3,3a,8,8a-hexa-hydropyrrolo[2,3-b] indoles having an alkoxy group at the 3a-position

Received, 11th May, 2005, Accepted, 23rd June, 2005, Published online, 24th June, 2005

THREE NEW SYNTHETIC METHODS FOR THE 1,2,3,3a,8,8a-HEXAHYDROPYRROLO[2,3-*b*]INDOLES HAVING AN ALKOXY GROUP AT THE 3a-POSITION[1]

Takako Iwaki, Fumio Yamada, Shiho Funaki, and Masanori Somei*

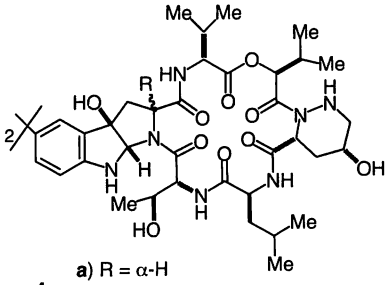
Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa, 920-1192, Japan
e-mail address: somei@mail.p.kanazawa-u.ac.jp

Abstract – Three methods have been newly developed for the synthesis of 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles. Employing them, 3a-chloro-, 3a-bromo-, 3a-hydroxy-, and various 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles are now readily available.

Himastatin[2] (**1a**), *iso*-himastatin[2] (**1b**), FP1[3] (**2**), and (+)-okaramine J[4] (**3**) are typical examples belonging to 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole alkaloids having an alkoxy group at the 3a-position (Figure 1). We have been much interested in the alkaloids from the point of creating our own biologically active lead compounds[5] and challenged for some time to develop new and simple synthetic methods for the compounds shown in general formula[6] (**4**). Now we have found three kinds of useful synthetic methods for 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles.

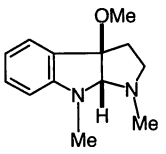
The first method is the treatment of 1-hydroxy-*N*-methoxycarbonyltryptamine[7] (**5**) in refluxing Ac_2O resulting in the formation of 3a-acetoxy-8-acetyl-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indole (**8**) in 72% yield (Scheme 1). The formation of **8** can be explained by a series of reactions; 1) acetylation of 1-hydroxy group of **5** to afford **6**, 2) followed by the [3,3] sigmatropic rearrangement[8] to give the imine (**7**), and 3) finally, cyclization of the nitrogen on the aminoethyl substituent to the imine carbon. The structure of **8** was determined unequivocally by X-Ray single crystallographic analysis and the results are shown in Figure 2.[9] Mild hydrolysis of **8** with aqueous $NaHCO_3$ provided the corresponding 8-acetyl-3a-hydroxy-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**9a**) in 96% yield. Further alkylation of **9a** with EtI in dry DMF in the presence of NaH (1 mol eq.) produced the 3a-ethoxy compound (**9b**) in 31% yield together with 46% yield of recovery of starting material.

Figure 1

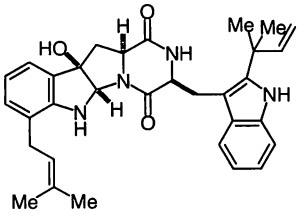


a) R = α-H
b) R = β-H

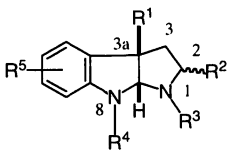
1



2



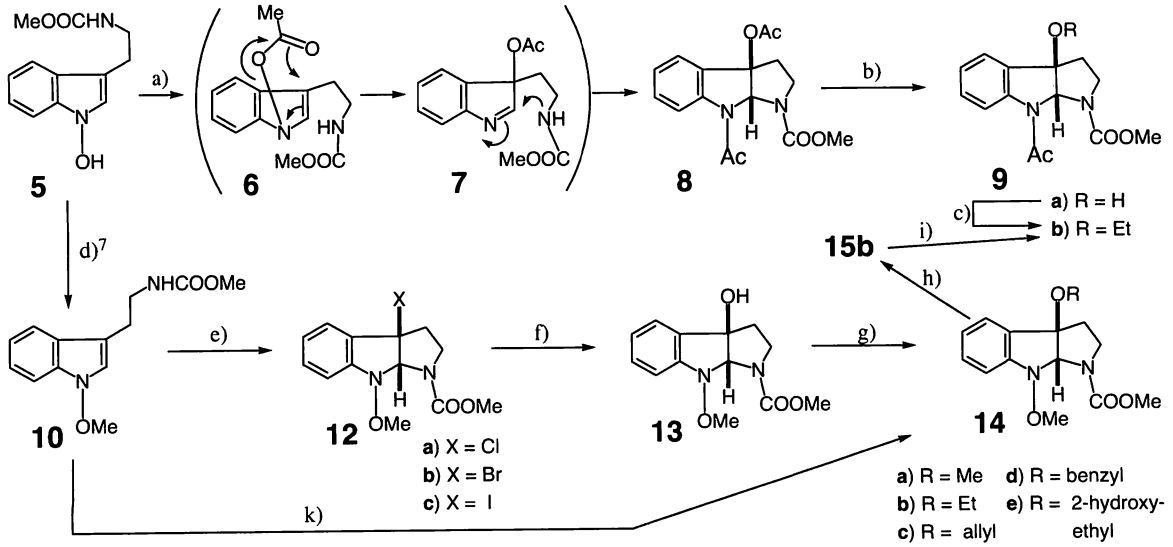
3



R^{1-5} = an appropriate substituent

4

Scheme 1

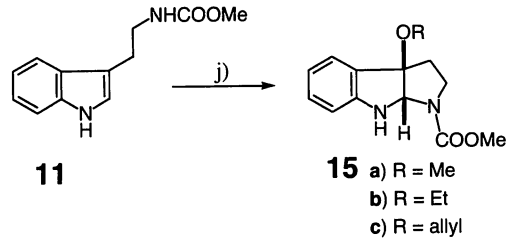


5 **6** **7** **8** **9** **10** **11** **12** **13** **14** **15b**

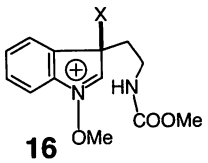
a) R = H
b) R = Et

a) X = Cl
b) X = Br
c) X = I

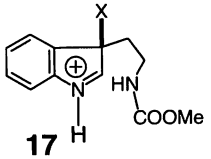
a) R = Me
b) R = Et
c) R = allyl
d) R = benzyl
e) R = 2-hydroxy-ethyl



15 a) R = Me
b) R = Et
c) R = allyl



16

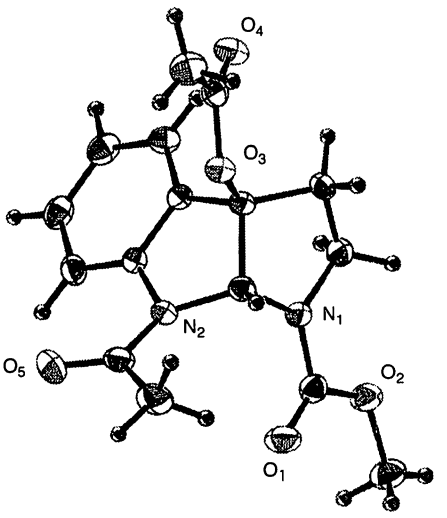


17

a) Ac_2O, reflux; b) $NaHCO_3$, H_2O; c) NaH, DMF, then EtI;
d) Me_2SO_4, K_2CO_3; e) NCS, NBS, or NIS in an appropriate solvent;
f) AgCN, MeCN, H_2O; g) NaH, DMF, then MeI, EtI, or allyl bromide;
h) H_2, 10% Pd/C; i) Ac_2O, pyridine; j) NCS or NBS in MeOH or EtOH:
I_2, morpholine, in MeOH or allyl alcohol; k) I_2, morpholine, in an appropriate alcohol (See Table 1).

Figure 2 X-Ray Analysis of 8

ORTEP Drawing (R=0.033)



As the second method, we examined the halogenation of 1-methoxy-*N*-methoxycarbonyltryptamine[7] (**10**) and *N*-methoxycarbonyltryptamine (**11**) as substrates in the presence of alcohols. No matter which substrates were employed, we found the yields of 3a-bromo- and 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles were extremely poor together with many kinds of brominated compounds, as long as bromine was employed as a brominating reagent under various tested reaction conditions.[10]

In contrast to the above results, the reaction of **10** with NCS (1 mol eq.) in MeOH afforded 3a-chloro-1,2,3,3a,8,8a-hexahydro-8-methoxy- (**12a**) and 1,2,3,3a,8,8a-hexahydro-3a,8-dimethoxy-1-methoxycarbonylpyrrolo[2,3-*b*]indole (**14a**) in 64 and 4% yields, respectively. The same reaction in MeCN gave **12a** as a sole product in 92% yield. When NBS (0.9 mol eq.) was employed in MeOH instead of NCS, 3a-bromo-1,2,3,3a,8,8a-hexahydro-8-methoxy-1-methoxycarbonylpyrrolo[2,3-*b*]indole (**12b**) and **14a** were produced in 12 and 59% yields, respectively. The same reaction in MeCN produced only **12b** in 85% yield. In a similar reaction of **10** in EtOH, **12b** and **14b** were obtained in 8 and 39% yields, respectively. The reaction of **10** with NIS in MeOH afforded **14a** in 58% yield, while the formation of **12c** was not observed at all. The same reaction with NIS in MeCN formed only tar.

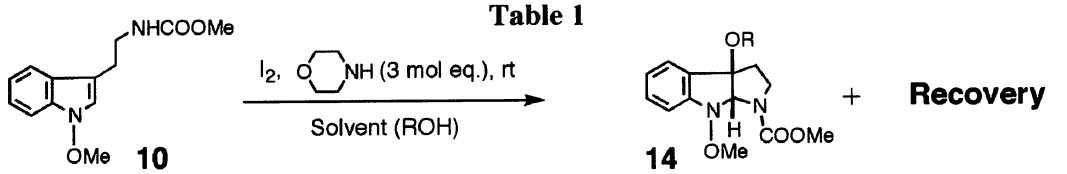
It should be noted that the results of halogenation of **10** are always superior to those of **11** in every corresponding reactions. For examples, the reaction of **11** with NCS in MeOH or EtOH afforded **15a** and **15b** in 49 and 15% yields, respectively, together with concomitant formation of tar. In the reactions of **11** with NBS in MeOH or EtOH, yields of **15a** and **15b** dropped down to less than 10% in addition to much quantity of tar. These findings suggest that the presence of the methoxy oxygen at the 1-position on the indole nucleus makes the intermediate (**16**) more stable than the corresponding immonium salt (**17**) and makes it possible for the first preparation of the 3a-halogeno-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles (**12a** and **12b**).

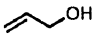
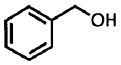
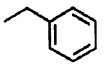
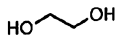
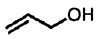
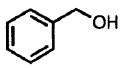
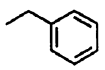
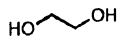
With **12a** and **12b** in hand, we next tried to convert them into 3a-hydroxycompound (**13**) with silver salt. Among the examined reagents, silver cyanide was found to be the reagent of choice. Thus, in MeCN-H_2O, **12a** and **12b** were transformed to **13** in the respective yields of 85 and 94%. Subsequent treatments of **13** with MeI, EtI, and allyl bromide in the presence of NaH afforded **14a**, **14b**, and **14c** in 94, 68, and 92% yields, respectively.

As the third method, we have examined the direct one step conversion of **10** to **14a-e**. After various trials,[6] we have succeeded in finding that the treatment of **10** with iodine and morpholine in an appropriate alcoholic solvent at room temperature meets our end, and the results are summarized in Table 1. As can be seen from the Table, the quantity of iodine governs the yields of the desired products (**14a-e**). Thus, treatment of **10** with about 1.5 molar eq. of iodine generated **14a-e** in the range of 11—37% yields in addition to the unreacted **10** (Entries 1—5). On the other hand, when the amount of iodine was increased to ten molar eq. (Entries 6—10), the yields of **14** were dramatically improved. Consequently, **14a**, **14b**, **14c**, **14d**, and **14e** are now available in 98, 97, 96, 97, and 92% yields, respectively.

Even when the above best reaction conditions were employed for the reaction of **11** with iodine in MeOH and allyl alcohol in the presence of morpholine, the yields of **15a** and **15c** were 60 and 4% yields together with much quantity of tars, respectively.

Table 1



Entry	Iodine (mol eq.)	Solvent (ROH)	Reaction Time (h)	Product 14	R	Yield (%) of Product	Recovery (%)	Total Yield (%)
1	1.5	MeOH	21	a)	Me	36	45	81
2	1.6	EtOH	5	b)	Et	37	55	92
3	"		5	c)		17	79	96
4	1.5		24	d)		28	26	54
5	"		24	e)		11	48	59
6	10	MeOH	1/6	a)	Me	98	0	98
8	"	EtOH	1/6	b)	Et	97	0	97
7	"		1/2	c)		96	0	96
9	"		1/6	d)		97	0	97
10	"		3/2	e)		92	0	92

The structure of **14b**, as a representative of **14a-e**, was confirmed by leading it to **9b**. First, **14b** was hydrogenated to **15b** in 81% yield in the presence of 10% Pd/C at room temperature and 1 atm hydrogen. Subsequent treatment of **15b** with acetic anhydride provided 76% yield of **9b**, which was identical with the sample derived from **8**. As a result, we could develop a simple direct synthetic method for 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles from **10**.

In conclusion, 3a-halogeno-, 3a-hydroxy-, and 3a-alkoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles are now readily available. Biological evaluations of them and their synthetic applications 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) This report is Part 125 of a series entitled "The Chemistry of Indoles". b) Part 124: M. Somei, F. Yamada, Y. Suzuki, S. Ohmoto, and H. Hayashi, *Heterocycles*, 2004, **64**, 483. c) All new compounds gave satisfactory spectral and elemental analysis or high-resolution MS spectral data for crystals or oils, respectively. **8**) mp 137—138°C; **9a**) mp 199—200°C; **9b**) oil; **12a**) oil; **12b**) oil; **13**) oil; **14a**) oil; **14b**) oil; **14c**) oil; **14d**) oil; **14e**) oil; **15a**) mp 114—118°C; **15b**) oil.
2. 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.
3. H. Takayama, I. Mori, M. Kitajima, and N. Aimi, Abstract Papers 2, The 124th Annual Meeting of Pharmaceutical Society, Osaka, 2004, p. 147.
4. Y. Shiono, K. Akiyama, and H. Hayashi, *Biosci. Biotechnol. Biochem.*, 2000, **64**, 103.
5. New compounds for cerebral infarction and myocardial infarction: JP Patent 157475 (1996) [*Chem. Abstr.*, **125**, 195426y]; JP Patent 31257 (1991) [*Chem. Abstr.*, **114**, 247138a]. New compounds for osteoporosis: JP Patent 2004-64408, applied March, 2004. New compounds for ED (erectile dysfunction): JP Patent 2004-280104, applied Sept. 2004; JP Patent 2002-255963 (2001) [*Chem. Abstr.*, **137**, 217126c].
6. This is partly reported: Abstracts of Papers, The 30th Symposium on Progress in Organic Reactions and Syntheses, Sapporo, October, 2004, p. 155.
7. Readily available from tryptamine in three steps in 63% overall yield; a) M. Somei, *J. Synth. Org. Chem.*, 1991, **49**, 205; b) M. Somei, *Heterocycles*, 1999, **50**, 1157; c) M. Somei, Advances in Heterocyclic Chemistry, Vol. 82, ed. by A. R. Katritzky, Elsevier Science, USA, 2002, pp. 101—155.
8. Examples of [3,3] sigmatropic rearrangement of 1-hydroxyindoles: M. Somei, K. Noguchi, and F. Yamada, *Heterocycles*, 2001, **55**, 1237; Y. Fukui and M. Somei, *ibid.*, 2001, **55**, 2055.
9. The reflection data were collected on a Rigaku AFC5R diffractometer over the range of $79.13°<2\theta<79.93°$ 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 **8** was solved by the direct method using MITHRIL[11] 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 0.033 and 0.041 for 1265 observed reflections [$I>3.00\sigma(I)$], respectively. Crystal data for **8**: $C_{16}H_{18}N_2O_5$, M=318.33; orthorhombic; space group, $P2_12_12_1$ (#19); a=12.0955 (9) Å, b=15.231 (1) Å, c=8.4361 (5) Å; V=1554.1 (2) Å^3, Z=4, D_{calc}=1.360 g/cm^3.
10. The results were reported: Abstracts of Papers, The 33rd Congress of Heterocyclic Chemistry, Sapporo, October, 2003, p. 142.
11. C. J. Gilmore, *J. Appl. Cryst.*, 1984, **17**, 42.