1-HYDROXYINDOLES

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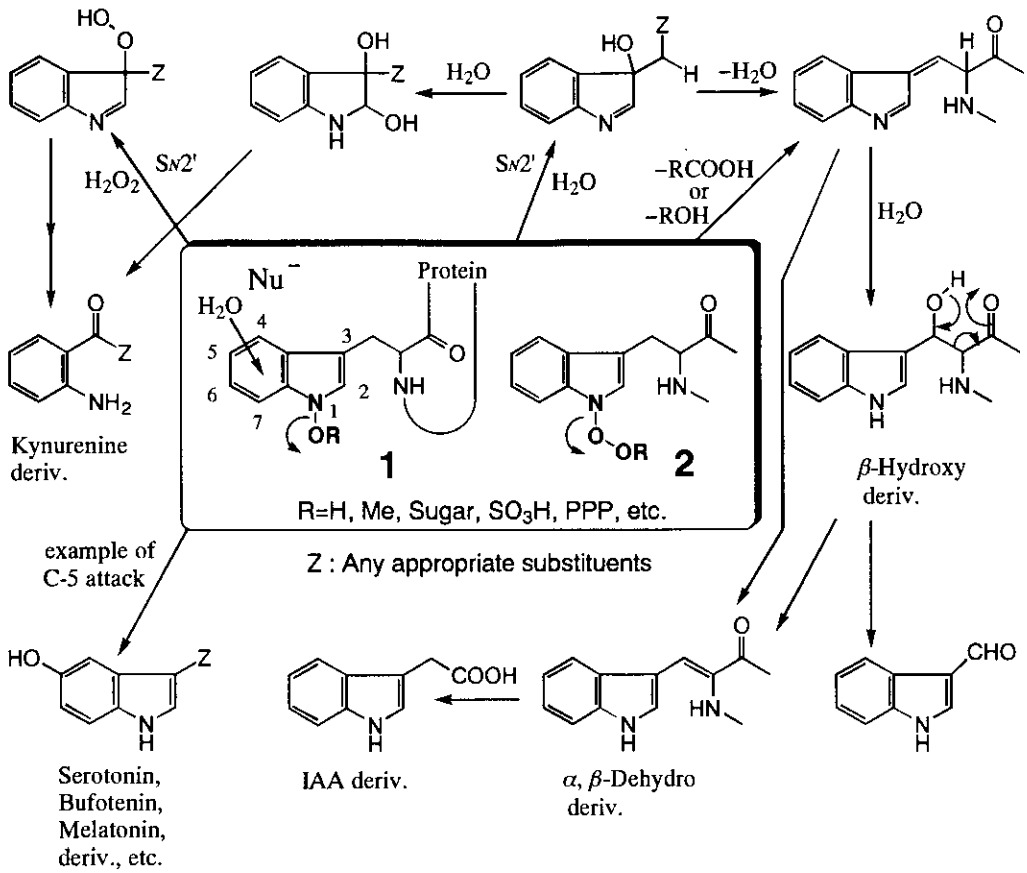
Abstract - This review summarizes our hypotheses, syntheses, physical and chemical properties, and chemical reactions of 1-hydroxyindoles. Syntheses of natural products having 1-methoxyindole nucleus and 1-methoxy derivatives of indole alkaloids are also included. Application of the chemistry of 1-hydroxyindoles to the syntheses of biologically active substances, syntheses of tryptophan-4,5-diones and their reactions, and biological evaluation of 1-hydroxyindoles are reviewed.

1. Introduction and 1-Hydroxyindole Hypotheses

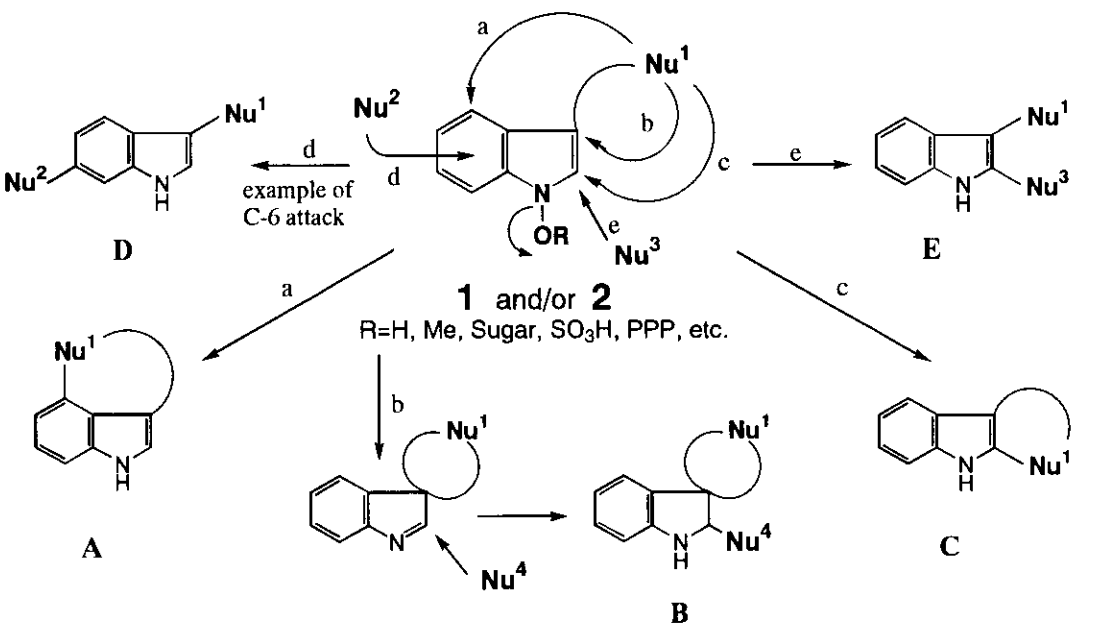
Not a single compound having 1-hydroxyindole structure has yet been isolated as a natural product. Does it mean that 1-hydroxy- and 1-hydroperoxyindoles, as well as the corresponding tryptophan derivatives, can not exist in nature? In 1971, in spite of various discouraging facts, we advanced[1] "1-Hydroxyindole Hypotheses" where we imagined the existence of 1-hydroxytryptophan derivatives in living organisms and supposed that they could undergo nucleophilic substitution reactions with 1-hydroxy moiety as a leaving group, although no example of nucleophilic substitution reaction on indole nucleus was reported at that time.

The hypotheses, illustrated in Scheme 1, seem to explain uniformly the metabolism and/or biosyntheses of biologically important indoles such as kynurenine, serotonin, melatonin, indole-3-acetic acid (IAA), β-hydroxy- and α,β-dehydrotryptophans, etc., by the nucleophilic substitution reaction of 1-hydroxy- (**1**) and/or 1-hydroperoxytryptophan (**2**) as a common intermediate. Biosyntheses of various indole alkaloids, such as 4-substituted indoles including ergot alkaloids and teleocidins (**A**), 4-oxoazetidine-2-spiro-3'-(2'-oxindole) derivatives (**B**), pyrrolo[2,3-*b*]indoles (**C**), 6-substituted (**D**), 2-substituted indoles (**E**), and so on, might also be explained by the nucleophilic attack of either the intramolecular side chain in **1** or intermolecular nucleophiles on

Scheme 1



Scheme 2



Scheme 3

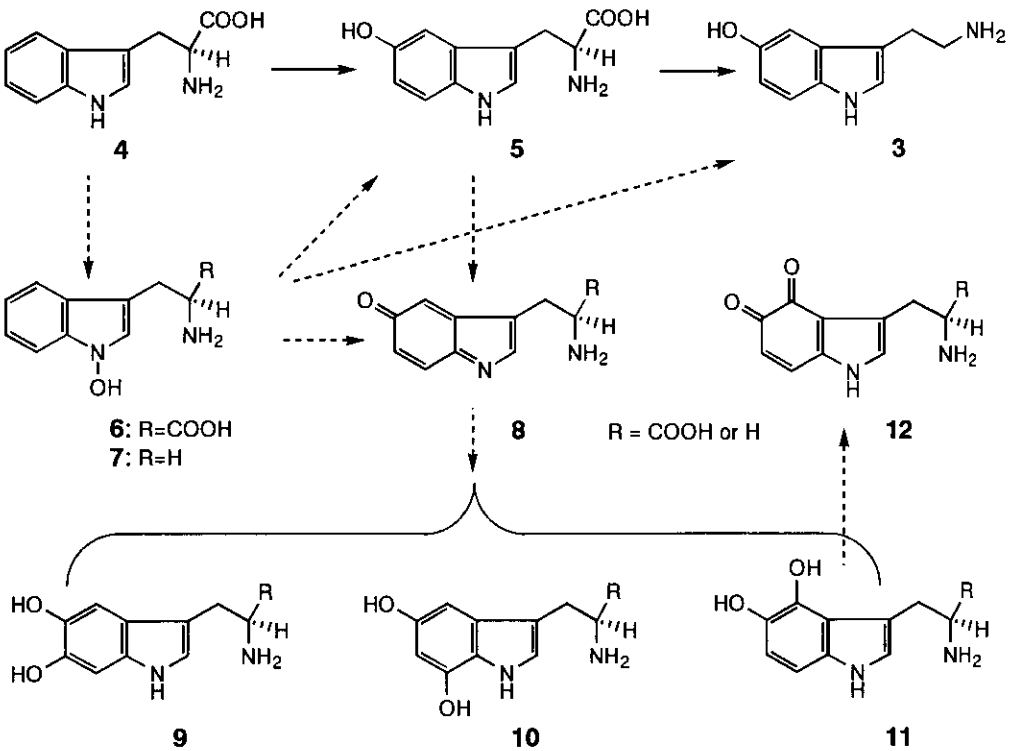
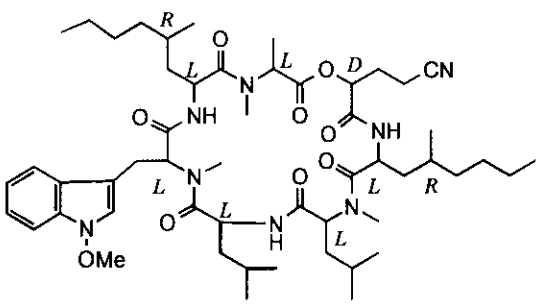


Figure 1



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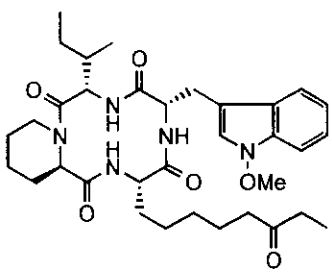

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indole nucleus, as shown in Scheme 2.

In the central nervous system, synaptic vesicles are acidic (pH about 5.5)[2a] and believed to function as storation of serotonin (**3**), whose formation *in vivo* from tryptophan (**4**) through 5-hydroxytryptophan (**5**) was established (Scheme 3).[2b] We speculated, however, an alternative possibility that **3** could be formed in synaptic vesicles by acid catalyzed elimination of 1-hydroxy group of **1**, **6** and/or 1-hydroxytryptamine (**7**), followed by nucleophilic addition of water to the 5-position. If the nucleophiles happened to be reactive oxygen species (oxygen, hydrogen peroxide, superoxide, etc.), **6** or **7** should produce indolequinoneimine (**8**). Subsequent nucleophilic addition of water to **8** could generate 5,6- (**9**), 5,7- (**10**), and/or 4,5-dihydroxyindoles[3] (**11**), and further oxidation of them would lead to 4,5-diones (**12**), and so on. Since these diones are expected to be neurotoxic substances,[4] they would cause neuro-degenerative diseases.[5] On the other hand, blood platelets are known to contain **3**. If **1**, **6**, and/or **7** were associated with **3** as stated above, they could be imagined to have closely related biological activity to the function of blood platelets.

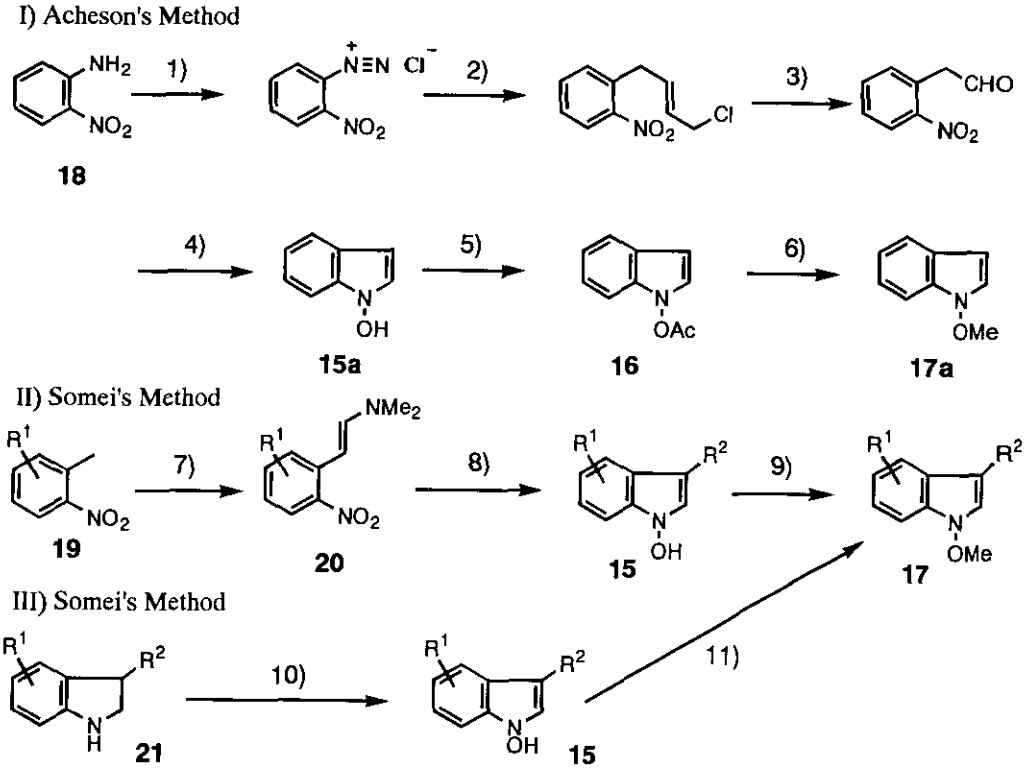
In order to determine whether "1-Hydroxyindole Hypotheses" are imaginary story or not, we challenged the seemingly impossible theme, "how to prepare 1-hydroxyindoles, especially imaginary 1-hydroxytryptophan derivatives". Fortunately, we could create a general synthesis method suitable for our purposes and consequently prove that 1-hydroxytryptophan derivatives are no longer imaginary compounds. They actually underwent unprecedented nucleophilic substitution reactions on indole nucleus. They also exhibited not only interesting rearrangement reactions and chemical behaviors, but also potent inhibition of blood platelets aggregation as expected.

Although we are still on the way to verify "1-Hydroxyindole Hypotheses", to our pleasure, two peptides, HUN-7293[6a] (**13**) and apicidin[6b] (**14**), having 1-methoxytryptophan residue, were isolated and determined as natural products in 1996 (Figure 1). These facts seem to support the presence of **1** and/or **2** in nature. We now wish to describe our results obtained thus far briefly in this review.

2. Syntheses of 1-Hydroxyindoles

Thus far, three major methods are reported for the synthesis of 1-hydroxyindoles. In 1974, Acheson and co-workers[7] succeeded in the first preparation of 1-hydroxy- (**15a**), 1-acetoxy- (**16**), and 1-methoxyindoles (**17a**) as shown in Scheme 4, utilizing coupling of diazonium salts with butadiene as a key reaction starting from 2-nitroaniline (**18**). With **16** in hand, they produced some 1-hydroxyindole derivatives stabilized with electron withdrawing group at the 3-position. Their works on 1-hydroxy- and 1-methoxyindoles are summarized in their

Scheme 4



1) $NaNO_2$, H^+; 2) butadiene; 3) O_3; 4) Zn, NH_4Cl; 5) Ac_2O; 6) MeI, NaOMe; 7) DMFDMA, DBU; 8) $TiCl_3$ or Zn and NH_4Cl; 9) MeI, phase transfer catalyst; 10) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2, MeOH, H_2O; 11) CH_2N_2.

excellent reviews.[8] Unfortunately, Acheson's method is not applicable for the general syntheses of 1-hydroxyindoles, but they have disclosed the unstable nature of **15a** which was useful for researchers in this field.

In 1981, we discovered the second method[9] reacting 2-nitrotoluene (**19**) with *N,N*-dimethylformamide dimethyl acetal (DMFDMA), followed by reduction of the intermediate nitroenamine (**20**) with either titanium chloride ($TiCl_3$) or zinc (Zn) and ammonium chloride (NH_4Cl). Employing the method, 1-hydroxy- (**15**) and 1-methoxyindoles (**17**) were produced[9] and they are summarized in Table 1. As can be seen from the Table, the method was applied to the limited kind of 1-hydroxyindoles and was not applicable for the direct preparation of 1-hydroxytryptophan derivatives. Besides, utilization of an expensive DMFDMA and anhydrous reaction conditions remained to be improved.

Hoping to obtain 1-hydroxyindoles, we examined direct oxidation of indoles with various reagents for some time *in vain*. Based on the failures, however, we succeeded in 1989 in creating a simple and general synthetic

method for **15**[10] which consisted of oxidation of 2,3-dihydroindoles (**21**) in methanol-water (MeOH-H_2O) with 30% aqueous hydrogen peroxide (30% H_2O_2) in the presence of a catalytic amount of sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$) (Scheme 4): we abbreviate the method as the tungstate method in the following text. The tungstate method could give birth to thus far imagined 1-hydroxyindoles for the first time including our long desired compounds such as methyl 1-hydroxyindole-3-acetate (**15c**), *Nb*-methoxycarbonyl-1-hydroxytryptamine (**15l**), (±)- (**15t**) and (*S*)-(+)-*Nb*-acetyl-1-hydroxytryptophan methyl ester (**15u**). Typical examples are listed in Tables 2 and 3 together with their 1-methoxyindole derivatives.[10] Oxone as well as *m*-chloroperbenzoic acid (MCPBA) can be used as oxidizing reagents, but they are generally inferior to the tungstate method except the following one case. The oxidation of **27** by the tungstate method afforded 1,4-dihydroxy-5-nitroindole (**28**) in only 14% yield, whereas with MCPBA 66% yield was attained (Scheme 5).

The tungstate method could produce halogen containing 1-hydroxyindoles (**25c-f**, Table 2) and 1-hydroxytryptamines,[11] **30a** (57%) and **30b** (51%), from **29a** and **29b**, respectively, as shown in Scheme 5. Preparation of tricyclic 5-acetyl-1,3,4,5-tetrahydro-1-hydroxypyrrolo[4,3,2-*de*]quinoline (**32**, 69%) was also attained from **31**. 9-Hydroxy-1,2,3,4-tetrahydrocarbazole[10f] (**34**, 65%), 9-hydroxy-*N*-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline[10f] (**36**, 31%), 9-hydroxy-β-carboline[12] (**38**, 15%), 9-hydroxy-3,4-dihydro-[12] (**39**, 29%), and 9-hydroxy-β-carboline-*N*-oxide[12] (**40**, 9%) were produced from **33**, **35**, and **37**, respectively. The mildness of the tungstate method allowed even the preparation of 1-hydroxymelatonin[12] (**25g**, 58%), 1-hydroxy-3-allylsulfinylmethyl-[12] (**42**, 22%), and 1-hydroxy-3-methylsulfinylmethylindoles[11] (**44a**, 27%) from the corresponding 2,3-dihydroindoles (**24g**, **41**, and **43**), respectively. In the oxidation of **43**, concomitant formation of quite unstable 1-hydroxy-3-methylsulfonylmethylindole (**44b**) was confirmed by leading it to stable 1-methoxy derivative (15%), but the isolation of **44b** was unsuccessful.[11]

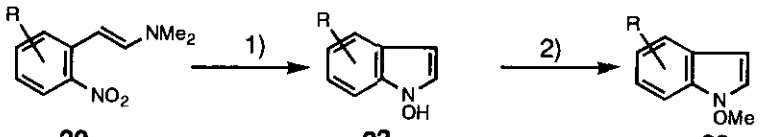
3. Physical and Chemical Properties of 1-Hydroxyindoles

3-1. Stability of 1-Hydroxy- and 1-Methoxyindoles

We often encountered the cases where isolations of 1-hydroxyindoles were impossible due to their instability. Generally speaking, when they carry an electron withdrawing group or resonance stabilizing substituent on the indole nucleus, they become sufficiently stable for isolation and characterization. When they have an electron donating group, their stabilities decrease significantly.[1f,9,10,13] General trends in stability order can be summarized as shown in Figure 2.

Alkylation, especially methylation changes unstable 1-hydroxyindoles into stable 1-methoxyindoles as shown in

Table 1. Typical Examples of 1-Hydroxyindoles and 1-Methoxyindoles



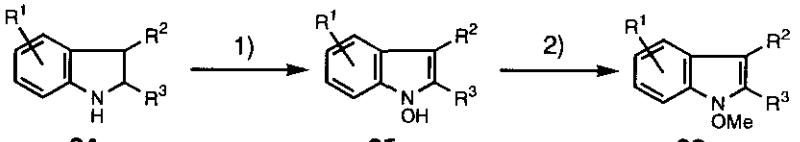
20 **22** **23**

	R	**22** Yield (%)	**23** Yield (%)
a	4-NO_2	57	97
b	4-OCH_2Ph	unstable oil (hard to purify)	77
c	4-COOMe	65, unstable oil	78
d	4-NH_2	unstable oil (hard to purify)	91*[a] unstable oil
e	5-COOMe	26	59
f	6-CHO	29, unstable oil	36*[b]

*a: Obtained by the reduction of 1-methoxy-4-nitroindole with $TiCl_3$.

*b: Overall yield from nitroenamine. 1) $TiCl_3$, H_2O, AcOH or MeOH; 2) CH_2N_2 or Me_2SO_4 or MeI and K_2CO_3.

Table 2. Typical Examples of 1-Hydroxyindoles and 1-Methoxyindoles



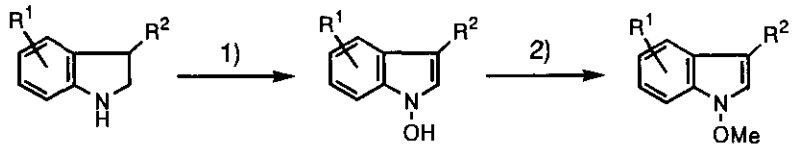
24 **25** **26**

	R^1	R^2	R^3	**25** Yield (%)	**26** Yield (%)
a	H	Me	H	37, unstable oil	50*[a]
b	H	H	Ph	56	86
c	5-Br	H	H	unstable oil	60*[a]
d	6-Br	H	H	unstable oil	83*[a]
e	5,7-diBr	H	H	unstable oil	17*[a]
f	7-I	H	H	unstable oil	26*[a]
g	5-OMe	CH_2CH_2NHAc	H	58	75

*a: Overall yield from the corresponding 2,3-dihydroindole.

1) $Na_2WO_4 \cdot 2H_2O$, 30% aq. H_2O_2, MeOH, H_2O; 2) CH_2N_2 or Me_2SO_4 or MeI and K_2CO_3.

Table 3. Typical Examples of 1-Hydroxyindoles and 1-Methoxyindoles



21 **15** **17**

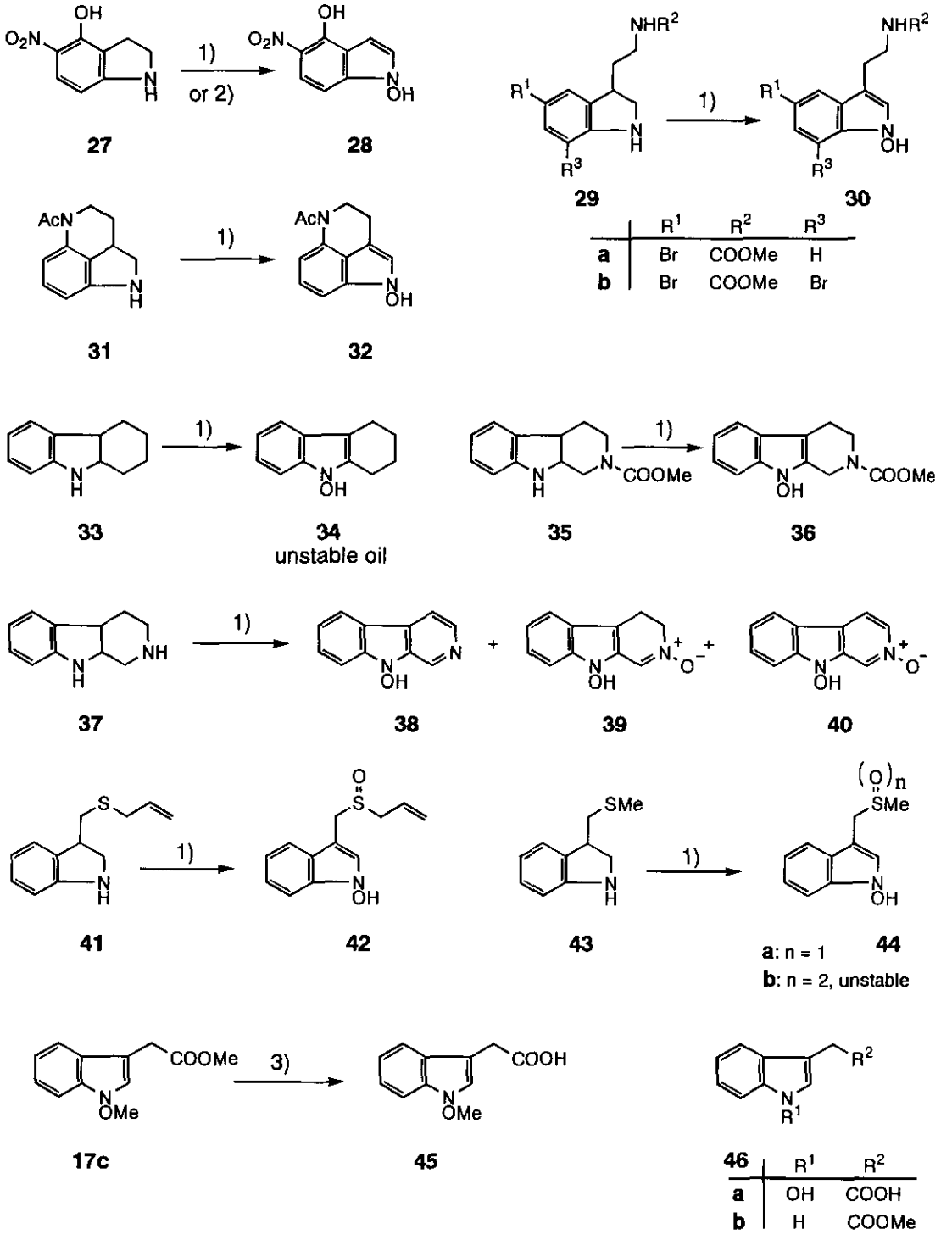
	R^1	R^2	**15** Yield (%)	**17** Yield (%)
a	H	H	unstable (hard to purify)	52
b	H	*CHO*	39*[a]	93
c	H	CH_2COOMe	73	91
d	H	CH_2CONMe_2	74	-
e	H	$CH_2NHCOMe$	66	85
f	H	$CH_2NHCOCF_3$	65	96
g	H	CH_2NHTs	67	95
h	H	$CH_2NHCOCH_2CH_2COOMe$	63	96
i	H	$CH_2CH_2NHCOOMe$	67	83
j	H	$CH_2CH_2NHCOMe$	55	82
k	H	$CH_2CH_2NHCOCF_3$	72	78
l	H	$CH_2CH_2NHCH_2CH_2Me$	57	65
m	H	$CH_2CH_2NMe_2$	55	57
n	H	$CH_2CH_2CH_2NMe_2$	56	59
o	H	$CH_2CH_2CH_2CH_2NMe_2$	65	69
p	H	CH_2CH_2COOMe	59	57*[b]
q	H	$CH_2CH_2CH_2COOMe$	52	49*[b]
r	H	CH_2 $CH_2CH_2CH_2OCOMe$	57	75
s	H	$CH_2CH_2NHCO(CH_2)_{14}Me$	50	41
t	H	(±)-$CH_2CH(NHAc)COOMe$	73	63
u	H	(*S*)-(+)-$CH_2CH(NHAc)COOMe$	53	78
v	H	(±)-$CH_2CH(NHAc)CH_2OH$	86	77
w	5-NO_2	H	42	98
x	6-NO_2	H	79	96
y	6-NO_2	$CH_2CH_2NHCOOMe$	80	85
z	6-NO_2	$CH_2CH_2NHCOCF_3$	78	84

* a: Prepared by the Vilsmeier reaction of 1-benzoyloxyindole.

* b: Overall yield from the corresponding 2,3-dihydroindole.

1) $Na_2WO_4 \cdot 2H_2O$, 30% aq. H_2O_2, MeOH, H_2O; 2) CH_2N_2 or MeI and K_2CO_3

Scheme 5



	R^1	R^2	R^3
a	Br	COOMe	H
b	Br	COOMe	Br

46	R^1	R^2
a	OH	COOH
b	H	COOMe

1) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2, MeOH, H_2O; 2) MCPBA; 3) aq. NaOH, MeOH.

Tables 1, 2, and 3. The representative example is 1-hydroxyindole (**15a**) itself. Although Kikugawa and co-workers[14] succeeded in taking the spectra of **15a**, it is very unstable as Acheson's group observed.[7] However, once it is converted to 1-methoxyindole (**17a**), stability increases to the extent which makes its storage possible for eleven years at room temperature without any detectable decomposition under protection of light.[10a] We believe this is the most probable reason why 1-hydroxyindoles are not reported as natural products, while various 1-methoxyindole compounds have been isolated, mainly from the plant family *Cruciferae*.[15]

During the investigation to prepare 1-hydroxyindole-3-acetic acid (**46a**), alkaline hydrolysis of methyl 1-methoxyindole-3-acetate (**17c**) was carried out (Scheme 5). Monitoring on TLC clearly showed a formation of an extremely unstable product, presumed to be 1-methoxyindole-3-acetic acid (**45**), which rapidly collapsed to many unidentified products. This result indicates that there is a case where even a methoxy group can not satisfactorily stabilize the structure.

Considering the instability of 1-hydroxy-3-methylindole (**25a**) and general trends shown in Figure 2, we had worried that methyl 1-hydroxyindole-3-acetate (**15c**), *Nb*-acetyl-1-hydroxytryptamine (**15j**), (±)- (**15t**), (*S*)-(+)-*Nb*-acetyl-1-hydroxytryptophan methyl ester (**15u**), etc. would be unstable because of having electron donating alkyl substituents in the 3-position. To our surprise and luckily, these were actually stable crystalline compounds and their stabilities are in the increasing order of **15c**, **15j**, and **15t** =**15u**.[10b] These results suggest that not only the electrostatic effect but also the bulkiness of the 3-substituent governs the stability of 1-hydroxyindoles.

It is well known, as illustrated in Scheme 6, that indoles (**F**, **G**) carrying a heteroatom leaving group at the indolylmethyl carbon are unstable because lone pair electrons of nitrogen facilitates its departure and stabilizes the resultant indolenine type intermediate (**H**). Trapping of **H** with nucleophiles has been a versatile method for manipulating indolylmethyl carbon. However, without suitable nucleophiles, handlings of both indole-3-methanols (**F**) and -3-methanamines (**G**) often result in the formation of polymers. On the contrary, 1-hydroxy or 1-alkoxy group would destabilize the intermediate (**L**) owing to the electron withdrawing effect of oxygen and retard the departure of a heteroatom leaving group from the indolylmethyl carbon. This means that 1-methoxyindole-3-methanols (**J**) and -3-methanamines (**K**) can be utilized as they are for building blocks in synthetic study. A typical example is illustrated in the synthesis of marine alkaloid, (±)-chelonin A, and 1-methoxychelonin A in Section 6-3.

3-2. Acidity of 1-Hydroxyindoles

1-Hydroxyindoles are weak acids. The pKa value of 1-hydroxy moiety of (±)-*Nb*-acetyl-1-hydroxytryptophan methyl ester (**15t**) is measured to be 9.8 which is larger than that of succinimide and smaller than phenol. They can

Figure 2. Stability Order of 1-Hydroxyindoles and Its Derivatives

I. Effect of R^1 on the stability of 1-hydroxyindoles is the following order.

$R^1=NO_2 >> COOMe >> OCH_2Ph > H >> NH_2$

II. Effect of R^2.

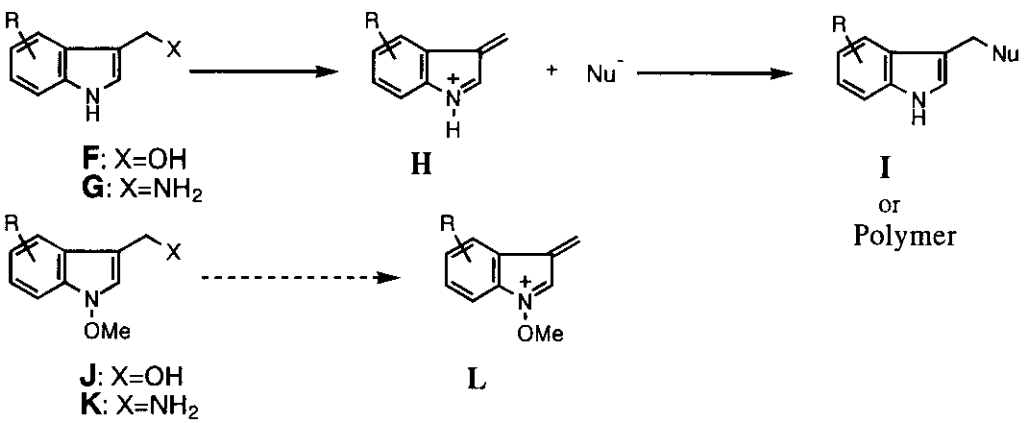
When R^1 is an electron withdrawing group such as NO_2 or COOMe, stability is the following order.

$R^2=Me >> H > Ac$

When R^1 is an electron donating group such as OCH_2Ph, H, or NH_2, stability is the following order.

$R^2=Me >> Ac > H$

Scheme 6



therefore react with alkylating and acylating reagents in the presence of weak bases. Several examples are illustrated in Section 4-1.

3-3. Spectral Data of 1-Hydroxyindoles

UV, IR absorption, and ^{1}H-NMR spectra of 1-hydroxyindoles are superimposable with those of the corresponding indoles. As a typical example, UV spectrum of **15c** is shown in Figure 3 comparing with that of methyl indole-3-acetate (**46b**). Considering the similarities of these spectral data, we worry that when 1-hydroxyindoles happen to

be isolated as natural products, they are likely to be regarded as indoles. If we are not cautious, they might be actually isolated as indole compounds after decomposition to indoles on standing or during work-up. MS spectral data play an important role to determine 1-hydroxyindole structures which show both molecular ion (M^{+}) and characteristic fragment ion $(M-16)^{+}$. Methylation with diazomethane to 1-methoxyindoles is also helpful as noted in Section 4-1.

3-4. Structure of 1-Hydroxytryptophan Derivatives in Crystals

We have assumed that the stability of 1-hydroxytryptophan derivatives is due to hydrogen bondings in intra- or intermolecular fashion between 1-hydroxy moiety and the side chain at the 3-position. To confirm the view, the first X-Ray crystallographic analysis of 1-hydroxyindoles was carried out on **15t**.[10b] The results shown in Figures 4-(a) and 4-(b), however, do not show any expected hydrogen bonds.

Bond length between N(1) and C(1) (X-Ray analysis) and the ABX coupling pattern (^{1}H-NMR) of H(6), H(7), and H(8) signals of **15t** prove that the contribution of its tautomer, nitrone (**47**) structure, is negligible both in solution and solid states. It should be noted that the oxygen atom of the 1-hydroxy group deviates from the plane of the indole nucleus by 14° as Figure 4-(b) shows. A similar result was reported by Acheson's group[16] in the case of 1-benzoyloxyindole. The fact might be the cause of the interesting chemical reactions observed in the following Sections.

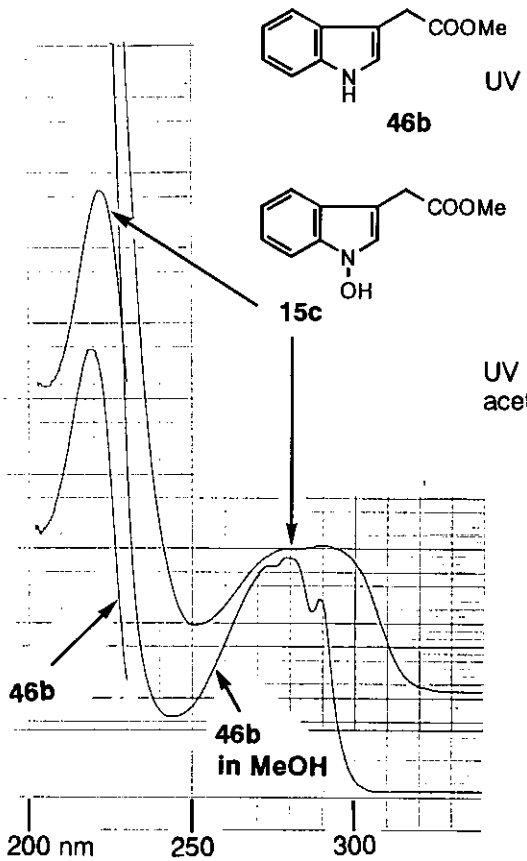
4. Chemical Reactions of 1-Hydroxyindoles and 1-Methoxyindoles

4-1. Methylation, Alkylation, and Acylation

Although 1-hydroxyindole itself (**15a**) is an unstable compound, it can be handled as either MeOH, benzene, or CH_2Cl_2 solution without any special precautions. A MeOH solution of **15a** is directly obtained by the tungstate method as described in Chapter 2. The MeOH solution contains a catalytic amount of Na_2WO_4 and unreacted 30% H_2O_2, but it is sufficient to use for further alkylation and acylation. Thus, the addition of ethereal CH_2N_2 or alkylating reagents to the MeOH solution of **15a** in the presence of base produced various 1-alkoxyindole derivatives (**48a-e**).[10c] Typical examples are listed in Table 4. Interestingly, when benzyl bromide, (*E*)-cinnamyl bromide, or prenyl bromide were used, concomitant formations of **49a-c** were observed.

The benzene solution of **15a** was obtained by adding benzene and H_2O to the MeOH solution of **15a**, followed by separation of an organic layer and drying it over anhydrous Na_2SO_4. A CH_2Cl_2 solution of **15a** could also be obtained by the same separating procedure. An alternative way to obtain CH_2Cl_2 solution of **15a** was found by

Figure 3



UV Spectrum of Methyl Indole-3-acetate (**46b**)

λ_{max}^{MeOH} nm (log ε)	λ_{min}^{MeOH} nm (log ε)
219 (4.56)	244 (3.32)
274 (3.80)	
280 (3.81)	
289 (3.73)	

UV Spectrum of Methyl 1-Hydroxyindole-3-acetate (**15c**)

λ_{max}^{MeOH} nm (log ε)	λ_{min}^{MeOH} nm (log ε)
222 (4.52)	252 (3.36)
281 (3.69)	
291 (3.70)	

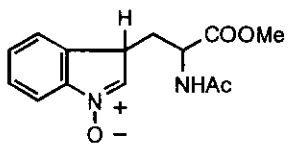


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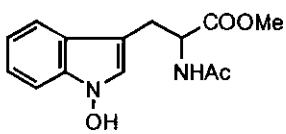
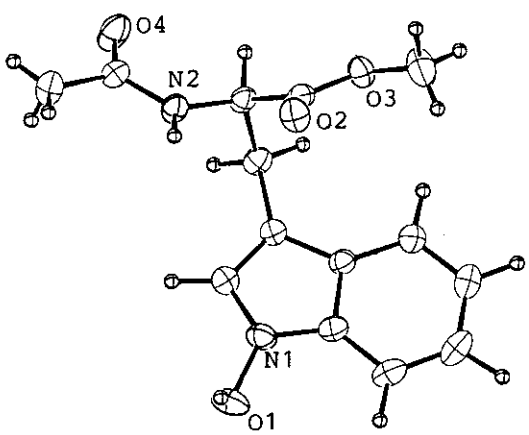
Figure 4

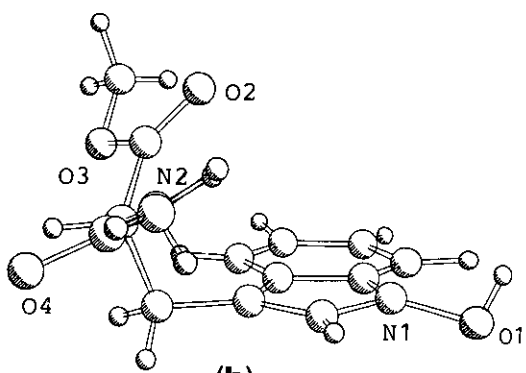
ORTEP Drawing and Side View of (±)-*N b* -Acetyl-1-hydroxytryptophan Methyl Ester (**15t**)



15t



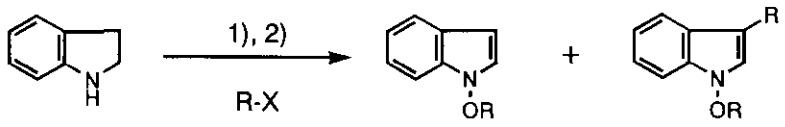
(a)



(b)

Bond Length (angstrom)
N1-C1, 1.372(2); C1-C2, 1.364(3);
C2-C3, 1.433(3); N1-C1, 1.388(2);
C3-C8, 1.408(3); N1-C8, 1.363(3).

Table 4. Alkylation and Acylation of 1-Hydroxyindoles

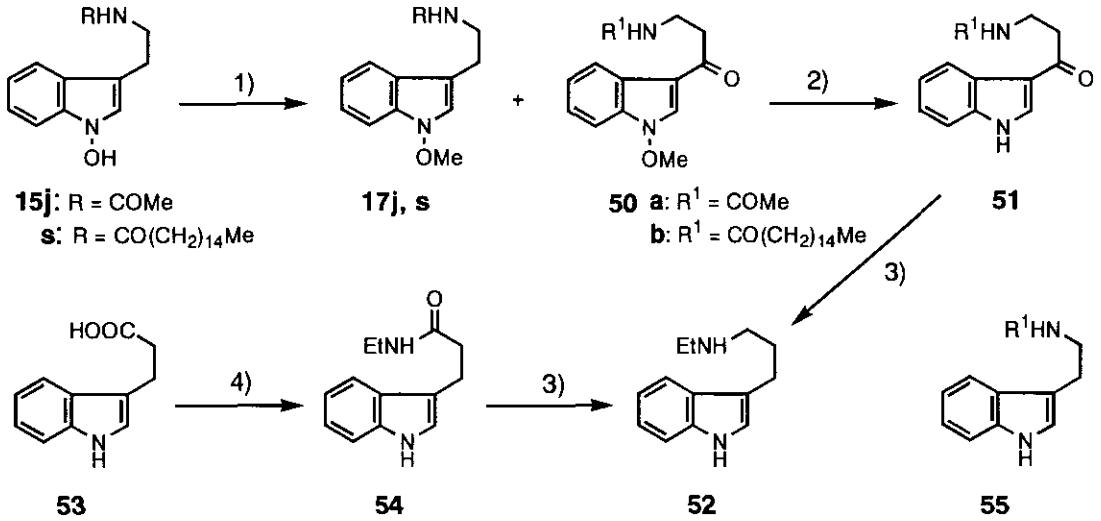


21a **48** **49**

	R-X	Yield (%) of **48**	**49**
a	$PhCH_2Br$	47	5
b	(*E*) $PhCH{=}CHCH_2Br$	25	10
c	$Me_2C{=}CHCH_2Br$	7	3
d	$CH_2{=}CHCH_2Br$	45	0
e	TsCl	10	0
f	*t*-$BuMe_2SiCl$	47	0
g	PhCOCl	49	0
h	$MeOCH_2Cl$	39	0
i	$MeOCH_2CH_2OCH_2Cl$	11	0

1) $Na_2WO_4{\cdot}2H_2O$, 30% H_2O_2, MeOH, H_2O; 2) R-X, K_2CO_3.

Scheme 7



15j: R = COMe
s: R = $CO(CH_2)_{14}Me$

17j, s

50 **a**: R^1 = COMe
b: R^1 = $CO(CH_2)_{14}Me$

51

53 **54** **52** **55**

1) CH_2N_2, $CHCl_3$ or CH_2Cl_2; 2) H_2, 10% Pd/C; 3) $LiAlH_4$, THF; 4) $EtNH_2$.

oxidizing 2,3-dihydroindole (**21a**) with MCPBA in CH_2Cl_2, though the concentration of **15a** was low (20-30%). Treating the benzene solution of **15a** with tosyl chloride, *t*-butyldimethylsilyl chloride, benzoyl chloride, methoxymethyl chloride, and 2-methoxyethoxymethyl chloride successfully produced the expected products (**48e-i**), respectively.[10c,17]

Acylation and tosylation generally take place as expected. There is a case, however, where the product is too unstable to characterize. Tosylation of 1-hydroxyindole-3-carbaldehyde (**15b**) is a good example and the results are described in Section 4-4.[10c]

4-2. Homologation of Side Chain

Generally, the structures of 1-hydroxyindoles are confirmed by converting it to the corresponding 1-methoxyindoles by the reaction with CH_2N_2 in MeOH. However, when **15j** was reacted in CH_2Cl_2 at room temperature, a homologation product (**50a**, 9%) was generated in addition to the normal 1-methoxyindole (**17j**, 36%) and two unknown products (Scheme 7).[18] A homologation product (**50b**) (23%) was similarly observed in the reaction of **15s** with CH_2N_2 in $CHCl_3$ or CH_2Cl_2 together with **17s** (62%). In MeOH, however, all 1-hydroxy compounds afforded normal products, exclusively.

In order to establish the structures of **50a,b**, the compound (**50a**) was catalytically hydrogenated over 10% Pd/C to remove 1-methoxy group giving **51** (quantitative). Reduction of **51** with $LiAlH_4$ afforded *N*-ethyl-3-(indol-3-yl)-propylamine (**52**, 64%). On the other hand, authentic 3-indolepropionic acid (**53**) was derived to ethyl amide (**54**, 98%). Its reduction with $LiAlH_4$ gave authentic **52** (91%), which was identical with the sample derived from **50a**.

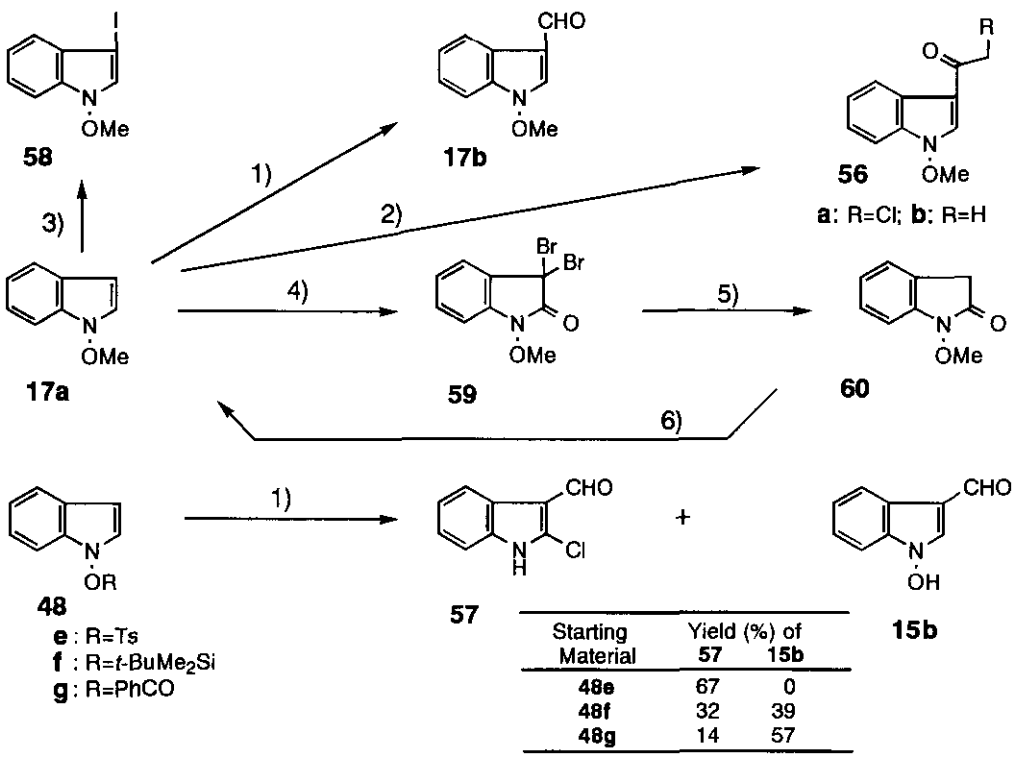
It should be noted that the attempted reactions of both **17j** and **17s** with CH_2N_2 in $CHCl_3$ did not produce **50a** and **50b** even in a trace amount and unreacted starting materials were recovered quantitatively. Similarly, neither **55a** nor **55b** formed **51a** or **51b**, respectively, and quantitative recoveries were observed in both cases. These facts clearly indicate that the side chain homologation is characteristic to 1-hydroxyindole structure, though the reaction mechanism is under investigation.

4-3. Electrophilic Substitution Reaction

4-3-1. Vilsmeier-Haack Reaction and Acylation

1-Methoxyindole (**17a**) underwent Vilsmeier-Haack reaction smoothly to give 1-methoxyindole-3-carbaldehyde (**17b**, 91%) as shown in Scheme 8. Chloroacetyl chloride reacted with **17a** giving 3-chloroacetyl-1-methoxyindole[8c] (**56a**, quantitative), but acetyl chloride did not give 3-acetyl-1-methoxyindole (**56b**, 2%)

Scheme 8



Starting Material	Yield (%) of 57	15b
48e	67	0
48f	32	39
48g	14	57

1) DMF, $POCl_3$; 2) $ClCH_2COCl$ for **56a**, CH_3COCl for **56b**; 3) I_2, morpholine; 4) NBS, *t*-BuOH; 5) Zn, AcOH; 6) $LiAlH_4$.

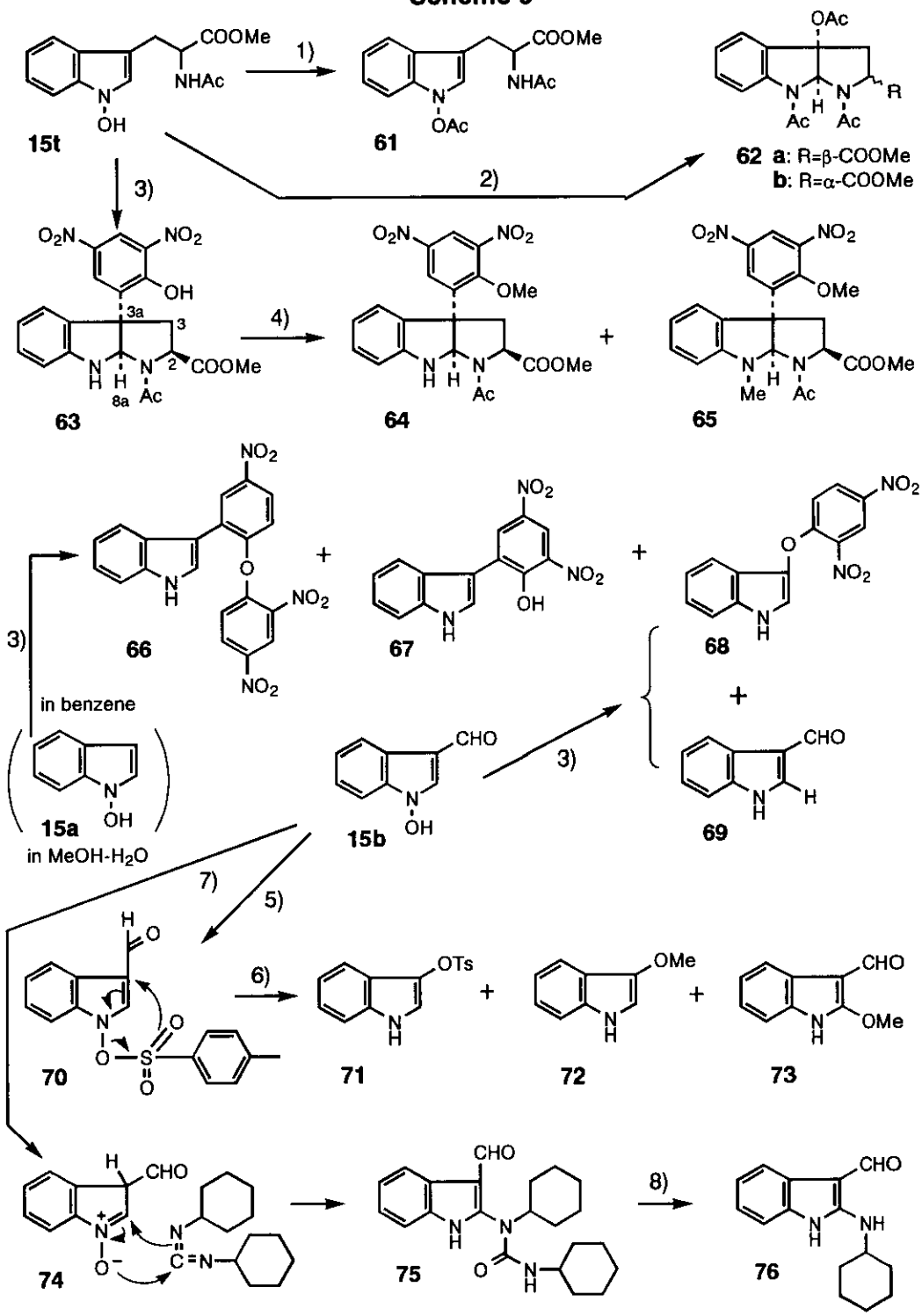
satisfactorily. Vilsmeier-Haack reaction of 1-tosyloxyindole (**48e**) produced 2-chloroindole-3-carbaldehyde (**57**) as a sole product, while 1-*t*-butyldimethylsilyloxyindole (**48f**) and 1-benzoyloxyindole (**48g**) produced **57** and 1-hydroxyindole-3-carbaldehyde (**15b**) in varied yields depending on the reaction conditions.[10c]

4-3-2. Halogenation

Halogenation of 1-methoxyindoles (**17a**) afforded relatively unstable 3-halo-1-methoxyindoles (Scheme 8). For example, the reaction of 1-methoxyindole (**17a**) with iodine (I_2) and morpholine gave 3-iodo-1-methoxyindole[9d] (**58**, 27%), which was then applied to the synthesis of (±)-paniculidine B (Section 5-4).[9e] Interestingly, bromination of **17a** with *N*-bromosuccinimide afforded 3,3-dibromo-1-methoxy-2-oxindole (**59**, 60%).[10c] Reduction of **59** with Zn in acetic acid (AcOH) produced 1-methoxy-2-oxindole (**60**, 65%).[10c] Since **60** was reduced to **17a**, interconversion between **17a** and **60** was attained.

4-4. Rearrangement Reaction

Scheme 9

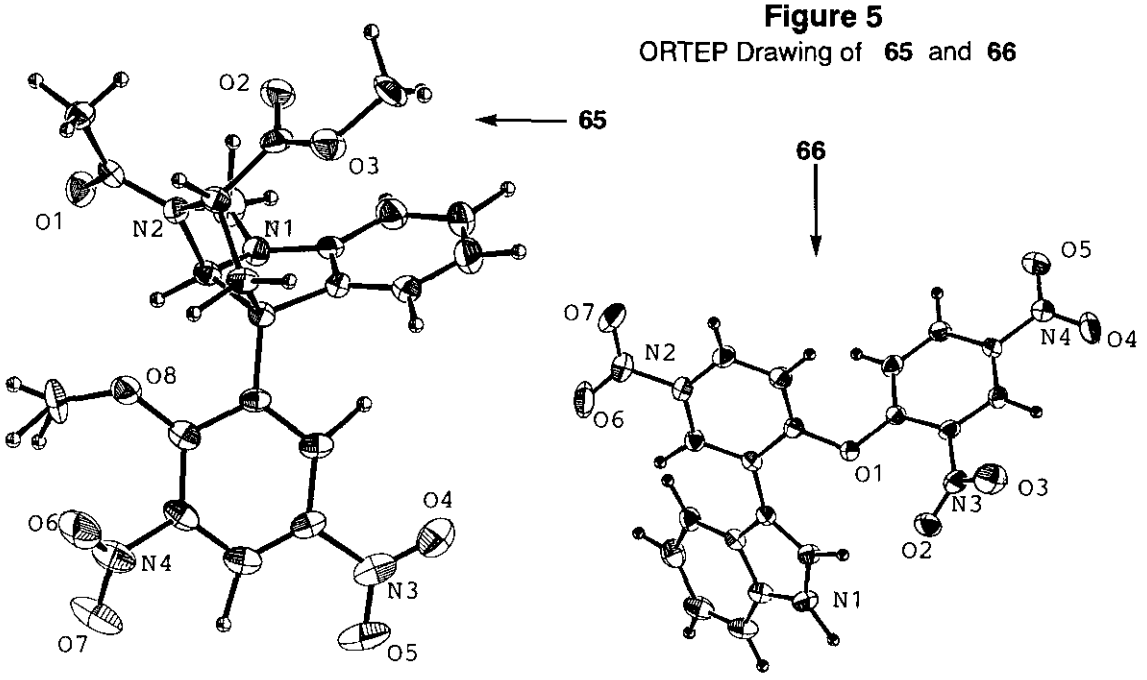


1) Ac_2O; 2) Ac_2O, NaOAc; 3) 2,4-DNF; 4) CH_2N_2; 5) TsCl, pyridine; 6) NaOMe, MeOH; 7) DCC, Et_3N; 8) 20% NaOH, MeOH.

The reaction of **15t** with refluxing Ac_2O afforded 1-acetoxy derivative (**61**, quantitative), while the addition of NaOAc in the reaction mixture dramatically changed the reaction pathway (Scheme 9): a series of [3,3] sigmatropic rearrangement of 1-acetoxy group and subsequent nucleophilic addition of the *Nb*-side chain to the 2-position took place giving 3a-acetoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles (**62a** (17%) and **62b** (21%)).[1c] Similar [3,3] sigmatropic rearrangements were encountered in the reaction of **15t** with 2,4-dinitrofluorobenzene (2,4-DNF) to produce **63** (35%). Methylation of **63** with CH_2N_2 gave monomethyl (**64**, 32%) and dimethyl compounds (**65**, 30%).[1c] X-Ray single crystallographic analysis of **65** proved its structure. The results shown in Figure 5 exhibit that the two pyrrolidine nuclei are *cis* fused and methoxycarbonyl group at the 2-position is thermodynamically stable *trans* configuration concerning to 3a and 8a hydrogens.[1c]

1-Hydroxyindole (**15a**) itself in benzene solution reacted with 2,4-DNF to produce 1:2 adduct (**66**, 6%), 3-arylindole (**67**, 17%), and 3-aryloxyindole (**68**, 6%). The structure of **66** was established by X-Ray single crystallographic analysis and the results are shown in Figure 5.[1c] 1-Hydroxyindole-3-carbaldehyde (**15b**) also reacted with 2,4-DNF producing **68** (31%) and indole-3-carbaldehyde (**69**, 48%). In the reaction with tosyl chloride, **15b** produced unstable 1-tosyloxyindole-3-carbaldehyde (**70**, 93%), which collapsed to many unknown products. In the presence of NaOMe in MeOH, it transformed to 3-tosyloxyindole (**71**, 16%), 3-methoxyindole (**72**,

Figure 5
ORTEP Drawing of **65** and **66**



12%), and 2-methoxyindole-3-carbaldehyde (**73**, 8%).[10c]

In the reaction of **15b** with DCC, rearranged products were not observed, instead *N,N'*-dicyclohexyl-*N*-(3-formylindol-2-yl)urea (**75**, 83%) was formed.[10c] Its formation may be explained by the 1,3-dipolar [2+3] cycloaddition reaction of a nitrone (**74**), a tautomer of **15b**, with DCC. Upon treatment with aqueous sodium hydroxide, **75** led to 2-cyclohexylaminoindole-3-carbaldehyde (**76**, 37%).

Nucleophilic substitutions of 1-methoxyindole-3-carbaldehyde (**17b**) with sodium allylalkoxides and the attempted [3,3] sigmatropic rearrangement of the resultant 2-allyloxyindoles to 3-allyl-2-oxindoles are described in Sections 4-9-3 and 7-3.

4-5. Functioning as Active Esters and Nucleophilic Oxidizing Reagents

1-Hydroxy-4-nitroindole (**22a**) is one of the most stable 1-hydroxyindoles.[9b] It forms esters (**78**) by the reaction with carboxylic acids (**77**) in the presence of DCC (Scheme 10). These esters have the activated carbonyl groups which are reactive toward various nucleophiles.

When hydride ($NaBH_4$) was employed as a nucleophile, **78** led to alcohols (**79**) and **22a**.[1f] If the amines (**81**) were employed, **80** provided amides (**82**) and **22a**.[1f] Since recovered **22a** in both reactions can be recycled, effective methods for transforming carboxylic acids to alcohols and amides are developed.

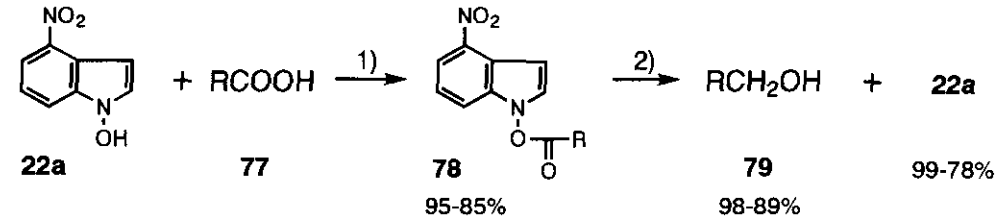
In our "1-Hydroxyindole Hypotheses", we have imagined the existence of 1-hydroxytryptophan derivatives in peptides and/or enzymes, and their probability to function as a catalyst for the formation of amides (peptides), phosphates, sulfates, etc. In accord with the expectation, 1-hydroxy-5-nitroindole (**15w**) and particularly *Nb*-acetyl-1-hydroxytryptophan methyl ester (**15t**) showed the similar reactivity with that of 1-hydroxy-4-nitroindole (**22a**).[12] Comparative study of them (**15w** and **15t**) with well known 1-hydroxybenzotriazole (**84**) concerning the ability to produce amides by the reaction of tryptamine (**83**) with heptanoic acid in the presence of DCC showed almost the same effectiveness as can be seen in Scheme 10.[12]

On the other hand, **22a** was found to react with α-bromoacetyl compounds (**86**) to give 4-nitro-1-(2-oxoalkyl)oxyindole (**87**, quantitative). Upon treatment with weak base such as triethylamine, **87** splitted into two parts, glyoxals (**88**) and 4-nitroindole (**89**).[9c] Thus, 1-hydroxyindoles can function as nucleophilic oxidizing reagents for some substrates.

4-6. Lithiation

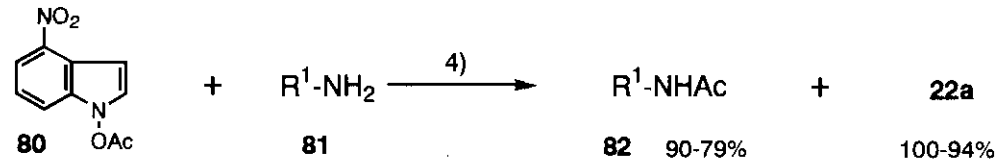
4-6-1. Preparation of 2- and 4-Substituted 1-Methoxyindoles

Scheme 10

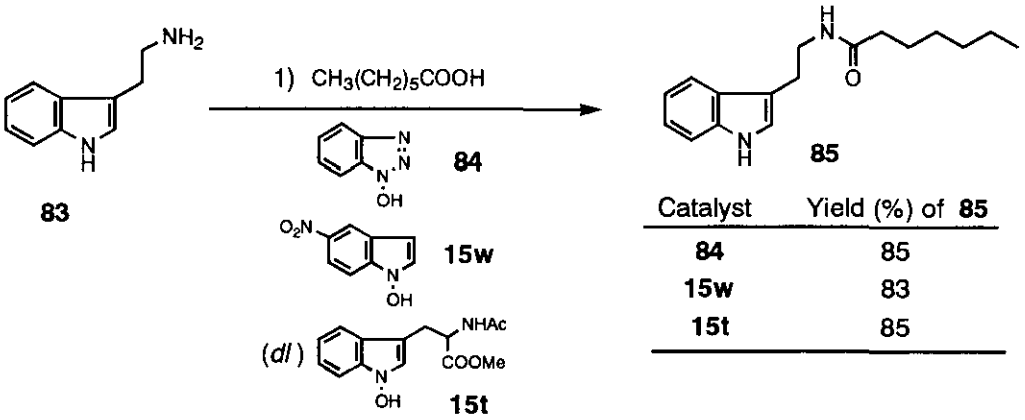


3) 84%

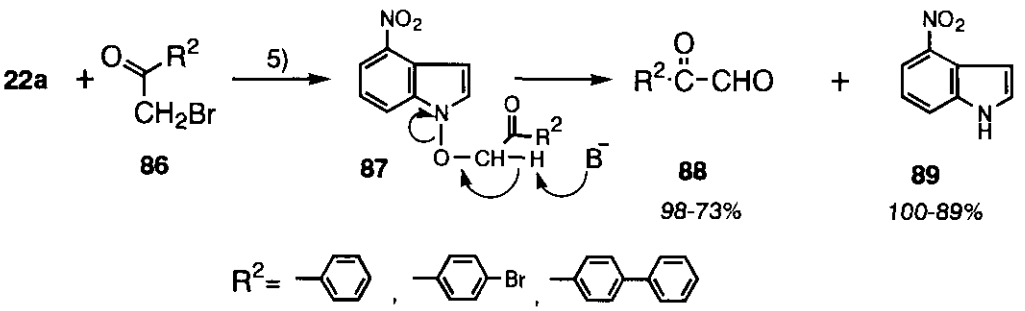
RCOOH: palmitic acid, stearic acid, indole-3-acetic acid, N_b-acetyltryptophan, 2-methyl-3-nitrobenzoic acid, 4-methyl-3-nitrobenzoic acid, methyl 2-carboxyphenylacetate, etc.



R^1-NH_2: tryptamine, benzylamine, cyclohexylamine, pyrrolidine, N_b-methyltryptamine, etc.

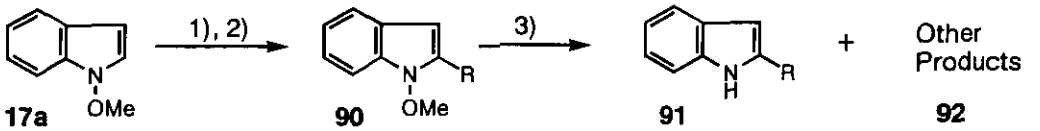


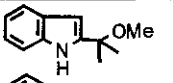
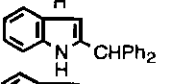
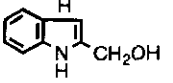
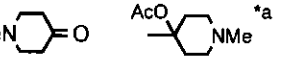
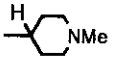
Catalyst	Yield (%) of **85**
84	85
15w	83
15t	85



1) DCC, THF; 2) $NaBH_4$, THF; 3) Ac_2O, pyridine; 4) THF, rt; 5) Et_3N, THF.

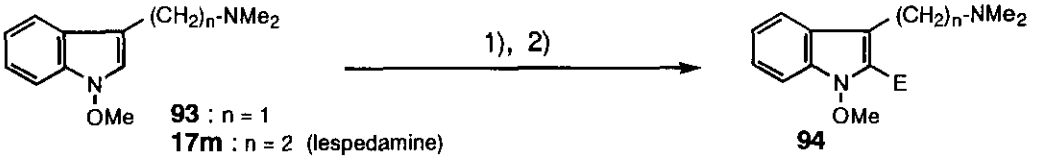
Table 5



	Electrophile	R	Yield (%) of 90	R	91	Yield (%) of Other Product	92
a	$Me_2C{=}O$	$C(OH)Me_2$	90		85		7
b	$(Ph)_2C{=}O$	$C(OH)Ph_2$	81		69		19
c	$Me_2NCH{=}O$	CHO	99		62		22
d		*a	68		97	–	–
e	$(MeO)_2C{=}O$	COOMe	60		90	–	–
f	I_2	I	89		–	–	–

*a: The product was isolated after acetylation with Ac_2O-pyridine.
1) *n*-BuLi, Ar, THF or ether,-18°C; 2) electrophile; 3) H_2, 10% Pd/C.

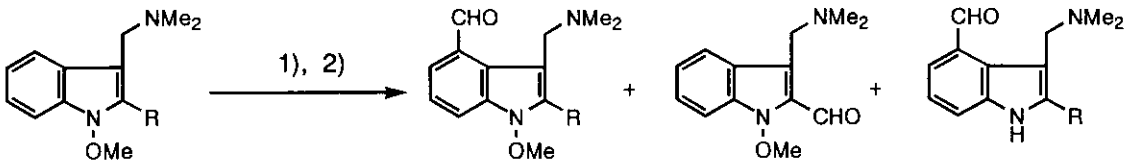
Table 6



Entry	Starting Material	Electrophile		E	Yield (%) of 94
1	93	$Me_2NCH{=}O$	a	CHO	96
2	〃	Me_3SiCl	b	$SiMe_3$	91
3	〃	$(Ph\text{-}S)_2$	c	SPh	97
4	〃	$(Me\text{-}S)_2$	d	SMe	96
5	〃	$(sec\text{-}Bu\text{-}S)_2$	e	S-*sec*-Bu	99
6	〃	Me_3SnCl	f	$SnMe_3$	96
7	17m	$Me_2NCH{=}O$	g	CHO	91
8	〃	Me_3SiCl	h	$SiMe_3$	86

1) *n* -BuLi, THF or ether, Ar, -18°C; 2) electrophile, rt, Ar.

Table 7

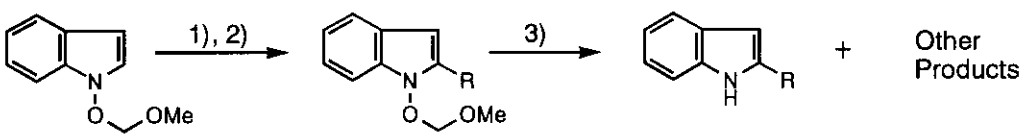


94 **95** **96** **97**

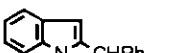
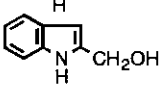
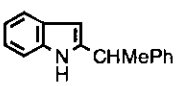
Entry	Starting Material	Lithiation Condition *n* - BuLi (mol eq.)	Reaction Temp. (°C)		R	Yield (%) of **95**	**96**	**97**
1	**94b**	3.1	reflux	**a**	$SiMe_3$	70	14	0
2	**94c**	1.7	reflux	**b**	SPh	67	0	6
3	**94d**	3.0	20	**c**	SMe	43	13	0
4	**94e**	3.0	reflux	**d**	S-*sec*-Bu*a	67	0	0

*a : Formation of 2-*sec*-butyl-4-hydroxy-1-methoxy-3-dimethylaminomethylindole was observed in 10% yield. 1) *n* -BuLi, Ar, ether; 2) DMF, 0°C~rt, Ar.

Table 8



48h **98** **91** **92**

	Electrophile	R	Yield (%) **98**	**91**	of Other Product	**92**
a	$Me_2C{=}O$	$C(OH)Me_2$	89*a	87	–	–
b	$(Ph)_2C{=}O$	$C(OH)Ph_2$	99	90		6
c	$Me_2NCH{=}O$	CHO	96	67		26
g	Me_3SiCl	$SiMe_3$	91	86	–	–
h	$MePhC{=}O$	C(OH)MePh	88*a	76		10

*a: Starting material was recovered in 10% yield, respectively.

1) *n*-BuLi, Ar, THF or ether, 0°C; 2) electrophile; 3) H_2, 10% Pd/C.

1-Methoxy group stabilizes a 2-lithio species and facilitates regioselective lithiation of indoles at the 2-position.[17,19] Low reaction temperatures (-76°C) and the use of pyrophoric *t*-BuLi are not required. For example, 1-methoxyindole (**17a**) was lithiated with *n*-BuLi at -18°C (ice and sodium chloride bath) for 10 min. The 2-lithiated indole reacts with a wide range of electrophiles giving 2-substituted 1-methoxyindoles (**90a-f**) in good to excellent yields. The results are summarized in Table 5.[17,19a]

Lithiation at the 2-position becomes much easier if an additional activating group is introduced at the 3-position. The example is the lithiation of 3-dimethylaminomethyl-1-methoxyindole (**93**) as shown in Table 6.[19b] Thus, lithiation of **93** in THF (or ether) took place exclusively at the 2-position. Even when an excess amount of *n*-BuLi was used, extra lithiation at the 4- or 7-position was not observed. Subsequent reactions of the 2-lithiated indole with electrophiles such as DMF, TMS chloride, diphenyl disulfide, dimethyl disulfide, di-*sec*-butyl disulfide, and trimethyltin chloride produced **94a-f** in excellent yields (Table 6, Entries 1-6). The other example was an indole alkaloid, lespedamine (**17m**, 3-dimethylaminoethyl-1-methoxyindole), which was also lithiated readily, and subsequent trapping with DMF and TMS chloride afforded 2-substituted indoles, **94g** and **94h**, respectively (Entries 7 and 8).[19b]

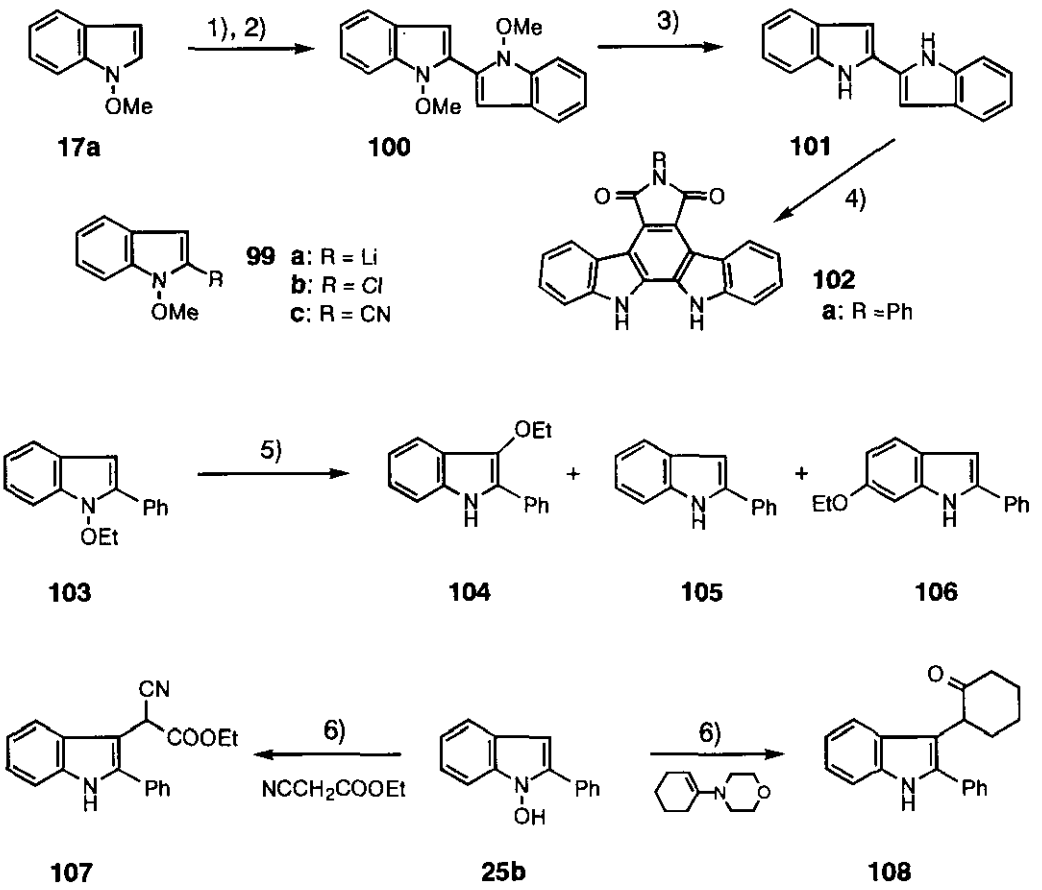
With the expectation that a bulky 2-substituent in the compounds (**94b-e,h**), would force the direction of dimethylamino group towards the 4-position, attempts to lithiate them at the 4-position were made, and an interesting solvent dependence was discovered.[19b] In fact, as long as THF was used as a solvent, lithiation at the 4-position never took place. Once a solvent was changed to ether, the desired lithiation occurred easily as shown in Table 7. The lithiated solution of **94b** reacted with DMF to afford 4-formyl- (**95a**, 70%) and 2-formylindole derivatives (**96a**, 14%, Entry 1). Under similar reaction conditions, **94c-e** produced 4-formylindoles (**95b-d**) as major products (Entries 2-4). While at present all attempts to lithiate **94h** at the 4-position are unsuccessful under various examined reaction conditions, employing *t*-, *sec*-, or *n*-BuLi in either THF or ether at from -78°C to refluxing temperatures.[19b]

4-6-2. Preparation of 2-Substituted 1-Methoxymethoxyindoles

Lithiation of **17a** was performed with *n*-BuLi at about -18°C (ice-sodium chloride) in excellent yields. Nevertheless, when the reaction was carried out at 0°C, the yields of products dropped down to 30-50%. However, using 1-methoxymethoxyindole (**48h**), regioselective lithiation of indoles at the 2-position was relatively more readily attained. Due to the superiority of 1-methoxymethoxy group as a lithium ligand to the 1-methoxy group, lithiation could be carried out at 0°C (ice cooling) with *n*-BuLi. Subsequent reactions with electrophiles produced 2-

substituted 1-methoxymethoxyindoles (**98**) in good to excellent yields. The results are summarized in Table 8.[17]

Scheme 11



1) *n*-BuLi, THF; 2) $CuSO_4$, O_2, ultrasound; 3) 10% Pd/C, H_2; 4) *N*-phenylmaleimide; 5) hυ, MeOH; 6) TsCl, DMF, pyridine.

4-6-3. Oxidation of 1-Methoxyindol-2-yllithium

Treatment of the yellow THF solution of 1-methoxyindol-2-yllithium (**99a**), generated from **17a** and *n*-BuLi, with anhydrous $CuSO_4$ under oxygen atmosphere with ultrasound stirring at 0°C produced 2,2'-bi(1-methoxyindolyl) (**100**, 54%) (Scheme 11).[19a] Quantity of $CuSO_4$ had an important effect on the coupling yield, and 0.5 mol eq. was found to be recommendable. Although cupric chloride and cuprous cyanide were examined as a coupling reagent, the yield of **100** was poor (6-38%), and either 2-chloro- (**99b**, 4-21%) or 2-cyano-1-methoxyindole (**99c**, 3-10%) was produced as a by-product, respectively.

Catalytic hydrogenation of **100** over 10% Pd/C under atmospheric hydrogen afforded 2,2'-biindolyl (**101**, 79%)

and its application to the preparation of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (**102a**) is described in Section 7-1.

4-7. Reduction

Removal of 1-hydroxy and 1-methoxy group is attained generally by catalytic hydrogenation at room temperature and atmospheric pressure over 10% Pd/C. Some examples are listed in Tables 5 and 8.[10c] Raney nickel is also used successfully. In some cases, over reduction occurs. For example, reduction of **90a** produced 2-(1-hydroxy-1-methyl)- (**91a**, 85%), 2-(1-methoxy-1-methyl)- (**92a**, 7%), and 2-(1-methyl)ethylindoles (4%). Similarly, **98c** gave **91c** (67%) and indole-2-methanol (**92c**, 26%). Consequently, combination of the reaction of 1-alkoxyindol-2-yllithium with electrophiles (Sections 4-6-1 and 4-6-2) and the removal of the 1-alkoxy group provides a versatile preparation method for 2-substituted indoles.

1-Methoxy group on indoles having electron donating group is quite sensitive and removed under milder reduction conditions. Typical examples are shown in the syntheses of both methoxybrassinin and (±)-paniculidine B in Sections 5-2 and 5-4.

4-8. Photoreaction

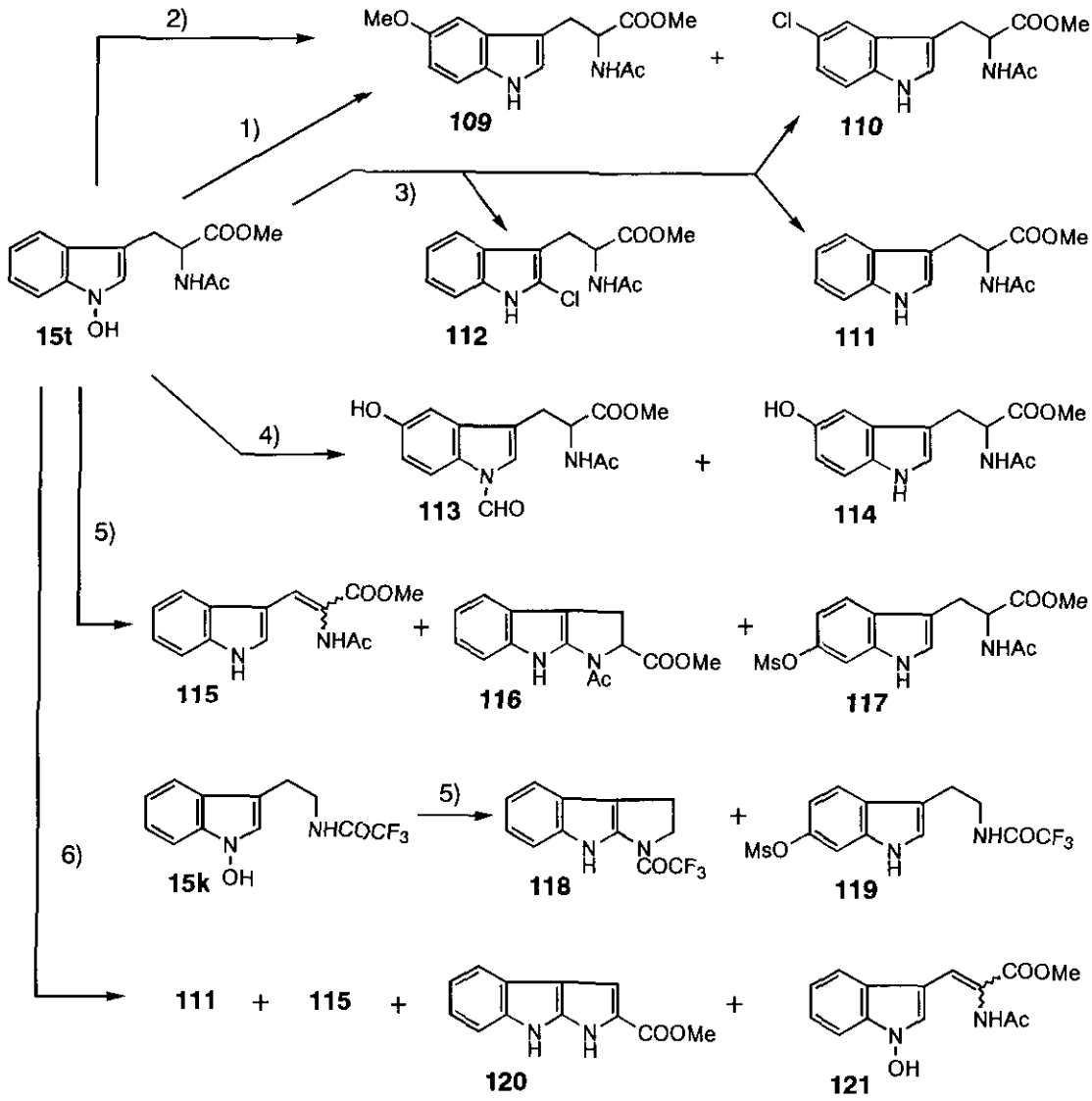
UV irradiation is an useful means for breaking N-O bond and successfully applied for removing 1-hydroxy and 1-methoxy group. In 1973, we attempted the rearrangement of 1-ethoxy group to 3 and other positions (Scheme 11). This is the first report of our research based on "1-Hydroxyindole Hypotheses".[20] Irradiation of 1-ethoxy-2-phenylindole (**103**) in methanol with Hannovia UV lamp produced 3-ethoxy-2-phenyl- (**104**), 2-phenylindole (**105**), and the other rearranged product (**106**) carrying an ethoxy group on the benzene part.[20] Quite recently, we have succeeded in proving that **106** is 6-ethoxy-2-phenylindole.[12] Consequently, we can conclude that any substituents at the 1-position of indoles, including 1-alkoxy group, have the possibility of migration to 3-, 4-, and/or 6 -positions upon photoirradiation.[20]

4-9. Nucleophilic Substitution Reaction

Nucleophilic substitution reactions are rarely known in the indole chemistry.[1,10,21] In 1981, Hamana and co-workers[22] disclosed that 1-hydroxy-2-phenylindole (**25b**) afforded 3-substituted indoles (for example **107** and **108**) by its reaction with tosyl chloride in the presence of nucleophiles (Scheme 11). Moody and co-workers reported that 1-substituted 2-chloroindole-3-carbaldehyde underwent nucleophilic substitution reaction.[23]

Indole-chromium carbonyl complexes were also found to react with nucleophiles by Kozikowski and Semmelhack groups.[24]

Scheme 12



1) 10% H_2SO_4, MeOH; 2) 3% HCl, MeOH; 3) $SOCl_2$; 4) 85% HCOOH; 5) MsCl, pyridine; 6) *o*-dichlorobenzene, 180°C; 7) 20% BF_3·MeOH.

4-9-1. Acid Catalyzed Nucleophilic Substitution Reaction of *Nb*-Acetyl-1-hydroxytryptophan Methyl Ester and Its Derivatives

We imagined nucleophilic substitution reactions as one of the characteristics of 1-hydroxyindoles in our hypotheses".[1] Our imaginary reactions actually occurred at least chemically on 1-hydroxytryptophan derivatives as

illustrated in Scheme 12.[1c]

Treatment of (±)-*Nb*-acetyl-1-hydroxytryptophan methyl ester (**15t**) with 10% H_2SO_4 in MeOH produced 5-methoxy compound (**109**, 71%). When 3% hydrochloric acid was employed, the products were **109** (32%) and 5-chloro compound (**110**, 18%). Thionyl chloride reacted with **15t** generating 2-chloro compound (**112**, 35%) accompanied by **110** (9%) and **111** (3%). Bromide was also employed successfully as a nucleophile and the typical example is illustrated in the preparation of 5-bromo-*N,N*-dimethyltryptamine in Section 5-5.

To our most delighted, when the 1-hydroxy compound (**15t**) was treated with 85% HCOOH, the dreamt reaction took place to give (±)-*Nb*-acetyl-1-formyl- (**113**, 12%) and (±)-*Nb*-acetyl-5-hydroxytryptophan methyl esters (**114**, 67%). The compound (**15t**) also reacted with mesyl chloride to produce α,β-dehydrotryptophan (**115**, 3:2 mixture of isomers, 2%), 2,3-dihydropyrrolo[2,3-*b*]indole (**116**, 47%), and 6-mesyloxytryptophan derivative (**117**, 9%). Under similar reaction conditions, 1-hydroxy-*Nb*-trifluoroacetyltryptamine (**15k**) produced **118** (45%) and **119** (8%). Thermolysis of **15t** in *o*-dichlorobenzene at 180°C afforded **111** (16%), **115** (17%), pyrrolo[2,3-*b*]indole (**120**, 8%), and 1-hydroxy-α,β-dehydrotryptophan derivative (**121**, 39%).

4-9-2. Preparation of Melatonin, Serotonin, *N*-Methylserotonin, and Bufotenine through 1-Hydroxytryptamines

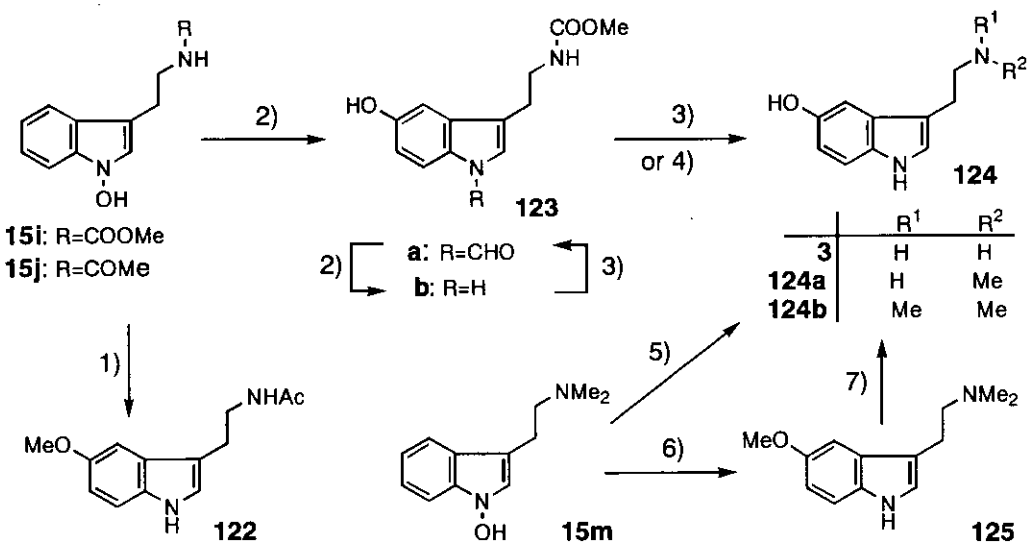
Biologically important amines such as melatonin (**122**), serotonin (**3**), *N*-methylserotonin (**124a**), and bufotenine (**124b**) were also prepared directly through the corresponding 1-hydroxytryptamines as imagined in our hypotheses[1] (Scheme 13).[25]

Melatonin (**122**), being attracted much attention as a hydroxyl radical scavenger, a regulator of circadian rhythms, etc.,[26] was produced regioselectively in more than 80% yield by the reaction of *Nb*-acetyl-1-hydroxytryptamine (**15j**) with BF_3·MeOH complex in refluxing MeOH.

While *Nb*-methoxycarbonyl-1-hydroxytryptamine (**15l**) led to **123a** (15%) and **123b** (50%) by the reaction with 85% HCOOH at room temperature. Hydrolysis of **123b** to serotonin (**3**, 73%) was attained by hydrolysis, while reduction of **123b** with $LiAlH_4$ in refluxing Et_2O-THF afforded *N*-methylserotonin (**124a**, 65%). An attempt to convert *N,N*-dimethyl-1-hydroxytryptamine (**15m**) into bufotenine (**124b**, 47%) was realized by treatment with 5% aqueous H_2SO_4 at reflux. When the solvent was changed to MeOH under similar reaction conditions, **15m** afforded **125** (57%) and **124b** (7%). The cleavage of the methoxy group of **125** using BBr_3 in CH_2Cl_2-toluene is an alternative route to **124b** (63%).

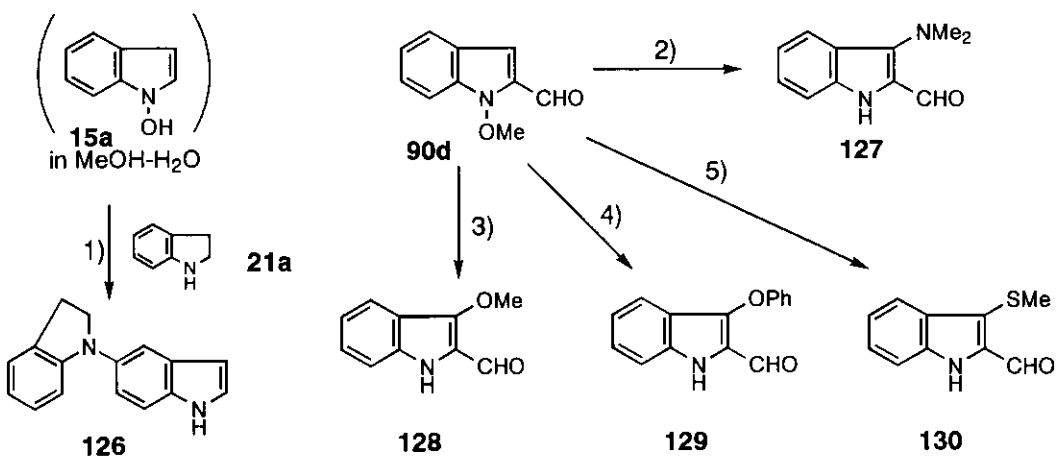
4-9-3. Preparation of 2- and 3-Substituted Indoles

Scheme 13



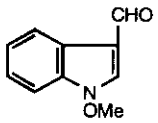
1) BF_3·MeOH, reflux; 2) 85% HCOOH; 3) NaOH, MeOH for **124a**; 4) $LiAlH_4$, Et_2O, THF for **124b**; 5) 5%H_2SO_4, H_2O for **124c**; 6) 5%H_2SO_4, MeOH; 7) BBr_3, CH_2Cl_2-toluene.

Scheme 14



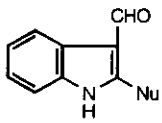
1) MeOH, standing at rt; 2) Me_2NH, MeOH; 3) NaOMe, MeOH; 4) PhOH, KO*t*-Bu; 5) NaSMe, MeOH.

Table 9



17b

Nucleophiles (NuH)
Base



131

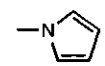
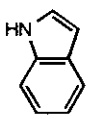
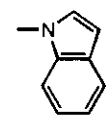
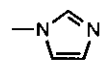
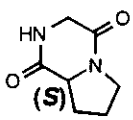
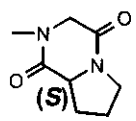
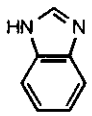
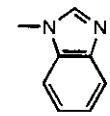
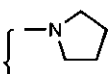
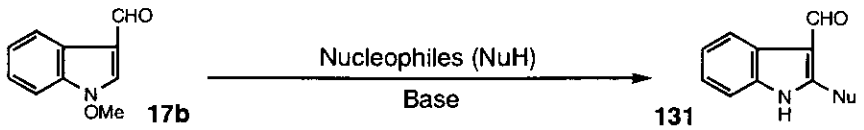
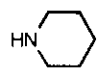
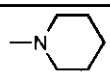
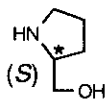
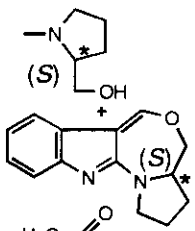
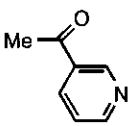
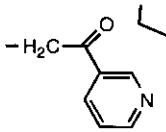
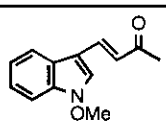
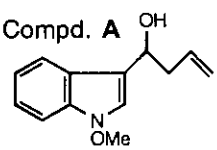
Entry	NuH	Base	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Results Nu		Yield (%)
1	MeOH	NaOMe	MeOH	reflux	2	—OMe	**a**	90
2	EtOH	NaOEt	EtOH	reflux	2	—OEt	**b**	95
3	MeSH	NaSMe	MeOH-H_2O	reflux	2	—SMe	**c**	94
4	$HOCH_2CH_2OH$	Na	$HOCH_2CH_2OH$	60	19	$-OCH_2CH_2OH$	**d**	50
5	$HO(CH_2)_3OH$	NaH	DMF	70	5	$-OCH_2CH_2CH_2OH$	**e**	76
6	$HOCH_2CH(OH)CH_2OH$	Na	$HOCH_2CH(OH)CH_2OH$	70	5	$-OCH_2CH(OH)CH_2OH$	**f**	30
7	$HO(CH_2)_2NMe_2$	Na	THF	70	2	$-O(CH_2)_2NMe_2$	**g**	36
8		NaH	DMF	rt	3		**h**	99
9		NaH	DMF	rt	24		**i**	95
10		NaH	DMF	rt	48		**j**	81
11		NaH	DMF	rt	6		**k**	63
12		NaH	DMF	rt	120		**l**	30
13		NaH	DMF	rt	6	 + **131a**	**m**	71 24

Table 10

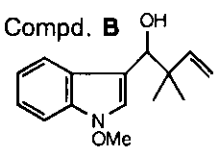


Entry	NuH	Base	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Results Nu		Yield (%)
1		NaH	DMF	rt	6	 + **131a**	**o**	26 64
2		NaH	DMF	rt	0.5		**p** **q**	14 23
3		KH	THF	rt	3		**r**	56
4	$SiMe_3$ $CH_2CH{=}CH_2$	$(n\text{-}Bu)_4NF$	THF	rt	6	$-CH_2CH{=}CH_2$ + Compd. **A**	**s** **t**	23 28
5	$SiMe_3$ $CH_2CH{=}CMe_2$	$(n\text{-}Bu)_4NF$	THF	rt	3	$-CH_2CH{=}CMe_2$ + $-C(Me)_2CH{=}CH_2$ + Compd. **B** + Recovery	**k** **u** **v**	7 12 14 38
6	OH $CH_2CH{=}CMe_2$	NaH	DMF	rt	24	Compd. **C**	**w**	41
7	MeCOMe	KH	THF	rt	2	$-CH_2COMe$	**x**	48
8	COMe CH_2COOMe	NaOMe	MeOH	75	2	$-CH_2COOMe$	**y**	38
9	MeCOMe	8% NaOH	MeOH	rt	6		**132**	96

Compd. **A**



Compd. **B**



Compd. **C**

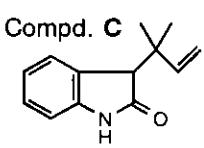
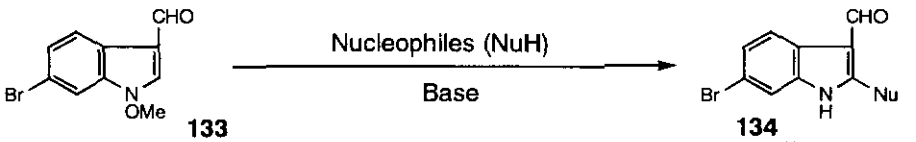
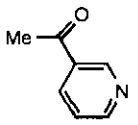
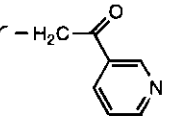
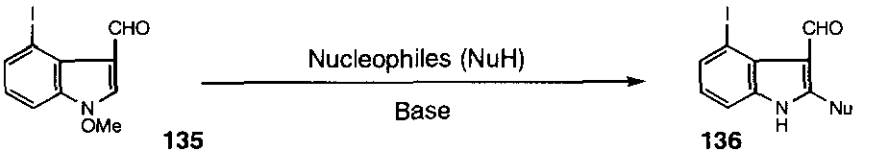


Table 11

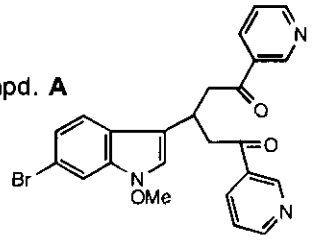


Entry	NuH	Base	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Results Nu	Results Yield (%)
1		KH	THF	rt	1	 + Compd. **A**	62 + 3
2	$CH_2(COOMe)_2$	KO*t*Bu	DMF	70	2.5	$-CH(COOMe)_2$ + Recovery	78 + 5
3	MeCOMe	KH	THF	rt	3	$-CH_2COMe$	51
4	$HOCH_2CH{=}CMe_2$	NaH	DMF	rt	14	Compd. **B**	47

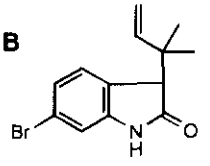


Entry	NuH	Base	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Results Nu		Results Yield (%)
1	$CH_2(COOMe)_2$	KO*t*Bu	DMF	rt	2	$-CH(COOMe)_2$	**a**	96
2	MeOH	NaOMe	MeOH	rt	2	—OMe	**b**	87

Compd. **A**



Compd. **B**



Even under basic conditions, both 1-hydroxy and 1-methoxy groups can function as a leaving group. A typical example is 1-hydroxyindole itself (**15a**). When it was allowed to stand in MeOH in the presence of excess 2,3-dihydroindole (**21a**), formation of 5-(2,3-dihydroindol-1-yl)indole (**126**, 8%) was observed accompanied by many unidentified products (Scheme 14).[1c]

Indole-2- and -3-carbaldehydes will not react with nucleophiles even under forced reaction conditions. In contrast, introduction of 1-methoxy group changes natures of indole-2- and -3-carbaldehydes to be susceptible to nucleophilic substitution.[10d] Thus, 1-methoxyindole-2-carbaldehyde (**90d**) reacted with nucleophiles such as dimethylamine, NaOMe, potassium phenoxide, and sodium thiomethoxide (NaSMe) to produce the corresponding 3-substituted indoles (**127**, 90%; **128**, 85%; **129**, 51%; **130**, 73%). The results are illustrated in Scheme 14.

Similar reaction of 1-methoxyindole-3-carbaldehyde (**17b**) with NaOMe or NaOEt produced 2-methoxy- (**131a**, 90%) or 2-ethoxyindole-3-carbaldehyde (**131b**, 95%), respectively (Table 9, Entries 1 and 2).[10d] Brassicanal A (**131c**) and **17b** are phytoalexins isolated from plant family *Cruciferae*.[15q] Considering our hypotheses and coexistence of **131c** with **17b** in the same plant, biosynthetic pathway of **131c** from **17b** could be assumed.[1c] Actually, the transformation of **17b** to **131c** (94%) proceeded successfully by the reaction with NaSMe (Entry 3).

Substitution reactions of **17b** with other oxygen and nitrogen containing nucleophiles were also successful and typical results are listed in Tables 9 and 10.[10d,e] Nucleophiles, such as pyrrole, indole, imidazole, and (8a*S*)-octahydropyrrolo[1,2-*a*]pyrazine-1,4-dione, afforded **131h-k** in excellent to good yields (Entries 8-11). The reaction rate of benzimidazole was slow and even after 5 days, starting material was recovered as a major product (62%) together with **131l** (30%, Entry 12).

The reaction of **17b** with carbon nucleophiles including allylsilanes and active methylene compounds are also summarized in Table 10.[10d] When sodium allylalkoxide was employed, 2-allyloxyindole was isolated as an intermediate, which readily underwent thermal [3,3] sigmatropic rearrangement to produce 2-oxindole (**131w**, Entry 6). This finding is applied to the synthesis of (±)-debromoflustramine B in Section 7-3.

Interestingly, in the reaction of **17b** with acetone, products are governed by the base used. Thus, when KH was used (Entry 7), **131x** (48%) was produced as a sole product, while 4-(1-methoxyindol-3-yl)-3-buten-2-one (**132**, 96%) was obtained if 8% NaOH was employed (Entry 9). Furthermore, the reaction of **17b** with methyl acetoacetate and NaOMe afforded **131y** (38%) without formation of **131x** (Entry 8). These results are applied for the synthesis of (±)-paniculidine B as illustrated in Section 5-4.

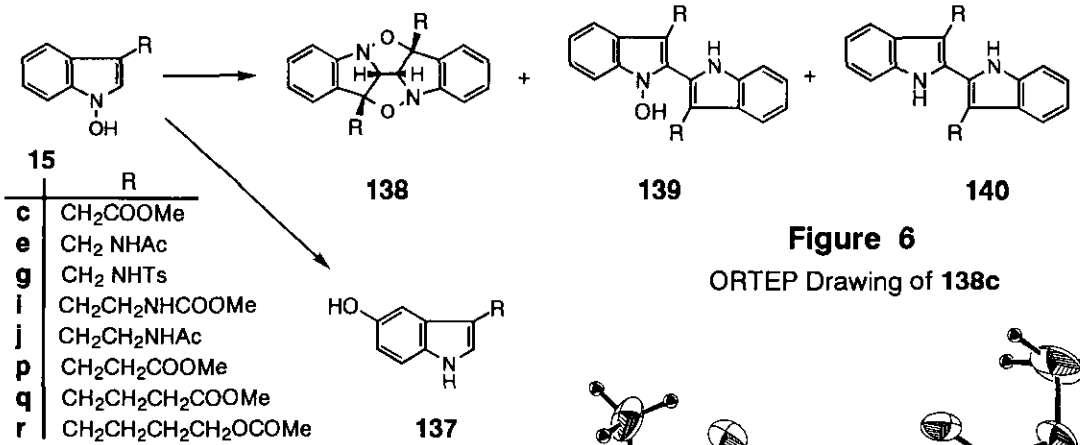
In the cases of 6-bromo- (**133**) and 4-iodo-1-methoxyindole-3-carbaldehyde (**135**), similar nucleophilic substitution reactions took place to give 2-substituted 6-bromo- (**134**) and 4-iodoindole-3-carbaldehydes (**136**). The results

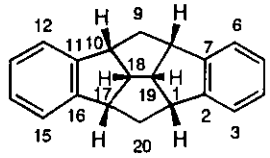
are summarized in Table 11.

4-10. Acid Catalyzed Dimerization

As noted in Section 4-9, we disclosed that 1-hydroxytryptophan (**15t**) and 1-hydroxytryptamine derivatives (**15l,j**) produced the corresponding 5-hydroxy compounds (**114**, **123**, and **122**) in the reaction with 85% HCOOH. According to these facts, we expected methyl 5-hydroxyindole-3-acetate (**137c**) as a major product in the reaction of methyl 1-hydroxyindole-3-acetate (**15c**) with 85% HCOOH (Scheme 15). Surprisingly, **137c** was not observed at all, instead a novel type of dimerization occurred forming hexacyclic dimer (**138c**, 20%), 1-hydroxy dimer (**139c**, 8%), and methyl indole-3-acetate (**46b**,14%),[27] while a mixture of TFA and acetonitrile (1:1, v/v) led **15c** to afford another dimer (**140c**, 3%) together with **138c** (27%), **139c** (5%), and **46b** (14%). When TFA alone was used at room temperature, formation of **138c** was not observed, and **139c** (48%) and **140c** (17%) were produced.

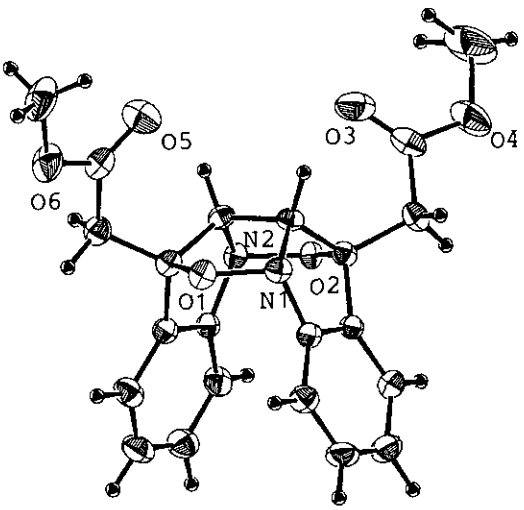
Scheme 15





141 kabutane
all-*cis* -dibenzo[*b,g*]tetracyclo-
[7.2.1.$0^{4,11}$. $0^{6,10}$]dodecane

Figure 6
ORTEP Drawing of **138c**



Methyl 1-hydroxyindole-3-propionate (**15p**) also afforded **138p** (39%) and **139p** (11%) by the reaction with 85%

HCOOH. Under similar reaction conditions, methyl 1-hydroxyindole-3-butylate (**15q**) gave **138q** (47%) and **139q** (28%), while 1-hydroxy-3-(4-acetoxybutyl)indole (**15r**) produced **138r** (36%) and **139r** (41%). By contrast, 3-aminomethyl-1-hydroxyindole *derivatives (***15e** *and* **g***) gave no isolable products forming* tars in the reaction with 85% HCOOH.

The structure of **138a** was determined by X-Ray single crystallographic analysis. The results shown *in Figure 6* clearly show that **138a** has C_2 symmetry and characteristic Kabuto (Japanese ancient soldiers helmet) like structure in shape. So, we gave kabutane as the short name for the parent skeleton, all-*cis*-dibenzo[*b,g*]-tetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (**141**).[27] As a result, 1-hydroxyindole compounds were found to be sensitive to acids and undergo four types of competing reactions; dehydroxylation, nucleophilic substitution, dimerization, and formation of 8,17-disubstituted 1,10-diaza-9,20-dioxakabutanes (**138**).

Why do only tryptamine derivatives undergo nucleophilic substitution reactions effectively under mild acidic conditions? These phenomena are one of the most important facts in accord with our "1-Hydroxyindole Hypotheses". Although we can not explain the reason at present, we have concluded that the C—C—N structure *in the side chain* at the 3-position is essential for realizing regioselective nucleophilic substitution reaction at the 5-position.

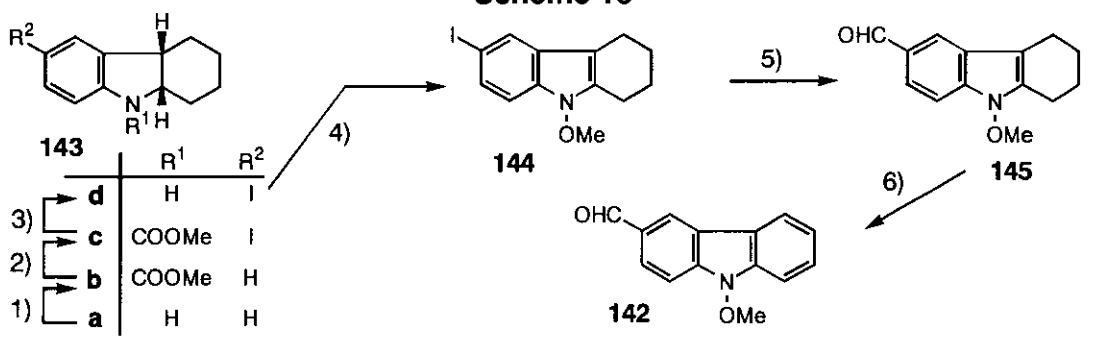
5. Syntheses of Natural Products Having 1-Methoxyindole Structure

Alkaloids and glucosinolates having 1-methoxyindole nucleus have been isolated from microorganisms and plants as phytoalexins, alterating substances of chemically induced carcinogenesis, and so on.[15] It is therefore necessary to establish synthetic methods for supplying them in much quantities so as to pursue thorough and systematic biological evaluations.

5-1. 9-Methoxycarbazole-3-carbaldehyde

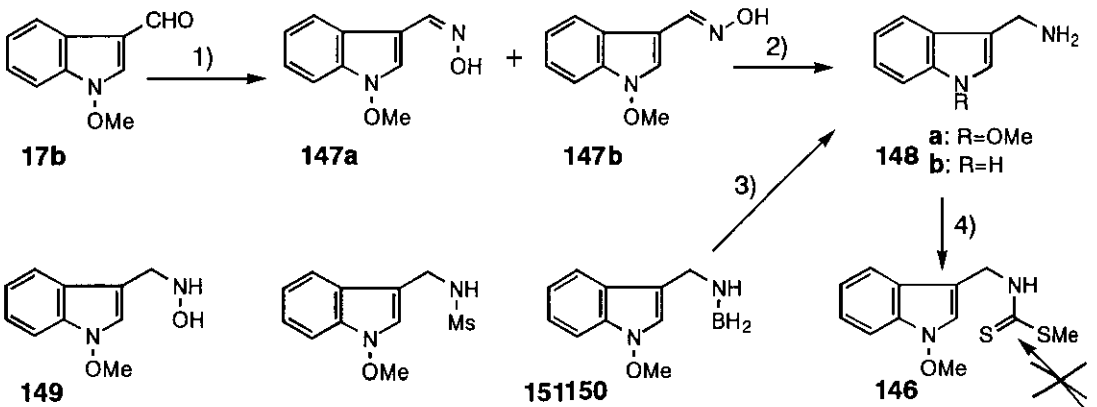
Furukawa and co-workers isolated 9-methoxycarbazole-3-carbaldehyde (**142**) from *Murraya euchrestifolia* in *1988.*[15n] *Starting from 4a,9a-cis-*1,2,3,4,4a,9a-hexahydrocarbazole (**143a**), its synthesis was carried out as shown in Scheme 16.[28a] First, **143a** was converted to 9-methoxycarbonyl compound **143b** (89%) and then to 6-iodo compound (**143c**, 61%) with iodine and sodium periodate. *Alkaline hydrolysis of* **143c** *led to 6-iodo* compound (**143d**) (85%). Application of the tungstate method to **143d**, followed by methylation with CH_2N_2, gave 1,2,3,4-tetrahydro-6-iodo-9-methoxycarbazole (**144**, 37%). Lithiation of **144** with *n*-BuLi and quenching with DMF afforded **145** (50%). Dehydrogenation of **145** was achieved with 2,3-dichloro-5,6-dicyano-1,4-benzo-

Scheme 16



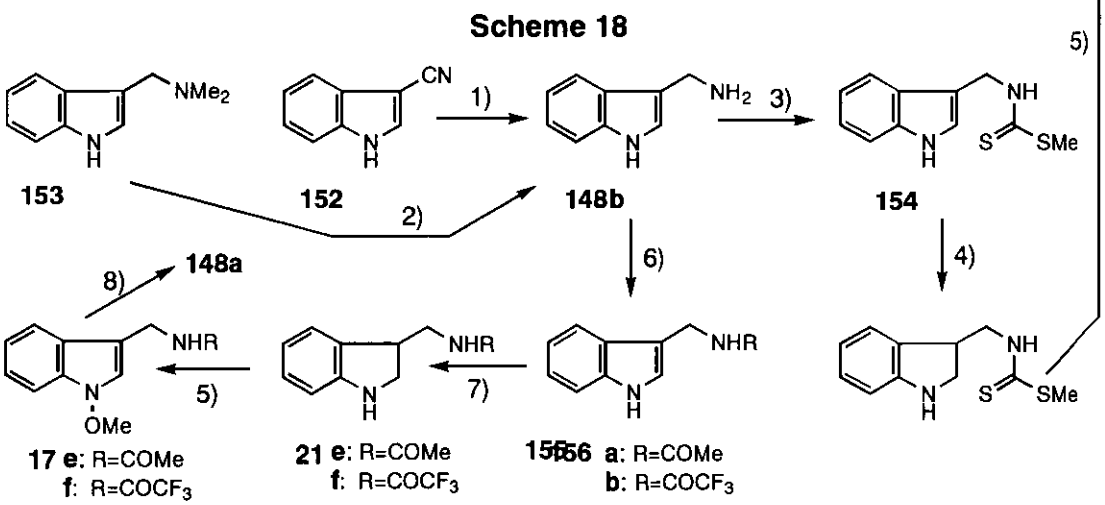
1) ClCOOMe; 2) I_2, $NaIO_4$; 3) 8% NaOH; 4) i. $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2; ii. CH_2N_2; 5) i. *n*-BuLi; ii. DMF; 6) DDQ.

Scheme 17



1) $NH_2OH \cdot HCl$, pyridine; 2) $NaBH_4$ (3 mol), MsCl (3 mol), rt; 3) HCOOH, rt; 4) i. CS_2, Et_3N; ii. MeI.

Scheme 18



1) $LiAlH_4$; 2) MeI, aq. NH_3; 3) i. CS_2, Et_3N; ii. MeI; 4) $NaBH_3CN$, AcOH; 5) i. $NaWO_4 \cdot 2H_2O$, 30% H_2O_2; ii. CH_2N_2; 6) Ac_2O for **156a**; CF_3COOEt for **156b**; 7) $NaBH_3CN$, AcOH for **21e**; Et_3SiH, CF_3COOH for **21f**; 8) aq. NaOH, MeOH.

quinone in benzene to give **142** (29%).

5-2. Methoxybrassinin

5-2-1. The First Synthesis

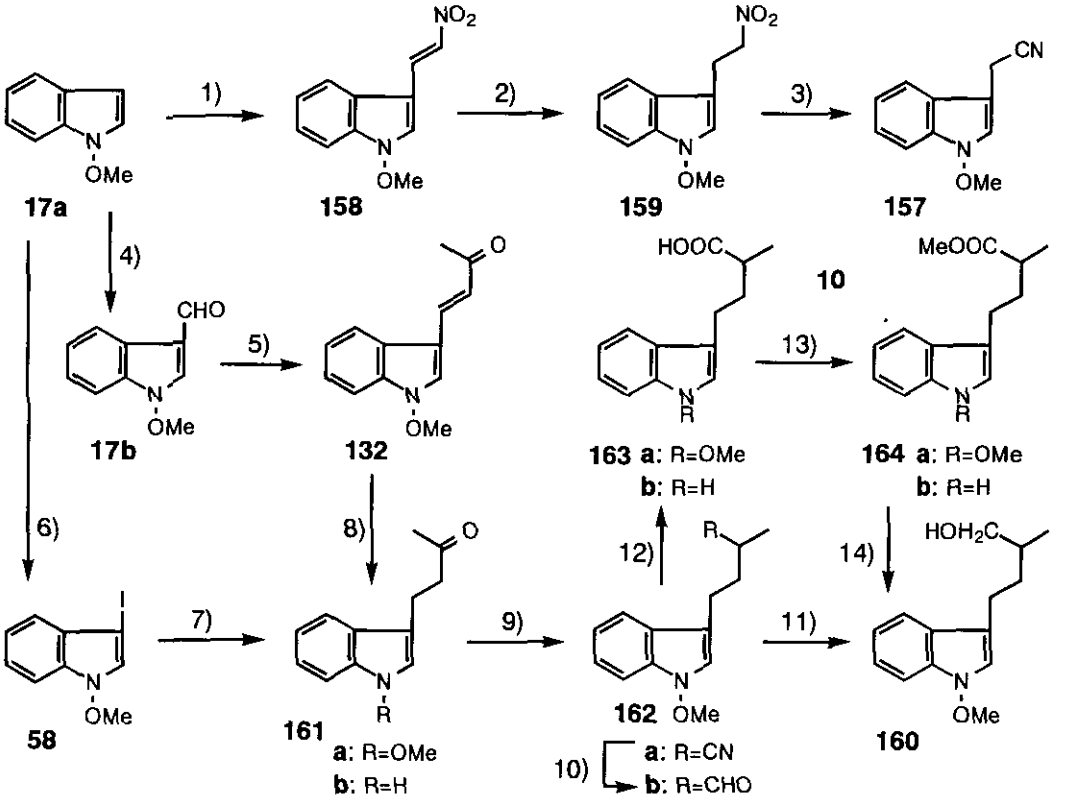
In 1988, Takasugi and co-workers isolated methoxybrassinin (**146**) from chinese cabbage *Brassica campestris* L. ssp. pekinensis[150] and established the structure (Scheme 17). Its synthesis required 3-aminomethyl-1-methoxyindole (**148a**) as a key intermediate. So, the readily available 1-methoxyindole-3-carbaldehyde (**17b**) was converted to oximes (**147a** and **147b**, 1:1.6, 98%) with hydroxylamine.[28a] Subsequent reduction of the oximes were, however, troublesome step due to the instability of the N-OMe bond. Reduction with $LiAlH_4$, Zn (Hg)-HCl, or $NiCl_2$-$NaBH_4$ completely eliminated 1-methoxy group culminating in the formation of 3-aminomethylindole (**148b**). Although reduction with B_2H_6-THF, $NaBH_3CN$-AcOH, or $ZrCl_4$-$NaBH_4$ afforded 3-hydroxyaminomethyl-1-methoxyindole (**149**), formation of **148a** was not observed. Finally, we developed a novel and mild reducing method for converting oximes to amines using $NaBH_4$ and mesyl chloride in dry THF. Employing the method, the oximes (a mixture of **147a** and **147b**) were converted to **148a** (21%) accompanied by its borane complex (**150**, 12%) and 3-mesylaminomethyl-1-methoxyindole (**151**, 16%). Borane complex (**150**) was converted to **148a** (quantitative) by the reaction with formic acid. Subsequent treatment of **148a** with carbon disulfide, followed by the reaction with MeI, achieved the first total synthesis of methoxybrassinin (**146**, 64%).

5-2-2. Improved Synthesis of Methoxybrassinin

Reduction of indole-3-carbonitrile (**152**) with $LiAlH_4$ was a conventional synthetic method for unstable 3-aminomethylindole (**148b**) (69%). We developed a novel and simpler one pot synthetic method for **148b** (60%) from gramine (**153**) by converting it to (indol-3-ylmethyl)trimethylammonium iodide, followed by treatment with aqueous ammonia.[28c] Based on the method, improved synthesis of **146** was attained as illustrated in Scheme 18.[28b,c]

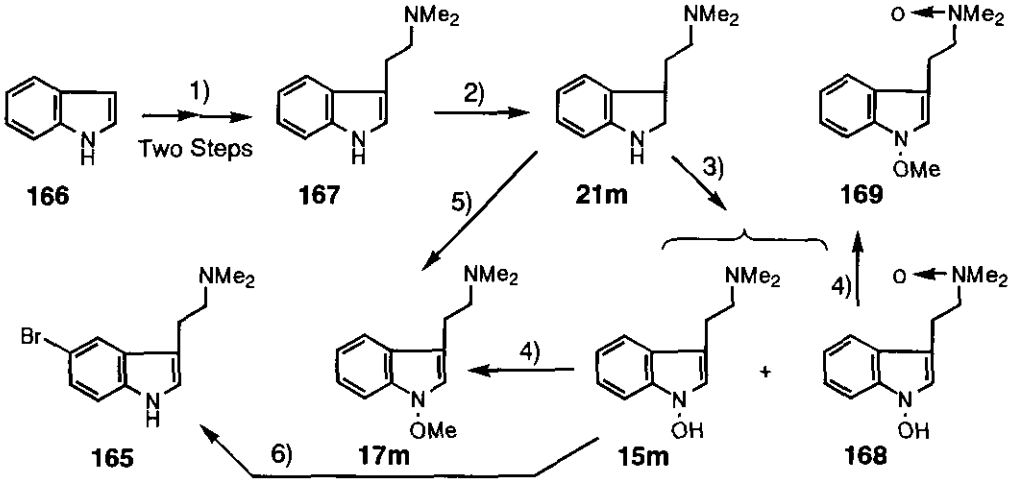
The reaction of **148b** with carbon disulfide, followed by the treatment with MeI, afforded brassinin (**154**, 89%). Unfortunately, 2,3-dihydrobrassinin (**155**), prepared by the reduction of **154** with $NaBH_3CN$ in AcOH, did not afford 1-hydroxybrassinin by the tungstate method. Therefore, 3-aminomethylindole (**148b**) was converted to acetyl (**156a**, 88%) or trifluoroacetyl derivative (**156b**, 91%). Reduction of **156a** with $NaBH_3CN$ in AcOH and **156b** with Et_3SiH in TFA afforded 2,3-dihydroindoles (**21e** (93%) and **21f** (82%)), respectively. Subsequent oxidation of **21e** and **21f** with the tungstate method, followed by methylation with CH_2N_2, produced **17e** (59%) and **17f**

Scheme 19



1) 1-dimethylamino-2-nitroethylene, CF_3COOH; 2) $NaBH_4$, silica gel; 3) $(Me_2N)_3P$, Et_3N; 4) $POCl_3$, DMF; 5) acetone, 2N-NaOH; 6) I_2, morpholine; 7) 3-buten-2-ol, $Pd(OAc)_2$ (cat.), phase transfer catalyst; 8) 10% Pd/C, $CHCl_3$, rt; 9) TosMIC; 10) DIBAL; 11) $NaBH_4$, MeOH; 12) NaOH, H_2O; 13) CH_2N_2; 14) $LiAlH_4$.

Scheme 20



1) i. $(COCl)_2$, Me_2NH; ii. $LiAlH_4$; 2) Et_3SiH, CF_3COOH; 3) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2, MeOH, H_2O; 4) CH_2N_2; 5) one pot operation of the procedures 3 and 4; 6) 47% HBr.

(77%), respectively. Alkaline hydrolysis of both compounds produced 3-aminomethyl-1-methoxyindole (**148a**, 34% from **17e**, 98% from **17f**), which was converted to **146** by the same procedure as described in Section 5-2-1.

5-3. 1-Methoxyindole-3-acetonitrile

1-Methoxyindole-3-acetonitrile (**157**) is a natural auxin isolated from chinese cabbage in 1970 by Nomoto and co-workers.[15e] Its synthesis was achieved as illustrated in Scheme 19[9d] starting from the reaction of 1-methoxyindole (**17a**) with 1-dimethylamino-2-nitroethylene producing 1-methoxy-3-(2-nitrovinyl)indole (**158**, 72%). Further reduction with $NaBH_4$ afforded 1-methoxy-3-(2-nitroethyl)indole (**159**, 72%), which was then converted to **157** (53%) by the reaction with hexamethylphosphorus triamide.

5-4. (±)-Paniculidine B and A

Kinoshita and co-workers[15m] isolated paniculidine B from *Murraya paniculata* (Linn.) Jack and determined its structure to be 2-methyl-4-(1-methoxyindol-3-yl)-1-butanol (**160**, Scheme 19). Its synthesis started from 4-(1-methoxyindol-3-yl)-3-buten-2-one (**132**, 96%),[9e] obtained from **17b** as described in Section 4-9-3.

Selective hydrogenation of the conjugated double bond in **132** was the challenging problem in the presence of the intrinc unstable N-OMe bond. Various reduction methods with such reagents as pyridine-$NaBH_4$, CuI/$LiAlH_4$, $PdCl_2$/$NaBH_4$, and Zn(Hg)/HCl were unsuccessful, while catalytic hydrogenation over 10% Pd/C in $CHCl_3$ (other solvents are invalid) was finally discovered to give the desired 4-(1-methoxyindol-3-yl)-2-butanone (**161a**, 36%) together with demethoxy compound (**161b**, 16%). As an alternative route, **161a** was produced in 36% yield by the improved Heck reaction of 3-iodo-1-methoxyindole (**58**) with 3-buten-2-ol in the presence of tetra-*n*-butylammonium bromide. By the reaction with TosMIC, **161a** was then converted to 4-(1-methoxyindol-3-yl)-2-methylbutanenitrile (**162a**, 84%). Its reduction with DIBAL produced 4-(1-methoxyindol-3-yl)-2-methylbutyraldehyde (**162b**, 88%), which was finally transformed with $NaBH_4$ to (±)-paniculidine B (**160**, 98%).

1-Methoxy group of **162a** was interestingly so sensitive to base that even mild alkaline hydrolysis mainly produced demethoxy compound (**163b**) (49%) and the yield of the desired carboxylic acid (**163a**) was only 22%. Both carboxylic acids (**163a** and **163b**) were methylated quantitatively with CH_2N_2 to yield methyl 4-(1-methoxyindol-3-yl)-2-methylbutylate (**164a**) and (±)-paniculidine A (**164b**), respectively. Reduction of **164a** with $LiAlH_4$ afforded (±)-paniculidine B (94%) as an alternative route.

5-5. Lespedamine and 5-Bromo-*N,N*-dimethyltryptamine

Lespedamine (**17m**) is an alkaloid isolated from *Lespedeza bicolor* var. japonica Nakai in 1965 by Morimoto and co-workers (Scheme 20).[15b] In 1980, 5-bromo-*N,N*-dimethyltryptamine (**165**) was isolated from marine sponge *Smenospongia aurea* by Faulkner and co-workers.[29] The alkaloid (**165**) is a suitable target for testing the predicted nucleophilic substitution of 1-hydroxy-*N,N*-dimethyltryptamine (**15m**). So, *N,N*-dimethyltryptamine (**167**), prepared from indole (**166**) in two steps, was reduced to 2,3-dihydro-*N,N*-dimethyltryptamine (**21m**, 92%). Subsequent oxidation by the tungstate method generated **15m** (36%) as stable crystals accompanied by 1-hydroxy-*N,N*-dimethyltryptamine *N*-oxide (**168**, 30%). Then, as expected, **15m** underwent nucleophilic substitution of 1-hydroxy group for bromide with 47% aqueous HBr at room temperature producing **165** (25%) regioselectively. Methylation of **15m** and **168** with CH_2N_2 produced lespedamine[10f,30] (**17m**, 53%) and 1-methoxy-*N,N*-dimethyltryptamine *N*-oxide (**169**, 78%), respectively.

6. Syntheses of 1-Methoxy Derivatives of Biologically Active Indoles

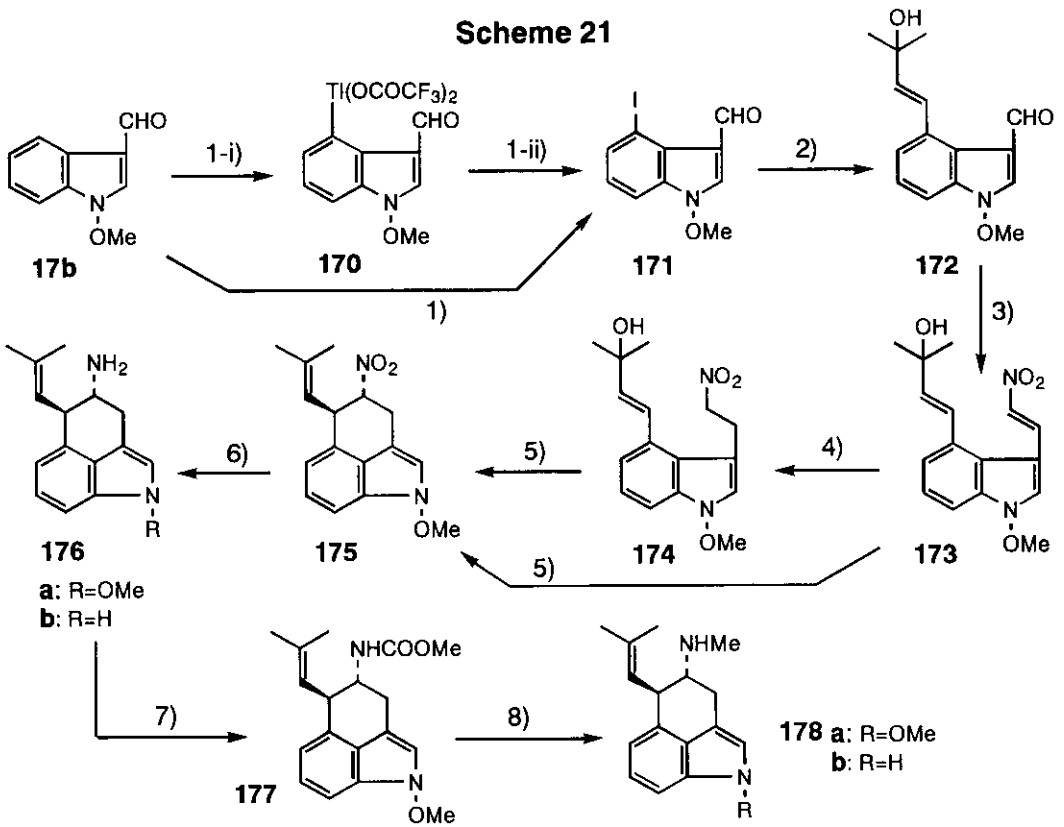
We believe that preparations of 1-hydroxy and/or 1-methoxy (or 1-alkoxy, etc.) derivatives of thus far known biologically active indoles and indole alkaloids guide us to new lead compounds.[1f] Based on the belief, the following synthetic studies have been carried out.

6-1. Ergot Alkaloid, (±)-6,7-Secoagroclavine, and (±)-1-Methoxy-6,7-secoagroclavine

Syntheses of 1-methoxy derivatives of biologically important ergot alkaloids were attempted as illustrated in Scheme 21.[9f] Regioselective thallation at the 4-position of **17b** with thallium tristrifluoroacetate and subsequent treatment with aqueous potassium iodide provided 4-iodo-1-methoxyindole-3-carbaldehyde (**171**, 91% overall yield) through **170**. Introduction of 5-carbon unit into the 4-position was attained by Heck reaction, using 2-methyl-3-buten-2-ol as an olefin component affording 4-(3-hydroxy-3-methyl-1-butenyl)-1-methoxyindole-3-carbaldehyde (**172**, 93%). Its aldol condensation with nitromethane gave **173** (97%) and subsequent reduction with $NaBH_4$ afforded **174** (79%). Intramolecular cyclization of **174** with $NaBH_4$-HCl produced thermodynamically stable 4,5-*trans*-1-methoxy-5-(2-methyl-1-propenyl)-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**175**, 64%) as a sole product. Under the same reaction sequences, **175** (64%) was prepared directly from **173**. Reduction of **175** with zinc (Hg) in refluxing methanolic HCl produced 1-methoxy-6-nor-6,7-secoagroclavine (**176a**, 86%) and 6-nor-6,7-secoagroclavine (**176b**, 14%). Due to the unstable N-OMe bond, the yield of **176a** increased in proportion to the shorter reaction time. After conversion of **176a** to 1-methoxy-6-methoxycarbonyl-6-nor-6,7-secoagroclavine (**177**, 93%) by the reaction with methyl chloroformate, its reduction with $LiAlH_4$ produced the desired (±)-1-

methoxy-6,7-secoagroclavine (**178a**, 77%) and (±)-6,7-secoagroclavine[31] (**178b**, 20%).

Scheme 21



1) i. $Tl(OCOCF_3)_3$, TFA; ii. aq. KI.; 2) $Pd(OAc)_2$, 2-methyl-3-buten-2-ol, DMF; 3) $MeNO_2$, NH_4OAc; 4) $NaBH_4$; 5) i. $NaBH_4$, MeOH; ii. 6% HCl; 6) Zn(Hg), HCl; 7) Et_3N, ClCOOMe; 8) $LiAlH_4$, THF.

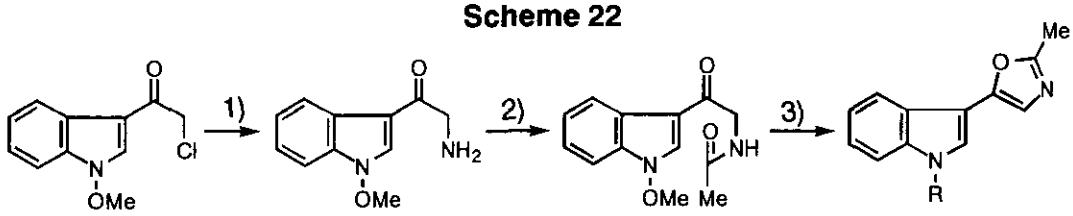
6-2. Pimprinine and 1-Methoxypimprinine

Pimprinine (**179b**) is an antibiotic isolated from *Streptomyces pimprina* in 1960 by Bhate and co-workers (Scheme 22).[32] Biological activity might therefore be expected to 1-methoxypimprinine (**179a**). Its synthesis started from the reaction of 3-(2-chloroacetyl)-1-methoxyindole (**50a**) with aqueous ammonia in a sealed tube to yield 3-(2-aminoacetyl)-1-methoxyindole (**180a**, 35%).[9d] Since **180a** was unstable and polymerized on standing, it reacted immediately after preparation with acetyl chloride to produce 3-(*N*-acetyl-2-aminoacetyl)-1-methoxyindole (**181**, 44% overall yield). Polyphosphate ester cyclized **181** to 1-methoxypimprinine (**179a**, 78%). Its hydrogenolysis over 10% Pd/C afforded pimprinine (**179b**, 99%).

6-3. Marine Alkaloid, (±)-Chelonin A, and (±)-1-Methoxychelonin A

Chelonin A (**182a**) was isolated from marine sponge *Chelonaplysilla* sp. as anti-fungi substances and its structure

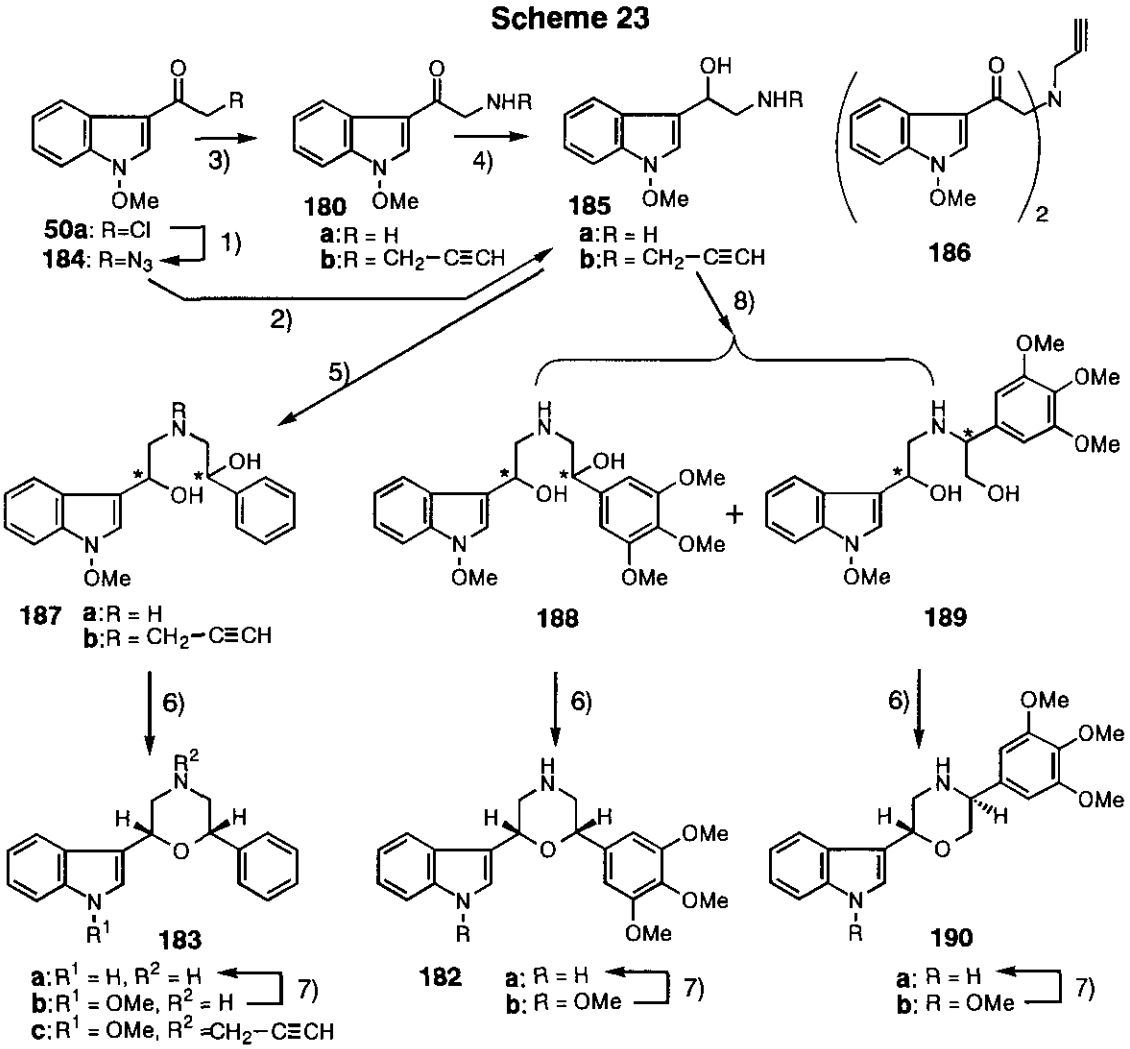
Scheme 22



50a **180a** **181** **179** **a**: R = OMe
b: R = H

1) NH_4OH, sealed tube; 2) MeCOCl, Et_3N; 3) PPE, $CHCl_3$.

Scheme 23



1) NaN_3; 2) $LiAlH_4$; 3) NH_4OH, sealed tube for **180a**; propargyl amine for **180b**; 4) $NaBH_4$; 5) styrene oxide; 6) 6% HCl, MeOH; 7) H_2, 10% Pd/C; 8) 3,4,5-trimethoxystyrene oxide.

was determined as shown in Scheme 23 by Faulkner and co-workers.[33] Aiming at (±)-1-methoxychelonin A (**182b**) and its analogs, the synthesis of model compounds, 2,6-*cis*-2-(1-methoxyindol-3-yl)-6-phenylmorpholine (**183b**) and its *N*-propargyl derivative (**183c**), was first attempted[34] relied on the reasoning illustrated in Section 3-1.

3-(2-Chloroacetyl)-1-methoxyindole[9d] (**50a**) was first converted to 3-(2-azidoacetyl)-1-methoxyindole (**184**, 87%) by treatment with NaN_3. Its reduction with $LiAlH_4$ led to **185a** (48%), which was alternatively produced by reduction of **180a** with $NaBH_4$ (72%). When **50a** reacted with excess propargylamine, monomer (**180b**, 53%) and dimer (**186**, 32%) were produced. Reduction of **180b** with $NaBH_4$ afforded **185b** (57%). Subsequent reaction of **185a** with styrene oxide produced **187a** (57%, 1:1 mixture of diastereoisomers). Similar reaction of **185b** with styrene oxide afforded **187b** (80%, 1:1 mixture of diastereoisomers). Treatments of **187a** and **187b** with 6% HCl smoothly underwent cyclization to the desired **183b** (74%) and **183c** (70%) as a single isomer in both cases. Catalytic hydrogenation of **183b** over 10% Pd/C produced **183a** (51%).

Based on the above results, **185a** was treated with 3,4,5-trimethoxystyrene oxide[35] to give regioisomers (**188** (9%) and **189** (9%)). Acid cyclization of them produced **182b** (89%) and **190b** (81%), respectively. Since **188** and **189** were unstable and polymerized during purification, acid cyclization of them immediately after their preparation resulted in giving better yields of **182b** (16%) and **190b** (15%). Catalytic hydrogenation of them over 10% Pd/C produced **182a** (59%) and **190a** (57%), respectively.

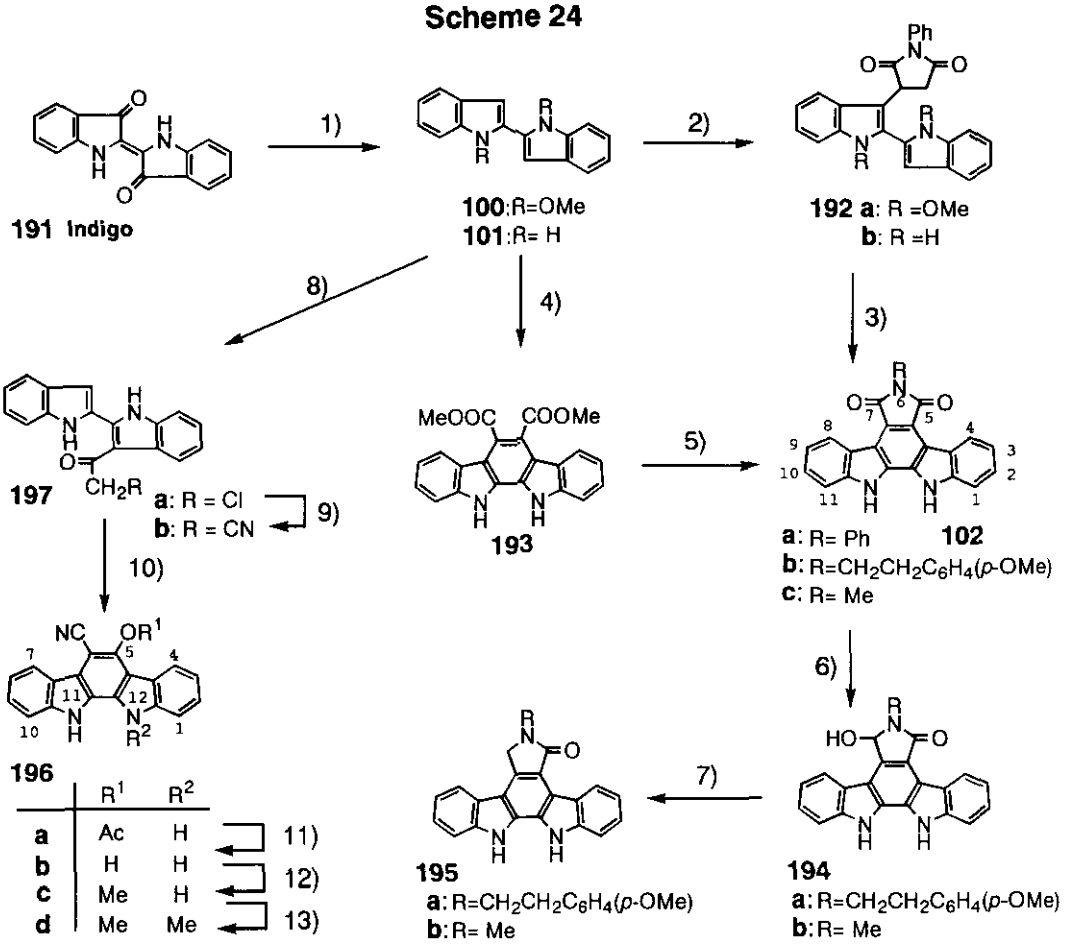
7. Application of the Chemistry of 1-Hydroxyindoles to the Syntheses of Biologically Active Substances

Unprecedented nucleophilic substitution reactions and novel rearrangement reactions, observed in the chemistry of 1-hydroxyindoles, supplied various types of indoles which were difficult to obtain thus far. Since these compounds are versatile building blocks in indole chemistry, further extentions to the syntheses of natural products and other biologically active substances were attempted as follows.

7-1. Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-diones and 6-Cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole

2,2'-Bi(1-methoxyindolyl) (**100**) is now readily available from 2,3-dihydroindole and its catalytic hydrogenation afforded 2,2'-biindolyl (**101**, 79%) as described in Section 4-6-3. We have alternatively succeeded in developing a new one step synthesis of 2,2'-biindolyl (**101**, 46%) from indigo (**191**) (Scheme 24).[36]

Scheme 24



1) Zn, AcOH, Ac_2O, Ar; 2) *N* -phenylmaleimide, $BF_3{\cdot}Et_2O$; 3) 10% Pd/C, xylene, reflux; 4) dimethyl acetylenedicarboxylate, 10% Pd/C, *o*-dichlorobenzene, reflux; 5) aniline, reflux for **102a**; *p* -methoxyphenethylamine for **102b**; methylamine for **102c**; 6) $NaBH_4$, DMF, MeOH; 7) H_2, 10% Pd/C; 8) $ClCH_2COCl$; 9) NaCN, NH_2CHO, MeOH; 10) Ac_2O, AcOH, 10% Pd/C, reflux; 11) NaOH, H_2O; 12) CH_2N_2; 13) MeI, K_2CO_3.

With **100** in hand, its reaction with *N*-phenylmaleimide in the presence of $BF_3{\cdot}Et_2O$ was examined to afford Michael adduct (**192a**, 68%), which was then converted to 6-phenylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (**102a**, 32%) and 1,1'-demethoxy Michael adduct (**192b**, 14%) by heating in xylene with 10% Pd/C. Diels-Alder approach to **102a** was also successful. The reaction of **100** with *N*-phenylmaleimide in the presence of 10% Pd/C formed **102a** (6%), while the reaction of **101** with dimethyl acetylenedicarboxylate in *o*-dichlorobenzene at reflux gave **193** (36%). Treatment of **193** with aniline produced **102a** (48%) together with unreacted **193** (49%). Similarly, amines such as *p*-methoxyphenethylamine and methylamine reacted with **193** to afford **102b** (92%) and **102c** (90%). Subsequent hydride reduction of **102b** and **102c** with $NaBH_4$ produced 7-

hydroxy compounds (**194a** (80%) and **194b** (67%)), respectively. From them, indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5(6*H*)-ones (**195a** (54%) and **195b** (58%)), were readily accessible by catalytic hydrogenation.

2,2'-Biindolyl (**101**) was also useful for the first total syntheses of cytotoxic and antiviral 6-cyano-5-methoxy- (**196c**) and -12-methylindolo[2,3-*a*]carbazoles (**196d**), isolated from blue-green alga *Nostoc sphaericum* (strain EX-5-1) by Moore and co-workers.[37] Chloroacetylation of **101** gave **197a** (87%), which was then converted to **197b** (77%) by the reaction with NaCN. Subsequent treatment of **197b** with refluxing Ac_2O in the presence of 10% Pd/C formed **196a** (35%). Alkaline hydrolysis of **196a**, followed by methylation of the resutant **196b** (97%) with CH_2N_2, attained the synthesis of **196c** (90%). Methylation of **196c** with MeI and K_2CO_3 discerned the difference in acidity of nitrogens at the 11 and 12 positions to produce **196d** as major product

7-2. 5*H*-pyrido[4,3-*b*]indoles (γ-Carbolines)

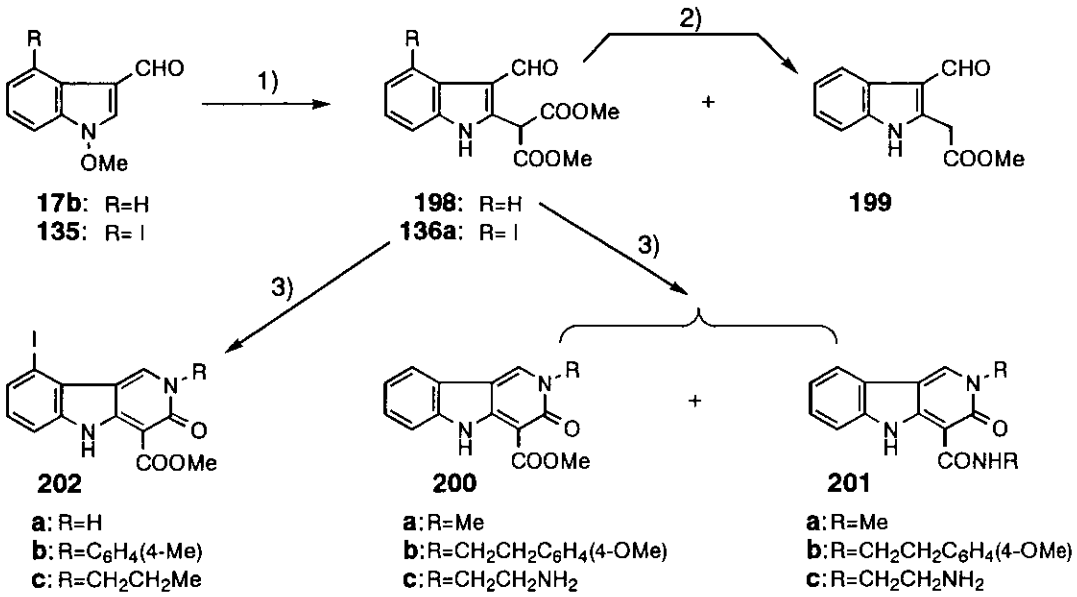
Although γ-Carbolines have attracted less interest than the related 9*H*-pyrido[3,4-*b*]indoles (β-carboline), various biologically active substances are involved as the members of the group. Aiming at developing simple γ-carboline synthetic method, the nucleophilic substitution reactions of 1-methoxyindole-3-carbaldehydes were applied successfully (Scheme 25).[38]

The reaction of **17b** with methyl malonate using NaOMe as a base gave dimethyl 2-(3-formylindol-2-yl)malonate (**198**, 53%) and methyl 2-(3-formylindol-2-yl)acetate (**199**, 7%). Treatment of **198** with NaOMe in refluxing MeOH afforded **199** (56%) together with unreacted **198** (31%). The reaction of 4-iodo-1-methoxyindole-3-carbaldehyde (**135**) with methyl malonate and NaOMe gave dimethyl 2-(3-formyl-4-iodoindol-2-yl)malonate (**136a**, 88%) predominantly. When the same reaction was carried out in DMF with KO*t*-Bu as a base at room temperature, exclusive production of **136a** (98%) was realized.

The reaction of **198** with an excess amount of methylamine in refluxing MeOH produced methyl 2,3-dihydro-2-methyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylate (**200a**, 72%) and its carboxamide (**201a**, 22%). Similarly, 4-methoxyphenethylamine afforded **200b** (73%) and **201b** (17%) and ethylenediamine gave **200c** (75%) and **201c** (22%). The reaction of **136a** with ammonium acetate gave methyl 2,3-dihydro-9-iodo-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylate (**202a**, 66%). 4-Methylaniline and propylamine also reacted with **136a** to give **202b** (91%) and **202c** (91%), respectively. Further reactions of **198** with various amines and interesting reactions of **199** with alcohols in the presence of amines are described in our report.[38]

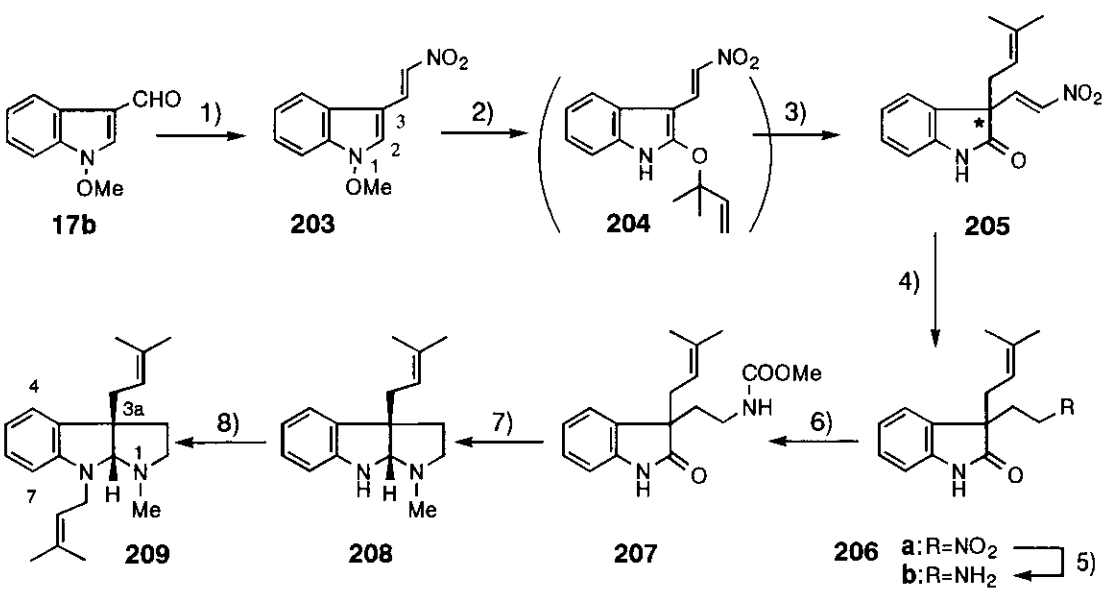
7-3. (±)-Debromoflustramine B

Scheme 25



1) $CH_2(COOMe)_2$, NaOMe, for **198** and **199**; $CH_2(COOMe)_2$, KO*t*-Bu, DMF for **136a**; 2) NaOMe, MeOH; 3) amines, MeOH.

Scheme 26



1) $MeNO_2$; 2) 2-methyl-3-buten-2-ol, KH, HMPA; 3) heating; 4) $NaBH_4$, MeOH; 5) Zn(Hg), HCl; 6) ClCOOMe, Et_3N; 7) $LiAlH_4$, THF; 8) *n*-BuLi, prenyl bromide.

It is desirable to have one's own synthetic method for pyrrolo[2,3-*b*]indole compounds, which are expected to have biological activities.

Aldol reaction of **17b** with nitromethane produced 1-methoxy-3-(2-nitrovinyl)indole (**203**, 91%) (Scheme 26). We discovered that **203** underwent the same nucleophilic substitution reactions with nucleophiles regioselectively at the 2-position as observed with **17b**. Employing the reaction to allylalkoxides as a nucleophile, a novel synthetic method of pyrrolo[2,3-*b*]indoles was elaborated.[39]

The reaction of **203** with potassium 2-methyl-3-buten-2-oxide in HMPA afforded 3-(3,3-dimethylallyl)-3-(2-nitrovinyl)-2-oxindole (**205**, 39%) through [3,3] sigmatropic rearrangement of the intermediate (**204**). After reduction of the conjugated double bond of **205** with $NaBH_4$ giving **206a** (92%), its nitro group was reduced to amine (**206b**, 83%) with amalgamated zinc. Methoxycarbonylation of **206b** to **207** (77%) and subsequent reduction with $LiAlH_4$ led to pyrrolo[2,3-*b*]indole (**208**, 61%). Finally, the treatment of **208** with BuLi and then with prenyl bromide achieved the total synthesis of (±)-debromoflustramine B[40] (**209**, 54%).[39]

7-4. Multi-Linked Heterocycles

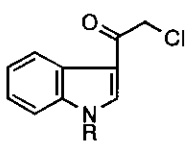
In order to develop biologically active new leads, we have designed a novel type of compounds which are consisted of plural heterocycles connected each other through single bond. We can classify these compounds as multi-linked heterocycles.[41] A simple method to approach them was developed based on the chemistry of 1-hydroxyindoles (Scheme 27).

3-Chloroacetyl-1-methoxyindole (**50a**) was converted to 4-(1-methoxyindol-3-yl)-2-aminothiazole (**211a**, 68%) by reaction with thiourea. Similarly, **211b** (95%) and **211c** (94%) were prepared from **210a** and **210b**, respectively.

We have disclosed that their 5-positions of 2-aminothiazole part have a characteristic nucleophilic character.[41] When **211a** was treated with a mixture of pyridine and Ac_2O at room temperature, tris-linked heterocycle, 2-acetylamino-5-(1-acetyl-1,4-dihydropyridin-4-yl)-4-(1-methoxyindol-3-yl)thiazole (**212a**, 36%), was produced together with **213a** (55%). Under similar reaction conditions, 4-(indol-3-yl)- (**211b**) and 4-(1-methylindol-3-yl)-2-aminothiazoles (**211c**) afforded **212b** (65%) and **212c** (42%) in addition to **213b** (34%) and **213c** (46%), respectively. The structures of tris-linked heterocycles were determined by pursuing X-Ray single crystallographic analysis of **212c**. The results are shown in Figure 7.

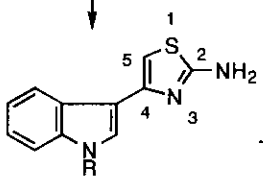
The above results are remarkable findings because acetylpyridinium acetate (**214**), *in situ* formation upon mixing pyridine and Ac_2O, has not been reported to react at the pyridine part with nucreophiles except one case.[42] This is the reason why a mixture of pyridine and Ac_2O is used as an acetylating reagent. Further application of 2-

Scheme 27

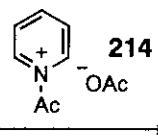


50a: R=OMe
210a: R=H
210b: R=Me

1)

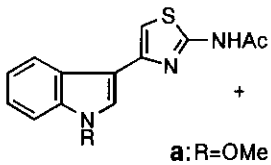


211 a: R=OMe
b: R=H
c: R=Me



214

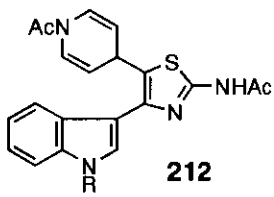
2)



213

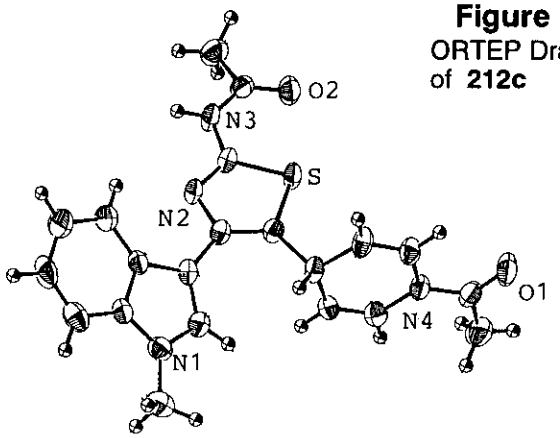
a: R=OMe
b: R=H
c: R=Me

+



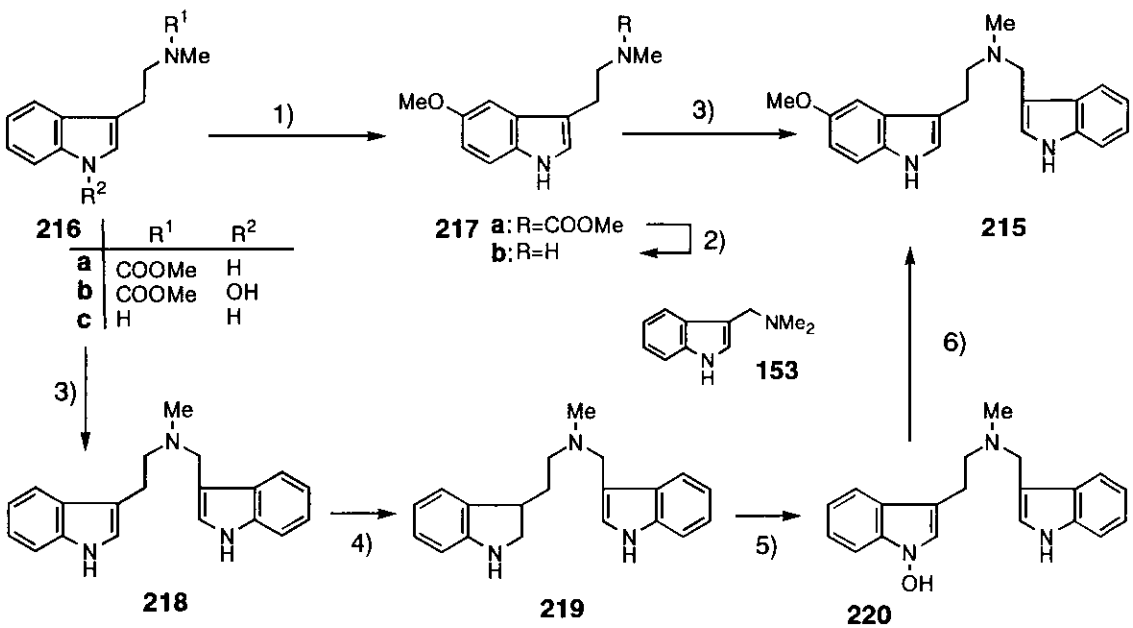
212

Figure 7
ORTEP Drawing of **212c**



1) thiourea, MeOH, reflux; 2) pyridine, Ac_2O, rt.

Scheme 28



216

	R^1	R^2
a	COOMe	H
b	COOMe	OH
c	H	H

217 **a**: R=COOMe
b: R=H

2)

153

215

218

219

220

1) 5% H_2SO_4, MeOH; 2) aq. NaOH; 3) (n-Bu)$_3$P, **153**, MeCN, reflux; 4) $NaBH_3CN$, AcOH, TFA; 5) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2, MeOH, H_2O; 6) $BF_3 \cdot$MeOH, MeOH, reflux.

aminothiazoles (**211a-c**) to the syntheses of various multi-linked heterocycles are described in our report.[41]

7-5. *N*-(Indol-3-yl)methyl-*N*-methyl-5-methoxytryptamine

In 1995, Weniger and co-workers[43] isolated and determined *N*-(indol-3-yl)methyl-*N*-methyl-5-methoxytryptamine (**215**), as a member of tryptamine alkaloid family, from the roots of *Antirhea lucida* (Sw.) Hook (Rubiaceae). Total synthesis of **215** was attained by the following two routes applying 1-hydroxyindole chemistry (Scheme 28). Reduction of **216a** with Et_3SiH-TFA, followed by oxidation by the tungstate method, afforded **216b** (73% overall yield). Treatment of **216b** with 5% methanolic H_2SO_4 and subsequent hydrolysis of the resultant **217a** (39%) with 40% NaOH produced **217b** (93%). Application of our tri-*n*-butylphosphine[44] (n-Bu)$_3$P catalyzed functionalization method of gramine (**153**) to **217b** achieved the first total synthesis of **215** (78%).

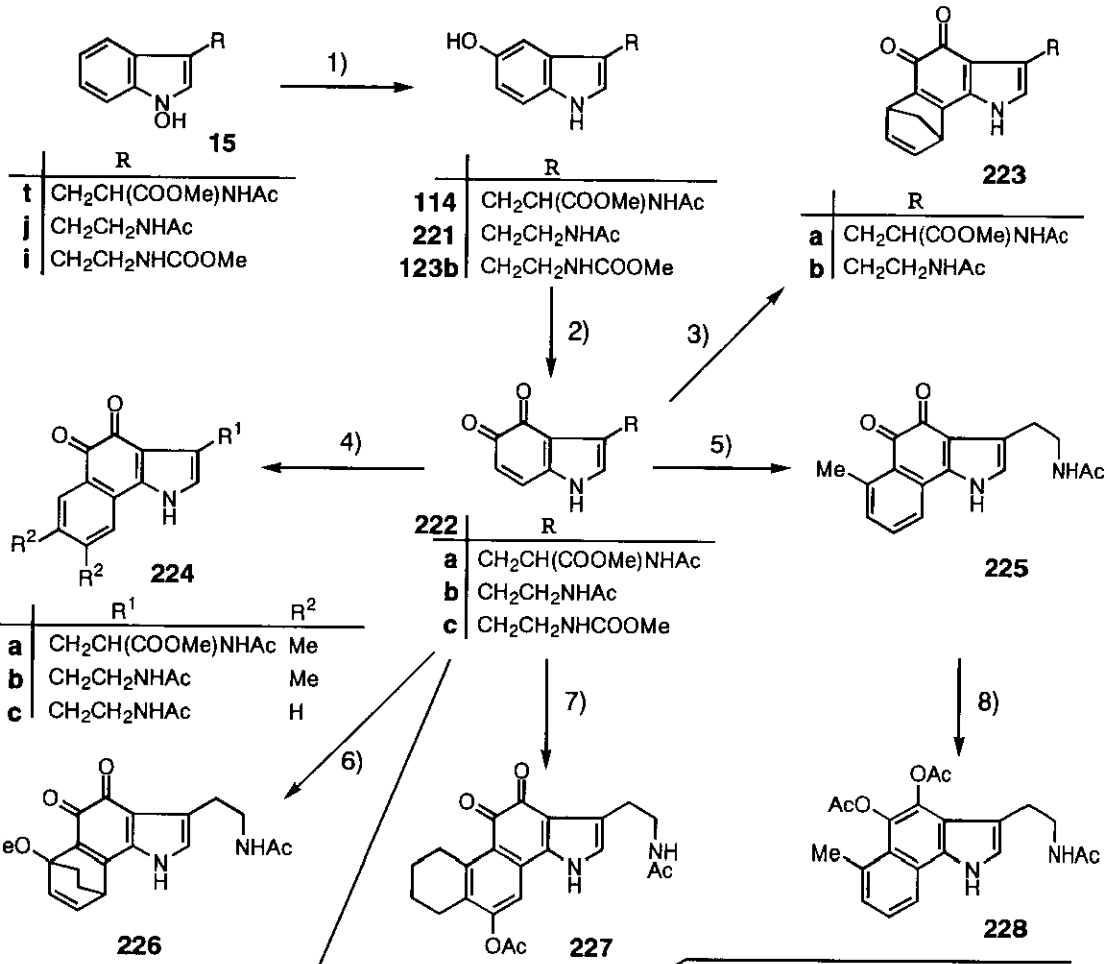
The above (n-Bu)$_3$P catalyzed method was also employed to **216c** giving **218** (67%). It is interesting to note that selective reduction of tryptamine part of **218** was realized with $NaBH_3CN$ in AcOH-TFA (3:1, v/v) resulting in the formation of **219** (71%). Subsequent oxidation of **219** by the tungstate method gave **220** (51%), which was then transformed to **215** (15%) by treatment with BF_3·MeOH in refluxing MeOH.

8. Formation of Tryptophan-4,5-dione and Its Reactions

As described in Section 4-9, 5-hydroxytryptophan derivatives ((±)-**114**, **123b**, and **221**) were produced from the corresponding 1-hydroxytryptophans (**15t, l**, and **j**) by acidic nucleophilic substitution reactions (Scheme 29). Generally, these 5-hydroxy compounds were unstable on exposure to air and so sensitive to oxidizing reagents that ceric ammonium nitrate, $FeCl_3$, $K_3Fe(CN)_6$, and Fenton reagent did not afford any isolable products except for tars. Iodosylbenzene was, however, found to be suitable reagent for obtaining (±)-*Nb*-acetyltryptophan-4,5-dione methyl ester (**222a**, 39%) from (±)-**114** and *Nb*-acetyltryptamine-4,5-dione (**222b**, 38%) from **221**.[45] In the oxidation of **221**, Fremy's salt (4 mol eq.) is the reagent of choice for producing **222b** (99%), whereas the oxidation of (±)-**114** with Fremy's salt gave only tars under various examined reaction conditions.

Indole-4,5-diones ((±)-**222a**) and (**222b**) were excellent dienophiles.[45] They produced Diels-Alder adducts, which were highly sensitive to air and oxidized during work-up to 6,7-disubstituted indole-4,5-dione derivatives. These results sharply contrasted to the chemical behavior reported by Cai and co-workers[46] using **222c**. For example, **222b** reacted with cyclopentadiene to produce **223b** (81%), while (±)-**222a** afforded (±)-**223a** (2:1 mixture of diastereomers) in 35% overall yield from (±)-**114**. In the reaction with 2,3-dimethylbutadiene, **222b** afforded **224b** (quantitative), whereas (±)-**222a** afforded (±)-**224a** (33% overall yield from (±)-**114**). Interestingly,

Scheme 29



1) 85% HCOOH; 2) PhIO or Fremy's salt; 3) cyclopentadiene; 4) 2,3-dimethylbutadiene or 1-acetoxybutadiene; 5) 1,3-pentadiene; 6) 1-methoxy-1,3-cyclohexadiene; 7) 1-(1-acetoxyvinyl)cyclohexane; 8) Zn, Ac_2O, Et_3N; 9) nucleophiles (see the text).

Figure 8

ORTEP Drawing of **228**

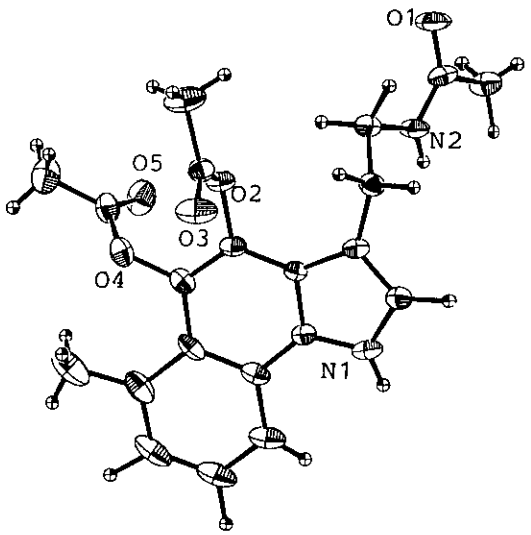
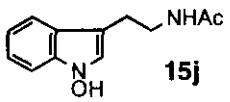
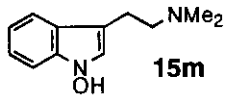
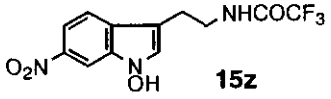
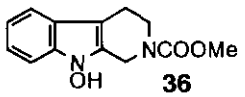
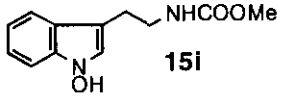
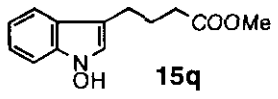
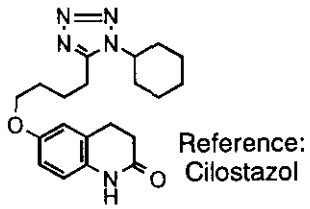


Table 12. Effects of 1-Hydroxyindoles on Arachidonic Acid Induced Platelet Aggregation in Rabbit PRP

Entry	Compound	Inhibition Percent of Control Platelet Aggregation				
		10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4} (M)
1	 **15j**	-	-	2.2	92.1	93.5
2	 **15m**	-	-	11.3	95.1	95.8
3	 **15z**	-	-	2.3	94.0	94.7
4	 **36**	-	-	51.4	94.9	94.2
5	 **15i**	1.5	6.2	93.3	92.3	92.3
6	 **15q**	2.9	4.4	94.1	89.7	92.6
7	 Reference: Cilostazol	-	-	7.1	94.3	92.9

the reaction of **222b** with 1-acetoxybutadiene afforded **224c** (40%). Similarly, **222b** underwent Diels-Alder reaction with 1,3-pentadiene, 1-methoxy-1,3-cyclohexadiene, and 1-(1-acetoxyvinyl)cyclohexene to give the expected **225** (22%), **226** (41%), and **227** (39%), respectively. To determine the structures of these Diels-Alder products, **225** was subjected to reductive acetylation with Zn in Ac_2O and Et_3N to give **228** (81%). Its structure was unequivocally proved by X-Ray single crystallographic analysis as shown in Figure 8.

On the other hand, (±)-**222a** and **222b** underwent nucleophilic addition reactions and spontaneous oxidation of the resultant addition products culminating in the formation of 7-substituted tryptamine-4,5-diones. Thus, (±)-**222a** reacted with MeSH to afford (±)-**229a** (69% overall yield from (±)-**114**). Similarly, **222b** reacted with methyl

malonate, ethyl cyanoacetate, and methyl acetoacetate, in the presence of KO*t*-Bu to afford **229b** (83%), **229c** (88%), and **229d** (71%), respectively.

9. Biological Evaluation of 1-Hydroxyindoles

With various 1-hydroxyindoles in hand,[2,10] biological evaluations of six samples composed of stable 1-hydroxytryptamines and related derivatives were examined. As can be seen from Table 12,[11] all of the tested compounds show inhibition on arachidonic acid induced platelet aggregation in rabbit PRP. Among them, the potencies of **15j**, **15m**, **15z**, and **36** are equivalent to that of the reference medicine, cilostazol, while **15l** and **15q** exhibit more potent effects. So we assure, at least, a part of our hypotheses hit the target.

Biological evaluations of compounds described in the present review are in progress.

10. Conclusions and Future Plans

We have given birth to 1-hydroxyindoles and 1-hydroxytryptophan derivatives by creating an economcal and general synthetic method and discovered them as lead compounds for potent inhibitor of blood platelet aggregation. Chemically, we have shown the possibility that 1-hydroxyindoles might be transformed to 5-hydroxyindoles (serotonin, melatonin, etc.) in the central nervous system or in the acidic particles in the cell. They are known to play important roles in our body.[47] If those 5-hydroxyindoles happened to be oxidized *in vivo* with reactive oxygen species (oxygen, hydrogen peroxide, superoxide, etc.) to indole-4,5-diones, etc., they should react as both electrophiles and dienophiles with near proteins, alkadienoic acids, leucotrienes, and so on, resulting in the malfunction of nerves and neuro-degenerative diseases.[48] Along these hypotheses,[1] we are planning to examine the reactions of (*S*)-**222a** and **222b** with proteins and nucleic acids.

The other important and urgent subject is to determine whether 1-methoxyindoles are good or harmful for our health, considering that they are contained in the plant family *Cruciferae* and we eat them in a significant quantity from vegetables (cabbage, radish, turnip, etc.) every day.[15o,p,49] We should also investigate whether 1-hydroxyindoles and 1-hydroxytryptophans are contained in the *Cruciferae* vegetables. If their existences were confirmed, eating vegetables would have such an important meaning that it helps people to protect from cerebral thrombosis and/or myocardial infarction by taking antiaggregating substances for platelet.

Recent report[50] about the interaction of melatonin and amyloid peptides gives us courage to pursue the study of 1-hydroxymelatonin (**25g**) and related derivatives. The existence of biologically active peptides containing 1-methoxytryptophan as a component[6a,b] seems to reinforce "1-Hydroxyindole Hypotheses".[1] Although they

might be erroneous because of originating from imaginations, they have thus far led us to a frontier and a fruitful chemistry of 1-hydroxyindoles. A lot of novel treasures are buried in the field, we believe.

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