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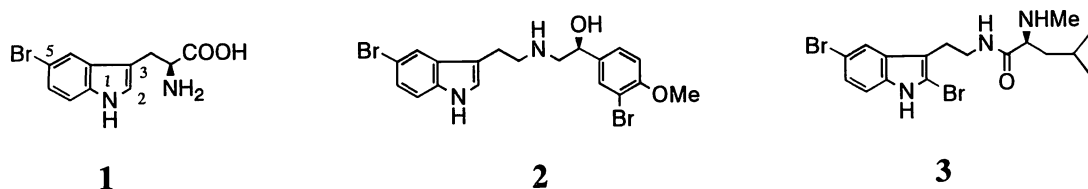
A NOVEL METHODOLOGY FOR PREPARING 5-CHLORO- AND 5-BROMO-TRYPTAMINES AND TRYPTOPHANS, AND ITS APPLICATION TO THE SYNTHESIS OF (\pm)-BROMOCHELONIN B¹

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Abstract — A novel methodology for introducing chlorine or bromine into the 5-position of tryptamines was found through 1-hydroxytryptamines. The chemistry was applied to the syntheses of (\pm)-5-chloro-, -5-bromotryptophan derivatives, and (\pm)-bromochelonin B.

Many biologically active tryptamines are reported such as 5-bromotryptophan² (**1**), bromochelonin B³ (**2**), alternatamide C⁴ (**3**), cyclocinamide A⁵ and so on, containing halogen at the 5-position of indole nucleus (Figure 1).⁶ Their total syntheses would require suitably halogenated indolic building blocks. We have thusfar disclosed unprecedented acid promoted nucleophilic substitution reactions of 1-hydroxyindoles⁷ and succeeded in preparing 5-hydroxy- and 5-methoxytryptamines (**I** and **II**) as summarized in Table 1.⁷ Now, we wish to describe that the reaction of 1-hydroxytryptamines with hydrogen halides is a suitable synthetic methodology for 5-chloro- and 5-bromotryptamines (**4a,b** and **5a,b**), and its applications to the syntheses of (\pm)-5-chloro- and -5-bromotryptophan derivatives (**6a,b** and **7**), and (\pm)-**2**.

Figure 1

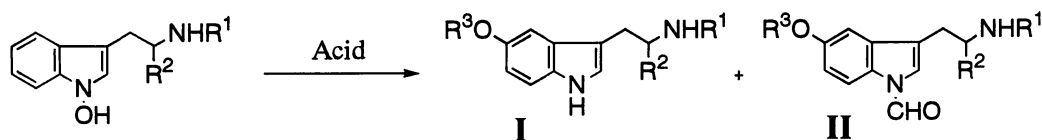


According to our method,⁷ 1-hydroxy- (**8a, e** and **9a**), 1-methoxytryptamines (**8b, f** and **9b**), 1-hydroxy- (**9a** and **10a**), and 1-methoxytryptophan derivatives (**9b** and **10b**) were prepared as substrates. 1-(2-Methoxycarbonyl)ethoxy- (**8c**) and 1-(2-methoxycarbonyl-1-methyl)ethoxytryptamine (**8d**) were prepared in 69 and 72% yields, respectively, using conjugate addition reaction of *N*b-acetyl-1-hydroxytryptamine (**8a**) to methyl acrylate and methyl 3-methylacrylate in the presence of 4-*N,N*-dimethylaminopyridine.

The reactions of **8a-f** with HCl were examined and the results are summarized in Table 2. As can be seen from the Table, the 1-substituent is found to be an important factor in determining the yield of 5-chloro-tryptamines (**4a,b**). As the substituent changes from hydroxy to methoxy, 1-(2-methoxycarbonyl)ethoxy,

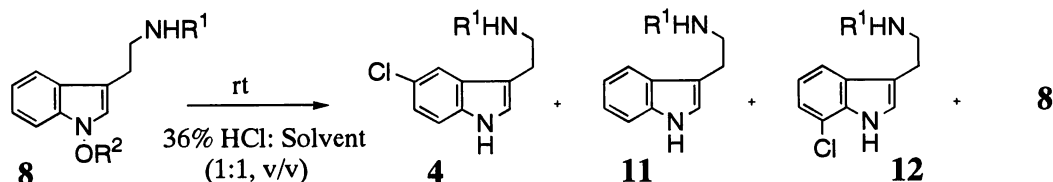
and 1-(2-methoxycarbonyl-1-methyl)ethoxy group (Entries 1—4), the yield of **4a** increased dramatically and yield 73% was attained under the reaction conditions described in the Entry 4. It is worthy to note that under similar reaction conditions *Nb*-substituent of the side chain at the 3-position functions as the other increasing factor in the yield of **4**. Thus, comparing the results in the Entries 5 and 7, much more quantity of **4b** having *Nb*-methoxycarbonyl group was produced than **4a** having *Nb*-acetyl group. As a result, we can now achieve regioselective chlorination at the 5-position in 80% yield by reacting HCl with 1-hydroxytryptamine (**8f**) which has both 1-methoxy and *Nb*-methoxycarbonyl group (Entry 7).

Table 1



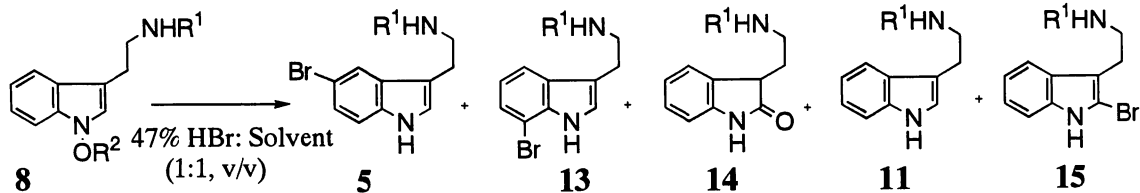
Entry	R ¹	R ²	R ³	Acid	Yield (%) I	of II
1	Ac	H	Me	20% BF ₃ ·MeOH	80	0
2	COOMe	"	"	"	85	0
3	Ac	COOMe	"	H ₂ SO ₄ -MeOH	71	0
4	"	"	H	85% HCOOH	67	12

Table 2



Entry	Substrate	R ¹	R ²	Reaction Solvent	Conditions Time (h)	Product	Yield (%) 4	11	12	8
1	a	Ac	H	MeOH	3.5	a) R ¹ = Ac	17	20	0	0
2	b	"	Me	"	7.5	"	55	0	4	8
3	c	"	CH ₂ CH ₂ COOMe	"	17	"	59	0	0	6
4	d	"	CH(Me)CH ₂ COOMe	"	120	"	73	0	0	6
5	b	"	Me	<i>t</i> -BuOH	6	"	54	0	5	10
6	e	COOMe	H	"	1/6	b) R ¹ = COOMe	48	8	7	0
7	f	"	Me	"	1/6	"	80	0	0	0

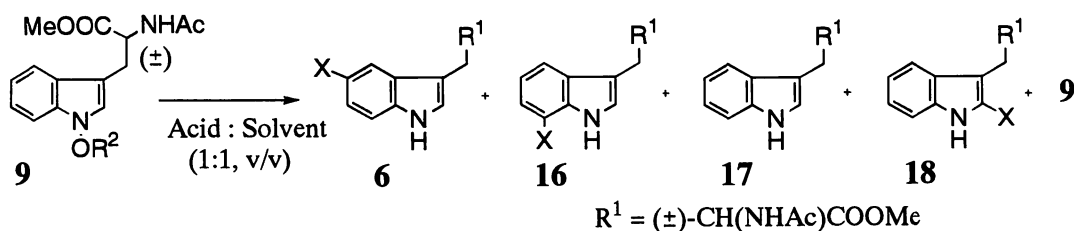
Table 3



Entry	Substrate	R ¹	R ²	Reaction Solvent	Reaction Conditions		Product	Yield (%) of				
					Temp. (°C)	Time (h)		5	13	14	11	15
1	a	Ac	H	MeCN	80	3	a) R ¹ = Ac	5	4	19	3	0
2	c	"	CH ₂ CH ₂ COOMe	MeOH	rt	20	"	51	8	18	11	0
3	d	"	CH(Me)CH ₂ COOMe	"	rt	55	"	38	8	0	10	0
4	e	COOMe	H	<i>t</i> -BuOH	80	1/12	b) R ¹ = COOMe	17	8	15	6	23
5	"	"	"	DMF	80	1/12	"	27	8	13	19	0
6	"	"	"	MeCN	80	1/12	"	24	6	41	14	0
7	"	"	"	HCONH ₂	80	1/6	"	39	6	15	10	0
8	"	"	"	HCONHMe	80	1/12	"	36	9	9	19	0
9	f	"	Me	HCONH ₂	rt	1/6	"	45	8	5	9	0
10	e	"	H	MeNO ₂ *	rt	1	"	5	23	35	11	2

* BBr₃ (1.1 mol eq) was used as a brominating reagent.

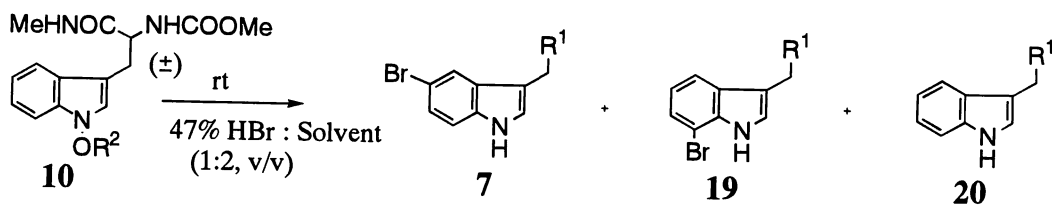
Table 4



Entry	Substrate	R ²	Acid	Reaction Solvent	Reaction Conditions		Product	Yield (%) of				
					Temp. (°C)	Time (min)		6	16	17	18	9
1	a	H	36% HCl	MeCN *	80	5	a) X = Cl	19	8	13	0	8
2	b	Me	"	<i>t</i> -BuOH	rt	420	"	52	0	7	0	11
3	a	H	47% HBr	MeCN	80	5	b) X = Br	13	2	20	8	0
4	b	Me	"	MeCN	80	10	"	20	5	10	0	0

* Acid and solvent were used in the ratio of 1:2 (v/v).

Table 5



Entry	Substrate	R ²	Reaction Solvent	Conditions Time (min)	7	Yield (%) 19	20	of Other Product
1	a	H	<i>t</i> -BuOH	60	28	0	14	10 (7)
2	b	Me	<i>t</i> -BuOH	60	50	12	17	0
3	b	Me	MeCN	15	15	13	17	Unknown Product

Table 3 shows typical results obtained from the reactions of **8a,c-f** with HBr. Even in these reactions, both 1-substituent and *Nb*-substituent play significant roles on the yield of 5-bromotryptamines (**5a,b**) (Entries 1—3, 6, 7, and 9). The solvent was found to be another important factor. As the solvent polarity (ϵ) increases from *tert*-BuOH (11) to DMF (37), MeCN (38), HCONH₂ (111), and HCONHMe (182) (Entries 4—8), the yield of **5b** has a tendency to increase, though it is not proportional. Considering the balance of these factors, **5a** and **5b** are now available in 45—51% yield by reacting 1-hydroxytryptamines (**8a,f**) with HBr under the reaction conditions in Entries 2 and 9. It is interesting to note that when BBr₃ was employed as a brominating reagent (Entry 10), the production of 7-bromotryptamine (**13b**) was raised to 23% yield though the major product was 2-oxindole (**14b**).

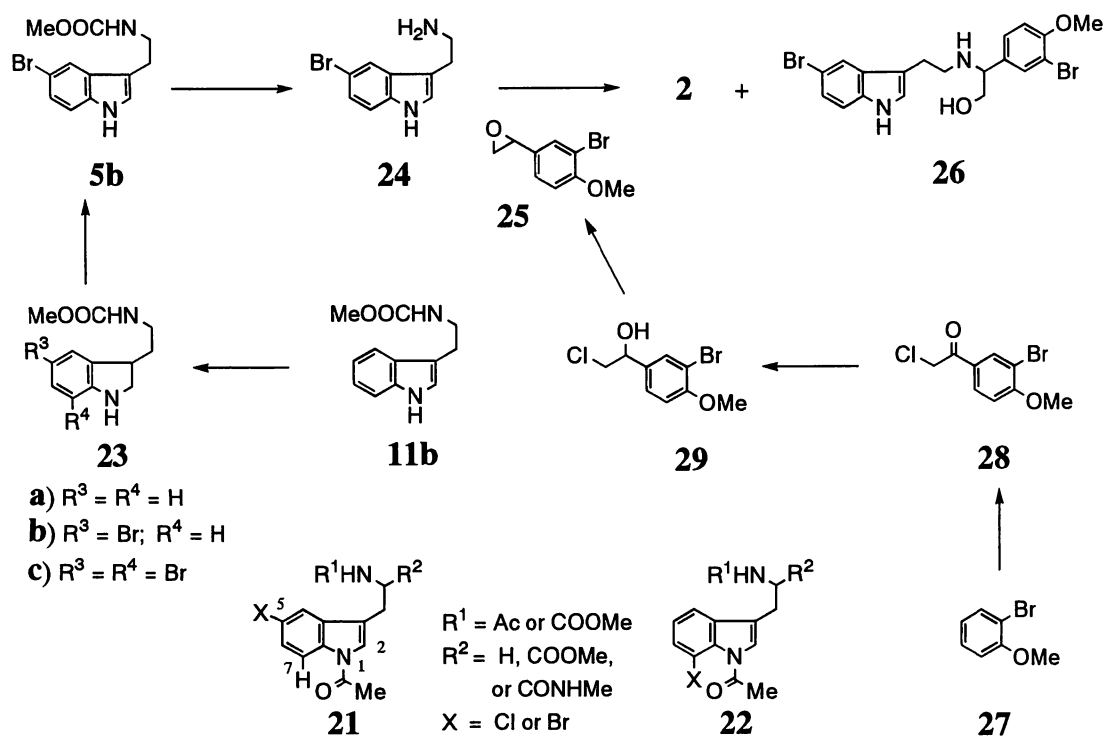
The similar substituent effects as described above were observed in the reactions of (\pm)-1-hydroxytryptophan derivatives (**9a,b** and **10a,b**) (Tables 4 and 5). Consequently, (\pm)-*Nb*-acetyl-5-chlorotryptophan methyl ester (**6a**) and (\pm)-5-bromo-*Nb*-methoxycarbonyltryptophan methyl amide (**7**) were obtained in the respective yields of 52 and 50% by reacting **9b** or **10b** with HCl or HBr under reaction conditions described in Entries 2 in Tables 4 and 5, respectively. Establishment of the optimum reaction conditions and further examinations of *Nb*-substituent effect are now in progress.

The structures of 5- and 7-halogenated indoles were unequivocally confirmed as usual.⁷ Treatments of 5-halogenated tryptamines and tryptophans with NaH in DMF, followed by acetylation with AcCl provided the corresponding 1-acetyl derivatives (**21**, Scheme 1). Utilizing the same reaction sequence, 7-halogenated tryptamines and tryptophans afforded the corresponding 1-acetyl derivatives (**22**). In the former compounds, comparisons of each set of NMR spectra of the starting material and its 1-acetyl derivative clearly show that the C-7 protons (*d*, $J = 7\text{--}8$ Hz) are deshielded by 1 ppm, proving that these compounds have a substituent at the 5-position of indole nucleus. In cases of the latter compounds, however, deshielded protons are not observed comparing each set of NMR spectra. These facts demonstrate that the latter compounds are 7-substituted tryptamines. Structures of 2-oxindoles⁸ (**14a,b**) and 2-halogenated indoles (**15b**, **18b**) were determined by their spectral data.

Structure of **5b** was further confirmed by employing alternative synthesis as shown in Scheme 1. Treatment of 2,3-dihydro-*N*b-methoxycarbonyltryptamine (**23a**), prepared from the corresponding tryptamine (**11b**), with bromine-AcOH afforded 5-bromo- (**23b**) and 5,7-dibromo derivatives (**23c**) in 61 and 31% yields, respectively. Salcomine catalyzed oxidation of **23b** with molecular oxygen provided 89% yield of **5b**. Thus, **5b** is available by two different routes in almost the same overall yield from **11b**.

With **5b** in hand, we set out the synthesis of (\pm)-bromochelonine B (**2**). Alkaline hydrolysis of **5b** with 5% NaOH-MeOH at reflux afforded 5-bromotryptamine (**24**) in 88% yield. Subsequent reaction of **24** with 3-bromo-4-methoxystyrene oxide (**25**) in the presence of DBU in refluxing *tert*-BuOH provided (\pm)-**2** and its (\pm)-isomer (**26**) in 28 and 14 % yields, respectively. Compound (**25**) was readily prepared from bromoanisole (**27**) by the following three steps: 1) Friedel-Crafts chloroacetylation of **27** in 53% yield, 2) reduction of the resultant **28** with NaBH₄ to chlorohydrin (**29**) in 98% yield, 3) epoxide formation with *tert*-BuOK in 47% yield.

Scheme 1



In conclusion, regioselective introduction of either chlorine, bromine, hydroxy,⁷ or methoxy⁷ group onto the 5-position of tryptamines is now possible by the following sequence of reactions: 1) conversion of tryptamine to 2,3-dihydroindole, 2) transformation to 1-hydroxyindole, and 3) subsequent reaction with acids. The most impressive fact through these studies is that the 1-hydroxyindoles having C—C—Nb side chain at the 3-position can only undergo the acid promoted nucleophilic substitution reactions effectively,

otherwise other types of reactions such as pyrrolo[2,3-*b*]indole formation,^{7a} dimerization,^{7b} kabutane formation,^{7d} and so on,⁷ take place depending on the structures of substrates and reaction conditions. The reason why is an interesting subject for further investigation.⁹ Furthermore, our results thusfar obtained⁷ and the present study suggest that use of acids for the isolation of indolic alkaloids and peptides should be done very carefully because if 1-hydroxy or 1-methoxy substituted tryptamines or tryptophans were involved as a component, they would be isolated as 5-substituted indole derivatives resulted by acid promoted nucleophilic substitution reactions.

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All new compounds gave satisfactory spectral and elemental analysis or high-resolution MS data for crystals or oils, respectively. **2**, mp 172-173°C (AcOEt-hexane); **4a**, mp 140—141°C (CH₂Cl₂-hexane); **4b**, oil; **5a**, mp 154—155°C (CH₂Cl₂-MeOH); **5b**, oil; **6a**, oil; **6b**, oil; **7**, mp 202°C (MeOH); **8c**, oil; **8d**, oil; **10a**, mp 157—158°C (CHCl₃-hexane); **10b**, mp 154—156°C (CHCl₃-hexane); **12a**, oil; **12b**, oil; **13a**, oil; **13b**, mp 68.5—69.5°C (CH₂Cl₂-hexane); **14a**, mp 146—147°C (CH₂Cl₂-MeOH); **14b**, mp 123.5—125.0°C (CH₂Cl₂-MeOH); **15b**, oil; **16a**, mp 167—168°C (CH₂Cl₂-MeOH); **16b**, mp 161—162°C (CH₂Cl₂-hexane); **18b**, oil; **19**, mp 178—180°C (CH₂Cl₂-hexane); **23b**, oil; **23c**, oil; **24**, oil; **25**, oil; **26**, mp 98.5—100.0°C (CH₂Cl₂-hexane); **28**, mp 104—106°C (CH₂Cl₂-hexane); **29**, oil.
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8. There is a possibility that 2-oxindoles are formed through the hydrolysis of the corresponding 2-halogenated indoles during work-up.
9. Our working hypothesis is the following. The first and fast protonation occurs on the side chain Nb

nitrogen atom no matter whether it is amine or amide nitrogen. The protonated *Nb* nitrogen inhibits electrostatically the addition of the second proton to the 3-position of indole nucleus. As a result, the second protonation occurs selectively on the 1-alkoxy oxygen atom, situated far from the protonated *Nb* nitrogen, culminating in the departure of 1-alkoxy group and then followed by the nucleophilic substitution reaction. In the cases of indoles lacking *Nb* nitrogen, preferential proton addition occurs at the 3-position directing toward pyrrolo[2,3-*b*]indole formation, dimerization, kabutane formation, etc.⁷

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