

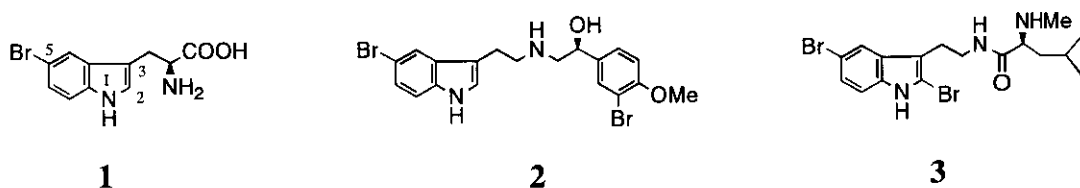
A NOVEL METHODOLOGY FOR PREPARING 5-CHLORO- AND 5-BROMO-TRYPTAMINES AND TRYPTOPHANS, AND ITS APPLICATION TO THE SYNTHESIS OF ( $\pm$ )-BROMOCHELONIN B<sup>1</sup>

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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-bromotryptophan<sup>2</sup> (**1**), bromochelonin B<sup>3</sup> (**2**), alternatamide C<sup>4</sup> (**3**), cyclocinamide A<sup>5</sup> and so on, containing halogen at the 5-position of indole nucleus (Figure 1).<sup>6</sup> Their total syntheses would require suitably halogenated indolic building blocks. We have thusfar disclosed unprecedented acid promoted nucleophilic substitution reactions of 1-hydroxyindoles<sup>7</sup> and succeeded in preparing 5-hydroxy- and 5-methoxytryptamines (**I** and **II**) as summarized in Table 1.<sup>7</sup> 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

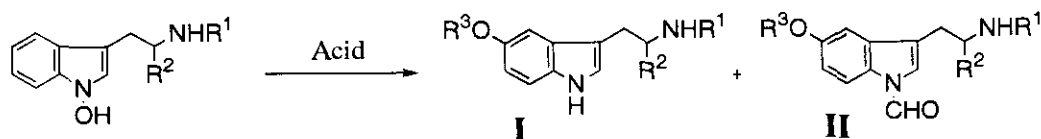


According to our method,<sup>7</sup> 1-hydroxy- (**8a, e** and **9a**), 1-methoxytryptamines (**8b, f** and **9b**), 1-hydroxy- (**9a** and **10a**), and 1-methoxytryptophan derivatives (**9b** and **10b**) were prepared as substrates. 1-(2-Methoxycarbonyl)ethoxy- (**8c**) and 1-(2-methoxycarbonyl-1-methyl)ethoxytryptamine (**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-chlorotryptamines (**4a,b**). As the substituent changes from hydroxy to methoxy, 1-(2-methoxycarbonyl)ethoxy,

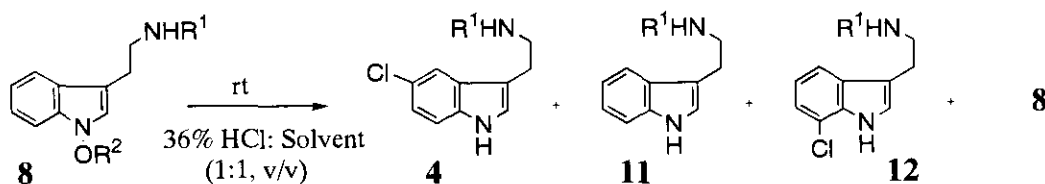
and 1-(2-methoxycarbonyl-1-methyl)ethoxy group (Entries 1—4), the yield of **4a** increased dramatically and yield 73% was attained under the reaction conditions described in the Entry 4. It is worthy to note that under similar reaction conditions *Nb*-substituent of the side chain at the 3-position 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



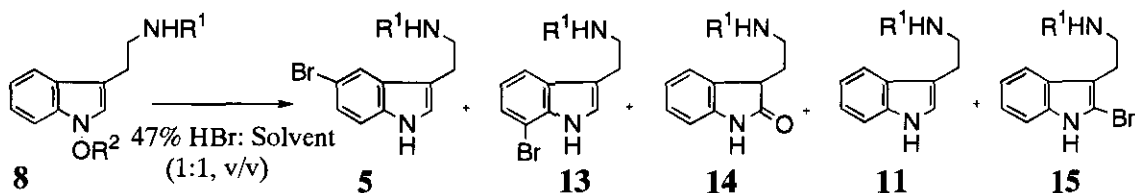
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Acid	Yield (%) of	
					I	II
1	Ac	H	Me	20% BF <sub>3</sub> ·MeOH	80	0
2	COOMe	"	"	"	85	0
3	Ac	COOMe	"	H <sub>2</sub> SO <sub>4</sub> -MeOH	71	0
4	"	"	H	85% HCOOH	67	12

Table 2



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

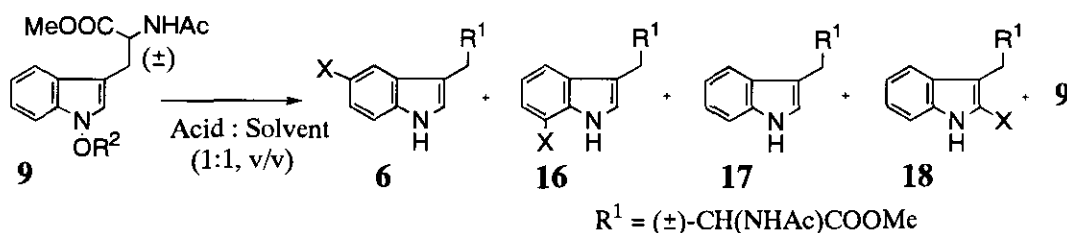
Table 3



Entry	Substrate	$\text{R}^1$	$\text{R}^2$	Reaction Solvent	Conditions		Product	Yield (%) of				
					Temp. ( $^{\circ}\text{C}$ )	Time (h)		<b>5</b>	<b>13</b>	<b>14</b>	<b>11</b>	<b>15</b>
1	<b>a</b>	Ac	H	MeCN	80	3	<b>a)</b> $\text{R}^1 = \text{Ac}$	5	4	19	3	0
2	<b>c</b>	"	$\text{CH}_2\text{CH}_2\text{COOMe}$	MeOH	rt	20	"	51	8	18	11	0
3	<b>d</b>	"	$\text{CH}(\text{Me})\text{CH}_2\text{COOMe}$	"	rt	55	"	38	8	0	10	0
4	<b>e</b>	COOMe	H	<i>t</i> -BuOH	80	1/12	<b>b)</b> $\text{R}^1 = \text{COOMe}$	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	"	"	"	$\text{HCONH}_2$	80	1/6	"	39	6	15	10	0
8	"	"	"	$\text{HCONHMe}$	80	1/12	"	36	9	9	19	0
9	<b>f</b>	"	Me	$\text{HCONH}_2$	rt	1/6	"	45	8	5	9	0
10	<b>e</b>	"	H	$\text{MeNO}_2^*$	rt	1	"	5	23	35	11	2

\*  $\text{BBR}_3$  (1.1 mol eq) was used as a brominating reagent.

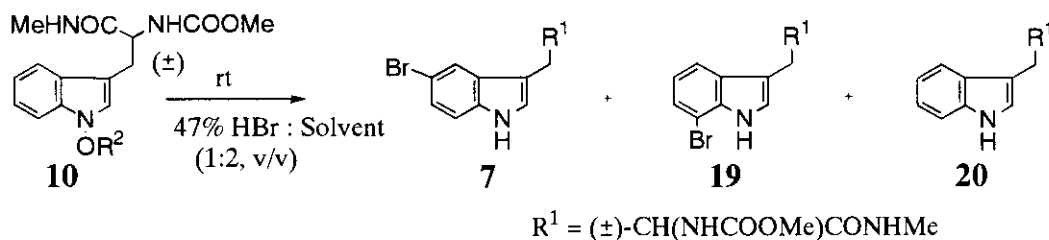
Table 4



Entry	Substrate	$\text{R}^2$	Acid	Reaction Solvent	Conditions		Product	Yield (%) of				
					Temp. ( $^{\circ}\text{C}$ )	Time (min)		<b>6</b>	<b>16</b>	<b>17</b>	<b>18</b>	<b>9</b>
1	<b>a</b>	H	36% HCl	MeCN*	80	5	<b>a)</b> $\text{X} = \text{Cl}$	19	8	13	0	8
2	<b>b</b>	Me	"	<i>t</i> -BuOH	rt	420	"	52	0	7	0	11
3	<b>a</b>	H	47% HBr	MeCN	80	5	<b>b)</b> $\text{X} = \text{Br}$	13	2	20	8	0
4	<b>b</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)	Yield (%) of			Other Product
					7	19	20	
1	<b>a</b>	H	<i>t</i> -BuOH	60	28	0	14	<b>10</b> (7)
2	<b>b</b>	Me	<i>t</i> -BuOH	60	50	12	17	0
3	<b>b</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 ( $\epsilon$ ) increases from *tert*-BuOH (11) to DMF (37), MeCN (38), HCONH<sub>2</sub> (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 BBr<sub>3</sub> 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**).

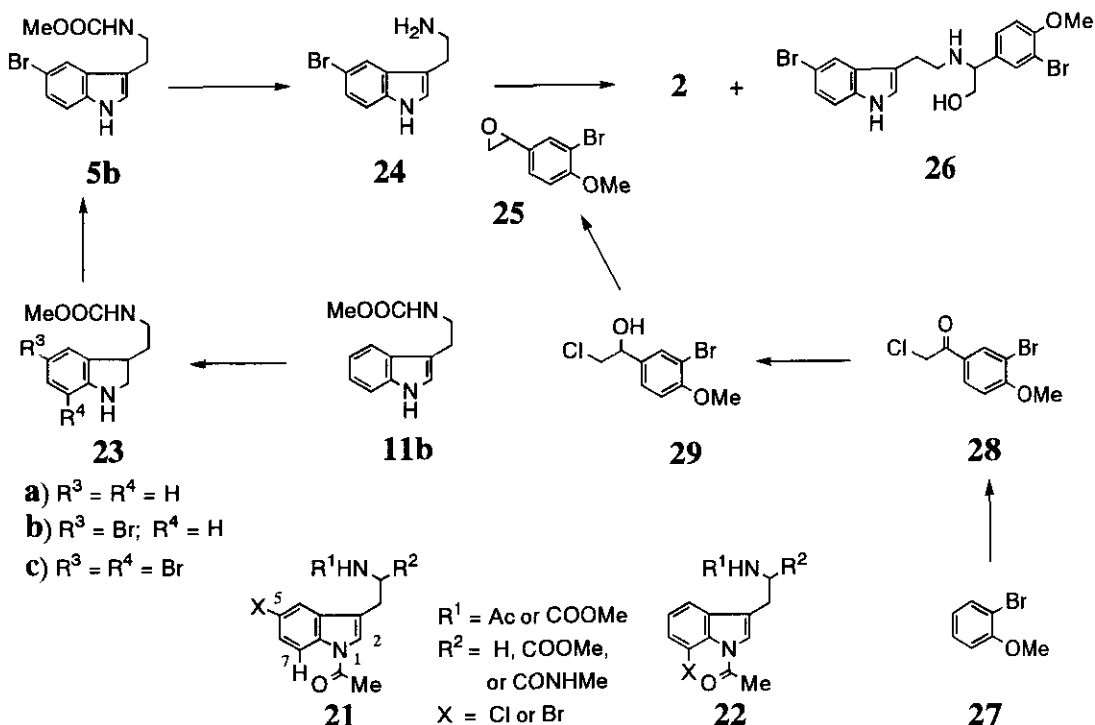
The similar substituent effects as described above were observed in the reactions of ( $\pm$ )-1-hydroxytryptophan derivatives (**9a,b** and **10a,b**) (Tables 4 and 5). Consequently, ( $\pm$ )-*Nb*-acetyl-5-chlorotryptophan methyl ester (**6a**) and ( $\pm$ )-5-bromo-*Nb*-methoxycarbonyltryptophan methyl 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.<sup>7</sup> 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-oxindoles<sup>8</sup> (**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 NaBH<sub>4</sub> 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,<sup>7</sup> or methoxy<sup>7</sup> 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,<sup>7a</sup> dimerization,<sup>7b</sup> kabutane formation,<sup>7d</sup> and so on,<sup>7</sup> take place depending on the structures of substrates and reaction conditions. The reason why is an interesting subject for further investigation.<sup>9</sup> Furthermore, our results thusfar obtained<sup>7</sup> 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.

## ACKNOWLEDGMENT

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## REFERENCES AND NOTES

1. This is Part 94 of a series entitled "The Chemistry of Indoles". Part 93: M. Somei, M. Nakajou, T. Teramoto, A. Tanimoto, and F. Yamada, *Heterocycles*, 1999, **51**, 1949.  
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 (CH<sub>2</sub>Cl<sub>2</sub>-hexane); **4b**, oil; **5a**, mp 154–155°C (CH<sub>2</sub>Cl<sub>2</sub>-MeOH); **5b**, oil; **6a**, oil; **6b**, oil; **7**, mp 202°C (MeOH); **8c**, oil; **8d**, oil; **10a**, mp 157–158°C (CHCl<sub>3</sub>-hexane); **10b**, mp 154–156°C (CHCl<sub>3</sub>-hexane); **12a**, oil; **12b**, oil; **13a**, oil; **13b**, mp 68.5–69.5°C (CH<sub>2</sub>Cl<sub>2</sub>-hexane); **14a**, mp 146–147°C (CH<sub>2</sub>Cl<sub>2</sub>-MeOH); **14b**, mp 123.5–125.0°C (CH<sub>2</sub>Cl<sub>2</sub>-MeOH); **15b**, oil; **16a**, mp 167–168°C (CH<sub>2</sub>Cl<sub>2</sub>-MeOH); **16b**, mp 161–162°C (CH<sub>2</sub>Cl<sub>2</sub>-hexane); **18b**, oil; **19**, mp 178–180°C (CH<sub>2</sub>Cl<sub>2</sub>-hexane); **23b**, oil; **23c**, oil; **24**, oil; **25**, oil; **26**, mp 98.5–100.0°C (CH<sub>2</sub>Cl<sub>2</sub>-hexane); **28**, mp 104–106°C (CH<sub>2</sub>Cl<sub>2</sub>-hexane); **29**, oil.
2. P. Z. DeCroos, P. Sangdee, B. L. Stockwell, L. Kar, E. B. Thompson, M. E. Johnson, and B. L. Currie, *J. Med. Chem.*, 1990, **33**, 3138.
3. S. C. Bobzin and D. J. Faulkner, *J. Org. Chem.*, 1991, **56**, 4403.
4. N. -K. Lee, W. Fenical, N. Lindquist, *J. Nat. Prod.*, 1997, **60**, 697.
5. W. D. Clark, T. Corbett, F. Valeriote, and P. Crews, *J. Am. Chem. Soc.*, 1997, **119**, 9285.
6. H. H. Sun and S. Sakemi, *J. Org. Chem.*, 1991, **56**, 4307; L. H. Franco, E. B. der Kier Joffe, L. Puricelli, M. Tatian, A. M. Seldes, and J. A. Palermo, *J. Nat. Prod.*, 1998, **61**, 1130.
7. a) M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles*, 1992, **34**, 1877; b) M. Somei and Y. Fukui, *ibid.*, 1993, **36**, 1859; c) M. Somei, K. Kobayashi, K. Tanii, T. Mochizuki, Y. Kawada, and Y. Fukui, *ibid.*, 1995, **40**, 119; d) M. Hasegawa, M. Tabata, K. Satoh, F. Yamada, and M. Somei, *ibid.*, 1996, **43**, 2333; e) M. Somei, F. Yamada, and H. Morikawa, *ibid.*, 1997, **46**, 91; f) Review: M. Somei, *ibid.*, 1999, **50**, 1157 and references cited therein; g) M. Somei, N. Oshikiri, M. Hasegawa, and F. Yamada, *ibid.*, 1999, **51**, 1237.
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 *N*b

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.<sup>7</sup>

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