A novel methodology for preparing 5-chloro- and 5-bromotryptamines and tryptophans, and its application to the synthesis of (±)-bromochelonin B

A NOVEL METHODOLOGY FOR PREPARING 5-CHLORO- AND 5-BROMO-TRYPTAMINES AND TRYPTOPHANS, AND ITS APPLICATION TO THE SYNTHESIS OF (±)-BROMOCHELONIN B[1]

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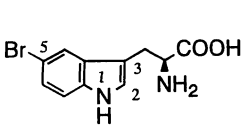
Abstract — A novel methodology for introducing chlorine or bromine into the 5-position of tryptamines was found through 1-hydroxytryptamines. The chemistry was applied to the syntheses of (±)-5-chloro-, -5-bromotryptophan derivatives, and (±)-bromochelonin B.

Many biologically active tryptamines are reported such as 5-bromotryptophan[2] (**1**), bromochelonin B[3] (**2**), alternatamide C[4] (**3**), cyclocinamide A[5] 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-hydroxyindoles[7] 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 (±)-5-chloro- and -5-bromotryptophan derivatives (**6a,b** and **7**), and (±)-**2**.

Figure 1



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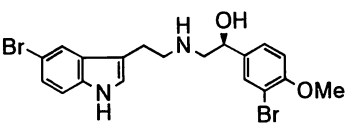

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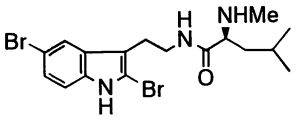


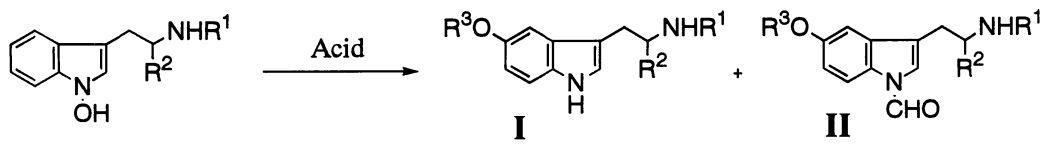
3

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 summarizedd 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,

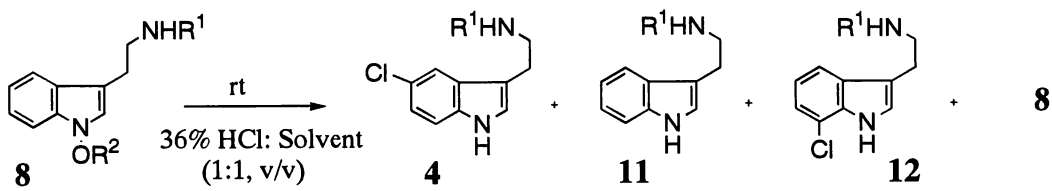
and 1-(2-methoxycarbonyl-1-methyl)ethoxy group (Entries 1—4), the yield of **4a** increased dramatically and yield 73% was attained under the reaction conditions described in the Entry 4. It is worthy to note that under similar reaction conditions *N*b-substituent of the side chain at the 3-position 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 *N*b-methoxycarbonyl group was produced than **4a** having *N*b-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 *N*b-methoxycarbonyl group (Entry 7).

Table 1



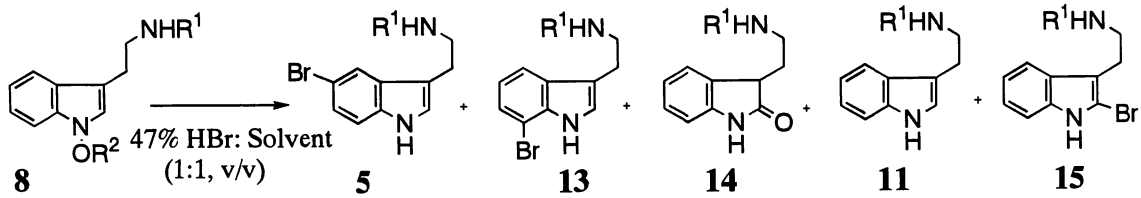
Entry	R^1	R^2	R^3	Acid	Yield (%) of I	Yield (%) of II
1	Ac	H	Me	20% BF_3·MeOH	80	0
2	COOMe	"	"	"	85	0
3	Ac	COOMe	"	H_2SO_4-MeOH	71	0
4	"	"	H	85% HCOOH	67	12

Table 2



Entry	Substrate	R^1	R^2	Reaction Solvent	Conditions Time (h)	Product	Yield (%) 4	11	of 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_2CH_2COOMe	"	17	"	59	0	0	6
4	**d**	"	$CH(Me)CH_2COOMe$	"	120	"	73	0	0	6
5	**b**	"	Me	*t*-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

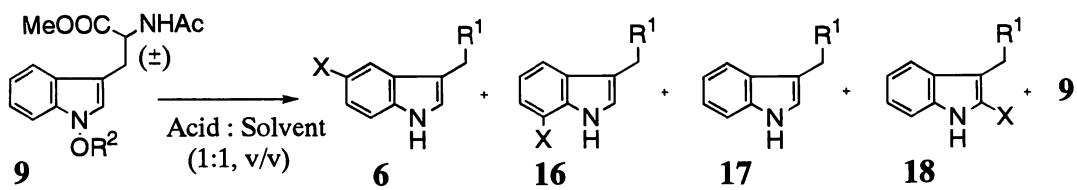


8 **5** **13** **14** **11** **15**

Entry	Substrate	R^1	R^2	Reaction Conditions: Solvent	Temp. (°C)	Time (h)	Product	Yield (%) of 5	13	14	11	15
1	**a**	Ac	H	MeCN	80	3	**a)** R^1 = Ac	5	4	19	3	0
2	**c**	"	CH_2CH_2COOMe	MeOH	rt	20	"	51	8	18	11	0
3	**d**	"	$CH(Me)CH_2COOMe$	"	rt	55	"	38	8	0	10	0
4	**e**	COOMe	H	*t*-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

* BBr_3 (1.1 mol eq) was used as a brominating reagent.

Table 4



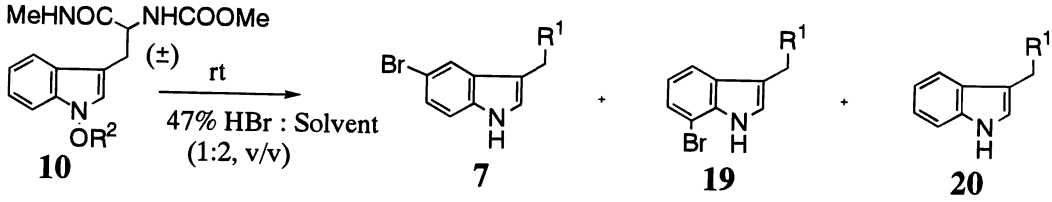
9 **6** **16** **17** **18**

R^1 = (±)-CH(NHAc)COOMe

Entry	Substrate	R^2	Acid	Reaction Conditions: Solvent	Temp. (°C)	Time (min)	Product	Yield (%) of 6	16	17	18	9
1	**a**	H	36% HCl	MeCN *	80	5	**a)** X = Cl	19	8	13	0	8
2	**b**	Me	"	*t*-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



R^1 = (±)-CH(NHCOOMe)CONHMe

Entry	Substrate	R^2	Reaction Conditions Solvent	Time (min)	Yield (%) of 7	19	20	Other Product
1	**a**	H	*t*-BuOH	60	28	0	14	**10** (7)
2	**b**	Me	*t*-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 *N*b-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), $HCONH_2$ (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_3 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**).

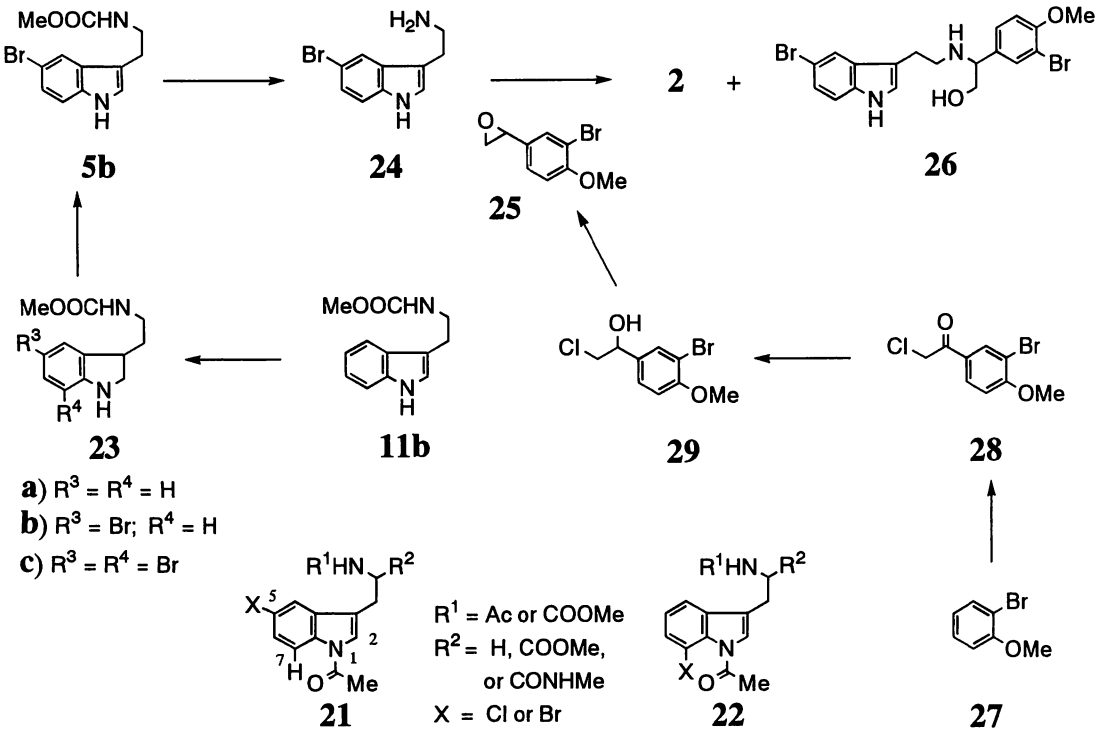
The similar substituent effects as described above were observed in the reactions of (±)-1-hydroxytryptophan derivatives (**9a,b** and **10a,b**) (Tables 4 and 5). Consequently, (±)-*N*b-acetyl-5-chlorotryptophan methyl ester (**6a**) and (±)-5-bromo-*N*b-methoxycarbonyltryptophan methyl amide (**7**) 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 *N*b-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 = 7-8 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[8] (**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 (±)-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 (±)-**2** and its (±)-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 $NaBH_4$ 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 methoxy[7] 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 obtained[7] 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

This work is supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, which is gratefully acknowledged.

REFERENCES AND NOTES

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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℃ (AcOEt-hexane); **4a**, mp 140—141℃ (CH_2Cl_2-hexane); **4b**, oil; **5a**, mp 154—155℃ (CH_2Cl_2-MeOH); **5b**, oil; **6a**, oil; **6b**, oil; **7**, mp 202℃ (MeOH); **8c**, oil; **8d**, oil; **10a**, mp 157—158℃ ($CHCl_3$-hexane); **10b**, mp 154—156℃ ($CHCl_3$-hexane); **12a**, oil; **12b**, oil; **13a**, oil; **13b**, mp 68.5—69.5℃ (CH_2Cl_2-hexane); **14a**, mp 146—147℃ (CH_2Cl_2-MeOH); **14b**, mp 123.5—125.0℃ (CH_2Cl_2-MeOH); **15b**, oil; **16a**, mp 167—168℃ (CH_2Cl_2-MeOH); **16b**, mp 161—162℃ (CH_2Cl_2-hexane); **18b**, oil; **19**, mp 178—180℃ (CH_2Cl_2-hexane); **23b**, oil; **23c**, oil; **24**, oil; **25**, oil; **26**, mp 98.5—100.0℃ (CH_2Cl_2-hexane); **28**, mp 104—106℃ (CH_2Cl_2-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 *N*b

nitrogen atom no matter whether it is amine or amide nitrogen. The protonated *N*b nitrogen inhibits electrostatistically 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 *N*b nitrogen, culminating in the departure of 1-alkoxy group and then followed by the nucleophilic substitution reaction. In the cases of indoles lacking *N*b nitrogen, preferential proton addition occurs at the 3-position directing toward pyrrolo[2,3-*b*]indole formation, dimerization, kabutane formation, etc. [7]

Received, 30th July, 1999