TOTAL SYNTHESIS OF TOPSENTIN, ANTIVIRAL AND ANTITUMOR BIS(INDOLYL)IMIDAZOLE[1]

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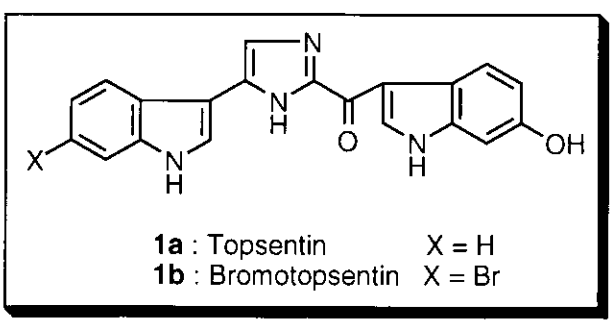
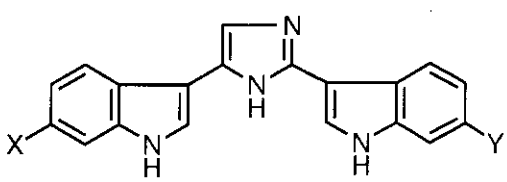
Abstract-Topsentin (**1**), which was isolated from marine sponges and has antiviral and antitumor activities, was synthesized *via* a cross coupling reaction in the presence of palladium catalyst at the 5-position and an acylation at the 2-position of imidazole ring.

Topsentins (**1**) were isolated from marine sponges and show antitumor and antiviral activity.[2] Rinehart *et al.* reported a total synthesis of **1a** *via* condensation of 3-glyoxalylindole with 6-benzyloxy-3-glyoxalylindole in the presence of ammonia in 1988, but this synthesis was low yield and non-regioselective.[2b] We have been developed the methods for regioselective introduction of carbogenic or functional group at 2-, 4,- or 5-position of imidazole ring, and total synthesis of several marine products containing imidazole ring was performed by the application of these methods.[3] Recently, we reported the first total synthesis of nortopsentins (**2**), having a characteristic 2,4-bis(indolyl)imidazole skeleton, *via* arylation of the imidazole ring.[3d,f] The structure of topsentins (**1**) resembles that of nortopsentins (**2**). In this paper, we describe a total synthesis of **1a** by successive introduction of indolyl and indolylcarbonyl groups on imidazole ring.



1a : Topsentin X = H
1b : Bromotopsentin X = Br

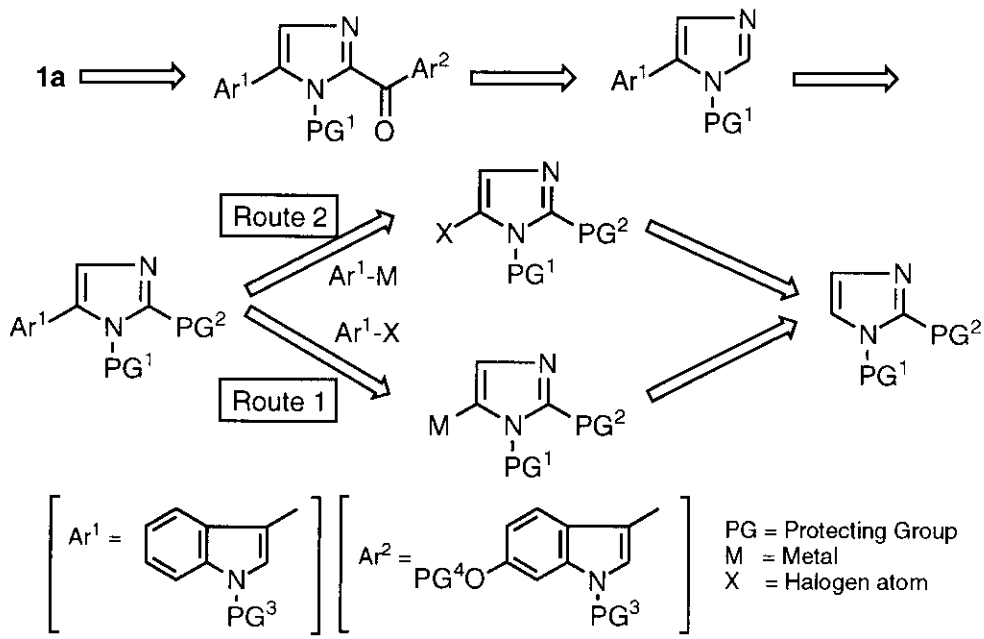


2a : Nortopsentin A X = Y = Br
2b : Nortopsentin B X = H, Y = Br
2c : Nortopsentin C X = Br, Y = H
2d : Nortopsentin D X = Y = H

Figure 1

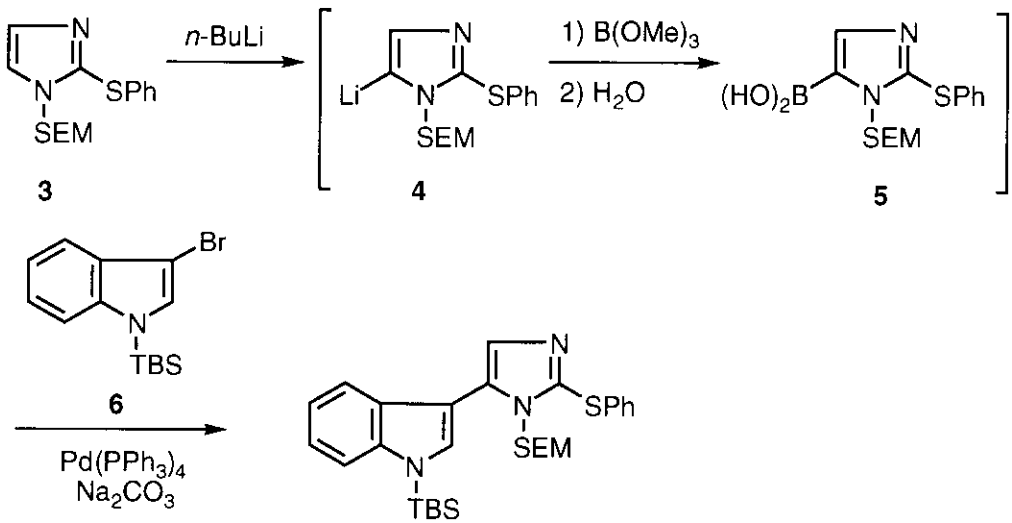
A retrosynthetic route is shown in Scheme 1. The indolyl group (Ar^1) would be introduced at the 5-position of the imidazole by a cross coupling reaction in the presence of palladium catalyst. Two

combinations of the starting materials are possible for the cross coupling. One is condensation of the indolyl halide with imidazolylboronic acid (Route 1), and the other is condensation of the imidazoyl halide with indolylboronic acid (Route 2). Introduction of the indolylcarbonyl group (Ar^2-CO) would be done by acylation of 2-lithioimidazole with an appropriate 3-indolecarboxylic acid derivative.



Scheme 1

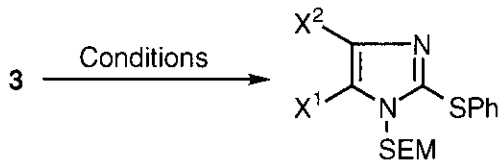
First, we tried Route 1. After lithiation of the 1,2-protected imidazole (**3**)[4] with *n*-BuLi, addition of trimethyl borate followed by hydrolysis afforded the imidazolylboronic acid (**5**).



Scheme 2

The boronic acid (**5**) was subjected to the Suzuki reaction[5] without further purification. The 3-bromo-1-(*tert*-butyldimethylsilyl)indole (**6**)[6] was treated with the boronic acid (**5**) in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium. However, the cross coupling product (**7a**) was obtained only in 7% yield (Scheme 2). This low yield might be attributable to the instability of **6**.[7]

Next, we tried Route 2. The 1,2-protected imidazole (**3**) was halogenated by the methods shown in Scheme 3, and the corresponding halogenoimidazoles (**8a** - **c**) were obtained in moderate to good yields.



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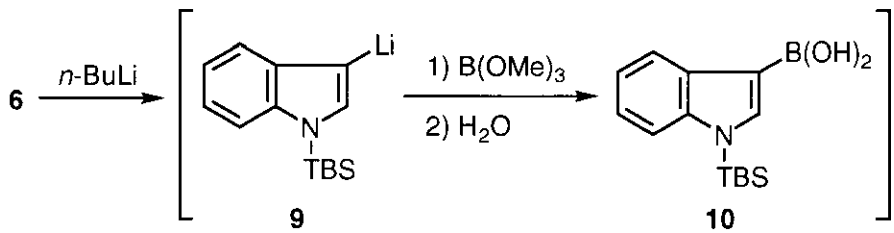
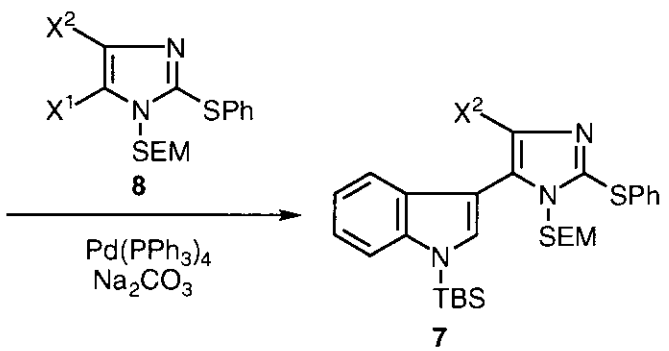
Run	Conditions	Product	X^1	X^2	Yield (%)
1	1) *n*-BuLi 2) Br_2 (1 eq.)/ -78°C	**8a**	Br	H	84
2	NBS (2 eq.) / 0°C	**8b**	Br	Br	54
3	1) *n*-BuLi 2) I_2 (1 eq.)/ -78°C	**8c**	I	H	98

Scheme 3





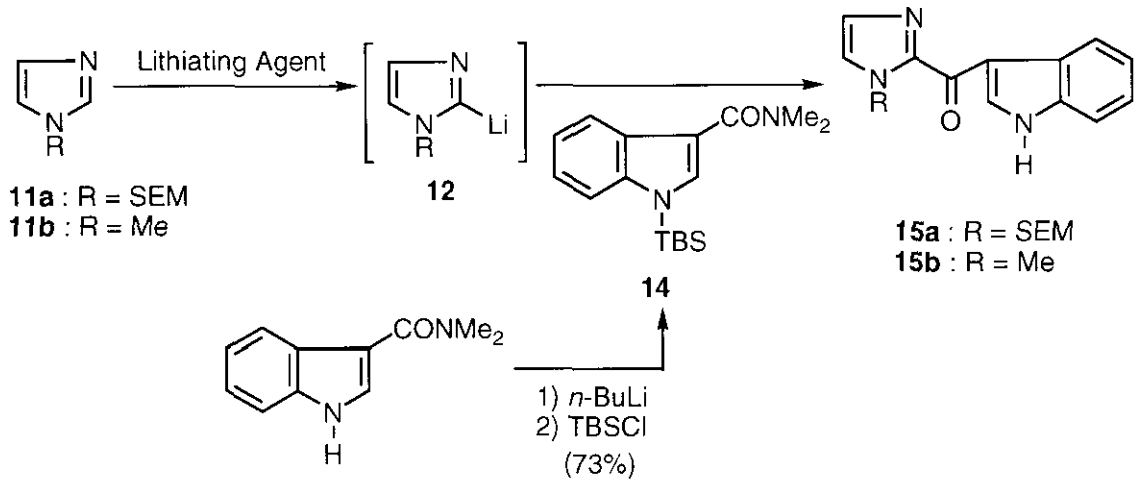
Substrate	Product
8a	**7a** : X^2 = H 79 %
8b	**7b** : X^2 = Br 39 %
8c	**7a** : X^2 = H 79 %

Scheme 4

The compound (**6**) was lithiated with *n*-BuLi,[6] and then the lithio compound was treated with trimethyl borate followed by hydrolysis to afford the indolylboronic acid (**10**). The halogenated imidazoles (**8**) were

treated with **10** in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium. As shown in Scheme 4, the reaction of the 5-bromo- and the 5-iodoimidazoles (**8a** and **8c**) gave the desired 5-(3-indolyl)imidazole (**7a**) in high yields. In the case of the 4,5-dibromoimidazole (**7b**), however, the desired product **7b** was obtained in low yield (39%) (Scheme 4).

To introduce the indolylcarbonyl group to the 2-position of imidazole ring, we examined the acylation of the 1-protected imidazoles (**11**) with the 3-indolecarboxylic acid derivative as a model reaction. It has been known that tertiary amides are good acylation agents for the imidazole ring.[8] The 2-lithioimdazoles (**12**) was prepared by treatment of **11** with lithiating agents such as *n*-BuLi and LDA, and treated with the 3-amidoindole (**14**), which was prepared by protecting the 1-position of the amide (**13**)[9] with TBS group in the usual manner. Interestingly, the TBS groups on the indole ring were lossed probably during isolation step to give **15a** and **15b**. The results are shown in Scheme 5. When *n*-BuLi was used as the lithiating agent, the yields of **15a** and **15b** were relatively good. We selected *n*-BuLi as the lithiation agent for the acylation.

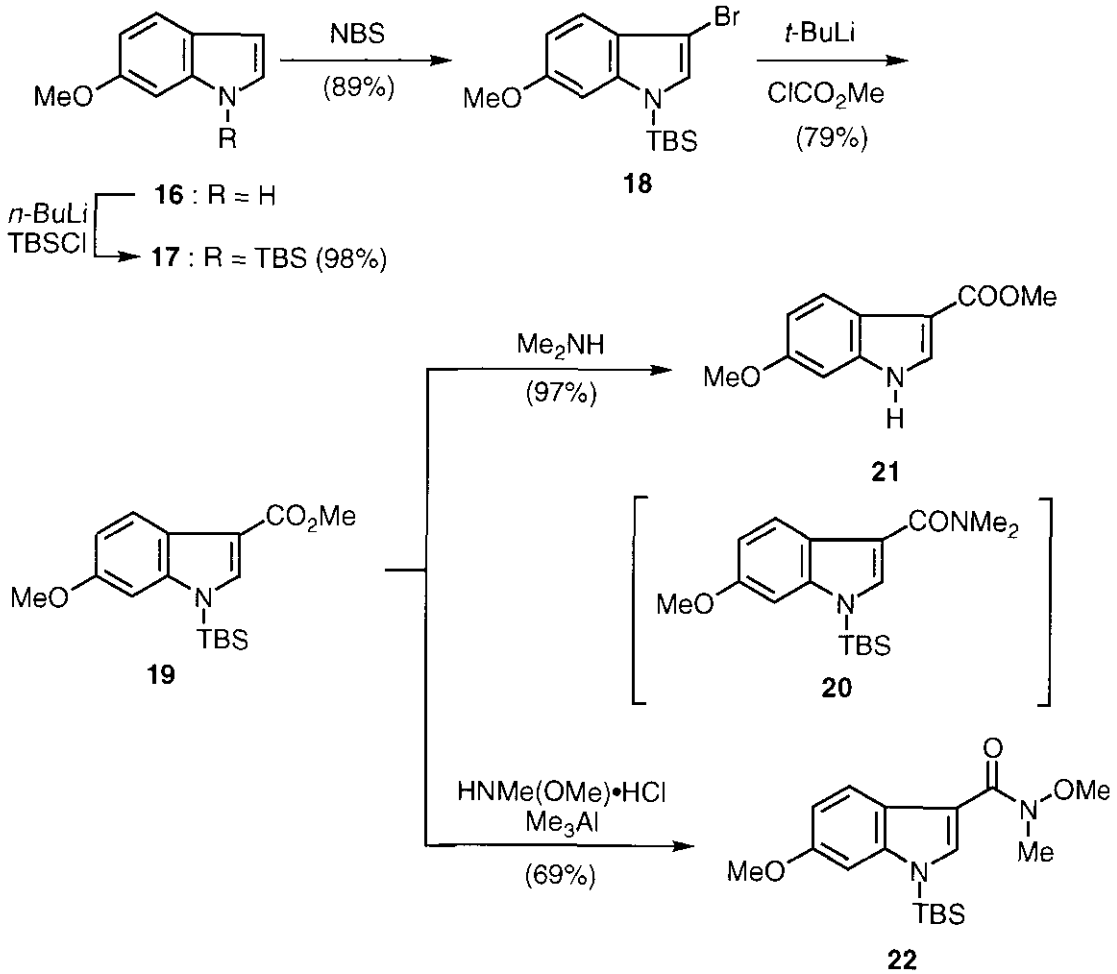


Substrate	Lithiating Agent	Temp. (°C)	Product : Yield (%)
11a	*n* -BuLi	-78 to rt	**15a** : 58
11a	LDA	-78 to rt	**15a** : 42
11b	*n* -BuLi	-78 to rt	**15b** : 87
11b	LDA	-78 to rt	**15b** : 69

Scheme 5

Next, the 6-methoxyindolecarboxamide was prepared as follows. The 6-methoxyindole ester (**19**) was prepared according to the Amat's method.[6] The 1-position of the 6-methoxyindole (**16**)[10] was protected with TBS group and the product (**17**) was brominated with NBS to give the 3-bromo compound (**18**). The 3-bromo compound (**18**) was lithiated with *tert*-BuLi followed by treatment with methyl chloroformate

to give the indolecarboxylate (**19**). In order to transform the ester (**19**) to the amide (**20**), **19** was treated with dimethylamine solution. Disappointedly, the obtained product was not the desired one (**20**) but the *N*-deprotected one (**21**, 97%). On the other hand, the ester (**19**) could be transformed to the corresponding Weinreb amide (**22**) in 69% yield by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum (Scheme 6).[11]



Scheme 6

Desulfurization of **7a** with sodium borohydride in the presence of nickel(II) chloride afforded **23** in 79% yield.[12]

Moreover, **23** was obtained through another route starting from the 2,4,5-triiodoimidazole (**24**). The 2,4,5-triiodoimidazole (**24**) was protected with SEM group, and the obtained **25** was treated with the boronic acid (**10**) in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium to give **26** in 75% yield and **26** was dehalogenated by treatment with ethylmagnesium bromide to give **23** in 84% yield. For the preparation of **23**, this route is shorter than the former route starting from **3**.

Lithiation of **23** with *n*-BuLi followed by addition of the Weinreb amide (**22**)[11] afforded a mixture of **27a**,

27b, and **27c** in 34, 33, and 6% yields, respectively.

The structures of **27a**, **27b** and **27c** were determined on the basis of their spectral data. In the NOE experiment of **27b**, NOE (3.7%) was observed between 2'-H of the indolyl group at the 5-position of the imidazole ring and methylene protons on SEM group as shown in Figure 2.

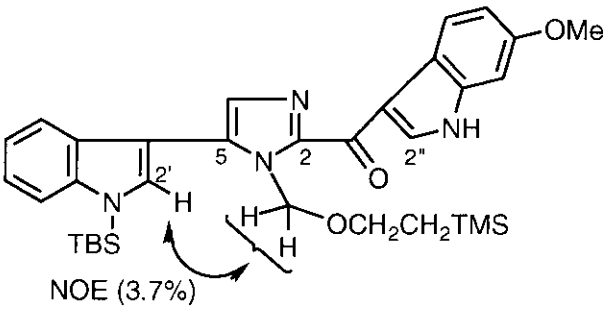
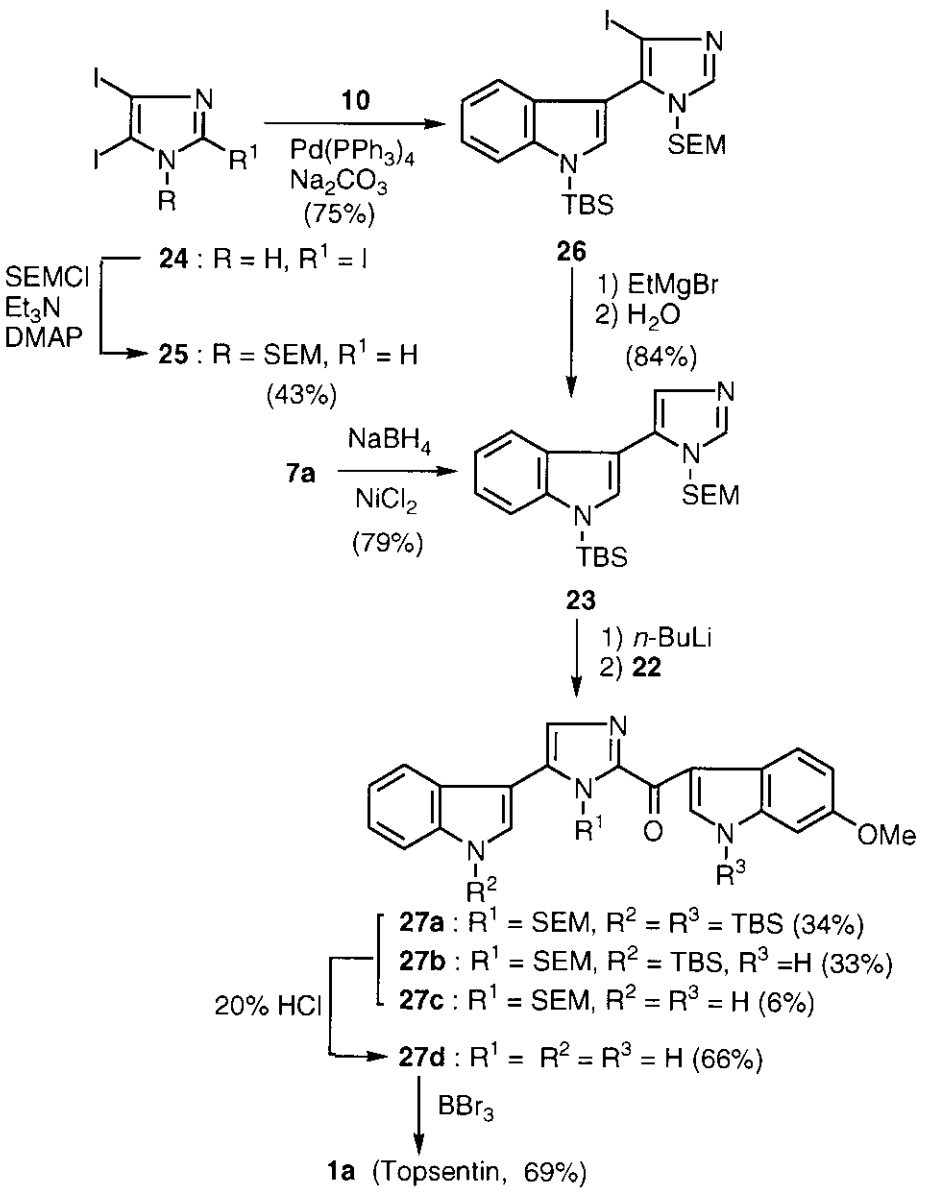


Figure 2. Observed NOE of **27b**



Scheme 7

A mixture of these three products (**27a** - **c**) was treated with 20% HCl in ethanol to give the*O*-methyltopsentin (**27d**) in 66% yield. Finally, topsentin (**1a**) was obtained in 69% yield by treatment of **26d** with BBr_3.[13] The structure of the synthetic **1a** was confirmed by comparison of its spectral data with those of the natural product.[2b]

EXPERIMENTAL

Melting points were measured with a Yanaco MP micro-melting point apparatus and are uncorrected. IR spectra were taken with a Shimadzu IR-435 spectrophotometer. NMR spectra were measured on a Varian XL-300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) with tetramethylsilane as an internal standard and chemical shifts are reported in ppm. MS were recorded with a JEOL JMS-SX 102A QQ spectrometer. Silica gel 60 (Merck) for column chromatography and Silica gel 60 PF_{254} (Nacalai Tesque Inc.) for preparative TLC (PTLC) were used. All extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure.

5-[1-(*tert*-Butyldimethylsilyl)indol-3-yl]-2-phenylthio-1-[2-(trimethylsilyl)ethoxy]-methyl-1*H*-imidazole (7a): To a solution of 2-phenylthio-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole (**3** : 153 mg, 0.50 mmol) in THF (1 mL) was added dropwise *n*-BuLi (0.38 mL, 1.6 M solution in *n*-hexane, 0.60 mmol) at -78°C under an nitrogen atmosphere and the whole was stirred for 15 min at the same temperature. A solution of trimethyl borate (208 mg, 0.23 mL, 2.0 mmol) in THF (2 mL) was added to the mixture and the whole was stirred for additional 1 h at -78°C. After addition of MeOH-H_2O (1 : 1) (0.25 mL), the whole was stirred for 1 h at rt. H_2O (5 mL) was added and the mixture was extracted with ether. The combined organic extracts were washed with H_2O, dried, and evaporated to give crude 2-phenylthio-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazolylboronic acid (**5**), which was used in the next reaction without further purification. A mixture of **6** (155 mg, 0.50 mmol), **5**, $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), 2M Na_2CO_3 aqueous solution (0.5 mL), methanol (2 mL), and benzene (10 mL) was refluxed under stirring for 8 h. The mixture was dried and evaporated. The residue was chromatographed on PTLC (ethyl acetate / *n*-hexane =1 / 2) to give **7a** (20 mg, 7 %) as colorless oil. IR ($CHCl_3$) : 2941, 1449, 1255, 1080 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.06 (s, 9H), 0.64 (s, 6H), 0.85 (t, 2H, *J* = 8.2 Hz), 0.96 (s, 9H), 3.51 (t, 2H, *J* = 8.2 Hz), 5.37 (s, 2H), 7.18 - 7.27 (m, 7H), 7.49 (s, 1H), 7.54 - 7.57 (m, 1H), 7.69 (s, 1H), 7.74 - 7.77 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ : -4.0, -1.5, 18.1, 19.4, 26.3, 66.0, 73.2, 107.4, 114.1, 119.4, 120.7, 122.3, 126.6, 127.9, 129.1, 129.2, 129.7, 130.6, 131.3, 135.5, 137.9, 141.2. HRMS *m/z* : Calcd for $C_{29}H_{41}N_3OSSi_2$, 535.2510. Found, 535.2514 (M^+).

5-Bromo-2-phenylthio-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole (8a): To a solution of **3** (919 mg, 3.0 mmol) in THF (30 mL) was added dropwise *n*-BuLi (1.9 mL, 1.6 M solution in *n*-hexane, 3.0 mmol) at -78°C under an nitrogen atmosphere and the whole was stirred for 30 min at the same temperature. A solution of bromine (476 mg, 155 μL, 3.0 mmol) in THF (9 mL) was added to the mixture and the whole was stirred for additional 2 h at -78°C. After addition of 5% $Na_2S_2O_3$ aqueous solution, the mixture was extracted with ethyl acetate. The combined organic extracts were washed with H_2O, dried,

and evaporated. The residue was chromatographed with ethyl acetate / *n*-hexane (1 / 8) to give **8a** (971 mg, 84 %) as colorless oil. IR ($CHCl_3$) : 2941, 1478, 1247, 1086 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.06 (s, 9H), 0.81 (t, 2H, *J* = 8.2 Hz), 3.46 (t, 2H, *J* = 8.2 Hz), 5.41 (s, 2H), 7.18 (s, 1H), 7.20 - 7.28 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ : -1.5, 17.8, 66.6, 74.1, 106.0, 127.2, 128.9, 129.3, 131.3, 133.9, 140.2. LRMS *m/z* : 384 (M^+), 386 $(M+2)^+$. HRMS *m/z* : Calcd for $C_{15}H_{21}N_2OBrSSi$, 384.0347. Found, 384.0337 (M^+).

4,5-Dibromo-2-phenylthio-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole (8b): To a solution of **3** (110 mg, 0.36 mmol) in THF (6 mL) was added portionwise NBS (128 mg, 0.72 mmol) at 0°C under an nitrogen atmosphere and the whole was stirred for 3 h at the same temperature. After addition of ethyl acetate and H_2O, the mixture was extracted with ethyl acetate. The combined organic extracts were washed with H_2O, dried, and evaporated. The residue was chromatographed on PTLC (ethyl acetate/*n*-hexane =1 / 10) to give **8b** (90 mg, 54 %) as colorless oil. IR ($CHCl_3$) : 2941, 1477, 1247, 1089 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.08 (s, 9H), 0.79 (t, 2H, *J* = 8.3 Hz), 3.44 (t, 2H, *J* = 8.3 Hz), 5.39 (s, 2H), 7.21 - 7.31 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ : -1.5, 17.8, 66.9, 75.2, 107.0, 118.6, 127.6, 129.2, 129.4, 133.1, 140.0. HRMS *m/z* : Calcd for $C_{15}H_{20}N_2OBr_2SSi$, 463.9412. Found, 463.9418 $(M+2)^+$.

5-Iodo-2-phenylthio-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole (8c): The reaction was carried out in a similar manner to that used for the above-mentioned preparation of **8a** except for use of iodine instead of bromine. Purification by the column chromatograpy with ethyl acetate / *n*-hexane (1 / 10) gave **8c** (98 %) as colorless oil. IR ($CHCl_3$) : 2948, 1475, 1246, 1084 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.05 (s, 9H), 0.82 (t, 2H, *J* = 8.2 Hz), 3.46 (t, 2H, *J* = 8.2 Hz), 5.42 (s, 2H), 7.22 - 7.32 (m, 6H). ^{13}C-NMR ($CDCl_3$) δ : -1.4, 17.8, 66.5, 75.6, 127.2, 128.1, 128.5, 128.9, 129.3, 134.0, 138.4. HRMS *m/z* : Calcd for $C_{15}H_{21}N_2OISSi$, 432.0190. Found, 432.0174 (M^+).

5-[1-(*tert*-Butyldimethylsilyl)indol-3-yl]-2-phenylthio-1-[2-(trimethylsilyl)ethoxy]-methyl-1*H*-imidazole (7a): To a solution of **6** (186 mg, 0.60 mmol) in THF (2 mL) was added dropwise *tert*-BuLi (0.76 mL, 1.57 M solution in *n*-pentane, 1.2 mmol) at -78°C under an nitrogen atmosphere and the whole was stirred for 15 min at the same temperature. A solution of trimethyl borate (250 mg, 0.27 mL, 2.4 mmol) in THF (4 mL) was added to the mixture and the whole was stirred for additional 1 h at -78°C. After addition of MeOH-H_2O (1 : 1) (0.5 mL), the whole was stirred for 1 h at rt. H_2O (5 mL) was added and the mixture was extracted with ether. The combined organic extracts were washed with H_2O, dried, and evaporated to give 1-(*tert*-butyldimethylsilyl)indolyl-3-boronic acid (**10**), which was used without further purification. The mixture of **8a** (77 mg, 0.20 mmol), **10**, $Pd(PPh_3)_4$ (35 mg, 0.03 mmol), 2M Na_2CO_3 aqueous solution (0.2 mL), methanol (0.8 mL), and benzene (4 mL) was refluxed under stirring for 15 h. The mixture was dried and evaporated. The residue was chromatographed on PTLC (ethyl acetate / *n*-hexane =1 / 10) to give **7a** (85 mg, 79 %), which was identical with the product prepared above.

When the reaction was carried out using **8c** instead of **8a**, **7a** was obtained in 79 % yield.

4-Bromo-5-[1-(*tert*-butyldimethylsilyl)indol-3-yl]-2-phenylthio-1-[2-(trimethylsilyl)-ethoxy]methyl-1*H*-imidazole (7b): The reaction was carried out in a similar manner to that used for the above-mentioned preparation of **7a** except for use of **8b** instead of **8a**. Purification by PTLC (ethyl acetate / *n*-hexane = 1 / 20) gave **7b** (39 %) as colorless oil. IR ($CHCl_3$) : 2942, 1449, 1254, 1081 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.11 (s, 9H), 0.64 (s, 6H), 0.72 (t, 2H, *J* = 8.3 Hz), 0.95 (s, 9H), 3.33 (t, 2H, *J* = 8.3 Hz), 5.25 (s, 2H), 7.15 - 7.36 (m, 7H), 7.48 (s, 1H), 7.50 - 7.57 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ : -4.0, -1.5, 17.9, 19.4, 26.3, 66.3, 73.8, 105.3, 114.3, 116.8, 120.3, 120.5, 122.2, 127.0, 128.5, 128.8, 129.3, 129.5, 133.3, 134.5, 138.3, 141.0. HRMS *m/z* : Calcd for $C_{29}H_{40}N_3OBrSSi_2$, 613.1620. Found, 613.1599 (M^+).

***N,N*-Dimethyl-1-(*tert*-butyldimethylsilyl)indole-3-carboxamide (14)**: To a solution of **13** (941 mg, 5.0 mmol) in THF (10 mL) was added dropwise *n*-BuLi (3.5 mL, 1.6 M solution in *n*-hexane, 5.5 mmol) followed by addition of *tert*-butyldimethylsilyl chloride (829 mg, 5.5 mmol) at 0°C under an nitrogen atmosphere and the whole was stirred for 2 h at rt. After addition of H_2O (10 mL), the mixture was extracted with ethyl acetate. The combined organic extracts were washed with H_2O, dried, and evaporated to give solid. The solid was chromatographed (ethyl acetate / *n*-hexane =5 / 1) to give **14** (1.11g, 73 %) as colorless crystals. mp 126.5 - 128.0°C (*n*-hexane). IR ($CHCl_3$) : 2912, 2847, 1605, 1448 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.61 (s, 6H), 0.94 (s, 9H), 3.15 (s, 6H), 7.16 - 7.22 (m, 2H), 7.45 (s, 1H), 7.49 - 7.52 (m, 1H), 7.73 - 7.76 (m, 1H). *Anal.*Calcd for $C_{17}H_{26}N_2OSi$: C, 67.50; H, 8.66; N, 9.26. Found: C, 67.04; H, 8.76; N, 9.49.

2-(3-Indolyl)-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole (15a): To a solution of **11a** (238 mg, 1.2 mmol) in THF (3 mL) was added dropwise *n*-BuLi (0.83 mL, 1.6 M solution in *n*-hexane, 1.32 mmol) at -78°C under an nitrogen atmosphere. A solution of **14** (454 mg, 1.5 mmol) in THF (3 mL) was added to the mixture and the whole was stirred overnight at an ambient temparature. After addition of H_2O (3 mL), the mixture was extracted with ethyl acetate. The combined organic extracts were washed with H_2O, dried, and evaporated. The residue was chromatographed with PTLC (ethyl acetate / *n*-hexane = 3 / 2) to give **15a** (240 mg, 58 %) as colorless oil. IR ($CHCl_3$) : 3439, 2941, 1611, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.05 (s, 9H), 0.94 (t, 2H, *J* = 8.3 Hz), 3.63 (t, 2H, *J* = 8.3 Hz), 5.92 (s, 2H), 7.21 - 7.38 (m, 5H), 8.50 - 8.53 (m, 1H), 8.83 (d, 1H, *J* = 3.2 Hz), 9.35 (br s, 1H). HRMS *m/z* : Calcd for $C_{18}H_{23}N_3O_2Si$, 341.1560. Found, 341.1563 (M^+).

The reaction was carried out in a similar manner to that used for the reaction of **15a** except for use of LDA instead of *n*-BuLi as base. Yield: 42 %.

2-(3-Indolyl)-1-methyl-1*H*-imidazole (15b): The reaction was carried out in a similar manner to that used for the reaction of **15a** except for use of **11b** instead of **11a**. Purification of the crude product by

PTLC (ethyl acetate) gave **15b** (87 %) as colorless crystals. mp 232.0 - 233.0°C (ethyl acetate / *n*-hexane). IR (KBr) : 3117, 2870, 1604, 1450 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ : 4.02 (s, 3H), 7.13 (s, 1H), 7.19 - 7.26 (m, 2H), 7.46 (s, 1H), 7.50 - 7.53 (m, 1H), 8.34 - 8.37 (s, 1H), 12.02 (br s, 1H). *Anal.*Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.47; H, 5.06; N, 18.71.
The reaction was carried out in a similar manner to that used for the reaction of **15a** except for use of LDA instead of *n*-BuLi as base. Yield: 69 %.

1-(*tert*-Butyldimethylsilyl)-6-methoxyindole (17) : To a solution of 6-methoxyindole (**16**) (1.47 g, 10 mmol) in THF (100 mL) was added dropwise *n*-BuLi (6.25 mL, 1.6 M solution in *n*-hexane, 10 mmol) at 0°C under an nitrogen atmosphere and the whole was stirred for 15 min. *tert*-Butyldimethylsilyl chloride (1.51 g, 10 mmol) was added to the mixture and the whole was stirred for additional 10 h at rt. After addition of H_2O (10 mL), the solvent was concentrated under reduced pressure and the residue was extracted with ethyl acetate. The combined organic extracts were washed with H_2O, dried, and evaporated. The residue was chromatographed (ethyl acetate / *n*-hexane =1 / 50) to give **17** (2.55g, 98%) as colorless oil. IR ($CHCl_3$) : 2918, 1612, 1480, 1131 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.59 (s, 6H), 0.94 (s, 9H), 3.84 (s, 3H), 6.53 (d, 1H, *J* = 3.2 Hz), 6.79 (dd, 1H, *J* = 2.2, 8.6 Hz), 7.04 (d, 1H, *J* = 2.0 Hz), 7.07 (d, 1H, *J* = 3.2 Hz), 7.49 (d, 1H, *J* = 8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ : -4.0, 19.6, 26.4, 55.8, 98.5, 104.6, 109.1, 120.8, 125.7, 129.9, 141.8, 155.7. HRMS *m/z* : Calcd for $C_{15}H_{23}NOSi$, 261.1550. Found, 261.1566 (M^+).

3-Bromo-1-(*tert*-butyldimethylsilyl)-6-methoxyindole (18) : To a solution of **17** (2.61 g, 10 mmol) in THF (100 mL) was added oneportion NBS (1.78 g, 10 mmol) at -78°C under an nitrogen atmosphere and the whole was stirred for 3 h at the same temperature. The solvent was evaporated and the residue was chromatographed (ether / *n*-hexane =1 / 100) to give **18** (3.03 g, 89 %) as colorless crystals. mp 62.0 - 63.0°C (EtOH-H_2O). IR ($CHCl_3$) : 2921, 1616, 1480, 1127 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.59 (s, 6H), 0.95 (s, 9H), 3.85 (s, 3H), 6.87 (dd, 1H, *J* = 2.2, 8.8 Hz), 6.98 (d, 1H, *J* = 2.1 Hz), 7.05 (s, 1H), 7.43 (d, 1H, *J* = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ : -4.0, 19.5, 26.2, 55.8, 93.5, 98.5, 109.9, 119.5, 124.4, 128.5, 141.0, 156.6. *Anal.*Calcd for $C_{15}H_{22}NOBrSi$: C, 52.94; H, 6.52; N, 4.12. Found: C, 53.05; H, 6.30; N, 4.19.

Methyl 1-(*tert*-Butyldimethylsilyl)-6-methoxyindole-3-carboxylate (19) : To a solution of **18** (1.46 g, 4.28 mmol) in THF (17 mL) was added dropwise *tert*-BuLi (5.45 mL, 1.57 M solution in *n*-pentane, 8.56 mmol) at -78°C under an nitrogen atmosphere and the whole was stirred for 15 min. A solution of methyl chloroformate (809 mg, 0.66 mL, 8.56 mmol) in THF (5 mL) was added to the mixture and the whole was stirred for additional 2 h at -78°C. After addition of H_2O (10 mL), the mixture was extracted with ether. The combined organic extracts were washed with H_2O, dried, and evaporated. The residue was chromatographed (ether / *n*-hexane =1 / 10) to give **19** (1.08g, 79%) as colorless crystals. mp 78.0 - 80.0°C (ether-*n*-hexane). IR ($CHCl_3$) : 2942, 1689, 1531, 1189 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.63 (s, 6H), 0.95 (s, 9H), 3.85 (s, 3H), 3.90 (s, 3H), 6.93 (dd, 1H, *J* = 2.2, 8.8 Hz), 7.01 (d, 1H, *J* = 2.2

Hz), 7.79 (s, 1H), 8.04 (d, 1H, J = 8.8 Hz). ^{13}C-NMR ($CDCl_3$) δ : -4.0, 19.3, 26.3, 51.0, 55.7, 98.8, 110.5, 110.7, 121.9, 123.0, 137.3, 142.2, 156.3, 165.6. HRMS *m/z* : Calcd for $C_{17}H_{25}NO_3Si$, 319,1600. Found, 319.1584 (M^+). *Anal.*Calcd for $C_{17}H_{25}NO_3Si$: C, 63.91; H, 7.89; N, 4.38. Found: C, 63.89; H, 7.92; N, 4.49.

Methyl 6-Methoxyindolyl-3-carboxylate (21) : A solution of **19** (37 mg, 0.12 mmol) and 50% dimethylamine solution (116 μL, 1.2 mmol) in THF (1 mL) was stirred for 3 h at rt under an nitrogen atmosphere. The solvent was evaporated to give solid. The solid was dissolved in ether and washed with H_2O. The organic extracts were dried, and evaporated. The residue was chromatographed (ether) to give **21** (23 mg, 97%) as colorless crystals. mp 144.5 - 146.0°C (ether/*n*-hexane). IR ($CHCl_3$) : 3442, 2934, 1689,1531 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.83 (s, 3H), 3.91 (s, 3H), 6.87 (d, 1H, J = 2.0 Hz), 6.93 (dd, 1H, J = 2.3, 8.7 Hz), 7.80 (d, 1H, J = 2.9 Hz), 8.04 (d, 1H, J = 8.7 Hz), 8.66 (br s, 1H). HRMS *m/z* : Calcd for $C_{11}H_{11}NO_3$, 205.0740. Found, 205.0747 (M^+).

***N*-Methoxy-*N*-methyl-1-(*tert*-butyldimethylsilyl)-6-methoxyindole-3-carboxamide (22)** : Trimethylaluminum solution (0.16 mL, 2.0 M in *n*-hexane, 0.32 mmol) was added dropwise to a suspension of *N,O*-dimethylhydroxylamine hydrochloride (32 mg, 0.32 mmol) in benzene (0.5 mL) at 0°C and the whole was stirred for 2 h at rt. To the mixture, a solution of **19** (51 mg, 0.16 mmol) in benzene (2 mL) was added and the whole was refluxed for 3 h. After addition of H_2O (1 mL), the mixture was extracted with ether. The combined extracts were washed with H_2O, dried, and evaporated. The residue was chromatographed (ether / *n*-hexane = 2 / 3) to give **22** (39 mg, 69 %) as colorless oil. IR ($CHCl_3$) : 2919, 1615, 1520, 1179 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.63 (s, 6H), 0.96 (s, 9H), 3.39 (s, 3H), 3.68 (s, 3H), 3.85 (s, 3H), 6.91 (dd, 1H, J = 2.2, 8.8 Hz), 7.00 (d, 1H, J = 2.2 Hz), 7.86 (s, 1H), 8.24 (d, 1H, J = 8.8 Hz). ^{13}C-NMR ($CDCl_3$) δ : -4.0, 19.3, 26.2, 33.2, 55.7, 60.6, 98.3, 110.2, 110.7, 122.7, 124.8, 135.5, 141.3, 156.2, 165.8. HRMS *m/z* : Calcd for $C_{18}H_{28}N_2O_3Si$, 348.1870. Found, 348.1858 (M^+).

5-[1-(*tert*-Butyldimethylsilyl)indol-3-yl)-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole (23) : Sodium borohydride (672 mg, 17.9 mmol) was added portionwise to a solution of **7a** (450 mg, 0.84 mmol) and nickel(II) chloride hexahydrate (1.40 g, 5.89 mmol) in THF (6 mL) and MeOH (18 mL) at 0°C and the whole was stirred for 10 min. The mixture was passed through a Celite column and the filtrate was evaporated. The residue was chromatographed ($CHCl_3$ / MeOH = 40 / 1) to give **23** (284 mg, 79%) as colorless crystals. mp 118.0 - 120.0 8C (ethyl acetate/*n*-hexane). IR ($CHCl_3$) : 2942, 1451, 1255, 1082 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.02 (s, 9H), 0.64 (s, 6H), 0.92 (t, 2H, J = 8.3 Hz), 0.97 (s, 9H), 3.53 (t, 2H, J = 8.3 Hz), 5.25 (s, 2H), 7.16 - 7.25 (m, 2H), 7.30 (d, 1H, J = 0.8 Hz), 7.53 - 7.54 (m, 1H), 7.56 (s, 1H), 7.69 - 7.70 (m, 1H), 7.72 (d, 1H, J = 0.8 Hz). ^{13}C-NMR ($CDCl_3$) δ : -4.0, -1.4, 17.8, 19.5, 26.3, 65.9, 73.9, 107.1, 114.0, 119.5, 120.5, 122.2, 126.9, 128.0, 129.9, 130.7, 137.9, 141.3. HRMS *m/z* : Calcd for $C_{23}H_{37}N_3OSi_2$, 427.2480. Found, 247.2459 (M^+).

4,5-Diiodo-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole (25) : To a mixture of 2,4,5-triiodo-1*H*-imidazole (892 mg, 2.0 mmol),[14] triethylamine (304 mg, 3.0 mmol), and DMAP (244 mg, 2.0 mmol) in DMF (5 mL) was added dropwise [2-(trimethylsilyl)ethoxy]methyl chloride (367 mg, 2.2 mmol) at rt and the whole was heated at 100 °C for 2 h. After addition of H_2O, the mixture was extracted with ethyl acetate. The combined extracts were washed with H_2O, dried, and evaporated. The residue was chromatographed (ethyl acetate / *n*-hexane = 1 / 3) to give **25** (383 mg, 43%) as colorless oil. IR ($CHCl_3$): 2965, 2940, 1242, 1093, 1041 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.18 (s, 9H), 0.92 (t, 2H, *J* = 8.4 Hz), 3.52 (t, 2H, *J* = 8.4 Hz), 5.29 (s, 2H), 7.72 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ : -1.4, 17.7, 66.8, 77.7, 81.8, 97.0, 141.6. HRMS *m/z* : Calcd for $C_9H_{16}N_2OI_2Si$, 449.9120. Found, 449.9124 (M^+).

5-[1-(*tert*-Butyldimethylsilyl)indol-3-yl)-4-iodo-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole (26) : The reaction was carried out in a similar manner to that used for the reaction of **7** except for use of **25** instead of **8**. Purification of the crude product by PTLC (ethyl acetate / *n*-hexane = 1 / 3) gave **26** (75 %) as colorless oil. IR ($CHCl_3$) : 2948, 1447, 1243, 1089, 838 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.08 (s, 9H), 0.65 (s, 6H), 0.81 (t, 2H, *J* = 8.3 Hz), 0.96 (s, 9H), 3.37 (t, 2H, *J* = 8.3 Hz), 5.16 (s, 2H), 7.14 - 7.25 (m, 2H), 7.37 (s, 1H), 7.45 (dd, 1H, *J* = 1.2, 6.8 Hz), 7.57 (d, 1H, *J* = 8.0 Hz), 7.76 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ : -3.9, -1.5, 17.8, 19.4, 26.3, 66.4, 74.7, 105.7, 114.3, 120.2, 120.5, 122.2, 125.1, 129.8, 130.1, 133.2, 139.4, 141.2. HRMS *m/z* : Calcd for $C_{23}H_{36}N_3OISi_2$, 553.1440. Found, 553.1426 (M^+).

5-[1-(*tert*-Butyldimethylsilyl)indol-3-yl)-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole (23) : To a solution of **26** (374 mg, 0.68 mmol) in THF (30 mL) was added dropwise a solution of ethylmagnesium bromide (1.5 mL, 1.67 mmol, 0.9 M in THF solution) at rt and the whole was stirred for 30 min at rt. After addition of H_2O, the mixture was extracted with ethyl acetate. The combined extracts were washed with H_2O, dried, and evaporated. The residue was purified with PTLC (ethyl acetate / *n*-hexane = 1 / 1) to give **23** (243 mg, 84%).

6''-*O*-Methyl-1',1''-di(*tert*-butyldimethylsilyl)-1-[[(2-trimethylsilyl)ethoxy]methyl]-topsentin (27a), 6''-*O*-Methyl-1'-(*tert*-butyldimethylsilyl)-1-[[(2-trimethylsilyl)ethoxy]-methyl]topsentin (27b), and 6''-*O*-Methyl-1-[[(2-trimethylsilyl)ethoxy]methyl]topsentin (27c) : *n*-BuLi (0.17 mL, 0.28 mmol, 1.6 M solution in *n*-hexane) was added dropwise to a solution of **23** (107 mg, 0.25 mmol) in THF (2 mL) at -78°C under a nitrogen atmosphere and the whole was stirred for 15 min at -78°C. A solution of **22** (108 mg, 0.31 mmol) in THF (1 mL) was added dropwise to the mixture at the same temperature and the whole was stirred for 12 h at an ambient temperature. After addition of H_2O, the mixture was extracted with ethyl acetate. The combined extracts were washed with H_2O, dried, and evaporated. The residue was chromatographed (ethyl acetate / *n*-hexane = 1 / 10) to give **27a** (61 mg, 34.0%, Rf = 0.5) as colorless oil, **27b** (49 mg, 33%, Rf = 0.3) as colorless oil, and **27c** (7 mg, 6%, Rf = 0.1) as colorless oil.

27a : IR ($CHCl_3$) : 2943, 1611, 1511, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.07 (s, 9H), 0.67 (s, 6H), 0.69 (s, 6H), 0.93 - 1.01 (m, 20H), 3.73 (t, 2H, J = 8.3 Hz), 3.88 (s, 3H), 5.94 (s, 2H), 6.98 (dd, 1H, J = 2.2, 8.7 Hz), 7.06 (d, 1H, J = 2.0 Hz), 7.20 - 7.29 (m, 2H), 7.47 (s, 1H), 7.57 - 7.60 (m, 1H), 7.80 - 7.83 (m, 2H), 8.45 (d, 1H, J = 8.7 Hz), 8.79 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ : -4.0, -1.5, 18.1, 19.3, 19.4, 26.3, 26.4, 55.6, 65.8, 73.0, 98.8, 106.7, 110.5, 114.1, 118.6, 119.5, 120.7, 122.3, 122.9, 124.2, 127.9, 129.9, 131.9, 132.1, 141.3, 142.1, 143.0, 144.4, 156.4, 178.9. HRMS *m/z* : Calcd for $C_{39}H_{58}N_4O_3Si_3$, 714.3820. Found, 714.3831 (M^+).

27b : IR ($CHCl_3$) : 3442, 2944, 1612, 1518 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.10 (s, 9H), 0.67 (s, 6H), 0.91 - 0.98 (m, 11H), 3.67 - 3.73 (m, 5H), 5.90 (s, 2H), 6.76 (d, 1H, J = 2.1 Hz), 6.93 (dd, 1H, J = 2.3, 8.8 Hz), 7.20 - 7.29 (m, 2H), 7.46 (s, 1H), 7.57 - 7.60 (m, 1H), 7.77 - 7.80 (m, 2H), 8.39 (d, 1H, J = 8.8 Hz), 8.56 (d, 1H, J = 3.1 Hz), 9.88 (br, 1H). ^{13}C-NMR ($CDCl_3$) δ : -3.9, -1.5, 18.1, 19.4, 26.3, 55.5, 65.9, 73.0, 94.9, 106.5, 112.0, 114.2, 116.5, 119.4, 120.8, 120.9, 122.4, 123.1, 127.5, 129.9, 132.0, 132.3, 135.5, 137.0, 141.3, 144.3, 157.2, 178.8. HRMS *m/z* : Calcd for $C_{33}H_{44}N_4O_3Si_2$, 600.2950. Found, 600.2963 (M^+).

27c : IR ($CHCl_3$) : 3447, 2988, 1609, 1516 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.10 (s, 9H), 0.93 (t, 2H, J = 8.3 Hz), 3.74 (t, 2H, J = 8.3 Hz), 3.85 (s, 3H), 5.98 (s, 2H), 6.90 (d, 1H, J = 2.2 Hz), 6.97 (dd, 1H, J = 2.3, 8.7 Hz), 7.21 - 7.32 (m, 2H), 7.46 - 7.49 (m, 2H), 7.79 - 7.82 (m, 2H), 8.43 (d, 1H, J = 8.7 Hz), 8.54 (br, 1H), 8.77 (d, 1H, J = 2.9 Hz), 8.79 (br, 1H). ^{13}C-NMR ($CDCl_3$) δ : -1.5, 18.0, 55.5, 66.1, 72.9, 94.9, 104.5, 111.5, 112.0, 116.5, 119.5, 120.8, 120.9, 123.0, 123.1, 125.0, 126.6, 127.6, 132.3, 135.5, 136.1, 137.0, 144.4, 157.2, 178.9. HRMS *m/z* : Calcd for $C_{27}H_{30}N_4O_3Si$, 486.2090. Found, 486.2068 (M^+).

6''-O-Methyltopsentin (27d) : A solution of **27a-c** (33 mg, 0.051 mmol) in EtOH (3 mL) and 20 % HCl (3 mL) was refluxed for 1 h. After neutralization with saturated $NaHCO_3$ aqueous solution, the mixture was extracted with ethyl acetate. The combined extracts were washed with H_2O, dried, and evaporated. The residue was purified with PTLC (ethyl acetate / *n*-hexane = 1 / 2) to give **27d** (12 mg, 66%) as pale yellow crystals. mp 304 - 306°C (ethyl acetate-*n*-hexane). IR (KBr) : 3396, 2903, 1582, 1516 cm^{-1}. ^{1}H-NMR ($(CD_3)_2CO$) δ : 3.79 (s, 3H), 6.84 - 6.87 (m, 2H), 7.08 - 7.20 (m, 2H), 7.41 - 7.48 (m, 2H), 7.67 (s, 1H), 8.18 (d, 1H, J = 7.3 Hz), 8.29 - 8.33 (m, 2H), 10.96 (br, 1H), 12.00 (br, 1H). ^{1}H-NMR (DMSO-d_6 + 1% TFA) δ : 3.82 (s, 3H), 6.92 (dd, 1H, J = 2.2, 8.7 Hz), 7.06 (d, 1H, J = 2.6 Hz), 7.13 - 7.23 (m, 2H), 7.48 (d, 1H, J = 7.4 Hz), 7.86 (s, 1H), 8.03 (br d, 1H, J = 7.0 Hz), 8.04 (br, 1H), 8.21 (d, 1H, J = 8.7 Hz), 8.93 (br, 1H), 11.51 (br, 2H). HRMS *m/z* : Calcd for $C_{21}H_{16}N_4O_2$, 356.1270. Found, 356.1249 (M^+).

Topsentin (1a) : To a solution of **27d** (30 mg, 0.08 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of BBr_3 (2 mL, 1.0 M solution in CH_2Cl_2, 2.0 mmol) and the whole was refluxed for 8 h. After neutralization with saturated $NaHCO_3$ aqueous solution, the mixture was extracted with ethyl acetate. The combined extracts were washed with H_2O, dried, and evaporated. The residue was purified with PTLC (ethyl acetate) to give **1a** (20 mg, 69%) as pale yellow crystals. mp 265.0 - 268.0°C. IR (KBr) : 3336,

3193, 1622, 1582, 1519, 1156 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + 1% TFA) δ : 6.80 (dd, 1H, J = 2.2, 8.7 Hz), 6.92 (d, 1H, J = 2.2 Hz), 7.15 - 7.25 (m, 2H), 7.50 (d, 1H, J = 7.4 Hz), 8.01 (br d, 1H, J = 7.6 Hz), 8.02 (s, 1H), 8.06 (d, 1H, J = 8.5 Hz), 8.09 (br, 1H), 8.65 (d, 1H, J = 2.5 Hz), 11.63 (br, 1H), 12.14 (br, 1H). HRMS *m/z* : Calcd for $C_{20}H_{14}N_4O_2$, 342.1120. Found, 342.1108 (M^+).[15]

REFERENCES AND NOTES

1. Preliminary report of the present work: I. Kawasaki, H. Katsuma, Y. Nakayama, M. Yamashita, and S. Ohta, *Heterocyclic Commun.*, 1996, **2**, 189.
2. a) K. Bartik, J.-C. Braekman, D. Daloze, C. Stoller, J. Huysecom, G. Vandevyver, and R. Ottinger, *Can. J. Chem.*, 1987, **65**, 2118; b) S. Tsujii, K. L. Rinehart, S. P. Gunasekera, Y. Kashman, S. S. Cross, M. S. Lui, S. A. Pomponi, and M. C. Diaz, *J. Org. Chem.*, 1988, **53**, 5446.
3. a) S. Ohta, T. Yamamoto, I. Kawasaki, M. Yamashita, H. Katsuma, R. Nasako, K. Kobayashi, and K. Ogawa, *Chem. Pharm. Bull.*, 1992, **40**, 2681; b) S. Ohta, T. Yamamoto, I. Kawasaki, M. Yamashita, Y. Nagashima, and T. Yoshikawa, *Chem. Pharm. Bull.*, 1994, **42**, 821; c) I. Kawasaki, N. Taguchi, T. Yamamoto, M. Yamashita, and S. Ohta, *Tetrahedron Lett.*, 1995, **36**, 8251; d) I. Kawasaki, M. Yamashita, and S. Ohta, *J. Chem. Soc., Chem. Commun.*, **1994**, 2085; e) I. Kawasaki, N. Taguchi, Y. Yoneda, M. Yamashita, and S. Ohta, *Hetrocycles*, 1996, **43**, 1375; f) I. Kawasaki, M. Yamashita, and S. Ohta, *Chem. Pharm. Bull.*, 1996, **44**, 1831; g) I. Kawasaki, N. Taguchi, M. Yamashita, and S. Ohta, *Chem. Pharm. Bull.*, 1997, **45**, 1393; and our literatures cited therein.
4. B. A. Horenstein, R. F. Zabinski, and V. L. Schramm, *Tetrahedron Lett.*, 1993, **34**, 7213.
5. N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; A. Suzuki and N. Miyaura, *Yuki Gosei Kagaku Kyokaishi*, 1993, **51**, 1043; N. Miyaura, K. Yamada, H. Suginome, and A. Suzuki, *J. Am. Chem. Soc.*, 1985, **107**, 972; N. Miyaura, T. Yanagi, and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513.
6. M. Amat, S. Hadida, S. Sathyanarayana, and J. Bosch, *J. Org. Chem.*, 1994, **59**, 10.
7. In ref. 6, it is stated that **6** easily decomposed on heating in solution.
8. N. J. Curtis and R. S. Brown, *J. Org. Chem.*, 1980, **45**, 4038; S. Ohta, S. Hayakawa, H. Moriwaki, S. Tsuboi, and M. Okamoto, *Heterocycles*, 1985, **23**, 1759; Ohta, S. Hayakawa, H. Moriwaki, S. Harada, and M. Okamoto, *Chem. Pharm. Bull.*, 1986, **34**, 4916.
9. The treatment of 3-indolecarboxylic acid with 1,1-carbonyldiimidazole (CDI) followed by addition of 50% dimethylamine solution afforded tertiary amide (**13**) in 95% yield.
10. P. L. Feldman and H. Rapoport, *Synthesis*, **1986**, 735.
11. J. I. Levin, E. Turos, and S. M. Weinreb, *Synth. Commun.*, 1982, **12**, 989; P. A. Jacobi , L. M. Armacost, H. L. Brielmann, R. O. Cann, J. I. Kravitz, and M. J. Martinelli, *J. Org. Chem.*, 1994, **59**, 5292.
12. T. G.Back, D. L. Baron, and K.Yang, *J. Org. Chem.*, 1993, **58**, 2407.
13. R. A.Hill, R. H. Carter, and J. Staunton, *J. Chem. Soc., Perkin Trans. I*, **1981**, 2571.

14 K. J. Brunings, *J. Am. Chem. Chem.*, 1947, **69**, 205.

15 Spectral data of **1a** stated in ref. 2b; IR (KBr) : 3397, 1626, 1576, 1522, 1159, 1091 cm^{-1}. ^1H-NMR (DMSO-d_6 + 1% TFA) δ : 6.81 (dd, 1H, J = 1.8, 8.6 Hz), 6.93 (d, 1H, J = 1.8 Hz), 7.19 (m, 2H), 7.50 (br d, 1H, J = 7.0 Hz), 7.96 (s, 1H), 8.02 (d, 1H, J = 7.0 Hz), 8.07 (d, 1H, J = 2.6 Hz), 8.10 (d, 1H, J = 8.4 Hz), 8.74 (d, 1H, J = 3.0 Hz), 11.64 (d, 1H, J = 2.6 Hz), 12.11 (d, 1H, J = 3.0 Hz). HRMS m/z : Calcd for $C_{20}H_{14}N_4O_2$, 342.1120. Found, 342.1107 (M^+).

Received, 18th May, 1998