Introduction of Carbogenic Substituent into the 4-Position of 1-Methyl-1*H*-imidazole

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The 4-position of the 1-methyl-1*H*-imidazole ring was lithiated by treatment of the corresponding 4-bromo derivatives with *tert*-butyllithium. This procedure was applied to synthesis of the left-hand part of pyronaamidine (1), which is a biologically interesting marine alkaloid.

Keywords lithiation; substituted imidazole; alkylation; bromination; hydrogenolysis; pyronaamidine

Pyronaamidine (**1**) and kealliquinone (**2**) are marine imidazole-containing alkaloids recently isolated from a sponge and the former shows anti-cancer activity.[1] The characteristic feature of the structures of **1** and **2** from the view point of total synthesis is that the imidazole ring has four different substituents at the 1-, 2-, 4- and 5-positions. Since we are interested in the synthesis and biological activities of imidazole and triazole compounds,[2] we planned the total synthesis of **1** and **2** starting from 1-methyl-1*H*-imidazole (**3**). Previously, we reported a method for the selective introduction of substituents at the 5-position of **3**,[3] but we needed to develope a method for the introduction of different carbogenic substituents into the 4- and 5-positions of 1-methyl-1*H*-imidazole prior to total synthesis of **1** and **2**. Imidazolyl anions are generated relatively readily on C-2[4] and C-5[3,5] by direct metalation and metal-halogen exchange, but generation of thermodynamically less stable C-4 anions is much more difficult. The known procedures for substitution at the 4-position seemed inconvenient, especially for our present purpose, because of the requirement of a proper directing group at the 1-position for C-5 metalation,[5] the requirement of a halogen atom at the 4-position[6-8] low selectivity (low yield) for C-4 substitution in particular[7,8] or poor accessibility of starting materials.[6,7] Here we present a solution to the problem of the selective introduction of carbogenic substituents into the 4- and 5-positions of **3**, leading to a synthesis of the left-hand part of the structure in **1** (Fig. 1).

Attempts at lithiation of the 4-position of 1-methyl-2,5-bis(phenylthio)-1*H*-imidazole (**4a**) or 5-(α-alkoxybenzyl)-1-methyl-2-phenylthio-1*H*-imidazole (**4b, c**) by treatment with various lithiating agent such as lithium diisopropylamide (LDA), lithium 2,2,6,6-tetramethylpiperidide (LTMP), *n*-, *sec*-, and *tert*-butyllithium resulted in recovery of **4** or gave a complex mixture. The attempted lithiation of the ethers **4b** and **4c** was based on the *ortho*-directing metalation effect of these groups, but they were not effective. In the literature, metal–halogen exchange of halogenoimidazoles has been extensively explored mainly

TABLE I. Conversion of **5a** to **6a** ($R^2 = C_6H_5$)

Entry	Metalation reagent	eq	Temp. (°C)	Solvent	Yield (%)[a]
1	Mg	1	0	Ether	N.R.[b]
2	*n*-BuLi	2	−78	THF	58
3	*n*-BuLi	2	0	THF	—[c]
4	*sec*-BuLi	2	−78	THF	44
5	*tert*-BuLi	2	−78	THF	66
6	*n*-BuLi	2	−78	Ether	70
7	*tert*-BuLi	2	−78	Ether	84

a) Isolated yield. *b*) Recovery of **5a**. *c*) A complex mixture was obtained.

TABLE II. Conversion of **5a, b** to **6a—j**

Entry		Product R^1	Product R^2	mp (°C)	Isolated yield (%)
1	**6a**	C_6H_5S	C_6H_5	Viscous oil	84
2	**6b**	C_6H_5S	Me_3C	Viscous oil	83
3	**6c**	C_6H_5S	$4\text{-}MeOC_6H_4$	Viscous oil	84
4	**6d**	C_6H_5S	$2,4\text{-}Cl_2C_6H_3$	140—142	71
5	**6e**	C_6H_5S	$3,4\text{-}(OCH_2O)C_6H_3$	Viscous oil	77
6	**6f**	$C_6H_5CH_2$	C_6H_5	137—139	89
7	**6g**	$C_6H_5CH_2$	$2,4\text{-}Cl_2C_6H_3$	163—164	37
8	**6h**	$C_6H_5CH_2$	$4\text{-}MeOC_6H_4$	144—145	45
9	**6i**	$C_6H_5CH_2$	C_2H_5	Viscous oil	65
10	**6j**	$C_6H_5CH_2$	Me_3C	Viscous oil	66

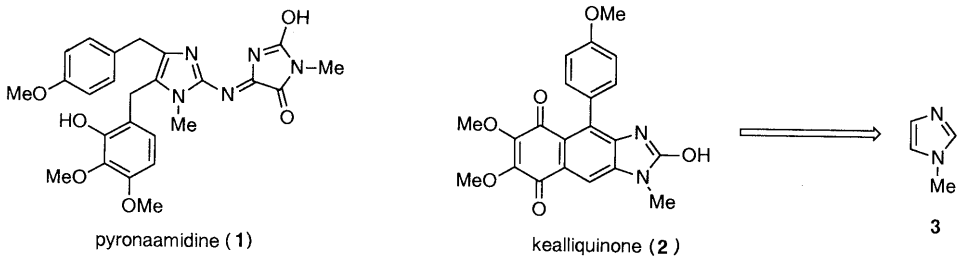


Fig. 1

by Iddon and colleagues.[4d,5,9] So we tried bromination of **4** and lithiation of the bromide (**5**) by the metal–halogen exchange principle. Thus, the bissulfide (**4**) was treated with *N*-bromosuccinimide (NBS) to give the brominated product (**5a**) almost quantitatively. Bromination of the 4-position was confirmed by the absence of the 4-position proton signal in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. Halogen–metal exchange under various conditions was examined by using benzaldehyde as a trapping agent of the produced imidazolyl carbanion. The best yield (84%) of **6a** was obtained under the conditions of entry 7 in Table I. Reaction of the carbanion with other aldehydes under the best conditions (entry 7 in Table I) gave other 4-substituted imidazoles (**6b—e**) in 71—84% yields (entries 2—5 in Table II). 5-Benzyl-1-methyl-2-phenylthio-1*H*-imidazole (**4d**) could be similarly converted to the corresponding 4-substituted imidazoles (**6f—j**) *via* the brominated intermediate (**5b**) in usable yields (entries 6—10 in Table II), and it is noteworthy that imidazoles having a range of carbogenic substituents could

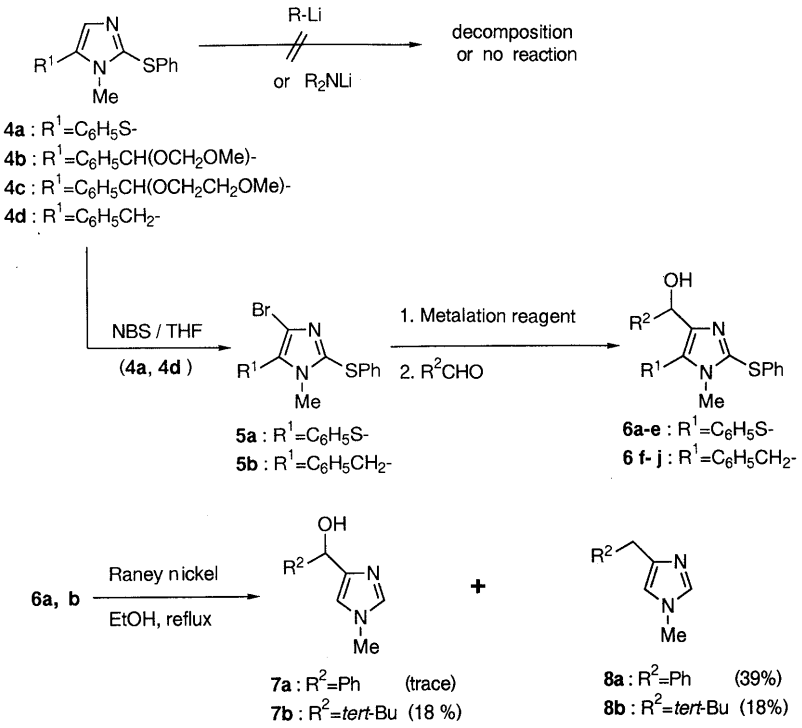
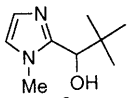
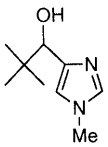
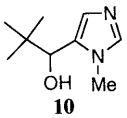
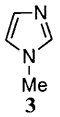


Chart 1

TABLE III. Physical and Spectral Data for **9**, **7b**, **10** and **3**

	mp (°C)	IR ν_{max} [a] ($CHCl_3$)	UV λ_{max} (nm) (log ε)	^{1}H-NMR (in $CDCl_3$) 2H	4H	5H	^{13}C-NMR (in $CDCl_3$) NCH_3	C-2	C-4	C-5
 **9**	82—83	1485	215 (3.88)	—	6.91	6.76	33.44	148.82	126.79	120.75
 **7b**	100—101	1503	207 (3.62) *ca.* 220 (s)	7.33	—	6.72	33.19	136.08	143.38	116.77
 **10**	150—152	1500	216 (3.79) *ca.* 210 (s)	7.29	6.94	—	32.38	137.50	127.04	133.10
 **3**	Oil (bp 198)	1512	212 (3.61)	7.41	7.03	6.87[b]	34.2	138.7	130.2	121.0[c]

a) This absorption band is usually observed in IR spectra of imidazole compounds and is presumed to be that of $\nu_{C=N}$. *b*) Ref. 1. *c*) Ref. 13.

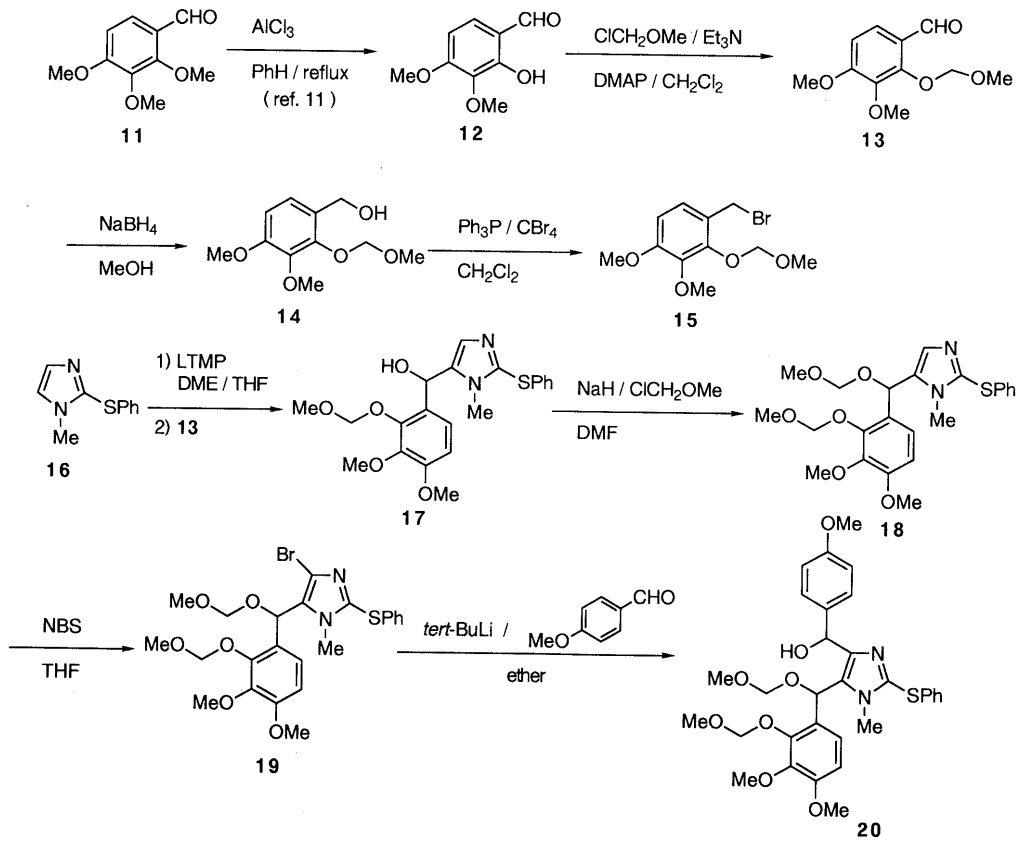


Chart 2

be prepared.

The products (**6a** and **6b**) were treated with a large excess of Raney nickel in refluxing ethanol to give the desulfurized 4-substituted imidazoles (**7a** and **7b**) and their dehydroxylated products (**8a** and **8b**) in low yields. Table III shows physical and spectral data for 1-methyl-1*H*-imidazole (**3**) and 2-, 4- and 5-(2,2-dimethyl-1-hydroxypropyl)-1-methyl-1*H*-imidazole (**9**,[10] **7b** and **10**[3]), some of which may be useful for the determination of substituent position.

Next, we planned synthesis of the left-hand part of pyronaamidine (**1**) and kealliquinone (**2**) by utilizing the above-mentioned methodology. First, we wished to prepare the benzyl bromide (**15**) as an alkylating agent for the 5-position of 1-methyl-2-phenylthio-1*H*-imidazole (**16**). Thus, 2-hydroxy-3,4-dimethoxybenzaldehyde (**12**) was prepared from 2,3,4-trimethoxybenzaldehyde (**11**) according to the reported procedure,[11] and the hydroxyl group was protected with a methoxymethyl (MOM) group in the usual manner to give the aldehyde **13** in 70% yield from commercially available **11**. The aldehyde (**13**) was reduced to the alcohol (**14**) by treatment with sodium borohydride. However, the use of the bromide as the alkylating agent was unsuitable because the conversion of the alcohol (**14**) to the corresponding bromide (**15**) occurred only in very poor yield. On the other hand, 1-methyl-2-phenylthio-1*H*-imidazole (**16**) was lithiated by LTMP according to the previously reported procedure,[3] and the aldehyde (**13**) was added to the reaction mixture to give the 5-substituted imidazole (**17**) in 89% yield. The hydroxyl group of **17** was protected with a MOM group in the usual manner to give **18** in 88% yield, and the 4-position of the compound (**18**) was brominated in 62% yield by treatment with NBS. The bromide (**19**) was converted to a diastereomeric mixture (2 : 1; on the basis of ^{1}H-NMR) of the alcohol (**20**) according to the above-mentioned procedure in 37% yield (Chart 2).

Thus, we have developed a generally applicable procedure for selective introduction of carbogenic substituent into the 4- and 5-position of 1-methyl-1*H*-imidazole. Conversion of the alcohol (**20**) to the natural products **1** and **2** is under study.

Experimental

All melting points are uncorrected. IR spectra were taken with a Shimadzu IR-410 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a JEOL EX-270 spectrometer or on a Varian XL-300 spectrometer, and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). UV spectra were obtained on a Shimadzu UV-240 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Hitachi M-80 spectrometer. All solvents were removed under reduced pressure in the usual work-up procedure. Anhydrous sodium sulfate was used as a drying agent. A Kugel–Rohr apparatus was used for vacuum distillations of oily crude products. Silica gel 60 (Merck Art. 7734) and Silica gel 60 PF 254 (Nakalai Tesque Co., Ltd.) were used in column chromatography and preparative thin-layer chromatography (PTLC), respectively.

4-Bromo-1-methyl-2,5-bis(phenylthio)-1*H*-imidazole (5a) NBS (2.14 g, 12 mmol) was added in small portions at room temperature to a solution of **4a**[3] (3.58 g, 12 mmol) in tetrahydrofuran (THF) (25 ml), and the mixture was stirred for 1 h. The reaction mixture was diluted with AcOEt (50 ml), and the solution was washed with 10% K_2CO_3. The organic layer was dried over Na_2SO_4, then the solvent was evaporated off under reduced pressure. The residual oil was purified by column chromatography (AcOEt : *n*-hexane = 1 : 5) to give **5a** as a viscous oil. Yield, 4.45 g

(98%). IR ($CHCl_3$): 1581, 1477, 1439, 1237 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.55 (s, 3H, $-NCH_3$), 7.05—7.33 (m, 10H, Ar-H). HRMS *m/z*: Calcd for $C_{16}H_{13}BrN_2S_2$: 375.9700. Found: 375.9733 (M^+).

5b: This was obtained in a similar manner to that used for the synthesis of **5a**, starting from **4d**[3] (1.12 g, 4 mmol). Purification by column chromatography (AcOEt : *n*-hexane = 5 : 1) and recrystallization from *n*-hexane gave colorless crystals, mp 56—57 °C. Yield, 1.26 g (87%). IR ($CHCl_3$): 2974, 1580, 1451 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.37 (s, 3H, $-NCH_3$), 4.01 (s, 2H, $-CH_2-$), 7.10—7.35 (m, 10H, Ar-H). *Anal.* Calcd for $C_{17}H_{15}BrN_2S$: C, 56.83; H, 4.21; N, 7.80. Found: C, 56.95; H, 4.13; N, 7.93.

General Procedure for Introduction of Carbogenic Substituents into the 4-Position of 5a and 5b: Synthesis of 5-Benzyl-4-(1-hydroxy-2,2-dimethylpropyl)-1-methyl-2-phenylthio-1*H*-imidazole (6j) as an Example A solution of *tert*-BuLi in *n*-hexane (1.57 M; 0.64 ml, 1.0 mmol) was added dropwise at −78 °C under an N_2 atmosphere to a solution of the bromide **5b** (180 mg, 0.5 mmol) in ether (5 ml), and the mixture was stirred for 1 h. Pivalaldehyde (56 μl, 0.52 mmol) was added and the mixture was stirred for 1 h. Water (5 ml) was added and the product was extracted with AcOEt (10 ml × 2). The organic layer was dried over Na_2SO_4 and evaporated to give a viscous oily residue. The crude product was purified by column chromatography ($CHCl_3$) to give **6j** as a colorless viscous oil. Yield, 121 mg (66%). IR ($CHCl_3$): 2944 (OH), 1580, 1474, 1452, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.99 (s, 9H, $-C(CH_3)_3$), 2.89 (d, 1H, $-OH$, J = 7.9 Hz), 3.28 (s, 3H, $-NCH_3$), 3.94 and 4.14 (d each, 1H each, $-CH_2-$, J = 17.2 Hz), 4.37 (d, 1H, $-CH(OH)-$, J = 7.9 Hz), 7.04—7.31 (m, 10H, Ar-H). HRMS *m/z*: Calcd for $C_{22}H_{26}N_2OS$: 366.1700. Found: 366.1775 (M^+).

6a: This was obtained in a similar manner to that used for the synthesis of **6j** starting from **5a** and benzaldehyde. Solvent for column chromatography, $CHCl_3$: MeOH = 50 : 1. Yield, 84%. A colorless viscous oil. IR ($CHCl_3$): 3450 (OH), 1581, 1477, 1439 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.44 (s, 3H, $-NCH_3$), 3.60 (d, 1H, $-OH$, J = 7.9 Hz), 5.96 (d, 1H, $-CH(OH)$, J = 7.9 Hz), 6.84—7.46 (m, 15H, Ar-H). HRMS *m/z*: Calcd for $C_{23}H_{20}N_2OS_2$, 404.1020. Found: 404.1023 (M^+).

6b: This was obtained in a similar manner to that used for the synthesis of **6j** starting from **5a** and pivalaldehyde. Yield, 83%. A colorless viscous oil. IR ($CHCl_3$): 3450 (OH), 2951 (CH_3), 1581, 1477, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.98 (s, 9H, $-C(CH_3)_3$), 2.86 (d, 1H, $-OH$, J = 9.2 Hz), 3.46 (s, 3H, $-NCH_3$), 4.54 (d, 1H, $-CH(OH)$, J = 9.2 Hz), 6.96—7.31 (m, 10H, Ar-H). HRMS *m/z*: Calcd for $C_{21}H_{24}N_2OS_2$: 384.1330. Found: 384.1343 (M^+).

6c: This was obtained in a similar manner to that used for the synthesis of **6j** starting from **5a** and *p*-anisaldehyde. Yield, 84%. A colorless viscous oil. IR ($CHCl_3$): 3450 (OH), 1610 (C_6H_5-), 1582, 1509, 1477, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.44 (s, 3H, $-NCH_3$), 3.57 (d, 1H, $-OH$, J = 7.6 Hz), 5.92 (d, 1H, $-CH(OH)$, J = 7.6 Hz), 6.75—7.38 (m, 14H, Ar-H). HRMS *m/z*: Calcd for $C_{24}H_{22}N_2O_2S_2$: 434.1120. Found: 434.1152 (M^+).

6d: This was obtained in a similar manner to that used for the synthesis of **6j** starting from **5a** and 2,4-dichlorobenzaldehyde. After purification by column chromatography ($CHCl_3$: MeOH = 50 : 1), the product was recrystallized from CH_2Cl_2–*n*-hexane. Yield, 71%. Colorless crystals, mp 140—142 °C. IR ($CHCl_3$): 3450 (OH), 1582, 1474, 1454 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.46 (s, 3H, $-NCH_3$), 3.66 (d, 1H, $-OH$, J = 5.3 Hz), 6.32 (d, 1H, $-CH(OH)$, J = 5.3 Hz), 6.80—7.65 (m, 13H, Ar-H). *Anal.* Calcd for $C_{23}H_{18}C_2N_2OS$: C, 58.35; H, 3.83; N, 5.92. Found: C, 58.26; H, 3.76; N, 6.12.

6e: This was obtained in a similar manner to that used for the synthesis of **6j** starting from **5a** and piperonal. Yield, 77%. A colorless viscous oil. IR ($CHCl_3$): 3450 (OH), 1580, 1500, 1477, 1439, 1039 (C–O–C) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.46 (s, 3H, $-NCH_3$), 3.61 (d, 1H, $-OH$, J = 7.6 Hz), 5.87 (d, 1H, $-CH(OH)$, J = 7.6 Hz), 5.88 (s, 2H, $-OCH_2O-$), 6.63—7.32 (m, 13H, Ar-H). HRMS *m/z*: Calcd for $C_{24}H_{20}N_2O_3S_2$: 448.0920. Found: 448.0905 (M^+).

6f: This was obtained in a similar manner to that used for the synthesis of **6j** starting from **5a** and benzaldehyde. After purification by PTLC (solvent, $CHCl_3$: MeOH = 50 : 1), the product was recrystallized from AcOEt–*n*-hexane. Yield, 89%. Colorless crystals, mp 137—139 °C. IR ($CHCl_3$): 3450 (OH), 2885, 1581, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.26 (s, 3H, $-NCH_3$), 3.87 (s, 2H, $-CH_2-$), 5.85 (s, 1H, $-CH(OH)$), 6.88—7.45 (m, 15H, Ar-H). *Anal.* Calcd for $C_{24}H_{22}N_2OS$: C, 74.58; H, 5.74; N, 7.25. Found: C, 74.44; H, 5.77; N, 7.19.

6g: This was obtained in a similar manner to that used for the synthesis of **6j** starting from **5a** and 2,4-dichlorobenzaldehyde. After purification by PTLC ($CHCl_3$: MeOH = 50 : 1), the product was recrystallized from AcOEt–*n*-hexane. Yield, 37%. Colorless crystals, mp 140—142 °C. IR ($CHCl_3$): 3120 (OH), 1580, 1456, 1028 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.29 (s, 3H, $-NCH_3$), 3.72 (d, 1H, $-OH$, J = 5.9 Hz), 3.87 and 4.01 (d each, 2H each, $-CH_2-$, J = 17.0 Hz), 6.20 (d, 1H, $-CH(OH)$, J = 5.9 Hz), 6.90—7.73 (m, 13H, Ar-H). *Anal.* Calcd for $C_{24}H_{20}Cl_2N_2OS$: C, 63.30; H, 4.43; N, 6.15. Found: C, 63.19; H, 4.51; N, 6.03.

6h: This was obtained in a similar manner to that used for the synthesis of **6j** starting from **5a** and *p*-anisaldehyde. After purification by PTLC ($CHCl_3$: MeOH = 50 : 1), the product was recrystallized from AcOEt–*n*-hexane. Yield, 45%. Colorless crystals, mp 144—145 °C. IR ($CHCl_3$): 3120 (OH), 2986, 1610 (C_6H_5- and $C_6H_4<$), 1581, 1508, 1452, 1243 (C–O–C) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.29 (s, 3H, $-NCH_3$), 3.61 (d, 1H, $-OH$, J = 6.3 Hz), 3.77 (s, 3H, $-OCH_3$), 3.87 (s, 2H, $-CH_2-$), 5.79 (d, 1H, $-CH(OH)$, J = 6.3 Hz), 6.80—7.76 (m, 14H, Ar-H). *Anal.* Calcd for $C_{25}H_{24}N_2O_2S$: C, 72.01; H, 5.81; N, 6.72. Found: C, 72.62; H, 5.79; N, 6.72.

6i: This was obtained in a similar manner to that used for the synthesis of **6j** starting from **5a** and propionaldehyde. Yield, 65%. A colorless viscous oil. IR ($CHCl_3$): 3450 (OH), 2954, 1580, 1450, 1097 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.93 (t, 3H, $-CH_2CH_3$, J = 7.4 Hz), 1.87—1.98 (m, 2H, $-CH_2CH_3$), 3.31 (s, 3H, $-NCH_3$), 4.05 (s, 2H, $C_6H_5CH_2-$), 4.62 (t, 1H, $-CH(OH)$, J = 6.8 Hz), 7.04—7.31 (m, 10H, Ar-H). HRMS *m/z*: Calcd for $C_{20}H_{22}N_2OS$: 338.1450. Found: 338.1476 (M^+).

Desulfurization of 6b A mixture of **6b** (960 mg, 2.5 mmol), Raney nickel catalyst (W2, 6.0 g) and EtOH (10 ml) was refluxed for 7 h, then the catalyst was filtered off. The filtrate was evaporated to give a viscous oily residue, which was purified by column chromatography ($CHCl_3$: MeOH = 20 : 1) to give two fractions. Evaporation of the first fraction gave **8b** as a colorless oily residue, which was further purified by vacuum distillation, bp 69 °C (3 mmHg). Yield, 70 mg (18%). IR ($CHCl_3$): 2942, 1505, 1473, 1362 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 0.93 (s, 9H, $-C(CH_3)_3$), 2.42 (s, 2H, $-CH_2-$), 3.62 (s, 3H, $-NCH_3$), 6.59 (s, 1H, C^5-H), 7.32 (s, 1H, C^2-H). HRMS *m/z*: Calcd for $C_9H_{16}N_2$, 152.1310. Found: 152.1323 (M^+). Evaporation of the second fraction gave **7b** as a crystalline residue, which was further purified by recrystallization from *n*-hexane to give colorless crystals. Yield, 74 mg (18%). mp 100—101 °C. IR ($CHCl_3$): 3400 (OH), 2951, 1504, 1477, 1362 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 0.93 (s, 9H, $-C(CH_3)_3$), 3.30 (s, 1H, $-OH$), 3.66 (s, 3H, $-NCH_3$), 4.29 (s, 1H, $-CH(OH)-$), 6.72 (s, 1H, C^5-H), 7.33 (s, 1H, C^2-H). ^{13}C-NMR ($CDCl_3$, 67.8 MHz): 25.59 ($-C(CH_3)_3$), 33.19 ($-NCH_3$), 35.35 ($-C(CH_3)_3$), 76.52 ($-CH(OH)-$), 116.77 (C-5), 136.08 (C-2), 143.38 (C-4). UV λ_{max} nm (log ε): 207 (3.62). *Anal.* Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.71. Found: C, 64.36; H, 9.79; N, 16.71.

Desulfurization of 6a This reaction was carried out in a similar manner to that used for **6b**. In this case, **8a** was obtained in 39% yield, but **7a** was obtained only in a trace amount.

8a: A colorless oil, bp 118 °C (3 mmHg). IR ($CHCl_3$): 2935, 1507, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 3.52 (s, 3H, $-NCH_3$), 3.89 (s, 2H, $C_6H_5CH_2-$), 6.45 (s, 1H, C^5-H), 7.15—7.30 (m, 6H, C^2-H and Ar-H). HRMS *m/z*: Calcd for $C_{11}H_{12}N_2$: 172.1000. Found: 172.0988 (M^+).

3,4-Dimethoxy-2-(methoxymethoxy)benzaldehyde (13) Chloromethyl methyl ether (10.7 ml, 141 mmol) was added dropwise under N_2 atmosphere at 0 °C to a solution of **12**[7] (8.55 g, 47 mmol), Et_3N (32.8 ml, 235 mmol) and 4-*N*,*N*-dimethylaminopyridine (574 mg, 4.7 mmol) in CH_2Cl_2 (80 ml), and the mixture was stirred overnight at room temperature. After evaporation of the solvent, AcOEt (150 ml) and 0.5 N HCl (100 ml) were added to the residue. The mixture was shaken, then the organic layer was washed with water (30 ml) and 10% NaOH. The AcOEt layer was dried and evaporated to give a colorless crystalline residue, which was purified by recrystallization from *n*-hexane. Yield, 6.72 g (79%). mp 54—55 °C. IR ($CHCl_3$): 2930, 1674 (>C=O), 1590, 1286, 1069 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.57 (s, 3H, $-CH_2OCH_3$), 3.86 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.28 (s, 2H, $-CH_2OCH_3$), 6.80 (d, 1H, 5-H, J = 8.9 Hz), 7.63 (d, 1H, 6-H, J = 8.9 Hz), 10.30 (s, 1H, $-CHO$). *Anal.* Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.09; H, 6.31.

3,4-Dimethoxy-2-(methoxymethoxy)benzyl Alcohol (14) $NaBH_4$ (1.49 g, 39.5 mmol) was added in small portions to a stirred solution of **13** (1.79 g, 7.9 mmol) in MeOH (30 ml), and the whole was stirred at room

temperature for 1 h. After addition of ice-water (20 ml), methanol was evaporated off. The product was extracted with $CHCl_3$, and the organic layer was dried. Evaporation of the solvent gave an oily residue, which was purified by vacuum distillation to give **14** as a colorless oil. Yield, 1.58 g (88%). bp 110 °C (0.05 mmHg). IR ($CHCl_3$): 3447 (OH), 2995, 1601 (benzene ring), 1495, 1460, 1275, 1099 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 3.01 (t, 1H, –OH, J=6.6 Hz), 3.57 (s, 3H, $-CH_2OCH_3$), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.59 (d, 2H, $-CH_2OH$, J=6.6 Hz), 5.17 (s, 2H, $-CH_2OCH_3$), 6.69 (d, 1H, 5-H, J=8.6 Hz), 7.02 (d, 1H, 6-H, J=8.6 Hz). HRMS m/z: Calcd for $C_{11}H_{16}O_5$: 228.1000. Found: 228.0994 (M^+).

3,4-Dimethoxy-2-(methoxymethoxy)benzyl Bromide (15) A solution of triphenylphosphine (525 mg, 2 mmol) in CH_2Cl_2 (1 ml) was added dropwise to a solution of **14** (456 mg, 2 mmol) and CBr_4 (663 mg, 2 mmol) in CH_2Cl_2 (2 ml), and the mixture was stirred for 2 h at room temperature. Water (3 ml) and CH_2Cl_2 (10 ml) were added, and the whole was shaken. The organic layer was dried and the solvent was evaporated off to give an oily residue, which was purified by column chromatography (AcOEt : n-hexane = 1 : 5). The solvent of the main fraction was evaporated off to give **15** as a colorless oil. Yield, 67 mg (12%). IR ($CHCl_3$): 2984, 1598 (benzene ring), 1494, 1459, 1279, 1086 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 3.64 (s, 3H, $-CH_2OCH_3$), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.60 (s, 2H, $-CH_2Br$), 5.26 (s, 2H, $-CH_2OCH_3$), 6.67 (d, 1H, 5-H, J=8.6 Hz), 7.09 (d, 1H, 6-H, J=8.6 Hz). HRMS m/z: Calcd for $C_{11}H_{15}BrO_4$: 290.0150. Found: 290.0165 (M^+).

5-[1-[3,4-Dimethoxy-2-(methoxymethoxy)phenyl]-1-hydroxymethyl]-1-methyl-2-phenylthio-1*H*-imidazole (17) A solution of n-BuLi in hexane (1.6 M, 1.88 ml, 3 mmol) was added dropwise at −78 °C under an N_2 atmosphere to a stirred solution of 2,2,6,6-tetramethylpiperidine (557 μl, 3.3 mmol) in 1,2-dimethoxyethane (6 ml). The mixture was stirred for 15 min at −78 °C, then a solution of **16** (570 mg, 3 mmol) in THF (1 ml) was added. Stirring was continued for 1 h at −78 °C, then the aldehyde **13** (678 mg, 3 mmol) was added to the mixture. The whole was stirred overnight at room temperature, then water (15 ml) and AcOEt (20 ml) were added, and the organic layer was dried. Evaporation of the solvent gave a viscous oily residue, which was purified by column chromatography ($CHCl_3$: MeOH = 50 : 1) and recrystallization from AcOEt–n-hexane to give **17** as colorless crystals. Yield, 1.11 g (89%), mp 113—115 °C. IR ($CHCl_3$): 3554 (–OH), 2932, 1599 (benzene ring), 1493, 1455, 1283, 1096 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 3.43 and 3.53 (s each, 3H each, $>NCH_3$ and $-CH_2OCH_3$), 3.83 and 3.86 (s each, 3H each, $-OCH_3 \times 2$), 4.17 (br, 1H, –OH), 5.11 (d, 1H, $-CH_2OCH_3$, J=5.6 Hz), 5.15 (d, 1H, $-CH_2OCH_3$, J=5.6 Hz), 6.07 (s, 1H, –CH(OH)–), 6.66 (d, 1H, benzene 5-H, J=8.9 Hz), 6.91 (d, 1H, benzene 6-H, J=8.9 Hz), 6.92 (s, 1H, imidazole 4-H), 7.09—7.27 (m, 5H, Ar-H). *Anal.* Calcd for $C_{21}H_{24}N_2O_5S$: C, 60.56; H, 5.81; N, 6.73. Found: C, 60.36; H, 5.84; N, 6.65.

5-[1-[3,4-Dimethoxy-2-(methoxymethoxy)phenyl]-1-(methoxy-methoxy)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (18) This was prepared in a usual manner (**17**/NaH/$ClCH_2OCH_3$/*N*,*N*-dimethylformamide (DMF)), starting from 980 mg (2.35 mmol) of **17**. The crude product was purified by column chromatography (AcOEt : n-hexane = 1 : 1) to give **18** as a viscous colorless oil. Yield, 950 mg (88%). IR ($CHCl_3$): 2934, 1598 (benzene ring), 1493, 1452, 1284, 1087 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 3.39 (s, 3H, $-CH_2OCH_3$), 3.43 (s, 3H, $-CH_2OCH_3$), 3.63 (s, 3H, $>NCH_3$), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.63 and 4.68 (d each, 1H each, $-CH_2OCH_3$, J=6.9 Hz each), 5.01 and 5.16 (d each, 1H each, $-CH_2OCH_3$, J=5.6 Hz each), 6.13 (s, 1H, –CH(OMOM)–), 6.76 (d, 1H, benzene 5-H, J=8.6 Hz), 6.84 (s, 1H, imidazole 4-H), 7.12—7.27 (m, 6H, Ar-H). HRMS m/z: Calcd for $C_{23}H_{28}N_2O_6S$: 460.1670. Found: 460.1679 (M^+).

4-Bromo-5-[1-[3,4-dimethoxy-2-(methoxymethoxy)phenyl]-1-(methoxymethoxy)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (19) This was prepared in a similar manner to that used for the synthesis of **5a** starting from **18** (539 mg, 1.0 mmol). The crude product was purified by column chromatography (AcOEt : n-hexane = 1 : 2) to give **19** as a colorless viscous oil. Yield, 332 mg (62%). IR ($CHCl_3$): 2932, 1598 (benzene ring), 1491, 1285, 1098, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 3.36 (s, 3H, $-CH_2OCH_3$), 3.44 (s, 3H, $-CH_2OCH_3$), 3.50 (s, 3H, $>NCH_3$), 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.71 (s, 2H, $-CH(OCH_2OCH_3)$–), 4.99 and 5.16 (d each, 1H each, Ar-OCH_2OCH_3, J=5.3 Hz each), 6.15 (s, 1H, –CH(OMOM)-Ar), 6.68 (d, 1H, benzene 5-H, J=8.6 Hz), 7.12—7.31 (m, 6H, Ar-H). HRMS m/z: Calcd for $C_{23}H_{27}BrN_2O_6S$: 538.0770. Found: 538.0795 (M^+).

5-[1-[3,4-Dimethoxy-2-(methoxymethoxy)phenyl]-1-(methoxymethoxy)methyl]-4-[1-hydroxy-1-(4-methoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (20) This was prepared in a similar manner to that used for the synthesis of **6j** starting from **19** (183 mg, 0.34 mmol). The crude product was purified by PTLC ($CHCl_3$: MeOH = 50 : 1) to give **20** as a diastereomeric mixture as a viscous oil. Yield, 74 mg (37%). IR ($CHCl_3$): 3406 (–OH), 3015, 1601 (benzene ring), 1452, 1089 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) of the major isomer δ: 3.24, 3.44 and 3.51 (s each, 3H each, $-OCH_3 \times 2$ and $>NCH_3$), 3.65 (br d, 1H, –OH, J=7.9 Hz), 3.73, 3.75 and 3.83 (s each, 3H each, $-OCH_3 \times 3$), 4.54 (d-like, 1H, $-CH_2OCH_3$, J=6.6 Hz), 4.59 (d-like, 1H, $-CH_2OCH_3$, J=6.6 Hz), 4.82 (d-like, 1H, Ar-OCH_2OCH_3, J=5.1 Hz), 5.05 (d-like, 1H, Ar-OCH_2OCH_3, J=5.1 Hz), 5.91 (d, 1H, $-CH(OH)$–, J=7.3Hz), 6.17 (s, 1H, –CH(OMOM)-Ar), 6.57—7.38 (m, 11H, Ar-H). ^{1}H-NMR ($CDCl_3$, 270 MHz) of the minor isomer: 3.23, 3.42 and 3.56 (s each, 3H each, $-OCH_3 \times 2$ and $>NCH_3$), 3.65 (br d, 1H, –OH, J=7.9 Hz), 3.77, 3.80 and 3.86 (s each, 3H each, $-OCH_3 \times 3$), 4.38 (d-like, 1H, $-CH_2OCH_3$, J=6.9 Hz), 4.43 (d-like, 1H, $-CH_2OCH_3$, J=6.9 Hz), 4.90 (d-like, 1H, Ar-OCH_2OCH_3, J=5.3 Hz), 5.09 (d-like, 1H, Ar-OCH_2OCH_3, J=5.3 Hz), 5.75 (d, 1H, $-CH(OH)$–, J=7.6 Hz), 6.20 (s, 1H, –CH(OMOM)-Ar), 6.57—7.38 (m, 11H, Ar-H). HRMS m/z: Calcd for $C_{31}H_{36}N_2O_8S$: 596.2190. Found: 596.2217 (M^+). The diastereomer ratio of this product was estimated to be 2 : 1 on the basis of the ^{1}H-NMR spectrum.

2-(2,2-Dimethyl-1-hydroxypropyl)-1-methyl-1*H*-imidazole (9) This was prepared from 1-methyl-1*H*-imidazole (0.40 ml, 5 mmol) and pivalaldehyde (0.54 ml, 5 mmol) in a similar manner to the reported procedure.[10] The crude product was recrystallized from n-hexane to give **9** as colorless crystals. Yield, 730 mg (87%). mp 82—83 °C. IR ($CHCl_3$): 3530 (–OH), 2952, 1485, 1363, 1279 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.97 (s, 9H, $-C(CH_3)_3$), 3.67 (s, 3H, $>NCH_3$), 3.96—4.51 (br, 1H, –OH), 4.39 (s, 1H, $-CH(OH)$–), 6.76 (d, 1H, C^5-H, J=1.3 Hz), 6.91 (d, 1H, C^4-H, 1.3 Hz). ^{13}C-NMR ($CDCl_3$, 67.8 MHz): 25.77 ($-C(CH_3)_3$), 33.44 ($>NCH_3$), 37.13 ($-C(CH_3)_3$–), 73.96 ($-CH(OH)$–), 120.75 (C-5), 126.79 (C-4), 148.82 (C-2). UV λ_{max} nm (log ε): 215 (3.88). *Anal.* Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.71. Found: C, 64.22; H, 9.68; N, 16.50.

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