Synthesis of a regio-isomer of kealiiquinone, a marine benzimidazole alkaloid

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Received (in Cambridge, UK) 18th September 2000, Accepted 3rd January 2001
First published as an Advance Article on the web 31st January 2001

Treatment of 1,3-dialkyl-2-(phenylthio)benzimidazolium salts **3** and 1,3-dialkyl-2-phenylthio-1*H*-imidazolium salts **7** with aq. K_2CO_3 gives 1,3-dialkyl-1,3-dihydrobenzimidazol-2-ones **4** and 1,3-dialkyl-1,3-dihydroimidazol-2-ones **8**, respectively, in 22–94% yield. A regio-isomer **17** of kealiiquinone, a marine benzimidazole alkaloid, where the 4-methoxyphenyl group at the 4-position migrates to the 9-position, is synthesized by application of the reaction. Cytotoxity of **17** and kealiiquinone against 39 human cancer cells is evaluated. They have weak activity but a unique mechanism of action.

Recently, many marine imidazole and benzimidazole alkaloids have been isolated from sponges, and their antitumour and antibacterial activities have been investigated.[1,2] Hitherto, we have reported the total syntheses of several marine imidazole and benzimidazole alkaloids such as nortopsentins A–D,[3] topsentin,[4] kealiiquinone,[5] clathridine A,[6] naamine A,[7] and naamidine A,[7] which are shown in Fig 1.

In this paper, we would like to report the development of a new method for the introduction of an oxo group into the 2-position of imidazole and benzimidazole rings, and its application to the preparation of a regio-isomer **17** of kealiiquinone, the biological activity of which has not been reported.

Results and discussion

1-Methyl-2-(phenylthio)benzimidazole **2** was prepared in 71% yield by lithiation of 1-methylbenzimidazole **1** with *n*-BuLi followed by treatment with diphenyl disulfide. The sulfide **2** was refluxed with benzyl bromide to yield the corresponding benzimidazolium salt **3a** in 70% yield. A solution of the salt **3a** in aq. K_2CO_3 was stirred at 80 °C for 3 h to give 1-benzyl-3-methyl-1,3-dihydrobenzimidazol-2-one **4a** in 81% yield as shown in Scheme 1. After the sulfide **2** had been refluxed with either 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) or allyl bromide, attempts to obtain pure benzimidazolium salts **3b** and **3c** failed. However, subsequent treatment of the crude salts **3b** and **3c** with aq. K_2CO_3 gave the 1,3-dihydrobenzimidazol-2-ones **4b** and **4c** in 94 and 51% yield, respectively, from **2**. The SEM group of **4b** could be readily removed in 70% yield by treatment with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) to give 1-methylbenzimidazolidin-2-one **5**, which was also obtained by hydrogenolysis of **4a** in the presence of Pd catalyst in 31% yield (Scheme 1).

As shown in Scheme 1 and Table 1, some imidazoles **6** could be quaternized with various alkyl halides and the obtained crude 1,3-dialkyl-1*H*-imidazolium salts **7a**–**h** were subjected to

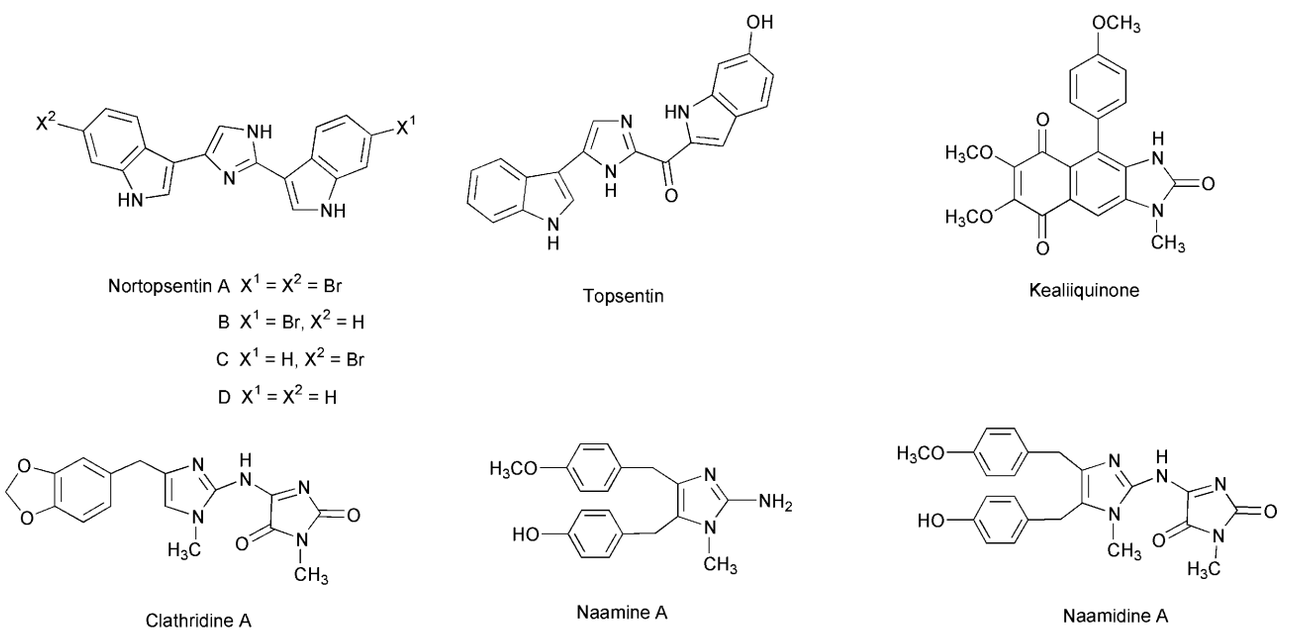
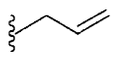
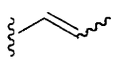
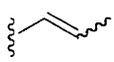


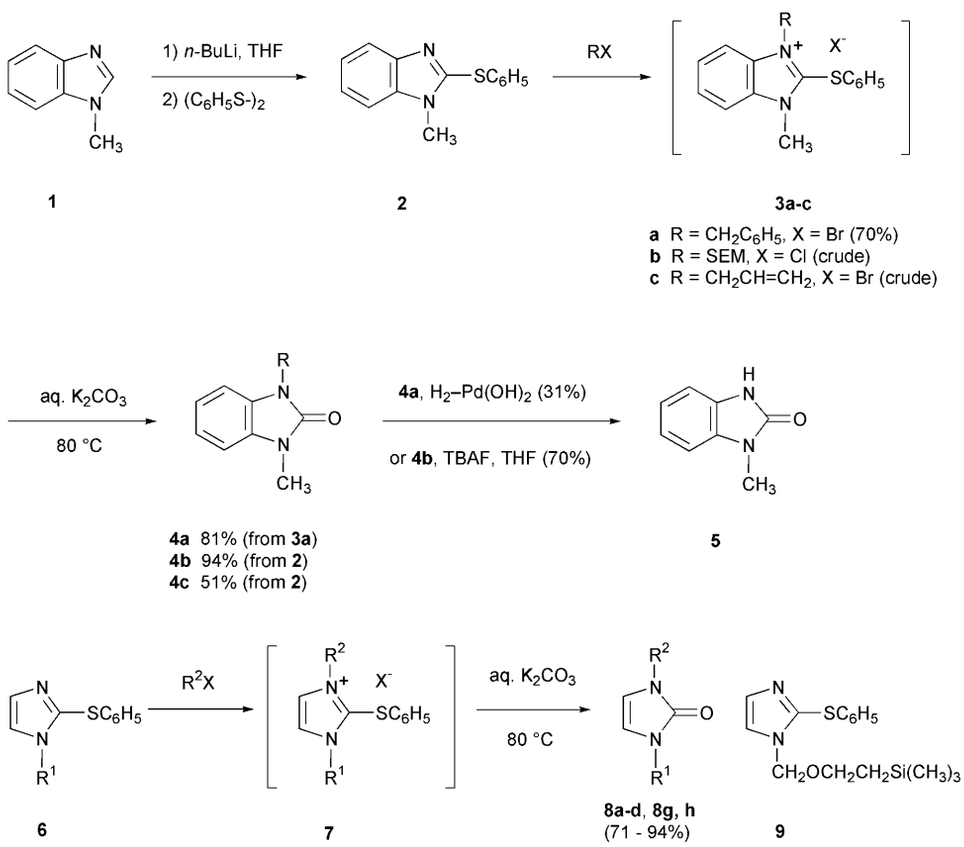
Fig. 1

DOI: 10.1039/b007560o

Table 1 Synthesis of 1,3-dialkyl-1,3-dihydroimidazol-2-ones **8**

	Imidazolium salt[a]				Product	
Entry	Compd.	R^1	R^2	X	Compd.	Isolated yield (%)[b]
1	**7a**	CH_3	CH_3	I	**8a**	76
2	**7b**[c]	CH_3	$C_6H_5CH_2$	Br	**8b**	76[d]
3	**7c**	CH_3	SEM	Cl	**8c**	77
4	**7d**	CH_3		Br	**8d**	71
5	**7e**	MOM	SEM	Cl	**8e**	26[e]
6	**7f**	MOM	$C_6H_5CH_2$	Br	**8f**	22
7	**7g**		SEM	Cl	**8g**	94[f]
8	**7h**		$C_6H_5CH_2$	Br	**8h**	75[f]

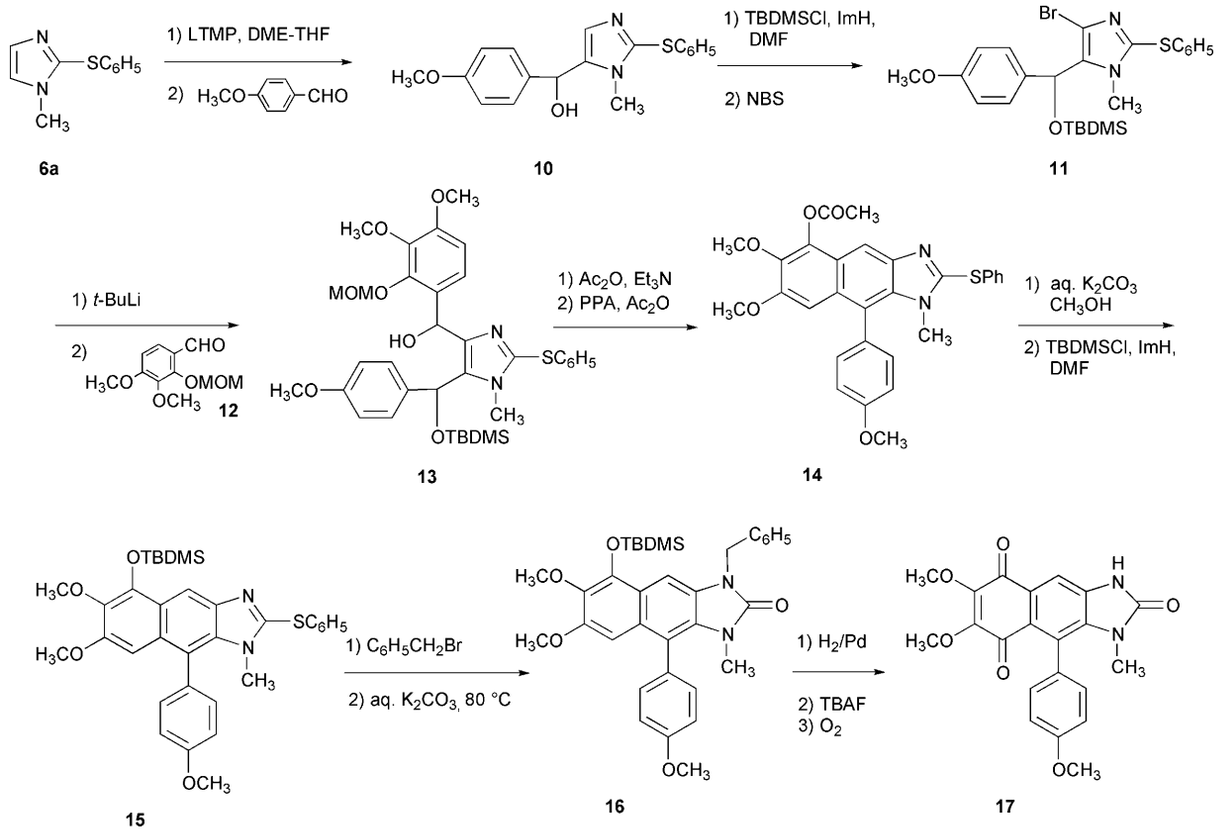
[a] Crude salts were used except for **7b**. [b] The yields are calculated on the basis of 1-alkyl-1*H*-imidazoles **6**. [c] Crude **7b** was purified by recrystallization from AcOEt–*n*-hexane. Isolated yield 89%. [d] Isolated yield from **7b**. [e] A by-product (**9**; R = SEM) was also obtained in 14% yield. [f] Total yield of *Z* and *E* isomers (ratio ≈1 : 1).



Scheme 1

similar alkaline hydrolysis with aq. K_2CO_3 as that used for **3** to give 1,3-dialkyl-1,3-dihydroimidazol-2-ones **8a**–**d**, **8g** and **8h** in 71–94% yield, but only low yields in the cases where R^1 (or R^2) = methoxymethyl group (MOM) (**8e**, **8f**). A small amount of 2-phenylthio-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-imidazole[4,8] **9** was obtained along with the main product **8e** in the case of Entry 5. It is suggested that the low yields of **8e** and **8f** might be due to deprotection of the 1-MOM group by small amounts of HCl generated *in situ* before and/or after quaternization.

Kealiiquinone in Fig. 1 has a unique and interesting chemical structure, but its biological activity has not been reported.[2e–g] So, we planned to synthesize several analogues of kealiiquinone and to examine their antitumour activity including that of the previously reported synthetic kealiiquinone. A regio-isomer **17** of kealiiquinone was selected as a synthetic target. 1-Methyl-2-phenylthio-1*H*-imidazole **6a** was converted into the 5-substituted imidazole **10** by the previously reported procedure,[9] and then protection of the hydroxy group of **10** by a *tert*-butyldimethylsilyl (TBDMS) group followed by bromination with *N*-bromosuccinimide (NBS) gave the bromide **11** in 41% yield from **6a**. Lithiation at the 4-position of **11** with *tert*-butyllithium followed by trapping with 3,4-dimethoxy-2-(methoxymethoxy)benzaldehyde **12** gave the tetra-substituted imidazole **13** in 77% yield as a diastereomeric mixture (≈4 : 3, on the basis of ^{1}H NMR analysis). After acetylation of the hydroxy group of **13**, Friedel–Crafts-type cyclization with polyphosphoric acid (PPA) in the presence of acetic anhydride gave the tricycle **14** in 93% yield as pale yellow crystals. Alkaline hydrolysis of the ester group of **14** followed



Scheme 2

by conversion of the produced phenolic hydroxy group into a TBDMSO group afforded the silyl ether **15** in 71% yield. Quaternization of **15** with benzyl bromide followed by heating in aq. K_2CO_3 successfully afforded the 2-oxo compound **16** in 51% yield as a viscous oil. The benzyl group and the TBDMS group of **16** were removed by Pd/C-catalyzed hydrogenation followed by treatment with TBAF, and then the product was autoxidized in the presence of salcomin[10] in THF to give our target compound **17** as yellow needles, mp 261–262 °C (Scheme 2). Spectral and physical data of **17** and kealiiquinone are listed in Table 2.

Growth-inhibitory activity of the regio-isomer **17** and the synthetic kealiiquinone against a panel of 39 human cancer cell lines was evaluated in the Japanese Foundation for Cancer Research.[11] The mean concentrations of **17** required to achieve GI_{50}, TGI, and LC_{50} levels against the panel were 51.3, 91.2, and 100 μM, respectively. Those of kealiiquinone were 39.8, 79.4, and 97.7 μM, respectively. The Foundation has operated its screening system with the panel and the database analysis, by which anticancer activity of the tested compounds can be evaluated in not only strength but also their uniqueness in mechanism of action by comparison with the cumulated data. They reported to us on their analysis that compound **17** and the synthetic kealiiquinone both have relatively weak activity but a unique mechanism of action.[12]

Experimental

All mps were measured with a Yanaco MP micro-melting-point apparatus and are uncorrected. IR spectra were taken with a Shimadzu IR-435 spectrometer. ^{1}H NMR spectra were measured on a Varian XL-300 (^{1}H: 300 MHz, ^{13}C: 75.4 MHz) or a Varian UNITY INOVA 400NB (^{1}H: 400 MHz, ^{13}C: 100.6 MHz) spectrometer with tetramethylsilane as internal standard, and chemical shifts δ are reported in ppm. Low-resolution mass spectra (LRMS) and high-resolution MS (HRMS) were measured on JEOL JMS-SX 102A QQ or JEOL JMS BU-20 spectrometers. Silica gel (Merck Art. 7734) was used for column chromatography.

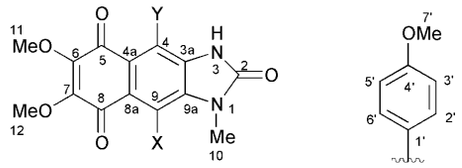
1-Methyl-2-(phenylthio)benzimidazole 2

n-BuLi (1.6 M in *n*-hexane; 18.8 mL, 30.0 mmol) was added dropwise to a solution of 1-methylbenzimidazole **1** (3.97 g, 30.0 mmol) in THF (60 mL) under N_2 at −78 °C. After stirring of the mixture for 15 min at the same temperature, diphenyl disulfide (6.55 g, 30.0 mmol) was added and the whole was stirred for 30 min at −78 °C. The mixture was acidified with 10% HCl and washed with diethyl ether. The aqueous layer was basified with K_2CO_3 powder and extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane 1 : 1) to give sulfide **2** (5.11, 71%), mp 65–67 °C (colourless needles, recrystallized from *n*-hexane); ν_{max} ($CHCl_3$) 2947, 1579, 1439, 1323, 1078 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.74 (s, 3H, NCH_3), 7.23–7.38 (m, 8H, ArH), 7.76–7.79 (m, 1H, ArH); δ_C (100.6 MHz; $CDCl_3$) 30.8, 109.4, 119.9, 122.4, 123.2, 127.6, 129.4, 130.2, 132.2, 136.5, 143.1, 147.6 (Calc. for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66. Found: C, 69.84; H, 5.06; N, 11.37%. HRMS *m/z* Calc. for $C_{14}H_{12}N_2S$: *M*, 240.0721. Found: M^+, 240.0711).

1-Benzyl-3-methyl-2-(phenylthio)benzimidazolium bromide 3a

A mixture of sulfide **2** (100 mg, 0.42 mmol) and benzyl bromide (0.07 mL, 0.62 mmol) in AcOEt (1 mL) was refluxed under stirring for 3 h. The solvent was evaporated off to give a solid mass, which was recrystallized from AcOEt–Pr^{i}OH to give salt **3a** (97 mg, 70%), mp 160–164 °C (colourless needles); ν_{max} (KBr) 3014, 1471, 776, 562 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 4.06 (s, 3H, NCH_3), 5.87 (s, 2H, NCH_2Ar), 7.17–8.09 (m, 14H, ArH); δ_C (100.6 MHz; DMSO-d_6) 34.1, 54.1, 113.7, 114.0, 114.3, 127.5, 127.7, 127.9, 128.5, 129.0, 129.8, 130.5, 131.5, 131.9, 133.0, 134.1, 147.1 [Calc. for $C_{21}H_{19}BrN_2S$: C, 61.31; H, 4.66; N, 6.81. Found: C, 60.89; H, 4.93; N, 6.46%. HRMS *m/z*

Table 2 Physical and spectral data of kealiiquinone and **17**



Kealiiquinone X = H, Y = 4-methoxyphenyl,
Regio-isomer (**17**) X = 4-methoxyphenyl, Y = H

		Kealiiquinone[5]		Regioisomer **17** of kealiiquinone	
Appearance		Orange needles		Yellow needles	
Mp		290–292 °C		261–262 °C	
IR: ν_{max}/cm^{-1} in $CHCl_3$		1719, 1657, 1624, 1511, 1458, 1339, 1302, 1243, 1219, 1172, 1103, 1053		2984, 1706, 1662, 1624, 1510, 1457, 1345, 1285, 1242, 1172, 1067, 1032	
UV (MeOH) λ_{max} (log ε)		209 (4.53), 286 (4.63), 369 (3.48)		203 (4.57), 287 (4.63), 360 (3.47)	
	Position	^{1}H	^{13}C	^{1}H	^{13}C
NMR in DMSO-d_6 [δ (ppm)]	2		154.76		155.01
	3a		133.97		132.25
	4		126.46	7.55 (s, 1H)	105.84
	4a		122.64		124.12
	5		181.31		181.17
	6		147.79		133.30
	7		132.60		148.08
	8		181.13		181.34
	8a		123.49		123.12
	9	7.68 (s, 1H)	104.56		126.46
	9a		129.86		145.36
	10	3.39 (s, 3H)	26.80	3.33 (s, 3H)	29.06
	11	3.94 (s, 3H)	60.76	3.83 (s, 3H)	60.95
	12	3.85 (s, 3H)	60.76	3.92 (s, 3H)	60.95
	1′		126.50		127.99
	2′, 6′	7.13 (d, 2H)[a]	127.66	7.19 (d, 2H)[a]	130.76
	3′, 5′	6.98 (d, 2H)[a]	113.89	6.97 (d, 2H)[a]	113.22
	4′		158.53		158.83
	7′	3.82 (s, 3H)	55.04	3.83 (s, 3H)	55.26
	3-NH	11.03 (br, 1H)		11.73 (br, 1H)	

[a] J = 8.8 Hz.

Calc. for $C_{21}H_{19}N_2S$ (M − Br), 331.1269. Found: 331.1278 (M − Br)$^+$].

1-Benzyl-3-methyl-1,3-dihydrobenzimidazol-2-one 4a

A mixture of salt **3a** (50 mg, 0.15 mmol) and aq. K_2CO_3 (41 mg, 0.30 mmol in 1 mL) was stirred at 80 °C for 3 h. The mixture was extracted with AcOEt, and the organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane 1 : 1) to give the urea **4a** (29 mg, 81%), mp 87–88 °C (colourless needles from AcOEt–*n*-hexane); ν_{max} ($CHCl_3$) 2981, 1687, 1494, 1171, 555 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.47 (s, 3H, NCH_3), 5.08 (s, 2H, NCH_2Ar), 6.86–7.33 (m, 9H, ArH); δ_C (100.6 MHz; $CDCl_3$) 27.1, 44.8, 107.3, 108.1, 121.1, 121.2, 127.4, 127.5, 128.6, 129.1, 130.0, 136.3, 154.4 (Calc. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.83; H, 5.95; N, 11.31%. HRMS *m/z* Calc. for $C_{15}H_{14}N_2O$: M, 238.1106. Found: M$^+$, 238.1104).

1-Methyl-3-[2-(trimethylsilyl)ethoxymethyl]-1,3-dihydrobenzimidazol-2-one 4b

A mixture of sulfide **2** (400 mg, 1.66 mmol) and SEMCl (0.44 mL, 2.50 mmol) in AcOEt (2 mL) was refluxed with stirring for 3 h. The solvent was evaporated off to give benzimidazolium salt **3b**. A mixture of the benzimidazolium salt and aq. K_2CO_3 (460 mg, 3.33 mmol in 2 mL) was stirred at 80 °C for 3 h. The mixture was extracted with AcOEt, and the organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane 1 : 1) to afford the urea **4b** as a colourless, viscous oil (435 mg, 94%); ν_{max} ($CHCl_3$) 2950, 1697, 1493, 1247, 1072, 834 cm^{-1}; δ_H (400 MHz; $CDCl_3$) −0.04 [s, 9H, $Si(CH_3)_3$], 0.92 (t, J 8.2 Hz, 2H, CH_2CH_2Si), 3.43 (s, 3H, NCH_3), 3.61 (t, J 8.2 Hz, 2H, CH_2CH_2Si), 5.32 (s, 2H, NCH_2O), 6.98–7.19 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$) −1.45, 17.8, 27.1, 66.1, 70.7, 107.4, 108.7, 121.5, 121.9, 128.8, 130.1, 154.4 (HRMS *m/z* Calc. for $C_{14}H_{22}N_2O_2Si$: M, 278.1450. Found: M$^+$, 278.1454).

1-Allyl-3-methyl-1,3-dihydrobenzimidazol-2-one 4c

This was prepared in a similar manner as that used for the preparation of **4b** except for use of allyl bromide (0.22 mL, 2.50 mmol) instead of SEMCl. Title compound was obtained as a colourless, viscous oil (160 mg, 51%); ν_{max} ($CHCl_3$) 2930, 1686, 1494, 1124, 925, 563 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.43 (s, 3H, NCH_3), 4.51 (dt, J 5.3, 1.7 Hz, 2H, NCH_2CH), 5.20 (ddt, J 1.3, 16.9, 1.6 Hz, 1H, $CH{=}CH_2$), 5.23 (ddt, J 1.1, 10.6, 1.6 Hz, 1H, $CH{=}CH_2$), 5.90 (ddt, J 9.8, 17.7, 5.4 Hz, 1H, $CH{=}CH_2$), 6.95–

7.12 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$) 27.1, 43.5, 107.3, 108.1, 117.4, 121.1, 121.2, 129.2, 130.0, 132.0, 154.2 (HRMS *m/z* Calc. for $C_{11}H_{12}N_2O$: *M*, 188.0950. Found: M^+, 188.0946).

1-Methyl-1,3-dihydrobenzimidazol-2-one 5

(a) Synthesis from 4a. A mixture of **4a** (42 mg, 0.18 mmol) and 20% $Pd(OH)_2$–C (400 mg) in EtOH (2 mL) was stirred for 24 h under H_2 (4 kg cm^{-2}) at room temperature. After filtration, the filtrate was evaporated. The crude product was purified by column chromatography (AcOEt–*n*-hexane 1 : 2) to give title compound **5** as a colourless, viscous oil (8 mg, 31%); ν_{max} ($CHCl_3$) 3400, 2979, 1686, 1495, 1123, 560 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.43 (s, 3H, NCH_3), 6.96–7.15 (m, 4H, ArH), 10.57 (s, 1H, NH); δ_C (100.6 MHz; $CDCl_3$) 26.8, 107.6, 109.6, 121.2, 121.6, 128.0, 130.9, 156.0 (HRMS *m/z* Calc. for $C_8H_8N_2O$: *M*, 148.0637. Found: M^+, 148.0642).

(b) Synthesis from 4b. A stirred solution of **4b** (126 mg, 0.45 mmol) and TBAF (1 M in THF; 0.91 mL, 0.91 mmol) in THF (1 mL) was refluxed for 3 h. After addition of water, the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt) to afford title compound **5** (26 mg, 70%). This compound was identical with the sample obtained in (a).

1,3-Dimethyl-1,3-dihydroimidazol-2-one 8a

A solution of sulfide **6a** (R^1 = Me; 200 mg, 1.05 mmol) and methyl iodide (0.11 mL, 1.58 mmol) in AcOEt (1 mL) was refluxed under stirring for 3 h. The solvent was evaporated off to give imidazolium salt **7a**. An analytical sample was recrystallized from acetone–Et_2O to give colourless crystals, mp 196–197 °C; ν_{max} ($CHCl_3$) 2920, 1561, 1497, 1228, 657 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.06 (s, 6H, NCH_3), 7.21–7.24 (m, 2H, ArH), 7.38–7.43 (m, 3H, ArH), 8.14 (s, 2H, ArH); δ_C (100.6 MHz; $CDCl_3$) 37.6, 125.9, 128.5, 129.4, 129.9, 130.6, 139.3 (Calc. for $C_{11}H_{13}IN_2S$: C, 39.77; H, 3.94; N, 8.43. Found: C, 39.79; H, 3.97; N, 8.33%).

A mixture of the imidazolium salt **7a** and aq. K_2CO_3 (291 mg, 2.10 mmol in 1 mL) was stirred at 80 °C for 3 h. After cooling, the reaction mixture was extracted with AcOEt, and the organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$–MeOH 20 : 1) to give compound **8a** as a colourless, viscous oil (90 mg, 76%); ν_{max} ($CHCl_3$) 2968, 1671, 1479, 1231, 650 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.25 (s, 6H, NCH_3), 6.16 (s, 2H, ArH); δ_C (100.6 MHz; $CDCl_3$) 30.3, 111.0, 153.4 (HRMS *m/z* Calc. for $C_5H_8N_2O$: *M*, 112.0637. Found: M^+, 112.0641).

1-Benzyl-3-methyl-2-(phenylthio)imidazolium bromide 7b

A stirred solution of compound **6a** (R^1 = Me; 190 mg, 1.00 mmol) and benzyl bromide (0.18 mL, 1.50 mmol) in AcOEt (1.5 mL) was refluxed for 3 h. The solvent was evaporated off to give imidazolium salt **7b**, which was recrystallized from methyl ethyl ketone (322 mg, 89%), mp 106–107 °C (colourless crystals); ν_{max} (KBr) 3055, 1493, 1436, 1249, 730 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.87 (s, 3H, NCH_3), 5.53 (s, 2H, NCH_2Ar), 7.24–7.39 (m, 10H, ArH), 8.10 (d, *J* 2.2 Hz, 1H, ArH), 8.13 (d, *J* 2.0 Hz, 1H, ArH); δ_C (100.6 MHz; DMSO-d_6) 37.1, 53.5, 124.9, 126.8, 128.4, 128.7, 129.1, 129.2, 129.3, 129.5, 130.5, 132.9, 138.1 (Calc. for $C_{17}H_{17}BrN_2S$: C, 56.51; H, 4.74; N, 7.75. Found: C, 56.35; H, 4.86; N, 7.57%).

1-Benzyl-3-methyl-1,3-dihydroimidazol-2-one 8b

This was prepared from salt **7b** in a similar manner as that used to prepare **8a**. Yield 151 mg (76%), mp 63–64 °C (colourless needles, recrystallized from *n*-hexane); ν_{max} ($CHCl_3$) 2969, 1669, 1470, 1231, 651 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.28 (s, 3H, NCH_3), 4.78 (s, 2H, NCH_2Ar), 6.10 (d, *J* 2.9 Hz, 1H, ArH), 6.16 (d, *J* 2.9 Hz, 1H, ArH), 7.25–7.35 (m, 5H, ArH); δ_C (100.6 MHz; $CDCl_3$) 30.3, 47.0, 109.7, 111.5, 127.5, 127.7, 128.5, 136.9, 153.2 (Calc. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.35; H, 6.48; N, 14.85%. HRMS *m/z* Calc. for $C_{11}H_{12}N_2O$: *M*, 188.0950. Found: M^+, 188.0955).

1-Methyl-3-[2-(trimethylsilyl)ethoxymethyl]-1,3-dihydroimidazol-2-one 8c

This was prepared from sulfide **6a** in a similar manner as that used to prepare **8a** except for the use of SEMCl (0.28 mL, 1.58 mmol) instead of methyl iodide. The crude product was purified by column chromatography (AcOEt–*n*-hexane 1 : 1) to give compound **8c** as a colourless, viscous oil (185 mg, 77%); ν_{max} ($CHCl_3$) 2971, 1674, 1467, 1243, 1080, 834, 652 cm^{-1}; δ_H (400 MHz; $CDCl_3$) −0.04 [s, 9H, $Si(CH_3)_3$], 0.88 (t, *J* 8.2 Hz, 2H, CH_2CH_2Si), 3.23 (s, 3H, NCH_3), 3.54 (t, *J* 8.2 Hz, 2H, CH_2CH_2Si), 4.97 (s, 2H, NCH_2O), 6.17 (d, *J* 2.9 Hz, 1H, ArH), 6.30 (d, *J* 3.1 Hz, 1H, ArH); δ_C (100.6 MHz; $CDCl_3$) −1.5, 17.8, 30.2, 65.9, 72.6, 109.6, 112.2, 153.4 (HRMS *m/z* Calc. for $C_{10}H_{20}N_2O_2Si$: *M*, 228.1294. Found: M^+, 228.1299).

1-Allyl-3-methyl-1,3-dihydroimidazol-2-one 8d

This was prepared from sulfide **6a** in a similar manner as that used to prepare **8a** except for the use of allyl bromide (0.14 mL, 1.58 mmol) instead of methyl iodide. The crude product was purified by column chromatography (AcOEt–*n*-hexane 1 : 1) to give the urea **8d** as a colourless, viscous oil (98 mg, 71%); ν_{max} ($CHCl_3$) 2971, 1673, 1470, 1230, 650 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.27 (s, 3H, NCH_3), 4.23 (dt, *J* 5.9, 1.5 Hz, 2H, NCH_2CH), 5.19 (dq, *J* 16.9, 1.5 Hz, 1H, $CH{=}CH_2$), 5.21 (dq, *J* 10.4, 1.5 Hz, 1H, $CH{=}CH_2$), 5.87 (ddt, *J* 10.4, 16.9, 5.8 Hz, 1H, $CH{=}CH_2$), 6.18 (s, 2H, ArH); δ_C (100.6 MHz; $CDCl_3$) 30.4, 45.8, 109.7, 111.4, 117.7, 133.1, 153.1 (HRMS *m/z* Calc. for $C_7H_{10}N_2O$: *M*, 138.0793. Found: M^+, 138.0789).

1-Methoxymethyl-3-[2-(trimethylsilyl)ethoxymethyl]-1,3-dihydroimidazol-2-one 8e and 2-phenylthio-1-[2-(trimethylsilyl)-ethoxymethyl]imidazole 9

A stirred solution of sulfide **6b** (R^1 = MOM; 200 mg, 0.91 mmol) and SEMCl (0.24 mL, 1.36 mmol) in AcOEt (1 mL) was refluxed for 3 h. The solvent was evaporated off to give imidazolium salt **7e**. A mixture of this imidazolium salt and aq. K_2CO_3 (251 mg, 1.82 mmol in 2 mL) was stirred at 80 °C for 3 h. The mixture was extracted with AcOEt, and the organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane 1 : 1). Compound **8e**: Colourless, viscous oil (60 mg, 26%); ν_{max} ($CHCl_3$) 2976, 1687, 1456, 1370, 1248, 1078, 834, 655 cm^{-1}; δ_H (400 MHz; $CDCl_3$) −0.02 [s, 9H, $Si(CH_3)_3$], 0.92 (t, *J* 8.2 Hz, 2H, CH_2CH_2Si), 3.32 (s, 3H, OCH_3), 3.56 (t, *J* 8.2 Hz, 2H, CH_2CH_2Si), 4.98 (s, 2H, NCH_2O), 5.02 (s, 2H, NCH_2O), 6.35 (d, *J* 3.1 Hz, 1H, ArH), 6.37 (d, *J* 3.1 Hz, 1H, ArH); δ_C (100.6 MHz; $CDCl_3$) −1.5, 17.8, 56.2, 66.1, 72.5, 74.3, 110.7, 110.9, 153.6 (HRMS *m/z* Calc. for $C_{11}H_{22}N_2O_3Si$: *M*, 258.1400. Found: M^+, 258.1390).

Compound **9**: Colourless viscous oil (40 mg, 14%); ν_{max} ($CHCl_3$) 2937, 1578, 1474, 1247, 1077, 835 cm^{-1}; δ_H (400 MHz; $CDCl_3$) −0.04 [s, 9H, $Si(CH_3)_3$], 0.83 (t, *J* 8.2 Hz, 2H, CH_2CH_2Si), 3.38 (t, *J* 8.3 Hz, 2H, CH_2CH_2Si), 5.39 (s, 2H, NCH_2O), 7.18–7.30 (m, 7H, ArH); δ_C (75.4 MHz; $CDCl_3$) −1.5, 17.7, 66.4, 75.6, 122.3, 126.8, 128.3, 129.2, 130.8, 134.7, 138.3 (HRMS *m/z* Calc. for $C_{15}H_{22}N_2OSSi$: *M*, 306.1222. Found: M^+, 306.1213).

1-Benzyl-3-methoxymethyl-1,3-dihydroimidazol-2-one 8f

This was prepared in a similar manner as that used to prepare **8e**, except for the use of benzyl bromide (0.16 mL, 1.36 mmol)

instead of SEMCl. The crude product was purified by column chromatography ($CHCl_3$–MeOH 20:1) to give the urea **8f** as a colourless, viscous oil (38 mg, 22%); ν_{max} ($CHCl_3$) 2921, 1675, 1460, 1226, 1097, 671 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.34 (s, 3H, OCH_3), 4.79 (s, 2H, NCH_2O), 5.00 (s, 2H, NCH_2Ar), 6.14 (d, *J* 3.1 Hz, 1H, ArH), 6.31 (d, *J* 3.1 Hz, 1H, ArH), 7.24–7.35 (m, 5H, ArH); δ_C (100.6 MHz; $CDCl_3$) 47.1, 56.2, 74.4, 110.1, 111.1, 127.78, 127.80, 128.8, 136.7, 153.5 (HRMS *m/z* Calc. for $C_{12}H_{14}N_2O_2$: *M*, 218.1055. Found: M^+, 218.1059).

A diastereomeric mixture of 1-(prop-1-enyl)-3-[2-(trimethylsilyl)-ethoxymethyl]-1,3-dihydroimidazol-2-one 8g

A stirred solution of sulfide **6c** (R^1 = CH=$CHCH_3$; 433 mg, 2.00 mmol) and SEMCl (0.53 mL, 3.00 mmol) in AcOEt (2 mL) was refluxed for 3 h. The solvent was evaporated off to give imidazolium salt **7g**. A mixture of **7g** and aq. K_2CO_3 (553 mg, 4.00 mmol in 2 mL) was stirred at 80 °C for 3 h. After cooling, the reaction mixture was extracted with AcOEt, and the organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography (AcOEt–*n*-hexane 1:1). (*Z*)-**8g**: Colourless, viscous oil (247 mg, 49%); ν_{max} ($CHCl_3$) 2937, 1687, 1450, 1245, 1074, 834, 653 cm^{-1}; δ_H (400 MHz; $CDCl_3$) −0.04 [s, 9H, $Si(CH_3)_3$], 0.90 (t, *J* 8.2 Hz, 2H, CH_2CH_2Si), 1.76 (dd, *J* 1.7, 7.2 Hz, 3H, CH=$CHCH_3$), 3.56 (t, *J* 8.2 Hz, 2H, CH_2CH_2Si), 5.00 (s, 2H, NCH_2O), 5.28 (dq, *J* 8.9, 7.3 Hz, 1H, CH=$CHCH_3$), 6.37 (d, *J* 3.1 Hz, 1H, ArH), 6.40 (dq, *J* 9.0, 1.8 Hz, 1H, CH=$CHCH_3$), 6.48 (d, *J* 3.1 Hz, 1H, ArH); δ_C (100.6 MHz; $CDCl_3$) −1.4, 12.4, 17.9, 66.2, 72.5, 110.5, 111.0, 115.7, 122.1, 152.3 (HRMS *m/z* Calc. for $C_{12}H_{22}N_2O_2Si$: *M*, 254.1450. Found: M^+, 254.1445).

(*E*)-**8g**: Colourless, viscous oil (231 mg, 45%); ν_{max} ($CHCl_3$) 2976, 1687, 1455, 1244, 1079, 834, 651 cm^{-1}; δ_H (400 MHz; $CDCl_3$) −0.04 [s, 9H, $Si(CH_3)_3$], 0.88 (t, *J* 8.2 Hz, 2H, CH_2CH_2Si), 1.74 (dd, *J* 1.7, 6.6 Hz, 3H, CH=$CHCH_3$), 3.54 (t, *J* 8.2 Hz, 2H, CH_2CH_2Si), 4.97 (s, 2H, NCH_2O), 5.45 (dq, *J* 14.3, 6.8 Hz, 1H, CH=$CHCH_3$), 6.35 (d, *J* 3.1 Hz, 1H, ArH), 6.43 (d, *J* 3.1 Hz, 1H, ArH), 6.67 (dq, *J* 14.5, 1.7 Hz, 1H, CH=$CHCH_3$); δ_C (100.6 MHz; $CDCl_3$) −1.4, 15.0, 17.8, 66.1, 72.4, 107.6, 109.4, 111.4, 122.3, 151.4 (HRMS *m/z* Calc. for $C_{12}H_{22}N_2O_2Si$: *M*, 254.1450. Found: M^+, 254.1444).

A diastereomeric mixture of 1-benzyl-3-(prop-1-enyl)-1,3-dihydroimidazol-2-one 8h

Similarly prepared from sulfide **6c** as used for the preparation of **8g** except for the use of benzyl bromide (0.36 mL, 3.00 mmol) instead of SEMCl. (*Z*)-**8h**: Colourless, viscous oil (168 mg, 39%); ν_{max} ($CHCl_3$) 2975, 1682, 1447, 1229, 672 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.79 (dd, *J* 1.8, 7.3 Hz, 3H, CH=$CHCH_3$), 4.80 (s, 2H, NCH_2Ar), 5.29 (dq, *J* 9.0, 7.2 Hz, 1H, CH=$CHCH_3$), 6.17 (d, *J* 3.1 Hz, 1H, ArH), 6.48 (d, *J* 3.1 Hz, 1H, ArH), 6.47–6.51 (m, 1H, CH=$CHCH_3$), 7.26–7.37 (m, 5H, ArH); δ_C (100.6 MHz; $CDCl_3$) 12.4, 47.0, 110.3, 110.6, 114.8, 122.2, 127.77, 127.84, 136.6, 152.2 (HRMS *m/z* Calc. for $C_{13}H_{14}N_2O$: *M*, 214.1106. Found: M^+, 214.1111).

(*E*)-**8h**: Colourless, viscous oil (153 mg, 36%); ν_{max} ($CHCl_3$) 2977, 1683, 1449, 1237, 647 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.78 (dd, *J* 1.8, 6.8 Hz, 3H, CH=$CHCH_3$), 4.79 (s, 2H, NCH_2Ar), 5.47 (dq, *J* 14.3, 6.8 Hz, 1H, CH=$CHCH_3$), 6.15 (d, *J* 3.1 Hz, 1H, ArH), 6.42 (d, *J* 3.1 Hz, 1H, ArH), 6.74 (dq, *J* 14.4, 1.6 Hz, 1H, CH=$CHCH_3$), 7.24–7.36 (m, 5H, ArH); δ_C (100.6 MHz; $CDCl_3$) 14.9, 46.9, 106.9, 109.0, 111.5, 122.5, 127.72, 127.73, 128.7, 136.5, 151.3 (HRMS *m/z* Calc. for $C_{13}H_{14}N_2O$: *M*, 214.1106. Found: M^+, 214.1118).

4-Bromo-5-[(*tert*-butyldimethylsiloxy)-(4-methoxyphenyl)-methyl]-1-methyl-2-phenylthio-1*H*-imidazole 11

A mixture of the alcohol **10**[9a] (prepared from **6a** in 67% yield, 1.95 g, 6.00 mmol), imidazole (3.06 g, 45.0 mmol) and TBDMSCl (2.89 g, 19.2 mmol) in dimethylformamide (DMF; 16 mL) was stirred for 12 h at 60 °C. Water (10 mL) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane 1:2). This product was the corresponding silyl ether of **10**, a colourless, viscous oil (2.62 g, 99%); ν_{max} ($CHCl_3$) 2938, 1505, 1246, 1067, 853 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.05 [s, 3H, $Si(CH_3)_2$], 0.06 [s, 3H, $Si(CH_3)_2$], 0.90 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], 3.31 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 5.88 [s, 1H, ArC*H*(OTBDMS)Ar], 6.84–7.24 (m, 10H, ArH); δ_C (100.6 MHz; $CDCl_3$) −5.1, −5.0, 18.2, 25.7, 32.1, 55.2, 68.2, 113.6, 126.3, 127.1, 127.6, 129.1, 129.3, 133.3, 135.0, 136.9, 139.4, 158.8 (HRMS *m/z* Calc. for $C_{24}H_{32}N_2O_2SSi$: *M*, 440.1954. Found: M^+, 440.1951).

NBS (144 mg, 0.81 mmol) was added to a solution of the silyl ether (297 mg, 0.67 mmol) in THF (1 mL) under N_2 at 0 °C, and the whole was stirred for 7 h at 0 °C. Water (2 mL) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane 1:2). Bromide **11** was a pale yellow, viscous oil (216 mg, 62%); ν_{max} ($CHCl_3$) 2939, 1506, 1245, 1070, 852 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.05 [s, 3H, $Si(CH_3)_2$], 0.18 [s, 3H, $Si(CH_3)_2$], 0.91 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], 3.32 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 6.08 [s, 1H, ArC*H*(OTBDMS)Ar], 6.86 (d, *J* 8.9 Hz, 2H, ArH), 7.06–7.25 (m, 7H, ArH); δ_C (100.6 MHz; $CDCl_3$) −5.3, −5.1, 18.1, 25.8, 32.7, 55.3, 67.0, 113.8, 115.6, 126.3, 126.7, 127.9, 129.3, 132.8, 134.1, 134.2, 139.1, 158.8 (HRMS *m/z* Calc. for $C_{24}H_{31}BrN_2O_2SSi$: *M*, 518.1058. Found: M^+, 518.1060).

5-[(*tert*-Butyldimethylsiloxy)-(4-methoxyphenyl)methyl]-4-{[3,4-dimethoxy-2-(methoxymethoxy)phenyl]hydroxymethyl}-1-methyl-2-phenylthio-1*H*-imidazole 13

A solution of *tert*-BuLi in *n*-pentane (1.64 M; 2.8 mL, 4.50 mmol) was added dropwise to a stirred solution of bromide **11** (1.17 g, 2.24 mmol) in diethyl ether (18 mL) under N_2 at −78 °C. Stirring was continued for 1 h, and a solution of 3,4-dimethoxy-2-(methoxymethoxy)benzaldehyde **12** (1.09 g, 4.50 mmol) in diethyl ether (6 mL) was added dropwise at −78 °C. Stirring was continued for 3 h at −78 °C, water (20 mL) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane 1:2) to give title compound **13**, a diastereomeric mixture (≈4:3), as a pale yellow, viscous oil (1.15 g, 77%); ν_{max} ($CHCl_3$) 3400, 2925, 2842, 1604, 1505, 1454, 1278, 1244, 1164, 1064, 988, 854 cm^{-1}; δ_H (300 MHz; $CDCl_3$) of the major isomer: −0.35 [s, 3H, $Si(CH_3)_2$], −0.07 [s, 3H, $Si(CH_3)_2$], 0.84 [s, 9H, $Si(CH_3)_2(CH_3)_3$], 3.34 (s, 3H, NCH_3), 3.55 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.21 (d, *J* 15.1 Hz, 1H, OCH_2O), 5.23 (d, *J* 15.1 Hz, 1H, OCH_2O), 6.30 [s, 1H, ArC*H*(OTBDMS)Ar], 6.34 [d, *J* 5.9 Hz, 1H, ArC*H*(OH)Ar], 6.62–7.24 (m, 11H, ArH) (HRMS *m/z* Calc. for $C_{35}H_{46}N_2O_7SSi$: *M*, 666.2795. Found: M^+, 666.2791).

5-Acetoxy-6,7-dimethoxy-9-(4-methoxyphenyl)-1-methyl-2-phenylthio-1*H*-naphtho[2,3-*d*]imidazole 14

Triethylamine (0.48 mL, 3.43 mmol) and acetic anhydride (0.29 mL, 3.09 mmol) were added dropwise to a solution of alcohol **13** (1.15 g, 1.72 mmol) in $CHCl_3$ (5 mL) under N_2 at 0 °C, and the whole was stirred for 3 h at room temperature. Water (4 mL) was added, and the mixture was extracted with $CHCl_3$. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane 1:2) to give the

corresponding acetyl ester of **13**, a diastereomeric mixture (≈4:3), as a pale yellow, viscous oil (1.22 g, 81%); ν_{max} ($CHCl_3$) 2937, 1725, 1506, 1474, 1285, 1241, 1213, 1067 cm^{-1}; δ_H (400 MHz; $CDCl_3$) of the major isomer: −0.01 [s, 3H, $Si(CH_3)_2$], 0.25 [s, 3H, $Si(CH_3)_2$], 0.96 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], 2.06 (s, 3H, OAc), 3.35 (s, 3H, NCH_3), 3.50 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.22 (d, *J* 11.5 Hz, 1H, OCH_2O), 5.23 (d, *J* 11.7 Hz, 1H, OCH_2O), 6.22–7.62 (m, 13H, ArCH × 2 and ArH) (HRMS *m/z* Calc. for $C_{37}H_{48}N_2O_8SSi$: *M*, 708.2900. Found: M^+, 708.2897).

PPA (0.3 mL) was added to a solution of the acetyl ester (140 mg, 0.20 mmol) in acetic anhydride (2 ml) under N_2 at 0 °C, and the whole was stirred for 12 h. Saturated aq. $NaHCO_3$ was added to neutralize the mixture, which was then extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt). The product was recrystallized from AcOEt–*n*-hexane to afford title compound **14** (95 mg, 93%), mp 167–168 °C (pale yellow crystals); ν_{max} ($CHCl_3$) 2930, 1759, 1456, 1201, 1074, 1017, 834 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 2.49 (s, 3H, OAc), 3.22 (s, 3H, NCH_3), 3.71 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.75 (s, 1H, ArH), 7.05 (d, *J* 8.8 Hz, 2H, ArH), 7.32–7.39 (m, 5H, ArH), 7.51–7.55 (m, 2H, ArH), 8.04 (s, 1H, ArH); δ_C (100.6 MHz; $CDCl_3$) 20.6, 33.0, 55.3, 55.5, 60.8, 102.4, 109.1, 113.7, 118.7, 120.3, 127.5, 128.0, 128.5, 129.5, 130.0, 132.2, 132.3, 134.6, 138.2, 139.2, 142.1, 151.2, 154.6, 159.4, 169.1 (Calc. for $C_{29}H_{26}N_2O_5S$: C, 67.69; H, 5.09; N, 5.44. Found: C, 67.60; H, 5.10; N, 5.48%. HRMS *m/z* Calc. for $C_{29}H_{26}N_2O_5S$: *M*, 514.1562. Found: M^+, 514.1552).

5-(*tert*-Butyldimethylsiloxy)-6,7-dimethoxy-9-(4-methoxyphenyl)-1-methyl-2-phenylthio-1*H*-naphtho[2,3-*d*]imidazole 15

Potassium carbonate (81 mg, 0.58 mmol) was added to a solution of acetate **14** (100 mg, 0.19 mmol) in MeOH–water (5:1) (3 mL) at 0 °C, and the whole was stirred for 3 h at room temperature. The mixture was extracted with $CHCl_3$, and the organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. A mixture of the residue, imidazole (66 mg, 0.97 mmol), and TBDMSCl (88 mg, 0.58 mmol) in DMF (1 mL) was stirred for 6 h under N_2 at 60 °C. Water (2 ml) was added, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$–MeOH 100:1) to give compound **15** (80 mg, 71%), mp 183–184 °C (pale yellow crystals, recrystallized from AcOEt–*n*-hexane); ν_{max} ($CHCl_3$) 2918, 1458, 1251, 1100, 834 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 0.29 [s, 6H, $Si(CH_3)_2$], 1.13 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], 3.19 (s, 3H, NCH_3), 3.71 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.50 (s, 1H, ArH), 7.03 (d, *J* 8.6 Hz, 2H, ArH), 7.37–7.40 (m, 7H, ArH), 8.50 (s, 1H, ArH); δ_C (100.6 MHz; $CDCl_3$) −4.0, 18.9, 26.3, 33.3, 55.3, 55.4, 60.7, 97.5, 111.6, 113.6, 118.6, 122.4, 127.7, 128.4, 128.6, 129.5, 130.4, 132.0, 132.4, 134.3, 136.3, 141.2, 143.6, 151.4, 152.1, 159.3 (Calc. for $C_{33}H_{38}N_2O_4SSi$: C, 67.54; H, 6.53; N, 4.77. Found: C, 67.27; H, 6.64; N, 4.78%. HRMS *m/z* Calc. for $C_{33}H_{38}N_2O_4SSi$: *M*, 586.2321. Found: M^+, 586.2316).

3-Benzyl-5-(*tert*-butyldimethylsiloxy)-6,7-dimethoxy-9-(4-methoxyphenyl)-1-methyl-1,3-dihydronaphtho[2,3-*d*]imidazol-2-one 16

A mixture of compound **15** (24 mg, 0.04 mmol) and benzyl bromide (0.008 mL, 0.06 mmol) in AcOEt (0.8 mL) was refluxed with stirring for 6 h. The solvent was evaporated off to give the corresponding benzimidazolium salt. A mixture of the benzimidazolium salt and aq. K_2CO_3 (12 mg, 0.08 mmol in 1.0 mL) was stirred at 80 °C for 1 h. The mixture was extracted with AcOEt, and the organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$–MeOH 20:1) to afford the urea **16** as a colourless, viscous oil (12 mg, 51%); ν_{max} ($CHCl_3$) 1692, 1460, 1104 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 0.16 [s, 6H, $Si(CH_3)_2$], 1.02 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], 2.92 (s, 3H, NCH_3), 3.66 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.14 (s, 2H, NCH_2Ar), 6.42 (s, 1H, ArH), 7.03 (d, *J* 8.6 Hz, 2H, ArH), 7.25–7.39 (m, 7H, ArH), 7.48 (s, 1H, ArH); δ_C (100.6 MHz; $CDCl_3$) −4.3, 18.8, 26.1, 29.8, 45.0, 55.3, 55.4, 60.6, 98.6, 99.0, 113.5, 117.4, 120.2, 127.0, 127.2, 127.6, 127.7, 128.0, 128.1, 128.8, 132.5, 136.3, 136.6, 143.0, 151.2, 156.0, 159.4 (HRMS *m/z* Calc. for $C_{34}H_{40}N_2O_5Si$: *M*, 584.2706. Found: M^+, 584.2708).

Regioisomer 17 of kealiiquinone

A mixture of compound **16** (8 mg, 0.0014 mmol) and 20% $Pd(OH)_2$/C (4 mg) in EtOH (0.4 mL) was stirred for 48 h under H_2 (4.2 kg cm^{-2}) at room temperature. The catalyst was removed by filtration with AcOEt and the filtrate was evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$–MeOH 20:1). This product was the corresponding 3-unsubstituted naphthoimidazole (2 mg, 29%), mp 290–291 °C (pale yellow crystals, recrystallized from AcOEt–*n*-hexane); ν_{max} ($CHCl_3$) 3200, 2916, 1704, 1459, 1243, 1113, 1077, 830 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 0.26 [s, 6H, $Si(CH_3)_2$], 1.10 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], 2.87 (s, 3H, NCH_3), 3.69 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.44 (s, 1H, ArH), 7.03 (d, *J* 8.8 Hz, 2H, ArH), 7.32 (d, *J* 8.8 Hz, 2H, ArH), 7.67 (s, 1H, ArH), 9.09 (s, 1H, NH); δ_C (100.6 MHz; $CDCl_3$) −4.2, 18.9, 26.2, 29.3, 55.3, 55.4, 60.6, 98.6, 99.7, 113.5, 117.5, 120.4, 126.2, 127.6, 127.9, 129.1, 132.5, 136.7, 143.1, 151.2, 156.0, 159.4 (Calc. for $C_{27}H_{34}N_2O_5Si$: C, 65.56; H, 6.93; N, 5.66. Found: C, 65.27; H, 6.83; N, 5.72%. HRMS *m/z* Calc. for $C_{27}H_{34}N_2O_5Si$: *M*, 494.2237. Found: M^+, 494.2232).

A solution of TBAF in THF (1 M; 0.07 mL, 0.073 mmol) was added dropwise to a solution of the above 3-unsubstituted naphthoimidazole (18 mg, 0.036 mmol) in THF at room temperature. The mixture was stirred for 5 min at room temperature, salcomine (1 mg, 0.004 mmol) was added, and the whole was stirred for 1 h at room temperature. The solvent was evaporated off, and the crude product was purified by column chromatography ($CHCl_3$–MeOH 20:1) to give the target compound **17** (5 mg, 35%), mp 261–262 °C (yellow needles, recrystallized from AcOEt) (Calc. for $C_{21}H_{18}N_2O_6 \cdot 1/2H_2O$: C, 62.53; H, 4.75; N, 6.94. Found: C, 62.62; H, 4.59; N, 6.76%. HRMS *m/z* Calc. for $C_{21}H_{18}N_2O_6$: *M*, 394.1165. Found: M^+, M^+, 394.1166).

in vitro Growth inhibition of 39 human cancer cell lines

39 Human cancer cells were five breast cancers (HBC-4, BSY-1, HBC-5, MCF-7, and MDA-MB-231), six central-nervous-system cancers (U251, SF-268, SF-295, SF-539, SNB-75, and SNB-78), five colon cancers (HCC2998, KM-12, HT-29, HCT-15, and HCT-116), seven lung cancers (NCI-H23, NCI-H226, NCI-H522, NCI-H460, A549, DMS273, and DMS114), melanoma (LOX-IMVI), five ovarian cancers (OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3), two renal cancers (RXF-631L and ACHN), six stomach cancers (St-4, MKN1, MKN7, MKN28, MKN45, and MKN74), and two prostate cancers (DU-145 and PC-3). The cells were plated at appropriate density in 96-well plates in RPMI-1640 medium with 10% foetal bovine serum, and allowed to attach overnight. Kealiiquinone and the regio-isomer **17** were dissolved in DMSO, and further diluted with RPMI-1640 medium. The cells in the wells were treated with the samples at concentrations of 0.01 to 100 μM. After 48 h, cell growth was determined by means of the sulforhodamine B assay described by Skehan *et al.*[13] Data treatment followed the method described by Monks *et al.*[14] The LC_{50} is given as the concentration at which

only 50% of the cells are viable, the GI_{50}-value is given as the concentration that yields 50% growth, and the total growth inhibition (TGI) is given as the concentration at which no growth is observed.

Acknowledgements

We are grateful to Dr Takao Yamori (Japanese Foundation for Cancer Research, Screening Committee of New Anticancer Agents supported by Grant-in-Aid for Scientific Research on Priority Area 'Cancer' from The Ministry of Education, Science, Sports and Culture of Japan) for evaluation of antitumour activity. This research was financially supported in part by the Frontier Research Program of the Ministry of Education, Science, Sports and Culture of Japan.

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