Total Synthesis of Kealiiquinone, an Imidazole Marine Alkaloid

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Received February 27, 1997; accepted May 23, 1997

The total synthesis of kealiiquinone (1), a highly substituted imidazole marine alkaloid isolated from sponge, was achieved *via* nine reaction steps starting from 1-methyl-1*H*-imidazole (5). The synthesis is based on the selective introduction of appropriate carbogenic substituents and protecting groups into the imidazole ring followed by an intramolecular cyclization of the substituents on the *C*4- and the *C*5-positions. The structure of the synthesized kealiiquinone was confirmed by X-ray crystallographic analysis.

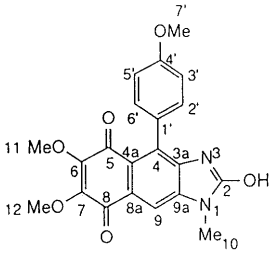
Key words imidazole; 1-methyl-1*H*-imidazole; marine alkaloid; kealiiquinone; lithiation; total synthesis

Many marine imidazole alkaloids have recently been isolated, and most of them exhibit biological activities such as antibacterial and antitumor activities.[1] The imidazole alkaloids, kealiiquinone (**1**)[2] and pyronaamidine (**2**), were isolated from a marine sponge, *Leucetta-chagosensis*, by Scheuer's group in 1990.[3] Compound **2** is cytotoxic to KB cells, and compound **1** is regarded as a metabolite of **2**. The structure elucidation of **1** was finally achieved by X-ray crystallographic analysis (Fig. 1).[3] We have investigated the synthesis and biological activities of imidazole compounds and related natural products.[4] During recent years, the metalation chemistry of the imidazole ring has been developed,[5] and in this paper we wish to report the total synthesis of **1** starting from 1-methyl-1*H*-imidazole (**5**) *via*/*C*2-, *C*4- and *C*5-lithiations of the imidazole nucleus.

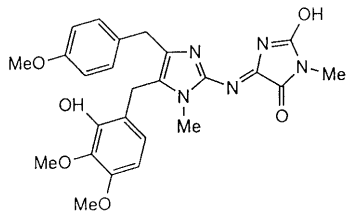
Our strategy for the total synthesis of **1** is shown in Chart 1. A tetra-substituted imidazole (**4**) can be derived from **5** by successive introductions of two different types of benzyl groups at the 5- and 4-positions of the imidazole ring by application of the previously reported procedure for the introduction of carbogenic substituents into the 4- and/or 5-position of imidazole.[5b,5c] The fused tricyclic compound (**3**) should be obtained *via* intramolecular Friedel-Crafts alkylation of **4** followed by aromatization of the central ring and subsequent oxidation of the 2-position of the imidazole ring (Chart 1).

First, we planned the introduction of a carbogenic substituent into the 5-position of the imidazole nucleus by using an appropriate lithioimidazole. As shown in Chart 2, the 5-substituted imidazole (**9**) was prepared according to the previous paper starting from 1-methyl-2-phenylthio-1*H*-imidazole (**6**) in 89% yield.[5c] The secondary alcoholic hydroxy group of **9** was protected with a methoxymethyl (MOM) group,[5c] *tert*-butyldimethylsilyl (TBS) group or methyl group in the usual manner to give **10a**,[5c] **10b** and **10c** in good yields, respectively.

Next, we attempted to generate the corresponding carbanion at the 4-position of **10a—c** with various lithiating agents such as lithiumdiisopropylamide (LDA), lithium-2,2,6,6-tetramethylpiperidine (LTMP), *n*-BuLi, *sec*-BuLi and *tert*-BuLi; however, most of the starting material was recovered in all cases.[5b] The direct lithiation of **10a—c** was difficult, so we next planned indirect lithiation at the 4-position of the imidazole ring *via* 4-bromoimidazole.[5b] Thus, the corresponding bromides (**11a**,[5b] **11b**, **11c**) were prepared by treatment with *N*-bromosuccinimide (NBS) in tetrahydrofuran (THF) or ether at −30 °C to room temperature in moderate yields (59—64%). The corresponding 4-lithioimidazoles (**12a—c**) could be generated by treatment with the bromide (**11a—c**) with two equivalents of *tert*-BuLi in ether at −78 °C, and then the reaction was quenched with *p*-anisaldehyde to give a diastereomeric mixture of the 4,5-di(hydroxyphenylmethyl)imidazoles (**4a**,[5b] **4b**, **4c**) (diastereomeric ratio



Kealiiquinone (1)



Pyronaamidine (2)

Fig. 1

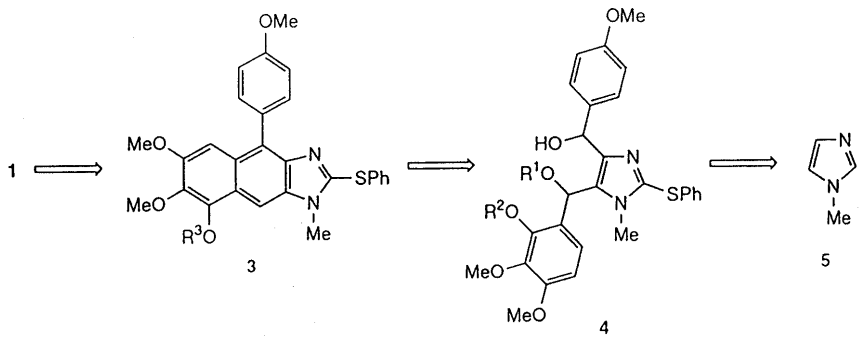


Chart 1

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= *ca.* 1 : 2; estimated from the NMR spectra of these mixtures) in moderate to good yields (37—80%) (Chart 2).

Compounds **4a** and **4b** with protecting groups such as MOM and TBS were treated with polyphosphoric acid (PPA) for intramolecular Friedel–Crafts type alkylation, but in every case only a complex mixture was obtained. These poor results may be due to use of the acid-sensitive protecting groups (MOM and/or TBS). On the other hand, the imidazole (**4c**) with an acid-stable methoxy group was smoothly cyclized in the presence of PPA in acetic anhydride at 0 °C for 5 min to give the desired tricyclic naphthoimidazole (**13**) in 99% yield (Chart 3).

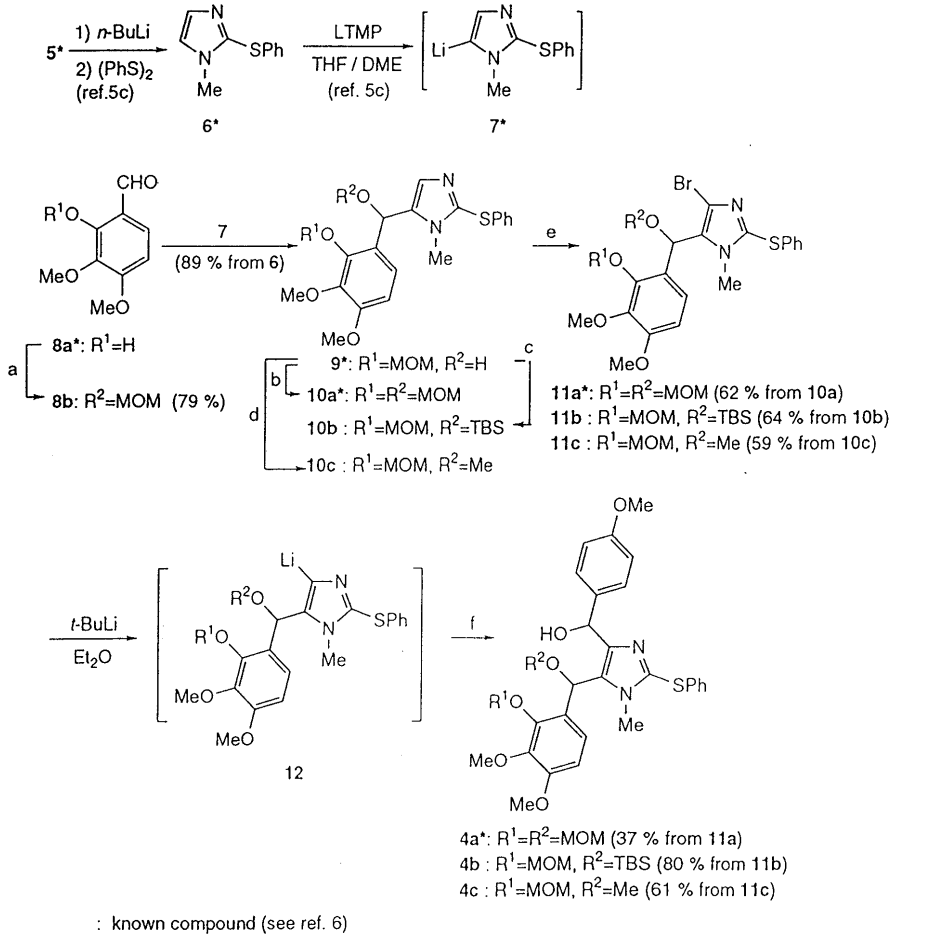

Chart 2. a: $MOMCl/Et_3N/DMAP/CH_2Cl_2$; b: NaH/MOMCl/DMF (88%); c: TBSCl/imidazole/DMF (100%); d: NaH/MeI/DMF (99%); e: NBS/THF or Et_2O; f: *p*-anisaldehyde

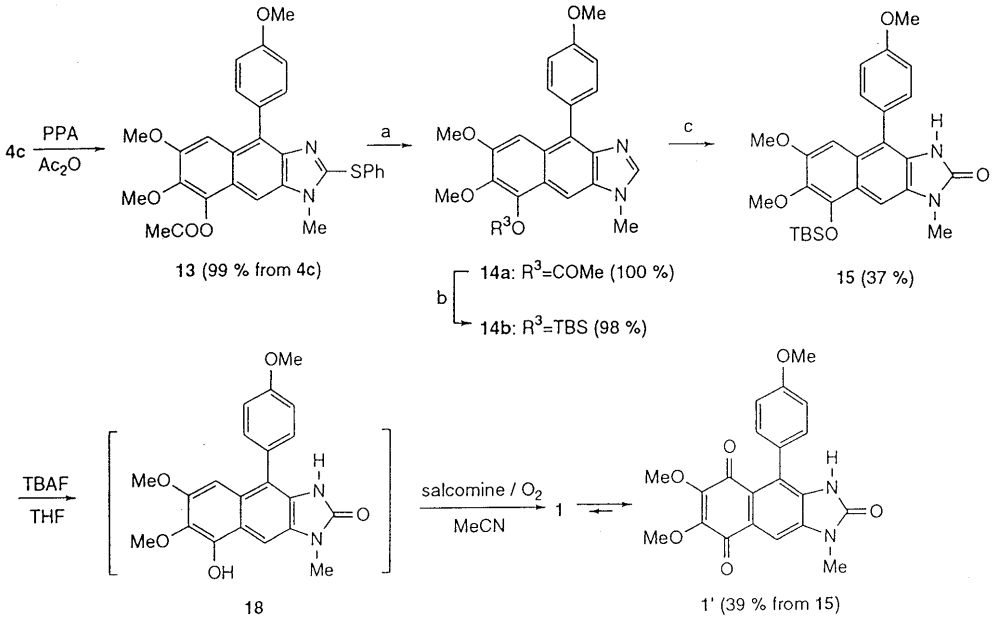

Chart 3. a: $NaBH_4/NiCl_2/MeOH/THF$; b: 1) $K_2CO_3/MeOH/H_2O$, 2) TBSCl/imidazole/DMF; c: 1) $LDA/(PhCH_2OCOO)_2$, 2) H_2O

A possible reaction mechanism for the conversion of **4c** to **13** is shown in Chart 4. This mechanism involves an intramolecular Friedel-Crafts type cyclization of **4c**, the benzylic hydroxy group of which is protected by the acid-stable methoxy group. The phenolic hydroxy group of the initially formed intermediate is quickly acetylated *in situ*. The acetylation may help to prevent possible side-reactions such as phosphorylation and autooxidation of the intermediate.

Compound **13** was treated with nickel boride[7] at 0 °C for reductive desulfurization to give **14a** in quantitative yield. Conversion of the acetyl group of **14a** to a siloxy group was performed by hydrolysis with aqueous sodium carbonate, followed by treatment with TBS chloride in the presence of 1*H*-imidazole to give **14b** in 98% overall yield from **14a**. Reaction conditions for the introduction of a hydroxy group into the 2-position of **14b** *via* the corresponding 2-lithio intermediate, generated from **14b** by treatment with LDA,[8] were examined by using several oxidizing agents, such as oxygen gas,[9] camphorsulfonyloxaziridine (Davis reagent),[10] (TMSO)[11] and dibenzylperoxydicarbonate.[12] The hydroxynaphthoimidazole (**15**) was obtained in 37% yield by oxidation with dibenzylperoxydicarbonate and LDA at −78 °C in THF. The silyloxy group of **15** was removed by treatment with tetrabutylammonium fluoride (TBAF) to give the dihydroxynaphthoimidazole (**18**), which was finally subjected to salcomin-mediated autooxidation under an oxygen atmosphere[13] to afford red needles [mp 290—292 °C (lit. mp 300 °C (dec.)[3])] of kealiiquinone in 39% overall yield from **15**.

Melting point and ^{1}H-NMR spectral data of the synthetic kealiiquinone were similar to the reported values for the natural product, but the IR, UV and ^{13}C-NMR spectral data were somewhat different from the reported values, as shown Table 1.[2] These deviations may reflect different conditions for the spectral measurements, and we speculate that a tautomeric equilibrium as shown in Chart 3 may also be significant. Thus, we conducted an X-ray crystallographic analysis of the synthetic sample of **1**. It was clarified that the synthetic kealiiquinone takes a dimeric structure consisting of two imidazolone

Table 1. Spectral Data for Kealiiquinone

	Synthetic product	Natural product
^{1}H-NMR[a]	11.03 (br, 1H), 7.68 (s, 1H), 7.13 (d, 2H, J=8.8 Hz), 6.98 (d, 2H, J=8.8 Hz), 3.94 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.39 (s, 3H)	7.69 (s, 1H), 7.12 (d, 3H), 6.88 (d, 2H), 3.92 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.58 (s, 3H)
^{13}C-NMR[a]	181.31, 181.13, 158.53, 154.76, 147.79, 133.97, 132.60, 129.86, 127.66, 126.50, 126.46, 123.49, 122.64, 113.89, 104.56, 60.76, 55.04, 26.80	182.39, 181.83, 158.97, 158.28, 148.20, 147.82, 145.96, 137.89, 131.06, 130.64, 129.44, 124.07, 122.88, 113.27, 105.46, 61.04, 55.43, 29.18
IR[b]: ν_{max} (cm^{-1})	1719, 1657, 1624, 1511, 1458, 1339, 1302, 1243, 1219, 1197, 1172, 1103, 1053	1654, 1647, 1618, 1597, 1541, 1511, 1353, 1309, 1286, 1235, 1176, 1033
UV[c]: λ_{max} (log ε)	209 (4.53), 286 (4.63), 369 (3.48)	230 (4.18), 296 (4.35), 388 (3.14)

a) Measured in DMSO-d_6. *b*) Measured for a thin film from $CHCl_3$ and also in a KBr tablet: 1722, 1665, 1632, 1601, 1529, 1335, 1305, 1253, 1201, 1054 (cm^{-1}). *c*) Measured in MeOH.

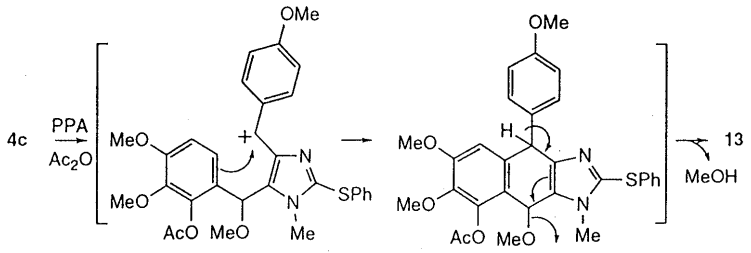

Chart 4

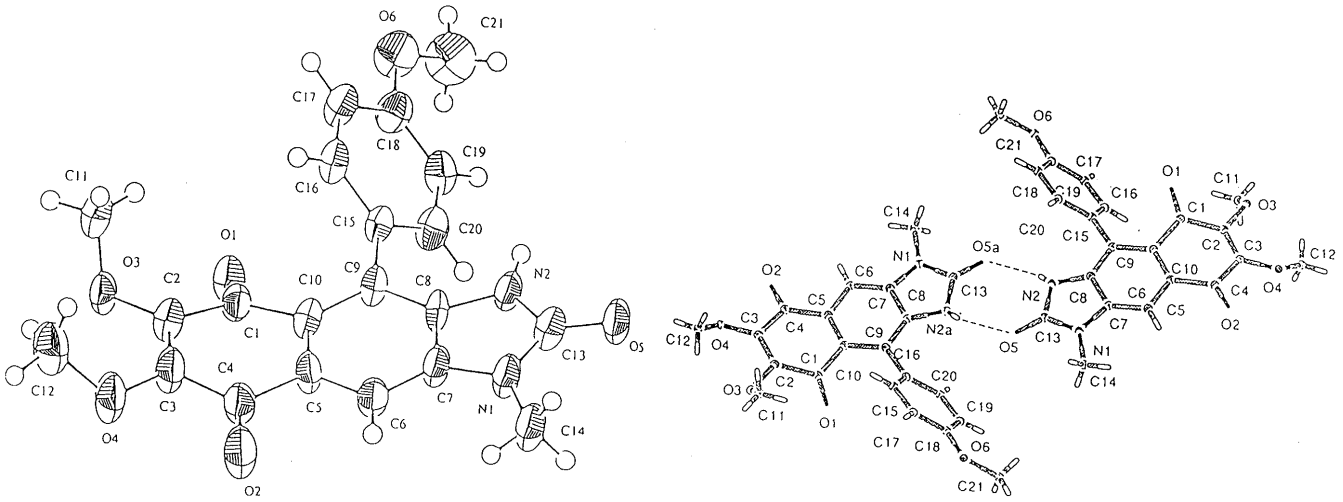

Fig. 2. X-Ray Structure of Synthetic Kealiiquinone **1'**

Table 2. Atomic Coordinates and B_{iso}/B_{eq}

Atom	x	y	z	B_{eq}
O(1)	0.5769 (3)	0.3297 (3)	−0.152 (1)	4.4 (1)
O(2)	0.4285 (4)	0.1034 (3)	0.236 (2)	6.1 (2)
O(3)	0.3909 (3)	0.3972 (3)	0.021 (1)	4.0 (1)
O(4)	0.3091 (3)	0.2679 (3)	0.191 (2)	5.2 (1)
O(5)	0.9633 (3)	−0.0914 (3)	0.538 (1)	4.6 (1)
O(6)	0.9215 (4)	0.4115 (3)	0.018 (1)	5.3 (2)
N(1)	0.7979 (4)	−0.0497 (3)	0.428 (2)	4.1 (2)
N(2)	0.8683 (4)	0.0466 (4)	0.342 (2)	3.7 (2)
C(1)	0.5509 (5)	0.2830 (4)	0.019 (2)	3.6 (2)
C(2)	0.4456 (5)	0.3119 (4)	0.087 (2)	3.8 (2)
C(3)	0.4053 (5)	0.2526 (5)	0.156 (2)	4.2 (2)
C(4)	0.4660 (5)	0.1581 (5)	0.201 (2)	4.1 (2)
C(5)	0.5727 (4)	0.1344 (4)	0.210 (2)	3.5 (2)
C(6)	0.6271 (5)	0.0482 (4)	0.299 (2)	3.8 (2)
C(7)	0.7257 (5)	0.0270 (4)	0.329 (2)	3.7 (2)
C(8)	0.7703 (5)	0.0895 (4)	0.278 (2)	3.6 (2)
C(9)	0.7189 (5)	0.1755 (4)	0.177 (2)	3.4 (2)
C(10)	0.6158 (5)	0.1970 (4)	0.146 (2)	3.5 (2)
C(11)	0.4139 (5)	0.4639 (5)	0.227 (2)	4.5 (2)
C(12)	0.2506 (5)	0.3509 (6)	0.342 (2)	5.5 (2)
C(13)	0.8849 (5)	−0.0362 (5)	0.446 (2)	4.1 (2)
C(14)	0.7842 (5)	−0.1313 (4)	0.512 (2)	5.0 (2)
C(15)	0.7717 (5)	0.2385 (4)	0.139 (2)	3.2 (2)
C(16)	0.7418 (5)	0.3247 (4)	0.276 (2)	3.8 (2)
C(17)	0.7933 (5)	0.3801 (4)	0.238 (2)	4.3 (2)
C(18)	0.8760 (5)	0.3502 (5)	0.050 (2)	3.9 (2)
C(19)	0.9084 (5)	0.2649 (5)	−0.078 (2)	3.9 (2)
C(20)	0.8556 (5)	0.2097 (4)	−0.038 (2)	3.8 (2)
C(21)	1.0079 (7)	0.3818 (6)	−0.161 (3)	6.4 (3)
H(2N)	0.908 (5)	0.073 (4)	0.36 (2)	3.7000
H(6)	0.5971	0.0060	0.3382	3.8000
H(11A)	0.4794	0.4583	0.2004	4.5000
H(11B)	0.3724	0.5213	0.1637	4.5000
H(11C)	0.4048	0.4568	0.4530	4.5000
H(12A)	0.2752	0.3575	0.5625	5.6000
H(12B)	0.2522	0.3983	0.2157	5.6000
H(12C)	0.1858	0.3521	0.3470	5.6000
H(14A)	0.7176	−0.1247	0.4817	5.0000
H(14B)	0.8215	−0.1795	0.3717	5.0000
H(14C)	0.8048	−0.1428	0.7382	5.0000
H(16)	0.6844	0.3461	0.3991	3.9000
H(17)	0.7727	0.4388	0.3397	4.4000
H(19)	0.9670	0.2429	−0.1943	4.0000
H(20)	0.8777	0.1504	−0.1337	3.8000
H(21A)	1.0541	0.3320	−0.0577	6.5000
H(21B)	0.9939	0.3646	−0.3841	6.5000
H(21C)	1.0337	0.4286	−0.1616	6.5000

molecules **1′**, as shown in Fig 2. The 2-imidazolone structure **1′** is also supported by the presence of a $\nu C=O$ absorption in the IR spectra both in KBr tablet (1722 cm^{-1}) and in $CHCl_3$ solution (1719 cm^{-1}). In the case of the intermediate 2-hydroxynaphthoimidazole (**15**), a strong absorption assigned to its carbonyl function was also observed at 1709 cm^{-1} (in $CHCl_3$). Furthermore, the heat of formation of these tautomers (**1**, **1′**) was calculated by using the PM3 method (MOPAC Ver. 6.01),[14] which indicated that the keto form (**1′**; −138.1 kcal/mol) is more stable than the enol form (**1**; −124.7 kcal/mol). Scheuer reported the hydroxy structure (**1**) for kealiiquinone[3] on the basis of an X-ray crystallographic analysis.[15] At the present stage, it can be presumed that the kealiiquinone molecule takes two forms (**1**, **1′**) in a tautomeric equilibrium, which is influenced by the medium conditions.

Table 3. Bond Lengths (Å)

O1–C1	1.219 (8)	O2–C4	1.206 (8)	O3–C2	1.357 (8)
O3–C11	1.423 (9)	O4–C3	1.365 (8)	O4–C12	1.426 (9)
O5–C13	1.237 (8)	O6–C18	1.381 (8)	O6–C21	1.421 (9)
N1–C7	1.381 (8)	N1–C13	1.367 (9)	N1–C14	1.452 (9)
N2–C8	1.381 (9)	N2–C13	1.354 (8)	C1–C2	1.494 (9)
C1–C10	1.481 (10)	C2–C3	1.334 (9)	C3–C4	1.482 (9)
C4–C5	1.481 (9)	C5–C6	1.393 (9)	C5–C10	1.403 (9)
C6–C7	1.370 (9)	C7–C8	1.404 (10)	C8–C9	1.396 (9)
C9–C10	1.433 (9)	C9–C15	1.491 (9)	C15–C16	1.380 (9)
C15–C20	1.385 (9)	C16–C17	1.372 (10)	C17–C18	1.395 (10)
C18–C19	1.356 (9)	C19–C20	1.385 (9)	N2–H2N	0.82 (7)
C6–H6	0.95	C11–H11A	0.95	C11–H11B	0.95
C11–H11C	0.95	C12–H12A	0.95	C12–H12B	0.95
C12–H12C	0.95	C14–H14A	0.95	C14–H14B	0.95
C14–H14C	0.95	C16–H16	0.95	C17–H17	0.95
C19–H19	0.95	C20–H20	0.95	C21–H21A	0.95
C21–H21B	0.95	C21–H21C	0.95		

Table 4. Bond Angles (°)

C2–O3–C11	115.0 (5)	C3–O4–C12	119.0 (6)
C18–O6–C21	116.9 (6)	C7–N1–C13	109.2 (5)
C7–N1–C14	125.9 (6)	C13–N1–C14	124.9 (5)
C8–N2–C13	110.3 (6)	O1–C1–C2	117.6 (6)
O1–C1–C10	124.2 (6)	C2–C1–C10	118.0 (6)
O3–C2–C1	116.8 (6)	O3–C2–C3	121.5 (6)
C1–C2–C3	120.8 (6)	O4–C3–C2	127.1 (6)
O4–C3–C4	112.4 (6)	C2–C3–C4	120.5 (6)
O2–C4–C3	120.2 (6)	O2–C4–C5	121.7 (6)
C3–C4–C5	118.0 (6)	C4–C5–C6	116.2 (6)
C4–C5–C10	121.4 (6)	C6–C5–C10	122.3 (6)
C5–C6–C7	116.9 (6)	N1–C7–C6	130.9 (6)
N1–C7–C8	107.1 (6)	C6–C7–C8	121.9 (6)
N2–C8–C7	106.0 (5)	N2–C8–C9	131.0 (6)
C7–C8–C9	123.0 (6)	C8–C9–C10	114.7 (6)
C8–C9–C15	119.5 (6)	C10–C9–C15	125.6 (5)
C1–C10–C5	116.9 (6)	C1–C10–C9	121.7 (6)
C5–C10–C9	121.2 (5)	O5–C13–N1	125.0 (6)
O5–C13–N2	127.7 (7)	N1–C13–N2	107.3 (6)
O9–C15–C16	123.1 (6)	C9–C15–C20	119.3 (6)
C16–C15–C20	117.6 (6)	C15–C16–C17	121.1 (6)
C16–C17–C18	120.0 (6)	O6–C18–C17	115.8 (6)
O6–C18–C19	124.4 (6)	C17–C18–C19	119.8 (6)
C18–C19–C20	119.5 (6)	C15–C20–C19	121.8 (6)
C8–N2–H2N	123 (4)	C13–N2–H2N	124 (4)
C5–C6–H6	121.6	C7–C6–H6	121.5
O3–C11–H11A	109.5	O3–C11–H11B	109.4
O3–C11–H11C	109.4	H11A–C11–H11B	109.5
H11B–C11–H11C	109.4	H11C–C11–H11A	109.6
O4–C12–H12A	109.4	O4–C12–H12B	109.4
O4–C12–H12C	109.5	H12A–C12–H12B	109.5
H12B–C12–H12C	109.5	N12C–C12–H12A	109.5
N1–C14–H14A	109.5	N1–C14–H14B	109.4
N1–C14–H14C	109.3	H14A–C14–H14B	109.7
H14B–C14–H14C	109.5	H14C–C14–H14A	109.5
C15–C16–H16	119.4	C17–C16–H16	119.5
C16–C17–H17	120.0	C18–C17–H17	120.0
C18–C19–H19	120.3	C20–C19–H19	120.2
C15–C20–H20	119.0	C19–C20–H20	119.1
O6–C21–H21A	109.4	O6–C21–H21B	109.5
O6–C21–H21C	109.5	H21A–C21–H21B	109.4
H21B–C21–H21C	109.5	H21C–C21–H21A	109.4

Experimental

All melting points were measured with a Yanaco MP micro-melting point apparatus, without correction. IR were taken with a Shimadzu IR-410 spectrometer. ^{1}H-NMR spectra and ^{13}C-NMR spectra were obtained on a Varian XL-300 (300 MHz for ^{1}H and 75.4 MHz for ^{13}C). The chemical shifts are given 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); m (multiplet). Mass spectra (MS) and high-resolution mass spectra (HR-MS) were obtained on a JEOL JMS-SX 102A QQ spectrometer. Silica gel (Merck Art. 7734) and Nacalai Tesque Silica gel 60 PF_{254} was used for column chromatography and preparative thin layer chromatography (PTLC), respectively.

5-[1-(*tert*-Butyldimethylsiloxy)-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (10b) A mixture of **9** (1.251 g, 3.0 mmol), imidazole (1.53 g, 22.5 mmol) and TBS chloride (1.440 g, 9.6 mmol) in dimethylformamide (DMF) (4 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. The crude product was purified by column chromatography (AcOE/*n*-hexane = 1/3). Yield, 1.59 g (100%). Colorless viscous oil. IR ($CHCl_3$): 2947, 2920, 1282, 1083, 1067. ^{1}H-NMR ($CDCl_3$): −0.09 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 3.43 (s, 3H), 3.54 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 4.99 (d, 1H, J = 5.5 Hz), 5.11 (d, 1H, J = 5.5 Hz), 6.17 (s, 1H), 6.73 (d, 1H, J = 8.7 Hz), 6.89 (s, 1H), 7.05—7.30 (m, 6H). HR-MS m/z: Calcd for $C_{27}H_{38}N_2O_5SSi$, 530.2270. Found, 530.2280 (M^+).

5-[1-Methoxy-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)]-1-methyl-2-phenylthio-1*H*-imidazole (10c) Sodium hydride (29 mg, 1.2 mmol) was added to a solution of **9** (417 mg, 1.0 mmol) in DMF (4 ml) under an N_2 atmosphere at 0 °C. The mixture was stirred for 15 min at room temperature, then recooled to 0 °C. Iodomethane (170 mg, 1.2 mmol) was added dropwise to the solution, and the whole was stirred for 1 h at room temperature. Water (3 ml) was added, and the mixture was extracted with ether. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography (AcOE/*n*-hexane = 1/1). Yield, 427 mg (99%). Colorless viscous oil. IR ($CHCl_3$): 2973, 1598, 1491, 1450, 1284, 1154, 1084. ^{1}H-NMR ($CDCl_3$): 3.35 (s, 3H), 3.39 (s, 3H), 3.63 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 4.99 (d, 1H, J = 5.5 Hz), 5.17 (d, 1H, J = 5.5 Hz), 5.67 (s, 1H), 6.69 (s, 1H), 6.78 (d, 1H, J = 8.6 Hz), 7.13—7.28 (m, 6H). HR-MS m/z: Calcd for $C_{22}H_{26}N_2O_5S$, 430.1560. Found, 430.1536 (M^+).

4-Bromo-5-[1-(*tert*-butyldimethylsiloxy)-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)-methyl]-1-methyl-2-phenylthio-1*H*-imidazole (11b) NBS (178 mg, 1.0 mmol) was added to a solution of **10b** (530 mg, 1.0 mmol) in THF (4 ml) under an N_2 atmosphere at −30 °C, and the whole was stirred for 3 h at −30 °C. Then water (3 ml) was added, and the mixture was extracted with ether. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by PTLC (AcOE/*n*-hexane = 1/2). This product was recrystallized from *n*-hexane. Yield, 390 mg (64%). mp 127—129 °C (colorless needles). IR ($CHCl_3$): 2932, 2920, 1243, 1202, 1086. ^{1}H-NMR ($CDCl_3$): −0.04 (s, 3H), 0.15 (s, 3H), 0.90 (s, 9H), 3.39 (s, 3H), 3.40 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 5.01 (d, 1H, J = 5.3 Hz), 5.16 (d, 1H, J = 5.3 Hz), 6.17 (d, 1H, J = 0.8 Hz), 6.68 (d, 1H, J = 8.8 Hz), 7.05—7.20 (m, 5H), 7.41 (1H, dd, J = 0.9, 8.7 Hz). *Anal.* Calcd for $C_{27}H_{37}BrN_2O_5SSi$: C, 53.19; H, 6.12; N, 4.60. Found: C, 53.13; H, 6.16; N, 4.58.

4-Bromo-5-[1-methoxy-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)]-1-methyl-2-phenylthio-1*H*-imidazole (11c) This compound was obtained from **10c** in a similar manner to that used for the above synthesis of **11a**. The crude product was purified by column chromatography (AcOEt/*n*-hexane = 1/2). Yield, 59%. Pale yellow viscous oil. IR ($CHCl_3$): 2977, 1597, 1490, 1456, 1285, 1156, 1089. ^{1}H-NMR ($CDCl_3$): 3.40 (s, 3H), 3.46 (s, 6H), 3.80 (s, 3H), 3.85 (s, 3H), 5.03 (d, 1H, J = 5.3 Hz), 5.16 (d, 1H, J = 5.3 Hz), 5.72 (s, 1H), 6.66 (d, 1H, J = 8.9 Hz), 7.11—7.26 (m, 6H). EI-MS m/z (relative intensity): 45 (32), 181 (38), 353 (100), 354 (22), 508 (84, M^+), 509 (23, $M^+ + 1$), 510 (89, $M^+ + 2$), 511 (22, $M^+ + 3$). HR-MS m/z: Calcd for $C_{22}H_{25}BrN_2O_5S$, 508.0670. Found, 508.0642 (M^+).

5-[1-(*tert*-Butyldimethylsiloxy)-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)methyl]-4-[1-hydroxy-1-(4-methoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (4b) A solution of *tert*-BuLi in *n*-pentane (1.57 M; 0.43 ml, 0.68 mmol) was added dropwise to a solution of **11b** (207 mg, 0.34 mmol) in ether (13.6 ml) under an N_2 atmosphere at 23 °C. The mixture was stirred for 2 min, then a solution of *p*-anisaldehyde (93 mg, 0.68 mmol) in ether (0.5 ml) was added dropwise at 23 °C. Stirring was continued for 1 h at −78 °C, then water (5 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. The crude product was purified by PTLC (AcOE/*n*-hexane = 1/2) to give **4b** as a diastereomeric mixture (*ca.* 2 : 1). Pale yellow viscous oil. Yield, 181 mg (80%). IR ($CHCl_3$): 2920, 1450, 1241, 1082, 1022. ^{1}H-NMR ($CDCl_3$) of the major isomer: −0.28 (s, 3H), −0.07 (s, 3H), 0.84 (s, 9H), 3.40 (s, 3H), 3.56 (s, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 4.91 (d, 1H, J = 4.9 Hz), 5.10 (d, 1H, J = 4.9 Hz), 6.00 (d, 1H, J = 2.2 Hz) 6.28 (s, 1H), 6.67 (d, 1H, J = 8.7 Hz), 6.80 (d, 2H, J = 8.7 Hz), 7.03—7.38 (m, 9H). HR-MS m/z: Calcd for $C_{35}H_{46}N_2O_7SSi$, 666.2800. Found, 666.2778 (M^+).

4-[1-Hydroxy-1-(4-methoxyphenyl)]-5-[1-methoxy-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)]-1-methyl-2-phenylthio-1*H*-imidazole (4c) This compound was obtained from **11c** in a similar manner to that used for the above synthesis of **4a**. The crude product was purified by PTLC (AcOEt/*n*-hexane = 1/3) to give **4c** as a diastereomeric mixture (*ca.* 2 : 1). Pale yellow viscous oil. Yield, 61%. IR ($CHCl_3$): 2926, 1506, 1451, 1282, 1241, 1213, 1085, 979. ^{1}H-NMR ($CDCl_3$) of the major isomer: 3.17 (s, 3H), 3.44 (s, 3H), 3.46 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 4.95 (d, 1H, J = 5.3 Hz), 5.10 (d, 1H, J = 5.3 Hz), 5.69 (s, 1H), 5.89 (d, 1H, J = 7.6 Hz), 6.57—7.35 (m, 12H). HR-MS m/z: Calcd for $C_{30}H_{34}N_2O_7S$, 566.2090. Found, 566.2098 (M^+).

8-Acetoxy-6,7-dimethoxy-4-(4-methoxyphenyl)-1-methyl-2-phenylthio-1*H*-naphtho[2,3-*d*]imidazole (13) PPA (0.5 ml) was added to a solution of **4c** (192 mg, 0.34 mmol) in acetic anhydride (17 ml) under an N_2 atmosphere at 0 °C, and the whole was stirred for 5 min. Saturated sodium bicarbonate aqueous solution was added to neutralize the mixture, and the product was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give a solid residue, which was recrystallized from AcOEt–*n*-hexane. Yield, 173 mg (99%). mp 191—193 °C (colorless needles). IR ($CHCl_3$): 2980, 1761, 1619, 1482, 1267. ^{1}H-NMR ($CDCl_3$): 2.54 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 7.09 (d, 2H, J = 8.6 Hz), 7.23—7.33 (m, 6H), 7.51 (s, 1H), 7.59 (d, 2H, J = 8.8 Hz). ^{13}C-NMR ($CDCl_3$): 20.8, 31.0, 55.3, 55.7, 60.9, 97.6, 103.5, 113.9, 121.4, 125.6, 127.4, 127.9, 128.4, 129.3, 129.5, 132.3, 132.4, 135.9, 137.8, 139.8, 141.6, 150.5, 151.2, 159.0, 169.3. *Anal.* Calcd for $C_{29}H_{26}N_2O_5S$: C, 67.69; H, 5.09; N, 5.44. Found: C, 67.39; H, 5.05; N, 5.11.

8-Aetoxy-6,7-dimethoxy-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho-[2,3-*d*]imidazole (14a) Sodium borohydride (159 mg, 4.2 mmol) was added to a solution of **13** (103 mg, 0.20 mmol) and nickel(II) chloride hexahydrate (333 mg, 1.4 mmol) in MeOH/THF = 3/1 (10 ml) under an N_2 atmosphere at 0 °C, and the whole was stirred for 1 h. The solvent was evaporated off, then water (3 ml) was added to the residue. The 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 PTLC ($CHCl_3$/MeOH = 20/1). This product was recrystallized from AcOEt–*n*-hexane. Yield, 81 mg (100%). mp 219—221 °C (colorless needles). IR ($CHCl_3$): 2937, 1761, 1625, 1483, 1279. ^{1}H-NMR ($CDCl_3$): 2.56 (s, 3H), 3.82 (s, 3H), 3.91 (s, 6H), 3.96 (s, 3H), 7.11 (d, 2H, J = 8.8 Hz), 7.30 (s, 1H), 7.55 (d, 2H, J = 8.8 Hz), 7.62 (s, 1H), 7.96 (s, 1H). ^{13}C-NMR ($CDCl_3$): 20.8, 31.2, 55.4, 55.7, 60.9, 97.8, 103.3, 114.0, 121.3, 125.4, 128.4, 128.8, 132.0, 134.0, 137.9, 139.7, 142.5, 147.0, 150.5, 159.0, 169.3. *Anal.* Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 67.94; H, 5.33; N, 6.55.

8-(*tert*-Butyldimethylsilyloxy)-6,7-dimethoxy-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho[2,3-*d*]imidazole (14b) Sodium carbonate (41 mg, 0.30 mmol) was added to a solution of **14a** (41 mg, 0.10 mmol) in MeOH/H_2O = 5/1 (12 ml) under an N_2 atmosphere at 0 °C, and the whole was stirred for 1 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 a solid. A mixture of the whole of the solid, imidazole (34 mg, 0.50 mmol), and *tert*-TBS chloride (45 mg, 0.30 mmol) in DMF (1 ml) was stirred for 12 h at 60 °C. Then water (1 ml) was added, and the mixture was extracted with ether. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography ($CHCl_3$/MeOH = 10/1). This product was recrystallized from AcOEt–*n*-hexane. Yield, 47 mg (98%). mp 206—208 °C (colorless needles). IR ($CHCl_3$): 2942, 1619, 1243, 1113, 833. ^{1}H-NMR ($CDCl_3$): 0.30 (s, 6H), 1.18 (s, 9H), 3.81 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 7.04 (s, 1H), 7.11 (d, 2H, J = 8.7 Hz), 7.57 (d, 2H, J = 8.8 Hz), 7.95 (s, 1H), 8.09 (s, 1H). *Anal.* Calcd for $C_{27}H_{34}N_2O_4Si$: C, 67.75; H, 7.16; N, 5.85. Found: C, 67.56; H, 7.15; N, 5.84. HR-MS m/z: Calcd for $C_{27}H_{34}N_2O_4Si$, 478.2290. Found, 478.2282 (M^+).

8-(*tert*-Butyldimethylsiloxy)-2-hydroxy-6,7-dimethoxy-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho[2,3-*d*]imidazole (15) A solution of *n*-BuLi in *n*-hexane (1.6 M; 0.09 ml, 0.15 mmol) was added dropwise to a

solution of diisopropylamine (15 mg, 0.15 mmol) in THF (2 ml) under an N_2 atmosphere at −78 °C. The mixture was stirred for 15 min at −78 °C, then **14b** (70 mg, 0.15 mmol) in THF (1 ml) was added dropwise at −78 °C. Stirring was continued for 2 h at −78 °C, then dibenzylperoxydicarbonate (45 mg, 0.15 mmol) was added, and the whole was stirred for 1 h at room temperature. Water (1 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. The crude product was purified by PTLC (AcOEt/*n*-hexane = 2/1). This product was recrystallized from AcOEt. Yield, 27 mg (37%). mp 228—229 °C (pale yellow needles). IR ($CHCl_3$): 3425, 2924, 1709, 1606, 1468. ^{1}H-NMR ($CDCl_3$): 0.28 (s, 6H), 1.15 (s, 9H), 3.46 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 3.91 (s, 3H), 6.78 (s, 1H), 7.09 (d, 2H, J = 8.7 Hz), 7.39 (d, 2H, J = 8.7 Hz), 7.49 (br, 1H), 7.59 (s, 1H). ^{13}C-NMR ($CDCl_3$): −4.2, 18.9, 26.2, 26.8, 55.4, 55.6, 60.7, 98.0, 98.3, 114.7, 116.6, 121.0, 125.9, 126.4, 127.4, 129.6, 131.1, 136.8, 143.4, 151.5, 155.2, 159.3. HR-MS *m/z*: Calcd for $C_{27}H_{34}N_2O_5Si$, 494.2240. Found, 494.2235 (M^+).

Kealiiquinone (1) A solution of TBAF in THF (1 M; 0.15 ml, 0.15 mmol) was added dropwise to a solution of **15** (15 mg, 0.03 mmol) in THF (1 ml) at room temperature. The mixture was stirred for 5 min at room temperature, then water (1 ml) was added. The whole was extracted with AcOEt and the organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. A mixture of the residue and salcomine (1 mg, 0.003 mmol) in acetonitrile (7 ml) was stirred for 2 h under an O_2 atmosphere at room temperature. The crude product was purified by column chromatography (AcOEt/*n*-hexane = 2/1). This product was recrystallized from AcOEt. Yield, 4.6 mg (39%). mp 290—292 °C (red needles) (lit. mp 300 °C (dec.)). ^{1}H-NMR, ^{13}C-NMR, IR and UV spectral data are given in Table 1. FAB-MS *m/z*: Calcd for $C_{21}H_{18}N_2O_6$, 394.1170. Found, 395.1241 (M + 1). *Anal.* Calcd for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10. Found: C, 63.92; H, 4.70; N, 7.13.

X-Ray Analysis of Kealiiquinone (1) Reflection data were collected on a Rigaku AFC5R diffractometer with filtered Cu/$K\alpha$ radiation and a 12 kW rotating anode generator using the ω-2θ scan mode. Of the total of 2635 reflections, 1181 with intensity above the 3.00s(I) level were used for the structure determination. The structure was solved by a direct method (SHELX86) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen atoms are refined anisotropically. Positional parameters, bond lengths, bond angles and an ORTEP drawing of the molecule are given in Tables 2, 3 and 4, and Fig. 2, respectively. Crystal data: $C_{21}H_{18}N_2O_6$, triclinic, a = 14.713(10) Å, b = 15.995(8) Å, c = 4.026(2) Å, V = 885.6(9) Å^3, Dc = 1.479 g/cm^3, Z = 2. Space group, $P1$(#2). R = 0.066.[16]

Acknowledgement The authors are grateful to Dr. Motoo Shiro (Rigaku Corporation) for the X-ray crystallographic analysis.

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