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Total Synthesis of Kealiiquinone, an Imidazole Marine Alkaloid

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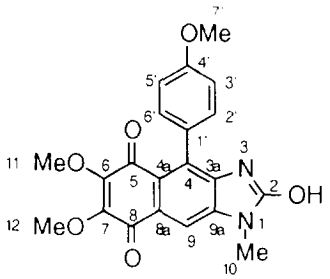
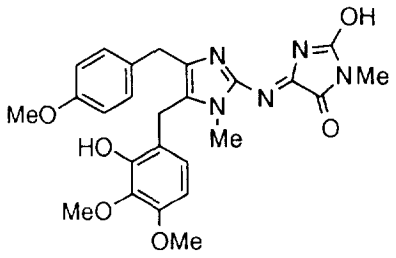
Abstract: The first total synthesis of kealiiquinone 1, the marine alkaloid of a sponge, was achieved starting from 5-[1-hydroxy-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (**5**).

Kealiiquinone **1** and pyrronaamidine **2** are imidazole-containing marine alkaloids, recently isolated from a sponge, *Leucetta* sp., and it was reported that the 2-hydroxyimidazole structure **1** was determined by X-ray crystallography.[1]



kealiiquinone **1**



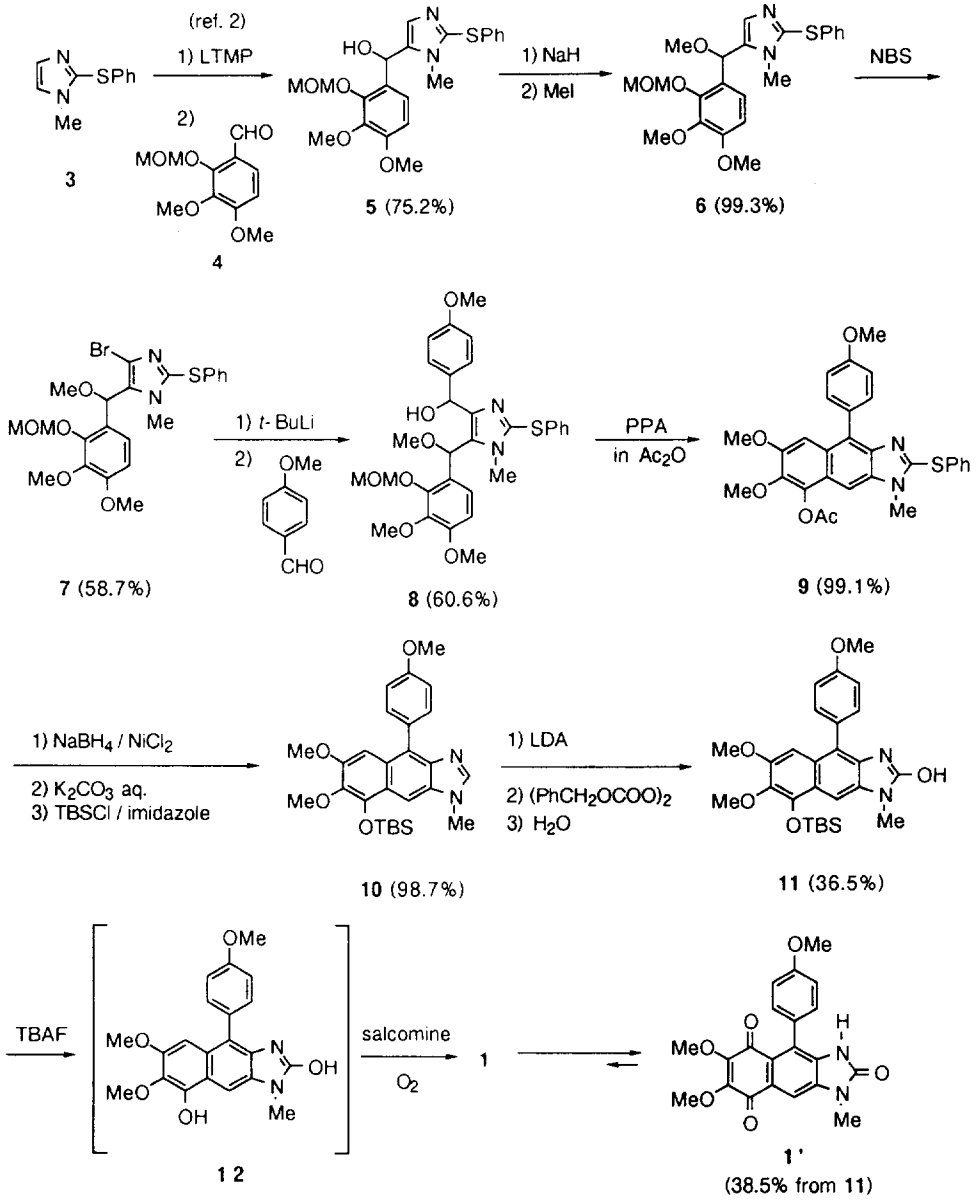
pyronaamidine **2**

Fig. 1

We have been interested in the synthesis and biological activities of imidazole and triazole compounds,[2] and planned the total synthesis of **1** and **2** starting from 1-methyl-1*H*-imidazole. We previously reported a regioselective synthesis of 5-[1-hydroxy-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (**5**) starting from 1-methyl-1*H*-imidazole.[2] The hydroxyl group of the alcohol (**5**) was treated with methyl iodide in the presence of sodium hydride to give quantitatively the methyl ether (**6**), the 4-position of which was brominated with *N*-bromosuccinimide to give the bromide (**7**) in 58.7%. The bromide (**7**) was treated with *t*-BuLi, and the intermediate lithioimidazole was quenched with 4-methoxybenzaldehyde to give a diastereomixture of the alcohol (**8**; diastereomeric ratio = 1 : 2; calculated from its ^{1}H-NMR) in 60.6% yield. Intramolecular Friedel-Crafts alkylation of **8** by treatment with polyphosphoric acid (PPA) furnished a complex mixture probably because of the presence of an acid-sensitive MOM group. When the alcohol (**8**) was treated with a mixture of PPA and acetic anhydride at 0 ℃, the expected cyclization reaction successfully proceeded to give **9** (colorless needles; mp 191 - 193 ℃) as the sole product in quantitative yield. From ^{1}H-NMR,[3] IR and HRMS spectra, the structure of **9** was confirmed to have the same tricyclic skeleton as kealiiquinone (**1**). The success of the cyclization in the system of PPA/acetic anhydride may be attributed to

the simultaneous acetylation of the intermediately formed phenolic hydroxyl group and subsequent aromatization at the central ring.

Scheme



After desulfurization of **9** by reduction with sodium borohydride in the presence of $Ni(II)Cl_2$,[4] hydrolysis of the acetyl ester with an aqueous potassium carbonate, followed by treatment with TBSCl, gave

10 in 98.7 % yield. Next, oxidation of the imidazole ring of **10** was examined, and the best yield (36.5 %) of the desired hydroxy compound (**11**; pale yellow needles, mp 228 - 229 ℃)[5] was obtained by lithiation with LDA followed by oxidation with dibenzyl peroxydicarbonate.[6] The introduction of the hydroxyl group was confirmed by ^{1}H-NMR, in which the signal of the C2 proton of the imidazole ring was not observed. The TBS group of the hydroxyimidazole (**11**) was removed by treating with tetrabutylammonium fluoride (TBAF) to give the dihydroxy compound (**12**), which was finally subjected to autooxidation in the presence of salcomine[7] to afford kealiiquinone [red needles, mp 290 - 292 ℃ (lit. mp 300 ℃ decomp.)[1]] in 38.5 % yield from **11**. Satisfactory spectral and elemental analysis data of the product were obtained,[8] but these data are considerably diferent from those of **1** reported in ref. 1a.[9] X-ray crystallography[10] of the synthetic kealiiquinone indicated that imidazole portion of kealiiquinone has the 2-imidazolone structure **1'** (not the 2-hydroxyimidazole structure **1**) and two molecules of **1'** associate as shown in Fig. 2.[11]

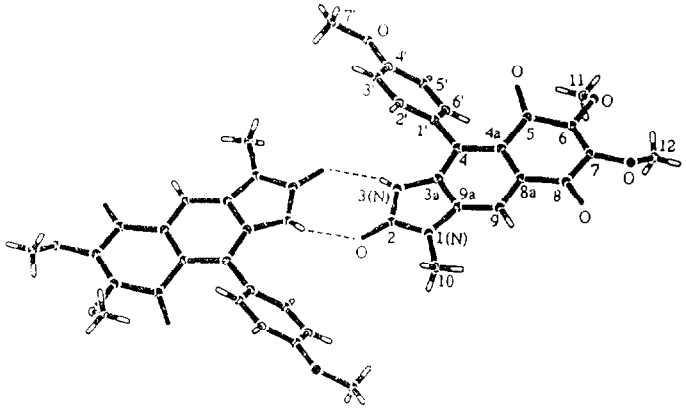


Fig. 2

ACKNOWLEDGEMENT

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2. Ohta, S.; Yamamoto, T.; Kawasaki, I.; Yamashita, M.; Nagashima, Y.; Yoshikawa, T.*Chem. Pharm. Bull.*, **1994**, 42, 821; and literature cited therein.
3. *in* $CDCl_3$ δ: 2.54 (s, 3H, $COCH_3$), 3.73 (s, 3H, $>NCH_3$), 3.82 , 3.90, 3.95 (s each; 3H each, OCH_3 x 3), 7.09 (d, 2H, C3'-H and C5'-H, *J*=8.6Hz), 7.23-7.33 (m, 6H, C5-H and $-SC_6H_5$), 7.51 (s, 1H, C9-H), 7.59 ppm (d, 2H, C2'-H and C6'-H, *J*=8.6Hz).
4. Back, T. G.; Baron, D.L.; Yang, K. *J. Org. Chem.*, **1993**, 58, 2407.
5. IR ($CHCl_3$) ν max: 3425 cm^{-1} (OH). HRMS *m/z*: Calcd for M^+, 494.2240. Found, 494.2235.

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8. Spectral and analytical data of synthetic kealiiquinone (values in [ ] are those of natural one reported in ref. 1a): IR ($CHCl_3$) ν max: 1719, 1657, 1624, 1602, 1511, 1458, 1339, 1302, 1243, 1219, 1197, 1172, 1103, 1053 cm^{-1} [1654, 1647, 1618, 1597, 1541, 1511, 1353, 1309, 1286, 1235, 1176, 1033 cm^{-1}]; IR (KBr) 1722, 1665, 1632, 1601, 1529, 1335, 1305, 1253, 1201, 1054 cm^{-1}; UV (MeOH) λ max (log ε): 209 (4.53), 286 (4.53), 369 nm (3.48) [230 (4.18), 296 (4.35), 388 nm (3.14)]; FABMS *m/z*: Calcd for M+1 ($C_{21}H_{19}N_2O_6$), 395.1240. Found, 395.1241; ^{1}H-NMR (300MHz, DMSO-d_6) δ: 3.39 (s, 3H, 10-Me), 3.82 (s, 3H, 7'-Me), 3.85 (s, 3H, 12-Me), 3.94 (s, 3H, 11-Me), 6.98 (d, 2H, 3'-H and 5'-H, J = 8.8 Hz), 7.13 (d, 2H, 2'-H and 6'-H, J = 8.8 Hz), 7.68 (s, 1H, 9-H), 11.03 ppm (br, 1H, NH) [3.58 (s, 3H, 10-Me), 3.78 (s, 3H, 7'-Me), 3.83 (s, 3H, 12-Me), 3.92 (s, 3H, 11-Me), 6.88 (d, 2H, 3'-H and 5'-H), 7.12 (d, 2H, 2'-H and 6'-H), 7.69 ppm (s, 1H, 9-H)]; ^{13}C NMR (DMSO-d_6) δ: 26.80 (C10), 55.04 (C7'), 60.76 (C11 and C12), 104.56 (C9), 113.89 (C3' and C5'), 122.64 (C4a), 123.49 (C8a), 126.46 (C4), 126.50 (C1'), 127.66 (C2' and C6'), 129.86 (C9a), 132.60 (C7), 133.97 (C3a), 147.79 (C6), 154.76 (C2), 158.53 (C4'), 181.13 (C8), 181.31 ppm (C5) [29.18 (C10) 55.43 (C7'), 61.04 (C11 and C12), 105.46 (C9), 113.27 (C3' and 5'), 122.88 (C4a), 124.07 (C8a), 129.44 (C4), 130.64 (C1'), 131.06 (C2' and C6'), 137.89 (C9a), 145.96 (C7), 147.82 (C3a), 148.20 (C6), 158.28 (C2), 158.97 (C4'), 181.83 (C8), 182.39 ppm (C5)]; *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.

9. The presence of relatively stable tautomers (1 and 1'; see Scheme) at the imidazole ring and certain association with kealiiquinone itself and with the medium may be reasons for the difference. We are now trying to isolate another tautomer (**1**).

10. Empirical Formula: $C_{21}H_{18}N_2O_6$; FW 394.38; crystal system, triclinic; space group, P1(#2); lattice parameter, a = 14.713(10), b = 15.995(8), c = 4.026(2) Å, α = 94.09(5)°, β = 93.78(5)°, γ = 69.74(5)°, V = 885.6(9) $Å^3$; Z value, 2; D_{calc}, 1.479 g/cm^3; Radiation, CuKα (λ = 1.54178 Å); m, 9.21 cm^{-1}; F(000), 412; T, 298; R, 0.066 for 1181 observations. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre.

11. Spectral and analytical data of the new compounds prepared were consistent with the given structures.

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