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New Synthetic Approach to Pyrroloiminoquinone Marine Alkaloids. Total Synthesis of Makaluvamines A, D, I, and K

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Abstract: A new entry into pyrroloiminoquinone marine alkaloids, makaluvamines, has been developed. The key 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline intermediates **11** and **18** were prepared by aryne-mediated cyclization of the 4-chloro-6-methoxytryptamine derivatives **10** and **17**, respectively. The requisite substituents at the indole 4- and 3-positions of **10** and **17** were efficiently assembled by sequential use of directed lithiation of 1-triisopropylsilyl-6-methoxygramine (**6**) and fluoride ion-induced elimination-addition of the methiodide of 4-chloro-1-triisopropylsilyl-6-methoxygramine (**7**) as key reactions.

INTRODUCTION

Pyrroloiminoquinone marine alkaloids based upon 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline nucleus have been received considerable attention due to their unique structures and potentially valuable biological activities.[1] This class of alkaloids comprises discorhabdins,[1a-d] prianosins,[1e-f] isobatzellines,[1g] wakayin,[1h] makaluvamines,[1i-k] tsitsikammanines,[1l] epinardins,[1m] and veiutamine.[1n] Makaluvamines A-F were isolated for the first time by Ireland in 1993 from the Fijian sponge *Zyzzya* cf. *marsailis.*[1i] In the same year, makaluvamine G was isolated from the Indonesian sponge *Histodermella* sp.[1j] More recently, six additional alkaloids, makaluvamines H-M, were isolated by Faulkner from the Pohnpeian sponge *Zyzzya fuliginosa.*[1k] Makaluvamines exhibit *in vitro* cytotoxicity toward the human colon tumor cell-line HCT 116, show differential toxicity toward the topoisomerase II sensitive CHO cell-line xrs, and inhibit topoisomerase II *in vitro.*[1i,2] Makaluvamine A and C exhibit *in vivo* antitumor activity against the human ovarian carcinoma Ovcar 3 implanted in athymic mice.[1i,2]

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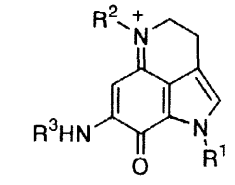
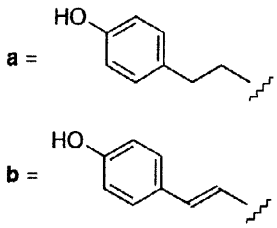
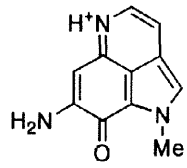


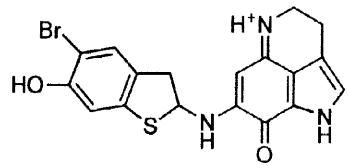
makaluvamines

	R^1	R^2	R^3
A	Me	H	H
C	H	Me	H
D	H	H	a
E	Me	H	b
G	Me	Me	b
H	Me	Me	H
I	H	H	H
J	H	Me	a
K	Me	H	a
L	H	Me	b
M	H	H	b



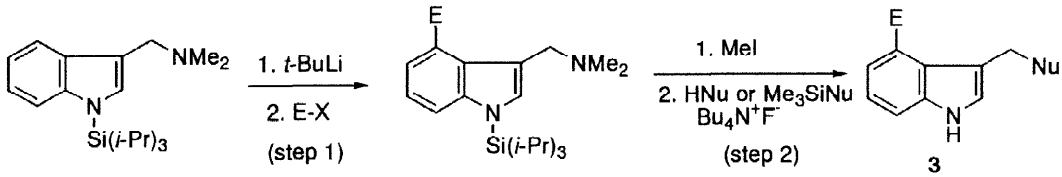


makaluvamine B



makaluvamine F

The synthetic studies toward makaluvamines were carried out by several groups, and the total or formal syntheses of some makaluvamines have been achieved.[3] In this paper, we present a novel approach to the pyrroloiminoquinone nucleus and its application to the total synthesis of makaluvamines A, D, I, and K. The strategy is based upon our own methodology[4] for the synthesis of 3,4-differentially substituted indoles **3**, which consists of two sequential steps; 1) C-4 selective functionalization of the indole ring *via* directed lithiation of 1-(triisopropylsilyl)gramine (**1**) to produce 4-substituted gramines **2** (step 1)[4a] ; 2) functionalization of C-3 side chain by quaternization of **2** followed by fluoride ion-induced elimination-addition reaction with nucleophiles to give **3** (step 2)[4b] (**Scheme 1**). We planned to synthesize 4-halogeno-6-methoxytryptamines from 1-triisopropylsilyl-6-methoxygramine (**6**) by using this methodology and subsequently construct the key tricyclic 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline system *via* aryne-mediated cyclization.[5]

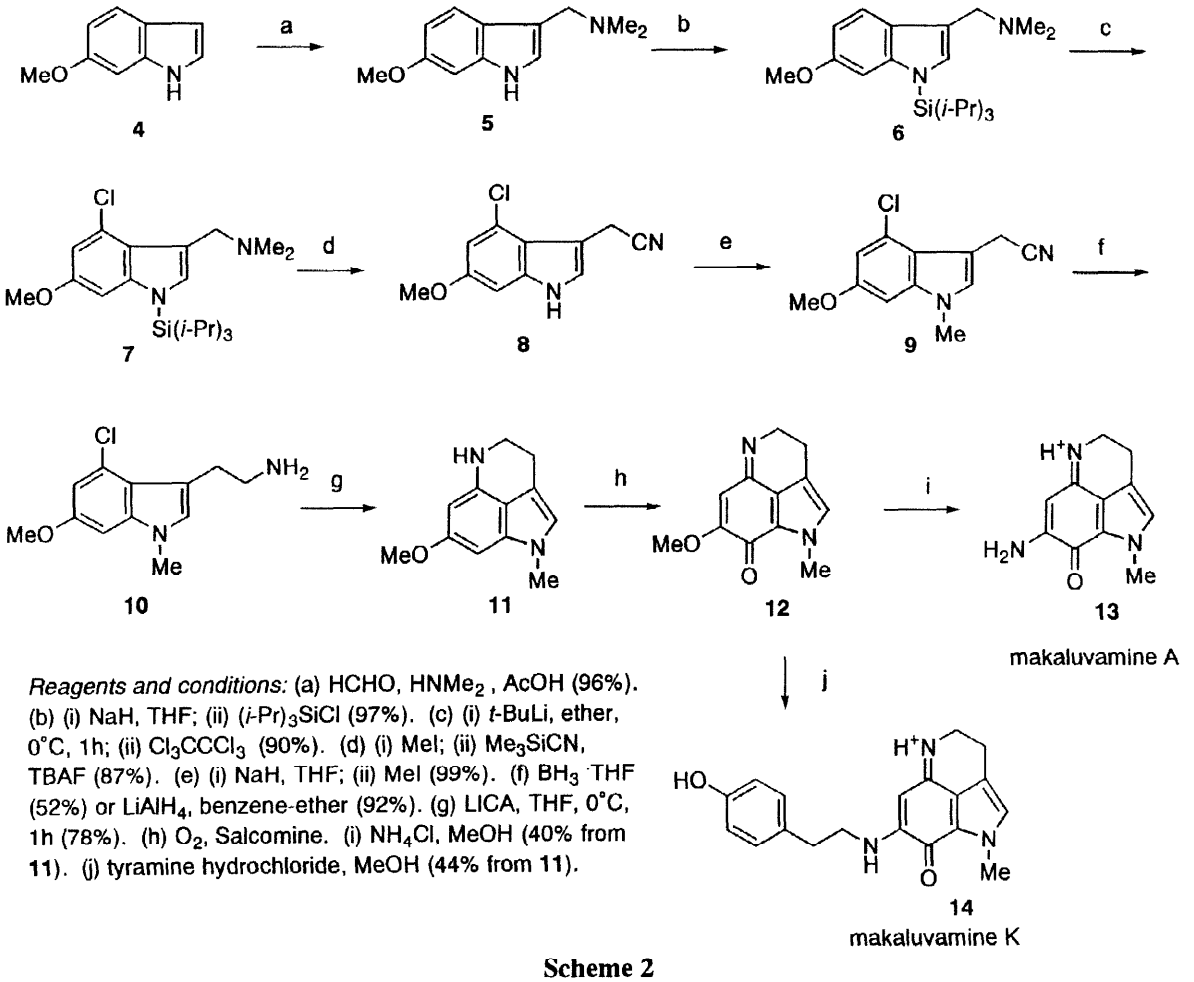


Scheme 1

RESULTS AND DISCUSSION

The total synthesis of makaluvamines A and K (**13** and **14**) is shown in **Scheme 2**. The starting material, 6-methoxyindole (**4**), was readily synthesized from *p*-anisaldehyde in large scale following a procedure of Cook, *et al.* [6] Mannich reaction of **4** afforded 6-methoxygramine (**5**) in 96% yield. Protection of the indole nitrogen with triisopropylsilyl group was effected by the reaction of **5** with NaH and triisopropylsilyl chloride to provide 1-triisopropylsilyl-6-methoxygramine (**6**) in 97% yield. Directed lithiation of **6** under the standard conditions[4a] (1.2 equiv *t*-BuLi, ether, 0°C, 1h) followed by a reaction with hexachloroethane gave the 4-chlorinated compound **7** in 90% yield. The lithiation was highly regioselective and none of the product

derived from other lithiated species was isolated. Quaternization of **7** with MeI, followed by fluoride ion-induced elimination-addition reaction[4b] with trimethylsilyl cyanide in the presence of tetrabutylammonium fluoride (TBAF) produced the nitrile **8** in 87% yield. The indole nitrogen of **8** was methylated by sequential treatment with 1.2 equiv of NaH and 2.0 equiv of MeI at 0°C to give **9** in 99% yield. Reduction of **9** with BH_3·THF complex[7] gave the tryptamine derivative **10** in 52% yield. The yield of **10** was much improved to 92% by heating **9** with large excess of $LiAlH_4$ (LAH) in diluted benzene-ether mixed solvent system.[8]

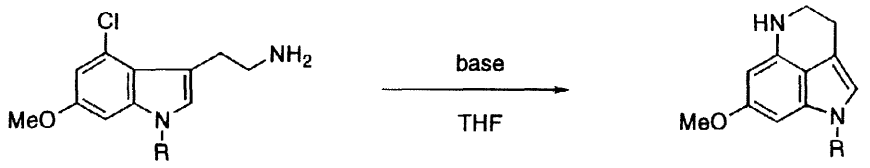


Reagents and conditions: (a) HCHO, $HNMe_2$, AcOH (96%). (b) (i) NaH, THF; (ii) $(i\text{-Pr})_3SiCl$ (97%). (c) (i) *t*-BuLi, ether, 0°C, 1h; (ii) Cl_3CCCl_3 (90%). (d) (i) MeI; (ii) Me_3SiCN, TBAF (87%). (e) (i) NaH, THF; (ii) MeI (99%). (f) BH_3·THF (52%) or $LiAlH_4$, benzene-ether (92%). (g) LICA, THF, 0°C, 1h (78%). (h) O_2, Salcomine. (i) NH_4Cl, MeOH (40% from **11**). (j) tyramine hydrochloride, MeOH (44% from **11**).

Scheme 2

The aryne-mediated cyclization[5] of **10** into the key 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline derivative **11** was examined by using excess (5 equiv) of lithium dialkylamide bases in THF. The results were summarized in **Table 1**. When **10** was allowed to react with lithium diisopropylamide (LDA) at -50~0°C, the cyclized compound **11** was obtained in 54% yield (entry 1). The yields of **11** were slightly improved under the similar conditions (-50~0°C) by using more bulky bases, such as lithium 2,2,6,6-tetramethylpiperidide (LTMP) or lithium isopropylcyclohexylamide (LICA) (entries 2, 3). On the other hand, **11** was produced in much better yield (78%) by allowing **10** to react with LICA at 0°C for 1h (entry 4). Thus, the temperature for aryne generation seems to be critical to achieve successful cyclization. Similar observation has been reported in a related aryne-mediated reaction.[9]

Table 1. Aryne-mediated Cyclization of 4-Chloro-6-methoxytryptamines **10** and **17**.



10: R=Me
17: R=Si(*t*-Bu)Me_2

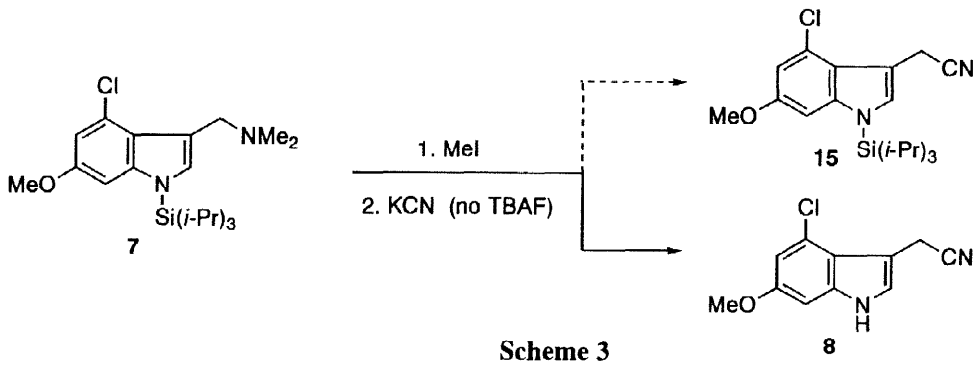
11: R=Me
18: R=Si(*t*-Bu)Me_2

entry	tryptamine	base[a]	temp./time	pyrroloquinoline	yield (%)
1	**10**	LDA	-50°C/1h → 0°C/1h	**11**	54
2	**10**	LTMP	-50°C/1h → 0°C/1h	**11**	56
3	**10**	LICA	-50°C/1h → 0°C/1h	**11**	58
4	**10**	LICA	0°C/1h	**11**	78
5	**17**	LDA	-50°C/1h → 0°C/1h	**18**	18
6	**17**	LDA	0°C/1h	**18**	58
7	**17**	LICA	0°C/1h	**18**	75

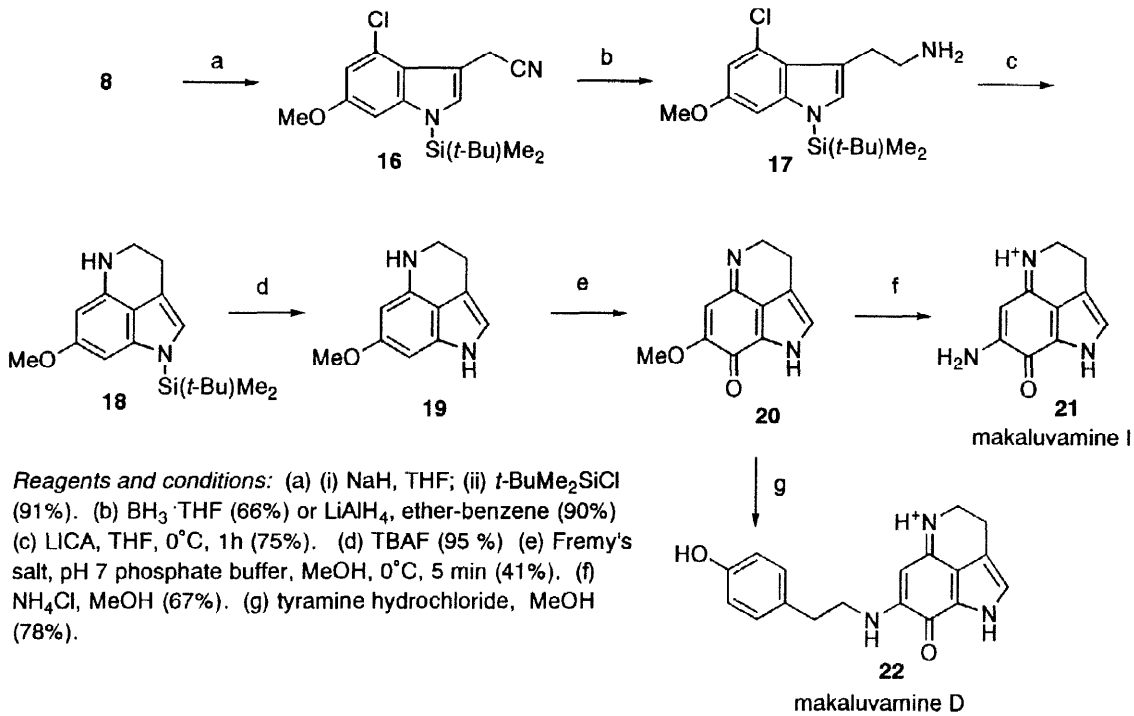
a) The base was used in 5.0 mole equivalents to the tryptamine.

The Fremy's salt oxidation of some aniline derivatives to iminoquinones has been reported.[10] Recently Somei, *et al.* described a successful oxidation of 6-chloro-1-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline to the corresponding iminoquinone with Fremy's salt.[3e] Therefore, we applied Fremy's salt for the oxidation of **11** at first. However, the desired iminoquinone **12** was obtained in very poor yields (<10%) though we had examined a variety of conditions. In contrast, the salcomine-catalyzed O_2 oxidation[11] found to be suitable for this conversion. When oxygen was passed through a mixture of **11** and salcomine in DMF for 2 h, the iminoquinone **12** was produced as a major product. Since it was difficult to isolate pure **12** from some other impurities by chromatography, the impure **12** was used for the next reactions without further purification. The conversion of **12** to makaluvamine A (**13**) has been reported by Yamamura, *et al.* [3a,b] Thus, following the Yamamura's conditions, the crude **12** was reacted with large excess (*ca.* 10 equiv) of ammonium chloride in methanol at room temperature overnight. After chromatographic purifications, makaluvamine A (**13**) was isolated as trifluoroacetate in 40 % overall yield from **11**. The impurities in **12** were readily removed at this stage. A similar reaction of the crude **12** with tyramine hydrochloride produced makaluvamine K (**14**) in 44 % overall yield from **11**. The spectroscopic data (^1H and ^{13}C NMR) of **13** and **14** were identical with those reported for the natural products.[1i,k]

Next, we turned our attention to the synthesis of 1-unsubstituted makaluvamines. Initially we planned to construct the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline **19** by using analogous transformations as described above, keeping the readily removable triisopropylsilyl protecting group of **7** intact until the stage of aryne-mediated cyclization. Thus, we tried a simple nucleophilic substitution of the methiodide of **7** with potassium cyanide *in the absence of TBAF* in order to produce [4-chloro-1-(triisopropylsilyl)-6-methoxyindol-3-yl]acetonitrile (**15**). Although we tested two different conditions (KCN/MeOH/reflux/1 h or KCN/18-crown-6/MeCN/r.t./48 h), the sole isolated product was the desilylated nitrile **8** (*ca.* 60% yields in both cases) (**Scheme 3**).



Scheme 3



Reagents and conditions: (a) (i) NaH, THF; (ii) *t*-$BuMe_2SiCl$ (91%). (b) BH_3·THF (66%) or $LiAlH_4$, ether-benzene (90%) (c) LICA, THF, 0°C, 1h (75%). (d) TBAF (95 %) (e) Fremy's salt, pH 7 phosphate buffer, MeOH, 0°C, 5 min (41%). (f) NH_4Cl, MeOH (67%). (g) tyramine hydrochloride, MeOH (78%).

Scheme 4

Since it was difficult to avoid undesirable desilylation under conventional cyanation conditions, we decided to use **8** as the starting point for further transformations (**Scheme 4**). Thus, the indole nitrogen of **8** was reprotected with *t*-butyldimethylsilyl group by a reaction with NaH and *t*-butyldimethylsilyl chloride to give **16** in 91% yield. Reduction of the cyano group with BH_3·THF complex[7] afforded the tryptamine derivative

17 in 66% yield. The LAH reduction[8] of **16** gave **17** in 90% yield accompanied by desilylated 4-chloro-6-methoxytryptamine (5%). Aryne-mediated cyclization[5] of **17** underwent in 75% yield to give **18** by using 5 equiv of LICA in THF at 0°C for 1 h (**Table 1**; entry 7). Under other reaction conditions **18** was obtained in lower yields (entries 5, 6). Again, the temperature for aryne formation (0°C) is critical for the successful cyclization. It is also revealed that LICA is particularly useful, compared to LDA, for the cyclization of **17**.[12] Deprotection of *t*-butyldimethylsilyl group of **18** with TBAF afforded **19** in 95% yield. To our surprise, the salcomine-catalyzed O_2 oxidation[11] of **19** produced only a complex mixture. Fortunately, however, Fremy's salt oxidation in pH 7 phosphate buffer[10] afforded the pyrroloiminoquinone **20** in 41% yield. Reaction of **20** with ammonium chloride in a similar manner as described above gave makaluvamine I (**21**) in 67% yield. Makaluvamine D (**22**) was also synthesized by a reaction with tyramine hydrochloride in 78% yield. The spectroscopic data (^1H and ^{13}C NMR) of **21** and **22** were identical with those reported for the natural products.[1i,k]

In conclusion, we have developed a new efficient route to 1-methyl and 1-normakaluvamines. The total yields of makaluvamines A, D, I, and K (**13**, **22**, **21**, and **14**) from 6-methoxyindole (**4**) were 21%, 14%, 12%, and 23%, respectively. Although we have synthesized relatively simple pyrroloiminoquinone marine alkaloids, our synthetic route would be further expanded for the synthesis of more complex alkaloids *via* ring functionalizations of the key tricyclic 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline intermediates (**11** and **18**). The studies along this line are in progress in our laboratories.

EXPERIMENTAL

General. Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were recorded with Perkin Elmer System 2000 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained with JEOL JNM-GX400 or Varian Gemini-300 or Gemini-200 machine using TMS as an internal standard. Mass spectra (MS) were recorded with JEOL JMS-DX303 or JMS-SX/SX 102 A spectrometer. Elemental analyses were performed at the microanalytical laboratory in Nagasaki University. For flash chromatography, FL60D silica gel (Fuji Silysia) was used, except otherwise mentioned. Dry ether and THF were distilled from Na-benzophenone ketyl under N_2 before use.

6-Methoxygramine (5). A mixed solution of 50% aqueous dimethylamine (4.76 g, 53 mmol), acetic acid (7 mL), and 37% aqueous formaldehyde (4.17 g, 51 mmol) was added to powdered 6-methoxyindole (**4**) (7.36 g, 50 mmol) with vigorous stirring. After stirring for 15 h at room temperature, the solution was poured into a mixture of 10% aqueous NaOH (100 mL) and crushed ice (100 g), and the product was extracted with ether. The combined extracts were washed with water and brine solution, dried over Na_2SO_4, and evaporated to give 9.76 g (96%) of **5**, mp 91-92°C (ether-pentane) (lit.[13] mp 93°C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 6H), 3.59 (s, 2H), 3.84 (s, 3H), 6.80 (dd, 1H, *J*=8.6 and 2.3 Hz), 6.85 (d, 1H, *J*=2.3 Hz), 7.01 (d, 1H, *J*=2.3 Hz), 7.57 (d, 1H, *J*=8.6 Hz), 8.00 (br s, 1H). The crude **5** thus obtained was used for the next reaction without further purification.

1-Triisopropylsilyl-6-methoxygramine (6). Under an atmosphere of Ar, a solution of **5** (9.26 g, 45.3 mmol) in dry THF (20 mL) was added dropwise at 0 °C to a stirred suspension of NaH (60% dispersion in mineral oil, 2.73 g, 68.3 mmol, prewashed with dry pentane) in dry THF (70 mL) over 20 min. After stirring at the same temperature for 1 h, triisopropylsily chloride (9.26 g, 49.9 mmol) was added dropwise and the stirring at 0 °C was continued overnight. The reaction mixture was carefully quenched with water and the product was extracted with ether. The combined extracts were washed with water and brine solution, dried over Na_2SO_4, and evaporated. The residue was purified by Kügelrohr distillation to give 15.83 g (97%) of **6** as yellow oil : bp 160°C/0.2 mmHg; IR (neat) 2946, 2868, 1619, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, 18H, *J*=7.4 Hz), 1.68 (sept, 3H, *J*=7.4 Hz), 2.25 (s, 6H), 3.58 (s, 2H), 3.83 (s, 3H), 6.80 (dd, 1H, *J*=8.5 and 2.2 Hz), 7.00 (d, 1H, *J*=2.2 Hz), 7.03 (s, 1H), 7.54 (d, 1H, *J*=8.5 Hz). *Anal.* Calcd for $C_{21}H_{36}N_2OSi$: C, 69.94; H, 10.06; N, 7.77. Found: C, 69.60; H, 10.11; N, 7.69.

4-Chloro-1-triisopropylsilyl-6-methoxygramine (7). Under an atmosphere of Ar, *t*-BuLi (1.4 *M* in pentane, 17 mL, 24 mmol) was added dropwise to a stirred solution of **6** (7.21 g, 20.0 mmol) in dry ether (100 mL) at -78°C. After being stirred for 20 min, dry ice-acetone bath was removed. The mixture was allowed to warm to 0°C and stirred at this temperature for 1h. After cooling to -78°C, a solution of hexachloroethane (7.10 g, 30.0 mmol) in dry ether (20 mL) was added dropwise over 18 min. After 1h, dry ice-acetone bath was removed and the mixture was stirred for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl and, after dilution with water, the product was extracted with ether. The combined extracts were washed with water and brine solution, dried over Na_2SO_4, and evaporated. After exposure to oil pump vacuum at 50°C to remove unreacted hexachloroethane, the residue was purified by column chromatography over alumina [hexane-ethyl acetate (20:1~5:1)] to give 7.11 g (90%) of **7** as viscous oil; IR (neat) 2947, 2869, 1614, 1555 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 (d, 18H, *J*=7.4 Hz), 1.67 (sept, 3H, *J*=7.4 Hz), 2.31 (s, 6H), 3.75 (s, 2H), 3.80 (s, 3H), 6.79 (d, 1H, *J*=2.1 Hz), 6.89 (d, 1H, *J*=2.1 Hz), 7.02(s, 1H). *Anal.* Calcd for $C_{21}H_{35}ClN_2OSi$: C, 63.85; H, 8.93; N, 7.09. Found: C, 63.71; H, 8.79; N, 7.03.

(4-Chloro-6-methoxy-1*H*-indol-3-yl)acetonitrile (8). To a stirred solution of **7** (7.11 g, 18.0 mmol) in benzene (54 mL) was added MeI (5.11 g, 36.0 mmol) and the mixture was stirred at room temperature overnight. Benzene was removed under reduced pressure and the residual white solid of the methiodide was suspended in THF (85 mL). To the stirred suspension were added sequentially TMS-CN (2.68 g, 27.0 mmol) and TBAF (1.0 *M* in THF, 54 mL, 54 mmol), and the mixture was stirred for 1h. THF was removed under reduced pressure and the residue was partitioned between ether and water. The organic layer was washed with water (three times) and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel using CH_2Cl_2 as an eluent to give 3.46 g (87%) of **8**, mp 136°C (ether-pentane); IR (KBr) 3379, 3314, 2277, 2259, 2252 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.83 (s, 3H), 4.11 (d, 2H, *J*=1.2 Hz), 6.76 (d, 1H, *J*=2.1 Hz), 6.80 (d, 1H, *J*=2.1 Hz), 7.17(m, 1H), 8.13 (br s, 1H). *Anal.* Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.93; H, 4.15; N, 12.70.

(4-Chloro-6-methoxy-1-methylindol-3-yl)acetonitrile (9). Under an atmosphere of Ar, a solution of **8** (3.09 g, 14.0 mmol) in dry THF (15 mL) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 0.68 g, 17.1 mmol, prewashed with dry pentane) in dry THF (60 mL) at 0°C.

After being stirred for 30 min, MeI (1.75 mL, 28.1 mmol) was added.The mixture was stirred for 30 min at 0°C, quenched with water, and extracted with ether. The combined extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silca gel using CH_2Cl_2 as eluent to give 3.25 g (99%) of **9**, mp 124-125°C (ethyl acetate-hexane); IR (KBr) 2250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.86 (s, 3H), 4.10 (d, 2H, *J*=1.1 Hz), 6.64 (d, 1H, *J*=2.1 Hz), 6.79 (d, 1H, *J*=2.1 Hz), 7.03 (s, 1H). *Anal.* Calcd for $C_{12}H_{11}ClN_2O$: C, 61.42; H, 4.72; N, 11.94. Found: C, 61.62; H, 4.86; N, 11.96.

4-Chloro-6-methoxy-1-methyltryptamine (10). *BH_3·THF complex reduction.* Under an atmosphere of Ar, BH_3·THF complex (1.0 *M* in THF, 16 mL, 16 mmol) was added to a solution of **9** (1.88 g, 8.00 mmol) in dry THF (64 mL). The mixture was stirred at ambient temperature for 16 h, quenched with MeOH (30 mL), and evaporated. Diluted NH_4OH was added to the residue and the product was extracted with ether. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel ($CHCl_3$-MeOH-concd NH_4OH=75:25:1) to give 1.01 g (52%) of **10**, mp 89.5-90.5°C (ether); IR (KBr) 3366 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.44 (br s, 2H), 3.02 (m, 4H), 3.66 (s, 3H), 3.85 (s, 3H), 6.62 (d, 1H, *J*=2.1 Hz), 6.76 (d, 1H, *J*=2.1 Hz), 6.77 (s, 1H). *Anal.* Calcd for $C_{12}H_{15}ClN_2O$: C, 60.38; H, 6.33; N, 11.74. Found: C, 60.20; H, 6.22; N, 11.57.

$LiAlH_4$ reduction. Under an atmosphere of Ar, a solution of **9** (235 mg, 1.00 mmol) in dry benzene (30 mL) was added dropwise to a suspension of $LiAlH_4$ (569 mg, 15.0 mmol) in dry ether (30 mL) over 15 min, and the mixture was refluxed for 5 h. After cooling, water (1.2 mL) and then 10% aqueous NaOH (1.2 mL) were added. The mixture was stirred overnight, and resulting white precipitates were removed by decantation. The organic solution was washed with water and brine, dried over K_2CO_3, and evaporated to give 220 mg (92%) of essentially pure **10** as white crystalline solid.

7-Methoxy-1-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (11). Under an atmosphere of Ar, BuLi (1.13 *M* in hexane, 19.0 mL, 21.5 mmol) was added dropwise to a solution of *N*-isopropylcyclohexylamine (3.57 g, 25.3 mmol) in dry THF (190 mL) at -20 °C. After 1 h, the mixture was allowed to warm to 0°C (ice-water bath) and, to this solution, was added a solution of **10** (1005 mg, 4.21 mmol) in dry THF (20 mL) over 14 min. After being stirred for 1 h, saturated NH_4Cl was added and the mixture was diluted with water. Organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel (hexane-ethyl acetate = 3:1) to give 667 mg (78%) of **11** as unstable oil; IR (neat) 3368 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.96 (t, 2H, *J*=5.8 Hz), 3.45 (t, 2H, *J*=5.8 Hz), 3.65 (s, 3H), 3.82 (s, 3H), 5.92 (d, 1H, *J*=1.6 Hz), 6.16 (d, 1H, *J*=1.6 Hz), 6.46 (s, 1H); MS *m/z* 202 (M^+); HRMS calcd for $C_{12}H_{14}N_2O$ 202.1106, found 202.1098.

Makaluvamine A (13). Oxygen gas was passed through a mixture of **11** (105 mg, 0.52 mmol), salcomine (40 mg, 0.12 mmol), and DMF (3.5 mL) at ambient temperature. After 1 h, salcomime (40 mg, 0.12 mmol) was added and the reaction was continued for an additional 1 h. DMF was removed *in vacuo* and the residue was chromatographed over silica gel using $CHCl_3$-MeOH (20:1) as an eluent to give 86 mg of the crude iminoquinone **12**. ^1H NMR (200 MHz, $CDCl_3$) δ 2.73 (t, 2H, *J*=8.0 Hz), 3.83 (3H, s), 3.96 (s, 3H), 4.13

(t, 2H, *J*=8.0 Hz), 6.07 (s, 1H), 6.34 (s, 1H).

A mixture of the crude **12** (86 mg), powdered NH_4Cl (214 mg, 4.00 mmol), and MeOH (20 mL) was stirred at room temperature for 13 h. MeOH was evaporated and the residue was chromatographed over silica gel using $CHCl_3$-MeOH (5:1) as an eluent to give 50 mg of green solid (presumably hydrochloride of makaluvamine A), which was passed through a column of Chromatorex® NH-DM1020 silica gel (Fuji Silysia) using $CHCl_3$-MeOH (10:1) as an eluent to produce the free base of makaluvamine A. The orange solid thus obtained was dissolved in MeOH and the solution was treated with 15 drops of CF_3COOH. The whole was evaporated *in vacuo* to give 65 mg (40% overall yield from **11**) of the trifluoroacetate of makaluvamine A (**13**) as deep purple solid; IR (KBr) 3429, 3372, 3106, 1682, 1616, 1548, 1199, 1147 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.84 (t, 2H, *J*=7.5 Hz), 3.76 (td, 2H, *J*=7.5 and 2.9 Hz), 3.90 (s, 3H), 5.61 (s, 1H), 7.30 (s, 1H), 8.36 (br s, 1H), 9.07 (br s, 1H), 10.38 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.0, 35.8, 42.0, 86.5, 117.8, 122.3, 123.0, 131.0, 156.0, 156.8, 168.3; MS *m/z* 201 (M^+-H); HRMS calcd for $C_{11}H_{11}N_3O$ 201.0902, found 201.0910.

Makaluvamine K (14). A mixture of the crude iminoquinone **12** (73 mg) prepared from 101 mg (0.50 mmol) of **11** as described above, tyramine hydrochloride (71 mg, 0.41 mmol), and MeOH (14 mL) was stirred at room temperature for 23 h. To this mixture was added saturated aqueous $NaHCO_3$ (7 mL) and, after dilution with water, the orange precipitates were extracted successively with a mixture of CH_2Cl_2 and MeOH. The extracts were dried (Na_2SO_4) and evaporated. The residual solid was dissolved in MeOH, and the solution was treated with 20 drops of CF_3COOH and evaporated. The residue was chromatographed over silica gel ($CHCl_3$-MeOH-CF_3COOH=100:10:0.1) to give 124 mg (44% overall yield from **11**) of the trifluoroacetate of makaluvamine K (**14**) as deep purple solid; IR (KBr) 3297, 3124, 2927, 1678, 1627, 1600, 1559, 1517, 1437, 1201, 1136 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.79 (t, 2H, *J*=7.5 Hz), 2.86 (t, 2H, *J*=7.5 Hz), 3.47 (td, 2H, J=7.5 and 6.2 Hz), 3.79 (td, 2H, *J*=7.5 and 2.6 Hz), 3.91 (s, 3H), 5.51 (s, 1H), 6.70 (d, 2H, *J*=8.4 Hz), 7.04 (d, 2H, *J*=8.4 Hz), 7.32 (s, 1H), 8.91 (br t, 1H, *J*=6.2 Hz), 10.54 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.1, 32.4, 35.8, 42.2, 45.1, 84.2, 115.2, 118.0, 122.3, 123.0, 128.1, 129.5, 131.3, 152.8, 156.0, 156.5, 167.7; MS(FAB) *m/z* 322 (M^+); HRMS(FAB) calcd for $C_{19}H_{20}N_3O_2$ 322.1556, found 322.1556.

[1-(*tert*-Butyldimethylsilyl)-4-chloro-6-methoxyindol-3-yl]acetonitrile (16). Under an atmosphere of Ar, a solution of **8** (1.40 g, 6.3 mmol) in dry THF (5.0 mL) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 0.42 g, 10. 4 mmol, prewashed with dry pentane) in dry THF (5.6 mL) at 0°C. After being stirred for 30 min, a solution of *tert*-butyldimethylsilyl chloride (1.18 g, 7.8 mmol) in dry THF (2.0 mL) was added. The mixture was stirred for 1 h at 0°C, quenched with water, and the product was extracted with ether. The combined extracts were washed with water and brine solution, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel using hexane-ethyl acetate (5:1) as an eluent to give 1.92 g (91%) of **16**, mp 93-94°C (ether-pentane); IR (KBr) 2249 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.59 (s, 6H), 0.94 (s, 9H), 3.82 (s, 3H), 4.10 (d, 2H, *J*=1.1 Hz), 6.80 (d, 1H, *J*=2.0 Hz), 6.88 (d, 1H, *J*=2.0 Hz), 7.08 (t, 1H, *J*=1.1 Hz). *Anal.* Calcd for $C_{17}H_{23}ClN_2OSi$: C, 60.97; H, 6.92; N, 8.36. Found: C, 60.92; H, 6.83; N, 8.39.

1-(*tert*-Butyldimethylsilyl)-4-chloro-6-methoxytryptamine (17). *BH_3·THF complex reduction.* Under an atmosphere of Ar, BH_3·THF complex (1.0 *M* in THF, 11.4 mL, 11.4 mmol) was added to a solution of **16** (1.92 g, 5.72 mmol) in dry THF (45 mL). The mixture was stirred at ambient temperature for 18 h, quenched with MeOH (30 mL), and evaporated. Diluted NH_4OH was added to the residue and the product was extracted with ether. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel ($CHCl_3$-MeOH=10:1 then $CHCl_3$-MeOH-concd NH_4OH=100:10:1) to give 1.26 g (66%) of **17** as a viscous oil; IR (neat) 3361 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.55 (s, 6H), 0.91 (s, 9H), 1.44 (br s, 2H), 3.03 (m, 4H), 3.81 (s, 3H), 6.78 (d, 1H, *J*=2.1 Hz), 6.87 (s, 1H), 6.89 (d, 1H, *J*=2.1 Hz); MS *m/z* 338 (M^+); HRMS calcd for $C_{17}H_{27}ClN_2OSi$ 338.1581, found 338.1584.

$LiAlH_4$ reduction. Under an atmosphere of Ar, a solution of **16** (196 mg, 0.59 mmol) in dry benzene (5.9 mL) was added dropwise to a suspension of $LiAlH_4$ (111 mg, 2.93 mmol) in dry ether (5.9 mL), and the mixture was refluxed for 30 min. After cooling, water (0.23 mL) and then 10% aqueous NaOH (0.20 mL) were added, and the mixture was stirred for 30 min. After removal of white precipitates by decantation, the organic solution was washed with water and brine, dried over K_2CO_3, and evaporated. The residue was purified by flash chromatography over silica gel ($CHCl_3$-MeOH-concd NH_4OH=100:10:1) to give 178 mg (90%) of **17** and 7 mg (5%) of 4-chloro-6-methoxytryptamine, mp 119.5-120.5°C (CH_2Cl_2-hexane); IR (KBr) 3339 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.58 (br s, 2H), 3.04 (m, 4H), 3.81 (s, 3H), 6.74 (d, 1H, *J*=2.1 Hz), 6.77 (d, 1H, *J*=2.1 Hz), 6.91 (br s, 1H), 8.24 (br s, 1H); *Anal.* Calcd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.66; H, 5.76; N, 12.46.

1-(*tert*-Butyldimethylsilyl)-7-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (18). Under an atmosphere of Ar, BuLi (1.13 *M* in hexane, 17.9 mL, 20.3 mmol) was added dropwise to a solution of *N*-isopropylcyclohexylamine (3.43 g, 24.3 mmol) in dry THF (150 mL) at -20°C. After stirring for 1 h at -20°C, the mixture was allowed to warm to 0°C (ice-water bath). A solution of **17** (1370 mg, 4.04 mmol) in dry THF (20 mL) was added dropwise over 14 min, and the mixture was stirred for 1 h. After quenching with saturated NH_4Cl, THF was evaporated and the residue was partitioned between ether and water. Organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel (hexane-ethyl acetate = 3:1) to give 918 mg (75%) of **18**, mp 116.5-117 °C (ether-pentane); IR (KBr) 3370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.54 (s, 6H), 0.94 (s, 9H), 2.97 (t, 2H, *J*=5.8 Hz), 3.45 (t, 2H, *J*=5.8 Hz), 3.79 (s, 3H), 5.98 (d, 1H, *J*=1.6 Hz), 6.36 (d, 1H, *J*=1.6 Hz), 6.58 (s, 1H); *Anal.* Calcd for $C_{17}H_{26}N_2OSi$: C, 67.50; H, 8.66; N, 9.26. Found: C, 67.58; H, 8.72; N, 9.31.

7-Methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (19). To a solution of **18** (191 mg, 0.63 mmol) in THF (3.2 mL) was added TBAF (1.0 M in THF, 0.76 mL, 0.76 mmol) at room temperature and the mixture was stirred for 10 min. THF was removed by evaporation and the residue was partitioned between ether and water. The organic layer was separated, washed sequentially with water and brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed over silica gel using hexane-ethyl acetate (3:1) as an eluent to give 113 mg (95%) of **19**, mp 96.5-97°C; IR (KBr) 3392, 3358 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.98 (td, 2H, *J*=5.8 and 1.1 Hz), 3.47 (t, 2H, *J*=5.8 Hz), 3.79 (s, 3H), 4.05 (br

s, 1H), 5.95 (d, 1H, *J*=1.5 Hz), 6.26 (d, 1H, *J*=1.5 Hz), 6.61 (dt, 1H, *J*=1.8 and 1.1 Hz), 7.66 (br s, 1H); *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.04; H, 6.45; N, 14.85.

7-Methoxy-1,3,4,8-tetrahydro[4,3,2-*de*]quinolin-8-one (20). A precooled solution of potassium nitrosodisulfonate (455mg, 60~75% purity, Wako Pure Chemical Industries) in phosphate buffer (pH=7, 16.5 mL) was added to a solution of **19** (94 mg, 0.50 mmol) in MeOH (8.3 mL) at 0°C over 2 min. After being stirred for 2 min, the mixture was diluted with CH_2Cl_2 and filtered through Celite. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 for several times. The combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography over silica gel ($CHCl_3$:MeOH=10:1) to give 41 mg (41%) of **20**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (t, 2H, *J*=7.8 Hz), 3.86 (s, 3H), 4.19 (t, 2H, *J*=7.8 Hz), 6.18 (s, 1H), 6.91 (s, 1H). This material was used in the next reactions without further purification.

Makaluvamine I (21). A mixture of **20** (41 mg, 0.20 mmol), powdered NH_4Cl (108 mg, 1.96 mmol), and MeOH (10 mL) was stirred for 39 h at room temperature. MeOH was evaporated and the residue was chromatographed over silicagel using $CHCl_3$-MeOH (5:1) as an eluent to give 40 mg of purple solid (presumably hydrochloride of makaluvamine I), which was passed through a column of Chromatorex® NH-DM1020 silica gel (Fuji Silysia) using $CHCl_3$-MeOH (10:1) as an eluent to produce the free base of makaluvamine A. The red solid thus obtained was dissolved in MeOH and the solution was treated with 15 drops of CF_3COOH. The whole was evaporated *in vacuo* to give 41 mg (67%) of the trifluoroacetate of makaluvamine I (**21**) as deep purple solid; IR (KBr) 3316, 3153, 1679, 1610, 1533, 1203, 1177, 1139 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.86 (t, 2H, *J*=7.5 Hz), 3.78 (t, 2H, *J*=7.5 Hz), 5.61 (s, 1H), 7.30 (d, 1H, *J*=2.4 Hz), 8.43 (br s, 1H), 9.10 (br s, 1H), 10.45 (br s, 1H), 13.05 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.1, 42.2, 86.4, 118.5, 122.6, 123.7, 126.6, 156.2, 157.4, 167.9; MS *m/z* 187 (M^+-H); HRMS calcd for $C_{10}H_9N_3O$ 187.0746, found 187.0746.

Makaluvamine D (22). A mixture of **20** (37 mg, 0.18 mmol), tyramine hydrochloride (39 mg, 0.22 mmol), and MeOH (8 mL) was stirred at room temperature for 14 h. To this mixture was added saturated aqueous $NaHCO_3$ and the product was extracted with a mixture of CH_2Cl_2 and MeOH. The extracts were dried (Na_2SO_4) and evaporated. The residual solid was dissolved in MeOH, and the solution was treated with CF_3COOH and evaporated. The residue was chromatographed over silica gel ($CHCl_3$-MeOH-CF_3COOH=100:10:0.1) to give 60 mg (78%) of the trifluoroacetate of makaluvamine D (**22**) as deep purple solid; IR (KBr) 3126, 3014, 1678, 1629, 1602, 1558, 1516, 1437, 1203 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.80 (t, 2H, *J*=7.5 Hz), 2.89 (t, 2H, *J*=7.5 Hz), 3.48 (td, 2H, *J*=7.5 and 6.2 Hz), 3.81 (t, 2H, *J*=7.5 Hz), 5.47 (s, 1H), 6.70 (d, 2H, *J*=8.3 Hz), 7.04 (d, 2H, *J*=8.3 Hz), 7.31 (s, 1H), 8.98 (br t, 1H, *J*=6.2 Hz), 9.23 (s, 1H), 10.43 (br s, 1H), 13.07 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.1, 32.3, 42.4, 45.0, 84.0, 115.2, 118.6, 122.5, 123.7, 126.8, 128.1, 129.5, 153.0, 155.9, 157.0, 167.4; MS(FAB) *m/z* 308 (M^+); HRMS(FAB) calcd for $C_{18}H_{18}N_3O_2$ 308.1399, found 308.1399.

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