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1,2,3,4-Tetrahydro-8-Hydroxymanzamines, Alkaloids from Two Different Haplosclerid Sponges

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Abstract: The isolation and characterization of two new sponge alkaloids, 1,2,3,4-tetrahydro-2-*N*-methyl-8-hydroxymanzamine A (**2**) and 1,2,3,4-tetrahydro-8-hydroxymanzamine A (**3**), is described. These compounds were obtained from Papua New Guinea sponges of the genera *Petrosia* and *Cribochalina*, which are in different families of the order Haplosclerida. These new manzamines are close in structure to 8-hydroxymanzamine (**4**) recently reported from *Pachypellina*, a Haplosclerid sponge belonging to a different family than that of the two preceding sponges. The cytotoxicity of **2** is described and the biogenetic relationship of **2** or **3** to manzamine A (**1**) and to nine other related polycyclic diamine and one monoamine type alkaloids is described.

INTRODUCTION

A continuing emphasis in our natural products program at UCSC is the collection and examination of Indo-Pacific sponges suspected to contain alkaloids.[1] Initially, we believed that sponges in orders such as the Dictyoceratida[2] or Dendroceratida[3], known to be excellent sources of terpenoids, ought to be avoided because they would be devoid of alkaloids. Likewise, once a group of sponges had been identified as yielding new alkaloids, ideally in high concentration, then our supposition was that other related compounds would not be obtained from specimens of distant taxonomic groups (*i.e.* sponges of different families or orders). While such ideas have been valuable guides to our discovery of a number of new bioactive compound classes[4], over time, there have been exceptions[5]. We are now beginning to appreciate that a complex relationship probably exists between the taxonomic placement of sponges and the alkaloids they afford. There are several polycyclic alkaloids whose rings are lacking methyl substituents[6] which illustrate this association.

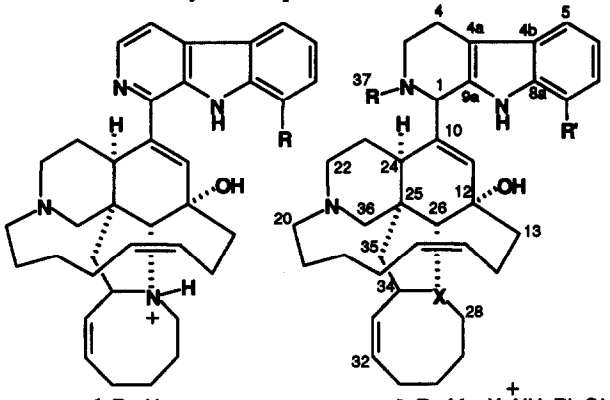
The first member of this exclusively sponge-derived alkaloid family was reported independently by Higa *et al.*[7] in 1986 and by Nakamura *et al.*[8] in 1987. The same compound was described in each case, but was given different names; manzamine A, isolated from a *Haliclona* sp. (family, Chalinidae), and keramamine A, obtained from *Pellina* sp. (family, Oceanapiidae), respectively. The structure **1** assigned to both compounds includes a pentacyclic diamine joined to C1 of a β-carboline moiety. Likewise, another manzamine derivative, again with two different names but with the same structure was obtained from different sources, as keramamine B (*Pellina* sp.: family, Oceanapiidae[8]) and manzamine F (*Xestospongia* sp.: family, Petrosiidae[9]).

The UCSC and UO groups have separately studied different genera of sponges from Papua New Guinea identified as *Petrosia contignata* (family, Petrosiidae) and *Cribochalina* sp. (family, Niphatidae), respectively, but each sponge yields the same partially reduced and hydroxylated derivative of **1**, which we have named 1,2,3,4-tetrahydro-2-*N*-methyl-8-hydroxy-manzamine A (**2**). The demethylated compound, **3**, was also found in *P. contignata*. In this report we will describe the structures of **2** and **3** which are related to 8-hydroxymanzamine A (**4**), recently isolated from a sponge belonging to the genus *Pachypellina* (family, Oceanapiidae),[10] and manzamine D (**5**), isolated from two sponges, *Ircinia* sp (family, Thorectidae)[11a] and

Haliclona (family, Chalinidae)[12]. Also presented is a summary of how the various diamine alkaloids occur as a function of the taxonomy of their sponge sources.

RESULTS AND DISCUSSION

The isolation work undertaken by the UCSC group began after a gray, oval sponge (coll no. 91160), having a compound oscule on top as one of its distinguishing features, was collected at Milne Bay in Papua New Guinea. It should be noted that our repository contains numerous samples of *P. contignata* which are variable in morphology and have not been a source of the chemistry reported below. The sponge was preserved by our standard procedure[13] and then returned to UCSC for extraction with methanol. The hexanes:EtOAc (1:1) solubles of the CH_2Cl_2 solvent partition fraction were purified by HPLC (normal phase column, hexanes:EtOAc 1:1) to afford **2** and **3**. The former was a salt whose counter ion was not identified, whereas **3** was isolated as the free base, and organic solutions of **2** extracted with saturated Na_2CO_3 also afforded it as the free base. The molecular formula of $C_{37}H_{51}N_4O_2$ for **2** was based on an HREIMS *m/z* = 582.3936 $[M-H]^+$, (Δ 0.2 mmu of calcd.), and an APT NMR count of $C_{37}H_{47}$. There were four hetero atom protons (δ 4.59, 7.24, 9.97, and 10.51) which could be identified as they did not show correlation peaks in an HMQC spectrum. The OH/NH functionality and the presence of an aromatic residue were also evident from the IR and UV data.



The ^1H NMR spectrum of pure **2**, while quite complex, contained several features that facilitated our structure elucidation efforts. That a new manzamine-type compound was in hand was suggested by the HRMS count of four nitrogens and three features in the ^1H NMR spectrum: the lack of aliphatic methyl resonances, the presence of a plethora of aliphatic multiplets, and the appearance of peaks in the aromatic region. A further indication of how **2** differed from a normal manzamine was that its 15 computed unsaturation equivalents was less than that of the 17 computed for **4** but was the same as that calculated for **5**. The characteristic low field ^{13}C NMR signals for the vinyl carbons of **4** at C1 (δ 143.3), C3 (δ 137.9) and C4 (δ 114.7) were missing in the NMR spectrum of **2**, instead signals for these carbons were observed at 69.5 (C1), 53.0 (C3) and 21.9 (C4) indicating the presence of a 1,2,3,4-tetrahydro system. Eventually, we realized that most of the remaining ^{13}C NMR signals of **2**, especially the fourteen signals in the olefinic/aromatic chemical shift region (106.9-144.9 ppm) and the three low field signals in the aliphatic region (between δ 80 -70), were similar to those reported for **4** as can be seen in Table 1.

Data from 2D NMR experiments provided additional support to justify the gross structure shown for **2** and further confirmed that it differed from **4** by the presence of a tetrahydro β-carboline ring. The ^1H signal at δ 9.97 (NH27) displayed an HMBC correlation to δ 78.9 (C26) further highlighting that **2** had been isolated as a quaternary ammonium salt. Data from the ^1H-^1H COSY, TOCSY and HMQC-TOCSY NMR spectra confirmed various substructures including: $CH_2$13-$CH_2$20, NH27-CH34-$CH_2$35, NCH3-$CH_2$4, NCH$_2$22-$CH_2$24 and CH5-CH7. The HMBC results shown in Table 1 enabled assignment of the indole ring constellation consisting of quaternary carbons 4a, 4b, 8, 8a, and 9a. A combination of HMBC data and analogy to prior literature assignments of **4** (our revisions are represented with a # symbol in Table 1) were used to interpret the resonances for the remaining isolated spin systems and quaternary carbons at: δ 70.9 ($CH_2$36), δ 131.6 (C10), δ

132.1 (CH11), δ 71.1 (C12OH), δ 69.5 (CH1), δ 44.6 (C25), δ 44.4 (NMe37). The connectivities between these various atom sets reflected in the final structure **2** were unequivocally established by the remaining HMBC correlations shown in Table 1. The relative stereochemical features shown for **2** are justified by the parallel ^{13}C NMR shifts observed between this compound and that of **1** whose structure was established by X-ray crystallography.

The same structural conclusions were reached by the UO group using a mixed solvent system (DMSO-d_6:Acetone-d_6) for NMR analyses on **2**. While this solvent system gave convenient proton signal dispersion, the proton shifts were sensitive to sample concentration and solvent ratios and hence the data for the alkaloid salt in $CDCl_3$ are recorded here. Comparison of the NMR spectra of the two samples of **2** confirmed that they are the same.

The molecular formula, $C_{36}H_{48}N_4O_2$, of the second compound, **3**, was based on the HRFABMS *m/z*=569.3832 $(M+H)^+$ (Δ 2.3 mmu of calcd.). Its ^{13}C NMR spectrum showed one resonance less than that of **2**. Further changes were observed in the carbon chemical shifts of C1 and C3 (60.8 and 43.9) in support that the NMe was not present. The ^1H NMR of **3** includes signals for H26 and H34 with different multiplicity than those of **2**, suggesting that **3** was present as free base.

The new alkaloid **2** was cytotoxic to leukemia cells, P388 and exhibited an ED_{50} of 0.8 μg/mL. This compound is of further interest as it provides yet another intermediate in the biosynthetic path from acyclic precursors to the fully aromatized manzamines.[14] Furthermore, the circumstance of isolating **2** and **3** from sponges of different families can be added to an overall interesting picture which is emerging for several of the other members of this structural family. In addition to the manzamines there are at least ten additional related alkaloid frameworks which have been described to date[11,12,15-26] and some of them have been synthesized[28-31]. Retro-biogenetic analyses appearing in several recent publications[1,6,11,14,15,16] have outlined how their seemingly varying diamine frameworks are actually analogous. Several years ago Baldwin[14] suggested that some of these could be derived by a process commencing with one or more condensation reactions between acyclic aldehydes and two ammonia atoms. An overview of the various marine sponge derived alkaloids which fit this pattern is presented in Chart 1 and the related literature appears in Table 2. Examining the overall scope of the taxonomic origins of the sponges which are a source of these compounds gives an interesting perspective. In particular, there is an unusually broad diversity represented in the sponges which are a source of these compounds. As is evident from the data in Table 2, these alkaloids have been isolated from several Haplosclerida order sponges. In addition, there are several instances wherein the same structural type has been observed from Haplosclerid sponges classified in different families, and this is especially true for the manzamine (a.k.a. keramamine) derivatives. Another most unusual observation from Table 2 is that compounds of the haliclamine [HCL] (≈ halitoxin [≡CST] and cyclostellettamine [CST]) group have been isolated from sponges classified in different subclasses.

EXPERIMENTAL

General Experimental Procedures

The NMR spectra were recorded at 250, 300 or 500 MHz for ^1H and 62.5, 75 or 125 MHz for ^{13}C respectively. Low and high resolution EI and FAB mass spectra (using a mixture of dithiothreitol:dithioerythritol 3:1) were obtained either at UCSC, the University of Illinois or the University of Oklahoma mass spectrometry facilities. High performance liquid chromatography (HPLC) was performed on 10 μm silica columns.

Collection and Identification

The UCSC group obtained sponges from open reef habitats in the Milne Bay province of Papua New Guinea (coll. no. 91160) which were identified as *Petrosia contignata* by Ms. M. C. Diaz. The voucher specimen was barely compressible and round with a compound oscule on top. The color of the sponge was gray

Table 1. NMR Data ($CDCl_3$) of **2**, **3** and **4** (Ref. 10).

	2	**2**	**2**	**3**	**3**	**4**
Atom #	^{13}C	^1H (δ, mult., *J*, Hz)	HMBC	^{13}C	^1H (δ, mult., *J*, Hz)	^{13}C
1	69.5	3.92, s	H11	60.8	4.80, bs	143.3
3	53.0	3.00, dd, 11.0, 4.0; 2.44, dd, 12.0, 3.0		43.9	2.94, dt, 11.0; 3.27, bd, 11.0	137.9
4	21.9	2.85, t, 12.0; 2.65, bd, 15.0		22.3	2.81, m; 2.62, bd, 13.8	114.7
4a	110.3		H1, H3, H4-H4', H5	110.3		129.8
4b	129.0		H5, H6	129.5		123.2
5	109.3	6.96, d, 8.0	H6, 8-OH	109.5	6.96, d, 8.0	112.6
6	119.9	6.91, dt, 8.0, 4.0	H7	119.9	6.91, dt, 8.1,4.0	120.7
7	106.9	6.64, d, 8.0	H6	106.8	6.63, d, 8.1	114.3
8	143.1		H7	143.0		143.8
8a	125.3		H7	125.1		130.6
9a	144.9		H1	144.8		141.9#
10	131.6		H1, H24	132.8		132.9#
11	132.1	5.91, s	H26	132.7	5.84, s	134.6
12	71.1		H11, H26	70.6		71.2
13	39.8	1.92, m; 1.75,m	H26, H15, H14	39.6	2.00, m; 1.52, m	39.2
14	20.6	2.17, m	H15	20.6	2.13, m	20.7
15	126.8	5.56, dt, 8.0, 3.0		127.6	5.55, m	126.7
16	132.9	5.54, dt, 11.0, 4.0		131.7	5.53, m	133.0
17	24.8	2.36, m; 1.55, m		24.9	2.38, m; 1.42, m	24.7
18	26.3	1.45, m; 1.14, m		26.4	1.38, m; 1.13, m	26.5
19	24.4	1.72, m; 1.40, m		24.4	1.85, m; 1.42, m	25.5
20	53.2	2.26, m; 2.48, dd, 13.0, 5.0	H22, H18, H19-19'	53.3	2.27, m; 2.45, dd, 12.0, 5.1	53.4
22	49.1	2.75, m; 1.61, bt, 11.0	H36, H20, H23-23', H24	49.1	2.77, m; 1.67, m	49.1
23	33.4	2.16, m; 1.43, m		33.7	2.16, m; 1.33, m	33.4
24	37.4	1.86, m	H1, H11, H22	37.5	1.97, m	41.3
25	44.6		H23, H36-36', H35-35'	46.7		47.1
26	78.9	3.56, d, 7.5	NH27, H11, H24, H28	78.9	3.55, s	78.2
28	53.3	3.88, m; 3.16,q, 10.0	H26, H30, H29-29'	53.5	3.82, m; 3.16, t, 11.4	53.7
29	26.3	2.44, m; 1.91, m		26.3	2.45, m; 1.84, m	26.4
30	24.0	1.97, m; 1.42, m	H32, H28-28'	24.0	1.90, m; 1.42, m	24.2
31	28.7	2.34, m; 2.20, m	H32, H33	28.6	2.32, m	28.4
32	142.1	6.17, dt, 12.0, 6.0	H30-30', H31-31', H33, H34	142.5	6.14, m	142.8
33	123.6	5.18, t, 10.0	H32	123.6	5.18, t, 9.9	123.3
34	57.5	4.73, q, 8.1	H28, H33	57.5	4.70, t ,8.7	57.4
35	42.5	1.69, dd, 14.0, 8.0; 1.30, bd, 14.0	H33, H26	43.2	1.71, m; 1.42, m	44.8
36	70.9	2.74, bd, 12.1; 2.09, bd, 12.0	H35-35', H26	70.9	2.78, m; 2.10, m	70.2
37	44.4	2.26, s	H1, H3		-	
NH27		9.97, bs				
12-OH		10.51, bs			10.21, bs	
8-OH		7.24, bs				
NH		4.59, bs				

Revision of assigments of reference 10.

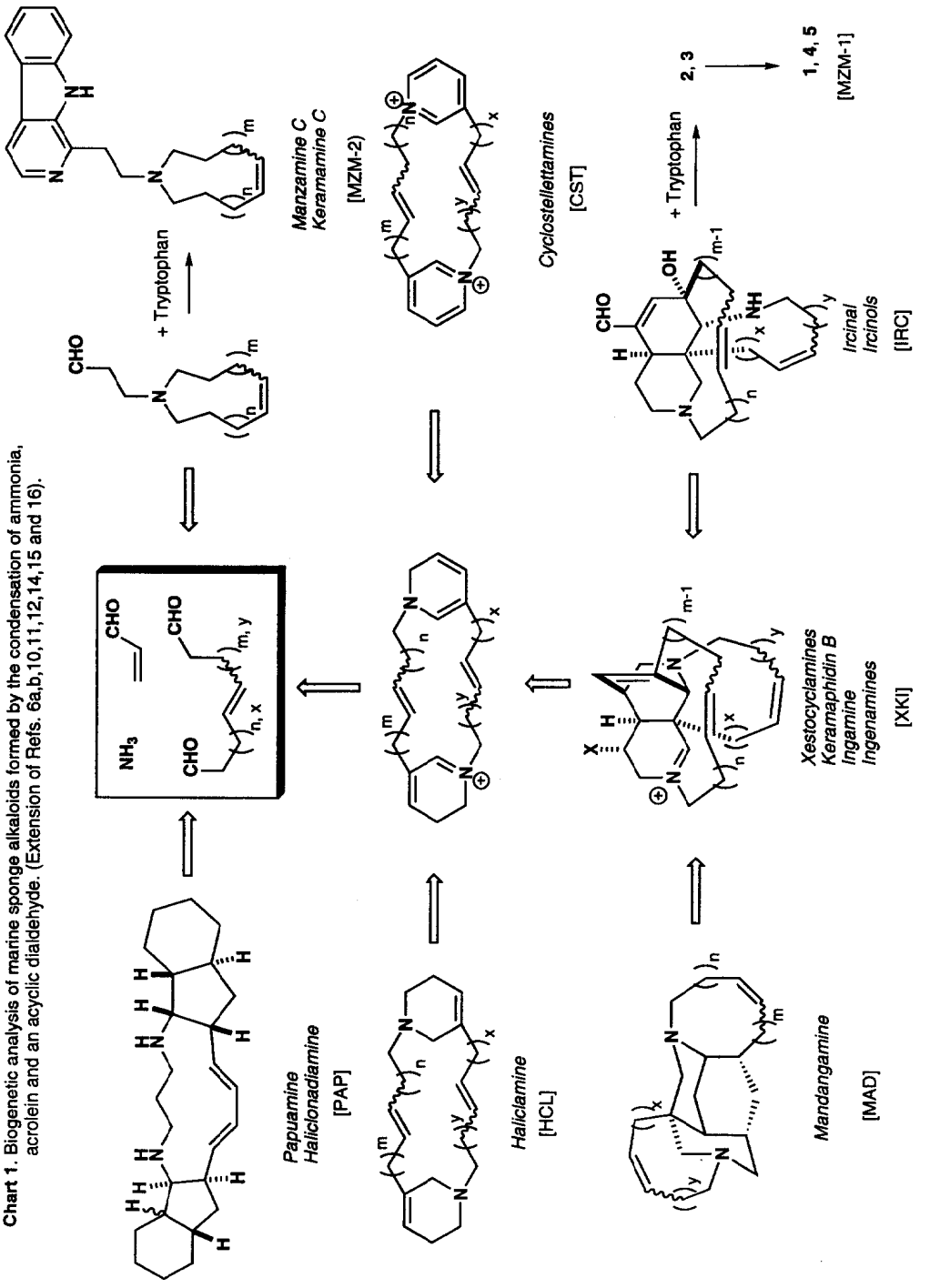


Chart 1. Biogenetic analysis of marine sponge alkaloids formed by the condensation of ammonia, acrolein and an acyclic dialdehyde. (Extension of Refs. 6a,b,10,11,12,14,15 and 16).

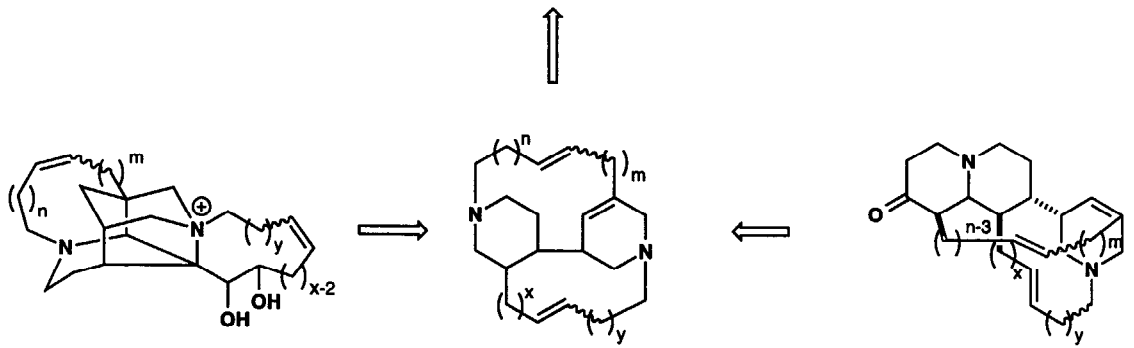


Table 2. Taxonomy of Sponges Producing Alkaloid Structural Types of Chart 1.

CLASS	SUBCLASS	ORDER	FAMILY	GENUS	STRUCTURE TYPE	REFERENCES ISOLATION	REFERENCES SYNTHESIS
Demospongiae	Ceractinomorpha	Dictyoceratida	Thorectidae	*Ircinia*	IRC, MZM-1	11, 12	28
		Haplosclerida	Oceanapiidae	*Pellina*	MZM-1	8	
				Pachypellina	MZM-1	10	
			Petrosiidae	*Petrosia*	MZM	This work	
			Niphatidae	*Cribochalina*	MZM	This work	
				Amphimedon	MZM-2, XKI, IRC	11, 17, 18, 19	29
				Xestospongia	MZM-1	9	
					XKI	1, 15	
					MAD	16	
			Callyspongiidae	*Callyspongia*	HCL	20	
			Chalinidae	*Haliclona*	HCL	21	
					MZM-1	7	
					PAP	22a, 22b	30
					MZM-2	23	
					HCY	6b	
				Reneira	SAR-A, SAR-1	24, 25	31
	Tetractinomorpha	Choristida	Stelletidae	*Stelletta*	CST	26	

to tan. The surface of the specimen was microhispid with a non specialized ectosome and a dense, isotropic, multispicular reticulated choanosome. The skeleton was formed from oxeas: oxea I (140x8), (150x8), (160x5); oxea II (80x5), (70x3), (70x3). A drawing along with an additional morphological description of this sponge appears in the literature.[27] The UO group obtained specimens in 1987 and 1989 near Madang, Papua New Guinea. The voucher specimen (coll. no FJS-5-NG-89) was identified as *Cribochalina* sp. by Prof. P. Bergquist (University of New Zealand).

Extraction and Isolation

Sponges studied by the UCSC group were preserved immediately after collection by being immersed in an alcohol:H_2O 1:1 solution. After approximately 24 h this solution was decanted and discarded. The damp organisms were placed in Nalgene™ bottles and shipped back to the home lab at ambient temperature. Next 100% MeOH was added and the organisms were soaked for 24 h. This procedure was repeated two more times and the combined MeOH extracts were concentrated. The combined organic extract yielded a crude oil, which was successively partitioned between equal volumes of aqueous MeOH, percent adjusted to produce a biphasic solution, and a solvent series of hexanes, and CH_2Cl_2. The methylene chloride fraction (522 mg) was chromatographed on silica gel (Hexane:EtOAc 2:1 and then EtOAc:MeOH 1:1) to yield six sub fractions. The third and sixth sub fractions were purified by HPLC (normal phase, hexane:EtOAc 1:1) to give 35 mg of **2** and 40 mg of **3**. Sponges studied by the UO group were frozen after collection and shipped back to the home lab in a frozen state. The material (28 g, wet wt) was subsequently cut into small pieces and soaked in MeOH for 24 h. This procedure was repeated one more time and the combined MeOH extracts were concentrated. The crude oil was then partitioned between equal volumes H_2O:EtOAc. The EtOAc solubles (397 mg) were chromatographed in portions over a silica gel Sep-Pak™ using acetone:hexane 4:1. Manzamine-containing fractions were combined and further resolved with HPLC using a silica gel column and acetone:hexane 1:4. A less polar fraction was rechromatographed on silica gel HPLC (acetone:hexane 1:5) to give 50 mg of **2** white powder. Compound **2**: IR (KBr) ν_{max}; 3005, 2935, 2847, 1648, 1627, 1578 cm^{-1}. UV (MeOH) λ_{max}; 240, 270, 326, 370 nm. $[\alpha]_D$ 5° (*c* 0.03, CH_2Cl_2). HREIMS, m/z $[M]^+$ 582.3948, $C_{37}H_{50}O_2N_4$ requires 582.3934; $[\alpha]_D$ 46° (*c* 0.006, CH_2Cl_2) $[M+H]^+$ 583.4025, $C_{37}H_{51}O_2N_4$ requires 583.4012; ^1H and ^{13}C NMR data are in Table 1. Compound **3**: HRFABMS, m/z $[M+H]^+$ 569.3832, $C_{36}H_{48}O_2N_4$ requires 569.3855. ^1H and ^{13}C NMR data are in Table 1.

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