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PHYTOCHEMICAL INVESTIGATION OF *Iphiona aucheri.* STRUCTURAL REVISION OF DONINE

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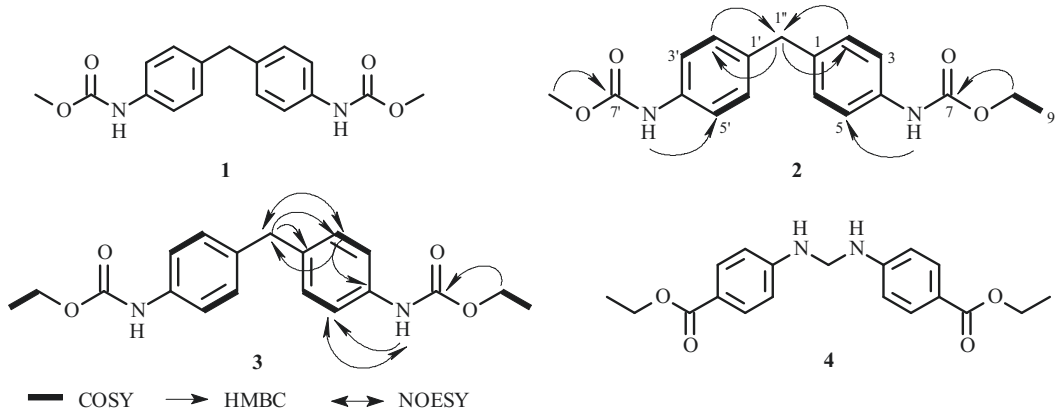
Investigation of an extract of Iphiona aucheri *afforded compounds **1–3**. These compounds were identified by detailed spectroscopic and spectrometric analysis, however, a literature search revealed that NMR and mass data similar to those of compound **3** have been reported for donine alkaloid **4**. Investigation of the experimental and calculated NMR data of compound **4** revealed that the proposed structure should be revised to **3**. This was further confirmed by synthesis of compounds **3** and **4**.*

Keywords: *Iphiona aucheri*, donine, GIAO-NMR calculation, structure revision.

Iphiona aucheri belongs to the family Compositae and is distributed in Iran, the Arabian Peninsula, and North-East Africa [1]. The plant has been reported to be toxic to animals [2]. Previous phytochemical investigations of this species resulted in the identification of different secondary metabolites including the pyrrolizidine alkaloid isotussilagine and several terpenoids including the diterpenoids atractyloside and carboxyatractyloside [3]. The latest metabolite, carboxyatractyloside, was identified to be responsible for the plant toxicity [3]. In this study, investigation of the extract of *I. aucheri* resulted in the identification of compounds **1–3**. The mass and NMR data of compound **1** were identical to the reported values of dimethyl (methylenedi-4,1-phenylene)biscarbamate which has been purified from *Magnolia kachirachirai* and Cortex Mori [4–6]. Compounds **2** and **3** were identified as analogues of compound **1**; however, we noticed that NMR data similar to those of compound **3** have been reported for the alkaloid donine (**4**) with a different structure [7]. Alkaloid **4** has been identified from *Arundo donax* [7], and there is no other report on the isolation of donine or related alkaloids from any other natural sources. A close investigation of the data reported for compound **4** revealed that the structure of the metabolite was misassigned and should be revised to compound **3**.



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Compound **1** is symmetrical and shows only four proton and seven carbon chemical shifts. The LR-ESI-MS of compound **2** showed a 14 Da mass difference from that of compound **1**. A molecular formula of $C_{18}H_{20}O_4N_2$ was established for compound **2** by analysis of HR-ESI-MS and NMR data, establishing that **2** differed from compound **1** by a methylene. Comparative analysis of the NMR data of compounds **1** and **2** showed that **2** was nonsymmetrical and possessed an additional methyl (δ_C 15.2, δ_H 1.18), a methylene (δ_C 61.1, δ_H 4.25), and a quaternary carbon signal at δ_C 155.2 in the NMR spectra of compound **2**. Investigation of the COSY and HMBC correlations showed that an ethoxy group replaced one of the methoxy groups of compound **1**. One side of the unsymmetrical molecule **2** showed HMBC correlation between the protons of methyl (H-8′) at δ 3.74 and the carbonyl C-7′ at δ 155.6, while the other side showed correlation between the methylene protons of the ethyl group (H-8) at δ 4.25 and the quaternary carbon of carbonyl C-7 at δ 155.2. The unsymmetrical character of the compound was obvious in the splitting pattern of the aromatic protons as well. While the aromatic protons of the symmetric molecule **1** showed two doublets, compound **2** showed two unresolved methene doublets at δ_H 7.29 and 7.87.

The HR-ESI-MS analysis of compound **3** showed a mass at *m/z* 365.1468 $[M + Na]^+$ corresponding to the cationized molecule with the molecular formula $C_{19}H_{22}O_4N_2Na$ (calcd 365.1471). The mass difference of 14 Da from compound **2** indicated the addition of a CH_2 unit in compound **3**. The ^1H and ^{13}C NMR spectroscopic data revealed that the molecule is symmetric. The ^{13}C NMR spectrum (pyridine-d_5) of compound **3** in conjunction with the HSQC showed eight carbon signals, including one methyl at δ 15.2, two methylenes at δ 41.3 and 61.2, two methines at δ 119.8 and 130.2, and three quaternary carbons at δ 136.7, 139.0, and 155.2. The ^1H NMR spectroscopic data (pyridine-d_5) displayed five signals corresponding to a triplet methyl at δ 1.18 (J = 7.1 Hz), a quartet methylene at δ 4.25 (J = 7.1 Hz), one singlet methylene at δ 3.93, and two aromatic protons at δ 7.29 (d, J = 8.4 Hz) and 7.89 (d, J = 8.4 Hz). The COSY correlation indicated an ethoxy moiety and a *para*-substituted benzene ring. The HMBC experiment revealed a ^2J correlation from proton H_2-1″ at δ 3.93 to the quaternary carbon C-1, 1′ at δ 136.7 and ^3J correlation to C-2, 6, 2′, 6′ at δ_C 130.2 ppm, indicating the direct connection of the methylene at the center of the molecule to the benzene ring. Protons H-2, 6, 2′, 6′ at δ 7.29 ppm showed ^3J correlations to C-1″ at δ 41.3 and C-4, 4′ at δ 139.0, as well as ^2J correlations to C-3, 5, 3′, 5′ at δ 119.8 ppm. The HMBC correlation between the NH protons at δ 10.57 to C-3, 5, 3′, 5′ revealed that NH is connected to the quaternary carbons C-4, 4′. The NOESY correlations between H_2-1″ and H-2, 6, 2′, 6′ as well as NH and H-3, 5, 3′, 5′ also confirmed that NH is between benzene rings and carbonyl groups. All data indicated that compound **3** is an analog of compounds **1** and **2**; however, it was noted that the ^1H and ^{13}C NMR values obtained for compound **3** are very similar to those reported for the donine alkaloid (**4**) isolated from the plant *Arundo donax* [7]. The structure of donine had been assigned as a symmetric compound with two *para*-substituted benzene rings and two ethyl ester groups on two sides of the compound with a methylene group at the center of the molecule. The difference between donine and compound **3** is the position of the NH groups in the structure. While two NH groups in compound **3** are positioned between benzene rings and the carbonyl groups to form carbamate, in donine they are placed between benzene rings and the methylene group at the center of the molecule. The similarities between our NMR data for compound **3** and reported values for compound **4** prompted us to investigate the reported structure.

The structure of **4** had been assigned mostly based on one-dimensional NMR data and mass spectrometry results. The authors reported ten carbon signals instead of eight. Two additional signals had been identified as possible alternative signals for the methine carbons of the benzene rings (Table 1). A close investigation of the reported carbon chemical shifts identified three carbon resonances of the deuterated pyridine, which has been used as NMR solvent at δ_C 123.4, 135.5 and 149.8 with about 0.5 ppm downfield shift due to incorrect referencing. Excluding the solvent′s carbon chemical shifts, seven carbons remained. Although not all of the carbon resonances of compound **4** have been annotated to their carbon, a comparative analysis of the remaining seven carbon resonances of compound **4** to that of compounds **3** revealed a 0.5 ppm downfield shift of the carbons of compound **3** compare to the molecule **4** (Table 1). The carbon that was not reported by the previous researchers is a quaternary carbon at δ 136.7 (C-1, 1′) of compound **3**.

The chemical shift reported for the carbonyl of compound **4** (δ 154.7) is too upfield for an ester group. This shift in the carbon signal had been wrongly correlated to the inductive effect of the nitrogen atom in the para position of the benzene ring, while the carbonyl carbon in a similar scaffold such as ethyl 4-aminobenzoate resonates at 166.9 ppm ($CDCl_3$) [8]. The reported chemical shift is more consistent for a carbamate. For instance, in compound **1** the carbon of carbonyl resonates at δ 155.6 ppm (in both $CDCl_3$ and pyridine-d_5) and that in 2-[4′-[ethylcarbamoyl)phenyl]-*N*-acetylglycine resonates at δ 154.3 ppm (DMSO-d_6) [4, 9]. The reported value for the carbon of the methylene (δ 40.8) at the center of compound **4** is also more consistent with the values reported for the compounds with methylene directly attached to the benzene ring. Two examples are molecule **1** (δ_C 41.2, pyridine-d_6) and bis-(4-octanoylphenyl)methane (δ_C 41.8, $CDCl_3$) [4, 10]. If the methylene is connected from both sides to the nitrogen attached to a benzene ring, the carbon resonates more than 10 ppm downfield [11, 12].

TABLE 1. Comparison of the δ_C Chemical Shifts for Isolated and Synthesized Compound **3** and Also Reported Resonances for Donine (**4**) and Synthesized Compound **4** (pyridine-d_5, δ, ppm)

C atom	Isolated **3**	Synthesized **3**	Reported **4***	Synthesized **4**
1″	41.3	41.3	40.8	53.3
1, 1′	136.7	136.7	Not reported/identified	152.9
2, 6, 2′, 6′	130.2	130.3	129.7**	112.8
3, 5, 3′, 5′	119.8	119.8	119.3**	132.4
4, 4′	139.0	139.0	138.5	119.5
7, 7′	155.2	155.2	154.7	167.3
8, 8′	61.2	61.2	60.6	60.7
9, 9′	15.2	15.2	14.7	15.0

*The extra carbon resonances of 123.4, 135.5, and 149.8 ppm belonging to the deuterated pyridine were also reported for donine. **These resonances as well as the resonances at 123.4 and 135.5 ppm were reported as "possible alternative assignment of the signals" of the carbon on the benzene ring of the donine.

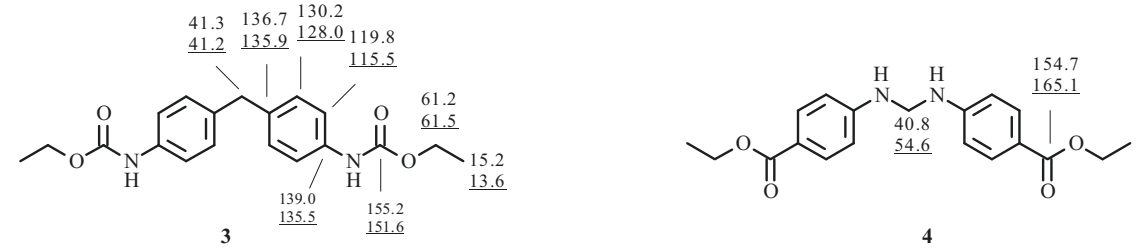


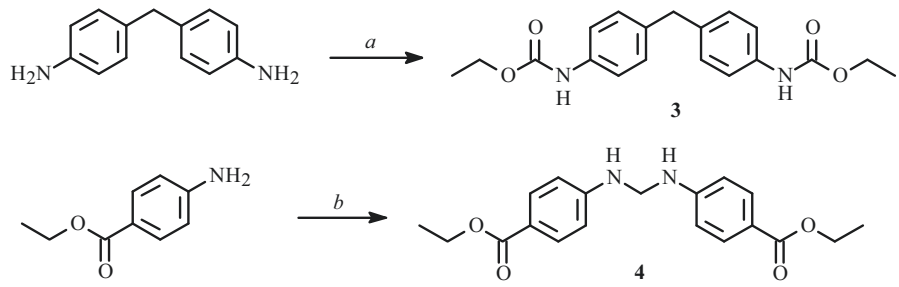
Fig. 1. Comparison of the experimental and calculated ^{13}C NMR chemical shifts of compound **3** and the reported structure **4**. Calculated chemical shifts are underlined.

In addition, the proton resonance of the methylene at the center of the donine structure was reported as a singlet at 3.89 ppm (compound **3** shows a singlet at 3.93 ppm). Considering the fact that in the proposed structure of donine this methylene is directly attached to the NH and pyridine-d_5 has been used as NMR solvent, which is not a suitable solvent for proton-deuterium exchange, the methylene should appear as a doublet instead of a singlet.

This finding was also supported by GIAO-NMR calculation of the correct **3** and incorrect **4** structures. The method developed by Tantillo and co-workers was used for NMR calculation [13]. Following conformational searches, the low-energy conformers were optimized at the B3LYP/6-31+G(d,p) level in pyridine using the PCM model. Then the ^{13}C NMR chemical shifts of the low-energy conformers (19 conformers for compound **3** and 31 conformers for compound **4**) with Boltzmann populations greater than 1% were calculated at the mPW1PW91/6-311+G(2d,p) level in pyridine using the PCM model. The calculated carbon chemical shifts of compound **3** were very close to the experimental values (Fig. 1).

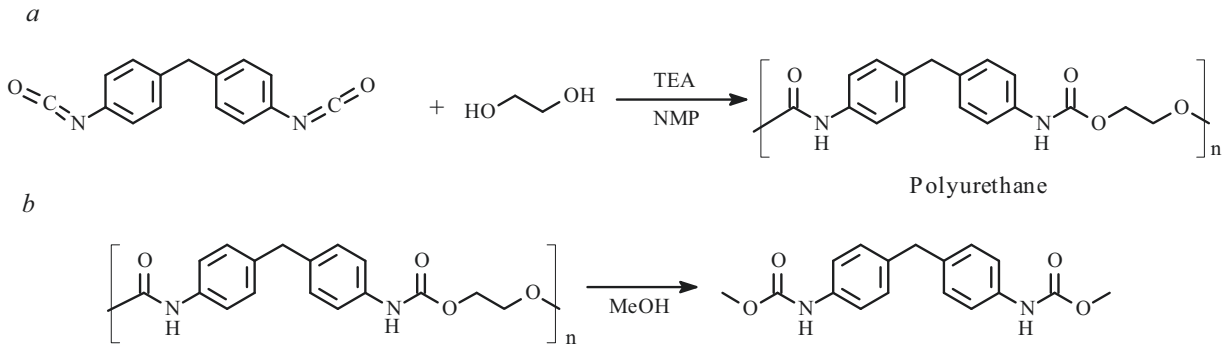
Since the experimental carbon chemical shifts of compound **4** had not been clearly annotated to their corresponding carbon atoms [7], comparison of the experimental and calculated chemical shifts is unreliable. However, the carbon chemical shifts of the methylene at the center of the molecule (40.8 ppm) and the quaternary carbon of the carbonyl (154.7 ppm) are identifiable. As expected, the calculated carbon chemical shifts of these two carbons in **4** showed more than a 10 ppm downfield shift compared to the experimental values. Except for the close values for the ethoxy group, no other correlations were found between the calculated and the experimental carbon chemical shifts of compound **4**.

Compounds **3** and **4** were then synthesized using one-step literature procedures (Scheme 1) [14, 15], and the carbon chemical shifts of the synthetic compounds were compared to the values obtained for the isolated compound **3** and reported values for compound **4** (Table 1). This comparison clarified the identical chemical shifts for the synthesized and isolated compound **3**, while the carbon chemical shifts of the synthesized compound **4** were different from the values reported for donine **4**. All this information revealed that the reported structure for alkaloid **4** is not correct, and therefore the structure of donine should be revised to compound **3**.



a. Ethyl chloroformate, Et_3N, DCM; *b*. CH_2O, EtOH

Scheme 1. Procedures used for synthesis of compounds **3** and **4**.



Scheme 2. *a*) synthesis of polyurethane; *b*) possible degradation by methanol. TEA – triethylamine, NMP – *N*-methylpyrrolidinone.

Compounds **1–3** have an unusual structural backbone that is not common in natural products; therefore, we sought to investigate if they are real natural products or are contaminations of extraction process. Specifically, we suspected that these compounds might be plasticizers as a plastic bucket was used for extraction. As shown in Scheme 2, polyurethane, which is a component of many plastics, under exposure to methanol or ethanol might undergo methanolysis or ethanolysis to yield compounds **1** and **3**, respectively, and a mixture of methanol and ethanol might yield compound **2**. We thus collected *Iphiona aucheri* again from the same place at the same time of the year as it was previously collected. An extraction was performed under previous conditions, but this time in a glass container instead of a plastic bucket. Upon investigation of the extract with LC-MS, none of these compounds were detected. As we did not have access to the plastic container that was used for extraction, we synthesized the polyurethane polymer based on a reported procedure [16] and then exposed it to methanol and ethanol separately. Analysis by LC-MS after 1, 3, and 7 days did not show the target mass for compounds **1** and **3**. Based on these data, it was not possible to conclude whether compounds **1–3** are secondary metabolites produced by plants or extraction artifact, and therefore more investigation needs to be performed to clarify whether these type of compounds are genuine natural products or plasticizers.

In conclusion, three compounds were purified from extract of *Iphiona aucheri*. The structures of the compounds were assigned by analysis of 1 and 2 D NMR and HR-ESI-MS data. It was noticed that mass and NMR data similar to those of compound **3** have been reported for donine alkaloid **4** isolated from *Arundo donax*. Reinvestigation of the NMR data reported for donine, GIAO-NMR calculations, and also synthesis of **3** and **4** revealed that the structure of donine should be revised to **3**.

EXPERIMENTAL

General Procedure. UV spectra were acquired on a Jasco V650 UV/vis spectrophotometer. Infrared spectra were obtained on a FT-IR JASCO A-302 spectrophotometer in $CHCl_3$ solvent. One- and two-dimensional NMR spectra were recorded on a Varian spectrometer operating at 500 (^{1}H NMR) and 125 (^{13}C NMR) MHz. A Waters ZQ electrospray mass spectrometer with a Phenomenex Luna C_{18} column (4.6 × 50 mm, 3 μm) was used for LC-MS analysis. A Betasil C_{18} column (21.2 × 150 mm) was used for semipreparative HPLC separation. All HPLC and LC-MS experiments were performed with

MeOH–H_2O gradient solvent system. Silica gel mesh size 70–230 (E. Merck) was used for column chromatography. Precoated silica gel plates (DC-Alugram 60 UV254, E. Merck) were utilized for thin-layer chromatography (TLC), and detection was performed under UV (254 nm) and cerium(IV) sulfate spray reagent.

Extraction and Isolation. Aerial parts of *I. aucheri* were collected from Karri Village in Bushehr Province, Iran. The plant material was air-dried under the shed and powdered. About 2 kg of the powdered material was extracted with 80% EtOH (3 × 4.5 L) overnight at room temperature. After filtration, the extract was concentrated by rotary evaporation to yield 160 g crude extract. The crude extract was then fractionated by vacuum liquid chromatography (VLC) using silica gel as stationary phase and eluted with stepwise-gradient solvents hexane, hexane–$CHCl_3$, $CHCl_3$–MeOH, and MeOH to give 12 main fractions. The polarity was first increased by 10%, then by 20% from 60% $CHCl_3$–hexane, to 20% MeOH–$CHCl_3$ followed by 50:50 MeOH–$CHCl_3$, and then finished by 100% MeOH. Subsequently, fraction 10 (60 mg) obtained from 20% MeOH–$CHCl_3$ was subjected to silica gel column chromatography with hexane–acetone as solvent system (from 5% to 50% acetone–hexane), resulting in nine subfractions.

Subfraction 2 (18 mg) was then chromatographed by HPLC using a semipreparative reversed-phase C_{18} Betasil column (21.2 mm × 150 mm). Initially isocratic conditions of 10% MeOH were used for 10 min, then a linear gradient from 10 to 100% MeOH was performed over 40 min and continued isocratically for 10 min at a flow rate of 9 mL/min. Sixty fractions were collected in 1 min increments over 60 min. Compound **1** (4 mg) eluted in fraction 31, **2** (6 mg) in fractions 32 and 33, and **3** (5 mg) in fraction 34.

Ethyl Methyl (Methylenedi-4,1-phenylene)biscarbamate (2). White amorphous solid. IR ($CHCl_3$, λ_{max}, cm^{-1}): 3298, 2926, 1715, 1603, 1531, 1227, 1070. UV (MeOH, λ_{max}, nm) (log ε): 206 (4.42), 246 (4.36). ^{1}H NMR (500 MHz, pyridine-d_5, δ, ppm, J/Hz): 1.18 (3H, t, J = 7.1, H-9), 3.74 (3H, s, H-8′), 3.93 (2H, s, H-1″), 4.25 (2H, q, J = 7.1, H-8), 7.29 (4H, dd, J = 8.5, 1.9, H-2, 6, 2′, 6′), 7.87 (4H, t, J = 8.5, H-3, 5, 3′, 5′), 10.56 (NH), 10.65 (NH). ^{13}C NMR (125 MHz, pyridine-d_5, δ, ppm): 15.2 (C-9), 41.3 (C-1″), 52.3 (C-8′), 61.1 (C-8), 119.8 (C-3, 5, 3′, 5′), 130.2 (C-2, 6, 2′, 6′), 136.6 (C-1, 1′), 139.0 (C-4, 4′), 155.2 (C-7), 155.6 (C-7′). HR-ESI-MS *m/z* 351.1315 $[M + Na]^+$ (calcd for $C_{18}H_{20}O_4N_2Na$, 351.1315).

Diethyl (Methylenedi-4,1-phenylene)biscarbamate (3). White amorphous solid. IR ($CHCl_3$, λ_{max}, cm^{-1}): 3296, 2926, 1712, 1600, 1531, 1226, 1068. UV (MeOH, λ_{max}, nm) (log ε): 206 (4.47), 246 (4.45). ^{1}H NMR (500 MHz, pyridine-d_5, δ, ppm, J/Hz): 1.18 (6H, t, J = 7.1, H-9, 9′), 3.93 (2H, s, H-1″), 4.25 (4H, q, J = 7.1, H-8, 8′), 7.29 (4H, d, J = 8.4, H-2, 6, 2′, 6′), 7.89 (4H, d, J = 8.4, H-3, 5, 3′, 5′), 10.57 (NH). ^{13}C NMR (125 MHz, pyridine-d_5, δ, ppm): 15.2 (C-9, 9′), 41.3 (C-1″), 61.2 (C-8, 8′), 119.8 (C-3, 5, 3′, 5′), 130.2 (C-2, 6, 2′, 6′), 136.7 (C-1, 1′), 139.0 (C-4, 4′), 155.2 (C-7, 7′). HR-ESI-MS *m/z* 365.1468 $[M + Na]^+$ (calcd for $C_{19}H_{22}O_4N_2Na$, 365.1471).

Synthesized Diethyl 4,4′-(Methylenebis(azanediyl))-dibenzoate (4). White amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.26 (6H, t, J = 7, H-9, 9′), 4.20 (4H, q, J = 7, H-8, 8′), 4.57 (2H, t, J = 5.5, H-1″), 6.72 (4H, d, J = 8.5, H-2, 6, 2′, 6′), 7.25 (2H, t, J = 5.5, NH), 7.70 (4H, d, J = 8.5, H-3, 5, 3′, 5′). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 14.3 (C-9, 9′), 51.2 (C-1″), 59.6 (C-8, 8′), 111.6 (C-2, 6, 2′, 6′), 117.0 (C-4, 4′), 130.8 (C-3, 5, 3′, 5′), 151.6 (C-1, 1′), 165.8 (C-7, 7′). ^{1}H NMR (500 MHz, pyridine-d_5, δ, ppm, J/Hz): 1.22 (6H, t, J = 7, H-9, 9′), 4.32 (4H, q, J = 7, H-8, 8′), 4.97 (2H, t, J = 5.5, H-1″), 7.02 (4H, d, J = 8.5, H-2, 6, 2′, 6′), 7.87 (2H, t, J = 5.5, NH), 8.15 (4H, d, J = 8.5, H-3, 5, 3′, 5′). ^{13}C NMR (125 MHz, pyridine-d_5, δ, ppm): 15.0 (C-9, 9′), 53.3 (C-1″), 60.7 (C-8, 8′), 112.8 (C-2, 6, 2′, 6′), 119.5 (C-4, 4′), 132.4 (C-3, 5, 3′, 5′), 152.9 (C-1, 1′), 167.3 (C-7, 7′). HR-ESI-MS *m/z* 365.1471 $[M + Na]^+$ (calcd for $C_{19}H_{22}O_4N_2Na$, 365.1472).

Computational Methods. Conformational searches were performed in Schrodinger MacroModel 9.1 using the OPLS 2005 (Optimized Potential for Liquid Simulations) force field in H_2O. Gaussian 09 was used for optimization and NMR calculations. Conformers occurring within a 2 kcal/mol energy window from the global minimum were chosen for geometrical optimization with the B3LYP functional and the 6-31+G(d,p) basis set in the gas-phase with the Gaussian 09 program. Vibrational analysis was done at the same level to confirm minima, and frequency lists were checked to ensure that no imaginary frequencies were present. The NMR calculations were performed in Gaussian 09 using the gauge-independent atomic orbitals (GIAO) method and SCRF-mPW1PW91/6-311+G(2d,p) level of theory in pyridine as solvent. The calculated NMR isotopic shifts were empirically scaled according to the following formula:

$$\delta = (b - \sigma)/-m,$$

where δ is the calculated chemical shift referenced to the TMS, b is the y-intercept, σ is the calculated isotopic chemical shielding value, and m is the slope. The scaling factors used for ^{13}C shifts were m = –1.0533 and b = 186.5242, obtained from the CHESHIRE CCAT website (http://cheshirenmr.info/). The calculated chemical shifts were obtained from the Boltzmann-averaged chemical shift of all the conformers.

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