Stemoninines from the Roots of *Stemona tuberosa*

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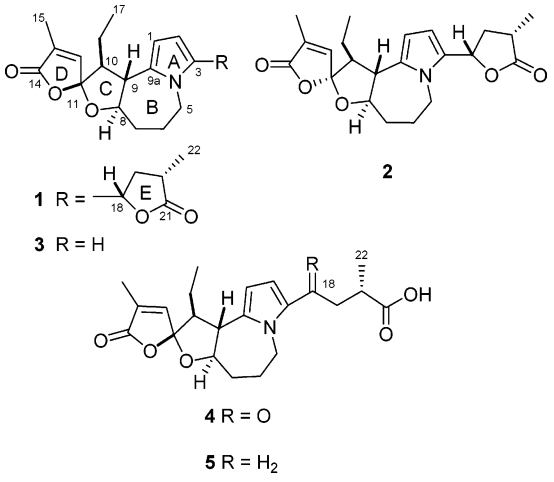
Five new stemoninine-type alkaloids, bisdehydrostemoninine (**1**), isobisdehydrostemoninine (**2**), bisdehydroneostemoninine (**3**), and bisdehydrostemonininines A (**4**) and B (**5**), were isolated from the crude-alkaloid extract of the roots of *Stemona tuberosa*. Their structures were elucidated on the basis of one- and two-dimensional NMR and other spectroscopic studies. The relative configuration of **4** was determined by X-ray diffraction. Alkaloid **1** displayed significant antitussive activity in the citric acid-induced guinea pig cough model.

The roots of *Stemona tuberosa* Lour. (Stemonaceae) have been used as an antitussive agent and insecticide for thousands of years in Traditional Chinese Medicine.[1,2] Alkaloids, present as the main components in the roots of this plant, are believed to be responsible for its bioactivities. Chemical investigations have been carried out extensively, and more than twenty alkaloids possessing an azaazulene ring basic skeleton were identified.[2] Most of the reported alkaloids are tuberostemonine-type alkaloids,[4−7] and only two are stemoninine-type.[2] In 2003 a pharmacological study revealed that some representative tuberostemonine-type alkaloids exhibited significant antitussive activity in the guinea pig after cough induction by citric acid aerosol stimulation.[9]

As a part of our systematic chemical investigation of alkaloids in the plants of the Stemonaceae family in China, alkaloids in *S. tuberosa* Lour. collected from Hainan province were investigated in the present study. Five new stemoninine-type alkaloids (**1**−**5**) were isolated. Their structures were determined by one- and two-dimensional NMR and other spectroscopic studies. The structure of **4** was confirmed by X-ray diffraction. The antitussive activity of the major alkaloid **1** was investigated by using the citric acid-induced guinea pig cough model.



Results and Discussion

The HRESIMS of bisdehydrostemoninine (**1**) afforded the molecular formula as $C_{22}H_{27}NO_5$ (*m*/*z* 386.1952 $[M + H]^+$) with 10 degrees of unsaturation. The ^{13}C NMR and DEPT spectra (Table 1) indicated **1** had 22 carbons, including three CH_3, five CH_2, eight CH, and six quaternary carbons. The low-field carbonyl carbons (δ_C 179.1 and 171.6), coupled with the strong and sharp IR absorption at 1763 cm^{-1}, suggested the presence of two γ-lactone moieties in **1**. The ^1H NMR of **1** (Table 2) showed three methyl signals at δ_H 0.81 (3H, t, $J = 7.6$), 1.19 (3H, d, $J = 7.0$), and 1.81 (3H, d, $J = 1.3$) and three olefinic proton signals at δ_H 5.88 (1H, d, $J = 3.5$), 6.13 (1H, d, $J = 3.5$), and 7.18 (1H, d, $J = 1.3$). The triplet methyl suggested the existence of an ethyl group. The coupling relation between the vinylic methyl (δ_H 1.81) and the olefinic proton (δ_H 7.18) indicated the presence of an allylic moiety. The evidence revealed that compound **1** contained the basic skeleton of stemoninines.[2] In a comparison of its ^1H and ^{13}C NMR spectra with those of stemoninine,[8] the signals of the spiro unsaturated γ-lactone (rings C and D) and α-methyl-γ-lactone (ring E) were similar. The major differences involved the signals of ring A. Two conjugated olefinic protons (δ_H 5.88 and 6.13) in **1**, instead of the signals of a pyrrolidine ring in stemoninine, suggested that **1** contained a dehydroazaazulene ring.[5] Thus, the gross structure of **1** was constructed, and the key HMBC correlations are shown by broken arrows in Figure 1. The relative configuration was revealed by the ROESY spectrum (broken arrows in Figure 2a). The correlations between H-9 and H-5b and H-7b indicated that the

Table 1. ^{13}C NMR Data of Alkaloids **1**−**5** (100 MHz)

C	**1**[a]	**2**[a]	**3**[b]	**4**[b]	**5**[b]
1	103.9 CH	103.7 CH	104.1 CH	104.9 CH	102.2 CH
2	107.0 CH	106.9 CH	106.1 CH	119.4 CH	104.4 CH
3	132.8 C	131.5 C	121.9 CH	140.1 C	132.1 C
5	44.3 CH_2	44.4 CH_2	48.9 CH_2	45.3 CH_2	44.0 CH_2
6	26.1 CH_2	25.7 CH_2	26.7 CH_2	25.9 CH_2	26.5 CH_2
7	35.0 CH_2	34.4 CH_2	35.1 CH_2	35.6 CH_2	35.4 CH_2
8	84.2 CH	83.0 CH	84.6 CH	84.5 CH	84.9 CH
9	46.5 CH	51.1 CH	47.3 CH	47.2 CH	47.4 CH
9a	128.8 C	128.9 C	129.6 C	130.4 C	129.6 C
10	49.3 CH	51.1 CH	50.9 CH	50.5 CH	50.8 CH
11	113.4 C	114.7 C	113.2 C	113.0 C	113.2 C
12	147.1 CH	145.2 CH	145.4 CH	144.9 CH	145.5 CH
13	132.8 C	132.6 C	133.2 C	133.6 C	133.2 C
14	171.6 C	171.2 C	171.6 C	171.4 C	171.7 C
15	10.2 CH_3	10.1 CH_3	10.5 CH_3	10.6 CH_3	10.5 CH_3
16	19.9 CH_2	22.8 CH_2	19.9 CH_2	19.9 CH_2	19.9 CH_2
17	12.6 CH_3	12.1 CH_3	13.0 CH_3	13.0 CH_3	13.1 CH_3
18	71.4 CH	71.3 CH		188.7 C	33.1 CH_2
19	34.5 CH_2	33.4 CH_2		42.3 CH_2	24.3 CH_2
20	35.7 CH	35.8 CH		35.0 CH	38.7 CH
21	179.1 C	179.1 C		181.3 C	181.0 C
22	15.6 CH_3	15.5 CH_3		17.1 CH_3	17.2 CH_3

[a] In DMSO-d_6. [b] In $CDCl_3$.

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Table 2. ^{1}H NMR Data of Alkaloids **1**−**5** (400 MHz)

C	**1**[a]	**2**[a]	**3**[b]	**4**[b]	**5**[b]
1	5.88, d (3.5)	5.91, d (3.6)	5.89, m	5.94, d (4.0)	5.80, d (4.7)
2	6.13, d (3.5)	6.11, d (3.6)	6.02, t (2.0)	6.95, d (4.1)	5.85, d (4.7)
3			6.58, t (3.3)		
5a	4.20, dd (5.3, 14.6)	4.20, dd (5.3, 14.4)	4.05, dd (4.8, 14.3)	5.80, dd (5.7, 14.7)	4.18, dd (5.3, 14.8)
5b	3.83, dd (11.8, 14.6)	3.78, dd (11.8, 14.4)	3.89, dd (11.6, 14.3)	3.68, dd (2.8, 14.3)	3.70, m
6a	2.02, m	2.00, m	2.08, m	2.08, m	2.08, m
6b	1.60, m	1.63, m	1.58, m	1.62, m	1.50, m
7a	2.19, m	2.20, m	2.31, m	2.31, m	2.30, m
7b	1.72, m	1.65, m	1.80, m	1.85, m	1.80, m
8	3.58, ddd (3.6, 9.9, 9.9)	3.68, ddd (3.6, 9.9, 9.9)	3.71, dt (3.4, 11.1)	3.70, m	3.67, dd (3.7, 15.2)
9	3.21, dd (9.9, 12.0)	3.05, dd (10.6, 20.9)	3.20, dd (3.2, 11.0)	3.25, m	3.20, dd (10.0, 12.1)
10	2.60, m	2.60, m	2.72, dt (3.2, 9.3)	2.58, ddd (3.5, 8.9, 12.5)	2.55, m
12	7.18, d (1.3)	7.23, d (1.4)	6.75, d (1.5)	6.75, d (1.6)	6.75, d (1.6)
15	1.81, d (1.3)	1.81, d (1.4)	1.98, d (1.5)	1.98, d (1.5)	1.98, d (1.6)
16	1.43, m	1.45, m	1.61, m	1.72, m	1.60, m
16	1.38, m	1.38, m	1.77, m	1.64, m	1.80, m
17	0.81, t (7.6)	0.79, t (7.6)	0.90, t (7.6)	0.91, t (7.5)	0.87, t (7.6)
18	5.53, dd (5.3, 11.1)	5.52, dd (5.4, 11.3)			a2.00, m
					b1.77, m
19a	2.68, m	2.72, m		3.25, m	2.58, m
19b	2.11, m	2.12, m		2.92, m	
20	2.82, m	2.80, m		3.12, dq (2.0, 7.3)	2.68, m
22	1.19, d (7.0)	1.18, d (6.9)		1.27, d (7.2)	1.25, d (6.3)

[a] In DMSO-d_6. [b] In $CDCl_3$.

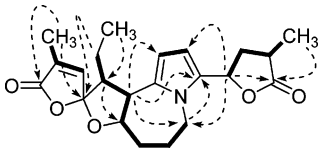

Figure 1. ^{1}H−^{1}H correlations (bold lines) and key HMBC correlations (broken arrows) of **1**.

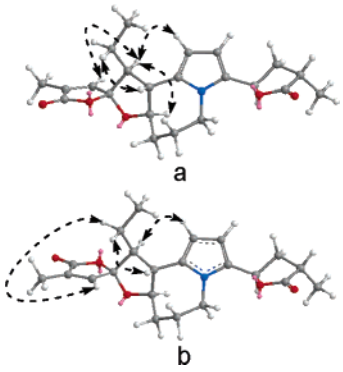

Figure 2. Key NOE correlations (broken arrows) and possible conformations of **1** (a) and **2** (b).

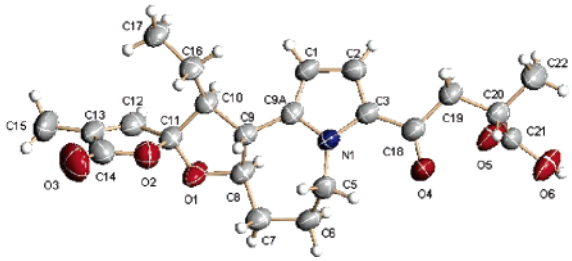

Figure 3. X-ray diffraction of compound **4**.

seven-membered ring was in a stable chair conformation. The β-orientation of H-18 was revealed by its correlation with H-5a. The configuration of C-11 was determined by the NOE correlation between H-10 and H-12. Thus the structure of **1** was established and further confirmed by a single-crystal X-ray diffraction experiment (Figure 5, Supporting Information). The detailed assignments of the ^{1}H and ^{13}C NMR signals were determined by a HMQC experiment (Tables 1 and 2).

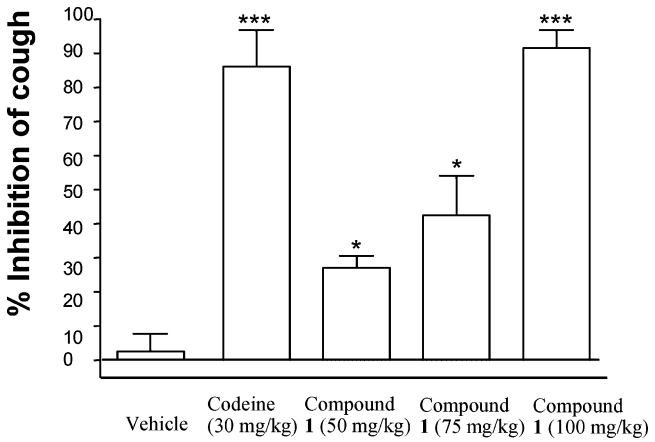

Figure 4. Antitussive activity of compound **1** in guinea pigs treated with a single ip dose. Cough was induced by 0.5 M citric acid aerosol at flow rate of 0.5 mL/min. Data were expressed as mean ± SEM (standard error of the mean). *p < 0.05, **p < 0.01, ***p < 0.001 compared with vehicle control.

The HRESIMS of isobisdehydrostemoninine (**2**) indicated the molecular formula to be $C_{22}H_{27}NO_5$ (*m*/*z* 386.1985 [M + H]$^+$), which was the same as **1**. Careful analysis of spectroscopic data resulted in the conclusion that compound **2** was a stereoisomer of **1**. The relative configuration was disclosed by a ROESY experiment (broken arrows in Figure 2b). NOE correlations between H-10 and H-1, H-9, and H-16 showed that the configuration of the ethyl group was the same as in **1** and β-oriented. The configuration at C-11 was unequivocally assigned on the basis of the NOE correlation between H-12 and H-16, which was different from **1**. The correlation between H-5a and H-18 disclosed that H-18 was in the β-orientation. The structure of **2** was established, and the detailed assignments of the ^{1}H and ^{13}C NMR signals were determined by a HMQC experiment (Tables 1 and 2).

The molecular formula $C_{17}H_{21}NO_3$ of bisdehydroneostemoninine (**3**) was inferred from the HRESIMS (*m*/*z* 288.1607 [M + H]$^+$) and supported by ^{13}C NMR and DEPT data (Table 1). An IR absorption at 1766 cm^{-1}, coupled with a low-field carbonyl carbon (δ_C 171.6), suggested the presence of a lactone moiety. The similarity in the ^{1}H and ^{13}C NMR spectra of compounds **1** and **3** revealed that they shared the same basic skeleton. The ^{1}H−^{1}H correlations between H-1 and H-2 and between H-2 and H-3 in

the $^1H-^1H$ COSY spectrum clearly indicated a dehydroazaazulene ring constructed by the three olefinic protons. The relative configuration of **3** was also confirmed by a NOESY experiment. Thus, the structure of **3** was established, and assignments of the ^1H and ^{13}C NMR signals were determined by a HMQC experiment.

The molecular formula of bisdehydrostemoninine A (**4**) was determined to be $C_{22}H_{27}NO_6$ from its HRESIMS. Its IR spectrum indicated the presence of a γ-lactone (1761 cm^{-1}), a carbonic acid (3427, 1705, 1481 cm^{-1}), and an α,β-unsaturated ketone (1641 cm^{-1}). The ^1H and ^{13}C NMR spectra revealed that **4** contained the basic skeleton of stemoninine-type alkaloids. The dehydroazaazulene ring and spiro unsaturated γ-lactone fragments were similar to those of **1**. In the ^{13}C NMR spectrum a carbonyl carbon (δ_C 188.7) in **4** instead of the methine [δ_C 71.5 (C-18)] in **1** was inferred to be an α,β-unsaturated ketone signal. The HMBC correlations between the carbonyl carbon and H-19 and H-20 confirmed the conclusion. The location of the carbonic acid group (δ_C 181.3) at C-21 was supported by HMBC correlations between C-21 and H-22. The evidence revealed that the γ-lactone annexed to C-3 in **1** was opened to form a five-carbon carbonic acid side chain in **4**. The relative configuration of **4** was determined by a ROESY experiment and further confirmed by X-ray diffraction, as shown in Figure 3. The methyl group at C-20 was α-oriented and the same as in **1**.

The molecular formula of bisdehydrostemoninine B (**5**) was established as $C_{22}H_{29}NO_5$ by HRESIMS. Strong IR absorptions at 1766 and 3431 cm^{-1} indicated the presence of γ-lactone and hydroxyl groups. The ^1H and ^{13}C NMR spectra of **5** were very similar to those of **4**, except that a methylene (δ_C 33.1) was present in **5** instead of the carbonyl carbon (C-18) in **4**. The C-18 methylene was established by the correlation between the H-18a, H-18b, and the olefinic carbon (C-3) in the HMBC spectrum. In comparison with **4**, upfield shifts of the H-2, C-2, and C-3 NMR signals supported the above deduction. The configuration of **5** was revealed by a ROESY experiment. Detailed assignments of the ^1H and ^{13}C NMR signals of **5** were performed using HMQC.

Compounds **4** and **5**, found for the first time, possess a five-carbon linear side chain moiety annexed to C-3 of the azaazulene ring. Co-occurrence of alkaloids with the typical C-3 α-methyl-γ-lactone moiety and those with a five-carbon linear chain moiety in the same plant suggested a common biogenetic origin.

Compound **1** was chosen as a representative for the study of antitussive activity in the citric acid-induced guinea pig cough model. Compound **1** showed significant antitussive activity in a dose-dependent manner (Figure 4), and about 90% cough inhibition was achieved at a single intraperitoneal (ip) dose of 100 mg/kg. Furthermore, the ED_{50} of compound **1** was estimated to be 188 $\pm$ 13 μmol/kg (ip). Comparing the results from our previous study[9] on the tuberostemonine-type alkaloid neotuberostemonine (66 $\pm$ 7 μmol/kg, ip), compound **1** exhibited markedly lower potency in cough suppression. Nevertheless, the results demonstrated that a stemoninine-type alkaloid (compound **1**) is also an active component, which may contribute to the antitussive effect of herbal *S. tuberosa*.

Experimental Section

General Experimental Procedures. Optical rotations were taken on a Perkin-Elmer 341 polarimeter. IR spectra were recorded on Nicolet Magna FT-IR 750 spectrophotometer using KBr disks. NMR spectra were recorded on Bruker AM-400 and INVOR-600 NMR spectrometers. The chemical shift (δ) values are given in ppm with TMS as internal standard, and coupling constants (J) are in Hz. EIMS and HREIMS spectra were recorded on a Finnigan MAT-95 mass spectrometer. ESIMS and HRESIMS spectra were recorded on a Micromass LC-MS-MS mass spectrometer. Silica gel was used for flash chromatography and was produced by Qingdao Marine Chemical Industrials. TLC was carried out on precoated silica gel GF254 plates (Yantai Chemical Industrials), and the TLC spots were viewed at 254 nm and visualized by spraying with Dragendorff reagent.

Plant Material. The plant material was collected in Hainan Province, China, and was identified by Professor Yi Zhong. A voucher was deposited at the herbarium of Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

Extraction and Isolation. Air-dried roots of *S. tuberosa* (7.0 kg) were ground into powder and extracted with 95% EtOH. After evaporation of the collected percolate, the crude extract was acidified with dilute HCl (4%) to pH 1−2 and partitioned between CH_2Cl_2 and H_2O. The aqueous part was basified with aqueous NH_3 to pH 9−10 and extracted with CH_2Cl_2 to afford 88 g of crude alkaloid. The crude alkaloid (80 g) was subjected to column chromatography over silica gel and eluted with petroleum ether−acetone (4:1, 3:1, 2:1, 1:1, 1:2), acetone, and MeOH (each 5 L) to yield nine major fractions (ST1−ST9). Fraction ST4 was subjected to repeated column chromatography over silica gel and then Sephadex LH-20 to afford bisdehydrostemoninine (**1**) (1.85 g), isobisdehydrostemoninine (**2**) (1.52 g), bisdehydroneostemoninine (**3**) (26 mg), bisdehydrostemoninine A (**4**) (22 mg), and bisdehydrostemoninine B (**5**) (19 mg).

Antitussive Activity of Compound 1. Our previously established citric acid-induced guinea pig cough model[9] with modifications was used in the study. This animal cough model is generally recognized as the most relevant model for predicting the clinical efficacy of drugs treating cough in man.[10,11] Briefly, unrestrained, conscious Dunkin-Hartley guinea pigs of both sexes (300−350 g) were randomly divided into groups with at least 5 animals in each group. Compound **1** (dose of 50, 75, and 100 mg/kg) was given to the guinea pigs in different groups respectively via a single ip injection. The treated animal was individually placed into a transparent Perspex airtight chamber. At 30 min after treatment, each animal was exposed to 0.5 M citric acid aerosols for 8 min with a flow rate of 0.5 mL/min. During the aerosol exposure, the animal was continuously monitored, and cough sounds were recorded via a microphone connected to a personal computer and analyzed by Cool Edit 2000 software (Syntrillium, Phoenix, Az). Cough episodes were determined. The antitussive activity of codeine phosphate as the positive control and response of the vehicle control (Tween 80 in saline (5:95, v/v)) were also tested in parallel studies. Antitussive activity was evaluated and expressed as the percentage of cough inhibition based on the comparison of numbers of cough episodes recorded in the alkaloid-treated group with the corresponding vehicle control group. Statistical analysis between the alkaloid-treated and control group was calculated using Mann−Whitney test. A p value less than 0.05 was considered to be significant difference.

Bisdehydrostemoninine (1): colorless cubic crystals (EtOAc); mp 138−140 °C; $[\alpha]_D^{20}$ −57 (*c* 0.13, $CHCl_3$); IR ν_{max} (KBr) 2935, 1762, 1169, 968 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1 and Table 2; ESIMS *m/z* 386.3 $[M + 1]^+$, 770.5 $[2M]^+$, 793.1 $[2M + Na]^+$; HRESIMS *m/z* 386.1952 (calcd for $C_{22}H_{28}NO_5$, 386.1967).

Isobisdehydrostemoninine (2): colorless needle crystals (EtOAc); mp 178−182 °C; $[\alpha]^{20}_D$ 0 (*c* 0.15, $CHCl_3$); IR ν_{max} (KBr) 2935, 1766, 1161, 960 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1 and Table 2; ESIMS *m/z* 386.2 $[M + 1]^+$, 770.8 $[2M]^+$; HRESIMS *m/z* 386.1985 (calcd for $C_{22}H_{28}NO_5$, 386.1967).

Bisdehydroneostemoninine (3): yellow amorphous solid; $[\alpha]^{20}_D$ −132 (*c* 0.06, $CHCl_3$); IR ν_{max} (KBr) 3354, 2925, 1766, 1456, 1284, 972 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1 and Table 2; ESIMS *m/z* 288.1 $[M + 1]^+$; HRESIMS *m/z* 288.1607 (calcd for $C_{17}H_{22}NO_3$, 288.1600).

Bisdehydrostemoninine A (4): colorless cubic crystals (hexanes−EtOAc); $[\alpha]^{20}_D$ −186 (*c* 0.05, $CHCl_3$); IR ν_{max} (KBr) 3427, 2947, 1761, 1705, 1641, 1481, 1261, 1059, 972 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1 and Table 2; ESIMS *m/z* 402.1 $[M + 1]^+$, 424.1 $[M + Na]^+$, 400.3 $[M - 1]^-$; HRESIMS *m/z* 402.1905 (calcd for $C_{22}H_{28}NO_6$, 402.1917).

Bisdehydrostemoninine B (5): yellow amorphous solid; $[\alpha]^{20}_D$ −122 (*c* 0.14, $CHCl_3$); IR ν_{max} (KBr) 3431, 2925, 1766, 1464, 1286, 1167, 972 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1 and Table 2; ESIMS *m/z* 388.2 $[M + 1]^+$, 410.2 $[M + Na]^+$, 426.2 $[M + K]^+$; 386.4 $[M - 1]^-$; HRESIMS *m/z* 388.2143 (calcd for $C_{22}H_{30}NO_5$, 388.2124).

X-ray Crystal Structure Determination of 4. A colorless cubic of **4** was obtained by recrystallization from hexane−EtOAc. A single crystal with dimensions of 0.52 × 0.46 × 0.32 mm was used for X-ray diffraction studies on a Bruker AXS diffractometer employing graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structure was

solved by a direct method using SHELXL-97 (Sheldrick, 1990) and refined also by SHELXL-97 (Sheldrick, 1997)[12] using 2420 reflections [$I > 2.00\sigma(I)$] for 297 parameters. The final R value is 0.053.

Crystal Data: $C_{88}H_{108}N_4O_{24}$, $M = 1605.78$, monoclinic, space group $C2$, with $a = 20.289(2)$ Å, $b = 7.599(8)$ Å, $c = 16.572(17)$ Å, $V = 2074(4)$ Å^3, and D_c ($Z = 1$) = 1.286 g/cm^3. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 603428). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposite@ccdc.cam.ac.uk).

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Supporting Information Available: Figure 5 along with the crystallographic data for structures **1** and **4** are available free of charge via the Internet at http://pubs.acs org.

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