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Total Synthesis of Clathculins A and B

Rebecca C. Hoye,* Gretchen L. Anderson, Susan G. Brown, and Erica E. Schultz

Department of Chemistry, Macalester College, 1600 Grand Avenue, Saint Paul, Minnesota 55105, United States

hoye@macalester.edu

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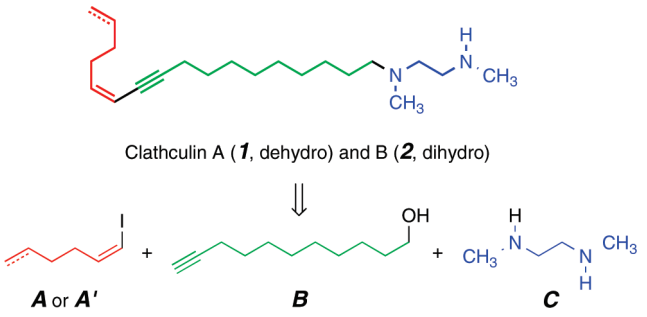


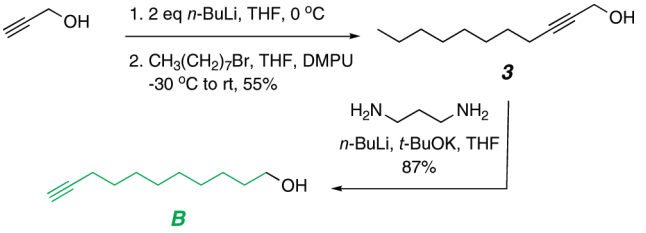
Clathculins A and B represent a new class of *vic*-diamine alkaloids containing a PA2 unit as the basic structure. We report the first total syntheses of **1** and **2**, which confirm the assigned structure of each. Dependence of their NMR spectroscopic behavior as a function of protonation state has been observed.

Clathculins A and B were isolated from the Indo-Pacific sponge *Clathrina* aff. reticulum collected in Sodwana Bay, South Africa.[1] They were described as an unstable (and, not surprisingly, inseparable) mixture of compounds **1** and **2**.[1] Structures were assigned on the basis of NMR spectroscopy (COSY, TOCSY, and HMBC correlations) of the mixture as well as by acetylation and reduction to the common saturated analog. Clathculins A and B are the first reported examples of acyclic long-chain marine metabolites containing a $>NCH_2CH_2N<$ (PA2) moiety.[2] Additionally, there appear to be no known examples of natural substances containing the array of substituents $R^1R^2NCH_2CH_2NHR^3$ where R^1, R^2, and R^3 are any combination of Me and $-CH_2R$ substituents. This contrasts with the 1,3-diaminopropane (PA3) and 1,4-diaminobutane (PA4) elements common to the spermidine and spermine classes of polyamines. Other key structural features are the presence of an internal enyne moiety in a C-17 chain and the differentiating alkene vs alkane chain termini. Clathculin A is the only known natural product to have a terminal $CH_2{=}CH(CH_2)_2CH{=}CHC{\equiv}CCH_2-$ subunit.

Given these unique structural features as well as their inherent inseparability, we decided to prepare each of the natural products by chemical synthesis. Our retrosynthetic approach is shown above. It was anticipated that palladium-catalyzed coupling of alkyne **B** with the appropriate vinyl iodide **A** or **A′** would create a precursor for C−N bond formation with commercially available *N*,*N*′-dimethylethylenediamine (**C**).

The α,ω-alkynyl alcohol (**B**) was prepared as shown in Scheme 1. The dianion of propargyl alcohol was generated in THF and treated with 1-bromooctane in DMPU[3] to yield 3-undecyn-1-ol (**3**) in 60% yield. Zipper isomerization to the terminal alkyne **B** was effected in 87% yield in THF with 5.0 equiv of diaminopropane in the presence of 4.0 equiv of *n*-BuLi and 4.0 equiv of *t*-BuOK. These conditions are operationally simpler than the standard zipper isomerization conditions[4] and also avoid the use of noxious 1,3-diaminopropane as the reaction solvent.

SCHEME 1. Preparation of Compound B



Vinyl iodides **A** and **A′** were prepared as shown in Scheme 2. Following a strategy first reported by Kluge, Untch, and Fried,[5] 1-iodohexyne,[6] **4**, was reduced with diimide[7] to give (*Z*)-1-iodohexene, **A**, in 55% yield. Similarly, 5-hexyn-1-ol was converted to iodide **5**[8] and reduced with diimide to give **6**. Formation of the tosylate[9] **7** and conversion to the selenide **8** followed by oxidation and elimination[10] afforded **A′**.

Clathculins A and B were obtained as shown in Scheme 3. Sonogashira coupling[11] of iodide **A** or **A′** with **B** afforded the enynes **9** and **10**, respectively. Formation of the corresponding tosylates **11** and **12** and reaction of each with *N*,*N*′-dimethylethylenediamine afforded clathculins A (**1**) and B (**2**), respectively.

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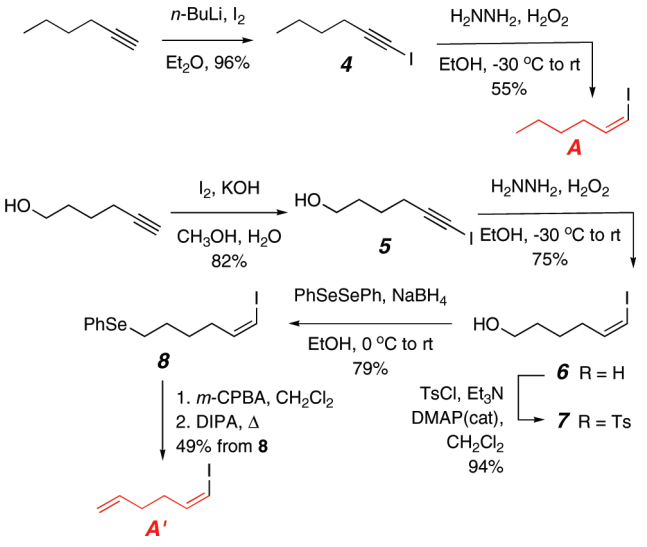
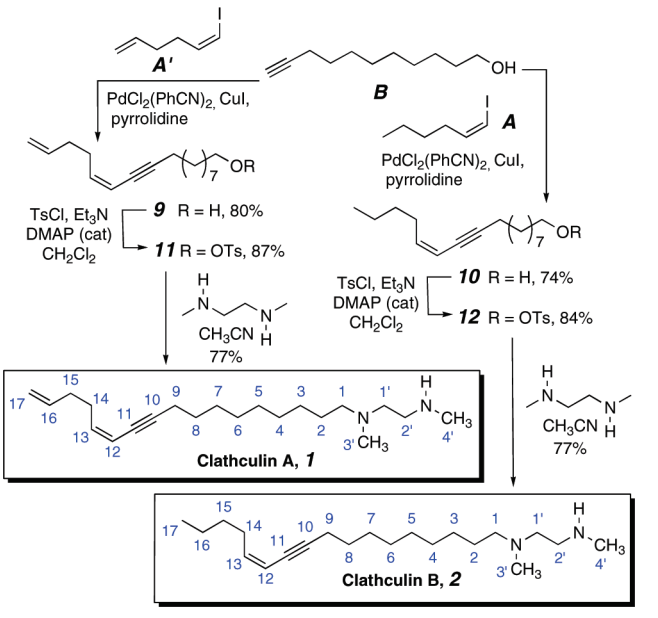
TABLE 1. ^{1}H NMR Data (300 MHz) of Clathculins A and B (1 and 2) in $CDCl_3$

δ	1 synthetic	1 synthetic	1 natural[1]	2 synthetic	2 synthetic	2 natural[1]
		(with 2% TFA)			(with 2% TFA)	
1	2.33 ~t (7.0)	3.26 ddd (12.5, 6.5, 10.5); 3.08 ddd (12.5, 6.5, 10.5)	2.45 q (7.1)	In 2.37 – 2.25 m	3.23 m, 3.08 m	
9	2.33 dt (2.2, 7.0)	2.33 dt (2.0, 7.0)	2.25 m	In 2.37 – 2.25 m	2.32 dt (2.1, 6.8)	
12	5.47 ddt (10.1, 2.2, 1.5)	5.46 ddt (10.7, 1.3, 2.2)	5.44 d (10.8)	5.43 dtt (10.7, 2.2, 1.3)	5.42 dtt (10.7, 2.3, 1.6)	5.43 d (9.8)
13	5.83 dt (10.7, 7.2)	5.82 dt (10.7, 7.2)	5.81 dt (10.8, 7.0)	5.80 dt (10.7, 7.4)	5.82 dt (10.7, 7.4)	5.80 dt (9.8, 7.0)
14	2.39 br dt (7.5, 7.5)	2.39 br dt (7.5, 7.5)	2.30 m	In 2.37 – 2.25 m	2.28 ddt (7.3, 1.3, 7.3)	2.20 m
15	2.16 br dt (6.5, 7.5)	2.16 br dt (6.5, 7.5)	2.05 q (7.1)	1.60 – 1.23 m	1.70 – 1.25	1.25 m
16	5.84 ddt (17.1, 10.3, 6.5)	5.83 ddt (17.1, 10.2, 6.5)	5.84 ddt (17.1, 10.2, 7.1)	1.60 – 1.23 m	1.70 – 1.25	2.25 m
17a	5.05 ddt (17.1, 1.8, 1.6)	5.04 ddt (17.1, 2.0, 1.6)	5.05 d (17.1)	0.91 t (6.9)	0.90 t (7.0)	0.80 t (7.5)
17b	4.97 ddt (10.2, 2.1, 1.7)	4.97 ddt (10.2, 2.0, 1.7)	4.95 d (10.2)			
1'	2.49 t (6.2)	3.75 m, 3.56 m	2.70 t (6.8)	2.50 t (6.1)	3.75 m, 3.56 m	
2'	2.68 t (6.2)	3.59 brs	2.95 t (6.8)	2.66 t (6.2)	3.60 brs	
3'	2.21 s	2.94 s	2.25 s	2.20 s	2.93 s	
4'	2.47 s	2.87 s	2.60 s	2.46 s	2.87 s	

SCHEME 2. Preparation of Vinyl Iodides A and A′



SCHEME 3. Convergent Couplings Leading to 1 and 2



^{1}H NMR chemical shifts data for selected protons of **1** and **2** in $CDCl_3$ (synthetic vs natural[1]) and in 2% TFA in $CDCl_3$ (synthetic) are shown in Table 1. Our initial concern over differences in chemical shifts between those reported for natural vs those we observed for the synthetic samples led us to probe the question of protonation. It has been shown that chemical shifts of protons[12] and carbons[13] in close proximity to amines are dependent on degree of protonation. To give confidence that we were observing the free-base forms of the synthetic materials, the crude reaction products were chromatographed on silica gel using CMA [chloroform/methanol/ammonia (83: 17: 0.5)] as eluent,

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and the NMR spectra were recorded in $CDCl_3$ that had been stored over K_2CO_3. We have investigated the ^1H NMR spectral behavior of clathculins A and B in $CDCl_3$ in the presence of 2% trifluoroacetic and 2% acetic acid-d_4. Upon addition of trifluoroacetic acid (2% TFA in $CDCl_3$), full (i.e., double) protonation of clathculins was observed, as judged by the diastereotopic nature of the methylene protons at C1 and at C1′ adjacent to the stereogenic nitrogen of the tertiary ammonium ion. The salient differences are highlighted in gray boxes. In contrast, in the presence of the weaker acetic acid, less than full protonation was observed (see the Supporting Information). The chemical shifts reported for the natural sample[1] fall between those we observed for the free-base versus in the presence of either TFA or AcOH. The most reasonable explanation is that the spectral data for the natural material were recorded for a sample that was slightly protonated.

Although the natural material was described as a mixture of two unstable compounds,[1] we have not observed instability with either crude or purified synthetic samples in either the free-base or protonated forms. We do not have a good explanation for the original observations; our samples of clathculins A and B, each in 2% TFA in $CDCl_3$, were allowed to stand at room temperature for 3 weeks, during which time they showed no evidence of change by ^1H NMR analysis.

We have achieved a convergent synthesis of the natural enyne diamines clathculins A (**1**) and B (**2**). We have also shown the value of recording and reporting NMR data of basic amine-containing compounds both as the free-base as well as in the presence of excess acid (here 2% TFA in $CDCl_3$).

Experimental Section

Undec-10-yn-1-ol (B). To a solution of 1,3-diaminopropane (2.40 g, 2.7 mL, 32.3 mmol, 5.0 equiv) in 10 mL of THF at 0 °C was added dropwise *n*-BuLi (2.48 M in hexanes, 10.5 mL, 26.0 mmol, 4.0 equiv). The resulting mixture was stirred for 20 min, and *t*-BuOK (1.0 M in THF, 26.0 mL, 26.0 mmol, 4.0 equiv) was added dropwise. The resulting yellow solution was warmed to room temperature, and **3** (1.08 g, 6.51 mmol, 1 equiv) in 2.0 mL of THF was added dropwise via cannula. The solution was stirred for 3 h (red-brown color), poured into 100 mL of satd aq NH_4Cl, and extracted with ether. The combined organic extracts were washed with 5% HCl, satd aq $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Flash chromatography [hexanes/ethyl acetate (8:2)] afforded **B**[14] as a colorless liquid (0.94 g, 5.66 mmol, 87%).

(*Z*)-6-Iodohex-5-en-1-yl 4-methylbenzenesulfonate (7). Compound **6** (13.85 g, 61.3 mmol, 1 equiv), Et_3N (17.00 mL, 122.6 mmol, 2.0 equiv), and DMAP (375 mg, 3.1 mmol, 0.5 equiv) were combined in 150 mL of CH_2Cl_2 and cooled to 0 °C. *p*-Toluenesulfonyl chloride (17.46 g, 91.9 mmol, 1.5 equiv) was added in one portion. The solution was allowed to warm to room temperature and stirred overnight. Saturated aq $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash chromatography [hexanes/ethyl acetate (8:2)] provided **7** as a yellow oil (20.48 g, 53.0 mmol, 88%): IR (neat) 3294, 3066, 2945, 2865, 1598 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, J = 8.4 Hz), 7.36 (d, J = 8.1 Hz), 6.26 (dt, J = 7.3, 1.4 Hz), 6.08 (dt, J = 7.1, 7.0 Hz), 4.04 (t, J = 6.3 Hz,), 2.45 (s), 2.10 (ddt, J = 1.1, 7.0, 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6, 140.2 133.0, 129.8, 127.8, 83.1, 70.1, 33.7, 28.0, 23.6, 21.5; HRMS (ESI) calcd for $C_{13}H_{17}IO_3S$ $[M + Na]^+$ 402.9835, found 402.9858.

(*Z*)-(6-Iodohex-5-en-1-yl)(phenyl)selane (8). With modification of a literature procedure,[15] diphenyl diselenide (4.92 g, 15.8 mmol, 0.6 equiv) in 200 mL of absolute ethanol was treated with $NaBH_4$ (1.45 g, 38.2 mmol) in portions until the solution became colorless. The solution was cooled in an ice bath, and a solution of **7** (10.03 g, 26.3 mmol, 1 equiv) in 30 mL of THF was added. The reaction was gradually warmed to room temperature and stirred overnight. The reaction mixture was poured into 500 mL of 5% Na_2CO_3 and 100 mL of brine and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash chromatography (hexanes) afforded a light yellow oil (7.27 g, 20.0 mmol, 76%): IR (neat) 3069, 3014, 2929, 2853, 1609, 1578 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.58 − 7.45 (m), 7.29 − 7.23 (m), 6.19 (dt, J = 7.3, 11.1 Hz), 6.13 (dt, J = 7.2, 6.3 Hz), 2.93 (t, J = 7.6 Hz), 2.15 (q, J = 7.1 Hz), 1.75 (quintet, J = 7.2 Hz) 1.56 (quintet, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.7, 132.5, 130.3, 128.9, 126.7, 82.8, 34.0, 29.4, 27.9, 27.6; GC−MS 366 (M^+), 239 (base, $M^+ - I$).

(*Z*)-1-Iodohexa-1,5-diene (A′). *m*-CPBA (478 mg, 2.31 mmol, 1.2 equiv) was added portionwise to a solution of **8** (839 mg, 2.31 mmol, 1 equiv) in 5 mL of CH_2Cl_2 at 0 °C. The solution was stirred for 15 min, diluted with 10 mL of CH_2Cl_2, and extracted with satd $NaHCO_3$. The organic solution was washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo to give a light yellow oil that was dissolved in 3 mL of CH_2Cl_2 and added to a refluxing solution of 10 mL CCl_4 and diisopropylamine (270 mg, 0.390 mL, 2.77 mmol, 1.2 equiv). After being refluxed for 30 min, the reaction mixture was poured into 30 mL of water and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo to give a bright orange oil that was purified by flash chromatography (pentane) to yield **A′** as a colorless liquid (235.0 mg, 1.13 mmol, 49%): IR (neat) 3076, 2979, 2924, 2847, 1641, 2609, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.23−6.14 (m, 2H), 5.82 (ddt, J = 17.1, 10.2, 6.4 Hz), 5.04 (ddt, J = 17.2, 1.8, 1.6 Hz), 5.00 (ddt, 10.2, 1.9, 1.1 Hz), 2.28−2.13 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.5, 137.4, 115.3, 82.7, 33.9, 32.0; GC−MS 208 (M^+), 126 $(M - C_3H_5)^+$, 81 $(M - I)^+$.

(*Z*)-Heptadeca-12,16-dien-10-yn-1-ol (9). $PdCl_2(PhCN)_2$ (52.0 mg, 0.136 mmol, 0.05 equiv) and CuI (52 mg, 0.272 mmol, 0.10 equiv) were combined and purged with argon. Pyrrolidine (2 mL) was added, and after the mixture was stirred for 5 min, the iodide **A′** (680.0 mg, 3.27 mmol, 1.2 equiv) in 1 mL of pyrrolidine was added followed by the addition of alkyne **B** (451.5 mg, 2.72 mmol, 1.0 equiv) in 1 mL of pyrrolidine. The solution was stirred overnight in the dark and then poured into 50 mL of satd aq NH_4Cl. The mixture was extracted (EtOAc), and the combined extracts were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash chromatography [hexanes/ethyl acetate (8:2)] gave a colorless oil (541.1 mg, 2.18 mmol, 80%): IR (neat) 3332, 3077, 3021, 2931, 2855, 2212, 1641, 1617, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.83 (ddt, J = 17.3, 10.2, 6.5 Hz), 5.82 (dt, J = 10.6, 7.2 Hz), 5.46 (dtt, J = 10.6, 2.2, 1.5 Hz), 5.04 (ddt, J = 17.1, 1.9, 1.6 Hz), 4.98 (ddt, J = 10.2, 2.0, 1.3 Hz), 3.64 (t, J = 6.5 Hz), 2.39 (ddt, J = 7.3, 1.5, 7.3 Hz), 2.34 (dt, J = 6.9, 2.2 Hz), 2.16 (br dt, J = 6.5, 7.5 Hz), 1.60−1.28 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.4, 138.0, 114.8, 109.8, 94.8, 77.2, 63.0, 32.9, 32.8, 29.5, 29.3, 29.2, 29.0, 28.8, 25.7, 19.5; HRMS (ESI) calcd for $C_{17}H_{28}O$ $[M + Na]^+$ 271.2032, found 271.2004.

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(*Z*)-Heptadeca-12-en-10-yn-1ol (10). According to the procedure for **9**, iodide **A** (1.87 g, 8.9 mmol, 1.5 equiv) and alkyne **B** (986 mg, 5.94 mmol, 1.0 equiv) were added to a solution of $PdCl_2(PhCN)_2$ and CuI (113 mg, 0.594 mmol, 0.1 equiv) in 10.0 mL of pyrrolidine. Flash chromatography of the crude reaction mixture gave the product (1.095 g, 4.41 mmol, 74%) as a colorless oil: IR (neat) 3333, 3020, 2928, 2856, 2215, 1617, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (dt, J = 10.7, 7.4 Hz), 5.44 (dtt, J = 10.7, 2.2, 1.4 Hz), 3.63 (dt, J = 3.3, 6.4 Hz, CH_2OH), 2.33 (dt, J = 2.2, 7.0 Hz), 2.29 (ddt, J = 7.4, 1.5, 7.3), 1.60−1.46 (m, 4H), 1.44−1.25 (m, 12H), 0.90 (t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 109.3, 94.4, 77.4, 63.0, 32.8, 31.0, 29.7, 29.5, 29.4, 29.1, 28.84, 28.82, 25.7, 22.3, 19.5, 13.9; HRMS (ESI) Calcd for $C_{17}H_{30}O$ $[M + Na]^+$ 273.2189, found 273.2187.

(*Z*)-Heptadeca-12,16-dien-10-yn-1-yl 4-Methylbenzenesulfonate (11). According to the procedure for **7**, *p*-toluenesulfonyl chloride (564.2 mg, 2.97 mmol, 1.5 equiv), alcohol **9** (491.1 mg, 1.98 mmol, 1.0 equiv), Et_3N (400 mg, 0.55 mL, 3.96 mmol, 2.0 equiv), and DMAP (12.2 mg, 0.10 mmol, 0.05 equiv) were reacted in 5 mL of CH_2Cl_2. Purification of the crude reaction mixture by flash chromatography [hexanes/ethyl acetate (8:2)] gave **11** as a colorless oil (693.0 mg, 1.72 mmol, 87%): IR (neat) 3075, 3021, 2929, 2856, 2211, 1640, 1599, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, J = 8.3 Hz), 7.34 (d, J = 8.3 Hz), 5.83 (ddt, J = 17.0, 10.2, 6.5), 5.82 (dt, J = 10.6, 7.2 Hz), 5.46 (dtt, J = 10.7, 2.1, 1.4 Hz), 5.04 (ddt, J = 17.1, 1.9, 1.7 Hz), 4.98 (ddt, J = 10.2, 1.9, 1.3 Hz), 4.02 (t, J = 7.3 Hz), 2.45 (s), 2.39 (ddt, J = 7.3, 1.5, 7.3 Hz), 2.33 (dt, J = 7.0, 2.2 Hz), 2.16 (dddt, J = 6.5, 1.5, 1.5, 2.5 Hz), 1.68−1.46 (m, 4H), 1.43−1.29 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6, 141.4, 138.0, 133.2, 129.7, 127.8, 114.8, 109.8, 94.7, 77.2, 70.6, 32.9, 29.3, 29.2, 28.8, 28.76, 28.75, 28.73, 25.3, 21.6, 19.5; HRMS (EI) calcd for $C_{24}H_{34}O_3S$ $[M + Na]^+$ 425.2121, found 425.2120.

(*Z*)-Heptadeca-12-en-10-yn-1-yl 4-Methylbenzenesulfonate (12). According to the procedure for **7**, *p*-toluenesulfonyl chloride (912 mg, 4.80 mmol, 1.5 equiv), alcohol **10** (794.7 mg, 3.20 mmol, 1 equiv), Et_3N (646 mg, 0.87 mL, 6.4 mmol, 2.0 equiv), and DMAP (19.5 mg, 0.16 mmol, 0.05 equiv) were reacted in 10 mL of CH_2Cl_2. Purification by flash chromatography [hexanes/ethyl acetate (8:2)] gave **12** as a light yellow oil (1.0885 g, 2.50 mmol, 84%): IR (neat) 3019, 2028, 2857, 2213, 1653, 1599, 1495, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 8.4 Hz), 7.33 (d, J = 8.5 Hz), 5.80 (dt, J = 10.7, 8.4 Hz), 5.41 (dtt, J = 10.7, 2.2, 1.4 Hz), 4.01 (t, J = 6.5 Hz), 2.44 (s), 2.32 (dt, J = 6.8, 2.2 Hz), 2.28 (dt, J = 7.3, 1.4 Hz), 1.68 − 1.29 (m, 18H), 0.91 (t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6, 142.6, 133.2, 129.8, 127.8, 109.3, 94.3, 77.4, 70.6, 31.1, 29.7, 29.2, 28.9, 28.85, 28.79, 28.78, 28.75, 25.3, 22.2, 21.6, 19.5, 14.0; HRMS (ESI) calcd for $C_{24}H_{36}O_3S$ $[M + Na]^+$ 427.2277, found 427.2297.

Clathculin A (1). To a solution of tosylate **11** (625.0 mg, 1.55 mmol, 1 equiv) in 5.0 mL of CH_3CN was added *N*,*N*′-dimethylethylenediamine (687 mg, 0.84 mL, 7.77 mmol, 5 equiv). The solution was stirred overnight, concentrated in vacuo, and transferred (EtOAc) to a separatory funnel containing 30 mL of satd aq $NaHCO_3$. The aqueous solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. Purification by flash chromatography [CMA: chloroform/methanol/ammonia (83:17:0.5)] gave two components, the less polar dialkylated diamine **13** (81.0 mg, see the Supporting Information for complete characterization) and clathculin A (374.6 mg, 1.18 mmol, 77%). These two compounds had R_f values of 0.40 and 0.05 in CMA: IR (neat) 3328, 3077, 3020, 2929, 2854, 2797, 2212, 1641, 1470 cm^{-1}; ^1HNMR ($CDCl_3$, 300 MHz) δ 5.84 (ddt, J = 17.1, 10.3, 6.5 Hz, H_2C═CH), 5.83 (dt, J = 10.7, 7.2 Hz, CH═CHC≡C), CH_2CH═CHC≡C), 5.47 (dtt, J = 10.7, 2.2, 1.4 Hz, CH═CHC≡C), 5.05 (ddt, J = 17.1, 1.9, 1.6 Hz, HCH═CH), 4.97 (ddt, J = 10.2, 2.1, 1.2 Hz, HCH═CH), 2.68 (t, J = 6.2, NCH_2CH_2N), 2.49 (t, J = 6.2, NCH_2CH_2N), 2.47 (s, NCH_3), 2.39 (ddt, J = 7.3, 1.5, 7.5, CH_2CH═CHC≡C), 2.34 (∼t with some evidence of nonfirst order character, J = 7.0 Hz, $CH_2CH_2CH_2N$), 2.33 (dt, J = 2.2, 7.0, C≡CCH_2), 2.16 (dddt, J = 6.5, 1.6, 1.2, 7.5, CH_2═CHCH_2), 1.58−1.22 (m, 7 CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 137.9, 114.7, 109.8, 94.8, 77.2, 58.1, 56.7, 49.2, 42.2, 36.2, 29.46, 29.44, 29.21, 29.20, 29.03, 28.78, 28.76, 27.4, 27.3, 19.4; HRMS (ESI) calcd for $C_{21}H_{38}N_2$ $[M + H]^+$ 319.3108, found 319.3111.

Clathculin B (2). Following the procedure for **1**, tosylate **10** (536.6.mg, 1.33 mmol, 1 equiv), and *N*,*N*′-dimethylethylenediamine (469.9 mg, 0.57 mL, 4.0 equiv) in 5.0 mL of CH_3CN afforded two components upon flash chromatography [chloroform/methanol/ammonia (83:17:0.5), the less polar dialkylated diamine **14** (50.7 mg, see the Supporting Information for full characterization) and clathculin B (328.1 mg, 1.03 mmol, 78%). These two compounds had R_f values of 0.40 and 0.05 in CMA: IR (neat) 3329, 3019, 2928, 2854, 2787, 2215, 1466 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.80 (dt, J = 10.7, 7.4 Hz, CH_2CH═), 5.43 (dtt, J = 10.7, 2.2, 1.3 Hz, CH═CHC≡C), 2.66 (t, J = 6.2 Hz, NCH_2CH_2N), 2.50 (t, J = 6.1 Hz, NCH_2CH_2N), 2.46 (s, NCH_3), 2.37−2.25 (m. 6H, 3CH_2), 2.20 (s, NCH_3), 1.97 (brs, 1H, *NH*) 1.60−1.23 (m, 9 CH_2), 0.91 (t, J = 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.5, 109.3, 94.3, 77.3, 58.1, 56.9, 49.4, 42.3, 36.4, 31.0, 29.7, 29.50, 29.49, 29.1 28.83, 28.82, 27.4, 27.3, 22.2, 19.5, 13.9; HRMS (ESI) calcd for $C_{21}H_{40}N_2$ $[M + H]^+$ 321.3264, found 321.3270.

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Supporting Information Available: General experimental conditions, ^1H NMR and ^{13}C NMR spectra for all new compounds, experimental procedures for preparation and zipper isomerization of **3**, and our interpretative assignments for selected ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org."