Ring-Closing Alkyne Metathesis. Stereoselective Synthesis of the Cytotoxic Marine Alkaloid Motuporamine C

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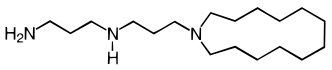
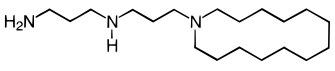
Bioassay-guided fractionation of the extracts of the tropical sponge *Xestospongia exigua* (Kirkpatrick) collected off the coast of Papua New Guinea led to the isolation of three novel alkaloids called motuporamine A−C (**1**−**3**).[1] These compounds combine a spermine-type unit with a macrocyclic entity and exhibit cytotoxicity in vitro against a panel of human cancer cell lines. The uncertainty in the original report as to the actual position of the (*Z*)-configured double bond in the most abundant member of this family was recently overcome by total synthesis of compound **3** and the $\Delta^{15,16}$-isomer **4** and comparison of their spectra with those of the natural product.[2,3] This led to the unambiguous assignment of the structure of motuporamine C as it appears in **3**.[2]



1



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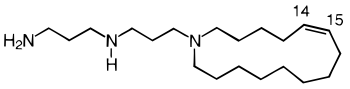

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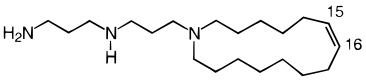

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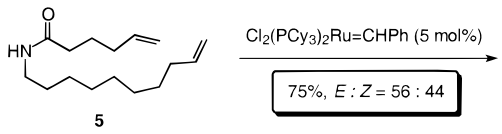
This preparative study relies on a ring-closing metathesis reaction (RCM)[4] as the key step (Scheme 1), which is known to be a highly attractive method for the formation of macrocycles in general.[4,5] The excellent yield obtained in the formation of the 15-membered lactam **6** from the diene precursor **5** is very much in line with this notion; the fact, however, that **6** is obtained as an (*E*,*Z*)-mixture with the undesired (*E*)-alkene predominating detracts from the preparative appeal of this approach.[2]

Scheme 1



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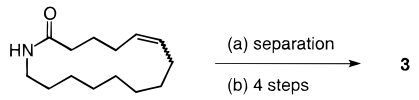

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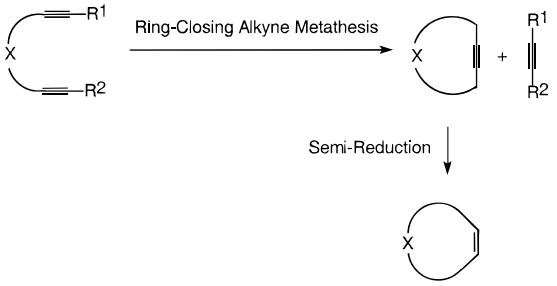
Scheme 2



Therefore this example highlights the eminent problem of RCM, that the catalysts presently available do not allow to control the stereochemistry of the newly formed double bond during macrocyclization.[4]

We have recently proposed an indirect solution for this significant shortcoming: ring-closing metathesis of a *diyne* substrate followed by Lindlar-type reduction of the resulting cycloalkyne product results in the *stereoselective* formation of macrocyclic (*Z*)-alkenes (Scheme 2).[6−8] We were tempted to scrutinize the validity of this new concept by an application to the case of motuporamine C because this particular example allows a detailed assessment of its efficacy by direct comparison with the alkene metathesis route previously described in the literature.[2]

Our synthesis (Scheme 3) starts from commercially available 9-undecyn-1-ol **7**, which is converted into amine **8** by a Mitsunobu reaction[9] with phthalimide and treatment of the resulting product with hydrazine. *N*-Alkylation of **8** with mesylate **9** in THF followed by protection of the resulting secondary amine with a Fmoc group in the presence of aqueous $NaHCO_3$ as the base was carried out in one pot, delivering urethane **10** in good overall yield.

(1) Williams, D. E.; Lassota, P.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 4838.

(2) Goldring, W. P. D.; Weiler, L. *Org. Lett.* **1999**, *1*, 1471.

(3) For a synthesis of the saturated analogues **1** and **2**, see: Baldwin, J. E.; Vollmer, H. R.; Lee, V. *Tetrahedron Lett.* **1999**, *40*, 5401.

(4) For recent reviews on RCM, see the following for leading references: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Top. Catal.* **1997**, *4*, 285. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37. (e) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, 2nd ed.; Academic Press: New York, 1997.

(5) For RCM-based macrocycle syntheses from our laboratory, see: (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (b) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005. (c) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (d) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746. (e) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (f) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010. (g) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424. (h) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215. (i) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275. (j) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361. (k) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814.

(6) Fürstner, A.; Seidel, G. *Angew. Chem.* **1998**, *110*, 1758; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1734.

(7) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108.

(8) (a) Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453. (b) Fürstner, A.; Grela, K. *Angew. Chem.*, in press.

(9) Mitsunobu, O. *Synthesis* **1981**, 1.

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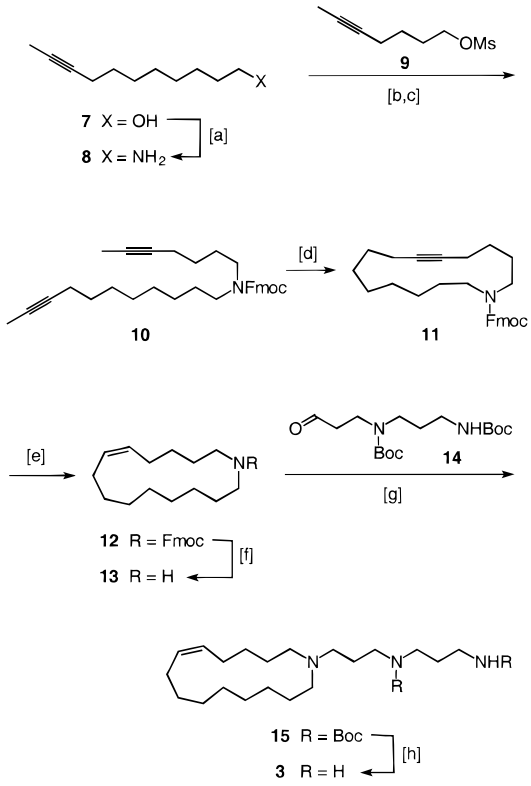
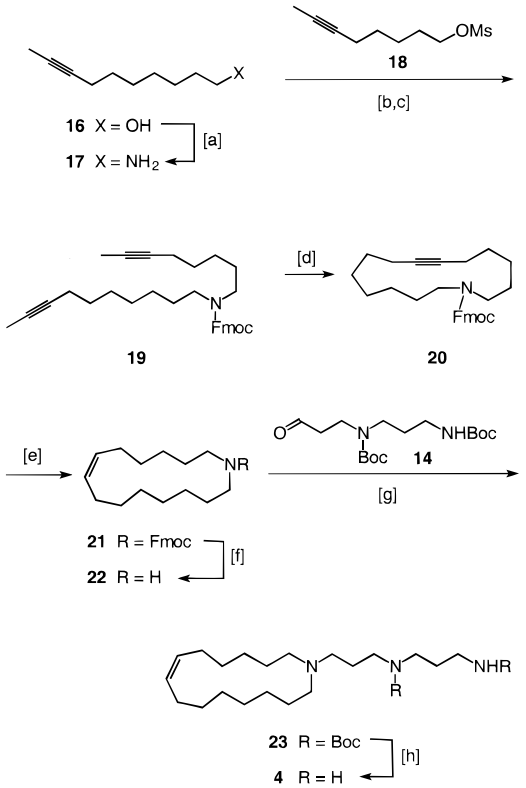
Scheme 3[a]



[a] [a] (i) Phthalimide, PPh_3, DEAD, THF; (ii) hydrazine hydrate, EtOH, reflux, 55% (over both steps). [b] Compound **9**, THF, reflux, 2 days. [c] FmocCl, aq. $NaHCO_3$, 6 h, 58% (over both steps). [d] (i) $(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3$ (10 mol %), chlorobenzene, 1 h, 80 °C, 62% *or* (ii) $Mo(CO)_6$ (5 mol %), *p*-chlorophenol (1 equiv), chlorobenzene, 140 °C, 30 h, 68%. [e] Lindlar catalyst, quinoline cat., H_2 (1 atm), MeOH, 97%. [f] $n\text{Bu}_4\text{NF}{\cdot}3\text{H}_2\text{O}$, aq. THF, rt, 1 h, 89%. [g] Aldehyde **14**, $NaBH(OAc)_3$, 1,2-dichloroethane, rt, 2 h, 74%. [h] HCl, MeOH/EtOAc, 30 min, 84%.

Scheme 4[a]



[a] [a] (i) Phthalimide, PPh_3, DEAD, THF; (ii) hydrazine hydrate, EtOH, reflux, 56% (over both steps). [b] Compound **18**, THF, reflux, 2 d. [c] FmocCl, aq. $NaHCO_3$, 6 h, 54% (over both steps). [d] (i) $(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3$ (10 mol %), chlorobenzene, 1 h, 80 °C, 65% *or* (ii) $Mo(CO)_6$ (5 mol %), *p*-chlorophenol (1 equiv), chlorobenzene, 140 °C, 30 h, 67%. [e] Lindlar catalyst, quinoline cat., H_2 (1 atm), MeOH, 98%. [f] $n\text{Bu}_4\text{NF}{\cdot}3\text{H}_2\text{O}$, aq. THF, rt, 1 h, 76%. [g] Aldehyde **14**, $NaBH(OAc)_3$, 1,2-dichloroethane, rt, 2 h, 81%. [h] HCl, MeOH/EtOAc, 30 min, 84%.

This diyne was subjected to ring-closing alkyne metathesis using two different catalyst systems. We were pleased to see that exposure of **10** to catalytic amounts of the Schrock alkylidyne complex $(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3$[10] in chlorobenzene at 80 °C for 1 h provides the desired product **11** in 62% isolated yield on a gram scale. Similar results are obtained with a structurally unknown catalyst species formed in situ from $Mo(CO)_6$ and *p*-chlorophenol, although this system requires much more forcing conditions (chlorobenzene at 140 °C) and rather long reaction times (30 h).[11,12] Subsequent Lindlar reduction of cycloalkyne **11** provides the required (*Z*)-alkene **12** in a stereoselective manner and in almost quantitative yield. Cleavage of the Fmoc group with $\text{Bu}_4\text{NF}{\cdot}3\text{H}_2\text{O}$ and reductive amination of the cyclic amine **13** thus formed with aldehyde **14**[13] followed by deprotection of the resulting product **15** proceeds readily and affords the bishydrochloride of motuporamine C (**3**·2HCl) as a colorless solid. The small number of steps, the efficiency of the metal-catalyzed ring closure, and the excellent overall yield of this *stereoselective* synthesis of **3** demonstrates the relevance of alkyne metathesis[6−8] as an emerging new tool for target-oriented syntheses that complements conventional RCM[4] in terms of stereochemistry and rivals its efficiency in other preparative respects.[14]

As shown in Scheme 4, the unnatural isomer **4** of motuporamine C can be prepared analogously starting from 1-amino-8-decyne **17** and 8-mesyloxy-2-octyne **18**. The crucial alkyne metathesis of substrate **19** is once again effected either by Schrock's tungsten alkylidyne complex $(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3$[10] or by the in situ system of $Mo(CO)_6$ and *p*-chlorophenol, which were found to be essentially equipotent in terms of yield but rather different in terms of reactivity. Cycloalkyne **20** thus obtained is processed into product **4** as outlined above. Comparison of the ^{13}C NMR spectra of **3** [δ 133.0 (d),

(10) (a) Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645. (b) Freudenberger, J. H.; Schrock, R. R.; Churchill, M. R.; Rheingold, A. L.; Ziller, J. W. *Organometallics* **1984**, *3*, 1563. (c) Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, *4*, 74. (d) Schrock, R. R. *Polyhedron* **1995**, *14*, 3177.

(11) The combination of $Mo(CO)_6$ and phenol additivies has originally been proposed by Mortreux et al., cf.: (a) Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun.* **1974**, 786. (b) Mortreux, A.; Dy, N.; Blanchard, M. *J. Mol. Catal.* **1975**, *1*, 101.

(12) For applications and further optimizations of the Mortreux system, see: (a) Villemin, D.; Cadiot, P. *Tetrahedron Lett.* **1982**, *23*, 5139. (b) Du Plessis, J. A. K.; Vosloo, H. C. M. *J. Mol. Catal.* **1991**, *65*, 51. (c) Vosloo, H. C. M.; du Plessis, J. A. K. *J. Mol. Catal. A* **1998**, *133*, 205. (d) Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett.* **1999**, *40*, 2481. (e) Kaneta, N.; Hirai, T.; Mori, M. *Chem. Lett.* **1995**, 627. (f) Kaneta, N.; Hikichi, K.; Asaka, S.-I.; Uemura, M.; Mori, M. *Chem. Lett.* **1995**, 1055. (g) Kloppenburg, L.; Song, D.; Bunz, U. H. F. *J. Am. Chem. Soc.* **1998**, *120*, 7973.

(13) The analogous aldehyde bearing Z-groups instead of Boc-groups on nitrogen was described by Baldwin et al., cf. ref 3; compound **14** was prepared by following this literature route.

(14) For a short discussion of our strategic goals in target-oriented syntheses in general, see: Fürstner, A. *Synlett* **1999**, 1523.

130.5 (d)] and **4** [δ 131.9 (d), 130.0 (d)] obtained during this study with those of authentic motuporamine C (δ 133.0, 130.6)[1] fully confirm the conclusion previously reached by Goldring et al. with regard to the position of the double bond in the natural product.[2]

Further applications of alkyne metathesis to the total synthesis of bioactive targets are underway and will be reported in due course.

Experimental Section

General. All reactions were carried out under Ar in predried glassware using Schlenk techniques. The solvents were dried by distillation over the drying agents indicated and were stored and transferred under Ar: CH_2Cl_2 (P_4O_{10}), toluene (Na/K), THF (magnesium/anthracene), DMF (Desmodur, Bayer AG; dibutyltin dilaurate), NEt_3, pyridine (KOH), EtOH (Mg), and MeOH (Mg). Flash chromatography was performed on Merck silica gel (230−400 mesh) or activated aluminum oxide (Aldrich, neutral, Brockmann I, STD grade, ~150 mesh) using hexane/ethyl acetate or hexane/Et_2O in various proportions as eluent. For the instrumentation used and the spectra formats see the Supporting Information. The multiplicity in the ^{13}C NMR spectra refers to the geminal protons (DEPT). Commercially available reagents (Aldrich, Fluka) were used as received.

7-(Methanesulfonyloxy)-hept-2-yne (9). Mesyl chloride (3.05 mL, 39.20 mmol) was slowly added to a solution of 5-heptyn-1-ol (4.00 g, 35.72 mmol) and Et_3N (5.51 mL, 39.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After 30 min, the reaction was quenched with H_2O, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were successively washed with 10% HCl, aqueous saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. Flash chromatography (hexane/EtOAc, 10:1) afforded compound **9** as a colorless liquid (6.51 g, 96%): ^1H NMR (300 MHz,$CDCl_3$) δ 4.23 (t, 2H, J = 6.4 Hz), 2.99 (s, 3H), 2.16 (m, 2H), 1.81 (quint, 2H, J = 2.4 Hz), 1.74 (t, 3H, J = 2.5 Hz), 1.56 (quint, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.4 (s), 76.7 (s), 70.1 (t), 37.6 (t), 28.5 (t), 25.1 (t), 18.5 (t), 3.7 (q).

8-(Methanesulfonyloxy)-oct-2-yne (18). Prepared as described above from 6-octyn-1-ol (5.00 g, 39.68 mmol) and mesyl chloride (3.39 mL, 43.65 mmol) as a colorless liquid (7.53 g, 93%): ^1H NMR (300 MHz, CD_2Cl_2) δ 4.19 (t, 2H, J = 6.6 Hz), 2.97 (s, 3H), 2.12 (q, 2H, J = 2.5 Hz), 1.74 (t, 3H, J = 2.8 Hz), 1.72 (m, 2H), 1.49 (m, 4H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 78.9 (s), 75.9 (s), 70.7 (t), 37.6 (q), 29.0 (t), 28.8 (t), 25.0 (t), 18.8 (t), 3.4 (q); HRMS ($C_9H_{16}O_3S$ + H) calcd 205.089841, found 205.09253.

9-Undecynylamine (8). Diethyl azodicarboxylate (6.55 mL, 41.6 mmol) was added to a solution of 9-undecyn-1-ol **7** (7.00 g, 41.6 mmol), phthalimide (6.12 g, 41.6 mmol), and PPh_3 (10.91 g, 41.6 mmol) in THF (90 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature and was stirred overnight. After evaporation of the solvent, Et_2O was added to precipitate triphenylphosphine oxide, which was filtered off and thoroughly washed with Et_2O. The combined filtrates were evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 10:1 → 4:1), providing *N*-(9-undecynyl)-phthalimide as a colorless solid (11.15 g, 90%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, 2H, J = 5.5 and 3 Hz), 7.69 (dd, 2H, J = 5.5 and 3 Hz), 3.66 (t, 2H, J = 7.3 Hz), 2.08 (m, 2H), 1.76 (t, 3H, J = 2.5 Hz), 1.68−1.30 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (s), 133.8 (d), 132.1(s), 123.1 (d), 79.3 (s), 75.3 (s), 38.0 (t), 29.0 (t), 28.9(t), 28.7 (t), 28.6 (t), 26.8 (t), 18.6 (t), 3.4 (q); IR (neat) υ 1767; MS m/z (rel intensity) 297 ([M^+], 5), 160 (100).

Hydrazine hydrate (2.63 g, 52.42 mmol) was added to a solution of *N*-(9-undecynyl)-phthalimide (13.00 g, 43.77) in EtOH (150 mL), and the resulting mixture was refluxed for 1 h. After cooling to ambient temperature, the white suspension was treated with concentrated HCl (10 mL), and the precipitate was filtered off. The filtrate was evaporated, and the residue was dissolved in H_2O. The aqueous phase was extracted with CH_2Cl_2, and the organic washings were discarded. The aqueous layer was treated with aqueous NaOH (1 M) until a pH of ca. 10 was reached and was then repeatedly extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, the solvent was evaporated, and the residue was distilled in vacuo to afford amine **8** as a colorless liquid (4.53 g, 62%): ^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (t, 2H, J = 6.8 Hz), 2.06 (m, 2H), 1.73 (t, 3H, J = 2.6 Hz), 1.44−1.16 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.3 (s), 75.2 (s), 42.2 (t), 33.7 (t), 29.3 (t), 29.0 (t), 28.9 (t), 28.7 (t), 26.7 (t), 18.6 (t), 3.4 (q).

8-Decynylamine (17). Prepared as described above from *N*-(8-decynyl)-phthalimide (11.00 g, 38.86 mmol) and hydrazine hydrate (2.40 g, 46.67 mmol) as a colorless liquid (4.95 g, 63%): ^1H NMR (300 MHz, $CDCl_3$) δ 2.60 (t, 2H, J = 6.8 Hz), 2.10 (m, 2H), 1.71 (t, 3H, J = 2.6 Hz), 1.43−1.13 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.2 (s), 75.1 (s), 42.2 (t), 33.8 (t), 29.3 (t), 29.0 (t), 28.6 (t), 26.7 (t), 18.5 (t), 3.4 (q); HRMS ($C_{10}H_{19}N$ + H) calcd 154.159574, found 154.159074.

***N*-(9-Fluorenylmethyloxycarbonyl)-*N*-(9-undecynyl)-5-heptynamine (10).** A solution of mesylate **9** (1.00 g, 5.26 mmol) and amine **8** (966 mg, 5.79 mmol) in THF (6 mL) was refluxed for 2 days. After cooling, 9-fluorenylmethyl chloroformate (1.79 g, 6.93 mmol) and aqueous $NaHCO_3$ (10% w/w, 20 mL) were added, and the resulting mixture was stirred for 6 h. Extraction with *tert*-butylmethyl ether, drying of the combined organic layers (Na_2SO_4), evaporation of the solvent, and flash chromatography (hexane/Et_2O 10:1) delivered compound **10** as a colorless syrup (1.47 g, 58% over both steps): ^1H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.76 (d, 2H, J = 7.4 Hz), 7.58 (d, 2H, J = 7.4 Hz), 7.33 (m, 4H), 4.49 (d, 2H, J = 5.9 Hz), 3.19 (m, 2H), 3.01 (m, 2H), 2.08 (m, 4H), 1.77 (t, 6H, J = 2.5 Hz), 1.37 (m, 26H); ^{13}C NMR (75.4 MHz, $CDCl_3$, rotamers) δ 156.0 (s), 144.2 (s), 141.4 (s), 127.5 (d), 126.9 (d), 124.7 (d), 119.8 (d), 79.3 (s), 75.7 (s), 66.5 (t), 47.4 (d), 46.9 (t), 46.5 (t), 29.2 (t), 29.0 (t), 28.8 (t), 28.6 (t), 28.0 (t), 27.8 (t), 27.3 (t), 26.8 (t), 26.1 (t), 18.6 (t), 18.5 (t), 3.4 (q).

***N*-(9-Fluorenylmethyloxycarbonyl)-*N*-(9-decynyl)-5-octynamine (19).** Prepared as described above from mesylate **18** (1.52 g, 7.45 mmol), amine **17** (1.46 g, 9.57 mmol), and FmocCl (5.45 g, 10.50 mmol) as a colorless syrup (1.94 g, 54% over both steps): ^1H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.75 (d, 2H, J = 5.5 Hz), 7.59 (d, 2H, J = 6.8 Hz), 7.39 (t, 2H, J = 5.5 Hz), 7.30 (t, 2H, J = 5.5 Hz), 4.49 (d, 2H, J = 5.9 Hz), 4.22 (t, 1H, J = 5.9 Hz), 3.19 (m, 2H), 2.99 (m, 2H), 2.11 (m, 4H), 1.77 (t, 6H, J = 2.5 Hz), 1.46−1.12 (m, 16H); ^{13}C NMR (300 MHz, $CDCl_3$, rotamers) δ 156.0 (s), 144.2 (s), 141.4 (s), 127.5 (d), 126.9 (d), 124.7 (d), 119.8 (d), 110.2 (d), 79.3 (s), 79.0 (s), 75.6 (s), 66.5 (t), 47.5 (t), 47.1 (t), 46.9 (t), 28.9 (t), 28.7 (t), 28.1 (t), 27.7 (t), 26.7 (t), 26.0 (t), 18.7 (t), 3.4 (q); HRMS ($C_{32}H_{39}NO_2$ + H) calcd 484.321553, found 484.320596.

***N*-(9-Fluorenylmethyloxycarbonyl)-1-azacyclopentadec-6-yne (11). Method A.** A solution of (tBuO)$_3$W≡CCMe$_3$ (92 mg, 0.24 mmol) in chlorobenzene (5 mL) was added to a solution of diyne **10** (1.20 g, 2.4 mmol) in the same solvent (600 mL). The resulting brown mixture was kept at 80 °C for 1 h. The solvent was evaporated, and the crude product was chromatographed (hexane/Et_2O, 15:1 → 10:1) to afford cycloalkyne **11** as a colorless syrup (660 mg, 62%). **Method B.** A solution of diyne **10** (100 mg, 0.24 mmol), *p*-chlorophenol (32 mg, 0.24 mmol), and Mo(CO)$_6$ (4 mg, 0.012 mmol) in chlorobenzene (50 mL) was refluxed for 30 h while a gentle stream of Ar was bubbled though the reaction mixture. For workup, the solvent was evaporated under reduced pressure, and the residue was chromatographed (hexane/Et_2O, 20:1 → 15:1) to give compound **11** (60 mg, 68%) as a colorless syrup: ^1H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.75 (d, 2H, J = 7.2 Hz), 7.58 (d, 2H, J = 7.2 Hz), 7.41 (m, 4H), 4.56 (d, 1H, J = 5.5 Hz), 4.49 (d, 1H, J = 5.9 Hz), 4.22 (d, 1H, J = 2.4 Hz), 3.28 (d, 1H, J = 6.4 Hz), 3.20 (t, 1H, J = 8 Hz), 3.12 (t, 1H, J = 6.9 Hz), 2.91 (m, 3H), 2.20 (m, 3H), 2.12 (t, 1H, J = 6.4 Hz), 1.75 (m, 1H), 1.49−1.20 (m, 13H), 1.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 156.3 (s), 156.2 (s), 144.2 (s), 141.4 (d), 127.5 (d), 126.9 (d), 124.8 (d), 124.7 (t), 119.8 (d), 81.0 (s), 80.8 (s), 79.9 (s), 79.8 (s), 66.5 (t), 66.2 (t), 49.8 (t), 49.3 (t), 49.3 (t), 48.6 (t), 47.5 (d), 28.6 (t), 28.1 (t), 28.0 (t), 28.0 (t), 27.6 (t), 27.4 (t), 27.3 (t), 27.0 (t), 26.4 (t), 26.2 (t), 25.6 (t), 24.5 (t), 24.4 (t), 18.3 (t), 18.2 (t), 18.0 (t); HRMS ($C_{29}H_{35}NO_2$ + H) calcd 430.274603, found 430.273975.

***N*-(9-Fluorenylmethyloxycarbonyl)-1-azacyclopentadec-7-yne (20). Method A.** A solution of (tBuO)$_3$W≡CCMe$_3$ (80 mg, 0.20 mmol) in chlorobenzene (5 mL) was added to a solution of

diyne **19** (1.00 g, 2.0 mmol) in chlorobenzene (600 mL). The resulting brown mixture was stirred at 80 °C for 1 h. The solvent was evaporated, and the residue was chromatographed (hexane/Et_2O, 15:1 → 10:1) to afford cycloalkyne **20** as a colorless oil (576 mg, 65%). **Method B.** A solution of diyne **19** (150 mg, 0.31 mmol), *p*-chlorophenol (41 mg, 0.31 mmol), and $Mo(CO)_6$ (4.5 mg, 0.015 mmol) in chlorobenzene (50 mL) was refluxed for 30 h while a gentle stream of Ar was bubbled though the reaction mixture. For workup, the solvent was evaporated, and the residue was chromatographed (hexane/Et_2O, 20:1 → 15:1) to give compound **20** (88 mg, 67%): ^{1}H NMR (300 MHz, CD_2Cl_2, rotamers) δ 7.61 (m, 2H), 7.55 (m, 2H), 7.36−7.16 (m, 4H), 4.42 (bd, 2H, J = 5.5 Hz), 4.14 (t, 1H, J = 5.8 Hz), 3.48 (m. 3H), 2.98 (m, 2H), 2.10 (m, 4H), 1.68−0.75 (m, 16H); ^{13}C NMR (75 MHz, CD_2Cl_2, rotamers) δ 157.8, 156.2, 144.2, 141.8, 140.6, 129.8, 127.5, 127.4, 126.9, 126.3, 124.7, 120.0, 119.8, 90.5, 80.7, 80.5, 80.3, 80.1, 66.5, 65.1, 49.2, 49.0, 48.8, 48.6, 47.4, 31.8, 28.7, 28.3, 28.0, 27.4, 26.9, 26.8, 26.5, 26.3, 26.2, 25.8, 24.7, 24.6, 22.6, 18.2, 18.1, 14.0; HRMS ($C_{29}H_{35}NO_2$ + H) calcd 430.274603, found 430.273938.

***N*-(9-Fluorenylmethyloxycarbonyl)-1-azacyclopentadec-6-ene (12).** To a solution of compound **11** (400 mg, 0.93 mmol) and quinoline (68 μL) in MeOH (20 mL) was added Lindlar catalyst (65 mg). The flask was flushed with H_2 (two freeze/thaw cycles), and the reaction was stirred for 1 h under H_2 (1 atm) at ambient temperature. For workup, the mixture was filtered through a pad of Celite, the Celite was carefully washed with MeOH, and the combined filtrates were evaporated. The residues were washed with 10% HCl, dried (Na_2SO_4), and evaporated. Flash chromatography of the resulting crude product (hexane/Et_2O, 20:1) afforded alkene **12** as a colorless syrup (389 mg, 98%): ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.76 (d, 2H, J = 7.5 Hz), 7.58 (d, 2H, J = 7.3 Hz), 7.39 (t, 2H, J = 7.4 Hz), 7.30 (t, 2H, J = 7.4 Hz), 5.29 (m, 2H), 4.47 (bd, 2H, J = 2.9 Hz), 4.22 (t, 1H, J = 6 Hz), 3.18 (q, 2H, J = 6.8 Hz), 2.99 (q, 2H, J = 7.4 Hz), 2.06 (m, 4H), 1.58−1.21 (m, 20); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 144.2 (s), 141.4 (s), 131.4 (d), 131.0 (d), 130.3 (d), 130.0 (d), 129.9 (d), 127.5 (d), 126.9 (d), 124.7 (d), 119.9 (d), 66.5 (t), 47.5 (d), 28.1 (t), 26.9 (t), 26.5 (t), 26.1 (t), 26.0 (t), 25.5 (t), 24.4 (t); HRMS ($C_{29}H_{37}NO_2$ + H) calcd 432.290246, found 432.289938.

***N*-(9-Fluorenylmethyloxycarbonyl)-7-azacyclopentadec-6-ene (21).** The Lindlar reduction was carried out as described above using compound **20** (300 mg, 0.93 mmol), quinoline (50 μL), and Lindlar catalyst (50 mg) in MeOH (20 mL) under H_2 (1 atm) to afford **21** as a colorless oil (295 mg, 98%): ^{1}H NMR (300 MHz, CD_2Cl_2, rotamers) δ 7.77 (m, 2H), 7.62 (m, 2H), 7.43−7.29 (m, 4H), 5.33 (m, 2H), 4.45 (bd, 2H, J = 5.9 Hz), 4.24 (t, 1H, J = 6.0 Hz), 3.12 (m, 4H), 2.06 (m, 4H), 1.62−1.16 (m, 16H); ^{13}C NMR (75 MHz, CD_2Cl_2, rotamers) δ 144.8 (s), 141.7 (s), 130.5 (d), 130.4 (d), 127.8 (d), 127.3 (d), 125.2 (d), 120.2 (d), 66.8 (t), 48.8 (t), 48.3 (t), 47.9 (d), 28.6 (t), 28.4 (t), 27.8 (t), 27.5 (t), 27.2 (t), 26.7 (t), 25.8 (t), 25.4 (t); HRMS ($C_{29}H_{37}NO_2$ + H) calcd 432.290253, found 432.289938.

Compound 15. TBAF·$3H_2O$ (330 mg, 1 mmol) was added to a solution of the alkene **12** (300 mg, 0.70 mmol) in THF (15 mL), and the resulting mixture was stirred for 1 h. The reaction was then quenched with H_2O, the aqueous layer was extracted with *tert*-butylmethyl ether, the combined organic layers were dried (Na_2SO_4) and concentrated, and the remaining residue was filtered through a small pad of silica (hexane/EtOAc 4:1 → EtOAc) to give amine **13** as a red oil (116 mg, 89%). This compound was used in the next step without further purification.

Sodium triacetoxyborohydride (65 mg, 0.31 mmol) was added to a solution of aldehyde **14** (97 mg, 0.31 mmol) and amine **13** (60 mg, 0.31 mmol) in 1,2-dichloroethane (15 mL), and the resulting mixture was stirred at ambient temperature for 2 h. The reaction was quenched by adding aqueous saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), the solvent was evaporated, and the residue was chromatographed (hexanes/EtOAc 4:1 → EtOAc) to afford compound **15** as a colorless syrup (117 mg, 74%): ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 5.31 (m, 2H), 3.07 (m, 6H), 2.30 (m, 6H), 2.02 (m, 4H), 1.61 (m, 4H), 1.43 (s, 9H), 1.41 (s, 9H), 1.32−1.28 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 155.9 (s), 130.3 (d), 130.2 (d), 79.3 (s), 78.8 (s), 54.1 (t), 53.0 (t), 52.7 (t), 45.6 (t), 43.8 (t), 37.3 (t), 28.4 (q), 28.1 (t), 27.5 (t), 27.4 (t), 27.1 (t), 27.0 (t), 26.9 (t), 26.5 (t), 25.8 (t), 25.7 (t), 25.2 (t).

Compound (23). Prepared in 81% yield as a colorless syrup from alkene **21** (200 mg, 0.70 mmol) as described above: ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 5.31 (m, 2H), 3.07 (m, 6H), 2.30 (m, 6H), 2.02 (m, 4H), 1.61 (m, 4H), 1.43 (s, 9H), 1.41 (s, 9H), 1.32−1.28 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 155.9 (s), 130.3 (d), 130.2 (d), 79.3 (s), 78.8 (s), 54.1 (t), 53.0 (t), 52.7 (t), 45.6 (t), 43.8 (t), 37.3 (t), 28.4 (q), 28.1 (t), 27.5 (t), 27.4 (t), 27.1 (t), 27.0 (t), 26.9 (t), 26.5 (t), 25.8 (t), 25.7 (t), 25.2 (t).

Motuporamine C (3). A solution of compound **15** (100 mg, 0.19 mmol) in EtOAc was slowly added to a solution of HCl in CH_3OH/AcOMe (2 mL, freshly prepared by addition of acetyl chloride (4.4 mL) to dry CH_3OH (15.6 mL) at 0 °C), and the mixture was stirred for 30 min. For workup, Et_2O was added to the reaction mixture until a white solid started to precipitate. The slurry was immersed in an ice−water bath and the solid formed was collected by filtration (67 mg, 84%). The analytical data are in agreement with those reported in the literature:[1] ^{1}H NMR (300 MHz, CD_3OD) δ 5.30 (m, 2H), 3.25 (m, 4H), 3.07 (m, 10H), 2.24−2.03 (m, 8H), 1.69 (m, 4H), 1.58−1.20 (m, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 133.0 (d), 130.5 (d), 53.9 (t), 53.5 (t), 53.0 (t), 46.0 (t), 37.9 (t), 29.2 (t), 27.8 (t), 26.5 (t), 25.3 (t), 25.0 (t), 23.7 (t), 23.1 (t), 22.4 (t).

Compound 4. Prepared as described above from compound **23** (60 mg, 0.09 mmol) as a colorless solid (42 mg, 84%): ^{1}H NMR (300 MHz, CD_3OD) δ 5.29 (m, 2H), 3.25−3.00 (m, 14H), 2.07−2.00 (m, 8H), 1.65 (m, 4H), 1.49−1.17 (m, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 131.9, 130.0, 53.1, 52.8, 46.1, 37.9, 29.5, 27.7, 27.4, 27.2, 25.9, 25.3, 22.9, 22.5, 22.1.

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Supporting Information Available: Compilation of the IR and MS data and copies of the NMR spectra of all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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