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Amphimedosides A–C: Synthesis, Chemoselective Glycosylation, And Biological Evaluation

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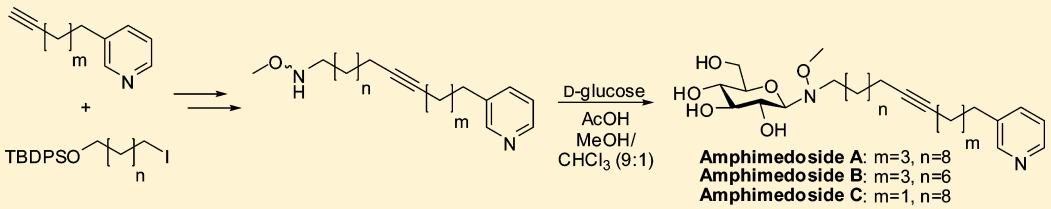
Supporting Information



ABSTRACT: The amphimedosides, discovered in 2006, are the first examples of naturally occurring glycosylated alkoxyamines. We report syntheses of amphimedosides A–C that feature a stereoselective oxyamine neoglycosylation and found that these alkaloids display modest cytotoxicity toward seven diverse human cancer cell lines, exhibiting IC_{50} values ranging from 3.0 μM to greater than 100 μM.

Marine sponges have long been a source of biologically active natural products, including cytotoxic alkaloids. Many such alkaloids are 3-alkylpyridine derivatives[1] containing an aliphatic chain terminated by functional groups including amines,[2] *N*-methoxyamines,[3] *N*-methyl-*N*-methoxyamines,[4] *N*-methyl-*N*-hydroxylamines,[3a] oximes,[3c] or aldehydes.[3c] In 2006, Matsunaga, Fusetani, and co-workers reported the first examples of glycosylated 3-alkylpyridines, which they named the amphimedosides.[5] These secondary metabolites contain unique *O*-methyl-*N*-(β-D-glucopyranosyl)hydroxylamine termini and are modest cytotoxins toward murine leukemia cells. We and others have previously shown that glycosylated hydroxylamines can be generated using oxyamine neoglycosylation, a chemoselective glycosylation methodology that employs reducing sugars to form closed ring neoglycosides, thus revealing a synthetic route to these interesting alkaloids.[6−11] Motivated by their unique glycosidic linkages, we pursued a synthesis of amphimedosides A–C (Figure 1) by using oxyamine neoglycosylation. The promising biological activities of amphimedosides A–C led us to examine the cytotoxicity of these alkaloids toward several human cancer cell lines.

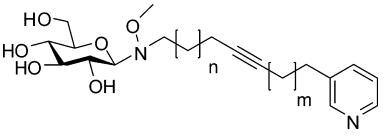


Figure 1. Amphimedosides A–C are 3-alkylpyridines that contain unique *O*-methyl-*N*-(β-D-glucopyranosyl)hydroxylamine termini.

We planned to generate amphimedosides A–C (**1a–c**) through chemoselective glycosylation of the corresponding aglycons (**12a–c**; Figure 4). These in turn would be generated from protected iodoalcohols and pyridylalkynes using methodologies similar to those developed by Baldwin and Lee for the generation of the hachijodines.[12]

To begin, pyridylalkyne **4a** was synthesized from commercial 3-(pyridine-3-yl)propanol (**2**) using Swern oxidation[13] followed by Seyferth–Gilbert homologation[11] with Bestmann's reagent (Figure 2).[14] Since 5-(pyridin-3-yl)pentanol is not commercially available for conversion to pyridylalkyne **4b**, we generated **4b** from lithiated 3-picoline as was reported previously.[11]

To assemble the requisite pyridylalcohols **7a–c**, we coupled deprotonated pyridylalkynes **4** with protected iodo alcohols **5a** and **5b** using the conditions developed by Baldwin and Lee (Figure 3).[12] Isolated yields for **6a** and **6b** were good, but the highest yield we obtained for **6c** was 28% (with 21% recovery of **4a**). Despite this low yield, deprotection using ammonium fluoride in methanol[15] afforded pyridyl alcohols **7a–c** in adequate enough amounts for us to proceed.

We were uncertain how to convert alcohols **7a–c** to the corresponding methoxyamines most efficiently. We considered two options, nucleophilic displacement using deprotonated *N*-(*tert*-butoxycarbonyl)-protected methoxyamine[9c,16] and oxidation followed by reductive amination.[9e,17] To explore the viability of the first option, we conducted a model study that explored different leaving groups and reaction conditions (Table 1). Unfortunately, isolated yields were low for all the conditions we investigated; the highest yield obtained was 54%. Concerned that the conversion of alcohols **7a–c** to the

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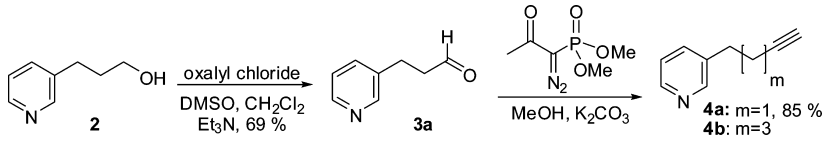


Figure 2. Generation of pyridylalkyne intermediates.

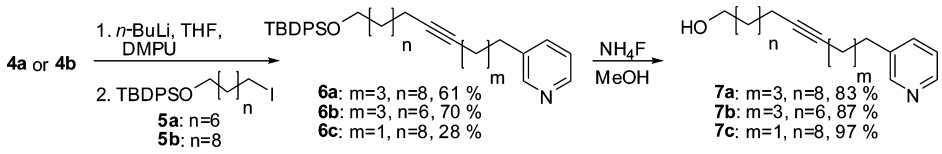
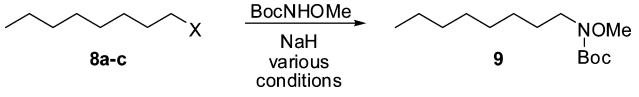


Figure 3. Synthesis of pyridyl alcohols **7a–c**.

Table 1. Effect of Reaction Conditions on Isolated Yield of *N*-Boc-Protected-*O*-methoxyamine[a]



entry	X	conditions	isolated yield[b] (%)
1	OTs (**8a**)	THF, 40 °C	39
2	OMs (**8b**)	THF, 40 °C	17
3	OMs (**8b**)	THF, rt	17
4	OMs (**8b**)	NaI, THF, rt	33
5	OMs (**8b**)	THF/DMPU (3:1), rt	38
6	OMs (**8b**)	NaI, THF/DMPU (3:1), rt	34
7	Br (**8c**)	THF, 40 °C	25
8	Br (**8c**)	THF, rt	37
9	Br (**8c**)	NaI, THF, rt	32
10	Br (**8c**)	THF/DMPU (3:1), rt	39
11	Br (**8c**)	NaI, THF/DMPU (3:1), rt	54

[a]Reactions were run with *N*-(*tert*-butoxycarbonyl)-*O*-methoxyamine (1.5 equiv), sodium hydride (2.7 equiv), and substrate **8** (1.0 equiv) in the indicated solvent (1 mL/mmol substrate) at the indicated temperature for 3–6 d. [b]Following SiO_2 column chromatography.

corresponding bromides would lower further the overall yield of the methoxyamine installation sequence, we turned our attention to reductive amination.

Alcohols **7a–c** were oxidized using Swern conditions, and the resulting aldehydes (**10a–c**) were converted to the corresponding *O*-methyl oxime ethers (**11a–c**) using methoxyamine hydrochloride in the presence of pyridine (Figure 4).[7] Oximes **11a–c** were subsequently reduced using sodium cyanoborohydride in acetic acid to provide the aglycons of amphimedosides A–C (**12a–c**) in excellent yields. The overall yields of **12a–c** from **7a–c** (three steps) ranged from 40 to 65%.

Since the late 1990s, it has been known that secondary alkoxyamines react with unprotected and unactivated reducing sugars under mild conditions to provide cyclic neoglycosides.[6−11] This methodology, known as oxyamine neoglycosylation, has been shown to favor formation of β-pyranosides when D-glucose is used. Based on the desired β-anomeric stereochemistry of amphimedosides A–C and the fact that this strategy can be employed without the use of activating or protecting groups, we used this glycosylation method. As shown in Figure 5, we treated aglycons **12a–c** with D-glucose under mildly acidic conditions for 2 days, providing amphimedosides A–C (**1a–c**) in excellent stereoselectivities (100% β-anomer). The ^1H and ^{13}C NMR spectroscopic data for **1a–c** are identical to published data for the natural products.[5] Unfortunately, the yields of the neoglycosylation reactions were low, and our attempts to improve them were not fruitful.[18]

Fusetani and co-workers found that amphimedosides A–C (**1a–c**) displayed significant cytotoxicity against P388 murine leukemia cells (IC_{50} = 21.7, 23.0, and 10.4 μM, respectively).[5] Related, but nonglycosylated, 3-alkylpyridines display similar potency. For example, methoxyamines niphatesine H (the aglycon of amphimedoside C, **12c**) and niphatyne A (**13**) are moderately cytotoxic (IC_{50} = 6.0 μM, 1.5 μM)[3b,c] as are *O*-methyl oximes niphatesine E (**14**) and niphatesine F (**15**) (Figure 6).[3b]

Based on these preliminary findings, we decided to assess the cytotoxicity of oximes **11a–c**, methoxyamines **12a–c**, and amphimedosides A–C (**1a–c**) toward human cancer cell lines representing a range of tumor types including lung, prostate, liver, colon, breast, and skin (Figure 7). Amphimedosides A–C (**1a–c**) displayed modest cytotoxicity (IC_{50} = 10 to greater than 100 μM) toward the seven cell lines tested. Interestingly, **1a–c** were at least three times more potent against Hep3B cells than any other cell line examined. Oxime ethers displayed cytotoxicity profiles similar to **1a–c** but with slightly

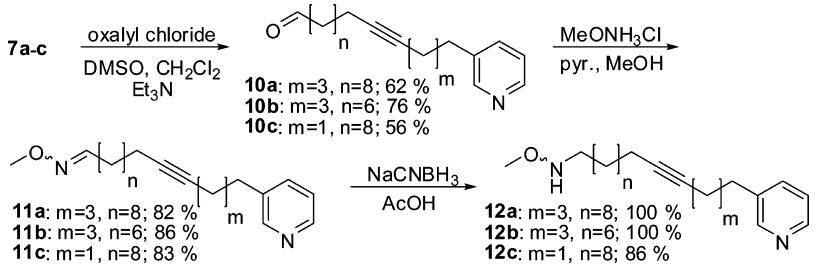


Figure 4. Amphimedoside aglycons **12a–c** were produced from **7a–c** via oxidation followed by reductive amination.

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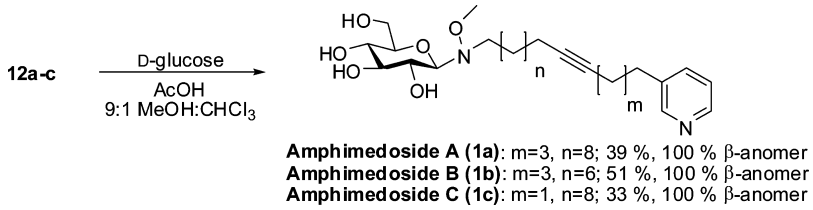

Figure 5. Oxyamine neoglycosylation of **12a–c** produced amphimedosides **1a–c** in excellent stereoselectivities but in low yields.

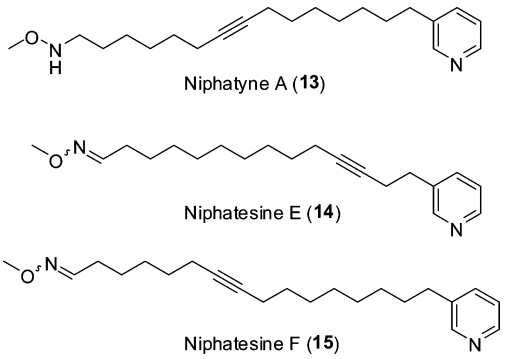

Figure 6. Structures of nonglycosylated 3-alkylpyridines that are related to amphimedosides A–C.

diminished potency. In contrast, amphimedoside aglycons **12a–c** were nonselective but more potent than **1a–c** (IC_{50} = 2–36 μM). Thus, it appears glucosylation may slightly enhance cell line selectivity but may diminish overall potency. It is possible that efforts to glycorandomize[10] the amphimedosides or to generate linkage-diversified derivatives[7a,c] might provide cytotoxins with improved activities.

In summary, amphimedosides A–C were synthesized in overall yields ranging from 3 to 20% (7–9 steps). The amphimedosides, as well as the corresponding oximes and methoxyamines, displayed modest cytotoxicity against a panel of human cancer cell lines. Given our demonstration that **12a–c** can be glycosylated to form the amphimedosides in the absence of activating and protecting groups, it is interesting to consider the biosynthesis of this glycosidic linkage. Typically, the glycosylation of secondary metabolites is mediated by glycosyltransferases using activated nucleotide diphosphosugar (NDP-sugar) donors. However, because of the unique reactivity of secondary alkoxyamines, it is also theoretically possible that glucose itself serves as the sugar donor in amphimedoside biosynthesis. Such a transformation seems less likely than the canonical enzymatic process since oxyamine neoglycosylations require high sugar concentrations, acid, and heat, and since secondary alkoxyamine glycosylation can be accomplished in vitro using glycosyltransferases and NDP-sugar donors.[19]

EXPERIMENTAL SECTION

General Procedure for Model Study To Produce *O*-Methyl-*N*-octyl-*N*-(*tert*-butoxycarbonyl)hydroxylamine (9). NaH (2.7 equiv) was added to a solution of THF or 3:1 THF/DMPU (1 mL/mmol of **8**), and the resulting mixture was cooled to 0 °C. *N*-(*tert*-Butoxycarbonyl)-*O*-methoxyamine (1.5 equiv) was added dropwise, and the mixture was warmed to rt. A substrate (**8**) was added, and the solution was stirred at the temperature shown in Table 1 for 3–6 d. The reaction mixtures were diluted with water and extracted with EtOAc (4×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixtures were purified by SiO_2 column chromatography eluting with 49:1 toluene/EtOAc to provide **9** (TLC R_f = 0.36 in 49:1 toluene/EtOAc) as an oil: IR ν_{max} (thin film) 2930, 2857, 1705, 1458, 1367, 1252, 1168, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.67 (s, 3H), 3.41 (dd, 2H, J = 7.3 Hz), 1.58 (m, 2H), 1.49 (s, 9H), 1.28 (m, 10H), 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.5, 81.1,

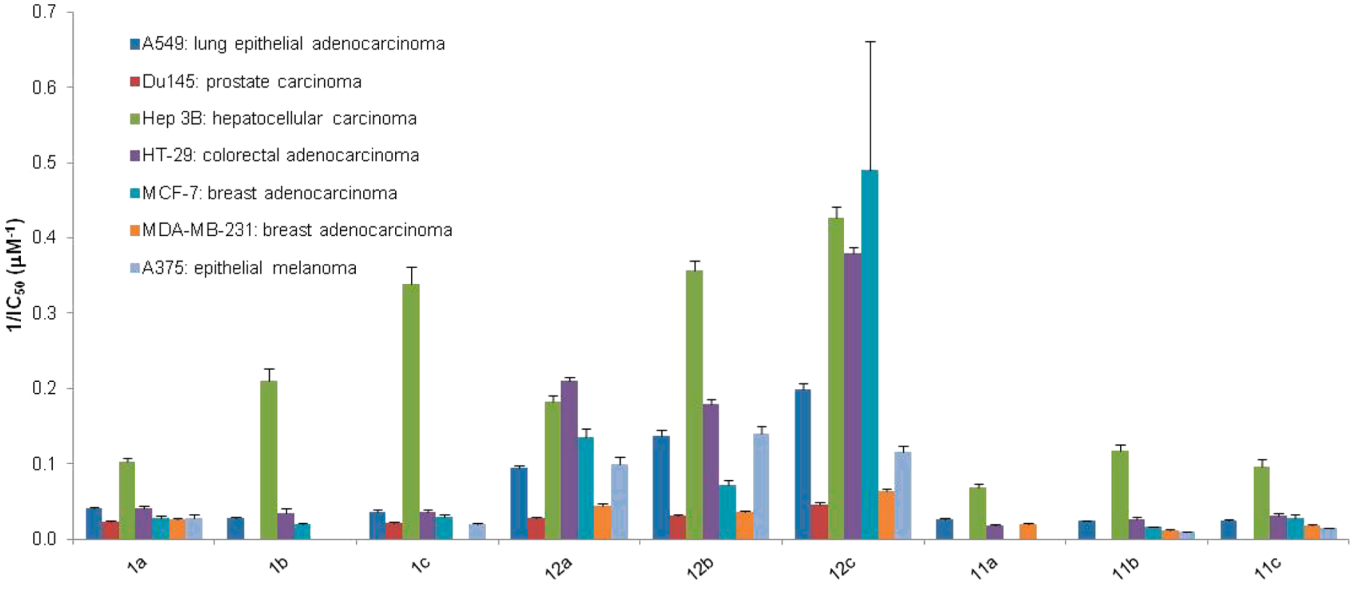

Figure 7. Summary of IC_{50} data from cytotoxicity assays. Reciprocal IC_{50} values are shown for clarity, and error bars indicate the calculated standard error. Where bars are not visible, the IC_{50} values were >100 μM. A table containing IC_{50} values can be found in the Supporting Information.

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62.3, 49.2, 31.9, 29.42, 29.36, 28.5, 27.3, 26.9, 22.8, 14.2; HRMS (ESI, TOF) m/z (M + Na) calcd for $C_{14}H_{29}NO_3Na$ 282.2045, obsd 282.2042.

3-(Pyridin-3-yl)propanal (3a). Oxalyl chloride (0.52 mL, 6.20 mmol) was added to CH_2Cl_2 (4.4 mL) and cooled to −78 °C. DMSO (0.55 mL, 7.75 mmol) was added dropwise followed by a solution of 3-pyridinepropanol (0.4 mL, 3.10 mmol) in CH_2Cl_2 (0.72 mL). The resulting mixture was stirred at −78 °C for 45 min, and then triethylamine (1.73 mL, 12.4 mmol) was added dropwise. The solution was warmed to rt and was stirred for 30 min, diluted with diethyl ether (100 mL), filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane to provide **7a** (TLC R_f = 0.33 in EtOAc) as an oil (290.0 mg, 69% yield). Spectral data for **3a** matched those previously reported.[20]

3-(Pyridin-3-yl)but-1-yne (4a). A solution of dimethyl-1-diazo-2-oxopropylphosphonate[14] (2.36 g, 12.26 mmol) in anhydrous MeOH (7.8 mL) was added to aldehyde **3a** (1.38 g, 10.22 mmol) under nitrogen. Anhydrous K_2CO_3 (2.70 g, 20.44 mmol) was added, and the resulting mixture was stirred overnight. The reaction was quenched with water and then extracted with diethyl ether (4×). The combined organic layers were washed with satd aq $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane to provide **4a** (TLC R_f = 0.40 in 1:1 EtOAc/hexane) as an oil (1.15 g, 85% yield). Spectral data for **4a** matched those previously reported.[21]

16-(Pyridin-3-yl)-1-(*tert*-butyldiphenylsilyloxy)hexadec-11-yne (6a). Alkyne **4b**[12] (0.515 g, 3.23 mmol) was dissolved in THF (6.6 mL) and DMPU (2.02 mL, 16.8 mmol), and the resulting mixture was cooled to −78 °C. After 10 min, *n*-BuLi in hexanes (2.88 mL, 3.88 mmol, 1.348 M) was added dropwise. After 30 min at −78 °C, a solution of **5b**[12] (4.39 g, 8.41 mmol) in THF (13.2 mL) was added dropwise via cannula, and the reaction was stirred overnight at rt. The reaction mixture was quenched with water and extracted with petroleum ether (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 3:7 EtOAc/hexane to provide **6a** (TLC R_f = 0.41 in 3:7 EtOAc/hexane) as an oil (1.02 g, 57% yield): IR ν_{max} (thin film) 3071, 2925, 2854, 1575, 1472, 1462, 1427, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.44 (m, 2H), 7.67 (m, 4H), 7.49 (ddd, 1H, J = 7.8, 2.2, 1.8 Hz), 7.39 (m, 6H), 7.20 (ddd, 1H, J = 7.7, 4.8, 0.6 Hz), 3.65 (t, 2H, J = 6.4 Hz), 2.62 (t, 2H, J = 7.6 Hz), 2.19 (m, 2H), 2.13 (m, 2H), 1.73 (m, 2H), 1.57−1.24 (m, 18H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.0, 147.3, 137.6, 135.8, 135.6, 134.2, 129.5, 127.6, 123.3, 80.8, 79.5, 64.0, 32.6, 32.5, 30.2, 29.6, 29.5, 29.4, 29.2, 29.1, 28.9, 28.5, 26.9, 25.8, 19.2, 18.7, 18.6; HRMS (ESI, TOF) m/z (M + H) calcd for $C_{37}H_{52}NOSi$ 554.3818, obsd 554.3818.

14-(Pyridine-3-yl)-1-(*tert*-butyldiphenylsilyloxy)tetradec-9-yne (6b). Alkyne **4b**[12] (1.37 g, 8.63 mmol) was dissolved in THF (17.6 mL) and DMPU (5.39 mL, 44.7 mmol), and the resulting mixture was cooled to −78 °C. After 10 min, *n*-BuLi in hexanes (8.0 mL, 10.35 mmol, 1.30 M) was added dropwise. After 30 min at −78 °C, a solution of **5a**[12] (11.36 g, 23.0 mmol) in THF (35.2 mL) was added dropwise via cannula, and the reaction was stirred overnight at rt. The reaction mixture was quenched with water and extracted with petroleum ether (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 3:7 EtOAc/hexane to provide **6b** (TLC R_f = 0.25 in 3:7 EtOAc/hexane) as an oil (3.16 g, 70% yield). Spectral data for **6b** matched those previously reported.[12b]

14-(Pyridine-3-yl)-1-(*tert*-butyldiphenylsilyloxy)tetradec-11-yne (6c). Alkyne **4a** (1.14 g, 8.70 mmol) was dissolved in THF (17.7 mL) and DMPU (5.44 mL, 45.2 mmol), and the resulting mixture was cooled to −78 °C. After 10 min, *n*-BuLi in hexanes (8.0 mL, 10.4 mmol, 1.30 M) was added dropwise. After 30 min at −78 °C, a solution of **5a**[12] (11.82 g, 22.6 mmol) in THF (35.5 mL) was added dropwise via cannula, and the reaction was stirred overnight at rt. The reaction mixture was quenched with water and extracted with petroleum ether (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 3:7 EtOAc/hexane to provide **6c** (TLC R_f = 0.47 in 3:7 EtOAc/hexane) as an oil (1.26 g, 28% yield): IR ν_{max} (thin film) 3070, 2934, 2856, 1574, 1472, 1427, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.49 (d, 1H, J = 2.1 Hz), 8.46 (dd, 1H, J = 4.8, 1.6 Hz), 7.67 (m, 4H), 7.55, (ddd, 1H, J = 7.8, 2.3, 1.8 Hz), 7.39 (m, 6H), 7.21 (ddd, 1H, J = 7.8, 4.8, 0.7 Hz), 3.65 (t, 2H, J = 6.6 Hz), 2.79 (t, 2H, J = 7.3 Hz), 2.46 (tt, 2H, J = 7.2, 2.3 Hz), 2.11 (tt, 2H, J = 7.0, 2.3 Hz), 1.64−1.21 (m, 16H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.4, 148.0, 136.4, 136.2, 135.8, 134.5, 129.7, 127.8, 123.4, 82.2, 78.8, 64.3, 32.9, 29.9, 29.86, 29.77, 29.7, 29.4, 29.3, 29.1, 27.1, 26.0, 21.0, 19.5, 18.9; HRMS (ESI, TOF) m/z (M + H) calcd for $C_{35}H_{48}NOSi$ 526.3505, obsd 526.3502.

16-(Pyridin-3-yl)-hexadec-11-yn-1-ol (7a). Protected alkyne **6a** (1.02 g, 1.85 mmol) was dissolved in MeOH (10.3 mL), NH_4F (1.08 g, 34.8 mmol) was added, and the resulting mixture was stirred at reflux overnight. Additional NH_4F (1.00 g, 32.2 mmol) was added at 3 and 4 h to promote reaction completion. The reaction was diluted with satd aq $NaHCO_3$ and water (1:1) and extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane followed by 95:5 EtOAc/MeOH to provide **7a** (TLC R_f = 0.17 in 3:7 EtOAc/hexane) as an oil (0.484 g, 83% yield): IR ν_{max} (thin film) 3339, 2928, 2855, 1578, 1463, 1425 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.44 (m, 2H), 7.50 (ddd, 1H, J = 7.7, 2.1, 1.7 Hz), 7.21 (ddd, 1H, J = 7.8, 4.8, 0.7 Hz), 4.06 (t, 1H, J = 6.7 Hz), 3.64 (t, 2H, J = 6.6 Hz), 2.63 (dd, 2H, J = 7.6, 7.6 Hz), 2.20 (m, 2H), 2.14 (m, 2H), 1.76−1.23 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.6, 146.9, 137.7, 136.0, 123.3, 80.7, 79.5, 62.5, 32.8, 32.4, 30.1, 29.5, 29.41, 29.40, 29.1, 29.0, 28.8, 28.4, 25.8, 18.7, 18.5; HRMS (ESI, TOF) m/z (M + H) calcd for $C_{21}H_{34}NO$ 316.2640, obsd 316.2650.

14-(Pyridin-3-yl)tetradec-9-yne-1-ol (7b). Protected alkyne **6b** (3.20 g, 6.10 mmol) was dissolved in MeOH (33.9 mL), NH_4F (3.56 g, 114.7 mmol) was added, and the resulting mixture was stirred at reflux overnight. Additional NH_4F was added at 4 and 6 h to promote reaction completion (1.2 g, 38.7 mmol and 1.0 g, 32.2 mmol, respectively). The reaction was diluted with satd aq $NaHCO_3$ and water (1:1) and extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane followed by 95:5 EtOAc/MeOH to provide **7b** (TLC R_f = 0.13 in 3:7 EtOAc/hexane) as an oil (1.53 g, 87% yield). Spectral data for **7b** matched those previously reported.[12b]

14-(Pyridin-3-yl)tetradec-11-yn-1-ol (7c). Protected alkyne **6c** (1.26 g, 2.39 mmol) was dissolved in MeOH (3.3 mL), NH_4F (1.40 g, 45.0 mmol) was added, and the resulting mixture was stirred at reflux overnight. Additional NH_4F (0.50 g, 16.1 mmol) was added at 3 and 4 h to promote reaction completion. The reaction was diluted with satd aq $NaHCO_3$ and water (1:1) and extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane followed by 95:5 EtOAc/MeOH to provide **7c** (TLC R_f = 0.45 in 7:3 EtOAc/hexane) as an oil (0.666 g, 97% yield): IR ν_{max} (thin film) 3326, 3050, 2932, 2855, 1742, 1578, 1425, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.49 (d, 1H, J = 1.9 Hz), 8.46 (dd, 1H, J = 4.8, 1.6 Hz), 7.56 (ddd, 1H, J = 7.8, 2.2, 1.7 Hz), 7.22 (ddd, 1H, J = 7.8, 4.8, 0.7 Hz), 3.64 (t, 2H, J = 6.6 Hz), 2.79 (t, 2H, J = 7.2 Hz), 2.47 (tt, 2H, J = 7.1, 2.3 Hz), 2.11 (tt, 2H, J = 7.0, 2.3 Hz), 1.66−1.21 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.1, 147.7, 136.1, 123.2, 82.0, 78.5, 63.1, 32.8, 32.5, 29.5, 29.39, 29.36, 29.1, 28.9, 28.8, 25.7, 20.6, 18.6; HRMS (ESI, TOF) m/z (M + H) calcd for $C_{19}H_{30}NO$ 288.2327, obsd 288.2319.

16-(Pyridin-3-yl)hexadec-11-yn-1-al (10a). Oxalyl chloride (17.0 μL, 0.103 mmol) was added to CH_2Cl_2 (0.15 mL) and cooled to −78 °C. DMSO (18.0 μL, 0.257 mmol) was added dropwise

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followed by a solution of **7a** (32.4 mg, 0.103 mmol) in CH_2Cl_2 (0.1 mL). The resulting mixture was stirred at −78 °C for 45 min, and then triethylamine (57.0 μL, 0.411 mmol) was added dropwise. The solution was allowed to warm to rt and was stirred for 30 min, diluted with diethyl ether (4 mL), filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 2:3 EtOAc/hexane to provide **8a** (TLC R_f = 0.27 in 3:2 hexane/EtOAc) as an oil (20.1 mg, 62% yield): IR ν_{max} (thin film) 3425, 2932, 2855, 2719, 1723, 1423 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.77 (t, 1H, *J* = 1.8 Hz), 8.44 (m, 2H), 7.50 (ddd, 1H, *J* = 7.8, 2.2, 1.8 Hz), 7.21 (ddd, *J* = 7.8, 4.8, 0.7 Hz), 2.63 (dd, 2H, *J* = 7.7, 7.7 Hz), 2.42 (td, 2H, *J* = 7.1, 1.9 Hz), 2.19 (m, 2H), 2.13 (m, 2H), 1.77−1.24 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.0, 149.7, 147.0, 137.9, 136.1, 123.4, 80.7, 79.5, 62.6, 43.9, 32.5, 30.1, 29.3, 29.13, 29.09, 29.07, 28.8, 28.4, 22.1, 18.7, 18.5; HRMS (ESI, TOF) *m*/*z* (M + H) calcd for $C_{21}H_{32}NO$ 314.2483, obsd 314.2487.

14-(Pyridin-3-yl)tetradec-9-yn-1-al (10b). Oxalyl chloride (0.81 mL, 1.62 mmol) was added to CH_2Cl_2 (0.5 mL) and cooled to −78 °C. DMSO (0.14 mL, 2.03 mmol) was added dropwise followed by a solution of **7b** (233.1 mg, 0.811 mmol) in CH_2Cl_2 (0.2 mL). The resulting mixture was stirred at −78 °C for 45 min, and then triethylamine (0.45 mL, 3.24 mmol) was added dropwise. The solution was allowed to warm to rt and was stirred for 30 min, diluted with diethyl ether (30 mL), filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 2:3 EtOAc/hexane to provide **8b** (TLC R_f = 0.15 in 3:2 hexane/EtOAc) as an oil (175.7 mg, 76% yield): IR ν_{max} (thin film) 3423, 2930, 2858, 1723, 1423 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.76 (t, 1H, *J* = 1.9 Hz), 8.45 (m, 2H), 7.50 (ddd, 1H, *J* = 7.7, 2.1, 1.6 Hz), 7.21 (ddd, *J* = 7.7, 4.8, 0.6 Hz), 2.63 (dd, 2H, *J* = 7.6, 7.6 Hz), 2.42 (td, 2H, *J* = 7.3, 1.8 Hz), 2.19 (m, 2H), 2.14 (m, 2H), 1.77−1.20 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.0, 150.1, 147.4, 137.7, 135.9, 123.4, 80.7, 79.8, 44.0, 32.6, 30.3, 29.14, 29.08, 29.0, 28.7, 28.5, 22.1, 18.8, 18.6; HRMS (ESI, TOF) *m*/*z* (M + H) calcd for $C_{19}H_{28}NO$ 286.2170, obsd 286.2175.

14-(Pyridin-3-yl)tetradec-11-yn-1-al (10c). Oxalyl chloride in CH_2Cl_2 (0.72 mL, 1.43 mmol, 2 M) was added to CH_2Cl_2 (0.45 mL) and cooled to −78 °C. DMSO (0.13 mL, 1.79 mmol) was added dropwise followed by a solution of **7c** (206.0 mg, 0.717 mmol) in CH_2Cl_2 (0.2 mL). The resulting mixture was stirred at −78 °C for 45 min, and then triethylamine (0.40 mL, 2.87 mmol) was added dropwise. The solution was allowed to warm to rt and was stirred for 30 min, diluted with diethyl ether (30 mL), filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 2:3 EtOAc/hexane to provide **8c** (TLC R_f = 0.35 in 3:2 hexane/EtOAc) as an oil (115.1 mg, 56% yield): IR ν_{max} (thin film) 2918, 2850, 1463, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.77 (t, 1H, *J* = 1.8 Hz), 8.49 (d, 1H, *J* = 1.8 Hz), 8.47 (dd, 1H, *J* = 4.8, 1.5 Hz), 7.56 (ddd, 1H, *J* = 7.8, 2.1, 1.8 Hz), 7.22 (ddd, 7.7, 4.8, 0.6 Hz), 2.63 (t, 2H, *J* = 7.3 Hz), 2.46 (tt, 2H, *J* = 7.2, 2.3 Hz), 2.43 (td, 2H, *J* = 7.4, 1.9 Hz), 2.11 (td, 2H, *J* = 7.0, 2.3 Hz), 1.67−1.23 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.2, 150.2, 147.9, 137.5, 136.2, 123.3, 78.7, 44.1, 32.7, 29.5, 29.4, 29.3, 29.2, 29.1, 28.9, 25.6, 22.2, 20.8, 18.8; HRMS (ESI, TOF) *m*/*z* (M + H) calcd for $C_{19}H_{28}NO$ 286.2170, obsd 286.2198.

16-(Pyridin-3-yl)hexadec-11-yn-1-al *O*-Methyl Oxime (11a). Aldehyde **10a** (70.7 mg, 0.226 mmol) was dissolved in MeOH (0.5 mL) and pyridine (400 μL, 0.496 mmol). $MeONH_3Cl$ (28.2 mg, 0.338 mmol) was added, and the solution was stirred for 3 h and then concentrated. The resulting residue was dissolved in CH_2Cl_2, washed with satd aq $NaHCO_3$ (3×) and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane to provide a diastereomeric mixture (1:2.1 *E*/*Z* by ^1H NMR) of **11a** (TLC R_f = 0.51 and 0.25 in 1:1 hexane/EtOAc) as an oil (63.3 mg, 82% yield): IR ν_{max} (thin film) 2934, 2855, 1744, 1575, 1464, 1423, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.39 (m, 2H), 7.44 (m, 1H), 7.29 (t, 0.3H, *J* 6.7), 7.15 (dd, 1H, *J* = 7.8, 4.8 Hz), 6.55 (t, 0.7H, *J* = 5.6 Hz), 3.79 (s, 2.3H), 3.74 (0.5H); 2.56 (t, 2H, *J* = 7.7 Hz), 2.26 (td, 1.4H, *J* = 7.3, 5.4 Hz), 2.15−2.04 (m, 4.7H), 1.70−1.18 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0, 151.1, 149.8, 147.1, 137.7, 135.9, 124.2, 123.3, 80.7, 79.5, 61.5, 61.2, 32.5, 30.2, 29.4, 29.32, 29.27, 29.2, 29.1, 28.9, 28.5, 26.7, 26.2, 25.5, 18.7, 18.5; HRMS (ESI, TOF) *m*/*z* (M + H) calcd for $C_{22}H_{35}N_2O$ 343.2749, obsd 343.2765.

14-(Pyridin-3-yl)tetradec-9-yn-1-al *O*-Methyl Oxime (11b). Aldehyde **10b** (50.8 mg, 0.178 mmol) was dissolved in MeOH (0.4 mL) and pyridine (320 μL, 0.392 mmol). $MeONH_3Cl$ (22.3 mg, 0.267 mmol) was added, and the solution was stirred for 3 h then concentrated. The resulting residue was dissolved in CH_2Cl_2, washed with satd aq $NaHCO_3$ (3×) and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane to provide a diastereomeric mixture (1.5:1 *E*/*Z* by ^1H NMR) of **11b** (TLC R_f = 0.58 and 0.39 in 1:1 hexane/EtOAc) as an oil (38.8 mg, 70% yield): IR ν_{max} (thin film) 2936, 2857, 1726, 1575, 1463, 1422, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.45 (m, 2H), 7.50 (m, 1H), 7.36 (t, 0.6H, *J* = 6.2 Hz), 7.21 (dd, 1H, *J* = 7.7, 4.1 Hz), 6.62 (t, 0.4H, *J* = 5.4 Hz), 3.86 (s, 1.2H), 3.81 (s, 1.7H), 2.63 (dd, 2H, *J* = 7.6, 7.6 Hz), 2.30 (td, 0.86H, *J* = 7.5, 5.5 Hz), 2.16 (m, 5.2H), 1.77−1.25 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.1, 151.2, 150.1, 147.5, 137.7, 135.9, 32.7, 30.3, 29.2, 29.1, 29.0, 28.8, 28.6, 26.8, 25.5, 18.9, 18.7; HRMS (ESI, TOF) *m*/*z* (M + H) calcd for $C_{20}H_{31}N_2O$ 315.2436, obsd 315.2426.

14-(Pyridin-3-yl)tetradec-11-yn-1-al *O*-Methyl Oxime (11c). Aldehyde **10c** (115.1 mg, 0.403 mmol) was dissolved in MeOH (0.9 mL) and pyridine (130.4 μL, 1.612 mmol). $MeONH_3Cl$ (50.5 mg, 0.605 mmol) was added, and the solution was stirred for 3 h and then concentrated. The resulting residue was dissolved in CH_2Cl_2, washed with satd aq $NaHCO_3$ (3×) and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane to provide a diastereomeric mixture (1.5:1 *E*/*Z* by ^1H NMR) of **11c** (TLC R_f = 0.54 and 0.35 in 1:1 hexane/EtOAc) as an oil (105.2 mg, 83% yield): IR ν_{max} (thin film) 3413, 2930, 2855, 1634, 1465, 1424, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.49 (d, 1H, *J* = 2.0 Hz), 8.47 (dd, 1H, *J* = 4.7, 1.5 Hz), 7.56 (dt, 1H, *J* = 7.6, 1.9 Hz), 7.36 (t, 0.6H, *J* = 6.3 Hz), 7.22 (ddd, 1H, *J* = 7.6, 4.7, 0.5 Hz), 6.63 (t, 0.4H, *J* = 5.4 Hz), 3.86 (s, 1.2H), 3.82 (s, 1.7H), 2.79 (t, 2H, *J* = 7.3 Hz), 2.46 (tt, 2H, *J* = 7.1, 2.4 Hz), 2.30 (m, 0.8H), 2.20−2.09 (m, 3.2H), 1.51−1.23 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.2, 151.2, 150.2, 147.8, 136.3, 136.1, 123.3, 82.0, 78.6, 62.8, 61.7, 61.3, 32.7, 29.6, 29.50, 29.46, 29.42, 29.38, 29.2, 29.1, 28.9, 26.9, 26.4, 25.7, 20.8, 18.8; HRMS (ESI, TOF) *m*/*z* (M + H) calcd for $C_{20}H_{31}N_2O$ 315.2436, obsd 315.2440.

***O*-Methyl-*N*-(16-(pyridin-3-yl)hexadec-11-ynyl)hydroxylamine (12a).** Oxime **11a** (37.4 mg, 0.109 mmol) was dissolved in AcOH (0.7 mL), and $NaCNBH_3$ (117.0 mg, 0.186 mmol) was added. After 1 h, the reaction mixture was diluted with CH_2Cl_2 and washed with satd aq $NaHCO_3$ (2×). The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane to provide **12a** (TLC R_f = 0.25 in 1:1 hexane/EtOAc) as an oil (38.0 mg, 100% yield): IR ν_{max} (thin film) 2930, 2855, 1757, 1427, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.44 (m, 2H), 7.50 (dt, 1H, *J* = 7.7, 1.8 Hz), 7.20 (dd, 1H, *J* = 7.7, 4.6 Hz), 5.57 (br s, 1H), 3.54 (s, 3H), 2.91 (dd, 1H, *J* = 7.2, 7.2 Hz), 2.63 (dd, 1H, *J* = 7.7, 7.7 Hz), 2.19 (m, 2H), 2.13 (m, 2H), 1.73 (m, 2H), 1.58−1.17 (18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.9, 147.3, 137.5, 135.7, 123.2, 80.7, 79.5, 61.8, 51.9, 32.5, 30.1, 29.7, 29.50, 29.46, 29.12, 29.11, 28.9, 28.4, 27.3, 27.2, 18.7, 18.5; HRMS (ESI, TOF) *m*/*z* (M + H) calcd for $C_{22}H_{37}N_2O$ 345.2905, obsd 345.2892.

***O*-Methyl-*N*-(14-(pyridin-3-yl)tetradec-9-ynyl)hydroxylamine (12b).** Oxime **11b** (185.9 mg, 0.616 mmol) was dissolved in AcOH (3.8 mL), and $NaCNBH_3$ (65.8 mg, 1.046 mmol) was added. After 1 h, the reaction mixture was diluted with CH_2Cl_2 and washed with satd aq $NaHCO_3$ (2×). The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane to provide **12b** (TLC R_f = 0.28 in 1:1 hexane/EtOAc)

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as an oil (123.9 mg, 67% yield): IR ν_{max} (thin film) 2932, 2856, 1575, 1463, 1423, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ δ 8.45 (m, 2H), 7.50 (m, 1H), 7.21 (dd, 1H, J = 7.7, 4.7 Hz), 4.57 (br s, 1H), 3.54 (s, 3H), 2.91 (dd, 1H, J = 7.3, 7.3 Hz), 2.63 (dd, 1H, J = 7.6, 7.6 Hz), 2.19 (m, 2H), 2.13 (m, 2H), 1.73 (m, 2H), 1.56−1.26 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.9, 147.2, 137.6, 135.8, 123.3, 80.7, 79.5, 61.8, 51.9, 32.5, 30.1, 29.4, 29.1, 29.0, 28.8, 28.4, 27.2, 27.1, 18.7, 18.5; HRMS (ESI, TOF) m/z (M + H) calcd for $C_{20}H_{33}N_2O$ 317.2592, obsd 317.2578.

***O*-Methyl-*N*-(14-(pyridin-3-yl)tetradec-11-ynyl)hydroxylamine (12c).** Oxime **11c** (80.3 mg, 0.256 mmol) was dissolved in AcOH (1.6 mL), and $NaCNBH_3$ (27.3 mg, 0.435 mmol) was added. After 1 h, the reaction mixture was diluted with CH_2Cl_2 and washed with satd aq $NaHCO_3$ (2×). The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane to provide **12c** (TLC R_f = 0.26 in 1:1 hexane/EtOAc) as an oil (80.9 mg, 86% yield): IR ν_{max} (thin film) 3054, 2987, 1421, 1354 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.48 (m, 2H), 7.56 (ddd, 1H, J = 7.7, 2.1, 1.7 Hz), 7.22 (ddd, 1H, J = 7.7, 4.8, 0.6 Hz), 5.54 (br s, 1H), 3.54 (s, 3H), 2.91 (dd, 2H, J = 7.3, 7.3 Hz), 2.79 (dd, 2H, J = 7.7, 7.7 Hz), 2.46 (tt, 2H, J = 7.1, 2.3 Hz), 2.11 (tt, 2H, J = 7.0, 2.5 Hz), 1.67−1.22 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.1, 147.7, 136.1, 136.0, 123.2, 81.9, 78.5, 62.6, 61.8, 52.0, 32.6, 29.52, 29.46, 29.2, 29.0, 28.8, 27.3, 27.2, 20.7, 18.7; HRMS (ESI, TOF) m/z (M + H) calcd for $C_{20}H_{33}N_2O$ 317.2592, obsd 317.2580.

***O*-Methyl-*N*-(16-(pyridin-3-yl)hexadec-11-ynyl)hydroxylamine-β-D-glucopyranoside (1a).** Methoxyamine **12a** (24.6 mg, 71.4 μmol) and D-glucose (14.2 mg, 78.5 μmol) were dissolved in 9:1 MeOH/$CHCl_3$ (714 μL), AcOH (4.1 μL, 71.4 μmol) was added, and the resulting mixture was stirred for 2 d at 40 °C. $NaHCO_3$ (7.2 mg, 85.7 μmol) was added, and the reaction mixture was stirred 5 min. The mixture was concentrated onto silica gel (175 mg) and purified by SiO_2 column chromatography eluting with 12:1 CH_2Cl_2/MeOH to provide **1a** (TLC R_f = 0.13 in 12:1 CH_2Cl_2/MeOH) as a white powder (14.0 mg, 39% yield). ^1H and ^{13}C NMR data for **1a** matched those previously reported:[5] IR ν_{max} (thin film) 3369, 2920, 2853, 1731, 1462, 1082, 1026 cm^{-1}; HRMS (ESI, TOF) m/z (M + H) calcd for $C_{28}H_{47}N_2O_6$ 507.3434, obsd 507.3417.

***O*-Methyl-*N*-(14-(pyridin-3-yl)tetradec-9-ynyl)hydroxylamine-β-D-glucopyranoside (1b).** Methoxyamine **12b** (40.0 mg, 132.3 μmol) and D-glucose (26.2 mg, 145.5 μmol) were dissolved in 9:1 MeOH/$CHCl_3$ (1.3 mL), AcOH (7.6 μL, 132.3 μmol) was added, and the resulting mixture was stirred for 2 d at 40 °C. $NaHCO_3$ (13.3 mg, 158.7 μmol) was added and the reaction mixture was stirred 5 min. The mixture was concentrated onto silica gel (175 mg) and purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to provide **1b** (TLC R_f = 0.34 in 10:1 CH_2Cl_2/MeOH) as a white powder (32.2 mg, 51% yield). ^1H and ^{13}C NMR data for **1b** matched those previously reported. IR ν_{max} (thin film) 3369, 2934, 2857, 1426, 1082, 1027 cm^{-1}; HRMS (ESI, TOF) m/z (M + H) calcd for $C_{26}H_{43}N_2O_6$ 479.3121, obsd 479.3121.

***O*-Methyl-*N*-(14-(pyridin-3-yl)tetradec-11-ynyl)hydroxylamine-β-D-glucopyranoside (1c).** Methoxyamine **12c** (48.6 mg, 153.5 μmol) and D-glucose (30.4 mg, 168.9 μmol) were dissolved in 9:1 MeOH/$CHCl_3$ (1.5 mL), AcOH (8.8 μL, 153.5 μmol) was added, and the resulting mixture was stirred for 2 d at 40 °C. $NaHCO_3$ (15.5 mg, 184.2 μmol) was added, and the reaction mixture was stirred 5 min. The mixture was concentrated onto silica gel (175 mg) and purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to provide **1c** (TLC R_f = 0.34 in 10:1 CH_2Cl_2/MeOH) as a white powder (24.5 mg, 33% yield). ^1H and ^{13}C NMR data for **1c** matched those previously reported: IR ν_{max} (thin film) 3369, 2934, 2855, 1427, 1083, 1027 cm^{-1}; HRMS (ESI, TOF) m/z (M + H) calcd for $C_{26}H_{42}N_2O_6Na$ 501.2940, obsd 501.2935.

Cytotoxicity assays. Compounds **1a-c**, **11a-c**, and **12a-c** were dissolved in DMSO (30 mM). Assays were conducted as previously reported (see Supporting Information for IC_{50} values).[7c]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectral data of all new compounds and IC_{50} values for **1a−c**, **11a−c**, and **12a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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