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Synthesis of Triazole-Epothilones by Using Cu_2O Nanoparticles to Catalyze 1,3-Dipolar Cycloaddition

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We report the total synthesis of a triazole-epothilone analogue **1**. The key step to generate the macrocyclic ring and the triazole ring was to apply Cu_2O nanoparticles (Cu_2O-NPs) to catalyze the 1,3-dipolar cycloaddition. The conformation of **1** and its bioactivity in MCF cancer cell lines were investigated.

Introduction

The copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction is increasingly being used to generate vast libraries of materials, new applications, and chemical modifications.[1,2] In particular, the click reaction provides a facial approach for construction of macrocyclic molecules through intramolecular cycloaddition. The catalyst systems that are employed in this type of ring formation includes: $CuSO_4$/NaAsc,[2c] CuI/DIEA,[3] $Cu(CN)_4PF_6$,[4] and CuBr/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[5] Chen and Kong[6] recently reported the use of Cu_2O nanoparticles (Cu_2O-NPs) to catalyze this reaction either under physiological conditions or in acetonitrile. This Cu_2O-NP catalyst demonstrates less cytotoxicity and superior efficiency than traditional $CuSO_4$/NaAsc systems.

Epothilones, which were isolated in 1993 from myxobacteria by Höfle et al., are polyketide macrolides.[7] Compared to paclitaxel, the epothilones possess improved water solubility and activity against various human cancer cells. These advantages have evoked large-scale research efforts within both academic and pharmaceutical research groups and this has resulted in numerous total syntheses, structure activity relationship (SAR) studies, and computational modeling.[8] For example, epothilone D (Scheme 1), in which the C12–C13 olefin is replaced by cyclopropane[7b–7f] or aziridine[7g] moieties shows a slight improvement in biological activity against cancer cell lines. These results suggest that the type of replacement is largely conformational. On the other hand, the CuAAC product, 1,5-triazole or 1,4-triazole, was reported to be isostatic to amides and olefins in drugs with linear structure, and the resulting analogues maintain significant biological activity.[9]

Here we report the first synthesis of a triazole-epothilone analogue through a Cu_2O-NP catalyzed CuAAC reaction to simultaneously generate the macrocyclic ring and the triazole ring. The resulting triazole analogue (Scheme 1) may be suitable for exploring the conformational and biological effects in more complex polyketide macrolide systems.

Inspection of the structure of triazole-epothilone analogue **1** reveals the possibility of applying the click reaction with precursor **2** (Scheme 1). The aldol moiety in **2** allows the indicated disconnection of the reported aldehyde **3**[10] and ester **4** as potential intermediates. An esterification reaction was identified to disconnect **4** from its components: the known carboxylic acid **6**[11] and secondary alcohol **5**. The latter may be derived from the ketone alcohol **7** and known thiazole fragment derivative **8**.[12]

The key step in the synthesis of target compound **1** is the utilization of intramolecular 1,3-dipolar cycloaddition to construct the sixteen-membered macrocycle. A model reaction to form a fourteen-membered heterocycle **10** was applied to explore the best conditions for the intramolecular CuAAC reaction (Scheme 2). Exposure of the key intermediate **9** to CuI/DIEA[3] or $[Cu(CN)_4PF_6]$[4] either provided the cyclization product in only trace amounts or no reaction was observed. However, compound **10** was successfully obtained in 64% yield when the reaction was catalyzed by Cu_2O-NPs. The success of the study with the model system demonstrates that the use of Cu_2O-NPs is feasible for intramolecular CuAAC reactions.

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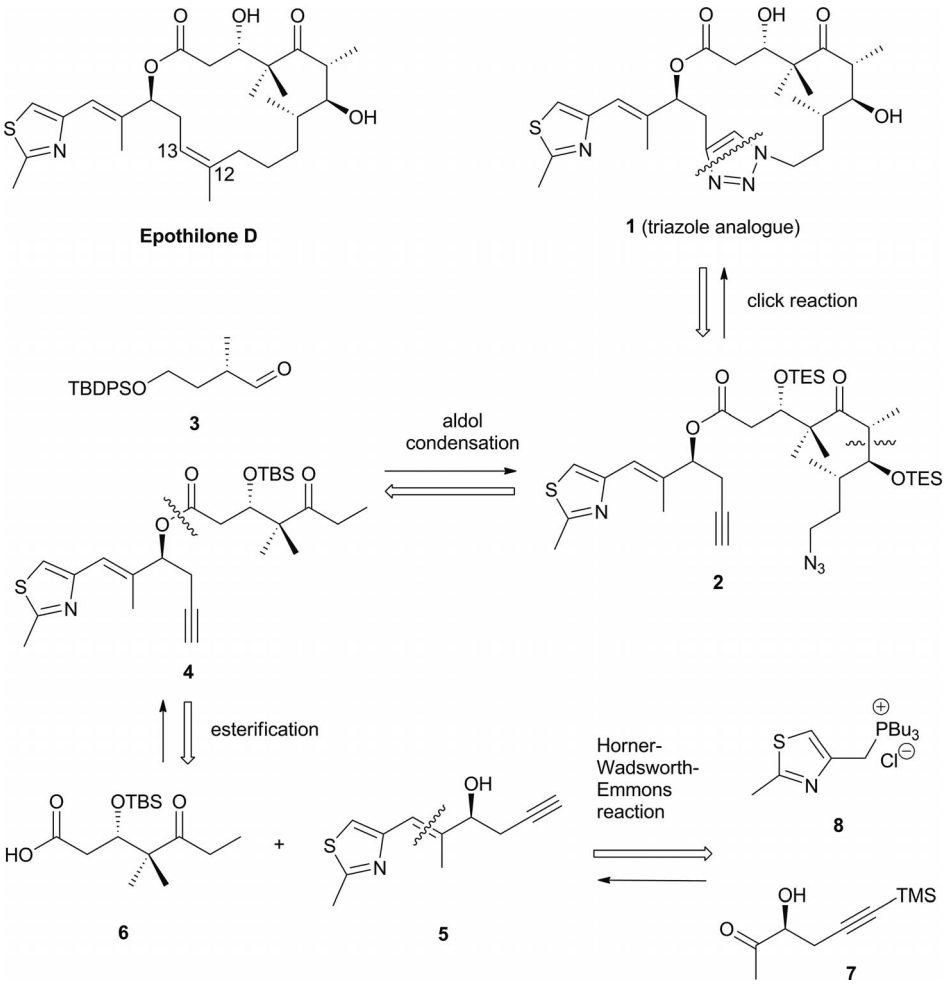
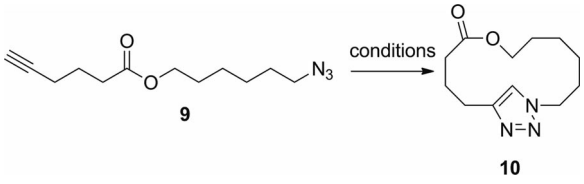


Scheme 1. Retrosynthetic analysis.



Scheme 2. Model system used to study the conditions for the intramolecular CuAAC reaction.

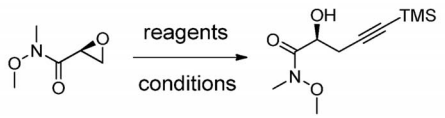
Results and Discussion

The preparation of fragment **12** started with the Weinreb amide **11** (Scheme 3), which was synthesized according to Chen and Li.[13] The nucleophile (trimethylsilyl)ethyn-1-ide was generated using (trimethylsilyl)acetylene and *n*BuLi, and the following alkynylation of epoxide **11** was tested under various reaction conditions. However, the expected epoxide product was either not formed or generated in trace amounts with BF_3·OEt[14] or Me_3Al[15] as the catalyst. Finally, an organo-aluminum species, which was prepared with iBu_2AlCl and (trimethylsilyl)ethyn-1-ide, provided the desired alcohol **12** in 75% yield.

Addition of MeMgBr to **12** afforded keto alcohol **7** in 87% yield (Scheme 4), and subsequent Horner–Wadsworth–Emmons reaction with tributyl[(2-methylthiazol-4-yl)methyl]phosphonium chloride (**8**) to provide (*E*)-olefin **13** in 97% yield.[16] Desilylation of the latter using tetrabutylammonium fluoride (TBAF) furnished alcohol **5** (95%). Thus, the coupling reaction between fragments **5** and **6** led to the formation of ester **4** in 85% yield.[17] Aldol condensation of the Ti enolate of keto **4** (generated by $TiCl_4$ under basic conditions) and aldehyde **3** provided adduct **14** (73%, *dr* = 8:1).[18] Desilylation of **14** with trifluoroacetic acid at 0 °C furnished the intermediate **15**, which was treated with $NaHCO_3$ in CH_2Cl_2/MeOH to afford triol **16** (80% for two steps).

After protection of triol **16** with a combination of TESOTf and 2,6-lutidine to obtain compound **17** (Scheme 5), the less sterically hindered TES group in **17** was selectively removed with pyridinium *p*-toluenesulfonate (PPTS) to provide primary alcohol **18** in 80% yield for two steps.[19] Treatment of **18** with *p*-toluenesulfonyl chloride (TsCl) to generate a TsO leaving group, followed by NaN_3 replacement, afforded **2** in 87% yield for two steps.[20]

Exposure of the key intermediate **2** to conventional catalyst systems (Scheme 6, entries 1–3), CuI/DIEA,[3] $CuSO_4$/NaAsc,[2c] or CuBr/DBU,[5] either provided the cyclization

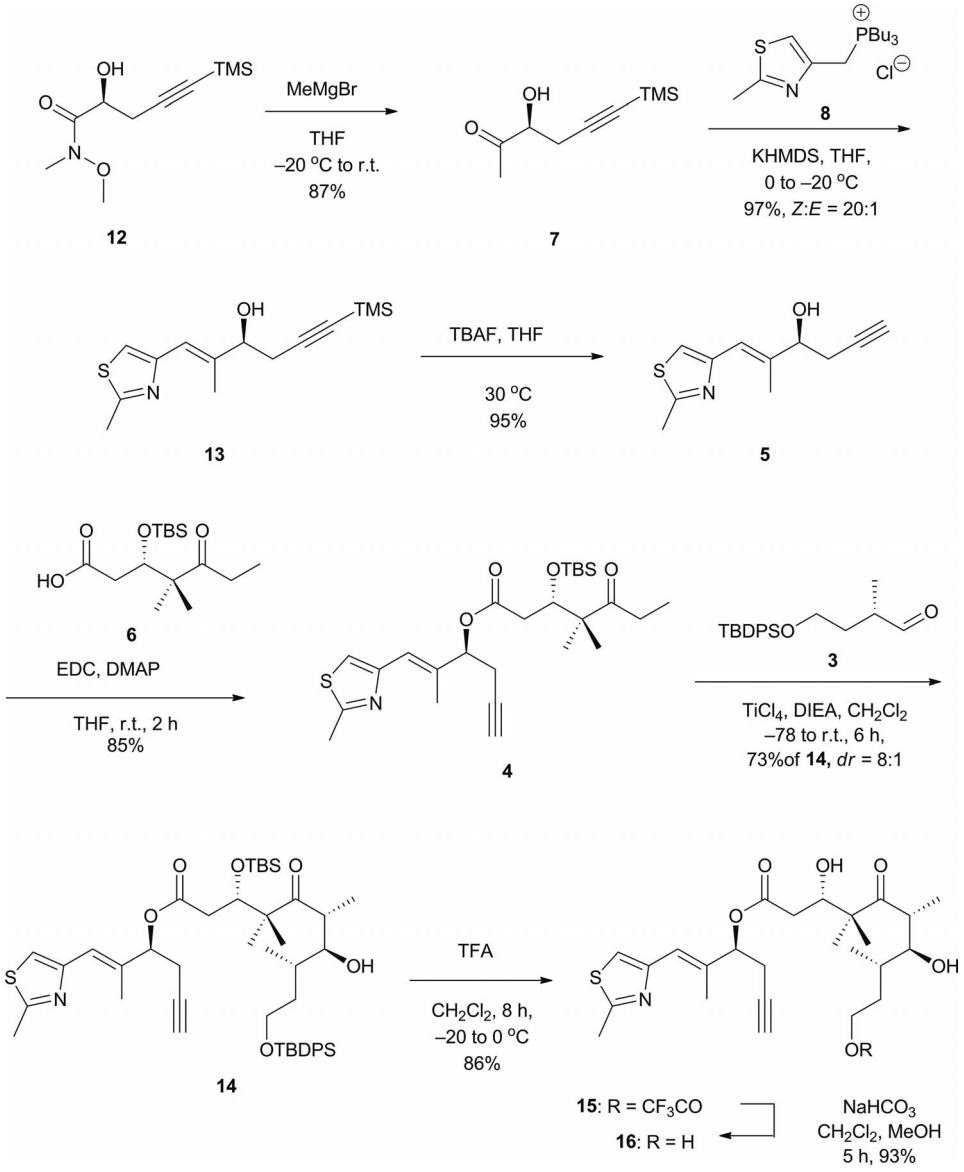


11 12

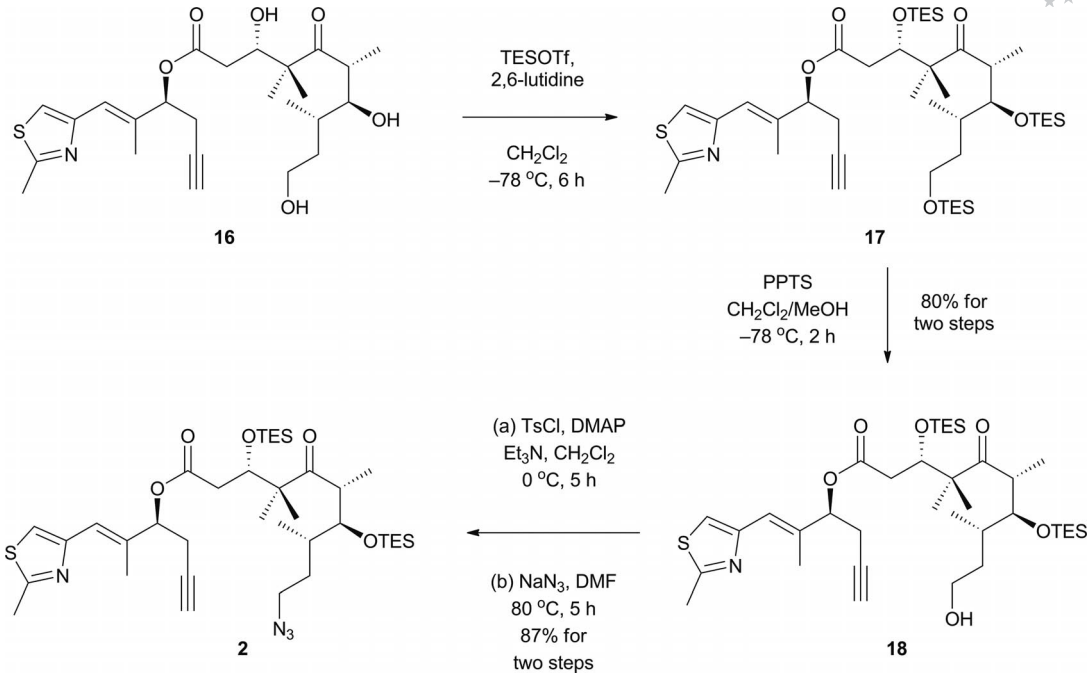
Entry	Reagents	Conditions	Yield[a] of **12**
1	TMS-acetylene, *n*BuLi, THF	–78 to –60 °C	0
2	TMS-acetylene, *n*BuLi, BF_3·OEt THF	–78 to –60 °C	0
3	TMS-acetylene, *n*BuLi, Me_3Al, THF	–78 to 0 °C	trace product[b]
4	**TMS-acetylene, *n*BuLi, *i*Bu_2AlCl, THF**	**0 °C**	**75%**

[a] Isolated yields after silica gel chromatography. [b] Unreacted starting martial is recovered.

Scheme 3. Preparation of **12** from the Weinreb amide **11**.



Scheme 4. Preparation of **16** from **12**.



Scheme 5. Preparation of **2** from **16**.

product in only trace amounts or no reaction was observed. The best approach was to apply $[Cu(CN)_4PF_6]$ (Scheme 6, entry 4), which provided the product **19** in 36% yield.[4] Interestingly, for the first time, we applied this Cu_2O-NP catalyst in a ring-closure click reaction (Scheme 6, entry 5), and found the result to be satisfactory: using acetonitrile as solvent, the desired monomer **19** was isolated in 74% yield and dimer **20** was isolated in 6% yield. Both compounds were treated with trifluoroacetic acid at 0 °C to furnish the target molecule **1** in 92% yield and compound **21** in 87% yield.

The absolute structure of **1** was confirmed by X-ray analysis (Figure 1). Computational modeling (see Figure S2 in the Supporting Information) suggests that the conformation of compound **1** in solution is similar to that in the solid-state, and this conformation is significantly different from the solid-state structure of epothilones[21] and the suggested bioactive conformations.[22] This comparison is further confirmed by the NMR analysis of compound **1** in solution. The main feature of **1** is a rigid and planar conformation of the C10–C14 region, which contrasts with the same region in natural epothilones which is flexible and has at least two conformers.[22] Furthermore, there is also a conformational change in the C1–C7 region, which is probably vital to the biological activity of epothilone.[23] The best docking of **1** to the structure of α,β-tubulin (PDB ID: 1TVK) using the software AutoDock v.4.2 (http://autodock.scripps.edu) (Figure 2) requires a reversal of conformation compared to natural epothilones (for the docking procedure, see the Supporting Information). Moreover, the binding energy of **1** to the structure of α,β-tubulin is 2.7 kcal/mol higher than that of natural epothilones.[24] It is therefore not surprising to find that compound **1** had reduced biological activity against MCF-7 cancer cell lines ($IC_{50} > 50$ μM). However, it was interesting to find that the dimer **21** is active against MCF-7 ($IC_{50} = 10$ μM, which is about 200 times less potent than Epothilone D in the same assay).

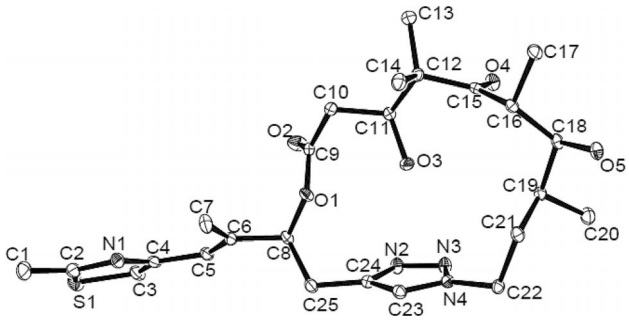


Figure 1. X-ray ORTEP illustration of compound **1**.

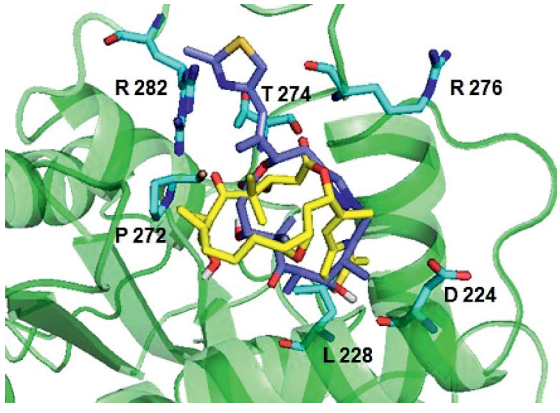
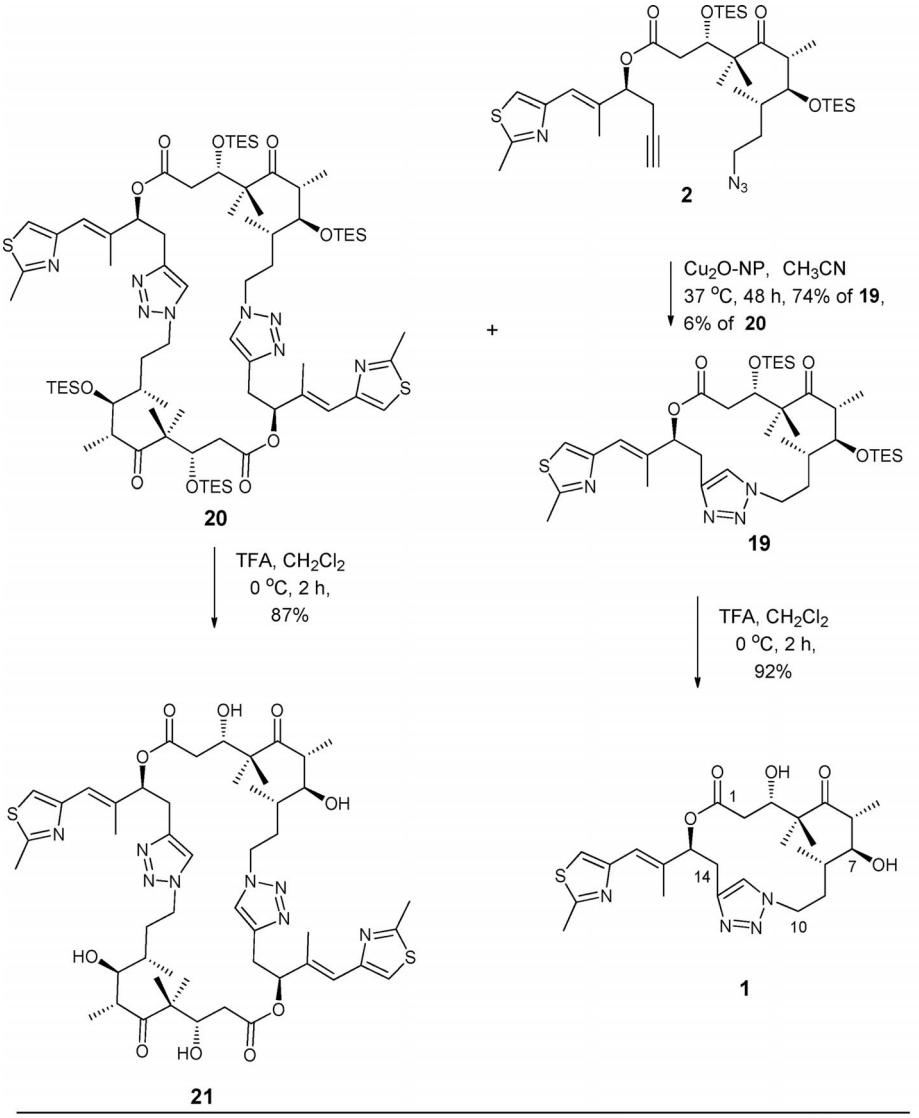


Figure 2. Superposition of best docking position of **1** (light purple) and natural Epothilone A (yellow) to α,β-tubulin.



Entry	Reagent	Conditions	Yield[a] of **19**	Yield[a] of **20**
1	CuI/DIEA	CH_3CN, 40 °C, 72 h	trace product [b]	0
2	$CuSO_4$/sodium ascrobate	CH_2Cl_2, r.t.,72 h	no reaction[b]	0
3	CuBr/DBU	CH_2Cl_2, r.t., 72 h	no reaction [b]	0
4	$Cu(CN)_4PF_6$	toluene, 60 °C, 48 h	36%	0
5	**Cu_2O-NP**	**CH_3CN 37 °C, 48 h**	**74%**	**6%**

[a] Isolated yields after silica gel chromatography. [b] Unreacted starting martial is recovered.

Scheme 6. Preparation of **1** and the dimer **21**.

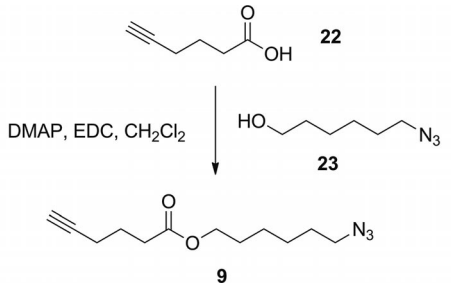
Conclusions

A novel type of triazole-epothilone analogue was synthesized through Cu_2O-NP catalyzed 1,3-dipolar cycloaddition as the key step. This is the first time that the efficiency of Cu_2O-NPs has been evaluated in the cyclization of large ring systems. The superior yield of this reaction demonstrates that Cu_2O-NPs are a feasible catalyst for intramolecular macrocyclic ring formation.

Experimental Section

General: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. The used solvents were purified and dried according to common procedures. Polyvinylpyrrolidone (PVP) coated copper(I) oxide nanoparticle (Cu_2O-NPs) were synthesized according to Chen and Kong's procedures.[6] Other chemicals and solvents are commercially available. The phosphate buffer solution (pH 7.2, 0.1 M) was prepared by dissolving disodium hydrogen phosphate ($Na_2HPO_4{\cdot}12H_2O$, 25.79 g) and sodium dihydrogen phosphate ($NaH_2PO_4{\cdot}2H_2O$, 4.37 g) in distilled, deionized water (1000 mL). High-resolution mass spectra (HRMS) were obtained with a FTICR-MS (Ionspec 7.0T) spectrometer. ^{1}H NMR spectra were obtained with a Bruker AC-P 300, AV 400, AV 600, or a Varian Mercury Plus 400 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to either a tetramethylsilane internal standard or solvent signals. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants, and integration. ^{13}C NMR spectra were recorded with a Bruker AC-P 300 (75 MHz) or AV 400 spectrometer (100 MHz) using $CDCl_3$ or MeOD as the solvent. Chemical shifts (δ) are reported in ppm measured relative to the solvent peak. IR spectra were recorded with a Bio-Rad FTS 6000 Fourier infrared spectrometer.

Synthesis of 9



To a solution of acid **22** (391 mg, 3.49 mmol) at 0 °C, was added a solution of 4-(dimethylamino)pyridine (4-DMAP; 641 mg, 5.24 mmol) and alcohol **23** (500 mg, 3.49 mmol) in CH_2Cl_2 (20 mL), and the mixture was treated with 1-ethyl-3-[(dimethylamino)propyl]carbodiimide hydrochloride (EDC; 1.3 g, 6.98 mmol). The reaction mixture was stirred at 0 °C for 2 h and then at 25 °C for 12 h. The solution was concentrated under reduced pressure and the residue was taken up in EtOAc (20 mL) and water (100 mL). The organic layer was sequentially washed with saturated NH_4Cl (10 mL) and water (10 mL), and dried with $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography (silica gel; EtOAc/hexanes, 7%) to give ester **9** (700 mg, 84%) as a yellow oil. R_f = 0.67 (hexanes/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (t, J = 6.6 Hz, 2 H), 3.16 (t, J = 6.8 Hz, 2 H), 2.33 (t, J = 7.4 Hz, 2 H), 2.16–2.13 (m, 2 H), 1.89 (s, 1 H), 1.76–1.69 (m, 2 H), 1.55–1.48 (m, 4 H), 1.29–1.28 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 83.1, 69.0, 64.0, 51.1, 32.7, 28.5, 28.3, 26.2, 25.3, 23.5, 17.6 ppm. HRMS (ESI): calcd. for $C_{12}H_{19}N_3O_2$ [M + H^+] 238.1550; found 238.1552.

Synthesis of 10: To a solution of freshly prepared polyvinylpyrrolidone (PVP) coated copper(I) oxide nanoparticle (Cu_2O-NP; 75 mg, 0.71 mmol) in CH_3CN (355 mL, c = 211 μg/mL), was added **9** (170 mg, 0.71 mmol) in CH_3CN (5 mL) at 37 °C in 24 h. The mixture was stirred at 37 °C for 48 h (TLC indicated the disappearance of **9**). The mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by column chromatograph (silica gel; EtOAc/hexanes, 30%) to give **10** (108 mg, 64%) as a white solid. R_f = 0.4 (EtOAc/hexanes, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (s, 1 H), 4.34–4.31 (m, 2 H), 3.99–3.96 (m, 2 H), 2.84–2.81 (m, 2 H), 2.28–2.26 (m, 2 H), 2.14–2.08 (m, 2 H), 1.96–1.89 (m, 2 H), 1.49–1.44 (m, 2 H), 1.28–1.21 (m, 2 H), 0.94–0.89 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 145.8, 122.8, 63.7, 50.1, 32.6, 28.1, 27.6, 25.2, 25.0, 24.7, 22.2 ppm. HRMS (ESI): calcd. for $C_{12}H_{19}N_3O_2$ [M + H^+] 238.1550; found 238.1552.

Synthesis of 12: To a solution of (trimethylsilyl)acetylene (6.8 mL, 48 mmol) in toluene (150 mL) at 0 °C, was added *n*BuLi (17.6 mL, 44 mmol) by using a syringe over 30 min under Ar. The resulting mixture was stirred for 30 min then *iso*-Bu_2AlCl (60 mL, 48 mmol) was added. The resulting solution was stirred at room temperature for 2 h, then recooled to 0 °C and epoxy amide **9** (5.24 g, 40 mmol) was added. The solution was stirred at 0 °C for 2 h, then the mixture was diluted with diethyl ether (200 mL) and acidified with 1 M HCl (pH 4). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layer was dried with Na_2SO_4, filtered through Celite, and the solvents were removed under reduced pressure. The residue was purified by a flash column chromatography (silica gel; EtOAc/hexanes, 20%) to give **12** (6.89 g, 75%) as a yellow oil. R_f = 0.24 (EtOAc/hexanes, 20%). $[\alpha]_D^{20}$ = –67.4 (c = 1.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3429, 2959, 2901, 2822, 2177, 1658, 1443, 1370, 1249, 1179, 1077, 1046, 983, 839, 759 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51 (s, 1 H), 3.72 (s, 3 H), 3.59–3.58 (m, 1 H), 3.25 (s, 3 H), 2.66 (q, J = 16.9 Hz, 2 H), 0.13 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.67, 101.69, 87.40, 67.18, 61.52, 32.46, 26.37, 0.07 ppm. HRMS (ESI): calcd. for $C_{10}H_{19}NO_3Si$ [M + H^+] 230.1207; found 230.1214.

Synthesis of 7: To a solution of amide **12** (6 g, 26.1 mmol) in THF (200 mL) under N_2 was added methylmagnesium bromide (1.53 mL, 1.96 mmol) at –20 °C. The reaction mixture was warmed to room temperature and stirred for 8 h. EtOAc (100 mL) was added slowly, followed by saturated aqueous oxalic acid (100 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layer was washed with brine (120 mL), dried with Na_2SO_4, filtered through Celite, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel; EtOAc/hexanes, 10%) to give **7** (4.2 g, 87%) as a yellow oil. R_f = 0.83 (EtOAc/hexanes, 50%) $[\alpha]_D^{20}$ = +39.0 (c = 0.8, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3445, 2959, 2900, 2177, 1717, 1411, 1358, 1249, 1181, 1095, 1046, 948, 840, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28 (q, J = 5.4 Hz, 1 H), 3.67 (d, J = 5.5 Hz, 1 H), 2.63–2.49 (m, 2 H), 2.29 (s, 3 H), 0.13 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.9, 101.1, 87.6, 74.7, 25.6, 25.0, –0.4 ppm. HRMS (ESI): calcd. for $C_9H_{16}O_2Si$ [M + Na^+] 207.0812; found 207.0816.

Synthesis of 13: To a solution of Wittig reagent **8** (22 g, 65.2 mmol) in THF (100 mL), was added KHMDS (65.2 mL, 65.2 mmol) at 0 °C. After stirring for 0.5 h, the reaction mixture was cooled to –78 °C and a solution of ketone **7** (3 g, 16.3 mmol) in THF (40 mL) was added. The reaction mixture was warmed to –20 °C, and, after 1 h, TLC indicated the disappearance of keto **7**. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL), the aqueous layer was extracted with EtOAc (100 mL), and the combined organic layer was washed with brine (120 mL), and dried with Na_2SO_4. The solvent was removed under vacuum and the resi-

due was purified by a flash column chromatography (silica gel; hexane/EtOAc, 3:1) to give **13** (4.82 g, 97%) as a yellow oil. R_f = 0.21 (EtOAc/hexanes, 30%). $[\alpha]_D^{20}$ = –1.0 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3290, 3118, 2957, 2902, 2175, 1654, 1506, 1438, 1422, 1248, 1030, 999, 837, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 1 H), 6.53 (s, 1 H), 4.27–4.24 (m, 1 H), 3.95–3.92 (m, 1 H), 2.63 (s, 3 H), 2.51–2.49 (m, 2 H), 1.94 (s, 3 H), 0.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 152.4, 140.7, 119.3, 115.5, 103.6, 87.0, 75.2, 27.5, 18.9, 14.2, 0.04 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}NOSSi$ [M + H^+] 280.1186; found 280.1189.

Synthesis of 5: To a solution of TBAF (92 g, 294 mmol) in THF (200 mL), was added a solution of alcohol **13** (27 g, 98 mmol) in THF (3 mL) at 30 °C, and the reaction mixture was stirred for 2 h. The reaction was quenched by addition of water (50 mL) and the aqueous layer was extracted with Et_2O (3 × 60 mL). The combined organic layer was dried with Na_2SO_4 and the solvent was removed under vacuum to give a residue that was purified by flash chromatography on silica gel (hexane/EtOAc, 10:1) to give product **5** (19 g, 95%) as a yellow oil. R_f = 0.19 (EtOAc/hexanes, 30%). $[\alpha]_D^{20}$ = –2.1 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3296, 2917, 2118, 1655, 1508, 1441, 1377, 1270, 1191, 1036 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1 H), 6.61 (s, 1 H), 4.36 (t, *J* = 6.2 Hz, 1 H), 2.71 (s, 3 H), 2.57–2.54 (m, 2 H), 2.42 (s, 1 H), 2.07–2.06 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 152.3, 140.4, 119.7, 115.8, 81.0, 75.4, 70.6, 25.9, 19.0, 14.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{13}NOS$ [M + H^+] 208.0791; found 208.0794.

Synthesis of 4: To a solution of acid **6** (8.88 g, 29.4 mmol) at 0 °C, was added a solution of DMAP (5.4 g, 44.1 mmol) and alcohol **5** (7.3 g, 35.2 mmol) in CH_2Cl_2 (40 mL), and then treated with EDC (11.3 g, 58.8 mmol). The reaction mixture was stirred at 0 °C for 2 h and then at 25 °C for 12 h. The solution was concentrated to dryness in vacuo and the residue was taken up in EtOAc (100 mL) and water (100 mL). The organic layer was sequentially washed with saturated NH_4Cl (50 mL) and water (50 mL), and dried with $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography (silica gel; EtOAc/hexanes, 7%) to give **4** (12 g, 85%) as a yellow oil. R_f = 0.74 (hexanes/EtOAc, 5:1). $[\alpha]_D^{20}$ = –15.6 (*c* = 0.23, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3506, 3310, 3071, 2957, 2932, 2857, 1740, 1686, 1505, 1470, 1428, 1386, 1293, 1255, 1177, 1106, 1089, 996, 834, 777, 703, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1 H), 6.54 (s, 1 H), 5.35 (t, *J* = 6.6 Hz, 1 H), 4.46 (dd, *J* = 4.0, 5.8 Hz, 1 H), 2.67 (s, 3 H), 2.61 (t, *J* = 5.8 Hz, 2 H), 2.57–2.30 (m, 3 H), 2.33 (dd, *J* = 6.3, 16.8 Hz, 1 H), 2.08 (s, 3 H), 1.96 (s, 1 H), 1.08 (s, 3 H), 1.04 (s, 3 H), 0.97–0.94 (t, *J* = 7.1 Hz, 3 H), 0.82 (s, 9 H), 0.03 (d, *J* = 7.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.4, 170.7, 164.4, 152.2, 135.3, 121.7, 116.8, 79.2, 77.0, 73.3, 70.8, 52.4, 39.3, 31.6, 25.8, 23.3, 20.7, 20.6, 19.1, 17.9, 14.3, 7.6, –4.4, –5.2 ppm. HRMS (ESI): calcd. for $C_9H_{16}O_2Si$ [M + H^+] 492. 2598; found 492.2601.

Synthesis of 14: To a solution of **4** (5.37 g, 11 mmol) in CH_2Cl_2 (250 mL), was added $TiCl_4$ (13.2 mL, 13.2 mmol, 1 mmol/mL) at –78 °C, followed by addition of DIEA (2.2 mL, 13.2 mmol). After stirring for 1.5 h at –78 °C, a solution of aldehyde **3** (3.71 g, 11 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was warmed slowly to room temperature and then diluted with Et_2O (100 mL) and quenched with phosphoric buffer solution (30 mL). The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried with $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography (silica gel; EtOAc/hexanes, 5%) to afford **14** (6.6 g, 73%) as a yellow oil and **14a** (822 mg, 9%) as a yellow oil. Compound **14**: R_f = 0.68 (hexanes/EtOAc, 5:1). $[\alpha]_D^{20}$ = –44.8 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3506, 3310, 3071, 2957, 2932, 2857, 1740, 1686, 1505, 1470, 1428, 1386, 1293, 1255, 1177, 1106, 1089, 996, 834, 777, 738, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.66 (m, 4 H), 7.39–7.37 (m, 6 H), 6.98 (s, 1 H), 6.57 (s, 1 H), 5.39 (t, *J* = 6.5 Hz, 1 H), 4.42 (m, 1 H), 3.72 (dd, *J* = 6.3, 12.7 Hz, 2 H), 3.38 (s, 1 H), 3.31–3.26 (m, 2 H), 2.68 (s, 3 H), 2.64 (s, 2 H), 2.50 (dd, *J* = 3.5, 17.3 Hz, 1 H), 2.37 (dd, *J* = 5.8, 17.2 Hz, 1 H), 2.10 (s, 3 H), 1.98 (s, 1 H), 1.70 (m, 2 H), 1.20 (s, 3 H), 1.09 (s, 3 H), 1.04 (m, 12 H), 0.88 (m, 12 H), 0.80 (d, *J* = 6.8 Hz, 3 H), 0.11 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 221.5, 170.9, 164.8, 162.4, 152.4, 135.7, 135.6, 134.2, 134.1, 129.6, 127.8, 127.7, 121.9, 117.0, 79.5, 77.3, 74.9, 73.6, 70.9, 62.4, 53.9, 41.7, 40.3, 35.6, 32.9, 29.8, 26.9, 26.1, 23.6, 22.3, 20.0, 19.4, 19.3, 18.3, 15.9, 14.7, 10.0, –4.1, –4.7 ppm. HRMS (ESI): calcd. for $C_{47}H_{69}NO_6SSi_2$ [M + H^+] 832.4457; found 832.4450.

Synthesis of 16: To a solution of **14** (228 mg, 0.274 mmol) was added a freshly prepared 20% CF_3COOH solution in CH_2Cl_2 (8 mL) at –20 °C. The reaction mixture was allowed to reach 0 °C and stirred for 1 h. The reaction mixture was diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$ to adjust the pH to 7. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layer was washed with brine, dried with $MgSO_4$, filtered through Celite and the solvents removed under reduced pressure to give the crude product **15**. To a solution of crude **15** in a mixture of CH_2Cl_2 (8 mL) and MeOH (2 mL) was added $NaHCO_3$ (500 mg) at 0 °C. The mixture was stirred until the starting martial was completely converted. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with brine, dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatograph on silica gel (hexanes/EtOAc, 1:2) to obtain **16** (104 mg, 80% for two steps) as a colorless oil. R_f = 0.23 (hexanes/EtOAc, 1:2). $[\alpha]_D^{20}$ = –43.6 (*c* = 1.0, $CHCl_3$) IR (KBr): $\tilde{\nu}$ = 3299, 2956, 2918, 2849, 1784, 1736, 1697, 14723, 1463, 1378, 1295, 1261, 1220, 1169, 1018, 801, 719, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 1 H), 6.58 (s, 1 H), 5.46 (t, *J* = 6.6 Hz, 1 H), 4.27 (d, *J* = 8.7 Hz, 1 H), 3.76–3.71 (m, 1 H), 3.64–3.60 (m, 1 H), 3.49–3.45 (m, 2 H), 3.40 (s, 1 H), 3.27 (dd, *J* = 6.3, 13.0 Hz, 1 H), 2.70 (s, 3 H), 2.66–2.63 (m, 2 H), 2.54–2.42 (m, 2 H), 2.10 (s, 3 H), 2.01 (m, 1 H), 1.79–1.73 (m, 2 H), 1.58–1.53 (m, 1 H), 1.22–1.20 (m, 3 H), 1.13 (s, 3 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 221.9, 171.8, 164.9, 151.9, 135.5, 121.7, 116.9, 79.3, 77.2, 75.4, 72.3, 70.9, 60.8, 52.2, 41.4, 37.0, 36.8, 33.6, 23.6, 21.6, 19.2, 18.6, 17.2, 14.7, 10.5 ppm. HRMS (ESI): calcd. for $C_{25}H_{37}NO_6S$ [M + H^+] 480.2414; found 480.2412.

Synthesis of 18: To a solution of **16** (930 mg, 1.94 mmol) in CH_2Cl_2 (50 mL) was added 2,6-lutidine (2.7 mL, 23.3 mmol), followed by TESOTf (4 mL, 17.5 mmol) at –78 °C. The resulting solution was stirred at –78 °C for 5 h before being quenched by addition of saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layer was washed with brine, dried with $MgSO_4$, filtered through Celite, and the solvent removed under reduced pressure to obtain crude product **17** as a yellow oil, which was used immediately in the next step without further purification. To a solution of crude **17** in a mixture of MeOH/CH_2Cl_2 (4 mL/12 mL) was added pyridinium 4-toluenesulfonate (137 mg, 0.54 mmol) at –10 °C. The mixture was stirred until the starting martial was completely converted. The mixture was quenched with saturated aqueous NH_4Cl (16 mL) and the aqueous phase was extracted with Et_2O (3 × 16 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by

column chromatograph on silica gel (EtOAc/hexanes, 20%) to obtain **18** (1.1 g, 80% for two steps) as a colorless oil. R_f = 0.27 (EtOAc/hexanes, 20%) $[\alpha]_D^{20}$ = –33 (*c* = 1.0, $CHCl_3$) IR (KBr): $\tilde{\nu}$ = 3314, 2956, 2917, 2877, 1737, 1690, 1458, 1379, 1293, 1238, 1096, 988, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1 H), 6.56 (s, 1 H), 5.38 (t, *J* = 6.4 Hz, 1 H), 4.36 (dd, *J* = 1.4, 4.4 Hz, 1 H), 3.81 (d, *J* = 7.7 Hz, 1 H), 3.66 (br., 1 H), 3.52–3.51 (m, 1 H), 3.20–3.17 (m, 1 H), 2.69 (s, 3 H), 2.64–2.60 (m, 2 H), 2.48 (dd, *J* = 2.7, 17.1 Hz, 1 H), 2.34 (dd, *J* = 7.3, 17.0 Hz, 1 H), 2.09 (s, 3 H), 1.96 (t, *J* = 2.5 Hz, 1 H), 1.63–1.60 (m, 1 H), 1.52–1.49 (m, 2 H), 1.21 (s, 3 H), 1.08 (s, 3 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.94 (m, 21 H), 0.66–0.58 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.4, 171.2, 164.8, 152.4, 135.7, 122.1, 116.9, 79.4, 78.7, 77.1, 73.6, 70.8, 60.1, 53.5, 45.7, 39.9, 34.8, 33.6, 29.8, 23.5, 19.8, 19.3, 18.2, 15.6, 14.6, 7.2, 7.1, 5.5, 5.2 ppm. HRMS (ESI): calcd. for $C_{37}H_{65}NO_6SSi_2$ [M + H^+] 708.4144; found 708.4147.

Synthesis of 2: To a solution of **18** (323 mg, 0.45 mmol) in CH_2Cl_2 (10 mL), was added Et_3N (0.39 mL, 2.7 mmol) and DMAP (5.5 mL, 0.045 mmol) at 0 °C, followed by addition of TsCl (435 mg, 2.3 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at room temperature for 6 h, then the reaction was quenched with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the extracts were washed with brine, dried with Na_2SO_4, and the solvent was removed under vacuum to give the crude product. To a solution of the 4-methylbenzenesulfonyl crude product in DMF (16 mL) was added NaN_3 (87.7 mg, 1.35 mmol) under Ar, and the mixture was heated to 80 °C and stirred for 5 h. The reaction mixture was diluted with Et_2O and quenched with saturated aqueous NaCl, the aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layer was washed with H_2O (2 × 10 mL), dried with $MgSO_4$, filtered through Celite, and the solvent was removed under reduced pressure. The residue was purified by column chromatograph (silica gel; EtOAc/hexanes, 1:30 → 1:10) to obtain **2** (288 mg, 87% for two steps) as a colorless oil. R_f = 0.64 (EtOAc/hexanes, 15%). $[\alpha]_D^{20}$ = –45.2 (*c* = 1.0, $CHCl_3$) IR (KBr): $\tilde{\nu}$ = 3401, 3314, 2962, 2918, 2849, 2663, 2096, 1945, 1739, 1691, 1621, 1472, 1462, 1415, 1379, 1337, 1260, 872, 743, 722, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1 H), 6.56 (s, 1 H), 5.39 (t, *J* = 6.6 Hz, 1 H), 4.34 (dd, *J* = 3.0, 7.1 Hz, 1 H), 3.78 (d, *J* = 7.6 Hz, 1 H), 3.36–3.30 (m, 1 H), 3.22–3.17 (m, 1 H), 3.13–3.06 (m, 1 H), 2.70 (s, 3 H), 2.65–2.60 (m, 2 H), 2.51 (dd, *J* = 2.9, 17.0 Hz, 1 H), 2.33 (dd, *J* = 7.2, 17.0 Hz, 1 H), 2.10 (s, 3 H), 1.97 (t, *J* = 2.6 Hz, 1 H), 1.74–1.67 (m, 1 H), 1.39 (br., 2 H), 1.24 (s, 3 H), 1.06–1.03 (m, 6 H), 0.97–0.90 (m, 21 H), 0.65–0.69 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.1, 171.1, 164.8, 152.5, 135.7, 122.1, 117.0, 79.5, 78.6, 77.1, 73.9, 70.8, 53.3, 50.0, 45.8, 39.9, 35.3, 29.8, 23.5, 23.3, 20.1, 19.3, 17.9, 15.3, 14.5, 7.2, 7.1, 5.6, 5.2 ppm. HRMS (ESI): calcd. for $C_{37}H_{64}N_4O_5SSi_2$ [M + H^+] 733.4209; found 733.4206.

Synthesis of 19 with Cu_2O-NP: To a solution of freshly prepared polyvinylpyrrolidone (PVP) coated copper(I) oxide nanoparticle (Cu_2O-NP, 48 mg) in CH_3CN (160 mL, *c* = 300 μg/mL), was added **2** (238 mg, 0.32 mmol) in CH_3CN (20 mL) at 37 °C in 24 h. The mixture was stirred at 37 °C for 48 h, when TLC indicated the disappearance of **2**. The mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by column chromatograph (silica gel; EtOAc/hexanes, 30%) to give **19** (174 mg, 74%) as a white solid and **20** as a white solid. Compound **19**: R_f = 0.15 (EtOAc/hexanes, 30%). $[\alpha]_D^{20}$ = –14.7 (*c* = 2.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2961, 2917, 2873, 2849, 1728, 1600, 1580, 1462, 1380, 1261, 1074, 1020, 865, 799, 745, 724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 1 H), 6.92 (s, 1 H), 6.58 (s, 1 H), 5.53 (d, *J* = 9.6 Hz, 1 H), 4.42 (t, *J* = 12.2 Hz, 1 H), 4.30–4.28 (m, 2 H), 3.58 (d, *J* = 2.9 Hz, 1 H), 3.19–3.07 (m, 2 H), 2.73–2.71 (m, 1 H), 2.67 (s, 3 H), 2.45–2.36 (m, 2 H), 2.19 (s, 3 H), 1.71–1.61 (m, 2 H), 1.53–1.50 (m, 1 H), 1.03–1.01 (m, 6 H), 0.96–0.90 (m, 21 H), 0.81 (s, 3 H), 0.65–0.59 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.3, 169.7, 164.7, 152.7, 144.1, 137.8, 122.2, 120.3, 116.5, 79.1, 77.1, 72.8, 53.5, 47.6, 45.9, 42.0, 32.3, 31.2, 30.5, 20.3, 19.3, 18.9, 18.3, 16.7, 14.8, 7.1, 7.0, 5.4, 5.1 ppm. HRMS (ESI): calcd. for $C_{37}H_{64}N_4O_5SSi_2$ [M + H^+] 733.4209; found 733.4191.

Synthesis of 19 with $Cu(CN)_4PF_6$: To a solution of $[Cu(CN)_4PF_6]$ (15 mg, 0.04 mmol) in toluene (14 mL), was added **2** (28 mg, 0.04 mmol) in toluene (3 mL) at 80 °C in 12 h. The mixture was stirred at 37 °C for 48 h, when TLC indicated the disappearance of **2**. The mixture was filtered through Celite, concentrated under reduced pressure, and the residue was purified by column chromatograph (silica gel; EtOAc/hexanes, 30%) to give **19** (10 mg, 36%).

Synthesis of 1: To a solution of **19** (164 mg, 0.22 mmol), was added a freshly prepared 20% CF_3COOH solution in CH_2Cl_2 (8 mL) at –20 °C. The reaction mixture was allowed to reach 0 °C and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$ to adjust the pH to 7. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layer was washed with brine, dried with $MgSO_4$, filtered through Celite, and the solvent was concentrated under reduced pressure. The residue was purified by column chromatograph (silica gel; EtOAc/hexanes, 50%) to provide **1** (101 mg, 92%) as a white solid. R_f = 0.24 (EtOAc/hexanes, 80%). $[\alpha]_D^{20}$ = –26.7 (*c* = 1.0, $CHCl_3$). M.p. 198–199 °C. IR (KBr): $\tilde{\nu}$ = 3577, 3335, 3138, 2958, 2920, 1742, 1690, 1432, 1365, 1292, 1175, 1145, 1012, 982, 938 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1 H), 6.99 (s, 1 H), 6.59 (s, 1 H), 5.61 (dd, *J* = 3.6, 10.0 Hz, 1 H), 4.46–4.43 (m, 2 H), 3.62 (br., 2 H), 3.18–3.06 (m, 3 H), 2.71 (s, 3 H), 2.37 (m, 2 H), 2.17 (s, 3 H), 2.00 (br., 2 H), 1.70–1.64 (m, 1 H), 1.25 (s, 3 H), 1.07–1.04 (m, 6 H), 1.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 219.7, 170.7, 164.9, 152.1, 143.2, 137.0, 123.4, 120.2, 116.7, 78.4, 75.3, 74.4, 51.3, 47.3, 44.4, 38.1, 32.1, 30.1, 29.6, 22.3, 19.2, 18.9, 16.7, 15.1, 13.9 ppm. HRMS (ESI): calcd. for $C_{25}H_{36}N_4O_5S$ [M + H^+] 505.2479; found 505.2480.

Synthesis of 21: To a solution of **20** (14 mg, 0.009 mmol), was added a freshly prepared 20% CF_3COOH solution in CH_2Cl_2 (1 mL) at –20 °C. The reaction mixture was allowed to reach 0 °C and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$ to adjust the pH to 7. The aqueous phase was extracted with CH_2Cl_2 (3 mL), and the combined organic layer was washed with brine, dried with $MgSO_4$, filtered through Celite, and the solvent was concentrated under reduced pressure. The residue was purified by column chromatograph (silica gel; EtOAc/hexanes, 50%) to provide **21** (8 mg, 87%) as a white solid. ^1H NMR (400 MHz, MeOD): δ = 7.89 (s, 2 H), 7.21 (s, 2 H), 6.49 (s, 2 H), 5.51 (t, *J* = 5.8 Hz, 2 H), 4.47–4.35 (m, 4 H), 4.30 (dd, *J* = 2.5, 9.7 Hz, 2 H), 3.57 (t, *J* = 5.5 Hz, 2 H), 3.28–3.27 (m, 4 H), 3.16 (d, *J* = 5.9 Hz, 4 H), 2.68 (s, 6 H), 2.49–2.37 (m, 4 H), 2.20–2.13 (m, 4 H), 2.10 (s, 6 H), 1.74–1.65 (m, 2 H), 1.53–1.50 (m, 2 H), 1.18 (s, 6 H), 1.09 (s, 6 H),1.06 (d, *J* = 6.8 Hz, 6 H), 0.96 (d, *J* = 6.7 Hz, 6 H) ppm. ^{13}C NMR(100 MHz, MeOD): δ = 221.6, 172.9, 166.9, 153.1, 138.5, 124.7, 120.1, 117.9, 78.9, 76.7, 73.9, 53.8, 48.8, 44.2, 34.7, 33.7, 30.8, 21.5, 20.0, 18.7, 17.1, 15.5, 12.8 ppm. HRMS (ESI): calcd. for $C_{50}H_{72}N_8O_{10}S_2$ [M + H^+] 1009.4886; found 1009.4908.

Supporting Information (see footnote on the first page of this article): Experimental procedure, ^1H and ^{13}C NMR spectra, X-ray data, molecular modeling methods, and data for compound **1**.

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