Visible Light-Driven Photocatalytic Initiation of Radical Thiol-Ene Reactions using Bismuth-oxide

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Olugbeminiyi Fadeyi*, James J. Mousseau, Yiqing Feng, Christophe Allais, Philippe Nuhant, Ming Z. Chen, Betsy Pierce, Ralph Robinson.

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Pfizer Worldwide MedChem
Pfizer, Inc.
445 Eastern point Road, Groton, CT 06340, USA

E-mail: olugbeminiyi.fadeyi@pfizer.com

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SUPPORTING INFORMATION

General Procedures and characterization of new compounds

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General information

General Methods

Dimethylformamide was purchased from EMD Chemicals Inc. (DriSolv) and used as received. Methanol, dichloromethane, diethyl ether, ethyl acetate and heptane were purchased from Fisher Scientific and used as received. Bismuth oxide 99.999% trace metals basis (202827) and bromotrichloromethane (B82251) were purchased from Aldrich and used as received. Unless specified, all commercially available alkenes and thiols were used as received. Spiral light bulb (25W) can be purchased from any grocery store. Standard techniques for handling air-sensitive compounds were employed for indicated operations. Removal of solvents was accomplished on a rotary evaporator at reduced pressure.

Physical Properties and Spectroscopic Measurements

All NMR spectra were collected on either a Bruker 400 Avance III with a 5 mm BBFO probe (400 MHz for ^{1}H; 101 MHz for ^{13}C) or a Bruker 500 Avance III HD with a 5 mm BBO Nitrogen cryoprobe (500 MHz for ^{1}H; 126 MHz for ^{13}C). The proton signal for non-deuterated solvent (δ 7.27 for $CHCl_3$, δ 2.50 for DMSO) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.00 resonance of $CDCl_3$ or δ 39.51 resonance of DMSO-*d6*. Deuterated solvents ($CDCl_3$ and DMSO-*d6*) were purchased from Cambridge Isotope Laboratories Inc. and used as received.

Low-Resolution Mass Spectrometry analyses were conducted on Waters Acquity UPLC (Acquity Binary Solvent Manager, 2777C-Autosampler, Acquity PDA, Acquity ELS and Acquity Column Manager) and Waters Acquity SQ systems from Waters Corporation, Milford, MA. Signal acquisition conditions included: Waters Acquity HSS T3, 2.1mmx50mm, C18, 1.7µm; Column Temperature 60 °C as the column; 0.1% formic acid in water (v/v) as the mobile phase A; 0.1% formic acid in acetonitrile (v/v) as the mobile phase B; 1.25mL/min as the flow and ESCI (ESI+/-, APCI+/-), 100-2000m/z scan, 0.4sec scan time, Centroid as the MS method.

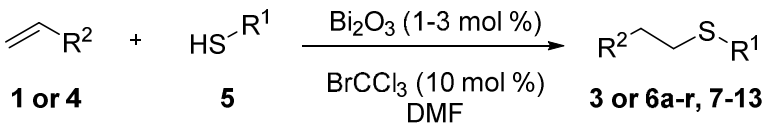
High-Resolution Mass Spectrometry analyses were conducted on an Agilent 6220 TOF mass spectrometer (Agilent Technologies, Wilmington, DE) in positive or negative electrospray mode. The system was calibrated to greater than 1ppm accuracy across the mass range prior to analyses according to manufacturer's specifications. The samples were separated using UHPLC on an Agilent 1200 (Agilent Technologies, Wilmington, DE) system prior to mass spectrometric analysis. The resulting spectra were automatically lockmass corrected and the target mass ions and any confirming adducts (Na+, NH4+) were

extracted and combined as a chromatogram. The mass accuracy was calculated for all observed isotopes against the theoretical mass ions derived from the chemical formula using MassHunter software (Agilent Technologies, Wilmington, DE).

Analytical thin layer chromatography (TLC) was performed on 60 F_{254} glass plates precoated with a 0.25-mm thickness of silica gel purchased from EMD chemical Inc. and TLC plates were visualized with UV light. Column chromatography was performed on TELEDYNE ISCO devices; *CombiFlash® Rf+* version: 2.0.4.

General Procedure for Radical Thiol-Ene Reactions:

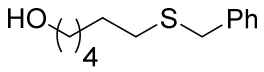
Scheme 1. Bismuth-catalyzed thiol-ene reaction



1 or 4 **5** **3 or 6a-r, 7-13**

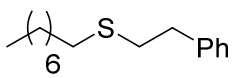
A vial was charged with an olefin (0.5 mmol), a thiol (2.00 mmol) and bismuth oxide (1-3 mol%) in the dark. Dimethylformamide (0.7 mL) was added and the resulting mixture was degassed for 5 minutes (nitrogen stream). Bromotrichloromethane (10 mol%) was then added and the mixturewas irradiated with household bulb lamp (25 W). Upon completion of the reaction, the mixture was concentrated and purified on ISCO to provide the corresponding thioether or thioester (**6a-r**, **7**-**13**).

Characterization of compounds 3, 6a-r and 7-13



3

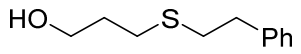
6-(benzylthio)hexan-1-ol (**3**): This compound was obtained using general procedure from 0.50 mmol of hex-5-en-1-ol. **3** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane in **98%** yield (110 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.32 (d, *J* = 4.4 Hz, 4H), 7.26 - 7.22 (m, 1H), 3.71 (s, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 1.61 - 1.52 (m, 4H), 1.41 - 1.33 ppm (m, 4H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 138.6, 128.8, 128.4, 126.8, 62.8, 36.3, 32.5, 31.2, 29.1, 28.5, 25.3. HRMS (ESI), m/z: calculated for $C_{13}H_{21}OS$ $[M+H]^+$ 225.1308, found 225.1305.



6a

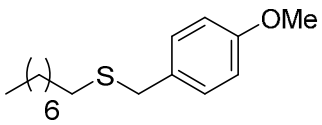
Octyl(phenethyl)sulfane (**6a**): This compound was obtained using general procedure from 0.25 mmol of 1-octene. **6a** was isolated after purification on ISCO with 30:1 heptane/Et_2O in **93%** yield (58 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.35 - 7.28 (m, 2H), 7.26 - 7.20 (m, 3H), 2.94 - 2.86 (m, 2H), 2.82 - 2.75 (m, 2H), 2.55 (t, *J* = 7.4 Hz, 2H), 1.65 - 1.56 (m, 2H), 1.43 - 1.35 (m, 2H), 1.29 (d, *J* = 7.4 Hz, 8H), 0.91 ppm (t, *J* = 7.0 Hz, 3H). ^{13}C NMR

($CDCl_3$, 126 MHz) δ ppm 140.7, 128.4, 128.4, 126.3, 36.4, 33.7, 32.3, 31.8, 29.7, 29.2, 29.2, 28.9, 22.6, 14.1. HRMS (ESI), m/z: calculated for $C_{16}H_{27}S$ $[M+H]^+$ 251.1828, found 251.1755.



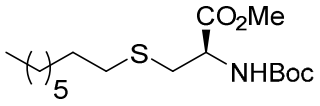
6b

3-(phenethylthio)propan-1-ol (**6b**): This compound was obtained using general procedure from 0.25 mmol of allyl-alcohol. **6b** was isolated after purification on ISCO with 30:1 heptane/Et_2O in **82%** yield (40 mg) as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 7.35 - 7.28 (m, 2H), 7.26 - 7.18 (m, 3H), 3.76 (t, *J* = 6.2 Hz, 2H), 2.95 - 2.87 (m, 2H), 2.85 - 2.77 (m, 2H), 2.66 (t, *J* = 7.0 Hz, 2H), 1.90 - 1.82 (m, 2H), 1.68 ppm (s, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 140.5, 128.4, 126.3, 61.8, 36.2, 33.6, 31.9, 29.0. LRMS (ESI), m/z 197.4 $[M+H]^+$.



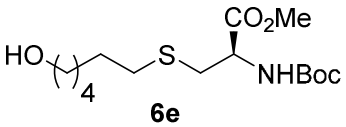
6c

(4-methoxybenzyl)(octyl)sulfane (**6c**): This compound was obtained using general procedure from 0.25 mmol of 1-octene. **6b** was isolated after purification on ISCO with 30:1 heptane/Et_2O in **92%** yield (61 mg) as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 7.24 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.81 (s, 3H), 3.67 (s, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.56 (quint, *J* = 7.2 Hz, 2H), 1.40 - 1.31 (m, 2H), 1.31 - 1.19 (m, 8H), 0.89 ppm (t, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 158.5, 130.7, 129.8, 113.8, 55.2, 35.6, 31.8, 31.3, 29.3, 29.2, 29.1, 28.9, 22.6, 14.1. LRMS (ESI), m/z 267.6 $[M+H]^+$.



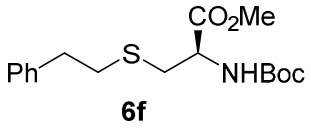
6d

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-octyl-*L*-cysteinate (**6d**): This compound was obtained using general procedure from 0.25 mmol of 1-octene. **6d** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane in **94%** yield (82 mg) as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 5.39 - 5.32 (br. s., 1H), 4.53 (br. s., 1H), 3.77 (s, 3H), 2.96 (br. s., 2H), 2.52 (t, *J* = 7.4 Hz, 2H), 1.59 - 1.53 (m, 2H), 1.46 (s, 9H), 1.40 - 1.20 (m, 10H), 0.89 ppm (t, *J* = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 171.6, 155.0, 52.5, 34.5, 32.8, 31.8, 29.5, 29.12, 29.11, 28.7, 28.3, 22.6, 14.0. HRMS (ESI), m/z: calculated for $C_{17}H_{33}NNaO_4S$ $[M+Na]^+$ 370.2023, found 370.2027.



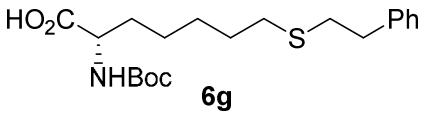
6e

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(6-hydroxyhexyl)-*L*-cysteinate (**6e**): This compound was obtained using general procedure from 0.25 mmol of hex-5-en-1-ol. **6e** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane in **99%** yield (83 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.42 - 5.31 (br. s., 1H), 4.55 - 4.43 (br. s., 1H), 3.74 (s, 3H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.92 (d, *J* = 4.3 Hz, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 1.85 (s, 1H), 1.60 - 1.49 (m, 4H), 1.43 (s, 9H), 1.39 - 1.34 ppm (m, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 171.6, 155.1, 80.1, 62.6, 53.2, 52.4, 34.4, 32.5, 32.4, 29.3, 28.3, 28.2, 25.2. HRMS (ESI), m/z: calculated for $C_{15}H_{29}NNaO_5S$ $[M+Na]^+$ 358.1659, found 358.166.



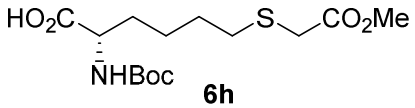
6f

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-phenethyl-*L*-cysteinate (**6f**): This compound was obtained using general procedure from 0.25 mmol of styrene. **6f** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane in **91%** yield (77 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.32 - 7.28 (m, 2H), 7.24 - 7.18 (m, 3H), 5.39 - 5.31 (m, 1H), 4.59 - 4.51 (m, 1H), 3.76 (s, 3H), 2.99 (br. s., 2H), 2.90 - 2.85 (m, 2H), 2.81 – 2.77 (m, 2H), 1.45 ppm (s, 9H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 171.5, 155.1, 140.1, 128.5, 128.5, 126.4, 80.2, 53.3, 52.5, 36.2, 34.6, 34.2, 28.3**.** HRMS (ESI), m/z: calculated for $C_{17}H_{25}NNaO_4S$ $[M+Na]^+$ 362.1397, found 362.1398.



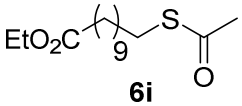
6g

(*S*)-2-((*tert*-butoxycarbonyl)amino)-7-(phenethylthio)heptanoic acid (**6g**): This compound was obtained using general procedure from 0.25 mmol of (*S*)-2-((*tert*-butoxycarbonyl)amino)hept-6-enoic acid. **6g** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane in **88%** yield (77 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.34 - 7.29 (m, 2H) 7.26 - 7.21 (m, 3H) 5.07 (d, *J* = 8.31 Hz, 1H) 4.33 (d, *J* = 5.13 Hz, 1H) 2.92 - 2.88 (m, 2H) 2.81 - 2.77 (m, 2H) 2.54 (t, *J* = 7.09 Hz, 2H) 1.95 - 1.00 (m, 1H) 1.75 - 1.55 (m, 3H) 1.54 - 1.35 (m, 14H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 177.6, 155.7, 140.7, 128.54, 128.52, 126.3, 80.3, 53.3, 36.4, 33.7, 32.4, 32.1, 29.4, 28.4, 28. 3, 25.0. LRMS (ESI), m/z: 380.5 $[M-H]^-$.



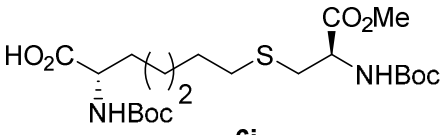
6h

(*S*)-2-((tert-butoxycarbonyl)amino)-6-((2-methoxy-2-oxoethyl)thio)hexanoic acid (**6h**): This compound was obtained using general procedure from 0.25 mmol of (*S*)-2-((*tert*-butoxycarbonyl)amino)hex-5-enoic acid. **6h** was isolated after purification on ISCO with 0-70% gradient EtOAc/heptane in **86%** yield (75 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.04 (d, *J* = 7.6 Hz, 1H), 4.30 (d, *J* = 5.6 Hz, 1H), 3.75 (s, 3H), 3.23 (s, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 1.85 (d, *J* = 5.1 Hz, 1H), 1.69 (br. s., 1H), 1.65 - 1.57 (m, 2H), 1.45 (s, 9H), 1.43 (br. s., 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 176.8, 171.1, 155.6, 80.2, 53.2, 52.4, 33.4, 32.4, 32.1, 29.7, 28.6, 28.3, 28.2, 24.8. LRMS (ESI), m/z 372.31 $[M+Na]^+$.



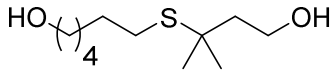
6i

Ethyl 11-(acetylthio)undecanoate (**6i**): This compound was obtained using general procedure from 0.50 mmol of ethyl undec-10-enoate. **6i** was isolated after purification on ISCO with 0-20% gradient EtOAc/heptane **99%** yield (143 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 4.11 (q, *J* = 7.1 Hz, 2H), 2.85 (t, *J* = 7.3 Hz, 2H), 2.31 (s, 3H), 2.27 (t, *J* = 7.6 Hz, 2H), 1.65 - 1.49 (m, 4H), 1.35 - 1.18 (m, 15H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 195.9, 173.8, 60.1, 34.3, 30.6, 29.4, 29.3, 29.3, 29.2, 29.1, 29.05, 29.01, 28.7, 24.9, 14.2. HRMS (ESI), m/z: calculated for $C_{15}H_{29}O_3S$ $[M+H]^+$ 289.1832, found 289.1828.



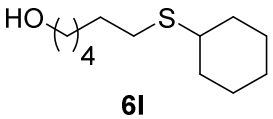
6j

(*S*)-2-((*tert*-butoxycarbonyl)amino)-7-(((R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)thio)heptanoic acid (**6j**): This compound was obtained using general procedure from 0.25 mmol of (*S*)-2-((*tert*-butoxycarbonyl)amino)hept-6-enoic acid. **6j** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane **90%** yield (115 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.44 (d, *J* = 7.8 Hz, 1H), 5.15 (d, *J* = 8.3 Hz, 1H), 4.57 - 4.51 (m, 1H), 4.33 - 4.30 (m, 1H), 3.78 (s, 3H), 3.08 - 2.78 (m, 2H), 2.56 - 2.49 (m, 2H), 1.91 - 1.77 (m, 1H), 1.75 - 1.65 (m, 1H), 1.62 - 1.52 (m, 2H), 1.50 - 1.35 (m, 22H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 171.8, 163.3, 155.6, 155.3, 138.0, 115.1, 81.5, 80.4, 80.1, 54.8, 54.4, 53.3, 52.8, 36.9, 34.4, 32.4, 31.8, 28.4, 28.3, 28.2, 24.8. HRMS (ESI), m/z: calculated for $C_{21}H_{41}N_2O_8S$ $[M+H]^+$ 478.2469, found 478.2446.



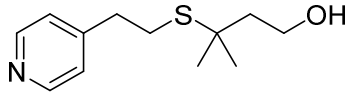
6k

6-((4-hydroxy-2-methylbutan-2-yl)thio)hexan-1-ol (**6k**): This compound was obtained using general procedure from 0.25 mmol of hex-5-en-1-ol. **6k** was isolated after purification on ISCO with 0-70% gradient EtOAc/heptane in **55%** yield (30 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 3.81 (t, *J* = 6.2 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.06 (br. s., 2H), 1.81 (t, *J* = 6.2 Hz, 2H), 1.62 - 1.53 (m, 4H), 1.46 - 1.35 (m, 4H), 1.32 (s, 6H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 62.7, 60.1, 43.9, 43.1, 32.5, 29.4, 29.2, 28.8, 27.8, 25.2. HRMS (ESI), m/z: calculated for $C_{11}H_{24}NaO_2S$ $[M+Na]^+$ 243.1389, found 243.1390.



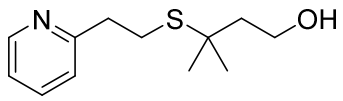
6l

6-(cyclohexylthio)hexan-1-ol (**6l**): This compound was obtained using general procedure from 0.25 mmol of hex-5-en-1-ol. **6l** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane in **89%** yield (48 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 3.64 (t, *J* = 6.6 Hz, 2H), 2.66 - 2.59 (m, 1H), 2.53 (t, *J* = 7.3 Hz, 2H), 2.01 - 1.91 (m, 2H), 1.82 - 1.71 (m, 2H), 1.65 - 1.54 (m, 5H), 1.48 (s, 1H), 1.46 - 1.34 (m, 4H), 1.34 - 1.18 (m, 5H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 62.86, 43.5, 33.7, 32.6, 30.0, 29.9, 28.8, 26.1, 25.8, 25.3. LRMS (ESI), m/z 217.33 $[M+H]^+$.



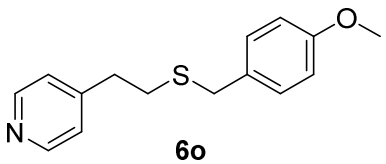
6m

3-Methyl-3-((2-(pyridine-4-yl)ethyl)thio)butan-1-ol (6m): This compound was obtained using general procedure from 0.476 mmol of 4-vinylpyridine. **6m** was isolated after purification on ISCO with 0-100% gradient EtOAc/heptane in **50%** yield (54 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.54 (d, *J* = 5.1 Hz, 2H), 7.17 (d, *J* = 5.0 Hz, 2H), 3.82 (t, *J* = 6.4 Hz, 2H), 2.93 - 2.79 (m, 4H), 1.84 (t, *J* = 6.4 Hz, 2H), 1.35 (s, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ ppm 149.8, 123.9, 59.9, 44.5, 43.6, 35.1, 29.3, 28.2. LRMS (ESI), m/z 226.3 $[M+H]^+$.



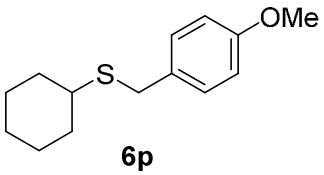
6n

3-Methyl-3-((2-(pyridine-2-yl)ethyl)thio)butan-1-ol (6n): This compound was obtained using general procedure from 0.476 mmol of 2-vinylpyridine. **6n** was isolated after purification on ISCO with 0-100% gradient EtOAc/heptane in **46%** yield (49 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.56 (d, *J* = 4.2 Hz, 1H), 7.66 (td, *J* = 7.6, 1.8 Hz, 1H), 7.23 - 7.17 (m, 2H), 3.79 (t, *J* = 6.5 Hz, 2H), 3.11 - 3.03 (m, 2H), 3.03 – 2.95 (m, 2H), 1.84 (t, *J* = 6.5 Hz, 2H), 1.33 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 159.7, 148.9, 136.9, 123.5, 121.7, 59.9, 44.4, 43.6, 37.7, 29.4, 27.5. LRMS (ESI), m/z 226.3 $[M+H]^+$.



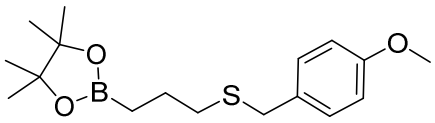
6o

4-(2-((4-methoxybenzyl)thio)ethyl)pyridine (6o): This compound was obtained using general procedure from 0.5 mmol of 4-vinylpyridine. **6o** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane then 9:1 CH_2Cl_2: MeOH in **96%** yield (124 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.52 - 8.47 (m, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 6.2 Hz, 2H), 6.89 - 6.82 (m, 2H), 3.87 - 3.74 (m, 3H), 3.69 (s, 2H), 2.86 - 2.74 (m, 2H), 2.72 - 2.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 158.7, 149.78, 149.2, 149.2, 129.95, 129.94, 129.90, 123.8, 113.9, 55.3, 35.9, 35.1, 31.4. LRMS (ESI), m/z 260.4 $[M+H]^+$.



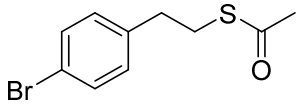
6p

Cyclohexyl(4-methoxybenzyl)sulfane (**6p**): This compound was obtained using general procedure from 0.50 mmol of cyclohexene. **6p** was isolated after purification on ISCO with 30:1 heptane/Et_2O in **89%** yield (105 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.26 - 7.22 (m, 2H), 6.87 - 6.83 (m, 2H), 3.81 (s, 3H), 3.71 (s, 2H), 2.56 (tt, *J* = 3.7, 10.5 Hz, 1H), 1.98 - 1.91 (m, 2H), 1.79 - 1.71 (m, 2H), 1.63 - 1.58 (m, 1H), 1.39 - 1.22 (m, 5H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 158.41, 130.9, 130.5, 129.7, 113.9, 113.8, 55.2, 42.8, 33.9, 33.4, 26.0, 25.9. LRMS (ESI), m/z 237.4 $[M+H]^+$.



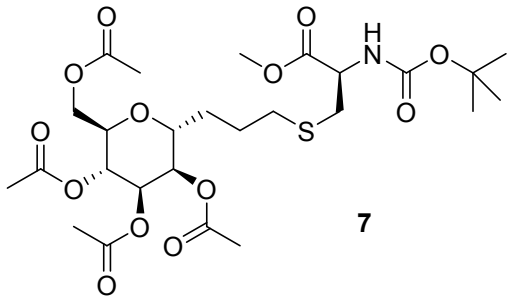
6q

2-(3-(4-methoxybenzylthio)propyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6q**): This compound was obtained using general procedure from 0.50 mmol of allylboronic acid pinacol ester. **6q** was isolated after purification on ISCO with 0-20% gradient EtOAc/heptane in **90%** yield (143 mg) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.23 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.71 - 3.60 (m, 2H), 2.41 (t, *J* = 7.8 Hz, 2H), 1.70 (quint., *J* = 7.8 Hz, 2H), 1.23 (s, 12H), 0.86 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 158.3, 130.6, 129.8, 113.7, 82.9, 55.1, 35.2, 33.3, 24.7, 23.7, 10.5 (broad multiplet, coupling with boron). GCMS (ESI), m/z 322.2 [$C_{17}H_{27}BO_3S$].



6r

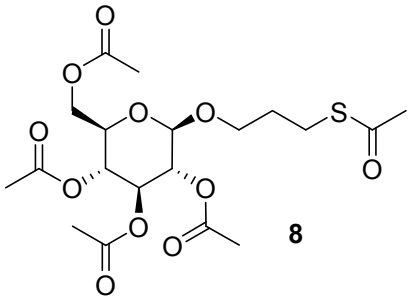
***S*-(4-bromophenethyl) ethanethioate** (**6r**): This compound was obtained using general procedure from 0.50 mmol of 1-bromo-4-vinylbenzene. **6r** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane in **85%** yield (110 mg) as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.43 (d, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 3.11 - 3.07 (m, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 62.9, 43.5, 33.7, 32.6, 30.0, 29.9, 28.7, 26.1, 25.8, 25.3. LRMS (ESI), m/z 260.18 $[M+H]^+$.



7

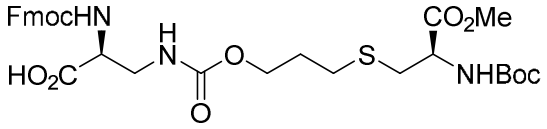
(2*R*,3*R*,4*R*,5*R*,6*R*)-2-(acetoxymethyl)-6-(3-(((*R*)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)thio)propyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**7**): This compound was obtained using general procedure from 0.537 mmol of (2*R*,3*R*,4*R*,5*R*,6*R*)-2-(acetoxymethyl)-6-allyltetrahydro-2H-pyran-3,4,5-triyl triacetate. **7** was isolated after purification on ISCO with 0-100% gradient EtOAc/heptane in **65%** yield (212 mg) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 5.35 (br. s, 1H), 5.31 (t, *J* = 9.2 Hz, 1H), 5.08 (dd, *J* = 5.7, 9.6 Hz, 1H), 4.98 (t, *J* =

9.2 Hz, 1H), 4.52 (br. s., 1H), 4.25 (dd, *J* = 5.3, 12.3 Hz, 1H), 4.17 (ddd, *J* = 3.1, 5.8, 11.8 Hz, 1H), 4.09 (dd, *J* = 2.5, 12.3 Hz, 1H), 3.85 - 3.80 (m, 1H), 3.78 (s, 3H), 3.02 - 2.91 (m, 2H), 2.67 - 2.52 (m, 2H), 2.10 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.90 - 1.83 (m, 1H), 1.76 - 1.59 (m, 3H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ ppm 171.4, 170.5, 170.0, 169.5, 169.4, 155.0, 80.0, 72.1, 70.23, 70.20, 68.7, 68.6, 62.2, 53.2, 52.4, 34.3, 32.0, 28.2, 24.7, 23.9, 20.59, 20.57, 20.54, 20.5. HRMS (ESI), m/z: calculated for $C_{26}H_{42}NO_{13}S$ $[M+H]^+$ 608.2371, found 608.2387.



8

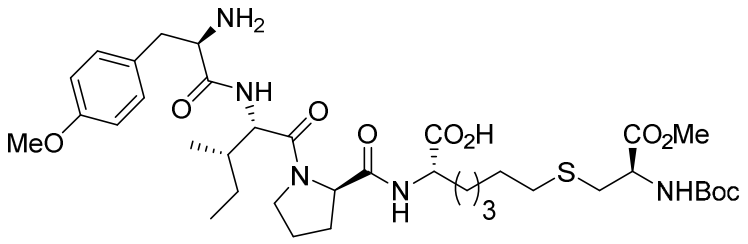
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(3-(acetylthio)propoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**8**): This compound was obtained using general procedure from 0.772 mmol of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(allyloxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate. **8** was isolated after purification on ISCO with 0-100% gradient EtOAc/heptane in **74%** yield (266 mg) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 5.21 (t, *J* = 9.6 Hz, 1H), 5.09 (t, *J* = 9.6 Hz, 1H), 4.99 (dd, *J* = 8.0, 9.6 Hz, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 4.27 (dd, *J* = 4.7, 12.1 Hz, 1H), 4.15 (dd, *J* = 2.6, 12.2 Hz, 1H), 3.92 (td, *J* = 5.6, 10.0 Hz, 1H), 3.70 (ddd, *J* = 2.8, 4.8, 9.9 Hz, 1H), 3.56 (ddd, *J* = 5.3, 7.5, 9.9 Hz, 1H), 2.96 - 2.88 (m, 2H), 2.33 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.95 - 1.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ ppm 195.3, 170.4, 170.0, 169.2, 169.1, 100.5, 72.6, 71.6, 71.1, 68.2, 68.0, 61.7, 30.4, 29.1, 25.4, 20.5, 20.41, 20.36. HRMS (ESI), m/z: calculated for $C_{19}H_{29}NO_{11}S$ $[M+H]^+$ 465.1425, found 465.1437.



9

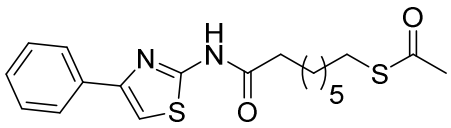
(6*R*,16*S*)-16-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-6-(methoxycarbonyl)-2,2-dimethyl-4,13-dioxo-3,12-dioxa-8-thia-5,14-diazaheptadecan-17-oic acid (**9**): This compound was obtained using general procedure from 0.25 mmol of (*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(((allyloxy)carbonyl)amino)propanoic acid. **9** was isolated after purification on ISCO with 0-10% gradient MeOH/CH_2Cl_2 in **91%** yield (147 mg) as white foam. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 12.85 - 12.62 (br. s., 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.71 (d, *J* = 7.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.45 - 7.39 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.16 (t, *J* = 5.7 Hz, 1H), 4.32 - 4.27 (m, 2H), 4.25 - 4.20 (m, 1H), 4.17 - 4.06 (m, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.63 (s, 3H), 3.40 - 3.27 (m, 2H), 2.87 - 2.81 (m, 1H), 2.77 - 2.69 (m, 1H), 2.54 (t, *J* = 7.1 Hz, 2H), 1.81 - 1.73 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (DMSO-d_6,

126 MHz) δ ppm 1712.0, 171.6, 156.2, 155.9, 155.3, 143.8, 143.8, 140.7, 127.6, 127.07, 125.23, 120.12, 78.43, 65.71, 62.59, 53.89, 53.63, 51.98, 46.59, 41.43, 32.47, 28.58, 28.11, 27.83. HRMS (ESI), m/z: calculated for $C_{31}H_{40}N_3O_{10}S$ $[M+H]^+$ 646.2429, found 646.2441.



10

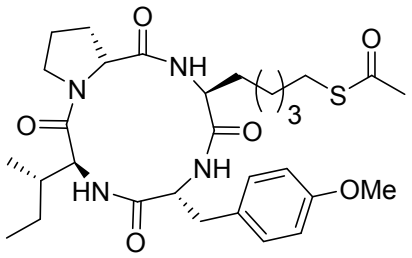
(*S*)-2-((*R*)-1-(((*R*)-2-amino-3-(4-methoxyphenyl)propanoyl)-*L*-isoleucyl)pyrrolidine-2-carboxamido)-7-(((*R*)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)thio)heptanoic acid (**10**): This compound was obtained using general procedure from 0.125 mmol of **S5**. **10** was isolated after purification on ISCO with 0-10% gradient MeOH/CH_2Cl_2 in **75%** yield (72 mg) as white solid. ^{1}H NMR (MeOD, 500 MHz) δ ppm 7.19 (d, *J* = 8.6 Hz, 2H), 6.92 - 6.88 (m, 2H), 4.89 (br. s., 7H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.41 (d, *J* = 10.5 Hz, 1H), 4.34 - 4.28 (m, 1H), 4.16 (t, *J* = 8.8 Hz, 1H), 4.09 (t, *J* = 5.4 Hz, 1H), 3.98 (t, *J* = 7.8 Hz, 1H), 3.80 - 3.76 (m, 3H), 3.73 (s, 3H), 3.65 - 3.57 (m, 1H), 3.08 - 3.02 (m, 2H), 2.93 (dd, *J* = 5.3, 13.8 Hz, 1H), 2.80 (dd, *J* = 7.9, 13.8 Hz, 1H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.33 - 2.27 (m, 1H), 2.04 - 1.93 (m, 2H), 1.92 - 1.81 (m, 2H), 1.79 - 1.61 (m, 2H), 1.60 - 1.51 (m, 2H), 1.45 (s, 9H), 1.36 (d, *J* = 3.7 Hz, 3H), 1.27 - 1.17 (m, 1H), 1.05 - 0.95 (m, 1H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 4.9 Hz, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz) δ ppm 178.3, 173.5, 173.4, 171.6, 169.9, 160.8, 157.9, 131.7, 127.8, 115.5, 80.9, 61.5, 56.8, 56.2, 55.9, 55.8, 55.3, 53.0, 38.1, 36.9, 34.7, 33.3, 30.5, 29.8, 29.3, 28.9, 25.7, 25.6, 25.3, 15.5, 11.1. HRMS (ESI), m/z: calculated for $C_{37}H_{60}N_5O_{10}S$ $[M+H]^+$ 766.4055, found 766.4066.



11

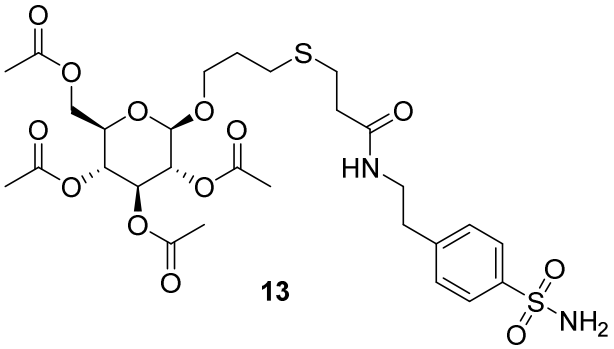
***S*-(7-oxo-7-((4-phenylthiazol-2-yl)-l2-azanyl)heptyl) ethanethioate (11)**: This compound was obtained using general procedure from *N*-(4-phenylthiazol-2-yl)hept-6-enamide (3.5 mmol) **S9**. **11** was isolated after purification on ISCO with 0-20% gradient EtOAc/heptane as white solid in **61%** yield (775 mg). 256 mg of *N*-(4-phenylthiazol-2-yl)hept-6-enamide **S9** was recovered, BRSM yield **82%**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.70 (br. s., 1H), 7.83 (d, *J* = 7.4 Hz, 2H), 7.46 - 7.27 (m, 3H), 7.16 (s, 1H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 1.89 (t, *J* = 7.6 Hz, 2H), 1.49 - 1.33 (m, 4H), 1.26 - 1.07 (m, 2H), 1.04 - 0.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ ppm 195.6, 171.2, 159.5, 149.0, 133.9, 128.6, 127.9, 125.9, 107.5, 76.7, 76.4, 35.1, 30.2, 28.8,

28.6, 27.9, 27.9, 24.0. HRMS (ESI), m/z: calculated for $C_{18}H_{23}N_2O_2S_2$ $[M+H]^+$ 363.1195, found 363.1204.



12

S-(5-((3S,6R,9S,14aR)-9-((S)-sec-butyl)-6-(4-methoxybenzyl)-1,4,7,10-tetraoxotetradecahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)pentyl) ethanethioate (**12**): This compound was obtained using general procedure from 0.045 mmol of **S6**. **12** was isolated after purification on ISCO with 0-10% gradient MeOH/CH_2Cl_2 in **87%** yield (23 mg) as white foam. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.17 (d, *J* = 10.3 Hz, 1H), 7.13 - 7.10 (m, 2H), 6.83 - 6.78 (m, 2H), 6.27 (d, *J* = 10.3 Hz, 1H), 6.20 (d, *J* = 9.8 Hz, 1H), 4.75 - 4.66 (m, 2H), 4.48 (t, *J* = 10.8 Hz, 1H), 4.24 (td, *J* = 7.5, 10.1 Hz, 1H), 4.05 - 3.98 (m, 1H), 3.78 (s, 3H), 3.51 (td, *J* = 7.6, 10.0 Hz, 1H), 3.16 (dd, *J* = 7.8, 14.4 Hz, 1H), 2.85 - 2.80 (m, 2H), 2.80 - 2.76 (m, 1H), 2.80 - 2.76 (m, 1H), 2.45 - 2.39 (m, 1H), 2.32 (s, 3H), 2.00 - 1.81 (m, 4H), 1.81 - 1.72 (m, 1H), 1.65 - 1.49 (m, 4H), 1.38 - 1.30 (m, 2H), 1.27 - 1.20 (m, 1H), 1.15 - 1.05 (m, 1H), 0.89 - 0.83 (m, 6H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ ppm 195.9, 173.6, 173.5, 173.2, 171.8, 158.3, 129.9, 128.7, 113.9, 57.7, 57.4, 55.2, 53.1, 52.8, 47.1, 33.8, 33.5, 30.6, 29.2, 28.9, 28.8, 28.3, 25.1, 25.0, 24.9, 24.7, 15.6, 10.5. LRMS (ESI), m/z 589.5 $[M+H]^+$ and 611.5 $[M+Na]^+$.



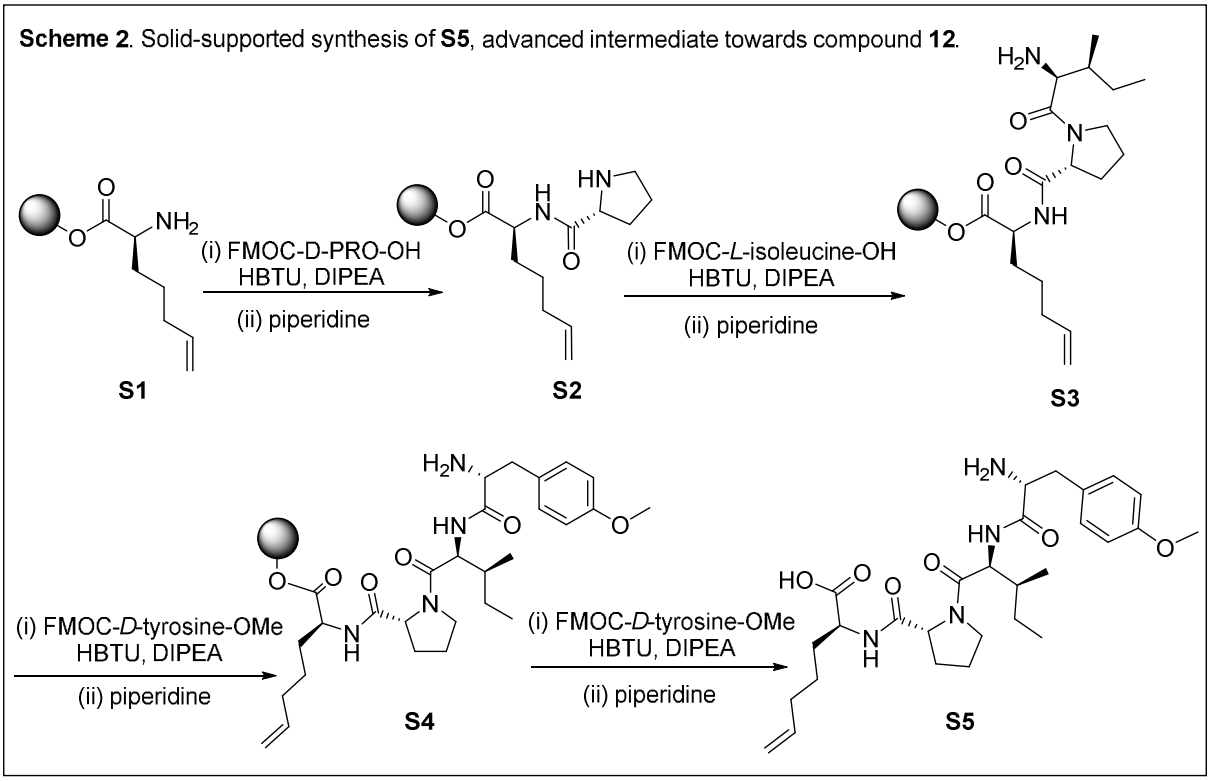
13

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(3-((3-oxo-3-((4-sulfamoylphenethyl)amino)propyl)thio)propoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (13): This compound was obtained using general procedure from (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(allyloxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (0.13 mmol). **13** was isolated after purification on ISCO with 20:1 DCM/MeOH as white solid in **87%** yield (76 mg).

^{1}H NMR (DMSO-d$_6$, 400 MHz,) δ ppm 8.02 - 7.96 (m, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.28 (s, 2H), 5.26 (t, *J* = 9.4 Hz, 1H), 4.89 (t, *J* = 9.8 Hz, 1H), 4.82 - 4.71 (m, 2H), 4.22 - 4.12 (m, 1H), 4.06 - 3.93 (m, 2H), 3.84 - 3.71 (m, 1H), 3.62 - 3.49 (m, 1H), 3.37 - 3.25 (m, 2H), 2.81 - 2.76 (m, 2H), 2.69 - 2.59 (m, 2H), 2.48 - 2.44 (m, 1H), 2.39 - 2.22 (m, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.92 (s, 3H), 1.83 - 1.67 (m, 2H). ^{13}C NMR (DMSO-*d*$_6$) δ ppm 170.4, 170.2, 170.0, 169.5, 169.2, 169.0, 162.3, 143.7, 142.0, 129.1, 125.6, 99.4, 72.0, 70.9, 70.5, 68.2, 67.7, 61.7, 35.70, 34.8, 30.7, 29.0, 27.3, 27.0, 20.5, 20.3, 20.2, 19.9. HRMS (ESI), m/z: calculated for $C_{28}H_{44}N_3O_{13}S_2$ $[M+NH_4]^+$ 694.2310, found 694.2316.

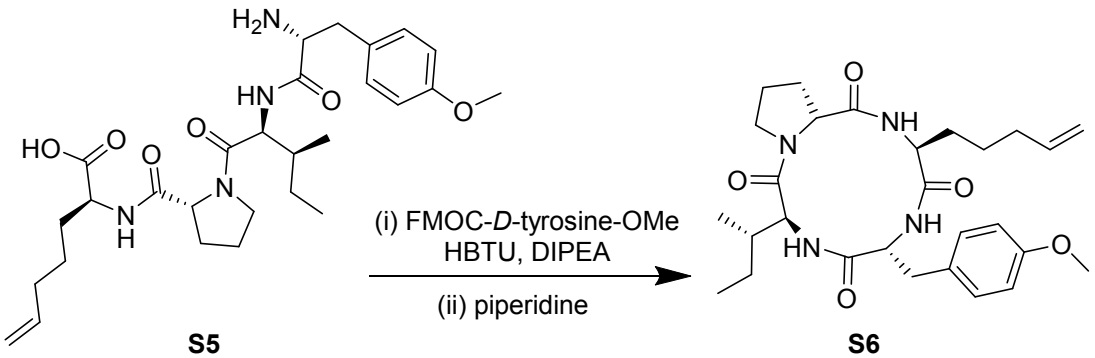
Synthesis and characterization of novel intermediates

Scheme 2. Solid-supported synthesis of **S5**, advanced intermediate towards compound **12**.



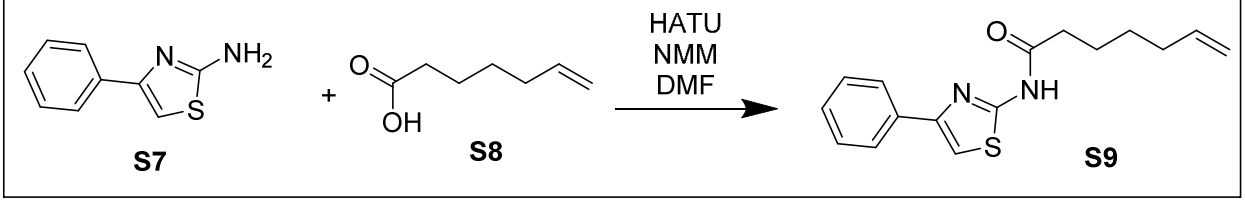
((*S*)-2-((*R*)-1-(((*R*)-2-amino-3-(4-methoxyphenyl)propanoyl)-*L*-isoleucyl)pyrrolidine-2-carboxamido)hept-6-enoic acid (**S5**): This compound was obtained using typical Fmoc-2CTC resin solid phase peptide synthesis following the sequence shown in Scheme 2 from 1.2 mmol of **S1**. **S5** was obtained in **93%** yield (592 mg) as off-white foam. ^{1}H NMR (DMSO-d$_6$, 500 MHz) δ ppm 8.71 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 7.1 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.75 (dd, *J* = 10.3, 17.1 Hz, 1H), 5.01 - 4.88 (m, 2H), 4.48 (d, *J* = 7.3 Hz, 1H), 4.21 (dd, *J* = 9.2, 10.1 Hz, 1H), 4.00 - 3.90 (m, 2H), 3.80 - 3.74 (m, 1H), 3.71 (s, 3H), 3.50 (q, *J* = 7.3 Hz, 1H), 2.93 (dd, *J* = 5.5, 13.3 Hz, 1H), 2.85 - 2.77 (m, 1H), 2.28 - 2.20 (m, 1H), 2.00 - 1.93 (m, 2H), 1.90 - 1.85 (m, 1H), 1.78 - 1.60 (m, 4H), 1.54 - 1.45 (m, 1H), 1.41 - 1.30 (m, 1H), 1.30 - 1.18 (m, 1H), 0.88 - 0.75 (m, 2H), 0.71 (d, *J* = 6.6 Hz, 3H), 0.58 (d, *J* = 4.6 Hz, 3H). ^{13}C NMR (DMSO-d$_6$, 126 MHz) δ ppm 174.1, 172.0, 171.0, 168.5, 168.2, 158.3, 138.8, 130.4, 127.0, 114.7, 113.7, 59.2, 54.9, 54.5, 54.1, 53.1, 46.9, 36.6, 34.8, 33.3, 31.9, 27.1, 24.2, 23.8, 23.6, 21.1, 14.7, 10.3. HRMS (ESI), m/z: calculated for $C_{28}H_{43}N_4O_6$ $[M+H]^+$ 531.3177, found 531.3183.

Scheme 3. Macrocyclization towards **S6**, precursor of compound **12**.



(3*S*,6*R*,9*S*,14a*R*)-9-((*S*)-sec-butyl)-6-(4-methoxybenzyl)-3-(pent-4-en-1-yl)decahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecine-1,4,7,10-tetraone (**S6**): To a solution of TPTU (288 mg, 0.969 mmol) and HOBTM (166 mg, 1.09 mmol) in 180 ml DMF, was added DIPEA to adjust the pH of the mixture to 7. **S5** (200 mg, 0.377 mmol) was dissolved in 115 ml DMF was then added dropwise using a dropping funnel. After 1 hr LC/MS showed reaction was done. The mixture was quenched with water and extract with EtOAc (4x). Combined organic layers were washed with diluted sodium bicarbonate solution, 20% citric acid and then brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified on ISCO using MeOH:CH_2Cl_2 (0% – 10%) to give **S6** as a white solid in **82%** yield. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 8.75 (d, *J* = 9.3 Hz, 1H), 7.26 (d, *J* = 9.3 Hz, 1H), 7.18 - 7.13 (m, 2H), 7.06 (d, *J* = 10.0 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.77 - 5.66 (m, 1H), 4.99 - 4.89 (m, 2H), 4.74 (d, *J* = 7.6 Hz, 1H), 4.48 (dt, *J* = 6.4, 9.0 Hz, 1H), 4.37 (t, *J* = 10.4 Hz, 1H), 4.27 - 4.18 (m, 1H), 3.79 - 3.73 (m, 1H), 3.69 (s, 3H), 3.56 - 3.48 (m, 1H), 2.89 (dd, *J* = 6.1, 14.2 Hz, 1H), 2.74 (dd, *J* = 9.2, 14.3 Hz, 1H), 2.24 - 2.18 (m, 1H), 2.09 - 1.99 (m, 1H), 1.99 - 1.93 (m, 2H), 1.93 - 1.87 (m, 1H), 1.87 - 1.77 (m, 1H), 1.72 (ddd, *J* = 4.0, 7.6, 11.1 Hz, 1H), 1.56 - 1.46 (m, 2H), 1.45 - 1.36 (m, 1H), 1.25 - 1.11 (m, 2H), 1.11 - 1.01 (m, 1H), 0.81 (t, *J* = 7.5 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz) δ ppm 173.4, 173.2, 172.7, 171.5, 157.7, 138.3, 130.0, 129.8, 114.9, 113.4, 56.9, 56.0, 54.9, 53.4, 53.1, 46.0, 33.7, 32.5, 32.5, 29.5, 24.5, 24.4, 24.1, 24.0, 15.0, 10.3. HRMS (ESI), m/z: calculated for $C_{28}H_{41}N_4O_5$ $[M+H]^+$ 513.3071, found 513.3075.

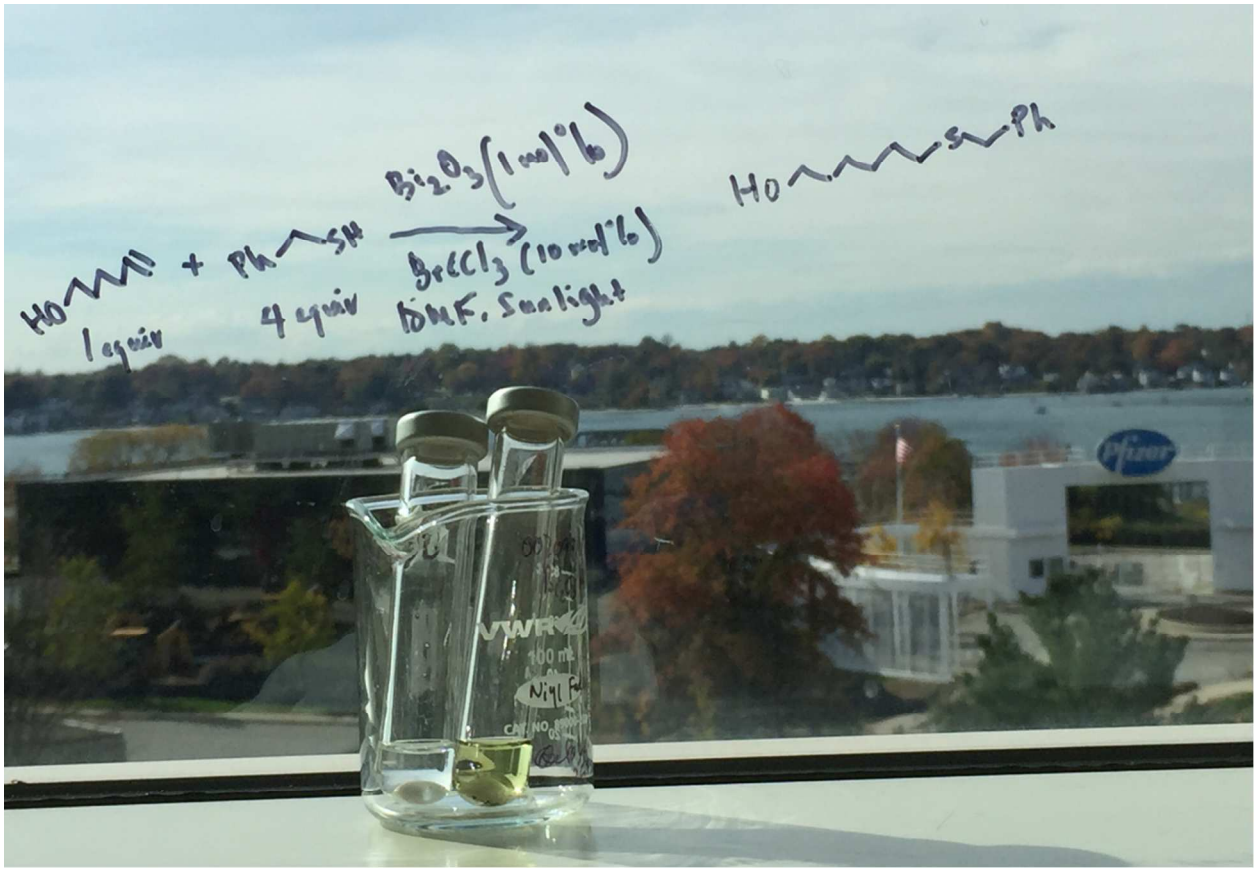
Scheme 4. Synthesis of **S9**, precursor of compound **11**.



***N*-(4-phenylthiazol-2-yl)hept-6-enamide (S9)**: A solution of hept-6-enoic acid (**S8**) (803 mg, 6.26 mmol) in DMF (6 mL) were stirred with *N*-methyl morpholine (1.84 mL, 16.7 mmol) at rt for 5 min. HATU (2.38 g, 6.26 mmol) solid was then added and mixture was stirred at rt for 15 min to afford a bright yellow solution. Solid 4-phenylthiazol-2-amine (**S7**) (736 mg, 4.18 mmol) was added, and the resulting bright orange mixture was stirred at rt for 48 h. The reaction mixture was diluted with ether, the organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford an oily residue, which was purified by ISCO using 0-20% gradient EtOAc/heptane to afford **S9** as a white solid in **58%** yield (1.04 g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.68 (br. s., 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.47 - 7.33 (m, 3H), 7.16 (s, 1H), 5.74 - 5.63 (m, 1H), 4.96 - 4.88 (m, 2H), 1.97 - 1.78 (m, 4H), 1.43 (td, *J* = 7.8, 15.6 Hz, 2H), 1.06 (q, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.5, 159.9, 149.4, 138.2, 134.3, 128.9, 128.3, 126.2, 114.6, 107.8, 77.3, 76.7, 35.5, 33.1, 28.0, 24.1. HRMS (ESI), m/z: calculated for $C_{16}H_{19}N_2OS$ $[M+H]^+$ 287.1213, found 287.1212.

Control Experiment with Sunlight

6-(benzylthio)hexan-1-ol (**3**): This compound was obtained using general procedure with the exception that sunlight was used as the light source for 6 h from 0.50 mmol of hex-5-en-1-ol. **3** was isolated after purification on ISCO with 0-50% gradient EtOAc/heptane in 94% yield (105 mg) as colorless oil. A control experiment with no catalyst proceeded with <20% conversion.


HO
1 equiv
+ Ph SH
4 equiv
Bi2O3 (1 mol%)
BrCCl3 (10 mol%)
DMF, Sunlight
HO
Ph