

Supplementary Material

Application of a novel small scale UV LED photochemical batch reactor for the thiol-yne reaction

Nils Griebenow, Stefan Bräse and Alica M. Dilmac

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Flash chromatography was done on silica gel 60 (0.063–0.200 mm) from Merck KgaA, Darmstadt, Germany. Preparative HPLC chromatography was done on a 250 mm x 30 mm column packed with YMC gel ODS-AQ S5 / 15 μ M, with acetonitrile / water as eluent and UV-detection. All ^1H NMR and ^{13}C NMR spectra were recorded in $\text{DMSO-}d_6$. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet) as well as br (broad).

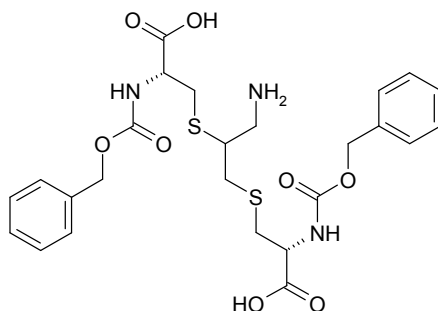
For running small scale batch reactions under inert gas atmosphere and in standard glassware a UV LED curing pen (Omnicure LX 400, $d=12$ mm, $l=130$ mm) was used. The LED pen was mounted into the neck (NS 14/23) of a 10-50 ml two-neck round-bottom flask sealed with a Teflon tape. The LED pen (wavelength of 365 nm) was equipped with a 10 mm focusing lens to deliver an irradiance of about 500 mW/cm² at a distance of 40 mm.

Procedures for the synthesis of compounds 3a-e.

General procedure 1 (3a-e). N-[(benzyloxy)carbonyl]-L-cysteine (0.37 mmol, 2 eq.) and (2,4,6-trimethylbenzoyl)phosphine oxide (20 mol %) were introduced in a two necked round bottom flask, put under an argon atmosphere and dissolved in 0.5 mL of methanol (anhyd.). The alkyne (0.18 mmol, 1 eq.) was added. An OmniCure LX400 LED lamp was introduced into one of the neck of the flask and the reaction mixture was irradiated with UV-light (365 nm) for one to two hours. The reaction mixture was dissolved with a small amount of methanol and purified over preparative HPLC (Eluent: Gradient Water + 0.1% TFA / Acetonitrile).

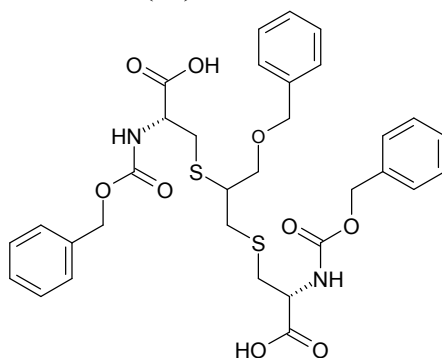
General procedure 2 (3e). N,N'-bis[(benzyloxy)carbonyl]-L-cystine (0.19 mmol, 1 eq.), and TCEP.HCl (80.0 mg, 0.279 mmol) were introduced in a two necked round bottom flask under an argon atmosphere and dissolved in a 1:1 mixture of water/methanol (1 mL). The mixture was stirred at rt for 2h30. The alkyne (1 eq.) was added, followed by Irgacure[®] 819 (0.05 eq.). An OmniCure LX400 LED lamp was introduced into one of the neck of the flask and the reaction mixture was irradiated with UV-light (365 nm) for one hour. The reaction mixture was dissolved with a small amount of methanol and purified over preparative HPLC (Eluent: Gradient Water + 0.1% TFA / Acetonitrile).

(5R,12R)-8-(aminomethyl)-12-[[[(benzyloxy)carbonyl]amino]-5-carboxy-3-oxo-1-phenyl-2-oxa-7,10-dithia-4-azatridecan-13-oic acid (3a):



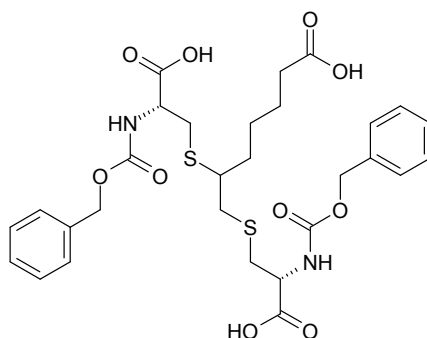
Prepared according general procedure 1 with one hour of irradiation. Isolated yield: 32%. LC/MS: 2.04 min, $m/z = 566$ $[M+H]^+$. 1H NMR (MeOD- d_4 , 500 MHz): $\delta/ppm = 2.65-2.82$ (m, 2H), 2.83-3.02 (m, 6H), 3.02-3.17 (m, 7H), 3.16-3.25 (d, $J = 12.5$ Hz, 1H), 3.34-3.48 (m, 2H), 4.34-4.50 (m, 4H), 5.06-5.18 (2 s, 8H), 7.25-7.40 (m, 20H). ^{13}C NMR (MeOD- d_4 , 125.77 MHz), δ (ppm): 174.2, 174.0, 174.9, 174.7, 158.9, 158.6, 158.6, 158.3, 138.2, 138.1, 128.7-129.7, 68.0, 67.9, 55.8, 55.6, 55.5, 45.5, 44.9, 42.7, 42.6, 37.1, 37.0, 35.8, 35.6, 35.2, 33.9.

(5R,12R)-12-{{(benzyloxy)carbonyl}amino}-8-[(benzyloxy)methyl]-5-carboxy-3-oxo-1-phenyl-2-oxa-7,10-dithia-4-azatridecan-13-oic acid (3b):



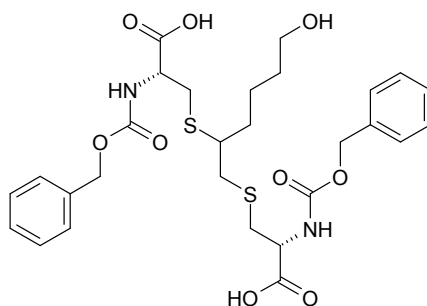
Prepared according general procedure 1 with one hour of irradiation. Isolated yield: 55%. LC/MS: 3.66 min, $m/z = 656$ $[M+H]^+$. 1H NMR (MeOD- d_4 , 500 MHz): $\delta/ppm = 2.70-3.20$ (m, 7H), 3.52-3.75 (m, 2H), 4.30-4.45 (m, 2H), 4.46-4.55 (s, 2H), 5.02-5.20 (m, 4H), 7.20-7.44 (m, 15H). ^{13}C NMR (MeOD- d_4 , 500 MHz) $\delta/ppm = 174.12$, 174.08, 158.60, 139.63, 139.60, 138.30, 134.51, 130.86, 129.78, 129.62, 129.53, 129.14, 129.06, 129.04, 128.99, 128.82, 74.29, 74.27, 72.97, 72.89, 67.91, 67.88, 55.92, 55.76, 55.73, 47.97, 47.60, 36.51, 36.34, 35.97, 35.91, 34.75, 34.51.

(5R,12R)-12-{{(benzyloxy)carbonyl}amino}-5-carboxy-8-(4-carboxybutyl)-3-oxo-1-phenyl-2-oxa-7,10-dithia-4-azatridecan-13-oic acid (3c):



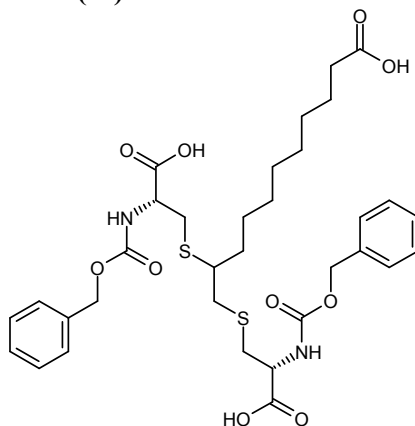
Prepared according general procedure 1 with one hour of irradiation. Isolated yield: 19%. LC/MS: 2.79 min, $m/z = 636$ $[M+H]^+$. 1H NMR (MeOD- d_4 , 500 MHz): $\delta/ppm = 1.35-1.79$ (m, 6H), 2.24-2.28 (m, 2H), 2.36-3.11 (m, 7H), 4.35-4.40 (m, 2H), 5.08-5.14 (m, 4H), 7.23-7.37 (m, 10H).

(5R,12R)-12-{{(benzyloxy)carbonyl}amino}-5-carboxy-8-(4-hydroxybutyl)-3-oxo-1-phenyl-2-oxa-7,10-dithia-4-azatridecan-13-oic acid (3d):



Prepared according general procedure 1 with one hour of irradiation. Isolated yield: 45%. LC/MS: 2.74 min, $m/z = 609$ $[M+H]^+$. HRMS: calculated: 609.1940, measured: 609.1945 : $C_{28}H_{37}N_2O_9S_2$. 1H NMR (MeOD- d_4 , 500 MHz): $\delta/ppm = 1.33-1.62$ (m, 5H), 1.68-1.89 (m, 1H), 2.64-2.76 (m, 1H), 2.75-2.97 (m, 4H), 2.97-3.15 (m, 2H), 3.48-3.58 (m, 2H), 4.30-4.45 (m, 2H), 5.04-5.21 (m, 4H), 7.23-7.43 (m, 10H). ^{13}C NMR (MeOD- d_4 , 500 MHz): $\delta/ppm = 174.13, 174.11, 174.04, 158.62, 158.60, 158.57, 158.54, 138.31, 138.29, 129.62, 129.14, 129.04, 129.00, 67.89, 67.88, 62.97, 56.16, 55.80, 55.75, 55.67, 47.77, 47.35, 39.74, 35.72, 34.67, 34.49, 33.87, 33.75, 33.55, 24.25, 24.17$.

(5R,12R)-12-((benzyloxy)carbonylamino)-5-carboxy-8-(8-carboxyoctyl)-3-oxo-1-phenyl-2-oxa-7,10-dithia-4-azatridecan-13-oic acid (3e)



Prepared according general procedure 2. Isolated yield: 49% of two Isomers (1:1). LC/MS: 3.43 min, $m/z = 693$ $[M+H]^+$. 1H -NMR (400 MHz, MeOD- d_4): $\delta/ppm = 1.21-1.52$ (m, 12H), 1.53-1.63 (m, 2H), 1.69-1.82 (m, 1H), 2.21-2.31 (m, 2H), 2.66-3.18 (m, 7H), 4.31-4.46 (m, 2H), 5.05-5.19 (m, 4H), 7.24-7.43 (m, 10H). The two isomers were separated by chiral preparative chromatography. (Eluent: 65% *iso*-Hexane, 35% Ethanol + 0.2% TFA + 1% H_2O). **Isomer 1**. Isolated yield: 17%. 1H -NMR (400 MHz, MeOD- d_4): $\delta/ppm = 1.19-1.52$ (m, 12H), 1.53-1.64 (m, 2H), 1.67-1.82 (m, 1H), 2.22-2.33 (m, 2H), 2.66-3.17 (m, 7H), 4.31-4.46 (m, 2H), 5.05-5.19 (m, 4H), 7.24-7.43 (m, 10H). ^{13}C -NMR (125.78 MHz, MeOD- d_4): $\delta/ppm = 177.88, 174.17, 158.63, 158.56, 138.32, 129.62, 129.14, 128.96, 128.95, 67.87, 67.85, 55.67, 47.28, 39.75, 35.74, 35.11, 34.64, 33.76, 30.57, 30.49, 30.38, 27.81, 26.25$. **Isomer 2**. Isolated yield: 20%. 1H -NMR (400 MHz, MeOD- d_4): $\delta/ppm = 1.21-1.52$ (m, 12H), 1.54-1.62 (m, 2H), 1.69-1.82 (m, 1H), 2.23-2.32 (m, 2H), 2.69 (dd, $J = 12.8, 8$ Hz, 1H), 2.75-2.96 (m, 4H), 3.00-3.06 (m, 2H), 4.31-4.45 (m, 2H), 5.05-5.18 (m, 4H), 7.24-7.43 (m, 10H). ^{13}C -NMR (125.78 MHz, MeOD- d_4): $\delta/ppm = 177.90, 174.14, 174.08, 158.61, 158.56, 138.30, 138.29, 129.63, 129.15, 129.00, 128.98, 67.90, 56.22, 55.78, 47.76, 39.74, 35.71, 35.11, 34.79, 33.84, 30.58, 30.56, 30.49, 30.38, 27.75, 26.25$.