Supporting Information

Selective strain-promoted azide–alkyne cycloadditions through transient protection of bicyclo[6.1.0]nonynes with silver or gold

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Contents

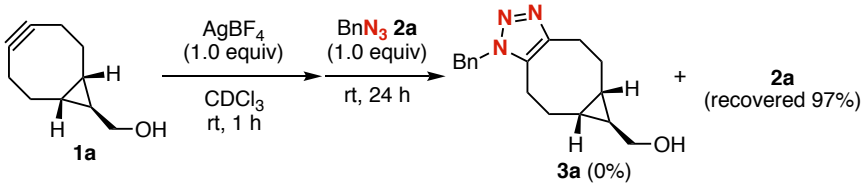
General Remarks

All reactions were performed in a dry glassware under atmosphere of argon otherwise noted. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica-gel plates (Merck Chemicals, Silica Gel 60 F_{254}, Cat. No. 1.05715). Column chromatography was conducted using silica-gel (Kanto Chemical Co., Inc., Silica Gel 60N, spherical neutral, particle size 40–50 μm, Cat. No. 37563-85 or particle size 63–210 μm, Cat. No. 37565-85). Preparative thin-layer chromatography (PTLC) was performed on silica-gel (Wako Pure Chemical Industries Ltd., Wakogel B5-F, Cat. No. 230-00043). ^{1}H NMR spectra were obtained with a Bruker AVANCE 500 spectrometer at 500 MHz or Bruker AVANCE 400 spectrometer at 400 MHz. ^{13}C NMR spectra were obtained with a Bruker AVANCE 500 spectrometer at 126 MHz. Chemical shifts (δ) are given in parts per million (ppm) downfield from $(CH_3)_4Si$ (δ 0.00 for ^{1}H NMR in $CDCl_3$) or the solvent peak (δ 77.0 for ^{13}C NMR in $CDCl_3$) as an internal reference with coupling constants (*J*) in hertz (Hz). The abbreviations s, d, m, and br signify singlet, doublet, multiplet, and broad, respectively. IR spectra were measured by diffuse reflectance method on a Shimadzu IRPrestige-21 spectrometer attached with DRS-8000A with the absorption band given in cm^{-1}. High-performance liquid chromatography (HPLC) was performed on a Shimadzu Prominence HPLC system (CBM-20A lite, LC-20AD × 2, DGU-20A3R, SUS316L, and CTO-20A) equipped with a Shimadzu SPD-20A UV/Vis detector. High-resolution mass spectra (HRMS) were measured on a Bruker micrOTOF mass spectrometer under positive electrospray ionization (ESI^+) conditions.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. SiliaMetS Thiourea (ca. 1.24 mmol/g, Cat. No. R69530B) was purchased from SiliCycle Inc. Resin(polystyrene)–PPh_2 (PS–TPP) (~3.0 mmol/g, Cat. No. 366455) was purchased from Sigma–Aldrich. (1α,8α,9α)-Bicyclo[6.1.0]non-4-yn-9-ylmethanol (**1a**),[S1] 5,6-didehydro-11,12-dihydrodibenzo[*a*,*e*]cyclooctene (**1b**),[S2] 4,8-ditosyl-4,8-diazacyclononyne (**1c**),[S3] (1α,8α,9α)-bicyclo[6.1.0]non-4-yn-9-ylmethyl 3,6,9-trioxa-12-azadodecylcarbamate (**S1**),[S1] 11,12-didehydro-5,6-dihydrodibenzo[*a*,*e*]cycloocten-5-yl 4-nitrophenyl carbonate (**S2**),[S2] and 3-(4-tosyl-4,8-diazacyclononyne-8-ylcarbonyl)propionic acid (**S3**)[S4] were prepared according to the reported methods.

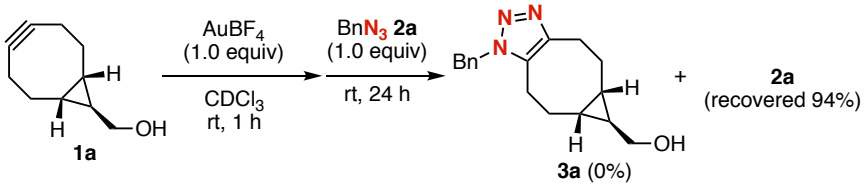
Experimental Procedures

A typical procedure for protection of cycloalkynes from click reaction via complexation with silver



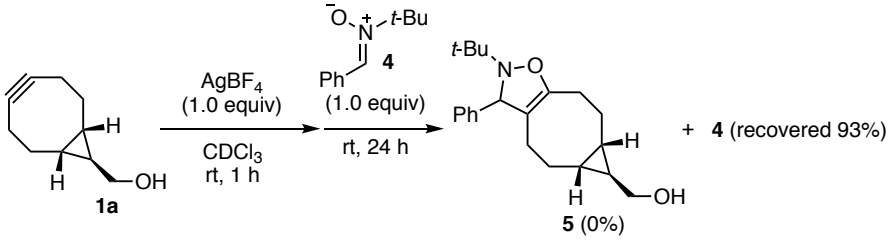
To a mixture of bicyclo[6.1.0]nonyne derivative **1a** (15.0 mg, 99.9 μmol) and 1,1,2,2-tetrachloroethane (14.3 mg, 85.1 μmol) as an internal standard dissolved in $CDCl_3$ (1.0 mL) was added silver(I) tetrafluoroborate (19.4 mg, 99.7 μmol) at room temperature. After stirring for 1 h at the same temperature, to the mixture was added a solution of benzyl azide (**2a**) (13.3 mg, 0.100 mmol) dissolved in $CDCl_3$ (1.0 mL) at room temperature. After stirring for 24 h at the same temperature, ^{1}H NMR analysis (400 MHz) was performed. From the ^{1}H NMR analysis of the mixture were determined the yields of triazole **3a** (0%) and recovered azide **2a** (97%) by comparing the relative values of integration for the peaks observed at 5.46 ppm (s, 2H, for **3a**) and 4.34 ppm (s, 2H, for **2a**) with that of 1,1,2,2-tetrachloroethane observed at 5.95 ppm (s, 2H).

A typical procedure for protection of cycloalkynes from click reaction via complexation with gold



To a mixture of silver(I) tetrafluoroborate (19.4 mg, 99.7 μmol) and gold(I) chloride (23.2 mg, 99.8 μmol) was added $CDCl_3$ (1.0 mL) at room temperature. After stirring for 30 min at the same temperature, to the resulting mixture was added a solution of bicyclo[6.1.0]nonyne derivative **1a** (15.0 mg, 99.9 μmol) and 1,1,2,2-tetrachloroethane (15.3 mg, 91.2 μmol) as an internal standard dissolved in $CDCl_3$ (1.0 mL). After stirring for 1 h at the same temperature, to the mixture was added a solution of benzyl azide (**2a**) (13.3 mg, 0.100 mmol) dissolved in $CDCl_3$ (1.0 mL) at room temperature. After stirring for 24 h at the same temperature, ^{1}H NMR analysis (400 MHz) was performed. From the ^{1}H NMR analysis of the mixture were determined the yields of triazole **3a** (0%) and recovered azide **2a** (94%) by comparing the relative values of integration for the peaks observed at 5.46 ppm (s, 2H, for **3a**) and 4.34 ppm (s, 2H, for **2a**) with that of 1,1,2,2-tetrachloroethane observed at 5.95 ppm (s, 2H).

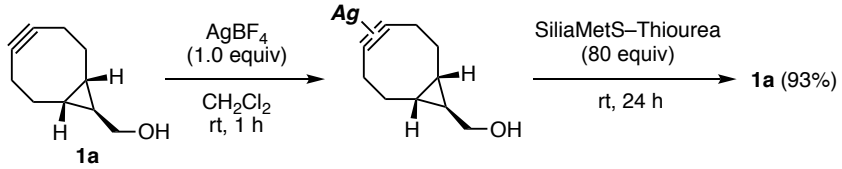
*A typical procedure for protection of bicyclo[6.1.0]nonyne derivative **1a** from formation of isoxazole **5** via complexation with metal salts*



To a mixture of bicyclo[6.1.0]nonyne derivative **1a** (15.4 mg, 0.103 mmol) and 1,1,2,2-tetrachloroethane (16.3 mg, 97.1 μmol) as an internal standard dissolved in $CDCl_3$ (2.0 mL) was added silver(I) tetrafluoroborate (20.0 mg, 0.103 mmol) at room temperature. After stirring for 1 h at the same temperature, to the mixture was added a solution of benzyl azide (**2a**) (18.1 mg, 0.102 mmol) dissolved in $CDCl_3$ (1.0 mL) at room temperature. After stirring for 24 h at the same temperature, ^{1}H NMR analysis (400 MHz) was performed. From the ^{1}H NMR analysis of the mixture were determined

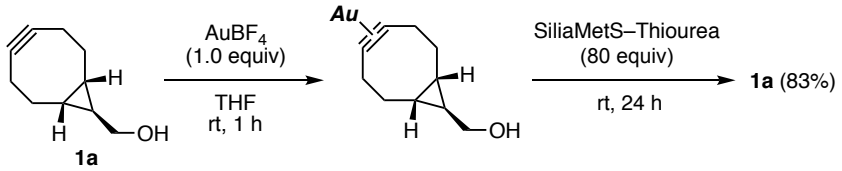
the yields of isoxazole **5** (0%) and recovered azide **2a** (93%) by comparing the relative values of integration for the peaks observed at 3.41–3.52 ppm (m, 2H, for **5**) and 4.34 ppm (s, 2H, for **2a**) with that of 1,1,2,2-tetrachloroethane observed at 5.95 ppm (s, 2H).

A typical procedure for decomplexation of a silver–cycloalkyne complex with SiliaMetS–Thiourea



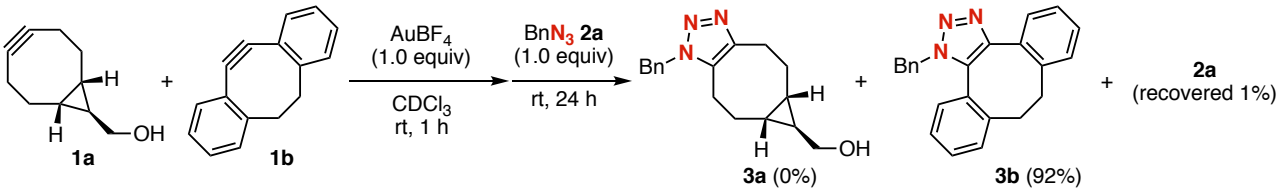
To a solution of bicyclo[6.1.0]nonyne derivative **1a** (15.0 mg, 99.9 μmol) dissolved in CH_2Cl_2 (2.0 mL) was added silver(I) tetrafluoroborate (19.5 mg, 0.100 mmol) at room temperature. After stirring for 1 h at the same temperature, to the reaction mixture were added CH_2Cl_2 (8.0 mL) and SiliaMetS–Thiourea (ca. 1.24 mmol/g, 6.4 g, ca. 8.0 mmol). After stirring for 24 h at the same temperature, the reaction mixture was filtered through a Celite pad, and then the filtrate was concentrated under reduced pressure. To the residue was added 1,1,2,2-tetrachloroethane (16.0 mg, 95.3 μmol) as an internal standard, dissolved in $CDCl_3$, and ^1H NMR analysis (400 MHz) was performed. The yield of bicyclo[6.1.0]nonyne derivative **1a** was determined to be 93% by comparing the relative values of integration for the peaks observed at 3.54 ppm (d, J = 6.4 Hz, 2H, for **1a**) with that of 1,1,2,2-tetrachloroethane observed at 5.95 ppm (s, 2H).

A typical procedure for decomplexation of a gold–cycloalkyne complex with SiliaMetS–Thiourea



To a mixture of silver(I) tetrafluoroborate (9.7 mg, 50 μmol) and gold(I) chloride (11.6 mg, 49.9 μmol) was added THF (1.0 mL) at room temperature. After stirring for 30 min at the same temperature, to the resulting mixture was added bicyclo[6.1.0]nonyne derivative **1a** (7.5 mg, 50 μmol). After stirring for 1 h at the same temperature, to the reaction mixture were added THF (10 mL) and SiliaMetS–Thiourea (ca. 1.24 mmol/g, 3.2 g, ca. 4.0 mmol). After stirring for 24 h at the same temperature, the reaction mixture was filtered through a Celite pad, and then the filtrate was concentrated under reduced pressure. To the residue was added 1,1,2,2-tetrachloroethane (18.8 mg, 0.112 mmol) as an internal standard, dissolved in $CDCl_3$, and ^1H NMR analysis (400 MHz) was performed. The yield of bicyclo[6.1.0]nonyne derivative **1a** was determined to be 83% by comparing the relative values of integration for the peaks observed at 3.54 ppm (d, J = 6.4 Hz, 2H, for **1a**) with that of 1,1,2,2-tetrachloroethane observed at 5.95 ppm (s, 2H).

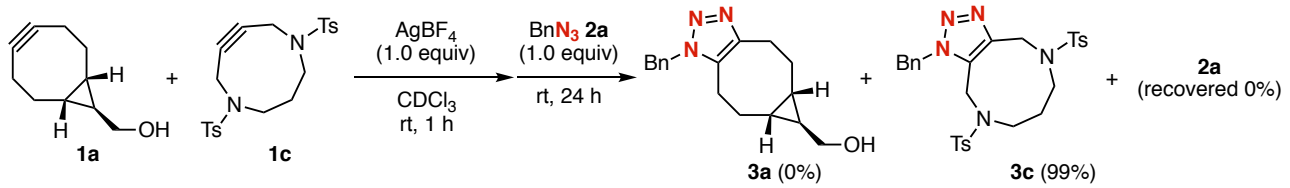
*A typical procedure for the competition reaction between bicyclo[6.1.0]nonyne derivative **1a** and 5,6-didehydro-11,12-dihydrodibenzo[a,e]cyclooctene (**1b**) in the cycloaddition with benzyl azide (**2a**) via complexation with gold*



To a mixture of silver(I) tetrafluoroborate (19.4 mg, 99.7 μmol) and gold(I) chloride (23.2 mg, 99.8 μmol) were added $CDCl_3$ (2.0 mL) and 1,1,2,2-tetrachloroethane (15.3 mg, 91.2 μmol) as an internal standard at room temperature. After stirring for 30 min at the same temperature, to a mixture was added a solution of bicyclo[6.1.0]nonyne derivative **1a** (15.0 mg, 99.9 μmol) and 5,6-didehydro-

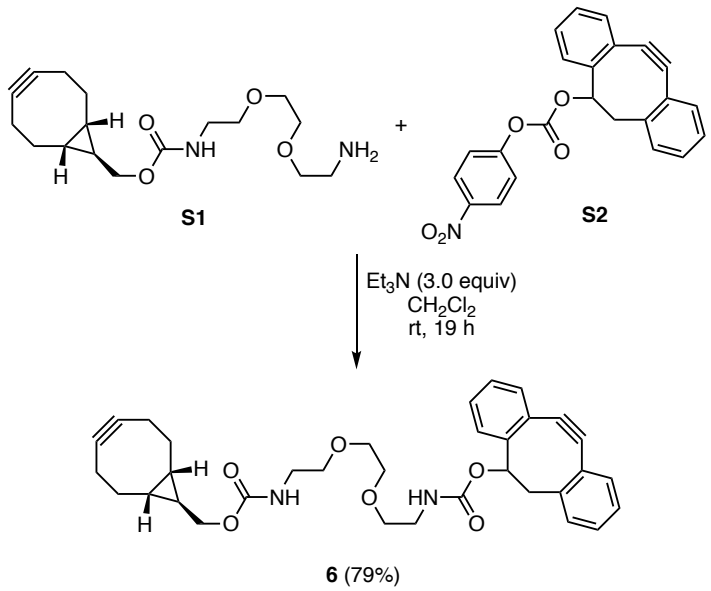
11,12-dihydrodibenzo[*a,e*]cyclooctene (**1b**) (20.4 mg, 99.9 μmol) dissolved in $CDCl_3$ (1.5 mL). After stirring for 1 h at the same temperature, to the mixture was added a solution of benzyl azide (**2a**) (13.3 mg, 0.100 mmol) dissolved in $CDCl_3$ (1.0 mL) at room temperature. After stirring for 24 h at the same temperature, ^{1}H NMR analysis (400 MHz) was performed. From the ^{1}H NMR analysis of the mixture were determined the yields of triazoles **3a** (0%) and **3b** (92%) and recovered azide **2a** (1%) by comparing the relative values of integration for the peaks observed at 5.46 ppm (s, 2H, for **3a**), 5.59 ppm (s, 2H, for **3b**) and 4.34 ppm (s, 2H, for **2a**) with that of 1,1,2,2-tetrachloroethane observed at 5.95 ppm (s, 2H).

*A typical procedure for the competition reaction between bicyclo[6.1.0]nonyne derivative **1a** and N,N′-bis(p-toluenesulfonyl)-4,8-diazacyclononyne (**1c**) in the cycloaddition with benzyl azide (**2a**) via complexation with silver*



To a mixture of bicyclo[6.1.0]nonyne derivative **1a** (15.0 mg, 99.9 μmol), *N,N′*-bis(*p*-toluenesulfonyl)-4,8-diazacyclononyne (**1c**) (43.2 mg, 99.9 μmol), and 1,1,2,2-tetrachloroethane (16.3 mg, 97.1 μmol) as an internal standard dissolved in $CDCl_3$ (1.0 mL) was added silver(I) tetrafluoroborate (19.4 mg, 99.7 μmol) at room temperature. After stirring for 1 h at the same temperature, to the mixture was added a solution of benzyl azide (**2a**) (13.3 mg, 0.100 mmol) dissolved in $CDCl_3$ (1.0 mL). After stirring for 24 h at the same temperature, ^{1}H NMR analysis (400 MHz) was performed. From the ^{1}H NMR analysis of the mixture were determined the yields of triazoles **3a** (0%) and **3c** (99%) and recovered azide **2a** (0%) by comparing the relative values of integration for the peaks observed at 5.46 ppm (s, 2H, for **3a**), 5.72 ppm (s, 2H, for **3c**) and 4.34 ppm (s, 2H, for **2a**) with that of 1,1,2,2-tetrachloroethane observed at 5.95 ppm (s, 2H).

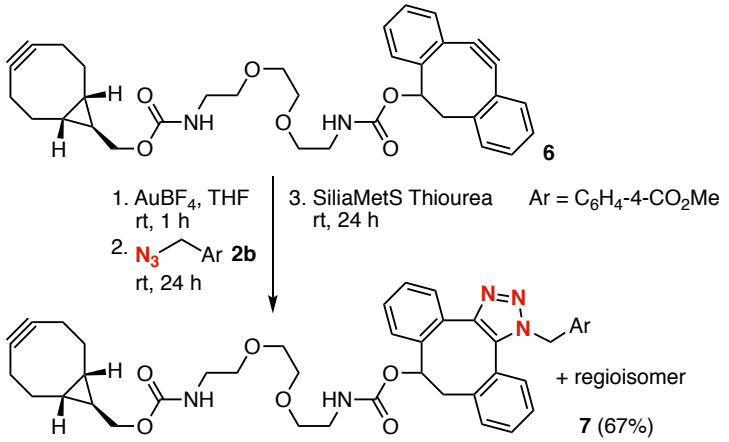
*Synthesis of diyne **6** from bicyclo[6.1.0]nonyne derivative **S1** and dibenzo-fused cyclooctyne derivative **S2***



To a solution of bicyclo[6.1.0]nonyne derivative **S1** (87.6 mg, 0.270 mmol) and triethylamine (113 μL, 0.810 mmol) dissolved in CH_2Cl_2 (2.7 mL) was added a solution of dibenzo-fused cyclooctyne derivative **S2** (105 mg, 0.272 mmol) dissolved in CH_2Cl_2 (4.0 mL) at room temperature. After stirring for 19 h at the same temperature, the mixture was extracted with CH_2Cl_2 (10 mL × 3), and the combined organic extract was washed with brine (10 mL), dried (Na_2SO_4), and after filtration,

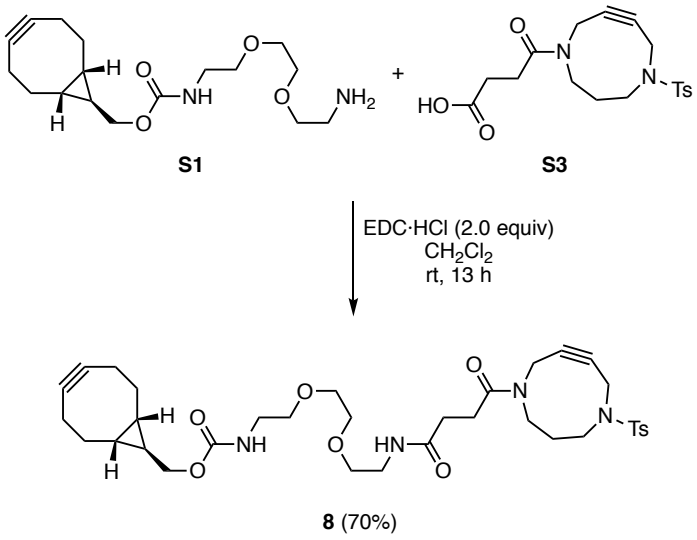
the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 38 g, CH_2Cl_2/MeOH = 20/1) to give diyne **6** (122 mg, 214 μmol, 79%) as a colorless oil.

*Selective SPAAC reaction of diyne **6** via protection of bicyclo[6.1.0]nonyne moiety with gold*



To a mixture of silver(I) tetrafluoroborate (9.7 mg, 50 μmol) and gold(I) chloride (11.6 mg, 49.9 μmol) was added THF (0.50 mL) at room temperature. After stirring for 30 min at the same temperature, to the resulting mixture was added a solution of diyne **6** (27.5 mg, 48.1 μmol) in THF (1.0 mL). After stirring for 1 h at the same temperature, to the reaction mixture was added a solution of azide **2b** (8.2 mg, 43 μmol) dissolved in THF (1.0 mL). After stirring for 24 h at the same temperature, to the reaction mixture were added THF (6.0 mL) and SiliaMetS–Thiourea (ca. 1.24 mmol/g, 2.7 g, ca. 3.4 mmol). After stirring for 24 h at the same temperature, the reaction mixture was filtered through a Celite pad, and then the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/EtOAc/MeOH = 20/3/1) to give triazole **7** (21.9 mg, 28.7 μmol, 67%) as a colorless oil.

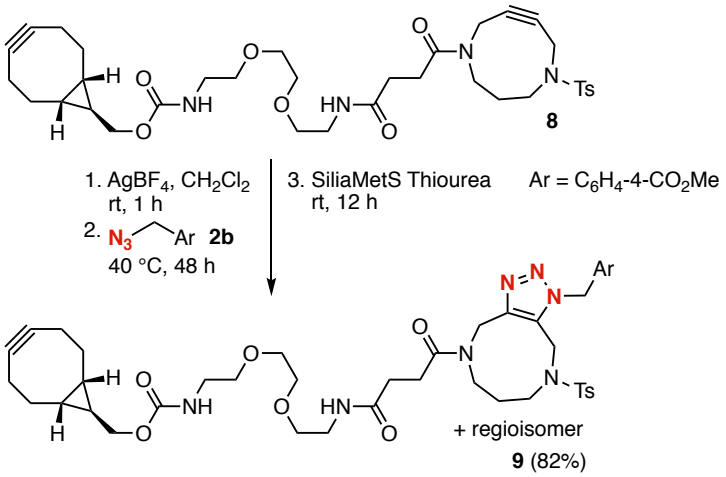
*Synthesis of diyne **8** from bicyclo[6.1.0]nonyne derivative **S1** and diazacyclononyne derivative **S3***



To a solution of bicyclo[6.1.0]nonyne derivative **S1** (341 mg, 1.05 mmol) and diazacyclononyne derivative **S2** (362 mg, 1.05 mmol) dissolved in CH_2Cl_2 (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) (403 mg, 2.10 mmol) at room temperature. After stirring for 13 h at the same temperature, to the mixture was added water (15 mL). The mixture was extracted with CH_2Cl_2 (10 mL × 3), and the combined organic extract was washed with brine (10 mL), dried (Na_2SO_4), and after filtration, the filtrate was concentrated under reduced

pressure. The residue was purified by flash column chromatography (silica-gel 36 g, CH_2Cl_2/MeOH = 30/1) to give diyne **8** (500 mg, 0.730 mmol, 70%) as a colorless oil.

*Selective SPAAC reaction of diyne **8** via protection of bicyclo[6.1.0]nonyne moiety with silver*

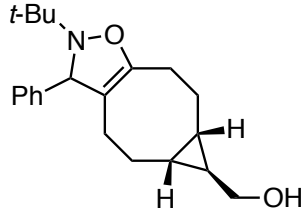


To a solution of diyne **8** (28.1 mg, 41.0 μmol) dissolved in CH_2Cl_2 (1.0 mL) was added silver (I) tetrafluoroborate (4.8 mg, 25 μmol) at room temperature. After stirring for 1 h at the same temperature, to the reaction mixture was added a solution of azide **2b** (6.3 mg, 33 μmol) dissolved in CH_2Cl_2 (1.0 mL) at 40 ˚C. After stirring for 2 days at the same temperature, to the reaction mixture was added SiliaMetS–Thiourea (ca. 1.24 mmol/g, 1.6 g, ca. 2.0 mmol) at room temperature. After stirring for 12 h at the same temperature, the reaction mixture was filtered through a Celite pad, and then the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/EtOAc/MeOH = 4/4/1) to give triazole **9** (23.6 mg, 26.9 μmol, 82%) as a colorless oil.

Characterization Data of New Compounds

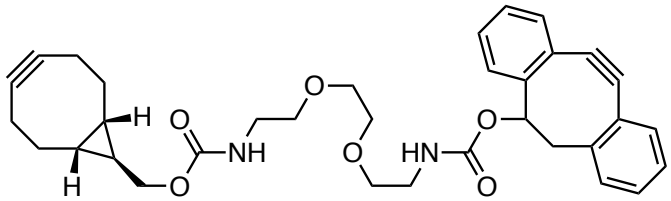
((5*aR**,6*R**,6*aS**)-1-Benzyl-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6]cycloocta[1,2-*d*][1,2,3]triazol-6-yl)methanol (**3a**),[S1] 1-benzyl-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (**3b**),[S5] and 1-benzyl-4,5,6,7,9,10-hexahydro-4,8-ditosyl-4,8-diazacyclonona[*d*][1,2,3]triazole (**3c**)[S3] were identical in spectra data with those reported in the literature.

((5a*S**,6*R**,6a*R**)-2-(*tert*-Butyl)-3-phenyl-3,4,5,5a,6,6a,7,8-octahydro-*2H*-cyclopropa[5,6]cycloocta[1,2-*d*]isoxazol-6-yl)methanol (**5**)



Colorless oil; R_f = 0.37 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR for a mixture of two diastereomers (500 MHz, $CDCl_3$) δ 0.45–0.54 (m, 0.3H), 0.57–0.65 (m, 1H), 0.66–0.81 (m, 1.7H), 1.09 (s, 3H), 1.10 (s, 6H), 1.19–1.35 (m, 2H), 1.38–1.52 (m, 1H), 1.64–1.74 (m, 0.3H), 1.80–1.94 (m, 1.7H), 1.96–2.07 (m, 1H), 2.12–2.22 (m, 1H), 2.26–2.52 (m, 2H), 3.41–3.52 (m, 2H), 4.73 (s, 0.7H), 4.78 (s, 0.3H), 7.20–7.25 (m, 1H), 7.28–7.35 (m, 4H); ^{13}C NMR for a mixture of two diastereomers (126 MHz, $CDCl_3$) δ 20.9, 21.26, 21.28, 21.4, 24.1, 24.4, 25.0, 25.11, 25.12, 25.2, 25.3, 26.0, 26.1, 26.5, 26.7, 59.9, 66.6, 75.0, 75.1, 106.3, 106.6, 127.1, 127.6, 127.7, 128.3, 144.3, 144.4, 146.8, 147.0; IR (KBr, cm^{-1}) 1026, 1225, 1265, 1364, 1377, 1526, 1545, 1705, 2928, 2972, 3301; HRMS (ESI^+) *m/z* 328.2266 ($[M+H]^+$, $C_{21}H_{30}NO_2^+$ requires 328.2271).

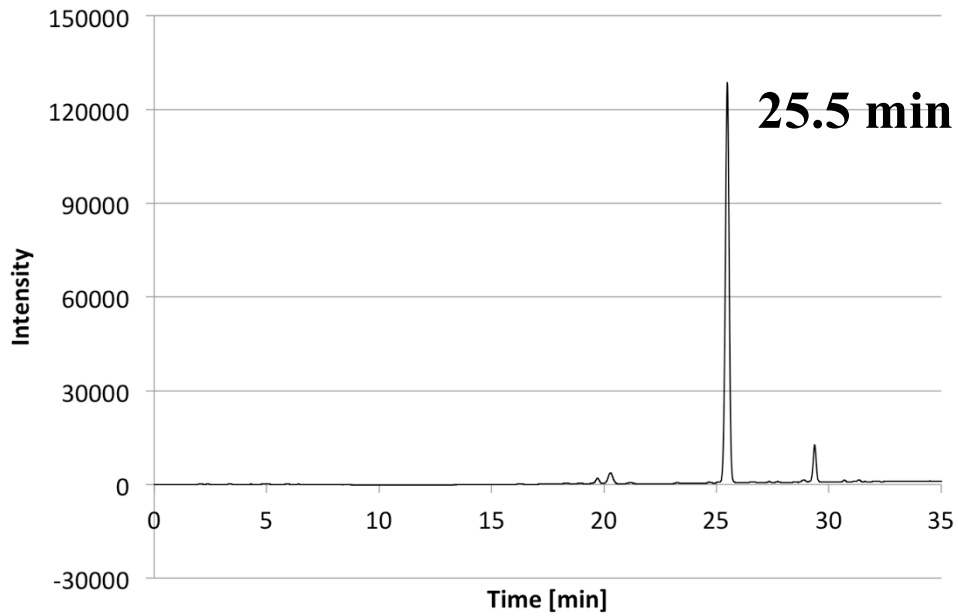
11,12-Didehydro-5,6-dihydrodibenzo[*a*,*e*]cycloocten-5-yl *N*-(2-(2-((((1*R**,8*S**,9*R**)-bicyclo[6.1.0]non-4-yn-9-yl)methyl)oxycarbonylamino)ethoxy)ethoxy)ethylcarbamate (**6**)



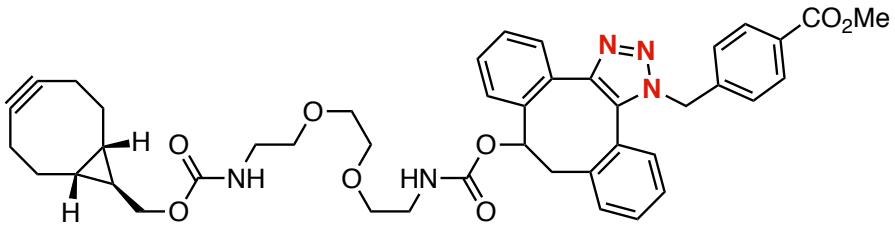
Colorless oil; R_f = 0.39 (CH_2Cl_2/MeOH = 20/1); Compound **6** is a mixture of diastereomers and conformational isomers were also observed in NMR analyses; ^{1}H NMR for major isomer (500 MHz, $CDCl_3$) δ 0.63–0.77 (m, 3H), 1.29–1.41 (m, 2H), 2.10–2.17 (m, 2H), 2.22–2.31 (m, 2H), 2.34–2.42 (m, 2H), 2.90 (dd, 1H, *J* = 15.0, 3.6 Hz), 3.18 (d, 1H, *J* = 14.0 Hz), 3.33–3.46 (m, 4H), 3.52–3.74 (m, 8H), 4.03 (d, 2H, *J* = 6.3 Hz), 5.20–5.29 (br, 1H), 5.45–5.57 (m, 2H), 7.27–7.40 (m, 7H), 7.45–7.55 (m, 1H); ^{13}C NMR for major isomer (126 MHz, $CDCl_3$) δ 21.3 (2C), 22.8 (2C), 23.7 (1C), 33.2 (2C), 40.7 (1C), 40.9 (1C), 46.1 (1C), 67.0 (1C), 69.1 (1C), 70.0 (1C), 70.1 (1C), 70.2 (2C), 98,7 (2C), 109.9 (1C), 112.9 (1C), 121.3 (1C), 123.7 (1C), 123.8 (1C), 125.9 (1C), 126.2 (1C), 127.0 (1C+1C, two signals overlapped), 127.9 (1C), 128.0 (1C), 129.9 (1C), 150.9 (1C), 152.1 (1C), 155.5 (1C), 156.8 (1C); IR (KBr, cm^{-1}) 739, 760, 1103, 1140, 1254, 1263, 1449, 1522, 1717, 2930; HRMS (ESI^+) *m/z* 593.2610 ($[M+Na]^+$, $C_{34}H_{38}N_2NaO_6^+$ requires 593.2622).

HPLC analysis: The diastereomers did not separate and observed as a single peak with R*t* = 25.5 min [column: *SHISEIDO* CAPCELL PAK MG II (4.6 mm × 150 mm); mobile phase: CH_3CN:H_2O = 40:60 (0–5 min), linear gradient from 40:60 to 99:1 (5–25 min), 99:1 (25–35 min); flow rate: 1.00 mL/min; detection: UV at 254 nm]

HPLC chart:



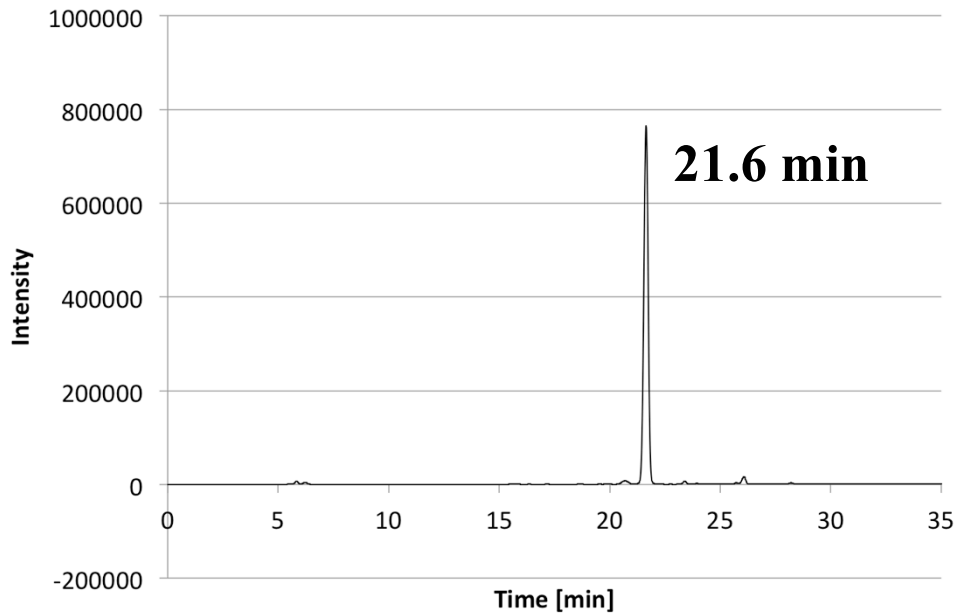
Methyl 4-((8-(((1-((1*R**,8*S**,9*R**)-bicyclo[6.1.0]non-4-yn-9-yl)-3-oxo-2,7,10-trioxa-4-azadodecan-12-yl)carbamoyl)oxy)-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazol-1-yl)methyl)benzoate (**7**)



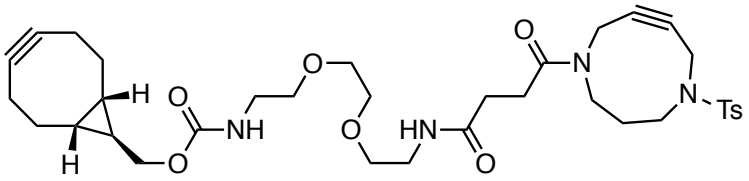
Colorless oil; R_f = 0.34 (CH_2Cl_2/MeOH = 20/1); Compound **7** is a mixture of diastereomers, regioisomers, and conformational isomers, which were observed in NMR analyses; IR (KBr, cm^{-1}) 752, 763, 1020, 1111, 1247, 1280, 1435, 1512, 1521, 1719; HRMS (ESI^+) *m/z* 784.3301 ($[M+Na]^+$, $C_{43}H_{47}N_5NaO_8^+$ requires 784.3317).

HPLC analysis: The diastereomers and regioisomers did not separate and observed as a single peak with R*t* = 21.6 min [column: *SHISEIDO* CAPCELL PAK MG II (4.6 mm × 150 mm); mobile phase: CH_3CN:H_2O = 40:60 (0–5 min), linear gradient from 40:60 to 99:1 (5–25 min), 99:1 (25–35 min); flow rate: 1.00 mL/min; detection: UV at 254 nm]

HPLC chart:



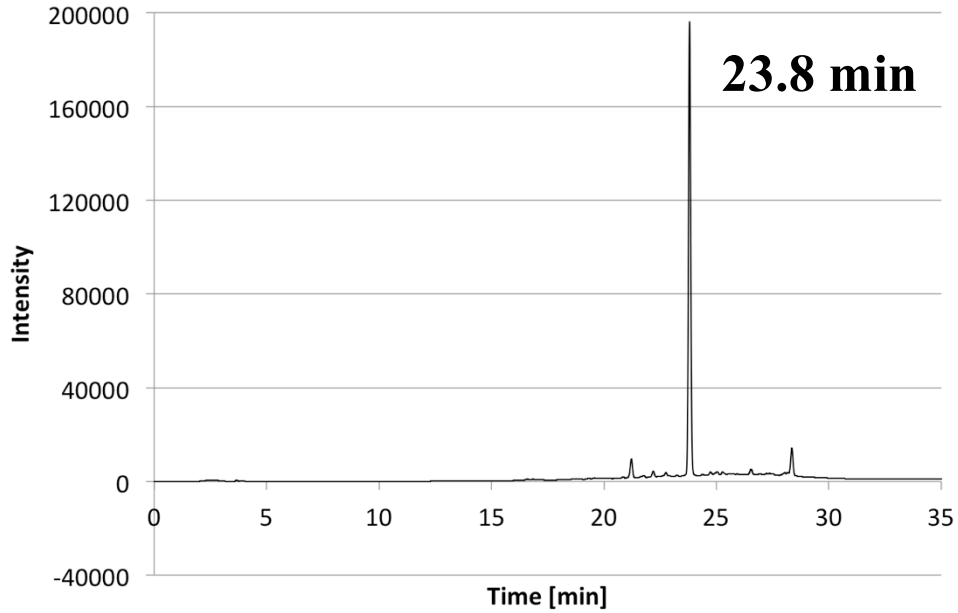
8-(1-((1*R**,8*S**,9*R**)-Bicyclo[6.1.0]non-4-yn-9-yl)-3,14-dioxo-2,7,10-trioxa-4,13-diazaheptadecan-17-oyl)-4-tosyl-4,8-diazacyclononyne (**8**)



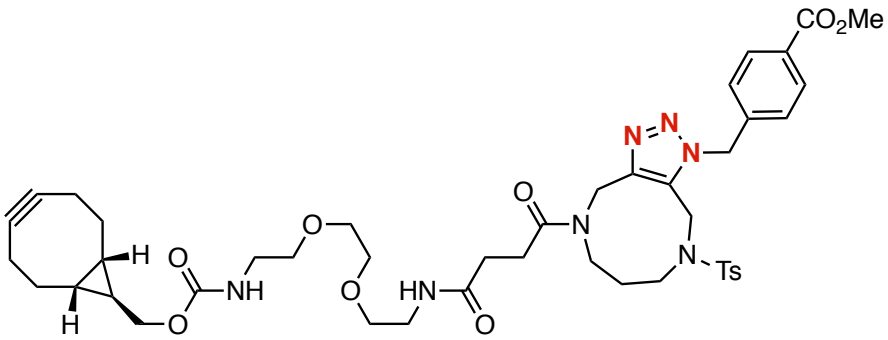
Colorless oil; R_f = 0.48 (CH_2Cl_2/MeOH = 10/1); Compound **8** is a mixture of rotamers, which were observed in NMR analyses; ^{1}H NMR for a mixture of rotamers (500 MHz, $CDCl_3$) δ 0.63–0.78 (m, 3H), 1.30–1.42 (m, 2H), 2.08–2.19 (m, 4H), 2.24–2.32 (m, 2H), 2.36–2.42 (m, 2H), 2.44 (s, 3H), 2.47–2.58 (m, 2H), 2.61–2.68 (m, 2H), 3.15–3.19 (m, 0.8H), 3.25–3.29 (m, 1.2H), 3.34–3.48 (m, 4H), 3.52–3.65 (m, 10H), 3.83–3.89 (m, 2H), 3.95–4.01 (m, 2H), 4.05–4.08 (m, 0.8H), 4.18–4.24 (m, 1.2H), 5.29–5.44 (br, 0.6H), 5.50–5.64 (br, 0.4H), 6.22–6.39 (br, 0.6H), 6.97–7.12 (br, 0.4H), 7.31–7.37 (m, 2H), 7.64–7.71 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 21.6, 22.8, 23.7, 29.0, 29.1, 30.1, 31.0, 31.2, 32.1, 33.3, 36.7, 39.3, 39.4, 40.7, 40.8, 41.0, 43.7, 43.8, 45.4, 69.1, 69.8, 70.1, 70.2, 86.8, 88.3, 88.4, 89.2, 98.8, 127.28, 127.33, 129.9, 130.0, 134.5, 134.6, 143.8, 143.9, 156.9, 171.3, 172.08, 172.13, 172.5; IR (KBr, cm^{-1}) 1096, 1136, 1159, 1256, 1337, 1350, 1445, 1535, 1649, 1713; HRMS (ESI^+) *m/z* 707.3078 ($[M+Na]^+$, $C_{35}H_{48}N_4NaO_8^+$ requires 707.3085).

HPLC analysis: R*t* = 23.8 min [column: *SHISEIDO* CAPCELL PAK MG II (4.6 mm × 150 mm); mobile phase: CH_3CN:H_2O = 20:80 (0–5 min), linear gradient from 20:80 to 99:1 (5–25 min), 99:1 (25–35 min); flow rate: 1.00 mL/min; detection: UV at 254 nm]

HPLC chart:



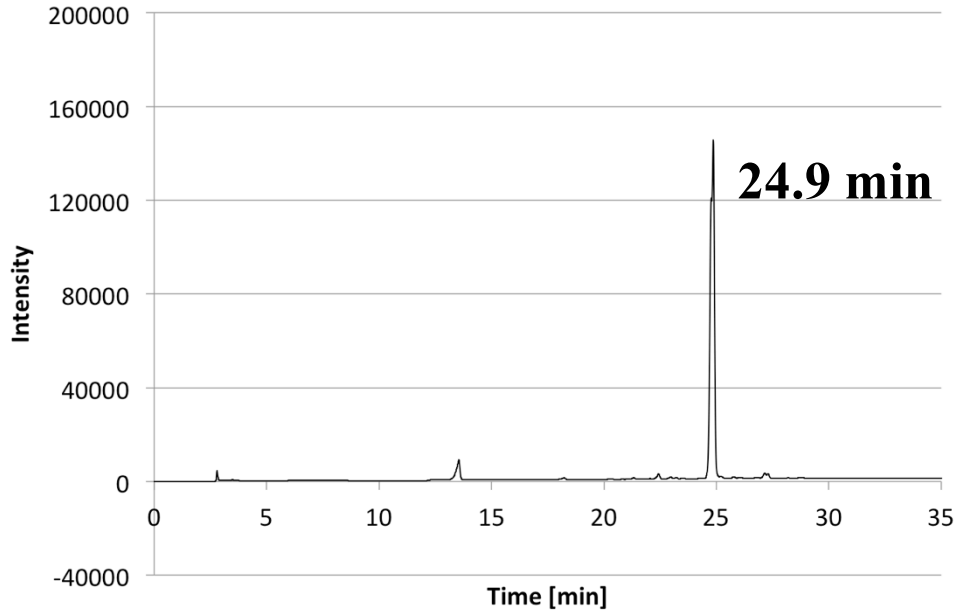
Methyl 4-((5-(1-((1*R**,8*S**,9*R**)-bicyclo[6.1.0]non-4-yn-9-yl)-3,14-dioxo-2,7,10-trioxa-4,13-diazaheptadecan-17-oyl)-9-tosyl-5,6,7,8,9,10-hexahydro-[1,2,3]triazolo[4,5-*g*][1,5]diazonin-1(4*H*)-yl)methyl)benzoate (**9**)



Colorless oil; R_f = 0.45 (CH_2Cl_2/MeOH = 10/1); Compound **9** is a mixture of regioisomers and rotamers, which were observed in NMR analyses; IR (KBr, cm^{-1}) 733, 914, 1094, 1109, 1161, 1256, 1281, 1344, 1437, 1647, 1719; HRMS (ESI^+) *m/z* 898.3776 ($[M+Na]^+$, $C_{44}H_{57}N_7NaO_{10}S^+$ requires 898.3780).

HPLC analysis: The regioisomers did not separate and observed as a single peak with R*t* = 24.9 min [column: *SHISEIDO* CAPCELL PAK MG II (4.6 mm × 150 mm); mobile phase: CH_3CN:H_2O = 20:80 (0–5 min), linear gradient from 20:80 to 99:1 (5–25 min), 99:1 (25–35 min); flow rate: 1.00 mL/min; detection: UV at 254 nm]

HPLC chart:



References for Supporting Information

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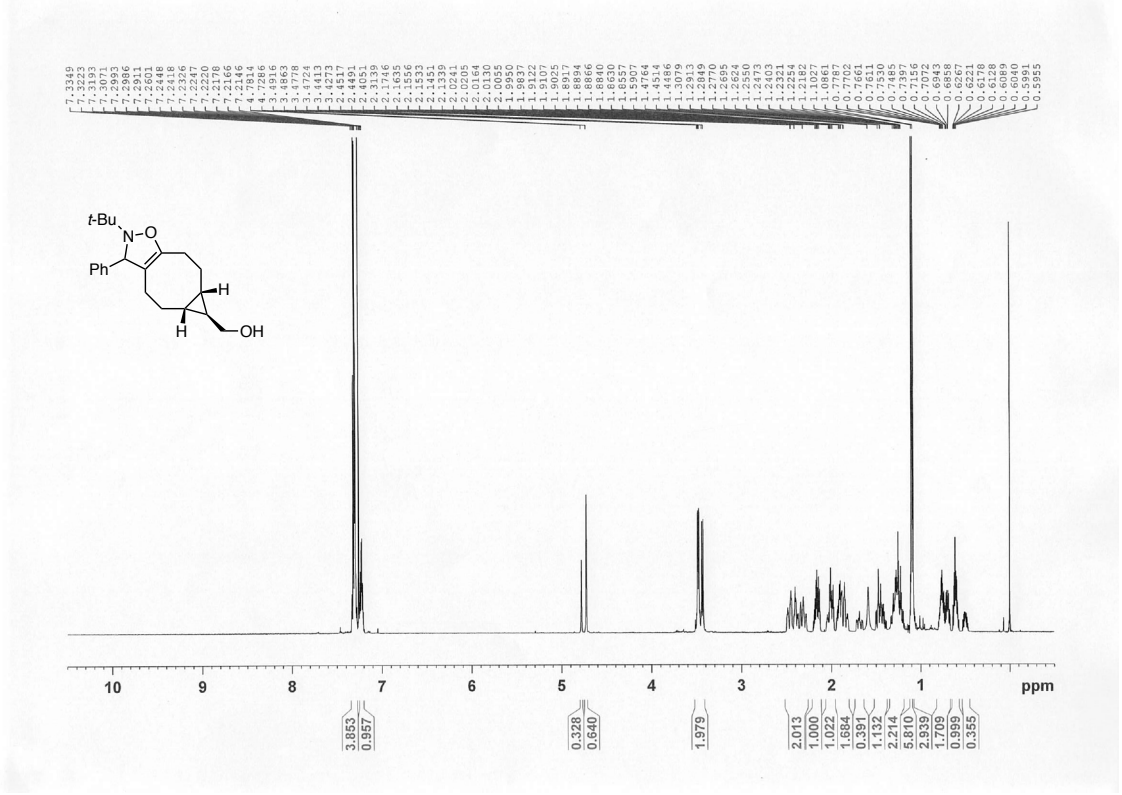
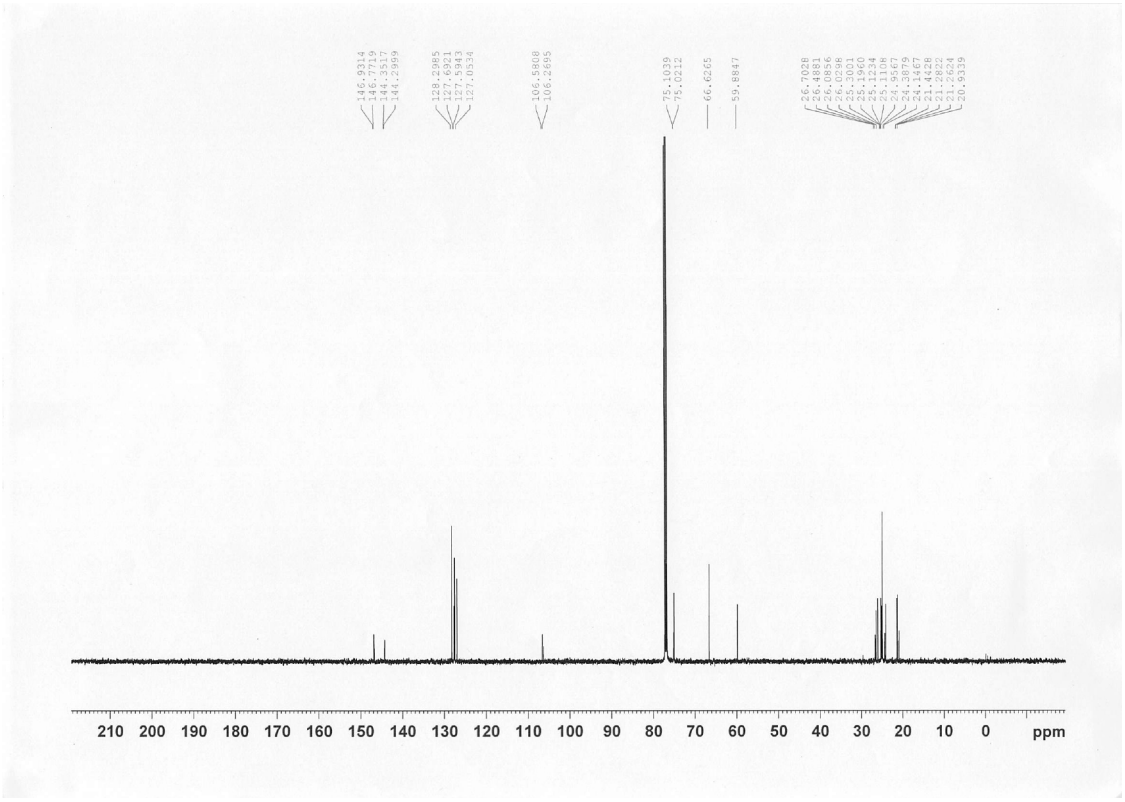
S2) G.-J. Boons, J. Guo, X. Ning and M. Wolfert, WO 2009/067663, 2009.
S3) R. Ni, N. Mitsuda, T. Kashiwagi, K. Igawa and K. Tomooka, *Angew. Chem., Int. Ed.,* 2014, **54**, 1190.
S4) K. Igawa, S. Aoyama, Y. Kawasaki, T. Kashiwagi, Y. Seto, R. Ni, N. Mitsuda and K. Tomooka, *Synlett,* **2017**, *28*, 2110.
S5) Q. Li, T. Dong, X. Liu and X. Lei, *J. Am. Chem. Soc.,* 2013, **135**, 4996.

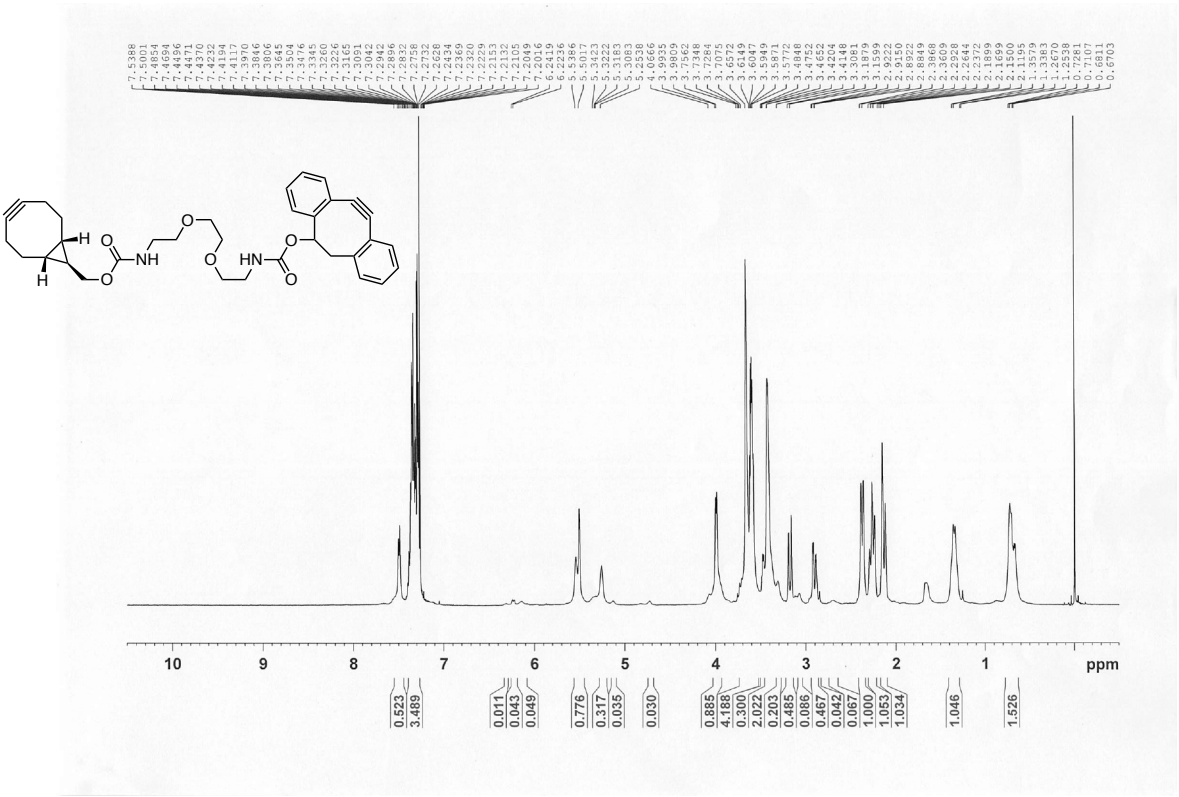
NMR Spectra of New Compounds

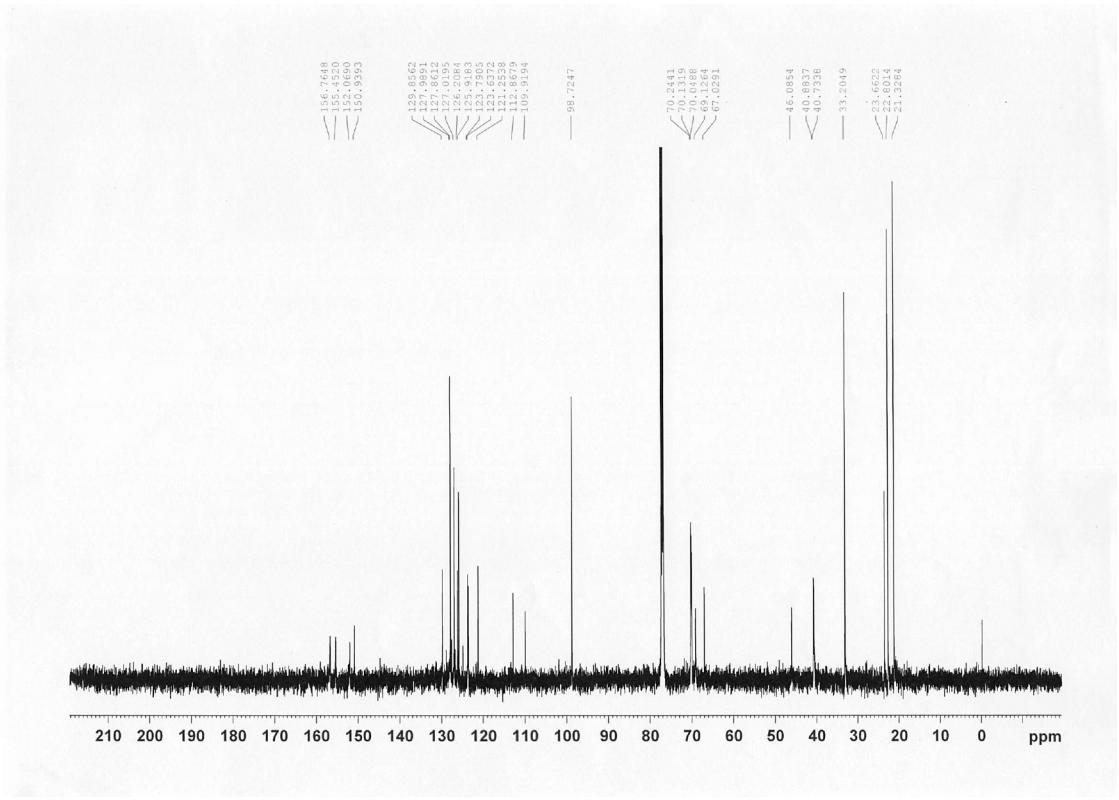
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of ((5a*S**,6*R**,6a*R**)-2-(*tert*-butyl)-3-phenyl-3,4,5,5a,6,6a,7,8-octahydro-*2H*-cyclopropa[5,6]cycloocta[1,2-*d*]isoxazol-6-yl)methanol (**5**) ($CDCl_3$)



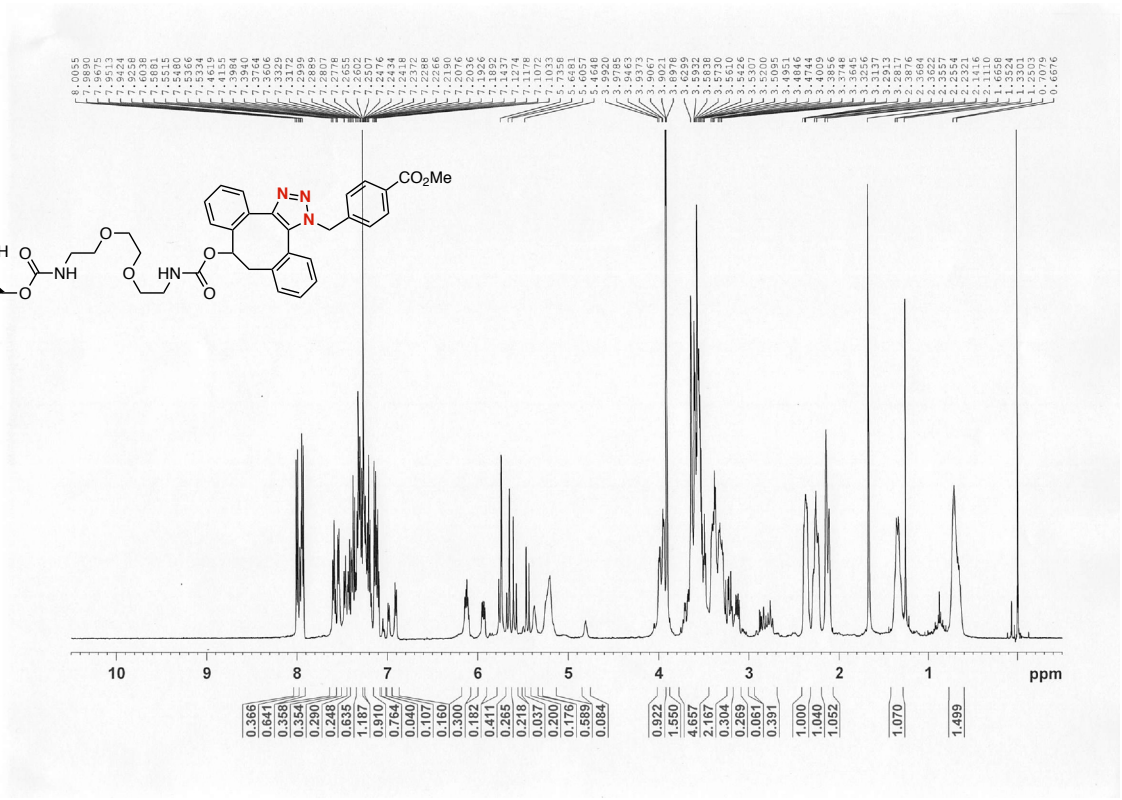


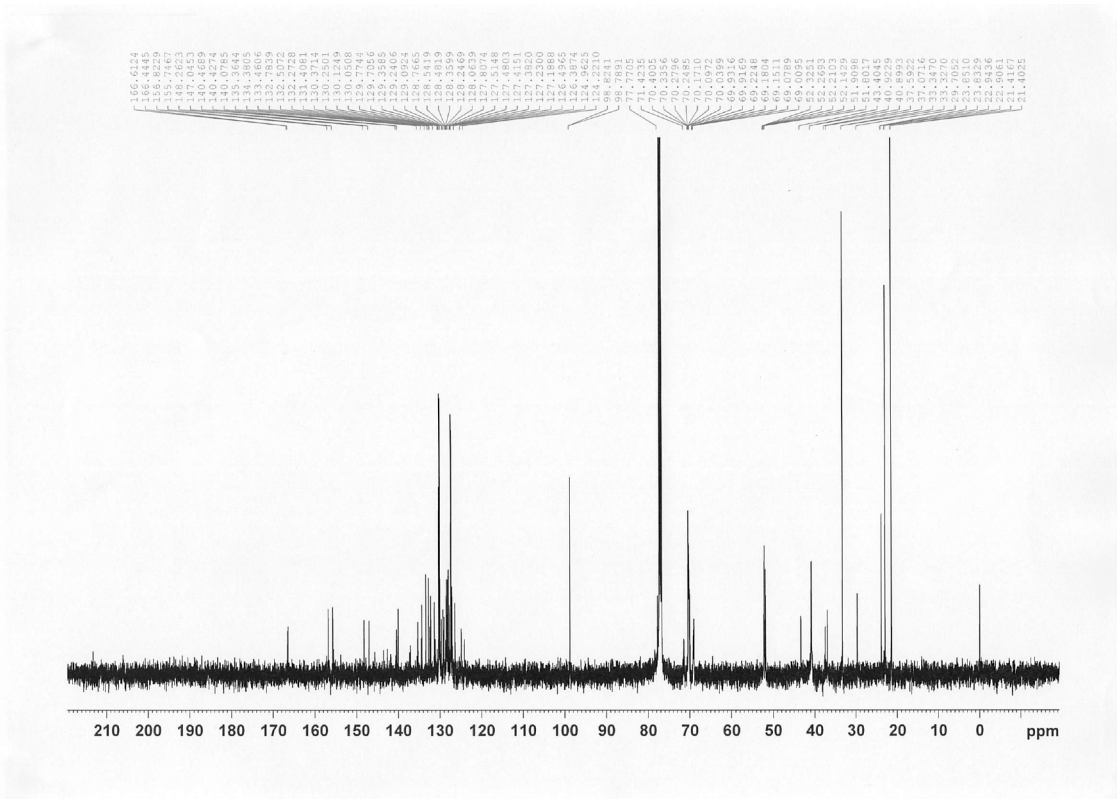
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 11,12-didehydro-5,6-dihydrodibenzo[*a*,*e*]cycloocten-5-yl *N*-(2-(2-((((1*R**,8*S**,9*R**)-bicyclo[6.1.0]non-4-yn-9-yl)methyl)oxycarbonylamino)ethoxy)ethoxy)ethylcarbamate (**6**) ($CDCl_3$)



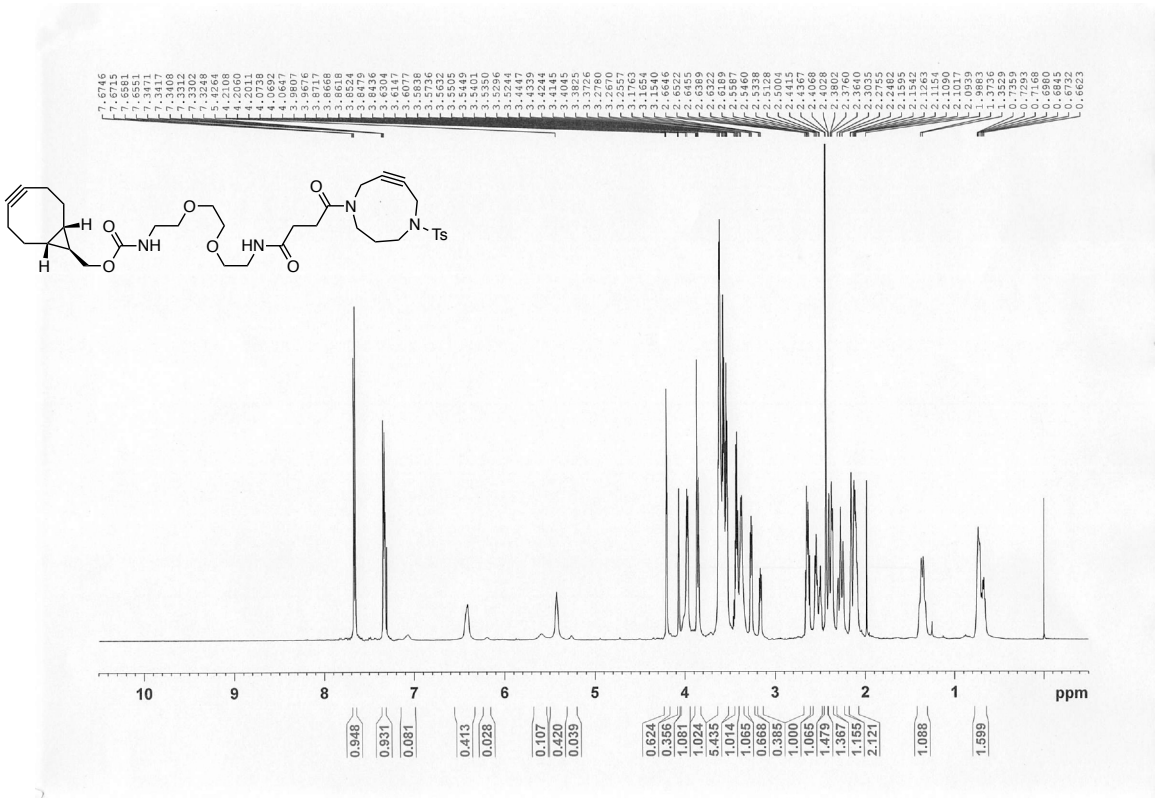


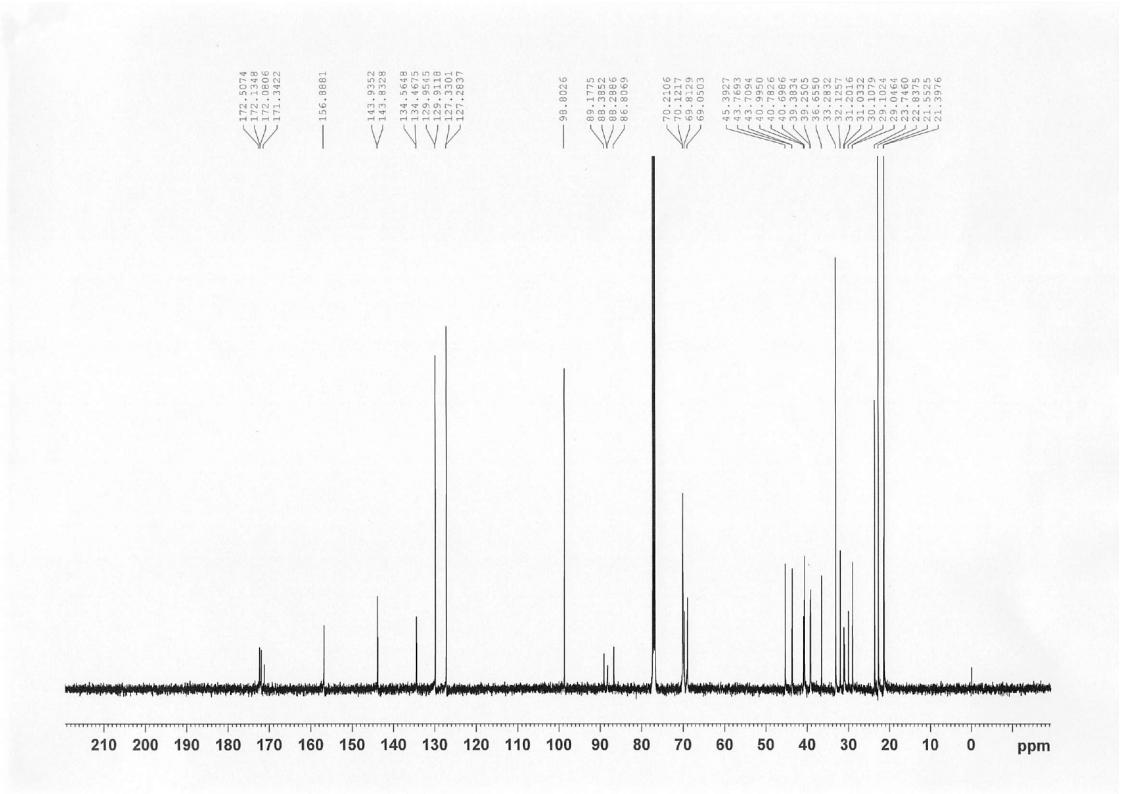
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of methyl 4-((8-(((1-((1*R**,8*S**,9*R**)-bicyclo[6.1.0]non-4-yn-9-yl)-3-oxo-2,7,10-trioxa-4-azadodecan-12-yl)carbamoyl)oxy)-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cyclooctа[1,2-*d*][1,2,3]triazol-1-yl)methyl)benzoate (**7**) ($CDCl_3$)





^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 8-(1-((1*R**,8*S**,9*R**)-bicyclo[6.1.0]non-4-yn-9-yl)-3,14-dioxo-2,7,10-trioxa-4,13-diazaheptadecan-17-oyl)-4-tosyl-4,8-diazacyclononyne (**8**) ($CDCl_3$)





^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of methyl 4-((5-(1-((1*R**,8*S**,9*R**)-bicyclo[6.1.0]non-4-yn-9-yl)-3,14-dioxo-2,7,10-trioxa-4,13-diazaheptadecan-17-oyl)-9-tosyl-5,6,7,8,9,10-hexahydro-[1,2,3]triazolo[4,5-*g*][1,5]diazonin-1(4*H*)-yl)methyl)benzoate (**9**) ($CDCl_3$)