Electronic Supplementary Information

A tri(ethylene glycol)-tethered Morita-Baylis-Hillman dimer in the formation of macrocyclic crown ether-paracyclophane hybrid structures

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Mass spectrometry

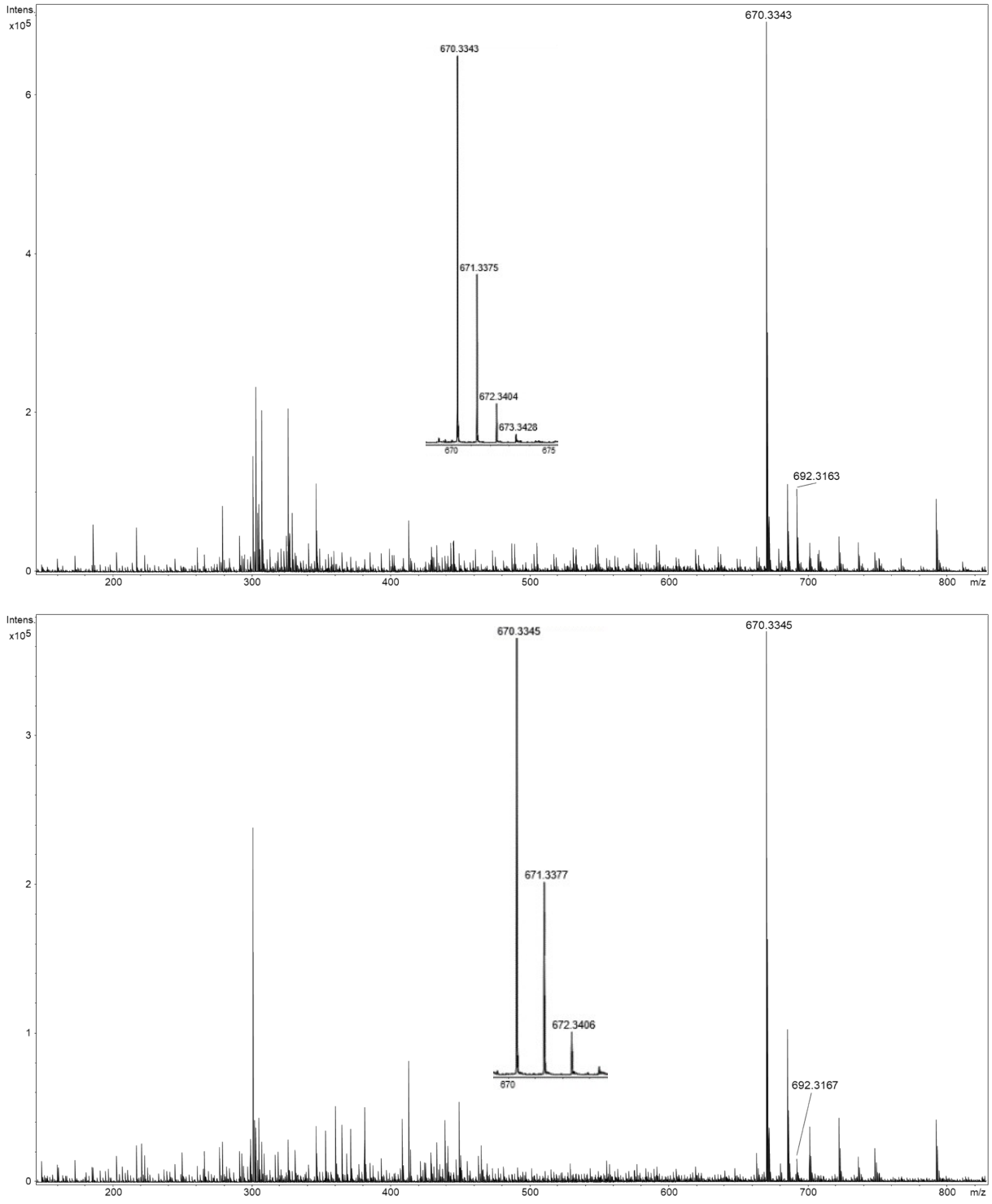

Figure ESI-1. ESI(+) timsTOF mass spectrum of **2a** (top) and **2b** (bottom).

Table ESI-1. Data analysis from timsTOF mass spectra.

	m/z	Molecular Formula	Error (ppm)	RDB[a]	e⁻ conf	Resolution
2a	670.3343	$C_{36}H_{44}N_7O_6$	0.7	19.0	EVEN	39344
	692.3163	$C_{36}H_{43}N_7O_6Na$	-0.5	19.0	EVEN	35954
2b	670.3345	$C_{36}H_{44}N_7O_6$	0.3	19.0	EVEN	37351
	692.3167	$C_{36}H_{43}N_7O_6Na$	0.0	19.0	EVEN	34332

[a] Double bond/ring equivalents.

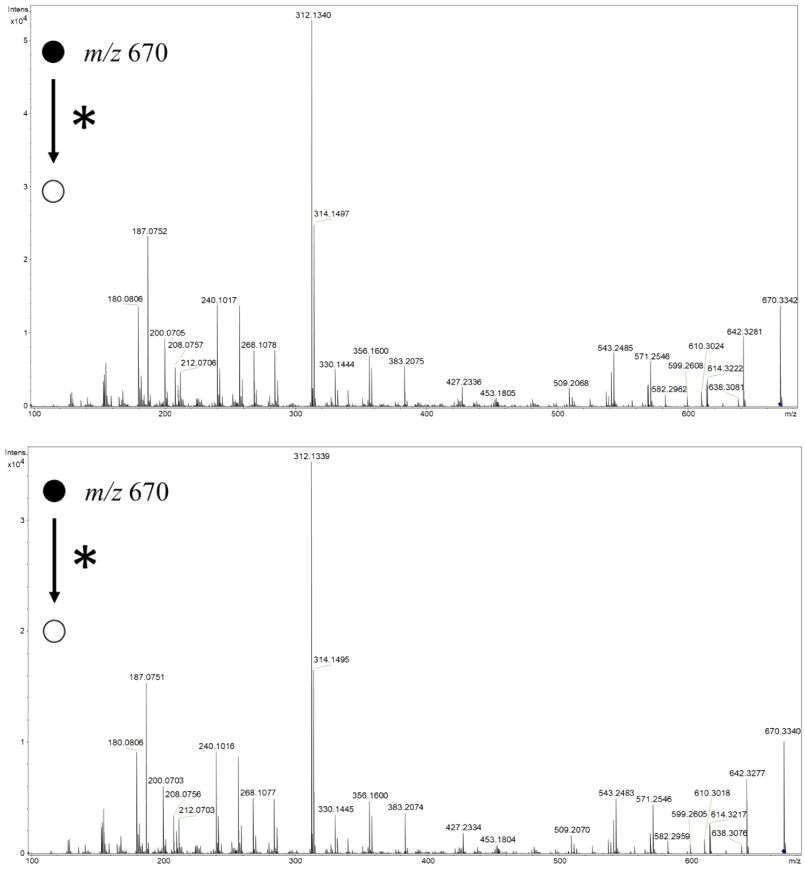

Figure ESI-2. ESI(+) timsTOF MS^2 spectra of **2a** (top) and **2b** (bottom).

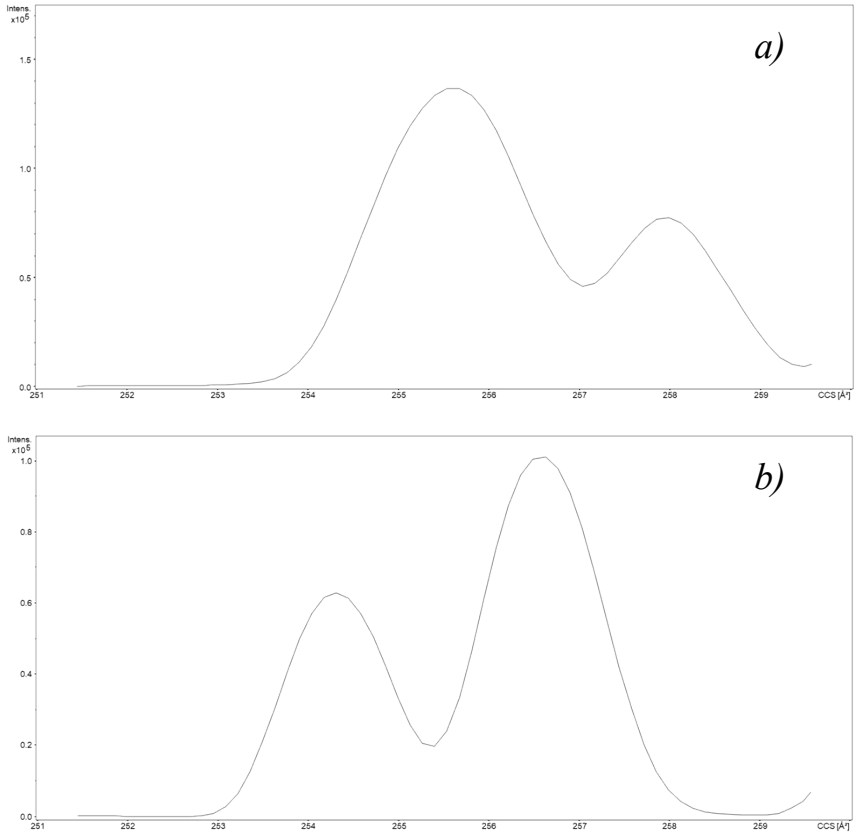

Figure ESI-3. ESI(+) timsTOF ion mobility spectra on the extracted ion mobilogram of ions at *m/z* 670 for: ***a)*** **2a**; ***b)*** **2b**.

Table ESI-2. TIMS data from the extracted ion mobilograms of $[M+H]^+$ at *m/z* 670.

	CCS (Å^2)	1/K$_0$ (V·s/cm^2)	Resolution 1/K$_0$
2a	255.6	1.251	130.161
	258.0	1.262	155.311
2b	254.3	1.244	183.515
	256.6	1.255	169.493

CCS stands for collision cross section; 1/K$_0$: inversed reduced mobility.

Characterization of photophysical features of macrocyclic compounds 2a,b.

The photophysical features of macrocyclic compounds **2a**,**b** were characterized in terms of their absorption spectra in methanol (Figure ESI-4).

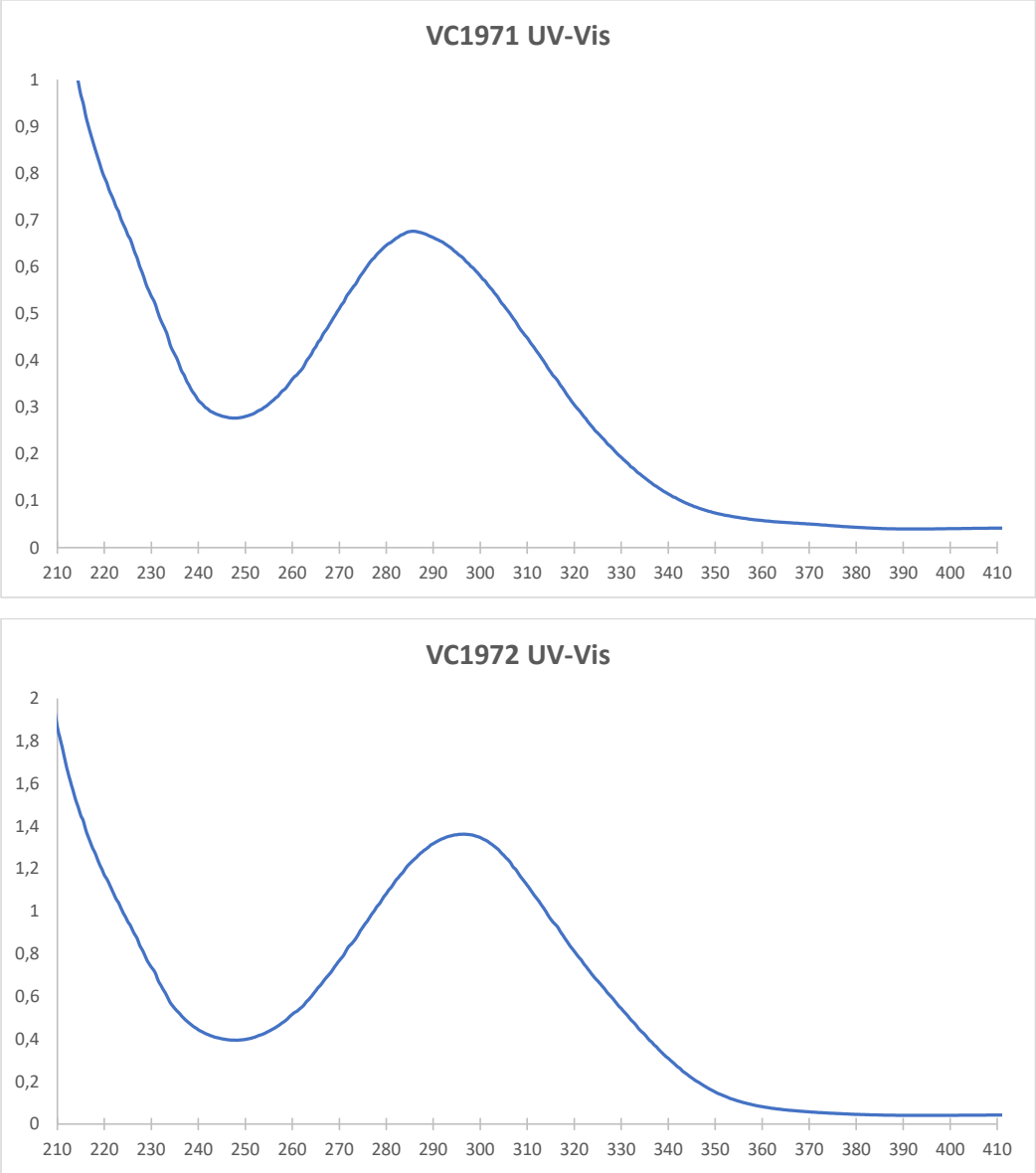

Figure ESI-4. Absorption spectra of **2a** (bottom) and **2b** (top). The spectra were recorded with solutions of **2a**,**b** at the concentration of 10^{-4} M in methanol by using a Specord 210 Analytik Jena.

Characterization of photochemical features of macrocyclic compound 2a by ^{1}H NMR spectroscopy studies.

The (*E*,*E*) diastereomer **2a** was dissolved in deuterated methanol into a 5 mm NMR tube and the resulting solutions were exposed to UV-B light into an appropriate photoreactor (Multirays, Helios Quartz). ^{1}H NMR spectra were registered at regular time intervals, elaborated, and compared in Figure ESI-5.

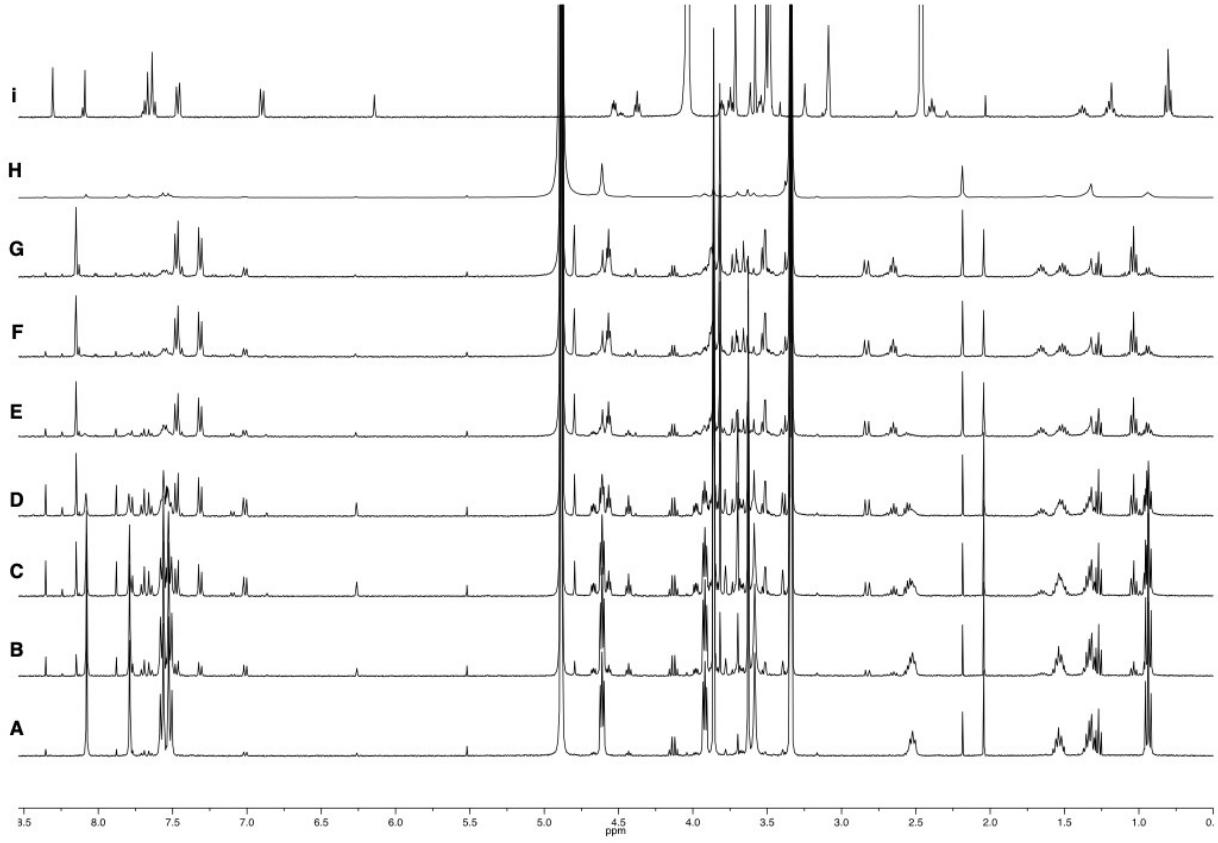

Figure ESI-5. Comparison of the ^{1}H NMR spectra recorded (400 MHz) with the solution of **2a** in deuterated methanol exposed to UV-B irradiation for increasing times (i. e. trace A: t = 0 min; B: t = 5 min; C: t = 10 min; D: t = 15 min; E: t = 20 min; F: t = 25 min; G: t = 30 min). After 15 min exposition to UV-B irradiation, the formation of a white precipitate was noticed that increased with the UV-B exposition. Trace H: the spectrum was recorded after storing the NMR tube containing the mixture at room temperature for three weeks. Trace I: the spectrum was recorded after dissolving the white precipitate with deuterated DMSO.

The comparison of the ^{1}H NMR spectra recorded with the solution of **2a** in deuterated methanol exposed to UV-B irradiation for increasing times (i. e. from 5 to 30 min) supported the liability of the (*E*,*E*) diastereomer to undergo photoisomerization with the formation of an almost insoluble compound, which precipitated from the reaction mixture. In fact, after 15 min exposition to UV-B irradiation, the formation of a white precipitate was observed, and the amount of this material appeared to increase in the time with the UV-B exposition. After storing the NMR tube containing the mixture at room temperature for three weeks, the spectrum (trace H) suggested that negligible amounts of materials remained in the solution. Thus, a spectrum was recorded after dissolving the white precipitate with deuterated DMSO (trace I), and this spectrum supported the formation of (*E*,*Z*) diastereomer **2b** by photoisomerization with UV-B light of (*E*,*E*) diastereomer **2a** in methanol.

Experimental Procedures

Synthesis

All chemicals used were of reagent grade. Yields refer to purified products and are not optimized. Melting points were determined in open capillaries on a Gallenkamp apparatus and are uncorrected. Merck silica gel 60 (230-400 mesh) was used for flash chromatography purifications. Merck TLC plates, silica gel 60 F_{254} were used for TLC. NMR spectra were recorded with a Bruker DRX-400 AVANCE or a Bruker DRX-500 AVANCE spectrometer in the indicated solvents (TMS as internal standard): the values of the chemical shifts are expressed in ppm and the coupling constants (*J*) in Hz. Mass spectra were recorded on an Agilent 1100 LC/MSD operating with an electrospray source.

4-((Trimethylsilyl)ethynyl)benzaldehyde (4). VC1891

To a degassed solution of *p*-bromobenzaldehyde (Sigma Aldrich, 1.00 g, 5.41 mmol) in 9.0 mL of THF-TEA (5:1), $Pd(PPh_3)_2Cl_2$ (266 mg, 0.38 mmol), CuI (74 mg, 0.39 mmol), and finally trimethylsilylacetylene (1.12 mL, 8.11 mmol) were added in the sequence. The resulting mixture was maintained under stirring in a nitrogen atmosphere at room temperature for 3 h. Subsequently, the reaction mixture was concentrated under reduced pressure and the obtained residue was partitioned between CH_2Cl_2 and H_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting organic residue was purified by flash chromatography with petroleum ether-ethyl acetate (9:1) as the eluent to obtain **4** (896 mg, yield 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 0.26 (s, 9H), 7.59 (d, J = 8.2, 2H), 7.81 (d, J = 8.2, 2H), 9.99 (s, 1H) in full agreement with the data described in the literature.[1]

MS (ESI): *m/z* 203.1 [M + H^+].

4-Ethynylbenzaldehyde (5). VC1892

A mixture of **4** (861 mg, 4.25 mmol) and K_2CO_3 (59 mg, 0.425 mmol) in MeOH (15 mL) was maintained under stirring in a nitrogen atmosphere at room temperature overnight. Subsequently, the reaction mixture was concentrated under reduced pressure and the resulting residue was partitioned between CH_2Cl_2 and H_2O acidulated with 1N HCl. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash chromatography with petroleum ether-ethyl acetate (8:2) as the eluent to obtain **5** (242 mg, yield 44%) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 3.28 (s, 1H), 7.63 (d, J = 8.1, 2H), 7.83 (d, J = 8.2, 2H), 10.01 (s, 1H) in full agreement with the data described in the literature.[2]

MS (ESI): *m/z* 153.1 [M + Na^+].

Methyl 2-((4-ethynylphenyl)(hydroxy)methyl)acrylate (6). VC1893

A mixture of compound **5** (216 mg, 1.66 mmol) in methyl acrylate (0.30 mL, 3.32 mmol) containing 1,4-diazabicyclo[2.2.2]octane (DABCO) (223 mg, 1.99 mmol) and 7.2 µL of MeOH was

maintained under stirring at room temperature and in the dark for 72 h. Subsequently, the reaction mixture was concentrated under reduced pressure and the obtained residue was redissolved in CH_2Cl_2 and washed with a saturated solution of NH_4Cl. Then, the organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The organic residue was purified by flash chromatography with petroleum ether-ethyl acetate (7:3) as the eluent to obtain **6** (201 mg, yield 56%) as pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 3.05 (m, 2H), 3.72 (s, 3H), 5.54 (d, *J* = 5.8, 1H), 5.81 (s, 1H), 6.33 (s, 1H), 7.33 (d, *J* = 8.2, 2H), 7.47 (d, *J* = 8.2, 2H). MS (ESI): *m/z* 239.1 [M + Na^+].

Methyl 2-(acetoxy(4-ethynylphenyl)methyl)acrylate (7). VC1894

To a solution of **6** (199 mg, 0.92 mmol) in dry CH_2Cl_2 (5.0 mL), triethylamine (TEA) (0.32 mL, 2.3 mmol) and acetyl chloride (0.13 mL, 1.84 mmol) were added dropwise. The resulting mixture was stirred at room temperature in a nitrogen atmosphere for ninety minutes. Subsequently, the reaction mixture was washed with H_2O and the organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash chromatography with petroleum ether-ethyl acetate (7:3) as the eluent mixture to obtain **7** (194 mg, yield 82%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 2.10 (s, 3H), 3.06 (s, 1H), 3.70 (s, 3H), 5.86 (s, 1H), 6.39 (s, 1H), 6.64 (s, 1H), 7.32 (d, *J* = 8.2, 2H), 7.45 (d, *J* = 8.2, 2H). MS (ESI): *m/z* 281.1 [M + Na^+].

Dimethyl 2,2'-(((((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(1H-1,2,3-triazole-1,4-diyl))bis(4,1-phenylene))bis(acetoxymethylene))diacrylate (1). VC1956

To a solution of **7** (193 mg, 0.747 mmol) and **10** (75 mg, 0.37 mmol) in anhydrous CH_3CN (11 mL), DIPEA (52 µL, 0.30 mmol) and CuBr(I) (43 mg, 0.30 mmol) were added in the sequence. The resulting mixture was maintained under stirring in a nitrogen atmosphere at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was

dissolved in CH_2Cl_2 and washed with NH_4OH. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The organic residue was purified by flash chromatography with ethyl acetate-methanol (95:5) as the eluent mixture to obtain **1** as a colorless oil (187 mg, yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.08 (s, 6H), 3.52 (s, 4H), 3.68 (s, 6H), 3.82 (t, *J* = 5.1, 4H), 4.50 (t, *J* = 5.1, 4H), 5.88 (s, 2H), 6.39 (s, 2H), 6.66 (s, 2H), 7.41 (d, *J* = 8.2, 4H), 7.78 (d, *J* = 8.1, 4H), 7.85 (s, 2H). MS (ESI): *m/z* 739.2 [M + Na^+].

(Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl) dimethanesulfonate (9).

To a solution of tri(ethylene glycol) **8** (Sigma Aldrich, 509 mg, 3.39 mmol) in CH_2Cl_2 (10 mL) cooled in an ice bath, TEA (2.82 mL, 20.3 mmol) and CH_3SO_2Cl (0.79 mL, 10.2 mmol) were added sequentially drop by drop. The resulting mixture was maintained under stirring in a nitrogen atmosphere at room temperature for 3 h. Subsequently, the reaction crude was washed with a saturated solution of NH_4Cl and the organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography with ethyl acetate-methanol (9:1) as the eluent to obtain **9** as a pale-yellow oil (973 mg, yield 94%). ^{1}H NMR (400 MHz, $CDC1_3$): 3.07 (s, 6H), 3.68 (s, 4H), 3.74-3.80 (m, 4H), 4.34-4.41 (m, 4H). MS (ESI): *m/z* 329.0 [M + Na^+].

1,2-Bis(2-azidoethoxy)ethane (10).

To a solution containing **9** (2.21 g, 7.22 mmol) in CH_3CN (30 mL) and DMF (5.0 mL), NaN_3 (2.82 g, 43.3 mmol) was added, and the resulting mixture was maintained under stirring in a nitrogen atmosphere at reflux temperature overnight. Subsequently, the reaction mixture was concentrated under reduced pressure and the resulting residue was partitioned between CH_2Cl_2 and a saturated solution of NH_4Cl. The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure and the organic residue was purified by flash chromatography with ethyl acetate-

petroleum ether (9:1) as the eluent mixture to obtain **10** as a yellow oil (981 mg, yield 68%). ^{1}H NMR (400 MHz, $CDCl_3$): 3.34-3.37 (m, 4H), 3.51-3.75 (m, 8H). MS (ESI): *m/z* 223.1 [M + Na^+].

Reaction of the reactive homodimer 1 with n-butylamine.

Compound **1** (185 mg, 0.258 mmol) was solubilized in $CHCl_3$ (31 mL) and subsequently n-butylamine (51 µL, 0.52 mmol) was added. The resulting mixture was refluxed for 24 h, and then concentrated under reduced pressure. The organic residue was purified by flash chromatography with ethyl acetate-methanol (95:5) as the eluent.

Dimethyl (1^{4}Z,11^{4}Z,3E,8E)-6-butyl-1^{1}H,11^{1}H-14,17-dioxa-6-aza-1,11(4,1)-ditriazola-2,10(1,4)-dibenzenacyclononadecaphane-3,8-diene-4,8-dicarboxylate (2a). VC1972

Compound **2a** was obtained as a yellowish-white solid (60 mg, yield 35%) as the most polar fraction of the chromatographic purification. ^{1}H NMR (400 MHz, DMSO-d_6): 0.82 (t, *J* = 7.3, 3H), 1.17-1.28 (m, 2H), 1.42-1.48 (m, 2H), 2.41 (t, *J* = 7.1, 2H), 3.44 (s, 4H), 3.51 (s, 4H), 3.74 (s, 6H), 3.79 (t, *J* = 4.9, 4H), 4.52 (t, *J* = 4.9, 4H), 7.50 (d, *J* = 8.4, 4H), 7.71 (d, *J* = 8.3, 4H), 7.74 (s, 2H), 8.18 (s, 2H). MS (ESI): *m/z* 670.3 [M + H^+].

Dimethyl (1^{4}Z,11^{4}Z,3Z,8E)-6-butyl-1^{1}H,11^{1}H-14,17-dioxa-6-aza-1,11(4,1)-ditriazola-2,10(1,4)-dibenzenacyclononadecaphane-3,8-diene-4,8-dicarboxylate (2b). VC1971

Compound **2b** was obtained as a white solid (29 mg, yield 17%) as the least polar fraction of the chromatographic purification. ^{1}H NMR (400 MHz, DMSO-d_6): 0.84 (t, *J* = 7.3, 3H), 1.18-1.27 (m, 2H), 1.38-1.45 (m, 2H), 2.43 (t, *J* = 6.9, 2H), 3.28 (s, 2H), 3.52-3.54 (m, 2H), 3.57-3.59 (m, 2H), 3.61 (s, 3H), 3.65 (s, 2H), 3.75 (s, 3H), 3.79 (t, *J* = 5.8, 2H), 3.84 (t, *J* = 4.7, 2H), 4.42 (t, *J* = 5.8, 2H), 4.57 (t, *J* = 5.8, 2H), 6.17 (s, 1H), 6.93 (d, *J* = 8.2, 2H), 7.50 (d, *J* = 8.3, 2H), 7.67 (s, 1H), 7.68 (d, *J* = 8.4, 2H), 7.72 (d, *J* = 8.5, 2H), 8.20 (s, 1H), 8.36 (s, 1H). MS (ESI): *m/z* 670.3 [M + H^+].

References

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2. Pelletier, G; Bechara, W. S.; Charette, A. B. Controlled and Chemoselective Reduction of Secondary Amides. *J. Am. Chem. Soc*. **2010**, *132*, 12817-12819. https://doi.org/10.1021/ja105194s