Synthesis of Macrocycles Containing 1,2,3-Triazole Motifs

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Abstract: A new procedure for the preparation of macrocycles containing 1,2,3-triazole motifs is developed. The macrocyclic precursor is constructed by repetition of a series of steps which include cycloaddition of an azide with an alkyne, alkylation of a carboxylic acid with propargyl bromide and formation of an azide from an amino group. The order of the steps and the size of the connected fragments are determined by the desired ring size. Chromatographic purification techniques for the poorly soluble final products are also described.

Key words: macrocycles, 1,2,3-triazole, cycloaddition, azidobenzoate, propargyl ester

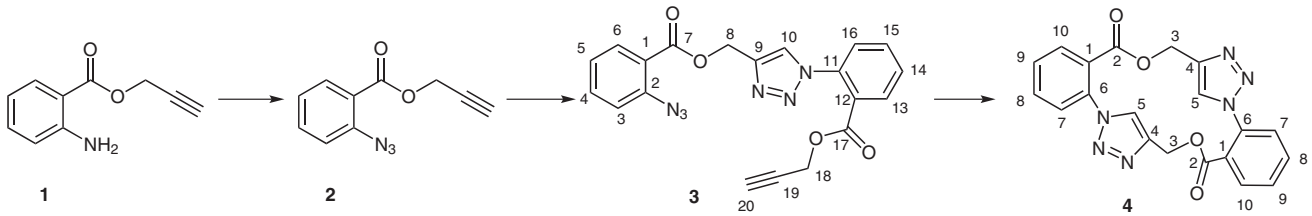
Numerous naturally occurring macrocyclic molecules are known, with examples comprising porphyrins, cyclopeptides and cyclic diterpenes. Some of these compounds display remarkable biological activity, and many of them (or their derivatives) are used as drugs.[1,2] Several other classes of macrocyclic compounds, including cyclophanes, crown ethers and glycophanes, are synthesized primarily in the laboratory.

Macrocycles containing a heterocyclic ring system possess a favorable binding site for metal ions[3] and can potentially act as molecular hosts.[4] Cyclophanes with triazole rings might be expected to exhibit increased complexing, chelating and solubilizing abilities due to the presence of a greater number of heteroatoms.[5] Macrocyclic compounds possessing triazole rings have been applied as optical and electrochemical chemosensors.[6] Intramolecular dipolar cycloaddition between azides and alkynes is a commonly used method for the synthesis of various macrocycles in which the 1,2,3-triazole moiety is a part of the macrocyclic unit.[7–12] This strategy has been well documented in a review article.[13]

The formation of macrocycle **4**, which contains a 16-membered ring, was observed during the preparation of 4*H*,6*H*-[1,2,3]triazolo[1,5-*a*][4,1]benzoxazepin-6-one derivatives.[14,15] The spontaneous dimerization of propargyl azidobenzoate **2** into dimer **3** requires a very long reaction time. The method employed for the cyclization of dimer **3** is useful for the preparation of macrocycle **4**, but it is not appropriate for the synthesis of molecules containing a larger ring system (Scheme 1).[14]

Based on our previous experience in this field,[14] we decided to develop a general method for the preparation of triazole-containing macrocycles of this type with various ring sizes.

The stepwise construction of the macrocycles was found to be a suitable strategy, and compound **4** was selected as the initial target. 2-Azidobenzoic acid (**6**) was used as the starting material and was itself prepared according to a previously described procedure.[16] This azido derivative was coupled with propargyl anthranilate (**1**),[14] and alkylation of the resulting carboxylic acid **7** with propargyl bromide yielded ester **8**. This ester was then transformed into azido derivative **3** via the diazonium salt. Compound **3** underwent cycloaddition to afford macrocycle **4**, as described previously[14] (Scheme 2). Azido derivative **3** and macrocycle **4** were compared with the previously prepared compounds and showed identical melting points, NMR spectra and high-resolution mass spectrometric data.



Scheme 1 Original preparation of macrocycle **4**

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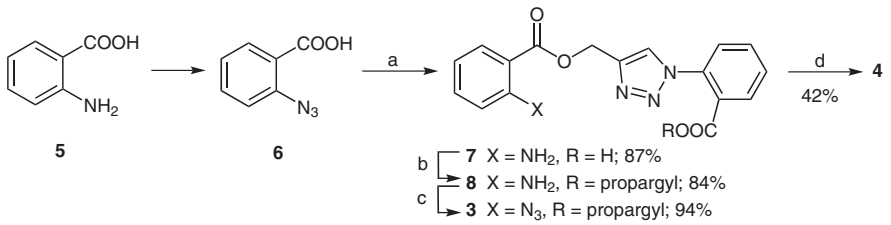
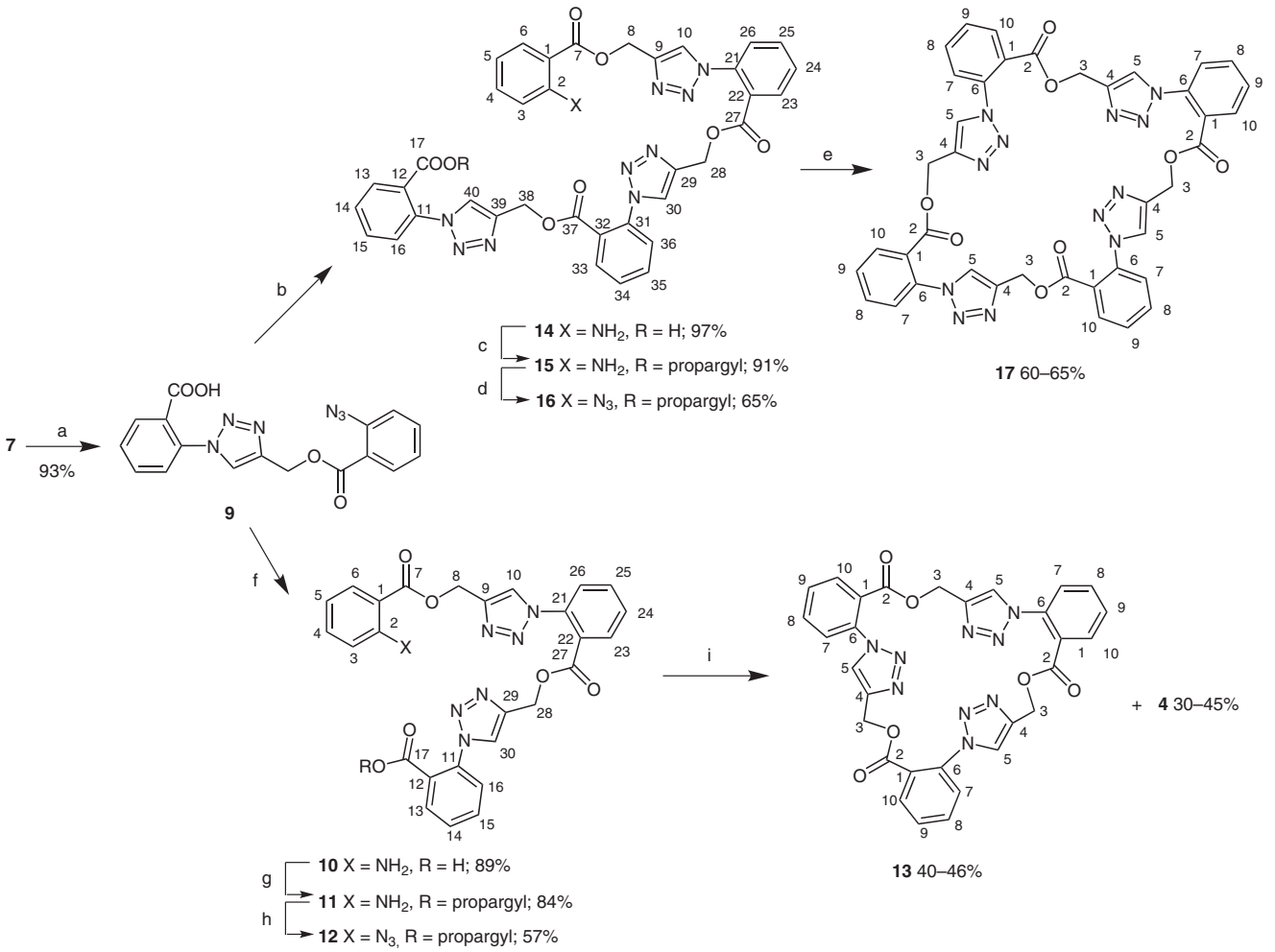


Scheme 2 Newly designed synthesis of macrocycle **4**. *Reagents and conditions*: (a) *n*-BuOH, H_2O, $CuSO_4$, ascorbic acid, **1**, r.t., 1 h; (b) DMF, K_2CO_3, propargyl bromide, r.t.; (c) acetone, HCl, $NaNO_2$, H_2O, 0 °C, then NaN_3, r.t., 0.5 h; (d) DMF, reflux, 1.5 h.

This experiment verified that it was possible to construct a macrocyclic ring via several consecutive steps. However, it was not practical to use the same approach for the construction of larger rings because the synthesis would be too long. Therefore, larger structural units were prepared in advance by cyclization of key azide **9**, itself prepared from amine **7**, with the appropriate propargyl esters to give **10** or **14**. The carboxylic acid group was then alkylated to form propargyl ester **11** or **15**, and the amino group was transformed into an azide to afford compounds **12** or **16**. The final macrocyclization was achieved via intramolecular dipolar cycloaddition (Scheme 3). Macrocycles **4**, **13** and **17** were produced in moderate yields ranging from 40–65%. The ^1H and ^{13}C NMR spectral data of compounds **4** and **7**–**17** are collated in Table 1. During the macrocyclization of derivative **12**, a significant amount of macrocycle **4** was formed in addition to the expected product **13**. The exact mechanism for this particular transformation is not known, but it probably involves initial formation of macrocycle **13** followed by a transesterification step to form the smaller ring macrocycle **4**.



Scheme 3 Synthesis of macrocycles **4**, **13** and **17**. *Reagents and conditions*: (a) acetone, HCl, $NaNO_2$, H_2O, 0 °C, then NaN_3, r.t., 0.5 h; (b) DMF, **8**, ascorbic acid, $CuSO_4$, H_2O, r.t.; (c) DMF, K_2CO_3, propargyl bromide, r.t.; (d) acetone, HCl, $NaNO_2$, H_2O, 0 °C, then NaN_3, r.t., 0.5 h; (e) DMF, reflux, or DMF, ascorbic acid, $CuSO_4$, H_2O, r.t., 0.5 h; (f) DMF, **1**, ascorbic acid, $CuSO_4$, H_2O, r.t.; (g) DMF, K_2CO_3, propargyl bromide, r.t.; (h) acetone, HCl, $NaNO_2$, H_2O, 0 °C, then NaN_3, r.t., 0.5 h; (i) DMF, reflux, or DMF, ascorbic acid, $CuSO_4$, H_2O, r.t.

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Table 1 ^{1}H and ^{13}C NMR Spectral Data (δ, ppm, DMSO-d_6) for Compounds **4** and **7**–**17**

	Product	Position	1	2	3	4	5	6	7	8	9	10	11
Amine	**7**[a]	δ_H	–	–	6.84	7.31	6.57	7.77	–	5.47	–	8.74	–
		δ_C	108.4	151.7	116.6	134.4	114.9	130.9	167.1	57.1	142.5	126.3	135.5
	10[b]	δ_H	–	–	6.83	7.30	6.55	7.72	–	5.44	–	8.71	–
		δ_C	108.4	151.7	116.7	134.4	114.9	130.9	167.1	57.2	142.6	126.2	135.5
	14[c]	δ_H	–	–	6.83	7.28	6.52	7.72	–	5.43	–	8.74	–
		δ_C	108.4	151.7	116.7	134.4	114.9	130.9	167.1	57.2	142.6	126.2	135.4
Ester	**8**[d]	δ_H	–	–	6.84	7.31	6.57	7.77	–	5.49	–	8.74	–
		δ_C	108.4	151.7	116.6	134.4	114.9	130.9	167.1	57.1	142.5	126.3	135.5
	11[e]	δ_H	–	–	6.82	7.29	6.54	7.78	–	5.43	–	8.72	–
		δ_C	108.4	151.6	116.6	134.4	114.9	130.9	167.0	57.1	142.6	126.2	135.4
	15[f]	δ_H	–	–	6.83	7.29	6.55	7.76	–	5.43	–	8.72	–
		δ_C	108.4	151.6	116.6	134.4	114.9	130.9	167.1	57.1	142.6	126.1	135.4
Azide	**9**	δ_H	–	–	7.47	7.71	7.33	7.85	–	5.52	–	8.75	–
		δ_C	122.2	139.2	120.9	133.8	125.1	131.3	164.4	58.1	141.8	126.5	135.3
	12	δ_H	–	–	7.45	7.68	7.30	7.85	–	5.46	–	8.74	–
		δ_C	122.1	139.2	120.8	133.8	125.0	130.8	164.2	58.0	142.1	126.4	135.4
	16	δ_H	–	–	7.45	7.68	7.30	7.85	–	5.46	–	8.74	–
		δ_C	121.1	139.2	120.8	133.8	125.0	130.8	164.2	58.0	142.1	126.4	135.4
Macro-cycle	**4**	δ_H	–	–	7.65	7.90	7.84	8.15	–	5.22	–	8.44	–
		δ_C	127.0	135.5	127.3	133.7	130.6	131.5	165.0	58.1	141.4	127.1	–
	13	δ_H	–	–	7.67	7.89	7.81	8.11	–	5.23	–	8.37	–
		δ_C	127.0	134.9	126.1	133.5	130.5	131.0	165.1	58.5	141.7	126.6	–
	17	δ_H	–	–	7.67	7.82	7.73	7.94	–	5.24	–	8.21	–
		δ_C	126.7	134.9	126.1	133.3	130.6	130.9	165.1	58.5	141.4	125.8	–

	Product	Position	12	13	14	15	16	17	18	19	20	21	22
Amine	**7**[a]	δ_H	–	8.03	7.79	7.90	7.76	–	–	–	–	–	–
		δ_C	126.5	130.8	130.3	133.5	126.8	164.3	–	–	–	–	–
	10[b]	δ_H	–	8.03	7.78	7.80	7.76	–	–	–	–	–	–
		δ_C	127.0	130.8	130.3	133.4	126.8	166.6	–	–	–	–	–
	14[c]	δ_H	–	g	h	i	j	–	–	–	–	–	–
		δ_C	126.9	g	h	i	j	164.7	–	–	–	135.4	126.2
Ester	**8**[d]	δ_H	–	8.03	7.79	7.90	7.76	–	4.79	–	3.59	–	–
		δ_C	126.5	130.8	130.3	133.5	126.8	164.3	53.0	78.3	77.6	–	–
	11[e]	δ_H	–	8.05	7.77	7.88	7.77	–	4.79	–	3.60	–	–
		δ_C	126.4	130.8	130.4	133.4	126.8	164.2	53.0	78.3	77.7	133.4	126.9
	15[f]	δ_H	–	l	m	n	o	–	4.79	–	3.59	–	–
		δ_C	126.3	l	m	n	o	164.2	53.0	78.3	77.7	135.4	126.9

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Table 1 ^{1}H and ^{13}C NMR Spectral Data (δ, ppm, DMSO-d_6) for Compounds **4** and **7**–**17**

	Product	Position	12	13	14	15	16	17	18	19	20	21	22
Azide	**9**	δ_H	–	8.00	7.73	7.81	7.69	–	–	–	–	–	–
		δ_C	128.7	130.6	130.2	132.6	126.7	–	–	–	–	–	–
	12	δ_H	–	8.05	7.78	7.89	7.76	–	4.79	–	3.60	–	–
		δ_C	126.4	130.8	130.3	133.5	126.8	164.4	53.0	78.3	77.6	135.4	126.9
	16	δ_H	–	[q]	[r]	[s]	[t]	–	4.77	–	3.59	–	–
		δ_C	126.9	[q]	[r]	[s]	[t]	164.2	53.0	78.3	77.7	–	–
	Product	Position	23	24	25	26	27	28	29	30	31	32	33
Amine	**10**[b]	δ_H	8.03	7.78	7.80	7.76	–	–	–	–	–	–	–
		δ_C	130.8	130.3	133.4	126.8	166.6	–	–	–	–	–	–
	14[c]	δ_H	[g]	[h]	[i]	[j]	–	5.28	–	8.38	–	–	[g,k]
		δ_C	[g]	[h]	[i]	[j]	164.7	58.5	141.5	126.6	135.4	126.9	[g,k]
Ester	**11**[e]	δ_H	8.02	7.88	7.88	7.77	–	5.36	–	8.55	–	–	–
		δ_C	130.8	130.3	133.4	126.8	164.7	58.3	141.5	126.4	–	–	–
	15[f]	δ_H	[l]	[m]	[n]	[o]	–	5.35	–	8.55	–	–	[l,p]
		δ_C	[l]	[m]	[n]	[o]	164.7	58.3	141.5	126.3	135.4	126.9	[l,p]
Azide	**12**	δ_H	8.01	7.76	7.89	7.76	–	5.34	–	8.64	–	–	–
		δ_C	130.8	130.2	134.4	126.8	164.7	58.2	141.5	126.4	–	–	–
	16	δ_H	[q]	[r]	[s]	[t]	–	5.46	–	8.74	–	–	[q,u]
		δ_C	[q]	[r]	[s]	[t]	164.2	58.2	142.1	126.4	135.4	126.9	[q,u]

[a] δ_H 6.76 (NH_2).
[b] δ_H 6.74 (NH_2).
[c] δ_H 6.76 (NH_2).
[d] δ_H 6.76 (NH_2).
[e] δ_H 6.74 (NH_2).
[f] δ_H 6.74 (NH_2).
[g] δ_H 8.01–8.05, δ_C 2 × 130.84, 130.82.
[h] δ_H 7.74–7.78, δ_C 130.34, 130.29 or 130.27 [+ C(34)H].
[i] δ_H 7.80–7.88, δ_C 2 × 133.35, 133.32 [+ C(35)H].
[j] δ_H 7.74–7.78, δ_C 126.78, 126.75 or 126.67 [+ C(36)H].
[k] δ_H –, δ_C 164.7 (37); δ_H 5.31, δ_C 58.3 (38); δ_H –, δ_C 141.3 (39); δ_H 8.54, δ_C 126.5 (40).
[l] δ_H 8.01–8.06, δ_C 130.83, 130.81 or 130.74.
[m] δ_H 7.73–7.79, δ_C 130.35, 130.29, 130.21 [+ C(34)H].
[n] δ_H 7.84–7.94, δ_C 133.54, 133.33 or 133.31 [+ C(35)H].
[o] δ_H 7.73–7.79, δ_C 126.81, 126.71 or 126.68 [+ C(36)H].
[p] δ_H –, δ_C 164.7 (37); δ_H 5.31, δ_C 58.3 (38); δ_H –, δ_C 141.5 (39); δ_H 8.53, δ_C 126.3 (40).
[q] δ_H 8.00–8.04, δ_C 130.80, 130.36, 130.27.
[r] δ_H 7.73–7.79, δ_C 130.35, 130.29 or 130.25 [+ C(34)H].
[s] δ_H 7.82–7.90, δ_C 133.82, 133.56 or 133.34 [+ C(35)H].
[t] δ_H 7.73–7.78, δ_C 126.86, 126.84, 126.82 [+ C(36)H].
[u] δ_H –, δ_C 164.2 (37); δ_H 5.46, δ_C 58.2 (38); δ_H –, δ_C 142.1 (39); δ_H 8.74, δ_C 126.4 (40).

Purification of the prepared macrocycles was problematic as their solubility in organic solvents was quite low. For example, they were found to precipitate from hot *N*,*N*-dimethylformamide. The best method found to purify the products was to prepare solutions of the macrocycles in acetic acid or acetic acid containing hydrochloric acid and then to purify the solution by column chromatography. A detailed purification procedure is described below.

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The major contribution of the article is the new method that makes it possible to synthesize these macrocycles from simple compounds such as 2-azidobenzoic acid, propargyl bromide and propargyl anthranilate through sequential steps. These macrocycles may be interesting owing to their ability to form very strong complexes with metals.

Analytical TLC was performed on DC-Fertigfolien Polygram Sil G/UV254 plates from Macherey-Nagel. The products were purified by column chromatography on Silia Flash P60 230–400 mesh silica gel from company Silicycle. Melting points were recorded on a Köfler apparatus and are uncorrected. IR spectra were recorded with a Nicolet iS10 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C) and on a Bruker Avance II 400 spectrometer (400.13 MHz for ^{1}H, 100.56 MHz for ^{13}C) in DMSO-d_6. The ^{1}H and ^{13}C chemical shifts were referenced to TMS as the internal standard (δ = 0.0). All 2D experiments [gradient-selected (gs)-COSY, NOESY, gs-HMQC, gs-HMBC] were performed using Topspin 2.1 software. The numbering of carbons for NMR purposes is shown in Schemes 1 and 3. The numbering of the propargyl group is shown in Scheme 1. HRMS was performed on a Thermo Exactive (Orbitrap) instrument under ESI-MS conditions. All azides, especially **12** and **16**, have limited stability and must be used for another step as soon as possible. Petroleum ether (PE) refers to the fraction boiling in the 30–70 °C range. **CAUTION:** Although no problems were observed while handling the azido derivatives, these compounds may be explosive and are potentially dangerous!

Propargylation of Carboxylic Acids; General Procedure (GP 1)
To a soln of carboxylic acid **7**, **10** or **14** (6 mmol) in DMF (30 mL) was added K_2CO_3 (0.83 g, 6 mmol) and the mixture heated at reflux temperature for 5 min. After cooling to r.t., 80% propargyl bromide (0.89 g, 6 mmol) was added and the resulting mixture was stirred at the same temperature. Following complete consumption of the starting material (TLC, toluene–EtOAc–HCO_2H, 25:25:1), the mixture was filtered, poured into H_2O (400 mL) and the precipitated solid removed by filtration. If an emulsion formed, the mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layer separated and evaporated under reduced pressure. The oily residue was dissolved in EtOH–H_2O (6 mL, 1:2) after which PE (20 mL) was added to the soln. The precipitated solid was isolated by filtration and washed with H_2O and PE.

Azido Derivatives; General Procedure (GP 2)
Amino derivative **7**, **8**, **11** or **15** (2.5 mmol) was dissolved in acetone (20 mL) and treated with concd HCl (1 mL). The resulting mixture was cooled below 0 °C after which a soln of $NaNO_2$ (0.18 g, 2.6 mmol) in H_2O (3 mL) was added. The mixture was stirred for 5 min, and then a soln of NaN_3 (0.17 g, 2.6 mmol) in H_2O (3 mL) was added dropwise at the same temperature. The resulting mixture was stirred at r.t. until no starting material remained (ca. 30 min) (TLC, toluene–EtOAc–HCO_2H, 25:25:1), and was then poured into H_2O (50 mL). The precipitated crystalline material was filtered, washed with H_2O and air-dried. If an emulsion formed, the mixture was extracted with EtOAc (4 × 50 mL), and the combined extracts dried, concentrated and purified by column chromatography on silica gel (toluene–EtOAc, 2:1).

Cycloaddition; General Procedure (GP 3A)
Azido derivative **3**, **12** or **16** (2.5 mmol) was dissolved in DMF (40 mL) and the mixture heated at reflux temperature until the starting material had been consumed (TLC, toluene–EtOAc–HCO_2H, 25:25:1). The mixture was then poured into H_2O (400 mL), and the precipitated solid was filtered, washed with H_2O (3 × 50 mL) and purified.

Cycloaddition; General Procedure (GP 3B)
Azido derivative **12** or **16** (2.5 mmol), or a mixture of azido derivative **6** or **9** (2.5 mmol) and propargyl derivative **1** or **8** (2.5 mmol) was dissolved in DMF (25 mL). A soln of ascorbic acid (0.15 g, 0.85 mmol) in H_2O (2.5 mL) and a soln of $CuSO_4$ (0.09 g, 0.36 mmol) in H_2O (2.5 mL) were added, and the mixture was stirred at r.t. until the starting material had been consumed (ca. 30 min) (TLC, toluene–EtOAc–HCO_2H, 25:25:1). The soln was poured into a mixture of H_2O (200 mL) and ice (50 g) and the resulting solid precipitate was filtered, washed with H_2O and purified by column chromatography on silica gel (EtOAc).

Chromatographic Purification of the Macrocycles; General Procedure (GP 4)
The dried solid compound was dissolved in AcOH. If the product was insoluble in AcOH then it was instead dissolved in a minimal amount of a mixture of concd HCl–AcOH (15:85). This soln was separated on a silica gel column. The column was first eluted with toluene–EtOAc–HCO_2H (25:25:1) to remove unidentified impurities. The macrocyclic products were then gradually eluted with a mixture of EtOAc–HCO_2H (50:1). The fractions containing the product were separated and concentrated to dryness. The solid product was then stirred in a 5% aq soln of $(NH_4)_2CO_3$, filtered, washed with H_2O and dried to a constant weight.

Prop-2-yn-1-yl 2-(4-{[(2-Azidophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoate (3)
Azide **3** was prepared from **8** according to GP 2.

IR (neat, ATR): 3203, 2122, 2089, 1726, 1707, 1600, 1448, 1258, 1087, 1049, 775, 774 cm^{-1}.

Yield: 0.95 g (94%); white solid; mp 126–129 °C (Lit.[14] mp 131–133 °C).

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{15}N_6O_4$: 403.11493; found: 403.11487.

9,22-Dioxa-1,12,13,14,25,26-hexaazapentacyclo[22.2.1.1^{11,14}.0^{2,7}.0^{15,20}]octacosa-2,4,6,11(28),12,15,17,19,24(27),25-decaene-8,21-dione (4)
Macrocycle **4** was prepared from **3** according to GP 3A. The reaction time was 1.5 h.

Yield: 0.42 g (42%); white solid; mp 328–330 °C (DMF) (Lit.[14] mp 328–331 °C).

IR (neat, ATR): 3152, 3114, 1708, 1601, 1505, 1289, 1266, 1241, 1230, 1126, 1044, 833, 767, 710 cm^{-1}.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{15}N_6O_4$: 403.11493; found: 403.11465.

2-(4-{[(2-Aminophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic Acid (7)
To a soln of 2-azidobenzoic acid (**6**) (2.30 g, 14.10 mmol) in *n*-BuOH (100 mL) was added propargyl anthranilate (**1**) (2.47 g, 14.10 mmol) followed by ascorbic acid (0.8 g, 4.54 mmol) in H_2O (10 mL) and $CuSO_4$ (0.4 g, 1.6 mmol) in H_2O (5 mL). The mixture was stirred at r.t. until the complete disappearance of the starting material (ca. 1 h). The extent of reaction was monitored by TLC (*n*-hexane–EtOAc–HCO_2H, 7:3:0.2). A soln of Na_2SO_3 (0.5 g, 6.4 mmol) in H_2O (10 mL) was added, and the copper sulfide that precipitated was filtered and washed with EtOAc (10 mL). The aq layer was separated and extracted with EtOAc (2 × 25 mL). The combined organic layer was concentrated under reduced pressure. The resulting oily residue was dissolved in a mixture of EtOH (16 mL) and H_2O (34 mL), and then PE (50 mL) was added. After 1 h at r.t., the mixture was cooled to 0 °C and the precipitated crystals were filtered and washed with H_2O and PE.

Yield: 4.13 g (87%); yellow solid; mp 149–153 °C.

IR (neat, ATR): 3456, 3354, 2922, 2478, 1709, 1682, 1618, 1589, 1487, 1454, 1294, 1238, 1227, 1092, 1067, 1054, 765, 748, 693 cm^{-1}.

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ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{17}H_{15}N_4O_4$: 339.10878; found: 339.10863.

Prop-2-yn-1-yl 2-(4-{[(2-Aminophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoate (8)
Compound **8** was prepared from carboxylic acid **7** according to GP 1.

Yield: 1.9 g (84%); light-yellow solid; mp 106–109 °C.

IR (neat, ATR): 3441, 3327, 3246, 3116, 2123, 1721, 1684, 1620, 1488, 1373, 1289, 1243, 1162, 1121, 1095, 1052, 757, 705, 693 cm^{-1}.

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{20}H_{17}N_4O_4$: 377.12443; found: 377.12399.

2-(4-{[(2-Azidophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic Acid (9)
Azide **9** was prepared from **7** according to GP 2. The resulting emulsion was extracted and the solvent was removed. The residue was then dissolved in a soln of EtOH and H_2O (6 mL, 1:2), and the title compound was precipitated by the addition of PE.

Yield 0.85 g (93%); off-white solid; mp 73–76 °C.

IR (neat, ATR): 3145, 2936, 2607, 2137, 2102, 1723, 1578, 1490, 1246, 1232, 1125, 1069, 1052, 833, 762, 749, 693 cm^{-1}.

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{17}H_{13}N_6O_4$: 365.09928; found: 365.09914.

2-[4-({[2-(4-{[(2-Aminophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)phenyl]carbonyloxy}methyl)-1*H*-1,2,3-triazol-1-yl]benzoic Acid (10)
Carboxylic acid **10** was prepared from **9** according to GP 3B.

Yield: 1.2 g (89%); white solid; mp 92–95 °C.

IR (neat, ATR): 3466, 3369, 3150, 1731, 1683, 1614, 1505, 1290, 1265, 1232, 1163, 1124, 1083, 1047, 824, 793, 761 cm^{-1}.

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{27}H_{22}N_7O_6$: 540.16261; found: 540.16248.

(1-{2-[(Prop-2-yn-1-yloxy)carbonyl]phenyl}-1*H*-1,2,3-triazol-4-yl)methyl 2-(4-{[(2-Aminophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoate (11)
Compound **11** was prepared from carboxylic acid **10** (1.0 g, 1.85 mmol) in DMF (20 mL) according to GP 1. The oily residue was purified by column chromatography on silica gel (toluene–EtOAc, 3:1).

Yield: 0.9 g (84%); ochre solid; mp 81–87 °C.

IR (neat, ATR): 3476, 3380, 3275, 3147, 2126, 1727, 1683, 1612, 1587, 1505, 1289, 1258, 1232, 1161, 1123, 1086, 1045, 823, 794, 757, 696 cm^{-1}.

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{30}H_{24}N_7O_6$: 578.17826; found: 578.17840.

(1-{2-[(Prop-2-yn-1-yloxy)carbonyl]phenyl}-1*H*-1,2,3-triazol-4-yl)methyl 2-(4-{[(2-Azidophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoate (12)
Azide **12** was prepared from compound **11** according to GP 2. The resulting emulsion was extracted, the solvent removed and the residue purified by column chromatography.

Yield: 0.86 g (57%); yellow oil.

IR (neat, ATR): 2983, 2125, 1728, 1446, 1372, 1290, 1237, 1123, 1081, 1041, 760, 702 cm^{-1}.

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{30}H_{22}N_9O_6$: 604.16876; found: 604.16898.

9,22,35-Trioxa-1,12,13,14,25,26,27,38,39-nonaazaheptacyclo[35.2.1.1^{11,14}.1^{24,27}.0^{2,7}.0^{15,20}.0^{28,33}]dotetraconta-2,4,6,11(42),12,15,17,19,24(41),25,28(33),29,31,37(40),38-pentadecaene-8,21,34-trione (13) and 9,22-Dioxa-1,12,13,14,25,26-hexaazapentacyclo[22.2.1.1^{11,14}.0^{2,7}.0^{15,20}]octacosa-2,4,6,11(28),12,15,17,19,24(27),25-decaene-8,21-dione (4)
Macrocycles **13** and **4** were prepared from **12** according to GP 3A using a reaction time of 4.5 h. The two major products were separated by column chromatography according to GP 4.

Macrocycle 13
Yield: 0.6 g (40%); white solid; mp 129–133 °C.

IR (neat, ATR): 3143, 3010, 1717, 1603, 1503, 1460, 1381, 1287, 1252, 1122, 1083, 1043, 940, 761, 700 cm^{-1}.

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{30}H_{22}N_9O_6$: 604.16876; found: 604.16875.

Macrocycle 4
Yield: 0.45 g (45%).

Macrocycles **13** [0.7 g (46%)] and **4** [0.3 g (30%)] were also prepared by reacting azide **12** (1.5 g, 2.5 mmol) with ascorbic acid (0.176 g, 1 mmol) and a soln of $CuSO_4$ (0.10 g, 0.40 mmol) in H_2O (2.5 mL) according to GP 3B. The isolated solid was purified by column chromatography according to GP 4.

2-{4-[({2-[4-({[2-(4-{[(2-Aminophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)phenyl]carbonyloxy}methyl)-1*H*-1,2,3-triazol-1-yl]phenyl}carbonyloxy)methyl]-1*H*-1,2,3-triazol-1-yl}benzoic Acid (14)
Carboxylic acid **14** was prepared from compounds **9** and **8** according to GP 3B.

Yield: 1.8 g (97%); ochre solid; mp 110–114 °C.

IR (neat, ATR): 3467, 3367, 2961, 1720, 1689, 1616, 1603, 1503, 1456, 1289, 1240, 1122, 1085, 1042, 757, 701 cm^{-1}.

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{37}H_{29}N_{10}O_8$: 741.21643; found: 741.21590.

[1-(2-{[(1-{2-[(Prop-2-yn-1-yloxy)carbonyl]phenyl}-1*H*-1,2,3-triazol-4-yl)methoxy]carbonyl}phenyl)-1*H*-1,2,3-triazol-4-yl]methyl 2-(4-{[(2-Aminophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoate (15)
Compound **15** was prepared from carboxylic acid **14** (1.0 g, 1.35 mmol) in DMF (20 mL) according to GP 1.

Yield: 0.96 g (91%); white solid; mp 58–64 °C.

IR (neat, ATR): 3489, 3145, 1720, 1688, 1616, 1603, 1504, 1289, 1243, 1122, 1083, 1042, 758, 702 cm^{-1}.

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{40}H_{31}N_{10}O_8$: 779.23208; found: 779.23193.

[1-(2-{[(1-{2-[(Prop-2-yn-1-yloxy)carbonyl]phenyl}-1*H*-1,2,3-triazol-4-yl)methoxy]carbonyl}phenyl)-1*H*-1,2,3-triazol-4-yl]methyl 2-(4-{[(2-Azidophenyl)carbonyloxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoate (16)
Azide **16** was prepared from **15** according to GP 2. The resulting emulsion was extracted, the solvent removed and the residue purified by column chromatography.

Yield: 1.3 g (65%); yellow oil.

IR (neat, ATR): 2983, 2126, 1728, 1603, 1506, 1446, 1372, 1290, 1237, 1123, 1082, 1041, 762, 703 cm^{-1}.

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{40}H_{29}N_{12}O_8$: 805.22258; found: 805.22210.

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9,22,35,48-Tetraoxa-1,12,13,14,25,26,27,38,39,40,51,52-dodecaazanonacyclo[48.2.1.1^{11,14}.1^{24,27}.1^{37,40}.0^{2,7}.0^{15,20}.0^{28,33}.0^{41,46}]hexapentaconta-2,4,6,11(56),12,15,17,19,24(55),25,28,30,32,37(54),38,41(46),42,44,50(53),51-icosaene-8,21,34,47-tetrone (17)

Macrocycle **17** was prepared from **16** according to GP 3A using a reaction time of 2.5 h. The product was dissolved in AcOH–HCl (85:15), and this soln was purified by column chromatography (EtOAc).

Yield: 1.3 g (65%); white solid; mp 277–280 °C.

IR (neat, ATR): 3139, 3068, 1738, 1717, 1601, 1503, 1457, 1287, 1264, 1239, 1142, 1127, 1094, 1047, 764, 757, 767 cm^{-1}.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{29}N_{12}O_8$: 805.22258; found: 805.22247.

Macrocycle **17** was also prepared by reacting azide **16** (2.01 g, 2.5 mmol) in DMF (60 mL) with $CuSO_4$ (0.16 g, 0.64 mmol) and ascorbic acid (0.3 g, 1.7 mmol) according to GP 3B. The reaction time was 30 min.

Yield: 1.2 g (60%); mp 276–280 °C.

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