Macrocyclic Peptoids by Selective S-Acylation of Cysteine Esters

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Abstract: Optimized selective S-acylations of cysteine esters gave intermediates for the synthesis of macrocyclic peptoids by a benzotriazole-based method.

Key words: acylations, amino acids, macrocycles, heterocycles

Cysteine residues are common components of natural products such as insulin.[1] S-Acylated cysteines are potentially useful as intermediates for the synthesis of oxytocin-like peptides[2] or proteins through native chemical ligation. Cysteine β-thioesters are *S*-acyl isopeptides that can be converted into natural peptides through S-to-N intramolecular acyl-migration reactions.

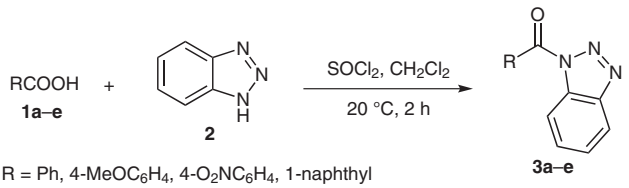
There are several previous reports on selective S-acylation reactions of cysteine esters. For example, Zervas and co-workers S-acylated cysteine esters in 52% overall yield through the reaction of an acyl chloride with a cysteine residue, followed by esterification;[1] Hedrick and co-workers synthesized *S*-acylcysteine esters through the reaction of an excess of an acyl chloride with ethyl cysteinate hydrochloride under vigorous conditions, followed by removal of residual acyl chloride by evaporation;[3] and Clark and co-workers selectively S-acylated α-cysteine amides with an acyl chloride in trifluoroacetic acid.[4]

In drug discovery, cyclic peptides and cyclic peptidomimetics are of interest as protein-binding molecules, because they have a greater conformational rigidity than their linear counterparts.[5] Small proteins frequently contain intermolecular side-chain constraints, often in the form of disulfide bonds between cysteine residues. Such disulfide bridges stabilize three-dimensional structures in otherwise flexible systems. Cyclotides[6,7] are small proteins that contain cysteine knot motifs that can be engineered to form β-hairpins.[8] Cyclization of oligopeptides can enhance their resistance to proteases[9] and improve their cell permeability.[10] Chemical strategies that have been employed to develop novel covalent intermolecular constraints include the formation of lactam or lactone bridges,[11,12] ring-closing olefin metathesis,[13] click chemistry,[14–16] and several other approaches.[11,17–19]

The importance of *S*-acylcysteines in various applications justifies the development of a mild and efficient method for the selective S-acylation of cysteine esters. In a previous communication,[2] we reported a preferential selective S-acylation (over N-acylation) of free cysteine with *N*-acylbenzotriazoles. Here, we report the selective S-acylation of cysteine esters under optimized conditions, the synthesis of macrocyclic peptoids by using the benzotriazole method, and the use of S-acylated cysteine esters as active intermediates.

Many reports describe the synthesis of cyclic peptides, but few include the use of functional groups in the side chain of the amino acid cysteine to build the ring. We succeeded in optimizing the reaction conditions for S-acylation of cysteine derivatives **7a**–**j** to give the corresponding thio esters **8a**–**h**, and we used the acylated derivatives **8b**, **8c**, and **8e** as active intermediates for the synthesis of macrocyclic peptoids.

First, we synthesized the *N*-acylbenzotriazoles **3a**–**e** by our previously reported method (Scheme 1).[20,21]



Scheme 1 Synthesis of *N*-acylbenzotriazoles **3a**–**e**

We then prepared the bisbenzotriazoles **5a**–**f** in 52–85% yield by treatment of the corresponding dicarboxylic acid with eight equivalents of 1*H*-1,2,3-benzotriazole and 2.2 equivalents of thionyl chloride in tetrahydrofuran at 20 °C for two hours (Table 1).

Treatment of the L-cysteine ester hydrochlorides **6a** and **6b** with the *N*-acylbenzotriazoles **3a**–**e** at 20 °C in aqueous tetrahydrofuran for three hours gave the corresponding *S*-acylcysteine esters **7a**–**j** exclusively in 50–73% yield (Table 2).

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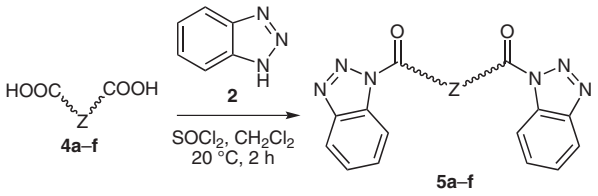
Table 1 Preparation of *N*-Acylbisbenzotriazoles **5a–f**



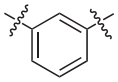
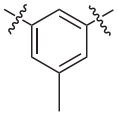
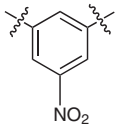
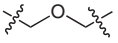
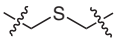
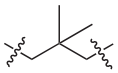
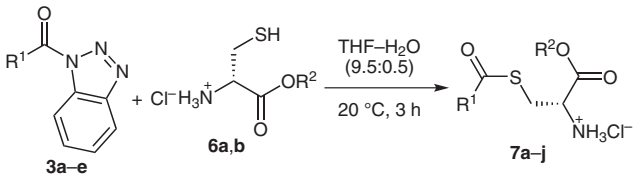
Product	Z	Yield (%)	Mp (°C)
5a		52	189–190[22]
5b		70	183–185
5c		68	200–202
5d		60	142–144[22]
5e		85	151–153[22]
5f		72	100–101[22]

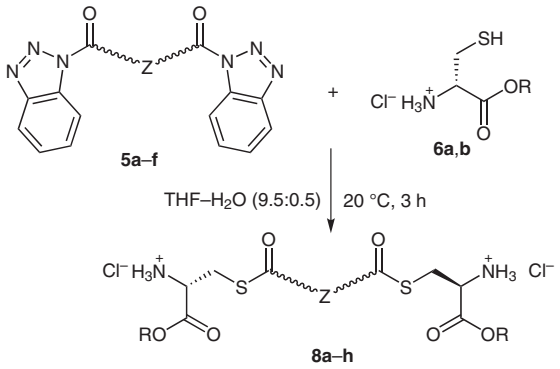
Table 2 Selective S-Acylation of Cysteine Ester Hydrochlorides **6a** and **6b** with *N*-Acylbenzotriazoles **3a–e**

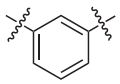
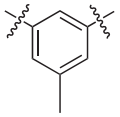
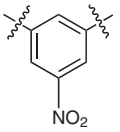
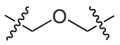
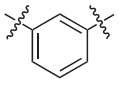
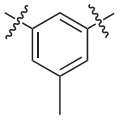
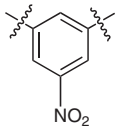
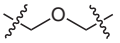


Product	R^1	R^2	Yield (%)	Mp (°C)
7a	Ph	Me	50	oil[4]
7b	4-Tol	Me	52	oil
7c	4-$MeOC_6H_4$	Me	51	177–79
7d	4-$O_2NC_6H_4$	Me	61	182–184
7e	1-naphthyl	Me	66	176–178
7f	Ph	Et	71	oil[23]
7g	4-Tol	Et	54	110–112
7h	4-$MeOC_6H_4$	Et	57	175–177
7i	4-$O_2NC_6H_4$	Et	68	oil
7j	1-naphthyl	Et	73	oil

Similarly, treatment of L-cysteine ester hydrochlorides **6a** and **6b** with the *N*-acylbisbenzotriazoles **5a–f** in aqueous tetrahydrofuran at room temperature for three hours gave the corresponding *S*-acylcysteines **8a–h** exclusively in 59–92% yields (Table 3).

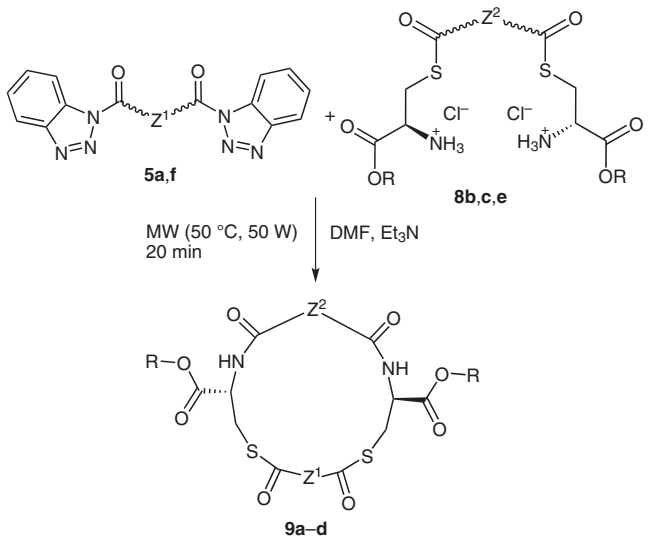
Table 3 Selective S-Acylation of Cysteine Ester Hydrochlorides **6a** and **6b** with *N*-Acylbisbenzotriazoles **5a–f**

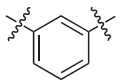
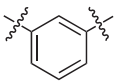
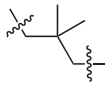
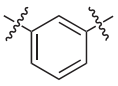
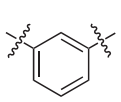
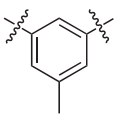
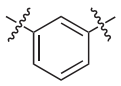
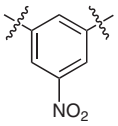


Product	Z	R	Yield (%)	Mp (°C)
8a		Me	70	163–164
8b		Me	61	165–167
8c		Me	66	219–220
8d		Me	65	oil
8e		Et	70	203–204
8f		Et	59	190–192
8g		Et	92	218–220
8h		Et	72	oil

Compounds **5a** and **5f** were treated with cysteine ester hydrochlorides **8b**, **8c**, and **8e** in the presence of four equivalents of triethylamine in *N*,*N*-dimethylformamide with microwave irradiation at 50 °C and 50 W power for 20 minutes to give the novel macrocyclic peptoids **9a–d** (64–72%) (Table 4). In this reaction sequence, compounds **8b**,

Table 4 Preparation of Macrocyclic Peptoids **9a–d**



Product	Z^1	Z^2	R	Yield (%)	Mp (°C)
9a			Et	64	oil
9b			Et	70	oil
9c			Me	72	oil
9d			Me	67	oil

8c, and **8e** underwent *S*- to *N*-acyl migration in the presence of triethylamine,[2] which reacted further with **5a** and **5f** *in situ* to give the desired macrocyclic peptoids **9a–d.** Examples of similar *S*- to *N*-acyl rearrangements have been previously observed.[24]

In summary, we have developed a method for selectively synthesizing *S*-acylcysteine esters in good yields by using *N*-acylbenzotriazoles and *N*-acylbisbenzotriazoles. The bis-*S*-acylcysteine esters were used as precursors for the synthesis of macrocyclic peptoids.

Commercial reagents were purchased from Sigma-Aldrich and were used without purification. Solvents were purified by distillation. Melting points were determined on a capillary melting-point apparatus equipped with a digital thermometer. NMR spectra were recorded in $CDCl_3$, or CD_3OD on Mercury or Gemini NMR spectrometers operating at 300 MHz for ^1H NMR (with TMS as an internal standard) or 75 MHz for ^{13}C NMR. Elemental analyses were performed on a Carlo Erba-EA1108 instrument.

All microwave-assisted reactions were carried out with a single-mode-cavity Discover Microwave Synthesizer (CEM Corp., Matthews, NC). The reaction mixtures were transferred into a 10-mL glass pressure microwave tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum, and the mixture was subjected to microwave irradiation (Discover mode; run time: 60 s; PowerMax-cooling mode).

Bis-1*H*-benzotriazoles 5a–f; General Procedure
The compounds were synthesized by using our established procedure.[22]

(5-Methylbenzene-1,3-diyl)bis(1*H*-benzotriazol-1-ylmethanone) (5b)
White microcrystals; yield: 0.150 g (70%); mp 183–185 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.82 (br s, 1 H), 8.38 (d, *J* = 8.4 Hz, 2 H), 8.31 (br s, 2 H), 8.14 (d, *J* = 8.4 Hz, 2 H), 7.71 (t, *J* = 7.7 Hz, 2 H), 7.54 (t, *J* = 7.8 Hz, 2 H), 2.60 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 146.0, 139.2, 136.9, 132.5, 132.4, 132.1, 130.8, 126.8, 120.5, 115.0, 21.7.

Anal. Calcd for $C_{21}H_{14}N_6O_2$: C, 65.96; H, 3.69; N, 21.98. Found: C, 65.64; H, 3.66; N, 21.96.

(5-Nitrobenzene-1,3-diyl)bis(1*H*-benzotriazol-1-ylmethanone) (5c)
White microcrystals; yield: 0.170 g (68%); mp 200–202 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.41–9.40 (m, 1 H), 9.38 (d, *J* = 1.5 Hz, 2 H), 8.44 (d, *J* = 8.1 Hz, 2 H), 8.22 (d, *J* = 8.4 Hz, 2 H), 7.80 (t, *J* = 7.7 Hz, 2 H), 7.63 (t, *J* = 7.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 146.1, 139.8, 133.9, 132.1, 132.0, 131.5, 130.6, 127.4, 120.9, 115.0.

Anal. Calcd for $C_{20}H_{11}N_7O_4$: C, 58.11; H, 2.68; N, 23.72. Found: C, 58.08; H, 2.36; N, 23.60.

Alkyl *S*-Aroyl-L-cysteinates 7a–j; General Procedure
A solution of the cysteine ester hydrochloride **6a** or **6b** (0.843 mmol) in H_2O (0.5 mL) was added to a soln of the *N*-acylbenzotriazole derivative **3a–e** (0.843 mmol) in THF (10 mL), and the heterogeneous mixture was stirred at r.t. for 3 h. The solid was then collected by filtration, washed with Et_2O (3 × 30 mL), and dried in a desiccator under vacuum.

Methyl *S*-(4-Methylbenzoyl)-L-cysteinate Hydrochloride (7b)
Colorless oil; yield: 0.128 g (52%).

^1H NMR (300 MHz, CD_3OD): δ = 7.82 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 4.37 (t, *J* = 5.4 Hz, 1 H), 3.80 (s, 3 H), 3.68 (dd, *J* = 14.7, 4.8 Hz, 1 H), 3.52 (dd, *J* = 15.0, 6.3 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 191.3, 169.3, 147.0, 134.9, 130.8, 128.8, 54.3, 54.2, 29.4, 21.8.

HRMS: *m/z* $[M - HCl + Na]^+$ calcd for $C_{12}H_{15}NNaO_3S$: 276.0665; found: 276.0665.

Methyl *S*-(4-Methoxybenzoyl)-L-cysteinate Hydrochloride (7c)
White microcrystals; yield: 0.133 g (51%); mp 177–179 °C.

^1H NMR (300 MHz, CD_3OD): δ = 7.87 (d, *J* = 9.0 Hz, 2 H), 6.94 (d, *J* = 9.0 Hz, 2 H), 4.34 (t, *J* = 5.4 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.63 (dd, *J* = 14.9, 4.7 Hz, 1 H), 3.48 (dd, *J* = 14.9, 6.5 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 190.0, 169.3, 166.3, 131.0, 130.1, 115.3, 56.4, 54.3, 54.2, 29.4.

HRMS: *m/z* $[M - HCl + Na]^+$ calcd for $C_{12}H_{15}NNaO_4S$: 292.0614; found: 292.0623.

Methyl *S*-(4-Nitrobenzoyl)-L-cysteinate Hydrochloride (7d)
White microcrystals; yield: 0.165 g (61%); mp 182–184 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.39 (d, *J* = 9.0 Hz, 2 H), 8.22 (d, *J* = 9.0 Hz, 2 H), 4.52 (t, *J* = 5.6 Hz, 1 H), 3.89 (s, 3 H), 3.81 (dd, *J* = 13.3, 8.6 Hz, 1 H), 3.69 (dd, *J* = 15.0, 6.3 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 190.9, 169.1, 152.5, 141.9, 129.9, 125.3, 54.3, 54.1, 29.9.

HRMS: *m/z* [M – HCl + H]$^+$ calcd for $C_{11}H_{13}N_2O_5S$: 285.0545; found: 285.0545.

Methyl *S*-2-Naphthoyl-L-cysteinate Hydrochloride (7e)
White microcrystals; yield: 0.180 g (66%); mp 176–178 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.46 (d, *J* = 8.1 Hz, 1 H), 8.14 (d, *J* = 7.2 Hz, 1 H), 8.08 (d, *J* = 8.1 Hz, 1 H), 7.90 (d, *J* = 8.1 Hz, 1 H), 7.60–7.49 (m, 3 H), 4.51 (t, *J* = 5.6 Hz, 1 H), 3.84 (s, 3 H), 3.80–3.64 (m, 2 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 193.5, 169.3, 135.3, 135.1, 130.3, 129.9, 129.7, 129.4, 128.0, 126.2, 126.0, 125.8, 54.0, 31.0, 30.5.

HRMS: *m/z* [M – HCl + H]$^+$ calcd for $C_{15}H_{16}NO_3S$: 290.0845; found: 290.0846.

Ethyl *S*-(4-Methylbenzoyl)-L-cysteinate Hydrochloride (7g)
White microcrystals; yield: 0.139 g (54%); mp 110–112 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.90 (d, *J* = 8.7 Hz, 2 H), 7.36 (d, *J* = 7.8 Hz, 2 H), 4.45 (t, *J* = 5.4 Hz, 1 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 3.76 (dd, *J* = 14.9, 4.7 Hz, 1 H), 3.63 (dd, *J* = 15.0, 6.0 Hz, 1 H), 2.43 (s, 3 H), 1.33 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 191.2, 168.8, 146.9, 135.0, 130.8, 128.8, 64.3, 54.3, 29.4, 21.8, 14.5.

Anal. Calcd for $C_{13}H_{18}ClNO_3S·H_2O$: C, 48.52; H, 6.26; N, 4.35. Found: C, 49.10; H, 6.01; N, 4.87.

Ethyl *S*-(4-Methoxybenzoyl)-L-cysteinate Hydrochloride (7h)
White microcrystals; yield: 0.155 g (57%); mp 175–177 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.97 (d, *J* = 9.0 Hz, 2 H), 7.05 (d, *J* = 9.0 Hz, 2 H), 4.43 (t, *J* = 6.3 Hz, 1 H), 4.31 (q, *J* = 6.8 Hz, 2 H), 3.89 (s, 3 H), 3.73 (dd, *J* = 14.9, 5.0 Hz, 1 H), 3.59 (dd, *J* = 14.9, 6.2 Hz, 1 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 189.8, 168.7, 166.1, 130.9, 130.0, 115.3, 64.1, 55.9, 29.4, 25.3, 14.6.

HRMS: *m/z* [M – HCl + Na]$^+$ calcd for $C_{13}H_{17}NNaO_4S$: 306.0770; found: 306.0763.

Ethyl *S*-(4-Nitrobenzoyl)-L-cysteinate Hydrochloride(7i)
Colorless oil; yield: 0.192 g (68%).

^{1}H NMR (300 MHz, CD_3OD): δ = 8.39 (d, *J* = 9.0 Hz, 2 H), 8.22 (d, *J* = 9.0 Hz, 2 H), 4.51 (t, *J* = 5.6 Hz, 1 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 3.84 (dd, *J* = 15.0, 4.8 Hz, 1 H), 3.70 (dd, *J* = 15.0, 6.2 Hz, 1 H), 1.35 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 190.8, 168.6, 152.5, 141.9, 129.9, 125.3, 64.4, 54.1, 29.9, 14.5.

HRMS: *m/z* [M – HCl + Na]$^+$ calcd for $C_{12}H_{14}N_2NaO_5S$: 321.0516; found: 321.0526.

Ethyl *S*-2-Naphthoyl-L-cysteinate Hydrochloride (7j)
Colorless oil; yield: 0.210 g (73%).

^{1}H NMR (300 MHz, CD_3OD): δ = 8.51 (d, *J* = 8.1 Hz, 1 H), 8.18 (d, *J* = 7.2 Hz, 1 H), 8.12 (d, *J* = 8.1 Hz, 1 H), 7.94 (d, *J* = 8.4 Hz, 1 H), 7.66–7.53 (m, 3 H), 4.53 (t, *J* = 5.6 Hz, 1 H), 4.33 (q, *J* = 7.0 Hz, 2 H), 3.82 (dd, *J* = 15.0, 5.1 Hz, 1 H), 3.72 (dd, *J* = 14.9, 5.9 Hz, 1 H), 1.33 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 193.4, 168.8, 135.3, 135.1, 130.3, 129.9, 129.7, 129.4, 128.0, 126.0, 125.8, 64.3, 54.0, 30.4, 14.5.

HRMS: *m/z* [M – HCl + Na]$^+$ calcd for $C_{16}H_{17}NNaO_3S$: 326.0821; found: 326.0812.

Dialkyl *S*,*S*′-Arylene- and *S*,*S*′-Alkylenebis-L-cysteinates 8a–h; General Procedure
A soln of cysteine ester hydrochloride **6a** or **6b** (0.542 mmol) in H_2O (0.5 mL) was added to a soln of a bisbenzotriazole derivative **5a–f** (0.271 mmol) in THF (10 mL), and the heterogeneous mixture was at r.t. for 3 h. The solid collected by filtration, washed with Et_2O (3 × 30 mL), and dried in a desiccator under vacuum.

Dimethyl (2*S*,2′*S*)-3,3′-[Benzene-1,2-diylbis(carbonylsulfanediyl)]bis(2-aminopropanoate) Dihydrochloride (8a)
White microcrystals; yield: 0.180 g (70%); mp 163–164 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.43 (s, 1 H), 8.21 (d, *J* = 7.8 Hz, 2 H), 7.68 (t, *J* = 8.0 Hz, 1 H), 4.44 (t, *J* = 5.4 Hz, 2 H), 3.80 (s, 6 H), 3.75 (dd, *J* = 14.9, 4.7 Hz, 2 H), 3.61 (dd, *J* = 14.9, 6.2 Hz, 2 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 191.1, 169.2, 138.1, 133.9, 131.3, 127.0, 54.3, 54.1, 29.7.

Anal. Calcd for $C_{16}H_{22}Cl_2N_2O_6S_2·H_2O$: C, 39.11; H, 4.92; N, 5.70. Found: C, 39.33; H, 4.75; N, 5.13.

Dimethyl (2*S*,2′*S*)-3,3′-[5-Methylbenzene-1,2-diylbis(carbonylsulfanediyl)]bis(2-aminopropanoate) Dihydrochloride (8b)
White microcrystals; yield: 0.161 g (61%); mp 165–167 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.24 (br s, 1 H), 8.02 (br s, 2 H), 4.43 (t, *J* = 5.4 Hz, 2 H), 3.81 (s, 6 H), 3.74 (dd, *J* = 15.0, 4.8 Hz, 2 H), 3.60 (dd, *J* = 15.0, 6.0 Hz, 2 H), 2.44 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 199.6, 177.7, 150.5, 146.6, 142.7, 132.9, 62.8, 62.6, 38.2, 29.8.

Anal. Calcd for $C_{17}H_{24}Cl_2N_2O_6S_2$: C, 41.89; H, 4.96; N, 5.75. Found: C, 42.05; H, 4.84; N, 5.81.

Dimethyl (2*S*,2′*S*)-3,3′-[5-Nitrobenzene-1,2-diylbis(carbonylsulfanediyl)]bis(2-aminopropanoate) Dihydrochloride (8c)
White microcrystals; yield: 0.175 g (66%); mp 219–220 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.86 (d, *J* = 1.5 Hz, 2 H), 8.69 (t, *J* = 1.5 Hz, 1 H), 4.47 (t, *J* = 5.4 Hz, 2 H), 3.84–3.76 (m, 8 H), 3.65 (dd, *J* = 15.0, 6.3 Hz, 2 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 189.7, 169.0, 150.3, 139.4, 131.9, 127.5, 54.4, 54.0, 30.1.

Anal. Calcd for $C_{16}H_{21}Cl_2N_3O_8S_2·HCl$: C, 34.64; H, 4.00; N, 7.57. Found: C, 35.07; H, 3.51; N, 7.46.

Methyl (4*S*,14*S*)-4,14-Diamino-3,7,11-trioxo-2,9-dioxa-6,12-dithiapentadecan-15-oate Dihydrochloride (8d)
Colorless oil; yield: 0.156 g (65%).

^{1}H NMR (300 MHz, CD_3OD): δ = 4.40 (d, *J* = 1.5 Hz, 4 H), 4.34 (t, *J* = 5.6 Hz, 2 H), 3.79 (s, 6 H), 3.54 (dd, *J* = 14.9, 4.7 Hz, 2 H), 3.39 (dd, *J* = 14.7, 6.3 Hz, 2 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 199.6, 169.2, 77.4, 54.2, 54.1, 28.4.

HRMS: *m/z* [M – 2HCl + Na]$^+$ calcd for $C_{12}H_{20}N_2NaO_7S_2$: 391.0604; found: 391.0610.

Diethyl (2*S*,2′*S*)-3,3′-[Benzene-1,2-diylbis(carbonylsulfanediyl)]bis(2-aminopropanoate) Dihydrochloride (8e)
White microcrystals; yield: 0.190 g (70%); mp 203–204 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.42–8.39 (m, 1 H), 8.21–8.16 (m, 2 H), 7.65 (t, *J* = 7.8 Hz, 1 H), 4.40 (t, *J* = 5.4 Hz, 2 H), 4.23 (q, *J* = 7.1 Hz, 4 H), 3.72 (dd, *J* = 14.9, 4.7 Hz, 2 H), 3.60 (dd, *J* = 15.0, 6.0 Hz, 2 H), 1.23 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 190.9, 168.6, 138.1, 133.8, 131.3, 126.9, 64.3, 54.1, 29.7, 14.5.

Anal. Calcd for $C_{18}H_{26}Cl_2N_2O_6S_2$·HCl: C, 40.19; H, 5.06; N, 5.21. Found: C, 39.92; H, 4.90; N, 6.03.

Diethyl (2*S*,2′*S*)-3,3′-[5-Methylbenzene-1,2-diylbis(carbonylsulfanediyl)]bis(2-aminopropanoate) Dihydrochloride (8f)
White microcrystals; yield: 0.165 g (59%); mp 190–192 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.20 (s, 1 H), 7.98 (s, 2 H), 4.40 (t, *J* = 5.7 Hz, 2 H), 4.22 (q, *J* = 7.1 Hz, 4 H), 3.72 (dd, *J* = 15.0, 4.8 Hz, 2 H), 3.60 (dd, *J* = 14.9, 6.2 Hz, 2 H), 2.41 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 190.9, 168.6, 142.0, 138.0, 134.2, 124.4, 64.3, 54.1, 29.7, 21.4, 14.5.

Anal. Calcd for $C_{19}H_{28}Cl_2N_2O_6S_2$: C, 44.27; H, 5.47; N, 5.43. Found: C, 44.67; H, 5.44; N, 5.52.

Diethyl (2*S*,2′*S*)-3,3′-[5-Nitrobenzene-1,2-diylbis(carbonylsulfanediyl)]bis(2-aminopropanoate) Dihydrochloride (8g)
White microcrystals; yield: 0.237 g (92%); mp 218–220 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.90 (br s, 2 H), 8.73 (br s, 1 H), 4.48 (t, *J* = 5.4 Hz, 2 H), 4.28 (q, *J* = 7.2 Hz, 4 H), 3.83 (dd, *J* = 14.9, 4.7 Hz, 2 H), 3.69 (dd, *J* = 15.0, 6.3 Hz, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 189.7, 168.6, 150.3, 139.5, 131.9, 127.5, 64.5, 54.0, 30.1, 14.5.

Anal. Calcd for $C_{18}H_{25}Cl_2N_3O_8S_2$·HCl: C, 37.09; H, 4.50; N, 7.21. Found: C, 37.07; H, 4.05; N, 7.47.

Ethyl (5*S*,15*S*)-5,15-Diamino-4,8,12-trioxo-3,10-dioxa-7,13-dithiahexadecan-16-oate Dihydrochloride (8h)
Colorless oil; yield: 0.185 g (72%).

^{1}H NMR (300 MHz, CD_3OD): δ = 4.41 (d, *J* = 2.1 Hz, 4 H), 4.34 (t, *J* = 5.4 Hz, 2 H), 4.26 (q, *J* = 7.1 Hz, 4 H), 3.56 (dd, *J* = 15.0, 4.5 Hz, 2 H), 3.42 (dd, *J* = 14.9, 6.2 Hz, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 199.5, 168.7, 77.4, 64.3, 54.8, 28.4, 14.5.

HRMS: *m/z* [M – 2HCl + Na]$^+$ calcd for $C_{14}H_{24}N_2NaO_7S_2$: 419.0917; found: 419.0919.

Macrocycles 9a–d; General Procedure
A mixture of the *N*-acylbenzotriazole derivative **5a** or **5g** (0.399 mmol), *S*-acylated cysteine ester dihydrochloride **8b**, **8c**, or **8e** (0.399 mmol), and Et_3N (1.596 mmol) in DMF (5 mL) was irradiated in a microwave oven at 50 °C and 20 W for 20 min. The soln was poured onto crushed ice and the mixture was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with sat. aq Na_2CO_3, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography.

Diethyl (5*S*,15*S*)-2,7,13,18-Tetraoxo-3,17-dithia-6,14-diazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8(24),9,11,19,21-hexaene-5,15-dicarboxylate (9a)
Colorless oil; yield: 0.143 g (64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (t, *J* = 1.7 Hz, 1 H), 8.02–7.90 (m, 5 H), 7.57–7.47 (m, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 5.29–5.21 (m, 2 H), 4.29 (q, *J* = 7.2 Hz, 4 H), 3.90 (dd, *J* = 14.1, 4.2 Hz, 2 H), 3.40 (dd, *J* = 14.1, 8.7 Hz, 2 H), 1.35 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.7, 170.2, 166.8, 137.9, 134.6, 131.7, 130.6, 129.7, 129.4, 128.6, 126.3, 62.6, 52.0, 31.8, 14.4.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{26}H_{26}N_2NaO_8S_2$: 581.1023; found: 581.1036.

Diethyl (4*S*,14*S*)-9,9-Dimethyl-2,7,11,16-tetraoxo-6,12-dithia-3,15-diazabicyclo[15.3.1]henicosa-1(21),17,19-triene-4,14-dicarboxylate (9b)
Colorless oil; yield: 0.155 g (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 7.8 Hz, 1.5 Hz, 2 H), 7.74 (br s, 1 H), 7.50 (t, *J* = 7.7 Hz, 1 H), 7.03 (d, *J* = 7.2 Hz, 2 H), 4.96–4.89 (m, 2 H), 4.26–4.18 (m, 4 H), 3.54 (dd, *J* = 14.6, 4.1 Hz, 2 H), 3.43 (dd, *J* = 14.4, 6.3 Hz, 2 H), 2.74 (d, *J* = 15.0 Hz, 2 H), 2.68 (d, *J* = 15.3 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 6 H), 0.99 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.7, 170.2, 167.1, 134.5, 131.7, 129.5, 123.5, 62.3, 53.2, 52.2, 35.0, 30.4, 28.9, 14.3.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{25}H_{33}N_2O_8S_2$: 553.1673; found: 553.1651.

Dimethyl (5*S*,15*S*)-10-Methyl-2,7,13,18-tetraoxo-3,17-dithia-6,14-diazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8(24),9,11,19,21-hexaene-5,15-dicarboxylate (9c)
Colorless oil; yield: 0.156 g (72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.36 (t, *J* = 1.8 Hz, 1 H), 7.95 (dd, *J* = 8.4 Hz, 1.8 Hz, 2 H), 7.71–7.68 (m, 3 H), 7.49 (t, *J* = 7.7 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 5.28–5.20 (m, 2 H), 3.87–3.83 (m, 2 H), 3.81 (s, 6 H), 3.41 (dd, *J* = 14.3 Hz, 8.6 Hz, 2 H), 2.38 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.7, 170.8, 166.9, 139.6, 137.9, 134.5, 131.7, 131.3, 129.7, 128.6, 123.5, 53.3, 51.9, 31.7, 21.4.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{25}H_{25}N_2O_8S_2$: 545.1047; found: 545.1033.

Dimethyl (5*S*,15*S*)-10-Nitro-2,7,13,18-tetraoxo-3,17-dithia-6,14-diazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8(24),9,11,19,21-hexaene-5,15-dicarboxylate (9d)
Colorless oil; yield: 0.155 g (67%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (d, *J* = 1.5 Hz, 2 H), 8.35 (t, *J* = 1.7 Hz, 1 H), 8.27 (t, *J* = 1.4 Hz, 1 H), 7.99 (dd, *J* = 7.7, 1.7 Hz, 2 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 7.30 (d, *J* = 8.7 Hz, 2 H), 5.34–5.28 (m, 2 H), 3.99–3.90 (m, 2 H), 3.86 (s, 6 H), 3.41 (dd, *J* = 14.3 Hz, 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.7, 170.4, 164.7, 148.8, 137.7, 136.3, 131.9, 131.8, 129.9, 128.5, 125.3, 53.5, 52.3, 31.6.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{21}N_3NaO_{10}S_2$: 598.0561; found: 598.0572.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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