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# Diaminoterephthalates: Scaffolds for Combinatorial Chemistry

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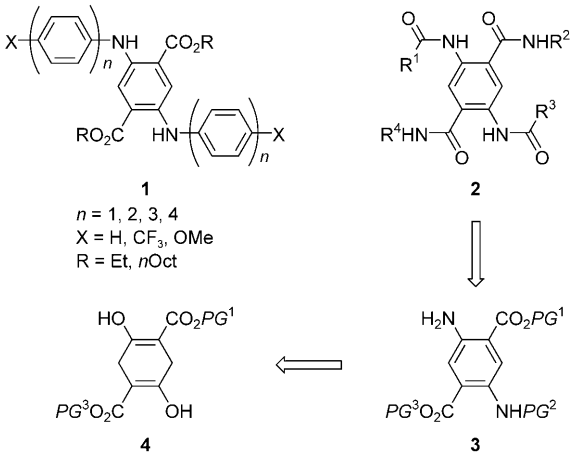
*In memory of Professor Peter Köll*

**Abstract:** 2,5-Diaminoterephthalates that possess four points of diversification are introduced as new scaffolds for combinatorial chemistry. A straightforward synthesis of an orthogonally protected platform compound was developed. This platform was transformed by stepwise deprotection and amidation of the two amino and two carboxylic acid moieties into tetra-amides with a central aromatic ring as a fluorescence chromophore.

**Keywords:** amino acids · carboxamides · combinatorial chemistry · fluorescence · terephthalates

## Introduction

2,5-Diaminoterephthalates are intensively colored fluorescent materials that are easily prepared by the enamine formation of succinyl succinates with primary amines followed by oxidative aromatization.[1] When anilines are used as amines, this reaction is a key step in the industrial synthesis of quinacridone pigments.[2] We recently prepared symmetric ($D_{2h}$) diaminoterephthalates **1** with two biphenyl, terphenyl, or quaterphenyl moieties as new fluorescent materials (Scheme 1).[3] In an extension of this study, we report the development of compounds **2** as colored and fluorescent scaffolds with four different effector groups $R^1$–$R^4$. Fluorescence is an interesting feature in high-throughput synthesis and biological essays. In particular, we aim to access tetra-amides **2** derived from two carboxylic acids $R^1CO_2H$ and $R^3CO_2H$ and two amines $R^2NH_2$ and $R^4NH_2$. A precondition for this project would be the availability of an orthogonally protected ($PG^1$–$PG^3$) platform, that is, compound **3**, which might be prepared from mixed succinyl succinate **4**.




Scheme 1. Synthetic plan for 2,5-diaminoterephthalate derivatives **2**. PG = protecting group.

## Results and Discussion

Succinyl succinates **4** are prepared by the Dieckmann condensation of succinates; however, only cases with two equal ester groups have been reported so far.[4] Herein, benzyl and methyl ester were chosen as carboxylate protective groups $PG^1$ and $PG^3$. Mixed ester **6** was prepared in almost quantitative yield by the methylation of mono-benzyl succinate **5** (Scheme 2). The preparation of compound **6** by a conjugate addition reaction has been reported previously.[5] The inter- and intramolecular Claisen condensation of mixed ester **6** gave a mixture of benzyl methyl succinyl succinates **4a–c**, which were separated by crystallization followed by column chromatography. Acidification of the reaction mixture

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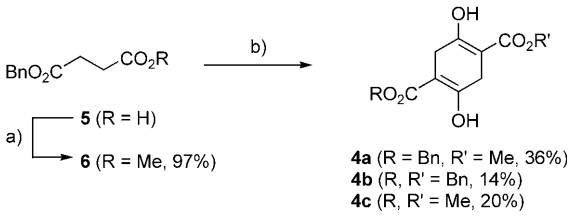
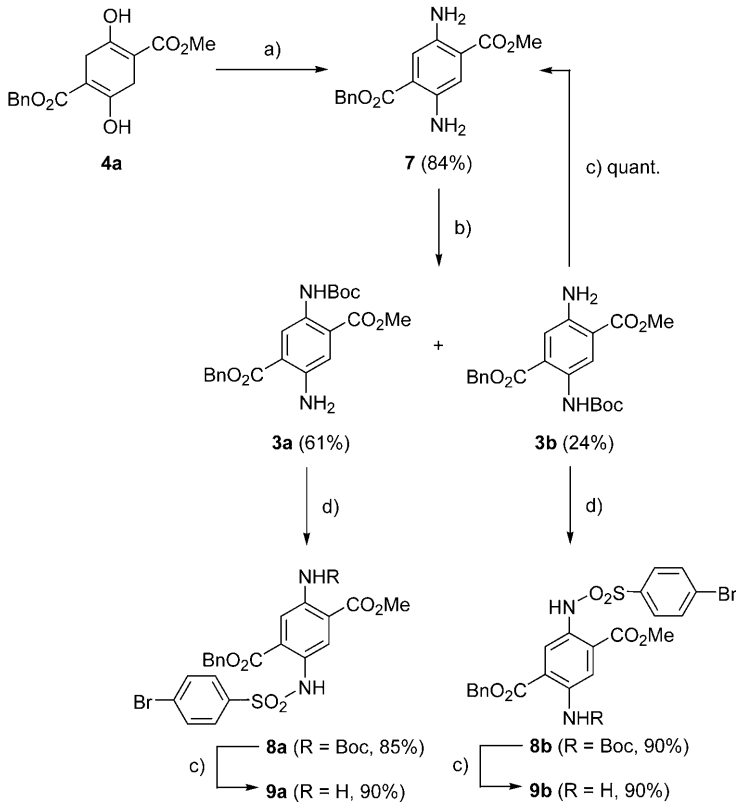



Scheme 2. Synthesis of succinyl succinates **4a–c**. a) MeI, $Na_2CO_3$, DMF, 4 h, 23 °C; b) 1. NaH, DMSO, 0.5 h, 0 °C; 3 h, 23 °C; 2. HCl, $H_2O$; 3. recrystallization; 4. isolation by column chromatography. DMSO = dimethyl sulfoxide.

during the workup must be carried out with cooling and careful control of the temperature. If the temperature raises significantly over 23 °C, the esters oxidize with air to give hydroquinone dicarboxylates. Symmetric esters **4b** and **4c** are known compounds,[4] mixed ester **4a** was obtained in moderate yield (36 %), though multigram amounts were obtained.

Oxidative aminolysis of diester **4a** was performed with an ethanolic solution of $NH_3$. Saponification or transesterification was not observed. The transformation has to be performed in the following manner: The bis-enamine was formed readily within one hour at 60 °C. The mixture was buffered by the addition of HCl, and oxidation proceeded slowly at 60 °C. If the reaction is performed with a buffered system from the beginning, enamine formation is slow relative to oxidation and hydroquinone dicarboxylates and aminophenol dicarboxylates are formed as hardly separable byproducts. A solution of $NH_3$ in EtOH (ca. 15 mol dm$^{-3}$ by titration) was prepared by storing a beaker of EtOH and a large amount of a 25 % aqueous $NH_3$ in a desiccator for two days. After chromatography, diamino terephthalate **7** was obtained in good yield (Scheme 3). The conversion of diamine **7** with one equivalent of $Boc_2O$ in dichloromethane gave regioisomeric carbamates **3a** and **3b**, which were separable by column chromatography. Only the major isomer **3a** was used in further studies. The other regioisomer **3b** was collected and deprotected with TFA to recycle diamine **7**. We planned to prove the constitution of major isomer **3a** (or by-product **3b**) by using X-ray single-crystal studies. To obtain crystalline materials, we prepared bromobenzene sulfonamides **8a** and **8b**, which did not, however, give suitable crystals. Therefore, we deprotected carbamates **8a** and **8b**, and, indeed, anilines **9a** and **9b** gave suitable single crystals. An ORTEP representation of the molecular structure of **9a** in the solid state is given in Figure 1.[6]

As the first explorative example of a final tetracarboxamide **2**, we prepared **2a** with four β-alanine (β-Ala) moieties bound to the central aromatic fluorescent scaffold (Scheme 4). The amidation of the aromatic $NH_2$ groups with *N*-protected amino acids proceeded with DCC/HOBt at elevated temperature. The conversion of the platform compound **3a** with *N*-Fmoc-β-Ala gave amide **10a** in 82 % yield (Scheme 5, Table 1, series a). After the deprotection of the Boc group (product: **11a** in 98 % yield), the second amidation was performed with *N*-Boc-β-Ala (product: **12a** in 75 % yield). Catalytic hydrogenolysis gave free carboxylic acid **13a** (94 % yield), which was amidated with β-Ala *tert*-butyl ester (β-Ala-O*t*Bu; product **14a** in 94 % yield). The amidation of aromatic carboxylic acids, such as **13** and **15**, required (as well as DCC/HOBt) the addition of catalytic amounts of DMAP to give satisfactory yields. The second last transformation was saponification of the methyl ester in compound **14**. The conversion with $K_2CO_3$ in EtOH/$H_2O$ proceeded very well within 2–4 hours at 50 °C; however, the workup




Scheme 3. Synthesis of platform **3a** from succinyl succinate **4a**. a) 1. $NH_3$, EtOH, 1 h, 60 °C, then addition of HCl, air, 3 d, 60 °C; b) $Boc_2O$ (1.0 equiv), dichloromethane, 16 h, 23 °C; c) TFA, dichloromethane, 16 h, 23 °C; d) 4-Br$C_6H_4SO_2$Cl, pyridine, cat. DMAP, dichloromethane, 16 h, 23 °C. DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid.

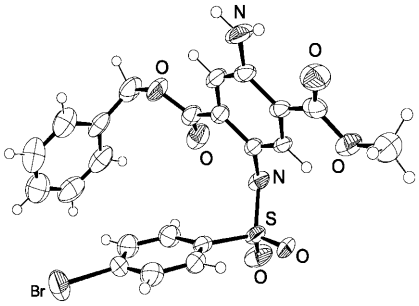
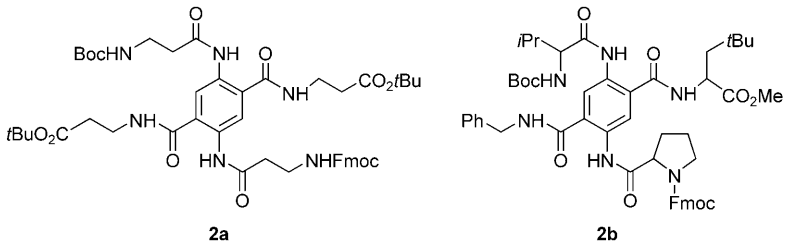


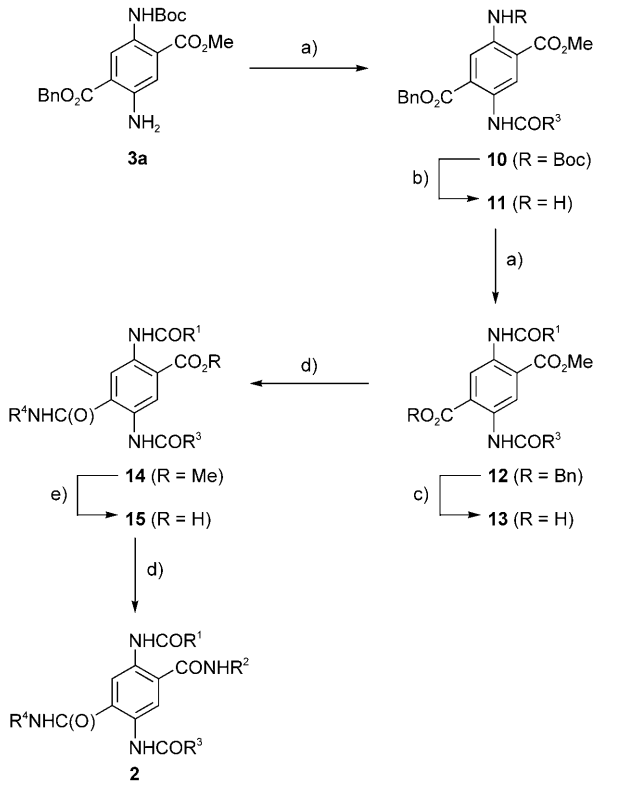

Figure 1. ORTEP view of **9a** in the solid state.




2a 2b

Scheme 4. Final compounds **2a** and **2b**. Fmoc = 9-fluorenylmethoxycarbonyl.




Scheme 5. Synthesis of final compounds **2a** and **2b** (see Table 1 for the yields and residues $R^1$–$R^4$). a) $R^3CO_2H$ or $R^1CO_2H$, DCC, HOBt, dichloromethane, 2 d, 80 °C; b) TFA, dichloromethane, 16 h, 23 °C; c) cat. Pd/C, $H_2$, ethyl acetate, 16 h, 23 °C; d) $R^4NH_2$ or $R^2NH_2$, DCC, HOBt, cat. DMAP, dichloromethane, 2 d, 80 °C; e) $K_2CO_3$, $H_2O$, EtOH, 2–4 h, 50 °C. Boc = *tert*-butoxycarbonyl, DCC = dicyclohexylcarbodiimide, HOBt = hydroxybenzotriazole.

Table 1. Yields for the preparation of **2a** and **2b** from **3a**.

| Series a | | | Series b | | |
|---|---|---|---|---|---|
| Coupling partner or deprotection reagent | Product | Yield [%] | Coupling partner or deprotection reagent | Product | Yield [%] |
| *N*-Fmoc-β-Ala | **10a** | 82 | *N*-Fmoc-L-Pro | **10b** | 78 |
| TFA | **11a** | 98 | TFA | **11b** | 90 |
| *N*-Boc-β-Ala | **12a** | 75 | *N*-Boc-L-Val | **12b** | 90 |
| $H_2$/Pd | **13a** | 94 | $H_2$/Pd | **13b** | 94 |
| β-Ala-O*t*Bu | **14a** | 94 | $BnNH_2$ | **14b** | 64 |
| $K_2CO_3$ | **15a** | 70 | $K_2CO_3$ | **15b** | 75 |
| β-Ala-O*t*Bu | **2a** | 93 | L-Npg-OMe | **2b** | 37 |

protocol turned out to be the crucial part of this step because acids **15** are already very soluble in $H_2O$. Finally, the fourth amidation with β-Ala-O*t*Bu gave **2a** in 93% yield. In summary, the final product **2a** was obtained from platform compound **3a** in seven steps and 35% overall yield.

In the second series (Table 1, series b), we changed the acids and amines for the amidation, but kept the order of the deprotecting transformations the same (Scheme 5). The coupling partners in their synthetic order were: *N*-Fmoc-L-Pro (Pro = proline), *N*-Boc-L-Val (Val = valine), benzylamine ($BnNH_2$), and L-neopentylglycine methyl ester (L-Npg-OMe). The final compound **2b** was obtained in lower overall yield (11%). Most products in this series (with optically active amino acid derivatives) show a doubled signal set in the NMR spectra in $CDCl_3$ at 23 °C. A single signal set was obtained (which was shown for **14b**) at 80 °C in [$D_6$]DMSO. Therefore, we assume hindered rotation along the aniline $sp^2$-C–N bond that results in atropisomerism (axial chirality), thus leading to diastereoisomeric conformers and a doubled signal set at 23 °C.

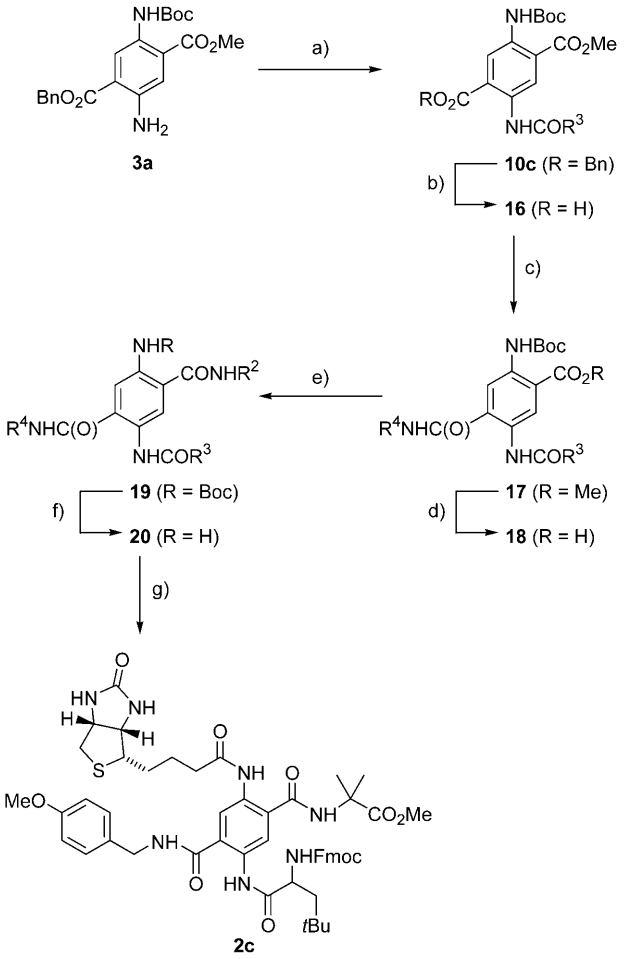
For the third series (Scheme 6), we changed the coupling partners and the sequence of the deprotecting operations to introduce the most challenging residue (biotin) as the last step. Moreover, sulfur compounds might influence the catalytic activity during hydrogenolytic debenzylation. First, the amidation was carried out using *N*-Fmoc-L-Npg from the platform compound **3a** (product: **10c** in 59% yield). After catalytic hydrogenolytic debenzylation (product: **16** in 98% yield), the acid was coupled with 4-$MeOC_6H_4CH_2NH_2$ (PMB-$NH_2$) (product: **17** in 61% yield). Methyl aminoisobutyrate (Aib-OMe) was introduced (product: **19** in 53% yield) after methyl ester saponification (product: **18** in 70% yield). Finally, the Boc group was cleaved (product: **20** in 95% yield) and the scaffold was coupled with (+)-biotin to give the final compound **2c** (34%). The overall yield in this series was 4%.

Finally, UV/vis and fluorescence spectra were recorded of the three final compounds **2a–c**. All the spectra showed, of course, a strong absorption at $\lambda = 230$–250 nm caused by the Fmoc groups. In addition, a weaker band was observed at $\lambda = 330$–350 nm (Table 2). Upon irradiation of this band, strong fluorescence was observed in the visible region at $\lambda =$ 410–450 nm.

## Conclusion

The fluorescence of single compounds is an interesting feature for high-throughput synthesis and screening. 2,5-Diaminoterephthalates are intensively colored, fluorescent materials. We have developed a combinatorial-like synthesis of tet-




Scheme 6. Synthesis and constitution of final compound **2c**. a) *N*-Fmoc-L-Npg, DCC, HOBt, dichloromethane, 2 d, 80 °C (59 %); b) cat. Pd/C, $H_2$, ethyl acetate, 16 h, 23 °C (98 %); c) PMB–$NH_2$, DCC, HOBt, cat. DMAP, dichloromethane, 2 d, 80 °C (61 %); d) $K_2CO_3$, $H_2O$, EtOH, 2–4 h, 50 °C, 70 %; e) Aib–OMe, DCC, HOBt, cat. DMAP, dichloromethane, 2 d, 80 °C (53 %); f) TFA, dichloromethane, 16 h, 23 °C (95 %); g) (+)-biotin, DCC, HOBt, dichloromethane, 2 d, 80 °C (35 %).

Table 2. Absorption and emission bands of **2a–c** recorded in $CH_2Cl_2$ at 23 °C.

| Compound | $\lambda_{max}$ [nm] | $\varepsilon$ [$dm^3 mol^{-1} cm^{-1}$] | $\lambda_{em}$ [nm] |
|---|---|---|---|
| **2a** | 352 | 1682 | 423 |
| **2b** | 329 | 944 | 440 |
| **2c** | 327 | 7247 | 447 |

racarboxamides that starts from an orthogonally protected platform compound **3a**. The two amino and two carboxylic acid groups were transformed by stepwise deprotection and amidation into three tetracarboxamides **2a–c** with different amino acids or amines as effector groups attached to the central aromatic fluorescence chromophore.

## Experimental Section

**General methods**: Preparative column chromatography was carried out using Merck $SiO_2$ (0.035–0.070 mm, type 60 A) with petroleum ether (PE; b.p. 40–60 °C) and ethyl acetate (EA) as eluents. TLC was performed on Merck $SiO_2$ $F_{254}$ plates on aluminum sheets. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker Avance DRX 500 and Avance DPX 300 spectrometers in $CDCl_3$ at 23 °C with trimethylsilane (TMS) as the internal standard, if not otherwise stated. Multiplicities were determined with DEPT experiments. EI-MS, CI-MS, and HRMS spectra were obtained with a Finnigan MAT 95 spectrometer, ESI-MS (HRMS) spectra with a Waters Q-TOF Premier. A Thermo system equipped with AS 3000 autosampler and Finnigan MAT ESI-MS was used for LC–MS. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond-ATR unit. Elemental analyses were measured with a Euro EA-CHNS from HEKAtech. UV and fluorescence spectra were recorded with a Perkin Elmer LS 50 spectrometer. Monobenzyl succinate **5**[7] and the following amino acid derivatives were prepared according to reported protocols: *N*-Fmoc-β-Ala,[8] *N*-Fmoc-L-Pro,[9] *N*-Fmoc-L-Npg,[10] *N*-Boc-β-Ala,[11] *N*-Boc-L-Val,[12] β-Ala-O*t*Bu,[13] L-Npg-OMe,[14] and Aib–OMe.[15] All other starting materials were commercially available. Spectroscopic and analytical data of **4b** and **4c** have been reported previously.[4b]

**Benzyl methyl succinate (6)**: MeI (9.40 mL, 21.3 g, 150 mmol, 1.1 equiv) and $Na_2CO_3$ (19.0 g, 136 mmol, 1.0 equiv) were added to a solution of mono-ester **5** (28.29 g, 136.0 mmol) in DMF (200 mL). The resulting mixture was stirred for 4 h at 23 °C, diluted with ethyl acetate (100 mL), and washed with $H_2O$ (3×200 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent evaporated to give di-ester **6** (30.48 g, 133.0 mmol, 97 %; >98 % purity by GC) as a yellow oil, which was used without further purification. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ = 2.64–2.68 (m, 4H), 3.66 (s, 3H), 5.13 (s, 2H), 7.31–7.37 ppm (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 28.78 ($CH_2$), 29.05 ($CH_2$), 51.68 ($CH_3$), 66.39 ($CH_2$), 128.07 (2 CH), 128.13 (CH), 128.42 (2 CH), 135.69 (C), 171.94 (C), 172.52 ppm (C); IR (ATR): $\tilde{\nu}$ = 3035 (w), 2954 (m), 1733 (vs), 1678 (s), 1439 (m), 1354 (m), 1213 (s), 1153 (vs), 997 (s), 847 (m), 700 $cm^{-1}$ (vs); MS (EI, 70 eV): *m*/*z* (%): 222 (8) [$M^+$], 194 (15), 115 (82), 107 (50), 91 (100); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{12}H_{14}O_4$: 222.0892; found: 222.0891 [$M^+$]; elemental analysis calcd for $C_{12}H_{14}O_4$ (222.24): C 64.85, H 6.35; found: C 64.30, H 6.41.

**Benzyl methyl 2,5-dihydroxycyclohexa-1,4-diene-1,4-dicarboxylate (4a)**: Succinate **6** (60 g, 270 mmol) was added to a cooled (icebath) suspension of NaH (21.6 g, 60 % dispersion in mineral oil, 540 mmol, 2.0 equiv) in DMSO (250 mL). After stirring for 30 min at 0 °C and 3 h at 23 °C, the reaction mixture was neutralized by the dropwise addition (icebath) of half-concentrated hydrochloric acid (50 mL). The precipitate was filtered off, collected on a glass frit, and washed portionwise with $H_2O$ (300 mL) until the red/brown color disappeared. The residue was stirred for 1 h at 50 °C with PE/dichloromethane (500 mL, 9:1) and the warm suspension was filtered through a glass frit. The residue was dibenzyl ester **4b** (7.20 g, 18.9 mmol, 14 %; $R_f$ = 0.55 ($SiO_2$, toluene)). The filtrate was evaporated and purified by column chromatography ($SiO_2$, toluene) to give benzyl methyl ester **4a** (14.7 g, 48.3 mmol, 36 %) as a colorless solid (m.p. 127 °C) in the first fraction ($R_f$ = 0.49). The second fraction ($R_f$ = 0.42) was dimethyl ester **4c** (6.16 g, 27.0 mmol, 20 %) also a colorless solid. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ = 3.18–3.24 (m, 4H), 3.79 (s, 3H), 5.23 (s, 2H), 7.33–7.41 (m, 5H), 12.11 ppm (s, 2H; OH); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 28.48 ($CH_2$), 28.58 ($CH_2$), 51.76 ($CH_3$), 66.28 ($CH_2$), 93.08 (C), 93.12 (C), 127.97 (2 CH), 128.34 (CH), 128.61 (2 CH), 135.52 (C), 168.43 (C), 168.87 (C), 170.92 (C), 171.55 ppm (C); IR (ATR): $\tilde{\nu}$ = 3086 (m, br; OH), 3035 (w), 2951 (m), 2899 (m), 1661 (vs), 1626 (vs), 1424 (s), 1320 (s), 1203 (s), 1121 (s), 1057 (vs), 801 (s), 702 $cm^{-1}$ (s); MS (EI, 70 eV): *m*/*z* (%): 304 (6) [$M^+$], 228 (7), 165 (3), 91 (100); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{16}H_{16}O_6$: 304.0947; found: 304.0945 [$M^+$]; elemental analysis calcd for $C_{16}H_{16}O_6$ (304.30): C 71.15, H 5.30; found: C 71.06, H 5.14.

**1-Benzyl 4-methyl 2,5-diaminoterephthalate (7)**: Succinyl succinate **4a** (10.00 g, 32.87 mmol) was added to a solution of $NH_3$ in EtOH (200 mL,

ca. 15 mol dm$^{-3}$) and the resulting mixture was heated for 1 h at 60 °C. Concentrated hydrochloric acid (10 mL) was added and the mixture was further stirred at 60 °C for 3 d. After cooling to ambient temperature, the solvent was evaporated and the residue diluted with dichloromethane (200 mL) and washed with $H_2O$ (200 mL). The aqueous layer was extracted with dichloromethane (3×200 mL), the combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was evaporated. The residue was purified by column chromatography ($Al_2O_3$, basic, activity 1; PE/EA/acetone 5:5:1, $R_f$=0.56) to give **7** (8.31 g, 27.7 mmol, 84%) as a red oil. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=3.86 (s, 3H), 5.07 (brs, 4H; $NH_2$), 5.30 (s, 2H), 7.27 (s, 1H), 7.30 (s, 1H), 7.33–7.37 (m, 2H), 7.38–7.43 ppm (m, 3H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=51.84 ($CH_3$), 66.53 ($CH_2$), 117.28 (C), 117.55 (C), 118.74 (CH), 118.67 (CH), 128.19 (2 CH), 128.29 (2 CH), 128.60 (CH), 135.70 (C), 140.46 (C), 140.69 (C), 166.89 (C), 167.53 ppm (C); IR (ATR): $\tilde{\nu}$=3476 (s), 3473 (s), 3034 (w), 2952 (m), 1690 (vs), 1584 (vs), 1501 (vs), 1439 (vs), 1379 (m), 1286 (s), 1201 (vs), 1096 (vs), 961 (m), 890 (m), 791 (s), 735 (s), 698 cm$^{-1}$ (s); MS (EI, 70 eV): *m*/*z* (%): 300 (100) [$M^+$], 209 (28), 165 (31), 133 (18), 91 (43), 86 (12); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{16}H_{16}N_2O_4$: 300.1110; found: 300.1110 [$M^+$]; 300.31 ($C_{16}H_{16}N_2O_4$).

**Introduction of the Boc protecting group (3a,b)**: A solution of $Boc_2O$ (1.88 g, 8.63 mmol) in dichloromethane (6 mL) was added dropwise to a solution of diamine **7** (2.59 g, 8.63 mmol) in dichloromethane (6 mL) and the resulting mixture was stirred for 16 h at 23 °C. The solution was diluted with dichloromethane (20 mL) and washed with $H_2O$ (20 mL). The aqueous layer was extracted with dichloromethane (3×20 mL), the combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was evaporated. The residue was purified by column chromatography ($Al_2O_3$, basic, activity 1; PE/EA 3:1) to give **3b** (0.83 g, 2.07 mmol, 24%) in the first fraction ($R_f$=0.48) and **3a** (2.11 g, 5.27 mmol, 61%) in the second fraction ($R_f$=0.43) as yellow solids.

**1-Benzyl 4-methyl 2-amino-5-(*tert*-butyloxycarbonylamino)terephthalate (3a)**: M.p. 146 °C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.51 (s, 9H), 3.91 (s, 3H), 5.38 (s, 2H), 5.46 (s, 2H; $NH_2$), 7.32 (s, 1H), 7.32–7.33 (m, 1H), 7.36–7.39 (m, 2H), 7.46–7.47 (m, 2H), 8.87 (s, 1H), 9.43 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=28.41 (3 $CH_3$), 52.51 ($CH_3$), 66.39 ($CH_2$), 80.16 (C), 115.68 (C), 118.54 (CH), 120.91 (C), 122.25 (CH), 127.87 (2 CH), 128.07 (CH), 128.54 (2 CH), 130.75 (C), 136.12 (C), 144.28 (C), 153.05 (C), 167.16 (C), 167.49 ppm (C); IR (ATR): $\tilde{\nu}$=3479 (s), 3369 (s), 3337 (m), 2978 (w), 2952 (w), 1695 (vs), 1625 (m), 1566 (s), 1528 (vs), 1452 (m), 1419 (s), 1316 (s), 1213 (vs), 1156 (vs), 1107 (vs), 1022 (m), 905 (m), 788 (vs), 731 (vs), 685 cm$^{-1}$ (s); MS (EI, 70 eV): *m*/*z* (%): 400 (17) [$M^+$], 344 (42), 300 (100), 252 (10), 238 (19), 209 (25), 165 (14), 133 (10), 91 (67); HRMS (CI, isobutane): *m*/*z*: calcd for $C_{21}H_{25}N_2O_6$: 401.1713; found: 401.1714 [$M$+H$^+$]; elemental analysis calcd for $C_{21}H_{24}N_2O_6$ (400.43): C 62.99, H 6.04, N 7.00; found: C 62.42, H 6.23, N 6.80.

**1-Benzyl 4-methyl 5-amino-2-(*tert*-butyloxycarbonylamino)terephthalate (3b)**: M.p. 144 °C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.52 (s, 9H), 3.89 (s, 3H), 5.33 (s, 2H), 5.47 (s, 2H; $NH_2$), 7.36 (s, 1H), 7.38–7.39 (m, 2H), 7.41–7.42 (m, 3H), 8.83 (s, 1H), 9.52 ppm (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=28.42 (3 $CH_3$), 52.09 ($CH_3$), 67.30 ($CH_2$), 80.20 (C), 115.81 (C), 118.70 (CH), 120.57 (C), 121.84 (CH), 128.36 (2 CH), 128.63 (CH), 128.77 (2 CH), 130.92 (C), 135.24 (C), 144.18 (C), 153.09 (C), 166.87 (C), 167.89 ppm (C); IR (ATR): $\tilde{\nu}$=3476 (m), 3358 (m), 2976 (w), 1690 (vs), 1620 (s), 1565 (m), 1526 (s), 1449 (m), 1415 (vs), 1311 (s), 1212 (s), 1152 (s), 1102 (s), 1019 (m), 898 (m), 780 (vs), 728 cm$^{-1}$ (s); MS (EI, 70 eV): *m*/*z* (%): 400 (12) [$M^+$], 344 (35), 300 (89), 209 (26), 165 (20), 133 (12), 91 (100); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{21}H_{24}N_2O_6$: 400.1634; found: 400.1634 [$M^+$]; 400.43 ($C_{21}H_{24}N_2O_6$).

**General procedure A**: **deprotection of the Boc group**: TFA (10 equiv) was added to a cooled (icebath) solution of the carbamate (1 equiv) in dichloromethane ($c$=0.1 mol dm$^{-3}$) and the mixture was stirred for 16 h at 23 °C. The solvent was evaporated and $H_2O$ (20 dm$^3$ mol$^{-1}$) and KOH (10% in $H_2O$) were added dropwise to the residue until pH>10 (ca. 2 dm$^3$ mol$^{-1}$) was reached. The aqueous layer was extracted with dichloromethane (4×50 dm$^3$ mol$^{-1}$), the combined organic layers dried ($MgSO_4$) and filtered, and the solvent evaporated to give the deprotected amines, which could be purified by chromatography.

**Deprotection of 3b**: Following general procedure A, **3b** (1.02 g, 2.55 mmol) was deprotected and the residue purified by column chromatography ($Al_2O_3$, basic, activity 1, PE/EA/acetone 5:5:1, $R_f$=0.56) to give **7** (730 mg, 2.42 mmol, 95%) as a red oil.

**1-Benzyl 4-methyl 2-(4-bromobenzenesulfonylamino)-5-(*tert*-butyloxycarbonylamino)terephthalate (8a)**: Pyridine (35 mg, 0.44 mmol), a solution of DMAP in dichloromethane (4 mL, c=1 mmol dm$^{-3}$, 4 μmol), and a solution of 4-Br$C_6H_4SO_2$Cl (112 mg, 0.44 mmol) in dichloromethane (2 mL) were subsequently added to a solution of amine **3a** (160 mg, 0.40 mmol) in dichloromethane (2 mL). The reaction mixture was stirred for 16 h at 23 °C and washed with $H_2O$ (10 mL). The organic layer was separated and dried ($MgSO_4$). After filtration, the solvent was evaporated, and the residue purified by column chromatography on $SiO_2$ (PE/EA 2:1, $R_f$= 0.49) to give **8a** (213 mg, 0.34 mmol, 85%) as a yellow solid. M.p. 175 °C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.43 (s, 9H), 3.90 (s, 3H), 5.23 (s, 2H), 7.29–7.34 (m, 7H), 7.41–7.47 (m, 2H), 8.28 (s, 1H), 8.95 (s, 1H), 9.86 (s, 1H; NH), 9.93 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$= 28.26 (3 $CH_3$), 52.98 ($CH_3$), 67.66 ($CH_2$), 81.12 (C), 119.00 (C), 121.47 (CH), 122.90 (C), 124.23 (CH), 128.11 (C), 128.40 (2 CH), 128.64 (CH), 128.67 (2 CH), 128.72 (2 CH), 132.06 (C), 132.20 (2 CH), 134.93 (C), 137.80 (C), 138.30 (C), 152.57 (C), 166.73 (C), 167.17 ppm (C); IR (ATR): $\tilde{\nu}$=3295 (w), 3174 (m), 2983 (w), 1722 (vs), 1685 (vs), 1583 (m), 1528 (vs), 1400 (s), 1226 (vs), 1107 (s), 1071 (s), 935 (m), 790 (s), 691 cm$^{-1}$ (s); MS (EI, 70 eV): *m*/*z* (%): 618 (34) [$M^+$], 576 (35), 562 (79), 518 (100), 500 (3); HRMS (CI, isobutane): *m*/*z*: calcd for $C_{27}H_{28}BrN_2O_8S$: 619.750; found: 619.0756 [$M$+H$^+$]; elemental analysis calcd for $C_{27}H_{27}BrN_2O_8S$ (619.48): C 52.35, H 4.39, N 4.52; found: C 51.74, H 4.45, N 4.45.

**1-Benzyl 4-methyl 5-(4-bromobenzenesulfonylamino)-2-(*tert*-butyloxycarbonylamino)terephthalate (8b)**: Following the procedure reported for sulfonamide **8a**, a solution of amine **3b** (0.2 g, 0.5 mmol) in dichloromethane (2.5 mL) was treated with pyridine (44 mg, 0.55 mmol), a solution of DMAP in dichloromethane (5 mL, $c$=1 mmol dm$^{-3}$, 5 μmol), and a solution of 4-Br$C_6H_4SO_2$Cl (124 mg, 0.55 mmol) in dichloromethane (2.5 mL) to give amide **8b** as a yellow solid (280 mg, 0.45 mmol, 90%) after chromatography ($SiO_2$, PE/EA 2:1, $R_f$=0.58). M.p. 174 °C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.51 (s, 9H), 3.86 (s, 3H), 5.38 (s, 2H), 7.37 (d, $J$=8.7 Hz, 2H), 7.46–7.47 (m, 5H), 7.54 (d, $J$=8.7 Hz, 2H), 8.30 (s, 1H), 8.97 (s, 1H), 9.95 (s, 1H; NH), 10.06 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=28.28 (3 $CH_3$), 53.01 ($CH_3$), 67.20 ($CH_2$), 81.13 (C), 118.96 (C), 121.31 (CH), 121.81 (C), 122.58 (CH), 128.13 (C), 128.33 (2 CH), 128.81 (CH), 128.88 (2 CH), 128.90 (2 CH), 132.35 (2 CH), 132.40 (C), 134.97 (C), 137.75 (C), 137.89 (C), 152.65 (C), 166.35 (C), 167.43 ppm (C); IR (ATR): $\tilde{\nu}$=3332 (w), 2982 (w), 1730 (s), 1694 (vs), 1574 (s), 1526 (vs), 1393 (vs), 1320 (m), 1228 (vs), 1152 (vs), 1111 (s), 1070 (s), 910 (s), 824 (m), 734 cm$^{-1}$ (vs); MS (EI, 70 eV): *m*/*z* (%): 618 (37) [$M^+$], 562 (73), 518 (100); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{27}H_{27}BrN_2O_8S$: 618.0671; found: 618.0668 [$M^+$]; elemental analysis calcd for $C_{27}H_{27}BrN_2O_8S$ (619.48): C 52.35, H 4.39, N 4.52; found: C 52.30, H 4.67, N 4.42.

**1-Benzyl 4-methyl 5-amino-2-(4-bromobenzenesulfonylamino)terephthalate (9a)**: Following general procedure A, **8a** (56 mg, 86 μmol) was deprotected and the residue purified by column chromatography ($SiO_2$, PE/EA 2:1, $R_f$=0.31) to give **9a** (40 mg, 77 μmol, 90%) as a yellow solid. M.p. 103 °C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=3.77 (s, 3H), 5.36 (s, 2H), 5.65 (s, 2H; $NH_2$), 7.16 (s, 1H), 7.34–7.37 (m, 2H), 7.40–7.44 (m, 2H), 7.45–7.48 (m, 3H), 7.52–7.53 (m, 2H), 8.19 (s, 1H), 9.29 ppm (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=52.66 ($CH_3$), 66.78 ($CH_2$), 114.91 (C), 118.84 (CH), 124.17 (C), 125.66 (CH), 126.92 (C), 127.77 (C), 128.19 (2 CH), 128.48 (CH), 128.76 (2 CH), 129.04 (2 CH), 132.01 (2 CH), 135.68 (C), 138.14 (C), 146.35 (C), 166.51 (C), 167.31 ppm (C); IR (ATR): $\tilde{\nu}$=3482 (m), 3373 (m), 2955 (w), 1696 (vs), 1593 (s), 1507 (s), 1404 (s), 1316 (m), 1235 (vs), 1167 (vs), 1108 (vs), 926 (m), 743 cm$^{-1}$ (s); MS (EI, 70 eV): *m*/*z* (%): 518 (8) [$M^+$], 299 (33), 91 (100), 57 (51); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{22}H_{19}BrN_2O_6S$: 518.0147; found:

518.0148 [$M^+$]; elemental analysis calcd for $C_{22}H_{19}BrN_2O_6S$ (519.37): C 50.88, H 3.69, N 5.39; found: C 50.51, H 3.71, N 5.81.

**1-Benzyl 4-methyl 2-amino-5-(4-bromobenzenesulfonylamino)terephthalate (9b)**: Following general procedure A, **8b** (280 mg, 0.45 mmol) was deprotected and the residue purified by column chromatography ($SiO_2$, PE/EA 2:1, $R_f$=0.27) to give **9b** (210 mg, 0.404 mmol, 90%) as a yellow solid. M.p. 106°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=3.76 (s, 3H), 5.35 (s, 2H), 5.67 (s, 2H; $NH_2$), 7.16 (s, 1H), 7.38–7.40 (m, 2H), 7.42–7.43 (m, 2H), 7.45–7.48 (m, 3H), 7.50–7.52 (m, 2H), 8.18 (s, 1H), 9.29 ppm (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=52.62 ($CH_3$), 66.73 ($CH_2$), 114.84 (C), 118.85 (CH), 124.14 (C), 125.59 (CH), 126.90 (C), 127.77 (C), 128.16 (2 CH), 128.45 (CH), 128.73 (2 CH), 129.01 (2 CH), 131.99 (2 CH), 135.66 (C), 137.94 (C), 146.82 (C), 166.53 (C), 166.90 ppm (C); IR (ATR): $\tilde{\nu}$=3482 (m), 3372 (m), 2953 (w), 1691 (vs), 1591 (s), 1504 (vs), 1399 (s), 1314 (m), 1229 (vs), 1163 (vs), 1104 (vs), 923 (m), 740 cm$^{-1}$ (s); MS (EI, 70 eV): *m*/*z* (%): 518 (11) [$M^+$], 299 (42), 91 (100); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{22}H_{19}BrN_2O_6S$: 518.0147; found: 518.0147 [$M^+$]; elemental analysis calcd for $C_{22}H_{19}BrN_2O_6S$ (519.37): C 50.88, H 3.69, N 5.39; found: C 50.53, H 3.68, N 5.61.

**General procedure B**: **amidation of aliphatic carboxylic acids**: *N*,*N*-Dicyclohexylcarbodiimide (DCC; 1.2 equiv) was added to a solution of carboxylic acid (1.1 equiv) in dichloromethane (0.30 mol dm$^{-3}$). After the reaction mixture was stirred at ambient temperature for 1 min, a colorless precipitate was formed and HOBt (88% purity, 1.2 equiv) was added. After further stirring for 1 min, the amine (1.0 equiv) was added. The reaction mixture was stirred in a tightly closed reaction flask for 2 d at 80°C. After cooling to 23°C, the mixture was diluted with dichloromethane (20 dm$^3$ mol$^{-1}$) and washed with saturated $NH_4Cl$ solution (20 dm$^3$ mol$^{-1}$), saturated $NaHCO_3$ solution (20 dm$^3$ mol$^{-1}$), and $H_2O$ (20 dm$^3$ mol$^{-1}$). After drying over $MgSO_4$ and filtration, the organic layer was evaporated and the residue purified by chromatography on $SiO_2$.

**1-Benzyl 4-methyl 5-(*tert*-butyloxycarbonylamino)-2-[3-(fluoren-9-ylmethyloxycarbonylamino)propanoylamino]terephthalate (10a)**: Following general procedure B, **3a** (470 mg, 1.17 mmol) was coupled with *N*-Fmoc-β-Ala (402 mg, 1.29 mmol) by using DCC (291 mg, 1.41 mmol) and HOBt (216 mg, 1.41 mmol) to give **10a** (670 mg, 0.97 mmol, 82%) after chromatography ($SiO_2$, PE/EA 2:1, $R_f$=0.20) as a yellow solid. M.p. 96°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.53 (s, 9H), 2.66 (t, $J$=5.4 Hz, 2H), 3.56 (q, $J$=5.6 Hz, 2H), 3.95 (s, 3H), 4.20 (t, $J$=6.9 Hz, 1H), 4.35 (d, $J$=7.0 Hz, 2H), 5.37 (s, 2H), 5.53 (s, 1H; NH), 7.25–7.28 (m, 2H), 7.33–7.40 (m, 5H), 7.46 (d, $J$=7.4 Hz, 2H), 7.57 (d, $J$=7.4 Hz, 2H), 7.73 (d, $J$=7.5 Hz, 2H), 9.17 (s, 1H), 9.27 (s, 1H), 10.01 (s, 1H; NH), 10.71 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=28.29 (3 $CH_3$), 36.73 ($CH_2$), 37.49 ($CH_2$), 47.23 (CH), 52.78 ($CH_3$), 66.71 ($CH_2$), 67.40 ($CH_2$), 80.82 (C), 118.99 (C), 119.90 (2 CH), 120.13 (C), 121.25 (C), 122.59 (C), 125.05 (2 CH), 126.97 (2 CH), 127.61 (2 CH), 128.01 (2 CH), 128.46 (2 CH), 128.64 (3 CH), 133.95 (C), 135.19 (C), 136.77 (C), 141.24 (C), 143.92 (C), 152.67 (C), 156.58 (C), 167.17 (C), 167.59 (C), 170.22 ppm (C); IR (ATR): $\tilde{\nu}$=3318 (m), 2952 (w), 1723 (s), 1692 (s), 1543 (vs), 1407 (s), 1321 (m), 1224 (vs), 1152 (vs), 1107 (s), 1070 (m), 1017 (m), 907 (s), 727 cm$^{-1}$ (vs); MS (EI, 70 eV): *m*/*z* (%): 693 (2) [$M^+$], 593 (12), 441 (7), 415 (14), 397 (70), 371 (12), 300 (71), 209 (11), 196 (25), 178 (91), 165 (61), 91 (100), 57 (15); HRMS (ESI): *m*/*z*: calcd for $C_{39}H_{40}N_3O_9$: 694.2765; found: 694.2758 [$M$+H$^+$]; elemental analysis calcd for $C_{39}H_{39}N_3O_9$ (693.74): C 67.52, H 5.67, N 6.06; found: C 67.61, H 5.93, N 5.86.

**1-Benzyl 4-methyl 5-(*tert*-butyloxycarbonylamino)-2-{[(*S*)-1-(fluoren-9-ylmethyloxycarbonyl)pyrrolidin-2-yl]carbonylamino}terephthalate (10b)**: Following general procedure B, **3a** (220 mg, 0.55 mmol) was coupled with *N*-Fmoc-L-Pro (202 mg, 0.60 mmol) by using DCC (124 mg, 0.60 mmol) and HOBt (92 mg, 0.60 mmol) to give **10b** (310 mg, 0.43 mmol, 78%) after chromatography ($SiO_2$, PE/EA 2:1, $R_f$=0.08) as a yellow solid. M.p. 71°C; a partly doubled signal set (ratio 1:1) was observed in the NMR spectra: $^1$H NMR ($CDCl_3$, 500 MHz), two isomers: $\delta$=1.51 (s, 9H), 1.53 (s, 9H), 1.90–1.93 (m, 2H), 2.00–2.03 (m, 2H), 2.21–2.23 (m, 2H), 2.27–2.31 (m, 2H), 3.62 (t, $J$=8.1 Hz, 2×1H), 3.71–3.74 (m, 1H), 3.82–3.84 (m, 1H), 3.93 (s, 3H), 3.97 (s, 3H), 4.09 (t, $J$=6.7 Hz, 2×1H), 4.29–4.32 (m, 2×2H), 4.54–4.55 (m, 2×1H), 5.14 (A part of an AB system, $J$=13.1 Hz, 1H), 5.17 (B part of an AB system, $J$=12.7 Hz, 1H), 5.31 (s, 2H), 7.01–7.05 (m, 2H), 7.15–7.17 (m, 2H), 7.23–7.27 (m, 2×2H), 7.30–7.34 (m, 2×2H), 7.36–7.40 (m, 2×4H), 7.55 (d, $J$=7.1 Hz, 1H), 7.61 (d, $J$=7.7 Hz, 1H), 7.64 (d, $J$=7.1 Hz, 1H), 7.73–7.74 (m, 1H), 7.75–7.76 (m, 2H), 9.15 (s, 2×1H), 9.34 (s, 1H), 9.39 (s, 1H), 10.00 (s, 1H; NH), 10.04 (s, 1H; NH), 11.18 (s, 1H; NH), 11.34 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz), two isomers: $\delta$=23.46 ($CH_2$), 24.40 ($CH_2$), 28.28 (2× 3 $CH_3$), 30.24 ($CH_2$), 31.46 ($CH_2$), 47.05 ($CH_2$), 47.08 ($CH_2$), 47.33 (CH), 47.42 (CH), 52.69 ($CH_3$), 52.73 ($CH_3$), 62.06 (CH), 62.40 (CH), 66.92 ($CH_2$), 67.30 ($CH_2$), 67.57 ($CH_2$), 67.76 ($CH_2$), 80.70 (C), 80.80 (C), 118.95 (2×C), 119.81 (CH), 119.91 (CH), 120.45 (C), 120.62 (C), 121.13 (2×2 CH), 122.54 (2×2 CH), 124.59 (CH), 124.74 (CH), 125.24 (CH), 125.37 (CH), 126.88 (2 CH), 126.96 (2 CH), 127.49 (2 CH), 127.67 (2 CH), 128.09 (2×CH), 128.16 (2×CH), 128.45 (2×2 CH), 133.73 (C), 133.92 (C), 135.19 (2×C), 136.78 (C), 136.85 (C), 141.11 (2 C), 141.25 (2 C), 143.66 (C), 143.73 (C), 144.28 (C), 144.33 (C), 152.62 (2×C), 154.97 (C), 155.61 (C), 166.93 (C), 167.10 (C), 167.70 (2×C), 170.96 (C), 171.10 ppm (C); IR (ATR): $\tilde{\nu}$=3318 (w), 2953 (m), 1689 (vs), 1538 (vs), 1407 (s), 1320 (m), 1222 (vs), 1152 (vs), 1107 (s), 908 (s), 727 cm$^{-1}$ (vs); MS (ESI): *m*/*z* (%): 742 (67) [$M$+Na$^+$], 593 (100), 422 (42); HRMS (ESI): *m*/*z*: calcd for $C_{41}H_{42}N_3O_9$: 720.2921; found: 720.2928 [M+H$^+$]; elemental analysis calcd for $C_{41}H_{41}N_3O_9$ (719.78): C 68.42, H 5.74, N 5.84; found: C 68.07, H 5.88, N 5.82.

**1-Benzyl 4-methyl 5-(*tert*-butyloxycarbonylamino)-2-[(*S*)-4,4-dimethyl-2-(fluoren-9-ylmethyloxycarbonylamino)pentanoylamino]terephthalate (10c)**: Following general procedure B, **3a** (880 mg, 2.20 mmol) was coupled with *N*-Fmoc-L-Npg (888 mg, 2.42 mmol) by using DCC (499 mg, 2.42 mmol) and HOBt (371 mg, 2.42 mmol) to give **10c** (966 mg, 1.29 mmol, 59%) after chromatography ($SiO_2$, PE/EA 2:1, $R_f$=0.09) as a yellow solid. M.p. 129°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.00 (s, 9H), 1.46–1.49 (m, 2H), 1.51 (s, 9H), 3.93 (s, 3H), 4.25 (t, $J$=6.8 Hz, 1H), 4.37–4.49 (m, 3H), 5.11 (d, $J$=7.9 Hz, 1H; NH), 5.22 (A part of an AB system, $J$=12.7 Hz, 1H), 5.26 (B part of an AB system, $J$=12.6 Hz, 1H), 7.27–7.29 (m, 6H), 7.36–7.40 (m, 3H), 7.61 (d, $J$=7.3 Hz, 1H), 7.66 (d, $J$=7.3 Hz, 1H), 7.75 (d, $J$=7.4 Hz, 2H), 9.16 (s, 1H), 9.35 (s, 1H), 10.00 (s, 1H; NH), 11.27 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=28.30 (3 $CH_3$), 29.65 (3 $CH_3$), 30.66 (C), 46.35 ($CH_2$), 47.31 (CH), 52.70 ($CH_3$), 54.34 (CH), 67.14 ($CH_2$), 67.19 ($CH_2$), 80.76 (C), 118.97 (C), 119.94 (2 CH), 120.52 (C), 121.53 (CH), 122.59 (CH), 125.14 (CH), 125.22 (CH), 127.00 (2 CH), 127.03 (CH), 127.69 (2 CH), 127.77 (CH), 128.25 (CH), 128.54 (2 CH), 133.84 (C), 135.06 (C), 135.19 (C), 136.19 (C), 141.27 (C), 143.65 (C), 144.06 (C), 152.65 (C), 155.86 (C), 167.04 (C), 167.67 (C), 171.63 ppm (C); IR (ATR): $\tilde{\nu}$=3303 (w), 2951 (m), 1731 (s), 1695 (s), 1548 (s), 1450 (w), 1409 (m), 1322 (w), 1227 (vs), 1154 (s), 1107 (s), 1073 (m), 789 (m), 738 (s), 696 cm$^{-1}$ (m); MS (ESI): *m*/*z* (%): 772 (100) [$M$+Na$^+$], 716 (14); HRMS (ESI): *m*/*z*: calcd for $C_{43}H_{47}N_3NaO_9$: 772.3210; found: 772.3227 [M+Na$^+$]; elemental analysis calcd for $C_{43}H_{47}N_3O_9$ (749.85): C 68.88, H 6.32, N 5.60; found: C 68.35, H 6.38, N 5.42.

**1-Benzyl 4-methyl 5-amino-2-[3-(fluoren-9-ylmethyloxycarbonylamino)-propanoylamino]terephthalate (11a)**: Following general procedure A, **10a** (1.21 g, 1.75 mmol) was deprotected and the crude product purified by column chromatography ($SiO_2$, PE/EA 1:1, $R_f$=0.44) to give **11a** (1.02 g, 1.72 mmol, 98%) as a yellow solid. M.p. 175°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=2.63 (t, $J$=5.0 Hz, 2H), 3.58 (q, $J$=5.2 Hz, 2H), 3.89 (s, 3H), 4.20 (t, $J$=6.8 Hz, 1H), 4.36 (d, $J$=7.0 Hz, 2H), 4.50 (brs, 1H; NH), 5.26 (s, 2H), 5.60 (brs, 2H; $NH_2$), 7.25–7.27 (m, 2H), 7.33–7.34 (m, 2H), 7.36–7.37 (m, 2H), 7.38–7.39 (m, 4H), 7.57 (d, $J$=7.3 Hz, 2H), 7.72 (d, $J$=7.4 Hz, 2H), 9.08 (s, 1H), 10.36 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=36.87 ($CH_2$), 37.36 ($CH_2$), 47.20 (CH), 52.08 ($CH_3$), 66.70 ($CH_2$), 67.48 ($CH_2$), 115.00 (C), 118.61 (C), 119.87 (2 CH), 121.11 (C), 123.37 (CH), 125.08 (2 CH), 126.96 (2 CH), 127.57 (2 CH), 128.40 (2 CH), 128.69 (2 CH), 128.73 (2 CH), 129.49 (C), 134.92 (C), 141.21 (C), 143.92 (2 C), 145.35 (C), 156.40 (C), 166.89 (C), 167.63 (C), 169.67 ppm (C); IR (ATR): $\tilde{\nu}$=3475 (m), 3364 (m), 3310 (m), 2948 (w), 1713 (s), 1692 (vs), 1645 (s), 1532 (vs), 1438 (s), 1233 (vs), 1109 (s), 1050 (m), 962 (m), 909 (m), 731 (vs), 695 cm$^{-1}$ (s); MS (EI, 70 eV): *m*/*z* (%): 593 (14) [$M^+$], 397 (39), 300 (20), 246 (4), 178 (29), 165 (100),

139 (5), 91 (45), 57 (3); HRMS (EI, 70 eV): *m/z*: calcd for $C_{34}H_{31}N_3O_7$: 593.2162; found: 593.2163 [$M^+$]; $C_{34}H_{31}N_3O_7$ (593.63).

**1-Benzyl 4-methyl 5-amino-2-{[(*S*)-1-(fluoren-9-ylmethyloxycarbonylamino)pyrrolidin-2-yl]carbonylamino}terephthalate (11b)**: Following general procedure A, **10b** (580 mg, 0.81 mmol) was deprotected and the crude product purified by column chromatography ($SiO_2$, PE/EA 1:2, $R_f$=0.19) to give **11b** (450 mg, 0.73 mmol, 90%) as a yellow solid. M.p. 55°C; a partly doubled signal set (ratio 1:1) was observed in the NMR spectra: $^1$H NMR ($CDCl_3$, 500 MHz), two isomers: $\delta$=1.92–1.99 (m, 2×2H), 2.17–2.30 (m, 2×2H), 3.61 (t, $J$=8.7 Hz, 1H), 3.63 (t, $J$=8.6 Hz, 1H), 3.72–3.74 (m, 2×1H), 3.86 (s, 3H), 3.90 (s, 3H), 4.14 (t, $J$=6.3 Hz, 2×1H), 4.29–4.39 (m, 2×2H), 4.53–4.57 (m, 2×1H), 4.67 (s, 2×2H; $NH_2$), 4.99 (A part of an AB system, $J$=12.2 Hz, 1H), 5.05 (B part of an AB system, $J$=12.3 Hz, 1H), 5.13 (A part of an AB system, $J$=12.1 Hz, 1H), 5.19 (B part of an AB system, $J$=12.1 Hz, 1H), 7.02 (t, $J$=6.8 Hz, 1H), 7.06 (t, $J$=7.0 Hz, 1H), 7.19–7.22 (m, 2×1H), 7.27–7.28 (m, 2×2H), 7.30–7.31 (m, 2×3H), 7.33–7.34 (m, 2×2H), 7.42 (d, $J$=7.8 Hz, 2H), 7.46 (d, $J$=7.8 Hz, 2H), 7.59–7.60 (m, 2×1H), 7.63–7.66 (m, 2×1H), 7.75 (s, 2×1H), 9.19 (s, 1H), 9.20 (s, 1H), 10.95 (s, 1H; NH), 11.06 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz), two isomers: $\delta$=23.43 ($CH_2$), 24.36 ($CH_2$), 30.16 ($CH_2$), 31.42 ($CH_2$), 47.03 (2×$CH_2$), 47.31 (CH), 47.45 (CH), 51.96 ($CH_3$), 52.02 ($CH_3$), 62.06 (CH), 62.32 (CH), 67.07 ($CH_2$), 67.35 ($CH_2$), 67.73 ($CH_2$), 67.81 ($CH_2$), 114.98 (C), 115.08 (C), 118.53 (2×CH), 119.75 (CH), 119.87 (CH), 121.16 (C), 121.42 (C), 123.12 (2 CH), 123.24 (2 CH), 124.76 (CH), 124.94 (CH), 125.24 (2 CH), 125.37 (2 CH), 126.88 (2×2 CH), 126.93 (2 CH), 127.48 (2 CH), 127.63 (CH), 127.97 (CH), 128.44 (2×CH), 128.55 (2×2 CH), 129.32 (C), 129.61 (C), 134.95 (2×C), 140.95 (2×C), 141.07 (C), 141.22 (C), 143.70 (C), 143.82 (C), 144.37 (C), 144.40 (C), 145.31 (C), 145.46 (C), 155.13 (C), 155.62 (C), 166.69 (C), 166.88 (C), 167.73 (2×C), 170.26 (C), 170.52 ppm (C); IR (ATR): $\tilde{\nu}$=3353 (w), 2951 (w), 1687 (vs), 1567 (m), 1525 (s), 1417 (s), 1314 (m), 1223 (vs), 1102 (vs), 910 (m), 736 cm$^{-1}$ (s). MS (ESI): *m/z* (%): 642 (35) [$M$+Na$^+$], 420 (100), 360 (40); HRMS (ESI): *m/z*: calcd for $C_{36}H_{33}N_3NaO_7$: 642.2216; found: 642.2243 [$M$+Na$^+$]; elemental analysis calcd for $C_{36}H_{33}N_3O_7$ (619.66): C 69.78, H 5.37, N 6.78; found: C 69.52, H 5.58, N 6.60.

**1-Benzyl 4-methyl 5-[3-(*tert*-butyloxycarbonylamino)propanoyl]amino-2-[3-(fluoren-9-ylmethyloxycarbonylamino)propanoyl]aminoterephthalate (12a)**: Following general procedure B, **11a** (400 mg, 0.674 mmol) was coupled with *N*-Boc-β-Ala (383 mg, 2.02 mmol) by using DCC (417 mg, 2.02 mmol) and HOBt (310 mg, 2.02 mmol) to give **12a** (390 mg, 0.508 mmol, 75%) as a yellow solid after chromatography ($SiO_2$, PE/EA 1:1, $R_f$=0.17). M.p. 155°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.42 (s, 9H), 2.63–2.66 (m, 4H), 3.49 (q, $J$=5.6 Hz, 2H), 3.57 (q, $J$=5.5 Hz, 2H), 3.91 (s, 3H), 4.17 (t, $J$=6.9 Hz, 1H), 4.36 (d, $J$=7.0 Hz, 2H), 5.28 (s, 1H; NH), 5.34 (s, 2H), 5.69 (t, $J$=6.0 Hz, 1H; NH), 7.21–7.24 (m, 2H), 7.31–7.34 (m, 3H), 7.37–7.40 (m, 2H), 7.46 (d, $J$=7.4 Hz, 2H), 7.55 (d, $J$=7.4 Hz, 2H), 7.69 (d, $J$=7.5 Hz, 2H), 9.27 (s, 1H), 9.37 (s, 1H), 10.78 ppm (s, 2H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=28.34 (3 $CH_3$), 36.28 ($CH_2$), 36.66 ($CH_2$), 37.58 ($CH_2$), 37.86 ($CH_2$), 47.15 (CH), 52.88 ($CH_3$), 66.62 ($CH_2$), 67.53 ($CH_2$), 79.19 (C), 119.47 (C), 119.58 (C), 119.82 (2 CH), 122.31 (C), 122.45 (C), 124.98 (2 CH), 126.89 (2 CH), 127.54 (2 CH), 128.08 (2 CH), 128.49 (2 CH), 128.66 (3 CH), 134.96 (C), 135.26 (C), 135.46 (C), 141.16 (C), 143.85 (C), 155.82 (C), 156.38 (C), 166.96 (C), 167.58 (C), 170.21 (C), 170.38 ppm (C); IR (ATR): $\tilde{\nu}$=3321 (m), 2932 (w), 1684 (vs), 1531 (s), 1404 (m), 1322 (m), 1224 (vs), 1176 (s), 1103 (s), 918 (m), 792 (s), 728 cm$^{-1}$ (m); MS (ESI): *m/z* (%): 787 (45) [M+Na$^+$], 694 (8), 563 (60), 517 (80), 471 (35), 293 cm$^{-1}$ (100); HRMS (ESI): *m/z*: calcd for $C_{42}H_{45}N_4O_{10}$: 765.3163; found: 765.3143 [$M$+H$^+$]; elemental analysis calcd for $C_{42}H_{44}N_4O_{10}$ (764.82): C 65.96, H 5.80, N 7.33; found: C 65.64, H 5.36, N 6.90.

**1-Benzyl 4-methyl 5-[(*S*)-2-(*tert*-butyloxycarbonylamino)-3-methylbutanoyl]amino-2-{[(*S*)-1-(fluoren-9-ylmethyloxycarbonylamino)pyrrolidin-2-yl]carbonylamino}terephthalate (12b)**: Following general procedure B, **11b** (420 mg, 0.678 mmol) was coupled with *N*-Boc-L-Val (295 mg, 1.36 mmol) by using DCC (280 mg, 1.36 mmol) and HOBt (208 mg, 1.36 mmol) to give **12b** (500 mg, 0.611 mmol, 90%) as a yellow solid after chromatography ($SiO_2$, PE/EA 1:2, $R_f$=0.44). M.p. 74°C; a partly doubled signal set (ratio 1:1) is observed in the NMR spectra: $^1$H NMR ($CDCl_3$, 500 MHz), two isomers: $\delta$=0.89–1.04 (m, 2×6H), 1.44 (s, 9H), 1.45 (s, 9H), 1.85–1.92 (m, 2×2H), 2.21–2.32 (m, 2×3H), 3.60–3.66 (m, 2×1H), 3.74–3.76 (m, 2×1H), 3.87 (s, 3H), 3.92 (s, 3H), 4.13–4.16 (m, 2×1H), 4.29–4.33 (m, 2×2H), 4.36–4.39 (m, 2×1H), 4.53–4.54 (m, 2×1H), 5.00–5.07 (m, 2H), 5.12–5.20 (m, 2H), 5.58 (br s, 1H, NH), 5.64 (br s, 1H, NH), 7.02 (t, $J$=7.0 Hz, 1H), 7.06 (t, $J$=7.2 Hz, 1H), 7.20–7.22 (m, 2×2H), 7.28–7.34 (m, 2×5H), 7.38–7.39 (m, 2×1H), 7.42–7.47 (m, 2×1H), 7.59–7.66 (m, 2×1H), 7.70–7.75 (m, 2×2H), 9.19 (s, 1H), 9.21 (s, 1H), 9.42 (s, 1H), 9.47 (s, 1H), 10.95 (s, 1H; NH), 11.06 (s, 1H; NH), 11.27 (s, 1H; NH), 11.34 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz), two isomers: $\delta$=19.42 (2 $CH_3$), 19.44 (2 $CH_3$), 23.47 (2×$CH_2$), 28.28 (3 $CH_3$), 28.31 (3 $CH_3$), 30.19 ($CH_2$), 30.21 ($CH_2$), 31.47 (CH), 31.49 (CH), 47.07 (CH), 47.09 (CH), 47.36 ($CH_2$), 47.39 ($CH_2$), 52.00 ($CH_3$), 52.06 ($CH_3$), 60.36 (2×CH), 62.08 (CH), 62.36 (CH), 67.10 (2×$CH_2$), 67.76 ($CH_2$), 67.85 ($CH_2$), 78.61 (2×C), 113.35 (2×CH), 115.05 (C), 115.07 (C), 118.52 (CH), 118.53 (CH), 119.01 (2×CH), 119.76 (CH), 119.92 (CH), 123.17 (C), 123.26 (C), 124.80 (CH), 124.97 (CH), 125.26 (CH), 125.41 (CH), 126.93 (2 CH), 126.96 (2 CH), 127.48 (CH), 127.66 (CH), 128.00 (2×2 CH), 128.44 (2 CH), 128.50 (2 CH), 128.58 (2×2 CH), 129.40 (C), 129.42 (C), 134.98 (2×C), 139.40 (2×C), 141.09 (C), 141.14 (C), 143.73 (C), 143.75 (C), 144.28 (C), 144.31 (C), 145.32 (C), 145.45 (C), 155.61 (C), 155.63 (C), 157.85 (C), 157.86 (C), 166.84 (C), 166.89 (C), 167.77 (2×C), 170.14 (C), 170.16 (C), 170.78 (C), 170.81 ppm (C); IR (ATR): $\tilde{\nu}$=3299 (w), 2953 (w), 1686 (vs), 1528 (s), 1404 (s), 1316 (m), 1225 (vs), 1104 (vs), 984 (w), 913 (m), 737 cm$^{-1}$ (vs); MS (ESI): *m/z* (%): 841 (67) [$M$+Na$^+$], 774 (60), 643 (48), 619 (100); HRMS (ESI): *m/z*: calcd for $C_{46}H_{50}N_4NaO_{10}$: 841.3425; found: 841.3440 [$M$+Na$^+$]; $C_{46}H_{50}N_4O_{10}$ (818.91).

**General procedure C**: **hydrogenolysis of benzyl ester**: A catalytic amount of Pd (5 w/w% on C, 5 g mol$^{-1}$ substrate) was added to a solution of benzyl ester in ethyl acetate ($c$=30 mmol dm$^{-3}$) and the mixture stirred for 16 h at 23°C in a $H_2$ atmosphere (1 atm, balloon). Subsequently, the catalyst was removed by filtration, the residue washed with ethyl acetate (100 dm$^3$ mol$^{-1}$), and the filtrate evaporated to give the crude hydrogenation product.

**5-[3-(*tert*-Butyloxycarbonylamino)propanoyl]amino-2-[3-(fluoren-9-ylmethyloxycarbonylamino)propanoyl]aminoterephthalic acid 4-methyl ester (13a)**: Following general procedure C, **12a** (420 mg, 0.547 mmol) was deprotected to give **13a** (350 mg, 0.516 mmol, 94%) as a yellow solid. M.p. 151°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.43 (s, 9H), 2.67–2.70 (m, 4H), 3.51–3.53 (m, 2H), 3.59–3.61 (m, 2H), 3.95 (s, 3H), 4.17 (t, $J$=6.6 Hz, 1H), 4.37 (q, $J$=7.0 Hz, 2H), 5.29 (br s, 1H), 5.45 (br s, 1H), 5.88 (br s, 1H), 7.23–7.25 (m, 1H), 7.31–7.38 (m, 3H), 7.56 (d, $J$=7.4 Hz, 2H), 7.69 (d, $J$=7.2 Hz, 2H), 9.27 (s, 1H), 9.33 (s, 1H), 10.82 (s, 1H), 11.16 ppm (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=24.74 ($CH_2$), 25.49 ($CH_2$), 28.38 (3 $CH_3$), 32.98 ($CH_2$), 33.59 ($CH_2$), 47.14 (CH), 52.89 ($CH_3$), 66.84 ($CH_2$), 79.35 (C), 119.31 (C), 119.85 (2 CH), 120.47 (C), 123.19 (CH), 123.95 (CH), 125.04 (2 CH), 126.95 (2 CH), 127.58 (2 CH), 135.25 (C), 135.62 (C), 140.46 (C), 141.20 (C), 143.84 (C), 148.94 (C), 156.78 (C), 157.76 (C), 167.79 (C), 169.94 (C), 170.34 (C), 170.48 ppm (C); IR (ATR): $\tilde{\nu}$=3341 (s), 2934 (m), 1678 (vs), 1529 (vs), 1437 (w), 1404 (s), 1320 (w), 1228 (vs), 1169 (s), 1104 (s), 955 (m), 910 (s), 790 (m), 729 cm$^{-1}$ (s); MS (ESI, neg. mode): *m/z* (%): 673 (100) [$M$−H$^+$], 573 (40), 533 (22), 506 (74), 391 (34), 293 (25), 206 (33); HRMS (ESI): *m/z*: calcd for $C_{35}H_{38}N_4NaO_{10}$: 697.2486; found: 697.2485 [$M$+Na$^+$]; elemental analysis calcd for $C_{35}H_{38}N_4O_{10}$ (674.70): C 62.31, H 5.68, N 8.30; found: C 62.72, H 5.75, N 8.02.

**5-[(*S*)-2-(*tert*-Butyloxycarbonylamino)-3-methylbutanoyl]amino-2-{[(*S*)-1-(fluoren-9-ylmethyloxycarbonylamino)pyrrolidin-2-yl]carbonylamino}terephthalic acid 4-methyl ester (13b)**: Following general procedure C, **12b** (500 mg, 0.611 mmol) was deprotected to give **13b** (418 mg, 0.574 mmol, 94%) as a yellow solid. M.p. 112°C; a partly doubled signal set (ratio 1:1) is observed in the NMR spectra: $^1$H NMR ($CDCl_3$, 500 MHz), two isomers: $\delta$=0.78–0.95 (m, 2×6H), 1.34 (s, 9H), 1.39 (s, 9H), 1.77–1.87 (m, 2×2H), 2.11–2.13 (m, 2×3H), 3.41–3.48 (m, 2×1H), 3.64–3.66 (m, 2×1H), 3.76 (s, 3H), 3.82 (s, 3H), 4.01–4.05 (m, 2×1H), 4.19–4.22 (m, 2×2H), 4.30–4.32 (m, 2×1H), 4.46–4.48 (m, 2×1H), 5.20 (br s, 2×1H),

5.50 (brs, 2×1H), 6.93 (t, $J$=7.3 Hz, 1H), 6.96 (t, $J$=7.3 Hz, 1H), 7.23–7.30 (m, 2×3H), 7.32–7.36 (m, 2×1H), 7.49 (t, $J$=7.2 Hz, 2×1H), 7.53 (t, $J$=7.0 Hz, 2×1H), 7.63 (t, $J$=6.8 Hz, 2×1H), 9.02 (s, 1H), 9.08 (s, 1H), 9.20 (s, 1H), 9.30 (s, 1H), 10.97 (s, 1H; NH), 11.01 (s, 1H; NH), 11.44 (s, 1H; NH), 11.46 ppm (s, 1H; NH); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz), two isomers: $\delta$=19.41 (2 $CH_3$), 19.53 (2 $CH_3$), 23.29 (2×$CH_2$), 28.23 (3 $CH_3$), 28.29 (3 $CH_3$), 30.44 (2×$CH_2$), 31.38 (2×CH), 47.09 (2×CH), 47.38 (2×$CH_2$), 51.92 ($CH_3$), 52.01 ($CH_3$), 60.39 (2×CH), 62.09 (2×CH), 68.03 ($CH_2$), 68.11 ($CH_2$), 80.09 (2×C), 114.76 (2×C), 117.96 (2×CH), 119.39 (C), 119.50 (C), 119.77 (CH), 119.88 (CH), 124.73 (CH), 124.87 (CH), 125.04 (CH), 125.20 (CH), 125.87 (2×2 CH), 126.92 (2×2 CH), 127.49 (2 CH), 127.64 (2 CH), 129.24 (2×C), 141.04 (C), 141.17 (C), 143.56 (C), 143.61 (C), 143.76 (2×C), 145.24 (C), 145.29 (C), 145.57 (2×C), 155.23 (C), 155.45 (C), 155.69 (C), 155.89 (C), 167.71 (C), 167.76 (C), 169.26 (C), 169.36 (C), 169.99 (C), 170.35 (C), 170.87 (C), 171.21 ppm (C); IR (ATR): $\tilde{\nu}$=3457 (m), 2970 (m), 1738 (vs), 1525 (s), 1437 (m), 1365 (s), 1228 (vs), 1205 (s), 1109 (m), 896 (m), 794 (m), 738 $cm^{-1}$ (m); MS (ESI, neg. mode): $m/z$ (%): 727 (88) [$M-H^+$], 527 (50), 306 (100); 728.79 ($C_{39}H_{44}N_4O_{10}$): elemental analysis calcd for $C_{39}H_{44}N_4O_{10}$: C 64.27, H 6.09, N 7.69; found: C 63.97, H 6.08, N 7.81.

**General procedure D**: **amidation of aromatic carboxylic acids with amino acid hydrochlorides**: A solution of DMAP in dichloromethane ($c$= 1 mmol $dm^{-3}$, 0.01 equiv) and DCC (2.0 equiv) were added to a solution of carboxylic acid (1.0 equiv) in dichloromethane (0.30 mol $dm^{-3}$). After the reaction mixture was stirred for 1 min at ambient temperature, a colorless precipitate was formed and HOBt (88% purity, 2.0 equiv) was added. In a separate flask, $NEt_3$ (1.2 equiv) was added to a suspension of the amino acid hydrochloride (1.1 equiv) in dichloromethane (0.30 mol $dm^{-3}$). This suspension was added to the first one and the resulting mixture was stirred in a tightly closed reaction flask for 2 d at 80 °C. After cooling to 23 °C, the mixture was diluted with dichloromethane (20 $dm^3 mol^{-1}$) and washed with saturated $NH_4Cl$ solution (20 $dm^3 mol^{-1}$), saturated $NaHCO_3$ solution (20 $dm^3 mol^{-1}$), and $H_2O$ (20 $dm^3 mol^{-1}$). After drying over $MgSO_4$ and filtration, the organic layer was evaporated and the residue purified by chromatography on $SiO_2$.

**5-[3-(*tert*-Butyloxycarbonylamino)propanoyl]amino-2-[3-(fluoren-9-ylmethyloxycarbonylamino)propanoyl]aminoterephthalic acid 1-[2-(*tert*-butyloxycarbonyl)ethyl]amide 4-methylester (14a)**: Following general procedure D, **13a** (114 mg, 0.168 mmol) was coupled with β-Ala-O*t*Bu·HCl (34 mg, 0.19 mmol) by using $NEt_3$ (19 mg, 0.19 mmol), DMAP (1.68 μmol, 1.68 mL), DCC (76 mg, 0.37 mmol), and HOBt (56 mg, 0.37 mmol) to give **14a** (120 mg, 0.149 mmol, 94%) as a yellow solid after chromatography ($SiO_2$, PE/EA/MeOH 2:2:1, $R_f$=0.46). M.p. 142 °C; $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$=1.43 (s, 9H), 1.46 (s, 9H), 2.57 (t, $J$= 5.8 Hz, 2H), 2.60–2.68 (m, 4H), 3.36 (q, $J$=6.0 Hz, 2H), 3.58 (q, $J$= 5.0 Hz, 2H), 3.64 (q, $J$=5.5 Hz, 2H), 3.91 (s, 3H), 4.17 (t, $J$=6.6 Hz, 1H), 4.36 (d, $J$=7.0 Hz, 2H), 5.20 (s, 1H; NH), 5.27 (s, 1H; NH), 5.73 (s, 1H; NH), 7.23–7.25 (m, 2H), 7.32–7.35 (m, 2H), 7.56 (d, $J$=7.3 Hz, 2H), 7.69 (d, $J$=7.3 Hz, 2H), 8.84 (s, 1H), 9.10 (s, 1H), 10.85 (s, 1H; NH), 10.95 ppm (s, 1H; NH); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$=24.81 ($CH_2$), 24.90 ($CH_2$), 25.46 ($CH_2$), 25.58 ($CH_2$), 28.06 (3 $CH_3$), 28.37 (3 $CH_3$), 33.07 ($CH_2$), 33.89 ($CH_2$), 47.21 (CH), 52.87 ($CH_3$), 66.50 ($CH_2$), 77.22 (C), 81.42 (C), 117.51 (C), 119.85 (2 CH), 120.25 (C), 123.28 (CH), 125.03 (2 CH), 126.93 (2 CH), 127.56 (2 CH), 128.97 (CH), 133.44 (C), 135.96 (C), 141.14 (C), 141.21 (C), 143.86 (C), 143.93 (C), 155.82 (C), 156.41 (C), 167.52 (C), 167.75 (C), 170.19 (C), 170.28 (C), 171.31 ppm (C); IR (ATR): $\tilde{\nu}$=3326 (m), 2932 (m), 2855 (w), 1697 (s), 1605 (s), 1541 (s), 1439 (m), 1401 (s), 1366 (m), 1323 (w), 1243 (vs), 1154 (vs), 912 (m), 729 $cm^{-1}$ (vs); MS (ESI): $m/z$ (%): 824 (17) [$M$+$Na^+$], 727 (9), 563 (25), 477 (86), 431 (100), 352 (39), 293 (19); HRMS (ESI): $m/z$: calcd for $C_{42}H_{52}N_5O_{11}$: 802.3663; found: 802.3658 [$M$+$H^+$]; 801.88 ($C_{42}H_{51}N_5O_{11}$).

**General procedure E**: **amidation of aromatic carboxylic acids with amines**: A solution of DMAP in dichloromethane ($c$=1 mmol $dm^{-3}$, 0.01 equiv) and DCC (1.2 equiv) was added to a solution of carboxylic acid (1.0 equiv) in dichloromethane (0.30 mol $dm^{-3}$). After the reaction mixture was stirred for 1 min at ambient temperature, a colorless precipitate was formed and HOBt (88% purity, 1.2 equiv) was added. After further stirring for 1 min, the amine (1.2 equiv) was added. The mixture was then stirred in a tightly closed reaction flask for 2 d at 80 °C. After cooling to 23 °C, the mixture was diluted with dichloromethane (20 $dm^3 mol^{-1}$), and washed with saturated $NH_4Cl$ solution (20 $dm^3 mol^{-1}$), saturated $NaHCO_3$ solution (20 $dm^3 mol^{-1}$), and $H_2O$ (20 $dm^3 mol^{-1}$). After drying over $MgSO_4$ and filtration, the organic layer was evaporated and the residue purified by chromatography on $SiO_2$.

**5-[(*S*)-2-(*tert*-Butyloxycarbonylamino)-3-methylbutanoyl]amino-2-{[(*S*)-1-(fluoren-9-ylmethyloxycarbonylamino)pyrrolidin-2-yl]carbonylamino}terephthalic acid 1-benzylamide 4-methyl ester (14b)**: Following general procedure E, **13b** (150 mg, 0.206 mmol) was coupled with $BnNH_2$ (26 mg, 0.25 mmol) by using DMAP (4 μmol, 2 mL solution), DCC (52 mg, 0.25 mmol), and HOBt (38 mg, 0.25 mmol) to give **14b** (160 mg, 0.131 mmol, 64%) as a yellow solid after chromatography ($SiO_2$, PE/EA/MeOH 2:2:1, $R_f$=0.35). M.p. 138 °C; $^1H$ NMR ([$D_6$]DMSO, 500 MHz, 80 °C, TMS): $\delta$=0.83–0.93 (m, 3H), 0.95–0.98 (m, 3H), 1.40 (s, 4.5H), 1.42 (s, 4.5H), 1.83–1.88 (m, 2H), 1.96–1.99 (m, 3H), 3.57–3.59 (m, 1H), 3.62–3.64 (m, 1H), 3.83 (s, 3H), 3.90–3.92 (m, 1H), 4.32 (A part of an AB system, $J$=7.6 Hz, 1H), 4.36–4.42 (m, 4H), 4.66 (B part of an AB system, $J$=7.6 Hz, 1H), 4.74 (s, 1H; NH), 5.28 (s, 1H; NH), 6.66–6.68 (m, 2H), 6.92–6.94 (m, 2H), 7.24–7.25 (m, 3H), 7.30–7.33 (m, 4H), 7.76–7.78 (m, 1H), 7.84–7.86 (m, 1H), 8.56 (s, 2H), 10.63 (s, 1H; NH), 10.88 ppm (s, 1H; NH); $^{13}C\{^1H\}$ NMR ([$D_6$]DMSO, 125 MHz, 80 °C, TMS): $\delta$=19.21 ($CH_3$), 19.24 ($CH_3$), 24.37 ($CH_2$), 28.30 (3 $CH_3$), 30.74 ($CH_2$), 32.86 (CH), 43.89 ($CH_2$), 44.10 (CH), 51.82 ($CH_3$), 55.65 ($CH_2$), 65.23 (CH), 65.35 (CH), 73.20 ($CH_2$), 73.74 ($CH_2$), 80.10 (C), 111.63 (2 CH), 116.34 (C), 116.86 (2 CH), 120.01 (C), 121.03 (C), 127.17 (CH), 127.54 (CH), 127.76 (CH), 127.94 (2 CH), 128.23 (CH), 128.70 (2 CH), 129.12 (CH), 130.01 (C), 130.94 (2 CH), 137.84 (C), 140.30 (C), 140.46 (C), 141.17 (2 C), 150.12 (2 C), 166.75 (C), 167.11 (C), 176.82 ppm (C); IR (ATR): $\tilde{\nu}$=3424 (m), 2923 (w), 2852 (w), 1694 (vs), 1539 (w), 1440 (s), 1244 (s), 1162 (m), 1024 (vs), 1004 (vs), 822 (s), 759 $cm^{-1}$ (s); MS (ESI): $m/z$ (%): 839 (18) [$M$−H+$Na^+$], 729 (89), 630 (39), 431 (23), 314 (100); HRMS (ESI): $m/z$: calcd for $C_{46}H_{50}N_5NaO_9$: 839.3506; found: 839.3505 [$M$−H+$Na^+$]; 817.93 ($C_{46}H_{51}N_5O_9$).

**General procedure F**: **saponification of methyl ester**: $K_2CO_3$ (10% aqueous solution, 1.1 equiv) was added to a solution of the respective methyl ester (1.0 equiv) in EtOH ($c$=0.1 mol $dm^{-3}$) and the mixture was stirred at 50 °C for 2 h. Subsequently, the reaction mixture was diluted with $H_2O$ (30 $dm^3 mol^{-1}$), acidified with concentrated hydrochloric acid (ca. 5–10 $dm^3 mol^{-1}$), and brine (30 $dm^3 mol^{-1}$) was added. The aqueous layer was extracted with dichloromethane (3×60 $dm^3 mol^{-1}$) and the combined organic layers were dried ($MgSO_4$) and filtered. The solvent was evaporated to give the crude carboxylic acids.

**5-[3-(*tert*-Butyloxycarbonylamino)propanoyl]amino-2-[3-(fluoren-9-ylmethyloxycarbonylamino)propanoyl]aminoterephthalic acid 1-[2-(*tert*-butyloxycarbonyl)ethyl]amide (15a)**: Following general procedure F, **14a** (80 mg, 0.10 mmol) was deprotected to give **15a** (55 mg, 0.70 mmol, 70%, purity >95% by LC–MS) as a colorless solid. M.p. 127 °C; $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$=1.43 (s, 9H), 1.45 (s, 9H), 2.38 (t, $J$= 4.8 Hz, 1H), 2.45 (t, $J$=4.7 Hz, 1H), 2.62–2.64 (m, 1H), 2.67–2.69 (m, 2H), 2.83–2.85 (m, 1H), 3.39–3.43 (m, 2H), 3.55–3.56 (m, 4H), 4.09–4.16 (m, 1H), 4.29–4.33 (m, 2H), 5.19 (brs, 1H), 5.30 (brs, 1H), 5.73 (brs, 1H), 6.77 (brs, 1H), 7.27–7.29 (m, 4H), 7.36–7.38 (m, 4H), 8.16 (s, 1H), 8.62 (s, 1H), 10.89 (s, 1H), 11.3 ppm (s, 1H); IR (ATR): $\tilde{\nu}$=3285 (w), 2985 (m), 1684 (vs), 1532 (vs), 1500 (s), 1452 (m), 1360 (w), 1231 (vs), 1150 (s), 1084 (m), 1021 (m), 967 (m), 722 $cm^{-1}$ (s); MS (ESI, neg. mode): $m/z$ (%): 786 (70) [$M-H^+$], 697 (100); HRMS (ESI, neg. mode): $m/z$: calcd for $C_{41}H_{48}N_5O_{11}$: 786.3350; found: 786.3358 [$M-H^+$]; 787.85 ($C_{41}H_{49}N_5O_{11}$).

**5-[(*S*)-2-(*tert*-Butyloxycarbonylamino)-3-methylbutanoyl]amino-2-{[(*S*)-1-(fluoren-9-ylmethyloxycarbonylamino)pyrrolidin-2-yl]carbonylamino}terephthalic acid 1-benzylamide (15b)**: Following general procedure F, **14b** (40 mg, 50 μmol) was deprotected to give **15b** (31 mg, 38 μmol, 75%, purity >95% by LC–MS) as a yellow oil. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$=0.76–0.94 (m, 6H), 1.35 (s, 4.5H), 1.37 (s, 4.5H), 1.79–1.85 (m, 2H), 2.18–2.21 (m, 3H), 3.39–3.42 (m, 1H), 3.76–3.82 (m, 1H), 4.36–4.38 (m, 1H), 4.46–4.48 (m, 2H), 4.51–4.57 (m, 2H), 4.75 (A part of an AB system, $J$=7.2 Hz, 1H), 5.08 (s, 1H, br), 5.23 (B part of an AB system,

$J$=7.0 Hz, 1H), 6.08 (brs, 1H), 6.81–6.86 (m, 2H), 7.24–7.28 (m, 6H), 7.31–7.34 (m, 5H), 7.71 (s, 2H), 7.94 (brs, 1H), 8.98 (brs, 1H), 9.04 ppm (brs, 1H); IR (ATR): $\tilde{\nu}$=3294 (m), 2950 (w), 1703 (s), 1526 (s), 1510 (vs), 1385 (m), 1224 (vs), 1152 (vs), 1077 (s), 1010 (m), 963 (m), 817 (m), 745 cm$^{-1}$ (m); MS (ESI, neg. mode): $m/z$ (%): 803 (100) [$M^+$], 651 (70), 445 (77), 391 (50); 803.91 ($C_{45}H_{49}N_5O_9$).

**5-[3-(*tert*-Butyloxycarbonylamino)propanoyl]amino-2-[3-(fluoren-9-ylmethyloxycarbonylamino)propanoyl]aminoterephthalic acid 1,4-bis[2-(*tert*-butyloxycarbonyl)ethyl]amide (2a)**: Following general procedure D, **15a** (10 mg, 13 μmol) was coupled with β-Ala-O*t*Bu·HCl (3 mg, 15 μmol), which was first treated with $NEt_3$ (2 mg, 15 μmol), by using DMAP (0.1 μmol, 0.1 mL), DCC (3 mg, 15 μmol), and HOBt (3 mg, 15 μmol) to give **2a** (11 mg, 12 μmol, 93%, 90% purity by LCMS) as a yellow oil. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.36 (s, 9H), 1.38 (s, 18H), 2.29 (t, $J$=6.2 Hz, 1H), 2.37 (t, $J$=5.8 Hz, 1H), 2.50–2.54 (m, 2H), 2.60–2.64 (m, 4H), 3.29–3.35 (m, 2H), 3.43–3.47 (m, 6H), 4.21–4.23 (m, 1H), 4.30–4.34 (m, 2H), 5.08 (brs, 1H), 5.22 (brs, 1H), 5.50 (brs, 1H), 6.52 (brs, 1H), 7.33–7.39 (m, 2H), 7.47–7.52 (m, 2H), 7.59–7.62 (m, 2H), 7.95–7.98 (m, 2H), 8.84 (s, 2H), 10.94 ppm (brs, 2H); IR (ATR): $\tilde{\nu}$=3250 (w), 2930 (s), 2855 (m), 1706 (s), 1618 (vs), 1548 (m), 1450 (m), 1366 (s), 1247 (s), 1153 (vs), 845 (w), 742 cm$^{-1}$ (m); MS (ESI): $m/z$ (%): 937 [$M$+Na$^+$]; 915.04 ($C_{48}H_{62}N_6O_{12}$).

**5-[(*S*)-2-(*tert*-Butyloxycarbonylamino)-3-methylbutanoyl]amino-2-{[(*S*)-1-(fluoren-9-ylmethyloxycarbonylamino)pyrrolidin-2-yl]carbonylamino}terephthalic acid 1-benzylamide 4-[(*S*)-1-(methoxycarbonyl)-3,3-dimethylbutyl]amide (2b)**: Following general procedure D, **15b** (25 mg, 0.031 mmol) was coupled with L-Npg-OMe·HCl (7 mg, 34 μmol), which was first treated with $NEt_3$ (3 mg, 34 μmol), by using DMAP (0.3 μmol, 0.3 mL), DCC (13 mg, 62 μmol), and HOBt (10 mg, 62 μmol) to give **2b** (10 mg, 11 μmol, 37%, purity >90% by HPLC) as a colorless solid. M.p. 124°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=0.88–0.96 (m, 6H), 1.13 (s, 9H), 1.47 (s, 4.5H), 1.49 (s, 4.5H), 1.66–1.84 (m, 5H), 1.90–1.96 (m, 2H), 3.16–3.31 (m, 1H), 3.60–3.67 (m, 1H), 3.75 (s, 3H), 4.19–4.20 (m, 1H), 4.30–4.38 (m, 2H), 4.22–4.45 (m, 1H), 4.56–4.67 (m, 2H), 4.80–4.89 (m, 1H), 5.30 (s, 1H; NH), 5.38–5.41 (m, 1H), 5.92 (s, 1H; NH), 6.37 (s, 1H; NH), 7.33–7.34 (m, 1H), 7.40–7.49 (m, 2H), 7.57–7.61 (m, 2H), 7.68 (d, $J$=8.4 Hz, 2H), 7.86 (d, $J$=8.3 Hz, 2H), 8.06 (d, $J$=8.4 Hz, 2H), 8.08 (d, $J$=8.4 Hz, 2H), 8.17 (s, 1H), 8.41 (s, 1H), 9.68 (s, 1H; NH), 9.76 ppm (s, 1H; NH); IR (ATR): $\tilde{\nu}$=3420 (m), 2896 (w), 1691 (vs), 1567 (s), 1440 (s), 1301 (m), 1162 (m), 1012 (s), 986 (m), 822 (s), 759 cm$^{-1}$ (s); MS (ESI): $m/z$ (%): 967 [$M$+Na$^+$] (10), 821 (42), 739 (79), 470 (100); 945.11 ($C_{53}H_{64}N_6O_{10}$).

**5-(*tert*-Butyloxycarbonylamino)-2-[(*S*)-4,4-dimethyl-2-(fluoren-9-ylmethyloxycarbonylamino)pentanoylamino]terephthalic acid 4-methyl ester (16)**: Following general procedure C, **10c** (320 mg, 0.427 mmol) was deprotected to give **16** (275 mg, 0.417 mmol, 98%) as a yellow solid. M.p. 138°C; a partly doubled signal set (ratio 1:1) was observed in the NMR spectra: $^1$H NMR ($CDCl_3$, 500 MHz), two isomers: $\delta$=0.90 (s, 9H), 0.99 (s, 9H), 1.54 (s, 9H), 1.56 (s, 9H), 1.94 (d, $J$=6.4 Hz, 2H), 1.97 (d, $J$=6.4 Hz, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 4.08 (t, $J$=6.9 Hz, 2×1H), 4.42–4.44 (m, 2×2H), 4.49–4.55 (m, 2×1H), 5.77 (d, $J$=6.2 Hz, 2×1H; NH), 7.10 (t, $J$=6.8 Hz, 2H), 7.22 (t, $J$=6.7 Hz, 2H), 7.28–7.33 (m, 2×2H), 7.47 (t, $J$=7.9 Hz, 2H), 7.54 (d, $J$=7.4 Hz, 1H), 7.59 (t, $J$=7.7 Hz, 2H), 7.63 (d, $J$=7.5 Hz, 1H), 7.68 (d, $J$=7.5 Hz, 2×1H), 8.85 (s, 1H), 9.09 (s, 1H), 9.19 (s, 1H), 9.28 (s, 1H), 9.42 (s, 1H; NH), 9.50 (s, 1H; NH), 10.03 (s, 1H; NH), 10.06 (s, 1H; NH), 11.26 (brs, 1H OH), 11.34 ppm (brs, 1H; OH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz), two isomers: $\delta$=28.31 (3 $CH_3$), 28.35 (3 $CH_3$), 29.52 (3 $CH_3$), 29.68 (3 $CH_3$), 30.67 (2×C), 45.87 ($CH_2$), 46.33 ($CH_2$), 47.17 (CH), 46.96 (CH), 52.72 ($CH_3$), 52.77 ($CH_3$), 54.32 (CH), 54.38 (CH), 67.22 ($CH_2$), 67.75 ($CH_2$), 80.48 (C), 80.99 (C), 118.89 (C), 118.94 (C), 119.86 (2 CH), 119.89 (2 CH), 120.66 (C), 120.68 (C), 121.18 (CH), 121.68 (CH), 122.21 (CH), 122.66 (CH), 124.56 (CH), 124.67 (CH), 125.04 (CH), 125.12 (CH), 126.89 (2 CH), 126.97 (2 CH), 127.63 (2 CH), 127.68 (2 CH), 133.95 (C), 134.00 (C), 136.63 (C), 136.78 (C), 141.20 (2×2 C), 143.25 (C), 143.30 (C), 143.56 (C), 143.78 (C), 152.62 (C), 152.80 (C), 156.25 (C), 156.84 (C), 167.40 (C), 167.67 (C), 169.68 (C), 170.70 (C), 171.97 ppm (2×C); IR (ATR): $\tilde{\nu}$=3319 (w), 2954 (m), 1692 (s), 1539 (vs), 1437 (m), 1410 (m), 1322 (w), 1239 (vs), 1152 (vs), 1111 (m), 1017 (m), 908 (s), 860 (w), 729 cm$^{-1}$ (vs); MS (ESI): $m/z$ (%): 682 (100) [$M$+Na$^+$], 634 (35), 485 (40), 437 (22), 271 (21); MS (ESI, neg. mode): $m/z$ (%): 658 (100) [$M$−H$^+$], 436 (54); HRMS (ESI): $m/z$: calcd for $C_{36}H_{41}N_3NaO_9$: 682.2740; found: 682.2740 [$M$+Na$^+$]; elemental analysis calcd for $C_{36}H_{41}N_3O_9$ (659.73): C 65.54, H 6.26, N 6.37; found: C 65.97, H 6.18, N 6.26.

**5-(*tert*-Butyloxycarbonylamino)-2-[(*S*)-4,4-dimethyl-2-(fluoren-9-ylmethyloxycarbonylamino)pentanoylamino]terephthalic acid 1-(4-methoxybenzyl)amide 4-methyl ester (17)**: Following general procedure E, **16** (530 mg, 0.80 mmol) was coupled with PMB–$NH_2$ (132 mg, 0.96 mmol) by using DMAP (4 μmol, 4 mL solution), DCC (199 mg, 0.96 mmol), and HOBt (148 mg, 0.96 mmol) to give **17** (385 mg, 0.49 mmol, 61%) as a yellow oil after chromatography ($SiO_2$, PE/EA 1:1, $R_f$=0.50). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.03 (s, 9H), 1.46 (s, 9H), 1.55–1.63 (m, 2H), 3.67 (s, 3H), 3.91 (s, 3H), 4.23 (t, $J$=7.1 Hz, 1H), 4.31–4.37 (m, 2H), 4.42–4.78 (m, 3H), 5.66 (brs, 1H; NH), 6.72–6.73 (m, 2H), 7.03 (brs, 1H; NH), 7.11–7.13 (m, 2H), 7.23–7.26 (m, 2H), 7.34–7.35 (m, 2H), 7.54 (d, $J$=7.4 Hz, 1H), 7.62 (d, $J$=7.5 Hz, 1H), 7.68 (d, $J$=7.5 Hz, 2H), 8.53 (s, 1H), 9.17 (s, 1H), 10.10 (s, 1H; NH), 11.49 ppm (s, 1H; NH); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=28.16 (3 $CH_3$), 29.62 (3 $CH_3$), 30.59 (C), 43.16 ($CH_2$), 46.27 ($CH_2$), 47.17 (CH), 52.51 ($CH_3$), 54.11 (CH), 55.04 ($CH_3$), 67.06 ($CH_2$), 80.79 (C), 113.86 (2 CH), 113.95 (C), 116.50 (CH), 116.80 (C), 119.76 (2 CH), 123.25 (CH), 124.90 (C), 125.09 (CH), 125.15 (CH), 125.66 (C), 126.89 (2 CH), 127.49 (2 CH), 128.96 (2 CH), 132.18 (C), 136.80 (C), 141.10 (C), 143.65 (C), 144.02 (C), 152.81 (C), 155.88 (C), 158.83 (C), 167.36 (C), 167.62 (C), 171.72 ppm (C); IR (ATR): $\tilde{\nu}$=3318 (m), 2953 (m), 1699 (s), 1656 (m), 1541 (s), 1512 (s), 1438 (m), 1406 (m), 1367 (w), 1322 (w), 1238 (vs), 1154 (vs), 1047 (m), 973 (s), 921 (s), 733 cm$^{-1}$ (vs); MS (ESI): $m/z$ (%): 801 (100) [$M$+Na$^+$], 557 (22), 471 (19), 389 (5), 304 (2), 238 (8); HRMS (ESI): $m/z$: calcd for $C_{44}H_{50}N_4NaO_9$: 801.3475; found: 801.3470 [$M$+Na$^+$]; 778.89 ($C_{44}H_{50}N_4O_9$).

**5-(*tert*-Butyloxycarbonylamino)-2-[(*S*)-4,4-dimethyl-2-(fluoren-9-ylmethyloxycarbonylamino)pentanoylamino]terephthalic acid 1-(4-methoxybenzyl)amide (18)**: Following general procedure F, **17** (220 mg, 0.282 mmol) was deprotected to give **18** (150 mg, 0.196 mmol, 70%) as a colorless solid. M.p. 72°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.01 (s, 9H), 1.37–1.40 (m, 2H), 1.49 (s, 9H), 3.74 (s, 3H), 4.04–4.06 (m, 1H), 4.34–4.42 (m, 3H), 4.49–4.53 (m, 2H), 5.21 (brs, 1H), 6.81–6.85 (m, 2H), 7.01 (brs, 1H), 7.25–7.33 (m, 4H), 7.41–7.44 (m, 2H), 7.56–7.58 (m, 2H), 7.67 (d, $J$=8.4 Hz, 2H), 8.03 (d, $J$=8.5 Hz, 2H), 9.88 (brs, 1H), 10.10 (brs, 1H), 11.41 ppm (brs, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$=28.28 (3 $CH_3$), 29.50 (3 $CH_3$), 30.65 (C), 42.81 ($CH_2$), 46.10 ($CH_2$), 47.31 (CH), 53.42 ($CH_3$), 55.26 (CH), 67.21 ($CH_2$), 85.07 (C), 109.41 (2 CH), 114.09 (CH), 114.32 (C), 118.84 (C), 120.07 (C), 120.21 (2 CH), 120.35 (C), 124.70 (CH), 125.05 (2 CH), 125.26 (CH), 127.08 (CH), 127.59 (CH), 128.71 (CH), 128.77 (2 CH), 128.96 (C), 129.42 (C), 136.70 (C), 141.53 (C), 143.49 (C), 144.32 (C), 152.32 (C), 157.82 (C), 159.03 (C), 166.91 (C), 168.23 ppm (C); IR (ATR): $\tilde{\nu}$=3297 (m), 2956 (m), 1691 (s), 1537 (vs), 1511 (vs), 1410 (w), 1367 (m), 1239 (vs), 1152 (vs), 1084 (m), 1021 (m), 968 (m), 826 (w), 737 cm$^{-1}$ (s); MS (ESI, neg. mode): $m/z$ (%): 763 [$M$−H$^+$]; HRMS calcd for $C_{43}H_{47}N_4NaO_9$: 786.3241; found: 786.3242 [$M$+Na$^+$]; 764.86 ($C_{43}H_{48}N_4O_9$).

**5-(*tert*-Butyloxycarbonylamino)-2-[(*S*)-4,4-dimethyl-2-(fluoren-9-ylmethyloxycarbonylamino)pentanoylamino]terephthalic acid 1-(4-methoxybenzyl)amide 4-[1-(methoxycarbonyl)-1-methylethyl]amide (19)**: Following general procedure D, **18** (40 mg, 53 μmol) was coupled with Aib–OMe·HCl (9 mg, 58 μmol), which was first treated with $NEt_3$ (6 mg, 58 μmol), by using DMAP (0.5 μmol, 0.5 mL), DCC (21 mg, 0.105 mmol), and HOBt (16 mg, 0.105 mmol) to give **19** (32 mg, 28 μmol, 53%, purity >98% by HPLC) as a yellow oil after chromatography ($SiO_2$, PE/EA/MeOH 2:2:1, $R_f$=0.29). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=0.92–1.04 (m, 2H), 0.97 (s, 9H), 1.51 (s, 6H), 1.55 (s, 9H), 3.76 (s, 3H), 3.80 (s, 3H), 3.86–3.88 (m, 1H), 4.37–4.42 (m, 3H), 4.53–4.56 (m, 2H), 5.01 (brs, 1H), 5.15 (brs, 1H), 6.78–6.91 (m, 2H), 7.15–7.23 (m, 4H), 7.45–7.47 (m, 2H), 7.57–7.59 (m, 2H), 7.86 (d, $J$=8.4 Hz, 2H), 8.10 (d, $J$=8.5 Hz, 2H), 9.16 (brs, 1H), 10.13 (brs, 1H), 10.20 ppm (brs, 1H); IR (ATR): $\tilde{\nu}$=3278 (m), 2945 (m), 1702 (vs), 1498 (s), 1356 (w), 1202 (s), 1098 (s), 1013 (m), 972

(m), 911 (m), 866 (w), 723 $cm^{-1}$ (s); MS (ESI): *m*/*z* (%): 886 (22) [*M*+$Na^+$], 786 (16), 690 (18), 586 (100), 410 (44), 305 (37); HRMS (ESI): *m*/*z*: calcd for $C_{48}H_{57}N_5NaO_{10}$: 886.4003; found: 886.3995 [*M*+$Na^+$]; 863.99 ($C_{48}H_{57}N_5O_{10}$).

**5-Amino-2-[(*S*)-4,4-dimethyl-2-(fluoren-9-ylmethyloxycarbonylamino)-pentanoylamino]terephthalic acid 1-(4-methoxybenzyl)amide 4-[1-(methoxycarbonyl)-1-methylethyl]amide (20)**: Following general procedure A, **19** (30 mg, 35 μmol) was deprotected and the residue purified by column chromatography (PE/EA/MeOH 2:2:1, $R_f$=0.27) to give **20** (25 mg, 33 μmol, 95%, purity >95% by HPLC) as a yellow oil. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=0.90–0.97 (m, 2H), 0.94 (s, 9H), 1.43 (s, 6H), 3.68 (s, 3H), 3.72 (s, 3H), 3.91–3.93 (m, 1H), 4.30–4.51 (m, 5H), 5.21 (brs, 1H), 5.93 (brs, 2H), 6.80–6.85 (m, 2H), 7.21–7.36 (m, 6H), 7.49–7.52 (m, 2H), 7.82–7.91 (m, 4H), 8.32 (brs, 1H), 9.56 (brs, 1H), 9.67 ppm (brs, 1H); IR (ATR): $\tilde{\nu}$=3287 (w), 2953 (w), 1691 (vs), 1510 (s), 1404 (s), 1326 (m), 1225 (vs), 1088 (vs), 984 (w), 913 (m), 720 $cm^{-1}$ (s); MS (ESI): *m*/*z* (%): 764 (100) [*M*+$H^+$]; HRMS (ESI): *m*/*z*: calcd for $C_{43}H_{49}N_5NaO_8$: 786.3479; found: 786.3485 [*M*+$Na^+$]: 763.88 ($C_{43}H_{49}N_5O_8$).

**2-[(*S*)-4,4-Dimethyl-2-(fluoren-9-ylmethyloxycarbonylamino)pentanoylamino]-5-[(3a*S*,4*R*,6a*R*)-5-(hexahydro-2-oxothieno[3.4-*d*]imidazol-4-yl)-pentanoylamino]terephthalic acid 1-(4-methoxybenzyl)amide 4-[1-(methoxycarbonyl)-1-methylethyl]amide (2c)**: Following general procedure B, **20** (20 mg, 26 μmol) was coupled with (+)-biotine (7 mg, 29 μmol) by using DCC (6 mg, 31 μmol) and HOBt (5 mg, 31 μmol) to give **2c** (9 mg, 9.2 μmol, 35%) as a colorless solid after chromatography ($SiO_2$, PE/EA/MeOH 2:2:1, $R_f$=0.17, purity >90% by HPLC). M.p. 89°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$=1.08–1.09 (m, 6H), 1.11 (s, 9H), 1.25–1.35 (m, 8H), 2.41–2.43 (m, 2H), 2.72–2.74 (m, 2H), 3.44–3.47 (m, 6H), 3.93–3.95 (m, 1H), 4.30–4.35 (m, 2H), 4.50–4.53 (m, 2H), 4.61–4.64 (m, 1H), 4.70–4.73 (m, 2H), 5.17 (brs, 1H), 5.24 (brs, 1H), 5.29 (brs, 1H), 5.66 (brs, 1H), 5.79 (brs, 2H), 6.10 (brs, 1H), 7.34–7.37 (m, 1H), 7.41–7.43 (m, 2H), 7.53–7.56 (m, 2H), 7.67–7.68 (m, 2H), 7.76–7.79 (m, 1H), 7.86–7.87 (m, 1H), 7.98–8.00 (m, 2H), 8.05–8.06 (m, 2H), 8.37–8.40 ppm (m, 2H); IR (ATR): $\tilde{\nu}$=3288 (m), 2927 (s), 2854 (m), 1696 (vs), 1640 (s), 1542 (s), 1450 (s), 1285 (m), 1094 (m), 1028 (m), 737 $cm^{-1}$ (s); MS (ESI): *m*/*z* (%): 1013 [*M*+$Na^+$]; 990.17 ($C_{53}H_{63}N_7O_{10}S$).

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