Synthesis of Orthogonally Protected Bis(aminomethyl)malonic Acid, and Its Use as a Key Building Block in the Preparation of Cyclic Peptide Conjugates of 2-*N*-Alkyl-1,2,3,4-tetrahydroisoquinoline on a Solid Support

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Orthogonally protected bis(aminomethyl)malonic acid (**1**) was synthesized and used as a key building block for the construction of cyclic peptide conjugates on a solid support. The applicability of the building block was demonstrated by preparation of 19 backbone cyclized/branched peptide conjugates of *N*-2-alkyl-5-(3-aminopropoxy)-1,2,3,4-tetrahydroisoquinoline as stereoisomeric pairs.

Introduction

Cyclic peptides are conformationally less flexible than their linear counterparts, which makes them useful tools for probing the structure of receptor targets.[1] Conjugation of small cyclic peptides to a core structure that is known to exhibit affinity towards a given receptor may therefore provide useful sets of lead compounds for structural studies of membrane receptors by chemical mapping. We have previously developed solid phase methods for the preparation of both linear and branched β-peptide conjugates of *N*-2-alkyl-1,2,3,4-tetrahydroisoquinoline for such purposes,[2] using α,α-dialkylated and α,α-bisaminomethylated β-alanines as the key building blocks. These conjugates were aimed at probing the structure of the α_2-adrenergic receptors. As an extension of this approach we now report on the preparation of similar cyclic peptide conjugates on a solid support. The methodology developed is based on utilization of an orthogonally protected bis(aminomethyl)malonic acid (**1**) , bearing conventional Fmoc and Boc protecting groups on the two amino functions, and with one of the carboxylic acid groups protected as an allyl ester (Figure 1). The Fmoc-protected amino group and the allyl-protected carboxylic acid group have been exploited in construction of a backbone-cyclized peptide moiety, while the Boc-protected amino group and the free carboxylic acid group have been used for insertion of this cyclic block into the linear peptide chain. Thanks to the two dissimilar protecting groups on the amino functions, **1** is chiral, and the peptide conjugates are hence obtained as stereoisomeric pairs. As previously,[2] 5-(3-aminopropoxy)-1,2,3,4-tetrahydroisoquinoline immobilized to hydroxymethyl polystyrene resin through a vinylsulfonyl linker[3] was used as a handle for the peptide chain assembly.

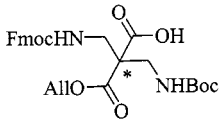

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Figure 1. Orthogonally protected bis(aminomethyl)malonic acid (**1**).

Results and Discussion

Synthesis of Bis(aminomethyl)malonic Acid (1)

The bis(aminomethyl)malonic acid building block (**1**) was synthesized from benzylidene-protected pentaerythritol[4] (**2**) as outlined in Scheme 1. 4-Methoxytritylation of one of the unprotected hydroxy groups (**3**) was followed by displacement of the other with phthalimide by a Mitsunobu reaction (**4**),[5] removal of the phthaloyl group by hydrazinolysis (**5**), and protection of the deblocked amino group with a Boc group (**6**). The next step, the opening of the 1,3-dioxane ring by a palladium-catalyzed *tert*-butyl hydroperoxide oxidation,[6] was the key step of the synthesis. One of the ring oxygens remained protected by a benzoyl group, while the other was released as a hydroxy group (**7**) and was subsequently displaced with phthalimide (**8**). Removal of phthaloyl and benzoyl groups in a single step by hydrazinolysis was attempted, but this proved to yield an *N*-benzoylated product instead of a free amine. For this reason, the benzoyl protecting group was removed by sodium methoxide-catalyzed transesterification (**9**) prior to hydrazinolysis of the phthaloyl group (**10**). After protection of the amino function with a Fmoc group (**11**), the hydroxy group was oxidized to a carboxylic acid group (**12**) with PDC (pyridinium dichromate) under neutral conditions.[7] The crude reaction product was used for esterification of the carboxylic acid function with allyl bromide **13**, because **12** tended to decompose during silica gel chromatography (several

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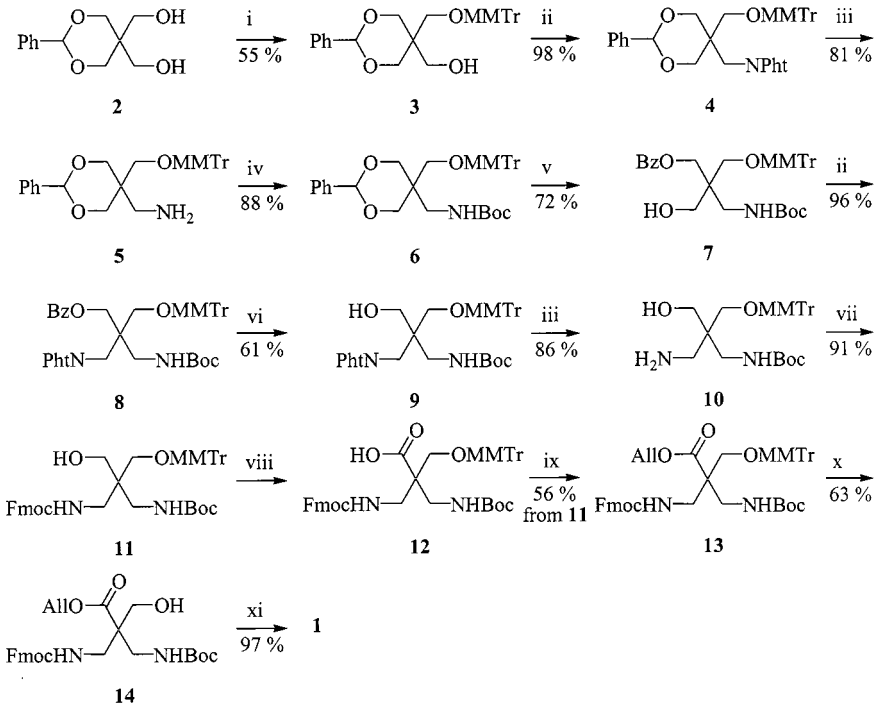


Scheme 1. Synthesis of building block **1**. (i) MMTrCl, Py, (ii) PhthNH, DEAD, Ph_3P, THF, (iii) NH_2NH_2, OH_2, EtOH, (iv) Boc_2O, NaOH, H_2O, MeCN, (v) *t*BuOOH, $Pd(OAc)_2$, benzene, (vi) NaOMe, MeOH, (vii) FmocCl, DIPEA, dioxane, (viii) PDC, DMF, (ix) AllBr, DIPEA, DMF, (x) I_2, MeOH, (xi) CrO_3, H_2SO_4, acetone.

methods were tried). The MMTr group of **13** was removed with iodine in methanol,[8] and Jones oxidation of the released hydroxy function (**14**) accomplished the synthesis.

The Solid Support 15

Hydroxymethyl polystyrene derivatized with *O*-(vinylsulfonylethyl) groups was employed as the solid support. *N*-(*tert*-butyloxycarbonyl)-protected 5-(3-aminopropoxy)-1,2,3,4-tetrahydroisoquinoline was immobilized through its *N*-2 atom by Michael addition onto the vinyl groups of this resin, as described previously.[3] The relative quantity of the tetrahydroisoquinoline compound was adjusted so that only about one third of the vinylsulfonyl groups on the support became derivatized. The final tetrahydroisoquinoline loading was hence about 80 μmol g^{-1}. The unchanged vinylsulfonyl groups were capped with methanol using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a base.

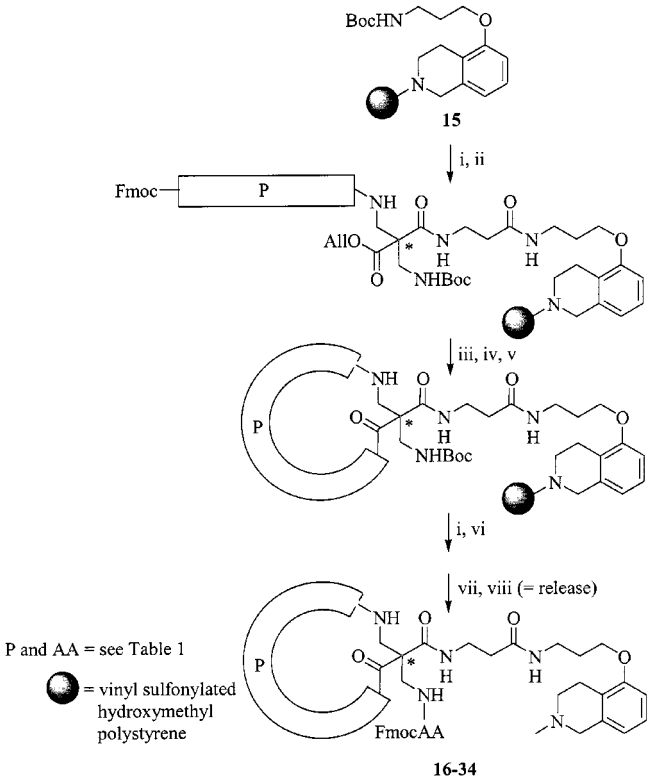
Removal of Protecting Groups on the Solid Support

Conventional peptide synthesis strategies on a solid support include removal of Fmoc and Boc groups with 20% piperidine in DMF and with 25% TFA in DCM (dichloromethane), respectively. The removal of the Fmoc protecting group from solid-supported **1** with piperidine proved to be rather readily accompanied by elimination of the unblocked aminomethyl group, resulting in formation of a methylenemalonate derivative, but no traces of this side product were observed during standard piperidine treatment with a reaction time of 15 min. Accordingly, unnecessarily basic conditions were carefully avoided. Hydroxymethyl derivatives of malonic acid have previously been reported to undergo a similar transformation.[9] The removal of the Boc group from **1** by TFA treatment did not, in turn, result in any detectable side products; no elimination of the aminomethyl group or hydrolysis of the allyl ester function could be observed. Allyl protecting groups are frequently removed by means of a tetrakis(triphenylphosphane)palladium(0)-catalyzed reaction when a three-dimensional orthogonal protecting strategy is applied.[10] This method could also be used without difficulty to remove the allyl protection from the carboxylic acid group of **1.**

Synthesis of the Peptide Conjugates 16−34

The 5-(3-aminopropoxy) side chain of the solid-supported tetrahydroisoquinoline core was first elongated with one N^{α}-Fmoc-β-alanine unit, and **1** was then coupled to the deprotected β-amino group using standard HATU [*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] procedures (Scheme 2.).[11] The Fmoc protection was removed from the solid-supported **1**, and a short (three amino acids) peptide sequence was assembled on the amino function. After this, the terminal Fmoc protection and the allyl protection of **1** were removed, and the cyclization (10 equiv. HATU, 20 equiv. DIPEA (*N*,*N*-diisopropylethylamine) in DMF, 15 h at room temperature) was performed. The Boc group was removed from **1**, and coup-

ling with an appropriate Fmoc-protected amino acid (Gly, Ala, and Phe) was carried out. Release from the support was achieved by *N*-2 quaternization of the tetrahydroisoquinoline moiety with methyl iodide and subsequent triethylamine treatment. Figure 2 shows an example of a crude reaction product (stereoisomer pair **33**).



Scheme 2. Synthesis of conjugates **16**−**34**. (i) TFA, DCM, (ii) peptide assembly using HATU/Fmoc chemistry, (iii) $(Ph_3P)_4Pd^0$, DMSO, THF, 0.5 M HCl, morpholine, (iv) piperidine, DMF, (v) HATU, DIPEA, DMF, (vi) Fmoc-AA-OH, HATU, DIPEA, DMF, (vii) MeI, DMF, (viii) Et_3N, DCM.

Cyclization of peptides of fewer than seven α-amino acids in length is usually difficult.[12] To evaluate the cyclization efficiency, all the possible tripeptides consisting of glycine and β-alanine were assembled on the amino group of **1** and cyclized using a shorter reaction time (4 h) than in the final library synthesis. It was clearly observed that the cyclization efficiency correlated with the number of β-alanine units in the peptide. When a Gly-Gly-Gly sequence was used, no cyclization could be observed, even though this type of cyclic backbone structure has been described previously.[12a] It was also noticed that additional space between the tetrahydroisoquinoline moiety and **1** facilitates the cyclization. This observation, in fact, prompted us to use one β-alanine unit between **1** and the aminopropoxy tail of tetrahydroisoquinoline. Table 1 summarizes the peptide conjugates finally prepared to demonstrate the applicability of the technique developed. The authenticity of the products was verified by HPLC/ESI-MS.

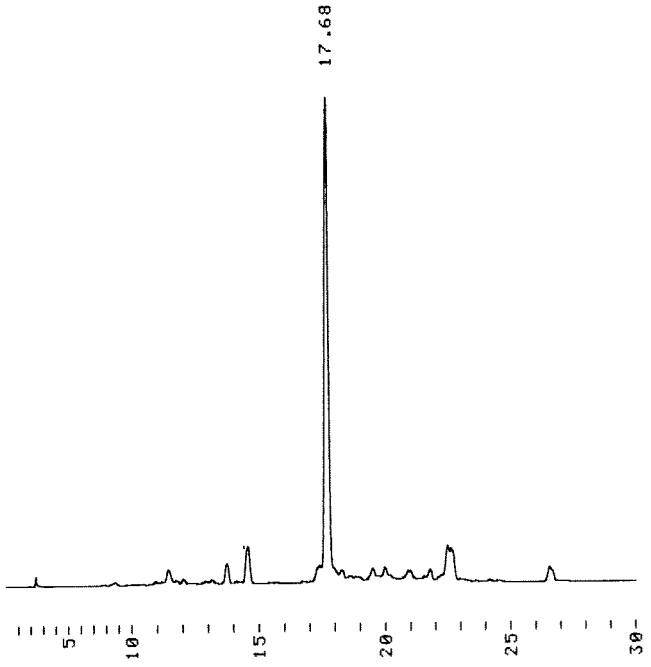


Figure 2. HPLC chromatogram of the crude synthesis product of conjugate **33** (refers to a pair of stereoisomers). Hypersil Hypurity C18 (150×4.6 mm, 5 μm), gradient from aqueous 0.1% TFA to acetonitrile in 30 min, flow 1.0 mL min^{-1}, detection at 276 nm.

Table 1. Required and found molecular weights (M_{req} and $[M + H]^+_{found}$) for the peptide conjugates synthesized (**16**−**34** cf. Scheme 2).

No.	P	AA	M_{req}	$[M + H]^+_{found}$
16	GlyGlyβ-Ala	Gly	881.4	882.7
17	Glyβ-AlaGly	Gly	881.4	882.7
18	β-AlaGlyGly	Gly	881.4	882.7
19	β-Alaβ-AlaGly	Gly	895.4	896.4
20	β-AlaGlyβ-Ala	Gly	895.4	896.4
21	Glyβ-Alaβ-Ala	Gly	895.4	896.4
22	$(β\text{-Ala})_3$	Gly	909.4	910.5
23	β-AlaLeuβ-Ala	Gly	951.5	952.6
24	β-AlaLeuβ-Ala	Ala	965.5	966.8
25	β-AlaLeuβ-Ala	Phe	1041.5	1042.9
26	β-AlaPheβ-Ala	Gly	985.5	986.8
27	β-AlaPheβ-Ala	Ala	999.5	1000.7
28	β-AlaPheβ-Ala	Phe	1075.5	1076.5
29	β-AlaGlnβ-Ala	Gly	966.5	967.3
30	β-AlaGlnβ-Ala	Ala	980.5	981.5
31	β-AlaGlnβ-Ala	Phe	1056.5	1057.8
32	β-AlaSerβ-Ala	Gly	925.4	926.4
33	β-AlaSerβ-Ala	Ala	939.4	940.8
34	β-AlaSerβ-Ala	Phe	1015.5	1016.8

Experimental Section

General: NMR spectra were recorded on Bruker 200 NMR or JEOL JNM-GX 400 spectrometers. The chemical shifts are given in ppm from internal TMS. − The mass spectra were recorded on 7070E VG or PE SCIEX API 365 LC/ESI-MS/MS mass spectrometers. − RP HPLC analyses were performed using a Hypersil 150 × 4.6 mm, 5 μm Hypurity™ Elite C18 column, gradient from aqueous 0.1% TFA to acetonitrile in 30 min, flow 1.0 mL min^{-1}, detection at 276 nm.

Solid Support 15: The hydroxymethyl polystyrene support derivatized with *O*-vinylsulfonylethyl groups[3] (1.0 g) was suspended in DMF (10 mL). 5-[3-(*tert*-Butyloxycarbonylamino)propoxy]-1,2,3,4-tetrahydroisoquinoline[2a] (40 mg, 0.13 mmol) in DMF (2 mL) was added dropwise and the mixture was shaken at ambient temperature for 20 h. The solid support was washed with DCM and methanol, and resuspended in a mixture of DCM (8.0 mL), methanol (4.0 mL), and DBU (0.5 mL). The suspension was shaken at ambient temperature for 20 h, washed with DCM and methanol, and dried under reduced pressure. According to RP HPLC analysis of the tetrahydroisoquinoline derivative released from the support, the loading was 80 μmol g^{-1}.

Synthesis of Peptide Conjugates 16−34: The Boc group was first removed from support-bound 5-[3-(*tert*-butyloxycarbonylamino)propoxy]-1,2,3,4-tetrahydroisoquinoline (**15** in Scheme 2) with the aid of 25% TFA in DCM (1 h at room temperature). The fully protected acyclic peptide chains containing **1** as the penultimate *C*-terminal residue were then assembled using HATU/Fmoc chemistry (1 μmol scale). The support and $(Ph_3P)_4Pd^0$ (5.8 mg, 5 mol. equiv.) were then suspended in a mixture of DMSO, THF, aq. 0.5 M HCl, and morpholine (580 μL, 1:1:0.5:0.1, *v*/*v*/*v*/*v*), and the mixture was shaken at room temperature for 45 min. This reaction time was sufficient to complete the allyl deprotection. The support was then filtered and washed successively with DMSO, DMF, 30% Et_3N in DMF, DMF, DCM, MeOH, and DMF, in that order. The Fmoc group was removed with 20% piperidine in DMF (15 min at room temperature), and the support was subjected to successive washings with DMF, 30% Et_3N in DMF, DMF, DCM, and MeOH. The dried support was suspended in DMF (200 μL), and HATU (3.8 mg, 10 molar equiv. in 180 μL DMF) and DIPEA (3.5 μL, 20 molar equiv. in 10 μL DMF) were added. The support was shaken in this solution at room temperature for 15 h, and then filtered off, washed with DMF, DCM, and MeOH, and dried. The Boc group was removed by using 25% TFA in DCM (1 h at room temperature), washed with DCM, 10% pyridine in DCM, DCM, and MeOH, and dried. The appropriate amino acid (5 molar equiv. in 100 μL DMF), HATU (1.9 mg, 5 molar equiv. in 100 μL DMF), and DIPEA (1.8 μL, 10 molar equiv. in 10 μL DMF) were added. The mixture was shaken for 1 h at room temperature, and the solid support was then filtered, washed with DMF, DCM, and MeOH, and dried. The support was then shaken with a solution of methyl iodide in DMF (MeI:DMF, 1:9, *v*/*v*) for 1 h, filtered off, washed with DCM and MeOH, and dried. Triethylamine in DCM (Et_3N:DCM, 1:1, *v*/*v*) was added, and the mixture was shaken for 20 min. The solution was collected by filtration, and the solvents evaporated off, producing **16−34** as crude reaction products. Prior to HPLC analysis, the residue was diluted with 0.1% aq. TFA. The authenticity of the products was verified by HPLC/ESI-MS (Table 1). The yield of each coupling was determined by assessing the Fmoc released before addition of the next residue, by UV spectroscopy. On this basis the coupling efficiency was higher than 95%, also when using **1** as a building block. In addition, the product was in some cases (**16**, **22**, **23**, **28**, **33**) released from an aliquot of the solid support after each coupling and analyzed by HPLC. Only minor impurities gradually appeared. Accordingly, the overall yield of the synthesis was approximately 50−70%. The chromatogram depicted in Figure 2 illustrates the situation at the end of the synthesis.

5-Hydroxymethyl-5-(4-methoxytrityloxy)methyl-2-phenyl-1,3-dioxane (3): Benzylidene-protected pentaerythritol[4] (**2**) (15 g, 67 mmol) was coevaporated twice with dry pyridine, and dissolved in the same solvent (60 mL). 4-Methoxytrityl chloride (13.7 g, 44 mmol) was added to this solution. The reaction mixture was stirred at room temperature for 3 h, and the solvents were evaporated off. The residue was dissolved in DCM (200 mL), and the organic phase was washed with saturated aq. $NaHCO_3$ and brine, and evaporated to dryness. The product was purified by silica gel chromatography (30% EtOAc in petroleum ether), yielding 12.2 g (55%) of **3** as a white, solid foam. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (t, *J* = 6.0 Hz, 1 H, OH), 3.45 (d, *J* = 5.9 Hz, 2 H, C*H*$_2$OH), 3.62 (s, 2 H, CH_2OMMTr), 3.78 (s, 3 H, OCH_3), 3.79 (d, *J* = 11.8 Hz, 2 H, 2 × OC*H*HC_q), 4.25 (d, *J* = 11.8 Hz, 2 H, 2 × OCH*H*C_q), 5.42 (s, 1 H, PhCH), 6.85 (m, 2 H, MMTr), 7.21−7.51 (m, 17 H, MMTr and Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.0 (C_q, pentaerythritol), 55.2 (OCH_3), 63.7 (CH_2OMMTr), 65.8 (CH_2OH), 70.4 (O*C*H_2C_q), 86.8 (C_q, MMTr), 102.2 (PhCH), 113.2 (MMTr), 126.3, 127.0, 128.0, 128.2, 128.2, 129.1, 130.4 (MMTr and Ph), 135.2 (MMTr), 138.2 (Ph), 144.2, 158.7 (MMTr). − HRMS (EI): M^+ found 496.2236. $C_{32}H_{32}O_5$ requires 496.2236.

5-(4-Methoxytrityloxy)methyl-2-phenyl-5-phthalimidomethyl-1,3-dioxane (4): Diethyl azodicarboxylate (DEAD; 7.6 mL, 48 mmol) was added dropwise to a solution of **3** (12.1 g, 24 mmol), triphenylphosphane (12.8 g, 48 mmol), and phthalimide (7.2 g, 48 mmol) in THF (70 mL). The reaction mixture was stirred overnight at room temperature, and evaporated to dryness. The crude reaction product was purified by silica gel chromatography (30 to 50% EtOAc in petroleum ether), yielding 15.0 g (98%) of **4** as a white, solid foam. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.58 (s, 2 H, CH_2NPhth), 3.65 (s, 2 H, CH_2OMMTr), 3.78 (s, 3 H, OC*H*$_3$), 3.82 (d, *J* = 11.9 Hz, 2 H, 2 × OC*H*HC_q), 4.37 (d, *J* = 11.9 Hz, 2 H, 2 × OCH*H*C_q), 5.35 (s, 1 H, PhCH), 6.81 (m, 2 H, MMTr), 7.17−7.53 (m, 17 H, MMTr and Ph), 7.69−7.87 (m, 4 H, Phth). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.8, 40.1 (CH_2NPhth and C_q, pentaerythritol), 55.1 (OCH_3), 63.2 (CH_2OMMTr), 70.6 (O*C*H_2C_q), 86.4 (C_q, MMTr), 101.7 (PhCH), 113.0 (MMTr), 123.4 (Phth), 126.3, 126.7, 127.7, 128.1, 128.5, 129.0, 130.5 (MMTr and Ph), 131.9, 134.1 (Phth), 135.4 (MMTr), 138.0 (Ph), 144.3, 158.4 (MMTr), 168.6 (C=O, Phth). − HRMS (EI): M^+ found 625.2461. $C_{40}H_{35}NO_6$ requires 625.2464.

5-Aminomethyl-5-(4-methoxytrityloxy)methyl-2-phenyl-1,3-dioxane (5): Hydrazine monohydrate (3.7 mL, 76 mmol) was added to a solution of **4** (12.1 g, 19 mmol) in 150 mL EtOH, and the reaction mixture was stirred overnight at room temperature. The solution was evaporated to dryness, dissolved in DCM (200 mL), filtered, and washed with brine (200 mL). The organic phase was dried over Na_2SO_4, and evaporated to dryness. The product was purified by silica gel chromatography (5% MeOH, 0.5% Et_3N in DCM), yielding **5** (8.3 g, 81%) as a white, solid foam. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.59 (s, 2 H, C*H*$_2$NH$_2$), 3.51 (s, 2 H, CH_2OMMTr), 3.70 (d, *J* = 11.2 Hz, 2 H, 2 × OC*H*HC_q), 3.78 (s, 3 H, OCH_3), 4.24 (d, *J* = 11.3 Hz, 2 H, 2 × OCH*H*C_q), 5.40 (s, 1 H, PhCH), 6.84 (m, 2 H, MMTr), 7.15−7.53 (m, 17 H, MMTr and Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.5 (C_q, pentaerythritol), 44.1 (CH_2NH_2), 55.1 (OCH_3), 61.3 (CH_2OMMTr), 71.6 (O*C*H_2C_q), 86.1 (C_q, MMTr), 102.2 (PhCH), 113.1 (MMTr), 126.4, 126.8, 127.8, 128.2, 128.4, 129.0, 130.4 (MMTr and Ph), 135.6 (MMTr), 138.3 (Ph), 144.5, 158.5 (MMTr). − HRMS (EI): M^+ found 495.2411. $C_{32}H_{33}NO_4$ requires 495.2410.

5-(*tert*-Butyloxycarbonylamino)methyl-5-(4-methoxytrityloxy)-methyl-2-phenyl-1,3-dioxane (6): Compound **5** (7.3 g, 15 mmol) was dissolved in 75% aq. acetonitrile (120 mL). Di-*tert*-butyl dicarbonate (3.5 g, 16 mmol) and 2 M aqueous NaOH (9.5 mL, 19 mmol) were added, and the reaction mixture was stirred at room temperature overnight. DCM (300 mL) was added, and the organic phase

was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The crude product was purified by silica gel chromatography (1% MeOH in DCM), yielding **6** (7.7 g, 88%) as a white, solid foam. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $(CH_3)_3$], 3.00 (d, *J* = 6.1 Hz, 2 H, C*H*$_2$NHBoc), 3.51 (s, 2 H, CH_2OMMTr), 3.78 (d, *J* = 11.7 Hz, 2 H, 2 × OC*H*HC$_q$), 3.79 (s, 3 H, OCH_3), 4.17 (d, *J* = 11.7 Hz, 2 H, 2 × OCH*H*C$_q$), 4.64 (t, *J* = 6.1 Hz, 1 H, NHBoc), 5.41 (s, 1 H, PhCH), 6.83 (m, 2 H, MMTr), 7.21–7.54 (m, 17 H, MMTr and Ph). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3 [$(CH_3)_3$], 38.5, 41.9 (CH_2NHBoc and C_q, pentaerythritol), 55.2 (OCH_3), 61.4 (CH_2OMMTr), 70.6 (O*C*H$_2$C$_q$), 79.2 (C_q, Boc), 86.5 (C_q, MMTr), 102.2 (PhCH), 113.2 (MMTr), 126.3, 126.9, 127.8, 128.2, 128.3, 129.2, 130.3 (MMTr and Ph), 135.4 (MMTr), 138.2 (Ph), 144.3, 158.6 (MMTr), 156.2 (C=O, Boc). – HRMS (EI): M^+ found 595.2935. $C_{37}H_{41}NO_6$ requires 595.2934.

2-Benzoyloxymethyl-2-(*tert*-butyloxycarbonylamino)methyl-3-(4-methoxytrityloxy)propan-1-ol (7): A solution of *tert*-butyl hydroperoxide in benzene (15 mL, 6 M, 90 mol) and a catalytic amount of palladium acetate were added to a solution of **6** (7.6 g, 13 mmol) in benzene (50 mL). The reaction mixture was stirred at room temperature for 17 days, and concentrated by evaporation. The mixture was dissolved in DCM (200 mL), washed with 10% aq. Na_2SO_3 (4 × 150 mL) and brine (2 × 200 mL), and evaporated to dryness. The crude reaction product was purified by silica gel chromatography (30% EtOAc in petroleum ether), yielding **7** (5.8 g, 72%) as a white, solid foam. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 [s, 9 H, $(CH_3)_3$], 3.04 (d, *J* = 9.0 Hz, 1 H, C*H*HOMMTr), 3.20 (m, 2 H, C*H*HOH and C*H*HNHBoc), 3.39 (d, *J* = 9.0 Hz, 1 H, CH*H*OMMTr), 3.54 (m, 2 H, CH*H*OH and CH*H*NHBoc), 3.69 (s, 3 H, OCH_3), 4.08 (m, 1 H, OH), 4.40 (d, *J* = 11.0 Hz, 1 H, C*H*HOBz), 4.54 (d, *J* = 11.0 Hz, 1 H, CH*H*OBz), 4.88 (m, 1 H, NH), 6.78 (m, 2 H, MMTr), 7.20–7.70 (m, 15 H, MMTr and Bz), 7.93 (m, 2 H, Bz). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.0 [$(CH_3)_3$], 39.7 (CH_2NHBoc), 45.4 (C_q, pentaerythritol), 54.7 (OCH_3), 60.7, 60.8 (CH_2OMMTr and CH_2OH), 63.4 (CH_2OBz), 79.6 (C_q, Boc), 86.0 (C_q, MMTr), 112.9 (MMTr), 126.6, 127.6, 128.0, 129.0, 129.4, 129.6, 130.1 (MMTr and Bz), 132.8 (Bz), 134.8 (MMTr), 143.9, 144.1 (MMTr and Bz), 157.3 (C=O, Boc), 158.3 (MMTr), 166.2 (C=O, Bz). – HRMS (EI): M^+ found 611.2881. $C_{37}H_{41}NO_7$ requires 611.2883.

2-Benzoyloxymethyl-*N*-(*tert*-Butyloxycarbonyl)-2-(4-methoxytrityloxy)methyl-*N*′-phthaloylpropane-1,3-diamine (8): DEAD (2.9 mL, 19 mmol) was added dropwise to a solution of **7** (9.4 g, 15 mmol), triphenylphosphane (4.4 g, 17 mmol), and phthalimide (2.5 g, 17 mmol) in THF (100 mL). The reaction mixture was stirred at room temperature for 2 days, with addition of reagents or refluxing sometimes being necessary to complete the reaction. The reaction solvents were evaporated to dryness, and the residue was purified by silica gel chromatography (30 to 50% EtOAc in petroleum ether), yielding 11.0 g (96%) of **8** as a white solid foam. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $(CH_3)_3$], 3.13–3.42 (m, 4 H, CH_2NHBoc and CH_2OMMTr), 3.71 (d, *J* = 14.4 Hz, 1 H, C*H*HNPhth), 3.71 (s, 3 H, OCH_3), 4.05 (d, *J* = 14.4 Hz, 1 H, CH*H*NPhth), 4.45 (d, *J* = 11.6 Hz, 1 H, C*H*HOBz), 4.59 (d, *J* = 11.6 Hz, 1 H, CH*H*OBz), 5.61 (t, *J* = 6.5 Hz, 1 H, NHBoc), 6.74 (m, 2 H, MMTr), 7.12–7.50 (m, 15 H, MMTr and Bz), 7.62–7.88 (m, 6 H, Phth and Bz). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3 [$(CH_3)_3$], 39.6, 41.9 (CH_2NPhth, CH_2NHBoc), 45.3 (C_q, pentaerythritol), 55.0 (OCH_3), 63.4 (CH_2OMMTr), 65.7 (CH_2OBz), 79.0 (C_q, Boc), 86.6 (C_q, MMTr), 113.1 (MMTr), 123.4 (Phth), 126.8, 127.8, 128.2, 128.4, 129.6, 130.4, 131.7 (MMTr and Bz), 132.8, 134.1 (Phth), 135.0 (MMTr), 144.0 (MMTr and Bz), 156.0 (C=O, Boc), 158.5 (MMTr), 166.1 (C=O, Bz), 169.0 (C=O, Phth). – HRMS (EI): M^+ found 740.3096. $C_{45}H_{44}N_2O_8$ requires 740.3098.

2-(*tert*-Butyloxycarbonylamino)methyl-3-(4-methoxytrityloxy)-2-phthalimidomethylpropan-1-ol (9): Compound **8** was dissolved in sodium methoxide in methanol (1 M, 100 mL), and the reaction mixture was stirred at room temperature for 2 h. DCM (100 mL) was added, and the mixture was directly loaded onto a silica gel column. The column was eluted with DCM, yielding **9** (2.7 g, 61%) as a white, solid foam. – ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.41 [s, 9 H, $(CH_3)_3$], 3.24 (s, 2 H, CH_2OMMTr), 3.29–3.34 (m, 3 H, C*H*$_2$OH and C*H*HNHBoc), 3.40 (dd, *J* = 12.4, *J* = 7.0, 1 H, CH*H*NHBoc), 3.62 (d, *J* = 14.3 Hz, 1 H, C*H*HNPhth), 3.70 (d, *J* = 14.3 Hz, 1 H, CH*H*NPhth), 3.76 (s, 3 H, OCH_3), 4.01 (m, 1 H, OH), 5.26 (m, 1 H, NHBoc), 6.76 (m, 2 H, MMTr), 7.14–7.33 (m, 12 H, MMTr), 7.70–7.89 (m, 4 H, Phth). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3 [$(CH_3)_3$], 39.8, 41.1 (CH_2NHBoc and CH_2NPhth), 46.3 (C_q, pentaerythritol), 55.1 (OCH_3), 62.8 (CH_2OMMTr), 64.9 (CH_2OH), 79.6 (C_q, Boc), 86.6 (C_q, MMTr), 113.0 (MMTr), 123.4 (Phth), 126.8, 127.7, 128.4, 130.4 (MMTr), 132.0, 134.2 (Phth), 143.8 (MMTr), 157.3 (C=O, Boc), 158.4 (MMTr), 169.2 (C=O, Phth). – HRMS (EI): M^+ found 636.2837. $C_{38}H_{40}N_2O_7$ requires 636.2836.

3-Amino-2-(*tert*-butyloxycarbonylamino)methyl-2-(4-methoxytrityloxy)methylpropan-1-ol (10): Compound **9** (5.2 g, 8.3 mmol) was dissolved in ethanol. Hydrazine monohydrate (2.0 mL, 42 mmol) was added, and the reaction mixture was stirred at room temperature overnight. Volatile components were removed by evaporation, and the residue was purified by silica gel chromatography (0 to 10% MeOH, 0.5% Et_3N in CH_2Cl_2), yielding **10** (3.6 g, 86%) as a white, solid foam. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $(CH_3)_3$], 2.72 (s, 2 H, C*H*$_2$NH$_2$), 2.96 (s, 2 H, CH_2OH), 3.11 (dd, *J* = 14.5, *J* = 6.2, 1 H, C*H*HNHBoc), 3.33 (dd, *J* = 14.5, *J* = 7.4, 1 H, CH*H*NHBoc), 3.56 (d, *J* = 11.6 Hz, 1 H, C*H*HOMMTr), 3.61 (d, *J* = 11.6 Hz, 1 H, CH*H*OMMTr), 3.79 (s, 3 H, OCH_3), 4.46 (m, 1 H, NHBoc), 7.42 (m, 2 H, MMTr), 7.21–7.33 (m, 8 H, MMTr), 7.40–7.43 (m, 4 H, MMTr). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3 [$(CH_3)_3$], 40.5 (CH_2NHBoc), 44.2 (CH_2NH_2), 45.9 (C_q, pentaerythritol), 55.2 (OCH_3), 63.0 (CH_2OMMTr), 65.4 (CH_2OH), 79.5 (C_q, Boc), 86.3 (C_q, MMTr), 113.2, 127.0, 128.0, 128.2, 130.2, 135.0, 144.0 (MMTr), 157.2 (C=O, Boc), 158.6 (MMTr). – HRMS (ES): $[M + H]^+$ found 507.2869. $C_{30}H_{39}N_2O_5$ requires 507.2859.

2-(*tert*-Butyloxycarbonylamino)methyl-2-(9-fluorenylmethoxycarbonylamino)methyl-3-(4-methoxytrityloxy)propan-1-ol (11): 9-Fluorenylmethoxycarbonyl chloride (1.9 g, 7.3 mmol) was added portionwise to a solution of **10** (3.7 g, 7.2 mmol) and DIPEA (1.3 mL, 7.2 mmol) in dioxane (40 mL). The reaction mixture was stirred overnight at room temperature and evaporated to dryness. The product was purified by silica gel chromatography (DCM), yielding **11** (4.8 g, 91%) as a white, solid foam. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 [s, 9 H, $(CH_3)_3$], 2.60 (dd, *J* = 14.3, *J* = 5.3, 1 H, C*H*HNHBoc), 2.77 (dd, *J* = 14.3, *J* = 5.3, 1 H, CH*H*NHBoc), 2.93 (d, *J* = 9.1 Hz, 1 H, C*H*HOMMTr), 3.10 (d, *J* = 9.1 Hz, 1 H, CH*H*OMMTr), 3.17 (m, 2 H, CH_2NHFmoc), 3.40 (m, 2 H, CH_2OH), 3.74 (s, 3 H, OCH_3), 4.04 (m, 1 H, OH), 4.17 (m, 1 H, OCH$_2$C*H*, Fmoc), 4.34 (m, 2 H, OC*H*$_2$CH, Fmoc), 4.97 (m, 2 H, NHFmoc and NHBoc), 6.86 (m, 2 H, MMTr), 7.16–7.52 (m, 18 H, MMTr and Fmoc), 7.78 (m, 2 H, Fmoc). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3 [$(CH_3)_3$], 39.3, 40.2 (CH_2NHBoc and CH_2NHFmoc), 46.1 (C_q, pentaerythritol), 47.2 (OCH$_2$*C*H, Fmoc), 55.2 (OCH_3), 61.3 (CH_2OH), 66.9 (CH_2OMMTr), 67.1 (O*C*H$_2$CH, Fmoc), 79.7 (C_q, Boc), 86.3 (C_q,

MMTr), 113.3 (MMTr), 120.0, 125.0 (Fmoc), 127.1, 127.7, 128.0, 128.3 (MMTr and Fmoc), 130.1, 135.3 (MMTr), 141.3 (Fmoc), 143.9, 144.1 (MMTr and Fmoc)157.8, 157.8 (C=O, Fmoc and Boc), 158.6 (MMTr). − HRMS (ES): $[M + H]^+$ found 729.3528. $C_{45}H_{49}N_2O_7$ requires 729.3540.

2-(*tert*-Butyloxycarbonylamino)methyl-2-(9-fluorenylmethoxycarbonylamino)methyl-3-(4-methoxytrityloxy)propanoic Acid (12): Compound **11** (0.65 g, 0.89 mmol) and PDC (3.4 g, 9 mmol) were dissolved in DMF (10 mL) and the reaction mixture was stirred overnight at room temperature. Water (100 mL) was added, and the organic components were extracted into diethyl ether (4 × 20 mL). The organic phase was dried over $NaSO_4$, and evaporated to dryness. The resulting oil was purified by silica gel chromatography (0 to 20% MeOH in DCM), yielding **12** (82 mg, 12%) as a colorless oil. The reason for this low yield was that **12** partially decomposed on silica gel. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $(CH_3)_3$], 3.25−3.45 (m, 4 H, CH_2NHBoc and CH_2OMMTr), 3.45−3.60 (m, 2 H, CH_2NHFmoc), 3.71 (s, 3 H, OCH_3), 4.14 (t, *J* = 6.0 Hz, 1 H, OCH_2CH, Fmoc), 4.26 (d, *J* = 6.0 Hz, 2 H, OCH_2CH, Fmoc), 5.12, 5.62 (m, 1H and m, 1 H, NHFmoc and NHBoc) 6.77 (m, 2 H, MMTr), 7.10−7.56 (m, 18 H, MMTr and Fmoc) 7.75 (m, 2 H, Fmoc). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3 $[(CH_3)_3]$, 40.5, 41.0 (CH_2NHBoc and CH_2NHFmoc), 47.1 (OCH_2CH, Fmoc), 55.1 (C_q, pentaerythritol), 55.1 (CH_2OMMTr), 63.8 (CH_2OMMTr), 66.9 (OCH_2CH, Fmoc), 79.5 (C_q, Boc), 86.5 (C_q, MMTr), 113.2 (MMTr), 119.9, 125.2 (Fmoc), 127.0, 127.6, 127.8, 128.1, 128.3 (MMTr and Fmoc), 130.2, 135.1 (MMTr), 141.2 (Fmoc), 143.9 (MMTr and Fmoc), 156.6, 156.9 (C=O, Boc and Fmoc), 158.5 (MMTr), 176.0 (COOH). − HRMS (ES): $[M + K]^+$ found 781.2882. $C_{45}H_{46}N_2O_8K$ requires 781.2891.

Allyl 2-(*tert*-Butyloxycarbonylamino)methyl-2-(9-fluorenylmethoxycarbonylamino)methyl-3-(4-methoxytrityloxy)propanoate (13): Crude **12** (from 4.8 g/6.6 mmol of **11**, not purified by silica gel chromatography) was dissolved in DMF (10 mL). Freshly distilled allyl bromide (2.8 mL, 33 mmol) and DIPEA (0.55 mL, 3.3 mmol) were added. The reaction mixture was stirred for 50 hours at room temperature, and evaporated to dryness. The product was purified by silica gel chromatography (0 to 1.5% MeOH in DCM), yielding **13** (2.9 g, 56% from **11**) as a white, solid foam. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $(CH_3)_3$], 3.20 (dd, *J* = 14.7, *J* = 7.1, 1 H, C*H*HNHBoc), 3.31 (m, 3 H, CH*H*NHBoc and CH_2OMMTr), 3.49 (dd, *J* = 14.3, *J* = 6.7, 1 H, C*H*HNHFmoc), 3.56 (dd, *J* = 14.3, *J* = 6.5, 1 H, CH*H*NHFmoc), 3.74 (s, 3 H, OCH_3), 4.15 (m, 1 H, OCH_2CH, Fmoc), 4.28 (m, 2 H, OCH_2CH, Fmoc), 4.69 (m, 2 H, $OCH_2CH=CH_2$), 5.03 (m, NHFmoc), 5.41−5.23 (m, 2 H, $OCH_2CH=CH_2$), 5.48 (m, 1 H, NHBoc), 5.98 (m, 1 H, $OCH_2CH=CH_2$) 6.81 (m, 2 H, MMTr), 7.58−7.11 (m, 18 H, MMTr and Fmoc), 7.76 (m, 2 H, Fmoc). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3 $[(CH_3)_3]$, 36.2, 37.0 (CH_2NHBoc and CH_2NHFmoc), 47.2 (OCH_2CH, Fmoc), 53.4 (C_q, pentaerythritol), 55.1 (OCH_3), 66.0 ($OCH_2CH=CH_2$), 66.9 (OCH_2CH, Fmoc), 79.4 (C_q, Boc), 86.3 (C_q, MMTr), 113.2 (MMTr), 118.8 ($OCH_2CH=CH_2$), 119.9, 125.2 (Fmoc), 127.0, 127.7, 127.9, 128.3 (MMTr and Fmoc), 130.2 (MMTr), 132.0 ($OCH_2CH=CH_2$), 135.0 (MMTr), 141.3 (Fmoc), 143.9 (MMTr and Fmoc), 156.5, 156.9 (C=O, Boc and Fmoc), 158.6 (MMTr), 173.7 (COOAll). − HRMS (ES): $[M + Na]^+$ found 805.3516. $C_{48}H_{50}N_2O_8Na$ requires 805.3465.

Allyl 2-(*tert*-Butyloxycarbonylamino)methyl-2-(9-fluorenylmethoxycarbonylamino)methyl-3-hydroxypropanoate (14): Compound **13** (2.9 g, 3.7 mmol) was stirred in methanolic iodine (100 mL, 1% iodine in MeOH, *m*/*v*) overnight at room temperature. The solution was evaporated to dryness, and the residue was dissolved in DCM (200 mL), and washed several times with neutral aq. Na_2SO_3 (10%, *m*/*v*). The organic phase was dried over Na_2SO_4, and evaporated to dryness. The product was purified by silica gel chromatography (20 to 50% EtOAc in petroleum ether), yielding **14** (1.2 g, 63%) as a white, solid foam. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 [s, 9 H, $(CH_3)_3$], 3.09 (dd, *J* = 14.6, *J* = 5.6, 1 H, C*H*HNHBoc), 3.19 (dd, *J* = 14.6, *J* = 5.4, 1 H, CH*H*NHBoc), 3.55 (d, *J* = 7.8 Hz, 2 H, CH_2OH), 3.59 (m, 2 H, CH_2NHFmoc), 4.25 (m, 2 H, OH and OCH_2CH, Fmoc), 4.42 (m, 2 H, OCH_2CH, Fmoc), 4.65 (m, 2 H, $OCH_2CH=CH_2$), 5.22−5.39 (m, 2 H, $OCH_2CH=CH_2$), 5.54 (m, 2 H, NHFmoc and NHBoc), 5.90 (m, 1 H, $OCH_2CH=CH_2$) 7.26−7.44 (m, 4 H, Fmoc), 7.58 (m, 2 H, Fmoc), 7.77 (m, 2 H, Fmoc). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3 $[(CH_3)_3]$, 39.4, 40.3 (CH_2NHFmoc and CH_2NHBoc), 47.2 (OCH_2CH, Fmoc), 55.0 (C_q, pentaerythritol), 62.4 (CH_2OH), 65.7 ($OCH_2CH=CH_2$), 67.1 (OCH_2CH, Fmoc), 80.3 (C_q, Boc), 118.6 ($OCH_2CH=CH_2$), 120.0, 125.0, 127.1, 127.8 (Fmoc), 131.7 ($OCH_2CH=CH_2$), 141.3, 143.7 (Fmoc), 157.6, 157.8 (C=O, Boc and Fmoc), 172.8 (COOAll). − HRMS (ES): $[M + Na]^+$ found 533.2253. $C_{28}H_{34}N_2O_7Na$ requires 533.2264.

2-(*tert*-Butyloxycarbonylamino)methyl-2-(9-fluorenylmethoxycarbonylamino)methylmalonic Acid Monoallyl Ester (1): A solution of CrO_3 (0.34 g, 3.4 mmol) and H_2SO_4 (0.34 mL) in the minimum possible amount of water was added dropwise to a solution of **14** (1.2 g, 2.3 mmol) in acetone (40 mL). The reaction mixture was stirred at room temperature for 4 hours. The reaction was quenched using 2-propanol, and the mixture concentrated by evaporation. Chloroform was added (150 mL), and the organic phase was washed with water (2 × 30 mL) and brine (2 × 30 mL), dried over Na_2SO_4, and evaporated to dryness. Compound **14** was obtained as a white, solid foam in an almost quantitative yield (1.2 g, 97%). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, $(CH_3)_3$], 3.70−3.79 (m, 4 H, CH_2NHBoc and CH_2NHFmoc), 4.22 (m, 1 H, OCH_2CH, Fmoc), 4.34 (m, 2 H, OCH_2CH, Fmoc), 4.63 (m, 2 H, $OCH_2CH=CH_2$), 5.18−5.34 (m, 2 H, $OCH_2CH=CH_2$), 5.34, 6.02 (m, 1 H and m, 1 H, NHBoc and NHFmoc), 5.89 (m, 1 H, $OCH_2CH=CH_2$), 7.26−7.42 (m, 4 H, Fmoc), 7.58 (m, 2 H, Fmoc), 7.75 (m, 2 H, Fmoc). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.5 $[(CH_3)_3]$, 41.2, 41.6 (CH_2NHBoc and CH_2NHFmoc), 47.1 (OCH_2CH, Fmoc), 59.1 (C_q, malonic acid), 66.7 ($OCH_2CH=CH_2$), 67.3 (OCH_2CH, Fmoc), 80.4 (C_q, Boc), 119.0 ($OCH_2CH=CH_2$), 120.0, 125.2, 127.1, 127.8 (Fmoc), 131.3 ($OCH_2CH=CH_2$), 141.3, 143.8 (Fmoc), 128.5, 128.9 (C=O, Boc and Fmoc), 168.6 (COOH), 171.6 (COOAll). − HRMS (ES): [M + Na] found 547.2059. $C_{28}H_{32}N_2O_8Na$ requires 547.2056.

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