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Cross-Claisen Condensation of *N*-Fmoc-Amino Acids – A Short Route to Heterocyclic γ-Amino Acids

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4-Amino(methyl)-1,3-thiazole-5-carboxylic acids (ATCs) are a new class of constrained heterocyclic γ-amino acids built around a thiazole ring; these compounds are valuable as design mimics of the secondary structures of proteins such as helices, β-sheets, turns, and β-hairpins. We report herein a short and versatile chemical route to orthogonally protected ATCs. The synthesis is centered on cross-Claisen condensations between *N*-Fmoc-amino acids and sterically hindered 1,1-dimethylallyl acetate. The optimized conditions are compatible with aliphatic, aromatic, acidic, and basic amino acids. The resulting *N*-Fmoc-β-keto ester intermediates were engaged in a two-step process to give ATCs in 45–90% yields. The synthetic protocol provides a highly flexible method for the introduction of a wide variety of lateral chains either on the γ-carbon atom or on the thiazole core of the γ-amino acids.

Introduction

Over recent decades, peptidomimetic oligomers have been pursed to identify potent therapeutic agents, because they might overcome the poor pharmacokinetic profiles often attributed to peptides with their potency and selectivity toward biological targets maintained. In consequence, synthetic oligomers that adopt stable and predictable conformations in solution and are able to mimic the secondary structures of proteins such as helices, β-sheets, turns, and β-hairpins have been extensively described.[1–3] A wide range of scaffolds derived from β-amino acids have been characterized,[4–11] whereas homo- or heterogeneous sequences incorporating γ-amino acids have received far less attention, in part because of the difficulty to access stereochemically pure γ building blocks.[8,9,12–23] In this context, we recently described a new class of constrained heterocyclic γ-amino acids named 4-amino(methyl)-1,3-thiazole-5-carboxylic acids or ATCs (**1**), which are built around a thiazole ring.[24,25] Owing to the low conformational flexibility of the γ-amino acids, ATC-containing oligomers adopt predictable secondary structures that are stabilized by C_9 intramolecular hydrogen-bonding networks.

To modulate the physicochemical properties of the oligomers and to drive molecular recognition, the designed ATC chemical route has to be versatile for the deployment of a wide variety of side chains. In addition, a judicious choice of orthogonal protecting groups is required for peptide elongation. In our previous work, 9-fluorenylmethyloxycarbonyl (Fmoc) was chosen as the transient protecting group of the N-terminal position, as it has become the preferred method for most solid- and solution-phase peptide synthetic processes. The lateral chains were protected with acid-labile groups [e.g., *t*Bu, *tert*-butyloxycarbonyl (Boc), trityl (Trt), and 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf)]. The chemical route for the ATC motif consisted of a six-step synthesis starting from *N*-Fmoc-protected α-amino acids to take advantage of their ready availability, low cost, and high enantiomeric purity (Scheme 1). However, the major issue of the process was the preparation of the key *N*-Fmoc-amino-β-keto ester intermediates, which were obtained in three steps with 25 to 56% overall yields.[24–26] Furthermore, a partial racemization of the γ stereocenter occurred, because the key tin-mediated diazo coupling reaction involved a *N*-Fmoc-aminoaldehyde intermediate (Scheme 1, Route A).

To speed up the overall synthesis and avoid racemization, we reconsidered the chemical route to N-protected γ-amino-β-keto esters. The most commonly used route involves a neutral C-acylation of acyl imidazoles with a magnesium enolate that is generated in situ from a monoalkyl malonate and magnesium chloride (Scheme 1, Route B).[27–29] Although amino acids protected with carboxybenzyl (Cbz), Boc, and Bz groups are readily converted, Fmoc-protected amino acids degrade slowly during the acylation. Additionally, the reactions are relatively slow and usually require 1–2 d of stirring. Reducing the reaction time by increasing the temperature results in racemiza-

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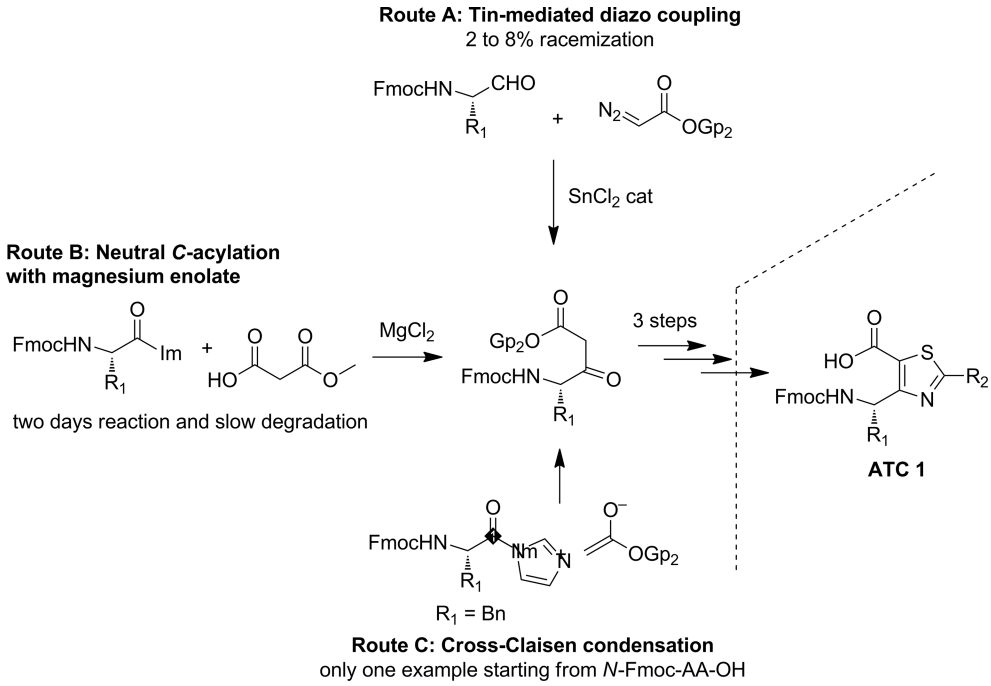


Scheme 1. Strategies to access *N*-Fmoc-protected γ-amino-β-keto ester intermediates as precursors for ATCs.

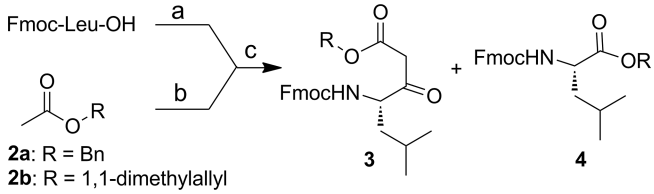
tion.[29] Another classical strategy for the chain extension of amino acid skeletons consists of cross-Claisen condensations between activated carboxylic acids and a lithium enolate prepared from an alkyl acetate (Scheme 1, Route C). Whereas positive results have been obtained for *N*-Boc-[30] or *N*-Cbz-amino acids,[31–34] only one example of a cross-Claisen reaction has been reported to date for *N*-Fmoc-protected amino acids.[35] The success of this method highly depends on functional-group compatibility, harsh reaction conditions, and longer reaction durations. As a consequence, to the best of our knowledge, effective cross-Claisen condensations with amino acids with functionalized lateral chains are exceptional.

As we considered that cross-Claisen condensations between *N*-Fmoc-amino acids and alkyl acetates might be worthy of investigation, we report herein our efforts to develop compatible conditions for cross-Claisen reactions of *N*-Fmoc-amino acids. The optimized methodology was applied for the preparation of ten *N*-Fmoc-amino-β-keto esters with diverse lateral chains, including acidic and basic amino acids. In a second part, these β-keto esters were used as precursors to prepare a representative set of highly diverse orthogonally protected ATC building blocks.

Results and Discussion

To study the cross-Claisen condensation, *N*-Fmoc-Leu-OH was selected as a model amino acid. Considering the previous work in β-keto ester preparation,[36] *N*,*N*′-carbonyldiimidazole (CDI) was first chosen for the carbonyl activation. The *N*-Fmoc-Leu-imidazolide was condensed with the lithium enolate **2a**, which was prepared from benzyl acetate and lithium bis(trimethylsilyl)amide (LiHMDS) in tetrahydrofuran (THF) at –78 °C. The reaction gave the desired β-keto ester **3** in only 33% yield (Table 1, Entry 1). The major product was the *N*-Fmoc-leucine benzyl ester **4**, probably resulting from the reaction of the imidazolide and

Table 1. Optimization of the cross-Claisen condensation.



Entry	a: Amino acid activation (equiv.)[a]	b: Enolate formation[b]		c: Condensation time [min]	Ratio **3**/**4**	Yield [%][c]
		Acetate	Base			
1	CDI (1.05)	**2a**	LiHMDS	45	1:3	33
2	CDI (1.05)	**2b**	LiHMDS	45	1:0	55
3	PyBOP (1.1) / DIEA (1.1)	**2b**	LiHMDS	30	1:0	6
4	DIC (1.1) / HOBt (1.1)	**2b**	LiHMDS	30	1:0	9
5	CDI (1.05)	**2b**	LDA	45	1:0	57
6	CDI (1.05)	**2b**	LiTMP	45	1:0	dec.
7	CDI (1.2)	**2b**	LiHMDS	90	1:0	47
8	CDI (1.05) / DMAP (0.03)	**2b**	LiHMDS	15	1:0	73

[a] The activation of Fmoc-Leu-OH (1.0 equiv., 28 mmol) was performed at room temp. in anhydrous THF (50 mL) for 1 h. [b] The enolate formation was performed at –78 °C for 10 min, then at r.t. for 10 min, and at –78 °C for 20 min starting from 1,1-dimethylallyl acetate (4.0 equiv., 112 mmol) and base (3.5 equiv.) in anhydrous THF (190 mL). The activated amino acid was added dropwise to the enolate at –78 °C. [c] Determined for the isolated β-keto ester **3**; dec. = decomposition.

the benzyl alcoholate, which was released because of acetate autocondensation. Usually, the autocondensation side reaction can be avoided by using the sterically hindered *tert*-butyl acetate.[32,37,38] However, as the resulting *tert*-butyl ester is sensitive to acidic conditions, the orthogonality of the protections would not be preserved. Thus, we considered the use of another sterically hindered acetate, that is, 1,1-dimethylallyl acetate (**2b**); the resulting 1,1-dimethylallyl ester could be selectively deprotected under mild conditions with a palladium catalyst.

Compound **2b** was synthesized from 2-methyl-3-buten-2-ol by the procedure of Watson et al.[39] The 1,1-dimethylallyl acetate was isolated by distillation in 71% yield. After the generation of the enolate and subsequent condensation with the Fmoc-Leu-imidazolide, the *N*-Fmoc-amino-β-keto ester **3** was recovered in 55% yield. Despite the use of a large excess of reagent, we did not detect the formation of *N*-Fmoc-Leucine ester **4**.

To optimize the cross-Claisen reaction, we explored some other conditions for amino acid activation, that is, (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate/*N*,*N*-diisopropylethylamine (PyBOP/DIEA) and diisopropylcarbodiimide/1-hydroxybenzotriazole (DIC/HOBt), but these conditions led to drastic decreases in the yield (Table 1, Entries 3–4). Therefore, CDI was kept as the best activation reagent. We also tested the influence of the base used for the enolate formation. Although lithium diisopropylamide (LDA) and LiHMDS gave similar results, lithium 2,2,6,6-tetramethylpiperidine (LiTMP) yielded a complex mixture (Table 1, Entries 2, 5, and 6). Finally, the best-identified conditions consisted of activation of the *N*-Fmoc-protected amino acid with CDI (1.10 equiv.) and 4-dimethylaminopyridine (DMAP; 3 mol-%) at room temp. in anhydrous THF. At the same time, the enolate was generated from 1,1-dimethylallyl acetate and LiHMDS. The activated amino acid was then added dropwise to the enolate solution. A strict control of the temperature and the reaction time was essential to avoid any Fmoc deprotection. After 15 min of stirring, the reaction mixture was quenched with an aqueous citric acid solution to afford the *N*-Fmoc-amino-β-keto ester **3**, which was isolated in 73% yield by chromatography. The scope of the reaction was extended to nine other *N*-Fmoc-amino acids, namely, Fmoc-Gly-OH, Fmoc-Ala-OH, Fmoc-Phe-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(*t*Bu)-OH, Fmoc-Asp(*t*Bu)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Trp(Boc)-OH, and Fmoc-Arg(Pbf)-OH, to afford the *N*-Fmoc-amino-β-keto esters **3b**–**3j** in overall yields of 34–80% (Table 2). The conditions were compatible with aliphatic and aromatic as well as acidic and basic amino acids. Finally, the reaction was scaled up to almost 10 g for **3a** without the yield decreasing.

Monohalogenation of the malonic position of the *N*-Fmoc-amino-β-keto esters **3a**–**3j** was another important issue for accessing ATCs. As supported by Honda et al.[32] and by our previous studies on ATC synthesis, sulfuryl chloride was first considered as the halogenating reagent. The desired α-chloro-β-keto ester **5a** was isolated in 67% yield, but we also observed 33% overchlorination (Table 3).

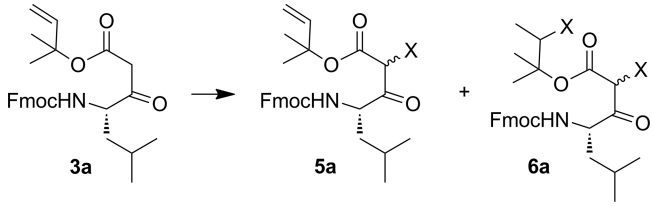
Table 2. Scope of the cross-Claisen condensation between *N*-Fmoc-protected α-amino acids and 1,1-dimethylallyl acetate.[a]

Fmoc-AA-OH	β-Keto ester	Yield [%][b]
Fmoc-(L)-Leu-OH	**3a**	73
Fmoc-Gly-OH	**3b**	59
Fmoc-(L)-Ala-OH	**3c**	80
Fmoc-(L)-Phe-OH	**3d**	66
Fmoc-(L)-Lys(Boc)-OH	**3e**	55
Fmoc-(L)-Glu(*t*Bu)-OH	**3f**	53
Fmoc-(L)-Asp(*t*Bu)-OH	**3g**	72
Fmoc-(L)-Cys(Trt)-OH	**3h**	45
Fmoc-(L)-Trp(Boc)-OH	**3i**	49
Fmoc-(L)-Arg(Pbf)-OH	**3j**	34

[a] Experimental conditions: the activation of Fmoc-AA-OH (1.0 equiv.) was performed at room temp. in anhydrous THF (50 mL) for 1 h. The enolate was prepared from 1,1-dimethylallyl acetate (4.0 equiv.) and base (3.5 equiv.) in anhydrous THF at –78 °C for 10 min, then at 20 °C for 10 min, and at –78 °C for 20 min. The cross-Claisen condensation was performed at –78 °C. [b] Determined for isolated compound.

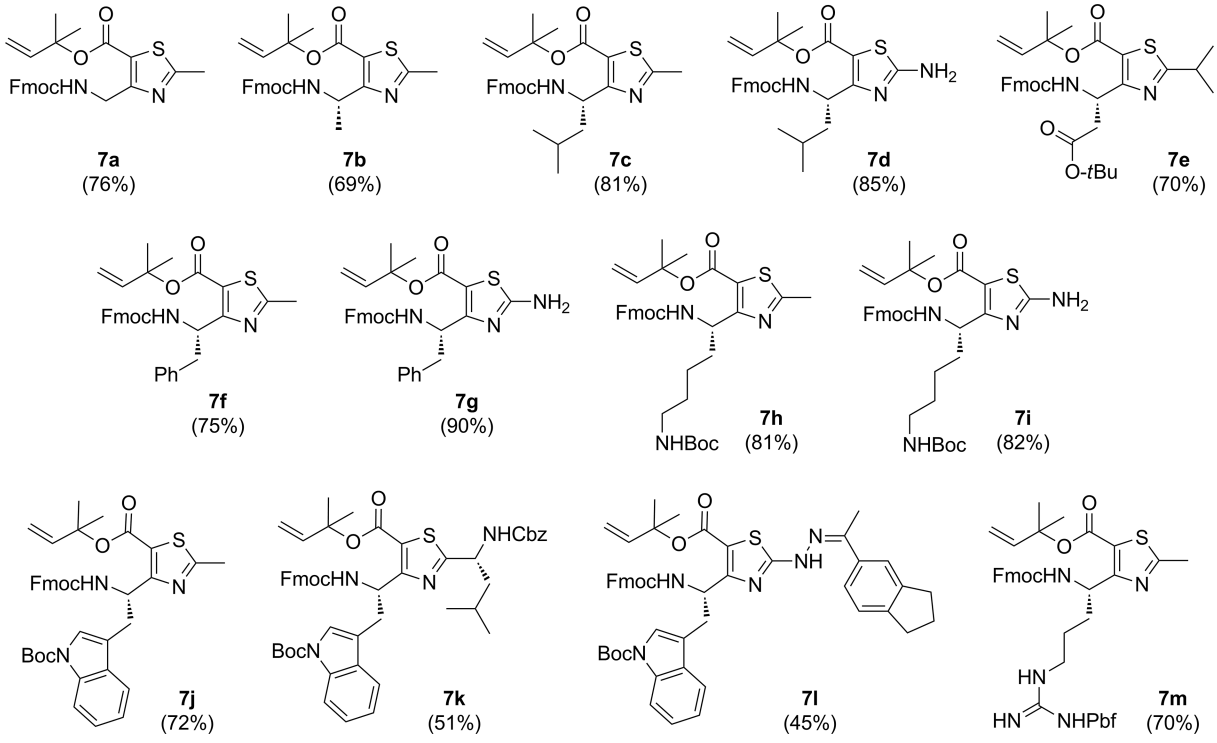
Such a result was surprising as no dichlorinated compound was detected for the reaction of a benzyl β-keto ester. This suggested that overchlorination did not occur at the malonic position. Consequently, we reinvestigated the conditions for selective monohalogenation (Table 3). Confirmation that the dimethylallyl protecting group was very sensitive to halogenation was achieved by isolation of the byproduct **6a** (see Supporting Information). Bromodimethylsulfonium bromide (BDMS) was tested according to the procedure described by Khan et al.[40] but did not give any reaction. We found that the bromination conditions reported by Yang et al.,[41] that is $Mg(ClO_4)_2$ Lewis acid catalysis combined with *N*-bromosuccinimide (NBS) afforded mild, fast monohalogenation of the β-keto ester. An improvement of the selectivity was obtained by decreasing the temperature to –45 °C.

Table 3. Results of halogenation of the *N*-Fmoc-amino-β-keto ester **3a**.[a]



X	Reagent (equiv.)	Conditions	Ratio **5a**/**6**
Cl	SO_2Cl_2 (1.1)	CH_2Cl_2, 0–20 °C	67:33
Br	BDMS (1.25)	CH_2Cl_2, 0–20 °C	–
Br	NBS (1.05)/$Mg(ClO_4)_2$ (1.05)	CH_3CN, 20 °C	86:14
Br	NBS (1.05)/$Mg(ClO_4)_2$ (0.5)	CH_3CN, 20 °C	85:15
Br	NBS (1.05)/$Mg(ClO_4)_2$ (0.3)	CH_3CN, 20 °C	85:15
Br	NBS (1.05)/$Mg(ClO_4)_2$ (0.3)	CH_3CN, –35 °C	89:11
Br	NBS (1.05)/$Mg(ClO_4)_2$ (0.3)	*i*BuCN, –65 °C	93:7
Br	NBS (1.05)/$Mg(ClO_4)_2$ (0.3)	CH_3CN, –45 °C	97:3[b]

[a] Yields determined by HPLC. [b] Determined for isolated compound.



Scheme 2. Scope of the ATC synthesis (yields determined for isolated compounds).

Finally, the optimized bromination conditions were used to convert the *N*-Fmoc-amino-β-keto esters **3** into α-bromo-β-keto esters **5**, which were engaged without any purification in Hantzsch heterocyclizations. Thiazole rings were formed after 2 h in ethanol at 40 °C. Starting from a representative set of primary thioamides, thiourea, and thiosemicarbazones, the ATCs **7a**–**7m** were isolated in 45–86% yields over the last two steps (Scheme 2). The enantioselectivity of the overall synthesis was ascertained by chiral HPLC. The compounds are usually stocked as fully protected ATC **7**. The removal of the dimethylallyl ester is classically done under Tsuji–Trost conditions with palladium tetrakis(triphenylphosphine) (3 mol-%) and phenylsilane (1.2 equiv.) just before ATC oligomerization (see Supporting Information).

Conclusions

We have developed an efficient and stereoselective method for the preparation of ATCs in 34 to 52% overall yield starting from *N*-Fmoc-amino acids. The three-step synthesis is based on a cross-Claisen condensation between *N*-Fmoc-amino acids and 1,1-dimethylallyl acetate to provide *N*-Fmoc-γ-amino-β-keto ester intermediates. We demonstrated that the choice of the sterically hindered 1,1-dimethylallyl acetate was crucial to improve the condensation yield and maintain orthogonal protection. The synthetic protocol provides a highly versatile and flexible method for the introduction of a wide variety of lateral chains either on the γ-carbon atom or on the thiazole core of the ATC.

Experimental Section

General: Commercially available reagents and solvents were used without any further purification. Reactions were monitored by HPLC with an analytical Chromolith Speed Rod RP-C18 185 Pm column (50 × 4.6 mm, 5 μm) and 100:0 to 0:100 A/B gradient elution over 3 (conditions A) or 5 min (conditions B) at a flow rate of 5.0 mL/min; eluent A is H_2O/trifluoroacetic acid 0.1% (H_2O/TFA 0.1%) and eluent B is CH_3CN/TFA 0.1%. Detection was performed at λ = 214 and 254 nm with a photodiode array detector. The retention times are reported as follows: LC: t_R = [min]. The ^1H and ^{13}C NMR spectra were recorded at room temperature with samples in deuterated solvents. The chemical shifts (δ) are given in parts per million relative to tetramethylsilane (TMS) or relative to the solvent [^1H: δ ($CDCl_3$) = 7.24 ppm; ^{13}C: δ ($CDCl_3$) = 77.2 ppm]. The following abbreviations are used to designate the signal multiplicities: s (singlet), d (doublet), dd (doublet doublet), t (triplet), q (quartet), m (multiplet), and br. (broad). Analytical TLC was performed with aluminium-backed silica gel plates coated with a 0.2 mm thickness of silica gel or with aluminium oxide 60 F254, neutral. LC–MS spectra (ESI) were recorded with an HPLC instrument with an analytical Chromolith Speed Rod RP-C18 185 Pm column (50 × 4.6 mm, 5 μm) and 100:0 to 0:100 A/B gradient elution over 2.5 min at a flow rate of 3.0 mL/min; eluent A is H_2O/HCOOH 0.1% and eluent B is CH_3CN/HCOOH 0.1%. High-resolution mass spectrometric analyses were performed with a time-of-flight (TOF) mass spectrometer fitted with an electrospray ionization source (ESI). All measurements were performed in the positive-ion mode. Melting points were recorded with a capillary melting point apparatus. Enantiomeric excesses were determined by chiral HPLC analysis with a Chiracel OD-R column (250 × 4.6 mm) with H_2O, TFA 0.1%/CH_3CN, TFA 0.1% (40:60) as eluent and a flow rate of 1 mL/min.

General Procedure for Synthesis of β-Keto Ester 3

Imidazolide Formation: In a 250 mL two-neck flask under a nitrogen atmosphere was dissolved the Fmoc-AA-OH (28.57 mmol) in dry THF. Then, CDI (5.096 g, 31.41 mmol, 1.1 equiv.) was added in three portions. A catalytic amount of DMAP (105 mg, 0.8571 mmol, 3 mol-%) was added 2–3 min later, and the solution was stirred for 1 h at room temp.

Enolate Formation: Under a nitrogen atmosphere, a 500 mL three-neck flask was charged with LiHMDS (100 mL, 100 mmol, 1 M solution in THF) followed by dry THF (100 mL). After cooling at –78 °C 1,1-dimethylallyl acetate (14.650 g, 114.3 mmol) was added dropwise over 10 min. The solution was stirred at –78 °C for 5–10 min, then at room temp. for 10 min, and finally at –78 °C for 20 min.

Condensation: The imidazolide solution was added dropwise to the enolate solution at –78 °C over 5–10 min. After stirring for 15 min (HPLC monitoring), the mixture was removed from the cold bath and poured onto a solution of 10% aqueous citric acid (200 mL) until pH 7. The crude was extracted with EtOAc (2× 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (1× 100 mL) and brine (3× 150 mL), dried, filtered, and evaporated under reduced pressure to yield the crude product. Purification by flash column chromatography afforded the pure β-keto ester.

1,1-Dimethylprop-2-en-1-yl (4*S*)-4-(Fmoc-amino)-6-methyl-3-oxoheptanoate (3a): White solid, yield 73%, m.p. 117–118 °C. $[\alpha]_D^{20\,°C}$ = –10.2 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (t, *J* = 6.2 Hz, 6 H), 1.41 (m, 2 H), 1.53 (s, 6 H), 1.68 (m, 1 H), 3.41 (AB, *J* = 15.6 Hz, 1 H), 3.49 (AB, *J* = 15.6 Hz, 1 H), 4.22 (t, *J* = 6.6 Hz, 1 H), 4.42 (s, 1 H), 4.45 (d, *J* = 6.6 Hz, 2 H), 5.09 (d, *J* = 10.8 Hz, 1 H), 5.19 (d, *J* = 17.4 Hz, 1 H), 5.19 (s, 1 H), 6.08 (dd, *J* = 10.9, 17.4 Hz, 1 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.59 (m, 2 H), 7.78 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.7, 23.4, 25.0, 26.5 (2 C), 40.3, 47.5 (2 C), 58.8, 67.0, 82.7, 113.5, 120.2 (2 C), 125.1 (2 C), 127.2 (2 C), 127.9 (2 C), 141.5 (2 C), 142.0, 143.9 (2 C), 156.2, 165.7, 202.7 ppm. LC (conditions A): t_R = 2.29 (major) and 2.52 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m*/*z* (%) = 464.3 (100) $[M + H]^+$, 486.3 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{28}H_{34}NO_5$ $[M + H]^+$ 464.2437; found 464.2416. FTIR: $\tilde{\nu}_{max}$ = 3375, 3041, 2958, 1739, 1717, 1536, 1452, 1353, 1249, 1237, 1222, 1126, 1098, 1038, 942, 760, 737, 730 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl (Fmoc-amino)-3-oxobutanoate (3b): White solid, yield 59%, m.p. 99–100 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 6 H), 3.43 (s, 2 H), 4.23 (m, 3 H), 4.41 (d, *J* = 7.0 Hz, 2 H), 5.12 (dd, *J* = 0.6, 10.9 Hz, 1 H), 5.21 (d, *J* = 17.5 Hz, 1 H), 5.46 (br., 1 H), 6.08 (dd, *J* = 10.9, 17.5 Hz, 1 H), 7.30 (t, *J* = 7.4 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.59 (d, *J* = 7.4 Hz, 2 H), 7.76 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.4 (2 C), 47.3, 47.8, 51.0, 67.3, 83.0, 113.7, 120.1 (2 C), 125.2 (2 C), 127.2 (2 C), 127.9 (2 C), 141.5, 141.7 (2 C), 143.9 (2 C), 156.3, 165.4, 198.5 ppm. LC (conditions A): t_R = 2.19 (major) and 2.40 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m*/*z* (%) = 408.2 (17) $[M + H]^+$, 430.1 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{24}H_{26}NO_5$ $[M + H]^+$ 408.1811; found 408.1811. FTIR: $\tilde{\nu}_{max}$ = 3357, 3041, 2979, 1724, 1704, 1449, 1436, 1394, 1306, 1288, 1252, 1109, 1073, 1050, 988, 969, 760, 739 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl (4*S*)-4-(Fmoc-amino)-3-oxo-5-pentanoate (3c): Pale orange solid, yield 80%, m.p. 68–70 °C. $[\alpha]_D^{20\,°C}$ = +6.61 (*c* = 2.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (d, *J* = 7.1 Hz, 3 H), 1.54 (s, 6 H), 3.45 (AB, *J* = 16.0 Hz, 1 H), 3.50 (AB, *J* = 16.0 Hz, 1 H), 4.22 (t, *J* = 6.9 Hz, 1 H), 4.38–4.50 (m, 3 H), 5.10 (d, *J* = 11.0 Hz, 1 H), 5.20 (d, *J* = 17.5 Hz, 1 H), 5.47 (d, *J* = 7.2 Hz, 1 H), 6.08 (dd, *J* = 11.0, 17.5 Hz, 1 H), 7.32 (td, *J* = 0.7, 7.5 Hz, 2 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 7.4 Hz, 2 H), 7.75 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.4, 26.4 (2 C), 47.0, 47.3, 56.0, 67.1, 82.8, 113.6, 120.1 (2 C), 125.1 (2 C), 127.2 (2 C), 127.9 (2 C), 141.5, 141.8 (2 C), 143.9 (2 C), 155.8, 165.6, 202.2 ppm. LC (conditions A): t_R = 2.25 (major) and 2.48 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m*/*z* (%) = 422.3 (100) $[M + H]^+$, 444.2 (70) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{25}H_{28}NO_5$ $[M + H]^+$ 422.1972; found 422.1967. FTIR: $\tilde{\nu}_{max}$ = 3309, 2983, 2939, 1717, 1685, 1533, 1450, 1316, 1254, 1123, 1048, 923, 833, 757, 737 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl (4*S*)-4-(Fmoc-amino)-3-oxo-5-phenylpentanoate (3d): Pale pink solid, yield 66%, m.p. 101–102 °C. $[\alpha]_D^{20\,°C}$ = +0.55 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.52 (s, 6 H), 3.01 (ABX, *J* = 7.0, 14.0 Hz, 1 H), 3.18 (ABX, *J* = 7.0, 14.0 Hz, 1 H), 3.40 (d, *J* = 5.3 Hz, 2 H), 4.17 (t, *J* = 6.9 Hz, 1 H), 4.40 (m, 2 H), 4.67 (m, 1 H), 5.10 (d, *J* = 10.8 Hz, 1 H), 5.19 (d, *J* = 17.5 Hz, 1 H), 5.34 (d, *J* = 7.6 Hz, 1 H), 6.07 (dd, *J* = 10.8, 17.5 Hz, 1 H), 7.14 (d, *J* = 7.0 Hz, 1 H), 7.23–7.33 (m, 6 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.53 (t, *J* = 7.4 Hz, 2 H), 7.77 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.4 (2 C), 37.1, 47.3, 48.0, 60.9, 67.1, 82.8, 113.5, 120.1 (2 C), 125.2 (2 C), 127.2 (2 C), 127.3, 127.9 (2 C), 128.9 (2 C), 129.4 (2 C), 135.9, 141.4 (2 C), 141.8, 143.8 (2 C), 155.8, 165.6, 201.7 ppm. LC (conditions A): t_R = 2.04 (major) and 2.19 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m*/*z* (%) = 498.2 (100) $[M + H]^+$, 520.2 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{31}H_{31}NO_5Na$ $[M + Na]^+$ 520.2100; found 520.2098. FTIR: $\tilde{\nu}_{max}$ = 3313, 2984, 1738, 1713, 1692, 1534, 1323, 1254, 1124, 1031, 929, 836, 755, 741, 703 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl (4*S*)-4-(Fmoc-amino)-8-[(*tert*-butyloxycarbonyl)amino]-3-oxooctanoate (3e): Yellow gel, yield 55%. $[\alpha]_D^{20\,°C}$ = –4.7 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.35 (br., 2 H), 1.43 (s, 9 H), 1.53 (s, 6 H), 1.62 (br., 2 H), 1.92 (m, 2 H), 3.11 (br., 2 H), 3.42 (AB, *J* = 15.7 Hz, 1 H), 3.49 (AB, *J* = 15.7 Hz, 1 H), 4.21 (t, *J* = 6.6 Hz, 1 H), 4.42 (br., 1 H), 4.46 (br., 2 H), 4.58 (br., 1 H), 5.10 (d, *J* = 10.9 Hz, 1 H), 5.19 (d, *J* = 17.4 Hz, 1 H), 5.51 (br., 1 H), 6.08 (dd, *J* = 10.9, 17.4 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.60 (d, *J* = 7.6 Hz, 2 H), 7.76 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.3, 26.5, 27.1, 28.6 (3 C), 29.8, 30.6, 40.0, 47.4 (2 C), 60.0, 67.1, 79.4, 82.8, 113.6, 120.1 (2 C), 125.2 (2 C), 127.2 (2 C), 127.9 (2 C), 141.5 (2 C), 141.9, 143.9 (2 C), 156.2, 156.3, 165.7, 202.1 ppm. LC (conditions A): t_R = 2.29 (major) and 2.46 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m*/*z* (%) = 579.3 (100) $[M + H]^+$, 601.3 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{33}H_{43}N_2O_7$ $[M + H]^+$ 579.3039; found 579.3031. FTIR: $\tilde{\nu}_{max}$ = 3375, 3041, 2958, 2934, 1739, 1717, 1695, 1511, 1450, 1364, 1247, 1165, 1084, 974, 759, 740, 708 cm^{-1}.

1-(1,1-Dimethylprop-2-en-1-yl) 7-*tert*-Butyl (4*S*)-4-(Fmoc-amino)-3-oxoheptan-1,7-dioate (3f): Orange oil, yield 53%. $[\alpha]_D^{20\,°C}$ = +4.72 (*c* = 2.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.44 (s, 9 H), 1.53–1.57 (m, 6 H), 1.82–1.90 (m, 1 H), 2.17–2.38 (m, 3 H), 3.47 (AB, *J* = 16.0 Hz, 1 H), 3.54 (AB, *J* = 16.0 Hz, 1 H), 4.21 (t, *J* = 6.6 Hz, 1 H), 4.38–4.47 (m, 3 H), 5.09 (d, *J* = 11.3 Hz, 1 H), 5.18 (d, *J* = 17.4 Hz, 1 H), 5.60 (d, *J* = 7.4 Hz, 1 H), 6.08 (dd, *J* = 11.3, 17.4 Hz, 1 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.59 (d, *J* = 7.4 Hz, 2 H), 7.76 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.1, 26.4, 26.5, 28.2 (3 C), 31.2, 47.4 (2 C), 59.7, 67.1, 81.1, 82.8, 113.5, 120.2 (2 C), 125.2 (2 C), 127.2 (2 C), 127.9 (2 C), 141.5, 141.9 (2 C), 143.8, 143.9, 156.2, 165.6, 172.3,

201.7 ppm. LC (conditions A): t_R = 2.54 (major) and 2.73 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m/z* (%) = 558.3 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{31}H_{38}NO_7$ $[M + H]^+$ 536.2648; found 536.2648. FTIR: $\tilde{\nu}_{max}$ = 3334, 2979, 1714, 1515, 1450, 1367, 1320, 1243, 1150, 1123, 1042, 927, 844, 759, 739 cm^{-1}.

1-(1,1-Dimethylprop-2-en-1-yl) 7-*tert*-Butyl (4*S*)-4-(Fmoc-amino)-3-oxoheptan-1,7-dioate (3g): Brown oil, yield 72%. $[\alpha]_D^{20\,°C}$ = –11.0 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.44 (s, 9 H), 1.53 (s, 6 H), 2.71 (ABX, *J* = 5.0, 17.1 Hz, 1 H), 2.90 (ABX, *J* = 5.0, 17.1 Hz, 1 H), 3.50 (s, 2 H), 4.23 (t, *J* = 6.7 Hz, 1 H), 4.47 (m, 2 H), 4.57 (m, 1 H), 5.08 (d, *J* = 10.9 Hz, 1 H), 5.18 (d, *J* = 17.5 Hz, 1 H), 5.89 (br., 1 H), 6.08 (dd, *J* = 10.9, 17.5 Hz, 1 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 7.5 Hz, 2 H), 7.76 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.4 (2 C), 28.2 (3 C), 36.7, 47.1, 47.4, 56.9, 67.3, 82.2, 82.6, 113.4, 120.2 (2 C), 125.2 (2 C), 127.2 (2 C), 127.9 (2 C), 141.5 (2 C), 142.0, 143.8 (2 C), 156.1, 165.7, 170.5, 201.2 ppm. LC (conditions A): t_R = 2.44 (major) and 2.60 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m/z* (%) = 522.1 (100) $[M + H]^+$, 544.2 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{30}H_{36}NO_7$ $[M + H]^+$ 522.2491; found 522.2492. FTIR: $\tilde{\nu}_{max}$ = 3335, 2979, 1714, 1505, 1451, 1367, 1319, 1238, 1151, 1123, 1047, 927, 844, 759, 738 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl (4*S*)-4-(Fmoc-amino)tritylthio-3-oxopentanoate (3h): Orange solid, yield 45%, m.p. 70–71 °C. $[\alpha]_D^{20\,°C}$ = –0.24 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.51 (m, 6 H), 2.52 (ABX, *J* = 7.4, 13.1 Hz, 1 H), 2.78 (ABX, *J* = 4.3, 13.1 Hz, 1 H), 3.15 (AB, *J* = 16.0 Hz, 1 H), 3.21 (AB, *J* = 16.0 Hz, 1 H), 4.22 (br., 2 H), 4.41 (br., 2 H), 5.06 (d, *J* = 10.9 Hz, 1 H), 5.14 (d, *J* = 17.6 Hz, 1 H), 5.23 (br., 1 H), 6.05 (m, 1 H), 7.18–7.31 (m, 12 H), 7.39 (br., 7 H), 7.61 (d, *J* = 7.2 Hz, 2 H), 7.75 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.4, 26.8, 32.8, 47.1, 47.3, 59.1, 67.1, 67.4, 82.6, 113.4, 120.1 (2 C), 125.2 (2 C), 127.1 (3 C), 127.2 (2 C), 127.9 (2 C), 128.2 (6 C), 129.6 (6 C), 141.4 (2 C), 141.9, 143.8 (2 C), 144.3 (3 C), 155.8, 165.4, 200.3 ppm. LC (conditions A): t_R = 2.38 (major) and 2.53 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m/z* (%) = 718.3 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{44}H_{41}NO_5SNa$ $[M + Na]^+$ 718.2603; found 718.2589. FTIR: $\tilde{\nu}_{max}$ = 3391, 3058, 2980, 2927, 1714, 1490, 1446, 1412, 1319, 1239, 1121, 1033, 926, 845, 739, 699 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl (4*S*)-4-(Fmoc-amino)-5-(*N*-Boc-1*H*-indol-3-yl)-3-oxopentanoate (3i): Orange solid, yield 49%, m.p. 64–67 °C. $[\alpha]_D^{20\,°C}$ = –3.6 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.50 (m, 6 H), 1.64 (s, 9 H), 3.17 (ABX, *J* = 6.8, 14.8 Hz, 1 H), 3.28 (ABX, *J* = 6.8, 14.8 Hz, 1 H), 3.39 (AB, *J* = 16.0 Hz, 1 H), 3.45 (AB, *J* = 16.0 Hz, 1 H), 4.18 (t, *J* = 6.6 Hz, 1 H), 4.39 (d, *J* = 6.9 Hz, 2 H), 4.78 (m, 1 H), 5.08 (d, *J* = 10.9 Hz, 1 H), 5.16 (d, *J* = 17.5 Hz, 1 H), 5.46 (d, *J* = 7.8 Hz, 1 H), 6.04 (dd, *J* = 10.9, 17.5 Hz, 1 H), 7.23–7.35 (m, 4 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.45 (s, 1 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 7.5 Hz, 1 H), 7.75 (d, *J* = 7.5 Hz, 2 H), 8.13 (br., 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.4 (2 C), 26.9, 28.3 (3 C), 47.3, 48.0, 59.8, 67.2, 82.8, 83.9, 113.5, 115.1, 115.5, 119.0, 120.1 (2 C), 123.0, 124.4, 124.9, 125.2 (2 C), 127.2 (2 C), 127.9 (2 C), 130.3, 135.6, 141.4 (2 C), 141.8, 143.8 (2 C), 149.6, 155.9, 165.7, 201.9 ppm. LC (conditions A): t_R = 2.28 (major) and 2.43 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m/z* (%) = 637.3 (100) $[M + H]^+$, 659.3 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{38}H_{41}N_2O_7$ $[M + H]^+$ 637.2914; found 637.2918. FTIR: $\tilde{\nu}_{max}$ = 2981, 2936, 1718, 1508, 1451, 1368, 1310, 1252, 1226, 1154, 1122, 1083, 1044, 929, 855, 739 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl (4*S*)-4-(Fmoc-amino)-7-(*N*-Pbf-guanidino)-3-oxooctanoate (3j): Yellow solid, yield 34%, m.p. 86–88 °C. $[\alpha]_D^{20\,°C}$ = –0.5 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.43 (s, 6 H), 1.49 (s, 6 H), 1.58 (br., 3 H), 1.90 (br., 1 H), 2.07 (s, 3 H), 2.49 (s, 3 H), 2.56 (s, 3 H), 2.91 (s, 2 H), 3.20 (br., 2 H), 3.48 (d, *J* = 3.8 Hz, 2 H), 4.16 (t, *J* = 6.8 Hz, 1 H), 4.35 (m, 3 H), 5.06 (d, *J* = 10.9 Hz, 1 H), 5.15 (d, *J* = 17.6 Hz, 1 H), 6.02 (m, 1 H), 6.55 (br., 1 H), 7.26 (m, 2 H), 7.36 (t, *J* = 7.5 Hz, 2 H), 7.57 (d, *J* = 7.5 Hz, 2 H), 7.73 (d, *J* = 7.5 Hz, 2 H) ppm; the HN Guanidine resonance was not observed. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.6, 18.1, 19.5, 25.0, 26.5 (2 C), 28.1, 28.7 (2 C), 41.0, 43.2, 47.0, 47.2, 60.5, 67.2, 82.9, 86.8, 113.5, 118.0, 120.1 (2 C), 125.1 (2 C), 125.2 (2 C), 127.2 (2 C), 127.9 (2 C), 133.0, 139.1, 141.4 (2 C), 141.8, 143.8 (2 C), 155.7, 156.7, 159.5, 166.3, 202.4 ppm. LC (conditions A): t_R = 2.07 (major) and 2.18 min (minor; keto–enol equilibrium). LC–MS (ESI+): *m/z* (%) = 759.4 (100) $[M + H]^+$, 781.5 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{41}H_{51}N_4O_8S$ $[M + H]^+$ 759.3428; found 759.3434. FTIR: $\tilde{\nu}_{max}$ = 2990, 2940, 1716, 1455, 1384, 1312, 1259, 1155, 1087, 761, 742, 731 cm^{-1}.

General Procedure for ATC Synthesis 7

Synthesis of Bromo-β-keto Esters 5: To a solution of the β-keto ester **3** (2.87 mmol) in acetonitrile (20 mL) was added magnesium perchlorate (210 mg, 0.95 mmol, 0.3 equiv.). The solution was stirred at –45 °C for 10 min. A solution of NBS (537 mg, 3.01 mmol, 1.1 equiv.) in acetonitrile (15 mL) was then added dropwise over 5 min. The reaction was complete after a few minutes of stirring at –45 °C (HPLC monitoring). The mixture was diluted with Et_2O (40 mL) and washed with water (2 × 40 mL) and brine (3 × 20 mL). The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed under vacuum to give the crude product, which was used in the next step without further purification.

Hantzsch Cyclization: To a solution of α-monobrominated β-keto ester (2 mmol) in absolute ethanol was added a solution of the thioamide (6.0 mmol, 3 equiv.) dissolved in absolute ethanol. The solution was heated for 2 h at 40 °C until completion of the reaction (HPLC and TLC monitoring). The EtOH was evaporated, and the yellowish solid was partitioned between EtOAc (25 mL) and water (25 mL). The organic layer was washed with water (3 × 20 mL) and brine (1 × 20 mL). The combined organic layers were dried with magnesium sulfate and filtered, and the solvents were evaporated under vacuum to yield the crude product. Purification by silica gel column chromatography afforded ATC **7**.

1,1-Dimethylprop-2-en-1-yl 4-[(Fmoc-amino)methyl]–2-methyl-1,3-thiazole-5-carboxylate (7a): White solid, yield 76%, m.p. 102–105 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.65 (s, 6 H), 2.69 (s, 3 H), 4.25 (m, 1 H), 4.38 (d, *J* = 7.2 Hz, 2 H), 4.75 (d, *J* = 5.7 Hz, 2 H), 5.16 (d, *J* = 10.9 Hz, 1 H), 5.26 (d, *J* = 17.5 Hz, 1 H), 5.86 (br., 1 H), 6.17 (dd, *J* = 10.9, 17.5 Hz, 1 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.76 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.6, 26.7 (2 C), 40.8, 47.4, 67.1, 83.2, 113.6, 120.1 (2 C), 124.2, 125.3 (2 C), 127.1 (2 C), 127.8 (2 C), 141.4, 142.0 (2 C), 144.2 (2 C), 156.4, 158.5, 160.7, 169.6 ppm. LC (conditions A): t_R = 2.39 min. LC–MS (ESI+): *m/z* (%) = 463.2 (100) $[M + H]^+$, 485.2 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{26}H_{27}N_2O_4S$ $[M + H]^+$ 463.1682; found 463.1692. FTIR: $\tilde{\nu}_{max}$ = 3213, 3047, 1710, 1541, 1451, 1280, 1241, 1191, 1158, 1133, 1082, 1056, 926, 825, 734 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl 4-[(1*S*)-1-(Fmoc-amino)ethyl]-2-methyl-1,3-thiazole-5-carboxylate (7b): White solid, yield 69%, m.p. 51–53 °C. $[\alpha]_D^{20\,°C}$ = +8.37 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.48 (d, *J* = 6.5 Hz, 3 H), 1.66 (s, 6 H), 2.68 (s, 3 H), 4.23 (t, *J* = 7.8 Hz, 1 H), 4.36 (d, *J* = 6.5 Hz, 2 H), 5.15 (d, *J* = 10.9 Hz, 1 H), 5.27 (d, *J* = 17.4 Hz, 1 H), 5.68 (m, 1 H), 6.01 (d, *J* = 8.7 Hz, 1 H), 6.18 (dd, *J* = 10.9, 17.4 Hz, 1 H), 7.30 (t, *J* =

7.5 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.76 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.5, 22.1, 26.7 (2 C), 46.6, 47.4, 66.8, 83.2, 113.5, 120.0 (2 C), 123.1, 125.3 (2 C), 127.1 (2 C), 127.7 (2 C), 141.4, 142.0 (2 C), 144.1, 144.2, 155.7, 160.3, 162.6, 169.8 ppm. LC (conditions A): t_R = 2.49 min. LC–MS (ESI+): *m*/*z* (%) = 477.2 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{27}H_{29}N_2O_4S$ $[M + H]^+$ 477.1844; found 477.1848. FTIR: $\tilde{\nu}_{max}$ = 3317, 2980, 1705, 1499, 1448, 1366, 1315, 1233, 1192, 1132, 1082, 923, 830, 758 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl 4-[(1*S*)-1-(Fmoc-amino)-3-methylbutyl]-2-methyl-1,3-thiazole-5-carboxylate (7c): White solid, yield 81%, m.p. 98–99 °C. $[\alpha]_D^{20°C}$ = –0.6° (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (d, *J* = 6.4 Hz, 3 H), 0.99 (d, *J* = 6.4 Hz, 3 H), 1.56 (m, 2 H), 1.66 (s, 6 H), 1.75 (m, 1 H), 2.67 (s, 3 H), 4.21 (t, *J* = 7.4 Hz, 1 H), 4.35 (m, 2 H), 5.14 (d, *J* = 10.5 Hz, 1 H), 5.26 (d, *J* = 17.5 Hz, 1 H), 5.70 (m, 1 H), 5.83 (m, 1 H), 6.19 (dd, *J* = 17.5, 10.5 Hz, 1 H), 7.29 (m, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.60 (m, 2 H), 7.75 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.5, 22.3, 23.3, 25.1, 26.7, 26.8, 45.1, 47.4, 48.8, 66.7, 83.3, 113.5, 120.0 (2 C), 123.8, 125.3 (2 C), 127.1 (2 C), 127.7 (2 C), 141.4 (2 C), 142.1, 144.1, 144.2, 155.9, 160.4, 162.2, 169.8 ppm. LC (conditions A): t_R = 2.45 min. LC–MS (ESI+): *m*/*z* (%) = 519.3 (100) $[M + H]^+$, 541.3 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{30}H_{35}N_2O_4S$ $[M + H]^+$ 519.2305; found 519.2318. FTIR: $\tilde{\nu}_{max}$ = 3326, 2956, 1699, 1507, 1450, 1327, 1278, 1251, 1191, 1082, 1044, 923, 830, 759, 736 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl 2-Amino-4-[(1*S*)-1-(Fmoc-amino)-3-methylbutyl]-1,3-thiazole-5-carboxylate (7d): White solid, yield 85%, m.p. 113–114 °C. $[\alpha]_D^{20\ °C}$ = –16.0 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (m, 6 H), 1.53 (m, 2 H), 1.61 (s, 3 H), 1.62 (s, 3 H), 1.73 (m, 1 H), 4.21 (m, 1 H), 4.32 (dd, *J* = 10.3, 7.0 Hz, 1 H), 4.40 (dd, *J* = 10.3, 7.0 Hz, 1 H), 5.12 (d, *J* = 10.9 Hz, 1 H), 5.23 (d, *J* = 17.6 Hz, 1 H), 5.42 (m, 1 H), 5.82 (br., 2 H), 6.04 (m, 1 H), 6.17 (dd, *J* = 17.6, 10.9 Hz, 1 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.59 (d, *J* = 7.4 Hz, 2 H), 7.75 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.3, 23.3, 25.1, 26.7, 27.0, 44.4, 47.4, 49.2, 66.7, 82.5, 113.1, 120.0 (2 C), 125.3 (3 C), 127.1 (2 C), 127.7 (3 C), 141.4 (2 C), 142.5, 144.1 (2 C), 156.1, 161.6, 170.1 ppm. LC (conditions A): t_R = 2.23 min. LC–MS (ESI+): *m*/*z* (%) = 520.2 (100) $[M + H]^+$, 542.2 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{29}H_{34}N_3O_4S$ $[M + H]^+$ 520.2270; found 520.2274. FTIR: $\tilde{\nu}_{max}$ = 3313, 2955, 1695, 1615, 1496, 1450, 1316, 1257, 1075, 1043, 923, 827, 758, 738 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl 4-[(1*S*)-1-(Fmoc-amino)-3-(*tert*-butyl)-propionate]-2-isopropyl-1,3-thiazole-5-carboxylate (7e): Yellow gel, yield 70%. $[\alpha]_D^{20\ °C}$ = –1.9 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (s, 6 H), 1.40 (s, 9 H), 1.67 (s, 6 H), 2.82 (m, 2 H), 3.29 (m, 1 H), 4.24 (br., 1 H), 4.33 (br., 2 H), 5.15 (d, *J* = 10.7 Hz, 1 H), 5.27 (d, *J* = 17.3 Hz, 1 H), 5.98 (br., 1 H), 6.19–6.25 (m, 2 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.60 (d, *J* = 7.4 Hz, 2 H), 7.75 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.0 (2 C), 26.7 (2 C), 28.1 (3 C), 33.7, 41.5, 47.3, 47.8, 67.1, 81.0, 83.6, 113.7, 120.0 (2 C), 123.7, 125.4 (2 C), 127.1 (2 C), 127.8 (2 C), 141.4 (2 C), 141.9, 144.2 (2 C), 155.7, 159.2, 160.3, 169.5, 181.7 ppm. LC (conditions A): t_R = 2.81 min. LC–MS (ESI+): *m*/*z* (%) = 605.3 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{34}H_{41}N_2O_6S$ $[M + H]^+$ 605.2685; found 605.2690. FTIR: $\tilde{\nu}_{max}$ = 2975, 1711, 1506, 1450, 1438, 1367, 1246, 1150, 1121, 1084, 1043, 845, 759, 738, 723, 695 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl 4-[(1*S*)-1-(Fmoc-amino)-2-phenethyl]-2-methyl-1,3-thiazole-5-carboxylate (7f): White solid, yield 75%, m.p. 50–51 °C. $[\alpha]_D^{20\ °C}$ = +2.9 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.62 (d, *J* = 5.7 Hz, 6 H), 2.67 (s, 3 H), 3.13 (d, *J* = 6.8 Hz, 2 H), 4.21 (m, 2 H), 4.39 (m, 1 H), 5.14 (d, *J* = 11.0 Hz, 1 H), 5.23 (d, *J* = 17.5 Hz, 1 H), 5.98 (m, 1 H), 6.11 (m, 2 H), 7.09 (m, 2 H), 7.18–7.23 (m, 3 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.55 (m, 2 H), 7.76 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.4, 26.5, 26.6, 42.2, 47.2, 51.2, 66.8, 83.2, 113.4, 120.0 (2 C), 124.4, 125.2, 125.3, 126.6, 127.0 (2 C), 127.7 (2 C), 128.2 (2 C), 129.4, 129.6, 137.2, 141.3 (2 C), 141.9, 144.1 (2 C), 155.7, 160.0 (2 C), 169.8 ppm. LC (conditions A): t_R = 2.18 min. LC–MS (ESI+): *m*/*z* (%) = 553.3 (100) $[M + H]^+$, 575.3 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{33}H_{33}N_2O_4S$ $[M + H]^+$ 553.2161; found 553.2166. FTIR: $\tilde{\nu}_{max}$ = 2925, 2310, 1703, 1501, 1449, 1319, 1245, 1131, 1083, 738, 699 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl 2-Amino-4-[(1*S*)-1-(Fmoc-amino)-2-phenethyl]-1,3-thiazole-5-carboxylate (7g): White solid, yield 90%, m.p. 119–120 °C. $[\alpha]_D^{20\ °C}$ = +0.07 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.56 (m, 6 H), 3.10 (d, *J* = 7.2 Hz, 2 H), 4.20 (m, 2 H), 4.29 (m, 1 H), 5.10 (d, *J* = 11.0 Hz, 1 H), 5.19 (d, *J* = 17.5 Hz, 1 H), 5.71 (q, *J* = 8.0 Hz, 1 H), 6.07 (br., 2 H), 6.10 (dd, *J* = 17.5, 11 Hz, 1 H), 6.16 (d, *J* = 9.2 Hz, 1 H), 7.13–7.26 (m, 5 H), 7.27 (t, *J* = 7.5 Hz, 2 H), 7.38 (t, *J* = 7.5 Hz, 2 H), 7.53 (d, *J* = 7.5 Hz, 2 H), 7.74 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.7, 26.8, 41.4, 47.3, 51.4, 66.9, 82.8, 113.2, 120.0 (2 C), 125.3, 125.4 (2 C), 126.7, 127.1 (2 C), 127.7 (2 C), 128.3 (2 C), 129.7 (2 C), 137.2, 141.4 (2 C), 142.3, 144.1 (2 C), 155.9, 158.1, 160.5, 169.8 ppm. LC (conditions A): t_R = 1.96 min. LC–MS (ESI+): *m*/*z* (%) = 554.2 (100) $[M + H]^+$, 576.2 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{32}H_{32}N_3O_4S$ $[M + H]^+$ 554.2114; found 554.2123. FTIR: $\tilde{\nu}_{max}$ = 3316, 3198, 2982, 1691, 1614, 1494, 1450, 1317, 1280, 1251, 1076, 1046, 923, 827, 758, 739, 699 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl 4-{(1*S*)-1-(Fmoc-amino)-[(*tert*-butoxycarbonyl)amino]pentyl}-2-methyl-1,3-thiazole-5-carboxylate (7h): White solid, yield 81%, m.p. 128–129 °C. $[\alpha]_D^{20\ °C}$ = –1.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (br., 2 H), 1.41 (s, 9 H), 1.52 (br., 2 H), 1.65 (s, 6 H), 1.80 (m, 2 H), 2.75 (s, 3 H), 3.08 (br., 2 H), 4.21 (t, *J* = 7.6 Hz, 1 H), 4.34 (m, 2 H), 4.60 (br., 1 H), 5.16 (d, *J* = 10.7 Hz, 1 H), 5.26 (d, *J* = 17.3 Hz, 1 H), 5.62 (m, 1 H), 6.16–6.19 (m, 2 H), 7.29 (m, 2 H), 7.38 (t, *J* = 7.6 Hz, 2 H), 7.60 (br., 2 H), 7.75 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.3, 23.1, 26.6 (2 C), 28.5 (3 C), 29.7, 35.7, 40.4, 47.3, 50.1, 66.9, 79.2, 83.5, 113.7, 120.0 (2 C), 123.6, 125.3 (2 C), 127.1 (2 C), 127.8 (2 C), 141.4 (2 C), 141.8, 144.0 (2 C), 156.1, 156.2, 160.2, 161.3, 170.1 ppm. LC (conditions A): t_R = 2.04 min. LC–MS (ESI+): *m*/*z* (%) = 634.3 (100) $[M + H]^+$, 656.3 (10) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{35}H_{44}N_3O_6S$ $[M + H]^+$ 634.2951; found 634.2955. FTIR: $\tilde{\nu}_{max}$ = 3298, 3069, 2978, 2934, 1695, 1511, 1450, 1364, 1247, 1165, 1084, 974, 831, 759, 740, 708 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl 2-Amino-4-{(1*S*)-1-(Fmoc-amino)-[(*tert*-butoxycarbonyl)amino]pentyl}-1,3-thiazole-5-carboxylate (7i): White solid, yield 82%, m.p. 147–148 °C. $[\alpha]_D^{20\ °C}$ = –15.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (br., 2 H), 1.43 (s, 9 H), 1.51 (br., 2 H), 1.62 (s, 6 H), 1.75 (m, 2 H), 3.09 (br., 2 H), 4.19 (t, *J* = 7.0 Hz, 1 H), 4.35 (d, *J* = 7.0 Hz, 2 H), 4.62 (br., 1 H), 5.12 (d, *J* = 10.9 Hz, 1 H), 5.23 (d, *J* = 17.6 Hz, 1 H), 5.39 (m, 1 H), 6.03 (br., 3 H), 6.16 (dd, *J* = 17.6, 10.9 Hz, 1 H), 7.28 (m, 2 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.59 (br., 2 H), 7.74 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.0, 26.8 (2 C), 28.6 (3 C), 29.7, 35.1, 40.3, 47.4, 50.5, 66.9, 79.3, 82.6, 113.2, 118.6, 120.0 (2 C), 125.3 (2 C), 127.2 (2 C), 127.7 (2 C), 141.4 (2 C), 142.4, 144.2 (2 C), 156.1 (2 C), 156.3, 160.9, 170.1 ppm. LC (conditions A): t_R = 2.08 min. LC–MS (ESI+): *m*/*z* (%) = 635.3 (100) [M +

H]$^+$, 657.3 (10) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{34}H_{43}N_4O_6S$ [M + H]$^+$ 635.2903; found 635.2908. FTIR: $\tilde{\nu}_{max}$ = 3316, 2933, 1685, 1498, 1450, 1364, 1248, 1165, 1077, 926, 858, 828, 758, 739 cm^{-1}.

1,1-Dimethylprop-2-en-1-yl 4-[(1*S*)-1-(Fmoc-amino)-2-(*N*-Boc-1*H*-indol-3-yl)ethyl]-2-methyl-1,3-thiazole-5-carboxylate (7j): Yellow solid, yield 72%, m.p. 149–150 °C. $[\alpha]_D^{20\,°C}$ = +0.56 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.53 (m, 6 H), 1.62 (s, 9 H), 2.67 (s, 3 H), 3.26 (m, 2 H), 4.20 (t, *J* = 7.1 Hz, 1 H), 4.25–4.35 (m, 2 H), 5.09 (d, *J* = 10.8 Hz, 1 H), 5.17 (d, *J* = 17.4 Hz, 1 H), 5.99–6.06 (m, 2 H), 6.11 (m, 1 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 7.24–7.40 (m, 6 H), 7.56 (m, 3 H), 7.75 (d, *J* = 7.7 Hz, 2 H), 8.08 (br., 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.3, 26.5 (2 C), 28.3 (3 C), 31.5, 47.3, 50.3, 67.0, 83.5 (2 C), 113.6, 115.2, 116.1, 119.0, 120.0 (2 C), 122.5, 124.3, 124.9, 125.5 (2 C), 127.2 (2 C), 127.7 (2 C), 127.9, 130.9, 135.4, 141.4 (2 C), 141.8, 144.1 (2 C), 149.8, 155.8, 159.9 (2 C), 170.0 ppm. LC (conditions B): t_R = 2.98 min. LC–MS (ESI+): *m*/*z* (%) = 692.4 (100) [M + H]$^+$, 714.4 (10) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{40}H_{42}N_3O_6S$ [M + H]$^+$ 692.2794; found 692.2798. FTIR: $\tilde{\nu}_{max}$ = 3376, 2978, 2932, 1718, 1504, 1451, 1368, 1331, 1252, 1155, 1082, 936, 855, 833, 758, 739 cm^{-1}.

Compound 7k: White solid, yield 51%, m.p. 134–135 °C. $[\alpha]_D^{20\,°C}$ = –0.98 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (br., 6 H), 1.25 (s, 6 H), 1.42 (m, 1 H), 1.57 (m, 2 H), 1.62 (br., 9 H), 3.23 (m, 2 H), 4.21 (br., 1 H), 4.33 (m, 2 H), 4.98 (br., 1 H), 5.09 (m, 2 H), 5.12 (s, 2 H), 5.97 (br., 1 H), 6.00 (m, 1 H), 6.07 (br., 2 H), 7.07–7.39 (m, 12 H), 7.50–7.61 (m, 3 H), 7.75 (d, *J* = 7.8 Hz, 2 H), 8.06 (br., 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.9 (2 C), 26.6 (2 C), 28.3 (3 C), 29.9 (2 C), 32.1, 45.8, 47.4, 50.7, 67.1, 67.4, 83.5, 83.6, 113.6, 115.3, 116.1, 117.6, 120.1 (2 C), 122.7, 124.3, 124.4, 125.3 (2 C), 127.2 (2 C), 127.8 (2 C), 128.2 (2 C), 128.4, 128.7 (2 C), 129.8, 130.4, 132.2, 136.2, 141.4 (2 C), 142.0, 144.2 (2 C), 149.8, 155.8, 155.9, 161.5, 161.9, 165.4 ppm. LC (conditions B): t_R = 3.16 min. LC–MS (ESI+): *m*/*z* (%) = 897.1 (100) [M + H]$^+$, 919.1 (10) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{52}H_{57}N_4O_8S$ [M + H]$^+$ 897.3897; found 897.3899. FTIR: $\tilde{\nu}_{max}$ = 2917, 2851, 1728, 1593, 1522, 1451, 1368, 1254, 1191, 1143, 1081, 937, 831, 758, 740, 721 cm^{-1}.

Compound 7l: White solid, yield 45%, m.p. 121–122 °C. $[\alpha]_D^{20\,°C}$ = –0.80 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (s, 6 H), 1.66 (s, 9 H), 2.12 (m, 3 H), 2.47 (s, 3 H), 2.95 (m, 4 H), 3.27 (m, 2 H), 4.16 (br., 1 H), 4.25 (m, 2 H), 5.17 (d, *J* = 10.8 Hz, 1 H), 5.25 (d, *J* = 17.4 Hz, 1 H), 6.04 (m, 1 H), 6.12 (m, 1 H), 6.24 (br., 1 H), 7.21–7.38 (m, 7 H), 7.46–7.58 (br., 4 H), 7.64–7.76 (m, 4 H), 8.13 (br., 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 25.6, 26.6, 28.3 (3 C), 29.9 (2 C), 30.3, 33.0, 47.1, 49.0, 67.6, 84.0, 84.6, 114.2, 114.6, 115.5, 118.6, 120.0 (2 C), 122.8, 122.9, 124.5, 124.6, 124.8, 124.9, 125.2, 125.5 (2 C), 127.2 (2 C), 127.8 (2 C), 130.0 (2 C), 135.5, 141.3, 143.7, 143.9 (2 C), 145.1 (2 C), 147.8, 149.7, 155.8, 157.6, 159.1, 163.3, 169.6 ppm. LC (conditions A): t_R = 2.84 and 2.87 min. LC–MS (ESI+): *m*/*z* (%) = 850.7 (100) [M + H]$^+$, 872.7 (10) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{50}H_{52}N_5O_6S$ [M + H]$^+$ 850.3638; found 850.3633. FTIR: $\tilde{\nu}_{max}$ = 2917, 2850, 1728, 1594, 1522, 1451, 1368, 1252, 1191, 1143, 1081, 938, 832, 758, 740, 721 cm^{-1}.

Compound 7m: White solid, yield 70%, m.p. 140–142 °C. $[\alpha]_D^{20\,°C}$ = –0.99 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.44 (s, 6 H), 1.60 (d, *J* = 8.1 Hz, 6 H), 1.72 (br., 2 H), 1.92 (br., 2 H), 2.08 (s, 3 H), 2.51 (s, 3 H), 2.57 (s, 3 H), 2.67 (s, 3 H), 2.92 (s, 2 H), 3.23 (br., 2 H), 4.19 (t, *J* = 7.0 Hz, 1 H), 4.39 (m, 2 H), 5.14 (d, *J* = 10.9 Hz, 1 H), 5.28 (d, *J* = 17.6 Hz, 1 H), 5.54 (br., 1 H), 6.04 (br., 1 H), 6.12 (dd, *J* = 17.6, 10.9 Hz, 1 H), 7.15–7.32 (m, 2 H), 7.38 (m, 5 H), 7.57 (m, 2 H), 7.75 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.6, 18.0, 19.4, 19.5, 25.3, 26.5, 26.9, 28.7 (2 C), 33.8, 40.6, 43.4, 47.3, 49.2, 67.0, 83.5, 86.4, 113.6, 117.5, 120.1 (2 C), 122.7, 124.6 (2 C), 125.2 (2 C), 127.2 (2 C), 127.8 (2 C), 132.4, 133.3, 138.5, 141.4, 142.0, 143.8, 144.0, 156.2, 156.6, 158.7, 160.6, 161.8, 170.1 ppm. LC (conditions A): t_R = 2.54 min. LC–MS (ESI+): *m*/*z* (%) = 814.4 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{43}H_{52}N_5O_7S_2$ [M + H]$^+$ 814.3308; found 814.3312. FTIR: $\tilde{\nu}_{max}$ = 2921, 2853, 1719, 1539, 1452, 1370, 1251, 1135, 1083, 759, 740 cm^{-1}.

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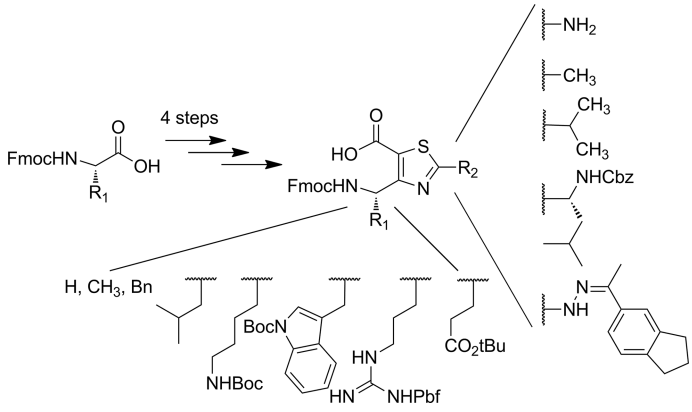

Cross-Claisen condensations between *N*-Fmoc-amino acids and sterically hindered 1,1-dimethylallyl acetate provide a short route to 4-amino(methyl)-1,3-thiazole-5-carboxylic acids (ATCs), a new class of constrained heterocyclic γ-amino acids built around a thiazole ring. A wide variety of lateral chains can be introduced on the γ-carbon atom or on the thiazole core.

Keywords: Peptidomimetics / Amino acids / Heterocycles / Cross-Claisen reactions

