A Simple Synthesis of N^{β}-Fmoc/Z-Amino Alkyl Thiols and their use in the Synthesis of N^{β}-Fmoc/Z-Amino Alkyl Sulfonic Acids

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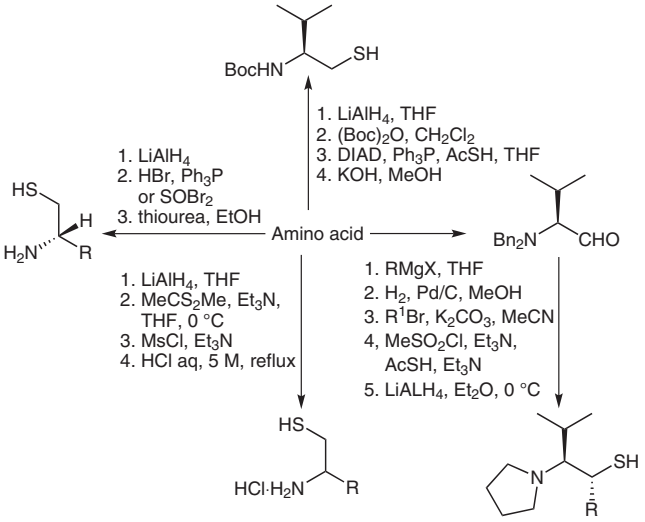
Abstract: A simple and efficient protocol for the synthesis of N^{β}-Fmoc/Z-amino alkyl thiols is described. The approach uses sodium pyrosulfite-mediated hydrolysis of isothiouronium salts resulting from the reaction between N-protected aminoalkyl iodides and thiourea. N-Protected taurines were prepared through performic acid oxidation of the thiols and the products were further utilized for the synthesis of dipeptidosulfonamides.

Key words: alkyl iodides, thiourea, alkyl thiols, N-protected taurines, isothiuronium salts

Thiols are important structural motifs in various biologically active molecules.[1] Compounds containing this functionality have served as key starting materials in the synthesis of a variety of organosulfur compounds that demonstrate pesticidal, fungicidal, antimicrobial, antibacterial, and antiviral activities.[2] Chiral β-amino alkyl thiols have found application as enzyme inhibitors,[3] radio-protective agents,[4] and also as intermediates for the synthesis of libraries of biological interest.[5] In peptide chemistry, the thiol group of cysteine is utilized in various synthetic applications, such as in the construction of *S*-glycopeptides.[6] Often, oxygen or nitrogen atoms of native peptides are replaced with sulfur to obtain novel thio-analogs,[7] several of which possess higher biological activities than the corresponding natural materials. For example, replacement of an amide bond in peptides by CH_2–S linkages has lead to surrogates that are potent inhibitors of aminopeptidase M.[8] The amino thiols: cysteine, homocysteine and pencillamine, are present in many complex biomolecules,[9] and alkyl thiols are key precursors in the preparation of many medicinally important classes of molecules, such as: thiocarbamates,[10] thiocarbonates,[11] and taurines.[12] They are also being employed as catalysts for enantioselective organic synthesis.[13]

Thiols can be synthesized through deprotection of thioacetates by heating at reflux with $NaBH_4$,[14] by reaction of an alkyl halide with NaSH,[15] or through reaction of an activated alcohol in the form of tosylate/mesylate or that of alkyl bromides with thiourea followed by hydrolysis using 1 N NaOH.[16] However, in the latter cases, the harsh conditions employed for such deprotection often leads to dialkyl sulfides.[17]



Scheme 1

Some of the important routes employed for the synthesis of amino alkyl thiols from amino acids are depicted in Scheme 1. One example of an *N*-urethane-protected amino alkyl thiol was reported by Myllamaki et al., who synthesized Boc-Val-ψ[CH_2SH] starting from valine. The methodology involved the conversion of Boc-valinol into the corresponding thioacetate using thioacetic acid under Mitsunobu conditions, followed by KOH-mediated hydrolysis.[18] Yang's group described the synthesis of 1,2-substituted amino thiols using dibenzyl-protected 1,2-substituted β-amino thioacetates.[19] An alternative route for the synthesis of amino thiols employing methyl dithioacetate as a sulfur transfer reagent is also known.[20] Otto's group has isolated free amino alkyl thiols (derived from L-Ala, L-Val, L-Leu, L-Ile, and L-Phe) in three steps by treating bromoalkylammonium hydrobromides with thiourea.[21] In that report, the isolated yield of amino thiols was in the range of 38–48% only. Although the authors employed various brominating reagents, such as HBr, PBr_3 and $SOBr_2$, for the conversion of the alcohols into bromides, the reaction was not complete, which made the isolation of the intermediates tedious. Overall, the multi-step sequences, low yields, formation of byproducts and consequent tedious product isolation procedures involved in the above protocols, evoke the need for alternative methodologies to be developed.

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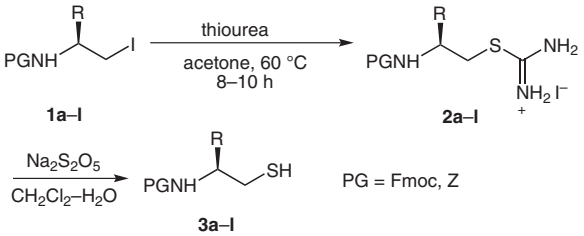
Aminoalkylsulfonic acids,[22] known as taurines, have a significant role in various physiological processes[23] and are found in mammalian tissues and other organisms.[24] They can serve as starting materials for the synthesis of sulfonopeptides,[25] wherein the peptide linkage is replaced with a sulfonamide. Thus, owing to the vast number of synthetic applications of amino acid derived thiols and taurines, we report herein, a simple and high-yielding approach to the synthesis of N^{β}-Fmoc/Z-amino alkyl thiols via the isothiouronium intermediate. Furthermore, subsequent oxidation leading to N^{β}-protected amino alkyl sulfonic acids is described, the utility of which in the preparation of a few *N*-Fmoc-protected dipeptidosulfonamides is also demonstrated.

In view of the general stability of the Fmoc group, its immense utility in solid-phase peptide synthesis and handling advantages associated with these compounds,[26] we initiated our study employing Fmoc chemistry. Fmoc-amino acids were reduced to the corresponding alcohols via the mixed anhydride using the *N*-methyl morpholine/ethyl chloroformate system, followed by treatment with $NaBH_4$.[27] The resulting *N*-Fmoc aminols were then converted into the corresponding alkyl iodides[28] under Mitsunobu conditions (Ph_3P/imidazole/I_2) in quantitative yield. The next step was to insert a thiol group in place of the iodide functionality, to afford the title molecules. We chose *N*-Fmoc-Phe-ψ[CH_2-I] (**1c**) as a typical example to establish the optimal reaction conditions. To this end, treatment of a solution of **1c** in acetone with thiourea under reflux (argon atmosphere) for 8–10 hours led to the formation of isothiouronium salt **2c** (Scheme 2).[40] Evaporation of the solvent followed by a single recrystallization of the crude material, afforded the intermediate isothiouronium salt as a pure white, stable solid in good yield (91%). Similar results with respect to both yield and purity were observed when the reaction was repeated with several other N-protected amino acids (Table 1); all the products were characterized by ^1H, ^{13}C NMR and mass analyses,[41] and all were found to be stable for several weeks at room temperature.



Scheme 2

In the next set of experiments, we carried out the hydrolysis of the isothiouronium salts leading to the title molecules. Although base hydrolysis is widely used for this,[29] such conditions are not compatible with Fmoc chemistry. During our quest for an alternative procedure, a literature survey revealed that aqueous sodium pyrosulfite is a mild reagent for carrying out such hydrolysis under neutral conditions.[30] The method also facilitates the isolation of product with a simple work-up. Accordingly, treatment of **2c** with sodium pyrosulfite in CH_2Cl_2–H_2O (5:2) at reflux for 30 minutes brought about complete hydrolysis of the isothiouronium salt. A simple aqueous work-up, followed by column purification, led to the desired thiol **3c** as a pure solid in 88% yield.[42,43] The generality of this protocol was demonstrated by the synthesis of several examples of thiols derived from *N*-Fmoc amino acids, including two bifunctional products: Lys (**2f**) and Glu(OBn) (**2g**) (Table 1).

Table 1 Isothiouronium Salts **2**

Product	PG	R	HRMS [M – I]$^+$		Yield (%)
			Calcd	Found	
2a	Fmoc	H	341.1198	341.1172	92
2b	Fmoc	Me	355.1354	355.1310	94
2c	Fmoc	Bn	431.1667	431.1651	91
2d	Fmoc	*i*-Pr	383.1667	383.1621	94
2e	Fmoc	*i*-Bu	397.1824	397.1801	88
2f	Fmoc	$(CH_2)_4NHZ$	546.2301	546.2271	94
2g	Fmoc	$(CH_2)_2CO_2Bn$	503.1879	503.1771	93
2h	Fmoc	$-(CH_2)_3-$	382.1589	382.1534	91
2i	Z	Bn	344.1433	344.1409	92
2j	Z	*s*-Bu	310.1589	310.1558	87
2k	Z	CH_2CO_2Bn	402.1488	402.1471	93
2l	Z	Ph	330.1276	330.1245	94

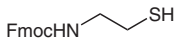
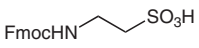
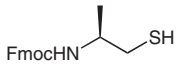
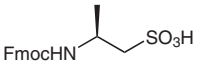
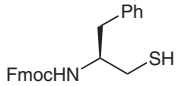
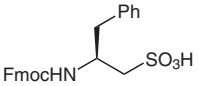
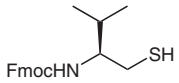
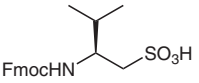
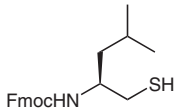
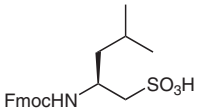
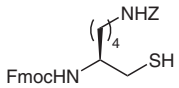
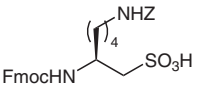
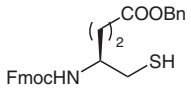
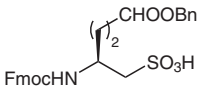
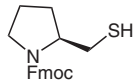
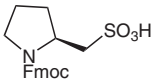
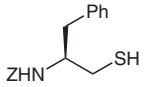
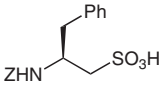
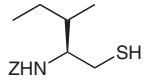
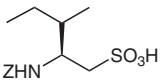
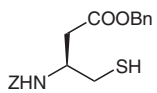
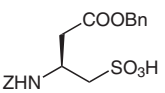
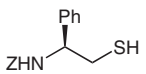
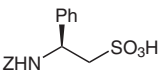
In a continuation of this study, several Z-amino alkyl iodides were also converted into their corresponding thiols (**3i–l**) in good yields. All the thiols synthesized were found to be stable for long periods on storage at low temperatures. However, efforts to simplify this two-step protocol into a one-pot procedure starting from N-protected amino alkyl iodide, obviating the isolation of the isothiouronium salt intermediate, gave only low overall yields.

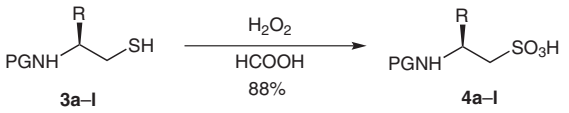
Having established a protocol for the conversion of *N*-Fmoc-amino alkyl iodides into the corresponding isothiouronium salts, leading to the preparation of thiols, we examined the feasibility of following a similar protocol with related intermediates such as *N*-Fmoc amino alkyl tosylates and mesylates. For this, Fmoc-Phe-ψ[CH_2OH] was converted into its tosylate by employing a reported procedure.[31] On treatment of this intermediate with thiourea under similar conditions to those described for the iodide counterpart, the formation of the isothiouronium salt was observed with no more than 50–60% conversion even after continuing the reaction for longer periods at reflux (>18 h). Moreover, the isolation of the intermediate was tedious due to the formation of several byproducts. A similar result was obtained with Fmoc-amino acid derived

mesylate {Fmoc-Phe-ψ[CH_2OMs]}. Owing to the low yield and other synthetic difficulties encountered in the synthesis of the isothiouronium salt itself, the -OTs and -OMs intermediates were judged to be less attractive for the efficient preparation of thiols.

The next part of the study involved the synthesis of N-protected taurines. Among the various methods available for their preparation, direct conversion of amino alcohols via sulfite displacement[32] and performic acid oxidation of Boc/Z-β-amino thioacetates are attractive.[33] Gude et al., prepared a Boc-NH-Xaa-ψ[SO_2Cl] series via betaines obtained from mesylates of Boc-β-amino alcohols.[34] Liskamp's group reported the synthesis of *N*-Fmoc-β-aminoethanesulfonyl chlorides via the oxidation of *N*-Fmoc-β-amino thioacetates generated by Cs_2CO_3-promoted reaction of *N*-Fmoc-β-amino alkyl mesylate with thioacetic acid. This intermediate step requires 18 hours and the yields of corresponding thioacetates are usually low.[35] Previously, the same group had reported a few other procedures.[36] Xu et al. have established a route for the synthesis of substituted taurines via oxidation of Z-β-amino thioacetates employing performic acid.[37] Aziridine ring-opening with thioacetic acid leading to the formation of acetyl-β-amino thiols followed by oxidation is also known.[38] Although taurines have been prepared from Boc- and Z-protected compounds, their synthesis using Fmoc-chemistry has yet to be demonstrated. It was envisaged that performic acid oxidation would be a suitable method for the conversion of our thiols into N^{β}-Fmoc/Z-amino alkane sulfonic acids (Scheme 3). Accordingly, in a typical reaction, a solution of thiol **3c** in 98% formic acid was added slowly to the oxidant solution at 0 °C; the mixture was then allowed to warm to room temperature and then stirred for one day. After removal of the solvent, the crude material was purified on a silica gel column to afford *N*-Fmoc-Phe-ψ[CH_2SO_3H] (**4c**) in 78% yield.[44] The protocol was successfully employed for the synthesis of a

Table 2 Thiols **3** and Sulfonic Acids **4**

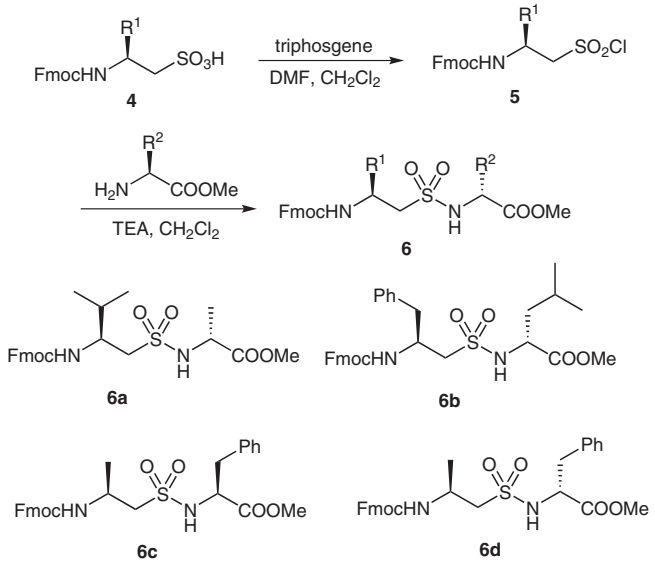
Entry	Thiol **3**	Mp (°C)	$[\alpha]_D^{25}$ (*c* 1, $CHCl_3$)	Yield (%)	N-Protected Taurines **4**	Yield (%)	$[\alpha]_D^{25}$ (*c* 1, $CHCl_3$)	Mp (°C)
a		118	–	86		85	–	136
b		96	–11.6	92		79	–23.1	148
c		109	+3.0	88		88	–28.0	133
d		98	–0.70	91		82	–41.3	129
e		81	–20.1	84		86	–10.8	135
f		113	+5.6	88		81	–7.4	119
g		92	+3.4	94		71	–14.5	113
h		78	–28.3	79		87	–39.2	125
i		105	+6.8	91		69	–41.0	131
j		96	–10.8	88		70	–9.5	115
k		72	+7.1	85		65	+1.2	98
l		104	–48.3	90		73	+20.0	137



Scheme 3

series of N-protected taurines in good yield and purity (Table 2).[45]

In the next set of experiments, the utility of taurines for the preparation of dipeptidosulfonamides was demonstrated by coupling Fmoc-protected sulfonic acids with amino acid esters. In a typical reaction, *N*-Fmoc-Val-ψ[CH_2SO_3H] (**4d**) was converted into its sulfonyl chloride by treatment with triphosgene and a catalytic amount of DMF.[39,46] The resulting sulfonylchloride was obtained in 71% yield after purification by flash chromatography.[47] *N*-Fmoc-Val-ψ[CH_2SO_2Cl] (**5d**) was then coupled with alanyl methyl ester in the presence of Et_3N to obtain dipeptidosulfonamide **6a** in 72% yield after column purification (Scheme 4).[48] In a similar manner, *N*-Fmoc-Phe-ψ[CH_2SO_2]-Leu-OMe (**6b**) was also obtained in good yield. Additionally, two epimeric sulfonopeptides **6c** and **6d** were prepared by coupling *N*-Fmoc-Ala-ψ[CH_2SO_2Cl] (**3b**) with H-Phg-OMe (both L and D) in a separate set of experiments and their ^{1}H NMR spectra were recorded.[49] Distinct alanyl methyl group doublets were observed for each of the epimers (δ = 1.16 and 1.18 ppm for **6c**; δ = 1.23 and 1.26 ppm for **6d**), which confirmed the absence of the undesired epimer in both the samples, suggesting that the protocol is free from epimerization.



Scheme 4

This, in turn, also implies that *N*-Fmoc-Ala-ψ[CH_2SH] is optically pure. Therefore, it was concluded that the present protocol, starting from the synthesis of thiols and leading to the generation of taurines and peptidosulfonamides is free from racemization at levels detectable by NMR analysis.

In summary, we have demonstrated a mild and efficient route for the synthesis of *N*-Fmoc/Z-amino alkyl thiols starting from the corresponding iodides. Performic acid oxidation of the thiols afforded the respective taurines, which were employed as precursors for the preparation of a number of N-protected dipeptidyl sulfonamides. All the products, including the isothiouronium salts, were isolated and adequately characterized.

Acknowledgment

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(40) **General procedure for 2a–l**: A solution of N^{β}-Fmoc/Z-amino alkyl iodide **1a–l** (1.0 mmol) and thiourea (2.1 g, 3.0 mmol) in anhydrous acetone (10.0 mL) was heated at reflux under an argon atmosphere for 8–10 h. The consumption of the iodide was monitored by TLC. The solvent was evaporated under vacuum and the isothouronium salt was isolated as the pure compound by recrystallization from acetone–diethyl ether.
(41) **Spectroscopic data for 2d**: IR (KBr): 1703, 1657, 3211 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 0.91 (2 × d, *J* = 6.1 Hz, 6 H), 1.76–2.08 (m, 1 H), 2.98–3.10 (m, 2 H), 3.96–4.01 (m, 1 H), 4.18 (t, *J* = 6.9 Hz, 1 H), 4.39 (d, *J*= 4.9 Hz, 2 H), 5.01 (br, 1 H), 6.94–7.77 (m, 8 H), 9.10 (br, 2 H), 9.32 (br, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.8, 25.4, 30.1, 47.3, 55.2, 66.1, 119.5, 124.8, 125.5, 127.0, 127.9, 141.0, 143.8, 144.2, 156.3, 161.2.
(42) **General procedure for 3a–l**: Isothiouronium salt **2** (1.0 mmol) and sodium pyrosulfite (1.5 mmol) were dissolved in CH_2Cl_2 (10.0 mL) and H_2O (2.0 mL) and heated at reflux under argon atmosphere until completion of reaction. The mixture was diluted with excess CH_2Cl_2, and the organic extract was washed with H_2O (2 × 10 mL) and brine (10 mL), and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel; 100–150 mesh; EtOAc–hexane, 15%).
(43) **Selected spectroscopic data: 3c**: IR (KBr): 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.23 (s, 1 H), 2.81–3.05 (m, 4 H), 3.65 (d, *J* = 3.5 Hz, 2 H), 3.71–3.97 (m, 1 H), 4.17 (t, *J* = 6.8 Hz, 1 H), 5.02 (br, 1 H), 6.97–7.67 (m, 13 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8, 40.3, 47.1, 52.8, 67.4, 120.4, 125.6, 127.0, 127.8, 128.5, 129.3, 137.0, 141.7, 144.5, 155.8. **3j**: IR (KBr): 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 2.8 Hz, 3 H), 0.96 (d, *J*= 4.2 Hz, 3 H), 1.12–1.35 (m, 2 H), 2.05 (s, 1 H), 2.32–2.45 (m, 1 H), 2.71 (dd, *J* = 2.7 Hz, 1 H), 3.01 (dd, *J* = 3.1 Hz, 1 H), 3.56–3.71 (m, 1 H), 4.90 (br, 1 H), 5.05 (s, 2 H), 7.21 (s, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.5, 13.6, 24.2, 28.6, 39.4, 57.6, 64.8, 127.2, 128.0, 128.8, 137.6, 155.8.
(44) **General experimental procedure for 4a–l**: H_2O_2 (30%, 15.0 mL) was dissolved in 98% formic acid (35.0 mL) at 0 °C and the mixture was stirred at this temperature for 1 h to afford performic acid. Fmoc/Z-amino alkyl thiol in 98% formic acid (3.0 mL) solution was added dropwise to the performic acid solution and the resulting reaction mixture was stirred at r.t. for 1 d. After removal of the solvent, the product was purified by column chromatography ($CHCl_3$–MeOH, 8:1) to afford N-protected taurines as colorless solids.
(45) **Selected spectroscopic data: 4b**: IR (KBr): 1708, 1211, 1118 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.11 (d, *J* = 6.53 Hz, 3 H), 2.58 (dd, *J* = 2.9 Hz, 1 H), 2.78 (dd, *J* = 3.0 Hz, 1 H), 3.25–3.45 (m, 1 H), 4.15 (t, *J* = 6.8 Hz, 1 H), 4.41 (d, *J* = 4.8 Hz, 2 H), 6.13 (br, 1 H), 7.02–7.57 (m, 8 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.5, 41.2, 46.8, 57.5, 64.8, 120.1, 125.2, 126.9, 127.8, 141.1, 142.8, 155.03. **4j**: IR (KBr): 1691, 1217, 1170 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 0.76 (t, *J* = 2.3 Hz, 3 H), 0.98 (d, *J* = 5.0 Hz, 3 H), 1.31–1.40 (m, 2 H), 2.12–2.31 (m, 1 H), 2.75 (dd, *J* = 2.5 Hz, 1 H), 3.03 (dd, *J* = 3.1 Hz, 1 H), 3.57–3.62 (m, 1 H), 4.68 (s, 2 H), 5.92 (br, 1 H), 6.98 (s, 5 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 0.2, 13.6, 24.6, 37.8, 45.8, 55.3, 64.4, 128.1, 128.8, 137.5, 154.8.
(46) **General procedure for the synthesis of Fmoc-Xaa-ψ[CH_2SO_2Cl](5)**: To a suspension of **4** (1.0 mmol) in anhydrous CH_2Cl_2 (10.0 mL) at 0 °C, triphosgene (0.7 mmol) and a catalytic amount of DMF were added and the mixture was stirred overnight. The mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with H_2O (2 × 10 mL) and brine (10 mL), then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 100–150 mesh; EtOAc–hexane, 10%).
(47) **Spectroscopic data for 5a**: Yield 78%; white solid; mp 151 °C. IR (KBr): 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.0 Hz, 3 H), 3.58 (dd, *J* = 2.8 Hz, 1 H), 3.65 (d, *J* = 3.5 Hz, 2 H), 3.97–4.08 (m, 1 H), 4.20 (t, *J* = 6.8 Hz, 1 H), 4.31–4.39 (m, 1 H), 5.11 (br, 1 H), 7.04–7.70 (m, 8 H); ^{13}C NMR (100, MHz, $CDCl_3$): δ = 19.3, 44.0, 46.9, 66.8, 69.1, 119.5, 125.6, 127.2, 128.0, 141.2, 143.8, 155.5.
(48) **General procedure for the synthesis of 6**: To an ice-cooled solution of *N*-Fmoc-Xaa-ψ[CH_2SO_2Cl] (1.0 mmol) in anhydrous CH_2Cl_2, was added a solution of amino acid methyl ester in CH_2Cl_2 (1.0 mmol, obtained by neutralizing the corresponding hydrochloride salt using zinc dust), followed by Et_3N (1.0 mmol). The resulting suspension was stirred for 6–8 h. After dilution with excess CH_2Cl_2 (25 mL), it was washed with 1M HCl (2 × 10 mL), sat. $NaHCO_3$ (2 × 10 mL), and brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by column

chromatography (silica gel, 100–150 mesh; EtOAc–hexane, 30%).

(49) **Selected spectroscopic data: 6a**: White solid; mp 163 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.98–1.12 (m, 6 H), 1.23 (d, *J* = 5.9 Hz, 3 H), 2.08–2.15 (m, 1 H), 3.06 (d, *J* = 4.5 Hz, 1 H), 3.21 (s, 3 H), 3.78 (dd, *J* = 2.6 Hz, 1 H), 3.98 (t, *J* = 3.8 Hz, 1 H), 4.01 (dd, *J* = 3.0 Hz, 1 H), 4.12 (d, *J* = 5.8 Hz, 2 H), 4.21–4.31 (m, 1 H), 5.06–5.11 (br, 2 H), 7.12–7.69 (m, 8 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 7.0, 18.2, 30.6, 37.2, 47.3, 50.3, 63.2, 66.7, 120.2, 125.6, 127.3, 127.8, 141.3, 143.6, 154.6, 170.2. **6c**: White solid; mp 143 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.17 (d, *J* = 5.4 Hz, 3 H), 3.10 (s, 3 H), 3.59 (dd, *J* = 2.2 Hz, 1 H), 3.63–3.75 (m, 1 H), 4.04 (s, 1 H), 4.12 (d, *J* = 5.6 Hz, 2 H), 5.23–5.64 (br, 2 H), 7.12–7.82 (m, 13 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.9, 34.5, 50.6, 54.8, 62.7, 66.1, 47.4, 120.6, 125.1, 127.4, 127.1, 141.0, 143.1, 155.0, 170.1.