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Efficient synthesis of new α-β-unsaturated alkyl-ester peptide-linked chiral amines †

Oscar Villanueva-Kasis[1,2], Denisse A. de Loera[2], Sandra L. Castañón-Alonso[1], Armando Domínguez-Ortíz[1], Leticia Lomas-Romero[1], Ilich A. Ibarra[3,*], Eduardo González-Zamora[1,*], and Alejandro Islas-Jácome[1,*]

[1] Departamento de Química, Universidad Autónoma Metropolitana-Iztapalapa, San Rafael Atlixco 186, Col. Vicentina, C.P. 09340, Iztapalapa, Ciudad de México.
[2] Facultad de Ciencias Químicas, Universidad Autónoma de San Luís Potosí, Av. Manuel Nava 6, Zona Universitaria, C.P. 78210, San Luis Potosí, S.L.P., México.
[3] Laboratorio de Fisicoquímica y Reactividad de Superficies, Instituto de Investigaciones en Materiales, Universidad Nacional Autónoma de México, Circuito Exterior S/N, Ciudad Universitaria, C.P. 04510, Coyoacán, Ciudad de México.
* Correspondence: argel@unam.mx (I.A.I.); egz@xanum.uam.mx (E.G.-Z.); aij@xanum.uam.mx (A.I.-J.); Tel.: +52-55-5622-4595 (I.A.I.); +52-55-5804-4913 (E.G.-Z; A.I.-J.)
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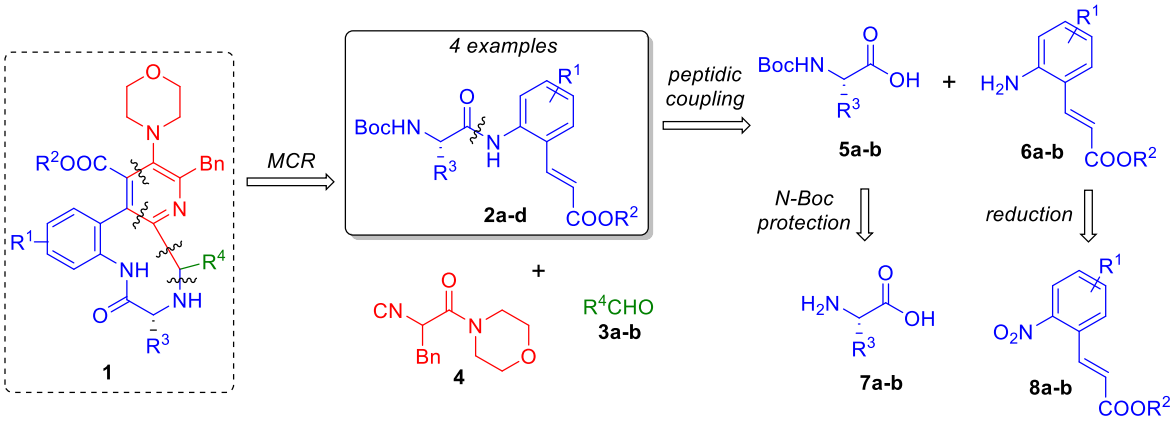
Abstract: Four new α-β-unsaturated alkyl-ester chiral amines were synthesized in excellent yields (77–95%) via peptide couplings from their corresponding α-β-unsaturated alkyl-ester anilines and *N*-Boc protected chiral aminoacids. To our delight, these polyfunctionalized compounds are being used as starting reagents in Ugi-type three-component reactions (Ugi-3CR), together with alkyl- and aryl-aldehydes, and a chain-ring tautomerizable aminoacid-containing isocyanide to synthesize novel oxazole-based macrocycle precursors. Thus, the aim of this communication is to show our most recent results of the synthesis and use of new and complex chiral amines to assemble macrocyclic polypeptides with potential application in medicinal chemistry, such as the post-surgical antibiotic Vancomycin.

Keywords: Chiral amines; α-β-Unsaturated alkyl-ester anilines, Peptide synthesis; *N*-Boc protection-deprotection; Multicomponent reactions; Ugi-3CR, Chemoselective reductions.

1. Introduction

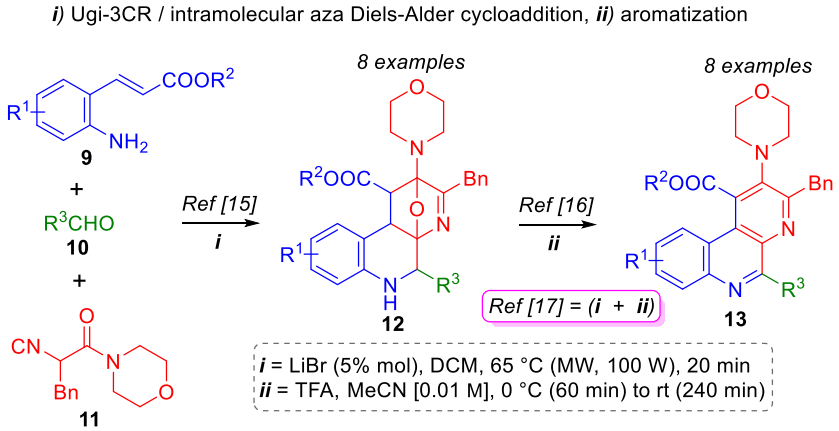
Multicomponent reactions (MCRs) are highly convergent one-pot processes [1] in which three or more reagents are combined sequentially to construct complex products [2] having most of the atoms present in the starting materials [3]. Thus, MCRs are commonly used to synthesize compounds with potential applications in various fields of science and technology. However, most of the MCR's synthetic targets are prepared thinking in their potential pharmaceutical properties [4], from a combinatorial chemistry [5], diversity-oriented synthesis [6] or target-directed synthesis [7] approaches. In this context, we have recently reviewed the use of MCR-based strategies to synthesize novel bioactive products, for example, pharmacophore-containing polyheterocycles [8]. Particularly, there are reports describing the use of MCRs to synthesize often efficiently series of new/novel sugar-containing products [9], peptide-based compounds [10], macrocycles [11], macro-polyheterocycles [12], as well as polycyclic analogues of natural products [13], all of them using exotic amines as starting reagents.

Thus, the aim of this communication is to show our most recent results about the synthesis of the four new *α-β*-unsaturated alkyl-ester chiral amines **2a-d**, which have begun to be used as precursors of the chiral macrocyclic polypeptides **1**, compounds with potential application in medicinal chemistry, **scheme 1**. It is worthy to note that the amines **2a-d** have not been synthesized or isolated anywhere. In the same way, the use of chiral amines as starting reagents for Ugi-type reactions (or other MCRs) has been little reported in comparison to *non*-chiral amines [14].



Scheme 1. Retrosynthetic analysis

As direct background of the results that we are communicating here, in collaboration with Zhu and co-workers (2001), eight new *oxa*-bridged 5-alkyl-benzo[*f*][1,7]naphthyridines **12** (R^3 = alkyl) were synthesized efficiently via an Ugi-3CR / intramolecular aza Diels-Alder cycloaddition [15], **scheme 1**. Then, in collaboration also with Zhu and co-workers (2007), the optimal conditions to aromatize the *oxa*-bridged 5-alkyl-benzo[*f*][1,7]naphthyridine system to synthesize the 5-alkyl-benzo[*f*][1,7] naphthyridines **13** (R^3 = alkyl) were investigated [16], **scheme 1**. Finally, in 2018, we reported the synthesis of eight new *oxa*-bridged 5-aryl-benzo[*f*][1,7]naphthyridines **12** (R^3 = aryl) and their corresponding aromatic analogues **13** (R^3 = aryl) via a coupled cascade process Ugi-3CR / intramolecular aza Diels-Alder cycloaddition / aromatization [17], **scheme 1**.

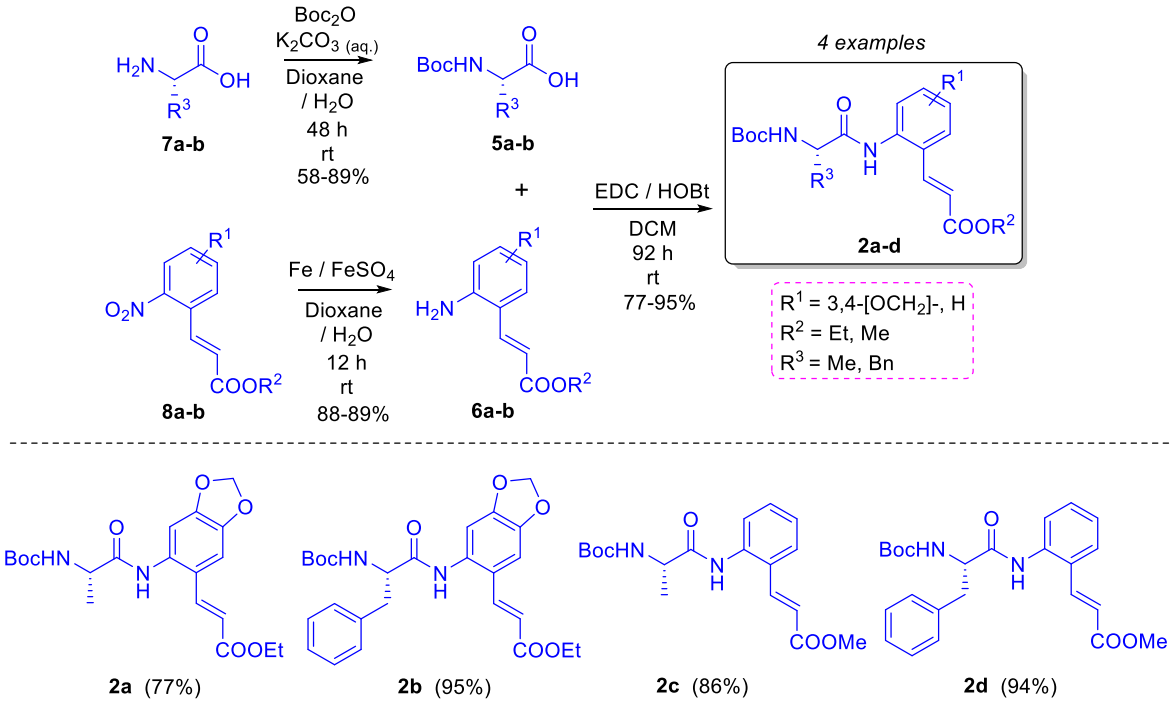


Scheme 2. Own previous work

Then, based on our previously reported methodologies, we hypothesized that by placing smartly *N*-Boc protected chiral aminoacids in the amine moiety **9**, it would be possible to synthesize the chiral peptidic macro-polyheterocycles with potential application in medicinal chemistry.

2. Results and Discussion

To prepare the desired *α-β*-unsaturated alkyl-ester chiral amines **2a-d**, it was necessary first to synthesize the *N*-Boc protected aminoacids **5a-d** from its corresponding chiral aminoacids **7a-b**, as well as the *ortho*-aminocinnamates **6a-b** from their corresponding *ortho*-nitrocinnamates **8a-b**. Thus, the L-phenylalanine and L-alanine were *N*-protected following the protocol described by Ragnarsson and co-workers [18] using di-*tert*-butyl dicarbonate (Boc_2O) in basic conditions for 48 hours at room temperature to give the *N*-Boc protected aminoacids **5a-b** in 58% (*phe*) and 89 (*ala*) yields, respectively, **scheme 3**. It is worthy to note that both aminoacids **5** were used for further peptidic couplings, and for this reason, they had to be *N*-protected to avoid the inherent formation of by-products just under peptidic coupling conditions. Besides, the *α-β*-unsaturated *ortho*-nitrocinnamates **8a-b** were reduced chemoselectively via a modified version of the method reported by Porter and co-workers [19] using Fe[0] and $FeSO_4$ in aqueous media for 12 hours at room temperature to afford the *α-β*-unsaturated *ortho*-aminocinnamates **6a-b**, yielding 88 (R^2 = Et) and 89% (R^2 = Me), **scheme 3**. Then, having in hand the compounds **5** and **6**, peptidic couplings were carried out to afford the *α-β*-unsaturated alkyl-ester chiral amines **2a** (77%)**, 2b** (95%), **2c** (86%) and **2d** (94%), which are excellent yields considering: *i)* that the formation of by-products were kept to a minimum, *ii)* asymmetric centers were retained, and *iii)* the molecular complexity of the final products, **scheme 3**. As seen, better yields were observed for the L-phenylalanine derivatives **2b** (95%) and **2d** (94%), **scheme 3**.



Scheme 3. *α-β*-unsaturated alkyl-ester chiral amines

The products **2a-d** were characterized by their physicochemical properties, as well as by the classical spectroscopic techniques (*See the experimental part for further details*). The ethyl (*S*,*E*)-3-(6-(2-((*tert*-butoxycarbonyl)amino)propanamido)benzo[*d*][1,3]dioxol-5-yl)acrylate) **2a** was selected to discuss in succinctly manner the key signals from their ^1H and ^{13}C NMR spectra. Thus, with respect to the ^1H NMR spectrum (**figure 1a**), there are two doublets at 7.72 and 6.21 ppm with *J* = 15.7 Hz, which are attributed to the *trans*-alkene system. Besides, with respect to the ^{13}C NMR spectrum (figure 1b), there are two peaks at 172.0 and 166.9 ppm, which are attributed to both carbonyls, **figure 1b**.

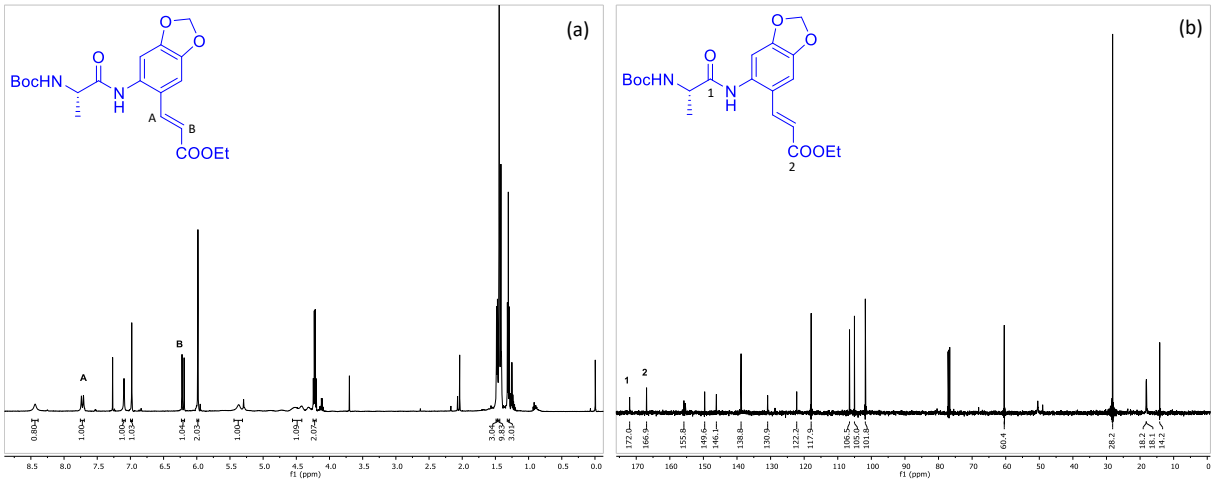
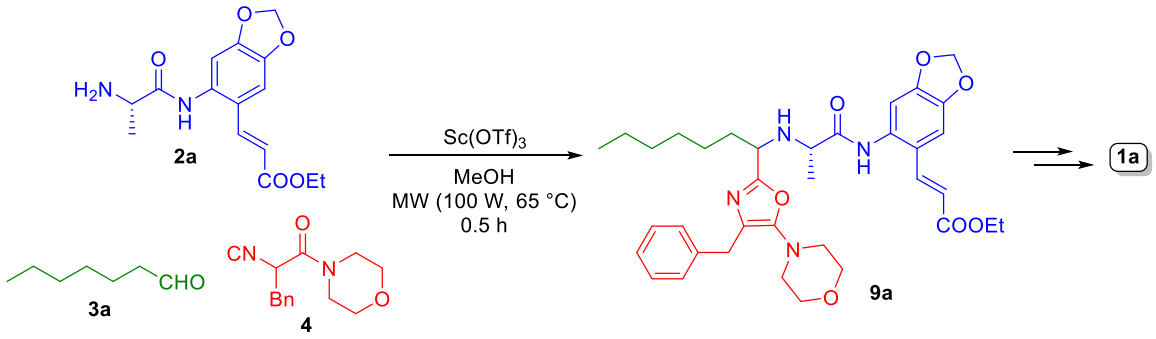


Figure 1. (a) ^{1}H NMR spectrum of the compound **2a**, (b) ^{13}C NMR spectrum of the compound **2a**.

The first attempts using the chiral amine **2a** as reagent in a Ugi-3CR are being performed. Thus, the amine **2a** is first *N*-Boc deprotected using TFA and then, combined sequentially with heptanaldehyde **3a** and the chain-ring tautomerizable isocyanide to give the polyfunctionalized oxazole **9a**, which in turn may perform an aza Diels-Alder cycloaddition coupled to a further aromatization process to construct the peptide-containing macrocyclic structure **1a**, **scheme 4**. The results will be published soon.



Scheme 4. Multicomponent reactions

3. Conclusions

Four new exotic and polyfunctionalyzed *α*-*β*-unsaturated alkyl-ester chiral amines were synthesized in excellent yields (77–95%) via peptidic couplings from their corresponding *ortho*-aminocinnamates and *N*-Boc protected chiral aminoacids. The use of chiral and complex amines as starting reagents in MCRs toward macro-polyheterocyclic architectures is the main contribution of this work, which is a practically unexplored field in the MCR chemistry. To our delight, the first attempts are being performed, giving a product which seems to be an oxazole-based precursor of the desired peptide-containing macrocycles **1**.

4. Experimental part

4.1 General information, instrumentation and chemicals

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Advance III (500 MHz) spectrometer. The solvent was deuterated chloroform ($CDCl_3$). Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is respect to TMS at 0.0 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). NMR data was treated using the MestReNova software (12.0.0-20080). IR spectra were acquired on a Perkin-Elmer series 1600 spectrophotometer. The absorbance peaks are reported in reciprocal centimeters (cm^{-1}). Elemental analyses were performed using a Cole-Palmer 2400 Series II. Reaction progress was monitored by TLC on precoated Kieselgel 60 F_{254} plates and the spots were visualized under UV lights (254 or 365 nm). Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Structure drawings were done using the ChemDraw software (15.0.0.106). Mixtures of hexanes with ethyl acetate in 3:1 proportion (*v*/*v*) were used as mobile phase to perform flash column chromatography. All starting materials were purchased from Sigma-Aldrich-Merck and used without further purification. The solvents were distilled and dried according to standard procedures. The *N*-Boc protections of aminoacids [18] and chemoselective reductions of *ortho*-nitrocinnamates were carried out using classical reported conditions [19].

4.2 Synthesis and characterization of the α-β-unsaturated alkyl-ester chiral amines **2a-d**

General Method: In a round-bottomed flask equipped with a magnetic stirring bar under inert atmosphere (Ar), 1.0 equiv. (1.0 mmol) of the corresponding *N*-Boc protected aminoacids **5**, 1.2 equiv. of *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC), and 1.5 equiv. of hydroxybenzotriazole (HOBt) were added sequentially into 2 mL of anhydrous dichloromethane. After one hour, 1.0 equiv. of the corresponding *ortho*-aminocinnamates **6** were carefully added. The reaction mixture was stirred at room temperature for 92 hours keeping the inert atmosphere. Then, the reaction was stopped by adding 5 mL of a concentrated aqueous solution of sodium bicarbonate ($NaHCO_3$). Further extractions with dichloromethane (3 x 5 mL) were performed and the organic phase was collected, washed with brine, dried using anhydrous sodium sulfate, filtered over a celite pad and concentrated to dryness under vacuum. The crude is purified by flash column chromatography using mixtures of hexanes with ethyl acetate (3:1 v/v) to afford the products **2a-d** as white solids.

Ethyl-(*S*,*E*)-3-(6-(2-((*tert*-butoxycarbonyl)amino)propanamido)benzo[*d*][1,3]dioxol-5-yl)acrylate (**2a**): yield = 77%; mp = 144–146 °C; IR (ν_{max}) = 3426, 3012, 3001, 2348, 2321, 1788, 1692, 1603, 1507, 1494, 1385, 1367, 1179, 1042 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (bs, 1H), 7.72 (d, *J* = 15.4 Hz, 1H), 7.10 (s, 1H), 6.98 (s, 1H), 6.21 (d, *J* = 15.7 Hz, 1H), 5.99 (s, 2H), 5.37 (bs, 1H), 4.55–4.41 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.44 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 166.9, 155.8, 149.6, 146.1, 138.8, 130.9, 122.2, 117.9, 106.5, 105.0, 101.8, 60.4, 28.2, 18.2, 18.1, 14.2 ppm; Elem. Anal. calcd. for $C_{20}H_{26}N_2O_7$ = C (59.10), H (6.45), N (6.89%); found = C (57.74), H (6.71), N (6.61%).

Ethyl-(*S*,*E*)-3-(6-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)benzo[*d*][1,3]dioxol-5-yl)acrylate (**2b**): yield = 95%; mp = 143–145 °C; IR (ν_{max}) = 3400, 3005, 2328, 1800, 1745, 1516, 1501, 1474, 1398, 1187, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (bs, 1H), 7.54 (d, *J* = 15.7 Hz, 1H), 7.34–7.30 (m, 1H), 7.29–7.23 (m, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 6.18 (d, *J* = 15.7 Hz, 1H), 5.99 (s, 2H), 5.10 (bs, 1H), 4.54–4.49 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.24–3.13 (m, 1H), 1.42 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 166.6, 155.7, 149.7, 146.2, 138.4, 136.4, 130.5, 129.3, 128.9, 127.2, 122.1, 118.8, 106.1, 105.4, 101.9, 60.5, 56.6, 38.1, 29.7, 28.2, 14.3 ppm; Elem. Anal. calcd. for $C_{26}H_{30}N_2O_7$ = C (64.72), H (6.27), N (5.81%); found = C (64.97), H (7.02), N (5.49%).

Methyl-(*S*,*E*)-3-(2-(2-((*tert*-butoxycarbonyl)amino)propanamido)phenyl)acrylate (**2c**): yield = 86%; mp = 145–147 °C; IR (ν_{max}) = 3450, 2400, 1792, 1501, 1456, 1398, 1245, 1198, 1003 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89–7.81 (m, 2H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.41–7.37 (m, 1H), 7.22–7.18 (m, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 5.07–5.01 (m, 1H), 4.40–4.29 (m, 1H), 3.81 (s, 3H), 1.50–1.49 (m, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 162.6, 155.6, 139.7, 130.8, 127.2, 125.8, 124.5, 120.4, 113.1, 111.8, 65,1, 51.8, 49.1, 28.3, 18.3 ppm; Elem. Anal. calcd. for $C_{18}H_{24}N_2O_5$ = C (62.05), H (6.94), N (8.04%); found = C (61.85), H (6.30), N (8.18%).

Methyl-(*S*,*E*)-3-(2-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)phenyl)acrylate (**2d**): yield = 94%; mp = 133–135 °C; IR (ν_{max}) = 3452, 3012, 2412, 1802, 1699, 1521, 1504, 1498, 1386, 1234, 1000 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (bs, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 15.8 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.39–7.35 (m, 1H), 7.34–7.23 (m, 4H), 7.22–7.17 (m, 2H), 6.33 (d, *J* = 15.8 Hz, 1H), 5.16–5.09 (m, 1H), 4.60–4.51 (m, 1H), 3.81 (s, 3H), 3.23–3.14 (m, 2H), 1.43 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8, 170.5, 167.0, 155.8, 139.6, 136.5, 135.5, 130.7, 129.5, 129.3, 128.8, 128.4, 127.2, 127.1, 125.9, 124.5, 120.4, 56.7, 51.8, 38.3, 37.9, 28.2 ppm; Elem. Anal. calcd. for $C_{24}H_{28}N_2O_5$ = C (67.91), H (6.65), N (6.60%); found = C (66.79), H (6.87), N (6.30%).

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