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Stereoselective Synthesis of Functional Dehydrophenylalanine Derivatives from Novel β-Chloroamino Esters

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ABSTRACT: *New functional dehydrophenylalanines* **3** *were prepared from* β*-amino alcohols* **1** *in a two-step reaction sequence. The synthesis involved chlorination of the starting amino alcohols* **1** *to afford the intermediate erythro* β*-chloroamines* **2.** *Treatment of the latter with an appropriate base led to a highly stereoselective elimination reaction, giving the corresponding (E)-dehydrophenylalanine derivatives* **3** *in high yields.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 23:91–98, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20756

INTRODUCTION

Dehydroamino acids are gaining substantial interest because they are important constituents of many fungal metabolites with antibiotic or phytotoxic proprieties, such as nisin and subtilin [1,2]. In addition, dehydroamino acids are versatile precursors for the asymmetric synthesis of amino acids and peptides [3].

Introduction of dehydroamino acid residues into peptide chains has been found to influence the three-dimensional structure of both main chains and side chains dramatically due to the presence of the $C^{\alpha}=C^{\beta}$ double bond [4]. This has become a useful tool to study a structure–function relationship and to provide new bioactive peptide sequences of enhanced activity. In this field, dehydrophenylalanine is of potential use in designing peptides with preferred secondary structures and commonly serves as a pharmacophore [5]. For example, Latajka et al. have recently reported on the synthesis and evaluation of peptides containing either (*E*)-dehydrophenylalanines in place of (*Z*)-dehydrophenylalanines [6] or both of them [7] as inhibitors and substrates of cathepsin C.

Several methods have been developed for the synthesis of dehydroamino acid derivatives. The most widely used approach is the dehydration of β-hydroxy amino acid derivatives, which involves activation of the hydroxy group, followed by elimination [8–14]. The reaction can be performed in a one-pot procedure, and even tertiary alcohols are stereoselectively transformed into α, β-dehydroamino esters [15]. Most of the procedures [16,17] involved the synthesis of dehydroalanine and dehydroaminobutyric acid derivatives from serine and threonine, respectively, but they are of low to moderate yields, and the active intermediates are quite reactive. Ferreira et al. [14a] have reported a mild and high yielding procedure for the direct elimination of serine and threonine derivatives using Boc_2O and 4-dimethylaminopyridine to corresponding dehydroamino acid derivatives. Recently, an antiselective β-elimination of serine and threonine to the

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corresponding α, β-dehydroamino acids has been reported using K_2CO_3 in dimethylformamide (DMF) [18]. More recently, a nucleophilic addition to nitroacrylates has been applied to the synthesis of 2,3-dehydroamino acids [19]. Ramesh et al. have also reported an improved procedure for the synthesis of dehydroamino acids and dehydropeptides from the carbonate derivatives of serine and threonine using tetrabutylammonium fluoride [20]. In addition, a valuable method for the synthesis of the *E*-isomer of β-substituted dehydroalanines by controlled potential electrolysis of the corresponding β-halo-β-substituted derivatives has been reported [21].

In continuation of our previous study on the reactivity of *N*-benzyl-β-amino alcohols **1** [22a] as key intermediates, we report herein on the stereoselective synthesis of new dehydrophenylalanines **3** from the chlorination of the same amino alcohol intermediates **1** with mesyl chloride, followed by treatment with sodium ethoxide in ethanol.

RESULTS AND DISCUSSION

In a more recent study [22b], we reported the synthesis of *trans*-aziridine-2-carboxylates via the formation of a mesylate intermediate, obtained after treatment of amino alcohols [22a] with mesyl chloride. This intermediate is not very stable in the reaction medium, which gives a second type of aziridinium intermediate. The latter is easily deprotonated by the base added initially to provide aziridines. Following this study, we thought that it would be possible to obtain β-chloro amines **2** from *N*-benzyl amino alcohols **1** using the same strategy as for aziridines. Therefore, the treatment of a series of racemic *N*-benzyl amino alcohols **1** with mesyl chloride in the presence of diisopropylethylamine afforded the corresponding racemic diastereomeric (1:1) mixture of β-chloro amines **2** (Scheme 1). These were derived from the diastereomeric (1:1) mixture of **1** [22a].

The choice of *N*-benzyl amino alcohols **1** for this reaction is justified by the fact that the aziridinium ion formed from these compounds does not contain a hydrogen on the nitrogen atom and thus would undergo a nucleophilic attack by the chloride ion regenerated in the reaction medium, leading to its opening and the formation of β-chloro amines **2** (Table 1).

TABLE 1 Synthesis of β-Chloroamine Diesters **2a–f**

Entry	*R*	*Product* **2**[a]	*Time (h)*	*Yield (%)*[b]
1	H	**2a**	6	95
2	CH_3	**2b**	12	96
3	C_2H_5	**2c**	12	86
4	*i*Pr	**2d**	12	90
5	*n*Pr	**2e**	12	91
6	Ph	**2f**	12	92

[a]**2b–f** were (1:1) mixtures of two diastereomers (α + β) derived from the 1:1 mixture of **1**.
[b]Yields refer to chromatographically isolated pure compounds.

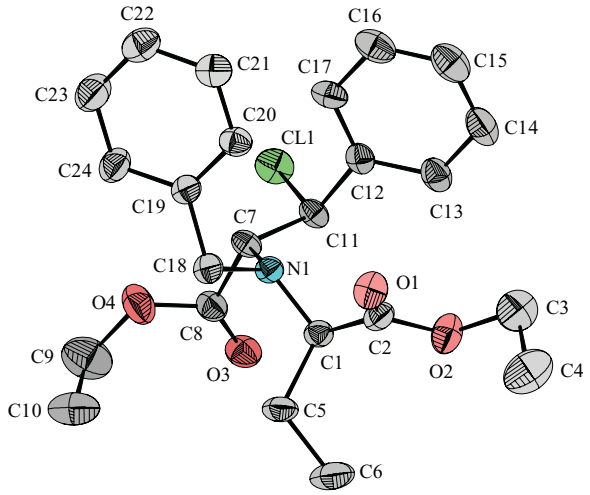
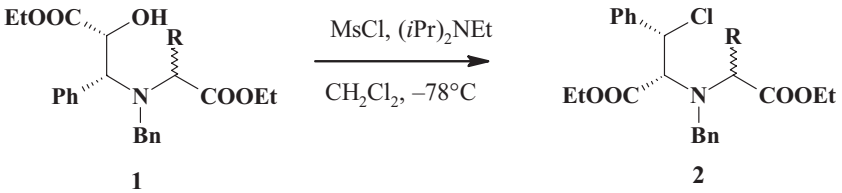


FIGURE 1 ORTEP drawing of compound **2c** (α) showing thermal ellipsoids at 50% probability. Hydrogen atoms were omitted for clarity.

Importantly, the structure of diastereoisomer **2c** (α) was determined by X-ray analysis, and it showed an erythro configuration for this product (Fig. 1). This suggested, as expected, that the chlorination reaction passed through an aziridinium intermediate, which was confirmed by the rearrangement observed (change in position of the phenyl group from C_7 to



SCHEME 1 Synthesis of β-chloroamine diesters **2**.

TABLE 2 Various Conditions for the Synthesis of **3a**

Entry	Conditions	*E*/*Z*[a]	Yield (%)[b]
1	$(Et)_3N$, (CH_3CN or CH_2Cl_2), reflux	–	–
2	$(iPr)_2NEt$, (CH_3CN or CH_2Cl_2), reflux	–	–
3	DABCO, (CH_3CN or CH_2Cl_2), reflux	–	–
4	K_2CO_3, DMF, reflux, 24 (h)	51/49	70
5	NaH, anhydrous THF, 25°C, 3 h	60/40	73
6	EtO^-Na^+/EtOH, 0°C, 0.5 h	63/37	90
7	KHMDS, anhydrous THF, −78°C, 1 h	70/30	85

[a]The isomer ratio was determined by ^1H NMR.
[b]Overall yields.

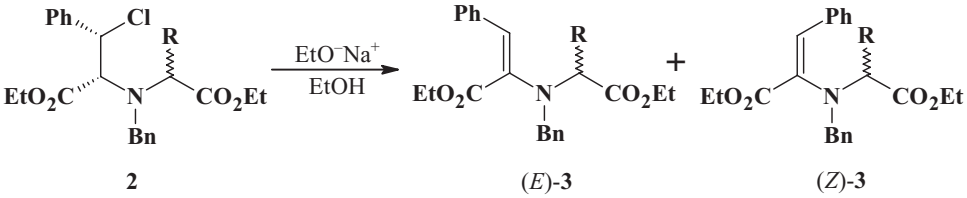
C_{11}). Such a nucleophilic attack of the chloride ion occurring exclusively at the benzylic position with a high regio- and stereoselectivity is well established in the literature [23].

The synthesis of dehydrophenylalanines **3** from β-chloro amines **2** was first attempted on β-chloro amine **2a** (R = H). Whatever operating conditions were used, in all instances, the reaction lead to a mixture of two diastereoisomers, (*Z*) and (*E*) (Table 2). To maximize the yield of this reaction and improve the stereoselectivity, various tests were performed using different bases, solvents, and temperatures (Table 2). We started this investigation using tertiary amines as bases in different solvents, but the reaction did not provide the expected dehydrophenylalanine **3a**, and the starting material was totally recovered in all cases. The use of potassium carbonate in DMF at reflux resulted in the formation of dehydrophenylalanine **3a** in a 70% yield. However, the reaction was slow and gave a mixture of two diastereoisomers with similar proportions. We thought then that using a stronger base and operating at a lower temperature could improve the efficiency of this reaction and possibly its diastereoselectivity. Therefore, when sodium hydride was used in anhydrous tetrahydrofuran (THF) at room temperature, dehydrophenylalanine **3a** was obtained with a 73% yield, with the *E*-diastereoisomer being the major product. Finally, we found that both sodium ethoxide in ethanol at 0°C (Table 2, entry 6) and potassium hexamethyldisilazane (KHMDS) in anhydrous THF at −78°C (Table 2, entry 7) significantly increased the yield (90% and 85%, respectively) and improved the stereoselectivity, giving (*E*)-**3a** as the major isomer (see Table 2).

The above reaction was then generalized using a series of β-chloro amines **2b–f**. The results showed that the use of sodium ethoxide in ethanol gave good yields and high stereoselectivity. However, when KHMDS was used, dehydrophenylalanines **3a** and **3b** were obtained in 85% and 87% yields, respectively, and no elimination reaction was observed for β-chloro amines **2c–f**. This could be interpreted in terms of steric hindrance caused by both KHMDS and the R group in β-chloro amines **2c–f**. The use of sodium ethoxide in ethanol (as in Table 2, entry 6) was thus selected as the best reaction condition (Scheme 2). Various dehydrophenylalanines were prepared in this way, and the different results are presented in Table 3.

As shown in Table 3, the reaction provides two diastereoisomers, (*Z*) and (*E*), when R = H or CH_3 (Scheme 1), whereas the presence of bulkier groups (R = C_2H_5, *i*Pr, *n*Pr, or Ph) leads to a high stereoselectivity, with only the *E*-diastereoisomer being obtained. We also noted that it was necessary to operate at a temperature above 0°C when R was different from H.

The stereochemistry of products **3a–f** was confirmed by two-dimensional nuclear overhauser enhancement spectroscopy–nuclear magnetic resonance (2D NOESY–NMR) experiments. For example, the 2D NOESY experiments for **3c** in $CDCl_3$ show positive cross-peaks between the vinylic proton and benzyl protons, which confirmed the *E* configuration of this product (Fig. 2). Furthermore, the chemical shifts for the vinylic proton of (*E*)-**3a,b** are in the δ-range 5.50–5.74 ppm, whereas the same signals for the (*Z*)-**3a,b** appear in the range 6.54–6.91 ppm. *Z*-isomers thus show a downfield shift (∼1 ppm) with respect to their *E*-isomers. This is in good agreement with the results obtained for related systems [24].



2 (*E*)-**3** (*Z*)-**3**

SCHEME 2 Formation of dehydrophenylalanines **3**.

TABLE 3 Synthesis of Dehydrophenylalanines **3a–f**

Entry	*R*	*Product*[a]	*Temperature (°C)*	*Time (h)*	*Yield*[b]*(%)*	*E/Z*
1	H	**3a**	0	0,5	90	63/37
2	CH_3	**3b**	25	1	86	93/7
3	C_2H_5	**3c**	80	1	84	100/0
4	*i*Pr	**3d**	80	3	91	100/0
5	*n*Pr	**3e**	80	3	90	100/0
6	Ph	**3f**	80	3	95	100/0

[a]Elimination was carried out on a 1:1 mixture of diastereomers ($\alpha + \beta$) for **3b–f**.
[b]Yields refer to products isolated after column chromatography.

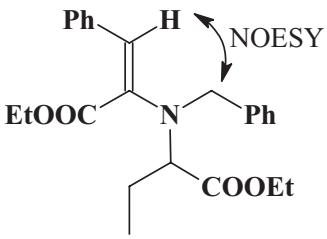


FIGURE 2 *E* configuration of **3c** as shown by the NOESY experiment.

CONCLUSION

The chlorination of β-amino alcohols **1** proceeded with high stereo- and regioselectivity, providing access to erythro β-chloro amines **2** in high yields. The latter were easily converted to the new dehydrophenylalanine derivatives **3** by a highly stereoselective elimination reaction. Unfortunately, the use of these compounds is limited by the fact that they can only be in the *N*-terminal position of a peptide chain. However, the scope and the synthetic utility of these dehydrophenylalanines using other substrates having substituted aromatic rings are underway in our laboratory.

EXPERIMENTAL

All reagents were purchased from Acros (Germany). Reaction progress was monitored by thin-layer chromatography on silica-gel plates (Fluka Kieselgel 60 F_{254} [Switzerland]). For column chromatography, Fluka Kieselgel (70–230 mesh) was used. The infrared (IR) spectra were determined on a Perkin–Elmer Paragon 1000 PC. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. Mass spectra (GC-MS and GC-HRMS) were measured on a HP 5890 A mass spectrometer at 70 eV.

Preparation of β-Chloro Amine Diesters **2a–f**

General Procedure. To a solution of **1** [19a] (2.5 mmol) and $(i\text{Pr})_2\text{NEt}$ (3 mmol) in CH_2Cl_2 (5 mL) cooled at −78°C, MsCl (3 mmol) was added slowly in CH_2Cl_2 (5 mL). After the addition, the reaction was allowed to warm to room temperature, the mixture was filtered, and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel with ether/petroleum ether (1/9) as the eluent to give **2a** and **2c–f** (α) as white solids and **2b** and **2c–f** (**β**) as colorless oils.

*Ethyl 2 - [N - Benzyl - N - (ethoxycarbonylmethyl) amino]-3-chloro-3-phenylpropionate (***2a***).* White solid, mp 59–60°C. IR ($CHCl_3$, ν cm^{-1}): 1728. MS *m/z* (%): 332 ($M^+(^{37}Cl)$ – ($2CH_3CH_2O$), 5), 330 ($M^+(^{35}Cl)$ – ($2CH_3CH_2O$), 16), 294 (4), 278 (100), 222 (3), 130 (10), 91 (88). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.34–6.73 (m, 10H), 5.18 (d, 1H, J = 10.7 Hz), 4.31, 4.04 (2q, 4H, J = 7.1 Hz), 3.96 (d, 1H, J = 10.7 Hz), 3.92 and 3.68 (AB, 2H, J = 13.6 Hz), 3.35 and 3.28 (AB, 2H, J = 18.1 Hz), 1.38, 1.18 (2t, 6H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.8, 169.9 (*2CO*$_2$), 138.3, 137.5 (*2Carom*), 128.7, 128.6, 128.3, 128.2, 127.4 (*10CHarom*), 69.0 (*CHN*), 61.1 (*CHCl*), 60.0, 59.9 (*2CH*$_2$*O*), 56.0 (*CH*$_2$*Ph*), 50.1 (*CH*$_2$*N*), 14.3, 14.2 (*2CH*$_3$*CH*$_2$*O*). HRMS (*m/z*): calcd for $C_{22}H_{26}ClNO_4$: 403.1550, found: 403.1520.

*Ethyl 2-[N-Benzyl-N-[(ethoxycarbonyl-1-methyl) methyl]amino]-3-chloro-3-phenylpropionate (***2b***).* IR and MS spectra were identical for α- and β-isomers. IR (CHCl3, ν cm^{-1}): 1728. MS *m/z* (%): 347 ($M^+(^{37}Cl)$ – ($2CH_3CH_2O$), 7), 345 ($M^+(^{35}Cl)$ – ($2CH_3CH_2O$), 23), 292 (100), 236 (4), 144 (8), 103 (5), 91 (95).

α-Isomer. A colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.16–6.98 (m, 10H), 5.10 (d, 1H, J = 10.5 Hz), 4.32 (q, 2H, J = 7.1 Hz), 4.06 (s, 2H), 3.99 (d, 1H, J = 10.5 Hz), 3.90–3.85 (m, 2H), 3.72 (q, 1H, J = 7.0 Hz), 1.21 (d, 3H, J = 7.0 Hz), 1.39, 1.13

(2t, 6H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.0, 170.9 (*2CO*$_2$), 138.1, 138.0 (*2Carom*), 129.5, 128.4, 128.3, 128.1, 127.1 (*10CHarom*), 66.6 (*CHN*), 61.0 (*CHCl*), 60.9, 59.9 (*2CH*$_2$*O*), 55.8 (*CHCH*$_3$) 52.1 (*CH*$_2$*Ph*), 17.5 (*CH*$_3$*CH*), 14.3, 13.5 (*2CH*$_3$*CH*$_2$*O*). HRMS (*m/z*): calcd for $C_{23}H_{28}ClNO_4$: 417.1707, found: 417.1717.

β-Isomer. A colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22–7.03 (m, 10H), 5.16 (d, 1H, J = 10.5 Hz), 4.27 (q, 2H, J = 7.1 Hz), 4.15–4.05 (m, 2H), 3.96 (d, 1H, J = 10.5 Hz), 3.91 and 3.72 (AB, 2H, J = 12.8 Hz), 3.68 (q, 1H, J = 7.0 Hz), 1.38, 1.26 (2t, 6H, J = 7.1 Hz), 1.12 (d, 3H, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$)δ = 173.8, 170.1 (*2CO*$_2$), 138.4, 138.1 (*2Carom*), 129.1, 128.4, 128.2, 128.0, 126.9 (*10CHarom*), 66.4 (*CHN*), 60.8 (*CHCl*), 60.4, 60.0 (*2CH*$_2$*O*), 54.3 (*CHCH*$_3$) 51.5 (*CH*$_2$*Ph*), 17.4 (*CH*$_3$*CH*), 14.3, 13.5 (*2CH*$_3$*CH*$_2$*O*).

*Ethyl 2 - [N - Benzyl - N - [(ethoxycarbonyl-1-ethyl) methyl]amino]-3-chloro-3-phenyl propionate (***2c***)*. IR and MS spectra were identical for α- and β-isomers. IR ($CHCl_3$, ν cm^{-1}): 1726. MS *m/z* (%): 358 (M$^+$(^{37}Cl) – (2CH_3CH_2O), 22), 356 (M$^+$(^{35}Cl) – (2CH_3CH_2O), 7), 306 (100), 250 (4), 160 (7), 103 (5), 91 (91).

α-Isomer. A white solid, mp 53–54°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.20–6.09 (m, 10H), 5.08 (d, 1H, J = 10.9 Hz), 4.31 (q, 2H, J = 7.1 Hz), 4.00 (d, 1H, J = 10.9 Hz), 4.06–3.92 (m, 2H), 4.13 and 3.77 (AB, 2H, J = 14.1 Hz), 3.51 (dd, 1H, J = 9.6 and = 4.4 Hz), 1.77–1.48 (2m, 2H), 1.39, 1.16 (2t, 6H, J = 7.1 Hz), 0.83 (t, 3H, J = 7.4 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.4, 170.8 (*2CO*$_2$), 138.3, 138.2 (*2Carom*), 129.4, 128.5, 128.3, 128.1, 128.0, 127.1 (*10CHarom*), 67.1 (*CHN*), 63.1 (*CHCH*$_2$*CH*$_3$), 61.0 (*CHCl*), 60.3, 60.2 (*2CH*$_2$*O*), 51.31 (*CH*$_2$*Ph*), 21.7 (*CH*$_2$*CH*$_3$), 14.3, 14.1 (*2CH*$_3$*CH*$_2$*O*), 11.2 (*CH*$_3$*CH*$_2$*CH*). HRMS (*m/z*): calcd for $C_{24}H_{30}ClNO_4$: 431.1863, found: 431.1862.

β-*Isomer*. A colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49–6.09 (m, 10H), 5.08 (d, 1H, J = 10.9 Hz), 4.32 (q, 2H, J = 7.2 Hz), 3.99 (d, 1H, J = 10.9 Hz), 4.08–3.91 (m, 2H), 4.09 and 3.78 (AB, 2H, J = 14.1 Hz) 3.51 (dd, 1H, J = 10.1 and J = 4.5 Hz), 1.79–1.50 (2m, 2H), 1.39, 1.17 (2t, 6H, J = 7.2 Hz), 0.81 (t, 3H, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.4, 171.0 (*2CO*$_2$), 138.3, 138.2 (*2Carom*), 129.4, 128.5, 128.3, 128.1, 128.0, 127.0 (*10CHarom*), 67.1 (*CHN*), 63.1 (*CHCH*$_2$*CH*$_3$), 61.0 (*CHCl*), 60.3, 60.2 (*2CH*$_2$*O*), 51.3 (*CH*$_2$*Ph*), 21.7 (*CH*$_2$*CH*$_3$), 14.3, 14.1 (*2CH*$_3$*CH*$_2$*O*), 11.2 (*CH*$_3$*CH*$_2$*CH*).

*Ethyl 2-[N-Benzyl-N-[(ethoxycarbonyl-1-i-propyl) methyl]amino]-3-chloro-3-phenylpropionate (***2d***)*. IR and MS spectra were identical for α- and β-isomers. IR ($CHCl_3$, ν cm^{-1}): 1731. MS *m/z* (%): 374 (M$^+$(^{37}Cl) – (2CH_3CH_2O), 9), 372 (M$^+$(^{35}Cl) – (2CH_3CH_2O), 27), 320 (100), 292 (4), 264 (4), 172 (6), 130 (6), 103 (5), 91(80).

α-Isomer. A white solid, mp 109–110°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34–7.25 (m, 10H), 4.81 (d, 1H, J = 11.0 Hz), 4.47 (d, 1H, J = 11.0 Hz), 4.26 and 3.86 (AB, 2H, J = 14.1 Hz), 4.25, 4.06, 3.70, 3.46 (4qd, 4H, J = 7.2 and = 10.9 Hz), 3.10 (d, 1H, J = 9.8 Hz), 2.08–2.03 (m, 1H), 1.24, 1.06 (2t, 6H, J = 7.2 Hz), 0.98, 0.84 (2d, 6H, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.5, 168.5 (*2CO*$_2$), 139.0, 134.0 (*2Carom*), 130.0, 129.7, 128.3, 128.0, 127.8, 127.3 (*10CHarom*), 66.0 (*CHN*), 65.0 (*CHCH*), 62.0 (*CHCl*), 60.2, 60.0 (*2CH*$_2$*O*), 52.2 (*CH*$_2$*Ph*), 29.0 (*CH*(*CH*$_3$)$_2$), 20.6, 19.8 (*2CH*$_3$*CH*), 13.9, 13.7 (*2CH*$_3$*CH*$_2$*O*). HRMS (*m/z*): calcd for $C_{25}H_{32}ClNO_4$: 445.2020, found: 445.2016.

β-*Isomer*. A colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31–7.03 (m, 10H), 5.23 (d, 1H, J = 10.5 Hz), 4.30–4.14 (m, 4H), 4.04 (d, 1H, J = 10.5 Hz), 4.22 and 4.04 (AB, 2H, J = 14.3 Hz), 2.97 (d, 1H, J = 9.5 Hz), 1.93–1.86 (m, 1H), 1.40, 1.32 (2t, 6H, J = 7.2 Hz), 0.78, 0.40 (2d, 6H, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.0, 170.4 (*2CO*$_2$), 138.3, 137.8 (*2Carom*), 129.9, 128.7, 128.6, 128.4, 128.1, 127.3 (*10CHarom*), 65.7 (*CHN*), 65.2 (*CHCH*), 60.8 (*CHCl*), 60.3, 60.2 (*2CH*$_2$*O*), 51.9 (*CH*$_2$*Ph*), 28.9 (*CH*(*CH*$_3$)$_2$), 19.8, 19.7 (*2CH*$_3$*CH*), 14.4, 14.3 (*2CH*$_3$*CH*$_2$*O*).

*Ethyl 2 - [N - Benzyl - N - [(ethoxycarbonyl - 1 - n-propyl)methyl]amino]-3-chloro-3-phenylpropionate (***2e***)*. IR and MS spectra were identical for α- and β-isomers. IR ($CHCl_3$, ν cm^{-1}): 1732. MS *m/z* (%): 374 (M$^+$(^{37}Cl) – (2CH_3CH_2O), 9), 372 (M$^+$(^{35}Cl) – (2CH_3CH_2O), 29), 336 (4), 320 (100), 264 (4), 170 (5), 91 (75).

α-Isomer. A white solid, mp 95–96°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22–6.92 (m, 10H), 5.19 (d, 1H, J = 10.9 Hz), 4.29, 4.11 (2q, 4H, J = 7.1 Hz), 4.09 (S, 2H), 3.96 (d, 1H, J = 10.9 Hz), 3.38 (t, 1H, J = 7.2 Hz), 1.65–1.55 (m, 2H), 1.39, 1.28 (2t, 6H, J = 7.1 Hz), 0.97–0.88 (m, 2H), 0.71 (t, 3H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.7, 170.2 (*2CO*$_2$), 138.4, 138.0 (*2Carom*), 129.6, 128.6, 128.5, 128.3, 128.1, 127.1 (*10CHarom*), 65.8 (*CHN*), 60.5 (*CHCl*), 60.1, 60.0 (*2CH*$_2$*O*), 59.1 (*CHCH*$_2$*CH*$_2$), 51.7 (*CH*$_2$*Ph*), 33.6 (*CH*$_2$*CH*$_2$*CH*$_3$), 19.4 (*CH*$_2$*CH*$_3$), 14.3, 14.2 (*2CH*$_3$*CH*$_2$*O*), 14.0 (*CH*$_3$*CH*$_2$*CH*$_2$). HRMS (*m/z*): calcd for $C_{25}H_{32}ClNO_4$: 445.2020, found: 445.2005.

β-*Isomer*. A colorless oil.^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.12–6.81 (m, 10H), 5.00 (d, 1H, J = 10.9 Hz), 4.27–4.21 (m, 4H), 3.93 (d, 1H,

J = 10.9 Hz), 3.85 and 3.70 (AB, 2H, J = 14.3 Hz), 3.49 (dd, 1H, J = 10.1 and J = 4.3 Hz), 1.75–1.50 (2m, 2H), 1.12, 1.06 (2t, 6H, J = 7.2 Hz), 0.90–0.78 (m, 2H), 0.63 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.4, 169.7 (*2CO*$_2$), 137.3, 136.8 (*2Carom*), 127.5, 127.2, 127.1, 127.0, 126.1 (*10CHarom*), 67.1 (*CHN*), 61.3 (*CHCl*), 60.1, 60.0 (*2CH*$_2$*O*), 59.1 (*CHCH*$_2$*CH*$_2$), 50.6 (*CH*$_2$*Ph*), 32.6 (*CH*$_2$*CH*$_2$*CH*$_3$), 18.9 (*CH*$_2$*CH*$_3$), 13.3, 13.0 (*2CH*$_3$*CH*$_2$*O*), 12.9 (*CH*$_3$*CH*$_2$*CH*$_2$).

Ethyl 2-[N-Benzyl-N-[(ethoxycarbonyl-1-phenyl) methyl]amino]-3-chloro-3-phenylpropionate (**2f**). IR and MS spectra were identical for α- and β-isomers. IR ($CHCl_3$, ν cm^{-1}): 1731. MS *m/z* (%): 408 (M$^+$(^{37}Cl) – (2CH_3CH_2O), 5), 406 (M$^+$(^{35}Cl) – (2CH_3CH_2O), 17), 370 (6), 354 (100), 280 (4), 206 (10), 163 (18), 135 (9), 107 (7), 91 (65).

α-Isomer. A white solid, mp 103–104°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25–6.85 (m, 15H), 5.05 (d, 1H, J = 10.4 Hz), 4.74 (s, 1H), 4.20 (d, 1H, J = 10.4 Hz), 4.31–4.00 (m, 4H), 4.10 and 3.78 (AB, 2H, J = 14.8 Hz), 1.31, 1.18 (2t, 6H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.6, 169.8 (*2CO*$_2$), 139.0, 138.3, 136.2 (*3Carom*), 129.5, 129.4, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.0 (*15CHarom*), 69.6 (*CHPh*), 68.6 (*CHN*), 60.8 (*CHCl*), 60.7, 60.6 (*2CH*$_2$*O*), 51.1 (*CH*$_2$*Ph*), 14.2, 14.0 (*2CH*$_3$*CH*$_2$*O*). HRMS (*m/z*): calcd for $C_{28}H_{30}ClNO_4$: 479.1863, found: 479.1852.

β-*Isomer*. A colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21–6.65 (m, 15H), 5.35 (d, 1H, J = 10.9 Hz), 4.61 (s, 1H), 4.45–4.15 (m, 4H), 4.04 (d, 1H, J = 10.9 Hz), 4.11 and 3.94 (AB, 2H, J = 14.3 Hz), 1.44, 1.19 (2t, 6H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.0, 170.3 (*2CO*$_2$), 138.0, 137.4, 136.2 (*3Carom*), 129.6, 129.2, 128.8, 128.7, 128.5, 128.2, 128.0, 127.9, 127.6, 127.2, (*15CHarom*), 63.9 (*CHPh*), 63.6 (*CHN*), 60.9 (*CHCl*), 60.4, 60.1 (*2CH*$_2$*O*), 51.2 (*CH*$_2$*Ph*), 14.3, 14.2 (*2CH*$_3$*CH*$_2$*O*).

Preparation of Dehydrophenylalanines **3a–f**

General Procedure. A solution of β-chloro amine **2** (5.45 mmol) in ethanol (3 mL) was added to a solution of sodium ethoxide (Na (6 mmol) in dry ethanol (5 mL)) and cooled at 0°C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and was stirred for a fixed time and at the temperature indicated in Table 3. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography using petroleum ether to give **3a–f** as colorless oils (for the separation of *Z*- and *E*-isomers, we used ether/petroleum ether (9/1) as the eluent).

Ethyl 2 - [N - Benzyl - N - (ethoxycarbonylmethyl) amino]-3-phenylprop-2-enoate (**3a**). IR and MS spectra were identical for E- and Z-isomers. IR ($CHCl_3$, ν m^{-1}): 1731. MS *m/z* (%): 367 (M$^+$, 21), 338 (2), 294 (29), 280 (11), 220 (7), 206 (10), 202 (21), 181 (7), 130 (11), 116 (8), 101 (9), 91 (100).

E-Isomer. Yield 57%; a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35–7.08 (m, 10H), 5.73 (s, 1H), 4.37 (s, 2H), 4.18, 4.08 (2q, 4H, J = 7.1 Hz), 3.72 (s, 2H), 1.25, 1.03 (2t, 6H, J = 7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.0, 167.0 (*2CO*$_2$), 141.7, 137.1 (*2Carom*), 128.4, 128.2, 128.1, 128.0, 127.6, 127.5 (*10CHarom*), 125.7 (*N—C*=), 107.5 (*Ph—C*=), 61.4, 60.8 (*2CH*$_2$*O*), 54.8 (*CH*$_2$*–N*), 50.6 (*CH*$_2$*Ph*), 14.3, 13.5 (2*CH*$_3$*CH*$_2$*O*). HRMS (*m/z*): calcd for $C_{22}H_{25}NO_4$: 367.1784, found: 367.1768.

Z-Isomer. Yield 33%; a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37–7.19 (m, 10H), 6.92 (s, 1H), 4.21, 4.14 (2q, 4H, J = 7.1 Hz), 4.12 (s. 2H), 3.75 (s, 2H), 1.31, 1.24 (2t, 6H, J = 7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.2, 166.6 (*2CO*$_2$), 137.7, 135.0 (*2Carom*), 130.3, 129.1, 128.4, 128.2, 127.3, (*10CHarom*), 125.8 (*N—C*=), 110.8 (*Ph—C*=), 61.0, 60.6 (*2CH*$_2$*O*), 57.6 (*CH*$_2$ *– N*), 53.6 (*CH*$_2$*Ph*), 14.3, 14.2 (*2CH*$_3$*CH*$_2$*O*).

Ethyl 2 - [N - Benzyl - N - [(1 - ethoxycarbonyl - 1-methyl)methyl]amino]-3-phenylprop-2-enoate (**3b**). IR and MS spectra were identical for E- and Z-isomers. 1732. MS *m/z* (%): 381 (M$^+$, 15), 308 (100), 290 (9), 280 (21), 234 (17), 204 (12), 200 (9), 144 (7), 119 (9), 91 (74), 101 (9), 91 (100).

E-Isomer. Yield 80%; a colorless oil. IR ($CHCl_3$, ν m^{-1}): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75–6.98 (m, 10H), 5.67 (s, 1H), 4.38 (s. 2H), 4.22, 4.01 (m, 5H), 1.48 (d, 3H, J = 7.1 Hz), 1.29, 1.03 (2t, 6H, J = 7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.7, 167.4 (*2CO*$_2$), 140.1, 138.1 (*2Carom*), 130.8, 129.3, 128.3, 128.0, 127.8, 127.1 (*10CHarom*), 125.7 (*N—C*=), 110.7 (*Ph—C*=), 61.3, 61.0 (*2CH*$_2$*O*), 58.2 (*CH–CH*$_3$), 53.8 (*CH*$_2$*Ph*), 15.8 (*CH*$_3$*–CH*), 14.3, 13.5 (*2CH*$_3$*CH*$_2$*O*). HRMS (*m/z*): calcd for $C_{23}H_{27}NO_4$: 381.1940, found: 381.1940.

Z-Isomer. Yield 6%; a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.74–7.02 (m, 10H), 6.52 (s, 1H), 4.34 (q, 1H, J = 7.1 Hz), 4.22, 4.15 (m, 4H), 4.02 (q, 2H, J = 7.1 Hz), 1.37 (d, 3H, J = 7.1 Hz), 1.28, 1.26 (2t, 6H, J = 7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.0, 166.8 (*2CO*$_2$), 138.2, 135.7 (*2Carom*), 130.8, 129.3, 128.4, 128.0, 127.9, 127.5 (*10CHarom*), 125.9 (*N—C*=), 110.7 (*Ph—C*=), 60.8, 60.7 (*2CH*$_2$*O*), 60.5 (*CH–CH*$_3$), 53.7 (*CH*$_2$*Ph*), 16.5 (*CH*$_3$*–CH*), 14.3, 14.2 (*2CH*$_3$*CH*$_2$*O*).

*(E) - Ethyl 2 - [N - Benzyl - N - [(1 - ethoxycarbonyl-1-ethyl)methyl]amino]-3-phenylprop-2-enoate (**3c**).* Colorless oil. IR ($CHCl_3$, ν m^{-1}): 1724. MS *m/z* (%): 395 (M^+, 4), 266 (21), 235 (15), 234 (99), 206 (5), 105 (4), 91 (100). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.39–6.97 (m, 10H), 5.71 (s, 1H), 4.40 (s, 2H), 4.16, 4,07 (2q, 4H, J = 7.1 Hz), 3.38 (dd, 1H, J = 6.7 and = 8.2 Hz), 1.99–1.84 (m, 2H), 1.26, 1.05 (2t, 6H, J = 7.1 Hz), 1.02 (t, 3H, J = 7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.1, 167.4 (*2CO*$_2$), 140.3, 138.0 (*2Carom*), 128.0, 127.9, 127.7, 127.4, 127.3, 126.8 (*10CHarom*), 125.7 (*N—C=*), 111.8 (*Ph—C=*), 61.2, 60.8 (*2CH*$_2$*O*), 50.00 (*CH*$_2$*Ph*), 23.1 (*CH*$_2$*CH*$_3$), 14.3, 13.6 (*2CH*$_3$*CH*$_2$*O*).11.10 (*CH*$_3$*CH*$_2$). HRMS (*m/z*): calcd for $C_{24}H_{29}NO_4$: 395.2097, found: 395.2099.

*(E)-Ethyl 2-[N-Benzyl-N-[(1-ethoxycarbonyl-1-i-propyl)methyl]amino]-3-phenylprop-2-enoate (**3d**).* Colorless oil. IR ($CHCl_3$, ν m^{-1}): 1730. MS *m/z* (%): 409 (MH^+, 43), 362 (57), 334 (13), 316 (27), 302 (43), 273 (26), 227 (10), 105 (21), 91 (100). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.64–6.94 (m, 10H), 5.75 (s, 1H),), 4.49 and 4.38 (AB, 2H, J = 12.8 Hz), 4.24–4.01 (m, 4H), 3.43 (d, 1H, J = 10.6 Hz), 2.38–2.32 (m, 1H), 1.26, 1.01 (2t, 6H, J = 7.2 Hz), 1.10, 0.91 (2d, 6H, J = 7.0 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.1, 167.2 (*2CO*$_2$), 140.2, 137.7 (*2Carom*), 128.4, 128.2, 128.0, 127.8, 127.8, 127.3 (*10CHarom*), 125.7 (*N—C=*), 113.2 (*Ph—C=*), 70.0 (*CHCH*), 61.1, 60.5 (*2CH*$_2$*O*), 48.9 (*CH*$_2$*Ph*), 28.2 (*CH*(*CH*$_3$)$_2$), 19.9, 19.3 (2(*CH*$_3$)$_2$*CH*$_2$), 14.3, 13.6 (*2CH*$_3$*CH*$_2$*O*). HRMS (*m/z*): calcd for $C_{25}H_{31}NO_4$: 409.2253, found: 409.2251.

*(E)-Ethyl 2-[N-Benzyl-N-[(1-ethoxycarbonyl-1-n-propyl)methyl]amino]-3-phenylprop-2-enoate (**3e**).* Colorless oil. IR ($CHCl_3$, ν m^{-1}): 1730. MS *m/z* (%): 409 (M^+, 13), 337 (25), 336 (100), 318 (7), 280 (18), 206 (10), 91 (57). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.40–6.97 (m, 10H), 5.71 (s, 1H),), 4.40 (s, 2H), 4.22–4.04 (m, 4H), 3.87 (t, 1H, J = 7.5 Hz), 1.91–1.83 (m, 2H), 1.72–1.68 (m, 2H), 1.26, 1.25 (2t, 6H, J = 7.1 Hz), 1.02 (t, 3H, J = 7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.3, 166.7 (*2CO*$_2$), 136.1, 134.8 (*2Carom*), 129.3, 128.3, 128.0, 127.8, 127.4, 127.2 (*10CHarom*), 125.7 (*N—C=*), 111.8 (*Ph—C=*), 65.6 (*CHCH*$_2$*CH*$_2$), 61.2, 60.8 (*2CH*$_2$*O*), 53.5 (*CH*$_2$*Ph*), 33.1 (*CHCH*$_2$*CH*$_2$), 19.7 (*CH*$_2$*CH*$_3$),, 14.3, 14.0 (*2CH*$_3$*CH*$_2$*O*), 13.5 (*CH*$_3$*CH*$_2$*CH*$_2$). HRMS (*m/z*): calcd for $C_{25}H_{31}NO_4$: 409.2253, found: 409.2045.

*(E)-Ethyl 2-[N-Benzyl-N-[(1-ethoxycarbonyl-1-phenyl)methyl]amino]-3-phenylprop-2-enoate (**3f**).* Colorless oil. IR ($CHCl_3$, ν m^{-1}): 1732. MS *m/z* (%): 443 (M^+, 5), 370 (87), 352 (9), 296 (13), 267 (25), 206 (38), 193 (32), 178 (12), 91 (100).^1H NMR (300 MHz, $CDCl_3$) δ = 7.28–6.95 (m, 10H), 5.80 (s, 1H), 5.18 (s, 1H), 4.24 (q, 2H, J = 7.10 Hz), 4,47 and 4.14 (AB, 2H, J = 16.0 Hz), 4.07–4.03 (m, 2H), 1.27, 1.03 (2t, 6H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.0, 167.5 (*2CO*$_2$), 139.2, 137,7, 136.9 (*3Carom*), 128.8, 128.6, 128,4, 128.1, 127.9, 127.5, 127.3, 126,7 (*15CHarom*), 125.9 (*N—C=*), 115.3 (*Ph—C=*), 66.6 (*CHPh*), 61.3, 61.1 (*2CH*$_2$*O*), 50.4 (*CH*$_2$*Ph*), 14.3,13.6 (*2CH*$_3$*CH*$_2$*O*). HRMS (*m/z*): calcd for $C_{28}H_{29}NO_4$: 443.2097, found: 443.2088.

SUPPLEMENTARY MATERIAL

CCDC 752143 (**3c** (α)) contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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