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Highly Selective Synthesis of Enantiopure (*S*,*E*)-α,β-Unsaturated γ-Amino Esters Through a Sequential Reaction of Ethyl Dibromoacetate with α-Amino Aldehydes Promoted by Chromium Dichloride

José M. Concellón*[a] and Carmen Méjica[a]

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A sequential reaction of ethyl dibromoacetate with various enantiopure *N*,*N*-dibenzyl- or *N*-Boc-α-amino aldehydes (derived from natural α-amino acids), promoted by chromium dichloride, afforded optically active (*S*,*E*)-α,β-unsaturated γ-amino esters. The C=C double bond was generated with total or very high *E*-selectivity and the (*S*,*E*)-α,β-unsaturated γ-amino esters were obtained with complete enantiomeric purity, except from *N*-Boc-phenylalaninal (as determined by chiral HPLC). A mechanism is proposed to explain this transformation.

Introduction

The transformation of natural α-amino acids into γ-amino acids is of interest owing to their potential biological activity, for example, as GABA analogues.[1] Thus, enantiopure vinylogous amino acid derivatives are important building blocks in organic synthesis and a great deal of effort has been invested in the conjugate addition reactions of α,β-unsaturated γ-amino esters.[2]

Most commonly, α,β-unsaturated γ-amino esters with the amino function dibenzylated or *N*-Boc-protected can be prepared from α-amino aldehydes by the Horner–Wittig reaction[3] or by the Wittig reaction.[4] In some cases, α,β-unsaturated γ-amino esters have been obtained with partial racemization.[4a] Hence, an alternative synthesis of enantiopure α,β-unsaturated γ-amino esters, without racemization, starting from amino aldehydes and commercially available compounds such as ethyl dibromoacetate and chromium dichloride, obviating the use of phosphorus compounds, would be desirable.

Moreover, chromium dichloride has been used to perform a variety of organic transformations, including carbon–carbon bond formation or β-elimination reactions.[5] In this context, we recently reported a completely stereoselective synthesis of (*E*)-α,β-unsaturated esters by reaction of a variety of aldehydes with ethyl dibromoacetate promoted by $CrCl_2$.[6] This transformation took place as two sequential reactions: an aldol-type reaction in the first step followed by a β-elimination reaction in the second step.[7]

These results prompted us to apply this synthetic method to the synthesis of α,β-unsaturated γ-amino esters with complete optical purity and with the C=C double bond generated with total *E* selectivity. There were two main objectives of this proposed study. On the one hand, to test the use of enantiopure α-amino aldehydes (highly prone to racemization) as starting materials, conserving their enantiomeric purity during the course of the reaction. On the other hand, to develop an easy and efficient sequential reaction to prepare α,β-unsaturated γ-amino esters which could constitute an alternative to the previously reported methods.

Thus, we describe herein a $CrCl_2$-mediated sequential reaction of ethyl dibromoacetate with a variety of optically active *N*,*N*-dibenzyl- or *N*-Boc-α-amino aldehydes derived from natural amino acids which readily affords the corresponding enantiopure (*S*,*E*)-α,β-unsaturated *N*,*N*-dibenzyl- or *N*-Boc-γ-amino esters, respectively. Unsaturated γ-amino esters (*N*,*N*-dibenzyl- or *N*-Boc-protected) were obtained with complete or high enantiomeric purity, except from *N*-Boc-phenylalaninal (as determined by chiral HPLC), and the C=C double bond was generated with total or very high *E* selectivity (assessed by NMR and/or GC). A mechanism is proposed to explain this transformation.

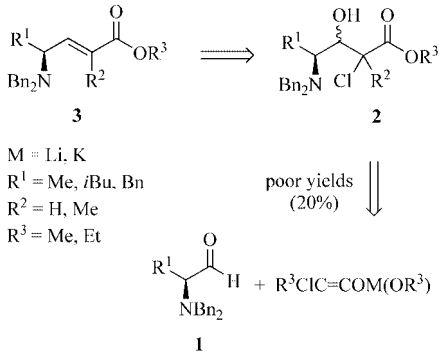
Results and Discussion

Our first approach to enantiopure α,β-unsaturated γ-amino esters was conceptually very simple and was based on a previous methodology developed by our group in which α,β-unsaturated esters were obtained in high yields with complete *E* selectivity by treatment of α-chloro-β-hydroxy esters with $CrCl_2$.[8] Therefore, we expected that the reaction of $CrCl_2$ with an appropriate optically active

[a] Department of Organic Chemistry, University of Oviedo, Faculty of Chemistry,
Julián Clavería, 8, 33071, Oviedo, Spain
Fax: +34-985-10-34-46
E-mail: jmcg@uniovi.es

amino-containing compound such as α-chloro-β-hydroxy-γ-dibenzylamino ester **2**, which theoretically could be readily available, should allow access to the corresponding alkyl γ-dibenzylaminoalk-2-enoate **3**.

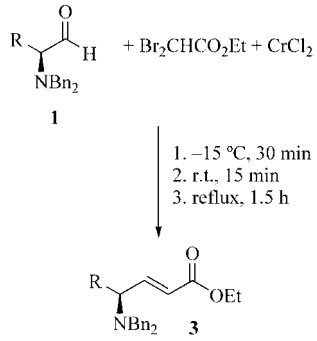
Consequently, various attempts were made to prepare the starting α-chloro-β-hydroxy-γ-dibenzylamino esters **2** by reaction of lithium or potassium enolates derived from chloroacetate or 2-chloropropanoate esters with a range of α-dibenzylamino aldehydes **1**, such as alaninal, phenylalaninal or leucinal, under various reaction conditions. Surprisingly, the reactions led to the requisite compounds **2** in very low yields. Under the best reaction conditions (lithium ethyl acetate enolate and leucinal in THF at –90 °C for 7 h), the corresponding α-chloro-β-hydroxy-γ-dibenzylamino esters **2** were obtained in only 20% yield (based on the starting amino aldehyde **1**). Therefore, owing to the lack of access to the starting compounds **2**, this synthetic route to γ-amino α,β-unsaturated esters was abandoned (Scheme 1).



Scheme 1. Failed initial synthesic proposal for obtaining α,β-unsaturated γ-amino esters.

Synthesis of Enantiopure (*S*,*E*)-α,β-Unsaturated γ-Dibenzylamino Esters 3

Consequently, bearing the above result in mind and taking into account our previous work on the synthesis of α,β-unsaturated esters,[6] we examined an alternative method for obtaining α,β-unsaturated γ-amino esters through a $CrCl_2$-mediated sequential process (C–C bond formation followed by an elimination reaction). Taking into account our previous experience in the development of synthetic applications of *N*,*N*-dibenzylated α-amino aldehydes **1**,[9] initially we tested the sequential reaction using *N*,*N*-dibenzylated aldehydes **1**. Thus, treatment of a suspension of 6 equiv. of $CrCl_2$ in 10 mL of THF with a solution of various α-dibenzylamino aldehydes **1**[10] (1 equiv.) and ethyl dibromoacetate (1.2 equiv.) in 8 mL of THF at –15 °C for 30 min followed by stirring for 15 min at room temperature and heating at reflux for 1.5 h afforded the corresponding (*S*,*E*)-α,β-unsaturated γ-dibenzylamino esters **3** with high or total *E* selectivity and in moderate-to-good yields (Scheme 2 and Table 1).



Scheme 2. Synthesis of (*S*,*E*)-α,β-unsaturated γ-dibenzylamino esters **3**.

Table 1. Synthesis of (*S*,*E*)-α,β-unsaturated γ-dibenzylamino esters **3**.

3	R	% Yield[a]	% *de*[b]	Enantiomeric purity[c]
3a	Me	60	>99	–[d]
3b	*i*Bu	58	95	99:1
3c	$BnOCH_2$	64	>99	97.5:2.5

[a] Isolated yield after column chromatography (based on the starting α-amino aldehyde **1**). [b] Determined by GC–MS and/or 300 MHz ^{1}H NMR analysis of the crude products. [c] Ratio of enantiomers, as determined by HPLC analysis (see ref.[12]). [d] The enantiomeric purity of this product was not determined.

The *E* stereochemistry of compounds **3** was established on the basis of the value of the ^{1}H NMR coupling constant between the olefinic protons, ranging between 15.6 and 15.9 Hz, in accordance with literature values.[11] In addition, the spectroscopic data of compound **3a** were in agreement with those previously reported in the literature.[3a] The diastereomeric excess (*de*) of the C=C double bond was determined by ^{1}H NMR spectroscopy (300 MHz) and/or GC of the crude reaction mixtures. The determined *de* values are compiled in Table 1 and show that the β-elimination reaction takes place with very high or complete diastereoselectivity.

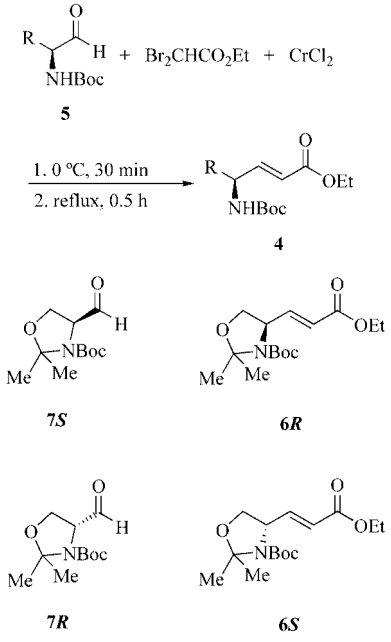
The enantiomeric purity of **3b** and **3c** was determined by chiral HPLC analysis, showing an enantiomeric ratio of 99:1 and 97.5:2.5, respectively. A racemic mixture of **3b** and **3c** was used as a reference to exclude the possibility of the coelution of both enantiomers.[12] The enantiomeric purity of **3a** was not determined as a result of the very high enantiomeric purity of **3b** and **3c** and the configurational stability of the α-dibenzylalaninal **1a**. Both values (enantiomeric purity and *de*) demonstrate that the sequential process promoted by $CrCl_2$ is effective in the synthesis of enantiopure (*S*,*E*)-α,β-unsaturated γ-dibenzylamino esters **3**, giving complete *E* selectivity and very high or complete enantiomeric purity (enantiomeric ratio >97.5:2.5).

This sequential reaction is an attractive synthetic method due to its simplicity. In general, sequential reactions are the methods of choice due to their experimental advantages in comparison with the most conventional multistep methodologies. Thus, this synthesis takes place in a shorter time, the starting materials are, in general, commercially avail-

able, higher overall yields are obtained and time and effort are saved. In addition, this method negates the use of phosphorus derivatives which is advantageous (in comparison to the Wittig or Horner reactions). For these reasons, we tested the generality of the reaction by using 2-amino aldehydes with other nitrogen-protecting groups.

Synthesis of Enantiopure (*S,E*)-α,β-Unsaturated γ-(*tert*-Butoxycarbonyl)amino Esters 4 or 6

We selected *tert*-butyloxycarbonyl (Boc) as the protecting group of the amino function as a result of its extensive use in organic synthesis.[13] Thus, the reaction of freshly prepared *N*-Boc-α-amino aldehyde **5**[14] (1 equiv.) with ethyl dibromoacetate (1.2 equiv.) in 8 mL of THF in the presence of a solution of 6 equiv. of $CrCl_2$ in 10 mL of THF at 0 °C for 2 h and at reflux for 30 min afforded the corresponding (*S,E*)-α,β-unsaturated γ-(*tert*-butyloxycarbonyl)amino ester **4** with high *E* selectivity and in good yield (Scheme 3 and Table 2).



Scheme 3. Synthesis of (*S,E*)-α,β-unsaturated γ-(*tert*-butyloxycarbonyl)amino esters **4** and **6**.

In the case of serinal, two enantiomers of the corresponding *N*-Boc-α,β-unsaturated γ-amino esters **6*R*** and **6*S*** were prepared from the two commercially available enantiomers, Gardner's aldehydes **7*S*** and **7*R***.[15]

The results obtained are shown in Table 2 and demonstrate that the method, starting from the *N*-Boc-amino aldehydes, is general and works efficiently. Indeed, no important differences were observed in the synthesis of (*S,E*)-α,β-unsaturated γ-(*tert*-butyloxycarbonyl)amino esters **4** or **6** on varying the structure of R in the starting amino aldehyde. In all cases, only the *E* diastereoisomer of **4** or **6** was detected by ^{1}H NMR spectroscopy (300 MHz) of the crude reaction mixtures. Similarly as indicated above, the relative

Table 2. Synthesis of (*S,E*)-α,β-unsaturated γ-(*tert*-butoxycarbonyl)amino esters **4** and **6**.

4 or **6**	R	% Yield[a]	% *de*[b]	% Enantiomeric purity[c]
4a	Me	54	>99	>99
4b	*i*Bu	55	>99	98
4c	$PhCH_2$	57	>99	86
4d[c]	$MeSCH_2CH_2$	52	>99	>99
6*S*	– CH_2OCMe_2–	57	>99	>99
6*R*	– CH_2OCMe_2–	51	94	>99

[a] Isolated yield of the pure compounds **4** or **6** after column chromatography (based on the starting α-amino aldehyde **5** or **7**). [b] Determined by GC–MS and/or 300 MHz ^{1}H NMR analysis of the crude products. [c] Determined by chiral HPLC analysis (see ref.[19]).

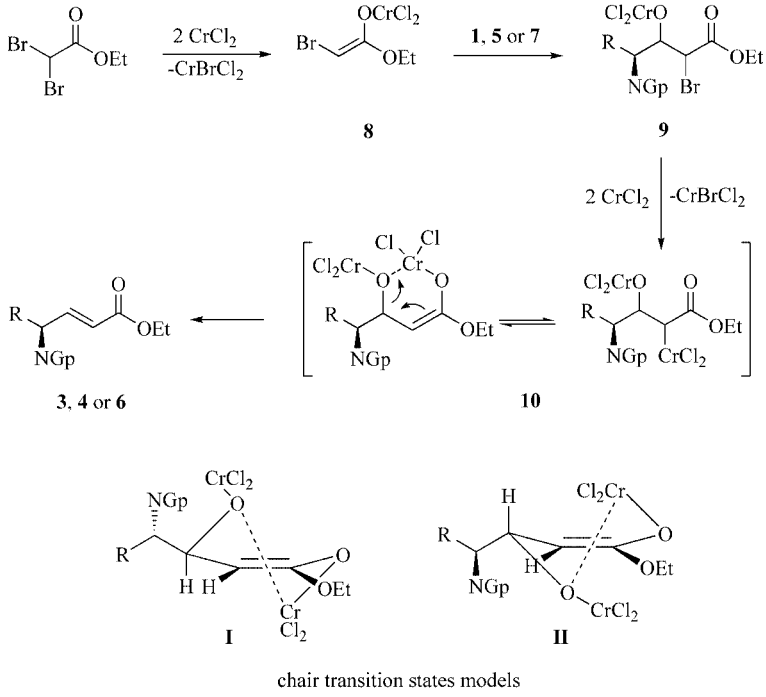
E configuration of **4** or **6** was established on the basis of the value of the ^{1}H NMR coupling constant between the olefinic protons.[11] The spectroscopic data of compounds **4a**,[3c,3d,16] **4c**,[17] **6*R***[4g,4k] and **6*S***[4f] are in agreement with those previously reported in the literature.

The optical instability of the *N*-Boc-protected α-amino aldehydes **5** (especially phenylalaninal) has been carefully documented[18] and, for this reason, to reproduce the results shown in Table 2, it was essential to carry out the sequential reaction with the corresponding *N*-Boc-amino aldehyde immediately after its preparation. Storage at low temperatures for 0.5–12 h produced partial racemization of the *N*-Boc-amino aldehydes (especially phenylalaninal).

Compounds **4a–d**, **6*R*** and **6*S*** were analysed by chiral HPLC[19] to check their enantiomeric purity. Racemic mixtures of each compound were used as a reference to exclude the possibility of coelution of both enantiomers. These determinations showed the presence of only one enantiomer in all cases except for compound **4c** which suffered partial racemization (*ee* = 86%) during its synthesis. This loss of enantiomeric purity could be explained by the low configurational stability of the *N*-Boc-phenylalaninal.[18] However, it is noteworthy that the *ee* of **4c** is higher than the values obtained by using other previously reported methodologies.[4a]

Mechanism

This reaction may be rationalised by assuming a sequential process comprising two steps. Thus, in the first step of the reaction 2 equivalents of $CrCl_2$ react with ethyl dibromoacetate to generate a chromium enolate **8** which reacts with the starting α-amino aldehyde **1**, **5** or **7**, affording the corresponding intermediate α-bromo ester **9** as a mixture of *syn* and *anti* diastereoisomers. In the second step, another metallation of **9** with a further 2 equivalents of $CrCl_2$ gives the amino enolate intermediate **10** (as a mixture of diastereoisomers) which undergoes spontaneous β-elimination to give the α,β-unsaturated γ-amino esters **3**, **4** or **6** (Scheme 4).



Scheme 4. Proposed reaction mechanism.

To explain the *E* selectivity, we tentatively propose a chelation of the Cr^{III} centre of both diastereoisomeric enolates **10** with the oxygen atom of the alcoholate group which could produce a six-membered ring. This coordination of the Cr^{III} centre with the leaving oxygen could facilitate the elimination reaction. Thus, the elimination from each diastereoisomer **10** could take place through half-chair transition-state models **I** or **II** with the bulkier RCH(NGp) group in the equatorial orientation in both diastereoisomeric transition states. Owing to steric hindrance, both transition states would be favoured above those in which the RCH(NGp) group was in an axial position. Elimination from **I** and **II** affords the same (*S*,*E*)-α,β-unsaturated γ-amino esters **3**, **4** or **6**. Supporting this explanation, the synthesis of α,β-unsaturated esters with total *E* selectivity by β-elimination of a diastereoisomeric mixture of α-halo-β-hydroxy esters has been previously reported.[8] This mechanism has also been previously proposed to explain other β-elimination reactions promoted by $CrCl_2$.[6,7]

Conclusions

We have presented an easy, rapid, straightforward, general method for the preparation of enantiopure (*S*,*E*)-α,β-unsaturated γ-amino esters in good yields, with very high or total *E* stereoselectivity and with high or complete enantiomeric purity, except from *N*-Boc-phenylalaninal. This synthesis takes place by the reaction of dibromoacetate with *N*,*N*-dibenzyl- or *N*-Boc-α-amino aldehydes promoted by chromium dichloride. The described transformation takes place through a sequential process: an aldol-type reaction as the first step followed by a very high or totally *E* stereoselective β-elimination reaction as the second step. A mechanism to explain the high or total *E* selectivity of the elimination reaction has been proposed.

Experimental Section

General: Reactions requiring an inert atmosphere were conducted under dry nitrogen and the glassware was oven-dried (120 °C). THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were purchased in the highest quality available and were used without further purification. ^{1}H NMR spectra were recorded at 300 or 400 MHz. ^{13}C NMR spectra and DEPT experiments were recorded at 75 MHz. GC-MS spectra were measured at 70 eV with an Agilent 5973 N A.

General Procedure for the Synthesis of Compounds 3: Anhydrous $CrCl_2$ (6 mmol) was suspended in THF (10 mL) under nitrogen. A solution of the corresponding aldehyde (1 mmol) and ethyl dibromoacetate (1.2 mmol) in THF (8 mL) was added dropwise to this suspension at –15 °C. After stirring for 30 min, the reaction mixture was warmed to room temperature and after 15 min was refluxed for 1.5 h and the reaction mixture was hydrolysed with 0.1 N HCl and extracted with diethyl ether (3 × 10 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Then the organic layer was filtered through a pad of Celite® and the solvents removed in vacuo. Purification by column chromatography on silica gel afforded the (*S*,*E*)-α,β-unsaturated γ-dibenzylamino esters **3**.

Ethyl (*S*,*E*)-4-(Dibenzylamino)pent-2-enoate[3a] (3a): Yellow oil. $[\alpha]_D^{25}$ = –66.2 (*c* = 0.7, $CHCl_3$). R_f = 0.49 (hexane/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.3–57.11 (m, 10 H), 7.10 (dd, *J* = 15.9, 6.0 Hz, 1 H), 5.94 (dd, *J* = 15.9, 1.6 Hz, 1 H), 4.24 (q, *J* =

7.1 Hz, 2 H), 3.67 (d, J = 13.9 Hz, 2 H), 3.60 (d, J = 13.9 Hz, 2 H), 3.58–3.48 (m, 1 H), 1.34 (t, J = 7.1 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4 (C), 150.2 (CH), 139.8 (2×C), 128.4 (4×CH), 128.2 (4×CH), 128.0 (CH), 126.8 (CH), 121.8 (CH), 60.3 (CH_2), 53.6 (CH), 53.6 (2×CH_2), 14.2 (CH_3), 14.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2927, 2360, 2342, 1717 cm^{-1}. MS (70 eV, EI): m/z (%) = 323 (<1) $[M]^+$, 308 (66), 232 (71), 91(100). $C_{21}H_{25}NO_2$ (323.43): calcd. C 77.98, H 7.79, N 4.33; found C 78.20, H 7.91, N 4.28.

Ethyl (*S*,*E*)-4-(Dibenzylamino)-6-methylhep-2-enoate[3a] (3b): Yellow oil. $[\alpha]_D^{25}$ = –26.9 (c = 0.2, $CHCl_3$). R_f = 0.56 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 10 H), 7.00 (dd, J = 15.7, 8.4 Hz, 1 H), 5.86 (d, J = 15.7 Hz, 1 H), 4.25 (q, J = 7.2 Hz, 2 H), 3.92–3.88 (m, 1 H), 3.82 (d, J = 13.7 Hz, 2 H), 3.42 (d, J = 13.7 Hz, 2 H), 1.77–1.63 (m, 2 H), 1.35 (t, J = 7.1 Hz, 3 H), 0.89–0.86 (m, 1 H), 0.79 (d, J = 6.5 Hz, 3 H), 0.70 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3 (C), 147.5 (CH), 139.8 (2×C), 128.6 (2×CH), 128.2 (2×CH), 128.0 (4×CH), 126.9 (2×CH), 123.2 (CH), 60.4 (CH_2), 56.6 (CH), 53.7 (2×CH_2), 40.5 (CH2), 24.4 (CH), 22.7 (CH_3), 22.4 (CH_3), 14.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3355, 2979, 2932, 1717, 1519 cm^{-1}. MS (70 eV, EI): m/z (%) = 365 (<1) $[M]^+$, 320 (10), 308 (100), 274 (32), 181 (17), 91 (99). $C_{24}H_{31}NO_3$ (381.51): calcd. C 75.56, H 8.19, N 3.67; found C 75.39, H 8.28, N 3.71.

Ethyl (*S*,*E*)-5-Benzyloxy-4-(dibenzylamino)pent-2-enoate (3c): Yellow oil. $[\alpha]_D^{25}$ = –18.5 (c = 0.4, $CHCl_3$). R_f = 0.47 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.11 (m, 15 H), 6.96 (ddd, J = 15.9, 6.5, 2.8 Hz, 1 H), 5.95 (d, J = 15.9 Hz, 1 H), 4.39 (s, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.91–3.73 (m, 1 H), 3.87 (d, J = 14.0 Hz, 2 H), 3.72–3.55 (m, 2 H), 3.53 (d, J = 14.0 Hz, 2 H), 1.24 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2 (C), 145.7 (CH), 139.6 (2×C), 138.0 (C), 128.4 (4×CH), 128.2 (5×CH), 127.6 (2×CH), 127.5 (2×CH), 126.9 (2×CH), 123.8 (CH), 73.1 (CH_2), 70.1 (CH_2), 60.3 (CH_2), 58.1 (CH), 54.5 (2×CH_2), 14.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3345, 2989, 1719 cm^{-1}. $C_{28}H_{31}NO_3$ (429.56): calcd. C 78.29, H 7.27, N 3.26; found C 78.17, H 7.32, N 3.31.

General Procedure for the Synthesis of Compounds 4 or 6: Anhydrous $CrCl_2$ (6 mmol) was suspended in THF (10 mL) under nitrogen. A solution of the corresponding aldehyde **5** or **7** (1 mmol) and ethyl dibromoacetate (1.2 mmol) in THF (8 mL) was added dropwise to this suspension at 0 °C. After stirring for 2 h, the reaction mixture was refluxed for 0.5 h. Then the reaction mixture was hydrolysed with 0.1 N HCl and extracted with diethyl ether (3×10 mL). The combined extracts were dried with Na_2SO_4 and concentrated. The organic layer was filtered through a pad of Celite® and the solvents were removed in vacuo. Purification by column chromatography on silica gel afforded the (*S*,*E*)-α,β-unsaturated γ-(*tert*-butoxycarbonylamino) esters **4** or **6**.

Ethyl (*S*,*E*)-4-(*tert*-Butoxycarbonylamino)pent-2-enoate[3c,3d,16] (4a): Yellow oil. $[\alpha]_D^{25}$ = –17.2 (c = 0.7, $CHCl_3$). R_f = 0.51 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.87 (dd, J = 15.7, 4.9 Hz, 1 H), 5.89 (dd, J = 15.7, 1.6 Hz, 1 H), 4.74 (s, 1 H), 4.41 (s,1 H), 4.19 (q, J = 7.0 Hz, 2 H), 1.44 (s, 9 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.26 (d, J = 8.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3 (C), 154.8 (C), 149.3 (CH), 120.0 (CH), 79.7 (C), 60.3 (CH_2), 46.9 (CH), 28.2 (3×CH_3), 20.2 (CH_3), 14.1 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3437, 3360, 2980, 2931, 1708 cm^{-1}. MS (70 eV, EI): m/z (%) = 244 (8) $[M + 1]^+$, 188 (100), 144 (48), 57 (94). HRMS (70 eV): m/z calcd. for $C_{12}H_{21}NO_4$ 243.1471; found 243.1236.

Ethyl (*S*,*E*)-4-(*tert*-Butoxycarbonylamino)-6-methylhep-2-enoate (4b): Yellow oil. $[\alpha]_D^{25}$ = +2.63 (c = 0.5, $CHCl_3$). R_f = 0.47 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81 (dd, J = 15.6, 5.4 Hz, 1 H), 5.90 (d, J = 15.6 Hz, 1 H), 4.47 (s, 1 H), 4.32 (s, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 1.83–1.62 (m, 2 H), 1.42 (s, 9 H), 1.36–1.28 (m, 1 H), 1.26 (t, J = 7.1 Hz, 3 H), 0.91 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3 (C), 155.0 (C), 148.8 (CH), 120.3 (CH), 79.6 (C), 60.3 (CH_2), 49.7 (CH), 43.7 (CH_2), 28.3 (3×CH_3), 24.6 (CH), 22.6 (CH_3), 22.1 (CH_3), 14.1 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3356, 2960, 2930, 1717, 1522 cm^{-1}. MS (70 eV, EI): m/z (%) = 285 (<1) $[M]^+$, 187 (12), 228 (24), 212 (8), 128 (100), 57 (32). HRMS (70 eV): m/z calcd. for $C_{15}H_{27}NO_4$ 285.1940; found 285.1705.

Ethyl (*S*,*E*)-4-(*tert*-Butoxycarbonylamino)-5-phenylpent-2-enoate[17] (4c): Yellow oil. $[\alpha]_D^{25}$ = +9.52 (c = 0.4, $CHCl_3$). R_f = 0.47 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.16 (m, 5 H), 7.20 (dd, J = 16.5, 6.7 Hz, 1 H), 5.87 (d, J = 15.6 Hz, 1 H), 4.59 (s, 2 H), 4.19 (q, J = 7.0 Hz, 2 H), 3.01–2.85 (m, 2 H), 1.40 (s, 9 H), 1.28 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1 (C), 154.9 (C), 147.5 (CH), 136.3 (C), 129.3 (2×CH), 128.5 (2×CH), 126.8 (CH), 121.0 (CH), 79.8 (C), 60.4 (CH_2), 40.8 (CH_2), 28.2 (3×CH_3), 14.1 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3355, 2979, 2932, 1717, 1519 cm^{-1}. MS (70 eV, EI): m/z (%) = 319 (<1) $[M]^+$, 228 (52), 128 (100), 57 (62). HRMS (70 eV): m/z calcd. for $C_{18}H_{25}NO_4$ 319.1784; found 319.1880.

Ethyl (*S*,*E*)-4-(*tert*-Butoxycarbonylamino)-6-methylsulfanylhex-2-enoate (4d): Yellow oil. $[\alpha]_D^{25}$ = –4.89 (c = 0.5, $CHCl_3$). R_f = 0.30 (hexane/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86 (dd, J = 15.6, 5.1 Hz, 1 H), 5.96 (dd, J = 15.6, 1.6 Hz, 1 H), 4.58 (s, 1 H), 4.33 (s, 1 H), 4.21 (q, J = 7.0 Hz, 2 H), 3.49 (q, J = 7.0 Hz, 2 H), 2.42 (t, J = 6.9 Hz, 2 H), 2.13 (s, 3 H), 1.46 (s, 9 H), 1.27 (t, J = 9.3, 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1 (C), 155.0 (C), 147.4 (CH), 121.2 (CH), 79.9 (C), 60.5 (CH_2), 50.8 (CH), 33.9 (CH_2), 30.3 (CH_2), 28.3 (3×CH_3), 15.5 (CH_3), 14.1 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2963, 2923, 2853, 1717 cm^{-1}. MS (70 eV, EI): m/z (%) = 303 (9) $[M]^+$, 247 (43), 156 (100), 128 (56). HRMS (70 eV): m/z calcd. for $C_{14}H_{25}NO_4S$ 303.1504. found 303.1502.

Ethyl (*R*,*E*)-3-(3-*tert*-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl)propenoate[4g,4k] (6*S*): Pale yellow oil. $[\alpha]_D^{25}$ = +56.46 (c = 1.0, $CHCl_3$). R_f = 0.32 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81 (d, J = 15.4 Hz 1 H), 5.91 (t, J = 15.4 Hz, 1 H), 4.56–4.42 (m, 1 H), 4.21–4.19 (m, 2 H), 4.08 (dd, J = 9.0, 6.6 Hz, 1 H), 3.78 (ddd, J = 11.2, 9.0, 2.2 Hz, 1 H), 1.63 (s, 3 H), 1.48 (s, 3 H), 1.42 (s, 9 H), 1.29 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2 (C), 146.0 (CH), 145.7 (C), 122.3 (CH), 94.5 (C), 80.4 (C), 67.3 (CH_2), 60.5 (CH_2), 58.0 (CH), 28.4 (3×CH_3), 26.4 (CH_3), 23.6 (CH_3), 14.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2855, 1719, 1520 cm^{-1}. MS (70 eV, EI): m/z (%) = 299 (<1) $[M]^+$, 284 (9), 184 (100), 96 (27), 57 (98). $C_{15}H_{25}NO_5$ (299.37): calcd. C 60.18, H 8.42, N 4.68; found C 60.27, H 8.36, N 4.60.

Ethyl (*S*,*E*)-3-(3-*tert*-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl)propenoate[4f] (6*R*): Yellowish oil. $[\alpha]_D^{25}$ = –55.92 (c = 0.3, $CHCl_3$). R_f = 0.32 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82 (d, J = 15.4 Hz, 1 H), 5.91 (t, J = 15.4 Hz, 1 H), 4.55–4.44 (m, 1 H), 4.20–4.19 (m, 2 H), 4.08 (dd, J = 9.0, 6.6 Hz, 1 H), 3.77 (ddd, J = 11.2, 9.0, 2.2 Hz, 1 H), 1.63 (s, 3 H), 1.48 (s, 3 H), 1.42 (s, 9 H), 1.30 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2 (C), 146.0 (CH), 145.6 (C), 122.3 (CH), 94.6 (C), 80.4 (C), 67.3 (CH_2), 60.4 (CH_2), 58.0 (CH), 28.5 (3×CH_3), 26.4 (CH_3), 23.6 (CH_3), 14.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2854, 1720, 1519 cm^{-1}. MS (70 eV, EI): m/z (%) = 299 (<1) $[M]^+$, 284 (9), 184 (100), 96 (27), 57 (98). $C_{15}H_{25}NO_5$ (299.37): calcd. C 60.18, H 8.42, N 4.68; found C 60.39, H 8.32, N 4.61.

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