*Article*

*J. Mex. Chem. Soc.* **2011**, *55(3),* 148-153

ISSN 1870-249X

# Diastereoselective Alkylation of Chiral Glycinate Derivatives Containing the α-Phenylethyl Group

Cristina Rodríguez-Garnica, Heraclio López-Ruiz,* Susana Rojas-Lima, Alejandro Álvarez-Hernández, Rafael Tapia-Benavides, and María Concepción García-López

Área Académica de Química, Ciudad Universitaria Carretera Pachuca-Tulancingo Km. 4.5. Mineral de la Reforma, Hidalgo, México. heraclio@uaeh.edu.mx

Received October 1, 2010; accepted February 28, 2011

**Abstract.** Novel chiral glycinate derivatives (*S*)-**6** and (*S*)-**7** containing the α-phenylethyl group, were prepared and studied as potential precursors of enantiopure α-substituted-α-amino acids. In particular, the alkylation of enolate (*S*)-**7**-Li showed substantial (78:22 dr) stereoinduction by the *N*-(1-phenylethyl)benzamide chiral auxiliary. Addition of DMPU showed no appreciable effect upon the diastereoselectivity.
**Keywords:** Alkylation; diastereoselective; enantioselective; lithium enolates; glycinate; amino acids.

**Resumen.** Derivados quirales novedosos de glicinato (*S*)-**6** y (*S*)-**7** conteniendo el grupo α-feniletil fueron preparados y estudiados como precursores potenciales de α-aminoácidos α-sustituidos. En particular el auxiliar quiral *N*-(1-feniletil)benzamida mostró estereoinducción sustancial (78:22 dr) en la alquilación del enolato (*S*)-**7**-Li. La adición de DMPU no mostró un efecto apreciable en la diastereoselectividad.
**Palabras clave:** Alquilación, diastereoselectiva, enantioselectiva, enolatos de litio, glicinato, amino ácidos.

## Introduction

The preparation of enantiopure α-substituted α-amino acids has received substantial attention in recent years due to the important biological properties of these compounds [1]. For example, α-substituted α-amino acids are used in pharmaceuticals such as L-DOPA (**1**) [2], fungicides such as polyoxin (**2**) [3] and food additives such as glutamic acid (**3**) [4]. Furthermore, α-substituted α-amino acids are essential peptide precursors [5].

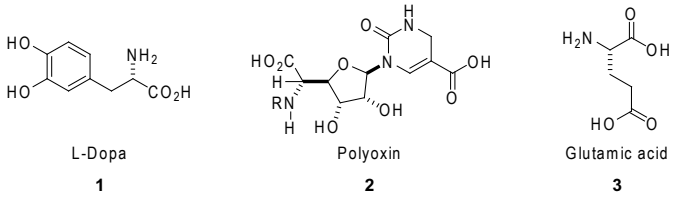



**Fig. 1.**

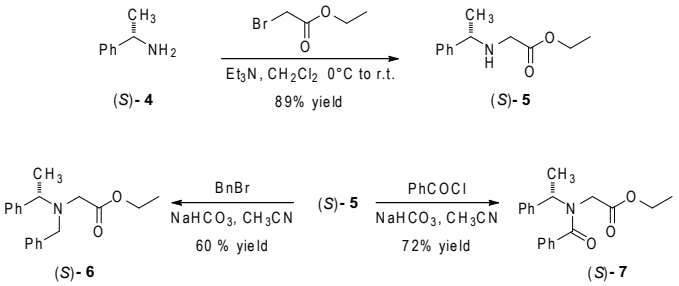
At present, a number of methodologies are available for the enantioselective synthesis of α-substituted α-amino acids [4]. We decided to study the alkylation of enolates derived from glycinate bearing the chiral auxiliary α-phenylethylamino group, namely (*S*)-**6** and (*S*)-**7,** as an alternative method to achieve enantioselective synthesis of α-substituted α-amino acids. Both (*R*)- and (*S*)-α-phenylethylamines are simple, hitherto efficient chiral auxiliaries in asymmetric synthesis [6], and have been used for the preparation of enantiopure α-substituted β-amino acids [7].

## Results and Discussion

### Stereoselectivity of alkylation of (*S*)-6

At the beginning of this work, we set up to prepare *N*-substituted glycinate bearing the chiral auxiliary α-phenylethylamine. Thus, as outlined in Scheme 1, (*S*) α-phenylethylamine **4** was treated with ethyl bromoacetate to give the corresponding optically pure ethyl glycinate derivative (*S*)-**5**, which in turn was converted into the benzyl derivative (*S*)-**6** [8] and the benzoyl derivative (*S*)-**7**.

Alkylation experiments started with the generation of the lithium enolate of ethyl *N*-α-methylbenzylglycinate (*S*)-**6** by treatment with LiHMDS in THF at low temperature followed by addition of several alkyl halides at low temperature. The chemical yields of alkylated glycinates under these conditions were 88-92% and modest diastereoselectivities were obtained. The diastereomeric excess was calculated by integration of signals in $^1$H NMR spectra of crude products as % of the major




**Scheme 1.**

diastereomer-% of minor diastereomer. The results are summarized in Table I.

Since the addition of DMPU has been found to affect the stereoselectivity of alkylation reactions [7] several experiments were performed in the presence of DMPU in order to improve diastereoselectivity (see Table I). Disappointingly, the diastereomeric excess did not improve (see entries 2-6) and the chemical yields were substantially lower (see Table I).

Although modestly, the $\alpha$-phenylethyl chiral auxiliary induced alkylation on the *Si* face of enolate (*S*)-**6**-Li, i.e. stereoinduction favored the *like* stereoisomer. To rationalize this stereoselection, we resorted to molecular modeling studies (Becke3LYP/6-311G (2d,2p) DFT level with Gaussian 98) [9] of the lithium enolate (*S*)-**6**-Li and Figure 2 shows its calculated minimum energy conformation.

According to this calculated model, the lithium cation is coordinated preferentially to the (*Re*) face of the enolate, because it interacts with the benzene ring of the *N*-benzyl group and with all three (C-C-O) atoms of the enolate system. This set of interactions overcomes allylic $A^{1,3}$ strain of the phenylethyl group. These interactions of lithium leave the (*Si*) face (top face in Figure 2) of the enolate less hindered to approach of electrophiles and induce the "*like*" stereochemistry of alkylation that is observed. A similar interaction of lithium on the (*Re*) face of the enolate (not shown) lacks a favorable interaction with the benzene ring but suffers from a non-bonding interaction of lithium with the methyl group on the chiral auxiliary. Thus, it is the *Si* face of the reactive enolate that is preferentially alkylated.

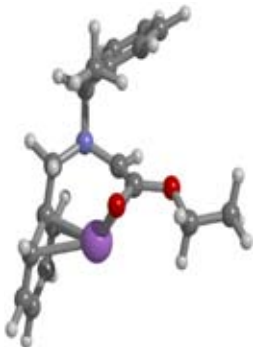


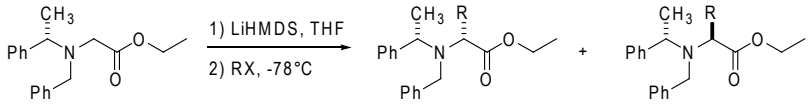
**Fig. 2.** Calculated minimum energy conformation of enolate (*S*)-**6**-Li.

### Stereoselectivity of alkylation of (*S*)-7

*N*-Benzoyl glycinate (*S*)-**7** was prepared to study the effect of a more rigid chiral auxiliary on alkylation diastereoselectivity. Thus, treatment of (*S*)-**7** with LiHMDS was followed by addition of alkyl halides at low temperature. (Table II) *N*-benzoyl glycinate (*S*)-**7** shows the same direction and magnitude of stereo induction as in the case of its less rigid analog, *N*-benzyl glycinate (*S*)-**6**, favoring the "like" alkylated stereoisomer. Alkylation experiments using MeI were conducted with different amounts of DMPU which showed no effect upon diastereoselection; again the only effect of DMPU was to slightly decrease the chemical yield of the alkylation (compare entries 1 vs 2-6 on Table II).

Molecular modeling studies of enolate (*S*)-**7**-Li by means of Becke3LYP/6-311G (2d,2p) DFT level with Gaussian 98 [9] gave the minimum energy conformation calculated for enolate (*S*)-**7**-Li Figure 3. The global energy minimum of (*S*)-**7**-Li shows that lithium is bridged to both oxygen atoms on the enolate and the carbonyl oxygen of the benzamide moiety. As a result of these interactions, the (*Si*) face of the enolate is less

**Table I.** Diastereoselectivity of Enolate (*S*)-**6**-Li Alkylations.

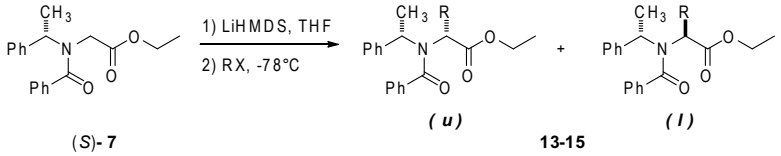



(*S*)- **6** ( *u* ) **8-12** ( *l* )

| Entry | RX | DMPU | Products | Diastereomer ratio (*u*:*l*)[a] | yield[b] (%) |
|---|---|---|---|---|---|
| **1** | $CH_3I$ | — | **8** | 33:67 | 92 |
| **2** | $CH_3I$ | 1 Equiv. | **8** | 32:68 | 78 |
| **3** | $CH_3I$ | 2 Equiv. | **8** | 48:52 | 80 |
| **4** | $CH_3I$ | 3 Equiv. | **8** | 25:75 | 63 |
| **5** | $CH_3I$ | 6 Equiv. | **8** | 33:67 | 70 |
| **6** | $CH_3I$ | 7 Equiv. | **8** | 28:72 | 62 |
| **7** | $PhCH_2Br$ | — | **9** | 26:74 | 88 |
| **8** | $CH_2{=}CHCH_2Br$ | — | **10** | 35:65 | 92 |
| **9** | $BrCH_2CO_2CH_2CH_3$ | — | **11** | 30:70 | 91 |
| **10** | $CH_3CH_2Br$ | — | **12** | 33:67 | 92 |

[a](l) means like, (u) means unlike configuration, taking the configuration of the initial stereogenic C as reference.
[b]Combined yield after purification.

**Table II.** Diastereoselectivity of Enolate (*S*)-**7**-Li Alkylations.




| Entry | RX | DMPU | Product | Diastereomer ratio (*u*:*l*) | yield[a] (%) |
|---|---|---|---|---|---|
| **1** | $CH_3I$ | — | **13** | 23:77 | 95 |
| **2** | $CH_3I$ | 1 Equiv. | **13** | 25:75 | 86 |
| **3** | $CH_3I$ | 2 Equiv. | **13** | 24:76 | 85 |
| **4** | $CH_3I$ | 3 Equiv. | **13** | 24:76 | 86 |
| **5** | $CH_3I$ | 6 Equiv. | **13** | 22:78 | 87 |
| **6** | $CH_3I$ | 7 Equiv. | **13** | 22:78 | 89 |
| **7** | $PhCH_2Br$ | — | **14** | 22:78 | 90 |
| **8** | $BrCH_2CO_2CH_2CH_3$ | — | **15** | 34:66 | 92 |

[a]Combined yield after purification.

hindered to react with alkylating agents. Overall, the sense and magnitude of stereoinduction is essentially the same as in the case of (*S*)-**6**-Li.

### Assignment of configuration of diastereoisomeric products

The diastereomeric ratios reported on Table I and Table II were determined by integration of the signals in the $^1$H NMR spectra of crude products **8-15** and assignment of absolute configuration of the major diastereomer **8(*l*)** was established by chemical correlation with known (*S*)-**16** obtained by hydrogenolysis of both benzyl and methylbenzyl groups followed by hydrolysis of ethyl ester functionality (Scheme 2).

In summary, chiral glycinate derivatives (*S*)-**6** and (*S*)-**7** containing the $\alpha$-phenylethyl group were prepared in good yields from benzyl bromide or benzoyl chloride and (*S*)-ethyl-2-(1-phenylethylamino)acetate (*S*)-**5**, respectively. Enolates (*S*)-**6**-Li and (*S*)-**7**-Li were alkylated in high yields and moderate diastereoselectivity with various electrophiles. Addition of DMPU did not improve diastereoselection of alkylation.

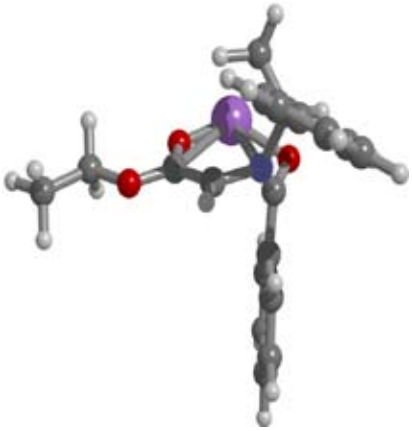


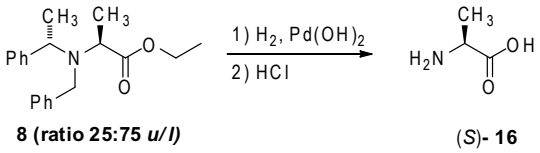
**Fig. 3.** Calculated minimum energy conformation of enolate (*S*)-**7**-Li.

## Experimental section

The glassware used for the generation and reactions of organolithium compounds were oven-dried ca. 12 h at 120°C. Anhydrous solvents were obtained by distillation from benzophenone ketyl. TLC was performed on Merck-DC-$F_{254}$ plates; detection was made by UV light. Flash column chromatography was performed using Merck silica gel (230-240 mesh). All melting points are uncorrected. $^1$H NMR spectra were recorded on a JEOL Eclipse+400 (400 MHz) spectrometer. $^{13}$C NMR spectra were recorded on a JEOL Eclipse+400 (100 MHz) spectrometer. Chemical shifts ($\delta$) are indicated in ppm downfield from internal TMS used as reference; the coupling constants (*J*) are given in Hz. Optical rotations were measured in a Perkin-Elmer Model 341 Polarimeter, using the sodium D-line (586 nm). Elemental analyses were performed on a Perkin-Elmer Serie II CHNS/O Analyzer 2400.

### Ethyl *N*-[(*S*)-$\alpha$-phenylethyl] glycinate (*S*-5)

To a solution of (*S*)-$\alpha$-phenylethylamine (**4**) (1.0 g, 8.25 mmol) and triethylamine (1.38 mL, 9.90 mmol) in dry $CH_2Cl_2$ (15 mL)




**Scheme 2.**

under nitrogen, was added ethyl bromoacetate (0.915 mL, 8.25 mmol) in $CH_2Cl_2$ (15 mL) at 0ºC. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. After the addition of 2M HCl (5 mL), the product was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were dried over anh. $Na_2SO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography (hexane-EtOAc, 9:1). Colorless oil, yield (1.52 g, 89%); $[\alpha]_D^{20}$ = –64.1 (c = 1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.22 (t, $J$ = 7.0 Hz, 3H), 1.36 (d, $J$ = 6.6 Hz, 3H), 1.98 (b, 1H), 3.20 (d, $J$ = 17.4 Hz, 1H), 3.26 (d, $J$ = 17.4 Hz, 1H), 3.77 (q, $J$ = 6.6 Hz, 1H), 4.13 (q, $J$ = 7.0 Hz, 2H), 7.20-7.33 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.2, 24.3, 48.9, 57.8, 60.7, 126.8, 127.2, 128.6, 144.7, 172.6. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.40; H, 8.30; N, 6.74%.

**(*S*)-Ethyl 2-[benzyl (1-phenylethyl) amino] acetate (*S*-6)**

A suspension of chiral amine (*S*)-**5** (1.0 g, 4.83 mmol) and $NaHCO_3$ (0.52 g, 4.83 mmol) in acetonitrile (15 mL), under nitrogen was cooled at 0ºC; then benzyl bromide (0.69 mL, 5.80 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated and the residue suspended in water (50 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried over anh. $Na_2SO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography (hexane-EtOAc, 9:1). White solid, yield (0.86 g, 60%), mp 61-63 ºC; $[\alpha]_D^{20}$ = –37 (c = 0.785, MeOH). (Lit [8b]. $[\alpha]_D^{20}$ = –37 (c = 0.785, MeOH)).

$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.25 (t, $J$ = 7.1 Hz, 3H), 1.40 (d, $J$ = 6.8 Hz), 3.21 (d, $J$ = 17.4 Hz, 1H), 3.42 (d, $J$ = 17.4 Hz, 1H), 3.73 (d, $J$ = 13.9 Hz, 1H), 3.76 (d, $J$ = 13.9 Hz, 1H), 4.12 (q, $J$ = 6.8 Hz, 1H), 4.14 (q, $J$ = 7.1 Hz, 2H), 7.20-7.47 (m, 10H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 14.4, 18.9, 50.6, 54.9, 59.9, 60.2, 127.0, 127.7, 128.3, 128.4, 128.8, 139.8, 144.7, 172.1. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.77; H, 7.96; N, 4.60%.

**(*S*)-Ethyl 2-[*N*-(1-phenylethyl)benzamido]acetate (*S*-7)**

A solution of the chiral amine (*S*)-**5** (1.0 g, 4.83 mmol) and $NaHCO_3$ (2.03 g, 24.15 mmol) in acetonitrile (50 mL) was cooled to 0ºC under nitrogen. Then benzoyl chloride (1.68 mL, 14.49 mmol) was added dropwise and the reaction mixture stirred at room temperature for 48 h. The solvent was removed in a rotary evaporator and the residue suspended in water (50 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried over anh. $Na_2SO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography (hexane-EtOAc, 9:1). Yellow oil, yield (1.081 g, 72% yield); $[\alpha]_D^{20}$ = –42.9 (c = 2.1, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.15 (t, $J$ = 7. 3 Hz, 3H), 1.57 (d, $J$ = 7.0 Hz, 3H), 3.76 (d, $J$ = 17.6 Hz, 1H), 4.00 (d, $J$ = 17.6 Hz, 1H), 4.05 (q, $J$ = 7.3 Hz, 2H), 5.23 (q, $J$ = 7.0 Hz, 1H) 7.20-7.97 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 14.4, 17.8, 49.2, 55.8, 61.0, 126.8, 127.0, 127.5, 128.3, 128.8, 129.0, 137.3, 141.0, 169.5, 171.78. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.47; H, 6.75; N, 4.60%.

**General procedure for the reaction of glicine enolates [(*S*)-6-Li or (*S*)-7-Li] with electrophiles**

A mixture of (*S*)-**6** or (*S*)-**7** (1.0 eq.) in dry THF (30 mL) was stirred at −78 ºC under nitrogen and 1.0 M LiHMDS (1.0 eq.) added. The resulting solution was allowed to react for 30 min. then the electrophile was added. The reaction mixture was stirred at −78 ºC for additional 2 h, then allowed to warm to room temperature and stirring continued overnight. The reaction was quenched with saturated aq. $NH_4Cl$ (5.0 mL), and the product extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried over anhydrous $Na_2SO_4$, and concentrated. Final purification was accomplished by flash chromatography. In all cases, the diastereomeric mixture could not be separated by chromatography but NMR spectroscopic analysis of the major product was feasible.

**Ethyl 2-(benzyl ((*S*)-1-phenylethyl)amino)propanoate (8)**

The general procedure was followed using (*S*)-**6** (0.2 g, 0.67 mmol), 1.0 M LiHMDS (0.67 mL, 0.67 mmol) and methyl iodide (0.05 mL, 0.81 mmol). $^1$H NMR analysis of the crude product showed a mixture of two diastereomeric products in a 33:67 ratio. The major product was assigned the (*S*) configuration by chemical correlation with (*S*)-**16** (see text). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.25 (t, $J$ = 7.2 Hz, 3H), 1.32 (d, $J$ = 6.8 Hz, 3H), 1.37 (d, $J$ = 7.0 Hz, 3H), 3.54 (q, $J$ = 6.8 Hz, 1H), 3.56 (d, $J$ = 14.5 Hz, 1H), 3.95 (d, $J$ = 14.5 Hz, 1H), 4.06 (q, $J$ = 7.0 Hz, 1H), 4.19 (q, $J$ = 7.2 Hz, 2H), 7.25-7.42 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 14.4, 15.8, 21.4, 51.5, 54.7, 60.1, 126.8, 126.9, 127.0, 127.7, 128.3, 128.4, 141.34, 174.6. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.12; H, 8.15; N, 4.60%.

**Ethyl 2-(benzyl ((*S*)-1-phenylethyl) amino)-3-phenylpropanoate (9)**

The general procedure was followed using (*S*)-**6** (0.2 g, 0.67 mmol), 1.0 M LiHMDS (0.67 mL, 0.67 mmol) and benzyl bromide (0.10 mL, 0.81 mmol). $^1$H NMR analysis of the crude product showed a mixture of two diastereomeric products in a 26:74 ratio. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.19 (t, $J$ = 7.1 Hz), 1.42 (d, $J$ = 7.0 Hz, 3H), 3.14 (dd, $J$ = 13.6 Hz, $J$ = 8.8 Hz, 1H), 3.17 (dd, $J$ = 13.6 Hz, $J$ = 8.1 Hz, 1H), 3.54 (d, , $J$ = 13.7 Hz, 1H), 3.68 (d , $J$ = 13.7 Hz, 1H), 3.82 (dd, $J$ = 7.6 Hz, $J$ = 7.4 Hz, 1H), 4.07 (q, $J$ = 7. Hz, 2H), 4.28 (q, $J$ = 7.0 Hz, 2H), 7.22-7.49 (m, 15H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 14.3, 21.2, 37.6, 56.3, 58.1, 60.7, 62.9, 126.3, 126.9, 127.0, 128.0, 128.3, 128.9, 129.5, 138.6, 140.6, 144.0, 173.3. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.68; H, 7.31; N, 3.68%.

**Ethyl 2-(benzyl ((*S*)-1-phenylethyl)amino)pent-4-enoate (10)**

The general procedure was followed using (*S*)-**6** (0.2 g, 0.67 mmol), 1.0 M LiHMDS (0.67 mL, 0.67 mmol) and allyl bromide (0.07 mL, 0.81 mmol). $^1$H NMR analysis showed a mixture of two diastereomeric products in a 35:65 ratio. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.17 (t, $J$ = 7.1 Hz, 3H), 1.34 (d, $J$ = 7.0 Hz, 3H); 2.27-2.52 (m, 2H), 3.49 (dd, $J$ = 7.7 Hz, $J$ = 7.3 Hz, 1H), 3.95 (q, $J$ = 7.1 Hz, 2H), 4.03 (d, $J$ = 13.5 Hz, 1H), 4.09 (d, $J$ = 13.5 Hz, 1H), 4.14 (q, $J$ = 7.0 Hz, 1H), 4.95-5.01 (m, 2H), 5.51-5.78 (m, 1H), 7.17-7.47 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.5, 21.4, 35.7, 51.7, 56.4, 60.1, 61.2, 117.1, 127.0, 127.2, 128.0, 128.2, 128.3, 128.9, 135.6, 142.5, 144.2, 173.4. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.54; H, 8.05; N, 4.12%.

**Diethyl 2-(benzyl ((*S*)-1-phenylethyl) amino) succinate (11)**

The general procedure was followed using (*S*)-**6** (0.2 g, 0.67 mmol), 1.0 M LiHMDS (0.67 mL, 0.67 mmol) and ethyl bromoacetate (0.09 mL, 0.81 mmol). $^1$H NMR analysis showed a mixture of two diastereomeric products in a 30:70 ratio. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.18 (t, $J$ = 7.3 Hz, 3H), 1.27 (t, $J$ = 7.1 Hz, 3H), 1.39 (d, $J$ = 6.6 Hz, 3H), 2.78 (dd, $J$ = 15.9 Hz, $J$ = 8.9 Hz, 1H), 2.80 (dd, $J$ = 15.8 Hz, $J$ = 7.7 Hz, 1H), 3.81 (d, $J$ = 14.6 Hz, 1H), 3.85 (d, $J$ = 14.6 Hz, 1H), 3.94-3.99 (m, 1H), 4.02 (q, $J$ = 6.6 Hz, 1H), 4.12 (q, $J$ = 7.3 Hz, 2H), 4.17 (q, $J$ = 7.1 Hz, 2H), 7.20-7.41 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.2, 14.3, 21.0, 36.5, 51.9, 56.4, 58.1, 60.6, 60.7, 127.2, 127.8, 127.9, 128.0, 128.3, 128.8, 141.5, 143.7, 171.3, 172.7. Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.37; H, 7. 52; N, 3.55%.

**Ethyl 2-(benzyl ((*S*)-1-phenylethyl) amino) butanoate (12)**

The general procedure was followed using (*S*)-**6** (0.2 g, 0.67 mmol), 1.0 M LiHMDS (0.67 mL, 0.67 mmol) and ethyl bromide (0.09 mL, 0.81 mmol). $^1$H NMR analysis showed a mixture of two diastereomeric products in a 33:67 ratio.

$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.91 (t, $J$ = 7.3 Hz, 3H), 1.24 (t, $J$ = 7.00 Hz, 3H), 1.27-1.29 (m, 2H), 1.40 (d, $J$ = 7.0 Hz, 3H), 3.12 (d, $J$ = 13.5 Hz, 1H), 3.47 (d, $J$ = 13.5 Hz, 1H), 3.73 (dd, $J$ = 7.2 Hz, $J$ = 7.2 Hz, 1H), 3.95 (q, $J$ = 7.0 Hz, 1H), 4.20 (q, $J$ = 7.0 Hz, 2H), 7.14-7.34 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.6, 14.0, 18.7, 29.8, 50.0, 51.4, 56.0, 59.8, 126.8, 127.8, 127.9, 128.1, 128.5, 140.9, 142.8, 172.6. Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.30; H, 8.66; N, 4.55%.

**Ethyl 2(*N*-((*S*)-1-phenylethyl) benzamido) propanoate (13)**

The general procedure was followed using (*S*)-**7** (0.2 g, 0.64 mmol), 1.0 M LiHMDS (0.64 mL, 0.64 mmol) and methyl iodide (0.05 mL, 0.77 mmol). $^1$H NMR analysis showed a mixture of two diastereomeric products in a 23:77 ratio. The major product was assigned the *S* configuration by chemical correlation with (*S*)-**16** (see text). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.12 (d, $J$ = 7.0 Hz, 3H), 1.29 (t, $J$ = 7.3 Hz, 3H), 1.59 (d, $J$ = 6.8 Hz, 3H),3.62 (q, $J$ = 7.0 Hz, 1H), 4.20 (q, $J$ = 7.3 Hz, 2H), 5.06 (q, $J$ = 6.8 Hz, 1H); 7.25-7.50 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 14.3, 16.8, 29.8, 52.2, 56.8, 61.2, 126.0, 127.6, 128.0, 128.2, 128.7, 129.3, 137.0, 139.3, 170.6, 171.6. Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.92; H, 7.15; N, 4.41%.

**Ethyl 3-phenyl-2-(*N*-((*S*)-1-phenylethyl) benzamido) propanoate (14)**

The general procedure was followed using (*S*)-**7** (0.2 g, 0.64 mmol), 1.0 M LiHMDS (0.64 mL, 0.64 mmol) and benzyl bromide (0.09 mL, 0.77 mmol). $^1$H NMR analysis showed a mixture of two diastereomeric products in a 22:78 ratio. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.05 (t, $J$ = 7.1 Hz, 3H), 1.58 (d, $J$ = 7.0 Hz, 3H), 2.48-2.77 (m, 1H), 3.52-3.82 (m, 1H), 4.07 (q, $J$ = 7.1 Hz, 2H), 5.00 (dd, $J$ = 7.4 Hz, $J$ = 7.0 Hz, 1H), 5.25 (q, $J$ = 7.0 Hz, 1H), 7.07-7.80 (m, 15H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.1, 17.4, 35.7, 50.0, 57.3, 60.9, 126.3, 128.2, 128.6, 128.9, 131.4 137.2, 139.5, 170.0, 171.5. Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.57; H, 6.77; N, 3.47%.

**Diethyl 2-(*N*-((*S*)-1-phenylethyl) benzamido) succinate (15)**

The general procedure was followed using (*S*)-**7** (0.2 g, 0.64 mmol), 1.0 M LiHMDS (0.64 mL, 0.64 mmol) and ethyl bromoacetate (0.09 mL, 0.77 mmol). $^1$H NMR analysis showed a mixture of two diastereomeric products in a 34:66 ratio. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.25 (t, $J$ = 7.0 Hz, 6H), 1.60 (d, $J$ = 7.0 Hz, 3H), 2.76 (dd, $J$ = 16.3 Hz, $J$ = 5.6 Hz, 1H), 3.04 (dd, $J$ = 16.3 Hz, $J$ = 5.6 Hz, 1H), 4.17 (q, $J$ = 7.0 Hz, 4H), 5.13 (q, $J$ = 7.0 Hz, 1H), 5.33 (dd, $J$ = 7.3 Hz, $J$ = 7.3 Hz, 1H), 7.25-7.77 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.2, 21.8, 29.8, 44.1, 49.3, 61.2, 126.4, 127.2, 127.4, 127.9, 128.5, 128.7, 134.6, 143.2, 166.7, 169.2, 172.2. Anal. Calcd. for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.53. Found: C, 69.61; H, 6.63; N, 3.59%.

**2-Amino-propionic acid (16)**

The hydrogenation of **8** (25:75 ***u***/***l*** ratio) (0.1 g, 0.32 mmol) was carried out under $H_2$ pressure 60 psi., using 10% $Pd(OH)_2$ over charcoal (0.01 g) water (2.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was shaked for 8 h then filtered over Celite and concentrated to afford the deprotected amine. This product was dissolved in 6 N HCl (10 mL) and heated to 95°C for 5 h. The crude product was washed with $CH_2Cl_2$ (3 × 20 mL), the aqueous phase was concentrated, and the residue adsorbed into acid ion-exchange resin Dowex 50W X4. The resin was washed with distilled water until the washings came out neutral. Then the free amino acid was recovered with 0.1 N aqueous $NH_4OH$. Evaporation or the solution afforded the chiral $\alpha$-amino acid

(*S*)-**16**. Yield **(**0.022 g, 62%). $[\alpha]_D^{20}$ = +7.25 (c = 6, 6 M HCl; for this rotation $[\alpha]_D^{20}$ value an *ee* of 67% can be calculated), Lit[10]. $[\alpha]_D^{20}$ = +14.5 (c = 6 M HCl). $^1$H NMR ($D_2O$, 400 MHz) δ 3.81 (d, *J* = 7.0 Hz, 3H), 6.12 (q, *J* = 7.0 Hz, 1H). $^{13}$C NMR ($D_2O$, 100 MHz) δ 16.3, 50.8, 176.0.

## Acknowledgments

We are indebted to Conacyt, Mexico for financial support via grants J49336-Q and 84453. We are indebted to Prof. Joseph M. Muchowski for many discussions.

## References

1. a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517-3599. b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645-732. c**)** Joksović, M. D.; Marković, V.; Juranić, Z. D.; Stanojković, T.; Jovanović, L. S.; Damljanović, I. S.; Szécsényi, K. M.; Todorović, N.; Trifunović, S.; Vukićević, R. D. ***J.*** *Organomet. Chem.* **2009,** *694*, 3935-3942.
2. Coskun, A.; Acalla, E. U. *Org. Lett.* **2004**, *6*, 3107-3109.
3. Savage, I.; Tomas, E. J.; Wilson, P. D. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3291-3303.
4. a) Yiotakis, A.; Magriotis, P. A.; Vassilious, S. *Tetrahedron: Asymmetry* **2007**, *18*, 873-877. b) Reyes, A.; Juaristi, E. *Tetrahedron: Asymmetry* **2000**, *11*, 1411-1423. c) Juaristi, E.; León-Romo, J. L.; Ramírez-Quirós, Y. *J. Org. Chem.* **1999**, *64*, 2914-2918. d) Orena, M. Porzi; G. Sandri, S. *J. Org. Chem.* **1992**, *57*, 6532-6536. e) Williams, R. M. *Synthesis of Optically Active α-Amino Acids;* Pergamon Press: Oxford, **1989**.
5. Nájera, C. *Synlett* **2002**, *9*, 1388-1403.
6. a) Juaristi, E.; Leon-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441-2495. b) Bandala, Y.; Juaristi, E. *Aldrichim. Acta*, **2010**, *43*, 65-78.
7. a) Gutierrez-García, V. M.; López-Ruiz, H.; Reyes-Rangel, G.; Juaristi, E. *Tetrahedron* **2001**, *57*, 6487-6496. b) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439-4486.
8. a) Ordoñez, M.; González-Morales, A.; Salazar-Fernández, H. *Tetrahedron: Asymmetry* **2004**, *15*, 2719-2725. b) Yamashita, A.; Norton, E. B.; Williamson, R. T.; Ho, D. M.; Sinishtaj, S.; Mansour, T. S. *Org. Lett.* **2003**, *5*, 3305-3308.
9. Gaussian 98, Revision A.11, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rubuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.
10. a) Chapman & Hall, *Dictionary of Organic Compounds* **1996**, 6$^{th}$ Ed. b) *Aldrich Chemical Co*, Inc. Wisconsin, USA. **2010**, pp. 63.