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Facile Synthesis of (*R*,*R*) and of (*R*,*S*) Tricarballylic Acid Anhydride and Imide Derivatives

Abdel-Sattar S. Hamad Elgazwy

Department of Chemistry, Faculty of Science, University of Ain Shams, Abbassia 11566, Cairo, Egypt
Tel.: (00)202-4831836, Fax: (00)202-4831836, E-mail: hamad@asunet.shams.eun.eg

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Abstract: The diastereomeric mixture of (*R*)-2-(methoxycarbonylmethyl)-*N*-(*R*)-1-(1-phenylethyl) succinimide **11s** and (*S*)-2-(methoxycarbonylmethyl)-*N*-(*R*)-1-(1-phenylethyl) succinimide **11a** was synthesized by reaction of 2-(carboxymethyl)succinic anhydride **6** with (*R*)-(*a*)-methylbenzylamine in dry THF/room temperature/24 hrs. The diastereomeric mixture of 1-[(*R*)-(*a*)-Methylbenzylamideformyl)]propane-2,3-dicarboxylic acid anhydride **9s** and 1-[(*R*)-(*a*)-methylbenzylamideformyl)]propane-2,3-dicarboxylic acid anhydride **9a** was isolated as an intermediate under the reaction conditions. This diastereomeric mixture **9s**/**9a** was also prepared by a different route via reaction of 1-(chloroformyl)propane-2,3-dicarboxylic acid anydride **12** with (*R*)-(*a*)-methylbenzylamine in the presence of DMA at 0^{o}C for 24 hrs.

Keywords: Fumonisin, AAL Toxin T_A, Actinoplanic acid, Diastereomers of Tricarballylic acid, Sphingosine analogs.

Introduction

Tricarballylic acid (TCA) **5** is found as a fragment in several mycotoxin natural products such as Fumonisin B_1 (**1a**), Fumonisin B_2 (**2b**), and AAL Toxin T_A (**3**) and a macrocyclic polycarboxylic acid which is an inhibitor of Ras Farnesyl-Protein Transferase (FPTase) [1] like Actinoplanic acid (**4**), (Figure 1). Fumonisins and AAL toxins are sphingosine analog mycotoxins characterized by tricar-

ballylic acid side chains.[2] Most notably, fumonisins are known to be natural cancer promoters, and have been linked to human esophageal cancer in parts of China and southern Africa.[3] The occurrence and biological activity of the tricarballylic acid molecule has been studied extensively.[4]

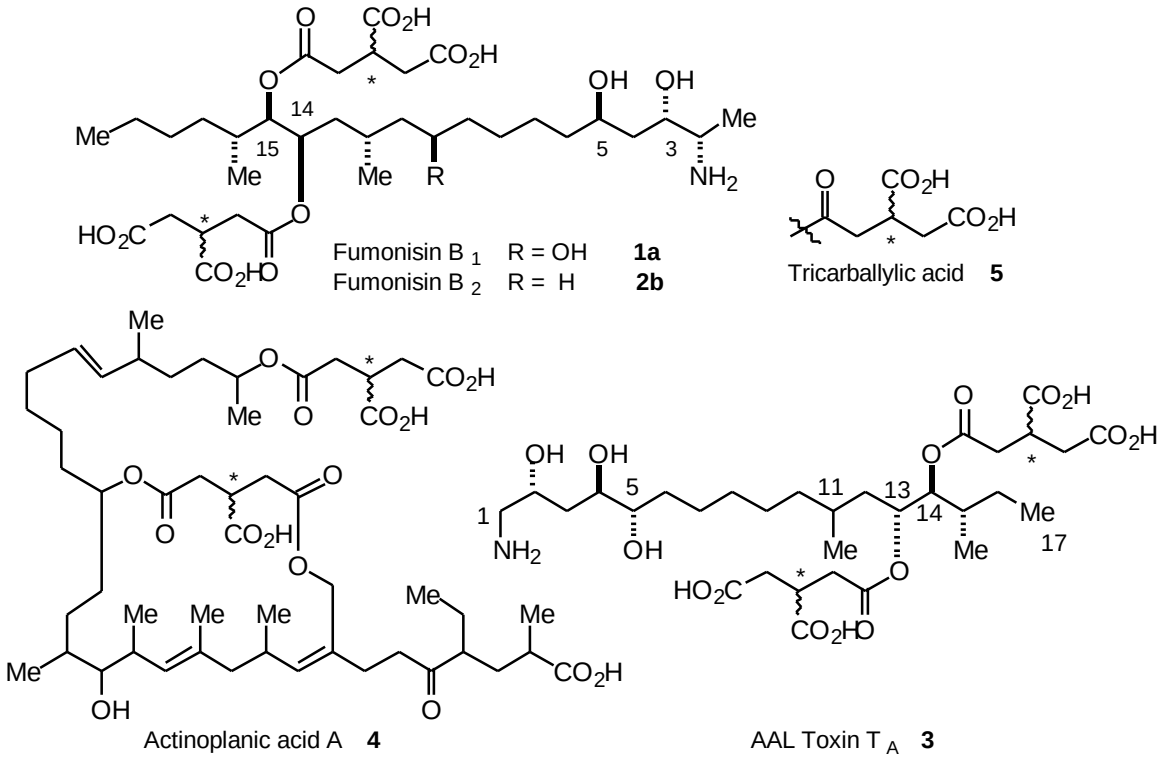


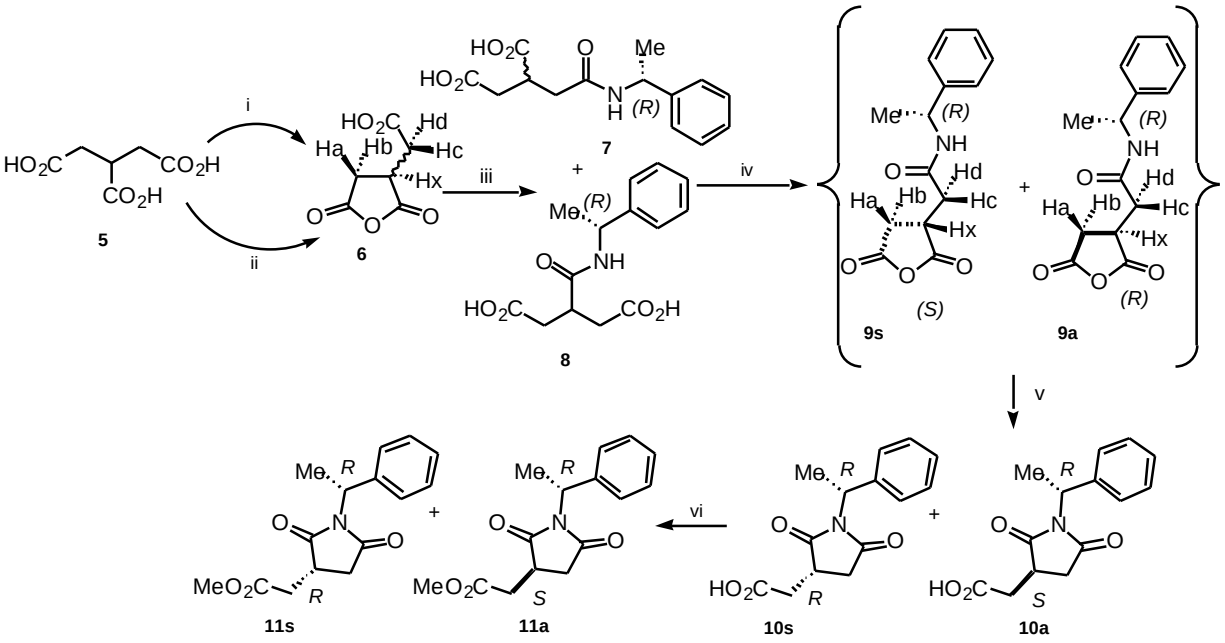
Figure 1.

It has been established that TCA **5** is produced by rumen bacteria and that it influences ruminant tissue metabolism.[5,6] Previously [7] we have described the synthesis of the 4-(5-nonyloxycarbonyl)-3-substituted butanoic acids and methyl esters like those found in Fumonisin B_1 (**1a**), B_2 (**2b**), AAL Toxin T_A (**3**) and Actinoplanic acid **4** (Figure 1) as a part of sphingosine analogs.

We now report the preparation of the diastereomeric mixture of (*R*)-2-(methoxycarbonyl-methyl)-*N*-(*R*)-1-(1-phenylethyl)succinimide **11s** and (*S*)-2-(methoxycarbonylmethyl)-*N*-(*R*)-1-(1-phenylethyl)-succinimide **11a**.

Results and Discussion

Ring-opening of 2-(carboxymethyl) succinic anhydride **6** with (*R*)-(*a*)-methylbenzylamine in dry THF (RT, 24 h) gave a white sticky material of diastereomeric and regioisomeric mixture of amides upon concentration (Scheme 1).



i) Ac_2O / 24 h, RT, ii) Ac_2O at 45 ^{0}C/ 1h.AcOH at 60 ^{0}C/ 1h., iii) (R)-(α)-methyl benzylamine/ dry THF, RT , 24 hrs. iv) fusion at 129-132 ^{0}C and then solidified, v) fusion at 158-160 ^{0}C, vi) $Me_2NCH(OMe)_2$, dry THF, RT, 24 hrs.

Scheme 1.

The ^{1}H NMR spectrum allowed us to suggest that the mixture of diastereomeric and regioisomeric amides were the *a*-amide and *b*-amide derivatives **7** and **8**, respectively. NMR data for these structures **7** and **8** were consistent with the results described by Hoye et al.[8] for the determination of absolute configuration of 3-substituted carboxylic acids (*b*-chiral acids). The resulting products **7** and **8** were melted at 129-132^{o}C, re-solidified by cooling, transferred into a NMR tube and finally analyzed. The spectrum shows doublet peaks downfield for (RC<u>H</u>c-R') and (RC<u>H</u>d-R') at δ 2.86 (dd, *J* = 6.86, 16.90 Hz) and δ 3.30 (dd, *J* = 9.75, 18.54 Hz) of the compound **9s**, respectively. The ^{1}H NMR spectrum of **9a** was virtually the same as for **9s** with the following differences: δ (RC<u>H</u>c-R') and (RC<u>H</u>d-R') at δ 2.75 (dd, J = 9.76, 17.90 Hz) and δ 3.22 (dd, J = 9.93, 18.42 Hz) ppm. This was considered to be due to the anisotropic shielding effect of the aromatic ring of the phenyl group attached to the succinimide. The major product of the diastereomeric mixture of anhydride was assigned to be **9s** (1.3:1). The intermediate compounds **9s**/**9a** were re-melted at 158-160^{o}C, and gave the expected assignment of the diastereomeric mixture of succinimide derivatives **10s**/**10a** in a 1:1 ratio. The product was quite pure after spectroscopic analysis and no attempt was made to purify this diastereomeric mixture further. Esterification of the diastereomeric mixture **10s**/**10a** was achieved with *N*,*N*′-dimethylformamide dimethylacetal in dry THF (RT, 24h). Concentration gave a white sticky material of diastereomeric mixture **11s**/**11a** in a 1.2:1 ratio. The diastereomeric mixture was purified by MPLC (1:9 Hexane:EtOAc) to provide compounds (*R*)-2-(methoxycarbonylmethyl)-*N*-(*R*)-1-(1-phenylethyl)-succin-

imide **11s** and (*S*)-2-(methoxycarbonylmethyl)-*N*-(*R*)-1-(1-phenyl-ethyl) succinimide **11a** in 82% yield. We have developed a reliable method for determining the absolute configuration of carboxylic acids containing a stereogenic center at C(3) of the tricarballylic acid derivatives.[8,9]. Figure 2 shows the application of this method to identify a heterotopic group attached to C(3) that contains readily distinguishable ^{1}H NMR resonances in the diastereomeric pair of 1-arylethylsuccinimides (e.g. the methoxycarbonyl methyl group in **11**). The C(3)-configuration has been deduced by comparing the relative shifts of these resonances. For example, in the *anti* isomer **11** of the CH_2CO_2Me-succinimide of generic *anti-(3S)* diastereomer, the methoxyl resonance will be observed at higher field than in the *syn* -(3*R*) diastereomer.

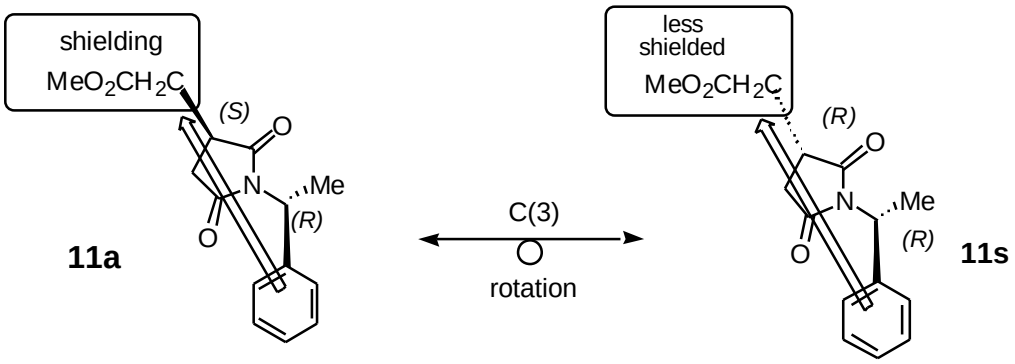
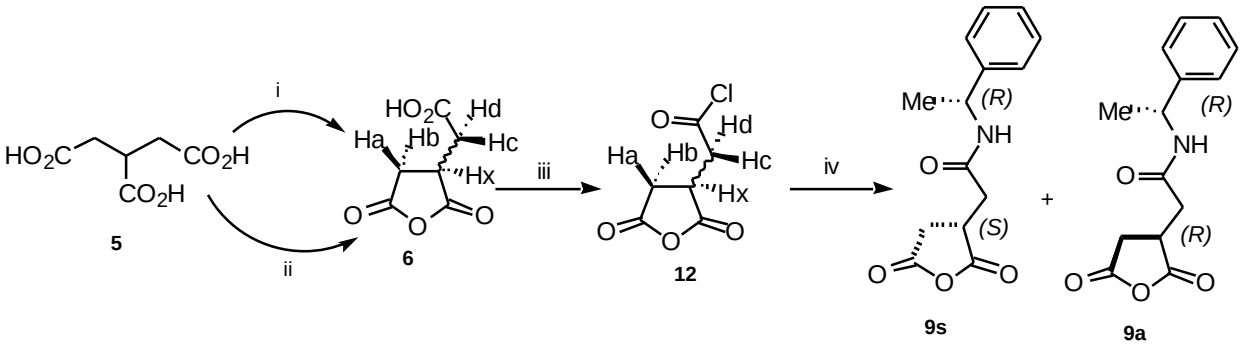


Figure 2.

Similarly, the ^{1}H NMR spectrum of compounds **11s**/**11a** shows the (CO_2Me) of **11s** as a singlet downfield (high chemical shift) at δ (3.66) and the **11a** was a singlet upfield (low chemical shift) at δ (3.62), due to the anisotropic shielding effect of the aromatic ring of the phenyl group attached to the succinimide derivatives. We attempted to further separate these diastereomers and confirmed the present of two diastereomers by using gas chromatography at different temperatures (250, 270^{o}C) and also with different retention times, but we obtained a broad peak which included a shoulder of the other diastereomer. HPLC was used for the separation of those diastereomeric mixture of **11s/11a,** unfortunately those diastereomeric mixture was enriched to each other.

The intermediate compounds **9s** and **9a** were also prepared via a different route as shown in (Scheme 2), by treatment of the 1-(chloroformyl) propane-2,3-dicarboxylic acid anhydride **12** with (*R*)-*a*-methylbenzylamine in the presence of DMA and CH_2Cl_2 at 0°C. The reaction mixture was vigorously stirred at room temperature overnight to provide a good yield of the crude product which was purified further by flash chromatography (2:1 Hexane:EtOAc) to afford the diastereoisomeric mixture in 60% yield.



i) Ac_2O / 24 hrs, RT; ii) AC_2O at 45 ^oC/1 h., AcOH at 60 ^oC/1 h.; iii) $SOCl_2$/refluxed for 48 hrs.; iv) (*R*)-(*a*)-methylbenzylamine, dry CH_2Cl_2, DMA, 0 ^oC

Scheme 2.

Experimental

General

^1H and ^{13}C NMR spectra were taken on an IBM NR-200 or IBM NR-300-AF spectrometer. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in hertz. ^1H-chemical shifts (300MHz) were referenced to the residual $CHCl_3$ signal (7.24). ^{13}C-chemical shifts (75 MHz) were referenced to $CDCl_3$ (77.0). Optical rotations were measured on a Perkin Elmer 1420 ratio recording spectrometer, 1-2% solution in $CHCl_3$. MPLC refers to medium pressure liquid chromatography (25-60 psi) using hand packed columns of E. Merck silica gel (230-400 mesh) and a Fluid Metering Inc. pump, an ISCO Model 2361 gradient programmer, and a differential refractive index detector (Waters R401). Flash column chromatography was performed as described by Still [10] using E. Merck silica gel (230-400 mesh). The R_f value reported for TLC analysis was determined on Macherey-Nagel 0.25 mm layer fluorescent UV_{254} plates with the indicated solvent system. Infrared IR spectra listed as recorded 'neat' refer to a thin film of material on NaCl disks. Infrared spectra were recorded on a MIDAC Prospect spectrometer. IR spectrum peaks are reported in cm^{-1}. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ) and the Central Lab.of Ain Shams University, Cairo, Egypt. Tandem gas chromatography/ low resolution mass spectrometry (GC/LRMS) using electron impact (EI) ionization was performed on a Hewlett-Packard 5890 series II gas chromatography and 5971A mass selective detector at 70 eV. Gas chromatography retention time is reported along with the capillary column configuration using the following convention: Column C = DB-5.6 m x 0.1 mm ID x 0.1 m film + 1 guard column with a 1 mL/in flow rate.

Propane-1,2,3-tricarboxylic Acid (1,2-Anhydride) **6**

Tricarballylic acid **5** (1.76 g, 0.01 mol) was dissolved in acetic anhydride (1.78 mL, 2.04 g, 0.02

mol). The reaction mixture was stirred overnight at room temperature, then excess acetic anhydride was removed under reduced pressure and the product was recrystallized twice from ethyl acetate to give of the title compound as a white micro-crystalline solid (1.37 g, 0.0087 mol, 77.8% yield) that had mp. 132-133°C, lit.[11]: 132-134°C. ^{1}H NMR**:** (200 MHz, acetone-d$_6$): δ 2.89 [dd, J = 2.6 and 18.2 Hz, 1H, RCHa-R'(ax)], 2.91 [dd, J = 6.6 and 18.6 Hz, 1H, RCHc-R'(ax)], 3.002 [dd, J = 5.4 and 18.2 Hz, 1H, RCHd-R'(eq)], 3.27 [dd, J = 10.4 and 18.2 Hz, 1H, RCHb-R'(eq)], 3.62 [dddd, J = 10.4, 6.6, 5.4, and 2.6 Hz, R-CH$_2$CHxCH$_2$-R'(eq)], 11.3 (s, R-CO$_2$H) ppm. ^{13}C NMR**:** (50 MHz, acetone-d$_6$): δ 176.7, 174.2, 173.4 , 38.2, 35.3 and 35.2 ppm. IR**:** (KBr pellet): 1727 (vs), 1790 (s), and 1833 (m) cm^{-1} Anal. Calcd for $C_6H_6O_5$: C, 45.58; H, 3.84; O, 50.59% Found: C, 45.55; H, 4.08.

1-(Chloroformyl)propane-2,3-dicarboxylic anhydride **12**

Propane-1,2,3-tricarboxylic acid (1,2-anhydride) **6** (0.01 mol) was refluxed with $SOCl_2$ (1 mol) for 48 hours. The $SOCl_2$ was evaporated and the residue distilled under reduced pressure. Purification of the fraction collected at b.p. 132-136°C (1.5 mmHg) required the use of a Buchi Kugelrohr apparatus which afforded the product which later crystallized from CH_2Cl_2 upon being cooled to room temperature to give the title product (1.58 g, 0.009 mol, 90% yield), m.p. 96-98°C, lit.[12] 97-98°C; ^{1}H NMR (200 MHz, acetone-d6): δ 2.63 (dd, J = 6.2 and 17 Hz, RCHa-R'), 2.80 (dd, J = 6.8 and 17 Hz, RCHc-R'), 3.07 (dd, J = 7.2 and 18.6 Hz, RCHd-R'), 3.33 (dd, J = 10 and 18.8 Hz, RCHb-R'), 3.86 (dddd, J = 6.2, 6.8, 7, and 10 Hz, RCH$_2$CHxCH$_2$-R') ppm. IR (KBr pellet); 1760 (vs) and 1835 (m) cm^{-1}. Anal. Calcd for $C_6H_5ClO_4$: C, 40.82; H, 2.85; Cl, 20.08; O, 36.25% Found: C, 45.55; H, 4.08; Cl, 20.93.

*3-Carboxypentane-1,5-dioic acid, mono-[1-(*R*)-(1-phenylethyl)]amide* **7**, *and 3-mono-[(*R*)-(1-phenylethyl)]amide pentane-1,5-dioic acid* **8**

Tricarballylic acid anhydride (TCA) **6** (47.4 mg, 0.3 mmol) was placed into an oven dried culture tube (25 mL r.b.), dissolved in dry THF (1.2 mL, 0.25 M), and then treated with (R)-(+)-α-methylbenzyl amine (46.4 μL, 43.6 mg, 0.36 mmol). The resulting solution was stirred overnight at room temperature. The solvent was removed under reduced pressure to give 84.3 mg (92% mass recovery) of a white sticky of diastereoisomer **7** and regioisomeric amides **8** as determined by ^{1}H NMR analysis and no attempt was made to purify this material further and isolate the diastereoisomers.

Compound **7**

^{1}H NMR (200 MHz, acetone-d6, from the mixture) : δ 1.43–1.40 (d, J = 7.0 Hz, 3H, Ar CHCH$_3$), 2.43–2.54 (m, 2H, RCH$_2$-CONH), 2.61-2.68 (m, 2H, RCH$_2$-CO$_2$H), 3.18-3.22 (m, 1H, RCH$_2$CHCH$_2$-R'), 5.03 (dq, J = 6.8 Hz, ArCH-), 5.34 (d, J = 7.23 Hz, -NH-), 7. 16-7.52 (m, 5H, Ph-H) ppm.

Compound **8**

^{1}H NMR (200 MHz, acetone-d6, from the mixture) : δ 1.62–1.59 (d, 3H, J = 6.8 Hz, Ar CHC<u>H</u>$_3$), 2.43–2.54 (m, 2H, RC<u>Ha</u><u>H</u>b-CO_2H), 2.61–2.68 (m, 2H, RC<u>Ha'H</u>b'-CO_2H), 3.2-3.3 (m, 1H, RC<u>H</u>R'), 5.0-5.08 [dq, J = 6.65 Hz, 1H, ArC<u>H</u>NHMe], 5.63 (d, J = 7.23 Hz, 1H, -<u>NH</u>-), 7.19-7.49 (m, Ph-H) ppm.

The mixture of compounds **7** and **8**, were placed into an oven dried melting point tube, fused (129-135ºC), solidified, and then transferred into the NMR tube. The diastereoisomers were determined by ^{1}H NMR analysis. The structural assignments were made by comparison of the spectral data of compounds **9s**/**9a** which were obtained by the reaction of tricarballylic anhydride acid chloride **12** with (*R*)-(+)-α-methylbenzyl amine. The ratio of the distereoisomers was ~1:1 according to the integration. No attempt was made to resolve the diastereoisomers further, m.p. 129-135^{o}C. The ^{1}H NMR spectra data was identical consistent with authentic samples **9s/9a** in all aspects.

1-[(R)-(a)-methylbenzylamido)formylpropane-(R)-2,3-dicarboxylic-anhydride **9s** *and 1-[(R)-(a)-methylbenzylamido)formylpropane-(S)-2,3-dicarboxylic anhydride* **9a**

Into an oven dried flask (50 mL r.b.) equipped with a stirring bar were placed tricarballylic anhydride acid chloride (85.7 mg, 0.5 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred until dissolution was complete. (R)-α–methylbenzylamine (60.5 mg, 0.5 mmol) and *N,N'*-dimethylaniline (DMA) (70 μL, 66.5 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) were added dropwise to the acid chloride solution at 0ºC with vigorous stirring. The reaction mixture was warmed slowly to RT and stirred overnight. The solvent was removed under reduced pressure, the residue dissolved in CH_2Cl_2, extracted three times with cooled dilute HCl (2 mol dm^{-3}), and several times with water. The organic layer was dried on Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. No attempts were made to purify this material. The compounds **9s** and **9a** were obtained as mixture of diastereoisomers in 1:1 ratio (NMR).

Compond **9s**

LRMS (EI): m/z 148 [M^+-113, (20)], 106 (20), 94 (20), 77 (25), 44 (100). ^{1}H NMR (200 MHz, acetone-d_6): δ 1.62 (d, J = 7.2 Hz, ArCHCH_3), 2.65 (dd, J = 6.39 and 16.93 Hz, RC<u>H</u>a-R'), 2.86 (dd, J = 6.86 and 16.90 Hz, RC<u>H</u>c-R'), 3.09 (dd, J = 7.13 and 18.59 Hz, RC<u>H</u>b-R'), 3.30 (dd, J = 9.75 and 18.54 Hz, RC<u>H</u>d-R'), 3.84 (dddd, J = 12.20, 7.31, 5.16, and 2.21 Hz, RCH_2<u>CHx</u>CH_2-R'), 5.37 (q, J = 7.20 and 14.36 Hz, ArC<u>H</u>-), 7.42 (m, Ar-H) ppm.; Cap gc; t_R = 7.21 min.; column: DB-5 5 m+ 1m guard ~1 mL / min.; gum temp prog: To = 50ºC / 2 min. / 20ºC $min.^{-1}$ / 250ºC / 5 min.

The ^{1}H NMR spectrum of **9a** was virtually the same as for **9s** with the following differences**.** δ 2.75 (dd, J = 9.76 and 17.90 Hz, RC<u>H</u>c-R'), 3.22 (dd, J = 9.93 and 18.42 Hz, RC<u>H</u>d-R') ppm. Anal. Calcd

for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; O, 24.49% Found: C, 64.03; H, 4.99; N, 5.01.

The solidified materials **9s/9a** were again melted at 158-160°C, and transferred into a NMR tube. The ^{1}H NMR spectral data was identical with those for compounds **10s** and **10a**. Tlc: R_f = 0.2 in 2:1:Hex:EtOAc. LRMS (EI): m/z 275 (M^+, (100), 260 (<3), 244 (20), 232 (55), 215 (20), 200 (15), 172 (20), 146 (40), 120 (65), 105 (100), 104 (100), 94 (12), 77 (60), 59 (75), and 41 (25). The compounds **10s** and **10a** were obtained as a diastereoisomeric mixture in 1.2:1 ratio (NMR). **(10s)** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, 1H, J = 8.5 Hz, Ar-H), 7.87 (d, 1H, J = 8.0 Hz, Ar-H), 7.80 (d, 1H, J = 1 and 7 Hz, Ar-Hp), 5.42 (dq, J = 7.5 Hz, Ar-CH-Me), 3.66 (s, RR'CHCOOCH_3)$_2$ 3.51 (dddd, J = 2.3, 3.6, 3.8, and 9.3 Hz, R_2CHCO$_2$Me), 2.99 (dd, J = 3.73 and 15.31 Hz, RCHaHbCONHCHAr), 2.9-2.75 (m, 2H, RCHaHbCOOMe), 2.47-2.44 (dd, J = 6.0 and 7.5 Hz, 2H, RCHcHdCONHAr), 2.43-2.41 (dd, J = 5.5 and 7.5 Hz, RCHcHdCONHAr), 1.827 -1.812 (d, J = 7.5 Hz, 3H, ArCH-Me) ppm. The ^{1}H NMR spectrum of **10a** was virtually the same as that for **10s** with the following differences: δ 3.62 (s, 3H, RCH$_2$COOMe) and 1.821-1.807 (d, J = 7.0 Hz, 3H, ArCH-CH_3) ppm.; Cap gc: t_R = 10.44 min.; column: DB-5 5mL = 1m guard ~ 1mL / min.; gum temp prog: To = 50°C / 2 min. / 20°C min.$^{-1}$ / 250°C / 5 min.

*(*R*)-2-Carboxymethyl*-N-*[(*R*)-1-(phenylethyl)succinimide* **11s** *and (*S*)-2-Carboxymethyl*-N-*[(*R*)-1-(phenylethyl)succinimide* **11a**

Diastereomeric acid mixture **10s/10a** (115 mg, 0.44 mmol) was dissolved or suspended in dry THF (1 mL). N,N'-dimethylformamide dimethylacetal (209 mg, 1.76 mmol, 0.5 mL) was added dropwise to the suspended solution within 20 min. The reaction mixture was allowed to stir overnight at room temperature and then the solvent was removed. The residue was washed with water (15 mL) and then the product was extracted with ethyl acetate, washed with saturated $NaHCO_3$ solution (2x10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$ anhydrous. The solvent was removed, to afford 110.5 mg of crude semi-oily product. The residue was purified by MPLC (with pure EtOAc) to provide the diastereoisomeric products **11s** and **11a** (95 mg, 0.35 mmol., 20 mole% and 82% yield). The material proved to be a 1.2:1 mixture of diastereoisomers according to ^{1}H NMR analysis. TLC; R_f = 0.2 in 2:1:Hex:EtOAc.; LRMS (EI): m/z 275 (M^+, (100), 260 (<3), 244 (20), 232 (55), 215 (20), 200 (15), 172 (20), 146 (40), 120 (65), 105 (100), 104 (100), 94 (12), 77 (60), 59 (75), and 41 (25).

Compound **11s**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.07 (d, 1H, J = 8.5 Hz, Ar-H), 7.87 (d, 1H, J = 8.0 Hz, Ar-H), 7.80 (d, 1H, J = 1 and 7 Hz, Ar-Hp), 5.42 (dq, J = 7.5 Hz, Ar-CH-Me), 3.66 (s, RR'CHCOOCH_3)$_2$ 3.51 (dddd, J = 2.3, 3.6, 3.8, and 9.3,Hz, R_2CHCO$_2$Me), 2.99 (dd, J = 3.73 and 15.31 Hz, RCHaHbCONHCHAr), 2.9-2.75 (m, 2H, RCHaHbCOOMe), 2.47-2.44 (dd, J = 6.0 and 7.5 Hz, 2H, RCHcHdCONHAr), 2.43-2.41 (dd, J = 5.5 and 7.5 Hz, RCHcHdCONHAr), 1.827 -1.812 (d, J = 7.5

Hz, 3H, ArCH-Me) ppm.

The ^{1}H NMR spectrum of **11a** was virtually the same as for **11s** with the following differences: δ 3.62 (s, 3H, RCH_2COOMe) and 1.821-1.807 (d, J = 7.0 Hz, 3H, ArCH-CH_3) ppm.; Cap gc: t_R = 10.44 min.; column: DB-5 5mL = 1m guard ~ 1mL / min; gum temp prog.: To = 50ºC / 2 min. / 20ºC min.$^{-1}$ / 250ºC / 5 min. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 66.44; H, 6.22; N, 5.09; O, 23.25% Found: C, 66.55; H, 6.09; N, 4.99.

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Sample Availability: Samples not available.