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ENANTIOSELECTIVE SYNTHESIS OF α -METHYLENE- γ -BUTYROLACTAMS USING *N*-*TERT*-BUTANESULFINAMIDES

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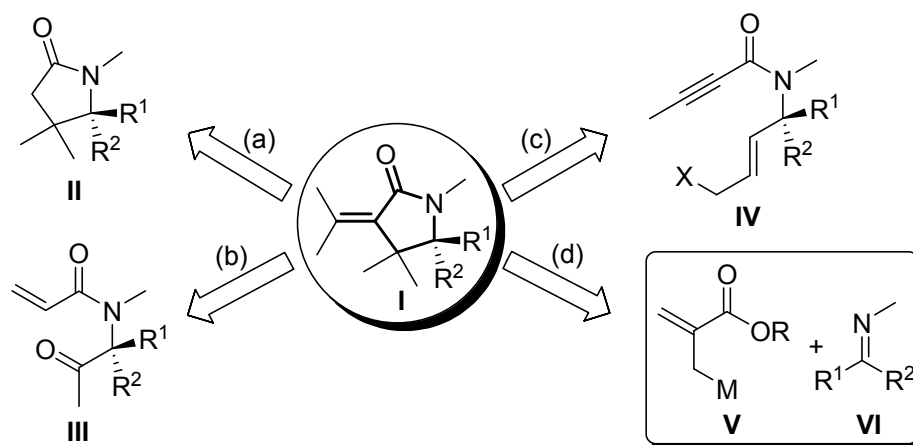
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Abstract – Indium-mediated coupling of ethyl 2-(bromomethyl)acrylate (**1**) and chiral *N*-*tert*-butanelsulfinylimines **2** in a saturated sodium bromide aqueous solution leads to *N*-*tert*-butanesulfinyl aminoesters **3** in high yields and diastereoselectivities. After column chromatography purification, enantiomerically pure aminoesters **3** were converted into the expected α -methylene- γ -butyrolactams **4** in a one-pot process.

INTRODUCTION

The development of synthetic methodologies which allow an easy access in a stereoselective fashion to α -methylene- γ -butyrolactams is of interest because many of them exhibit promising biological activities, and lower cytotoxicity when comparing with the corresponding, and more abundant in Nature, lactones.¹ Four main different strategies have been employed for the stereoselective synthesis of α -methylene- γ -butyrolactams of type **I** (Scheme 1): (a) α -methylenation of chiral γ -butyrolactams **II** under Horner–Wadsworth–Emmons conditions² or using the Bredereck reagent, followed, in this case by reduction with LiAlH_4 ;³ (b) intramolecular Baylis-Hillman coupling of chiral acrylamides **III**;⁴ (c) intramolecular cyclisation of amides of type **IV** promoted by transition metals, mostly Pd, in the presence of a chiral ligand;⁵ and (d) nucleophilic addition of allylic organometallic compounds of type **V**, derived from metacrylic acid (metacrylates and metacrylamides), to imine derivatives **VI**. Among organometallic compounds of type **V**, allylzinc intermediates⁶ are the most commonly used, along with allylboranes.⁷ Due to our interest in indium-promoted reactions,⁸ we report here the use of this metal for the stereoselective preparation of α -methylene- γ -butyrolactams⁹ from ethyl 2-(bromomethyl)acrylate (**1**) and chiral *N*-*tert*-butanelsulfinamides (**2**). These chiral electrophilic reagents have found high applicability in

synthesis¹⁰ due to the possibility of preparing their both enantiomers¹¹ and also because the chiral auxiliary can be easily removed under acidic conditions.¹² In addition, practical processes for recycling the *tert*-butanesulfinyl group upon deprotection of *N-tert*-butanesulfinylamines have been reported recently, making this chiral auxiliary of interest for large scale industrial processes.¹³



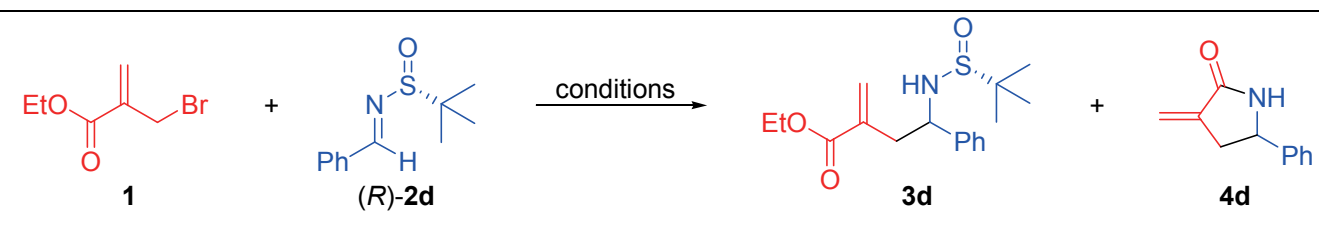
Scheme 1. General strategies for the stereoselective synthesis of α -methylene- γ -butyrolactams

RESULTS AND DISCUSSION

We first investigated the reaction conditions for the allylation of *N-tert*-butanesulfinamide (*R*)-**2d** by treatment with ethyl 2-(bromomethyl)acrylate (**1**) in the presence of indium metal. Based on our previous experience with indium-mediated allylation of these type of aldimines, we used 1.1 equiv of indium metal and 1.2 equiv of the allylic bromide, THF being the solvent of choice at 60 °C.^{8c-g} However, under these reaction conditions the allylation did not take place, even after 3 days (Table 1, entry 1). It was supposed that in these processes the formation of an allylindium intermediate¹⁴ was facilitated in aqueous media, although in the case of using a 1:1 water/THF mixture, hydrolysis of the starting aldimine **2d** occurred, yielding benzaldehyde and other reaction products derived from it (Table 1, entry 2). Regarding the temperature, although the reaction does not progress at 60 °C in THF while at 80 °C it takes 7 days to drive it to an only 15% conversion (Table 1, entry 3), complete conversion was achieved at 100 °C after 48 hours to give a mixture of the expected aminoester derivative **3d** and the butyrolactam **4d** in and 3:1 ratio (Table 1, entry 4).¹⁵ Under these reaction conditions, compound **3d** could partially cyclise to give α -methylene- γ -butyrolactam **4d**. Overall yields and selectivities were not improved when the allylation was performed at 100 °C in acetonitrile, *N,N*-dimethylformamide and toluene (Table 1, entries 5, 6 and 7, respectively), meanwhile in ethanol decomposition of aldimine **2d** occurred without formation of the expected aminoester derivative **3d** (Table 1, entry 8). Surprisingly, total conversion occurred when the reaction was carried out in a saturated aqueous sodium bromide solution in the presence of 4 equivalents

of indium at room temperature for 48 hours,¹⁶ and compound **3d** was the only isolated reaction product in 79% yield (Table 1, entry 9). On the other hand, a 46% yield was obtained when zinc was used instead of indium under the same reaction conditions (Table 1, entry 10).

Table 1. Optimization of the reaction conditions

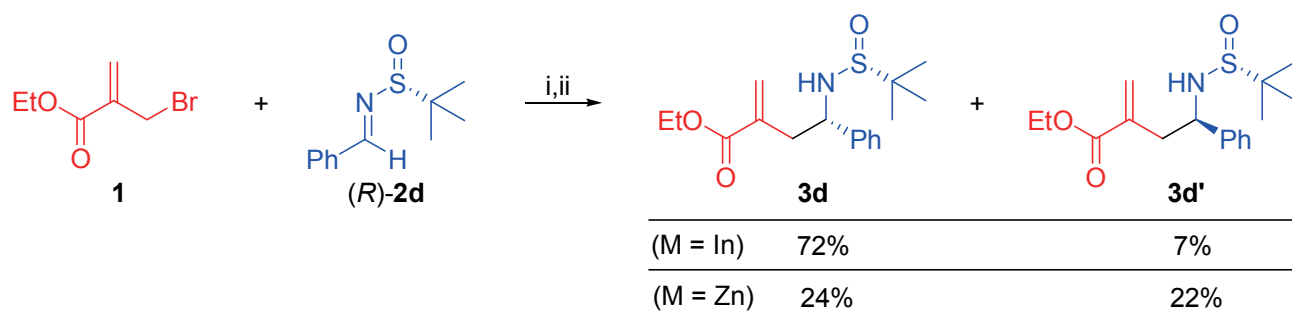


The reaction scheme shows the reaction of bromoester **1** (ethyl 2-bromo-3-methylacrylate) and aldimine **(R)-2d** (N-(2-phenylpropan-2-ylideneamino)acetamide) under various conditions to produce products **3d** (ethyl 2-(2-phenylpropan-2-ylideneamino)acrylate) and **4d** (2-phenylpropan-2-ylideneacetamide).

Entry	Conditions ^a	Conversion ^b	Reaction products (%) ^c	
			3d	4d
1	In (1.1 equiv), THF (2 mL), 60 °C, 72 h	0	--	--
2 ^d	In (1.1 equiv), THF:H ₂ O (2 mL, 1:1), 60 °C, 72 h	100	--	--
3	In (1.1 equiv), THF (2 mL), 80 °C, 168 h	15	15	--
4	In (1.1 equiv), THF (2 mL), 100 °C, 48 h	100	51	17
5	In (1.1 equiv), MeCN (1.5 mL), 100 °C, 48 h	100	35	43
6	In (1.1 equiv), DMF (1.5 mL), 100 °C, 48 h	88	32	12
7	In (1.1 equiv), PhMe (1.5 mL), 100 °C, 48 h	100	29	35
8 ^d	In (1.1 equiv), EtOH (1.5 mL), 100 °C, 48 h	100	--	--
9	In (4 equiv), saturated NaBr-H ₂ O (2 mL), 23 °C, 48 h	100	79	--
10	Zn (4 equiv), saturated NaBr-H ₂ O (2 mL), 23 °C, 48 h	86	46	--

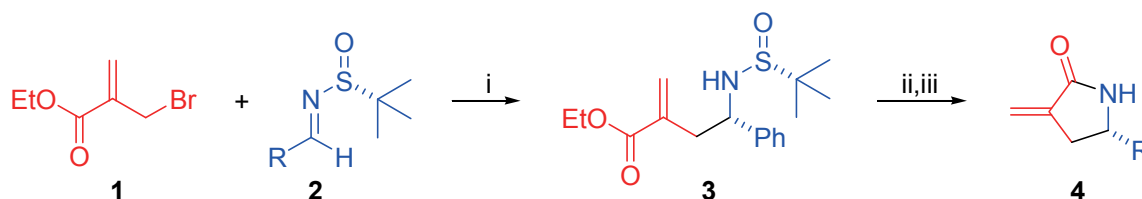
^a All the reactions were carried out using 0.2 mmol of aldimine **(R)-2d** and 0.25 mmol of bromoester **1**. ^b Conversion is given based on the disappearance of the starting **(R)-2d**. ^c Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **(R)-2d**. ^d Decomposition of the starting aldimine **(R)-2d** occurred.

Not only the yield but the stereoselectivity was considerable much higher in the case of using indium metal instead of zinc when the allylation was performed in a saturated aqueous sodium bromide solution. A diastereomeric mixture of aminoester derivatives **3d** and **3d'** was obtained in an almost 1:1 ratio with zinc, meanwhile diastereoselectivity was 91:1 with indium (Scheme 2). The diastereomeric ratio was easily determined by ¹H-NMR analysis of the crude reaction mixture paying attention to the integrals of the *t*-Bu group and the N-H of the diastereoisomers (the largest chemical shift difference has been always observed for the N-H).



Scheme 2. Reagents and conditions: (i) M (4 equiv), saturated NaBr-H₂O (2 mL), 23 °C, 48 h

The reaction of ethyl 2-(bromomethyl)acrylate (**1**) with different chiral *N*-sulfinyl aldimines **2** under the optimized conditions (Table 1, entry 9) led to compounds **3** in good yields (Scheme 3, Table 2) and diastereomeric ratios ranging between 86:14 and 95:5 (Table 2, entries 2 and 1, respectively). The major diastereomer was easily isolated after column chromatography and fully characterized in all cases. Finally, aminoester derivatives **3** were converted into butyrolactams **4** upon removal of the *tert*-butylsulfinyl by treatment first with a 4M HCl dioxane solution in methanol and then with sodium methoxide in methanol until basic pH. Yields were in all cases over 90% and ee ≥ 95% (Scheme 3 and Table 2).



Scheme 3. Reagents and conditions: (i) In (4 equiv), saturated NaBr-H₂O (2 mL), 23 °C, 48 h; (ii) HCl-dioxane, MeOH, 0 °C, 2 h; (iii) NaOMe/MeOH, 0 °C, 1 h

Regarding the configuration of the newly created stereogenic centre in the major diastereoisomer **3d** (Scheme 2) it was determined by comparing the specific rotation of **4d** $\{[\alpha]_D^{23} +14 (c 0.50, \text{CHCl}_3)\}$, which derived from **3d**, with that provided in the literature for (*R*)-3-methylene-5-phenylpyrrolidin-2-one $\{[\alpha]_D^{26} -17 (c 1.35, \text{CHCl}_3)\}$.^{6b} This result is consistent with an approach of the nucleophile, an allylindium sesquihalide of type **VII** (Figure 1), through a six-membered ring model **TSI** or **TSII** (Figure 1), with a four-membered metallacycle, in which the metal is chelated both by the oxygen and the nitrogen atoms of the imine moiety. We assume that the nucleophilic attack occurs predominantly to the *Si*-face of the imine unit for *R_S*-isomers (Table 1, entries 1-4) and to the *Re*-face in the case of *S_S*-derivatives (Table 1, entries 5-8). The stereochemical pathway under the reaction conditions described in Scheme 3 is the opposite to that obtained when the reaction is performed in THF at 100 °C as we have previously reported.¹⁵

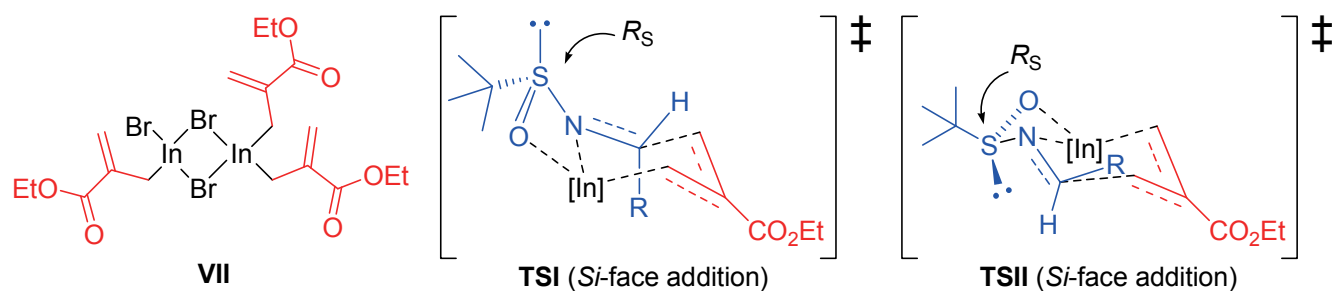


Figure 1. Proposed allylindium sesquihalide intermediate **VII** and possible transition state **PSI**

Table 2. Preparation of amino ester derivatives **3** and α -methylene- γ -butyrolactams **4**

Entry	Aldimine 2	Aminoester 3 ^a				Butyrolactam 4 ^{a,b}		
		No.	Structure	Yield (%) ^c	dr ^d	No.	Structure	Yield (%) ^c
1	(<i>R</i>)- 2a	3a		80	95:5	4a		92
2	(<i>R</i>)- 2b	3b		73	86:14	4b		91
3	(<i>R</i>)- 2c	3c		82	93:7	4c		94
4	(<i>R</i>)- 2d	3d		72	91:9	4d		93
5	(<i>S</i>)- 2a	3e		79	89:11	4e		93
6	(<i>S</i>)- 2b	3f		77	91:9	4f		90
7	(<i>S</i>)- 2c	3g		77	88:12	4g		95
8	(<i>S</i>)- 2d	3h		75	93:7	4h		92

^a All products were >95% pure (GLC and/or 300 MHz ¹H RMN). ^b ee ≥ 95%, as determined by HPLC using a Chiralcel OD-H column (conditions: hexane/isopropanol, 9:1; 0.5 mL/min). ^c Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **2**. ^d Ratio determined by ¹H-NMR analysis of the crude reaction mixture. ^e Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the aminoester **3**.

In conclusion, we have reported herein an enantioselective synthesis of α -methylene- γ -butyrolactams **4** from ethyl 2-(bromomethyl)acrylate (**1**) and chiral *N*-*tert*-butanesulfinyl aldimines **2**. The key step of the process is an indium promoted nucleophilic addition to the chiral imine. The resulting aminoesters **3** were purified by column chromatography and the major diastereoisomers converted in high yields in a one-pot process to the corresponding butyrolactam **4**.

EXPERIMENTAL

All chemicals were commercially available (Acros, Aldrich). TLC was performed on Merck silica gel 60 F₂₅₄, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Chromatographic purification was performed by flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and hexane/EtOAc as eluent. IR spectra were measured (film) with a Nicolet Impact 510 P-FT Spectrometer. Melting points were recorded on an OptiMelt (Stanford Research Systems) apparatus and reported without corrections. HPLC analyses were performed on a JASCO 200-series equipped with a Chiralcel OD-H column (conditions: hexane/isopropanol, 9:1; 0.5 mL/min). NMR spectra were recorded with a Bruker AC-300 or a Bruker ADVANCE DRX-500 using CDCl₃ as the solvent and TMS as internal standard. HRMS (EI) were recorded on a Finnigan MAT 95S.

Preparation of aminoesters **3**. General procedure.

A mixture of the corresponding aldimine **2** (0.5 mmol), ethyl 2-(bromomethyl)acrylate (**1**, 0.128 g, 0.65 mmol) and indium powder (0.226 g, 2.0 mmol) in a saturated aqueous NaBr solution (5 mL) was stirred for 48 h at 23 °C. Then, the resulting mixture was hydrolyzed with water (10 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous MgSO₄ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **3**. Yields, physical and spectroscopic data follow.

(4*R*,*R*_s)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylenedodecanoate (3a**):** Colourless oil; R_f 0.46 (hexane/EtOAc: 1/1); IR ν (film) 3223, 2924, 2855, 1715, 1627, 1464, 1364, 1303, 1150, 1053, 942 cm⁻¹; δ _H 0.88 (3H, t, *J* = 7.1 Hz, CH₃CH₂), 1.19 [9H, s, (CH₃)₃C], 1.31 (3H, t, *J* = 7.1 Hz, CH₃CH₂O), 1.25-1.50 (14H, m, 7×CH₂), 2.59 (2H, d, *J* = 6.2 Hz, CH₂CHNH), 3.40-3.44 (1H, m, CHNH), 3.52 (1H, d, *J* = 6.0 Hz, NH), 4.21 (2H, c, *J* = 7.1 Hz, CH₃CH₂O), 5.68 (1H, s, C=CHH), 6.30 (1H, s, C=CHH); δ _C 14.0, 14.1, (CH₃), 22.6 (CH₂), 22.65 (CH₃), 25.4, 29.1, 29.3, 29.4, 31.7, 35.4, 38.3 (CH₂), 55.2 (CH), 55.6 (C), 60.9 (CH₂), 128.0 (CH₂), 137.3 (C), 167.4 (CO); LRMS (EI) *m/z* 303 [M⁺-(CH₃)₂C=CH₂, 6%], 285 (19), 258 (11), 212 (100), 300 (17), 189 (72), 187 (76), 140 (14), 133 (22), 114 (28), 100 (33), 84 (23), 70 (30), 55 (18); [α]_D²⁰ -41 (c 1.43, CH₂Cl₂).

(4*S*,*R*_S)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-5-methyl-2-methylenehexanoate (3b): Colourless liquid; R_f 0.40 (hexane/EtOAc: 1/1); IR ν (film) 3274, 2959, 1713, 1628, 1465, 1366, 1315, 1153, 1057, 904 cm^{-1} ; δ_H 0.91 (3H, d, $J = 6.8$ Hz, CH_3CH), 0.92 (3H, d, $J = 6.9$ Hz, CH_3CH), 1.21 [9H, s, $(\text{CH}_3)_3\text{C}$], 1.31 (3H, t, $J = 7.1$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 1.83-1.90 (1H, m, CHCH_3), 2.48-2.51 (2H, m, $\text{CH}_2\text{C}=\text{CH}_2$), 3.26-3.33 (1H, m, CHNH), 3.56 (1H, d, $J = 5.5$ Hz, NH), 4.21 (2H, c, $J = 7.0$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 5.70 (1H, s, $\text{C}=\text{CHH}$), 6.31 (1H, s, $\text{C}=\text{CHH}$); δ_C 14.1, 17.3, 18.1, 22.7 (CH_3), 31.8 (CH), 34.7 (CH_2), 55.8 (C), 60.6 (CH), 61.0 (CH_2), 127.9 (CH_2), 137.7 (C), 167.6 (CO); LRMS (EI) m/z 233 [$\text{M}^+(\text{CH}_3)_2\text{C}=\text{CH}_2$, 23%], 215 (21), 186 (36), 172 (29), 142 (76), 123 (54), 100 (100), 94 (38), 72 (45), 57 (61); $[\alpha]_D^{20}$ -97 (c 0.70, CH_2Cl_2).

(4*R*,*R*_S)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-6-phenylhexanoate (3c): Colourless oil; R_f 0.34 (hexane/EtOAc: 1/1); IR ν (film) 3222, 3061, 3026, 2951, 1712, 1454, 1176, 1052, 699 cm^{-1} ; δ_H 1.23 [9H, s, $(\text{CH}_3)_3\text{C}$], 1.28 (3H, t, $J = 7.2$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 1.74-1.85 (2H, m, CH_2CHN), 2.59-2.80 (4H, m, PhCH_2 , $\text{CH}_2\text{C}=\text{CH}_2$), 3.46-3.52 (1H, m, CHNH), 3.67 (1H, d, $J = 5.5$ Hz, NH), 4.20 (2H, c, $J = 7.2$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 5.68 (1H, s, $\text{C}=\text{CHH}$), 6.30 (1H, s, $\text{C}=\text{CHH}$), 7.15-7.30 (5H, m, ArH); δ_C 14.1, 22.7 (CH_3), 31.8, 37.3, 38.3 (CH_2), 55.0 (CH), 55.8 (C), 61.0 (CH_2), 125.8, 128.2 (CH), 128.3 (CH_2), 128.4 (CH), 137.0, 141.6 (C), 167.4 (CO); LRMS (EI) m/z 295 [$\text{M}^+(\text{CH}_3)_2\text{C}=\text{CH}_2$, 4%], 277 (27), 204 (100), 181 (18), 117 (62), 91 (87), 65 (14); $[\alpha]_D^{20}$ -33 (c 0.98, CH_2Cl_2).

(4*S*,*R*_S)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-4-phenylbutanoate (3d): Colourless oil; R_f 0.29 (hexane/EtOAc: 1/1); IR ν (film) 3301, 3094, 3028, 2983, 1720, 1629, 1454, 1363, 1315, 1193, 1172, 1052, 916, 868, 698 cm^{-1} ; δ_H 1.19 [9H, s, $(\text{CH}_3)_3\text{C}$], 1.30 (3H, t, $J = 7.2$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 2.71 (1H, dd, $J = 14.1$, 7.9 Hz, $\text{CHHC}=\text{CH}_2$), 2.80 (1H, dd, $J = 14.1$, 6.2 Hz, $\text{CHHC}=\text{CH}_2$), 4.08 (1H, br s, NH), 4.19 (2H, c, $J = 7.2$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 4.59-4.64 (1H, m, CHNH), 5.52 (1H, s, $\text{C}=\text{CHH}$), 6.25 (1H, s, $\text{C}=\text{CHH}$), 7.26-7.33 (5H, m, ArH); δ_C 14.1, 22.6 (CH_3), 41.1 (CH_2), 55.5 (C), 57.7 (CH), 61.1 (CH_2), 127.5, 127.6, 128.3 (CH), 128.6 (CH_2), 136.6, 141.5 (C), 167.2 (CO); LRMS (EI) m/z 267 [$\text{M}^+(\text{CH}_3)_2\text{C}=\text{CH}_2$, 2%], 249 (21), 176 (100), 153 (69), 136 (16), 115 (12), 104 (35), 77 (28), 69 (21), 51 (16); $[\alpha]_D^{20}$ -101 (c 0.96, CH_2Cl_2).

(4*R*,*R*_S)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-4-phenylbutanoate (3d'): Colourless oil; R_f 0.32 (hexane/EtOAc: 1/1); IR ν (film) 3305, 3095, 3029, 2984, 1721, 1631, 1455, 1362, 1312, 1190, 1173, 1052, 915, 870, 697 cm^{-1} ; δ_H 1.19 [9H, s, $(\text{CH}_3)_3\text{C}$], 1.26 (3H, t, $J = 7.2$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 2.73 (1H, dd, $J = 13.8$, 7.3 Hz, $\text{CHHC}=\text{CH}_2$), 2.98 (1H, dd, $J = 13.8$, 7.3 Hz, $\text{CHHC}=\text{CH}_2$), 3.60 (1H, d, $J = 5.0$ Hz, NH), 4.12 (2H, c, $J = 7.2$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 4.54-4.59 (1H, m, CHNH), 5.45 (1H, s, $\text{C}=\text{CHH}$), 6.17 (1H, s, $\text{C}=\text{CHH}$), 7.28-7.33 (5H, m, ArH); δ_C 14.2, 22.6 (CH_3), 39.8 (CH_2), 56.1 (C), 58.9 (CH), 60.8 (CH_2), 127.5, 127.6, 128.3 (CH), 128.1 (CH_2), 136.9, 141.7 (C), 171.2 (CO); LRMS (EI) m/z 267 [$\text{M}^+(\text{CH}_3)_2\text{C}=\text{CH}_2$, 6%], 207 (14), 176 (12), 163 (15), 153 (100), 136 (22), 131 (19), 129 (16), 115 (15),

104 (35), 91 (13), 77 (16); $[\alpha]_{\text{D}}^{20} +17$ (c 0.35, CH_2Cl_2).

(4*S,S*)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylenedodecanoate (3e): Physical and spectroscopic data were found to be the same than for **3a**; $[\alpha]_{\text{D}}^{20} +38$ (c 0.78, CH_2Cl_2).

(4*R,S*)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-5-methyl-2-methylenehexanoate (3f): Physical and spectroscopic data were found to be the same than for **3b**; $[\alpha]_{\text{D}}^{20} +84$ (c 1.30, CH_2Cl_2).

(4*S,S*)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-6-phenylhexanoate (3g): Physical and spectroscopic data were found to be the same than for **3c**; $[\alpha]_{\text{D}}^{20} +33$ (c 0.34, CH_2Cl_2).

(4*R,S*)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-4-phenylbutanoate (3h): Physical and spectroscopic data were found to be the same than for **3d**; $[\alpha]_{\text{D}}^{20} +102$ (c 0.89, CH_2Cl_2).

Preparation of butyrolactams **4** from aminoesters **3**. General procedure.

To a solution of the corresponding aminoester **3** (0.2 mmol) in MeOH (1 mL) was added a 4M HCl dioxane solution (0.5 mL) at 0 °C. After 2 h stirring at the same temperature, a 2M NaOMe MeOH solution (2 mL) was added and the resulting mixture was stirred for 1 h at 0 °C. After that, it was hydrolyzed with water (10 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous MgSO_4 and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **4**. Yields, physical and spectroscopic data follow. (min)

(*R*)-3-Methylene-5-octylpyrrolidin-2-one (4a): White solid; mp 47-48 °C (pentane/ CH_2Cl_2); R_f 0.45 (hexane/EtOAc: 1/1); IR ν (film) 3176, 3090, 2916, 2849, 1697, 1659, 1466, 1396, 1307, 917 cm^{-1} ; δ_{H} 0.88 (3H, t, $J = 7.1$ Hz, CH_3CH_2), 1.19-1.34 (12H, m, $6 \times \text{CH}_2$), 1.41-1.48 (1H, m, CHH), 1.52-1.56 (1H, m, CHH), 2.39-2.45 (1H, m, $\text{CHHC}=\text{CH}_2$), 2.91-2.99 (1H, m, $\text{CHHC}=\text{CH}_2$), 3.60-3.66 (1H, m, CHNH), 5.32 (1H, s, $\text{C}=\text{CHH}$), 5.95 (1H, t, $J = 2.5$ Hz, $\text{C}=\text{CHH}$), 7.58 (1H, br s, NH); δ_{C} 14.0 (CH_3), 22.6, 25.4, 29.1, 29.4, 31.8, 33.0, 37.3 (CH_2), 51.4 (CH), 115.5 (CH_2), 139.7 (C), 170.7 (CO); LRMS (EI) m/z 209 (M^+ , 8%), 97 (14), 96 (100), 68 (11), 53 (25); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{23}\text{NO}$ 209.1780, found 209.1753; $[\alpha]_{\text{D}}^{20} +21$ (c 0.55, CH_2Cl_2); HPLC t_{ret} (min) 16.89.

(*S*)-5-Isopropyl-3-methylenepyrrolidin-2-one (4b): White solid; mp decomposed >300 °C (pentane/ CH_2Cl_2); R_f 0.27 (hexane/EtOAc: 1/1); IR ν (film) 3211, 2960, 2926, 2874, 1696, 1658, 1391, 1284, 1042, 807 cm^{-1} ; δ_{H} 0.90 (3H, d, $J = 7.0$ Hz, CH_3CH), 0.93 (3H, d, $J = 7.0$ Hz, CH_3CH), 1.65 (1H, heptet, $J = 6.7$ Hz, CHCH_3), 2.48-2.57 (1H, m, $\text{CHHC}=\text{CH}_2$), 2.85-2.95 (1H, m, $\text{CHHC}=\text{CH}_2$), 3.38-3.44 (1H, m, CHNH), 5.34 (1H, br s, $\text{C}=\text{CHH}$), 5.97 (1H, t, $J = 2.7$ Hz, $\text{C}=\text{CHH}$), 6.18 (1H, br s, NH); δ_{C} 17.8, 18.1 (CH_3), 30.6 (CH_2), 33.6, 56.9 (CH), 115.6 (CH_2), 139.5 (C), 170.6 (CO); LRMS (EI) m/z 96 [$\text{M}^+ - i\text{-Pr}$, 100%], 95 (17), 68 (11), 67 (14), 53 (36); HRMS (EI) calcd for $\text{C}_8\text{H}_{13}\text{NO}$ 139.0997, found 139.0982; $[\alpha]_{\text{D}}^{20} +3$ (c 0.46, CH_2Cl_2); HPLC t_{ret} (min) 20.26.

(R)-3-Methylene-5-(2-Phenylethyl)pyrrolidin-2-one (4c): White solid; mp 69-70 °C (pentane/CH₂Cl₂); R_f 0.36 (hexane/EtOAc: 1/1); IR ν (film) 3229, 3061, 3026, 2926, 1692, 1650, 1494, 1442, 1331, 1299, 1030, 936, 697 cm⁻¹; δ_{H} 1.74-1.95 (2H, m, CH₂CHN), 2.42-2.50 (1H, m, CHHC=CH₂), 2.61-2.76 (2H, m, PhCH₂), 2.92-3.02 (1H, m, CHHC=CH₂), 3.62-3.70 (1H, m, CHNH), 5.32 (1H, br s, C=CHH), 5.97 (1H, t, $J = 2.4$ Hz, C=CHH), 7.75 (1H, br s, NH); δ_{C} 31.8, 33.0, 38.9 (CH₂), 50.8 (CH), 115.8 (CH₂), 126.0, 128.3, 128.5 (CH), 139.4, 140.9 (C), 170.7 (CO); LRMS (EI) m/z 201 (M⁺, 21%), 132 (11), 123 (15), 117 (10), 110 (29), 103 (18), 97 (30), 96 (100), 91 (34), 77 (17), 65 (15), 53 (36); HRMS (EI) calcd for C₁₃H₁₅NO 201.1154, found 201.1142; $[\alpha]_{\text{D}}^{20} +25$ (c 0.53, CH₂Cl₂); HPLC t_{ret} (min) 43.84.

(S)-3-Methylene-5-phenylpyrrolidin-2-one (4d): White solid; mp 172-174 °C (pentane/CH₂Cl₂) [mp 191-192 °C (hexano/EtOAc)];^{6b} R_f 0.34 (hexane/EtOAc: 1/1); IR ν (film) 3184, 3094, 3028, 2923, 2852, 1696, 1657, 1452, 1337, 1282, 935, 763 cm⁻¹; δ_{H} 2.64-2.80 (1H, m, CHHC=CH₂), 3.26-3.36 (1H, m, CHHC=CH₂), 4.75 (1H, dd, $J = 8.1, 4.7$ Hz, CHNH), 5.38 (1H, br s, C=CHH), 6.06 (1H, t, $J = 2.7$ Hz, C=CHH), 6.55 (1H, br s, NH), 7.27-7.40 (5H, m, ArH); δ_{C} 36.8 (CH₂), 54.8 (CH), 116.6 (CH₂), 125.7, 128.1, 129.0 (CH), 138.6, 142.6 (C), 170.6 (CO); LRMS (EI) m/z 173 (M⁺, 100%), 172 (59), 144 (33), 128 (12), 104 (61), 96 (22), 78 (23), 77 (40), 68 (28), 51 (37); HRMS (EI) calcd for C₁₁H₁₁NO 173.0841, found 173.0848; $[\alpha]_{\text{D}}^{20} +14$ (c 0.50, CH₂Cl₂); HPLC t_{ret} (min) 36.92.

(S)-3-Methylene-5-octylpyrrolidin-2-one (4e): Physical and spectroscopic data were found to be the same than for **4a**; $[\alpha]_{\text{D}}^{20} -21$ (c 0.51, CH₂Cl₂); HPLC t_{ret} (min) 12.25.

(R)-5-Isopropyl-3-methylenepyrrolidin-2-one (4f): Physical and spectroscopic data were found to be the same than for **4b**; $[\alpha]_{\text{D}}^{20} -2$ (c 1.00, CH₂Cl₂); HPLC t_{ret} (min) 14.20.

(S)-3-Methylene-5-(2-Phenylethyl)pyrrolidin-2-one (4g): Physical and spectroscopic data were found to be the same than for **4c**; $[\alpha]_{\text{D}}^{20} -29$ (c 0.56, CH₂Cl₂); HPLC t_{ret} (min) 12.01.

(R)-3-Methylene-5-phenylpyrrolidin-2-one (4h): Physical and spectroscopic data were found to be the same than for **4d**; $[\alpha]_{\text{D}}^{20} -13$ (c 0.40, CH₂Cl₂); HPLC t_{ret} (min) 33.20.

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