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

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Abstract – Indium-mediated coupling of ethyl 2-(bromomethyl)acrylate (1) and chiral N-tert-butanesulfinylimines 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 LiAlH4;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 metacycramides), 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-butanesulfinamides (2). These chiral electrophilic reagents have found high applicability in

This paper is dedicated to Professor Dr. Albert Eschenmoser on occasion of his 85th birthday.
synthesis\textsuperscript{10} due to the possibility of preparing their both enantiomers\textsuperscript{11} and also because the chiral auxiliary can be easily removed under acidic conditions.\textsuperscript{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.\textsuperscript{13}

\begin{center}
\textbf{Scheme 1.} General strategies for the stereoselective synthesis of $\alpha$-methylene-$\gamma$-butyrolactams
\end{center}

\textbf{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 (I) 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.\textsuperscript{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 intermediate\textsuperscript{14} 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).\textsuperscript{15} Under these reaction conditions, compound 3d could partially cyclise to give $\alpha$-methylene-$\gamma$-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, 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conversion b</th>
<th>Reaction products (%) c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3d</td>
<td>4d</td>
</tr>
<tr>
<td>1</td>
<td>In (1.1 equiv), THF (2 mL), 60 °C, 72 h</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>2d</td>
<td>In (1.1 equiv), THF:H2O (2 mL, 1:1), 60 °C, 72 h</td>
<td>100</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>In (1.1 equiv), THF (2 mL), 80 °C, 168 h</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>In (1.1 equiv), THF (2 mL), 100 °C, 48 h</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>In (1.1 equiv), MeCN (1.5 mL), 100 °C, 48 h</td>
<td>100</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>In (1.1 equiv), DMF (1.5 mL), 100 °C, 48 h</td>
<td>88</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>In (1.1 equiv), PhMe (1.5 mL), 100 °C, 48 h</td>
<td>100</td>
<td>29</td>
</tr>
<tr>
<td>8d</td>
<td>In (1.1 equiv), EtOH (1.5 mL), 100 °C, 48 h</td>
<td>100</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>In (4 equiv), saturated NaBr-H2O (2 mL), 23 °C, 48 h</td>
<td>100</td>
<td>79</td>
</tr>
<tr>
<td>10</td>
<td>Zn (4 equiv), saturated NaBr-H2O (2 mL), 23 °C, 48 h</td>
<td>86</td>
<td>46</td>
</tr>
</tbody>
</table>

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 considerably 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).
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 \( \geq 95\% \) (Scheme 3 and Table 2).

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 \( \{[\alpha]_D^{26} -17 (c 1.35, \text{CHCl}_3)\} \). This result is consistent with an approach of the nucleophile, an allylindium sesquisihalide 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 \(^\circ\)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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldimine 2 No.</th>
<th>Aminoester 3</th>
<th>Yield (%)</th>
<th>dr</th>
<th>Butyrolactam 4</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-2a 3a</td>
<td>EtO₂C HN</td>
<td>80</td>
<td>95:5</td>
<td>4a</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>(R)-2b 3b</td>
<td>EtO₂C HN</td>
<td>73</td>
<td>86:14</td>
<td>4b</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>(R)-2c 3c</td>
<td>EtO₂C HN</td>
<td>82</td>
<td>93:7</td>
<td>4c</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>(R)-2d 3d</td>
<td>EtO₂C HN</td>
<td>72</td>
<td>91:9</td>
<td>4d</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>(S)-2a 3e</td>
<td>EtO₂C HN</td>
<td>79</td>
<td>89:11</td>
<td>4e</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>(S)-2b 3f</td>
<td>EtO₂C HN</td>
<td>77</td>
<td>91:9</td>
<td>4f</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>(S)-2c 3g</td>
<td>EtO₂C HN</td>
<td>77</td>
<td>88:12</td>
<td>4g</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>(S)-2d 3h</td>
<td>EtO₂C HN</td>
<td>75</td>
<td>93:7</td>
<td>4h</td>
<td>92</td>
</tr>
</tbody>
</table>

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-butanesulfanyl 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 (condition: 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.


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.

(4R,R5)-Ethyl N-(tert-butylsulfanyl)-4-amino-2-methyleneundecanoate (3a): Colourless oil; Rf 0.46 (hexane/EtOAc: 1/1); IR ν (film) 3223, 2924, 2855, 1715, 1646, 1364, 1303, 1150, 1053, 942 cm⁻¹; δH 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); δC 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 (12), 114 (28), 100 (33), 84 (23), 70 (30), 55 (18); [α]D20 -41 (c 1.43, CH2Cl2).
(4S,R S)-Ethyl N-(tert-butyldisulfinyl)-4-amino-5-methyl-2-methylenehexanoate (3b): Colourless liquid; Rf 0.40 (hexane/EtOAc: 1/1); IR ν (film) 3274, 2959, 1713, 1628, 1465, 1366, 1315, 1153, 1057, 904 cm⁻¹; δ t 0.91 (3H, d, J = 6.8 Hz, CH₃CH), 0.92 (3H, d, J = 6.9 Hz, CH₃CH), 1.21 [9H, s, (CH₃)₃C], 1.31 (3H, t, J = 7.1 Hz, CH₂CH₂O), 1.83-1.90 (1H, m, CH=CH₂), 2.48-2.51 (2H, m, CH₂C=CH₂), 3.26-3.33 (1H, m, C=CH₂), 3.56 (1H, d, J = 5.5 Hz, NH), 4.21 (2H, c, J = 7.0 Hz, CH₂CH₂O), 5.70 (1H, s, C=CHH), 6.31 (1H, s, C=CHH); δ: 14.1, 17.3, 18.1, 22.7 (CH₃), 31.8 (CH), 34.7 (CH₂), 55.8 (CH), 60.6 (CH), 61.0 (CH₂), 127.9 (CH₂), 137.7 (C), 167.6 (CO); LRMS (EI) m/z 233 [M⁺-(CH₃)₂C=CH₂, 23%], 215 (21), 186 (36), 172 (29), 142 (76), 123 (54), 100 (100), 94 (38), 72 (45), 57 (61); [α]D²⁰ -97 (c 0.70, CH₂Cl₂).

(4R,R S)-Ethyl N-(tert-butyldisulfinyl)-4-amino-2-methylene-6-phenylhexanoate (3c): Colourless oil; Rf 0.34 (hexane/EtOAc: 1/1); IR ν (film) 3222, 3061, 3026, 2951, 1712, 1454, 1176, 1052, 699 cm⁻¹; δ t 1.23 [9H, s, (CH₃)₃C], 1.28 (3H, t, J = 7.2 Hz, CH₂CH₂O), 1.74-1.85 (2H, m, CH₂CHN), 2.59-2.80 (4H, m, PhCH₂, CH₂C=CH₂), 3.46-3.52 (1H, m, C=CH₂), 3.67 (1H, d, J = 5.5 Hz, NH), 4.20 (2H, c, J = 7.2 Hz, CH₂CH₂O), 5.68 (1H, s, C=CHH), 6.30 (1H, s, C=CHH), 7.15-7.30 (5H, m, ArH); δ: 14.1, 22.7 (CH₃), 31.8, 37.3, 38.3 (CH₂), 55.0 (CH), 55.8 (C), 61.0 (CH₂), 125.8, 128.2 (CH), 128.3 (CH₂), 128.4 (CH), 137.0, 141.6 (C), 167.4 (CO); LRMS (EI) m/z 295 [M⁺-(CH₃)₂C=CH₂, 4%], 277 (27), 204 (100), 181 (18), 117 (62), 91 (87), 65 (14); [α]D²⁰ -33 (c 0.98, CH₂Cl₂).

(4S,R S)-Ethyl N-(tert-butyldisulfinyl)-4-amino-2-methylene-4-phenylbutanoate (3d): Colourless oil; Rf 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 t 1.19 [9H, s, (CH₃)₃C], 1.30 (3H, t, J = 7.2 Hz, CH₂CH₂O), 2.71 (1H, dd, J = 14.1, 7.9 Hz, CHH=CH₂), 2.80 (1H, dd, J = 14.1, 6.2 Hz, CHH=CH₂), 4.08 (1H, br s, NH), 4.19 (2H, c, J = 7.2 Hz, CH₂CH₂O), 4.59-4.64 (1H, m, CH=CH₂), 5.52 (1H, s, C=CHH), 6.25 (1H, s, C=CHH), 7.26-7.33 (5H, m, ArH); δ: 14.1, 22.6 (CH₃), 41.1 (CH₂), 55.5 (C), 57.7 (CH), 61.1 (CH₂), 127.5, 127.6, 128.3 (CH), 128.6 (CH₂), 136.6, 141.5 (C), 167.2 (CO); LRMS (EI) m/z 267 [M⁺-(CH₃)₂C=CH₂, 2%], 249 (21), 176 (100), 153 (69), 136 (16), 115 (12), 104 (35), 77 (28), 69 (21), 51 (16); [α]D²⁰ -101 (c 0.96, CH₂Cl₂).

(4R,R S)-Ethyl N-(tert-butyldisulfinyl)-4-amino-2-methylene-4-phenylbutanoate (3d'): Colourless oil; Rf 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 t 1.19 [9H, s, (CH₃)₃C], 1.26 (3H, t, J = 7.2 Hz, CH₂CH₂O), 2.73 (1H, dd, J = 13.8, 7.3 Hz, CHH=CH₂), 2.98 (1H, dd, J = 13.8, 7.3 Hz, CHH=CH₂), 3.60 (1H, d, J = 5.0 Hz, NH), 4.12 (2H, c, J = 7.2 Hz, CH₂CH₂O), 4.54-4.59 (1H, m, CH=CH₂), 5.45 (1H, s, C=CHH), 6.17 (1H, s, C=CHH), 7.28-7.33 (5H, m, ArH); δ: 14.2, 22.6 (CH₃), 39.8 (CH₂), 56.1 (C), 58.9 (CH), 60.8 (CH₂), 127.5, 127.6, 128.3 (CH), 128.1 (CH₂), 136.9, 141.7 (C), 171.2 (CO); LRMS (EI) m/z 267 [M⁺-(CH₃)₂C=CH₂, 6%], 207 (14), 176 (12), 163 (15), 153 (100), 136 (22), 131 (19), 129 (16), 115 (15),
104 (35), 91 (13), 77 (16); $[\alpha]_D^{20} +17$ (c 0.35, CH$_2$Cl$_2$).

(4S,S)-Ethyl $N$-(tert-butylsulfinyl)-4-amino-2-methyleneoctanoate (3c): Physical and spectroscopic data were found to be the same than for 3a; $[\alpha]_D^{20} +38$ (c 0.78, CH$_2$Cl$_2$).

(4R,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; $[\alpha]_D^{20} +84$ (c 1.30, CH$_2$Cl$_2$).

(4S,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; $[\alpha]_D^{20} +33$ (c 0.34, CH$_2$Cl$_2$).

(4R,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; $[\alpha]_D^{20} +102$ (c 0.89, CH$_2$Cl$_2$).

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 ºC. 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 ºC. After that, it was hydrolyzed with water (10 mL), extracted with EtOAc (3 x 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 ºC (pentane/CH$_2$Cl$_2$); R$_f$ 0.45 (hexane/EtOAc: 1/1); IR $\nu$ (film) 3176, 3090, 2916, 2849, 1697, 1659, 1466, 1396, 1307, 917 cm$^{-1}$; $\delta$$_H$ 0.88 (3H, t, $J$ = 7.1 Hz, C$_3$H$_7$CH$_2$), 1.19-1.34 (12H, m, 6xCH$_2$), 1.41-1.48 (1H, m, CHH), 1.52-1.56 (1H, m, CHH), 2.39-2.45 (1H, m, CHH=CH$_2$), 2.91-2.99 (1H, m, CHH=CH$_2$), 3.60-3.66 (1H, m, CHNH), 5.32 (1H, s, C=CHH), 5.95 (1H, t, $J$ = 2.5 Hz, C=CH$_2$), 7.58 (1H, br s, NH); $\delta$$_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 C$_{13}$H$_{23}$NO 209.1780, found 209.1753; $[\alpha]_D^{20} +21$ (c 0.55, CH$_2$Cl$_2$); HPLC $t_{ret}$ (min) 16.89.

(S)-5-Isopropyl-3-methylenepyrroolidin-2-one (4b): White solid; mp decomposed $>300$ ºC (pentane/CH$_2$Cl$_2$); R$_f$ 0.27 (hexane/EtOAc: 1/1); IR $\nu$ (film) 3211, 2960, 2926, 2874, 1696, 1658, 1391, 1284, 1042, 807 cm$^{-1}$; $\delta$$_H$ 0.90 (3H, d, $J$ = 7.0 Hz, CH$_3$CH), 0.93 (3H, d, $J$ = 7.0 Hz, CH$_3$CH), 1.65 (1H, heptet, $J$ = 6.7 Hz, CHCH$_3$), 2.48-2.57 (1H, m, CHHC=CH$_2$), 2.85-2.95 (1H, m, CHHC=CH$_2$), 3.38-3.44 (1H, m, CHNH), 5.34 (1H, br s, C=CHH), 5.97 (1H, t, $J$ = 2.7 Hz, C=CH$_2$), 6.18 (1H, br s, NH); $\delta$$_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 [(M$^+$-i-Pr), 100%], 95 (17), 68 (11), 67 (14), 53 (36); HRMS (EI) calcd for C$_{8}$H$_{13}$NO 139.0997, found 139.0982; $[\alpha]_D^{20} +3$ (c 0.46, CH$_2$Cl$_2$); HPLC $t_{ret}$ (min) 20.26.
(R)-3-Methylene-5-(2-Phenylethyl)pyrrolidin-2-one (4c): White solid; mp 69-70 °C (pentane/CH$_2$Cl$_2$); R$_f$ 0.36 (hexane/EtOAc: 1/1); IR $\nu$ (film) 3229, 3061, 3026, 2926, 1692, 1650, 1494, 1442, 1331, 1299, 1030, 936, 697 cm$^{-1}$; $\delta$H 1.74-1.95 (2H, m, C$_2$H$_2$CHN), 2.42-2.50 (1H, m, CHHC=CH$_2$), 2.61-2.76 (2H, m, PhCH$_2$), 2.92-3.02 (1H, m, CHNH), 5.32 (1H, br s, C=CHH), 5.97 (1H, t, J = 2.4 Hz, C=CH/H), 7.75 (1H, br s, NH); $\delta$C 31.8, 33.0, 38.9 (CH$_2$), 50.8 (CH), 115.8 (CH$_2$), 126.0, 128.3, 128.5 (CH), 139.2, 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 C$_{13}$H$_{15}$NO 201.1154, found 201.1142; $[\alpha]_D^{20}$ +25 (c 0.53, CH$_2$Cl$_2$); HPLC t$_{ret}$ (min) 43.84.

(S)-3-Methylene-5-phenylpyrrolidin-2-one (4d): White solid; mp 172-174 °C (pentane/CH$_2$Cl$_2$) [mp 191-192 °C (hexano/EtOAc)], R$_f$ 0.34 (hexane/EtOAc: 1/1); IR $\nu$ (film) 3184, 3094, 3028, 2923, 2852, 1696, 1657, 1452, 1337, 1282, 935, 763 cm$^{-1}$; $\delta$H 2.64-2.80 (1H, m, C$_2$H$_2$CH), 3.26-3.36 (1H, m, CH$_2$C=CH$_2$), 4.75 (1H, dd, J = 8.1, 4.7 Hz, CHNH), 5.38 (1H, br s, C=CH/H), 6.01 (1H, t, J = 2.7 Hz, C=CH/H), 6.55 (1H, br s, NH), 7.27-7.40 (5H, m, ArH); $\delta$C 36.8 (CH$_2$), 54.8 (CH), 116.6 (CH$_2$), 125.7, 128.1, 129.0 (CH), 138.6, 142.6 (C), 170.6 (CO); LRMS (EI) m/z 173 (M$^+$, 100%), 144 (33), 104 (61), 96 (22), 78 (23), 77 (40), 68 (28), 51 (37); HRMS (EI) calcd for C$_{11}$H$_{11}$NO 173.0841, found 173.0848; $[\alpha]_D^{20}$ +14 (c 0.50, CH$_2$Cl$_2$); 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; $[\alpha]_D^{20}$ -21 (c 0.51, CH$_2$Cl$_2$); 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; $[\alpha]_D^{20}$ -2 (c 1.00, CH$_2$Cl$_2$); 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; $[\alpha]_D^{20}$ -29 (c 0.56, CH$_2$Cl$_2$); 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; $[\alpha]_D^{20}$ -13 (c 0.40, CH$_2$Cl$_2$); HPLC t$_{ret}$ (min) 33.20.

ACKNOWLEDGEMENTS

This work was generously supported by the Spanish Ministerio de Educación y Ciencia (MEC; grant no. Consolider Ingenio 2010-CSD2007-00006 and CTQ-2007-65218) and the Generalitat Valenciana (grant no. PROMETEO/2009/039). H. K. D. thanks to the Generalitat Valenciana for a predoctoral fellowship (programa Santiago Grisolía). We also thank MEDALCHEMY S.L. for a gift of chemicals.
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