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Efficient Synthesis of β-Aryl-γ-lactams and Their Resolution with (S)-Naproxen: Preparation of (R)- and (S)-Baclofen

Iris J. Montoya-Balbás †, Berenice Valentín-Guevara †, Estefanía López-Mendoza †, Irma Linzagá-Elizalde *, Mario Ordoñez † and Perla Román-Bravo †

Received: 31 October 2015; Accepted: 2 December 2015; Published: 10 December 2015

Academic Editor: Derek J. McPhee

Centro de Investigaciones Químicas CIQ-IICBA, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, 62209 Cuernavaca, Morelos, Mexico; natzelane_k@hotmail.com (I.J.M.-B.); b.valentininguevara@gmail.com (B.V.-G.); fa_pple@hotmail.com (E.L.-M.); palacios@uaem.mx (M.O.); rperl@uaem.mx (P.R.-B.)

* Correspondence: linzagá@uaem.mx; Tel.: +52-777-329-7997
† These authors contributed equally to this work.

Abstract: An efficient synthesis of enantiomerically-pure β-aryl-γ-lactams is described. The principal feature of this synthesis is the practical resolution of β-aryl-γ-lactams with (S)-Naproxen. The procedure is based on the Michael addition of nitromethane to benzylidenemalonates, which was easily obtained, followed by the reduction of the γ-nitroester in the presence of Raney nickel and the subsequent saponification/decarboxylation reaction. The utility of this methodology was highlighted by the preparation of enantiomerically-pure (R)- and (S)-Baclofen hydrochloride.

Keywords: β-aryl-γ-lactams; Michael addition; resolution; (S)-naproxen; baclofen; phenibut

1. Introduction

γ-lactams have attracted considerable attention due to their fascinating properties and potential applications in many fields, especially in organic synthesis and medicinal chemistry [1–3]. In particular, enantiomerically-pure β-aryl-γ-lactams, such as the (R)-Rolipram 1, considered as a cyclic derivative of GABA, which has shown antipsychotic [4–6], antidepressive [7,8], anti-inflammatory, immunosuppressive, and antitumor activity. Additionally, the β-aryl-γ-lactams 2a and 2b are precursors for the synthesis of Phenibut 3 and Baclofen 4, two β-aryl-γ-amino butyric acids (GABA analogues), which are important biological active compounds Figure 1. Phenibut is used as a psychotrophic drug, anticonvulsant, antidepressant, and for its anti-neuropathic pain properties [9,10], whereas Baclofen is a GABAB receptor agonist and is marketed for the treatment of multiple neurological disorders, and acts as a muscle relaxant [11]. The biological activity of these compounds depends on its absolute configuration, and the (R)-enantiomer is much more active than the (S)-enantiomer [12–15]. Additionally, the β-aryl-γ-lactams are also important key intermediates for the synthesis of more complex compounds [1,16].

Due to the utility of β-aryl-γ-lactams as key synthetic intermediates for the synthesis of γ-amino acids [17] in conjunction with their biological activity, several methods have been reported for the synthesis of γ-lactams [18–22]; however, it is yet highly desirable to develop convenient and milder protocols for its preparation, especially with various substitution patterns and enantiomerically purity. In this paper, we report an efficient synthesis of a series of β-aryl-γ-lactams and its resolution by derivatization with (S)-Naproxen. The utility of this methodology was highlighted by the preparation of enantiomerically-enriched (R)- and (S)-Baclofen hydrochloride.
2. Results and Discussion

For the synthesis of the target β-aryl-γ-lactams (2a–f), we first carried out the Knoevenagel reaction of diethyl or methyl malonate with different aromatic aldehydes in toluene at reflux in the presence of a catalytic amount of piperidine, leading to the expected arylidenemalonates (5a–f) in 80% to 92% yield. The reaction proceeds efficiently with electron-rich and electron-withdrawing aromatic substituents. The Michael addition of nitromethane to arylidenemalonates (5a–f) in the presence of K₂CO₃ as a base in toluene at room temperature, furnished the γ-nitro derivatives 6a–f in 60% to 76% yield (Scheme 1) [23,24].

Catalytic hydrogenation of the nitro derivatives (6a–f) in the presence of catalytic amounts of Raney nickel at 60 psi proceeds efficiently to produce the racemic γ-lactams (7a–f) in 75% to 95% yield (Scheme 2).

Figure 1. Structures of γ-lactams and GABA derivatives used as pharmaceuticals.

Scheme 1. Preparation of nitro derivatives (6a–f).

Scheme 2. Catalytic reduction of γ-nitroesters 6a–f.
The racemic γ-lactams with trans-stereochemistry were obtained as major product, according to the coupling constants ($J = 10$ Hz) for the hydrogens H2 and H3. Additionally, suitable crystals for the γ-lactams 7c and 7e were obtained, which were subjected to X-ray analysis (Supplementary Materials) [25], in which it has been confirmed that the orientation of the hydrogens in C7 and C10 are in a trans relationship (Figure 2).

![X-ray structures of γ-lactams 7c (a) and 7e (b).](image)

Figure 2. X-ray structures of γ-lactams 7c (a) and 7e (b).

In the next step we carried out the hydrolysis and decarboxylation of the ester moiety, by treatment of (7a–f) with $1 \text{ N NaOH}$ in ethanol followed by the protonation, obtaining the carboxylic acids derivatives (8a–f) in 53% to 100% yield which, by heating in toluene, afforded the β-aryl-γ-lactams (2a–f) in excellent yield (Scheme 3).

![Scheme 3. Preparation of racemic γ-lactams (2a–f).](image)

With the racemic β-aryl-γ-lactams (2a–f) in hand, the next step was to explore the scope of (S)-Naproxen as a resolution agent [26–30]. For this purpose, and after several attempts using Et$_3$N/DMAP as base, we found that the reaction of the racemic β-phenyl-γ-lactam (2a) with lithium diisopropylamide (LDA) in dry tetrahydrofuran at $-78^\circ$C, followed by the addition of (S)-Naproxen acyl chloride 9 freshly prepared after reaction of (S)-Naproxen with oxalyl chloride, produced the imides (R,S)-10a and (S,S)-10a as a diastereoisomeric mixture which, by careful separation by column chromatography, afforded the diastereoisomerically pure imides (R,S)-10a as minor polar and (S,S)-10a as more polar in 26% and 27% yield, respectively. Under identical conditions, the resolution of the β-aryl-γ-lactams (2c–d) with 9, afforded the diastereoisomerically pure imides (R,S)-10b–d and (S,S)-10b–d in good yields (Scheme 4).
Subsequently removing the chiral agent in the diastereoisomerically-pure imides (R,S)-10a–d and (S,S)-10a–d was carried out using 1 N potassium hydroxide in THF to obtain the enantiomerically-pure β-aryl-γ-lactams (R)-2a–d and (S)-2a–d in excellent yield (Scheme 5). The absolute configuration of γ-lactams (R)-2a–b [(R)-2a: [α]_{D}^{20} – 19.21; (R)-2b: [α]_{D}^{20} – 24.2] and (S)-2a: [α]_{D}^{20} + 19.78; (S)-2b: [α]_{D}^{20} + 13.53 was assigned by comparing the sign of optical rotation with those reported in the literature [31–35]. The other β-aryl-γ-lactams showed similar characteristics in NMR and the configuration was also assigned by comparing the sign of optical rotation.

Scheme 4. Resolution of γ-lactams 2a–d with (S)-Naproxen.

Scheme 5. Preparation of enantiomerically-pure β-aryl-γ-lactams (R)- and (S)-2a–d.
Finally, the hydrolysis of the β-chlorophenyl-γ-lactam (R)-2b with 6N HCl, gave the (R)-baclofen hydrochloride 4 in 79% yield. Under identical conditions, the β-chlorophenyl-γ-lactam (S)-2b was transformed into (S)-Baclofen hydrochloride 4 in 97% yield (Scheme 6).

Scheme 6. Preparation of (R-) and (S)-Baclofen hydrochloride 4.

3. Materials and Methods

3.1. General Comments

Reagents were obtained from commercial suppliers and were used without further purification. Melting points were determined in a Fischer Johns apparatus (Pittsburgh, PA, USA) and are uncorrected. NMR spectra were recorded on Varian System instrument (Palo Alto, CA, USA), 400 MHz for ¹H and 100 MHz for ¹³C) and Varian Gemini 200 MHz, 200 MHz for ¹H and 50 MHz for ¹³C). The spectra were obtained in CD₃OD and CDCl₃ solution using TMS as an internal reference. High-resolution CI⁺ and FAB⁺ mass experiments were made in a JEOL HRMS-station JHRMS-700 (Akishima, Tokyo, Japan). X-ray diffraction studies were performed on a Bruker-APEX diffractometer (Madison, WI, USA) with a CCD area detector at 100 K (λMo Kα = 0.71073 Å, monochromator:graphite). Specific rotations were measured in a Perkin-Elmer 341 polarimeter (Shelton, CT, USA) at room temperature and λ = 589 nm. The purification of all compounds was carried out by column chromatography using silica gel 70-230. The dichloromethane was refluxed on phosphorous pentoxide and THF with sodium and benzophenone.

3.2. General Procedure for the Preparation of Arylidenemalonates 5a–f

A mixture of dialkyl malonate (1 eq.), toluene, aryl aldehyde (1 eq.), and 10 drops of piperidine, was refluxed for 48 h. Then, the reaction mixture was acidified to pH = 6–7 by addition of 1M HCl, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography. ¹H- and ¹³C-NMR data for the compounds 5a,d [36], 5b,c [37], are identical with those described in the literature.

3.2.1. Diethyl 2-(2-Chlorobenzylidene)malonate 5e

According to the general procedure, diethyl malonate (3.0 g, 18.7 mmol), toluene (35 mL), 2-chlorobenzaldehyde (2.63 g, 18.7 mmol), and piperidine were reacted. The crude product was purified by column chromatography using hexane/AcOEt (9:1) as eluent to afford 5e (4.2 g, 80%) as a slightly yellow liquid. IR (cm⁻¹): 2983, 1724, 1632, 1469, 1248, 1200, 756. ¹H-NMR (CDCl₃, 400 MHz) δ: 1.18 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 4.22 (q, J = 7.2 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 4.64 (q, J = 7.2 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 8.06 (s, 1H).
2H), 7.21–7.33 (m, 1H), 7.29–7.33 (m, 1H), 7.41–7.45 (m, 2H), 8.02 (s, 1H). $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ: 14.0, 14.3, 61.8, 61.9, 127.0, 129.1, 129.5, 130.0, 131.3, 132.3, 134.9, 139.4, 163.9, 165.9. MS (Cl$^+$): m/z 283 (10%), 237 (100%), 219 (12%), 173 (30%). HRMS (Cl): calculated for C$_{14}$H$_{16}$ClO$_4$ [M+H]$^+$, m/z 283.0737; found for [M + H]$^+$, m/z 283.0712.

3.2.2. Diethyl 2-(2-Nitrobenzylidene)malonate 5f

According to the general procedure, diethyl malonate (3.0 g, 18.7 mmol), toluene (35 mL), 2-nitrobenzaldehyde (2.82 g, 18.7 mmol), and piperidine were reacted. The crude product was recrystallized (hot EtOH) to give 5f as a white crystalline solid, m.p.: 64–66°C. HRMS (FAB): calculated for C$_{14}$H$_{16}$NO$_6$ [M + H]$^+$, m/z 294.0978; found for [M + H]$^+$, m/z 294.0959.

3.3. General Procedure for the Preparation of Nitroderivatives 6a–f

To a solution of arylidenemalonates 5a–f in toluene (20 mL) was added nitromethane (5.0 eq.) and potassium carbonate (1.7 eq.). The reaction mixture was stirred at room temperature for 48 h, and then the solvent was evaporated under reduced pressure. The crude product was treated with water (20 mL) and extracted with AcOEt (4 × 25 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, evaporated, and purified by column chromatography. $^1$H- and $^{13}$C-NMR data for the compounds 6a, 6b [38], 6c, d [39], 6e, f [23,40], are identical with those described in the literature.

3.4. General Procedure for the Synthesis of the $\gamma$-Lactams 7a–f

A mixture of 6a–f in MeOH (15 mL) and a catalytic amount of Ra-Ni was hydrogenated at room temperature for 2.5 h at 60 psi. The catalyst was filtered off in vacuum through Celite and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography or by recrystallization. $^1$H- and $^{13}$C-NMR data for the compound 7a was identical with those described in the literature [41].

3.4.1. Ethyl 2-Oxo-4-(4-chlorophenyl)-pyrrolidine-3-carboxylate (±)-7b

Following the general procedure, 6b (0.9 g, 2.8 mmol) was treated with Ra-Ni in MeOH. The crude product was recrystallized (hot EtOH) to give (±)-7b as a white solid (0.54 g, 75%), m.p.: 131–133°C. IR (cm$^{-1}$): 3193, 3095, 2953, 1740, 1701, 1518, 1158, 1196, 815. $^1$H-NMR (CDCl$_3$, 400 MHz) δ: 3.40 (ddd, J = 10.0, 8.4, 6.0 Hz, 1H), 3.54 (d, J = 10 Hz, 1H), 3.78–3.83 (m, 1H), 3.77 (s, 3H), 4.09 (dd, J = 18.0, 8.4 Hz, 1H), 7.20 (d, J = 8.8, 2H), 7.32 (d, J = 8.0, 2H), 7.43 (bs, 1H). $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ: 43.9, 47.8, 53.1, 55.3, 128.6, 129.4, 133.7, 138.3, 169.6, 172.7. ME (FAB$^+$): m/z 254 (60%), 235 (<10%), 222 (<10%), 176 (<10%), 154 (100%), 136 (65%), 107 (18%), 89 (15%), 77 (12%), 65 (<10%), 51 (<10%). HRMS (FAB) calculated for C$_{12}$H$_{13}$ClNO$_3$ (M + 1): 254.0584, found 254.0596.

3.4.2. Methyl 2-Oxo-4-(4-methylphenyl)-pyrrolidine-3-carboxylate (±)-7c

Following the general procedure, 6c (1.8 g, 6.09 mmol) was treated with Ra-Ni in MeOH. The crude product was recrystallized (CH$_2$Cl$_2$/hexane) to give (±)-7c as a beige solid (1.2 g, 87%), m.p.: 120–123°C. IR (cm$^{-1}$): 3186, 3095, 2953, 1742, 1701, 1518, 1158, 1196, 815. $^1$H-NMR (CDCl$_3$, 400 MHz) δ: 2.33 (s, 3H), 3.40 (dd, J = 17.6, 9.2 Hz, 1H), 3.57 (d, J = 9.2 Hz, 1H), 3.77–7.80 (m, 1H), 4.07 (ddd, J = 9.2, 9.2, 8.8 Hz, 1H), 7.15 (s, 4 H). $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ: 21.2, 44.2, 48.1, 53.0, 55.5, 127.1, 129.8, 136.9, 137.5, 169.9, 173.0. ME (Cl$^+$): m/z 234 (100%), 233 (5%), 202 (30%), 174 (30%). HRMS (Cl) calculated for C$_{13}$H$_{16}$NO$_3$ (M + 1): 234.1130, found 234.1136.
3.4.3. Methyl 2-Oxo-4-(3-methylphenyl)-pyrrolidine-3-carboxylate (±)-7d

According to the general procedure, 6d (0.8 g, 2.7 mmol) was hydrogenated in the presence of a catalytic amount of Ra-Ni in MeOH (15 mL). The crude product was recrystallized from hot EtOH, to give (±)-7d (0.56 g, 88%) as a white solid, m.p.: 105–109 °C. IR (cm⁻¹): 3208, 2948, 1739, 1694, 1433, 1167, 786, 775, 701. ¹H-NMR (CDCl₃, 400 MHz): δ: 2.34 (s, 3H), 3.40–3.44 (m, 1H), 3.60 (d, J = 9.6 Hz, 3H), 3.78 (dd, J = 17.6, 9.2 Hz, 1H), 3.79 (s, 3H), 4.07 (dd, J = 17.6, 8.4 Hz, 1H), 7.04–7.10 (m, 2H), 7.21–7.26 (m, 2H), 7.34 (bs, 1H). ¹³C-NMR (CDCl₃, 100 MHz): δ: 12.6, 40.4, 48.9, 53.0, 55.4, 124.2, 127.9, 128.5, 129.1, 138.9, 139.9, 169.8, 173.0. MS (FAB): calculated for C₂₄₈ (27%), 203 (28%), 175 (40%), 149 (100%), 132 (<10%), 113 (15%), 71 (35%), 57 (47%). HRMS (FAB) calculated for C₁₃H₁₇NO₃ [M + H]⁺, m/z 234.1130; found for [M + H]⁺, m/z 234.1135.

3.4.4. Ethyl 2-Oxo-4-(2-chlorophenyl)-pyrrolidine-3-carboxylate (±)-7e

According to the general procedure, 6e (1.2 g, 3.5 mmol) was hydrogenated in the presence of a catalytic amount of Ra-Ni in MeOH (18 mL). The crude product was recrystallized from hexane/CH₂Cl₂ mixture, to give (±)-7e (0.77 g, 83%) as a white solid, m.p.: 108–110 °C. IR (cm⁻¹): 3207, 3100, 2868, 1732, 1698, 1481, 1175, 1152, 757. ¹H-NMR (CDCl₃, 400 MHz): δ: 1.28 (t, J = 7.2 Hz, 3H), 3.40 (dd, J = 9.6, 7.6 Hz, 1H), 3.66 (d, J = 7.6 Hz, 1H), 3.92 (dd, J = 9.6, 8.8 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.52 (dd, J = 8.8, 7.6, 7.6 Hz, 1H), 7.21–7.33 (m, 3H), 7.39–7.41 (d, J = 7.6 Hz, 1H), 7.51 (bs, 1H). ¹³C-NMR (CDCl₃, 100 MHz): δ: 14.2, 41.4, 47.1, 54.1, 62.1, 127.6, 128.0, 129.0, 130.4, 134.1, 169.2, 173.0. MS (CI⁺): m/z 268 (100%), 267 (5%), 222 (45%), 194 (20%). HRMS (CI) calculated for C₁₃H₁₃ClNO₃ [M + H]⁺, m/z 268.0740; found for [M + H]⁺, m/z 268.0745.

3.4.5. Ethyl 2-Oxo-4-(2-aminophenyl)-pyrrolidine-3-carboxylate (±)-7f

According to the general procedure, 6f (0.7 g, 1.9 mmol) was hydrogenated in the presence of a catalytic amount of Ra-Ni in MeOH (15 mL). The crude product was recrystallized from Et₂O/CH₂Cl₂/hexane to give the trans-7f (0.40 g, 83%) as a white solid, m.p.: 102–105 °C. IR (cm⁻¹): 3458, 3352, 3210, 3105, 2956, 1721, 1701, 1470, 1178, 787. ¹H-NMR (CDCl₃, 400 MHz): δ: 1.27 (t, J = 7.2 Hz, 3H), 3.39 (m, 1H), 3.54 (d, J = 9.6 Hz, 3H), 3.76 (m, 1H), 3.98 (dd, J = 17.6, 8.4 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.59 (m, 3H), 7.11 (m, 1H), 7.24 (bs, 1H). ¹³C-NMR (CDCl₃, 100 MHz): δ: 14.3, 44.5, 47.9, 55.4, 62.0, 113.7, 114.4, 117.1, 130.1, 141.3, 147.2, 169.6, 173.1. MS (FAB⁺): m/z 249 (75%), 248 (27%), 203 (28%), 175 (40%), 149 (100%), 132 (<10%), 113 (15%), 71 (35%), 57 (47%). HRMS (FAB) calculated for C₁₃H₁₃N₂O₃ [M + H]⁺, m/z 249.1239; found for [M + H]⁺, m/z 249.1251.

3.5. General Procedure for The Preparation of the Carboxylic Acids 8a–f

To a suspension of 7a–f in ethanol (2 mL) was added 1 N NaOH (0.8 mL) was stirred at room temperature for 48 h. The ethanol was removed at reduced pressure and the residue was acidified with 1M HCl. The precipitate formed was filtered under vacuum.

3.5.1. 2-Oxo-4-phenyl-pyrrolidine-3-carboxylic Acid 8a

According to the general procedure, 7a (0.38 g, 1.7 mmol) was treated with 1 N NaOH (1.5 mL) to give 8a (0.31 g, 89%) as a white solid, m.p.: 158–162 °C. IR (cm⁻¹): 3283, 1686, 1489, 766, 703. ¹H-NMR (MeOD, 400 MHz): δ: 3.39 (dd, J = 9.2, 8.8 Hz, 1H), 3.58 (d, J = 10.0 Hz, 1H), 3.75 (dd, J = 9.2, 8.8 Hz, 1H), 4.01 (ddd, J = 10.0, 8.8, 8.8 Hz, 1H), 7.24–7.35 (m, 5H). ¹³C-NMR (MeOD, 100 MHz): δ: 46.4, 48.9, 56.9, 128.2, 128.6, 130.1, 141.6, 172.8, 175.1. MS (FAB⁺): m/z 206 (100%), 188 (20%), 154 (55%), 136 (38%), 107 (11%), 77 (14%). HRMS (FAB) calculated for C₁₁H₁₂NO₃ [M + H]⁺, m/z 206.0817, found for [M + H]⁺, m/z 206.0815.
3.5.2. 2-Oxo-4-(4-chlorophenyl)-pyrrolidine-3-carboxylic Acid 8b

According to the general procedure, 7b (0.2 g, 0.79 mmol) was treated with 1 N NaOH (0.8 mL) to give 8b (0.15 g, 82%) as a beige solid, m.p.: 140–142 °C. IR (cm⁻¹): 3283, 2932, 1724, 1686, 1511. 1H-NMR (MeOD, 400 MHz) δ: 3.32 (t, J = 9.6 Hz, 1H), 3.57 (d, J = 9.6 Hz, 1H), 3.75 (dd, J = 9.6, 8.8 Hz, 1H), 4.01 (t, J = 8.8 Hz, 1H), 7.32 (s, 4H). 13C-NMR (MeOD, 100 MHz) δ: 45.9, 48.7, 56.8, 130.0, 130.1, 134.4, 140.3, 172.7, 175.0. MS (FAB⁺): m/z 240 (98%), 222 (20%), 176 (10%), 154 (100%), 137 (70%), 107 (23%), 89 (22%), 77 (20%), 65 (<10%), 51 (<10%). HRMS calculated for C₁₁H₁₁ClNO₃ [M + H]⁺; m/z 240.0427; found for [M + H]⁺, m/z 240.0431.

3.5.3. 2-Oxo-4-(4-methylphenyl)-pyrrolidine-3-carboxylic Acid 8c

According to the general procedure, 7c (0.2 g, 0.85 mmol) was treated with 1 N NaOH (0.8 mL) to give 8c (0.17 g, 94%) as a white solid, m.p.: 166–169 °C. IR (cm⁻¹): 3255, 2964, 1738, 1667, 1488, 808. 1H-NMR (MeOD, 400 MHz) δ: 2.30 (s, 3H), 3.30–3.31 (m, 1H), 3.36 (t, J = 9.6 Hz, 1H), 3.57 (d, J = 9.6 Hz, 1H), 3.72 (t, J = 9.6 Hz, 1H), 3.93–4.00 (m, 1H), 7.12–7.20 (m, 4H). 13C-NMR (MeOD, 100 MHz) δ: 21.2, 46.1, 49.0, 56.0, 128.0, 128.8, 130.1, 130.5, 138.3, 172.8, 175.1. MS (CI⁺): m/z 219 (<10%), 202 (18%), 175 (100%), 145 (10%), 118 (85%), 91 (<10%). HRMS (CI⁺) calculated for C₁₂H₁₄NO₃ [M + H]⁺; m/z 220.0794; found for [M + H]⁺, m/z 220.0796.

3.5.4. 2-Oxo-4-(3-methylphenyl)-pyrrolidine-3-carboxylic Acid 8d

According to the general procedure, 7d (0.2 g, 0.85 mmol) was treated with 1 N NaOH (0.8 mL) to give 8d (0.18 g, 100%) as a white solid, m.p.: 173–177 °C. IR (cm⁻¹): 3332, 2891, 1731, 1666, 1427, 731, 686, 642. 1H-NMR (MeOD, 400 MHz) δ: 2.32 (s, 3H), 3.38 (dd, J = 10.0, 8.8 Hz, 1H), 3.56 (d, J = 10.0 Hz, 1H), 3.73 (dd, J = 10.0, 8.8 Hz, 1H), 3.97 (ddd, J = 10.0, 8.8, 8.8 Hz, 1H), 7.07–7.14 (m, 3H), 7.20–7.25 (m, 1H). 13C-NMR (MeOD, 50 MHz) δ: 21.6, 46.6, 48.9, 57.0, 125.3, 128.9, 129.3, 130.0, 141.5, 172.9, 175.3. MS (FAB⁺): m/z 220 (100%), 202 (37%), 154 (65%), 136 (55%), 89 (25%), 77 (23%), 57 (12%). HRMS (FAB⁺) calculated for C₁₂H₁₄ClNO₃ [M + H]⁺; m/z 220.0794; found for [M + H]⁺, m/z 220.0796.

3.5.5. 2-Oxo-4-(2-chlorophenyl)-pyrrolidine-3-carboxylic Acid 8e

According to the general procedure, 7e (0.2 g, 0.79 mmol) was treated with 1 N NaOH (0.8 mL) to give 8e (0.89 g, 53%) as a white solid, m.p.: 154–156 °C. IR (cm⁻¹): 3290, 2887, 1751, 1656, 1478, 760. 1H-NMR (MeOD, 400 MHz) δ: 3.61 (dd, J = 10.0, 7.6 Hz, 1H), 3.68 (d, J = 8.4 Hz, 1H), 3.85 (dd, J = 10.0, 8.4 Hz, 1H), 4.44–4.50 (m, 1H), 7.24–7.29 (m, 1H), 7.31–7.35 (m, 1H), 7.41–7.47 (m, 2H). 13C-NMR (MeOD, 50 MHz) δ: 43.1, 48.0, 55.6, 128.9, 129.3, 130.1, 131.2, 135.1, 138.9, 172.6, 174.9. MS (FAB⁺): m/z 240 (85%), 222 (25%), 154 (100%), 136 (80%), 107 (25%), 89 (26%), 77 (23%). HRMS calculated for C₁₂H₁₃ClNO₃ [M + H]⁺, m/z 240.0427; found for [M + H]⁺, m/z 240.0429.

3.5.6. 2-Oxo-(4-aminophenyl)-pyrrolidine-3-carboxylic Acid 8f

According to general procedure, 7f (0.2 g, 0.8 mmol) was treated with 1 N NaOH (0.8 mL) to give 8f (0.14 g, 80%) as a brown liquid. IR (cm⁻¹): 3366, 2883, 1674, 1493, 793. 1H-NMR (MeOD, 400 MHz) δ: 3.44 (dd, J = 9.6, 8.8 Hz, 1H), 3.63 (d, J = 10 Hz, 1H), 3.81 (dd, J = 9.6, 9.2 Hz, 1H), 4.08–4.12 (m, 1H), 7.34 (d, J = 7.2, 1H), 7.41 (s, 1H), 7.48–7.56 (m, 2H). 13C-NMR (MeOD, 100 MHz) δ: 45.9, 47.0, 56.6, 123.1, 123.2, 129.1, 132.0, 133.0, 144.3, 172.4, 174.6. MS (FAB⁺) m/z 220 (<10%), 203 (<10%), 176 (10%), 154 (100%), 136 (85%), 120 (12%) 107 (18%), 89 (<10%). HRMS (FAB⁺) calculated for C₁₁H₁₃N₂O₃ [M + H]⁺, m/z 221.0926; found for [M + H]⁺, m/z 221.0976.

3.6. General Procedure of the Synthesis of β-Aryl-γ-lactams (±)-2a–f

A suspension of carboxylic acid in toluene was heated to reflux for 5 h. After cooling to room temperature, the solvent was evaporated and the pure product was obtained. 1H- and 13C-NMR data for the compounds (±)-2a–c [42], are identical with those described in the literature.
3.6.1. 4-(3-Methylphenyl)-pyrrolidin-2-One (±)-2d

According to the general procedure 8d (0.15 g, 0.7 mmol) was refluxed to give (±)-2d (0.12 g, 100%) as a beige solid, m.p.: 103–104 °C. IR (cm⁻¹): 3211, 3095, 2892, 1677, 1498, 790, 706, 684. ¹H-NMR (CDCl₃, 200 MHz) δ: 2.35 (s, 3H), 2.49 (dd, J = 16.8, 8.6 Hz, 1H), 2.72 (dd, J = 16.8, 8.6 Hz, 1H), 3.41 (dd, J = 16.8, 8.6 Hz, 1H), 3.57–3.68 (m, 1H), 3.77 (dd, J = 16.8, 8.6 Hz, 1H), 7.03–7.08 (m, 2H), 7.19–7.27 (m, 2H). ¹³C-NMR (CDCl₃, 50 MHz) δ: 36.9, 37.3, 48.5, 127.2, 127.5, 128.4, 130.0, 133.9, 139.6, 178.0. MS (FAB) calculated for C₁₁H₁₄NO [M + H]^+, m/z 176.1075; found for [M + H]^+, m/z 176.1077.

3.6.2. 4-(2-Chlorophenyl)-pyrrolidin-2-One (±)-2e

According to general procedure, 8e (0.11 g, 0.46 mmol) was refluxed to give (±)-2e (80 mg, 86%) as a beige solid, m.p.: 112–115 °C. IR (cm⁻¹): 3174, 3080, 2884, 1686, 1486, 746. ¹H-NMR (CDCl₃, 200 MHz) δ: 2.48 (dd, J = 17.2, 7.4 Hz, 1H), 2.74 (dd, J = 17.2, 8.8 Hz, 1H), 3.41 (dd, J = 9.8, 6.2 Hz, 1H), 3.85 (dd, J = 9.8, 8.4 Hz, 1H), 4.18–7.25 (m, 1H), 7.33–7.34 (d, J = 8.8 Hz, 1H), 7.38–7.40 (d, J = 7.6 Hz, 2H). ¹³C-NMR (CDCl₃, 50 MHz) δ: 36.9, 37.3, 48.5, 127.2, 127.5, 128.4, 130.0, 133.9, 139.6, 178.0. MS (FAB) calculated for C₁₀H₁₂ClNO [M + H]^+, m/z 196.0529; found for [M + H]^+, m/z 196.0541.

3.6.3. 4-(2-Aminophenyl)-pyrrolidin-2-one (±)-2f

According to general procedure, 8f (0.2 g, 0.7 mmol) was refluxed in toluene for five hours to give (±)-2f (60 mg, 18%) as a beige solid, m.p.: 122–125 °C. IR (cm⁻¹): 3422, 3347, 3243, 2923, 1668, 1773, 1722, 1629, 1543, 1371, 1072, 777, 684. ¹H-NMR (CDCl₃, 200 MHz) δ: 2.84 (dd, J = 17.2, 7.4 Hz, 1H), 2.95 (dd, J = 17.2, 8.8 Hz, 1H), 3.41 (dd, J = 9.8, 6.2 Hz, 1H), 3.85 (dd, J = 9.8, 8.4 Hz, 1H), 4.18–7.25 (m, 1H), 7.03–7.08 (m, 2H), 7.19–7.27 (m, 2H). ¹³C-NMR (CDCl₃, 50 MHz) δ: 38.0, 40.3, 49.6, 113.4, 114.0, 117.0, 129.8, 143.6, 147.0, 178.4. MS (CI): m/z 177 (100%), 176 (78%) 160 (11%), 119 (45%). HRMS (CI) calculated for C₁₀H₁₃N₂O [M + H]^+, m/z 177.1028; found for [M + H]^+, m/z 177.1025.

3.7. Synthesis of (S)-Naproxen Acyl Chloride 9

To a solution of (S)-Naproxen (2.5 eq.) in anhydrous CH₂Cl₂ (15 mL) and N,N-dimethyl formamide (one drop), oxalyl chloride (3 eq.) at 0 °C was added. The reaction mixture was stirred at room temperature for 2.5 h under a nitrogen atmosphere, and after this time, the solvent and residual oxalyl chloride were removed under reduced pressure to continue the reaction, obtaining the (S)-Naproxen acyl chloride 9, which was not isolated and used immediately in the next reaction.

3.8. General Procedures for The Resolution of β-Aryl-γ-lactams (±)-2a–d

A solution of 8a–d (1 eq.) in anhydrous tetrahydrofuran (10 mL) was added dropwise to a freshly prepared LDA (1.1 eq.) at −78 °C. The reaction mixture was stirred for 30 min at room temperature under a nitrogen atmosphere. Then, the mixture was cooled to −78 °C followed by the addition of crude (S)-9. The reaction mixture was allowed to room temperature and stirred for 2 h under a nitrogen atmosphere. After, a saturated solution of ammonium chloride was added and extracted with dichloromethane (3 × 15 mL). Finally the solvent was removed under reduced pressure and purified by column chromatography, to obtain the diastereoisomeric pure (R,S)- and (S,S)-imides 10a–d.

3.8.1. (R)-1-((S)-2-(6-Methoxynaphth-2-yl)propionyl)-4-phenyl-pyrrolidin-2-one (R,S)-10a and (S)-1-((S)-2-(6-methoxynaphth-2-yl)propionyl)-4-phenyl-pyrrolidin-2-one (S,S)-10a

According to the general procedure, the reaction of 8a (50 mg, 0.31 mmol) with LDA (39 mg, 0.37 mmol) and (S)-9 (190 mg, 0.77 mmol), followed by purification in column chromatography using
hexane/AcOEt (90:10), afforded the diastereoisomers (R,S)-10a (30 mg, 26%) and (S,S)-10a (31 mg, 27%), both as an amber liquid.

(R,S)-10a: [α]D20 + 87.13 (c 0.95, CHCl3). IR (cm⁻¹): 2933, 1734, 1685, 1604, 1482, 1190, 760, 698.

1H-NMR (CDCl3, 400 MHz) δ: 1.57 (d, J = 7.2 Hz, 3H), 2.76 (dd, J = 17.6, 10.4 Hz, 1H), 2.84 (dd, J = 17.6, 8.4 Hz, 1H), 3.38 (dddd, J = 10.4, 8.8, 8.4, 8.4 Hz, 1H), 3.79 (dd, J = 12.0, 8.8 Hz, 1H), 3.91 (s, 3H), 4.19 (dd, J = 12.0, 8.4 Hz, 1H), 5.25 (q, J = 7.2 Hz, 1H), 7.11–7.20 (m, 4H), 7.25–7.29 (m, 1H), 7.29–7.36 (m, 2H), 7.48–7.51 (m, 1H), 7.70–7.75 (m, 3H). 13C-NMR (CDCl3, 100 MHz) δ: 19.4, 35.8, 41.1, 44.7, 52.5, 55.3, 105.6, 118.9, 126.6, 126.7, 127.0, 127.1, 127.4, 129.0, 129.4, 133.7, 136.2, 140.3, 157.6, 173.4, 175.4. MS (Cl⁺): m/z 374 (100%), 373 (38%) 212 (70%), 185 (23%), 162 (18%). HRMS (CI) calculated for C24H34ClNO3 [M + H]+, m/z 408.1366; found for [M + H]+, m/z 408.1383.

According to the general procedure, the reaction of 8c (0.2 g, 1.14 mmol) with LDA (0.14 g, 1.37 mmol) and (S)-9 (0.709 g, 2.85 mmol), followed by purification in column chromatography using hexane/AcOEt (90:10), afforded the diastereoisomers (R,S)-10c (0.21 g, 49%) as a colorless liquid, and (S,S)-10c (0.19 g, 44%) as a beige solid, m.p.: 61–64 °C.
3.8.4. (R)-1-((S)-2-(6-Methoxynaphth-2-yl)propionyl)-4-(3-methylphenyl)-pyrrolidin-2-one (R,S)-10d and (S)-1-((S)-2-(6-Methoxynaphth-2-yl)propionyl)-4-(3-methylphenyl)-pyrrolidin-2-one (S,S)-10d

According to the general procedure, the reaction of 8d (50 mg, 0.28 mmol) with LDA (36 mg, 0.34 mmol) and (S)-9 (0.17 g, 0.7 mmol), followed by purification in column chromatography using hexane/ACOEt (90:10), afforded the diastereoisomers (R,S)-10d (33 mg, 31%) and (S,S)-10d (30 mg, 28%), both as an amber liquid.

(R,S)-10d: \([\alpha]_D^{20} + 87.14\) (c 0.95, CHCl₃). IR (cm⁻¹): 2931, 1735, 1686, 1604, 1482, 1198, 727, 701, 672. ¹H-NMR (CDCl₃, 400 MHz) δ: 1.55 (d, J = 7.2 Hz, 3H), 2.33 (s, 3H), 2.75 (dd, J = 17.6, 10.4 Hz, 1H), 3.78 (dd, J = 10.4, 4.8 Hz, 1H), 3.90 (s, 3H), 4.19 (dd, J = 7.2 Hz, 1H), 6.74–7.14 (m, 4H), 7.68–7.73 (m, 3H). ¹³C-NMR (CDCl₃, 100 MHz) δ: 19.3, 21.4, 35.7, 41.2, 44.7, 52.5, 55.3, 105.5, 118.9, 123.7, 126.6, 127.0, 128.1, 128.9, 129.4, 133.6, 136.2, 138.7, 140.2, 157.6, 173.6, 175.4. MS (CI⁺): m/z 388 (100%), 387 (45%) 212 (90%), 185 (25%), 176 (12%). HRMS (CI) calculated for C₂₅H₂₆NO₃ [M + H]⁺, m/z 388.1913; found for [M + H]⁺, m/z 388.1904.

(S,S)-10d: \([\alpha]_D^{20} + 83.53\) (c 0.8, CHCl₃). IR (cm⁻¹): 2931, 1734, 1686, 1604, 1482, 1197, 727, 701, 672. ¹H-NMR (CDCl₃, 400 MHz) δ: 1.55 (d, J = 7.2 Hz, 3H), 2.40 (s, 3H), 2.60 (dd, J = 17.6, 8.4 Hz, 1H), 2.91 (dd, J = 17.6, 8.4 Hz, 1H), 3.46 (m, 1H), 3.68 (dd, J = 12.0, 6.8 Hz, 1H), 3.91 (s, 3H), 4.31 (dd, J = 12.0, 8.0 Hz, 1H), 5.23 (q, J = 6.8 Hz, 1H), 6.74–7.14 (m, 4H), 7.68–7.73 (m, 3H). ¹³C-NMR (CDCl₃, 100 MHz) δ: 19.4, 21.2, 35.9, 41.3, 44.6, 52.5, 53.5, 105.5, 118.8, 123.4, 126.5, 127.0, 127.1, 127.9, 128.7, 129.4, 133.6, 136.0, 138.6, 140.1, 157.6, 173.6, 175.3. MS (CI⁺): m/z 388 (100%), 387 (45%) 212 (77%), 185 (20%), 176 (12%). HRMS (CI) calculated for C₂₅H₂₆NO₃ [M + H]⁺, m/z 388.1913; found for [M + H]⁺, m/z 388.1935.

3.9. General Procedure for the Preparation of Enantiomerically-Pure β-Aryl-γ-lactams 2a–d

To a solution of (R,S)-10a–d or (S,S)-10a–d in tetrahydrofuran (0.6 mL) was added 1 N KOH (0.3 mL) and the reaction mixture was stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure and extracted with CH₂Cl₂ (4 × 3 mL), the organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give the corresponding γ-lactams (R)-2a–d or (S)-2a–d.
3.9.1. (R)-4-Phenylpyrrolidin-2-one 2a

According to the general procedure (R,S)-10a (23 mg, 0.06 mmol) in THF (0.6 mL) was reacted with 1 N KOH (0.3 mL), to give (R)-2a (7 mg, 100%) as a white solid, m.p.: 84–86 °C. [α]D20 = 19.2 (c 0.9, CHCl3) [31]. 1H- and 13C-NMR data are identical to (±)-2a.

3.9.2. (S)-4-Phenylpyrrolidin-2-one 2a

According to the general procedure (S,S)-10a (20 mg, 0.056 mmol) in THF (0.6 mL) was reacted with 1 N KOH (0.3 mL) to give (S)-11a (8 mg, 95%) as a white solid, m.p.: 87–89 °C [43,44]. [α]D20 = 24.2 (c 1.15, CHCl3). 1H- and 13C-NMR data are identical to (R)-2a.

3.9.3. (R)-4-(Chlorophenyl)-pyrrolidin-2-one 2b

According to the general procedure (R,S)-10b (19 mg, 0.05 mmol) in THF (0.5 mL) was reacted with 1 N KOH (0.3 mL) to give (R)-11b (7 mg, 79%) as a white solid, m.p.: 102–105 °C. [α]D20 = 13.5 (c 0.9, CHCl3) [45]. 1H- and 13C-NMR data are identical to (±)-2b.

3.9.4. (S)-4-(Chlorophenyl)-pyrrolidin-2-one 2b

According to the general procedure (S,S)-10b (28 mg, 0.07 mmol) in THF (0.5 mL) was reacted with 1 N KOH (0.3 mL) to give (S)-2b (12 mg, 94%) as a white solid, m.p.: 99–101 °C. [α]D20 = 33.7 (c 0.95, CHCl3). IR (cm⁻¹): 3189, 2917, 1685, 804. 1H-NMR (CDCl3, 400 MHz) δ: 2.28 (s, 3H), 2.48 (dd, J = 17.2, 9.2 Hz, 1H), 2.71 (dd, J = 17.2, 8.4 Hz, 1H), 3.39 (dd, J = 9.2, 7.6 Hz, 1H), 3.66 (dd, J = 9.2, 8.4, 8.0, 7.6 Hz, 1H), 3.73–3.80 (m, 1H), 7.1 (s, 1H). 13C-NMR (CDCl3, 100 MHz): δ 21.2, 38.1, 40.2, 49.8, 126.8, 129.7, 137.0, 139.2, 177.9. MS (FAB⁺): m/z 176 (100%), 149 (25%), 113 (<10%), 73 (<10%), 57 (<10%). HRMS (FAB) calculated for C11H14NO [M + H]⁺, m/z 176.1075; found for [M + H]⁺, m/z 176.1083.

3.9.5. (R)-4-(Methylphenyl)-pyrrolidin-2-one 2c

According to the general procedure (R,S)-10c (30 mg, 0.06 mmol) in THF (0.6 mL) was reacted with 1 N KOH (0.3 mL) to give (R)-2c (12 mg, 98%) as a white solid, m.p.: 108–110 °C. [α]D20 = 33.7 (c 0.95, CHCl3). IR (cm⁻¹): 3189, 2917, 1685, 804. 1H-NMR (CDCl3, 400 MHz) δ: 2.28 (s, 3H), 2.48 (dd, J = 17.2, 9.2 Hz, 1H), 2.71 (dd, J = 17.2, 8.4 Hz, 1H), 3.39 (dd, J = 9.2, 7.6 Hz, 1H), 3.66 (dd, J = 9.2, 8.4, 8.0, 7.6 Hz, 1H), 3.73–3.80 (m, 1H), 7.1 (s, 1H). 13C-NMR (CDCl3, 100 MHz): δ 21.2, 38.1, 40.5, 49.7, 123.9, 127.7, 128.0, 128.9, 138.7, 142.3, 177.9. MS (FAB⁺): m/z 176 (100%), 147 (76%), 73.5 (58%), 57 (13%). HRMS (FAB) calculated for C11H13NOH [M + H⁺], m/z 176.1075; found for [M + H⁺], m/z 176.1043.

3.9.6. (S)-4-(Methylphenyl)-pyrrolidin-2-one 2c

According to the general procedure (S,S)-10c (26 mg, 0.054 mmol) in THF (0.6 mL) was reacted with 1 N KOH (0.3 mL) to give (S)-2c (11 mg, 100%) as a white solid, m.p.: 100–103 °C. [α]D20 = 30.3 (c 1.04, CHCl3). IR (cm⁻¹): 3191, 2918, 1685, 804. 1H-NMR (CDCl3, 200 MHz) δ: 2.33 (s, 3H), 2.47 (dd, J = 16.8, 7.8 Hz, 1H), 2.70 (dd, J = 16.8, 9.0 Hz, 1H), 3.38 (dd, J = 8.2, 6.6 Hz, 1H), 3.56–3.80 (m, 2H), 7.14 (s, 4H). 13C-NMR (CDCl3, 50 MHz): δ 21.6, 38.1, 40.5, 49.7, 123.9, 127.7, 128.0, 128.9, 138.7, 142.3, 177.9. MS (FAB⁺): m/z 176 (100%), 147 (76%), 73.5 (58%), 57 (13%). HRMS (FAB) calculated for C11H13NOH [M + H⁺], m/z 176.1075; found for [M + H⁺], m/z 176.1043.

3.9.7. (R)-4-(3-Methylphenyl)-pyrrolidin-2-one 2d

According to the general procedure (R,S)-10d (24 mg, 0.06 mmol) in THF (0.6 mL) was reacted with 1 N KOH (0.3 mL) to give (R)-2d (8 mg, 72%) as an amber liquid. [α]D20 = 20.0 (c 0.68, CHCl3). IR (cm⁻¹): 3228, 2922, 1686, 784, 700, 637. 1H-NMR (CDCl3, 200 MHz) δ: 2.35 (s, 3H), 2.50 (dd, J = 17.2, 9.0 Hz, 1H), 2.71 (dd, J = 17.2, 8.6 Hz, 1H), 3.41 (dd, J = 8.2, 6.6 Hz, 1H), 3.62–3.70 (m, 2H), 7.04–7.09 (m, 2H). 13C-NMR (CDCl3, 50 MHz): δ 21.6, 38.0, 40.4, 49.6, 123.9, 127.7, 128.0, 128.9, 138.7, 142.3, 177.9. MS (FAB⁺): m/z 176 (20%), 175 (15%), 145 (<10%), 131 (<10%), 118 (100%), 117 (30%), 91 (15%). HRMS (FAB) calculated for C11H14NO [M + H]⁺, m/z 176.1075; found for [M + H]⁺, m/z 176.1069.
3.9.8. (S)-4-(3-Methylphenyl)-pyrrolidin-2-one 2d

According to general procedure (S,S)-10d. (29 mg, 0.16 mmol) in THF (0.5 mL) was reacted with 1 N KOH (0.3 mL) to give (S)-2d (13 mg, 100%) as an amber liquid. \( [\alpha]_{D}^{20} + 17.5 \) (c 0.94, CHCl3). IR (cm\(^{-1}\)): 3222, 2919, 1682, 783, 699, 637. \( ^1\)H-NMR (CDCl3, 200 MHz) \( \delta \): 2.34 (s, 3H), 2.46 (dd, \( J = 16.8, 9.0 \) Hz, 1H), 2.69 (dd, \( J = 16.8, 8.6 \) Hz, 1H), 3.37 (dd, \( J = 8.6, 7.2 \) Hz, 1H), 3.53-3.76 (m, 2H), 6.66 (bs, 1H), 7.02–7.09 (m, 2H), 7.19–7.27 (m, 2H). \( ^{13}\)C-NMR (CDCl3, 50 MHz) \( \delta \): 21.6, 38.1, 40.5, 49.7, 123.9, 127.7, 128.0, 128.9, 138.7, 142.3, 177.9. MS (FAB\(^{+}\)): \( m/z \) 176 (20%), 175 (30%), 145 (<10%), 131 (<10%), 118 (100%), 117 (25%), 91 (12%). HRMS (FAB) calculated for C\(_{11}\)H\(_{14}\)NO \([M + H]\)^{+}, \( m/z \) 176.1075; found for \([M + H]\)^{+}, \( m/z \) 176.1076.

3.10. (R)-(−)-Baclofen Hydrochloride 4

The \( \gamma \)-lactam (R)-2b (7 mg, 0.03 mmol) and 6N HCl (2 mL) was refluxed for 3.5 h. After this time, the mixture reaction was concentrated in vacuum to afford (R)\(-12b (10 mg, 79%) as a colorless solid, m.p.: 190–192 °C. \( [\alpha]_{D}^{20} + 2.0 \) (c 0.6, H\(_2\)O) [31,45]. \( ^1\)H- and \( ^{13}\)C-NMR data are identical to those reported in the literature [46].

3.11. (S)-(−)-Baclofen Hydrochloride 4

The \( \gamma \)-lactam (S)-2b (18 mg, 0.09 mmol) and 6N HCl (2 mL) was refluxed for 5.0 h. After this time, the mixture reaction was concentrated in vacuum to afford (S)-4 (23 mg, 97%) as a white solid, m.p.: 188–189 [47]. \( [\alpha]_{D}^{20} + 2.9 \) (c 0.76, H\(_2\)O) [32,48]. \( ^1\)H- and \( ^{13}\)C-NMR data are identical to (S)-(−)-Baclofen hydrochloride [46].

4. Conclusions

In conclusion, we have demonstrated the utility of (S)-Naproxen as an excellent resolution agent of \( \beta \)-aryl-\( \gamma \)-lactams, which are easily obtained through four steps from diethyl or methyl malonate and the appropriate aromatic aldehyde. The utility of this methodology was highlighted by the preparation of enantiomerically-pure (R)- and (S)-Baclofen hydrochloride in excellent yields. Additionally, we anticipate that the use of this procedure could be used in the preparation of \( \beta \)-aryl-\( \gamma \)-lactams as key intermediates in the synthesis of compounds with important pharmacological properties.

Supplementary Materials: Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/20/12/19830/s1.

Acknowledgments: The authors thank CONACyT of México, for their financial support via Projects 181816, and Laboratorio Nacional de Estructura de Macromoléculas (LANEM) 251613. We thank to Blanca E. Domínguez-Mendoza and V. Labastida-Galván for the determination of the NMR spectra and HRMS. I.J.M-B. also thank CONACyT for a Graduate Scholarship.

Author Contributions: I.L.-E. and M.O. provided the concepts of the work, interpreted the results and prepared the manuscript, I.J.M.-B, B.V.-G., E.L.-M., carried out the experimental work and interpreted the results, P.R.-B., determined the X-ray structures. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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25. CCDC 1048102 and 1048101 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

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**Sample Availability:** Samples of the compounds are not available from the authors.

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