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Optimized Methodologies in Asymmetric Organic Synthesis Applying Microwaves

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Dedicated to the memory of Ernest L. Eliel, caring mentor and friend

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Abstract. The use of microwave heating is a valuable tool for synthetic chemists. Being able to reduce reaction times and to increase product yield, this methodology offers to organic chemists the potential to optimize reaction processes. Additionally, microwave-assisted reactions provide more environmentally friendly reaction conditions. In this report, we describe results in the optimization of several organic reactions employed in the synthesis of various chiral molecules such as heterocycles, β-amino acids, and β-peptides, among others.
Keywords: Microwaves, Reaction Optimization, Organocatalysts, β-amino Acids, β-peptides.

Resumen. El uso de calentamiento por microondas es una valiosa herramienta para los químicos sintéticos. Esta metodología permite reducir los tiempos de reacción e incrementar el rendimiento de los productos, lo que equivale a optimizar los procesos de interés. Aunado a esto, las reacciones asistidas por microondas son más amigables al medio ambiente. En este trabajo se describen algunos resultados obtenidos en la optimización de varias reacciones orgánicas utilizadas para la síntesis de diversas moléculas quirales tales como heterociclos, β-aminoácidos y β-péptidos, entre otros.
Palabras Clave: Microondas, optimización de reacción, organocatalizadores, β-aminoácidos, β-péptidos.

Introduction

Asymmetric synthesis has become a central field in basic and applied research, especially because of the increasing necessity to avoid the formation of racemic products in chiral drug elaboration. The search for strategies that lead to the improvement and optimization of the preparation of a chiral product, traditionally has included the evaluation of temperature, reaction times, addition of additives, and concentration effects, among other parameters. Nevertheless, there is presently a new parameter to be considered: the use of microwaves [1].

Since the first reports on the use of microwave heating in organic synthesis by Gedye [2] and Giguere [3], the number of works related to this procedure has therefore increased dramatically, therefore, several research groups are already using microwaves for fast reaction optimization and efficient synthesis of new compounds [4]. Microwave irradiation frequently gives rise to products of higher purity and with a considerable decrease in reaction time, which is of great advantage over conventional heating methods, so, this strategy has allowed the optimization of various synthetic processes [5].

In this sense, the advantages offered by microwave irradiation have been applied successfully on asymmetric organic synthesis. Thus, for example, microwaves have allowed the synthesis of unsymmetrical diketopiperazines [6], alkaloids [7] or β-carboline derivatives [8]. In equal form, several asymmetric reactions such as the asymmetric versions of Suzuki-Miyaura [9], Negishi [9], Mannich [10], aldol [11], conjugate additions [11], Diels-Alder [11], α-aminations [12], addition of alkylzinc to aldehydes [13] among others, have been optimized with this methodology. Nevertheless, microwave effects on the production of asymmetric molecules by means of reactions involving the addition, hydrolysis, reduction, esterification, and saponification of substrates has been less examined. Therefore, the primary target of this report is to illustrate the benefit of microwave irradiation in the preparation of various chiral derivatives.

Results and Discussion

(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]heptanes

Diazabicyclo[2.2.1]heptanes have emerged as an attractive framework in the area of asymmetric catalysis, mainly when acting as ligands. Some features of these compounds are their structural rigidity, the presence of two stereogenic centers, and suitable coordination sites, that render them as attractive analogs of the steroid sparteine [14]. The conventional route for the synthesis of (1*S*,4*S*)-2,5-diazabicyclic derivatives described by Portoghese [15a] and Braish [15b] involves tosylation of the amino group in the (*S*)-*trans*-4-hydroxyproline **1**, followed by reduction of the carboxylic acid fragment with sodium borohydride. The subsequent tosylation of the two hydroxyl groups with *p*-toluenesulfonyl chloride and cyclization by treatment with a primary amine generates the corresponding heterocycles **5** (Scheme 1) [16].

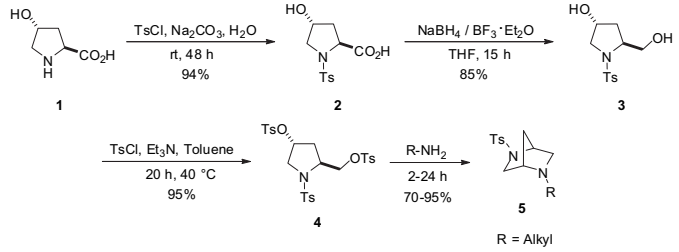
The long reaction times required for the synthesis of **5** (cf. Scheme 1) motivated the search for alternative strategies; indeed, the use of microwave irradiation turned out to be an ideal option. Thus, the first and final steps were optimized with microwave irradiation: the tosylation of the amino group

in **1** was realized in 30 min instead of 48 h and the cyclization step was carried out in 30-90 min instead of 2-24 h. Desired **5a-c** derivatives were obtained in good overall yields (Scheme 2) [14].

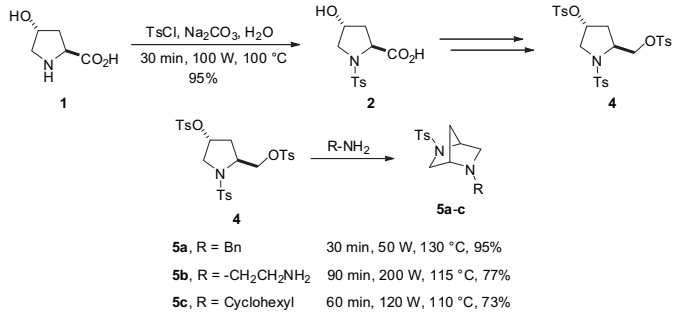
N-Benzyl-*N'*-tosyl-(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan e **5a** is a suitable precursor of several heterocyclic derivatives [14]. To this end, **5a** was detosylated under microwave irradiation over 30 min in the presence of hydrobromic acid at reflux to give 98% yield of **6** (Scheme 3). By comparison, conventional heating requires 2-6 h at reflux for complete reaction [14].

Motivated by the success of (–)-sparteine as a chiral ligand in stereoselective organolithium chemistry [16], we applied these conformationally rigid diamines as potential ligands in the enantioselective addition of diethylzinc (Et_2Zn) to benzaldehyde [14], the cycloaddition reaction between cyclopentadiene and 3-acryloyloxazolidin-2-one [14], and the Biginelli reaction [17] with good results [14]. In this last multicomponent reaction, *N*-methyl-(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane **7** was employed as catalyst under microwave irradiation for the enantioselective synthesis of **8** requiring only 8 h (in comparison with the 5 days that is usually required for this reaction), in 42% yield and 27% *ee*. To our knowledge, this is the first example of a multicomponent asymmetric reaction facilitated under microwave irradiation (Scheme 4) [18].

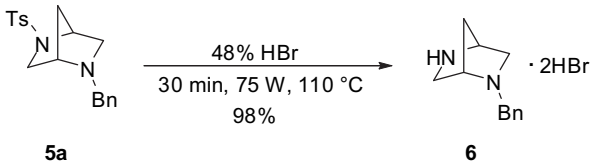
The slight difference in reaction rates and yields between reactions carried out under conventional conditions and microwave irradiation, results from the dependence of Biginelli's reaction to the reaction conditions as described by Kappe [19], so the investigation on this procedure is already in process.



Scheme 1. Conventional route for the synthesis of (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane derivatives [15].



Scheme 2. Synthesis of (1*S*,4*S*)-2,5-diazabicyclo derivatives **5a-c** via microwave irradiation [14].

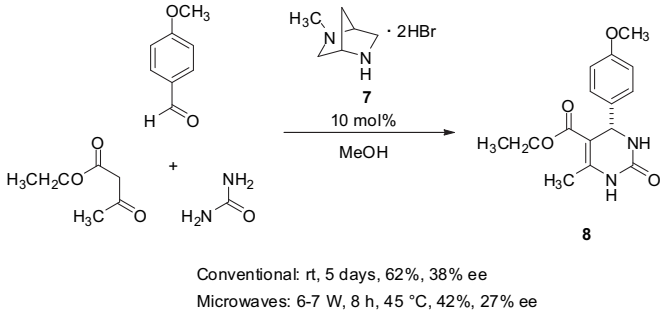


Scheme 3. Detosylation of **5a** using microwaves [14].

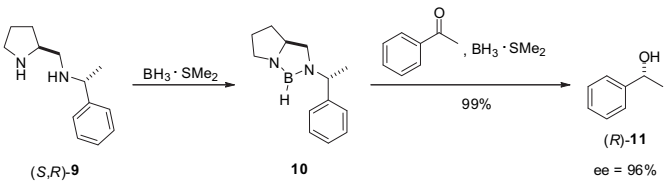
Enantioselective reduction of prochiral ketones

The asymmetric reduction of prochiral ketones is an important methodology for the synthesis of chiral secondary alcohols. In particular, the application of chiral diamine borane-based chiral reducing agents has led to the enantioselective reduction of prochiral ketones by means of the corresponding diazaborolidine complexes [20]. In this regard, diazaborolidine **10** induced enantiomeric excesses greater than 96% (Scheme 5) [21].

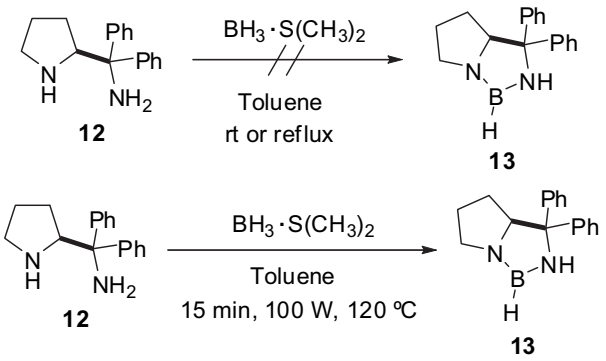
In this respect, an initial attempt to prepare the diazaborolidine **13** under conventional heating failed, as evidenced by the lack of change in the ^{11}B NMR shift in the starting borane-dimethyl sulfide reagent (-20.1 ppm relative to boron trifluoride etherate). The desired diazaborolidine reagent was obtained under microwave irradiation [22], as revealed by the difference in ^{11}B NMR chemicals shifts in the starting borane-dimethyl sulfide reagent, -20.1 ppm, and the corresponding signal in the diazaborolidine, -28.3 ppm. Furthermore, the infrared spectrum of **13** in toluene shows a characteristic B–H stretching band at 2404 cm^{-1}, as well as N–H stretching at 3584 cm^{-1}, in line with Corey's observations in oxazaborolidine analogs (Scheme 6) [23].



Scheme 4. Use of chiral organocatalysts **7** in the asymmetric Biginelli reaction under microwave heating [18].



Scheme 5. Reduction of prochiral ketones employing chiral diamines derivates from proline [21].



Scheme 6. Synthesis of diazaborolidine complexes using microwave irradiation [21].

1-Phenyl and 2-phenyl-1,2-pyrazolidin-3-ones

Motivated by the extraordinary success of the α-amino acid L-proline as organocatalyst in several reactions [24], we deemed it important to look for novel chiral analogs as potential organocatalysts. For this reason, we prepared a set of chiral pyrazolidinones employing microwave irradiation in good yields and short reaction times. For example, the methodology described by Ficken [25] involves 16 h of reflux for the synthesis of isomer **14** from methyl maleate and phenylhydrazine. By contrast, under microwave irradiation at 50 W and 70 °C, the reaction requires only 10 minutes (Scheme 7).

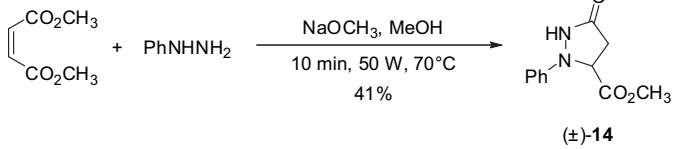
Similarly, the synthesis of the isomeric 2-phenyl-1,2-pyrazolidin-3-one **15** was carried out in two steps. Initially, intermediate **16** was prepared by conventional stirring during 48 h. By contrast, under microwave heating this reaction required only 30 min. On the other hand, the reaction of **16** with MeONa and reflux, and subsequent saponification under conventional conditions, gave product **15**, whereas using microwaves this procedure was completed in 15 min with 83% yield (Scheme 8).

In this regard, compound **17** was subjected to several modifications including saponification, esterification, and formation of novel amide derivatives, using microwaves with excellent results and short reaction times (Scheme 9).

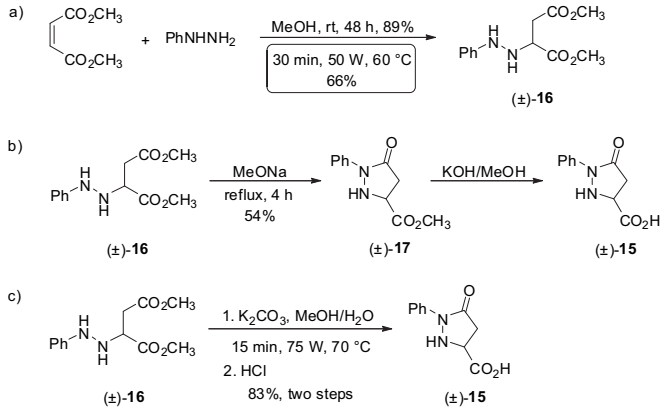
β-Amino acids and β-peptides

The search for novel β-amino acids and β-peptides is an important area in chemistry, principally because of their application as organocatalysts [26], in supramolecular chemistry [27], as intermediates in the synthesis of novel derivatives [28], and in view of their potential application in medicine [29]. Therefore, it is necessary to develop new methodologies and strategies for the synthesis of non-racemic β-amino acids and β-peptides, looking for the reduction of reaction times, increased yields, and preservation of the enantiomeric purity in the final products.

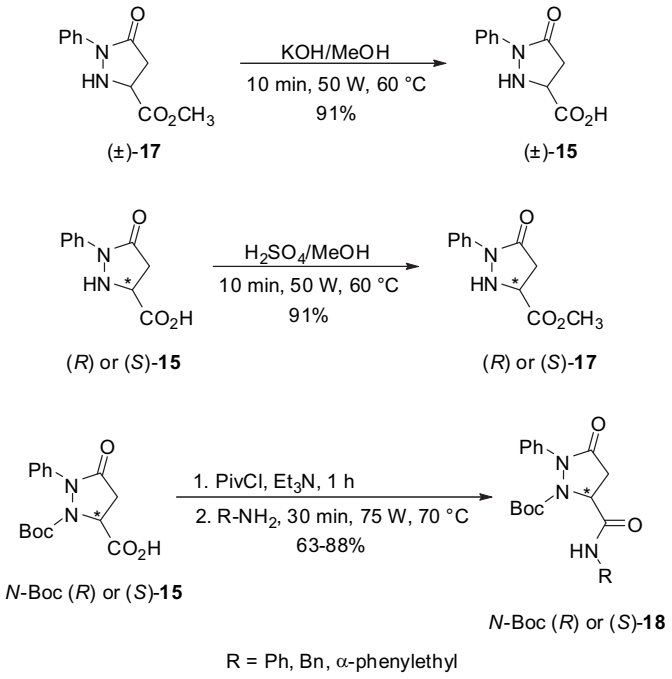
With this purpose, our research group has developed several methodologies for the preparation of β-amino acids [30]. Such methodology became an ideal model for the exploration of new conditions using microwave irradiation. In first place, the synthesis of cyclic β-dipeptide **19** was initiated with the



Scheme 7. Synthesis of pyrazolidinone **14** by means of microwaves.



Scheme 8. Optimized procedure for the synthesis of novel 2-phenyl-1,2-pyrazolidin-3-one **15**. a) Preparation of intermediate **16**; b) synthesis of **15** by conventional methods, and c) under microwave irradiation.



Scheme 9. Saponification, esterification, and preparation of amide derivatives of pyrazolidinone **15**, employing microwave irradiation.

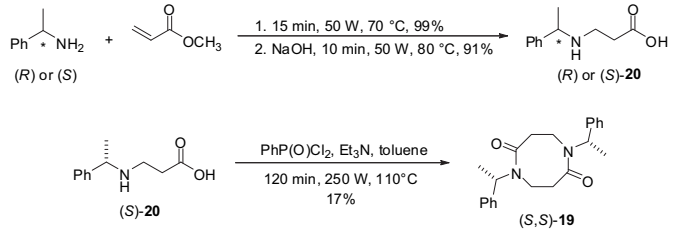
addition of (*R*) or (*S*)-α-phenylethylamine to methyl acrylate, followed by saponification with NaOH to afford the chiral β-amino acid derivatives **20** in a total reaction time of 25 min. Secondly, the reaction of (*S*)-**20** with $PhP(O)Cl_2$ and Et_3N in anhydrous toluene provided compound (*S*,*S*)-**19** in only 2 h. By comparison, 24 h are required for this reaction under conventional heating conditions (Scheme 10) [28, 31].

As showed in figure 1, the presence of chiral segments, and suitable coordination sites in **19** motivated us to investigate their potential as ligands. In this way, **19** was subjected to two modifications: (1) the substitution of C=O groups by C=S groups with Lawesson reagent and (2) the reduction of amide functions to amines using $LiAlH_4$. Both transformations proceeded best under microwave heating, to give the new heterocyclic derivatives **21** and **22**, incorporating the (*R*) or (*S*)-α-phenylethylamine chiral auxiliary (Scheme 11).

On the other hand, the synthesis of β^2-amino acids in enantioenriched form has been possible with microwave heating. For example, the conventional acid hydrolysis of **23** and **24** leads the corresponding products (*S*)-2-benzyl and (*S*)-2-(2-phenylethyl) β-alanine derivatives **25** and **26**, in enantiomeric excess of 77% and 88% respectively and reaction times of 5 days. By contrast, a modified procedure using microwave irradiation afforded **25** and **26** with enantiomeric excess greater than 96%, in 15 and 6 h respectively (Scheme 12a) [33, 34]. In this sense, the synthesis of the chiral auxiliary (*R*,*R*)-bis-α-phenylethylamine **27** required for the preparation of **23** was realized under microwave heating (Scheme 12b) [33].

Miscellaneous applications

Additional optimization processes using microwave heating developed in our research group include the transesterification reaction of methyl to benzyl esters in the preparation of linear β-dipeptide **28**, which required only 4.5 h in comparison



Scheme 10. Synthesis of chiral cyclo β-dipeptide **19** and β-amino acid **20** via microwave irradiation.

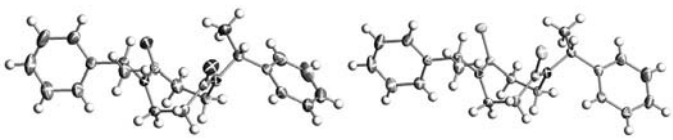
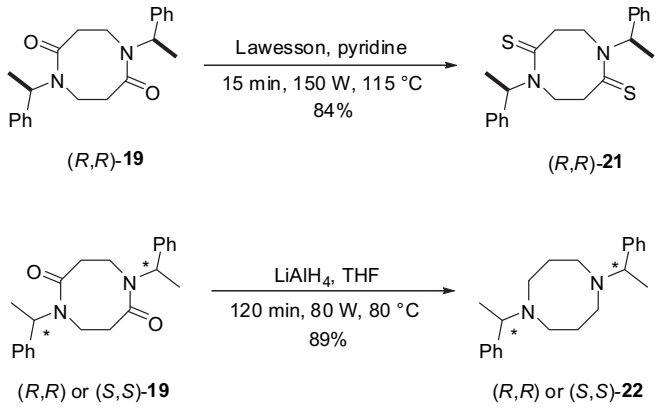
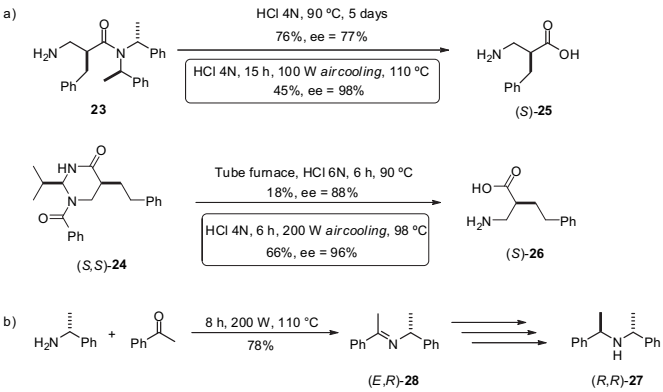


Fig. 1. X-ray structure of cyclo β-dipeptide (*R*,*R*)-**19** and cyclo β-dipeptide derivative (*R*,*R*)-**21** [32].



Scheme 11. Application of microwave irradiation in the preparation of potential chiral ligands based on cyclo β-dipeptides.



Scheme 12. Microwave heating in the synthesis of enantioenriched β-amino acids. a) Hydrolysis reactions [33, 34], b) preparation of (*R*,*R*)-bis-α-phenylethylamine **27** [33].

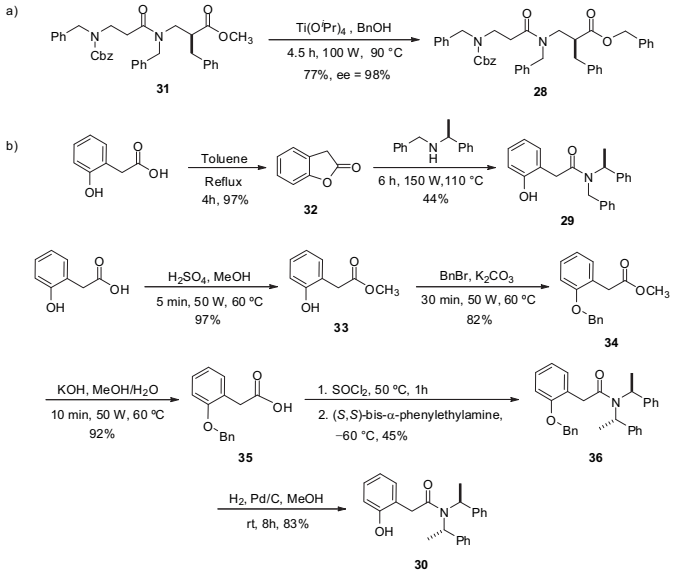
with conventional conditions that involved 20 h [35]. On the other hand, several steps were optimized in the synthesis of phenolic-amide derivatives **29** and **30** via microwaves in good yields (Scheme 13) [36]. The X-ray structure of **29** is showed in figure 2.

Conclusions

Microwave irradiation is a powerful tool whose effect is more prominent in the extraordinary acceleration of reactions, which cannot be reproduced by conventional methods. This translates into a significant reduction of reaction times, minimizing thermal decomposition of products or reagents, leading to higher yields under mild reaction.

Experimental

General Information. Commercially available reagents and solvents were used as received. Anhydrous solvents were



Scheme 13. Miscellaneous synthetic procedures optimized with microwaves. a) Transesterification reaction; b) application of microwave irradiation in the synthesis of phenolic derivatives **29** and **30**.

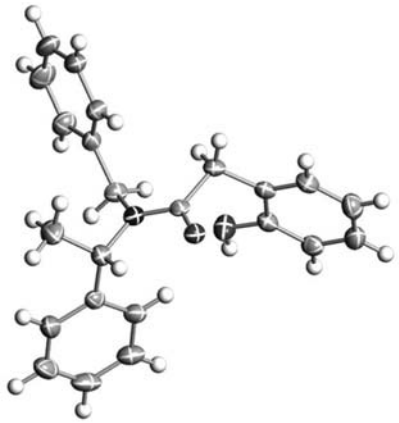


Fig. 2. X-ray structure of **29**.[3]

obtained using conventional methodologies. Purification was realized using flash column chromatography on silica gel (230-400 mesh) or by distillation in a Kugelrohr apparatus. Melting points were measured with a Melt-Temp Electrothermal apparatus and are uncorrected. Optical rotations were determined on Perkin-Elmer Polarimeter model 241 at room temperature. IR spectra were recorded on a Perkin-Elmer FT-IR 1600 instrument. NMR spectra were obtained with JEOL GSX-270 (270 MHz), Bruker Advance 300 (300 MHz), and JEOL Eclipse+400 (400 MHz) spectrometers. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as reference. MS were registered on a Hewlett-Packard 5989-AMS-ENGINE, and Thermo Electron Trace-DSQ, both at 20 eV. HRMS were recorded on Agilent-MSD-TOF1069A spectrometer. Elemental analyses were obtained with a Thermo Finnigan CHNS/O-1112 apparatus. Analytical HPLC was carried out with Waters 600 controller and Waters 2487 UV/Vis detector using several chiral columns, conditions and flows. Microwave heating was carried out with a single-mode cavity Discover Microwave Synthesizer (CEM Corporation, NC) provided with BenchMate and CoolMate accessories, using high-purity quartz tubes or round-bottom flasks. The preparation of compounds **5**, **6**, **8**, **10**, **25**, **26**, and **30** using microwave irradiation was reported previously by us [14, 18, 21, 33, 34, 36].

Methyl 5-oxo-2-phenylpyrazolidine-3-carboxylate (14). In a 10 mL quartz tube provided with magnetic stirrer was dissolved 0.95 g (6.6 mmol) of dimethyl maleate in 3 mL of MeOH; subsequently, a solution of 0.07 g (3.3 mmol) of metallic sodium in 6 mL of absolute MeOH was added. After that, 0.59 g (5.5 mmol, 0.54 mL) of phenylhydrazine were added into the solution and the resulting mixture introduced to the microwave synthesizer under the next conditions: 10 min, 50 W, and 70 °C. The reaction mixture was cooled to ambient temperature, concentrated in a rotary evaporator, washed with distilled water (1 × 10 mL) and EtOAc (2 × 20 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated, and the residue was purified by column (hexane/EtOAc, 8:2) to obtain 0.48 g (41% yield) of **14** as a yellow solid, mp = 86-88 °C (Lit.[25] mp = 86-87 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.7 (dd, 1H, J = 2.2, 17.2 Hz), 3.0 (dd, 1H, J = 9.5, 16.8 Hz), 4.3 (m, 2H), 3.8 (s, 3H), 4.4 (dd, 1H, J = 2.2, 9.5 Hz), 7.0-7.3 (m, 5H), 8.5 (br, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ: 32.0, 53.1, 68.1, 116.4, 123.6, 129.5, 150.9, 171.2, 173.4. MS, m/z: 220 (57), 161 (100), 133 (25), 119 (18), 104 (31), 91 (24), 77 (45), 55 (17).

Dimethyl 2-(2-phenylhydrazinyl)succinate (16). In a round-bottom flask with magnetic stirrer was placed 10 g (69.3 mmol) of dimethyl maleate in MeOH (70 mL), before the slow addition of 5.76 g (53.3 mmol) of phenylhydrazine via syringe. The resulting mixture was placed into the microwave synthesizer using the next conditions: 30 min, 50 W, and 60 °C. The reaction mixture was concentrated in a rotary evaporator and then cooled to 0 °C in an ice bath to induce the precipitation of dimethyl fumarate. The precipitate was filtered and washed with cold MeOH (2 × 15 mL); the filtered was evaporated, and purified by column chromatography (hexane/EtOAc, 9:1) to obtain 8.86 g (66% yield) of **16** as a yellow solid, mp = 44-46 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.8 (dd, 1H, J = 6.8, 16.3 Hz), 2.8 (dd, 1H, J = 5.1, 16.3 Hz), 3.7 (s, 3H), 3.8 (s, 3H), 3.9 (dd, 1H, J = 4.9 Hz), 4.4 (br, 1H), 5.7 (br, 1H), 6.8 (m, 1H), 6.9 (m, 2H).^{13}C NMR ($CDCl_3$, 100.5 MHz) δ: 35.6, 52.0, 52.5, 59.2, 113.1, 119.4, 129.1, 149.0, 171.5, 173.7. MS, m/z: 252 (88), 193 (46), 161 (37), 133 (15), 119 (70), 107 (100), 92 (99), 77 (67). $C_{12}H_{16}N_2O_4$: calcd. C 57.13, H 6.39, N 11.10; found C 57.42, H 6.31, N 11.18.

5-Oxo-1-phenylpyrazolidine-3-carboxylic acid (15). In a round-bottom flask equipped with magnetic stirrer and condenser was placed 3.12 g (12.3 mmol) of **16** in 30 mL of

MeOH, before the addition of 1.70 g (12.3 mmol) of K_2CO_3 in distilled water (18 mL). The reaction mixture was placed in the microwave synthesizer (15 min, 75 W, 70 °C). The reaction mixture was cooled to room temperature and concentrated under vacuum before the addition of 50 mL of water. The solution was washed with CH_2Cl_2 (2 × 20 mL), the aqueous phase was heated at 30 °C for 10 min, acidified with conc. HCl to pH = 2.0, and stirred 20 min. The precipitate was filtered, washed with water until pH = 3-4, and dried at 40 °C under vacuum to give 2.10 g (83% yield) of **15** as a yellow solid, mp = 210-212 °C (Lit. [37] mp = 197-199 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.7 (dd, 1H, *J* = 5.9, 16.5 Hz), 2.9 (dd, 1H, *J* = 8.5, 16.5 Hz), 4.2 (dd, 1H, *J* = 5.9, 8.1 Hz), 6.5 (br, 1H), 7.1 (t, 1H, *J* = 7.2 Hz), 7.3 (t, 2H, *J* = 7.5 Hz), 7.8 (d, 2H, *J* = 7.6 Hz), 13.0 (br, 1H). ^{13}C NMR (DMSO-d_6, 100.5 MHz) δ: 37.8, 55.4, 118.4, 124.1, 129.0, 139.5, 170.6, 172.9. MS, m/z: 206 (100), 161 (55), 118 (13), 107 (35), 91 (17), 77 (20), 55 (5).

Methyl 5-oxo-1-phenylpyrazolidine-3-carboxylate (17). In a round-bottom flask with magnetic stirrer was placed 1 g (8.4 mmol) of **15** in 30 mL of MeOH (partial dissolution), before treatment with 5 drops of conc. H_2SO_4. The resulting mixture was placed in the microwave apparatus, employing 50 W, 10 min, and 60 °C. The reaction mixture was cooled to room temperature and concentrated in a rotary evaporator and the residue treated with 25 mL of water and 25 mL of EtOAc. The reaction mixture was basified (pH = 8.0) with satd. $NaHCO_3$ and extracted with EtOAc (3 × 25 mL). The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuum to give 0.96 g (91% yield) of **17** as a white solid, mp = 76-78 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.9 (dd, 1H, *J* = 9.5, 16.8 Hz), 3.0 (dd, 1H, *J* = 8.4, 16.8 Hz), 3.8 (s, 3H), 4.3 (q, 1H, *J* = 9.2 Hz), 5.3 (d, 1H, *J* = 9.5), 7.1 (t, 1H, *J* = 7.4 Hz), 7.3 (t, 2H, *J* = 8.4 Hz), 7.8 (d, 2H, *J* = 7.7 Hz). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ: 38.0, 53.0, 55.4, 118.6, 124.8, 128.9, 138.3, 168.4, 171.4. MS, m/z: 220 (100), 178 (9), 161 (96), 119 (15), 107 (17), 91 (10), 77 (8), 55 (5). $C_{11}H_{12}N_2O_3$: calcd. C 59.99, H 5.49, N 12.72; found C 60.08, H 5.28, N 12.70.

General procedure for the preparation of amide derivatives (18) with microwave irradiation. In a round-bottom flask provided with magnetic stirrer and condenser, was placed the corresponding *N*-protected pyrazolidinone **15** (1 equiv) in anhydrous THF and Et_3N (1 equiv). The resulting solution was stirred for 10 min, before the addition of pivaloyl chloride (1 equiv, 5-10 min). The reaction mixture was stirred 1 h at 0-5 °C before treatment with the corresponding amine (1 equiv), and heated to reflux with microwave irradiation (75 W, 70 °C) for 30 min. The reaction mixture was cooled to room temperature, diluted with distilled water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated under vacuum. The product was precipitated from cold hexane/EtOAc solution (9:1), filtered, and dried at 40 °C under vacuum.

3-[(*R*) or (*S*)-α-Phenylethylamino)propanoic acid (20). In a microwave tube provided with magnetic stirrer, was placed 0.10 mL (0.8 mmol) of (*R*) or (*S*)-α-phenylethylamine and 0.07 mL (0.8 mmol) of methyl acrylate in 1 mL of MeOH. The resulting solution was placed in the microwave synthesizer (50 W, 70 °C, 15 min). Methyl 3-[(*R*) or (*S*)-α-phenylethylamine)propionic ester was obtained by Kugelrohr distillation as a colorless oil in 99% yield (0.17 g). Optical rotation: (*R*), $[a]_D$ = +41.0 (c = 1.0, $CHCl_3$); (*S*), $[\alpha]_D$ = -39.0 (c = 1.0, $CHCl_3$). Lit. [38] (*R*), $[\alpha]_D$ = +42.6 (c = 1.0, $CHCl_3$); (*S*), $[\alpha]_D$ = -42.0 (c = 1.0, $CHCl_3$). In a second step, 0.10 g (0.5 mmol) of (*R*) or (*S*)-methyl propionic ester was dissolved in 0.8 mL of MeOH, cooled to 0 °C, treated with 0.05 g (1.2 mmol) of NaOH (dissolved in the minimum amount of water), and subject to microwave irradiation (50 W, 70 °C, 10 min). Finally, the solution was acidified with HCl 0.1 N to pH = 4.0, extracted vigorously with CH_2Cl_2, the organic phase dried over anhydrous Na_2SO_4, filtered, evaporated, and purified by column chromatography (EtOAc/EtOH, 9:1). The product was obtained as white foam in 91% yield (0.09 g). Optical rotation: (*R*), $[\alpha]_D$ = +20.0 (c = 1.0, MeOH); (*S*), $[\alpha]_D$ = -19.6 (c = 1.0, MeOH). Lit. [39] (*R*), $[\alpha]_D$ = +8.3 (c = 1.0, MeOH). ^{1}H NMR (D_2O, 300 MHz) δ: 1.5 (d, 3H, *J* = 6.7 Hz), 2.5 (t, 2H, *J* = 6.6 Hz), 2.8 (m, 1H), 3.0 (m, 1H), 4.2 (q, 1H, *J* = 6.6 Hz), 7.3 (m, 5H). ^{13}C NMR (D_2O, 75.4 MHz) δ: 18.6, 31.1, 41.7, 58.8, 127.8, 129.7, 130.0, 135.9, 175.5. MS, m/z: 194 (14), 192 (1000), 118 (538), 105 (489).

1,5-Bis[(*S*)-α-phenylethyl]-1,5-diazocane-2,6-dione [(*S*,*S*)-19]. In a round-bottom flask provided with magnetic stirrer was placed 0.10 g (0.5 mmol) of (*S*)-**20** under nitrogen atmosphere before addition of anhydrous toluene (51.8 mL) with vigorous stirring. The resulting solution was treated with 0.14 mL (0.9 mmol) of Et_3N and 1.1 mL (0.8 mmol) of $PhP(O)Cl_2$. Immediately, a condenser was adapted and the reaction apparatus positioned in the microwave reactor with the next conditions: 250 W, 110 °C, and 2 h. The reaction mixture was cooled to room temperature, concentrated, and purified by column chromatography (EtOAc/hexane, 1:1 to 7:3). Finally, the product was crystallized from EtOAc/hexane and isolated as a white solid (17% yield, 0.015 g), mp = 195-197 °C, $[\alpha]_D$ = -222.0 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 1.5 (d, 6H, *J* = 7.1 Hz), 2.7 (br, 4H), 3.2 (ddd, 2H, *J* = 15, 6.0, 6.0 Hz), 3.4 (ddd, 2H, ^2J = 15, 8.0, 6.0 Hz), 5.9 (q, 2H, *J* = 7.1 Hz), 7.2-7.3 (m, 10H). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ: 17.0, 39.3, 39.3, 51.4, 127.5, 127.6, 128.6, 140.5, 170.7. MS, m/z: 351 (11), 350 (29), 322 (93), 245 (59), 217 (60), 146 (56), 105 (100). IR (KBr, cm^{-1}): 1622, 1646 C=O. $C_{22}H_{26}N_2O_2$: calcd. C 75.40, H 7.48, N 7.99; found C 75.22, H 7.75, N 7.99.

1,5-Bis[(*R*)-α-phenylethyl]-1,5-diazocane-2,6-dithione [(*R*,*R*)-21]. In a microwave tube provided with magnetic stirrer was placed 0.10 g (0.3 mmol) of (*R*,*R*)-**19**, 0.23 g (0.6 mmol) of Lawesson reagent, and 1.2 mL of anhydrous pyridine under nitrogen atmosphere, and placed in the microwave synthesizer (150 W, 115 °C, 15 min). The resulting solution was cooled to room temperature and treated with MeOH for the precipitation of the product. The precipitate was filtered, washed with MeOH, and dried under vacuum to obtain the

product (0.092 g, 84% yield) as a white solid, mp = 218-220 °C. $[\alpha]_D$ = +647.7 (c = 1.3, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 270 MHz, 120 °C) δ: 1.6 (d, 6H, *J* = 7.1 Hz), 3.3 (br, 4H), 3.5 (m, 2H), 3.8 (m, 2H), 6.8 (q, 2H, *J* = 7.1 Hz), 7.2-7.3 (m, 10H). ^{13}C NMR (DMSO-d_6, 67.9 MHz, 120 °C) δ: 15.0, 44.4, 46.7, 58.6, 126.3, 126.8, 127.8, 138.9, 200.5. MS, m/z: 383 (5), 349 (886), 317 (1000), 132 (449), 105 (567), 91 (263). IR (KBr, cm^{-1}): 1493, 1441 C=S. HRMS-TOF $[M+Na]^+$ $C_{22}H_{26}N_2NaS_2$: calcd. 405.1429; found 405.1441.

1,5-Bis[(*R*) or (*S*) α-phenylethyl)]-1,5-diazocane [(*R*,*R*) or (*S*,*S*)-22]. In a round-bottom flask provided with magnetic stirrer and nitrogen atmosphere was placed 0.16 g (1.7 mmol) of $LiAlH_4$ in 20 mL of anhydrous THF at 0 °C, before the slow addition of 0.30 g (0.9 mmol) of (*R*,*R*) or (*S*,*S*)-**19** in 10 mL of anhydrous THF. The solution was stirred for 10 min at 0 °C, and placed in the microwave reactor (80 W, 80 °C, 120 min). Unreacted $LiAlH_4$ was destroyed with 2M NaOH and the product was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, the solvent evaporated under vacuum, and purified by column chromatography (CH_2Cl_2/MeOH, 9:1 to CH_2Cl_2/MeOH/AcOH, 9:1:0.5) to obtain the product as a yellow oil in 89% yield (0.25 g). Optical rotation: (*R*,*R*) $[\alpha]_D$ = +29.0 (c = 1.1, $CHCl_3$); (*S*,*S*), $[\alpha]_D$ = -28.0 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.3 (d, 6H, *J* = 6.5 Hz), 1.5 (m, 4H), 2.7 (m, 8H), 3.8 (m, 2H), 7.2-7.3 (m, 10H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ: 18.7, 28.0, 49.6, 62.9, 126.6, 127.7, 128.1, 145.2. MS, m/z: 322 (2), 217 (45), 160 (33), 105 (100). HRMS-TOF $[M+H]^+$ $C_{22}H_{31}N_2$: calcd. 323.2482; found 323.2483.

***N*,*N'*-Dibenzyl-*N'*-benzyloxycarbonyl (*S*)-2-benzyl-di-β-alanine benzyl ester (28).** In a round-bottom flask provided with magnetic stirrer was placed 0.03 g (0.08 mmol) of the corresponding chiral β-dipeptide **31** as methyl ester, 2 mL of benzyl alcohol, and 0.05 mL (0.16 mmol) of titanium(IV)isopropoxide. The solution was heated under microwave irradiation (4.5 h, 100 W, 90 °C). The benzyl alcohol was removed under vacuum and the residue was purified by column chromatography (hexane/EtOAc, 6:4) to obtain 0.04 g (77% yield) of **28** as a yellow oil and with 98% *ee* (HPLC, Chiralcel OD, λ = 210 nm, 85:15 hexane/^{i}PrOH , 0.5 mL/min, $tr_{(S)}$ = 29.0 min). Optical rotation: $[\alpha]_D$ = + 12.0 (c = 1.0, CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC) δ: 2.5 (t, 2H, *J* = 7.1 Hz); 2.7 (dd, 2H, *J* = 6.1, 14.0 Hz); 2.8 (dd, 2H, *J* = 14.0, 8.4 Hz); 3.1 (ddd, 1H, *J* = 14.3, 8.4, 5.9 Hz); 3.5 (t, 2H, *J* = 7.2 Hz); 4.4 (m, 2H); 2.5 (t, 2H, *J* = 12.7 Hz); 5.0 (dd, 2H, *J* = 14.3, 12.4 Hz); 5.1 (s, 2H); 7.1-7.7 (m, 25 H). ^{13}C NMR (DMSO-d_6, 75.4 MHz, 120 ºC) δ: 32.7, 36.7, 44.5, 46.8, 49.2, 51.5, 66.7, 67.4, 127.0, 127.3, 127.8, 127.9, 128.1, 128.2, 128.5, 128.7, 128.8, 129.0, 129.1, 129.2, 129.3, 129.4, 136.7, 137.8, 138.2, 139.0, 139.2, 156.5, 171.9, 173.9. MS, m/z: 654 (12), 519 (76), 358 (100), 160 (28), 91 (96). HRMS $[M+H]^+$ $C_{42}H_{43}N_2O_5$: calcd. 655.3172; found 655.3172.

(*S*)-*N*-benzyl-2-(2-hydroxyphenyl)-*N*-(1-phenylethyl)acetamide (29). In a round-bottom flask provided with magnetic stirrer and condenser was placed 1.38 g (6.5 mmol) of *N*-benzyl-(*S*)-α-phenylethylamine, 0.87 g (6.5 mmol) of benzofuran-2(3H)-one **32**, and 5 mL of toluene. The resulting solution was placed in the microwave synthesizer (150 W, 110 °C, 6 h). The reaction mixture was cooled to room temperature and the formed precipitate was filtered, washed with hexane, and dried under vacuum. The product was obtained as a white solid (44% yield, 0.95 g), mp = 140-142 °C, $[\alpha]_D$ = -122.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 400 MHz, 120 °C) δ: 1.4 (d, 3H, *J* = 7.2 Hz), 3.6 (d, 1H, *J* = 14.8 Hz), 3.8 (d, 1H, *J* = 15.2 Hz), 4.2-4.7 (dd, 2H, *J* = 16.7 Hz), 5.7 (br, 1H, *J* = 7.0 Hz), 6.7-6.8 (m, 2H), 7.0-7.3 (m, 12H), 9.1 (br, 1H). ^{13}C NMR (DMSO-d_6, 100.5 MHz, 120 °C) δ: 18.4, 35.8, 47.4, 54.6, 116.2, 119.6, 123.1, 127.0, 127.2, 127.5, 127.6, 128.1, 128.6, 128.4, 130.9, 139.7, 141.9, 155.8, 172.5. MS, m/z: 345 (24), 254 (45), 241 (100), 105 (100), 91 (41). IR (KBr, cm^{-1}): 3087, 1616, 1590, 1456, 1168. $C_{23}H_{23}NO_2$: calcd. C 79.97, H 6.71, N 4.05; found C 80.25, H 6.93, N 3.95.

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32. Crystal data for **19**: $C_{22}H_{26}N_2O_2$, monoclinic, space group P 2(1), a = 10.9924(11)Å, b = 6.5469(19)Å, c = 13.2954(09)Å, $\alpha = \gamma = 90°$, β = 96.4848(68)°, V = 950.6Å^3, crystal size: 0.3 × 0.2 × 0.1 mm^3, R1 = 0.0441 (*w*R2 = 0.1087). Crystal data for **21**: $C_{22}H_{26}N_2S_2$, monoclinic, space group P 2(1), a = 12.56660(50)Å, b = 6.03300(20)Å, c = 13.00150(59)Å, $\alpha = \gamma = 90°$, β = 92.3405(15)°, V = 984.8776(68)Å^3, crystal size: 0.88x0.20x0.15 mm^3, R1 = 0.0427 (*w*R2 = 0.1223). Crystal data for **29**: $C_{23}H_{23}NO_2$, monoclinic, space group P 2(1), a = 9.8525(20)Å, b = 6.0365(12)Å, c = 16.2635(33)Å, $\alpha = \gamma = 90°$, β = 104.788(30)°, V = 935.225Å^3, crystal size: 0.3 × 0.2 × 0.1 mm^3, R1 = 0.0379 (*w*R2 = 0.0932). CCDC 740273 (**19**), CCDC 740274 (**21**), and CCDC 740275 (**29**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.
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