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(R)- and (S)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, New Chiral Auxiliaries for the Asymmetric Synthesis of α-Arylpropanoic Acids.

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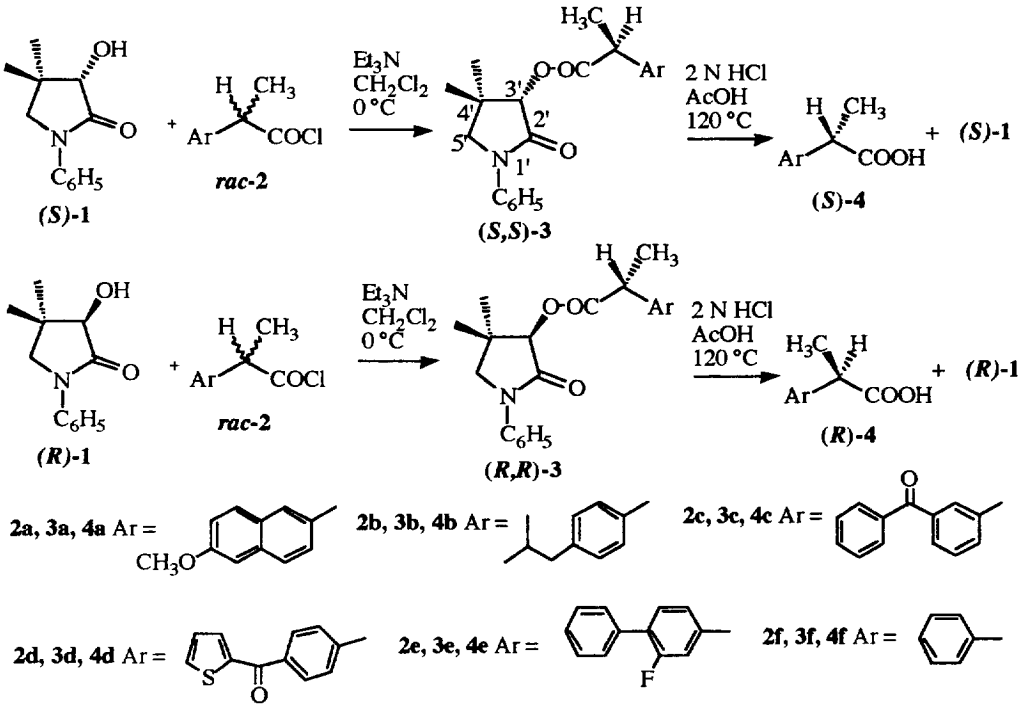
Abstract: Reaction of rac-α-arylpropanoyl chlorides with (*R*)- and (*S*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone (***R***)- and (***S***)-**1**, in the presence of triethylamine, under standard esterification conditions, gave (***R,R***)- and (***S,S***)-**3**, respectively, with high diastereoselectivity. Controlled acidic hydrolysis afforded the corresponding (*R*)- or (*S*)-α-arylpropanoic acids with high enantioselectivity, the chiral auxiliary being recovered efficiently.

Some time ago, the use of (R)-pantolactone and other homochiral alcohols, such as ethyl (S)-lactate, for the asymmetric synthesis of α-arylpropanoic acids from the corresponding racemic mixtures was described.[1] The key-step of this transformation was the diastereoselective addition of the homochiral alcohol to an aryl methyl ketene preformed by reaction of the corresponding acid chloride with a tertiary amine. The higher diastereoselectivities (around 95-99%) were obtained with (R)-pantolactone. After hydrolysis of the esters thus obtained, (R)-α-arylpropanoic acids were obtained. On the other hand, it is known that the eutomers of the antiinflammatory α-arylpropanoic acids are the (S)-enantiomers, which could be derived from the less easily available (S)-pantolactone or from ethyl (S)-lactate, although in the last case with a lower degree of diastereoselectivity during the addition of the alcohol to the ketene. No mention was made about the recovery of the chiral auxiliaries used in these transformations.

In the preceding paper we have described a synthesis, that can be easily performed on a multigram scale, of both enantiomers of 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, ***(R)***- and ***(S)***-**1**, through the enantioselective enzymatic acetylation of the (*S*)-enantiomer of *rac*-**1**, and their configurational assignment by X-ray diffraction analysis of ***(R)***-**1** and its *p*-bromobenzoyl derivative. These compounds contain the structural characteristics of pantolactone, but offer several advantages as chiral auxiliaries: 1) Both enantiomers of **1**, while only (*R*)-pantolactone, are easily available, 2) Contrary to pantolactone, ***(R)***- and ***(S)***-**1** are easily crystallizable non-hygroscopic solids what greatly facilitates their recovery, 3) Due to the presence of the aniline chromophore, the enantiomeric excesses of these chiral auxiliaries are easily determined by HPLC under chiral conditions and UV detection.

In this paper we report the use of ***(R)***- and ***(S)***-**1** as chiral auxiliaries for the asymmetric synthesis of α-arylpropanoic acids from the corresponding racemic mixtures, under reaction conditions that could be easily performed on an industrial scale (Scheme 1).



Scheme 1

Table 1. Yields[a], diastereomeric[b] or enantiomeric[c] excesses of esters **3**, acids **4**, and recovered chiral auxiliary, from the reaction of *rac*-**2** with *(R)*- or *(S)*-**1**.

Entry	Starting	ester **3**			acid **4**			recovered **1**		
	rac-**2**	Conf.	% yield	% de	Conf.	% yield	% ee	Conf.	% yield	% ee
1	*rac*-**2a**	S,S	91	89	S	86	95	S	88	>99
2	*rac*-**2b**	S,S	93	91	S	95	90	S	93	>99
3	*rac*-**2c**	S,S	93	>99	S	92	>99	S	97	>99
4	*rac*-**2d**	S,S	89	88	S	94	95	S	82	>99
5	*rac*-**2e**	S,S	87	>99	S	100	>99	S	95	>99
6	*rac*-**2f**	S,S	77	74	S	72	>99	S	97	>99
7	*rac*-**2b**	R,R	89	90	R	83	92	R	98	>99

[a] Yields refer always to isolated product. For the acids **4**, yields are for the hydrolysis step. [b] The de's of the esters **3** were determined by HPLC under achiral conditions (see experimental). [c] The ee's of acids **4** and recovered **1** were determined by chiral HPLC using different columns and conditions (see experimental).

The key features of the procedure herein described as compared with the one reported by Larsen et al.[1] are: 1) The aryl methyl ketene is not preformed, thus avoiding its hydrolysis or dimerization before reacting with the chiral auxiliary. 2) The esterification reaction is performed always at 0 °C, just by mixing at this temperature anhydrous CH_2Cl_2 solutions of the undistilled acid chloride, ***(R)***- or ***(S)*-1**, and triethylamine. 3) After hydrolysis of the esters **3**, the acid **4** is isolated from its mixture with the chiral auxiliary by precipitation as cyclohexylamine salt, and 4) The chiral auxiliary is easily recovered from the above solution, after filtering the acid salt, by concentration and crystallization from ethanol.

As expected, starting from ***(S)*-1**, (*S*)-α-arylpropanoic acids were obtained (entries 1 to 6), while from ***(R)*-1**, the corresponding (*R*)-acids were obtained, as is shown for (*R*)-ibuprofen (entry 7). As can be seen from Table 1, in general: 1) The yields of formation of esters **3** were around 90%, 2) The diastereoselectivities during the formation of esters **3** were around 90%, what can be considered a good diastereoselectivity taking into account the reaction temperature (0 °C) and the possible concurrence of other esterification mechanisms not involving ketene formation, thus lacking or having low diastereoselectivity, 3) The ee's of the isolated acids **4** were greater than the de's of the corresponding esters due to enrichment during the crystallization of the cyclohexylamine salt, while the yields were good, 4) The chiral auxiliaries were always recovered without epimerization (ee's greater than 99%) in high yields.

The de's of esters **3** were obtained by HPLC under achiral conditions, by asuming the ratio of areas to be equal to their molar ratio, in good agreement with the values obtained by ^1H NMR spectroscopy. For the NMR study of esters **3**, *rac*-acids **4** were esterified with *rac*-**1** in the presence of dicyclohexylcarbodiimide (DCC) obtaining mixtures of the two enantiomeric pairs (*R,R*)/(*S,S*)-**3** and (*R,S*)/*S,R*)-**3**, with a variable small preference of one of the enantiomeric pairs. In all cases, the protons of the alcohol moiety and the β-methyl of the acid rest were clearly observed, being worth of mention the differences in chemical shift observed for the 4'α- and 4'β-CH_3 protons of the diastereomers of **3**. In the pair (*R,S*)/*S,R*)-**3**, the 4'α-CH_3 protons appear upfield shifted by 0.24-0.30 ppm with respect to the corresponding signals of the pair (*R,R*)/(*S,S*)-**3**. The same situation, but less pronounced (0.11-0.16 ppm), was observed for the 4'β-CH_3 protons. Less significant were the ^{13}C chemical shift differences. The ee's of the acids **4** and of the recovered chiral auxiliaries were established by HPLC using the chiral columns and conditions indicated in the experimental part.

The new compounds ***(S,S)*-3a-f** and ***(R,R)*-3b** have been fully characterized through their spectroscopic data and elemental analysis. The NMR spectra of these compounds have been fully assigned on the basis of COSY $^1H/^1H$ and $^1H/^{13}C$ experiments. The aromatic quaternary carbon atoms from the acid rest have been assigned by comparison with the NMR data of the acid, for which COSY $^1H/^{13}C$ experiments were performed by using the HMBC or HMQC sequences with an indirect detection probe. The assignment of the pairs of protons 4α-CH_3 / 4β-CH_3 and 5α-H / 5β-H was carried out on the same grounds described in the preceding paper for ***(R)*-** or ***(S)*-1**.

In conclusion, a simple procedure for the enantioselective synthesis of α-arylpropanoic acids, that could be useful from an industrial view-point, through the intermediacy of (*R*)- or (*S*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, ***(R)***- or ***(S)*-1**, has been developed, while the advantages derived from the use of these new chiral auxiliaries over (*R*)- or (*S*)-pantolactone have been proved, i.e.: ease of recovery of the chiral auxiliary without loss of enantiomeric purity and both enantiomers equally available.

EXPERIMENTAL

Melting points were determined on a MFB 595010 M Gallenkamp melting point apparatus. 500 MHz ^1H NMR spectra and COSY $^1H/^1H$ and $^1H/^{13}C$ experiments were determined on a Varian VXR 500 MHz spectrometer and 200 MHz ^1H and 50.3 MHz ^{13}C NMR spectra on a Varian Gemini 200, always in $CDCl_3$. COSY $^1H/^1H$ experiments were performed using standard procedures while for the COSY $^1H/^{13}C$ experiments, the HMQC and HMBC sequences with indirect detection probe were used. Chemical shifts (δ) are reported in ppm related to the tetramethylsilane. Optical rotations were measured on a Perkin Elmer 241 polarimeter. HPLC analyses were performed on a Hewlet-Packard apparatus, with UV detection at λ=249 nm using column A for the non-stereospecific analyses and columns B and C for the stereospecific HPLC analyses. Column A: Tracer Analytical column ODS-2, 15 x 0.39 cm, 4 μm silica gel; column B: CHIRALCEL OD-H column (25 x 0.46 cm) containing the chiral stationary phase cellulose tris-(3,5-dimethylphenylcarbamate); column C: Chiral-AGP (10 x 0.40 cm, 5 μm) containing the chiral stationary phase silica-bonded α_1-acid glycoprotein. Conditions A: Column A, H_2O / acetonitrile in a ratio of 40 / 60 as eluent, flow 0.5 ml / min; Conditions B: Column A, H_2O / acetonitrile in a ratio of 50 / 50 as eluent, flow 0.9 ml / min; Conditions C: Column A, H_2O / acetonitrile in a ratio of 40 / 60 as eluent, flow 0.6 ml / min; Conditions D: Column A, H_2O / acetonitrile in a ratio of 65 / 35 as eluent, flow 0.4 ml / min; Conditions E: Column A, H_2O / acetonitrile in a ratio of 50 / 50 as eluent, flow 0.4 ml / min; Conditions F: column B, mixture of hexane / isopropanol in the ratio of 93 / 7 as eluent, flow 0.8 ml / min. Conditions G: column B, mixture of hexane / isopropanol / trifluoroacetic acid in the ratio of 90 / 10 / 0.5 as eluent, flow 0.5 ml / min. Conditions H: Column C, sodium phosphate buffer 25 mM, pH = 7.0, flow 0.9 ml / min. Conditions I: Column C, sodium phosphate buffer 100 mM, pH = 7.0, flow 0.9 ml / min. Conditions J: Column C, mixture of potassium phosphate buffer 10 mM, pH = 5.5 / isopropanol in the ratio of 99 / 1, flow 0.9 ml / min. Conditions K: Column C, mixture of sodium phosphate buffer 25 mM, pH = 7.0 / isopropanol in the ratio of 99 / 1, flow 0.9 ml / min. Conditions L: Column C, potassium phosphate buffer 25 mM, pH = 5.0, flow 0.3 ml / min. Solvents were of analytical grade.

General procedure for the preparation of rac-α-arylpropionyl chlorides.

A mixture of the *rac*-α-arylpropionic acid, *rac*-**4**, (1 equiv) and PCl_5 (1.1 equiv) in CCl_4 (1.5 ml / mmol) was stirred at 40 °C for 30 min. Evaporation of the volatile products gave the corresponding *rac*-α-arylpropionyl chloride, *rac*-**2**, that was used as such in the following step.

General procedure for the reaction of rac-α-arylpropionyl chlorides with (R)- or (S)-1.

To a dried (1 g of 3 Å molecular sieves / mmol) and cooled solution (ice-water bath) of ***(R)***- or ***(S)*-1** (1 equiv) in CH_2Cl_2 (3 ml / mmol) under an argon atmosphere, dried solutions (1 g of 3 Å molecular sieves / mmol) of the *rac*-α-arylpropionyl chloride, *rac*-**2**, (1 equiv) in CH_2Cl_2 (3 ml / mmol) and triethylamine (2.2 equiv) in CH_2Cl_2

(4 ml / mmol) were successively added and the mixture was magnetically stirred for 3 h at 0°C. The mixture was washed with N HCl (2 x 5 ml / mmol), saturated aqueous solution of $NaHCO_3$ (2 x 5 ml / mmol), dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed [silica gel (50 g / g residue), hexane / diethyl ether] and the diastereomeric excess of the ester **3** thus obtained was determined by HPLC under conditions A-E.

(3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (αS)-α-(6-methoxy-2-naphthyl)propionate (S,S)-3a

Following the general procedure, from *(S)*-**1** (410 mg, 2.00 mmol) and *rac*-**2a** (510 mg, 2.05 mmol), **(*S,S*)-3a** (757 mg, 91% yield, 89% de, conditions A, r.t. 20.10 min.) was obtained as an oil, $[\alpha]_D^{20}$ (c = 1.7, $CHCl_3$) = -16.8 . ^{1}H NMR (500 MHz) δ = 1.01 (s, 3 H, 4'α-CH_3), 1.21 (s, 3 H, 4'β-CH_3), 1.70 (d, J = 7.5 Hz, 3 H, C*H*$_3$-CHCOO), 3.46 (d, J = 9.5 Hz, 1 H, 5'α-H), 3.54 (d, J = 9.5 Hz, 1 H, 5'β-H), 3.89 (s, 3H, OCH_3), 4.04 (q, J = 7.5 Hz, 1 H, CH_3-C*H*COO), 5.38 (s, 1 H, 3'-H), 7.09 (d, J = 2.5 Hz, 1 H, 5-H), 7.12 (dd, J = 9.0 Hz, J' = 2.5 Hz, 1 H, 7-H), 7.14 (tt, J = 7.5 Hz, J' = 1.0 Hz, 1 H, H*para* N-phenyl), 7.34 (dd, J = 9.0 Hz, J' = 7.5 Hz, 2 H, H*meta* N-phenyl), 7.48 (dd, J = 8.5 Hz, J' = 1.5 Hz, 1 H, 3-H), 7.58 (dd, J = 9.0 Hz, J' = 1.0 Hz, H*ortho* N-phenyl), 7.70 (m, 2 H, 4-H and 8-H), 7.73 (d, J = 1.5 Hz, 1 H, 1-H). ^{13}C NMR (50.3 MHz) δ = 18.5 (CH_3, *C*H_3CHCOO), 21.0 (CH_3, 4'α-CH_3), 24.8 (CH_3, 4'β-CH_3), 37.3 (C, C4'), 45.5 (CH, CH_3*C*HCOO), 55.2 (CH_3, CH_3O), 57.7 (CH_2, C5'), 78.3 (CH, C3'), 105.5 (CH, C5), 118.8 (CH, C7), 119.4 (CH, C*ortho* N-phenyl), 124.8 (CH, C*para* N-phenyl), 126.1 (CH, C1), 126.4 (CH, C3), 127.0 (CH, C4), 128.9 (CH, C*meta* N-phenyl), 129.3 (CH, C8), 133.7 (C, C4a), 134.8 (C, C2), 139.0 (C, C*ipso* N-phenyl), 157.6 (C, C6), 168.7 (C, C2'), 173.9 (C, COO) (C8a was not observed); IR ($CHCl_3$) ν = 1743 and 1713 (C=O st) cm^{-1}. $C_{26}H_{27}NO_4$ (417.51): calcd. C 74.79% H 6.52% N 3.35%. Found C 74.79% H 6.61% N 3.31%.

(3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (αS)-α-[4-(2-methylpropyl)phenyl]propionate (S,S)-3b

Following the general procedure, from *(S)*-**1** (320 mg, 1.56 mmol) and *rac*-**2b** (350 mg, 1.56 mmol), **(*S,S*)-3b** (570 mg, 93% yield, 91% de, conditions B, r.t. 108.8 min.) was obtained as a solid, m.p. 77-80 °C (ethanol), $[\alpha]_D^{20}$ (c = 1.1, $CHCl_3$) = -22.3 . ^{1}H NMR (500 MHz) δ = 0.89 [d, J = 7.0 Hz, 6 H, (CH_3)$_2$CHCH$_2$], 1.01 (s, 3 H, 4'α-CH_3), 1.21 (s, 3 H, 4'β-CH_3), 1.63 (d, J = 7.0 Hz, 3 H, C*H*$_3$-CHCOO), 1.85 [m, 1 H, (CH_3)$_2$C*H*CH$_2$], 2.45 (d, J = 7.0 Hz, 1 H, (CH_3)$_2$CHC*H*$_2$], 3.47 (d, J = 9.5 Hz, 1 H, 5'α-H), 3.55 (d, J = 9.5 Hz, 1 H, 5'β-H), 3.90 (q, J = 7.0 Hz, 1 H, CH_3-C*H*COO), 5.36 (s, 1 H, 3'-H), 7.11 [d, J = 8.0 Hz, 2H, 3(5)-H], 7.15 (tt, J = 7.5 Hz, J' = 1.0 Hz, 1 H, H*para* N-phenyl), 7.29 [d, J = 8.0 Hz, 2 H, 2(6)-H], 7.36 (dd, J = 8.5 Hz, J' = 7.5 Hz, 2 H, H*meta* N-phenyl), 7.61 (dd, J = 8.5 Hz, J' = 1.0 Hz, 2 H, H*ortho* N-phenyl). ^{13}C NMR (50.3 MHz) δ = 18.3 (CH_3, *C*H_3CHCOO), 20.9 (CH_3, 4'α-CH_3), 22.3 [CH_3, (*C*H_3)$_2$CHCH$_2$], 24.8 (CH_3, 4'β-CH_3), 30.1 [CH, (CH_3)$_2$*C*HCH$_2$], 37.3 (C, C4'), 45.0 [CH_2, (CH_3)$_2$CH*C*H$_2$], 45.2 (CH, CH_3*C*HCOO), 57.6 (CH_2, C5'), 78.2 (CH, C3'), 119.4 (CH, C*ortho* N-phenyl), 124.8 (CH, C*para* N-phenyl), 127.3 [CH, C2(6)], 128.8 (CH, C*meta* N-phenyl), 129.2 [CH, C3(5)], 136.8 (C, C1), 139.0 (C, C*ipso* N-phenyl), 140.5 (C, C4), 168.7 (C, C2'), 173.9 (C, COO); IR ($CHCl_3$) ν = 1744 and 1720 (C=O st) cm^{-1}. $C_{25}H_{31}NO_3$ (393.53): calcd. C 76.30% H 7.94% N 3.56%. Found C 76.21% H 8.03% N 3.51%.

(3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (αS)-α-(3-benzoylphenyl)propionate (S,S)-3c

Following the general procedure, from *(S)*-**1** (475 mg, 2.31 mmol) and *rac*-**2c** (630 mg, 2.31 mmol), **(*S,S*)-3c** (947 mg, 93% yield, > 99% de, conditions C, r.t. 17.6 min.) was obtained as an oil, $[\alpha]_D^{20}$ (c = 1.4, isopropanol)

= -27.2 . ^{1}H NMR (500 MHz) δ = 1.03 (s, 3 H, 4'α-CH_3), 1.23 (s, 3 H, 4'β-CH_3), 1.64 (d, J = 7.0 Hz, 3 H, C*H*$_3$-CHCOO), 3.47 (d, J = 9.5 Hz, 1 H, 5'α-H), 3.55 (d, J = 9.5 Hz, 1 H, 5'β-H), 3.97 (q, J = 7.0 Hz, 1 H, CH_3-C*H*COO), 5.36 (s, 1 H, 3'-H), 7.13 (tt, J = 7.0 Hz, J' = 1.0 Hz, 1 H, H*para* N-phenyl), 7.33 (m, 2 H, H*meta* N-phenyl), 7.45 (m, 3 H, H*meta* benzoyl and 5-H), 7.55 (tt, J = 7.5 Hz, J' = 1.5 Hz, 1 H, H*para* benzoyl), 7.58 (dd, J = 9.0 Hz, J' = 1.0 Hz, 2 H, H*ortho* N-phenyl), 7.63 (dt, J = 7.5 Hz, J' = 1.5 Hz, 1 H, 6-H), 7.68 (dt, J = 7.5 Hz, J' = 1.5 Hz, 1 H, 4-H), 7.80 (dd, J = 8.5 Hz, J' = 1.5 Hz, 2 H, H*ortho* benzoyl), 7.81 (broad s, 1 H, 2-H). ^{13}C NMR (50.3 MHz) δ = 18.5 (CH_3, *C*H_3CHCOO), 20.9 (CH_3, 4'α-CH_3), 24.6 (CH_3, 4'β-CH_3), 37.1 (C, C4'), 45.2 (CH, CH_3*C*HCOO), 57.4 (CH_2, C5'), 78.3 (CH, C3'), 119.2 (CH, C*ortho* N-phenyl), 124.7 (CH, C*para* N-phenyl), 128.1 (CH, C*meta* benzoyl), 128.4 (CH, C5), 128.7 (CH, C*meta* N-phenyl), 128.9 (CH, C4), 129.1 (CH, C2), 129.9 (CH, C*ortho* benzoyl), 131.7 (CH, C6), 132.3 (CH, C*para* benzoyl), 137.3 (C, C*ipso* benzoyl), 137.6 (C, C3), 138.8 (C, C*ipso* N-phenyl), 140.0 (C, C1), 168.3 (C, C2'), 173.1 (C, COO), 196.3 (C, Ar-CO-Ar'); IR ($CHCl_3$) ν = 1739, 1716 and 1659 (C=O st) cm^{-1}. $C_{28}H_{27}NO_4$ (441.53): calcd. C 76.17% H 6.16% N 3.17%. Found C 75.97% H 6.16% N 3.04%.

*(3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (αS)-α-[4-(2-thenoyl)phenyl]propionate (S,S)-***3d**

Following the general procedure, from *(S)-***1** (243 mg, 1.18 mmol) and *rac-***2d** (330 mg, 1.18 mmol), **(*S,S*)-3d** (472 mg, 89% yield, 88% de, conditions D, r.t. 11.2 min.) was obtained as an oil, $[\alpha]_D^{20}$ (c = 1.3, $CHCl_3$) = -15.9 . ^{1}H NMR (500 MHz) δ = 1.06 (s, 3 H, 4'α-CH_3), 1.26 (s, 3 H, 4'β-CH_3), 1.68 (d, J = 7.0 Hz, 3 H, C*H*$_3$-CHCOO), 3.50 (d, J = 9.5 Hz, 1 H, 5'α-H), 3.58 (d, J = 9.5 Hz, 1 H, 5'β-H), 4.02 (q, J = 7.0 Hz, 1 H, CH_3-C*H*COO), 5.40 (s, 1 H, 3'-H), 7.15 (m, 2 H, H*para* N-phenyl and 4-H thenoyl), 7.36 (dd, J = 8.5 Hz, J' = 7.5 Hz, 2 H, H*meta* N-phenyl), 7.53 [d, J = 8.0 Hz, 2 H, 2(6)-H], 7.60 (dd, J = 8.5 Hz, J' = 1.0 Hz, 2 H, H*ortho* N-phenyl), 7.65 (dd, J = 4.0 Hz, J' = 1.5 Hz, 1 H, 3-H thenoyl), 7.70 (dd, J = 5.5 Hz, J' = 1.5 Hz, 1 H, 5-H thenoyl), 7.86 [d, J = 8.0 Hz, 2 H, 3(5)-H]. ^{13}C NMR (50.3 MHz) δ = 18.4 (CH_3, *C*H_3CHCOO), 20.9 (CH_3, 4'α-CH_3), 24.6 (CH_3, 4'β-CH_3), 37.1 (C, C4'), 45.3 (CH, CH_3*C*HCOO), 57.4 (CH_2, C5'), 78.4 (CH, C3'), 119.3 (CH, C*ortho* N-phenyl), 124.7 (CH, C*para* N-phenyl), 127.7 [CH, C2(6)], 127.8 (CH, C4 thenoyl), 128.8 (CH, C*meta* N-phenyl), 129.4 [CH, C3(5)], 134.0 (CH, C5 thenoyl), 134.7 (CH, C3 thenoyl), 136.8 (C, C4), 138.8 (C, C*ipso* N-phenyl), 143.4 (C, C2 thenoyl), 144.1 (C, C1), 168.3 (C, C2'), 173.0 (C, COO), 187.5 (C, Ar-CO); IR ($CHCl_3$) ν = 1743, 1714 and 1631 (C=O st) cm^{-1}. $C_{26}H_{25}NO_4S \cdot 0.75\ H_2O$ (461.06): calcd. C 67.73% H 5.79% N 3.04% S 6.95%. Found C 67.49% H 5.61% N 2.97% S 6.56.

*(3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (αS)-α-(3-fluorobiphenyl-4-yl)propionate (S,S)-***3e**

Following the general procedure, from *(S)-***1** (390 mg, 1.90 mmol) and *rac-***2e** (490 mg, 1.87 mmol), **(*S,S*)-3e** (703 mg, 87% yield, > 99% de, conditions A, r.t. 32.3 min.) was obtained as a solid, m.p. 131-132 °C (ethanol), $[\alpha]_D^{20}$ (c = 2.8, $CHCl_3$) = -18.2 . ^{1}H NMR (500 MHz) δ = 1.07 (s, 3 H, 4'α-CH_3), 1.26 (s, 3 H, 4'β-CH_3), 1.65 (d, J = 7.5 Hz, 3 H, C*H*$_3$-CHCOO), 3.49 (d, J = 9.5 Hz, 1 H, 5'α-H), 3.58 (d, J = 9.5 Hz, 1 H, 5'β-H), 3.95 (q, J = 7.5 Hz, 1 H, CH_3-C*H*COO), 5.39 (s, 1 H, 3'-H), 7.15 (broad t, J = 7.5 Hz, 1 H, H*para* N-phenyl), 7.20 (dd, $^3J_{H,F}$ = 11.5 Hz, J' = 1.5 Hz, 1 H, 2-H), 7.23 (dd, J = 8.0 Hz, J' = 1.5 Hz, 1 H, 6-H), 7.35 (m, 3 H, H*para* Ar-phenyl and H*meta* N-phenyl), 7.42 (m, 3 H, H*meta* Ar-phenyl and 5-H), 7.53 (dm, J = 7.5 Hz, 2 H, H*ortho* Ar-phenyl), 7.60 (dd, J = 8.5 Hz, J' = 1.0 Hz, 2 H, H*ortho* N-phenyl). ^{13}C NMR (50.3 MHz) δ = 18.5 (CH_3, *C*H_3CHCOO), 21.0 (CH_3, 4'α-CH_3), 24.7 (CH_3, 4'β-CH_3), 37.2 (C, C4'), 44.9 (CH, CH_3*C*HCOO), 57.5 (CH_2, C5'), 78.5 (CH, C3'), 115.4 (CH, d, $^2J_{C,F}$ = 28.8 Hz, C2), 119.3 (CH, C*ortho* N-phenyl), 123.8 (CH, C6), 124.8

(CH, C_{para} N-phenyl), 127.5 (CH, C_{para} Ar-phenyl), 128.0 (C, d, $^3J_{C,F}$ = 9.8 Hz, C4), 128.3 (CH, C_{meta} Ar-phenyl), 128.9 (CH, C_{meta} N-phenyl and C_{ortho} Ar-phenyl), 130.7 (CH, C5), 135.4 (C, C_{ipso} Ar-phenyl), 138.9 (C, C_{ipso} N-phenyl), 141.0 (C, d, $^3J_{C,F}$ = 7.7 Hz, C1), 159.5 (C, d, $^1J_{C,F}$ = 248.3 Hz, C3), 168.5 (C, C2'), 173.2 (C, COO); IR ($CHCl_3$) ν = 1745 and 1717 (C=O st) cm^{-1}. $C_{27}H_{26}FNO_3$ (431.51): calcd. C 75.15% H 6.07% N 3.25% F 4.40%. Found C 75.24% H 6.19% N 3.26% F 4.20%.

*(3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (αS)-α-phenylpropionate (S,S)-**3f***

Following the general procedure, from *(S)*-**1** (410 mg, 2.00 mmol) and *rac*-**2f** (340 mg, 2.02 mmol), **(*S,S*)-3f** (516 mg, 77% yield, 74% de, conditions E, r.t. 49.5 min.) was obtained as a solid, m.p. 88-90 °C (ethanol), $[\alpha]_D^{20}$ (c = 1.2, $CHCl_3$) = -28.1 . ^1H NMR (500 MHz) δ = 1.01 (s, 3 H, 4'α-CH_3), 1.21 (s, 3 H, 4'β-CH_3), 1.62 (d, J = 7.0 Hz, 3 H, CH_3-CHCOO), 3.46 (d, J = 9.5 Hz, 1 H, 5'α-H), 3.53 (d, J = 9.5 Hz, 1 H, 5'β-H), 3.91 (q, J = 7.0 Hz, 1 H, CH_3-CHCOO), 5.36 (s, 1 H, 3'-H), 7.13 (tt, J = 7.0 Hz, J' = 1.0 Hz, 1 H, H_{para} N-phenyl), 7.24 (tt, J = 7.0 Hz, J' = 1.0 Hz, 1 H, 4-H), 7.33 [m, 4 H, 3(5)-H and H_{meta} N-phenyl], 7.37 [m, 2 H, 2(6)-H], 7.59 (dd, J = 8.5 Hz, J' = 1.0 Hz, 2 H, H_{ortho} N-phenyl). ^{13}C NMR (50.3 MHz) δ = 18.2 (CH_3, CH_3CHCOO), 20.6 (CH_3, 4'α-CH_3), 24.4 (CH_3, 4'β-CH_3), 36.9 (C, C4'), 45.2 (CH, CH_3CHCOO), 57.2 (CH_2, C5'), 78.0 (CH, C3'), 119.1 (CH, C_{ortho} N-phenyl), 124.5 (CH, C_{para} N-phenyl), 126.9 (CH, C4), 127.4 [CH, C2(6)], 128.2 [CH, C3(5)], 128.6 (CH, C_{meta} N-phenyl), 138.7 (C, C_{ipso} N-phenyl), 139.4 (C, C1), 168.4 (C, C2'), 173.4 (C, COO); IR ($CHCl_3$) ν = 1728 and 1711 (C=O st) cm^{-1}. $C_{21}H_{23}NO_3$ (337.42): calcd. C 74.75% H 6.87% N 4.15%. Found C 74.68% H 6.80% N 4.04%.

*(3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (αR)-α-[4-(2-methylpropyl)phenyl]propionate (R,R)-**3b***

Following the general procedure, from *(R)*-**1** (205 mg, 1.00 mmol) and *rac*-**2b** (220 mg, 0.98 mmol), **(*R,R*)-3b** (343 mg, 89% yield, 90% de, conditions B) was obtained as a solid, m.p. 79-80 °C (ethanol), $[\alpha]_D^{20}$ (c = 1.0, $CHCl_3$) = + 23.2 . The IR and NMR data coincide with those of ***(S,S)*-3b**. $C_{25}H_{31}NO_3$ (393.53): calcd. C 76.30% H 7.94% N 3.56%. Found C 76.19% H 7.97% N 3.61%.

*General procedure for the reaction of rac-α-arylpropionic acids with rac-**1**.*

A mixture of the *rac*-α-arylpropionic acid (1 equiv), dicyclohexylcarbodiimide (1 equiv), *rac*-**1** (1 equiv) and 4-dimethylaminopyridine (0.05 equiv) in CH_2Cl_2 (6 ml / mmol) was magnetically stirred at room temperature for 3 h following the reaction by tlc. The mixture was filtered and the filtrate was washed with saturated aqueous solution of citric acid (3 x 6 ml/mmol) and saturated aqueous $NaHCO_3$ (3 x 6 ml / mmol), dried with Na_2SO_4 and concentrated in vacuo. The residue containing the mixture of **(*R,R*)**-, **(*S,S*)**-, **(*R,S*)**-, and **(*S,R*)-3** was analyzed by HPLC under conditions A-E, and by NMR spectroscopy.

In all cases, the reaction was performed starting from 200 mg of the acid, and the oily stereoisomeric mixtures of esters were obtained in the following yields: **3a** (76%), **3b** (63%), **3c** (71%), **3d** (73%), **3e** (84%), and **3f** (65%). The enantiomeric pair **(*R,S*)/(*S,R*)** in the cases of **3a**, **3b**, and **3d**, and the **(*R,R*)/(*S,S*)** in the cases of **3c**, **3e**, and **3f** was slightly more abundant.

Significant analytical and NMR data of the enantiomeric pair (R,S)/(S,R)-3, deduced from the data of the above mixtures: **(*R,S*)/(*S,R*)-*3a***: HPLC (conditions A), r.t. 17.9 min. ^1H NMR (200 MHz) δ: = 0.72 (s, 3 H, 4'α-CH_3), 1.07 (s, 3 H, 4'β-CH_3), 1.65 (d, J = 7.2 Hz, 3 H, CH_3-CHCOO), 3.37 (d, J = 9.6 Hz, 1 H, 5'α-H), 3.52 (d, J =

9.6 Hz, 1 H, 5'β-H), 4.06 (q, J = 7.2 Hz, 1 H, CH_3-C*H*COO), 5.43 (s, 1 H, 3'-H). ^{13}C NMR (50.3 MHz) δ = 18.3 (CH_3, *C*H_3CHCOO), 20.6 (CH_3, 4'α-CH_3), 24.6 (CH_3, 4'β-CH_3), 37.5 (C, C4'), 45.2 (CH, CH_3*C*HCOO), 57.6 (CH_2, C5'), 78.1 (CH, C3'), 169.0 (C, C2'), 174.0 (C, COO).

(***R,S***)/(***S,R***)-***3b***: HPLC (conditions B), r.t. 99.7 min. ^1H NMR (200 MHz) δ = 0.71 (s, 3 H, 4'α-CH_3), 1.06 (s, 3 H, 4'β-CH_3), 1.55 (d, J = 7.1 Hz, 3 H, C*H*$_3$-CHCOO), 3.36 (d, J = 9.6 Hz, 1 H, 5'α-H), 3.52 (d, J = 9.6 Hz, 1 H, 5'β-H), 3.89 (q, J = 7.1 Hz, 1 H, CH_3-C*H*COO), 5.39 (s, 1 H, 3'-H). ^{13}C NMR (50.3 MHz) δ = 18.0 (CH_3, *C*H_3CHCOO), 20.4 (CH_3, 4'α-CH_3), 24.6 (CH_3, 4'β-CH_3), 37.6 (C, C4'), 44.8 (CH, CH_3*C*HCOO), 57.5 (CH_2, C5'), 77.9 (CH, C3'), 169.0 (C, C2'), 174.1 (C, COO).

(***R,S***)/(***S,R***)-***3c***: HPLC (conditions C), r.t. 16.0 min. ^1H NMR (200 MHz) δ = 0.82 (s, 3 H, 4'α-CH_3), 1.13 (s, 3 H, 4'β-CH_3), 1.61 (d, J = 7.2 Hz, 3 H, C*H*$_3$-CHCOO), 3.42 (d, J = 9.6 Hz, 1 H, 5'α-H), 3.55 (d, J = 9.6 Hz, 1 H, 5'β-H), 4.02 (q, J = 7.2 Hz, 1 H, CH_3-C*H*COO), 5.41 (s, 1 H, 3'-H). ^{13}C NMR (50.3 MHz) δ = 18.2 (CH_3, *C*H_3CHCOO), 20.7 (CH_3, 4'α-CH_3), 24.6 (CH_3, 4'β-CH_3), 37.5 (C, C4'), 45.1 (CH, CH_3*C*HCOO), 57.5 (CH_2, C5'), 78.2 (CH, C3'), 168.7 (C, C2'), 173.4 (C, COO), 195.8 (C, Ar-CO-Ar').

(***R,S***)/(***S,R***)-***3d***: HPLC (conditions D), r.t. 10.3 min. ^1H NMR (200 MHz) δ = 0.81 (s, 3 H, 4'α-CH_3), 1.13 (s, 3 H, 4'β-CH_3), 1.62 (d, J = 7.2 Hz, 3 H, C*H*$_3$-CHCOO), 3.43 (d, J = 9.6 Hz, 1 H, 5'α-H), 3.56 (d, J = 9.6 Hz, 1 H, 5'β-H), 4.01 (q, J = 7.2 Hz, 1 H, CH_3-C*H*COO), 5.42 (s, 1 H, 3'-H). ^{13}C NMR (50.3 MHz) δ = 18.2 (CH_3, *C*H_3CHCOO), 20.7 (CH_3, 4'α-CH_3), 24.7 (CH_3, 4'β-CH_3), 37.5 (C, C4'), 45.2 (CH, CH_3*C*HCOO), 57.5 (CH_2, C5'), 78.3 (CH, C3'), 168.7 (C, C2'), 173.4 (C, COO), 187.4 (C, Ar-CO).

(***R,S***)/(***S,R***)-***3e***: HPLC (conditions A), r.t. 30.2 min. ^1H NMR (200 MHz) δ = 0.86 (s, 3 H, 4'α-CH_3), 1.15 (s, 3 H, 4'β-CH_3), 1.61 (d, J = 7.2 Hz, 3 H, C*H*$_3$-CHCOO), 3.42 (d, J = 9.6 Hz, 1 H, 5'α-H), 3.55 (d, J = 9.6 Hz, 1 H, 5'β-H), 3.98 (q, J = 7.3 Hz, 1 H, CH_3-C*H*COO), 5.42 (s, 1 H, 3'-H). ^{13}C NMR (50.3 MHz) δ = 18.2 (CH_3, *C*H_3CHCOO), 20.7 (CH_3, 4'α-CH_3), 24.7 (CH_3, 4'β-CH_3), 37.5 (C, C4'), 44.8 (CH, CH_3*C*HCOO), 57.6 (CH_2, C5'), 78.3 (CH, C3'), 168.7 (C, C2'), 173.3 (C, COO).

(***R,S***)/(***S,R***)-***3f***: HPLC (conditions E), r.t. 46.7 min. ^1H NMR (200 MHz) δ = 0.75 (s, 3 H, 4'α-CH_3), 1.09 (s, 3 H, 4'β-CH_3), 1.56 (d, J = 7.0 Hz, 3 H, C*H*$_3$-CHCOO), 3.40 (d, J = 9.6 Hz, 1 H, 5'α-H), 3.52 (d, J = 9.6 Hz, 1 H, 5'β-H), 3.91 (q, J = 7.0 Hz, 1 H, CH_3-C*H*COO), 5.40 (s, 1 H, 3'-H). ^{13}C NMR (50.3 MHz) δ = 18.1 (CH_3, *C*H_3CHCOO), 20.5 (CH_3, 4'α-CH_3), 24.6 (CH_3, 4'β-CH_3), 37.5 (C, C4'), 45.3 (CH, CH_3*C*HCOO), 57.5 (CH_2, C5'), 78.0 (CH, C3'), 168.5 (C, C2'), 173.4 (C, COO).

General procedure for the hydrolysis of α-arylpropionates ***(S,S)-3*** *or* ***(R,R)-3****: (S)- or (R)-α-arylpropionic acids* ***(S)-4*** *or* ***(R)-4*** *and recovery of the chiral auxiliary* ***(S)-1*** *or* ***(R)-1****.*

A mixture of the α-arylpropionate (1 equiv), acetic acid (8ml / mmol) and 2 N HCl (3.2 ml / mmol) was heated at 120°C (bath temperature) till completion of the hydrolysis (2.5 h), following the reaction by tlc. The mixture was allowed to cool to room temperature and the volatile products were distilled at reduced pressure. Water (8 ml / mmol) was added to the residue, and the mixture was extracted with CH_2Cl_2 (3 x 8 ml / mmol). The combined organic phases were treated with cyclohexylamine (1 equiv) and the precipitate thus formed was filtered.

The solid was treated with N HCl until pH = 1, and the mixture was extracted with CH_2Cl_2 (3 x 8 ml / mmol). The combined organic extracts were washed with water (2 x 8 ml / mmol), dried with Na_2SO_4 and concentrated in vacuo to give the (S)- or (R)-α-arylpropionic acid.

The filtrate was concentrated in vacuo and the residue consisting of the chiral auxiliary ***(S)*-1** or ***(R)*-1** was crystallized from ethanol (0.2 ml / mmol).

The ee of the α-arylpropionic acid was obtained by HPLC under the chiral conditions indicated in each case, while the ee of the recovered chiral auxiliary was obtained by HPLC under the chiral conditions F.

(αS)-α-(6-Methoxy-2-naphthyl)propionic acid (S)-**4a**

Following the general procedure described above, from ***(S,S)*-3a** (520 mg, 1.25 mmol), **(*S*)-4a** (246 mg, 86% yield, 95% ee) and **(*S*)-1** (225 mg, 88% yield, > 99% ee) were obtained.

HPLC (conditions H): **(*S*)-4a**: r.t. 11.63 min; **(*R*)-4a**: r.t. 6.61 min;

$[\alpha]_D^{20}$ ($CHCl_3$, c = 1.00) = + 65.8 . Lit.[2]: $[\alpha]_D^{20}$ ($CHCl_3$, c = 1.00) = + 65.5 .

(αS)-α-[4-(2-Methylpropyl)phenyl]propionic acid (S)-**4b**

Following the general procedure described above, from ***(S,S)*-3b** (350 mg, 0.89 mmol), **(*S*)-4b** (175 mg, 95% yield, 90% ee) and **(*S*)-1** (170 mg, 93% yield, > 99% ee) were obtained.

HPLC (conditions I): **(*S*)-4b**: r.t. 11.98 min; **(*R*)-4b**: r.t. 8.88 min;

$[\alpha]_D^{20}$ (ethanol, c = 1.00) = + 59.9 °. Lit.[3]: $[\alpha]_D^{20}$ (ethanol, c = 1.00) = + 60.2 .

(αS)-α-(3-Benzoylphenyl)propionic acid (S)-**4c**

Following the general procedure described above, from ***(S,S)*-3c** (390 mg, 0.88 mmol), **(*S*)-4c** (205 mg, 92% yield, > 99% ee) and **(*S*)-1** (175 mg, 97% yield, > 99% ee) were obtained.

HPLC (conditions J): **(*S*)-4c**: r.t. 47.48 min; **(*R*)-4c**: r.t. 34.65 min;

$[\alpha]_D^{20}$ (isopropanol, c = 1.00) = + 49.3 . Lit.[3]: $[\alpha]_D^{20}$ (isopropanol, c = 1.00) = + 49.8 .

(αS)-α-[4-(2-Thenoyl)phenyl]propionic acid (S)-**4d**

Following the general procedure described above, from ***(S,S)*-3d** (146 mg, 0.33 mmol), **(*S*)-4b** (80 mg, 93% yield, 95% ee) and **(*S*)-1** (55 mg, 82% yield, > 99% ee) were obtained.

HPLC (conditions G): **(*S*)-4d**: r.t. 23.43 min; **(*R*)-4d**: r.t. 20.73 min;

$[\alpha]_D^{20}$ ($CHCl_3$, c = 1.00) = + 40.8 . Lit.[4]: $[\alpha]_D^{28}$ ($CHCl_3$, c = 1.00) = + 39.5 (93% ee).

(αS)-α-(3-Fluorobiphenyl-4-yl)propionic acid (S)-**4e**

Following the general procedure described above, from ***(S,S)*-3e** (500 mg, 1.16 mmol), **(*S*)-4e** (120 mg, quantitative yield, > 99% ee) and **(*S*)-1** (140 mg, 95% yield, > 99% ee) were obtained.

HPLC (conditions K): **(*S*)-4e**: r.t. 22.44 min; **(*R*)-4e**: r.t. 20.25 min;

$[\alpha]_D^{20}$ (isopropanol, c = 1.00) = + 44.6 . Lit.[3]: $[\alpha]_D^{20}$ (isopropanol, c = 1.00) = + 44.7 .

(αS)-α-Phenylpropionic acid (S)-4f

Following the general procedure described above, from ***(S,S)*-3f** (392 mg, 1.16 mmol), **(*S*)-4f** (125 mg, 72% yield, 99% ee) and **(*S*)-1** (230 mg, 97% yield, > 99% ee) were obtained.

HPLC (conditions L): **(*S*)-4f**: r.t. 17.66 min; **(*R*)-4f**: r.t. 16.12 min;
$[\alpha]_D^{20}$ (acetone, c = 1.50) = + 95.1 . Lit.[5]: $[\alpha]_D^{25}$ for **(*S*)-4f** (acetone, c = 1.50) = - 95.5 . **(para R)**

(αR)-α-[4-(2-Methylpropyl)phenyl]propionic acid **(*R*)-4b**
Following the general procedure described above, from **(*R,R*)-3b** (274 mg, 0.70 mmol), **(*R*)-4b** (120 mg, 83% yield, 92% ee) and **(*R*)-1** (140 mg, 98% yield, > 99% ee) were obtained.
$[\alpha]_D^{20}$ (ethanol, c = 1.00) = - 60.0 .

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