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ASYMMETRIC SYNTHESIS OF β-SUBSTITUTED γ-LACTAMS EMPLOYING THE SAMP-/RAMP-HYDRAZONE METHODOLOGY. APPLICATION TO THE SYNTHESIS OF (*R*)-(–)-BACLOFEN

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Abstract – A short and efficient asymmetric synthesis of β-substituted γ-lactams is described. Key steps are the α-alkylation of aldehyde SAMP-hydrazones with alkyl bromoacetates, their MMPP mediated conversion to the corresponding nitriles and a reductive cyclization with Raney Ni or Ni boride to the title pyrrolidin-2-ones. The β-substituted γ-lactams are obtained in three steps, good overall yields (27-78%) and excellent enantiomeric excesses (*ee* = 93-99%). The applicability of this procedure for the asymmetric synthesis of GABAs (γ-aminobutyric acids) is demonstrated for (*R*)-(–)-baclofen hydrochloride, which is obtained in 4 steps, 55% yield and 94% *ee*.

INTRODUCTION

The lactam group is a characteristic structural feature of many natural products and biologically active compounds. For example, β-lactams are of enormous importance as antibiotics.[1] The extensive use of classical β-lactam antibiotics in medicine led to an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer. Therefore, the homologeous γ-lactams[2] are popular targets as analogues of β-lactam antibiotics.[3] The pyrrolidin-2-one moiety is also often found in bioactive compounds.[4] Among the drugs bearing a γ-lactam ring, for instance (±)-rolipram,[5] which has been originally developed as an antidepressant by the Schering AG, is a selective inhibitor of phosphodiesterase (PDE) type IV.[6] The (*R*)-enantiomer of rolipram is primarily responsible for the pharmacological effects.[7] The amide bond of lactams can be easily hydrolysed to the corresponding acyclic amino acids. GABAs (γ-aminobutyric acids) are the acyclic forms of γ-lactams and play important roles in various nervous

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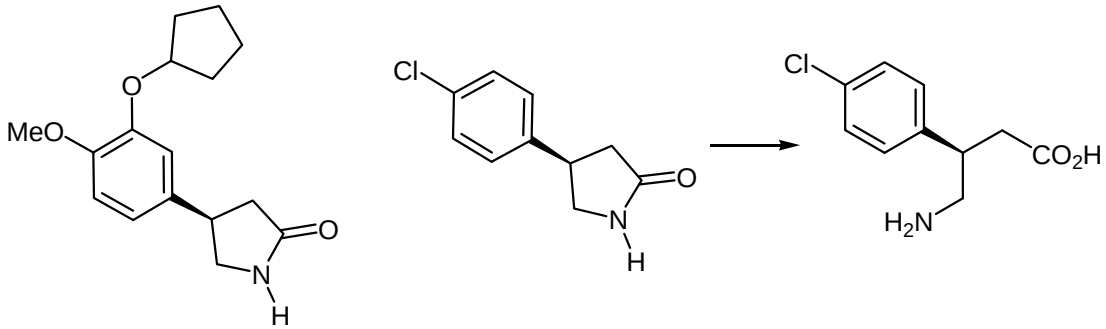
Dedicated to the memory of Professor Kenji Koga

system functions.[8] They are used in the regulation of neurological disorders such as Parkinson´s disease and epilepsy.[9] The strongly lipophilic β-substituted GABA derivative baclofen [γ-amino-β-(4-chlorophenyl)butyric acid] is the only available selective agonist of the $GABA_B$ receptor[10] and is used as a muscle relaxant in the treatment of spasticy caused by diseases at the spinal cord (Figure 1).



(*R*)-Rolipram (*R*)-Baclofen

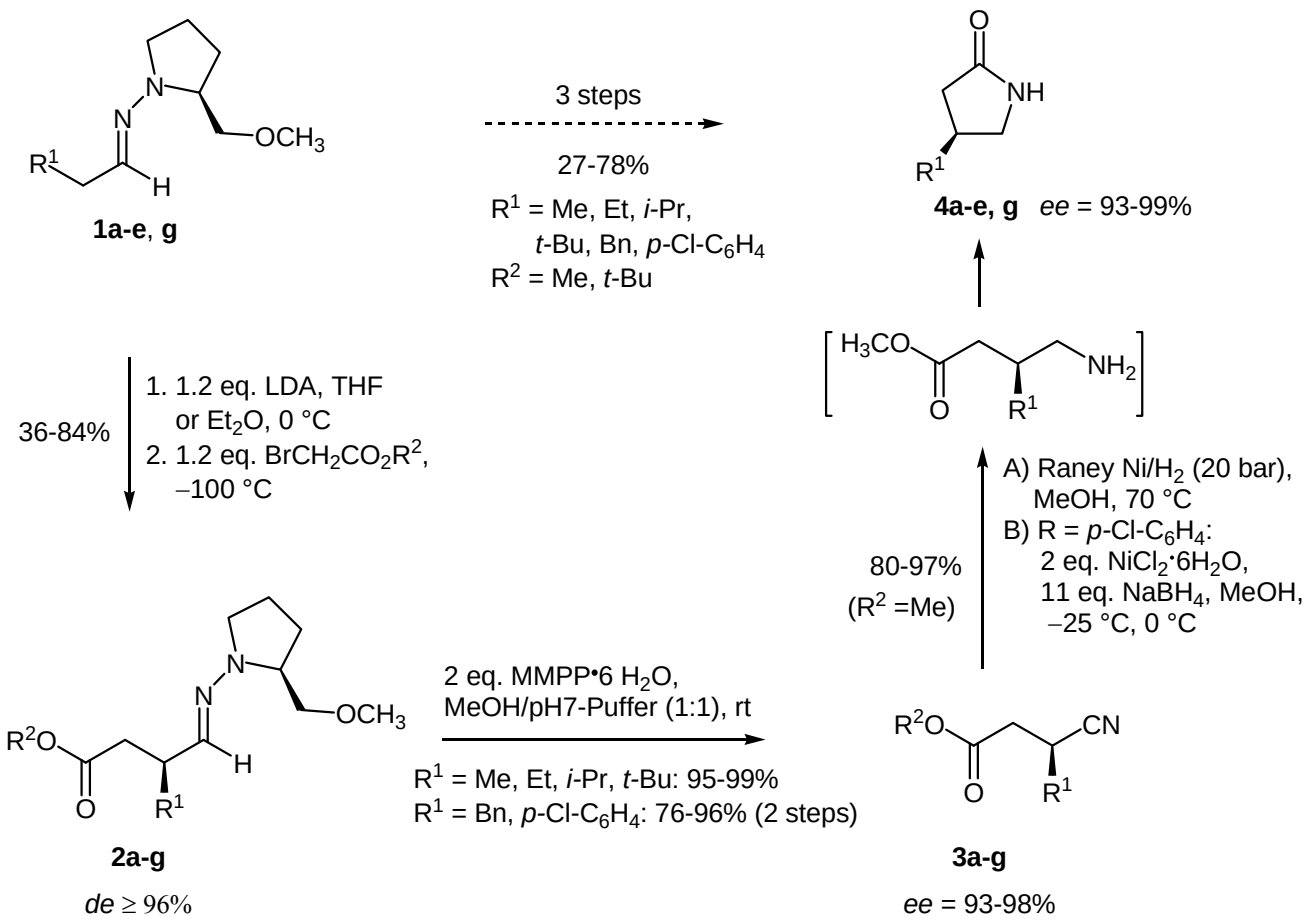
Figure 1

Baclofen is commercially available in its racemic form (Lioresal® and Baclon®), but the biological activity is known to residue in the (*R*)-enantiomer.[11] Some syntheses of (±)-baclofen and its enantiomers have been reported in the literature[12] as well as some stereoselective syntheses of β-alkyl- or β-aryl-substituted γ-lactams.[13] In contrast, protocols for a stereoselective entry with a broad substitution pattern are rather rare. Intrigued by the manifold properties of γ-lactams and their derivatives and our own efforts in the synthesis of lactams,[14] we wish to report a short and efficient asymmetric synthesis of β-substituted 2-pyrrolidinones as well as its application to the synthesis of (*R*)-(−)-baclofen employing the SAMP/RAMP-hydrazone methodology.[15]

RESULTS AND DISCUSSION

The synthetic three step strategy leading to the β-substituted γ-lactams is outlined in Scheme 1. Starting from the aldehyde SAMP-hydrazones (**1a-e**, **g**), α-alkylation with methyl or *tert*-butyl bromoacetate[16] and subsequent oxidative removal of the auxiliary with magnesium monoperoxyphthalate (MMPP) gave the corresponding nitriles (**3a-g**).[17] Reduction of the nitriles to the corresponding amines and *in situ* cyclization afforded the target lactams in moderate to good yields (27-78%) and high enantiomeric excesses (*ee* = 93-99%) .

The α-alkylation of the aldehyde-SAMP-hydrazones (**1a-e**, **g**) with methyl or *tert*-butyl 2-bromoacetate proceeded smoothly either in Et_2O or THF. After deprotonation with lithium diisopropylamide the resulting azaenolates were trapped with the bromoacetate at −100 °C. Aqueous work up and purification by flash chromatography gave the alkylated hydrazones (**2a-g**) in acceptable to good yields and excellent diastereomeric excesses (*de* ≥ 96%) (Table 1).



Scheme 1

Table 1

2	R^1	R^2	Yield [%]	*de* [%][a]	Config.
a	Me	Me	36	≥ 96	*S*, *S*
b	Et	Me	49 (73)[b,c]	≥ 96	*S*, *S* (*R*, *R*)[c]
c	*i*-Pr	Me	83	≥ 96	*S*, *R*
d	*t*-Bu	Me	76 (93)[b,c]	≥ 96	*S*, *R* (*R*, *S*)[c]
e	Bn	Me	70	≥ 96	*S*, *S*
f	Bn	*t*-Bu	78	≥ 96	*S*, *S*
g	*p*-Cl-C_6H_4	Me	97[b] (84)[c]	≥ 96	*S*, *R* (*R*, *S*)[c]

a) Determined by ^{1}H and ^{13}C NMR spectroscopy.

b) Conversion determined by GC.

c) Utilizing the corresponding RAMP-hydrazone.

The configuration of the newly formed stereogenic center was assigned as *R* (**2a**, **b**, **e**, **f**) or *S* (**2c**, **d**, **g**) starting from the corresponding SAMP-hydrazones and opposite utilizing the RAMP-auxiliary, respectively. Two different electrophiles (methyl and *tert*-butyl 2-bromoacetates) were employed in the α-alkylation step of the 3-phenylpropionaldehyde SAMP-hydrazone (**1e**) to the alkylated hydrazones (**2e**) and (**2f**). They could serve as model substrates in the chemoselective reduction of the nitrile to the amine functionality and subsequent cyclization to the desired γ-lactam.

Oxidative conversion of the α-substituted aldehyde hydrazones (**2a-g**) to the corresponding nitriles (**3a-g**) was achieved with magnesium monoperoxyphthalate hexahydrate (MMPP) without racemization.[17,18] Attempts for a direct reductive transformation of the aldehyde hydrazone (**2f**) to the corresponding amine with BH_3·THF in refluxing THF produced a complex reaction mixture.[19] The hydrazones were added to a rapidly stirred suspension of MMPP in a methanol/pH 7 phosphate buffer at 0 °C and the reaction mixture was stirred until complete conversion (TLC control). After work up and flash chromatography the nitriles (**3a-g**) were obtained with high yields and enantiomeric excesses (Table 2).

Table 2

3	R^1	R^2	Yield [%]	*ee*[a] [%]	Config.
a	Me	Me	95	93	*S*
b	Et	Me	99 (46)[b,c]	98 (98)[c]	*S* (*R*)[c]
c	*i*-Pr	Me	97	98	*R*
d	*t*-Bu	Me	98 (71)[b,c]	97 (97)[c]	*R* (*S*)[c]
e	Bn	Me	66[b]	96	*S*
f	Bn	*t*-Bu	75[b]	95	*S*
g	*p*-Cl-C_6H_4	Me	92[b] (98)[b,c]	95 (93)[c]	*R* (*S*)[c]

a) Determined by GC with a chiral stationary phase.

b) Yield over 2 steps starting from the corresponding hydrazone (**1**).

c) Utilizing the corresponding RAMP-hydrazone.

The nitriles (**3e**) and (**3f**) were used in initial experiments to find sufficient reaction conditions for a one pot reduction / cyclization process to the desired γ-lactams (**4a-e, g**). Hydrogenation of the *tert*-butyl ester (**3f**) with Raney Ni in methanol at 70 °C led to a mixture of the amine and lactam (**4e**)**.** Addition of 10% of aqueous NH_4OH-solution (30%) to favor the cyclization under more basic condition resulted in slighty higher amounts of the cyclized product (Table 3).

Table 3

R^2	Conditions	Amine : Lactam[a]	Yield [%]
***t*-Bu**	Raney Ni (W2), H_2 (20 bar), MeOH, 70 °C, 6 h	50 : 50	-
***t*-Bu**	Raney Ni (W2), H_2 (20 bar), MeOH/NH_4OH, 70 °C, 6 h	40 : 60[b]	-
***t*-Bu**	1. Raney Ni (W2), H_2 (20 bar), MeOH, 70 °C, 16 h 2. Na_2CO_3, MeOH, Δ, 24 h	0 : 100	66
Me	Raney Ni (W2), H_2 (20 bar), MeOH, 70 °C, 16 h	0 : 100	89

a) Conversion determined by GC.

b) Utilizing of a 30% aqueous NH_4OH-solution/MeOH (1:10).

To increase the amount of the lactam the obtained reaction mixture was refluxed for 24 h in methanol basified with sodium carbonate leading to the cyclic product in moderate yield. This two step procedure could be optimized by employing the methyl ester which directly cyclized after reduction to the amine.

Using the optimized conditions the methyl ester substituted nitriles (**3a-e**) were converted to the corresponding γ-lactams (**4**) in high yields and without racemization (Table 4).

Table 4

4	R^1	Yield [%]	*ee*[a] [%]	Config.
a	Me	80	93	*S*
b	Et	95 (46)[b,c]	97 (97)[c]	*S* (*R*)[c]
c	*i*-Pr	97	97	*R*
d	*t*-Bu	90 (71)[b,c]	99 (97)[c]	*R* (*S*)[c]
e	Bn	89[b]	95	*S*

a) Determined by HPLC with a chiral stationary phase.

b) Yield over 2 steps starting from the corresponding hydrazone (**1**).

c) Utilizing the corresponding RAMP-hydrazone.

Unfortunately, the more reactive α-*p*-Cl-C_6H_4-substituted nitrile (**4g**) decomposed under these reaction conditions. Investigations for a milder reduction with Raney Ni at room temperature resulted in a low yield of the desired product. Efforts for a reduction using catalytic amounts of PtO_2 also afforded a complex mixture of products. A two step procedure using 10% Pd/C and subsequent cyclization of the amine led to the corresponding dechlorinated γ-lactam in high yields. Rh on Al_2O_3 seemed also not to be a suitable

catalyst for the reduction, because the desired lactam was obtained as a racemate but with a high yield (99%). A mild method for the reduction of nitriles to primary amines is the reaction with Co or Ni boride using $NaBH_4$.[20] With Co boride in a THF/H_2O-mixture at room temperature the desired product was formed, but a significant racemization occurred (*ee* = 58%). Using the same reaction conditions with the more reactive Ni boride led to decomposition of the nitrile even if methanol as solvent was used as reported in the literature.[21] Perfoming the reaction at −25 °C and addition of the $NaBH_4$ in small portions over a period of 30 min finally led to the γ-lactam (**4f**) in good yield (80%) and still high enantiomeric excess (94%) (Table 5).

Table 5

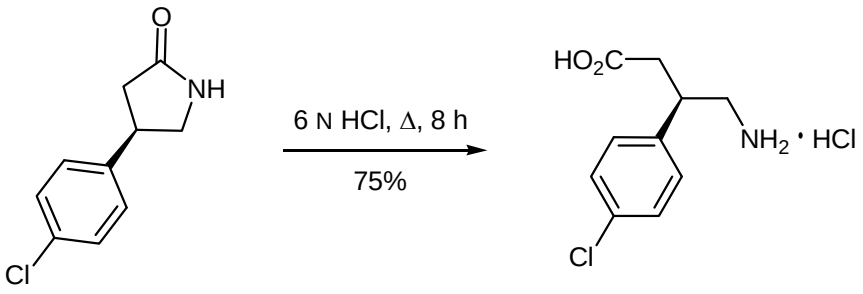
Conditions	Yield of 4g [%]	*ee*[a] [%]
Raney Ni (W2), H_2 (20 bar), MeOH, 70 °C, 15 h	complex mixture	-
Raney Ni (W2), H_2 (20 bar), MeOH, rt, 15 h	50	-
PtO_2, H_2 (3.5 bar), EtOH, HCl, rt, 3 h	complex mixture	-
1. 10% Pd/C, H_2 (3.5 bar), MeOH, rt, 5h 2. 3 N NaOH, MeOH, rt , 1h	97[b]	-
5% Rh/Al_2O_3, H_2 (1 bar), EtOH, NH_3, rt , 22h	99	0
$CoCl_2 \cdot 6H_2O$, $NaBH_4$, THF/H_2O, 0 °C to rt, 24 h	96[c]	58
$NiCl_2 \cdot 6H_2O$, $NaBH_4$, THF/H_2O, rt, 1 h	complex mixture	-
$NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, rt, 1 h	complex mixture	-
$NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, −25 to 0 °C, 1 h	80	94

a) Determined by HPLC with a chiral stationary phase with the corresponding *N*-Boc-protected γ-lactam.

b) Yield of the corresponding dechlorinated γ-lactam.

c) Conversion determined by GC.

The β-substituted γ-lactams serve as precursors for the synthesis of GABA derivatives. To show the applicability of our method the *p*-chlorophenyl-substituted γ-lactam (**4g**) was hydrolysed with 6 N HCl to the pharmaceuticaly active (*R*)-baclofen hydrochloride (**5**) in good yield (75%). By this method (*R*)-baclofen was synthesized in only 4 steps with an excellent overall yield of 55% and 94% enantiomeric excess.



(*R*)-4g **(*R*)-5**

Scheme 2

CONCLUSION

In conclusion, we have developed an efficient and short asymmetric synthesis of β-aryl- and β-alkyl-substituted γ-lactams employing the SAMP-/RAMP-hydrazone methodology. The title γ-lactams were obtained in moderate to good overall yields and excellent enantiomeric excesses. The application of this procedure as an entry to GABAs could be demonstrated for the asymmetric synthesis of (*R*)-baclofen hydrochloride.

EXPERIMENTAL

The enantiopure aldehyde SAMP- or RAMP-hydrazones (**1a-e**, **g**) were synthesized by direct condensation of equimolar amounts of the corresponding commercially available aldehydes and (*S* or *R*)-1-amino-2-methoxymethylpyrrolidine (SAMP or RAMP). The reactions were performed neat at 0 °C and stirred at room temperature until complete conversion (TLC control). After purification by column chromatography on silica gel (ether / *n*-pentane) the aldehyde hydrazones were obtained in virtually quantitative yields as colorless liquids. 4-Chlorobenzaldehyde was prepared from the corresponding alcohol by *Dess-Martin* oxidation.[22] *Swern* or *Collins*[23] oxidation did not give acceptable yields.

(*S*)-*N*-(3,3-Dimethylbutylidene)-2-methoxymethylpyrrolidin-1-amine (1d): $[\alpha]_D^{24} = -93.2$ (c = 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.95 (s, 9H, C(C*H*$_3$)$_3$), 1.80-2.00 (m, 4H, NCH$_2$C*H*$_2$, NCHC*H*$_2$), 2.11 (d, 2H, *J* = 5.9 Hz, (CH$_3$)$_3$CC*H*$_2$), 2.75 (dd, 1H, *J* = 16.6/8.2 Hz, NCH*H*CH$_2$), 3.34-3.46 (m, 3H, CH$_3$OCH*H*, NC*H*CH$_2$, NC*H*HCH$_2$), 3.38 (s, 3H, C*H*$_3$O), 3.54-3.60 (m, 1H, CH$_3$OC*H*H), 6.72 (t, 1H, *J* = 6.2 Hz, NC*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.19, 26.59 (*C*H$_2$), 29.46 (*C*H$_3$), 31.05 (CH$_3$*C*), 46.77 (*C*H$_2$), 50.76 (N*C*H$_2$), 59.20 (*C*H$_3$), 63.53 (*C*H), 74.92 (O*C*H$_2$), 137.64 (N*C*H) ppm; IR (film) $\tilde{\upsilon}$ = 2954 (vs), 2876 (vs), 2828 (s), 1602 (w), 1466 (s), 1365 (m), 1342 (m), 1283 (vw), 1242 (vw), 1197 (m), 1120 (vs), 973 (w), 911 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 212 (9) [M$^{+\bullet}$], 168 (10), 167 (100), 70 (14). *Anal.* Calcd for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 68.04; H, 11.67; N, 13.28.

(*S*)-*N*-(2-(4-Chlorophenyl)ethylidene)-2-methoxymethylpyrrolidin-1-amine (1g): $[\alpha]_D^{23}$ = –98.5 (c = 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.75-2.01 (m, 4H, NCH_2CH_2, $NCHCH_2$), 2.76 (dt, 1H, *J* = 8.4/8.4 Hz, $NCHHCH_2$), 3.30-3.37 (m, 1H, $NCHHCH_2$), 3.40 (s, 3H, CH_3O), 3.42-3.49 (m, 2H, CH_3OCHH, $NCHCH_2$), 3.53 (d, 2H, *J* = 5.7 Hz, $NCHCH_2$), 3.58 (dd, 1H, *J* = 7.9/2.7 Hz, CH_3OCHH), 6.63 (t, 1H, *J* = 5.7 Hz, NC*H*), 7.14-7.28 (m, 4H, arom C*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.19, 26.63, 38.95 (CH_2), 50.16 (NCH_2), 59.24 (CH_3), 63.36 (*C*H), 74.80 (OCH_2), 128.56, 130.14 (arom *C*H), 132.05 (arom *C*Cl), 135.38 (N*C*H), 137.47 (arom *C*) ppm; IR (film) $\tilde{\upsilon}$ = 2972 (vs), 2881 (vs), 2826 (vs), 1597 (m), 1490 (vs), 1458 (s), 1408 (w), 1343 (m), 1304 (w), 1284 (w), 1197 (vs), 1118 (vs), 1015 (m), 973 (w), 924 (w), 902 (vw), 871 (vw), 825 (s), 717 (w), 692 (w), 649 (w), 549 (w), 490 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 266 (11) [$M^{+\bullet}$], 223 (31), 222 (15), 221 (100), 125 (22). *Anal.* Calcd for $C_{14}H_{19}N_2OCl$: C, 63.03; H, 7.18; N, 10.50. Found: C, 63.22; H, 6.97; N, 10.53.

General procedure 1 (GP1) for α-alkylation of aldehyde SAMP-hydrazones with alkyl bromoacetates (**2a-g**):

To a solution of diisopropylamine (1.2 mmol/mmol hydrazone) in Et_2O or THF (5 mL/mmol) was added dropwise *n*-buthyllithium (2.5 M in hexane) (1.2 mmol/mmol hydrazone) at 0 °C. The solution was stirred for 15 min and the aldehyde hydrazone (**1a-f**) was added dropwise. The reaction mixture was stirred for an additional 1 h and then cooled to –100 °C. Methyl or *tert*-butyl 2-bromoacetate (1.2 mmol/mmol hydrazone) in Et_2O or THF (1 mL/mmol) was added slowly over a period of 30 min and the reaction mixture was left over night while allowing to warm to rt. It was quenched with saturated aqueous NH_4Cl solution and extracted three times with Et_2O. The organic layer was then washed with H_2O and brine and the aqueous layers were reextracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography.

(*S*)-Methyl 4-((*S*)-2-methoxymethylpyrrolidin-1-ylimino)-3-methylbutanoate (2a): According to GP1 hydrazone (**1a**) (1.70 g, 10 mmol) and methyl 2-bromoacetate (1.84 g, 12 mmol) were added to a solution of lithium diisopropylamide (12 mmol) in Et_2O (45 mL). Purification by column chromatography (ether / *n*-pentane 1:3, 3% triethylamine) afforded **2a** (869 mg, 36%) as a colorless liquid. *de* ≥ 96% (determined by ^{1}H NMR and ^{13}C NMR spectrum). $[\alpha]_D^{23}$ = –121.5 (c = 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.11 (dd, 3H, *J* = 6.9/1.4 Hz,CH_3), 1.74-1.98 (m, 4H, $NCHCH_2$, NCH_2CH_2), 2.30 (ddd, 1H, *J* = 15.1/7.2/1.4 Hz, NCHCHCH*H*), 2.58 (ddd, 1H, *J* = 15.4/7.1/1.4 Hz, NCHCHC*H*H), 2.69 (dt, 1H, J = 8.5/8.5 Hz, $NCHHCH_2$), 2.81-2.90 (m, 1H, NCHC*H*), 3.29-3.37 (m, 1H, $NCHHCH_2$), 3.37 (d, 3H, *J* = 1.4 Hz, CH_3O), 3.40-3.45 (m, 2H, CH_3OCHH, $NCHCH_2$), 3.54-3.58 (m, 1H, CH_3OCHH), 3.67 (d, 3H, *J* = 1.6 Hz, CH_3OCO), 6.55 (d, 1H, J = 4.7 Hz, NC*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 18.75 (CH_3),

21.98, 26.49 (*C*H_2), 33.65 (*C*H), 39.31 (*C*H_2), 49.77 (NCH_2), 51.28 (*C*H_3OCO), 59.11 (*C*H_3O), 63.31 (*C*H), 74.46 (O*C*H_2), 139.95 (N*C*H), 172.90 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 2963 (vs), 2879 (vs), 1739 (vs), 1603 (w), 1456 (s), 1364 (w), 1343 (w), 1280 (m), 1196 (s), 1172 (s), 1121 (m), 1047 (vw), 1008 (m), 972 (vw), 900 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 242 (13) [$M^{+\bullet}$], 198 (10), 197 (100), 96 (18), 70 (27), 59 (5). *Anal.* Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.50; H, 8.87; N, 11.55.

(*S*)-Methyl 3-(((*S*)-2-methoxymethylpyrrolidin-1-ylimino)methyl)pentanoate (2b): According to GP1 hydrazone (**1b**) (1.84 g, 10 mmol) and methyl 2-bromoacetate (1.84 g, 12.0 mmol) were added to a solution of lithium diisopropylamide (12 mmol) in Et_2O (45 mL). Purification by column chromatography (ether / *n*-pentane 1:4, 3% triethylamine) afforded **2b** (1.257 g, 49%) as a colorless liquid. *de* ≥ 96% (determined by ^{1}H NMR and ^{13}C NMR spectrum). $[\alpha]_D^{23}$ = –97.3 (c = 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.93 (t, 3H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.51 (dq, 2H, *J* = 7.2/7.2 Hz, CH$_3$C*H*$_2$), 1.73-2.00 (m, 4H, NCHC*H*$_2$, NCH$_2$C*H*$_2$), 2.39 (dd, 1H, *J* = 15.1/6.1 Hz, NCHCHCH*H*), 2.54 (dd, 1H, *J* = 15.1/8.2 Hz, NCHCHC*H*H), 2.64-2.75 (m, 2H, NCH*H*CH$_2$), NCHC*H*), 3.30-3.40 (m, 2H, NC*H*CH$_2$, NC*H*HCH$_2$), 3.38 (d, 3H, *J* = 0.5 Hz, C*H*$_3$O), 3.43 (dd, 1H, *J* = 9.2/7.2 Hz, CH$_3$OCH*H*), 3.56 (dd, 1H, *J* = 8.7/3.2 Hz, CH$_3$OC*H*H), 3.67 (s, 3H, C*H*$_3$OCO), 6.56 (d, 1H, *J* = 5.0 Hz, NC*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.26 (*C*H$_3$), 22.00, 26.35, 26.52, 37.35 (*C*H$_2$), 40,28 (*C*H), 49.96 (NCH$_2$), 51.36 (*C*H$_3$OCO), 59.20 (*C*H$_3$O), 63.42 (*C*H), 74.60 (O*C*H$_2$), 129.43 (N*C*H), 173.33 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 2961 (vs), 2877 (vs), 1739 (vs), 1602 (w), 1458 (s), 1340 (m), 1251 (s), 1194 (s), 1170 (vs), 1122 (vs), 1013 (w), 972 (w), 902 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 256 (12) [$M^{+\bullet}$], 212 (13), 211 (100), 110 (21), 82 (6), 70 (28). *Anal.* Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 60.53; H, 9.87; N, 11.05.

(*S*)-Methyl 3-(((*R*)-2-methoxymethylpyrrolidin-1-ylimino)methyl)-4-methylpentanoate (2c): According to GP1 hydrazone (**1c**) (1.983 g, 10 mmol) and methyl 2-bromoacetate (1.84 g, 12 mmol) were added to a solution of lithium diisopropylamide (12 mmol) in Et_2O (45 mL). Purification by column chromatography (ether / *n*-pentane 1:4, 3% triethylamine) afforded **2c** (2.248 g, 83%) as a colorless liquid. *de* ≥ 96% (determined by ^{1}H NMR and ^{13}C NMR spectrum). $[\alpha]_D^{24}$ = –83.2 (c = 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.91 (d, 3H, *J* = 6.0 Hz, C*H*$_3$CHCH$_3$), 0.93 (d, 3H, *J* = 6.0 Hz, CH$_3$CHC*H*$_3$), 1.74-1.98 (m, 5H, NCHC*H*$_2$, NCH$_2$C*H*$_2$, C*H*), 2.38 (dd, 1H, *J* = 15.1/5.0 Hz, NCHCHCH*H*), 2.56 (dd, 1H, *J* = 14.8/9.3 Hz, NCHCHC*H*H), 2.63-2.73 (m, 2H, NCH*H*CH$_2$, NCHC*H*), 3.29-3.36 (m, 2H, NC*H*CH$_2$, NC*H*HCH$_2$), 3.36 (s, 3H, CH$_3$O), 3.40 (dd, 1H, *J* = 9.1/6.6 Hz, CH$_3$OCH*H*), 3.55 (dd, 1H, *J* = 9.1/3.6 Hz, CH$_3$OC*H*H), 3.65 (s, 3H, C*H*$_3$OCO), 6.57 (d, 1H, *J* = 5.2 Hz, NC*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.29, 19.82 (*C*H$_3$), 21.93, 26.46 (*C*H$_2$), 30.78 (*C*H), 34.67 (*C*H$_2$), 44.61 (*C*H), 49.92 (NCH$_2$), 51.27 (*C*H$_3$OCO), 59.11 (*C*H$_3$O), 63.36 (*C*H), 74.49 (O*C*H$_2$), 138.18 (N*C*H), 173.41 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ =

2958 (vs), 2877 (vs), 1740 (vs), 1601 (w), 1461 (s), 1439 (m), 1370 (w), 1340 (m), 1291 (w), 1258 (s), 1194 (s), 1168 (vs), 1119 (s), 998 (w), 973 (w), 892 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 270 (9) [$M^{+\bullet}$], 226 (14), 225 (100), 124 (18), 96 (5), 70 (36), 69 (7). High Resol. MS Calcd for $C_{14}H_{26}N_2O_3$: 270.1943. Found: 270.1943.

(*S*)-Methyl 3-(((*R*)-2-methoxymethylpyrrolidin-1-ylimino)methyl)-4,4-dimethylpentanoate (2d): According to GP1 hydrazone (**1d**) (2.123 g, 10 mmol) and methyl 2-bromoacetate (1.84 g, 12 mmol) were added to a solution of lithium diisopropylamide (12 mmol) in Et_2O (45 mL). Purification by column chromatography (ether / *n*-pentane 1:4) afforded **2d** (2.163 g, 76%) as a colorless liquid. *de* ≥ 96% (determined by ^{1}H NMR and ^{13}C NMR spectrum). $[\alpha]_D^{24}$ = –56.1 (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.93 (s, 9H, (CH_3)$_3$C), 1.75-1.99 (m, 4H, NCHCH_2, NCH_2CH_2), 2.40-262 (m, 3H, NCHC*H*, NCHCHCH_2), 2.69 (dt, 1H, *J* = 8.4/8.4 Hz, NCH*H*CH_2), 3.29-3.49 (m, 3H, CH_3OCHH, NC*H*CH_2, NC*H*HCH_2), 3.36 (s, 3H, CH_3O), 3.55 (dd, 1H, *J* = 8.9/3.2 Hz, CH_3OCHH), 3.63 (s, 3H, CH_3OCO), 6.60 (d, 1H, *J* = 4.5 Hz, NC*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.97, 26.49 (CH_2), 27.67 (CH_3), 33.29 (CH_2, (CH_3)*C*), 48.73 (*C*H), 50.09 (NCH_2), 51.37 (CH_3OCO), 59.20 (CH_3O), 63.53 (*C*H), 74.65 (OCH_2), 138.00 (N*C*H), 173.96 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 2959 (vs), 2875 (vs), 1741 (vs), 1600 (w), 1464 (m), 1438 (m), 1368 (m), 1292 (w), 1252 (w), 1197 (s), 1159 (s), 1120 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 284 (11) [$M^{+\bullet}$], 240 (15), 239 (100), 227 (9), 138 (7), 70 (18). *Anal.* Calcd for $C_{15}H_{28}N_2O_3$: C, 63.35; H, 9.92; N, 9.85. Found: C, 63.51; H, 10.22; N, 10.17.

(*S*)-Methyl 4-((*S*)-2-methoxymethylpyrrolidin-1-ylimino)-3-benzylbutanoate (2e): According to GP1 hydrazone (**1e**) (493 mg, 2.0 mmol) and methyl 2-bromoacetate (367 mg, 2.4 mmol) were added to a solution of lithium diisopropylamide (2.4 mmol) in Et_2O (9 mL). Purification by column chromatography (ether / *n*-pentane 1:4, 3% triethylamine) afforded **2e** (443 mg, 70%) as a colorless liquid. *de* ≥ 96% (determined by ^{1}H NMR and ^{13}C NMR spectrum). $[\alpha]_D^{24}$ = –102.5 (c = 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.72-1.99 (m, 4H, NCHCH_2, NCH_2CH_2), 2.38 (dd, 1H, *J* = 15.6/5.7 Hz, NCHCHCH*H*), 2.56 (dd, 1H, *J* =15.6/8.2 Hz, NCHCHC*H*H), 2.59-2.66 (m, 1H, NCH*H*CH_2), 2.71 (dd, 1H, *J* = 13.6/7.9 Hz, arom CCH*H*), 2.87 (dd, 1H, *J* = 13.6/6.9 Hz, arom CC*H*H), 3.03-3.15 (m, 1H, NCHC*H*), 3.22-3.30 (m, 1H, NC*H*HCH_2), 3.30-3.41 (m, 2H, CH_3OCHH, NC*H*CH_2), 3.36 (s, 3H, CH_3O), 3.46-3.56 (m, 1H, CH_3OCHH), 3.62 (s, 3H, CH_3OCO), 6.56 (d, 1H, *J* = 4.5 Hz, NC*H*), 7.16-7.32 (m, 5H, arom C*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.97, 26.56, 36.80, 39.82 (CH_2), 40.30 (*C*H), 49.73 (NCH_2), 51.33 (CH_3OCO), 59.20 (CH_3O), 63.28 (*C*H), 74.50 (OCH_2), 126.17 (*p*-arom *C*H), 128.31, 129.33 (arom *C*H), 138.04 (N*C*H), 139.45 (arom *C*), 173.17 (*C*O) ppm; IR ($CHCl_3$) $\tilde{\upsilon}$ = 3061 (w), 3025 (s), 2949 (vs), 1737 (vs), 1602 (m), 1495 (m), 1453 (s), 1339 (s), 1257 (s), 1200 (vs), 1152 (vs), 1120 (vs), 1018 (m),

973 (w), 880 (w), 754 (vs), 702 (s), 667 (w), 544 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 318 (7) [$M^{+\bullet}$], 274 (18), 273 (100), 172 (7), 144 (7), 117 (6), 91 (9), 70 (25). *Anal.* Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.70; H, 8.58; N, 9.04.

(*S*)-*tert*-Butyl 4-((*S*)-2-methoxymethylpyrrolidin-1-ylimino)-3-benzylbutanoate (2f): According to GP1 hydrazone (**1e**) (2.46 g, 10 mmol) and *tert*-butyl 2-bromoacetate (2.34 g, 12 mmol) were added to a solution of lithium diisopropylamide (12 mmol) in Et_2O (45 mL). Purification by column chromatography (ether / *n*-pentane 1:4, 3% triethylamine) afforded **2f** (2.805 g, 78%) as a colorless liquid. *de* ≥ 96% (determined by ^{1}H NMR and ^{13}C NMR spectrum). $[\alpha]_D^{23}$ = –83.3 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.42 (s, 9H, ((C*H*$_3$)$_3$C), 1.72-1.96 (m, 4H, NCHC*H*$_2$, NCH$_2$C*H*$_2$), 2.29 (dd, 1H, *J* = 15.4/6.0 Hz, NCHCHCH*H*), 2.43 (dd, 1H, *J* = 15.4/8.3 Hz, NCHCHC*H*H), 2.65-2.75 (m, 1H, NCH*H*CH$_2$), 2.72 (dd, 1H, *J* = 13.6/7.7 Hz, arom CCH*H*), 2.84 (dd, 1H, *J* = 13.7/7.1 Hz, arom CC*H*H), 2.97-3.05 (m, 1H, NCHC*H*), 3.27 (ddd, 1H, *J* = 9.9/7.4/3.3 Hz, NC*H*HCH$_2$), 3.32-3.39 (m, 2H, CH$_3$OCH*H*, NC*H*CH$_2$), 3.35 (s, 3H, C*H*$_3$O), 3.50-3.55 (m, 1H, CH$_3$OC*H*H), 6.54 (d, 1H, *J* = 5.2 Hz, NC*H*), 7.16-7.29 (m, 5H, arom C*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.01, 26.59 (*C*H$_2$), 28.12 ((*C*H$_3$)$_3$C), 38.38, 39.58 (*C*H$_2$), 40.49 (*C*H), 49.91 (N*C*H$_2$), 59.09 (*C*H$_3$O), 63.21 (*C*H), 74.55 (O*C*H$_2$), 79.98 ((CH$_3$)$_3$*C*), 125.87 (*p*-arom *C*H), 128.06, 129.19 (arom *C*H), 138.44 (N*C*H), 139.42 (arom *C*), 171.67 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 3061 (w), 3025 (m), 2974 (vs), 2927 (vs), 1728 (vs), 1602 (w), 1455 (s), 1414 (w), 1367 (vs), 1340 (s), 1255 (s), 1146 (vs), 1032 (w), 958 (m), 905 (w), 845 (w), 749 (m), 702 (s), 544 (vw) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 360 (17) [$M^{+\bullet}$], 316 (23), 315 (100), 287 (12), 260 (10), 259 (62), 190 (6), 123 (6), 62 (91), 70 (24), 57 (9). *Anal.* Calcd for $C_{21}H_{32}N_2O_3$: C, 69.97; H, 8.95; N, 7.77. Found: C, 69.59; H, 9.12; N, 7.86.

(*S*)-Methyl 3-(4-chlorophenyl)-4-((*R*)-2-methoxymethylpyrrolidin-1-ylimino)butanoate (2g): According to GP1 hydrazone (**1f**) (450 mg, 1.7 mmol) and methyl 2-bromoacetate (310 mg, 2 mmol) were added to a solution of lithium diisopropylamide (2 mmol) in THF (7.6 mL). Purification by column chromatography (ether / *n*-pentane 1:4) afforded **2g** (483 mg, 84%) as a colorless liquid. *de* ≥ 96% (determined by ^{1}H NMR and ^{13}C NMR). $[\alpha]_D^{23}$ = –156.5 (c = 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.75-2.00 (m, 4H, NCHC*H*$_2$, NCH$_2$C*H*$_2$), 2.59 (dd, 1H, *J* = 15.8/7.2 Hz, NCHCHCH*H*), 2.72 (dt, 1H, *J* = 8.2/8.2 Hz, NCH*H*CH$_2$), 3.05 (dd, 1H, *J* = 15.8/7.9 Hz, NCHCHC*H*H), 3.24-3.32 (m, 1H, NC*H*HCH$_2$), 3.37 (s, 3H, C*H*$_3$O), 3.40-3.49 (m, 2H, CH$_3$OCH*H*, NC*H*CH$_2$), 3.51-3.57 (m, 1H, CH$_3$OC*H*H), 3.63 (s, 3H, C*H*$_3$OCO), 4.04 (dt, 1H, *J* = 7.4/4.0 Hz, NCHC*H*), 6.61 (d, 1H, *J* = 4.0 Hz, NC*H*), 7.16-7.29 (m, 4H, arom C*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.96, 26.58, 38.64 (*C*H$_2$), 44.21 (*C*H), 49.52 (N*C*H$_2$), 51.49 (*C*H$_3$OCO), 59.22 (*C*H$_3$O), 63.26 (*C*H), 74.49 (O*C*H$_2$), 128.75, 129.39

(arom *C*H), 132.59 (arom *C*Cl), 136.00 (N*C*H), 140.54 (arom *C*), 172.52 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 2950 (s), 2881 (s), 1739 (vs), 1596 (vw), 1490 (s), 1483 (m), 1412 (w), 1362 (w), 1304 (vw), 1249 (m), 1198 (m), 1164 (m), 1119 (w), 1093 (w), 1016 (m), 971 (w), 912 (vw), 831 (m), 726 (vw), 563 (vw) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 340 (6) [$M^{+\bullet}$+2], 339 (7) [$M^{+\bullet}$+1], 338 (16) [$M^{+\bullet}$], 296 (6), 295 (34), 294 (18), 293 (100), 166 (12), 164 (36), 157 (8), 155 (25), 116 (8), 70 (18), 59 (6), 45 (6). *Anal.* Calcd for $C_{17}H_{23}N_2O_3Cl$: C, 60.26; H, 6.84; N, 8.27. Found: C, 60.49; H, 6.78; N, 8.27.

General procedure 2 (GP2) for the MMPP-mediated hydrazone nitrile conversion of aldehyde hydrazones (**2a-g)**:
MMPP·$6H_2O$ (2.0 mmol/mmol hydrazone) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (1:1, 5 mL/mmol MMPP each) at 0 °C. The corresponding hydrazone was dissolved in MeOH (4 mL/mmol hydrazone) and added dropwise. The mixture was stirred at 0 °C until the reaction was complete (TLC control). The suspension was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous phase extracted three times with Et_2O. The combined organic phases were washed with H_2O and brine and dried over $MgSO_4$. Evapuration and purification by column chromatography affords the pure nitrile as a colorless liquid.

(*S*)-Methyl 3-cyanobutanoate (3a): According to GP2 a solution of hydrazone (**2a**) (300 mg, 1.24 mmol) in MeOH (5 mL) was added to a solution of magnesium monoperoxyphthalate hexahydrate (1.225 g, 2.48 mmol) in MeOH (12.5 mL) and pH7-buffer (12.5 mL). Purification by column chromatography (diethyl ether / *n*-pentane 1:4) afforded **3a** (150 mg, 95%) as a colorless liquid. *ee* = 93% (determined by GC on a chiral stationary phase (Lipodex E)). $[\alpha]_D^{23}$ = +35.3 (c = 1.05, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.39 (d, 3H, *J* = 7.1 Hz, C*H*$_3$), 2.55 (dd, 1H, *J* = 16.8/7.1 Hz, CH*H*), 2.73 (dd, 1H, *J* = 16.5/7.1 Hz, C*H*H), 3.10 (ddq, 1H, *J* = 7.1/7.1/7.1 Hz, C*H*), 3.75 (s, 3H, C*H*$_3$O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 17.69 (*C*H$_3$), 21.73 (*C*H), 37.89 (*C*H$_2$), 52.17 (*C*H$_3$O), 121.62 (N*C*), 169.83 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 3640 (vw), 2989 (m), 2955 (m), 2888 (w), 2852 (vw), 2244 (w), 1741 (vs), 1441 (s), 1367 (s), 1280 (s), 1202 (vs), 1125 (vw), 1077 (w), 1004 (s), 944 (vw), 888 (w), 709 (vw), 603 (vw) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 128 (1) [$M^{+\bullet}$+1], 112 (11), 97 (6), 96 (100), 95 (6), 74 (94), 69 (7), 68 (83), 67 (6), 59 (25), 54 (6), 52 (6). *Anal.* Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.55; H, 7.05; N, 10.84.

(*S*)-Methyl 3-cyanopentanoate (3b): According to GP2 a solution of hydrazone (**2b**) (550 mg, 2.15 mmol) in MeOH (9 mL) was added to a solution of magnesium monoperoxyphthalate hexahydrate (2.12 g, 4.29 mmol) in MeOH (21 mL) and pH7-buffer (21 mL). Purification by short way flash chromatography (ether / *n*-pentane 1:4) afforded **3b** (300 mg, 99%) as a colorless liquid. *ee* = 98%

(determined by GC on a chiral stationary phase (Lipodex G)). $[\alpha]_D^{24}$ = +11.8 (c = 1.00, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.12 (t, 3H, *J* = 7.4 Hz, C*H*$_3$), 1.62-1.77 (m, 2H, CH_3CH_2), 2.62 (dd, 1H, *J* = 16.8/6.9 Hz, CH*H*), 2.73 (dd, 1H, *J* = 16.6/7.7 Hz, C*H*H), 2.94-3.04 (m, 1H, C*H*), 3.76 (s, 3H, C*H*$_3$O) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.37 (*C*H$_3$), 25.20 (*C*H$_2$), 29.16 (*C*H), 36.21 (*C*H$_2$), 52.27 (*C*H$_3$O), 120.94 (N*C*), 170.30 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 3639 (vw), 3552 (vw), 2970 (s), 2881 (m), 2243 (w), 1741 (vs), 1440 (s), 1368 (s), 1253 (s), 1180 (vs), 1100 (vw), 1018 (w), 977 (w), 918 (vw), 706 (vw) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 142 (3) [$M^{+\bullet}$+1], 126 (5), 113 (13), 110 (65), 101 (18), 82 (54), 81 (10), 80 (7), 74 (100), 68 (27), 59 (17), 55 (38), 54 (68), 53 (9), 52 (5). *Anal.* Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.50; H, 7.67; N, 10.22.

(*R*)-Methyl 3-cyano-4-methylpentanoate (3c): According to GP2 a solution of hydrazone (**2c**) (1.85 g, 6.84 mmol) in MeOH (28 mL) was added to a solution of magnesium monoperoxyphthalate hexahydrate (6.77 g, 13.7 mmol) in MeOH (68 mL) and pH7-buffer (68 mL). Purification by short way flash chromatography (ether / *n*-pentane 1:4) afforded **3c** (1.034 g, 97%) as a colorless liquid. *ee* = 98% (determined by GC on a chiral stationary phase (Lipodex E)). $[\alpha]_D^{23}$ = +27.7 (c = 1.05, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.07 (d, 3H, *J* = 6.9 Hz, CH_3CHCH_3), 1.10 (d, 3H, *J* = 6.7 Hz, CH_3CHCH_3), 1.86-1.97 (m, 1H, CH_3CH), 2.57 (dd, 1H, *J* = 16.8/6.3 Hz, CH*H*), 2.71 (dd, 1H, *J* = 16.5/8.5 Hz, C*H*H), 2.96-3.01 (m, 1H, C*H*), 3.75 (m, 3H, C*H*$_3$O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 18.24, 20.80 (*C*H$_3$), 29.72 (*C*H), 34.65 (*C*H$_2$), 34.71 (*C*H), 52.20 (*C*H$_3$O), 119.78 (N*C*), 170.26 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 2966 (s), 2879 (w), 2241 (w), 1742 (vs), 1465 (m), 1439 (m), 1370 (m), 1255 (s), 1177 (s), 994 (w), 896 (vw), 734(vw) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 156 (17) [$M^{+\bullet}$], 140 (5), 124 (28), 115 (18), 114 (6), 113 (100), 108 (8), 96 (23), 82 (29), 81 (16), 80 (14), 74 (19), 71 (12), 69 (8). *Anal.* Calcd for $C_8H_{14}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.18; H, 8.82; N, 9.05.

(*R*)-Methyl 3-cyano-4,4-dimethylpentanoate (3d): According to GP2 a solution of hydrazone (**2d**) (1.90 g, 6.66 mmol) in MeOH (27 mL) was added to a solution of magnesium monoperoxyphthalate hexahydrate (6.59 g, 13.3 mmol) in MeOH (67 mL) and pH7-buffer (67 mL). Purification by short way flash chromatography (ether / *n*-pentane 1:4) afforded **3d** (1.109 g, 98%) as a colorless liquid. *ee* = 97% (determined by GC on chiral stationary phase (Lipodex E)). $[\alpha]_D^{23}$ = +59.8 (c = 1.10, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H, C*H*$_3$), 2.61 (dd, 2H, *J* = 8.2/6.7 Hz, C*H*$_2$), 2.89 (dd, 1H, *J* = 8.4/6.7 Hz, C*H*), 3.76 (s, 3H, C*H*$_3$O) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.14 (*C*H$_3$), 32.82 (*C*H$_2$), 32.89 ($(CH_3)_3C$), 39.45 (*C*H), 52.36 (*C*H$_3$O), 120.45 (N*C*), 171.02 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 2966 (vs), 2877 (m), 2241 (w), 1743 (vs), 1471 (m), 1439 (s), 1372 (s), 1323 (vw), 1287 (s), 1265 (m), 1207 (vs), 1163 (s), 987 (m), 881 (vw), 694 (vw) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 170 (3) [$M^{+\bullet}$+1], 154 (12), 138 (14), 122

(13), 113 (9), 94 (28), 57 (100), 54 (11), 53 (5). *Anal.* Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 64.37; H, 8.66; N, 8.56.

(*S*)-Methyl 3-cyano-4-phenylbutanoate (3e): According to GP2 a solution of crude hydrazone (**2e**) (3.0 g, 9.42 mmol) in MeOH (40 mL) was added to a solution of magnesium monoperoxyphthalate hexahydrate (9.40 g, 19 mmol) in MeOH (100 mL) and pH7-buffer (100 mL). Purification by column chromatography (ether / *n*-pentane 1:4) afforded **3e** (1.109 g, 58% over 2 steps, 76% per step) as a colorless liquid. *ee* = 96% (determined by GC on a chiral stationary phase (Lipodex E)). $[\alpha]_D^{24} = -2.2$ (c = 1.25, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.58 (dd, 1H, *J* = 16.8/6.6 Hz, arom CCH*H*), 2.67 (dd, 1H, *J* = 17.0/7.7 Hz, aromC C*H*H), 2.93 (dd, 1H, *J* = 13.7/6.9 Hz, CH*H*), 2.97 (dd, 1H, *J* = 13.7/7.4 Hz, C*H*H), 3.23-3.30 (m, 1H, C*H*), 3.72 (s, 3H, CH_3), 7.22-7.37 (m, 5H, arom C*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 29.37 (*C*H), 35.58 (arom C*C*H_2), 37.51 (*C*H_2), 52.20 (*C*H_3), 120.47 (N*C*), 127.36 (*p*-arom *C*H), 128.67, 128.95 (arom *C*H), 135.77 (arom *C*), 169.87 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 3062 (vw), 3029 (w), 2953 (w), 2244 (w), 1739 (vs), 1603 (vw), 1497 (w), 1440 (m), 1368 (m), 1262 (m), 1208 (s), 1080 (vw), 996 (w), 983 (vw), 749 (m), 703 (s), 484 (vw) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 203 (27) [$M^{+\bullet}$], 176 (18), 172 (12), 131 (9), 130 (90), 129 (15), 117 (9), 92 (7), 91 (100), 74 (39), 65 (12). *Anal.* Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.02; H, 6.42; N, 7.07.

(*S*)-*tert*-Butyl 3-cyano-4-phenylbutanoate (3f): According to GP2 a solution of crude hydrazone (**2f**) (3.82 g, 10.5 mmol) in MeOH (40 mL) was added to a solution of magnesium monoperoxyphthalate hexahydrate (9.91 g, 20 mmol) in MeOH (100 mL) and pH7-buffer (100 mL). Purification by column chromatography (ether / *n*-pentane 1:8) afforded **3f** (1.84 g, 75% over 2 steps, 87% per step) as a colorless liquid. *ee* = 95% (determined by GC on a chiral stationary phase (Lipodex E)). $[\alpha]_D^{24} = +1.2$ (c = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.48 (s, 9H, (CH_3)$_3$C), 2.48 (dd, 1H, *J* = 16.5/6.9 Hz, arom CCH*H*), 2.57 (dd, 1H, *J* = 16.8/7.4 Hz, aromC C*H*H), 2.94 (d, 2H, *J* = 7.1 Hz, CH_2), 3.20 (pent, 1H, *J* = 7.1 Hz, C*H*), 7.23-7.37 (m, 5H, arom C*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.99 ((*C*H_3)$_3$C), 29.56 (*C*H), 36.93 (arom C*C*H_2), 37.54 (*C*H_2), 81.99 ((CH$_3$)$_3$*C*), 120.62 (N*C*), 127.29 (*p*-arom *C*H), 128.64, 128.96 (arom *C*H), 135.96 (arom *C*), 168.55 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 3063 (vw), 3030 (w), 2979 (s), 2932 (m), 2243 (vw), 1730 (vs), 1603 (vw), 1496 (w), 1455 (m), 1369 (s), 1257 (m), 1152 (vs), 1082 (vw), 1033 (vw), 951 (vw), 847 (w), 771 (m), 702 (m), 617 (vw) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 245 (25) [$M^{+\bullet}$], 189 (14), 173 (8), 172 (68), 163 (9), 162 (92), 145 (10), 144 (6), 130 (15), 129 (13), 117 (15), 91 (39), 65 (8), 59 (5), 57 (100). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.83; H, 7.79; N, 5.98.

(*R*)-Methyl 3-(4-chlorophenyl)-3-cyanopropanoate (3g): According to GP2 a solution of crude hydrazone (**2g**) (2.06 g, 6.08 mmol) in MeOH (27 mL) was added to a solution of magnesium monoperoxyphthalate hexahydrate (6.63 g, 13.4 mmol) in MeOH (67 mL) and pH7-buffer (67 mL). Purification by column chromatography (ether / *n*-pentane 1:2) afforded **3g** (1.246 g, 92% over 2 steps, 96% per step) as a colorless liquid. *ee* = 95% (determined by GC on a chiral stationary phase (Chirasil-dex)). $[\alpha]_D^{23}$ = +8.7 (c = 1.11, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.83 (dd, 1H, *J* =16.6/6.9 Hz, CH*H*), 3.02 (dd, 1H, *J* = 16.8/7.9 Hz, C*H*H), 3.72 (s, 3H, CH_3), 4.29 (t, 1H, *J* = 7.4 Hz, C*H*), 7.30-7.39 (m, 4H, arom C*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 32.58 (*C*H), 39.62 (*C*H_2), 52.43 (*C*H_3), 119.48 (N*C*), 128.79, 129.51 (arom *C*H), 132.91 (arom *C*Cl), 134.71 (arom *C*), 169.38 (*C*O) ppm; IR (film) $\tilde{\upsilon}$ = 3876 (vw), 2992 (vw), 2950 (m), 2248 (w), 1914 (vw), 1736 (vs), 1594 (vw), 1494 (m), 1440 (m), 1411 (m), 1366 (m), 1256 (m), 1204 (vs), 1092 (m), 998 (m), 911 (w), 829 (vs), 711 (w), 671 (vw), 626 (w), 550 (w), 505 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 225 (18) [$M^{+\bullet}$+2], 224 (8) [$M^{+\bullet}$+1], 223 (58) [$M^{+\bullet}$], 194 (11), 192 (5), 180 (6), 166 (7), 165 (35), 164 (20), 163 (100), 152 (14), 150 (41), 139 (9). *Anal.* Calcd for $C_{11}H_{10}NO_2Cl$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.23; H, 4.52; N, 6.22.

General procedure 3 (GP3) for the Raney Ni catalysed reduction of nitriles (**3a-e**) to β-substituted γ-lactams (**4a-e)**:
Strongly basic W2 Raney Ni catalyst was freshly prepared according to a known literature procedure.[24] A steel autoclave with a glass inlet was charged with Raney Ni (500 mg/mmol nitrile) and MeOH (10 mL/g Raney Ni). The nitrile was added and the mixture was hydrogenated at 20 bar H_2 pressure and 70 °C for 16 h. The reaction mixture was cooled to rt and filtered over celite. Evapuration of the solvent and purification by column chromatography affords the pure product.

(*R*)-4-Isopropylpyrrolidin-2-one (4c): According to GP3 nitrile (**3c**) (230 mg, 1.47 mmol) was added to a mixture of Raney Ni (740 mg) in MeOH (8 mL) and was hydrogenated. Purification by short way flash chromatography (ethyl acetate) afforded **4c** (182 mg, 97%) as a colorless solid; mp = 91 °C. *ee* = 97% (determined by HPLC on chiral stationary phase (Chiralpak AS)). $[\alpha]_D^{23}$ = +16.9 (c = 1.05, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.91 (d, 3H, *J* = 6.4 Hz, CH_3CHCH_3), 0.93 (d, 3H, *J* = 6.7 Hz, CH_3CHCH_3), 1.52-1.72 (m, 1H, CH_3CHCH_3), 2.06 (dd, 1H, *J* = 16.1/9.4 Hz, NHCH*H*), 2.13-2.27 (m, 1H, C*H*), 2.37 (dd, 1H, *J* = 15.8/8.2 Hz, NHC*H*H), 3.07 (dd, 1H, *J* = 9.7/7.9 Hz, COCH*H*), 3.42-3.49 (m, 1H, COC*H*H), 6.51 (1H, br s, 1H, N*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.07, 20.63 (*C*H_3), 32.54 (CH_3CH), 35.15 (*C*H_2), 42.29 (*C*H), 46.62 (*C*H_2), 78.69 (*C*O) ppm; IR (KBr) $\tilde{\upsilon}$ = 3967 (vw), 3655 (vw), 3439 (m), 3206 (s), 3101 (m), 2957 (s), 2871 (s), 1685 (vs), 1490 (w), 1466 (w), 1422 (vw), 1384 (m), 1365 (m), 1313 (m), 1267 (m), 1169 (w), 1080 (vw), 1047 (vw), 1028 (vw), 974 (vw), 886 (vw), 800 (m), 692 (m), 528

(m) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 128 (11) [$M^{+\bullet}$+1], 127 (100) [$M^{+\bullet}$], 112 (5), 110 (16), 97 (20), 85 (7), 84 (33), 83 (5), 71 (6), 70 (42), 69 (22), 68 (6). *Anal.* Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.68; H, 10.76; N, 10.69.

(*R*)-4-*tert*-Butylpyrrolidin-2-one (4d): According to GP3 nitrile (**3d**) (600 mg, 3.47 mmol) was added to a mixture of Raney Ni (1.80 g) in MeOH (20 mL) and was hydrogenated. Purification by column chromatography (ethyl acetate) afforded **4d** (487 mg, 90%) as a colorless solid; mp = 112 °C. *ee* = 99% (determined by HPLC on a chiral stationary phase (S,S-Whelk O1)). $[\alpha]_D^{23}$ = –14.1 (c = 1.03, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.90 (s, 9H, C*H*$_3$), 2.16 (dd, 1H, *J* = 16.8/10.4 Hz, NHCH*H*), 2.25 (dd, 1H, *J* = 17.1/8.9 Hz, NHC*H*H), 2.29-2.41 (m, 1H, C*H*), 3.17 (dd, 1H, *J* = 9.7/7.9 Hz, COCH*H*), 3.34 (dd, 1H, *J* = 9.7/8.2 Hz, COC*H*H), 6.61 (s, br, 1H , N*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 26.87 (*C*H_3), 31.63 ((CH_3)$_3$*C*), 32.12, 43.78 (*C*H_2), 45.38 (*C*H), 178.60 (*C*O) ppm; IR (KBr) $\tilde{\upsilon}$ = 3183 (s), 3102 (s), 2957 (s), 2905 (s), 2870 (s), 1697 (vs), 1494 (w), 470 (w), 1366 (m), 1284 (m), 1257 (w), 1194 (vw), 1068 (vw), 802 (m), 695 (w), 533 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 142 (23) [$M^{+\bullet}$+1], 141 (100) [$M^{+\bullet}$], 126 (22), 111 (14), 85 (75), 84 (85), 70 (10), 69 (43), 57 (68), 56 (6), 55 (19). *Anal.* Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.15; H, 10.49; N, 9.54.

(*S*)-4-Benzylpyrrolidin-2-one (4e): According to GP3 nitrile (**3e**) (1.0 g, 4.92 mmol) was added to a mixture of Raney-Ni (2.50 g) in MeOH (25 mL) and was hydrogenated. Purification by column chromatography (ethyl acetate) afforded **4e** (768 mg, 89%) as a colorless solid; mp = 98 °C. *ee* = 95% (determined by HPLC on a chiral stationary phase (Chiralpak AD)). $[\alpha]_D^{24}$ = +5.4 (c = 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.07-2.16 (m, 1H, NHCH*H*), 2.38-2.45 (m, 1H, NHC*H*H), 2.70-2.83 (m, 3H, C*H*, arom CC*H*$_2$), 2.98 (dd, 1H, *J* = 9.6/7.1 Hz, COCH*H*), 3.09-3.13 (m, 1H, COC*H*H), 6.58 (br s, 1H, N*H*), 7.14-7.32 (m, 5H, arom C*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 36.28 (*C*H), 36.48, 40.35, 47.41 (*C*H_2), 126.28 (*p*-arom *C*H), 128.40, 128.52 (arom *C*H), 139.06 (arom *C*), 177.94 (*C*O) ppm; IR (KBr) $\tilde{\upsilon}$ = 3231 (vs), 3119 (m), 3063 (w), 3027 (w), 2996 (vw), 2901 (w), 1657 (vs), 1495 (w), 1451 (m), 1373 (vw), 1304 (w), 1283 (w), 1251 (w), 1065 (w), 789 (m), 757 (w), 738 (m), 701 (m), 624 (w), 550 (vw), 501 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 176 (16) [$M^{+\bullet}$+1], 175 (89) [$M^{+\bullet}$], 132 (5), 118 (7), 117 (25), 115 (9), 93 (6), 92 (77), 91 (91), 84 (100), 83 (17), 65 (13). *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.26; H, 7.70; N, 7.78.

(*R*)-4-(4-Chlorophenyl)pyrrolidin-2-one (4g):

A solution of $NiCl_2 \cdot 6H_2O$ (106 mg, 0.45 mmol) in MeOH (2.25 mL) under argon was cooled to –25 °C. The nitrile (**3g**) (50 mg, 0.22 mmol) was added and the green solution was stirred for 15 min at this temperature. 91 mg (2.4 mmol) of $NaBH_4$ was added in small portions over a period of 30 min and the

black reaction mixture was stirred for additional 30 min at –25 °C and for 45 min at 0 °C. After completion of the reaction (TCL control) the solvent was evaporated and the residue was dissolved in a mixture of DCM and H_2O (1:1). After separation of the phases the aqueous phase was extracted four times with DCM. The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. Purification by column chromatography (ethyl acetate) afforded 35 mg (80%) of the pure product; mp = 111 °C [lit.,[25] 112 °C]. *ee* = 94% (determined by HPLC on a chiral stationary phase (Chiralcel OJ)). $[\alpha]_D^{26}$ = –32.7 (c = 1.00, EtOH), lit.,[25] $[\alpha]_D^{23}$ = –39 (c = 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.45 (dd, 1H, *J* = 17.0/8.8 Hz, NHCH*H*), 2.73 (dd, 1H, *J* = 17.0/9.1 Hz, NHC*H*H), 3.38 (dd, 1H, *J* = 9.6/7.1 Hz, COCH*H*), 3.67 (pent, 1H, *J* = 8.2 Hz, C*H*), 3.76-3.81 (m, 1H, COC*H*H), 6.89 (br s, 1H , N*H*), 7.17-7.21 (m, 2H, arom C*H*), 7.28-7.33 (m, 2H, arom C*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 37.91 (*C*H_2), 39.60 (*C*H), 49.39 (*C*H_2), 127.94, 128.79 (arom *C*H), 132.68 (arom *C*Cl), 140.42 (arom *C*), 177.37 (*C*O) ppm; The spectroscopic data were in accordance with those reported in the literature.[25]

Synthesis of (*R*)-4-Amino-3-(4-chlorophenyl)butanoic acid hydrochloride [(R)-baclofen hydrochloride] (5):

The γ-lactam (**4f**) (100 mg, 0.51 mmol) was heatet in 6 N HCl (3 mL) at 100 °C for 10 h. The excess of water in the reaction mixture was removed under reduced pressure to obtain a solid redidue, which was trituated in isopropanol affording 95 mg (75%) of (*R*)-(–)-baclofen hydrochloride as a colorless solid; mp = 194 °C [lit.,[26] 195 °C].

$[\alpha]_D^{23}$ = –1.7 (c = 0.60, H_2O), lit.,[26] $[\alpha]_D^{20}$ = –2.0 (c = 0.60, H_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.90 (s, 9H, C*H*$_3$), 2.16 (dd, 1H, *J* = 16.8/10.4 Hz, NHCH*H*), 2.25 (dd, 1H, *J* = 17.1/8.9 Hz, NHC*H*H), 2.29-2.41 (m, 1H, C*H*), 3.17 (dd, 1H, *J* = 9.7/7.9 Hz, COCH*H*), 3.34 (dd, 1H, *J* = 9.7/8.2 Hz, COC*H*H), 6.61 (br s, 1H , N*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 26.87 (*C*H_3), 31.63 ((CH$_3$)$_3$*C*), 32.12 (*C*H_2), 43.78 (*C*H_2), 45.38 (*C*H), 178.60 (*C*O) ppm; The spectroscopic data were in accordance with those reported in the literature.[26]

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