From Paracetamol to Rolipram and Derivatives: Application of Deacetylation–Diazotation Sequences and Palladium-Catalyzed Matsuda–Heck Reaction

Bernd Schmidt,* Nelli Elizarov, René Berger, Monib H. Petersen

Universität Potsdam, Institut für Chemie (Organische Synthesechemie), Karl-Liebknecht-Straße 24–25, 14476 Potsdam-Golm, Germany
Fax +49(331)9775059; E-mail: bernd.schmidt@uni-potsdam.de

Received: 30.01.2013; Accepted after revision: 01.03.2013

Abstract: A six-step synthesis of the antidepressant rolipram from the popular analgetic 4-acetamidophenol (paracetamol) is described. The steps include oxidative functionalization of the aromatic core, diazonium salt formation via deacetylation-diazotation, Matsuda–Heck reaction, conjugate addition of nitromethane, and hydrogenative cyclization.

Key words: acetanilides, deacetylation, diazonium salts, palladium, Matsuda–Heck reaction

Rolipram (Figure 1) is a phosphodiesterase-IV (PDE-IV) inhibitor, which was developed in the 1970s as a potential drug against depression, multiple sclerosis, or inflammatory diseases.[1] Although rolipram has never been used as a therapeutic for the clinical treatment of PDE-IV related diseases, it still attracts considerable attention today as an experimental drug for the study of their underlying molecular mechanisms.[2–5]

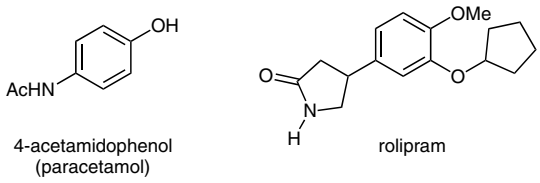


Figure 1 . 4-Acetamidophenol (paracetamol) and rolipram

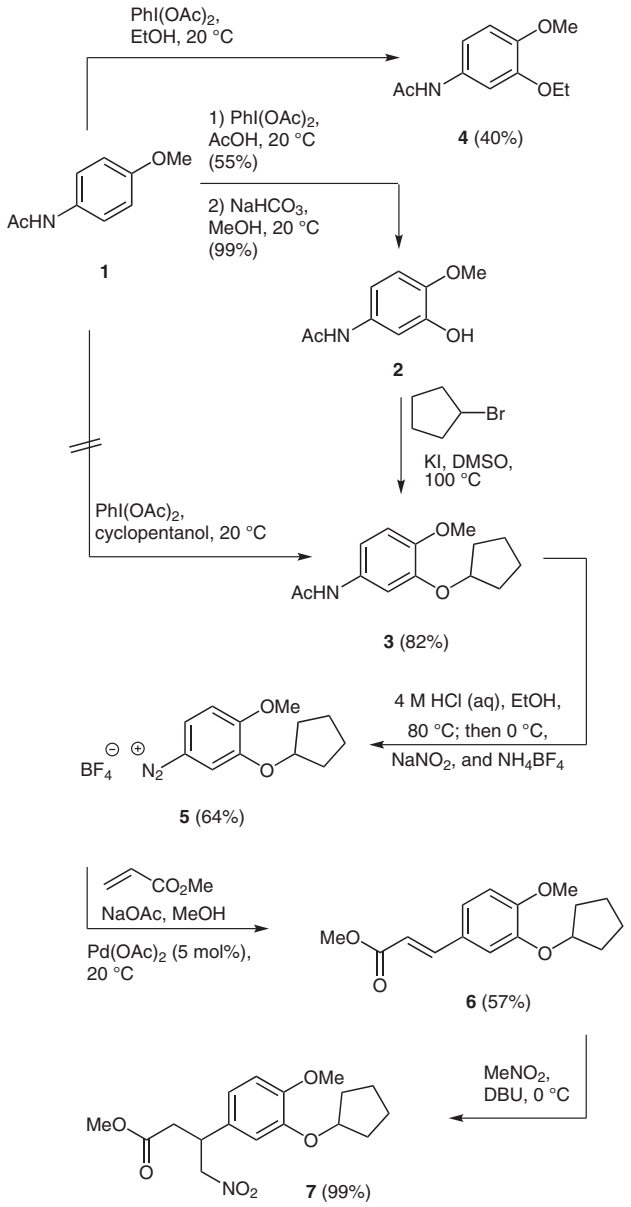
Several syntheses of rolipram proceed via addition of nitromethane to an α,β-unsaturated ester or amide[2,6–8] or via addition of an enolate to a nitrostyrene.[9,10] Recently, an enantioselective Pd-catalyzed allylic alkylation of nitromethane has been used, followed by hydroboration-oxidation to establish the required carboxylic acid.[11] In all these cases, lactam formation occurs spontaneously upon reduction of the nitro group.

A few years ago we found that commercially available 4-acetamidophenol, which is better known as paracetamol,[12] and other acetanilides derived from it can be efficiently transformed into isolable, microcrystalline diazonium tetrafluoroborates via a one-flask deacetylation–diazotation–precipitation sequence.[13–16] The diazonium salts derived from paracetamol are particularly useful building blocks for the direct Pd-catalyzed incorporation of phenols or alkoxybenzenes into target molecules.[17–21] Diazonium tetrafluoroborates in general are highly reactive arylating reagents, which are useful alternatives to aryl halides or triflates in Pd-catalyzed coupling and cross-coupling reactions.[22–29] The Pd-catalyzed arylation of alkenes with arenediazonium salts is often referred to as the 'Matsuda–Heck reaction'. For instance, a Matsuda–Heck coupling of an appropriately substituted benzenediazonium salt (obtained from 2-methoxy-5-nitrophenol in three steps) and *N*-Boc-2,5-dihydropyrrole had previously been used for the synthesis of rolipram by Correia's group.[30] In this contribution, we report how rolipram and some derivatives can be synthesized from paracetamol in few steps, using the deacetylation–diazotation sequence for the generation of the required arene diazonium salt, which is subsequently coupled with an acrylate.

Starting from the methyl ether of paracetamol **1**, the acetamide **2** was obtained in two steps by iodoacetoxylation in acetic acid (giving the corresponding acetate) and subsequent cleavage of the acetate with methanol and $NaHCO_3$.[31] Replacing acetic acid by ethanol as a solvent for the iodoacetoxylation resulted in the formation of ethyl ether **4** in 40% yield. Obviously, the alcohol serves as a nucleophile in this transformation, and the reaction was therefore repeated in propan-2-ol and cyclopentanol, with the intention of direct access to the required acetanilide **3**. Unfortunately, the reaction fails completely with both branched alcohols, resulting in the complete recovery of unreacted **1**. Therefore, **3** was synthesized by Williamson ether synthesis from **2** and cyclopentyl bromide. Acetanilide **3** was then subjected to the conditions of the one-flask deacetylation–diazotation sequence. To this end, **3** was treated sequentially with hydrochloric acid at elevated temperature, cooled to 0 °C, and diazotized using $NaNO_2$. The diazonium salt was precipitated as the tetrafluoroborate **5** by addition of NH_4BF_4 and isolated in 64% yield. In the next step, **5** was reacted with methyl acrylate in a ligand-free Matsuda–Heck reaction, using $Pd(OAc)_2$ as precatalyst, to give the cinnamate **6**. As mentioned above, the 1,4-addition of nitromethane to similar α,β-unsaturated carbonyl compounds such as enals,[7] *N*-acylpyrroles[8] or *N*-acylimidazoles[6] has previously been exploited for the synthesis of rolipram, but to the best of our knowledge this particular cinnamate **6** has never been used for this transformation. Therefore, we needed to complete the synthesis of rolipram by performing the 1,4-addition of nitromethane to **6** and subsequent reduction of the nitro group in the addition product **7**. The conjugate addition of

SYNTHESIS 2013, 45, 1174–1180
Advanced online publication: 14.03.2013
DOI: 10.1055/s-0032-1316874; Art ID: SS-2013-T0092-OP

nitromethane to **6** could be accomplished in quantitative yield by using DBU as a base (Scheme 1).

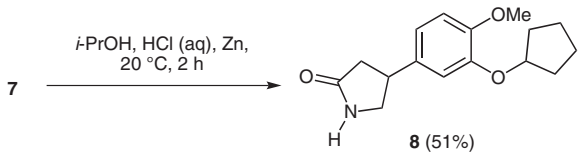


Scheme 1 First part of the synthesis of rolipram from paracetamol

A previous synthesis of **7** via methanolysis of an appropriately substituted *N*-acylpyrrole was reported by Vakulya et al.[8] These authors also described the hydrogenation of **7** in the presence of Pd/C in methanol at 10 atmospheres of hydrogen pressure, with concomitant cyclization of the resulting primary amine to give rolipram (**8**). Palomo et al. obtained rolipram from **7** at 1 bar of hydrogen in ethanol and Pd/C as a catalyst,[7] while Felluga et al. used Raney-Ni as a catalyst in ethanol under 1 bar of hydrogen to achieve the reduction of the nitro group in a structurally related baclofen precursor.[32] Against the background of these literature reports we were quite surprised that none of these conditions worked in our hands. While both Ra-Ni and Pd/C as catalysts at low hydrogen pressures resulted in the quantitative recovery of unreacted starting material, higher pressures at elevated temperatures led to the formation of **8**, contaminated with varying amounts of *N*-methylrolipram (**9**) and occasionally the tertiary amine **10** (Table 1). The methyl groups incorporated in these products are obviously the result of a nitro group reduction, simultaneous dehydrogenation of methanol, and a reductive methylation. Unfortunately, reproducibility of the exact product composition is quite poor, however, *N*-methylrolipram was always observed as a by-product when methanol was used as a solvent at hydrogen pressures of or above 10 bars. We investigated various conditions to obtain the desired product rolipram (**8**) selectively. The composition of the product mixtures was analyzed qualitatively by GC-MS coupling, and the results are summarized in Table 1. With hydrogen pressures up to 5 bars, neither Ra-Ni nor Pd/C led to a significant conversion of the starting material in methanol. Increasing the pressure to 10 bars at 60 °C in the same solvent resulted in a full conversion of the nitro compound **7** into rolipram (**8**) and its *N*-methyl analogue **9** in significantly varying ratios. It was possible to isolate and characterize the hitherto unknown *N*-methylrolipram (**9**) from one reaction mixture in 12% yield, along with 51% of rolipram (**8**) (Table 1, entry 4). Increasing the hydrogen pressure further to 50 bars does not improve the selectivity. Occasionally, the tertiary amine **10** was observed as an additional by-product, which could not be isolated on a preparative scale (entry 6). Changing the catalyst to $Pd(OH)_2$ did not result in a significant improvement, because either incomplete conversion (entry 7), or formation of the by-products (entry 8) was observed. We therefore decided to investigate different solvents for the hydrogenation. With ethanol at 20 bars of hydrogen and Pd/C as catalyst the desired product **8** was not observed, but the ethyl analogues of compounds **9** and **10** were detected by means of GC-MS coupling (entry 9). The use of THF, dichloromethane, and ethyl acetate was completely unsuccessful, because only unreacted starting material was recovered. Eventually, a breakthrough was achieved with the solvent mixture *tert*-butyl alcohol–water: with this solvent mixture and Pd/C as a catalyst and 10 bars of hydrogen the selective formation of rolipram (**8**) was observed. It was isolated from the reaction mixture on preparative scale in 76% yield (Table 1, entry 13). The occasional unreliability of alkene hydrogenation and hydrogenative debenzylation reactions catalyzed by commercial Pd/C has also been addressed by Felpin and Fouquet, who proposed the in situ generation of the catalyst for improved reproducibility.[33]

Parallel to this optimization alternative reduction methods were also investigated. By using elemental zinc in propan-2-ol/hydrochloric acid[34] the desired lactam could be obtained reliably without using hydrogen at elevated pressures, albeit in somewhat lower yields (Scheme 2).

We applied these reduction–cyclization conditions to three other nitromethane adducts **12a–c** derived from cinnamates **11a–c**, which we had previously synthesized from paracetamol derived phenol diazonium salts via Pd-

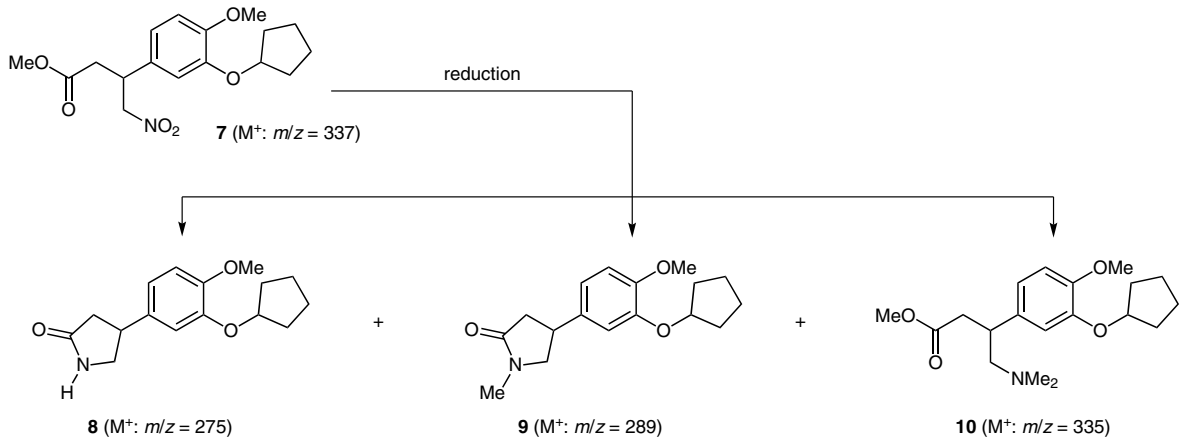


Scheme 2 Reduction–cyclization of **7** to rolipram (**8**) using Zn

catalyzed Matsuda–Heck coupling and subsequent O-methylation (Scheme 3).[16] All nitromethane adducts underwent reduction and cyclization with zinc in the presence of aqueous HCl. In the case of **12c** with an additional nitro group at the aromatic substituent both nitro groups were reduced and the aniline **13c** could be isolated in moderate yield.

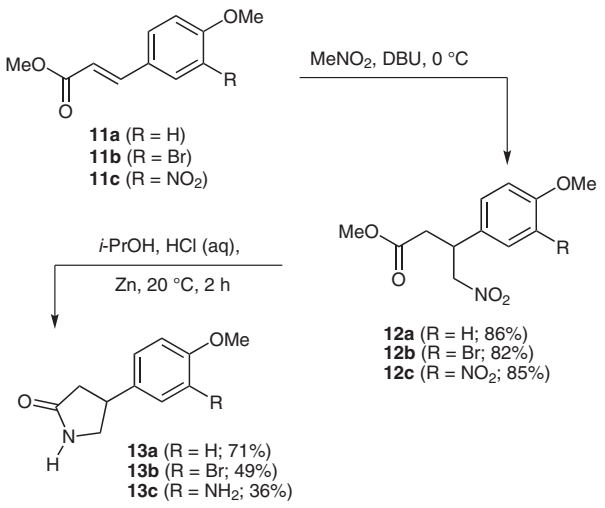
In summary, we have developed a synthesis of the PDE-IV inhibitor rolipram and three analogues from the well-known analgetic 4-acetamidophenol. The synthesis illustrates the utility of the deacetylation–diazotation sequence for the preparation of electron-rich diazonium salts and their application in target molecule synthesis. In the course of this study, *tert*-butyl alcohol–water mixtures were used as alternative solvent for Pd/C-catalyzed hydrogenation reactions. This allowed us to overcome a hydrogenative methylation, which was a prominent side reaction in methanol.

Table 1 Optimization of Conditions for the Hydrogenation of Nitro Compound **7**[a,b]



Entry	Solvent	H_2 pressure (bar)	Cat.	**7**	**8**	**9**	**10**	Isolated product(s) (yield)[c]
1	MeOH	1	Raney-Ni	++	–	–	–	n.d.
2	MeOH	2	Pd/C	++	–	–	–	n.d.
3	MeOH	5	Pd/C	++	–	–	–	n.d.
4[d]	MeOH	10	Pd/C	–	+	+	+	**8** (51%); **9** (12%)
5	MeOH	20	Pd/C	–	+	+	+	n.d.
6	MeOH	50	Pd/C	–	+	+	+	n.d.
7	MeOH	2	$Pd(OH)_2$	+	+	–	–	n.d.
8	MeOH	7	$Pd(OH)_2$	–	–	+	+	n.d.
9[e]	EtOH	20	Pd/C	+	–	+	+	n.d.
10	THF	20	Pd/C	++	–	–	–	n.d.
11	CH_2Cl_2	20	Pd/C	++	–	–	–	n.d.
12	EtOAc	20	Pd/C	++		–	–	n.d.
13[d]	*t*-BuOH–H_2O	10	Pd/C	–	++	–	–	**8** (76%)

[a] Reaction conditions: solvent, catalyst (10 wt%), H_2 (bar), 20 °C, unless otherwise stated.
[b] Analysis is based on GC-MS measurements and not quantitative. ++: Product was formed exclusively or predominantly; +: product was detected in GC; –: product was not observed.
[c] n.d. = not detected.
[d] Reaction was conducted at 60 °C.
[e] In EtOH the corresponding *N*-ethyl or *N*,*N*-diethyl analogues of **9** and **10** were formed.



Scheme 3 Synthesis of rolipram derivatives

All experiments were conducted in dry reaction vessels under an atmosphere of dry argon. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ with $CHCl_3$ (δ = 7.26) as an internal standard, in DMSO-d_6 with DMSO-d_5 (δ = 2.50) as an internal standard, or in methanol-d_4 with residual CD_2HOD (δ = 3.31) as an internal standard. Coupling constants (*J*) are given in Hz. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.0) as an internal standard, in DMSO-d_6 with DMSO-d_6 (δ = 39.5) as an internal standard, or in methanol-d_4 with CD_3OD (δ = 49.2) as an internal standard. IR spectra were recorded as films on NaCl or KBr plates, or as KBr discs. Wavenumbers are given in cm^{-1}. Mass spectra were obtained at 70 eV. Caution: Although we have never experienced decomposition of arene diazonium salts, we strongly advise against heating neat samples.

5-Acetamido-2-methoxyphenyl Acetate

To a solution of phenyliodoso diacetate (11.7 g, 36.3 mmol) in glacial AcOH (50 mL) was added **1** (5.00 g, 30.3 mmol) over a period of 0.5 h. After stirring for 24 h at r.t, the solution was concentrated in vacuo and the residue was partitioned between EtOAc (50 mL) and H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and all volatiles were evaporated. The residue was purified by column chromatography (SiO_2, EtOAc–MTBE, 1:3) to give the acetate as a colorless solid (3.70 g, 16.7 mmol, 55%); mp 158 °C.

IR (KBr): 3291 (m), 1756 (s), 1660 (s), 1506 (s), 1200 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 7.29 (d, *J* = 2.6 Hz, 1 H), 7.12 (dd, *J* = 2.6, 8.8 Hz, 1 H), 6.81 (d, *J* = 8.9 Hz, 1 H), 3.75 (s, 3 H), 2.28 (s, 3 H), 2.01 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 168.6, 147.8, 139.6, 131.8, 118.5, 115.8, 112.7, 56.3, 24.3, 20.9.

MS (EI): *m*/*z* (%) = 139 (36), 181 (65), 223 (M^+, 16).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}NO_4$: 223.0845; found: 223.0865.

Anal. Calcd for $C_{11}H_{13}NO_4$ (223.23): C, 59.1; H, 5.8; N, 6.2. Found: C, 58.6; H, 5.8; N, 6.2.

(3-Hydroxy-4-methoxyphenyl)acetamide (2)

A suspension of 5-acetamido-2-methoxyphenyl acetate (774 mg, 3.5 mmol) prepared as above and $NaHCO_3$ (641 mg, 7.6 mmol) in anhyd MeOH (16 mL) was stirred at r.t. for 2 h. The mixture was concentrated in vacuo and the residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous layer was treated with 4 M aq HCl (10 mL) and then extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and all volatiles were evaporated. The residue was purified by column chromatography (SiO_2, EtOAc–MTBE, 1:1) to give **2** as a colorless solid (628 mg, 3.5 mmol, 99%); mp 163–168 °C.

IR (KBr): 3326 (w), 1607 (m), 1241 (s), 1219 (s), 792 cm^{-1} (s).

^{1}H NMR (300 MHz, CD_3OD): δ = 7.10 (d, *J* = 2.4 Hz, 1 H), 6.91 (dd, *J* = 2.4, 8.7 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 1 H), 3.82 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 171.4, 147.7, 146.1, 133.6, 113.0, 112.9, 109.8, 56.8, 23.8.

MS (EI): *m*/*z* (%) = 124 (100), 139 (70), 149 (17), 150 (8), 181 (M^+, 95).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_{11}NO_3$: 181.0736; found: 181.0739.

Anal. Calcd for $C_9H_{11}NO_3$ (181.19): C, 59.6; H, 6.1; N, 7.7. Found: C, 59.6; H, 5.9; N, 7.4.

3-Cyclopentyloxy-4-methoxyacetanilide (3)

A mixture of **2** (1.23 g, 6.7 mmol), K_2CO_3 (1.38 g, 10.0 mmol), KI (0.22 g, 2.0 mmol), and cyclopentyl bromide (1.39 g, 1.00 mL, 10.0 mmol) in anhyd DMF (17 mL) was heated to 100 °C for 6 h. The solution was concentrated in vacuo, and the residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (SiO_2, EtOAc–MTBE, 1:3) to give **3** (1.37 g, 5.5 mmol, 82%) as a colorless solid; mp 95–96 °C.

IR (KBr): 3291 (m), 2958 (m), 1510 (s), 1286 (s), 1267 cm^{-1} (s).

^{1}H NMR (300 MHz, CD_3OD): δ = 7.26 (d, *J* = 2.4 Hz, 1 H), 7.00 (dd, *J* = 2.4, 8.7 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 1 H), 4.76 (m, 1 H), 3.79 (s, 3 H), 2.09 (s, 3 H), 1.98–1.49 (m, 8 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 171.5, 148.9, 148.3, 133.7, 114.1, 113.8, 110.0, 82.0, 57.1, 33.8, 25.0, 23.8.

MS (ESI): *m*/*z* (%) = 250 (M^+, 100), 218 (7), 167 (20), 149 (10).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_3$: 250.1443; found: 250.1429.

Anal. Calcd for $C_{14}H_{19}NO_3$ (249.31): C, 67.4; H, 7.6; N, 5.6. Found: C, 67.4; H, 7.7; N, 5.6.

3-Ethoxy-4-methoxyacetanilide (4)

To a solution of phenyliodoso diacetate (1.87 g, 5.8 mmol) in EtOH (5 mL) was added **1** (800 mg, 4.9 mmol) over a period of 0.5 h. The solution was stirred at r.t. for 24 h, concentrated in vacuo, and the residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (SiO_2, EtOAc–MTBE, 1:3) to give **4** as a colorless solid (410 mg, 2.0 mmol, 40%); mp 146 °C.

IR (KBr): 3249 (m), 1653 (s), 1515 (s), 1422 (s), 1234 cm^{-1} (s).

^{1}H NMR (300 MHz, CD_3OD): δ = 7.26 (d, *J* = 2.4 Hz, 1 H), 7.00 (dd, *J* = 2.4, 8.7 Hz, 1 H), 6.88 (d, *J* = 8.7 Hz, 1 H), 4.04 (q, *J* = 7.0 Hz, 2 H), 3.80 (s, 3 H), 2.09 (s, 3 H), 1.39 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 171.5, 149.9, 147.8, 133.8, 114.0, 113.9, 108.49, 65.9, 57.0, 23.8, 15.2.

MS (ESI): *m*/*z* (%) = 168 (10), 182 (11), 210 (M^+, 100).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{16}NO_3$: 210.1130; found: 210.1120.

Anal. Calcd for $C_{11}H_{15}NO_3$ (209.24): C, 63.1; H, 7.2; N, 6.6. Found: C, 63.1; H, 7.2; N, 6.5.

3-Cyclopentyloxy-4-methoxybenzene Diazonium Tetrafluoroborate (5)

A suspension of **3** (880 mg, 3.5 mmol) in 4 M aq HCl (4.0 mL) and EtOH (2.0 mL) was heated at 80 °C for 5 h. The solution was cooled to 0 °C, and NH_4BF_4 (556 mg, 5.3 mmol) and then $NaNO_2$ (109 mg, 1.6 mmol) were added slowly over a period of 15 min. Stirring at 0 °C was continued for 0.5 h, and the precipitate was filtered, washed with cold H_2O (20 mL), EtOH (20 mL), and Et_2O (20 mL) to give **5** as a colorless solid (692 mg, 2.3 mmol, 64%).

IR (KBr): 3126 (w), 2946 (w), 2260 (m), 1067 (s), 1029 cm^{-1} (s).

^1H NMR (300 MHz, DMSO-d_6): δ = 8.41 (dd, *J* = 2.5, 9.1 Hz, 1 H), 8.15 (d, *J* = 2.4 Hz, 1 H), 7.50 (d, *J* = 9.2 Hz, 1 H), 4.81 (m, 1 H), 4.03 (s, 3 H), 1.87–1.52 (m, 8 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.2, 147.4, 130.4, 114.4, 113.7, 102.7, 81.4, 57.5, 31.9, 23.5.

MS (ESI): *m*/*z* (%) = 218 (12).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}N_2O_2$: 219.1128; found: 219.1134.

(*E*)-3-(3-Cyclopentyloxy-4-methoxyphenyl)acrylic Acid Methyl Ester (6)

A suspension of **5** (405 mg, 1.3 mmol), methyl acrylate (228 mg, 0.24 mL, 2.6 mmol), NaOAc (325 mg, 4.0 mmol), and $Pd(OAc)_2$ (15 mg, 5 mol%) in anhyd MeOH (8 mL) was stirred at r.t. for 16 h under an atmosphere of N_2. The mixture was concentrated in vacuo and the residue was partitioned between MTBE (20 mL) and H_2O (20 mL). The aqueous layer was extracted with MTBE (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (SiO_2, hexane–MTBE, 3:1) to give **6** (209 mg, 0.8 mmol, 57%) as a colorless solid; mp 54–57 °C.

IR (KBr): 2956 (m), 1712 (s), 1510 (s), 1262 (s), 1169 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 15.9 Hz, 1 H), 7.06 (dd, *J* = 2.0, 8.2 Hz, 1 H), 7.03 (d, *J* = 2.0 Hz, 1 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 6.26 (d, *J* = 15.9 Hz, 1 H), 4.83–4.72 (m, 1 H), 3.85 (s, 3 H), 3.77 (s, 3 H), 2.06–1.71 (m, 6 H), 1.71–1.50 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 152.5, 148.2, 145.2, 127.5, 122.5, 115.6, 113.9, 112.0, 80.9, 56.3, 51.8, 33.0, 24.3.

MS (ESI): *m*/*z* (%) = 177 (80), 245 (12), 277 (M^+, 20).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}O_4$: 277.1440; found: 277.1443.

Anal. Calcd for $C_{16}H_{20}O_4$ (276.33): C, 69.5; H, 7.3. Found: C, 69.6; H, 7.1.

Methyl 3-(3-Cyclopentyloxy-4-methoxyphenyl)-4-nitrobutanoate (7)

A solution of **6** (100 mg, 0.4 mmol) in nitromethane (0.5 mL) was cooled to 0 °C and DBU (0.54 mL, 0.36 mmol) was added slowly. The reaction mixture was allowed to warm to r.t. and stirred for 16 h. The solution was partitioned between MTBE (10 mL) and 1 M aq HCl (10 mL). The aqueous layer was extracted with MTBE (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, hexane–MTBE, 2:1) to give **7** (122 mg, 0.4 mmol, 99%) as a colorless solid; mp 86–88 °C.

IR (KBr): 2961 (s), 1727 (s), 1589 (s), 1437 (s), 1140 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 8.0 Hz, 1 H), 6.73–6.67 (m, 2 H), 4.73 (tt, *J* = 3.0, 6.3 Hz, 1 H), 4.67 (dd, *J* = 7.0, 12.4 Hz, 1 H), 4.58 (dd, *J* = 7.9, 12.4 Hz, 1 H), 3.88 (pent, *J* = 7.4 Hz, 1 H), 3.79 (s, 3 H), 3.61 (s, 3 H), 2.78–2.66 (2 H), 1.96–1.73 (6 H), 1.65–1.54 (2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4, 149.9, 148.0, 130.7, 119.4, 114.5, 112.4, 80.7, 79.9, 56.2, 52.2, 40.0, 37.9, 32.9, 32.9, 24.2.

MS (EI): *m*/*z* (%) = 338 (M^+, 25), 270 (69), 191 (83), 163 (28), 98 (25).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{24}NO_6$: 338.1604; found: 338.1621.

Anal. Calcd for $C_{17}H_{23}NO_6$ (337.37): C, 60.5; H, 6.8; N, 4.1. Found: C, 60.3; H, 6.7; N, 4.3.

Rolipram (8)

Reduction–Cyclization with Zn and HCl: To a solution of **7** (297 mg, 0.9 mmol) in propan-2-ol (17.6 mL) was added 1 M aq HCl (8.8 mL). Zn dust (1.15 g, 17.6 mmol) was then added over a period of 20 min, and the mixture was stirred at r.t. for 2 h. The mixture was carefully neutralized with sat. aq $NaHCO_3$ (30 mL) and filtered through a pad of Celite. The pad was subsequently washed with EtOAc (20 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (SiO_2, EtOAc) to give **8** (123 mg, 0.45 mmol, 51%) as a colorless solid.

Reduction–Cyclization with H_2 and Pd/C: To a solution of **7** (60 mg, 0.2 mmol) in *t*-BuOH (5 mL) and H_2O (5 mL) was added Pd/C (10 wt%, 6.0 mg). The mixture was degassed and saturated with H_2, transferred to an autoclave, and pressurized with H_2 (10 bar) and kept at 60 °C for 5 h. The mixture was filtered through Celite and washed with EtOAc (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (SiO_2, EtOAc) to give **8** (38 mg, 0.14 mmol, 76%) as a colorless solid; mp 134 °C.

IR (KBr): 3208 (w), 2959 (w), 1677 (s), 1515 (s), 1264 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 6.81 (d, *J* = 6.5 Hz, 1 H), 6.75 (dd, *J* = 2.0, 6.5 Hz, 2 H), 6.18 (s, 1 H), 4.82–4.69 (m, 1 H), 3.81 (s, 3 H), 3.73 (dd, *J* = 7.2, 9.1 Hz, 1 H), 3.67–3.52 (m, 1 H), 3.36 (dd, *J* = 7.2, 9.1 Hz, 1 H), 2.68 (dd, *J* = 8.9, 16.9 Hz, 1 H), 2.44 (dd, *J* = 8.9, 16.9 Hz, 1 H), 2.01–1.47 (8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.7, 149.6, 148.3, 134.9, 119.1, 114.3, 112.7, 81.0, 56.4, 49.9, 40.2, 38.2, 33.0, 24.2.

MS (ESI): *m*/*z* (%) = 276 (M^+, 100), 208 (21), 191 (83).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_3$: 276.1600; found: 276.1595.

Anal. Calcd for $C_{16}H_{21}NO_3$ (275.34): C, 69.7; H, 7.6; N, 5.0. Found: C, 69.4; H, 7.5; N, 5.1.

***N*-Methylrolipram (9)**

To a solution of **7** (60 mg, 0.2 mmol) in MeOH (10 mL) was added Pd/C (10 wt%, 6.0 mg). The mixture was degassed and saturated with H_2, transferred to an autoclave and pressurized with H_2 (10 bar) and kept at 60 °C for 5 h. The mixture was filtered through Celite and washed with EtOAc (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (SiO_2, EtOAc) to give **9** (6.3 mg, 0.02 mmol, 12%) as a colorless solid, mp 66 °C, along with rolipram (**8**; 28 mg, 0.1 mmol, 51%).

IR (KBr): 3410 (w), 2957 (m), 1670 (s), 1512 (s), 1264 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 8.6 Hz, 1 H), 6.69 (2 H), 4.80–4.65 (m, 1 H), 3.78 (s, 3 H), 3.67 (dd, *J* = 8.7, 8.7 Hz, 1 H), 3.45 (dt, *J* = 8.2, 16.4 Hz, 1 H), 3.31 (dd, *J* = 7.1, 9.2 Hz, 1 H), 2.85 (s, 3 H), 2.74 (dd, *J* = 9.0, 16.8 Hz, 1 H), 2.46 (dd, *J* = 8.2, 16.8 Hz, 1 H), 1.97–1.68 (6 H), 1.57 (2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 149.4, 148.2, 135.2, 118.9, 114.1, 112.6, 80.8, 57.1, 56.3, 39.1, 37.0, 33.0, 32.9, 29.7, 24.1.

MS (ESI): *m*/*z* (%) = 290 (100), 222 (13).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{24}NO_3$: 290.1756; found: 290.1751.

Anal. Calcd for $C_{17}H_{23}NO_3$ (289.37): C, 70.5; H, 8.0; N, 4.8. Found: C, 69.9; H, 7.8; N, 4.7.

Methyl 3-(4-Methoxyphenyl)-4-nitrobutanoate (12a)
Following the procedure for the synthesis of **7**, the cinnamate **11a** (850 mg, 4.4 mmol) was converted into **12a** (964 mg, 3.8 mmol, 86%); colorless solid; mp 65–68 °C.

IR (KBr): 3443 (w), 1730 (s), 1551 (s), 1252 (m), 833 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 4.67 (dd, *J* = 12.4, 7.5 Hz, 1 H), 4.57 (dd, *J* = 12.4, 7.5 Hz, 1 H), 4.02–3.84 (m, 1 H), 3.76 (s, 3 H), 3.61 (s, 3 H), 2.81–2.60 (2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 159.3, 130.3, 128.4, 114.5, 79.7, 55.3, 52.0, 39.6, 37.8.

MS (ESI): *m*/*z* (%) = 207 (80), 147 (100).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{15}NO_5$ + Na: 276.0848; found: 276.0868.

Anal. Calcd for $C_{12}H_{15}NO_5$ (253.10): C, 56.9; H, 6.0; N, 5.5. Found: C, 57.0; H, 6.0; N, 5.4.

Methyl 3-(3-Bromo-4-methoxyphenyl)-4-nitrobutanoate (12b)
Following the procedure for the synthesis of **7**, the cinnamate **11b** (780 mg, 2.9 mmol) was converted into **12b** (790 mg, 2.4 mmol, 82%); colorless solid; mp 98–100 °C.

IR (KBr): 3167 (w), 1727 (s), 1498 (s), 1284 (m), 1018 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 2.3 Hz, 1 H), 7.12 (dd, *J* = 8.5, 2.3 Hz, 1 H), 6.83 (d, *J* = 8.5 Hz, 1 H), 4.79–4.49 (2 H), 3.90 (m, 1 H), 3.85 (s, 3 H), 3.63 (s, 3 H), 2.74 (dd, *J* = 16.3, 7.2 Hz, 1 H), 2.68 (dd, *J* = 16.3, 7.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 155.8, 144.2, 132.2, 131.9, 127.8, 112.4, 79.5, 56.4, 52.2, 39.3, 37.7.

MS (ESI): *m*/*z* (%) = 98 (15), 146 (62), 160 (100), 332 (M + H^+, 14).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{15}BrNO_5$: 332.0134; found: 332.0109.

Anal. Calcd for $C_{12}H_{14}BrNO_5$ (332.15): C, 43.4; H, 4.2; N, 4.2. Found: C, 43.2; H, 4.1; N, 4.2.

Methyl 3-(4-Methoxy-3-nitrophenyl)-4-nitrobutanoate (12c)
Following the procedure for the synthesis of **7**, the cinnamate **11c** (10.0 g, 42 mmol) was converted into **12c** (10.7 g, 36 mmol, 85%); colorless solid; mp 96–100 °C.

IR (KBr): 2954 (w), 1732 (m), 1529 (s), 1268 (s), 1014 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 2.4 Hz, 1 H), 7.44 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.06 (d, *J* = 8.7 Hz, 1 H), 4.75 (dd, *J* = 12.9, 6.5 Hz, 1 H), 4.63 (dd, *J* = 12.9, 8.4 Hz, 1 H), 4.05–3.93 (m, 1 H), 3.94 (s, 3 H), 3.64 (s, 3 H), 2.79 (dd, *J* = 16.5, 7.0 Hz, 1 H), 2.73 (dd, *J* = 16.5, 7.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 152.7, 139.7, 133.6, 130.8, 124.5, 114.3, 78.9, 56.7, 52.2, 39.1, 37.3.

MS (EI): *m*/*z* (%) = 146 (67), 193 (86), 251 (100), 298 (M^+, 3).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{14}N_2O_7$: 298.0801; found: 298.0794.

Anal. Calcd for $C_{12}H_{14}N_2O_7$ (298.25): C, 48.3; H, 4.7; N, 9.4. Found: C, 48.4; H, 4.6; N, 9.4.

4-(4-Methoxyphenyl)pyrrolidin-2-one (13a)
Following the procedure for the synthesis of **8** via reduction-cyclization with Zn and aq HCl, **12a** (224 mg, 0.9 mmol) was converted into **13a** (120 mg, 0.6 mmol, 71%); colorless solid; mp 131–132 °C.

IR (KBr): 3203 (m), 2952 (m), 1679 (s), 1541 (s), 1247 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.41 (s, 1 H), 3.80 (s, 3 H), 3.75 (dd, *J* = 9.0, 8.3 Hz, 1 H), 3.71–3.58 (m, 1 H), 3.38 (dd, *J* = 9.1, 7.2 Hz, 1 H), 2.71 (dd, *J* = 16.9, 8.7 Hz, 1 H), 2.46 (dd, *J* = 16.9, 8.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.7, 158.8, 134.3, 127.8, 114.4, 55.4, 49.8, 39.8, 38.1.

MS (EI): *m*/*z* (%) = 191 (M^+, 40), 134 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}NO_2$: 191.0946; found: 191.0943.

Anal. Calcd for $C_{11}H_{13}NO_2$ (191.23): C, 69.1; H, 6.8; N, 7.3. Found: C, 68.8; H, 6.7; N, 7.3.

4-(3-Bromo-4-methoxyphenyl)pyrrolidin-2-one (13b)
Following the procedure for the synthesis of **8** via reduction-cyclization with Zn and aq HCl, **12b** (146 mg, 0.4 mmol) was converted into **13b** (58 mg, 0.2 mmol, 49%); colorless solid; mp 153–155 °C.

IR (KBr): 3196 (m), 1687 (s), 1497 (m), 1256 (s), 1054 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 2.2 Hz, 1 H), 7.15 (dd, *J* = 8.5, 2.2 Hz, 1 H), 6.86 (d, *J* = 8.5 Hz, 1 H), 6.69 (s, 1 H), 3.88 (s, 3 H), 3.75 (dd, *J* = 9.3, 8.3 Hz, 1 H), 3.68–3.52 (m, 1 H), 3.36 (dd, *J* = 9.4, 7.1 Hz, 1 H), 2.70 (dd, *J* = 16.9, 8.8 Hz, 1 H), 2.43 (dd, *J* = 16.9, 8.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 155.2, 135.9, 131.8, 126.8, 112.4, 112.2, 56.4, 49.6, 39.4, 38.0.

MS (EI): *m*/*z* (%) = 89 (41), 197 (24), 214 (100), 269 (M^+, 46).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{12}BrNO_2$: 269.0051; found: 269.0062.

Anal. Calcd for $C_{11}H_{12}BrNO_2$ (270.12): C, 48.9; H, 4.5; N, 9.2. Found: C, 49.0; H, 4.3; N, 5.1.

4-(3-Amino-4-methoxyphenyl)pyrrolidin-2-one (13c)
Following the procedure for the synthesis of **8** via reduction-cyclization with Zn and aq HCl, **12c** (100 mg, 0.3 mmol) was converted into **13c** (25 mg, 0.1 mmol, 36%); colorless solid; mp 163–166 °C.

IR (KBr): 3340 (m), 2938 (w), 1689 (s), 1518 (m), 1230 cm^{-1} (m).

^1H NMR (300 MHz, DMSO-d_6): δ = 7.63 (s, 1 H), 6.71 (d, *J* = 8.2 Hz, 1 H), 6.55 (dd, *J* = 2.1 Hz, 1 H), 6.43 (dd, *J* = 8.2, 2.1 Hz, 1 H), 4.66 (s, 2 H), 3.72 (s, 3 H), 3.54 (dd, *J* = 8.2, 8.2 Hz, 1 H), 3.35–3.47 (m, 1 H), 3.10 (dd, *J* = 9.4, 7.1 Hz, 1 H), 2.44 (dd, *J* = 16.4, 8.7 Hz, 1 H), 2.17 (dd, *J* = 16.3, 8.9 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 176.0, 145.2, 137.6, 135.3, 114.3, 112.2, 110.6, 55.3, 48.9, 39.2, 37.9.

MS (EI): *m*/*z* (%) = 106 (23), 134 (98), 149 (89), 206 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{14}N_2O_2$: 206.1055; found: 206.1052.

Acknowledgment

We thank Evonik Oxeno for generous donation of solvents and Umicore (Hanau, Germany) for generous donation of palladium catalysts.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Karppanen, H.; Paakkari, P.; Orma, A.-L.; Paakkari, I. *Agents Actions* **1979**, *9*, 84.
(2) Day, J. P.; Lindsay, B.; Riddell, T.; Jiang, Z.; Allcock, R. W.; Abraham, A.; Sookup, S.; Christian, F.; Bogum, J.; Martin, E. K.; Rae, R. L.; Anthony, D.; Rosair, G. M.; Houslay, D. M.; Huston, E.; Baillie, G. S.; Klussmann, E.;

Houslay, M. D.; Adams, D. R. *J. Med. Chem.* **2011**, *54*, 3331.
(3) Ortiz, J. L.; Milara, J.; Lluch, J.; De Diego, A.; Sanz, C.; Cortijo, J. *Allergy* **2013**, *68*, 64.
(4) Fehrholz, M.; Bersani, I.; Kramer, B. W.; Speer, C. P.; Kunzmann, S. *PLoS One* **2012**, *7*, 11.
(5) Oliva, A. A.; Kang, Y.; Furones, C.; Alonso, O. F.; Bruno, O.; Dietrich, W. D.; Atkins, C. M. *J. Neurochem.* **2012**, *123*, 1019.
(6) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394.
(7) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, Á.; Vera, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8431.
(8) Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475.
(9) Oliveira, A. R. M.; Villar, J. A. F. P.; Simonelli, F.; Gariani, R. A.; Wosch, C. L.; Zarbin, P. H. G. *Tetrahedron Lett.* **2007**, *48*, 1507.
(10) Wu, B.; Kuhen, K.; Ngoc Nguyen, T.; Ellis, D.; Anaclerio, B.; He, X.; Yang, K.; Karanewsky, D.; Yin, H.; Wolff, K.; Bieza, K.; Caldwell, J.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3430.
(11) Yang, X.-F.; Ding, C.-H.; Li, X.-H.; Huang, J.-Q.; Hou, X.-L.; Dai, L.-X.; Wang, P.-J. *J. Org. Chem.* **2012**, *77*, 8980.
(12) Morse, H. N. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 232.
(13) Schmidt, B.; Berger, R.; Hölter, F. *Org. Biomol. Chem.* **2010**, *8*, 1406.
(14) Schmidt, B.; Berger, R.; Hölter, F.; Böge, N.; Kreipl, A. Int. Patent Appl. WO 2010/122105 A1, **2009**; *Chem. Abstr.* **2010**, 1336884.
(15) Schmidt, B.; Hoelter, F. Int. Patent Appl. WO 2008055927, **2008**; *Chem. Abstr.* **2008**, 590195.
(16) Schmidt, B.; Hölter, F.; Berger, R.; Jessel, S. *Adv. Synth. Catal.* **2010**, *352*, 2463.
(17) Schmidt, B.; Berger, R.; Kelling, A.; Schilde, U. *Chem. Eur. J.* **2011**, *17*, 7032.
(18) Schmidt, B.; Hölter, F.; Kelling, A.; Schilde, U. *J. Org. Chem.* **2011**, *76*, 3357.
(19) Schmidt, B.; Hölter, F. *Org. Biomol. Chem.* **2011**, *9*, 4914.
(20) Schmidt, B.; Geißler, D. *Eur. J. Org. Chem.* **2011**, 4814.
(21) Schmidt, B.; Elizarov, N. *Chem. Commun.* **2012**, *48*, 4350.
(22) Bonin, H.; Fouquet, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2011**, *353*, 3063.
(23) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159.
(24) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622.
(25) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403.
(26) Felpin, F.-X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815.
(27) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305.
(28) Felpin, F.-X.; Miqueu, K.; Sotiropoulos, J.-M.; Fouquet, E.; Ibarguren, O.; Laudien, J. *Chem. Eur. J.* **2010**, *16*, 5191.
(29) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem. Eur. J.* **2002**, *8*, 3901.
(30) Garcia, A. L. L.; Carpes, M. J. S.; de Oca, A. C. B. M.; dos Santos, M. A. G.; Santana, C. C.; Correia, C. R. D. *J. Org. Chem.* **2005**, *70*, 1050.
(31) Kokil, P. B.; Patil, S. D.; Ravindranathan, T.; Nair, P. M. *Tetrahedron Lett.* **1979**, *20*, 989.
(32) Felluga, F.; Gombac, V.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **2005**, *16*, 1341.
(33) Felpin, F.-X.; Fouquet, E. *Chem. Eur. J.* **2010**, *16*, 12440.
(34) Hoshiko, T.; Ishihara, H.; Shino, M.; Mori, N. *Chem. Pharm. Bull.* **1993**, *41*, 633.

