JOC Article
pubs.acs.org/joc

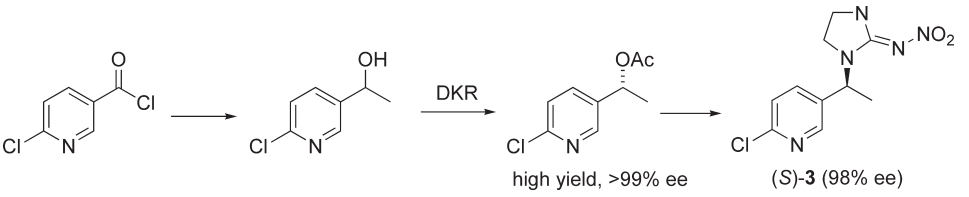
Synthesis of a Neonicotinoide Pesticide Derivative via Chemoenzymatic Dynamic Kinetic Resolution

Patrik Krumlinde,[†] Krisztián Bogár,[‡] and Jan-E. Bäckvall*,[†]

[†]*Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden, and* [‡]*Medicinal Chemistry, Discovery, AstraZeneca R&D Södertälje, SE-151 85 Södertälje, Sweden*

jeb@organ.su.se

Received July 8, 2009



Chemoenzymatic dynamic kinetic resolution (DKR) via combined ruthenium and enzyme catalysis was used in the key step of a synthesis of a neonicotinoid pesticide derivative (*S*)-**3**. The DKR was carried out under mild conditions with low catalyst loading. The method gives (*S*)-**3** in high enantiomeric excess (98%).

Introduction

As a result of the chiral environment in biological systems, the two enantiomers of a chemical compound will in many cases have different biological activity. Therefore it is desirable to have access to enantiomerically pure pharmaceuticals, pesticides, perfumes, and flavors, and during the past three decades asymmetric synthesis has emerged as one of the most important research areas in organic chemistry.[1]

In industry, resolution of enantiomers is still the predominant method for producing enantiomerically pure compounds. However, resolution is limited to give a maximum theoretical yield of 50% of the enantiomerically pure product, and furthermore, the product has to be separated from the starting material. Combined enzyme- and transition metal-catalyzed dynamic kinetic resolution (DKR)[2] of secondary alcohols[3] and primary amines[4] as well as of primary alcohols[5] has in recent years proved to be an efficient route to enantiopure compounds. This method relies on a catalytic in situ racemization of the remaining substrate, thereby enabling 100% yield of enantiomerically pure product.

Several different racemization catalysts have been explored, and in our group we have focused on the ruthenium catalysts shown in Figure 1.

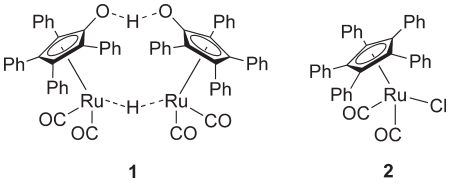


FIGURE 1. Ruthenium-based racemization catalysts.

Ever since Bayer released imidacloprid onto the market in 1991, neonicotinoid insecticides have been the fastest growing family of insecticides.[6] The in vivo action of this type of compounds is similar to that of epibatidine and nicotine (Figure 2), and the common target is the nicotinic acetylcholine receptor (nAChR).[7]

(1) (a) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.

(2) Pàmies, O.; Bäckvall, J. -E. *Chem. Rev.* **2003**, 3247–3262.

(3) (a) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825. (b) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972–1977. (c) Martín-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226–232.

(4) (a) Paetzold, J.; Bäckvall, J. -E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621. (b) Thalén, L. K.; Zhao, D.; Sortais, J. B.; Paetzold, J.; Hoben, C.; Bäckvall, J. -E. *Chem.—Eur. J.* **2009**, *15*, 3403–3410. (c) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668–669. (d) Choi, Y. K.; Kim, M. J.; Ahn, Y.; Kim, M. J. *Org. Lett.* **2001**, *3*, 4099–4101.

(5) Strübing, D.; Krumlinde, P.; Bäckvall, J. -E. *Adv. Synth. Catal.* **2007**, *349*, 1577–1581.

(6) Jeschkel, P.; Nauen, R. *Pest Manage. Sci.* **2008**, *64*, 1084–1098.

(7) Matsuda, K.; Buckingham, S. D.; Kleier, D.; Rauh, J. J.; Grauso, M.; Sattelle, D. B. *Trends Pharmacol. Sci.* **2001**, *22*, 573–580.

DOI: 10.1021/jo9014276 Published on Web 09/02/2009

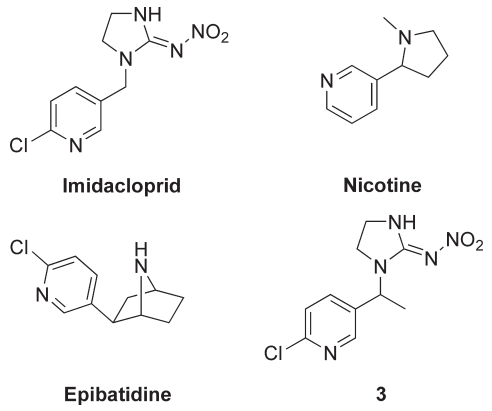
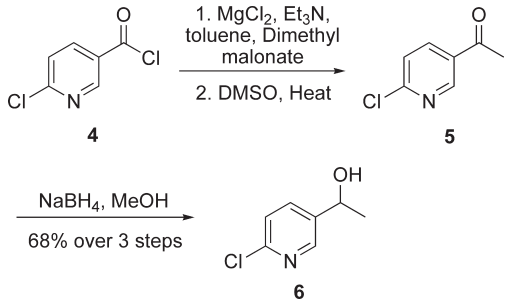


FIGURE 2. Compounds known to act on the nicotinic acetylcholine receptor (nAChR).

SCHEME 1. Synthesis of 6 on 100 mmol Scale



The release of imidacloprid to the market stimulated the development of different derivatives of the neonicotinoid motif. Recently, Kagabu et al. presented a racemic synthesis of a chiral chloronicotinyl insecticide, Me-imidacloprid (**3**).[8] The biological activity of this compound is slightly lower than that of imidacloprid; however, (*S*)-**3** has a higher potency compared with that of (*R*)-**3**. In this paper we present an easy and efficient synthesis of enantiopure (*S*)-**3** using DKR in the key step.

Results and Discussion

Alcohol **6** (Scheme 1) is a key intermediate in the synthesis of (*S*)-**3** using our approach. Racemic **6** was expected to work as substrate in a DKR reaction, and hence enantiopure (*R*)-**6** would be readily accessible. The synthesis of alcohol **6** was changed compared to the previously described route[7] because the new route (Scheme 1) was thought to be easier in a scale-up procedure. Ketone **5** was synthesized according to the method developed by Kuo.[9,10] The $NaBH_4$ reduction of **5** yielded **6** in 68% total yield over 3 steps on a 100 mmol scale. This corresponds to an average yield of 88% in each step. Alcohol **6** was then employed in the subsequent DKR without further purification.

SCHEME 2. DKR of 6

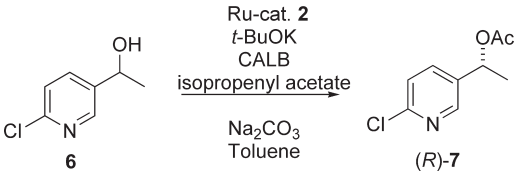


TABLE 1. Screening of Conditions for the DKR of 6[a]

entry	scale (mmol)	Ru-**2** (mol %)	Na_2CO_3 (mol %)	CALB (mg/mmol substrate)	[**6**] (M)	time (h)	conv (%)	yield (%)	ee (%)
1[b]	0.2	5	100	25	0.2	48	90	ND	95
2	0.2	5	100	25	0.2	15	100	ND	98
3	6	0.5	100	10	0.5	40	100	86	98
4	10	0.25	20	2	0.5	41	>99	96	>99
5	10	0.5	20	2	0.5	36	100	91	>99

[a]Reaction conditions: unless otherwise noted the reaction was carried out at 50 °C in toluene with 1.5 equiv of isopropenyl acetate and an equimolar amount of *t*-BuOK to ruthenium catalyst **2** loading. [b]The reaction was carried out at room temperature.

Candida antarctica lipase B (CALB) has been shown to have an excellent enantioselectivity for the 1-phenyl ethanol motif, and DKR has been carried out on a large number of derivatives. As expected the enantioselectivity in the transesterification[11] of **6** in toluene was excellent, both at room temperature and at 50 °C. DKR using Ru-catalyst **2** is often performed at room temperature, but sometimes the temperature has to be elevated when electron-deficient substrates are employed.

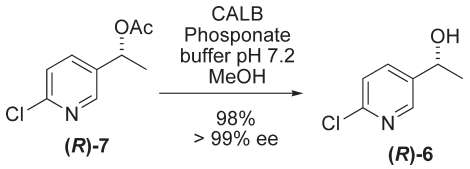
The DKR of **6** was carried out with the enzyme CALB and ruthenium catalyst **2** in toluene using isopropenyl acetate as acyl donor (Scheme 2). Reaction at room temperature was slow and gave 90% conversion and 95% ee after 45 h (Table 1, entry 1). Increasing the temperature to 50 °C greatly enhanced the rate of the reaction and also the enantioselectivity (Table 1, entry 2). The improved enantioselectivity is due to the faster racemization at higher temperatures, which makes the balance between the acylation rate and racemization better. In an attempt to make the process more cost-effective, the catalyst loading was decreased from 5 to 0.5 mol % (entry 3 compared to 1 and 2).

The amount of CALB was also decreased from 25 to 10 mg CALB/mmol substrate to keep the acylation rate relatively low compared to racemization. Because of the low catalyst loading the reaction time had to be extended, and after 40 h complete conversion had been obtained. In an attempt to decrease the catalyst loading even further (0.25 mol %, entry 4), the CALB loading was also decreased to 2 mg/mmol substrate to keep the racemization and resolution rates balanced. The result was a slower reaction, but with excellent yield and enantiomeric excess. To ensure complete conversion within a reasonable reaction time the Ru-catalyst loading was again increased to 0.5 mol %, and this time the reaction was finished within 36 h with >99% ee (entry 5).

To avoid purification between steps, direct hydrolysis of product **7** to (*R*)-**6** in the crude reaction mixture was investigated.

(8) Kagabu, S.; Kiriyama, K.; Nishiwaki, H.; Kumamoto, Y.; Tada, T.; Nishimura, K. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 980–988.
(9) Kuo, D. L. *Tetrahedron* **1992**, *48*, 9233–9236.
(10) For a scale-up synthesis of **5** to 100 g with this method, see: Lee, C. -H.; Jiang, M.; Cowart, M.; Gfesser, G.; Perner, R.; Kim, K. H.; Gu, Y. G.; Williams, M.; Jarvis, M. F.; Kowaluk, E. A.; Stewart, A. O.; Bhagwat, S. S. *J. Med. Chem.* **2001**, *44*, 2133–2138.
(11) For transesterification in organic solvents, see: (a) Faber, K. *Biotransformations in Organic Chemistry*, 5th ed.; Springer: Berlin, 2004. (b) Bornscheuer, U. T., Kazlauskas, R. J. *Hydrolases in Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2005.

SCHEME 3. Hydrolysis of (*R*)-7

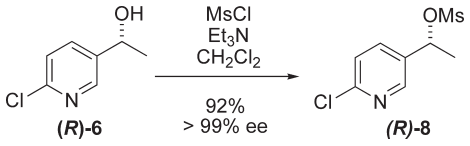


Hydrolysis under alkaline conditions (NaOH in MeOH) resulted in racemization of the product, most probably catalyzed by remaining ruthenium species. The hydrolysis of **7** was therefore carried out with CALB in a phosphate buffer (pH 7.2),[12] which leads to very mild reaction conditions (Scheme 3). An additional benefit of using CALB for the hydrolysis is that a second resolution is introduced, thereby yielding a mixture consisting of traces of the (*S*)-enantiomer of **7** and the enantiopure (*R*)-**6** as the major component. This poses no problem in the following reactions since the acetate **7** is more or less unreactive to those reaction conditions and is easily removed in the final purification. Attempts to perform the S_N2 substitution directly on (*R*)-**7** (DMSO, K_2CO_3 (2 equiv) 90 °C, 16 h) with nitroguanidine derivative **9** (see Scheme 5 for the structure) as nucleophile were unsuccessful and gave only a hydrolysis product (**6**) in small amounts.

In the article by Kagabu et al.[8] alcohol **6** was transformed to the tosylate to provide a good leaving group for the final S_N2 substitution. All efforts to reproduce the tosylation procedure were unsuccessful, since the tosylate was found to be unstable and difficult to purify. We therefore turned our attention to the mesylate group, a good alternative to the tosylate group. Even though mesylate **8** was more stable than the corresponding tosylate, **8** is still rather unstable. If it is stored at room temperature, it decomposes within weeks, where one of the decomposition products is the vinyl compound. Mesylate **8** also racemizes at room temperature, probably via elimination and readdition of the mesylate group. After 2 days at room temperature, the ee drops from >99% to 97%. Elimination and racemization is also a severe problem if **8** is subjected to column chromatography purification. These problems have been noticed before with similar types of compounds and have been solved by precipitation and filtration of the salts in the mesylation procedure as the only purification.[13] In the case of **8** it is possible to make an aqueous workup with retained ee and high yield. In this workup the inorganic salts are removed and will not interfere in the subsequent reaction. Aqueous workup afforded (*R*)-**8** in 92% yield with no or a small decrease in enantiopurity (>99% ee). This material has to be used quickly or stored in a freezer.[14]

The final step in the synthesis is an S_N2 substitution of the mesylate. Substitutions in the benzylic position are known to have a competing S_N1 pathway. Depending on the substituents

SCHEME 4. Mesylation of (*R*)-6



SCHEME 5. S_N2 Substitution of Mesylate (*R*)-8 by Nitroguanidine 9 To Yield the Final Product (*S*)-3

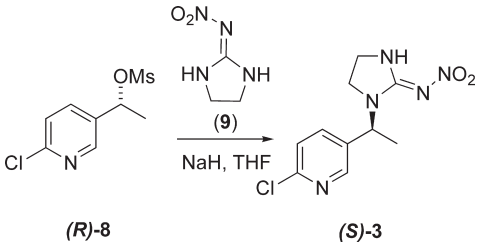


TABLE 2. Screening of Conditions for the Substitution of (*R*)-8

entry	solvent	temp (°C)	concn (M)	time (h)	yield (%)	ee (%)
1[a]	MeCN	reflux	0.1	14	40	85
2[a,d]	MeCN	50	0.1	50	34	91
3[a]	1,4-dioxane	90	0.1	4	53	94
4[b]	THF	50	0.2	20	51	98
5[c]	THF	50	0.2	16	58	98
6[c]	DMSO	50	0.1	1	63	92
7[c]	DMSO	25	0.1	3	69	96

[a]Base: K_2CO_3 (2 equiv), **9** (1 equiv). [b]Base: NaH (1 equiv), **9** (1 equiv). [c]Base: NaH (3 equiv), **9** (3 equiv). [d]Full conversion was not obtained.

on the reactant and the reaction conditions, this can in many cases be the dominating pathway.[15] With electron-deficient substrates the cationic intermediate is destabilized and the reaction is more likely to proceed according to the S_N2 model. In the case of nucleophilic substitutions in the pyridylmethyl position, which is positionally equivalent to a benzylic position but electron-deficient, the S_N2 pathway should be followed. However, the position of the nitrogen is important for the degree of electron deficiency. Pyridyl-2-methyl and pyridyl-4-methyl cations are destabilized both inductively and by resonance, but the pyridyl-3-methyl cation is destabilized only by induction. This can be seen in case of 1-(*x*-pyridyl)ethyl methanesulfonates ($x = 2, 3, 4$) where the 2- and 4-positioned ethyl methanesulfonates are stable enough to enable silica gel chromatography. However, having the substituent in 3-position destabilizes the molecule to such a degree that not even aqueous workup is possible.[13]

In the case of mesylate **8** the chlorine in the 2-position seems to destabilize the pyridylmethyl cation compared to the non-halogenated pyridine since aqueous workup is possible.

Kagabu et al. obtained 9% yield of **3** in the substitution performed in acetonitrile with K_2CO_3 as base. In their case they used the tosylate as leaving group. As mentioned above, we experienced this group to be less stable than the mesylate, which could explain the low yield. Using the similar conditions for reaction of mesylate **8** with **9** yielded (*S*)-**3** in 40% yield with an ee of 85% (entry 1, Table 2). In an attempt to increase both the yield and ee, the temperature was lowered to 50 °C, but the reaction did not go to completion within 50 h (entry 2). The yield was also lower, which could be

(12) It is important to point out that this method requires full conversion in the DKR reaction (>99%); otherwise the nonconverted racemic alcohol will deteriorate the ee after hydrolysis.

(13) Uenishi, J.; Hamada, M.; Aburatani, S.; Matsui, K.; Yonemitsu, O.; Tsukube, H. *J. Org. Chem.* **2004**, *69*, 6781–6789.

(14) At −18 °C no loss of ee or decomposition could be detected after 1 month.

(15) (a) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 4513–4519. (b) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383–1396. (c) Zieger, H. E.; Bright, D. A.; Haubenstock, H. *J. Org. Chem.* **1986**, *51*, 1180–1184. (d) Lim, C.; Kim, S. -H.; Yoh, S. -D.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* **1997**, *38*, 3243–3246.

explained by the interrupted reaction, but the ee was improved to 91%. Since a large amount of nonidentified byproducts was obtained in acetonitrile, we turned our attention to less ionizing solvents such as dioxane and THF. These gave indeed better results, both in terms of yield and ee. The best result was obtained in THF (50 °C for 16 h) using 3 equiv of **9**, which had been pretreated with NaH in situ (entry 5; Scheme 5). Lowering the temperature to 25 °C gave a very slow reaction (not included in the table). A standard solvent for S_N2 reactions is DMSO, and employing it gave a very fast reaction, at both 50 and 25 °C (entry 6 and 7 respectively). The best result was obtained at 25 °C with a yield of 69% and ee of 96%.

Conclusion

In conclusion, we have presented an easy, scalable, and highly stereoselective process (98% ee) of an imidacloprid derivative in 32% total yield over 7 steps (85% average yield in each step), which could be of importance for future development of pesticides.

Experimental Section

(*R*)-1-(6-Chloropyridin-3-yl)ethyl Acetate ((*R*)-7). *t*-BuOK (0.5 M in THF, 103 μL, 0.052 mmol) was added to a flame-dried Schlenk flask under argon. THF was removed under vacuum, and the flask refilled with argon. Ru-catalyst **2** (33 mg, 0.052 mmol), CALB (20 mg), Na_2CO_3 (220 mg, 2.1 mmol), and toluene (16 mL) were added, and the mixture was stirred for 5 min at 50 °C followed by the addition of alcohol **6** (1.6 g, 10.3 mmol) in 5 mL of toluene. The reaction was stirred for another 5 min at 50 °C, and then isopropenyl acetate (1.7 mL, 15.5 mmol) was charged to the flask. The reaction was stirred at 50 °C for 36 h. The conversion was checked by both ^{1}H NMR (>99.9%) and GC (>99.7%). The solids were removed by filtration through Celite using EtOAc as eluent. The solvent was evaporated, yielding 1.88 g of an orange liquid, which upon standing turned green, yield 91%, ee >99%. The product was used without further purification. A small sample was purified by silica gel column chromatography (CH_2Cl_2 used as eluent) for analysis. $[\alpha]^{20}_D = +87.44$ (*c* 1.4, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (1 H, app dt, *J* = 2.5, 0.6 Hz), 7.63 (1 H, ddd, *J* = 8.3, 2.5, 0.4 Hz), 7.30 (1 H, dd, *J* = 8.3, 0.5 Hz), 5.85 (1 H, q, *J* = 6.7 Hz), 2.06 (3 H, s), 1.53 (3 H, d, *J* = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 151.0, 148.0, 136.9, 136.2, 124.3, 69.5, 22.0, 21.2. HRMS (ESI) (M + Na)$^+$: *m*/*z* calcd for $C_7H_8ClNNaO$ 222.0292, obsd 222.0297. Chiral GC gradient (carrier gas H_2, flow 1.8 mL/min): 110 °C, 0 min; 2 °C/min to 135 °C, 0 min; 80 °C/min to 200 °C, 6 min. Retention times: (*S*)-**7**, 12.62 min; (*R*)-**7**, 12.87 min.

(*R*)-1-(6-Chloropyridin-3-yl)ethanol ((*R*)-6). (*R*)-**7** (1.9 g, 9.4 mmol) and CALB (20 mg) were suspended in a mixture of MeOH (10 mL) and phosphate buffer (pH 7.2, 10 mL). The mixture was stirred 44 h at ambient temperature, monitored by TLC. Water (20 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 1.49 g of a green oil: 98 mol % of (*R*)-**6** and 2 mol % of **7**. This was used without further purification. A small sample was purified by silica gel column chromatography (eluent CH_2Cl_2/EtOAc 1:1) for analysis. $[\alpha]^{20}_D = +46.05$ (*c* 2.1, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (1 H, app dt, *J* = 2.5, 0.8 Hz), 7.68 (1 H, ddd, *J* = 8.3, 2.5, 0.5 Hz), 7.27 (1 H, d, *J* = 8.3 Hz), 4.92 (1 H, q, *J* = 6.5 Hz), 3.03 (1 H, s), 1.48 (3 H, d, *J* = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 147.2, 140.3, 136.4, 124.3, 67.4, 25.4. HRMS (ESI) (M + Na)$^+$: *m*/*z* calcd for $C_7H_8ClNNaO$ 180.0187, obsd 180.0193. Chiral GC gradient (carrier gas H_2, flow 1.8 mL/min): 110 °C, 10 min; 1 °C/min to 135 °C, 0 min; 80 °C/min to 200 °C, 6 min. Retention times: (*R*)-**6**, 32.63 min; (*S*)-**6**, 34.11 min.

(*R*)-1-(6-Chloropyridin-3-yl)ethyl Methanesulfonate ((*R*)-8). (*R*)-**6** (0.39 g, 2.5 mmol) and Et_3N (0.52 mL, 3.7 mmol) were dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. MsCl (0.21 mL, 2.7 mmol) was added dropwise to the solution upon which a white precipitate was formed. After being stirred at 0 °C for 1 h, 10 mL of CH_2Cl_2 and 10 mL of H_2O were added. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to yield 0.55 g of a yellow oil that solidified upon standing. Yield 92%, ee >99%. For a pure sample it is possible to run silica gel column chromatography (CH_2Cl_2/EtOAc 19:1), although the majority of **8** will decompose. Compound **8** also racemized to some extent on column chromatography. $[\alpha]^{20}_D$ (ee 97%) = +70.42 (*c* 1.2, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (1 H, app dt, *J* = 2.5, 0.6 Hz), 7.72 (1 H, ddd, *J* = 8.3, 2.5, 0.4 Hz), 7.37 (1 H, dd, *J* = 8.3, 0.6 Hz), 5.76 (1 H, q, *J* = 6.6 Hz), 2.91 (3 H, s), 1.72 (3 H, d, *J* = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 147.9, 136.9, 134.3, 124.7, 76.8, 39.2, 23.2. HRMS (ESI) (M + Na)$^+$: *m*/*z* calcd for $C_8H_{10}ClNNaO_3S$ 257.9962, obsd 257.9961. Chiral HPLC: AS (isocratic, isohexane/isopropanol 70:30, flow 0.5 mL/min). Retention times: (*R*)-**8**, 30.1 min; (*S*)-**8**, 37.0 min.

(*S*)-Me Imidacloprid ((*S*)-3). Method A. Compound **9** (160 mg, 1.2 mmol) and NaH (60% suspension in mineral oil, 48 mg, 1.2 mmol) were suspended in THF (2 mL). The mixture was stirred for 4 h at 50 °C until the gas evolution had ceased. Mesylate (*R*)-**8** (94 mg, 0.40 mmol) was added in one portion, and the reaction was stirred for an additional 16 h at 50 °C. The solids were filtered off, the solution was evaporated onto silica, and the product was purified by silica gel column chromatography using EtOAc as eluent. Yield 63 mg (58%), ee 98%.

Method B. Compound **9** (160 mg, 1.2 mmol) and NaH (60% suspension in mineral oil, 48 mg, 1.2 mmol) were suspended in DMSO (4 mL). The mixture was stirred for 2 h at 25 °C until the gas evolution had ceased. Mesylate (*R*)-**8** (94 mg, 0.40 mmol) was added in one portion, and the reaction was stirred for an additional 3 h at 25 °C. Water and EtOAc were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and then dried over $MgSO_4$. The solids were filtered off, and the solution was evaporated onto silica and purified by silica gel column chromatography using EtOAc as eluent. Yield 63 mg (69%), ee 96%. $[\alpha]^{20}_D$ (ee = 98%) = −130.68 (*c* 0.73, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (1 H, app d, *J* = 2.6 Hz), 8.18 (1 H, bs), 7.65 (1 H, ddd, *J* = 8.3, 2.5, 0.4 Hz), 7.31 (1 H, d, *J* = 8.3 Hz), 5.50 (1 H, q, *J* = 7.4 Hz), 3.82−3.57 (3 H, m), 3.25−3.18 (1 H, m), 1.58 (3 H, d, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 151.3, 148.4, 138.1, 133.5, 124.5, 48.9, 41.5, 40.7, 15.8. HRMS (ESI) (M + Na)$^+$: *m*/*z* calcd for $C_{10}H_{12}ClN_5NaO_2$ 292.0572, obsd 292.0586. Chiral HPLC: AS (isocratic, isohexane/isopropanol 50:50, flow 0.5 mL/min). Retention times: (*R*)-**3**, 46.6 min; (*S*)-**3**, 57.3 min.

Acknowledgment. The Swedish Research Council, the Berzelius Center EXSELENT, and K & A Wallenberg foundation are gratefully acknowledged for financial support.

Supporting Information Available: General procedures and copies of ^{1}H and ^{13}C NMR spectra and chromatograms of compounds (*R*)-**6**, (*R*)-**7**, (*R*)-**8**, and (*S*)-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.