



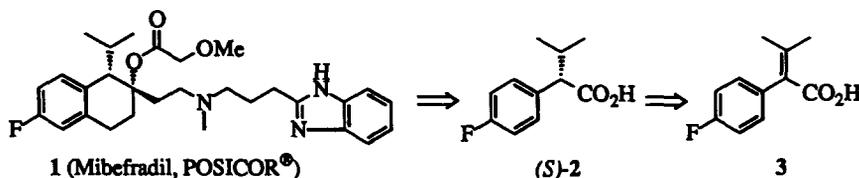
Practical synthesis of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid, key building block for the calcium antagonist Mibefradil

Yvo Cramer, Joseph Foricher, Michelangelo Scalone* and Rudolf Schmid

Pharmaceuticals Division, Process Research, F. Hoffmann–La Roche AG, CH-4070 Basel, Switzerland

Abstract: A short, technically feasible route was developed for the synthesis of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid (*S*)-2 with an overall yield of 80% starting from 4-fluorophenylacetic acid. Asymmetric hydrogenation of the easily accessible unsaturated acid **3** in the presence of ruthenium(II) carboxylato complexes containing chiral atropisomeric diphosphines afforded (*S*)-2 in up to 94% ee. The ee of (*S*)-2 was upgraded to 98% by crystallization of its sodium salt. The same protocol was also applied to the synthesis of (*S*)-2-(4-chlorophenyl)-3-methylbutanoic acid. © 1997 Elsevier Science Ltd

Mibefradil **1**^{1,2} is a new type of calcium antagonist³ which has been approved in several countries for the treatment of hypertension and angina pectoris (Scheme 1). Previously, the key intermediate for the introduction of the chirality, the acid (*S*)-2, had been obtained by resolution of the racemate.^{1,2,4} However, this procedure, although being quite efficient (70% overall yield), required five chemical steps. Therefore we envisaged the preparation of (*S*)-2 by a shorter route employing the asymmetric hydrogenation of the unsaturated acid **3** as the key step.



Scheme 1.

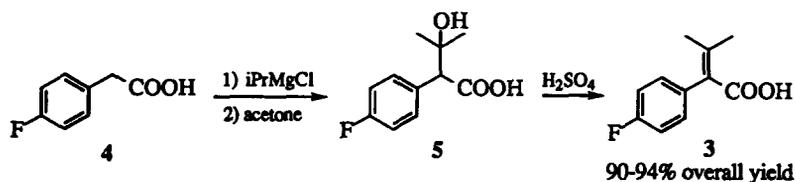
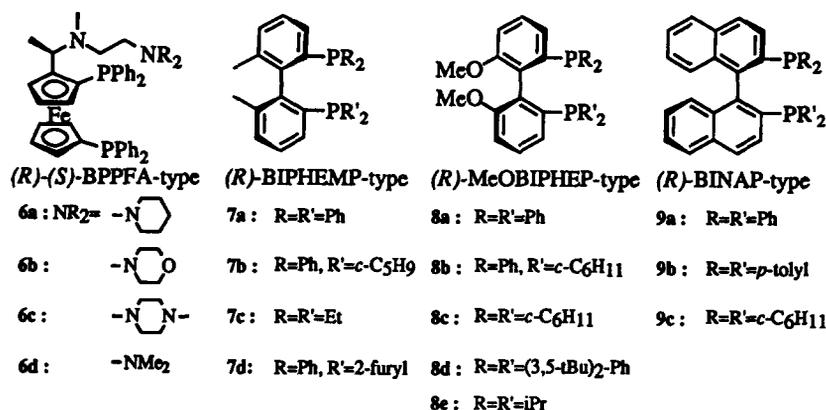
The asymmetric hydrogenation of trisubstituted acrylic acids of type **3**—although not **3** itself—has been described with rhodium catalysts. Up to 98% ee was achieved with chiral (aminoalkyl)ferrocenyldiphosphines,⁵ whereas with atropisomeric diphosphines (BINAP and analogues) the highest ee was 80%.⁶ With chiral ruthenium catalysts, the asymmetric hydrogenation of a trialkyl-substituted acrylic acid, i.e. 2,3-dimethyl-2-butanoic acid, has been reported to proceed with 70% and 88% ee with BINAP⁷ or octahydroBINAP⁸ as the chiral ligand, respectively.

Using methods published for the synthesis of trisubstituted acrylic acids analogous to the hydrogenation substrate **3**,⁹ the conversion of **4** to **3** was achieved in only moderate yields ($\leq 67\%$). Specifically, the racemic alcohol **5** was obtained in high yields by reaction of **4** with LDA and acetone. However, the conversion of **5** to **3** in the presence of dilute mineral acids,¹⁰ *p*-toluenesulphonic acid or Amberlyst 15 was accompanied by the formation of substantial amounts of β,β -dimethyl-*p*-fluorostyrene by loss of CO₂ and water.

After considerable experimentation we found that the dehydration of **5** proceeded selectively in conc. sulfuric acid at room temperature.¹¹ In this reaction, sulfuric acid has a triple role of proton

* Corresponding author. Email: michel.scalone@roche.com

source, solvent and water scavenger. Finally, replacement of expensive LDA with *i*-propylmagnesium chloride¹² rendered the synthesis of **3** a short and efficient process (Scheme 2).



Scheme 2.

The rhodium catalyzed asymmetric hydrogenation of **3** in the presence of modified ferrocenyl-type ligands proceeded, as expected, very enantioselectively, affording (*S*)-**2** in up to 98% ee (Table 1). With **6a** as the diphosphine the rate and the ee of (*S*)-**2** remained constant over a wide range of pressure (10–100 bar), concentration (5–20%) and temperature (20–50°C). In contrast, the ruthenium catalyzed asymmetric hydrogenation of **3** was very responsive to parameter variation (Table 2). Highly active and enantioselective catalysts were obtained when at least one of the phosphorus atoms contained aromatic substituents. A hydrogen pressure of 180 bar was necessary for reaching the highest ee-values of 94% with **7a** and 92% with **8a** or **9a** as the chiral diphosphines.

The presence in the catalyst of diphosphine ligands with *R* configuration led to the formation of acid **2** with *S* configuration. In two instances, however, when the substituents on the phosphorus atom were bulky alkyl (*i*-propyl) or aryl groups [bis(3,5-*t*Bu)-phenyl] (Entries 12 and 13 in Table 2), acid **2** with *R* configuration was formed. This observation, together with the dependence of the ee on

Table 1. Asymmetric hydrogenation of **3** catalyzed by chiral ferrocenylphosphine–rhodium complexes

Entry	Diphosphine	% Conv.	%ee (<i>S</i>)
1	6a	> 99	98
2	6b	68	74
3	6c	83	75
4	6d	75	89
5	BPPFA	42	38

Conditions: [Rh(COD)₂]BF₄/*R,S*-diphosphine, MeOH/THF 1:4 (*c* = 5%), 20°C, 50 bar, 20h, substrate/catalyst molar ratio (S/C) = 200. In entries 2,3 and 4, 5% of triethylamine (relative to **3**) was added.

Table 2. Asymmetric hydrogenation of **3** catalyzed by Ru(OAc)₂((*R*)-diphosphine) complexes

Entry	Diphosphine	P (bar)	conc. (%)	S/C	% Conv.		%ee (<i>S</i>)
					4h	20h	
1	7a	5	2	1000	-	95	35
2	"	40	2	1000	98	100	85
3	"	60	8	2000	56	100	88
4	"	180	30	4000	83	100	94
5	7b	60	5	2000	99	100	88
6	7c	60	5	2000	48	82	41
7	7d	60	5	2000	100	-	90
8	8a	60	30	2000	60	100	80
9	"	180	30	4000	85	100	92
10	8b	60	5	2000	100	-	91
11	8c	60	5	2000	6	10	30
12	8d	60	5	1000	100	-	22 ^{a)}
13	8e	60	5	1000	n.d.	55	11 ^{a)}
14	9a	60	30	2000	39	100	81
15	"	180	30	4000	50	99	91
16	9b	60	5	1000	93	100	77
17	9c	60	8	1000	2	13	63

Conditions: MeOH, 20°C; ^{a)} (*R*) configuration.

Table 3. Ruthenium-catalyzed asymmetric hydrogenation of **3** in the presence of base

Entry	Base	Amount of base ^{a)}	% Conv.		%ee (<i>S</i>)
			1h	4h	
1	NEt ₃	0.3	68	100	94
2	"	0.6	84	100	94
3	"	0.9	56	100	94
4	NaOMe	0.1	55	98	92
5	"	0.5	66	99	92
6	"	0.9	64	99	92
7	none	-	42	85	92

Conditions: MeOH (c = 30%), 20°C, 180 bar, S/C 4000. ^{a)} Molar equivalents relative to **3**.

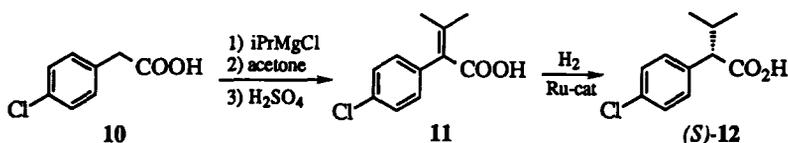
pressure and base (*vide infra*) indicate that the mechanism of the ruthenium catalyzed hydrogenation of trisubstituted acrylic acids is more complex than so far proposed for unsaturated acids.¹³

Due to its better availability, the chiral diphosphine **8a** (MeOBIPHEP) was chosen for further optimization. A screening of organic (primary, secondary and tertiary amines) and inorganic (MOH, MOCH₃) bases showed that the addition of triethylamine or sodium methoxide had a beneficial effect on the hydrogenation rate and, in the case of triethylamine, also on the ee (Table 3). Under the best conditions (entries 2 and 5 in Table 3) the hydrogenation was conducted on a 300 g scale at an S/C-ratio of 8000. Complete conversion was achieved within 8–10 h, (*S*)-**2** was obtained in 92% (NaOCH₃) and 94% ee (Et₃N). Further studies towards scale-up and technical development of the hydrogenation have been carried out using a CSTR cascade system.^{2,14}

The ee of (*S*)-**2** was upgraded by crystallization of its sodium salt¹⁵ from methanol/tetrahydrofuran, affording finally (*S*)-**2** of 98% ee in 83–86% isolated yield. The potassium salt of (*S*)-**2** was too soluble

in polar organic solvents, whereas the calcium salt gave a crystalline paste which was difficult to handle.

The protocol adopted for (*S*)-**2** was also applied to the preparation of the 4-chloro analogue (*S*)-**12**, which is a potential intermediate in the synthesis of enantiomerically pure fenvalerate (Scheme 3).¹⁶ The hydrogenation substrate **11** was prepared in 77% yield by reaction of 4-chlorophenylacetic acid **10** with *i*-propylmagnesium chloride and acetone followed by dehydration. The ruthenium catalyzed hydrogenation ([Ru(OAc)₂(**7a**)], same conditions as in Table 3) afforded (*S*)-**12** of 91% ee in 92% yield. The rhodium catalyzed hydrogenation of **11**, which had already been described,^{5a} was reproduced uneventfully ([Rh(COD)₂]BF₄/**6a**, same conditions as in Table 1) and afforded (*S*)-**12** of 98% ee in 96% yield.



Scheme 3.

In conclusion, we have developed a new, efficient route to (*S*)-**2** which compares favourably with the resolution route, since it is shorter (three versus five chemical steps), higher yielding (80 versus 70%) and requires less multipurpose equipment and unit operations. The resulting significant cost reduction renders the process attractive for technical implementation.

Experimental section

All manipulations of oxygen- and moisture-sensitive materials were conducted under an argon atmosphere. All solvents were distilled under argon before use. Hydrogen and argon were of 99.9999% purity. The ferrocenyl-type^{5a} and the atropisomeric diphosphines¹⁷ as well as the Ru(OAc)₂(diphosphine) complexes¹⁸ were prepared according to reported procedures. Nuclear magnetic resonance (NMR) spectra were taken on a Bruker 250E (¹H 250 MHz and ³¹P 101.26 MHz) spectrometer using TMS (¹H) as internal standard and 85% H₃PO₄ (³¹P) as an external standard. Optical rotations were measured on a Perkin–Elmer 241 spectrometer. Melting points were determined on a Büchi 510 and are uncorrected.

2-(4-Fluorophenyl)-3-hydroxy-3-methylbutanoic acid **5**

To a suspension of magnesium turnings (24.30 g, 1.00 mol) in tetrahydrofuran (50 mL) was added under vigorous stirring 1,2-dibromoethane (0.5 mL) followed by a solution of isopropyl chloride (86.4 g, 1.10 mol) in tetrahydrofuran (225 mL) within 90 min at 30°C. The resulting gray suspension was stirred during 18 h at room temperature, then a solution of 4-fluorophenylacetic acid (73.0 g, 0.473 mol) in tetrahydrofuran (150 mL) was added at 25°C during 90 min. The resulting thick suspension was stirred at 40°C for 1 h, treated with acetone (30.0 g, 0.516 mol) at 25°C during 30 min and stirred at 40°C for 1 h. Addition of a 14.2% aqueous solution of sulfuric acid (350 mL) under ice cooling, extraction of the aqueous phase with tetrahydrofuran (200 mL) and evaporation of the organic phase afforded crude 2-(4-fluorophenyl)-3-hydroxy-3-methylbutanoic acid (**5**) (110 g) as a dark oil. Crystallization from toluene (70 mL)/hexane (300 mL) (50–0°C) afforded **5** (97.0 g, 96.5%) as a white crystalline material, mp 86–88°C. ¹H NMR (250 MHz, CDCl₃, 20°C): δ 1.07 (*s*, 3 H, Me), 1.37 (*s*, 3 H, Me), 3.61 (*s*, 1 H), 7.01 (*m*, 2 H), 7.36 (*m*, 2 H). MS (EI) *m/z* 194 (M⁺–H₂O, 5%), 154 (M⁺–C₃H₆O, 100%), 136 (M⁺–C₃H₆O–H₂O, 60%). Anal. Calcd for C₁₁H₁₃FO₃: C, 62.26; H, 6.19. Found: C, 62.26; H, 6.17.

2-(4-Fluorophenyl)-3-methylcrotonic acid 3

To a solution of **5** (96.5 g, 0.455 mol) in dichloromethane (200 mL) was added under stirring sulfuric acid (240 g, 2.45 mol) at 15–20°C during 30 min. Dichloromethane was evaporated at 20°C, the yellow solution was stirred for 45 min at room temperature and then poured on ice water. The white precipitate was filtered off, washed with water and hexane and dried. 2-(4-Fluorophenyl)-3-methylcrotonic acid (**3**) (75.4 g, 97%) was isolated as a white crystalline material, mp 124–126°C. ¹H NMR (250 MHz, CDCl₃, 20°C): δ 1.69 (*s*, 3 H, Me), 2.23 (*s*, 3 H, Me), 6.99–7.15 (*m*, 4 H), 12.0–12.5 (*br*, 1 H). MS (EI) *m/z* 194 (M⁺, 100%), 136 (M⁺–C₃H₆OH, 60%). Anal. Calcd for C₁₁H₁₁FO₂: C, 67.96; H, 5.67. Found: C, 68.03; H, 5.71.

(*S*)-2-(4-Fluorophenyl)-3-methylbutanoic acid 2 (ruthenium catalyst, triethylamine as base)

A 2 L Hastelloy autoclave was charged with a solution of **3** (310.0 g, 1.60 mol) in methanol (0.790 L) and triethylamine (0.133 L, 0.958 mol), and with Ru(OAc)₂/**8a** (0.160 g, 0.20 mmol). The autoclave was sealed, purged with argon and pressurized with 180 bar of hydrogen. The hydrogenation was carried out at 20°C with a constant pressure of 180 bar. After 8 h the conversion was complete and (*S*)-**2** of 94.1% ee had formed. The autoclave was purged with argon, the contents were drained off and the autoclave was rinsed with methanol (0.34 L). To the hydrogenated mixture a sodium methylate solution in methanol (307.0 g, 30% w/w, 1.70 mol) was added and solvent mixture (720 g) was distilled off (170–245 mbar, 30–32°C). Then THF (1.4 L) was added dropwise during 1.5 h under normal pressure at 90°C bath temperature simultaneously removing the solvent mixture (1.05 L) by distillation. The resulting suspension was cooled to 2°C and stirred at this temperature for 2 h. The precipitate was collected by filtration, washed with THF (800 mL) and dried, affording 363.8 g of the white, crystalline sodium salt of (*S*)-**2** with an ee of 98.5%. Treatment with charcoal, removal of THF *in vacuo* and acidification of an aqueous solution of the sodium salt with hydrochloric acid (220 mL, 25% w/w, 1.7 mol) at room temperature afforded (*S*)-**2** (258.2 g, 85.5%) as a white crystalline solid of 98.5% ee.

Sodium salt of (*S*)-**2**: mp >250°C, ¹H NMR (250 MHz, DMSO, 20°C): δ 0.54 (*d*, 3 H, Me, *J*=1.3), 0.95 (*d*, 3 H, Me, *J*=1.3), 2.10 (*m*, 1 H, CHMe₂), 2.70 (*d*, 1 H, CH, *J*=3.1), 6.96 (*m*, 2 H), 7.32 (*m*, 2 H). [α]_D²¹ +3.3 (*c* 1, MeOH). MS (ESI) *m/z* 195.3 ((M–Na)[–], 100%). Anal. Calcd for C₁₁H₁₂FNao₂·0.76 THF: C, 61.77; H, 6.68; F, 6.96. Found: C, 61.65; H, 6.78; F, 6.66. Ruthenium content <2 ppm (X-ray fluorescence).

(*S*)-**2**: Mp 55–57°C, ¹H NMR (250 MHz, CDCl₃, 20°C): δ 0.69 (*d*, 3 H, Me, *J*=1.9), 1.06 (*d*, 3 H, Me, *J*=1.0), 2.30 (*m*, 1 H, CHMe₂), 3.12 (*d*, 1 H, CH, *J*=1.7), 6.99 (*m*, 2 H), 7.28 (*m*, 2 H), 9.5–10.5 (*br*, 1 H). [α]_D²⁰ +50.7 (*c* 1, CHCl₃) (lit.⁴ [α]_D²¹ +46.8 (*c* 1, CHCl₃)). MS (EI) *m/z* 196 (M⁺, 24%), 154 (M⁺–C₃H₆, 100%), 136 (M⁺–C₃H₆–H₂O, 25%), 109, (M⁺–C₃H₆–COOH, 50%). Anal. Calcd for C₁₁H₁₃FO₂: C, 67.33; H, 6.68; F, 9.68. Found: C, 67.23; H, 6.72; F, 9.80. Ruthenium content <2 ppm (X-ray fluorescence).

(*S*)-2-(4-Fluorophenyl)-3-methylbutanoic acid 2 (ruthenium catalyst, sodium methylate as base)

A 2 L Hastelloy autoclave was charged with a solution of **3** (300.0 g, 1.545 mol) in methanol (0.760 L), a sodium methylate solution in methanol (139.0 g, 30% w/w, 0.772 mol) and with Ru(OAc)₂/**8a** (0.155 g, 0.193 mmol). The autoclave was sealed, purged with argon and pressurized with 180 bar of hydrogen. The hydrogenation was carried out at 20°C with a constant pressure of 180 bar. After 10 h the conversion was complete and (*S*)-**2** of 92.5% ee had formed. The autoclave was purged with argon, the contents were drained off and the autoclave was rinsed with methanol (0.10 L). After addition of a sodium methylate solution in methanol (167.0 g, 30% w/w, 0.927 mol), an analogous work-up of the hydrogenated mixture as described above afforded 357.7 g of sodium salt of (*S*)-**2** with an ee of 98.2% and finally 248.2 g (82.8%) of (*S*)-**2** as a white crystalline material of 98.1% ee, mp 54–57°C.

2-(4-Chlorophenyl)-3-methylcrotonic acid **11**

The reaction was carried out as described above for **5** and **3**. Treatment of 4-chlorophenylacetic acid (80.6 g, 0.473 mol) with *i*-propylmagnesium chloride and acetone afforded crude 2-(4-chlorophenyl)-3-hydroxy-3-methylbutanoic acid (120.9 g), which was treated with sulfuric acid. 2-(4-Chlorophenyl)-3-methylcrotonic acid **11** (75.4 g, 97%) was isolated as a white crystalline material, mp 144–145°C (lit.¹⁹ 141°C). Anal. Calcd for C₁₁H₁₁ClO₂: C, 62.72; H, 5.26; Cl, 16.83. Found: C, 62.74; H, 5.31; Cl, 16.61.

(*S*)-2-(4-Chlorophenyl)-3-methylbutanoic acid **12** (ruthenium catalyst)

In a glove-box (argon, <1 ppm oxygen) a 180 mL stainless steel autoclave equipped with a magnetically driven stirrer was charged successively with **11** (5.0 g, 23.74 mmol), methanol (23 mL) and a catalyst solution of Ru(OAc)₂(**7a**) (0.0914 g, 0.119 mmol) in methanol (50 mL). The autoclave was sealed and the hydrogenation run at 20°C at a constant pressure of 60 bar. After 4 h the conversion was complete. The hydrogenated mixture was rotary evaporated and the residue distilled (kugelrohr, 150°C, 0.2 mbar), affording 4.6 g (92%) of (*S*)-**13** of 90.5% ee, [α]_D²⁰ +42.3 (*c* 1, MeOH) (lit.⁴ [α]_D²³ 46.8 (*c* 1, CHCl₃)).

General procedure for the rhodium catalyzed hydrogenations

In a glove-box (argon, <1 ppm oxygen) a 180 mL stainless steel autoclave equipped with a magnetically driven stirrer was charged successively with the substrate (5.00 g of **3** or **11**), the solvent and the catalyst solution. The hydrogenations were run under the conditions given in Table 1. The products were isolated by distillation (kugelrohr, 150°C, 0.2 mbar). With **6a** as the chiral diphosphine ligand the following results were achieved: (*S*)-**2**: [α]_D²⁰ +52.4 (*c* 1, CHCl₃), 98% ee; (*S*)-**12**: [α]_D²⁰ +49.7 (*c* 1, CHCl₃), 98% ee.

Analytical methods

The enantiomeric excesses of **2** and **12** were determined by GC using a Hewlett Packard instrument equipped with a 2,6-dimethyl-3-pentyl β -cyclodextrin column (30% on OV 61, 10 m, 0.32 mm ID; H₂ gas). A sample of (*S*)-**2** (ca. 20 mg, residue from a hydrogenated solution after evaporation or solid sample homogenized by trituration in a mortar) was dissolved in an ethereal solution of diazomethane (1.5 mL). After having been stirred for 10 min, 0.75 mL of this solution were evaporated to dryness and the residue dissolved in ethyl acetate (1.0 mL); 0.5 μ L of this solution were injected. A sample of sodium salt of (*S*)-**2** (ca. 25 mg) was treated with an excess of methanolic hydrogen chloride and, after evaporation, converted to the methyl ester as above. Temperature program: 80°C→180°C, 2°C/min. The retention times were 11.1 min ((*S*)-**2**), 11.5 min ((*R*)-**2**), 14.5 min (**3**), 14.2 min ((*S*)-**12**), 14.7 min ((*R*)-**12**), 18.6 min (**11**).

The enantiomeric excess of **2** was also determined by HPLC using a Hewlett Packard instrument equipped with a CHIRACEL OD column (250×4.6 mm, 5 μ m). The mobile phase was prepared by charging isopropanol (10 ml) and trifluoroacetic acid (1.0 ml) in a 1 L measuring flask and adding hexane to the mark. The flow rate was 0.6 mL/min, the detection wavelength was 210 nm. The sample was prepared by dissolving **2** or its sodium salt (ca. 10 mg) in the mobile phase (10 mL); 20 μ L of this solution were injected. The retention times were 25.1 min ((*R*)-**2**), 26.7 min ((*S*)-**2**), 31.0 min (**3**). The ee-values for **2** obtained by GC and HPLC differed by less than 0.5%.

Acknowledgements

We wish to thank our colleagues from the Analytical Services for NMR spectra (Dr W. Arnold), elemental analyses (Dr S. Müller), GC analyses (Dr W. Walther) and HPLC analyses (Mr J. Bögli). We thank M. Häss, M. Lalonde, P. Meier, A. Meili, Ms S. Müller, A. Rageot, D. Spiess and J. Stadelmann for skillful technical assistance. We are also grateful to Dr S. Wang for helpful discussions.

References

1. (a) Hengartner, U.; Ramuz, U. to *F. Hoffmann-La Roche AG*, EP 177'960 (10 October 1985). (b) Branca, Q.; Jaunin, R.; Märki, H.P.; Marti, F.; Ramuz, H. to *F. Hoffmann-La Roche AG*, EP 268'148 (4 April 1987).
2. Cramer, Y.; Foricher, J.; Hengartner, U.; Jenny, Ch.; Kienzle, F.; Ramuz, H.; Scalone, M.; Schlageter, M.; Schmid, R.; Wang, S. *Chimia* **1997**, *51*, 303.
3. Mishra, S. K.; Hermsmeyer, K. *Circ. Res.* **1994**, *75*, 144.
4. Miyakado, M.; Ohno, N.; Okuno, Y.; Hirano, M.; Fujimoto, K.; Yoshioka, H. *Agr. Biol. Chem.* **1975**, *39*, 267.
5. (a) Hayashi, T.; Kawamura, N.; Ito, Y. *J. Am. Chem. Soc.* **1987**, *109*, 7876. (b) Hayashi, T.; Kawamura, N.; Ito, Y. *Tetrahedron Lett.* **1988**, *46*, 5969.
6. Takemoto, I.; Kawamura, N.; Kaminaka, H. *Biosci. Biotech. Biochem.* **1994**, *58*, 2071.
7. Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174.
8. Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 5510.
9. Petrignani, N.; Yonashiro, M. *Synthesis*, **1982**, 523 and references therein.
10. Noyce, D. S.; Heller, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 4325.
11. Foricher, J.; Schmid, R., *F. Hoffmann-La Roche AG*, EP Appl. 97100843.8 (21 January 1997).
12. (a) Blagoev, B.; Ivanov, D. *Synthesis* **1970**, 615; (b) Weston, A. W.; DeNet, R. W. *J. Am. Chem. Soc.* **1951**, *73*, 4221.
13. (a) Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1990**, *49*, 7189; (b) Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589; (c) Saburi, M.; Takeuchi, H.; Ogasawara, M.; Tsukahara, T.; Ishii, Y.; Ikariya, T.; Takahashi, T.; Uchida, Y. *J. Organometal. Chem.* **1992**, *428*, 155; (c) Chan, A. S. C.; Chen, C. C.; Yang, T. K.; Huang, J. H.; Lin, Y. C. *Inorg. Chim. Acta* **1995**, *234*, 95.
14. Kienzle, F.; Wang, S., *F. Hoffmann-La Roche AG*, unpublished results.
15. The optical purification of Prophen drugs by crystallization of their sodium salts has been reported: Manimaran, T.; Stahly, G. *Tetrahedron: Asymmetry* **1993**, *4*, 1949.
16. (a) Nakayama, I. *Advances in Pesticide Sciences*, Geissbühler, H. Ed., Pergamon Press, Oxford, 1978, part 2, p. 174 ff; (b) Yoshioka, H. *CHEMTECH* **1985**, 482.
17. (a) Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897; (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370; (c) Cereghetti, M.; Arnold, W.; Broger, E. A.; Rageot, A. *Tetrahedron Lett.* **1996**, *37*, 5347; (d) Schmid, R.; Broger, E. A.; Cereghetti, M.; Cramer, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure & Appl. Chem.* **1996**, *68*, 131.
18. Heiser, B.; Broger, E. A.; Cramer, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51.
19. Cekovic, Z.; Saicic, R. *J. Serb. Chem.* **1985**, *50*, 211.

(Received in UK 21 August 1997; accepted 7 October 1997)