Ethyl 2,4-Dioxo-4-phenylbutyrate: A Versatile Intermediate for the Large-Scale Preparation of Enantiomerically Pure α-Hydroxy and α-Amino Acid Esters

Hans-Ulrich Blaser,*[a] Stephan Burkhardt,[a,b] Hans Jürg Kirner,[b] Tanja Mössner,[b] Martin Studer[a]

[a] Solvias AG, Postfach 4002 Basel, Switzerland
Fax +41(61)68666100 ; E-mail: Hans-Ulrich.Blaser@solvias.com

[b] Ciba Specialty Chemicals, Postfach 4002 Basel, Switzerland

Received 12 June 2003

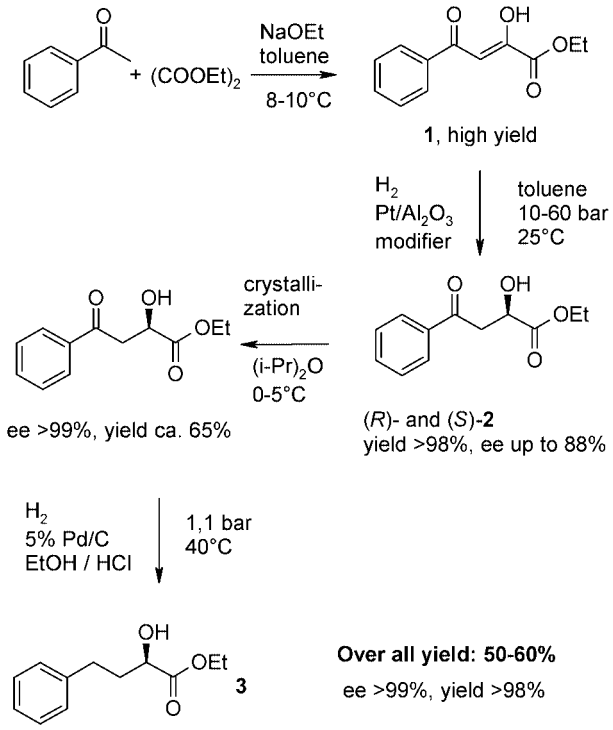
Abstract: Starting from ethyl 2,4-dioxo-4-phenylbutyrate, both enantiomers of six enantiomerically pure α-hydroxy and α-amino acid esters (homophenylalanine derivatives) were prepared on >100 g scale. The key step involves a Pt-cinchona catalyzed enantioselective hydrogenation followed by enrichment via crystallization. All derivatives are commercially available.

Key words: hydrogenation, enantioselective synthesis, α-keto ester, α-hydroxy ester, homophenylalanine

Enantiomerically pure homophenylalanine derivatives and the related hydroxy estes are of high interest for chemists working in the area of medicinal and combinatorial chemistry, one the one hand as amino acid building blocks,[1] on the other hand as intermediates for the synthesis of ACE inhibitors.[2] Until recently, these derivatives were available only at very high prices or in the case of the ring hydrogenated compounds not at all.

Having an efficient technology in hand to produce both enantiomers of the very versatile ethyl 2-hydroxy-4-phenylbutyrate (**3**, HPB-ester) (Scheme 1),[2] we set out to synthesize a series of analogous building blocks. This contribution describes the 100–200 g scale preparation of **2**–**7**, all of which are now available from Fluka.

The synthesis of **1**, as described before,[2] was scaled up without any problem, and three 8 kg batches were produced. Compound **1** was isolated in 92% yield as a solid with a melting point of 35–37 °C. The enantioselective hydrogenation of **1** to (*R*)-**2** was also carried out in analogy to Ref.[2] on a 20 kg scale with HCd (hydrocinchonidine) (Figure 1) as a modifier. The preparation of the corresponding (*S*)-**2** proved to be more problematic. It is well known that the pseudoenantiomeric HCn (hydocinchonione) gives significantly lower ee's in the enantioselective hydrogenation of activated ketones than HCd.[3] In fact, the ee observed with HCn under our conditions was only 59% for the *S* compared to 84% ee with HCd for the *R* derivative. With only 59% ee, enrichment to >99% ee by crystallization was not possible. We therefore converted Cn to iso-Cn (iso-cinchonine), a derivative known to give higher ee's than HCn for similar substrates.[4] Indeed,



Scheme 1 Synthesis of HPB-ester **3**

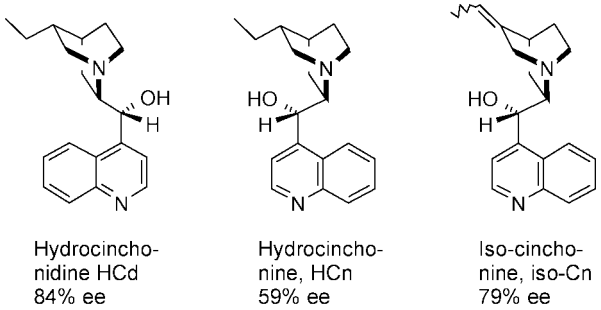
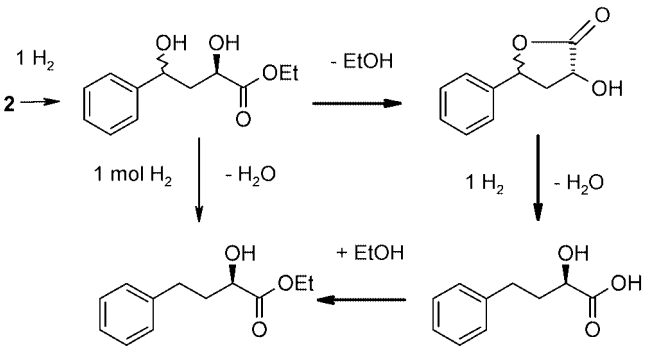


Figure 1 Structure of modifiers and ee's observed in the hydrogenation of **1**. *Reagents and conditions*: 5% Pt/Al_2O_3, 60 bar H_2, 25 °C, toluene. Values for HCd and HCn from Ref.[3]

Synthesis 2003, No. 11, Print: 05 08 2003.
Art Id.1437-210X,E;2003,0,11,1679,1682,ftx,en;C03703SS.pdf.

on a 2.5 kg scale, 79% ee and a strong increase in rate compared to HCn was obtained with iso-Cn as a chiral modifier.

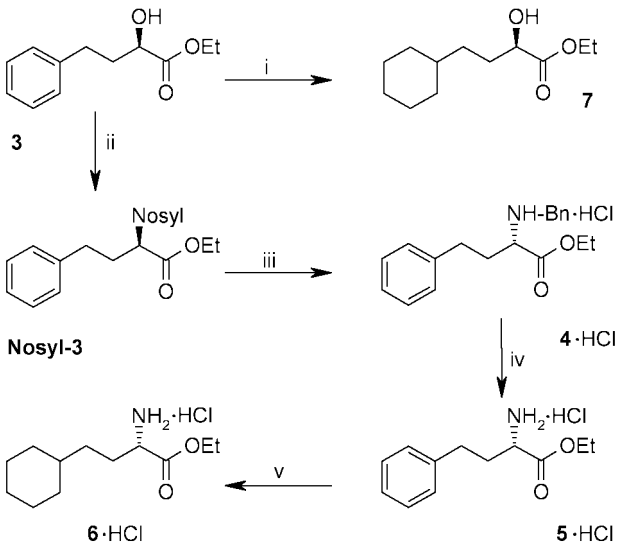
Enrichment of **2** by crystallization was unproblematic on a 7.4 kg scale, and (*S*)-**2** was obtained with an ee of 99.6% and >99% purity in 63% yield starting from (*S*)-**2** with 79% ee. The scale-up of the deoxygenation from **2** to **3** in EtOH/HCl was not as straightforward as expected. To our surprise, the product of three 1.3 kg batches contained 44% of the corresponding acid directly after the deoxygenation. To obtain 100% of the ester, the reaction products were evaporated to dryness and the resulting oil was dissolved in EtOH/HCl. After one day at room temperature, all the acid had been reconverted to the ester (98% over all yield, ee 99.2%). A possible explanation for the observed hydrolysis is that under our reaction conditions the pathway through the lactone is favored (Scheme 2).



Scheme 2 Possible formation of a lactone intermediate in the hydrolysis of the ester **2**

Both enantiomers of **Nosyl-3** were synthesized on up to 700 g scale in 99% yield and high purity in analogy to Ref.[5] using 4-nitrobenzenesulfonyl chloride and Et_3N in toluene. **Nosyl-3** was converted to **4** by reacting it with two equivalents benzylamine on 390 g scale (Scheme 3). The solid product mixture was suspended in dibutyl ether and the benzylammonium 4-nitrobenzene sulfonate could be separated quantitatively by filtration and recycled after reconverting it to the acid chloride. Compound **4**·HCl was isolated in high yield by filtration after introducing one equivalent of gaseous HCl to the dibutyl ether solution. Compound **4**·HCl was debenzylated in absolute EtOH using Pd/C at room temperature and 1.1 bar hydrogen pressure on >500 g scale, and **5**·HCl could be isolated in 99% yield after removal of the solvent.

A few preliminary 100 mg experiments showed that the best results for the ring saturation of **5**·HCl were obtained with the Nishimura catalyst (Pt–Rh oxide) in water containing small amounts of HCl (100 bar and r.t.). These conditions were scaled up to 144 g. The yield of **6**·HCl was 89%, and the chemical purity of the product was 90% (>99% ee). For the isolation of the product, it was important to neutralize the acidic solution to pH 7 before evaporating the water, to prevent ester hydrolysis. Similar conditions (Nishimura catalyst, EtOH, 100 bar, r.t.)



Scheme 3 Synthesis of derivatives **4**–**7**. *Reagents and conditions*: i) Nishimura catalyst (Pt–Rh oxide), EtOH, H_2 (100 bar), r.t.; ii) NosCl, Et_3N, toluene; iii) a. $PhCH_2NH_2$ (2 equiv), b. dibutyl ether, HCl (g) (1 equiv); iv) 5% Pd/C, EtOH/HCl, H_2 (1.1 bar), 25 °C; v) Nishimura catalyst (Pt–Rh oxide), HCl (small amount), H_2 (100 bar), r.t.

proved to be optimal for the ring hydrogenation of **3** to **7**. Here the yield in a 450 g experiment was 95%, and the purity of **7** was >95% according to ^{1}H NMR spectroscopy (ee of 99.6% after recrystallization).

The final products, meant for commercial use, were purified where necessary either by crystallization or distillation as described in the experimental part. While distilling compounds **3** and **7**, the addition of small amounts of a weakly basic ion exchanger proved to be very beneficial. Without this additive, distillation yields were considerably lower due to di- and polymerization and other side reactions. From Table 1 and 2 it can be seen that the procedures developed allow the synthesis of >100 g amounts of both enantiomers of **2**–**7** in very high chemical and enantiomeric purity.

All commercial reagents were employed as supplied. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker dpx 300 spectrometer. Chemical shifts (δ) are given in ppm. All ee's were determined using chiral HPLC or GC columns. Table 2 lists the methods used and the retension times for these experiments.

Iso-Cn[4]

$RuCl_3 \cdot H_2O$ (2.5 g) and Ph_3P (10.5 g) were dissolved in DMF (3 L) under argon. Over 50 min, the mixture was heated to 150 °C (reflux) and kept at this temperature for 10 min (black solution turned orange). After cooling to 110 °C, cinchonine (200 g, containing 15% HCn, Fluka) in DMF (1.0 L) was added. This mixture was heated to 140 °C (clear yellow solution), kept at this temperature for 20 min and then cooled to 100 °C. This warm solution was poured onto ice-cooled H_2O (8 L). After stirring for 2 h, the suspension was filtered. The white residue was washed with cold H_2O (2 ×) and then dried overnight under reduced pressure at r.t.; yield: 175.8 g. This material was recrystallized in two batches from dimethoxyethane giving a pooled yield of 127.7 g (64%). According to ^{1}H NMR analysis, the product contained a mixture of 16% hydrocinchonine [δ =

Table 1 Enantiomeric and Chemical Purity and Characterization Data of **2**–**7**

Product	ee[a] (%)	Purity[a] (%)	$[\alpha]_D^{20}$[b]	mp (°C)	bp (°C)/ 1Torr
(*S*)-**2**	99.6	>98	+5.7	36	–
(*R*)-**2**	>99.9	>98	–5.4	36	–
(*S*)-**3**	99.2	>98	+20.9	–	120
(*R*)-**3**	99.8	>98	–20.8	–	120
(*S*)-**4**·HCl	>99.9	>98	+27.4	144	–
(*R*)-**4**·HCl	99.6	>98	–28.4	144	–
(*S*)-**5**·HCl	99.1	>98	+37.9	154	–
(*R*)-**5**·HCl	99.7	>98	–38.4	154	–
(*S*)-**6**·HCl	99.8	>98	+9.7	156	–
(*R*)-**6**·HCl	>99.9	>98	–10.1	156	–
(*S*)-**7**	99.6	>98	+2.4	–	88
(*R*)-**7**	>99.9	>98	–2.7	–	88

[a] Determined by HPLC.
[b] c = 1 in $CHCl_3$ (hydroxy compounds) or doubly distilled H_2O (amino compounds).

Table 2 Ee Determination for **2**–**7**

Product	Column	Hexane	EtOH	UV Det. (nm)	t_R (*R*) (min)	t_R (*S*) (min)
2	Chiracel OD-H	985	15	254	48.2	45.3
3	Chiracel OD-H	985	15	254	18.8	14.6
4[a]	Chiracel OD	950	50	254	5.2	5.6
5[a]	Chiracel OD-H	900	100	254	11.4	9.4
6[a]	Chiracel AD	970	30	230	8.8	9.7
7	B-DM[b]	–	–	–	35.0	38.9

[a] For HPLC analysis, the free bases were liberated by stirring a small sample of the hydrochloride salt in a mixture of aq. $NaHCO_3$ and hexane and filtering the hexane phase through anhyd Na_2SO_4. The flow was 1 mL/min in all HPLC experiments.
[b] GC (30 m BD-M dimethyl β-cyclodextrin column from Astec-chiraldex), 80–110 °C (1 °C/min), then 40 min isothermic at 110 °C.

1.0, t, 3 H, and 84% of a 45:55 *E*/*Z* mixture of the isomerized product (δ = 5.65 and 5.75, m, 1 H each)]. For full characterization, see Ref.[4]

(+)-Ethyl (*S*)-2-Hydroxy-4-oxo-4-phenylbutyrate [(*S*)-2][2]

5% Pt/Al_2O_3 (Type JMC 94, 84 g, preheated for 2 h at 400 °C under H_2) and iso-Cn (8.4 g) were placed in a 16 L stainless steel autoclave. After closing and testing for leaks with H_2 and purging with N_2, compound **1** (2.5 kg) dissolved in toluene (10 L) was added through an addition valve. Then, the autoclave was purged with N_2 (3 ×) and H_2 (3 ×). The hydrogenation at 25 °C was started immediately after pressurizing the autoclave to 60 bar. After 1.5 h, the H_2 uptake had ceased (it is important to stop the hydrogenation after the uptake of 105–110% of the theoretical amount of H_2, otherwise, over-hydrogenation to the corresponding diol might occur) and the pressure was released. After purging the autoclave with N_2, the catalyst was filtered off and the filtrate was evaporated to dryness. The ee for (*S*)-**2** was 79% and the conversion was 99% according to ^{1}H NMR spectroscopy. The yield for three pooled batches starting from totally 7.65 kg of **1** was 7.64 kg (99%).

Enrichment of (*S*)-2 by Crystallization[2]

Compound (*S*)-**2** (7.39 kg) with an ee of 79% was dissolved in diisopropyl ether (11.09 kg) in a 30 L email-Belatec apparatus. The reaction mixture was cooled to 15 °C using an ice-water mixture. Then, seeding crystals of enantiomerically pure (*S*)-**2** (36 g) were added. The mixture was cooled to 5 °C, stirred overnight at 5 °C and then filtered. After washing the residue with cold (5 °C) diisopropyl ether (4 L), the crystals were sucked dry during 2 min, and then washed with hexane (7 L). The yellowish crystals were air-dried; yield: 4.64 kg (63%, ee 99.6%).

(+)-Ethyl (*S*)-2-Hydroxy-4-phenylbutyrate [(*S*)-3][2]

Compound (*S*)-**2** (1.2 kg) was dissolved in EtOH (2.2.L) in a 6 L glass shaker. After the addition of EtOH/HCl (106 mL, 15% w/v) and 5% Pd/C (128 g, Engelhard 4522), the shaker was evacuated and flushed with H_2 (3 ×). The hydrogenation was carried out at 25 °C and 1.1 bar H_2 pressure. After 11.5 h, the H_2 uptake had ceased and the catalyst was filtered off. A sample withdrawn showed that the reaction mixture contained 56% ester and 44% acid according to ^{1}H NMR spectroscopy. After pooling 3 batches of the same size, the mixture was evaporated to dryness giving 3.56 kg of a yellow oil containing 93% ester and 7% of the corresponding acid. This residue was treated with a mixture of absolute EtOH (3 L) and EtOH/HCl (100 mL, 12% w/v) and kept for 24 h at r.t. ^{1}H NMR analysis showed that the acid had been converted quantitatively to the ester; yield: 3.59 kg (98%). To obtain analytically pure material, (*S*)-**3** was vacuum distilled at 120 °C/1 Torr after addition of a small amount of a weakly basic ion exchange resin with a yield of >95% and a purity of >98% (ee = 99.2%).

Nosyl-(*R*)-3[5]

A 2 L round-bottom flask was charged with (*R*)-**3** (208 g, 1 mol), 4-nitrobenzenesulfonyl chloride (222 g, 1 mol), and toluene (580 mL). The reaction mixture was cooled to 3–5 °C under stirring and Et_3N (136 g) was slowly added over a period of 30 min (<10 °C). During this addition, triethylammonium chloride precipitated as a cloudy solid. After the addition was complete, the stirring was continued for 1 h at r.t. Then, the reaction mixture was quenched with de-ionized H_2O (800 mL) and stirred for 15 min. The reaction mass was transferred to a separatory funnel and the phases were allowed to separate. The aqueous phase was removed and the organic layer was washed with 1 N HCl (500 mL), brine (500 mL), and then with pure H_2O (500 mL). The organic layer was transferred to a 2 L round-bottom flask and evaporated to dryness; yield: 390 g (99%); orange, viscous liquid; >99.5% pure by HPLC.

(+)-Ethyl (*S*)-2-*N*-Benzylamino-4-phenylbutyrate Hydrochloride [(*S*)-4·HCl]

The **nosyl-3** oil obtained above was mixed under vigorous stirring at r.t. with benzylamine (214.4 g). The reaction was exothermic, and the temperature rose in 15–20 min to 120 °C, and a solid, pale-yellow clay was obtained. After the reaction mixture had cooled to <70 °C, dibutyl ether (800 mL) was added and the resulting suspension was stirred for 1 h at 80 °C. After cooling to 25 °C, the mixture was filtered and the filter cake was washed with dibutyl ether (2 × 100 mL). ^{1}H NMR analysis of a small sample of the filtrate showed pure **4**. The hydrochloride salt could be precipitated by introducing gaseous HCl (1 equiv) at 0 °C. The yield after filtration and air-dry-

ing was 95–97%. To obtain analytically pure (*S*)-**4**·HCl, the isolated solid was recrystallized from EtOAc in 81% yield (ee = 99.6%).

^{1}H NMR (D_2O): δ = 1.14–1.19 (t, *J* = 7 Hz, 3 H), 2.11–2.19 (m, 2 H), 2.49–2.70 (m, 2 H), 3.74–3.79 (t, *J* = 6.0 Hz, 1 H), 4.03–4.11 (q, *J* = 7 Hz, 2 H), 4.12 (br s, 2 H), 7.07–7.38 (m, 10 H).

^{13}C NMR (D_2O): δ = 13.64 (CH_3), 30.54 (CH_2), 30.93 (CH_2), 50.34 (CH_2), 58.28 (CH_2), 64.06 (CHN), 126.93 (CH), 128.74 (CH), 129.00 (CH), 129.53 (CH), 129.75 (CH), 130.16 (CH), 130.38 (CH), 139.59 (C), 169.29 (C=O).

The benzylammonium 4-nitrobenzenesulfonate isolated above could be reconverted to nosyl chloride and recycled.

(+)-Ethyl (*S*)-2-Amino-4-phenylbutyrate Hydrochloride [(*S*)-5·HCl]

Compound (*S*)-**4**·HCl (286 g) was dissolved in absolute EtOH (2.6 L) in a 6 L shaker. After the addition of 5% Pd/C (58 g, Engelhard 4522), the shaker was evacuated and flushed with H_2 (3 ×). The hydrogenation was carried out at 25 °C and 1.1 bar H_2 pressure for 17.25 h. After pooling two identical batches, the catalyst was filtered off and the EtOH was removed at reduced pressure. The white product was dried at 10^{-2} bar; yield: 414.5 g (99%). ^{1}H NMR analysis showed a purity of about 98% (ee 98.2%) (HPLC). To obtain analytically pure (*S*)-**5**·HCl, the isolated solid was recrystallized from *i*-PrOH in 80–82% yield (ee = 99.7%).

(+)-Ethyl (*S*)-2-Amino-4-cyclohexylbutyrate Hydrochloride [(*S*)-6·HCl]

Compound (*S*)-**5**·HCl (144.2 g) was dissolved in H_2O (2 L). After the addition of 1 N HCl (15–20 mL), and Nishimura catalyst (1 g, Degussa, 45.6% Rh and 18.8% Pt by weight), the 8 L autoclave was closed and purged with N_2 (3 ×) and H_2 (3 ×). The hydrogenation was carried out at 100 bar for 23 h at r.t. After 1 h, an additional amount of catalyst (2 g) and 1 N HCl (20 mL) were added. After 18 h, another batch of catalyst (2 g) was added and the hydrogenation was continued for 1 h. After this, the H_2 was replaced by N_2 and the catalysts was filtered off. The filtrate was neutralized with a weakly basic ion-exchanger Amberlite IRA93 to pH 7. The resulting solution was evaporated under reduced pressure and dried; yield: 132 g (89%, some handling loss); purity 90% (^{1}H NMR). To obtain analytically pure (*S*)-**6**·HCl, the isolated solid was recrystallized from EtOAc–EtOH 10/:1 in 75–80% yield (ee = 99.8%).

^{1}H NMR (DMSO-d_6) : δ = 0.75–0.88 (m, 2 H), 1.07–1.22 (m, 4 H), 1.19–1.23 (t, *J* = 7 Hz, 3 H), 1.25–1.33 (m, 2 H), 1.53–1.58 (m, 1 H), 1.57–1.65 (m, 4 H), 1.74–1.88 (m, 2 H), 3.35 (br s, 2 H, NH_2), 3.84–3.88 (t, *J* = 6 Hz, 1 H), 4.09–4.26 (m, 2 H).

^{13}C NMR (DMSO-d_6): δ = 14.80 (CH_3), 26.48 (2 CH_2), 26.89 (CH_2), 28.17 (CH_2), 33.31 (2 CH_2), 37.38 (CH_2), 52.71 (CH), 52.93 (CH), 62.29 (CH), 169.97 (C=O).

(+)-Ethyl (*S*)-2-Hydroxy-4-cyclohexylbutyrate [(*S*)-7]

Compound (*S*)-**3** (450 g) was dissolved in EtOH (4 L). After the addition of Nishimura catalyst (4.5 g, Degussa, 45.6% Rh and 18.8% Pt by weight), the 6.3 L autoclave was closed and purged with N_2 (3 ×) and H_2 (3 ×). The hydrogenation was carried out for 4.25 h at 100 bar and r.t. After this, the H_2 was replaced by N_2 and the catalysts were filtered off and the EtOH was evaporated to dryness. Upon standing, small amounts of colorless crystals were formed. Therefore, the product mixture was filtered for a second time and the solvent was evaporated; yield 440 g (95%). The product was >95% pure according to ^{1}H NMR spectroscopy. To obtain analytically pure material, (*S*)-**7** was vacuum distilled at 88 °C/1 Torr, after addition of a small amount of a weakly basic ion exchange resin, with a yield of >95% and a purity of >98% (ee = 99.6%).

^{1}H NMR ($CDCl_3$): δ = 0.74–0.81 (m, 2 H), 1.03–1.13 (m, 4 H), 1.15–1.20 (t, *J* = 7 Hz, 3 H), 1.19–1.24 (m, 2 H), 1.47–1.62 (m, 4 H), 1.60–1.70 (m, 1 H), 3.14 (br s, 1 H, OH), 4.00–4-05 (m, 1 H), 4.05–4.15 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.44 (CH_3), 26.55 (CH_2), 26.57 (CH_2), 26.88 (CH_2), 32.04 (CH_2), 32.52 (CH_2), 33.36 (CH_2), 33.60 (CH_2), 37.70 (CH), 61.47 (CH_2), 70.88 (CH), 175.27 (C=O).

Acknowledgments

The authors would like to thank the Syngenta Kilo lab (P. Riebli) for the skillful experimental work.

References

(1) Garrett, C. E.; Jiang, X.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **2002**, *43*, 4161.
(2) (a) Herold, P.; Indolese, A. F.; Studer, M.; Jalett, H. P.; Siegrist, U.; Blaser, H. U. *Tetrahedron* **2000**, *56*, 6497. (b) Studer, M.; Herold, P.; Indolese, A.; Burkhardt, S. Ciba Specialty Chemicals Holding, Inc., Switzerland, PCT Int. Appl. WO 9950223, **1999**; *Chem. Abstr*. **1999**, *131*, 243073.
(3) Studer, M.; Burkhardt, S.; Indolese, A. F.; Blaser, H.-U. *Chem. Commun.* **2000**, 1327.
(4) Exner, C.; Pfaltz, A.; Studer, M.; Blaser, H.-U. *Adv. Synth. Catal.*, submitted.
(5) Blaser, H.-U.; Jalett, H.-P.; Sedelmeier, G. Eur. Pat. Appl. EP 206993 A1, **1986**; *Chem. Abstr*. **1987**, *107*, 77434.