Asymmetric Hydrogenation of 2-Benzylidenesuccinic Acid 4-[(4-BOC-amino)-1-piperidide] Monoamide: Key Step in a Process for Large Scale Preparation of a Renin Inhibitor

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The *N*-terminal component **4** of an orally active renin inhibitor is prepared on kg-scale by asymmetric hydrogenation of the title compound **3**. Enantioselectivities of several homogeneous homochiral rhodium(I)- and ruthenium(II)-diphosphine catalysts are compared.

Recently, processes for large scale preparation of optically pure *N*-terminal[1] and C-terminal component[2] of an orally active renin inhibitor[3] were communicated. The BOC-protected *N*-terminal component **4** can be prepared by asymmetric hydrogenation of 2(*E*)-benzylidenesuccinic acid **(1)**.[1,4] However, on pilot plant scale the asymmetric hydrogenation of title compound **3** is advantageous[1] for several reasons:

- The di(*p*-nitrophenyl) ester of dicarboxylic acid **2** must be prepared to achieve highly regioselective transformation[4] to the monoamide **4**.[1] Small amounts of relatively toxic *p*-nitrophenol in aqueous washings and mother liquors are problematic.
- Although there are more than twenty reports on the use of rhodium(I)-diphosphine catalysts for hydrogenation of unsubstituted or substituted methylenesuccinic acids, products with the desired (*R*)-configuration (e.g. **2**) were not obtained with sufficient enantioselectivity, or the catalysts were not readily accessible.[1,4-11]

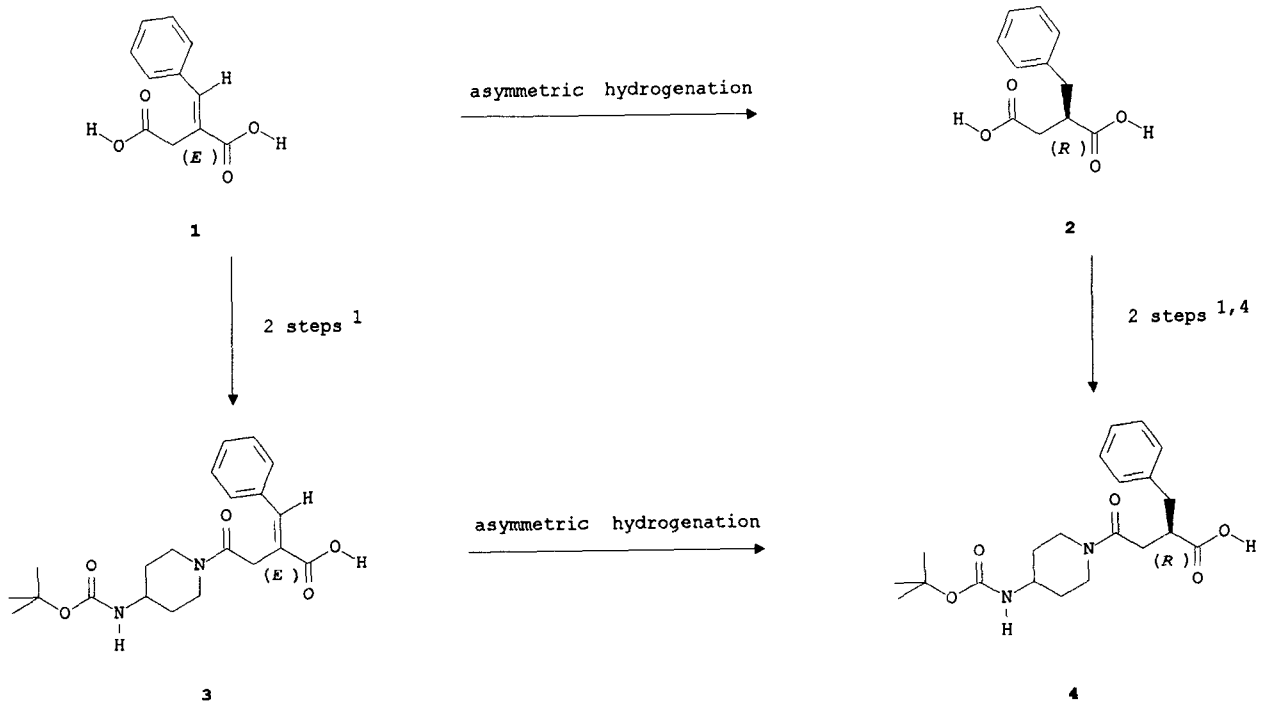
After our work was initiated,[12] ruthenium(II)–BINAP (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) complexes were reported to hydrogenate methylenesuccinic acid (derivatives) with good enantioselectivity: The binuclear complex **5** gives **2** with 90% ee, however, with a reported substrate/catalyst (s/c) ratio of 50–90:1.[13,14]

Asymmetric transfer hydrogenation of **1** catalyzed by pentacoordinate ruthenium hydride complex **6** (s/c = 100:1)[14] gives (*R*)-**2** with up to 82% ee.[15] An enantioselective transfer hydrogenation with catalyst **7** furnishes (*R*)-2-methylsuccinic acid with 93.5% ee, however, **1** is only 10% hydrogenated.[16]

Similarly, transfer hydrogenation of **1** with rhodium(I)-diphosphine catalysts and formic acid/triethylamine (3:1) as hydrogen-transferring agent in dimethyl sulfoxide at 45°C leads to less than 50% hydrogenation.[17] Kinetic analysis of this reaction indicates that **1** is a weakly binding substrate.[17]

In this paper asymmetric hydrogenations of monoamide **3** with different homogeneous homochiral rhodium(I)- and ruthenium(II)-diphosphine catalysts are reported.[18]

Commercially available ligands **8**[19] and **9**[20] were transformed in situ to the cationic rhodium(I) catalysts **11** by reaction with 0.91 equivalent of bis(1,5-cyclooctadiene)-rhodium(I) tetrafluoroborate **(10)**[21] in deaerated methanolic solution (25°C/15 min) before substrate **3** was added. Ligand **13** was prepared from (2*R*,4*R*)-BPPM **(12)**[22] [(2*R*,4*R*)-*N*(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine] by removal of the BOC-group and subsequent reaction with phenylisocyanate, as described by Ojima et al[23] for the enantiomer of **13**. Ligand **13** was transformed to neutral rhodium(I) catalyst **15** in situ by reaction with 0.93 equivalent (0.465 mol) of commercial di-μ-chloro-bis[(cycloocta-1c,5c-diene)-rhodium(I)] **(14)** in deaerated methanolic



$Ru_2Cl_4[(R)\text{-BINAP}]_2NEt_3$

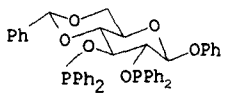
5

$[RuH((S)\text{-BINAP})_2]^+ PF_6^-$

6

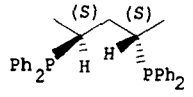
$Ru[((S)\text{-BINAP})_2(CF_3COCHCOCF_3)_2(CH_2CHCH_2)]$

7



"(R)(-)-Phenyl-ß-glup"

8



"(2S,4S)(-)-BDPP"

9

$[Rh(COD)_2]^+ BF_4^-$

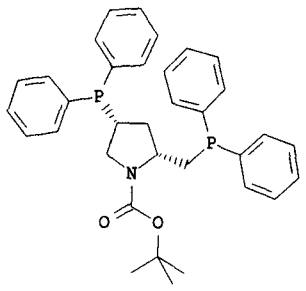
10

$[Rh(COD)(diphosphine)]^+ BF_4^-$

diphosphine

8 11a

9 11b



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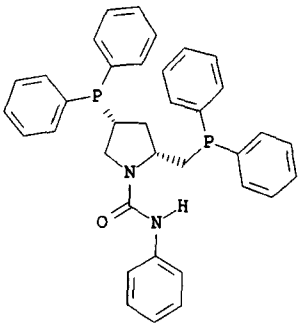
1. CF_3CO_2H, 0°C
2. PhNCO



"(2R,4R)(+)-Phenyl-CAPP"

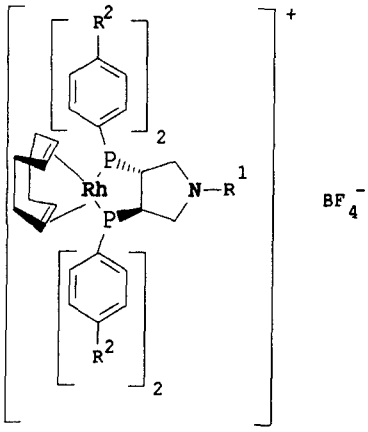
13

$[Rh(COD)Cl]_2$

14

$\{Rh[(2R,4R)(+)\text{-Phenyl-CAPP}]Cl\}_2$

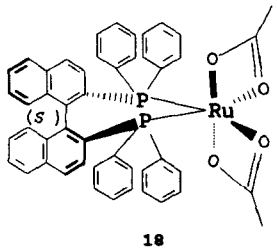
15



R^1	R^2	
-CO-CH_3	CH_3	16a
-CO-NH-Ph	CH_3	16b
-CO-NH-Ph	H	16c

$[RuCl(PPh_3)(S)(-)\text{BINAP}]_2Cl_2$

17



18

solution (25°C, 5 min, ultrasound), before substrate **3** was added. Catalysts **16a**,[24] **16b**,[25] **16c**,[1] **17**[26] and **18**[27] were prepared and isolated according to literature procedures. The results of the asymmetric hydrogenations of monoamide **3** are summarized in the Table.

Ligand **8**[29] led to the saturated amide **4** with only low asymmetric induction (entry 1). Likewise (2*S*,4*S*)-BDPP (**9**) [(2*S*,4*S*)-bis(diphenylphosphinopentane] was inefficient (entry 2). Excellent asymmetric inductions were obtained with the neutral rhodium(I) complexes of (2*R*,4*R*)-BPPM (**12**) or its phenylurea derivative **13** as catalysts (entries 3 and 5). However, the preparation of (2*R*,4*R*)-BPPM[22] is too lengthy and laborious to be of technical interest. The presence of one equivalent of triethylamine decelerated the hydrogenation and deteriorated the enantioselectivity (entry 4); the presence of a non-polar cosolvent decreased the enantioselectivity slightly (entry 6). Catalyst **16a**, with an *N*-acetyl substituent R^1, gave product **4** with moderate stereochemical control (entry 7). Good enantioselectivity (up to 86% ee) was attained when the acetyl was replaced by a phenylaminocarbonyl substituent (entries 8–12). There was no significant difference in asymmetric inductions of catalysts **16b** and **16c**, carrying di(*p*-tolyl)phosphino and diphenylphosphino groups, respectively. Since **16b** and **16c** are easily prepared[1,24] from natural (*R*,*R*)-(+)-tartaric acid, they are acceptable for the process. Attempts to enhance the molar ratio of substrate **3** to catalyst **16c** significantly above 300:1 led to incomplete hydrogenation and distinctly lower optical purity of the crude product **4**, at least on laboratory scale.[30] In isopropanol (or methan-

Table. Asymmetric Hydrogenation of **3**

Entry	Substrate **3** (mmol)	Catalyst (μmol)	s/c[a]	Solvent (mL)[b]	Temp. (°C)	H_2 (bar)	Reaction Time (h)	Hydrogenation (%, HPLC)[c]	ee of Product (%, HPLC)
1	10.0	**8** (55), **10** (50)	200	150	25	1	20	100	8
2	12.5	**9** (68), **10** (62)	200	55	25	1	16	100[d]	31
3	3.1	**12** (34), **14** (16)	100	17	20	1	2	100	93
4	3.1[e]	**12** (34), **14** (16)	100	17	20	1	5	100	9
5	40.2	**13** (271), **14** (126)	160	110	25	1	3	100	95
6	12.5	**13** (135), **14** (62)	100	35[f]	25	1	2	100	87
7	10.0	**16a** (100)	100	50	20	50	24	100	67
8	10.0	**16b** (100)	100	50	20	50	24	100	81
9	2160	**16c** (21600)	100	11000	20	50	24	100	81
10	10.0	**16c** (50)	200	50	15	100	24	100	86
11	4000	**16c** (21000)	190	17000	15	100	24	100	86
12	20.0	**16c** (67)	300	100	25	100	24	100	78
13	20.6[g]	**16c** (82)	250	150[h]	25	100	96	100[d]	56
14	1.0	**17** (5)[i]	100	25	40	100	16	100[j]	28
15	1.5	**18** (15)	100	20	40	100	16	100[j]	20
16	1.5[k]	**18** (15)	100	20	40	100	48	60[j]	n.d.

[a] Mmol **3**/g-atom Rh or Ru.
[b] Methanol (abs.) unless otherwise indicated.
[c] < 5% Byproducts were detected, unless otherwise indicated.
[d] 5–10% Byproducts detected.
[e] Triethylamine (96 mol%) added.
[f] Methanol/benzene 2.5 : 1.
[g] Na_2CO_3 (10.3 mmol) added.
[h] Isopropanol/water 1 : 2.
[i] Quality of catalyst **17** was checked by test hydrogenation (> 98% ee) of methyl acetoacetate.[26,28]
[j] 20–25% Byproducts detected.
[k] Triethylamine (15 μmol) added.

ol)-water mixtures[31] hydrogenation was decelerated and the amount of byproduct was enhanced proportionally to the percentage of water. Formation of byproduct is acid-catalyzed.[32] Isopropanol/water (1 : 2) in the presence of 50 mol% of sodium carbonate gave an acceptably small amount of byproduct, but the hydrogenation was slow and the enantioselectivity depressed (entry 13).

Two different ruthenium(II)–BINAP catalysts led to enhanced byproduct formation and low enantioselectivity (entries 14 and 15). Addition of 1 mol% of triethylamine decelerated the hydrogenation drastically and did not suppress the formation of byproducts[33] (entry 16).

Importantly, in more than twenty independent experiments, all crude products **4** of > 72% ee consistently gave crystals of > 97% ee in excellent yield on single recrystallization from mixtures of methanol and ethers (diisopropyl or diethyl ether or THF).[34] In an optimized procedure, crude product **4** (86% ee, entry 11) was recrystallized from methanol/diethyl ether/diisopropyl ether to give optically pure **4** (> 99.5% ee) in 75% yield based on starting material **3**.[1,35]

The following commercial reagents were used: $[Rh(COD)Cl]_2$[38] (Aldrich), (*S*)-BINAP[39] and **9**[20] (Strem Chemicals) and **8**[19] (ISIS-Chemie, Zwickau). Substrate **3** was prepared according to literature.[1] **3**; mp 158–160°C (dec) Lit.[1] mp 158–160°C (dec).

MS (ESI, compound dissolved in H_2O/MeCN/HCO_2H (50 : 50 : 0.5) and measured within 30 sec[32]): *m/z* (%) = 389.1 (M^+H^+, 100), 333.0 ($M^+H^+ - Me_2C{=}CH_2$, 75).

Ligands and catalysts were prepared according to the literature procedures. **10**,[21,37] **12**,[22] **13**,[23] **16a**,[24] **16b**,[25] **16c**,[1] **17**[26] and **18**.[27] Catalyst **17** (0.015 mol) was used in the hydrogenation (100 bar H_2, 24°C, 40 h) of methyl acetoacetate (30 mmol) in MeOH (20 mL) to give methyl (*S*)-3-hydroxybutyrate (**19**); yield: 95% (after distillation); $[\alpha]_D^{25}$ + 23.8° (neat, 98% ee). A sample of the product **19** was derivatized with isopropyl isocyanate and then analyzed on a fused silica capillary GC column Chirasil L Val (80°C, injector and FID 220°C, 0.55 bar He carrier gas). The 3*S*-product (t_{ret} 41.87 min) was present in > 99% yield and < 1% of 3*R*-product (t_{ret} 40.90 min) was observed. The spectral data of the ligands **16a,b** and catalysts **17** are given below:

16a:

^1H NMR (270 MHz, CD_2Cl_2/TMS): δ = 1.77 (s, 3H, $COCH_3$), 2.10–2.25 (m, 4H, CH_2 of COD), 2.30–2.60 (m, 4H, CH_2 of COD), 2.43 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.70–2.85 (m, 1H, NCH), 2.87–3.23 (m, 3H, 3 × NCH), 3.56 (br t, 1H, PCH), 3.70–3.80 (m, 1H, PCH), 4.45–4.62 (br t, 2H, =CH), 5.08–5.22 (m, 2H, =CH), 7.23–7.51 (m, 12H_{arom}), 7.71–7.82 (m, 4H_{arom}).

16b:

^1H NMR (270 MHz, CD_2Cl_2/TMS): δ = 2.00–2.60 (m, 8H, CH_2 of COD), 2.47 (s, 6H, 2 × CH_3), 2.51 (s, 6H, 2 × CH_3), 2.90–3.15 (m, 4H, NCH_2), 3.70 (br d, 2H, PCH), 4.47–4.60 (m, 2H, =CH), 5.16 (br t, 2H, =CH), 6.47 (s, 1H, NH), 6.9–7.9 (m, 21H_{arom}).
$^{31}P\{^1H\}$NMR (161.98 MHz, CD_2Cl_2/external 85% H_3PO_4): δ = + 32.78 (d, $J_{Rh,P}$ = 150.3 Hz).

17:

$^{31}P\{^1H\}$NMR [109.35 MHz, $Cl(CH_2)_2Cl$/external DMSO]: δ = + 26.8 (s); traces of free PPh_3 (δ = − 5.6, s) and of free BINAP (δ = − 15.7, s) were observed.

Preparations of chiral diphosphines, of rhodium and ruthenium complexes, as well as preparation of reaction solutions for asymmetric hydrogenations were conducted in carefully deaerated solvents under an Ar atmosphere. Solutions (solvents) were deaerated in large scale reactions by bubbling a stream of Ar through the solution with stirring for 20 min. In small scale reactions either the same technique or two "freeze – pump – thaw" – cycles were applied. MeOH p.A. (Riedel de Haen, > 99.8% (GC) < 0.05% H_2O) was used as the solvent.

Procedures for Asymmetric Hydrogenation:
A: Under 1 Bar of Hydrogen (Table, Entries 1 to 6):
Asymmetric hydrogenations under 1 bar of H_2 were conducted in a glass flask ("Hydrierente") attached to an air (3 bar)-driven

shaking device (E. Bühler, Tübingen, type SML) and connected via a tube to a H_2 reservoir above a column of H_2O in a calibrated glass tube. This hydrostatic hydrogenation apparatus is similar to the one described in the literature.[36]

B: Small Scale Hydrogenations Under Hydrogen Pressure (Table, Entries 7, 8, 10, 12 to 16):

These were run in a 2 L autoclave (Deutsch & Neumann, Berlin) equipped with a shaking device. The deaerated reaction mixture was contained in a 800 mL cylindrical glass insert with a NS 29-(engl.: Quickfit B29) joint. A bent glass tube, integrated into a "NS 29" gas stopper, provided a connection of the gas phase inside glass insert with the gas phase inside autoclave and at the same time it ensured that no liquid could spill out of the glass insert when shaken. The reaction mixture in the glass insert was sealed under an Ar atmosphere by a layer of Parafilm® on the outer end of the bent glass tube. This sealed glass reactor was inserted into the autoclave, which was purged with N_2 during this process. The autoclave was sealed and N_2 purge was continued for 5 min, followed by a H_2 purge for 2 min. Then a H_2 pressure of 50 or 100 bar (according to the Table) was applied. This leads to the disruption of the Parafilm® seal and allows for the access of H_2 into the glass reactor where it displaces the former Ar atmosphere. The autoclave was shaken for the time indicated in the Table, after which H_2 was released and the autoclave was purged with N_2. The autoclave was opened and the glass insert removed.

C: Large Scale Hydrogenations Under Hydrogen Pressure (Table 1, Entries 9 and 11):

These were conducted in a 30 L stainless steel autoclave with a concentric agitator shaft ("Rührwelle") carrying three sets of stirrer blades (Uhde, 1969). The autoclave was evacuated, then purged with N_2. The deaerated reaction solution, kept under a N_2 atmosphere, was sucked into the autoclave applying slight vacuum. Great care was taken, not to suck air into the autoclave during this operation. The vacuum was released with N_2. The autoclave was sealed, purged with N_2, then with H_2. The H_2 pressure indicated in the Table was then applied and the contents of the autoclave were stirred. Pressure dropped while hydrogenation was progressing, due to consumption of H_2. The pressure was readjusted to the initial value before it had dropped by more than 5 bar. After the time indicated in the Table, the pressure was released. The autoclave was purged with N_2. The reaction solution was drained into a glass container.

2(*R*)-Benzylsuccinic Acid 4-[4-(*tert*-Butoxycarbonylamino)-1-piperidide Monoamide (4):

A: Prepared According to Entry 5:

A solution of **3**[1] (15.6 g, 40.2 mmol) in MeOH (100 mL) was deaerated with Ar. In a second flask, MeOH (10 mL) was deaerated with Ar under ultrasonic irradiation (Elma Transsonic TS 540® ultrasonic bath, filled with H_2O). Diphosphine **13** (155 mg, 0.271 mmol) and rhodium complex **14** (62 mg, 0.126 mmol) were added to give, after 5 min of ultrasonic irradiation under Ar, a clear yellow solution which was added under argon to the solution of substrate **3**. The resulting mixture was hydrogenated under 1 bar of H_2 according to method A (*vide supra*). A H_2 consumption of 880 mL was measured (~ 39.3 mmol, 98% of theory). HPLC [250 × 4.0 mm Nucleosil 100 C18, particle size 7 μm; eluent: 1.6 L H_2O, 0.9 L MeCN + 5.5 g $NH_4H_2PO_4$, adjusted to pH 3.5 with 85% H_3PO_4; flow 1.5 mL/min; detector 215 nm; t_{ret}: **3** (11.14 min),[32] **4** (10.55 min)[32]] indicated quantitative hydrogenation. The solvent was evaporated in vacuo. *i*-Pr_2O (100 mL) was added to the residue to give a clear solution from which the product crystallized after a few min. The suspension was kept at 0 °C for 2 h. The crystals were suction-filtered and dried in vacuo; crude yield: 15.0 g (96%); mp 119–133 °C; 95.3% ee [HPLC of methyl ester, prepared with CH_2N_2/Et_2O, Chiralcel OC; eluent: hexane/*i*-PrOH, 56:44; 40 °C; flow 0.8 mL/min; t_{ret} **4** (8.74 min), *ent*-**4** (13.74 min)]. Recrystallization from MeOH/Et_2O/*i*-Pr_2O (*vide infra*) gave colourless crystals; yield: 14.1 g (90%); mp 136–137 °C, > 99.5% ee (HPLC).

$C_{21}H_{30}N_2O_5$	calc.	C 64.60	H 7.74	N 7.17
(390.5)	found	64.42	7.80	7.05

^{1}H NMR (270 MHz, DMSO-d_6/TMS): δ = 1.05–1.25 (m, 2H), 1.36 (s, 9H), 1.68 (br t, 2H), 2.27 (dd, 1H), 2.53–3.05 (m, 6H), 3.43 (br s, 1H), 3.71 (br d, 1H), 4.15 (br d, 1H), 6.75–6.90 (br dd, 1H), 7.15–7.32 (m, 5H), 12.05 (s, 1H).

MS (ESI, compound dissolved in H_2O/MeCN/HCO_2H, 50:50:0.5): *m/z* (%) = 391.1 ($M + H^+$, 100), 335.0 ($M + H^+ - Me_2C{=}CH_2$, 99).

B: Prepared According to Entry 11:

A solution of substrate **3** (1.55 kg, 4.0 mol) and catalyst **16c** (18 g, 21.0 mmol) in MeOH (17 L) was hydrogenated as described in method C (*vide supra*, 50 bar H_2, 15 °C, 20 h). The solvent was evaporated in vacuo. The residue was dissolved in *tert*-butyl methyl ether (TBM-ether) (30 L) and stirred for 2 min with 0.5 N HCl (8 L). The organic layer was separated and the aqueous layer was extracted with TBM-ether (5 L). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give crude **4** (1.53 kg, 3.92 mol, 98% yield; 86% ee, HPLC). This solid was suspended in MeOH (1.4 L), and after stirring for 15 min, Et_2O (20 L) was added. After a further 15 min *i*-Pr_2O (4.4 L) was added and the suspension was cooled to 0 °C. The solid was collected by suction-filtration, washed with cold *i*-Pr_2O (2 × 2 L) and dried in vacuo; yield: 1.17 kg (75%); mp 134–136 °C, > 99.5% ee (HPLC).

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The maximum s/c ratio for hydrogenation of **3** has not yet been determined on pilot plant scale.
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