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A practical synthesis of enantiopure ethyl *cis*-2-amino-1-cyclohexanecarboxylate via asymmetric reductive amination methodology

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Abstract: A simple and practical method for large scale preparation of optically pure ethyl 2-amino-1-cyclohexanecarboxylate was developed via a reductive amination of 2-oxo-cyclohexanecarboxylate with a chiral α-methylbenzylamine. The major diastereomer was isolated in optically pure form by a simple and efficient crystallization as its HBr salt. The diastereoselectivity as well as the *cis/trans* selectivity was also improved. © 1997 Elsevier Science Ltd

Introduction

2-Amino-1-cyclohexanecarboxylic acid, an important non-proteogenic β-amino acid, has found many applications in syntheses of natural products, biologically active compounds, and peptide mimetics.[1,2] Its derivatives have been used in asymmetric synthesis either as chiral auxilaries or as ligands in catalytic systems.[3] A practical method for making enantiomerically pure 2-amino-1-cyclohexanecarboxylic acids on large scale is needed.

There are several methods reported for the synthesis of the enantiopure 2-amino-1-cyclohexanecarboxylic acids or their derivatives. These methods are conceptually different in establishing the chirality and include 1) chemical or enzymatic approaches to the optically active 1,2-cyclohexanedicarboxylic acid mono ester, followed by a Curtius rearrangement and other chemical transformations to obtain the desired amino acid,[4] 2) chemical or enzymatic resolution of *cis*-2-benzamidocyclohexanecarboxylic acid or *cis*-2-aminocyclohexanecarboxylate,[5] 3) Michael addition of chiral amines to α,β-unsaturated esters,[6] and 4) diastereoselective reductive amination of 2-oxo-cyclohexanecarboxylate with α-methylbenzylamine.[7] The latter method reported by Palmieri and coworkers[7] attracted our attention for a large scale synthesis as it utilizes inexpensive and readily available starting materials. The only drawback of this method is the necessity of a chromatographic purification to isolate the desired diastereomer. The similar chromatographic properties of the diastereomers (two *cis* diastereomers and two *trans* diastereomers) makes the chromatographic separation relatively inefficient especially for preparative scale. We have found that the major diastereomer, **1** (*R,S,S*), or its enantiomer, can be preferentially precipitated from the reaction mixture as its HBr salt (Scheme 1) in good chemical yield and excellent optical purity. In addition, the diastereoselectivity as well as the *cis/trans* selectivity was further improved by altering the reduction conditions. These results leading to a large scale preparation of ethyl (1*R*,2*S*)-2-amino-1-cyclohexanecarboxylate are disclosed herein.

Results and discussion

Selectivity

Before optimizing the reductive amination for the diastereomeric and *cis/trans* selectivity, we searched for a reliable analytical method for monitoring the reaction and determining the diastereomeric

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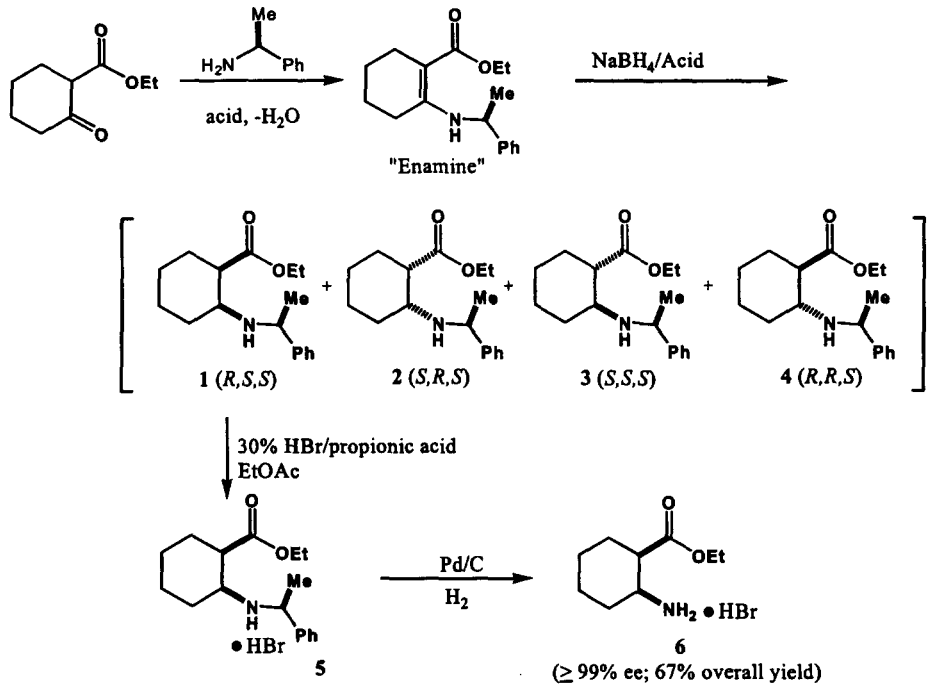

Scheme 1. Reductive amination approach to 2-amino-1-cyclohexanecarboxylate.

ratio. Towards this end, all four diastereomers were made in pure form. First, the two *cis* isomers, **1** and **2**, were isolated from the reaction mixture by a preparative silica gel TLC by eluting twice with 8% ethyl acetate in hexane. Each *cis* isomer was isomerized independently with NaO*t*-Bu in THF/*t*-BuOH,[3a] and the resulting *trans* isomer was purified by a preparative TLC. Since NMR was used in the literature for the diastereoselectivity determination,[3a,8] the ^{1}H NMR spectra of all four isomers were carefully studied. A relevant portion of the ^{1}H NMR spectra is shown in Figure 1. The proton adjacent to the nitrogen on the cyclohexane ring appears at 2.82 ppm for the major *cis* isomer **1**, at 2.77 ppm for the minor *cis* isomer **2**, at 2.72 ppm for the major *trans* isomer **3**, and at 2.48 ppm for the minor *trans* isomer **4**. The proton next to the ester group on the cyclohexane ring shows relatively larger differences in chemical shifts among the isomers. They are as follows: **1**: 2.75 ppm, **2**: 2.50 ppm, **3**: 2.14 ppm, and **4**: 2.16 ppm (in **4**, overlaping with a proton from the cyclohexane ring). Because of the extensive overlapping of the signals, the isomeric ratios could not be determined directly from the NMR spectra. However, the three of the four possible isomers can be baseline-resolved on a DB-5 column by a gas chromatography method (Figure 2; GC conditions: see Experimental part; retention time[min]: minor *cis* isomer, 24.76; major *cis* isomer, 24.90; major *trans* isomer, 25.27). The minor *trans* isomer (*R,R,S*) (retention time[min]: 24.93) partially overlaps with the major *cis* isomer (*R,S,S*) under the GC conditions. However, as the minor *trans* isomer is present only in trace quantity in the reaction mixture, we disregarded this component in selectivity determinations. The isomeric ratios in this work were all determined by this GC method.

Optimization of selectivity

The diastereoselectivity of the two *cis* isomers and the *cis/trans* selectivity were found to depend on the carboxylic acid, co-solvent, the acid/substrate ratio, and the reaction temperature (Table 1). Among the carboxylic acids studied (entries 1 to 6), pivalic acid offered the best result both in terms of diastereomeric excess of the *cis* isomers and the *cis/trans* ratio. The diastereoselectivity is monotonically correlated with the *cis/trans* selectivity with higher *cis* selective system giving better *de*

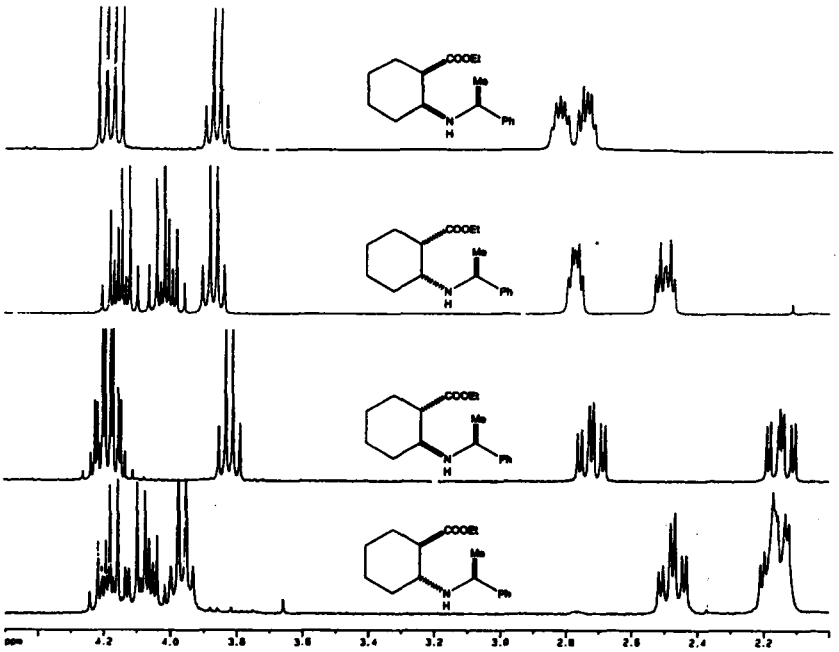

Figure 1. Selected portion of NMR spectra for all four isomers.

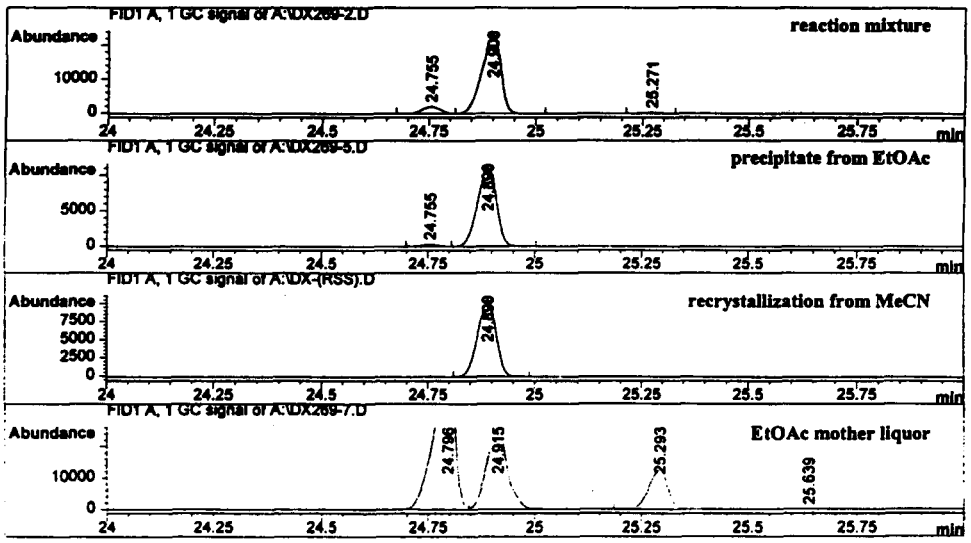

Figure 2. GC Traces for reaction mixture and the progress of purifications.

except in the case of trifluoroacetic acid (entry 5). This probably reflects the extent of the intramolecular hydride delivery in competition with the intermolecular hydride delivery according to the Palmieri model.[7b] Using acetic acid (entry 7), only 75% *de* was achieved under the literature conditions as opposed to the reported 81% *de*. The discrepancy could be due to different methods used in measuring the selectivity.[8] With toluene as a co-solvent, isobutyric acid offered the same selectivity as pivalic acid (entries 8 and 9) and due to easier handling, isobutyric acid was selected for further optimization.

The optimal reaction temperature was found to be 0 °C; selectivity decreased at temperatures either

Table 1. Selectivity optimization

Entry	Acid	Substrate/$NaBH_4$ /Acid (mmol)	Co-solvent	Temp (°C)	*de* (*cis* isomer)	*cis/trans*[a]
1	acetic acid	1/5/50	MeCN; 5 mL	20	72%	29/1
2	isobutyric acid	1/5/50	MeCN; 5 mL	20	79%	48/1
3	pivalic acid	1/5/50	MeCN; 5 mL	20	82%	74/1
4	benzoic acid	1/5/50	MeCN; 5 mL	20	64%	17/1
5	trifluoroacetic acid	1/5/50	MeCN; 5 mL	20	66%	4/1
6	phenylacetic acid	1/5/50	MeCN; 5 mL	20	72%	37/1
7[b]	acetic acid	3/9/87	MeCN, 5 mL	0	75%	32/1
8	isobutyric acid	1/5/25	toluene, 5 mL	0	80%	45/1
9	pivalic acid	1/5/25	toluene, 5 mL	0	80%	43/1
10	isobutyric acid	1/5/50	MeCN, 5 mL	-15	74%[c]	25/1
11	isobutyric acid	1/5/50	MeCN, 5 mL	0	81%	46/1
12	isobutyric acid	1/5/20	MeCN, 5 mL	0	60%	8/1
13	isobutyric acid	1/5/50	none	0	84%	48/1
14[d]	isobutryic acid	1/3/20	toluene, 0.5 mL	0	84%	60/1

a) Only the major *trans* isomer is taken into account. The overall *cis/trans* selectivity is somewhat lower.
b) Conditions reported in reference 7.
c) The reaction did not go to completion (about 60% conversion).
d) Conditions selected for a one-mole scale-up run.

higher or lower than 0 °C (entries 2, 10, and 11). This is a clear indication of the existence of the competing intermolecular and intramolecular hydride transfer processes. At lower temperatures, the ligand exchange between the enolate and the acetoxy group on the boron may be slow allowing the intermolecular hydride transfer to occur to a significant extent. At higher temperatures, the intrinsic selectivity of the intramolecular process is probably deteriorated.

Large excess in acid is clearly beneficial to the selectivity (entries 11 and 12). The highest selectivity (84% *de*) was achieved when the reaction was run in neat isobutyric acid (entry 13). Coupling this result with the fact that the enamine is made in toluene, we tried conditions shown in entry 14 using a minimum amount of co-solvent toluene (coming from enamine preparation). To our delight, these conditions offered the best selectivity and were adopted for a scale-up to one mole (see Experimental).

Preparation of 5

As the diastereomeric mixture resulting from the reductive amination is in oily form, we tried to enrich the diastereomeric purity through salt formation. Attempts with weak acids such as acetic acid, citric acid, (*S*)-mandelic acid, and tartaric acid were unsuccessful. Treatment of the amino esters with HCl under anhydrous conditions in diethyl ether gave only a gelatinous material. Addition of a stoichiometric amount of 48% aqueous HBr into an acetone solution of the amino esters resulted in a precipitation of the amino ester HBr salt, albeit in low yield. We fortuitously discovered that *the HBr salt 5 can be obtained in both excellent chemical yield and optical purity if the crude ethyl acetate extract from the aqueous workup was treated directly with the commercially available 30% of HBr in propionic acid at 0°C.* The precipitated salt was determined to have an optical purity of ≥ 94% *de*. One recrystallization from acetonitrile enriched the optical purity to ≥ 99% *de*. The efficiency of the HBr salt formation and recrystallization is illustrated through GC monitoring as shown in Figure 2. The precipitation removed essentially all of the available major *cis*-isomer, leaving behind in the mother liquor the minor *cis* isomer and two *trans* isomers. The overall yield of the HBr salt of the optically pure ethyl (*R,S,S*)-2-(α-methylbenzylamino)-1-cyclohexanecarboxylate, **5**, is about 75%, which represents 90% of the total available diastereomer in the reaction mixture.

The isolation of the major *cis* isomer as the HBr salt offered one additional advantage. While the corresponding HCl salt needed 2 days for the deprotection at 50 °C using 10% Pd/C, the HBr salt

needed only two hours under similar conditions. The two step sequence offers the title compound in enantiopure form in 67% overall yield.

Summary

A simple and a practical method for large scale preparation of optically pure ethyl 2-amino-1-cyclohexanecarboxylate has been developed based on the Palmieri's asymmetric reductive amination method starting from a β-ketoester. Diastereomeric enrichment *via* its HBr salt crystallization is the key for making this procedure into a practical method. The optimized reductive amination conditions, although tested for one particular system, should be applicable to other related examples as well.

Experimental

Selectivity optimization (Table 1)

Appropriate amount of an acid was mixed with a co-solvent in a round-bottomed flask and cooled to 0 °C followed by portionwise addition of $NaBH_4$. The mixture was stirred at 0 °C for 30 minutes and then brought to the desired temperature. The enamine (purified) was added with a specified amount of co-solvent. The mixture was stirred at the same temperature for 2 hours. A sample (~0.1 mL) was withdrawn from the mixture and mixed with excess of saturated Na_2CO_3 aquous solution (2 mL). The product was extracted into ethyl acetate (2 mL) and analyzed by GC (column: DB-5, 0.25 mm×30m; temperature gradient: 150 °C, 20 min; 20 °C/min; 200 °C, 10 min; injection temperature: 180 °C; detector (FID) temperature: 280 °C; retention time[min]: minor *cis* isomer, 24.76; major *cis* isomer, 24.90; minor *trans* isomer, 24.93; major *trans* isomer, 25.27; starting material enamine, 29.97).

Preparation of all four pure diastereomers

A quantity of 0.34 g (9 mmol) of $NaBH_4$ was added in portions to glacial acetic acid (5 mL) while keeping the internal termperature at 10 °C. The mixture was further stirred at this temperature for 1 hour. Acetonitrile (5 mL) was added and the solution was cooled to 0 °C. The enamine (0.82 g, 3.0 mmol) was added, and the solution was stirred at 0 °C for 2 hours. Saturated Na_2CO_3 aqueous solution (50 mL) was added and the mixture was extracted with 2×20 mL of ethyl acetate. The extracts were dried with $MgSO_4$, filtered and all of the solvent removed. Portion of the remaining oil was applied to a silica gel preparative TLC and eluted twice with 8% ethyl acetate in hexane. Pure *cis* isomers were collected, and a portion of each was subjected to epimerization independently. Thus, a quantity of 27 mg of the (*S,R,S*) isomer (0.1 mmol) was mixed with 1 mL of anhydrous THF containing 74 mg (1.0 mmol) of *t*-BuOH. To this solution was added 50 mg (0.5 mmol) of NaO*t*-Bu under nitrogen. The mixture was stirred at room temperature for 6 hours. A *cis/trans* ratio of 1:1.2 was achieved. (a 1:3.5 ratio was obtained for the (*R,S,S*) isomer under the same conditions). To the mixture was added the brine solution (5mL) and ethyl acetate (5 mL). The organic layer was collected and dried with $MgSO_4$. The *trans* isomer was isolated by preparative TLC, eluting with 12% ethyl acetate in hexane to give 8 mg of the pure *trans* isomer (*R,R,S*).

1 (*R,S,S*): oil; ^{1}H NMR ($CDCl_3$, 300 MHz), δ:1.27 (3H, d, *J*=7.5 Hz), 1.30 (3H, t, *J*=7.1 Hz), 1.19–1.34 (2H, m)1.42–1.70 (5H, m), 1.85–1.91 (1H, m), 2.74 (1H, m), 2.82 (1H, m), 3.85 (1H, q, *J*=7.5 Hz), 4.18 (2H, q, *J*=7.2 Hz), 7.19–7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 14.3, 22.8, 23.2, 24.6, 25.5, 29.8, 44.4, 53.3, 54.9, 59.9, 126.6, 126.7, 128.3, 146.5, 174.5.

2 (*S,R,S*): oil; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.18 (3H, t, *J*=7.0 Hz), 1.29 (3H, d, *J*=6.6 Hz) 1.25–1.46 (3H, m), 1.55–1.62 (3H, m), 1.82–1.90 (2H, m), 2.50 (1H, dt, *J*=9.4, 3.8 Hz), 2.77 (1H, dt, *J*=6.1, 3.6 Hz), 3.86 (1H, q, *J*=6.6 Hz), 4.00 (1H, dq, *J*=14.3, 7.0 Hz), 4.15 (1H, dq, *J*=14.3, 7.0 Hz), 7.18–7.30 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz), L: 14.1, 21.4, 24.0, 24.7, 25.4, 27.5, 46.4, 51.7, 54.2, 59.9, 126.6, 126.7, 128.1, 145.9, 174.6.

3 (*S,S,S*): oil; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 0.84–0.97 (1H, m), 1.10–1.25 (2H, m), 1.26 (3H, d, *J*=6.6 Hz), 1.30 (3H, t, *J*=7.0 Hz), 1.40–1.55 (1H, m), 1.64–1.68 (2H, m), 1.83–1.91 (2H, m), 2.15 (1H, ddd, *J*=13.8, 10.3, 3.6 Hz), 2.72 (1H, td, *J*=10.8, 3.9 Hz), 3.82, (1H, q, *J*=6.6 Hz), 4.12–4.24

(2H, m), 7.18–7.31 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 14.3, 23.9, 24.9, 25.0, 29.2, 33.2, 51.8, 55.7, 56.1, 60.1, 126.4, 126.7, 128.3, 147.1, 175.8.

4 (*R,R,S*): oil; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 0.85–1.42 (5H, m), 1.23 (3H, t, *J*=7.1 Hz), 1.28 (3H, d, *J*=6.6 Hz), 1.62–1.69 (2H, m), 1.83–1.90 (1H, m), 2.12–2.21 (2H, m), 2.48 (1H, td, *J*=10.6, 3.9 Hz), 3.97 (1H, q, *J*=6.6 Hz), 4.07 (1H, dq, *J*=10.8, 7.1 Hz), 4.19 (1H, dq, *J*=10.8, 7.1 Hz), 7.19–7.35 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 14.2, 24.5, 25.2, 25.7, 29.1, 31.4, 51.4, 53.8, 54.4, 60.2, 126.6, 126.7, 128.2, 148.3, 175.4.

Reductive amination and isolation of the pure HBr salt 5

To a 3-L, 4-necked round-bottomed flask were added 170.2 g (1.0 mol) of ethyl 2-oxocyclohexanecarboxylate, 1.0 L of toluene, and 96.9 g, (1.1 mol) of isobutyric acid. A quantity of 133.3 g (1.1 mol) of *S*(−)-1-phenylethylamine was added over 10 min at 20 to 30 °C (internal temperature) to obtain a cloudy solution. The reaction mixture was heated at 70 °C for 2 hours and then refluxed under nitrogen for 2 hours with azeotropic removal of water. A quantity of about 500 mL of toluene was distilled off. The solution was cooled to room temperature and added to the reducing medium prepared as follows.

To a 5-L, 4-necked round-bottomed flask containing 1.86 L (1762.2 g, 20 mol) of isobutyric acid, was added 113.4 g (3.0 mol) of sodium borohydride powder portionwise under nitrogen at 0–10 °C. The mixture was further stirred at 15–20 °C for 0.5 hours and then cooled to 0 °C. Under nitrogen the above enamine solution in toluene was added dropwise at 0 °C. The mixture was stirred at 0 °C for two hours. The reaction was quenched by dropwise addition of 0.5 L of 4 N hydrochloric acid. The organic layer was removed, and the aqueous layer was washed with 1.0 L of 1:1 (v/v) of ethyl acetate and heptane. The aqueous layer was basified to pH 10 with 10 N sodium hydroxide solution. The aqueous layer was extrated two times with 0.5-L portions of ethyl acetate. The pooled organic layers was washed two times with a saturated sodium chloride solution.

The organic extract was cooled to 0 °C and 324 g of 30% (w/w) hydrogen bromide (1.2 mol) in propionic acid was added dropwise at 0 °C. The resulting solid was filtered and washed two times with 300-mL portions of ethyl acetate. The mother liquor and the washings were combined and condensed to about 400 mL in volume. The resulting suspension was cooled and stirred at 0 °C for 1 hour. The solid was filtered and washed twice with 20-mL portions of ethyl acetate to get a second crop of the product. The combined crops were suspended in 2.5 L of acetonitrile and heated to reflux. The solution was filtered and cooled at 0 °C for 1 hour. The suspension was filtered and washed two times with 100-mL portions of acetonitrile. The solid was further dried under vacuum to give 265.1 g of **5** as a white crystalline solid (≥99.0% *de*, 74.4% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.08–1.41 (3H, m), 1.30 (3H, t, *J*=7.1 Hz), 1.55–1.69 (2H, m), 1.80–1.87 (1H, m), 1.92 (3H, d, *J*=6.7 Hz), 2.29–2.42 (2H, m), 3.20–3.27 (1H, m), 3.45–3.47 (1H, m), 4.21 (1H, dq, *J*=10.7, 7.1 Hz), 4.29 (1H, dq, *J*=10.7, 7.1 Hz), 4.38 (1H, q, *J*=6.7 Hz), 7.36–7.48 (3H, m), 7.73–7.78 (2H, m), 9.16 (1H, s, br), 9.33 (1H, s, br); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 14.0, 19.7, 21.8, 24.2, 25.5, 27.1, 39.7, 56.1, 56.4, 62.1, 127.8, 129.6, 135.9, 148.0, 174.4; mp: 192–193 °C (melts with gas evolution); $[\alpha]^{20}_D$=−58.0 (c=1.00, MeOH); free base: $[\alpha]^{20}_D$=−65.0 (c=2.07, 95% EtOH); $[\delta]^{20}_D$=−68.8 (c=2.04, MeOH).

Hydrogenolysis

To a 2-L hydrogenolysis bottle were added under nitrogen 10 g of 10% Pd/C, 1.0 L of 95% ethanol, and 100 g of **5**. The bottle was connected to a Parr hydrogenation apparatus and pressurized to 50 psi with hydrogen. The shaking was started and the reaction was heated to 50 °C. The reaction generally took 2 hours. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give 74.38 g of a pasty solid, which was crystallized from 250 mL of ethyl acetate at 0 °C to give 70.79 g (89%) of **6** as white crystals. The enantio purity of the amino ester can determined by analyzing the corresponding benzamide derivative on a Chiralcel OF column (0.46×25 cm): mobile phase 20% IPA/HEX, 0.8 mL/min; retention time [min]: major isomer, 15.8; minor isomer, 21.1. ^{1}H NMR ($CDCl_3$, 300 MHz), δ:

1.20–1.35 (1H, m), 1.30 (3H, t, J=7.1 Hz), 1.40–1.70 (3H, m), 1.82–1.95 (2H, m), 2.10–2.18 (1H, m), 2.25–2.33 (1H, m), 3.20–3.24 (1H, m), 3.64 (1H, dt, J=10.4, 4.0 Hz), 4.21 (1H, dq, J=9.9, 7.1 Hz), 4.27 (1H, dq, J=9.9, 7.1 Hz), 8.25 (3H, s, br); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 14.1, 22.2, 23.2, 26.6, 27.1, 41.5, 51.0, 61.6, 173.8; mp: 137–138°C; $[\alpha]^{20}_D$=+8.9 (c=1.0, MeOH); free base: $[\alpha]^{20}_D$=−2.7 (c=1.08, 95% EtOH).

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8. The method used for determining the selectivity was not specified in reference 7.

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