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An Improved Process for Repaglinide *via* an Efficient and One Pot Process of (1*S*)-3-methyl-1-(2-piperidin-1-ylphenyl)butan-1-amine – A Useful Intermediate

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Abstract: The development of a large-scale synthesis for (1*S*)-3-methyl-1-(2-piperidin-1-ylphenyl)butan-1-amine (*S*-(+)-**1**), a key intermediate of repaglinide (**2**), is described. The process conditions for *S*-(+)-**1** involving nucleophilic substitution, Grignard reaction, reduction and resolution were optimized and telescoped. The racemization of the undesired enantiomer *R*-(–)-**1** offers a distinctive advantage in terms of cost and overall yield over the existing process. This communication also describes the control of a DCU byproduct obtained during the condensation of *S*-(+)-**1** with phenyl acetic acid derivative **3** in the synthesis of **2**.

Keywords: 1,3-Dicyclohexyl urea impurity · Grignard reaction · Racemization · Repaglinide · Resolution · SNAR reaction · Telescopic process

1. Introduction

Process research plays an important role in the pharmaceutical industry and helps companies gain a competitive advantage in the production of Active Pharmaceutical Ingredients (APIs). The overall thrust of the scientists engaged in process chemistry is to develop a scalable, low-cost, safe and environmentally friendly route to manufacture APIs. In the generic API industry developing a route that meets targeted manufacturing costs, in the context of strong economic pressures and existing patent protected commercial processes, is a challenging task for the process chemist. Exploration of new and efficient chemical routes or exploitation of existing chemical schemes to enhance yield and purity are daily fare. In the present article, we will discuss our attempts at Dr. Reddy's to meet the chemical synthesis aspects of this goal for repaglinide (**2**), a well-known API for the treatment of type-2 non-insulin dependent diabetes mellitus (NIDDM) [1][2] available on the market as Prandin®. Specifically, we describe the process development studies for developing (1*S*)-3-methyl-1-(2-piperidin-1-ylphenyl)butan-1-amine (*S*-(+)-**1**), a major cost contributing intermediate for **2**.

Grell *et al.* [3] reported a general process for the synthesis of **2** in a convergent approach that involves condensation of enantiomerically pure *S*-(+)-benzylamine derivative *S*-(+)-**1** with phenyl acetic acid derivative **3** in the presence of N,N-dicyclohexylcarbodidimide (DCC) by ejection of 1,3-dicyclohexylurea (DCU) as a byproduct. Saponification of the resulting amide derivative **4** produces **2** (Scheme 1).

The said JMC process reported a four-step synthesis for *S*-(+)-**1** (Scheme-2) and a five-step synthesis for **3** with an overall yield of 14% and 30% respectively [3]. Of the two compounds, intermediates *S*-(+)-**1** is very expensive and involves a tedious process whereas a commercially viable process for **3** has been recently reported [4].

The reported synthesis [3] for the preparation of *S*-(+)-**1** (Scheme 2, paths a, b, c, d and e) involves nucleophilic substitution of the chlorine of 2-chlorobenzonitrile (**5**) by piperidine in presence of N-formylpiperidine at 125–130 °C for 65 h to afford crude **7**. Purification of crude **7** by silica gel slurry followed by high vacuum distillation of the resulting oil yields pure **7** in 84% yield. Grignard reaction of **7** with isobutyl magnesium bromide yields the unstable imine intermediate **8**, which upon reduction using sodium borohydride provided the corresponding amine derivative (±)-**1** as an impure residue in 64% yield, which was purified *via* formation of its glutamate salt. Hydrolysis of the (±)-**1**.glutamate salt and subsequent resolution of the resulting pure amine (±)-**1** using N-acetyl-L-glutamic acid (L-NAGA) in a mixture of acetone and methanol (93:7) provides enantiomerically enriched desired *S*-(+)-**1**. The resulting *S*-(+)-**1** is further recrystallized with acetone and methanol (5:1) to obtain enantiomerically pure *S*-amine (+)-**1** in 60% yield (w.r.t. *S*-isomer).

The aforementioned process suffers from the following disadvantages:

a) Condensation of piperidine with **5** does not go to completion and requires very long reaction times;
b) Silica gel slurry and fractional distillation are required for purification of **7** at high temperature and vacuum conditions;

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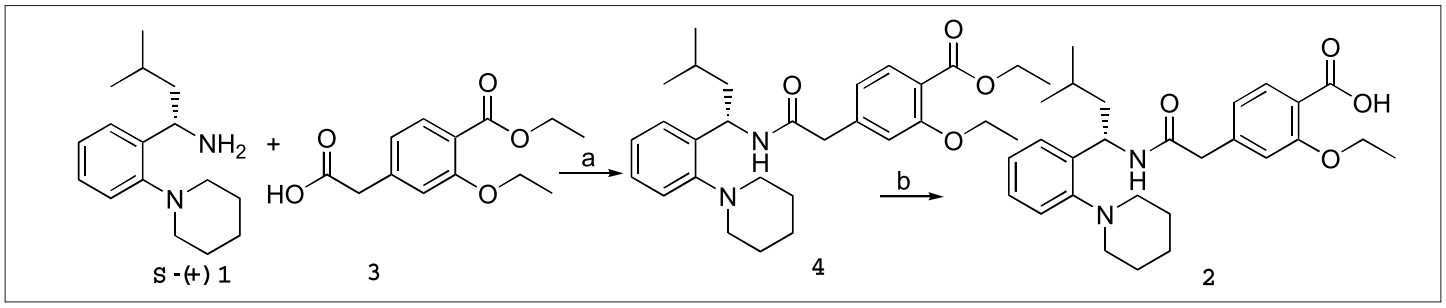
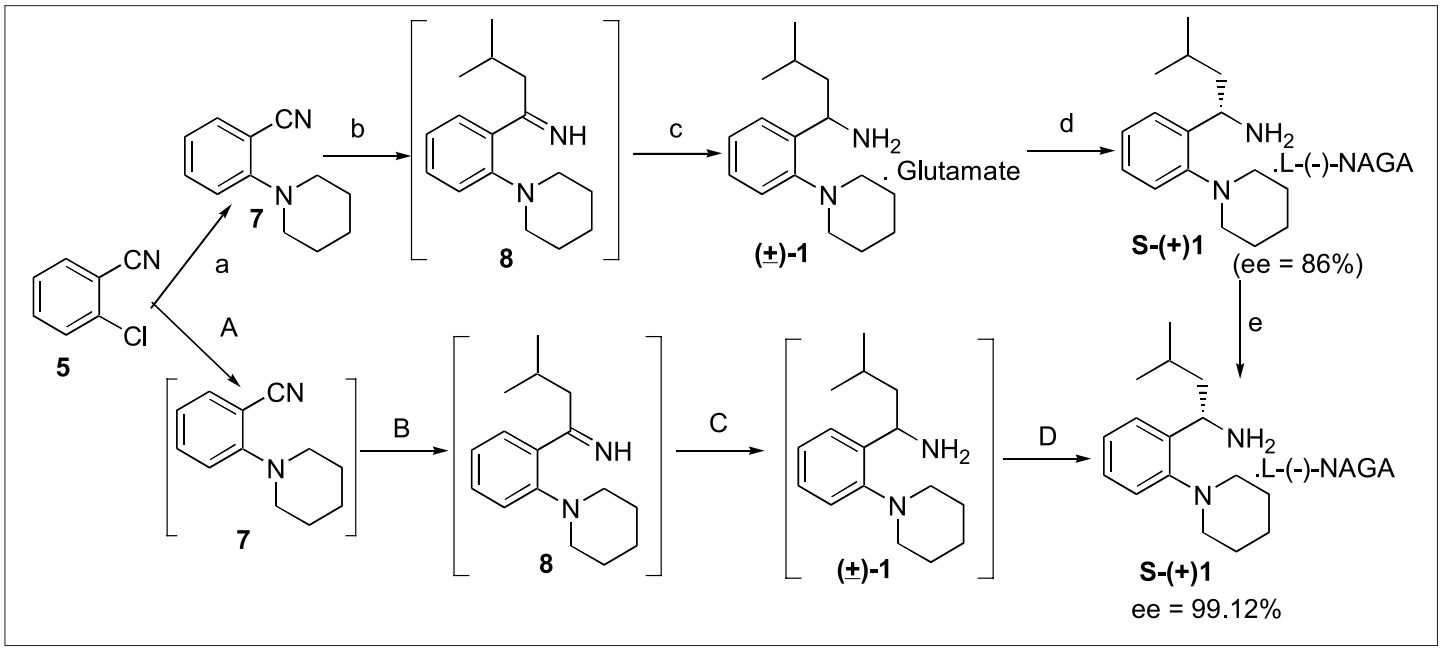


Scheme 1. Repaglinide synthesis from intermediates *S*-(+)-**1** and **3**. Reagents and conditions: a) dicyclohexylcarbodiimide/CH_2Cl_2/25–35 °C; b) NaOH/isopropanol/water/60–65 °C.



Scheme 2. JMC and DRL route comparison for the synthesis of S-(+)-**1** intermediate of repaglinide. Reagents and conditions: a) N-formyl piperidine/piperidine, 125–130 °C, 65 h; b) *i*-BuMgBr/toluene:THF (4:1), 90–95 °C, 4 h; c) $NaBH_4$/MeOH, 0–5 °C, 2–3 h, glutamic acid/acetone, reflux; d) aqueous NH_3/toluene, L-(–)-NAGA/acetone:MeOH (8.2:0.65), 12–14 h; e) acetone:MeOH (10:2); A) piperidine, 220–225 °C, 6–8 h, pressure 3–3.5 kg/cm_2; B) *i*-BuMgBr/toluene:THF (4:1), 98–102 °C, 14–16 h; C) $NaBH_4$/MeOH, 0–5 °C, 2–3 hrs; D) L-(–)-NAGA/acetone:water (8.2:0.55), 3 h.

c) Diethyl ether used in the isobutyl magnesium bromide preparation is hazardous and not recommended on scale;
d) Grignard reaction using isobutyl magnesium bromide prepared in other solvents such as THF does not lead to reaction completion and the yields are highly inconsistent;
e) Amine (±)-**1** obtained after borohydride reduction is highly impure, requiring a glutamate salt purification;
f) Yields of the resolution step were poor and required an additional recrystallization step to attain enantiomeric purity (>98.0 %);
g) Finally, the DCU byproduct formed during the condensation step of *S*-(+)-**1** and **3** was found to exceed the ICH limit (<0.15%) in the final API [5].

Herein we report a scalable and economic process for large-scale synthesis of *S*-(+)-**1** (Scheme 2, path A, B, C and D). The overall process incorporates a procedure to racemize the unwanted isomer *R*-(–)-**1**, from which additional *S*-(+)-**1** can be recovered. To ensure final API purity, a procedure for controlling the DCU byproduct formed during the condensation step of *S*-(+)-**1** and **3** is developed.

2. Results and Discussion

In our approach, we began by exploring the original route, as we were clear about its many disadvantages. The ready commercial availability of the raw materials for the existing route also prompted us to expend significant efforts at optimizing this route. Our approach focused on identification of the critical reaction parameters at each step with emphasis on those that drive the reaction towards complete conversion. The details of the optimization studies we carried out are discussed here.

2.1. *Condensation of 5 with Piperidine*

Following the original route, the substitution of the chlorine in 2-chlorobenzonitrile (**5**) by piperidine in presence of N-formyl piperidine at reflux (125–130 °C) displayed around 70–75% conversion of **5**. Furthermore, no additional progress of reaction was observed even after prolonged maintenance of the reaction conditions. This incomplete reaction progress posed a serious problem of low yield and necessitated the removing of unreacted **5** by fractional distillation at 160–170 °C and 30–40 mbar vacuum. The unreacted **5** still bears a nitrile group and therefore undergoes similar reactions in next stages, which produces the respective chloro impurity **6** (Fig. 1), and requires its removal/exclusion at as early a stage as possible. The conversion rate of **5** with and without the presence

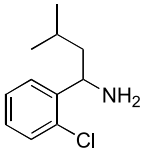


Fig. 1. Structure of chloro impurity

of N-formylpiperidine is same and the usage of N-formylpiperidine is not preferred on the basis of the experimental results in Table 1. Thus, we opted to use piperidine as solvent as well as reagent for this reaction. Interestingly, complete conversion of **5** to **7** in piperidine as solvent, is attained by optimizing the reaction at higher temperature than the boiling point of piperidine (220–225 °C) in a closed autoclave system under *in situ* pressure (closed system) of 3.0–3.5 kg/cm^2 within 6–8 h. This study enabled us to obtain **7** in quantitative yield with a purity of >98.0% without any silica gel slurry or high vacuum distillation purification. The reaction was monitored by on-line gas chromatography [6] and it was found that the content of **5** is always less than 0.05% and in many cases absent in the reaction mass itself after 6 h. The major parameter that drives the reaction was found to be the temperature (220–225 °C), which can be attained by conducting the reaction in a closed vessel.

2.2. *Grignard Reaction of Isobutyl Magnesium Bromide to 8 and Reduction of 8*

Initially, we were successful in repeating the described Grignard reaction to obtain imine **8** with 2.5 equiv. of isobutyl magnesium bromide prepared in diethyl ether, which is not an industrially friendly solvent. Alternatively we reinvestigated the addition reaction between **7** and isobutyl magnesium bromide, prepared in neat THF, to obtain **8** and found that under similar conditions to those reported in the literature procedure the addition did not proceed to completion. An exhaustive optimization of reaction conditions using Grignard complex prepared in THF then ensued; the mole ratio of isobutyl magnesium bromide, temperature and reaction time were found to be critical parameters to attain the complete conversion.

An optimized process was found, wherein the usage of 5.0 equiv. of isobutyl magnesium bromide at reflux temperature of 98–102 °C for 14–16 h in a mixture of toluene:THF (4:1) affords imine **8** in essentially quantitative yield. From our experimental observation a minimum of 98 °C is essential for completion of this reaction. Even though we could achieve temperatures above 98 °C by increasing the ratio of toluene as a co-solvent, reaction with 3.0 equiv. of isobutyl magnesium bromide did not proceed to completion, indicating the need for a large excess of Grignard reagent. Interestingly, using the same combination of toluene:THF (4:1) it is observed that the temperature of 98–102 °C is reached when 5.0 equiv. of isobutyl magnesium bromide is used. On the basis of these experimental results it was understood that the excess amount of Grignard reagent helped to elevate the boiling point of resulting solvent mixture and in turn facilitated the complete conversion of **8**. Usage of high boiling xylene in place of toluene resulted in the production of a number of impurities due to instability of the Grignard reagent and the imine **8** at high temperatures. The resulting imine **8** obtained after usual work up as a thick syrup was directly reduced with sodium borohydride in methanol to give the amine intermediate (±)-**1**, with reasonably good purity and was further used directly for resolution.

2.3. *Resolution of Amine (±)-1*

In our hands the resolution procedure mentioned by the Grell and co-workers produced poor yields (40–45%) and optical purities (<97.0 %). According to the literature process a mixture of amine (±)-**1** and L-NAGA was refluxed in mixture of acetone:methanol (93:7) and the resulting clear solution is stirred overnight at room temperature. The resulting solid having a enantiomeric purity of ~75% was further recrystallized in mixture of acetone:methanol (5:1) to achieve *S*-(+)-**1** in 60% yield with respect to the *S*-isomer content and 98.0% enantiomeric purity.

During our initial test-tube screening of this resolution procedure, addition of a single drop of water produced dramatic changes in optical purity of the resulting product. Consequently, as a result of various experiments, the resolution step can be optimized to a single-step procedure using the combination of acetone:methanol:water (8.2:1.2:0.2) with >98.0% ee and 70–75% yield with respect to the *S*-isomer content (Table 2).

An alternative process also developed for the same resolution step in acetone: water (15:1). The enantiomeric purity of *S*-(+)-**1** is found to be directly proportional to quantity of water used >0.55 times with respect to the amount of (±)-**1**, whereas the yield displayed an inverse proportionality with the quantity of water. An optimized experimental procedure involves refluxing a mixture of amine (±)-**1** and L-NAGA in

Table 1. Conversion rate of **5** at different temperatures and pressure

Entry	Temp [°C]	Time [h]	Yield [%]	In-built pressure [Kg/cm^2]	Contents by GC			
					Before HVD		After HVD	
					7	5	7	5
1	118–120	67	65	[b]	76	20.6	95.8	ND
2[c]	125–130	68	66	[b]	58.2	21.2	[a]	–
3[c]	125–130	66	65	1.0–1.2	56.4	19.2	[a]	–
4	118–120	67	65	1.0–1.2	77.4	19.8	96.3	ND
5	118–120	78	68	3.0–4.0[d]	73.4	21.6	[a*]	–
6	145–150	44	90	2.0–2.2	94.6	1.94	[a]	–
7	178–180	14	90	3.0–3.5	98.2	ND	[a]	–
8	220–225	8	92	3.4–3.8	98.3	0.002	[a]	–

[a] High vacuum distillation (HVD) not performed; [b] Reactions performed in round bottom flask at atmospheric pressure; [c] Reactions in which both N-formyl piperidine and piperidine were used; [d] External N_2 pressure was applied; ND = not detected

Table 2. Role of methanol and water on resolution efficiency

Entry	Solvent ratio[a]			Yield[b] [%]	SOR[c] $[\alpha]^{20}_D$	Enantiopurity
	Acetone	MeOH	H_2O			
1	8.2	0.65	–	66.7	14.6	75.2
2	8.2	0.8	–	59.1	23	81.4
3	8.2	0.6	0.2	52	28	86.4
4	8.2	1.2	0	38.2	30.1	91
5	8.2	1.2	0.2	35.3	33.2	98.9
6	8.2	–	0.55	37.8	33.5	99.1
7	8.2	–	0.6	28.6	33.4	99.2
8	8.2	–	0.45	45.4	26.4	85.0

[a]Quantities of acetone, methanol and water are calculated on the basis of the amount of (±)-**1** added; [b]Yield [%] is calculated with respect to the racemic compound; [c]SOR analysis is carried out at c = 1% in methanol.

a mixture of acetone:water (15:1) followed by stirring of the resulting clear solution for 3 h at room temperature. The resulting solid is filtered to obtain *S*-(+)-**1** in 75% yield with an enantiomeric purity of >98.5 %. In both of the above processes, crystallization below 15 °C resulted in co-precipitation of the undesired *R*-isomer, *R*-(–)-**1**, as evidenced by the steady drop in optical rotation. Therefore, we opted to crystallize the desired isomer at room temperature.

2.4. *Racemization of Undesired Amine Enantiomer R-(–)-1 and Recovery of L-NAGA*

The undesired isomer *R*-(–)-**1** recovered from the mother liquor is racemized by heating in a solution of dimethylsulfoxide in presence of potassium hydroxide for 10–12 h to obtain (±)-**1** in quantitative yield. The racemate so obtained is then subjected to resolution in the aforementioned process to obtain additional pure *S*-(+)-**1**. Furthermore, the chiral auxiliary L-NAGA is also recovered from the aqueous layers obtained after hydrolysis of *S*-(+)-**1** and *R*-(–)-**1**. L-(–)-NAGA salts can be isolated as crystalline solids directly by adjusting pH of the respective aqueous layers to 2–3 using concentrated hydrochloric acid at 0–5 °C.

The combined improvements of nucleophilic substitution, Grignard reaction, single-step resolution process and racemization of the recovered undesired enantiomer isomer allowed the use of this process to produce *S*-(+)-**1** in short cycle time, with easier handling, without special isolations/purifications in better yield and purity (Scheme 2).

2.5. *Control of Dicyclohexylurea (DCU) Impurity*

Finally, *S*-(+)-**1** and **3** were condensed using DCC in dichloromethane and the by-product DCU was filtered off at room temperature. The resulting amide derivative **4** was hydrolyzed to afford **2**. Despite the care taken to filter off the DCU impurity at the end of the condensation step, DCU as impurity was still found at a level of >1.0 % in the final API. Understanding that the low particle size of the DCU impurity was the root cause, the reaction mass was filtered over a Hyflo bed at 0–5 °C. repaglinide prepared according to this process is free from DCU without any yield loss in direct contrast to previous multiple crystallization techniques that required the sacrifice of some product yield in order to reach comparable levels of purity.

In conclusion, the improved process for *S*-(+)-**1**, a key intermediate en route to repaglinide offers distinct advantages over the existing process. The new process proceeds in an overall yield of 50%, including the recovery of unwanted *R*-isomer and a shorter time cycle of 55 h; this in turn gives a substantial cost advantage to the total synthesis of repaglinide The potential DCU impurity is controlled in the process itself without involving multiple crystallizations, which reduce product yield.

3. Experimental Section

The ^{1}H and ^{13}CNMR spectra were measured in $CDCl_3$ using 200 and 50 MHz, respectively, on a Varian Gemini 200 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on HP-5989a LC-MS spectrometer. The melting points were determined by using the capillary method on a POLMON (model MP-96) melting point apparatus. The solvents and reagents were used without any purification.

3.1. *(1S)-3-Methyl-1-(2-piperidin-1-ylphenyl)butan-1-amine (S-(+)-1)*

A mixture of 2-chloro-benzonitrile (5, 50.0 g, 0.364 mol) and piperidine (93.0 g, 1.09 mol) was refluxed at 220–225 °C for 6–8 h in an autoclave under *in situ* pressure conditions. After completion of the reaction piperidine was distilled off and the resulting thick residue was dissolved in toluene (50.0 ml), filtered to remove the by product piperidine hydrochloride. The filtercake was washed with toluene (3 × 50.0 ml). Water (100.0 ml) was added to the filtrate and acidified to a pH of 3–5 using conc. HCl (~ 0.5–0.6 ml). The combined organic layers are washed with water (2 × 50.0 ml) and distilled off under vacuum to obtain 64.5 g of **7** as a residue.

To prepare isobutyl magnesium bromide, a separate flask was charged with a mixture of Mg (41.5 g, 1.73 mol), iodine (3.0 g) in THF (194 ml), isobutyl bromide (7 ml) was added to initiate Grignard complex formation under N_2 atmosphere. After initiation, a solution of isobutyl bromide (237.4 g, 1.73 mol) in THF (65 ml) was slowly added to the flask and the resulting reaction mixture heated at reflux (*ca.* 60–65 °C) for 1 h. A solution of 2-piperidino-benzonitril (**7**, 64.5 g, 0. 34 mol) in toluene:THF (516:130 ml) was added to the reaction mixture and heated under reflux (*ca*. 98–102 °C) for 14–16 h. The reaction mixture was cooled to 25–35 °C and slowly quenched in a cold mixture of concentrated ammonia and saturated ammonium chloride (484:484 ml) between –10 to 0 °C. The resulting emulsion is filtered through a Hyflo bed and the filtrate was concentrated under vacuum to obtain 80.6 g of **8** as a residue.

The obtained residue of **8** was dissolved in methanol (645 ml) and cooled to 0–5 °C. To the resulting solution, $NaBH_4$ (6.5 g, 0.17 mol) was added in portions over a period of 45–60 min at 0–5 °C. The reaction mixture is heated to 10–15 °C and stirred for 2–3 h. The solvent from the resulting reaction mixture was distilled off under vacuum, water (167.6 ml) was added and then the reaction pot acidified with conc. HCl (58–61.2 ml). The obtained acidic solution was washed with dichloromethane (3 × 113 ml). The resulting DCM layer was extracted with 3.0 N HCl solution (160 ml) to recover (+)-**1** and to remove undesired impurities. The combined aqueous layers were neutralized using lye (58–60 ml) and the product was extracted into dichloromethane (3 × 150 ml). The final organic layer was washed with water (2 × 95 ml) and then the solvent was removed under vacuum to obtain 68.9 g of (+)-**1** as a residue.

Amine (±)-**1** was dissolved in acetone (565 ml), N-acetyl-L-glutamic acid (52.9 g, 0.28 mol) and water (37.8 ml) was then added and the resulting suspension was heated at reflux for 1 h. The resultant clear solution was slowly cooled to room temperature and held there for 3–4 h. The separated diastereomeric salt was filtered and washed with chilled acetone (–10 °C) to obtain 45.6 g of *S*-(+)-**1**. L-(–)-NAGA salt. Yield [%]: 57.5 (calculated relative to theoretical amount, which is half of the starting racemate); SOR $[\alpha]_D$: + 33.5 (c 1.0, methanol); enantiomeric purity [7] 99.1%; mp 169–171 °C.

3.2. *Alternative Process for Resolution of 3-Methyl-1-(2-piperidin-1-ylphenyl)butan-1-amine ((±)-1)*

To a solution of (±)-**1** in acetone (565 ml), N-acetyl-L-glutamic acid (52.9 g, 0.28 mol) was added and the mixture slowly heated to reflux at which point methanol (82.7 ml) was added in three portions over 10 min. To the resulting suspension, water (13.8 ml) was also charged to obtain a clear solution. The solution was aged for 12 h and the resulting solid was filtered and washed with chilled acetone (–10 °C): yield 42.6 g, 70.6 % (calculated related to theoretical amount, which is half of the starting racemate); SOR $[\alpha]_D$: + 33.2 (c 1.0, methanol); enantiomeric purity [7] 98.89%; mp 169–171 °C. ^{1}H NMR (50 MHz, $CDCl_3$): δ 0.85 (d, 3H, J = 6.2 Hz), 0.93 (d, 3H, J = 6.2 Hz), 1.3–1.6 (m, 1H), 1.3–1.9 (m, 8H), 1.82 (s, 3H), 2.19 (q, 2H, J = 7.2 Hz), 2.65 (m, 2H), 2.9 (m, 4H), 4.1 (q, 1H, J = 7.0 Hz), 4.7 (t, 1H, J = 7.2 Hz), 7.1–7.4 (m, 2H), 7.52 (d, 1H, J = 7.2 Hz), 7.66 (d, 1H, J = 7.2 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 22.2, 22.6, 22.7, 23.6, 24.1, 26.1, 45.1, 46.4, 52.8, 54.3, 121.2, 124.7, 126.8, 128.7, 135.5, 152.4, 168.4, 174.2, 174.8; MS: m/z = 247 [M^++1].

3.3. *(S)-Ethyl 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate (4) Free from 1,3-Dicyclohexyl Urea*

To a stirred solution of enantiomerically pure freebase of *S*-benzyl amine derivative [8] (*S*-(+)-**1**, 28.2 g, 0.114 mol) and phenylacetic acid derivative (**3**, 31.8 g, 0.125 mol) in dichloromethane (250 ml) was charged N,N'-dicylcohexylcarbodiimide (28.4 g, 0.136 mol) and stirred at room temperature for 2–3 h. After the reaction completion, reaction mass was cooled to 0–5 °C and then 1,3-dicyclohexylurea was separated by filtration over Hyflo bed. The resultant filtrate was washed with water (2 × 50.0 ml), distilled and recrystallized from IPA/n-heptane to obtain 44.8 g of **4** as a solid. Yield: 80.0 %; purity by HPLC 98.5 %; DCU content: not detected; mp: 120–121.8 °C; $[\alpha]_D$ + 8.0 (c 1.0, methanol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (d, 6H), 1.35 (t, 3H, *J* = 7.4 Hz), 1.4 (t, 3H, *J* = 7.4 Hz), 1.4–1.8 (m, 6H), 1.6 (q, 2H, *J* = 7.4 Hz), 1.7 (m, 1H), 2.63 (m, 1H), 2.91 (m, 2H), 3.5 (s, 2H), 4.0 (m, 2H), 5.35 (m, 1H), 6.81 (d, 1H, *J* = 6.8 Hz), 6.83 (s, 1H), 7.0-7.3 (m, 4H), 7.72 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.21, 14.59, 22.4, 22.7, 24.0, 24.9, 26.6, 44.1, 46.6, 49.5, 54.8, 60.6, 64.5, 113.8, 120.7, 122.6, 124.9, 127.5, 127.8, 131.9, 138.6, 141.0, 152.4, 158.7 (2C), 166.1, 168.7; MS: m/z = 481 [M^++1].

3.4. *Racemization of (R)-Amine Derivative R-(–)-1*

To a solution of R-benzyl amine derivative *R*-(–)-**1**, 10.0 g, 0.04 mol) in DMSO (50 ml), KOH flakes (2.5 g, 0.044 mol) were added and stirred at 130–140 °C for 10–12 h. The reaction mixture was cooled to 25–35 °C and then mixed with water (50 ml). The whole reaction mass was extracted into toluene (2 × 30 ml) and the resulting organic layer is washed with water (2 × 25 ml). The final organic layer was distilled off under vacuum to obtain 9.5 g of (±)-**1** as syrup. Yield 95.0%; $[\alpha]_D$ –0.8 (c 1.0, methanol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (d, 3H), 0.95 (d, 3H, *J* = 3.2 Hz), 1.4 (m, 3H), 1.6 (m, 4H), 2.7 (m, 6H), 4.38 (t, 1H), 4.7(s, 1H), 7.0–7.4 (m, 4H); MS: m/z = 247 [M^++1].

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[6] The progress of the first stage of reaction was monitored by gas chromatography analysis performed with AT5, 30 × 0.53 mm, 5.0 μ column.

[7] Enantiopurity of **1** was performed on chiral HPLC analysis with chiral pak AD-H, 250 × 4.6 mm, 5.0 μ; mobile phase: n-hexane, 2-propanol and triflouro acetic acid in the ratio of 80:20: 0.04 (v/v); 1.2 ml/min; 240 nm.

[8] Liberation of the (+)-**1** L-(–) NAGA salt was carried out to obtain enantiomerically pure *S*-amine freebase in dichloromethane and aqueous sodium carbonate medium. The obtained organic layer can be used directly without distillation or syrup obtained after distillation in next condensation step.