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# Enantiopure β$^3$-neopentylglycine: synthesis and resolution

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ABSTRACT

A procedure has been developed for the large scale synthesis of enantiopure β$^3$-neopentylglycine and its *Cbz*-protected derivative. The synthetic route developed in our laboratory features *Cbz*-protection of the racemic β-amino acid followed by resolution with L-norephedrine and provides the enantiomerically pure *Cbz*-β-neopentylglycine in good yield and excellent enantiopurity. No toxic or dangerous chemicals are used, allowing the scale-up of this procedure without major safety concerns.



## 1. Introduction

α-Amino acids dominate life on a molecular level, as they are the basic structural components of enzymes and proteins. On a macroscopic scale, α-amino acids are produced by the chemical industry on enormous scales and are of immense economic importance; for example, as food supplements, feed additives and building blocks for active pharmaceutical ingredients.

Compared to α-amino acids, the use of β-amino acids is very low. However, interest in β-amino acids is steadily increasing, as can be seen from the large number of investigations concerning the chemistry and properties of β-amino acids, β-peptides and their derivatives.[1,2] In Nature, β-amino acids and β-peptides are not uncommon compounds. In fact, some β-amino acids, such as β-alanine, occur relatively often in naturally occurring peptides. Well known classes of natural products, which are important because of their antibiotic activity, are the penicillins and the cephalosporins, both contain a β-lactam ring in their structures. Another natural compound containing a β-amino acid moiety is the anticancer drug Taxol.

Apart from the naturally occurring substances, the pharmaceutical industry has investigated and developed a number of physiologically active compounds which incorporate a β-amino acid residue. Examples include Sitagliptin phosphate[3] (Januvia™, Merck & Co.) for treatment of type 2 diabetes and the peptide deformylase inhibitor LBM415 (Novartis).[4]

Despite the increased interest in β-amino acids, β-peptides and their derivatives, only limited information can be found in the literature concerning large-scale preparative procedures. Historically, many of the β-amino acids have been prepared by the Arndt–Eistert homologation sequence using the highly toxic and dangerous diazomethane. Since then, a large number of different approaches have been established for the synthesis of enantiomerically pure β-amino acids, the most successful being the asymmetric hydrogenation of dehydroamino acid derivatives,[5–9] the asymmetric conjugate addition of nitrogen nucleophiles[10] and the enzymatic resolution of ester-[11,12] or amide-derivatives.[13] Furthermore, over the past few years, organocatalysed reactions have become increasingly successful, and a number of reports describing approaches towards β-amino carbonyl compounds have appeared.[14–19] Although organocatalysis sometimes suffers from relatively inaccessible ligands, long reaction times and dilute conditions, it is becoming more attractive and efficient. More 'classical' approaches towards β-amino acids and their derivatives involve syntheses with, for example, chiral Lewis acids and chiral auxiliaries.[20–29] The majority of these routes suffer from long synthetic sequences, expensive chemicals, long reaction times and protecting groups that are difficult to remove. Despite all efforts, there have until now been no general routes found for large-scale preparations of β-amino acids. We became interested in β$^3$-neopentylglycine, which we considered useful as a potential building block for physiologically active compounds due to its sterically demanding and lipophilic *tert*-butyl substituent. However, the lipase resolution protocol, which has been found to be very useful for the resolution and large-scale manufacture of aromatic β$^3$-amino acids, could not be applied to the synthesis of β$^3$-neopentylglycine as attempted enzymatic resolution afforded only racemic material. We therefore concentrated our efforts on the synthesis of this aliphatic β$^3$-amino acid via the formation of diastereomeric salts.

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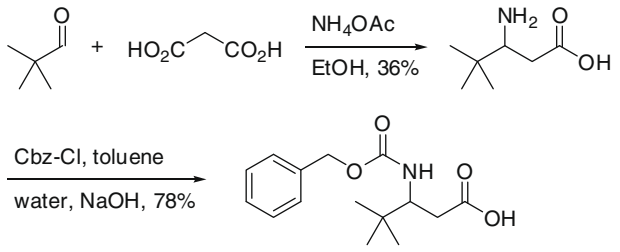
## 2. Results and discussion

For a synthesis to be applied on an industrial scale, the chemistry of choice should be safe, easy to perform and not involve any hazardous or toxic chemicals. Moreover, raw materials should be cost-attractive and readily available, and the number of steps and isolations should be limited as much as possible. With these considerations in mind, we started our investigations towards the synthesis of enantiomerically pure β$^3$-neopentylglycine via diastereomeric resolution.[30]

There are many good reasons to opt for diastereomeric resolution. Diastereomeric resolutions can be performed on a large scale and are generally robust and safe processes. The resolving agent can, after re-isolation and purification, be used for new resolutions and does not need to be discarded. Moreover, the undesired enantiomer can often be racemised after the resolution and resolved again, if economically attractive.

The resolution of diastereomers has become a well known method since the first resolution experiments by Pasteur,[31] and has been used many times for a large number of compounds.[32] Although commonly used in practice, such resolutions have received considerably less attention in the literature. Detailed investigations to find the rationale behind diastereomeric resolutions were undertaken by Collet in the 1980's.[33,34] Nevertheless, the development of new methodologies for diastereoselective salt formation has remained a topic of considerable interest, as shown by the work on 'Dutch resolution' by Kellogg et al.[35] For the investigations presented herein, we also deviated slightly from the 'classical' conditions by using only half an equivalent of the resolving agent for economic reasons.

In the first step of our synthesis, we condensed malonic acid, pivaldehyde and ammonium acetate in ethanol to give the racemic β-amino acid according to the so-called Rodionov synthesis, as depicted in Scheme 1.[36]




**Scheme 1.** Synthesis of racemic, *Cbz*-protected β$^3$-neopentylglycine.

The yield of 36% was somewhat low, due to the tedious separation of the β-amino acid from acetate, malonate and ammonium salts. Once pure, the racemic β-amino acid was protected with *Cbz*-chloride under Schotten–Baumann conditions in 78% yield. The *Cbz*-group was chosen as the protective group for the amine functionality as it can be removed easily by catalytic hydrogenation and after completion of the reaction and separation of the catalyst no undesired by-products remain in the reaction mixture. Moreover, the *Cbz*-group is a good chromophore, which facilitates analysis by HPLC and provides an analytical handle for the molecule. Both the synthesis of *rac*-β$^3$-neopentylglycine and its *Cbz*-protection were conducted on multi-kilogram scales. Having protected the amine moiety, the carboxylic acid functionality can be used for the formation of diastereomeric salts with a chiral base. For the assignment of the correct stereochemistry, we prepared enantiopure (*R*)-β$^3$-neopentylglycine from *Cbz*-L-*tert*-leucine through an Arndt–Eistert homologation sequence to function as a reference with defined stereochemistry during our resolution experiments.[37]

In an initial screening, various chiral amines (e.g., β-amino alcohols, phenylethylamines, norephedrine) were tested for their capability to form diastereomerically pure salts. Relatively early on, it became clear that the best results were obtained using commercially available L-(−)-norephedrine and (*R*)-phenylethylamine. Compared with other frequently used resolving agents, these bases offer the additional advantages that they have relatively low molecular weights (compared with e.g., quinine), are non-toxic (compared with e.g., strychnine and brucine) and that both enantiomers are readily available.

It should be noted that in almost all cases, no salt formation occurred in polar solvents such as water, ethanol, *iso*-propanol or acetone. We therefore concentrated on apolar solvents such as toluene, ethers and esters. In order to have a closer look at the physical properties of the salts, experiments were performed using 10.0 g of *rac-Cbz*-β$^3$-neopentylglycine. The results of these experiments using half an equivalent of (*R*)-phenylethylamine in various solvents are depicted in Table 1.[38]

**Table 1**
Results of the resolution of *rac-Cbz*-β$^3$-neopentylglycine with (*R*)-phenylethylamine

| Solvent | Yield[a] | Yield[b] | Ratio (*R*):(*S*) | | Diastereomeric excess | *S*-factor |
|---|---|---|---|---|---|---|
| *n*-BuOAc | 57.7 | 26.9 | 85.2 | 14.8 | 70.4 | 0.41 |
| EtOAc | 78.7 | 39.4 | 85.7 | 14.4 | 71.3 | 0.56 |
| Toluene | 69.1 | 34.6 | 87.7 | 12.4 | 75.3 | 0.52 |
| MiBK | 80.3 | 40.2 | 81.9 | 18.2 | 63.7 | 0.51 |
| IPAc | 83.1 | 41.6 | 84.4 | 15.6 | 68.8 | 0.57 |
| MTBE | 97.4 | 48.8 | 73.0 | 27.0 | 46.0 | 0.45 |
| THF | 74.6 | 37.3 | 86.4 | 13.6 | 72.8 | 0.54 |

[a] Yields based on (*R*)-phenylethylamine.
[b] Yields based on *Cbz*-β$^3$-neopentylglycine.

Although these results appeared to be quite promising, a subsequent recrystallisation of the diastereomerically enriched salt would probably not be sufficient to give diastereomerically pure material. Furthermore, it was noticed that the salt pair formed with (*R*)-phenylethylamine was difficult to filter and wash and, therefore, was likely to give problems during centrifugation on a large scale.

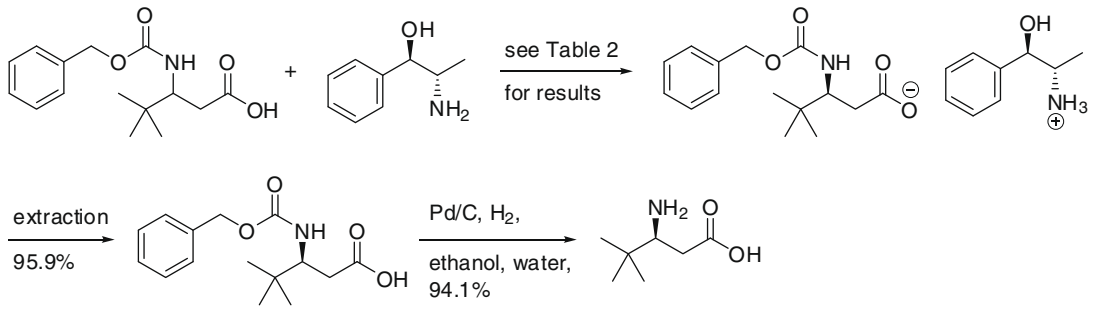
Similarly, experiments using L-(−)-norephedrine as the resolving base were performed using 10.0 g of *rac-Cbz*-β$^3$-neopentylglycine. Although the product was similarly fluffy, it was more easily filtered and could be washed without problems. However, it required extended drying times at 50 °C. The results of these resolution experiments are shown in Table 2.[38]

**Table 2**
Results of the resolution of *rac-Cbz*-β$^3$-neopentylglycine with L-(−)-norephedrine

| Solvent | Yield[a] | Yield[b] | Ratio (*R*):(*S*) | | Diastereomeric excess | *S*-factor |
|---|---|---|---|---|---|---|
| Toluene | 75.4 | 37.8 | 4.3 | 95.7 | 91.4 | 0.69 |
| MTBE | 84.5 | 42.3 | 23.0 | 77.0 | 54.0 | 0.46 |
| IPAc | 62.2 | 31.1 | 3.7 | 96.3 | 92.6 | 0.58 |
| EtOAc | 61.6 | 30.8 | 4.9 | 95.1 | 90.3 | 0.56 |
| MiBK | 51.3 | 25.7 | 4.9 | 95.1 | 90.3 | 0.46 |
| *n*BuOAc | 60.7 | 32.6 | 6.2 | 93.8 | 87.7 | 0.53 |

[a] Yields based on L-(−)-norephedrine.
[b] Yields based on *rac-Cbz*-β$^3$-neopentylglycine.

As the experiments using L-(−)-norephedrine and toluene gave the best overall results, with respect to yields and purities, it was decided to focus on this particular combination of reagent and solvent. Various experiments performed on larger scales afforded the salt pair in around 74% yield and with diastereomeric ratios (*R*):(*S*) ca. 2.5:97.5 and *S*-factors of around 0.70–0.74. Yields could be improved further by addition of 0.55 equiv of L-(−)-norephedrine instead of 0.5 equiv. Based on the amount of *rac-Cbz*-β-neopentylglycine employed, yields improved from 37% to 41%, while the diastereoselectivity of the salt formation remained unchanged. Although various other experiments were performed




**Scheme 2.** Resolution of racemic *Cbz*-β$^3$-neopentylglycine and hydrogenation of the enantiomerically pure derivative to obtain enantiomerically pure (*S*)-β$^3$-neopentylglycine.

using different concentrations of the amino acid or amounts of the resolving agent, these did not result in substantial further improvements with respect to the selectivity of the salt formation or the yield of the product. Diastereomerically pure material was therefore obtained by recrystallisation of the salt, for which a mixture of toluene and ethanol proved to be best. During the recrystallisation, a small amount of the material was lost, ranging typically from 5% to 10% of the initially isolated material.

The (*S*)-*Cbz*-β-neopentylglycine was liberated from its salt by extraction of the L-(−)-norephedrine into an acidic water layer while the amino acid derivative was taken up in ethyl acetate. This step proceeded without any significant loss. Re-isolation of L-(−)-norephedrine was not investigated at this point. Subsequent cleavage of the *Cbz*-group using a Pd–C catalyst under a hydrogen atmosphere was achieved without any problems, as is depicted in Scheme 2. The free enantiomerically pure β-amino acid was isolated as a white solid in high yields and in high enantiomeric purity, and no racemisation of the chiral centre was observed, as determined by GC.[38]

## 3. Conclusion

Herein, we have demonstrated that enantiomerically pure (*S*)-β-neopentylglycine can be obtained efficiently by resolution of its *Cbz*-derivative with L-(−)-norephedrine. This methodology allows for easy access to both enantiomers of β-neopentylglycine, as both D-(+)- and L-(−)-norephedrine are commercially available. Although the emphasis has been on synthesis of the enantiomerically pure β-amino acids, the (*S*)-*Cbz*-β-neopentylglycine itself, obtained after the resolution, could be of even more interest. As its amine functionality is already protected, it could serve directly as a building block for the construction of new β$^3$-peptides or other pharmaceutically active compounds using well-established peptide chemistry.

All reactions have been performed on a multi-gram, while at other times early in the synthetic sequence, on a multi-kilogram scale. No particularly dangerous, unstable or toxic chemicals were used, which allows a safe transfer of this procedure to production scale. All chemicals used in this synthesis are readily available in commercial quantities.

This resolution represents, to the best of our knowledge, the only example of a resolution of an aliphatic β-amino acid reported in the literature.

## 4. Experimental

### 4.1. *rac*-3-Amino-4,4-dimethylpentanoic acid; *rac*-β-neopentylglycine

A 50 l vessel was charged with ethanol (33.8 l), malonic acid (5.55 kg, 53.3 mol), pivaldehyde (4.56 kg, 52.9 mol) and ammonium acetate (6.60 kg, 85.7 mol). The reaction mixture was heated for 16 h at 80 °C and cooled to room temperature. Filtration of the reaction mixture and washing of the cake with a small amount of ethanol (0.8 l) were followed by the removal of the volatiles by distillation under reduced pressure at 80 °C. The subsequent residue was slurried in ethyl acetate (76 l), filtered and washed with a second amount of ethyl acetate (11.5 l). The cake was reslurried in acetone (52 l) and filtered. The residue was then dissolved in a hot (75 °C) mixture of ethanol (18.3 l) and water (4.8 l). After cooling to room temperature, the solids were isolated to give a first crop of crude product (3.2 kg). The filtrate was concentrated under reduced pressure and cooled to give a second crop (0.45 kg). At this point, the crude products still contained some malonic acid. Therefore, the whole was taken up in hot ethanol. After cooling, the solid was isolated by filtration and was dried to give 3-amino-4,4-dimethylpentanoic acid (2.77 kg, 18.6 mol, 36.1%) as a white crystalline solid. A small sample was recrystallised from a mixture of acetone, ethanol and water for analytical purposes; $^1$H NMR (500 MHz, DMSO-$d_6$ + HCl) $\delta$: 0.91 (s, 9H, *t*-Bu), 2.44 (dd; $J$ = 17.7, 7.7 Hz; 1H; $H_2$), 2.64 (dd, $J$ = 17.7, 4.4 Hz, 1H, $H_{2'}$), 3.18–3.25 (m, 1H, $H_3$), 7.98 (s, 3H, $NH_3^+$); $^{13}$C NMR (125 MHz, DMSO-$d_6$ + HCl) $\delta$: 26.1 (q), 33.4 (t), 34.0 (s), 56.5 (d), 172.6 (s); IR (KBr), $\lambda^{-1}$ (cm$^{-1}$): 3398, 2960, 1582, 1559, 1396.

### 4.2. *rac*-3-Benzyloxycarbonylamino-4,4-dimethylpentanoic acid; *rac-Cbz*-β$^3$-neopentylglycine

Racemic β-neopentylglycine (3.5 kg, 24.1 mol) was dissolved in water (18.2 l) and the pH of the solution was adjusted to 11 with concentrated NaOH (50% in water). At 0 °C, a 50% solution of *Cbz*-chloride (9.6 kg, 28.2 mol) in toluene was added while maintaining the pH of the solution between 10.5 and 11.5 with 50% sodium hydroxide. After the reaction was complete, the toluene layer was separated and the aqueous layer was washed with toluene (3 × 6 l). Acidification of the aqueous layer with aq. HCl (32%, 4.0 l) to pH 2 resulted in the separation of some solids that were extracted with two portions of toluene (17 and 14 l). The organic layer was isolated, and toluene was removed under reduced pressure. Water (25 l) was added to the residue and heating was continued to distill off all toluene. The cake isolated after cooling of the mixture was reslurried in water (20 l) and stirred for 6 h. The final product (5.23 kg, 18.7 mol, 77.6%) was obtained as a white solid after drying at 80 °C under reduced pressure; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 0.83 (s, 9H, *t*-Bu), 2.18 (dd, $J$ = 15.3, 10.7 Hz, 1H, $H_2$), 2.46 (dd, $J$ = 15.3, 3.0 Hz, 1H, $H_{2'}$), 3.72–3.82 (m, 1H, $H_3$), 4.99 (d, $J$ = 12.7 Hz, 1H, $H_{benzyl}$), 5.03 (d, $J$ = 12.7 Hz, 1H, $H_{benzyl'}$), 6.80 (d, $J$ = 9.6 Hz, 1H, $NH_{minor\ rotamer}$), 7.14 (d, $J$ = 9.6 Hz, 1H, $NH_{major\ rotamer}$), 7.25–7.39 (m, 5H, arom.); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 26.6 (q), 35.2 (t), 35.8 (s), 56.7 (d), 65.3 (t), 127.8 (d), 128.0 (d), 128.7 (d), 137.8 (s), 156.4 (s), 173.5 (s); IR (KBr), $\lambda^{-1}$ (cm$^{-1}$): 3320, 2966, 1730, 1697, 1544, 1260, 1058, 697.

### 4.3. (*S*)-3-Benzyloxycarbonylamino-4,4-dimethylpentanoic acid, L-(−)-Norephedrine salt

Racemic *Cbz*-protected β-neopentylglycine (150 g, 537 mmol) was suspended in toluene (1.5 l). This mixture was heated to 80–90 °C and L-(−)-norephedrine (44.7 g, 296 mmol, 0.55 equiv) was added to the slightly turbid solution as a solid. The resulting solution was allowed to reach room temperature in 4 h and was then cooled in an ice bath for 1 h. The solids were filtered off, washed with cold toluene (2 × 100 ml) and dried at 50 °C under reduced pressure. It should be noted that complete removal of all the toluene can take up to 2 days. The dried solid was weighed (95.3 g, 221 mmol, 41.2%) and analysed by HPLC (ratio (*R*):(*S*) = 2.8:97.2). In order to obtain a diastereomerically pure product, the product was recrystallised from a mixture of toluene (720 ml) and ethanol (190 ml). The salt dissolved at close to 100 °C in the solvent mixture and was heated at reflux for 20 min. On cooling to room temperature over ca. 3 h, a fluffy solid formed. After further cooling in an ice bath and stirring for an additional hour, the solids were isolated by filtration and then dried at 50 °C to give the diastereomerically pure product as a fluffy solid (83.9 g, 194 mmol, 36.1%); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 0.83 (s, 9H, *t*-Bu, β-AA), 0.86 (d, *J* = 6.5 Hz, 3H, Me, L-nor.), 2.13 (dd, *J* = 15.0, 9.6 Hz, 1H, $H_2$, β-AA), 2.34 (dd, *J* = 15.0, 3.5 Hz, 1H, $H_{2'}$, β-AA), 3.02–3.12 (m, 1H, $H_2$, L-nor.), 3.68–3.82 (m, 1H, $H_3$, β-AA), 4.56 (d, *J* = 4.2 Hz, 1H, $H_1$, L-nor.), 4.95 (d, *J* = 12.7 Hz, 1 H, $H_{benzyl}$, β-AA), 5.02 (d, *J* = 12.7 Hz, 1H, $H_{benzyl'}$, β-AA), 6.83 (d, *J* = 9.6 Hz, 1H, $NH_{minor\ rotamer}$, β-AA), 7.20–7.38 (m, 11H, arom., 5H β-AA, 5H L-nor., 1H $NH_{major\ rotamer}$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 16.1 (q, L-nor.), 26.7 (q, β-AA), 35.4 (t, β-AA), 37.0 (s, β-AA), 50.2 (d, L-nor.), 57.0 (d, β-AA), 65.2 (t, β-AA), 75.4 (d, L-nor.), 126.7 (d, L-nor.), 127.1 (d, L-nor.), 127.8 (d, β-AA), 127.9 (d, β-AA), 128.2 (d, L-nor.), 128.6 (d, β-AA), 137.9 (s, β-AA), 143.3 (s, L-nor.), 156.4 (s, β-AA), 174.8 (s, β-AA); $[\alpha]_D^{20} = -6.4$ (*c* 1, EtOH); IR (KBr), $\lambda^{-1}$ (cm$^{-1}$): 3369, 2965, 1692, 1543, 1401, 1259, 1062, 738, 700.

### 4.4. (*S*)-3-Benzyloxycarbonylamino-4,4-dimethylpentanoic acid; (*S*)-Cbz-β-*neopentylglycine*

The L-(−)-norephedrine salt of (*S*)-3-benzyloxycarbonylamino-4,4-dimethylpentanoic acid (83.4 g, 194 mmol) was added to a mixture of ethyl acetate (300 ml) and water (250 ml) in a three-necked flask. The pH was adjusted to 2 by the dropwise addition of hydrochloric acid (32%, 22 ml), while the mixture was vigorously stirred. The water phase was separated and extracted twice with ethyl acetate (2 × 100 ml). The combined organic layers were washed with brine (8%, 200 ml) and dried over sodium sulfate. Removal of the solvent afforded the protected amino acid as a white solid (51.9 g, 186 mmol, 95.9%); The shifts in the $^1$H and $^{13}$C NMR spectra were identical to those reported for the racemate above; Elemental Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.34; H, 7.61; N, 5.28; $[\alpha]_D^{20} = +13.4$ (*c* 1.4, $CHCl_3$); determination of the enantiomeric purity was performed by HPLC using a Chiralcel AD Column as the stationary phase and a mixture of *i*-hexane/*i*-propanol/trifluoroacetic acid = 850:150:1 as the eluent using a flow of 1 ml min$^{-1}$ at 30 °C. The separations were performed using ca. 10 mg of the substance, dissolved in 10 ml of the eluent. The detection was performed at 215 nm; the enantiomeric purity of the sample proved to be 99.9% for the (*S*)-enantiomer; IR (KBr), $\lambda^{-1}$ (cm$^{-1}$): 3419, 3092, 2967, 1723, 1668, 1541, 1255, 756, 625, 546.

### 4.5. (*S*)-3-Amino-4,4-dimethylpentanoic acid; (*S*)-β-neopentylglycine

(*S*)-3-Benzyloxycarbonylamino-4,4-dimethylpentanoic acid (20.0 g, 71.6 mmol) was dissolved in a mixture of ethanol (160 ml) and water (40 ml) and filled into an autoclave. Palladium on carbon (1.0 g, 5%) was added, and the mixture was flushed three times with hydrogen. The reaction mixture was left to stir at 50 °C for 24 h under 10 bar hydrogen. The catalyst was removed by filtration, leaving a colourless solution. Removal of all volatiles left the enantiomerically pure amino acid as a white solid (9.77 g, 67.4 mmol, 94.1%); The shifts in the $^1$H and $^{13}$C NMR spectra were identical to those reported for the racemate above; $[\alpha]_D^{20} = -67.7$ (*c* 1, $H_2O$). The determination of the enantiomeric purity was performed by GC using a Chirasil Dex CB column. Sample preparation: 2.5 mg of the sample was treated with 500 µl 3 M hydrochloric acid in ethanol (prepared by mixing 37 ml of ethanol and 10 ml of acetyl chloride) for 45 min at 110 °C. All solvents were removed in a nitrogen stream and the residue was subsequently treated with a mixture of 200 µl dichloromethane and 200 µl trifluoroacetic acid anhydride for 10 min at 110 °C. After removal of all volatiles, the remaining material was dissolved in 150 µl of toluene and analysed. Temperature program: 70 °C for 1 min then an increase of 3 °C min$^{-1}$ until 160 °C; then at 160 °C for 1 min; sample volume 0.2 µl; hydrogen gas as mobile phase; split 70:1; The enantiomeric purity of the sample proved to be 99.9% for the (*S*)-enantiomer; IR (KBr), $\lambda^{-1}$ (cm$^{-1}$): 2966, 1639, 1494, 1464, 1387, 1146.

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38. The absolute configuration of the resolved *Cbz*-$\beta^3$-amino acid was assigned by comparison with a reference sample of (*R*)-*Cbz*-$\beta^3$-neopentylglycine.