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An efficient synthesis of (*S*)-3-aminomethyl-5-methylhexanoic acid (Pregabalin) via quinine-mediated desymmetrization of cyclic anhydride

Zdenko Hameršak,[a,*] Irena Stipetić[a] and Amir Avdagić[b]

[a]*Department of Organic Chemistry and Biochemistry, Rudjer Bošković Institute, PO Box 180, 10002 Zagreb, Croatia*
[b]*PLIVA Research and Development Ltd, Prilaz Baruna Filipovića 29, 10000 Zagreb, Croatia*

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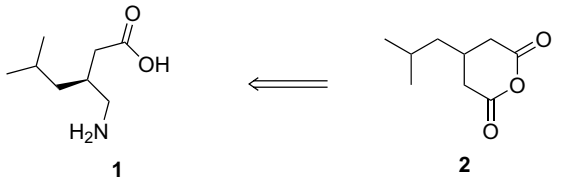
Abstract—A highly enantioselective synthesis of (*S*)-3-aminomethyl-5-methylhexanoic acid **1** (Pregabalin) is reported. The key step of the synthesis is a quinine-mediated ring opening of 3-isobutylglutaric anhydride with cinnamyl alcohol. A Curtius rearrangement and subsequent deprotection provides **1** in high yield and excellent enantiomeric excess.

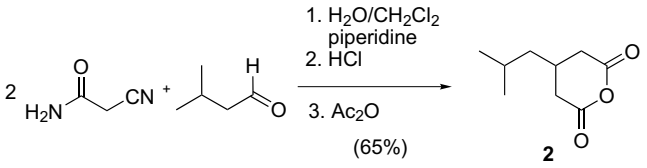
1. Introduction

(*S*)-3-Aminomethyl-5-methylhexanoic acid **1** (Pregabalin), was designed as a more potent gabapentine substitute, an anticonvulsant drug used for neuropatic pain treatment. It has also been found to be more active in preclinical models of epilepsy.[1] Since only the (*S*)-enantiomer possesses the required biological activity, stereoselective syntheses of (*S*)-pregabalin are of great interest. The first syntheses were evaluated by Hoekstra et al.[2] in the Warner–Lambert laboratories, including several manufacturing processes. More recent examples of stereoselective syntheses of (*S*)-pregabalin and its analogues are covered by a review of Ordónez and Cativiela.[3] One of the preferred processes comprises of the aminolysis of 3-isobutylglutaric anhydride **2** followed by a Hoffman rearrangement.[2] Enantiopurity was obtained either by the resolution of the intermediary amide with (*R*)-(+)-1-phenylethylamine or racemic 3-aminomethyl-5-methylhexanoic acid *rac*-**1** with (*S*)-(+)-mandelic acid. The fact that the resolutions provide Pregabalin in about 30% yield motivated us to explore the option of an enantioselective desymmetrization of **2**.

2. Results and discussion

3-Isobutylglutaric anhydride **2** was prepared starting from cyanoacetamide and isovaleraldehyde by a modified procedure of Day and Thorpe,[4] without the isolation of intermediates (Scheme 1). The piperidine catalyzed condensation of 2 equiv of cyanoacetamide with isovaleraldehyde was performed in a two-phase system (water–dichloromethane, emulsion), which ensured acceptable fluidity of the reaction mixture. Upon hydrolysis with 6 M hydrochloric acid, the crude product was converted to the anhydride by the action of acetic anhydride. Pure 3-isobutylglutaric anhydride **2** was obtained by vacuum distillation in 65% yield.





Scheme 1.

* Corresponding author. Fax: +385 1 4680108; e-mail: hamer@irb.hr

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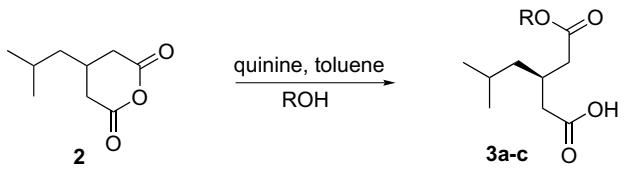
Desymmetrization of *meso* compounds has proven to be a valuable approach in the synthesis of chiral compounds.[5] The first catalytic ring opening of cyclic anhydrides was reported by Oda[6] and shortly thereafter by Aitken.[7] When cinchona alkaloids were used as catalysts and methanol as the nucleophile, monoesters were obtained in about 70% ee. Deng[8] has reported excellent enantioselectivities (90–98%) using modified bis-cinchona alkaloids—$(DHQ)_2AQN$ and $(DHQD)_2AQN$. Since the use of catalytic quantities of alkaloids is practically limited to methanol as the nucleophile and requires several days for completion, we decided to utilize Bolm's[9] findings and use an equimolar quantity of base. As the stereochemical outcome of the desymmetrization of cyclic anhydrides was found to be highly predictable,[9–11] quinine was employed as the base.

In preliminary experiments (Table 1, Scheme 2) the influence of base quantity, temperature and the choice of nucleophile on the reaction was examined. The alcoholic nucleophiles used were chosen for the reason of their specific cleavage as protective groups.[12] Comparable results were obtained with benzyl and cinnamyl alcohols. A decrease in temperature of 10 °C resulted in an increase of ee by more than 5% with all nucleophiles. The reaction with *p*-methoxybenzyl alcohol was significantly faster, however, in these cases, lower ees were obtained. The lower ee resulting from the use of just 1 equiv of the base was noticed by Bolm[13] with methanol as the nucleophile. Nevertheless, we wanted to verify if the same effect was present with cinnamyl alcohol. Lower yields on isolated monoesters **3a–c** compared to the conversion can be attributed to the emulsification properties of their potassium salts during the work-up.

Table 1. Influence of base quantity, conditions and nucleophile on opening of anhydride **2**[a]

	R/equiv	Quinine (equiv)	°C	Time (h)	Yield[b] (%)	ee[c] (%)
3a	Cinnamyl/2	1.2	−15	22	78	61
3b	*p*-Metoxybenzyl/2	1.2	−15	8	74	50
3c	Benzyl/2	1.2	−15	18	69	58
3a	Cinnamyl/2	1.2	−25	23	78	67
3b	*p*-Metoxybenzyl/2	1.2	−25	12	68	58
3c	Benzyl/2	1.2	−25	23	72	64
3a	Cinnamyl/2	1.0	−25	23	68	62
3a	Cinnamyl/1.3	1.1	−25	25	85	69

[a] The reactions were performed with 1.0 g of anhydride in 50 mL of toluene and were quenched with 5% HCl when over 95% of the anhydride had been consumed.
[b] Isolated yield.
[c] Determined by chiral HPLC.



Scheme 2.

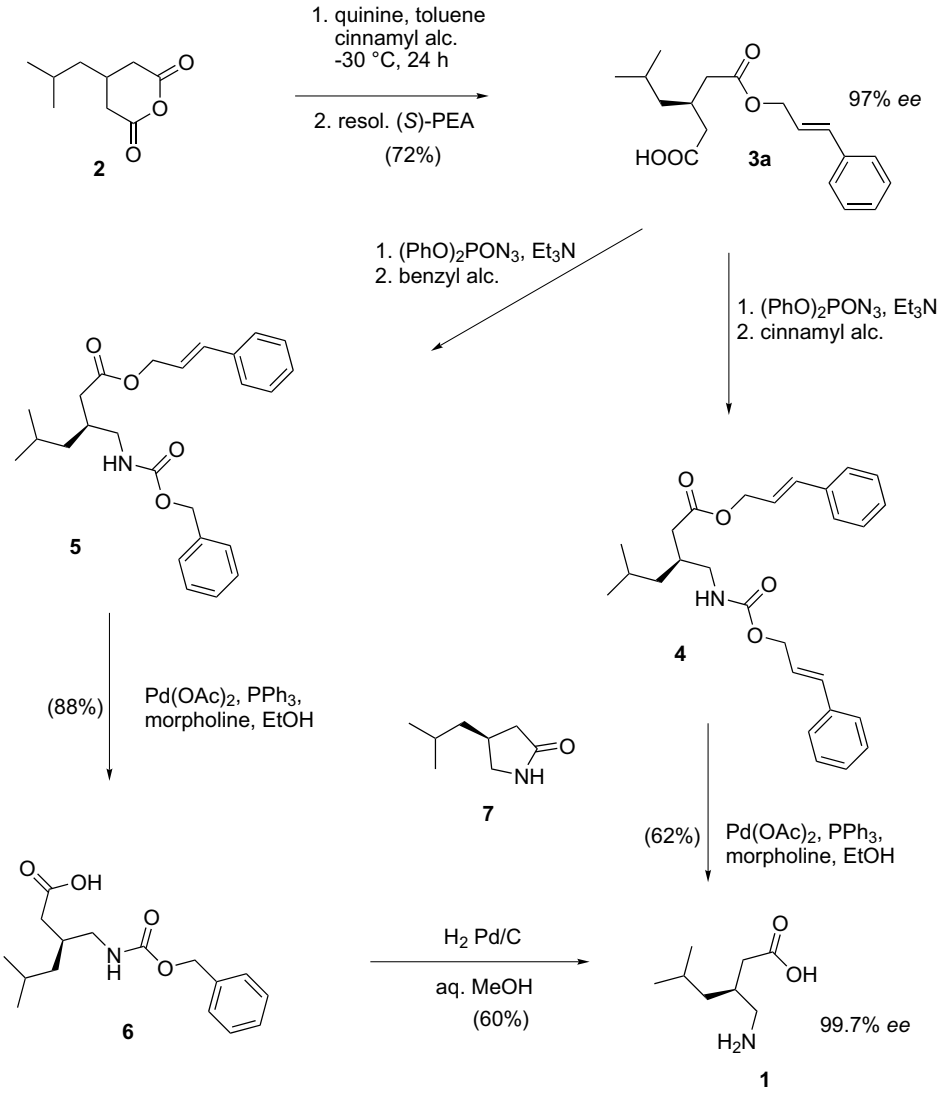
All racemic and enantiomerically enriched monoesters appeared to be oily materials; consequently further enantiomeric enrichment needed to be performed via diastereomeric salts. Amongst the variety of chiral amines screened, (*S*)-1-phenylethylamine [(*S*)-PEA] proved to be the best choice in combination with the cinnamyl monoester.

On a preparative scale, the reactions were performed at −30 °C in toluene with 1.1 equiv of quinine and 1.3 equiv of cinnamyl alcohol (Scheme 3). After 28 h, the reaction was stopped by dil. HCl and solvent was evaporated. HPLC analysis revealed 72% ee. The oily residue was dissolved in MTBE, warmed to 45 °C and (*S*)-PEA then added, followed by seed crystals. The crystal slurry was stirred for another 12 h at 25 °C to yield pure *S*-PEA salt in 73% yield and 97% ee upon filtration. This method ensures not only an acceptable enrichment of enantiopurity, but also opens up the possibility of avoiding the usual tedious work-up, which comprises of successive washing of alkaline aqueous solution of the monoester with organic solvent to remove residual alcohol.[9]

In the next step, the liberated monoester ester **3a** was converted into the protected β-amino acid ester derivative **4** by a Curtius rearrangement using diphenyl phosphoryl azide-triethylamine followed by reaction of the intermediate isocyanate with cinnamyl alcohol in refluxing toluene. The crude oily product contained about 10% cinnamyl alcohol, together with some minor impurities and was used in the next step without purification. Small quantities of the material were purified by chromatography, although the method is highly impractical for scale-up.

In the last step, the protective groups in **4** were removed by transallylation of morpholine as a nucleophile in refluxing ethanol, catalyzed with palladium acetate-triphenyl phosphine. The precipitated product was crystallized from aqueous 2-propanol. Pregabalin **1** was obtained in 62% yield (calculated from monoester **3a**) and 99.7% ee. It was reported by Hoekstra et al.[2] that, when a free amino group exists in the neighbourhood of an ester group during Pregabaline syntheses, a significant amount of lactame **7** is formed. However, during the synthesis of cyclic β-amino acids by the same reaction sequence,[14] we observed that the cinnamyl ester group was cleaved faster than the carbonylamino protection. With that fact in mind we hoped that the lactam formation would be largely suppressed. Indeed, only about 5% of lactam **7** was formed during the reaction.

The fact that the starting compound **4** was to be used as a crude material and that, under such circumstances present impurities can influence the efficiency of palladium acetate-triphenyl phosphine catalyzed deprotection and enlarge the quantity of lactam by-product, forced us to examine an alternative route from **3a** to **1**. Therefore, instead of cinnamyl alcohol, the benzyl alcohol was used in the Curtius rearrangement. Cinnamyl protection of **5** was cleaved by palladium acetate-triphenyl phosphine as before, to afford amino-protected acid **6**, which was purified via its sodium salt. Finally, Pregabalin **1** was obtained by Pd/C catalyzed



Scheme 3.

hydrogenation in 53% yield (calculated from monoester **3a**) and 99.7% ee.

3. Conclusion

In conclusion, a convenient enantioselective synthesis of (*S*)-3-aminomethyl-5-methylhexanoic acid **1** (Pregabalin) was developed. The key step of the synthesis was a quinine-mediated opening of 3-isobutylglutaric anhydride with cinnamyl alcohol. The Curtius rearrangement of the intermediary monoester and subsequent cleavage of protective groups afforded Pregabalin in 45% overall yield and 99.7% ee.

4. Experimental

4.1. General

Melting points were determined on Electrothermal 9100 apparatus in open capillaries and are not corrected. Optical rotations were measured using Optical Activity AA-10 automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 300 and AV 600 spectrometers, IR spectra on a Bruker ABB Bomen instrument. For the chemical purity determination, and monitoring of the progress of the reactions HP 5890 GC, and HP 1090 HPLC chromatographs were used. Ees of monoestes **3a**–**c** were determined on Chiralpak AS column (*n*-hexane–EtOH–TFA, 95:5:0.2). The enantiomeric purity of **1** was determined by conversion to its derivative with Marfey's reagent (*N*-α-(2,4-dinitro-5-fluorophenyl)-L-alaninimide)[15] followed by analysis on a Nucleosil 100-5 C18 column (0.05 M aqueous triethylamine (pH adjusted to 3 with H_3PO_4)–acetonitrile, 55:45). All other reagents and solvents were purchased from commercial sources and used without purification.

4.2. 3-Isobutylglutaric anhydride 2

Cyanoacetamide (52.0 g, 0.62 mol) was suspended in 220 mL of water and heated to 30 °C until it dissolved.

The solution was cooled to 20 °C, after which piperidine (2 mL, 1.72 g, 20.2 mmol) was added, followed by isovaleraldehyde (33.6 mL, 26.8 g, 0.31 mol) over 10 min while keeping the temperature below 25 °C. After 15 min of stirring, the reaction mixture became turbid and 160 mL of dichloromethane was added. The resulting thick emulsion was stirred for another 6 h at 22–25 °C. Concd HCl (220 mL) was added, after which dichloromethane was distilled out, followed by a few millilitres of aq HCl until the reaction mixture temperature reached 108 °C. The reaction mixture was refluxed for 20 h after which an oily product was collected with dichloromethane (50 + 30 mL). Most of the solvent was distilled. Acetic anhydride (110 mL) was then added and the reaction mixture kept at gentle reflux for 2 h accompanied by separation of residual dichloromethane and acetic acid formed. The majority of the acetic anhydride was removed by vacuum distillation at 20 mmHg and then upon rejection of the small prefraction, the main fraction was collected at 100–105 °C/0.5 mmHg to yield 34 g (65%) of anhydride **2**, which was >98% pure by GC. ^{1}H NMR ($CDCl_3$), δ/ppm: 0.91 (d, 6H, $J = 6.6$ Hz), 1.27 (t, 2H, $J = 7.1$ Hz), 1.61–1.75 (m, 1H), 2.12–2.50 (m, 3H), 2.85 (dd, 2H, $J_1 = 17$ Hz, $J_2 = 4.1$ Hz). ^{13}C NMR ($CDCl_3$), δ/ppm: 21.8, 24.2, 25.9, 35.4, 43.1, 166.5.

4.3. (−)-(*R*)-3-Isobutyl-pentanedioic acid mono-(3-phenyl-allyl) ester 3a

To a suspension of quinine (31.5 g, 97 mmol) and cinnamyl alcohol (17.7 g, 132 mmol) in toluene (370 mL), a solution of anhydride **2** (15.0 g, 88 mmol) in 10 mL of toluene was added over 10 min while keeping the temperature at −30 °C. The reaction mixture was stirred at the same temperature for 24 h after which it was then allowed to warm-up (for 4–5 h) to −5 °C. The toluene solution was washed with 5% HCl (250 mL), brine (150 mL) and evaporated. HPLC analysis revealed 72% ee. The oily residue was dissolved in 200 mL of MTBE, warmed to 45 °C and (*S*)-phenylethyl amine (8.6 g, 70 mmol) was added, followed by few milligrams of seed crystals. The crystal slurry was stirred at 45 °C for an hour and then at rt overnight. Filtration yielded 27.3 g (73%) of amine salt (97% ee). $[\alpha]_D^{25} = -7.0$ (*c* 1, EtOH), mp = 108.5–110 °C. ^{1}H NMR ($CDCl_3$), δ/ppm: 0.85 (d, 6H, $J = 6.4$ Hz), 1.12–1.15 (m, 2H), 1.50–1.60 (m, 6H), 2.01–2.14 (m, 2H), 2.21–2.40 (m, 3H), 4.19 (q, 1H, $J = 6.7$ Hz), 4.69 (d, 2H, $J = 6.2$ Hz), 6.25 (dt, 1H, $J_1 = 15.8$ Hz, $J_2 = 6.5$ Hz), 6.62 (d, 1H, $J = 15.8$ Hz), 7.18–7.43 (m, 10H). ^{13}C NMR ($CDCl_3$), δ/ppm: 22.4, 22.5, 22.6, 25.0, 30.2, 38.9, 40.7, 43.5, 50.8, 64.7, 123.2, 126.2, 126.4, 127.7, 127.8, 128.4, 128.6, 133.9, 136.1, 142.3, 172.8, 178.0. IR (KBr): 2952, 2923, 2867, 2702, 1742, 1541, 1401, 1161, 1142, 970, 751, 698 cm^{-1}.

The (*S*)-PEA salt was suspended in toluene (150 mL) and stirred with 3% HCl (100 mL) until a clear solution was obtained. The organic layer was washed once again with 3% HCl (30 mL) and brine (50 mL). The toluene solution can be used directly in the subsequent reaction; otherwise evaporation of solvent provides monoester **3a** quantitatively.

Compound **3a**: $[\alpha]_D^{25} = -0.53$ (neat) ^{1}H NMR ($CDCl_3$), δ/ppm: 0.87 (d, 6H, $J = 6.5$ Hz), 1.21–1.27 (m, 2H), 1.56–1.70 (m, 1H), 2.38–2.48 (m, 5H), 4.73 (dd, 2H, $J_1 = 6.5$ Hz, $J_2 = 1.2$ Hz), 6.27 (dt, 1H $J_1 = 15.8$ Hz, $J_2 = 6.5$ Hz), 6.65 (d, 1H, $J = 15.8$ Hz), 7.22–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$), δ/ppm: 22.3, 25.1, 29.6, 38.3, 38.5, 43.3, 64.9, 122.9, 126.5, 127.9, 128.5, 134.18, 136.1, 172.2, 178.6. IR (film on KBr): 2956, 2927, 2871, 1734, 1707, 1168, 966, 745, 692 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_4$ (304.38): C, 71.03; H, 7.95. Found: C, 70.86; H, 8.02.

4.4. (−)-(*S*)-5-Methyl-3-[(3-phenyl-allyloxycarbonilamino)-methyl]-hexanoic acid 3-phenyl-allyl ester 4

To a dry toluene solution (140 mL) of monoester **3a** (18.6 g, 60.6 mmol) and triethylamine (8.3 mL, 60.6 mmol) diphenylphosphoryl azide (13.0 mL, 60.6 mmol) was added at 20 °C. The reaction mixture was stirred for 30 min and then slowly warmed to 90 °C. When nitrogen evolution ceased (30–45 min), cinnamyl alcohol (9.7 g, 72.7 mmol) was added and the mixture was refluxed overnight. The reaction mixture was washed with a solution of 1% $NaNO_2$ and 1.5% $NaHCO_3$ in H_2O (2 × 100 mL) and with H_2O (100 mL). Evaporation of the solvent yielded 24.9 g of crude oily carbamate, which was used without further purification in the next step. For characterization, the product was purified on silica gel using EtOAc–hexane (1:1) as eluent. Mp 53.5–54.5 °C; $[\alpha]_D^{25} = -4.3$ (*c* 20, EtOH). ^{1}H NMR ($CDCl_3$), δ/ppm: 0.88 (d, 3H, $J = 6.4$ Hz), 0.90 (d, 3H, $J = 6.4$ Hz), 1.09–1.25 (m, 2H), 1.63–1.71 (m, 1H), 2.15–2.38 (m, 3H), 3.05–3.18 (m, 1H), 3.25–3.33 (m, 1H), 4.68–4.75 (m, 4H), 4.96 (br s, 1H), 6.22–6.32 (m, 2H), 6.62 (d, 1H, $J = 15.8$ Hz), 6.65 (d, 1H, $J = 15.8$ Hz), 7.15–7.50 (m, 10H). ^{13}C NMR ($CDCl_3$), δ/ppm: 22.5, 25.0, 33.5, 37.3, 41.3, 44.6, 65.0, 65.3, 122.9, 123.8, 126.45, 126.5, 127.8, 127.9, 128.4, 128.5, 133.4, 134.2, 136.0, 136.2, 156.3, 172.8. IR (KBr): 3355, 3026, 2957, 1726, 1692, 1682, 1534, 1252, 1178, 968, 751, 691 cm^{-1}. Anal. Calcd for $C_{27}H_{33}NO_4$ (435.56): C, 74.45; H, 7.64; N, 3.22. Found: C, 74.65; H, 7.88; N, 3.02.

4.5. (+)-(*S*)-3-Aminomethyl-5-methyl-hexanoic acid 1

A solution of crude carbamate **4** (24.9 g) in abs EtOH (100 mL) was refluxed for 10 min, and then cooled to 70 °C. Morpholine (21 mL, 230 mmol) was added followed by triphenylphosphine (120 mg, 0.46 mmol) and $Pd(OAc)_2$ (3 mg, 0.01 mmol). The reaction mixture was refluxed for 3 h, and then slowly cooled to room temperature. After 5 h, the product was collected by filtration and dried at reduced pressure (6.9 g, 71%, 99.1% ee). Crystallization from aqueous 2-PrOH afforded 6.0 g (62% from **3a**) of pure amino acid (99.7% ee). Mp 195 °C (decomp.) lit.[2] 177–179 °C (decomp.), $[\alpha]_D^{25} = +10.8$ (*c* 1, H_2O), (lit.[2] $[\alpha]_D^{25} = +10.1$ (*c* 1.1, H_2O). ^{1}H NMR (D_2O), δ/ppm: 0.87 (d, 3H, $J = 6.5$ Hz), 0.89 (d, 3H, $J = 6.5$ Hz), 1.21 (t, 2H, $J = 7.0$ Hz), 1.58–1.72 (m, 1H), 2.07–2.35 (m, 3H), 2.90–3.05 (m, 2H). ^{13}C NMR (D_2O), δ/ppm: 21.6, 22.1, 24.5, 41.8, 40.7, 40.9, 43.8, 181.3. IR (KBr): 2956, 2925, 1641, 1549, 1390, 1332, 1278, 700 cm^{-1}. Anal. Calcd for $C_8H_{17}NO_2$ (159.23): C, 60.35; H, 10.76; N, 8.80. Found: C, 60.61; H, 10.53; N, 8.99.

4.6. (−)-(*S*)-3-(Benzyloxycarbonylamino-methyl)-5-methyl-hexanoic acid 3-phenyl-allyl ester 5

To a dry toluene solution (100 mL) of monoester **3a** (15.0 g, 49 mmol), triethylamine (6.7 mL, 49 mmol) and diphenylphosphoryl azide (10.5 mL, 49 mmol) were added at 20 °C. The reaction mixture was stirred for 30 min and then slowly warmed to 90 °C. When nitrogen evolution ceased (30–45 min), benzyl alcohol (6.3 g, 49 mmol) was added and the mixture refluxed overnight. The reaction mixture was washed with a solution of 1% $NaNO_2$ and 1.5% $NaHCO_3$ in H_2O (2×100 mL), then with H_2O (100 mL) and evaporated under reduced pressure to yield 18.4 g of crude oily carbamate, which was used without further purification in the next step. For spectroscopic determination the product was purified by chromatography on silica gel. $[\alpha]_D^{25} = -4.2$ (*c* 20, EtOH). ^{1}H NMR ($CDCl_3$), δ/ppm: 0.82–0.93 (m, 6H), 1.13–1.20 (m, 2H), 1.60–1.70 (m, 1H), 2.14–2.42 (m, 3H), 3.06–3.16 (m, 1H), 3.23–3.33 (m, 1H), 4.70–4.75 (m, 2H), 4.95 (br s, 1H), 5.06–5.10 (m, 2H), 6.26 (dt, 1H, $J_1 = 15.8$ Hz, $J_2 = 6.5$ Hz), 6.63 (d, 1H, $J = 15.8$ Hz), 7.13–7.45 (m, 10H). ^{13}C NMR ($CDCl_3$), δ/ppm: 22.5, 22.6, 25.0, 33.5, 37.2, 41.3, 44.6, 65.0, 66.5, 122.9, 126.5, 128.0, 128.4, 128.5, 134.2, 136.0, 156.4, 172.7. IR (film on KBr): 3346, 3033, 2954, 2935, 2867, 1726, 1523, 1247, 1169, 967, 746, 694 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_4$ (409.52): C, 73.32; H, 7.63; N, 3.42. Found: C, 73.03; H, 7.50; N, 3.21.

4.7. (−)-(*S*)-3-(Benzyloxycarbonylamino-methyl)-5-methyl-hexanoic acid 6

A solution of crude carbamate **5** (18.4 g) in abs EtOH (100 mL) was refluxed for 10 min, and then cooled to 70 °C. Morpholine (8.1 mL, 90 mmol) was added followed by triphenylphosphine (95 mg, 0.36 mmol) and $Pd(OAc)_2$ (2 mg, 0.009 mmol). The reaction mixture was refluxed for 3 h. Most of the solvent was evaporated at a reduced pressure, 200 mL of 3% Na_2CO_3 and 80 mL of EtOAc were added. The mixture was stirred for 15 min, after which the aqueous layer was separated and washed again with EtOAc. Upon acidification to pH 1.5 with concd HCl, extraction with CH_2Cl_2 afforded 12.7 g (88% from monoester **3a**) of oily benzyl-carbamate **6**. $[\alpha]_D^{25} = -4.4$ (*c* 25, EtOH). ^{1}H NMR (DMSO), δ/ppm: 0.81–0.85 (m, 6H), 1.00–1.16 (m, 2H), 1.55–1.66 (m, 1H), 1.91–2.27 (m, 3H), 2.84–3.09 (m, 2H), 5.01 (s, 2H), 7.26–7.28 (m, 5H). ^{13}C NMR (DMSO), δ/ppm: 22.9, 23.2, 25.1, 33.6, 37.6, 41.4, 44.3, 65.6, 128.1, 128.2, 128.7, 137.8, 156.8, 174.4. IR (film on KBr): 3340, 2956, 2929, 2871, 1708, 1534, 1258, 697 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_4$ (293.36): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.78; H, 8.12; N, 4.51.

4.8. (+)-(*S*)-3-Aminomethyl-5-methyl-hexanoic acid 1 from 6

Benzyl-carbamate **6** (12.7 g, 43 mmol) was dissolved in 100 mL of methanol, 0.6 g of Pd/C (10%) was added, after which the mixture was hydrogenated at rt and 10 bar of hydrogen pressure.

After 15 h, 50 mL of water was added, warmed to 50 °C and filtered hot. The filter was carefully washed with hot aqueous methanol. The filtrate was concentrated to 25 mL. 2-Propanol (100 mL) was added and left to crystallize for 3 h. Filtration yielded 4.1 g (60%) of Pregabaline **1** (99.7% ee). The IR, ^{1}H NMR and ^{13}C NMR spectra are coincidental to those of **1** obtained from **4**.

Acknowledgements

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