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Development of a Chemoenzymatic Route to (*R*)-Allyl-(3-amino-2-(2-methylbenzyl)propyl)carbamate

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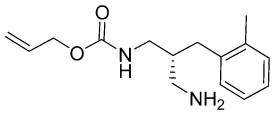
ABSTRACT: A chemoenzymatic route to (*R*)-allyl-(3-amino-2-(2-methylbenzyl)propyl)carbamate (**1**-(*R*)) has been developed on a kilogram scale. The key intermediate, 2-(2-methylbenzyl)propane-1,3-diamine **4**, was isolated as a tartrate salt in a three-step sequence starting from 2-methylbenzyl chloride. The subsequent lipase-catalyzed desymmetrization was optimized, and **1**-(*R*) was isolated as the D-tartrate salt.

INTRODUCTION

To support preclinical and clinical studies in an internal drug discovery program, a kilogram amount of (*R*)-allyl-(3-amino-2-(2-methylbenzyl)propyl)carbamate **1**-(*R*) was needed (Figure 1).

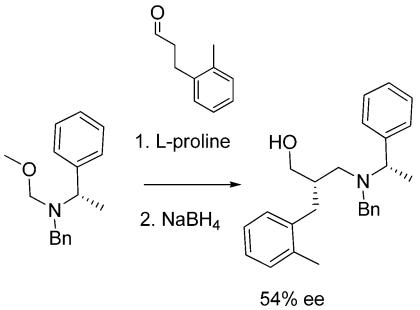


1-(*R*)

Figure 1. Structure of **1**-(*R*).

Initially, the material was prepared by a six-step route, starting from 3-(*o*-tolyl)propanal.[1] The key step was a proline-catalyzed diastereoselective aminomethylation (Scheme 1). In our hands, the diastereoselectivity obtained was 54% ee. The combination of poor diastereoselectivity, the need for chromatography, and the number of steps limited the applicability of this organocatalyzed route on scale.

Scheme 1. Proline-Catalyzed Diastereoselective Aminomethylation



54% ee

DISCUSSION

The work of Riva[2] and Gotor[3a−d] prompted us to investigate the hydrolase-catalyzed desymmetrization of 2-(2-methylbenzyl)propane-1,3-diamine **4** as an alternative and scaleable route to **1**-(*R*). The substrate **4** and closely related precursors have been prepared in a number of ways: malonicesters[4] or malononitrile[5] have been alkylated with benzyl halides, benzaldehydes have been condensated with nitromethane[6,3c] and malononitrile,[7a−c] and alkoxycarbonylation of aryl alkyl acids[3a−c] has also been reported.

Investigated Routes to Diamine 4. Three routes were chosen for a more thorough investigation: (1) condensation of malonitrile and 2-methylbenzaldehyde (malononitrile route), (2) alkylation of a dialkylmalonate with 2-methylbenzyl chloride (malonicester route), and (3) alkylation of malonamide with 2-methylbenzyl chloride (malonamide route) (Scheme 2).

The Malononitrile Route. Condensation of 2-methylbenzaldehyde and malonitrile in ethanol gave 2-(2-methylbenzylidene)malononitrile **2** in high yield, and subsequent reduction with sodium borohydride afforded 2-(2-methylbenzyl)malononitrile **3** in 95% yield. The two steps could be telescoped, although the obtained product **3** was of lower purity. The direct reduction of dinitrile **3** to diamine **4** was challenging. When using borane, dinitrile **3** was reduced to diamine **4** in a very low yield, probably due to dimerization and strong borane complexation with intermediates and product. The reduction of **3** was also attempted with PtO_2, H_2 in EtOH/CCl_4 (5:1), $LiAlH_4$ in THF, and Zn,$NaBH_4$ in MeOH,[8] but, in all cases, it failed or gave complex reaction mixtures. As an alternative to the direct reduction of **3** to **4**, dinitrile **3** could be efficiently hydrated with acetamide, $PdCl_2$ in THF/water (3:1),[9] to diamide **6** and then reduced with borane to afford diamine **4** in a good yield. In this way, diamine **4** was obtained

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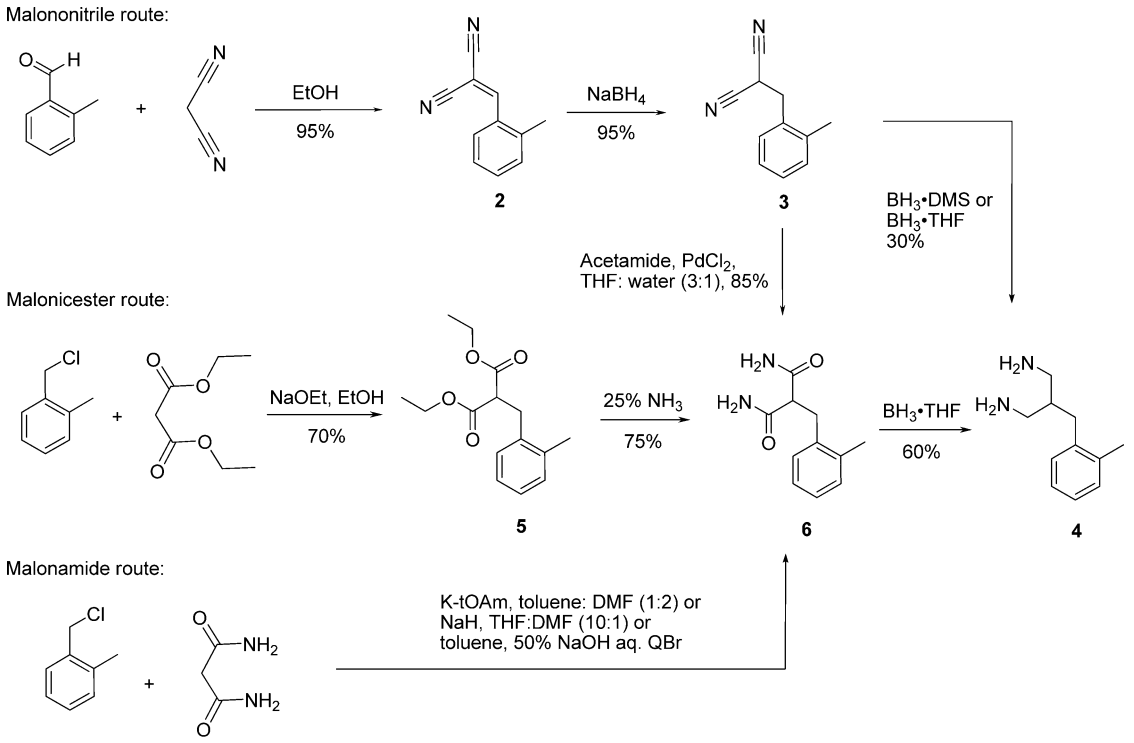
Scheme 2. Investigated Routes to Diamine 4



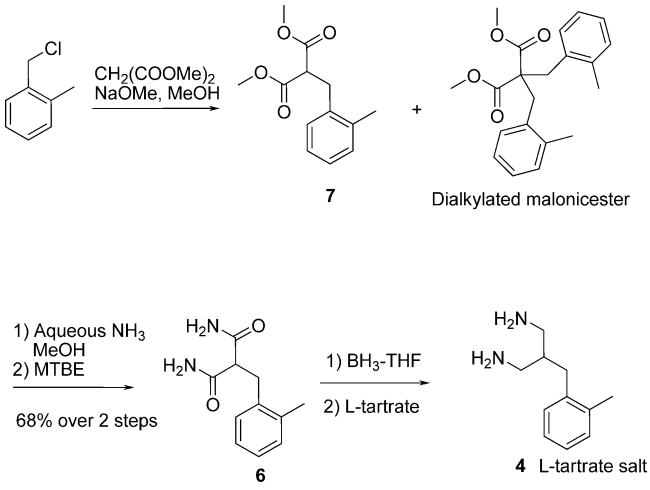
in a four-step sequence from 2-methylbenzaldehyde in a 46% overall yield.

The Malonicester Route. Diethylmalonate was alkylated with 2-methylbenzyl chloride to diethyl 2-(2-methylbenzyl)-malonate **5** in a good yield and then treated with aqueous ammonia to give diamide **6** in 53% overall yield. Borane reduction of **6**, similar to the malononitrile route, gave 2-(2-methylbenzyl)propane-1,3-diamine **4** in 32% overall yield over three synthetic steps.

The Malonamide Route. Attempts were made to alkylate malonamide with 2-methylbenzyl chloride, which would provide a very direct route to 2-(2-methylbenzyl)propane-1,3-diamine **4**. Three different reaction conditions were tried: potassium *tert*-amylate in toluene/DMF (1:2), sodium hydride in THF/DMF (10:1), and biphasic conditions using toluene, 50% aqueous NaOH, and tetra-*n*-butylammonium bromide (QBr). Unfortunately, a lot of byproducts were formed in all reactions, and this approach was abandoned. Both the malononitrile and the malonicester routes were efficient routes to diamine **4**, but the malonicester route in particular proved to be an operationally simple and effective way of producing diamine **4** and was chosen for further optimization.

Optimization of the Malonicester Route to Diamine 4. In early development work, diethyl malonate was used for the synthesis of **4**, but we quickly substituted it with dimethylmalonate since the synthesis was higher yielding and produced fewer byproducts. After alkylation and ammonolysis, diamide **6** could be isolated in 53% overall yield starting from diethylmalonate and in 68% yield starting from dimethyl malonate (Scheme 3). In the alkylation of dimethyl malonicester, the major byproduct was dialkylated malonicester. After ammonolysis, diamide **6** could be precipitated from methyl *t*-butyl ether, leaving the dialkylated byproduct in the supernatant. To increase the rate of reaction in the ammonolysis of **7**, we found it to be beneficial to increase the

Scheme 3. Optimization of the Malonicester Route



amount of added ammonia from 15 to 25 equiv and to increase the reaction temperature from 20 to 25 °C. Under these conditions, the reaction was completed within 24 h, yielding diamide **6** in high yield and purity. The borane reduction of diamide **6** was tested under a variety of conditions. Addition of the borane−THF complex was tested at 0, 30, and 40 °C. At 0 °C, the reaction proceeded to completion after reflux. However, when adding the borane complex at 30 or 40 °C, the reaction stalled after 80% conversion. After adding borane−THF at 0 °C, the reduction was tested at 20 °C, 50 °C, and reflux. After 24 h, the reaction at 20 °C contained a 6:1 ratio of product **4** to starting material **6** (plus a significant amount of byproducts), at 50 °C, a 50:1 ratio, and at reflux, a 25:1 ratio, using 5 equiv of borane−THF. The use of 4 equiv of borane−THF gave a cleaner conversion compared to that with 5 equiv, but with 3 equiv the reduction was much slower and gave a 1:1 ratio of **4**

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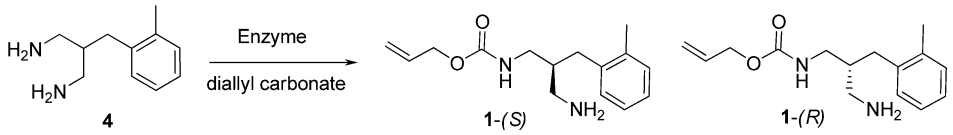
Table 1. Immobilized Lipase Screen[a]



enzyme	conv.[b] (%)	1-(*S*) ee (%)[c]	1-(*R*) ee (%)[c]	enzyme units (U/g)
IMM CALB[d]	33.2	6.8		2000[g]
IMM CALBY[d]	52.8	10.7		4000[g]
Novozym 435[e]	75.8		27.6	>5000
Amano Lipase PS-C1[f]	31.4		81.4	>30 000
Amano Lipase PS-IM[f]	21.2		66.6	>5000
Amano Lipase PS-D[f]	33.4		85	>3000
no enzyme (control)				

[a]See text or Experimental Section for a detailed description of conditions. [b]Percentage of conversion to monoallyl carbamate calculated by HPLC from area peaks. [c]Measured by HPLC with chiral stationary phase. [d]*Candida antartica* lipase B from Chiralvision. [e]*Candida antartica* lipase B from Novozymes. [f]*Burkholderia cepacia* lipase from Sigma-Aldrich. [g]TriButyrin units/g.

to **6** after 16 h as well as more byproducts. The reduction of **6** to **4** with 4 equiv of borane−THF added at 0 °C followed by reaction at 50 °C was first scaled up to 5 L and then to 10 L scale successfully. No significant exotherm was noted when heating the reaction mixture. As an alternative to a MeOH quench, quenching with 4 M KOH was tried and gave equally pure material. Furthermore, quenching the reaction mixture into 4 M KOH gave a well-controlled quench, and the organic phase could be separated and concentrated under reduced pressure. Subsequent acidic and basic workup was used to minimize the amount of borate species. To increase the purity of diamine **4**, a salt screen was performed, identifying the tartrate salt as a good alternative. The L-tartrate salt of **4** precipitated in quantitative yield from ethanol, increasing the purity from 70 to 90 wt %.

Enzymatic Desymmetrization of 4. With an effective synthesis of diamine **4** at hand, we turned our attention to the enzymatic desymmetrization of **4** using diallyl carbonate.[3b] A large set of immobilized lipases was screened for activity in dioxane (1 mass equivalent enzyme, 30 °C), but only six immobilized enzymes showed more than 20% conversion after 3 days (Table 1).

The best enzymes for the transformation originated from *Candida antarctica* and *Burkholderia cepacia*. Amano Lipase PS-C1 and Amano Lipase PS-D displayed especially good enantioselectivity. Unfortunately, these enzymes were no longer commercially available, and a new series of experiments was initiated using the currently available Amano Lipase PS-IM in a range of solvents (Table 2).

Table 2. Solvent Screen with Amano PS-IM[a]

solvent	conversion[b]	1-(*R*) ee (%)[c]
TBME/THF (1:1)	72.8	72
heptane/THF (1:1)	88.4	69
cyclohexane/THF (1:1)	89.8	74
toluene	52.5	74
THF	36.8	66
2-MeTHF	86.2	75
2-MeTHF (no enzyme)	24.8	

[a]See text or Experimental Section for a detailed description of conditions. [b]Percentage of conversion to monoallyl carbamate calculated by HPLC from area peaks. [c]Measured by HPLC with chiral stationary phase.

Diamine **4** was not very soluble in nonpolar solvents, such as methyl *t*-butyl ether, heptanes, and cyclohexane. Addition of THF to each of the solvents did, however, allow **4** to dissolve, and a set of 1:1 solvent mixtures was tested (Table 2). The conversion after 6 days suggested that 2-MeTHF gave the best enantioselectivity, despite some background reaction without any enzyme. In order to minimize the background carboxylation in 2-MeTHF, a gram scale experiment was carried out at 30 °C with excess Amano lipase PS-IM (3 mass equivalents immobilized lipase, 1.2 equiv diallyl carbonate, 20 rel. vol. 2-MeTHF). The reaction proceeded to completion within 3 days, and after workup, crude (*R*)-monoallylcarbamate **1**-(*R*) was isolated with 85% ee. Converting crude **1** into the corresponding D-tartarate salt in ethanol increased the enantiomeric excess to 91.0% (58% overall yield from **4**). Further enrichment of the enantiomeric excess to 99% ee was achieved in a subsequent four-step sequence by isolating the corresponding the product as a dibenzoyl-D-tartrate salt.

Kilogram Synthesis of 1-(*R*). The described developments formed the basis of a multikilogram campaign of **1**-(*R*) (Scheme 4). On a 4 kg scale, 2-methylbenzyl chloride was alkylated with 1.5 equiv of dimethylmalonate, affording monoalkylated product **7** and dialkylated malonicester in an 8:1 ratio. Ammonolysis of the crude product mixture with an excess (36 equiv) of ammonium hydroxide afforded the corresponding amides, and upon addition of methyl *t*-butyl ether, the monoalkylated amide **6** precipitated and was isolated in 75% overall yield starting from 2-methylbenzyl chloride. 2-(2-Methylbenzyl)malonamide **6** was reduced using 4 equiv of borane−THF to give the crude key diamine **4** in a 70% yield. Treatment with L-tartrate in ethanol then gave **4** L-tartrate salt in quantitative yield.

After basification of **4** L-tartrate salt with NaOH, lipase-mediated desymmetrization of **4** with diallyl carbonate gave **1**-(*R*) with 82% ee. Converting **1**-(*R*) into the corresponding D-tartrate salt increased the ee to 88% and resulted in 3 kg of **1**-(*R*) D-tartrate salt in 62% yield, starting from **4** L-tartrate salt.

CONCLUSIONS

We have developed a scaleable route affording (*R*)-allyl-(3-amino-2-(2-methylbenzyl)propyl)carbamate **1**-(*R*) D-tartrate salt in four synthetic steps from 2-methylbenzyl chloride in 32% overall yield. The route has been optimized to support multikilogram production and features a key enzymatic

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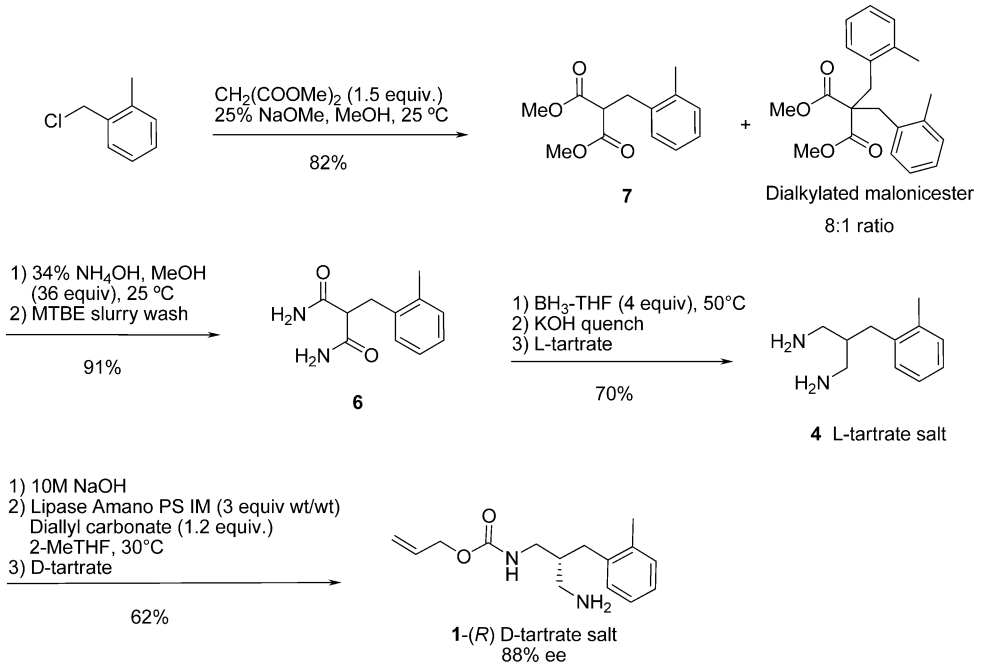
Scheme 4. Kilogram Campaign



desymmetrization of 2-(2-methylbenzyl)propane-1,3-diamine **4** using Amano PS-IM and diallyl carbonate.

EXPERIMENTAL SECTION

Commercially available solvents and reagents were used without purification. Enzymes were supplied by Amano Enzyme Europe Ltd., Sigma-Aldrich, and Chiralvision. Unless otherwise noted, temperature is the mantle temperature of the reactor. When weight percent (wt %) is noted, the yields have been corrected; wt % was determined with quantitative NMR using 1,2,4,5-tetrachloro-3-nitrobenzene as an internal standard. LC was performed on an Agilent 1100 coupled with a Bruker Esquire 3000 Plus Ion Trap MS, with a Zorbax Eclipse XDB-C18 column (4.6 × 50 mm, 1.8 μm) at 35 °C, using a gradient of water and methanol containing 0.1% formic acid. Absorbance was measured at 220 nm. HPLC with chiral stationary phase was performed on an Agilent 1100 with a Chiralpak IC column (4.6 × 250 mm, 5 μm) at 40 °C, using heptane/*i*PrOH/triethylamine (75:25:0.1) as the mobile phase. Retention times: **1**-(*S*) = 10.3 min and **1**-(*R*) = 13.0 min. Absorbance was measured at 268 nm. ^{1}H NMR measurements were performed on a Jeol 270 MHz.

Immobilized Lipase Screen. Diallyl carbonate (502 mg, 3.53 mmol) was added to a solution of diamine **4** (0.60 g, 3.37 mmol) in 1,4-dioxan (30 mL). 1.0 mL aliquots of this solution were added to 10 mL screw cap test tubes containing the enzymes (0.02 g) described in Table 1. The tubes were shaken at 500 rpm/30 °C for 3 days. Each tube was sampled and analyzed by reverse phase HPLC (4.6 × 50 mm Thermoquest Hypercarb; UV detection at 260 nm) and HPLC with a chiral stationary phase (4.6 × 250 mm Chiralpak IC3; UV detection at 260 nm).

Solvent Screen with Amano Lipase PS-IM. Solvent screen with Amano PS-IM was carried out in each of the solvents (2 mL, 20 rel. vol.) with diallyl carbonate (87.7 mg, 0.679 mmol), Amano PS-IM (0.1 g, 100 wt %), and diamine **4** (0.1 g, 0.561 mmol). After 6 days at 30 °C, the experiments were sampled using the same methods asthose described for the lipase screen.

Dimethyl 2-(2-Methylbenzyl)malonate (7). A reactor was charged with dimethylmalonate (6.00 kg, 45.4 mol) and methanol (21.3 L). 25% NaOMe/MeOH (10.37 L, 45.2 mol) was added over 10 min, and then 2-methyl benzyl chloride (4.26 kg, 30.3 mol) was added over 1.5 h, maintaining a reaction temperature below 30 °C. Saturated NH_4Cl (53.1 L) was added to the reaction, resulting in pH 8.5. The product was extracted with isopropyl acetate (3 × 25 L), and the combined organic layers were washed with 10% brine (10 L) and concentrated under reduced pressure to afford an oil of **7** and dialkylated malonate in an 8:1 ratio (8.63 kg, 68 wt % **7**, 82% yield). Purity by HPLC: 86 area %; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 7.17−7.05 (4H, m), 3.60 (6H, s), 3.82 (1H, t), 3.12 (2H, s), 2.21 (3H, s); ^{13}C NMR (DMSO-d_6, 67.5 MHz) δ 169.5 (2C), 136.6, 136.3, 130.8, 129.5, 127.3, 126.4, 52.8 (2C), 52.0, 31.8, 19.4; HRMS (ESI): $[M + H]^+$ m/z calcd for $C_{13}H_{16}O_4$, 237.1127; found, 237.1116.

2-(2-Methylbenzyl)malonamide (6). A reactor was charged with dimethyl-2-(2-methylbenzyl) malonate (**7**) (5.90 kg, 68 wt %, 17.0 mol) and methanol (14.8 L). 34% ammonium hydroxide (24 L, 36 equiv) was added, and the reaction was stirred at 25 °C until it was considered to be complete by HPLC (16 h). The solids (product **6** and dialkylated malonamide) were filtered off and then slurried in MTBE (15.3 L). After 30 min, the solids were filtered off, washed with MTBE (2 × 15.3 L), and dried under reduced pressure at 60 °C to give **6** as a white solid (3.2 kg, 100 wt %, 91% yield). Purity by HPLC: 99.6 area %; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 7.32−7.21 (2H, br s), 7.15−7.00 (6H, m), 3.33 (1H, t), 2.96 (2H, d), 2.28 (3H, s); ^{13}C NMR (DMSO-d_6, 67.5 MHz) δ 171.0 (2C), 137.5, 136.0, 129.9, 128.9, 126.1, 125.6, 53.2, 32.5, 19.1; HRMS (ESI): $[M + H]^+$ m/z calcd for $C_{11}H_{14}N_2O_2$, 207.1133; found, 207.1132

2-(2-Methylbenzyl)propane-1,3-diamine (4). A reactor was charged with 2-(2-methylbenzyl)malonamide (**6**) (1.32 kg, 100 wt %, 6.40 mol) and THF (5.4 L). The viscous mixture was

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cooled to 0 °C, and 1 M borane−THF (25.6 L, 25.6 mol) was added during 2 h, maintaining a reaction temperature below 2 °C. The reaction was initially warmed to 15 °C to ensure no exothermic reaction would occur and was then stirred at 50 °C for 16 h. When HPLC analysis indicated that less than 8% of **6** remained, the reaction mixture was quenched into 4 M KOH (8 L), maintaining a temperature below 30 °C. The organic layer was concentrated under reduced pressure, and the aqueous layer was extracted twice with MTBE (2 × 10 L). The combined MTBE extract was added to the concentrated organic layer, and the combined organic layers were then charged to a solution of 6 M HCl (10 L), maintaining a temperature below 30 °C. The aqueous phase was washed with MTBE (10 L) and then basified with 6 M KOH (12 L). The aqueous phase was extracted twice with THF (10 L and then 5 L), and the combined organic phase was concentrated under reduced pressure. Toluene (5 L) was added and then azeotrope distilled off to remove any residual water. The mixture was triturated with toluene (5 L), and the solids were filtered off and washed with toluene (3 L). The filtrate was concentrated under reduced pressure, affording **4** as the free amine (1.13 kg, 71 wt %, 70% yield). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.12−7.00 (4H, m), 2.72−2.59 (4H, m), 2.52 (2H, d), 2.27 (3H, s), 1.64 (1H, m), 1.48−1.25 (4H, br s); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 139.0, 136.3, 130.5, 129.9, 126.2, 125.9, 44.7 (2C), 43.8, 34.3, 19.6; HRMS (ESI): $[M + H]^+$ m/z alcd for $C_{11}H_{18}N_2$, 179.1548; found, 179.1553

2-(2-Methylbenzyl)propane-1,3-diamine (4) L-Tartrate Salt. Crude diamine **4** (2.28 kg, 71 wt %, 9.1 mol) was added to ethanol (4 L). A solution of L-tartaric acid (1.62 kg, 10.8 mol) in ethanol (11 L) was added, keeping the temperature below 40 °C. The mixture was stirred for 16 h at 25 °C, and then the solids were filtered off, washed with ethanol (2 × 2 L), and dried under reduced pressure 50 °C to give the L-tartrate salt of **4** (3.21 kg, 94 wt %, quantitative yield). ^{1}H NMR (D_2O, 270 MHz) δ 7.30−7.15 (4H, m), 4.27 (2H, s), 3.20−3.07 (2H, dd), 3.04−2.94 (2H, dd), 2.79 (2H, d), 2.41 (1H, m), 2.27 (3H, s); ^{13}C NMR (D_2O, 67.5 MHz) δ 178.4 (2C), 137.2, 135.7, 131.0, 130.0, 127.6, 126.7, 73.9 (2C), 40.5 (2C), 35.9, 32.8, 18.7; HRMS (ESI): $[M + H]^+$ m/z calcd for $C_{11}H_{18}N_2$, 179.1548; found, 179.1553

(*R*)-Allyl (3-Amino-2-(2-methylbenzyl)propyl)-carbamate (1-(*R*)) D-Tartrate Salt. A reactor was charged with 2-(2-methylbenzyl)propane-1,3-diamine (**4**) L-tartrate salt (3.79 kg, 94 wt %, 10.9 mol) and water (17 L). 10 M NaOH (17 L, 170 mol) was added, maintaining a reaction temperature below 25 °C. The mixture was stirred for 30 min at 25 °C, and then 2-MeTHF (14 L) was added. The layers were separated, and the aqueous phase was extracted with 2-MeTHF (14 L). The combined organic phase was dried (sodium sulfate), filtered, and concentrated under reduced pressure, affording the free diamine **4**. A reactor was charged with **4**, 2-MeTHF (37.4 L), and diallyl carbonate (1.80 kg, 12.6 mol). Immobilized lipase Amano PS IM (5.61 kg, 3 wt equivalents) was added in portions over 30 min, and the temperature was set at 30 °C. After 4 days, ^{1}H NMR indicated less than 5% starting material left, and the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford **1**-(*R*) (2.68 kg, 82% ee). To the crude (*R*)-allyl (3-amino-2-(2-methylbenzyl)-propyl)carbamate (**1**-(*R*); 2.68 kg) was added EtOH (7.1 L). A solution of D-tartaric acid (1.53 kg, 10.2 mol) in EtOH (8 L) was added, keeping the temperature below 25 °C. After 16 h at 25 °C, acetonitrile CH_3CN (5 L) was added. The solids were filtered off, washed with CH_3CN (2 × 5 L), and dried under reduced pressure at 40 °C to afford 2.94 kg of **1**-(*R*) D-tartrate salt (95 wt %, 62% yield from **4**, 88% ee). ^{1}H NMR (DMSO-d_6, 270 MHz) δ 7.50 (1H, t), 7.22−7.05 (4H, m), 5.98−5.85 (1H, m), 5.35−5.12 (2H, m), 4.48 (2H, d), 3.95 (2H, s), 3.13−2.99 (2H, m), 2.90−2.79 (1H, m), 2.75−2.58 (2H, m), 2.26 (3H, s), 2.08 (1H, m); ^{13}C NMR (DMSO-d_6, 67.5 MHz) δ 174.6 (2C), 156.6, 137.4, 136.1, 133.7, 130.3, 129.7, 126.3, 125.8, 117.0, 71.8 (2C), 64.4, 65.5, 37.6, 32.7, 19.1, 18.9; HRMS (ESI): $[M + H]^+$ m/z calcd for $C_{15}H_{22}N_2O_2$, 263.1760; found, 263.1769

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Notes

The authors declare no competing financial interest.

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