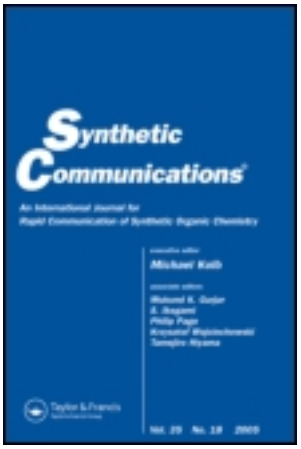

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ENANTIOSELECTIVE SYNTHESIS OF (*R*)- AND (*S*)-1-^{2}H-1-OCTANOL AND THEIR CORRESPONDING AMINES

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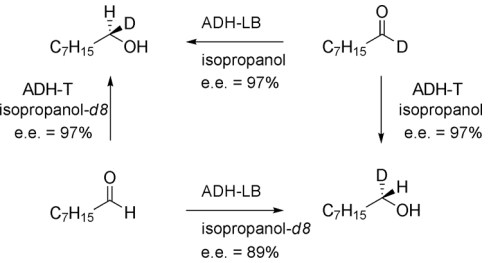
GRAPHICAL ABSTRACT



Abstract *Both enantiomers of 1-^{2}H-1-octanol were obtained by the enzymatic reduction of deuterated octanal in the presence of alcohol dehydrogenases (ADH) (ADH-T or ADH-LB) as the biocatalyst in good yield, purity, and enantiomeric excess (>95%). The cofactor nicotinamide adenine dinucleotide phosphate was regenerated by the addition of isopropanol. To simplify the synthetic route, the direct reduction of octanal using the same enzymes and the same cofactor but adding deuterated isopropanol was evaluated. This provided a one-step procedure from a commercially available starting compound to both enantiomers of 1-^{2}H-1-octanol in good yields (>80%) and good enantiomeric excess (~97%). The (*S*)-alcohols were converted to their corresponding (*R*)-amines, which showed* ee*'s around 90%.*

Keywords Asymmetric synthesis; biocatalysis; deuterium; NMR spectroscopy

INTRODUCTION

Chiral, deuterated compounds are useful mechanistic probes to elucidate chemical and biological pathways.[1,2] Recently we became interested in chiral

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deuterated alkyl amines to prepare chiral C_3-symmetrical benzene-1,3,5-tricarboxamides (BTAs).[3] BTAs have received a lot of interest because of their highly cooperative self-assembly and strong chiral amplification effects in dilute solution.[4–6] In our ongoing quest to understand BTA self-assembly, we found it desirable to synthesize both enantiomers of a deuterated BTA derivative. For this, we required an easy and fast route to chiral (*R*)- and (*S*)-1-^{2}H-1-octylamine of high enantiomeric purity.

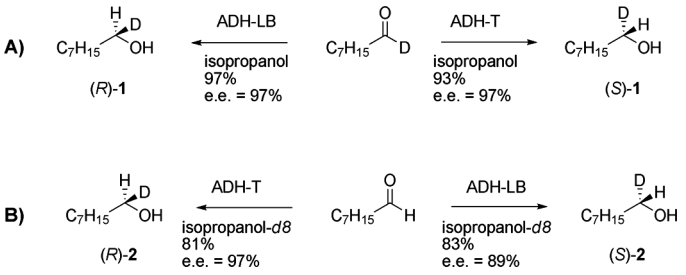
Several chemical reductions are known to afford deuterated alcohols enantioselectively and the *ee*'s are usually moderate to good (typically $ee < 92\%$).[2,7–12] In addition, the biocatalytic synthesis of enantioenriched (*S*)-1-^{2}H-1-hexanol via the reduction of 1-^{2}H-hexanal with Baker's yeast, a well-known alcohol dehydrogenase, was described but the *ee* of the product was not determined.[13] Later, Baker's yeast was applied for the reduction of 1-^{2}H-octanal, affording (*S*)-1-^{2}H-1-octanol with an $ee > 99\%$.[14] An alternative approach to obtain enantiopure deuterated alcohols was found by reducing hexanal with alcohol dehydrogenases from horse liver (HL-ADH) and *Pseudomonas* (PADH) using a deuterated cofactor to the corresponding (*R*)-1-^{2}H-1-hexanol and (*S*)-1-^{2}H-1-hexanol, respectively.[15] The deuterated cofactor was regenerated by the deuterium transfer from a deuterated solvent such as isopropanol or ethanol. The *ee*'s of the deuterated alcohols were >97%, but the conversions were far from quantitative and long reaction times were required.

Recently, new alcohol dehydrogenases from *Lactobacillus brevis* (ADH-LB, *R*-selective) and *Thermoanaerobacter* sp. (ADH-T, *S*-selective), which are highly active and show excellent enantioselectivity in the reduction of ketones ($ee > 99\%$),[16] have become commercially available. These enzymes depend on nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor, which serves as reduction equivalent. Both enzymes are able to oxidize isopropanol for cofactor regeneration, and therefore only catalytic amounts of NADPH are needed. The reaction equilibrium is driven by using an excess of isopropanol in buffer. To date, these ADHs have not been explored to access optically pure deuterated alcohols.

Here we report the use of ADH-T and ADH-LB in the reduction of 1-^{2}H-octanal and (by applying a deuterated cofactor) of octanal to (*R*) and (*S*)-1-^{2}H-1-octanol with high *ee* and in good yields. The *ee*'s of all (*R*)- and (*S*)-1-^{2}H-1-octanol obtained were determined by using (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl) derivatization, a useful chemical reagent for determining the *ee*'s of the chiral alcohols via the formation of diastereomeric esters.[7,8] Finally, we converted the (*S*)-alcohols into the corresponding (*R*)-amines and evaluated how this procedure affects the enantiomeric excess.

RESULTS AND DISCUSSION

We first evaluated the reductions of deuterated octanal employing ADH-T and ADH-LB (Scheme 1). Deuterated octanal was obtained following a previously described three-step synthesis.[13] Reductions were performed in isopropanol and potassium phosphate buffer (pH = 7, 23–29% v/v) at substrate concentrations of 46–48 mM (Table 1). The reactions were monitored by gas chromatography–mass spectrometry (GC-MS), and after 4 days the conversions were >98%. The alcohols (*R*)-**1** and (*S*)-**1** were isolated in good yields (93–97%) and high purity as evidenced by NMR spectroscopy and GC-MS.



Scheme 1. (a) Synthesis of (*R*)-**1**: ADH-LB, isopropanol, NADPH, phosphate buffer solution, $MgCl_2$ solution, 36 °C, 48 h, 97%; (*S*)-**1**: ADH-T, isopropanol, NADPH, phosphate buffer solution, 36 °C, 48 h, 93%. (b) Synthesis of (*R*)-**2**: ADH-T, NADPH, isopropanol-*d8*, phosphate buffer solution, 36 °C, 4 d, 81%; (*S*)-**2**: ADH-LB, NADPH, isopropanol-*d8*, phosphate buffer solution, 36 °C, 4 d, 83%.

To avoid the lengthy synthesis of deuterated octanal, the reduction of octanal using isopropanol-*d8* to regenerate the cofactor was performed (Scheme 1). In this case, ADH-LB affords (*S*)-**2** while ADH-T affords (*R*)-**2**. We performed the reaction at a lower isopropanol concentration and at a two times higher substrate concentration. Within 4 days, quantitative conversions were obtained and the isolated yields were >80% (Table 1). Both enantiomers were of high purity as evidenced by NMR spectroscopy and GC-MS.

Subsequently, alcohols (*R*)-**1**, (*S*)-**2**, and (*R*)-**2** were converted to their corresponding chiral amines (*S*)-**3**, (*R*)-**4**, and (*S*)-**4**, respectively, following a previously described procedure by tosylation, azidation, and reduction (Scheme 2).[13] All steps proceeded in good yields and high purity as evidenced by NMR and GC-MS.

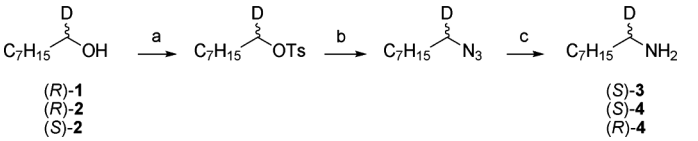
The optical purity of all alcohols and amines (*S*)-**3** and (*S*)-**4** was assessed by derivatization employing MTPA-Cl (Scheme 3).[7,8] The NMR spectra of the diastereomeric compounds were quantified to determine the *ee*'s. To facilitate the interpretation of the NMR spectra of the enantiomers, we synthesized the racemic alcohol (*rac*)-**5** and its amine derivative (*rac*)-**6**, which were converted to their MTPA ester and amide derivatives.

In the ^{1}H NMR spectrum of MTPA ester of *rac*-**5**, the –OC*H*– proton resonates as two overlapping triplets with equal intensity (Fig. 1). Deconvolution of the overlapping peaks gave an *ee* of 0% (Table 2, entry 1). Following this procedure, the *ee*'s of (*R*)-**1**, (*S*)-**1** and (*R*)-**2**, (*S*)-**2** (Table 2, entries 2–5) were found to be $97 \pm 1\%$, $97 \pm 1\%$, $97 \pm 1\%$, and $89 \pm 1\%$, respectively. Alcohol (*R*)-**2** (synthesized via reduction with a deuterated cofactor) shows the same *ee* as (*R*)-**1** synthesized

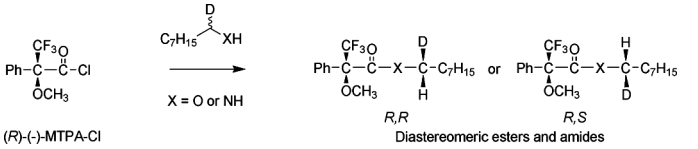
Table 1. Enzymatic reduction of (deuterated) octanal

Substrate	Solvent (%v/v)[a]	Concentration (mM)	Enzyme	Alcohol	Isolated yield (%)
D-octanal	IPA/H_2O, 23	46	ADH-LB	(*R*)-**1**	97
D-octanal	IPA/H_2O, 29	48	ADH-T	(*S*)-**1**	93
Octanal	IPA-d_8/H_2O, 11	93	ADH-T	(*R*)-**2**	81
Octanal	IPA-d_8/H_2O, 12	103	ADH-LB	(*S*)-**2**	83

[a]IPA, isopropanol.



Scheme 2. Synthesis of (*R*)- and (*S*)-1-^{2}H-1-octylamine. Experimental conditions: (a) TsCl, pyridine, 4 °C, 5 h, 89%; (b) NaN_3, DMF, 70 °C, overnight, 85%; and (c) $LiAlH_4$, ether, reflux, 2 h, 85%.



Scheme 3. Synthesis of diastereomeric MTPA-esters and amides.

via the normal enzymatic reduction process. The slightly lower *ee* of 89% measured for (*S*)-**2** is presumably the result of nonoptimal reduction conditions. The high concentration (103 mM) employed in this reaction may have negatively influenced its enantioselectivity.

We then analyzed the MTPA amides of (*rac*)-**6**, (*S*)-**3**, and (*S*)-**4** (Fig. 2). Two (overlapping) quartet peaks with equal intensities at 3.32 and 3.28 ppm were identified for the MTPA amide of (*rac*)-**6** which, after deconvoluting the spectra, gave an *ee* of 0% (Table 2, entry 6). The ^{1}H NMR spectra of the MTPA amide of (*S*)-**3** and (*S*)-**4** show a large quartet at 3.32 ppm and a small partially overlapping quartet at 3.28 ppm. In these cases, the *ee*'s were around 90%, indicating that the inversion of configuration that takes place when converting the chiral alcohol into the chiral amine proceeds with high selectivity.

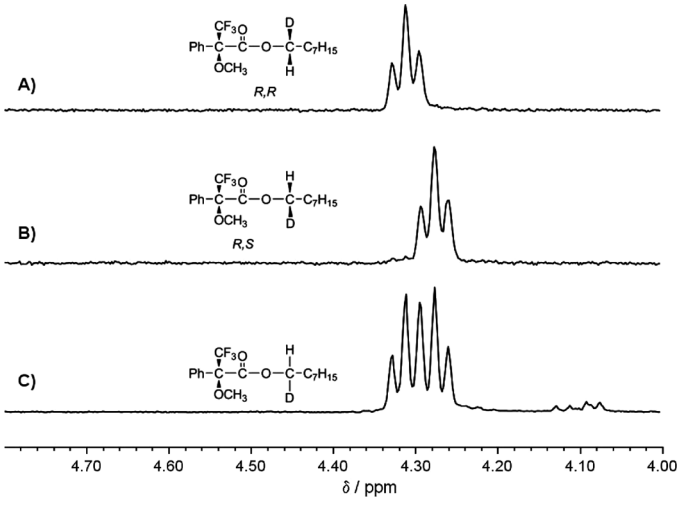


Figure 1. ^{1}H NMR spectra of MTPA esters of (a) (*R*)-**1**, (b) (*S*)-**2**, and (c) (*rac*)-**5**.

Table 2. The *ee*'s of chiral deuterated alcohols and amines

Entry	Alcohol/amine[a]	$Ee^{b,c}$ (%)
1	(*rac*)-**5**	0
2	(*R*)-**1**	97 ± 1
3	(*S*)-**1**	97 ± 1
4	(*R*)-**2**	97 ± 1
5	(*S*)-**2**	89 ± 1
6	(*rac*)-**6**	0
7	(*S*)-**3**	89 ± 1
8	(*S*)-**4**	90 ± 1

[a]All compounds were converted into their MTPA ester or amide derivatives.

[b]*Ee* [=(R − S)/(R + S)] was calculated from the intensities of –XC*H*– signals in the ^{1}H NMR spectra of the diastereomeric MTPA derivatives by using deconvolution to resolve overlapping peaks.

[c]The error on the *ee* by deconvolution of the spectra was determined by performing an error propagation analysis assuming that the intensity of the ^{1}H NMR signals possesses an uncertainty of 10%.

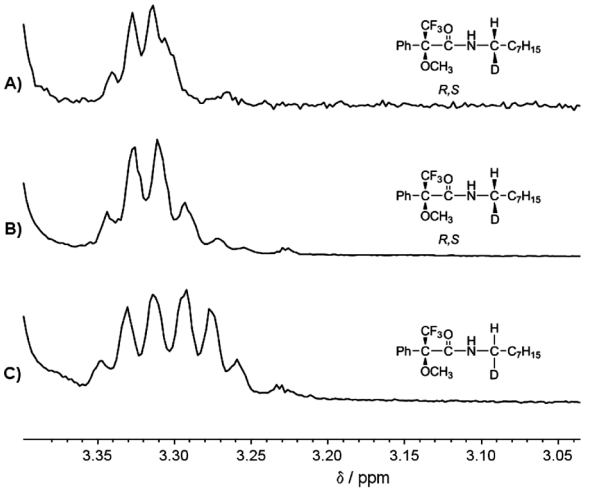


Figure 2. ^{1}H NMR spectra of MTPA amides of (a) (*S*)-**3**, (b) (*S*)-**4**, and (c) (*rac*)-**6**.

CONCLUSIONS

Both enantiomers of 1-^{2}H-1-octanol are accessible in good yields and purity by applying alcohol dehydrogenases ADH-T or ADH-LB in the reduction step. Moreover, the use of a deuterated cofactor allows the one-step synthesis of (*R*)-1-^{2}H-1-octanol and (*S*)-1-^{2}H-1-octanol starting from octanal whereby the synthesis of deuterated octanal can be avoided. In all cases, excellent *ee*'s of ~97% were achieved. The conversion of (*R*)-1-^{2}H-1-octanol to (*S*)-1-^{2}H-1-octylamine proceeded in good yields and enantiomeric excess (~90%). This biocatalytic route provides a simple and fast

access to stereoselectively labeled deuterated amines from commercially available aldehydes.

EXPERIMENTAL

^{1}H NMR (400 MHz and 500 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Varian spectrometers (Varian Mercury Vx 400 or Varian Unity Inova 500) in deuterated chloroform unless stated otherwise. ^{2}H NMR was measured on a Varian Unity Inova 500 spectrometer by dissolving the sample in chloroform and adding 10 μL of deuterated chloroform in the NMR tube. The spectra were referenced to deuterated chloroform (7.26 ppm). Chemical shifts are reported in parts per million (ppm) and referenced to tetramethylsilane (TMS). Peaks are noted as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qui), or heptet (h), and broadened peaks are noted as (br). Deconvolution was performed by using the linefit in MestReNova version 6.0.3-5604. To verify to upper and lower values of the *ee*'s, considering the uncertainty of the ^{1}H NMR signals, an error propagation analysis was performed. GC-MS was performed on a Shimadzu GC-MS-QP5000 equipped with a Zebron ZB-5 column and an autosampler. All GC-MS measurements were done with injector temperature at 300 °C and detector temperature at 300 °C. Infrared (IR) spectra were recorded on a Perkin-Elmer spectrum 1 using a universal attenuated total reflectance (ATR).

Deuterated octanal was prepared according to Ref. 13. Octanal, ethyl octanoate, $LiAlD_4$, phosphate buffered saline, and isopropanol-*d8* were obtained from Sigma-Aldrich. Cofactor NADPH and alcohol dehydrogenases from *Lactobacillus brevis* [ADH-LB, (*R*)-selective, 4100 U/mL] and *Thermoanaerobacter sp.* [ADH-T, (*S*)-selective, 331 U/mL] were purchased from Julich Chiral Solutions GmbH. (*R*)-(−)-α-Methoxy-α-trifluoromethylphenylacetyl chloride [(*R*)-(–)-MTPA-Cl] was purchased from Acros. All other chemicals were purchased from Sigma-Aldrich and used as received unless otherwise noted. All solvents were purchased from Biosolve. Ether was dried over molsieves. Phosphate buffered saline was dissolved in deionized water to prepare phosphate buffer solution (pH 7.4, 50 mM) and was used for the enzymatic reduction reactions. All alcohols and amines [except (*R*)-**1** and **2**] were converted to their diastereomeric MTPA ester and amide derivatives by treating with commercially available (*R*)-(–)-MTPA-Cl following a modified literature procedure.[8]

(*R*)-1-^{2}H-1-Octanol [(*R*)-1]

Deuterated octanal (1.16 g, 9 mmol) was dissolved in isopropanol (45 mL). To this mixture, phosphate buffer solution (150 mL) and NADPH (265 mg) were added. A few drops of $MgCl_2$ solution in distilled water (0.1 M) was added to the reaction mixture. When the temperature was set to 36 °C, the enzyme ADH-LB (308 U) was added to the reaction mixture. The mixture was left stirring at that temperature for 48 h. The mixture was washed with ether (3 × 50 mL), and the combined organic layers were dried with $MgSO_4$. After the solvent was evaporated, (*R*)-**1** was obtained as a colorless oil (1.14 g, 97%). *ee* = 97 ± 1%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (tt, *J* = 6.8 and 1.2 Hz, 1H, -CH_2CHDOH), 1.51 [q, *J* = 6.8 Hz, 2H, -$(CH_2)_5CH_2$CHDOH], 1.27 [m, 10H, $CH_3(CH_2)_5CH_2$-], 0.85 [t, *J* = 7.2 Hz, 3H, $CH_3(CH_2)_5$-] ppm. ^{2}H NMR

(500 MHz, $CDCl_3$): $\delta = 3.65$ (s, -CD) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 62.0$ (t), 32.5, 31.7, 29.3, 26.1, 25.6, 22.5, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 2.64$ min, purity >99.5%, major peaks: [M^+-CHDOH] = 99, [M^+-CH_2CHDOH] = 84, [M^+-CH_4CHDOH] = 70, [M^+-CH_6CHDOH] = 57, [M^+-CH_8CHDOH] = 43. FT-IR: $\nu = 3336$ (br), 2956 (s), 2856 (s), 2157 (w), 1711 (s), 1466 (m), 1069 (m), 939 (m), 723 (w).

(*S*)-1-^{2}H-1-Octanol [(*S*)-1]

Deuterated octanal (1.29 g, 10 mmol) was dissolved in isopropanol (60 mL). To this mixture, phosphate buffer solution (150 mL) and NADPH (326 mg) were added. Instead of using ADH-LB for the reduction, ADH-T (155 U) was used. $MgCl_2$ solution was not required for this enzyme. (*S*)-**1** was obtained as a colorless oil (1.22 g, 93%). *ee* = 97 ± 1%. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.56$ (tt, $J = 6.8$ and 1.2 Hz, 1H, -CH_2CHDOH), 1.51 [q, $J = 6.8$ Hz, 2H, -$(CH_2)_5CH_2$CHDOH], 1.27 [m, 10H, $CH_3(CH_2)_5CH_2$-], 0.85 [t, $J = 7.2$ Hz, 3H, $CH_3(CH_2)_5$-] ppm. ^2H NMR (500 MHz, $CDCl_3$): $\delta = 3.65$ (s, -CD) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 62.0$ (t), 32.5, 31.7, 29.3, 26.1, 25.6, 22.5, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 2.64$ min, purity >99.5%, major peaks: [M^+-CHDOH] = 99, [M^+-CH_2CHDOH] = 84, [M^+-CH_4CHDOH] = 70, [M^+-CH_6CHDOH] = 57, [M^+-CH_8CHDOH] = 43. FT-IR: $\nu = 3336$ (br), 2956 (s), 2856 (s), 2157 (w), 1711 (s), 1466 (m), 1069 (m), 939 (m), 723 (w).

(*S*)-1-^{2}H-1-Octylamine [(*S*)-3]

(R)-1-^{2}H-Octyl 4-methylbenzenesulfonate. p-Toluenesulfonyl chloride (1.56 g, 8.4 mmol) was dissolved in dry pyridine (10 mL) in a round-bottom flask and cooled down to 0 °C. (*R*)-**1** (1.0 g, 7.6 mmol) was added dropwise to this mixture. The reaction mixture was left stirring overnight at 4 °C. The mixture was quenched with ice and extracted with ether (3 × 50 mL). The combined organic layers were washed sequentially with 1 M HCl solution, water, and brine. The organic layer was dried over $MgSO_4$. The solvent was removed by in vacuo at 50 °C. The isolated product yielded a yellowish oil (1.95 g, 89%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ [d, $J = 8.4$ Hz, 2H, -$SO_2C(CH)_2CCH_3$], 7.33 [d, $J = 8.4$ Hz, 2H, -$SO_2C(CHCH)_2CCH_3$], 3.99 (t, $J = 6.6$ Hz, 1H, -CH_2CHDO-), 2.45 [s, 3H, -$SO_2C(CHCH)_2CCH_3$], 1.66 [q, $J = 6.6$ Hz, 2H, $(CH_2)_5CH_2$CHDO], 1.23 [m, 10H, $CH_3(CH_2)_5CH_2$], 0.86 [t, $J = 7.2$ Hz, 3H, $CH_3(CH_2)_5$-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.6$, 133.2, 129.8, 71.5 (t), 31.7, 29.0, 28.8, 28.5, 25.3, 127.8, 22.5, 21.6, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 7.39$ min, purity = >99.5%, major peaks: [M^+-C_7H_{15}CDH] = 127, [M^+-OTs] = 113, [M^+-C_4H_9] = 99, [M^+-CH_2CHDOTs] = 84, [M^+-CH_4CHDOTs] = 70, [M^+-CH_6CHDOTs] = 57, [M^+-CH_8CHDOTs] = 43.

(S)-1-^{2}H-1-Azidooctane. The tosylate (1.95 g, 6.8 mmol) was dissolved in DMF (30 mL). While stirring the reaction mixture at room temperature, NaN_3 (4.4 g, 68 mmol) was added as a solid in proportions to this solution. The reaction mixture was left stirring at 70 °C overnight. Subsequently the mixture was poured

into ice water (200 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with water and brine. The organic layer was dried over $MgSO_4$. After removal of solvent, the product was obtained as clear oil (0.9 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): 3.23 (tt, $J = 7.2$ and 1.6 Hz, 1H, -CH_2CDHN_3), 1.56 [q, $J = 7.2$ Hz, 2H, -$(CH_2)_5CH_2CDHN_3$], 1.28 [m, 10H, $CH_3(CH_2)_5CH_2$-], 0.85 [t, $J = 7.2$ Hz, 3H, $CH_3(CH_2)_5$-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 51.1 (t), 31.7, 29.2, 26.6, 22.5, 15.2, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 2.73$ min, purity = 88%, major peaks: $[M^+\text{-}N_2] = 127$, $[M^+\text{-}N_3] = 113$, $[M^+\text{-}C_4H_9] = 99$, $[M^+\text{-}CH_2CHDN_3] = 84$, $[M^+\text{-}CH_4CHDN_3] = 70$, $[M^+\text{-}CH_6CHDN_3] = 57$, $[M^+\text{-}CH_8CHDN_3] = 43$. FT-IR: 2956 (s), 2856 (s), 2157 (w), 2092 (s), 1677 (m), 1466 (m), 1069 (m), 939 (m), 723 (w).

(S)-1-^{2}H-1-Octylamine. $LiAlH_4$ solution (9.9 mL, 1.0 M in ether) was placed in a round-bottom flask under argon atmosphere and diluted with additional ether (10 mL). The mixture was cooled down to 0 °C. To this solution, (*S*)-1-^{2}H-octylazide (0.7 g, 4.5 mmol) in ether (40 mL) was added dropwise. The mixture was refluxed for 2 h, cooled down using an ice bath, and quenched slowly with ice water. The mixture was extracted with ether (3 × 50 mL). The combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was isolated as a clear oil (0.5 g, 85%). $Ee = 89 \pm 1\%$. ^{1}H NMR (400 MHz, $CDCl_3$): 2.62 (t, $J = 6.8$ Hz, 1H, -CH_2CDHNH_2), 1.60 (br. s, 2H, -CH_2CDHNH_2), 1.40 [q, $J = 6.8$ Hz, $CH_3(CH_2)_5CH_2CDHNH_2$], 1.20 [m, 10H, $CH_3(CH_2)_5CH_2CDHNH_2$], 0.85 [t, $J = 7.2$, 3H, $CH_3(CH_2)_5CH_2CDHNH_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 41.7 (t), 33.6, 31.7, 29.2, 26.8, 22.6, 15.2, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 2.00$ min, purity = 94%, major peaks: $[M^+] = 130$, $[M^+\text{-}NH_2] = 113$, $[M^+\text{-}C_2H_5] = 101$, $[M^+\text{-}CH_2CHDNH_2] = 84$, $[M^+\text{-}CH_4CHDNH_2] = 70$, $[M^+\text{-}CH_6CHDNH_2] = 57$, $[M^+\text{-}CH_8CHDNH_2] = 43$. FT-IR: 2956 (s), 2856 (s), 2157 (w), 1466 (m), 1069 (m), 939 (m), 723 (w).

(*R*)-1-^{2}H-1-Octanol [(*R*)-2]

Octanal (3.0 g, 23 mmol) was dissolved in isopropanol-*d8* (28 mL). To this solution, phosphate buffer solution (220 mL) and NADPH (1.0 g) were added. Then, the temperature was set to 36 °C; ADH-T (331 U) was added to the reaction mixture, which was left stirring at 36 °C for 4 days. The reaction was monitored by GC-MS and NMR spectroscopy. The mixture was extracted with ether (3 × 50 mL), and the organic layer was dried over $MgSO_4$. The solvent was evaporated, and the desired alcohol (*R*)-2 was obtained as a colorless oil (2.50 g, 81%). The alcohol was used without further purification. $Ee = 97 \pm 1\%$. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.56$ (tt, $J = 6.8$ and 1.2 Hz, 1H, -CH_2CHDOH), 1.51 [q, $J = 6.8$ Hz, 2H, -$(CH_2)_5CH_2$ CHDOH], 1.27 [m, 10H, $CH_3(CH_2)_5CH_2$-], 0.85 [t, $J = 7.2$ Hz, 3H, $CH_3(CH_2)_5$-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 62.0$ (t), 32.5, 31.7, 29.3, 26.1, 25.6, 22.5, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R =$ 2.64 min, purity >99.5%, major peaks: $[M^+\text{-}CHDOH] = 99$, $[M^+\text{-}CH_2CHDOH] =$ 84, $[M^+\text{-}CH_4CHDOH] = 70$, $[M^+\text{-}CH_6CHDOH] = 57$, $[M^+\text{-}CH_8CHDOH] = 43$.

FT-IR: $\nu = 3336$ (br), 2956 (s), 2856 (s), 2157 (w), 1711 (s), 1466 (m), 1069 (m), 939 (m), 723 (w).

(*S*)-1-^{2}H-1-Octylamine [(*S*)-4]

The desired amine (*S*)-**4** was obtained from **(*R*)-2** by following the same procedure as described previously. $Ee = 90 \pm 1\%$. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.62$ (t, $J = 6.8$ Hz, 1H, -CH_2CDHNH_2), 1.60 (br. s, 2H, -CH_2CDHNH_2), 1.40 [q, $J = 6.8$ Hz, $CH_3(CH_2)_5CH_2CDHNH_2$], 1.2 [m, 10H, $CH_3(CH_2)_5CH_2CDHNH_2$], 0.85 [t, $J = 7.2$, 3H, $CH_3(CH_2)_5CH_2CDHNH_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 41.7$ (t), 33.6, 31.7, 29.2, 26.8, 22.6, 15.2, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 2.00$ min, purity = 94%, major peaks: $[M^+] = 130$, $[M^+\text{-}NH_2] = 113$, $[M^+\text{-}C_2H_5] = 101$, $[M^+\text{-}CH_2CHDNH_2] = 84$, $[M^+\text{-}CH_4CHDNH_2] = 70$, $[M^+\text{-}CH_6CHDNH_2] = 57$, $[M^+\text{-}CH_8CHDNH_2] = 43$. FT-IR: $\nu = 2956$ (s), 2856 (s), 2157 (w), 1466 (m), 1069 (m), 939 (m), 723 (w).

(*S*)-1-^{2}H-1-Octanol [(*S*)-2]

Octanal (1.5 g, 11.7 mmol) was dissolved in isopropanol-*d8* (14 mL). To this solution, phosphate buffer solution (100 mL), NADPH (0.5 g), and a few drops of $MgCl_2$ (0.1 M in distilled water) were added. The temperature was set to 36 °C, ADH-LB (380 U) was added, and the reaction mixture was left stirring at 36 °C for 4 days. The same procedure was followed to obtain alcohol (*S*)-**2** as colorless oil (1.25 g, 83%). $Ee = 89 \pm 1\%$. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.56$ (tt, $J = 6.8$ and 1.2 Hz, 1H, -CH_2CHDOH), 1.51 [q, $J = 6.8$ Hz, 2H, -$(CH_2)_5CH_2CHDOH$], 1.27 [m, 10H, $CH_3(CH_2)_5CH_2$-], 0.85 [t, $J = 7.2$ Hz, 3H, $CH_3(CH_2)_5$-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 62.0$ (t), 32.5, 31.7, 29.3, 26.1, 25.6, 22.5, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 2.64$ min, purity >99.5%, major peaks: $[M^+\text{-}CHDOH] = 99$, $[M^+\text{-}CH_2CHDOH] = 84$, $[M^+\text{-}CH_4CHDOH] = 70$, $[M^+\text{-}CH_6CHDOH] = 57$, $[M^+\text{-}CH_8CHDOH] = 43$. FT-IR: $\nu = 3336$ (br), 2956 (s), 2856 (s), 2157 (w), 1711 (s), 1466 (m), 1069 (m), 939 (m), 723 (w).

(*R*)-1-^{2}H-1-Octylamine [(*R*)-4]

The desired amine (*R*)-**4** was obtained from (*S*)-**2** by following the same procedure as described previously. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.62$ (t, $J = 6.8$ Hz, 1H, -CH_2CDHNH_2), 1.60 (br. s, 2H, -CH_2CDHNH_2), 1.40 [q, $J = 6.8$ Hz, $CH_3(CH_2)_5CH_2CDHNH_2$], 1.2 [m, 10H, $CH_3(CH_2)_5CH_2CDHNH_2$], 0.85 [t, $J = 7.2$, 3H, $CH_3(CH_2)_5CH_2CDHNH_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 41.7$ (t), 33.6, 31.7, 29.2, 26.8, 22.6, 15.2, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 2.00$ min, purity = 94%, major peaks: $[M^+] = 130$, $[M^+\text{-}NH_2] = 113$, $[M^+\text{-}C_2H_5] = 101$, $[M^+\text{-}CH_2CHDNH_2] = 84$, $[M^+\text{-}CH_4CHDNH_2] = 70$, $[M^+\text{-}CH_6CHDNH_2] = 57$, $[M^+\text{-}CH_8CHDNH_2] = 43$. FT-IR: $\nu = 2956$ (s), 2856 (s), 2157 (w), 1466 (m), 1069 (m), 939 (m), 723 (w).

(*rac*)-1-^{2}H-1-Octanol [(*rac*)-5]

Octanal (2.0 g, 16.5 mmol) in ether (20 mL) was added dropwise to a solution of $LiAlD_4$ (0.43 g, 10.1 mmol) in ether (10 mL) at 0 °C. The reaction mixture was

refluxed for 2 h and then quenched with ice water (10 mL) slowly. The mixture was extracted with ether (3 × 50 mL). The combined organic layers were washed with HCl (1 M) solution, water, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was isolated as clear oil (1.95 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.56$ (tt, $J = 6.8$ and 1.2 Hz, 1H, -CH_2CHDOH), 1.51 [q, $J = 6.8$ Hz, 2H, -$(CH_2)_5CH_2CHDOH$], 1.27 [m, 10H, $CH_3(CH_2)_5CH_2$-], 0.85 [t, $J = 7.2$ Hz, 3H, $CH_3(CH_2)_5$-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 62.0$ (t), 32.5, 31.7, 29.3, 26.1, 25.6, 22.5, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 2.64$ min, purity >99.5%, major peaks: $[M^+\text{-}CHDOH] = 99$, $[M^+\text{-}CH_2CHDOH] = 84$, $[M^+\text{-}CH_4CHDOH] = 70$, $[M^+\text{-}CH_6CHDOH] = 57$, $[M^+\text{-}CH_8CHDOH] = 43$.

(*rac*)-1-^{2}H-1-Octylamine [(*rac*)-6]

The desired racemic amine was obtained from (*rac*)-**5** (3.53 g, 27 mmol) as a yellowish oil (3.50 g, 99%) by following the same procedure as described previously. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.62$ (t, $J = 6.8$ Hz, 1H, -CH_2CDHNH_2), 1.60 (br. s, 2H, -CH_2CDHNH_2), 1.40 [q, $J = 6.8$ Hz, $CH_3(CH_2)_5CH_2CDHNH_2$], 1.2 [m, 10H, $CH_3(CH_2)_5CH_2CDHNH_2$], 0.85 [t, $J = 7.2$, 3H, $CH_3(CH_2)_5CH_2CDHNH_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 41.7$ (t), 33.6, 31.7, 29.2, 26.8, 22.6, 15.2, 14.0 ppm. GC-MS temperature program: 50 °C | 15 min → 300 °C, 10 °C/min. $t_R = 2.00$ min, purity = 94%, major peaks: $[M^+] = 130$, $[M^+\text{-}NH_2] = 113$, $[M^+\text{-}C_2H_5] = 101$, $[M^+\text{-}CH_2CHDNH_2] = 84$, $[M^+\text{-}CH_4CHDNH_2] = 70$, $[M^+\text{-}CH_6CHDNH_2] = 57$, $[M^+\text{-}CH_8CHDNH_2] = 43$.

General Synthesis Procedure for MTPA Derivatives

The desired alcohol or amine (0.10 mmol) was dissolved in dry chloroform (300 μL) under an argon atmosphere. To this solution, dry pyridine (300 μL) and (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(*R*)-(−)-MTPA-Cl] (26 μL, 0.14 mmol) were injected using a syringe. The reaction mixture was stirred overnight at room temperature. A few drops of water were added, and the mixture was left stirring for 10 min. The mixture was diluted with ether (10 mL) and washed with cold HCl (1 M), Na_2CO_3, and saturated brine solution. The combined organic layers were dried on $MgSO_4$, and subsequently the solvent was removed under reduced pressure. The desired ester or amide was obtained as a colorless oil in quantitative yield. The NMR spectra of these samples were recorded, and the relative proportions of the diastereomers were determined from the integrals of the proton signals.

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