

Synthesis of (*S*)-Ketamine via [1,3]-Chirality Transfer of a Stereocenter Created by Enantioselective Aldol Reaction

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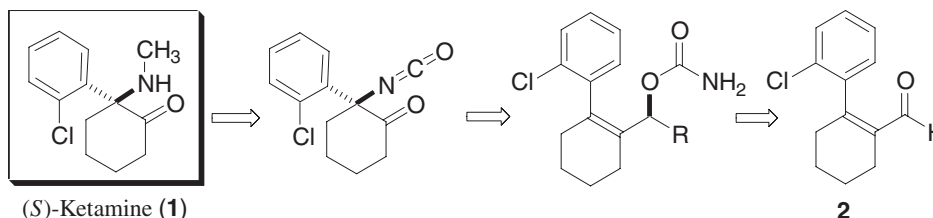
The stereocenter in the intermediate alcohol (86% ee), created by enantioselective oxazaborolidinone-promoted aldol reaction, was transferred to the stereocenter in the cyclohexanone ring, necessary for (*S*)-ketamine, via allyl cyanate-to-isocyanate rearrangement. The second asymmetric synthesis of (*S*)-ketamine has been achieved (87% ee).

Ketamine (**1**) has been widely used since 1963 as an anesthetic and analgesic in human and veterinary medicine under the trade name Ketalar.¹ The preparation of racemic **1** was reported by Stevens through thermal isomerization of 1-[(2-chlorophenyl)(methylimino)methyl]cyclopentanol.^{2–5} Commercially available ketamine is a racemic mixture of two enantiomers. The *S* enantiomer is shown to be more potent with an approximately 3- to 4-fold anesthetic potency compared to the *R* enantiomer. (*R*)-**1** causes undesirable side effects, including agitation, hallucination, and restlessness in contrast to (*S*)-**1**.⁶ However, the effective (*S*)-**1** is only obtainable via optical resolution of the tartaric acid salt,⁷ leaving the undesired (*R*)-**1** as a by-product. Therefore, development of an enantioselective synthesis for the *S* enantiomer is highly desirable.

We have recently reported⁸ the first asymmetric synthesis of (*S*)-**1** in which the chirality of the precursor allyl alcohol, introduced by an enantioselective reduction,⁹ was utilized for the construction of the nitrogen-substituted quaternary carbon by an allyl cyanate-to-isocyanate rearrangement.¹⁰ The enantioselective reduction supplying chiral allyl alcohols is useful for the strategy but is limited for the construction of bioactive compounds having various types of side chains. Then, we planned to apply an enantioselective aldol reaction for the purpose of chirality introduction.

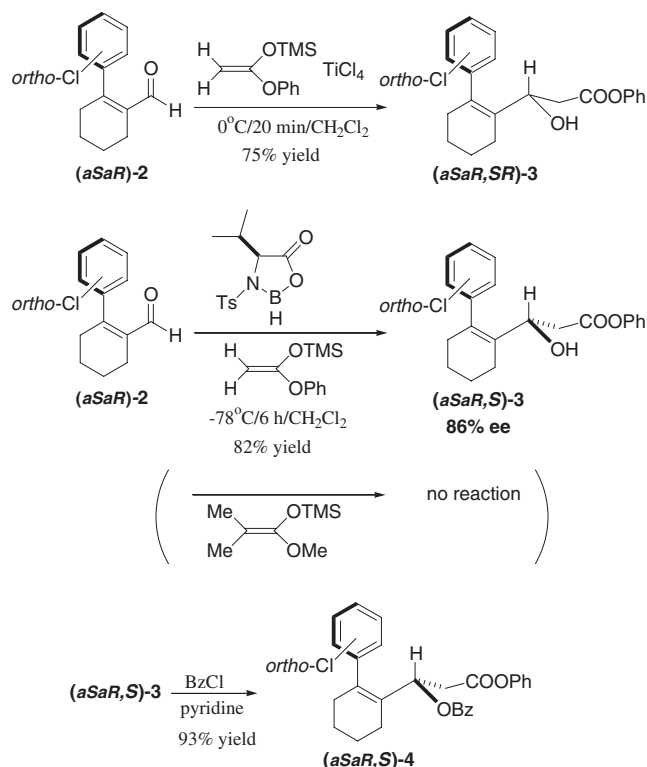
Results and Discussion

The retrosynthesis of (*S*)-**1** suggested that aldehyde **2** is suitable as a synthetic intermediate for the reaction sequence



Scheme 1. Target molecule and retrosynthetic overview.

(Scheme 1). A precursor nitrile to **2** was prepared from ethyl 2-chlorobenzoylacetate,¹¹ according to Fleming's procedure.¹² DIBAL reduction of the nitrile at -78°C gave the aldehyde **2** in a good yield.¹³ The chiral oxazaborolidinone-promoted enantioselective aldol reaction¹⁴ of **2** with 1-phenyloxy-1-(trimethylsilyloxy)ethene proceeded to give the corresponding aldol product **3** in 82% yield (Scheme 2), while dimethylketene methyl trimethylsilyl acetal did not work presumably owing to its steric bulkiness. The ^1H NMR spectra of **3** indicated that the product was a mixture (ca. 3:2) of diastereomers. The appearance of the diastereoisomers is evidently attributable to a new stereocenter associated with atropisomerism¹⁵ on the hindered rotation about the single bond between the ortho substituted phenyl and cyclohexene rings. The diastereomers could not be resolved by silica gel column chromatography. The difficulty of the separation can be suspected to arise from epimerization around the atropic axis during silica gel chromatography. When the standard sample of the atropisomeric mixture, (*aSaR,SR*)-**3**, provided by the corresponding TiCl_4 -mediated aldol reaction, was introduced to a chiral HPLC column, a couple of diastereomeric pairs were observed and epimerization turned out to take place between the atropisomeric pairs, **A** and **B** (Figure 1). The aldol products **3** from the chiral oxazaborolidinone-promoted reaction also underwent the interconversion so that the chiral HPLC measurement of **3** would not indicate correct values of the enantioselectivity. Then, the level of the enantioselectivity was determined after conversion of the aldols (*aSaR,SR*)-**3** to their benzoates



Scheme 2. Introduction of the chiral center necessary for (*S*)-ketamine by enantioselective aldol reaction.

(*aSaR,SR*)-4 and the chiral HPLC analysis without epimerization revealed to be 86% ee as a pair of (*aS,S*)-4 and (*aR,S*)-4, as shown in Figure 2.¹⁶ Here the four peaks could not completely correspond to the structures corresponding to the four enantiomers but larger peaks be apparently confirmed to *S* enantiomers from the results of the absolute configuration and the level of the enantioselectivity of the final product (*S*)-1. In addition, the diastereomeric ratio of 4 changed to ca. 3:1 through epimerization occurring during benzylation.

Completion of the synthesis directed toward (*S*)-1 is as follows (Scheme 3). The aldol 3 was converted by lithium aluminum hydride reduction to diol 5 (96% yield), followed by benzylation to give the corresponding mono-benzyl derivative 6 (87% yield). Reaction of 6 with trichloroacetyl isocyanate in dichloromethane and subsequent hydrolysis with potassium carbonate in aqueous methanol provided carbamate (*aSaR,S*)-7 in 95% yield.^{8,10} The carbamate 7, consisting of the atropisomers, was employed as a precursor of the allyl cyanates 8 for the successive allyl cyanate-to-isocyanate rearrangement. Dehydration of 7 was performed with triphenylphosphine, carbon tetrabromide, and triethylamine at 0 °C for 20 min. During the one-pot procedure, the expected [3,3]-sigmatropic rearrangement with the 1,3-chirality transfer took place via the transient (*aS,S*)- and (*aR,S*)-8 to give the corresponding isocyanate (*R*)-9. The quite stable isocyanate 9 was isolated as a single isomer in 86% yield. Treatment of 9 with lithium aluminum hydride in THF provided the methylamine (*R*)-10 in 87% yield. Avoiding reaction of the basic allylic amino function with the intermediate ozonide, the hydrogen chloride salt of (*R*)-10 was used for the ozonolysis in the final step to ketamine.⁸ Ozonolysis of 10 in methanol at −18 °C followed by reductive work-up with

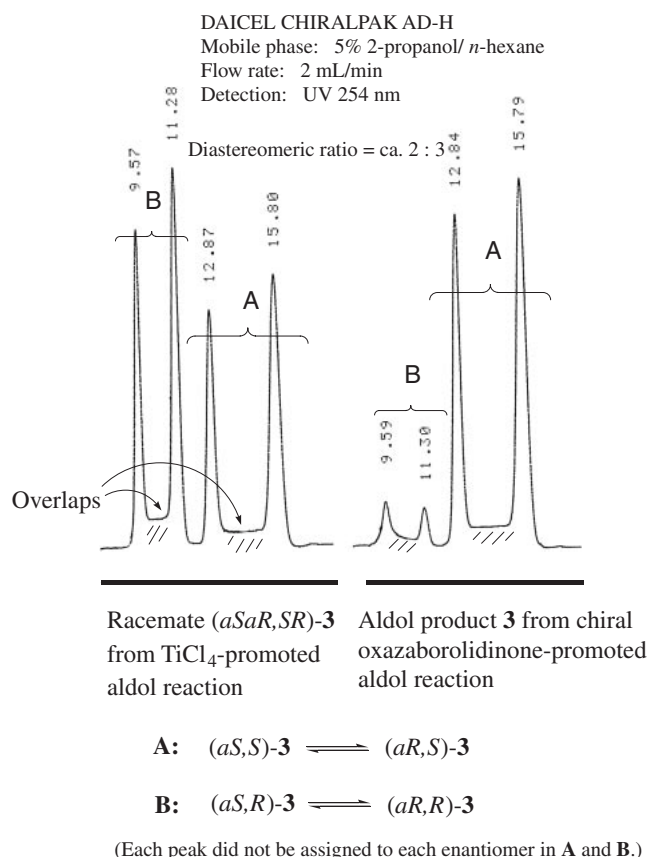


Figure 1. Epimerization between two atropisomeric pairs involving four enantiomers, indicated by the rise of their base lines, observed during HPLC measurement.

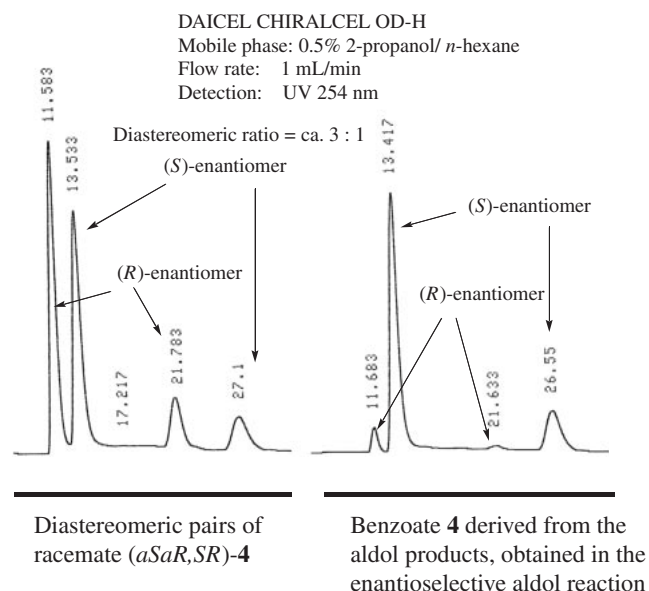
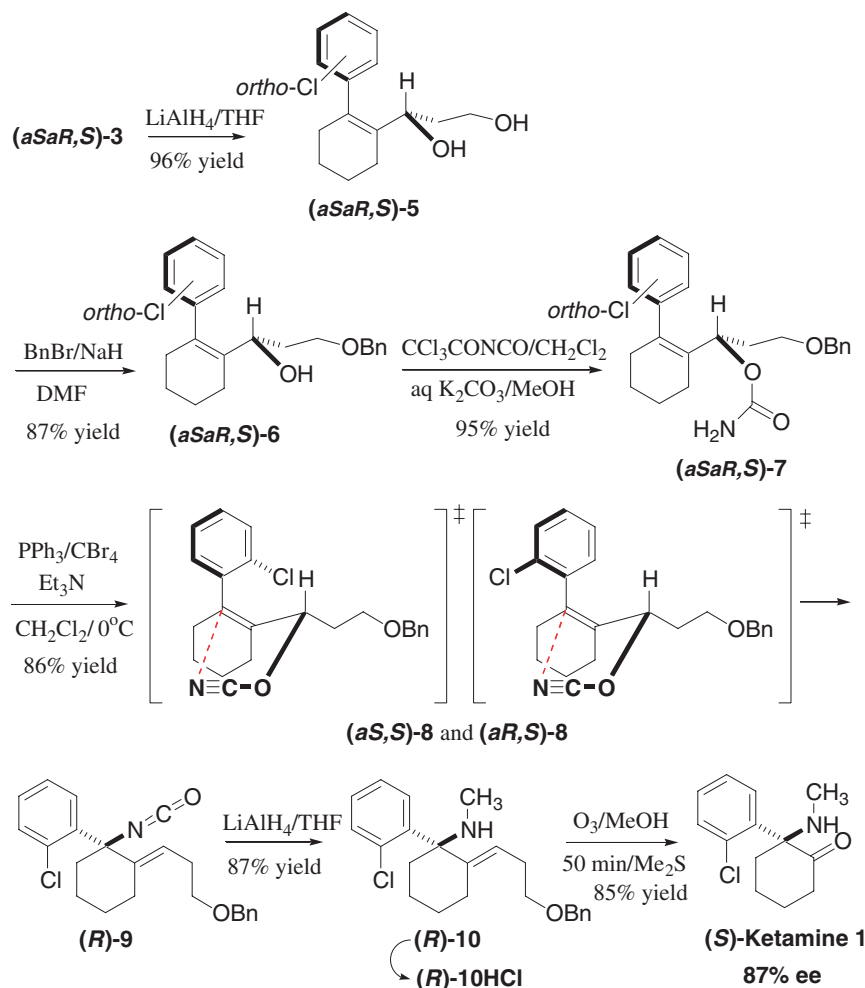


Figure 2. Determination (86% ee of *S*) of enantioselectivity by chiral HPLC with the benzoates 4 derived from the aldols 3.

dimethyl sulfide proceeded smoothly to give the final product 1 as its hydrogen chloride salt which was crystallized from ethanol/*n*-hexane in 85% yield. The synthetic ketamine 1

Scheme 3. Completion of asymmetric synthesis of (*S*)-ketamine.

was determined by chiral HPLC (DAICEL CHIRALCEL OD-H/5% 2-propanol/*n*-hexane) analysis to be 87% ee of *S* configuration (Figure 3). Throughout the synthetic process, the optical purity of the compounds: **5**, **6**, **7**, **9**, and **10**, is retentively regarded as the same level (86% ee) of **3**.

The enantioselectivity of the aldol product was transferred with the same level to that of the final product where the stereospecific sigmatropic rearrangement proceeded without any influence of the *ortho*-chloro substituent. Thus, the second asymmetric synthesis of (*S*)-**1** has been accomplished with high selectivity. Although the aldol moiety was finally eliminated for the purpose of the ketamine synthesis, this enantioselective aldol-reaction approach toward the construction of nitrogen-substituted quaternary carbons will develop profitable routes extending various side chains in the forthcoming synthesis of bioactive natural products.

Experimental

General. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. All reagent solutions were handled under an argon atmosphere by using syringes. All reactions unless otherwise noted were carried out under an argon atmosphere. Merck silica gel 60 TLC aluminum sheets were used for thin layer chromatography. Flash column chromatography was carried out with Merck 60 silica gel

(230–400 mesh). Infrared spectra (IR) were recorded on a JASCO FT/IR-460 and only partial data are listed. Optical rotations were determined with a JASCO DIP-370 digital polarimeter. ¹H NMR spectra were obtained in CDCl₃ with a JNM-LA 400 (400 MHz) spectrometer; chemical shifts (δ) are expressed in ppm relative to internal standard tetramethylsilane and coupling constants are reported in Hz. ¹³C NMR spectra were measured at 100 MHz with a JNM-LA 400 spectrometer with complete proton decoupling; chemical shifts are reported in ppm relative to tetramethylsilane with the solvent resonance as the internal standard (CDCl₃, δ 77.0). Enantiomeric excess (ee) was determined by HPLC analysis using DAICEL CHIRALCEL OD-H and CHIRALPAK AD-H columns.

(*aSaR,S*)-Phenyl 3-[2-(2-Chlorophenyl)-1-cyclohexenyl]-3-hydroxypropionate ((*aSaR,S*)-3**) from Chiral Oxazaborolidinone-Promoted Enantioselective Aldol Reaction of (*aSaR*)-**2**.** To a stirred solution of *N*-(*p*-toluenesulfonyl)-(*S*)-valine (772 mg, 2.85 mmol) in dry CH₂Cl₂ (8 mL) at 0 °C was added BH₃·THF (2.59 mL, 2.59 mmol, 1 M in THF). The solution was allowed to stir for 30 min at 0 °C and an additional 30 min at room temperature. The solution was then cooled to −78 °C and aldehyde **2** (571 mg, 2.59 mmol) [IR (film): 1676 cm^{−1}; ¹H NMR (400 MHz, CDCl₃): δ 1.70–1.84 (m, 4H), 2.27–2.32 (m, 1H), 2.34–2.37 (m, 2H), 2.57–2.65 (m, 1H), 7.16–7.21 (m, 1H), 7.28–7.30 (m, 2H), 7.38–7.45 (m, 1H), 9.32 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 21.3, 21.7, 22.1, 33.1, 126.7, 129.2, 129.7, 130.1, 132.6, 136.4, 138.4, 157.0, 192.8] in CH₂Cl₂ (1 mL) was added slowly over

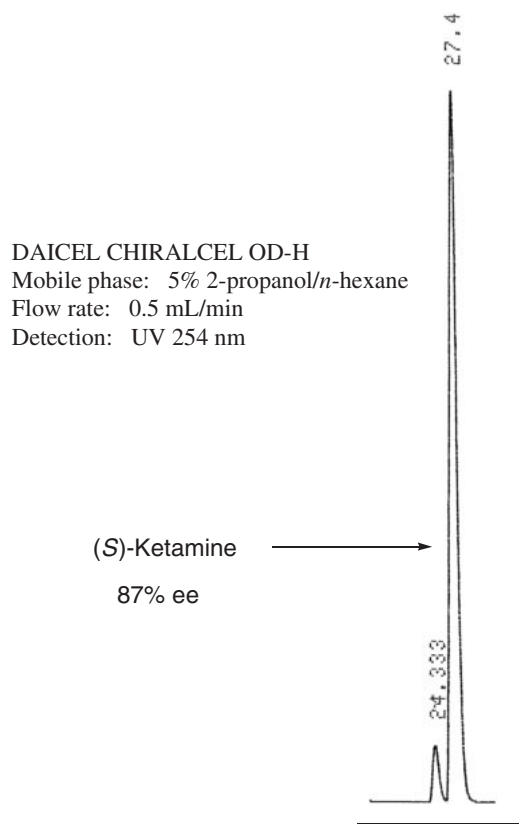


Figure 3. Determination of enantiopurity of synthetic (S)-ketamine.

5 min. After stirring for 5 min, 1-phenyloxy-1-(trimethylsilyloxy)ethene (593 mg, 2.85 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 5 min and the reaction mixture was stirred for 6 h before quenching with a buffer solution (5 mL, pH 6.86). The resulting mixture was allowed to warm to room temperature. The organic layer was extracted with ether, washed with aqueous saturated NaHCO_3 solution and brine. The resulting solution was dried over MgSO_4 and evaporated in vacuo. Flash column chromatography (20% ethyl acetate/*n*-hexane) provided a mixture (4:1) of aldols **3** (758 mg, 82%). **3**: Colorless oil, IR (film): 3465, 1758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): a mixture of major and minor isomers (a hydroxy proton is overlapping); δ 1.51–1.73 (m, 4H), 1.96 (m, 2H), 2.12–2.19 (m, 1H), 2.32 (m, 1H), 2.51 (ddd, $J = 15.8, 4.8, 1.8$ Hz, 1H), 2.73 (ddd, $J = 16.7, 10.6, 8.8$ Hz, 1H), 4.34 and 4.95 (major dd, $J = 8.4, 5.6$ Hz and minor d, $J = 2.5$ Hz, respectively, 2H), 6.86–7.23 (m, 9H); ^{13}C NMR (100 MHz, CDCl_3): major: δ 22.2, 22.4, 22.7, 31.4, 39.1, 67.9, 121.4 ($\times 2$), 125.8, 127.1, 128.2, 129.3 ($\times 2$), 129.5, 129.5, 132.5, 134.4, 134.5, 141.1, 150.3, 170.0; minor: δ 22.1, 22.4, 22.8, 31.4, 39.1, 68.4, 121.4 ($\times 2$), 125.8, 127.0, 128.2, 129.3 ($\times 2$), 129.5, 129.6, 130.2, 131.7, 133.9, 141.1, 150.4, 171.7. Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{O}_3\text{Cl}$: C, 70.68; H, 5.93%. Found: C, 70.43; H, 6.01%.

(*aSaR,S*)-1-[2-(2-Chlorophenyl)-1-cyclohexyl]-1,3-propanediol ((*aSaR,S*)-5). To a slurry of large excess LiAlH_4 (50 mg, 1.31 mmol) in THF (1 mL) was added dropwise a solution of (*aSaR,S*)-**3** (148 mg, 0.421 mmol) in THF (1 mL). The resulting solution was stirred at room temperature for 1 h and then refluxed for 30 min. After cooling, a 30% NaOH solution (1 mL) was added and the mixture was stirred for 1 h. The reaction mixture was extracted with ether (10 mL $\times$ 3). The combined organic layers

were washed with brine and dried (Na_2SO_4). Concentration under reduced pressure gave a residue, which was purified by flash chromatography to afford the corresponding diol (*aSaR,S*)-**5** (106 mg, 96%). **5**: Colorless oil, IR (film): 3366 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): a mixture of major and minor isomers; δ 1.44–1.90 (m, 6H), 1.96–2.13 (m, 2H), 2.22–2.41 (m, 2H), 3.15 (brs, 2H), 3.47–3.65 (m, 2H), 4.08–4.14 (m, 1H), 7.10–7.40 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): major: δ 22.2, 22.4 ($\times 2$), 22.7, 30.9, 35.8, 61.6, 71.9, 126.8, 127.9, 129.2, 129.6, 132.6, 135.7, 141.4; minor: δ 22.0, 22.4, 22.8, 23.0, 35.9, 61.0, 71.7, 126.8, 127.9, 129.3, 130.2, 131.7, 132.8, 136.0, 141.3. Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{O}_2\text{Cl}$: C, 67.54; H, 7.18%. Found: C, 67.359; H, 7.21%.

(*aSaR,S*)-3-Benzoyloxy-1-[2-(2-chlorophenyl)-1-cyclohexyl]-1-propanol ((*aSaR,S*)-6). To a DMF-washed solution of excess NaH (40 mg of 60% dispersion in mineral, 1.00 mmol) in DMF (7 mL) was added dropwise a solution of diol **5** (160 mg, 0.600 mmol) in DMF (1 mL). The resulting solution was stirred at room temperature for 1 h. After cooling, a 30% NaOH solution (1 mL) was added and the mixture was heated at 90 $^\circ\text{C}$ for 1 h. A solution of benzyl bromide (78 mg, 0.662 mmol) was added and the mixture was heated at 50 $^\circ\text{C}$ for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (10 mL $\times$ 3). The combined organic layers were washed with brine and dried (Na_2SO_4). Concentration under reduced pressure gave a residue, which was purified by flash chromatography to afford the corresponding mono-benzyl compound **6** (186 mg, 87%). **6**: Colorless oil, IR (film): 3434 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): a mixture of major and minor isomers; δ 1.60–1.84 (m, 6H), 1.90–2.13 (m, 2H), 2.25–2.45 (m, 2H), 2.67 (brs, 1H), 3.40–3.62 (m, 2H), 4.12–4.18 (m, 1H), 4.35–4.46 (m, 2H), 7.12–7.39 (m, 9H); ^{13}C NMR (100 MHz, CDCl_3): major: δ 22.3, 22.5, 22.8, 31.0, 34.1, 69.4, 71.5, 72.9, 126.9, 127.5 ($\times 2$), 127.9, 128.3 ($\times 2$), 129.3, 129.8, 130.4, 132.9, 133.2, 135.9, 137.9, 141.7; minor: δ 22.0, 22.5, 22.8, 31.4, 34.0, 68.0, 70.1, 72.8, 126.9, 127.4 ($\times 2$), 127.9, 128.2 ($\times 2$), 129.4, 129.8, 130.4, 132.8, 133.2, 136.2, 138.2, 141.7. Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{O}_2\text{Cl}$: C, 74.04; H, 7.06%. Found: C, 73.91; H, 7.11%.

(*aSaR,S*)-3-Benzoyloxy-1-[2-(2-chlorophenyl)-1-cyclohexenyl]-propyl Carbamate ((*aSaR,S*)-7). To a solution of alcohol (*aSaR,S*)-**6** (152 mg, 0.426 mmol) in CH_2Cl_2 (3 mL) at 0 $^\circ\text{C}$ was added trichloroacetyl isocyanate (101 μL , 0.852 mmol) and the reaction mixture was stirred at 0 $^\circ\text{C}$ for 15 min. After stirring at room temperature for 15 min, evaporation of the solvent gave a crude material. The residue was dissolved in an aqueous K_2CO_3 (474 mg) solution in water (2 mL) and MeOH (3 mL). The reaction mixture was stirred at room temperature for 1.5 h. After extraction with ether (10 mL $\times$ 3), the combined organic layers were washed with brine and dried (MgSO_4). Evaporation of the solvent under reduced pressure gave a crude product which was purified by flash chromatography on silica gel (30% AcOEt/*n*-hexane) to afford allyl carbamate (*aSaR,S*)-**7** (161 mg, 95%). **7**: Colorless oil, IR (film): 3350, 1715, 1599 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): a mixture of major and minor isomers; δ 1.64–2.15 (m, 10H), 4.32 and 4.40 (dd, $J = 20.5, 12.0$ Hz and dd, $J = 15.0, 12.5$ Hz, respectively, 2H), 5.07–5.11 (m, 1H), 7.15–7.35 (m, 9H); ^{13}C NMR (100 MHz, CDCl_3): major: δ 22.3, 22.6, 22.8, 30.8, 32.2, 66.7, 72.3, 73.0, 126.8, 127.3, 127.4 ($\times 2$), 128.1 ($\times 3$), 128.2, 129.2, 130.4, 132.8, 134.3, 138.4, 140.9, 156.1, minor: δ 22.3, 22.7, 23.3, 31.2, 33.2, 66.9, 72.6, 72.8, 126.4, 127.4, 127.6, 127.7 ($\times 2$), 128.1 ($\times 2$), 128.5, 129.5, 130.1, 132.6, 134.9, 138.3, 141.0, 156.1.

(1*R*,2*E*)-2-(3-Benzoyloxypropylidene)-1-(2-chlorophenyl)-cyclohexyl Isocyanate ((1*R*,2*E*)-9). To a solution of carbamate **7** (150 mg, 0.375 mmol), triphenylphosphine (301 mg, 1.15 mmol),

and triethylamine (306 μ L, 2.20 mmol) in CH_2Cl_2 (6 mL) cooled to 0 °C was added a solution of carbon tetrabromide (369 mg, 1.11 mmol) in CH_2Cl_2 (3.5 mL). After stirring at 0 °C for 30 min, the reaction mixture was diluted with hexane (20 mL). The resulting reaction mixture was washed with H_2O and aqueous saturated NaHCO_3 solution, and dried (MgSO_4). Evaporation of the solvent under reduced pressure gave a crude product which was purified by flash chromatography on silica gel (20% EtOAc/*n*-hexane) to afford isocyanate **9** (123 mg, 86%). **9**: Colorless oil, $[\alpha]_{\text{D}}^{18}$ -81.1 (*c* 1.17, CHCl_3); IR (film): 2255 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.26–1.57 (m, 1H), 1.74–1.91 (m, 4H), 2.26–2.42 (m, 3H), 2.61 (dt, *J* = 14.6, 3.6 Hz, 1H), 2.69–2.76 (m, 1H), 3.40 (t, *J* = 6.6 Hz, 2H), 4.45 (s, 2H), 5.05 (t, *J* = 6.6 Hz, 1H), 7.21–7.31 (m, 7H), 7.37 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.72 (dd, *J* = 8.0, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.6, 25.4, 25.5, 28.1, 39.2, 68.9, 69.5, 72.8, 122.5, 126.9, 127.4, 127.5 ($\times 3$), 128.3 ($\times 2$), 128.8, 129.3, 132.0, 132.9, 138.4, 138.6, 139.8. Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{NO}_2\text{Cl}$: C, 72.34; H, 6.33%. Found: C, 72.10; H, 6.57%.

(1R,2E)-2-(3-Benzyloxypropylidene)-1-(2-chlorophenyl)-1-methylaminocyclohexane ((1R,2E)-10**)**. To a slurry of a large excess LiAlH_4 (59 mg, 1.52 mmol) in THF (1 mL) was added dropwise a solution of isocyanate **9** (83 mg, 0.220 mmol) in THF (1 mL). The resulting solution was stirred at room temperature for 1 h and then refluxed for 30 min. After cooling, a 30% NaOH solution (1 mL) was added and the mixture was heated at 90 °C for 1 h. The reaction mixture was extracted with ether (10 mL $\times 3$). The combined organic layers were washed with brine and dried (Na_2SO_4). Concentration under reduced pressure gave a residue, which was purified by flash chromatography to afford the corresponding methyl amine **10** (70 mg, 87%). **10**: Colorless liquid, $[\alpha]_{\text{D}}^{18}$ -8.2 (*c* 0.97, CHCl_3); IR (film): 3385, 1101 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.45–1.52 (m, 1H), 1.60–1.85 (m, 4H), 1.90 (brs, 1H), 2.04 (s, 3H), 2.27–2.32 (m, 2H), 2.35–2.43 (m, 3H), 3.43 (t, *J* = 7.4 Hz, 2H), 4.47 (s, 2H), 4.97 (t, *J* = 7.3 Hz, 1H), 7.17 (dt, *J* = 7.1, 1.8 Hz, 1H), 7.23–7.38 (m, 7H), 7.51 (dd, *J* = 8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.4, 25.8, 27.2, 28.1, 29.3, 36.5, 65.6, 70.1, 72.3, 119.8, 126.4, 127.4, 127.5 ($\times 2$), 127.6, 128.3 ($\times 2$), 130.4, 131.7, 133.9, 138.6, 140.9, 141.5.

(S)-Ketamine 1. Amine **10** (72 mg, 0.262 mmol) was dissolved in 10% HCl solution (2 mL). Concentration under reduced pressure gave the corresponding amine HCl salt. Ozone was passed into a solution of the amine HCl salt in MeOH (5 mL) at -78°C , terminating the ozonolysis upon observing the distinctive blue color of ozone. After purging with nitrogen, dimethyl sulfide (400 μ L) was added at -78°C . The solution was allowed to warm up to room temperature and concentrated under reduced pressure to give a crude material. The crude was dissolved in a 10% NaOH solution (3 mL) and the corresponding amine was extracted with ether (10 mL). After evaporation of the solvent, the amine was purified by flash chromatography (50% AcOEt/*n*-hexane) to afford (S)-ketamine (63 mg, 85%). The enantiomeric excess was determined to be 87% by HPLC (DAICEL CHIRALCEL OD-H column, Mobile phase 5% 2-propanol/*n*-hexane, Flow rate 0.5 mL min^{-1} , *Rt* (min) 24.3 (R), 27.4 (S)). **1**: Colorless crystals, Mp 120 °C (*n*-hexane); $[\alpha]_{\text{D}}^{21}$ -49.3 (*c* 1.50, EtOH) (Lit. value, $[\alpha]_{\text{D}}^{25}$ -56.9 (*c* 2.00, EtOH));¹⁷ IR (film): 3353, 1701, 752 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.72–1.78 (3H, m), 1.82–1.90 (1H, m), 1.96–2.05 (1H, m), 2.06–2.15 (1H, m), 2.11 (3H, s), 2.44–2.55 (2H, m), 2.76–2.82 (1H, m), 7.24 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.32 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.38 (dd, *J* = 7.5, 1.5 Hz, 1H),

7.55 (dd, *J* = 7.5, 1.5 Hz, 1H); ^{13}C NMR (CDCl_3): δ 21.7, 28.0, 29.0, 38.5, 39.4, 70.0, 126.5, 128.6, 129.3, 131.1, 133.6, 137.7, 209.1.

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