Synthesis of Enantiomerically Pure 8-Substituted 5,6,7,8-Tetrahydro quinolines

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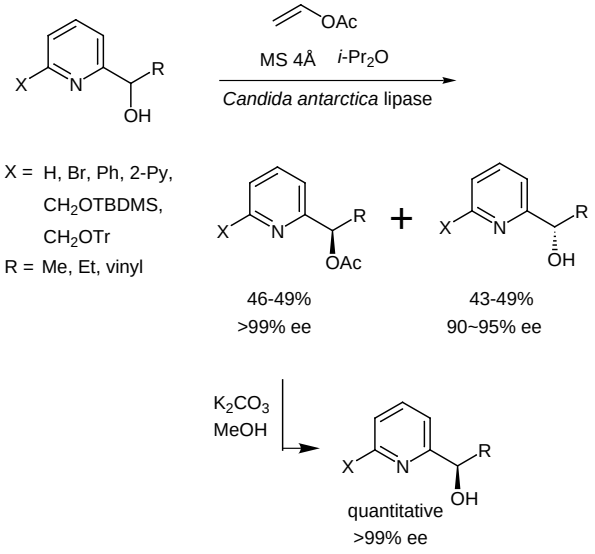
Abstract: Enantiomerically pure (*S*)-5,6,7,8-tetrahydroquinolin-8-ol [(*S*)-**1**] and (*R*)-8-acetoxy-5,6,7,8-tetrahydroquinoline [(*R*)-**2**] have been prepared by the lipase-catalyzed kinetic acetylation of racemic 5,6,7,8-tetrahydroquinolin-8-ol [(±)-**1**] in excellent chemical yields. The mesylation of (*R*)-**1** followed by a substitution reaction with the azide, thioacetate, and dimethyl malonate anions and benzylamine gives the corresponding substituted products in an enantiomerically pure form with an inversion of the configuration in good yields. The methanolysis of (*S*)-5,6,7,8-tetrahydroquinolin-8-yl acetate in the presence of potassium carbonate and alkylation of the resulting thiol anion with alkyl halides in a one-pot reaction gives the 5,6,7,8-tetrahydroquinolin-8-yl thioether.

Key words: 8-substituted quinolines, enzymatic acetylation, nucleophiles, stereospecific substitutions, asymmetric synthesis

Quinolines and hydrogenated quinolines are very important components of alkaloids, and medicines.[1] We became interested in 8-substituted 5,6,7,8-tetrahydroquinolines, because of their potent and unique biological activities present in their 8-nitrogen,[2] 8-sulfur,[3] and 8-carbon[4] substituted analogues. There are a number of synthetic methods for the 5,6,7,8-tetrahydroquinolines, including i) the construction of the pyridine ring from cyclohexanone oxime or other functional groups,[5,6] ii) the Diels–Alder reaction of an enamine,[7] and iii) the reduction of quinoline.[8] However, these methods have not been used directly for the synthesis of the 8-substituted 5,6,7,8-tetrahydroquinolines. Most syntheses were performed by the direct introduction of a functional group on the 8-position of 5,6,7,8-tetrahydroquinoline.[9,10] Surprisingly, to date, an enantiomerically pure derivative has never been prepared. Therefore, an asymmetric synthesis of the 8-substituted 5,6,7,8-tetrahydroquinolines is highly desired.

In this paper, we report the preparation of the enantiomerically pure 5,6,7,8-tetrahydroquinolin-8-ol (**1**) and the first synthesis of the enantiomerically pure 8-amino, acylthio, alkylthio, and bis(methoxycarbonyl)methyl substituted 5,6,7,8-tetrahydroquinolines by the stereospecific substitution reactions of the enantiomerically pure 5,6,7,8-tetrahydroquinolin-8-ol methanesulfonate ester.

Our synthetic approach began with the preparation of an enantiomerically pure **1**. Recently, we have reported the *Ca*l (*Candida antarctica* lipase)-catalyzed kinetic acetylation of racemic 1-(2-pyridinyl)ethanols, in which the (*R*)-acetate and the recovered (*S*)-1-(2-pyridinyl)ethanol were obtained in 45–49% yields with over 90% enantiomeric purities (Scheme 1).[11]



Scheme 1

This method has a number of advantages including a simple and convenient recipe, a clean reaction, an excellent enantioselectivity, a high chemical yield, and the availability of both the *R*- and *S*-enantiomers in one reaction. However, the enantiomeric discrimination reaction of 1-(2-pyridinyl)alkanol is limited to the length of the alkanol chain having less than three linear carbons.[11a] Although four methylene carbons at the C2 and C4 positions on the pyridine ring are present in **1**, the conformational flexibility of **1** would be more restricted than that of the 1-(2-pyridinyl)butanol. We believed that the lipase-catalyzed enantiomeric discrimination would work for the racemic **1**.

The racemic 5,6,7,8-tetrahydroquinolin-8-ol [(±)-**1**][12] was treated with vinyl acetate in the presence of *Ca*l and molecular sieves 4Å in diisopropyl ether at 60 °C. The reaction was complete in 30 hours, and gave the acetate (*R*)-**2** and the unreacted (*S*)-quinolinol (*S*)-**1** in 43% and 44% yields, respectively (Scheme 2). The enantiomeric purities were determined to be >99% ee for both the acetate and alcohol by HPLC analysis using a chiral stationary phase column.[13] These absolute configurations were as-

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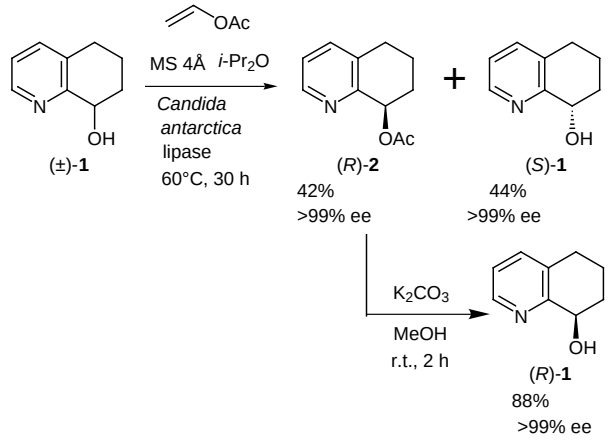
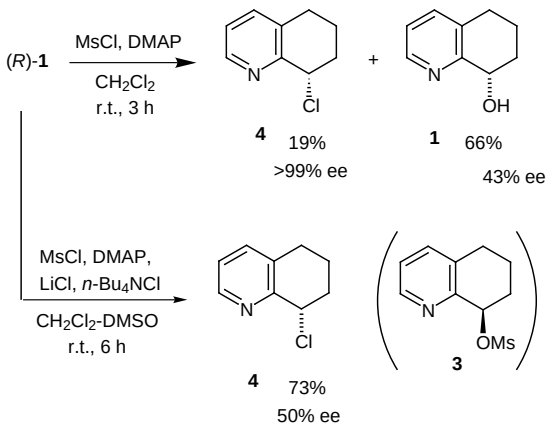
sumed based on the previous results.[14] This stereochemical result may provide additional information on the empirical rule for the stereoselectivity of the lipase-catalyzed acetylation reactions.[15] The acetate (*R*)-**2** was quantitatively hydrolyzed to (*R*)-**1** by treating with K_2CO_3 in methanol (Scheme 2). Thus, both enantiomers for (*R*)- and (*S*)-**1** are now available.



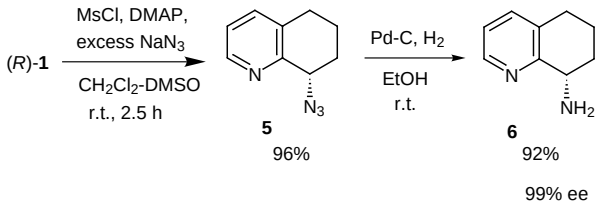
Scheme 2

Mesylation of the alcohol (*R*)-**1** with methanesulfonyl chloride was conducted in CH_2Cl_2 at room temperature in the presence of DMAP. However, the desired methanesulfonate **3** could not be obtained. Instead, 8-chloro-5,6,7,8-tetrahydroquinoline (**4**) was produced in 19% with 99% ee along with 66% yield of the stereo-inverted alcohol (*S*)-**1** with 43% ee. These results suggest that i) the mesylate is not stable enough for isolation like the 1-(2-pyridinyl)ethyl derivatives,[16] and ii) it is surely formed under the given reaction conditions, but hydrolyzed during the workup. When the reaction was performed in the presence of lithium chloride and tetrabutylammonium chloride, **4** was the main product in 73% yield with 50% ee, being formed by the substitution of **3** and/or **4** with an excess of chloride anions (Scheme 3). Although the chloride **4** was obtained with a high enantiomeric purity in the initial stage, the purity was gradually lost by further substitution with an excess of chloride anions resulting in a partially racemized **4**, eventually.

This disappointing result, however, suggested an alternative approach. If another nucleophile is present in the reaction media, it would react with the mesylate and the desired substitution product could be produced. Therefore, the mesylation of (*R*)-**1** was examined in the presence of an excess NaN_3. In fact, the reaction proceeded nicely to give the azide **5** in 99% yield. Catalytic hydrogenation of **5** under a hydrogen atmosphere in the presence of Pd-charcoal afforded 8-amino-5,6,7,8-tetrahydroquinoline (**6**) in 92% yield (Scheme 4). The enantiomeric purity of **6** was confirmed to be over 99% ee by ^1H NMR spectrum after the conversion to the corresponding MTPA-amide.

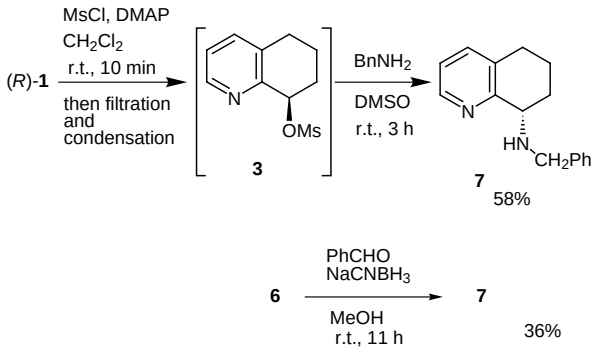


Scheme 3



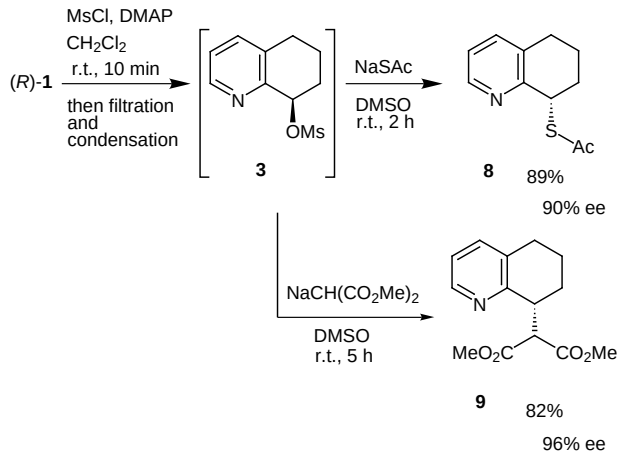
Scheme 4

Unfortunately, this technique is limited to the azide anion. When a primary amine was used, methanesulfonamide was obtained exclusively, instead of the desired aminoquinoline. However, this problem was overcome by another technical approach by removing the formed DMAP hydrochloride by simple filtration. The resulting salt free mesylate **3** was reacted with an excess of benzylamine in DMSO to give 8-benzylamino-5,6,7,8-tetrahydroquinoline (**7**) in 58% yield. Alternatively, the N-benzylation of **6** with benzaldehyde in the presence of sodium cyanoborohydride gave **7** in 36% yield (Scheme 5). Since specific rotations of both of the above 8-benzylamino-5,6,7,8-tetrahydroquinolines (**7**) obtained by two different methods indicated consistency, the substitution reaction of **3** had taken place stereospecifically with an inversion of the configuration similar to the case of the 1-(2-pyridinyl)ethyl methanesulfonate ester.[16]



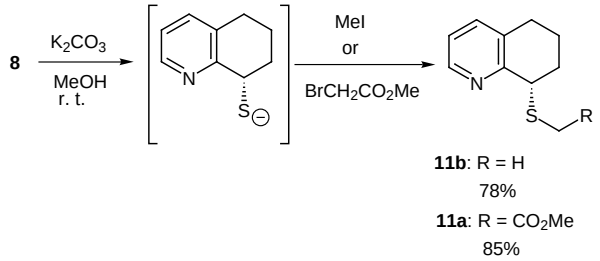
Scheme 5

Since it was gratifyingly found that the mesylate survived during the partial purification process, this method was subjected to other substitution reactions with *S*- and *C*-nucleophiles. Treatment of the mesylate (*R*)-**3** with NaSAc instead of benzylamine gave the 5,6,7,8-tetrahydroquinolin-8-thiol acetate, [(*S*)-**8**] in 89% yield with 90% ee. The partial formation of the (*R*)-isomer originated due to the formation of a small amount of chloride (*S*)-**4**, which reacted with NaSAc in this case. Since other nucleophiles such as benzylamine or malonate ester were poorly reactive with (*S*)-**4**, they were exclusively reacted with the mesylate (*R*)-**3** and gave the corresponding substituted enantiomer without loss of the high enantiomeric purity. In fact, the substituted reaction with the dimethyl malonate sodium salt led to the corresponding *C*-substituted product **9** in 82% yield with 96% ee (Scheme 6).



Scheme 6

The methanolysis of thioacetate **8** was somehow unsuccessful and produced complex mixtures, and no thiol was obtained. However, the reaction mixture was directly treated with idodomethane in a one-pot reaction to give methyl sulfide **11a** in 78% yield with 90% ee. The S-alkylation with methyl bromoacetate also took place to afford the corresponding sulfide **11b** in 85% yield with 90% ee (Scheme 7).



Scheme 7

The enantiomerically pure (*R*)- and (*S*)-5,6,7,8-tetrahydroquinolin-8-ols [(*R*)- and (*S*)-**1**] were obtained in good yields by the lipase-catalyzed kinetic acetylation. The alcohol was converted to a substantially unstable mesylate, and the salt-free partially purified mesylate was immediatelty reacted with NaN_3, NaSAc, $NaCH(CO_2Me)_2$, and benzylamine, to give the corresponding 8-substituted 5,6,7,8-tetrahydroquinolines in high yield. The reaction proceeded stereospecifically with an inversion of the configuration. These methods would be valuable for the synthesis of optically active 8-substituted 5,6,7,8-tetrahydroquinolines.

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on JEOL LA-300 spectrometers in $CDCl_3$ with TMS as an internal standard. MS spectra were obtained on JASCO JMS-GC-mate (EI) and JMS-SX 102A QQ instruments. IR spectra were obtained on JASCO FT/IR-410 spectrometer. Optical rotations were measured on a JASCO DIP-360 instrument. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under N_2. CH_2Cl_2 was distilled fleshly over P_2O_5 under N_2. DMSO and *i*-Pr_2O were dried over CaH_2, and distilled before use. TLC was performed with Merck $60F_{254}$ precoated silica gel plates. Flash column chromatography was carried out using Merck silica gel 60 (230–410 mesh). Ee values of all chiral compounds except **6** were determined by HPLC analysis using chiral-pack columns (Daicel OJ or AD-RH). *Cal* (Novozym 435) was purchased from Novo Nordisk Bioindustry.

Lipase-Catalyzed Kinetic Acetylation of (±)-5,6,7,8-Tetrahydroquinolin-8-ol (1)

A mixture of racemic **1** (1.49 g, 10 mmol), vinyl acetate (4.30 g, 50 mmol), *Cal* (620 mg), and molecular sieves 4Å (1.48 g) in *i*-Pr_2O (400 mL) was stirred at 60 °C for 30 h. *Cal* and molecular sieves were removed by filtration through a Celite pad, the filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel eluting with 30% EtOAc in hexane to give the (*R*)-acetate **2** (820 mg, 43%) and the unreacted (*S*)-alcohol **1** (656 mg, 44%).

(*R*)-8-Acetoxy-5,6,7,8-tetrahydroquinoline [(*R*)-2][17]

R_f 0.50 (80% EtOAc in hexane); $[\alpha]_D^{26}$ +86 (*c* = 1.12, $CHCl_3$).

IR (neat): 1734 cm^{-1} (C=O).

^{1}H NMR (300 MHz): δ = 1.80–2.05 (m, 3 H), 2.11 (s, 3 H, CH_3), 2.70–2.92 (m, 3 H), 5.97 (t, *J* = 4.8 Hz, 1 H, H-8), 7.19 (dd, *J* = 7.7, 4.8 Hz, 1 H, H-3), 7.48 (d, *J* = 7.7 Hz, 1 H, H-4), 8.52 (dd, *J* = 4.8, 1.1 Hz, 1 H, H-2).

^{13}C NMR (75 MHz): δ = 18.4, 21.3, 28.4, 29.0, 70.6, 123.2, 133.8, 137.5, 147.4, 153.0, 170.5.

MS (EI): *m*/*z* (%) = 191 (M^+, 0.3), 149 (30), 148 (100), 132 (11), 131 (10), 130 (11).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{13}NO_2$: 191.0946 (M^+). Found: 191.0947.

Chiral-packed column and separation conditions: Daicel AD-RH, eluent; 20% MeCN in H_2O; flow rate; 1.0 mL/min, retention time for (*R*)-**2**; 10.8 min [(*S*)-**2**; 13.5 min].

(*S*)-5,6,7,8-Tetrahydroquinolin-8-ol [(*S*)-1][18]

R_f 0.29 (80% EtOAc in hexane); $[\alpha]_D^{26}$ +76 (*c* = 1.40, $CHCl_3$).

IR (neat): 3389 cm^{-1} (OH).

^{1}H NMR (300 MHz): δ = 1.73–1.91 (m, 2 H), 2.00 (m, 1 H), 2.26 (m, 1 H), 2.70–2.92 (m, 2 H), 4.18 (br s, 1 H, OH), 4.72 (t, *J* = 6.1 Hz, 1 H, H-8), 7.12 (dd, *J* = 7.7, 4.8 Hz, 1 H, H-3), 7.42 (d, *J* = 7.7 Hz, 1 H, H-4), 8.39 (d, *J* = 4.8 Hz, 1 H, H-2).

^{13}C NMR (75 MHz): δ = 19.3, 28.4, 30.7, 68.7, 122.4, 131.7, 137.0, 146.6, 158.0.

MS (EI): *m*/*z* (%) 149 (M^+, 13), 130 (4), 121 (43), 93 (100).

HRMS (EI): *m*/*z* calcd for $C_9H_{11}NO$: 149.0841 (M^+). Found: 149.0834.

Chiral-packed column and separation conditions: Daicel AD-RH, eluent; 20% MeCN in H_2O; flow rate; 1.0 mL/min, retention time for (*S*)-**1**; 4.9 min [(*R*)-**1**; 5.7 min].

(*R*)-5,6,7,8-Tetrahydroquinolin-8-ol [(*R*)-1]

A mixture of (*R*)-**2** (120 mg, 0.63 mmol) and K_2CO_3 (347 mg, 2.51 mmol) was stirred for 2 h in MeOH (4 mL) at r.t. After removal of the MeOH, H_2O was added and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried ($MgSO_4$). After the solvent was removed, the residue was purified by column chromatography on silica gel (50% EtOAc in hexane) to give (*R*)-**1** (83 mg, 88%); $[\alpha]_D^{23}$ –75 (*c* = 1.16, $CHCl_3$).

Mesylation of (*R*)-5,6,7,8-Tetrahydroquinolin-8-ol [(*R*)-1]

To a solution of (*R*)-**1** (60 mg, 0.40 mmol) and DMAP (295 mg, 2.41 mmol) in CH_2Cl_2 (6 mL) was added MsCl (184 mg, 1.61 mmol) at 0 °C and the mixture was stirred at r.t. for 3 h. The mixture was quenched with aq sat. $NaHCO_3$ and extracted with EtOAc. The extract was washed with H_2O and brine, dried ($MgSO_4$) and concentrated. The residual oil was purified by column chromatography on silica gel using 20% EtOAc in hexane as eluent to give (*S*)-**4** (13 mg, 19%) as an oil. Elution with 30% EtOAc in hexane gave (*S*)-**1** (40 mg, 66%); $[\alpha]_D^{23}$ +32.0 (*c* = 0.55, $CHCl_3$).

(*S*)-8-Chloro-5,6,7,8-tetrahydroquinoline [(*S*)-4][19]

R_f 0.66 (50% EtOAc in hexane); $[\alpha]_D^{23}$ +0.7 (*c* = 0.61, $CHCl_3$).

^{1}H NMR (300 MHz): δ = 1.89 (m, 1 H), 2.17–2.19 (m, 2 H), 2.41 (m, 1 H), 2.72–2.94 (m, 2 H), 5.30 (t, *J* = 3.1 Hz, 1 H, H-8), 7.14 (dd, *J* = 7.7, 4.8 Hz, 1 H, H-3), 7.43 (d, *J* = 7.3 Hz, 1 H, H-4), 8.48 (d, *J* = 4.4 Hz, 1 H, H-2).

^{13}C NMR (75 MHz): δ = 17.4, 28.0, 32.4, 58.9, 123.2, 132.2, 137.6, 147.8, 154.5.

MS (EI): *m*/*z* (%) 169 (M^+, 6), 167 (M^+, 20), 132 (100), 130 (28), 117 (23).

HRMS (EI): *m*/*z* calcd for $C_9H_{10}{}^{35}ClN$: 167.0502 (M^+). Found: 167.0500.

Chiral-packed column and separation conditions: Daicel OJ, eluent; 10% propan-2-ol in hexane; flow rate; 0.3 mL/min, retention time for (*S*)-**4**; 25.0 min [(*R*)-**4**; 23.2 min].

Mesylation of 1 in the Presence of Chloride and Azide Anions

To a mixture of (*R*)-**1** (60 mg, 0.40 mmol), DMAP (295 mg, 2.41 mmol), Bu_4NCl (168 mg, 0.60 mmol), and LiCl (85 mg, 2.01 mmol) in CH_2Cl_2 (8 mL) was added MsCl (184 mg, 1.61 mmol) at 0 °C. The mixture was stirred at r.t. for 30 min. Then, DMSO (4 mL) was added and the mixture was stirred for an additional 6 h. The mixture was quenched with H_2O and extracted with 30% EtOAc in hexane. The extract was washed with H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 20% EtOAc in hexane to give **4** (49 mg, 73%). The major enantiomer was determined to be (*S*)-isomer with 50% ee by HPLC using Daicel OJ column as described above.

In the case of the reaction with azide anions, NaN_3 (1.3 g, 20 mmol) was used instead of Bu_4NCl, and LiCl. Elution with 15% EtOAc in hexane for flash chromatography gave **5** in 99% yield.

(*S*)-8-Azido-5,6,7,8-tetrahydroquinoline (5)

R_f 0.54 (30% EtOAc in hexane); $[\alpha]_D^{22}$ –97 (*c* = 0.75, $CHCl_3$).

IR (neat): 2099 cm^{-1} (N_3).

^{1}H NMR (300 MHz): δ = 1.75–2.12 (m, 4 H), 2.68–2.90 (m, 2 H), 4.71 (t, *J* = 4.4 Hz, 1 H, H-8), 7.17 (dd, *J* = 7.7, 4.8 Hz, 1 H, H-3), 7.45 (d, *J* = 7.7 Hz, 1 H, H-4), 8.49 (dd, *J* = 4.8, 0.7 Hz, 1 H, H-2).

^{13}C NMR (75 MHz): δ = 18.4, 28.1, 29.0, 60.3, 123.1, 132.6, 137.3, 147.5, 153.7.

MS (EI): *m*/*z* (%) 174 (M^+, 3), 146 (98), 144 (44), 132 (100), 118 (97).

HRMS (EI): *m*/*z* calcd for $C_9H_{10}N_4$: 174.0905 (M^+). Found: 174.0908.

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05, H, 5.79, N, 32.16. Found: C, 61.95, H, 6.00, N, 31.89.

Chiral-packed column and separation conditions: Daicel AD-RH, eluent; 20% MeCN in H_2O; flow rate; 1.0 mL/min, retention time for (*S*)-**5**; 37.4 min [(*R*)-**5**; 36.1 min].

(*S*)-8-Amino-5,6,7,8-tetrahydroquinoline (6)

A mixture of (*S*)-**5** (14 mg, 0.08 mmol) and Pd/C (5%, 5 mg) in EtOH (3 mL) was stirred under a H_2 atmosphere at r.t. After the H_2 uptake was over, the Pd/C was filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel eluting with 20% MeOH in $CHCl_3$ to give (*S*)-**6** (11 mg, 92%) as an oil; R_f 0.08 (50% MeOH in $CHCl_3$); $[\alpha]_D^{22}$ +51 (*c* = 0.55, $CHCl_3$).

^{1}H NMR (300 MHz): δ = 1.68–1.75 (m, 2 H), 1.96 (m, 1 H), 2.24 (m, 1 H), 2.68–2.88 (m, 2 H), 3.45 (br, 2 H, NH_2), 4.05 (t, *J* = 6.8 Hz, 1 H, H-8), 7.07 (dd, *J* = 7.3, 4.4 Hz, 1 H, H-3), 7.37 (d, *J* = 7.3 Hz, 1 H, H-4), 8.39 (d, *J* = 4.4 Hz, 1 H, H-2).

^{13}C NMR (75 MHz): δ = 19.8, 28.7, 31.3, 51.2, 121.8, 131.7, 136.8, 146.9, 158.3.

MS (EI): *m*/*z* (%) = 148 (M^+, 100), 147 (77), 131 (21), 120 (78), 119 (60), 93 (36).

HRMS (EI): *m*/*z* calcd for $C_9H_{12}N_2$: 148.1000 (M^+). Found: 148.0989.

5,6,7,8-Tetrahydroquinolines 7, 8, and 9 from 1; General Procedure

To a mixture of (*R*)-**1** (100 mg, 0.67 mmol) and DMAP (817 mg, 6.70 mmol) in CH_2Cl_2 (6.7 mL) was added MsCl (384 mg, 3.35 mmol) at 0 °C and the mixture was stirred at r.t. for 15 min. It was diluted with anhyd Et_2O–pentane (1:1, 12 mL), and the resulting precipitate was filtered under suction. The filtrate was concentrated to give an oily mesylate, which was quickly dissolved in DMSO (6 mL). To this solution was added nucleophiles (8–10 equiv), $BnNH_2$ (neat), NaSAc (in THF solution), or $NaCH(CO_2Me)_2$ (in THF solution) at r.t., and the mixture was stirred for 3 h, 2 h and 5 h, respectively. H_2O was added to the mixture and it was extracted with $CHCl_3$ in the case of $BnNH_2$ and 30% EtOAc in hexane solution for others. The organic extract was washed with H_2O and brine, dried (Na_2SO_4 or $MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 50% EtOAc in hexane for **7**, 20% EtOAc in hexane for **8**, and 15% EtOAc in hexane for **9**. The compounds **7**, **8**, and **9** were obtained as an oil in 58%–89%, and 82% yields, respectively.

(*S*)-*N*-Benzylamino-5,6,7,8-tetrahydroquinolin-8-ylamine (7)

R_f 0.32 (5% Et_3N in EtOAc); $[\alpha]_D^{22}$ +46 (*c* = 0.44, $CHCl_3$).

^{1}H NMR (300 MHz): δ = 1.65–1.90 (m, 2 H), 2.05 (m, 1 H), 2.20 (m, 1 H), 2.77–2.90 (m, 3 H), 3.85 (t, *J* = 6.2 Hz, 1 H, H-8), 3.89 (d, *J* = 13.2 Hz, 1 H, C*H*$_2$Ph), 3.99 (d, *J* = 13.2 Hz, 1 H, C*H*$_2$Ph), 7.04 (dd, *J* = 7.7, 4.8 Hz, 1 H, H-3), 7.20–7.42 (m, 6 H, C_6H_5 and H-4), 8.37 (d, *J* = 4.8 Hz, 1 H, H-2).

^{13}C NMR (75 MHz): δ = 19.6, 28.6, 28.8, 51.8, 57.5, 121.8, 126.8, 128.2 (2 C), 128.3 (2 C), 132.4, 136.8, 140.6, 146.8, 157.4.

MS (CI, isobutene): *m*/*z* (%) = 239 (M^+ + H, 22), 133 (100), 132 (41).

HRMS (CI, isobutene): *m*/*z* calcd for $C_{16}H_{19}N_2$: 239.1548 (M^+ + H). Found: 239.1545.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63, H, 7.61, N, 11.75. Found: C, 80.47, H, 7.57, N, 11.75.

(*S*)-*S*-5,6,7,8-Tetrahydroquinolin-8-ylacetate (8)
R_f 0.30 (30% EtOAc in hexane); $[\alpha]_D^{22}$ –32 (*c* = 0.18, $CHCl_3$).

IR (neat): 1686 cm^{-1} (C=O).

^{1}H NMR (300 MHz): δ = 1.85–2.00 (m, 2 H), 2.10 (m, 1 H), 2.30 (m, 1 H), 2.36 (s, 3 H, CH_3), 2.70–2.90 (m, 2 H), 4.99 (t, *J* = 4.8 Hz, 1 H, H-8), 7.07 (dd, 7.7, 4.8 Hz, 1 H, H-3), 7.38 (d, *J* = 7.7 Hz, 1 H, H-4), 8.44 (dd, *J* = 4.8, 1.1 Hz, 1 H, H-2).

^{13}C NMR (75 MHz): δ = 19.8, 28.3, 30.4, 30.6, 45.6, 122.1, 133.3, 137.1, 147.7, 154.1, 194.7.

MS (EI): *m*/*z* (%) = 207 (M^+, 35), 165 (46), 164 (72), 132 (100).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{13}NOS$: 207.0718 (M^+). Found: 207.0719.

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.49; H, 6.51; N, 6.64.

Chiral-packed column and separation conditions: Daicel AD-RH, eluent; 30% MeCN in H_2O; flow rate; 1.0 mL/min, retention time for (*S*)-**8**; 17.1 min [(*R*)-**8**; 13.8 min].

Dimethyl (*R*)-5,6,7,8-Tetrahydroquinolin-8-ylmalonate (9)
R_f 0.53 (20% EtOAc in hexane); $[\alpha]_D^{22}$ +71 (*c* = 2.00, $CHCl_3$).

IR (neat): 1735 cm^{-1} (C=O).

^{1}H NMR (300 MHz): δ = 1.65–2.10 (m, 4 H), 2.70–2.90 (m, 2 H), 3.65 (m, 1 H, H-8′), 3.67 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3), 4.38 (d, *J* = 6.2 Hz, 1 H, 2-H), 7.01 (dd, *J* = 7.7, 4.8 Hz, 1 H, H-3′), 7.34 (d, *J* = 7.7 Hz, 1 H, H-4′), 8.29 (d, *J* = 4.8 Hz, 1 H, H-2′).

^{13}C NMR (75 MHz): δ = 21.8, 25.9, 28.8, 41.4, 52.0, 52.3, 54.6, 121.3, 132.5, 136.5, 146.3, 156.5, 169.2, 170.0.

MS (EI): *m*/*z* (%) = 263 (M^+, 22), 232 (11), 204 (100), 172 (55), 132 (16).

HRMS (EI) *m*/*z* calcd for $C_{14}H_{17}NO_4$: 263.1157 (M^+). Found: 263.1152.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87, H, 6.51, N, 5.32. Found: C, 63.57, H, 6.45, N, 5.40.

Chiral-packed column and separation conditions: Daicel AD-RH, eluent; 40% MeCN in H_2O; flow rate; 1.0 mL/min, retention time for (*R*)-**8**; 7.8 min [(*S*)-**8**; 6.5 min].

8-Alkylthio-5,6,7,8-tetrahydroquinolines 11
To a solution of (*S*)-**8** (15 mg, 0.07 mmol) in MeOH (1 mL) was added K_2CO_3 (53 mg, 0.39 mmol) at 0 °C. The mixture was stirred at r.t. for 15 min and recooled to 0 °C. To the mixture was added MeI (5 equiv) or methyl bromoacetate (5 equiv) at the same temperature and the mixture was stirred at r.t. for an additional 30 min. H_2O was added and the mixture was extracted with EtOAc. The extract was washed with brine and dried ($MgSO_4$). After the solvent was removed, the residue was purified by flash column chromatography on silica gel (15% EtOAc in hexane) to give the corresponding sulfides **11a** in 78% yield and **11b** in 85% yield as an oil.

(*S*)-8-Methylthio-5,6,7,8-tetrahydroquinoline (11a)
R_f 0.52 (30% EtOAc in hexane); $[\alpha]_D^{22}$ +5 (*c* = 0.40, $CHCl_3$).

^{1}H NMR (300 MHz): δ = 2.00–2.15 (m, 4 H), 2.17 (s, 3 H, SCH_3), 2.67–2.77 (m, 2 H), 4.20 (t, *J* = 3.7 Hz, 1 H, H-8), 6.99 (dd, 7.7, 4.6 Hz, 1 H, H-3), 7.30 (d, *J* = 7.0 Hz, 1 H, H-4), 8.34 (dd, *J* = 4.8, 0.9 Hz, 1 H, H-2).

^{13}C NMR (75 MHz): δ = 15.5, 18.7, 28.2, 28.6, 47.4, 121.9, 132.2, 137.1, 147.1, 156.5.

MS (EI): *m*/*z* (%) = 179 (M^+, 0.4), 133 (100), 132 (40).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{13}NS$: 179.0769 (M^+). Found: 179.0763.

Anal. Calcd for $C_{10}H_{13}NS$: C, 66.99; H, 7.31; N, 7.81. Found: C, 66.25; H, 7.35; N, 7.78.

Chiral-packed column and separation conditions: Daicel AD-RH, eluent; 30% MeCN in H_2O; flow rate; 1.0 mL/min, retention time for (*S*)-**11a**; 12.8 min [(*R*)-**11a**; 15.2 min].

Methyl (*S*)-5,6,7,8-Tetrahydroquinolin-8-ylthioacetate (11b)
R_f 0.28 (30% EtOAc in hexane); $[\alpha]_D^{26}$ –73 (*c* = 0.70, $CHCl_3$).

IR (neat): 1738 cm^{-1} (C=O).

^{1}H NMR (300 MHz): δ = 1.82 (m, 1 H), 2.03–2.23 (m, 3 H), 2.69–2.90 (m, 2 H), 3.45 (d, *J* = 15.2 Hz, 1 H, C*H*H), 3.71 (d, *J* = 15.2 Hz, 1 H, CH*H*), 3.74 (s, 3 H, CH_3), 4.35 (t, *J* = 4.4 Hz, 1 H, H-8′), 7.07 (dd, *J* = 7.7, 4.6 Hz, 1 H, H-3′), 7.38 (br d, *J* = 7.5 Hz, 1 H, H-4′), 8.38 (br d, *J* = 4.8 Hz, 1 H, H-2′).

^{13}C NMR (75 MHz): δ = 19.0, 28.2, 29.0, 33.7, 45.9, 52.4, 122.1, 131.9, 137.2, 146.9, 156.4, 171.1.

MS (EI): *m*/*z* (%) = 237 (M^+, 2), 206 (4), 164 (5), 133 (100), 132 (40).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}NO_2S$: 237.0823 (M^+). Found: 237.0821.

Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.51; H, 6.66; N, 5.95.

Chiral-packed column and separation conditions: Daicel OJ, eluent; 10% 2-propanol in hexane; flow rate; 1.5 mL/min, retention time for (*S*)-**11b**; 9.3 min [(*R*)-**11b**; 10.3 min].

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