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# Diastereodivergent Synthesis of (+)- $\alpha$ -Conhydrine and (-)- $\beta$ -Conhydrine from a $\eta,\gamma$ -Dibromo- $\beta$ -ketosulfoxide

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Supporting information for this article is given via a link at the end of the document.

**Abstract:** Diastereodivergent synthesis of enantiopure hemlock alkaloid (+)- $\alpha$ -conhydrine and its diastereomer (-)- $\beta$ -conhydrine is reported. Our approach relied on efficient Crystallization-Induced Diastereomer Transformation (CIDT) of an epimeric mixture of a  $\eta,\gamma$ -dibromo- $\beta$ -ketosulfoxide, optically pure only at the sulfur atom, that provided a stable  $\alpha$ -bromoketone, and diastereoselective  $\beta$ -ketosulfoxide reduction that led to the corresponding *anti* and *syn*-bromohydrins with high level of asymmetric induction.

## Introduction

2-(1-Hydroxyalkyl)-piperidine (**1**, Figure 1) represents an important structural motif featured in natural products such as homopumiliotoxin 223 G<sup>[1]</sup> and indolizidine alkaloids (-)-swainsonine, lentiginosine, (-)-castanospermine and (-)-slaframine.<sup>[2]</sup> (+)- $\alpha$ -Conhydrine (**2**), which also falls into this category, is one of the poisonous alkaloids of the hemlock *Conium maculatum*.<sup>[3]</sup> The extracts of this plant, which cause paralysis of the skeletal musculature, were used in the ancient Greece for the execution of criminals and caused the death of the Greek philosopher Socrates.<sup>[4]</sup>

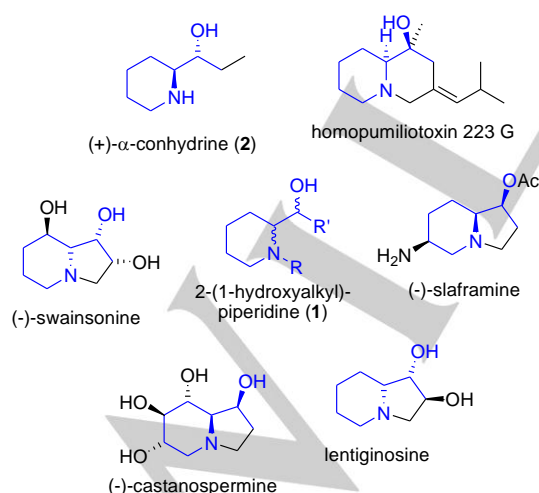


Figure 1. 2-(1-Hydroxyalkyl)-piperidine alkaloids.

Since its isolation by Wertheim in 1856<sup>[3]</sup> and structure determination in 1933,<sup>[5]</sup> (+)- $\alpha$ -conhydrine (**2**) and its three stereoisomers (Figure 2) have attracted a great deal of interest

from the synthetic community.<sup>[6]</sup> Since different stereoisomers of a chiral molecule may exhibit totally different biological and pharmacological activities,<sup>[7]</sup> despite these synthetic advances, developing alternative strategies allowing access to the four stereoisomers of conhydrine remains an important research goal to enable structure-activity relationship studies of conhydrine family members.<sup>[8]</sup> In particular, diastereodivergent strategies, in which more than one stereoisomer of conhydrine could be obtained from a common precursor via a diastereoselective reaction by varying the reaction conditions, would bring an effective solution in terms of atom and synthetic steps economy.<sup>[9]</sup>

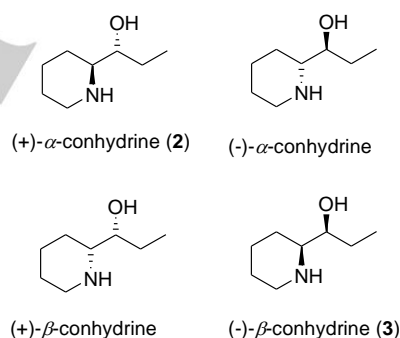
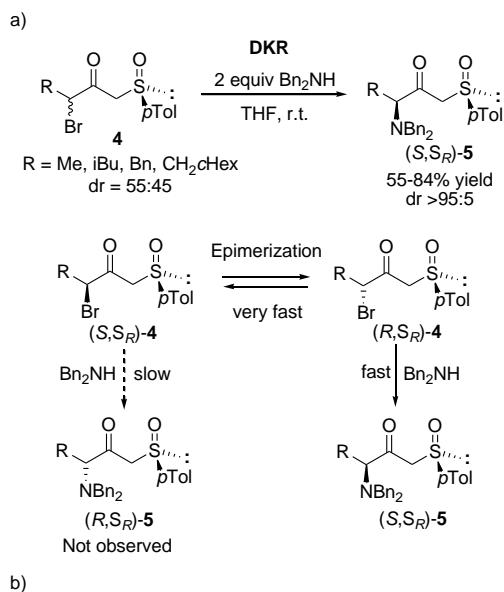


Figure 2. Conhydrine stereoisomers.

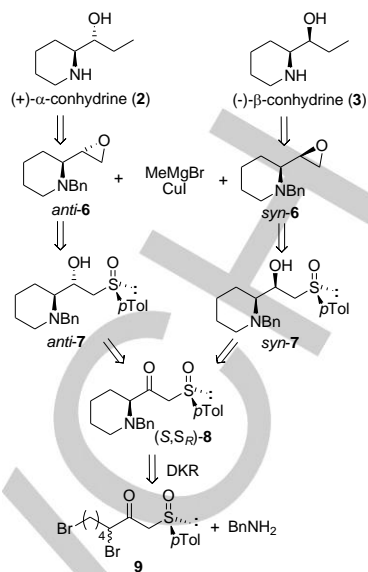
As part of a program directed at exploring the scope of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones as chiral building blocks for the synthesis of natural products containing 1,2-amino alcohol moieties,<sup>[10]</sup> we reported in a recent communication<sup>[11]</sup> on a diastereodivergent synthesis of (+)- $\alpha$ -conhydrine (**2**) and (-)- $\beta$ -conhydrine (**3**). Herein, we provide full details of our efforts that culminated in the total synthesis of both conhydrine stereoisomers.

In an earlier study (Scheme 1),<sup>[12]</sup> we described a Dynamic Kinetic Resolution (DKR) of epimeric mixtures of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones (**4**), optically pure only at the sulfur atom, with dibenzylamine that afforded the corresponding enantiopure  $\alpha$ -(*S*)-dibenzylamino  $\alpha'$ -(*R*)-sulfinyl ketones (*S,S<sub>R</sub>*)-**5** by  $S_N2$ -displacement of the bromine atom in the faster reacting epimer (*R,S<sub>R</sub>*)-**4** and simultaneous epimerization of the slower reacting (*S,S<sub>R</sub>*)-**4**.



**Scheme 1.** a) Dynamic Kinetic Resolution (DKR) of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones (**4**) with dibenzylamine. b) X-ray ORTEP of compound (*S,S<sub>R</sub>*)-**5a** (R = Me).<sup>[12]</sup>

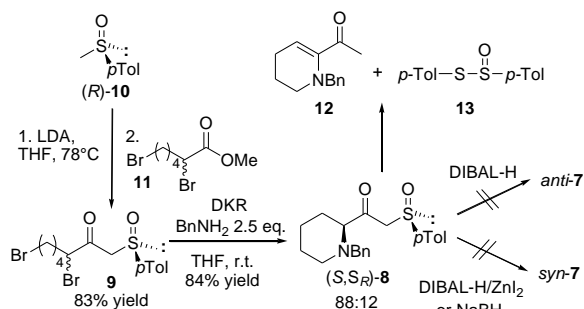
Based on this study, we set out to develop a diastereodivergent synthetic approach to (+)- $\alpha$ -conhydrine (**2**) and (-)- $\beta$ -conhydrine (**3**) based on DKR of  $\eta,\gamma$ -dibromo- $\beta$ -ketosulfoxide **9** by reaction with benzylamine (Figure 3). Thus, we anticipated that **2** and **3** could be derived from 2-(oxiran-2-yl)piperidines *anti*-**6** and *syn*-**6**, respectively, via copper (I)-catalyzed regioselective oxirane ring-opening upon attack with MeMgBr followed by amine debenzylation. Delaying the introduction of the side-chain until a late stage, would enable the synthesis of a broad variety of analogues of (+)- $\alpha$ -conhydrine (**2**) and (-)- $\beta$ -conhydrine (**3**) since 2-(oxiran-2-yl)piperidines *anti*-**6** and *syn*-**6** offer the opportunity for the incorporation of a multitude of substituents as side-chain. *Anti*-**6** and *syn*-**6** would result from sulfinyl group elimination in 2-(1-hydroxyalkyl)-piperidines *anti*-**7** and *syn*-**7**, which in turn would be accessed by diastereodivergent reduction of the  $\beta$ -ketosulfoxide moiety in the pivotal 2-acylated piperidine (*S,S<sub>R</sub>*)-**8** by the appropriate choice of the diastereoselective carbonyl reduction conditions. Finally, (*S,S<sub>R</sub>*)-**8** was envisioned to be accessible via DKR of **9** involving the S<sub>N</sub>2-displacement of  $\gamma$  bromine atom by benzylamine from more reactive (*R,S<sub>R</sub>*)-**9** epimer and simultaneous epimerization of (*S,S<sub>R</sub>*)-**9**. To this first substitution would follow the *in situ* piperidine ring formation by displacement of terminal bromine atom by the resulting secondary amine.



**Figure 3.** First retrosynthesis of (+)- $\alpha$ -conhydrine (**2**) and (-)- $\beta$ -conhydrine (**3**) from  $\eta,\gamma$ -dibromo- $\beta$ -ketosulfoxide **9**.

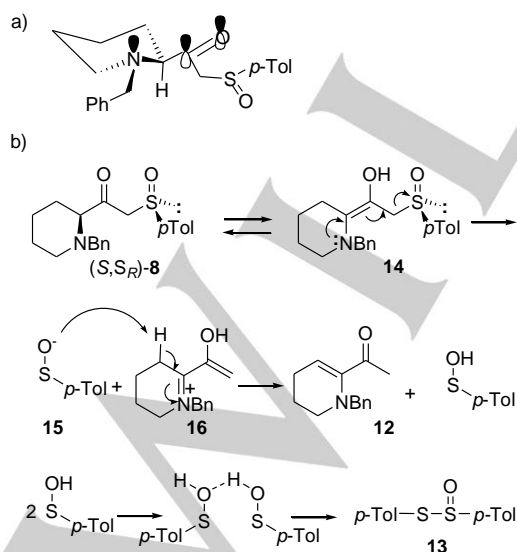
## Results and Discussion

With this initial retrosynthetic plan in mind, focus was placed on the synthesis of precursor **9**. Thus, as shown in Scheme 2, addition of dibromo ester **11**<sup>[13]</sup> to the lithium anion of (*R*)-methyl-*p*-tolylsulfoxide **10**, prepared using LDA as a base at -78°C, provided **9** in 83% yield as a 55:45 mixture of epimers at C-3. As aforementioned, for the synthesis of the pivotal precursor (*S,S<sub>R</sub>*)-**8**, DKR of **9** with benzylamine was envisaged, expecting to control the stereochemistry at C-3 stereocenter and triggering the piperidine ring formation. Thus, exposure of **9** to 2.5 equivalents of benzylamine provided, after extractive workup, clean (*S,S<sub>R</sub>*)-**8** in 84% yield as a 88:12 mixture of epimers. (*S,S<sub>R</sub>*)-**8** proved to be very unstable and had to be used without delay since it quickly decomposed into 2-acetyltetrahydropyridine **12** and thiosulfinate **13**. Thus, we attempted to perform the diastereoselective reduction of the carbonyl group in (*S,S<sub>R</sub>*)-**8** using DIBAL-H at -78°C,<sup>[14]</sup> but poor conversion and diastereoselectivity were observed and a rather unmanageable mixture of unreacted (*S,S<sub>R</sub>*)-**8**, **12**, **13**, *syn*-**7** along with a number of side products was obtained. Exposure to NaBH<sub>4</sub> or DIBAL-H in the presence of ZnI<sub>2</sub> at -78°C<sup>[15]</sup> also failed to effect total conversion of (*S,S<sub>R</sub>*)-**8**, even when excess of reducing agents were used, and resulted in the formation of *syn*-**7** as the single stereoisomer along with **12**, **13** and a number of non-identified side or decomposition products, which hampered the purification of *syn*-**7**.



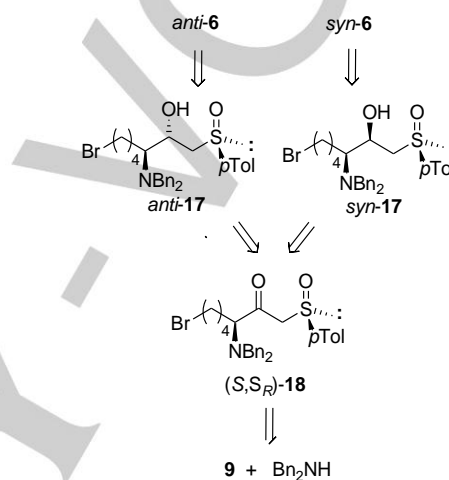
**Scheme 2.** First synthetic approach to 2-(1-hydroxyalkyl)-piperidines *anti*-7 and *syn*-7.

The spontaneous transformation of 2-acylated piperidine ( $S,S_R$ )-**8** into 2-acetyltetrahydropyridine **12** and thiosulfinate **13** was somewhat surprising since dibenzylamino ketones ( $S,S_R$ )-**5** (Scheme 1) have proved to be stable.<sup>[12]</sup> To account for this transformation, we proposed a plausible mechanism that is detailed in Scheme 3. According to X-ray crystal structure of compound ( $S,S_R$ )-**5** (Scheme 1b), tetrahedral nitrogen atom is located in such a way that the  $sp^3$  orbital containing the non-bonding electron pair is almost perpendicular to the  $\pi$  orbital of the carbonyl. However, we speculate that in compound ( $S,S_R$ )-**8** the conformational rigidity provided by the piperidinic ring (Scheme 3a) would force the nitrogen  $sp^3$  orbital containing the non-bonding electron pair to be practically parallel to the  $\pi$  orbital of the carbonyl. This geometry would give rise to a keto-enol equilibrium (Scheme 3b) favored by the conjugated system of the enol form **14** in which the donor character of the enamine moiety would trigger the C-S bond cleavage leading to anion **15** and ammonium ion intermediate **16**. Finally, an acid-base reaction between **15** and **16** would lead to 2-acetyltetrahydropyridine **12** and *p*-tolylsulfenic acid. The latter would self-condense to thiosulfinate **13** according to a known rearrangement.<sup>[16]</sup>



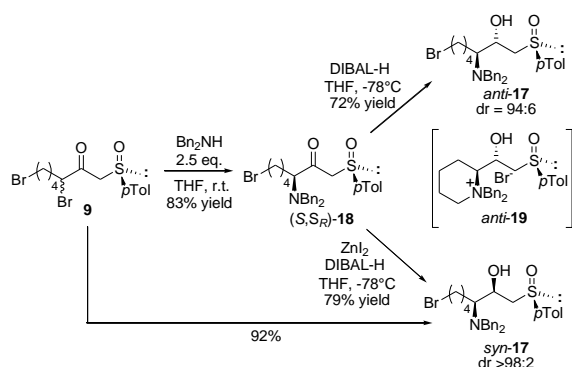
**Scheme 3.** Proposed mechanism for the transformation of 2-acylated piperidine ( $S,S_R$ )-**8** into 2-acetyltetrahydropyridine **12** and thiosulfinate **13**.

This frustrating outcome prompted us to reconsider our strategy. Rather than targeting the unstable 2-acylated piperidine ( $S,S_R$ )-**8** as pivotal intermediate, and considering our precedent work<sup>[12]</sup> that proves the stability of dibenzylamino ketones ( $S,S_R$ )-**5** (Scheme 1), we envisioned that dibenzylamino ketone ( $S,S_R$ )-**18** (Figure 4) might actually be more appropriate. This new pivotal intermediate should allow access, by diastereodivergent reduction of the  $\beta$ -ketosulfoxide moiety, to dibenzylamino alcohols *anti*-**17** and *syn*-**17** that would be used as precursors of 2-(oxiran-2-yl)piperidines *anti*-**6** and *syn*-**6**. This synthetic strategy would hinge on the DKR of  $\eta,\gamma$ -dibromo- $\beta$ -ketosulfoxide **9** by reaction with dibenzylamine that would lead to linear  $\eta$ -bromo- $\gamma$ -dibenzylamino- $\beta$ -ketosulfoxide ( $S,S_R$ )-**18**, delaying the piperidinic ring formation for a later stage.



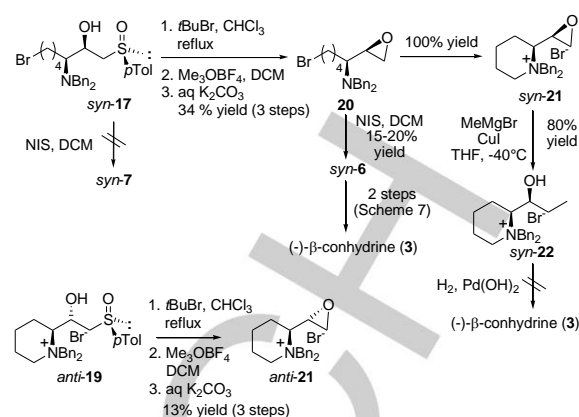
**Figure 4.** Second synthetic approach to 2-(oxiran-2-yl)piperidines *anti*-**6** and *syn*-**6**.

Our second synthetic approach to 2-(oxiran-2-yl)piperidines *anti*-**6** and *syn*-**6** began by the synthesis of dibenzylamino alcohols *anti*-**17** and *syn*-**17** (Scheme 4). Thus, DKR of **9** by exposure to 2.5 equivalents of dibenzylamine in THF at room temperature afforded ( $S,S_R$ )-**18** as a sole stereoisomer in 83% yield. Diastereoselective carbonyl reduction by reaction with DIBAL-H in THF at  $-78^\circ\text{C}$ <sup>[14]</sup> provided *anti*-**17** in a 72% yield and 94:6 diastereoisomeric ratio. *Anti*-**17** was not stable and smoothly transformed into *anti*-**19**. In parallel, reduction of ( $S,S_R$ )-**18** with DIBAL-H in the presence of  $\text{ZnI}_2$  at  $-78^\circ\text{C}$ <sup>[15]</sup> gave rise to the stable dibenzylamino alcohol *syn*-**17** in 79% yield and excellent diastereoselectivity (dr >98:2). We improved the yield of this two-step sequence by reacting crude ( $S,S_R$ )-**18** without prior isolation (92% yield from **9**). It is noteworthy that, by preparing *anti*-**17** and *syn*-**17**, we have extended the scope of our reported methodology concerning the Dynamic Kinetic Resolution (DKR) with dibenzylamine of epimeric mixtures of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones bearing an alkyl substituent (Scheme 1)<sup>[12]</sup> to a substrate with a functionalized side-chain.



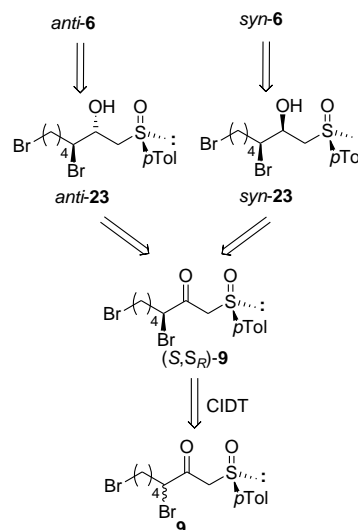
**Scheme 4.** Synthesis of dibenzylamino alcohols *anti*-17 and *syn*-17.

We next focused on the elaboration of *syn*-17 into 2-(oxiran-2-yl)piperidine *syn*-6 via 2-(1-hydroxyalkyl)-piperidine *syn*-7, according to the strategy depicted in Figure 3. Thus, we expected that monodebenzylation of *syn*-17 (Scheme 5) following the procedure described by Grayson and Davis<sup>[17]</sup> would result in the formation of *syn*-7 by intramolecular cyclization of the resulting secondary monobenzylated amine. Unfortunately, exposure of *syn*-17 to NIS in anhydrous dichloromethane failed in delivering the desired *syn*-7 and led to a complex mixture of unidentified side or decomposition products. We eventually deduced that the sulfoxide group did not tolerate these oxidative conditions and was responsible for the decomposition issues. Consequently, we decided to convert *syn*-17 into dibenzyl amino epoxide **20**. Thus, exposure of *syn*-17 to an excess of *t*BuBr at refluxing chloroform,<sup>[18]</sup> followed by methylation of the ensuing sulfide with Me<sub>3</sub>OBF<sub>4</sub> in dichloromethane and treatment of the resulting sulfonium salt with aqueous K<sub>2</sub>CO<sub>3</sub>, provided dibenzylamino epoxide **20** in 34% yield after 3 steps. The latter was somewhat unstable and transformation into ammonium salt *syn*-21 occurred smoothly. Treatment of freshly prepared **20** with NIS in anhydrous DCM led to not satisfying yields (15–20%) of 2-(oxiran-2-yl)piperidine *syn*-6, after column chromatography. Reaction with CAN<sup>[19]</sup> failed in affording the desired compound *syn*-6 and only degradation of the starting material was observed. *Syn*-6 was used to complete the synthesis of (-)-β-conhydrine, as it will be discussed further below (third synthetic approach, Scheme 7). Next, *syn*-21 was treated with MeMgBr in the presence of CuI in THF at -40°C providing alcohol *syn*-22 in 80% yield. Debenzylation of *syn*-22 should deliver (-)-β-conhydrine (**3**). Unfortunately, exposure of *syn*-22 to 10% Pd(OH)<sub>2</sub>/C (10 mol%) or 10% Pd/C (10 mol%) under hydrogen atmosphere didn't allow the hydrogenolysis of benzyl groups. Moreover, β-hydroxysulfoxide *anti*-19 was converted into epoxide *anti*-21, following the aforementioned sequence used to transform *syn*-17 into **20**, with a poor 13% yield (3 steps).



**Scheme 5.** Elaboration of amino alcohols *syn*-17 and *anti*-19.

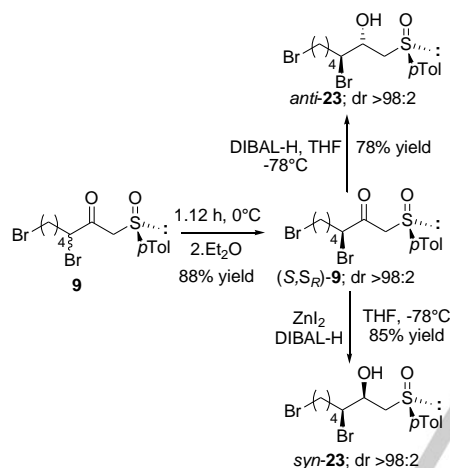
Prompted by these disappointing results, an alternative strategy to access 2-(oxiran-2-yl)piperidines *anti*-6 and *syn*-6 was pursued (Figure 5). More specifically, we envisioned both compounds could be constructed from bromohydrins *anti*-23 and *syn*-23 respectively, which contain appropriate functionality for late-stage installation of the piperidinic ring by a bisnucleophilic substitution of both bromine atoms using benzylamine as a nucleophile. *Anti*-23 and *syn*-23 would be divergently derived from the diastereoselective ketone reduction of enantiopure (S,S<sub>R</sub>)-**9**, the new pivotal intermediate, which, in turn, would be issued from the epimeric mixture **9** via Crystallization-Induced Diastereomer Transformation (CIDT).



**Figure 5.** Third synthetic approach to 2-(oxiran-2-yl)piperidines *anti*-6 and *syn*-6.

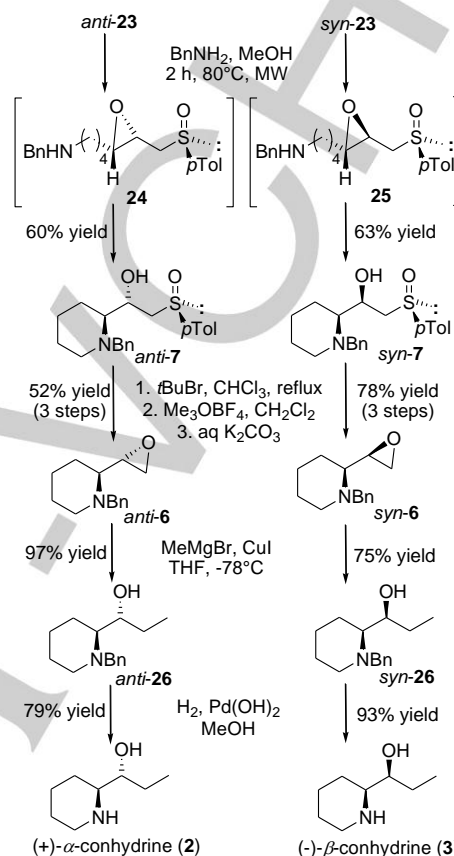
Crystallization-Induced Diastereomer Transformation (CIDT) is a practical way to realize a diastereoenrichment, which has attracted considerable attention in the synthetic community.<sup>[20]</sup> This hybrid process involves mixtures of two diastereomeric compounds and combines the selective crystallization of a desired diastereomer and the epimerization of the undesired one. In contrast to classical resolution, which affords yields lower than

50%, CIDT provides a theoretical yield of 100%. As reported in a previous communication,<sup>[11]</sup> we serendipitously discovered that an epimeric mixture of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones enantiopure only at the sulfur stereogenic center can be resolved via a CIDT. In this context, we envisioned the required enantiopure bromo ketone (*S,S<sub>R</sub>*)-**9** to be accessed via CIDT of the epimeric mixture **9**. Thus, after 12 h at 0°C, the yellowish liquid 55:45 epimeric mixture **9** led to a precipitate that was crushed and washed with diethyl ether giving rise to (*S,S<sub>R</sub>*)-**9** as single epimer. (*S,S<sub>R</sub>*)-**9** was configurationally stable and could be stored several months at refrigerator temperatures without any epimerization occurs. Ketone diastereoselective reduction using DIBAL-H in THF at -78°C<sup>[14]</sup> delivered bromohydrin *anti*-**23** in 78% yield with an excellent diastereoselectivity (dr >98:2). Reduction of (*S,S<sub>R</sub>*)-**8** by reaction with the system ZnI<sub>2</sub>/DIBAL-H in THF at -78°C<sup>[15]</sup> led uneventfully to bromohydrin *syn*-**23** in 85% yield (dr >98:2).



**Scheme 6.** Synthesis of bromohydrins *anti*-**23** and *syn*-**23**.

Having bromohydrins *anti*-**23** and *syn*-**23** in hand, we proceeded to complete the synthesis of (+)- $\alpha$ -conhydrine (**2**) and (-)- $\beta$ -conhydrine (**3**) (Scheme 7). For this purpose, both bromohydrins were reacted with benzylamine in methanol at 80°C under microwave irradiation conditions and 2-(1-hydroxyalkyl)piperidines *anti*-**7** and *syn*-**7** were obtained in the moderated 60 and 63% yields, respectively, *via* the amino epoxide intermediates **24** and **25** in a double inversion process of the C-3 stereocenter. The synthesis of 2-(oxiran-2-yl)piperidines *anti*-**6** and *syn*-**6** from *anti*-**7** and *syn*-**7** followed the same three-step sequence of transformations described above for the synthesis of **20** from *syn*-**17** (Scheme 5) involving sulfonyl reduction, subsequent sulfide methylation and elimination of the resulting sulfonium group leading to *anti*-**6** and *syn*-**6** in 52 and 78% yield for the three steps, respectively. The synthesis were completed in two steps. Thus, *anti*-**6** and *syn*-**6** were subjected to CuI catalyzed reaction with MeMgBr giving the corresponding amino alcohols *anti*-**26** and *syn*-**26** in 97% and 75% yield. Benzyl removal under hydrogen atmosphere using Pd(OH)<sub>2</sub> as catalyst afforded (+)- $\alpha$ -conhydrine (**2**) and (-)- $\beta$ -conhydrine (**3**) in 79 and 93% yield, respectively. The spectroscopic and physical data of both compounds were in accordance with the reported literature values.<sup>[21]</sup>



**Scheme 7.** Completion of the synthesis of (+)- $\alpha$ -conhydrine (**2**) and (-)- $\beta$ -conhydrine (**3**).

## Conclusion

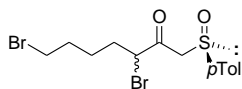
In conclusion, we have studied three different diastereodivergent approaches to the synthesis of hemlock alkaloids (+)- $\alpha$ -conhydrine (**2**) and (-)- $\beta$ -conhydrine (**3**) starting from  $\eta,\gamma$ -dibromo- $\beta$ -ketosulfoxide **9**. The first two involved DKR of **9** by bromo atom displacement employing either benzyl or dibenzylamine as the nucleophiles. The use of benzylamine led to 2-acylated piperidine (*S,S<sub>R</sub>*)-**8**, which was unstable. However, by using dibenzylamine, we illustrated the synthetic potential of this methodology for the synthesis of dibenzylamino ketones, that can be used as pivotal intermediates for the diastereodivergent synthesis of *anti* and *syn* 1,2-amino alcohols bearing a functionalized side-chain, extending the scope of our previous studies with substrates bearing alkyl side-chains.<sup>[12]</sup> The low yields obtained in this second synthetic approach prompted us to develop a third strategy. Thus, we demonstrated that the CIDT of an epimeric mixture of a  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketone can be efficiently used for the synthesis of natural products containing 1,2-amino alcohol moieties as we illustrated with the diastereodivergent synthesis of alkaloids (+)- $\alpha$ -conhydrine (**2**) and (-)- $\beta$ -conhydrine (**3**) with good yields and excellent

diastereoselectivities. Further investigation into  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones derivatization and application of this chemistry to natural and unnatural product synthesis is ongoing.

## Experimental Section

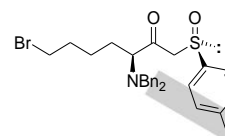
**General information:** All reagents and solvents were purchased from commercial sources. THF was distilled on sodium/benzophenone. Diisopropylamine was distilled on KOH. Solvents for chromatography were of technical grade and distilled prior to use. Reactions requiring anhydrous conditions were conducted in flame-dried glassware under an argon atmosphere using standard syringe techniques.  $^1\text{H}$  NMR spectra were recorded at 400 MHz in  $\text{CDCl}_3$ .  $^{13}\text{C}$  NMR spectra were recorded at 101 MHz in  $\text{CDCl}_3$ . Chemical shifts are given in ppm and reported to the residual solvent peak ( $\text{CDCl}_3$  7.26 ppm for  $^1\text{H}$  NMR and 77.16 ppm for  $^{13}\text{C}$  NMR). Data are reported as follows: chemical shift ( $\delta$ ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, and integration. Analytical TLC were performed on silica gel 60 F254 plates. Compounds were visualized by charring with ethanolic vanillin/ $\text{H}_2\text{SO}_4$  or ethanolic ninhydrin. Chromatography columns were carried out on silica gel 60 (63-200  $\mu\text{m}$ ) using air pressure. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and Q-ToF detection. Melting points were measured with a Büchi apparatus and are reported uncorrected. Optical rotations were measured with a Perkin-Elmer apparatus at 20°C, 589 nm (sodium ray), and concentrations are given in g/100 mL. Microwave-assisted reactions were performed with a Biotage Initiator 60 EXP®. The temperature was measured with an IR sensor on the outer surface of the reaction vial.

### (*R,S,S<sub>R</sub>*)-1-(*p*-tolylsulfinyl)-3,7-dibromoheptan-2-one (**9**)



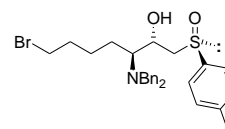
Diisopropylamine (1.75 mL, 12.5 mmol, 2.1 equiv) was dissolved in 20 mL of dry THF and *n*-butyllithium (8 mL, 1.6M in hexanes, 12.8 mmol, 2.1 equiv) was added rapidly via syringe, at -78°C. The reaction mixture was stirred at -78°C for 30 min, and then a solution of (*R*)-methyl-*p*-tolylsulfinyl (*R*)-**10** (1.93 g, 12.5 mmol, 2.1 equiv) in 8 mL anhydrous THF was added via cannula over a 15-min period, whereupon the reaction mixture turned yellow. After stirring 1 h at -78°C, methyl ester **11** (1.71 g, 5.9 mmol, 1 equiv) in 5 mL THF was added via cannula over a 5-min period. The resulting solution was stirred for 2 additional h at -78°C, and then quenched with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (50 mL). The cooling bath was removed and the reaction allowed to warm gradually to room temperature. The aqueous layer was separated and extracted with EtOAc (3x100 mL). The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 10:1) to afford a 55:45 mixture of epimers **9** (2.0 g, 4.9 mmol, 83%) as a pale yellow oil.  $R_f$  = 0.54 and 0.49 (cyclohexane/EtOAc, 2:1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.57 (d,  $J$  = 8.1 Hz, 2H), 7.49 (d,  $J$  = 8.2 Hz, 2H), 7.36 (d,  $J$  = 8.0 Hz, 2H), 7.35 (d,  $J$  = 8.1 Hz, 2H), 4.38 (d,  $J$  = 13.4 Hz, 0.5H), 4.30-4.24 (m, 1H), 4.22 (d,  $J$  = 13.6 Hz, 0.5H), 3.87 (d,  $J$  = 13.5 Hz, 0.5H), 3.84 (d,  $J$  = 13.4 Hz, 0.5H), 3.39 (t,  $J$  = 6.6 Hz, 1H), 3.38 (t,  $J$  = 6.6 Hz, 1H), 2.43 (s, 1.5H), 2.42 (s, 1.5H), 2.4-1.78 (m, 4H), 1.64-1.34 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 194.8, 194.3, 142.7, 142.6, 139.8, 138.7, 130.4, 130.3, 124.2, 124.1, 66.2, 63.7, 54.1, 54.0, 33.2, 33.1, 32.0, 31.9, 31.4, 25.8, 25.7, 21.6. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{14}\text{H}_{19}\text{O}_2\text{SBr}_2^+$  408.9467, found 408.9470.

### (*S,S<sub>R</sub>*)-1-(*p*-tolylsulfinyl)-7-bromo-3-(dibenzylamino)heptan-2-one ((*S,S<sub>R</sub>*)-**18**)



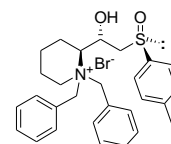
Dibenzylamine (0.8 mL, 4.15 mmol, 2.2 equiv) was added to a solution of **9** (766 mg, 1.87 mmol, 1 equiv) in THF (25 mL). The reaction mixture was stirred for 30 h at room temperature. A saturated aqueous solution of  $\text{KHCO}_3$  (20 mL) was added. The organic phase was separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layers were washed with an aqueous solution of 10%  $\text{KHSO}_4$  (20 mL), dried over  $\text{MgSO}_4$ , and concentrated. The crude reaction mixture was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 10:1) to afford (*S,S<sub>R</sub>*)-**18** (0.812 g, 1.54 mmol, 83%) as a pale yellow oil.  $R_f$  = 0.57 (cyclohexane/EtOAc, 2:1).  $[\alpha]_D^{20}$  = -65 ( $c$  = 1.2,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.41-7.22 (m, 12H), 7.15 (d,  $J$  = 8.0 Hz, 2H), 4.18 (d,  $J$  = 13.0 Hz, 1H), 4.07 (d,  $J$  = 13.0 Hz, 1H), 3.63 (d,  $J$  = 13.3 Hz, 2H), 3.41-3.29 (m, 2H), 3.37 (d,  $J$  = 13.1 Hz, 2H), 2.67 (dd,  $J$  = 9.5, 2.7 Hz, 1H), 2.37 (s, 3H), 1.78-1.62 (m, 3H), 1.51-1.43 (m, 1H), 1.10-0.99 (m, 1H), 0.87-0.76 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 201.4, 142.2, 139.6, 138.4, 130.0, 129.1, 128.6, 127.6, 124.7, 67.6, 66.2, 54.8, 33.4, 32.5, 25.5, 21.5, 20.3. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{28}\text{H}_{33}\text{BrNO}_2\text{S}^+$  526.1410, found 526.1414.

### (2*R,3S,S<sub>R</sub>*)-1-(*p*-tolylsulfinyl)-7-bromo-3-(dibenzylamino)heptan-2-ol (*anti*-**17**)



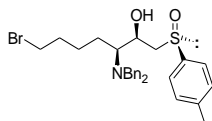
In a dried two-necked round-bottom flask under argon atmosphere, compound (*S,S<sub>R</sub>*)-**18** (134 mg, 0.25 mmol, 1 equiv) was solubilised in 3 mL of anhydrous THF and the resulting solution was cooled at -78°C. DIBAL-H (0.55 mL; 1.5 M in toluene, 0.81 mmol, 3.2 equiv) was added dropwise via syringe over a 5-min period. Stirring at the same temperature was continued for 4 h, and then the reaction was quenched with 2 mL MeOH and warmed up to room temperature. The solvents were evaporated and 10 mL of a saturated aqueous solution of potassium sodium *L*-tartrate tetrahydrate and 10 mL of EtOAc were added and the reaction mixture was stirred vigorously for 15 h at room temperature. The aqueous layer was separated and extracted with EtOAc (3x15 mL). The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The resulting crude reaction mixture was purified by flash chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) to afford *anti*-**17** as a white solid (96 mg, 0.18 mmol, 72%).  $R_f$  = 0.39 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 200:1). M.p. 44-46°C.  $[\alpha]_D^{20}$  = +45.3 ( $c$  = 1.06,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.51 (d,  $J$  = 8.2 Hz, 2H), 7.33 (d,  $J$  = 8.2 Hz, 2H), 7.29-7.19 (m, 6H), 7.13-7.11 (m, 4H), 4.56 (br s, 1H), 4.46-4.45 (m, 1H), 3.58 (d,  $J$  = 13.7 Hz, 2H), 3.46 (d,  $J$  = 13.9 Hz, 2H), 3.40 (t,  $J$  = 6.7 Hz, 2H), 2.93-2.78 (m, 2H), 2.49-2.44 (m, 1H), 2.42 (s, 3H), 1.82-1.73 (m, 3H), 1.69-1.60 (m, 1H), 1.57-1.45 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 141.6, 139.7, 130.1, 129.2, 129.0, 128.3, 127.0, 124.2, 66.4, 60.9, 54.4, 33.9, 33.1, 29.8, 26.7, 25.3, 21.5. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{28}\text{H}_{35}\text{NO}_2\text{BrS}$  528.1572, found 528.1575.

### (*S,S<sub>R</sub>*)-2-(*p*-tolylsulfinyl)-1-((*S*)-1-dibenzylpiperidinium-2-yl)ethanol bromide (*anti*-**19**)



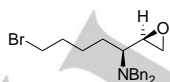
After 30 days of storage in fridge, *anti*-**17** spontaneously converted into *anti*-**19** in a quantitative yield. White solid. M.p. 135-137°C.  $[\alpha]_D^{25} = +14.3$  ( $c = 0.5$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.77-7.75 (m, 2H), 7.63 (d,  $J = 8.2$  Hz, 2H), 7.51-7.35 (m, 8H), 7.32 (d,  $J = 8.0$  Hz, 2H), 6.32 (d,  $J = 8.2$  Hz, 1H), 5.94-5.89 (m, 1H), 5.53-5.46 (m, 2H), 4.98 (d,  $J = 13.7$  Hz, 1H), 3.98 (d,  $J = 13.7$  Hz, 1H), 3.29 (dd,  $J = 13.0, 9.5$  Hz, 2H), 3.21-3.11 (m, 2H), 2.64 (dd,  $J = 13.1, 3.1$  Hz, 1H), 2.61-2.50 (m, 1H), 2.44-2.31 (m, 1H), 2.39 (s, 3H), 2.02-1.93 (m, 3H), 1.34-1.22 (m, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 141.8, 141.1, 133.7, 133.6, 131.1, 130.9, 130.2, 129.7, 129.6, 127.3, 126.0, 124.0, 71.8, 64.7, 64.5, 62.5, 58.1, 56.8, 21.9, 21.5, 21.0, 20.2. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{28}\text{H}_{34}\text{NO}_2\text{S}$  448.2305, found 448.2309.

**(2*R*,3*S*,*S*<sub>R</sub>)-1-(*p*-tolylsulfinyl)-7-bromo-3-(dibenzylamino)heptan-2-ol (*syn*-**17**)**



To a solution of  $\text{ZnI}_2$  (411 mg, 1.25 mmol, 1.1 equiv) in 6 mL anhydrous THF under argon at room temperature was added via canula a solution of (*S*,*S*<sub>R</sub>)-**18** (614 mg, 1.17 mmol, 1 equiv) in 10 mL THF. After being stirred for 50 min at room temperature, the mixture was cooled to -78°C. Then, DIBAL-H (1.96 mL, 1.5M solution in toluene, 3.00 mmol, 2.5 equiv) was added dropwise via syringe over a 5-min period and the solution was maintained at -78°C for 3 h. Excess of MeOH (10 mL) was then added dropwise via pipet, the cooling bath was removed and the solution was allowed to warm to room temperature. The solvents were evaporated under vacuum and the resulting solid was treated with a saturated aqueous solution of sodium potassium tartrate (50 mL) and EtOAc (50 mL). After the mixture was stirred vigorously overnight, the aqueous layer was separated and extracted with EtOAc (3x25 mL). The organic extracts were combined, washed with brine (25 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexanes/EtOAc, 5:1) to afford *syn*-**17** as a pale yellow oil (489 mg, 0.93 mmol, 79%).  $R_f = 0.33$  (cyclohexane/EtOAc, 2:1).  $[\alpha]_D^{25} = +28$  ( $c = 1$ , acetone).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.51 (d,  $J = 8.2$  Hz, 2H), 7.53 (d,  $J = 7.9$  Hz, 2H), 7.29-7.27 (m, 4H), 7.25-7.22 (m, 6H), 4.25 (br s, 1H), 3.91 (d,  $J = 13.3$  Hz, 2H), 3.89-3.86 (m, 1H), 3.47 (d,  $J = 13.3$  Hz, 2H), 3.46-3.40 (m, 2H), 3.13 (dd,  $J = 13.1, 8.8$  Hz, 1H), 2.64-2.60 (m, 2H), 2.43 (s, 3H), 1.89-1.84 (m, 2H), 1.72-1.66 (m, 1H), 1.58-1.53 (m, 2H), 1.51-1.45 (m, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 141.8, 140.9, 139.5, 130.1, 129.2, 128.5, 127.3, 124.4, 68.5, 62.2, 62.0, 55.0, 33.5, 32.9, 26.6, 24.6, 21.6. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{28}\text{H}_{35}\text{NO}_2\text{BrS}$  528.1572, found 528.1559.

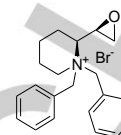
**(*S*,*S*<sub>R</sub>)-*N*,*N*-dibenzyl-5-bromo-1-(*R*)-oxiran-2-yl)pentan-1-amine (**20**)**



A mixture of *syn*-**17** (176 mg, 0.33 mmol, 1 equiv) and *t*BuBr (0.31 mL, 2.66 mmol, 8 equiv) in dry  $\text{CHCl}_3$  (5 mL) was heated at 85°C under argon, using an oil bath, for 15 h. The mixture was allowed to cool to room temperature and the excess *t*BuBr and solvent were removed under reduced pressure. The residue was dissolved in 1.9 mL dry  $\text{CH}_2\text{Cl}_2$  and 160 mg (1.08 mmol, 3.3 equiv) of  $\text{Me}_3\text{OBF}_4$  were added. After stirring for 6 h at room temperature under argon, 3 ml of a saturated aqueous solution of  $\text{K}_2\text{CO}_3$  was added and the mixture was stirred vigorously for further 16 h at the same temperature. Then, the aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3x20 mL). The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 18:1) affording 44 mg (0.11 mmol, 34%) of **20** as a yellow oil.  $R_f = 0.52$  (cyclohexane/EtOAc, 9:1).  $[\alpha]_D^{25} = +30.1$  ( $c = 1$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.33-7.13 (m, 10H), 3.80 (d,  $J = 13.4$  Hz, 1H), 3.69 (d,  $J = 13.4$  Hz, 1H), 3.25 (t,  $J = 6.4$

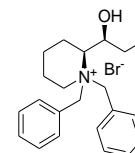
Hz, 1H), 3.08-3.04 (m, 1H), 2.65 (dd,  $J = 5.0, 4.3$  Hz, 1H), 2.33 (dd,  $J = 5.1, 2.6$  Hz, 1H), 2.33-2.24 (m, 1H), 1.63-1.51 (m, 4H), 1.37-1.19 (m, 2H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 140.2, 129.1, 128.3, 127.9, 59.0, 54.5, 52.4, 44.1, 33.8, 32.5, 27.9, 25.1. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{21}\text{H}_{27}\text{NOBr}$  388.1276, found 388.1289.

**(*S*)-1-dibenzyl-2-((*S*)-oxiran-2-yl)piperidinium bromide (*syn*-**21**)**



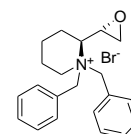
After 40 days of storage in fridge, **20** spontaneously converted into *syn*-**21** in a quantitative yield. M.p = 154-156°C.  $[\alpha]_D^{25} = +40.8$  ( $c = 1$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.73-7.70 (m, 2H), 7.57-7.51 (m, 6H), 7.45-7.43 (m, 2H), 5.47 (d,  $J = 12.9$  Hz, 2H), 4.72-4.67 (m, 1H), 4.60-4.57 (m, 1H), 4.40 (d,  $J = 13.4$  Hz, 2H), 4.17 (d,  $J = 13.4$  Hz, 2H), 4.10-4.06 (m, 1H), 3.40-3.30 (m, 2H), 2.40-2.32 (m, 1H), 1.87-1.76 (m, 2H), 1.56-1.31 (m, 6H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 133.2, 132.5, 131.1, 130.6, 129.8, 129.7, 127.9, 127.8, 77.7, 64.7, 63.8, 62.0, 60.3, 33.4, 32.0, 23.4, 21.1. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{21}\text{H}_{26}\text{NO}$  308.2014, found 308.2032.

**(*S*)-1-((*S*)-1-dibenzylpiperidinium-2-yl)propan-1-ol bromide (*syn*-**22**)**



To a solution of *syn*-**21** (24 mg, 0.06 mmol, 1 equiv) in 3 mL of THF under argon, CuI (6 mg, 0.015 mmol, 0.50 equiv) was added. The suspension was cooled at -78°C, and then 0.05 mL of a 3.0 M solution of MeMgBr in Et<sub>2</sub>O (0.15 mmol, 2.5 equiv) were introduced dropwise via cannula over a 10-min period. The reaction mixture was allowed to warm to -20°C overnight. Then, the mixture was treated with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (5 mL). The aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3x10 mL). The organic extracts were combined, dried ( $\text{MgSO}_4$ ), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) to afford 20 mg (0.049 mmol, 80%) of *syn*-**22** as a pale yellow oil.  $R_f = 0.20$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 40:1).  $[\alpha]_D^{25} = +30.1$  ( $c = 1$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.70-7.68 (m, 2H), 7.54-7.52 (m, 2H), 7.43-7.32 (m, 6H), 6.13 (d,  $J = 12.3$  Hz, 1H), 5.62 (d,  $J = 6.3$  Hz, 1H), 5.44 (d,  $J = 13.1$  Hz, 1H), 4.75 (d,  $J = 13.0$  Hz, 1H), 4.39-4.32 (m, 1H), 3.53 (d,  $J = 12.3$  Hz, 1H), 3.31-3.25 (m, 1H), 3.07-2.93 (m, 2H), 2.32-2.22 (m, 1H), 1.85-1.63 (m, 5H), 1.50-1.41 (m, 2H), 1.06 (t,  $J = 7.3$  Hz, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 134.7, 133.9, 130.8, 130.7, 129.6, 129.1, 127.8, 127.1, 70.5, 68.5, 67.3, 56.9, 56.3, 29.1, 25.0, 22.0, 21.0, 9.3. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{22}\text{H}_{30}\text{NO}$  324.2322, found 324.2329.

**(*S*)-1-dibenzyl-2-((*R*)-oxiran-2-yl)piperidinium bromide (*anti*-**21**)**

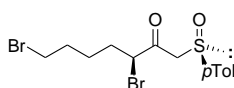


A mixture of *anti*-**19** (102 mg, 0.19 mmol, 1 equiv) and *t*BuBr (0.21 mL, 1.86 mmol, 10 equiv) in dry  $\text{CHCl}_3$  (1.5 mL) was heated at 85°C under argon, using an oil bath, for 15 h. The mixture was allowed to cool to room temperature and the excess *t*BuBr and solvent were removed under reduced pressure. The residue was dissolved in 1.5 mL dry  $\text{CH}_2\text{Cl}_2$  and 176 mg (1.19 mmol, 6.3 equiv) of  $\text{Me}_3\text{OBF}_4$  were added. After



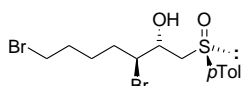
stirring for 6 h at room temperature under argon, 3 ml of a saturated aqueous solution of  $K_2CO_3$  was added and the mixture was stirred vigorously for further 16 h at the same temperature. Then, the aqueous layer was separated and extracted with  $CH_2Cl_2$  (3x20 mL). The organic extracts were combined, dried over  $MgSO_4$ , filtered and concentrated under reduced pressure. The crude beige solid was purified by washing with  $CHCl_3$  affording 10 mg (0.026 mmol, 13%) of *anti*-**21** as a white solid.  $R_f = 0.45$  ( $CH_2Cl_2/MeOH$ , 10:1). M.p 200-202°C.  $[\alpha]_D^{20} = +25.3$  ( $c = 1$ , MeOH).  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  (ppm) = 7.74-7.72 (m, 2H), 7.63-7.46 (m, 8H), 5.30 (d,  $J = 13.6$  Hz, 1H), 5.19 (d,  $J = 13.5$  Hz, 1H), 4.64 (dd,  $J = 13.5$ , 1.1 Hz, 1H), 4.22-4.20 (m, 1H), 4.09 (d,  $J = 13.7$  Hz, 1H), 3.82 (dd,  $J = 12.1$ , 3.3 Hz, 1H), 3.42-3.38 (m, 1H), 3.26-3.19 (m, 1H), 3.05 (t,  $J = 4.5$  Hz, 1H), 2.87 (dd,  $J = 4.5$ , 2.6 Hz, 1H), 2.46-2.33 (m, 1H), 2.09-1.98 (m, 1H), 1.91-1.85 (m, 1H), 1.60-1.56 (m, 1H), 1.35-1.23 (m, 1H).  $^{13}C$  NMR (101 MHz,  $CD_3OD$ )  $\delta$  (ppm) = 134.6, 134.4, 132.0, 131.9, 130.6, 128.4, 127.9, 67.4, 65.1, 59.0, 57.3, 48.6, 44.6, 22.1, 21.2, 19.1. HRMS (ESI+):  $m/z$  calc. for  $C_{21}H_{26}NO$  308.2009, found 308.2010.

### (*S,S*)-1-(*p*-tolylsulfinyl)-3,7-dibromoheptan-2-one ((*S,S*)-**9**)



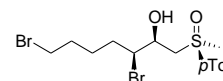
1.2 g (4.2 mmol) of yellowish oil 55:45 mixture of epimers **9** was kept 12 h at 0°C and the resulting solid was crushed and washed three times with diethyl ether yielding 1.05 g (2.6 mmol) of a white solid (88%).  $R_f = 0.54$  (cyclohexane/EtOAc, 2:1). M.p. 69-71°C.  $[\alpha]_D^{20} = +131$  ( $c$  1.03, acetone).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm) = 7.49 (d,  $J = 8.3$  Hz, 2H), 7.35 (d,  $J = 8.0$  Hz, 2H), 4.38 (d,  $J = 13.4$  Hz, 1H), 4.29 (dd,  $J = 8.1$ , 6.1 Hz, 1H), 3.85 (d,  $J = 13.4$  Hz, 1H), 3.38 (t,  $J = 6.6$  Hz, 2H), 2.43 (s, 3H), 1.97-1.75 (m, 4H), 1.64-1.33 (m, 2H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  (ppm) = 194.1, 142.5, 138.7, 130.2, 124.2, 63.7, 53.9, 33.0, 31.9, 31.3, 25.7, 21.5. HRMS (ESI+):  $m/z$  calc. for  $C_{14}H_{19}O_2SBr_2$  408.9473, found 408.9478.

### (2*R*,3*S*,*S*)-1-(*p*-tolylsulfinyl)-3,7-dibromoheptan-2-ol (*anti*-**23**)



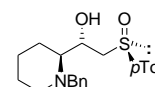
In a dried two-necked round-bottom flask under argon atmosphere, compound (*S,S*)-**9** (411 mg, 1 mmol, 1 equiv) was solubilised in 10.5 mL of anhydrous THF and the resulting solution was cooled at -78°C. DIBAL-H (1.7 mL; 1.5 M in toluene, 2.5 mmol, 2.5 equiv) was added dropwise via syringe over a 5-min period. Stirring at the same temperature was continued for 1.5 h, and then the reaction was quenched with 10 mL MeOH and warmed up to room temperature. The solvents were evaporated and 25 mL of a saturated aqueous solution of potassium sodium *L*-tartrate tetrahydrate and 25 mL of EtOAc were added and the reaction mixture was stirred vigorously for 15 h at room temperature. The aqueous layer was separated and extracted with EtOAc (3x25 mL). The organic extracts were combined, dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. The resulting crude reaction mixture was purified by flash chromatography on silica gel (cyclohexanes/Et<sub>2</sub>O, 2:1) to afford *anti*-**23** as a pale yellow oil (323 mg, 0.79 mmol, 78%).  $R_f = 0.35$  (cyclohexane/EtOAc, 3:1).  $[\alpha]_D^{20} = +126$  ( $c$  1.4,  $CHCl_3$ ).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm) = 7.53 (d,  $J = 8.2$  Hz, 2H), 7.37 (d,  $J = 8.0$  Hz, 2H), 4.23-4.17 (m, 1H), 4.07-4.00 (m, 1H), 3.88 (br s, 1H), 3.38 (t,  $J = 6.7$  Hz, 2H), 3.18 (dd,  $J = 13.5$ , 9.2 Hz, 1H), 3.02 (dd,  $J = 13.5$ , 2.0 Hz, 1H), 2.44 (s, 3H), 2.00-1.65 (m, 5H), 1.56-1.40 (m, 1H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  (ppm) = 142.1, 138.9, 130.4, 124.2, 70.3, 59.6, 58.9, 33.3, 33.2, 32.1, 26.2, 21.6. HRMS (ESI+):  $m/z$  calc. for  $C_{14}H_{21}O_2SBr_2$  410.9629, found 410.9637.

### (2*R*,3*S*,*S*)-1-(*p*-tolylsulfinyl)-3,7-dibromoheptan-2-ol (*syn*-**23**)



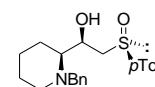
To a solution of  $ZnI_2$  (600 mg, 1.88 mmol, 1.1 equiv) in 9 mL anhydrous THF under argon at room temperature was added via canula a solution of (*S,S*)-**9** (700 mg, 1.71 mmol, 1 equiv) in 9 mL THF. After being stirred for 30 min at room temperature, the mixture was cooled to -78°C. Then, DIBAL-H (2.8 mL, 1.5M solution in toluene, 4.27 mmol, 2.5 equiv) was added dropwise via syringe over a 5-min period and the solution was maintained at -78°C for 1.5 h. Excess of MeOH (20 mL) was then added dropwise via pipet, the cooling bath was removed and the solution was allowed to warm to room temperature. The solvents were evaporated under vacuum and the resulting solid was treated with a saturated aqueous solution of sodium potassium tartrate (80 mL) and EtOAc (80 mL). After the mixture was stirred vigorously overnight, the aqueous layer was separated and extracted with EtOAc (3x25 mL). The organic extracts were combined, washed with brine (25 mL), dried over  $MgSO_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexanes/EtOAc, 3:1) to afford *syn*-**23** as a pale yellow oil (599 mg, 1.5 mmol, 85%).  $R_f = 0.18$  (cyclohexane/EtOAc, 3:1).  $[\alpha]_D^{20} = +65.2$  ( $c$  1.05, acetone).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm) = 7.55 (d,  $J = 8.2$  Hz, 2H), 7.34 (d,  $J = 8.0$  Hz, 2H), 4.28-4.23 (m, 1H), 4.14-4.08 (m, 1H), 3.92 (sl, 1H), 3.39 (t,  $J = 6.6$  Hz, 2H), 3.11 (dd,  $J = 13.2$ , 8.2 Hz, 1H), 3.02 (dd,  $J = 13.2$ , 3.7 Hz, 2H), 4.42 (t, 3H), 2.05-1.65 (m, 5H), 1.61-1.46 (m, 1H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  (ppm) = 142.4, 139.9, 130.4, 124.1, 70.3, 60.8, 60.3, 33.6, 33.3, 32.0, 26.5, 21.6. HRMS (ESI+):  $m/z$  calc. for  $C_{14}H_{21}O_2SBr_2$  410.9629, found 410.9631.

### (*S,S*)-2-(*p*-tolylsulfinyl)-1-((*S*)-1-benzylpiperidin-2-yl)ethanol (*anti*-**7**)



326 mg (0.79 mmol, 1 equiv) of *anti*-**23** and 0.30 mL (2.74 mmol, 3.5 equiv) of benzylamine in 3 mL MeOH were heated in a microwave oven at 80°C for 2 h. The reaction mixture was allowed to cool to room temperature and it was added to 50 mL of a saturated aqueous solution of NaCl. Then, 50 mL of  $CH_2Cl_2$  were added, the aqueous layer was separated and extracted with  $CH_2Cl_2$  (3x25 mL). The organic extracts were combined, dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel ( $CH_2Cl_2/MeOH$ , 100:1) affording 170 mg (0.48 mmol, 60%) of *anti*-**7** as a white solid.  $R_f = 0.75$  ( $CH_2Cl_2/MeOH$ , 10:1). M.p. 99-101°C.  $[\alpha]_D^{20} = +100$  ( $c$  2.0, acetone).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm) = 7.47 (d,  $J = 8.2$  Hz, 2H), 7.27-7.17 (m, 7H), 4.58-4.54 (m, 1H), 4.16 (d,  $J = 13.7$  Hz, 1H), 3.66 (br s, 1H), 3.15 (d,  $J = 13.7$  Hz, 1H), 2.88 (dd,  $J = 13.3$ , 9.8 Hz, 1H), 2.73 (dd,  $J = 13.3$ , 1.8 Hz, 1H), 2.73-2.67 (m, 1H), 2.34 (s, 3H), 2.31-2.25 (m, 1H), 2.06-1.98 (m, 1H), 1.62-1.58 (m, 1H), 1.45-1.41 (m, 3H), 1.29-1.13 (m, 2H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  (ppm) = 141.5, 140.8, 130.1, 128.9, 128.5, 127.1, 124.1, 65.0, 63.6, 60.9, 57.6, 52.0, 24.0, 23.7, 23.2, 21.5. HRMS (ESI+):  $m/z$  calc. for  $C_{21}H_{28}NO_2S$  358.1841, found 358.1841.

### (*R,S*)-2-(*p*-tolylsulfinyl)-1-((*S*)-1-benzylpiperidin-2-yl)ethanol (*syn*-**7**)



410 mg (0.99 mmol, 1 equiv) of *syn*-**23** and 0.38 mL (3.48 mmol, 3.5 equiv) of benzylamine in 4 mL MeOH were heated in a microwave oven at 80°C for 2 h. The reaction mixture was allowed to cool to room temperature and it was added to 50 mL of a saturated aqueous solution of NaCl. Then, 50 mL of  $CH_2Cl_2$  were added, the aqueous layer was

separated extracted with  $\text{CH}_2\text{Cl}_2$  (3x25 mL). The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) affording 225 mg (0.63 mmol, 63%) of *syn-7* as a white solid.  $R_f = 0.65$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 10:1). M.p. 119-121°C.  $[\alpha]_D^{20} = +23.1$  (c 1, acetone).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.56 (d,  $J = 8.2$  Hz, 2H), 7.35-7.27 (m, 7H), 4.27-4.24 (m, 1H), 3.83 (d,  $J = 13.6$  Hz, 1H), 3.69 (d,  $J = 13.6$  Hz, 1H), 3.01-2.96 (m, 2H), 2.77 (dd,  $J = 13.2, 8.2$  Hz, 1H), 2.67 (dd,  $J = 13.2, 3.7$  Hz, 1H), 2.44-2.40 (m, 1H), 2.43 (s, 3H), 1.91-1.86 (m, 1H), 1.64-1.57 (m, 1H), 1.51-1.41 (m, 2H), 1.33-1.24 (m, 2H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 141.8, 141.0, 139.3, 130.0, 128.7, 128.6, 127.3, 124.4, 65.0, 63.3, 61.2, 57.6, 48.7, 21.9, 21.7, 21.5, 21.4. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{21}\text{H}_{28}\text{NO}_2\text{S}^+$  358.1841, found 358.1841.

#### (*S,S*)-1-benzyl-2-((*S*)-oxiran-2-yl)piperidine (*anti-6*)



A mixture of *anti-7* (121 mg, 0.34 mmol, 1 equiv) and *t*BuBr (0.31 mL, 2.76 mmol, 8 equiv) in dry  $\text{CHCl}_3$  (2.5 mL) was heated at 85°C under argon, using an oil bath, for 15 h. The mixture was allowed to cool to room temperature and the excess *t*BuBr and solvent were removed under reduced pressure. The residue was dissolved in 1.9 mL dry  $\text{CH}_2\text{Cl}_2$  and 187 mg (1.26 mmol, 3.7 equiv) of  $\text{Me}_3\text{OBF}_4$  were added. After stirring for 6 h at room temperature under argon, 3 ml of a saturated aqueous solution of  $\text{K}_2\text{CO}_3$  was added and the mixture was stirred vigorously for further 16 h at the same temperature. Then, the aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3x20 mL). The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 200:1) affording 38 mg (0.018 mmol, 52%) of *anti-6* as a yellow oil.  $R_f = 0.65$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 50:1).  $[\alpha]_D^{20} = -100$  (c 0.56,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.28-7.13 (m, 5H), 4.06 (d,  $J = 13.3$  Hz, 1H), 3.02 (d,  $J = 13.3$  Hz, 1H), 2.80-2.71 (m, 3H), 2.54 (dd,  $J = 5.1, 2.8$  Hz, 1H), 1.93-1.78 (m, 2H), 1.74-1.62 (m, 2H), 1.55-1.32 (m, 3H), 1.26-1.11 (m, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 139.7, 128.8, 128.3, 127.0, 65.4, 60.0, 54.7, 52.7, 49.3, 29.9, 25.6, 23.5. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{14}\text{H}_{20}\text{NO}^+$  218.1545, found 218.1554.

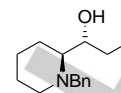
#### (*S,S*)-1-benzyl-2-((*S*)-oxiran-2-yl)piperidine (*syn-6*)



A mixture of *syn-7* (157 mg, 0.44 mmol, 1 equiv) and *t*BuBr (0.40 mL, 1.10 mmol, 2.5 equiv) in dry  $\text{CHCl}_3$  (3 mL) was heated at 85°C under argon, using an oil bath, for 15 h. The mixture was allowed to cool to room temperature and the excess *t*BuBr and solvent were removed under reduced pressure. The residue was dissolved in 2.4 mL dry  $\text{CH}_2\text{Cl}_2$  and 242 mg (1.63 mmol, 3.7 equiv) of  $\text{Me}_3\text{OBF}_4$  were added. After stirring for 6 h at room temperature under argon, 3 ml of a saturated aqueous solution of  $\text{K}_2\text{CO}_3$  was added and the mixture was stirred vigorously for further 16 h at the same temperature. Then, the aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3x20 mL). The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2$ ) affording 74 mg (0.34 mmol, 78%) of *syn-6* as a pale yellow oil.  $R_f = 0.45$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 50:1).  $[\alpha]_D^{20} = -72.0$  (c 1.15, acetone).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.40-7.20 (m, 5H), 4.39 (d,  $J = 13.7$  Hz, 1H), 3.25 (d,  $J = 13.7$  Hz, 1H), 3.06-3.01 (m, 1H), 2.85-2.82 (m, 1H), 2.79 (dd,  $J = 4.7, 4.4$  Hz, 1H), 2.49 (dd,  $J = 4.8, 2.8$  Hz, 1H), 1.90-1.36 (m, 7H), 1.32-1.17 (m, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$

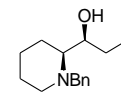
(ppm) = 139.6, 129.3, 128.2, 126.8, 65.8, 59.7, 56.0, 52.3, 44.0, 29.4, 25.5, 23.9. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{14}\text{H}_{20}\text{NO}^+$  218.1545, found 218.1544.

#### (*R*)-1-((*S*)-1-benzylpiperidin-2-yl)propan-1-ol (*anti-26*)



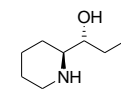
To a solution of *anti-6* (48 mg, 0.22 mmol, 1 equiv) in 1.05 mL of THF under argon,  $\text{CuI}$  (18 mg, 0.09 mmol, 0.4 equiv) was added. The suspension was cooled at -78°C, and then 0.52 mL of a 3.0 M solution of  $\text{MeMgBr}$  in  $\text{Et}_2\text{O}$  (1.56 mmol, 7.1 equiv) were introduced dropwise via cannula over a 10-min period. The reaction mixture was allowed to warm to -20°C overnight. Then, the mixture was treated with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (5 mL). The aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3x10 mL), the organic extracts were combined, dried ( $\text{MgSO}_4$ ), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) to afford 50.3 mg (0.21 mmol, 97%) of *anti-26* as a pale yellow oil.  $R_f = 0.50$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 30:1).  $[\alpha]_D^{20} = -59.1$  (c 1.7  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.27-7.16 (m, 5H), 4.20 (d,  $J = 13.3$  Hz, 1H), 3.99-3.95 (m, 1H), 3.28 (br s, 1H), 3.01 (d,  $J = 13.3$  Hz, 1H), 2.86-2.81 (m, 1H), 2.14 (dt,  $J = 11.2, 3.2$  Hz, 1H), 1.94 (td,  $J = 11.9, 2.7$  Hz, 1H), 1.70-1.67 (m, 1H), 1.60-1.22 (m, 6H), 1.18-1.07 (m, 1H), 0.93 (t,  $J = 7.4$  Hz, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 138.7, 129.1, 128.4, 127.1, 70.3, 63.7, 57.8, 53.2, 25.6, 25.5, 23.9, 23.4, 11.0. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{15}\text{H}_{24}\text{NO}^+$  234.1858, found 234.1869.

#### (*S*)-1-((*S*)-1-benzylpiperidin-2-yl)propan-1-ol (*syn-26*)



To a solution of *syn-6* (40 mg, 0.18 mmol, 1 equiv) in 0.6 mL of THF under argon,  $\text{CuI}$  (15 mg, 0.08 mmol, 0.4 equiv) was added. The suspension was cooled at -78°C, and then 0.37 mL of a 3.0 M solution of  $\text{MeMgBr}$  in  $\text{Et}_2\text{O}$  (1.11 mmol, 6.2 equiv) were introduced dropwise via cannula over a 10-min period. The reaction mixture was allowed to warm to -20°C overnight. Then, the mixture was treated with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (5 mL). The aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3x10 mL). The organic extracts were combined, dried ( $\text{MgSO}_4$ ), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) to afford 27.3 mg (0.12 mmol, 75%) of *syn-26* as a pale yellow oil.  $R_f = 0.25$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 50:1).  $[\alpha]_D^{20} = -22.2$  (c 3, acetone).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 7.27-7.14 (m, 5H), 4.00 (sl, 1H), 3.85 (d,  $J = 13.2$  Hz, 1H), 3.73 (d,  $J = 13.2$  Hz, 1H), 3.72-3.65 (m, 1H), 1.78-1.48 (m, 5H), 1.39-1.32 (m, 1H), 1.28-1.08 (m, 2H), 0.93 (t,  $J = 7.4$  Hz, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 139.3, 128.9, 128.6, 127.3, 68.2, 62.6, 56.2, 45.5, 27.0, 21.2, 20.0, 19.0, 10.3. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_{15}\text{H}_{24}\text{NO}^+$  234.1858, found 234.1861.

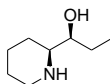
#### (+)- $\alpha$ -conhydrine (2)



A round-bottom flask, equipped with a stir bar, was charged with *anti-26* (31 mg, 0.13 mmol),  $\text{Pd}(\text{OH})_2$  on carbon (20 w%, 1 mg, 0.3 equiv), and  $\text{MeOH}$  (1.5 mL). The flask was purged with hydrogen (1 atm, balloon) for 10 min; then, the mixture was stirred vigorously (under hydrogen atmosphere) at room temperature for 4.5 h. The reaction mixture was

filtered onto a pad of Celite and washed with  $\text{CHCl}_3$ . The filtrate was concentrated in vacuo to afford 15 mg (0.10 mmol, 79%) of (+)- $\alpha$ -conhydrine (**2**) as a viscous colourless oil in an analytically pure form.  $[\alpha]_{\text{D}}^{20} = +8.0$  (c 0.82, EtOH) (lit.<sup>21</sup>  $[\alpha]_{\text{D}}^{20} = +8.3$  (c 0.81, EtOH)).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 3.52-3.48 (m, 1H), 3.18-3.15 (m, 1H), 3.06 (br s, 2H), 2.70 (td,  $J = 12.0, 2.9$  Hz, 1H), 2.64-2.60 (m, 1H), 1.85-1.84 (m, 1H), 1.63-1.56 (m, 2H), 1.52-1.29 (m, 5H), 0.97 (t,  $J = 7.4$  Hz).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 75.3, 60.4, 46.8, 26.0, 25.6, 24.6, 24.2, 10.7. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_8\text{H}_{18}\text{NO}^+$  144.1383, found 144.1389.

### (-)- $\beta$ -conhydrine (**3**)



A round-bottom flask, equipped with a stir bar, was charged with *syn*-**26** (28 mg, 0.12 mmol),  $\text{Pd}(\text{OH})_2$  on carbon (20 w%, 1 mg, 0.3 equiv), and MeOH (1.3 mL). The flask was purged with hydrogen (1 atm, balloon) for 10 min; then, the mixture was stirred vigorously (under hydrogen atmosphere) at room temperature for 4.5 h. The reaction mixture was filtered onto a pad of Celite and washed with  $\text{CHCl}_3$ . The filtrate was concentrated in vacuo to afford 16 mg (0.011 mmol, 93%) of (-)- $\beta$ -conhydrine (**3**) as a white solid in an analytically pure form. Mp 68-69°C.  $[\alpha]_{\text{D}}^{20} = -8.0$  (c 0.89, EtOH) (lit.<sup>21</sup>  $[\alpha]_{\text{D}}^{20} = +8.1$  (c 1.0, EtOH) for (+)- $\beta$ -conhydrine).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 3.52 (br s, 2H), 3.31 (ddd,  $J = 8.4, 8.4, 3.3$  Hz, 1H), 3.20-3.14 (m, 1H), 2.62 (ddd,  $J = 11.9, 11.9, 2.9$  Hz, 1H), 2.44 (ddd,  $J = 10.6, 7.7, 2.8$  Hz, 1H), 1.84-1.79 (m, 1H), 1.70-1.15 (m, 7H), 0.98 (t,  $J = 7.4$  Hz, 3H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) = 72.7, 62.0, 45.3, 26.4, 25.5, 22.5, 22.2, 9.6. HRMS (ESI+):  $m/z$  calc. for  $\text{C}_8\text{H}_{18}\text{NO}^+$  144.1383, found 144.1387.

## Acknowledgements

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## Conflict of Interest

The author declare no conflict of interest.

**Keywords:** Asymmetric synthesis • Chiral auxiliaries • Chiral sulfoxide • Crystallization-Induced Diastereomer Transformation • Conhydrine

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