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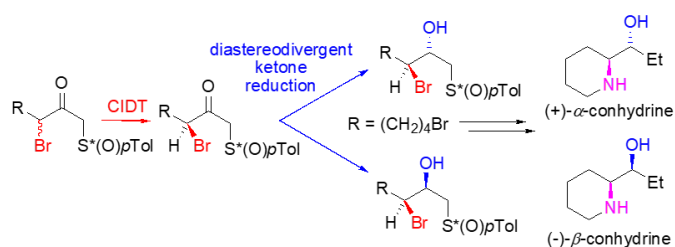
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# Crystallization-Induced Diastereomer Transformation of $\alpha$ -Bromo $\alpha'$ -Sulfinyl Ketones. Diastereodivergent Synthesis of (+)- $\alpha$ -Conhydrine and (-)- $\beta$ -Conhydrine

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Supporting Information Placeholder



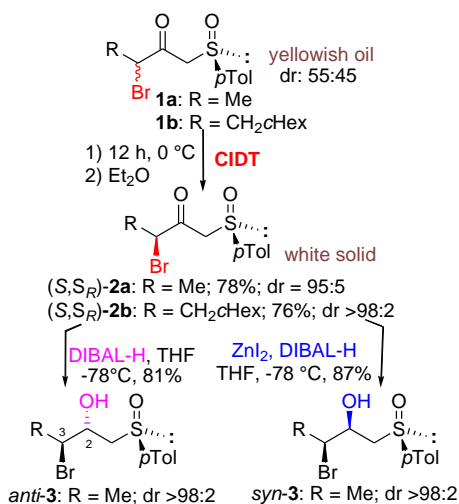
**ABSTRACT:** Crystallization-Induced Diastereomer Transformation (CIDT) of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinylketones is reported. This process provides not readily accessible enantiopure stereolabile  $\alpha$ -bromoketones, which after diastereoselective carbonyl group reduction lead to the corresponding highly value-added *anti* and *syn*-bromohydrins with excellent diastereoselectivities. As an application, a diastereodivergent synthesis of enantiopure hemlock alkaloid (+)- $\alpha$ -conhydrine and its diastereomer (-)- $\beta$ -conhydrine is also described.

The different stereoisomers of a chiral molecule can exhibit different pharmacological, toxicologic, pharmacokinetic and metabolic properties. For this reason, it is important to ensure that only the biologically active stereoisomer of a chiral molecule is present in a final drug preparation. It is also crucial to demonstrate that if other stereoisomers are present they do not imply any danger for the patients health.<sup>1</sup> Therefore, the development of enantiopure chiral drugs has become an essential aspect in pharmaceutical industry research. Particularly, for economical reasons, there has been an increase interest in processes centered on the transformation of racemates or diastereomeric mixtures into a single stereoisomeric product by crystallization. In this context, Crystallization-Induced Diastereomer Transformation (CIDT) is a practical, cost-effective and green technique to achieve a diastereoenrichment.<sup>2</sup> In this hybrid process involving mixtures of two diastereomeric compounds, one combines the selective crystallization or precipitation of a desired diastereomer and the simultaneous epimerization of the undesired one. In contrast to classical resolution, which affords yields lower than 50%, CIDT provides a theoretical yield of 100%, mostly in a single crystallization step, entirely avoiding the occurrence of an undesired stereoisomer.

In an earlier study,<sup>3</sup> we reported on the synthesis of  $\alpha$ -(*S*)-dibenzylamino ketones from non racemic  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones optically pure only at the sulfur atom (**1**, Scheme 1) via combined *in situ* substitution-epimerization in a so-called Dynamic Kinetic Resolution (DKR). During the course of that study, a serendipitous discovery was made when the 55:45 epimeric mixtures **1a** and **1b**, stored for 12 h at 0

$^{\circ}C$ , precipitated. The resulting yellowish solids were crushed and washed with diethyl ether providing, on a multigram scale, enantiopure epimers (*S,S<sub>R</sub>*)-**2a** and (*S,S<sub>R</sub>*)-**2b**, resulting from an efficient CIDT of **1a** and **1b**, as white solids. (*S,S<sub>R</sub>*)-**2a** and (*S,S<sub>R</sub>*)-**2b** were isolated in 78 and 76% yields, respectively, with excellent diastereoselectivities (dr = 95:5 for (*S,S<sub>R</sub>*)-**2a** and >98:2 for (*S,S<sub>R</sub>*)-**2b**). This process opens a new access to stereolabile  $\alpha$ -bromoketones.<sup>4</sup> It is well-known that the crystalline products arising from CIDTs are prone to epimerize when redissolved.<sup>2a</sup> Nonetheless, we wondered if it would be possible to perform diastereoselective reduction of the carbonyl group, by keeping bromo carbon stereochemistry untouched, opening access to the corresponding bromohydrins, which are known to be useful synthetic intermediates.<sup>5</sup> Thus, we carried out the well-known diastereoselective reduction of  $\beta$ -ketosulfoxides by treating (*S,S<sub>R</sub>*)-**2a** with DIBAL-H<sup>6</sup> or with DIBAL-H in the presence of  $ZnI_2$ <sup>7</sup> in THF at  $-78^{\circ}C$  and to our delight, bromohydrins *anti*-**3** and *syn*-**3** could be readily obtained in 81 and 87% yields, respectively, with excellent diastereoselectivities (dr >98:2). The absolute configurations of the newly generated carbinol stereocenters were confidently assigned by reference to the well-established outcome of this diastereoselective carbonyl reduction when applied to  $\beta$ -ketosulfoxides,<sup>8</sup> and confirmed from the  $^1H$  NMR spectroscopic data for the methylene protons  $\alpha$  to the sulfinyl group.<sup>9</sup>

Scheme 1. CIDT of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones **1a** and **1b** and diastereodivergent carbonyl reduction of (*S,S<sub>R</sub>*)-**2a** and (*S,S<sub>R</sub>*)-**2b** giving rise to bromohydrins *anti*-**3** and *syn*-**3**



However, at this point the stereochemistry at the bromo carbon stereocenter in *anti-3* and *syn-3* was not known. Thus, for the assignment of C-3 absolute configuration, we took advantage of the vicinal alcohol and triggered the intramolecular cyclization by treating bromohydrins *anti-3* and *syn-3* with  $\text{K}_2\text{CO}_3$  in a 8:5 mixture of  $\text{CH}_3\text{CN}$  and  $\text{MeOH}$  obtaining the corresponding epoxy sulfoxides *anti-4* and *syn-4* in good yields (Scheme 2). The coupling constants values between H-2 and H-3 confirmed the *anti* relative configuration in epoxide *anti-4* ( $^3J_{2,3} = 2.1$  Hz) and the *syn* configuration could be assigned to epoxide *syn-4* ( $^3J_{2,3} = 4.2$  Hz).<sup>10</sup> These stereochemistries were also confirmed by NOESY spectra. As shown in Scheme 2, NOE correlations between H-2 hydrogen and C-4 methyl group were observed in *anti-4* and between C-1 hydrogens and C-4 methyl group in *syn-4*. Furthermore, when reactions of bromohydrins *anti-3* and *syn-3* with  $\text{K}_2\text{CO}_3$  were run during seven days, (*E*)- $\gamma$ -hydroxy- $\alpha,\beta$ -unsaturated sulfoxide **5** was obtained in both cases, confirming that stereochemistry at the bromo carbon atom was kept during the diastereoselective reduction of the carbonyl group. Finally, the absolute stereochemistry of ( $S,S_R$ )-**2b** was unequivocally confirmed by X-ray crystallographic analysis (Figure 1).

Scheme 2. Synthesis of epoxides *anti-4* and *syn-4* and allylic alcohol **5**

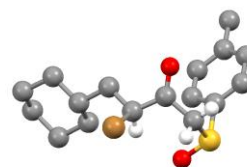
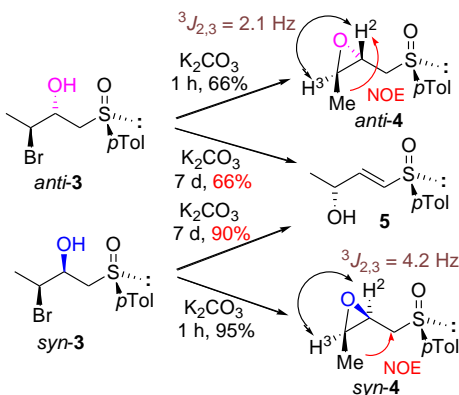


Figure 1. X-ray ORTEP of compound ( $S,S_R$ )-**2b**

At this point, we anticipated that the CIDT observed with compounds **1a** and **1b** having a small and a steric demanding side chain ( $\text{CH}_3$  and  $\text{CH}_2\text{cHex}$ , respectively) could be extended to a  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketone bearing a functionalized side chain. If that was the case, the remarkable stereocontrol observed on the synthesis of enantiopure bromohydrins *anti-3* and *syn-3* along with the synthetic versatility of the sulfoxide, which can be transformed into other functional groups, could increase the interest of our methodology for synthetic applications. In this context, 2-(1-hydroxyalkyl)-piperidine structure, commonly encountered in alkaloids<sup>11</sup> emerged as potential target. This class of compounds includes (+)- $\alpha$ -conhydrine (**6**, Figure 2), isolated from the seeds and leaves of hemlock *Conium maculatum* L. Umbelliferae in 1856,<sup>12</sup> a highly poisonous plant used in ancient Greece for the execution of criminals, which caused the death of the Greek philosopher Socrates in 399 B.C.<sup>13</sup> Due to its diverse biological activities and following the first synthesis of racemic conhydrine in 1948,<sup>14</sup> the synthetic community has demonstrated considerable interest in (+)- $\alpha$ -conhydrine (**6**) and its three stereoisomers.<sup>15</sup> We now report on a new approach for the diastereodivergent synthesis of hemlock alkaloid (+)- $\alpha$ -conhydrine (**6**) as well as its diastereomer (-)- $\beta$ -conhydrine (**7**), which takes advantage of our newly developed protocol involving CIDT of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones.

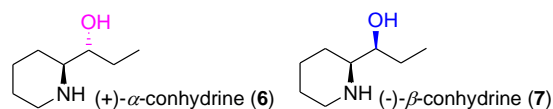


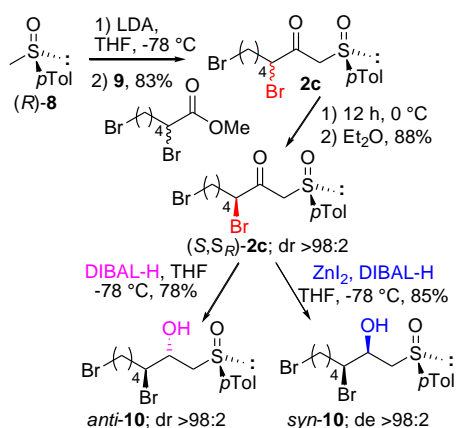
Figure 2. (+)- $\alpha$ -Conhydrine (**6**) and (-)- $\beta$ -conhydrine (**7**)

We envisioned (+)- $\alpha$ -conhydrine (**6**) and (-)- $\beta$ -conhydrine (**7**) could be synthesized from the common intermediate ( $S,S_R$ )-**2c** (Scheme 3) that would contain appropriate terminal electrophilic methylene for late-stage construction of the piperidine ring. Indeed, our expectation was that ( $S,S_R$ )-**2c** could be obtained by CIDT of an epimeric mixture of  $\eta,\gamma$ -dibromo- $\beta$ -ketosulfoxide **2c**. The stereochemistry in carbinol stereocenters of (+)- $\alpha$ -conhydrine (**6**) and (-)- $\beta$ -conhydrine (**7**) would result from diastereodivergent reduction of the ketone in ( $S,S_R$ )-**2c**.

Consequently, our synthesis began by the preparation of requisite dibromo ketosulfoxide **2c** by addition of racemic dibromo ester **9**<sup>16</sup> to two equivalents of lithium anion of (-)-(*R*)-methyl

*p*-tolylsulfoxide (*R*)-**8** affording, after column chromatography, **2c** in 83% yield as an expected mixture of epimerizable diastereomers. The equilibrium ratio of diastereomers was determined to be 55:45 by <sup>1</sup>H NMR in CDCl<sub>3</sub>, with (*S,S*)-**2c** as major epimer. To our delight, CIDT of mixture **2c**, following our newly developed protocol, selectively provided epimer (*S,S*)-**2c** in 88% yield from **2c** as a single diastereomer. The white solid (*S,S*)-**2c** was configurationally stable and could be stored several months in a refrigerator without any epimerization occurs. However, upon standing in CDCl<sub>3</sub> at room temperature, (*S,S*)-**2c** epimerization occurred smoothly. Indeed, a <sup>1</sup>H NMR sample of enantiopure (*S,S*)-**2c** was reanalysed after 48 h showing a 84:16 epimeric mixture (see the Supporting Information for details).

Scheme 3. Synthesis of bromohydrins *anti*-**10** and *syn*-**10**

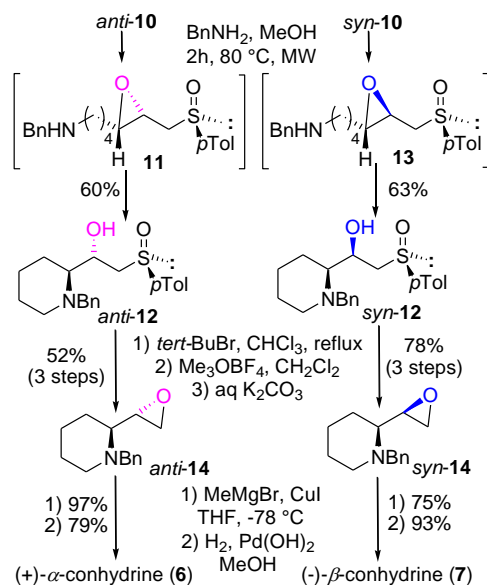


Next, we focussed our attention in the diastereoselective ketone reduction of (*S,S*)-**2c** aiming the preparation of bromohydrins *anti*-**10** and *syn*-**10**, which would be used as the precursors of (+)-*α*-conhydrine (**6**) and (-)-*β*-conhydrine (**7**), respectively. Thus, (*S,S*)-**2c** was submitted to DIBAL-H<sup>6</sup> in THF at -78 °C delivering bromohydrin *anti*-**10** in 78% yield and in a completely diastereoselective way (dr >98:2). The required C-2/C-3 *syn* stereoarray was secured by carbonyl reduction using DIBAL-H in the presence of ZnI<sub>2</sub><sup>7</sup> providing bromohydrin *syn*-**10** in 85% yield with equally high level of asymmetric induction.<sup>9</sup>

With the required bromohydrins *anti*-**10** and *syn*-**10** in hand, elaboration to the targets was pursued by examining first their conversion to piperidinic alcohols *anti*-**12** and *syn*-**12** (Scheme 4). For this purpose, *anti*-**10** and *syn*-**10** were separately exposed to an excess of benzyl amine under microwave irradiation at 80 °C using methanol as a solvent, giving rise to *anti*-**12** and *syn*-**12** in moderated yields (60 and 63% respectively). This transformation took place *via* the regioselective ring opening of epoxide intermediates **11** and **13** in a 6-*exo-tet*-type cyclization involving a double inversion process of the bromo carbon stereocenter. *Anti*-**12** and *syn*-**12** were then submitted to a three-step sequence involving, (1) sulfonyl group reduction by treatment with an excess of *tert*-BuBr in refluxing chloroform for 15 h; (2) methylation of the resulting sulfides

with trimethyl oxonium tetrafluoroborate (Me<sub>3</sub>OBF<sub>4</sub>) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> and (3) treatment of the corresponding sulfonium salts with aqueous K<sub>2</sub>CO<sub>3</sub> to afford amino epoxides *anti*-**14** and *syn*-**14** in 52 and 78% isolated yields, respectively, over 3-steps.

Scheme 4. Syntheses of (+)-*α*-conhydrine (**6**) and (-)-*β*-conhydrine (**7**)



From this point, all that remained to obtain (+)-*α*-conhydrine (**6**) and (-)-*β*-conhydrine (**7**) was lateral chain introduction and amine debenylation. Thus, *anti*-**14** and *syn*-**14** were separately subjected to copper (I)-catalyzed regioselective oxirane ring-opening upon attack with MeMgBr, which exclusively occurred at the less substituted carbon, giving rise to the corresponding amino alcohols in 97% and 75% yield, respectively. Completion of the synthesis was achieved through benzyl group hydrogenolysis by catalytic hydrogenation over 10% Pd(OH)<sub>2</sub>/C in methanol under hydrogen-filled balloon at room temperature affording, uneventfully, enantiomerically pure (+)-*α*-conhydrine (**6**) and its diastereomer (-)-*β*-conhydrine (**7**) in 79 and 93% yield, respectively. The spectroscopic and physical data of both compounds were in accordance with the reported literature values.<sup>17</sup> Hence, the stereochemical assignments of all the intermediate compounds (*S,S*)-**2c**, *anti*-**10** and *syn*-**10**, from which piperidine alkaloids **6** and **7** were derived, were also validated. It is noteworthy that amino epoxide intermediates *anti*-**14** and *syn*-**14** enable the synthesis of a broad variety of analogues of (+)-*α*-conhydrine (**6**) and (-)-*β*-conhydrine (**7**) since they offer the opportunity of the incorporation of a multitude of substituents as side chain late in the synthesis.

In conclusion, we have developed an efficient CIDT of epimeric mixtures of *α*-bromo-*α'*-(*R*)-sulfinyl ketones, which combined to diastereoselective *β*-ketosulfoxides reduction allowed access to enantiopure bromohydrins, known by their

large synthetic potential. These molecular scaffolds can be used as precursors for the synthesis of natural products containing 1,2-aminoalcohols moieties as we have illustrated with the diastereodivergent synthesis of hemlock alkaloid (+)- $\alpha$ -conhydrine (**6**) and its diastereomer (-)- $\beta$ -conhydrine (**7**). On the basis of previous reported syntheses, it is interesting to note that our route avoids the use of a protecting group for the hydroxyl function. However, the obvious synthetic potential of this diastereodivergent strategy arises from the use of (*S,S*)-**2c** as a common building block to access both alkaloids and the adaptability for the preparation of analogues of varying side chain. Moreover, the ready availability of methyl-*p*-tolylsulfoxide in either enantiomerically pure form renders this approach equally applicable to the preparation of the remaining two stereoisomeric forms of conhydrine. Additional studies with regard to the scope of this new CIDT are currently investigated.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, compound characterization and copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (PDF)

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### Author Contributions

†All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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