

# Crystallization-induced asymmetric transformation (CIAT) with simultaneous epimerization at two stereocenters. A short synthesis of conformationally constrained homophenylalanines

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**Abstract**—CIAT of aza-Michael adducts allows simultaneous build up of two stereocenters. A consequent short and efficient synthesis affords simple access to the both antipodes of various conformationally restricted homophenylalanines.  
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Crystallization-induced asymmetric transformation (CIAT)<sup>1,2</sup> is an attractive mode of stereoselective synthesis since it relies on the action of thermodynamic control, and not kinetics, as is usually observed in various methods of asymmetric synthesis. In other words, it is not necessary to work at low temperatures and simple and readily available chiral auxiliaries can be used to build anew stereogenic center. Over the last decade, several papers have appeared indicating its' industrial potential.<sup>3</sup>

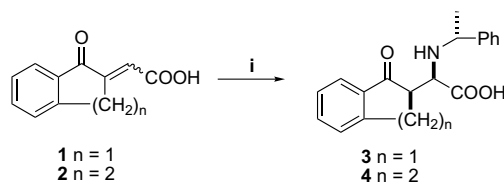
Our research program is focused on applications of CIAT to the synthesis of  $\alpha$ -amino acids.<sup>4</sup> At the end of 1998, being inspired by the results of Urbach and Henig,<sup>5</sup> we developed a method for the asymmetric synthesis of homophenylalanine derivatives based on a reversible aza-Michael reaction. However, Kaneka researchers were a step ahead.<sup>6</sup> We have decided to continue research in this field and have turned our attention to stereoselective reductions of  $\gamma$ -oxo- $\alpha$ -amino acids<sup>4a</sup> and the application of aminoalcohols as auxiliaries in CIAT.<sup>4b</sup> Here we would like to present a remarkable phenomenon, whereby simultaneous epimerization at two stereocenters leads to only one of four stereoisomers

in high yields and purity (Scheme 1).<sup>7,8</sup> The first and the last example of this kind was described forty years ago by Openshaw and Whittaker, in an elegant synthesis of (–)-emetine.<sup>9</sup>

CIAT is essentially in its fundament a process of equilibration, with crystallization causing continuous disequilibrium in the solution. Thus the equilibrium of the whole system is shifted toward one isomer.<sup>10</sup> The reaction itself runs in solution and therefore the medium used can play a crucial role in its success or failure.<sup>11</sup>

For successful CIAT there are four basic conditions which should be kept in mind:

1. The reaction must be reversible.
2. At least one of the final stereoisomers must crystallize under the reaction conditions.



**Scheme 1.** Reagents and conditions: (i) 1.1 equiv (*R*)-phenylethylamine, MeOH/H<sub>2</sub>O, 5 days, 81% (**3**), resp. 80% (**4**); >95% of the major diastereomer in both cases.

**Keywords:** Amino acids and derivatives; Asymmetric synthesis; Crystallization; Michael reactions; Reduction.

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3. The driving force of the process is based on the equation  $v_1 \neq v_2$ , where  $v_1$  and  $v_2$  are overall rates of interconversion between stereoisomers A and B. However, rate constants of interconversion  $k_1$ ,  $k_2$  can be equal.
4. The stereoisomers A and B may not preferentially co-crystallize in a form of mixed crystals  $x\text{A} \cdot y\text{B}$ .<sup>12</sup>

In our case, CIAT is based on a reversible aza-Michael reaction, the retro-Michael being catalyzed by excess of the base. A strong point of this system is that in the course of the reaction the amino acid formed has a dramatically different solubility in comparison with the mixture of starting compounds. Therefore, it is not a serious problem to find reaction conditions to meet the first three points mentioned above. These circumstances lead us to the conclusion that, unlike most cases, CIAT of covalent diastereomers could be more than just a coincidentally observed phenomenon. Aza-Michael addition to substrates of general formula **5** (Fig. 1), under the conditions of CIAT, has the potential to become apart of the efficient asymmetric synthesis of various amino acids. However, the concept has to be proven. A first step toward this aim was achieved through successful application of the method to substrates **6**.<sup>4c</sup>

The configuration of derivatives **3** and **4** was assigned by means of their structural modification (Schemes 2, 3, vide supra) as well as by X-ray crystallography (derivative **4**; Fig. 2).<sup>13</sup>

The  $\gamma$ -oxo- $\alpha$ -amino acids **3** and **4** were further used for synthesis of conformationally restricted homophenylalanines (Hfe) **9** and **12** (Schemes 2, 3). Generally, constrained amino acids are widely employed as a subunit of unnatural peptides and peptidomimetics with the aim of studying ligand–receptor interactions and finding a selective/potent receptor agonist/antagonist.

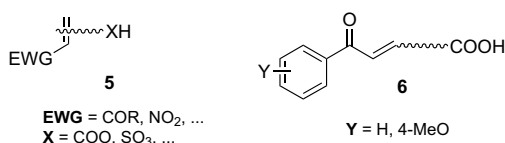
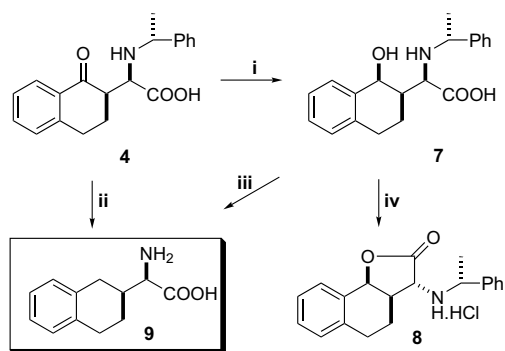
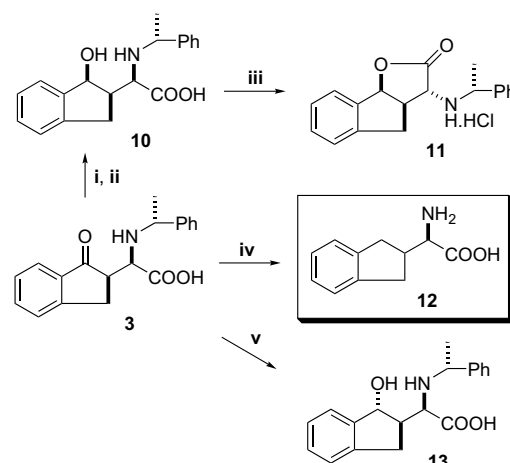


Figure 1.



**Scheme 2.** Reagents and conditions: (i) NaBH<sub>4</sub>/MnCl<sub>2</sub>, MeOH, 88%, dr >97:3; (ii) H<sub>2</sub>/Pd/C, 1 M HCl/MeOH, 71% (unoptimized); (iii) H<sub>2</sub>/Pd/C, 4 M HCl/THF, 63% (unoptimized); (iv) 4 M HCl, 82%, dr >95:5.



**Scheme 3.** Reagents and conditions: (i) NaBH<sub>4</sub>/MnCl<sub>2</sub>, MeOH, 0–5 °C, dr = 3:2; (ii) crystallization, 45%, dr = 11:1; (iii) 4 M HCl, 70%, dr >95:5; (iv) H<sub>2</sub>/Pd/C, 1 M HCl/MeOH, 63% (unoptimized); (v) NaBH<sub>4</sub>, MeOH, 64% (unoptimized), dr >97:3.

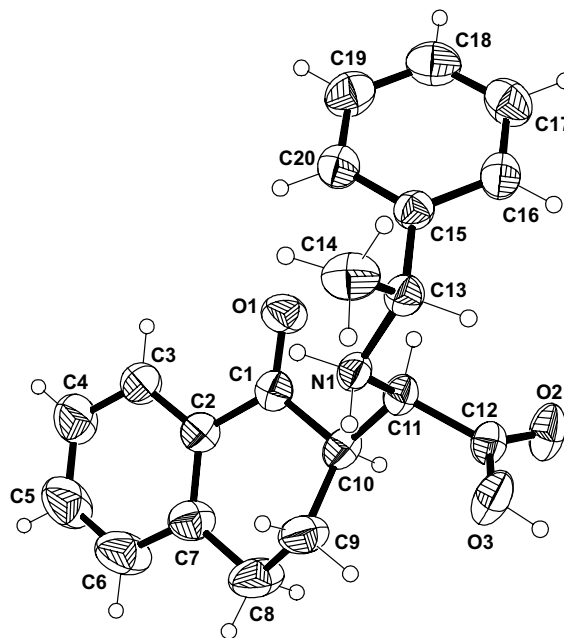


Figure 2.

2-Indanylglycine (Igl) **12** has been used as a component of peptides interacting with tachykinin,<sup>14a</sup> bradykinin,<sup>14b–d</sup> and somatostatin<sup>14e</sup> receptors. What is noteworthy is that its presence is crucial for a selective antagonistic interaction with the B1-receptor, with affinity in the picomolar range.<sup>14d</sup> To the best of our knowledge, the synthesis and application of the amino acid **9** have not yet been described.<sup>15</sup>

The reduction of amino acid **4** in the system NaBH<sub>4</sub>/MnCl<sub>2</sub><sup>4a</sup> is highly stereoselective (dr >97:3), as a result of concurring 1,2-induction and chelation.<sup>16</sup> The lactonization of hydroxy acid **7** leads to cyclic derivative **8**. This allows application of NOE-experiments to assign the relative configuration of the newly built stereocenters.<sup>17</sup> The hydrolysis of lactone **8** results again in

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