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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.

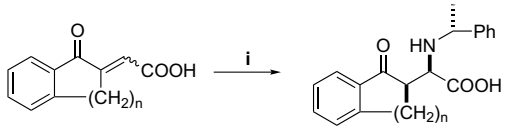
Crystallization-induced asymmetric transformation (CIAT)[1,2] is an attractive mode of stereoselective synthesis since it relies on the action of thermodynamic control, and not kinetics, as is usually observed in various methods of asymmetric synthesis. In other words, it is not necessary to work at 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.[3]

Our research program is focused on applications of CIAT to the synthesis of α-amino acids.[4] At the end of 1998, being inspired by the results of Urbach and Henig,[5] 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.[6] We have decided to continue research in this field and have turned our attention to stereoselective reductions of γ-oxo-α-amino acids[4a] and the application of aminoalcohols as auxiliaries in CIAT.[4b] 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).[7,8] The first and the last example of this kind was described forty years ago by Openshaw and Whittaker, in an elegant synthesis of (−)-emetine.[9]

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

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.



1 n = 1
2 n = 2

3 n = 1
4 n = 2

Scheme 1. Reagents and conditions: (i) 1.1 equiv (*R*)-phenylethylamine, MeOH/H_2O, 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 xA·yB.[12]

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**.[4c]

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).[13]

The γ-oxo-α-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.

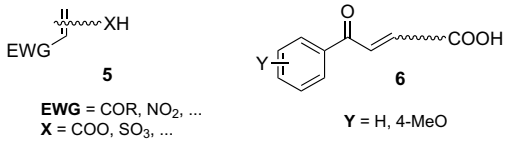
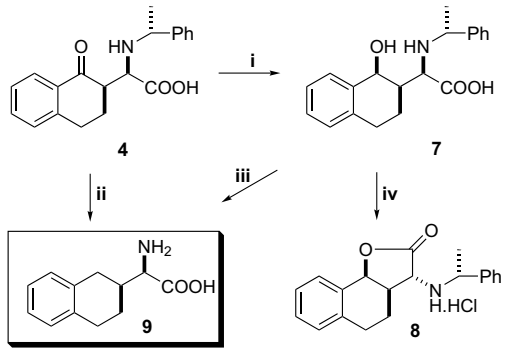
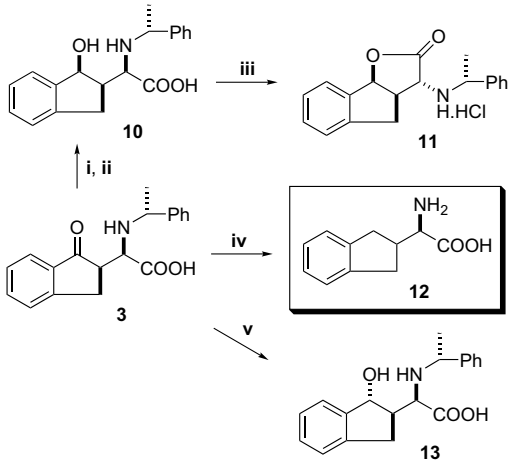


Figure 1.



Scheme 2. Reagents and conditions: (i) $NaBH_4/MnCl_2$, MeOH, 88%, dr >97:3; (ii) H_2/Pd/C, 1 M HCl/MeOH, 71% (unoptimized); (iii) H_2/Pd/C, 4 M HCl/THF, 63% (unoptimized); (iv) 4 M HCl, 82%, dr >95:5.



Scheme 3. Reagents and conditions: (i) $NaBH_4/MnCl_2$, MeOH, 0–5 °C, dr = 3:2; (ii) crystallization, 45%, dr = 11:1; (iii) 4 M HCl, 70%, dr >95:5; (iv) H_2/Pd/C, 1 M HCl/MeOH, 63% (unoptimized); (v) $NaBH_4$, MeOH, 64% (unoptimized), dr >97:3.

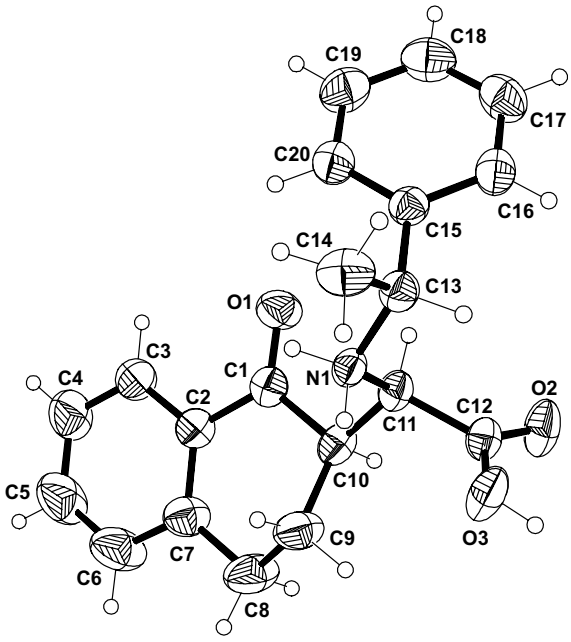


Figure 2.

2-Indanylglycine (Igl) **12** has been used as a component of peptides interacting with tachykinin,[14a] bradykinin,[14b–d] and somatostatin[14e] 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.[14d] To the best of our knowledge, the synthesis and application of the amino acid **9** have not yet been described.[15]

The reduction of amino acid **4** in the system $NaBH_4/MnCl_2$[4a] is highly stereoselective (dr >97:3), as a result of concurring 1,2-induction and chelation.[16] 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.[17] The hydrolysis of lactone **8** results again in

formation of hydroxy acid **7**, as determined by HPLC, and thus the potential inversion of configuration at C-1′ in the course of lactonization could be excluded. Removal of the activating carbonyl group of acid **4** as well as the auxiliary can be smoothly accomplished in one step, even though employing acidic conditions.[18] Analysis on column CROWNPACK CR(+) confirms that epimerization at C-2′ operates only in small scale (~4%). As an alternative a two step reductive sequence (i–iii) can be used.

Unlike acid **4**, oxo acid **3** (Scheme 3) is reduced by $NaBH_4/MnCl_2$ with low stereoselectivity (dr = 3:2). This result can be rationalized by the fact that the five-membered ring fused with benzene is rather planar and affords low stereodiscrimination in a chelation model. Due to its higher planarity, acid **10** possessing the *syn*-1′,2′-configuration has a rather high torsional strain. Another factor worth mentioning is that, when compared with oxo acid **4**, the space distance between the nitrogen and carbonyl oxygen in **3** is higher. This potentially prevents efficient chelation. However, this aspect was not studied further using other Lewis acids with higher ionic radii. Anyway, it is possible to isolate hydroxy acid **10** in much better purity (dr = 11:1) and reasonable yield (45%) after crystallization.[19]

Again, as in the case of acid **7**, the relative configuration of stereocenters in **10** can be assigned via cyclization and NOE experiments. Remarkably, reduction of oxo acid **3** with $NaBH_4$ alone is highly stereoselective and leads to hydroxy acid **13**. The configuration of derivative **13** deduced by comparison with a sample of acid **10** (NMR, HPLC) as well as studies of its' ability to lactonize. Lactonization of **13** is, as expected, much slower (ca. 2 days vs 4 h for the hydroxy acid **10**) and leads to derivative **11**. In other words, formation of a lactone with the *trans*-configuration is not observed and a slow epimerization allows preparation of **11**.[20] The absolute configuration of the amino acid **12** was assigned by comparison with the published optical rotation[15a] as well as by comparative analysis of racemic and chiral samples on column CROWNPACK CR(+).

In summary, we have described CIAT in conjunction with the syntheses of various conformationally constrained homophenylalanines. Applications of CIAT to other conjugate systems are being studied.

Acknowledgements

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7. Typical experimental procedure: (*R*)-Phenylethylamine (1.1 equiv) was added to a stirred suspension of requisite acid in 50% aqueous MeOH ($c = 0.2$ mol dm^{-3}). The resulting mixture was stirred for 5–6 days at room temperature, dr being monitored by HPLC. Precipitated crystalline solid was filtered off, washed with a small amount of MeOH and Et_2O, and dried under reduced pressure.*(2R,2′R,1″R)-(1′-Oxo-1′,2′,3′,4′-tetrahydronaphthalen-2′-yl)-(1″-phenylethylamino)ethanoic acid* (**4**). White crystalline solid, mp = 163–164 °C; yield = 80%; $[\alpha]_D^{20}$ −88 (*c* 0.8, THF/1 M HCl = 4/1); ^{1}H NMR (DCl, acetone-d_6): δ 7.90 (d, 1H, $J = 7.8$, H–Ar), 7.75 (m, 2H,

H–Ar), 7.60–7.45 (m, 4H, H–Ar), 7.35–7.31 (m, 2H, H–Ar), 4.86 (d, 1H, J = 6.6, H-1″), 4.12 (d, 1H, J = 1.8, H-2), 3.67 (m, 1H, H-2′), 3.12–2.98 (m, 2H, H-4′), 2.46 (m, 1H, H-3′A), 2.15 (m, 1H, H-3′B), 1.90 (d, 3H, J = 6.6, H-2″); ^{13}C NMR (DCl, acetone-d_6): δ 196.1 (C-1′); 169.2 (C-1); 144.9, 136.2, 134.8, 132.2, 130.3, 129.9, 129.7, 129.4, 127.8, 127.3 (C–Ar); 60.4, 58.1 (C-1″, C-2); 49.7 (C-2′); 29.6, 26.7 (C-3′, C-4′); 20.4 (C-2″).

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13. Crystal data for **4**: $C_{20}H_{22}ClNO_3$, M = 359.84, 0.26 × 0.24 × 0.12 mm, monoclinic, space group $P2_1$ (No. 4), a = 6.069(1), b = 12.217(2), c = 12.833(2) Å, β = 98.688(2)°, V = 940.5(2) Å^3, Z = 2, D_c = 1.271 g cm^{-3}, μ (Mo K$_\alpha$) = 2.21 cm^{-1}, T = 298 K, $2\theta_{max}$ = 46.54°, 4103 reflections measured, 2364 unique (R_{int} = 0.0140). The refinement (228 variables, one restriction) based on F converged with R = 0.0242, R_w = 0.0248, and GOF = 1.101 using 2316 unique reflections ($I > 2\sigma(I)$).
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17. As mentioned above, the structure of **4** is fully characterized by X-ray crystallography.
18. *(2R,2′S)-Amino-(1′,2′,3′,4′-tetrahydronaphthalen-2′-yl)-ethanoic acid* (**9**). White solid, mp = 246–248 °C; $[\alpha]_D^{20}$ −137 (*c* 0.6, THF/1 M HCl = 4/1); ^{1}H NMR (DCl, DMSO-d_6): δ 7.12–6.96 (m, 4H, H–Ar), 3.88 (br s, 1H, H-2), 2.90–2.48 (m, 4H, H-2′, H-4′A, H-4′B, H-1′A), 2.32–2.16 (m, 1H, H-1′B), 1.96–1.86 (m, 1H, H-3′A), 1.64–1.46 (m, 1H, H-3′B); ^{13}C NMR (DCl, DMSO-d_6): δ 170.4 (C-1); 136.1, 135.1, 129.5, 129.3, 126.6, 126.4 (C–Ar); 56.7 (C-2); 36.0 (C-2′); 31.3, 29.1, 25.8 (C-1′, C-3′, C-4′).
19. Experimental data: The starting amino acid **3** (2.00 mmol, 0.619 g) was suspended in MeOH (30 mL). $MnCl_2{\cdot}4H_2O$ (0.20 equiv, 0.40 mmol, 0.079 g) was added and the mixture was placed on an ultrasonic reactor for 0.5 min to attain a finer suspension of the reagents. The mixture was cooled down to 0 °C and whilst being stirred, $NaBH_4$ (2.00 equiv, 4.00 mmol, 0.151 g) was added over 10 min. The mixture was stirred for a subsequent 10 min (t = 0–5 °C). In the same manner, an additional two portions of $NaBH_4$ (2 × 2.00 equiv) were added, one after another. Later on, cooling was removed and the last 2 equiv of $NaBH_4$ were added at 20 °C. After a short period of stirring (30 min), the mixture was quenched with water (30 mL) and 10% K_2CO_3 (5 mL), the precipitated salts were filtered off and the pH of the filtrate adjusted to 6 (4 M HCl). Crystallization was initiated by ultrasound and the pH value was concurrently adjusted to 6. The product was filtered off, washed with a small amount of EtOH and dried under reduced pressure, yielding 0.28 g (45%) of a white powdery solid **10** (dr = 11:1). Mp = 187–188 °C; $[\alpha]_D^{20}$ +35 (*c* 0.4, 1 M NaOH); ^{1}H NMR (NaOD, D_2O): δ 7.55–7.25 (m, 9H, H–Ar), 3.76 (q, 1H, J = 6.6, H-1″), 3.27 (d, 1H, J = 6.6, H-2), 2.91 (d, 2H, J = 9.0, H-3′), 2.52–2.40 (m, 1H, H-2′), 1.41 (d, 3H, J = 6.6, H-2″); H-1′ in signal of H_2O; ^{13}C NMR (NaOD, D_2O): δ 183.7 (C-1); 146.5, 146.3, 146.3, 131.8, 131.6, 130.4, 130.3, 129.8, 128.0, 127.5 (C–Ar); 79.7 (C-1′); 64.5, 59.5 (C-2, C-1″); 48.3 (C-2′); 35.0 (C-3′); 26.0 (C-2″).
20. Selected data: *(1′R,3R,3aR,8bS)-3-(1′-Phenylethylamino)-3,3a,4,8b-tetrahydroindeno[1,2-b]furan-2-one hydrochloride* (**11**). White solid, mp = 189–192 °C; $[\alpha]_D^{20}$ +150 (*c* 0.5, DMSO); ^{1}H NMR (acetone-d_6): δ 7.86–7.79 (m, 2H, H–Ar), 7.51–7.38 (m, 4H, H–Ar), 7.34–7.19 (m, 3H, H–Ar), 6.22 (d, 1H, J = 8.1, H-8b), 5.18 (q, 1H, J = 6.9, H-1′), 4.08 (dddd, 1H, $J_{3,3a}$ = 7.5, $J_{4A,3a}$ = 8.4, $J_{4B,3a}$ = 1.5, $J_{8b,3a}$ = 8.1, H-3a), 3.55 (d, 1H, J = 7.5, H-3), 3.35 (dd, 1H, $J_{4A,3a}$ = 8.4, $J_{4A,4B}$ = 17.4, H-4A), 3.01 (dd, 1H, $J_{4B,3a}$ = 1.5, $J_{4A,4B}$ = 17.4, H-4B), 1.93 (d, 3H, J = 6.9, H-2′); ^{13}C NMR (DMSO-d_6): δ 171.5 (C-2); 141.9, 141.9, 137.8, 130.0, 129.1, 129.0, 128.1, 127.4, 125.7, 125.5 (C–Ar); 85.9 (C-8b); 57.6, 56.0 (C-3, C-1′); 41.0 (C-3a); 36.0 (C-4); 19.9 (C-2′).
(R)-Aminoindan-2-yl ethanoic acid (**12**). White solid, mp = 254–256 °C (lit.[14a] mp = 225 °C); $[\alpha]_D^{20}$ −54 (*c* 0.4, THF/1 M HCl = 4/1) [lit.[14a] +28 for (*S*)-configuration (1 N HCl, *c* 0.11)]; ^{1}H NMR (DCl, DMSO-d_6): δ 7.22–7.06 (m, 4H, H–Ar), 3.99 (d, 1H, J = 4.5, H-2), 3.06–2.78 (m, 5H, H-1′, H-2′, H-3′); ^{13}C NMR (DCl, DMSO-d_6): δ 170.4 (C-1); 141.8, 141.7, 126.9, 124.7 (C–Ar); 55.2 (C-2); 40.6 (C-2′); 35.5, 35.2 (C-1′, C-3′).