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Crystallization-induced asymmetric transformation. Application to conjugate addition of benzylamine to amides of benzoylacrylic acid

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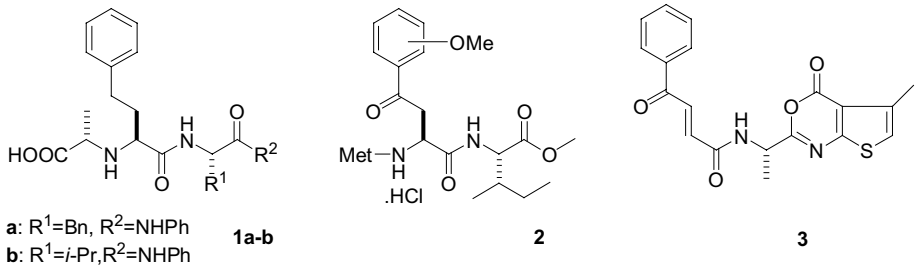
Abstract—Adducts of the conjugate addition of benzylamine to enantiopure amides of aroylacrylic acid possess high enantiomeric and diastereomeric purity. A high degree of stereoselectivity has been achieved by means of crystallization-induced asymmetric transformation. A practical synthesis leading to dipeptides containing homophenylalanine is depicted.

1. Introduction

Crystallization-induced asymmetric transformation (CIAT) is a promising methodology for the control of the stereochemical outcome of diverse chemical reactions. There are number of intriguing applications where CIAT has been used to obtain enantiomerically and diastereomerically pure molecules simply by crystallization of one of two equilibrating isomers. Recoveries can approach 100% based on the mixture regardless of the equilibrium constant in solution.[1] The CIAT approach has been used for control of the absolute configuration of stereogenic carbons[2] or other heteroelements.[3]

Our attention has been focused on the application of CIAT to the reversible conjugate addition of chiral *N*-nucleophiles to aroylacrylic acids.[4,5] It represents a direct and straightforward way to diverse homophenylalanine (Hfe) derivatives.[6,7] Now we would like to present an enlargement of this methodology to the direct preparation of *N*-substituted dipeptides with a Hfe subunit starting from enantiomerically pure aroylacrylic amides **6** (Scheme 2) derived from commercial amino acids.

The synthesis of modified oligopeptides has attracted significant attention (Scheme 1). *N*-Substituted dipeptides **1a**,**b** with L-Hfe incorporated represent a new class



Scheme 1.

Keywords: Crystallization-induced; Asymmetric transformation; Dipeptide; Homophenylalanine.
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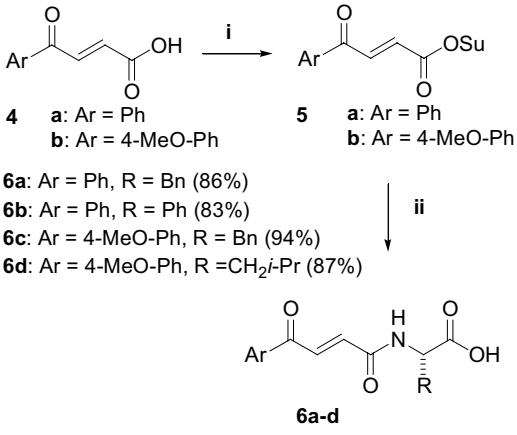
of potent inhibitors of matrix metalloproteinases, a novel class of drugs for the treatment of arthritis.[8,9] D-Hfe based dipeptides are useful in the design of a new class of stable efflux pump inhibitors.[10] Tripeptides **2** with oxo-substituted L-Hfe incorporated have been synthesized as a structural framework for subsequent elaboration into anti-inflammatory oligopeptides.[11] Already, amino acid based amides of aroylacrylic acids **3** have shown significant activity such as, for example, nanomolar inhibitors of the cytomegalovirus protease.[12]

2. Results and discussion

The synthesis of amides of benzoylacrylic acids **6a**–**d** is outlined in Scheme 2. (*E*)-3-Aroylacrylic acid **4** was treated with DCC and *N*-hydroxysuccinimide[13] at 20 °C in tetrahydrofuran for 24 h.[14]

The isolated active ester **5** was then coupled to an amino acid in dimethoxyethane.[15] The amides **6a**–**d** were isolated sufficiently pure for subsequent conjugate addition and were used directly without crystallization in the next step.



Scheme 2. Reagents and conditions: (i) *N*-Hydroxysuccinimide, DCC, THF, 24 h, −20 °C; (ii) α-amino acid, $NaHCO_3$, dimethoxyethane, 1 h.

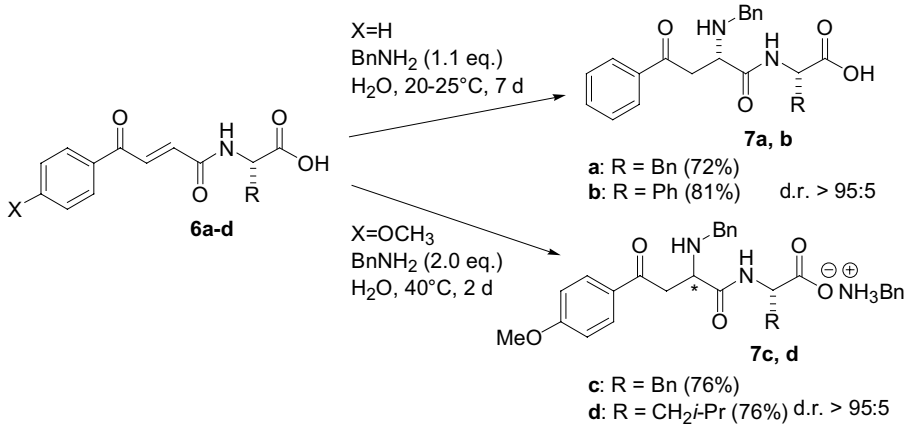
Table 1. Conjugate addition of benzylamine to amides **6a**–**d**

Entry	Ar	R	Yield (%)	Dr	Configuration
7a	Ph	Bn	72	>95:5	(2*S*,2′*S*)
7b	Ph	Ph	81	>95:5	(2*S*,2′*S*)
7c	4-MeOPh	Bn	76	>95:5	(2*S*,2′*S*)
7d	4-MeOPh	CH_2i-Pr	76	>95:5	(2*S*,2′*R*)

The conjugate addition of an *N*-nucleophile to chiral α,β-unsaturated acyclic amides leading to α-amino acids is not common in the literature and the known examples have low stereoselectivity.[16] On the other hand, the CIAT process has served well in the synthesis of α-amino acids using aroylacrylic acids as substrates for conjugate addition of *N*-nucleophiles.[4,5] We supposed that the success of previously published CIAT on this conjugate addition to aroylacrylic acids is based on the formation of only slightly soluble amino acids at their isoelectric point. This scenario can be applied to the reaction of amides of aroylacrylic acids with a free carboxyl function. The product of such addition has also to be the slightly soluble zwitterionic structure. Our anticipation was correct for the phenyl substituted amides **6a**,**b**.[17] Addition of benzylamine to amides **6a**,**b** were successful with only 1.1 molar equiv of base. The best results are summarized in Table 1. The same conditions when applied to 4-methoxyphenyl substituted amides **6c**,**d** led to very low conversion and poor diastereoselectivity.

It was necessary to increase the temperature to 40 °C and to use 2 equiv of amine to achieve sufficient conversion and dr. The corresponding adducts **7c**,**d** were obtained as crystalline salts with an excess of benzylamine (Scheme 3).

The course of the addition and the CIAT process has been monitored for the addition of benzylamine to the amide **6a**. As can be seen from Figure 1 the mixture of both diastereomers was initially formed with a prevalence for the (2*S*,2*R*′)-**7a** isomer (dr = 60:40). However, CIAT changed the sense of stereo induction and as a result the less soluble (2*S*,2*S*′)-**7a** was finally isolated in



Scheme 3. Conjugate addition of benzylamine to unsaturated amides **6a**–**d**.

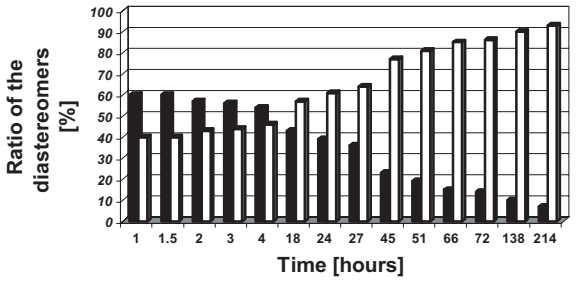


Figure 1. The stereochemical course of addition of benzylamine to amides **6a**, ■—(2*S*,2′*R*)-diastereomer **7a**, □—(2*S*,2′*S*)-diastereomer **7a**.

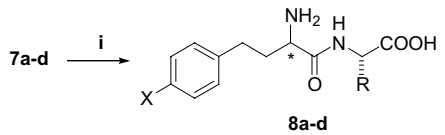
high excess (dr>95:5) after filtration. The crystallization of the less soluble diastereomer was successful in all the examples studied. As can be seen for compound **7d** there is no rule for prediction of the sense of stereo induction. No specific intramolecular role is required for the auxiliary or its proximity to the equilibrating stereogenic centre. The most important function of the existing stereogenic centre is to influence the intermolecular interactions that govern crystal packing.[3] The absolute configuration of C-2 is opposite to the other examples (**7a**–**c**) studied. However in this case also the diastereomeric purity of the isolated product is comparable to the purity of all the other adducts **7a**–**c**.

Adducts **7a**–**d** are stable in the solid state, but are prone to slow epimerization in solution, therefore we decided to use them directly in follow up reactions. Reduction of the carbonyl group and simultaneous debenzylation was accomplished by catalytic hydrogenation (Table 2). In the case of phenyl substituted derivatives **7a**,**b** (X = H) the stable dipeptides **8a**,**b** were obtained by hydrogenation in EtOH/water/HBr[18] (Scheme 4).

The same process failed for **7c**,**d** and led only to a mixture of unidentified products. The best results for the methoxyphenyl substituted derivatives (X = OMe) with only negligible racemization were obtained in the EtOH/H_2SO_4 system (Scheme 4).

Table 2. Preparation of dipeptides **8a**–**d**

Entry	Ar	R	Yield (%)	Dr	Configuration
8a	Ph	Bn	68	>95:5	(2*S*,2′*S*)
8b	Ph	Ph	62	>95:5	(2*S*,2′*S*)
8c	4-MeOPh	Bn	64	>95:5	(2*S*,2′*S*)
8d	4-MeOPh	CH_2*i*-Pr	77	>95:5	(2*S*,2′*R*)



Scheme 4. Reagents and conditions: (i) (for **7a**,**b**): EtOH/water 5:1, HBr (48%), 10% Pd/C, H_2, 40 °C, 30 h; (i) (for **7c**,**d**): EtOH/1 N H_2SO_4 1:3, 10% Pd/C, H_2, 50 °C, 24 h.

3. Elucidation of absolute configuration

After hydrolysis of dipeptides **8a**–**d** under standard conditions[19] (6 M HCl, reflux, 6 h), it was possible to confirm the absolute configuration of the newly synthesized stereogenic centre by means of chiral column chromatography using Crownpak CR(+) and the appropriate Hfe standard.

4. Summary

The use of reversible conjugate addition of benzylamine to chiral unsaturated amides and CIAT represents a straightforward method for the preparation of enantiomerically enriched dipeptides with homophenylalanine residues. This chemistry requires no special precautions and can be run on a multi-gram scale. Applications to the synthesis of metalloproteinase inhibitors are in progress.

Acknowledgements

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14. Typical procedure: A solution of the acid **4a** (0.192 g, 1 mmol) and *N*-hydroxysuccinimide (0.115 g, 1 mmol) in dry THF (10 mL) was cooled in an ice-water bath and dicyclohexylcarbodiimide (0.217 g, 1.05 mmol) was added with stirring. The mixture was kept in a refrigerator (−20 °C) for 24 h. The separated *N*,*N*′-dicyclohexylurea was removed by filtration and the solvent evaporated in vacuo. The crude product was recrystallized from isopropanol (yellow solid, 80–91%, mp 105–107 °C, ^{1}H NMR (300 MHz, DMSO-d_6): 2.88 (s, 4 H); 7.02 (d, 1H, $J_{2',3'} = 15.9$ Hz, H-2′); 7.57–7.76 (m, 5H, H-Arom); 8.29 (d, 1H, $J_{3',2'} = 15.9$ Hz, H-3), ^{13}C NMR (75 MHz, DMSO-d_6): 25.41 (C-3, C-4); 124.74; 128.97; 134.30; 135.45 (Ph, C-2′); 142.13 (C-3′); 161.06 (C-1′); 169.90 (C-2,5); 188.46 (C-4′)).
15. Typical procedure: A mixture of phenylalanine (0.661 g, 4 mmol) and sodium hydrogen carbonate (0.339 g, 4 mmol) in water was treated with a solution of ester **5a** (1.011 g, 3.7 mmol) in dimethoxyethane (20 mL). One hour later water (30 mL) was added and the solution acidified to pH 2 with 4 M hydrochloric acid. The crude oily product solidified on cooling. The crystals were washed on the filter with cold water and dried to afford **6a** (1.196 g, 86%, 139–142 °C, $[\alpha]_D$ −4.4 ± 0.2 (*c* 1.0, MeOH at 20 °C), ^{1}H NMR (300 MHz, $CDCl_3$): 3.14 (dd, 1H, $J_{3A,3B} = 13.8$, $J_{3A,2} = 6.6$ Hz, H-3A); 3.26 (dd, 1H, $J_{3B,3A} = 14.4$ Hz, $J_{3B,2} = 5.1$ Hz, H-3B); 5.03 (m, 1H, H-2); 7.03 (d, 1H, $J_{2',3'} = 15.0$, H-2′); 7.14–7.60 (m, 10H, H-Arom); 7.90 (d, 1H, $J_{3',2'} = 15.0$ Hz, H-3′); 7.98 (d, 1H, $J_{NH,2} = 6.9$ Hz, N*H*), ^{13}C NMR (75 MHz, $CDCl_3$): 37.3 (C-3); 53.7 (C-2); 127.3; 128.7; 128.8; 129.0; 129.3; 133.9; 134.0; 134.6; 135.5; 134.5 (C-Arom, C-2′, C-3′); 164.5 (C-1′); 174.2 (C-1); 190.0 (C-4′)).
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17. Typical procedure: Amide **6a** (2.619 g, 8.1 mmol) was suspended in water (90 mL). To this suspension benzylamine (0.972 mL, 8.9 mmol) was added. The resulting mixture was vigorously stirred for 7 days at 20–25 °C. The precipitated **7a** was filtered off, washed with Et_2O and dried. The same result was achieved when the mixture was stirred for 2 days at 40 °C. (1.918 g, 72%, dr >95:5, 72%, mp 180–182 °C, $[\alpha]_D$ +25.5 ± 0.1 (*c* 1.0, MeOH/1 M HCl = 3:1 at 20 °C), ^{1}H NMR (300 MHz, acetone-d_6/DCl): 3.03 (dd, 1H, $J_{3A,2} = 10.0$, $J_{3A,3B} = 14.1$, H-3A); 3.29 (dd, 1H, $J_{3B,2} = 4.8$ Hz, $J_{3B,3A} = 14.1$ Hz, H-3B); 3.88 (dd, 1H, $J_{3'A,2'} = 6.6$ Hz, $J_{3'A,3'B} = 18.6$, H-3′ A); 4.06 (d, 1H, $J = 12.9$ Hz, $PhCH_2NH$-A); 4.08 (dd, 1H, $J_{3'B,2'} = 5.7$ Hz, $J_{3'B,3'A} = 18.9$ Hz, H-3′ B); 4.19 (d, 1H, $J = 13.2$ Hz, $PhCH_2NH$-B); 4.57 ('t', 1H, $J_{2',3'B} = 6.0$ Hz, $J_{2',3'A} = 6.0$ Hz, H-2′); 4.79 (dd, 1H, $J_{2,3B} = 4.7$ Hz, $J_{2,3A} = 10.0$ Hz, H-2); 7.05–7.94 (m, 15H, H-Arom), ^{13}C NMR acetone-d_6/DCl: 37.5 (C-3); 39.7 (C-3′); 50.6 (Ph*C*H$_2$NH); 54.7 (C-2); 56.2 (C-2′); 127.3; 128.9; 129.0; 129.6; 130.1; 131.1; 131.3; 134.6; 136.3; 137.9 (C-Arom); 167.5 (C-1′); 172.5 (C-1); 196.9 (C-4′)).
18. Typical procedure: Peptide **7a** (1.507 g, 3.5 mmol) was suspended in a mixture of EtOH/water (75 mL/15 mL) and 48% hydrobromic acid (1.174 g, 7.0 mmol) and 10% Pd/C (0.301 g) were added. The suspension was stirred under H_2 (1.1 bar) for 30 h at 40 °C. Thereafter the catalyst was filtered off and the volume of residue was reduced in vacuo to about 10 mL and the pH of the solution was adjusted to about 6. The precipitated **8a** was filtered off, washed with Et_2O and dried (white solid, 68%, mp 276–279 °C $[\alpha]_D$ +19.8 ± 0.1 (*c* 0.5, MeOH/1 M HCl = 3:1 at 20 °C), ^{1}H NMR (300 MHz, D_2O/DCl): 2.14 (m, 2H, H-4′); 2.67 (m, 2H, H-3′); 3.08 (dd, 1H, $J_{3A,2} = 9.0$ Hz, $J_{3A,3B} = 14.1$ Hz, H-3A); 3.25 (dd, 1H, $J_{3B,2} = 5.6$ Hz, $J_{3B,3A} = 14.1$ Hz, H-3B); 3.98 (t, 1H, $J_{2',3'} = 6.4$ Hz, H-2′); 4.58 (dd, 1H, $J_{2,3B} = 5.6$ Hz, $J_{2,3A} = 9.0$ Hz, H-2); 7.23–7.42 (m, 10H, H-arom), ^{13}C NMR (DMSO-d_6/DCl): 30.4 (C-4′); 33.7 (C-3); 36.6 (C-3′); 52.2 (C-2′); 54.5 (C-2); 126.6, 127.1, 128.7, 128.9, 129.0, 129.6, 137.7, 141.4 (C-Arom); 168.9 (C-1′); 172.9 (C-1)).
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