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Crystallization-induced dynamic resolution (CIDR) and its application to the synthesis of unnatural *N*-substituted amino acids derived from aroylacrylic acids

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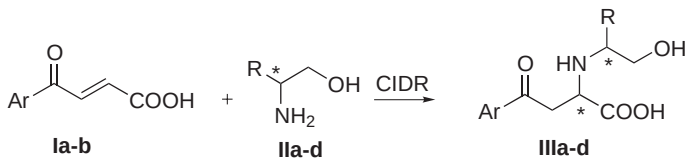
Abstract—A highly stereoselective conjugate addition of chiral amino alcohols affords a simple and inexpensive access to a wide variety of *N*-functionalized homophenylalanine derivatives. Limitations and conditions for application of CIDR to this system were studied.

Over the last decade the synthesis of non-proteinogenic unnatural amino acids has attracted significant attention of organic chemists, who have tried to find synthetic pathways with time and financial requirements as low as possible. From this point of view, application of the method CIDR[1] seems to be an attractive alternative since it uses easily accessible and relatively inexpensive chiral auxiliaries to build a new stereogenic center.



Scheme 1.

Table 1. Michael-type addition of amino alcohols (**IIa–d**) to aroylacrylic acids[a]

Comp.	Ar	Amino alcohol	Solvent	Yield (%)	d.r.[b]	Config.
IIIa	4-MeO-C_6H_4- (**Ia**)	(*R*)-2-Aminobutanol (**IIa**)	CH_2Cl_2	83	>95:5	(2*S*,2′*R*)
IIIb	Ph (**Ib**)	(*S*)-Leucinol (**IIb**)	CH_2Cl_2	77	>95:5	(2*R*,2′*S*)
IIIc	Ph (**Ib**)	(*S*)-Prolinol (**IIc**)	CH_2Cl_2/Et_2O	80	>95:5	(2*S*,2′*S*)
IIId	Ph (**Ib**)	(*S*)-Phenylalaninol (**IId**)	EtOH	81	>95:5	(2*R*,2′*S*)

[a] A typical procedure for preparation of **IIIb** is as follows: To a solution of **Ib** (10.00 g, 56.8 mmol) in 250 ml of CH_2Cl_2, aminoalcohol **IIb** (7.32 g, 62.4 mmol, 1.1 equiv.) was added. The resulting solution was stirred for 7 days at 25–30°C. The precipitate was then filtered off, washed with ether and dried to afford 12.82 g (77%) of **IIIb** as a white solid (mp 157–159°C; d.r. >95:5). ^{1}H NMR (300 MHz, DCl, D_2O/TMS): 7.91 (m, 2H, H-arom.); 7.65 (m, 1H, H-arom.); 7.49 (m, 2H, H-arom.); 4.61 (t, 1H, $J_{2,3A}=5.3$ Hz, $J_{2,3B}=5.3$ Hz, H-2); 3.85–3.95 (m, 3H, H-3, H-1′A); 3.63 (dd, 1H, $J_{1'B,2'}=7.2$ Hz, $J_{1'A,1'B}=12.9$ Hz, H-1′B); 3.40–3.50 (m, 1H, H-2′); 1.50–1.65 (m, 3H, H-3′, H-4′); 0.88 (d, 3H, $J_{4',5'A}=5.9$ Hz, H-5′A); 0.84 (d, 3H, $J_{4',5'B}=5.8$ Hz, H-5′B); ^{13}C NMR (75 MHz, DCl, D_2O/TMS): 201.7 (C-4); 173.8 (C-1); 137.7, 137.5, 131.8, 131.2 (C-arom.); 62.6 (C-1′); 62.2 (C-2); 56.6 (C-2′); 41.4 (C-3′); 38.4 (C-3); 27.1 (C-4′); 25.3 (C-5′A); 23.4 (C-5′B).

[b] d.r. values were readily determined by a reverse phase HPLC analysis on Waters Symmetry C18 5 μm column by using pH 2.5 phosphate buffer–CH_3CN=4:1 (v/v).

Keywords: amino acid derivatives; asymmetric induction; dynamic resolution; addition; amino alcohols.

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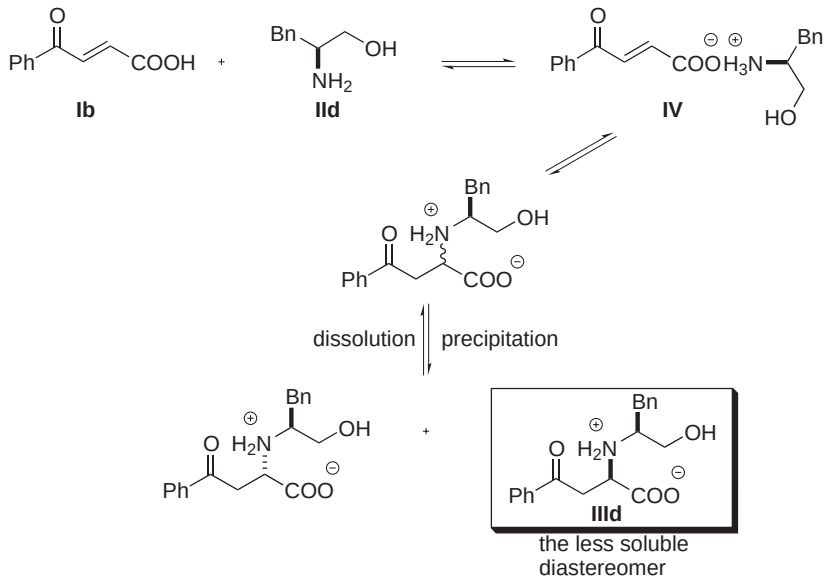


Scheme 2.

Table 2. Diastereoselectivity of the addition of (*R*)-2-aminobutanol (**IIa**) to aroylacrylic acids (rt, 7 days)

Solvent	EtOH	CH_2Cl_2	THF	Dioxane	CH_2Cl_2/Et_2O
Ar = Ph (d.r.)	[a]	[a]	65:35	91:9	[b]
Ar = 4-MeO-C_6H_4- (d.r.)	97:3	96:4	88:12	84:16	94:6

[a] The product does not precipitate out of solution.
[b] A mixture of reagents and products falls out.

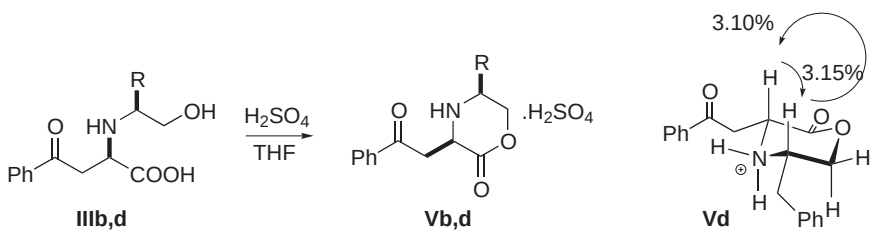
Until now, the CIDR processes for the synthesis of γ-oxo-α-amino acids have been applied in special cases only.[2,3] However, without application of CIDR, the addition of phenylethylamine to aroylacrylic acid esters confirms the low stereo-discriminating environment of this chiral auxiliary in Michael-type additions.[4] In connection with our previous work,[5] we have decided to study the stereoselectivity of addition of easily accessible chiral amino alcohols and to seek out the limitations of CIDR in this reaction system (Scheme 1). The best results are indicated in Table 1.

According to the nomenclature suggested by Eliel,[6] this process of equilibration can be characterized as an asymmetric transformation of the second kind (Scheme 2). In our case, it is based on a reversible Michael-type addition, the equilibration being catalyzed by an excess of base (1.1 equiv.).

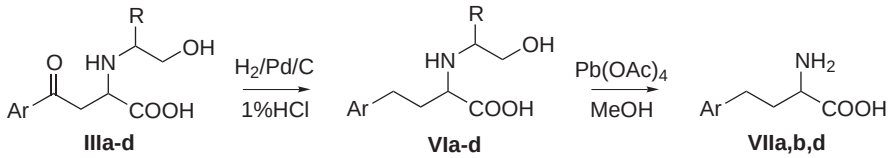
The solvent plays an important role when searching for the appropriate conditions for CIDR. It is necessary to find one in which the solubility of the arising amino acid is as low as possible but, at the same time, high enough to permit the equilibration processes. The example of (*R*)-2-aminobutanol (**IIa**) shows that the ability of the product to precipitate from solution is highly dependent on structural modification of the aroylacrylic acid (Table 2).

The impact of distance between asymmetric centers in the arising adduct on the progress of the dynamic resolution has also been studied. It is known that the proximity of a chiral auxiliary to a labile stereocenter in the CIDR process is sometimes not so important.[1] However, this was not so in our case and shifting of an asymmetric center by one bond had a fatal impact on the diastereoselectivity of the process. Addition of (±)-2-amino-1-phenylethanol to benzoylacrylic acid in various solvents (CH_2Cl_2, EtOH, MeOH/H_2O) led to a mixture of diastereomers with a d.r. of approximately 1:1.

The asymmetric induction of primary amino alcohols leads to (*R*,*S*)-derivatives. This stereoselectivity is opposite to that observed when alanine benzyl ester was



Scheme 3.



Scheme 4.

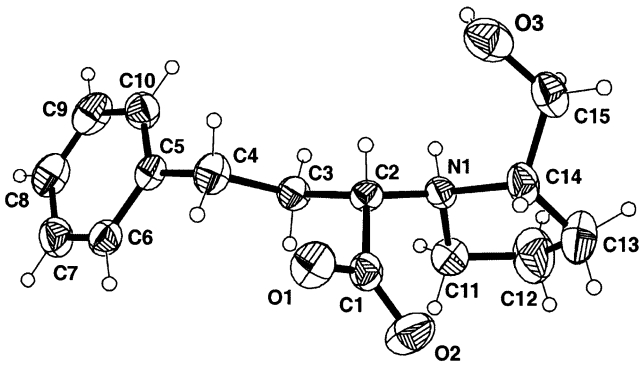


Figure 1. ORTEP view of the molecular structure of **VIc** (50% probability thermal ellipsoids).

added to ethyl benzoylacrylate.[2] (*S*)-Prolinol (**IIc**), surprisingly, represents a special case and forms the amino acid **IIIc** with the (*S*,*S*)-configuration.

The absolute configuration of the adducts **IIIa–d** could not be assigned by the usual spectroscopic methods. In order to determine the configuration of the newly-built stereogenic center in derivatives **IIIa–d** we therefore used three different methods.

For the adducts it is distinctive that they are on the one hand thermolabile, on the other unstable both in alkaline and neutral medium. However, we succeeded in finding mild acidic conditions for transformation of adducts **IIIb**,**d** into the corresponding lactones (Scheme 3), leading to pure compounds via precipitation.‡ After simple isolation of these sensitive compounds we succeeded in elucidating the absolute configuration of adduct **IIId** by NOE. In the case of amino acid **IIIb** we failed due to signal overlap.

After removal of the activating carbonyl group, we were able to prepare stable amino acids **VIa–d** with negligible epimerization (Scheme 4).§ Derivative **VIc** afforded suitable crystals of the hemihydrate and thereafter the absolute stereochemistry was assigned by single crystal X-ray analysis (Fig. 1).¶

In the case of leucinol and aminobutanol derivatives **VIa**,**b** the sense of asymmetric induction has been determined after their transformation to the known homophenylalanines **VIIa**,**b** using a convenient oxidative degradation with $Pb(OAc)_4$ (Scheme 4).[7] Amino acids **VIIa**,**b** were identified and their enantiomeric purity was determined by HPLC on a chiral CROWNPAK® CR(+) column.

In summary, the highly stereoselective conjugate addition of chiral amino alcohols described here represents a simple synthetic route to both antipodes of a variety of *N*-functionalized homophenylalanine derivatives. The application of this method to other conjugate systems is currently in progress.

‡ A typical procedure for the preparation of **Vd** is as follows: Amino acid **IIId** (980 mg, 3 mmol) was dissolved in a mixture of THF (50 ml) and 96% H_2SO_4 (310 mg, 3 mmol). The mixture was stirred for 3 days at room temperature. A precipitate was filtered off and dried to afford 730 mg (60%) of **Vd** as a white solid (mp 185–188°C; d.r. >95:5). ^{1}H NMR (300 MHz, DMSO-d_6/TMS): 8.05 (m, 2H, H-arom.); 7.73 (m, 1H, H-arom.); 7.60 (m, 2H, H-arom.); 7.35 (m, 5H, H-arom.); 4.69 (dd, 1H, $J_{3,1'A}$=3.7 Hz, $J_{3,1'B}$=4.4 Hz, H-3); 4.63 (dd, 1H, $J_{6A,6B}$=12.1 Hz, $J_{6A,5}$=12.1 Hz, H-6A); 4.45 (dd, 1H, $J_{6A,6B}$=12.1 Hz, $J_{6B,5}$=2.8, Hz, H-6B); 4.17–4.29 (m, 1H, H-5); 3.99 (dd, 1H, $J_{1'A,1'B}$=19.0 Hz, $J_{3,1'A}$=4.4 Hz, H-1′A); 3.82 (dd, 1H, $J_{1'A,1'B}$=19.0 Hz, $J_{3,1'B}$=3.7 Hz, H-1′B); 3.08 (dd, 1H, $J_{1''A,1''B}$=13.9 Hz, $J_{5,1''A}$=6.0 Hz, H-1″A); 2.95 (dd, 1H, $J_{1''A,1''B}$=13.9 Hz, $J_{5,1''B}$=8.3 Hz, H-1″B); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): 196.1 (C-2′); 165.9 (C-2); 135.0, 135.0, 134.5, 129.4, 129.1, 128.9, 128.5, 127.4 (C-arom.); 68.5 (C-6); 53.1 (C-5); 51.4 (C-3); 39.4 (C-1′); 33.7 (C-1″).

§ A typical procedure for preparation of **VIa** is as follows: Amino acid **IIIa** (2.46 g, 8.3 mmol) was dissolved in 1% HCl (75 ml) and 10% Pd/C was added (0.50 g). The suspension was stirred under H_2 (1.1 atm) for 1 day. Thereafter the catalyst was filtered off and washed with 1% HCl (50 ml). The resulting solution was added to the filtrate, partially concentrated under reduced pressure and its pH adjusted to 6.5 with 1N NaOH. A precipitate was filtered off, washed with Et_2O and dried to afford 1.71 g (73%) of amino acid **VIa** (d.r. >95:5) as a white solid. An analytical sample was obtained by recrystallization from EtOH with several drops of water: mp 220–222°C, ^{1}H NMR (300 MHz, CD_3OD, DCl/TMS): 7.21 (m, 2H, H-arom.); 6.89 (m, 2H, H-arom.); 4.12 ('t', 1H, $J_{2,3A}$=6.3 Hz, $J_{2,3B}$=6.3 Hz, H-2); 3.83 (dd, 1H, $J_{1'A,2'}$=3.3 Hz, $J_{1'A,1'B}$=12.4 Hz, H-1′A); 3.79 (s, 3H, OMe); 3.72 (dd, 1H, $J_{1'B,2'}$=5.6 Hz, $J_{1'A,1'B}$= 12.4 Hz, H-1′B); 3.15–3.25 (m, 1H, H-2′); 2.82 (m, 1H, H-3A); 2.74 (m, 1H, H-3B); 2.26 (m, 2H, H-4); 1.76 (dq, 2H, $J_{3',4'}$=7.4 Hz, $J_{2',3'}$=7.4 Hz, H-3′); 1.01 (t, 3H, $J_{3',4'}$=7.4 Hz, H-4′); ^{13}C NMR (75 MHz, CD_3OD, DCl/TMS): 171.4 (C-1); 159.8, 133.1, 130.5, 115.1 (C-arom.); 62.4 (C-2′); 59.9 (C-1′); 58.4 (C-2); 55.8 (OMe); 33.1 (C-3); 31.3 (C-4); 21.5 (C-3′); 10.4 (C-4′).

¶ Crystal data for **VIc**: $C_{30}H_{44}N_2O_7$, M=544.67, 0.03×0.06×0.50 mm, monoclinic, space group $P2_1/a$ (No. 14), a=11.442(3), b=7.390(2), c=16.861(4) Å, β=95.313(5)°, V=1419.6(6) Å^3, Z=2, D_c=1.274 g cm^{-3}, μ(Mo Kα)=0.90 cm^{-1}, T=298 K, $2\theta_{max}$=46.62°, 8169 reflections measured, 3952 unique (R_{int}=0.0423). The refinement (362 variables, three restrictions) based on F converged with R=0.0446, R_w=0.0683, and GOF=0.940 using 2911 unique reflections (I>$2\sigma(I)$).

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References

1. Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 447–456.
2. Urbach, H.; Henning, R. *Tetrahedron Lett.* **1984**, *25*, 1143–1146.
3. Yamada, M.; Nagashima, N.; Hasegawa, J.; Takahashi, S. *Tetrahedron Lett.* **1998**, *39*, 9019–9022.
4. Knollmüller, M.; Ferencic, M.; Gärtner, P.; Girreser, U.; Klinge, M.; Gaischin, L.; Mereiter, K.; Noe, Ch. R. *Monatsh. Chem.* **1999**, *130*, 769–782.
5. Berkeš, D.; Kolarovič, A.; Považanec, F. *Tetrahedron Lett.* **2000**, *41*, 5257–5260.
6. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp. 364–365.
7. Hegedus, L. S.; Schmeck, C. *J. Am. Chem. Soc.* **1994**, *116*, 9927–9934.