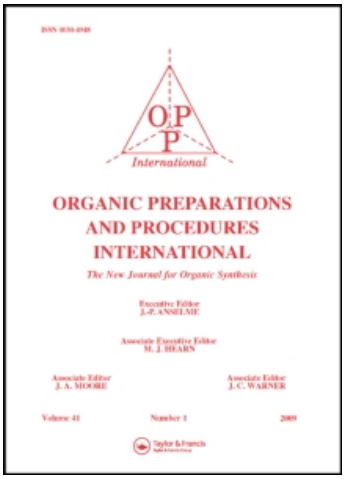

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STEREOSPECIFIC ONE-POT SYNTHESIS OF 5-CARBOXY-3,4-DIPHENYLIMIDAZOLIDIN-2-ONE, A USEFUL PRECURSOR TO THE CORRESPONDING 2,3-DIAMINOPROPANOIC ACID

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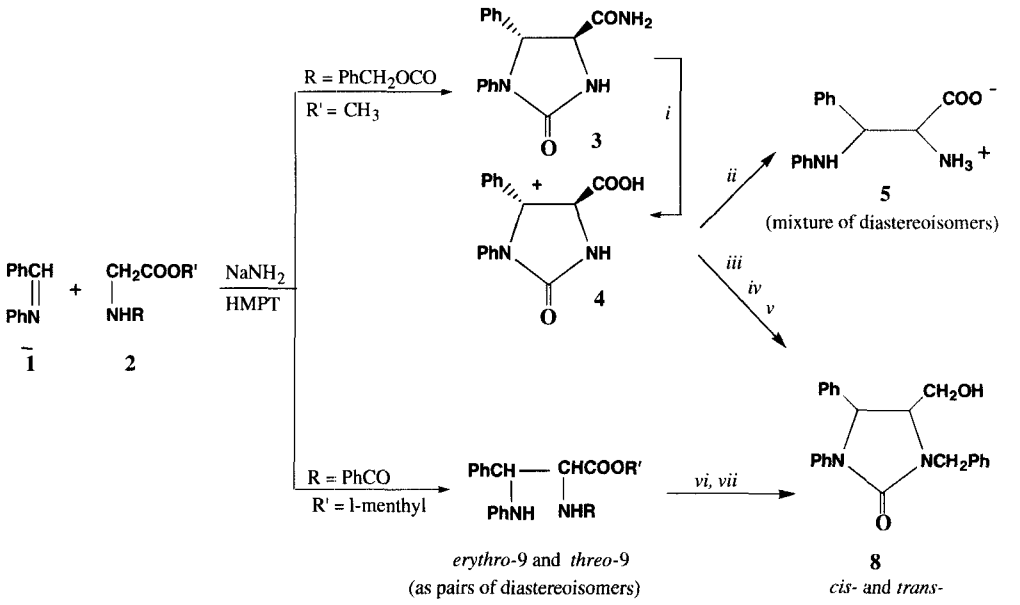
Recently we reported on the synthesis of 2-benzoylamino-3-phenyl-3-phenylamino-propanoic acid menthyl esters and the corresponding chiral diamino propanols[1] which are of interest as tridendate auxiliaries in asymmetric synthesis. They were readily obtained in a two-step procedure starting from *N*-benzylideneaniline and menthyl hippurate in the presence of sodium amide. The high yield and diastereoselectivity of this reaction prompted us to study the aldol-like condensation of *N*-benzylideneaniline with other glycine equivalents such as *N*-carbobenzoxyglycine methyl ester **2** as the CH-acidic component. We expected this reaction to provide an easy access to imidazolidine derivatives similar to the previously reported[2] aldol-type reaction between benzaldehyde and *N*-carbobenzoxyglycine methyl ester leading to the corresponding *trans*-oxazolidin-2-one. Imidazolidine derivatives are usually products of multi-step reactions and are desirable precursors for the preparation of 2,3-diamino acids.[3] The latter are uncommon, naturally occuring amino acids that have recently attracted considerable interest. We now report the stereospecific one-pot synthesis of *trans*-5-carboxy-3,4-diphenylimidazolidin-2-one (**4**) and its further hydrolysis to the corresponding 2-amino-3-phenyl-3-phenylaminopropanoic acid (**5**).

When the dianion of **2** obtained from the reaction with two equivalents of sodium amide was allowed to react with *N*-benzylideneaniline in hexamethylphosphoramide (HMPT), compounds **3** and **4** were obtained as single diastereoisomers. The formation of carboxamide **3** is probably due to partial ammonolysis of the initially formed methoxycarbonylimidazolidin-2-one. When heated with dilute sulfuric acid, the carboxamide **3** chemoselectively gave the cyclic acid **4** as a sole product. The imidazolidin-2-one ring in compounds **3** and **4** proved to be highly resistant to both acidic and alkaline hydrolysis under various conditions. Obviously the 3,4-disubstitution makes the hydrolysis much more difficult, as 3- or 4- monosubstituted 5-carboxyimidazolidin-2-ones afforded the open-chain acids when heated with conc. hydrochloric acid.[3a,3b] The 2-amino-3-phenyl-3-phenyaminopropanoic acid **5** was obtained in a 40% yield as a (1:1.2) diastereoisomeric mixture only on treatment of **4** with 4N NaOH at 110 for 6 days. We assigned the configuration of acid **4** by correlating it with the two



Reagents: i) 20% H_2SO_4, heat; *ii,*) 4N NaOH, heat; *iii)* MeOH, BF_3/Et_2O, heat; *iv,*) BzBr/Ag_2O, DMF; *v)* $NaBH_4$, MeOH; *vi)* $LiAlH_4$, Et_2O; *vii)* $COCl_2$, 10% KOH, toluene.

isomeric imidazolidin-2-one derivatives **8** (Scheme) through a series of transformations not affecting the two chiral centres. For their synthesis, we employed our previously reported preparation of the four diastereoisomeric 2-benzoylamino-3-phenyl-3-phenylaminopropanoic acid menthyl esters.[1] The major, slower eluting pair of *threo* diastereoisomers **9a** as well as the faster eluting, minor *erythro* pair **9b** were separated by preparative HPLC. They were further transformed first to the racemic alcohols **10a** and **10b**, then to the corresponding diastereoisomeric imidazolidin-2-ones **8a** and **8b**. The configuration of the cyclic compounds **8** was established on the basis of parallel quantitative NOE measurements. A 15% enhancement of the signal of the 5-H proton upon irradiation of 4-H was observed for **8b**, indicating its *cis* configuration and a 3% enhancement for the *trans* isomer **8a**. From the configuration of the cyclic products **8** thus established, the *threo* configurations of the related open-chain compounds **9a** and **10a** and the *erythro* configurations of **9b** and **10b** follows. The imidazolidinecarboxylic acid **4** and the carboxamide **3**, being related with *trans*-**8**, also proved to have a *trans* configuration.

Although the yield is not high, this one-pot procedure for the synthesis of 3,4-diphenylimidazolidin-2-one derivatives of *trans* configuration, starting from easily available materials, is promising. These compounds could further be useful as reagents for the preparation of α-branched 2,3-diamino acids and as chiral auxiliaries in asymmetric synthesis when they are optically active.

EXPERIMENTAL SECTION

Mps. were determined on a Kofler microscope. IR spectra were recorded on a Specord 71 IR Karl Zeiss Iena spectrometer in $CHCl_3$. ^1H NMR spectra were obtained on a Bruker WM 250 MHz spec-

trometer in $CDCl_3$, using $SiMe_4$ as an internal standard. Mass spectra were determined on a Jeol IMSD 300 mass spectrometer at 70 ev. Preparative HPLC was performed on an HPLC Perkin-Elmer 2/2 chromatograph: stationary phase, Si 100-7; mobile phase, hexane-diethyl ether (85:15 v/v); , 254 nm; flow rate, 6 mL/min^{-1}. IR, ^{1}H NMR and mass spectral data of products are given in Table.

***trans*-5-Carboxamide-3,4-diphenylimidazolidin-2-one (3) and *trans*-5-Carboxy-3,4-diphenylimidazolidin-2-one (4).**- To a stirred solution of *N*-benzylideneaniline (**1**) (2.5 mmol) and *N*-carbobenzoxyglycine methyl ester[4] (**2**) (2.5 mmol) in HMPT (1 mL) was added sodium amide (5.0 mmol). The reaction mixture was stirred for 1hr at room temperature, hydrolyzed with water and extracted with ethyl acetate. The ethyl acetate solution was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. ^{1}H NMR of the residue showed the presence of *trans*-5-carboxamide-3,4-diphenylimidazolidin-2-one **3** (a single diastereoisomer) and *N*-benzylideneaniline in a ratio 1:1.5. Crystallization from ethanol afforded pure **3** in 22% yield, mp. 230-232°. An analytically pure sample had mp. 231-232°.

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.44; H, 5.54; N, 15.17

The alkaline solution was acidified with 5N HCl. ^{1}H NMR of the ethyl acetate extract of an aliquot sample from the solution showed the presence of **4** (a single diastereoisomer) and *N*-carbobenzoxyglycine in a ratio 1:1. The precipitate was filtered off and washed with water. **4** was obtained in 29% yield, mp. 93-96°. An analytically pure sample had mp. 95-98° (aq. ethanol).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.13; H, 5.00; N, 9.92. Found: C, 68.13; H, 5.21; N, 9.98

A stirred suspension of **3** (0.35 mmol) in 5mL 20% H_2SO_4 was heated at 100° for 2 hrs. The cooled mixture was diluted with water, the product was filtered off and washed with water. **4** was isolated in 99% yield, mp. 93-96°, identical with the obtained above.

2-Amino-3-phenyl-3-phenylaminopropanoic Acid (5).- The imidazolidinecarboxylic acid **4** (1.4 mmol) in 10mL 4N NaOH was heated for 6 days at 110° in a stoppered teflon tube.The solution was acidified with 5N HCl and extracted with methylene chloride. The acidic water solution was evaporated to dryness and the residue was extracted at boiling with dry ethanol (3 x 40mL). The solvent was evaporated under reduced pressure, the residual solid dissolved in 5mL of water and absorbed onto a strongly acidic cation exchanger. The column was washed with water to neutral reaction, then the aminoacid **5** was eluated with 12.5% aqueous NH_3. Ninhydrin-positive fractions were combined and concentrated to dryness *in vacuo*. Compound **5** was obtained in 40% yield, mp. >230° (dec.).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.69; H, 6.85; N, 10.59

***trans*-5-Methoxycarbonyl-3,4-diphenylimidazolidin-2-one (6).**- A solution of **4** (1.4 mmol) and BF_3-etherate (3.3 mmol) in dry methanol (8 mL) was heated under reflux for 1 hr. The solvent was evaporated, the residue was treated with ice-water and extracted with methylene chloride. The extract was washed with 1M aqueous sodium hydrogencarbonate solution and water and dried ($MgSO_4$). After removal of the solvent *in vacuo* and trituration of the residue with pentane **6** was obtained in 93% yield, mp. 122-124°. An analytically pure sample had mp. 122-124° (aq. ethanol).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.88; H, 5.41; N, 9.42

TABLE. Spectral Data of Products

Product	IR (cm^{-1})	^1H NMR (δ)[a]	*m/z*
3	1667, 1693, 3126, 3247, 3353, 3359 [b,c]	3.78 (d, 1H, 5-H, J 3.9), 5.34 (d, 1H, 4-H, J 3.9), 6.90-7.51(m, $10H_{arom.}$), 7.66 (s, 1H, NH, D_2O exch.).[d]	281 (M^+, 46%), 237 (100), 194 (60), 182 (40), 118 (48), 104 (19), 91 (52), 77 (14).
4	1650, 1720, 3425	3.57 (br.s, 1H, NH, D_2O exch.), 4.02 (d, 1H, 5-H, J 3.5), 5.56 (d, 1H, 4-H, J 3.5), 5.57 (s, 1H, COOH, D_2O exch.), 6.95-7.45 (m, $10H_{arom.}$).	282 (M^+, 100%), 237 (49), 94 (47), 181 (51), 118 (30), 191 (47), 77 (55).
5	1450, 1540, 165, 3, 3434 (br.)[b,c]	3.67 (d, 1H, CH, J 4.3, diastereoisomer 1), 3.95 (d, 1H, CH, J 8.9, diastereoisomer 2), 4.04 (d, 1H, CH, J 4.3, diastereoisomer 1), 4.18 (d, 1H, CH, J 8.9, diastereoisomer 2), 5.95-6.32 (m, $10H_{arom.}$).[e]	256 (M^+, 2%), 221 (2), 210 (2), 182 (100), 104 (21), 76 (52).
6	1710, 1745, 3440	3.88 (s, 3H, CH_3), 4.09 (d, 1H, 5-H, J 3.4), 5.49 (d, 1H, 4-H, J 3.5), 5.52 (s, 1H, NH, D_2O exch.), 6.99-7.46 (m, $10H_{arom.}$).	296 (M^+, 100%), 253 (6), 237 (89), 194 (60), 182 (47), 118 (40), 91 (30), 77 (28).
7	1705, 1745	3.75 (s, 3H, CH_3), 3.79 (d, 1H, 5-H, J 3.7), 4.24 (d, 1H, CH_2Ph, J 15.2), 5.06 (d, 1H, CH_2Ph, J 15.2), 5.24 (d, 1H, 4-H, J 3.7), 6.96-7.47 (m, $15H_{arom.}$).	386 (M^+, 26%), 327 (61), 194 (4), 91 (100), 77 (7).
cis-**8**	1702, 3587 [b]	1.56 (s, 1H, OH, D_2O exch.), 3.27-3.43 (m, 2H, CH_2OH), 3.88-3.96 (m, 1H, 5-H), 4.34 (d, 1H, CH_2Ph, J 15.3), 4.90 (d, 1H, CH_2Ph, J 15.3), 5.31 (d, 1H, 4-H, J 9.0), 6.93-7.47 (m, $15H_{arom.}$).	358 (M^+, 10%), 327 (54), 194 (4), 104 (4), 91 (100), 77 (8).
trans-**8**	1695, 3550	2.21 (br.s, 1H, OH, D_2O exch.), 3.9-3.34 (m, 1H, 5-H), 3.53-3.77 (m, 2H, CH_2OH), 4.36 (d, 1H, CH_2Ph, J 15.3), 4.66 (d, 1H, CH_2Ph,J 15.3), 5.17 (d, 1H, 4-H, J 6.3), 6.95-7.49 (m, $15H_{arom.}$).	358 (M^+, 10%), 327 (50), 194 (4), 104 (8), 91 (100), 77 (15).
erythro-**10**	3348, 3411 [b]	1.95 (s, 3H, NHPh, $NHCH_2$Ph, OH, D_2O exch.), 2.99 (dd, 1H, 2-H, J 4.8 /9.6), 3.48-3.63 (m, 2H, CH_2OH), 3.85 (s, 2H, CH_2Ph), 4.62 (d, 1H, 3-H, J 5.1), 6.49-7.35 (m, $15H_{arom.}$).	332 (M^+, 1%), 181 (57), 150 (100), 104 (9), 91 (68), 77 (15).
threo-**10**	3377, 3397[b]	2.12 br.s, 2H, $NHCH_2$Ph, OH, D_2O exch.), 2.89-2.95 (m, 1H, 2-H), 3.44-3.79 (m, 4H, CH_2Ph, CH_2OH), 4.48 (d, 1H, 3-H, J 6.3), 4.78 (br.s, 1H, NHPh, D_2O exch.), 6.51-7.41 (m, $15H_{arom.}$).	332 (M^+, 1%), 181 (34), 150 (100), 104 (6), 91(53), 77(11).

a) J in Hz. b) Obtained on Bruker ISF 193V. c) KBr disc. d) In $[^2H_6]Me_2SO$. e) In ^2HCl.

***trans*-1-Benzyl-5-methoxycarbonyl-3,4-diphenylimidazolidin-2-one (7).**- To a stirred solution of **6** (0.7 mmol) in DMF (1 mL) were added Ag_2O (0.9 mmol) and benzylbromide (2.0 mmol). The mixture was stirred at room temperature for 5 hrs, then evaporated *in vacuo*. The residue was dissolved in chloroform, the solution was washed with water, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Crystallization from isopropyl ether-pentane afforded **7** in 70% yield, mp. 92-95°. An analytically pure sample had mp. 96-98° (benzene-hexane).

Anal. Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.45; H, 5.54; N, 7.25

***threo*- and *erythro*- 2-Benzoylamino-3-phenyl-3-phenylaminopropanoic acid Menthyl Esters (9a and 9b)** were separated by preparative HPLC from the crude mixture of diastereoisomers obtained acc. to 1) (t_r/ s 279 and 359 for *threo*-**9** and 153 and 171 for *erythro*-**9**).

***threo*- and *erythro*- 2-Benzylamino-3-phenyl-3-phenylaminopropan-1-ols (10a and 10b).**- A suspension of *threo*-**9** (1 mmol) and $LiAlH_4$ (10 mmol) in diethyl ether (10 mL) was stirred for 6 hrs at room temperature and then hydrolyzed with water. The dried ($MgSO_4$) solution was evaporated and the crude product was steam-distilled on a rotary evaporator for separation of the menthol formed. The residue was dissolved in chloroform and dried ($MgSO_4$). Evaporation of the solvent and recrystallization from ethanol afforded a 63% yield of *threo*-**10**, mp. 105-106°.

Anal. Calcd. for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43. Found: C, 79.29; H, 7.40; N, 8.65

Erythro-**10** was obtained analogously from 0.2 mmol of the crude *erythro*-**9** in 49% yield, mp.127-129°. An analytically pure sample had mp. 130-132° (ethanol).

Anal. Calcd. for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43. Found: C, 79.62; H, 7.42; N, 8.63

***trans*-1-Benzyl-5-hydroxymethyl-3,4-diphenylimidazolidin-2-one (8a).**- *(a)* To a mixture of *threo*-**10** (0.5 mmol) in benzene (5 mL) and 10% potassium hydroxide (3 mL), a toluene solution of phosgene (3 mL) was added in portions at 0° and the emulsion was stirred at 0° for 4 hrs. The organic layer was separated, washed with water and dried ($MgSO_4$). Evaporation and recrystallization from benzene-hexane afforded *trans*-**8** in 55% yield, mp. 153-155°.

Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 77.12; H, 6.24; N, 7.65

(b) A suspension of **7** (0.1 mmol) and $NaBH_4$ (1.0 mmol) in methanol (2 mL) was stirred for 2 hrs at room temperature. Water was added, the methanol was evaporated *in vacuo* and the mixture was extracted with methylene chloride. The dried ($MgSO_4$) solution was evaporated to dryness and the crude reaction product was recrystallized from benzene-hexane to give *trans*-**8** in 72% yield, mp. 153-155°, identical with the described above.

***cis*-1-Benzyl-5-hydroxymethyl-3,4-diphenylimidazolidin-2-one (8b).**- Obtained analogously with *(a)* in the above protocol in 39% yield from 0.1 mmol of *erythro*-**10** and purified by PTLC over silica gel [eluent hexane-diethyl ether (1:1 v/v)] before recrystallization. Mp. 130-132° (benzene-hexane).

Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C,77.14; H, 6.20; N, 7.78

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