Synthesis of Chiral *N*- and *N,N'*-Substituted Diamines and Diamino Alcohols from Amino Acids

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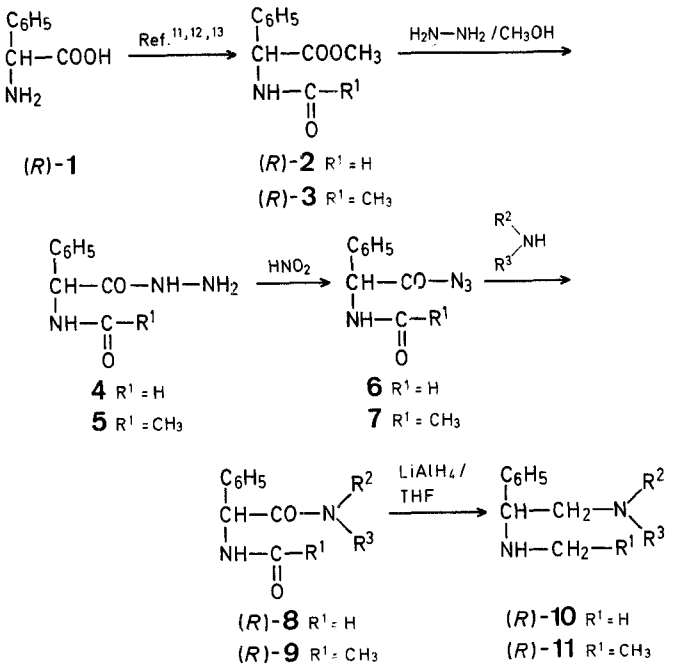
Chiral amino acids are generally used for configurational correlation[1], synthesis of optically active compounds[2], and, more recently for reagent preparation in order to induce asymmetric synthesis[3]. In this context we now describe some of the possibilities offered by peptide segment condensation carried out by the azide method[4]. Reduction of the amides thus obtained by lithium aluminium hydride yields a variety of chiral *N*- and *N,N'*-substituted diamines and diamino alcohols which are potentially useful for asymmetric synthesis. Furthermore, these new chiral compounds are versatile precursors in the synthesis of chiral bis-diaminophosphines which have been successfully used in asymmetric homogeneous catalysis[5,6,7].

The comparatively low tendency of racemization is the prime consideration for selecting the inexpensive azide procedure from the known methods for peptide bond formation[4]. As shown in this paper, this method is required for formyl or acetyl protecting groups to achieve a "racemization free" coupling step. On the contrary, the *N,N'*-carbonyldiimidazole[8] and dicyclohexylcarbodiimide[9] methods proceeding via 5(4*H*)-oxazolones are associated with considerable racemization, as shown in the experimental section. Furthermore, in the case of the dicyclohexylcarbodiimide method, it is very difficult to recover the diamides **8c** and **9b** from dicyclohexylurea during the workup. It is worth mentioning that the reaction of *N*-trifluoroacetylamino acids with *N,N'*-carbonyldiimidazole proceeds with racemization[10]. The azide method affords various possibilities for the amine condensation as outlined below. The reactions are carried out with (*R*)-phenylglycine **(1)**, which serves as a convenient source of numerous chiral substituted diamines and diamino alcohols.



Chiral starting materials are the *N*-formyl **(2)** and the *N*-acetyl **(3)** methyl esters of optically pure (*R*)-phenylglycine **(1)**. The *N*-acetyl compound **(3)** is obtained by acetylation of the methyl ester hydrochloride of **1** with either acetic anhydride or acetyl chloride in the presence of triethylamine (90% yield) in the same way as described for the free acid[11,12]. Formylation to **2** is achieved with the mixed formic acetic anhydride[13] (95% yield). Under these conditions less than 5% of acetylation occurs, as checked by ^{1}H-N.M.R. analysis.

The hydrazides **4** or **5** obtained from the reaction of hydrazine in methanol with the *N*-acylated (*R*)-phenylglycine methyl esters **2** or **3**, are readily transformed into the activated

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azides by generating nitrous acid in aqueous acetic acid solution[14]. The azides **6** or **7** are extracted with ether and immediately subjected to aminolysis. The dipeptides **8d** and **9c** (Table 1) are obtained in this way by reaction with (*R*)-phenylglycine methyl ester. Comparison of the ^{1}H-N.M.R. spectra of (*R*),(*R*)-**8d** and (*R*),(*R*)-**9c** with those of the corresponding racemic mixture revealed that no racemization had occurred during the coupling step[15].

So far, the azide compounds have not found any application in the formation of simple chiral diamides. As shown in Table 1, various diamides **8** or **9** have been obtained by reaction of **6** or **7** with amines. Reaction of ammonia, methylamine, *N,N*-dimethylamine, or ethylamine with the azide **6** or **7** afforded compounds **8a–c, 9a, b** in 65–75% yield from the hydrazides **4** or **5**. It is not possible to obtain direct evidence for the optical purity of the diamides **8** or **9**; however, the reduced compounds, **10a, 10b, 10c** and **11b** are optically pure as shown below.

The preparation of chiral diamides from amino acids by other methods is troubled by racemization. For instance, the synthesis of (*R*)-*N*-formylphenylglycine amide **(8a)** was reported by direct ammonia substitution on (*R*)-phenylglycine ethyl ester followed by formylation[16]. However, the intermediate α-aminophenylacetamide is easily subjected to base-catalyzed racemization[17]. This explains the lower rotatory power reported ($[\alpha]_D^{25}$: −19.25°, *c* 0.41, CH_3OH) compared with the one described herein ($[\alpha]_D^{25}$: −185°, *c* 0.58, CH_3OH).

Furthermore, we have observed that direct reaction of dimethylamine with (*R*)-*N*-formylphenylglycine methyl ester **(2)** in methanol solution provided readily the desired product **8c** (95% yield) but with about 90% racemization.

The diamines **10** and **11** are obtained from diamides **8** and **9** by reduction with lithium aluminium hydride in tetrahydrofuran (90% yield) (Table 2). Under the same conditions the dipeptides **8d** and **9c** lead to the corresponding diamino alcohols **10d** and **11c**. All compounds reported in the Tables 1 and 2 are new except diamide **8a** and diamine **10a**[16]. Lithium aluminium hydride reduction of chiral amino esters is known to occur without racemization[18]. It is also admitted that the reduction of chiral amides[19,6] gives similar results and some evidence of chirality conservation has been described[17]. In fact, N.M.R. analysis of the diamines **10a, 10b, 10c,** and **11b,** either by using a chiral shift reagent[20] or by preparing the Mosher amides[21] (see experimental section) demonstrates that these compounds are optically pure. These results prove, as expected, that no appreciable degree of racemization occurred during the preceding reduction and the azide aminolysis.

Diamides 8 or 9 by the Azide Method; General Procedure:
To a solution of (*R*)-*N*-formylphenylglycine hydrazide (**4**; $[\alpha]_D^{25}$: −161°, *c* 0.77, 0.1 normal hydrochloric acid) or (*R*)-*N*-acetylphenylglycine hydrazide (**5**; $[\alpha]_D^{20}$: −112°, *c* 1.00, water) (0.2 mol) in a mixture of acetic acid (200 ml) and aqueous 1 normal hydrochloric acid (800 ml) at around or just below 0 °C is slowly added sodium nitrite (0.22 mol) in water (75 ml). The solution is then kept at −5 °C for 2–4 h. The azide is extracted with cold diethyl ether (4 × 200 ml), the combined extracts are washed with water (200 ml) and an aqueous solution of sodium hydrogen carbonate (3% w/v, 200 ml). The azide solution is rapidly dried with magnesium sulfate at below 0 °C. The appropriate amine (0.25 mol) in diethyl ether (50 ml) is added to the azide

Table 1. (*R*)-Diamides **8** or **9** prepared

Product[a] No.	R^1	R^2	R^3	Yield [%][b]	m.p. [°C]	$[\alpha]_D^{25}$ (*c*, solvent)	Molecular formula[c]	^{1}H-N.M.R.[d] δ [ppm]
8a	H	H	H	60	164°	−185° (0.58, CH_3OH)[e]	$C_9H_{10}N_2O_2$ (178.2)	5.70 (d, 1H, *J*=7 Hz); 6.6 (br. s, 2H); 6.8 (br. d, 1H); 7.40 (s, 5H_{arom}); 8.25 (s, 1H)
8b	H	H	CH_3	75	222°	−126° (1.00, $CHCl_3$)	$C_{10}H_{12}N_2O_2$ (192.2)[f]	2.80 (s, 3H); 5.65 (d, 1H, *J*=7 Hz); 6.8 (br. s, 2H); 7.00 (s, 5H_{arom}); 8.20 (s, 1H)
8c	H	CH_3	CH_3	75	102°	−308° (1.30, $CHCl_3$)	$C_{11}H_{14}N_2O_2$ (206.2)	2.85, 2.95 (2s, 6H); 5.90 (d, 1H, *J*=7 Hz); 7.2–7.4 (br. s, 5H_{arom}); 7.6 (br. s, 1H); 8.12 (s, 1H)
8d	H	H	(*R*)-$H_3COOC—CH(C_6H_5)$—	72	228°	−210° (0.24, $CHCl_3$)[g]	$C_{18}H_{18}N_2O_4$ (326.3)	3.75 (s, 3H); 5.45 (d, 1H, *J*=7 Hz); 5.75 (d, 1H, *J*=8 Hz); 7.2, 7.4 (2 br. s, 2H); 7.6, 7.95 (2 br. s, 10H_{arom}); 8.10 (s, 1H)
9a	CH_3	H	C_2H_5	70	236°	−153° (1.00, C_2H_5OH)	$C_{12}H_{16}N_2O_2$ (220.3)[f]	1.18 (t, 3H, *J*=7 Hz); 2.30 (s, 3H); 3.40 (q, 2H); 5.75 (d, 1H, *J*=7 Hz); 6.6 (br. s, 1H); 7.40 (s, 5H_{arom}); 8.3 (br. s, 1H)
9b	CH_3	CH_3	CH_3	65	133°	−250° (1.00, C_2H_5OH)	$C_{12}H_{16}N_2O_2$ (220.3)	1.98 (s, 3H); 2.90, 3.00 (2s, 6H); 5.90 (d, 1H, *J*=8 Hz); 6.9 (br. s, 1H); 7.2–7.5 (br. s, 5H_{arom})
9c	CH_3	H	(*R*)-$H_3COOC—CH(C_6H_5)$—	75	273°	−209° (1.00, $CHCl_3$)[g]	$C_{19}H_{20}N_2O_4$ (340.4)	2.02 (s, 3H); 3.62 (s, 3H); 5.45 (d, 1H, *J*=7 Hz); 5.62 (d, 1H, *J*=8 Hz); 7.5, 7.95 (2 br. s, 2H); 7.1–7.3 (br. s, 10H_{arom})

[a] I.R. (KBr) for **8** and **9**: ν=3280 (NH); 1720 (C=O); 1660–1620 cm^{-1} (C=O).
[b] Yields based on hydrazides **4** or **5**, respectively.
[c] Satisfactory microanalyses obtained unless otherwise stated: C ±0.24, H ±0.05, N ±0.38.
[d] In $CDCl_3$ with 2–5% trifluoroacetic acid (v/v). Generally the NH chemical shifts occur between 7 at 8.5 ppm downfield *vs.* TMS. For the racemic compound **8d**, two methoxy signals at 3.68 and 3.75 ppm are observed.
[e] Ref.[16], $[\alpha]_D^{25}$: −19.2° (*c* 0.41, CH_3OH).
[f] Hygroscopic product could not be analyzed.
[g] Chloroform includes 5% trifluoroacetic (v/v) in order to dissolve the dipeptides.

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solution at 0 °C. The solution is then allowed to stand overnight at room temperature and the amide is either filtered off or extracted with ethyl acetate (3 × 50 ml) after addition of aqueous 1 normal hydrochloric acid (100 ml). The amide is crystallized from a mixture of ethyl acetate and petroleum ether; overall yield: 65–75% (based on the hydrazide).

For the synthesis of **8d** and **9c**, (*R*)-phenylglycine methyl ester is prepared from its hydrochloride by exchange reaction as follows: triethylamine (1.5 ml, 0.015 mol) is added to the hydrochloride (2 g) in chloroform (20 ml) and the mixture is shaken until the solid dissolves. The chloroform is removed by rotatory evaporation and the resulting amino ester is extracted with ether (2 × 50 ml). The solvent is evaporated in vacuo to afford the amino ester in quantitative yield.

Diamines and Diamino Alcohols 10 or 11; General Procedure:

The amide **8** or **9** (0.02 mol) is added to a stirred suspension of lithium aluminium hydride (0.75 equiv per function to be reduced) in tetrahydrofuran (100 ml) at 0 °C and then the reaction mixture is heated to reflux for 12 h. Aqueous 30% sodium hydroxide solution (5 ml) is added dropwise to the reaction mixture, which is previously cooled at 0 °C. The resulting white precipitate is removed by filtration. The filtrate is dried with anhydrous magnesium sulfate, and concentrated. The residue is subjected to bulb-to-bulb distillation (100–140 °C/0.1 torr) to afford pure diamines as colorless oils; yield: 85–90%.

The reduction of the dipeptides **8d** and **9c** is done in the same way. The oil **10d** thus obtained is shown to be pure by N.M.R. and **11c** is recrystallized from ethyl acetate/petroleum ether; m.p. 80 °C.

Diamides 8c, d or 9b, c by the *N,N'*-Carbonyldiimidazole Method[8]:

N,N'-Carbonyldiimidazole (4.45 g, 0.025 mol) is added to a solution of (*R*)-*N*-acetylphenylglycine (0.025 mol; $[\alpha]_D^{20}$: −211°, *c* 1.00, ethanol) or (*R*)-*N*-formylphenylglycine (0.025 mol; $[\alpha]_D^{20}$: −205°, *c* 0.98, $CHCl_3$ + 5% CF_3COOH) in tetrahydrofuran (30 ml) and when the evolution of carbon dioxide has stopped, stirring is continued for a further hour. Then *N,N*-dimethylamine or (*R*)-phenylglycine methyl ester (0.025 mol) is added. The solution is allowed to stand overnight at room temperature and the solvent is removed under vacuum. The oily residue is taken up with ether (100 ml) and the amide compounds which precipate are triturated and filtered off. The ether soluble compounds are obtained after washing the ether solution with sodium hydrogen carbonate solution, 0.5 normal hydrochloric acid, and water. The organic phase is dried with sodium sulfate and then evaporated to dryness under vacuum to give the amide compounds. The products are recrystallized from ethyl acetate/ethanol (1 : 1).

8c; yield: 3.9 g (75%); m.p. 130 °C
8d; yield: 6.1 g (76%); m.p. 193 °C
9c; yield: 6.0 g (70%); m.p. 270 °C
9b; yield: 4.6 g (85%); m.p. 150 °C

The compounds **8c** and **9b** are completely racemized under the above conditions. The compounds **8d** $[\alpha]_D^{25}$: −116.1°) and **9c** {$[\alpha]_D^{25}$: −132° (*c* 1.00, $CHCl_3$ + 5% CF_3COOH} are partly racemized with respect to the $[\alpha]_D$ values reported in the Table 1. Furthermore, the ^{1}H-N.M.R. spectra reval two equal signals for the methoxy groups of the **8d** and **9c** proving that racemization occurs by the *N,N'*-carbonyldiimidazole method.

Diamides 8d and 9c by the Dicyclohexylcarbodiimide Method[9]:

Dicyclohexylcarbodiimide (2.2 g, 0.011 mol) in chloroform (50 ml) is added at 0 °C to (*R*)-*N*-formylphenylglycine (1.8 g, 0.01 mol) in chloroform (50 ml). The reaction mixture is stirred for 1 h at 0.5 °C. (*R*)-Phenylglycine methyl ester (1.65 g, 0.01 mol) is added dropwise to the activated (*R*)-*N*-formylphenylglycine solution and the reaction mixture is stirred at 0 °C for 1 h, and then at room temperature overnight. The solvent is removed in vacuo and the dipeptide is extracted from dicyclohexylurea with ethanol/ethyl acetate (1 : 2, 50 ml). The amide compounds are recrystallized from ethyl acetate/ethanol

8d; yield: 1.5 g (45%); m.p. 195 °C; $[\alpha]_D^{25}$: −105° (*c* 0.90, $CHCl_3$ + 5% CF_3COOH)
9c; yield: 1.9 g (55%); m.p. 265 °C; $[\alpha]_D^{25}$: −120° (*c* 0.60, $CHCl_3$ + 5% CF_3COOH)

The compounds **8d** and **9c** are partly racemized (see Table 1).

Determination of Enantiomeric Purity of the Diamines 10a, 10b, 10c, and 11b:

N.M.R. Measurements: ^{1}H-N.M.R. spectra are obtained at 36 °C on a Perkin Elmer R 32 (at 90 MHz) using tetramethylsilane (TMS) as an

Table 2. Diamines and Diamino Alcohols **10** or **11** prepared

Product[a] No.	R^1	R^2	R^3	Configuration	Yield [%][b]	$[\alpha]_D^{25}$ (*c*, solvent)	Molecular formula[c]	^{1}H-N.M.R.[d] δ [ppm]
10a	H	H	H	*R*	80	−55° (0.32, $CHCl_3$)	$C_9H_{14}N_2$ (150.2)[e]	2.18 (s, 3H); 2.3 (br. s, 3H); 2.7 (ABX, 2H); 3.35 (dd, 1H, *J* = 6 Hz, 8 Hz); 7.7 (m, 5 H_{arom})
10b	H	H	CH_3	*R*	90	−50° (0.88, C_2H_5OH)	$C_{10}H_{16}N_2$ (164.2)	1.6 (br. s, 2H); 2.28, 2.40 (2s, 3H); 2.70 (d, 2H, *J* = 7 Hz); 3.60 (t, 1H); 7.3–7.4 (m, 5 H_{arom})
10c	H	CH_3	CH_3	*R*	90	−92° (0.82, C_2H_5OH)	$C_{11}H_{18}N_2$ (178.3)	2.00 (s, 6H); 2.10 (dd, 1H, *J* = 4 Hz, 12 Hz); 2.20 (s, 3H); 2.49 (dd, 1H, *J* = 11 Hz, 12 Hz); 3.53 (dd, 1H, *J* = 4 Hz, 11 Hz); 7.3 (m, 5 H_{arom}); 8.2 (br. s, 1H)
10d	H	H	$CH(C_6H_5)CH_2OH$	*R,R*	85	−109° (0.72, C_2H_5OH)	$C_{17}H_{22}N_2O$ (270.4)	2.20 (s, 3H); 2.66 (d, 2H, *J* = 7 Hz); 2.87 (br. s, 3H); 3.4–3.8 (m, 4H); 7.2, 7.25 (2 br. s, 10 H_{arom})
11a	CH_3	H	C_2H_5	*R*	85	−36° (1.00, C_2H_5OH)	$C_{12}H_{20}N_2$ (192.3)	1.03 (t, 6H, *J* = 7 Hz); 2.0 (2 br. s, 2H); 2.3–2.6 (m, 6H); 3.60 (dd, 1H, *J* = 5 Hz, 8 Hz); 7.3 (br. s, 5 H_{arom})
11b	CH_3	CH_3	CH_3	*R*	92	−71° (1.00, C_2H_5OH)	$C_{12}H_{20}N_2$ (192.3)	1.07 (t, 3H, *J* = 7 Hz); 2.0 (br. s, 1H); 2.24 (s, 6H); 2.45 (q, 2H); 2.0–2.5 (ABX, 2H); 3.65 (dd, 1H, *J* = 4 Hz, 11 Hz); 7.1–7.4 (m, 5 H_{arom})
11c[f]	CH_3	H	$CH(C_6H_5)CH_2OH$	*R,R*	90	−99° (1.00, C_2H_5OH)	$C_{18}H_{24}N_2O$ (284.4)	0.95 (t, 3H, *J* = 7 Hz); 2.15–2.5 (br. s, 3H); 2.48 (q, 2H); 2.68 (d, 2H, *J* = 6.2 Hz); 3.5–3.8 (m, 4H); 7.25 (2 br. s, 10 H_{arom})

[a] I.R. (film) of **10a–c, 11a, b**: ν = 3300 (NH), 1140 cm^{-1} (N—C).
I.R. (film or KBr) of **10d, 11c**: ν = 3400–3000 (NH, OH); 1140, 1050 cm^{-1} (N—C, O—C).
[b] Yields based on diamides **8** or **9**, respectively.
[c] Satisfactory microanalyses obtained: C ±0.35, H ±0.22, N ±0.40; except for **10d** which is an oil.
[d] In CCl_4, except for **10c** in $CDCl_3$ + 5% trifluoroacetic acid.
[e] Ref.[16]: levorotatory in ethanol.
[f] m.p. 80 °C.

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internal standard. When protons are resolved, relative peak height measurements give identical results as obtained by integration. The precision of all determinations is better than ± 1%.

Enantiomeric purity of **10b** is determined by using $Pr(tfc)_3$, tris[3-(trifluoromethylhydromethylene)-*d*-camphorato]praseodymium(III), as shift reagent. Solutions are made up by adding $Pr(tfc)_3$ (0.025 g) in benzene (300 µl) to the diamine (80 µl) in benzene (300 µl). Two equal *N*-methyl resonances are only observed for the enantiomer of diamine (*R*)-**10b** in the presence of $Pr(tfc)_3$ ($\delta = 1.97$ and 2.04 ppm) and four equal signals for the racemic compound ($\delta = 1.89$, 1.97, 1.99, and 2.04 ppm). It is also shown by this way that **10a** is optically pure.

Enantiomeric purity of **10c** is determined by using Mosher's reagent. The amine **10c** (0.025 g, $1.40 \cdot 10^{-4}$ mol) is added to α-methoxy-α-trifluoromethylphenylacetyl chloride ($[\alpha]_D^{24}$: +129°, *c* 4.5, CCl_4; 0.037 g, $1.46 \cdot 10^{-4}$ mol) dissolved in carbon tetrachloride (17 ml). The mixture is refluxed for 90 min. Dichloromethane (17 ml) is added to the cold mixture and the latter is washed with 1 normal sodium hydroxide solution (10 ml) and water (10 ml). The organic solution is dried with anhydrous magnesium sulfate. The solvent is removed and the residue is dissolved in deuteriochloroform for N.M.R. analysis. The diastereomeric amides from **10c** show sufficient N.M.R. chemical shift differences for the proton bonded to the asymmetric carbon of the diamine moiety to allow facile determination of the diastereomeric products. Two equal triplet resonances are observed for the racemic compound ($\delta = 5.3$ and 5.6 ppm) while only one signal ($\delta = 5.6$ ppm) is obtained for the amide of (*R*)-**10c**. The same experiment reveals that **11b** is optically pure. Both mentioned methods fail to provide an evidence of optical purity for compounds **11a**, **10d**, and **11c**.

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