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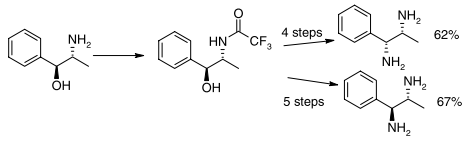
Graphical Abstract



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Synthesis of 1,2-Diamino-1-phenylpropane Diastereoisomers from *u-N*-Trifluoroacetyl-2-amino-1-phenylpropan-1-ol

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Summary. A new simple procedure for the synthesis of diastereomeric 1,2-diamino-1-phenylpropanes starting from *u-N*-trifluoroacetyl-2-amino-1-phenylpropan-1-ol (*N*-trifluoroacetylnorephedrine) is described. The trifluoroacetyl protecting group was particularly suitable for the protection of the amino group in order to reduce side reactions.

Keywords. Amino alcohols; Configuration; Diastereoselectivity; Diamines; Protecting groups.

Introduction

1,2-Diamines are of growing interest in organic synthesis, analytical chemistry, and also in medicinal chemistry [1]. Stereoisomers of 1,2-diamino-1-phenylpropane and their derivatives have been used as complexing agents for the synthesis of new platinum antitumor compounds like **1** (Fig. 1) [2, 3]. These molecules exist as two diastereoisomers that can be obtained by several methods. However, the best procedures are those starting from one precursor and leading with high selectivity to both diastereoisomers, *like* and *unlike*. Such methods have been quite rarely described and some of them present clear disadvantages such as the lack of diastereo- or regioselectivity, the use of elevated temperatures, or in application to structures different than **1** [2–10].

New ways for obtaining these diamines have been investigated, mainly, from β-aminoalcohols [4]. These educts can be quite easily obtained and the –OH group only has to be replaced by $-NH_2$ to give the diamines. The choice of a protecting group for the amine function is the critical step as the reaction on the benzylic carbon after activation of the alcohol can give rise to compounds with undesired

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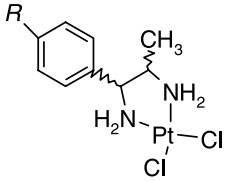

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R = H or F

Fig. 1. 1,2-Diamino-1-phenylalkanes complexed with platinum

configuration or structure. *Tert*-butoxycarbonyl (*BOC*) [11], acetyl [12], or benzoyl protecting groups are definitively not adequate for this purpose [13].

In the present paper trifluoroacetyl was considered as a possible protecting group for the amine function. The presence of three fluorine atoms on the amide group, which decreases the electronic density on the oxygen, was expected to prevent formation of *cis*- or *trans*-4,5-dihydro-4-methyl-5-phenyl-2-trifluoromethyl-oxazoles (oxazolines). Trifluoroacetyl can finally be easily removed under smooth conditions.

Results and Discussions

Starting from *u*-2-amino-1-phenylpropan-1-ol (norephedrine, *u*-**2**), *u*-*N*-trifluoro-acetyl-2-amino-1-phenylpropan-1-ol (*u*-**3**) could be obtained with an excellent yield according to a modified standard procedure (Fig. 2) [14]. From that compound, two methods were considered.

The first one, leading to *l*-*N*-trifluoroacetyl-2-amino-1-azido-1-phenylpropane (*l*-**6**), relied on a simple inversion of configuration on *u*-*N*-trifluoroacetyl-2-amino-1-phenylpropan-1-ol mesylate (*u*-**4**) with NaN_3. According to this procedure, the formation of variable amounts of *trans*-4,5-dihydro-4-methyl-5-phenyl-2-trifluoro-methyloxazole (*trans*-**7**) was expected. Three common aprotic polar solvents were investigated (see Table 1). As far as yield (∼65%) and diastereoselectivity (86 and 90%) were concerned, *DMSO* and *DMF* were quite equivalent with a moderate advantage for *DMF*. With *HMPA*, diastereoselectivity (48%) and yield (46%) were particularly poor.

Compound *u*-**6** could be obtained by a double inversion of configuration at the benzylic position of *u*-**3**. The first step was a *Mukaiyama* reaction with dibromo-triphenylphosphorane leading to *l*-*N*-trifluoroacetyl-2-amino-1-bromo-1-phenyl-propane (*l*-**5**), which reacted with NaN_3 to give *u*-**6** and *cis*-**7** as by-product [15]. Results obtained during the synthesis of *l*-**5** are listed in Table 2. When the reaction was carried on in acetonitrile and pyridine, a significant part of the starting compound was transformed into *trans*-**7** (entry 1). It is hypothesized that this cyclization was due to the basicity of the solvent (pyridine) and to the excess of imidazole. The replacement of the mixture pyridine/acetonitrile by toluene, and the use of stoechiometric amounts of imidazole avoided the formation of oxazoline. However, in spite of these modifications, *l*- and *u*-**5** were obtained with a 1:1 ratio (entry 2). Surprinsingly, no trace of *cis*-**7** was observed by analysis of the ^{1}H NMR

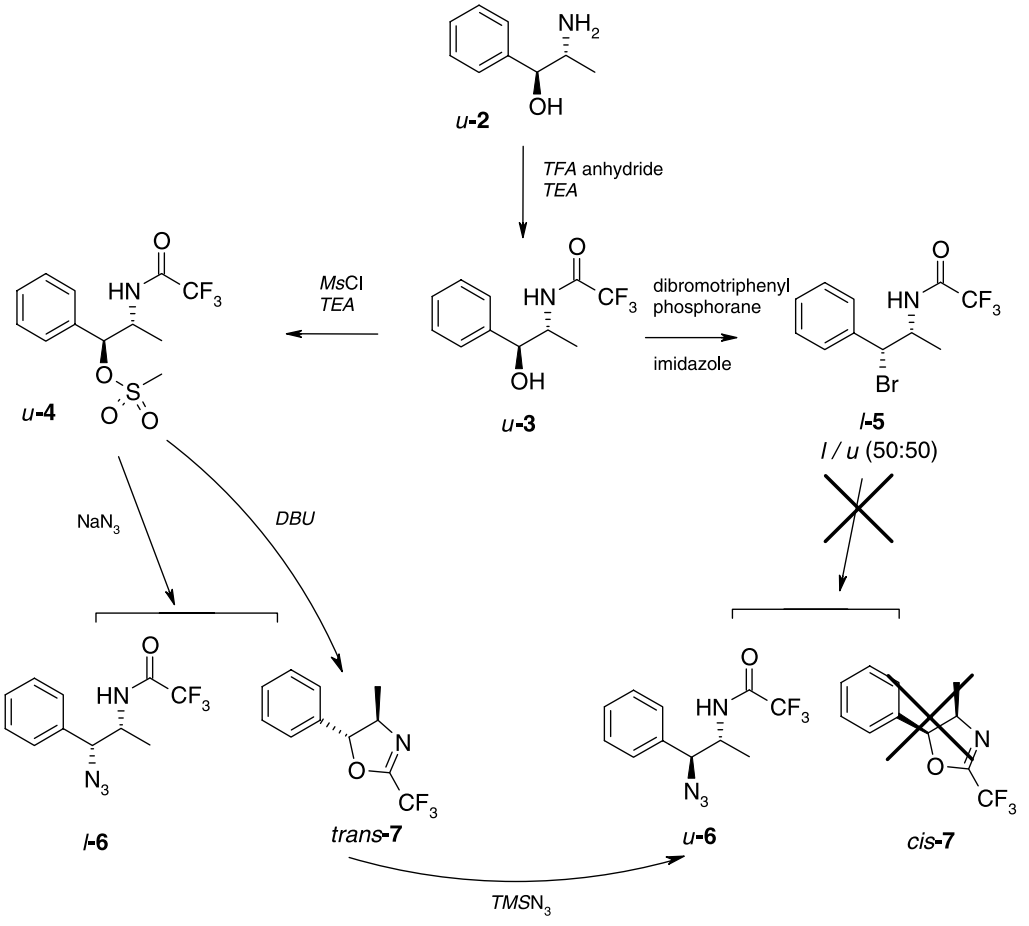

Fig. 2. Synthesis of the two diastereoisomers of *N*-trifluoroacetyl-2-amino-1-azido-1-phenylpropane (*l*- and *u*-**6**) from racemic *u*-2-amino-1-phenylpropan-1-ol (*u*-**2**)

Table 1. Synthesis of *l*-*N*-trifluoroacetyl-2-amino-1-azido-1-phenylpropane (*l*-**6**) from *u*-**4**: conditions and proportions of products obtained

Entry	Solvent[a]	*l*-**6**[b]	*u*-**6**[b]	*trans*-**7**[b]	Yield/%[c]
1	*DMF*	80 (95)	4 (5)	16	66
2	*DMSO*	76 (93)	6 (7)	18	64
3	*HMPA*	64 (74)	22 (26)	14	46

[a] All reactions carried out during 4 h at room temperature with 3 equivalents of NaN_3; [b] determined by ^1H NMR on the crude reaction mixture; [c] for isolated compounds

spectrum of the crude reaction products (entries 1 and 2) [16]. The method of *Hudson*, which uses thionyl chloride in *HMPT*, also gave bad results with a complex mixture of largely unidentified compounds [17]. Due to all these unfavourable features, this synthetic scheme had to be discontinued.

Table 2. Synthesis of *u*-*N*-trifluoroacetyl-2-amino-1-azido-1-phenylpropane (*u*-**6**): conditions and proportions of products obtained

Entry	Conditions	*l*-**5**[a]	*u*-**5**[a]	*trans*-**7**[a]	Yield/%[b]
	Starting from *u*-**3**				
1	Ph_3BBr_2 (2 eq.); imidazole (4 eq.); pyridine-acetonitrile; 80°C	19 (59)	13 (41)	68	17[c]
2	Ph_3BBr_2 (2 eq.); imidazole (1 eq.); toluene; 110°C	50 (50)	50 (50)	0	40[c]
	Starting from *trans*-**7**	*l*-**6**[a]	*u*-**6**[a]		Yield/%[b]
3	NaN_3 (8 eq.); *TMS*Cl (8 eq.); *DMF*; 110°C; 6 h	90 (90)	10 (10)		70

[a] Determined by ^{1}H NMR on the crude reaction mixture; [b] for isolated compounds; [c] compounds *l*- and *u*-**5** were not separable

The second procedure investigated for the synthesis of *u*-**6** consisted in the opening of *trans*-**7** with *TMS*N_3 produced *in situ* with *TMSCl* and NaN_3 in *DMF* instead of acetonitrile [18]. Indeed, the latter was not the ideal solvent for this synthesis. As a consequence of the poor solubility of the reagents, a long reaction time was needed which caused degradation or epimerization of the compounds. This procedure has a yield of 70% for *u*-**6** (entry 3).

In order to obtain the final products, both azido compounds *l*- and *u*-**6** were first reduced by catalytic hydrogenation into *l*- and *u*-N^2-trifluoroacetyl-1,2-diamino-1-phenylpropane (*l*- and *u*-**8**), and finally deprotected by hydrolysis (Fig. 3). It is interesting to note that compounds **8** were not deprotected under typically smooth conditions, *i.e.* 12 *M* HCl/*Me*OH/water (2:90:10) at 60°C [19]. Using the same

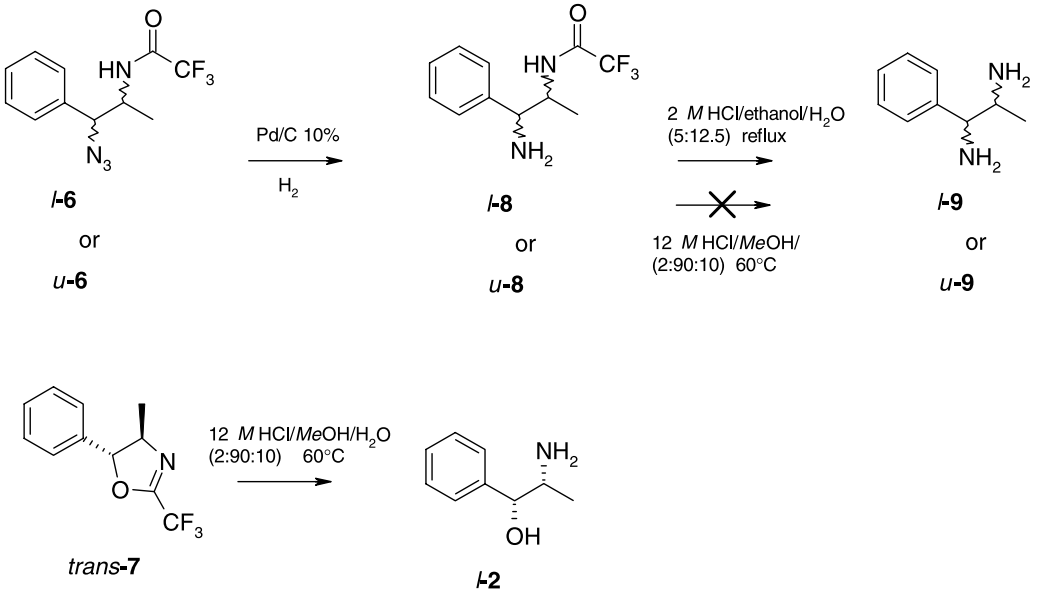

Fig. 3. Synthesis of the final compounds, *l*- and *u*-1,2-diamino-1-phenylpropane (*l*- and *u*-**9**)

reagents, oxazoline *trans*-**7** was easily hydrolyzed into the aminoalcohol *l*-**2**. Attempts to purify the mixture of azides and oxazolines by column chromatography on silicagel resulted also in hydrolysis of *trans*-**7**. These observations showed the fragility of the oxazolines in comparison to the trifluoroacetamides **8** and provided a good procedure to purify the mixture **7**/**8**.

One of the major problems encountered in the present study was the minimization of epimerization at benzylic position in the presence of basic molecules (*TEA*, imidazole, pyridine, N_3^-). The presence of good leaving groups ($CH_3SO_3^-$ and Br^-) in **4** and **5** can lead to SN_1 reactions. This was the case with *l*-**5** with a complete loss of diastereoselectivity, even with a limited amount of base. This phenomenon was probably stimulated by the high temperature.

These present observations herefore confirmed that trifluoroacetyl can be a useful protecting group for the amine in the synthesis of *l*- and *u*-diamines. It allowed to isolate **4** with a high degree of purity, which is rather difficult with such a structure [9, 20]. This intermediate could be conserved during weeks at $-20°C$. Despite the fact that *u*-**4** is rather unstable and therefore difficult to use, it can be the starting point of the synthesis of each diastereoisomer of 1,2-diamino-1-phenylpropane, with diastereoisomeric excess $\geq 80\%$ and yields between 60 and 70% from norephedrine.

Experimental

^1H and ^{13}C NMR spectra were taken on a Bruker Avance 300 MHz spectrometer with *TMS* as internal standard, at 293 K. IR analysis was performed with a Shimadzu IR-470 spectrophotometer. Melting points were measured with a Mettler FP1 apparatus. All flash and column chromatography purifications were done using silicagel Kieselgel® 100 (Merck). Thin layer chromatographies were performed on Kieselgel® 60 F_{254} plates (Merck). Mass spectra were recorded on a Thermo-Fisons VG Auto Spec (70 eV). Racemic norephedrine (*u*-**2**) from Aldrich was used as starting material. All the solvents and NaN_3 were dried before use.

u-N-Trifluoroacetyl-2-amino-1-phenylpropan-1-ol (*u*-**3**)

To a solution of 3.9 g of *u*-**2** (25.8 mmol) in 100 cm^3 of CH_2Cl_2, cooled with an ice bath, were added respectively 3.6 cm^3 of *TEA* (25.8 mmol) and 3.65 cm^3 of trifluoroacetic anhydride (25.8 mmol). The solution was stirred at room temperature during 15 h. Then, it was washed with 50 cm^3 of 2 *M* HCl, brine, dried over $MgSO_4$ and evaporated to give 6.38 g (quantitative) of *u*-**3** as a white solid. Mp 126.6°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.36$ (m, $5H_{aromatic}$), 6.72 (br, NH), 4.94 (d, $J = 3.2$ Hz, H-1), 4.30 (m, H-2), 2.33 (br, OH), 1.06 (d, $J = 6.9$ Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.2$ (q, $J = 36$ Hz, C=O), 140.6 ($C\text{-}1_{ar}$), 129.3 ($C\text{-}3_{ar}$, $C\text{-}5_{ar}$), 128.8 ($C\text{-}4_{ar}$), 126.5 ($C\text{-}2_{ar}$, $C\text{-}6_{ar}$), 116.3 (q, $J = 289$ Hz, CF_3), 75.7 (C-1), 51.9 (C-2), 13.8 (C-3) ppm; IR was identical to published one [21]; MS analysis gave data similar to those of Ref. [22].

u-N-Trifluoroacetyl-2-amino-1-phenylpropan-1-ol mesylate (*u*-**4**, $C_{12}H_{14}F_3NO_4S$)

A solution of 2.98 g of *u*-**3** (12.1 mmol) in 50 cm^3 of CH_2Cl_2 was cooled with an ice bath. To this, 1.7 cm^3 of *TEA* (12.1 mmol) and 1.0 cm^3 of methanesulfonyl chloride (13.3 mmol) were added. The solution was stirred at room temperature for 3 h. It was washed with brine, dried over $MgSO_4$, and evaporated to give 3.92 g (quantitative) of *u*-**4** as a yellowish oil. The product was not purified

and conserved at −20°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$ (m, $5H_{aromatic}$), 6.82 (br, NH), 5.78 (d, $J = 3.3$ Hz, H-1), 4.39 (m, H-2), 2.91 (s, CH_3), 1.22 (d, $J = 6.9$ Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.2$ (q, $J = 34$ Hz, C=O), 135.3 (C-1_{ar}), 129.9 (C-3_{ar}, C-5_{ar}), 129.6 (C-4_{ar}), 126.6 (C-2_{ar}, C-6_{ar}), 116.3 (q, $J = 288$ Hz, CF_3), 83.9 (CH_3S), 51.1 (C-1), 39.2 (C-2), 13.8 (C-3) ppm; IR (film): $\bar{\nu} = 3320$, 3060, 2925, 1789, 1725, 1700, 1549, 1453, 1365, 1212, 1143, 948, 848, 747, 700 cm^{-1}.

l- and u-N-Trifluoroacetyl-2-amino-1-bromo-1-phenylpropane (*l*- and *u*-**5**, $C_{11}H_{11}BrF_3NO$)

To a solution of 1 g of *u*-**3** (4 mmol) in 25 cm^3 of solvent 3.42 g of dibromotriphenylphosphorane (8 mmol) and imidazole were added (see Table 2 for exact conditions). The solvent was heated during 4 h. After cooling, toluene was added. The organic layer was washed with brine and evaporated. The residue was purified by flash chromatography (silicagel, CH_2Cl_2) to give **5** as a white solid. Analysis of the crude product: mixture *l*/*u* 50:50. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$ ($5H_{aromatic}$), 6.67* (br, NH), 6.58** (br, NH), 5.23 (d, $J = 4.6$ Hz, H-1),[a] 5.04 (d, $J = 6.2$ Hz, H-1),[b] 4.49* (m, H-2), 4.37** (m, H-2), 1.30* (d, CH_3), 1.28** (d, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.7$ (q, $J = 37$ Hz, C=O), 138.2* (C-1_{ar}), 137.5** (C-1_{ar}), 129.4, 129.2, 129.1, 129, 128.5, 128.2, 116 (q, $J = 288$ Hz, CF_3), 59.3* (C-1), 58** (C-1), 52* (C-2), 51.9** (C-2), 19.1* (C-3), 16.4** (C-3) ppm; IR (KBr): $\bar{\nu} = 3315$, 1718, 1696, 1558, 1448, 1248, 1217, 1160, 721, 694, 669 cm^{-1}; MS (70 eV): $m/z = 312$ (M+), 310 (M+), 230, 196, 169, 140, 117, 91, 69.

l-N-Trifluoroacetyl-2-amino-1-azido-1-phenylpropane (*l*-**6**, $C_{11}H_{11}F_3N_4O$)

To a solution of 120 mg of *u*-**4** (0.37 mmol) in 10 cm^3 of the appopriate solvent, 72 mg of NaN_3 (1.1 mmol) were added and the solution was stirred at room temperature during 4 h (see Table 1 for exact conditions). Then H_2O and toluene were added. After decantation, the organic layer was washed with H_2O, brine, dried over $MgSO_4$, and the solvent was evaporated. The crude residue was directly analyzed by ^{1}H NMR. The reaction products described in entries 1 to 3 (Table 1) were purified by column chromatography (silicagel, CH_2Cl_2). Diastereomer *l*-**6** could also be recrystallized from *Et*OH/H_2O 9/1. Mp 83.5°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$ (m, $5H_{aromatic}$), 6.52 (br, NH), 4.66 (d, $J = 5.5$ Hz, H-1), 4.25 (m, H-2), 1.23 (d, $J = 6.8$ Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.3$ (q, $J = 37$ Hz, C=O), 136.5 (C-1_{ar}), 129.7 (C-3_{ar}, C-5_{ar}), 129.6 (C-4_{ar}), 127.7 (C-2_{ar}, C-6_{ar}), 116.4 (q, $J = 288$ Hz, CF_3), 69.3 (C-1), 50.9 (C-2), 18.2 (C-3) ppm; IR (KBr): $\bar{\nu} = 3280$, 3070, 2100, 1724, 1698, 1556, 1447, 1721, 1205, 1180, 1147, 755, 725, 697 cm^{-1}; MS (70 eV): $m/z = 272$ (M+), 245, 230, 160, 152, 141, 132, 125, 117, 104, 91.

u-N-Trifluoroacetyl-2-amino-1-azido-1-phenylpropane (*u*-**6**, $C_{11}H_{11}F_3N_4O$)

*TMS*Cl, 1.24 cm^3 (9.8 mmol), and 0.64 g of NaN_3 (9.8 mmol) were poured into 5 cm^3 of *DMF*. This suspension was stirred for 1 h at room temperature. Then, a solution of 0.28 g of *trans*-**7** (1.22 mmol) in 5 cm^3 of *DMF* was added. The mixture was heated at 110°C during 6 h. After cooling, H_2O and toluene were added. The solvents were decanted and the organic layer was washed with H_2O, brine, dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (silicagel, CH_2Cl_2) to give 0.23 g (70%) of *u*-**6** as a yellowish solid. Mp 86°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$ (m, $5H_{aromatic}$), 6.93 (br, NH), 4.86 (d, $J = 4.6$ Hz, H-1), 4.26 (m, H-2), 1.13 (d, $J = 6.8$ Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.3$ (q, $J = 37$ Hz, C=O), 136.4 (C-1_{ar}), 129.6 (C-3_{ar}, C-5_{ar}), 128.9 (C-4_{ar}), 127.6 (C-2_{ar}, C-6_{ar}), 116.5 (q, $J = 288$ Hz, CF_3), 69 (C-1), 50.9 (C-2), 14.9 (C-3) ppm; IR and MS spectra were identical to those obtained for *l*-**6**.

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* isomer 1; ** isomer 2; [a] according to coupling constant: *u*-**5**; [b] according to coupling constant: *l*-**5**

trans-4,5-Dihydro-4-methyl-5-phenyl-2-trifluoromethyloxazole (*trans*-**7**, $C_{11}H_{10}F_3NO$)

To a solution of 200 mg of *u*-**4** (0.62 mmol) in 10 cm^3 of toluene, 0.1 cm^3 of *DBU* (0.67 mmol) were added. After 4 h of stirring at room temperature, the solution was washed with 10 cm^3 of 2 *M* HCl and brine, dried with $MgSO_4$, filtered, and evaporated to afford 0.14 g (quantitative) of a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$ (m, $5H_{aromatic}$), 5.22 (d, $J = 8.2$ Hz, H-1), 4.25 (m, H-2), 1.48 (d, $J = 6.8$ Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.5$ (q, $J = 37$ Hz, C-2), 138.8 (C-1_{ar}), 129.8 (C-3_{ar}, C-5_{ar}), 129.4 (C-4_{ar}), 126.2 (C-2_{ar}, C-6_{ar}), 117 (q, $J = 274$ Hz, CF_3), 91.1 (C-1), 71.3 (C-2), 21.3 (C-3) ppm; IR (film): $\bar{\nu} = 3060$, 2915, 1711, 1540, 1449, 1401, 1209, 1153, 1127, 942, 757, 698 cm^{-1}; MS (70 eV): $m/z = 229$ (M+), 222, 141, 117, 107, 86, 79, 69, 57.

l- and u-N^2*-Trifluoroacetyl-1,2-diamino-1-phenylpropane* (*l*- and *u*-**8**)

These compounds were not isolated and directly used in the last step.

l- and u-1,2-Diamino-1-phenylpropane (*l*- and *u*-**9**)

Pd on charcoal 10% (20 mg) was added to a solution of 200 mg of **6** (0.74 mmol) in 20 cm^3 of *Me*OH. The suspension was stirred under H_2 (60 psi) for 10 h. After filtration on celite, the solvent was evaporated. The residue was dissolved in 5 cm^3 of *Et*OH and 12.5 cm^3 of 2 *M* HCl were added. The solution was heated to reflux during 1 h. Ethanol was evaporated and the solution was neutralized with Na_2CO_3. NaOH (30% *m*/*v*) was added ($pH \sim 13$). After extraction with CH_2Cl_2, the organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford 105 mg (95%) of a yellowish oil. Analysis of *l*- and *u*-**9** by ^{1}H and ^{13}C NMR were identical to those already published [2]. IR (film): $\bar{\nu} = 3345$, 2860, 1585, 1443, 902, 755, 702 cm^{-1}; MS (70 eV): $m/z = 150$ (M+), 134, 118, 107, 91, 77, 63.

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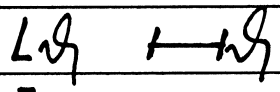
Delete character or ~~delete~~ word	
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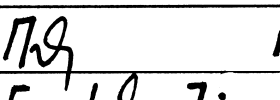
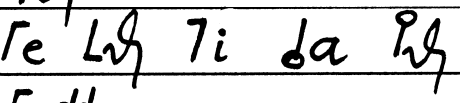
Group of characters to be ~~corrected~~	
Different errors on the same lines	
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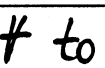
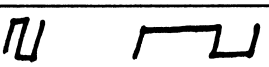
Word to be added	
Transpose characters words or	
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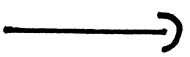
Reduce space between lines ~~Reduce space between lines~~	
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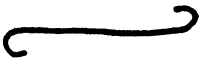
Text to run on (no new paragraph)	
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