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ENANTIOSPECIFIC AND DIASTEREOSELECTIVE SYNTHESIS OF *ANTI* α-HYDRAZINO- AND α-AMINO-β-HYDROXYACIDS THROUGH "ELECTROPHILIC AMINATION" OF β-HYDROXYESTERS

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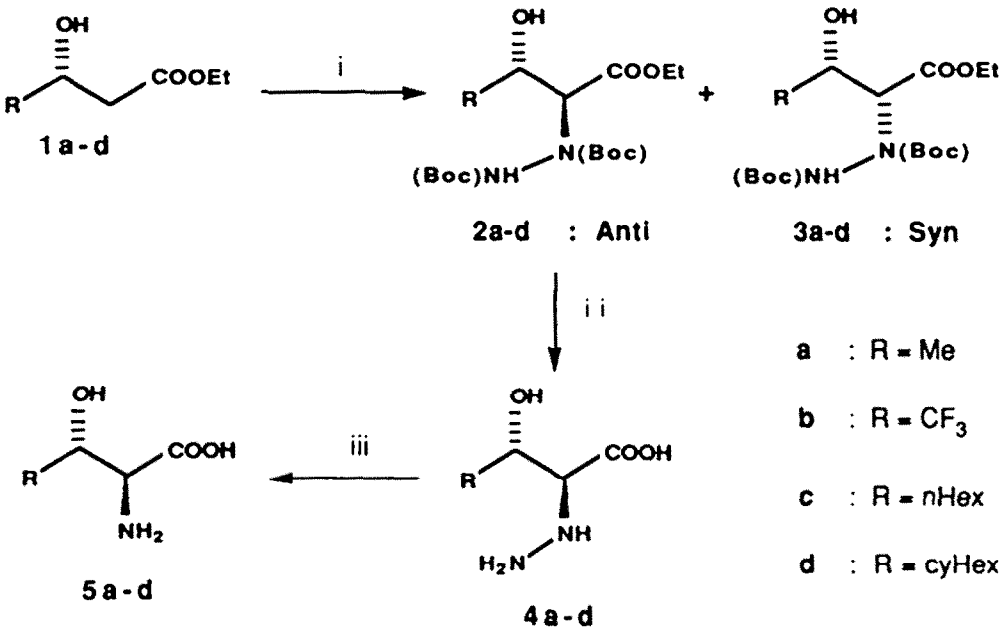
Summary: β-Hydroxyesters **1a-d** were transformed into corresponding dianions and condensed with di-*t*-butylazodicarboxylate to give *anti* protected α-hydrazino-β-hydroxyesters **2a-d** with good diastereoselectivities (up to 94:6). Cleavage of protecting groups followed by ester hydrolysis gave the previously unknown *anti* α-hydrazino-β-hydroxyacids **4a-d**, which were in turn converted by hydrogenolysis into *anti* α-amino-β-hydroxyacids **5a-d**. Starting from (*S*) **1a**, enantiomerically pure (2*S*,3*S*) *allo*-threonine **5a** was obtained in good overall yields. On the contrary, reaction of silyl ketene acetal **10**, derived from **1a**, with a diazonium salt furnished predominantly the *syn* isomer, but in unsatisfactory yield.

α-Amino-β-hydroxyacids are an important class of aminoacids both for their essential physiological role and their activity as enzymatic inhibitors.[1] Moreover these substances, having three different functional groups, can be elaborated in several ways and therefore they may be regarded also as useful precursors for other biological active molecules. Their use in the synthesis of sugars[2] and of β-lactam antibiotics[3] has been recently reported.

In the past, several methods for the stereoselective synthesis of these derivatives have been developed.[4-7] However, although recently some excellent asymmetric syntheses of *syn* (*threo*) α-amino-β-hydroxyacids in high optical purity have been reported,[5c-e,5g,5h] the preparation of *anti* (*allo*) diastereoisomers still remains a challenge. Actually this goal was previously achieved only in few cases,[5f,6a,6b,6f,5i] by methods requiring multi-step sequences and in some cases suffering from lack of generality[6a,6f] or low stereoselectivity.[6b,5i]

In continuation of a project directed towards the development of new methodologies for α-amino-β-hydroxyacid synthesis,[8] we envisaged that a possible straightforward entry to these compounds could be the C-α-amination of β-hydroxyesters with electrophilic aminating agents (that is $[NH_2]^+$ synthetic equivalents). β-Hydroxyesters are actually easily available building blocks which can be prepared in both enantiomerically pure forms through microbiological[9] or catalytic[10] reduction of β-ketoesters, as well as *via* depolymerization of a biopolymer,[11] microbiological hydration of unsaturated acids,[12] or asymmetric synthesis.[13] Moreover previous reports have shown that β-hydroxyesters dianions usually react with electrophiles to give *anti* adducts with good to excellent diastereoselectivities.[14]

SCHEME 1



I) 1) LDA; 2) TBAD; II) 1) CF_3COOH/CH_2Cl_2 1:1; 2) 0.5 N LiOH; III) 1) 1N HCl; 2) H_2, PtO_2, 1 bar

With regards to the amination reaction, some reagents for the introduction of $[NH_2]^+$ into a carbon skeleton are available,[15] but they generally suffer from some drawbacks. Recently a new type of synthetic equivalent of $[NH_2]^+$, di-*t*-butylazodicarboxylate (TBAD) was proposed.[16] This reagent appears to be particularly attractive, since it is stable, commercially available, and its reactions with ester enolates and silyl ketene acetals are described to occur smoothly and with good yields. Moreover by using this reagent also the hitherto unknown α-hydrazino-β-hydroxyacids should be accessible. The importance of L and D α-hydrazinoacids has been recognized since long time ago, especially in view of their strong biological activities as inhibitors of aminoacid decarboxylases.[17]

We report here the results of amination of some β-hydroxyesters with two $[NH_2]^+$ synthetic equivalents: TBAD and benzenediazonium tetrafluoroborate.

Treatment of the *O,O'-bis*-trimethylsilyl ketene acetal derived from (*S*) 3-hydroxybutyrate **1a**[18] with TBAD under the conditions described by Gennari[16a]($TiCl_4$, CH_2Cl_2, -78°C) led to a complex reaction mixture. On the contrary, when **1a** was converted by lithium diisopropylamide (LDA) in tetrahydrofuran (THF) into the corresponding dianion[14a] and then allowed to react with TBAD at low temperature, **2a** and **3a** were obtained in good overall yields (Table 1 and Scheme 1).

The *anti* isomer **2a** was the major product. The preference for the *anti* isomer can be explained either if its formation is kinetically or thermodynamically controlled. In the first case, on the reasonable assumption that in the most stable conformation of dianion a lithium atom is chelated by carboxyl and alkoxyl oxygens,[14a] attack of the electrophile should take place from the less encumbered face of the enolate, leading preferentially to transition state **6** (Scheme 2). In the second case the isomer ratio will reflect the relative stability of adducts **8** and **9**. Since **8** is expected to have a lower steric energy, the *anti* isomer should be favoured also under equilibrating conditions. In order to clarify this point, we performed this reaction under various conditions.

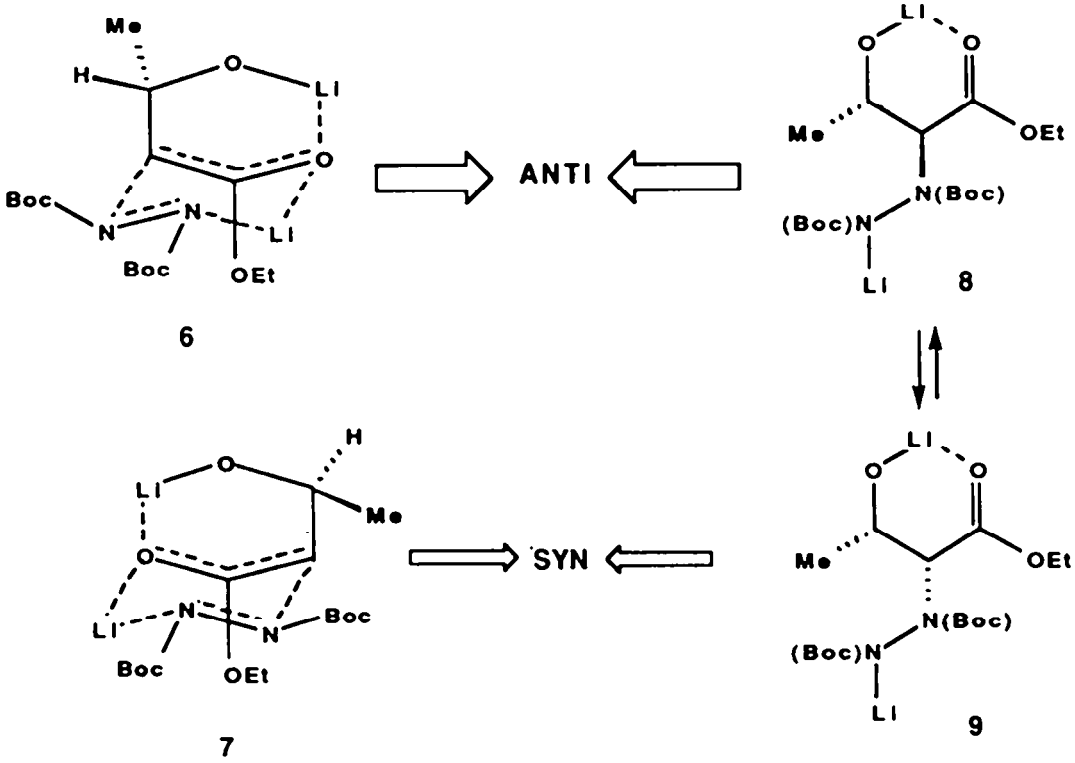
TABLE 1: Reaction of β-hydroxybutyrate 1a with TBAD under various conditions.

Entry	Temperature	Time	Eq LDA	Eq. TBAD	Overall yield[a]	Anti : syn[b]	$[\alpha]_D$[c]
1	-78°C	3 min	2.5	1.5	77%	75 : 25	+ 4.80°
2	-78°C	3 min	4.2	2.5	77%	77 : 23	+ 4.75°
3	-50°C	10 min	4.2	2.5	75%	84 : 16	+ 4.80°
4	-25°C	60 min	4.2	2.5	56%	94 : 6	+ 4.70°

a) Calculated from isolated yield of **2a**, taking into account the *anti* : *syn* ratio; b) Determined by CGC; c) c 2, $CHCl_3$, measured on chromatographed **2a**.

The results listed in Table 1 show that an increase of temperature, reaction times, and excess of LDA, favours to a higher extent the *anti* adduct, thus suggesting that the reaction control changes from kinetic to thermodynamic and that the two species **8** and **9** have a greater energy difference than **6** and **7**.

SCHEME 2



This thermodynamic control can derive from equilibration at C-2, through deprotonation-protonation, or from a *retro*-aldol reaction. In the latter case, however, we should have observed partial racemization, while, on the contrary, the optical purity of **2a** obtained under different conditions, is always the same (Table 1). An alternative hypothesis, explaining the increase of stereoselectivity with a selective destruction by excess LDA of the minor diastereoisomer can be ruled out since the overall yield is nearly constant passing from entry 1 to entry 3 in Table 1. Since a decrease in yield is observed at higher temperatures and longer reaction times, the best conditions turned out to be those of entry 3, which are a compromise between better induction and better overall yield, and which allowed the highest isolated yield of major diastereoisomer **2a** (63%).

The two isomers could be very easily separated by chromatography, thanks to the high ΔR_f value. Hydrolysis of major product **2a** with CF_3COOH/CH_2Cl_2 followed by *in situ* ester hydrolysis gave hydrazinoacid **4a** in 71% yield. Hydrogenolysis (PtO_2, 1 bar) of the hydrochloride then afforded in 80% yield (2*S*,3*S*) *allo*-threonine **5a**, identical in all respects with an authentic sample. ^1H NMR and t.l.c. showed that no epimerization occurred during hydrogenation. The optical rotatory power indicated an optical purity ≥ 95%.

In order to examine the scope of this new synthesis of *anti* α-hydrazino- and α-amino-β-hydroxyacids, we studied also the amination of β-hydroxyesters **1b-d**.[19] The results, listed in Table 2, showed that good diastereoselections for the *anti* isomers are commonly obtained. Once again, in every case the two diastereoisomers were well separated on silica gel, thus allowing easy obtainment of diastereomerically pure **2b-d**.

For R=CF_3 the relative configuration of major product was unambiguously assigned by its transformation into known[8c] *allo*-trifluorothreonine **5b**. For R= *n*-Hex and R= *cy*-Hex, the *anti* and *syn* configurations were tentatively assigned to **2c,d** and, respectively, **3c,d** on the basis of a t.l.c. behavior similar to **2a,b** and **3a,b** (the syn isomer is always faster running) and on the reasonable assumption that the stereochemical outcome of the amination reaction is the same for all β-hydroxyesters examined.

In conclusion, this three steps synthesis proved to be diastereoselective, enantiospecific, efficient and of general scope, thus allowing the conversion of easily available optically pure β-hydroxyesters into various *anti* α-hydrazino- and α-amino-β-hydroxyacids.

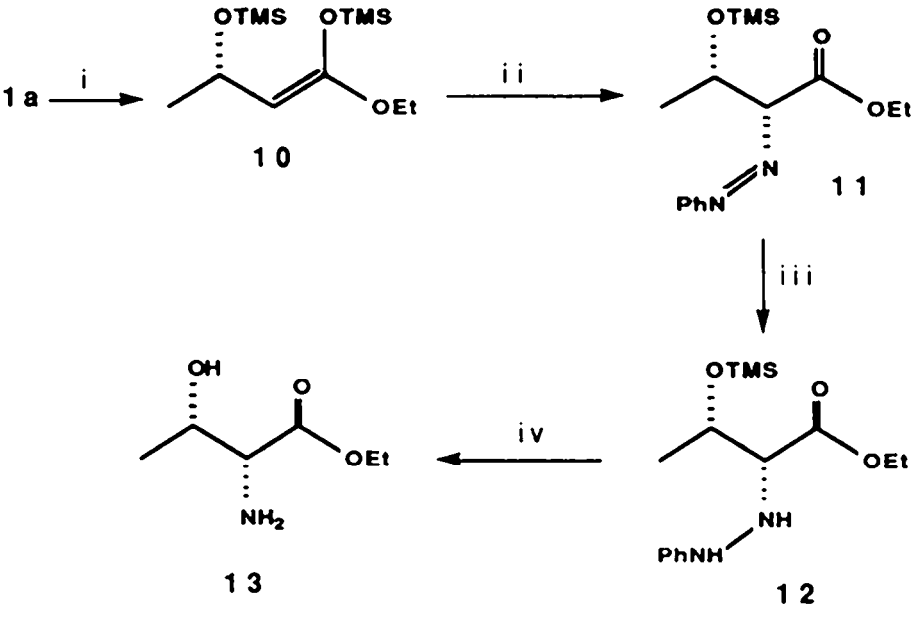
In order to develop a complementary method for the synthesis of *syn* α-hydrazino- and α-amino-β-hydroxyacids, we also studied the condensation of the *O,O'-bis*-trimethylsilyl ketene acetal **10**, derived from **1a**,[18] with benzenediazonium tetrafluoroborate, according to recent reports[15e,f] (Scheme 3).[20] Since we have previously demonstrated[18] that reaction of **10** with imines is *syn* selective, we hoped that this behaviour would have been confirmed also in this case.

TABLE 2 : Synthesis of hydrazinoacids 4 and aminoacids 5 *via* electrophilic amination of β-ketoesters with TBAD.

Entry	R	Product	Yield[a]	Anti : Syn	Hydrazinoacid	Yield[b]	Aminoacid	Yield[b]
1	Me	**2a + 3a**	75%[c]	84 : 16[e]	**4a**	71%	**5a**	80%
2	CF_3	**2b + 3b**	62%[d]	87 : 13[e]	**4b**	66%	**5b**	78%
3	*n*-Hex	**2c + 3c**	74%[d]	90 : 10[f]	**4c**	54%	**5c**	76%
4	*cy*-Hex	**2d + 3d**	81%[d]	85 : 15[f]	**4d**	56%	**5d**	76%

a) Isolated yields of *syn* + *anti* diastereoisomers; **b**) Isolated yields; **c**) Reaction carried out at -50°C, 10 min.; **d**) Reaction carried out at -78°C, 3 min.; **e**) Determined by CGC; **f**) Determined by weight of the two isolated diastereoisomers.

SCHEME 3



I) 1) LDA; 2) TMSCl; ii) PhN_2BF_4, pyridine, -35°C; III) H_2, Pd-C, CH_2Cl_2; Iv) 1) *n*-Bu_4NF, CH_2Cl_2; 2) H_2, Pd-C, 95% EtOH

When this condensation was carried out in pyridine, using 1.4 equivalents of diazonium salt, *syn* azo-derivative **11** was indeed obtained with excellent stereoselectivity (*syn* : *anti* ratio ≥ 95 : 5). However the yield was only modest (23%) and every attempt to increase it by changing reaction conditions was unsuccessful.[21] Attempts to obtain threonine ethyl ester **13** performing first the O-TMS cleavage and then the hydrogenation of the corresponding β-hydroxy-α-phenylazo-ester were fruitless because of extensive elimination during the OH deblocking. On the other hand hydrogenation could be carried out with good yield (82%) on the silylated azo compound **11**, to give **12**, which, after deprotection of the 3-hydroxyl group, was successfully hydrogenated to afford threonine ethyl ester **13**, identical in all respects with an authentic sample, in 52% yield from **12**. It should be pointed out that hydrogenolysis of **11** had to be stopped at the stage of hydrazine **12**, since when the reaction was allowed to proceed towards the N-N bond cleavage, extensive decomposition occurred.

Although this method proved to be complementary in terms of stereoselectivity with the electrophilic amination of β-hydroxyesters with *t*-butyl-azodicarboxylate, the low overall yield limits its synthetic utility.

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR spectra were recorded with a Varian FT-80 (80 MHz) instrument. Microanalyses were performed with a Perkin-Elmer 240 instrument, and are listed on Table 3. Optical rotatory powers were measured at 20°C in 1 dm cell using a Jasco DIP-181

polarimeter. CGC analyses were performed with a Carlo Erba Fractovap HRGC instrument, equipped with a RSL 150 capillary column.

All reactions employing dry solvents were run under a nitrogen atmosphere. Dry solvents were obtained by distillation under nitrogen atmosphere: tetrahydrofuran (THF) was distilled from potassium metal in the presence of benzophenone, dichloromethane from phosphorus pentoxide, pyridine from potassium hydroxide.

Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. 270-400 mesh silica gel (Merck) was used for flash chromatography.[22]

Racemic ethyl 4,4,4-trifluoro-3-hydroxybutanoate **1b**,[23] 3-hydroxynonanoate **1c**,[24] and 3-cyclohexyl-3-hydroxypropanoate **1d**[25] are known compounds.

(2*S* ,3*S*) and (2*R* ,3*S*) Ethyl 2-(*N*,*N'*-di-*tert*-butyloxycarbonyl)-hydrazino-3-hydroxybutanoates (2a) and (3a) -*Typical procedure* : (Entry 3 of Table 1) To a 0.5 N solution of lithium diisopropylamide in THF - *n*-hexane 2 : 1 (51.4 ml, 25.7 mmol), (*S*) ethyl 3-hydroxybutanoate **1a** (88% e.e.) (0.80 ml, 6.11 mmol) was added at -60°C, and the temperature allowed to reach -20°C during 30 min. The resulting dianion solution was cooled to -50°C and di-*tert*-butylazodicarboxylate (3.52 g, 15.3 mmol) in THF (7 ml) was added. After 10 min. the reaction was quenched with acetic acid (2.10 ml, 36.7 mmol), stirred for 15 min. at -50°C, and then allowed to reach room temperature. After dilution with water, extraction with Et_2O and usual work-up, flash chromatography (petroleum ether : Et_2O 1:1) afforded **2a** (R_f= 0.32) (1.39 g, 63%), which was crystallized from Et_2O/petroleum ether to give a white solid. M.p. 97-98°C; $[\alpha]_D$ = +4.8° (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS, exchanged with D_2O): δ 1.30 (t, 7.1 Hz, 3 H, *Me* CH_2), 1.31 (d, 6.6 Hz, 3 H, *Me* CH), 1.47 and 1.48 (2 s, 2 x 9 H, 2 x C*Me*$_3$), 4.24 (q, 7.1 Hz, 2 H, C*H*$_2$Me), 4.23-4.29 (m, 1 H, C*H* OH; $J_{2,3}$ = 6.0 Hz[26]), 4.60 - 5.10 (m, 1 H, C*H* N), 6.65 (bs, 1 H, N*H*).

We were not able to separate **3a** (R_f = 0.44) from di-*tert*-butylhydrazodicarboxylate, which is the main by-product, by column chromatography, but we obtained a pure sample of **3a** through Swern oxidation of **2a** [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -50°C to 0°C][27] followed by $NaBH_4$ reduction (EtOH : H_2O 3:1, NH_4Cl, R.T.)[8a] of the resulting β-ketoester to give a mixture of diastereoisomers separated by preparative t.l.c. (petroleum ether : Et_2O 4:6). ^1H NMR ($CDCl_3$, TMS, exchanged with D_2O): δ 1.28 (t, 7.1 Hz, 3 H, *Me* CH_2), 1.35 (d, 6.6 Hz, 3 H, *Me* CH), 1.47 & 1.49 (2 s, 2 x 9 H, 2 x C*Me*$_3$), 3.86-4.23 (m, 1 H, C*H* OH; $J_{2,3}$ = 8.8 Hz[26]), 4.20 (q, 7.1 Hz, 2 H, C*H*$_2$Me), 4.59 (d, 8.8 Hz, 1 H, C*H* N), 6.58 (bs, 1 H, N*H*).

(2*S* °, 3*R* °) and (2*S* °, 3*S* °) Ethyl 2-(*N*,*N'*-di-*tert*-butyloxycarbonyl)-hydrazino-3-hydroxy-4,4,4-trifluoro-butanoates (2b) and (3b) - The same procedure as for **2a** + **3a** was applied, with the following variations: molar ratio [LDA] : [**1b**] was 3 : 1, and the reaction between dianion and TBAD was run at -78°C for 3 min. Chromatography (dichloromethane - ethyl ether 95 : 5) gave **3b** (8%; R_f = 0.86) and **2b** (56%; R_f = 0.56). **2b** and **3b** were obtained as white solids from petroleum ether; **2b**: m.p. 101-103°C; ^1H NMR ($CDCl_3$, TMS, exchanged with D_2O): δ 1.26 (t, 7.1 Hz, 3 H, *Me*), 1.44 (s, 18 H, 2 x C*Me* $_3$), 4.21 (q, 7.1 Hz, 2 H, C*H* $_2$), 4.40-4.76 (m, 2 H, C*H* -C*H*), 6.62 (bs, 1H, N*H*); **3b**: m.p. 84-86°C; ^1H NMR ($CDCl_3$, TMS, exchanged with D_2O): δ 1.27 (t, 7.1 Hz, 3 H, *Me*), 1.45 & 1.46 (2 s, 2 x 9H, 2 x C*Me* $_3$), 4.23 (q, 7.1 Hz., 2 H, C*H* $_2$), 4.44-4.91 (m, 2 H, C*H* -C*H*), 6.63 (bs, 1H, N*H*).

(2*S* °, 3*S* °) and (2*S* °, 3*R* °) Ethyl 2- (*N*,*N'* - di - *tert* - butyloxycarbonyl) - hydrazino-3-hydroxynonanoates (2c) and (3c) - The same procedure as for **2b** + **3b** was applied. Chromatography (petroleum ether - AcOEt from 9 : 1 to 7 : 3) gave **2c** (67%, R_f = 0.47 with petroleum ether - AcOEt 75 : 25) and **3c** (7%, R_f = 0.60 with petroleum ether - AcOEt 75 : 25).

2c was obtained as a white solid from petroleum ether: m.p. 87-90°C; ^1H NMR ($CDCl_3$, TMS, exchanged with D_2O): δ 0.83-1.51 (m, 16 H, *n* -C_6H_{13} + CH_3CH_2O), 1.46 & 1.48 (2 s, 2 x 9 H, C*Me* $_3$), 3.98-4.21 (m, 1 H, C*H* OH), 4.23 (q, 7.1 Hz, 2 H, C*H* $_2$O), 4.76-5.01 (m, 1 H, C*H* N), 6.61 (bs,

1 H, N*H*). **3c**: ^{1}H NMR ($CDCl_3$, TMS, exchanged with D_2O): δ 0.87-1.49 (m, 16 H, *n*-C_6H_{13} + CH_3CH_2O), 1.47 & 1.49 (2 s, 2 x 9 H, CMe_3), 3.76-4.06 (m, 1 H, C*H* OH), 4.20 (q, 7.1 Hz, 2 H, CH_2O), 4.66 (d, 8 Hz., 1 H, C*H* N), 6.58 (bs, 1 H, N*H*).

(2*S*°, 3*S*°) and (2*S*°, 3*R*°) Ethyl 3-cyclohexyl-2-(*N,N'*-di-*tert*-butyloxycarbonyl)-hydrazino-3-hydroxypropanoates (2d) and (3d)- The same procedure as for **2b** + **3b** was applied. Flash chromatography (petroleum ether - Et_2O 7 : 3) gave **2d** (69%, R_f = 0.29) and **3d** (12%, R_f = 0.54).

2d was obtained as a white solid from petroleum ether: m.p. 91-93°C; ^{1}H NMR ($CDCl_3$, TMS, exchanged with D_2O): δ 0.72-1.77 (m, 11 H, *cy*-Hexyl), 1.19 (t, 7.1 Hz, 3 H, *Me*), 1.37 (s, 18 H, 2 x CMe_3), 3.79 (app t, 6.0 Hz, 1 H, C*H* OH), 4.12 (q, 7.1 Hz, 2 H, CH_2O), 4.68 (bs, 1 H, C*H* N), 6.52 (bs, 1 H, N*H*). **3d**: ^{1}H NMR ($CDCl_3$, TMS, exchanged with D_2O): δ 0.79-1.80 (m, 11 H, *cy*-Hexyl), 1.26 (t, 7.1 Hz, 3 H, *Me*), 1.44 & 1.45 (2 s, 2 x 9 H, CMe_3), 3.68 (dd, 8.3 & 0.5 Hz, 1 H, C*H* OH), 4.17 (q, 7.1 Hz, 2 H, CH_2O), 4.81 (d, 8.3 Hz, 1 H, C*H* N), 6.57 (bs, 1 H, N*H*).

(2*S*, 3*S*) 2-Hydrazino-3-hydroxybutanoic acid (4a) - **2a** (2.0 g, 5.52 mmol) was dissolved in dry CH_2Cl_2 (4 ml) and treated with CF_3COOH (4 ml) at room temperature. After 30 min, dichloromethane and trifluoroacetic acid were evaporated under reduced pressure, the residue taken up with 0.5 N aqueous LiOH (55 ml, 27.5 mmol) and stirred at room temperature for 4h. The solution was washed with ethyl ether (5 ml) and percolated through a column filled with Dowex 50 WX8 (H^+ form, 28 g). The resin was washed with water (200 ml) and then eluted with 10% NH_4OH. The fractions containing the hydrazinoacid (ninhydrin: pale pink) were evaporated to dryness to give **4a** as a solid (524 mg, 71%) which was crystallized from EtOH - H_2O: m.p. 154-155°C; $[\alpha]_D$ -20.9° (c 2, H_2O); ^{1}H NMR (D_2O, $Me_3SiCD_2CD_2COONa$): δ 1.18 (d, 6.7 Hz, 3 H, *Me*), 3.67 (d, 3.6 Hz, 1 H, C*H* N), 4.30 (dq, 3.6 & 6.7 Hz, 1 H, C*H* OH).

(2*S*°, 3*R*°) 2-Hydrazino-3-hydroxy-4,4,4-trifluorobutanoic acid (4b) - The same procedure as for **4a** was applied. The hydrazinoacid **4a** (66%) could be crystallized from absolute EtOH: m.p. 117-123°C (dec.); ^{1}H NMR (D_2O, $Me_3SiCD_2CD_2COONa$): δ 3.54 (d, 4.2 Hz, 1 H, C*H* N), 4.30-4.80 (m, 1 H, C*H* OH).

(2*S*°, 3*S*°) 2-Hydrazino-3-hydroxy-nonanoic acid (4c) - The same procedure used for **4a** was employed, except that ester hydrolysis was performed with 5 eq of 0.35 N LiOH in H_2O : THF 7:3 (yield = 54%). Trituration from EtOH - Et_2O gave a white solid: m.p. 180-190° (dec.); ^{1}H NMR (0.13 N DCl/D_2O, $Me_3SiCD_2CD_2COOH$): δ 0.78-1.52 (m, 13 H, *n*-C_6H_{13}), 3.90 (d, 3.3 Hz, 1 H, C*H* N), 3.92-4.22 (m, 1 H, C*H* OH).

(2*S*°, 3*S*°) 3-Cyclohexyl-2-hydrazino-3-hydroxypropanoic acid (4d) - The same procedure as for **4c** was followed. Yield = 56%; m.p. 191-193°C (dec.); ^{1}H NMR (0.13 N DCl/D_2O, $Me_3SiCD_2CD_2COOH$): δ 1.00-1.98 (m, 11 H, *cy*-Hexyl), 3.68 (dd, 8.5 & 3.0 Hz, 1 H, C*H*-OH), 4.05 (d, 3.0 Hz, 1 H, C*H* N).

(2*S*, 3*S*) 2-Amino-3-hydroxybutanoic acid (5a) - Hydrazinoacid **4a** (250 mg, 1.86 mmol) was dissolved in 2.3 ml of 1 N aqueous HCl (2.3 mmol); the solvent was evaporated to dryness, and the residue stripped for 2 h at 0.01 mmHg, dissolved in water (25 ml) and hydrogenated at atmospheric pressure in the presence of a catalytic amount of PtO_2. After 16 h, 0.5 N LiOH (11.5 ml, 5.75 mmol) was added, the catalyst filtered off, and the filtrate percolated through a column filled with Dowex 50 WX8 (H^+ form, 6 g). The resin was washed with water (30 ml) and then eluted with 10% NH_4OH. The fractions containing the aminoacid (ninhydrin: purple) were evaporated to dryness to give **5a** (177 mg, 80%) as a white solid, identical by ^{1}H NMR and t.l.c. (EtOH - NH_4OH 75 : 25) with an authentic sample of *allo*-threonine. The solid was triturated with EtOH to give a white solid, m.p. 273-276°C; $[\alpha]_D$ = + 8.7° (c 2, H_2O) (lit.[28] + 9.1°).

(2*S*°, 3*R*°) 2-Amino-3-hydroxy-4,4,4-trifluorobutanoic acid (5b) - The same procedure as for **5a** was applied. **5b** was obtained in 69% yield as a white solid, which was identical by

^{1}H NMR and t.l.c. (*n*-BuOH - H_2O - acetone - NH_4OH 8 : 6 : 1 : 1) with an authentic sample of 4,4,4-trifluoro-*allo*-threonine.[8c]

(2*S, 3*S**) 2-Amino-3-hydroxynonanoic acid (5c)** - The hydrogenation was carried out as for **5a**. After addition of LiOH and filtration of the catalyst, the filtrate was percolated on Dowex 50 WX8 as above, but the filter was further washed with 10% NH_4OH. The solution resulting from this operation was added to the one obtained by elution of the resin to give, after evaporation to dryness, **5c** as a white solid (61%), which was recrystallized from EtOH - Et_2O; m.p. 214-216°C (dec.); ^{1}H NMR (0.13 N DCl/D_2O, $Me_3SiCD_2CD_2COOH$): δ 0.82-1.59 (m, 13 H, *n*-C_6H_{13}), 4.00-4.17 (m, 2H, C*H* N + C*H*OH).

(2*S, 3*S**) 2-Amino-3-cyclohexyl-3-hydroxypropanoic acid (5d)** - It was prepared by the same method employed for **5c** (yield = 58%); m.p. 175-180°C (dec.) (EtOH - Et_2O); ^{1}H NMR (0.13 N DCl/D_2O, $Me_3SiCD_2CD_2COOH$): δ 0.94-2.00 (m, 11 H, *cy*-Hexyl), 3.64 (dd, 8.5 & 2.4 Hz, 1 H, C*H*OH), 4.21 (d, 2.4 Hz, 1H, C*H* N).

(2*R, 3*S**) Ethyl 2-(phenylazo)-3-trimethylsilyloxy-butanoate (11)** - To 939 mg of **10** (3.40 mmol) dissolved in anhydrous pyridine (10 ml), PhN_2BF_4 (939 mg, 4.89 mmol) was added as a solid at -35°C. After 18 h, the reaction was diluted with Et_2O and 1.5 N HCl (28 ml); the organic phase was separated and washed with brine. After usual work-up and flash chromatography (petroleum ether - Et_2O 1 : 1), **11** was obtained as a reddish yellow oil (226 mg, 0.73 mmol; 22%); ^{1}H NMR ($CDCl_3$, TMS) δ 0.12 (s, 9 H, *Me* $_3$Si), 1.16 (d, 6.0 Hz, 3 H, *Me* CH), 1.26 (t, 7.1 Hz, 3 H, *Me* CH_2), 4.19 (q, 7.1 Hz, 2 H, C*H* $_2$Me), 4.45 (d, 7.8 Hz, 1 H, C*H* N), 4.85 (dq, 7.8 & 6.0 Hz, 1 H, C*H* Me), 6.82-7.40 (m, 5 H, Ph). An isomer of **11** was isolated in about 1% yield (14 mg, 0.05 mmol); we did not ascertain if it was the *anti* diastereoisomer or a geometrical (at the N=N bond) isomer of **11**; ^{1}H NMR ($CDCl_3$, TMS): δ 0.02 (s, 9 H, *Me* $_3$Si), 1.28 (t, 7.1 Hz, 3 H, *Me* CH_2), 1.31 (d, 6.2 Hz, 3 H, *Me* CH), 4.24 (q, 7.1 Hz, 2 H, C*H* $_2$Me), 4.29 (d, 7.7 Hz, 1 H, C*H* N), 4.77 (dq, 7.7 & 6.2 Hz, 1 H, C*H* Me), 7.16-7.91 (m, 5 H, Ph).

(2*R, 3*S**) Ethyl 2-(phenylhydrazino)-3-trimethylsilyloxy-butanoate (12)** - 200 mg of **11** (0.65 mmol) were dissolved in anhydrous CH_2Cl_2 (20 ml) and hydrogenated at atmospheric pressure and room temperature in the presence of a catalytic amount of 10% palladium on charcoal. After 50 min, the catalyst was filtered off and the solvent evaporated to give a yellow oil. Chromatography (petroleum ether - Et_2O 9 : 1) afforded **12** in 82% yield (165 mg, 0.53 mmol); ^{1}H NMR ($CDCl_3$, TMS): δ 0.08 (s, 9 H, *Me* $_3$Si), 1.36 (t, 7.1 Hz, 3 H, *Me* CH_2), 1.44 (d, 6.3 Hz, 3 H, *Me* CH), 3.42 (d, 2.2 Hz, 1 H, C*H* N), 4.21 (q, 7.1 Hz, 2 H, C*H* $_2$Me), 4.29 (dq, 2.2 & 6.3 Hz, 1 H, C*H* Me), 6.74-7.29 (m, 5 H, Ph).

(2*R, 3*S**) Ethyl 2-amino-3-hydroxy-butanoate (13)** - 95 mg of **12** (0.31 mmol) dissolved in dry CH_2Cl_2 (12 ml) were treated with 6 ml of a 0.16 M solution of *n* -$Bu_4NF.3H_2O$ in dry CH_2Cl_2 (0.96 mmol) at room temperature. After 1 h, evaporation of solvent and flash chromatography (petroleum ether - Et_2O 1 : 1) afforded ethyl 3-hydroxy-2-(2-phenylhydrazino)butanoate in 62% yield (46 mg, 0.19 mmol); ^{1}H NMR ($CDCl_3$, TMS, exchanged with D_2O): δ 1.32 (t, 7.1 Hz, 3 H, *Me* CH_2), 1.40 (d, 6.5 Hz, 3 H, *Me* CH), 3.47 (d, 4.7 Hz, 1 H, C*H* N), 4.03-4.39 (m, 1 H, C*H* Me), 4.28 (q, 7.1 Hz, 2 H, C*H* $_2$Me), 6.72-7.33 (m, 5 H, Ph).

Ethyl 3-hydroxy-2-(phenylhydrazino)butanoate (40 mg, 0.17 mmol) was hydrogenated in 95% EtOH solution (2 ml) at atmospheric pressure and room temperature in the presence of a catalytic amount of 10% palladium on charcoal for 20 h. Filtration of catalyst and removal of solvent afforded (2*R**, 3*S**) ethyl 2-amino-3-hydroxybutanoate in 84% yield (21 mg, 0.14 mmol); ^{1}H NMR ($CDCl_3$, TMS, exchanged with D_2O) δ 1.24 (d, 6.2 Hz, 3 H, *Me* CH), 1.29 (t, 7.1 Hz, 3 H, *Me* CH_2), 3.25 (d, 5.3 Hz, 1 H, C*H* N), 3.87 (app quintet, 6.1 Hz, 1 H, C*H* Me), 4.22 (q, 7.2 Hz, 2 H, C*H* $_2$Me).

TABLE 3: Elemental Analyses of compounds 2,4, and 5

Compound	Found			Calculated		
	C%	H%	N%	C%	H%	N%
2a	52.94	8.22	7.77	53.02	8.84	7.73
2b	45.97	6.65	6.67	46.15	6.53	6.73
2c	58.02	9.16	6.56	58.31	9.32	6.48
2d	57.98	8.77	6.61	58.58	8.89	6.51
4a	35.64	7.46	20.67	35.82	7.51	20.88
4b	25.06	3.81	14.79	25.54	3.75	14.89
4c	52.99	9.38	13.72	52.92	9.89	13.71
4d	52.92	8.78	13.72	53.45	8.97	13.85
5c	56.83	9.94	7.34	57.12	10.12	7.40
5d	56.97	9.11	7.40	57.73	9.15	7.48

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