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Synthesis of Enantiomerically Pure Threo 1-Alkyl-2-benzyloxy-propylamines

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Abstract : *Pure (1S,2S)-1-Butyl- and (1S,2S)-1-isobutyl-2-benzyloxy-propylamine have been synthesized in 5 steps and 62% overall yield from (S)-ethyl lactate. It was found that BuLi and i-BuMgBr add readily and diastereoselectively (d.e.> 96 %) to α-benzyloxypropionaldehyde dimethylhydrazone and that hydrogenolysis proceeds in high yield and without epimerization.*

1-Alkyl-2-benzyloxy-propylamines **6** constitute an interesting class of chiral ligands which can be obtained in 5 steps from commercialy available and enantiomericaly pure α-hydroxyacids. Although Grignard reagents [1,2] and organo-lithium [3,4a] have been used for additions to hydrazones, organo-cerium reagents are often prefered [4b,5]. Since hydrogenolysis of the N-N bond[3-5] is difficult and/or leads to epimerization, various carbamates derivatives have been proposed to improve the yield of this step.[6]

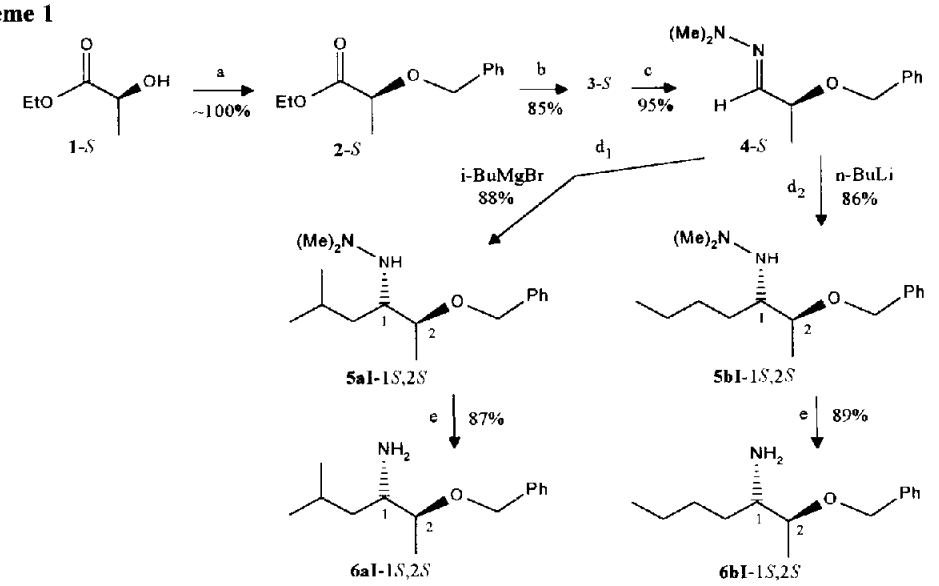
We report here easy, diastereoselective (de > 96%) and high yield additions of *i*-BuMgBr and *n*-BuLi to the α-benzyloxypropionaldehyde dimethylhydrazone **4**, Scheme 1. We also show that, while carbamates derivatives led to the undesired oxazolidones, direct hydrogenolysis of the unprotected hydrazines can be performed without epimerization and in high yield.

Results

The *E*-isomer (*cf.* below) of *S*-α-benzyloxypropionaldehyde dimethylhydrazone **4** was obtained in three steps, 81% overall yield and without racemization from *S*-ethyl lactate **1**, Scheme 1.

Various conditions were studied for the nucleophylic addition of *i*-BuMgBr and *n*-BuLi on **4**, and the results are gathered in Table 1. The dimethylhydrazines **5a** and **5b** were obtained in high yields (Table 1, lines 3 and 5) and as single diastereomers, **5aI** and **5bI** (from 200 MHz ^{1}H NMR of the crude products of the reactions), both additions were thus at least 96% diastereoselective. It must be noted that, although the organolithium reagent added quantitatively in five hours at 0°C, 35°C and 12 hours were necessary for the Grignard reagent to provide full conversion.

Scheme 1



a) $Ag_2O/PhCH_2Br/Et_2O$, 40°C. b) DIBAL-H, Et_2O/pentane (1/9), -78°C. c) $(Me)_2NNH_2/MgSO_4/CH_2Cl_2$ 0°C. d_1) i-BuMgBr/Et_2O, 35°C, 12 hrs. d_2) n-BuLi/Et_2O, 0°C, 5 hrs. e) Ni-Raney/H_2, 15 atm./MeOH, 50°C 2.5 hrs.

Table 1 : Nucleophylic additions to hydrazone 4.

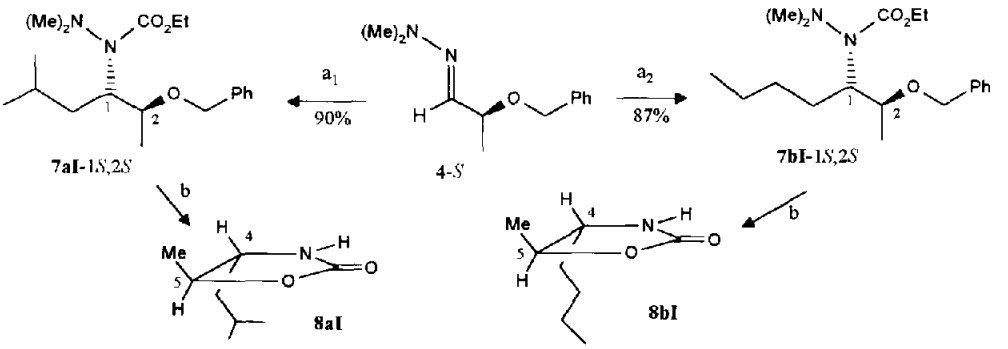
Reagent (equiv.)	Temp.	convers. %	**5I/5II**	Isolated yield %	Compnd
i-BuMgBr (2)	-20°C	0%			
i-BuMgBr (2)	20°C	60%[a]	98/2[b]		
i-BuMgBr (2)	35°C	100%	98/2[b]	88%[c]	**5aI**
i-BuMgBr (1)	35°C	40%[a]	98/2[b]		
n-BuLi (2)	0°C	100%	98/2[b]	86%[c]	**5bI**
n-BuLi (1)	0°C	47%[a]	98/2[b]		

a) Determined by ^1H NMR on the crude products of the reactions, the complement to 100% is the starting hydrazone **4**. b) **5I/5II** = 98/2 means that diastereomer II was not detected on ^1H NMR of the crude product of the reactions. c) After chromatography on Silica Gel (Et_2O/hex, 3/7).

Because carbethoxy-protected hydrazines were expected to be easier to handle and to undergo hydrogenolysis more readily[6], the intermediate adducts of the nucleophylic additions were, to begin with, trapped with ethyl chloroformate, Scheme 2. The protected-hydrazines **7a** and **7b** were isolated in high yields (87-90%), and, as expected, only one diastereomer (**7aI** or **7bI**) was detected in both

cases on the 200 MHz ^1H NMR spectra of the crude products. However, hydrogenolysis using Li/NH_3[6] afforded quantitatively and as a single diastereomer the corresponding oxazolidone, **8aI** and/or **8bI**, Scheme 2, instead of the benzyloxy- or hydroxy-amine. Moreover further hydrolysis of oxazolidones **8aI** and **8bI** was difficult, leading to poor yields in the amino-alcohols (~20%). The carbamate protection step was thus abandoned and the oxazolidones **8aI** and **8bI** have been used to determine the *threo*-structure of the parent compounds **5aI** and **5bI** (*cf.* below).

Scheme 2



a_1) i-BuMgBr/Et_2O, 40°C, 12 hrs ; $ClCO_2Et$, rt, 2 hrs. a_2) n-BuLi/Et_2O, 0°C, 5 hrs ; $ClCO_2Et$, rt, 2 hs. b) Li/NH_3, -78°C.

Table 2 : Hydrogenolysis of hydrazine 5aI

Catalyst	Solv.	Conditions	**6a (I/II)**	yield
H_2/Ra-Ni	EtOH	10 atm/12h/rt	79/21	85%
H_2/Ra-Ni	EtOH	30 atm/12h/rt	83/17	80%
H_2/Ra-Ni	MeOH	15 atm/2.5h/50°C	98/2[a]	87%
H_2 PtO_2	MeOH[b]	4 atm/12h/rt	87/13	85%
H_2 PtO_2	MeOH[b]	15 atm/2h/rt	77/23	80%

a) **I/II** = 98/2 means that diastereomer **II** was not detected on the ^1H NMR spectra of the crude product of the reaction. b) 1% AcOH (in volume) was added to MeOH.

The hydrogenolysis of dimethylhydrazine **5aI** was studied and the results are gathered in Table 2. It is worth noting that, with Ra-Ni and/or PtO_2/HOAc 1% as catalysts and under mild conditions (ambient, 12 hours), the N-N bond cleavage occured with extensive epimerization, in opposition with literature results[3]. However the use of Ra-Ni but at higher temperature (50°C) and with shorter reaction times (2.5 h) afforded the desired protected amino-alcohol **6aI** without epimerization (Table 2, line 3).

The same conditions applied to hydrazine **5bI** led to pure **6bI**, Scheme 1.

E-Structure of the dimethylhydrazone **4** *using NMR.*

Only one isomer was detected on the 200 MHz ^{1}H NMR of the crude product, with no splitting of any signal. The 24% nOe[7] obtained at the imino proton (doublet at 6.43 ppm) upon irradiation of the *gem*-dimethyl singlet (at 2.78 ppm) indicated that the *E*-isomer was the only isomer formed. On the other hand, the 7 Hz value for the $^3J_{1-2}$ coupling constant suggested that protons H1 and H2 are in a *trans* relationship, Figure 1, in consistency with literature results[8] and with molecular modeling. An MM2 analysis[9] using 4 search labels (θ1, 02, θ3, 04) followed by an MNDO conformational search around C1-C2 bond (θ4), on the most stable conformation found, led indeed to conformer **A1** as the most stable (12.94 kcal/mol) and most populated. A second minimum, **A2** (θ4 = -36°), was found ~2.2 kcal/mol above **A1** using a Rigid Search or **A2'** (θ4 = -12°) ~1.3 kcal/mol above **A1** using an Optimized Search.

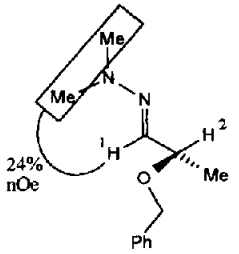
One must also note that the equivalence of the N-*gem*-dimethyl group, if not accidental[10], suggests that rotation around the N-N bond is rapid on the NMR time-scale or that the $N(Me)_2$ group is not coplanar with the C=N double bond. An MNDO conformational analysis around the N-N bond performed on conformer **A1** showed indeed, Figure 1, that in the most stable conformation **A1** (12.94 kcal/mol) θ ~ 114°, the nitrogen N2 is hybridized sp3 and the $N(Mc)_2$ group is perpendicular to the plane of the C=N double bond. The conjugated conformation was found at 15.1 kcal/mol with the N2 hybridized sp2 and corresponded neither to a minimum nor to a maximum. The less stable conformation (19.86 kcal/mol) has the lone pairs in a *cis* relationship and the nitrogen N2 is hybridized sp3.

Trans-structure of oxazolidones **8aI** *and* **8bI**.

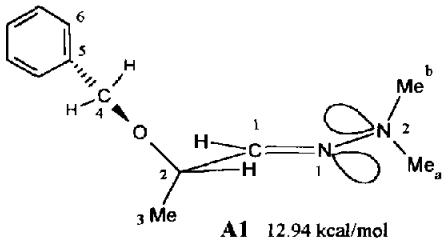
The J_{1-2} coupling constant was found to be 6 Hz in both compounds, **8aI** and **8bI**, suggesting a *trans*-structure ; but, because we had in hand only one diastereomer and because it had been found that *cis*-J_{1-2} and *trans*-J_{1-2} could be almost identical[11], the structure was determined using NOESY. It must be noted that in both cases 500 MHz ^{1}H NMR had to be used to avoid overlap between the CH_3 doublets and the CH_2 multiplet.

Examination of the NOESY map of oxazolidone **8aI** shows that the 4.25 ppm quintuplet corresponding to proton H5 correlates to the two protons of the CH_2 of the chain (ddd at 1.35 ppm and ddd at 1.48 ppm, AB part of an ABXM system) and that the 3.45 ppm double triplet corresponding to proton H4 correlates to the CH_3 (d at 1.40 ppm). More there is no correlation between the CH_3 and the CH_2 signals.

Figure 1



J_{12} = 7 Hz



A1 12.94 kcal/mol

θ1 C6-C5-C4-O = 90° ; θ2 C5-C4-O-C2 = -178°
θ3 C4-O-C2-C1 = -91° ; θ4 O-C2-C1-N1 = 132°
θ C1-N1-N2-Ca = -117° ; θ' C1-N1-N2-Cb = 114°

Similarly, examination of the NOESY map of **8bI** shows that the 4.26 ppm quintuplet corresponding to H5 correlates to the CH_2 quadruplet (1.52 ppm) and the 3.36 ppm double triplet corresponding to H4 correlates to the CH_3 doublet (1.39 ppm) while no correlation spot appears between the CH_2 quadruplet and the CH_3 doublet. One can thus conclude that oxazolidones **8aI** and **8bI** have a *trans* structure.

As a consequence both hydrazines **5aI** *and* **5bI** *as well as the derived benzyloxy-amines* **6aI** *and* **6bI** *have the* ***threo*** *structure.*

Conclusion

It was found that 2 equivalents of of *t*-BuMgBr and/or *n*-BuLi add readily with complete conversion (86-88% isolated yield) and complete *threo* diastereoselectivity (> 96% *threo*) to α-benzyloxypropionaldehyde dimethylhydrazone **4**. It was also shown that Ra-Ni catalyzed-hydrogenolysis of the corresponding dimethyl hydrazines **5aI** and **5bI** proceeds in high yields (87-89% isolated) and without epimerization provided conditions leading to rapid reactions are used (temperature around 50°C and 15 atm H_2).

Threo **and enantiomerically pure benzyloxyamines 6aI and 6bI have thus been obtained in 5 steps and high overall yields (~62%).**

Experimental.

For ^1H (200 MHz when not specified) and ^{13}C (50 MHz) NMR spectra, δ in ppm are referenced to TMS. Melting points are uncorrected. All starting materials were commercially available research-grade chemicals purchased from Aldrich and used without further purification. THF was distilled after

refluxing over Na/benzophenone, Et_2O was distilled from $LiAlH_4$ and CH_2Cl_2 from CaH_2. All reactions were run under argon. Silica gel 60 F_{254} was used for TLC and the spots were detected with UV. Flash chromatography was performed using silica gel 70-330 mesh from Merck. Microanalyses were performed in our Department.

The MM2 analysis with 4 search labels (θ1, θ2, θ3, θ4) was performed using the Sequential Search (one pass) method and led to conformation **A** which was then submitted to a MOPAC (MNDO) optimization followed by a conformational analysis around C1-C2 bond using the Rigid Search method : **A1**, 12.94 kcal/mol, θ1 = 90°, θ2 = -178°, θ3 = -91°, θ4 = 132° and **A2**, 15.11 kcal/mol, θ1 = 90°, θ2 = -178°, θ3 = -91°, θ4 = -36°). An Optimized Search was also performed and gave an identical structure , **A1**, for the most stable conformer ; the second minimum **A2'** was slightly different : 14.25 kcal/mol, θ1 = 93°, θ2 = -179°, θ3 = -88°, θ4 = -12°. Conformer **A1** was then submitted to an MNDO conformational analysis around the N-N bond using the Optimized Search method.

(*S*)-Ethyl O-benzyl lactate, 2 :

Ag_2O (1 eq., 11.4 mmol, 2.65 g) was added by portion to a mixture of (*S*)-ethyl lactate (1 eq., 11.4 mmol, 1.35 mL) and benzyl bromide (1.1 eq, 12.5 mL) dissolved in anhydrous Et_2O (20 mL). After stirring for one night under reflux the mixture is filtered. The organic layer is concentrated *in vacuo* and the residu (~100%) used for the next step without further purification. After chromatography (Et_2O/hex, 1/9) pure **2** was isolated (86%). Rf = 0.59 (Et_2O/hex, 4/6). $[\alpha]_D^{25}$ = -83 (c = 2.52, $CHCl_3$), lit.[12] : $[\alpha]_D$ = -74.5 (c = 2.92, $CHCl_3$). Enantiomeric purity ~99% , determined by ^1H NMR using $Eu(hfc)_3$. IR ($CHCl_3$) 1730. ^1H NMR ($CDCl_3$) : δ : 7.3 (5H, m) ; 4.57 (2H, AB system, ^2J = -11.5Hz, Δν=50Hz) ; 4.22 (2H, q, ^3J=7Hz) ; 4.05 (1H, q, ^3J=7Hz) ; 1.44 (3H, d) ; 1.3 (3H, t). ^{13}C NMR ($CDCl_3$) : δ : 128.5, 128 and 127.8 (CH) 74 (CH), 72 (CH_2), 60 (CH_2), 19 and 14 (CH_3). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21 ; H, 7.74. Found : C, 68.98 ; H, 7.82.

(*S*)-2 Benzyloxy-propionaldehyde, 3.:

A precooled (-78°C) 1M DIBAL-H solution in hexane (1.05 eq., 14.3 mmol, 14.3 mL) was added dropwise and rapidly to a cold (-78°C) solution of ester **2** (1 eq., 13 mmol, 2.67 g) in Et_2O/pentane (1/9, 100 mL). The mixture was stirred at -78°C for 15 mn then MeOH (10 mL), a saturated aqueous solution of sodium tartrate (30 mL) and ethyl acetate (50 mL) were added successively. After stirring for 0.5h at 0°C the organic phase was separated. The aqueous phase was extracted which ethylacetate (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and the residu chromatographied (Et_2O/hex, 2/8) : Colourless liquid. Yield : 85%. Rf = 0.52 (Et_2O/hex, 4/6). $[\alpha]_D^{25}$ = -65 (neat), lit.[12] : -66 (neat). IR (CCl_4) 1720. ^1H NMR ($CDCl_3$) : δ : 9.63 (1H, d, ^3J = 2 Hz) ; 7.25 (5H, m) ; 4.63 (2H, AB system, ^2J = -12Hz, Δν = 10Hz) ; 3.8 (1H, qd, ^3J = 7, 7, 7, 2 Hz); 1.34 (3H, d). ^{13}C NMR ($CDCl_3$) : δ : 200 (CO), 138 (C.), 128.5 and 128 (CH.), 79.5 (CH), 72 (CH_2), 15 (CH_3). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14 ; H, 7.36. Found : C, 72.67 ; H, 7.69.

(*S*)-2-benzyloxy-propionaldehyde-N,N-dimethylhydrazone, 4 :

To a solution of aldehyde **3** (1 eq., 21.9 mmol, 3.6 g) and N,N-dimethylhydrazine (1.05 eq., 22.9 mmol, 1.92 g) in CH_2Cl_2 (20 mL) was added dried $MgSO_4$ (0.95 eq. , 20.8 mmol, 2.5 g). The mixture was stirred at 0°C for 6h. After filtration the organic phase was concentrated in vacuo and the residu chromatographied (Et_2O/hex, 3/7). Yield : 95%. Rf = 0.47 (Et_2O/hex, 4/6). $[\alpha]_D^{25}$ = -89 (c = 2.17, CCl_4). IR (CCl_4) 1600. ^1H NMR ($CDCl_3$) : δ : 7.3 (5H, m) ; 6.43 (1H, d, ^3J=7 Hz) ; 4.51 (2H, AB system, ^2J = -12 Hz, Δν = 17 Hz) , 3.8 (1H, quint, J = 7 Hz) ; 2.78 (6H, s) ; 1.35 (3H, d). ^{13}C NMR ($CDCl_3$) : δ : 138 (C), 137 (CH), 128.5, 128 and 127.5 (CH), 76 (CH) ; 70 (CH_2), 43 (CH_3), 20 (CH_3). Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87 ; H, 8.79 ; N, 13.58. Found : C, 69.80 ; H, 8.64 ; N, 13.30.

(1*S*,2*S*)-N',N'-dimethyl- N-[1-isobutyl-2-benzyloxy] propylhydrazine, 5aI :

Isobutyl Grignard was prepared as usually from isobutyl bromide (2 eq., 3 mmol, 0.4 g, 0.324 mL) and Mg (2 eq., 3 mmol, 0.076 g) in anhydrous Et_2O (3 mL).Then hydrazone **4** (1 eq., 1.5 mmol, 0.309 g) in anhydrous Et_2O (5 mL) was added dropwise and the mixture was refluxed for 12h. After cooling to ambient, water (10 mL) was added. The ether layer was separated, the aqueous phase was saturated with NaCl and extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residu was chromatographied (Et_2O/hex, 3/7). Yield : 88%. Rf = 0.67 (Et_2O/hex, 4/6). $[\alpha]_D^{25}$ = -51 (c=2.17, $CHCl_3$). ^1H NMR ($CDCl_3$) only one diastereomer detected : δ : 7.3 (5H, m) ; 4.55 (2H, AB system, ^2J = -12 Hz, Δν = 22 Hz) ; 3.7 (1H, q.d, ^3J = 6, 7, 7, 7 Hz) ; 2.93 (1H, ddd, ^3J = 6, 4, 8.5 Hz) ; 2.38 (6H, s) ; 2.16 (1H, bs) ; 1.6 (1H, m) ; 1.3 (1H, ddd, ^3J = 4, 7 Hz, ^2J = -12.5 Hz) 1.17 (3H, d, ^3J = 7 Hz) ; 1.17 (1H, m) ; 0.94 (3H, d, J=6 Hz) ; 0.91 (3H, d, J=6Hz, CH_3). ^{13}C NMR ($CDCl_3$) : δ : 139 (C), 128.5, 128 and 127 (CH), 76 (CH), 74 (CH_2), 57.5 (CH), 48 (CH_3), 36 (CH_2), 24 (CH), 23 and 22 (CH_3). Anal. Calcd for $C_{16}H_{28}N_2O$: C, 72.68 ; H, 10.67. Found : C, 72.60 ; H, 10.80.

(1*S*,2*S*) -N',N'-dimethyl-N-[1-butyl-2-benzyloxy] propylhydrazine, 5bI :

To a solution of hydrazone **4** (1 eq., 1.5 mmol, 0.309 g) in anhydrous Et_2O (7 mL) was added dropwise at -40°C a 1.3 M solution in hexane of n-BuLi (2 eq., 3 mmol, 2.31 mL). After addition the temperature was allowed to reach 0°C and stirring was maintained at 0°C for 5h. Then the mixture was poured in cold water. The separated aqueous phase was saturated with NaCl and extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residu was chromatographied (Et_2O/hex, 3/7). Pale yellow liquid. Yield : 86%. Rf = 0.64 (Et_2O/hex, 1/1). $[\alpha]_D^{25}$ = +5 (c = 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$) : δ : 7.3 (5H, m) ; 4.53 (2H, AB system, ^2J = -11.5 Hz, Δν = 33 Hz) ; 3.7 (1H, quint, ^3J = 6 Hz) ; 2.78 (1H, td, ^3J = 6, 6, 4 Hz) ; 2.39 (6H, s) ; 1.6 (1H, m) ; 1.32 (6H, m) ; 1.15 (3H, d) ; 0.9 (3H, t). ^{13}C NMR ($CDCl_3$) : δ : 139 (C), 128, 127.5 and 127.2 (CH) ; 76 (CH), 71 (CH_2), 61 (CH), 48 (CH_3), 28.5, 28 and 23 (CH_2), 15 and 14 (CH_3). Anal. Calcd for $C_{16}H_{28}N_2O$: C, 72.68 ; H, 10.67. Found : C, 72.88 ; H, 10.80.

(1*S*,2*S*)-N',N'-dimethyl-N-[1-isobutyl-2-benzyloxy]propyl-N-carbethoxy-hydrazine, 7aI :

Isobutyl Grignard was prepared as usually. After addition of hydrazone **4** and reflux, ethyl chloroformate (2 eq.) was added and the mixture heated under reflux for 6h. Work-up was then

performed as above. Pale yellow liquid. Yield : 90%. Rf = 0.64 (Et_2O/hex, 3/7). IR (CCl_4) 1695. ^1H NMR ($CDCl_3$) : δ : 7.32 (5H, m.) ; 4.5 (2H, AB system, ^2J = -12 Hz, Δν = 50 Hz) ; 4.18 (3H, m) ; 3.69 (1H, broad m) ; 2.75, 2.73 and 2.64 (6H, three singlets, amide isomerism) ; 1.7 (2H, m), 1.25 (1H, m overlapped with CH_3) ; 1.24 (3H, d) ; 0.97 (3H, d, J = 6 Hz), 0.94 (3H, d, J=6 Hz). ^{13}C NMR ($CDCl_3$) : δ : 156 (CO), 139 (C), 128, 127.5 and 127 (CH), 75.5 and 75 (CH), 69 (CH_2), 61.5 (CH), 61 (CH_2), 45.2, 45, 44.5 and 44.2 (CH_3), 36.5 (CH_2), 25, 24.5, 24.2, 24, 22, 21.5, 16 and 15 (CH_3 and CH). Anal. Calcd for $C_{19}H_{32}N_2O_3$: C, 67.82 ; H, 9.58 ; N, 8.32. Found : C, 67.35 ; H, 9.84 ; N, 8.63.

(1*S*,2*S*)-N',N'-dimethyl-N-[1-butyl-2-benzyloxy]propyl-N-carbethoxy-hydrazine, 7bI :

The reaction was conducted as for the preparation of compound **5bI** but after stirring at 0°C for 5h ethylchloroformate (2 eq) was added dropwise and the temperature was allowed to reach ambient (5h). Work-up was then performed as usual. Pale yellow liquid. Yield : 87%. Rf = 0.61 (Et_2O/hex, 4/6). IR (CCl_4) 1690. ^1H NMR ($CDCl_3$) : δ : 7.28 (5H, m) ; 4.5 (2H, AB system, ^2J = -12 Hz, Δν=46 Hz) ; 4.16 (3H,m) ; 3.8 (1H, qd, ^3J = 7, 7, 7, 6 Hz) ; 2.74 and 2.64 (6H, two singlets, NCH_3), 1.6 and 1.27 (6H, bm, CH_2); 1.25 (d, J=7, CH_3) ; 0.91 (bt, CH_3). ^{13}C NMR ($CDCl_3$) : δ : 128 and 127 (CH) ; 75 (CH) ; 69 (CH_2), 63.5 and 63 (CH) ; 60 and 60.5 (CH_2) ; 45.2, 45, 44.5 and 44 (NCH_3) ; 39 (CH_2) ; 29, 27, 26, 23.5 and 23 (CH_2) ; 16.5, 15, 14.5 and 14 (CH_3). Anal. Calcd for $C_{19}H_{32}N_2O_3$: C, 67.82 ; H, 9.58. Found. C, 67.94 ; H, 9.86.

Synthesis of oxazolidone :

Lithium (15 eq., 30 mmol, 0.214 g) was added by portion at -78°C to liquid ammonia (15 mL). To the resulting purple solution was added dropwise the desired carbethoxy hydrazine, **7aI** or **7bI**, (1 eq., 2 mmol) dissolved in anhydrous THF (3 mL). Stirring was maintained and the temperature allowed to reach -30°C (4 to 5h). Then ammonia was evaporated, solid NH_4Cl (15 eq., 30 mmol, 1.6 g) was added and the mixture stirred for 15 mn. After addition of water (10 mL), the aqueous phase was extracted with Et_2O (2 x 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residu was chromatographied (Et_2O/hex/MeOH, 5/4/1).

***Trans-(4S,5S)*-4-isobutyl-5-methyl-oxazolidin-2-one, 8aI :**

Pale yellow oil. Yield 85%. Rf = 0.45 (Et_2O/hex/MeOH; 4/5/1). $[\alpha]_D^{25}$ = -30 (c = 1.34, $CHCl_3$). IR (CCl_4) 3250, 1750. ^1H NMR 500 MHz ($CDCl_3$) δ : 6.33 (1H, bs) ; 4.25 (1H, quint, ^3J = 6 Hz) ; 3.45 (1H, td, ^3J = 6, 6, 8 Hz) ; 1.64 (1H, d.oct., ^3J = 6 (7 times), 8 Hz) ; 1.48 (1H, ddd, ^2J = 13 Hz, ^3J = 8, 6 Hz) ; 1.40 (3H, d, ^3J = 6 Hz) ; 1.35 (1H, ddd, ^2J = 13 Hz, ^3J = 8, 6 Hz) ; 0.93 (3H, d, ^3J = 6 Hz) ; 0.91 (3H, d, ^3J = 6 Hz). ^{13}C NMR ($CDCl_3$) : δ : 155.5 (CO) ; 76 and 61.5 (CH) ; 42 (CH_2) ; 24.5 (CH) ; 24, 22 and 21 (CH_3). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12 ; H, 9.61 ; N, 8.90. Found : C, 61.26 ; H, 9.78 ; N, 8.76.

***Trans*-(4S,5S)-4-butyl-5-methyloxazolidin-2-one, 8bI :**

Pale yellow oil. Yield : 87%. Rf = 0.41 (Et_2O/hex/MeOH, 5/4/1). $[\alpha]_D^{25}$ = -28 (c=1.52, $CHCl_3$). IR (CCl_4) 3250, 1750. ^1H NMR 500 MHz ($CDCl_3$) δ : 6.60 (1H, bs) ; 4.26 (1H, quint, ^3J = 6 Hz) ; 3.36

(1H, q, ^3J = 6 Hz) ; 1.52 (2H, q, ^3J = 6 Hz) ; 1.39 (3H, d, ^3J = 6 Hz) ; 1.32 (4H, m) ; 0.89 (3H, t, ^3J = 6 Hz). ^{13}C NMR ($CDCl_3$) : δ : 160 (CO) ; 79 and 60 (CH) ; 34.5, 27.5 and 22.5 (CH_2) ; 20 and 14 (CH_3).

***Hydrogenolysis of hydrazines* 5aI *and* 5bI :**

Method 1 : Raney Nickel, previously rinsed with distilled water until pH 7, was added (2 spatulae) to a solution of the desired hydrazine (1.5 mmol) in EtOH or MeOH (10 mL). The mixture was then stirred in an autoclave at the desired temperature and under the desired pressure of H_2 for the desired amount of time. After filtration the catalyst was carefuly rinsed with EtOH or MeOH. The joined filtrates were concentrated *in vacuo* and the crude products were then analyzed by ^1H NMR.

Method 2 : As in method 1 but Raney Nickel was replaced by PtO_2 and 1% (in volume) of AcOH was added.

***Syn* (1*S*,2S) 1-isobutyl-2-benzyloxy-propylamine, 6aI :**

Pale yellow oil. Yield 87%. $[\alpha]_D^{25}$ = +17 (c=2.16, $CHCl_3$). Rf = 0.67 (Et_2O/hex, 4/6). IR (CCl_4) 3340. ^1H NMR ($CDCl_3$) δ : 7.3 (5H, m) ; 4.55 (2H, AB, ^2J = -11.5 Hz, Δν = 41 Hz) ; 3.28 (1H, quint, ^3J = 6 Hz) ; 2.74 (1H, q, ^3J = 6 Hz) ; 1.73 (1H, m) ; 1.23 (2H, t) ; 1.19 (3H, d, ^3J = 6 Hz) ; 0.91 (3H, d, ^3J = 7 Hz) ; 0.88 (3H, d, ^3J = 7Hz). ^{13}C NMR ($CDCl_3$) δ : 139 (C), 128.5, 128 and 127.5 (CH), 79.5 (CH), 71 (CH_2), 54 (CH), 43 (CH_2), 24.5 (CH), 24, 22 and 16 (CH_3). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97 ; H, 10.39. Found : C, 75.43 ; H, 10.61.

***Syn* (1*S*,2*S*) 1-butyl-2-benzyloxy-propylamine, 6bI**

Colourless oil. Yield : 89%. $[\alpha]_D^{25}$ = +26 (c=2.08, $CHCl_3$). IR (CCl_4) 3320. ^1H NMR ($CDCl_3$) : δ : 7.3 (5H, m) ; 4.50 (2H, AB, ^2J = -11.5 Hz, Δν = 40 Hz), 3.30 (1H, quint, ^3J = 6 Hz) ; 2.64 (1H, broad) ; 1.18 (6H, b m) 1.16 (3H, d, ^3J = 6 Hz) ; 0.88 (3H, bt). ^{13}C NMR ($CDCl_3$) : δ : 139 (C), 128.5, 128 and 127.5 (CH), 79 (CH), 71 (CH_2), 56 (CH), 33.5, 28.5 and 23 (CH_2) ; 16 and 15 (CH_3).

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