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Enantiomerically pure β,γ-epoxyesters from β-hydroxylactones: synthesis of β-hydroxyesters and (–)-GABOB.

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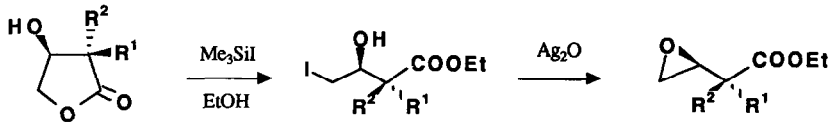
Abstract: *The preparation of enantiomerically pure β,γ-epoxyesters was achieved by chemoselective opening of β-hydroxybutanolides with trimethylsilyliodide followed by cyclisation of the resulting iodohydrins with silver oxide. The reaction of these epoxyesters with lithio or magnesiocuprates afforded stereochemically pure α-substituted β-hydroxyesters. Alternatively, (-)-GABOB was synthesized in optically pure form from the iodohydrin 2'a.*

Optically active epoxydes are very valuable synthetic intermediates due to their great facility to give both electrophilic and nucleophilic opening and to allow the access to chiral building-blocks possessing several chiral centers. They may be obtained by asymmetric epoxydation, by modification of natural products from the "chiral pool" [1] or by microbial reactions.[2] All these methods were applied with success to the preparation of α-functionalized epoxydes but frequently failed when applied to β-functionalized substrates. For example, the asymmetric epoxydation of homoallylic alcohols gives low enantiomeric excesses[3], and the resolution of racemic β,γ-epoxyesters by lipases or esterases is not general enough.[4]

We want to report here an efficient chemical method to prepare β,γ-epoxyesters based on the chemoselective opening of β-hydroxylactones followed by a basic cyclisation of the intermediate iodohydrines.[5]

β-hydroxybutanolides **1a** are easily obtained in R or S form from malic, aspartic and ascorbic acid,[6] or by microbial reduction of β-ketoesters.[7] They may be stereoselectively alkylated into the trans lactones **1b** or **1'b**.[8] Moreover, the cis isomer **1c** is available from the microbial reduction of α-methyl β-ketoester.[9]



1 **2** **3**

1' = ent-1 **2' = ent-2** **3' = ent-3**

a $R^1 = R^2 = H$ b $R^1 = H, R^2 = CH_3$ c $R^1 = CH_3, R^2 = H$

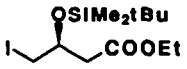
These lactones are very valuable precursors for the synthesis of epoxyester 3. Indeed, it is well-known that in the reaction of lactones with trimethylsilyl iodide the former undergoes mild cleavage of the carbone-oxygen bond to provide the corresponding iodoalkylcarboxylic acids after hydrolytic work-up.[10] This reaction is catalyzed by hydroiodic acid and it was shown that in some cases, by operating in the presence of alcohol, it was possible to isolate ω-iodocarboxylic ester.[11]

Upon reacting the lactones 1 in the presence of an excess of ethanol we succeeded in obtaining iodohydrines 2 without any protection of the free hydroxy function. Although alcohols are prone to further transformation into iodides with TMSI, we never observed the presence of diiodocompounds and the iodohydrines were isolated in about 80 % yield.[12] With trimethylsilyl bromide, however, yields decreased slightly (65 %).

The cyclisation of these iodohydrines was rather difficult to control. Indeed, the epoxy esters 3 are very sensitive to basic medium due to their great ability to isomerize into α,β-unsaturated γ-hydroxy ester. For example, the reaction with sodium carbonate affords total isomerisation in less than five minutes. In accordance with previous results[13], the most effective reagent was silver oxide (cf. Table 1). By operating in glyme at 80°C for four hours, we succeeded in obtaining the epoxyde 3 in 77 % yield. By comparison, the cyclisation of the silyl protected iodohydrine **4a** using anhydrous tetrabutylammonium fluoride in THF gives only a 55 % yield.

Table I: Cyclisation of iodohydrines **2a**

Reagent	Solvent	T°C	Yield %
Li_2CO_3	EtOH	50	no reaction
Cu_2O	diglyme	130	10
CH_3COOAg	THF	50	65
Ag_2O	glyme	85	77

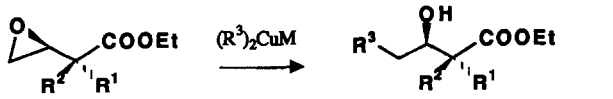


4a

The enantiomeric purity of the epoxyesters was checked by NMR with chiral shift reagents. However the method is not accurate enough and we prefered to measure the enantiomeric excesses by chiral VPC on the β-hydroxyesters obtained after opening with cuprates (vide infra). These excesses were in all cases better than 99 %.

Indeed, the β-hydroxyesters are important synthetic intermediates and enantiomerically pure β-hydroxybutanoates have been used as building-blocks for the synthesis of a wide variety of compounds.[14] However, the obtention of a stereochemically well-defined form of α-substituted β-hydroxyesters is not very easy. Besides the asymmetric aldol condensation, they may be obtained by the enantioselective ruthenium catalyzed reduction of β-keto esters (a reaction which has to be conducted under high pressure)[15] or by microbial reactions such as the resolution of racemic β-hydroxyesters (as *t*-Butyl esters)[16] or the microbiological reduction of α-methyl β-ketoesters.[17]

Alternatively, the reaction of homocuprates with the β,γ-epoxy esters previously described would furnish a very attractive method to prepare these β-hydroxy esters. Since the pioneering work of Johnson, cuprates are well-known to be the best carbon nucleophiles to achieve the opening of epoxides.[18] Despite their great sensitivity to basic media, β,γ-epoxyesters react very readily with lithiocuprates in ether or even with magnesiocuprates in THF to afford β-hydroxyesters in good yields (cf. Table 2).



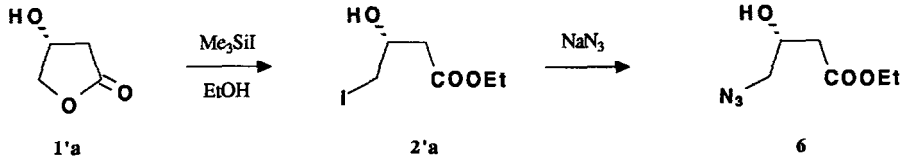
3 5 5' = ent-5

Table 2

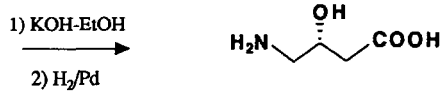
	M	R^3	Solvent	5 yield%	$[\alpha]_D^{20}$, c MeOH	
3a	Mg	C_2H_5	THF	73	-6.0°(3.1)	3R
3a	Li		ether	81	-7.1° (3.3)	3R
3'a	Li	n C_4H_9	ether	80	2.5° (1.9)	3S
3b	Mg	CH_3	THF	82	15.3° (2.8)	2S,3R
3'b	Li		ether	92	-28.8° (3.3)	2R,3S

As expected from previous results with glycidic esters[18d], cuprates afford exclusive attack on the less substituted carbon atom to give the β-hydroxyesters only. The enantiomeric purity was retained during the course of the reaction as indicated by VPC analysis of the derived isopropyl carbamates (XE60, S-Valine-α-phenylethylamide).[19]

A direct application of the hydroxylactones opening was found in the synthesis of (R)-γ-amino-β-hydroxy butanoic acid (GABOB). (R)-GABOB **7** is a compound of great pharmacological importance because of its biological function as a neuro mediator in the mammalian central nervous system and it has been shown to have a greater biological activity than its (S)-isomer.[20] The R isomer has been obtained by resolution of racemates[21] or by chemical modification of substances from the "chiral pool" such as ascorbic acid[20a,22], malic acid[23], hydroxyproline[24] and β-pinene[25]. It was also synthesized by chemoenzymatic methods by using a microbial hydrolysis[26] or a yeast reduction[27] as the enantioselective step.. Most of these previous synthesis were rather long and tedious and optical purities were not always satisfactory.



1'a **2'a** **6**



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The opening of the hydroxylactone **1'a** furnishes a very direct access to (R)-GABOB. Indeed, 4-halogeno-3-hydroxyesters are the direct precursors of GABOB and carnitine (the quaternary ammonium salt derived from GABOB).[3,28]

By substitution of iodine with sodium azide in water, we obtained the azidoester **6** in nearly quantitative yield. Catalytic hydrogenation of this ester did not furnish the required aminoester but afforded the corresponding cyclic lactame. However, GABOB **7** may be obtained in very good yield by saponification of the ester function followed by catalytic hydrogenation of the resulting azidoacid. In this manner, (-)-GABOB was obtained from the hydroxylactone ent-**1a** in a total yield of 56 %. The enantiomeric excess of the azide **6** was measured as >99% by HPLC of the Mosher derivatives[29] and we can assume that GABOB thus obtained is enantiomerically pure.

In conclusion, the above sequence is a practical alternative to the existing methods.

EXPERIMENTAL

Products were purified by distillation or by medium pressure liquid chromatography on a Jobin-Yvon Modulprep (Kieselgel 60H Merck) or by flash chromatography (Kieselgel 60 Merck: 230-400 Mesh; solvent : cyclohexane/ ethyl acetate) and analyzed by gas chromatography (10% SE30, 3m column or 10% SE52, 3m column) or by thin layer chromatography (silicagel 60F 254). Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ^{1}H-NMR spectra were recorded on a Bruker WP 80 or on a Bruker AM at 250 MHz for ^{1}H and 100.56 MHz for ^{13}C. Deuterochloroform was used as solvent with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer 599. Mass spectra were recorded on a Nermag R 10-10 (fitted with a VPC-mass coupling; column: CP Sil 5-40m).

- **(2S,3S)-2-methyl-3-hydroxy-4-butanolide 1b**

To diisopropylamine (1.23 g, 0.122 mol) at 0°C in THF (200 ml) under argon was added *n*-BuLi (2.2 M in hexane, 55 ml). The solution was stirred at room temperature for 30 minutes, cooled at -100°C and a solution of (S)-3-hydroxy-4-butanolide[6] (5 g, 49 mmol) in THF (120 ml) was added. After 45 minutes methyliodide (9.2 ml, 0.147 mol) in THF (100ml) was added and the solution was stirred at -100°C for two days and quenched with a saturated ammonium chloride solution. THF was evaporated *in vacuo* and the products were extracted with ether. The combined organic phases were dried ($MgSO_4$) and the solvent evaporated. The resulting oil was subjected to flash chromatography (cyclohexane/AcOEt : 2/8) to give **1b** (3.7 g, yield : 65 %). Bp 163-165°C/15 mm. IR (neat) ν = 3450 (OH) ; 1765 (C=O). ^{1}H NMR: 1.52 (d, 3H, J=7.5 Hz, C$\underline{H}_3$-CH)) ; 2.58 (dq, 1H, J=7.5 and 5.5 Hz, C$\underline{H}$-CH$_3$) ; 3.12 (s,1H, CHO$\underline{H}$) ; 4.10 (dd, 1H, J=10.0 and 5.0 Hz, CH$_2$-O) ; 4.30 (m, 1H, C$\underline{H}$OH) ; 4.50 (dd, 1H, J=10.0 and 6.0 Hz, CH$_2$-O). ^{13}C NMR: 12.85 ; 43.15 ; 73.47 ; 75.02 ; 179.38 ; MS : m/z 116 (3) ; 98 (4) ; 58 (64) ; 57 (100) ; 55 (14). Anal. calc for $C_5H_8O_3$: C, 51.72 H, 6.94 ; found : C, 51.90 H, 6.85. $[\alpha]_D^{20}$ - 58° (c=2.87 MeOH) ee > 97 % (by HPLC on the Mosher's esters).

- **(2R,3R)-2-methyl-3-hydroxy-4-butanolide 1'b**

The method was as described for **1b** using (R)-3-hydroxybutanolide. $[\alpha]_D^{20}$ 58.2° (c=2.93, MeOH).

- **(2S,3R)-2-methyl-3-hydroxy-4-butanolide 1'c**

Methyl 4-O-benzyl-2-methyl-3-hydroxybutanoate[9] (1.78 g, 7.5 mmol) in absolute ethanol (20 ml) was stirred under hydrogen with palladium on charcoal (10 %) for 12 hours. After filtration, solvent was evaporated *in vacuo* and the crude product diluted in CH_2Cl_2 (10 ml) was heated at 50°C for 3 hours with a small amount (3 drops) of trifluoroacetic acid. The solution was stirred with Na_2CO_3 and the solvent evaporated *in vacuo*. The resulting oil was subjected to flash chromatography (cyclohexane/AcOEt 3/7) to give the lactone **1'c** (680 mg, yield 83 %). Bp 115°C/0.1 mm IR (neat) ν=3430 (OH) ; 1765 (CO). ^{1}H NMR: d 1.28 (d, 3H, J=7 Hz, C$\underline{H}_3$-CH) ; 2.6-2.8 (m, 2H, OH and C$\underline{H}$-CH$_3$) ; 4.36 (2H, m, CH$_2$O) ; 4.6 (m, 1H, CHOH). ^{13}C NMR: 7.71 ; 40.09 ; 69.68 ; 74.54 ; 179.85. Anal. calc for $C_5H_8O_3$: C, 51.72 H, 6.94 ; found : C, 51.59 H, 6.98. $[\alpha]_D^{20}$ 77.8 (c=3.35, MeOH) ; ee 96 % (by HPLC on the Mosher's esters).

- **Ethyl (S)-3-hydroxy-4-iodobutanoate 2a**

To (S)-3-hydroxy-4-butanolide (2.5 g, 24 mmol) and absolute ethanol (3.4 g, 73 mmol) in methylene chloride (100 ml) under argon was slowly added freshly distilled trimethylsilyliodide (5.25 ml, 37 mmol). After stirring for a night, solvent was evaporated *in vacuo* and the residue was dissolved in ether. The solution was washed with sodium thiosulfate and evaporated. The resulting oil was subjected to flash chromatography (cyclohexane/AcOEt 75/25) to give **2a** as a colourless oil (5.4 g; yield 80 %). IR (neat) ν = 3500 (OH) ; 1725 (CO). ^{1}H NMR: d 1.3 (t, 3H, J=7 Hz, -CH$_2$C$\underline{H}_3$) ; 2.6 (d, 2H, CH$_2$CO) ; 3.0 (br, 1H, OH) ; 3.35 (d, 3H, J=7Hz, CH$_2$I) ; 4.0 (m, 1H, CHO) ; 4.17 (q, 2H, J=7 Hz, OCH$_2$). Anal. calc. for $C_6H_{11}IO_3$: C, 27.93 H, 4.18 ; found : C, 28.00 H, 4.22. $[\alpha]_D^{20}$ -10.7° (c=3.0, EtOH).

- **Ethyl (R)-3-hydroxy-4-iodobutanoate 2'a**

The method was as described for **2a** using (R)-hydroxy-4-butanolide. $[\alpha]_D^{20}$ 10.2° (c = 3.3, EtOH).

- **Ethyl (2S,3S)-3-hydroxy-4-iodo-2-methylbutanoate 2b**

The method was as described for **2a** using lactone **1b** (1.14 g, 10 mmol). Flash chromatography gave 2.1 g (yield: 78 %). IR (neat) ν = 3480 (OH) ; 1725 (CO). ^{1}H NMR: 1.2 (d, 3H, J=7 Hz, CH$_3$) ; 1.3 (t, 3H, CH$_2$CH$_3$) ; 2.7 (m, 1H, CHCH$_3$) ; 2.8 (br, 1H, OH) ; 3.2 (d, 3H, CH$_2$I) ; 3.95 (m, 1H, CHO) ; 4.1 (q, 2H, O-CH$_2$). Anal calc. for $C_7H_{13}IO_3$: C, 30.90 H, 4.82 ; found : C, 31.00 H, 4.82. $[\alpha]_D^{20}$ 22.8° (c=3.3, MeOH).

- **Ethyl (2R,3R)-3-hydroxy-4-iodo-2-methylbutanoate 2'b**

The method was as described for **2a** using (2R,3R)-lactone **1'b**. $[\alpha]_D^{20}$ -21.8° (c = 2.9, MeOH).

- **Ethyl (2S,3R)-3-hydroxy-4-iodo-2-methylbutanoate 2'c**

The method was as described for **2a** using (2S,3R)-lactone **1'c**. Anal. calc. for $C_7H_{13}IO_3$: C, 30.90 H, 4.82 found : C, 30.82 H, 4.76. $[\alpha]_D^{20}$ 16.3° (c = 4.4, MeOH).

Preparation of ethyl epoxybutanoates 3 and 3'

Iodohydrines **2** (33 mmol) and Ag_2O (34 mmol) were refluxed in monoglyme (100 ml) for 8 hours. After filtration, the solvent was distillated to give pure epoxydes after chromatography on silicagel.

- **Ethyl (S)-3,4-epoxybutanoate 3a**

From **2a** (8.5 g, 33 mmol), 3.26 g (yield 77 %) were isolated. IR (neat) ν = 1730 (CO) ; 1265 and 1180 (C-O-C) ; ^{1}H NMR (250 MHz): 1.3 (t, 3H, J=7.0 Hz, OCH$_2$C$\underline{H}_3$) ; 2.58 (d, 2H, J=5 Hz, CH$_2$CO) ; 2.62 (d, 1H, J=5.0 Hz, CH$\underline{H}$O) , 2.90 (dd, 1H, J=5.0 and 5.2 Hz, C$\underline{H}$HO) ; 3.32 (m, 1H, OCH) ; 4.22 (q, 2H, J=7.0 Hz, OC$\underline{H}_2$CH$_3$). MS : m/z 130 (3) ; 99 (100) ; 86 (60) ; 71 (80); 57 (51). $[\alpha]_D^{20}$ -25.3° (c=3.7, MeOH). calc. for $C_6H_{10}O_3$: C, 55.37 ; H, 7.75 ; found C, 55.20 ; H, 7.83.

- **Ethyl (R)-3,4-epoxybutanoate 3'a**

From **2'a** (8.5 g, 33 mmol), 3.2 g (yield 76 %) were isolated $[\alpha]_D^{20}$ 24.7° (c=3.93, MeOH).

- **Ethyl (2S,3S)-3,4-epoxy-2-methylbutanoate 3b**

From **2b** (8.16 g, 30 mmol) 3.45 g (yield 80 %) were isolated. IR (neat) ν = 1735 (CO) ; 1265 and 1175 (C-O-C) ; ^{1}H NMR (250 MHz): 1.32 (t+d, 6H, J=7.0 and 7.0 Hz, $OCH_2\underline{CH_3}$ + CH_3) ; 2.32 (m, 1H, CHCO) ; 2.70 (dd, 1H, J=2.5 and 5.0 Hz, C<u>H</u>HO) ; 2.88 (dd, 1H, J=5.0 and 5.0 Hz, CH<u>H</u>O) ; 3.12 (m, 1H, OCH) ; 4.22 (q, 2H, J=7.0 Hz, $OC\underline{H_2}CH_3$). $[\alpha]_D^{20}$ 24.9° (c=3.3, MeOH). Anal. calc. for $C_7H_{12}O_3$: C, 58.31 H, 8.39; found : C, 58.72 H, 8.68.

- Ethyl (2R,3R)-3,4-epoxy-2-methylbutanoate 3'b

From **2'b** (8.16 g, 30 mmol) 3.35 g (yield 78 %) were isolated. $[\alpha]_D^{20}$ -22° (c=3.9, MeOH).

- Ethyl (2S,3R)-3,4-epoxy-2-methylbutanoate 3'c

From **2'c** (6.8 g, 25 mmol) 2.56 g (yield 71 %) were isolated. IR (neat) ν = 1730 (CO) ; 1270 and 1170 (C-O-C) ; ^{1}H NMR: 1.23 (d, 3H, J=7.0 Hz, $\underline{CH_3}CH_2O$) ; 1.30 (t, 2H, J=7.0 Hz, CH_3) ; 2.38 (m, 1H, CHCO) ; 2.58 (dd, 1H, J=3.0 and 5.0 Hz, C<u>H</u>HO) ; 2.83 (dd, 1H, J=4.0 and 5.0 Hz, CH<u>H</u>O) ; 3.02 (m, 1H, OCH) ; 4.24 (q, 2H, J=7.0 Hz, $OC\underline{H_2}CH_3$). ^{13}C NMR 12.88 ; 14.15 ; 42.50 ; 45.40 ; 52.93 ; 60.80 ; 173.84. Anal. calc. for $C_7H_{12}O_3$: C, 58.31 H, 8.39 ; found : C, 58.42 H, 8.31. $[\alpha]_D^{20}$ 27.0° (c=4.25, MeOH).

Preparation of β-hydroxyesters 5

-Ethyl (R)-3-hydroxyhexanoate

To a suspension of CuI (418 mg, 2.2 mmol) in a mixture of THF (6 ml) and ether (12 ml) is added at -60°C a 0.8M THF solution of EtMgBr (5.5 ml, 4.4 mmol). After 1h at -30°C epoxyde **3a** (260 mg, 2 mmol) dissolved in a 1/1 (v/v) mixture of THF and ether (8 ml) is added at -45°C and reacted for 1 h at -30°C. The mixture was then hydrolyzed with aqueous ammoniacal ammonium chloride (conc. NH_4OH/sat. NH_4Cl : 1/1 v/v) until a clear ethereal layer and a deep blue aqueous layer formed (30 min). After extraction, the ethereal layer was washed with saturated NH_4Cl, dried ($MgSO_4$) and concentrated to afford after flash chromatography (cyclohexane/AcOEt 85/15) 233 mg of pure product (yield 73 %). Bp 101-104°C/14 mm. IR (neat) ν = 2970 (OH) and 1735 (CO) ; ^{1}H NMR: (250 MHz) 0.94 (t, 3H, J=7.0 Hz, $\underline{CH_3}$-CH_2) ; 1.3 (t, 3H, J=7.5 Hz, $\underline{CH_3}$-CH_2-O) ; 1.46 (m, 4H, CH_2-CH_2) ; 2.42 (dd, 1H, J=9.0 and 16.5 Hz, C<u>H</u>H) ; 2.54 (dd, 1H, J=3.5 and 16.5 Hz, CH<u>H</u>) ; 2.95 (br, 1H, OH) ; 4.06 (m, 1H, C<u>H</u>OH) ; 4.2 (q, 2H, J=7.0 Hz, $OC\underline{H_2}$-CH_3). ^{13}C NMR: 13.74 ; 13.94 ; 18.47 ; 38.50 ; 41.29 ; 60.40 ; 67.52 ; 172.83. MS : m/z 161 (M+1). $[\alpha]_D^{20}$ -6.0° (c=3.1, MeOH).Anal. calc. for $C_8H_{16}O_3$: C, 59.97 H, 10.06 ; found : C, 59.67 H, 10.74.

- Ethyl (2S,3R)-3-hydroxy-2-methylpentanoate

Similarly, 262 mg of ethyl (2S,3R)-3-hydroxy-2-methylpentanoate were obtained from the reaction of the epoxyde **3b** (288 mg, 2 mmol) with magnesium dimethylcuprate (yield 82 %). Bp 91-94°C/9 mm ; IR (neat) ν = 2980 (OH) ; 1735 (CO) ; ^{1}H NMR (250 MHz): 0.98 (t, 3H, J=7.0 Hz, $\underline{CH_3}$-CH_2-C) ; 1.20 (d, 2H, J=7.0 Hz, $\underline{CH_3}CH$) ; 1.29 (t, 3H, J=7.0 Hz, $\underline{CH_3}$-CH_2O) ; 1.48 (m, 2H, $CC\underline{H_2}$-CH-) ; 2.56 (qd, 1H, J=3.5 and 7.0 Hz, C<u>H</u>-CH_3) ; 2.6 (br, 1H, OH) ; 3.84 (m, 1H, C<u>H</u>OH) ; 4.2 (q, 2H, J=7.0 Hz, CH_3-$C\underline{H_2}O$). ^{13}C NMR: 10.20 ; 10.57 ; 14.00 ; 26.68 ; 43.88 ; 60.42 ; 75.09 ; 178.00. MS : m/z 161 (M+1) ; 102 ; 74 ; 57 ; 56. $[\alpha]_D^{20}$ 15.3° (c=2.8, MeOH). Anal. calc. for $C_8H_{16}O_3$: C, 59.97 H, 10.06 ; found : C, 59.28 H, 9.74.

-Ethyl (R)-3-hydroxy-6-methylhept-5-enoate

To a suspension of CuI (418 mg, 2.2 mmol) in anhydrous ether (12 ml) under argon at -50°C is added an ether solution of 2-methyl propenyllithium 0.5 M (8.8 ml, 4.4 mmol). After 1 hour at -35°C, the epoxyde **3a** (260 mg, 2 mmol) dissolved in ether (5 ml) is added and the mixture is stirred for 1 hour at -30°C. It was hydrolyzed with aqueous ammoniacal ammonium chloride (conc NH_4OH/sat. NH_4Cl : 1/1 v/v) for 30 min. After extraction, the ethereal layer is concentrated to afford after flash-chromatography (cyclohexane/AcOEt 8/2) 301 mg of a clear oil (yield 81 %). Bp 117-119°C/9 mm ; IR (neat) ν = 2980 (OH); 1735 (C=O) ; 980 (C=C) ; ^{1}H NMR: (250 MHz) 1.3 (t, 3H, J=7.0 Hz, $\underline{CH_3}CHO$) ; 1.65 (s, 3H, CH_3) ; 1.76 (d, 3H, J=1.0 Hz, CH_3) ; 2.26 (m, 2H, CH_2) ; 2.42 (dd, 1H, J=9.0 and 16.5 Hz, C<u>H</u>H) ; 2.56 (dd, 1H, J=3.0 and 16.5 Hz, CH<u>H</u>) ; 2.90 (br, 1H, OH) ; 4.07 (m, 1H, C<u>H</u>OH) ; 4.20 (q, 2H, J=7.0 Hz, $CH_3C\underline{H_2}O$) ; 5.2 (m, 1H, CH). ^{13}C NMR: 13.92 ; 17.67 ; 25.61 ; 35.09 ; 40.56 ; 60.37 ; 68.01 ; 119.25 ; 134.60 ; 172.68. MS : m/z 186. $[\alpha]_D^{20}$ -7.1° (c=3.3, MeOH). Anal. calc. for $C_{10}H_{18}O_3$: C, 64.49 H, 9.74; found : C, 64.29 H, 9.89.

-Ethyl (S)-3-hydroxyoctanoate

Similarly, from the reaction of the epoxyde **3'a** (260 mg, 2 mmol) and lithium dibutylcuprate 308 mg of a clear oil were isolated (yield 82 %). Bp : 117-119°C/9 mm ; IR (neat) ν = 2985 (OH), 1735 (CO) ; ^{1}H NMR: (250 MHz): 0.9 (m, 3H, $\underline{CH_3}CH_2C$), 1.3 (t, 3H, J=7.0 Hz, $\underline{CH_3}CH_2O$), 1.40 (m, 8H, $(\underline{CH_2})_4CH_3$), 2.41 (dd, 1H, J=9.0 and 16.5 Hz, C<u>H</u>H), 2.54 (dd, 1H, J=3.0 and 16.5 Hz CH<u>H</u>), 3.0 (br, 1H, OH), 4.04 (m, 1H, C<u>H</u>OH), 4.2 (q, 2H, J=7.0 Hz, CH_3-$C\underline{H_2}O$). ^{13}C NMR 13.88, 14.03, 22.46, 25.03, 31.59, 36.38, 41.26, 60.51, 67.90, 172.98 ; MS : m/z 189 (M+1). $[\alpha]_D^{20}$ 2.5° (c=1.9, MeOH) ; Anal. calc. for $C_{10}H_{20}O_3$: C, 63.79 H, 10.70 ; found : C, 63.36 H, 10.33.

-Ethyl (2R,3S)-3-hydroxy-2-methyldec-5-enoate

From the reaction of the epoxyde **3'b** (195 mg, 1.5 mmol) and lithium (Z)-hex-1-enyl cuprate[30], 300 mg of an oil were isolated (yield92%). Bp 140-142°C/10 mm ; IR (neat) ν = 2970 (OH), 1730 (CO) ; 980 (C=C) ; ^{1}H NMR (250 MHz): 0.96 (m, 3H, $\underline{CH_3}(CH_2)_3$) ; 1.28 (d, 2H, J=7.0 Hz, $\underline{CH_3}CH$) ; 1.34 (t, 3H, J=7.0 Hz, $\underline{CH_3}CH_2O$) ; 1.40 (m, 4H, $(\underline{CH_2})_2CH_3$) ; 2.02 (m, 2H, $C\underline{H_2}CH$) ; 2.22 (m, 2H, $CH\underline{CH_2}$) ; 2.62 (qd, 1H, J=4.0 and 7.0 Hz, C<u>H</u>CH_3) ; 2.7 (br, 1H, OH) ; 4.0 (m, 1H, CHOH) ; 4.24 (q, 2H, J=7.0 Hz, $CH_3C\underline{H_2}O$) ; 5.46 (m, 1H, CH) ; 5.62 (m, 1H, CH). ^{13}C NMR ($CDCl_3$) : 10.78 ; 13.80 ; 14.00 ; 22.19 ; 26.99 ; 31.79 ; 31.83 ; 43.60 ; 60.43 ; 71.48 ; 124.55 ; 133.04 ; 175.89. MS: m/z 229 (M+1). $[\alpha]_D^{20}$ -28.8° (c=3.29, MeOH). Anal. calc. for $C_{13}H_{24}O_3$: C, 68.38 H, 10.59 ; found : C, 68.23 H, 10.67.

Ethyl (R)-4-azido-3-hydroxybutanoate 6

To iodhydrine **2'a** (1g, 3.8 mmol) in acetonitrile (10 ml) and water (2 ml) was added sodium azide (1.0 g, 15.5 mmol). The solution was stirred at 80°C for six hours. Solvent was evaporated *in vacuo* and the residue was extracted with ether. After flash chromatography (cyclohexane/AcOEt 7/3) a pale yellow oil was isolated (670 mg, yield 100 %). IR (neat) ν = 3450 (OH) ; 2090 (N_3) ; 1730 (CO). ^{1}H NMR: 1.35 (t, 3H, J=7.0 Hz, CH_3) ; 2.58 (d, 2H, J=6.0 Hz, $COCH_2$) ; 3.38 (d, 2H, J=5.0 Hz, CH_2N_3) ; 3.45 (s, 1H, OH) ; 4.2 (m, 3H, CH_2O and CHO). $[\alpha]_D^{20}$ 7.4° (c=4.05, MeOH). ee > 99 % (measured by

HPLC after esterification of the hydroxyl function with (R)-Mosher's acid chloride). Anal. calc. for $C_6H_{11}N_3O_3$: C, 41.61 H, 6.40 N, 24.27 ; found: C, 41.81 H, 6.27 N, 24.40.

(R)-4-azido-3-hydroxybutanoic acid

To azide **6** (580 mg, 3.35 mmol) in water (5 ml) and ethanol (10 ml) was added solid potash (0.56 g, 10 mmol). After stirring for a night, ethanol was evaporated *in vacuo* and the residue was extracted with ether. After acidification with 3N HCl, water was evaporated *in vacuo* and the residue was dissolved in AcOEt. The solution was dried and evaporated to give an oil (490 mg, quantitative yield). IR (neat) ν = 3500 (OH) ; 2100 (N_3) ; 1730 (CO). ^1H NMR: 2.58 (d, 2H, J=6.0 Hz, CH_2CO) ; 3.35 (d, 2H, J=5.0 Hz, CH_2N_3) ; 4.18 (m, 1H, CHO) ; 6.6 (br, 2H, OH and COOH). $[\alpha]_D^{20}$ 3.02° (c=2.55, MeOH).

(R)-4-amino-3-hydroxybutanoic acid ((-)-GABOB)

To the acid (435 mg, 8 mmol) in methanol (9 ml) and water (1 ml) was added palladium on charcoal (10 %, 60 mg). The suspension was stirred under hydrogen for 5 hours. After filtration and evaporation under reduced pressure, the thick yellow oil was dissolved in a small amount of water. Dilution with absolute alcool provided 270 mg of white crystals (yield 75 %) which were recystallized from water-ethanol. m.p. 212°C. ^1H NMR (D_2O): d 2.7 (d, 2H, J=6.0 Hz, CH_2CO) ; 3.0-3.2 (m, 2H, NCH_2) ; 4.0-4.4 (m, 1H, CHO). $[\alpha]_D^{20}$ -20° (c=2.37, H_2O), (Lit.[23] 213-214°C ; $[\alpha]_D^{20}$ -20.5° (c=1.75, H_2O)).

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