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ASYMMETRIC SYNTHESIS OF *N*-METHYL-α-AMINO ESTERS FROM A GLYOXAL DERIVED CHIRAL HETEROCYCLE

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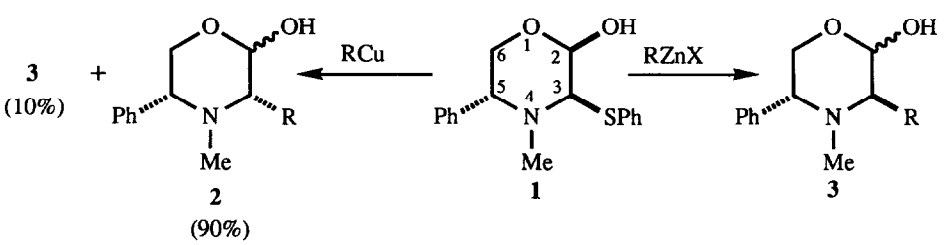
ABSTRACT- The reaction between a chiral template derived from glyoxal with organometallic reagents leads ultimately to the optically active title compounds The stereochemical outcome of the key-step which involves substitution of a thiophenol group depends on the organometallic predominantly inversion with alkyl copper or complete retention with alkyl zinc halides The stereodirecting effect of an allylic hydroxy group in an iminium intermediate is evidenced in the case of the organozinc reagent

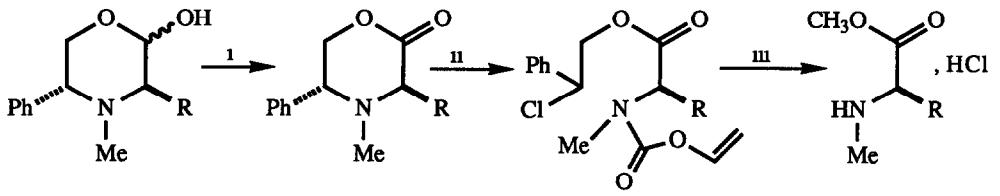
Of all the areas of asymmetric synthesis, the rapid expansion of that of α-aminoacids is self-evident The ever growing number of synthetically useful reactions involving these compounds as chiral inductors or building blocks[1] is a strong incitement for developing novel methods of synthesizing α-amino acids [2,3] In that respect we present here a synthesis of *N*-methyl-α-amino esters and *N*-methyl-β-amino alcohols [4] which exhibits two unusual features (i) glyoxal is enantioselectively functionalized, (ii) the stereochemistry of the overall process depends on the nature of an organometallic reagent

This synthesis belongs to a clearly defined class of reactions asymmetric derivatization of glycine-cation equivalents [5] The chiral substrate used here is the morpholine derivative **1** resulting from a one-pot condensation between glyoxal, *N*-methyl-(*R*)-phenylglycinol and thiophenol in aqueous solution [6] Substitution of the thioether moiety of **1** by organometallic reagents occurs either with complete retention (organozinc reagents) or with predominant inversion (alkyl copper reagents) as shown in Scheme I



Scheme I

A sequence of well-documented reactions then transforms the above alkylated product into the *N*-methyl α-aminoesters (Scheme II) [7]



3 4 5 6

(i) $(COCl)_2$, DMSO, Et_3N, 60-80% (ii) CH_2=CHOCOCl, 80-90% (iii) HCl, MeOH, 90%

Scheme II

RESULTS

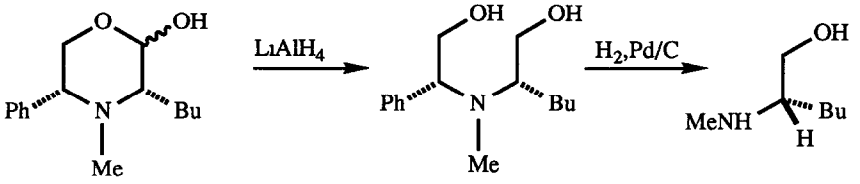
The key-step of the present asymmetric synthesis is the diastereoselective C-C bond formation resulting from reaction of compound **1** with organometallic reagents Actually substitution of acyclic amino thioethers by alkyl copper [8] and Grignard[9] reagents yielding amines has been reported but, to our knowledge, the stereochemical outcome of these reactions was not investigated Morpholine derivative **1** reacted with butylcopper and alkylzinc halides to give the corresponding hemiacetals **2** and **3** as shown in Table I Owing to ring-chain tautomerism, all hemiacetals were obtained as mixtures of epimers at C-2

Table I. Reactions of organometallic compounds with chiral compound 1

entry	organometallic reagent [a]	R	ratio of **2** **3**	yield %[b]
1	*n*-C_4H_9-Cu	*n*-Bu	90 10	50
2	*n*-C_4H_9-ZnI	*n*-Bu	<2 >98	56
3	*n*-C_3H_7-ZnI	*n*-Pr	<2 >98	80
4	*i*-C_4H_9-ZnI	*i*-Bu	<2 >98	55
5	CH_2=CH-ZnBr	CH_2=CH	<2 >98	78
6	CH_2=CH-CH_2-ZnBr	CH_2=CH-CH_2	46 54	69

[a] 4 equiv [b] Determined on isolated products

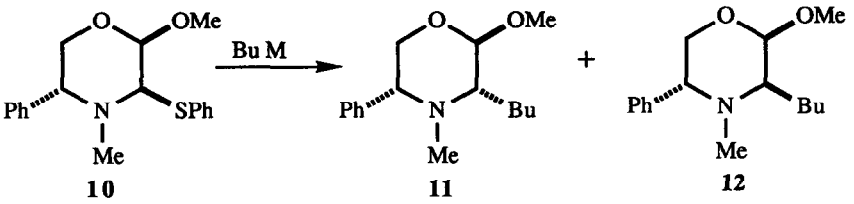
Stereochemistry at the new stereocenter in hemiacetals **3** was determined via conversion to the α–aminoesters **6** (see below) Hemiacetal **7** was obtained in a diastereoisomerically pure form by flash chromatography The resulting compound **7** (R =*n*-Bu) was transformed into the β-amino alcohol **9** (cf Scheme III) whose enantiomeric excess (>95%) and the absolute configuration (*S*) were established by chemical correlation with the aminoalcohol obtained by reduction of N-formyl-L-norleucine with $LiAlH_4$



7 8 9

Scheme III

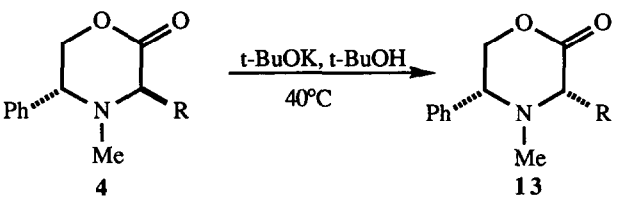
Reactions of the methyl acetal derivative **10** of compound **1** with butylzinc iodide and butylcopper are summarized in Scheme IV



	11	12
BuZnI	44%	56%
BuCu	90%	10%

Scheme IV

As shown on Scheme II, the mixture of epimeric hemiacetals **3** are transformed into tetrahydro oxazinones **4** which are diastereoisomerically pure in all cases except one (R=allyl, see entry 6 in Table I) Treatment of compounds **4** by potassium *t*-butoxide causes an almost complete epimerization at C-3 and yields the more stable diequatorial *cis* epimer **13** (Scheme V)



R	4 %de	13 %de
CH_2=$CHCH_2$	8	86
$CH_3CH_2CH_2$	>95	86

Scheme V

The final *N*-methyl aminoesters **6** were obtained from oxazinones **4** by treatment with vinyl chloroformate followed by an acid-catalyzed methanolysis of the intermediate carbamate **5** In the same way, the epimeric oxazinone **13** (R = allyl) led to *ent*-**6** Determination of the enantiomeric excess and abolute configurations were performed as follows (i) *R = n-Pr, i-Bu* chemical correlation with the corresponding *N*-methyl-α-amino esters made from commercially available amino acids and NMR spectroscopy on Mosher amide (ii) *R = vinyl, allyl* chemical correlations of the hydrogenated derivatives (H_2, Pd/C) with the corresponding *N*-methyl α-amino esters and NMR measurements on the Mosher derivatives *N*-Methyl-α-amino esters **6** (R = *n*-Pr, *i*-Bu) are enantiomerically pure and *ent*-**6** (R = allyl) shows a 86% ee, these enantiomeric excesses correspond to the diastereoisomeric excesses of the starting oxazinones **4** and **13** Steps ii and iii in Scheme II actually do not alter the stereochemistry of the substrate However this is not the case with the vinyl derivative **6** (R = vinyl) which was partly racemized during acidic methanolysis of carbamate **5** compound **6** (R = vinyl) was therefore obtained with a poor enantioselectivity (70% ee)

DISCUSSION

The dramatic difference of stereoselectivity which was observed during the diastereoselective C-C bond formation (Scheme I) according to the nature of the organometallic reagent clearly deserves a mechanistic interpretation The overall *inversion during substitution by butylcopper* can be accomodated by a S_N2-like process in which the thiophenyl moiety not only acts as a leaving group but also as a ligand for the metal atom The strong ability of sulfur compounds to coordinate on copper is well recognized,[10] it enhances the reactivity of the copper reagent towards a soft electrophilic center [11] The stereochemical outcome of such displacements is classically accomodated by a rate-determining nucleophilic attack on the carbon by copper (inversion), followed by reductive elimination (retention) [12]

It is worth mentioning that the use of lithium dibutyl cuprate instead of butylcopper failed contrary to a general feature in organocopper chemistry [13,14] In the present case this can be ascribed to reaction of the cuprate reagent with the hydroxy group of morpholinol **1** since alkylcopper compounds are known to be less basic than the corresponding cuprates [13,15] The fact that the hydroxy group in **1** is not instrumental to the thiophenyl displacement can also be deduced from Scheme IV (compare with entry 1 in Table I) Butylcopper shows the same stereoselectivity towards both the hemiacetal **1** and the derived methyl acetal **10**

On the other hand, a stereodirecting effect of the hydroxy group contributes to the *retention observed in the case of alkylzinc halides* (compare Scheme IV and entry 2 in Table I) Now an iminium ion intermediate **14** can account for the diastereoselectivity Formally resulting from the departure of phenylthiolate anion, this iminium ion is easily produced from the amino thioether precursor **1** owing to (i) an *internal assistance* by the nitrogen lone pair which is in a 1,2 *trans*-diaxial arrangement (Figure 1) with the SPh leaving group (kinetic anomeric effect [17]), (ii) an *external assistance* by a Lewis acid A (ZnX_2, RZnX, etc)

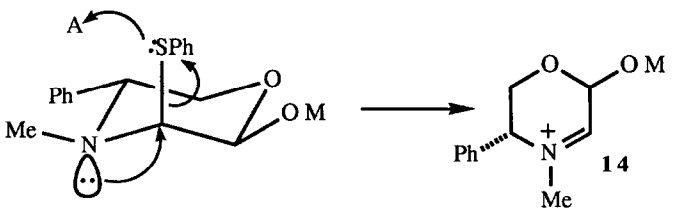
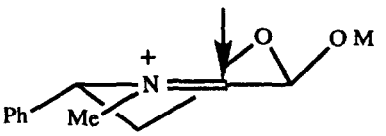


Figure 1

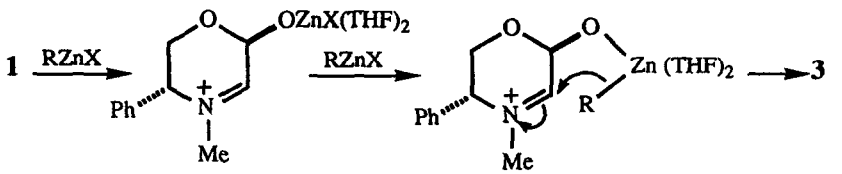
Stereochemistry of compounds **3** could therefore be ascribed to axial attack by nucleophilic organozinc halide following an antiperiplanar approach in relation to the nitrogen lone pair Hypotheses of these kind have frequently been advocated [18] for similar reactions but this feature was recently questioned [19] In the case at hand however, the axial attack (see Scheme VI) is strongly assisted by the hydroxy group (or more precisely by its metaloxy form, see below)[20] which is located in the suitable position Actually examples of such stereodirecting effects due to allylic hydroxy groups are so widely known [21,22] that collectively they constitute a new standard in organic synthesis [23]

No reaction of compound **1** with butylzinc iodide was observed when reactants are in 1 1 molar ratio an excess of organozinc reagent is mandatory for the reaction to occur The first equivalent of BuZnI reacts with hemiacetal **1** to generate a zinc alkoxide and a second organozinc molecule is needed to effect the alkylation



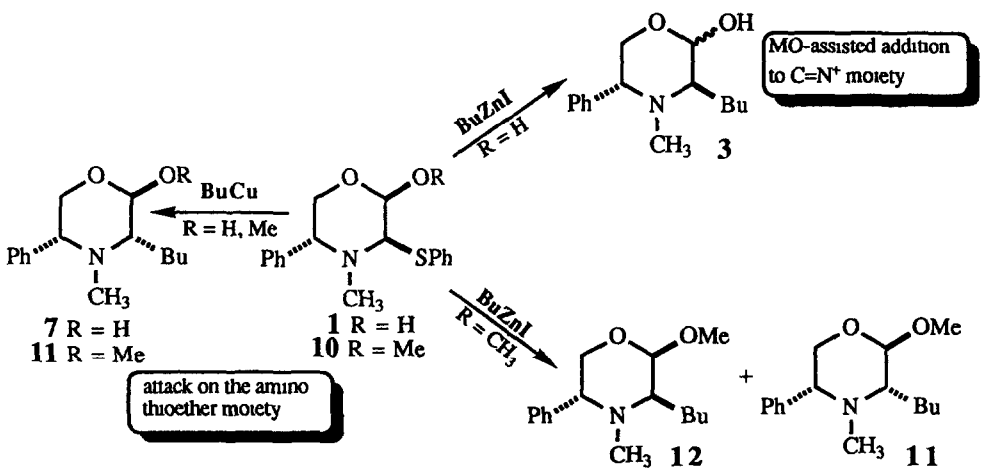
Scheme VI

This assumption is reminiscent of recent works by Noyori et al [24] reporting that alkylation of aldehydes by organozinc reagents, in the presence of a chiral ligand, proceeds via dinuclear zinc species Scheme VII tentatively rationalizes the above observations: i e., the *syn* attack of the double bond with respect to the HO group leading to an overall retention and the necessity of an excess of organozinc halide



Scheme VII

Scheme VIII resumes the differences of stereoselectivities in relation to the nature of the organometallic reagent and to the presence of a hemiacetal or an acetal moiety adjacent to the reactive amino thioether center



Scheme VIII

In contrast to the other alkylzinc halides, allylzinc bromide (entry 6 in Table I) reacted without stereoselectivity; this can be ascribed to the known reversibility [25] displayed by addition of such reagents on electrophilic double bonds (thermodynamic control) Nevertheless the base-catalyzed epimerization shown on Scheme V eventually led to *ent*-**6** (R = allyl) with a fair degree of enantioselectivity (86% ee)

Therefore, although starting from the same chiral substrate, either enantiomer of the α-amino ester can be synthesized via two different strategies (i) the choice of the organometallic reagent dictates the stereochemistry of the condensation (Scheme I) under kinetic control, (ii) epimerization of the intermediate oxazinone (Scheme V) allows a thermodynamic control of the overall process

EXPERIMENTAL SECTION

General comments

^1H , ^{13}C and ^{19}F NMR spectra ($CDCl_3$ solution unless otherwise stated) were respectively carried out on a Brucker AC 200 spectrometer at 200, 50 and 188 MHz , chemical shifts are reported in ppm downfield from TMS, unless otherwise stated Optical rotations were determined with a Perkin-Elmer 141 polarimeter Melting points were obtained with a Reichert apparatus (hot stage provided with a microscope) Mass spectra were performed on a Kratos MS 30 apparatus Microanalyses were obtained by the Laboratory of Microanalysis of the Université P et M Curie

All reactions were carried under nitrogen except those performed in aqueous solution Column chromatography was performed on silica gel, 230-400 mesh Mention of "usual workup" means (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic phases over $MgSO_4$, (iv) solvent evaporation under reduced pressure Compositions of stereoisomeric mixtures were achieved by NMR analysis on crude products before any purification

(2*R*,3*S*,5*R*) and (2*S*,3*S*,5*R*)-3-Butyl-4-methyl-5-phenyl-2-morpholinol (7)

A solution of 1 8 M butylmagnesium bromide in ether (1 47 ml, 2 65 mmol) was added dropwise to stirred suspension of copperbromide (381 mg, 2 65 mmol) in ether (3 ml), at -50°C After stirring at -40°C for 1 h , morpholine **1** (200 mg, 0 66 mmol) in ether (8 ml) was added The resulting mixture was allowed to reach r t within 1 h The black slurry was then quenched with 1 N buffer (pH 9) of NH_4Cl/NH_4OH (6 ml) and stirring was maintained during 1 h After filtration and usual workup, the residue was flash chromatographied (45% ether/petroleum ether), to give **7** as a clear oil (63/37 epimeric mixture at C-2, 82 mg, 50%) ^1H NMR 0 90-0 95 (m, 3H, CH_3CH_2) , 1 25-1 80 (m, 6H), 2 01 and 2 02 (s, 3H, NCH_3), 4 75 (d, J=8 Hz, OCHO), 5 02 (d, J=1 Hz, OCHO), 7 2-7 4 (m, 5H, Ph)

Aminodiol (8)

To a stirred suspension of $LiAlH_4$ (120 mg, 3 2 mmol) in ether (3 ml) was added dropwise a solution of **7** (239 mg, 0 96 mmol) in ether (10 ml) at r t After stirring for 5 h, the reaction was quenched by addition of water (5 ml) Workup gave **8** as an oil (223 mg, 93%) which was used without purification ^1H NMR 0 80 (t, J=6 2 Hz, 3H, CH_3CH_2), 1 1-1 3 (m, 6H), 2 11 (s, 3H, NCH_3), 2 95 (m, 1H, NCHBu), 3 3-4 0 (m, 7H), 7 20-7 35 (m, 5H, Ph), ^{13}C NMR 13 9, 22 9, 27 0, 29 1, 29 3, 61 8, 62 8, 63 5, 69 9, 127 6, 128 3, 128 4, 138 9

(*S*)-2-Methylaminohexanol (9)

A suspension of **8** (220 mg, 0 876 mmol) and 5% Pd/C (20 mg) in ethanol (10 ml) was vigourously stirred under a hydrogen atmosphere during 48 h After filtration on celite and evaporation, the residue was flash chromatographied (50% MeOH/Ether) to give amino alcohol **9** (65 mg, 57%), $[\alpha]_D^{20}$ +28 8° (*c* 3 2, $CHCl_3$) ^1H NMR 0 90 (t, J=6 5Hz, 3H, CH_3CH_2), 1 30-1 50 (m, 6H), 2 46 (s, 3H, NCH_3), 2 61 (m, 1H, CHN), 3 42 (dd, J=6 7 and 11 3Hz, 1H, CHHO), 3 70 (dd, J=3 6 and 11 3 Hz, 1H, CHHO), 4 30 (b s, 2H, OH and NH), ^{13}C NMR 13 8, 22 7, 28 0, 29 5, 32 5, 60 7, 61 9 m/z 131 (M^+), 128, 114, 100

(*S*)-2-Methylaminohexanol (9) obtained from (*S*)-norleucine

To a solution of (S)-norleucine (1 g, 7 6 mmol) in formic acid (3 ml), was added at 0°C formyl acetic anhydride [26] (2 g, 22 8 mmol) After stirring for 3 h at r t , the solution was evaporated under reduced pressure and the solid residue was added portionwise to a suspension of $LiAlH_4$ (1 14 g, 30 mmol) in THF (50 ml) at 60°C Stirring

was maintained 3 h at this temperature and 48 h at r t Water (1 5 ml), 2 5 N NaOH (1 5 ml) and water (1 5 ml) were then successively added. The suspension was filtered and the resulting solution was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (50% MeOH/ether) gave **9** as an oil (240 mg, 37%), $[\alpha]_D^{20}$ +30 3° (*c* 4 7, $CHCl_3$) ^1H and ^{13}C NMR data are identical with those reported above for **9** obtained from **8**

(2*R*,3*R*,5*R*) and (2*S*,3*R*,5*R*)-3-*n*-Butyl-4-methyl-5-phenyl-2-morpholinol (3, R = n-C_4H_9)
To a solution of **1** (1 5 g, 4 98 mmol) in THF (30 ml) was added *n*-BuZnI[27] (2 6 M in THF, 7 7 ml) at r t The resulting mixture was stirred for 18 h and was quenched with a saturated solution of ammonium sulfate (25 ml) The usual workup yielded a residue which was subjected to flash chromatography (70% ether/petroleum ether) **3** (R=*n*-Bu) was obtained as a white solid (90/10 epimeric mixture at C-2, 700 mg, 56%) ^1H NMR (major epimer) 0 92 (t, 3H, J=6 5 Hz, CH_3CH_2), 1 1-2 (m, 6H), 2 08 (s, 3H, NCH_3), 2.70 (dd, J=3 1 and 9 5 Hz, 1H, NCHBu), 3 50 (dd, J=3 8 and 11 Hz, 1H, NCHPh), 3 6-4 (m, 2H, CH_2O), 5 05 (d, J=0 9 Hz, 1H, OCHO), 7 3-7.6 (m, 5H, Ph), ^{13}C NMR (major epimer) 14.0, 20 8, 23 0, 29 4, 39 5, 61 5, 64 5, 64 6, 91 4, 128 0, 128 2, 128 6, 136 9

(2*R*,3*R*,5*R*) and (2*S*,3*R*,5*R*)-4-Methyl-5-phenyl-3-*n*-propyl-2-morpholinol (3, R = n-C_3H_7)
The same procedure as above was followed starting with **1** (4 g, 13 3 mmol) and *n*-PrZnI (1 62 M THF, 32 6 ml) Flash chromatography (70% ether/petroleum ether) afforded **3** (R = *n*-C_3H_7) as a white solid (84/16 epimeric mixture at C-2, 2 4 g, 80%) ^1H NMR (major epimer) 0 99 (t, J=6 5 Hz, 3H, CH_3CH_2), 1 15-2 0 (m, 4H), 2 13(s, 3H, NCH_3), 2 7-2 8 (m, 1H, NCHPr), 3 5-4 1 (m, 3H), 5 08 (b s, 1H, OCHO), 5 3 (b s , 1H, OH), 7 3-7 5 (m, 5H, Ph), ^{13}C NMR (major epimer) 14 3, 20 3, 23 6, 39 4, 61 3, 64 2, 91 3, 128 2, 128 7, 137 7

(2*R*,3*R*,5*R*) and (2*S*,3*R*,5*R*)-3-*i*-Butyl-4-methyl-5-phenyl-2-morpholinol (3, R = i-C_4H_9)
The above procedure was followed starting with **1** (3 g, 9 96 mmol) and *i*-BuZnI (1 48 M in THF, 27 ml) Flash chromatography gave **3** (R=*i*-Bu) as a white solid (70/30 epimeric mixture at C-2, 1 35 g, 55%) ^1H NMR (major epimer) 0 9-1 0 (m, 6H, $(CH_3)_2$), 1 2-1 8 (m, 3H), 2 06 (s, 3H, NCH_3), 2 75-2 80 (m, 1H, NCH*i*Bu), 3 40-3 70 (m, 2H), 3 80-3 90 (m, 1H), 4 40 (b s, 1H, OH), 5 01 (b s, 1H, OCHO), 7 20-7 45 (m, 5H, Ph), ^{13}C NMR 91 9 and 96 1 (OCHO for each epimer)

(2*R*,3*R*,5*R*) and (2*S*,3*R*,5*R*)-3-Ethenyl-4-methyl-5-phenyl-2-morpholinol (3, R = $CH{=}CH_2$)
A solution of CH_2=CH-MgBr (1 M in THF, 45 ml) was added dropwise to a stirred solution of dry zinc chloride (3 07 g, 22 5 ml) in THF (40 ml) The resulting solution was transferred *via* a syringe into a solution of **1** (3 g, 9 96 mmol) in THF (50 ml), at -40°C After stirring 2 h at 0°C, the reaction was quenched with a saturated solution of NH_4Cl (50 ml) Usual workup and flash chromatography (50% ether/petroleum ether) yielded **3** (R = $CH{=}CH_2$) as an oil (50/50 epimeric mixture at C-2, 1 65 g, 78%) ^1H NMR 2 01 and 2 02 (s, 3H, NCH_3), 3 1-4 2 (m, 4H), 4 9-5 0 (m, 1H), 5 2-5 6 (m, 2H, $CH{=}CH_2$), 6 05-6 30 (m, 1H, $CH{=}CH_2$), 7 25-7 35 (m, 5H, Ph), ^{13}C NMR 93 0 and 94 7 (OCHO), 121 0 and 123 6 ($CH{=}CH_2$), 128 4 and 129 3 ($CH{=}CH_2$) respectively for each epimer

Mixture of 4-methyl-5-phenyl-3-propenyl-2-morpholinols (2 and 3, R = $CH_2CH{=}CH_2$)
A solution of **1** (200 mg, 0 66 mmol) in THF (6 ml) was treated by a THF solution of CH_2=$CHCH_2$-ZnBr (1 5 M, 1 77 ml) at -20°C for 10 mn and was quenched by a saturated solution of ammonium sulfate (4 ml) at -10°C The usual workup gave a residue which was flash chromatographied (50% ether/petroleum ether) to yield **2** and **3** as an oil (107 mg, 69%) ^1H NMR 2 04, 2 09 and 2 12 (s, 3H, NCH_3), other protons resonnances appear as complex multiplets at 2 5-2 6, 3 2-4 0, 4 7-4 8, 5 00-5 25, 5 70-6 10, 7 2-7 4 (m, 5H, Ph), ^{13}C NMR 90 8, 91 8, 95 6 (OCHO)

(3*R*,5*R*)-2,3,4,6-Tetrahydro-3-propyl-5-phenyl-*N*-methyl-4*H*-1,4-oxazin-2-one(4,R=*n*-C_3H_7)
Dimethyl sulfoxide (539 mg, 6 39 mmol) was added dropwise to a solution of oxalyl chloride (406 mg, 3 19 mmol) in CH_2Cl_2 (5 ml) at -50°C After stirring 5 mn at -50°C, hemiacetal **3** (R = *n*-C_3H_7, 500 mg, 2 13 mmol) in CH_2Cl_2 (5 ml) was introduced *via* a syringe After 1 h at -50°C, triethylamine (1 03 g, 10 65 mmol) was added, and the mixture was allowed to warm to r t during 1h 30 Addition of water (20 ml) followed by usual workup yielded a residue which was purified by flash chromatography (30% ether/petroleum ether) **3** (R =*n*-C_3H_7) was obtained as white crystals (379 mg, 76%) mp 45°C, $[\alpha]_D^{20}$ +37 7° (*c* 1 2, $CHCl_3$), ^1H NMR 0 99 (t, J = 7 6Hz, 3H, CH_3CH_2), 1 35-1 90 (m, 4H), 2 28 (s, 3H, NCH_3), 3 55 (t, J = 6 4Hz, 1H, NCHCO), 4 00 (dd, J = 3 8 and 10 Hz, 1H, NCHPh), 4 37 (dd, J = 10 and 11 6 Hz, 1H, CH_2O), 4 55 (dd, J = 11 6 and 5 3 Hz, 1H, CH_2O), 7 3-7 4 (m, 5H, Ph), ^{13}C NMR 14 1, 19 5, 30 1, 38 7, 53 6, 60 8, 70 7,

127.6, 128 1, 128 8, 137 7, 171 7 Anal Calcd for $C_{14}H_{19}NO_2$ C, 72 07, H, 8 21, N, 6 00 Found C, 72 44, H, 8 26, N, 5 96

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-*i*-butyl-5-phenyl-*N*-methyl-4*H*-1,4-oxazin-2-one(4, R=*i*-C_4H_9)
The same procedure as above was followed starting with **3** (R = *i*-C_4H_9) (1 1 g, 4 4 mmol) Flash chromatography (35% ether/petroleum ether) yielded **4** (R =*i*-C_4H_9) as a white solid (860 mg, 80%) mp 30°C, $[\alpha]_D^{20}$ +48 4° (*c* 0 9, $CHCl_3$), ^1H NMR 0 99 (d, J = 6 6 Hz, 3H, CH_3), 1 01 (d, J = 6 6 Hz, 3H, CH_3), 1 7-2 0 (m, 3H), 2 27 (s, 3H, NCH_3), 3 64(t, J = 6 9 Hz, 1H, NCHCO), 4 00 (dd, J = 5 5 and 9 4 Hz, 1H, NCHPh), 4.40 (dd, J = 9 4 and 11 6 Hz, 1H, C*H*HO), 4 57 (dd, J = 5 5 and 11 6 Hz, 1H, CH*H*O), 7 3-7 4 (m, 5H, Ph), ^{13}C NMR 22 4, 22 6, 24 7, 36.5, 38 4, 59 0, 60.4, 70 1, 127 3, 128 0, 128 7, 137 8, 171 9 Anal Calcd for $C_{15}H_{21}NO_2$ C, 72 89; H, 8 55, N, 5 66 Found C, 72 40, H, 8 58, N, 5 66

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-ethenyl-5-phenyl-*N*-methyl-4*H*-1,4-oxazin-2-one (4, R = CH=CH_2)
Same procedure was followed as above starting with **3** (R = CH=CH_2) (3 3 g, 15 mmol) Flash chromatography (50% ether/petroleum ether) yielded **4** (R = CH=CH_2) as an oil (2 3 g, 71%) $[\alpha]_D^{20}$ -125 7° (*c* 1 1, $CHCl_3$), ^1H NMR 2.15 (s, 3H, NCH_3), 4 0 (dd, J = 4 8 and 7 8 Hz, 1H, NCHPh), 4 19 (b d, J = 7 5 Hz, 1H, NCHCO), 4.35-4 50 (m, 2H, CH_2O), 5 45-5 55 (m, 2H, CH=C*H*$_2$), 6 0-6 2 (m, 1H, C*H*=CH_2), 7 25-7 45 (m, 5H, Ph), ^{13}C NMR 38 2, 58 7, 66 5, 72 5, 121 5, 128 1, 128 3, 128 7, 130 2, 136 7, 168 7 Anal Calcd for $C_{13}H_{15}NO_2$ C, 71 85, H, 6 96, N, 6 44 Found C, 71 29, H, 7 00, N, 6 42

(3*R*,5*R*)-2,3,5,6-Tetrahydro-5-phenyl-3-propenyl-*N*-methyl-4H-1,4-oxazin-2-one(4, R = $CH_2CH=CH_2$) and (3*S*,5*R*)-2,3,5,6-Tetrahydro-5-phenyl-3-propenyl-*N*-methyl-4*H*-1,4-oxazin-2-one (13, R = $CH_2CH=CH_2$)
The same procedure was followed as above, starting with the mixture of **2** and **3** (R = $CH_2CH=CH_2$) (1 2 g, 5 15 mmol) Flash chromatography (30% ether/petroleum ether) gave a mixture of **4** and **13** (R = $CH_2CH=CH_2$) in a 54/46 respective ratio (745 mg, 63%) as an oil. ^1H NMR (major epimer) 2 30 (s, 3H, NCH_3), 2 6-2 7 (m, 2H), 3 6-3 7 (m, 1H, NCHCO), 4 0 (dd, J = 4 7 and 7 8 Hz, 1H, NCHPh), 4 38 (dd, J = 7 8 and 11 4 Hz, 1H, C*H*HO), 4 57 (dd, J = 5 and 11 4 Hz, 1H, CH*H*O), 5 15-5 25 (m, 2H, CH=C*H*$_2$), 5 85-5 95 (m, 1H, C*H*=CH_2), 7 15-7 50 (m, 5H, Ph), ^{13}C NMR 32 7, 38 6, 60 9, 61 4, 71 1, 77 8, 127 7, 128 2, 128 8, 134 2, 137 3, 170 8 ^1H NMR (minor epimer) 2 16 (s, 3H, NCH_3), 2 70-2 75 (m, 2H), 3 41 (t, J = 4 7 Hz, 1H, NCHCO), 3 61 (dd, J = 3.4 and 10 3 Hz, 1H, NCHPh), 4 05-4 25 (m, 2H, CH_2O), 5 15-5 25 (m, 2H, CH=C*H*$_2$), 5 90-6.15 (m, 1H, C*H*=CH_2), 7 25-7 40 (m, 5H, Ph), ^{13}C NMR 36 7, 41 1, 63 9, 66 0, 71 9, 118 4, 127 8, 128 4, 128 8, 133 6, 137 4, 170 1

Epimerization of 4 (R = $CH_2CH=CH_2$) to 13 (R = $CH_2CH=CH_2$)
To a solution of **4** and **13** (R = $CH_2CH=CH_2$) (54/46 epimeric mixture) obtained as described above (330 mg, 1 4 mmol) in *t*-BuOH (5ml) at 40°C, was added potassium *t*-butoxide (16 mg, 0 14 mmol) The mixture was stirred for 15 mn at 40°C and then neutralized with an NH_4Cl aqueous saturated solution Usual workup gave a mixture of **4** and **13** (R = $CH_2CH=CH_2$) in a 7/93 respective ratio (315 mg, 95%)

Epimerization of 4 (R = *n*-C_3H_7) to 13 (R = *n*-C_3H_7)
The above procedure was followed, starting with **4** (R = *n*-C_3H_7) (50 mg, 0 214 mmol). A mixture of **4** and **13** (R = *n*-C_3H_7) was obtained in a 7/93 ratio (30 mg, 60%) ^1H NMR 0 92 (t, J = 7 3 Hz, 3H, CH_3), 1 35-1 95 (m, 4H), 2 06 (s, 3H, NCH_3), 3 24 (t, J = 4 5 Hz, 1H, NCHCO), 3 52 (dd, J = 3 8 and 10 1 Hz, 1H, NCHPh), 4 0-4 2 (m, 2H, CH_2O), 7 1-7 4 (m, 5H, Ph), ^{13}C NMR 14 1, 18 5, 35 1, 41 6, 64 4, 65 9, 72 1, 128 0, 128 6, 129 0, 137 7, 170 2

(2*R*,3*R*,5*R*)-2-Methoxy-4-methyl-5-phenyl-3-phenylthiomorpholine (10)
To a solution of **1** (1 5 g, 5 mmol) in THF (10 ml), cooled at -70°C, was added *t*-BuOK (560 mg, 5 mmol), followed by methyl iodide (7 1 g, 50 mmol) The reaction mixture was then allowed to warm to r t during 30 min Water (3 ml) and ether (10 ml) were successively added Usual workup gave crude **10** Flash chromatography (20% ether/petroleum ether) yielded **10** as a white solid (950 mg, 60%) mp 152°C, $[\alpha]_D^{20}$ +156 2° (*c* 1 1, $CHCl_3$), ^1H NMR 2 11 (s, 3H, NCH_3), 3 4-3 9 (m, 3H), 3 64 (s, 3H, OCH_3), 4 48 (d, J = 1 5 Hz, 1H, NCHS), 4 80 (d, J = 1 5 Hz, 1H, OCHO), 7 15-7.65 (m, 10H, Ph), ^{13}C NMR 39 9, 56 6, 61 8, 71 4, 82 3, 102.6, 126 6, 128 0, 128 4, 128 6, 128 8, 133 2, 137 7, 138 0 Anal Calcd for $C_{18}H_{21}NO_2S$ C, 68 53, H, 6 71, N, 4 44 Found C, 68 40; H, 6 76, N, 4 31

(2*S*,3*S*,5*R*) and (2*S*,3*R*,5*R*)-2,3,5,6-Tetrahydro-2-methoxy-4-methyl-3-butyl-5-phenyl-4*H*-1,4-oxazines (11) and (12)

a Reaction with butylcopper
The procedure described above for the synthesis of **7** was used, starting with **10** (200 mg, 0 63 mmol) Flash chromatography (10% ether/petroleum ether) yielded a 90/10 epimeric mixture of **11** and **12** respectively (100 mg, 60%) ^{1}H NMR (major stereoisomer **11**) 0 93 (t, J = 6 7 Hz, 3H, CH_3), 1 15-1 80 (m, 6H), 2 00 (s, 3H, NCH_3), 2 05-2 10 (m, 1H, NCHCO), 3 23 (dd, J = 3 5 and 10 5 Hz, NCHPh), 3 44 (b t, J = 11,5 Hz,CH_2O), 3 52 (s, 3H, OCH_3), 3 75 (dd, J = 3 5 and 11 5 Hz, 1H, CH_2O), 4 34 (d, J = 8 Hz, 1H, OCHO), 7 2-7 4 (m, 5H, Ph), ^{13}C NMR 14 1, 23 4, 26 5, 27 8, 39 7, 56 6, 65 8, 68 0, 70 4, 103 2, 127 6, 128 1, 128 5, 140 2 Anal Calcd for $C_{16}H_{25}NO_2$ C, 72 96, H, 9 56, N, 5 31 Found C, 72 21, H, 9 71, N, 5 00

b Reaction with butylzinc iodide
The procedure described above for the synthesis of **3** (R = *n*-C_4H_9) was used, starting with **10** (400 mg, 1 27 mmol) Flash chromatography (10% ether/petroleum ether) yielded a 44/56 epimeric mixture of **11** and **12** respectively (190 mg, 57%) ^{1}H NMR (major stereoisomer **12**) 0 91 (t, J = 6 6 Hz, 3H, CH_3), 1 1-1 8 (m, 6H) , 2 11 (s, 3H, NCH_3), 2 70-2 85 (m, 1H, NCHCO), 3 50 (s, 3H, OCH_3), 3 40-3 65 (m, 2H), 3 90-4 05 (m, 1H, CH_2O), 4 64 (d, J = 2 2 Hz, 1H, OCHO), 7 25-7 35 (m, 5H, Ph), ^{13}C NMR 14 0, 21 7, 23 1, 31 5, 39 4, 56 2, 61 6, 69 2, 76 4, 103 0, 127 7, 128 0, 128 6, 137 8

Urethane derivative (5, R = *n*-C_3H_7)
A solution of **4** (379 mg, 1 63 mmol) and vinyl chloroformate (692 mg, 8 15 mmol) in CH_2Cl_2 (10 ml) was refluxed for 24 h. Evaporation and flash chromatography of the residue (10% ether/petroleum ether) yielded carbamate **5** (R = *n*-C_3H_7) as an oil (393 mg, 71%) ^{1}H NMR [28] 0 90-0 95 (m, 3H, CH_3), 1 2-2 0 (m, 4H), 2 82 (s, 3H, NCH_3), 4 40-4 85 (m, 5H), 5 07(t, J = 6 8 Hz, 1H, NCHCO), 7 1-7 3 (m, 1H, C*H*=CH_2), 7 3-7 4 (m, 5H, Ph), ^{13}C NMR 13 4, 19 2, 30 3, 30 5, 30 9, 58 2, 59 1, 68 1, 68 2, 95 7, 127 4, 128 8, 129 0, 137 3, 142 3, 142 5, 153 5, 154 3, 170 8 Anal Calcd for $C_{17}H_{22}NO_4Cl$ C, 60 08, H,6 53, N, 4 12 Found C, 60 19, H, 6 73, N, 4 02

Urethane derivative (5, R = *i*-C_4H_9)
The same procedure as above starting with **4** (R = *i*-C_4H_9) (600 mg, 2 43 mmol) gave, after refluxing for 72 h and flash chromatography (30% ether/petroleum ether), **5** (R = *i*-C_4H_9) as an oil (710 mg, 82%) ^{1}H NMR 0 9-1 0 (m, 6H), 1 35-1 80 (m, 3H), 2 81 (s, 3H, NCH_3), 4 40-4 55 (m, 3H), 4 7-4 9 (m, 2H), 5 07 (t, J = 6 8 Hz, 1H, NCHCO), 7 15-7 25 (m, 1H, C*H*=CH_2), 7 25-7 50 (m, 5H, Ph) ^{13}C NMR 21 1, 21 4, 23 2, 24 8, 30 3, 30 8, 37 3, 37 8, 56 8, 59.2, 68 2, 95 9, 127 5, 128 9, 129 1, 137 4, 142 4, 142 6, 154 3, 172 2 Anal Calcd for $C_{18}H_{24}NO_4Cl$ C, 61 08, H, 6 83, N, 3 95 Found C, 61 36, H, 6 98, N, 4 19

Urethane derivative (5, R = CH=CH_2)
The same procedure as above starting with **4** (R = CH=CH_2) (2 2 g, 10 1mmol) gave, after refluxing for 21 h and flash chromatography (30% ether/petroleum ether), **5** (R = CH=CH_2) as an oil (2 9 g, 88%) ^{1}H NMR 2 86 (s, 3H, NCH_3), 4 45-4 55 (m, 3H), 4 2-4 9 (m, 1H), 5 08 (t, J = 6 8 Hz, 1H, NCHCO), 5 1-5 4 (m, 3H), 5 8-6 0 (m, 1H), 7 05-7 30 (m, 1H, OC*H*=CH_2), 7 3-7 4 (m, 5H, Ph), ^{13}C NMR 31 6, 32 3, 58 9, 61 0, 68 2, 95 8, 119 8, 127 3, 128 6, 128 9, 129 8, 130 0, 137 1, 142 0, 142 3, 152 8, 153 8, 168 8 Anal Calcd for $C_{16}H_{18}NO_4Cl$ C, 59 35, H, 5 60, N, 4 32 Found C, 59 31, H, 5 70, N, 4 14

Urethane derivative (5, R = CH_2CH=CH_2)
The same procedure as above starting with a 7/93 epimeric mixture of **4** and **13** respectively (315 mg, 1 36 mmol) gave, after refluxing for 5 days and flash chromatography (20% ether/petroleum ether), **5** (R = CH_2CH=CH_2) as an oil (400 mg, 91%) ^{1}H NMR 2 30-2 95 (m, 5H), 4 45-4 50 (m, 3H), 4 65-4 95 (m, 2H), 5 05-5 15 (m, 3H), 5 60-5 85 (m, 1H), 7 10-7 55 (m, 6H), ^{13}C NMR 30 6, 31 3, 32 9, 33 4, 58 3, 58 5, 59 2, 68 2, 95 7, 118 2, 118 4, 127 4, 128 8, 129 0, 132 9, 133 1, 137 3, 142 2, 142 4, 153 5, 154 5, 169 9 Anal Calcd for $C_{17}H_{20}NO_4Cl$ C, 60 44, H, 5 97, N, 4 15 Found C, 60 76, H, 6 09, N, 4 46

Methyl (2R)-2-methylaminopentanoate hydrochloride (6, R = *n*-C_3H_7)
Urethane **5** (R = *n*-C_3H_7) (393 mg, 1 16 mmol) was refluxed for 3 days in MeOH HCl (10 ml, 6 N) Solvent was then evaporated so as to remove excess of HCl The residue was dissolved in water (10 ml) and the aqueous solution was extracted with ether (2 x 10 ml) Removal of water under reduced pressure and drying yielded **6** (R = *n*-C_3H_7) as a solid residue (199 mg, 95%), $[\alpha]_D^{20}$ -23 6° (*c* 0 51, MeOH), ^{1}H NMR (D_2O) 1 09 (t, J = 7 3 Hz, 3H, C*H*$_3$CH$_2$), 1 4-2 1 (m, 4H), 2 92 (s, 3H, NCH_3), 4 01 (s, 3H, OCH_3), 4 25 (t, J = 5 7 Hz, 1H, NCH), ^{13}C NMR (D_2O, dioxane) 15 6, 16 3, 31 3, 32 4, 54 4, 61 6, 170 9, m/z 145 (M^+-HCl)

Methyl (2R)-2-methylamino-4-methylpentanoate hydrochloride (6, R = *i*-Bu)
Urethane **5** (R = *i*-Bu) (215 mg, 0 61mmol) was treated as described above and gave **6** (R = *i*-Bu) as a white solid (114 mg, 97%), $[\alpha]_D^{20}$ -31 7° (*c* 1 3, EtOH) (lit [29] +31 4° for the *S* enantiomer)

Methyl (2R)-2-methylaminobuten-3-oate hydrochloride (6, R = CH=CH$_2$)
Urethane **5** (R = CH=CH$_2$) (516 mg, 1 6 mmol) was treated as described above and afforded **6** (R= CH=CH$_2$) as a solid residue (250 mg, 95%), $[\alpha]_D^{20}$ -113 7° (*c* 1 7, MeOH), ^{1}H NMR (D_2O) 2 88 (s, 3H, NCH_3), 4 01 (s, 3H, OCH3), 4 78 (d, J = 10 Hz, 1H, NCH), 5 7-6 1 (m, 3H, CH=CH$_2$), ^{13}C NMR (D_2O, dioxane) 31 5, 54 8, 63 6, 67 4, 126 2, 128 3, 169 4, m/z 129 (M^+-HCl)

Methyl (2S)-2-methylaminopenten-4-oate hydrochloride (6, R = CH$_2$CH=CH$_2$)
Urethane **5** (R = $CH_2CH=CH_2$) (365 mg, 1 13 mmol) was treated as described above and gave *ent*-**6** (R = $CH_2CH=CH_2$) as a solid residue (184 mg, 90%), $[\alpha]_D^{20}$ +0°7 (*c* 0 8, MeOH), ^{1}H NMR (D_2O) 2 9-3 0 (m, 5H, NCH_3 and $CH_2CH=CH_2$), 4 04 (s, 3H, OCH_3), 4 39 (t, J = 5 6 Hz, 1H, NCH), 5 4-5 5 (m, 2H, CH=CH_2), 5 8-6 0 (m, 1H, CH=CH_2), ^{13}C NMR (D_2O, dioxane) 32 3, 33 6, 54 5, 61 0, 122 5, 130 3, 170 2, m/z 143 (M^+-HCl), 102, 84

Determination of the absolute configuration of 6 (R= *n*-C$_3$H$_7$) and *ent*-6 (R = CH$_2$CH=CH$_2$), chemical correlation.

a Methyl (2S)-2-methylaminopentanoate hydrochloride from ent-6 (R = CH$_2$CH=CH$_2$)
A suspension of *ent*-**6** (R = $CH_2CH=CH_2$), (110 mg, 0 613 mmol) and 5% Pd/C (20 mg) in MeOH (10 ml) was vigourously stirred under a hydrogen atmosphere for 3 h Filtration on celite and evaporation gave title compound as a white solid (102 mg, 93%), $[\alpha]_D^{20}$ +20 3° (*c* 0 9, MeOH)

b Methyl (2S)-2-methylaminopentanoate hydrochloride from S-norvaline
(i) (2*S*)-2-Methylaminopentanoic acid
This compound was prepared from (*S*)-norvaline following the general method of Quitt et al [30] for synthesis of *N*-methyl α-aminoacids, $[\alpha]_D^{20}$ +28 3° (*c* 0 75, HCl 6 N), ^{1}H NMR (D_2O) 0 74 (t, J = 7 3 Hz, 3H, CH_3CH_2), 1 0-1 3 (m, 2H), 1.5-1 8 (m, 2H), 2 50 (s, 3H, NCH_3), 3 38 (t, J = 5 7 Hz, 1H, NCHCO), Anal Calcd for $C_6H_{13}NO_2$ C, 54 92, H, 9 98, N, 10 68 Found C, 54 88, H, 9 87, N, 10 45
(ii) Methyl (2*S*)-2-methylaminopentanoate hydrochloride
Title compound was prepared by refluxing a solution of the above (2*S*)-2-Methylaminopentanoic acid (100 mg, 0 763 mmol) in MeOH HCl (5 ml, 2 4 N) for 14 h Evaporation and drying gave the methyl ester hydrochloride as a white solid (137 mg, 99%), $[\alpha]_D^{20}$ +24 4° (*c* 0 9, MeOH) Spectral data (^{13}C and ^{1}H NMR) were identical to those showed by **6** (R = *n*-C_3H_7) and by the hydrogenated derivative of *ent*-**6** (R = $CH_2CH=CH_2$), both obtained by asymmetric synthesis

Determination of the absolute configuration of 6 (R = CH=CH$_2$), chemical correlation.

a. Methyl (2R)-2-methylaminobutanoate hydrochloride from 6 (R = CH=CH$_2$)
Same procedure was used as for methyl (2*S*)-2-methylaminopentanoate hydrochloride starting with **6** (R = CH=CH$_2$) (223 mg, 1 35 mmol) Title compound was obtained as a solid (184 mg, 82%), $[\alpha]_D^{20}$ -15 1° (*c* 1 1, MeOH), ^{1}H NMR (D_2O) 1 13 (t, J = 7 4 Hz, 3H, CH_3CH_2), 2 0-2 3 (m, 2H), 2 92 (s, 3H, NCH_3), 4 03 (s, 3H, OCH_3), 4 24 (t, J = 6 Hz, 1H, NCHCO), ^{13}C NMR (D_2O, dioxane) 8 9, 22 8, 32 4, 54 4, 62 7, 170 8, m/z 131 (M^+-HCl), 102, 72

b Methyl (2S)-2-methylaminobutanoate hydrochloride from (2S)-2-aminobutanoic acid
(i) (2*S*)-2-Methylaminobutanoic acid
This compound was prepared from (2*S*)-2-aminobutanoic acid following the general method of Quitt et al [30]
$[\alpha]_D^{20}$ +24 8° (*c* 0 85, HCl 6 N), ^{1}H NMR (D_2O) 1 09 (t, J = 7 6 Hz, 3H, CH_3CH_2), 2 0-2 1 (m, 2H), 2 85 (s, 3H, NCH_3), 3 70 (t, J = 7 3 Hz, 1H, NCHCO), Anal Calcd for $C_5H_{11}NO_2$ C, 51 26, H, 9 47, N, 11 96 Found C, 50 41, H, 9 35, N, 11 92
(ii) Methyl (2*S*)-2-methylaminobutanoate hydrochloride
Following the previously described procedure for methyl (2*S*)-2-methylaminopentanoate hydrochloride and starting with (2*S*)-2-methylaminobutanoic acid (50 mg, 0 43 mmol), title compound was obtained as a solid,

$[\alpha]_D^{20}$ +17 6° (*c* 1 2, MeOH) Spectral data (^{13}C and ^1H NMR) were identical to those showed by the hydrogenated derivative of **6** (R = $CH{=}CH_2$), obtained by asymmetric synthesis

Determination of optical purity of compounds (6)
A suspension of the aminoester hydrochloride (0 2 mmol) and triethylamine (0 28 ml, 0 2 mmol) in ether (1 ml) was stirred overnight. Triethylamine (0 28 ml, 0 2 mmol) and (+)- MTPACl (Mosher reagent) (0 175 M in THF, 1 15 ml) were successively added Stirring was continued for 7 h Addition of water (1 ml) and ether (3 ml) gave, after usual workup, a residue which was directly analysed by ^{19}F NMR ($CDCl_3$, trifluorotoluene) The following resonances appeared for **6** and *ent*-**6** Mosher amide derivatives R = *n*-C_3H_7 -8 14 and -7.75 (ee>95%); R = *i*-C_4H_9: -8 25 and -7 70 (ee>95%), R = *n*-C_2H_5 (from R = $CH{=}CH_2$) -8 22 and -7 75 (ee = 70%) For *ent*-**6** (R = C_3H_7 from R = $CH_2CH{=}CH_2$) -7 75 (ee = 86%)

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