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Stereospecific Preparation of Glycidic Esters from 2-Chloro-3-Hydroxyesters. Application to the Synthesis of (2*R*,3*S*)-3-Phenylisoserine

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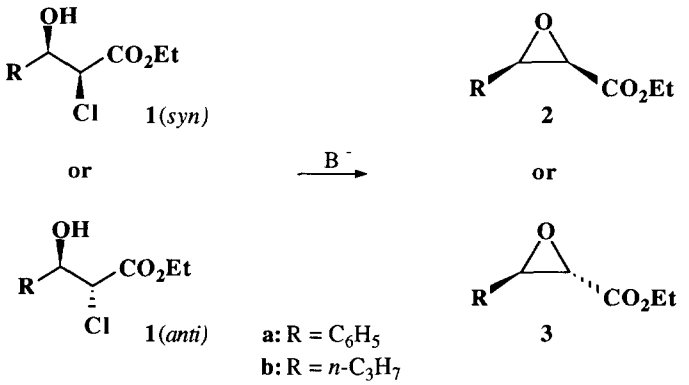
Abstract: *Cis*- and *trans*-glycidic esters may be synthesized in high enantiomeric purities by cyclisation with potassium carbonate in DMF of the corresponding *syn*- or *anti*-2-chloro-3-hydroxyesters, prepared by microbial reduction of 2-chloro-3-oxoesters. In contrast, more basic media such as sodium ethylate afford exclusively the *trans*-isomer, whatever the stereochemistry of the starting 2-chloro-3-hydroxyester is. Cyclisation of deuterated compounds showed that this result was due to a rapid isomerisation of the *syn* esters into *anti* isomers before cyclisation. An application of this reaction to the synthesis of (2*R*,3*S*)-3-phenylisoserine is described.

Optically active glycidic esters are versatile synthetic intermediates which may be regio- and stereoselectively opened with nucleophiles to afford various chiral synthons. They are generally prepared by enantioselective epoxidation of allylic alcohols, followed by oxidation of the resulting epoxyalcohols[1,2]. In some cases, the direct epoxidation of unsaturated esters was achieved[3,4]. An interesting alternative is offered by the cyclisation of β-hydroxyesters α-substituted by a leaving group such as an halide, a tosylate or an equivalent function. Such esters may be synthesized by stereocontrolled aldolisation[5-7], by modification of various diols obtained by enantioselective dihydroxylation[8,9] or issued from the chiral pool[10,11]. Alternatively, glycidic esters may be prepared by enzymatic resolution[12] or other chemoenzymatic methods[13].

In the preceding paper[14], we reported the stereoselective microbial reduction of 2-chloro 3-oxoesters, which allowed us to access in a stereoselective manner to 2-chloro-3-hydroxyesters in high enantiomeric purity. For example, from the corresponding chlorooxoester, using a reduction by *Mucor plumbeus*, the *anti* (2*R*,3*R*) ethyl 2-chloro-3-hydroxyhexanoate was obtained in 50% yield and 92% e.e., while both syn (2*S*,3*R*) and anti (2*R*,3*R*) ethyl 2-chloro-3-hydroxy-3-phenylpropionates were obtained in 45-50% yield (e.e.≥96%) using a reduction by *Mucor racemosus* or *Rhodotorula glutinis*, respectively. We describe now the stereospecific cyclisation of these 2-chloro-3-hydroxyesters into glycidic esters and present an application to the taxol side-chain synthesis.

When reacted in alkaline conditions, assuming an intramolecular SN2 reaction with inversion of configuration, the *anti* esters are expected to give the *trans* epoxides while the *syn* esters ought to afford the *cis* isomers. Although some examples of such cyclisations have been reported, they were restricted to the *anti*

compounds[15,16], and we did not find any example of stereospecific transformation of *syn* 2-halogeno-3-hydroxyesters into the corresponding *cis*-epoxides. It must be outlined that a very similar cyclisation of pure *syn*-2-chloro-3-hydroxyoxazolidinones was reported to give exclusively the corresponding *trans*-epoxides but not the *cis* isomers which would be the normal products resulting from an intramolecular SN2 substitution[16].



We thus decided to study the stereochemistry of such a cyclisation and, in a first attempt, ethyl 2-chloro-3-hydroxy-3-phenylpropionates were submitted to various basic media. The reaction was performed with optically active esters of defined purities and the results of this study are summarized in table 1.

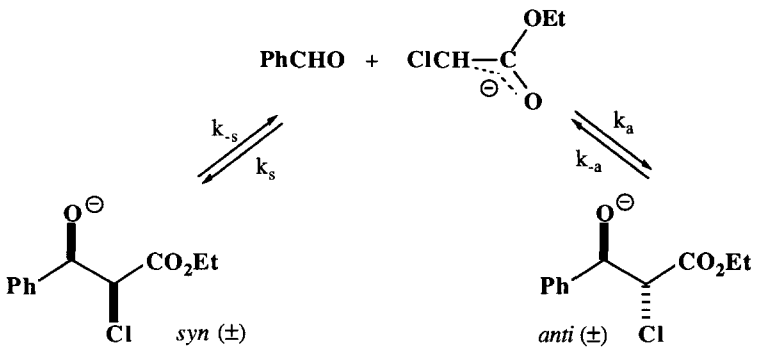
Table 1: Relative Configurations of 2,3-Epoxyesters Obtained by Cyclisation of 2-Chloro-3-hydroxyesters **1.**

Chlorohydroxyester *(syn/anti)*	Reagent	Reaction time (h)	Recovered chlorohydroxy-ester (%)	2,3-Epoxyester *cis* (**2**)	*trans* (**3**)
1a (83/17)	Ag_2O/DMF	24	100	-	-
1a (83/17)	CsF/THF	70	23	11	66
1a (100/0)	NaH/HMPT	20	32	47	21
1a (79/21)	K_2CO_3/EtOH	8	2	17	81
1a (79/21)	K_2CO_3/HMPT/cat.H_2O	23	-	74	26
1b (79/21)	DBU/CH_2Cl_2	2	-	22	78
1a (80/20)	K_2CO_3/DMF/cat.H_2O	6	-	79	21
1a[a] (100/0)	"	"	-	94 [a]	6
1a[a] (0/100)	"	"	-	-	100[a]
1b (76/24)	"	"	-	70	30
1b[b] (2/98)	"	"	-	2	98[b]
1a[a] (100/0)	NaOEt/EtOH	2	-	5	95[a]
1a[a] (0/100)	"	"	-	-	100[a]
1b (76/24)	"	"	-	6	94

[a] E.e. = 95%; [b] E.e.= 90%.

From this study, it results that a mixture of *cis*- and *trans*-epoxides was generally obtained from the *syn*-chlorohydroxyesters. However, the use of potassium carbonate in DMF, in the presence of a catalytic amount of water, allowed to obtain an almost stereospecific conversion into the *cis*-epoxide. In contrast, the cyclisation of the *anti* compounds afforded stereochemically pure *trans*-epoxides, whatever the alcaline medium was. It must be outlined that silver oxide, previously used to obtain some very sensitive epoxides, was completely inefficient[17].

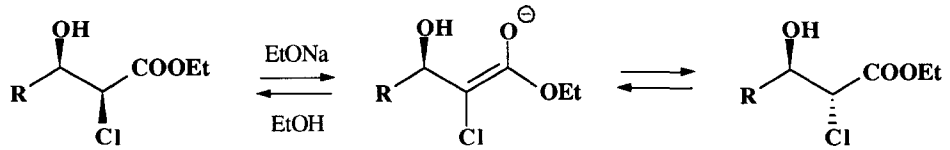
A possible explanation for these results could be found in the occurrence of a retroaldolisation reaction with formation of benzaldehyde and chloroester enolate. Such a reaction has been previously postulated by Seyden-Penne *et al.* in a study concerning the stereochemistry of the Darzens condensation[18], and it was demonstrated by deuterium incorporation that the final stereochemistry was depending on the relative cyclisation rates of the *syn* - and *anti* -chlorohydroxyesters.



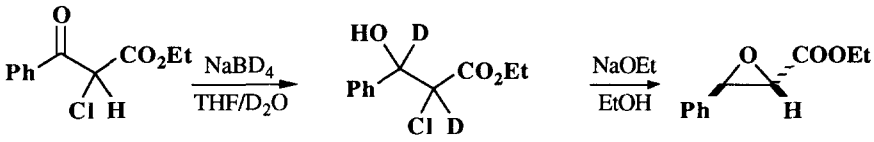
However, this study was performed exclusively with racemic chlorohydroxyesters.
When the *syn* (2*S*,3*R*)-chlorohydroxyester **1a** (95% e.e.) was treated with K_2CO_3/DMF-water, the *cis*-epoxide **2a** was isolated as the (2*R*,3*R*)-enantiomer with a 95% enantiomeric excess. Moreover, treatment of the same chlorohydroxyester or its *anti* (2*R*,3*R*) isomer with sodium ethylate in ethanol afforded the *trans*-(2*S*,3*R*)-phenylglycidate **3a** (95% e.e.). The same result was obtained with the *anti* (2*R*,3*R*)-ester **1b**.

Although they are of a great synthetic value, these results are in contradiction with a mechanism involving a retroaldolisation reaction, which would have given a mixture of racemic epoxyesters from enantiomerically pure chlorohydroxyesters.

A direct isomerisation of the epoxyester was not possible. Indeed, such isomerisations are known to require drastic conditions[19] and we have controlled that in our working conditions (NaOEt/EtOH; 0°C) both the *cis* and the *trans* epoxides were not isomerized. A mechanism involving an epimerisation of the C-2 position of the chlorohydroxyester, competitively with a SN2 ring closure, was the most credible. However, due to the fast cyclisation rate of the *anti* isomer, the direct observation of such an equilibrium during the reaction was not possible. In order to confirm this hypothesis, we synthesized a 2,3-dideutero-chlorohydroxyester, by reduction of a 2-chloro-3-oxoester with deuterated sodium borohydride[20].



We succeeded in isolating a 68:32 mixture of *syn* and *anti* dideuterated chlohydroxyester with a 75/25 deuterium/hydrogen ratio on C-2. The reaction of this compound with one equivalent of sodium ethylate in ethanol afforded a 8:92 mixture of *cis/trans* deuterated epoxides with a 31:69 deuterium/hydrogen ratio on carbon 2. Assuming that the very fast cyclisation of the deuterated *anti* isomer afforded the deuterated *trans* epoxide, the loss of deuterium found is in agreement with the postulated intermediate formation and equilibration of the α-chloro ester enolates[21].

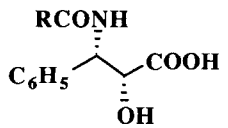


(±) syn/anti = 68/32

In conclusion, optically active *syn*- and *anti*-2-chloro-3-hydroxyesters may be stereospecifically cyclized into *cis*- and *trans*-epoxyesters respectively with conservation of the enantiomeric purity.

Synthesis of (2*R*,3*S*)-3-phenylisoserine

A direct application of the microbial reduction of α-chloro β-oxoesters was found in the synthesis of N-benzoyl and N-*tert*-butoxycarbonyl (2*R*,3*S*)-3-phenylisoserine which constitute the side chain at C-13 of taxol and taxotere® respectively. Such compounds have recently attracted much attention because of their efficiency in the treatment of various types of cancer. Chemical complexity has prohibited their commercial production by total synthesis, and semi-synthetic routes were developed involving coupling of synthetic side chains, which are essential for the potent antitumor activity, with 10-deacetylbaccatin[22].



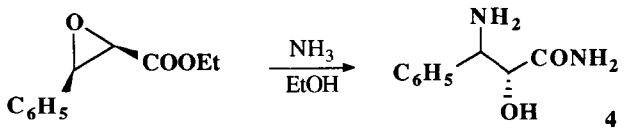
R = C_6H_5
R = *t*-C_4H_9O

Due to the recognized chemotherapeutic importance of these protected α-hydroxy β-aminoacids a number of syntheses have been reported. The first enantioselective synthesis was obtained in 8 steps and 23% yield *via* a Sharpless epoxidation from cinnamyl alcohol with a moderate enantiomeric excess (75-80%)[23]. This process has been further refined to give high yields of an optically pure (2*R*,3*S*)-phenylisoserine ester synthon[24]. A number of other imaginative syntheses, albeit not always suitable for large scale production, using β-lactam intermediates[25], enolate or ketene acetal condensation with imine[26], conjugate addition-electrophilic amination of a cinnamate ester[27], or chemoenzymatic methods[28] have been proposed.

However, a very direct method to access to phenylisoserine was offered by the regioselective opening of epoxides by nitrogenated nucleophiles[28,29]. In order to access to the desired (2*R*,3*S*) enantiomer, it was necessary to start from the *cis*-(2*R*,3*R*)-epoxide **2a**. Indeed, as previously reported[24,30], the reaction of the (2*R*,3*R*)-epoxide obtained after cyclisation of the *syn* 2-chloro-3-hydroxyester **1a** with sodium azide in ethanol afforded exclusively the (2*R*,3*S*)-2-hydroxy-3-azidophenylpropionic acid ethyl ester. This one provided directly the taxotere® side chain after a one-pot hydrogenation in the presence of di-*tert*-butyl dicarbonate[31].

However, the obtention of pure *cis*-epoxide being difficult enough, another approach based on the direct opening with ammonia[4,32], allowing the obtention of crystalline amides, was achieved in order to avoid the necessity of the separation of diastereomeric epoxides. Thus, when a 77/23 mixture of *cis*- and *trans*-epoxides was directly treated with ammonia in ethanol, a highly selective ring-opening process was observed and

3-phenylisoserinamide was isolated. As for the reaction with sodium azide, the reaction was completely regioselective, and the epoxide opening in position-3 was only observed.



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Moreover, the small amount of the diastereoisomeric impurity resulting from ring opening of the *trans*-epoxide was easily removed during recrystallization of the crude product. The pure (2*R*,3*S*)-3-phenylisoserinamide **4** was thus isolated in 54% yield. Such amides are known to be easily hydrolyzed without epimerization into 3-phenylisoserine. Thus, this methodology allows a very rapid access to the side-chain of taxol and taxotere®.

However, another strategy was also possible. Indeed, according to a recent report[33], the cyclically protected *anti*-(2*S*,3*S*)-phenylisoserines are isomerized during the coupling reaction with 10-desacetylbaccatin III, allowing the use of these isomers to access to taxol and taxotere®. This *anti* isomer was easily accessible by regioselective opening of the *trans*-epoxide **3a** obtained by cyclisation of the *syn* chlorohydroxyester **1a** in the presence of sodium ethylate or better by cyclisation of the *anti* ester, resulting from the microbial reduction of ethyl 2-chloro-3-oxo-3-phenylpropionic acid by the yeast *R. glutinis* [14].

Experimental

Products were purified by distillation, by flash chromatography (Kieselgel 60 Merck, 230-400 mesh, cyclohexane-ethyl acetate), or by medium pressure liquid chromatography on a Jobin-Yvon Modulprep (Kieselgel 60H, Merck), and analyzed by GC (BP 10, SGE, 15 m capillary column, or DBWax, J&W Scientific, 30 m capillary column) or by TLC (silicagel Merck $60F_{254}$).

Optical rotations were measured on a Perkin-Elmer 241 polarimeter. NMR spectra were recorded on a Bruker WM-250 at 250.1 MHz for ^1H and 62.9 MHz for ^{13}C with $CDCl_3$ as solvent. IR spectra were recorded on a Perkin-Elmer 783. Mass spectra were recorded on a Hewlett-Packard 5890-II/5972 fitted with a GC-mass coupling (30 m capillary HP 1 column), or on a Hewlett-Packard 5989A-MS instrument.

(2*R*,3*R*) Ethyl 3-phenylglycidate (2a)

Potassium carbonate (1.78 g, 12.8 mmol) was added to a solution of (2*S*,3*R*) ethyl 2-chloro-3-hydroxy-3-phenylpropionate **1a** (983 mg, 4.3 mmol) in DMF (21.3 mL) and water (387 µL). After stirring at room temperature for 6 h, 100 mL of a diethylether:pentane mixture (1:1) were added. The resulting solution was washed with water (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Yield: 79%. TLC: 0.21 (cyclohexane-EtOAc, 95:5) ; GC (DBWax, 220°C), Rt: 3.3 min ; IR (neat): 1755 cm^{-1} (CO_2Et) ; ^1H NMR, δ: 1.02 (t, 3H, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 3.83 (d, 1H, J = 4.5 Hz, $C\underline{H}CO$), 4.01 (m, 2H, $OC\underline{H_2}CH_3$), 4.28 (d, 1H, J = 4.5 Hz, $C\underline{H}Ph$), 7.32-7.41 (m, 5H, Ar-<u>H</u>) ; ^{13}C NMR, δ: 13.8 ($OCH_2\underline{C}H_3$), 55.7 ($\underline{C}HPh$), 57.3 ($\underline{C}HCO$), 61.1 ($O\underline{C}H_2CH_3$), 126.6 (Ar-<u>C</u> para), 127.9 (Ar-<u>C</u> meta), 128.3 (Ar-<u>C</u> ortho), 132.8 (Ar-<u>C</u>-1), 166.5 (CO) ; MS(EI) m/z (%): 135(100)[M-57]$^+$, 118(22)[M-74]$^+$, 107(79)[M-85]$^+$, 91(67)[M-101]$^+$, 89(49)[M-103]$^+$, 79(93)[M-113]$^+$, 77(35)[M-115]$^+$, 65(25)[M-127]$^+$, 63(22)[M-129]$^+$, 51(22)[M-141]$^+$; $[\alpha]_D^{20}$+25.0 (c 1.1, $CHCl_3$). E.e. = 95%, measured by HPLC (Chiralpack AD, Daicel, 250 mm ; hexane-*i*-PrOH, 95:5) Anal. calcd for $C_{11}H_{12}O_3$: C, 68.73 ; H, 6.29. Found: C, 68.65 ; H, 6.32.

(2*S*,3*R*) Ethyl 3-phenylglycidate (3a)

The same procedure with (2*R*,3*R*) **1a** gives the *trans* (2*S*,3*R*) isomer **3a**. TLC: 0.22 (cyclohexane-EtOAc, 95:5) ; GC (DBWax, 220°C), Rt: 3.8 min ; ^1H NMR, δ: 1.34 (t, 3H, J = 7.1 Hz, $OCH_2\underline{CH_3}$), 3.51 (d, 1H,

J = 1.8 Hz, CHCO), 4.10 (d, 1H, J = 1.8 Hz, CHPh), 4.34 (m, 2H, OCH_2CH_3), 7.28-7.40 (m, 5H, Ar-H) ; ^{13}C NMR δ: 14.1 (OCH_2CH_3), 56.7 (CHPh), 57.8 (CHCO), 61.7 (OCH_2CH_3), 125.8 (Ar-C para), 128.6 (Ar-C meta), 128.9 (Ar-C ortho), 135.0 (Ar-C-1), 168.1 (CO) ; $[\alpha]_D^{20}$ +152.0 (c 1.3, $CHCl_3$) E.e. = 95% measured by GC on a XE 60-*S*-valine-*S*-α-phenylethylamide capillary column (Chrompack, 50 m): Rt (2*R*,3*S*) = 30.8 min, Rt (2*S*,3*R*) = 31.3 min.

Alternatively, this isomer may be cyclized with NaOEt: a solution of (2*RS*,3*R*) ethyl 2-chloro-3-hydroxy-3-phenylpropionate (250 mg, 1.09 mmol) in ethanol (2.5 mL) was added at 0°C to a 2M solution of sodium ethylate (0.55 mL). After stirring for 2 h, ethanol was evaporated under reduced pressure. 0.5 N HCl (3 mL) was added and the epoxide was extracted with diethylether (3 x 10 mL). The organic phase was separated, washed with H_2O (5 mL), dried over $MgSO_4$ and concentrated. Yield: 62%.

Ethyl 2-chloro-2,3-dideutero-3-phenylpropionate

D_2O (5 mL) was added to ethyl 2-chloro-3-oxo-3-phenylpropionate (500 mg, 2.2 mmol) and the mixture was stirred for 5 h at room temperature. The excess of D_2O was eliminated by lyophilisation. The same procedure was performed twice. The crude product was dissolved in a mixture of D_2O (2.5 mL) and THF (7.5 mL) at -10°C; $NaBD_4$ (67 mg, 1.6 mmol) was then added. After stirring at -10°C for 1 h, the solution was hydrolyzed with conc. DCl (0.4 mL) and extracted with diethylether (3 x 10 mL). The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography. Yield: 71%. The product was determined by NMR to be a mixture of 68/32 *syn/anti* isomers with a D/H ratio of 75/25 on C-2 position .

Chlorohydroxyester (50 mg, 0.21 mmol) dissolved in abs. EtOH (0.25 mL) was then added to a solution of sodium (5 mg, 0.21 mmol) in abs. EtOH (0.5 mL) at -10°C and stirred for 1 h. After evaporation of EtOH, and addition of DCl in H_2O (2 mL), the mixture was extracted. The residue was determined by GC to be a mixture containing 11% phenylacetaldehyde, 7% *cis*-epoxyester, and 82% *trans*-epoxyester After purification by flash chromatography, 53% of a 8/92 *cis/trans* mixture of epoxides was isolated. The D/H ratio on C-2 position, measured by NMR, was 31/69.

(2*S*,3*R*) Ethyl 2,3-epoxyhexanoate (3b)

(2*R*,3*R*) ethyl 2-chloro-3-hydroxyhexanoate **1b** was cyclized with potassium carbonate as previously described to give *trans* (2*S*,3*R*) ethyl 2,3-epoxyhexanoate in 84% yield. TLC: 0.53 (pentane-diethylether, 95:5) ; GC (BP 10, 100°C), Rt: 7.0 min ; IR (neat): 1750 cm^{-1} (CO_2Et) ; bp 92°C/8 Torr ; ^1H NMR, δ: 0.95 (t, 3H, J = 7.1 Hz, $CH_2CH_2CH_3$), 1.27 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.37-1.69 (m, 4H, $CH_2CH_2CH_3$), 3.12 (m, 1H, *n*-PrCH), 3.17 (d, 1H, J = 1.9 Hz, CHCO), 4.20 (q, 2H, J = 7.1 Hz, OCH_2CH_3) ; ^{13}C NMR, δ: 13.65 ($CH_3CH_2CH_2$), 14.02 (OCH_2CH_3), 19.00 ($CH_3CH_2CH_2$), 33.34 ($CH_3CH_2CH_2$), 52.93 (*n*-PrCH), 58.16 (CHCO), 61.37 (OCH_2CH_3), 169.25 (CO) ; MS(EI) m/z (%): 130(18)[M-28]$^+$, 101(31)[M-57]$^+$, 85(46)[M-73]$^+$, 73(45)[M-85]$^+$, 71(21)[M-87]$^+$, 57(37)[M-101]$^+$, 55(100)[M-103]$^+$; $[\alpha]_D^{20}$ +23.3 (c 1.7, $CHCl_3$); E.e. = 90%.

Alternatively, the cyclisation was achieved by addition of DBU (3.22 mL, 21.6 mmol) to a solution of ethyl 2-chloro-3-hydroxyhexanoate (4.0 g, 20.6 mmol) in CH_2Cl_2 (30 mL). After stirring at room temperature for 2 h, the solution was washed with 0.5 N HCl and extracted with CH_2Cl_2. Yield after distillation: 80%.

From a mixture of racemic chlorohydroxyesters **1b**, the *cis* isomer **2b** was isolated. GC (BP 10, 100°C), Rt: 6.4 min ; ^1H NMR, δ: 0.93 (t, 3H, J = 7.2 Hz, $CH_2CH_2CH_3$), 1.27 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.41-1.72 (m, 4H, $CH_2CH_2CH_3$), 3.13 (m, 1H, *n*-PrCH), 3.48 (d, 1H, J = 4.7 Hz, CHCO), 4.23 (q, 2H, J = 7.1 Hz, OCH_2CH_3) ; ^{13}C NMR, δ: 13.55 ($CH_3CH_2CH_2$), 14.03 (OCH_2CH_3), 19.29 ($CH_3CH_2CH_2$), 29.03 ($CH_3CH_2CH_2$), 52.56 (*n*-PrCH) , 57.18 (CHCO), 61.13 (OCH_2CH_3), 168.15 (CO).

(2*RS*,3*S*) Ethyl 2-hydroxy-3-azido-3-phenylpropionate

Sodium azide (1.07 g, 16.5 mmol) and ammonium chloride (439 mg, 8.29 mmol) were added to a solution of 77/23 *cis*(2*R*,3*R*)/*trans*(2*S*,3*R*) ethyl 3-phenylglycidate (640 mg, 3.3 mmol) in 95% EtOH (10 mL). After

refluxing for 10 h, ethanol was evaporated. The mixture was diluted in diethylether (25 mL), washed with 1 N HCl (20 mL) and extracted. After drying over $MgSO_4$, the organic phase was concentrated and purified by flash chromatography to give the ethyl 2-hydroxy-3-azido-3-phenylpropionate in a 77/23 *syn/anti* ratio. Yield: 85% ; TLC: 0.29 (cyclohexane-EtOAc, 8:2) ; HPLC (Zorbax-Sil 3µm, isooctane-EtOAc, 85:15) Rt: 7.0 min (*syn*), 8.0 min (*anti*) ; IR (neat): 3450 (OH), 2140 (N_3), 1750 cm^{-1} (CO_2Et) ; ^1H NMR, δ (*syn*): 1.31 (t, 3H, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 3.15 (d, 1H, J = 6.7 Hz, OH), 4.30 (q, 2H, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 4.38 (dd, 1H, $J_{CH\text{-}OH}$ = 6.7 Hz, $J_{CH\text{-}CH}$ = 3.0 Hz, C<u>H</u>OH), 4.86 (d, 1H, J = 3.0 Hz, C<u>H</u>N_3), 7.37-7.48 (m, 5H, Ar-<u>H</u>) ; δ (*anti*): 1.21 (t, 3H, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 3.04 (d, 1H, J = 6.5 Hz, OH), 4.18 (q, 2H, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 4.54 (dd, 1H, $J_{CH\text{-}OH}$ = 6.5 Hz, $J_{CH\text{-}CH}$ = 3.9 Hz, C<u>H</u>OH), 4.90 (d, 1H, J = 3.9 Hz, C<u>H</u>N_3), 7.37-7.48 (m, 5H, Ar-<u>H</u>) ; ^{13}C NMR, δ (*syn*): 14.04 ($OCH_2\underline{C}H_3$), 62.39 ($O\underline{C}H_2CH_3$), 67.14 (<u>C</u>HN_3), 73.87 (<u>C</u>HOH), 127.87, 128.45, 128.7, 135.52 (Ar-<u>C</u>), 171.86 (CO) ; δ (*anti*): 13.96 ($OCH_2\underline{C}H_3$), 62.15 ($O\underline{C}H_2CH_3$), 67.20 (<u>C</u>HN_3), 73.72 (<u>C</u>HOH), 126.2, 128.5, 128.7, 134.37 (Ar-<u>C</u>), 171.29 (CO); MS(EI) m/z (%): 132(22)$[M\text{-}103]^+$, 104(94)$[M\text{-}131]^+$, 91(15)$[M\text{-}144]^+$, 77(100)$[M\text{-}158]^+$, 76(35)$[M\text{-}159]^+$, 51(22)$[M\text{-}184]^+$.

(2*R*,3*S*) Ethyl *N*-(*t*-butoxycarbonyl)-3-phenylisoserine

The previous *syn/anti* mixture of ethyl 2-hydroxy-3-azido-3-phenylpropionate (650 mg, 2.7 mmol) was dissolved in EtOAc (6.5 mL) and hydrogenated in the presence of *t*-butyl pyrocarbonate (725 mg, 3.3 mmol) and 10% palladium on charcoal (65 mg). After stirring for 69 h, the resulting mixture was filtered through a Celite pad; the filtrate was washed with water (10 mL), dried over $MgSO_4$ and chromatographed on silica gel. After recrystallisation from cyclohexane-CH_2Cl_2 (1:1), the pure (2*R*,3*S*) isomer was obtained in 68% overall yield. TLC: 0.27 (cyclohexane-EtOAc, 75:25) ; HPLC (Zorbax-Sil 3µm, isooctane-EtOAc, 85:15) Rt: 13.4 min ; IR (neat): 3495 (OH), 3380 (NH), 1720 (CO_2Et), 1680 cm^{-1} (NHCO) ; mp 121°C (lit.[30] 124°C); ^1H NMR, δ: 1.34 (t, 3H, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.42 (s, 9H, $C(C\underline{H}_3)_3$), 3.15 (br d, 1H, OH), 4.31 (m, 2H, $OC\underline{H}_2CH_3$, 4.46 (br s, 1H, NH), 5.24 (br d, 1H, J = 9.7 Hz, C<u>H</u>OH), 5.32 (br d, 1H, J = 9.7 Hz, C<u>H</u>NH), 7.29-7.38 (m, 5H, Ar-<u>H</u>) ; ^{13}C NMR, δ: 14.07 ($OCH_2\underline{C}H_3$), 28.20 ($C(\underline{C}H_3)_3$), 55.90 (<u>C</u>HNH), 62.41 ($O\underline{C}H_2CH_3$), 73.54 (<u>C</u>HOH), 79.74 (<u>C</u>$(CH_3)_3$), 126.6, 127.6, 128.5, 139.00 (Ar-<u>C</u>), 155.02 ($\underline{C}O_2C(CH_3)_3$), 172.87 ($\underline{C}O_2Et$); $[\alpha]_D^{25}$ +5.1 (c 1.1, $CHCl_3$) (lit.[30] +6.3) .

(2*R*,3*S*) 2-Hydroxy-3-amino-3-phenylpropionamide (4)

Ethyl 3-phenylglycidate (*cis/trans*:77/23) (375 mg, 1.5 mmol) was dissolved in a solution of 10 mL of ethanol saturated with ammonia at -20°C. This solution was placed in a stainless steel Parr reactor and heated to 100°C for 22 h. After filtration on Chelex 100 to eliminate the nickel salts, the solution was evaporated by lyophilisation and recristallized in anhydrous methanol to give pure (2*R*,3*S*) 2-hydroxy-3-amino-3-phenylpropionamide in 54% yield. Mp 177°C (lit.[4] 172°C); HPLC (Zorbax-Sil 5µm, CH_2Cl_2-*i*-PrOH-H_2O-Et_3N, 125:40:3:0.1) Rt: 5.75 min ; IR (neat): 3420 (OH), 3140 (NH_2), 1640 cm^{-1} (CONH) ; ^1H NMR (DMSO-d_6+D_2O), δ: 3.95 (d, 1H, J = 3.4 Hz, C<u>H</u>), 4.05 (d, 1H, J = 3.4 Hz, C<u>H</u>), 7.21-7.43 (m, 5H, Ar-<u>H</u>); ^{13}C NMR (DMSO-d_6+D_2O), δ: 57.06 (<u>C</u>HNH_2), 75.45 (<u>C</u>HOH), 127.06-128.18-142.85 (Ar-<u>C</u>), 176.05 (<u>C</u>ONH_2) ; MS(CI)NH_3 m/z (%): 217(32)$[M+37]^+$, 209(100)$[M+29]^+$, 134(12)$[M\text{-}46]^+$; $[\alpha]_D^{25}$ +0.5 (c 1.0, MeOH).

(2*RS*,3*RS*) 2-hydroxy-3-amino-3-phenylpropionamide

The same procedure was used to prepare the *anti* isomer from the (±)-*trans*-epoxide **3a**. Yield: 50%. Mp 199°C (lit.[28] 183°C); HPLC (Zorbax-Sil 5µm, CH_2Cl_2-*i*-PrOH-H_2O-Et_3N, 125:40:3:0.1) Rt: 7.45 min; ^1H NMR (DMSO-d_6+D_2O), δ: 4.00 and 4.05 (2d, 2H, J = 4.1Hz, C<u>H</u>), 7.20-7.40 (m, 5H, Ar-<u>H</u>).

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21. Assuming an exclusive formation of the *trans* epoxide from the [2,3-$^2H_2$] *syn* chlorohydroxyester, the maximum D/H ratio of the *trans* epoxide ought to be (32 x 0.75)/[68 + (32 x 0.25)] = 24/76.
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