Recl. Trav. Chim. Pays-Bas **111**, 069–074 (1992) 0165-0513/92/02069-06$2.00

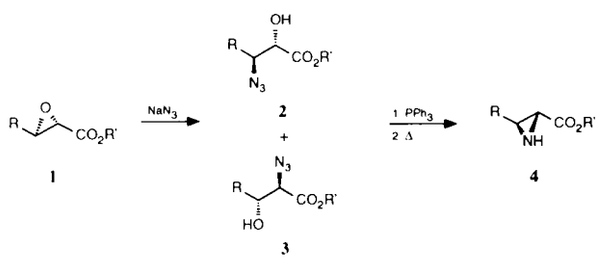
Synthesis of β-amino α-hydroxy carboxylic esters from oxiranecarboxylic esters

Johan Legters, Erik van Dienst, Lambertus Thijs and Binne Zwanenburg*

Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands
(Received March 27th, 1991)

Abstract. 3-Aryl-3-azido-2-hydroxypropanoic esters, prepared from the corresponding 3-aryloxirane-2-carboxylic esters by ring opening with sodium azide, were reduced with tin(II) chloride dihydrate in methanol to give 3-amino-3-aryl-2-hydroxypropanoic esters in good yields. Under these conditions, halogen substituents in the aromatic rings were not affected. The nitro group, however, was partially reduced to the amino group. Treatment of aliphatic oxirane-2-carboxylic esters with acetonitrile in the presence of boron trifluoride etherate led to regiospecific formation of 2,4-dialkyl-2-oxazoline-5-carboxylic esters, resulting from reaction of the nitrile at C3. Acidic hydrolysis of these oxazoline-5-carboxylic esters gave the corresponding 3-(acylamino)-2-hydroxy carboxylic esters. With these two complementary methods, both aryl- and alkyl-substituted β-amino α-hydroxy acid derivatives are accessible.

In recent publications[1], we have reported the synthesis of aziridine-2-carboxylic esters from the corresponding oxirane-2-carboxylic esters (Scheme 1). The first step in this synthesis involves ring opening of the epoxide function in



Scheme 1

substrate **1** with azide ion. The azido alcohols obtained in this manner are subsequently treated with triphenylphosphine to accomplish ring closure to the aziridines **4**. The regiochemistry of the ring-opening reaction is strongly dependent on the nature of the R substituent. For the synthesis of the aziridines **4**, this does not cause a problem, because both regioisomers **2** and **3** are converted into the same product. These aziridine-2-carboxylic esters can be used as starting materials for the preparation of a variety of β-substituted α-amino acid derivatives[2].

In those cases where the azide reaction with epoxy esters **1** proceeds regiospecifically, the azido alcohols can serve as potential starting materials for the corresponding amino alcohols. As demonstrated previously[1], aryl-substituted oxiranecarboxylic esters **1** exclusively yield azido hydroxy esters of type **2**. It is, therefore, of interest to investigate the preparation of β-amino α-hydroxy carboxylic esters from azido alcohols **2** where R is an aromatic substituent[3].

For this purpose, a series of 3-aryl-3-azido-2-hydroxypropanoic esters **2** was prepared from the corresponding oxiranecarboxylic esters **1** in the manner described earlier[1].

For the conversion of an azide function into an amino group, several methods have been reported[4], *e.g.*, reduction with hydrides, with phosphines, with sulfur derivatives and with low-valence metal ions, as well as catalytic hydrogenolysis. Most of these methods have serious drawbacks in the present case of the reduction of **2** (R = Ar), because of the presence of the hydroxyl and ester functions. Lithium aluminum hydride[5] will reduce the ester function, whereas sodium borohydride[4a,6] is too weak a reducting agent for an azide. When the latter reduction is carried out under conditions of phase-transfer catalysis, conversion to amine can be achieved; however, the methyl ester function will then also be affected[4a,6]. The Staudinger reaction[7], involving treatment with triphenylphosphine, in the present case will lead to aziridine-2-carboxylates and is, therefore, of no value for the desired amine synthesis (*cf.*, Ref. 1).

More success may be expected from reductions employing appropriate transition metal ions. In essence, the overall process involves the transfer of two protons and two electrons[8]. Little is known about the details of the mechanism of azide reduction with metal ions. Attempted reduction of substrate **2d** with an aqueous solution of $Cr^{II}Cl_2$, according to *Kaufmann* and *Thompson*[8], led to nitrogen evolution as well as a color change from blue (Cr^{2+}) to green (Cr^{3+}), but the desired amine could not be detected.

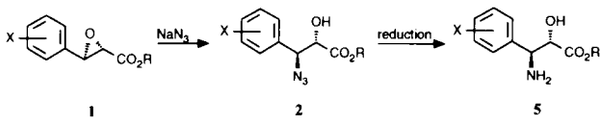
Good results were obtained when azido alcohols **2** were treated with an excess of tin(II) chloride dihydrate in boiling methanol or ethanol. This method is a modification of that recently reported by *Maiti* et al.[9]. The results are

Table I Preparation of α-hydroxy-β-amino esters **5** *by reduction of* **2**.

Entry	2	X	R	Method[a]	5	Yield (%)	Hydrochloride[b] yield (%)
i	**2a**	H	Me	A	**5a**	95	
ii	**2b**	H	Et	B	**5b**	72	83
iii	**2c**	4′-Br	Me	B	**5c**	47	45
iv	**2d**	4′-F	Me	B	**5d**	64	66
v	**2e**	4′-Cl	Me	B	**5e**	64	84
vi	**2f**	2′-Cl	Me	B	**5f**	77	
vii	**2g**	3′-Cl	Me	B	**5g**	71	
viii	**2h**	4′-MeO	Me	B	**5h**	51	
ix	**2i**	4′-NO_2	Me	C	**5i**	21	

[a] Method A: H_2/Pd(C), ethanol. Method B: $SnCl_2 \cdot 2H_2O$, ROH, reflux. Method C: $SnCl_2 \cdot 2H_2O$, ROH, room temperature. [b] Prepared by treatment of **5** with ethereal HCl.

collected in Table I. The yields are satisfactory to good for the various substrates **2**, except for 4-NO_2-substituted compound **2i**. In addition to reduction of the azide function, reduction of the nitro group also took place to give the corresponding 4-aminophenyl amino alcohol. In order to achieve better selectivity, reduction with 1.1 equivalents of tin(II) chloride dihydrate was attempted; however, no reaction took place.



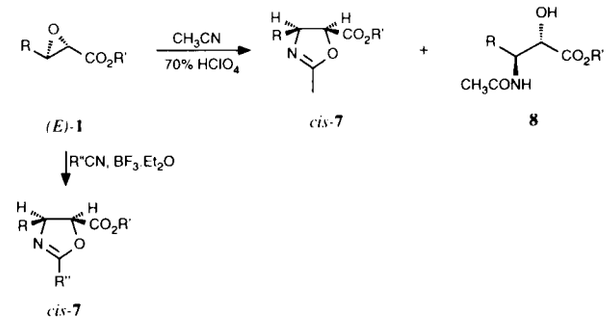
Scheme 2

It should be noted that substrate **2a**, containing an unsubstituted phenyl ring, can be converted into the corresponding amino alcohol **5a** on catalytic hydrogenation (*cf.*, ref. 10). This approach does not work for the halogen substituted compounds **2c–i**, because dehalogenation also took place.

The amino hydroxy esters could readily be converted into the corresponding hydrochlorides on treatment with ethereal hydrogen chloride (see Table I). The stereochemistry of the amino hydroxy esters can be deduced from the steric course of the azide epoxide opening reaction. It has been demonstrated[1] that these reactions take place via an S_N2-type reaction involving inversion of configuration at the site of attack (*cf.*, Scheme 1). Accordingly, the configuration of the products derived from the *trans*-substituted epoxy esters must be *anti* (*i.e.*, 2*R**,3*R**).

For the synthesis of aliphatic β-amino α-hydroxy carboxylic esters[3] **6**, the pathway via azido alcohols, obtained by reaction of oxiranecarboxylic esters with azide ions, cannot be used because of the lack of regiospecificity of this epoxide opening[1]. In the search for alternative approaches, the conversion of oxiranecarboxylic esters into oxazoline-5-carboxylic esters by a Ritter-type reaction with acetonitrile[11-13] was considered as an attractive possibility, because oxazolines are recognized as masked amino alcohols[14-20]. The reaction of epoxy esters with nitriles has previously been studied by *Zvonkova* et al.[14].

The aliphatic oxirane-2-carboxylic esters **1j-1n**, prepared as reported earlier[1], were subjected to a ring enlargement reaction with acetonitrile using various acid catalysts. Thus, treatment of **1j** with acetonitrile in the presence of perchloric acid, according to *Zvonkova* et al.[14], gave a mixture of oxazoline **7a** and amide **8a**, when the reaction was carried out at room temperature (Scheme 3). When this reaction was performed under reflux conditions, the main



Scheme 3

product was amide **8a**, which is the result of hydrolysis of the initially formed oxazolinecarboxylate **7a**. With sulfuric acid as catalyst (*cf.*, ref. 14), a mixture of products was produced, among which were oxazoline **7a** and amide **8a**. The Lewis-acid catalysts zinc chloride and zinc bromide gave very slow reactions, while titanium(IV) isopropoxide did not cause any reaction. With titanium(IV) chloride, epoxide opening to the hydroxy chloride was observed instead of ring expansion. The same product was obtained by treatment of **1j** with 2N hydrochloric acid in ether.

The best results were obtained with boron trifluoride etherate as catalyst. Treatment of **1j** with acetonitrile in the presence of 2 equivalents of boron trifluoride etherate at room temperature produced oxazoline **7a** in a yield of 71%. The results with the other aliphatically substituted oxirane-2-carboxylic esters are collected in Table II. It is of interest to note that the phenyl substituted oxirane **1a** leads only to a mixture of products in an attempted ring expansion reaction with acetonitrile in the presence of boron trifluoride etherate.

Chromatographic purification on silica led to a substantial hydrolysis on the column to give hydroxy amide **8** (*cf.*, ref. 21). Especially **7e**, which was left on a silica-gel column overnight, gave a considerable amount of hydroxy amide **8e** on elution. Immediately after preparation, oxazoline **7f** (the enantiomer of **7e**) was chromatographed rapidly; however, in this case hydrolysis also took place, resulting in 24% of **8f** as a by-product.

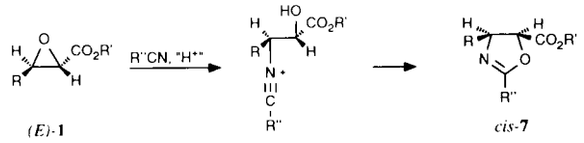
The structures of the oxazolines **7** were established on the basis of their ^{1}H NMR spectra. The coupling constants of C4–H and C5–H ($^3J_{4,5}$), which amount to *ca.* 10 Hz, are

Table II Conversion of oxirane-2-carboxylic esters **1** *into oxazolines* **7**.

Entry	1	R	R′	Config.	7	R″	Yield (%)[a]	Config.
i	**1j**	C_6H_{13}	Et	rac	**7a**	Me	71 (93)	
ii	**1j**	C_6H_{13}	Et	rac	**7b**	Et	71 (86)	
iii	**1j**	C_6H_{13}	Et	rac	**7c**	Ph	60	
iv	**1k**	C_6H_{13}	Me	2R,3*S*	**7d**	Et	40	4*R*,5*R*
v	**1l**	C_5H_{11}	Me	2*R*,3*S*	**7e**	Et	13[b] (100)	4*R*,5*R*
vi	**1m**	C_5H_{11}	Me	2*S*,3*R*	**7f**	Et	56[c] (96)	4*S*,5*S*
vii	**1n**	iC_3H_7	Et	rac	**7g**	Me	57 (73)	
viii	**1a**	Ph	Me	rac	**7h**	Me	mixture[d]	

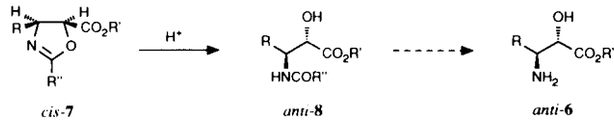
[a] Yields after purification. Numbers in parentheses refer to yields of crude product. [b] 58% of hydroxy amide **8e** was isolated. [c] 24% of hydroxy amide **8f** was isolated. [d] A complex mixture of products was obtained.

reliable evidence for the *cis* relationship of these protons[22]. The spectra reveal that the nitrile has reacted regiospecifically at C3 of the epoxide. The mechanistic pathway to the ring-expanded products can be deduced from these data. Initial opening of the epoxide by the nitrile at C3 in an S_N2 fashion, produces a nitrilium ion, which undergoes an intramolecular ring closure reaction (Scheme 4). This mechanism of formation agrees with that reported by *Wohl* et al.[13] for non-functionalized epoxides.



Scheme 4

For the hydrolysis of oxazolines various conditions have been reported, *e.g.*, 3N aqueous sulfuric acid in tetrahydrofuran (*Zvonkova*[14]), water (air moisture, *Lindsay Smith*[15]), 5–7% H_2SO_4 in ethanol (*Meyers*[23]), 3–6N aqueous sulfuric acid (*Meyers*[24]), 3–6N aqueous hydrochloric acid (*Meyers*[24], *Seebach*[16]), concentrated HCl in methanol (*Meyers*[24], *Ito*[18]). In most of these cases, formation of the corresponding hydroxy amines was reported; in some cases, however, the hydroxy amide was isolated. With oxazoline-5-carboxylates **7a**, **7b** and **7g** several hydrolytic conditions were investigated. The results are collected in Table III. When oxazoline **7a** was treated with concentrated hydrochloric acid in boiling ethanol for 24 h 54% of hydroxy amide **8a** was obtained as the principal product; no amino alcohol could be isolated (Table III, entry *i*).Treatment of **7a** with 70% perchloric acid in dichloromethane (room temperature, 4 days) gave amide **8a** in a lower yield (entry *ii*). Heating of a heterogeneous mixture of **7b**, silica-gel-60H and concentrated sulfuric acid in ether, resulted in the formation of amido hydroxy ester **8b** (entry *iv*). Similarly, **7g** gave, using 2N HCl instead of sulfuric acid, product **8g** in an acceptable yield (entry *v*). In the hydrolysis experiments described above, formation of amino hydroxy esters **6** may have occurred to some extent. However, their isolation may be rather difficult because of their high solubility in water.



Scheme 5

The best results for oxazoline hydrolysis were obtained using oxalic acid in boiling ethanol, a method described by *Meyers*[25]. This procedure is known to give hydroxy amides. Treatment of oxazoline **7a** with oxalic acid in boiling ethanol gave 90% of amide **8a** in a clean reaction (Table III, entry *iii*). On the basis of this experiment, hydrolysis to amido hydroxy esters **8** using oxalic acid is recommended. In conclusion, the results described above demonstrate that

Table III Hydrolysis of oxazolines **7**.

Entry	7	Method[a]	Product	Yield (%)
i	**7a**	A	**8a**	54
ii	**7a**	B	**8a**	37
iii	**7a**	C	**8a**	90
iv	**7b**	D	**8b**	44
v	**7g**	E	**8g**	74

[a] Method A: concd. HCl, ethanol, reflux, 24 h. Method B: 70% $HClO_4$, dichloromethane, room temperature, 4 days. Method C: oxalic acid, ethanol, reflux, 20 h. Method D: concd. H_2SO_4, silicagel-60H, ether, reflux, 40 h. Method E: 2N HCl, silicagel-60H, ether, reflux, 16 h.

β-amino α-hydroxy acid derivatives can readily be obtained from oxiranecarboxylic esters, either by an initial regioselective epoxide opening with azide ion for aromatically substituted substrates or by initial ring expansion to oxazolines for aliphatically substituted epoxy esters.

Experimental

General remarks

Mrs. *H. I. V. Amadtjais-Groenen* (el. anal.), Mr. *P. M. van Galen* (MS) and Mr. *A. E. M. Swolfs* (non-routine NMR) of our analytical department produced most of the analytical data under the supervision of Mr. *F. P. van der Meer*.

Elemental analyses were standard performed in triplicate.^{1}H NMR spectra were recorded on a Varian EM 390 (90 MHz, CW), a Bruker WH 90 (90 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as internal standard. IR spectra were run on a Perkin-Elmer 298 spectrophotometer. For mass spectroscopy a double focussing VG 7070E was used.

Melting points were determined on a Reichert Thermopan microscope and are uncorrected.

GC was performed on a Hewlett-Packard 5710A instrument equipped with a packed Chrompack SE 30 (10%, 6′ × 1/8″) column, or on a Hewlett-Packard 5790A or 5890 instrument equipped with a capillary HP cross-linked methyl silicone (25 m x 0.31 mm) column, connected to a HP 3390 or HP 5890 calculating integrator.

Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

For preparative chromatography a slightly modified version of the "flash"/chromatography technique as described by *Still* et al.[26] was used. The stationary phase was Silica gel 60H (Merck, art. No. 7736). A pressure of 1.5–2.0 bar was used to obtain the necessary flow rate. The column length was approximately 15 cm, column diameters varied between 2 and 5 cm.

Hexane was distilled from calcium hydride. Dichloromethane was distilled from phosphorus pentoxide. Diethyl ether was predried on calcium chloride, then distilled from calcium hydride and once more from sodium hydride. Acetonitrile was distilled from phosphorus pentoxide. Tin(II) chloride dihydrate *p.a.* was purchased from Janssen Chimica.

Azido alcohols **2**

Azido alcohols **2a-i** were prepared by treating oxiranecarboxylic esters **1** with sodium azide and ammonium chloride in ethanol (**2b**) or methanol (**2a**, **2c-i**), as described earlier[1a,c].

3-Phenyl-3-amino-2-hydroxypropanoic esters **5**

Methyl (2R,3R*)-3-phenyl-3-amino-2-hydroxypropanoate* (**5a**). To a solution of **2a** (0.46 g, 2.1 mmol) in absolute ethanol (25 ml) some Pd(C) was added. The mixture was shaken in a hydrogen atmosphere for 1 h. The catalyst was then removed by filtration through a Celite pad. The filtrate was concentrated, yielding 0.39 g (95%) of **5a** as a yellowish oil which crystallized on cooling. IR ($CHCl_3$): ν 3530 (OH), 3380/3320 (br, NH_2), 3060, 2950, 1730 (C=O), 1600, 1585, 1490, 1435, 1270 (br), 1100, 1070, 985, 905 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.8 (br s, 3H, N<u>H</u>$_2$, O<u>H</u>), 3.6 (s, 3H, $CO_2C\underline{H}_3$), 4.25 (d, 1H, *J* 4 Hz), 4.4 (d, 1H, *J* 4 Hz), 7.25 (m, 5H, $C_6\underline{H}_5$) ppm.

Ethyl (2R,3R*)-3-phenyl-3-amino-2-hydroxypropanoate* (**5b**)

General procedure using $SnCl_2 \cdot 2H_2O$. Tin(II) chloride dihydrate (0.60 g, 2.7 mmol) was added to a solution of **2b** (201 mg, 0.86 mmol) in ethanol (5 ml). The reaction mixture was heated at reflux for 1½ h and then cooled and concentrated. The residue was dissolved in dichloromethane (20 ml) and water (20 ml). After adjustment of the pH to 8 with 4N sodium hydroxide solution, the layers were separated and the aqueous layer was extracted with dichloromethane (5 x 10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. Yield 129 mg (72%) of **5b** as a colorless oil which solidified on cooling. IR as for **5a**. ^1H NMR ($CDCl_3$): δ 1.15 (t, 3H, $C\underline{H}_3$), 2.65 (br s, 3H, N<u>H</u>$_2$, O<u>H</u>), 4.05 (q, 2H, $OC\underline{H}_2CH_3$), 4.2 (d, 1H, *J* 4.5 Hz), 4.35 (d, 1H, *J* 4.5 Hz), 7.25 (s, 5H, $C_6\underline{H}_5$) ppm.

Ammonium chloride of **5b** *(general procedure).* Ethereal HCl solution (1 ml) was added to a solution of **5b** (41 mg, 0.20 mmol) in ether (10 ml). Immediately a white precipitate was formed. After concentration of the solution, the residue was dissolved in as little dichloromethane as possible. The ammonium chloride was then precipitated by addition of ether. The mother liquor was decanted. The precipitated salt was washed with ether and dried *in vacuo*. Yield 40 mg (83%) of the ammonium chloride as a white solid. M.p. 85–87°C. IR (KBr): ν 3370 (OH), 3700–2400 (br, NH_3^+), 1725 (C=O), 1595, 1495, 1465, 1380, 1325, 1295, 1240, 1230, 1210, 1150, 1085, 1005, 930, 915, 855, 790, 765, 705 (s), 635 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.05 (t, 3H, $C\underline{H}_3$), 3.3 (br s, 1H, O<u>H</u>), 3.95 (q, 2H, $OC\underline{H}_2CH_3$), 4.53 (d, 1H, *J* 4 Hz), 4.83 (d, 1H, *J* 4 Hz), 7.2 (s, 5H, $C_6\underline{H}_5$)), 8.8 (br s, 3H, $N\underline{H}_3^+$) ppm. ^1H NMR (DMSO-d_6 + D_2O): δ 1.05 (t, 3H, $C\underline{H}_3$), 3.95 (q, 2H, $OC\underline{H}_2CH_3$), 4.60 (d, 1H, *J* 4 Hz), 4.75 (d, 1H, *J* 4 Hz), 7.2 (s, 5H, $C_6\underline{H}_5$) ppm.

Methyl (2R,3R*)-3-(4-bromophenyl)-3-amino-2-hydroxypropanoate* (**5c**). Employing the general procedure, **2c** (0.66 g, 2.2 mmol) and tin(II) chloride dihydrate (0.60 g, 2.7 mmol) in methanol (10 ml) gave amino alcohol **5c** (0.28 g, 47%) as a colorless oil, which solidified on cooling (reaction time 1 h). The product was recrystallized from ether/dichloromethane. M.p. 120–122°C. IR ($CHCl_3$): ν 3530 (OH), 3375/3310 (NH), 3150, 2940, 1725 (C=O), 1590, 1435, 1375, 1275, 1200 (br), 1095, 1070, 1010, 900 (br), 645 cm^{-1}. IR (KBr): ν 3600–2500 (br, NH_2, OH), 3350, 3295, 2945, 2860, 2740, 1740 (C=O), 1585, 1485, 1450, 1310, 1215, 1195, 1165, 1095, 1070, 1010, 980, 970, 960, 915, 910, 835, 735, 720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.65 (br s, 3H, N<u>H</u>$_2$, O<u>H</u>), 3.65 (s, 3H, $CO_2C\underline{H}_3$), 4.2 (d, 1H, *J* 4.5 Hz), 4.4 (d, 1H, *J* 4.5 Hz), 7.1–7.5 (m, 4H, $C_6\underline{H}_4$) ppm. MS (CI): *m/e* (%) 274/276 (72/71, M + 1$^+$), 197/199 (20/20), 184/186 (100/98, $BrC_6H_4CH^+NH_2$), 169/171 (18/17). Calcd. for $C_{10}H_{12}BrNO_3$ (274.115): C 43.82, H 4.41, N 5.11; found: C 43.66, H 4.35, N 5.04%.

Ammonium chloride. From **5c** (102 mg, 0.37 mmol), 52 mg (45%) of the corresponding chloride was obtained. M.p. 108–110°C. IR (KBr): ν 3700–2400 (br, NH_3^+, OH), 1735 (C=O), 1590, 1485, 1435, 1415, 1380, 1250, 1235, 1140, 1070, 1010, 840, 725, 640 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.25 (br s, 1H, O<u>H</u>), 3.5 (s, 3H, $CO_2C\underline{H}_3$), 4.5 (d, 1H), 4.8 (br s, 1H), 7.2–7.6 (m, 4H, C_6H_4), 8.8 (br s, 3H, $N\underline{H}_3^+$) ppm. ^1H NMR (DMSO-d_6 + D_2O): δ 3.5 (s, 3H, $CO_2C\underline{H}_3$), 4.55 (d, 1H, *J* 4.5 Hz), 4.7 (d, 1H, *J* 4.5 Hz) 7.2–7.6 (m, 4H, C_6H_4) ppm. Calcd. for $C_{10}H_{13}BrClNO_3 \cdot H_2O$ (328.601): C 36.55, H 4.60, N 4.26; found: C 36.00, H 4.49, N 4.25%.

O,N-*Dibenzoate.* M.p. 156–160°C (hexane/diethyl-ether). IR (KBr): ν 3270 (br, NH), 1750. 1730, 1715, 1640 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.67 (s, 3H, $CO_2C\underline{H}_3$), 5.66 (d, 1H, CH–C<u>H</u>–CO_2Me, *J* 5 Hz), 5.87 (dd, 1H, NH–C<u>H</u>–CH), 7.3–8.1 (m, 15H, 2 $C_6\underline{H}_5$, $C_6\underline{H}_4$, N<u>H</u>). Calcd. for $C_{24}H_{20}BrNO_5$ (482.333): C 59.77, H 4.18, N 2.90; found: C 59.86, H 4.31, N 2.92%.

Methyl (2R,3R*)-3-(4-fluorophenyl)-3-amino-2-hydroxypropanoate* (**5d**). Employing the general procedure, azide **2d** (489 mg, 2.1 mmol) and tin(II) chloride dihydrate (0.70 g, 3.1 mmol) in methanol (7 ml) produced **5d** (279 mg, 64%) as a colorless oil, which solidified upon cooling (reaction time 1½ h). M.p. 95–96°C (diethyl ether). IR ($CHCl_3$): ν 3520 (OH), 3375/3310 (NH_2), 2950, 1725 (C=O), 1600, 1495, 1435, 1415, 1225 (br), 1090, 835, 665 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.8 (br s, 3H, N<u>H</u>$_2$, O<u>H</u>), 3.65 (s, 3H, $CO_2C\underline{H}_3$), 4.2 (d, 1H, *J* 4.5 Hz), 4.4 (d, 1H, *J* 4.5 Hz), 6.8-7.4 (m, 4H, $C_6\underline{H}_4$) ppm. Calcd. for $C_{10}H_{12}FNO_4$ (213.210): C 56.23, H 5.67, N 6.57; found: C 56.15, H 5.84, N 6.43%.

Ammonium chloride. From **5d** (134 mg, 0.63 mmol) 103 mg (66%) of hydrochloride was obtained, which was recrystallized from dichloromethane/MeOH/diethyl-ether. M.p. 155–157°C. IR (KBr): ν 3480, 3280, 3230, 3600–2500 (br, NH_3^+, OH), 1750 (C=O), 1600, 1575, 1510, 1450, 1435, 1215 (br), 1165, 1140, 1065, 985, 850, 845, 750, 730, 710 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.2 (br s, 1H, OH), 3.55 (s, 3H, $CO_2C\underline{H}_3$), 4.6 (d, 1H), 4.85 (br s, 1H), 7.0–7.7 (m, 4H, $C_6\underline{H}_4$), 8.7 (br s, 3H, $N\underline{H}_3^+$) ppm. ^1H NMR (DMSO-d_6 + D_2O): δ 3.55 (s, 3H, $CO_2C\underline{H}_3$), 4.6 (d, 1H), 4.7 (d, 1H), 7.0–7.7 (m, 4H, $C_6\underline{H}_4$) ppm. Calcd. for $C_{10}H_{13}ClFNO_3$ (249.671): C 47.78, H 5.04, N 5.58%; found: C 48.11, H 5.25, N 5.61%.

O,N-*Dibenzoate.* M.p. 145-146°C (hexane/diethyl-ether). IR (KBr): ν 3300 (br, NH), 1760 1730 1630 cm^{-1}. ^1H NMR ($CDCl_3$): 3.67 (s, 3H, $OC\underline{H}_3$), 5.66 (d, 1H, CH–C<u>H</u>–CO_2Me, *J* 5.1 Hz), 5.88 (dd, 1H, NH–C<u>H</u>–CH), 6.9–7.60 (m, 11H, 2 $C_6\underline{H}_5$, N<u>H</u>), 7.8 (m, 2H), 7.9 (m, 2H) ppm. Calcd. for $C_{24}H_{20}FNO_5$ (421.428): C 68.40, H 4.78, N 3.32%; found: C 68.32, H 4.93, N 3.34%.

Methyl (2R,3R*)-3-(4-chlorophenyl)-3-amino-2-hydroxypropanoate* (**5e**). Employing the general procedure, azide **2e** (578 mg, 2.3 mmol) and tin(II) chloride dihydrate (0.67 g, 3.0 mmol) in methanol (10 ml) gave 333 mg (64%) of **5e** as a colorless viscous oil (reaction time 1 h). IR ($CHCl_3$): ν 3525 (OH), 3385/3320 (NH_2), 3155, 2955, 1735 (C=O), 1600, 1485, 1440, 1375, 1265, 1220, 1095, 1015, 990, 905, 840, 650 cm^{-1}. ^1H MR ($CDCl_3$): δ 2.85 (br s, 3H, N<u>H</u>$_2$, O<u>H</u>), 3.6 (s, 3H, $CO_2C\underline{H}_3$), 4.67 (d, 1H, *J* 4.5 Hz), 4.85 (d, 1H, *J* 4.5 Hz), 7.2 (s, 4H, $C_6\underline{H}_4$) ppm.

Ammonium chloride. From **5e** (125 mg, 0.55 mmol) 122 mg (84%) of the corresponding chloride was obtained. M.p. 115–117°C. IR (KBr): ν 3650–2500 (NH_3^+, OH), 1735 (C=O), 1590, 1490, 1435, 1375, 1235, 1145, 1095, 1015, 840 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.4 (br s, 1H, O<u>H</u>), 3.55 (s, 3H, $CO_2C\underline{H}_3$), 4.60 (br s, 1H), 4.85 (d, 1H, *J* 4 Hz), 7.45 (s, 4H, $C_6\underline{H}_4$), 8.7 (br s, 3H, $N\underline{H}_3^+$) ppm. ^1H NMR (DMSO-d_6 + D_2O): δ 3.55 (s, 3H, $CO_2C\underline{H}_3$), 4.65 (d, 1H, *J* 4 Hz), 4.75 (d, 1H, *J* 4 Hz), 7.45 (m, 4H, $C_6\underline{H}_4$) ppm. Calc. for $C_{10}H_{13}Cl_2NO_3 \cdot H_2O$: C 42.27, H 5.32, N 4.93; found: C 42.95, H 5.03, N 4.91%.

Methyl (2R,3R*)-3-(2-chlorophenyl)-3-amino-2-hydroxypropanoate* (**5f**). Employing the general procedure, azide **2f** (481 mg, 1.9 mmol) and tin(II) chloride dihydrate (0.65 g, 2.9 mmol) in methanol (10 ml) gave 333 mg (77%) of **5f** as a colorless oil (reaction time 1 h). IR ($CHCl_3$): ν 3520 (OH), 3380/3320 (NH_2), 3030, 2945, 1725 (C=O), 1590, 1570, 1430, 1200 (br), 1080, 990, 955, 905, 850, 650 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.85 (br s, 3H, N<u>H</u>$_2$, O<u>H</u>), 3.55 (s, 3H,

$CO_2C\underline{H}_3$), 4.55 (d, 1H, *J* 4.5 Hz), 4.75 (d, 1H, *J* 4.5 Hz), 7.0–7.6 (m, 4H, $C_6\underline{H}_4$) ppm.
O,N-*Dibenzoate*. M.p. 175–177°C (hexane/diethyl-ether). IR (KBr): 3400 (s, NH), 1760 1710, 1670 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 3.64 (s, 3H, $CO_2C\underline{H}_3$), 5.65 (d, 1H, CH–C<u>H</u>–CO_2Me, *J* 5.8 Hz), 6.23 (dd, 1H, NH–C<u>H</u>–CH, *J* 5.8 Hz and *J* 7.7 Hz as appears by irradiation at 5.65 ppm), 7.2–7.6 (m, 11H, 2 $C_6\underline{H}_5$, NH), 7.8–8.05 (m, 4H, *o*-<u>H</u>'s). Calcd. for $C_{24}H_{20}ClNO_5$ (437.882): C 65.83, H 4.60, N 3.20; found: C 66.06, H 4.77, N 3.19%.

*Methyl (2*R*,*3*R*)*-3-(3-chlorophenyl)-3-amino-2-hydroxypropanoate* (**5g**). Employing the general procedure, azide **2g** (710 mg, 2.8 mmol) and tin(II) chloride dihydrate (0.90 g, 4.0 mmol) in methanol (10 ml) gave 454 mg (71%) of **5g** as a colorless oil (reaction time 2 h). IR ($CHCl_3$): ν 3520 (OH), 3380/3320 (NH_2), 2945, 1730 (C=O), 1595, 1570, 1430, 1225 (br), 1080, 995, 880 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 2.70 (br s, 3H, $N\underline{H}_2$, O<u>H</u>), 3.60 (s, 3H, $CO_2C\underline{H}_3$), 4.2 (d, 1H, *J* 4 Hz), 4.4 (d, 1H, *J* 4 Hz), 7.0–7.4 (m, 4H, $C_6\underline{H}_4$) ppm.
O,N-*Dibenzoate*. M.p. 149–151°C (hexane/diethyl-ether). IR (CCl_4): ν 3380 (s, NH), 3370–3300 (br, NH), 1740 1705 1665 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 3H, $CO_2C\underline{H}_3$), 5.65 (d, 1H, CH–C<u>H</u>–CO_2Me, *J* 5.0 Hz), 5.88 (dd, 1H, NH–C<u>H</u>–CH), 7.26–7.6 (m, 11H, 2 $C_6\underline{H}_5$, N<u>H</u>), 7.8 (m, 2H), 7.9 (m, 2H). Calcd. for $C_{24}H_{20}ClNO_5$ (437.882): C 65.83, H 4.60, N 3.20%; found: C 65.90, H 4.78, N 3.17%.

*Methyl (2*R*,*3*R*)*-3-(4-methoxyphenyl)-3-amino-2-hydroxypropanoate* (**5h**). Employing the general procedure, azide **2h** (211 mg, 0.84 mmol) and tin(II) chloride dihydrate (0.28 g, 1.24 mmol) in methanol (10 ml) produced 97 mg (51%) of **5h** as a yellowish oil (reaction time 1½ h). IR ($CHCl_3$): ν 3520 (OH), 3380/3315 (NH_2), 2940, 2835, 1730 (C=O), 1605, 1580, 1495, 1435, 1300–1175 (br), 1095, 1025, 830 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 2.45 (br s, 3H, $N\underline{H}_2$, O<u>H</u>), 3.60 (s, 3H, $CO_2C\underline{H}_3$), 3.75 (s, 3H, $OC\underline{H}_3$), 4.2 (d, 1H, *J* 4.5 Hz), 4.4 (d, 1H, *J* 4.5 Hz), 6.7–7.3 (m, 4H, $C_6\underline{H}_4$) ppm.

*Methyl (2*R*,*3*R*)*-3-(4-nitrophenyl)-3-amino-2-hydroxypropanoate* (**5i**).
A solution of azide **2i** (262 mg, 1.0 mmol) and tin(II) chloride dihydrate (0.55 g, 2.4 mmol) in methanol (5 ml) was stirred at room temperature for 18 h. After work-up as described in the general procedure, 49 mg (21%) of **5i** were obtained as a yellowish brown oil, which partly solidified. IR ($CHCl_3$): ν 3670, 3580, 2980, 1730 (C=O), 1600, 1505, 1345, 1190 (br), 1085, 905, 850 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 2.5 (br s, 3H, $N\underline{H}_2$, O<u>H</u>), 3.65 (s, 3H, $CO_2C\underline{H}_3$), 3.85 (d, 1H, *J* 4.5 Hz), 4.45 (d, 1H, *J* 4.5 Hz), 7.35–8.3 (m, 4H, $C_6\underline{H}_4$) ppm.

Oxazoline-5-carboxylic esters **7**

*Ethyl (4*R*,*5*R*)*-4-hexyl-2-methyl-2-oxazoline-5-carboxylate* (**7a**). Boron trifluoride etherate (1.47 g, 10.3 mmol) was added to a stirred solution of oxirane **1j** (1.03 g, 5.2 mmol) in acetonitrile (10 ml). The reaction mixture was stirred at room temperature for 4 h. Excess acetonitrile was evaporated. The residue was taken up in ether (50 ml) and washed with satd. sodium bicarbonate solution and water. The combined washings were reextracted with ether (25 ml). The combined organic layers were dried on $MgSO_4$ and concentrated, affording 1.16 g (93%) of crude oxazoline. After flash chromatography (hexane/ethyl acetate 1 : 1), 0.89 g (71%) of pure **7a** was obtained as a colorless oil. IR (CCl_4): ν 2955, 2925, 2855, 1755/1735 (C=O), 1685 (C=N), 1465, 1385, 1265, 1225, 1190, 1060, 1035, 915 cm $^{-1}$. ^{1}H NMR (CCl_4): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.6 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 1.95 (s, 3H, $C\underline{H}_3$C=N), 4.15 (m, 3H, C<u>H</u>CHCO$_2$Et, $OC\underline{H}_2CH_3$), 4.75 (d, 1H, CHC<u>H</u>CO$_2$Et, *J* 10 Hz) ppm. On storage in the refrigerator for several months the compound had hydrolyzed to the acetylamino alcohol **8a**, M.p. 69–70°C (hexane/diethyl ether).

*Ethyl (4*R*,*5*R*)*-4-hexyl-2-ethyl-2-oxazoline-5-carboxylate* (**7b**). A solution of **1j** (2.00 g, 10.0 mmol), propionitrile (1.7 g, 30 mmol) and boron trifluoride etherate (2.6 g, 19 mmol) in dichloromethane (100 ml) was stirred at room temperature for 18 h. After work-up, as described for the preparation of **7a**, 2.19 g (86%) of crude oxazoline was obtained, which after flash chromatography gave 1.82 g (71%) of pure **7b** as a yellowish oil. IR (CCl_4): ν 2980, 2950, 2925, 2860, 1755, 1735 (C=O), 1680 (C=N), 1495, 1465, 1380, 1270, 1190, 1125, 1060, 915 cm $^{-1}$. ^{1}H NMR (CCl_4): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.05–1.6 [m, 16H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$, $C\underline{H}_3CH_2$C=N], 2.25 (q, 2H, $CH_3C\underline{H}_2$C=N), 4.0–4.3 (m, 3H, C<u>H</u>CHCO$_2$Et, O$_2C\underline{H}_2CH_3$), 4.7 (d, 1H, CHC<u>H</u>CO$_2$Et, *J* 10 Hz) ppm.

*Ethyl (4*R*,*5*R*)*-4-hexyl-2-phenyl-2-oxazoline-5-carboxylate* (**7c**. Boron trifluoride etherate (0.80 g, 5.6 mmol) was added to a solution of **1j** (0.60 g, 3.0 mmol) and benzonitrile (1.10 g, 10.6 mmol) in dichloromethane (30 ml). The reaction mixture was stirred at room temperature for 17 h. After addition of satd. sodium bicarbonate solution the layers were separated. The aqueous layer was extracted with dichloromethane twice. The combined organic layers were dried on $MgSO_4$ and concentrated. The crude product was purified by chromatography (hexane/ethyl-acetate 15 : 1), which gave 0.55 g (60%) of pure **7c** as a colorless oil. IR (film): ν 3080, 1740 (C=O), 1655 (C=N) cm $^{-1}$. ^{1}H NMR (CCl_4): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)5$], 1.1–1.9 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 4.0–4.6 (q + m, 3H, C<u>H</u>CHCO$_2C\underline{H}_2CH_3$), 5.0 (d, 1H, CHC<u>H</u>CO$_2$Et, *J* 10.5 Hz), 7.4 [m, 3H, $C_6\underline{H}_3$(*m,p*)], 8.0 [m, 2H, $C_6\underline{H}_2$(*o*)] ppm.

*Methyl (4*R,*5*R*)-2-ethyl-4-hexyl-2-oxazoline-5-carboxylate* (**7d**). Following the procedure described for **7a**, oxirane (2*R*,3*S*)-(+)-**1k** (1.30 g, 7.0 mmol) gave 0.66 g (40%) of **7d** after chromatography. $[\alpha]_D^{20}$ +44.4° (*c* 1.0, EtOH). IR (film): ν 1760/1740 (C=O), 1675 (C=N) cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 0.85 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.0–1.7 [m, 13H, $CH_3(C\underline{H}_2)_5$, N=C–$CH_2C\underline{H}_3$], 2.26 (q, 2H, $CH_3C\underline{H}_2$C=N), 3.7 (s, 3H, $CO_2C\underline{H}_3$), 4.0–4.4 (m, 1H, C<u>H</u>CHCO$_2$Me), 4.85 (d, 1H, CHC<u>H</u>CO$_2$Me, *J* 10.5 Hz) ppm. MS (CI): *m/e* 242 (M + 1$^+$).

*Methyl (4*R,*5*R*)-2-ethyl-4-pentyl-2-oxazoline-5-carboxylate* (**7e**). From epoxide (2*R*,3*S*)-(+)-**1l** (2.60 g, 15.1 mmol) 3.93 g (100%) of crude product was obtained, using the procedure described for the synthesis of **7a**. It was chromatographed with petroleum ether (60–80)/ethyl acetate (starting with 2 : 1 and gradually increasing the polarity), after being kept on the column overnight. Yield 0.45 g (13%) of **7e**. After prolonged elution, 2.16 g (58%) of hydroxy amide **8e** were obtained as a white solid. **7e**: IR (film): ν 1760/1740 (C=O), 1675 (C=N) cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 0.85 [t, 3H, $C\underline{H}_3(CH_2)_4$], 1.0–1.7 [m, 11H, $CH_3(C\underline{H}_2)_4$, N=C–$CH_2C\underline{H}_3$], 2.24 (q, 2H, $CH_3C\underline{H}_2$C=N), 3.7 (s, 3H, $OC\underline{H}_3$), 4.0–4.43 (m, 1H, C<u>H</u>CHCO$_2$Me), 4.85 (d, 1H, CHC<u>H</u>CO$_2$Me, *J* 10.5 Hz) ppm. **8e**: M.p. 82°C (ether). $[\alpha]_D^{20}$ −5.37° (*c* 1.0, $CHCl_3$). IR (KBr): ν 3400–3200 (OH), 3280 (NH), 1740 (OC=O), 1645 (NC=O), 1545 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 0.85 [t, 3H, $C\underline{H}_3(CH_2)_4$), 1.0–1.6 [m, 11H, $CH_3C\underline{H}_2)_4$], NHCOC$H_2C\underline{H}_3$], 2.25 (q, 2H, NHCOC$\underline{H}_2CH_3$), 3.5 (d, 1H, O<u>H</u>, *J* 6 Hz), 3.8 (s, 3H, $CO_2C\underline{H}_3$), 4.3 [m, 2H, C<u>H</u>(NH)–C<u>H</u>(OH)], 5.7 (br d, 1H, N<u>H</u>, *J* 9 Hz) ppm. MS (CI): *m/e* 246 (M + 1$^+$). Calcd. for $C_{12}H_{23}NO_4$: C 58.75, H 9.45, N 5.71; found: C 58.69, H 9.65, N 5.68%.

*Methyl (4*S,*5*S*)-2-ethyl-4-pentyl-2-oxazoline-5-carboxylate* (**7f**). From oxirane (2*S*,3*R*)-(−)-**1m** (2.60 g, 15.1 mmol) 3.30 g (96%) of crude product was obtained, which was purified by chromatography immediately. Yield 1.92 g (56%) of **7f**; after continued elution, 0.89 g (24%) of **8f** were obtained as a white solid. **7f**: IR and ^{1}H NMR as for **7e**. **8f**: M.p. 82–83°C (ether). $[\alpha]_D^{20}$ +5.31° (*c* 1.0, $CHCl_3$). IR, ^{1}H NMR and MS as for **8e**. Calcd. for $C_{12}H_{23}NO_4$: C 58.75, H 9.45, N 5.71; found: C 58.33, H 9.44, N 5.55%.

*Ethyl (4*R*,*5*R*)*-4-isopropyl-2-methyl-2-oxazoline-5-carboxylate* (**7g**). Employing the procedure described for **7a**, oxirane **1n** (2.00 g, 12.7 mmol) gave 1.85 g (73%) of crude **7g**. Flash chromatography (hexane/ethyl acetate 2 : 1) gave 1.44 g (57%) of pure **7g** as a colorless oil. IR (CCl_4): ν 2980, 2955, 2930, 2870, 1750/1730 (C=O), 1680 (C=N), 1465, 1445, 1435, 1385, 1340, 1310, 1280, 1260, 1225, 1190, 1040, 920, 905 cm $^{-1}$. ^{1}H NMR (CCl_4): δ 0.93 [d, 6H, $(C\underline{H}_3)_2$CH], 1.33 (t, 3H, $OCH_2C\underline{H}_3$), 1.7 [m, 1H, $(CH_3)_2C\underline{H}$], 1.95 (s, 3H, $C\underline{H}_3$C=N), 3.7–4.0 (m, 1H, C<u>H</u>CHCO$_2$Et), 4.15 (q, 2H, $CO_2C\underline{H}_2CH_3$), 4.75 (d, 1H, CHC<u>H</u>CO$_2$Et, *J* 10 Hz) ppm.

2-Hydroxy-3-(acylamino)alkanoic esters **8**

*Ethyl (2*R*,*3*R*)*-2-hydroxy-3-(acetylamino)nonanoate* (**8a**). *Method A (hydrochloric acid/ethanol).* Concentrated hydrochloric acid (37%, 0.22 ml, 2.7 mmol) was added to a stirred solution of **7a** (0.60 g, 2.5

mmol) in ethanol (50 ml). The reaction mixture was then heated at reflux for 24 h. After cooling triethylamine (0.9 ml, 9 mmol) was added. The mixture was concentrated. The residue was dissolved in water and extracted with ether three times. The combined organic layers were dried over $MgSO_4$ and concentrated, giving 0.35 g (54%) of amide **8a** as a colorless oil.

Method B (perchloric acid/dichloromethane). Perchloric acid (70%, 0.15 ml) was added to a stirred solution of **7a** (0.10 g, 0.4 mmol) in dichloromethane (25 ml). The reaction mixture was stirred at room temperature for 4 days. The dichloromethane solution was washed with satd. sodium bicarbonate solution and water, dried over $MgSO_4$ and concentrated. Yield 40 mg (37%) of **8a** as a colorless oil.

Method C (oxalic acid/ethanol). A solution of **7a** (0.48 g, 2.0 mmol) and oxalic acid (1.0 g, 11 mmol) in ethanol (40 ml) was heated at reflux for 20 h. The solvent was evaporated. The residue was dissolved in ether (25 ml), washed with satd. sodium bicarbonate solution and water, dried on $MgSO_4$ and concentrated. Yield 0.46 g (90%) of **8a** as a colorless oil.

IR (CCl_4): ν 3510 (OH), 3430 (NH), 3320 (br, OH), 2950, 2920, 2850, 1720 (OC=O), 1655 (NC=O), 1495, 1445, 1365, 1245 (br), 1120, 1090, 1020, 860, 710 cm^{-1}. ^1H NMR (CCl_4): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.6 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 1.95 (s, 3H, $COC\underline{H}_3$), 4.0–4.4 (m, 5H, O<u>H</u>, C<u>H</u>C<u>H</u>$CO_2C\underline{H}_2CH_3$), 6.95 (d, 1H, N<u>H</u>, *J* 9 Hz) ppm.

Ethyl (2R,3R*)-2-hydroxy-3-(propionylamino)nonanoate* (**8b**).

Method D (silicagel-60H/H_2SO_4/ether). Silicagel-60H (2 g) and concentrated sulfuric acid (2 ml) were added to a solution of **7b** (0.30 g, 1.17 mmol) in ether (100 ml). The heterogeneous mixture was heated at reflux for 40 h. Silica gel was filtered off and washed with ethyl acetate twice. The filtrate was washed with satd. sodium bicarbonate solution, dried over $MgSO_4$ and concentrated. Residue 0.14 g (44%) of **8b** as a yellow oil. IR (CCl_4): ν 3530 (OH), 3435 (NH), 3350 (br, OH), 2950, 2920, 2850, 1725 (OC=O), 1680 (NC=O), 1495, 1460, 1365, 1260, 1215 (br), 1125, 1090, 1025, 865 cm^{-1}. ^1H NMR (CCl_4): δ 0.85 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.6 [m, 16H, $NHCOCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 2.15 (m, 2H, $COC\underline{H}_2CH_3$), 4.0–4.4 (m, 5H, O<u>H</u>, C<u>H</u>C<u>H</u>CO_2Et, $OC\underline{H}_2CH_3$), 5.75 (d, 1H, N<u>H</u>, *J* 9 Hz) ppm.

Ethyl (2R,3R*)-4-methyl-3-(acetylamino)-2-hydroxypentanoate* (**8g**).

Method E (2N HCl/silicagel-60H/ether). Silicagel-60H (2.17 g) and 2N HCl (0.2 ml) were added to a solution of **7g** (106 mg, 0.53 mmol) in ether (15 ml). The heterogeneous mixture was heated at reflux for 16 h. Silica gel was then filtered off and washed with ethyl acetate twice. The filtrate was washed with satd. sodium bicarbonate solution, dried over $MgSO_4$ and concentrated, affording 85 mg (74%) of amide **8g** as a colorless oil, which slowly solidified. M.p. 76–78°C (ether). IR (CCl_4): ν 3520 (OH), 3440 (NH), 3600–3100 (br), 2965, 2930, 2875, 1725 (OC=O), 1685 (NC=O), 1495, 1390, 1370, 1265 (br), 1195, 1135, 1105, 1025 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [d, 6H, $(C\underline{H}_3)_2CH$], 1.3 (t, 3H, $OCH_2C\underline{H}_3$, *J* = 7.5 Hz), 1.7–2.1 [m + s, 4H, $(CH_3)_2C\underline{H}$, $COC\underline{H}_3$], 3.95–4.4 (m, 5H, O<u>H</u>, C<u>H</u>C<u>H</u>$CO_2C\underline{H}_2CH_3$), 6.5 (d, 1H, N<u>H</u>, *J* 9 Hz) ppm.

Acknowledgement

These investigations were supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Research (NWO).

References and notes

[1a] *J. Legters, L. Thijs* and *B. Zwanenburg*, Tetrahedron Lett. **30**, 4881 (1989);
[b] *L. Thijs, J. J. M. Porskamp, A. A. W. M. van Loon, M. P. W. Derks, R. W. Feenstra, J. Legters* and *B. Zwanenburg*, Tetrahedron **46**, 2661 (1990);
[c] *J. Legters, L. Thijs* and *B. Zwanenburg*, Recl. Trav. Chim. Pays-Bas **111**, 1 (1992);
[2a] *J. Legters, L. Thijs* and *B. Zwanenburg*, Recl. Trav. Chim. Pays-Bas **111**, 16 (1992);
[b] *J. Legters, J. G. H. Willems, L. Thijs* and *B. Zwanenburg*, Recl. Trav. Chim. Pays-Bas **111**, 59 (1992).
[3] Other routes to β-amino α-hydroxy acids:
[a] *D.H. Rich, B. J. Moon* and *A. S. Boparai*, J. Org. Chem. **45**, 2288 (1980);
[b] *R. Herranz, J. Castro-Pichel* and *T. Garciá-López*, Synthesis 703 (1989);
[c] *R. Herranz, J. Castro-Pichel, S. Vinuesa* and *M. T. Garciá-López*, J. Chem. Soc. Chem. Commun. 938 (1989);
[d] *W. H. Pearson* and *J. V. Hines*, J. Org. Chem. **54**, 4235 (1989);
[e] *K. Kato, T. Saino, R. Nishizawa, T. Takita* and *H. Umezawa*, J. Chem. Soc. Perkin Trans. I 1618 (1980).
[4a] *K. Soai, S. Yokoyama* and *A. Ookawa*, Synthesis 48 (1987) and references cited therein;
[b] *M. Bartra, F. Urpi* and *J. Vilarrasa*, Tetrahedron Lett. **28**, 5941 (1987) and references cited therein.
[5a] *J. H. Boyer*, J. Am. Chem. Soc. **73**, 5865 (1951);
[b] *A. K. Bose, J. F. Kistner* and *L. Farber*, J. Org. Chem. **27**, 2925 (1962);
[c] *J. S. Brimacombe, J. G. H. Bryan, A. Husain, M. Stacey* and *M. S. Tolley*, Carbohydrate Res. **3**, 318 (1967).
[6] *F. Rolla*, J. Org. Chem. **47**, 4327 (1982).
[7] *M. Vaultier, N. Knouzi* and *R. Carrié*, Tetrahedron Lett. **24**, 763 (1983).
[8] *E. J. Kaufmann* and *R. C. Thompson*, J. Am. Chem. Soc. **99**, 1824 (1977).
[9] *S. N. Maiti, M. P. Singh* and *R. G. Micetich*, Tetrahedron Lett. **27**, 1423 (1986).
[10] *A. P. G. Kieboom* and *F. van Rantwijk*, "Hydrogenation and hydrogenolysis in synthetic organic chemistry", University Press, Delft, 1977.
[11] *L. I. Krimen* and *D. J. Coata*, Org. Reactions **17**, 213 (1969).
[12] *R. Oda, M. Okano, S. Tokiura* and *F. Mismui*, Bull. Chem. Soc. Jap. **35**, 1219 (1962).
[13] *R. A. Wohl* and *J. Cannie*, J. Org. Chem. **38**, 1787 (1973).
[14] *E. N. Zvonkova, A. S. Bushnev, N. E. Aksenov, N. K. Golovanova* and *R. P. Evstigneeva*, J. Org. Chem. of the USSR **10**, 1637 (1974).
[15] *J. R. Lindsay Smith, R. O. C. Norman* and *M. R. Stillings*, J. Chem. Soc. Perkin Trans. I 1201 (1975).
[16] *D. Seebach* and *J. D. Aebi*, Tetrahedron Lett. **24**, 3311 (1983).
[17] *C. Sund, J. Ylikoski* and *M. Kwiatkowski*, Synthesis 853 (1987).
[18] *Y. Ito, E. Shirakawa, K. Hayashizaki* and *T. Hayashi*, Tetrahedron Lett. **29**, 235 (1988).
[19] *C. Giordano, S. Cavicchioli, S. Levi* and *M. Villa*, Tetrahedron Lett. **29**, 5561 (1988).
[20] *S. Colonna, A. Manfredi, A. Solladié-Cavallo* and *S. Quazzotti*, Tetrahedron Lett. **31**, 6185 (1990).
[21] *E. N. Zvonkova* and *R. P. Evstigneeva*, J. Org. Chem. of the USSR **10**, 883 (1974).
[22] *M. Hesse, H. Meier* and *B. Zeeh*, "Spektroskopische Methoden in der organischen Chemie", Thieme, Stuttgart, 1979, p. 160.
[23] *A. I. Meyers* and *D. L. Temple*, J. Am. Chem. Soc. **92**, 6645 (1970).
[24] *A. I. Meyers, G. Knaus, K. Kamata* and *M. E. Ford*, J. Am. Chem. Soc. **98**, 567 (1976).
[25] *A. I. Meyers* and *D. Hoyer*, Tetrahedron Lett. **25**, 3667 (1984).
[26] *W. C. Still, M. Kahn* and *A. Mitra*, J. Org. Chem. **43**, 2923 (1978).