Synthesis of DL-Statine and DL-4-Amino-3-hydroxy-4-phenylbutanoic Acids via the Isoxazoline Route

Karen Halling,[a] Kurt B. G. Torssell*,[a] and Rita G. Hazell[b]

[a] Department of Organic Chemistry and [b] Department of Inorganic Chemistry, University of Aarhus, 8000 Århus C, Denmark

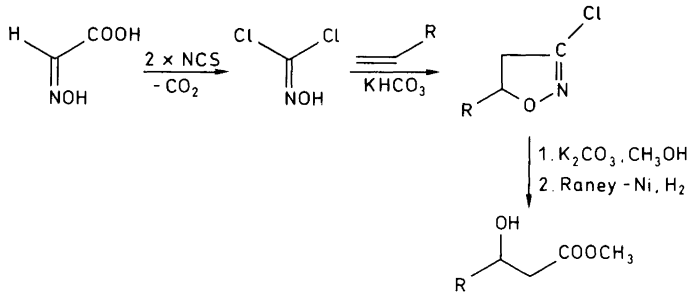
Halling, K., Torssell, K. B. G. and Hazell, R. G., 1991. Synthesis of DL-Statine and DL-4-Amino-3-hydroxy-4-phenylbutanoic Acids via the Isoxazoline Route. – Acta Chem. Scand. 45: 736–741.

1,3-Dipolar cycloaddition of chloronitrile oxide to *N*-allyltrichloroacetamides and subsequent reductive cleavage of the 3-methoxy-substituted isoxazolines gives methyl 3-hydroxy-4-trichloroacetamido esters which by acidic hydrolysis give the corresponding amino acids. The cycloaddition showed low stereospecificity; the diastereomeric ratio was 1.4–2.2:1. The *threo*-isomer was the major product when halonitrile oxides were cycloadded to *N*-(5-methylhex-1-en-3-yl)trichloroacetamide, whereas the *erythro* isomer became the major product when the *N*-(1-phenylprop-2-enyl)-trichloroacetamide was used for the cycloaddition. The stereostructure of 4-amino-3-hydroxy-4-phenylbutanoic acid was determined by X-ray diffraction. The reaction has been applied to the syntheses of DL-statine and analogues.

erythro-3-Methoxy-5-(α-trichloroacetamido)benzyl-2-isoxazoline, $C_{13}H_{13}Cl_3N_2O_3$: monoclinic, space group $P2_1/c$, with unit cell: $a = 12.173(2)$, $b = 6.018(1)$, $c = 22.224(4)$ Å, $\beta = 77.29(1)°$, $Z = 4$, $\mu_{(Mo\ K_\alpha)} = 5.88\ cm^{-1}$, $F(000) = 720$.

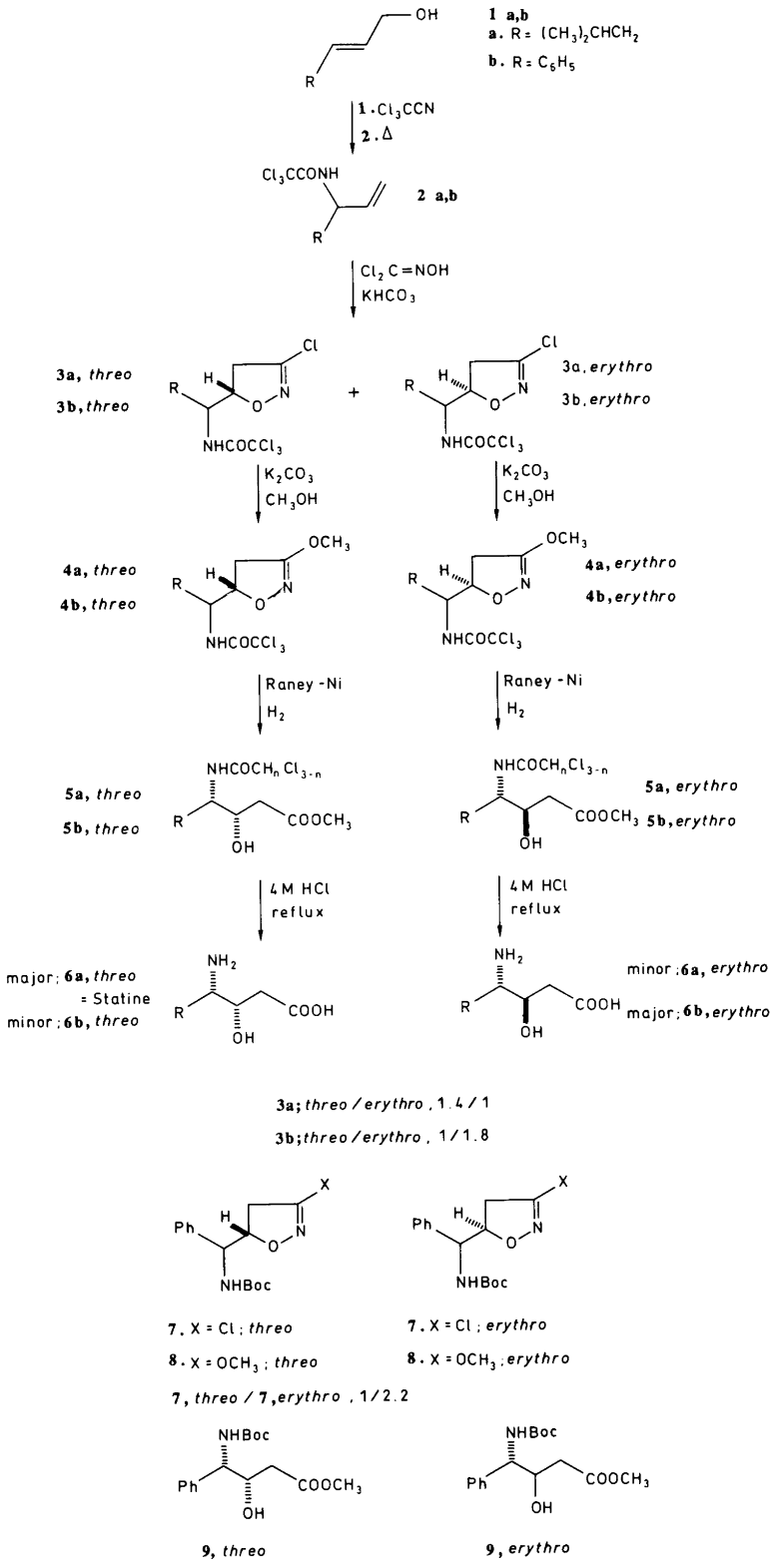
Several syntheses of statine and other γ-amino-β-hydroxy acids have recently been published.[1] These compounds are components of biologically active peptides. We have devised a facile carboxy–hydroxylation of olefins leading to β-hydroxy esters or acids,[2] Scheme 1, and this procedure has been applied to the syntheses of some γ-lactones and γ-amino acids;[2a] in the present work it was extended to the preparation of DL-statine and DL-γ-amino-β-hydroxy-γ-phenylbutanoic acid.

The 3-trichloroacetamido-1-alkenes **2** were prepared from the allylic alcohols **1** by reaction with trichloroacetonitrile and subsequent thermal rearrangement.[3] Phosgene oxime, generated *in situ* by chlorination of glyoxylic acid oxime with 2 mol *N*-chlorosuccinimide (NCS) or *t*-butyl hypochlorite, underwent cycloaddition to **2a,b** in the presence of potassium hydrogencarbonate to give the 3-chloro-2-isoxazolines **3a,b** as a diastereomeric mixture. The diastereomeric ratios were in the range 1.4–2.2:1. Compounds **3a,b** were transformed into the 4-amino-3-hydroxy acids **6a,b** in three steps as shown in Scheme 2. The catalytic reduction step led not only to cleavage of the isoxazoline ring but also to partial reduction of the CCl_3 group. Since the amino acids **6** were our primary goal, deacylation was carried out on the crude mixture of **5**. Naturally occurring 3*S*,4*S*-statine[4] has the *threo*-form **6a** and it turned out by comparison of NMR spectra that our major product actually had this structure. The allylic amide **2a** and allylic ethers thus have opposing directing effects. Compound **2b** gave a diastereomeric ratio of 1.8:1 for the cycloaddition



Scheme 1.

* To whom correspondence should be addressed.


1 a,b
a. R = (CH3)2CHCH2
b. R = C6H5
1. Cl3CCN
2. Δ
Cl3CCONH
2 a,b
Cl2C=NOH
KHCO3
3a, threo
3b, threo
3a, erythro
3b, erythro
K2CO3
CH3OH
4a, threo
4b, threo
4a, erythro
4b, erythro
Raney-Ni
H2
5a, threo
5b, threo
5a, erythro
5b, erythro
4M HCl
reflux
major; 6a, threo
= Statine
minor; 6b, threo
minor; 6a, erythro
major; 6b, erythro
3a; threo / erythro, 1.4 / 1
3b; threo / erythro, 1 / 1.8
7. X = Cl; threo
8. X = OCH3; threo
7. X = Cl; erythro
8. X = OCH3; erythro
7, threo / 7, erythro, 1 / 2.2
9, threo
9, erythro

Scheme 2.

products. Since the two isomers of **6b** were unknown, it was decided to carry out an X-ray investigation of **4b** major, which formed suitable crystals, to determine its relative configuration. By analogy it was then expected that **4b** or **6b** (major) also should have the *threo*-configuration. However, the X-ray structure showed that in this case the major product belonged to the *erythro*-series!

The trichloromethyl group did not influence the direction of the cycloaddition. The corresponding *t*-butoxycarbonyl (Boc) deriatives **7** were also prepared and the minor isomer could be transformed into the minor isomer **3b** by hydrolysis and trichloroacetylation.

It is thus difficult to predict the diastereoselection of the cycloaddition. It was previously found that allylic ethers predominantly gave the *erythro*-form[2,5] by adopting an 'inside' conformation[6] of the ether group in the transition state. Allylic esters show low stereoselectivity and the alcohols and amides tend to favour the *threo*-form by forming hydrogen bonds with the nitrile oxide oxygen in the transition state. Cycloaddition of nitrile oxides to rigid, 3-substituted cyclopentenes occurs preferentially on the sterically less hindred face, but if hydrogen bonds can be established in the transition state *syn*-addition is favoured, which, in this case, gives a high *threo/erythro* ratio.[7] Our results emphasize the need for caution, when extrapolating conclusions based on stereoelectronic considerations. Similar methodology has been used for the synthesis of (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid.[8]

The phenyl substituted γ-amino acids **6b** (*threo/erythro*) have, surprisingly, not been previously synthesized. They may show pharmacological effects.

Experimental

General. ^{1}H NMR spectra were obtained with a Varian Gemini 200 spectrometer. Tetramethylsilane was used as an internal standard. Chemical shifts are given in ppm. IR spectra were recorded on a Nicolet MS-S apparatus. Melting points were determined with a Electrothermal melting-point apparatus and are uncorrected. Preparative TLC was performed on silica gel 60 $PF_{254+360}$ (Art. No. 7748), layers (0.18×20×20 cm) on glass plates. Column chromatography was performed on Kieselgel 60 (0.063–0.200 mm) from Merck. Microanalyses were carried out by *Løvens Kemiske Fabrik,* DK-2750 Ballerup (*Microanalytisk laboratorium*).

(E)-Methyl 5-methyl-2-hexenoate was prepared by esterification of the acid with[9] methanol containing 5 % dry HCl at 25 °C for 24 h, 68 %, 65 °C/11 mmHg. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (6 H, d, *J* 6.5 Hz), 1.70 (1 H, nonet, *J* 6.5 Hz), 2.03 (2 H, t, *J* 6.5 Hz), 3.67 (3 H, s), 5.74 (1 H, d, *J* 15.0 Hz), 6.89 (1 H, dt, *J* 15.0, 6.5 Hz).

5-Methyl-2-hexenol (**1a**) was obtained in a yield of ca. 80 % by $LiAlH_4$ reduction, in diethyl ether, of the hexenoate above and by usual work-up, b.p. 88 °C/15 mmHg (lit.[10] b.p. 86–87 °C/26 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83 (6 H, d, *J* 6.5 Hz), 1.59 (1 H, nonet, *J* 6.5 Hz), 1.79–1.99 (3 H, m), 4.05 (2 H, d, *J* 5.0 Hz), 5.49–5.73 (2 H, m).

5-Methyl-3-trichloroacetamido-1-hexene (**2a**) was prepared in a yield of 62 % from 5-methyl-2-hexenol according to Overman's method.[3] White solid, m.p. 54–56 °C from light petroleum. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (6 H, d, *J* 7.0 Hz), 1.40–1.77 (3 H, m), 4.46 (1 H, m), 5.14 (1 H, d, *J* 10.9 Hz), 5.21 (1 H, d, *J* 17.1 Hz), 5.77 (1 H, ddd, *J* 17.1, 10.9, 5.7 Hz), 6.52 (1 H, br d, NH).

1-Phenylprop-2-enylamine. The corresponding trichloroacetamide[3] was hydrolysed according to the procedure described in Ref. 3. The yield was 68 %, light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98 (2 H, br s, NH_2), 4.50 (1 H, d, *J* 6.3 Hz), 5.11 (1 H, d, *J* 10.1 Hz), 5.23 (1 H, d, *J* 17.0 Hz), 6.18 (1 H, ddd, *J* 17.0, 10.1 and 6.3 Hz), 7.17–7.40 (5 H, m).

N-t-*Butoxycarbonyl-1-phenylprop-2-enylamine* was prepared by adding an equimolar amount of di-*t*-butyl dicarbonate (0.5 mmol, 0.11 g) to 1-phenylprop-2-enylamine (0.5 mmol, 0.07 g in 1 ml chloroform). The yield was 77 %, m.p. 61 °C from light petroleum. Purification was also carried out by preparative TLC or column chromatography (methanol–chloroform 1:99). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (9 H, s), 4.80 (1 H, br s), 5.13–5.29 (3 H, m), 5.97 (1 H, ddd, *J* 17.3, 9.6 and 5.3 Hz), 7.18–7.40 (5 H, m).

erythro-, threo-*3-Chloro-5-(1-trichloroacetamido-3-methyl)butyl-2-isoxazoline,* **3a**, were prepared from **2a** according to procedure described for compound **3b**. The crude yield of the diastereomeric mixture (*threo:erythro,* 1.4:1) was 64 %. Part of the *threo*-isomer was isolated by crystallization of the crude product from a small amount of diethyl ether at −20 °C overnight, m.p. 142–144 °C (from diethyl ether–ethyl acetate 9:1). The filtrate was evaporated and the diastereomeric mixture was separated on a silica column with dichloromethane as the eluent. The *erythro*-isomer was recrystallized from methanol, m.p. 140–141 °C. ^{1}H NMR (200 MHz, $CDCl_3$): **3a**, *threo*; δ 0.93 (3 H, d, *J* 6.0 Hz), 0.96 (3 H, d, *J* 6.0 Hz), 1.30–1.85 (3 H, m), 2.97 (1 H, dd, *J* 17.5, 7.5 Hz), 3.29 (1 H, dd, *J* 17.5, 10.5 Hz), 4.20 (1 H, td, *J* 10.0, 5.0 Hz), 4.83 (1 H, dd, *J* 10.5, 7.5 Hz), 6.54 (1 H, br d, *J* 10.0 Hz, NH). **3a**, *erythro*: 0.90 (3 H, d, *J* 6.5 Hz), 0.96 (3 H, d, *J* 6.5 Hz), 1.30–1.80 (3 H, m), 2.98 (1 H, dd, *J* 17.5, 7.5 Hz), 3.28 (1 H, dd, *J* 17.5, 11.0 Hz), 4.09 (1 H, m), 4.80 (1 H, ddd, *J* 11.0, 7.5 and 5.0 Hz), 6.60 (1 H, br d, *J* 10.0 Hz, NH).

3-Chloro-5-(α-trichloroacetamido)benzyl-2-isoxazoline (**3b**). Glyoxylic acid oxime[11] (20 mmol, 1.78 g), was dichlorinated with *t*-butyl hypochlorite (40 mmol, 4.32 g) in ethyl acetate (5 ml).[2a] **2b** (10 mmol, 2.77 g), potassium hydrogencarbo-

nate (8 g) and 3 drops of water were added, and the mixture was stirred for 12 h at 25 °C. Filtration, evaporation of the solvent *in vacuo* and purification by preparative TLC (SiO_2, chloroform) gave practically a quantitative yield of **3b**. We did not succeed in separating the diastereomers by crystallization in this step. The diastereomeric ratio, *erythro:threo*, was 1.8:1, according to the NMR spectrum. ^{1}H NMR (200 MHz, $CDCl_3$): **3b**, *erythro*: δ 2.85 (1 H, dd, *J* 17.4, 7.8 Hz), 3.26 (1 H, dd, *J* 17.4, 11.0 Hz), 4.99 (1 H, dd, *J* 9.0, 4.3 Hz), ca. 5.2 (1 H, m), 7.30–7.50 (5 H, m). **3b**, *threo*: 3.08 (1 H, dd, *J* 17.8, 7.7 Hz), 3.40 (1 H, dd, *J* 17.8, 10.6 Hz), ca. 5.2 (1 H, m).

threo-, erythro-*3-Methoxy-5-(1-trichloroacetamido-3-methyl)butyl-2-isoxazoline* (**4a**) were prepared from the corresponding 3-chloro derivatives, **3a**, by the method described for compound **4b**. The yields of the *threo-* and *erythro-*isomers were 91 and 96 %, respectively, m.p. 110 °C (from cyclohexane), 111–112 °C (from tetrachloromethane). ^{1}H NMR (200 MHz, $CDCl_3$): **4a**, *threo*: δ 0.94 (6 H, d, *J* 6.5 Hz), 1.32–1.82 (3 H, m), 2.75 (1 H, dd, *J* 16.5, 7.5 Hz), 3.09 (1 H, dd, *J* 16.5, 10.0 Hz), 3.80 (3 H, s), 4.12 (1 H, m), 4.70 (1 H, ddd, *J* 10.0, 7.5 and 1.0 Hz), 6.68 (1 H, br d, *J* 10.0 Hz). **4a**, *erythro*: 0.92 (3 H, d, *J* 6.0 Hz), 0.94 (3 H, d, *J* 6.0 Hz), 1.40–1.74 (3 H, m), 2.81 (1 H, dd, *J* 16.0, 6.5 Hz), 3.05 (1 H, dd, *J* 16.0, 10.0 Hz), 3.85 (3 H, s), 4.08 (1 H, ddd, *J* 14.5, 10.0 and 5.0 Hz), 4.64 (1 H, ddd, *J* 10.0, 6.5 and 5.0 Hz), 6.60 (1 H, br d, *J* 10.0 Hz). **4a**, *threo*: Found: C 39.70, H 5.04, N 8.37. Calc. C 39.81, H 5.16, N 8.44. **4a**, *erythro*: Found: C 39.73, H 5.08, N 8.44. Calc. as above.

erythro-, threo-*3-Methoxy-5-(α-trichloroacetamido)benzyl-2-isoxazoline* (**4b**). Compound **3b**, diastereomeric mixture (0.52 g, 1.5 mmol) and 0.8 g potassium carbonate in methanol (6 ml) were heated under reflux for 2.5 h. After the solution had been cooled to room temperature, the reaction mixture was filtered, evaporated *in vacuo* and suspended in chloroform. The chloroform suspension was washed with water and dried with magnesium sulphate. Removal of the solvent *in vacuo* and purification by preparative TLC (SiO_2, diethyl ether–light petroleum 2:1) gave two fractions: **4b**, *threo*: $R_f = 0.5$, 0.11 g, 0.31 mmol, m.p. 120 °C from tetrachloromethane–benzene 4:1. **4b**, *erythro*: $R_f = 0.4$, 0.17 g, 0.49 mmol, m.p. 148–150 °C from tetrachloromethane–benzene 4:1. Both compounds were white crystals, and the combined yield was 53 %. ^{1}H NMR (200 MHz, $CDCl_3$): **4b**, *threo*: δ 2.88 (1 H, dd, *J* 16.0, 6.5 Hz), 3.20 (1 H, dd, *J* 16.0, 10.0 Hz), 3.84 (3 H, s), 5.00–5.12 (2 H, m), 7.27–7.43 (6 H, m). **4b**, *erythro*: 2.64 (1 H, dd, *J* 16.0, 7.5 Hz), 3.03 (1 H, dd, *J* 16.0, 10.0 Hz), 3.65 (3 H, s), 4.90–5.13 (2 H, m), 7.30–7.43 (5 H, m), 7.50 (1 H, br d, *J* 7.5 Hz, NH). **4b**, *erythro*: Found: C 44.49, H 3.69, N 7.95. Calc. C 44.41, H 3.73, N 7.97. **4b**, *threo*: Found: C 44.34, H 3.66, N 7.79. Calc. as above.

erythro-, threo-*Methyl 3-hydroxy-6-methyl-4-trichloroacetamidoheptanoate* (**5a**) were prepared by catalytic hydrogenation of **4a** over Raney-Ni in methanol with boric acid (1.5 equivs. relative to the substrate). The solution was filtered through Celite and the solvent evaporated *in vacuo*. The oily product was freed from water by being suspended in chloroform, dried over Na_2SO_4 and concentrated *in vacuo*. **5a**, *erythro,* oil, crude yield ca. 73 %. **5a**, *threo,* oil, crude yield ca. 81 %. The crude product was used directly for the hydrolysis to **6a**. The trichloromethyl group was partially reduced to give a mixture of methyl, chloromethyl and dichloromethyl groups.

erythro-, threo-*Methyl 3-hydroxy-4-phenyl-4-trichloroacetamido)butanoate* (**5b**) were prepared by the procedure as described for **5a**. **5b**, *threo*; crude yield ca. 69 %, semisolid. **5b**, *erythro*; crude yield ca. 79 %, semisolid. The trichloromethyl group underwent partial reduction to give a mixture of dichloromethyl, chloromethyl and methyl groups. The crude product was used directly for the hydrolysis.

erythro-, threo-*4-Amino-3-hydroxy-6-methylheptanoic acid* (**6a**) were prepared by heating crude **5a**, *erythro* and *threo* respectively, under reflux in 4 M hydrochloric acid for ca. 1 h. Removal of the acid by evaporation *in vacuo* and purification of the residue by ion-exchange chromatography (DOWEX 50W-H) gave **6a**, *erythro,* m.p. 210–211 °C in an overall yield of 84 % from **4a**, *erythro* and **6a**, *threo*, m.p. 209–212 °C in an overall yield of 64 % from **4a**, *threo*. The NMR spectra of **6a**, *erythro* and *threo* agreed with the data found in the literature.[12] Our major product **6a**, *threo,* was identical with a commercial sample of (3*S*,4*S*)-statine.[6]

erythro-, threo-*4-Amino-3-hydroxy-4-phenylbutanoic acid* (**6b**) were prepared by hydrolysis of crude **5b** as described for **6a**. **6b**, *threo,* yield 61 %, white solid, m.p. 230–233 °C. **6b**, *erythro,* yield 54 %, white solid, m.p. 198–200 °C. ^{1}H NMR (200 MHz, D_2O): **6b**, *erythro*: δ 2.10–2.20 (2 H, m), 4.30–4.45 (2 H, m), 7.30–7.45 (5 H, m). **6b**, *threo*: 2.13 (1 H, dd, *J* 15.5, 7.0 Hz), 2.19 (1 H, dd, *J* 15.5, 4.5 Hz), 4.13 (1 H, d, *J* 9.0 Hz), 4.26 (1 H, ddd, *J* 9.0, 7.0 and 4.5 Hz), 7.30–7.50 (5 H, m). IR (KBr): **6b**, *erythro*: 1390 (s), 1550 (s), 2200–3500 (br) cm^{-1}. **6b**, *threo*: 1385 (s), 1540 (s), 1620 (m), 2150 (w), 2400–3200 (br), 3360 (m) cm^{-1}.

threo-, erythro-*5-(α-t-butoxycarbonylamino)benzyl-3-chloro-2-isoxazoline* (**7**). Glyoxylic acid oxime[11] (0.48 g, 5.4 mmol) was dichlorinated[2a] with *t*-butyl hypochlorite (1.17 g, 10.8 mmol) in ethyl acetate (2 ml), *t*-butoxycarbonyl-1-phenyl-2-propenylamine (0.62 g, 2.7 mmol) in ethyl acetate (2 ml), potassium hydrogen carbonate (2 g) and water (0.1 ml) were added, and the mixture was stirred for 24 h. The mixture was filtered, evaporated *in vacuo* and the residue purified on a short silica column (chloroform–methanol, 99:1). **7** was obtained as a diastereomeric mixture

(*erythro:threo*, 2.2:1, yield 64 %) which was separated by fractional crystallization. The minor diastereomer, **7**, *threo*, crystallized pure from methanol at −20 °C, m.p. 172–176 °C and the major diastereomer, **7**, *erythro*, was obtained practically pure as a semisolid product by evaporation of the filtrate. ^{1}H NMR (200 MHz, $CDCl_3$): **7**, *erythro*: δ 1.38 (9 H, s), 2.92 (1 H, dd, *J* 17.5, 8.5 Hz), 3.15 (1 H, dd, *J* 17.5, 10.5 Hz), 4.72 (1 H, dd, *J* 8.5, 5.0 Hz), 5.09 (1 H, ddd, *J* 10.5, 8.5 and 5.0 Hz), 5.39 (1 H, br d, NH), 7.30 (5 H, br s). **7**, *threo*: 1.40 (9 H, s), 3.19 (1 H, dd, *J* 17.0, 9.5 Hz), 3.25 (1 H, dd, *J* 17.0, 10.5 Hz), 4.86 (1 H, br d, *J* 10.0 Hz), 5.00–5.25 (3 H, m), 7.32 (5 H, br s).

erythro-, threo-*3-Methoxy-5-(α-t-butoxycarbonylamino)-benzyl-2-isoxazoline* (**8**) were prepared by heating the corresponding 3-chloro derivatives **7**, *erythro* and **7**, *threo* with an excess of solid potassium carbonate in methanol at reflux for 3 h. Usual work-up[2a] and purification by preparative TLC (SiO_2, ethyl acetate–light petroleum 2:3) gave **8**, *erythro* as white crystals, m.p. 138–141 °C (from methanol), 96 %, and **8**, *threo* as white crystals, m.p. 105 °C (from cyclohexane–benzene 1:1), 91 %. ^{1}H NMR (200 MHz, $CDCl_3$): **8**, *threo*: δ 1.39 (9 H, s), 2.95 (1 H, dd, *J* 16.1, 8.9 Hz), 3.00 (1 H, dd, *J* 16.1, 9.5 Hz), 3.83 (3 H, s), 4.78 (1 H, d, *J* 8.9 Hz), 4.89 (1 H, ddd, *J* 9.5, 8.9 and 2.9 Hz), 5.31 (1 H, d, *J* 8.8 Hz), 7.25–7.38 (5 H, m). **8**, *erythro*: 1.37 (9 H, s), 2.70 (1 H, dd, *J* 16.6, 7.9 Hz), 2.94 (1 H, dd, *J* 16.6, 9.9 Hz), 3.67 (3 H, s), 4.69 (1 H, dd, *J* 8.3, 5.0 Hz), 4.93 (1 H, ddd, *J* 9.9, 7.9 and 5.0 Hz), 5.31 (1 H, d, *J* 8.3 Hz), 7.22–7.38 (5 H, m).

threo-*Methyl 4-(t-butoxycarbonylamino)-3-hydroxy-4-phenylbutanoate* (**9**). **8**, *threo* (0.19 g, 0.6 mmol) was reduced over Raney-Ni in methanol–dioxane (5:2, 7 ml) in the presence of boric acid (40 mg) added. The solution was filtered through a thin layer of Celite, evaporated *in vacuo* and the residue purified by preparative TLC (SiO_2, chloroform–methanol 99:1). **9**, *threo* was obtained in a yield of 47 %, 0.3 mmol, 90 mg, m.p. 96–98 °C from cyclohexane–ethyl-acetate 3:1. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (9 H, s), 2.53 (1 H, dd, *J* 16.0, 4.5 Hz), 2.59 (1 H, dd, *J* 16.0, 9.0 Hz), 3.22 (1 H, br s), 3.67 (3 H, s), 4.27 (1 H, m), 4.61 (1 H, m), 5.50 (1 H, br d, *J* 7.5 Hz), 7.2–7.4 (5 H, m).

erythro-*Methyl 4-(t-butoxycarbonylamino)-3-hydroxy-4-phenylbutanoate* (**9**) was prepared according to the same procedure as the *threo*-derivative above. The yield of purified product was 46 %, m.p. 97–99 °C (from cyclohexane–diethyl ether 3:1), colourless crystals. ^{1}H NMR ($CDCl_3$): δ 1.36 (9 H, s), 2.21 (1 H, dd, *J* 16.0, 10.0 Hz), 2.47 (1 H, dd, *J* 16.0, 3.5 Hz), 3.22 (1 H, OH), 3.60 (3 H, s), 4.32 (1 H, m), 4.60 (1 H, br s), 5.54 (1 H, br d, *J* 7.5 Hz), 7.1–7.4 (5 H, m).

Transformation of **7**, threo *into* **3b**, threo. Compound **7**, *threo* was hydrolysed in 6 M HCl under reflux for 30 min. The acid was evaporated *in vacuo* and the residue suspended in a mixture of water and chloroform. The pH of the water phase was adjusted to ca. 8 with sodium hydrogencarbonate. The phases were separated and the chloroform phase was dried over Na_2SO_4, and triethylamine (1.3 equivs.) and trichloroacetyl chloride (2.3 equivs. relative to **7**, *threo*) in chloroform were added. The ^{1}H NMR spectrum of the trichloroacetamide formed was identical with the NMR spectrum of **3b**, *threo*.

Structure determination of **4b** *(major) by X-ray crystallography*. Crystals of **4b** (major) $C_{13}H_{13}Cl_3N_2O_3$, are monoclinic, space group $P2_1/c$, with unit cell: $a = 12.173(2)$, $b = 6.018(1)$, $c = 22.224(4)$, $\beta = 77.29(1)°$, $Z = 4$, $\mu_{(Mo\ K_\alpha)} = 5.88\ cm^{-1}$, $F(000) = 720$.

A crystal of dimensions 0.3×0.2×0.4 mm^3 was used for data collection on a HUBER diffractometer, using Nb filtered Mo radiation ($\lambda = 0.71073$ Å); 2333 reflections were measured in the ω–2θ scan mode, scan range in θ: 1.0 + 0.346 tan θ, 50 steps, 1 s per step; 3 test reflections measured every 100 reflections showed 25 % deterioration during the data collection, which was corrected for together with Lorenz, polarisation and absorption effects (transmissions in the range 0.84–0.90). Reflections measured were $-13 \le h \le 14$, $0 \le k \le 6$, $0 \le l \le 23$, $2\theta \le 50°$. The cell dimensions were determined from 25 reflections centered at positive and negative θ and at high and low χ.

The structure was solved by means of MULTAN[13] and refined by the full-matrix least-squares method.[14] Hydrogen atoms were found in a difference Fourier map close to calculated positions and included in refinements with isotropic temperature factors; heavier atoms were refined with anisotropic thermal parameters. The weighting scheme

Table 1. Fractional coordinates (×10^4) and equivalent isotropic thermal parameters, U_{eq}, in Å^2 × 10^{-3} for **4b** (major).

	x	*y*	*z*	U_{eq}
O1	3933(3)	1382(7)	2240(2)	62(3)
N2	3897(4)	2094(8)	1633(2)	52(3)
C3	4240(4)	472(10)	1269(3)	50(4)
C4	4570(7)	−1577(13)	1554(3)	64(5)
C5	4118(6)	−1013(12)	2234(3)	63(5)
C6	3011(5)	−2181(11)	2528(3)	54(4)
C7	2085(5)	−1920(10)	2186(3)	47(4)
C8	1422(5)	−12(12)	2228(3)	55(5)
C9	603(6)	201(13)	1896(4)	69(5)
C10	426(6)	−1489(16)	1516(4)	77(6)
C11	1063(7)	−3353(16)	1463(4)	77(6)
C12	1879(6)	−3579(13)	1798(3)	64(5)
N1	2677(5)	−1429(12)	3165(2)	65(4)
C13	2465(5)	−2805(12)	3633(3)	59(4)
O13	2568(5)	−4790(8)	3589(2)	117(4)
C14	2088(5)	−1791(9)	4292(3)	60(4)
Cl1	2093(1)	1139(3)	4300(1)	79(1)
Cl2	2962(2)	−2780(3)	4749(1)	108(2)
Cl3	704(1)	−2702(3)	4583(1)	98(1)
O3	4294(3)	530(7)	668(2)	69(3)
C15	3921(10)	2566(17)	438(4)	94(8)

Table 2. Interatomic distances (Å) and angles (degrees) for **4b** (major).

Bond		Angle	
N2–O1	1.427(6)	N2–O1–C5	108.9(5)
C3–N2	1.277(7)	O1–N2–C3	107.2(5)
C4–C3	1.481(9)	N2–C3–C4	116.6(6)
C5–O1	1.458(8)	N2–C3–O3	123.7(6)
C5–C4	1.527(9)	C3–O3–C15	115.6(6)
C6–C5	1.533(8)	C4–C3–O3	119.7(6)
C7–C6	1.501(8)	C3–C4–C5	99.5(6)
C8–C7	1.394(8)	C4–C5–O1	104.5(5)
C9–C8	1.371(9)	O1–C5–C6	109.3(6)
C10–C9	1.368(10)	C4–C5–C6	114.3(6)
C11–C10	1.354(11)	C6–C7–C8	122.7(7)
C12–C7	1.378(9)	C6–C7–C12	120.1(7)
C12–C11	1.373(11)	C7–C8–C9	121.2(7)
N1–C6	1.457(8)	C8–C9–C10	119.6(8)
C13–N1	1.308(8)	C9–C10–C11	120.3(8)
O13–C13	1.203(7)	C10–C11–C12	120.2(10)
C14–C13	1.560(8)	C11–C12–C7	121.3(8)
Cl1–C14	1.763(6)	C5–C6–N1	107.7(6)
Cl2–C14	1.729(6)	C7–C6–N1	112.3(6)
Cl3–C14	1.755(6)	C6–N1–C13	122.7(7)
O3–C3	1.323(7)	N1–C13–O13	124.4(7)
C15–O3	1.439(9)	N1–C13–C14	117.7(7)
		C13–C14–Cl1	113.6(5)
		C13–C14–Cl2	109.0(4)
		C13–C14–Cl3	106.5(4)

used was $w = 1/\sigma(F)^2$, $\sigma(F) = [\sigma(F^2) + 1.02\ F^2]^{1/2} - |F|$. The final agreement factors were $R = 0.046$, $R_w = 0.048$, $S = 1.87$ for 242 parameters and 1173 reflections with $I > 3\sigma(I)$. Final coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms are given in Table 1. The structure is shown in Fig. 1, bond lengths and angles are given in Table 2.

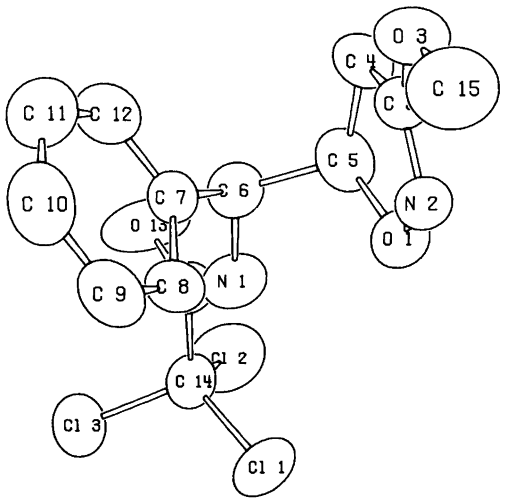


Fig. 1. Structure of *erythro*-3-methoxy-5-(α-trichloroacetamido)-benzyl-2-isoxazoline (**4b**, *erythro*).

Lists of observed and calculated structure factors and of anisotropic thermal parameters can be obtained from one of the authors (R.G.H.) on request.

Acknowledgements. This work was assisted financially by grants from *Århus Universitets Forskningsfond* and *Statens Naturvidenskabelige Forskningsråd.* We wish to thank Mr. Ib Thomsen for valuable experimental help.

References

1. For recent syntheses of statine and analogues see: (a) Schmidt, U., Kroner, M. and Greisser, H. *Synthesis* (1989) 832; (b) Sakaitani, M. and Ohfune, Y. *J. Am. Chem. Soc. 112* (1990) 1150; (c) Takemoto, Y., Matsumoto, T., Ito, Y. and Terashima, S. *Tetrahedron Lett. 31* (1990) 217 and references therein; (d) Kessler, H. and Schudok, M. *Synthesis* (1990) 457 and references therein; (e) Yanagisaw, H., Kanazaki, T. and Nishi, T. *Chem. Lett.* (1989) 687; (f) Saiah, M., Bessodes, M. and Antonakis, K. *Tetrahedron Asym. 2* (1991) 111 and references therein.
2. (a) Halling, K., Thomsen, I. and Torssell, K. G. B. *Liebigs Ann. Chem.* (1989) 985; (b) For a general introduction to the use of isoxazolines in organic synthesis see, e.g., Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis. Novel Strategies in Synthesis.* VCH Verlagsgesellschaft, Weinheim 1988.
3. Overman, L. E. *J. Am. Chem. Soc. 98* (1976) 2901.
4. Sigma Chemical Co.
5. (a) Das, N. B. and Torssell, K. B. G. *Tetrahedron 39* (1983) 2247; (b) Jäger, V., Müller, I., Schohe, R., Frey, M., Ehler, R., Häfele, B. and Schröter, D. *Lectures in Heterocyclic Chemistry*, Heterocorp, Tampa 1985, Vol. 8, p. 79; (c) Curran, D. P. and Goethe, S. A. *Tetrahedron 44* (1988) 3945.
6. Houk, K. N., Moses, S. R., Wu, Y. D., Rondan, N. G., Jäger, V., Schohe, R. and Fronczek, F. R. *J. Am. Chem. Soc. 106* (1984) 3880.
7. (a) Caramella, P. and Cellerino, G. *Tetrahedron Lett.* (1974) 229; (b) Caramella, P., Albini, F. M., Vitali, D., Rondan, N. G., Wu, Y.-D., Schwartz, T. R. and Houk, K. N. *Tetrahedron Lett. 25* (1984) 1875; (c) Curran, D. P., Sung-Mo, C., Goethe, S. A. and Fu-tyan Lin, *J. Org. Chem. 55* (1990) 3710.
8. Nishi, T. and Morisawa, Y. *Heterocycles 29* (1989) 1835.
9. v. Auwers, K., Meissner Th., Seydel, O. and Wissebach, H. *Liebigs Ann. Chem. 432* (1923) 46.
10. Delaby, R. and Lecomte, J. *Bull. Soc. Chim. Fr. 4* (1937) 743.
11. Wieland, H., *Ber. Dtsch. Chem. Ges. 43* (1910) 3362.
12. Rich, D. H., Sun, E. T. and Boparai, A. S. *J. Org. Chem. 43* (1978) 3624.
13. Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. and Woolfson, M. M. (1980). MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data, Univs. of York, England, and Louvain, Belgium.
14. Busing, W. R., Martin, K. O. and Levy, H. A. (1962) ORFLS. Report ORNL – TM 305. Oak Ridge National Laboratory, Tennessee.

Received December 17, 1990.