Amino Acids and Peptides; 70.[1] Optically Active α-Amino Acids, *N*-Boc-Aminoaldehydes and α-Amino-β-hydroxy Acids from 2,3-Epoxy Alcohols

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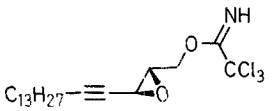
Trichloroacetimidic esters of 2,3-epoxy alcohols are transformed into oxazolines **5** and dihydrooxazines **6**, respectively, depending on the structure of the educts and the catalyst. The five-membered ring compounds **5** are transformed into *erythro*-α-amino-β-hydroxy acids (60–70% from epoxy alcohols) via oxazolidinones **11**, **12**, and **13**. α-Amino acids and α-substituted α-amino acids **10** are obtained from the dihydrooxazines **6** (50–60% from epoxy alcohols).

In connection with the syntheses of enzyme inhibitors and investigations on the mechanisms of enzyme reactions, a large number of non-ribosomal amino acids have been synthesized. These compounds have also been detected as building blocks of numerous, biologically highly active linear and cyclic peptides and peptolides from bacteria, fungi, plants and lower marine organisms, and have been prepared in the course of the total syntheses of these natural products. The preparations of optically active, non-ribosomal amino acids and α-alkylamino acids are generally based on the following methods 1–4. A survey of literature is given in references 2–12:

1. alkylation or amination of optically active enolates,[2–8]
2. alkylations with optically active, electrophilic glycine compounds,[9]
3. diastereoselective Strecker and Ugi reactions with optically active amines,[10,11] or
4. enantioselective hydrogenation of α,β-didehydroamino acid derivatives.[12]

Except for the last method, nearly all of the above processes give rise predominantly or exclusively to compounds of either the *S*- or the *R*-series. The enantiomer is then, if at all, considerably more difficultly accessible, since usually only one of the two enantiomers of the optically active auxiliary reagent employed (amino acids, amino alcohols) is "cheaply" available. We now report on the conversion of optically active 2,3-epoxy alcohols into amino acids. Since both enantiomeric epoxides are readily available by the Sharpless oxidation[13] of primary allylic alcohols, their transformation into amino acids provides a ready access to both the *S*- and the *R*-series. All dihydrooxazines **6** and oxazolines **5**, described in the following reactions, are easily purified crystalline compounds. Since the epoxides formed by the Sharpless oxidation have an optical purity of 90–95%, recrystallization of the corresponding dihydrooxazines **6** and oxazolines **5** affords optically pure products.

A selective transformation of 2,3-epoxy alcohols into 2-amino-1,3-diols can be realized through reactions with isocyanates to produce oxazolidinones and subsequent ring opening of the latter.[14–19] Primary aminodiols, however, are only difficultly accessible in this manner by reaction with benzyl isocyanate and subsequent hydrogenolytic cleavage of the benzyl group.[17] When the 3-hydroxy group in the oxazolidinone stage has to be masked for later synthetic steps, it must be taken into account that considerable amounts of the isomeric 4-hydroxymethyl-oxazolidinone are frequently formed simultaneously.[19] Both complications can be avoided when an epoxy alcohol **3** is allowed to react with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to furnish the imidic ester **4** in nearly quantitative yield and the epoxide ring present is then opened intramolecularly with methanesulfonic acid to give the oxazolines **5a–d**. To the best of our knowledge, the intramolecular opening of the epoxide ring by the trichloroacetimide group has only been described once before, by Vasella[20] who obtained the dihydrooxazine **2** from the acetylenic compound **1** and triethylaluminium.



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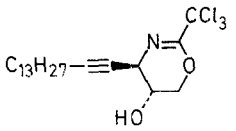

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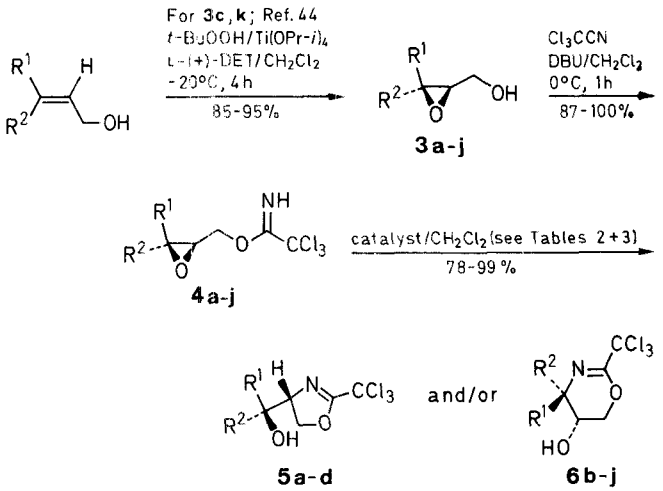
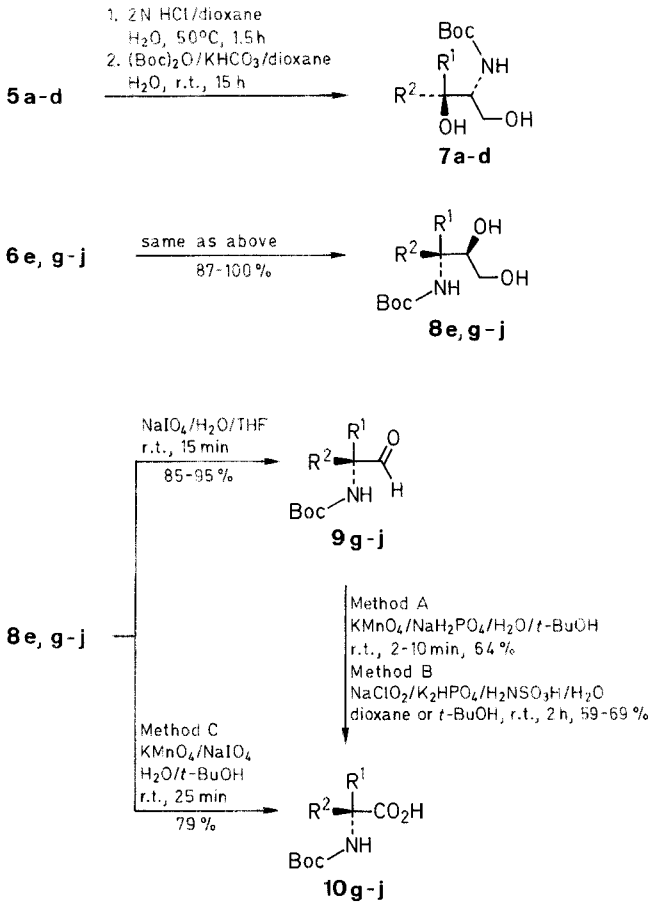
We have now found that the course of the reaction to form the five-membered ring **5** or the six-membered ring **6** is controlled by the structure of the epoxide **4** and, occasionally, also by the catalyst.



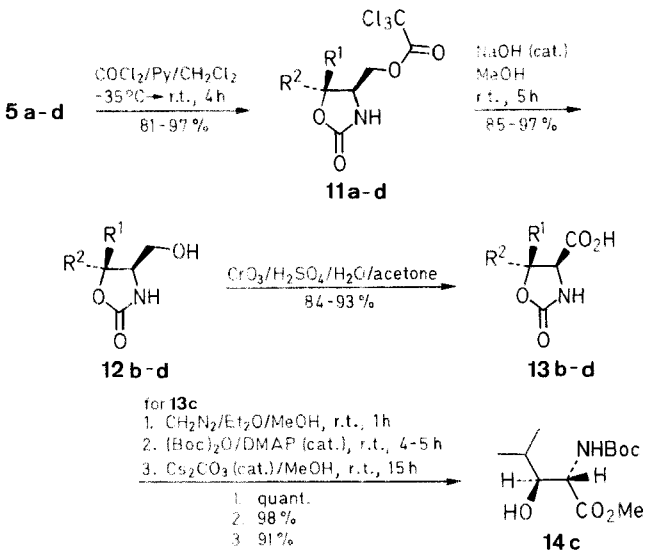
3–14	R^1	R^2	3–14	R^1	R^2
a	H	H	**f**	5-Br,2-MeOC$_6$H$_3$	H
b	*n*-C$_3$H$_7$	H	**g**	(CH$_3$)$_2$CH(CH$_2$)$_3$	CH$_3$
b'	H	*n*-C$_3$H$_7$	**h**	(CH$_3$)$_2$C=CH(CH$_2$)$_2$	CH$_3$
c	*i*-C$_3$H$_7$	H	**i**	HC≡C	CH$_3$
d	*t*-C$_4$H$_9$	H	**j**	CH$_3$(CH$_2$)$_2$C≡C	CH$_3$
e	Ph	H			

Scheme A

A reliable differentiation between the oxazoline **5** and the dihydroxazine **6** structures can be achieved by hydrolysis to the aminodiol, acylation at nitrogen to give **7** or **8**, respectively, and periodate oxidation to furnish the acylamino aldehyde **9**.



Scheme **B**



Scheme **C**

The latter product can only be formed from a dihydrooxazine **6**. Further proof of the two different ring structures is supplied by a rigorous ^{1}H-NMR analysis (see below).

As shown in Tables 2 and 3, imido esters of *cis*- and *trans*-2,3-epoxy alcohols with only *one aliphatic* substituent at the 3-position **(4a–d)** are transformed mainly to oxazolines **5a–d**. When methanesulfonic acid is used, the regioselectivity is high. Use of ether–boron trifluoride complex leads in the reactions of **4b–d** to a mixture of five- and six-membered ring products (1:1–9:1), whereas use of tin(IV)chloride in the reactions of **4b** and **4c** gives rise to a 3:7 mixture of five- and six-membered ring products. In contrast, dihydrooxazines **6** are exclusively obtained from *trans*-2,3-epoxy alcohols with an aromatic **(3e, f)** or acetylenic **(3i, j)** substituent or *two alkyl* groups **(3g, h)** in the 3-position. Both routes can be used for stereospecific amino acid syntheses: The oxazolines **5** react readily with phosgene to form the oxazolidinones **11**, which on hydrolysis and oxidation with the Jones reagent[21] give rise to the carboxylic acids **13**.

Acylation of the **13**-esters with di-*tert*-butyl dicarbonate and mild ring cleavage[22] with cesium carbonate produces *N*-*tert*-butyloxycarbonyl-β-hydroxy-α-amino acid esters. The more readily accessible, optically active *trans*-epoxy alcohols, which are formed in higher enantiomeric excesses by the Sharpless oxidation,[13] furnish, depending on the configuration of the tartaric acid ester used in their preparation, either, the (*R*, *R*)- or (*S*,*S*)-α-amino-β-hydroxycarboxylic acid compounds **14a–d**. The homologous serines with *R*,*S*- and *S*,*R*-configurations are readily accessible from the above products by inversion at the 3-position via oxazolines[23] or by rearrangement of the oxazolidinone-carboxylic ester (**13**-ester) at the 2-position with strong bases. The yields of α-amino-β-hydroxy acids thus obtained from 2,3-epoxy alcohols are in the range 60–70%.[24]

The dihydrooxazines **6** are rapidly hydrolyzed by dilute mineral acids to form aminodiols, which in aqueous basic media are transformed to the carbamic acid esters **8** (Scheme **B**). Periodate oxidation yields the α-acylamino aldehydes **9**. Thus, starting from the easily available (*R*,*R*)- and (*S*,*S*)-epoxy alcohols, (*R*)- and (*S*)-acylamino aldehydes, which are frequently used in natural products syntheses,[27–39] are accessible. By oxidation, preferably with buffered potassium permanganate[40] (Method A), (*R*)- or (*S*)-acylamino acids **10** are formed from these aldehydes in 50–60% yields (based on the epoxides).[41] In case of aldehydes bearing multiple bonds, this oxidation method fails, but this transformation can be performed in the same yields using sodium chlorite[43,44] (Method B). Aminodiols without olefinic or acetylenic substituents can be converted to the acylamino acids in a one-step process by using potassium permanganate/sodium metaperiodate (Method C).[45] β,γ-Acetylenic amino acids, and by their catalytic hydrogenation β,γ-didehydroamino acids, are accessible by this route. α-Methyl-β,γ-acetylenic amino acids are constructed from the commercial *trans*-3-methyl-2-penten-4-yn-1-ol.

The stereochemical assignment for all compounds encountered along our synthetic route is based on a numerical analysis of the respective ^{1}H-NMR spectra. The spectral data for the isopropyl series, $R^1 = CH(CH_3)_2$, are presented exemplarily in Table 8; the corresponding ^{13}C-NMR data are collected in Table 9.

The *trans* stereochemistry of the oxirane ring is established by the small ^3J coupling (2.2 Hz, see Table 8). The average ^3J value for the coupling between 3-H and the isopropyl methine proton argues for more or less free rotation of the isopropyl group in **4c**. The larger differentiation of the two vicinal couplings between 2-H and the two diastereotopic C-1 methylene protons, on the other hand, indicates a highly preferential conformation at this end of the oxirane moiety.

In the oxazoline **5c**, the geminal coupling appears numerically reduced as expected for an orthogonal orientation of one oxygen lone pair with respect to the bisecting plane of the CH_2 group. In this conformation of the five-membered ring, the dihedral angles between 1-H^A,H^B and 2-H are close to 30° and 150°, respectively, as borne out by the large values for these two vicinal couplings (see Table 8). With the O–H bonding to the C=N π system, the preferential conformation around the C-2/C-3 bond results in a dihedral angle between 2-H and 3-H close to 90°, and a correspondingly small vicinal coupling.

Table 1. (3-Substituted 2-Oxiranyl)methyl Trichloroacetimidates **4** Prepared

Allylic Alcohol Config.	Product	Yield (%)	bp (°C)/Torr	$[\alpha]_D^{a,b,c}$ (*c*, $CHCl_3$)	Molecular Formula[d]
	rac-**4a**	88	60–65/10^{-3}	–	$C_5H_6Cl_3NO_2$ (218.5)
(*E*)	(2*S*,3*S*)-**4b**	97	54–57/5 × 10^{-3}	−25.2[b] (5.34)	$C_8H_{12}Cl_3NO_2$ (260.6)
(*Z*)	*rac*-**4b′**	79	65–70/10^{-1}	–	$C_8H_{12}Cl_3NO_2$ (260.6)
(*E*)	(2*S*,3*S*)-**4c**	97	85–90/4 × 10^{-2}	−18.2[a] (3.8)	$C_8H_{12}Cl_3NO_2$ (260.6)
(*E*)	(2*S*,3*S*)-**4d**	87	75–80/10^{-3}	−13.9[a] (5.55)	$C_9H_{14}Cl_3NO_2$ (274.6)
(*E*)	(2*S*,3*S*)-**4e**	95	90/2 × 10^{-2}	−17.1[a] (2.4)	$C_{11}H_{10}Cl_3NO_2$ (294.6)
(*E*)	(2*S*,3*S*)-**4f**	99	–	−21.8[a] (1.2)	$C_{12}H_{11}BrCl_3NO_3$ (403.5)
(*E*)	(2*S*,3*S*)-**4g**	98	90/10^{-3}	− 9.6[a] (1.68)	$C_{12}H_{20}Cl_3NO_2$ (316.6)
(*E*)	(2*S*,3*S*)-**4h**	100	90/10^{-3}	−12.8[a] (2.26)	$C_{12}H_{18}Cl_3NO_2$ (314.6)
(*E*)	(2*S*,3*S*)-**4i**	91	70/5 × 10^{-2}	−13.35[b] (3.85)	$C_8H_8Cl_3NO_2$ (256.5)
(*E*)	(2*S*,3*S*)-**4j**	99	100–105/5 × 10^{-2}	− 5.45[a] (4.49)	$C_{11}H_{14}Cl_3NO_4$ (298.6)

[a] 20 °C.
[b] 25 °C.
[c] The optical purity was not determined.
[d] Satisfactory microanalyses obtained: C ±0.36, H ±0.19, N ±0.24; except **4d** (C + 0.46).

Table 2. Oxazolines **5** and 5,6-Dihydro-4*H*-oxazines **6** from Trichloroacetimidic Esters **4**

Product(s)	Catalyst	Yield **5** + **6** (%)
rac-**5a**	$Et_2O \cdot BF_3$	99
(1′*S*,4*R*)-**5b** : (4*R*,5*S*)-**6b** (50 : 50)	$Et_2O \cdot BF_3$	98
(1′*S*,4*R*)-**5b**	CH_3SO_3H	96
(1′*S*,4*R*)-**5b** : (4*R*,5*S*)-**6b** (30 : 70)	$SnCl_4$	91
rac-**5b′**	$Et_2O \cdot BF_3$	98
(1′*S*,4*R*)-**5c** : (4*R*,5*S*)-**6c** (92 : 8)	$Et_2O \cdot BF_3$	92
(1′*S*,4*R*)-**5c** : (4*R*,5*S*)-**6c** (90 : 10)	CH_3SO_3H	87
(1′*S*,4*R*)-**5c** : (4*R*,5*S*)-**6c** (25 : 75)	$SnCl_4$	91
(1′*S*,4*R*)-**5d** : (4*R*,5*S*)-**6d** (77 : 23)	$Et_2O \cdot BF_3$	98
(1′*S*,4*R*)-**5d** : (4*R*,5*S*)-**6d** (88 : 12)	CH_3SO_3H	100
(1′*S*,4*R*)-**5d** : (4*R*,5*S*)-**6d** (52 : 48)	$SnCl_4$	94
(4*R*,5*S*)-**6e**	$Et_2O \cdot BF_3$	98
(4*R*,5*S*)-**6e**	$SnCl_4$	97
(4*R*,5*S*)-**6f**	$Et_2O \cdot BF_3$	87
(4*R*,5*S*)-**6g**	$Et_2O \cdot BF_3$	99
(4*R*,5*S*)-**6h**	$Et_2O \cdot BF_3$	98
(4*R*,5*S*)-**6i**	$Et_2O \cdot BF_3$	98
(4*R*,5*S*)-**6j**	$Et_2O \cdot BF_3$	78

The oxazolidinone **11c** has the two substituents, and hence the two protons, on the five-membered ring in *cis* position (viz. ^3J = 6.9 Hz). Steric interaction between the two *cis* substituents holds the isopropyl group in a conformation with more or less perfect antiperiplanar orientation of 3-H and 4-H. The same restriction applies to the conformation about the C-1/C-2 bond, and this smoothly explains the divergent ^3J couplings between 1-H^A,H^B and 2-H in the two oxazolidinone compounds **11c** and **12c**.

In the oxazolidinone carboxylic acid **13c**, the steric restraint is considerably loosened, with a concomitant decrease in ^3J(3-H, 4-H), and an increase of the 2-H,3-H in-ring coupling.

The ^{1}H-NMR spectra were recorded on a Bruker WP 80 (80 MHz) and a Bruker CXP 300 (300 MHz). $[\alpha]_D$ values were determined with a Perkin Elmer 241 polarimeter. *trans*-3-Methyl-2-penten-4-yn-1-ol was purchased from Fluka AG. Petroleum ether with bp 40–60 °C was used in the chromatographic separations.

3-Substituted 2-Hydroxymethyloxiranes 3:
The epoxy alcohols **3c**, **3f**, **3i** and **3j** were obtained by the catalytic Sharpless oxidation.[46] Compounds **3b**, **3e**, **3h** are described in Ref. 46 and **3d** in Ref. 47. The optical purity was not determined. Satisfactory microanalyses obtained (C ± 0.32, H ± 0.23) for all epoxy alcohols **3** prepared.

Table 3. Oxazolines **5** and 5,6-Dihydro-4*H*-oxazines **6** Prepared

Product	Yield (%)	mp (°C)	$[\alpha]_D^{a,b}$ (*c*, $CHCl_3$)	Molecular Formula[c]
rac-**5a**	99	71–72	–	$C_5H_6Cl_3NO_2$ (218.5)
(1′*S*,4*R*)-**5b**	96	120	−41.4[b] (5.07)	$C_8H_{12}Cl_3NO_2$ (260.6)
rac-**5b′**	98		–	$C_8H_{12}Cl_3NO_2$ (260.6)
(1′*S*,4*R*)-**5c**	84	67	−70.5[a] (1.74)	$C_8H_{12}Cl_3NO_2$ (260.6)
(1′*S*,4*R*)-**5d**	88	99–101	−40.6[a] (1.97)	$C_9H_{14}Cl_3NO_2$ (274.6)
(4*R*,5*S*)-**6b**	69	95	+68.24[a] (2.85)	$C_8H_{12}Cl_3NO_2$ (260.6)
(4*R*,5*S*)-**6c**	68	92	+47.2[a] (1.23)	$C_8H_{12}Cl_3NO_2$ (260.6)
(4*R*,5*S*)-**6d**	49	94	+ 8.9[a] (0.88)	$C_9H_{24}Cl_3NO_2$ (274.6)
(4*R*,5*S*)-**6e**	98	120	+91.3[a] (2.4)	$C_{11}H_{10}Cl_3NO_2$ (294.6)
(4*R*,5*S*)-**6f**	87	152	+ 5.5[a] (1.2)	$C_{12}H_{11}BrCl_3NO_2$ (403.5)
(4*R*,5*S*)-**6g**	99	97	+ 9.47[a] (1.95)	$C_{12}H_{20}Cl_3NO_2$ (316.6)
(4*R*,5*S*)-**6h**	98	71	+16.78[a] (1.21)	$C_{12}H_{18}Cl_3NO_2$ (314.6)
(4*R*,5*S*)-**6i**	98	144	+98.9[b] (3.9)	$C_8H_8Cl_3NO_2$ (256.5)
(4*R*,5*S*)-**6j**	78	129	+192.35[a] (1.32)	$C_{11}H_{14}Cl_3NO_2$ (298.6)

[a] 20 °C. [b] 25 °C.
[c] Satisfactory microanalyses obtained: C ±0.29, H ±0.16, N ±0.36; except **6d** (H + 0.45).

Table 4. *N*-Boc-3-Amino-1,2-alkanediols **8** Prepared

Product	Yield (%)	mp (°C)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Molecular Formula[a]
(2*S*,3*R*)-**8e**	96	113	−53.36 (1.88)	$C_{14}H_{21}NO_4$ (267.3)
(2*S*,3*R*)-**8g**	94	82–83	+ 0.83 (1.92)	$C_{15}H_{31}NO_4$ (289.4)
(2*S*,3*R*)-**8h**	96	148	+ 2.38 (2.06)	$C_{15}H_{29}NO_4$ (287.4)
(2*S*,3*R*)-**8i**	87	95–96	−33.16 (2.72)	$C_{11}H_{19}NO_4$ (229.2)
(2*S*,3*R*)-**8j**	100	71–72	−12.89 (1.05)	$C_{14}H_{25}NO_4$ (271.4)

[a] Satisfactory microanalyses obtained: C ±0.28, H ±0.20, N ±0.16.

(2S,3S)-2-Hydroxymethyl-3-(1-methylethyl)oxirane (**3c**):
yield: 83%; bp 88°C/20 mbar; $[\alpha]_D^{20}$ −32.75 (*c* = 1.97, $CHCl_3$).
^{1}H-NMR (80 MHz, $CDCl_3$): δ = 0.98 (d, 3H, *J* = 6 Hz); 1.04 (d, 3H, *J* = 6 Hz); 1.3–1.9 (m, 1H); 2.7–2.9 (m, 2H); 2.9–3.1 (m, 1H); 3.45–4.1 (m, 2H).

Table 5. *N*-Boc-α-Amino Aldehydes **9** Prepared

Product	Yield (%)	Molecular Formula[a]	^{1}H-NMR (80 MHz, $CDCl_3$) δ, *J* (Hz)
(2*R*)-**9g**	97	$C_{14}H_{27}NO_3$ (257.4)	0.85 (d, 3H, *J* = 6.5); 0.87 (d, 3H, *J* = 6.5); 1.34 (s, 3H); 1.44 (s, 9H); 1.0–1.75 (m, 7H); 5.0 (br s, 1H); 9.35 (s, 1H)
(2*R*)-**9h**	95	$C_{14}H_{25}NO_3$ (255.4)	1.36 (s, 3H); 1.45 (s, 9H); 1.58 (s, 3H); 1.66 (s, 3H); 1.3–2.2 (m, 4H); 4.9–5.3 (m, 2H); 9.33 (s, 1H)
(2*R*)-**9i**	91	$C_{10}H_{15}NO_3$ (197.2)	1.45 (s, 9H); 1.6 (s, 3H); 2.6 (s, 1H); 5.7 (br s, 1H); 9.3 (s, 1H)
(2*R*)-**9j**	90	$C_{13}H_{21}NO_3$ (239.3)	0.98 (t, 3H, *J* = 8); 1.44 (s, 9H); 1.6 (s, 3H); 1.35–1.75 (m, 2H); 2.23 (t, 2H, *J* = 7); 5.3 (br s, 1H); 9.3 (s, 1H)

[a] Exact microanalyses and high resolution M^+ values have not been obtained. Usually the acylamino aldehydes have been reacted without further purification. Boc-Amino aldehydes are described as extremely instable.[29,35,39]

Table 6. *N*-Boc-α-Amino Acids **10** Prepared

Product	Substrate	Oxidation Method[a]	Yield (%)	$[\alpha]_D^{20}$ (*c*, solvent)	Molecular Formula[b]
(2*R*)-**10g**	**8g**	C	86	−2.71 (0.8, MeOH)	$C_{14}H_{27}NO_4$ (273.4)
	9g	A	93	−2.7 (1.34, MeOH)	$C_{14}H_{27}NO_4$ (273.4)
(2*R*)-**10h**	**9h**	B	70	−2.0 (0.55, $CHCl_3$)	$C_{14}H_{25}NO_4$ (271.4)
(2*R*)-**10i**	**9i**	B	62	+19.66 (0.72, MeOH)	$C_{10}H_{15}NO_4$ (213.2)
(2*R*)-**10j**	**9j**	B	67	+32.3 (2.2, MeOH)	$C_{13}H_{21}NO_4$ (255.3)

[a] Oxidation method:
A $KMnO_4$, NaH_2PO_4, H_2O, *t*-BuOH
B $NaClO_2$, K_2HPO_4, H_2NSO_3H, H_2O, dioxane or *t*-BuOH
C $KMnO_4$, $NaIO_4$, H_2O, *t*-BuOH.
[b] Satisfactory microanalyses obtained: C ±0.37, H ±0.19, N ±0.18.

(2S,3S)-2-Hydroxymethyl-3-methyl-3-(4-methylpentyl)oxirane (**3g**): is prepared from **3h** by catalytic hydrogenation with palladium on charcoal in dioxane at room temperature; yield 98%; bp 85–90°C/0.1 mbar; $[\alpha]_D^{20}$ −5.64 (*c* = 2.11, $CHCl_3$).
^{1}H-NMR (80 MHz, $CDCl_3$): δ = 0.85 (s, 3H); 0.93 (s, 3H); 1.3 (s, 3H); 1.0–1.75 (m, 7H); 2.5 (br s, 1H); 2.96 (dd, 1H, J_1 = 6 Hz, J_2 = 5 Hz); 3.6–3.9 (m, 2H).

(2S,3S)-3-Ethynyl-2-hydroxymethyl-3-methyloxirane (**3i**): yield: 80%; bp 55–60°C/0.05 mbar; $[\alpha]_D^{25}$ +11.36 (*c* = 4.4, $CHCl_3$).
^{1}H-NMR (80 MHz, $CDCl_3$): δ = 1.55 (s, 3H); 2.38 (s, 1H); 2.75 (br s, 1H); 3.39 (t, 1H, *J* = 5.5 Hz); 3.65–3.9 (m, 2H).

(2S,3S)-2-Hydroxymethyl-3-methyl-3-(1-pentynyl)oxirane (**3j**): yield: 80%; bp 60–61°C/10^{-3} mbar: $[\alpha]_D^{20}$ = +3.96 (*c* = 1.06, $CHCl_3$).
^{1}H-NMR (80 MHz, $CDCl_3$): δ = 0.98 (t, 3H, *J* = 6.5 Hz); 1.53 (s, 3H), 1.3–1.8 (m, 2H), 2.18 (t, 2H, *J* = 7 Hz), 2.46 (br s, 1H), 3.24–3.43 (m, 2H), 3.55–4.05 (m, 2H).

(3-Substituted 2-Oxiranyl)methyl Trichloroacetimidates 4; General Procedure:
To a stirred solution of epoxyalcohol **3** (10 mmol) and trichloroacetonitrile (1.62 g, 11.25 mmol) in CH_2Cl_2 (10 mL) at 0°C, DBU (0.17 g, 1.125 mmol) is added slowly. After 1 h, the reaction mixture is concentrated *in vacuo*, and the residue is filtered on silica gel (petroleum ether/EtOAc, 1:1). Evaporation of the eluent and Kugelrohrdestillation affords trichloroacetimidic ester **4** (Table 1). Sensitive products can easily be purified by column chromatography on silica gel (petroleum ether/EtOAc, 80:20).

4-(1-Hydroxyalkyl)-2-trichloromethyl-2-oxazolines 5 and 5,6-Dihydro-4*H*-oxazines 6; General Procedure:
Method A: Ether–boron trifluoride complex (1–3 mmol) at 0°C or methanesulfonic acid (1–2 mmol) at room temperature is added to a stirred solution of the trichloroacetimidic ester **4** (10 mmol) in CH_2Cl_2 (100 mL). The reaction mixture is stirred 1 h, washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Recrystallization from hexane or column chromatography on silica gel (petroleum ether/EtOAc, 70:30) affords oxazoline **5** or/and dihydrooxazine **6** (Tables 2, 3).
Method B: Trichloroacetimidic ester **4** (10 mmol) dissolved in CH_2Cl_2 (40 mL) is added to a stirred solution of tin(IV) chloride (1.3 g, 5 mmol) in CH_2Cl_2 (20 mL) at −10°C. After 15 min the reaction mixture is worked up as described in Method A (Tables 2, 3).

***N-tert*-Butoxycarbonyl-2-amino-1,3-alkanediols 7 and *N-tert*-Butoxycarbonyl-3-amino-1,2-alkanediols 8; General Procedure:**
Cleavage of oxazolines **5** or dihydrooxazines **6** can be performed acidic or alkaline. Compound **5** or **6** (10 mmol) dissolved in dioxane (10 mL) is treated with 2N HCl (10 mL) for 1.5 h at 50°C, or in case of the alkaline cleavage with 1N NaOH (10 mL) in EtOH (10 mL) at room temperature overnight. The reaction mixture is adjusted to pH 8 and treated with di-*tert*-butyl dicarbonate (2.4 g, 11 mmol) overnight at room temperature. The solvent is distilled and the aqueous layer is extracted several times with CH_2Cl_2. The combined organic layers are dried ($MgSO_4$), filtered, and evaporated to give crude compounds **7** or **8**, which can be purified by chromatography on silica gel (petroleum ether/EtOAc, 50:50) (Table 4). 1,3-Diols **7** are very hygroscopic and difficult to purify; their full characterization was not undertaken.

Table 7. 2-Oxazolidinones Prepared

Product	Substrate	Yield (%)	mp (°C)	$[\alpha]_D^{20}$ (*c*, solvent)	Molecular Formula[b]
rac-**11a**	**5a**	81	76	–	$C_6H_6Cl_3NO_4$ (262.5)
(4*R*,5*S*)-**11b**	**5b**	89	74	+10.73 (3.2, $CHCl_3$)	$C_9H_{12}Cl_3NO_4$ (304.5)
(4*R*,5*S*)-**12b**	**11b**	88	65	+10.39 (1.3, $CHCl_3$)	$C_7H_{13}NO_3$ (159.2)
(4*S*,5*S*)-**13b**[a]	**12b**	93	145	+12.9 (1.3, MeOH)	$C_7H_{11}NO_4$ (173.2)
(4*R*,5*S*)-**11c**	**5c**	92	122	+59.6 (1.77, $CHCl_3$)	$C_9H_{12}Cl_3NO_4$ (304.6)
(4*R*,5*S*)-**12c**	**11c**	97	91	+51.2 (0.78, MeOH)	$C_7H_{13}NO_3$ (159.2)
(4*S*,5*S*)-**13c**	**12c**	84	191	+16.94 (1.95, MeOH)	$C_7H_{14}NO_4$ (173.2)
(4*R*,5*S*)-**11d**	**5d**	97	182–183	+88.1 (0.9, $CHCl_3$)	$C_{10}H_{14}Cl_3NO_4$ (318.6)
(4*R*,5*S*)-**12d**	**11d**	85	96	+63.0 (0.4, MeOH)	$C_8H_{15}NO_3$ (173.2)
(4*S*,5*S*)-**13d**	**12d**	92	90	+8.86 (0.7, MeOH)	$C_8H_{13}NO_4$ (187.2)

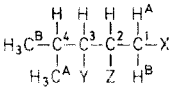
[a] Methyl ester of **13b**.
[b] Satisfactory microanalyses obtained: C ±0.27, H +0.19, N +0.32.

Table 8. ^{1}H-NMR Data[a] of the Isopropyl Series: Compounds **4c–6c** and **11c–13c**[b]

	4c	5c	6c	11c	12c	13c
1-H^A	4.508	4.676	4.335	4.561	3.674	–
1-H^B	4.259	4.622	4.099	4.325	3.606	–
2-H	3.165	4.512	3.95	4.072	3.765	4.366
3-H	2.737	3.727	3.307	4.267	4.200	4.403
4-H	1.597	1.715	1.920	1.977	2.094	1.939
CH_3^A	1.037	1.041	1.097	1.141	1.067	1.051
CH_3^B	0.977	0.936	0.990	1.018	0.976	1.030
OH		1.810	1.77		–	–
NH	8.375			5.96	–	–
^2J(1-H^A, 1-H^B)	-12.0_0	-8.4_5	-10.9_5	-11.4_0	-11.5_5	–
^3J(1-H^A, 2-H)	3.4_5	8.7_5	3.6_5	3.5_5	3.8_5	–
^3J(1-H^B, 2-H)	6.0_5	9.9_0	6.5_5	7.4_0	5.9_0	–
^3J(2-H, 3-H)	2.2_0	3.3_5	5.5_0	6.8_5	7.0_0	7.7_5
^3J(3-H, 4-H)	6.8_5	7.5_0	5.6_5	10.5_5	10.2_0	8.3_0
^3J(4-H, CH_3^A)	6.7_5	6.6_5	6.7_5	6.4_0	6.4_5	6.4
^3J(4-H, CH_3^B)	6.8_5	6.8_5	6.7_5	6.5_5	6.6_0	6.4
^4J(1-H^B, 3-H)			1.3_0			
^3J(2-H, NH)	–			0.5_0		–
^3J(3-H, OH)		3.5_5				

[a] Nominal frequency 300.13 MHz, 32 k interferograms and Fourier transforms, digital resolution 0.325 Hz ≙ 0.001 ppm/point; TMS as internal standard; ≤ 0.1 M in $CDCl_3$ (**12c** and **13c** in CD_3OD); 300 K. Chemical shift, δ, and coupling constant, J(Hz), values, as given in the table, are derived from an iterative numerical analysis (program Bruker PANIC, Aspect 2000); J values are rounded to $\pm 0.0_5$ Hz. Of the two diastereotopic CH_2 protons, and likewise the two CH_3 groups, the lower field signal is assigned as H^A and CH_3^A, respectively.

[b]



	X	Z	Y
4c	O–C^5(C^{6}Cl$_3$)=NH	–O–	
5c	–O–C^5(C^{6}Cl$_3$)=N–		OH
11c	O–C^{5}OC^{6}Cl$_3$	–NH–C^{7}O–O–	
12c	OH	–NH–C^{7}O–O–	
13c	(C^{1}O$_2$H)	–NH–C^{7}O–O–	

	X	Y	Z
6c	–O–C^5(C^{6}Cl$_3$)=N–		OH

Table 9. ^{13}C-NMR Data[a] of the Isopropyl Series: Compounds **4c–6c** and **11c–13c**[b]

	4c	5c	6c	11c	12c	13c
C-1	62.50	69.41[c]	68.73	67.13	61.27	173.05 (C=O)
C-2	53.88	71.51[c]	64.76[c]	53.39	57.90	59.47
C-3	61.77	75.67	62.81[c]	83.89	86.60	85.59
C-4	30.11	30.76	31.13	27.77	28.62	30.58
4-CH_3^A	18.95	18.94	19.72	19.68	20.07	19.18
4-CH_3^B	18.24	18.50	17.68	18.70	19.26	19.09
C-5 (C=O)	162.67	163.92	151.97	158.17	–	–
C-6 (CCl_3)	91.20	[d]	92.04	[d]	–	–
C-7 (C=O)	–	–	–	161.78	162.38	152.24

[a] Nominal frequency 75.47 MHz, 32 k interferograms and transforms, digital resolution 0.01 ppm/point; see also Table 8, footnote a.
[b] See Table 8, footnote b.
[c] Signal assignment may be reversed.
[d] Quaternary CCl_3 carbon signal not detectable.

***N-tert*-Butoxycarbonylalkanals 9; General Procedure:**

To a stirred solution of compound **8** (10 mmol) in THF (10 mL) is added at room temperature dropwise a solution of $NaIO_4$ (2.35 g, 11 mmol) in H_2O (10 mL). After 15 min the reaction mixture is evaporated, diluted with H_2O (25 mL) and extracted several times with Et_2O. The organic phase is dried ($MgSO_4$) and evaporated to give crude **9**, which can be purified by column chromatography on silica gel (petroleum ether/EtOAc 75:25) (Table 5).

***N-tert*-Butoxycarbonyl-α-amino Acids 10 from Diols 8 and Aldehydes 9; General Procedures:**

Method A[40]: $KMnO_4/NaH_2PO_4/H_2O/t$-BuOH.

Method B[43,44]: $NaClO_2/K_2HPO_4/H_2NSO_3H/H_2O/t$-BuOH or dioxane.

Method C[45]: $KMnO_4/NaIO_4/H_2O/t$-BuOH.

Oxidation by Methods A and B are performed as described in the literature. For the oxidation by Method C, a modified procedure is followed:

To a well stirred solution of *N*-Boc-3-amino-1,2-alkanediol **8** (10 mmol) in *t*-BuOH (50 mL) is added a solution of $NaIO_4$ (2.35 g, 11 mmol) in H_2O (15 mL) at room temperature. After 10 min, the resulting solution is diluted with 1.25 M aq. potassium phosphate buffer solution (40 mL); subsequently, 1 M aq. $KMnO_4$ solution (20 mL, 20 mmol) is added at room temperature with vigorous stirring. After 15 min the oxidation is quenched by the addition of a sat. aq. Na_2SO_3 solution (15 mL). The colloidal MnO_2 is filtered and the filtrate is concentrated *in vacuo*. The alkaline aq. solution is washed twice with CH_2Cl_2, then acidified with

solid citric acid to pH 5 and extracted several times with EtOAc. The organic layer is dried ($MgSO_4$) and evaporated to give pure acid **10**.

See Tables 4, 5.

5-Substituted 4-Trichloroacetoxymethyl-2-oxazolidinones 11; General Procedure:

To a stirred solution of oxazoline **5** (10 mmol) and pyridine (0.91 g, 11.5 mmol) in CH_2Cl_2 (20 mL) at −35 °C is added 2 M phosgene in CH_2Cl_2 (5.75 mL, 11.5 mmol). The reaction mixture is allowed to come to room temperature over a period of 4 h, then treated with H_2O (30 mmol) for 10 min, dried ($MgSO_4$) and evaporated. The residue is recrystallized from Et_2O/hexane to give oxazolidinone **11** (Table 7).

5-Substituted 4-Hydroxymethyl-2-oxazolidinones 12; General Procedure:

A solution of compound **11** (10 mmol) in MeOH (20 mL) is treated with NaOH (0.1 g, 2.5 mmol) at room temperature over 5 h. Evaporation of the solvent and recrystallization from Et_2O or chromatography on silica gel (petroleum ether/EtOAc, 50:50) gives **12** (Table 7).

5-Substituted 2-Oxazolidinone-4-carboxylic Acids 13; General Procedure:

Hydroxymethyloxazolidinone **12** (10 mmol) is dissolved in acetone (35 mL) and added dropwise to a Jones' reagent [prepared from chromium(VI) oxide (1.87 g, 18.7 mmol), conc. H_2SO_4 (1.6 mL) and H_2O (5 mL)] in acetone (20 mL) at 0 °C. The mixture is stirred for 3 h at 0 °C, then *i*-PrOH (3 mL) is added and stirring is continued for a further 0.5 h. The organic layer is evaporated, diluted with H_2O (25 mL) and extracted with EtOAc. The organic phase is extracted with 2 N $NaHCO_3$. The aqueous layer is separated, acidified, and extracted with EtOAc; drying ($MgSO_4$) and evaporation of the solvent gives pure compound **13** (Table 7).

Methyl (2*S*,3*S*)-*N*-*tert*-Butoxycarbonyl-3-hydroxyleucinate (14c):

Methyl (4S,5S)-5-Isopropyl-2-oxazolidinone-4-carboxylate: (4*S*,5*S*)-5-Isopropyl-2-oxazolidinone-4-carboxylic acid **(13c)** is esterified with excess diazomethane in MeOH to give quantitatively methyl ester **13c**; mp 70 °C; $[\alpha]_D^{20}$ + 5.8 (c = 0.98, CH_2Cl_2).

Methyl (4S,5S)-3-tert-Butoxycarbonyl-5-isopropyl-2-oxazolidinone-4-carboxylate: A stirred solution of methyl ester **13c** (1.87 g, 10 mmol) and di-*tert*-butyl dicarbonate (2.18 g, 10 mmol) in THF (10 mL) is treated with 4-dimethylaminopyridine (DMAP; 183 mg, 1.5 mmol) at room temperature for 4–5 h. After evaporation of the solvent, DMAP is separated by flash chromatography on silica gel (petroleum ether/EtOAc, 50:50); yield: 2.82 g (98%); mp 85 °C; $[\alpha]_D^{20}$ − 20.2 (c = 0.74, $CHCl_3$).

Methyl (2S,3S)-N-tert-Butoxycarbonyl-3-hydroxyleucinate **(14c)**: To a solution of the *N*-Boc derivative (2.87 g, 10 mmol) in MeOH (150 mL) solid Cs_2CO_3 (1.3 g, 4 mmol) is added at room temperature and stirring continued overnight. After neutralization with solid citric acid (1 g) the solvent is evaporated; the residue diluted with H_2O (20 mL) and extracted with CH_2Cl_2. The organic layer is washed with H_2O, dried ($MgSO_4$) and evaporated. The crude product is purified by column chromatography on silica gel (petroleum ether/EtOAc, 75:25) to give **14c**; yield: 2.23 g (91%); $[\alpha]_D^{20}$ + 23.6 (c = 0.45, $CHCl_3$).

$C_{12}H_{23}NO_4$	calc.	C 58.75	H 9.45	N 5.71
(245.3)	found	59.05	9.09	5.92

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