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Electrophilic ring opening of oxazolines derived from serine and threonine: A practical entry to N(N)-protected β-halogeno α-aminoesters

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Abstract

Treatment of oxazolines **4a–c** derived from serine or threonine with chloroformates, leads to the oxazoline ring opening and to the formation of N,N-protected β-chloro-α-aminoesters **1a–e** in 30–88% isolated yields. In the presence of NaI (0.9 equiv), oxazolines **4a,b,d** react with ethyl chloroformate to afford the N,N-protected β-iodo α-amino esters **1f–h** (67–89% yields), whereas the reaction of **4a,b** with trimethylsilyl halide gives the analogous *N*-benzoyl β-halogeno derivatives **1i,k** with 30–86% yields.

1. Introduction

2-Oxazolines are versatile heterocycles easily prepared from amino alcohols and carboxylic acids or derivatives, which have found extensive application in organic synthesis,[1] macromolecular[2] and coordination chemistry.[3] These heterocycles continue to present great interest as chiral auxiliaries in asymmetric synthesis,[1b,4] and as ligands in C–C bond formation catalysis.[3] In spite of the well-known chemistry, the reaction of oxazolines with electrophilic reagents has received little attention in synthesis, due to their polymerizability under such conditions. Nevertheless, among the electrophilic attacks[1a] and besides their acidolysis[5,6] or glycolysis,[7] one can mention the oxazoline ring opening with acyl chlorides,[6] or chloromethyl methyl ether.[8] Developing a new strategy to introduce an organophosphorus group on the lateral chain of aminoacids, we were interested by the N(N)-protected β-halogeno alanine derivatives **1** which are synthetic equivalents of the alanine β-anion, cation or radical (Scheme 1).[9] Considerable progress has been made recently in hemisynthesis of branched α-aminoacids using zinc reagents[10] prepared from *N*-Boc-β-iodo alanine **1** (P=Boc, Y=H, R_1=Me, X=I), and our preliminary results indicate that compounds **1** give also useful organometallic species.[11] As the preparation of these

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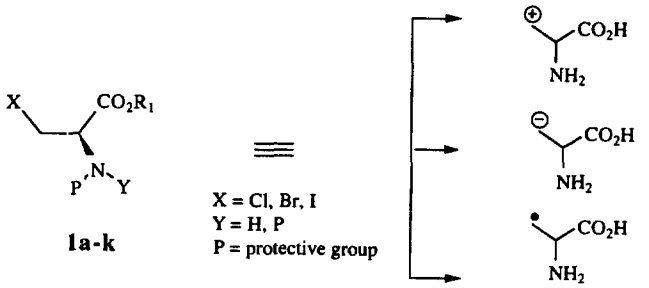
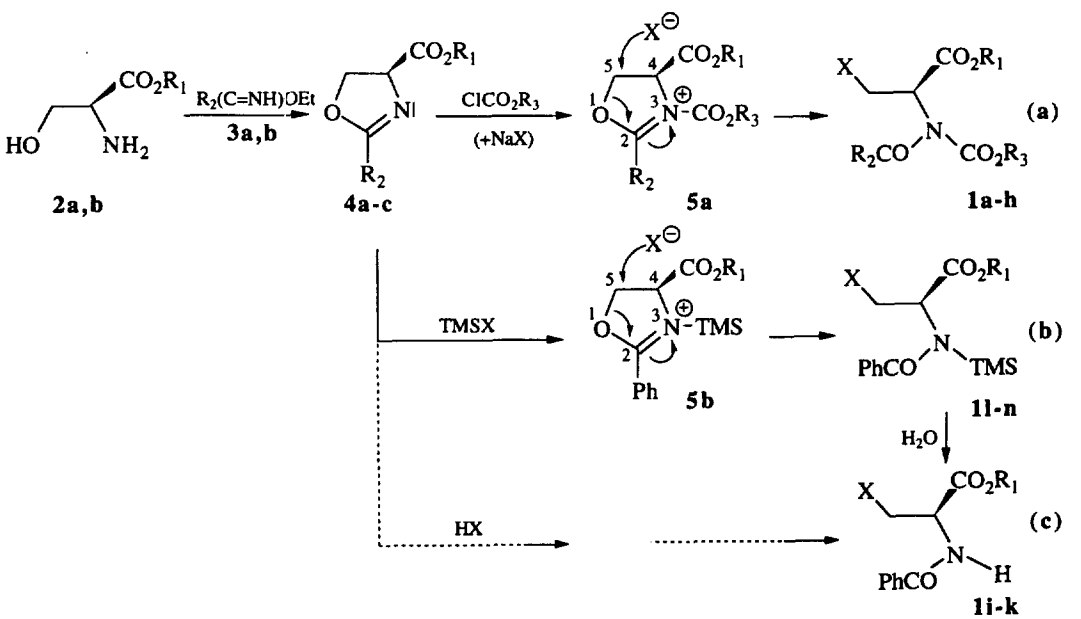
α-amino acid building blocks usually requires several steps from serine,[10b,12] cystine[13] or aspartic acid,[14] we report herein a simple and new method for the preparation of N,(N)-protected β-halogeno α-aminoesters **1**, by electrophilic ring opening of the oxazoline **4** with a chloroformate or a trimethylsilyl halide.



Scheme 1.

2. Results and discussion

The oxazolines **4a–d** have previously been synthesized in 80–95% yields, according to the classical condensation[15] of the appropriate iminoether hydrochlorides **3a,b**, with L and D,L aminoesters **2a–c** using triethylamine as a base (Scheme 2). Treatment of the oxazolines **4a,b,d** with 4 equivalents of ethyl chloroformate, provides the N,N-protected β-chloro aminoesters **1a–c** with 67–88% isolated yields (Table 1; entries 1–3). The reaction was explained by the formation of an oxazolinium intermediate **5a**, and the nucleophilic attack of the halide ion at the C(5) position of the ring, leading to the C(5)–O(1) bond cleavage (Scheme 2a).



Scheme 2.

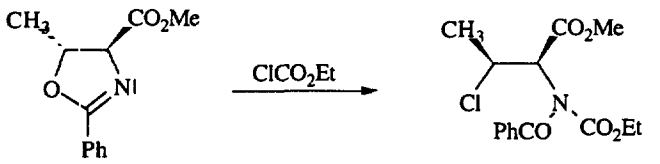
When $ClCO_2Bn$ was used, the reaction with the oxazoline (±)-**4b** gave a mixture of N,N-protected and N-protected β-chloro aminoesters **1d,i**, which can be isolated in 30 to 60% yields (entry 4). The

Table 1
Formation of N,N-protected β-halogeno α-aminoesters from reaction of oxazolines **4a–d** with $ClCO_2R_3$

Entry	Oxazoline 4			Electrophilic reagent	Conditions	N(N)-protected β-halogeno α-amino esters 1				
		R_1	R_2		solvent / T°C/ time		X	Y CO_2R_3	Y H	Yield [a]
1	(+)-**4a**	Me	Ph	Cl CO_2Et	THF/ 60°C/ 36h	**1a**	Cl	CO_2Et	-	85%
2	(+)-**4b**	Et	Ph	Cl CO_2Et	THF/ 60°C/ 36h	**1b**	Cl	CO_2Et	-	88%
3	(±)-**4d**	Me	Ph	Cl CO_2Et	THF/ 60°C/ 36h	**1c**	Cl	CO_2Et	-	67%
4	(±)-**4b**	Et	Ph	Cl CO_2Bn	THF/ 60°C/ 20h or CH_2Cl_2/ 40°C/24h	**1d** **1i**	Cl Cl	CO_2Bn -	- H	30-60%
5	(±)-**4b**	Et	Ph	$ClCO_2All$	THF/ 60°C/ 20h	**1e**	Cl	CO_2All	-	60%
6	(±)-**4b**	Et	Ph	Cl CO_2Et NaBr excess	THF/ 60°C/36h	**1b** **1j**	Cl Br	CO_2Et -	- H	48% 18%
7	(±)-**4a**	Me	Ph	Cl CO_2Et 0.9 equiv NaI	CH_2Cl_2/ 40°C/24h	**1f**	I	CO_2Et	-	89% (94%) [b]
8	(+)-**4b**	Et	Ph	Cl CO_2Et 0.9 equiv NaI	CH_2Cl_2/ 40°C/24h	**1g**	I	CO_2Et	-	78% (86%) [b]
9	(+)-**4c**	Et	t-Bu	Cl CO_2Et 0.9 equiv NaI	CH_2Cl_2/ 40°C/48h	**1h**	I	CO_2Et	-	67% (75%) [b]

[a] Isolated after purification by flash chromatography on silica gel.
[b] Calculated in regard to NaI

formation of the minor *N*-benzoyl product **1i**, was explained by the thermal decomposition of the benzyl chloroformate[16] and the dehydrochlorination of **1d** in the conditions of the reaction, leaving HCl responsible for the oxazoline ring opening[17] (Scheme 2c). Similar results were obtained with allyl chloroformate, since the oxazoline (±)-**4b** reacted to give the β-chloro alanine derivative **1e** (*N*-Alloc, *N*-benzoyl) isolated with 60% yield (entry 5). More interestingly, when the reaction between oxazolines **4a–c** and ethyl chloroformate occured in the presence of 0.9 equivalent of NaI, the N,N-protected β-iodo α-aminoesters **1f–h** were obtained in 67–89% yields (75–94% with regard to NaI; entries 7–9). The stereospecificity of the oxazoline ring opening has been controlled with **4d** prepared from D,L-threonine methyl ester **2c**, giving only one diastereoisomer of the N,N-protected β-chloro erythro derivative **1c**,[18] after reaction with the ethyl chloroformate (Scheme 3; Table 1, entry 3). Since it is well established that the acid solvolysis of **4d** involves a ring opening with complete inversion of configuration at the C(5) position,[5a] it is reasonable to assume that it is also the case here. Consequently, the formation of the pure erythro (±)-**1c** proves the absence of alteration of the α-carbon configuration in this reaction.[19]



(±)-**4d** (±)-**1c**

Scheme 3.

Table 2
Formation of *N*-benzoyl β-halogeno α-aminoesters from reaction of oxazolines **4a,b** with TMSX

Entry	Oxazoline 4	Electrophilic reagent TMSX	Conditions solvent / T°C/ Time	N-benzoyl-β-halogeno α-aminoesters 1 (Y= H) (Yield %)
1	(±)-**4b** R_1= Et; R_2= Ph	TMSCl	THF/ 60°C/ 8h	**1i** (86%)[a]
2	(+)-**4b** R_1= Et; R_2= Ph	TMSBr	THF/ 50°C/ 16h	**1j** (57%)[b]
3	(+)-**4b** R_1= Et; R_2= Ph	TMSBr	CH_2Cl_2/ 40°C/ 48h	**1j** (85%)[b]
4	(±)-**4a** R_1= Me; R_2= Ph	TMSI	CH_2Cl_2/ 40°C/ 36h	**1k** (30%)

[a] Isolated after purification by flash chromatography on silica gel. [b] Determined from NMR spectra of crude product.[20]

Since the reaction of ethyl chloroformate in the presence of NaBr proceeds with a poor efficiency (Table 1; entry 6), the ring opening of oxazolines **4a,b** has been performed with a trimethylsilyl halide as the electrophilic reagent (Scheme 2b, Table 2).

Thus, treatment of (±)-**4b** with trimethyl silyl chloride in refluxing THF led to the *N*-benzoyl β-chloro-α-aminoester **1i** with 86% yield (Table 2, entry 1). In similar conditions, the reaction of oxazoline (+)-**4b** with TMSBr afforded the β-bromo derivative **1j** with 57% yield, whereas in CH_2Cl_2 the yield increased to 85% (Table 2, entries 2 and 3). Finally, when TMSI reacted with the oxazoline (±)-**4a**, the *N*-benzoyl β-iodo-α-amino ester **1k** was isolated with a moderate yield of 30% (Table 2, entry 4). As in the case of chloroformates, we think that this reaction occurs via the formation of the *N*-trimethylsilyl oxazolinium salt **5b** (Scheme 2b), leading to the *N*-benzoyl β-halogeno products **1i–k** after hydrolysis of the *N*-trimethylsilyl-*N*-benzoyl intermediates **1l–n** (X=Cl, Br, I).

In summary, we have found a new and convenient method for the preparation of N,N-protected β-chloro-α-aminoesters **1a–e** in 30–88% overall yields, without alteration of the α-carbon configuration, and by reaction of chloroformates with oxazolines **4a,b,d** prepared from serine or threonine. It is noteworthy that in the presence of NaI, the N,N-protected β-iodo aminoesters **1f–h** were obtained in high yields (67–89%), whereas it was preferable to use TMSBr to obtain cleanly the analogous β-bromo alanine derivative **1j** (85% yield). The methodology described here, furnishes a general approach for the synthesis of enantiomerically pure β-halogeno α-aminoesters **1**, by simply changing the electrophilic reagent in the reaction with the oxazoline **4**. Finally, oxazolines derived from β-hydroxy α-aminoesters are promising chiral synthons for branched amino acids synthesis.

3. Experimental section

3.1. General

All reactions were carried out under an argon atmosphere in glassware dried overnight. Solvents were dried and freshly distilled under an argon atmosphere over sodium/benzophenone for THF and ether, and over CaH_2 for toluene, CH_2Cl_2 and $CHCl_3$. L and DL-serine, DL-threonine and trimethylsilyl bromide were purchased from Aldrich. Trimethylsilyl iodide, allyl, benzyl, ethyl chloroformates and pivalonitrile were purchased from Acros Organics. Trimethylsilylchloride was purchased from Lancaster. The phenyl and *tert*-butyl imino ethyl ether hydrochlorides **3a** and **3b** were obtained by bubbling HCl gas in a solution of the corresponding nitrile with ethanol.[4e,21] The serine and threonine esters **2a–c** were prepared from the reaction of acetyl chloride with the corresponding amino acid, in solution in methanol or ethanol.[15] Sodium iodide was dried by heating at 140°C under reduced pressure for 8 h in the dark. Flash chromatography was realized on silica gel (230–400 mesh; Merck) and when necessary pure samples were obtained by preparative TLC on commercially tapered silica gel plates $60F_{254+366}$(Merck). All NMR spectra data were obtained on Bruker DPX 250 and AM 400 spectrometers using TMS as an internal reference. Infrared spectra were recorded on a Perkin–Elmer 1600 FT spectrometer. Melting points were mesured on a Büchi melting point apparatus and are uncorrected. Optical rotations values were determined at 20°C on a Perkin–Elmer 241 polarimeter. Mass spectral analyses were performed on a NERMAG R10-10C and a KRATOS MS-50 for exact mass, at the Mass Spectroscopy Laboratories of ENSCP and the Structural Chemistry Laboratories of P. & M. Curie University (Paris). The major peak m/z is mentioned with the intensity as a percentage of the base peak in brackets. Elemental analyses were mesured with a precision superior to 0.3% at the Microanalysis Laboratories of P. & M. Curie University (Paris), and at the CNRS (Vernaison, France).

3.2. Typical procedure for oxazolines[15]

A 250 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with derivative **2** (22.5 mmol), 100 mL of chloroform, imino ethyl ether hydrochloride **3** (22.5 mmol) and 2.27 g of triethylamine (22.5 mmol). The mixture was refluxed for 30 h. The solvent was removed and the residue purified by chromatography on silica gel with cyclohexane:AcOEt (1:1) as the eluent to give compound **4**.

3.3. 2-Phenyl-4-carbomethoxy-2-oxazoline **4a**[4e,15]

Yield=80%; colourless oil; R_f=0.35 (cyclohexane:AcOEt=1:1); IR (neat, ν cm^{-1}): 2953 (m), 1742 (vs), 1644 (s), 1214 (vs), 1088 (s); ^1H NMR ($CDCl_3$): δ 7.99 (2H, d, ^3J=7.9, H arom), 7.43–7.33 (3H, m, H arom), 4.88 (1H, dd, ^3J=7.8, ^3J=10.5, C*H*N), 4.65 (1H, t, J=8.6, C(H)*H*), 4.52 (1H, dd, ^2J=8.7, ^3J=10.6, C*H*(H)), 3.76 (3H, s, CO_2CH_3); ^{13}C NMR ($CDCl_3$): δ 171.6 (CO_2Me), 166.1 (*C*N), 131.8 (*C*H arom), 128.6.(*C*H arom), 128.3 (*C*H arom), 127.0 (C arom), 69.6 (CHCH_2O), 68.6 (*C*HN), 52.6 (CO_2CH_3).

3.4. (S)-(+)-2-Phenyl-4-carboethoxy-2-oxazoline **4b**[22]

Yield=95%; crystals, mp<40°C; $[\alpha]_D^{20}$=+90.9 (c=0.2, $CHCl_3$); R_f=0.38 (cyclohexane:AcOEt=1:1); IR (neat, ν cm^{-1}): 2981 (m), 1736 (s), 1641 (s), 1194 (vs), 1089 (s); ^1H NMR ($CDCl_3$): δ 8.0 (2H, dd,

^3J=7, ^3J=8.5, H arom), 7.48–7.36 (3H, m, H arom), 4.91 (1H, dd, ^3J=7.9, ^3J=10.6, C*H*N), 4.67 (1H, t, J=8.4, OC(H)*H*), 4.56 (1H, dd, ^2J=8.8, ^3J=10.6, OC*H*(H)), 4.26 (2H, dq, ^3J=7.2, $CO_2CH_2CH_3$), 1.31 (3H, t, ^3J=7.1, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 171.2 (*C*O_2Et), 166.2 (*C*N), 132.2 (*C*H arom), 128.9 (*C*H arom), 128.7 (*C*H arom), 126.4 (C arom), 70.0 ($CHCH_2O$), 69.1 (*C*HN), 62.1 ($CO_2CH_2CH_3$), 14.5 ($CO_2CH_2CH_3$). Anal. calcd for $C_{12}H_{13}NO_3$ (219): C 65.74, H 5.97, N 6.39; found: C 65.64, H 5.95, N 6.36.

3.5. (S)-(+)-2-tert-Butyl-4-carboethoxy-2-oxazoline **4c**

Yield=80%; colourless oil; $[\alpha]_D^{20}$=+36.6 (c=2.1, $CHCl_3$); R_f=0.4 (cyclohexane:AcOEt=1:1); IR (neat, ν cm^{-1}): 2977 (vs), 1740 (s), 1651 (s), 1194 (vs), 1146 (s); ^{1}H NMR ($CDCl_3$): δ 4.68 (1H, dd, ^3J=7.5, ^3J=10.5, C*H*N), 4.40 (2H, 2dd, $CHCH_2O$), 4.22 (2H, dq, ^3J=7, $CO_2CH_2CH_3$), 1.30 (3H, t, ^3J=7, $CO_2CH_2CH_3$), 1.24 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 176.9 (*C*N), 171.5 (*C*O_2Et), 69.6 ($CHCH_2O$), 68.3 (*C*HN), 61.4 ($CO_2CH_2CH_3$), 33.4 ($C(CH_3)_3$), 27.6 ($C(CH_3)_3$), 14.1 ($CO_2CH_2CH_3$). Anal. calcd for $C_{10}H_{17}NO_3$ (199): C 60.30, H 8.54, N 7.04; found: C 60.24, H 8.48, N 7.03.

3.6. (±)-2-Phenyl-5-methyl-4-carbomethoxy-2-oxazoline **4d**[4b]

Yield=80%; colourless oil; R_f=0.52 ($CHCl_3$:Et_2O=7:3); IR (neat, ν cm^{-1}): 2953 (m), 1742 (s), 1642 (s), 1203 (vs); ^{1}H NMR ($CDCl_3$): δ 8.1–8 (2H, m, H arom), 7.6–7.3 (3H, m, H arom), 5.0 (1H, m, C*H*O), 4.45 (1H, d, ^3J=8, C*H*N), 3.8 (3H, s, CO_2CH_3), 1.5 (3H, d, ^3J=7, CH_3CH). HRMS (EI) calcd for $C_{12}H_{13}NO_3$ [M] 219.0895; found 219.0896.

*3.7. (R)-(−)-Methyl [2-(*N*-benzoyl-*N*-ethoxycarbonyl) amino-3-chloro] propanoate* **1a**

A 100 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 3 g of oxazoline (+)-**4a** (14.6 mmol), 9 mL of ethyl chloroformate (94.5 mmol) and 40 mL of THF. The mixture was refluxed for 36 h. The solvent was removed and the residue purified by chromatography on silica gel with cyclohexane:AcOEt (4:1) as the eluent to give 3.91 g of compound **1a** (85% yield). Colourless oil; $[\alpha]_D^{20}$=−40.7 (c=2.6, $CHCl_3$); R_f=0.73 (cyclohexane:AcOEt=1:1); IR (neat, ν cm^{-1}): 2955 (m), 1746 (s), 1682 (s), 1258 (s), 1069 (m), 1017 (s); ^{1}H NMR ($CDCl_3$): δ 7.65–7.38 (5H, m, H arom), 5.41 (1H, t, ^3J=7.6, C*H*N), 4.23 (2H, d, ^3J=7.6, CH_2Cl), 4.01 (2H, q, ^3J=7.1, $NCO_2CH_2CH_3$), 3.77 (3H, s, CO_2CH_3), 0.87 (3H, t, ^3J=7.1, $NCO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.5 (Ph*C*O), 168.2 (*C*O_2Me), 154.3 (N*C*O_2Et), 136.4 (C arom), 131.7 (*C*H arom), 128.2 (*C*H arom), 127.9 (*C*H arom), 63.4 ($NCO_2CH_2CH_3$), 59.3 (*C*HN), 52.9 (CO_2CH_3), 42.2 (CH_2Cl), 13.4 ($NCO_2CH_2CH_3$); MS (EI) m/z (relative intensity): 313 (M^+; 6), 278 ($M-Cl^+$; 31), 254 (14), 240 (10), 218 (11), 189 (17), 105 (100), 77 (100). Anal. calcd for $C_{14}H_{16}ClNO_5$ (313.5): C 53.60, H 5.14, N 4.46, O 25.49, Cl 11.30; found: C 53.88, H 5.32, N 4.79, O 25.24, Cl 10.97.

*3.8. (R)-(−)-Ethyl [2-(*N*-benzoyl-*N*-ethoxycarbonyl) amino-3-chloro] propanoate* **1b**

A 100 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 1.5 g of oxazoline (+)-**4b** (6.8 mmol), 2.6 mL of ethyl chloroformate (27.2 mmol) and 20 mL of THF. The mixture was refluxed for 36 h. The solvent was removed and the residue purified by chromatography on silica gel with cyclohexane:AcOEt (4:1) as the eluent to give 1.98 g of compound **1b** (88% yield). Colourless oil; $[\alpha]_D^{20}$=−35.3 (c=2.2, $CHCl_3$); R_f=0.55 (cyclohexane:AcOEt=1:1); IR (neat, ν cm^{-1}):

2983 (m), 1742 (s), 1686 (s), 1263 (s), 1022 (s); ^{1}H NMR ($CDCl_3$): δ 7.70–7.36 (5H, m, H arom), 5.40 (1H, dd, ^3J=6.3, ^3J=6.5, C*H*N), 4.28–4.22 (4H, m, CH_2Cl, $CO_2CH_2CH_3$), 4.01 (2H, q, ^3J=7.3, $NCO_2CH_2CH_3$), 1.27 (3H, t, ^3J=6.8, $CO_2CH_2CH_3$), 0.86 (3H, t, ^3J=7.3, $NCO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 171.3 (Ph*C*O), 166.4 (*C*O_2Et), 153.0 (N*C*O_2Et), 135.2 (C arom), 130.4 (*C*H arom), 127.2 (*C*H arom), 126.2 (*C*H arom), 62.4 ($NCO_2CH_2CH_3$), 60.9 ($CO_2CH_2CH_3$), 58.4 (*C*HN), 41.1 (*C*H_2Cl), 12.8 ($NCO_2CH_2CH_3$), 12.1 ($CO_2CH_2CH_3$). Anal. calcd for $C_{15}H_{18}ClNO_5$ (327.5): C 54.97, H 5.53, N 4.27; found: C 54.48, H 5.69, N 4.13.

3.9. (±)-Methyl erythro [2-(N-benzoyl-N-ethoxycarbonyl) amino-3-chloro] butanoate **1c**

A 100 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 2 g of oxazoline (±)-**4c** (8.6 mmol), 3 mL of ethyl chloroformate (31.4 mmol) and 30 mL of THF. The mixture was refluxed for 30 h. The solvent was removed and the residue purified by chromatography on silica gel to give 2.18 g of compound **1c** (67% yield). Colourless oil; R_f=0.66 (CH_2Cl_2); IR (neat, ν cm^{-1}): 2934 (m), 1742 (s), 1687 (s), 1227 (vs), 1033 (m). ^{1}H NMR ($CDCl_3$): δ 7.61 (2H, d, ^3J=7.6, H arom), 7.53 (1H, t, ^3J=7.4, H arom), 7.42 (2H, t, ^3J=7.6, H arom), 5.32 (1H, d, ^3J=7.4, C*H*N), 4.84 (1H, p, ^3J=6.8, CHCl), 4.02 (2H, q, ^3J=7.1, $NCO_2CH_2CH_3$), 3.79 (3H, s, CO_2CH_3), 1.58 (3H, d, ^3J=6.7, CH_3CHCl), 0.89 (3H, t, ^3J=7.2, $NCO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.4 (Ph*C*O), 168.3 (*C*O_2CH_3), 154.4 (N*C*O_2Et), 136.0 (C arom), 131.9 (*C*H arom), 128.3 (*C*H arom), 127.8 (*C*H arom), 63.7 (*C*HN), 63.4 ($NCO_2CH_2CH_3$), 54.6 (*C*HCl), 52.7 (CO_2CH_3), 21.6 (CH_3CHCl), 13.4 ($NCO_2CH_2CH_3$); MS (EI) m/z (relative intensity): 292 (M^+–Cl; 3); 232 (4); 105 (100); 85 (12); 83 (18); 77 (20); Anal. calcd for $C_{15}H_{18}ClNO_5$ (327.5): C 54.97, H 5.53, N 4.27, O 24.41; found: C 54.53, H 5.99, N 3.73, O 24.87.

3.10. (±)-Ethyl [2-(N-benzoyl-N-benzyloxycarbonyl) amino-3-chloro] propanoate **1d**

A 10 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 0.1 g of oxazoline (±)-**4b** (0.5 mmol), 0.28 mL of benzyl chloroformate (2 mmol) and 3 mL of THF. The mixture was refluxed for 24 h. The solvent was removed and the residue purified by chromatography on silica gel with cyclohexane:AcOEt (1:1) as the eluent to give 0.12 g of compound **1d** (60% yield). Colourless oil; R_f=0.63 (CH_2Cl_2); IR (neat, ν cm^{-1}): 3064 (m), 2982 (m), 1739 (vs), 1682 (s), 1449 (s), 1265 (vs), 1220 (s), 1164 (s), 1020 (s); ^{1}H NMR ($CDCl_3$): δ 7.63 (2H, d, ^3J=7.2, CH arom), 7.46–7.42 (1H, m, CH arom), 7.34–7.26 (2H, m, H arom), 7.23–7.18 (3H, m, H arom), 6.88 (2H, dd, ^4J=1.3, ^3J=7.2, CH arom), 5.41 (1H, dd, ^3J=6.4, 9.1, C*H*N), 4.98 (2H, s, CH_2Ph), 4.30–4.22 (2H m, CH_2Cl), 4.14 (2H, dq, ^3J=7.1, $CO_2CH_2CH_3$), 1.16 (3H, t, ^3J=7.1, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.3 (Ph*C*O), 167.5 (*C*O_2Et), 154.2 (N*C*O_2Bn), 136.0 (C arom), 133.9 (C arom), 131.8 (*C*H arom), 128.5 (*C*H arom), 128.4 (*C*H arom), 128.3 (*C*H arom), 128.0 (*C*H arom), 69.6 (O*C*H_2Ph), 62.6 ($CO_2CH_2CH_3$), 60.0 (*C*HN), 42.7 (*C*H_2Cl), 14.4 ($CO_2CH_2CH_3$). HRMS (EI) calcd for $C_{20}H_{20}ClNO_5$ [M] 389.1030; found 389.1030.

3.11. (±)-Ethyl [2-(N-allyloxycarbonyl-N-benzoyl) amino-3-chloro] propanoate **1e**

A 10 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 0.22 g of oxazoline (±)-**4b** (1 mmol), 0.5 mL of allyl chloroformate (4.7 mmol) and 3 mL of THF. The mixture was refluxed for 20 h. The solvent was removed and the residue purified by chromatography on silica gel with cyclohexane:AcOEt (1:1) as the eluent to give 0.21 g of compound **1e** (60% yield). Colourless oil; R_f=0.60 (cyclohexane:AcOEt=1:1); IR (neat, ν cm^{-1}): 2984 (m), 1746 (s), 1682 (s),

1381 (s), 1337 (s), 1260 (s), 1221 (s), 1170 (s), 1020 (s); ^{1}H NMR ($CDCl_3$): δ 7.67 (2H, d, ^3J=7.1, H arom), 7.53–7.39 (3H, m, H arom), 5.53–5.45 (1H, m, CH=C), 5.42 (1H, t, ^3J=8.2, CHN), 5.07 (1H, dd, ^4J=1.1, ^2J=10.3, CH(H_{cis})=CH), 5.02 (1H, dd, ^4J=1.2, ^3J=17.6, CH(H_{trans})=CH), 4.45 (2H, dd, ^4J=1.2, ^3J=5.9, CH_2CH=C), 4.29–4.19 (4H, m, CH_2Cl, $CO_2CH_2CH_3$), 1.26 (3H, t, ^3J=7.3, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.4 (PhCO), 167.6 (CO_2Et), 154.1 (NCO_2All), 136.1 (C arom), 131.88 (CH arom), 130.4 ($CH=CH_2$), 128.3 (CH arom), 128.0 (CH arom), 119.1 ($CH=CH_2$), 67.8 (NCO_2CH_2), 62.2 ($CO_2CH_2CH_3$), 59.5 (CHN), 42.2 (CH_2Cl), 14.1 ($CO_2CH_2CH_3$). HRMS (EI) calcd for $C_{16}H_{18}ClNO_5$ [M] 339.0873; found 339.0872.

3.12. (±)-Methyl [2-(N-benzoyl-N-ethoxycarbonyl) amino-3-iodo] propanoate 1f

A 100 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 3 g of oxazoline (±)-**4a** (14.63 mmol), 5.6 mL of freshly distilled ethyl chloroformate (58.52 mmol) and 50 mL of dichloromethane. Then 2 g of anhydrous NaI (13.1 mmol) was added and the mixture was refluxed for 24 h in the dark. The solution was cooled, the salt filtered and the filtrate evaporated. The residue was purified by chromatography on silica gel with dichloromethane as the eluent to give 5.03 g of compound **1f** (85% yield). Yellow oil; R_f=0.30 (cyclohexane:AcOEt=1:1); IR (neat, ν cm^{-1}): 2984 (m), 2953 (m), 1744 (vs), 1681 (s), 1263 (s), 1156 (m), 1057 (m); ^{1}H NMR ($CDCl_3$): δ 7.72 (2H, dd, ^4J=1.5, ^3J=8.5, H arom), 7.51–7.39 (3H, m, H arom), 5.36 (1H, dd, ^3J=5.7, ^3J=10.1, CHN), 4.03 (2H, q, ^3J=7.1, $CO_2CH_2CH_3$), 3.94–3.90 (2H, m, CH_2I), 3.78 (3H, s, CO_2CH_3), 0.89 (3H, t, ^3J=7.1, $NCO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.9 (PhCO), 168.5 (CO_2CH_3), 154.8 ($NCO_2CH_2CH_3$), 136.9 (C arom), 132.4 (CH arom), 129.1 (CH arom), 128.8 (CH arom), 64.1 ($NCO_2CH_2CH_3$), 60.2 (CHN), 53.7 (CO_2CH_3), 14.0 ($NCO_2CH_2CH_3$), 2.4 (CH_2I). Anal. calcd for $C_{14}H_{16}INO_5$ (405): C 41.50, H 3.98, N 3.46; found: C 41.64, H 4.01, N 3.47.

3.13. (R)-(−)-Ethyl [2-(N-benzoyl-N-ethoxycarbonyl) amino-3-iodo] propanoate 1g

A 100 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 3.2 g of oxazoline (+)-**4b** (14.63 mmol), 5.6 mL of freshly distilled ethyl chloroformate (58.52 mmol) and 50 mL of dichloromethane. Then 2 g of anhydrous NaI (13.71 mmol) was added and the mixture was refluxed for 24 h in the dark. The solution was cooled, the salt filtered and the filtrate evaporated. The residue was purified by chromatography on silica gel with dichloromethane as the eluent to give 4.8 g of compound **1h** (78% yield). Yellow oil; $[\alpha]_D^{20}$=−20.6 (c=1.2, $CHCl_3$); R_f=0.59 (CH_2Cl_2); IR (neat, ν cm^{-1}): 2983 (m), 1739 (vs), 1681 (vs), 1254 (vs), 1156 (s), 1110 (m), 1056 (s), 1019 (s); ^{1}H NMR ($CDCl_3$): δ 7.72 (2H, dd, ^4J=1.8, ^3J=7.9, H arom), 7.51–7.41 (3H, m, H arom), 5.35 (1H, dd, ^3J=6.1, ^3J=9.7, CHN), 4.27–4.20 (2H, m, $CO_2CH_2CH_3$), 4.02 (2H, q, ^3J=7.1, $NCO_2CH_2CH_3$), 3.97–3.86 (2H, m, CH_2I), 1.27 (3H, t, ^3J=7.1, $CO_2CH_2CH_3$), 0.89 (3H, t, ^3J=7.1, $NCO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.6 (PhCO), 167.7 (CO_2Et), 154.6 (NCO_2Et), 136.8 (C arom), 132.0 (CH arom), 128.8 (CH arom), 128.5 (CH arom), 63.8 ($NCO_2CH_2CH_3$), 62.6 ($CO_2CH_2CH_3$), 60.1 (CHN), 14.4 ($NCO_2CH_2CH_3$), 13.7 ($CO_2CH_2CH_3$), 2.4 (CH_2I); MS (EI) m/z: 420 (M+1), 374 (M−OEt), 292 (M−I), 105 (PhCO); Anal. calcd for $C_{15}H_{18}INO_5$ (419): C 42.98, H 4.32, N 3.34; found: C 43.15, H 4.32, N 3.30.

3.14. (R)-(−)-Ethyl [2-(N-ethoxycarbonyl-N-tert-butylcarbonyl) amino-3-iodo] propanoate **1h**

A 25 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 1.2 g of oxazoline (+)-**4d** (6.06 mmol), 2.3 mL of freshly distilled ethyl chloroformate (24 mmol) and 50 mL of dichloromethane. Then 0.83 g of anhydrous NaI (5.54 mmol) was added and the mixture was refluxed for 48 h in the dark. The solution was cooled, the salt filtered and the filtrate evaporated. The residue was purified by chromatography on silica gel with dichloromethane as the eluent to give 1.64 g of compound **1h** (75% yield). Yellow oil; $[\alpha]_D^{20}=-3.9$ (c=1.4, $CHCl_3$); $R_f=0.59$ (CH_2Cl_2); IR (neat, ν cm^{-1}): 2981 (s), 1739 (vs), 1693 (s), 1483 (m), 1465 (m), 1259 (s), 1178 (s), 1153 (s), 1064 (m), 1021 (m); ^1H NMR ($CDCl_3$): δ 4.98 (1H, dd, ^3J=4.4, ^3J=11.0, C*H*N), 4.29 (2H, q, ^3J=7.1, $CO_2CH_2CH_3$), 4.16 (2H, qd, J=2.6, J=7.2, $NCO_2CH_2CH_3$), 3.85 (1H, dd, ^3J=4.4, ^2J=10.9, C(H)*H*), 3.62 (1H, t, *J*=11.0, C*H*(H)), 1.38 (9H, s, $C(CH_3)_3$), 1.35 (3H, t, ^3J=7.2, $CO_2CH_2CH_3$), 1.25 (3H, t, ^3J=7.1, $NCO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 185.0 (t-Bu*C*O), 167.7 (*C*O_2Et), 154.4 (N*C*O_2Et), 63.4 ($NCO_2CH_2CH_3$), 62.1 ($CO_2CH_2CH_3$), 61.4 (*C*HN), 43.8 ($C(CH_3)_3$), 28.3 ($C(CH_3)_3$), 14.1 ($NCO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 2.1 (CH_2I); MS (CI, NH_3) m/z: 399 (M^+), 272 (M^+-I), 200 (M^+-I-CO_2Et), 85 (t-BuCO^+).

3.15. (±)-Ethyl [2-(N-benzoyl)amino-3-chloro] propanoate **1i** [13b,23]

A 25 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 0.23 g of oxazoline (±)-**4b** (1 mmol), 0.5 mL of trimethylsilyl chloride (4 mmol) and 3 mL of THF. The mixture was refluxed for 8 h and was hydrolyzed at room temperature. The solution was extracted with dichloromethane and dried over magnesium sulfate. The solvent was removed and the residue purified by chromatography on silica gel with dichloromethane as the eluent to give 0.22 g of compound **1i** (86% yield). White solid; mp=94°C; $R_f=0.45$ (cyclohexane:AcOEt=1:1); IR (KBr, ν cm^{-1}): 3322 (s), 1744 (s), 1639 (s), 1222 (s), 1040 (m); ^1H NMR ($CDCl_3$): δ 7.83 (2H, d, ^3J=7, H arom), 7.51–7.40 (3H, m, H arom), 7.21 (1H, d, ^3J=7, NH), 5.17–5.11 (1H, m, CHN), 4.33–4.24 (2H, m, $CO_2CH_2CH_3$), 4.05–4.03 (2H, m, CH_2Cl), 1.30 (3H, t, ^3J=7.1, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 168.9 (Ph*C*O), 167.1 (*C*O_2Et), 133.5 (C arom), 132.0 (*C*H arom), 128.6 (*C*H arom), 127.2 (*C*H arom), 62.4 ($CO_2CH_2CH_3$), 53.7 (*C*HN), 45.2 (CH_2Cl), 14.1 ($CO_2CH_2CH_3$).

3.16. (R)-(+)-Ethyl [2-(N-benzoyl)amino-3-bromo] propanoate **1j**

A 50 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with 2 g of oxazoline (+)-**4b** (9.13 mmol), 2 mL of trimethylsilyl bromide (15.2 mmol) and 30 mL of dichloromethane. The mixture was refluxed for 48 h and was hydrolyzed at room temperature. The solution was extracted with dichloromethane and dried over magnesium sulfate. The solvent was removed and the residue purified by chromatography on silica gel with dichloromethane as the eluent to give 2.33 g of compound **1j** (85% yield). White solid; mp=107°C; $[\alpha]_D^{20}=+45.9$ (c=2.2, $CHCl_3$); $R_f=0.38$ (cyclohexane:AcOEt=1:1); IR (KBr, ν cm^{-1}): 3299 (s), 2981 (w), 1733 (s), 1687 (s), 1327 (m), 1234 (m), 1151 (m), 1036 (m); ^1H NMR ($CDCl_3$): δ 7.84 (2H, d, ^3J=6.9, H arom), 7.60–7.40 (3H, m, H arom), 7.48 (1H, d, ^3J=6.5, N*H*), 5.22–5.16 (1H, m, C*H*N), 4.28 (2H, q, ^3J=7.2, $CO_2CH_2CH_3$), 3.91 (2H, d, ^3J=3.4, CH_2Br), 1.37 (3H, t, ^3J=7.2, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 169.0 (Ph*C*O), 167.0 (*C*O_2Et), 133.5 (C arom), 132.0 (*C*H arom), 128.8 (*C*H arom), 127.2 (*C*H arom), 62.4 ($CO_2CH_2CH_3$), 53.1 (*C*HN), 33.7 (CH_2Br), 14.2 ($CO_2CH_2CH_3$); MS (EI) m/z (relative intensity): 301 (M^++2; 1), 299

(M^+; 1), 219 (8), 146 (17), 105 (100), 77 (38), 51 (10). Anal. calcd for $C_{12}H_{14}BrNO_3$ (300): C 48.16, H 4.70, N 4.67; found: C 48.37, H 4.96, N 4.61.

3.17. (±)-Methyl [2-(N-benzoyl)amino-3-iodo] propanoate 1k

According to the same procedure as for compound **1i**, replacing TMSCl by TMSI, 0.1 g of **1k** was obtained (30% yield). Uncrystallized; R_f=0.48 (CH_2Cl_2); IR (KBr, ν cm^{-1}): 3294 (s), 2951 (w), 1735 (s), 1643 (s), 1224 (s), 1146 (s); ^1H NMR ($CDCl_3$): δ 7.85 (2H, d, ^3J=6.7, H arom), 7.56–7.48 (3H, m, H arom), 6.95 (1H, d, ^3J=7, N*H*), 4.99 (1H, td, ^3J=7, ^3J=3.6, C*H*N), 3.86 (3H, s, CO_2CH_3), 3.74 (2H, 2dd, ^2J=10.4, ^3J=3.6, CH_2I); ^{13}C NMR ($CDCl_3$): δ 169.7 (Ph*C*O), 167.1 (*C*O_2Me), 133.0 (C arom), 132.0 (*C*H arom), 128.6 (*C*H arom), 127.2 (*C*H arom), 53.1 (*C*HN), 52.6 (CO_2CH_3), 7.1 (CH_2I). Anal. calcd for $C_{11}H_{12}INO_3$ (333): C 39.64, H 3.60, N 4.20; found: C 39.72, H 3.66, N 4.14.

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