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Synthesis of enantiomerically pure (+)- and (−)-protected 5-aminomethyl-1,3-oxazolidin-2-one derivatives from allylamine and carbon dioxide

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Abstract—The stereoselective synthesis of enantiomerically pure (5*R*)- and (5*S*)-aminomethyl-oxazolidinones with different protecting groups have been carried out from an allyl amine as the source of the carbon backbone. The key reaction is the high yield iodiocyclization of enantiomerically pure allylphenethyl amine in the presence of carbon dioxide.

1. Introduction

Oxazolidin-2-ones are an important class of heterocyclic compounds containing a five-membered ring.[1] The use of these compounds as chiral auxiliaries was first introduced by Evans et al. in 1981 and subsequently by Seebach and Davies.[2] Nowadays, these systems are widely used in asymmetric synthesis for the preparation of homochiral molecules either in solution[3] or on solid supports.[4]

In addition, oxazolidin-2-ones are an important structural unit in peptidomimetics. The planar five-membered ring has recently been used to mimic proline units in non-natural peptide-like compounds. Thus oligomers of enantiomerically pure oxazolidin-2-one-4-carboxylic acid[5] and (2-oxo-1,3-oxazolidin-4-yl) acetic acid[6] were synthesized. Theoretical and experimental conformational studies show that these compounds fold in ordered helical structures.[7]

We have developed new mild conditions for the high yield synthesis of racemic functionalized oxazolidinones from allylamines and carbon dioxide.[8] Herein, we report a study on the diastereoselectivity of the reaction when enantiomerically pure allylamines are employed. In addition, the synthesis on a preparative scale of enantiomerically pure 5-aminomethyloxazolidinones that are ready for oligomerization is also presented.

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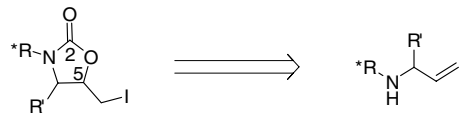
2. Results and discussion

The reaction between allylamines and carbon dioxide creates a new stereogenic centre at C^5. As a result, the synthesis of these compounds in enantiomerically pure form becomes straightforward. Initially, the possibility of obtaining the new stereogenic centre with a single absolute configuration through asymmetric induction was considered. The diastereoselectivity of the reaction between chiral allylamines and carbon dioxide under the conditions already developed, was therefore studied.

From a chemical point of view, the stereogenic centre required for the introduction of the new stereogenic centre can be located either on the allyl carbon chain or in another residue of the molecule. Both types of substrates were designed for this study. The first group of substrates consists of a small number of secondary alkylallylamines bearing a stereogenic centre in the *N*-alkyl moiety of the molecule ($R^* \neq H$, $R' = H$, Scheme 1). Thus, the influence of the stereogenic centre on the carbon chain, other than that where the formation of the ring takes place, can be assessed. In order to evaluate the effect of the stereogenic centre in a position closer to the olefin, a primary



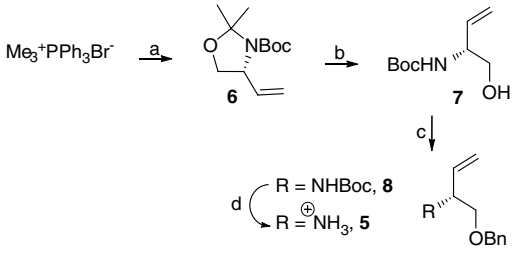
Scheme 1.

allylamine bearing a stereogenic centre on the allyl moiety ($R' \neq H$, $R^* = H$) was also synthesized (Scheme 1).

The preparation of enantiopure alkylallylamines was carried out by treating a range of chiral primary amines—either commercially available (1-phenylethylamine) or easily synthesized by amino acid derivatization (phenylalanine, phenylglycine)—with 60 mol % of allyl bromide in DMF. The corresponding monoallylamines **1**–**4** were obtained in moderate to good yield, together with a small amount of the diallylamines. The secondary and tertiary amines were easily separated by flash chromatography.

The allylamine with a stereogenic centre in the allylic position **5** was prepared through a less straightforward synthetic route. The Garner aldehyde was used as the starting material and was thus synthesized according to the well-established multigram scale procedure published by Hart.[9]

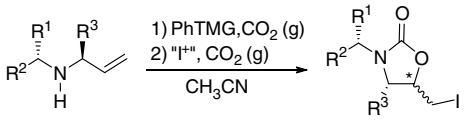
Once the aldehyde had been obtained, it was treated with the ylide derived from methyltriphenylphosphonium bromide to give olefin **6** in good yield. At this point, only manipulation of the protecting groups was necessary to obtain the chiral alkene. Thus, cleavage of the acetonide and protection of the amine as the *tert*-butoxycarbonyl derivative gave alcohol **7**. Finally, formation of the benzyl ether from the alcohol yielded the fully protected allylamine **8** (Scheme 2).[10] Allylamine **8** was finally treated with trifluoroacetic acid to remove the Boc group immediately prior to the cyclization reaction of amine **5**.



Scheme 2. Reagents and conditions: (a) (1) *n*-BuLi, THF, −78 °C; (2) Garner aldehyde, −78 °C to rt, overnight (45%); (b) (1) HCl, 6 M; (2) Boc_2O, Et_3N, DMAP, H_2O–THF (74%); (c) (1) NaH, DMF; (2) BnBr (64%); (d) TFA, CH_2Cl_2, rt, 5.5 h.

All of the allylamines were treated with 2-phenyl-1,1,3,3-tetramethylguanidine (PhTMG) and carbon dioxide in acetonitrile at low temperature followed by the addition of the electrophile (Scheme 3). The results of the experiments are summarized in Table 1.

Although the yields were not optimized they do warrant further comment. In our hands the reaction generally gave good to excellent yields. In a few examples the yields were rather poor. Although in most cases we were unable to find a convincing explanation, in such cases the yields could be greatly improved by either using more electrophilic iodine reagents (entries 11 and 12) such as *N*-iodosuccinimide or bis(pyridine)iodonium tetrafluoroborate (Barluenga's reagent)[11] or lowering the reaction temperature at the beginning of the reaction and then allowing the temperature to rise to room temperature (entries 2–4 and 6–8).



Scheme 3.

In entry **5**, a moderate yield (less than 50%) was obtained because two additional by-products were found (Scheme 4). The appearance of both by-products could be rationalized through a side reaction in which the C–N bond in the benzylic position of the products **2a** and **2b** is oxidized and further hydrolyzed. Since iodine was added in a small excess and the isolated yields of the by-products correlate very well with this excess, the amount of iodine added was reduced. Accordingly, when 90 mol % of iodine was used, the amount of by-products became negligible.

Diastereomeric ratios (dr) were measured by NMR through comparison of the integral of the H-5 multiplet in each diastereomer. In general, diastereomeric excesses were rather low, since diastereomeric ratios were close to 1:1 and could not be improved significantly by varying the reaction conditions (see below).

In chiral alkylallylamines, the presence of the stereogenic centre close to the nitrogen but in a carbon chain different to the alkene chain, is unable to distinguish sufficiently between the faces of the olefin.[12] Moreover, the reaction at lower temperatures does not improve the stereoselectivity at all. On the other hand, the structure of the substrate may influence the selectivity. For example, the presence of an alcohol group (entry 9) provides a better dr. This suggests the participation of the hydroxyl group in the transition state, possibly through complexation. A similar improvement in the dr could be obtained by changing the source of iodine. Thus, more electrophilic reagents (entries 11 and 12) not only improved the yields but also increased the diastereomeric excesses.

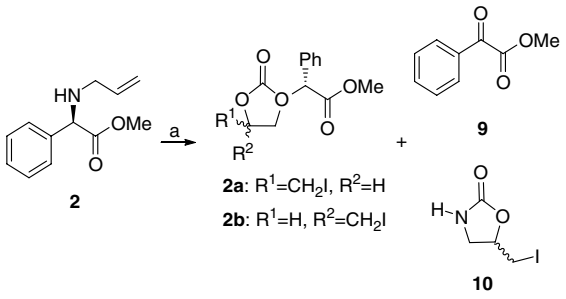
Entry 13 also shows a poor diastereomeric ratio, similar to those obtained in previous examples. In this case the substrate has a stereogenic centre at the allylic position and, in principle, the proximity to the double bond should enable differentiation between the olefin prochiral faces by means of allylic strain. However, the experimental results are rather disappointing.

Unfortunately, individual improvements are small and suggest that even a good combination of all of them would not give rise to a useful diastereomeric excess. Given that the synthesis of a single diastereomer with sufficiently high enantiomeric excess through diastereoselective cyclization is not feasible, we decided to turn our attention to the separation of diastereoisomers.

After a few attempts, the diastereomers obtained by reaction of amines **2**–**4** could be readily separated by silica gel column chromatography. Diastereomers from allylamine

Table 1. Results for the reaction via Scheme 3

Entry	Amine	Electrophile (mol %)	T (°C)	Product (dr)	Yield (%)
1	**1** R^1 = Bn, R^2 = COOMe, R^3 = H	I_2 (120)	0	**1a**:**1b** 1:1.08	69
2	**1** R^1 = Bn, R^2 = COOMe, R^3 = H	I_2 (120)	−20	**1a**:**1b** 1:1.10	91
3	**1** R^1 = Bn, R^2 = COOMe, R^3 = H	I_2 (120)	−40	**1a**:**1b** 1:1.18	92
4	**1** R^1 = Bn, R^2 = COOMe, R^3 = H	I_2 (120)	−45	**1a**:**1b** 1:1.10	91
5	**2** R^1 = COOMe, R^2 = Ph, R^3 = H	I_2 (120)	0	**2a**:**2b** 1:1.09	47
6	**2** R^1 = COOMe, R^2 = Ph, R^3 = H	I_2 (90)	−20	**2a**:**2b** 1:1.03	92
7	**2** R^1 = COOMe, R^2 = Ph, R^3 = H	I_2 (90)	−40	**2a**:**2b** 1:1.03	90
8	**2** R^1 = COOMe, R^2 = Ph, R^3 = H	I_2 (90)	−45	**2a**:**2b** 1:1.02	91
9	**3** R^1 = CH_2OH, R^2 = Ph, R^3 = H	I_2 (120)	0	**3a**:**3b** 1.24:1	61
10	**4** R^1 = Me, R^2 = Ph, R^3 = H	I_2 (120)	0	**4a**:**4b** 1.04:1	26
11	**4** R^1 = Me, R^2 = Ph, R^3 = H	NIS (120)	0	**4a**:**4b** 1.34:1	92
12	**4** R^1 = Me, R^2 = Ph, R^3 = H	Bis(pyridine)iodoniumtetrafluoroborate (120)	0	**4a**:**4b** 1.30:1	93
13	**5** R^1 = H, R^2 = H, R^3 = CH_2OBn	I_2 (120)	0	**5a**:**5b** 1:1.26	38



Scheme 4. Reagents and conditions: (a) PhTMG, CO_2 (g), I_2, CH_3CN, 0 °C to rt, overnight, **2a** and **2b** (47%), **9** (20%) and **10** (17%).

5 could be separated using a more difficult approach through semipreparative HPLC, whereas diastereomers from amine **1** could not be separated.

Both enantiomers of 5-aminomethyloxazolidinone can be obtained from the previously synthesized oxazolidinones by removing the chiral auxiliary and replacing the iodo-substituent by an amino group. While the second goal was easy to perform in all substrates, the removal of the chiral auxiliary proved otherwise. Finally, we decided to carry out the synthetic sequence on the compounds derived from allylamine **4**. The synthetic conditions from entry **11** were chosen as the optimal ones on the basis of the high yield obtained.

Once compounds **4a** and **4b** had been separated, each diastereomer was submitted to the same reaction sequence. The conversion of the iodide into the amine was easily achieved by the preparation of azides **11a** and **11b** by treatment of iodides **4a** and **4b** with sodium azide in DMF at 60 °C overnight. The azide was quantitatively reduced to give amines **12a** and **12b** by the hydrolysis of the iminophosphoranes obtained by the reaction of each azide with triphenylphosphine. Finally, the amines were protected as Boc derivatives by the standard procedure to yield compounds **13a** and **13b** in excellent yields.

The absolute configurations of all the substituted oxazolidinones could be easily deduced from molecular modelling, since the anisotropy of the aromatic ring produced an up-field chemical shift on the protons of the oxazolidinone ring that are close to the benzene ring (see Fig. 1). This effect was calculated using the equation proposed by McConnell and parameterized by Abraham.[13] The experimental value ($\Delta\delta$) was estimated by subtracting the chemical shift of protons H^4 and H^5 in diastereomeric oxazolidinones from their respective values in oxazolidinones without a chiral auxiliary (e.g., **10**). Table 2 presents the calculated values for the most stable conformation and the experimental ones in chloroform for the anisotropic effect of the benzene ring on protons H^4 and H^5 in the 5-iodomethyloxazolidinones **4a** and **4b**.

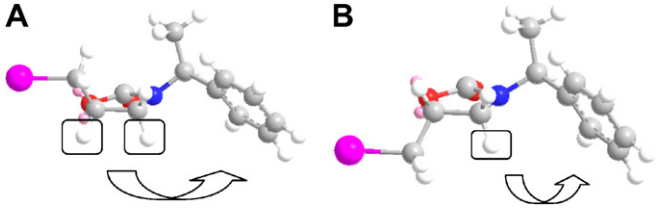


Figure 1. 3D-representation of compounds **4a** and **4b** showing the different proximities of H^4 and H^5 to the aromatic ring in each compound.

Although it is difficult to estimate the exact conformational composition, the calculated values for the most stable conformation and the trend in the data agree well with the experimental measurements.

Table 2. Protons H^4 were labelled 'H' and 'C' according to the *cis* position to H^5 and the ICH_2 group on C^5, respectively

Entry	Compound **4A**		Compound **4B**	
Proton	Calculated	Experimental	Calculated	Experimental
$\Delta\delta H^{4C}$	0.052	0.164	0.870	0.519
$\Delta\delta H^{4H}$	0.850	0.486	0.056	0.151
$\Delta\delta H^5$	0.138	0.268	0.053	0.168

The absolute configuration of each diastereomer was later confirmed by single crystal X-ray diffraction on compounds **4a** and **12b** (Fig. 2).

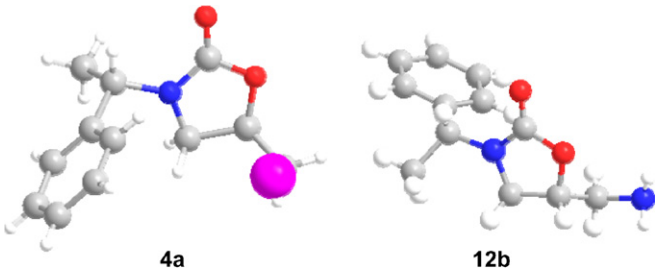
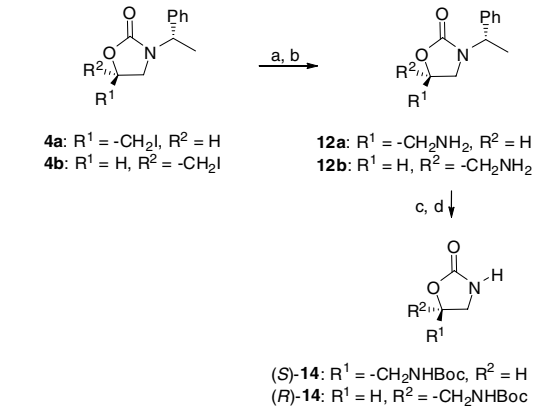


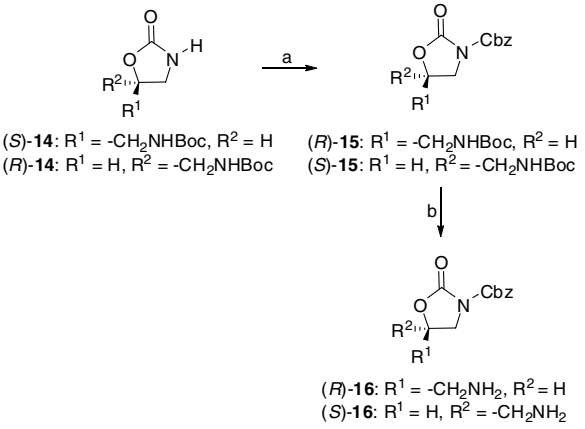
Figure 2. X-ray structures of compounds **4a** and **12b**.

The last step of the synthesis was the removal of the phenethyl group. Several attempts to achieve this goal were made using different conditions at all stages of the synthesis. We found that the two amines **12a** and **12b** and the protected amines **13a** and **13b** were the best substrates to run this reaction. Finally, cleavage was carried out by treating compounds **13a** and **13b** with lithium in ammonia to yield both enantiomers of compound **14** (Scheme 5).



Scheme 5. Reagents and conditions: (a) NaN_3, DMF, 60 °C, **11a** (97%), **11b** (95%); (b) 1. PPh_3, THF, rt; 2. H_2O, both **12** (100%); (c) Boc_2O, Et_3N, THF, rt, overnight, **13a** (99%), **13b** (100%); (d) Li, NH_3(l), THF, −78 °C, 10 min (*S*)-**14** (84%), (*R*)-**14** (97%).

Compounds (*S*)-**14** and (*R*)-**14** were modified to prepare orthogonally protected monomers (Scheme 6) ready for use in the synthesis of oligomers.



Scheme 6. Reagents and conditions: (1) *n*-BuLi, THF, −78 °C, 30 min; (2) benzyl chloroformate, 1–2 h (*R*)-**15** (76%), (*S*)-**15** (75%); (b) CF_3COOH, CH_2Cl_2, rt, 2 h (*R*)-**16** (65%), (*S*)-**16** (65%).

The fully protected oxazolidinone **15** was obtained by reaction of the oxazolidinone anion of **14** with benzyl chloroformate. Finally, the free amine **16** was obtained by cleavage of the *tert*-butoxycarbonyl group with TFA in dichloromethane.

All protected units have been used in the synthesis of a new type of oligomers, which will be reported in due course.

3. Experimental

3.1. General procedures

All reactions were carried out under a dry argon atmosphere. All glassware was dried in an oven at 150 °C prior to use. Solvents were freshly distilled prior to use. Tetrahydrofuran (THF) and toluene were distilled from sodium and benzophenone; dichloromethane, chloroform, acetonitrile, triethylamine and diisopropylamine were distilled from powdered calcium hydride; methanol was distilled from magnesium and iodine; acetone was distilled from potassium carbonate, and dimethylformamide (DMF) was distilled from calcium sulfate under reduced pressure.[14] Commercial *n*-BuLi was titrated with either diphenylacetic acid or *N*-pivaloyl-*o*-toluidine prior to use.[15] Carbon dioxide 4.0 (99.99%) was furnished in pressure cylinders. Flash chromatography was performed with 230–400 mesh silica gel. HPLC was performed with a semipreparative column (μPorasil™, 125 Å, 10 μm, 7.8 × 300 mm). Melting points were determined on a GALLENKAMP capillary melting point apparatus. IR spectra were obtained on a BRUKER VECTOR 22 FT-IR spectrophotometer. Mass spectra were obtained on a Hewlett–Packard HP5989A apparatus at 70 eV, a VG Autoespec M and an FT-ICR (ESI). ^{1}H NMR and ^{13}C NMR spectra were obtained on BRUKER AMX400 and BRUKER Avance-400 spectrometers. NMR signals are quoted in ppm (δ) relative to the residual solvent signal ($CDCl_3$ 7.27 for ^{1}H and 77.00 for ^{13}C) and are reported as follows; chemical shift, multiplicity (br = broad, s = singlet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. Optical rotations were obtained on a digital AUTOPOL-IV Rudolph and a JASCO P-1020 polarimeter. Data are reported as follows: $[\alpha]_D^T$ (concentration g/100 mL, solvent). Ultraviolet spectra were obtained using a Hewlett–Packard HP8452A spectrophotometer and samples were dissolved in chloroform. Elemental analysis was carried out in a Fisons EA-1108 analyzer. X-Ray diffraction was carried out on a CAD 4 Enraf-Nonius and Bruker SMART CCD diffractometer.

3.1.1. General procedure for the synthesis of iodooxazolidinones. CO_2 was bubbled into a solution of the allylamine and 2-phenyl-1,1,3,3-tetramethylguanidine (150–200 mol %) in acetonitrile (10 mL/mmol) in the dark at a low temperature. The electrophile (90–120 mol %) was added to the solution and CO_2 bubbled through for an additional 10 min. The temperature was allowed to rise to room temperature and the mixture was stirred overnight, in the dark, under a CO_2 atmosphere. The solvent was removed under reduced pressure and the crude product was dissolved in EtOAc. The organic phase was washed

with 5% HCl (2×) and then 10% $NaHSO_3$ (2×). The organic solution was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography.

3.1.2. (1′*R*,5*R*)- or (1′*R*,5*S*)-*N*-[(1′-Methoxycarbonyl-1′-phenyl)methyl]-5-iodomethyl-1,3-oxazolidin-2-one 2a and 2b. According to the general procedure, at −20 °C, the reaction of allylamine **2** (0.26 g, 1.25 mmol) with I_2 (0.29 g, 1.1 mmol, 90 mol %) yielded, after workup and chromatography (EtOAc–hexane, 1:3–3:1), compounds **2a** (190 mg) and **2b** (190 mg) as yellow oils in 92% yield. Compound **2a**: ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.42–7.23 (m, 5H, –Ph), 5.72 (s, 1H, –CHPh), 4.53 (m, 1H, –C^5H–), 3.78 (s, 3H, –Me), 3.68 (dd, $J = 5.9$ and 8.9 Hz, 1H, –C^4H_2–), 3.38 (dd, $J = 4.4$ and 10.0 Hz, 1H, –C^6H_2–), 3.30 (dd, $J = 9.1$ and 9.9 Hz, 1H, –C^6H_2–), 3.22 (t, $J = 8.7$ Hz, 1H, –C^4H_2–) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.3 (s, –CO–), 156.8 (s, –C^2O–), 132.9 (s, Ph), 129.2 (d, Ph), 129.1 (d, Ph), 128.5 (d, Ph), 73.3 (d, –C^5H–), 59.6 (q, –Me), 52.6 (d, –CHPh), 47.4 (t, –C^4H_2–), 5.1 (t, –C^6H_2–) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 317 (13), 316 ($M^+-COOCH_3$, 100), 272 (14), 146 (28), 144 (18), 117 (16), 84 (13); HRMS (EI^+): calcd for $C_{11}H_{11}NO_2I$, 315.9834; found, 315.9823; $[\alpha]_D^{24} = -43.0$ (*c* 1.11, $CHCl_3$); R_f: 0.55 (EtOAc–hexane 1:1). Compound **2b**: ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.41–7.23 (m, 5H, –Ph), 5.75 (s, 1H, –CHPh), 4.60 (m, 1H, –C^5H–), 4.04 (t, $J = 8.7$ Hz, 1H, –C^4H_2–), 3.77 (s, 3H, –Me), 3.23 (dd, $J = 4.0$ and 10.4 Hz, 1H, –C^6H_2–), 3.09 (dd, $J = 7.8$ and 10.4 Hz, 1H, –C^6H_2–), 2.80 (dd, $J = 6.2$ and 8.9 Hz, 1H, –C^4H_2–) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.3 (s, –CO–), 156.9 (s, –C^2O–), 132.9 (s, Ph), 129.2 (d, Ph), 129.2 (d, Ph), 128.5 (d, Ph), 72.5 (d, –C^5H–), 59.7 (q, –Me), 52.6 (d, –CHPh), 47.5 (t, –C^4H_2–), 5.9 (t, –C^6H_2–) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 316 ($M^+-COOCH_3$, 47), 146 (36), 146 (13), 117 (12), 105 (39), 91 (10), 86 (65), 84 (100), 77 (25); HRMS (EI^+): calcd for $C_{11}H_{11}NO_2I$, 315.9834; found, 315.9847; $[\alpha]_D^{24} = -30.9$ (*c* 0.38, $CHCl_3$); R_f: 0.43 (EtOAc–hexane 1:1).

3.1.3. (1′*R*,5*R*)- or (1′*R*,5*S*)-*N*-[(2′-Hydroxy-1′-phenyl)-ethyl]-5-iodomethyl-1,3-oxazolidin-2-one 3a and 3b. According to the general procedure, the reaction of allylamine **3** (118 mg, 0.67 mmol) with I_2 (163 mg, 0.67 mmol, 120 mol %) yielded, after workup and chromatography (EtOAc–hexane 1:1–2:1), compound **3a** (78 mg) as a white solid and compound **3b** (63 mg) as brownish solid (63% yield). Compound **3a**: ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.48–7.07 (m, 5H, –Ph), 4.90 (dd, $J = 4.8$ and 9.1 Hz, 1H, –CHPh), 4.56 (m, 1H, –C^5H–), 4.13 (dd, $J = 9.2$ and 11.9 Hz, 1H, –CH_2OH), 4.03 (dd, $J = 4.7$ and 11.9 Hz, 1H, –CH_2OH), 3.48 (t, $J = 8.8$ Hz, 1H, –C^4H_2–), 3.38–3.23 (m, 3H, –C^4H_2– and 2 × –C^6H_2–), 3.11 (br s, 1H, –OH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.8 (s, –CO–), 135.9 (s, Ph), 128.9 (d, Ph), 128.4 (d, Ph), 127.4 (d, Ph), 72.5 (d, –C^5H–), 61.8 (t, –CH_2OH), 59.7 (d, –CHPh), 48.1 (t, –C^4H_2–), 6.3 (t, –C^6H_2–) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 317 (26), 316 (M^+-CH_2OH, 100), 272 (16), 144 (30), 117 (36), 104 (12), 103 (13), 91 (26), 77 (15); HRMS (EI^+): calcd for $C_{11}H_{11}NO_2I$ (M^+-CH_2OH), 315.9834; found, 315.5821. MS (FAB^+): *m*/*e* (relative intensity, %) 348 (M^++1, 45), 307 (15), 289 (18), 252 (11), 242 (12), 241 (12), 240 (14), 239 (15), 228 (14), 228 (15), 227 (12), 226 (13), 221 (16), 219 (11), 215 (13), 203 (11), 202 (16), 192 (11), 191 (14), 190 (11), 189 (14), 181 (12), 180 (17), 179 (10), 178 (20), 168 (12), 167 (19), 166 (14), 165 (35), 155 (19), 154 (100); HRMS (FAB^+): calcd for $C_{12}H_{15}NO_3I$ (M^++1), 348.0097; found, 348.0081. Melting point: 96.4–100.8 °C; $[\alpha]_D^{23} = -6.4$ (*c* 0.97, $CHCl_3$); R_f: 0.54 (EtOAc). Compound **3b**: ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.48–7.07 (m, 5H, –Ph), 4.88 (dd, $J = 4.6$ and 9.1 Hz, 1H, –CHPh), 4.58 (m, 1H, –C^5H–), 4.12 (dd, $J = 9.2$ and 12.0 Hz, 1H, –CH_2OH), 4.00 (dd, $J = 4.7$ and 12.0 Hz, 1H, –CH_2OH), 3.73 (t, $J = 8.9$ Hz, 1H, –C^4H_2–), 3.40 (br s, 1H, –OH), 3.28 (dd, $J = 4.1$ and 10.4 Hz, 1H, –C^6H_2–), 3.19 (dd, $J = 7.8$ and 10.4 Hz, 1H, –C^6H_2–), 3.06 (dd, $J = 6.4$ and 8.9 Hz, 1H, –C^4H_2–) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.9 (s, –CO–), 135.9 (s, Ph), 129.0 (d, Ph), 128.4 (d, Ph), 127.4 (d, Ph), 72.4 (d, –C^5H–), 61.8 (t, –CH_2OH), 59.9 (d, –CHPh), 48.2 (t, –C^4H_2–), 6.4 (t, –C^6H_2–) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 317 (35), 316 (M^+-CH_2OH, 100), 272 (16), 144 (22), 117 (24), 91 (16); HRMS (EI^+): calcd for $C_{11}H_{11}NO_2I$ (M^+-CH_2OH), 315.9834; found, 315.9836. Melting point: 96.8–98.6 °C; $[\alpha]_D^{23} = -10.1$ (*c* 0.23, $CHCl_3$); R_f: 0.44 (EtOAc).

3.1.4. (1′*S*,5*S*)- and (1′*S*,5*R*)-5-Iodomethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 4a and 4b. According to the general procedure, the reaction of allylamine **4** (5.12 g, 31.75 mmol) and NIS (8.57 g, 38.10 mmol, 120 mol %) yielded, after workup and chromatography (EtOAc–hexane 18–40%), diastereomers **4a** and **4b** as a yellowish oil and a white solid, respectively (9.65 g, 92%, in a 1.34:1 ratio). Compound **4a**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H, –Ph), 5.21 (q, $J = 7.1$ Hz, 1H, –CHMe), 4.44 (m, 1H, –C^5H–), 3.36 (dd, $J = 3.8$ and 10.4 Hz, 1H, –C^6H_2–), 3.30–3.20 (m, 3H, 2 × –C^4H_2– and –C^6H_2–), 1.59 (d, $J = 7.1$ Hz, 3H, –Me) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 156.6 (s, –CO–), 139.2 (s, Ph), 128.8 (d, Ph), 128.0 (d, Ph), 127.0 (d, Ph), 71.6 (d, –C^5H–), 51.6 (d, –CHMe), 46.0 (t, –C^4H_2–), 16.2 (q, –Me), 6.9 (t, –C^6H_2–) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 331 (M^+, 12), 316 (22), 204 (59), 160 (15), 146 (13), 144 (17), 117 (22), 106 (11), 105 (100), 104 (18), 103 (13), 91 (16), 88 (10), 86 (61), 84 (97), 79 (17), 78 (11), 77 (59), 69 (29); HRMS (EI^+): calcd for $C_{12}H_{14}NO_2I$, 331.0069; found, 331.0069. UV ($CHCl_3$): λ_{max} 258, 253, 237 nm; $[\alpha]_D^{24} = -15.7$ (*c* 0.45, $CHCl_3$); R_f: 0.46 (EtOAc–hexane 1:1). Compound **4b**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H, –Ph), 5.20 (q, $J = 7.0$ Hz, 1H, –CHMe), 4.54 (m, 1H, –C^5H–), 3.61 (t, $J = 8.8$ Hz, 1H, –C^4H_2–), 3.27 (dd, $J = 4.0$ and 10.2 Hz, 1H, –C^6H_2–), 3.08 (dd, $J = 8.3$ and 10.2 Hz, 1H, –C^6H_2–), 2.87 (dd, $J = 6.3$ and 9.0 Hz, 1H, –C^4H_2–), 1.58 (d, $J = 7.1$ Hz, 3H, –Me) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 156.7 (s, –CO–), 139.0 (s, Ph), 128.7 (d, Ph), 128.0 (d, Ph), 127.1 (d, Ph), 72.1 (d, –C^5H–), 51.5 (d, –CHMe), 46.0 (t, –C^4H_2–), 16.4 (q, –Me), 6.1 (t, –C^6H_2–) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 331 (M^+, 18), 316 (41), 272 (14), 205 (12), 204 (95), 160 (20), 149 (26), 144 (22), 131 (11), 117 (25), 106 (12), 105 (100), 104 (19), 103 (14), 91 (17), 79 (15), 77 (28); HRMS (EI^+): calcd for $C_{12}H_{14}NO_2I$, 331.0069;

found, 331.0057. Elemental analysis: calcd for $C_{12}H_{14}NO_2I$: C, 43.52; H, 4.26; N, 4.23; O, 9.66; found, C, 43.81; H, 4.66; N, 4.26. UV ($CHCl_3$): λ_{max} 258, 253, 236 nm. Melting point: 133.9–135.7 °C; $[\alpha]_D^{24} = -3.3$ (*c* 0.12, $CHCl_3$); R_f: 0.34 (EtOAc–hexane 1:1).

3.1.5. (4*R*)-*N*-*tert*-Butoxycarbonyl-4-vinyl-2,2-dimethyloxazolidine 6. To a solution of methyltriphenylphosphonium bromide (479 mg, 1.34 mmol) in THF (15 mL) at −78 °C was slowly added *n*-BuLi (0.84 mL, 1.34 mmol). A solution of the aldehyde (326 mg, 1.34 mmol) in THF (10 mL) was added. The mixture was stirred at the same temperature for 1 h and then at rt overnight. The solvent was evaporated. The crude product was dissolved in EtOAc (15 mL) and washed with H_2O (15 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane 1:20) to give compound **6** as a clear yellow oil (137 mg, 45%). ^{1}H NMR (400.13 MHz, $CDCl_3$): mixture of rotamers δ 5.80 (m, 1H, =CH–), 5.24–5.12 (m, 2H, $=CH_2$), 4.32 (br s, 0.4H, –CH–), 4.25 (br s, 0.6H, –CH–), 4.03 (dd, $J = 6.2$ and 8.8 Hz, 1H, $-CH_2-$), 3.74 (dd, $J = 2.3$ and 8.8 Hz, 1H, $-CH_2-$), 1.59 (s, 3H, –Me), 1.50 (s, 3H, –Me), 1.44 (br s, 9H, –*t*Bu) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): mixture of rotamers δ 152.0 (s, –CO–), 137.4 and 136.8 (d, =CH–), 116.0 and 115.9 (t, $=CH_2$), 93.9 and 93.6 (s, $-C^2-$), 80.1 and 79.6 (s, –C*t*Bu), 68.1 (d, –CH–), 59.7 (t, $-CH_2-$), 28.4 (q, –*t*Bu), 27.2 and 26.5 (q, –Me), 24.8 and 23.7 (q, –Me) ppm. MS (FAB^+): *m*/*e* (relative intensity, %) 228 (M^++1, 27), 212 (22), 173 (11), 172 (100), 167 (12), 156 (36), 156 (26), 154 (78); HRMS (FAB^+): calcd for $C_{12}H_{22}NO_3$ (M^++1), 228.1600; found, 228.1595; $[\alpha]_D^{24} = 18.6$ (*c* 0.29, $CHCl_3$); R_f: 0.40 (EtOAc–hexane 1:5).

3.1.6. (2*R*)-2-(*N*-*tert*-Butoxycarbonylamino)-but-3-en-1-ol 7. A solution of alkene **6** (152 mg, 0.67 mmol) in HCl (6 M, 1.5 mL) was stirred at rt for 1.5 h. The solvent was evaporated and the residue redissolved in a mixture of THF–H_2O (1:1) (4 mL). Di-*tert*-butyl dicarbonate (180 mg, 0.82 mmol, 120 mol %) and triethylamine (0.19 mL, 1.37 mmol, 200 mol %) were added and the mixture stirred at rt for 7 h. The THF was removed under reduced pressure and the aqueous phase extracted with EtOAc (4×). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane 1:2–1:1) to give **7** as a clear yellow oil (93 mg, 74%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 5.80 (m, 1H, =CH–), 5.27–5.20 (m, 2H, $=CH_2$), 5.00 (br s, 1H, –NH–), 4.22 (br m, 1H, –CH–), 3.69 (dd, $J = 4.1$ and 11.1 Hz, 1H, $-CH_2-$), 3.61 (dd, $J = 5.5$ and 10.9 Hz, 1H, $-CH_2-$), 2.68 (br s, 1H, –OH), 1.44 (s, 9H, –*t*Bu) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 156.0 (s, –CO–), 135.5 (d, =CH–), 116.4 (t, $=CH_2$), 81 (s, –C*t*Bu), 65.1 (t, $-CH_2-$), 54.6 (d, –CH–), 28.3 (q, –*t*Bu) ppm. MS (FAB^+): *m*/*e* (relative intensity, %) 189 (12), 188 (M^++1, 71), 156 (15), 155 (22), 153 (72); HRMS (FAB^+): calcd for $C_9H_{18}NO_3$ (M^++1), 188.1287; found, 188.1290; $[\alpha]_D^{24} = 51.5$ (*c* 1.01, $CHCl_3$); R_f: 0.31 (EtOAc–hexane 1:1).

3.1.7. (2*R*)-2-(*N*-*tert*-Butoxycarbonylamino)-1-benzyloxybut-3-ene 8. To a solution of alkene **7** (80 mg, 0.43 mmol) in DMF (4 mL) at 0 °C was added NaH (20 mg, 0.51 mmol, 120 mol %). The mixture was stirred for 20 min. Benzyl bromide (0.06 mL, 0.51 mmol, 120 mol %) was added and the mixture stirred at rt for 6 h. The reaction mixture was then poured into saturated aqueous NaCl (10 mL) and the mixture extracted with EtOAc (3×). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane 1:10–1:1) to give **8** as a clear yellow oil (76 mg, 64%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.38–7.27 (m, 5H, –Ph), 5.85 (m, 1H, =CH–), 5.25 (dt, $J = 1.4$ and 17.2 Hz, 1H, $=CH_2$), 5.18 (dt, $J = 1.4$ and 10.4 Hz, 1H, $=CH_2$), 4.91 (br s, 1H, –NH–), 4.56 (d, $J = 12.1$ Hz, 1H, $-CH_2OBn$), 4.54 (d, $J = 12.0$ Hz, 1H, $-CH_2OBn$), 4.32 (br m, 1H, –CH–), 3.56 (dd, $J = 4.4$ and 9.5 Hz, 1H, $-CH_2-$), 3.51 (dd, $J = 4.7$ and 9.5 Hz, 1H, $-CH_2-$), 1.46 (s, 9H, –*t*Bu) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 155.4 (s, –CO–), 137.9 (s, Ph), 136.4 (d, =CH–), 128.4 (d, Ph), 127.7 (d, Ph), 127.6 (d, Ph), 115.6 (t, $=CH_2$), 79.4 (s, –C*t*Bu), 73.2 (t, $-CH_2-$), 72.1 (t, $-CH_2-$), 52.4 (d, –CH–), 28.4 (q, –*t*Bu) ppm. MS (FAB^+): *m*/*e* (relative intensity, %) 278 (M^++1, 82), 223 (15), 222 (100), 178 (39), 156 (13), 155 (19), 154 (64); HRMS (FAB^+): calcd for $C_{16}H_{24}NO_3$ (M^++1), 278.1756; found, 278.1743, $[\alpha]_D^{24} = -37.35$ (*c* 0.43, $CHCl_3$); R_f: 0.36 (EtOAc–hexane 1:5).

3.1.8. (4*S*,5*S*)- or (4*S*,5*R*)-4-Benzyloxymethyl-5-iodomethyl-1,3-oxazolidin-2-one 5a and 5b. Trifluoroacetic acid (0.06 mL, 0.72 mmol, 300 mol %) was added to a solution of alkene **8** (67 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) and the mixture then stirred at rt for 5.5 h. The solvent was evaporated. The crude product was dissolved in benzene, the solution concentrated under reduced pressure and the residue used directly in the next step. According to the general procedure, the reaction of crude alkene **5** with I_2 (74 mg, 0.29 mmol, 120 mol %) yielded, after workup and chromatography (EtOAc–hexane 1:10–1:1), a mixture of the two diastereomers **5a** and **5b** (24 mg, 38%) as a yellow oil together with unreacted starting material (25%). Compound **5a**: ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5H, –Ph), 5.75 (br s, 1H, –NH–), 4.54 (d, $J = 5.8$ Hz, 2H, 2 × $-CH_2Ph$), 4.33 (ddd, $J = 4.4$, 4.4 and 7.6 Hz, 1H, $-C^4HNH-$), 3.77 (ddd, $J = 4.5$, 4.6 and 6.6 Hz, 1H, $-C^5H-$), 3.53 (dd, $J = 4.8$ and 9.5 Hz, 1H, $-CH_2OBn$), 3.48 (dd, $J = 6.5$ and 9.5 Hz, 1H, $-CH_2OBn$), 3.34 (dd, $J = 4.3$ and 10.4 Hz, 1H, $-CH_2I$), 3.30 (dd, $J = 7.5$ and 10.4 Hz, 1H, $-CH_2I$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.7 (s, –CO–), 137.2 (s, Ph), 128.7 (d, Ph), 128.4 (d, Ph), 128.2 (d, Ph), 127.9 (d, Ph), 76.8 (d, $-C^4HNH-$), 73.7 (t, $-CH_2Ph$), 71.7 (t, $-CH_2OBn$), 57.5 (d, $-C^5H-$), 6.0 (t, $-CH_2I$) ppm; $[\alpha]_D^{24} = -38.7$ (*c* 0.13, $CHCl_3$); R_f: 0.21 (EtOAc–hexane 1:1). Compound **5b**: ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5H, –Ph), 5.67 (br s, 1H, –NH–), 4.85 (ddd, $J = 6.4$, 7.5 and 8.2 Hz, 1H, $-C^4HNH-$), 4.52 (d, $J = 5.8$ Hz, 2H, 2 × $-CH_2Ph$), 3.99 (ddd, $J = 4.5$, 6.0 and 7.7 Hz, 1H, $-C^5H-$), 3.63 (dd, $J = 4.4$ and 9.8 Hz, 1H, $-CH_2OBn$), 3.59 (dd, $J = 6.1$ and 9.7 Hz, 1H, $-CH_2OBn$), 3.35 (dd, $J = 6.3$ and 10.6 Hz,

1H, $-CH_2I$), 3.28 (dd, $J = 8.2$ and 10.5 Hz, 1H, $-CH_2I$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 158.2 (s, –CO–), 137.0 (s, Ph), 128.6 (d, Ph), 128.1 (d, Ph), 127.8 (d, Ph), 127.7 (d, Ph), 78.2 (d, $-C^4HNH-$), 73.7 (t, $-CH_2Ph$), 67.4 (t, $-CH_2OBn$), 54.7 (d, $-C^5H-$), −2.1 (t, $-CH_2I$) ppm; R_f: 0.21 (EtOAc–hexane 1:1).

3.1.9. (1′*S*,5*S*)-5-Azidomethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 11a. Sodium azide (1.62 g, 25 mmol, 150 mol %) was added to a solution of 5-iodomethyloxazolidinone **4a** (5.50 g, 16 mmol) in DMF (100 mL). The mixture was then stirred at 60 °C overnight. After cooling, the reaction was poured into water and the mixture was extracted with EtOAc (3×). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product gave, after column chromatography (EtOAc–hexane 1:1), azide **11a** as a yellow oil (3.82 g, 97%). ^1H NMR (400.16 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H, –Ph), 5.22 (q, $J = 7.1$ Hz, 1H, –CHMe), 4.53 (m, 1H, $-C^5H-$), 3.55 (dd, $J = 4.6$ and 13.1 Hz, 1H, $-C^6H_2-$), 3.44 (dd, $J = 4.5$ and 13.1 Hz, 1H, $-C^6H_2-$), 3.29 (dd, $J = 6.1$ and 8.8 Hz, 1H, $-C^4H_2-$), 3.20 (t, $J = 8.7$ Hz, 1H, $-C^4H_2-$), 1.59 (d, $J = 7.1$ Hz, 3H, –Me) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.6 (s, –CO–), 139.2 (s, Ph), 128.8 (d, Ph), 128.0 (d, Ph), 127.0 (d, Ph), 71.2 (d, $-C^5H-$), 53.3 (t, $-C^6H_2-$), 51.5 (d, –CHMe), 42.4 (t, $-C^4H_2-$), 16.1 (q, –Me) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 159 (11), 147 (73), 132 (99), 118 (12), 106 (22), 105 (75), 105 (100), 104 (95), 103 (90), 91 (40), 79 (80), 78 (68), 77 (98), 76 (10), 63 (10); HRMS (EI^+): calcd for $C_{12}H_{14}N_4O_2$, 246.1117; found, 246.1118. FT-IR (NaCl): ν 2104, 1744 cm^{-1}. UV ($CHCl_3$): λ_{max} 264, 258, 252, 236 nm; $[\alpha]_D^{24} = +22.6$ (*c* 0.19, $CHCl_3$); R_f: 0.44 (EtOAc–hexane 1:1).

3.1.10. (1′*S*,5*R*)-5-Azidomethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 11b. Following the same procedure used in the synthesis of **11a**, the reaction of 5-iodomethyloxazolidinone **4b** (4.11 g, 12 mmol) with NaN_3 (1.21 g, 19 mmol, 150 mol %) in DMF (60 mL) furnished after column chromatography (EtOAc–hexane 1:1) the azide **11b** as a yellow oil (2.82 g, 95%). ^1H NMR (400.16 MHz, $CDCl_3$): δ 7.39–7.26 (m, 5H, –Ph), 5.23 (q, $J = 7.1$ Hz, 1H, –CHMe), 4.60 (m, 1H, $-C^5H-$), 3.54 (t, $J = 8.9$ Hz, 1H, $-C^4H_2-$), 3.42 (dd, $J = 4.6$ and 13.1 Hz, 1H, $-C^6H_2-$), 3.33 (dd, $J = 4.8$ and 13.1 Hz, 1H, $-C^6H_2-$), 2.93 (dd, $J = 6.0$ and 8.8 Hz, 1H, $-C^4H_2-$), 1.59 (d, $J = 7.1$ Hz, 3H, –Me) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.5 (s, –CO–), 139.0 (s, Ph), 128.6 (d, Ph), 127.9 (d, Ph), 126.8 (d, Ph), 71.2 (d, $-C^5H-$), 53.1 (t, $-C^6H_2-$), 51.4 (d, –CHMe), 42.4 (t, $-C^4H_2-$), 16.2 (q, –Me) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 132 (39), 105 (100), 104 (72), 103 (50), 79 (28), 78 (34), 77 (62); HRMS (EI^+): calcd for $C_{12}H_{14}N_4O_2$, 246.1117; found, 246.1119. FT-IR (NaCl): ν 2104, 1745 cm^{-1}. UV ($CHCl_3$): λ_{max} 264, 258, 252, 235 nm; $[\alpha]_D^{24} = -220.65$ (*c* 0.10, $CHCl_3$); R_f: 0.35 (EtOAc–hexane 1:1).

3.1.11. (1′*S*,5*R*)-5-Aminomethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 12a. Triphenylphosphine (7.47 g, 28 mmol, 150 mol %) was added to a solution of 5-azidomethyloxazolidinone **11a** (4.67 g, 19 mmol) in THF (125 mL). The mixture was stirred at rt for 24 h. Water (8.54 mL, 470 mmol, 2500 mol %) was added and the mixture stirred at rt for another 24 h. The solvent was concentrated under reduced pressure and the crude product purified by column chromatography (MeOH–CH_2Cl_2 10%) to give amine **12a** as a white solid (4.20 g, 100%). ^1H NMR (400.16 MHz, $CDCl_3$): δ 7.30–7.19 (m, 5H, –Ph), 5.12 (q, $J = 7.1$ Hz, 1H, –CHMe), 4.34 (m, 1H, $-C^5H-$), 3.18 (dd, $J = 6.8$ and 8.5 Hz, 1H, $-C^4H_2-$), 3.11 (t, $J = 8.7$ Hz, 1H, $-C^4H_2-$), 2.90–2.78 (br m, 2H, $-C^6H_2-$), 1.49 (d, $J = 7.1$ Hz, 3H, –Me), 1.33 (br s, 2H, $-NH_2$) ppm: ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.2 (s, –CO–), 139.4 (s, Ph), 128.6 (d, Ph), 127.8 (d, Ph), 126.9 (d, Ph), 74.4 (d, $-C^5H-$), 51.4 (d, –CHMe), 45.2 (t, $-C^6H_2-$), 42.5 (t, $-C^4H_2-$), 16.1 (q, –Me) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 106 (14), 105 (100), 104 (36), 103 (20), 91 (13), 79 (10), 78 (12), 77 (25); HRMS (EI^+): calcd for $C_{12}H_{16}N_2O_2$, 220.1212; found, 220.1220. Elemental analysis: calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72; O, 14.53; found: C, 65.31; H, 7.27; N, 12.29. FT-IR (NaCl): ν 1739 cm^{-1}. UV ($CHCl_3$): λ_{max} 264, 258, 252, 234 nm. Melting point: 42–50 °C; $[\alpha]_D^{23} = -39.6$ (*c* 0.12, $CHCl_3$). R_f: 0.23 (MeOH–CH_2Cl_2 10%).

3.1.12. (1′*S*,5*S*)-5-Aminomethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 12b. Following the same procedure used in the synthesis of **12a**, the reaction of 5-azidomethyloxazolidinone **11b** (3.52 g, 14 mmol) with PPh_3 (5.63 g, 21 mmol, 150 mol %) in THF (100 mL) followed by hydrolysis with H_2O (6.43 mL, 360 mmol, 2500 mol %) provided, after column chromatography (MeOH–CH_2Cl_2 10%), amine **12b** as a white solid (3.16 g, 100%). ^1H NMR (400.16 MHz, $CDCl_3$): δ 7.29–7.17 (m, 5H, –Ph), 5.13 (q, $J = 7.1$ Hz, 1H, –CHMe), 4.41 (m, 1H, $-C^5H-$), 3.43 (t, $J = 8.7$ Hz, 1H, $-C^4H_2-$), 2.77 (dd, $J = 6.4$ and 8.2 Hz, 1H, $-C^4H_2-$), 2.74 (dd, $J = 3.5$ and 14.0 Hz, 1H, $-C^6H_2-$), 2.66 (dd, $J = 6.4$ and 13.7 Hz, 1H, $-C^6H_2-$), 1.49 (d, $J = 7.1$ Hz, 3H, –Me), 1.30 (br s, 2H, $-NH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.3 (s, –CO–), 139.3 (s, Ph), 128.6 (d, Ph), 127.8 (d, Ph), 126.9 (d, Ph), 74.4 (d, $-C^5H-$), 51.2 (d, –CHMe), 45.3 (t, $-C^6H_2-$), 42.5 (t, $-C^4H_2-$), 16.3 (q, –Me) ppm. MS (EI^+): *m*/*e* (relative intensity, %) 106 (12), 105 (100), 104 (10), 91 (10), 77 (13). HRMS (EI^+): calcd for $C_{12}H_{16}N_2O_2$, 220.1212; found, 220.1208. Elemental analysis: calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72; O, 14.53; found: C, 65.76; H, 7.04; N, 12.36. FT-IR (NaCl): ν 1739 cm^{-1}. UV ($CHCl_3$): λ_{max} 264, 258, 253, 240, 235 nm. Melting point: 76–79 °C; $[\alpha]_D^{24} = -139.2$ (*c* 0.10, $CHCl_3$); R_f: 0.22 (MeOH–CH_2Cl_2 10%).

3.1.13. (1′*S*,5*R*)-5-*tert*-Butoxycarbonylaminomethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 13a. Di-*tert*-butyl dicarbonate (8.32 g, 38 mmol, 200 mol %) and triethylamine (5.30 mL, 38 mmol, 200 mol %) were added to a solution of amine **12a** (4.20 g, 19 mmol) in THF (125 mL). The mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane 1:1) to give amine **13a** as a white solid (6.00 g, 100%). ^1H NMR (400.16 MHz, $CDCl_3$): δ 7.27–7.17 (m, 5H, –Ph), 5.14 (br s, 1H, –NH–), 5.11 (q, $J = 7.0$ Hz, 1H, –CHMe), 4.40 (m,

1H, –C^5H–), 3.32–3.28 (m, 2H, –C^6H_2–), 3.19 (dd, $J = 6.3$ and 8.8 Hz, 1H, –C^4H_2–), 3.09 (t, $J = 8.9$ Hz, 1H, –C^4H_2–), 1.46 (d, $J = 7.1$ Hz, 3H, –Me), 1.35 (s, 9H, –*t*Bu) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.8 (s, –CO–), 156.1 (s, –CO–), 139.1 (s, Ph), 128.5 (d, Ph), 127.6 (d, Ph), 126.7 (d, Ph), 79.5 (s, –C*t*Bu), 72.2 (d, –C^5H–), 51.2 (d, –CHMe), 43.1 (t, –C^6H_2–), 42.0 (t, –C^4H_2–), 28.1 (q, –*t*Bu), 16.1 (q, –Me) ppm. MS (EI^+): *m/e* (relative intensity, %) 220 (M^+−Boc, 16), 115 (11), 106 (13), 105 (100). HRMS (EI^+): calcd for $C_{17}H_{24}N_2O_4$, 320.1736; found, 320.1733. Elemental analysis: calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74; O, 19.98; found: C, 63.03; H, 7.82; N, 7.86. FT-IR (NaCl): ν 1743, 1707, 1517 cm^{-1}. Melting point: 124–126 °C; $[\alpha]_D^{26} = -32.7$ (*c* 0.06, $CHCl_3$); R_f: 0.39 (EtOAc–hexane 1:1).

3.1.14. (1′*S*,5*S*)-5-*tert*-Butoxycarbonylaminomethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 13b. Following the same procedure used in the synthesis of **13a**, the reaction of amine **12b** (3.16 g, 14 mmol) with Boc_2O (6.26 g, 29 mmol, 200 mol %) and Et_3N (4.00 mL, 29 mmol, 200 mol %) in THF (100 mL) furnished, after column chromatography (EtOAc–hexane 1:1), amine **13b** as a white solid (4.46 g, 100%). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.27–7.17 (m, 5H, –Ph), 5.11 (q, $J = 7.1$ Hz, 1H, –CHMe), 4.97 (br s, 1H, –NH–), 4.50 (m, 1H, –C^5H–), 3.43 (t, $J = 8.8$ Hz, 1H, –C^4H_2–), 3.26 (m, 1H, –C^6H_2–), 3.11 (dt, $J = 6.2$ and 12.8 Hz, 1H, –C^6H_2–), 2.79 (dd, $J = 6.9$ and 8.8 Hz, 1H, –C^4H_2–), 1.48 (d, $J = 7.1$ Hz, 3H, –Me), 1.29 (s, 9H, –*t*Bu) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.8 (s, –CO–), 155.8 (s, –CO–), 139.1 (s, Ph), 128.5 (d, Ph), 127.6 (d, Ph), 126.6 (d, Ph), 79.5 (s, –C*t*Bu), 72.3 (d, –C^5H–), 51.2 (d, –CHMe), 42.9 (t, –C^6H_2–), 42.2 (t, –C^4H_2–), 28.1 (q, –*t*Bu), 16.3 (q, –Me) ppm. MS (EI^+): *m/e* (relative intensity, %) 220 (M^+−Boc, 20), 115 (13), 106 (13), 105 (100). HRMS (EI^+): calcd for $C_{17}H_{24}N_2O_4$, 320.1736; found, 320.1739. Elemental analysis: calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74; O, 19.98; found: C, 63.00; H, 7.88; N, 7.83. FT-IR (NaCl): ν 1744, 1708, 1516 cm^{-1}. Melting point: 111–113 °C; $[\alpha]_D^{26} = -95.85$ (*c* 0.05, $CHCl_3$); R_f: 0.25 (EtOAc–hexane 1:1).

3.1.15. (5*S*)-5-*tert*-Butoxycarbonylaminomethyl-1,3-oxazolidin-2-one (*S*)-14. NH_3 gas was condensed at −78 °C over Li until the dark blue colour remained unchanged. A solution of the oxazolidinone **13a** (3.87 g, 12 mmol) in THF (120 mL) was added and the mixture stirred for 10 min. The reaction was quenched by the careful sequential addition of *tert*-butanol, ethanol, HCl (10%) and sodium carbonate (10%). The aqueous phase was extracted with EtOAc (4×). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Finally, the crude product was purified by column chromatography (EtOAc) to give amine (*S*)-**14** as a white solid (2.18 g, 84%). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 6.42 (s, 1H, –N^3H–), 5.22 (s, 1H, –NH–), 4.69 (br m, 1H, –C^5H–), 3.60 (t, $J = 8.8$ Hz, 1H, –C^4H_2–), 3.45 (br m, 1H, –C^6H_2–), 3.34–3.28 (m, 2H, –C^4H_2– and –C^6H_2–), 1.39 (s, 9H, –*t*Bu) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.7 (s, –C^2O–), 156.1 (s, –CO–), 79.8 (s, –C*t*Bu), 75.7 (d, –C^5H–), 43.2 (t, –C^6H_2–), 42.8 (t, –C^4H_2–), 28.2 (q, –*t*Bu) ppm. MS (EI^+): *m/e* (relative intensity, %) 160 (21), 143 (71), 130 (12), 116 (M^+−Boc, 53), 115 (10), 87 (100), 86 (17), 75 (13), 74 (22), 71 (13). HRMS (EI^+): calcd for $C_9H_{16}N_2O_4$, 216.1110; found, 216.1108. Elemental analysis: calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96; O, 29.60; found: C, 50.26; H, 7.72; N, 12.73. FT-IR (NaCl): ν 3319, 1752, 1695, 1520 cm^{-1}. Melting point: 112–114 °C; $[\alpha]_D^{26} = +1.4$ (*c* 2.02, $CHCl_3$); R_f: 0.23 (EtOAc).

3.1.16. (5*R*)-5-*tert*-Butoxycarbonylaminomethyl-1,3-oxazolidin-2-one (*R*)-14. Following the same procedure used in the synthesis of (*S*)-**14**, the reaction of amine **13b** (4.46 g, 14 mmol) with Li and NH_3 in THF (120 mL) furnished, after column chromatography (EtOAc), amine (*R*)-**14** as a white solid (2.92 g, 97%). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 6.42 (s, 1H, –N^3H–), 5.22 (s, 1H, –NH–), 4.69 (m, 1H, –C^5H–), 3.60 (t, $J = 8.8$ Hz, 1H, –C^4H_2–), 3.44 (br m, 1H, –C^6H_2–), 3.34–3.28 (m, 2H, –C^4H_2– and –C^6H_2–), 1.39 (s, 9H, –*t*Bu) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.7 (s, –C^2O–), 156.1 (s, –CO–), 79.8 (s, –C*t*Bu), 75.6 (d, –C^5H–), 43.2 (t, –C^6H_2–), 42.8 (t, –C^4H_2–), 28.2 (q, –*t*Bu) ppm. MS (EI^+): *m/e* (relative intensity, %) 160 (21), 143 (68), 130 (12), 116 (M^+−Boc, 52), 115 (11), 87 (100), 86 (16), 75 (12), 74 (21), 71 (12), 69(19); HRMS (EI^+): calcd for $C_9H_{16}N_2O_4$, 216.1110; found, 216.1108. Elemental analysis: calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96; O, 29.60; found: C, 50.17; H, 7.71; N, 12.74. FT-IR (NaCl): ν 3322, 1753, 1695, 1522 cm^{-1}. Melting point: 115–118 °C; $[\alpha]_D^{26} = -1.0$ (*c* 2.12, $CHCl_3$); R_f: 0.23 (EtOAc).

3.1.17. (5*R*)-5-*tert*-Butoxycarbonylaminomethyl-3-benzyloxycarbonyl-1,3-oxazolidin-2-one (*R*)-15. A solution of *n*-BuLi in hexanes (1.6 M) (3.70 mL, 5.54 mmol, 120 mol %) was added at −78 °C to a solution of oxazolidinone (*S*)-**14** (1 g, 4.62 mmol) in THF (40 mL). The mixture was stirred for 30 min, benzyl chloroformate (1.30 mL, 9.25 mmol, 200 mol %) was added, and the temperature was allowed to rise to rt over 1.5 h. Saturated NH_4Cl and saturated NaCl were sequentially added. The aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. After column chromatography (EtOAc–hexane 1:1), amine (*R*)-**15** was obtained as a white solid (1.229 g, 76%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.42–7.34 (m, 5H, –Ph), 5.28 (s, 2H, –CH_2Ph), 4.93 (br s, 1H, –NH–), 4.64 (m, 1H, –C^5H–), 4.02 (dd, $J = 8.9$ and 10.3 Hz, 1H, –C^4H_2–), 3.76 (dd, $J = 6.8$ and 10.5 Hz, 1H, –C^4H_2–), 3.47–3.40 (m, 2H, –C^6H_2–), 1.42 (s, 9H, –*t*Bu) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.0 (s, –CO–), 151.2 (s, –CO–), 150.6 (s, –CO–), 134.8 (s, Ph), 128.6 (d, Ph), 128.5 (d, Ph), 128.3 (d, Ph), 80.3 (s, –C*t*Bu), 72.4 (d, –C^5H–), 68.7 (t, –CH_2Ph), 45.6 (t, –C^4H_2–), 42.9 (t, –C^6H_2–), 28.2 (q, –*t*Bu) ppm. MS (ESI^+): *m/e* (%) 1074 (14), 1073 ($3 \times M^+$+23, 29), 724 (29), 723 ($2 \times M^+$+23, 15), 723 (75), 721 (14), 720 (15), 583 (10), 545 (13), 456 (45), 392 (21), 389 (15), 374 (17), 373 (M^++23, 97), 343 (12), 323 (10), 318 (15), 317 (100), 305 (13). HRMS (ESI^+): calcd for $C_{17}H_{22}N_2O_6Na$ (M^++23), 373.1370; found, 373.1372. Melting point: 114–115 °C; $[\alpha]_D^{20} = +11.9$ (*c* 0.05, $CHCl_3$); R_f: 0.33 (EtOAc–hexane 1:1).

3.1.18. (5*S*)-5-*tert*-Butoxycarbonylaminomethyl-3-benzyloxycarbonyl-1,3-oxazolidin-2-one (*S*)-15. Following the same procedure used in the synthesis of (*R*)-**15**, the reaction of oxazolidinone (*R*)-**14** (0.5 g, 2.31 mmol) with *n*-BuLi (1.80 mL, 2.77 mmol, 120 mol %) and benzyl chloroformate (0.78 mL, 5.55 mmol, 200 mol %) in THF (20 mL) furnished, after column chromatography (EtOAc–hexane 1:1), amine (*S*)-**15** as a white solid (611.2 mg, 75%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.42–7.26 (m, 5H, –Ph), 5.28 (s, 2H, $-CH_2Ph$), 4.95 (br s, 1H, –NH–), 4.64 (m, 1H, $-C^5H-$), 4.02 (dd, $J = 9.0$ and 10.2 Hz, 1H, $-C^4H_2-$), 3.76 (dd, $J = 6.7$ and 10.4 Hz, 1H, $-C^4H_2-$), 3.49–3.36 (m, 2H, $-C^6H_2-$), 1.42 (s, 9H, –*t*Bu) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.0 (s, –CO–), 151.2 (s, –CO–), 150.6 (s, –CO–), 134.8 (s, Ph), 128.6 (d, Ph), 128.5 (d, Ph), 128.3 (d, Ph), 80.3 (s, –C*t*Bu), 72.4 (d, $-C^5H-$), 68.7 (t, $-CH_2Ph$), 45.6 (t, $-C^4H_2-$), 42.9 (t, $-C^6H_2-$), 28.2 (q, –*t*Bu) ppm. MS (ESI$^+$): *m*/*e* (%) 1073 ($3\times M^+$+23, 12), 857 (10), 724 (35), 723 ($2\times M^+$+23, 100), 723 (15), 373 (M^++23, 33), 343 (12), 317 (36). HRMS (ESI$^+$): calcd for $C_{17}H_{22}N_2O_6Na$ (M^++23), 373.1370; found, 373.1363. Melting point: 113–114 °C; $[\alpha]_D^{20} = -13.55$ (*c* 0.05, $CHCl_3$); R_f: 0.33 (EtOAc–hexane 1:1).

3.1.19. (5*R*)-5-Aminomethyl-3-benzyloxycarbonyl-1,3-oxazolidin-2-one (*R*)-16. Trifluoroacetic acid (7 mL, 82.5 mmol, 2500 mol %) was added to a solution of the protected amine (*R*)-**15** (1.15 g, 3.30 mmol) in CH_2Cl_2 (20 mL). The solution was stirred for 2 h at rt. The solvent was concentrated under reduced pressure. Saturated sodium bicarbonate and sodium carbonate (10%) were then sequentially added. The aqueous phase was extracted with CH_2Cl_2 (5×). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to obtain, after column chromatography (MeOH–CH_2Cl_2 10%), compound (*R*)-**16** as a yellow oil (534.6 mg, 65%). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.39–7.26 (m, 5H, –Ph), 5.24 (s, 2H, $-CH_2Ph$), 4.51 (m, 1H, $-C^5H-$), 3.97 (t, $J = 9.4$ Hz, 1H, $-C^4H_2-$), 3.76 (dd, $J = 6.9$ and 9.8 Hz, 1H, $-C^4H_2-$), 2.99 (dd, $J = 3.6$ and 13.8 Hz, 1H, $-C^6H_2-$), 2.82 (dd, $J = 5.4$ and 13.8 Hz, 1H, $-C^6H_2-$), 1.22 (s, 2H, $-NH_2$) ppm. ^{13}C NMR (100.63 MHz, $CDCl_3$): δ 151.5 (s, –CO–), 150.6 (s, –CO–), 134.8 (s, Ph), 128.4 (d, Ph), 128.1 (d, Ph), 127.8 (d, Ph), 74.3 (d, $-C^5H-$), 68.4 (t, $-CH_2Ph$), 45.6 (t, $-C^4H_2-$), 44.3 (t, $-C^6H_2-$) ppm. MS (ESI$^+$): *m*/*e* (%) 1027 (10), 1019 (13), 1001 (12), 894 (11), 893 (26), 886 (12), 885 (25), 791 (16), 785 (10), 777 (16), 759 (14), 752 (17), 751 (43), 657 (23), 643 (34), 636 (19), 635 (56), 617 (15), 523 ($2\times M^+$+23, 16), 509 (13), 502 (19), 501 (77), 407 (17), 367 (21), 273 (M^++23, 11); HRMS (ESI$^+$): calcd for $C_{12}H_{14}N_2O_4Na$ (M^++23), 273.0846; found, 273.0851; $[\alpha]_D^{20} = +20.4$ (*c* 0.08, $CHCl_3$); R_f: 0.28 (MeOH–CH_2Cl_2 10%).

3.1.20. (5*S*)-5-Aminomethyl-3-benzyloxycarbonyl-1,3-oxazolidin-2-one (*S*)-16. Following the same procedure used for the synthesis of (*R*)-**16**, the reaction of oxazolidinone (*S*)-**15** (611.2 mg, 1.75 mmol) with TFA (5 mL, 43.75 mmol, 2500 mol %) in CH_2Cl_2 (15 mL) furnished, after column chromatography (MeOH–CH_2Cl_2 10%), compound (*S*)-**16** as a white solid (285.7 mg, 65%); ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H, –Ph), 5.23 (s, 2H, $-CH_2Ph$), 4.51 (m, 1H, $-C^5H-$), 3.97 (t, $J = 9.4$ Hz, 1H, $-C^4H_2-$), 3.74 (dd, $J = 6.9$ and 9.9 Hz, 1H, $-C^4H_2-$), 2.99 (dd, $J = 3.6$ and 13.8 Hz, 1H, $-C^6H_2-$), 2.82 (dd, $J = 5.4$ and 13.8 Hz, 1H, $-C^6H_2-$), 1.32 (s, 2H, $-NH_2$) ppm. ^{13}C NMR (100.63 MHz, $CDCl_3$): δ 151.5 (s, –CO–), 150.6 (s, –CO–), 134.7 (s, Ph), 128.4 (d, Ph), 128.1 (d, Ph), 127.8 (d, Ph), 74.3 (d, $-C^5H-$), 68.3 (t, $-CH_2Ph$), 45.5 (t, $-C^4H_2-$), 44.2 (t, $-C^6H_2-$) ppm. MS (ESI$^+$): *m*/*e* (%) 1027 (12), 1019 (10), 1001 (11), 893 (20), 886 (16), 885 (33), 791 (19), 785 (10), 777 (17), 752 (12), 751 (31), 657 (27), 643 (26), 636 (14), 635 (44), 617 (10), 523 ($2\times M^+$+23, 12), 502 (15), 501 (60), 407 (18), 367 (16), 273 (M^++23, 10); HRMS (ESI$^+$): calcd for $C_{12}H_{14}N_2O_4Na$ (M^++23), 273.0846; found, 273.0851; $[\alpha]_D^{20} = -20.0$ (*c* 0.05, $CHCl_3$); R_f: 0.28 (MeOH–CH_2Cl_2 10%).

4. X-ray data

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC 614294 and 614295 for compounds **4a** and **12b**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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