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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of 5-isopropyl-oxazoline-4-imide as *syn*-hydroxyleucine precursor

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Abstract—The synthesis of *syn N*-acetyl-hydroxyleucine methyl ester is reported through the ring expansion of aziridine-2-imides to oxazoline-4-imides. The key steps of the synthesis are the 1,4-addition of *O*-benzylhydroxylamine to unsaturated imides, promoted by Lewis acids, and the regio- and stereoselective ring expansion of *trans*-aziridines to *trans*-oxazolines.

1. Introduction

We have recently developed a new general method to prepare stereospecifically substituted oxazoline[1] derivatives which were used in the synthesis of naturally occurring non-proteinogenic β-hydroxy-α-amino acids.[2] Our strategy starts from the diastereoselective β-introduction of *O*-benzylhydroxylamine to α,β-unsaturated chiral imidates.[3] The diastereoselectivity of this step can be controlled by the use of (4*S*,5*R*)- or (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one as a chiral auxiliary,[4] that is commercially available in both enantiomerically pure forms. The 1,4-addition is followed by cyclisation to aziridines obtained in exclusive *trans*-configuration.[5] Their activation through *N*-acylation allowed ring expansion to the corresponding *trans*-oxazolines.[6] Since the configuration of the two new stereogenic centres exclusively depends on the initial addition of the nitrogen derivative, the chiral auxiliary and the Lewis acid selected for the 1,4-addition determine the stereochemical outcome of the whole sequence.

Herein, we report the synthesis of the enantiomeric *trans*-oxazolines **9** and **11**. Oxazoline **9** is a protected form of the corresponding β-hydroxy-α-amino acid, which is present in the antibiotic Lysobactin,[7] whose total synthesis is the object of much interest in our laboratory;[8] **11** has been recently reported as a starting material in the synthesis of the neurotrophic factor Lactacystin[9] (Fig. 1).

2. Results and discussion

The conjugate addition of nucleophiles to electron deficient α,β-unsaturated carboxylic acid derivatives provides an important route to β-substituted carbonyl compounds.[10] We have previously investigated the nucleophilic 1,4-addition and in our experience the rate of addition and the diastereomeric ratio strongly depend on the unsaturated substrate and on the Lewis acid selected.[3a] Concerning the addition of *O*-benzylhydroxylamine to 4-methylpentenoyl imidate, several Lewis acids have been tested in order to find the optimal conditions in terms of diastereomeric ratio and yield (Scheme 1). Some results are reported in Table 1.

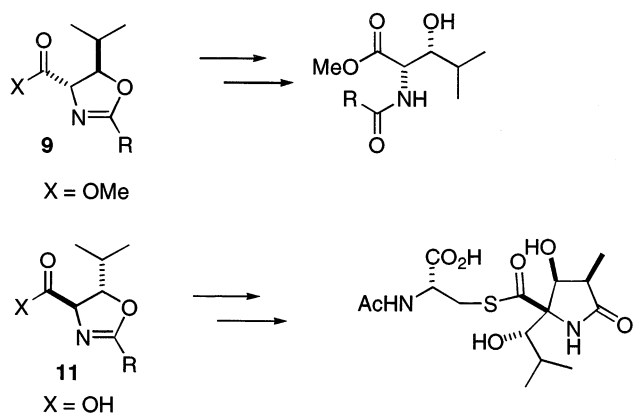

Figure 1.

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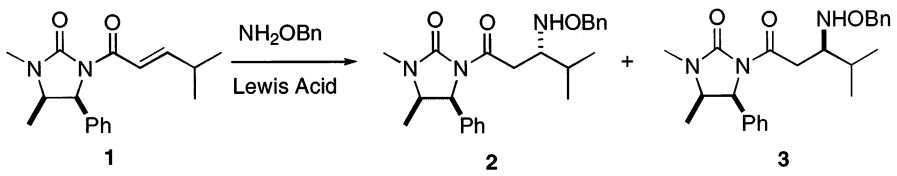


Scheme 1.

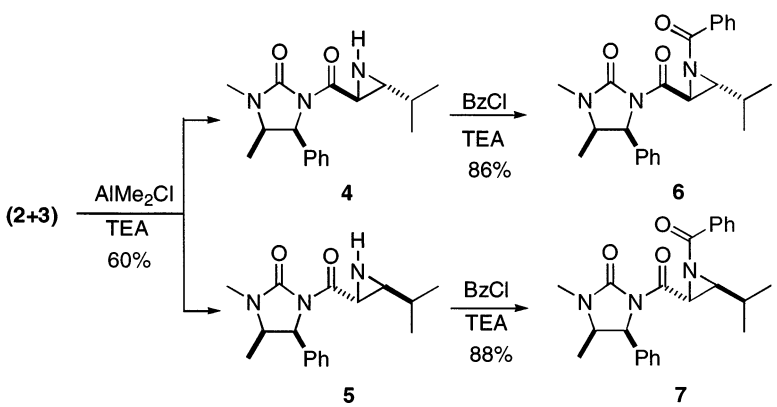
Table 1. Conjugate addition of *O*-benzylhydroxylamine to **1**

Entry	Lewis acid (equiv.)	*T* (°C)	Time (h)	Yield[a] (%)	D.r.[b] **2**/**3**
1	$AlMe_2Cl$ (1.1)	−78 to rt	18	95	70:30
2	$TiCl_4$ (1.1)	−60 to rt	18	10	46:54
3	$MgBr_2{\cdot}Et_2O$ (0.5)	−10 to rt	18	95	75:25
4	$Sc(OTf)_3$ (0.05)	−10 to rt	18	70	65:35
5	$BF_3{\cdot}Et_2O$ (1)	−10 to rt	72	50	90:10
6	$BF_3{\cdot}Et_2O$ (2)	−10 to rt	72	>95	90:10

[a] Calculated on isolated compounds.
[b] The diastereomeric ratio was determined at ^1H NMR through the evaluation of the signal corresponding to the H_4 in the chiral imidazolidinone for **2** (5.23 ppm) and **3** (5.15 ppm).

When $AlMe_2Cl$ or $MgBr_2{\cdot}Et_2O$ were used as Lewis acids, the conversion was almost quantitative and the preferential formation of **2** was observed (entries 1 and 3). On the other hand, performing the reaction in the presence of $TiCl_4$ proceeded slowly and with a very low diastereoselectivity (entry 2) affording **3** in slight excess. When $Sc(OTf)_3$ was used as catalyst, the preferential formation of **2** was observed and a good yield was obtained even with a catalytic amount of Lewis acid (entry 4). In general, the presence of the bulky isopropyl group lowered both the reaction rate and the d.r. in comparison to addition to crotonyl or acryloyl imidates (entry 1–5).[3] In fact, in this case we observed incomplete conversion of the starting material to hydroxylamino derivatives even after long reaction times. On the other hand, better results have been obtained utilising 2 equivalents of $BF_3{\cdot}Et_2O$ over 3 days. Under these conditions complete conversion and 9:1 d.r. was observed. These results are surprising since **2** was obtained as the major isomer in both aluminium or magnesium and boron catalysed reactions. Considering the behaviour of aluminium and magnesium, chelated intermediate structures have previously been proposed[11] and confirmed by us[3] and Castellino[11c] through NMR analysis. In these cases, as a consequence of the coordination of both carbonyl groups of unsaturated imides, nucleophilic attack on the less hindered face of the substrate–Lewis acid complex is preferred. In contrast, boron has long been regarded as a non-chelating Lewis acid and a reversal of diastereoselectivity would be expected.[12] The separation of **2** and **3** is not easy, so cyclisation to the corresponding aziridines was performed directly on the diastereomeric mixture using $AlMe_2Cl$ and triethylamine in CH_2Cl_2, following our previously reported protocol.[3b,5] This reaction afforded the two *trans*-aziridines **4** and **5** in 60% yield, the rest being unreacted starting material. The diastereomeric aziridines were separated by flash chromatography on silica gel (Scheme 2).

In order to prepare *N*-activated aziridines, each derivative was then treated with benzoyl chloride and triethylamine in CH_2Cl_2. Enantiomerically pure *N*-benzoylaziridines **6** and **7** were obtained after purification by flash chromatography in 86 and 88% yields, respectively.



Scheme 2.

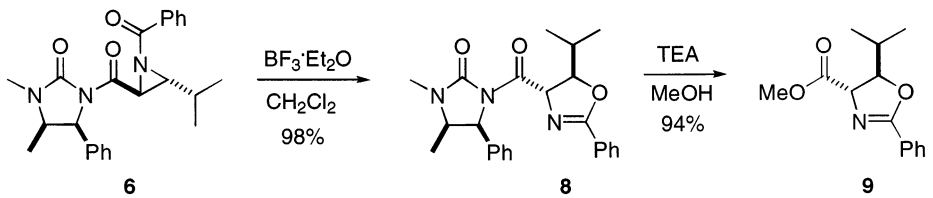
The ring expansion reaction of **6** and **7** to the corresponding *trans*-oxazolines easily occurs, under complete regio- and stereocontrol, by treatment with boron trifluoride–Et_2O in CH_2Cl_2.[13] The ring expansion of *N*-acyl-aziridines is a well known behaviour for this class of compounds and the mechanistic aspects of this reaction have been recently discussed by Hori et al.[6a] and by Lectka et al.[6b,c] We have successfully applied this kind of rearrangement in the synthesis of hydroxyamino acids present in the antibiotic Lysobactin. Oxazoline **8** was obtained from aziridine **6** as the exclusive product in 98% yield. To confirm the regiochemical course of the ring expansion reaction, **8** was stirred in refluxing MeOH in the presence of triethylamine.[14] This allowed complete removal and subsequent recovery of the chiral auxiliary and furnished the oxazoline methyl ester **9** in 94% yield. Comparison of the spectroscopic data and the specific rotation of **9** with the data reported in the literature confirmed both the regio- and stereochemical assignments[9] (Scheme 3).

The ring expansion of aziridine **7** to oxazoline was performed following the protocol reported above. In this case the *trans*-oxazoline **10** was isolated in 95% yield and subsequently treated with LiOOH in THF/H_2O.[15] The chiral imidazolidinone auxiliary was recovered in 90% yield from the basic organic layer, while oxazoline **11** was obtained in 95% yield after acidification of the aqueous layer and extraction with CH_2Cl_2 (Scheme 4). The ^1H NMR of compound **11** shows the exclusive presence of the *trans*-isomer, thus showing that the reaction proceeds without any racemisation.

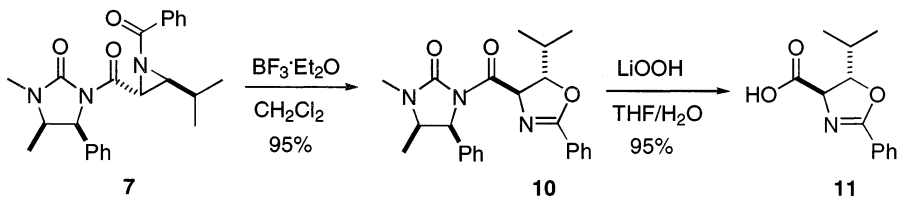
Aziridine **4** was also transformed into its *N*-acetyl derivative by treatment with acetyl chloride and triethylamine in CH_2Cl_2. The activated aziridine product **12** rapidly rearranged to the corresponding *trans*-oxazoline **13** in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 solvent. Ring expansion occurs as usual with complete regiocontrol and retention of configuration. The removal of the chiral imidazolidinone auxiliary, performed with triethylamine in refluxing MeOH, allowed us to obtain the oxazoline methyl ester **14**. During purification by flash chromatography on silica gel, spontaneous hydrolysis of the oxazoline ring occurred and (2*S*,3*R*)-*N*-acetyl-isoleucine methyl ester **15** was isolated in 90% yield (Scheme 5). No racemisation products were detected from the reaction mixture.

3. Conclusion

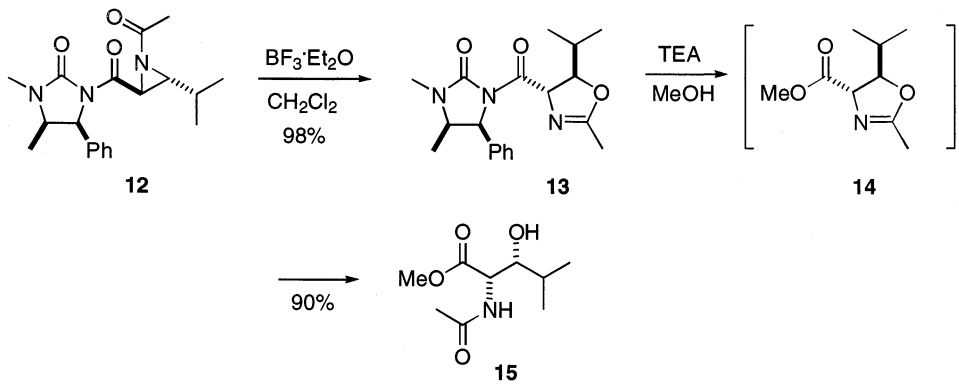
We have reported a methodology for the synthesis of *syn*-hydroxyleucine through the 1,4-addition of *O*-benzylhydroxylamine to α,β-unsaturated imides, followed by the cyclisation to *trans*-aziridines and ring expansion



Scheme 3.



Scheme 4.



Scheme 5.

to *trans*-oxazolines. The conjugate addition step is fundamental to the determination of the stereochemistry of the final product, since different enantiomers can be obtained by changing the configuration of the chiral auxiliary. The transformation of the addition products into aziridines and the ring expansion to oxazolines occurs with complete regio- and stereocontrol. The removal of the imidazolidinone auxiliary was performed following two different pathways in order to obtain oxazoline-4-esters and oxazoline-4-acids, which are useful precursors of *syn*-hydroxyleucine.

4. Experimental

4.1. General

Unless otherwise stated chemicals were obtained from commercial sources and used without further purification. CH_2Cl_2 was distilled from P_2O_5. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). NMR spectra were recorded with a Gemini Varian spectrometer at 300 or 200 MHz (^{1}H NMR) and at 75 MHz (^{13}C NMR). Chemical shifts were reported as δ values relative to the residual solvent peak of $CDCl_3$ set at $\delta=7.27$ (^{1}H NMR) or $\delta=77.0$ (^{13}C NMR). Infrared spectra were recorded with an FT-IR Nicolet 205 spectrometer. GC–MS analysis were performed on HP5890 series II chromatograph with a HP5971 mass detector. Optical rotation powers were recorded with Perkin–Elmer polarimeter 343. 4-Methyl-pentenoyl chloride was prepared following a procedure reported in the literature.[16]

4.2. (4*S*,5*R*)-3-(4′-Methyl-pentenoyl)-1,5-dimethyl-4-phenylimidazolidin-2-one 1

A mixture of (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one (2.00 g, 10.5 mmol), 4-methyl-pentenoyl chloride (1.53 g, 11.6 mmol), diisopropyl ethyl amine (2.02 mL, 11.6 mmol), and catalytic CuCl in dry CH_2Cl_2 (10 mL) was stirred under reflux under an inert atmosphere. After 6 h water (10 mL) was added and the mixture was extracted three times with CH_2Cl_2. The collected organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The oily residue was purified by flash chromatography (cyclohexane:EtOAc, 9:1) affording **1** (3.15 g, 95%).

(4*S*,5*R*)-**1**: IR (Nujol) ν 1716, 1669, 1628 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 0.78 (d, 3H, $J=6.6$ Hz); 1.06 (d, 3H, $J=6.9$ Hz); 2.43–2.58 (m, 1H); 2.80 (s, 3H); 3.90 (dq, 1H, $J=6.6$ Hz, 8.7 Hz); 5.32 (d, 1H, $J=8.7$ Hz); 6.90 (dd, 1H, $J=6.6$ Hz, 15.3 Hz); 7.14–7.35 (m, 5H); 7.44 (d, 1H, $J=15.3$ Hz); ^{13}C NMR (CD_2Cl_2) δ 15.1, 21.5, 21.6, 28.3, 31.6, 54.1, 119.6, 127.3, 128.0, 128.6, 137.6, 155.0, 156.1, 165.1; $[\alpha]_D^{20}=+40.4$ (*c* 1.1; $CHCl_3$); MS (*m*/*z*): 286 (M$^+$, 73), 217 (6), 191 (100), 132 (24), 117 (21), 96 (64); $C_{17}H_{22}N_2O_2$ (286.37); calcd: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.28; H, 7.75; N, 9.77%.

4.3. (4*S*,5*R*,3′*R*)-3-(3′-Benzyloxylamino-4′-methylpentanoyl)-1,5-dimethyl-4-phenylimidazolidin-2-one 2 and (4*S*,5*R*,3′*S*)-3-(3′-benzyloxylamino-4′-methylpentanoyl)-1,5-dimethyl-4-phenylimidazolidin-2-one 3

A mixture of **1** (1 g, 3.5 mmol) and Lewis acid in CH_2Cl_2 (15 mL) was stirred under an inert atmosphere. The amount of Lewis acid and the temperature of choice are reported in Table 1. After 30 min NH_2OBn (10.5 mL, 0.5 M in CH_2Cl_2, 5.25 mmol) was added and the reaction mixture was stirred for the time stated in Table 1, while the mixture was allowed to warm to rt. The reaction was quenched with sat. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2. The collected organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Compounds **2** and **3** were purified by flash chromatography on silica gel (cyclohexane:EtOAc, 8:2) and obtained as a mixture with the yield and the d.r. reported in Table 1.

(3′*R*)-**2**: IR (Nujol) ν 3480, 1719, 1673, 1383 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 (d, 3H, $J=6.6$ Hz); 0.91 (d, 3H, $J=6.9$ Hz); 0.93 (d, 3H, $J=6.9$ Hz); 1.94–2.23 (m, 1H); 2.80 (s, 3H); 3.00–3.28 (m, 3H); 3.80 (dq, 1H, $J=6.6$ Hz, 8.7 Hz); 4.58 (s, 2H); 5.23 (d, 1H, $J=8.7$ Hz); 5.80–6.05 (bs, 1H); 7.05–7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.9, 17.9, 19.4, 28.1, 28.9, 34.2, 53.8, 59.4, 62.4, 76.0, 126.9, 127.4, 128.0, 128.2, 128.2, 128.3, 136.5, 138.1, 155.8, 172.0; MS (*m*/*z*): 409 (M$^+$, 2), 366 (9), 302 (7), 232 (8), 191 (36), 132 (11), 91 (100), 58 (18); $C_{24}H_{31}N_3O_3$ (409.52); calcd: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.34; H, 7.65; N, 10.29%.

(3′*S*)-**3**: IR (Nujol) ν 3480, 1719, 1673, 1383 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (d, 3H, $J=6.6$ Hz); 0.91 (d, 3H, $J=6.9$ Hz); 0.93 (d, 3H, $J=6.9$ Hz); 1.94–2.23 (m, 1H); 2.76 (s, 3H); 3.00–3.28 (m, 3H); 3.62 (m, 1H); 4.58 (s, 2H); 5.15 (d, 1H, $J=8.4$ Hz); 5.45–5.60 (bs, 1H); 7.05–7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.9, 18.1, 19.4, 28.1, 29.1, 34.5, 53.7, 59.4, 62.4, 75.8, 126.9, 127.4, 127.9, 128.0, 128.2, 128.2, 128.3, 136.6, 138.1, 155.8, 172.0; MS (*m*/*z*): 409 (M$^+$, 2), 366 (9), 302 (7), 232 (8), 191 (36), 132 (11), 91 (100), 58 (18); $C_{24}H_{31}N_3O_3$ (409.52); calcd: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.34; H, 7.65; N, 10.29%.

4.4. (4*S*,5*R*,2′*S*,3′*R*)-1,5-Dimethyl-4-phenyl-3-[(2′-aziridinyl-3′-isopropyl)carbonyl]-imidazolidin-2-one 4 and (4*S*,5*R*,2′*R*,3′*S*)-1,5-dimethyl-4-phenyl-3-[(2′-aziridinyl-3′-isopropyl)carbonyl]-imidazolidin-2-one 5

To a solution of **2** and **3** (0.87 g, 2.12 mmol) in CH_2Cl_2 (15 mL), $AlMe_2Cl$ (2.33 mL, 1 M in hexane, 2.33 mmol) in CH_2Cl_2 (4 mL) was added dropwise at 0°C. The mixture was stirred for 20 min and then added via cannula to a solution of triethylamine (0.59 mL, 4.24 mmol) in CH_2Cl_2 (5 mL) at 0°C over 5 min. The reaction was quenched after 3 h with sat. $NaHCO_3$ (10 mL) and the mixture was extracted three times with CH_2Cl_2. The collected organic layers were dried over Na_2SO_4 and the solvent was evapo-

rated under reduced pressure. The mixture was purified by flash chromatography (AcOEt:cyclohexane, 7:3) giving **4** and **5** in a 60% yield. The ratio between **4** and **5** corresponds to the ratio between **2** and **3** in the starting material.

(4*S*,5*R*,2′*S*,3′*R*)-**4**: IR (film) *v* 3056, 1724, 1667, 1382 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, $J=6.6$ Hz); 1.03 (d, 3H, $J=6.7$ Hz); 1.04 (d, 3H, $J=6.7$ Hz); 1.39–1.51 (m, 1H); 1.73 (bs, 1H); 1.93 (dd, 1H, $J=2.4$ Hz, 7.5 Hz); 2.87 (s, 3H); 3.86 (d, 1H, $J=2.4$ Hz); 3.96 (dq, 1H, $J=6.6$ Hz, 8.7 Hz); 5.32 (d, 1H, $J=8.7$ Hz); 7.14–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.2, 19.6, 20.1, 28.3, 31.5, 35.0, 47.8, 54.1, 59.4, 126.9, 128.3, 128.6, 136.1, 155.6, 171.3; $[\alpha]_D^{20}=+79.7$ (*c* 1.0; $CHCl_3$); MS (*m*/*z*) 301 (M^+, 20), 258 (20), 231 (20), 191 (100); $C_{17}H_{23}N_3O_2$ (301.38) calcd: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.78; H, 7.66; N, 13.93%.

(4*S*,5*R*,2′*R*,3′*S*)-**5**: IR (film) *v* 2967, 1724, 1670, 1386 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, $J=6.6$ Hz); 1.02 (d, 3H, $J=6.7$ Hz); 1.04 (d, 3H, $J=6.7$ Hz); 1.38–1.47 (m, 1H); 1.74 (dd, 1H, $J=2.1$ Hz, 7.5 Hz); 1.75 (bs, 1H); 2.86 (s, 3H); 3.84 (d, 1H, $J=2.1$ Hz); 3.99 (dq, 1H, $J=6.6$ Hz, 8.4 Hz); 5.25 (d, 1H, $J=8.4$ Hz); 7.07–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.9, 19.5, 20.0, 28.1, 31.5, 35.3, 47.5, 54.5, 59.7, 127.1, 128.1, 128.5, 136.2, 155.8, 171.2; $[\alpha]_D^{20}=+78.6$ (*c* 0.6; $CHCl_3$); MS (*m*/*z*) 301 (M^+, 24), 258 (23), 231 (18), 191 (100); $C_{17}H_{23}N_3O_2$ (301.38); calcd: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.74; H, 7.69; N, 13.91%.

4.5. (4*S*,5*R*,2′*S*,3′*R*)-1,5-Dimethyl-4-phenyl-3-[(2′-*N*-benzoyl-aziridinyl-3′-isopropyl)carbonyl]-imidazolidin-2-one 6 and (4*S*,5*R*,2′*R*,3′*S*)-1,5-dimethyl-4-phenyl-3-[(2′-*N*-benzoyl-aziridinyl-3′-isopropyl)carbonyl]-imidazolidin-2-one 7

Benzoyl chloride (0.13 mL, 1.1 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of **4** or **5** (0.3 g, 1 mmol) and triethylamine (0.27 mL, 2 mmol) in CH_2Cl_2 (5 mL) at 0°C. The mixture was stirred for 2 h at room temperature and then rinsed twice with water. The organic layer, dried over anhydrous Na_2SO_4, was concentrated under reduced pressure. Aziridine **6** or **7** was purified by flash chromatography on silica gel (AcOEt:cyclohexane, 7:3).

(4*S*,5*R*,2′*S*,3′*R*)-**6** (0.35 g, 86%): IR (film) *v* 2959, 1787, 1731, 1689, 1375, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (d, 3H, $J=6.6$ Hz); 1.08 (d, 3H, $J=6.7$ Hz); 1.10 (d, 3H, $J=6.7$ Hz); 1.80–1.92 (m, 1H); 2.69 (dd, 1H, $J=2.7$ Hz, 6.6 Hz); 2.85 (s, 3H); 3.73 (dq, 1H, $J=6.6$ Hz, 8.4 Hz); 4.98 (d, 1H, $J=8.4$ Hz); 4.99 (d, 1H, $J=2.7$ Hz); 6.97–7.08 (m, 2H); 7.21–7.52 (m, 6H); 7.93–8.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 18.6, 19.7, 28.0, 29.8, 41.2, 49.7, 53.9, 59.1, 126.5, 128.0, 128.2, 128.4, 131.8, 134.3, 135.7, 155.3, 166.3, 176.2; $[\alpha]_D^{20}=+178.0$ (*c* 1.5; $CHCl_3$); MS (*m*/*z*) 405 (M^+, 2), 362 (11), 300 (9), 191 (17), 105 (83), 91 (32), 77 (100); $C_{24}H_{27}N_3O_3$ (405.49); calcd: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.11; H, 6.69; N, 10.35%.

(4*S*,5*R*,2′*R*,3′*S*)-**7** (0.36 g, 88%): IR (film) *v* 2940, 1786, 1731, 1687, 1374, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (d, 3H, $J=6.6$ Hz); 1.09 (d, 3H, $J=6.7$ Hz); 1.13 (d, 3H, $J=6.7$ Hz); 1.76–1.88 (m, 1H); 2.82–2.85 (m, 1H); 2.85 (s, 3H); 3.88 (dq, 1H, $J=6.6$ Hz, 8.7 Hz); 4.98 (d, 1H, $J=3.0$ Hz); 5.10 (d, 1H, $J=8.7$ Hz); 6.63–6.78 (m, 2H); 6.95–7.41 (m, 6H); 7.72–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.9, 19.2, 19.9, 28.2, 30.2, 41.6, 49.8, 54.0, 59.4, 126.1, 127.3, 128.1, 131.8, 133.9, 135.2, 155.2, 166.5, 176.2; $[\alpha]_D^{20}=+106.8$ (*c* 1.0; $CHCl_3$); MS (*m*/*z*) 405 (M^+, 2), 362 (11), 300 (9), 191 (17), 105 (83), 91 (32), 77 (100); $C_{24}H_{27}N_3O_3$ (405.49); calcd: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.08; H, 6.74; N, 10.34%.

4.6. (4*S*,5*R*,4′*S*,5′*R*)-4,5-Dihydro-2-phenyl-4-[(1′,5′-dimethyl-4′-phenylimidazolidin-2′-on-3′-yl)carbonyl]-5-isopropyl-oxazole 8 and (4*R*,5*S*,4′*S*,5′*R*)-4,5-dihydro-2-phenyl-4-[(1′,5′-dimethyl-4′-phenylimidazolidin-2′-on-3′-yl)carbonyl]-5-isopropyl-oxazole 10

To a solution of **6** or **7** (0.20 g, 0.49 mmol) in CH_2Cl_2 (7 mL), $BF_3{\cdot}Et_2O$ (62 μL, 0.49 mmol) was added at rt. After 1 h the reaction was quenched with sat. $NaHCO_3$ (4 mL), extracted three times with CH_2Cl_2 and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and **8** or **10** was obtained pure after flash chromatography (EtOAc:cyclohexane, 1:1).

(4*S*,5*R*,4′*S*,5′*R*)-**8** (0.195 g, 98%): IR (film) *v* 2926, 1739, 1713, 1686, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (d, 3H, $J=6.6$ Hz); 0.96 (d, 3H, $J=6.7$ Hz); 0.99 (d, 3H, $J=6.7$ Hz); 1.94–2.05 (m, 1H); 2.87 (s, 3H); 3.95 (dq, 1H, $J=6.6$ Hz, 8.7 Hz); 4.86 (dd≡t, 1H, $J=6.0$ Hz); 5.37 (d, 1H, $J=8.7$ Hz); 6.05 (d, 1H, $J=6.0$ Hz); 7.20–7.45 (m, 8H); 7.92–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.3, 17.1, 17.9, 28.3, 32.0, 53.9, 59.3, 70.4, 85.9, 126.9, 127.5, 127.9, 128.3, 128.4, 131.1, 135.7, 155.1, 165.0, 170.1; $[\alpha]_D^{20}=+137.5$ (*c* 0.4; $CHCl_3$); MS (*m*/*z*): 405 (M^+, 20), 362 (100), 215 (12), 191 (46), 188 (21), 104 (59), 76 (43), 57 (5), 43 (36); $C_{24}H_{27}N_3O_3$ (405.49); calcd: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.10; H, 6.71; N, 10.33%.

(4*R*,5*S*,4′*S*,5′*R*)-**10** (0.190 g, 95%): IR (film) *v* 2933, 1732, 1686, 1640, 1393 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, $J=6.6$ Hz); 0.95 (d, 3H, $J=6.7$ Hz); 0.98 (d, 3H, $J=6.7$ Hz); 1.98–2.10 (m, 1H); 2.88 (s, 3H); 3.99 (dq, 1H, $J=6.6$ Hz, 8.2 Hz); 4.65 (dd≡t, 1H, $J=6.9$ Hz); 5.31 (d, 1H, $J=8.2$ Hz); 6.19 (d, 1H, $J=6.9$ Hz); 7.08–7.18 (m, 2H); 7.20–7.48 (m, 6H); 7.87–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.9, 17.3, 17.8, 28.2, 32.1, 53.8, 59.8, 69.5, 87.4, 126.8, 128.0, 128.1, 128.5, 131.3, 136.5, 155.3, 165.7, 170.6; $[\alpha]_D^{20}=-4.8$ (*c* 1.3; $CHCl_3$); MS (*m*/*z*): 405 (M^+, 20), 362 (100), 215 (12), 191 (46), 188 (21), 104 (59), 76 (43), 57 (5), 43 (36); $C_{24}H_{27}N_3O_3$ (405.49); calcd: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.06; H, 6.74; N, 10.36%.

4.7. (4*S*,5*R*)-Methyl 5-isopropyl-2-phenyl-4,5-dihydro-oxazole-4-carboxylate 9

A solution of **8** (0.1 g, 0.25 mmol) and triethylamine (0.2 mL, 1.5 mmol) in MeOH (5 mL) was stirred under reflux

for 2 h. After removing the solvent under reduced pressure, the residue was dissolved in EtOAc and washed twice with water. The organic layer was dried over Na_2SO_4 and the solvent was removed. Purification by flash chromatography allowed recovery of the chiral imidazolidinone (47 mg, 99%) and isolation of oxazoline **9** in 94% yield (58 mg).

(4*S*,5*R*)-**9**: IR (film) *v* 1743, 1645, 1451, 1262 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3H, $J=6.7$ Hz); 1.04 (d, 3H, $J=6.7$ Hz); 1.91–2.02 (m, 1H); 3.82 (s, 3H); 4.58 (d, 1H, $J=6.6$ Hz); 4.69 (dd≡t, 1H, $J=6.6$ Hz); 7.39–7.53 (m, 3H); 7.96–8.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.3, 17.4, 32.4, 52.7, 71.2, 87.2, 128.2, 128.5, 131.7, 165.8, 171.9; $[\alpha]_D^{20}=+102.5$ (*c* 0.4; $CHCl_3$); MS (*m*/*z*) 247 (M^+, 4), 188 (41), 175 (14), 105 (80), 77 (100), 43 (74); $C_{14}H_{17}NO_3$ (247.29); calcd: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.02; H, 6.96; N, 5.67%.

4.8. (4*R*,5*S*)-5-Isopropyl-2-phenyl-4,5-dihydrooxazole-4-carboxylic acid 11

To a mixture of **10** (0.1 g, 0.25 mmol) in THF (4 mL) and water (1 mL), H_2O_2 (0.1 mL, 30% p/v, 1 mmol) and LiOH (12 mg, 0.5 mmol) were added at 0°C. The mixture was stirred at rt for 1 h. The reaction was quenched with sat. Na_2SO_3 (2 mL), and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to recover the chiral imidazolidinone (42 mg, 90%). The aqueous layer was acidified to pH 2, and extracted twice with EtOAc, then the solvent was removed under reduced pressure giving **11** (55 mg, 95%).

(4*R*,5*S*)-**11**: IR (film) *v* 3423, 2924, 1733, 1652, 1264 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, 3H, $J=6.0$ Hz); 1.04 (d, 3H, $J=6.0$ Hz); 1.95–2.09 (m, 1H); 4.61–4.75 (bm, 1H); 4.81–4.92 (bm, 1H); 6.60–7.2 (bs, 1H); 7.40–7.60 (m, 3H); 7.95–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.0 (2C), 29.7, 75.6, 80.0, 128.4, 128.7, 129.1, 133.4, 160.2, 173.0; $[\alpha]_D^{20}=-45$ ($c=1.2$; $CHCl_3$); MS (*m*/*z*) 233 (M^+, 1), 188 (42), 175 (11), 146 (36), 105 (83), 77 (100); $C_{13}H_{15}NO_3$ (233.26); calcd: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.96; H, 6.48; N, 6.02%.

4.9. (4*S*,5*R*,2′*S*,3′*R*)-1,5-Dimethyl-4-phenyl-3-[(2′-*N*-acetyl-aziridinyl-3′-isopropyl)carbonyl]-imidazolidin-2-one 12

Acetyl chloride (78 μL, 1.1 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of **4** (0.3 g, 1 mmol) and triethylamine (0.27 mL, 2 mmol) in CH_2Cl_2 (5 mL) at 0°C. The mixture was stirred for 2 h at room temperature and then washed twice with water. The organic layer, dried over anhydrous Na_2SO_4, was concentrated under reduced pressure. Aziridine **12** was purified by flash chromatography on silica gel (AcEtO:cyclohexane, 7:3).

(4*S*,5*R*,2′*S*,3′*R*)-**12** (0.29 g, 84%): IR (film) *v* 2920, 1780, 1733, 1682, 1221 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (d, 3H, $J=6.6$ Hz); 1.01 (d, 3H, $J=6.8$ Hz); 1.05 (d, 3H, $J=6.8$ Hz); 1.58–1.80 (m, 1H); 1.67 (s, 3H); 2.59 (dd, 1H, $J=2.6$ Hz, 7.0 Hz); 2.88 (s, 3H); 3.94 (dq, 1H, $J=6.6$ Hz, 8.8 Hz); 4.66 (d, 1H, $J=2.6$ Hz); 5.30 (d, 1H, $J=8.8$ Hz); 7.14–7.21 (m, 2H); 7.24–7.40 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 15.1, 19.1, 19.7, 24.0, 28.3, 30.2, 39.7, 50.8, 54.1, 59.5, 126.9, 128.2, 128.4, 135.9, 155.2, 167.2, 177.4; $[\alpha]_D^{20}=+143.6$ ($c=1.4$; $CHCl_3$); MS (*m*/*z*) 343 (M^+, 2), 330 (9), 300 (12), 191 (100), 102 (43), 43 (90); $C_{19}H_{25}N_3O_3$ (343.42); calcd: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.44; H, 7.36; N, 12.21%.

4.10. (4*S*,5*R*,4′*S*,5′*R*)-4,5-Dihydro-2-methyl-4-[(1′,5′-dimethyl-4′-phenylimidazolidin-2′-on-3′-yl)carbonyl]-5-isopropyl-oxazole 13

To a solution of **12** (0.20 g, 0.58 mmol) in CH_2Cl_2 (7 mL), $BF_3{\cdot}Et_2O$ (73 μL, 0.58 mmol) was added at rt. After 1 h the reaction was quenched with sat. $NaHCO_3$ (4 mL), extracted three times with CH_2Cl_2 and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and **13** was obtained pure after flash chromatography (EtOAc:cyclohexane, 1:1).

(4*S*,5*R*,4′*S*,5′*R*)-**13** (0.19 g, 95%): IR (film) *v* 1734, 1719, 1654, 1388 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, $J=6.6$ Hz); 0.90 (d, 3H, $J=6.6$ Hz); 0.94 (d, 3H, $J=6.7$ Hz); 1.85–1.92 (m, 1H); 1.96 (s, 3H); 2.87 (s, 3H); 3.95 (dq, 1H, $J=6.6$ Hz, 8.8 Hz); 4.70 (dd≡t, 1H, $J=6.2$ Hz); 5.35 (d, 1H, $J=8.8$ Hz); 5.79 (bd, 1H, $J=6.2$ Hz); 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.3, 17.1, 17.8, 28.3, 31.9, 53.9, 59.4, 70.2, 85.9, 127.0, 128.0, 128.4, 135.8, 155.0, 166.4, 170.2; $[\alpha]_D^{20}=+275.6$ ($c=0.9$; $CHCl_3$); MS (*m*/*z*): 343 (M^+, 4), 300 (13), 289 (45), 191 (100), 188 (6), 76 (31), 58 (76), 43 (37); $C_{19}H_{25}N_3O_3$ (343.42); calcd: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.42; H, 7.35; N, 12.24%.

4.11. (4*S*,5*R*)-Methyl 5-isopropyl-2-methyl-4,5-dihydro-oxazole-4-carboxylate 14 and (2*S*,3*R*)-*N*-acetyl-hydroxyleucine methyl ester 15

A solution of **13** (0.1 g, 0.29 mmol) and triethylamine (0.24 mL, 1.75 mmol) in MeOH (5 mL) was refluxed for 2 h. After removing the solvent under reduced pressure, the residue was dissolved in EtOAc and rinsed twice with water. The organic layer was dried over Na_2SO_4 and the solvent was removed to give oxazoline **14** and the chiral imidazolidinone in the crude reaction mixture. Purification by flash chromatography furnished exclusively **15** in 90% yield (0.053 g).

(4*S*,5*R*)-**14**: ^1H NMR ($CDCl_3$) δ 0.89 (d, 3H, $J=7.2$ Hz); 0.92 (d, 3H, $J=7.2$ Hz); 1.75–1.86 (m, 1H); 1.99 (s, 3H); 3.74 (s, 3H); 4.29 (d, 1H, $J=6.9$ Hz); 4.43 (dd≡t, 1H, $J=6.9$ Hz).

(2*S*,3*R*)-**15**: IR (film) *v* 3421, 1732, 1686, 1640, 1391 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, 3H, $J=6.6$ Hz); 1.02 (d, 3H, $J=6.6$ Hz); 1.62–1.75 (m, 1H); 2.08 (s, 3H); 3.73 (bdd, $J=9.3$ Hz, 2.0 Hz); 3.77 (s, 3H), 4.84 (dd, 1H, $J=2.0$ Hz, 9.5 Hz); 6.23 (d, 1H, $J=9.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 18.9 (2C), 23.2, 30.9, 52.6, 54.0, 77.2, 170.3, 172.2; $[\alpha]_D^{20}=+16.9$ (*c* 0.4; $CHCl_3$); MS (*m*/*z*):

144 (8), 131 (36), 99 (74), 59 (25), 43 (18); $C_9H_{17}NO_4$ (203.24); calcd: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.16; H, 8.44; N, 6.91%.

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