Synthesis of the Phenylserine−Leucine Dipeptide Fragment Present in the Antibiotic Lysobactin from an Aziridine-2-imide Precursor

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The ring expansion of (2*R*′,3*S*′) or (2*S*′,3*R*′)-*N*-(α-amino acyl)-aziridine-2-imides and the mild hydrolysis of the resulting oxazoline-4-imides gives (2*R*,3*S*)-phenylserine–leucine or (2*S*,3*R*)-phenylserine–leucine dipeptides. In particular, the latter fragment is present in the depsipeptide antibiotic Lysobactin.

Introduction

At present much attention has been focused on the stereoselective synthesis of naturally occurring unusual amino acids. Polyfunctionalized α- and β-amino acids are components of interesting and complex molecules that display high biological and pharmacological activity. For example, α-alkyl-β-amino acids are present in a number of macrocyclic polypeptides derived from marine sources. The α-hydroxy β-amino acid phenylisoserine with defined (2*R*,3*S*) configuration is a well-known component of the anticancer drug Taxol.[1] In addition, β-hydroxy α-amino acids are present in several important antibiotics.[2]

The antibiotic lactone Lysobactin[3] contains five hydroxy-amino acids in its backbone in the *syn* or *anti* configuration. Lysobactin activity has been compared with Vancomycin[4] antibiotic activity and it was shown that Vancomycin resistant bacteria could be controlled with Lysobactin. Therefore, the synthesis of a modified sequence which could show enhanced antibiotic activity, and the total synthesis of this macrocyclic polypeptide is of interest to many groups. In particular, Palomo et al. has developed the preparation of Lysobactin fragments containing β-hydroxy α-amino acids from chiral β-lactam frameworks.[5] In these last few years, we have developed new strategies for the synthesis of unusual α- and β- polyfunctionalized amino acids and, in many cases we have employed aziridine 2-carboxylate derivatives in enantiomerically pure forms as starting materials.[6] These heterocyclic rings are quite resistant to the nucleophilic attack at the α- and β-position. On the other hand, the introduction of an electron-withdrawing group on the nitrogen allows easy ring opening in the presence of an oxophilic Lewis acid.[7] Furthermore, nitrogen activation with an acyl group is responsible for another important reaction which is the ring expansion of the aziridine to the corresponding oxazoline.[8] This kind of reaction occurs spontaneously or in the presence of an azaphilic Lewis acid with retention of the pre-existing configuration and with preferential attack of the carbonyl group at the more substituted aziridine carbon atom (Figure 1).

Despite the interest in this last transformation, little attention has been paid to this kind of reaction which enables the preparation of a protected form of the hydroxy amino acid under high regio and stereocontrol in one step. On this basis, a new and efficient strategy for the synthesis of *syn* β-hydroxy-α-amino acid-containing dipeptides from *trans* *N*-α-acylamino-aziridine imides *via* ring expansion to the corresponding oxazolines, has been developed in our laboratory.[9]

We wish to report herein the synthesis of the *syn* phenylserine-containing dipeptide present in the lactone Lysobactin. The first step of this strategy deals with the synthesis of enantiomerically pure aziridines by using our well-established protocol (outlined in Figure 2), 1,4-addition of *O*-benzylhydroxylamine and subsequent cyclization to the *trans* aziridine *via* the corresponding enolate.

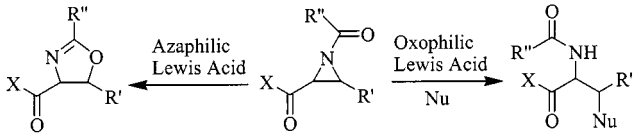

Figure 1. Reactivity of *N*-Acylaziridine-2-carboxylates

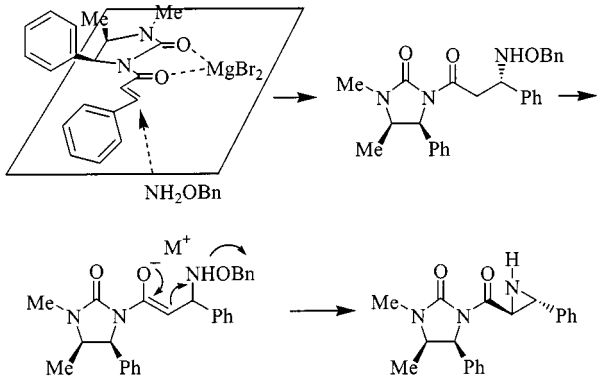

Figure 2. Synthetic protocol for optically pure aziridine-2-imides from α,β-unsaturated imides

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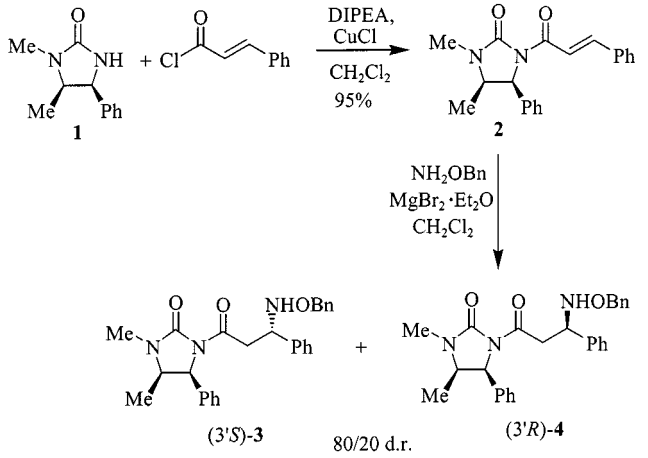
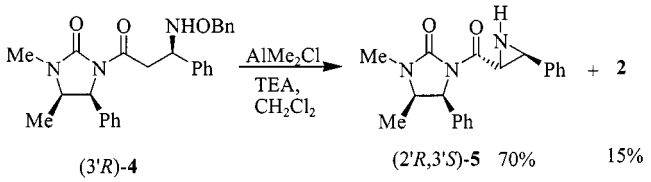
Results and Discussion

In order to obtain phenylserine in the (2*S*,3*R*) configuration as present in the Lysobactin backbone, our synthetic plan required the preparation of the (3′*S*)-benzylhydroxylamino imidate. This could be obtained from the chiral auxiliary (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one.[10] In a previous work,[11] we observed that the 1,4-addition of *O*-benzylhydroxylamine to cinnamoyl derivatives occurs in the presence of $MgBr_2$ with the preferential attack of the nucleophile on the less hindered face of the substrate-Lewis acid complex (Figure 2). Thus a synthetic procedure for the diastereoselective synthesis of phenylserine was carried out as outlined in Scheme 1.



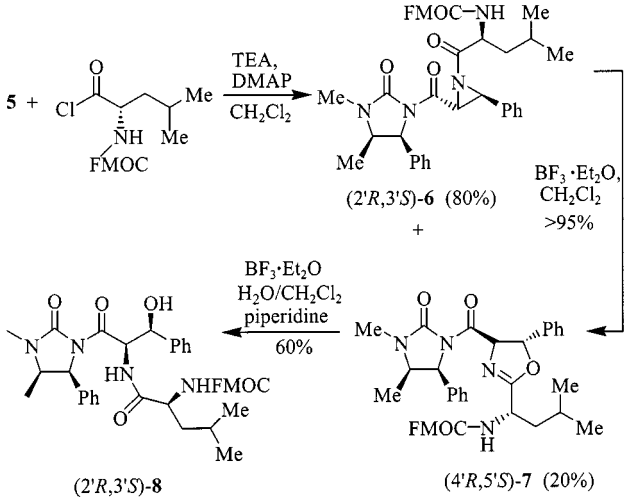
Scheme 1. Synthesis of compound (3′*S*)-**3** and (3′*R*)-**4** through conjugate addition of NH_2OBn in the presence of $MgBr_2$

The 1,4-addition of *O*-benzylhydroxylamine to the cinnamoyl derivative **2** in the presence of 0.5 equiv. of $MgBr_2$, in CH_2Cl_2 at reflux, gave an easily separated mixture of (3′*S*)-**3**/(3′*R*)-**4** isomers in 90% yield and 80:20 *dr*. Following our recently reported method for the synthesis of *trans* aziridines,[12] the minor isomer was treated with 1.1 equiv. of $AlMe_2Cl$ and two equiv. of TEA in CH_2Cl_2 at 0 °C. The intermediate enolate cyclized to aziridine (2′*R*,3′*S*)-**5**, which was obtained in 70% yield and exclusively in the *trans* configuration (J = 2.2 Hz, consistent with a *trans* configuration). This reaction also afforded compound **2** in 15% yield by an elimination process (Scheme 2).



Scheme 2. Ring closure of (3′*R*)-**4** to aziridine (2′*R*,3′*S*)-**5**

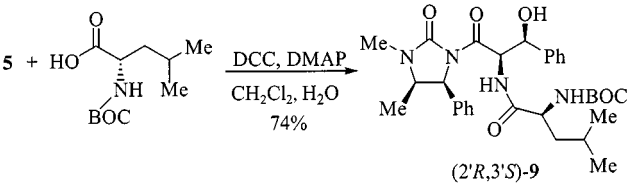
The *trans* aziridine (2′*R*,3′*S*)-**5** was treated with *N*-fluorenylmethoxycarbonyl-leucine chloride, prepared as described in the literature.[13] The reaction was carried out in CH_2Cl_2 with TEA and DMAP and gave 80% of the coupled aziridine (2′*R*,3′*S*)-**6** along with 20% of the *trans* oxazoline (4′*R*,5′*S*)-**7** produced in a ring expansion reaction. From this mixture the pure aziridine (2′*R*,3′*S*)-**6** and oxazoline (4′*R*,5′*S*)-**7** were isolated and characterized (Scheme 3).



Scheme 3. Coupling of aziridine (2′*R*,3′*S*)-**5** with *N*-FMOC-Leu and expansion to oxazoline (4′*R*,5′*S*)-**7**; hydrolysis of **7** to dipeptide derivative (2′*R*,3′*S*)-**8**

Treatment of (2′*R*,3′*S*)-**6** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 gave (4′*R*,5′*S*)-**7** in quantitative yield. The *trans* configuration of oxazoline (4′*R*,5′*S*)-**7** was unequivocally established on the basis of the H_4-H_5 coupling constant (J = 6.7 Hz). In order to obtain the desired amide, the hydrolysis of compound (4′*R*,5′*S*)-**7** was investigated and the method of choice found to be treatment with $BF_3{\cdot}Et_2O$ in the presence of piperidine, which gave (2*R*,3*S*)-phenylserine-containing dipeptide derivative (2′*R*,3′*S*)-**8** in 60% yield with retention of the configuration.[8c]

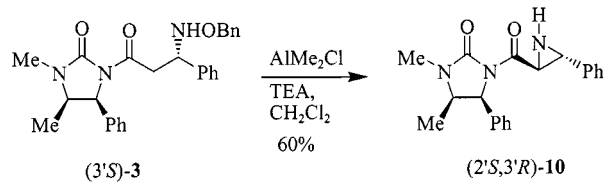
In an alternative approach *N*-*tert*-butoxycarbonyl-leucine was coupled with aziridine (2′*R*,3′*S*)-**5** by treatment with DCC and DMAP in CH_2Cl_2 in the presence of water. Under these conditions (2′*R*,3′*S*)-**9** was directly obtained (Scheme 4).



Scheme 4. Direct formation of dipeptide derivative (2′*R*,3′*S*)-**9**

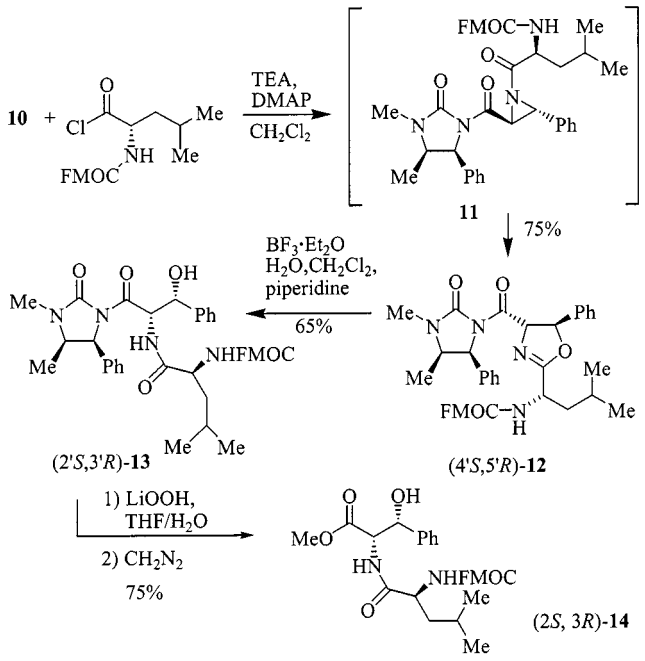
The procedure reported in Scheme 3 was applied to the synthesis of the (2*S*,3*R*)-phenylserine-isoleucine dipeptide derivative, a fragment of the Lysobactin antibiotic. Thus the (3′*S*)-**3** major isomer, when treated as reported above,

gave the *trans* aziridine (2′*S*,3′*R*)-**10** exclusively in 60% yield (J_{trans} = 2.2 Hz) (Scheme 5).



Scheme 5. Ring closure of (3′*S*)-**3** to aziridine (2′*S*,3′*R*)-**10**

The *trans* aziridine (2′*S*,3′*R*)-**10** was then treated with *N*-fluorenylmethoxycarbonyl-leucine in CH_2Cl_2 with TEA and DMAP, to afford the oxazoline (4′*S*,5′*R*)-**12** directly. The intermediate (2′*S*,3′*R*)-**11** *N*-leucyl-aziridine was not detected. Hydrolysis of the oxazoline with $BF_3{\cdot}Et_2O$ and piperidine in CH_2Cl_2/H_2O gave the (2*S*,3*R*)-phenylserine-containing dipeptide derivative (2′*S*,3′*R*)-**13** in 65% yield. Finally the nondestructive removal and recovery of the chiral auxiliary was carried out with lithium hydroperoxide in THF/H_2O[14] and the acid obtained converted into the corresponding methyl ester (2*S*,3*R*)-**14** with CH_2N_2 (Scheme 6). The *syn* stereochemistry of phenylserine derivative (2*S*,3*R*)-**14** was confirmed by comparison of its ^{1}H NMR spectrum with the ^{1}H NMR spectrum of the diastereomeric mixture of (±)-*syn*-phenylserine-*N*-fluorenylmethoxycarbonyl-leucine obtained by the coupling of commercially available (±)-*syn*-phenylserine methyl ester with *N*-fluorenylmethoxycarbonyl-leucine under standard condition in the presence of DCC.



Scheme 6. Coupling of aziridine (2′*S*,3′*R*)-**10** with *N*-FMOC-Leu and expansion to oxazoline (4′*S*,5′*R*)-**12**; synthesis of dipeptide (2′*S*,3′*R*)-**14**, fragment of the antibiotic Lysobactin

Conclusion

The ring expansion of *N*-activated 3-phenylaziridine-2-imides is regio and stereoselective and gives oxazoline-4-imides, which after hydrolysis, leads to phenylserine derivatives. When the activating group is a *N*-protected amino acid, this two steps procedure give rise to a dipeptide.

As the aziridine ring expansion occurs with retention of the configuration, thus *N*-leucyl-(2*R*′,3*S*′)-aziridine-2-imide affords the (2*R*,3*S*)-phenylserine-leucine dipeptide, whilst the product from the (2*S*′,3*R*′)-aziridine is the (2*S*,3*R*)-phenylserine-leucine dipeptide. The presence of this fragment in the depsipeptide antibiotic Lysobactin framework, and the easy accessibility of aziridine-2-imides as enantiomerically pure reagents, makes this last example of particular synthetic interest.

Experimental Section

General Remarks: Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. CH_2Cl_2 was distilled from P_2O_5. Toluene was distilled from molecular sieves. 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 are reported as δ values relative to the solvent peak of $CDCl_3$ set at δ = 7.27 (^{1}H NMR) or δ = 77.0 (^{13}C NMR). Infrared spectra were recorded with an FT-IR Nicolet 205 spectrometer.

(4*S*,5*R*)-3-Cinnamoyl-1,5-dimethyl-4-phenylimidazolidin-2-one (2): A mixture of **1** (2.00 g, 10.5 mmol), cinnamoyl chloride (1.92 g, 11.6 mmol), diisopropyl ethyl amine (2.02 mL, 11.6 mmol), and a catalytic amount of CuCl in dry CH_2Cl_2 (10 mL) was refluxed under an inert atmosphere. After 6 h, water (10 mL) was added and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and solvent evaporated at reduced pressure. The oily residue was purified by flash chromatography (cyclohexane/EtOAc 6:4) to afford **2** (3.18 g, 95%). m.p. 142−147 °C. − IR (nujol): $\tilde{\nu}$ = 1712, 1659, 1613 cm^{-1}. − ^{1}H NMR: δ = 0.85 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH*$_3$), 2.88 (s, 3 H, N*CH*$_3$), 3.95 (dq, 1 H, *J* = 6.6, 8.5 Hz, PhCH*CH*CH$_3$), 5.43 (d, 1 H, *J* = 8.5 Hz, Ph*CH*CHCH$_3$), 7.16−7.62 (m, 10 H, ArH), 7.70 (d, 1 H, *J* = 15.8 Hz, *CH*=CHPh), 8.18 (d, 1 H, *J* = 15.8 Hz, CH=*CH*Ph). − ^{13}C NMR: δ = 15.0, 28.2, 53.9, 59.6, 118.7, 126.9, 127.5, 128.0, 128.4, 128.6, 130.0, 135.0, 136.5, 144.3, 155.9, 164.8. − $[\alpha]_D^{20}$ = +22.6 (*c* = 1.9, $CHCl_3$).

(4*S*,5*R*)-3-(3′-Benzyloxylamino-3′-phenylpropanoyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (3, 4): A mixture of **2** (0.91 g, 2.84 mmol) and $MgBr_2{\cdot}OEt_2$ (0.37 g, 1.42 mmol) in CH_2Cl_2 (15 mL) at 0 °C was stirred under inert an atmosphere. After 30 min, NH_2OBz (6.89 mL, 0.5 M in CH_2Cl_2, 3.44 mmol) was added and the reaction stirred at room temp. for 72 h. The reaction was quenched with sat. $NaHCO_3$ (10 mL), the mixture filtered through Celite, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and solvent evaporated at reduced pressure. The mixture was purified by flash chromatography (CH_2Cl_2/acetone 95:5) to give **(3′*S*)-3** (0.91 g, 72%) and **(3′*R*)-4** (0.23 g, 18%).

(3′*S*)-3: m.p. 125−128 °C. − IR (nujol): $\tilde{\nu}$ = 3300, 1719, 1666 cm^{-1}. − ^{1}H NMR: δ = 0.77 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH*$_3$), 2.79 (s, 3 H, N*CH*$_3$), 3.48 (d, 2 H, *J* = 6.9 Hz, OC*CH*$_2$CHN), 3.79 (dq, 1 H, *J* = 6.6, 8.2 Hz, PhCH*CH*CH$_3$), 4.47 (d, 1 H, *J* = 11.4 Hz, OC*H*HPh), 4.52 (d, 1 H, *J* = 6.9 Hz, OCCH$_2$*CH*N), 4.55 (d, 1 H, *J* = 11.4 Hz, OCH*H*Ph), 5.18 (d, 1 H, *J* = 8.2 Hz,

Ph*CH*CHCH$_3$), 6.04−6.18 (br. s, 1 H, *NH*), 7.10−7.40 (m, 15 H, ArH). − ^{13}C NMR(CDCl3) δ = 14.8, 28.1, 39.7, 53.8, 59.3, 61.5, 76.4, 126.8, 127.4, 127.9, 128.1, 128.4, 136.3, 137.7, 140.7, 155.6, 170.3 . $[\alpha]_D^{20}$ = +26.0 (*c* = 1.2; $CHCl_3$). − $C_{27}H_{29}N_3O_3$ (443.54): calcd. C 73.11, H 6.59, N 9.47; found C 73.09, H 6.58, N 9.48.

(3′*R*)-4: IR (nujol): ṽ = 3300, 1717, 1668 cm^{-1}. − ^{1}H NMR: δ = 0.75 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH$_3$*), 2.78 (s, 3 H, N*CH$_3$*), 3.40 (dd, 1 H, *J* = 5.0, 16.3 Hz, OCC*H*HCHN), 3.57 (dd, 1 H, *J* = 9.0, 16.3 Hz, OCCH*H*CHN), 3.74 (dq, 1 H, *J* = 6.6, 8.5 Hz, PhCH*CH*CH$_3$), 4.48 (s, 2 H, O*CH$_2$*Ph), 4.56 (dd, 1 H, *J* = 5.0, 9.0 Hz, OCCH$_2$*CH*N), 5.21 (d, 1 H, *J* = 8.5 Hz, Ph*CH*CHCH$_3$), 6.05−6.17 (br. s, 1 H, *NH*), 6.98−7.43 (m, 15 H, ArH). − ^{13}C NMR: δ = 14.9, 28.2, 39.4, 53.8, 59.3, 61.5, 76.4, 126.8, 127.4, 127.7, 128.2, 128.4, 136.4, 137.9, 140.8, 154.5, 170.6. − $[\alpha]_D^{20}$ = +50.0 (*c* = 0.12, $CHCl_3$).

3-[(2′-Aziridinyl-3′-phenyl)carbonyl]-(4*S*,5*R*,2′*R*,3′*S*)-1,5-dimethyl-4-phenyl-imidazolidin-2-one (5): A solution of **4** (0.10 g, 0.23 mmol) in CH_2Cl_2 (7 mL) was treated dropwise at 0 °C with $AlMe_2Cl$ (0.25 mL, 1 M in hexane, 0.25 mmol) in CH_2Cl_2 (2 mL) . The mixture was stirred for 20 min, then a solution of triethylamine (0.06 mL, 0.46 mmol) in CH_2Cl_2 (2 mL) was added at 0 °C over 5 min. The reaction was quenched after 3 h with sat. $NaHCO_3$ (5 mL) and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and solvent evaporated under reduced pressure. The mixture was purified by flash chromatography (AcOEt/cyclohexane 7:3) to give **5** (54 mg, 70%). − ^{1}H NMR: δ = 0.81 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH$_3$*), 2.12−2.34 (br. s, 1 H, *NH*), 2.82 (s, 3 H, N*CH$_3$*), 3.00 (bd, 1 H, *J* = 2.2 Hz, OCCHN*CH*Ph), 3.99 (dq, 1 H, *J* = 6.6, 8.4 Hz, PhCH*CH*CH$_3$), 4.22 (bd, 1 H, *J* = 2.2 Hz, OC*CH*NCHPh), 5.30 (d, 1 H, *J* = 8.4 Hz, Ph*CH*CHCH$_3$), 7.12−7.41 (m, 10 H, ArH). − ^{13}C NMR: δ = 14.8, 27.9, 38.9, 41.4, 54.2, 59.7, 125.8, 126.4, 127.3, 127.9, 128.3, 128.6, 136.1, 138.1, 155.2, 170.0. − $[\alpha]_D^{20}$ = −135.0 (*c* = 1.0, $CHCl_3$).

(4*S*,5*R*,2′*R*,3′*S*,2′′*S*)-3-{[2′-Aziridinyl-1′-(2′′-fluorenylmethoxycarbonylamino-4′′-methylpentanoyl)-3′-phenyl-]carbonyl}-1,5-dimethyl-4-phenylimidazolidin-2-one (6): Triethylamine (0.13 mL, 0.9 mmol) and *N*-fluorenylmethoxycarbonyl-leucine chloride (0.27 g, 0.73 mmol) were added to a solution of **5** (0.15 g, 0.45 mmol) in CH_2Cl_2 (15 mL) at room temp. After stirring for 4 h, the solution was quenched with sat. $NaHCO_3$ (15 mL) and extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and solvent evaporated under reduced pressure. The mixture was purified by flash chromatography (CH_2Cl_2/acetone 95:5) to give **6** (0.24 g, 80%) and **7** (0.06 g, 20%).

6: ^{1}H NMR: δ= 0.75 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH$_3$*), 0.82 (d, 6 H, *J* = 6.3 Hz, $CH_2CH(CH_3)_2$), 1.50−1.75 (m, 3 H, *CH$_2$CH*$(CH_3)_2$), 2.78 (s, 3 H, N*CH$_3$*), 3.88 (d, 1 H, *J* = 2.1 Hz, OCCHN*CH*Ph), 3.93 (dq, 1 H, *J* = 6.6, 8.7 Hz, PhCH*CH*CH$_3$), 4.13−4.26 (m, 2 H, FMOC), 4.30−4.45 (m, 2 H, FMOC, HN*CH*CH$_2$), 5.08 (d, 1 H, *J* = 2.1 Hz, OC*CH*NCHPh), 5.27 (d, 1 H, *J* = 8.7 Hz, Ph*CH*CHCH$_3$), 5.29 (d, 1 H, *J* = 8.5 Hz, NHFMOC), 6.97−7.80 (m, 18 H, ArH). − $[\alpha]_D^{20}$ = −3.0 (*c* = 1.5; $CHCl_3$).

(4*R*,5*S*,4′*R*,5′*S*,1′′*S*)-4-[(1′,5′-Dimethyl-4′-phenylimidazolidin-2′-on-3′-yl)carbonyl]-2-(1′′-fluorenylmethoxycarbonylamino-3′′-methyl1′′-butyl)-4,5-dihydro-5-phenyloxazole (7): A solution of **6** (0.24 g, 0.36 mmol) in CH_2Cl_2 (5 mL) was treated with $BF_3{\cdot}Et_2O$ (0.045 mL, 0.36 mmol) at room temp. for 6 h. The reaction was quenched with sat. $NaHCO_3$ (3 mL), extracted three times with CH_2Cl_2 and dried over Na_2SO_4. The solvent was evaporated at reduced pressure to afford 7 (0.23 g, 96%) which required no further purification. − ^{1}H NMR: δ = 0.77 (d, 3 H, *J* = 6.8 Hz, PhCHCH*CH$_3$*), 0.87 (d, 6 H, *J* = 7.2 Hz, $CH_2CH(CH_3)_2$), 1.52−1.82 (m, 3 H, *CH$_2$CH*$(CH_3)_2$), 2.79 (s, 3 H, N*CH$_3$*), 3.89 (dq, 1 H, *J* = 6.8, 8.7 Hz, PhCH*CH*CH$_3$), 4.18−4.26 (m, 1 H, FMOC), 4.34−4.43 (m, 2 H, FMOC), 4.61−4.72 (bm, 1 H, HN*CH*CH$_2$), 5.25 (d, 1 H, *J* = 8.7 Hz, Ph*CH*CHCH$_3$), 5.31 (bd, 1 H, *J* = 9.6 Hz, NHFMOC), 5.83 (d, 1 H, *J* = 6.7 Hz, OC*CH*CHPh), 6.22 (d, 1 H, *J* = 6.7 Hz, OCCH*CH*Ph), 7.06−7.80 (m, 18 H, ArH). − $C_{41}H_{42}N_4O_5$ (670.80): calcd. C 73.41, H 6.31, N 8.35; found C 73.41, H 6.30, N 8.33.

(4*S*,5*R*,2′*R*,3′*S*,2′′*S*)-3-[2′-(2′′-Fluorenylmethoxycarbonylamino-4′′-methylpentanoyl)amino-3′-hydroxy-3′-phenylpropionyl]-1,5-dimethyl-4-phenylimidazolidin-2-one (8): Boron trifluoride−diethyl ether (95 μL, 0.75 mmol) and water (20 μL) were added to a mixture of **7** (0.10 g, 0.15 mmol) and piperidine (33 μL, 0.30 mmol) in CH_2Cl_2 (7 mL) at room temp. After 5 h the reaction was quenched with sat. $NaHCO_3$ (8 mL), extracted three times with CH_2Cl_2 and dried over Na_2SO_4. The solvent was evaporated at reduced pressure and, after flash chromatography (EtOAc/cyclohexane 1:1), pure **8** (62 mg, 60%) was obtained. − ^{1}H NMR: δ = 0.80 (d, 3 H, *J* = 6.0 Hz, $CH_2CH(CH_3)_2$), 0.84 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH$_3$*), 0.91 (d, 3 H, *J* = 7.8 Hz, $CH_2CH(CH_3)_2$), 1.20−1.46 (m, 3 H, *CH$_2$CH*$(CH_3)_2$), 2.72 (br. s, 1 H, OH), 2.89 (s, 3 H, N*CH$_3$*), 3.98 (dq, 1 H, *J* = 6.6, 7.7 Hz, PhCHCHCH$_3$), 4.07−4.22 (m, 3 H, OC*CH*NHFMOC, FMOC), 4.28−4.37 (m, 1 H, FMOC), 5.10 (bd, 1 H, *J* = 7.5 Hz, *NH*FMOC), 5.31 (d, 1 H, *J* = 7.7 Hz, Ph*CH*CHCH$_3$), 5.38 (br. s, 1 H, OCCHN*CHO*), 6.26 (bd, 1 H, *J* = 7.8 Hz, OC*CH*NCHO), 6.55 (bd, 1 H, *J* = 8.8 Hz, NHLeu), 7.52−7.78 (m, 18 H, ArH). − ^{13}C NMR: δ = 15.0, 22.8, 24.6, 28.3, 41.9, 47.1, 53.8, 54.2, 56.4, 59.5, 68.2, 72.8, 119.9, 125.2, 126.9, 127.0, 127.6, 128.0, 128.3, 128.7, 128.8, 136.1, 139.2, 141.2, 142.1, 154.0, 155.4, 169.2, 171.0. − $C_{41}H_{44}N_4O_6$ (688.81): calcd. C 71.49, H 6.44, N 8.13; found C 71.51, H 6.43, N 8.12.

(4*S*,5*R*,2′*R*,3′*S*,2′′*S*)-3-[2′-(2′′-*tert*-Butyloxycarbonylamino-4′′-methylpentanoyl)amino-3′-hydroxy-3′-phenylpropionyl]-1,5-dimethyl-4-phenylimidazolidin-2-one (9): Dicyclohexylcarbodiimide (27 mg, 0.13 mmol) and a cat. quantity of DMAP were added to a mixture of **5** (40 mg, 0.12 mmol) and BOC-leucine (30 mg, 0.13 mmol) in CH_2Cl_2 (10 mL) at room temp. The reaction was stirred overnight, filtered through Celite and water (1.0 mL) added to the filtrate. The mixture was then stirred for12 h. The organic layer was separated and dried over Na_2SO_4, and solvent evaporated at reduced pressure to afford an oily residue. The residue was purified by flash chromatography (EtOAc/cyclohexane 7:3) to give **9** (49 mg, 74%). − ^{1}H NMR: δ = 0.79 (d, 6 H, *J* = 6.3 Hz, $CH_2CH(CH_3)_2$), 0.85 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH$_3$*), 1.02−1.52 (bm, 3 H, *CH$_2$CH*$(CH_3)_2$), 1.39 (s, 9 H, *tert*-Butyl), 2.87 (s, 3 H, N*CH$_3$*), 3.95−4.10 (m, 1 H, OC*CH*NHBOC), 4.00 (dq, 1 H, *J* = 6.6, 8.5 Hz, PhCH*CH*CH$_3$), 4.75 (bd, 1 H, *J* = 7.7 Hz, *NH*BOC), 5.35 (d, 1 H, *J* = 8.5 Hz, Ph*CH*CHCH$_3$), 5.36 (d, 1 H, *J* = 3.3 Hz, OCCHN*CH*O), 6.24 (dd, 1 H, *J* = 3.3, 9.0 Hz, OC*CH*NCHO), 6.70 (bd, 1 H, *J* = 9.0 Hz, NHLeu), 7.16−7.21 (m, 10 H, ArH). − ^{13}C NMR: δ = 15.0, 22.9, 24.4, 24.9, 28.3, 33.8, 41.8, 43.3, 49.5, 54.2, 56.3, 59.4, 79.4, 126.1, 127.7, 128.1, 128.3, 128.7, 136.2, 138.8, 149.4, 164.0, 164.7, 170.8. − $[\alpha]_D^{20}$ = +32.0 (*c* = 1.4, $CHCl_3$). − $C_{31}H_{24}N_4O_6$ (566.69): calcd. C 65.70, H 7.47, N 9.89; found C 65.71, H 7.47, N 9.90.

(4*S*,5*R*,2′*S*,3′*R*)-1,5-Dimethyl-4-phenyl-3-[(3′-phenyl-2′-aziridinyl)-carbonyl]- imidazolidin-2-one (10): A solution of $AlMe_2Cl$ (0.51 mL, 1 M in hexane, 0.51 mmol) in CH_2Cl_2 (3 mL) was added dropwise at 0 °C to a solution of **3** (0.20 g, 0.46 mmol) in CH_2Cl_2

(13 mL). The mixture was stirred for 20 min and a solution of triethylamine (0.13 mL, 0.92 mmol) in CH_2Cl_2 (3 mL) added at 0 °C over 5 min. The reaction was quenched after 3 h with sat. $NaHCO_3$ (10 mL) and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and solvent evaporated under reduced pressure. The mixture was purified by flash chromatography (CH_2Cl_2:acetone 97:3) to give **10** (93 mg, 60%). m.p. 186−189 °C. − IR (nujol): $\tilde{\nu}$ = 3300, 1726, 1660 cm^{-1}. − ^1H NMR: δ = 0.82 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH*$_3$), 2.20 (bt, 1 H, *J* = 9.0 Hz, *NH*), 2.82 (s, 3 H, N*CH*$_3$), 3.15 (dd, 1 H, *J* = 2.2, 9.0 Hz, OCCHN*CH*Ph), 3.95 (dq, 1 H, *J* = 6.6, 8.7 Hz, PhCH*CH*CH$_3$), 4.27 (dd, 1 H, *J* = 2.2, 9.0 Hz, OC*CH*NCHPh), 5.34 (d, 1 H, *J* = 8.7 Hz, Ph*CH*CHCH$_3$), 7.12−7.41 (m, 10 H, ArH). − ^{13}C NMR: δ = 15.0, 28.2, 38.9, 42.0, 54.1, 59.7, 126.5, 126.9, 127.6, 128.4, 128.5, 128.6, 128.7, 136.0, 138.1, 155.4, 170.4. − $[\alpha]_D^{20}$ = +163.0 (*c* = 1.7, $CHCl_3$). − $C_{20}H_{21}N_3O_2$ (335.40): calcd. C 71.62, H 6.31, N 12.53; found C 71.64, H 6.30, N 12.53.

(4*R*,5*S*,4′*S*,5′*R*,1′′*S*)-4-[(1′,5′-Dimethyl-4′-phenylimidazolidin-2′-on-3′-yl)carbonyl]-2-(1′′-fluorenylmethoxycarbonylamino-3′′-methyl-1′′-butyl)-4,5-dihydro-5-phenyloxazole (12): *N*-Fluorenylmethoxycarbonyl-leucine chloride (0.33 g, 0.90 mmol) and a cat. amount of DMAP were added at room temp to a solution of **10** (0.15 g, 0.45 mmol) in CH_2Cl_2. After stirring for 4 h, the solution was quenched with sat. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and solvent evaporated under reduced pressure. The mixture was purified by flash chromatography (CH_2Cl_2/acetone 95:5) to give **12** (0.23 g, 75%). − ^1H NMR: δ = 0.81 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH*$_3$), 0.86 (d, 6 H, *J* = 5.1 Hz, $CH_2CH(CH_3)_2$), 1.48−1.74 (m, 3 H, *CH*$_2$*CH*(CH$_3$)$_2$), 2.81 (s, 3 H, N*CH*$_3$), 3.92 (dq, 1 H, *J* = 6.6, 8.7 Hz, PhCH*CH*CH$_3$), 4.19−4.28 (m, 1 H, FMOC), 4.34−4.48 (m, 2 H, FMOC), 4.56−4.68 (m, 1 H, HN*CH*CH$_2$), 5.37 (d, 1 H, *J* = 8.7 Hz, Ph*CH*CHCH$_3$), 5.39 (d, 1 H, *J* = 8.5 Hz, NHFMOC), 5.98 (d, 1 H, *J* = 6.6 Hz, OC*CH*CHPh), 6.09 (d, 1 H, *J* = 6.6 Hz, OCCH*CH*Ph), 7.15−7.80 (m, 18 H, ArH). − $[\alpha]_D^{20}$ = +82.0 (*c* = 1.3, $CHCl_3$). − $C_{41}H_{42}N_4O_5$ (670.80): calcd. C 73.41, H 6.31, N 8.35; found C 73.42, H 6.31, N 8.35.

(4*S*,5*R*,2′*S*,3′*R*,2′′*S*)-3[2′-(2′′-Fluorenylmethoxycarbonylamino-4′′-methylpentanoyl)amino-3′-hydroxy-3′-phenylpropionyl]-1,5-dimethyl-4-phenylimidazolidin-2-one (13): Boron trifluoride−diethyl ether (95 μL, 0.75 mmol) and water (20 μL) were added to a mixture of **12** (0.10 g, 0.15 mmol) and piperidine (33 μL, 0.30 mmol) in CH_2Cl_2 (10 mL) at room temp. After 4 h the reaction was quenched with sat. $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 and dried over Na_2SO_4. The solvent was evaporated at reduced pressure and, after flash chromatography (EtOAc/cyclohexane 1:1), pure **13** (67 mg, 65%) was obtained. − ^1H NMR: δ = 0.73 (d, 3 H, *J* = 6.6 Hz, PhCHCH*CH*$_3$), 0.77 (d, 6 H, *J* = 5.7 Hz, $CH_2CH(CH_3)_2$), 1.28−1.51 (bm, 3 H, *CH*$_2$*CH*(CH$_3$)$_2$), 2.76 (s, 3 H, N*CH*$_3$), 3.63 (dq, 1 H, *J* = 6.6, 8.1 Hz, PhCH*CH*CH$_3$), 4.02−4.21 (bm, 2 H, OC*CH*NHFmoc, FMOC), 4.25−4.43 (m, 2 H, FMOC), 5.08 (d, 1 H, *J* = 8.1 Hz, Ph*CH*CHCH$_3$), 5.10−5.20 (bm, 2 H, *NH*FMOC, OCCHN*CH*O), 6.39 (dd, 1 H, *J* = 3.3, 8.0 Hz, OC*CH*NCHO), 6.81 (bd, 1 H, *J* = 8.0 Hz, NHLeu), 7.03−7.81 (m, 18 H, ArH). − ^{13}C NMR: δ = 14.8, 22.8, 24.5, 28.2, 41.3, 47.1, 53.4, 54.0, 57.4, 59.9, 66.9, 75.3, 119.9, 126.3, 126.8, 127.0, 127.7, 128.1, 128.5, 135.7, 139.3, 141.2, 143.8, 154.9, 155.9, 169.3, 172.1. − $[\alpha]_D^{20}$ = +46.8 (*c* = 1.6, $CHCl_3$). − $C_{41}H_{44}N_4O_6$ (688.81): calcd. C 71.49, H 6.44, N 8.13; found C 71.50, H 6.45, N 8.13.

Methyl (2*S*,3*R*,2′*S*)-2-(2′-Fluorenylmethoxycarbonylamino-4′-methylpentanoyl)amino-3-hydroxy-3-phenylpropanoate (14): Hydrogen peroxide (45 μL, 30% p/v, 0.44 mmol) and LiOH (5.3 mg, 0.22 mmol) were added at 0 °C to a mixture of **13** (75 mg, 0.11 mmol) in THF (4 mL) and water (1 mL). The reaction was quenched with sat. Na_2SO_3 (2 mL), and the mixture extracted with EtOAc. The organic layer was dried over Na_2SO_4 and the solvent removed at reduced pressure to give **1** (19 mg, 90%). The aqueous layer was acidified to pH 2, extracted twice with EtOAc and the solvent removed at reduced pressure. The residue was treated with excess CH_2N_2 in Et_2O for 2 h and the solvent removed at reduced pressure to give **14** (44 mg, 75%). − ^1H NMR: (C_6D_6) δ = 0.76 (d, 6 H, *J* = 6.6 Hz, $CH_2CH(CH_3)_2$), 1.36 (s, 9 H, *tert*-Butyl), 1.38−1.68 (m, 3 H, *CH*$_2$*CH*(CH$_3$)$_2$), 3.16 (s, 3 H, COOCH$_3$), 3.65−3.71 (m, 2 H, OCC*HCH*Ph), 3.97−4.00 (m, 1 H, FMOC), 4.22−4.36 (m, 1 H, C*H*NFMOC), 4.39−4.51 (m, 2 H, FMOC), 4.75 (d, 1 H, *J* = 7.8 Hz, N*H*FMOC), 6.04 (bt. 1 H, N*H*Leu), 7.12−7.61 (m, 13 H, ArH). − ^{13}C NMR: (C_6D_6) δ = 21.9, 23.1, 24.8, 41.1, 41.2, 47.8, 51.6, 53.5, 60.0, 66.0, 120.2, 141.8, 144.3, 156.4, 170.0, 172.1. − MS: *m*/*z* = 530 (0.4) [M^+], 420 (3), 377 (4), 320 (7), 217 (8), 178 (100), 149 (79). − $C_{31}H_{34}N_2O_6$ (530.61): calcd. C 70.17, H 6.46, N 5.28; found C 70.15, H 6.46, N 5.29.

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