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Synthesis of Fmoc-protected (2*S*,3*S*)-2-hydroxy-3-amino acids from a furyl substituted chiral cyanohydrin

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Abstract—A stereoselective chemoenzymatic synthesis of Fmoc-protected (2*S*,3*S*)-2-hydroxy-3-amino acids **6** is described. After the formation of cyanohydrin **2** from 2-furaldehyde in the presence of R-oxynitrilase and subsequent protection, **3** was transformed into fully protected ethanolamines **5**. Ozonolysis provided the target compounds in good yields.

1. Introduction[1]

Although less abundant than α-amino acids, β-amino acids are also present in nature. While only a few occur in mammals, e.g. β-alanine and β-valine as catabolites of the cytosine or the thymine metabolism,[2] an increasing number is found in bacteria, sponges, tunicates and plants.[3] In the latter cases, the β-amino acids are not only catabolites, but also constituents of a variety of compounds that exhibit interesting biological properties. Among these is the anti-tumour active paclitaxel, first isolated from the bark of the pacific yew *Taxus brevifolia*.[4] Other examples are scytonemyn A from the blue-green alga *Scytonema* sp. with potential calcium antagonistic properties,[5] aminopeptidase B inhibitor bestatin, isolated from *Streptomyces olivoreticuli*,[6] aminopeptidase M inhibitor microginin 51-A, a hexapeptide from the cyanobacterium *Microcystis aeruginosa*,[7] and antimicrobially and insecticidally active jasplakinolide or jaspamide.[8]

Apart from this, β-peptides have attracted considerable attention since it was found that these compounds can fold to give stable secondary structures similar to those found in α-peptides.[9] Importantly, they are stable against enzymatic degradation.[10] Several biologically active β-peptides have been described.[11]

Here we describe a stereoselective chemoenzymatic synthesis of Fmoc-protected (2*S*,3*S*)-2-hydroxy-3-amino acids starting from 2-furaldehyde,[12] which were used in the solid phase synthesis of a completely α-hydroxylated β-hexapeptide.[1] So far, only two Fmoc-protected 2-hydroxy-3-amino acids have been described:[13] α-hydroxy-β-glycine[14] and 2-hydroxy-3-amino-pentanoic acid.[15]

To obtain the Fmoc-protected (2*S*,3*S*)-2-hydroxy-3-amino acids, a chemoenzymatic route described earlier[16] was further developed. The α-hydroxy-β-analogues of glycine, alanine, valine, leucine, phenylglycine, and phenylalanine (R′ = H, Me, *iso*-Pr, *iso*-Bu, Ph, and Bn, respectively) have been prepared.

2. Results and discussion

First, 2-furaldehyde was converted into (*S*)-cyanohydrin[17] **2** by an enzymatic reaction using R-oxynitrilase (E.C. 4.1.2.10) as present in ground, defatted almond meal[18] with high conversion and with high enantiomeric excess (99%) (Scheme 1). Subsequently, the crude cyanohydrin was protected at its hydroxyl function by means of *tert*-butyldimethylsilylchloride (TBS-Cl) and imidazole in DMF[19] to yield **3** in high yield after distillation (89% from **1**).

Next, the amine function and the amino acid side chain were introduced by either a two-step reduction[20] for **4a** or a Grignard addition–reduction sequence[21] **4b–f**.

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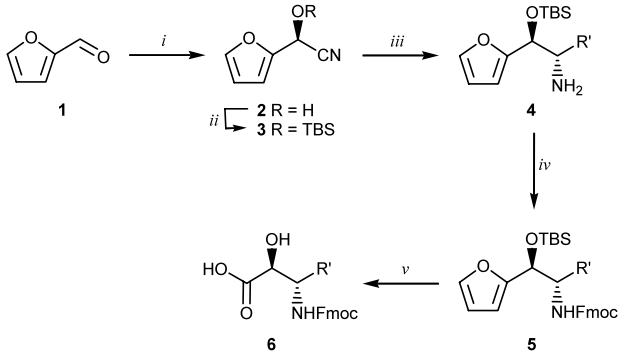


Scheme 1. *Reagents*: (*i*) R-Oxynitrilase, HCN, MTBE, pH 5.5; (*ii*) TBS-Cl, imidazole, DMF; (*iii*) 1. DibalH or R′MgX, Et_2O, 2. MeOH, 3. $NaBH_4$; (*iv*) Fmoc-Cl, CH_2Cl_2, $NaHCO_3$ (aq.); (*v*) 1. O_3, MeOH, 2. THF/MeCN/H_2O, 40°C.

To a solution of **3** in dry diethyl ether (−70°C) was added 1.2 equiv. of DIBALH in hexanes. The reaction was allowed to warm to −20°C before it was cooled again to −70°C. After addition of methanol and $NaBH_4$ at −70°C, the mixture was allowed to warm slowly to room temperature overnight, providing crude **4a** after work-up, which was used as such for Fmoc-protection.

For the introduction of the amino acid side chains R′ the appropriate Grignard reagent was added dropwise to a solution of **3** in diethyl ether. The reaction mixture was refluxed for 1 h, cooled to −20°C, and methanol was added. Subsequent stereoselective sodium borohydride reduction of the resulting imine provided the crude TBS protected ethanolamines **4b–f**, with the (1*S*,2*S*)-diastereoisomer as the major product (Table 1). The presence of the furan ring had a large positive influence on the stereoselectivity of the ethanolimine reduction by sodium borohydride compared to the synthesis starting from crotonaldehyde. In the latter case d.e.'s were found to be lower than 20% in the presence of hindered side groups like *iso*-propyl and *iso*-butyl.[22]

Table 1. Stereoselectivity of the addition–reduction sequence and yield after Fmoc-protection

	R =	(1*S*,2*S*)/(1*S*,2*R*)-**4**[a]	Yield **5**[b]
a	H	–	56
b	Me	95/5	80
c	*iso*-Propyl	90/10	48[c]
d	*iso*-Butyl	80/20	61
e	Phenyl	95/5	79
f	Benzyl	80/20	43

[a] (1*S*,2*S*)/(1*S*,2*R*)-Ratio determined by NMR.
[b] Yields after purification from **3**.
[c] See text.

At this stage, the crude *O*-protected ethanolamines **4** were *N*-protected using Fmoc-Cl in CH_2Cl_2/H_2O. Generally, the yield for the protected ethanolamines (from **3**) was good (Table 1). Introduction of the *iso*-propyl side chain followed by imine reduction and amine protection was problematic, with yields of 20–25% for **5c**. Yields were improved to 48% by adding a catalytic amount of copper(I) bromide and using THF as the solvent, as described by Weiberth and Hall[23] for sterically demanding Grignard reagents and by Fmoc-protection in the absence of water, using dry dichloromethane and DIPEA.[24]

Finally, the furan ring was readily oxidised by ozonolysis to obtain the carboxylic acid.[25] Taking advantage of the β-amide proton present,[26] a one-pot oxidation/silyl–deprotection step was foreseen to obtain the desired Fmoc-protected α-hydroxy-β-amino acids. Thus, a solution of the fully protected (2′-furyl)-ethanolamine **5** in methanol was cooled to −70°C. A mixture of oxygen and ozone was bubbled through until no more starting material could be observed (TLC). The mixture was left to warm to room temperature, while oxygen was passed through to remove all remaining ozone from the solution. To obtain complete deprotection by migration of the silyl group, the methanol was first evaporated, and the resulting yellow oil was dissolved in a mixture of THF, acetonitrile, and water (3/1/1, v/v/v), which was stirred for 2 h at 40°C. After work-up, the Fmoc-protected 2-hydroxy-3-amino acids **6** were obtained from the resulting yellow oil as white solids by crystallisation from EtOAc/pentane or, in the case of **6a**, simply by washing with diethyl ether (Table 2).

Table 2. Yield and (2*S*,3*S*)/(2*S*,3*R*)-ratio of **6** after ozonolysis–desilylation

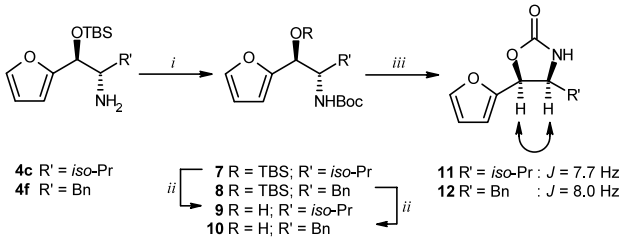
	R =	(2*S*,3*S*)/(2*S*,3*R*)[a]	Yield[b]
a	H	–	80
b	Me	95/5	61
c	*iso*-Propyl	88/12	52
d	*iso*-Butyl	80/20	61
e	Phenyl	95/5	69
f	Benzyl	80/20	52

[a] (2*S*,3*S*)/(2*S*,3*R*)-Ratio determined by NMR.
[b] Yields after purification from **5**.

2.1. Confirmation of the stereochemistry in 4

For the addition–reduction sequence discussed above, only formation of the *anti* diastereoisomer as the major isomer is described in literature, but all examples deal with sterically less demanding side chains (R′). Thus, in order to confirm the formation of sterically demanding (1*S*,2*S*)-ethanolamines crude ethanolamines **4c** and **4f** were converted into their respective oxazolidinones (Scheme 2). Protection with the *tert*-butyloxocarbonyl (Boc) function, using Boc-anhydride in dichloromethane and a saturated aqueous sodium hydrogencarbonate solution, yielded fully protected **7** and **8**. The alcohol function was desilylated with tetrabutylammonium fluoride (TBAF) in THF to yield **9** and **10** as white solids. Formation of the required oxazolidinones **9** and **10** was accomplished by sodium hydride assisted ring closure in a DMF/THF mixture.[27] Cou-

pling constants of the vicinal protons ($J=7.7$ Hz for **11** and 8.0 Hz for **12**) were in accordance with those reported in literature for *syn* orientated protons in oxazolidinones,[27,28] thus confirming the formation of the *anti*-diastereoisomers of the sterically hindered ethanolamines **4c** and **4f**.



Scheme 2. *Reagents*: (*i*) Boc_2O, CH_2Cl_2, $NaHCO_3$ (aq.); (*ii*) TBAF, THF; (*iii*) NaH, DMF, THF.

3. Concluding remarks

A direct chemoenzymatic route towards Fmoc-protected (2*S*,3*S*)-2-hydroxy-3-amino acids has been developed. 2-Furaldehyde was readily converted into its corresponding (*S*)-cyanohydrin with high enantioselectivity by R-oxynitrilase as present in defatted almond meal. Protection with the *tert*-butyldimethylsilyl group proceeded in high yield. Subsequent introduction of the amino acid side chain by a Grignard addition-reduction sequence, or by a two-step reduction (in the case of α-hydroxy-β-glycine), followed by Fmoc-protection of the crude ethanolamine gave in general good results, both with regard to yield and to diastereoselectivity. Introduction of the sterically demanding *iso*-propyl group was greatly facilitated by addition of a catalytic amount of copper(I) bromide to the Grignard reaction and by altering conditions for Fmoc-protection. Taking advantage of the tendency of the silyl-protecting group to migrate, both oxidation of the furan ring and desilylation could be achieved in one step to yield the required Fmoc-protected (2*S*,3*S*)-2-hydroxy-3-amino acids after crystallisation.

4. Experimental

4.1. General

Column chromatography was performed on Baker silica gel (0.063–0.200 mm). For TLC analysis, Schleicher and Schuell F1500/LS 254 silica plates were used. Spots were visualised with ultraviolet light, potassium permanganate spray [solution of $KMnO_4$ (5%) and $NaHCO_3$ (0.5%) in water] or by molybdene spray [solution of conc. sulfuric acid (10 mL) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (2.5 g) in 90 mL of water] and heating. ^1H and ^{13}C NMR were recorded with a Bruker AC 200 instrument. Tetramethylsilane was used as internal standard; δ in ppm, J in Hz. Infrared spectra were obtained with a Perkin–Elmer FT-IR Paragon 1000 spectrometer equipped with a Golden Gate Diamond ATR, using reflectance technique (neat, 4000–300 cm^{-1}, res. 4 cm^{-1}). Melting points were determined with a Büchi melting point apparatus and are uncorrected. The enantiomeric purity was determined by HPLC using a Daicel Chiralcel OD column; with hexane/2-propyl alcohol (99.75/0.25, v/v) as eluent. Optical rotations were measured with a Propol automatic polarimeter, at the sodium D line ($\lambda=589$ nm). Ozone was generated with a Fisher Ozon-Generator 500. Analytical samples of **6b–f** were prepared by recrystallisation from EtOAc/hexane.

4.1.1. (*S*)-2-(2′-Furyl)-2-hydroxy-acetonitrile 2. A suspension of 30 g almond meal in 45 mL of 0.10 M citric acid buffer pH 5.5, 19.2 g of freshly distilled 2-furaldehyde **1** (200 mmol) and 50 mL of MTBE was stirred at 4°C. Meanwhile a fresh solution of HCN in MTBE was prepared: a solution of 440 mmol of NaCN (2.1 equiv.) in 400 mL of H_2O was acidified to pH 5.5 with AcOH (**CAUTION**: toxic hydrogen cyanide gas may evolve. Work in a well ventilated hood.). The hydrogen cyanide solution was extracted three times with 175 mL of MTBE. The combined MTBE layers were transferred into a dropping funnel. After 1 h at 4°C the HCN solution was added dropwise to the enzyme mixture. The whole was allowed to stir over the weekend, filtered, and dried with $MgSO_4$. The solvent was evaporated to yield the crude product (26.1 g). E.e. 98.6% (HPLC; determined as TBDPS ether).—Yellow oil.—^1H NMR ($CDCl_3$) $\delta=3.54$ (br s, 1H, O*H*), 5.55 (s, 1H, *H-2*), 6.44 (dd, 1H, $J=1.8$, $J=3.3$, *H-4′*), 6.61 (d, 1H, $J=3.3$, *H-3′*), 7.49 (d, 1H, $J=1.8$, *H-5′*).—^{13}C NMR ($CDCl_3$) $\delta=56.4$ (*C-2*), 109.8, 110.6 (*C-3′*, *C-4′*), 116.9 (*C-1*), 143.9 (*C-5′*), 147.3 (*C-2′*).

4.1.2. (*S*)-2-(2′-Furyl)-2-*O*-(*tert*-butyldimethylsilyl)-acetonitrile 3. To a solution of 36 g of *tert*-butyldimethylsilylchloride (240 mmol; 1.2 equiv.) in 250 mL of DMF (0°C) was added 32.7 g of imidazole (480 mmol; 2.4 equiv.). After 15 min the crude cyanohydrin **2** was added and the mixture was allowed to warm to rt overnight. Water and diethyl ether were added and the layers separated. The organic phase was washed with water and brine, dried ($MgSO_4$) and the solvent was evaporated. The product was obtained by distillation under reduced pressure (96°C, 150 Pa) from the resulting oil. Yield: 88%.—Colourless oil.—IR: ν (cm^{-1}): 1500, 1473, 1464, 1254, 1146, 1070, 1014, 1006, 834, 779, 740.—^1H NMR ($CDCl_3$) $\delta=0.14$, 0.16 (2×s, 2×3H, 2×C*H*$_3$Si), 0.92 (s, 9H, (C*H*$_3$)$_3$C), 5.56 (s, 1H, *H-2*), 6.40 (dd, 1H, $J=1.8$, $J=3.3$, *H-4′*), 6.61 (d, 1H, $J=0.7$, $J=3.3$, *H-3′*), 7.49 (d, 1H, $J=0.7$, $J=1.8$, *H-5′*).—^{13}C NMR ($CDCl_3$) $\delta=-5.4$ (*C*H$_3$Si), 18.0 ((CH$_3$)$_3$*C*), 25.3 ((*C*H$_3$)$_3$C), 57.9 (*C-2*), 109.3, 110.6 (*C-3′*, *C-4′*), 117.1 (*C-1*), 143.6 (*C-5′*), 148.3 (*C-2′*).—$[\alpha]_D^{20}=18.9$ (*c* 5, $CHCl_3$).

4.1.3. (1*S*)-1-(2′-Furyl)-1-*O*-(*tert*-butyldimethylsilyl)-2-ethylamine 4a. To a solution (−70°C) of 4.74 g of **3** (20 mmol) in 150 mL of dry diethyl ether was added 24 mmol of DibalH (24 mL of 1 M in hexanes; 1.2 equiv.). The temperature was allowed to rise to −20°C, lowered to −70°C and 60 mL of MeOH was added, followed by 1.51 g of $NaBH_4$ (40 mmol; 2 equiv.). The mixture was

allowed to warm slowly to rt, diethyl ether was added and the organic layer was washed with 2N NaOH, water and brine, dried ($MgSO_4$) and the solvent evaporated. The resulting crude compound was used without purification in the next reaction.—Yellow oil.—^{1}H NMR ($CDCl_3$) $\delta = -0.05$, 0.07 (2×s, 2×3H, 2×CH_3Si), 0.89 (s, 9H, (CH_3)$_3$C), 1.37 (br s, 2H, NH_2), 2.90 (dd, 1H, $J = 4.9$, $J = 13.2$, *H-2*), 2.99 (dd, 1H, $J = 5.9$, $J = 13.2$, *H-2*), 4.6–4.71 (m, 1H, *H-1*), 6.21 (dd, 1H, $J = 0.9$, $J = 3.3$, *H-3′*), 6.32 (dd, 1H, $J = 1.8$, $J = 3.3$, *H-4′*), 7.35 (dd, 1H, $J = 0.9$, $J = 1.8$, *H-5′*).—^{13}C NMR ($CDCl_3$) $\delta = -5.5$, -5.3 (2×*C*H$_3$Si), 17.8 ((CH$_3$)$_3$*C*), 18.6 (*C-3*), 25.5 ((*C*H$_3$)$_3$C), 51.5 (*C-2*), 73.8 (*C-1*), 107.3, 109.7 (*C-3′*, *C-4′*), 141.3 (*C-5′*), 154.7 (*C-2′*).

4.2. General procedure for the Grignard reaction (except for 4.2.2)

Per mmol of **3** in 3 mL of dry diethyl ether was added dropwise 1.2 mmol of Grignard reagent in a total volume of 3 mL of dry diethyl ether. The mixture was refluxed for 1 h, cooled to −70°C and 2 mL of MeOH was added dropwise followed by 2 mmol of $NaBH_4$ (78 mg, 2 equiv.) and allowed to warm to rt overnight. Diethyl ether and water were added. The water layer was extracted three times with diethyl ether, the combined organic layers dried ($MgSO_4$), and the solvent was evaporated. The crude products were used without purification in the next step.

4.2.1. (1*S*,2*S*)-1-(2′-Furyl)-1-*O*-(*tert*-butyldimethylsilyl)-2-propylamine 4b. Yellow oil.—^{1}H NMR ($CDCl_3$) $\delta = -0.13$, 0.03 (2×s, 2×3H, 2×CH_3Si), 0.86 (s, 9H, (CH_3)$_3$C), 1.03 (d, 3H, $J = 6.6$, *H-3*), 1.50 (br s, 2H, NH_2), 3.12 (dq, 1H, $J = 5.9$, $J = 6.6$, *H-2*), 4.41 (d, 1H, $J = 5.9$, *H-1*), 6.21 (dd, 1H, $J = 0.7$, $J = 3.1$, *H-3′*), 6.31 (dd, 1H, $J = 1.8$, $J = 3.1$, *H-4′*), 7.36 (dd, 1H, $J = 0.7$, $J = 1.8$, *H-5′*).—^{13}C NMR ($CDCl_3$) $\delta = -5.5$, -5.3 (2×CH_3Si), 17.8 ((CH$_3$)$_3$*C*), 18.6 (*C-3*), 25.5 ((*C*H$_3$)$_3$C), 51.5 (*C-2*), 73.8 (*C-1*), 107.3, 109.7 (*C-3′*, *C-4′*), 141.3 (*C-5′*), 154.7 (*C-2′*).

4.2.2. (1*S*,2*S*)-1-(2′-Furyl)-1-*O*-(*tert*-butyldimethylsilyl)-3-methyl-2-butylamine 4c. Compound **3** (20 mmol) was dissolved in 40 mL of dry THF and the mixture was cooled to −35°C. Iso-propylmagnesiumchloride (2 M in diethyl ether, 11 mL, 1.1 equiv.) was added dropwise, followed by 0.34 mmol of Cu(I)Br (50 mg, 1.7 mol%). The mixture was allowed to slowly warm to rt. When the reaction had come to completion (TLC), the solution was cooled to −20°C and 20 mL of dry MeOH was added. After stirring for 5 min it was further cooled to −70°C and 1.52 g of $NaBH_4$ (40 mmol, 2 equiv.) was added. The mixture was allowed to warm to rt overnight. Diethyl ether, water and brine were added, the layers separated and the water layer extracted twice with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and the solvent evaporated.—Dark brown oil.—^{1}H NMR ($CDCl_3$) $\delta = 0.03$, 0.10 (2×s, 2×3H, 2×CH_3Si), 0.74–0.98 (m, 15H, (CH_3)$_3$C, (CH_3)$_2$C), 1.61–1.92 (m, 3H, *H-3*, NH_2), 2.82 (dd, 1H, $J = 5.5$, $J = 6.6$, *H-2*), 4.59 (d, 1H, $J = 6.6$, *H-1*), 6.32 (dd, 1H, $J = 0.7$, $J = 3.3$, *H-3′*), 6.24 (dd, 1H, $J = 1.8$, $J = 3.3$, *H-4′*), 7.37 (dd, 1H, $J = 0.7$, $J = 1.8$, *H-5′*).—^{13}C NMR ($CDCl_3$) $\delta = -5.4$ (s, 2×CH_3Si), 16.7, 20.2 ((*C*H$_3$)$_2$CH), 17.8 ((CH$_3$)$_3$*C*), 25.5 ((*C*H$_3$)$_3$C), 28.4 (*C-3*), 61.0 (*C-2*), 70.4 (*C-1*), 107.8, 110.0 (*C-3′*, *C-4′*), 141.4 (*C-5′*), 154.7 (*C-2′*).

4.2.3. (1*S*,2*S*)-1-(2′-Furyl)-1-*O*-(*tert*-butyldimethylsilyl)-4-methyl-2-pentylamine 4d. Dark brown oil.—^{1}H NMR ($CDCl_3$) $\delta = -0.12$, 0.03 (s, 3H, CH_3Si), 0.78–1.15 (m, 16H, (CH_3)$_3$C, (CH_3)$_2$CH, (CH$_3$)$_2$C*H*), 1.41–1.86 (m, 4H, NH_2, *H-3*), 3.03 (ddd, 1H, $J = 4.4$, $J = 5.1$, $J = 9.3$, *H-2*), 4.47 (d, 1H, $J = 5.1$, *H-1*), 6.21 (dd, 1H, $J = 0.7$, $J = 3.3$, *H-3′*), 6.33 (dd, 1H, $J = 1.8$, $J = 3.3$, *H-4′*), 7.40 (dd, 1H, $J = 0.7$, $J = 1.8$, *H-5′*).—^{13}C NMR ($CDCl_3$) $\delta = -5.5$, -5.3 (2×*C*H$_3$Si), 17.8 ((CH$_3$)$_3$*C*), 21.8, 23.3 ((*C*H$_3$)$_2$CH), 24.5 (*C-4*), 25.5 ((*C*H$_3$)$_3$C), 41.9 (*C-3*), 54.0 (*C-2*), 72.7 (*C-1*), 107.6, 109.7 (*C-3′*, *C-4′*), 141.4 (*C-5′*), 154.4 (*C-2′*).

4.2.4. (1*S*,2*S*)-1-(2′-Furyl)-1-*O*-(*tert*-butyldimethylsilyl)-2-phenyl-2-ethylamine 4e. Dark yellow oil.—^{1}H NMR ($CDCl_3$) $\delta = -0.27$, -0.24 (2×s, 2×3H, 2×CH_3Si), 0.71 (s, 9H, (CH_3)$_3$C), 1.51 (br s, 2H, NH_2), 4.21 (d, 1H, $J = 7.3$, *H-2*), 4.65 (d, 1H, $J = 7.3$, *H-1*), 6.22 (dd, 1H, $J = 0.7$, $J = 3.3$, *H-3′*), 6.32 (dd, 1H, $J = 1.8$, $J = 3.3$, *H-4′*), 7.32 (m, 6H, C*H* Ph, *H-5′*).—^{13}C NMR ($CDCl_3$) $\delta = -5.7$, -5.5 (2×CH_3Si), 17.8 ((CH$_3$)$_3$*C*), 25.5 ((*C*H$_3$)$_3$C), 60.5 (*C-2*), 73.8 (*C-1*), 107.9, 110.0 (*C-3′*, *C-4′*), 127.1, 127.6, 127.8 (*C*H Ph), 141.7 (*C-5′*), 142.4 (C_q Ph), 154.8 (*C-2′*).

4.2.5. (1*S*,2*S*)-1-(2′-Furyl)-1-*O*-(*tert*-butyldimethylsilyl)-3-phenyl-2-propylamine 4f. Brown oil.—^{1}H NMR ($CDCl_3$) $\delta = -0.14$, 0.04 (2×s, 2×3H, 2×CH_3Si), 0.89 (s, 9H, (CH_3)$_3$C), 1.26 (br s, 2H, NH_2), 2.45 (dd, 1H, $J = 9.3$, $J = 13.5$, *H-3a*), 3.04 (dd, 1H, $J = 4.4$, $J = 13.5$, *H-3b*), 3.31 (ddd, 1H, $J = 4.4$, $J = 6.0$, $J = 9.3$, *H-2*), 4.54 (d, 1H, $J = 6.0$, *H-1*), 6.28 (d, 1H, $J = 3.1$, *H-3′*), 6.36 (dd, 1H, $J = 1.8$, $J = 3.1$, *H-4′*), 7.25 (m, 6H, C*H* Ph, *H-5′*).—^{13}C NMR ($CDCl_3$) $\delta = -5.6$, -5.4 (2×*C*H$_3$Si), 17.7 ((CH$_3$)$_3$*C*), 25.4 ((*C*H$_3$)$_3$C), 38.8 (*C-3*), 57.1 (*C-2*), 71.7 (*C-1*), 107.8, 109.8 (*C-3′*, *C-4′*), 125.9, 127.9, 128.9 (*C*H Ph), 138.7 (C_q Ph), 141.5 (*C-5′*), 154.0 (*C-2′*).

4.3. General procedure for Fmoc-protection (except 4.3.3)

To a vigorously stirred mixture of 3 mL of dichloromethane and 6 mL of saturated $NaHCO_3$ (aq.) per mmol of **4** was added 1.4 equiv. of Fmoc-Cl. After the reaction had come to completion (TLC), 6 mL of dichloromethane and 3 mL of water were added, and the layers separated. The organic phase was washed once with brine, dried ($MgSO_4$), and the solvent evaporated. The crude compound was purified by column chromatography (pet. ether 40–60/EtOAc 95/5, v/v). Yields from **3**.

4.3.1. (1*S*)-2-*N*-(9*H*-Fluorenylmethoxycarbonyl)-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)-ethane 5a. Yield: 56%.—Yellowish oil.—IR: ν (cm^{-1}) 3346, 1706, 1508, 1472, 1463, 1450, 1250, 1148, 1083, 1005, 835, 777, 758,

735.—^{1}H NMR ($CDCl_3$) δ = −0.05, 0.07 (2×s, 2×3H, 2×CH_3Si), 0.89 (s, 9H, (CH_3)$_3$C), 3.39–3.65 (m, 2H, *H-2*), 4.17–4.27 (m, 1H, C*H* Fmoc), 4.34–4.41 (m, 2H, CH_2 Fmoc), 4.82 (dd, 1H, *J* = 5.1, *J* = 7.0, *H-1*), 5.08 (t, 1H, *J* = 5.7, N*H*), 6.24 (d, 1H, *J* = 3.1, *H-3′*), 6.32 (dd, 1H, *J* = 1.8, *J* = 3.1, *H-4′*), 7.34 (m, 5H, *CH* Ph Fmoc, *H-5′*), 7.58 (d, 2H, *J* = 7.3, C*H* Ph Fmoc), 7.76 (d, 2H, *J* = 7.0, C*H* Ph Fmoc).—^{13}C NMR ($CDCl_3$) δ = −5.6, −5.5 (2×CH_3Si), 17.7 ((CH$_3$)$_3$*C*), 25.3 ((*C*H$_3$)$_3$C), 45.7 (*C-2*), 46.7 (*C*H Fmoc), 66.2 (*C*H$_2$ Fmoc), 66.8 (*C-1*), 106.5, 109.7 (*C-3′*, *C-4′*), 119.5, 124.6, 126.5, 127.2 (*C*H Ph Fmoc), 140.8, 143.5 (2×C_q Fmoc), 141.5 (*C-5′*), 154.1 (*C-2′*), 155.9 (N*C*O).—HRMS (ESI) *m*/*z* Found: 486.2124 [M+Na]$^+$, calcd: 486.2077.—$[\alpha]_D^{20}$ = −21.6 (*c* 1, $CHCl_3$).

4.3.2. (1*S*,2*S*)-2-*N*-(9*H*-Fluorenylmethoxycarbonyl)-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)-propane 5b. Yield: 80%.—Colourless oil.—IR: *v* (cm^{-1}) 3337, 17.8, 1505, 1472, 1463, 1450, 1241, 1073, 1053, 1006, 835, 777, 758, 735.—^{1}H NMR ($CDCl_3$) δ = −0.08, 0.03 (2×s, 2×3H, 2×CH_3Si), 0.91 (s, 9H, (CH_3)$_3$C), 1.15 (d, 3H, *J* = 6.8, *H-3*), 4.01–4.14 (m, 1H, *H-2*), 4.26 (t, 1H, *J* = 6.8, C*H* Fmoc), 4.34–4.42 (m, 2H, CH_2 Fmoc), 4.90 (d, 1H, *J* = 3.7, *H-1*), 5.10 (d, 1H, *J* = 8.8, N*H*), 6.28 (d, 1H, *J* = 3.3, *H-3′*), 6.35 (dd, 1H, *J* = 1.8, *J* = 3.3, *H-4′*), 7.27–7.44 (m, 5H, *CH* Ph Fmoc, *H-5′*), 7.65 (d, 2H, *J* = 7.1, C*H* Ph Fmoc), 7.86 (d, 2H, *J* = 7.1, C*H* Ph Fmoc).—^{13}C NMR ($CDCl_3$) δ = −5.4, −5.1 (2×CH_3Si), 15.0 (*C-3*), 18.0 ((CH$_3$)$_3$*C*), 25.7 ((*C*H$_3$)$_3$C), 47.1 (*C*H Fmoc), 51.2 (*C-2*), 66.5 (*C*H$_2$ Fmoc), 71.0 (*C-1*), 107.0, 110.0 (*C-3′*, *C-4′*), 119.8, 125.0, 126.9, 127.5 (*C*H Ph Fmoc), 141.2, 143.9 (C_q Fmoc), 141.6 (*C-5′*), 154.5 (*C-2′*), 155.6 (N*C*O).—HRMS (ESI) *m*/*z* Found: 500.2287 [M+Na]$^+$, calcd: 500.2233.—$[\alpha]_D^{20}$ = −28.4 (*c* 1, $CHCl_3$).

4.3.3. (1*S*,2*S*)-2-*N*-(9*H*-Fluorenylmethoxycarbonyl)-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)-3-methyl-butane 5c. To a well stirred solution of crude **4c** in CH_2Cl_2 (10 mL per mmol) were added 2 mmol of Fmoc-Cl (0.52 g) and 1 mmol of DIPEA. When the reaction had come to completion (TLC), the mixture was washed with water and brine. The organic layer was dried ($MgSO_4$), the solvent evaporated and the crude compound purified by column chromatography. Yield: 48%.—Colourless oil.—IR: *v* (cm^{-1}) 3330, 1699, 1506, 1473, 1464, 1450, 1239, 1087, 1004, 836, 776, 757, 734.—^{1}H NMR ($CDCl_3$) δ = −0.15, 0.03 (2×s, 2×3H, 2×CH_3Si), 0.86 (s, 9H, (CH_3)$_3$C), 0.90 (d, 3H, *J* = 7.3, CH_3CH), 0.95 (d, 3H, *J* = 6.8, CH_3CH), 1.72–1.91 (m, 1H, *H-3*), 3.91 (ddd, 1H, *J* = 6.0, *J* = 10.4, *J* = 10.8, *H-2*), 4.09–4.36 (m, 2H, CH_2 Fmoc), 4.37–4.50 (m, 1H, C*H* Fmoc), 4.77 (d, 1H, J = 6.0, *H-1*), 4.85 (d, 1H, *J* = 10.8, N*H*), 6.26 (d, 1H, *J* = 3.1, *H-3′*), 6.31 (dd, 1H, *J* = 1.8, J = 3.1, *H-4′*), 7.25–7.46 (m, 5H, *CH* Ph Fmoc, *H-5′*), 7.56 (d, 1H, *J* = 5.1, C*H* Ph Fmoc), 7.64 (d, 1H, *J* = 8.2, C*H* Ph Fmoc), 7.77 (d, 2H, *J* = 6.9, C*H* Ph Fmoc).—^{13}C NMR ($CDCl_3$) δ = −5.6, −5.4 (2×CH_3Si), 16.8, 20.2 ((*C*H$_3$)$_2$C-3), 17.8 ((CH$_3$)$_3$*C*), 25.4 ((*C*H$_3$)$_3$C), 28.1 (*C-3*), 47.0 (*C*H Fmoc), 59.7 (*C-2*), 66.4 (*C*H$_2$ Fmoc), 69.0 (*C-1*), 107.4, 110.0 (*C-3′*, *C-4′*), 119.6, 124.8, 126.7, 127.3 (*C*H Ph Fmoc), 141.0, 143.7, 144.0 (C_q Fmoc), 141.5 (*C-5′*), 154.4 (*C-2′*), 156.3 (N*C*O).—HRMS (ESI) *m*/*z* Found: 528.2490 [M+Na]$^+$, calcd: 528.2546.—$[\alpha]_D^{20}$ = −41.6 (*c* 1, $CHCl_3$).

4.3.4. (1*S*,2*S*)-2-*N*-(9*H*-Fluorenylmethoxycarbonyl)-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)-4-methyl-pentane 5d. Yield: 61%.—Colourless oil.—IR: *v* (cm^{-1}) 3339, 1710, 1505, 1471, 1450, 1250, 1076, 1005, 836, 777, 758, 736.—^{1}H NMR ($CDCl_3$) δ = −0.08, 0.03 (2×s, 2×3H, 2×CH_3Si), 0.81–0.96 (m, 16H, (CH_3)$_3$C, CH_3CH, *H-4*), 1.12–1.33 (m, 2H, *H-3*), 3.96–4.09 (m, 1H, *H-2*), 4.18–4.26 (m, 1H, C*H* Fmoc), 4.36–4.45 (m, 2H, CH_2 Fmoc), 4.76 (br s, 1H, N*H*), 4.81 (d, 1H, *J* = 3.5, *H-1*), 6.22 (d, 1H, *J* = 3.1, *H-3′*), 6.31 (dd, 1H, *J* = 1.8, *J* = 3.1, *H-4′*), 7.29–7.33 (m, 5H, *CH* Ph Fmoc, *H-5′*), 7.61 (d, 2H, *J* = 7.3, C*H* Ph Fmoc), 7.64 (d, 2H, *J* = 8.2, C*H* Ph Fmoc), 7.77 (d, 2H, *J* = 7.1, C*H* Ph Fmoc).—^{13}C NMR ($CDCl_3$) δ = −5.3, −5.2 (2×CH_3Si), 18.1 ((CH$_3$)$_3$*C*), 21.5, 23.6 ((*C*H$_3$)$_2$C-4), 24.6 (*C-4*), 25.7 ((*C*H$_3$)$_3$C), 38.6 (*C-3*), 47.2 (*C*H Fmoc), 53.8 (*C-2*), 66.5 (*C*H$_2$ Fmoc), 71.3 (*C-1*), 107.2, 110.0 (*C-3′*, *C-4′*), 119.8, 125.0, 126.9, 127.5 (*C*H Ph Fmoc), 141.5, 143.8 (C_q Fmoc), 141.6 (*C-5′*), 154.5 (*C-2′*), 156.0 (N*C*O).—HRMS (ESI) *m*/*z* Found: 542.2672 [M+Na]$^+$, calcd: 542.2703.—$[\alpha]_D^{20}$ = −34.9 (*c* 1, $CHCl_3$).

4.3.5. (1*S*,2*S*)-2-*N*-(9*H*-Fluorenylmethoxycarbonyl)-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)-2-phenyl-ethane 5e. Yield: 79%.—White solid, mp 88°C.—IR *v* (cm^{-1}) 3320, 1690, 1542, 1472, 1450, 1258, 1241, 1087, 1027, 1009, 836, 778, 756, 731, 698.—^{1}H NMR ($CDCl_3$) δ = −0.13, −0.02 (2×s, 2×3H, 2×CH_3Si), 0.82 (m, 9H, (CH_3)$_3$C), 4.25 (m, 2H, CH_2 Fmoc), 4.40 (m, 1H, C*H* Fmoc), 5.01 (m, 2H, *H-1*, *H-2*), 5.63 (d, 1H, *J* = 6.8, N*H*), 5.95 (d, 1H, *J* = 3.1, *H-3′*), 6.23 (dd, 1H, *J* = 1.8, *J* = 3.1, *H-4′*), 7.30 (m, 10H, C*H* Ph Fmoc, C*H* Ph, *H-5′*), 7.57 (m, 2H, C*H* Ph Fmoc), 7.76 (d, 2H, *J* = 7.3, C*H* Ph Fmoc).—^{13}C NMR ($CDCl_3$) δ = −5.7, −5.4 (2×CH_3Si), 17.8 ((CH$_3$)$_3$*C*), 25.4 ((*C*H$_3$)$_3$C), 46.9 (*C*H Fmoc), 59.7 (*C-2*), 66.6 (*C*H$_2$ Fmoc), 72.5 (*C-1*), 107.8, 109.9 (*C-3′*, *C-4′*), 119.7, 124.8, 126.8, 127.3, 127.4, 127.9 (*C*H Ph, Fmoc), 138.9 (C_q Ph), 141.0, 143.7, 143.8 (C_q Fmoc), 141.5 (*C-5′*), 153.6 (*C-2′*), 155.5 (N*C*O).—HRMS (ESI) *m*/*z* Found: 562.2296 [M+Na]$^+$, calcd: 562.2390.—$[\alpha]_D^{20}$ = −26.1 (*c* 1, $CHCl_3$).

4.3.6. (1*S*,2*S*)-2-*N*-(9*H*-Fluorenylmethoxycarbonyl)-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)-3-phenyl-propane 5f. Yield: 43%.—Yellowish, viscous oil.—IR: *v* (cm^{-1}) 3336, 1710, 1504, 1471, 1465, 1450, 1250, 1074, 1041, 1005, 835, 777, 756, 734, 699.—^{1}H NMR ($CDCl_3$) δ = −0.10, 0.04 (2×s, 2×3H, 2×CH_3Si), 0.92 (m, 9H, (CH_3)$_3$C), 2.81 (dd, 1H, *J* = 9.1, *J* = 14.4, *H-3*), 2.87 (dd, 1H, *J* = 5.1, *J* = 14.4, *H-3*), 4.15 (t, 1H, *J* = 7.3, *CH* Fmoc), 4.25 (m, 3H, *CH*$_2$ Fmoc, *H-2*), 4.86 (d, 1H, *J* = 9.0, N*H*), 4.89 (d, 1H, *J* = 4.5, *H-1*), 6.29 (d, 1H, *J* = 3.1, *H-3′*), 6.36 (dd, 1H, *J* = 1.8, *J* = 3.1, *H-4′*), 7.29 (m, 10H, C*H* Ph Fmoc, C*H* Ph, *H-5′*), 7.49 (m, 2H, C*H* Ph Fmoc), 7.76 (d, 2H, *J* = 7.1, C*H* Ph Fmoc).—^{13}C NMR ($CDCl_3$) δ = −5.7, −5.4 (2×CH_3Si), 17.8 ((CH$_3$)$_3$*C*), 25.5 ((*C*H$_3$)$_3$C), 35.4 (*C-3*), 46.8 (*C*H Fmoc), 56.5 (*C-2*), 66.3 (*C*H$_2$ Fmoc), 69.9 (*C-1*), 107.5, 109.9 (*C-3′*, *C-4′*), 119.6, 125.0, 126.2, 127.8, 127.4,

128.2, 129.0 (*C*H Ph, Fmoc), 138.0 (C_q Ph), 141.0, 143.8 (C_q Fmoc), 141.8 (*C-5'*), 154.0 (*C-2'*), 155.6 (N*C*O).—HRMS (ESI) *m/z* Found: 576.2349 $[M+Na]^+$, calcd: 576.2546.—$[\alpha]_D^{20} = -17.6$ (*c* 1,$CHCl_3$).

4.4. General procedure for ozonolysis-deprotection

Compound **5** was dissolved in 10 mL of MeOH (**5e** was dissolved in 10 mL of $MeOH/CH_2Cl_2$, 1/1, v/v) per mmol and cooled to −70°C. A gas stream of O_3/O_2 was bubbled through until no starting material could be detected (TLC). To remove excess ozone, oxygen was bubbled through for 30 min, after which the mixture was allowed to warm to rt. The solvent was evaporated and the resulting oil stirred for 2 h in a mixture of $THF/CH_3CN/H_2O$ (3/1/1, v/v/v), 5 mL per mmol **5**, at 40°C. EtOAc was added and the layers were separated. The water layer was extracted three times with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent evaporated to yield a thick yellow oil. The crude product was purified by crystallisation from EtOAc/pentane or by washing with diethyl ether **6a**.

4.4.1. (2*S*)-3-*N*-(9*H*-Fluorenylmethoxycarbonyl)-2-hydroxylpropanoic acid 6a. Yield: 80%.—White solid, mp 162–164°C (dec.) (lit.: 168°C).[14]—IR: *v* (cm^{-1}) 3407, 3264, 1750, 1681, 1557, 1452, 1270, 1119, 761, 736.—^{1}H NMR (MeOD) $\delta = 3.35$ (dd, 1H, $J = 6.6$, $J = 13.9$, *H-3*), 3.52 (dd, 1H, $J = 4.4$, $J = 13.9$, *H-3*), 4.15–4.40 (m, 4H, *H-2*, C*H*, CH_2 Fmoc), 7.22–7.45 (m, 4H, C*H* Ph Fmoc), 7.65 (d, 2H, $J = 6.9$, C*H* Ph Fmoc), 7.79 (d, 2H, $J = 6.6$, C*H* Ph Fmoc).—^{13}C NMR (MeOD) $\delta = 45.5$ (*C-3*), 48.4 (*C*H Fmoc), 68.0 (CH_2 Fmoc), 71.0, (*C-2*), 120.9, 126.2, 128.2, 128.8 (*C*H Fmoc), 142.6, 145.3 (C_q Fmoc), 159.0 (N*C*O), 175.8 (*C-1*).—HRMS (ESI) *m/z* Found: 328.1156 $[M+H]^+$, calcd: 328.1184.—$[\alpha]_D^{20} = -17.8$ (*c* 0.1, MeOH).

4.4.2. (2*S*,3*S*)-3-*N*-(9*H*-Fluorenylmethoxycarbonyl)-2-hydroxyl-butanoic acid 6b. Yield: 61%.—White solid, mp 152–153°C (dec.).—IR: *v* (cm^{-1}) 3330, 1734, 1689, 1532, 1450, 1251, 1116, 1053, 736.—^{1}H NMR (MeOD) $\delta = 1.10$ (d, 3H, $J = 6.8$, *H-4*), 3.94–4.12 (m, 1H, *H-3*), 4.15–4.27 (m, 2H, *H-2*, C*H* Fmoc), 4.28–4.39 (m, 2H, CH_2 Fmoc), 7.04 (d, 1H, $J = 8.4$, N*H*), 7.24–7.43 (m, 4H, C*H* Ph Fmoc), 7.66 (d, 2H, $J = 7.1$, C*H* Ph Fmoc), 7.79 (d, 2H, $J = 7.7$, C*H* Ph Fmoc).—^{13}C NMR (MeOD) $\delta = 14.4$ (*C-4*), 48.4 (*C*H Fmoc), 50.3 (*C-3*), 67.6 (CH_2 Fmoc), 73.5, (*C-2*), 120.7, 126.0, 127.9, 128.5 (*C*H Fmoc), 140.8, 144.9 (C_q Fmoc), 157.7 (N*C*O), 175.4 (*C-1*).—HRMS (ESI) *m/z* Found: 364.1177 $[M+H]^+$, calcd: 364.1160.—$[\alpha]_D^{20} = -11.8$ (*c* 0.1, MeOH).

4.4.3. (2*S*,3*S*)-3-*N*-(9*H*-Fluorenylmethoxycarbonyl)-2-hydroxyl-4-methyl-pentanoic acid 6c. Yield: 52%.—White solid, mp 153–155°C (dec.).—IR: *v* (cm^{-1}) 3339, 1695, 1532, 1452, 1240, 1103, 1027, 758, 735.—^{1}H NMR ($MeOD/CDCl_3$ 9/1, v/v) $\delta = 0.90$ (d, 3H, $J =$ 5.11, CH_3CH), 0.94 (d, 3H, $J = 4.4$, CH_3CH), 1.96–2.16 (m, 1H, *H-4*), 3.71–3.89 (m, 1H, *H-3*), 4.12 (d, 1H, $J = 6.2$, *H-2*), 4.22 (d, 1H, $J = 5.8$, C*H* Fmoc), 4.26–4.38 (m, 2H, CH_2 Fmoc), 6.97 (d, 1H, $J = 9.7$, N*H*), 7.21–7.43 (m, 4H, C*H* Ph Fmoc), 7.60–7.71 (m, 2H, C*H* Ph Fmoc), 7.78 (d, 2H, $J = 7.1$, C*H* Ph Fmoc).—^{13}C NMR ($MeOD/CDCl_3$ 9/1, v/v) $\delta = 18.1$, 20.6 (CH_3CH), 29.5 (*C-4*), 48.3 (*C*H Fmoc), 59.8 (*C-3*), 67.7 (CH_2 Fmoc), 73.0 (*C-2*), 120.7, 126.1, 128.0, 128.6 (*C*H Ph Fmoc), 142.4, 145.0, 145.2 (C_q Ph Fmoc), 158.7 (N*C*O), 176.2 (*C-1*).—HRMS (ESI) *m/z* Found: 370.1652 $[M+H]^+$, calcd: 370.1654.—$[\alpha]_D^{20} = -5.9$ (*c* 0.1, MeOH).

4.4.4. (2*S*,3*S*)-3-*N*-(9*H*-Fluorenylmethoxycarbonyl)-2-hydroxyl-5-methyl-hexanoic acid 6d. Yield: 61%.—White solid, mp 154–155°C (dec.).—IR: *v* (cm^{-1}) 3379, 1715, 1696, 1520, 1452, 1245, 1224, 1105, 1082, 1048, 758, 735.—^{1}H NMR ($MeOD/CDCl_3$ 5/1, v/v) $\delta = 0.87$ (d, 3H, $J = 6.4$, CH_3CH), 0.92 (d, 3H, $J = 6.6$, CH_3CH), 1.01–1.19 (m, 1H, CH_3CH), 1.48–1.72 (m, 2H, *H-4*), 3.94–4.13 (m, 1H, *H-3*), 4.15–4.45 (m, 4H, *H-2*, C*H*-, CH_2 Fmoc), 7.02 (d, 1H, $J = 8.8$, N*H*), 7.22–7.44 (m, 4H, C*H* Ph Fmoc), 7.66 (d, 2H, $J = 6.8$, C*H* Ph Fmoc), 7.79 (d, 2H, $J = 6.9$, C*H* Ph Fmoc).—^{13}C NMR ($MeOD/CDCl_3$ 5/1, v/v) $\delta = 21.7$ (CH_3CH), 24.0 (CH_3CH), 24.4 (*C-5*), 38.5 (*C-4*), 48.2 (*C*H Fmoc), 52.9 (*C-3*), 67.5 (CH_2 Fmoc), 74.2 (*C-1*), 120.7, 126.0, 127.9, 128.5 (*C*H Ph Fmoc), 142.3, 144.9, 145.1 (C_q Ph Fmoc), 158.1 (N*C*O), 175.4 (*C-1*).—HRMS (ESI) *m/z* Found: 384.1795 $[M+H]^+$, calcd: 384.1811.—$[\alpha]_D^{20} = -19.2$ (*c* 0.1, MeOH).

4.4.5. (2*S*,3*S*)-3-*N*-(9*H*-Fluorenylmethoxycarbonyl)-2-hydroxyl-3-phenyl-propanoic acid 6e. Yield: 69%.—White solid, mp 134–135°C (dec.).—IR: *v* (cm^{-1}) = 3351, 1697, 1523, 1450, 1244, 1229, 1117, 1084, 1033, 738, 701.—^{1}H NMR (MeOD) $\delta = 4.14$–4.24 (m, 1H, C*H* Fmoc), 4.25–4.40 (m, 2H, CH_2 Fmoc), 4.46 (d, 1H, $J = 4.8$, *H-2*), 5.05 (d, 1H, $J = 4.8$, *H-3*), 7.16–7.44 (m, 9H, C*H* Ph Fmoc, Ph), 7.63 (d, 2H, $J = 7.3$, *C*H Ph Fmoc), 7.77 (d, 2H, $J = 7.3$, *C*H Ph Fmoc).—^{13}C NMR (MeOD) $\delta = 48.1$ (*C*H Fmoc), 58.5 (*C-3*), 67.8 (CH_2 Fmoc), 74.2 (*C-2*), 120.7, 126.0, 128.0, 128.6, 129.0 (*C*H Ph Fmoc, Ph), 139.1 (C_q Ph), 142.2, 144.9 (C_q Ph Fmoc), 157.7 (N*C*O), 174.8 (*C-1*).—HRMS (ESI) *m/z* Found: 404.1506 $[M+H]^+$, calcd: 404.1497.—$[\alpha]_D^{20} = -6.0$ (*c* 0.1, MeOH).

4.4.6. (2*S*,3*S*)-3-*N*-(9*H*-Fluorenylmethoxycarbonyl)-2-hydroxyl-4-phenyl-butanoic acid 6f. Yield: 52%.—White solid, mp 170–172°C (dec.).—IR: *v* (cm^{-1}) = 3329, 1690, 1532, 1428, 1247, 1110, 1034, 733, 702.—^{1}H NMR (MeOD) $\delta = 2.75$–2.86 (m, 2H, *H-4*), 4.02–4.29 (m, 5H, C*H*, CH_2 Fmoc, *H-2*, *H-3*), 7.07–7.42 (m, 9H, C*H* Ph, Fmoc), 7.54 (d, 2H, $J = 7.3$, C*H* Ph Fmoc), 7.76 (d, 2H, $J = 6.9$, C*H* Ph Fmoc).—^{13}C NMR ($MeOD/CDCl_3$ 1/1, v/v) $\delta = 35.5$ (*C-4*), 47.5 (*C*H Fmoc), 55.6 (*C-3*), 67.2 (CH_2 Fmoc), 73.1 (*C-2*), 120.3, 125.4, 126.8, 127.4, 128.0, 128.7, 128.9, 129.7 (*C*H Ph Fmoc, Ph), 138.3 (C_q Ph), 141.6, 144.3 (C_q Ph Fmoc), 157.2 (N*C*O), 174.8 (*C-1*).—HRMS (ESI) *m/z* Found: 418.1655 $[M+H]^+$, calcd: 418.1654.—$[\alpha]_D^{20} = -36.0$ (*c* 0.1, MeOH).

4.5. General procedure for Boc-protection

To a vigorously stirred mixture of crude ethanolamine **4** (1 mmol), 5 mL of dichloromethane, and saturated $NaHCO_3$ (aq.) was added 3 mmol of Boc-anhydride.

After stirring overnight, 10 mL of dichloromethane and 5 mL of water were added. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by column chromatography (pet. ether 40–60/EtOAc 99/1–95/5, v/v). Yields from **3**.

4.5.1. (1*S*,2*S*)-1-(2′-Furyl)-1-*O*-(*tert*-butyldimethylsilyl)-2-*N*-(*tert*-butyloxocarbonyl)-3-methyl-butane 7. Yield: 42%.—Colourless oil.—^{1}H NMR ($CDCl_3$) δ: −0.14, 0.04 (2×s, 2×3H, 2×CH_3Si), 0.85 (d, 3H, J=6.9, (CH_3CH), 0.87 (s, 9H, (CH_3)$_3$CSi), 0.91 (d, 3H, J=6.9, CH_3CH), 1.40 (s, 9H, (CH_3)$_3$CO), 1.65–1.81 (m, 1H, *H-3*), 3.75–3.86 (m, 1H, *H-2*), 4.59 (d, 1H, J=10.6, N*H*), 4.72 (d, 1H, J=5.9, *H-1*), 6.23 (d, 1H, J=3.3, *H-3′*), 6.31 (dd, 1H, J=1.8, J=3.3, *H-4′*), 7.36 (dd, 1H, J=0.7, J=1.8, *H-5′*).—^{13}C NMR ($CDCl_3$) δ: −5.6, −5.3 (2×s, 2×3H, 2×CH_3Si), 17.1, 20.4 ((*C*H$_3$C)$_2$CH), 18.0 ((CH$_3$)$_3$*C*Si), 28.3 ((*C*H$_3$)$_3$CO), 59.0 (*C-2*), 69.4 (*C-1*), 78.6 ((CH$_3$)$_3$*C*O), 107.3, 110.0 (*C-3′*, *C-4′*), 141.5 (*C-5′*), 154.8 (*C-2′*), 155.8 (N*C*O).

4.5.2. (1*S*,2*S*)-1-(2′-Furyl)-1-*O*-(*tert*-butyldimethylsilyl)-2-*N*-(*tert*-butyloxocarbonyl)-3-phenyl-propane 8. Yield: 28%.—Colourless oil.—^{1}H NMR ($CDCl_3$) δ: −0.13, 0.06 (2×s, 2×3H, 2×CH_3Si), 0.86 (s, 9H, (CH_3)$_3$CSi), 1.48 (s, 9H, (CH_3)$_3$CO), 2.61–2.94 (m, 2H, *H-3*), 4.03–4.21 (m, 1H, *H-2*), 4.61 (d, 1H, J=8.8, N*H*), 4.92 (d, 1H, J=3.7, *H-1*), 6.25 (d, 1H, J=2.9, *H-3′*), 6.32 (br s, 1H, *H-4′*), 7.16–7.33 (m, 5H, C*H* Ph), 7.40 (s, 1H, *H-5′*).—^{13}C NMR ($CDCl_3$) δ: −5.4, −5.2 (2×s, 2×3H, 2×CH_3Si), 18.1 ((CH$_3$)$_3$*C*Si), 25.7 ((*C*H$_3$)$_3$CSi), 28.2 ((*C*H$_3$)$_3$CO), 35.4 (*C-3*), 56.0 (*C-2*), 70.0 (*C-1*), 79.0 ((CH$_3$)$_3$*C*O), 107.5, 110.0 (*C-3′*, *C-4′*), 126.1, 128.2, 129.1 (*C*H Ph), 138.4 (C_q Ph), 141.8 (*C-5′*), 154.0 (*C-2′*), 155.2 (N*C*O).

4.6. General procedure for silyl deprotection

Compound **7** and **8** were dissolved in THF (4 mL per mmol) and 1.5 equiv. of TBAF·3H_2O was added. After the reaction had come to completion (TLC), ethyl acetate was added. The organic layer was washed with saturated $NaHCO_3$ (aq.), dried ($MgSO_4$), and the solvent evaporated. The crude product was purified by column chromatography (pet. ether 40–60/EtOAc 90/10–70/30, v/v).

4.6.1. (1*S*,2*S*)-1-(2′-Furyl)-2-*N*-(*tert*-butyloxocarbonyl)-3-methyl-1-butanol 9. Yield: 60%.—White solid.—^{1}H NMR ($CDCl_3$) δ=0.89 (d, 3H, J=6.6, (CH_3CH), 0.98 (d, 3H, J=6.6, CH_3CH), 1.44 (s, 9H, (CH_3)$_3$CO), 1.50–1.68 (m, 1H, *H-3*), 3.08 (d, 1H, J=6.2, O*H*), 3.75–3.87 (m, 1H, *H-2*), 4.66 (d, 1H, J=9.9, N*H*), 4.85 (dd, 1H, J=5.9, J=5.9, *H-1*), 6.31 (d, 1H, J=2.9, *H-3′*), 6.35 (dd, 1H, J=1.8, J=2.9, *H-4′*), 7.38 (dd, 1H, J=1.1, J=1.8, *H-5′*).—^{13}C NMR ($CDCl_3$) δ= 18.4, 20.1 ((*C*H$_3$C)$_2$CH), 28.3 ((*C*H$_3$)$_3$CO), 29.4 (*C-3*), 60.2 (*C-2*), 68.5 (*C-1*), 79.6 ((CH$_3$)$_3$*C*O), 107.7, 110.1 (*C-3′*, *C-4′*), 142.0 (*C-5′*), 154.3 (*C-2′*), 157.0 (N*C*O).

4.6.2. (1*S*,2*S*)-1-(2′-Furyl)-2-*N*-(*tert*-butyloxocarbonyl)-3-phenyl-1-propanol 10. Yield: 90%.—White solid.—^{1}H NMR ($CDCl_3$) δ=1.38 (s, 9H, (CH_3)$_3$CO), 2.77 (d, 2H, J=6.9, *H-3*), 3.49 (d, 1H, J=4.5, O*H*), 4.23–4.31 (m, 1H, *H-2*), 4.69–4.79 (m, 2H, *H-1*, N*H*), 6.33 (d, 1H, J=3.3, *H-3′*), 6.38 (dd, 1H, J=1.8, J=3.3, *H-4′*), 7.18–7.34 (m, 5H, C*H* Ph), 7.43 (s, 1H, J=0.7, J=1.8, *H-5′*).—^{13}C NMR ($CDCl_3$) δ=28.2 ((*C*H$_3$)$_3$CO), 36.5 (*C-3*), 56.4 (*C-2*), 69.9 (*C-1*), 79.9 ((CH$_3$)$_3$*C*O), 107.7, 110.2 (*C-3′*, *C-4′*), 126.4, 128.4, 129.2 (*C*H Ph), 137.4 (C_q Ph), 142.1 (*C-5′*), 154.0 (*C-2′*).

4.7. General procedure for oxazolidinone formation

The Boc-protected ethanolamine in DMF/THF (5 mL per mmol) was added to a stirred suspension (0°C) of 2 equiv. NaH in DMF (7.5 mL per mmol). After 1 h the reaction had come to completion and saturated NH_4Cl (aq.) was added. The title compound was extracted with diethyl ether. The organic layer was washed once with water, dried ($MgSO_4$), and the solvent was evaporated.

4.7.1. (4*S*,5*R*)-5-(2′-Furyl)-4-(*iso*-propyl)-oxazolidinone 11. ^{1}H NMR ($CDCl_3$) δ=0.73 (d, 3H, J=6.58, CH_3), 0.95 (d, 3H, J=6.58, CH_3), 1.48–1.74 (m, 1H, C*H*(CH$_3$)$_2$), 3.78 (t, 1H, J=8.0, *H-4*), 5.59 (d, 1H, J=7.7, *H-5*), 6.38 (dd, 1H, J=1.8, J=3.3, *H-4′*), 6.46 (d, 1H, J=3.3, *H-3′*), 7.44 (dd, 1H, J=0.7, J=1.8, *H-5′*).—^{13}C NMR ($CDCl_3$) δ=18.9, 19.5 (2×*C*H$_3$), 28.6 (*C*H(CH$_3$)$_2$), 63.1 (*C-4*), 74.9 (*C-5*), 110.2, 110.3 (*C-3′*, *C-4′*), 142.9 (*C-5′*), 148.8 (*C-2′*), 159.8 (O*C*ON).—MS (ESI) m/z found: [M+H]$^+$: 218.2, calcd: 218.1.

4.7.2. (4*S*,5*R*)-5-(2′-Furyl)-4-benzyl-oxazolidinone 12. ^{1}H NMR ($CDCl_3$) δ=2.53 (dd, 1H, J=10.2, J=13.9, CH_2Ph), 2.63 (dd, 1H J=4.8, J=13.9, CH_2Ph), 4.29 (ddd, 1H J=4.8, J=8.0, J=10.2, *H-4*), 5.72 (d, 1H, J=8.0, *H-5*), 6.43 (dd, 1H, J=1.8, J=3.3, *H-4′*), 6.51 (d, 1H, J=3.3, *H-3′*), 7.44 (dd, 1H, J=0.7, J=1.8, *H-5′*).—^{13}C NMR ($CDCl_3$) δ=18.9, 19.5 (2×*C*H$_3$), 28.6 (*C*H(CH$_3$)$_2$), 63.1 (*C-4*), 74.9 (*C-5*), 110.2, 110.3 (*C-3′*, *C-4′*), 142.9 (*C-5′*), 148.8 (*C-2′*), 159.8 (O*C*ON). MS (ESI) m/z found: 266.1 [M+Na]$^+$, calcd: 266.1.

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