Synthesis of Two Dipeptide Isosteres Containing Di- and Trisubstituted *E*-Configured Double Bonds

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Received 26 April 2007; revised 4 June 2007

Abstract: The stereoselective syntheses of a Tyr-Tyr and a Pro-Pro *E*-alkene isostere are described. While the Tyr-Tyr isostere was synthesized following a convergent olefination strategy, the trisubstituted *E*-configured double bond of the Pro-Pro isostere was generated by an Ireland–Claisen rearrangement. The configuration of all key intermediates containing new stereocenters was determined by X-ray crystallography.

Key words: tyrosine, proline, *E*-alkenes, Ireland–Claisen rearrangement, Julia–Kocienski olefination

The replacement of dipeptide units in bioactive peptides and proteins by synthetic isosteres is a useful tool for the investigation of biomolecular recognition processes. These backbone modifications generally consist in the isosteric replacement of the amide unit in a peptide chain possibly combined with the introduction of additional functional groups. Since biodegradation is a great limitation for the in vivo application of many biologically active peptides, replacements of this type are often used to increase the stability of the peptide towards proteolytic cleavage. In some cases they may also alter pharmacokinetics in a favorable manner.[1] In addition, the incorporation of amide bond isosteres is a convenient way to elucidate the role of selected amide bonds in receptor binding, as well as their influence on the secondary structure of peptides.

In this context, dipeptide isosteres, where the amide bond is capable of serving both as a hydrogen bond donor and the acceptor is replaced by an *E*-alkene which is incapable of hydrogen bonding, are ideal replacements. This is because they show a high degree of structural rigidity and hence closely resemble the amide bond with respect to bond lengths and angles.[2] However, hitherto this concept has been rarely realized particularly due to the difficulties associated with the stereoselective synthesis of *E*-alkene isosteres. Though various syntheses of these isosters have been published to date,[3] most of them are limited to specific amino acids and lack general applicability. The synthesis of such dipeptide isosteres consisting of amino acids with functionalized side chains is an even greater challenge since it requires a more complex protecting group strategy especially if a specific protecting group pattern is needed, for example, for the incorporation in a peptide by Fmoc-based solid-phase peptide synthesis (SPPS).

Herein, we present the full details of the stereoselective syntheses of a Tyr-Tyr and a Pro-Pro *E*-alkene isostere which was published in preliminary form.[3i,l] The amino acid tyrosine plays an important role, for example, in the stability and ligand binding of WW-domains.[4,5] These are small three-stranded antiparallel β-sheet structures of 34–40 amino acids that act as protein–protein interaction domains by recognizing specific proline-rich motifs.[4] Most types of WW-domains known to date contain one to three tyrosine residues as the most conserved residues in the second strand.[5]

A synthetic approach to an (*E*)-Tyr-Tyr isostere of type **1** containing a disubstituted double bond can rely on Wittig-type reactions,[2,3] whereas the stereoselective construction of the trisubstituted double bond in an (*E*)-Pro-Pro isostere of type **2** requires a different synthetic strategy (Figure 1). Our approach for **2** combines the stereoselective introduction of an allylic alcohol and a subsequent Ireland–Claisen rearrangement.[3f,i]

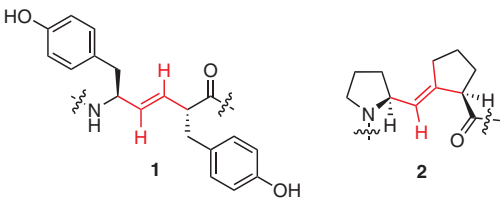
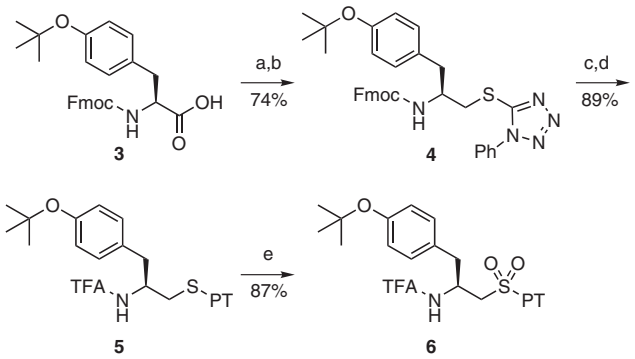


Figure 1 Two types of *E*-alkene isosteres

A protected L-tyrosine derivative was chosen as a versatile chiral pool material for entrance to the synthesis of the Tyr-Tyr *E*-alkene isostere. A stereoselective aldol reaction using an Evans auxiliary[6] to introduce the second stereocenter and a Julia–Kocienski olefination[7] to generate the *E*-configured double bond were applied as key steps. Sulfone **6** was prepared from the commercially available protected tyrosine derivative **3** (Scheme 1). A 1-phenyl-1*H*-tetrazolyl (PT) sulfonyl moiety was introduced for the Julia–Kocienski olefination.[7] Therefore, the acid **3** was first converted into the corresponding alcohol by reduction of an in situ generated mixed carbonic acid anhydride with sodium borohydride. The PT-thioether **4** was generated from the alcohol following the Mitsunobu protocol. Since the Fmoc protecting group turned out to be unstable towards the olefination conditions, it was replaced by the

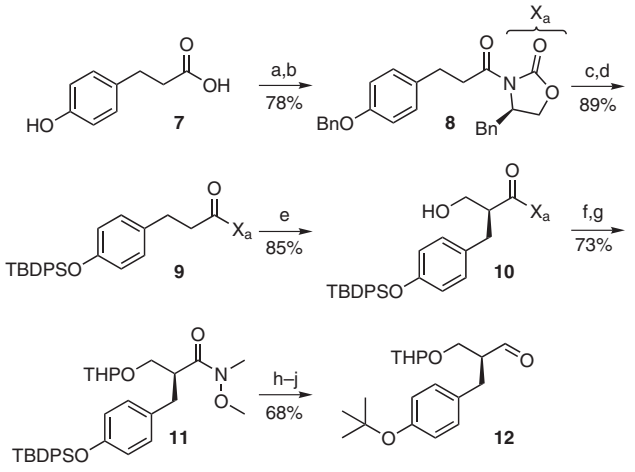
SYNTHESIS 2007, No. 17, pp 2720–2730
Advanced online publication: 12.07.2007
DOI: 10.1055/s-2007-983783; Art ID: T07607SS

trifluoroacetyl (TFA) group, which was introduced using trifluoroacetic acid anhydride (TFAA). Fmoc deprotection under standard conditions followed by TFA protection of the free amine yielded the thioether **5** which was then oxidized to the sulfone **6** with 3-chloroperbenzoic acid (MCPBA).



Scheme 1 *Reagents and conditions:* (a) i. $ClCO_2Et$, NMM, THF, –20 °C, ii. $NaBH_4$, H_2O, 0 °C; (b) PPh_3, DIAD, PT–SH, 0 °C → r.t.; (c) piperidine, DMF; (d) TFAA, pyridine, CH_2Cl_2, 0 °C → r.t.; (e) MCPBA, CH_2Cl_2, 0 °C → r.t.

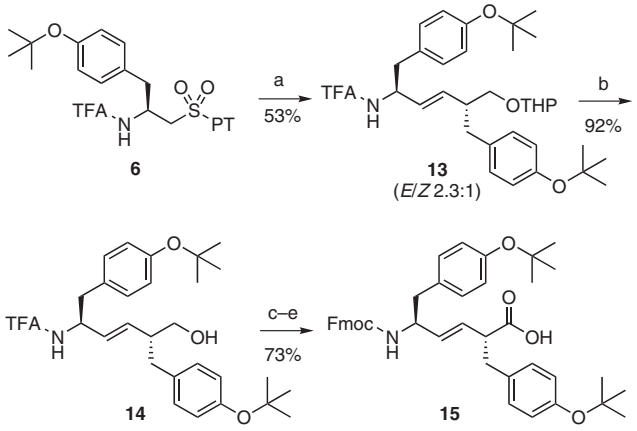
For the synthesis of the aldehyde **12** (Scheme 2), acyloxazolidinone **9**, which was available from 3-(4-hydroxyphenyl)propionic acid[1] (**7**) via the benzyl-protected intermediate **8**, was converted into the corresponding titanium enolate and allowed to react with *s*-trioxane as formaldehyde equivalent to give the aldol adduct **10** with a diastereoselectivity of >98:2.[8] The configuration was assigned by X-ray crystallography.[9] Transformation of **10** into the Weinreb amide in the presence of the free primary alcohol followed by THP protection furnished compound **11**.



Scheme 2 *Reagents and conditions:* (a) i. BnCl, KI, K_2CO_3, acetone, reflux., ii. aq NaOH, reflux; (b) i. pivaloyl chloride, Et_3N, THF, –20 °C; ii. X_a–H, LiCl, r.t.; (c) $Pd(OH)_2$, H_2, MeOH–EtOAc (1:1); (d) TBDPSCl, imidazole, DMF, 0 °C → r.t.; (e) i. $TiCl_4$, CH_2Cl_2, 0 °C, ii. DIEA, iii. *s*-trioxane, $TiCl_4$; (f) Me_3Al, Me(MeO)NH·HCl, CH_2Cl_2, –10 °C; (g) DHP, PPTS, CH_2Cl_2, 0 °C → r.t.; (h) TBAF, AcOH, THF, 0 °C → r.t.; (i) *t*-BuOTCA, PPTS, CH_2Cl_2, 0 °C → r.t.; (j) DIBAL-H, THF, –78 → –50 °C.

After TBDPS deprotection of **11**, the phenol formed needed to be transferred into a *tert*-butyl ether, but various attempts using isobutylene and catalytic amounts of different acids failed as well as the use of a *tert*-butyl halide combined with base. As previously reported, di-*tert*-butyl dicarbonate can be used for the introduction of phenolic *tert*-butyl ethers,[10] but in our hands this method only led to a 2:1 mixture of the *tert*-butyl ether and the corresponding mixed carbonate. Finally the reaction succeeded with *tert*-butyl 2,2,2-trichloroacetimidate (*t*-BuOTCA) in the presence of catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) after a prolonged reaction time of three days. Reduction of the intermediate Weinreb amide furnished aldehyde **12**.

Now the stage was set for the Julia–Kocienski olefination to connect the N-terminal sulfone **6** and the C-terminal aldehyde **12** (Scheme 3). To this end, model couplings were carried out with several aldehydes using different bases and solvents. But even for sterically nonhindered aldehydes such as butyraldehyde, the *E*/*Z* selectivity could not be improved beyond 2.1:1. The best results were obtained using NaHMDS in 1,2-dimethoxyethane (DME) as solvent, whereas the use of KHMDS which was reported to give higher selectivities,[7] only resulted in a decreased yield. Therefore, sulfone **6** was deprotonated with NaHMDS in DME and upon addition of aldehyde **12**, the desired alkene **13** was formed with modest *E*/*Z* selectivity of 2.3:1 after deprotection of the THP acetal leading to alcohol **14**, as determined by NMR spectroscopy. The chromatographic separation of *E*- and *Z*-isomer was carried out at the alcohol stage. The configuration of the double bond was assigned by ^1H NMR coupling constants. In order to introduce the *N*-Fmoc protection group for solid-phase synthesis, the TFA amide was cleaved with diisobutylaluminum hydride (DIBAL-H) followed by protection of the free amine using Fmoc-*N*-hydroxysuccinimide (FmocOSu). Oxidation with iodobenzene diacetate (IBDA) and 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) in the last step furnished the β,γ-unsaturated acid **15**.[11]

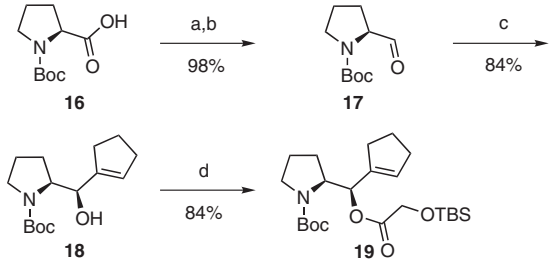


Scheme 3 *Reagents and conditions:* (a) NaHMDS, DME, –78 °C, then **12**, –78 °C → r.t.; (b) *p*-TsOH, MeOH; (c) DIBAL-H, THF, –78 → –50 °C; (d) FmocOSu, $NaHCO_3$, acetone, H_2O, 0 °C → r.t.; (e) IBDA, TEMPO, CH_2Cl_2.

The Pro-Pro isostere was addressed next. Proline, as the only secondary amino acid, has special properties that set it apart from the other natural amino acids. Because of both its cyclic structure and the secondary amino group it has specific conformational effects on the peptide and protein backbone and therefore often plays an important role in controlling the secondary structure of proteins.[12]

Peptide sequences adopting a left-handed helical polyproline II (PPII) conformation are often found at protein–protein interfaces where they play an important role in the recognition process.[13] Therefore, short PPII helical peptides and peptidomimetics are interesting synthetic targets because they can act as molecular probes for such recognition events and have already been investigated in recent years.[14] Among the numerous ligands for protein–protein interactions, the amino acid proline is crucial. The cognate protein interaction modules, such as Src3 homology (SH3) domains, Eps15 homology (EH15) domains, 14-3-3 proteins, and WW domains typically recognize linear regions of 3–9 amino acids.[4]

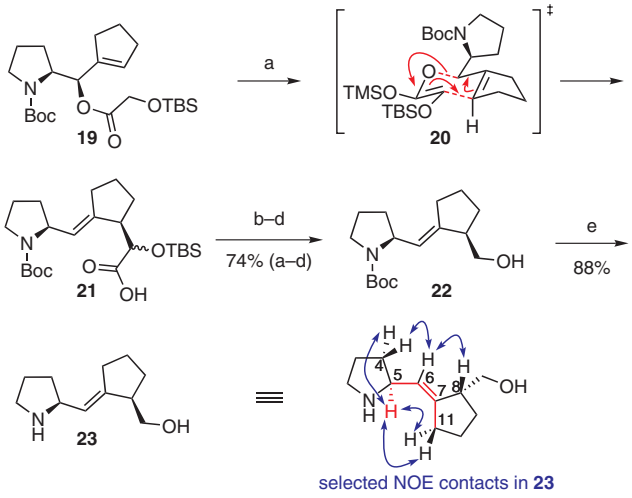
As a starting point of the synthesis of the Pro-Pro isostere, *N*-Boc-protected L-proline **16** was converted by borane reduction and subsequent Swern oxidation into the aldehyde **17**.[15] The alkenylation of **17** with cyclopent-1-enyllithium prepared from 1-iodocyclopent-1-ene by iodine–lithium exchange with *tert*-butyllithium gave the desired alcohol with a modest diastereoselectivity of 80:20 in 75% yield. If, however, the cyclopent-1-enyllithium was prepared in situ from 1-chlorocyclopent-1-ene and lithium metal,[16] the addition proceeded with high stereoselectivity (96:4) to give after chromatographic purification the *S*,*R*-alcohol **18** in 84% yield (Scheme 4). The stereochemical assignment of **18** was possible from an X-ray crystal structure.[3i]



Scheme 4 *Reagents and conditions:* (a) $BH_3{\cdot}SMe_2$, THF, reflux; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –63 °C; (c) cyclopent-1-enyllithium, Et_2O, –78 °C; (d) *tert*-butyldimethylsilyloxyacetyl chloride, pyridine, THF, 0 °C → r.t.

The Felkin–Anh selectivity observed in the addition of a lithium alkenyl compound to *N*-Boc-prolinal (**17** → **18**) is remarkably high.[17] In contrast, organomagnesium reagents show weak chelation control.[18] The alcohol **18** was then converted into the siloxy acetate **19** using *tert*-butyldimethylsilyloxyacetyl chloride.[19]

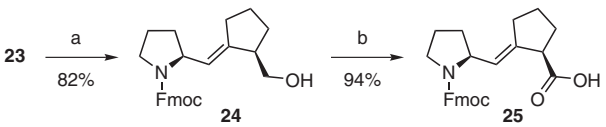
With the allyl acetate **19** in hand, the stereoselective Ireland–Claisen rearrangement into the acid **21** was investigated (Scheme 5).[3f,i] Treatment of ester **19** with LDA and TMSCl afforded the siloxy acid **21**.[3f,i,20] The Ireland–Claisen rearrangement proceeded via the proposed transition state **20** under 1,3-chirality transfer. The TBS ether in **21** was cleaved using tetrabutylammonium fluoride (TBAF) in THF. The resulting α-hydroxy acid underwent oxidative cleavage with $Pb(OAc)_4$ in $CHCl_3$–EtOAc. To prevent isomerization of the β,γ-unsaturated aldehyde thus obtained, it was reduced immediately with $NaBH_4$ in MeOH to give alcohol **22** in 74% yield over four steps. The structure of **22** in solid state was determined by X-ray crystallography.[3i] In order to get an isostere suitable for the incorporation in a peptide by Fmoc-based solid-phase peptide synthesis, alcohol **22** was transformed into the *N*-Fmoc protected acid **25**. N-Deprotection of **22** with 50% TFA in CH_2Cl_2 resulted in the secondary amine **23**. As shown for compound **22** by X-ray crystallography, the *E*-configured C(6,7) double bond leads to an antiperiplanar arrangement of H(C5) and H(C6) because of avoidance of an 1,3-allylic strain.[21] Selected NOE contacts observed for compound **23** confirm the antiperiplanar conformational lock between C5 and C6 in solution (Scheme 5).



Scheme 5 *Reagents and conditions:* (a) LDA, pyridine, TMSCl, then addition of **19**, THF, –100 °C → r.t.; (b) TBAF, THF, 0 °C → r.t.; (c) $Pb(OAc)_4$, $CHCl_3$, EtOAc, 0 °C; (d) $NaBH_4$, MeOH, 0 °C; (e) TFA, CH_2Cl_2.

To complete the synthesis of isostere **25**, amine **23** was treated with FmocOSu/$NaHCO_3$ in acetone–H_2O to give the Fmoc-protected alcohol **24**. The final oxidation of **24** using the Jones reagent yielded the desired carboxylic acid **25** in nearly quantitative yield (Scheme 6).

In summary, two novel *E*-alkene dipeptide isosteres were synthesized. Whereas the synthesis of the Tyr-Tyr isostere



Scheme 6 *Reagents and conditions:* (a) FmocOSu, $NaHCO_3$, acetone–H_2O (1:1), 0 °C → r.t.; (b) CrO_3, H_2SO_4, acetone, 0 °C.

15 relied on a convergent strategy highlighting a Julia–Kocienski olefination to generate the *E*-configured double bond, the synthesis of the Pro-Pro isostere **25** was accomplished by an efficient linear strategy containing an Ireland–Claisen rearrangement to establish the trisubstituted *E*-configured double bond. Both isosteres were synthesized with a protecting group pattern suitable for the use in Fmoc-based SPPS towards the synthesis of corresponding peptide analogues.

All nonaqueous reactions were carried out in an argon atmosphere using standard Schlenk techniques. All solvents were distilled by rotary evaporation. Solvents for nonaqueous reactions were dried following standard procedures and stored under argon prior to use. All commercially available reagents and reactants were used without purification unless otherwise noted. Boc-L-prolinal and *tert*-butyldimethylsilyloxyacetyl chloride were prepared according to literature procedures.[13,17] Chromatographic purification of products was performed on Merck Silica Gel 60 (230–400 mesh) unless otherwise noted using a forced flow of eluents. Neutral silica gel was purchased from Fuji Silysia (Chromatorex MB 100-40/75). Concentration under reduced pressure was performed by rotary evaporation at 40 °C and appropriate pressure. Yields refer to purified and spectroscopically pure products unless otherwise noted. Optical rotations were measured on a PerkinElmer 241 polarimeter using dried solvents and a 1 dm path length cell. IR spectra were recorded on a Bruker IFS 200 or a Nicolet Magna-IR 750 spectrometer. The absorption bands are given in wave numbers (cm^{-1}), with intensities reported as follows: s = strong, m = medium, w = weak, br = broad band. NMR spectra were recorded on a Bruker ARX300 or DRX500 spectrometer at room temperature. Chemical shifts are reported in ppm with the solvent resonance as internal standard. Data are reported as follows: s = singlet, d = doublet, t = triplet, qi = quintet, m = multiplet, br = broad signal, p = pseudo. Mass spectra were recorded on a Finnigan MAT TSQ 700 or MAT 95S (both mass service of Philipps-Universität Marburg) or an Applied Biosystems Model Q-Star (Prof. Marahiel, Philipps-Universität Marburg). Elemental analyses were determined on a Heraeus CHN-Rapid Analyzer (Philipps-Universität Marburg).

L-*O*-*tert*-Butyl-*N*-(9-fluorenylmethoxycarbonyl)tyrosinol

At –10 °C, a solution of Fmoc-Tyr(*t*-Bu)-OH (**3**; 2.30 g, 5.00 mmol) in THF (7 mL) was treated with NMM (0.69 mL, 6.25 mmol). After dropwise addition of ethyl chloroformate (0.48 mL, 5.00 mmol), the mixture was stirred at –10 °C for 30 min. After removing the solid by filtration, the solution was added dropwise to a slurry of $NaBH_4$ (473 mg, 12.50 mmol) in H_2O (7 mL) at 0 °C. After 4 h stirring at 0 °C, MTBE (40 mL) and aq sat. NH_4Cl were added. The aqueous layer was extracted with MTBE (2 × 40 mL) and the combined organic phases were washed with brine (20 mL), and dried (Na_2SO_4). The crude product was purified by flash column chromatography on silica gel (pentane–EtOAc, 2:1 → 1:1). The product alcohol (1.777 g, 80%) was obtained as a colorless solid; R_f = 0.23 (cyclohexane–EtOAc, 1:1); $[\alpha]_D^{19}$ –19.0 (*c* 1.11, $CHCl_3$).

IR (KBr): 3334 (br, m), 3062 (w), 2974 (m), 1689 (s), 1535 (s), 1505 (m), 1447 (w), 1365 (w), 1261 (m), 1233 (m), 1162 (m), 1085 (w), 1052 (w), 1023 (m), 739 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.3 Hz, 2 H), 7.55 (d, *J* = 7.3 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.30 (t, *J* = 7.3 Hz, 2 H), 7.08 (d, *J* = 7.6 Hz, 2 H), 6.91 (d, *J* = 7.8 Hz, 2 H), 5.12–4.91 (m, 1 H), 4.49–4.33 (m, 2 H), 4.19 (t, *J* = 6.6 Hz, 1 H), 3.99–3.82 (m, 1 H), 3.77–3.47 (m, 2 H), 2.87–2.74 (m, 2 H), 2.36–2.11 (m, 1 H), 1.32 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 154.0, 143.84, 143.80, 141.3 (2 C), 132.3, 129.6 (2 C), 127.7 (2 C), 127.0 (2 C), 125.0 (2 C), 124.2 (2 C), 119.9 (2 C), 78.3, 66.6, 63.9, 54.1, 47.2, 36.6, 28.8 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{31}NO_4$ + Na $[M + Na]^+$: 468.2145; found: 468.2153.

(*S*)-3-(4″-*tert*-Butoxyphenyl)-2-[*N*-(9‴fluorenylmethoxycarbonyl)amino]-1-(1′-phenyl-1*H*-tetrazol-5′-ylthio)propane (4)

Subsequently PPh_3 (1.10 g, 4.21 mmol) and 1-phenyl-1*H*-tetrazolyl-5-thiol (1.00 g, 5.61 mmol) were added to a solution of the above-prepared alcohol (1.25 g, 2.80 mmol) in THF (15 mL). At 0 °C, the mixture was treated dropwise with DIAD (1.06 mL, 5.05 mmol) and stirred for 2 h at r.t. The crude product was adsorbed onto silica gel and purified by flash column chromatography on silica gel (CH_2Cl_2–EtOAc, 10:1 or pentane–MTBE, 2:1) and the pure thioether **4** (1.56 g, 92%) was obtained as a colorless solid; R_f = 0.35 (cyclohexane–MTBE, 1:1); $[\alpha]_D^{19}$ –4.8 (*c* 1.22, $CHCl_3$).

IR (KBr): 3349 (m), 2975 (m), 1689 (s), 1529 (s), 1501 (s), 1450 (w), 1386 (m), 1365 (m), 1258 (s), 1228 (m), 1162 (m), 1103 (w), 1044 (m), 761 (m), 741 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.6 Hz, 2 H), 7.54–7.51 (m, 5 H), 7.49 (d, *J* = 7.6 Hz, 2 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.27 (t, *J* = 7.4 Hz, 2 H), 7.09 (d, *J* = 8.1 Hz, 2 H), 6.92 (d, *J* = 8.1 Hz, 2 H), 5.46 (br d, *J* = 8.1 Hz, 1 H), 4.31 (d, *J* = 7.1 Hz, 2 H), 4.28–4.19 (m, 1 H), 4.14 (t, *J* = 7.0 Hz, 1 H), 3.61 (dd, *J* = 13.8, 3.7 Hz, 1 H), 3.50 (dd, *J* = 13.8, 9.5 Hz, 1 H), 3.04 (dd, *J* = 13.7, 6.5 Hz, 1 H), 2.89 (dd, *J* = 13.7, 7.0 Hz, 1 H), 1.32 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 154.5, 154.3, 143.8 (2 C), 141.2 (2 C), 133.5, 131.4, 130.2, 129.8 (2 C), 129.7 (2 C), 127.6 (2 C), 127.0 (2 C), 125.1, 125.0, 124.2 (2 C), 123.8 (2 C), 119.9 (2 C), 78.4, 66.7, 52.8, 47.1, 39.8, 37.0, 28.8 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{35}H_{35}N_5O_3S$ + Na $[M + Na]^+$: 628.2353; found: 628.2371.

(*S*)-2-Amino-3-(4″-*tert*-butoxyphenyl)-1-(1′-phenyl-1*H*-tetrazol-5′-ylthio)propane

A solution of the thioether **4** (303 mg, 0.50 mmol) in DMF (5 mL) was treated with piperidine (1 mL) and stirred for 2 h. Afterwards, the solvent was evaporated, the residue was adsorbed onto silica gel, and purified by flash column chromatography on silica gel (pentane–MTBE, 1:1 → $CHCl_3$–MeOH, 10:1). The title compound free amine (192 mg, ~100%) was obtained as a colorless oil; R_f = 0.37 ($CHCl_3$–MeOH, 9:1); $[\alpha]_D^{20}$ +27.0 (*c* 1.35, $CHCl_3$).

IR (film): 3469 (br, m), 2976 (m), 2933 (m), 2860 (w), 1673 (s), 1501 (s), 1440 (w), 1388 (m), 1366 (w), 1388 (m), 1162 (m), 1092 (w), 897 (m), 763 (m), 694 cm^{-1} (w).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.53 (m, 5 H), 7.10 (pd, *J* = 8.3 Hz, 2 H), 6.94 (pd, *J* = 8.5 Hz, 2 H), 3.69 (dd, *J* = 13.3, 4.0 Hz, 1 H), 3.60–3.49 (m, 1 H), 3.33 (dd, *J* = 13.3, 7.4 Hz, 1 H), 2.95 (dd, *J* = 13.5, 5.2 Hz, 1 H), 2.69 (dd, *J* = 13.3, 4.0 Hz, 1 H), 2.52 (br s, 2 H), 1.33 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.3, 154.0, 133.5, 132.4, 130.0, 129.6 (2 C), 129.5 (2 C), 124.1 (2 C), 123.7 (2 C), 78.2, 51.8, 42.4, 40.5, 28.7 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{26}N_5OS$ + Na $[M + Na]^+$: 384.1853; found: 384.1859.

(*S*)-3-(4″-*tert*-Butoxyphenyl)-2-(trifluoroacetylamino)-1-(1′-phenyl-1*H*-tetrazol-5′-ylthio)propane (5)

To a solution of the above-prepared amine (1.06 g, 2.76 mmol) and pyridine (0.67 mL, 8.29 mmol) in CH_2Cl_2 (60 mL), was added trifluoroacetic anhydride (1.21 mL, 6.08 mmol) dropwise at 0 °C. The mixture was stirred for 1 h at r.t. and quenched by the addition of aq

sat. $NaHCO_3$ (30 mL). The layers were separated and the aqueous phase was extracted with additional CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with aq 1 M $NaHSO_4$ (10 mL) and brine (10 mL), and dried (Na_2SO_4). Purification of the crude product by flash column chromatography on silica gel (pentane–MTBE, 2:1) gave the amide **5** (1.18 g, 89%) as a colorless solid; R_f = 0.29 (cyclohexane–MTBE, 1:1); $[\alpha]_D^{19}$ –13.5 (*c* 1.02, $CHCl_3$).

IR (KBr): 3320 (m), 2978 (w), 1697 (s), 1598 (w), 1550 (m), 1501 (m), 1388 (w), 1367 (w), 1235 (m), 1218 (m), 1179 (s), 1103 (m), 898 (w), 766 (m), 692 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.01 (br d, *J* = 7.6 Hz, 1 H), 7.62–7.51 (m, 5 H), 7.16–7.09 (m, 2 H), 6.98–6.92 (m, 2 H), 4.58–4.43 (m, 1 H), 3.54 (dd, *J* = 14.8, 8.4 Hz, 1 H), 3.48 (dd, *J* = 14.9, 4.6 Hz, 1 H), 3.16 (dd, *J* = 13.8, 5.7 Hz, 1 H), 2.92 (dd, *J* = 13.8, 8.1 Hz, 1 H), 1.33 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.3 (q, *J* = 37 Hz), 154.6, 154.5, 133.2, 130.6, 130.5, 129.9 (2 C), 129.6 (2 C), 124.4 (2 C), 123.9 (2 C), 78.5, 52.6, 38.9, 35.8, 28.8 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{25}N_5O_2S$ + Na $[M + Na]^+$: 480.1676; found: 480.1696.

(*S*)-3-(4′′-*tert*-Butoxyphenyl)-2-(trifluoroacetylamino)-1-(1′-phenyl-1*H*-tetrazol-5′-ylsulfonyl)propane (6)

To a solution of thioether **5** (1.33 g, 2.70 mmol) in CH_2Cl_2 (30 mL), was added MCPBA (2.39 g, 9.70 mmol) at 0 °C. After stirring for 16 h at r.t., aq sat. $NaHCO_3$ (30 mL) and aq sat. $NaHSO_3$ (30 mL) were added. After phase separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL), and the combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2–EtOAc, 20:1) and the sulfone **6** (1.19 g, 87%) was obtained as a colorless solid; R_f = 0.11 (cyclohexane–MTBE, 2:1), 0.54 (cyclohexane–EtOAc, 1:1); $[\alpha]_D^{27}$ –9.1 (*c* 1.23, $CHCl_3$).

IR (film): 3323 (m), 2982 (m), 2932 (w), 1703 (s), 1559 (m), 1508 (m), 1354 (s), 1220 (m), 1156 (s), 899 (w), 879 (w), 764 (m), 689 (w), 639 (m), 522 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.53 (m, 5 H), 7.11–7.03 (m, 2 H), 6.99–6.89 (m, 3 H), 4.84–4.67 (m, 1 H), 4.13 (dd, *J* = 15.3, 9.1 Hz, 1 H), 3.97 (dd, *J* = 15.3, 3.6 Hz, 1 H), 3.11 (dd, *J* = 13.8, 7.0 Hz, 1 H), 3.04 (dd, *J* = 13.8, 6.8 Hz, 1 H), 1.33 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8 (q, *J* = 38 Hz), 155.1, 153.6, 132.7, 131.7, 129.75 (2 C), 129.72 (2 C), 129.3, 125.1 (2 C), 124.6 (2 C), 117.2, 78.8, 57.5, 47.5, 38.7, 28.8 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{24}F_3N_5O_4S$ + Na $[M + Na]^+$: 534.1393; found: 534.1401.

Anal. Calcd for $C_{22}H_{24}F_3N_5O_4S$: C, 51.66; H, 4.73; N, 13.69. Found: C, 50.99; H, 4.63; N, 13.54.

3-(4′-Benzyloxyphenyl)propionic Acid

A mixture of 3-(4′-hydroxyphenyl)propionic acid (**7**; 4.99 g, 30 mmol), benzyl chloride (13.9 mL, 120 mmol), KI (19.92 g, 120 mmol), and K_2CO_3 (16.59 g, 120 mmol) in acetone (70 mL) was heated to reflux for 2 d. After cooling to r.t., aq 20% NaOH (75 mL) was added and the mixture was again heated to reflux for 2 d. The resulting slurry was diluted with H_2O (250 mL), cooled to 0 °C, and treated with concd HCl until the solid had dissolved. The solution was extracted with $CHCl_3$ (3 × 100 mL) and the combined organic extracts were washed with brine (80 mL) and dried ($MgSO_4$). After recrystallization from refluxing EtOAc, 3-(4′-benzyloxyphenyl)propionic ccid (6.63 g, 86%) was obtained as a colorless crystalline solid; mp 122 °C (EtOAc).

IR (film): 3030 (w), 1692 (s), 1610 (w), 1581 (w), 1514 (m), 1427 (m), 1384 (w), 1308 (m), 1239 (m), 1111 (w), 1014 (m), 827 (m), 735 (m), 694 cm^{-1} (m).

^1H NMR (200 MHz, $CDCl_3$): δ = 11.66 (br s, 1 H), 7.05–7.28 (m, 5 H), 7.19–7.08 (m, 2 H), 6.98–6.86 (m, 2 H), 5.05 (s, 2 H), 2.91 (t, *J* = 7.8 Hz, 2 H), 2.66 (t, *J* = 7.9 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.1, 157.3, 137.0, 132.4, 129.2 (2 C), 128.6 (2 C), 127.9, 127.5 (2 C), 114.8 (2 C), 70.0, 35.8, 29.7.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}O_3$ $[M]^+$: 256.1099; found: 256.1102.

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.87; H, 6.28

(4*R*)-4-Benzyl-3-[3′-(4′′-benzyloxyphenyl)propionyl]-1,3-oxazolidin-2-one (8)

A solution of 3-(4′-benzyloxyphenyl)propionic acid (3.59 g, 14 mmol) in THF (170 mL) and Et_3N (5.82 mL, 42 mmol) was cooled to –20 °C. After dropwise addition of pivaloyl chloride (1.72 mL, 14 mmol), the resulting suspension was stirred for 2 h at –20 °C. Afterwards, LiCl (593 mg, 14 mmol) and (*R*)-4-benzyl-1,3-oxazolidin-2-one (2.48 g, 14.0 mmol) were added and the mixture was stirred for 14 h at r.t. After evaporation of the solvent in vacuo, the residue was redissolved in EtOAc (120 mL) and H_2O (50 mL). After phase separation, the organic phase was washed with aq 1 M $NaHCO_3$ (50 mL) and brine (30 mL), and dried (Na_2SO_4). The crude product was purified by flash column chromatography on silica gel (pentane–EtOAc, 2:1) or recrystallization from refluxing hexane–EtOAc (1:1) to give the acyloxazolidinone **8** (5.30 g, 91%) as a colorless solid; mp 106 °C (hexane–EtOAc); R_f = 0.14 (hexane–EtOAc, 3:1), 0.23 (hexane–EtOAc, 2:1); $[\alpha]_D^{24}$ –48.4 (*c* 1.01, $CHCl_3$).

IR (film): 3058 (w), 3027 (w), 2940 (m), 2071 (w), 1769 (s), 1694 (s), 1511 (s), 1447 (m), 1385 (m), 1353 (m), 1317 (m), 1236 (s), 1219 (m), 1201 (m), 1167 (m), 1099 (m), 1006 (m), 744 (s), 703 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.27 (m, 8 H), 7.23–7.14 (m, 4 H), 6.96–6.78 (m, 2 H), 5.05 (s, 2 H), 4.66 (dddd, *J* = 9.7, 6.1, 3.7, 3.6 Hz, 1 H), 4.23–4.12 (m, 2 H), 3.37–3.14 (m, 3 H), 3.04–2.92 (m, 2 H), 2.75 (dd, *J* = 13.3, 9.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 157.4, 153.4, 137.2, 135.2, 132.8, 129.6 (2 C), 129.4 (2 C), 128.9 (2 C), 128.5 (2 C), 127.9, 127.4 (2 C), 127.3, 114.9 (2 C), 70.1, 66.2, 55.1, 37.8, 37.3, 29.5.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{25}NO_4$ $[M + Na]^+$: 438.1676; found: 438.1684.

Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 75.19; H, 6.15; N, 3.24.

(4*R*)-4-Benzyl-3-[3′-(4′′-hydroxyphenyl)propionyl]-1,3-oxazolidin-2-one

$Pd(OH)_2$ on activated carbon (10 wt% Pd, 350 mg) was added to a solution of the benzyl ether **8** (3.45 g, 8.30 mmol) in MeOH–EtOAc (1:1, 200 mL) and the suspension was stirred vigorously under an H_2 atmosphere (1 bar) for 2 h. The catalyst was removed by filtration through a pad of Celite and the crude product was purified by flash column chromatography on silica gel (pentane–EtOAc, 1:1) to give the title compound (2.70 g, 100%) as a colorless solid; R_f = 0.33 (hexane–EtOAc, 1:1); $[\alpha]_D^{24}$ –62.3 (*c* 1.18, $CHCl_3$).

IR (film): 3411 (br, m), 3027 (w), 2954 (w), 1785 (s), 1762 (m), 1513 (m), 1443 (m), 1391 (s), 1374 (m), 1354 (m), 1305 (m), 1206 (s), 1115 (m), 1050 (m), 1015 (w), 979 (m), 826 (w), 743 (m), 704 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 3 H), 7.21–7.15 (m, 2 H), 7.14–7.07 (m, 2 H), 6.85–6.68 (m, 2 H), 5.47 (s, 2 H), 4.66

(dddd, *J* = 9.8, 6.0, 3.8, 3.8 Hz, 1 H), 4.23–4.09 (m, 2 H), 3.37–3.13 (m, 3 H), 3.04–2.85 (m, 2 H), 2.78 (dd, *J* = 13.4, 9.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 154.2, 153.6, 135.1, 132.3, 129.6 (2 C), 129.4 (2 C), 128.9 (2 C), 127.3, 115.3 (2 C), 66.2, 55.1, 37.8, 37.4, 29.5.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{19}NO_4$ + Na [M + Na]$^+$: 348.1206; found: 348.1211.

(4*R*)-4-Benzyl-3-[3′-(4″-*tert*-butyldiphenylsilyloxyphenyl)propionyl]-1,3-oxazolidin-2-one (9)

A solution of the above-prepared phenol (1.33 g, 4.1 mmol) and imidazole (737 mg, 12.3 mmol) in DMF (20 mL) was cooled to 0 °C and treated with TBDPSCl (1.59 mL, 6.2 mmol). After 14 h at r.t., H_2O (120 mL) was added and the mixture was extracted with MTBE (3 × 60 mL). The organic layers were pooled, washed with brine (60 mL) and dried (Na_2SO_4). After purification by flash column chromatography on silica gel (pentane–MTBE, 2:1), the TBDPS ether **9** (2.05 g, 89%) was obtained as a colorless viscous oil; R_f = 0.31 (cyclohexane–MTBE, 2:1); $[\alpha]_D^{25}$ –35.3 (*c* 1.08, $CHCl_3$).

IR (film): 3029 (w), 2958 (m), 2931 (m), 2858 (m), 1783 (s), 1700 (s), 1608 (m), 1510 (s), 1473 (w), 1428 (w), 1387 (s), 1352 (m), 1255 (s), 1213 (m), 1113 (s), 920 (s), 824 (m), 745 (m), 702 (s), 503 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.66 (m, 4 H), 7.46–7.23 (m, 9 H), 7.21–7.12 (m, 2 H), 7.02–6.94 (m, 2 H), 6.93–6.65 (m, 2 H), 4.69–4.57 (m, 1 H), 4.20–4.10 (m, 2 H), 3.30–3.07 (m, 3 H), 2.77–2.67 (m, 2 H), 2.72 (dd, *J* = 13.4, 9.6 Hz, 1 H), 1.09 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 154.0, 153.4, 135.5 (4 C), 135.2, 133.1, 132.8 (2 C), 129.8 (2 C), 129.4 (2 C), 129.2 (2 C), 128.9 (2 C), 127.7, 127.3, 119.6 (2 C), 66.1, 55.1, 37.8, 37.3, 29.5, 26.6 (3 C), 19.4.

HRMS (ESI): *m*/*z* calcd for $C_{35}H_{37}NSiO_4$ + Na [M + Na]$^+$: 586.2384; found: 586.2363.

(4*R*,2′*S*)-4-Benzyl-3-[3′-(4″-*tert*-butyldiphenylsilyloxyphenyl)-2′-hydroxymethylpropionyl]-1,3-oxazolidin-2-one (10)

To a solution of the oxazolidinone **9** (7.02 mmol, 3.96 g) in CH_2Cl_2 (40 mL) at 0 °C, was added dropwise $TiCl_4$ (7.72 mmol, 0.85 mL). After 5 min, *i*-Pr_2NEt (8.01 mmol, 1.4 mL) was added, whereupon the solution turned dark purple. After the mixture was stirred at 0 °C for 1 h, a solution of *s*-trioxane (8.01 mmol, 0.72 g) in CH_2Cl_2 (5 mL) was added, followed by $TiCl_4$ (7.37 mmol, 0.81 mL). The mixture was stirred for 3 h at 0 to 10 °C. Then aq sat. NH_4Cl (50 mL) was added and the layers were separated. After extraction with additional CH_2Cl_2 (3 × 50 mL), the organic layers were pooled and washed subsequently with H_2O (2 × 25 mL) and brine (50 mL). After drying (Na_2SO_4) and evaporation of solvents, the residue was purified by flash column chromatography on silica gel (MTBE–pentane, 1:2 → 1:1) to give compound **10** as a colorless foam; R_f = 0.14 (cyclohexane–MTBE, 2:1), 0.37 (cyclohexane–EtOAc, 1:1); $[\alpha]_D^{24}$ –75.0 (*c* 0.98, $CHCl_3$).

IR (KBr): 3506 (br, m), 3029 (w), 2930 (m), 2857 (m), 1780 (s), 1697 (s), 1510 (s), 1390 (m), 1350 (w), 1255 (s), 1210 (m), 1112 (m), 917 (m), 701 (s), 501 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.65 (m, 4 H), 7.43–7.26 (m, 9 H), 7.24–7.16 (m, 2 H), 6.96 (pd, *J* = 8.5 Hz, 2 H), 6.67 (pd, *J* = 8.5 Hz, 2 H), 4.44 (dddd, *J* = 9.4, 7.6, 3.5, 2.1 Hz, 1 H), 4.26–4.13 (m, 1 H), 4.03 (dd, *J* = 9.1, 2.1 Hz, 1 H), 3.90–3.70 (m, 2 H), 3.83 (dd, *J* = 8.2, 8.2 Hz, 1 H), 3.23 (dd, *J* = 13.5, 3.3 Hz, 1 H), 2.86 (dd, *J* = 13.4, 7.6 Hz, 1 H), 2.76 (dd, *J* = 13.4, 5.3 Hz, 1 H), 2.73 (dd, *J* = 13.3, 3.7 Hz, 1 H), 2.26 (br s, 1 H), 1.08 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5, 154.3, 153.2, 135.5 (4 C), 135.2, 133.0, 132.9, 130.5, 129.9 (2 C), 129.8 (2 C), 129.5 (2 C), 128.9 (2 C), 127.7 (4 C), 127.4, 119.6 (2 C), 66.0, 63.0, 55.5, 47.1, 37.9, 34.0, 26.5 (3 C), 19.4.

HRMS (ESI): *m*/*z* calcd for $C_{36}H_{39}NSiO_5$ + Na [M + Na]$^+$: 616.2490; found: 616.2492.

(2*S*)-3-(4′-*tert*-Butyldiphenylsilyloxyphenyl)-2-hydroxymethyl-*N*-methoxy-*N*-methylpropionamide

Me(MeO)NH·HCl (4.83 g, 49.51 mmol) was suspended in CH_2Cl_2 (70 mL) and cooled to –10 °C. After the addition of Me_3Al (2 M in toluene, 24.8 mL, 49.51 mmol), the resulting solution was stirred at r.t. for 1 h and again cooled to –10 °C. Afterwards, a solution of the acyloxazolidinone **10** (3.45 g, 7.07 mmol) in CH_2Cl_2 (70 mL) was added and the mixture was stirred for 72 h at –10 °C. The reaction was quenched by the addition of aq 1 M Na/K-tartrate solution (270 mL) and the resulting slurry was stirred vigorously for 1.5 h at r.t. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 180 mL) and MTBE (100 mL). The organic layers were pooled, washed with brine (150 mL), and dried (Na_2SO_4). Purification by flash column chromatography on silica gel (CH_2Cl_2–EtOAc, 4:1) yielded the title Weinreb amide (3.16 g, 94%) as a colorless oil; R_f = 0.24 (CH_2Cl_2–EtOAc, 2:1), 0.37 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –16.5 (*c* 1.04, $CHCl_3$).

IR (film): 3424 (br, m), 2932 (m), 2858 (m), 1636 (m), 1609 (m), 1510 (s), 1423 (w), 1428 (m), 1390 (w), 1255 (s), 1113 (m), 919 (m), 822 (m), 702 (s), 502 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.66 (m, 4 H), 7.46–7.31 (m, 6 H), 6.96–6.88 (m, 2 H), 6.72–6.63 (m, 2 H), 3.74–3.62 (m, 2 H), 3.38 (s, 3 H), 3.20–3.05 (m, 1 H), 3.11 (s, 3 H), 2.86 (dd, *J* = 13.6, 7.3 Hz, 1 H), 2.69 (dd, *J* = 13.3, 7.6 Hz, 1 H), 1.64 (br s, 1 H), 1.08 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 154.1, 135.5 (4 C), 133.00, 132.98, 131.6, 129.81 (2 C), 129.76 (2 C), 127.7 (4 C), 119.6 (2 C), 62.8, 61.2, 45.0, 33.9, 31.8, 26.5 (3 C), 19.4.

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{35}NSiO_4$ + Na [M + Na]$^+$: 500.2228; found: 500.2229.

(2*S*)-3-(4″-*tert*-Butyldiphenylsilyloxyphenyl)-*N*-methoxy-*N*-methyl-2-(tetrahydro-2*H*-pyran-2′-yloxymethyl)propionamide (11)

To a solution of the above-prepared amide (1.93 g, 4.04 mmol) and 3,4-dihydro-2*H*-pyran (0.50 mL, 5.26 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added PPTS (20 mg, 80 μmol) and the solution was stirred for 16 h at r.t. The reaction was quenched by the addition of aq sat. $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (50 mL) and dried (Na_2SO_4). After purification by flash column chromatography on silica gel (pentane–MTBE, 3:1 → 2:1), product **11** (1.84 g, 81%) was obtained as a colorless oil; R_f = 0.26 (cyclohexane–MTBE, 1:1).

IR (film): 2936 (m), 2859 (m), 1714 (m), 1657 (m), 1510 (s), 1472 (w), 1428 (w), 1256 (s), 1201 (w), 1172 (w), 1115 (s), 1032 (m), 920 (m), 734 (m), 702 (m), 503 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.64 (m, 4 H), 7.48–7.30 (m, 6 H), 6.95–6.83 (m, 2 H), 6.70–6.60 (m, 2 H), 4.61–4.56 (m, 0.5 H), 4.55–4.49 (m, 0.5 H), 3.85 (t, *J* = 8.8 Hz, 0.5 H), 3.86–3.71 (m, 1.5 H), 3.54 (t, *J* = 9.2 Hz, 0.5 H), 3.52–3.33 (m, 2.5 H), 3.28 (s, 1.5 H), 3.22 (m, 1.5 H), 2.99 (m, 1.5 H), 2.97 (m, 1.5 H), 2.83–2.70 (m, 1 H), 2.67–2.57 (m, 1 H), 1.82–1.42 (m, 6 H), 1.01 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 154.9, 135.5 (4 C), 133.08 + 133.05 (1 C), 129.80 (2 C), 129.76, 129.71, 127.7 (4 C), 119.5 (2 C), 99.4 + 97.0 (1 C), 68.8 + 68.0 (1 C), 62.4 + 61.5 (1 C), 61.1, 43.6, 34.5, 31.9, 30.6 + 30.4 (1 C), 26.5 (3 C), 25.4, 19.6 + 19.0 (1 C), 19.4.

HRMS (ESI): *m*/*z* calcd for $C_{33}H_{43}NSiO_5$ + Na [M + Na]$^+$: 584.2803; found: 584.2807.

(2*S*)-3-(4″-Hydroxyphenyl)-*N*-methoxy-*N*-methyl- 2-(tetrahydro-2*H*-pyran-2′-yloxymethyl)propionamide

A solution of the TBDPS ether **11** (878 mg, 1.56 mmol) in THF (25 mL) was cooled to 0 °C. Afterwards, a solution of TBAF (740 mg, 2.34 mmol) and AcOH (0.13 mL, 2.34 mmol) in THF (5 mL) was added and the mixture was stirred for further 30 min at 0 °C. After the addition of aq sat. $NaHCO_3$ (25 mL) and EtOAc (50 mL), the layers were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (30 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography on silica gel (EtOAc–pentane, 1:1) to give the title compound (505 mg, ~100%) as a colorless waxy solid; R_f = 0.12 (cyclohexane–EtOAc, 1:1).

IR (film): 3364 (br, s), 2946 (m), 1632 (s), 1594 (m), 1515 (m), 1446 (w), 1352 (w), 1260 (w), 1227 (m), 1202 (w), 1137 (w), 1120 (m), 1030 (s), 986 (w), 966 (m), 905 (m), 872 (w), 841 (m), 552 cm^{-1} (w).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07–6.97 (m, 2 H), 6.78–6.68 (m, 2 H), 6.47–6.26 (m, 1 H), 4.67–4.59 (m, 0.5 H), 4.58–4.58 (m, 0.5 H), 3.98 (t, *J* = 9.0 Hz, 0.5 H), 3.89–3.75 (m, 1.5 H), 3.66 (t, *J* = 9.2 Hz, 0.5 H), 3.59–3.36 (m, 2.5 H), 3.50 (s, 1.5 H), 3.46 (s, 1.5 H), 3.13 (s, 1.5 H), 3.11 (s, 1.5 H), 2.91–2.76 (m, 1 H), 2.74–2.61 (m, 1 H), 1.89–1.41 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 154.8, 130.7 + 130.5 (1 C), 130.1 + 130.0 (2 C), 115.3 (2 C), 99.6 + 98.0 (1 C), 68.8 + 68.0 (1 C), 62.6 + 61.6 (1 C), 61.3, 43.5, 34.4, 32.1, 30.6 + 30.4 (1 C), 25.4, 19.7 + 18.9 (1 C).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{25}NO_5$ + Na [M + Na]$^+$: 346.1625; found: 346.1629.

(2*S*)-3-(4″-*tert*-Butoxyphenyl)-*N*-methoxy-*N*-methyl-2-(tetrahydro-2*H*-pyran-2′-yloxymethyl)propionamide

A solution of the above-prepared phenol (288 mg, 0.89 mmol) in CH_2Cl_2 (2.5 mL) was cooled to 0 °C and treated with *t*-BuOTCA (0.32 mL, 1.78 mmol) and catalytic amounts of PPTS. After warming up to r.t., the mixture was stirred for 5 h, and three times at intervals of several hours the same amounts of *t*-BuOTCA and PPTS were added. The reaction was quenched by the addition of aq sat. $NaHCO_3$ (3 mL). After phase separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried (Na_2SO_4) and the crude product was purified by flash column chromatography on silica gel (pentane–MTBE, 2:1) to give the title *tert*-butyl ether (257 mg, 76%) as a colorless oil; R_f = 0.13 (cyclohexane–MTBE 2:1).

IR (film): 2975 (s), 2940 (s), 2871 (m), 1733 (s), 1655 (s), 1507 (s), 1389 (m), 1365 (m), 1236 (m), 1162 (s), 1137 (m), 1123 (m), 1077 (m), 1032 (s), 899 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07–6.97 (m, 2 H), 6.87–6.76 (m, 2 H), 4.57–4.52 (m, 0.5 H), 4.51–4.45 (m, 0.5 H), 3.97 (t, *J* = 8.8 Hz, 0.5 H), 3.81 (m, 1.5 H), 3.59 (m, *J* = 9.2 Hz, 0.5 H), 3.53–3.25 (m, 2.5 H), 3.42 (s, 1.5 H), 3.36 (s, 1.5 H), 3.09 (s, 1.5 H), 3.08 (s, 1.5 H), 2.86–2.73 (m, 1 H), 2.70–2.58 (m, 1 H), 1.80–1.36 (m, 6 H), 1.24 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 134.5 + 134.3 (1 C), 129.45, 129.39, 124.1 (2 C), 99.4 + 98.1 (1 C), 78.2, 68.8 + 68.1 (1 C), 62.5 + 61.6 (1 C), 61.2, 43.5, 34.7, 32.0, 30.6 + 30.4 (1 C), 28.8 (3 C), 25.4, 19.7 + 19.0 (1 C). C-1 was not observed.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}NO_5$ + Na [M + Na]$^+$: 402.2251; found: 402.2256.

(2*S*)-3-(4″-*tert*-Butoxyphenyl)-2-(tetrahydro-2*H*-pyran-2′-yloxymethyl)propanal (12)

A solution of the above-prepared Weinreb amide (338 mg, 891 μmol) in THF (6 mL) was cooled to –78 °C and DIBAL-H (1 M in petroleum ether, 0.98 mL, 0.98 mmol) was added dropwise. After stirring the mixture for 1.5 h, it was warmed up to –55 °C. Afterwards, the mixture was added slowly to aq K/Na-tartrate solution (1 M, 12 mL) at 0 °C. The resulting slurry was diluted with MTBE (30 mL) and stirred for 30 min at r.t. The layers were separated and the aqueous layer was extracted with MTBE (3 × 20 mL). The combined organic extracts were washed with brine (15 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography on neutral silica gel (pentane–MTBE, 4:1) to give the aldehyde **12** (243 mg, 85%) as a colorless oil; R_f = 0.38 (cyclohexane–MTBE, 2:1).

IR (film): 2976 (m), 1726 (s), 1608 (s), 1507 (s), 1389 (m), 1366 (m), 1236 (m), 1162 (s), 1136 (w), 1034 (m), 898 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.83–9.76 (m, 1 H), 7.11–7.01 (m, 2 H), 6.94–6.86 (m, 2 H), 4.60–4.51 (m, 1 H), 4.05–3.90 (m, 1 H), 3.82–3.71 (m, 1 H), 3.60–3.43 (m, 2 H), 3.09–2.97 (m, 1 H), 2.89–2.71 (m, 2 H), 1.86–1.44 (m, 6 H), 1.34 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.4 + 203.3 (1 C), 153.93 + 153.90 (1 C), 133.4 + 133.2 (1 C), 129.4, 129.3, 124.20, 124.19, 99.2 + 98.8 (1 C), 78.3, 65.3 + 65.1 (1 C), 62.1 + 62.0 (1 C), 53.7 + 53.6 (1 C), 31.4 + 31.1 (1 C), 30.43 + 30.37 (1 C), 28.8, 25.4 + 25.3 (1 C), 19.2 + 19.1 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{28}O_4$ + Na [M + Na]$^+$: 343.1880; found: 343.1883.

(*E*,2*R*,5*R*)-2-(4″-*tert*-Butoxybenzyl)-6-(4‴-*tert*-butoxyphenyl)-5-trifluoroacetylamino-1-(tetrahydro-2*H*-pyran-2′-yloxy)hex-3-ene (13)

A solution of the sulfone **6** (321 mg, 0.627 mmol) in DME (5 mL) was cooled to –78 °C and NaHMDS (2 m in THF, 0.69 mL, 1.379 mmol) was added dropwise whereupon the solution turned yellow. After 30 min at –78 °C, compound **12** (241 mg, 0.752 mmol) dissolved in DME (2.5 mL) was added dropwise. The cooling bath was removed and the mixture was stirred for 12 h at r.t. After the addition of phosphate buffer (pH 7, 2.5 mL), H_2O (2.5 mL) and MTBE (10 mL), the layers were separated and the aqueous layer was extracted with MTBE (3 × 5 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography on silica gel (pentane–MTBE, 10:1 → 6:1 and pentane–acetone 15:1 → 10:1) to give the olefin **13** (201 mg, 53%) as an inseparable *E*/*Z* mixture; R_f = 0.20 (cyclohexane–acetone, 5:1). The following spectral data were obtained from the diastereomeric mixture of **13**.

IR (film): 3303 (m), 2977 (m), 1705 (s), 1608 (w), 1550 (w), 1507 (s), 1444 (w), 1390 (w), 1366 (m), 1236 (m), 1162 (s), 1032 (m), 898 cm^{-1} (m).

The isomers were separated and analyzed after the cleavage of their THP acetals (see below).

(*E*,2*R*,5*R*)-2-(4′-*tert*-Butoxybenzyl)-6-(4″-*tert*-butoxyphenyl)-5-trifluoracetylaminohex-3-enol (14)

The acetal **13** (162 mg, 267 μmol) was dissolved in a mixture of Et_2O–MeOH (1:1, 8 mL) and treated with *p*-TsOH (4 mg, 20 μmol) at 0 °C. After warming up to r.t., the mixture was stirred for 4 h and quenched by the addition of aq sat. $NaHCO_3$ (10 mL). MTBE (20 mL) was added and the layers were separated. The aqueous layer was extracted with MTBE (2 × 10 mL) and the combined organic extracts were washed with brine (15 mL) and dried (Na_2SO_4). After evaporation of the solvent in vacuo, the *E*/*Z* mixture was separated by flash column chromatography on silica gel (pentane–MTBE, 4:1

→ 2:1) to give the *E*-isomer **14** (90 mg, 65%) as a colorless oil and the *Z*-isomer (39 mg, 28%) as a colorless waxy solid.

***E*-Isomer**

R_f = 0.41 (cyclohexane–MTBE, 2:1); $[\alpha]_D^{25}$ –31.2 (*c* 1.06, $CHCl_3$).

IR (film): 3442 (br, m), 3298 (br, m), 2978 (m), 2931 (w), 1705 (s), 1603 (w), 1555 (w), 1507 (s), 1367 (m), 1236 (m), 1161 (s), 1017 (w), 897 (m), 757 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.05–6.84 (m, 8 H), 6.23 (br d, *J* = 7.2 Hz, 1 H), 5.33 (dd, *J* = 15.5, 7.2 Hz, 1 H), 5.25 (dd, *J* = 15.4, 6.1 Hz, 1 H), 4.59 (ddd, *J* = 13.8, 7.0, 6.8 Hz, 1 H), 3.51 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.34 (dd, *J* = 10.3, 7.3 Hz, 1 H), 2.80 (dd, *J* = 13.6, 6.4 Hz, 1 H), 2.75 (dd, *J* = 13.0, 7.7 Hz, 1 H), 2.64 (dd, *J* = 12.9, 5.8 Hz, 1 H), 2.54–2.34 (m, 1 H), 2.49 (dd, *J* = 12.7, 8.0 Hz, 1 H), 1.67 (br s, 1 H), 1.32 (s, 9 H), 1.31 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3 (q, *J* = 37 Hz), 154.5, 153.7, 134.6, 134.1, 131.0, 129.9, 129.7 (2 C), 129.5 (2 C), 124.3 (2 C), 124.0 (2 C), 117.7, 78.5, 78.2, 64.9, 53.2, 47.1, 40.1, 36.7, 28.82 (3 C), 28.80 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{38}F_3NO_4$ + Na $[M + Na]^+$: 544.2645; found: 544.2655.

***Z*-Isomer**

R_f = 0.42 (cyclohexane–MTBE, 2:1); $[\alpha]_D^{24}$ +25.2 (*c* 1.04, $CHCl_3$).

IR (film): 3442 (br, m), 3298 (br, m), 2978 (m), 2932 (w), 1703 (s), 1608 (w), 1554 (w), 1507 (s), 1390 (w), 1367 (m), 1236 (m), 1161 (s), 1017 (w), 897 (m), 759 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.07–6.82 (m, 8 H), 6.39 (br d, *J* = 6.0 Hz, 1 H), 5.41 (dd, *J* = 10.8, 10.4 Hz, 1 H), 5.31 (dd, *J* = 10.8, 9.0 Hz, 1 H), 4.59 (ddd, *J* = 14.4, 7.9, 7.0 Hz, 1 H), 3.70 (dd, *J* = 10.5, 4.4 Hz, 1 H), 3.41 (dd, *J* = 10.1, 9.5 Hz, 1 H), 3.06–2.92 (m, 1 H), 2.63 (dd, *J* = 13.4, 5.1 Hz, 1 H), 2.37 (dd, *J* = 13.9, 7.3 Hz, 1 H), 2.30 (dd, *J* = 13.9, 6.0 Hz, 1 H), 2.25 (dd, *J* = 13.5, 9.2 Hz, 1 H), 1.70 (br s, 1 H), 1.29 (s, 9 H), 1.23 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8 (q, *J* = 37 Hz), 154.6, 153.7, 135.1, 134.3, 130.3, 129.7, 129.6 (2 C), 129.5 (2 C), 124.4 (2 C), 124.0 (2 C), 117.5, 78.5, 78.2, 65.9, 49.3, 43.8, 39.4, 37.2, 28.8 (3 C), 28.7 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{38}F_3NO_4$ + Na $[M + Na]^+$: 544.2645; found: 544.2651.

(*E*,2*R*,5*R*)-5-Amino-2-(4′-*tert*-butoxybenzyl)-6-(4″-*tert*-butoxyphenyl)hex-3-enol

To a solution of the amide **14** (107 mg, 0.251 mmol) in MeOH (5 mL) and H_2O (1 mL), was added K_2CO_3 (174 mg, 1.257 mmol), and the solution was heated to 50–60 °C for 3 h. Afterwards, the crude product was adsorbed onto silica gel and purified by flash column chromatography on silica gel ($CHCl_3$–MeOH, 10:1) to yield the title amine (81 mg, 95%) as a colorless oil; R_f = 0.10 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{22}$ –1.3 (*c* 1.23, $CHCl_3$).

IR (film): 3356 (br, m), 2976 (s), 2930 (m), 1607 (w), 1506 (s), 1389 (w), 1365 (m), 1235 (s), 1162 (s), 1017 (w), 924 (w), 898 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.04–6.96 (m, 4 H), 6.93–6.85 (m, 4 H), 5.44 (dd, *J* = 15.4, 6.7 Hz, 1 H), 5.26 (dd, *J* = 15.8, 7.8 Hz, 1 H), 3.54–3.45 (m, 2 H), 3.29 (dd, *J* = 10.7, 7.6 Hz, 1 H), 2.69–2.57 (m, 3 H), 2.56–2.37 (m, 2 H), 1.86 (br s, 3 H), 1.32 (s, 9 H), 1.31 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9, 153.5, 136.9, 134.6, 133.5, 130.9, 129.6 (2 C), 129.4 (2 C), 124.1 (2 C), 124.0 (2 C), 78.3, 78.1, 65.1, 55.3, 47.0, 43.8, 37.0, 28.8 (6 C).

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{40}NO_3$ + Na $[M + Na]^+$: 426.3003; found: 426.3011.

(*E*,2*R*,5*R*)-2-(4′-*tert*-Butoxybenzyl)-6-(4″-*tert*-butoxyphenyl)-5-(9‴-fluorenylmethyloxycarbonyl)aminohex-3-enol

A solution of the above-prepared amine (30.5 mg, 72 μmol) in H_2O–acetone (1:1, 2 mL) was cooled to 0 °C and treated with $NaHCO_3$ (6.0 mg, 72 μmol) and FmocOSu (24.2 mg, 72 μmol). After stirring for 16 h at r.t., phosphate buffer (pH 7, 3 mL) and $CHCl_3$ (5 mL) were added. The layers were separated and the aqueous phase was extracted with $CHCl_3$ (2 × 5mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The crude product was purified using flash column chromatography on silica gel (pentane–EtOAc, 2:1 or $CHCl_3$–MeOH, 49:1) to afford the title carbamate (45.2 mg, 97%) as a solid colorless foam; R_f = 0.35 (cyclohexane–EtOAc, 1:1), 0.26 ($CHCl_3$–MeOH, 49:1); $[\alpha]_D^{21}$ –15.9 (*c* 1.03, $CHCl_3$).

IR (film): 3429 (br, m), 3346 (br, m), 2977 (s), 2931 (m), 1704 (s), 1506 (s), 1476 (w), 1450 (m), 1390 (w), 1366 (m), 1236 (s), 1162 (s), 1032 (m), 897 (m), 758 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (pd, *J* = 7.6 Hz, 2 H), 7.57 (pd, *J* = 7.4 Hz, 2 H), 7.41 (pt, *J* = 7.6 Hz, 2 H), 7.32 (pt, *J* = 7.4 Hz, 2 H), 5.46–5.22 (m, 2 H), 4.83–4.66 (m, 1 H), 4.48–4.26 (m, 3 H), 4.20 (t, *J* = 6.6 Hz, 1 H), 3.54–3.42 (m, 1 H), 3.34–3.23 (m, 1 H), 2.91–2.34 (m, 5 H), 1.78–1.57 (m, 1 H), 1.314 (s, 9 H), 1.306 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 154.1, 153.5, 143.9 (2 C), 141.3 (2 C), 134.4, 132.5, 132.2, 132.0, 129.8 (2 C), 129.4 (2 C), 127.7 (2 C), 127.0 (2 C), 125.0 (2 C), 124.1 (2 C), 124.0 (2 C), 120.0 (2 C), 78.3, 78.1, 66.5, 64.8, 54.2, 47.3, 46.9, 40.9, 36.7, 28.8 (6 C).

HRMS (ESI): *m*/*z* calcd for $C_{42}H_{49}NO_5$ + Na $[M + Na]^+$: 670.3503; found: 670.3518.

(*E*,2*R*,5*R*)-2-(4′-*tert*-Butoxybenzyl)-6-(4″-*tert*-butoxyphenyl)-5-(9‴-fluorenylmethyloxycarbonyl)aminohex-3-enoic Acid (15)

To a solution of the above-prepared alcohol (280 mg, 432 mmol) in CH_2Cl_2 (6 mL) containing a small amount of H_2O (2 drops), were added iodobenzene diacetate (IBDA; 306 mg, 951 mmol) and TEMPO (3.4 mg, 22 mmol) added subsequently. After stirring for 6 h, the mixture was diluted with CH_2Cl_2 (15 mL) and after the addition of aq sat. $Na_2S_2O_4$ (5 mL), the resulting slurry was stirred vigorously for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). Purification by flash column chromatography on silica gel ($CHCl_3$–MeOH, 49:1 and EtOAc–pentane, 1:1) afforded the β,γ-unsaturated acid **15** (231 g, 79%); R_f = 0.24 (cyclohexane–EtOAc, 1:1); $[\alpha]_D^{19}$ –30.7 (*c* 0.32, $CHCl_3$).

IR (film): 3446 (m), 3324 (m), 2976 (s), 2913 (m), 1711 (s), 1506 (s), 1450 (w), 1365 (m), 1236 (s), 1161 (s), 1104 (w), 897 (m), 759 (m), 740 cm^{-1} (m).

^1H NMR (500 MHz, 343 K, DMSO-d_6): δ = 11.98 (br s, 1 H), 7.85 (pd, *J* = 7.6 Hz, 2 H), 7.63 (pd, *J* = 7.6 Hz, 2 H), 7.40 (pt, *J* = 7.4 Hz, 2 H), 7.31 (pt, *J* = 7.4 Hz, 2 H), 7.25–7.11 (m, 1 H), 7.05 (pd, *J* = 8.3 Hz, 2 H), 7.03–6.97 (m, 2 H), 6.83 (pd, *J* = 8.5 Hz, 2 H), 6.78 (pd, *J* = 8.5 Hz, 2 H), 5.57–5.42 (m, 2 H), 4.28–4.17 (m, 2 H), 4.15–4.07 (m, 1 H), 4.14 (t, *J* = 6.8 Hz, 1 H), 3.17–3.06 (m, 1 H), 2.90 (dd, *J* = 13.7, 7.6 Hz, 1 H), 2.69–2.57 (m, 3 H), 1.26 (s, 9 H), 1.22 (s, 9 H).

^{13}C NMR (125 MHz, 343 K, DMSO-d_6): δ = 177.4, 153.2, 153.1 (2 C), 143.61, 143.59, 140.4 (2 C), 133.1, 132.64, 132.58, 129.3 (2 C), 129.1 (2 C), 127.3, 127.1 (2 C), 126.6 (2 C), 124.7 (2 C), 122.7 (2 C), 122.6 (2 C), 119.6 (2 C), 77.2, 77.1, 65.1, 53.6, 49.6, 46.5, 37.0, 28.28 (3 C), 28.26 (3 C). One benzylic C-atom was not observed because of a superposition with the DMSO-d_6 signal.

HRMS (ESI): *m*/*z* calcd for $C_{42}H_{47}NO_6$ $[M + Na]^+$: 684.3296; found: 684.3290.

[(1*S*)-1-*tert*-Butyloxycarbonylpyrrolidine-2-yl]-(1′*R*)-cyclopent-1′-enylmethanol (18)

A piece of Li rod (1 cm diameter, 4.63 g, 0.67 mol) was flattened to a thickness of about 1 to 2 mm with a clean hammer. The flattened Li was cut into pieces of approximately 1 × 0.2 mm and kept under argon in a dry flask containing Et_2O (150 mL) and broken glass pieces. Freshly distilled (from $CaCl_2$) 1-chlorocyclopent-1-ene (23.74 g, 0.23 mol) was then added in one portion and the mixture was stirred at r.t. for 3 h (exothermic!) and heated at 50 °C oil bath temperature for 1 h. The resulting suspension was allowed to cool down to r.t. and the supernatant solution was transferred to another flask by a syringe and diluted with Et_2O (650 mL). The solution was cooled to –78 °C and the aldehyde **17** (19.8 g, 99.3 mmol) dissolved in Et_2O (400 mL) was added dropwise. The solution was maintained at –78 °C for 3 h, and then quenched by the addition of *i*-PrOH (10 mL) and warmed up to r.t. After adding aq sat. $NaHCO_3$ (400 mL), the mixture was vigorously stirred for 10 min. The aqueous layer was extracted with EtOAc (2 × 500 mL) and the combined organic extracts were washed with brine (300 mL), dried (Na_2SO_4) and concentrated. Flash column chromatography on silica gel (CH_2Cl_2–EtOAc, 10:1 → 4:1) yielded the alcohol **18** (22.28 g, 84%) as a colorless solid. A sample for X-ray was obtained by subsequent crystallization from CH_2Cl_2–cyclohexane; R_f = 0.22 (CH_2Cl_2–EtOAc 5:1); $[\alpha]_D^{24}$ –83.2 (*c* 2.03, $CHCl_3$).

^{1}H NMR (500 MHz, DMSO-d_6, 340 K): δ = 5.58–5.49 (m, 1 H), 4.58 (br s, 1 H), 4.48–4.39 (m, 1 H), 3.84–3.71 (m, 1 H), 3.38–3.31 (m, 1 H), 3.24–3.17 (m, 1 H), 2.33–2.17 (m, 4 H), 1.92–1.85 (m, 2 H), 1.82 (qi, *J* = 7.4 Hz, 2 H), 1.70–1.60 (m, 2 H), 1.41 (s, 9 H).

^{13}C NMR (125 MHz, DMSO-d_6, 340 K): δ = 145.9, 123.5, 77.7, 70.3, 59.7, 46.4, 31.9, 31.3, 27.9 (3 C), 24.3, 23.3, 22.7. The Boc-C=O signal was not observed.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{25}NO_3$ + Na $[M + Na]^+$: 290.1732; found: 290.1737.

[(2*S*)-1-*tert*-Butyloxycarbonylpyrrolidine-2-yl]-(*R*)-cyclopent-1′-enylmethyl *tert*-Butyldimethylsilyloxyacetate (19)

A solution of the alcohol **18** (22.14 g, 83.0 mmol) and pyridine (20 mL, 249 mmol) in THF (40 mL) was cooled to 0 °C and freshly prepared *tert*-butyldimethylsilyloxyacetyl chloride (17.39 g, 83.3 mmol) dissolved in THF (40 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h and at r.t. for further 30 min. Then the mixture was diluted with MTBE (250 mL) and washed with aq 0.5 N HCl (2 × 150 mL), aq sat. $NaHCO_3$ (80 mL), and brine (80 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography on silica gel (pentane–MTBE, 9:1) gave the ester **19** (30.65 g, 74%) as a colorless oil; R_f = 0.13 (cyclohexane–MTBE, 9:1), 0.54 (cyclohexane–MTBE, 2:1); $[\alpha]_D^{24}$ –62.7 (*c* 1.00, $CHCl_3$).

IR (film): 2955 (s), 2931 (s), 2856 (m), 1767 (m), 1740 (w), 1700 (s), 1473 (w), 1393 (s), 1366 (m), 1255 (m), 1146 (s), 839 (s), 780 cm^{-1} (m).

^{1}H NMR (500 MHz, DMSO-d_6, 340 K): δ = 5.89–5.85 (m, 1 H), 5.58–5.55 (m, 1 H), 4.28 (d, *J* = 16.6 Hz, 1 H), 4.22 (d, *J* = 16.6 Hz, 1 H), 4.02–3.91 (m, 1 H), 3.36–3.28 (m, 1 H), 3.19–3.12 (m, 1 H), 2.33–2.21 (m, 4 H), 1.90–1.79 (m, 5 H), 1.75–1.66 (m, 1 H), 1.40 (s, 9 H), 0.88 (s, 9 H), 0.064 (s, 3 H), 0.062 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6, 340 K): δ = 169.8, 153.0, 140.4, 125.6, 78.2, 72.8, 61.0, 57.7, 46.2, 32.1, 31.4, 27.8 (3 C), 25.3 (3 C), 25.0, 23.1, 22.4, 17.6, –5.81, –5.92.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{41}NO_5Si$ + Na $[M + Na]^+$: 462.2652; found: 462.2665.

{(*R*)-[1-((*S*)-1-*tert*-Butyloxycarbonylpyrrolidin-2-yl)-(*E*)-methylidene]cyclopentyl}methanol (22)

At 0 °C, *n*-BuLi (2.5 M in hexane, 143 mmol, 57 mL) was added dropwise to a solution of *i*-Pr_2NEt (22 mL, 156 mmol) in THF (250 mL). The solution was stirred at 0 °C for 15 min and cooled to –100 °C. A mixture of chlorotrimethylsilane (48.5 mL, 384 mmol) and pyridine (34 mL, 419 mmol) in THF (100 mL), which was previously prepared by the addition of chlorotrimethylsilane to a solution of pyridine in THF at 0 °C, was added dropwise to the LDA solution at –100 °C whereupon a white precipitate was formed. After 5 min, a solution of the ester **19** (15.34 g, 34.9 mmol) in THF (120 mL) was added dropwise and the solution was stirred at –100 °C for 30 min. The mixture was warmed up to r.t. over 1.5 h and stirred at r.t. for 1.5 h. The reaction was quenched with aq 1 M HCl (400 mL) at 0 °C and extracted with MTBE (3 × 600 mL). The combined organic extracts were washed with brine (400 mL), dried (Na_2SO_4) and concentrated to give the acid **21** (15.04 g, 98% crude yield) as a pale yellow oil. Without further purification, the acid was dissolved in THF (60 mL) and treated with Bu_4NF (17.82 g, 68.2 mmol) dissolved in THF (60 mL) at 0 °C. The mixture was warmed to r.t. and stirred for 1.5 h. After the addition of aq 0.5 M HCl (300 mL), the mixture was stirred for 10 min and extracted with EtOAc (2 × 300 mL). The organic layer was washed with brine (200 mL), dried (Na_2SO_4) and concentrated to give the intermediate α-hydroxy acid as a pale yellow oil. The crude α-hydroxy acid was dissolved in EtOAc (500 mL) and cooled to 0 °C. A solution of $Pb(OAc)_4$ (16.63 g, 37.5 mmol) dissolved in $CHCl_3$ (80 mL) was added dropwise. The mixture was stirred at 0 °C for 15 min, quenched with ethylene glycol (50 mL), diluted with EtOAc (1000 mL), and the EtOAc layer was washed with H_2O (4 × 100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated to yield the product aldehyde as a yellow oil. Due to its instability, the precursor β,γ-unsaturated aldehyde was used without purification and dissolved in MeOH (300 mL). The solution was cooled to 0 °C and $NaBH_4$ (2.58 g, 68.2 mmol) was added in small portions under vigorous gas evolution. The mixture was stirred for 30 min at 0 °C and again $NaBH_4$ (1.29 g, 34.1 mmol) was added. After stirring for further 30 min, aq sat. NH_4Cl (200 mL) was added and the mixture was extracted with EtOAc (2 × 300 mL). The combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4), and concentrated. Flash column chromatography on silica gel (pentane–EtOAc, 1:1) gave the alcohol **22** (7.07 g, 74% over 4 steps, 93% per step) as a colorless solid. A sample for X-ray crystal structure analysis was obtained by subsequent crystallization from CH_2Cl_2–cyclohexane; R_f = 0.23 (cyclohexane–EtOAc, 1:1); $[\alpha]_D^{22}$ +4.2 (*c* 1.01, $CHCl_3$).

IR (film): 3478 (s), 2965 (s), 2872 (m), 1671 (s), 1407 (s), 1366 (m), 1249 (w), 1223 (w), 1157 (s), 1118 (m), 1064 (w), 1030 (s), 878 (w), 772 (m), 576 cm^{-1} (m).

^{1}H NMR (500 MHz, DMSO-d_6, 340 K): δ = 5.20–5.13 (m, 1 H), 4.27 (dd, *J* = 5.3, 5.3 Hz, 1 H), 4.27–4.18 (m, 1 H), 3.39 (ddd, *J* = 10.5, 5.3, 5.3 Hz, 1 H), 3.31–3.16 (m, 3 H), 2.48–2.37 (m, 2 H), 2.13 (ddd, *J* = 15.5, 8.2, 7.5 Hz, 1 H), 2.04–1.93 (m, 1 H), 1.84–1.75 (m, 1 H), 1.74–1.59 (m, 3 H), 1.53–1.41 (m, 3 H), 1.34 (s, 9 H).

^{13}C NMR (125 MHz, DMSO-d_6, 340 K): δ = 153.3, 142.6, 123.0, 77.5, 64.4, 55.9, 46.5, 45.7, 32.3, 29.0, 28.3, 27.9 (3 C), 23.5, 22.9.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{27}NO_3$ $[M + Na]^+$: 304.1889; found: 304.1902.

Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 67.96; H, 9.60; N, 4.86.

[(*R*)-2′-((*S*)-1-Pyrrolidin-2-yl-(*E*)-methylidene)cyclopentyl]methanol (23)

Trifluoroacetic acid (7 mL) was added to alcohol **22** (1.00 g, 3.55 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred for

30 min at r.t. Then the pH of the mixture was adjusted to 9–10 with aq sat. Na_2CO_3 and aq 2 M NaOH and extracted with $CHCl_3$–*i*-PrOH (5:1, 10 × 50 mL). The combined organic extracts were washed with brine (20 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo. Flash column chromatography on silica gel ($CHCl_3$–*i*-PrOH–MeOH, 10:2:1 → $CHCl_3$–*i*-PrOH, 1:1) yielded the amino alcohol **23** (566 mg, 88%) as a colorless oil; R_f = 0.0 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –61.4 (*c* 2.20, $CHCl_3$).

IR (film): 3293 (br, m), 2954 (s), 2888 (s), 1431 (m), 1061 (m), 1032 (m), 753 cm^{-1} (w).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.18 (ddd, *J* = 8.0, 4.4, 2.3 Hz, 1 H), 3.45 (dd, *J* = 15.3, 8.0 Hz, 1 H), 3.38 (dd, *J* = 10.4, 5.5 Hz, 1 H), 3.16 (dd, *J* = 10.4, 8.9 Hz, 1 H), 2.86 (ddd, *J* = 9.9, 7.7, 5.3 Hz, 1 H), 2.68–2.60 (m, 1 H), 2.44–2.36 (m, 1 H), 2.31–2.23 (m, 1 H), 2.20–2.11 (m, 1 H), 1.83–1.74 (m, 1 H), 1.73–1.67 (m, 1 H), 1.66–1.54 (m, 3 H), 1.53–1.39 (m, 2 H), 1.22–1.11 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 143.6, 124.8, 64.6, 57.7, 46.6, 46.0, 32.4, 29.5, 29.1, 25.1, 23.8.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{19}NO$ $[M + H]^+$: 182.1545; found: 182.1545.

{(*R*)-2′-[1′-((*S*)-1-(9″-Fluorenylmethyloxycarbonyl)pyrrolidin-2-yl)-(*E*)-methylidene]cyclopentyl}methanol (24)

To a stirred solution of the amino alcohol **23** (634 mg, 3.5 mmol) and $NaHCO_3$ (294 mg, 3.5 mmol) in H_2O–acetone mixture (1:1, 10 mL) was added FmocOSu (1.18 g, 3.5 mmol) in one portion at 0 °C. The mixture was warmed up to r.t. and stirred overnight. The pH was adjusted to 2–3 with aq 2 M HCl and the acetone was evaporated in vacuo. The residue was taken up in $CHCl_3$ (100 mL), washed with aq 0.1 M HCl (50 mL), H_2O (50 mL), and brine (50 mL), and dried (Na_2SO_4). Flash column chromatography ($CHCl_3$–MeOH, 49:1 or pentane–EtOAc, 2:1) gave the alcohol **24** as a colorless foam; R_f = 0.23 (cyclohexane–EtOAc, 1:1), 0.53 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{22}$ +13.4 (*c* 1.10, $CHCl_3$).

IR (film): 3442 (br, s), 3065 (w), 2950 (s), 2871 (s), 1736 (m), 1693 (s), 1450 (s), 1416 (s), 1352 (s), 1243 (m), 1186 (m), 1099 (s), 1031 (m), 759 (m), 740 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.4 Hz, 2 H), 7.65–7.54 (m, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.35–7.24 (m, 2 H), 5.42–5.33 (m, 0.5 H), 5.32–5.23 (m, 0.5 H), 4.55–4.31 (m, 3 H), 4.29–4.16 (m, 1 H), 3.59–3.42 (m, 4 H), 2.76–2.58 (m, 2 H), 2.45–1.42 (m, 10 H). Due to the restricted rotation around the carbamate C–N bond at r.t., compound occurs as a 1:1 mixture of rotational isomers.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 144.20, 144.17, 143.8, 141.3, 141.2 (2 C), 127.6 (2 C), 126.9 (2 C), 125.1, 125.0, 119.9 (2 C), 66.9, 65.2, 56.9, 47.4, 46.8, 46.3, 33.8, 32.7, 29.1, 24.3, 23.5.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{29}NO_3$ $[M + Na]^+$: 426.2045; found: 426.2031.

(*R*)-2′-{1′-[(*S*)-1-(9″-Fluorenylmethyloxycarbonyl)pyrrolidin-2-yl]-(*E*)-methylidene}cyclopentanecarboxylic Acid (25)

The alcohol **24** (610 mg, 1.5 mmol) was dissolved in acetone (60 mL) and cooled to 0 °C. Jones reagent (2.7 M, 1.6 mL, 3.78 mmol) was added dropwise and the mixture was stirred for 30 min at 0 °C until the color changed from purple to green. *i*-PrOH (15 mL) was then added and the mixture was stirred for 5 min at r.t., diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The combined organic extracts were dried (Na_2SO_4). Flash column chromatography on silica gel ($CHCl_3$–MeOH, 19:1 and EtOAc–pentane, 1:1 → 2:1) gave acid **25** (550 mg, 94%) as a colorless foam; R_f = 0.21 (cyclohexane–EtOAc, 1:2), 0.25 ($CHCl_3$–MeOH, 10:1); t_R 10.2 min (Rainin Dynamax C8; A: H_2O, B: MeCN, 75 → 100% B in 25 min, 0.7 mL/min); $[\alpha]_D^{22}$ –31.2 (*c* 0.70, $CHCl_3$).

IR (film): 2955 (m), 2875 (m), 1699 (s), 1450 (m), 1417 (m), 1354 (m), 1243 (w), 1187 (m), 1116 (m), 758 (m), 741 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.4 Hz, 2 H), 7.61 (d, *J* = 7.4 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.30 (d, *J* = 7.4 Hz, 2 H), 5.65–5.53 (m, 0.5 H), 5.52–5.40 (m, 0.5 H), 4.54–4.31 (m, 3 H), 4.29–4.16 (m, 1 H), 3.58–3.28 (m, 3 H), 2.83–2.63 (m, 0.5 H), 2.44–2.15 (m, 1.5 H), 2.14–1.42 (m, 8 H). Due to the restricted rotation around the carbamate C–N bond at r.t., compound **25** occurs as a 1:1 mixture of rotational isomers.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.7, 154.9, 144.2, 144.1, 141.9, 141.31, 141.27, 127.6 (2 C), 126.97, 126.96, 125.1 (2 C), 125.0, 119.9 (2 C), 67.0, 57.0, 49.2, 47.4, 46.3, 32.0 29.9, 28.9, 25.1, 24.3.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{27}NO_4$ + Na $[M + Na]^+$: 440.1838; found: 440.1837.

Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft (Forschergruppe 475).

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