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. 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 unit in a peptide chain with respect to bond lengths and angles. 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 isosteres have been published to date, 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. The amino acid tyrosine plays an important role, for example, in the stability and ligand binding of WW-domains. 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. Most types of WW-domains known to date contain one to three tyrosine residues as the most conserved residues in the second strand.

A synthetic approach to an (E)-Tyr-Tyr isostere of type 1 containing a disubstituted double bond can rely on Wittig-type reactions, 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.

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 to introduce the second stereocenter and a Julia–Kocienski olefination 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-1H-tetrazolyl (PT) sulfonyl moiety was introduced for the Julia–Kocienski olefination. 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
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).

For the synthesis of the aldehyde 12 (Scheme 2), acyloxaazolidinone 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 aldehyde 11.

Scheme 1 Reagents and conditions: (a) i. CICO₂Et, NMM, THF, −20 °C; ii. NaBH₄, H₂O, 0 °C; (b) PPh₃, DIAD, PT–SH, 0 °C → r.t.; (c) piperidine, DMF; (d) TFAA, pyridine, CH₂Cl₂, 0 °C → r.t.; (e) MCPBA, CH₂Cl₂, 0 °C → r.t.

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 KHMS which was reported to give higher selectivities,11 only resulted in a decreased yield. Therefore, sulfone 6 was deprotonated with NaHMDS in DME and upon addition of aldehyde 12, the desired alkenene 15 was formed with modest E/Z selectivity of 2.3:1 after deprotection of the THP acetal leading to aldehyde 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 H 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 2 Reagents and conditions: (a) i. NaCl, KI, K₂CO₃, acetone, reflux.; ii. aq NaOH, reflux; (b) i. pivaloyl chloride, Et₃N, THF, −20 °C; ii. Xa–H, LiCl, r.t.; (c) Pd(OH)₂, H₂, MeOH–EtOAc (1:1); (d) TBDPSCl, imidazole, DMF, 0 °C → r.t.; (e) i. TiCl₄, CH₂Cl₂, 0 °C; ii. DIEA, iii. s-trioxane, TiCl₄; (f) Me₃Al, Me(MeO)NH.HCl, CH₂Cl₂, −10 °C; (g) DHP, PPTS, CH₂Cl₂, 0 °C → r.t.; (h) TBAF, AcOH, THF, 0 °C → r.t.; (i) s-BuOTCA, PPTS, CH₂Cl₂, 0 °C → r.t.; (j) DIBAL-H, THF, −78 → −50 °C.

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, NaHCO₃, acetone, H₂O, 0 °C → r.t.; (e) IBDA, TEMPO, CH₂Cl₂.
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 proline 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 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

As a starting point of the synthesis of the Pro-Pro isostere, N-Boc-protected 1-proline 16 was converted by borane reduction and subsequent Swern oxidation into the aldehyde 17.15 The allylation 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

The Felkin–Anh selectivity observed in the addition of a lithium alkényl 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).3i,l20 The Ireland–Claisen rearrangement proceeded via the proposed transition state 20 under 1,3-chirality transfer. The TBS ether in 21 was cleaved using tetraethylammonium fluoride (TBAF) in THF. The resulting α-hydroxy acid underwent oxidative cleavage with Pb(OAc)4 in CHCl3–EtOAc. To prevent isomerization of the β,γ-unsaturated aldehyde thus obtained, it was reduced immediately with NaBH4 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.24 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 CH2Cl2 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).

To complete the synthesis of isostere 25, amine 23 was treated with FmocOSu/NaHCO3 in acetone–H2O 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

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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-peptides and tert-butyldimethylsilyloxyacetyl chloride were prepared according to literature procedures.11,12 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 Siliysia (Chromatorex MB 100-40/75). Concentration under reduced pressure was performed by rotary evaporation. 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 280 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 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-O automatisches CHN-Biosystems Model Q-Star (Prof. Marahiel, Philipps-Universität Marburg) or an Applied Biosystems Model Q-Star (Prof. Marahiel, Philipps-Universität Marburg).

Elemental analyses were determined on a Heraeus CHN-O analyser (Heraeus-Universität Marburg).

1-O-Tert-Butyl-N-(9H-fluorenemethoxycarbonyl)ltyrosinol

At -10 °C, a solution of Fmoc-Tyr(ε-Bu)-OH (3; 2.30 g, 5.00 mmol) in THF (7 mL) was treated with NMM (0.69 mL, 5.00 mmol) and stirred for 30 min. After removing the solid by filtration, the solution was added dropwise to a slurry of NaBH₄ (473 mg, 12.50 mmol) in H₂O (7 mL) at 0 °C. After 4 h stirring at 0 °C, MTBE (40 mL) and aq sat. NH₄Cl were added. The aqueous layer was extracted with MTBE (2 x 40 mL) and the organic phases were washed with brine (20 mL), and dried (Na₂SO₄). The crude product was purified by flash column chromatography on silica gel (pentane–EtOAc, 2:1 → 1:1). The product alcohol (1.77 g, 80%) was obtained as a colorless solid; Rf = 0.23 (cyclohexane–EtOAc, 1:1; [ε]D) + 19.0 (c 0.11, CHCl₃).

IR (KBr): 3361, 1711, 1673, 1505, 1294, 1164, 1045 cm⁻¹


1H NMR (300 MHz, CDCl₃): 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), 4.49–3.33 (m, 2 H), 4.19 (t, J = 6.6 Hz, 1 H), 3.99–3.82 (m, 1 H), 3.71–3.07 (m, 2 H), 2.87–2.47 (m, 2 H), 2.36–2.11 (m, 1 H), 1.32 (s, 9 H).

11C NMR (75 MHz, CDCl₃): 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).

sat. NaHCO₃ (30 mL). The layers were separated and the aqueous phase was discarded. The organic layers were extracted with CH₂Cl₂ (2 × 30 mL) and brine (10 mL) and dried (Na₂SO₄). Purification of the crude product by flash column chromatography on silica gel (pentane–MTBE, 2:1) gave the amide S (1.18 g, 89%) as a colorless solid; Rₕ = 0.29 (cyclohexane–MTBE, 1:1); [α]D₁⁰ = +13.5 (c 1.02, CHCl₃).

IR (KBr): 3400 (br, m), 2951 (w), 1749 (s), 1597 (s), 1568 (s), 1467 (s), 1378 (s), 1321 (s), 1271 (s), 1104 (s), 959 (s), 833 (s), 805 (s), 735 (s), 694 cm⁻¹ (m).


Analytical: For C₂₃H₂₄F₄N₄O₄SNa: C, 63.37; H, 6.87; N, 3.93. Found: C, 63.33; H, 6.87; N, 3.93.

3-(4-Benzyloxyphenyl)propionic Acid

A mixture of 3-(4-hydroxyphenyl)propionic acid (7; 4.99 g, 30 mmol), benzyl chloride (13.9 g, 120 mmol), K₂CO₃ (16.9 g, 120 mmol) and K₂CO₃ (16.9 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 h. The resulting slurry was filtered and washed with brine (20 mL) and dried (Na₂SO₄). Recrystallization from refluxing EtOAc, 3-(4-benzyloxyphenyl)propionic acid (3.59 g, 80%) was obtained as a colorless solid; mp 106 °C (hexane–EtOAc); [α]D₁⁰ = +11.5 (c 0.02, CHCl₃).


Anal. Calcld for C₁₆H₁₆O₃Na: C, 74.87; H, 6.28; N, 3.28. Found: C, 74.91; H, 6.27; N, 3.27.
[49x136](dd, [49x147]J = 8.5 Hz, 2 H), 2.78 (dd, J = 13.4, 9.4 Hz, 1 H).

13C NMR (75 MHz, CDCl3): 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.


IR (film): 3423 (br, m), 2932 (m), 2858 (m), 1636 (m), 1609 (s), 1510 (s), 1423 (w), 1428 (m), 1390 (w), 1255 (s), 1113 (m), 919 (s), 822 (m), 702 (s), 503 cm−1 (m).

1H NMR (300 MHz, CDCl3): δ = 7.74–7.66 (m, 4 H), 7.46–7.31 (m, 2 H), 7.02–6.94 (m, 2 H), 6.93–6.65 (m, 2 H), 6.45–5.67 (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).

13C NMR (75 MHz, CDCl3): δ = 175.2, 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.


(4R,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 CH2Cl2 (40 mL) at 0 °C, was added dropwise TiCl4 (7.72 mmol, 0.81 mL). The mixture was stirred at 0 °C, then aq sat. NH4Cl (1.59 mL, 6.2 mmol) was added and the mixture was extracted with MTBE (3 × 60 mL). The organic layers were pooled, washed with brine (60 mL) and dried (Na2SO4). After purification by flash column chromatography on silica gel (pentane–MTBE, 3:1), the TBDS-tert-butylidiphenylsilyloxyphenyl)-2-hydroxymethylpropionamide (70 mL) and cooled to –10 °C. After the addition of Me3Al (2 M in toluene, 24.8 mL, 49.51 mmol), the resulting solution was stirred at r.t. for 1 h and then cooled to –10 °C. Afterwards, a solution of the acyloxazolidinone (10) (3.45 g, 7.07 mmol) in CH2Cl2 (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 CH2Cl2 (2 × 180 mL) and MTBE (100 mL). The organic layers were pooled, washed with brine (150 mL), and dried (Na2SO4).

Purification by flash column chromatography on silica gel (CH2Cl2–EtOAc, 4:1) yielded the title Weinreb amide (3.16 g, 81%) as a colorless oil; Rf = 0.24 (CH2Cl2–EtOAc, 2:1). 0.37 (CHCl3–MeOH, 10:1); [α]D20 = 16.5 (c 1.04, CH2Cl2).

IR (film): 3423 (br, m), 2932 (m), 2858 (m), 1636 (m), 1609 (s), 1510 (s), 1423 (w), 1428 (m), 1390 (w), 1255 (s), 1113 (m), 919 (s), 822 (m), 702 (s), 503 cm−1 (m).

1H NMR (300 MHz, CDCl3): δ = 7.74–7.66 (m, 4 H), 7.46–7.31 (m, 2 H), 7.02–6.94 (m, 2 H), 6.93–6.65 (m, 2 H), 6.38–3.05 (m, 1 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 (brs, 1 H), 1.08 (s, 9 H).

13C NMR (75 MHz, CDCl3): δ = 175.8, 154.1, 135.5 (4 C), 133.0, 131.6, 129.81 (2 C), 129.76 (2 C), 127.7 (4 C), 119.6 (2 C), 62.8, 61.2, 45.9, 33.9, 31.8, 26.5 (3 C), 19.4.


(2S)-3-[4'-tert-Butyldiphenylsilyloxyphenyl]-2-hydroxymethyl-N-methoxy-N-methylpropionamide (11)

To a solution of the above-prepared amide (1.93 g, 4.04 mmol) and 3,4-dihydro-2H-pyrain (0.50 mL, 5.26 mmol) in CH2Cl2 (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. NaHCO3 (50 mL). The layers were separated and the aqueous layer was washed with CH2Cl2 (2 × 100 mL) and brine (50 mL). The combined organic extracts were washed with brine (50 mL) and dried (Na2SO4). 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; Rf = 0.26 (cyclohexane–MTBE, 1:1).

IR (film): 2936 (m), 2859 (m), 1714 (m), 1657 (m), 1510 (s), 1472 (w), 1428 (w), 1396 (w), 1255 (s), 1113 (m), 919 (s), 822 (m), 702 (s), 503 cm−1 (m).

1H NMR (300 MHz, CDCl3): δ = 7.74–7.66 (m, 4 H), 7.46–7.31 (m, 2 H), 7.02–6.94 (m, 2 H), 6.93–6.65 (m, 2 H), 3.86–3.71 (m, 1 H), 3.32 (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 (brs, 1 H), 1.08 (s, 9 H).

13C NMR (75 MHz, CDCl3): δ = 175.8, 154.1, 135.5 (4 C), 133.0, 131.6, 129.81 (2 C), 129.76 (2 C), 127.7 (4 C), 119.6 (2 C), 62.8, 61.2, 45.9, 33.9, 31.8, 26.5 (3 C), 19.4.


Synthesis of E-Alkene Dipeptide Isosteres 2725

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(2S)-3-(4′-Hydroxyphenyl)-N-methoxy-N-methyl-2-(tetrahydro-2H-pyran-2′-yloxy)methylpropionamide

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. NaHCO3 (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 (Na2SO4). The crude product was purified by flash column chromatography on silica gel (pentane–MTBE, 4:1) to give the title diastereomer, 21: 1.02 (cyclohexane–EtOAc, 1:1). IR (film): 2938 (m), 2873 (m), 1780 (s), 1699 (w), 1550 (w), 1507 (w), 1446 (w), 1390 (w), 1366 (m), 1260 (w), 1227 (w), 1202 (w), 1137 (w), 1120 (w), 1077 (s), 1032 (s), 986 (w), 966 (m), 872 (w), 841 (m), 552 cm⁻¹ (w).


(2S)-3-(4′-tert-Butoxyphenyl)-2-(tetrahydro-2H-pyran-2′-yloxy)methylpropional (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 aqeous layer was extracted with MTBE (3 × 20 mL). The combined organic extracts were washed with brine (15 mL) and dried (Na2SO4). The crude product was purified by flash column chromatography on neutral silica gel (pentane–MTBE, 4:1) to give the title aldehyde 12 (243 mg, 85%) as a colorless oil; Rf = 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), 896 cm⁻¹ (m).

1H NMR (300 MHz, CDCl3): 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), 3.60–3.53 (m, 2 H), 2.90–2.71 (m, 2 H), 1.86–1.44 (m, 6 H), 1.34 (s, 9 H).

13C NMR (75 MHz, CDCl3): 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, 120.19, 99.2 + 98.8 (1 C), 78.3, 65.3 + 65.1 (1 C), 61.2 + 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).


(E,2R,SR)-2-(4′-tert-Butoxyphenyl)-6-(4′-tert-butoxyphenyl)-5-trifluorocetylaminol-1-(tetrahydro-2H-pyran-2-yl)hexahydropyrimidine-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 mL in THF, 0.69 mmol, 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), H2O (2.5 mL) and MTBE (10 mL), the layers were separated and the aqeous layer was extracted with MTBE (3 × 5 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na2SO4). The crude product was purified by flash column chromatography on silica gel (pentane–MTBE, 4:1) to give the olefin 13 (201 mg, 53%) as a separable EZ mixture; Rf = 0.20 (cyclohexane–acetone, 5:1). The following spectral data were obtained from the diastereomeric mixture of 13.

IR (film): 3303 (m), 2977 (m), 1727 (s), 1608 (w), 1507 (s), 1444 (w), 1390 (w), 1236 (m), 1162 (s), 1032 (m), 898 cm⁻¹ (m).

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

(E,2R,SR)-2-(4′-tert-Butoxyphenyl)-6-(4′-tert-butoxyphenyl)-5-trifluorocetylaminohexahydropyrimidine-3-ene (14)

The acetal 13 (162 mg, 267 μmol) was dissolved in a mixture of Et2O–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. NaHCO3 (10 mL). MTBE (20 mL) was added and the layers were separated. The aqeous layer was extracted with MTBE (2 × 10 mL) and the combined organic extracts were washed with brine (15 mL) and dried (Na2SO4). After evaporation of the solvent in vacuo, the EZ mixture was separated by flash column chromatography on silica gel (pentane–MTBE, 4:1

(2R,5R)-5-Amino-2-(4'-tert-butyloxy)-6-(4'-tert-butoxyphenyl)-hex-3-enoI

To a solution of the amide 14 (107 mg, 0.251 mmol) in MeOH (5 mL) and H2O (1 mL), was added K2CO3 (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 (CHCl3–MeOH, 10:1) to yield the title amine (81 mg, 95%) as a colorless oil; Rf 0.4 (cyclohexane–Me2CO, 10:1); [α]D25 –31.2 (c 1.06, CHCl3).

IR (film): 3356 (br, m), 2976 (s), 2930 (m), 1607 (w), 1554 (w), 1506 (s), 1389 (w), 1367 (m), 1236 (m), 1161 (s), 1017 (s), 987 (m), 757 cm–1 (m).


(E,2R,SR)-2-(4'-tert-Butyloxy)-6-(4'-tert-butoxyphenyl)-5-(9'-fluorenylethoxycarbonylamino)hex-3-enol (15)

A solution of the above-prepared amine (30.5 mg, 72 μmol) in H2O–acetonitrile (1:1, 2 mL) was cooled to 0 °C and treated with NaHCO3 (6.0 mg, 72 μmol) and Fomosol (24.2 mg, 72 μmol). After stirring for 16 h at rt., phosphate buffer (pH 7, 3 mL) and CHCl3 (5 mL) were added. The layers were separated and the aqueous phase was extracted with CHCl3 (2×5 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na2SO4). The crude product was purified by flash column chromatography on silica gel (pentane–EtOAc, 1:1) or CHCl3–MeOH, (9:1) to afford the title carbamate (45.2 mg, 97%) as a solid colorless foam; Rf 0.35 (cyclohexane–EtOAc, 1:1); 0.26 (CHCl3–MeOH, 49:1); [α]D25 –15.9 (c 1.03, CHCl3).

IR (film): 3429 (br, m), 3346 (br, m), 2977 (s), 2971 (m), 2960 (s), 2958 (s), 1608 (s), 1450 (m), 1441 (w), 1389 (w), 1367 (m), 1366 (m), 1292 (s), 1286 (s), 1280 (s), 1250 (w), 1240 (s), 1200 (s), 1178 (m), 1164 (s), 1105 (w), 897 (m), 757 cm–1 (s).

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 Et₂O (150 mL) and broken glass pieces. Freshly distilled (from CaCl₂) 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 Et₂O (650 mL). The solution was cooled to –78 °C and the aldehyde 17 (19.8 g, 99.3 mmol) dissolved in Et₂O (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 addingaq sat. NaHCO₃ (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 (Na₂SO₄) and concentrated. Flash column chromatography on silica gel (CH₂Cl₂–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 CH₂Cl₂–cyclohexane: Rf = 0.22 (CH₂Cl₂–EtOAc 5:1); [α]D²³ = –83.2 (c 2.03, CHCl₃).

¹H NMR (500 MHz, DMSO-d₆, 340 K): δ = 5.58–5.49 (m, 1 H), 4.58 (brs, 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 (q, J = 7.4 Hz, 2 H), 1.70–1.60 (m, 2 H), 1.41 (s, 9 H).

¹³C NMR (125 MHz, DMSO-d₆, 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.


IR (film): 2955 (s), 2931 (s), 2856 (m), 1767 (m), 1740 (w), 1700 (d), 1693 (w), 1673 (m), 1393 (m), 1366 (m), 1255 (m), 1146 (s), 839 (s), 780 cm⁻¹ (m).

A solution of the alcohol 18 (22.14 g, 83.0 mmol) and pyridine (34 mL, 419 mmol) in THF (100 mL) was added dropwise and the solution was stirred at r.t. 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 (Na₂SO₄) 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 CHCl₃ (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 H₂O (4 × 100 mL) and brine (100 mL). The organic layer was dried (Na₂SO₄) and concentrated to yield the product aldehyde as a yellow oil. Due to its instability, the precursor β₂-unsaturated aldehyde was used without purification and dissolved in MeOH (300 mL). The solution was cooled to 0 °C and NaBH₄ (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 NaBH₄ (1.29 g, 34.1 mmol) was added. After stirring for further 30 min, aq sat. NH₄Cl (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 (Na₂SO₄), and concentrated. Flash column chromatography on silica gel (pentane–EtOAc, 1:1) gave the ester 19 (30.65 g, 74%) as a colorless oil; Rf = 0.21 (cyclohexane–EtOAc, 1:1); [α]D⁰ = +4.2 (c 1.01, CHCl₃).

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


Anal. Calcd for C₁₆H₂₇NO₃: C, 68.29; H, 9.67; N, 4.98. Found: C, 67.96; H, 9.60; N, 4.86.

[(R)-1-(5S)-1-tert-Butyloxycarbonylpyrrolidin-2-yl]-(E)-methylidene[cyclopentyl]methanol (23)

Trifluoroacetic acid (7 mL) was added to alcohol 22 (1.00 g, 3.55 mmol) in CH₂Cl₂ (20 mL), and the mixture was stirred for...
1.54 (m, 3 H), 1.53–1.39 (m, 2 H), 1.22–1.11 (m, 1 H).
2.68–2.60 (m, 1 H), 2.44–2.36 (m, 1 H), 2.31–2.23 (m, 1 H), 3.16 (dd, J = 10.4, 5.5 Hz, 1 H), 3.45 (dd, J = 8.9, 7.7 Hz, 1 H), 7.54 (m, 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 H), 1.24–1.14 (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.

13C NMR (75 MHz, CDCl3): 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 calc for C9H8NO4 + Na [M + Na]+: 440.1838; found: 440.1837.

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References

(R)-2′-[2′-{[(S)-1′-(9′-Fluorenylmethoxy carbonyl)pyrrolidin-2-yl]-[E]-methylene]cyclopentyl]carboxylic Acid (25)
The alcohol 24 (610 mg, 1.5 mmol) was dissolved in acetonitrile (60 mL) and cooled to 0 °C. After addition of a solution of dry ice/acetone (15 mL) and stirring for 30 min at 0 °C until the color changed from purple to green, the mixture was diluted with H2O (100 mL) and extracted with CH2Cl2 (5 × 30 mL). The combined organic extracts were dried (Na2SO4). Flash column chromatography on silica gel (CHCl3–MeOH, 19:1 or EtOAc–pentane, 1:1 → 2:1) gave acid 25 (550 mg, 94%) as a colorless foam, Rf = 0.21 (cyclohexane–EtOAc, 1:2), 0.25 (CHCl3–MeOH, 10:1); tR 10.2 min (Rainin Dynamax C8; A: H2O, B: MeCN, 75 → 100% B in 25 min, 0.7 mL/min); [α]D20 +13.4 (c 0.70, CHCl3).

IR (film): 3392 (br, s), 3054 (w), 2950 (s), 2871 (s), 1736 (m), 1699 (s), 15366. (k) Reginato, G.; Gaggini, F.; Mordini, A.; Valacchi, M.; Kessler, H. Tetrahedron Lett. 2001, 42, 15366.


(9) Since the TBDPS-protected compound 6 was not crystalline, the Me-protected derivative was prepared and used to obtain a crystal structure. The crystal data has been deposited in the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 616493. Crystal data: C21H23NO5, M = 369.40, orthorhombic, P2_12_1_2, a = 7.0200(4) Å, b = 13.4213(10) Å, c = 19.5897(12) Å, α = 90°, β = 90°, γ = 90°, V = 1845.7(2) Å³, Z = 4, D_calcd = 1.329 g/cm³, 16972 collected reflections, 3696 independent (R_int = 0.0390), R1 = 0.0265, wR2 = 0.0686 (all data).


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