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ORIGINAL ARTICLE

Easy preparation of dehydroalanine building blocks equipped with oxazolidin-2-one chiral auxiliaries, and applications to the stereoselective synthesis of substituted tryptophans

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Abstract Chiral dehydroamino acid building blocks are versatile starting materials for the preparation of optically active unusual amino acids and other compounds of pharmacological interest. Herein we disclose the expedient preparation of dehydroalanines (ΔAla) equipped with oxazolidin-2-one (Oxd) chiral auxiliaries, Ts-Oxd-ΔAla-OMe. These compounds have been obtained in high yields from dipeptides Ts-Ser/Thr/phenylSer-Ser-OMe by the one-pot cyclization–elimination reaction with *N,N*-disuccinimidyl carbonate and catalytic DIPEA. To test the efficacy of the chiral auxiliaries in controlling asymmetric transformations, the Friedel–Crafts alkylations of indoles carrying diverse substituents were performed in the presence of Lewis and Brønsted acids. The reactions proceeded with good to excellent diastereomeric ratios giving (*S*)- or (*R*)-tryptophan derivatives, isolated very conveniently by simple flash chromatography. To verify the utility of this approach, optically pure (*S*)-2-methyltryptophan and (*S*)-5-fluorotryptophan were obtained and utilized to prepare analogues of endogenous opioid peptide endomorphin-1, H-Tyr-Pro-Trp-PheNH_2.

Keywords Dehydroamino acids · Oxazolidinone chiral auxiliary · Tryptophan · Friedel–Crafts alkylation · Endomorphin-1

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Introduction

Among the unusual amino acids, the α,β-dehydroamino acids (or Δaas) represent a noteworthy class for their presence in naturally occurring toxins and antibiotics, and for their important role in the biosynthesis of other non-proteinogenic amino acids (Stammer 1982; Schmidt et al. 1988; Humphrey and Chamberlin 1997; Bonauer et al. 2006). Δaas display unusual conformational features; when inserted into peptides, they induce conformational constrains which lead to changes in the secondary structure. The double bond rigidifies the conformation of the side chain; χ is fixed to 0° (*Z*) or 180° (*E*), and favors the formation of β- or γ-turns when the Δaas are placed at the $i + 2$ position of the putative turn sequence (Fig. 1a) (De Marco et al. 2013). Besides, the presence of these unnatural and constrained residues confers resistance to enzymatic degradation. The folding properties of Δaas have been utilized for the design of foldamers, oligomers which have a tendency to form well-defined secondary structures stabilized by non-covalent, non-adjacent interactions. For instance, it was reported that the sequential introduction in oligomers of ΔPhe gave repeated β-turns, forming a 3_{10} helix (Rajashankar et al. 1992).

Besides, Δaas have demonstrated their utility in organic synthesis as versatile intermediates, giving access to a variety of derivatives (Stammer 1982; Schmidt et al. 1988; Humphrey and Chamberlin 1997; Bonauer et al. 2006). The double bond permits to perform several reactions (Fig. 1b), which can be utilized for the preparation of interesting biologically active compounds, such as the oligosaccharide-peptide ligation by the addition of complex oligosaccharide thiolates to dehydroalanine (ΔAla)-containing peptides (Galonić et al. 2003), or the synthesis of a lanthionine-bridged enkephalin mimetics (Polinsky et al. 1992).

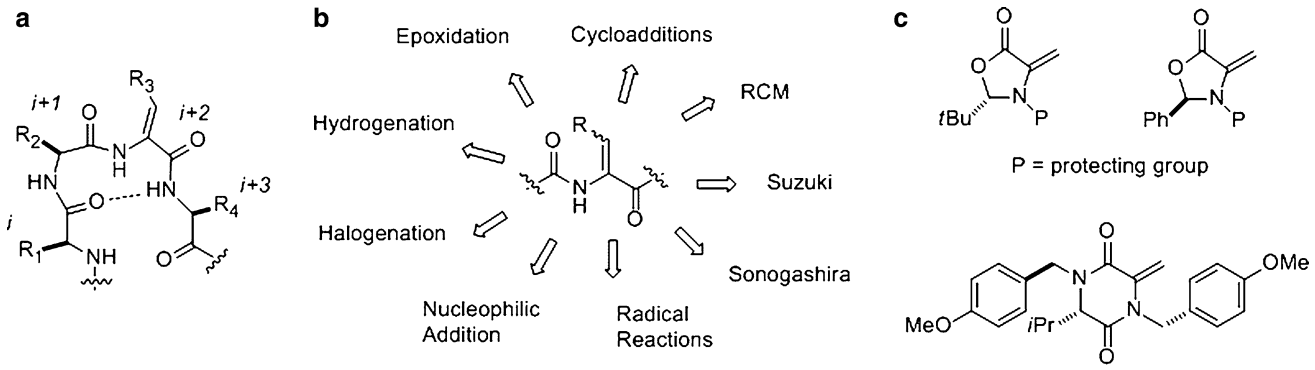


Fig. 1 **a** Δaas are β-turn inducers when placed at the position $i + 2$ of the putative turn; **b** Δaas as substrates for different synthetic reactions; **c** selected examples of chiral cyclic Δaas recently utilized for C–C bond formation (Michael additions)

Non-functionalized Δaas are enamines prone to hydrolysis; on the other hand, *N*-acyl derivatives or Δaas already incorporated into peptide sequences, are more stable, therefore several protocols for their preparations have been reported, including elimination reactions, Horner–Wadsworth–Emmons and Wittig reactions, Erlenmeyer synthesis and ring-opening of oxazolones, Schöllkopf formylaminomethylenation, etc. (Humphrey and Chamberlin 1997; Bonauer et al. 2006). One of the most direct methods is the dehydration of β-hydroxy-α-amino acids (e.g., Ser or Thr). For instance, Ferreira et al. reported the *anti*-selective elimination with Boc_2O/DMAP that afforded only one of the two possible *E*/*Z* isomers (Ferreira et al. 1999), the *Z* isomer being practically more accessible from *threo* reagents than the *E*.

Chiral ΔAla derivatives constitute suitable starting materials for many asymmetric transformations (Bonauer et al. 2006). Selected examples from the literature of compounds containing ΔAla recently utilized for diastereoselective Michael additions are shown in Fig. 1c. The addition of the benzophenone glycine-*tert*-butylester imine to 2-phenyloxazolidin-5-one gave the Michael adduct with control of the two new stereocenters and a diastereoselectivity of 97:3 (Javidan et al. 1997); the 2-*tert*-butyloxazolidin-5-one underwent addition of enamine in a preferentially *cis* manner with a ratio of 83:17 (Pyne et al. 1995); the organocuprate addition to dehydrodiketopiperazine gave the *cis* product in high yields and >95 % diastereomeric excess (Bull et al. 2001).

In this paper, we report the expedient preparation of ΔAla equipped with Oxd chiral auxiliaries (**3**), by one-pot cyclization–elimination of dipeptides of sequence Ts-Ser (or Thr, phenylSer)-Ser-OMe (**1**). To test the efficacy of these chiral building blocks for the preparation of non-racemic and non-natural amino acids, we performed the tandem Friedel–Crafts (F–C) alkylation/asymmetric protonation of substituted indoles (Bandini et al. 2005), to afford tryptophans functionalized at the indole with alkyl, aryl groups, halogens, or their combinations. Modified tryptophans are present in peptides of microbial or marine origins (e.g., halotryptophans: Yeh et al. 2005; Bittner et al. 2007), and unnatural Trp analogues have been utilized as important building blocks for the total synthesis of biologically active products (Xu et al. 2011; Artman et al. 2007; He et al. 2009; De Marco et al. 2014), as biological probes (Royer 2006), and finally as chiral small molecule catalysts (Ishihara et al. 2007). Several authors developed asymmetric syntheses of optically pure indole-substituted tryptophans (Perry et al. 1977; Li et al. 2004). Halotryptophans can be obtained by palladium-mediated heteroannulation of a chiral auxiliary (Ma et al. 2001), by electrochemical oxidation of proline followed by Fischer indole synthesis (Irie et al. 1984), from serine and commercially available microorganism containing tryptophan synthase (Goss and Newil 2006; Smith et al. 2014), by enzymatic resolutions (Porter et al. 1987; Konda-Yamada et al. 2002; Blaser et al. 2008). The F–C alkylation of substituted indoles with methyl acetamidoacrylate (Angelini et al. 2008) gave Trp derivatives in non-stereoselective fashion. On the other hand, non-racemic tryptophan derivatives were prepared with moderate stereoselectivities by F–C alkylation when ΔAla was incorporated into peptides (Gentilucci et al. 2010). Some asymmetric catalytic syntheses have been reported to afford with high levels of enantioselectivity (*S*)- or (*R*)-tryptophans carrying a limited number of distinct modifications (Drury et al. 1998; Castle and Srikanth 2003; Zheng et al. 2010). Heck reaction between *N*-Ts-indoles and methyl 2-acetamidoacrylate furnished the dehydrotryptophans, whose asymmetric catalytic hydrogenation with $[(COD)Rh(R,R)\text{-Et-DuPHOS}]^{+}TfO^{-}$ as catalyst furnished enantiomerically pure (*R*)-5-and 6-substituted tryptophans (Prieto et al. 2009). More recently, the F–C alkylation of methyl acetamidoacrylate catalyzed by 3,3-dibromo-BINOL·$SnCl_4$ complex furnished 2-substituted tryptophans

in good yields and high enantioselectivity (Kieffer et al. 2012).

Finally, herein we describe the synthesis of two analogues of the endogenous agonist of the μ-opioid receptor endomorphin-1 (EM1), H-Tyr-Pro-Trp-PheNH_2 (Zadina et al. 1997; Fichna et al. 2007). Among the opioid peptides, EM1 shows a unique sequence and extraordinary receptor affinity and selectivity. In the last years, we have been interested in the preparation, conformational analysis, and pharmacological characterization of EM1 analogues (Gentilucci et al. 2008, 2011a; De Marco et al. 2012a, 2014) as potential drugs for pain management (Gentilucci 2004; Lipkowski et al. 2004). Since none of the other endogenous opioid peptides contain a Trp in the sequence, SAR studies on EM1 analogues containing modified Trp could shed light into the role of this pharmacophore in ligand-receptor recognition (Keresztes et al. 2010). Besides, the introduction of substituents at the indole of Trp could improve metabolic stability, bioavailability, and CNS exposure (Witt et al. 2001; De Marco et al. 2014).

Materials and methods

Standard chemicals were purchased from commercial sources and used without further purification. The reactions were monitored by thin layer chromatography. Flash chromatography was performed on silica gel (230–400 mesh), using mixtures of distilled solvents. Analytical RP-HPLC was performed on an Agilent 1100 series apparatus, using a RP column Phenomenex mod. Gemini 3μ C18 110A 100 × 3.0 mm (P/No 00D-4439-Y0); column description: stationary phase octadecyl carbon chain-bonded silica (C18) with TMS endcapping, fully porous organo-silica solid support, particle size 3 μm, pore size 110 Å, length 100 mm, internal diameter 3 mm; DAD 210 nm; mobile phase: from a 9:1 H_2O-MECN to a 2:8 H_2O-MECN in 20 min at a flow rate of 1.0 mL min^{-1}, followed by 10 min at the same composition. Semi-preparative RP-HPLC was performed on an Agilent 1100 series apparatus, using an RP column ZORBAX mod. Eclipse XDB-C18 PrepHT cartridge 21.2 × 150 mm 7 μ (P/No 977150-102); column description: stationary phase octadecyl carbon chain-bonded silica (C18), double endcapped, particle size 7 μm, pore size 80 Å, length 150 mm, internal diameter 21.2 mm; DAD 210 nm; mobile phase from 8:2 H_2O-MeCN with 0.1 % TFA to 100 % MECN/0.1 % TFA in 10 min at a flow rate of 12 mL min^{-1}. Chiral HPLC analysis was performed on an Agilent 1200 series apparatus, using a CHIRALPAK IC column (P/No 83325); column description: chiral stationary phase cellulose *tris* (3,5-dichlorophenylcarbamate) immobilized on silica, particle size 5 μm, length 250 mm, internal diameter 4.6 mm, DAD 210/254 nm; mobile phase: 1:1 n-hexane/2-propanol, at 0.8 mL min^{-1}. Direct-phase HPLC analyses were performed on an Agilent 1100 series apparatus, using a Kromasil 60-5Diol column (P/No E42500); column description: stationary phase silica, particle size 5 μm, pore size 60 Å, length 250 mm, internal diameter 4.6 mm, DAD 210 nm; mobile phase hexane/2-propanol 60:40, at a flow rate of 0.6 mL min^{-1}. ESI analysis was performed using an MS single quadrupole HP 1100MSD detector, with a drying gas flow of 12.5 l/min, nebulizer pressure 30 psgi, drying gas temp. 350 °C, capillary voltage 4,500 (+) and 4,000 (-), scan 50–2,600 amu. Elemental analyses were performer using a Thermo Flash 2000 CHNS/O analyzer. The synthetic procedures by MW irradiation were performed using a microwave oven (MicroSYNTH Microwave Labstation for Synthesis) equipped with a built-in ATC-FO advanced fiber optic automatic temperature control. ^{1}H NMR spectra were recorded using a Varian Gemini apparatus at 400 MHz in 5 mm tubes, using 0.01 M peptide at room temperature. Solvent suppression was performed by the solvent presaturation procedure implemented in Varian (PRESAT). ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts are reported as δ values relative to residual $CHCl_3$ δH (7.26 p.p.m.), DMSO δH (2.50 p.p.m.) and $CDCl_3$ δC (77.16 p.p.m.) as internal standards. The unambiguous assignment of ^{1}H NMR resonances was performed by 2D gCOSY.

General procedure for the synthesis of Ts-Ser/Thr/phenylSer-Ser-OMe (**1**)

A stirred solution of the *N*-tosylamino acid (1.0 mmol) in 4:1 DCM/DMF (5 mL) was treated with HOBt (1.2 mmol) and HBTU (1.2 mmol), at r.t. and under inert atmosphere. After 5 min, the amino acid esters (1.1 mmol), and DIPEA (2.4 mmol) were added and the reaction was stirred under MW irradiation (Bacsa et al. 2008). The microwave-assisted reaction was performed by setting maximum irradiation power at 150 W and monitoring the internal reaction temperature at 80 °C. After 10 min, the mixture was concentrated at reduced pressure, and the residue was diluted with EtOAc (25 mL). The solution was washed with 0.1 M HCl (5 mL), and a saturated solution of $NaHCO_3$ (5 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude peptides (80–90 % yield, 70–80 % pure by analytical RP-HPLC) were identified by ESI–MS and ^{1}H NMR analysis, and were used without further purifications.

Ts-L-Ser-L-Ser-OMe (**1a**). ^{1}H NMR ($CDCl_3$) δ: 2.31 (s, 3H, TsMe), 3.49 (m, 1H, SerHα), 3.62 (s, 3H, OMe), 3.70–3.90 (m, 4H, SerHβ), 4.41 (m, 1H, SerHα), 6.66 (*d*, J = 7.2 Hz, 1H, SerNH), 7.18–7.22 (m, 2H, TsArH), 7.63–7.69 (m, 3H, TsArH + SerNH); ES–MS *m/z:* 361.1 $[M + H]^+$, calcd 361.0.

Table 1 Reactions of *1a–c* with DSC/DIPEA under different conditions

Entry	1	solvent	Temp (°C)	2 + 3 (%)[a]	2:3 (%)[b]
1	a	DCM/DMF	20	93	51.49
2	a	DCM	20	88	92:8
3	a	DMF	20	86	5:95
4[c]	a	DMF	0	94	2:98
5[c]	b	DMF	0	92	3:97
6[c]	c	DMF	0	90	2:98

[a] Determined after isolation by flash chromatography over silica gel

[b] Determined by RP- HPLC of the reaction mixtures

[c] Slow addition of DSC to 1

Ts-L-Thr-L-Ser-OMe (**1b**). ^{1}H NMR ($CDCl_3$) δ: 1.00 (*d*, $J = 6.4$ Hz, 3H, ThrMe), 2.38 (s, 3H, TsMe), 3.72 (s, 3H, OMe), 3.74 (*t*, $J = 3.0$ Hz, 1H, ThrHα), 3.85–3.89 (m, 2H, SerHβ), 4.18–4.24 (m, 2H, ThrHβ), 4.46 (*q*, $J = 3.8$ Hz, 1H, SerHα), 6.31 (*d*, $J = 8.0$ Hz, 1H, ThrNH), 7.21–7.25 (m, 2H, TsArH), 7.60 (*d*, $J = 7.6$ Hz, SerNH), 7.69–7.63 (m, 2H, TsArH); ES–MS *m/z:* 375.2 $[M + H]^+$, calcd 375.1.

Ts-L/D-phenylSer-L-Ser-OMe (**1c**). ^{1}H NMR ($CDCl_3$) δ (*two diastereoisomers*): 2.39 + 2.40 (s, 3H, TsMe), 3.80 (s, 3H, OMe), 3.90–4.06 (m, 3H, PhSerHβ + SerHβ), 4.63–4.65 (m, 1H, SerHα), 5.27 + 5.31 (m, 1H, PhSerHα), 7.02–7.40 (m, 10H, TsArH + PhSerArH + PhSerNH), 7.90 + 7.93 (*d*, $J = 7.6$ Hz, 1H, SerNH); ES–MS *m/z:* 437.3 $[M + H]^+$, calcd 437.1.

General procedure for the synthesis of Ts-Oxd-ΔAla-OMe (**3**)

N,N-disuccinimidyl carbonate (0.73 mmol) was added in 60 min using a temporized syringe to a stirred solution of **1** (0.33 mmol) in DMF (4 mL) and a catalytic amount of DIPEA (0.07 mmol) at 0 °C and under inert atmosphere. After 60 min, the solvent was removed under reduced pressure. The residue was diluted with 0.1 M HCl (5 mL), and the mixture was extracted three times with DCM (5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The residue was purified by flash chromatography over silica gel (eluant cyclohexane/EtOAc 70:30), giving **3** (yields: see Table 1; 94–96 % pure by analytical RP-HPLC) as waxy solids.

Ts-L-Oxd-ΔAla-OMe (**3a**). $[\alpha]_D^{20}$ −26.8 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ: 2.42 (s, 3H, Me), 3.88 (s, 3H, COOMe), 4.45 (dd, $J = 4.6$, 9.0 Hz, 1H, $OxdH_5$), 4.52 (*t*, $J = 9.1$ Hz, 1H, $OxdH_5$), 4.99 (dd, $J = 4.4$, 9.2 Hz, 1H, $OxdH_4$), 6.05 (s, 1H, =CH), 6.65 (s, 1H, =CH), 7.33–7.37 (m, 2H, TsArH), 7.92–7.96 (m, 2H, TsArH), 8.54 (s, 1H, ΔAlaNH); ^{13}C NMR ($CDCl_3$) δ: 21.4, 52.6, 57.9, 66.0, 111.0, 128.7, 128.9, 129.1, 129.1, 131.0, 133.8, 145.4, 151.5, 163.6, 166.8; ES–MS *m/z:* 369.1 $[M + H]^+$, calcd 369.1. Elem. Anal. for $C_{15}H_{16}N_2O_7S$, calcd: C 48.91, H 4.38, N 7.60, S 8.70; found: C 49.15, H 4.51, N 7.51, S 8.57.

Ts-L-5-Me-Oxd-ΔAla-OMe (**3b**). $[\alpha]_D^{20}$ −18.3 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ: 1.44 (*d*, $J = 12.4$ Hz, 3H, 5-Me), 2.44 (s, 3H, TsMe), 3.86 (s, 3H, COOMe), 4.54 (*d*, $J = 10.0$ Hz, 1H, $OxdH_4$), 4.71 (m, 1H, $OxdH_5$), 6.03 (s, 1H, =CH), 6.65 (s, 1H, =CH), 7.33–7.37 (m, 2H, TsArH), 7.92–7.96 (m, 2H, TsArH), 8.55 (s, 1H, ΔAlaNH); ^{13}C NMR ($CDCl_3$) δ: 20.7, 20.8, 53.5, 65.4, 75.1, 111.4, 129.2, 130.0, 130.1, 130.9, 133.8, 146.5, 151.4, 164.2, 166.2; ES–MS *m/z:* 400.2 [M + 18], calcd 400.4. Elem. Anal. for $C_{16}H_{24}N_2O_7S$, calcd: C, 50.26; H, 4.74; N, 7.33; S, 8.39; found: C, 49.97; H, 4.89; N, 7.45; S, 8.22.

Ts-L/D-5-Ph-Oxd-ΔAla-OMe (**3c**). ^{1}H NMR ($CDCl_3$) δ: 2.47 (s, 3H, TsMe), 3.88 (s, 3H, OMe), 4.71 (*d*, $J = 4.6$ Hz, 1H, $OxdH_4$), 5.64 (*d*, $J = 4.6$ Hz, 1H, $OxdH_5$), 6.08 (s, 1H, =CH), 6.72 (s, 1H, =CH), 7.14–7.21 (m, 2H, TsArH), 7.32–7.39 (m, 5H, 5-Ph), 7.86–7.90 (m, 2H, TsArH), 8.55 (s, 1H, ΔAlaNH); ^{13}C NMR ($CDCl_3$) δ: 21.8, 53.2, 66.3, 78.1, 111.1, 125.0, 128.8, 129.3, 129.6, 129.8, 130.6, 133.4, 136.5, 151.2, 163.7, 165.6; ES–MS *m/z* 445.2 $[M + H]^+$, calcd 445.1. Elem. Anal. for $C_{21}H_{20}N_2O_7S$, calcd: C, 56.75; H, 4.54; N, 6.30; S, 7.21; found: C, 56.45; H, 4.58; N, 6.33; S, 7.12.

General procedure for the Michael addition with substituted indoles

A flame-dried flask containing freshly activated powdered 4 Å molecular sieves (200 wt%) under inert atmosphere was charged with anhydrous DCM (5 mL), then the indole (Table 2 1.0 mmol), **3** (1.0 mmol) and, PhOH (0.20 mmol) were added under inert atmosphere at r.t. The Lewis acid (1 M in DCM, 1.0 mmol) was slowly added under inert atmosphere at 0 °C. The reaction was stirred at 0 °C for 24 h, and then it was quenched with 0.5 M HCl (5 mL). The mixture was filtered over Celite®, and concentrated at reduced pressure to a final volume of 5 mL. The residual aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with saturated $NaHCO_3$ (5 mL), and dried over Na_2SO_4. The solvent was evaporated at reduced pressure, and the crude residue was purified by flash chromatography over silica gel (eluant cyclohexane/EtOAc 70:20) giving **4** and **5** (Table 2, 94–97 % pure by analytical HPLC) as waxy solids.

Ts-L-Oxd-L-Trp-OMe (**4a**). $[\alpha]_D^{20}$ +44.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.40 (s, 3H, TsMe), 3.38 (*d*, $J = 5.0$ Hz, 2H, TrpHβ), 3.67 (s, 3H, OMe), 4.10–4.15 (m, 2H, $OxdH_5$), 4.73 (dd, $J = 6.4$, 7.6 Hz, 1H, $OxdH_4$),

Table 2 Yields and d.r. for the F–C reaction of R-indoles with *3a–c* with different Lewis Acids

Entry	3	L.A. (eq.)	R_1-Indole (Eq.)	4/5 (%)[a]	4, 5	4 (%)[b]	5 (%)[b]
1	**a**	$AlEt_2Cl$ (1.5)	H	18:82	**a**	10	45
2	**a**	$AlEtCl_2$ (1.5)	H	25:75	**a**	17	52
3	**a**	$SnCl_4$ (1.05)	H	10:90	**a**	7	67
4	**a**	$AlEt_2Cl$ (1.5)	2-Me	15:85	**b**	10	59
5	**a**	$AlEtCl_2$ (1.5)	2-Me	23:77	**b**	20	68
6	**a**	$SnCl_4$ (1.05)	2-Me	8:92	**b**	7	82
7	**a**	$AlEt_2Cl$ (1.5)	5-F	16:85	**c**	8	47
8	**a**	$AlEtCl_2$ (1.5)	5-F	22:78	**c**	17	62
9	**a**	$SnCl_4$ (1.05)	5-F	10:90	**c**	8	74
10	**a**	$AlEt_2Cl$ (1.5)	7-Br	11:89	**d**	6	51
11	**a**	$AlEtCl_2$ (1.5)	7-Br	8:92	**d**	6	69
12	**a**	$SnCl_4$ (1.05)	7-Br	6:94	**d**	4.5	71
13	**a**	$AlEt_2Cl$ (1.5)	1-Me	5:95	**e**	Traces[c]	77
14	**a**	$AlEtCl_2$ (1.5)	1-Me	9:91	**e**	7[c]	85
15	**a**	$SnCl_4$ (1.05)	1-Me	3:97	**e**	Traces[c]	94
16	**a**	$AlEt_2Cl$ (1.5)	7-Br-2-Me	17:83	**i**	12	61
17	**a**	$AlEtCl_2$ (1.5)	7-Br-2-Me	11:89	**i**	9	75
18	**a**	$SnCl_4$ (1.05)	7-Br-2-Me	14:86	**i**	12	71
19	**a**	$AlEt_2Cl$ (1.5)	5-Cl-2-Me	9:91	**l**	6	63
20	**a**	$AlEtCl_2$ (1.5)	5-Cl-2-Me	16:84	**l**	13	68
21	**a**	$SnCl_4$ (1.05)	5-Cl-2-Me	12:88	**l**	9	68
22	**b**	$AlEt_2Cl$ (1.5)	2-Me	19:81	**m**	11	46
23	**b**	$AlEtCl_2$ (1.5)	2-Me	27:73	**m**	16	43
24	**b**	$SnCl_4$ (1.05)	2-Me	15:85	**m**	9	51
25	**b**	$AlEt_2Cl$ (1.5)	7-Br-2-Me	18:82	**n**	49[d]	
26	**b**	$AlEtCl_2$ (1.5)	7-Br-2-Me	18:82	**n**	54[d]	
27	**b**	$SnCl_4$ (1.05)	7-Br-2-Me	22:78	**n**	60[d]	
28	**c**	$AlEt_2Cl$ (1.5)	1-Me	23:77	**o**	55[d]	
29	**c**	$AlEtCl_2$ (1.5)	1-Me	30:70	**o**	62[d]	
30	**c**	$SnCl_4$ (1.05)	1-Me	20:80	**o**	64[d]	
31	**c**	$AlEt_2Cl$ (1.5)	2-Ph	20:80	**p**	50[d]	
32	**c**	$AlEtCl_2$ (1.5)	2-Ph	25:75	**p**	64[d]	
33	**c**	$SnCl_4$ (1.05)	2-Ph	20:80	**p**	65[d]	
34	**c**	$AlEt_2Cl$ (1.5)	5-Cl-2-Me	16:84	**q**	54[d]	
35	**c**	$AlEtCl_2$ (1.5)	5-Cl-2-Me	28:72	**q**	60[d]	
36	**c**	$SnCl_4$ (1.05)	5-Cl-2-Me	21:79	**q**	66[d]	

n.d. Not determined

[a] Diastereomeric ratios determined by normal-phase HPLC of the reaction mixtures, using a Kromasil Diol column

[b] Yields calculated after isolation by flash chromatography over silica gel

[c] Not isolated

[d] The diastereoisomers were not separated

4.94 (dt, $J = 5.0$, 7.6 Hz, 1H, TrpHα), 6.94 (*d*, $J = 7.6$ Hz, 1H, TrpNH), 7.12 (*t*, $J = 7.6$ Hz, 1H, $TrpH_5$), 7.16 (m, 2H, $TrpH_{2,6}$), 7.21–7.23 (m, 2H, TsArH), 7.36 (*d*, $J = 8.0$ Hz, 1H, $TrpH_7$), 7.54 (*d*, $J = 8.0$ Hz, 1H, $TrpH_4$), 7.83–7.85 (m, 2H, TsArH), 8.47 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) *δ*: 21.7, 27.5, 52.6, 53.0, 57.8, 65.9, 108.8, 111.5, 118.2, 119.6, 122.2, 124.0, 127.2, 128.9, 129.6, 136.1, 151.8, 167.4, 171.9; ESI–MS *m/z* 486.2 $[M + H]^+$, calcd 486.1. Elem. Anal. for $C_{23}H_{23}N_3O_7S$, calcd: C, 56.90; H, 4.77; N, 8.65; S, 6.60; found: C, 57.47; H, 4.80; N, 8.59; S, 6.55.

Ts-L-Oxd-D-Trp-OMe (**5a**). $[\alpha]_D^{20}$ −22.0 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) *δ*: 2.41 (s, 3H, TsMe), 3.37 (dd, $J = 6.4$, 15.5 Hz, 1H, TrpHβ), 3.39 (dd, $J = 6.2$, 15.5 Hz, 1H, TrpHβ), 3.73 (s, 3H, OMe), 4.05 (dd, $J = 5.0$, 9.0 Hz, 1H, $OxdH_5$), 4.20 (m, 1H, $OxdH_5$), 4.77 (dd, $J = 5.0$, 9.0 Hz, 1H, $OxdH_4$), 4.93 (ddd, $J = 6.2$, 6.4, 7.6 Hz, 1H, TrpHα), 7.03 (*d*, $J = 7.6$ Hz, 1H, TrpNH), 7.10 (*t*, $J = 7.2$ Hz, 1H, $TrpH_6$), 7.12 (br.s, 1H, $TrpH_2$), 7.18 (*t*, $J = 7.4$ Hz, 1H, $TrpH_5$), 7.24–7.26 (m, 2H, TsArH), 7.35 (*d*, $J = 8.0$ Hz, 1H, $TrpH_7$), 7.49 (*d*, $J = 8.0$ Hz, 1H, $TrpH_4$), 7.84–7.86 (m, 2H, TsArH), 8.54 (br.s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) *δ*: 22.1, 27.6, 38.1, 53.5, 58.3, 66.1, 109.6, 111.9, 118.7, 120.0, 122.7, 123.9, 128.0, 129.3, 130.1, 133.9, 136.6, 146.5, 167.7, 170.2, 171.3; ESI–MS *m/z* 486.2 $[M + H]^+$,

calcd 486.1. Elem. Anal. for $C_{23}H_{23}N_3O_7S$, calcd: C, 56.90; H, 4.77; N, 8.65; S, 6.60; found: C, 56.34; H, 4.84; N, 8.73; S, 6.45.

Ts-L-Oxd-L-2-Me-Trp-OMe (**4b**): $[\alpha]_D^{20}$ −65.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ*: 2.39 (s, 3H, TrpMe), 2.40 (s, 3H, TsMe), 3.26 (dd, *J* = 6.2, 14.8 Hz, 1H, TrpHβ), 3.35 (dd, *J* = 6.0, 14.8 Hz, 1H, TrpHβ), 3.73 (s, 3H, OMe), 4.12 (m, 1H, $OxdH_5$), 4.29 (*t*, *J* = 9.0 Hz, 1H, $OxdH_5$), 4.75 (dd, *J* = 4.4, 9.0 Hz, 1H, $OxdH_4$), 4.91 (ddd, *J* = 6.0, 6.2, 8.0 Hz, 1H, TrpHα), 6.69 (*d*, *J* = 8.0 Hz, 1H, TrpNH), 7.10–7.17 (m, 6H, $TrpH_{4-7}$ + TsArH), 7.76–7.78 (m, 2H, TsArH), 8.00 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) *δ*: 11.6, 21.7, 29.7, 52.6, 57.7, 65.8, 105.2, 110.5, 117.6, 119.8, 121.5, 128.5, 128.9, 129.6, 133.2, 133.6, 135.3, 145.9, 151.6, 167.2, 171.9; ESI–MS *m/z* 500.2 $[M + H]^+$, calcd 500.1. Elem. Anal. for $C_{24}H_{25}N_3O_7S$, calcd: C, 57.70; H, 5.04; N, 8.41; S, 6.42; found: C, 58.68; H, 4.98; N, 8.52; S, 6.39.

Ts-L-Oxd-D-2-Me-Trp-OMe (**5b**): $[\alpha]_D^{20}$ +13.8 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ*: 2.40 (s, 3H, TrpMe), 2.41 (s, 3H, TsMe), 3.24 (dd, *J* = 6.6, 14.6 Hz, 1H, TrpHβ), 3.36 (dd, *J* = 5.8, 14.6 Hz, 1H, TrpHβ), 3.73 (s, 3H, OMe), 3.94 (dd, *J* = 4.8 8.8 Hz, 1H, $OxdH_5$), 4.11 (dd, *J* = 8.8, 9.4 Hz, 1H, $OxdH_5$), 4.64 (dd, *J* = 4.8, 9.4 Hz, 1H, $OxdH_4$), 4.88 (ddd, *J* = 5.8, 6.6, 7.2 Hz, 1H, TrpHα), 6.73 (*d*, *J* = 7.2 Hz, 1H, TrpNH), 7.08–7.18 (m, 4H, $TrpH_{4-7}$), 7.20–7.22 (m, 2H, TsArH), 7.80–7.82 (m, 2H, TsArH), 7.98 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) *δ*: 12.0, 22.1, 27.3, 53.0, 53.7, 58.1, 65.7, 105.7, 111.0, 118.0, 120.0, 121.8, 128.8, 129.2, 129.3, 130.0, 133.7, 135.7, 146.3, 152.0, 172.1, 172.3; ESI–MS *m/z* 500.2 $[M + H]^+$, calcd: 500.1. Elem. Anal. for $C_{24}H_{25}N_3O_7S$, calcd: C, 57.70; H, 5.04; N, 8.41; S, 6.42; found: C, 57.61; H, 5.10; N, 8.46; S, 6.30.

Ts-L-Oxd-L-5-F-Trp-OMe (**4c**). $[\alpha]_D^{20}$ +16.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ*: 2.44 (s, 3H, TsMe), 3.37 (*d*, *J* = 4.8 Hz, 2H, TrpHβ), 3.76 (s, 3H, OMe), 4.28 (dd, *J* = 4.4, 9.8 Hz, 1H, $OxdH_5$), 4.39 (*t*, *J* = 9.6 Hz, 1H, $OxdH_5$), 4.76 (dd, *J* = 4.4, 9.0 Hz, 1H, $OxdH_4$), 4.92 (m, 1H, TrpHα), 6.88 (br.d, 1H, TrpNH), 6.93 (*d*, *J* = 6.8 Hz, 1H, $TrpH_6$), 7.05 (s, 1H, $TrpH_2$), 7.12 (s, 1H, $TrpH_4$), 7.28–7.29 (m, 2H, TsArH), 7.53 (*d*, *J* = 6.8 Hz, 1H, $TrpH_7$), 7.84–7.86 (m, 2H, TsArH), 8.16 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) *δ*: 22.1, 30.1, 53.3, 53.8, 58.3, 66.1, 103.3, 110.4, 113.2, 115.0, 123.0, 127.6, 128.1, 129.3, 130.2, 133.7, 137.6, 151.9, 157.6, 170.2, 171.7; ES–MS *m/z* 504.0 $[M + H]^+$, calcd 504.1. Elem. Anal. for $C_{23}H_{22}FN_3O_7S$, calcd: C, 54.87; H, 4.40; N, 8.35; S, 6.37; found: C, 54.58; H, 4.68; N, 8.38; S, 6.33.

Ts-L-Oxd-D-5-F-Trp-OMe (**5c**) $[\alpha]_D^{20}$ +38.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ*: 2.44 (s, 3H, TsMe), 3.36 (*d*, *J* = 5.2 Hz, 2H, TrpHβ), 3.76 (s, 3H, OMe), 4.27 (dd, *J* = 5.6, 8.2 Hz, 1H, $OxdH_5$), 4.37 (dd, *J* = 8.2, 9.4 Hz, 1H, $OxdH_5$), 4.75 (dd, *J* = 5.6, 9.4 Hz, 1H, $OxdH_4$), 4.91 (m, 1H, TrpHα), 7.04 (br.d, 1H, TrpNH), 6.96–7.10 (m, 2H, $TrpH_{2,6}$), 7.12 (s, 1H, $TrpH_4$), 7.28–7.30 (m, 2H, TsArH), 7.54 (*d*, *J* = 8.0 Hz, 1H, $TrpH_7$), 7.84–7.87 (m, 2H, TsArH), 8.48 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) *δ*: 21.0, 28.0, 51.1, 52.9, 56.9, 60.8, 101.6, 107.9, 110.6, 113.2, 121.0, 125.5, 126.1, 127.1, 130.0, 131.5, 135.3, 149.3, 155.0, 168.6, 168.8; ES–MS *m/z* 504.0 $[M + H]^+$, calcd 504.1. Elem. Anal. for $C_{23}H_{22}FN_3O_7S$, calcd: C, 54.87; H, 4.40; N, 8.35; S, 6.37; found: C, 55.16; H, 4.43; N, 8.29; S, 6.30.

Ts-L-Oxd-L-7-Br-Trp-OMe (**4d**). $[\alpha]_D^{20}$ +51.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 2.40 (s, 3H, TsMe), 3.38 (*d*, *J* = 4.8 Hz, 2H, TrpHβ), 3.73 (s, 3H, OMe), 4.34 (dd, *J* = 4.4, 7.8 Hz, 1H, $OxdH_5$), 4.44 (dd, *J* = 7.8, 10.0 Hz, 1H, $OxdH_5$), 4.83 (dd, *J* = 4.4, 10.0 Hz, 1H, $OxdH_4$), 4.98 (m, 1H, TrpHα), 6.71 (br.d, 1H, TrpNH), 6.90 (*t*, *J* = 8.0 Hz, 1H, $TrpH_5$), 7.16 (br.s, 1H, $TrpH_2$), 7.22–7.31 (m, 3H, TsArH + $TrpH_6$), 7.51 (*d*, *J* = 8.0 Hz, 1H, $TrpH_4$), 7.81 (*d*, *J* = 8.0 Hz, 2H, TsAr), 8.30 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$, 400 MHz) *δ*: 20.8, 28.0, 50.9, 51.3, 56.6, 60.7, 98.1, 107.5, 115.4, 118.7, 120.5, 122.0, 125.7, 126.7, 127.0, 131.0, 132.8, 134.8, 149.0, 168.1, 168.3; ES–MS *m/z* 563.8/565.8 $[M + H]^+$, calcd 564.0/566.0. Elem. Anal. for $C_{23}H_{22}BrN_3O_7S$, calcd: C, 48.94; H, 3.93; N, 7.45; S, 5.68; found: C, 49.34; H, 3.96; N, 7.37; S, 5.61.

Ts-L-Oxd-D-7-Br-Trp-OMe (**5d**). $[\alpha]_D^{20}$ −11.0 (*c* 0.5, $CHCl_3^1$H NMR ($CDCl_3$) *δ*: 2.45 (s, 3H, TsMe), 3.40 (*d*, *J* = 4.8 Hz, 2H, TrpHβ), 3.73 (s, 3H, OMe), 4.30 (dd, *J* = 5.0, 8.4 Hz, 1H, $OxdH_5$), 4.38 (dd, *J* = 8.4, 9.0 Hz, 1H, $OxdH_5$), 4.75 (dd, *J* = 5.0, 9.0 Hz, 1H, $OxdH_4$), 4.93 (dt, *J* = 4.8, 7.6 Hz, 1H, TrpHα), 6.83 (*d*, *J* = 7.6 Hz, 1H, TrpNH), 6.91 (*t*, *J* = 7.8 Hz, 1H, $TrpH_5$), 7.16 (br.s, 1H, $TrpH_2$), 7.22–7.31 (m, 3H, TsArH + $TrpH_6$), 7.47 (*d*, *J* = 8.0 Hz, 1H, $TrpH_4$), 7.85–7.88 (m, 2H, TsArH), 8.30 (br.s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) *δ*: 21.0, 28.1, 51.1, 51.6, 57.0, 61.0, 98.5, 108.1, 116.1, 119.3, 121.2, 122.6, 126.4, 127.4, 127.7, 131.7, 133.5, 135.5, 149.6, 169.0, 169.2; ES–MS *m/z* 563.9/565.9 $[M + H]^+$, calcd 564.0/566.0. Elem. Anal. for $C_{23}H_{22}BrN_3O_7S$, calcd: C, 48.94; H, 3.93; N, 7.45; S, 5.68; found: C, 49.55; H, 3.90; N, 7.49; S, 5.63.

Ts-L-Oxd-D-1-Me-Trp-OMe (**5e**). $[\alpha]_D^{20}$ +20.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ*: 2.43 (s, 6H, TrpMe + TsMe), 3.41 (*d*, *J* = 4.4 Hz, 2H, TrpHβ), 3.73 (s, 3H, OMe), 4.24 (dd, *J* = 4.4, 9.6 Hz, 1H, $OxdH_5$), 4.35 (*t*, *J* = 9.2 Hz, 1H, $OxdH_5$), 4.74 (dd, *J* = 4.8, 9.0 1H, $OxdH_4$), 4.90 (dt, *J* = 4.4, 8.0 Hz, 1H, TrpHα), 6.51 (br.s, 1H, $TrpH_2$), 6.78 (*d*, *J* = 8.0 Hz, 1H, TrpNH), 7.02–7.12 (m, 2H, $TrpH_{5,7}$), 7.32–7.36 (m, 2H, TsArH), 7.48 (*d*, *J* = 8.0 Hz, 1H, $TrpH_6$), 7.59 (*d*, (*d*, *J* = 7.6 Hz, 1H, $TrpH_4$), 7.61–7.66 (m, 2H, TsArH); ^{13}C NMR ($CDCl_3$) *δ*: 20.9, 28.2, 33.3, 50.9, 52.7, 56.6, 60.7, 107.4, 107.5, 116.4, 117.4, 119.3, 122.7,

125.1, 125.7, 126.7, 131.0, 134.8, 135.0, 149.0, 168.1, 168.3; ESI–MS *m/z* 500.1 $[M + H]^+$, calcd: 500.1, Elem. Anal. for $C_{24}H_{25}N_3O_7S$, calcd: C, 57.70; H, 5.04; N, 8.41; S, 6.42; found: C, 58.54; H, 5.08; N, 8.35; S, 6.39.

Ts-L-Oxd-L-7-Br-2-Me-Trp-OMe (**4i**). $[\alpha]_D^{20}$ +7.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.42 (s, 3H, TrpMe), 2.44 (s, 3H, TsMe), 3.25 (dd, $J = 4.8$, 13.2 Hz, 1H, TrpHβ), 3.31 (dd, $J = 3.6$, 13.2 Hz, 1H, TrpHβ), 3.74 (s, 3H, OMe), 4.20 (dd, $J = 4.5$, 8.8 Hz, 1H, $OxdH_5$), 4.40 (dd, $J = 8.8$, 9.1 Hz, $OxdH_5$), 4.75 (dd, $J = 4.5$, 9.1 Hz, 1H, $OxdH_4$), 4.94 (ddd, $J = 3.6$, 4.8, 7.6, 1H, TrpHα), 6.63 (*d*, $J = 7.6$ Hz, 1H, TrpNH), 6.98–7.15 (m, 2H, $TrpH_{4,5}$), 7.22–7.24 (m, 2H, TsArH), 7.46 (*d*, $J = 7.6$ Hz, 1H, $TrpH_6$), 7.78–7.82 (m, 2H, TsArH), 8.03 (br.s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) δ: 12.2, 22.4, 28.0, 51.7, 53.8, 59.2, 62.5, 100.9, 108.0, 118.6, 121.8, 123.1, 128.0, 130.0, 131.5, 136.9, 138.7, 153.2, 170.7. ES–MS *m/z* 591.1 [M + Na] calcd 591.0, Elem. Anal. for $C_{24}H_{24}BrN_3O_7S$, calcd: C, 49.83; H, 4.18; N, 7.26; S, 5.54; found: C, 49.51; H, 4.21; N, 7.35; S, 5.49.

Ts-L-Oxd-D-7-Br-2-Me-Trp-OMe (**5i**). $[\alpha]_D^{20}$ −38.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.47 (s, 3H, TrpMe), 2.49 (s, 3H, TsMe), 3.24 (dd, $J = 5.8$, 14.9 Hz, 1H, TrpHβ), 3.34 (dd, $J = 6.4$, 14.9 Hz, 1H, TrpHβ), 3.73 (s, 3H, OMe), 4.19 (dd, $J = 4.8$, 8.8 Hz, 1H, $OxdH_5$), 4.26 (*t*, $J = 8.9$ Hz, $OxdH_5$), 4.68 (dd, $J = 4.8$, 8.9 Hz, 1H, $OxdH_4$), 4.93 (ddd, $J = 5.8$, 6.4, 7.2 Hz, 1H, TrpHα), 6.73 (*d*, $J = 7.2$ Hz, 1H, TrpNH), 7.00–7.20 (m, 2H, $TrpH_{4,5}$), 7.44 (m, 2H, TsArH), 7.46 (*d*, $J = 7.6$ Hz, 1H, $TrpH_6$), 7.84 (*d*, $J = 8.0$ Hz, 2H, TsArH), 8.47 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) δ: 12.2, 22.4, 28.0, 51.7, 53.8, 59.2, 62.5, 100.9, 108.0, 118.6, 121.8, 123.1, 127.9, 128.2, 130.0, 131.5, 136.9, 138.7, 153.2, 167.7, 170.7. ES–MS *m/z* 591.1 [M + Na] calcd 591.0, Elem. Anal. for $C_{24}H_{24}BrN_3O_7S$, calcd: C, 49.83; H, 4.18; N, 7.26; S, 5.54; found: C, 49.42; H, 4.22; N, 7.19; S, 5.54.

Ts-L-Oxd-L-5-Cl-2-Me-Trp-OMe (**4 l**). $[\alpha]_D^{20}$ −13.6 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.39 (s, 3H, TrpMe), 2.43 (s, 3H, TsMe), 3.23 (dd, $J = 7.0$, 14.6 Hz, 1H, TrpHβ), 3.28 (dd, $J = 6.0$, 14.6 Hz, 1H, TrpHβ), 3.76 (s, 3H, OMe), 4.26 (dd, $J = 4.5$, 9.2 Hz, 1H, $OxdH_5$), 4.37 (*t*, $J = 9.1$ Hz, $OxdH_5$), 4.75 (dd, $J = 4.5$, 9.0 Hz, 1H, $OxdH_4$), 4.89 (ddd, $J = 6.0$, 7.0, 7.6 Hz, 1H, TrpHα), 6.64 (*d*, $J = 7.6$ Hz, 1H, TrpNH), 7.10 (*d*, $J = 8.4$ Hz, $TrpH_6$), 7.18 (*d*, $J = 8.4$ Hz, 1H, $TrpH_7$), 7.19–7.23 (m, 2H, TsArH), 7.46 (s, 1H, $TrpH_4$), 7.75–7.79 (m, 2H, TsArH), 7.97 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) δ: 11.7, 21.7, 26.9, 52.7, 53.2, 57.8, 65.7, 105.2, 111.5, 117.2, 121.7, 125.5, 128.8, 129.6, 129.7, 133.6, 134.9, 151.5, 167.2, 171.7; ESI–MS *m/z* 534.0 $[M + H]^+$, calcd 534.1. Elem. Anal. for $C_{24}H_{24}ClN_3O_7S$, calcd: C, 53.98; H, 4.53; N, 7.87; S, 6.00; found: C, 54.58; H, 4.50; N, 7.79; S, 6.06.

Ts-L-Oxd-D-5-Cl-2-Me-Trp-OMe (**5 l**). $[\alpha]_D^{20}$ −12.0 (c 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.39 (s, 3H, TrpMe), 2.42 (s, 3H, TsMe), 3.22 (dd, $J = 5.8$, 14.6 Hz, 1H, TrpHβ), 3.33 (dd, $J = 6.2$, 14.6 Hz, 1H, TrpHβ), 3.78 (s, 3H, OMe), 4.15 (dd, $J = 4.6$, 8.8 Hz, 1H, $OxdH_5$), 4.29 (*t*, $J = 9.0$ Hz, 1H, $OxdH_5$), 4.70 (dd, $J = 4.6$, 9.0 Hz, 1H, $OxdH_4$), 4.87 (ddd, $J = 5.8$, 6.2, 7.6 Hz, 1H, TrpHα), 6.76 (*d*, $J = 7.6$ Hz, 1H, TrpNH), 7.08 (*d*, $J = 8.4$ Hz, 1H, $TrpH_6$), 7.19 (*d*, $J = 8.4$ Hz, 1H, $TrpH_7$), 7.20–7.24 (m, 2H, TsArH), 7.32 (s, 1H, $TrpH_4$), 7.80–7.83 (m, 2H, TsArH), 8.00 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) δ: 11.5, 21.5, 29.5, 52.2, 53.0, 57.3, 65.5, 105.2, 111.4, 117.0, 120.5, 124.3, 128.8, 129.2, 129.9, 133.4, 133.9, 135.0, 145.3, 151.6, 167.3, 171.7; ESI–MS *m/z* 534.0 $[M + H]^+$, calcd 534.1. Elem. Anal. for $C_{24}H_{24}ClN_3O_7S$, calcd: C, 53.98; H, 4.53; N, 7.87; S, 6.00; found: C, 53.67; H, 4.50; N, 7.91; S, 6.05.

Ts-L-5-Me-Oxd-L-2-Me-Trp-OMe (**4 m**). $[\alpha]_D^{20}$ +37.9 (c 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.11 (*d*, $J = 6.4$ Hz, 3H, OxdMe), 2.36 (s, 3H, TrpMe), 2.41 (s, 3H, TsMe), 3.29 (dd, $J = 6.4$, 14.8 Hz, 1H, TrpHβ), 3.32 (dd, $J = 6.0$, 14.8 Hz, 1H, TrpHβ), 3.70 (s, 3H, OMe), 4.26 (*d*, $J = 4.8$ Hz, 1H, $OxdH_4$), 4.36 (m, 1H, $OxdH_5$), 4.92 (ddd, $J = 6.0$, 6.4, 7.6 Hz, 1H, TrpHα), 6.71 (*d*, $J = 7.6$ Hz, 1H, TrpNH), 7.10–7.16 (m, 4H, $TrpH_{4-7}$), 7.18–7.22 (m, 2H, TsArH), 7.79–7.83 (m, 2H, TsArH), 7.95 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) δ: 11.6, 14.1, 21.6, 27.3, 52.3, 58.8, 64.0, 75.0, 105.2, 110.7, 118.5, 119.0, 120.7, 127.1, 128.5, 128.9, 129.4, 129.6, 133.9, 135.6, 137.5, 151.4, 167.3, 172.3; ESI–MS *m/z* 534.1 $[M + H]^+$, calcd 534.1. Elem. Anal. for $C_{25}H_{27}N_3O_7S$, calcd: C, 58.47; H, 5.30; N, 8.18; S, 6.24; found: C, 58.05; H, 5.33; N, 8.25; S, 6.18.

Ts-L-5-Me-Oxd-D-2-Me-Trp-OMe (**5 m**). $[\alpha]_D^{20}$ −6.5 (c 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.18 (*d*, $J = 6.4$ Hz, 3H, OxdMe), 2.41 (s, 3H, TrpMe), 2.41 (s, 3H, TsMe), 3.27 (dd, $J = 6.0$, 14.8 Hz, 1H, TrpHβ), 3.37 (dd, $J = 6.4$, 14.8 Hz, 1H, TrpHβ), 3.74 (s, 3H, OMe), 4.18 (*d*, $J = 4.4$ Hz, 1H, $OxdH_4$), 4.34 (m, 1H, $OxdH_5$), 4.87 (ddd, $J = 6.0$, 6.4, 7.2 Hz, 1H, TrpHα), 6.67 (*d*, $J = 7.2$ Hz, 1H, TrpNH), 7.10–7.15 (m, 4H, $TrpH_{4-7}$), 7.19–7.22 (m, 2H, TsArH), 7.80 (m, 2H, TsArH), 7.96 (s, 1H, $TrpH_1$); ^{13}C NMR ($CDCl_3$) δ: 11.7, 14.2, 21.7, 28.8, 53.3, 60.4, 64.4, 110.6, 117.5, 119.7, 121.4, 128.8, 129.7, 135.2, 164.5, 167.1, 171.8; ES–MS *m/z* 514.4 $[M + H]^+$, calcd 514.2. Elem. Anal. for $C_{25}H_{27}N_3O_7S$, calcd: C, 58.47; H, 5.30; N, 8.18; S, 6.24; found: C, 59.00; H, 5.26; N, 8.22; S, 6.19.

Ts-L-5-Me-Oxd-L/D-7-Br-2-Me-Trp-OMe (**4n**, **5n**). ^{1}H NMR ($CDCl_3$) δ (*two diastereoisomers*): 1.11 (*d*, $J = 6.4$ Hz, 3H, OxdMe), 2.40 (s, 3H, TsMe), 2.47 (s, 3H, TrpMe), 3.13 + 3.23 (*d*, $J = 6.0$ Hz, 2H, TrpHβ), 3.67 (s, 3H, OMe), 4.27 + 4.33 (*d*, $J = 4.6$ Hz, 1H, $OxdH_4$), 4.34 (m, 1H, $OxdH_5$), 4.71 + 4.79 (m, 1H, TrpHα), 6.94 + 7.00 (*t*, $J = 7.8$ Hz, 1H, $TrpH_5$), 7.08 (*d*, $J = 8.0$ Hz, 1H, $TrpH_4$), 7.06–7.09 (m, 1H, TrpNH), 7.22–7.31 (m, 3H, TsArH + $TrpH_6$), 7.65–7.69 (m, 2H, TsArH), 8.11 + 8.20 (s, 1H, $TrpH_1$). ES–MS *m/z* 609.2 [M + 18], calcd 609.1.

Ts-L/D-5-Ph-Oxd-L/D-1-Me-Trp-OMe (**4o**, **5o**). ^{1}H NMR ($CDCl_3$) δ (*racemic*, *two diastereoisomers*): 2.42 (s, 6H, TsMe + TrpMe), 3.35–3.46 (m, 2H, TrpHβ), 3.69 + 3.71 (s, 3H, OMe), 4.53 + 4.54 (*d*, $J = 4.0$ Hz, 1H, $OxdH_4$), 4.91–4.98 (m, 1H, TrpHα), 5.42 + 5.44 (*d*, $J = 4.0$ Hz, 2H, $OxdH_5$), 6.63 + 6.79 (*d*, $J = 7.0$ Hz, 1H, TrpNH), 6.81 + 6.82 (br.s, 1H, $TrpH_2$), 6.97 (*t*, $J = 7.2$ Hz, 1H, $TrpH_5$), 7.00–7.05 (m, 2H, TsArH), 7.30–7.61 (m, 8H, Ph + $TrpH_{4,6,7}$), 7.68–7.72 (m, 2H, TsArH); ES–MS *m/z* 576.3 $[M + H]^+$, calcd 576.2, found 576.3.

Ts-L/D-5-Ph-Oxd-L/D-2-Ph-Trp-OMe (**4p**, **5p**). ^{1}H NMR ($CDCl_3$) δ (*racemic*, *two diastereoisomers*): 2.43 + 2.47 (s, 3H, TsMe), 3.88 (s, 3H, OMe), 3.42–3.61 (m, 2H, TrpHβ), 4.83 + 4.87 (m, 1H, TrpHα), 4.90 (br.d, 1H, $OxdH_4$), 5.34 + 5.43 (br.d, 1H, $OxdH_5$), 6.91 (*d*, $J = 7.6$ Hz, 1H, TrpNH), 7.10 (*t*, $J = 7.2$ Hz, 1H, $TrpH_6$), 7.13–7.20 (m, 3H, $TrpH_5$ + TsArH), 7.22–7.40 (m, 10H, Ph), 7.52 + 7.54 (br.d, 1H, $TrpH_7$), 7.75 + 7.80 (*d*, $J = 7.8$ Hz, 1H, $TrpH_4$), 7.86–7.88 (m, 2H, TsArH), 8.57 (s, 1H, $TrpH_1$); ES–MS *m/z* 638.3 $[M + H]^+$, calcd 638.2.

Ts-L/D-5-Ph-Oxd-L/D-5-Cl-2-Me-Trp-OMe (**4q**, **5q**). ^{1}H NMR ($CDCl_3$) δ (*racemic*, *two diastereoisomers*): 2.37 + 2.39 (s, 3H, TsMe), 2.43 (s, 3H, TrpMe), 3.22–3.37 (m, 2H, TrpHβ), 3.77 + 3.78 (s, 3H, OMe), 4.51 + 4.52 (*d*, $J = 4.0$ Hz, 1H, $OxdH_4$), 4.88 + 4.95 (m, 1H, TrpHα), 5.44 + 5.50 (*d*, $J = 4.0$ Hz, 1H, $OxdH_5$), 6.62 + 6.86 (*d*, $J = 7.4$ Hz, 1H, TrpNH), 6.97 (*d*, $J = 7.2$ Hz, 2H, $TrpH_6$), 7.07–7.50 (m, 8H, Ph + TsArH + $TrpH_7$), 7.69–7.72 (m, 2H, TsArH), 7.95 + 7.99 (s, 1H, $TrpH_1$); ES–MS *m/z* 627.1 [M + Na], found 627.3.

(*S*)-*2-methyltryptophan* (***6b***), (*S*)-*5-fluorotryptophan* (***6c***). 10 % HBr (4.0 ml) was added to (*R*,*S*)-**5b** or (*R*,*S*)-**5c** (1.0 mmol), and the mixture was heated while stirring for 45 min by MW irradiation at 150 W, while monitoring the internal reaction temperature at 95 °C. The pH of the mixture was adjusted to about 3 with 1 M NaOH, and the aqueous mixture was washed three times with EtOAc (5 mL) to recover (*R*)-Ts-Ser-OH (not isolated). The aqueous layer was concentrated at reduced pressure and passed through Dowex 50X2-200 resin H^+ form. The resin washed with water (100 ml). The amino acids were eluted using 10 % ammonia in methanol (200 ml), and the solvent removed in vacuo to afford **6b** (0.73 mmol, 73 %) or **6c** (0.74 mmol, 74 %).

6b (commercially available). Optical rotation $[\alpha]_D^{20} = -9.8$ (*c* 0.26 in H_2O) was found to match with the literature (Yabe et al. 1979); NMR characterization was found to match with the literature (Mocek et al. 1993); ES–MS *m/z* 219.2 $[M + H]^+$, calcd 219.1.

6c. Optical rotation $[\alpha]_D^{20} = +5.6$ (*c* 1.0 in 0.1 M HCl) was found to match with the literature (Ma et al. 2001); NMR characterization was found to match with the literature (Blaser et al. 2008; Ma et al. 2001); ES–MS *m/z* 223.2 $[M + H]^+$, found 223.2.

N-Fmoc-(*S*)*-2-methyltryptophan* (***7b***), *N-Fmoc-*(*S*)*-5-fluorotryptophan* (***7c***). $NaHCO_3$ (118 mg, 1.4 mmol) and 9-fluorenylmethyloxycarbonyl succinimide (270 mg, 0.8 mmol) were added to the a suspension of amino acid **6b** or **6c** (0.7 mmol) in 1:1 water/dioxane (6 mL) at 0 °C, and the mixture was stirred overnight at r.t. Dioxane was removed at reduced pressure, and the pH of the aqueous mixture was adjusted to 3 with 1 M HCl. The mixture was extracted three times with EtOAc (10 mL), and the collected organic layers were dried over Mg_2SO_4. The solvent was evaporated at reduced pressure, affording the crude Fmoc-protected amino acid. The residues were purified by flash chromatography over silica gel (eluant: EtOAc/MeOH 97:3), giving **7b** or **7c** (for both 95 % yield, 92 % pure by RP-HPLC).

N-Fmoc-(*S*)-2-methyltryptophan (**7b**). ^{1}H NMR (DMSO-d_6) δ: 1.90 (s, 3H, TrpMe), 2.73 (dd, $J = 7.0$, 14.5 Hz, 1H, TrpHβ), 2.99 (dd, $J = 2.5$, 14.5 Hz, 1H, TrpHβ), 4.12–4.33 (m, 3H, FmocH), 4.65 (m, 1H, TrpHα), 6.05 (br.d, 1H, TrpNH), 7.00 (br.t, 1H, $TrpH_6$), 7.19–7.30 (m, 4H, FmocArH + $TrpH_{4,5}$), 7.36 (*t*, $J = 7.5$ Hz, 2H, FmocArH), 7.56 (*d*, $J = 7.5$ Hz, 2H, FmocArH), 7.76 (*d*, $J = 7.5$ Hz, 2H, FmocArH), 8.01 (*d*, $J = 7.0$ Hz, 1H, $TrpH_7$), 8.55 (s, 1H, $TrpH_1$); ES–MS m/z 441.3 $[M + H]^+$, calcd 441.2.

N-Fmoc-(*S*)-5-fluorotryptophan (**7c**). ^{1}H NMR characterization was found to match with the literature (Blaser et al. 2008); ES–MS *m/z* 444.2 $[M + H]^+$, calcd 444.2.

[*2-Me-Trp*^{3}]-*EM1* (***8***), [*5-F-Trp*^{3}]-*EM1* (***9***). A measure of Fmoc-Rink amide resin (0.3 g, 1.1 mmol/g, resin particle size: 100–200 mesh) was introduced into a reactor for solid-phase peptide synthesis (SPPS). Fmoc was removed with 4:1 DMF/piperidine (4 mL) under MW irradiation (40 W) for 1 min under mechanical shaking, monitoring the internal temperature at 45 °C. The suspension was filtered; the resin was washed with DCM (5 mL) and treated with a second portion of DMF/piperidine as above described. Then the suspension was filtered, and the resin was washed three times in sequence with DCM (5 mL) and MeOH (5 mL).

All coupling steps were performed according to the following general procedure. The resin was swollen in DCM (5 mL), and a solution of **7b** or **7c** (0.6 mmol) and HOBt (0.1 g, 0.7 mmol) in DMF (4 mL) was added at r.t. and under nitrogen atmosphere, followed by HBTU (0.26 g, 0.7 mmol) and DIPEA (0.2 mL, 1.2 mmol). The mixture was mechanically shaken under MW irradiation with an initial irradiation power of 40 W and monitoring the internal reaction temperature at 45 °C, and after 10 min the resin was filtered and washed three times with the sequence DCM (5 mL) and MeOH (5 mL). Coupling efficacy was determined by Kaiser or Chloranil test. All subsequent Fmoc deprotection steps were performed as

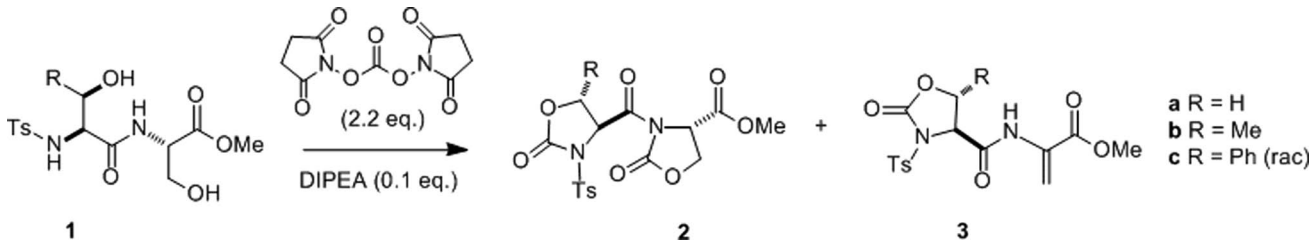


Fig. 2 One-pot synthesis of ΔAla equipped with Oxd chiral auxiliaries *3a–c*

above reported. The resin-bound peptide was suspended in a solution of TFA (9.0 mL), TIPS (0.40 mL), H_2O (0.40 mL), and PhOH (0.20 g), and mechanically shaken at r.t. After 2 h, the mixture was filtered, the resin was washed twice with 10 % TFA in Et_2O (10 mL) and twice Et_2O (10 mL). Filtrate and washes were collected and solvent and volatiles were removed under N_2 flow at r.t. The resulting residue was suspended in ice-cold Et_2O, and the crude solid which precipitated was triturated and collected by centrifuge. The peptide **8** or **9** was isolated by semi-preparative RP-HPLC (80 % yield based on the average resin loading; >95 % pure by analytical RP-HPLC, see general Methods).

[2-Me-Trp^3]-EM1 (**8**). ^{1}H NMR (DMSO-d6) δ (about *3:1 mixture of two conformers, t = major-trans isomer, c = minor-cis isomer*): 1.38–1.62 (m, $4H_c + 1H_t$), 1.72–1.84 (m, $2H_t$), 1.95 (m, $1H_t$), 2.09 (s, $3H_c$), 2.10 (s, $3H_t$), 2.62 (dd, $J = 6.5, 14.5$ Hz, $1H_t$), 2.65–2.76 (m, $3H_c$), 2.78 (dd, $J = 7.5, 15.0$ Hz, $1H_t$), 2.82 (dd, $J = 8.0, 14.0$ Hz, $1H_t$), 2.86 (m, $1H_c$), 2.90 (m, $1H_t$), 2.93 (m, $1H_c$), 2.95–3.09 (m, $2H_t + 1H_c$), 3.09 (dd, $J = 7.0, 15.5$ Hz, $1H_t$), 3.21-3.32 (m, $2H_c$), 3.45–3.61 (m, $1H_t + 2H_c$), 4.35–4.47 (m, $3H_t + 2H_c$), 4.55 (m, $1H_t$), 6.68 (m, $2H_t + 2H_c$), 6.90 (dd, $J = 4.8, 7.2$ Hz, $1H_t$), 6.98–7.05 (m, $2H_t + 1H_c$), 7.10 (m, $2H_t + 2H_c$), 7.10–7.25 (m, $7H_t + 7H_c$), 7.50 (*d*, $J = 7.2$ Hz, $1H_t + 1H_c$), 7.81 (*d*, $J = 7.8$ Hz, $1H_t$), 7.87 (br.d, $2H_t$), 7.94–8.05 (m, $3H_c$), 8.20 (br.d, $1H_c$), 8.21 (*d*, $J = 9.0$ Hz, $1H_t$), 9.31 (s, $1H_c$), 9.33 (s, $1H_t$), 10.60 (s, $1H_c$). 10.66 (s, $1H_t$); ES–MS m/z: 625.3 $[M + H]^+$; calcd: 625.3.

[5-F-Trp^3]-EM1 (**9**). ^{1}H NMR (DMSO-d6) δ (about *3:1 mixture of two conformers, t = major-trans isomer, c = minor-cis isomer*): 1.42–1.55 (m, $4H_c$), 1.62–1.73 (m, $3H_t$), 1.91 (m, $1H_t$), 2.68–2.83 (m, $3H_t + 2H_c$), 2.83–2.95 (m, $2H_t + 2H_c$), 2.95–3.05 (m, $2H_t + 2H_c$), 3.20 (m, $1H_c$), 3.30 (m, $1H_c$), 3.40–3.67 (m, $1H_t + 2H_c$), 4.15 (m, $1H_t$), 4.35 (dd, $J = 4.6, 8.2$ Hz, $1H_t$), 4.37–4.40 (m, $1H_t + 1H_c$), 4.40–4.48 (m, $1H_t + 1H_c$), 6.60 (m, $2H_t + 2H_c$), 6.87 (m, $2H_c$), 7.07 (m, $2H_t$), 7.10–7.35 (m, $9H_t + 9H_c$), 7.90 (*d*, $J = 8.4$ Hz, $1H_t$), 7.95 (*d*, $J = 8.0$ Hz, $1H_t$), 8.01 (br.s, $2H_t$), 8.11 (*d*, $J = 8.4$ Hz, $1H_c$), 8.25–8.32 (m, $3H_c$), 9.30 (br.s, $1H_t + 1H_c$), 10.80 (s, $1H_c$), 10.88 (s, $1H_t$); ES–MS m/z: 629.2 $[M + H]^+$; calcd: 629.7.

Results and discussion

Very recently (De Marco et al. 2012b), we observed that the reaction of the *N*-tosyl (Ts) dipeptide ester Ts-Ser-Ser-OMe (**1a**) with *N,N*-disuccinimidyl carbonate (DSC) and a catalytic amount of DIPEA in DCM/DMF, gave a 1:1 mixture of the compound containing two oxazolidin-2-one-4-carboxylate rings (Oxd), Ts-Oxd-Oxd-OMe (**2a**), and of the compound containing one Oxd and a ΔAla, Ts-Oxd-ΔAla-OMe (**3a**) (Fig. 2 and Table 1, entry 1). This compound **3a** can be regarded as a ΔAla equipped with an oxazolidin-2-one chiral auxiliary (Zappia et al. 2007), potentially useful for the asymmetric synthesis of optically active unusual α-amino acids (Gentilucci et al. 2010; Bonauer et al. 2006). This opportunity prompted us to preparare dipeptides Ts-Oxd-ΔAla-OMe carrying different substituents at the position 5 of the Oxd (Fig. 2).

The dipeptides **1a–c**, precursors of **3a–c** (Fig. 2), were easily prepared by coupling in solution Ts-Ser ($R = H$), Ts-Thr (R = Me), and (*S*/*R*)-Ts-phenylSer (R = Ph), respectively, with H-Ser-OMe. Amino acid tosylation was performed according to the literature (Ousmer et al. 2001; Deng and Mani 2006). The two β-hydroxy-α-amino acid building blocks were incorporated without a protection for the OH function, according to a protocol previously described by us (Greco et al. 2014a, b), using HOBt, HBTU, and DIPEA, as activating agents, at 80 °C under MW irradiation (Bacsa et al. 2008). Under these expedient conditions, acylation of the OH function and thus the formation of a depsipeptide side product was not observed, as confirmed by the ^{1}H NMR and RP-HPLC MS analyses of the crude reaction mixture.

The reaction of **1a** with DSC/DIPEA was performed in different solvents (Fig. 2), giving different outcomes: in pure DCM the reaction gave a 92:8 mixture of **2a** and **3a** (Table 1, entry 2), while in DMF the situation was completely reversed, giving a 5:95 ratio in favor of **3a** (entry 3). Finally, the slow addition of DSC to a solution of **1a–c** and catalytic DIPEA in DMF at 0 °C further reduced the amount of **2** (traces), as determined by HPLC–MS analysis of the reaction mixture, while the corresponding Ts-Oxd-ΔAla esters **3a** were obtained in almost quantitative yields after isolation by flash chromatography (entry 4). In a

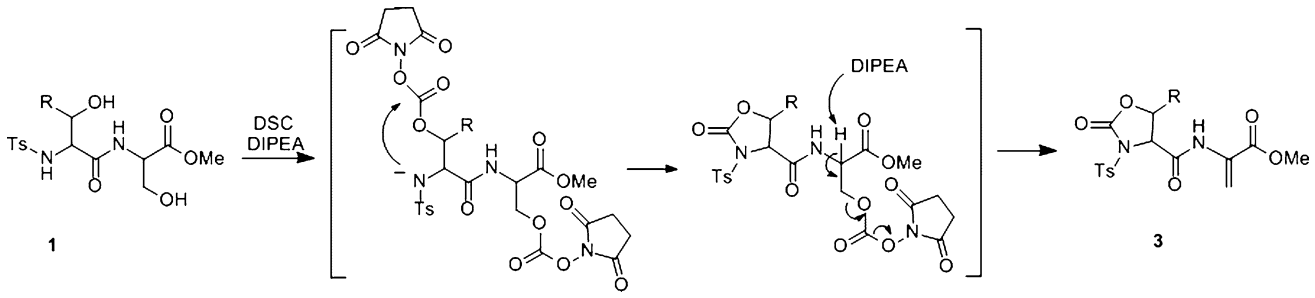


Fig. 3 Synthesis of peptides Ts-Oxd-ΔAlaOMe (*3*) from dipeptides Ts-Ser/Thr/PhSer-SerOMe. (**1**): Proposed two-step mechanism

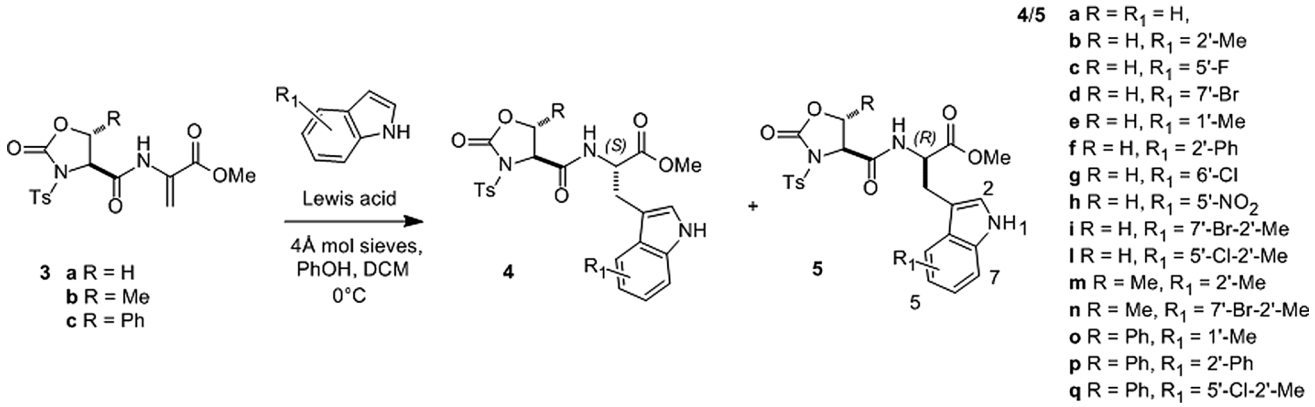


Fig. 4 Lewis–Brønsted acid-promoted asymmetric F–C alkylation of substituted indoles with dipeptides *3a–c*

similar way, the reaction of **1b** and **1c** performed under the same conditions gave the corresponding **3b** (entry 5) and **3c** (entry 6) in very good yields.

The analysis of the reaction mixtures at successive reaction times indicated that the reaction proceeds via the cyclization of Ts-Ser moiety promoted by DIPEA, followed by the dehydration of Ser-OMe to ΔAla (Fig. 3). It was proposed that the cyclization of the Ts-Ser moiety can be promoted by the presence of the arylsulfonyl group (Gentilucci et al. 2011b; De Marco et al. 2012a), while the comparatively higher acidity of the Hα of Ser-ester respect to that of the Hα of Ser-amide accounts for the elimination of the intermediate Ser-*O*-succinimidyl carbonate to ΔAla (Ferreira et al. 1999).

As anticipated in the introduction, we decided to assess the utility of the Oxd-equipped ΔAla as chiral building blocks for the preparation of non-racemic non-natural amino acids. In particular, we tested the efficacy of **3a** (R = H), **3b** (R = Me), or **3c** (R = Ph), to furnish optically active tryptophan derivatives by the Lewis acid-promoted F–C alkylation of substituted indoles (Bandini et al. 2005; Angelini et al. 2008; Gentilucci et al. 2010) in the presence of a Lewis acid-assisted Brønsted acid (Kieffer et al. 2012). In essence, the process consists in a tandem Michael addition-enolate protonation, a process which is very difficult to control under the point of view of the stereochemistry (Duhamel et al. 2004; Sibi et al. 2008; Xu et al. 2011; Kieffer et al. 2012). Initially, we screened different conditions for the reaction of **3a** with un-substituted indole. The reactions were carried out in DCM, in the presence of different Lewis acids (Angelini et al. 2008; Gentilucci et al. 2010; Kieffer et al. 2012), of molecular sieves (Sibi et al. 2008), of phenol as protonating agent (Lewis acid-assisted Brønsted acid, Kieffer et al. 2012), and afforded the dipeptide Ts-Oxd-Trp-OMe as a mixture of diastereoisomers (*S*,*S*)-**4a** and (*S*,*R*)-**5a** (Fig. 4).

Yields and d.r. strongly varied depending on the Lewis acid selected. $Yb(OTf)_3$, $Sc(OTf)_3$, $ZnCl_4$, $MgBr_2$, $SnBu_2Cl_2$, $ZnOTf_2$, $FeCl_3$, $InCl_3$, $CeCl_3$, $RuCl_3$ gave no products; other Lewis acids, $MgBr_2$, BBu_2OTf, $TiCl_4$, $Cu(OTf)_2$, gave **4a** and **5a** in traces. Finally, the reaction gave reasonable-to-good yields with $AlEtCl_2$, $AlEt_2Cl$ (Angelini et al. 2008; Gentilucci et al. 2010), or $SnCl_4$ (Kieffer et al. 2012), as reported in Table 2. The reaction with 1.5 equiv. of $AlEt_2Cl$ gave a 18:82 mixture of the diastreoisomers in favor of (*S*,*R*)-**5a** (entry 1), as determined by the HPLC analyses of the reaction mixtures; **4a** and **5a** were isolated by flash chromatography over silica gel in

10 and 45 % yield, respectively. The use of $AlEtCl_2$ gave a higher yield (**4a** 17 %, **5a** 52 %) but a reduced selectivity of 25:75 (entry 2). On the other hand, $SnCl_4$ (1.05 equiv.) gave **4a** and **5a** in good yield (7 and 67 %) after flash chromatography, with a d.r. of 90:10 in favor of (*S*,*R*)-**5a** (entry 3).

The configuration of the newly created stereocenter on Trp was determined by comparison with authentic samples of Ts-(*S*)-Oxd-(*S*)-Trp-OMe and Ts-(*S*)-Oxd-(*R*)-Trp-OMe, prepared by standard peptide synthesis in solution from the commercially available amino acids. The analyses of the crude reaction mixtures revealed no evidence of concurrent α-amidoalkylation reaction (Jia et al. 2007; Angelini et al. 2008). Increasing time and temperature did not lead to significantly higher yields; on the other hand, lower temperatures gave negligible improvements in terms of streoselectivity. The reduction of the amounts of Lewis acids to <1.0 equiv. gave reduced yields, consistent with the observation that stoichiometric Lewis–Brønsted acid was required due to its binding to the product, resulting in product inhibition (Kieffer et al. 2012). As for aluminum Lewis acids, a moderate excess was recommended for good reactivity and high selectivity in the conjugate addition reactions (Castellino and Dwight 1993). In the absence of molecular sieves, the reactions gave scarce d.r., and variable quantities of by-products arising from peptide bond and/or ester hydrolysis, as revealed by reversed phase (RP)-HPLC and electro-spray (ESI)-MS analyses. Finally, the absence of the proton donor phenol gave similar yields but accompanied by a significant drop of stereoselectivity, while the substitution of phenol with 2-naphthol or 2,2′-biphenol did not alter the reaction outcome.

Consequently, the reactions of **3a** with substituted indoles (Table 2, entries 4–25 were performed with $AlEt_2Cl$, or $AlEtCl_2$, or with $SnCl_4$ in the presence of phenol and activated molecular sieves in DCM. In all cases (including **4a**, **5a**), the analyses of the diastereoisomers **4** and **5** by reversed-phase HPLC under different conditions was unfeasible. However, the separation was possible by normal-phase HPLC using an analytical Kromasil Diol column, so allowing the determination of d.r. (Table 2). Gratifying, in most cases the diastereoisomers were easily isolated in preparative scale by low-pressure flash chromatography over silica gel using standard solvents.

The reaction of **3a** with 2-methylindole (entries 4–6) gave the dipeptides Ts-Oxd-(*S*)-2-Me-Trp-OMe (**4b**) and Ts-Oxd-(*R*)-2-Me-Trp-OMe (**5b**) in good to excellent yields and d.r. up to 8:92 with $SnCl_4$ in favor of the (*S*,*R*)-stereoisomer **5b** (entry 6), while $AlEt_2Cl$ and $AlEtCl_2$ gave inferior results (entries 4 and 5). A similar trend was observed for the reaction of **3a**, 5-fluoroindole, and the same Lewis acids, which gave **4c** and **5c** (entries 7–9). The reactions of **3a** with 7-bromoindole (entries 10–12) and 1-methylindole (entries 13–15) gave good yields and outstanding d.r. In particular, in the presence of $SnCl_4$ 7-bromoindole gave **4d/5d** in 6:94 ratio (entry 12). In a similar way, the reaction of 1-methylindole and **3a** with $SnCl_4$ (entry 15) afforded **5e** as the largely predominant product, being the diastereoisomer **4e** present only in traces.

On the contrary, 2-phenylindole or 6-chloroindole reacted with **3a** in the presence of $AlEtCl_2$ and $SnCl_4$, but not $AlEt_2Cl$, giving the corresponding products **4f/5f** (Kieffer et al. 2012), or **4 g/5 g** in modest yields, albeit the diastereoselectivities were comparable to that of the previous experiments (not shown). As for 5-nitroindole, the reaction with **3a** gave only traces of **4 h/5 h** with all of the Lewis acids utilized. For these low-yielding reactions, the analyses of the reaction mixtures by HPLC, ESI–MS, and ^{1}H NMR, excluded the formation of large quantities of by-products and confirmed the presence of un-reacted **3a**.

Finally, we tested the F–C alkylation of indoles carrying two substituents, 7-bromo-2-methylindole (entries 16–18) and 5-chloro-2-methylindole (entries 19–21). Interestingly, the reaction of 7-bromo-2-methylindole with **3a** afforded the best yield and d.r. with $AlEtCl_2$ (**4i** 9 % and **5i** 75 %, **4i/5i** 11:89, entry 17), while the reaction of 5-chloro-2-methylindole gave the best d.r. with $AlEt_2Cl$ (**4 l/5 l** 9:91, entry 19), but the best yield with $AlEtCl_2$ (**4 l** 13 % and **5 l** 68 %, entry 20).

Subsequently, to check any effects of diverse groups at the position 5 of the Oxd chiral auxiliary, we repeated the F–C alkylation of some selected substituted indoles with the dipeptides Ts-5-Me-Oxd-ΔAla-OMe (**3b**) and (*S*/*R*)-Ts-5-Ph-Oxd-ΔAla-OMe (**3c**) with $AlEt_2Cl$, $AlEtCl_2$, and $SnCl_4$, under the same conditions utilized for **3a**. The reaction of **3b** with 2-methylindole gave in all cases lower yields and reduced diastereoselectivities (entries 22–24) compared to the corresponding results observed for **3a** (entries 4–6). The isolation of the diastereomeric dipeptides **4 m** and **5 m** by flash chromatography over silica gel was still feasible. Similarly, moderate yields and d.r. were obtained also for the reaction of **3b** with 7-Br-2-Me-indole (entries 25–27). Nevertheless, the separation of the diastereoisomers by flash chromatography was not possible, and **4n**, **5n** were obtained as a mixture. Finally, the F–C reactions of **3c** and 1-methylindole (entries 28–30), 2-phenylindole (entries 31–33), and 5-Cl-2-Me-indole (entries 34–36) afforded the products **4o/5o**, **4p/5p**, and **4q/5q**, respectively. In all cases, the isolation of the diastereoisomers (*S*,*S*)-**4** and (*S*,*R*)-**5** by flash chromatography over silica gel was not possible. As observed for **3b**, yields and d.r. for the reactions of **3c** with 1-methylindole and 5-Cl-2-Me-indole were modest compared to the corresponding results for **3a**. In contrast, the moderate reactivity of 2-phenylindole with **3c** to give **4p/5p** (entries 31–33) can be

regarded as an improvement compared to the reaction with **3a**, since the latter gave inferior yields. Possibly, the moderate yields and d.r. of the reactions of **3b** and **3c** and all the indoles can be correlated to a significant instability of the respective 5-Me-Oxd and 5-Ph-Oxd auxiliaries; indeed, the analyses of the crude reaction mixtures (entries 26–40) by NMR and HPLC–ESI–MS revealed the presence of variable amounts of dipeptides containing Thr or phenylserine,

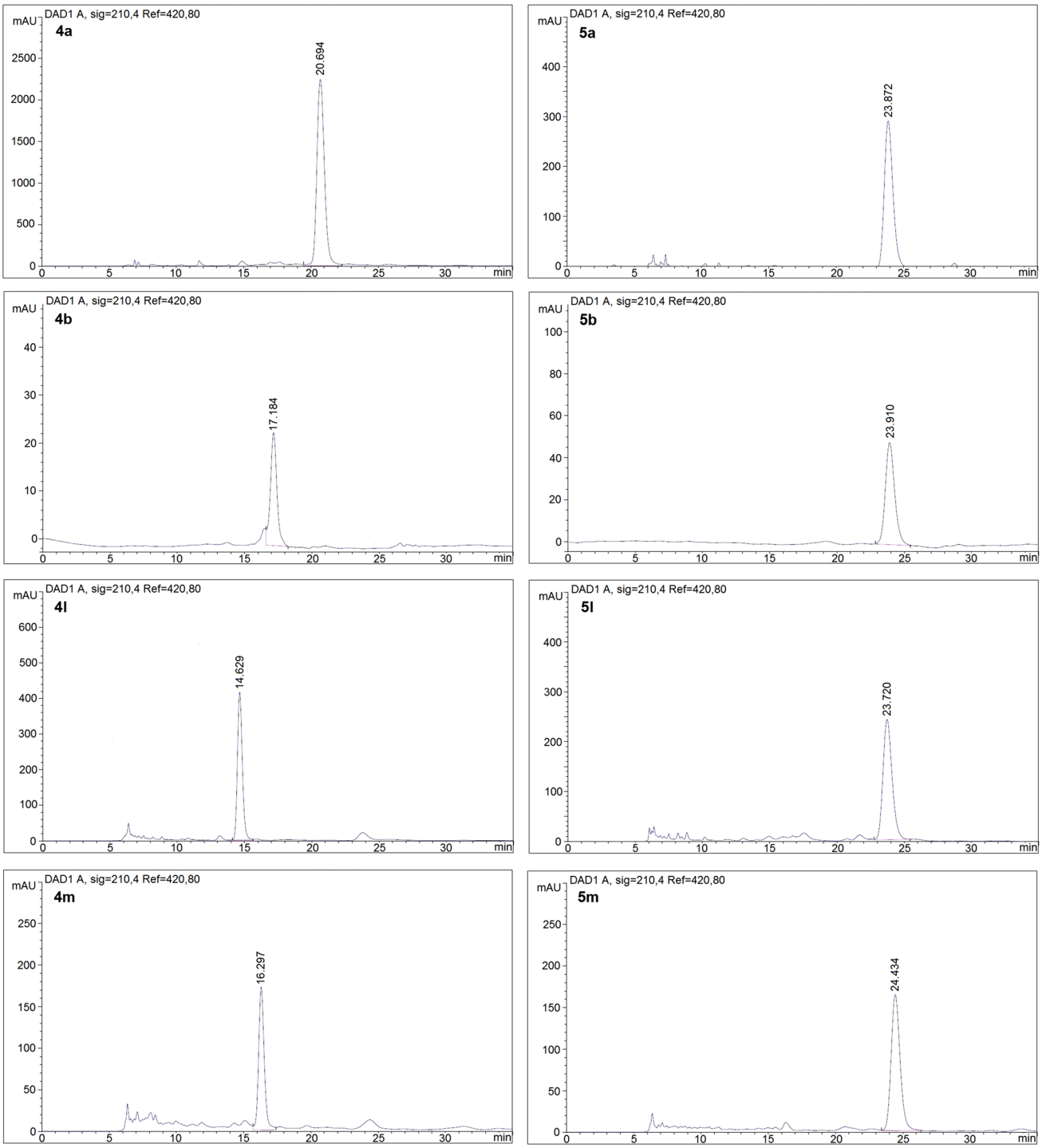


Fig. 5 HPLC analyses of the representative compounds *4a*, *5a 4b*, *5b*, *4l*, *5l*, *4m*, *5m*, performed on a chiral stationary phase, using CHIRALPAK IC column (cellulose *tris* 3,5-dichlorophenylcarbamate, particle size 5 µm, length 250 mm, internal diameter 4.6 mm, DAD 210); mobile phase: 1:1 n-hexane/2-propanol, at 0.8 mL min^{-1}

possibly resulting from the degradation of the 5-substituted Oxd rings.

In summary, from the comparison of the results of the tandem F–C alkylation/asymmetric enolate protonation reported in Table 2, it appears that in most cases the substrate **3a** is the most performing both in terms of yields and d.r. Besides, the un-substituted Ts-Oxd chiral auxilixary of **3a** allowed a very easy separation of the stereoisomers. Reaction yields strongly varied depending on the nature of the substituents at the indole ring. As expected, activating groups such as 1-methyl or 2-methyl gave very good yields, while weakly deactivating group such as 5-fluoro or 7-bromo still gave reasonable-to-good yields, in some cases superior to indole, albeit 6-chloroindole reacted poorly under the same conditions. Not surprisingly, the strongly deactivating 5-nitro group prevented the reaction. On the other hand, the modest reactivity of 2-phenylindole and **3a** with all of the Lewis acids tested was unexpected (Kieffer et al. 2012). Also unexpected was the comparatively higher reactivity of 2-phenylindole and **3c**. Possibly, these reactions can be improved by increasing the amounts of Lewis acid and/or indoles (Angelini et al. 2008); for the moment, the reactions have been not optimized further. As for the disubstituted indoles (5-Cl-2-Me-indole and 7-Br-2-Me-indole), the F–C reactions with **3a** proceeded with good yields possibly for the activating effect of the 2-methyl group.

In general, the stereochemical trend was very similar for all of the tested indoles, giving predominantly the (*S*,*R*)-**5** stereoisomers. For the monosubstituted indoles, the best d.r. were obtained with $SnCl_4$, including 7-bromoindole and 1-methylindole which reacted with **3a** very nicely giving an outstanding d.r., so that the minor (*S*,*S*)-stereoisomer could not be recovered after purification of the reaction mixture by flash chromatography. The disubstituted indoles behaved differently; for 7-bromo-2-methylindole and 5-chloro-2-methylindole the best d.r. were obtained with $AlEtCl_2$ and $AlEt_2Cl$, respectively.

The absolute configurations of all diastereoisomers **4** and **5** were determined by comparison of the HPLC analyses on Kromasil Diol column, and of the chiral HPLC analyses on CHIRALPAK IC column, with that of compounds **4a** and **5a**; the latter analysis also excluded racemization. Some representative examples of chiral HPLC analyses are reported in Fig. 5: the analyses of 2′-methyl substituted **4b** and **5b**, of 5′-chloro-2′-methyl-**4l** and -**5l**, and of compounds **4 m** and **5 m** equipped with 5-methyl oxazolidin-2-one, clearly match the analyses of **4a** and **5a**. The latter were confirmed in turn by comparison with authentic samples of Ts-(*S*)-Oxd-(*S*)-Trp-OMe (**4a**) and Ts-(*S*)-Oxd-(*R*)-Trp-OMe (**5a**), prepared from the commercially available (*S*)- or (*R*)-tryptophan. The absolute stereochemistry of **4b** and **5b**, and of **4c** and **5c**, was also confirmed after removal of the chiral auxiliary (see next paragraph and Fig. 7), by comparing the specific optical rotations of enantiopure (*S*)-2-methyltryptophan and (*S*)-5-fluorotryptophan with the values reported in the literature (Yabe et al. 1979; Porter

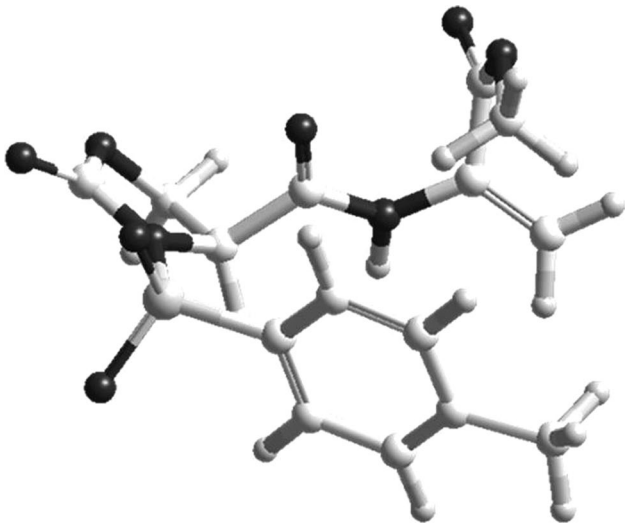


Fig. 6 Representative low-energy structure of *3a* consistent with ROESY analysis (see also Fig. 7), calculated by restrained molecular dynamics. The calculated geometry of the ΔAla residue matches the structures reported in the literature (Alemán and Casanovas 1995; Rzeszotarska et al. 2002; Padmanabhan et al. 1992)

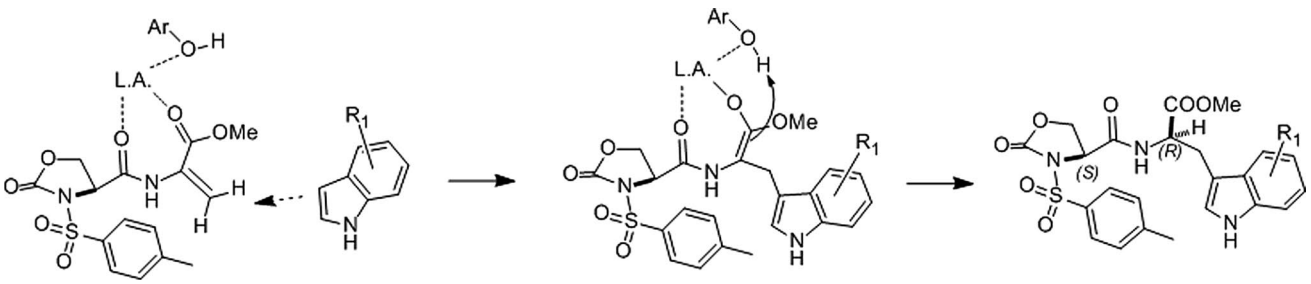
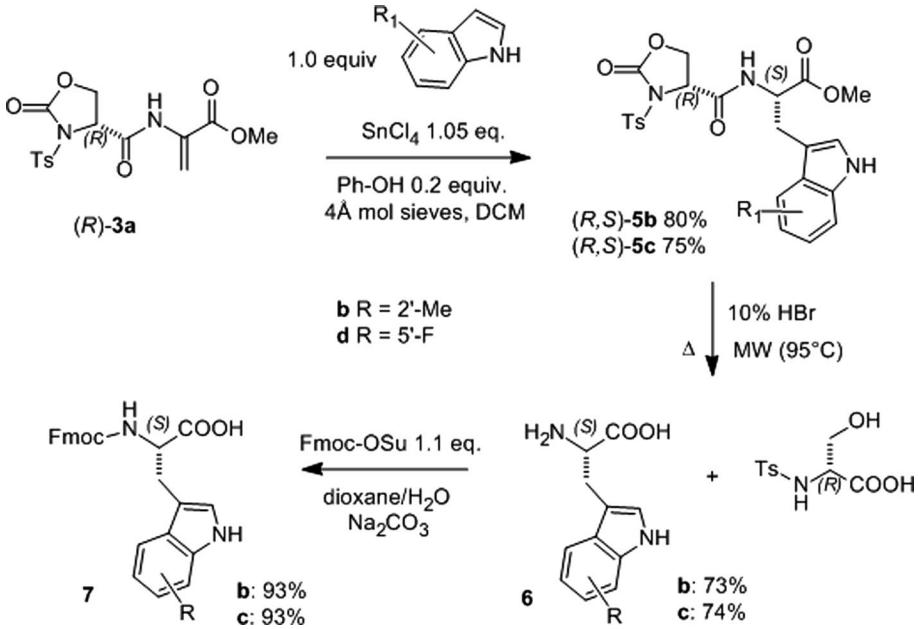


Fig. 7 Proposed model for the tandem Michael addition-enolate protonation of indoles and ΔAla, and role of the oxazolidin-2-one chiral auxilixary



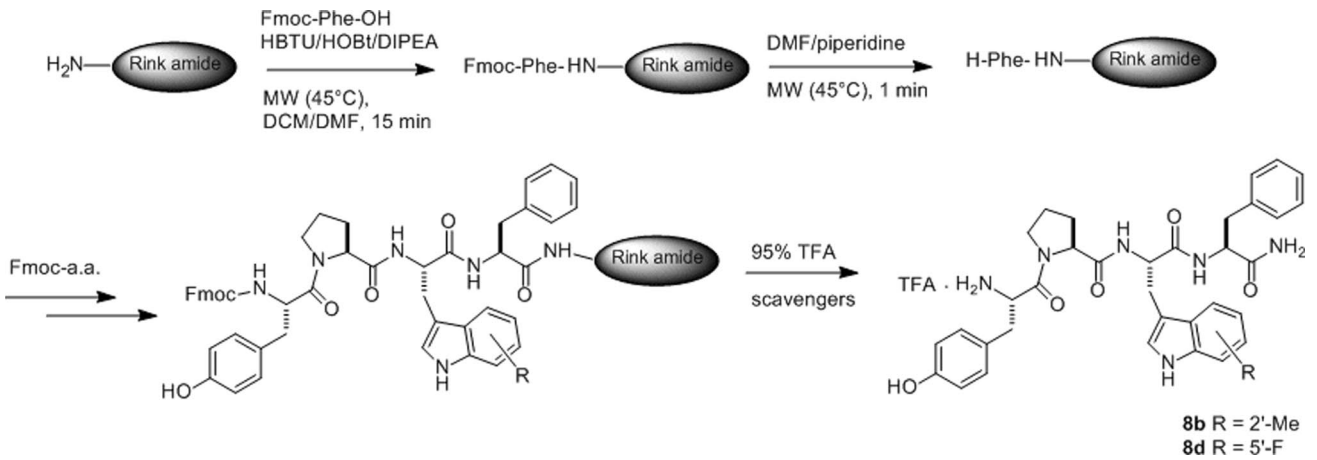


Fig. 8 Synthesis of Fmoc-2-Me-Trp-OH, and Fmoc-5-F-Trp-OH, by F–C reaction of the indoles with (*R*)-*3a*

Fig. 9 Solid-phase synthesis of the EM1 analogues *8b* and *8c* containing substituted Trp[3]

et al. 1987; Mocek et al. 1993; Ma et al. 2001; Goss and Newil 2006; Blaser et al. 2008; Smith et al. 2014).

To rationalize the stereochemical outcome of the reactions, we analyzed the in solution conformation of Ts-Oxd-ΔAla-OMe (**3a**). Previous analyses including Electronic Circular Dichroism, 2D NMR, and molecular dynamics computations (De Marco et al. 2012b) showed Ts group of **3a** facing the double bond of ΔAla at a distance of about 3.7 Å (Fig. 6), perfectly compatible with the values reported in the literature for π-stacking interactions (Jones and Chapman 1995).

Reasonably, the Lewis acid effectively promotes the conjugate addition of the indoles by forming a complex with the carbonyl oxygen of ΔAla (Tabatabaeian et al. 2007; Sibi et al. 2008; Angelini et al. 2008; Blay et al. 2012). The Michael addition gives rise to an intermediate enolate (Fig. 7). The ability of arylsulfonamide groups to form sandwich structures with enolates by π-stacking interactions is well known (Mahrwald 2004). Electron-poor aromatic rings have been reported to promote the reactivity of delocalized anions such as enolates by means of a donor–acceptor π-stacking stabilization of the transition states (Ojima and Kwon 1988; Marcaccini et al. 2009; Krenske and Houk 2013). As proposed in Fig. 7, the Ts group could shield the *Si* face of the enolate, leaving the *Re* face more accessible to the PhOH-Lewis acid complex that serves as a Brønsted acid to protonate the intermediate enolate (Ishihara et al. 2003; Xu et al. 2011; Kieffer et al. 2012).

The F–C reaction between the indoles and Ts-Oxd-ΔAla-OMe appears as a practical method to give access to peptides containing modified Trp. To exploit this opportunity, we

synthesized in a few steps the analogues of the opioid peptide H-Tyr-Pro-Trp-PheNH_2 (EM1) containing 2-methyltryptophan or 5-fluorotryptophan (Yabe et al. 1979; Porter et al. 1987; Mocek et al. 1993; Ma et al. 2001; Goss and Newil 2006; Blaser et al. 2008; Smith et al. 2014) [2-Me-Trp^3]-EM1 (**8**), and [5-F-Trp^3]-EM1 (**9**), respectively (Figs. 8, 9). Since we were interested in (*S*)-configures amino acids, we performed the F–C reactions of the indoles with the (*R*)-enantiomer of **3a**, in the presence of $SnCl_4$ and PhOH. (*R*)-**3a** was obtained in turn by treatment of (*R*,*R*)-**1a** with DSC and DIPEA as described for **3a**. The reactions of 2-methylindole and 5-fluoroindole afforded (*R*,*S*)-**5b** or (*R*,*S*)-**5c**, respectively, as the major products, with the same yields and d.r. as reported in Table 2, entries 6 and 9. After isolation by flash chromatography, (*R*,*S*)-**5b** or (*R*,*S*)-**5c** were treated with 10 % HBr at reflux under conventional heating, giving 2-methyltryptophan (**6b**) or 5-fluorotryptophan (**6c**) in moderate yields. Gratifyingly, heating at 95 °C under MW irradiation afforded **6b** or **6c** in more satisfactory yields (Fig. 8). The reaction mixture was adjusted to pH 3, and crude Ts-Ser-OH was easily separated from **6b** or **6c** and recovered in almost quantitative yield by extraction with EtOAc (Fig. 8). The tryptophans **6b** or **6c** were isolated using a Dowex H^+ form resin (Blaser et al. 2008). Spectroscopic characterization and specific optical rotation were found to match with the literature above reported, confirming the absolute stereochemistry attributed in the previous paragraph.

Finally, **6b** or **6c** were protected at the *N*-terminus with the Fmoc group under standard conditions (Blaser et al. 2008), and the resulting **7b** or **7c** were utilized for the SPPS of modified EM1.

The tetrapeptide-amides [2-Me-Trp^3]-EM1 (**8b**), and [5-F-Trp^3]-EM1 (**8c**) were rapidly obtained by standard SPPS on a Rink amide resin in DCM/DMF, using Fmoc-protected amino acids, and HBTU/HOBt/DIPEA as coupling agents (Fig. 9). The reaction was performed under MW-assisted conditions, keeping temperature at 45 °C while mechanically shaking, which allowed to complete the reactions in 10 min. Coupling efficiency was monitored by the Kaiser or Chloranil tests. After each coupling, Fmoc was removed very rapidly (1 min) with DMF/piperidine at 45 °C under MW irradiation. Peptide cleavage was performed by treatment with trifluoroacetic acid (TFA) in the presence of scavengers. After filtration, the crude peptides were precipitated from ice-cold Et_2O, and collected by centrifuge. The peptide **8b** or **8c** were isolated >95 % pure by semi-preparative RP-HPLC on a C18 column.

Conclusions

In summary, we proposed a practical route for the preparation of dehydroalanine equipped with an oxazolidinone chiral auxiliary, by one-pot cyclization–elimination of the dipeptide Ts-Ser-Ser-OMe, and we demonstrated the efficacy of the resulting Ts-Oxd-ΔAla-OMe chiral building block for the preparation of non-racemic non-natural amino acids. The F–C alkylation of substituted indoles with ΔAla carrying (*S*)-configured chiral auxiliary in the presence of Lewis/Brønsted acids allowed obtaining (*R*)-tryptophans with diverse substituents at different positions of the indole, in good to excellent d.r. over the (*S*)-isomers. The tryptophans were easily isolated in optical pure form after simple flash chromatography and cleavage of the chiral auxiliary. As a preliminary demonstration of the utility of this protocol, we introduced 2-methyl or 5-fluoro tryptophan into a peptide sequence of pharmacological interest, the opioid peptide EM1. The procedure will be utilized to synthesize a mini-library of EM1 analogues, aiming at obtaining new opioid peptides with improved in vivo performances, as well as to deduce information about the role of Trp in peptide–receptor recognition and activation by SAR studies. Further work is in progress to expand the scope of the Ts-Oxd-ΔAla-OMe chiral building block by exploring different reactions.

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Conflict of interest The authors declare that they have no conflict of interest.

References

Alemán C, Casanovas JCA (1995) Molecular conformational analyses of dehydroalanine analogues. Biopolymers 36:71–82. doi:10.1002/bip.360360107

Angelini E, Balsamini C, Bartoccini F, Lucarini S, Piersanti G (2008) Switchable reactivity of acylated α, β-dehydroamino ester in the friedel-crafts alkylation of indoles by changing the lewis acid. J Org Chem 73:5654–5657. doi:10.1021/jo800881u

Artman GD, Grubbs AW, Williams RM (2007) Concise, asymmetric, stereocontrolled total synthesis of stephacidins A, B and notoamide B. J Am Chem Soc 129:6336–6342. doi:10.1021/ja070259i

Bacsa B, Horváti K, Bõsze S, Andreae F, Kappe CO (2008) Solid-phase synthesis of difficult peptide sequences at elevated temperatures: a critical comparison of microwave and conventional heating technologies. J Org Chem 73:7532–7542. doi:10.1021/jo8013897

Bandini M, Melloni A, Tommasi S, Umani-Ronchi A (2005) A Journey across recent advances in catalytic and stereoselective alkylation of indoles. Synlett 8:1199–1222. doi:10.1055/s-2005-865210

Bittner S, Scherzer R, Harlev E (2007) The five bromotryptophans. Amino Acids 33:19–42. doi:10.1007/s00726-006-0441-8

Blaser G, Sanderson JM, Batsanov AS, Howard JAK (2008) The facile synthesis of a series of tryptophan derivatives. Tetrahedron Lett 49:2795–2798. doi:10.1016/j.tetlet.2008.02.120

Blay G, Cano J, Cardona L, Fernández I, Muñoz MC, Pedro JR, Vila C (2012) NMR spectroscopic characterization and dft

calculations of Zirconium(IV)-3,3-Br 2-BINOLate and related complexes used in an enantioselective Friedel–Crafts alkylation of indoles with α, β-unsaturated ketones. J Org Chem 77:10545–10556. doi:10.1021/jo3013594

Bonauer C, Walenzyk T, König B (2006) α, β-Dehydroamino acids. Synthesis 1:1–20. doi:10.1055/s-2005-921759

Bull SD, Davies SG, Garner AC, O'Shea MD (2001) Conjugate additions of organocuprates to a 3-methylene-6-isopropyldiketopiperazine acceptor for the asymmetric synthesis of homochiral α-amino acids. J Chem Soc Perkin Trans 1:3281–3287. doi:10.1039/B108621A

Castellino S, Dwight WJ (1993) Et_2AlCl complexes of an N-acyloxazolidinone: NMR investigation. J Am Chem Soc 115:2986–2987. doi:10.1021/ja00060a061

Castle SL, Srikanth GSC (2003) Catalytic asymmetric synthesis of the central tryptophan residue of celogentin C. Org Lett 5:3611–3614. doi:10.1021/ol035236x

De Marco R, Tolomelli A, Campitiello M, Rubini P, Gentilucci L (2012a) Expedient synthesis of pseudo-Pro-containing peptides: towards constrained peptidomimetics and foldamers. Org Biomol Chem 10:2307–2317. doi:10.1039/C2OB07172J

De Marco R, Tolomelli A, Spampinato S, Bedini A, Gentilucci L (2012b) Opioid activity profiles of oversimplified peptides lacking in the protonable N-terminus. J Med Chem 55(22):10292–10296. doi:10.1021/jm301213s

De Marco R, Greco A, Rupiani S, Tolomelli A, Tomasini C, Pieraccini S, Gentilucci L (2013) In-peptide synthesis of di-oxazolidinone and dehydroamino acid-oxazolidinone motifs as β-turn inducers. Org Biomol Chem 11:4316–4326. doi:10.1039/c3ob40357b

De Marco R, Bedini A, Spampinato S, Gentilucci L (2014) Synthesis of tripeptides containing D-Trp substituted at the indole ring, assessment of opioid receptor binding and in vivo central antinociception. J Med Chem 57(15):6861–6866. doi:10.1021/jm5002925

Deng X, Mani NS (2006) A facile, environmentally benign sulfonamide synthesis in water. Green Chem 8(9):835–838. doi:10.1039/b606127c

Drury WJ, Ferraris D, Cox C, Young B, Lectka T (1998) A novel synthesis of α-amino acid derivatives through catalytic, enantioselective ene reactions of α-imino esters. J Am Chem Soc 120:11006–11007. doi:10.1021/ja982257r

Duhamel L, Duhamel P, Plaquevent JC (2004) Enantioselective protonations: fundamental insights and new concepts. Tetrahedron Asymmetry 15:3653–3691. doi:10.1016/j.tetasy.2004.09.035

Ferreira PMT, Maia HLS, Monteiro LS, Sacramento J (1999) High yielding synthesis of dehydroamino acid and dehydropeptide derivatives. J Chem Soc Perkin Trans 1(24):3697–3703. doi:10.1039/A904730A

Fichna J, Janecka A, Costentin J, Do Rego JC (2007) The endomorphin system and its evolving neurophysiological role. Pharmacol Rev 59(1):88–123. doi:10.1124/pr.59.1.3

Galonić DP, van der Donk WA, Gin DY (2003) Oligosaccharide–peptide ligation of glycosyl thiolates with dehydropeptides: synthesis of s-linked mucin-related glycopeptide conjugates. Chem Eur J 9(24):5997–6006. doi:10.1002/chem.200305290

Gentilucci L (2004) New trends in the development of opioid peptide analogues as advanced remedies for pain relief. Curr Topics Med Chem 4:19–38. doi:10.2174/1568026043451663

Gentilucci L, Squassabia F, Demarco R, Artali R, Cardillo G, Tolomelli A, Spampinato S, Bedini A (2008) Investigation of the interaction between the atypical agonist c[YpwFG] and MOR. FEBS J 275:2315–2337. doi:10.1111/j.1742-4658.2008.06386.x

Gentilucci L, Cerisoli L, De Marco R, Tolomelli A (2010) A simple route towards peptide analogues containing substituted (S)- or (R)-tryptophans. Tetrahedron Lett 51:2576–2579. doi:10.1016/j.tetlet.2010.03.017

Gentilucci L, Tolomelli A, De Marco R, Spampinato S, Bedini A, Artali R (2011a) The inverse type II β-turn on D-Trp-Phe, a pharmacophoric motif for MOR agonists. ChemMedChem 6:1640–1653. doi:10.1002/cmdc.201100169

Gentilucci L, Tolomelli A, De Marco R, Tomasini C, Feddersen S (2011b) Synthesis of constrained peptidomimetics containing 2-Oxo-1,3-oxazolidine-4-carboxylic acids. Eur J Org Chem 25:4925–4930. doi:10.1002/ejoc.201100346

Goss RJM, Newil PLA (2006) A convenient enzymatic synthesis of L-halotryptophans. Chem Commun 47:4924–4925. doi:10.1039/B611929H

Greco A, Tani S, De Marco R, Gentilucci L (2014a) Synthesis and analysis of the conformational preferences of 5-aminomethyl-oxazolidine-2,4-dione scaffolds, first examples of β^2- and $\beta^{2,2}$-*homo*-Freidinger lactam analogs. Chem Eur J 20. doi:10.1002/chem.201402519

Greco A, De Marco R, Tani S, Giacomini D, Galletti P, Tolomelli A, Juaristi E, Gentilucci L (2014b) Convenient synthesis of the antibiotic linezolid via a oxazolidine-2,4-dione intermediate derived from the chiral building block *iso*serine. Eur J Org Chem submitted

He B, Hao S, Yu D, Yong Q (2009) Total synthesis of (-)-Ardeemin. J Org Chem 74:298–304. doi:10.1021/jo802216z

Humphrey JM, Chamberlin AR (1997) Chemical synthesis of natural product peptides: coupling methods for the incorporation of non-coded amino acids into peptides. Chem Rev 97(6):2243–2266. doi:10.1021/cr950005s

Irie K, Ishida A, Nakamura T, Oh-Ishi T (1984) Syntheses of substituted L- and D-tryptophans. Chem Pharm Bull 32(6):2126–2139. doi:10.1248/cpb.32.2126

Ishihara K, Nakashima D, Hiraiwa Y, Yamamoto HJ (2003) The crystallographic structure of a Lewis acid-assisted chiral Brønsted acid as an enantioselective protonation reagent for silyl enol ethers. J Am Chem Soc 125(1):24–25. doi:10.1021/ja021000x

Ishihara K, Fushimi N, Akakura M (2007) Rational design of minimal artificial diels–alderases based on the copper(ii) cation–aromatic π attractive interaction. Acc Chem Res 40(10):1049–1055. doi:10.1021/ar700083a

Javidan A, Schafer K, Pyne SG (1997) Diastereoselective michael reactions of azomethine ylides to chiral 4-methyleneoxazolidin-5-ones: synthesis of the four stereoisomers of 4-benzamindopyroglutamate. Synlett 1:100–102. doi:10.1055/s-1997-683

Jia YX, Zhong J, Zhu SF, Zhang CM, Zhou QL (2007) Chiral brønsted acid catalyzed enantioselective friedel–crafts reaction of indoles and α-aryl enamides: construction of quaternary carbon atoms. Angew Chem Int Ed 46:5565–5567. doi:10.1002/anie.200701067

Jones GB, Chapman BJ (1995) π stacking effects in asymmetric synthesis. Synthesis 5:475–497. doi:10.1055/s-002-328

Keresztes A, Borics A, Tóth G (2010) Recent advances in endomorphin engineering. ChemMedChem 5(8):1176–1196. doi:10.1002/cmdc.201000077

Kieffer ME, Repka LM, Reisman SE (2012) Enantioselective synthesis of tryptophan derivatives by a tandem Friedel–Crafts conjugate addition/asymmetric protonation reaction. J Am Chem Soc 134:5131–5137. doi:10.1021/ja209390d

Konda-Yamada Y, Okada C, Yoshida K, Umeda Y, Arima S, Sato N, Kai T, Takayanagi H, Harigaya Y (2002) Convenient synthesis of 7′ and 6-bromo-D-tryptophan and their derivatives by enzymatic optical resolution using D-aminoacylase. Tetrahedron 58(39):7851–7861. doi:10.1016/S0040-4020(02)00909-2

Krenske EH, Houk KN (2013) Aromatic interactions as control elements in stereoselective organic reactions. Acc Chem Res 46(4):979–989. doi:10.1021/ar3000794

Li X, Yin W, Srirama Sarma PVV, Zhou H, Ma J, Cook JM (2004) Synthesis of optically active ring-A substituted tryptophans

as IDO inhibitors. Tetrahedron Lett 45(46):8569–8573. doi:10.1016/j.tetlet.2004.09.113

Lipkowski AW, Misicka A, Carr DB, Ronsisvalle G, Kosson D, Bonney MI (2004) Neuropeptide mimetics for pain management. Pure Appl Chem 76(5):941–950. doi:10.1351/pac200476050941

Ma C, Liu X, Li X, Flippen-Anderson J, Yu S, Cook J (2001) Efficient asymmetric synthesis of biologically important tryptophan analogues via a palladium-mediated heteroannulation reaction. J Org Chem 66:4525–4542. doi:10.1021/jo001679s

Mahrwald R (2004) Modern aldol reactions vol 1: enolates, organocatalysis, biocatalysis and natural product synthesis. Wiley, Weinheim, pp 1–328

Marcaccini S, Neo AG, Marcos CF (2009) Sequential five-component synthesis of spiropyrrolidinochromanones. J Org Chem 74(17):6888–6890. doi:10.1021/jo900992w

Mocek U, Zeng Z, O'Hagan D, Zhou P, Fan LDG, Beale JM, Floss HG (1993) Biosynthesis of the modified peptide antibiotic thiostrepton in *Streptomyces azureus* and *Streptomyces laurentii*. J Am Chem Soc 115(18):7992–8001. doi:10.1021/ja00071a009

Ojima I, Kwon HB (1988) Remarkable effects of a pentafluorophenyl group on the stereoselective reactions of a chiral iron acyl complex. J Am Chem Soc 110:5617–5621. doi:10.1021/ja00225a004

Ousmer M, Braun NA, Bavoux C, Perrin M, Ciufolini MA (2001) Total synthesis of tricyclic azaspirane derivatives of tyrosine: FR901483 and TAN1251C. J Am Chem Soc 123:7534–7538. doi:10.1021/ja016030z

Padmanabhan B, Dey S, Khandelwal B, Rao GS, Singh TP (1992) Design of peptide : synthesis, crystal structure, molecular conformation, and conformational calculations of N-Boc-L-Phe-Dehydro-Ala-OME. Biopolymers 32:1271–1276. doi:10.1002/bip.360321002

Perry CW, Brossi A, Deitcher KH, Tautz W, Teitel S (1977) Preparation of R(+)- and S(-)-α-methyl-p-nitrobenzylamines and their use as resolving agents. Synthesis 7:492–493. doi:10.1055/s-1977-24459

Polinsky A, Cooney MG, Toy-Palmer A, Osapay G, Goodman M (1992) Synthesis and conformational properties of the lanthionine-bridged opioid peptide [D-AlaL2, AlaL5]enkephalin as determined by NMR and computer simulations. J Med Chem 35(22):4185–4194. doi:10.1021/jm00100a026

Porter J, Dykert J, Rivier J (1987) Synthesis, resolution and characterization of ring substituted phenylalanines and tryptophans. J Pept Prot Res 30(1):13–21. doi:10.1111/j.1399-3011.1987.tb03307.x

Prieto M, Mayor S, Lloyd-Williams P, Giralt E (2009) Use of the SPhos ligand to suppress racemization in arylpinacolboronate ester Suzuki couplings involving r-amino acids. Synthesis of biaryl derivatives of 4-Hydroxyphenylglycine, tyrosine, and tryptophan. J Org Chem 74:9202–9205. doi:10.1021/jo901899w

Pyne SG, Javidan A, Skeleton BW, White AH (1995) Asymmetric synthesis of proline derivatives from (2*R*) and (2*S*)-2-*tert*-butyl-3-benzoyl-4-methyleneoxazolidin-5-one. Tetrahedron 51(17):5157–5168. doi:10.1016/0040-4020(95)98711-P

Rajashankar KR, Ramakumar S, Chauhan VS (1992) Design of a helical motif using α,β-dehydrophenylalanine residues: crystal structure of Boc-Val-Δ-Phe-Phe-Ala-Phe-Δ-Phe-Val-Δ-Phe-Gly-OCH3, a 310-helical nonapeptide. J Am Chem Soc 114(23):9225–9226. doi:10.1021/ja00049a086

Royer CA (2006) Probing protein folding and conformational transitions with fluorescence. Chem Rev 106:1769–1784. doi:10.1021/cr0404390

Rzeszotarska B, Siodlak D, Broda MA, Dybala I, Koziol AE (2002) Conformational investigation of α, β-dehydropeptides. X. Molecular and crystal structure of Ac-ΔAla-NMe2 compared with those of Ac-l-Ala-NMe2, Ac-dl-Ala-NMe2 and other dimethylamides. J Pept Res 59:79–89. doi:10.1034/j.1399-3011.2002.10951.x

Schmidt U, Lieberknecht A, Wild J (1988) Didehydroamino acids (DDAA) and didehydropeptides (DDP). Synthesis 3:159–172. doi:10.1055/s-1988-27503

Sibi MP, Coulomb J, Stanley LM (2008) Enantioselective enolate protonations: Friedel-Crafts reactions with α-substituted acrylates. Angew Chem Int Ed 47(51):9913–9915. doi:10.1002/anie.200804221

Smith DR, Willemse T, Gkotsi DS, Schepens W, Maes BU, Ballet S, Goss RJ (2014) The first one-pot synthesis of l-7-iodotryptophan from 7-iodoindole and serine, and an improved synthesis of other l-7-halotryptophans. Org Lett 16(10):2622–2625. doi:10.1021/ol5007746

Stammer CH (1982) In chemistry and biochemistry of amino acids, peptides, and proteins; Weinstein B (Ed) Dekker, New York. pp 33–74

Tabatabaeian K, Mamaghani M, Mahmoodi NO, Khorshidi A (2007) RuIII-catalyzed double-conjugate 1,4-addition of indoles to symmetric enones. J Mol Cat A 270:112–116. doi:10.1016/j.molcata.2007.01.038

Witt KA, Gillespie TJ, Huber JD, Egleton RD, Davis TP (2001) Peptide drug modifications to enhance bioavailability and blood-brain barrier permeability. Peptides 22:2329–2343. doi:10.1016/S0196-9781(01)00537-X

Xu Z, Zhang F, Zhang L, Jia Y (2011) Total synthesis of (-)-indolactam V. Org Biomol Chem 9:2512–2517. doi:10.1039/C0OB01115K

Yabe Y, Miura C, Horikoshi H, Miyagawa H, Baba Y (1979) Synthesis and biological activity of LH-RH analogs substituted by alkyltryptophans at position 3. Chem Pharm Bull 27(8):1907–1911. doi:10.1248/cpb.27.1907

Yeh E, Garneau S, Walsh CT (2005) Robust in vitro activity of RebF and RebH, a two-component reductase/halogenase, generating 7-chlorotryptophan during rebeccamycin biosynthesis. Proc Natl Acad Sci USA 102:3960–3965. doi:10.1073/pnas.0500755102

Zadina JE, Hackler L, Ge LJ, Kastin AJ (1997) A potent and selective endogenous agonist for the mu-opiate receptor. Nature 383:499–502. doi:10.1038/386499a0

Zappia G, Cancelliere G, Gacs-Baitz E, Delle Monache G, Misiti D, Nevola L, Botta B (2007) Oxazolidin-2-one ring, a popular framework in synthetic organic chemistry part 2. applications and modifications. Curr Org Synth 4:238–307. doi:10.2174/157017907781369306

Zheng BH, Ding CH, Hou XL, Dai LX (2010) Ag-catalyzed diastereo- and enantioselective synthesis of β-substituted tryptophans from sulfonylindoles. Org Lett 12:1688–1691. doi:10.1021/ol100161n