

Synthesis of (*S,Z*)-3-[(1*H*-indol-3-yl)methylidene]hexahydropyrrolo-[1,2-*a*]pyrazin-4(1*H*)-one: an alternative, enaminone based, route to unsaturated cyclodipeptides

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Received 12 October 2007; received in revised form 19 December 2007; accepted 10 January 2008

Available online 16 January 2008

Abstract

A series of racemic and enantiopure (*S,Z*)-3-[(1*H*-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-one (cyclic Pro-ΔTrp) dipeptide analogues were prepared. Racemic analogues **6a–c** were prepared by direct coupling of racemic cyclodipeptide enaminone (*R,S*)-**5** with various indole derivatives. On the other hand, enantiopure analogues were prepared through a copper(I) catalyzed vinyl amidation reaction in which acyclic (*S*)-Pro-ΔTrp dipeptide analogues **20** and **21** were formed. Acyclic dipeptides were cyclized to enantiopure (*S*)-Pro-ΔTrp dipeptide analogues **24** and **25**. For coupling reactions, vinyl bromides were prepared in several steps. From ethyl acetate (**7**), enaminone **8** was prepared and coupled with 2-methylindole and 2-phenylindole to give **9** and **10**. Direct bromination of 3-(indole-3-yl)propenoates **9** and **10** at position 2 results in vinyl bromides **11** and **12**. The Boc protecting group on the indole nitrogen 1' in vinyl bromides **11** and **12** was introduced, before the copper(I) catalyzed coupling with *N*-Boc prolinamide **18** was performed. Enantiomeric purity of chiral intermediates and final products was determined mostly by HPLC or ¹H NMR spectroscopy and X-ray diffraction.

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Keywords: Cyclodipeptides; 3-[(Indol-3-yl)methylidene]piperazine-2,5-dione; Enaminones; Indoles; Copper(I) catalyzed coupling; Natural products

1. Introduction

The cyclodipeptide template, of which one amino acid residue α,β-didehydrotryptophan or its analogue, is a common structural element in the chemistry of secondary metabolites.¹

3-[(Indol-3-yl)methylidene]piperazine-2,5-dione is a structural element present in many indole alkaloids, possessing various biologically interesting activities. Among them are microtubule inhibiting spirotryprostatin B,² free radical scavenging dihydroisoechinulin A,³ immunosuppressing cristatin A,⁴ insecticidal okaramine R⁵ and antifouling acting⁶ baretin^{6b} and dipodazine^{6c} (Fig. 1). The unsaturated cyclodipeptides of such type not only represent simple indole alkaloids, they can be utilized also as precursors in the synthesis of more complex

indole alkaloids such as VM55599,^{7a} paraherquamide A,^{7b} or desmethoxy-(+)-verruculogen TR2.⁸

Most commonly 3-alkylidenepiperazine-2,5-diones are in most cases synthesized via Horner–Emmons reactions,^{7a,9} or via condensation reactions¹⁰ with suitable aldehydes, while coupling of the N-terminus of aromatic or heteroaromatic α,β-didehydro-α-amino acids with the C-terminus of activated esters or acylhalides of *N*-protected α-amino acids, is ineffective due to the impaired nucleophilicity of the N-terminal part.¹¹ It has to be also mentioned that chiral 3-ylidenepiperazine-2,5-diones are sensitive to the basic reaction conditions and are prone to racemization.^{10,12}

Recently enaminones and related compounds, such as β-dimethylamino-α,β-didehydroamino acid derivatives, have been demonstrated to be versatile reagents in the synthesis of various heterocyclic systems.^{13,14} This enaminone-based strategy has been also successfully applied for the preparation of several indole alkaloids and their analogues, such as aplysinopsins,^{15a–f,16,18} meridianins,^{17,18} and dipodazines.^{12b}

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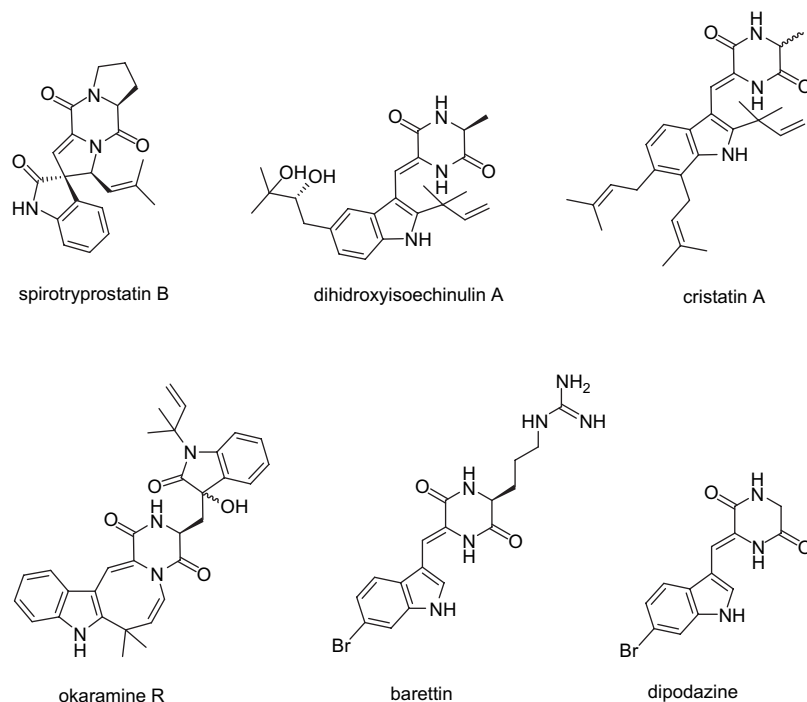


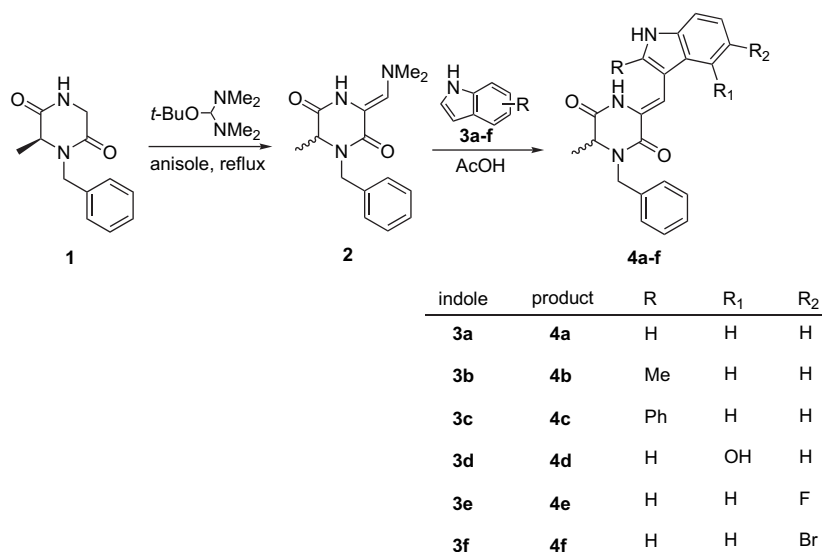
Figure 1.

2. Results and discussion

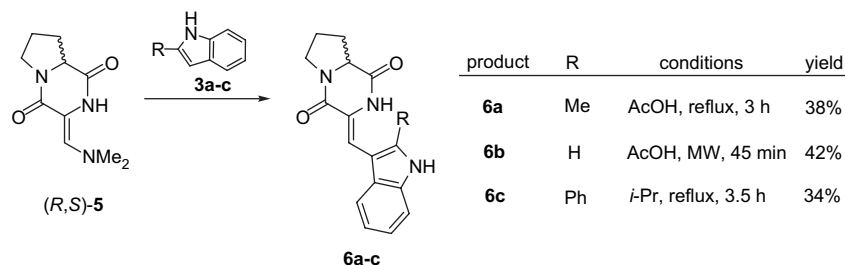
In our recent work on dipodazine analogues,^{12b} a problem with partial racemization was encountered. Namely, when we tried to introduce the chiral center with (*S*)-Ala into the dipodazine derivatives **4a–f** via (*S*)-1-benzyl-6-methylpiperazine-2,5-dione (**1**) and (*Z*)-1-benzyl-3-[(dimethylamino)methylidene]-6-methylpiperazine-2,5-dione (**2**), we observed partial racemization of this amino acid structural element in the transformation of **1** into **2** with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent),¹⁹ due to the basic reaction conditions (Scheme 1).

2.1. Preparation of racemic (*RS,Z*)-3-[(1*H*-indol-3-yl)-methylidene]hexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-ones (*Pro*– Δ Trp) cyclodipeptide analogues

To avoid racemization, we substituted (*S*)-Ala in **1**, for the conformationally more constrained (*S*)-Pro, hoping to obtain a (*Z*)-3-[(dimethylamino)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (*S*)-**5**, as a good chiral cyclodipeptide template, that would enable us to carry out further transformations. Unfortunately, racemization of (*S*)-**5** took place.²⁰ Nevertheless, racemic enaminone (*R,S*)-**5** was used in coupling reactions with different indoles, to afford three different racemic cyclic



Scheme 1.



Scheme 2.

Pro- Δ Trp analogues (*RS,Z*)-3-[(2-methyl-1*H*-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6a**), (*RS,Z*)-3-[(1*H*-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6b**), and (*RS,Z*)-3-[(2-phenyl-1*H*-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6c**) (Scheme 2).

2.2. Preparation of enantiopure (*S,Z*)-3-[(1*H*-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (*Pro-Δ*Trp) cyclodipeptide analogues

Since this synthetic approach toward desired enantiomerically pure Pro- Δ Trp cyclodipeptides was unsuccessful, a completely new synthesis was designed. For this purpose, a retrosynthetic analysis was made, accordingly to which the enaminone-based approach was preserved, and, on the other

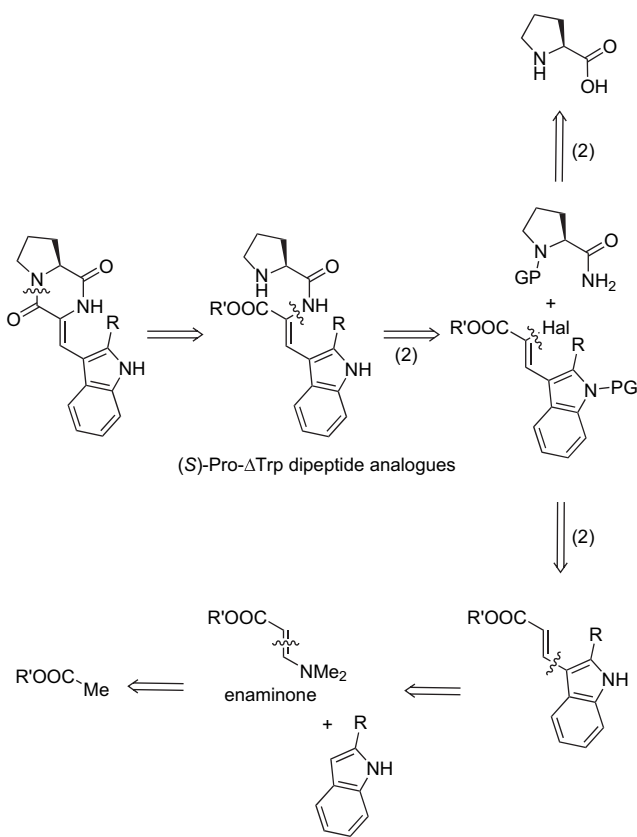
hand, enabled us to prepare enantiomerically pure acyclic Pro- Δ Trp dipeptides analogues (Scheme 3).

2.2.1. Synthesis

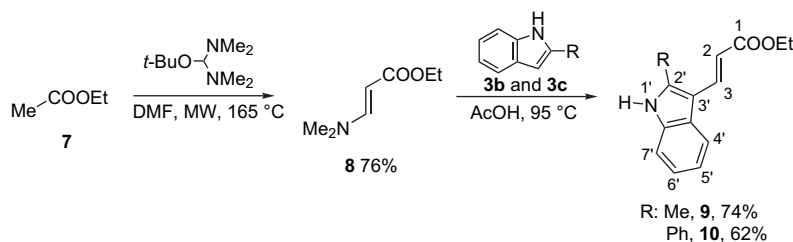
2.2.1.1. Synthesis of (*E*)-ethyl 3-(dimethylamino)propenoate (8**) and subsequent coupling with indoles **3b** and **3c**.** Ethyl acetate (**7**) selected as the starting material and reacted with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) in the presence of *N,N*-dimethylformamide under microwave irradiation, to afford the enaminone **8** in 76% yield. In the reaction of **8** with 2-methyl (**3a**) or 2-phenylindole (**3b**), (*E*)-ethyl 3-(2-methyl-1*H*-indol-3-yl)propenoate (**9**) and (*E*)-ethyl 3-(2-phenyl-1*H*-indol-3-yl)propenoate (**10**) were prepared (Scheme 4).

2.2.1.2. Synthesis of vinyl bromides **14–16.** Bromination of compound **9** with bromine in chloroform at 0 °C produced (*Z*)-ethyl 2-bromo-3-(5 or 6 bromo-2-methyl-1*H*-indol-3-yl)propenoate (**13**). Since a brominated indole nucleus could complicate the following coupling reactions, another method of bromination was introduced. We selected the simple procedure of Bocchi²¹ (used originally for the preparation for 3-haloindoles). In this manner, (*E*)-ethyl 3-(2-methyl-1*H*-indol-3-yl)propenoate (**9**) or (*E*)-ethyl 3-(2-phenyl-1*H*-indol-3-yl)propenoate (**10**) was dissolved in *N,N*-dimethylformamide, cooled to 0 °C, and then bromine was added dropwise. By treatment of the reaction mixture with aqueous ammonia and potassium disulfite, (*Z*)-ethyl 2-bromo-3-(2-methyl-1*H*-indol-3-yl)propenoate (**11**) or (*Z*)-ethyl 2-bromo-3-(2-phenyl-1*H*-indol-3-yl)propenoate (**12**) was obtained in 96 or 92% yield, respectively.

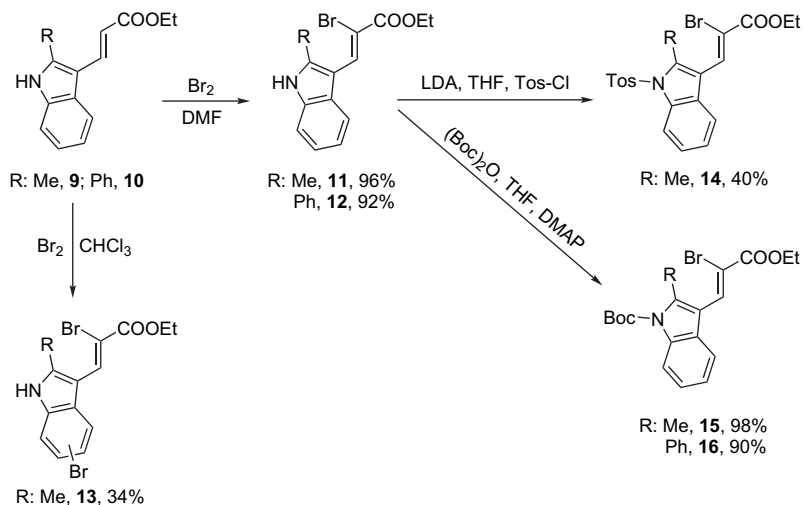
On prolonged heating of **11**, bromine is released resulting in a brown reaction mixture. This means that **11** is thermally unstable, like simple 3-haloindoles.²² To avoid thermal degradation of **11** and **12**, a push–pull system of indole nitrogen and bromine had to be blocked. For this purpose a tosyl protecting group was introduced on the indole nitrogen atom at position 1' of **11**. However, this tosyl protecting group turned out to be inconvenient for several reasons. The yield of its introduction was modest (40% in **14**) and more important, its removal resulted in racemization of the final product. Therefore, we introduced the Boc protecting group instead, according to the procedure reported in the literature²³ for other indole derivatives, to give **15** and **16** in 98 and 90% yields, respectively (Scheme 5).



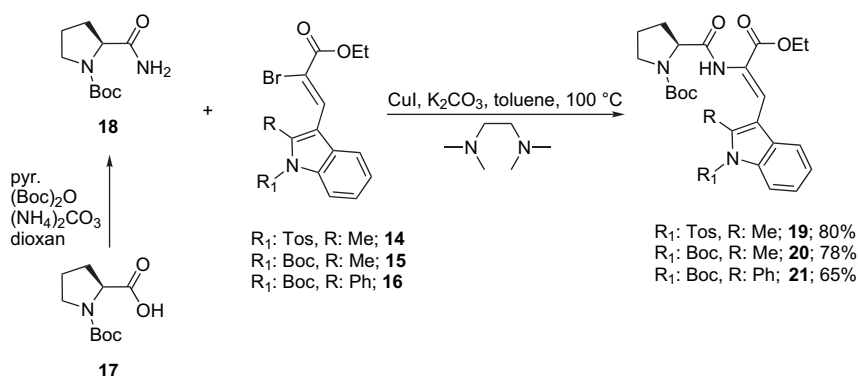
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

2.2.1.3. Copper(I) catalyzed vinyl amidation: synthesis of (S)-Pro-ΔTrp dipeptides analogues 19–21. The next synthetic step was the preparation of (S)-Pro-ΔTrp dipeptide analogues, that would allow us a simple cyclization to the final products. Having in mind the limitation and drawbacks of classical N-terminal coupling of α,β-unsaturated aromatic or heteroaromatic α-amino acids, we applied the Buchwald's copper(I) catalyzed vinyl amidation,²⁴ to couple (S)-N-Boc-prolinamide (**18**) with vinyl halides **14–16**, producing the desired (S)-Pro-ΔTrp

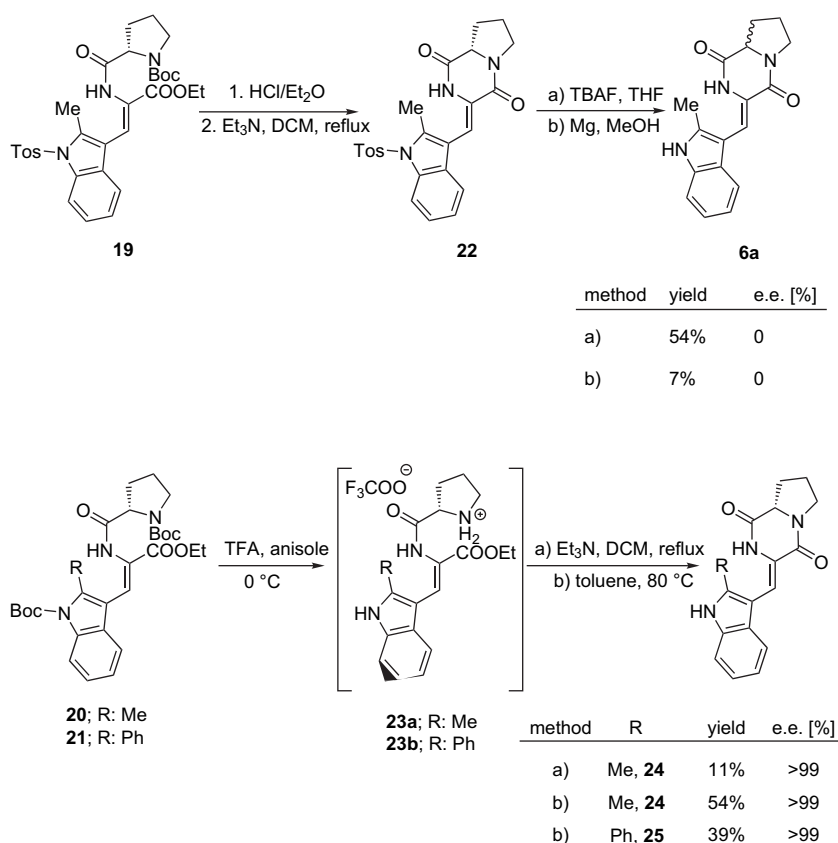
dipeptide analogues **19–21**. Looking through the literature, only one similar strategy was found in the synthesis of roquefortine C, where heteroaromatic α,β-unsaturated α-amino acid was incorporated in C-terminal part of the dipeptide.²⁵

(S)-N-Boc-prolinamide (**18**),^{26b–d} prepared from (S)-N-Boc-proline (**17**)^{26a} was coupled with vinyl bromides **14–16** in the presence of catalytic amounts of copper(I) iodide and N,N-dimethylethylenediamine as a ligand, in a Schlenk tube in toluene in an inert atmosphere at 100 °C. Using this protocol, three

(*S*)-Pro- Δ Trp analogues were prepared in good yields; (*S*)-*tert*-butyl 2-[3-ethoxy-1-(2-methyl-1-tosyl-1*H*-indol-3-yl)-3-oxoprop-1-en-2-ylcarbamoyl]-pyrrolidine-1-carboxylate (**19**) (80%), (*S*)-*tert*-butyl 3-[2-(1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)-3-ethoxy-3-oxoprop-1-enyl]-2-methyl-1*H*-indole-1-carboxylate (**20**) (78%), and (*S*)-*tert*-butyl 3-[2-(1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)-3-ethoxy-3-oxoprop-1-enyl]-2-phenyl-1*H*-indole-1-carboxylate (**21**) (65%), respectively (Scheme 6).

2.2.1.4. Cyclization of (*S*)-Pro- Δ Trp dipeptide analogues **19, **20** and **21** to **22** and final products, **24**, **25**.** Initial cyclization reactions were performed on dipeptide **19** with the 1' Tos protecting group on the indole moiety. The intention was to remove Boc protecting group from Pro part of the molecule first, then to perform cyclization to cyclodipeptide followed by detosylation of the indole 1' position in the last step. Removal of the Boc group was performed in dichloromethane with 2 M HCl in diethyl ether solution; the deprotected intermediate was not isolated. The volatile components were evaporated and the residue was immediately used in the cyclization reaction, which was performed in dichloromethane with 5 equiv of triethylamine added to the reaction mixture at reflux to produce (*S,Z*)-3-[(2-methyl-1-tosyl-1*H*-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**22**). Since the chiral piperazinediones are sensitive to racemization, we selected tetrabutylammonium fluoride (TBAF) in refluxing tetrahydrofuran as a mild method for detosylation. Reaction

proceeded slowly and after 6 h of reflux, the reaction mixture was stirred for additional 17 h at ambient temperature. To our surprise, racemic (*RS,Z*)-3-[(2-methyl-1*H*-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6a**) was isolated. The cause of racemization was probably due to a relatively strong basic nature of the fluoride anion²⁷ TBAF. The next attempt of detosylation was performed by using Mg turnings in methanol.²⁸ Since piperazinedione **22** was only slightly soluble in methanol, the yield of this reaction was very poor (7%) and the racemization again occurred, probably because of the magnesium methoxide formed during the reaction. Due to these unsuccessful experiments, we decided to use the Boc protecting group on both, the indole 1' position and proline part. Both Boc groups in dipeptide **20** were removed with trifluoroacetic acid according to the procedure described in literature for deprotecting of tryptophan.²⁹ Totally deprotected dipeptide **23a** without further purification was cyclized into (*S,Z*)-3-[(2-methyl-1*H*-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**24**) in the same manner as described above for the dipeptide **19** into **22**. In this procedure no racemization could be detected in the final product **24**, though the yield was only 11% over the two steps. Because of that, another method of cyclization was examined. After deprotection of dipeptide **20** with trifluoroacetic acid, the neutralization of dipeptide trifluoroacetate **23a** was performed with aqueous sodium hydroxide, to give the dipeptide, which was then cyclized in anhydrous toluene at 80 °C to piperazinedione **24** in 54% over two steps. Again, no racemization was



Scheme 7.

detected. Similarly dipeptide **21** was transformed to **23b** and then cyclized into (*S,Z*)-3-[(2-phenyl-1*H*-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**25**) in toluene at 80 °C. No racemization of piperazinedione **25** was observed (Scheme 7).

3. Structure determination

Due to problems with racemization, the enantiomeric purity of the chiral compounds had to be determined. This was done mostly by HPLC, in one case also by ¹H NMR spectroscopy and by X-ray analysis. For the HPLC analyses, Chiralcel OD-R chiral column was used with acetonitrile/water=40:60 as a mobile phase. For all analyses water was acidified with formic acid to pH 2 or 4. In all cases racemic analogues of analyzed compounds were prepared to be used as standards (Table 1).

For compound **19** no racemization could be seen, meaning that copper(I) catalyzed amidation of vinyl halide **14**, with

Table 1
HPLC data and optical rotations for listed compounds

Compound	Mobile phase	Retention time (min)		[α] _D	ee (%)
		<i>t</i> _R (<i>R</i>)	<i>t</i> _R (<i>S</i>)		
(<i>R,S</i>)- 19	MeCN/H ₂ O (pH 4)=40:60	14.7	15.4		0
(<i>S</i>)- 19	MeCN/H ₂ O (pH 4)=40:60	—	15.3	−116.5	>99
(<i>R,S</i>)- 22	MeCN/H ₂ O (pH 2)=40:60	8.8	8.5		0
(<i>S</i>)- 22	MeCN/H ₂ O (pH 2)=40:60	—	8.43	+42.3	>99
(<i>R,S</i>)- 6a ^a	MeCN/H ₂ O (pH 2)=40:60	6.5	5.2		0
(<i>S</i>)- 6a ^b	MeCN/H ₂ O (pH 2)=40:60	6.4	5.1	0	0
(<i>R,S</i>)- 24	MeCN/H ₂ O (pH 2)=40:60	6.4	5.1		0
(<i>S</i>)- 24	MeCN/H ₂ O (pH 2)=40:60	—	5.0	+387.1	>99
(<i>R,S</i>)- 25	MeCN/H ₂ O (pH 2)=40:60	19.0	26.9		0
(<i>S</i>)- 25	MeCN/H ₂ O (pH 2)=40:60	—	26.8	+357.5	>99

^a **6a** prepared according to Scheme 2.

^b **6a** prepared according to Scheme 7.

N-Boc prolinamide (**18**) was safe with respect to enantiomeric purity. This indicates that such formation of unsaturated dipeptides could perhaps be applied more generally. The

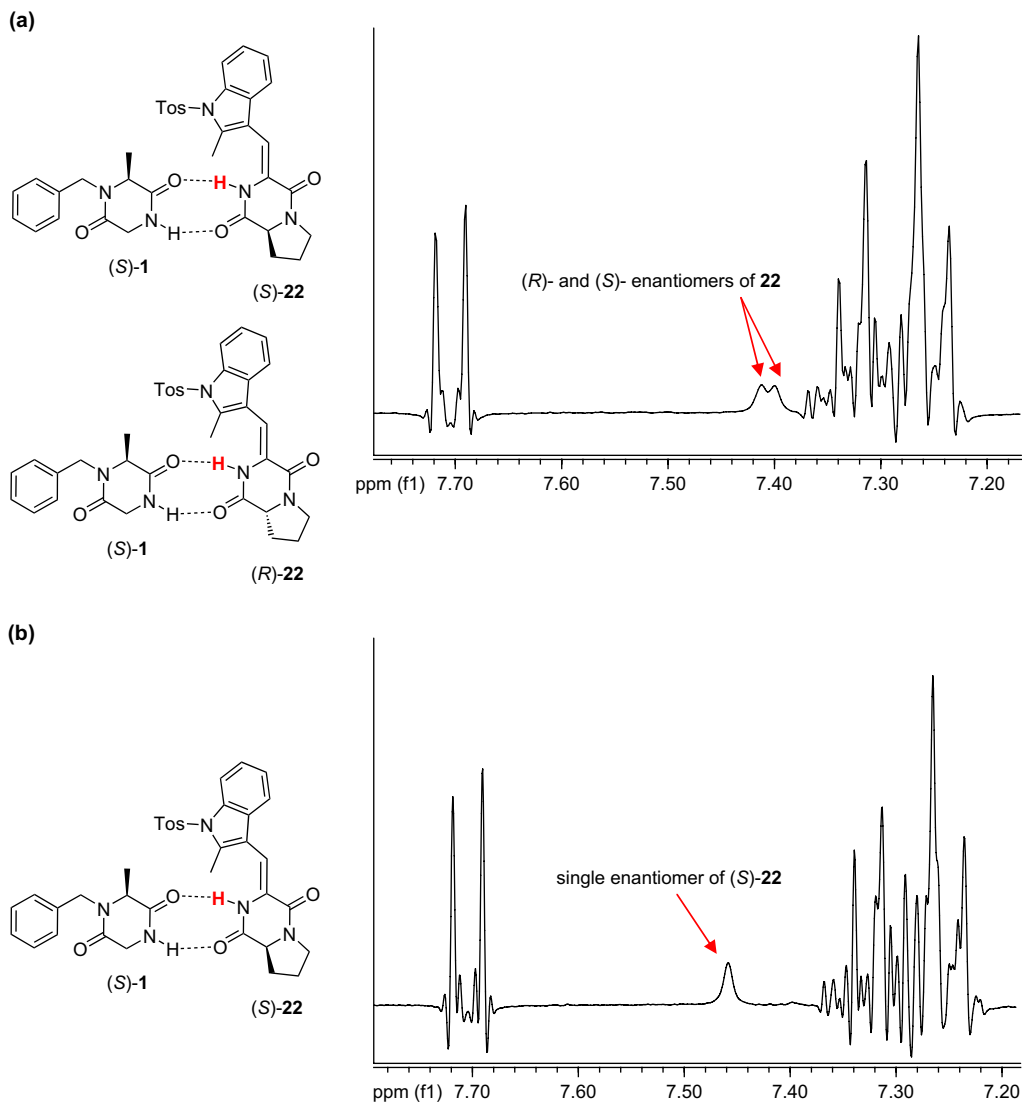


Figure 2. (a) Partial and apodized ¹H NMR spectrum, in CDCl₃ at 23 °C, of (*R,S*)-**22** with (*S*)-**1** as a CSA. Signals of amide protons for both enantiomers of (*R,S*)-**22** are visible. (b) Partial and apodized ¹H NMR spectrum, in CDCl₃ at 23 °C, of (*S*)-**22** with (*S*)-**1** as a CSA. Signal for only one amide proton of (*S*)-**22** is visible, meaning that (*S*)-**22** is enantiopure.

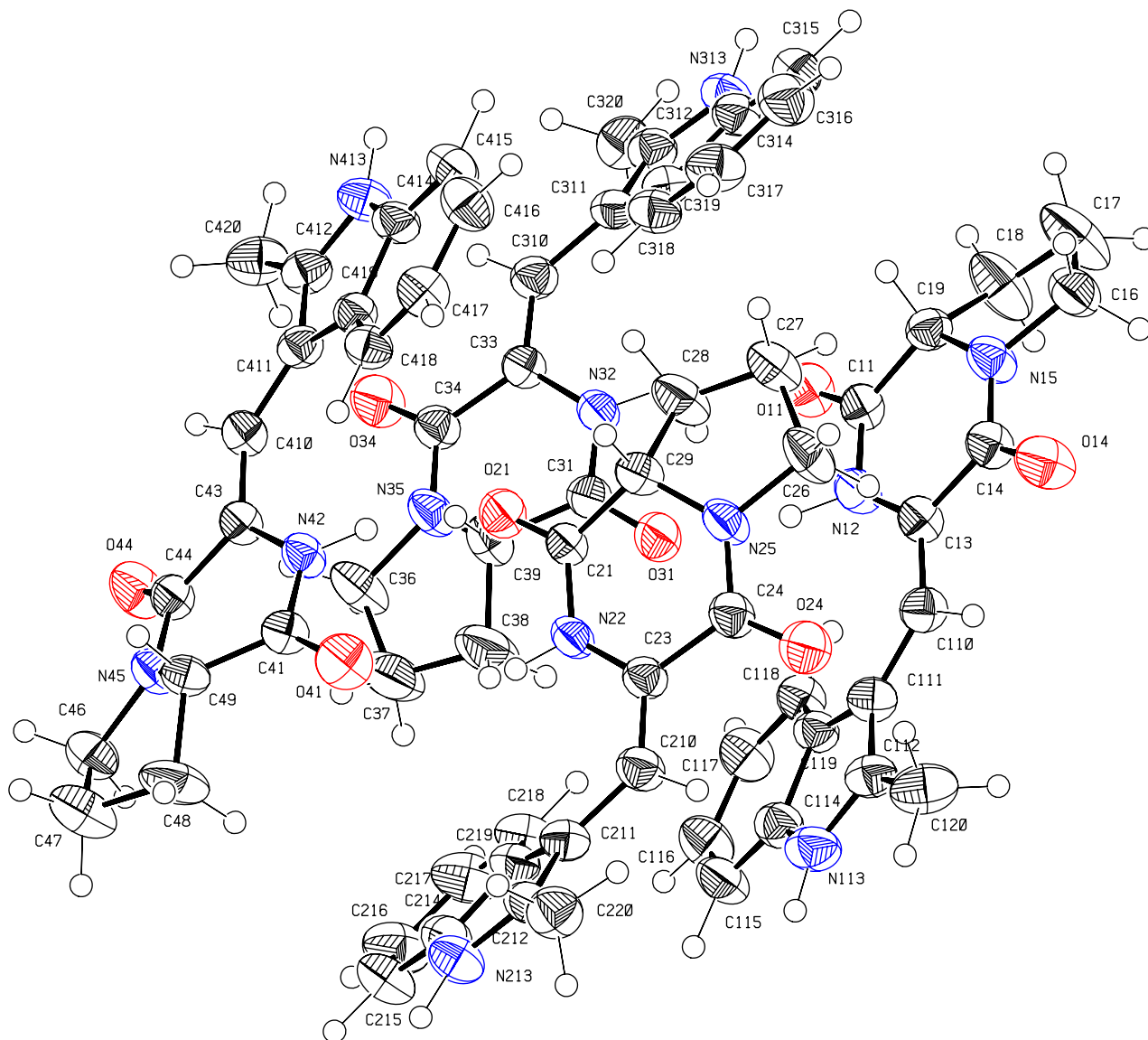


Figure 3. ORTEP plot of (*S*)-**24**. Cell packing is distinct for enantiomerically pure compounds. Also *Z* orientation around exocyclic double bond is visible. Ellipsoids are plotted at 50% probability.

enantiomeric purity of piperazinedione **24** was also confirmed by ^1H NMR spectroscopy using (*S*)-1-benzyl-6-methylpiperazine-2,5-dione, (our own chiral solvating agent (**1**)).^{16,30} From ^1H NMR spectroscopy, splitting of the signals for the amidic protons of (*R,S*)-**24** could be seen, while for the (*S*)-**24** this was not the case (Fig. 2).

The X-ray structure of piperazinedione **24** also showed that the final product was enantiomerically pure, since the cell packing of molecules in crystal was distinct for the enantiomerically pure compounds (Fig. 3).

Geometrical isomerization around the double bond was determined either by ^1H NMR spectroscopy or X-ray diffraction.

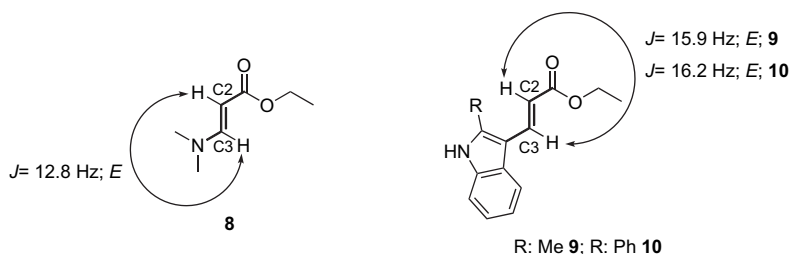


Figure 4.

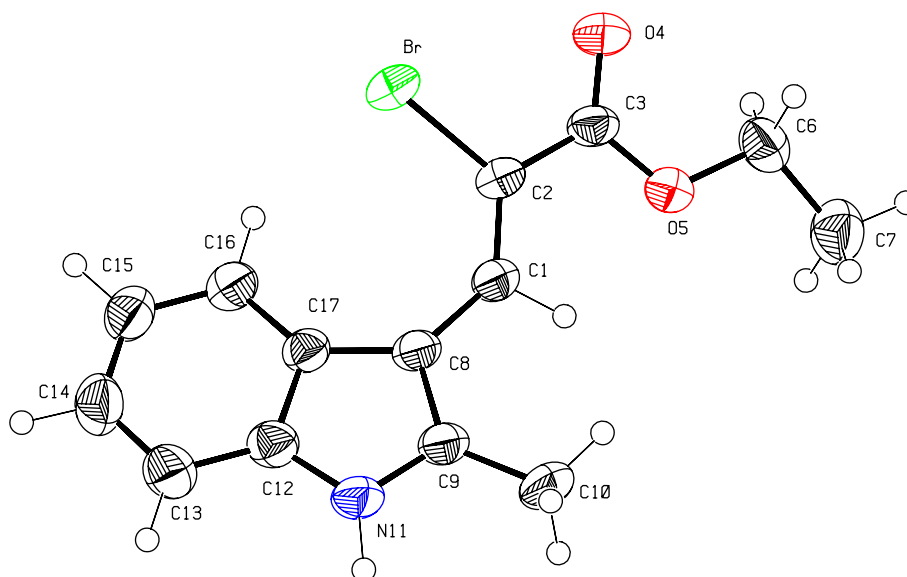


Figure 5. ORTEP plot of **11** showing Z orientation around exocyclic double bond. Ellipsoids are plotted at 50% probability.

Large coupling constants in propenoates **8–10** between hydrogen atoms on position C2 and C3 indicated that the *E* configuration was present (Fig. 4). For vinyl bromide **11**, X-ray diffraction revealed Z orientation (Fig. 5). Z orientation was also determined in an end product **24** (Fig. 3).

4. Conclusion

Analogues of cyclic Pro- Δ Trp were prepared via enamine-based synthesis. Cyclodipeptides **6a–c** were prepared in the racemic form, with coupling of indoles **3a–c** with racemic enaminone **5**. On the other hand, cyclodipeptides **22**, **24**, and **25** were prepared in their enantiopure form through copper(I) catalyzed vinyl amidation of *N*-Boc prolinamide (**18**) and vinyl bromides **14–16** as Δ Trp analogue precursors. This strategy represents a novel approach toward dipeptides, where an α,β -unsaturated heteroaromatic amino acid is in the C-terminal position. Cyclization of acyclic Pro- Δ Trp dipeptide analogues **19–21**, formed by vinyl amidation, was performed thermally. The enantiomeric purity of final products **24** and **25**, as well as intermediates **6a**, **19**, and **22** was determined by HPLC and in the case of **22** also with ^1H NMR spectroscopy, using **1** as a chiral solvating agent. X-ray crystal cell packing data on **24** also indicated on its optical purity.

5. Experimental

5.1. General

Melting points were determined on a Kofler micro hot stage. ^1H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^1H , and 75.5 MHz for ^{13}C nucleus, using DMSO- d_6 and CDCl_3 as solvents and TMS as the internal standard. HPLC analysis were performed on Hewlett Packard 1050 series Chromatographer, using Chiralcel OD-R $\Phi=0.46\times 25$ cm column. Optical rotations were determined on a Perkin–Elmer

241 MC Polarimeter. Microwave irradiations were performed on CEM Corporation Discover microwave unit. Mass spectra were recorded on an AutoSpecQ and QToF-premier spectrometers, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400. Column chromatography was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm).

5.2. Preparation of (RS,3Z)-3-[(dimethylamino)methylidene]-hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (**5**)

For preparation and characterization of this compound see Ref. 16.

5.3. Preparation of racemic cyclic Pro- Δ Trp analogues **6a–c**

5.3.1. (RS,Z)-3-[(2-Methyl-1H-indol-3-yl)methylidene]hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (**6a**)

A mixture of (RS,3Z)-3-[(dimethylamino)methylidene]-hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (**5**) (0.157 g, 0.75 mmol) and 2-methylindole (**3b**) (0.098 g, 0.75 mmol) was heated under reflux in 2 mL of glacial acetic acid for 3 h. The solvent was evaporated in vacuo and the product was purified by column chromatography (ethyl acetate) giving **6a**, which was recrystallized from ethanol. Yield 0.084 g (38%) of white solid, mp 270–271 $^\circ\text{C}$ (from ethanol); [Found: C, 68.93; H, 5.96; N, 14.18. $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2$ requires C, 69.14; H, 5.80; N, 14.23%]; R_f (ethyl acetate) 0.20; ν_{max} (KBr) 3285, 3256, 1687, 1670, 1626, 1611, 1440, 1398, 1249, 1133, 1100, 957, 744 cm^{-1} ; δ_{H} (300 MHz, DMSO- d_6) 1.80–2.00 (3H, m, Pro), 2.09–2.29 (1H, m, Pro), 2.37 (3H, s, CH_3), 3.41–3.53 (1H, m, Pro), 3.53–3.65 (1H, m, Pro), 4.37–4.49 (1H, m, Pro), 6.85 (1H, s, CH), 6.97–7.11 (2H, m, Ar), 7.28–7.35 (1H, m, Ar), 7.35–7.42 (1H, m, Ar), 9.21 (1H, s, CONH), 11.34 (1H, s, NH); MS (EI): m/z 295 (M^+).

5.3.2. (RS,Z)-3-[(1H-Indol-3-yl)methylidene]hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione (**6b**)

To a solution of (RS,3Z)-3-[(dimethylamino)methylidene]hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione (**5**) (0.098 g, 0.75 mmol) in 2 mL of glacial acetic acid, indole (**3a**) (0.088 g, 0.75 mmol) was added and the mixture was stirred in a closed vessel mode under microwave irradiation (CEM Discover, $P=300$ W, $T=125$ °C) for 45 min. The reaction mixture was cooled, volatile components were evaporated, and the product was purified by column chromatography (ethyl acetate) to give title compound **6b**, which was recrystallized from ethanol. Yield 0.089 g (42%) of yellow solid, mp 276–279 °C (from ethanol); [Found: C, 68.31; H, 5.48; N, 14.73. $C_{16}H_{15}N_3O_2$ requires C, 68.31; H, 5.37; N, 14.94%]; R_f (ethyl acetate) 0.20; $\nu_{\max}$ (KBr) 3345, 3055, 1673, 1601, 1533, 1444, 1397, 1243, 1133, 935, 764, 752, 710 cm^{-1} ; δ_H (300 MHz, DMSO- d_6) 1.75–2.05 (3H, m, Pro), 2.10–2.30 (1H, m, Pro), 3.40–3.60 (2H, m, Pro), 4.30–4.42 (1H, m, Pro), 6.99 (1H, s, CH), 7.06–7.13 (1H, m, Ar), 7.13–7.20 (1H, m, Ar), 7.40–7.45 (1H, m, Ar), 7.62–7.68 (1H, m, Ar), 7.92 (1H, d, $J=1.9$ Hz, Ar), 9.56 (1H, s, CONH), 11.62 (1H, s, NH); δ_C (75.5 MHz, DMSO- d_6) 21.5, 27.9, 44.9, 58.1, 107.9, 108.0, 111.7, 118.0, 119.7, 121.9, 124.1, 126.3, 126.8, 135.5, 159.1, 166.8; MS (EI): m/z 281 (M^+); HRMS (EI): M^+ , found 281.1170. $C_{16}H_{15}N_3O_2$ requires 281.1164.

5.3.3. (RS,Z)-3-[(2-Phenyl-1H-indol-3-yl)methylidene]hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione (**6c**)

A mixture of (RS,3Z)-3-[(dimethylamino)methylidene]hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione (**5**) (0.157 g, 0.75 mmol), 2-phenylindole (**3c**) (0.098 g, 0.75 mmol), and three drops of concentrated hydrochloric acid was heated under reflux in 4 mL of 2-propanol for 3.5 h. The reaction mixture was cooled, the solvent evaporated in vacuo, and the residue purified by column chromatography (ethyl acetate), giving title compound **6c**, which was then recrystallized from ethanol/water. Yield 0.092 g (34%) of pale yellow solid, mp 229–231 °C (from ethanol/water); [Found: C, 73.68; H, 5.44; N, 11.62. $C_{22}H_{19}N_3O_2$ requires C, 73.93; H, 5.36; N, 11.76%]; R_f (ethyl acetate) 0.39; $\nu_{\max}$ (KBr) 3341; 3299, 1695, 1663, 1622, 1449, 1432, 1379, 1310, 1229, 1114, 745, 699 cm^{-1} ; δ_H (300 MHz, DMSO- d_6) 1.80–2.00 (3H, m, Pro), 2.15–2.30 (1H, m, Pro), 3.40–3.52 (1H, m, Pro), 3.55–3.65 (1H, m, Pro), 4.40–4.47 (1H, m, Pro), 6.86 (1H, s, CH), 7.05–7.12 (1H, m, Ar), 7.16–7.30 (1H, m, Ar), 7.37–7.58 (5H, m, Ph), 7.64–7.68 (2H, m, Ar), 9.27 (1H, s, CONH), 11.77 (1H, s, NH).

5.4. Preparation of enantiomerically pure cyclic Pro- Δ Trp analogues

5.4.1. (E)-Ethyl 3-(dimethylamino)propenoate (**8**)

To ethyl acetate (**7**) (2 mL, 20 mmol) in a Pyrex vial, dimethylformamide (3 mL) and bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent, 1.044 mL, 5 mmol) were added. The vial was flushed with argon, closed with a rubber septum, and irradiated with microwave in a closed vessel mode (CEM Discover, $P=300$ W, $T=165$ °C) for 15 min. The cooled reaction mixture was transferred into round bottom flask and the

volatile components were evaporated in vacuo. The dark brown residue was purified by column chromatography (25% ethyl acetate/petroleum ether), giving a yellow oil **8**. Yield 0.542 g (76%); R_f (25% ethyl acetate/petroleum ether) 0.26; $\nu_{\max}$ (NaCl) 3530, 2930, 1676, 1617, 1499, 1388, 1255, 1158, 1096, 978, 764, 787 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 1.26 (3H, t, $J=7.2$ Hz, CH_3), 2.88 (6H, s, $N(CH_3)_2$), 4.13 (2H, q, $J=7.2$ Hz, CH_2), 4.52 (1H, d, $J=12.8$ Hz, CH), 7.44 (1H, d, $J=12.8$ Hz, CH); δ_C (75.5 MHz, $CDCl_3$) 14.8, 58.6, 84.2, 152.7, 169.4; MS (EI): m/z 143 (M^+); HRMS (EI): M^+ , found 143.0951. $C_7H_{13}NO_2$ requires 143.0946.

5.4.2. General procedure for coupling of indole **3b** and **3c** with propenoate **8**

(E)-Ethyl 3-(dimethylamino)propenoate (**8**) was dissolved in glacial acetic acid, one of the indole derivative **3b** or **3c** was added and the reaction mixture was heated at 95 °C.

5.4.2.1. (E)-Ethyl 3-(2-methyl-1H-indol-3-yl)propenoate (**9**). (E)-Ethyl 3-(dimethylamino)propenoate (**8**) (2.864 g, 20 mmol), 2-methylindole (**3b**) (2.624 g, 20 mmol), and glacial acetic acid (13 mL) were reacted according to the general procedure for 1.5 h. After cooling the reaction mixture to room temperature, the product **9** precipitated from the reaction mixture. This was collected by filtration, washed with water/ethanol=1:1 solution, and dried in a desiccator (over NaOH). Yield 3.410 g (74%) of pale white solid, mp 131 °C (solid becomes black), 190 °C (black solid melts); [Found: C, 73.36; H, 6.75; N, 6.07. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%]; $\nu_{\max}$ (KBr) 3292, 2980, 2897, 1688, 1607, 1575, 1454, 1363, 1323, 1279, 1175, 1149, 1027, 967, 741, 726 cm^{-1} ; δ_H (300 MHz, DMSO- d_6) 1.26 (3H, t, $J=7.2$ Hz, CH_3), 3.31 (3H, s, CH_3), 4.17 (2H, q, $J=7.2$ Hz, CH_2), 6.26 (1H, d, $J=15.8$ Hz, CH), 7.07–7.14 (2H, m, Ar), 7.33–7.39 (1H, m, Ar), 7.74–7.79 (1H, m, Ar), 7.85 (1H, d, 15.8 Hz, CH), 11.70 (1H, s, NH); δ_C (300 MHz, $CDCl_3$) 1.36 (3H, t, $J=7.2$ Hz, CH_3), 2.50 (3H, s, CH_3), 4.29 (2H, q, $J=7.2$ Hz, CH_2), 6.43 (1H, d, $J=15.9$ Hz, CH), 7.19 (2H, m, Ar), 7.30 (1H, m, Ar), 7.85 (1H, m, Ar), 7.95 (1H, d, $J=15.9$ Hz, CH), 8.49 (1H, s, NH); δ_C (75.5 MHz, $CDCl_3$) 12.3, 14.5, 60.1, 109.6, 110.9, 112.1, 119.9, 121.4, 122.4, 126.4, 135.7, 137.5, 140.0, 168.8; MS (EI): m/z 229 (M^+); HRMS (EI): M^+ , found 229.1110. $C_{14}H_{15}NO_2$ requires 229.1103.

5.4.2.2. (E)-Ethyl 3-(2-phenyl-1H-indol-3-yl)propenoate (**10**). (E)-Ethyl 3-(dimethylamino)propenoate (**8**) (1.718 g, 12 mmol), 2-phenylindole (**3c**) (2.319 g, 12 mmol), and glacial acetic acid (10 mL) were reacted according to the general procedure for 1.75 h. The volatile components were evaporated and yellow oily residue slowly crystallized. The solid was collected and recrystallized from methanol giving pure title product **10**. Yield 2.132 g (62%), mp 152–154 °C (from methanol); [Found: C, 78.09; H, 5.89; N, 4.65. $C_{19}H_{17}NO_2$ requires C, 78.33; H, 5.88; N, 4.81%]; $\nu_{\max}$ (KBr) 3295, 3054, 2977, 1667, 1619, 1455, 1391, 1365, 1233, 1052, 981, 841, 775, 741 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 1.33 (3H, t, $J=7.2$ Hz, CH_3), 4.25 (2H, q, $J=7.2$ Hz, CH_2), 6.59 (1H, d, $J=16.2$ Hz, CH), 7.25–7.35 (2H, m, Ar), 7.40–7.60 (6H, m, Ar), 7.95–8.04 (1H, m, Ar),

8.00 (1H, d, 16.2 Hz, CH); 8.47 (1H, br s, NH); δ_C (75.5 MHz, CDCl₃) 14.4, 60.1, 109.8, 111.5, 114.1, 120.8, 121.7, 123.4, 126.5, 128.9, 129.0, 129.1, 131.3, 136.4, 139.7, 142.4, 168.6; MS (EI): m/z 291 (M^+); HRMS (EI): M^+ , found 291.1268. C₁₉H₁₇NO₂ requires 291.1259.

5.4.3. (Z)-Ethyl 2-bromo-3-(5 or 6 bromo-2-methyl-1H-indol-3-yl)propenoate (**13**)

To (E)-ethyl 3-(2-methyl-1H-indol-3-yl)propenoate (**9**) (1.582 g, 6.90 mmol) dissolved in 75 mL of chloroform and cooled to 0 °C, bromine (0.461 mL, 8.97 mmol) was added dropwise. The reaction mixture was stirred for 25 min at 0 °C and then the volatile components were evaporated in vacuo, and the residue was purified by column chromatography (25% ethyl acetate/petroleum ether). On mobile phase evaporation the product **13**, while still wet, was yellow, but when dry it turned to violet. Yield 0.901 g (34%) of violet solid, mp 97 °C (decomposition, **13** is thermolabile); R_f (25% ethyl acetate/petroleum ether) 0.18; $\nu_{\max}$ (KBr) 3298, 2976, 1690, 1606, 1567, 1450, 1365, 1235, 1062, 897, 799, 752 cm⁻¹; δ (300 MHz, DMSO-*d*₆) 1.31 (3H, t, $J=7.2$ Hz, CH₃), 2.43 (3H, s, CH₃), 4.28 (2H, q, $J=7.2$ Hz, CH₂), 7.20 (1H, dd, $J_1=8.3$ Hz, $J_2=1.9$ Hz, Ar), 7.52 (1H, d, $J=1.9$ Hz, Ar), 7.58 (1H, d, $J=8.3$ Hz, Ar), 8.43 (1H, s, CH), 11.86 (1H, s, NH); MS (EI): m/z 387 (M^+); HRMS (EI): M^+ , found 384.9330. C₁₄H₁₃Br₂NO₂ requires 384.9313.

5.4.4. General procedure for preparation of vinyl bromides **11** and **12**

One of the propenoate **9** or **10** was dissolved in dimethylformamide, cooled to 0 °C, and bromine was added dropwise. The reaction mixture was left stirring at 0 °C for 0.5 h. After that it was poured into ice cold water in which ammonia (flushed for 1.5 min with gaseous ammonia), and potassium disulfite were dissolved. The product **11** or **12** precipitated as a solid and was collected by filtration.

5.4.4.1. (Z)-Ethyl 2-bromo-3-(2-methyl-1H-indol-3-yl)propenoate (**11**). (E)-Ethyl 3-(2-methyl-1H-indol-3-yl)propenoate (**9**) (2.293 g, 10 mmol), *N,N*-dimethylformamide (45 mL), bromine (0.581 mL, 10.1 mmol), ice cold water (350 mL), and potassium disulfite (0.5 g, 2.2 mmol) were reacted according to the general procedure. (Z)-Ethyl 2-bromo-3-(2-methyl-1H-indol-3-yl)propenoate (**11**) precipitated as a white solid and was collected by filtration. Yield 2.949 g (96%). For further purification, propenoate **11** was recrystallized from methanol. Total yield 1.911 g (62%) of colorless solid, mp 122 °C (decomposition); [Found: C, 54.34; H, 4.66; N, 4.33. C₁₄H₁₄BrNO₂ requires: C, 54.56; H, 4.58; N, 4.55%]; $\nu_{\max}$ (KBr) 3289, 2978, 1682, 1606, 1460, 1391, 1323, 1245, 1054, 901, 872, 741 cm⁻¹; δ_H (300 MHz, DMSO-*d*₆) 1.31 (3H, t, $J=7.2$ Hz, CH₃), 2.45 (3H, s, CH₃), 4.28 (2H, q, $J=7.2$ Hz, CH₂), 7.02–7.15 (2H, m, Ar), 7.32–7.37 (1H, m, Ar), 7.61–7.68 (1H, m, Ar), 8.47 (1H, s, CH), 11.73 (1H, s, NH); δ_C (75.5 MHz, DMSO-*d*₆) 13.1, 14.0, 61.9, 107.0, 107.8, 111.0, 119.5, 120.7, 121.2, 125.3, 135.6, 136.8, 139.6, 162.8; MS (EI): m/z 307

(M^+); HRMS (EI): M^+ , found 307.0219. C₁₄H₁₄BrNO₂ requires 307.0208.

5.4.4.2. (Z)-Ethyl 2-bromo-3-(2-phenyl-1H-indol-3-yl)propenoate (**12**). (E)-Ethyl 3-(2-phenyl-1H-indol-3-yl)propenoate (**10**) (1.681 g, 5.8 mmol), *N,N*-dimethylformamide (26 mL), bromine (0.300 mL, 5.8 mmol), ice cold water (250 mL), and potassium disulfite (0.264 g, 1.1 mmol) were reacted according to the general procedure. (Z)-Ethyl 2-bromo-3-(2-methyl-1H-indol-3-yl)propenoate (**11**) precipitated as a white solid and was collected by filtration. Yield 1.966 g (92%). For further purification, propenoate **12** was recrystallized from methanol. Yield 1.432 g (67%) as a yellow solid, mp 137–140 °C (decomposition); [Found: C, 61.67; H, 4.50; N, 3.64. C₁₉H₁₆BrNO₂ requires C, 61.64; H, 4.36; N, 3.78%]; $\nu_{\max}$ (KBr) 3305, 1682, 1607, 1452, 1390, 1260, 1235, 1075, 1048, 914, 872, 743 cm⁻¹; δ_H (300 MHz, CDCl₃) 1.37 (3H, t, $J=7.2$ Hz, CH₃), 4.35 (2H, q, $J=7.2$ Hz, CH₂), 7.18–7.26 (1H, m, Ar), 7.26–7.32 (1H, m, Ar), 7.32–7.37 (1H, m, Ar), 7.39–7.47 (2H, m, Ar), 7.48–7.53 (1H, m, Ar), 7.53–7.58 (1H, m, Ar), 7.78–7.84 (1H, m, Ar), 8.49 (1H, s, CH), 8.83 (1H, s, NH); δ_C (75.5 MHz, CDCl₃) 14.2, 62.5, 108.9, 111.3, 113.1, 120.6, 122.4, 123.1, 126.1, 128.2, 128.7, 129.0, 131.9, 136.1, 137.6, 139.1, 163.6; MS (EI): m/z 369 (M^+); HRMS (EI): M^+ , found 369.0376. C₁₉H₁₆BrNO₂ requires 369.0364.

5.4.5. (Z)-Ethyl 2-bromo-3-(2-methyl-1-tosyl-1H-indol-3-yl)propenoate (**14**)

To a dry 100 mL round bottom flask with magnetic stirrer, (Z)-ethyl 2-bromo-3-(2-methyl-1H-indol-3-yl)propenoate (**11**) (1.54 g, 5 mmol) was added and the flask was stoppered with a rubber septum. Through the septum, 18 mL of anhydrous tetrahydrofuran was added and the solution was cooled to –78 °C. Lithium diisopropylamide (3.25 mL of 2 M in tetrahydrofuran solution, 6.5 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 45 min, and then tosylchloride (1.144 g, 6 mmol) dissolved in 6 mL of anhydrous tetrahydrofuran was added rapidly. Stirring at –78 °C continued for 1 h, afterward the reaction mixture was left to stir at ambient temperature for 20 h, resulting in a yellow suspension. The reaction was quenched with 30 mL of 0.3 M aqueous solution of sodium hydrogencarbonate. The tetrahydrofuran was evaporated in vacuo and the water phase was extracted with 3 × 60 mL of diethyl ether. The organic phase was then washed with 20 mL of 0.1 M aqueous solution of sodium thiosulfate, 2 × 20 mL of water, 2 × 20 mL of brine, and dried with sodium sulfate. The volatile components were evaporated in vacuo and the yellow oily residue was purified by column chromatography (25% ethyl acetate/petroleum ether), and the oily product was recrystallized from methanol giving title product **14** as a colorless solid. Yield 0.915 g (40%), mp 113–115 °C (from methanol); [Found: C, 54.75; H, 4.50; N, 2.99. C₂₀H₂₁BrNO₄S requires: C, 54.55; H, 4.36; N, 3.03%]; R_f (25% ethyl acetate/petroleum ether) 0.40; $\nu_{\max}$ (KBr) 2928, 1725, 1622, 1453, 1377, 1243, 1177, 1090, 1043, 917, 812, 747 cm⁻¹; δ_H (300 MHz, DMSO-*d*₆): 1.31 (3H, t, $J=7.2$ Hz, CH₃), 2.33 (3H, s, CH₃), 2.55 (3H, s, CH₃), 4.30 (2H, q, $J=7.2$ Hz, CH₂), 7.27 (1H, ddd, $J_1=7.5$ Hz,

$J_2=7.5$ Hz, $J_3=1.2$ Hz, Ar), 7.30–7.40 (4H, m, 2H-Ar+2H-Tos), 7.74–7.81 (2H, m, Tos), 8.07 (1H, d, $J=8.1$ Hz, Ar), 8.28 (1H, s, CH); δ_C (75.5 MHz, $CDCl_3$) 13.9, 14.8, 20.9, 62.5, 114.0, 116.3, 118.5, 119.9, 123.6, 124.5, 126.2, 127.0, 130.2, 134.49, 134.52, 135.1, 135.3, 145.5, 161.7; MS (EI): m/z 463 (M^+); HRMS (EI): M^+ , found 461.0305. $C_{20}H_{21}BrNO_4S$ requires 461.0296.

5.4.6. General procedure for preparation of *N*-Boc protected vinyl bromides **15** and **16**

Di-*tert*-butyl dicarbonate was dissolved in 30 mL of anhydrous tetrahydrofuran, one of the vinyl bromide **11** or **12** and *N,N*-dimethylaminopyridine (DMAP) were added and the reaction mixture was stirred at room temperature for additional 0.5 h. The solvent was removed in vacuo, residue dissolved in 50 mL of dichloromethane, and washed with 3×100 mL of 1.5 M aqueous hydrochloric acid. The organic phase was dried with sodium sulfate, evaporated in vacuo, and an oily residue purified by column chromatography.

5.4.6.1. (Z)-tert-Butyl 3-(2-bromo-3-ethoxy-3-oxoprop-1-enyl)-2-methyl-1H-indole-1-carboxylate (15). Di-*tert*-butyl dicarbonate (1.753 g, 8 mmol), (Z)-ethyl 2-bromo-3-(2-methyl-1H-indol-3-yl)propenoate (**11**) (1.650 g, 5.4 mmol), and DMAP (65.4 mg, 0.54 mmol) were reacted according to the general procedure. Purified by column chromatography (90% chloroform/methanol). Yield 2.135 g (98%) of colorless oil that crystallized into white solid, mp 102–105 °C; R_f (90% chloroform/methanol) 0.33; ν_{max} (KBr) 2979, 2932, 1805, 1731, 1622, 1475, 1458, 1369, 1323, 1245, 1143, 1043, 841, 746 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 1.41 (3H, t, $J=7.2$ Hz, CH_3), 1.70 (9H, s, $C(CH_3)_3$), 2.57 (3H, s, CH_3), 4.38 (2H, q, $J=7.2$ Hz, CH_2), 7.18–7.33 (2H, m, Ar), 7.40–7.48 (1H, m, Ar), 8.08–8.15 (1H, m, Ar), 8.34 (1H, s, CH); δ_C (75.5 MHz, $CDCl_3$) 14.2, 16.5, 28.2, 62.7, 84.3, 115.0, 115.5, 117.4, 119.5, 122.7, 124.0, 127.2, 135.6, 135.8, 136.6, 150.3, 162.8; MS (EI): m/z 407 (M^+); HRMS (EI): M^+ , found 407.0746. $C_{19}H_{22}BrNO_4$ requires 407.0732.

5.4.6.2. (Z)-tert-Butyl 3-(2-bromo-3-ethoxy-3-oxoprop-1-enyl)-2-phenyl-1H-indole-1-carboxylate (16). Di-*tert*-butyl dicarbonate (1.689 g, 7.74 mmol), (Z)-ethyl 2-bromo-3-(2-phenyl-1H-indol-3-yl)propenoate (**12**) (1.432 g, 3.9 mmol), and DMAP (94.6 mg, 0.77 mmol) were reacted according to the general procedure. Purified by column chromatography (4.8% ethyl acetate/petroleum ether) gave **16**. Yield 1.635 g (90%) of yellow oil that crystallized over night, at +4 °C, into yellow solid, mp 115–118 °C; R_f (4.8% ethyl acetate/petroleum ether) 0.30; ν_{max} (KBr) 2978, 2937, 1736, 1721, 1615, 1475, 1455, 1354, 1331, 1224, 1154, 1083, 1044, 878, 849, 748 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 1.27 (9H, s, $C(CH_3)_3$), 1.32 (3H, t, $J=7.2$ Hz, CH_3), 4.29 (2H, q, $J=7.2$ Hz, CH_2), 7.28–7.50 (7H, m, 5H-Ph+2H-Ar), 7.62–7.70 (1H, m, Ar), 7.98 (1H, s, CH), 8.26 (1H, br d, $J=8.1$ Hz, Ar); δ_C (75.5 MHz, $CDCl_3$) 14.1, 27.4, 62.6, 84.0, 115.3, 116.2, 116.7, 121.9, 122.8, 124.9, 126.0, 127.9, 128.3, 129.7, 133.1, 136.6, 136.9, 139.6, 149.7, 162.8; MS (EI): m/z 471 (M^+); HRMS (EI): M^+ , found 469.0900. $C_{24}H_{24}BrNO_4$ requires 469.0889.

5.4.7. (S)-N-Boc proline (**17**)

(S)-Proline (2.303 g, 20 mmol) was suspended in 40 mL of dichloromethane. Triethylamine (3.733 mL, 26 mmol) was added, followed by di-*tert*-butyl dicarbonate (6.303 g, 28.9 mmol) solvated in 2 mL of dichloromethane. The mixture was stirred at room temperature for 2.5 h. Afterward, the reaction was quenched with 10 mL of saturated aqueous citric acid solution, washed with brine (2×15 mL) and water (15 mL). The organic layer was dried with sodium sulfate and evaporated in vacuo. The yellow syrup-like residue was dissolved in hot ethyl acetate (5 mL) and 50 mL of *n*-hexane was added. Upon cooling at –25 °C, (S)-N-Boc proline crystallized, and the solid was collected by filtration.^{26a} Yield 3.727 g (87%) of white solid, mp 133–134 °C (from ethyl acetate/*n*-hexane), lit.^{26a} mp 135–137 °C; ν_{max} (KBr) 2976, 2718, 1736, 1637, 1430, 1367, 1217, 1131, 1069, 978, 899, 852, 775 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 1.44 (3H, br s, $C(CH_3)_3$), 1.49 (6H, br s, $C(CH_3)_3$), 1.80–2.15 (3H, m, Pro), 2.18–2.51 (1H, m, Pro), 3.25–3.62 (2H, m, Pro), 4.20–4.41 (1H, m, Pro).

5.4.8. (S)-N-Boc prolinamide (**18**)

(S)-N-Boc proline (**17**) (3.702 g, 17.2 mmol) was dissolved in 85 mL of dioxane. Pyridine (0.860 mL), di-*tert*-butyl dicarbonate (4.875 g, 22.3 mmol), and ammonium carbonate (2.144 g; 22.3 mmol) were added. The reaction mixture was stirred at room temperature over night (19 h). The volatile components were evaporated in vacuo and 85 mL of ethyl acetate was added. The solution was washed with 81 mL of 20% aqueous citric acid solution and 85 mL of brine. The water phases were extracted with 3×100 mL of ethyl acetate, combined, dried with sodium sulfate, and evaporated in vacuo. The oily residue was purified by column chromatography (95% chloroform/methanol), giving clear oily product, which was recrystallized from hot diethyl ether. White solid was collected by filtration.^{26b,c} Yield 3.016 g (82%) of white solid, mp 108 °C (from diethyl ether), lit.^{26d} mp 104–106 °C; R_f [95% chloroform/methanol] 0.29; $[\alpha]_D^{25}$ –42.7 (*c* 1, EtOH), lit.^{26d} $[\alpha]_D^{26}$ –43.4 (*c* 1, EtOH); ν_{max} (KBr): 3385, 3204, 2976, 1676, 1412, 1362, 1174, 1121, 927, 780 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 1.75–2.45 (4H, m, Pro), 3.44 (2H, br s, Pro), 4.27 (1H, br s, Pro), 5.46 (2H, br s, $CONH_2$, trans), 6.00 (1H, br s, 1H of $CONH_2$, cis), 6.84 (1H, br s, 1H of $CONH_2$, cis); trans/cis=1:1.

5.4.9. General procedure for copper catalyzed coupling of *N*-protected vinyl bromides **14**–**16** with *N*-Boc prolinamide (**18**)

Cuprous iodide and finely powdered potassium carbonate were oven dried (100 °C) in vacuum for 2 h and were loaded into a Schlenk tube. One of the *N*-protected vinyl bromide **14**, **15** or **16** and (S)-N-Boc prolinamide (**18**) were dried in desiccator (over NaOH) over night and also loaded into a Schlenk tube, which was stoppered with a rubber septum. Air was evacuated under vacuum and the tube was backfilled with argon. This cycle was repeated twice. Then through the tube septum *N,N'*-dimethylethylenediamine and anhydrous toluene were added. The Schlenk tube was then heated in an oil bath at 100 °C. After

that heating was turned off and the reaction mixture was stirred continuously. The reaction mixture was then eluted through a 4 cm plug of silica gel with 40 mL of ethyl acetate. Volatile components were evaporated in vacuo and brown residue purified by column chromatography.

5.4.9.1. (S)-tert-Butyl 2-[3-ethoxy-1-(2-methyl-1-tosyl-1H-indol-3-yl)-3-oxoprop-1-en-2-ylcarbamoyl]-pyrrolidine-1-carboxylate (19). Cuprous iodide (19.8 mg, 0.1 mmol), potassium carbonate (0.257 g, 2 mmol), (Z)-ethyl 2-bromo-3-(2-methyl-1-tosyl-1H-indol-3-yl)propenoate (**14**) (0.462 g, 1.0 mmol), (S)-N-Boc prolinamide (**18**) (0.257 g, 1.2 mmol), *N,N'*-dimethylethylenediamine (21.5 μ L, 0.2 mmol), and anhydrous toluene (2 mL) were reacted according to the general procedure for 12 h at 100 °C and afterward for additional 11 h. Purified by column chromatography (25% ethyl acetate/petroleum ether). The colorless oily product was then dissolved in dichloromethane, *n*-heptane was added, and solvents were rapidly evaporated in vacuo. The product **19** was formed as a white foam. Yield 0.475 g (80%), mp 66–71 °C (from dichloromethane/*n*-heptane); R_f (25% ethyl acetate/petroleum ether) 0.14; $[\alpha]_D^{27}$ –116.5 (*c* 0.5, CHCl₃), ee>99%; $\nu_{\max}$ (KBr) 3369, 2978, 1698, 1494, 1476, 1454, 1396, 1366, 1260, 1176, 1121, 1080, 1020, 990, 748 cm^{–1}; δ_H (300 MHz, CDCl₃) 1.35 (3H, t, *J*=7.2 Hz, CH₃), 1.41 (9H, s, C(CH₃)₃), 1.46–1.77 (3H, m, Pro), 1.85–2.15 (1H, m, Pro), 2.33 (3H, s, CH₃), 2.58 (3H, s, CH₃), 3.00–3.35 (2H, m, Pro), 4.24 (1H, br s, Pro), 4.32 (2H, q, *J*=7.2 Hz, CH₂), 7.10–7.35 (6H, m, CH+2H-Tos+3H-Ar), 7.60–7.70 (2H, m, 2H-Tos), 8.10–8.18 (1H, m, Ar), 8.87 (1H, br s, CONH); δ_C (75.5 MHz, CDCl₃) 14.5, 14.7, 21.9, 23.1, 28.7, 32.3, 47.3, 60.2, 62.1, 81.1, 115.0, 116.6, 120.1, 121.4, 123.7, 124.5, 126.8, 127.3, 127.9, 130.3, 136.6, 136.8, 137.0, 145.1, 156.4, 164.8, 169.7; MS (EI): *m/z*=595 (M⁺); HRMS (EI): M⁺, found 595.2366. C₃₁H₃₇N₃O₇S requires 595.2352.

In the same manner (*R,S*)-**19** was prepared and used for HPLC analysis.

HPLC analysis using Chiralcel OD-R Φ =0.46×25 cm column and water (pH=4, HCOOH)/acetonitrile=60:40 as mobile phase. For (*R,S*)-**19** (flow=1.5 mL/min, λ =254 nm); t_R (*R*)=14.7 min, t_R (*S*)=15.4 min and for (*S*)-**19** (flow=1.5 mL/min, λ =254 nm); t_R (*S*)=15.3 min.

5.4.9.2. (S)-tert-Butyl 3-[2-(1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)-3-ethoxy-3-oxoprop-1-enyl]-2-methyl-1H-indole-1-carboxylate (20). Cuprous iodide (19.8 mg, 0.1 mmol), potassium carbonate (0.287 g, 2 mmol), (Z)-tert-butyl 3-(2-bromo-3-ethoxy-3-oxoprop-1-enyl)-2-methyl-1H-indole-1-carboxylate (**15**) (0.408 g, 1.0 mmol), (S)-N-Boc prolinamide (**18**) (0.297 g, 1.4 mmol), *N,N'*-dimethylethylenediamine (21.5 μ L, 0.2 mmol), and anhydrous toluene (1.8 mL) were reacted according to the general procedure for 12.5 h at 100 °C and afterward for additional 12 h. Purified by column chromatography (25% ethyl acetate/petroleum ether). The colorless oily product was then dissolved in dichloromethane, *n*-heptane was added, and solvents were rapidly evaporated in vacuo. The product **20** was formed as a white foam. Yield 0.421 g (78%), mp 60–63 °C (from dichloromethane/*n*-heptane); R_f (25% ethyl

acetate/petroleum ether) 0.27; $[\alpha]_D^{22}$ –85.6 (*c* 0.15, CHCl₃); $\nu_{\max}$ (KBr) 3288, 2978, 1732, 1695, 1477, 1458, 1396, 1322, 1258, 1158, 1118, 1028, 842, 770, 748 cm^{–1}; δ_H (300 MHz, CDCl₃) 1.36 (9H, s, C(CH₃)₃), 1.37 (3H, t, *J*=7.2 Hz, CH₃), 1.40–1.65 (3H, m, Pro), 1.69 (9H, s, C(CH₃)₃), 2.10–2.30 (1H, m, Pro), 2.58 (3H, s, CH₃), 3.10–3.25 (2H, m, Pro), 4.20–4.45 (3H, m, CH₂+1H-Pro), 7.10–7.20 (1H, m, Ar), 7.20–7.25 (1H, m, Ar), 7.30 (1H, d, *J*=7.5 Hz, Ar), 7.37 (1H, s, CH), 8.09 (1H, d, *J*=7.8 Hz, Ar), 8.73 (1H, br s, CONH); δ_C (75.5 MHz, CDCl₃) 14.1, 15.3, 28.1, 28.2, 29.0, 29.2, 46.9, 59.9, 61.5, 80.5, 84.1, 114.2, 115.5, 119.1, 122.1, 122.6, 123.6, 126.4, 127.2, 135.9, 137.4, 150.3, 164.6, 169.9; MS (EI): *m/z*=541 (M⁺); HRMS (EI): M⁺, found 541.2788. C₂₉H₃₉N₃O₇ requires 541.2777.

5.4.9.3. (S)-tert-Butyl 3-[2-(1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)-3-ethoxy-3-oxoprop-1-enyl]-2-phenyl-1H-indole-1-carboxylate (21). Cuprous iodide (19.8 mg, 0.1 mmol), potassium carbonate (0.287 g, 2 mmol), (Z)-tert-butyl 3-(2-bromo-3-ethoxy-3-oxoprop-1-enyl)-2-phenyl-1H-indole-1-carboxylate (**16**) (0.468 g, 1.0 mmol), (S)-N-Boc prolinamide (**18**) (0.257 g, 1.2 mmol), *N,N'*-dimethylethylenediamine (22 μ L, 0.2 mmol), and anhydrous toluene (2 mL) were reacted according to the general procedure for 13 h at 100 °C and afterward for additional 11 h. Purified by column chromatography (25% ethyl acetate/petroleum ether). The colorless oily product was then dissolved in dichloromethane, *n*-heptane was added, and solvents were rapidly evaporated in vacuo. The product **21** was formed as a yellow foam. Yield 0.389 g (65%), mp 65–68 °C (from dichloromethane/*n*-heptane); R_f (25% ethyl acetate/petroleum ether) 0.25; $[\alpha]_D^{22}$ –108.5 (*c* 0.18, CHCl₃); $\nu_{\max}$ (KBr): 3382, 2979, 1732, 1699, 1477, 1455, 1396, 1368, 1227, 1153, 1076, 1016, 755 cm^{–1}; δ_H (300 MHz, CDCl₃) 1.26 (9H, s, C(CH₃)₃), 1.27 (3H, t, *J*=7.2 Hz, CH₃), 1.41 (9H, s, C(CH₃)₃), 1.42–1.58 (2H, m, Pro), 1.58–1.72 (1H, m, Pro), 2.08–2.21 (1H, m, Pro), 3.08–3.28 (2H, m, Pro), 4.15–4.38 (3H, m, CH₂+1H-Pro), 7.03 (1H, s, CH), 7.21 (1H, br t, *J*=7.5 Hz, Ar), 7.28–7.35 (1H, m, Ar), 7.37–7.45 (6H, m, 5H-Ph+1H-Ar), 8.25 (1H, d, *J*=8.4 Hz, Ar), 9.01 (1H, br s, CONH); δ_C (75.5 MHz, CDCl₃) 14.2, 23.8, 27.4, 28.2, 47.0, 60.3, 61.4, 72.2, 80.6, 83.7, 115.4, 116.4, 120.4, 122.7, 123.4, 124.5, 125.5, 126.6, 127.7, 128.1, 130.2, 133.4, 136.9, 139.5, 149.8, 164.6, 169.6; MS (EI): *m/z*=603 (M⁺); HRMS (EI): M⁺, found 603.2959. C₃₄H₄₁N₃O₇ requires: 603.2945.

5.4.10. (S,Z)-3-[(2-Methyl-1-tosyl-1H-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (22)

(S)-tert-Butyl 2-[3-ethoxy-1-(2-methyl-1-tosyl-1H-indol-3-yl)-3-oxoprop-1-en-2-ylcarbamoyl]pyrrolidine-1-carboxylate (**19**) (0.882 g, 1.48 mmol) was dissolved in 120 mL dichloromethane, cooled to 0 °C, and 15 mL of 2 M hydrochloric acid in diethyl ether was added. The reaction mixture was then left to stir at room temperature for 20 h. The volatile components were evaporated in vacuo and to the remaining yellow oily residue, 120 mL of dichloromethane and triethylamine (1.1 mL, 7.4 mmol) were added. The reaction mixture was stirred under reflux for 3 h. The volatile components were then evaporated in vacuo thoroughly and the flask was backfilled with another

portion of dichloromethane (120 mL) and triethylamine (1.1 mL, 7.4 mmol). The reaction mixture was again stirred under reflux for 40 min, volatile components were evaporated in vacuo, and the residue purified by column chromatography (ethyl acetate), giving **22** as a white solid. Yield 0.472 g (71%), mp 125–127 °C (from 2-propanol); [Found: C, 64.28; H, 5.46; N, 9.16. $C_{24}H_{23}N_3O_4S$ requires C, 64.13; H, 5.16; N, 9.35%]; R_f (ethyl acetate) 0.26; $[\alpha]_D^{20} +42.3$ (c 0.3, $CHCl_3$), $ee > 99\%$; ν_{max} (KBr) 3463, 3188, 2957, 1693, 1636, 1454, 1374, 1242, 1176, 1089, 996, 812, 763, 746 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 1.85–2.20 (3H, m, Pro), 2.37 (3H, s, CH_3), 2.40–2.50 (1H, m, Pro), 2.56 (3H, s, CH_3), 3.58–3.67 (1H, m, Pro), 3.78–3.87 (1H, m, Pro), 4.22–4.32 (1H, m, Pro), 6.89 (1H, s, CH), 7.21 (1H, s, CONH), 7.22–7.38 (5H, m, 3H-Ar+2H-Tos), 7.68–7.76 (2H, m, 2H-Tos), 8.21–8.27 (1H, m, Ar); MS (EI): m/z =449 (M^+); HRMS (EI): M^+ , found 449.1421. $C_{24}H_{23}N_3O_4S$ requires 449.1409.

In the same manner (*R,S*)-**22** was prepared and used for HPLC analysis.

HPLC analysis of enantiomeric purity using Chiralcel OD-R $\Phi=0.46 \times 25$ cm column and water (pH=2, $HCOOH$)/acetonitrile=60:40 as mobile phase. For (*R,S*)-**22** (flow=1.5 mL/min, $\lambda=254$ nm); t_R (*R*)=8.78 min, t_R (*S*)=8.45 min and for (*S*)-**22** (flow=1.5 mL/min, $\lambda=254$ nm); t_R (*S*)=8.43 min.

1H NMR (300 MHz, $CDCl_3$) analysis of enantiomeric purity using (*S*)-1-benzyl-6-methylpiperazine-2,5-dione (**1**) as a CSA at 296 K. For (*R,S*)-**22**; δ_R (1H, br s, 7.40, NH), δ_S (1H, br s, 7.43, NH) and for (*S*)-**22**; δ_S (1H, br s, 7.46, NH).

5.4.11. (*RS,Z*)-3-[(2-Methyl-1H-indol-3-yl)methylidene]-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6a**)

For detosylation of (*S,Z*)-3-[(2-methyl-1-tosyl-1H-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**22**), two different methods were used, though both were unsuccessful with respect to the enantiomeric purity on (*S*)-proline residue.

5.4.11.1. Method A. (*S,Z*)-3-[(2-Methyl-1-tosyl-1H-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**22**) (0.135 g, 0.3 mmol) was dissolved in 5 mL of anhydrous tetrahydrofuran, tetrabutylammonium fluoride (0.75 mL of 1 M in THF, 0.75 mmol) was added and reaction mixture was heated to reflux for 6 h and stirred for another 17 h at ambient temperature. After that the volatile components were evaporated in vacuo and the residue purified by column chromatography (ethyl acetate). Yield 47.9 g (54%) of white solid; R_f (ethyl acetate) 0.16.

5.4.11.2. Method B. (*S,Z*)-3-[(2-Methyl-1-tosyl-1H-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**22**) (0.225 g, 0.5 mmol) was suspended in 12 mL anhydrous methanol and Mg turnings (0.304 g, 12.5 mmol) were added. When H_2 started to evolve, the reaction mixture was cooled to 0 °C and stirred at this temperature for 7 h. The reaction was quenched with 20 mL of saturated water solution of ammonium chloride and mixture extracted with 4 $\times$ 20 mL of dichloromethane. The combined organic phases were washed with 20 mL

of saturated aqueous sodium hydrogencarbonate and with 20 mL of brine. The volatiles were evaporated in vacuo and residue was purified by column chromatography (ethyl acetate). Yield 11 mg (7%) of white solid; R_f (ethyl acetate) 0.16.

Method A as well as method B proved to be unsatisfactory in retaining absolute configuration in (*S*)-proline residue. Both HPLC analyses and optical rotation showed complete racemization, thus giving racemic (*S,Z*)-3-[(2-methyl-1H-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6a**).

5.4.12. (*S,Z*)-3-[(2-Methyl-1H-indol-3-yl)methylidene]-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**24**)

First the (*S*)-*tert*-butyl 3-[2-(1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)-3-ethoxy-3-oxoprop-1-enyl]-2-methyl-1H-indole-1-carboxylate (**20**) was deprotected with trifluoroacetic acid in dichloromethane and then cyclized into (*S,Z*)-3-[(2-methyl-1H-indol-3-yl)methylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**24**) in two different manners.

5.4.12.1. Method A. Dipeptide **20** (0.492 g, 0.91 mmol) was dissolved in 3 mL of dichloromethane, 1 mL of anisole was added and the solution was cooled to 0 °C. Then 6 mL of trifluoroacetic acid was added and the reaction mixture was stirred at 0 °C for 5 h. The volatile components were evaporated thoroughly in vacuo at 35 °C. To the brown residue of **23a**, 70 mL of dichloromethane and triethylamine (0.637 mL, 4.6 mmol) were added and the reaction mixture was heated to reflux for 4 h. After that time, the volatile components were evaporated thoroughly, the reaction flask was backfilled with 70 mL of dichloromethane and a new portion of triethylamine (1.274 mL, 9.2 mmol). The reaction mixture was again refluxed for 1.5 h, the volatile components were removed, and residue was purified by column chromatography (ethyl acetate) to give **24** as a white solid. Yield 30.5 mg (11%) over two steps.

5.4.12.2. Method B. Dipeptide **20** (0.277 g, 0.51 mmol) was dissolved in 2 mL of dichloromethane, 0.6 mL of anisole was added and solution was cooled to 0 °C. Then 3.4 mL of trifluoroacetic acid was added and the reaction mixture was stirred at 0 °C for 5.5 h. To the deprotected dipeptide **23a**, dichloromethane (15 mL) was added and the reaction mixture was poured into 20 mL of ice cold water. The organic phase was then washed with 2 $\times$ 20 mL of 3 M aqueous hydrochloric acid. The combined water phases were cooled to 0 °C, and basified carefully to pH=8. The water phase was then extracted with 3 $\times$ 30 mL of dichloromethane, dried with sodium sulfate, and evaporated in vacuo. To the residue, 50 mL of anhydrous toluene was added and the solution was heated at 80 °C for 4.5 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (ethyl acetate) giving **24** as a white solid. Yield 81.3 mg (54%) over two steps, mp 256–258 °C (*n*-heptane/dichloromethane); [Found: C, 68.92; H, 5.76; N, 14.00. $C_{17}H_{17}N_3O_2$ requires C, 69.14; H, 5.80; N, 14.23%]; R_f (ethyl acetate) 0.15; $[\alpha]_D^{23} +387.1$ (c 0.06, DMSO); ν_{max} (KBr) 3286, 3256, 1687, 1670, 1650, 1612, 1441, 1249, 957, 744 cm^{-1} ; δ_H (300 MHz, $DMSO-d_6$) 1.77–1.97 (3H, m, Pro), 2.12–2.27 (1H, m, Pro), 2.37 (3H, s, CH_3), 3.40–3.50 (1H,

m, Pro), 3.50–3.62 (1H, m, Pro), 4.35–4.45 (1H, m, Pro), 6.86 (1H, s, CH); 7.02 (1H, ddd, $J_1=6$ Hz, $J_2=6$ Hz, $J_3=3$ Hz, Ar), 7.08 (1H, ddd, $J_1=6$ Hz, $J_2=6$ Hz, $J_3=3$ Hz, Ar), 7.32 (1H, br d, $J=6$ Hz, Ar), 7.39 (1H, d, $J_1=6$ Hz, Ar), 9.20 (1H, s, CONH), 11.33 (1H, s, NH); δ_C (75.5 MHz, DMSO- d_6) 12.5, 21.5, 28.0, 44.8, 58.4, 105.2, 109.1, 110.8, 118.8, 119.2, 120.6, 125.4, 126.5, 135.6, 136.4, 158.7, 166.0; MS (EI): $m/z=295$ (M^+); HRMS (EI): M^+ , found 295.1330. $C_{17}H_{17}N_3O_2$ requires: 295.1321.

HPLC analysis using Chiralcel OD-R $\Phi=0.46\times 25$ cm column and water (pH=2, HCOOH)/acetonitrile=60:40 as mobile phase. For (R,S)-**24** (flow=1.5 mL/min; $\lambda=254$ nm); t_R (R)=6.4 min, t_R (S)=5.1 min and for (S)-**24** (flow=1.5 mL/min, $\lambda=254$ nm); t_R (S)=5.0 min. Both cyclizations of **20–24**, in method A and in method B, did retained absolute configuration on proline residue, though yield in method B was much better. Enantiomeric purity was also confirmed by X-ray determination.

5.4.13. (S,Z)-3-[(2-Phenyl-1H-indol-3-yl)methylidene]-hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (**25**)

Dipeptide **21** (0.533 g, 0.88 mmol) was dissolved in 4 mL of dichloromethane, 1.1 mL of anisole was added and solution was cooled to 0 °C. Then 5.9 mL of trifluoroacetic acid was added and the reaction mixture was stirred at 0 °C for 7 h. To the deprotected dipeptide **23b**, dichloromethane (20 mL) was added and the reaction mixture was poured into 25 mL of ice cold water. The organic phase was then washed with 5×20 mL of water. The combined aqueous phases were cooled to 0 °C, and basified carefully to pH=8. The water phase was then extracted with 4×30 mL of dichloromethane, dried with sodium sulfate, and evaporated in vacuo. To the residue, 65 mL of anhydrous toluene was added and the solution was heated at 80 °C for 6 h. The volatile components were evaporated in vacuo and the residue was purified by column chromatography (66% ethyl acetate/petroleum ether) giving **25** as a yellow solid. Yield 0.124 g (39%) over two steps, mp 239–241 °C (ethanol/water); [Found: C, 73.71; H, 5.33; N, 11.67. $C_{22}H_{19}N_3O_2$ requires: C, 73.93; H, 5.36; N, 11.76%]; R_f (66% ethyl acetate/petroleum ether) 0.34; $[\alpha]_D^{19}+357.5$ (c 0.16, DMSO); ν_{max} (KBr) 3357, 3249, 2954, 1686, 1668, 1620, 1450, 1434, 1386, 1310, 1237, 1156, 743 cm^{-1} ; δ_H (300 MHz, DMSO- d_6) 1.80–2.00 (3H, m, Pro), 2.15–2.30 (1H, m, Pro), 3.40–3.50 (1H, m, Pro), 3.55–3.65 (1H, m, Pro), 4.42–4.47 (1H, m, Pro), 6.86 (1H, s, CH), 7.06–7.12 (1H, m, Ar), 7.17–7.27 (1H, m, Ar), 7.38–7.60 (5H, m, Ph), 7.65–7.69 (2H, m, Ar), 9.27 (1H, s, CONH), 11.77 (1H, s, NH); δ_C (75.5 MHz, DMSO- d_6) 21.8, 28.9, 45.8, 59.2, 105.7, 110.4, 111.6, 119.6, 121.2, 123.2, 126.3, 126.8, 127.8, 128.7, 129.0, 131.7, 136.2, 137.3, 158.2, 165.1; MS (EI): $m/z=357$ (M^+); HRMS (EI): M^+ , found 357.1485. $C_{22}H_{19}N_3O_2$ requires 357.1477.

HPLC analysis using Chiralcel OD-R $\Phi=0.46\times 25$ cm column and water (pH=2, HCOOH)/acetonitrile=60:40 as mobile phase. For (R,S)-**25** (flow=1.5 mL/min, $\lambda=254$ nm); t_R (R)=19.0 min, t_R (S)=26.9 min and for (S)-**25** (flow=1.5 mL/min, $\lambda=254$ nm); t_R (S)=26.8 min.

5.5. X-ray structure analysis for compounds **11** and **24**

Single crystal X-ray diffraction data of compounds **11** and **24** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.³¹ DENZO and SCALEPACK³² were used for indexing and scaling of the data and the structures were solved by means of SIR97.³³ Refinement was done using Xtal3.4³⁴ program package and the crystallographic plots were prepared by ORTEP-III.³⁵ Crystal structures were refined on F values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in all cases, while the positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. The Regina³⁶ weighting scheme was used in all cases.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 656803 and 656804. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

The financial support from Slovenian Research Agency through grants P0-0502-0103, P1-0179 and J1-6689-0103-04 is gratefully acknowledged. We thank pharmaceutical companies Krka d.d. (Novo mesto, Slovenia) and Lek d.d., a Sandoz Company (Ljubljana, Slovenia) for financial support. Crystallographic data were collected on the Kappa CCD Nonius diffractometer in the Laboratory of Inorganic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia. We acknowledge with thanks the financial contribution of the Ministry of Science and Technology, Republic of Slovenia through grant Packet X-2000 and PS-511-102, which thus made the purchase of the apparatus possible.

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