A Highly Stereoselective Synthesis of the Functionalized (*E*)-Alkene Dipeptide Isostere of Trp–Val *via* Organocyanocopper–Lewis Acid Mediated Reaction

Masaki NODA,*[a] Toshiro IBUKA,[b] Hiromu HABASHITA,[b] and Nobutaka FUJII[b]

Technology Research Laboratory, Shimadzu Co.,[a] Nishinokyo Kuwabaracho 1, Nakagyo-ku, Kyoto 604, Japan, and Faculty of Pharmaceutical Sciences, Kyoto University,[b] Kyoto 606, Japan.

Received February 17, 1997; accepted April 21, 1997

A stereocontrolled synthesis of the (*E*)-alkene dipeptide isostere of Trp–Val is described. The stereospecific α-alkylation of the δ-amino-γ-mesyloxy-α,β-unsaturated ester *via* the organocyanocopper–Lewis acid mediated reaction, based on 1,3-transfer of chirality, was successfully applied for the key step in the synthetic sequence.

Key words *trans* olefin dipeptide isostere; tryptophan; valine; 1,3-chirality transfer reaction

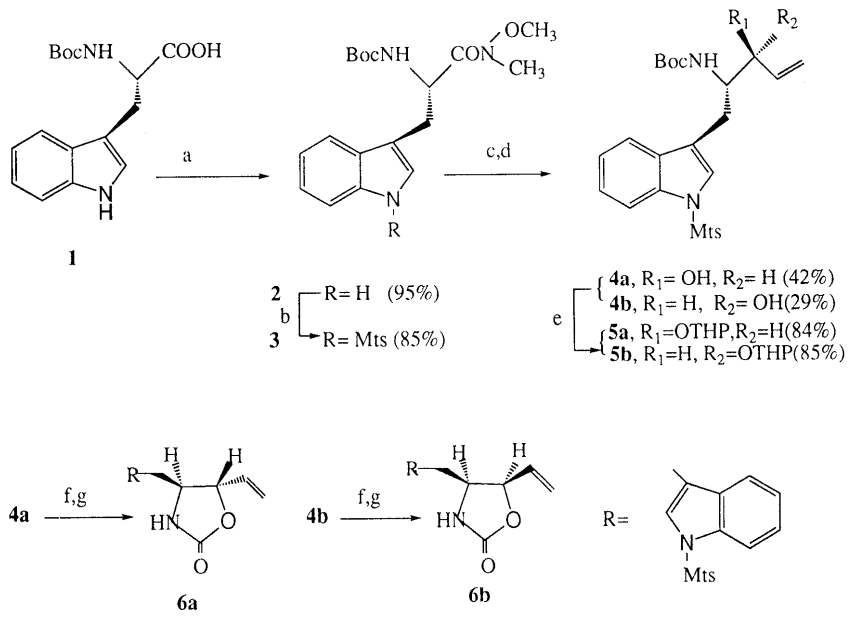
The replacement of a peptide amide bond by a *trans* olefin closely resembles the three-dimensional shape of the parent peptides.[1] It is postulated in this concept that it might be possible to modify one or more amide bonds in peptides such that conformation and binding ability to recepters are maintained, but enzymatic hydrolysis is prevented. Thus, increasing use of this concept in the designing of peptide analogues to probe structure–activity relationships has been reported.[2] We have approached the development of selective endothelin-converting enzyme (ECE) inhibitors by replacement of the Trp–Val cleavage site with a noncleavable *trans* olefin dipeptide isostere and incorporation into the substrate analogues of big endothelin-1.

An efficient synthetic route to such dipeptide mimics has been reported using a 1,3-chirality transfer reaction of γ-mesyloxy-α,β-enoates *via* RCu(CN)Li–BF_3-mediated reaction with high optical purity.[3] The reaction is highly controlled to maintain the double bond geometry at the β,γ-position and the stereochemistry of the chiral carbon center at the α-position. The γ-mesyloxy-α,β-enoates, the precursor of dipeptide mimics, are prepared from the homochiral substrate *via* steps containing ozone oxidation. However, tryptophan as a chiral starting material is easily oxidized with ozone to *N*-formyl kynurenine.[4] In fact, it gave unsatisfactory results because of the ring opening reaction of the indole moiety.[5] We now report the preparation of the functionalized (*E*)-alkene dipeptide isostere of Trp–Val using mild oxidizing reagents in combination with *N*-indole protection.

Boc–Trp-OH (**1**) was reacted with *O*,*N*-dimethylhydroxylamine hydrochloride salt in the presence of DCC/DMAP to yield Boc–Trp–$N(OCH_3)CH_3$ (**2**).[6] Compound **2** was converted to Boc–Trp(Mts)–$N(OCH_3)CH_3$ (**3**) by treatment with 2-mesitylenesulfonyl chloride (Mts-Cl) in the presence of NaH.[7] Compound **3** was reduced with diisobutylaluminum hydride (DIBAL) at −78 °C to yield the corresponding aldehyde, which was immediately reacted with vinylmagnesium chloride[8] at 0 °C to afford, after separation by silica gel column chromatography, (3*S*,4*S*)-5-3′-[*N*-mesitylene-2-sulfonyl(Mts)]indolyl-4-*tert*-butoxycarbonylamino(*N*-Boc)-3-hydroxy-1-pentene (**4a**) and (3*R*,4*S*)-5-3′-*N*-(Mts)indolyl-4-*N*-Boc-3-hydroxy-1-pentene (**4b**) in 42% and 29% yields (3*S*:3*R*=1.45:1), respectively. To assign the absolute stereochemistry of the diastereomers, **4a** and **4b**,[9] the oxazolidinones **6a** and **6b**[10] were prepared by cyclization of the free amino alcohols, obtained by removal of the Boc group of **4a** and **4b**, with triphosgen.[11] The assignment of the stereochemistry for **6a** and **6b** was designated as the *trans* and *cis* isomers, based on the ^{1}H-NMR chemical shifts of 5-H and the vicinal coupling constant $J_{4,5}$ between protons on the fourth and fifth carbons of **6a** (δ 4.70, $J_{4,5}$ = 6.0 Hz, H-5) and **6b** (δ 5.18, $J_{4,5}$ = 7.8 Hz, H-5), respectively (Chart 1).

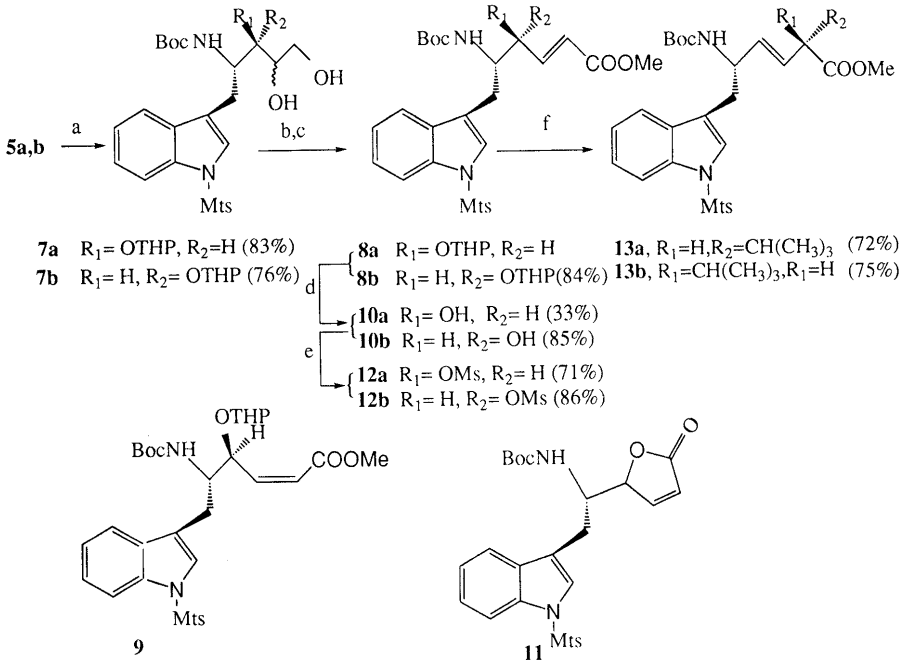
The treatment of **4a** with 3,4-dihydro-2*H*-pyran (DHP) in the presence of *p*-toluenesulfonic acid (PTS) gave (3*S*,4*S*)-5-3′-(*N*-Mts)indoyl-4-*N*-Boc-3-tetrahydropyranyloxy-1-pentene (**5a**), which was led to (3*S*,4*S*)-5-3′-(*N*-Mts)indoyl-4-*N*-Boc-3-tetrahydropyranyloxy-1,2-dihydroxypentane (**7a**), in 83% yield, by oxidation with *tert*-butylhydroxyperoxide (TBHP) in the presence of a catalytic amount of OsO_4.[12] Similarly, **4b** was converted to (3*R*,4*S*)-5-3′-(*N*-Mts)indolyl-4-*N*-Boc-3-tetrahydropyranyloxy-1-pentene (**5b**) with DHP–PTS. The compound **5b** was oxidized with TBHP–OsO_4 to give (3*R*,4*S*)- 5-3′-(*N*-Mts)indolyl-4-*N*-Boc-3-tetrahydropyranyloxy-1,2-dihydroxypentane (**7b**) in 76% yield. Oxidation of **7a** with sodium periodate[13] at 0 °C afforded (2*S*,3*S*)-4-3′-(*N*-Mts)-indolyl-3-*N*-Boc-2-tetrahydropyranyloxybutyl aldehyde. Without purification, the aldehyde was subsequently treated with Wittig reagent, methoxycarbonylmethylenetriphenylphosphorane,[14] to give a mixture of methyl (*E*,4*S*,5*S*)-6-3′-(*N*-Mts)indolyl-4-tetrahydropyranyloxy-5-*N*-Boc-2-hexenoate (**8a**) and methyl (*Z*,4*S*,5*S*)-6-3′-(*N*-Mts)indolyl-4-tetrahydropyranyloxy-5-*N*-Boc-2-hexenoate (**9**), (*E*:*Z*=1.1:1) in 76% yield. The mixture of *E* and *Z* forms of **8a** and **9** could be separated into two mixtures of the *E* and *Z* forms of the two diastereomers, arising from a chiral carbon of tetrahydropyranyl moiety, by silica gel column chromatography. The deprotection of the tetrahydropyranyloxy group of **8a** and **9** with AcOH–THF–H_2O (3:1:1) easily afforded methyl (*E*,-4*S*,5*S*)-6-3′-(*N*-Mts)indolyl-5-*N*-Boc-4-hydroxy-2-hexenoate (**10a**) and the ring cyclized product, (4*S*,5*S*)-6-3′-(*N*-Mts)indolyl-5-*N*-Boc-2-hexene-4-olide (**11**) in 33% and 42% yields, respectively. In a similar manner, after conversion of **7b** to the aldehyde by sodium periodate

* To whom correspondence should be addressed.



a; O,N-dimethylhydroxylamine-HCl, DIEA, DCC, DMAP/CH_2Cl_2, b; 2-mesitylenesulfonyl chloride, NaH (0°C)/DMF, c; DIBAL-H(-78°C)/THF, d; vinylmagnesium chloride(0°C)/THF, e; THP, cat.PTS/CH_2Cl_2 f; THF/CH_2Cl_2, g; triphosgene/TEA,

Chart 1



a; 70% *t*-butylhydroxyperoxide, cat. OsO_4/acetone-water, b; $NaIO_4$/MeOH, c;$(C_6H_5)_3P(O)CH_2CO_2CH_3$ /CH_2Cl_2, d; AcOH-THF-H_2O(3:1:1), e; methanesulfonyl chloride, TEA/THF, f; isopropylmagnesium bromide, CuCN, BF_3-Et_2O/THF-Et_2O

Chart 2

oxidation, the treatment of the aldehyde with a subsequent Wittig reaction gave the diastereomers of methyl (*E*,4*R*,5*S*)-6-3′-(*N*-Mts)indolyl-5-*N*-Boc-4-tetrahydropyranyloxy-2-hexenoate (**8b**) in 84% yield. In this case, none of the *Z* form of γ-tetrahydropyranyloxy-α,β-enoate was obtained. The treatment of **8b** with AcOH–THF–H_2O (3 : 1 : 1) afforded methyl (*E*,4*R*,5*S*)-6-3′-(*N*-Mts)indolyl-5-*N*-Boc-4-hydroxy-2-hexenoate (**10b**). The α,β-enoates (**10a** and **10b**) were converted to the Mosher's esters with optically active MTP-Cl.[9] The ^{1}H-NMR spectra of these esters showed only a single set of signals, indicating that no racemization had occurred during these manipulations. The requisite γ-mesyloxy-(*E*)-α,β-enoates (**12a** and **12b**) for the present isosteric dipeptide were prepared by the treatment of **10a** and **10b** with methanesulfonyl chloride. The reaction of the mesylates (**12a** and **12b**) with

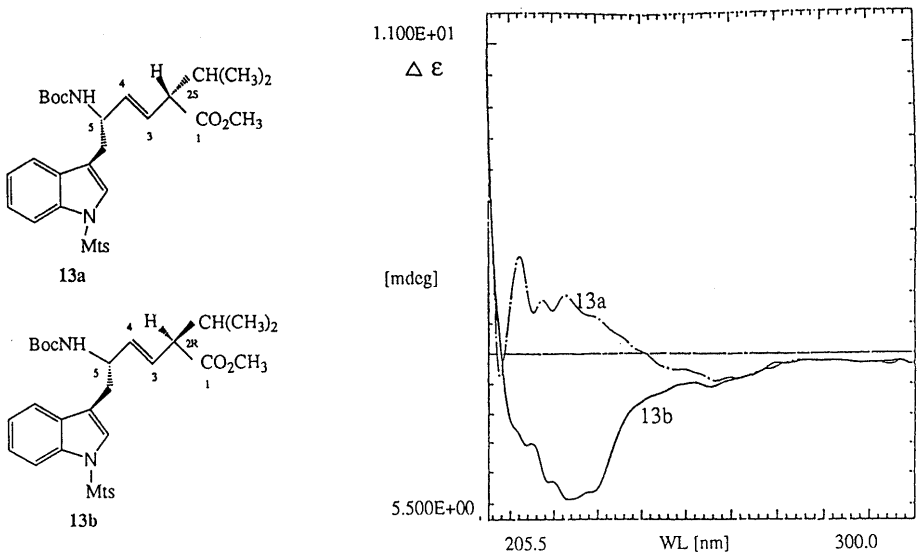


Fig. 1. CD Spectra of **13a** and **13b**

isopropyl Cu(CN)MgBr–BF_3 in tetrahydrofuran (THF) at −78 °C for 30 min gave the regio-, (*E*)-stereo- and diastereoselective 1,3-chirality transfer products **13a** and **13b** in 72% and 75% yields, respectively. The structures of **13a** and **13b** were characterized on the basis of their spectral data, particularly ^{1}H-NMR spectral comparison with the already reported (*E*)-alkene dipeptide isostere[15] (Chart 2).

The absolute configuration at the α-position of α-alkylated β,γ-unsaturated esters can be determined by circular dichroism (CD) measurement. (2*S*)-Compounds showed a positive $n\rightarrow\pi^*$ Cotton effect, whereas (2*R*)-compounds exhibit a negative $n\rightarrow\pi^*$ Cotton effect around 220 nm.[16] The CD spectra of **13a** in isooctane solution showed a positive Cotton effect; $\Delta\varepsilon_{max}$: +3.83 (nm: 212), whereas that of **13b** showed a negative Cotton effect; $\Delta\varepsilon_{max}$: −5.00 (nm: 225) as shown in Fig 1. Therefore, the configurations of **13a** and **13b** are confirmed as (2*S*) and (2*R*), respectively. Application of these structurally well-defined (*E*)-alkene dipeptide isosteres of Trp–Val to the structure–activity relationships (SAR) study of biologically active peptides is under investigation.

Experimental

All melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were determined with a Hitachi 660-30 spectrometer and mass spectra (MS) were measured with a JEOL JMC-OISG-2 instrument. ^{1}H-NMR spectra were recorded on JEOL FX-200 (200 MHz) and Bruker A-300 (300 MHz) spectrometers. Chemical shifts are reported as δ values relative to tetramethylsilane as an internal standard. All exchangeable protons were confirmed by addition of D_2O. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. CD spectra were recorded with JASCO J-720 spectropolarimeter. Kieselgel 60 Merck (70—230 mesh or 230—400 mesh for flash) was used for column chromatography. All reactions were carried out under a nitrogen or an argon atmosphere. The following abbreviations are used: DIEA, *N*,*N*-diisopropylethylamine; DCC, *N*,*N*-dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; DHP, 3,4-dihydro-2*H*-pyran; PTS, *p*-toluenesulfonic acid.

(*tert*-Butyloxycarbonyl)-L-tryptophan-*N*,*O*-Dimethylhydroxamate (2) Boc-L-Trp-OH (10.08 g, 33 mmol) was dissolved in CH_2Cl_2 (300 ml) containing *N*,*O*-dimethylhydroxylamine hydrochloride (3.552 g, 36 mmol), DMAP (0.324 g, 2.7 mmol) and DCC (7.43 g, 36 mmol). To the mixture was added DIEA (6.34 ml, 36 mmol) at −30 °C. The mixture was stirred at −30—−20 °C for 2 h and at room temperature for 16 h. The precipitate was filtered off, and the filtrate was evaporated *in vacuo*. The residue was chromatographed over silica gel (300 g) with hexane–AcOEt (1 : 1→1 : 2) as an eluent to give **2** (10.88 g, 95%), colorless needles, mp 137—138 °C (hexane–AcOEt). $[\alpha]_D^{20}$ −12.0° (*c*=0.828, MeOH). *Anal.* Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 62.12; H, 7.39; N, 12.24. IR ($CHCl_3$) cm^{-1}: 1665, 1705, 3470, 3520.

***N*-Mesitylene-2-sulfonyl-(*tert*-butyloxylcarbonyl)-L-tryptophan-*N*,*O*-dimethyl hydroxamate (3)** To a DMF (80 ml) solution of **2** (15.17 g, 43.7 mmol) was added NaH (60% in mineral oil, 1.89 g, 47.25 mmol) at 0 °C for 2 h. To this mixture was added 2-mesitylenesulfonyl chloride (11.46 g, 52.45 mmol). The mixture was stirred at 0 °C for 3 h, and at room temperature for 15 h, then poured into ice and water. The water layer was extracted with AcOEt. The solution was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give the crude product. The crude product was chromatographed over silica gel (300 g) eluting with AcOEt–hexane (1 : 1) to give **3** (19.84 g, 85%); colorless prisms, mp 129—130 °C (AcOEt–hexane), $[\alpha]_D^{21}$ −22.5° (*c*=1.09, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (9H, s, *tert*-Bu), 2.28 (3H, s, CH_3), 2.53 (6H, s, 2×CH_3), 3.11 (3H, s, N-CH_3), 3.01—3.23 (2H, m, CH_2), 3.65 (3H, s, OCH_3), 4.94—5.05 (1H, m, CH), 5.26 (1H, br d, *J*=8 Hz, NH), 6.94 (2H, s, Ar-H), 7.18—7.38 (3H, m, indole-H), 7.41 (1H, s, indole 2-H), 7.21—7.58 (1H, m, indole 7-H). IR ($CHCl_3$) cm^{-1}: 1603, 1653, 1703, 3460.

(3*S*,4*S*)-4-*tert*-Butyloxycarbonylamino-3-hydroxy-5-3′-(*N*-mesitylene-2-sulfonyl)indolyl-1-pentene (4a) and (3*R*,4*S*)-4-*tert*-Butyloxycarbonylamino-3-hydroxy-5-3′-(*N*-mesitylene-2-sulfonyl)indolyl-1-pentene (4b) A 1 M solution of DIBAL in toluene (75 ml, 75 mmol) was added to a solution of **3** (13.225 g, 25 mmol) in THF (40 ml) at −78 °C under an argon atmosphere, and the mixture was stirred at −78 °C for 1.5 h. AcOEt (9 ml) and MeOH (9 ml) were added successively to the reaction mixture and the whole mixture was stirred at −78 °C for 30 min. Water (70 ml) was added , and the mixture was stirred at 0 °C for 20 min, then filtered through a sintered glass funnel by use of Celite. The precipitate was washed with ether. The filtrate was separated, and the water layer was extracted with ether. The combined solution was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give the aldehyde. To a THF (150 ml) solution of the aldehyde was added 2.2 M vinyl magnesium chloride (39.8 ml, 87.5 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 20 h, and quenched with saturated $NaHCO_3$ solution (50 ml). AcOEt was added to the mixture and the organic layer was separated. The water layer was extracted with AcOEt. The combined solution was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give the crude product, which was chromatographed on silica gel (500 g) with AcOEt–hexane (1 : 3→1 : 1) as an eluent to give **4a** (5.244 g, 42%) and **4b** (3.61 g, 29%). Physical data for **4a**: mp 57—58 °C, amorphous powder, $[\alpha]_D^{21}$ −26.8° (*c*=0.97, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (9H, s, *tert*-Bu), 2.28 (3H, s, CH_3), 2.52 (6H, s, 2×CH_3), 2.96—3.09 (2H, m, CH_2), 3.87—3.96 (1H, m, 4-H), 4.16—4.21 (1H, m, 3-H), 4.91 (1H, br d, *J*=8 Hz, NH), 5.19

(1H, dd, J=10.6, 1.2 Hz, $\overset{H}{}>C=C<\overset{H}{\underline{H}}$), 5.27 (1H, dd, J=17.8, 1.2 Hz, $\overset{H}{}>C=C<\overset{\underline{H}}{H}$), 5.90 (1 H, dd, J=17.8, 10.6 Hz, 2-H), 6.94 (2H, s, Ar-H), 7.14—7.45 (3H, m, indole-H), 7.47 (1H, s, indole 2-H), 7.15—7.70 (1H, m, indole 7-H). MS m/z: 49 (M^+). High-resolution MS Calcd for $C_{27}H_{34}N_2O_5S$: 498.2188. Found: 498.2194. IR ($CHCl_3$) cm^{-1}: 1608, 1711, 3460. Physical data for **4b**: mp 55—57 °C, amorphous powder. $[\alpha]_D^{21}$ −19.4° (c=0.964, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (9H, s, *tert*-Bu), 2.28 (3H, s, CH_3), 2.52 (6H, s, 2×CH_3), 2.85—3.02 (2H, m, CH_2), 4.01—4.07 (1H, m, 4-H), 4.26—4.28 (1H, m, 3-H), 4.66 (1H, br d, J=8 Hz, NH), 5.19 (1H, dd, J=10.6, 1.2 Hz, $\overset{H}{}>C=C<\overset{H}{\underline{H}}$), 5.27 (1H, dd, J=17.8, 1.2 Hz, $\overset{H}{}>C=C<\overset{\underline{H}}{H}$), 5.90 (1H, ddd, J=17.8, 10.6, 5.4 Hz, 2-H), 6.94 (2H, s, Ar-H), 7.17—7.35 (3H, m, indole-H), 7.45 (1H, s, indole 2-H), 7.54—7.58 (1H, m, indole 7-H). MS m/z: 498 (M^+), High-resolution MS Calcd for $C_{27}H_{34}N_2O_5S$: 498.2188. Found: 498.2200. IR ($CHCl_3$) cm^{-1}: 1603, 1704, 3460.

(4*S*,5*S*)-3′-(*N*-Mesitylene-2-sulfonyl)indolylmethyl-5-vinyl-2-oxazolidinone (6a) To a solution of **4a** (0.12 g, 0.24 mmol) in CH_2Cl_2 (4 ml) was added CF_3COOH (1 ml). The reaction mixture was stirred at room temperature for 1 h. The solution was evaporated and the residue was dissolved in AcOEt. The solution was washed with 5% $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to give a solid. To a THF (3 ml) solution of the solid was added triethylamine (0.049 g, 0.49 mmol) and triphosgene (0.024 g, 0.08 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The precipitate was filtered off. The filtrate was dried over anhydrous $MgSO_4$ and evaporated to give the crude product, which was purified by silica gel column chromatography with AcOEt–hexane (1 : 3→1 : 2) as an eluant to give **6a** (0.048 g, 48%). mp 166—167 °C (ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, CH_3), 2.53 (6H, s, 2×CH_3), 2.96 (1H, dd, J=7.7, 14.5 Hz, CH_2), 3.03 (1H, dd, J=5.6, 14.5 Hz, CH_2), 3.86 (1H, ddd, J=7.7, 5.6, 6.0 Hz, 4-H), 4.70 (1H, dd, J=6.7, 6.0 Hz, 5-H), 5.19 (1H, br s, NH), 5.30 (1H, dt, J=10.4, 0.9 Hz, $\overset{H}{}>C=C<\overset{H}{\underline{H}}$), 5.37 (1H, dt, J=17, 0.9 Hz, $\overset{H}{}>C=C<\overset{H}{\underline{H}}$), 5.86 (1H, ddd, J=6.7, 10.4, 17 Hz, $\overset{\underline{H}}{}>C=C<\overset{H}{H}$), 6.97 (2H, s, Ar-H), 7.22—7.26 (2H, m, indole-H), 7.36—7.40 (1H, m, indole 4-H), 7.45 (1H, s, indole 2-H), 7.47—7.50 (1H, m, indole 7-H). MS m/z: 424 (M^+). High-resolution MS Calcd for $C_{23}H_{24}N_2O_4S$: 424.1457. Found: 424.1474.

(5*R*,4*S*)-3′-(*N*-Mesitylene-2-sulfonyl)indolylmethyl-5-vinyl-2-oxazolidinone (6b) To a solution of **4b** (0.1 g, 0.2 mmol) in CH_2Cl_2 (4 ml) was added CF_3COOH (1 ml). The reaction mixture was stirred at room temperature for 2 h. Work-up as described for the cleavage of Boc group of **4a** gave the crude product. To a THF (3 ml) solution of the crude product was added triethylamine (0.04 g, 0.4 mmol) and triphosgene (0.02 g, 0.067 mmol) at 0 °C, and then the reaction mixture was stirred at room temperature for 1 h. Work-up as described for the preparation of **6a** afforded **6b** (0.042 g, 50%), mp 90—92 °C (ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, CH_3), 2.53 (6H, s, 2×CH_3), 2.78 (1H, dd, J=10.4, 14.4 Hz, CH_2), 2.91 (1H, dd, J=3.9, 1.1 Hz, $\overset{H}{}>C=C<\overset{\underline{H}}{H}$, 5.58 (1H, dt, J=17.7, 1.1 Hz, $\overset{H}{}>C=C<\overset{H}{\underline{H}}$), 6.01 (1H, ddd, J=6.7, 10.5, 17.2 Hz, $\overset{\underline{H}}{}>C=C<\overset{H}{H}$), 6.97 (2H, s, Ar-H), 7.22—7.26 (2H, m, indole-H), 7.36—7.41 (1H, m, indole 4-H), 7.42 (1H, s, indole 2-H), 7.47—7.50 (1H, m, indole 7-H). MS m/z: 424 (M^+). High-resolution MS Calcd for $C_{23}H_{24}N_2O_4S$: 424.145. Found: 424.1474.

(3*S*,4*S*)-4-*tert*-Butyloxycarbonylamino-3-tetrahydropyranyloxy-5-3′-(*N*-mesitylene-2-sulfonyl)indolyl-1-pentene (5a) To a solution of **4a** (5.18 g, 10.4 mmole) and DHP (4.37 g, 52 mmol) in CH_2Cl_2 (60 ml) was added PTS (0.1 g, 0.52 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. The mixture was diluted with CH_2Cl_2, washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give the crude product, which was purified by silica gel column chromatography with AcOEt–hexane (1 : 5) as an eluant to give **5a** (4.89 g, 84%), amorphous powder $[\alpha]_D^{21}$ −25.7° (c=1.05, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.41 and 1.42 (9H, s, 3×CH_3, *tert*-Bu), 1.30—1.96 (6H, m, 3×CH_2), 2.28 (3H, s, CH_3), 2.25 (6H, s, 2×CH_3), 2.80—3.16 (2H, m, 5-CH_2), 3.40—3.62 (2H, m, –OCH_2–), 3.86—4.24 and 4.52—4.66 (3H, m, 3-H, 4-H, –OCHO–), 4.81—5.00 (1H, m, NH), 5.11—5.27 (2H, m, 1-H), 5.70—5.94 (1H, m, 2-H), 6.94 (1H, s, Ar-H), 7.11—7.41 (3H, m, indole-H), 7.42 and 7.57 (1H, s, indole 2-H), 7.56—7.77 (1H, m, indole 7-H). MS m/z: 582 (M^+). High-resolution MS Calcd for $C_{32}H_{42}N_2O_6S$: 582.2763. Found: 582.2778. IR ($CHCl_3$) cm^{-1}: 1605, 1703, 3480.

(3*R*,4*S*)-4-*tert*-Butyloxycarbonylamino-3-tetrahydropyranyloxy-5-3′-(*N*-mesitylene-2-sulfonyl)indolyl-1-pentene (5b) To a solution of **4b** (4.275 g, 8.58 mmol) and DHP (3.61 g, 42.9 mmol) in CH_2Cl_2 (50 ml) was added PTS (0.082 g, 0.43 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. Work-up as descrived for the preparation of **5a** gave the crude product, which was chromatographed on silica gel with AcOEt–hexane (1 : 5→1 : 3) as an eluent to give **5b** (3.99 g, 85%), mp 38—42 °C, amorphous powder, $[\alpha]_D^{21}$ −35.7° (c=0.85, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (9H, br s, *tert*-Bu), 1.17—1.90 (6H, m, 3×CH_2), 2.27 (3H, s, CH_3), 2.52 (6H, s, 2×CH_3), 2.84—3.15 (2H, m, 5-H), 3.35—5.55 (1H, m, –OCH_2–), 3.80—4.15 (2H, m, 4-H, –OCH_2–), 4.21—4.32 (1H, m, 3-H), 4.55—4.72 (1H, m, –OCHO–), 4.80—4.92 (1H, m, NH), 5.29 and 5.30 (1H, d, J=10.2 Hz, $\overset{H}{}>C=C<\overset{H}{\underline{H}}$), 5.40 and 5.41 (1 H, d, J=17 Hz, $\overset{H}{}>C=C<\overset{H}{\underline{H}}$), 5.78 and 5.97 (1H, ddd, J=6.0, 10.2, 17 Hz, $\overset{\underline{H}}{}>C=C<\overset{H}{H}$), 6.93 (1H, s, Ar-H), 7.11—7.38 (3H, m, indole-H), 7.45 and 7.51 (1H, s, indole 2-H), 7.47—7.62 (1H, m, indole 7-H). $[\alpha]_D^{21}$ −35.7° (c=0.85, MeOH). MS m/z: 582 (M^+). High-resolution MS Calcd for $C_{32}H_{42}N_2O_6S$: 582.276. Found: 582.275. IR ($CHCl_3$) cm^{-1}: 1605, 1705, 3475.

(3*S*,4*S*)-4-*tert*-Butyloxycarbonylamino-1,2-dihydroxy-3-tetrahydropyranyloxy-5-3′-(*N*-mesitylene-2-sulfonyl)indolylpentane (7a) A mixture of tetraethylammonium chloride (0.227 g, 1.37 mmol) and sodium acetate (0.224 g, 2.74 mmol) in acetone (30 ml) was stirred at room temperature for 1 h. To the mixture was added a solution of **5a** (3.184 g, 5.47 mmol) in acetone (40 ml) and 70% TBHP in water (3.75 ml, 27.35 mmol) under an argon atmosphere. The mixture was allowed to cool to 0 °C, and then a solution of OsO_4 in *tert*-BuOH (5 mg/ml of *tert*-BuOH, 2.08 ml, 0.041 mmol) was added. The whole mixture was stirred at 0 °C for 2 h, and at room temperature for 4 d. The solvent was evaporated and the residue was dissolved in water. The water layer was extracted with AcOEt. The solution was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give the crude product, which was purified by silica gel column chromatography with AcOEt–hexane (1 : 3→2 : 1) as an eluent to give **7a** (2.80 g, 83%), mp 62—64 °C, amorphous powder, $[\alpha]_D^{20}$ −13.9° (c=1.57, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.39 and 1.41 (9H, s, *tert*-Bu), 1.40—1.94 (6H, m, 3×CH_2), 2.28 (3H, s, CH_3), 2.51 (6H, s, 2×CH_3), 2.90—3.20 (2H, m, 5-H), 3.40—4.10 (7H, m, 1-H, 2-H, 3-H, 4-H, –OCH_2–), 4.28—4.55 (1H, m, –OCHO–), 4.85—4.90 (1H, m, NH), 6.93 and 6.94 (2H, s, Ar-H), 7.15—7.35 (3H, m, indole-H), 7.44 and 7.49 (1H, s, indole 2-H), 7.15—7.63 (1H, m, indole 7-H). MS m/z: 616 (M^+). High-resolution MS Calcd for $C_{32}H_{44}N_2O_8S$: 616.2818. Found: 616.2827. IR ($CHCl_3$) cm^{-1}: 1603, 1693, 1703, 3475, 3595.

(3*R*,4*S*)-4-*tert*-Butyloxycarbonylamino-1,2-dihydroxy-3-tetrahydropyranyloxy-5-3′-(*N*-mesitylene-2-sulfonyl)indolylpentene (7b) A mixture of tetraethylammonium chloride (0.235 g, 1.42 mmol) and sodium acetate (0.233 g, 2.84 mmol) in acetone (30 ml) was stirred at room temperature for 1 h. To this mixture was added a solution of **5b** (3.3 g, 5.67 mmol) in acetone (40 ml) and 70% TBHP in water (3.88 ml, 28.35 mmol) under an argon atmosphere. The reaction mixture was allowed to cool to 0 °C, and then a solution of OsO_4 in *tert*-BuOH (1 mg/ml of *tert*-BuOH, 2.16 ml, 0.085 mmole) was added. The whole mixture was stirred at 0 °C for 2 h, and at room temperature for 5 d. Work-up as described for the preparation of **7a** gave **7b** (2.663 g, 76%), mp 72—74 °C, amorphous powder, $[\alpha]_D^{21}$ −17.4° (c=0.784, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.33 and 1.35 (9H, s, *tert*-Bu), 1.40—1.93 (6H, m, CH_2), 2.26 and 2.28 (3H, s, CH_3), 2.52 (6H, s, 2×CH_3), 2.57—3.20 (4H, m, 2×CH_2), 3.43—3.60 (2H, m, CH_2), 3.60—4.19 (3H, m, 2-H, 3-H, 4-H), 4.43—4.51 (1H, m, –OCHO–), 4.60 and 5.81 (1H, br d, J=8 Hz, NH), 6.91 and 6.93 (2H, s, Ar-H), 7.29—7.35 (3H, m, indole-H), 7.45 and 7.51 (1H, s, indole 2-H), 7.52—7.68 (1H, m, indole 7-H). MS m/z: 616 (M^+). High-resolution MS Calcd for $C_{32}H_{44}N_2O_8S$: 616.2818. Found: 616.2805. IR ($CHCl_3$) cm^{-1}: 16.08, 1708, 1728, 3470. 3595.

Oxidation of 7a and 7b with $NaIO_4$ and Subsequent Wittig Reaction with Methoxycarbonylmethylenetriphenylphosphorane a) A water (50 ml) solution of $NaIO_4$ (1.78 g, 8.22 mmol) was added to a solution of **7a** (4.27 g, 6.93 mmol) in MeOH (500 ml)–water (200 ml) at 0 °C. The mixture

was stirred at 0 °C for 5 h, evaporated to *ca.* 200 ml, and then the solution was extracted with CH_2Cl_2. The solution was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give the crude aldehyde. To a CH_2Cl_2 (20 ml) solution of the aldehyde was added methoxycarbonylmethylenetriphenylphosphorane (6.95 g, 20.79 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h, and at room temperature for 16 h. The solvent was evaporated, and the residue was chromatographed on silica gel with AcOEt–hexane (1 : 5→1 : 1) as an eluent to give a mixture of **8a** and **9** (3.38 g, 76%), *E*:*Z* = 1.1 : 1, amorphous powder, $[\alpha]_D^{21}$ 19.64° (*c* = 0.84, MeOH). The mixture of **8a** and **9** (0.147 g) was chromatographed on silica gel with AcOEt–hexane (1 : 4) as an eluent to give mixtures of *E* and *Z* form of the two diastereomers; **8a** and **9** (0.052 g), and **8a′** and **9′** (0.047 g). Physical data for **8a** and **9**: amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.39 and 1.42 (9H, s, *tert*-Bu), 1.40—1.98 (6H, m, 3 × CH_2), 2.27 (3H, s, CH_3), 2.51 and 2.54 (6 H, 2 × CH_3), 2.27 (3H, s, CH_3), 2.51 and 2.54 (6H, 2 × CH_3), 2.92—3.16 (2H, m, 6-H), 3.19 (9/19 × 3H, s, $H\!>\!C\!=\!C\!<^{COOMe}_{H}$), 3.71 (10/19 × 3H, s, $H\!>\!C\!=\!C\!<^{H}_{COOMe}$), 3.41—3.54 (1H, m, –$OCH_2$–), 3.94—4.22 (2H, m, 4-H, 5-H), 4.43—4.56 (1H, m, –OCH_2–), 4.96—5.05 (1H, m, NH), 5.33 (1H, d, *J* = 8.4 Hz, –OCHO–), 5.93 (10/19 × 1H, d, *J* = 16 Hz, $\underline{H}\!>\!C\!=\!C\!<^{H}_{COOMe}$), 5.84 (9/19 × 1H, d, *J* = 12 Hz, $\underline{H}\!>\!C\!=\!C\!<^{COOMe}_{H}$), 6.17 (9/19 × 1H, dd, *J* = 12, 8 Hz, $H\!>\!C\!=\!C\!<^{COOMe}_{\underline{H}}$), 6.77 (10/19 × 1H, dd, *J* = 5.2, 16 Hz, $H\!>\!C\!=\!C\!<^{H}_{COOMe}$), 6.93 (2H, s, Ar-H), 7.12—7.34 (3H, m, indole-H), 7.57 and 7.62 (1H, s, indole 2-H), 7.63—7.78 (1H, m, indole 7-H). *trans* (**8a**) : *cis*(**9**) = 10 : 9, MS *m*/*z*: 640 (M^+). High resolution MS Calcd for $C_{34}H_{44}N_2O_8S$: 640.2818, Found: 640.2829. IR ($CHCl_3$) cm^{-1}: 1605, 1715, 1720, 3475. Physical data for **8a′** and **9′**: amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.38 and 1.41 (9H, s, *tert*-Bu), 1.45—1.96 (6H, m, 3 × CH_2), 2.28 (3H, s, CH_3), 2.52 and 2.54 (6H, s, 2 × CH_3), 2.94—3.07 (2H, m, 6-H), 3.32 (0.4 × 3H, s, $H\!>\!C\!=\!C\!<^{COOMe}_{H}$), 3.39—3.52 (2H, m, –$OCH_2$–), 3.72 (0.6 × 3H, s, $H\!>\!C\!=\!C\!<^{H}_{COOMe}$), 3.80—3.98 (1H, m, 5-H), 4.29—4.67 (1H, m, 4-H), 4.96—5.07 (1H, m, NH), 5.15 (1H, d, *J* = 8.4 Hz, –OCHO–), 5.75 (0.2 × 1H, d, *J* = 11.8 Hz, $\underline{H}\!>\!C\!=\!C\!<^{COOMe}_{H}$), 6.05 (0.3 × 1H, dd, *J* = 16, 1.2 Hz, $\underline{H}\!>\!C\!=\!C\!<^{H}_{COOMe}$), 6.38 (0.2 × 1H, dd, *J* = 12, 8 Hz, $H\!>\!C\!=\!C\!<^{COOMe}_{\underline{H}}$), 6.94 (2H, s, Ar-H) 6.95 (1H, dd, *J* = 16, 5.2 Hz, $H\!>\!C\!=\!C\!<^{\underline{H}}_{COOMe}$), 7.14—7.39 (3H, m, indole-H), 7.41 and 7.48 (1H, s, indole 2-H), 7.57—7.69 (1H, m, indole 7-H). *trans* (**8a′**) : *cis* (**9b′**) = 3 : 2, MS *m*/*z*: 640 (M^+). High-resolution MS Calcd for $C_{34}H_{44}N_2O_8S$: 640.2818, Found: 640.2848. IR ($CHCl_3$) cm^{-1}: 1608, 1716, 1723, 3475.

b) An aqueous (50 ml) solution of $NaIO_4$ (1.07 g, 4.99 mmol) was added to a solution of **7b** (2.56 g, 4.16 mmol), in MeOH (250 ml)–water (150 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h, and evaporated *in vacuo* to *ca.* 200 ml. The solution was extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give the crude aldehyde. Methoxycarbonylmethylenetriphenylphosphorane (4.17 g, 12.48 mmol) was added to a solution of the aldehyde in CH_2Cl_2 (20 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, and then at room temperature for 16 h. The solvent was evaporated, and the residue was chromatographed on silica gel with AcOEt–hexane (1 : 4→1 : 3) to give **8b** (2.25 g, 84%). mp 60—62 °C, amorphous powder, $[\alpha]_D^{21}$ −32.1° (*c* = 0.606, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (9H, s, *tert*-Bu), 1.49—1.86 (6H, m, 3 × CH_2), 2.27 (3H, s, CH_3), 2.51 and 2.52 (6H, s, 2 × CH_3), 2.89—2.98 (2H, m, 6-H), 3.47—3.71 (1H, m, –OCH_2–), 3.73 and 3.75 (3H, s, OCH_3), 3.80—4.17 (2H, m, –OCH_2–, 5-H), 4.52—4.73 (2H, m, –OCHO–, 4-H), 6.04 (0.5H, dd, *J* = 15.8, 1.6 Hz, 3-H), 6.21 (0.5H, dd, *J* = 15.8, 1.6 Hz, 3-H), 6.93 (2H, s, Ar-H), 6.87 (0.5H, dd, *J* = 15.8, 5.6 Hz, 2-H), 7.04 (0.5H, dd, *J* = 15.8, 5.4 Hz, 2-H), 7.15—7.35 (3H, m, indole-H), 7.45 and 7.50 (1H, s, indole 2-H), 7.48—7.53 (1H, m, indole 7-H). MS *m*/*z*: 640 (M^+). High-resolution MS Calcd for $C_{34}H_{44}N_2O_8S$: 640.2818. Found: 640.2824. *Anal.* Calcd for $C_{34}H_{44}N_2O_8S$: C, 63.73; H, 6.92; N, 4.37, Found: C, 63.72; H, 7.20; N, 4.15. IR ($CHCl_3$) cm^{-1}: 1603, 1710, 1720, 3460.

Methyl (*E*,4*S*,5*S*)-5-*tert*-Butyloxycarbonylamino-4-hydroxy-6-3′-(*N*-mesitylene-2-sulfonyl)indolyl-2-hexenoate (10a) and (4*S*,5*S*)-5-*tert*-Butyloxycarbonylamino-6-3′-(*N*-mesitylene-2-sulfonyl)indolyl-2-hexene-4-olide (11) A solution of the mixture of **8a** and **9** (3.23 g, 5 mmol) in AcOH–THF–H_2O [(3 : 1 : 1), 60 ml] was stirred at room temperature for 3 d under an N_2 atmosphere. The solvent was evaporated, the residue was dissolved in toluene, and the solution was evaporated to dryness. (This procedure was repeated three times). The residue was chromatographed on silica gel with hexane–AcOEt (3 : 1→2 : 1) as an eluent to give **10a** (0.91 g, 33%) and **11** (1.11 g, 42%). Physical data for **10a**: mp 73—77 °C, amorphous powder, (pentane–ether), $[\alpha]_D^{21}$ −41.5° (*c* = 0.678, MeOH). *Anal.* Calcd for $C_{29}H_{36}N_2O_7S$: C, 6.52; H, 62.57; N, 5.23, Found: C, 6.70; H, 62.64; N, 5.23. MS *m*/*z*: 556 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (9H, s, *tert*-Bu), 2.28 (3H, s, CH_3), 2.52 (6H, s, 2 × CH_3), 3.07 (2H, d, *J* = 7.4 Hz, CH_2), 3.72 (3H, s, CH_3), 3.80—4.12 (1H, m, 5-H), 4.39 (1H, br s, 4-H), 4.91—4.95 (1H, m, NH), 6.09 (2H, dd, *J* = 15.8, 2.0 Hz, 3-H), 6.93 (1H, dd, *J* = 15.8, 4.2 Hz, 2-H), 6.94 (1H, s, Ar-H), 7.18—7.36 (3H, m, indole-H), 7.47 (1H, s, indole 2-H), 7.61—7.65 (1H, m, indole 7-H). IR ($CHCl_3$) cm^{-1}: 1603, 1705, 1755 (sh), 3460. Physical data for **11**: mp 82—83 °C (hexane–ether), colorless needles. *Anal.* Calcd for $C_{28}H_{32}O_6N_2S$: C, 64.10; H, 6.15; N, 5.34, Found: C, 64.30; H, 6.43; N, 5.09. $[\alpha]_D^{21}$ −106.7° (*c* = 1.044, MeOH). MS *m*/*z*: 542 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (9H, s, *tert*-Bu), 2.28 (3H, s, CH_3), 2.52 (6H, s, 2 × CH_3), 3.09 (2H, d, *J* = 8.2 Hz, CH_2), 4.33 (1H, dd, *J* = 8.2, 9.6 Hz, 5-H), 4.58 (1H, d, *J* = 9.6 Hz, 4-H), 5.03 (1H, s, NH), 6.03 (1H, d, *J* = 3.8 Hz, 3-H), 6.95 (2H, s, Ar-H), 7.21—7.44 (4H, m, indole-H, 2-H), 7.51 (1H, s, indole 2-H), 7.62—7.66 (1H, m, indole 7-H). IR ($CHCl_3$) cm^{-1}: 1605, 1710, 1755, 1790 (sh), 3460.

Methyl (*E*,4*R*,5*S*)-5-*tert*-Butyloxycarbonylamino-4-hydroxy-6-3′-(*N*-mesitylene-2-sulfonyl)indolyl-2-hexenoate (10b) A solution of **8b** (2.215 g, 3.46 mmol) in AcOH–THF–H_2O [(3 : 1 : 1) 70 ml] was stirred at room temperature for 3 d under an N_2 atmosphere. Work-up as descrived for the preparation of **10a** gave the crude product, which was purified by silica gel column chromatography with hexane–AcOEt (3 : 1→1 : 1) as an eluent to give **10b** (1.637 g, 85%), mp 58—60 °C, amorphous powder (*n*-pentane–Ether). $[\alpha]_D^{21}$ 2.1° (*c* = 0.79, MeOH). *Anal.* Calcd for $C_{29}H_{36}N_2O_7S$: C, 62.57; H, 6.52; N, 5.23, Found: C, 62.41; H, 6.62; N, 5.03. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s, *tert*-Bu), 2.23 (3H, s, CH_3) 2.52 (6H, s, 2 × CH_3), 2.92 (2H, d, *J* = 7 Hz, CH_2), 3.76 (3H, s, OCH_3), 4.06—4.18 (1H, m, 5-H), 4.52 (1H, br s, 4-H), 4.68 (1H, br d, *J* = 8.0 Hz, NH), 6.21 (1H, dd, *J* = 15.6, 1.8 Hz, 3-H), 6.95 (2H, s, Ar-H), 7.03 (1H, dd, *J* = 15.6, 4.4 Hz, 2-H), 7.18—7.36 (3H, m, indole-H), 7.45 (1H, s, indole 2-H), 7.50—7.55 (1H, m, indole 7-H). MS *m*/*z*: 556 (M^+). IR ($CHCl_3$) cm^{-1}: 1608, 1713, 1763 (sh), 3460.

Methyl (*E*,4*S*,5*S*)-5-*tert*-Butyloxycarbonylamino-4-mesyloxy-6-3′-(*N*-mesitylene-2-sulfonyl)indolyl-2-hexenoate (12a) To a solution of **10a** (0.839 g, 1.5 mmol) and triethylamine (1.06 g, 10.5 mmol) in CH_2Cl_2 (10 ml) was added methanesulfonyl chloride (0.605 g, 5.28 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, and then water was added. The CH_2Cl_2 solution was separated, dried over anhydrous $MgSO_4$, and evaporated to give the crude product, which was purified by silica gel column chromatography with AcOEt–hexane (1 : 3) as an eluent to give **12a** (0.671 g, 71%), amorphous powder, $[\alpha]_D^{21}$ 32.7° (*c* = 0.76, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s, *tert*-Bu), 2.28 (3H, s, CH_3), 2.52 (6H, s, 2 × CH_3), 2.94—3.13 (2H, m, CH_2), 3.07 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 4.17—4.31 (1H, m, 5-H), 4.75 (1H, d, *J* = 8 Hz, NH), 5.31 (1H, br d, *J* = 4.8 Hz, 4-H), 6.11 (1H, d, *J* = 16 Hz, 3-H), 6.90 (1H, dd, *J* = 16, 5.8 Hz, 2-H), 6.94 (2H, s, Ar-H), 7.19—7.39 (3H, m, indole-H), 7.53 (1H, s, indole 2-H), 7.62—7.65 (1H, m, indole 7-H). MS *m*/*z*: 482 ($M^+ - SO_3CH_3$, −*tert*-Bu). IR ($CHCl_3$) cm^{-1}: 1608, 1713, 1723, 1758 (sh), 3470.

Methyl (*E*,4*R*,5*S*)-5-*tert*-butyloxycarbonylamino-4-mesyloxy-6-3′-(*N*-mesitylene-2-sulfonyl)indolyl-2-hexenoate (12b) To a solution of **10b** (1.537 g, 2.76 mmol) and triethylamine (1.674 g, 16.56 mmol) in CH_2Cl_2 (15 ml) was added methanesulfonyl chloride (0.948 g, 8.23 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Work-up as descrived for the preparation of **12a** gave the crude product, which was purified by silica gel column chromatography with AcOEt–hexane (1 : 3) as an eluent to give **12b** (1.497 g, 86%), amorphous powder, $[\alpha]_D^{21}$ −22.2° (*c* = 1.052, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (9H, s, *tert*-Bu), 2.28 (3H, s, CH_3), 2.52 (6H, s, 2 × CH_3), 2.88—3.05 (2H, m, CH_2), 3.07 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 4.18—4.24 (1H, m, 5-H), 4.73 (1H, d, *J* = 8.0 Hz, NH), 5.53—5.54 (1H, br s, 4-H), 6.21 (1H, dd, *J* = 15.8, 1.6 Hz,

3-H), 6.95 (2H, s, Ar-H), 6.95 (1H, dd, J=15.8, 5.4 Hz, 2-H), 7.18—7.46 (3H, m, indole-H), 7.47 (1H, s, indole 2-H), 7.41—7.52 (1H, m, indole 7-H). MS m/z: 482 ($M^+ - SO_3CH_3$, $-$*tert*-Bu), IR ($CHCl_3$) cm^{-1}: 1602, 1720, 1770 (sh), 3480.

Boc-(*N*-Mts)Trpψ(*E*-CH=CH)-D-valine Methyl Ester (13a) To a slurry of CuCN (0.382 g, 4.24 mmol) in dry THF (10 ml) was added 1.0 M THF solution of isopropylmagnesium bromide (4.24 ml, 4.24 mmol) at -78 °C under an argon atmosphere. The mixture was allowed to warm to 0 °C and stirred for 20 min. BF_3–Et_2O (0.522 ml, 4.24 mmol) was added at -78 °C, and the mixture was stirred for 10 min. A solution of **12a** (0.67 g, 1.06 mmol) in THF (10 ml) was added to the reaction mixture at -78 °C with stirring. The mixture was stirred for 30 min, and then quenched by addition of 28% NH_4OH (5 ml) and saturated NH_4Cl (5 ml). The mixture was extracted with CH_2Cl_2–ether (1 : 4). The solution was dried over anhydrous $MgSO_4$, and evaporated to give the crude product, which was chromatographed on silica gel with AcOEt–hexane (1 : 3) as an eluent to give **13a** (0.443 g, 72%), mp 49—51 °C, amorphous powder. *Anal.* Calcd for $C_{32}H_{42}N_2O_6S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.95; H, 7.56, N, 4.83. $[\alpha]_D^{21}$ 3.98° (c=1.046, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, d, J=6.9 Hz, CH_3), 0.84 (3H, d, J=6.9 Hz, CH_3), 1.42 (9H, s, *tert*-Bu), 2.28 (3H, s, CH_3), 1.89 (1H, dq, J=6.6 Hz, $CH_3C\underline{H}$), 2.52 (6H, s, 2 × CH_3), 2.63 (1H, t, J=8.4 Hz, 2-H), 2.90 (1H, dd, J=14.2, 6.6 Hz, 6-H), 3.00 (1H, dd, J=14.2, 4.9 Hz, 6-H), 3.63 (3H, s, OCH_3), 4.51 (2H, br s, NH and 5-H), 5.51 (1H, ddd, J=15.5, 5.0, 2.9 Hz, 4-H), 5.58 (1H, dd, J=15.5, 8.4 Hz, 3-H), 6.94 (2H, s, Ar-H), 7.16—7.21 (2H, m, indole-H), 7.31—7.34 (1H, m, indole 4-H), 7.40 (1H, s, indole 2-H), 7.55—7.57 (1H, m, indole 7-H). MS m/z: 582 (M^+). IR ($CHCl_3$) cm^{-1}: 1613, 1718, 1733, 3470.

Boc-(*N*-Mts)Trpψ(*E*-CH=CH)-valine Methyl Ester (13b) To a slurry of CuCN (0.792 g, 8.8 mmole) in dry THF (15 ml) was added 1.0 M THF solution of isopropylmagnesium bromide (8.8 ml, 8.8 mmol) at -78 °C under an argon atmosphere. The mixture was allowed to warm to 0 °C, and stirred for 20 min. BF_3–Et_2O (1.08 ml, 8.8 mmol) was added at -78 °C, and then the reaction mixture was stirred for 10 min. A solution of **12b** (1.4 g, 2.2 mmol) in THF (20 ml) was added to the reaction mixture at -78 °C with stirring. The reaction mixture was stirred at -78 °C for 30 min, and quenched with NH_4OH (10 ml) and saturated NH_4Cl (10 ml). Work-up as descrived for the preparation of **13a** gave the crude product, which was purified by silica gel column chromatography with AcOEt–hexane (1 : 5) as an eluent to give **13b** (0.954 g, 75%), mp 38—40 °C, amorphous powder, $[\alpha]_D^{21}$ -32.9° (c=1.172, MeOH). *Anal.* Calcd for $C_{32}H_{42}N_2O_6S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.65; H, 7.38; N, 4.59. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, J=6.6 Hz, CH_3), 0.86 (3H, d, J=6.6 Hz, CH_3), 1.42 (9H, s, *tert*-Bu), 2.28 (3H, s, CH_3), 2.51 (3H, s, 2 × CH_3), 2.96 (2H, d, J=5.4 Hz, 6-H), 3.62 (3H, s, OCH_3), 4.50 (2H, br s, NH, 5-H), 5.48 (1H, dd, J=4.8, 15.4 Hz, 3-H), 5.61 (1H, dd, J=8.8, 15.4 Hz, 4-H), 6.94 (2H, s, Ar-H), 7.13—7.24 (3H, m, indole-H), 7.26 (1H, s, indole 2-H), 7.29—7.57 (1H, m, indole 7-H). MS m/z: 582 (M^+). IR ($CHCl_3$) cm^{-1}: 1613, 1715, 1730, 3470.

References and Notes

1) Hann M. M., Sammer P. G., Kennewell R. D., Taylor J. B., *J. Chem. Soc., Chem. Commun.*, **1980**, 234—235.
2) *a*) Cox M. T., Gormley J. J., Hayward C. F., Petter N. N., *J. Chem. Soc., Chem. Commun.*, **1980**, 800—802; *b*) Johnon R. L., *J. Med. Chem.*, **27**, 1351—1354 (1984); *c*) Kaltenbronn J. S., Hudspeth J. P., Lunney E. A., Michniewicz B. M., Nicolaides E. D., Repine J. T., Roark W. H., Stier M. A., Tinney F. J., Woo P. K. W., Essenburg A, D., *J Med. Chem.*, **33**, 838—854 (1990); *d*) Shue Y. K., Carrera G. M., Tufano M. D., Nodzan A. M., *J. Org. Chem.*, **56**, 2107—2111 (1991).
3) *a*) Ibuka T., Tanaka M., Nishi S., Yamamoto Y., *J. Am. Chem. Soc.*, **111**, 4868—4872 (1989); *b*) Ibuka T., Akimoto N., Tanaka M., Nishi S., Yamamoto Y., *J. Org. Chem.*, **54**, 4055—4061 (1989); *c*) Ibuka T., Tanaka M., Nemoto H., Yamamoto Y., *Tetrahedron*, **45**, 435—442 (1989); *d*) Ibuka T., Habashita H., Otaka A., Fujii N., Oguchi Y., Uehara T., Yamamoto Y., *J. Org. Chem.*, **56**, 4370—4382 (1991); *e*) Kempf D. J., Wang X. C., Sparten S. G., *Int. J. Peptide Protein Res.*, **38**, 237—241 (1991).
4) Previero A., Coletti-Previero M. A., Cavadore J. C., *Biochim. Biophys. Acta*, **147**, 453—461 (1967).
5) The oxidized product of **4a** with ozone was subsequently reacted with methoxycarbonylmetylenetriphenylphosphorane to afford two products, the *N*-formyl kynurenine and kynurenine type derivatives.
6) Martinez J., Bali J. P., Rodriguez M., Castro B., Magous R.,Laur J., Lignon M. F., *J. Med., Chem.*, **28**, 1874—1876 (1985).
7) *a*) Fukuda T., Wakimatu M., Kobayashi S., Fujino M., *Chem. Pharm. Bull.*, **36**, 2825 (1982); *b*) Yajima H., Takayama M., Kanaki J., Mitani K., *J. Chem. Soc., Chem. Commun.*, **1978**, 482—483.
8) Ramusden H. E., Leebrick J. R., Rosenberg S. D., Miller E. H., Walburn J. J., Balint A. E., Cserr R., *J. Org. Chem.*, **22**, 1602—1605 (1957).
9) In order to determine the optical purity of **4a** and **4b**, ^{1}H-NMR spectra of the esters of these compounds with optically active α-methoxy-α-(trifluoromethyl)phenylacetyl-chloride (MTP-Cl) were recorded. No signals corresponding to the diastereomers of these compounds were observed.
10) *a*) Rich D. H., Sun E. T. O., Ulm E., *J. Med. Chem.*, **23**, 27—33 (1980); *b*) Sham H. L., Rempel C. H, Stein H., Cohen J., *J. Chem. Soc., Chem. Commun.*, **1990**, 904—905; *c*) Patel D. V., Gauvine K. G., Ryono D. E., *Tetrahedron Lett.*, **1990**, 5587—5590.
11) *a*) Imagawa T., *Yuki Gousei Kagaku Kyokai Shi*, **48**, 1058—1059 (1990); *b*) Sicken D., *Synthesis*, **1989**, 875—876.
12) Akashi K., Palermo R. E., Sharpless K. B., *J. Org. Chem.*, **43**, 2063—2066 (1978).
13) Brown J. B. Henbest H. B., Jones E. R. H., *J. Chem. Soc.*, **1952**, 3172—3176.
14) Ister O., Gutmann H., Montavon M., Ruegg R., Ryser G., Zeller P., *Helv. Chim. Acta*, **40**, 1242—1246 (1957).
15) Ibuka T., Habashita H., Funakoshi S., Fujii N., Oguchi T., Uehara T., Yamamoto Y., *Angew. Chem., Int. Ed. Engl.* **29**, 801—803 (1990).
16) *a*) Fujii N., Habashita H., Funakoshi S., Ibuka T., Yamamoto Y., Abstracts of Papers, The 28th Symposium on Peptide Chemistry, Shimonishi Y. (Ed) Protein Research Foundation, Osaka, 1991, p. 15; *b*) Ibuka T., Habashita H., Funakoshi S., Fujii N., Baba K., Kozawa M., Oguchi Y., Uehara T., Yamamoto Y., *Tetrahedron: Asymmetry*, **1**, 389—394 (1990).