Enantiospecific Synthesis of Optically Active 6-Methoxytryptophan Derivatives and Total Synthesis of Tryprostatin A[1]

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A concise preparation of optically active L or D-6-methoxytryptophan ethyl ester **21** was developed via the Fischer indole/Schöllkopf protocol from 6-methoxy-3-methylindole **16** (four steps, 58% overall yield). This method was extended to the enantiospecific total synthesis of tryprostatin A (**11**) via a regiospecific bromination process as a key step. In addition, 6-methoxy-2-bromotryptophan ethyl ester (**32**), a potential intermediate for indole alkaloid synthesis, was prepared via this strategy.

Introduction

Indole alkaloids have long held a prominent position in natural product chemistry because of their structural relationship to the essential amino acid tryptophan and the corresponding metabolites of tryptophan, such as the neurotransmitter serotonin.[2−4] One group of indole alkaloids studied intensely in recent years has been isolated from *Alstonia* species.[5,6] As shown in Figure 1, a number of these *Alstonia* alkaloids are ring-A oxygenated indole bases in the macroline/sarpagine series such as alstophylline (**1**),[7,8] N_b-desmethylalstophylline oxindole (**2**),[9] and 11-methoxy-N_a-methyldihydropericyclivine[10] (not shown). These bases could presumably be synthesized from 6-methoxy-D-tryptophan via the trans transfer of chirality in the asymmetric Pictet−Spengler reaction.[5,6]

In addition to the macroline/sarpagine monomeric alkaloids, 18 *Alstonia* bisindole alkaloids have also been reported.[5,6] At least three of these bisindole bases contain a 6-methoxytryptophan unit: macralstonine (**4**),[11−14] angusticraline,[15] and alkaloid H.[16,17] The alkaloid macralstonine (**4**) effects a progressively increasing drop in blood pressure when administered to dogs;[18,19] moreover the acetate derivative of macralstonine has been reported to exhibit antimalarial and antiamoebic activity.[20] A few of these bisindole alkaloids have been synthesized biomimetically from condensation of the two monomeric units by LeQuesne et al.[13,21,22] as well as in this laboratory.[23,24] The biomimetic coupling of macroline and alstophylline provided macralstonine (**4**)[13] while alkaloid H could be formed by coupling of macroline and N_b-desmethylalstophylline (**3**) in a similar process.[22]

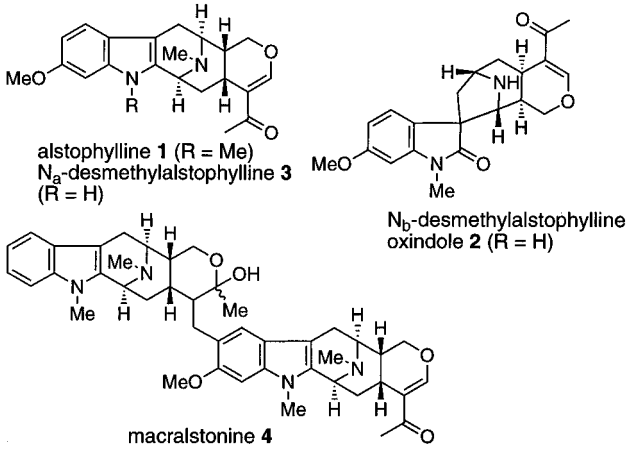

Figure 1.

Alstonia alkaloids represent only a small group of bases which could potentially be prepared from 6-methoxytryptophan derivatives. To illustrate the importance of a multigram synthetic route to optically active 6-methoxytryptophans, a number of other biologically active ring-A oxygenated alkaloids are presented in Figure 2. Most notable among these are the important *Catharanthus* antitumor alkaloids vinblastine (**5**) and vincristine (**6**). The pharmacology, structure−activity relationships, and

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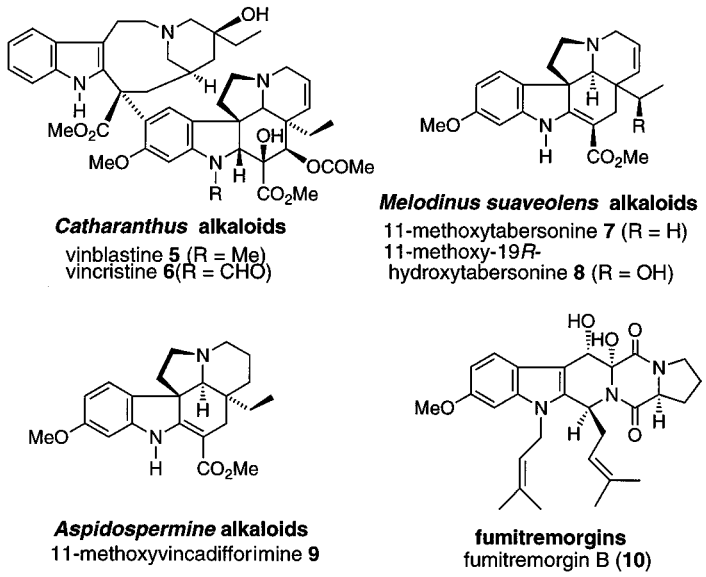

Figure 2.

therapeutic uses of these clinically important bisindoles have been reviewed extensively.[25] Certainly, 6-methoxytryptophan might serve as an important intermediate for the construction of 11-methoxytabersonine (**7**), the 19*R*-hydroxy derivative **8**, and 11-methoxyvincadifforimine (**9**). The active series of mycotoxins, the fumitremorgins, including the convulsant agent fumitremorgin B (**10**) have been isolated from a variety of *Aspergillus* and *Penicillium* species.[26] These alkaloids effect severe tremorgenic responses in mice on either intraperitoneal or oral administration.[27,28] It is known that at least one of these agents owes its activity to interaction in the GABA system.[29] As mentioned, for the total syntheses of the above indole alkaloids, optically active 6-methoxytryptophan could serve as an important building block.

In 1992, a method for the synthesis of 1-(benzenesulfonyl)-6-methoxy-D-(−)-tryptophan ethyl ester was reported[30] which employed the Moody azide pyrolysis followed by formylation under Vilsmeier−Haack conditions as key steps.[30,31] This approach required the synthesis of the intermediate azides on large scale as well as pyrolysis in refluxing xylene. Because this strategy required the potential storage of gram quantities of hazardous azidocinnimate intermediates, a new route to 6-methoxytryptophan was envisaged. Recently, a regiospecific bromination of 3-methylindole was developed in our laboratory[32] and this method was employed in the synthesis of optically active 5-methoxy-L-(−)- or D-(+)-tryptophan by utilizing the Japp−Klingmann/Fischer

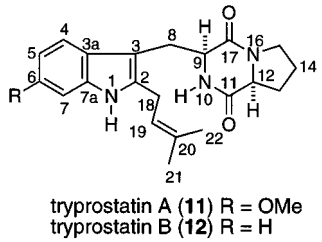

Figure 3.

indole protocol and a Schöllkopf chiral auxiliary.[33−35] This method appeared to be a more practical route for the synthesis of 6-methoxytryptophan and its derivatives on large scale. 6-Methoxytryptophan derivatives are not only important for the synthesis of indole alkaloids but also as potential inhibitors for the enzyme indoleamine 2,3-dioxygenase.[36]

More recently, tryprostatins A (**11**) and B (**12**) have been isolated as secondary metabolites of a marine fungal strain BM939 and shown to completely inhibit cell cycle progression of tsFT210 cells in the G2/M phase at a final concentration of 50 μg/mL of **11** and 12.5 μg/mL of **12**, respectively.[37−39] Tryprostatins A (**11**) and B (**12**) contain a 2-isoprenyltryptophan moiety and a proline residue, which comprise the diketopiperazine unit (Figure 3). These indole alkaloids differ from representatives of the fumitremorgin series for ring-C has not been formed between the positions designated C(18) and N(10).[26] Although bases in the fumitremorgin series have been studied extensively,[26] only a few natural products structurally related to **11** and **12** have been reported, to date.[26] The biological activity and unique 2-isoprenyltryptophan units of **11** and **12** prompted interest in such molecules.

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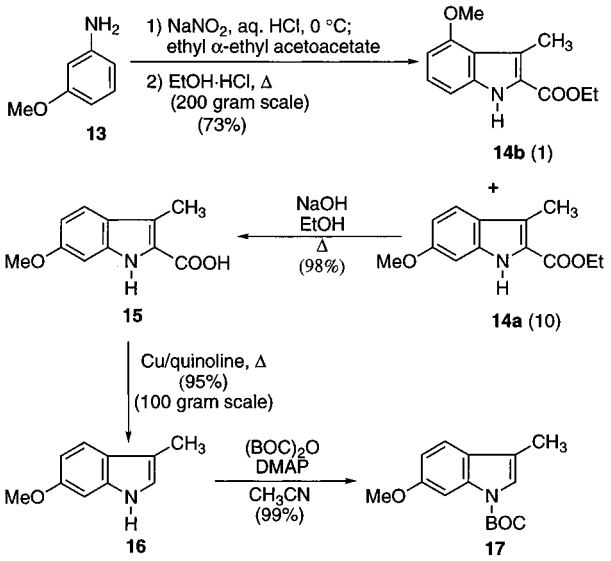
Scheme 1



Results and Discussion

We report here the enantiospecific synthesis of 6-methoxy-L- and D-tryptophan derivatives and its application to the synthesis of tryprostatin A (**11**) via a regiospecific bromination sequence as a key step. The synthesis began with the Fischer indole cyclization via a Japp−Klingmann azo-ester intermediate (Scheme 1). This sequence was originally reported by Abramovitch and Shapiro and reviewed.[40] When *m*-anisidine (**13**) was treated with sodium nitrite and concentrated aqueous HCl, followed by the addition of the anion of ethyl α-ethylacetoacetate, the Japp−Klingmann azo-ester intermediate was formed. When this intermediate was heated in a solution of 3 N ethanolic HCl, a mixture of ethyl 6-methoxy-3-methylindole-2-carboxylate (**14a**) and its 4-methoxy isomer **14b** was obtained in a ratio of 10:1. The desired 6-methoxyindole isomer **14a** was isolated from the mixture by simple crystallization. Although this sequence was exothermic, this method was far safer to execute on large scale than the Moody azide pyrolysis. Hydrolysis of the ester **14a** under alkaline conditions yielded the corresponding carboxylic acid **15** which was converted into indole **16** via the subsequent copper/quinoline-mediated decarboxylation sequence. This procedure provided the 6-methoxy-3-methylindole (**16**) in excellent yield.

To employ the Schöllkopf chiral auxiliary in the indole system, protection/deactivation of the indole N(H) moiety was required. When 6-methoxyindole **16** was stirred with di-*tert*-butyl dicarbonate in the presence of DMAP, *N*-BOC protected indole **17** was realized in 99% yield (Scheme 1). The protected 3-methylindole **17** was then treated with NBS in the presence of AIBN to provide the 3-(bromomethyl)indole **18**, as illustrated in Scheme 2. When bromide **18** was coupled with the anion of the Schöllkopf chiral auxiliary (**19**) (derived from D-valine),[30,31,33,41] only the desired trans diastereomer **20** was obtained. The pyrazine **20** was hydrolyzed with a 2 N aqueous HCl solution/THF to remove the D-valine ethyl ester, and then the BOC protecting group was removed on stirring with a 4 N aqueous HCl solution/MeOH in a one-pot reaction. D-Valine ethyl ester can readily be recovered by Kugelrohr distillation and reused. In this manner, 6-methoxy-L-tryptophan ethyl ester (**21**) was synthesized enantiospecifically in four steps from 6-methoxy-3-methylindole (**16**) in 58% overall yield. Use of the Schöllkopf chiral auxiliary derived from L-valine provided the D-enantiomer of **21**.

For the total synthesis of tryprostatin A (**11**), 2-isoprenyltryptophan derivatives were required. Since the regiospecific bromination of 3-methylindoles were achieved at the indole 2-position via an electrophilic process or at the 3-methyl position under free radical conditions,[32] this method appeared to be useful for the preparation of a 2-isoprenyltryptophan. The 2-bromo group could serve as synthetic equivalent for the isoprenyl group, and the 3-bromomethyl function could be coupled with the anion of the Schöllkopf chiral auxiliary **19** to obtain the desired tryptophan moiety. Consequently, the total synthesis of **11** began with regiospecific bromination of **17** at the indole C(2) position to yield 2-bromoindole **22** in 95% yield under electrophilic conditions (Scheme 3). Furthermore, when 2-bromoindole **22** was reacted with NBS under free radical conditions (AIBN, Δ), dibromide **23** was obtained as illustrated in 93% yield. When dibromide **23** was coupled with the anion of the Schöllkopf chiral auxiliary **19** at −78 °C, a mixture of diastereomers **24a** and **24b** in a ratio of 4:1 was obtained in 91% yield. The structures of **24a** and **24b** were established by proton and carbon NMR spectroscopy and by comparison to indoles in the 5-methoxy series.[41] Since the enantioselectivity of formation of **24a**:**24b** was disappointing, another approach for the preparation of **11** was envisaged.

It was decided to return to the 6-methoxy-3-(bromomethyl)indole **18** as the starting template since **18** had earlier been shown to react with the anion of Schöllkopf chiral auxiliary **19** to provide only the desired trans diastereomer **20** (Scheme 2). Regiospecific bromination of **20** at the indole C(2) position to furnish **24a** was accomplished in 85% yield when **20** was stirred with NBS in CH_2Cl_2 at room temperature (Scheme 4). Initially, it was feared that competitive bromination would take place both at the indole C(2) position and the C(3) methylene group, but fortunately the latter process did not occur under these conditions. It was believed the 6-methoxy group increased the electron density at the indole C(2) position; therefore, electrophilic substitution took place smoothly. In contrast, in the 5-methoxypyrazine series treatment of the indole with NBS in CH_2Cl_2 led to multibromination.[42] This indicated, as expected, that the 6-methoxy group played a major role in the regiospecific bromination at C(2). The regiospecific bromination at the indole C(2) position of **20** provided a route to the 6-methoxy-2-bromo trans pyrazine **24a** in enantiospecific fashion. When bromide **24a** was treated with *n*-butyllithium at −78 °C, followed by addition of isoprenyl bromide (4-bromo-2-methylbutene) **25**, 2-isoprenylpyrazine **26** was isolated in 86% yield. Since the Schöllkopf chiral auxiliary can tolerate strongly alkaline conditions,[33] again it served as a protecting group for the amino acid functionality to prevent any racemization. The pyrazine group from **26** was removed under acidic conditions (aqueous HCl, THF) in 94% yield to provide D-valine ethyl ester and the 2-isoprenyltryptophan **27** (Scheme 4).

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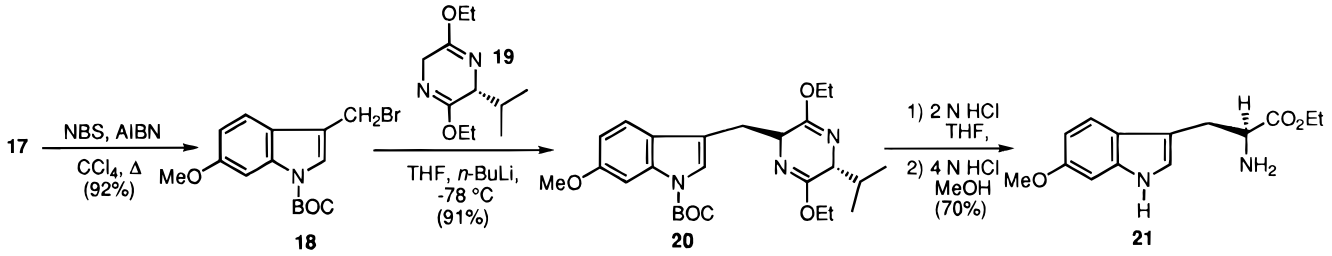
Scheme 2



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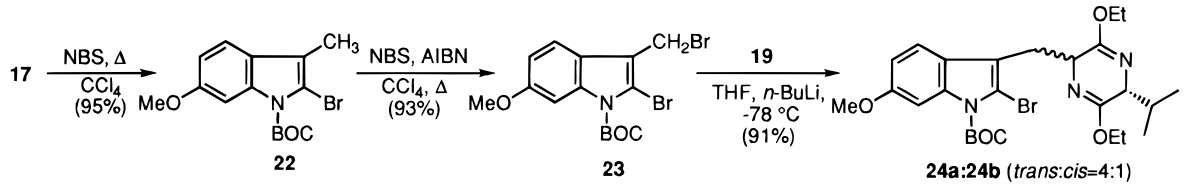

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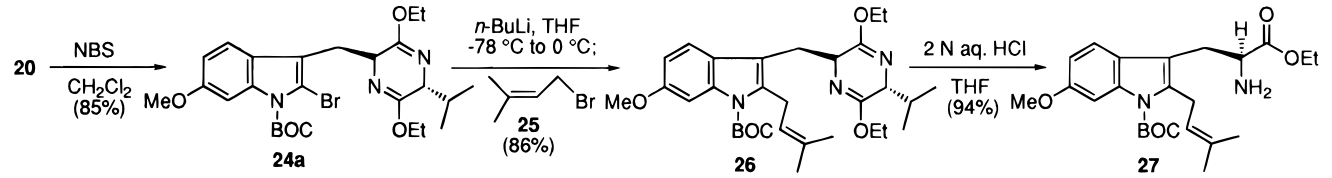

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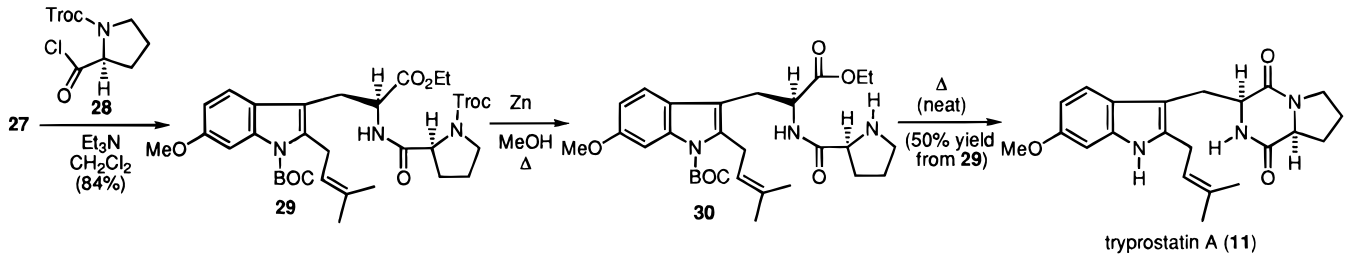
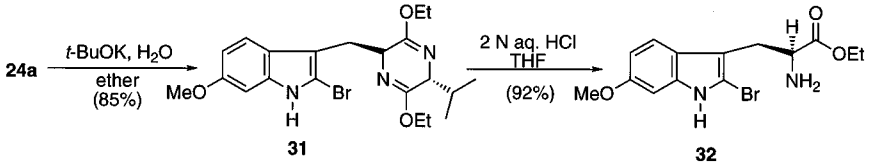


Scheme 6



As illustrated in Scheme 5, when the 6-methoxy-2-isoprenyltryptophan **27** was stirred with *N*-(trichloroethoxycarbonyl)(Troc)-L-prolyl chloride (**28**)[43] in the presence of triethylamine in CH_2Cl_2 at 0 °C, the desired dipeptide **29** was obtained. The Troc protecting group was then removed under reductive conditions when **29** was heated with Zn (dust) in refluxing MeOH.[43] Finally, formation of the diketopiperazine unit and removal of BOC protecting group from the indole N(H) function were achieved when dipeptide **30** was heated at 160 °C (neat) to furnish tryprostatin A (**11**) in 50% overall yield [from **29** (Scheme 5)].

In addition to tryprostatin A (**11**) and the 6-methoxy-2-isoprenyltryptophan ethyl ester (**27**), the 6-methoxy-2-bromotryptophan ethyl ester (**32**) was also prepared by removal of the BOC function with potassium *tert*-butoxide and water,[44] followed by acid-mediated hydrolysis of the pyrazine group (Scheme 6). These bromo derivatives (**31** and **32**) may be important intermediates for the preparation of unusual tryptophan derivatives with various substituents at the indole 2-position via palladium-catalyzed coupling reactions. These types of unusual tryptophan derivatives may also be potential inhibitors for the enzyme indoleamine 2,3-dioxygenase.[36]

In summary, a concise preparation of optically active L- or D-6-methoxytryptophan ethyl ester **21** was developed via the Fischer indole/Schöllkopf chiral auxiliary from 6-methoxy-3-methylindole (**16**). This method was extended to the first enantiospecific total synthesis of tryprostatin A (**11**) via a regiospecific bromination process as a key step. In addition, 6-methoxy-2-bromotryptophan ethyl ester (**32**) was prepared. This approach should also provide a route for the synthesis of other unusual tryptophans or indoles which carry substituents at the indole 2-position. Further work in this areas is in progress and will be reported in due course.

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Experimental Section

Melting points are reported uncorrected. The ^{1}H NMR spectra were recorded at 250 MHz or 500 MHz.

Analytical TLC plates employed were E. Merck Brinkman UV active silica gel (Kieselgel 60 F254) on plastic while silica gel 60b for flash chromatography was purchased from E. M. Laboratories.

Alkaloids were visualized with Dragendorf's reagent or a saturated solution of ceric ammonium sulfate in 50% sulfuric acid or with an aqueous solution of (2,4-dinitrophenyl)hydrazine in 30% sulfuric acid. Methanol (MeOH) and ethanol (EtOH) were dried by distillation over magnesium metal and iodine. Tetrahydrofuran (THF), benzene, toluene, dioxane, and diethyl ether were dried by distillation from sodium−benzophenone ketyl. Methylene chloride was dried over $MgSO_4$ and then distilled over P_2O_5. Triethylamine was dried over CaH_2 and then distilled over KOH. All chemicals were purchased from Aldrich Chemical Co. unless otherwise indicated.

Ethyl 6-Methoxy-3-methylindole-2-carboxylate (14a). To a mixture of *m*-anisidine **13** (12.3 g, 0.1 mol), concd aqueous HCl (25 mL), and water (40 mL) was added a solution of $NaNO_2$ (7.6 g, 0.11 mol in 10 mL of water) in a dropwise manner at −5 °C. After addition, the mixture was stirred at 0 °C for 15 min and brought to pH 3−4 by addition of sodium acetate (8.3 g, 0.1 mol). In a separate flask, a solution of ethyl α-ethylacetoacetate (15.8 g, 0.1 mol) in ethanol (80 mL) at 0 °C was treated with an aqueous solution of KOH (0.1 mol in 10 mL of H_2O), followed by addition of ice (200 g). The diazonium salt prepared above was immediately added to the alkaline solution of ethyl α-ethylacetoacetate. The mixture was then adjusted to pH 5−6 and stirred at 0 °C for 4 h. After the mixture was kept a further 12 h at 4 °C, it was extracted with ethyl acetate (4 × 200 mL). The combined extracts were washed with brine and dried ($MgSO_4$). Most of the solvent was removed under reduced pressure, and the liquid residue which remained was added dropwise to a solution of anhydrous 3 N ethanolic HCl at 70 °C. This is an exothermic process, and the addition was carried out at a rate at which the temperature remained at 70 °C. After addition, the mixture was held at 78 °C for 2 h. The solvent was removed under reduced pressure, and the residue which remained was treated with water (20 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine and dried (Na_2SO_4). Purification on a short wash column (silica gel, ethyl acetate/hexane, 1:3) gave a mixture of **14a** and **14b** (10:1 ratio as determined by ^{1}H NMR) as a dark brown solid. Recrystallization of this mixture from ethyl acetate furnished pure **14a** as brown crystals. Additional quantities of **14a** could be obtained by chromatography of the mother liquor followed by crystallization (combined 17.1 g, 73.5%). **14a**: mp 122−124 °C (lit.[46] mp 122 °C); IR (KBr) 3330, 1669, 1467 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.4 (t, 3 H, J = 7.1 Hz), 2.6 (s, 3 H), 3.81 (s, 3 H), 4.4 (q, 2 H, J = 7.1 Hz), 6.78 (d, 1 H, J = 1.8 Hz), 6.8 (dd, 1 H, J = 8.8 and 1.9 Hz), 7.5 (d, 1 H, J = 8.4 Hz), 8.55 (br, 1 H, D_2O exchangeable); MS (EI) *m/e* (relative intensity) 233 (48), 187 (100), 159 (53), 144 (21), 116 (23). This reaction was run on a 300 g scale with no loss in yield.

6-Methoxy-3-methylindole (16). A mixture of **14a** (72 g, 0.3 mol), EtOH (150 mL), KOH pellets (85%, 60 g, 0.9 mol), and water (100 mL) was heated to reflux for 1 h. The volume was reduced to 100 mL under reduced pressure and acidified with an aqueous solution of 3 N HCl. The precipitate which resulted was collected on a filter, washed with distilled water, and dried in a vacuum oven at 80 °C to afford 6-methoxy-3-methylindole-2-carboxylic acid (**15**) as a white solid (61.5 g, 100%): mp 202−203 °C (lit.[47] mp 200−201 °C). This acid **15** (59.5 g, 0.29 mol) was then heated to reflux in a well-stirred (mechanical stirrer) mixture of distilled quinoline (125 mL) and copper powder (2.5 g) under nitrogen for 2.5 h. The copper powder was removed by filtration, after which the filtrate was brought to pH 2−3 with an aqueous solution of 6 N HCl, and the solution which resulted was extracted with diethyl ether (4 × 100 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford **16** as a brown solid (43.7 g, 93.6%): mp 129−131 °C (lit.[48] mp 127 °C); IR (KBr) 2915, 1625, 1455 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 3.79 (s, 3 H), 6.78 (dd, 1 H, J = 1.8 and 8.6 Hz), 6.83 (m, 2 H), 7.43 (d, 1 H, J = 8.5 Hz), 7.72 (s, br, 1 H); MS (EI) *m/e* (relative intensity) 161 (84), 146 (100), 118 (42).

1-(*tert*-Butyloxycarbonyl)-6-methoxy-3-methylindole (17). To a solution of 6-methoxy-3-methylindole **16** (5.0 g, 31 mmol) in distilled acetonitrile (150 mL) were added di-*tert*-butyl dicarbonate (7.44 g, 34.1 mmol) and DMAP (0.195 g, 1.6 mmol). The reaction mixture was stirred at rt for 12 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with an aqueous solution of 1 N HCl (2 × 50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (K_2CO_3). After removal of solvent under reduced pressure, the residue was solidified to afford **17** (8.12 g, 99%) as a yellow solid: mp 45−46 °C; IR (KBr) 2950, 1720, 1620, 1455 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.65 (s, 9 H), 2.22 (s, 3 H), 3.87 (s, 3 H), 6.87 (dd, 1 H, J = 2.2 and 8.6 Hz), 7.22 (s, 1 H), 7.54 (d, 1 H, J = 8.6 Hz), 7.72 (br, s, 1 H); MS (EI) *m/e* (relative intensity) 261 (M^+, 42), 205 (100), 161 (52), 146 (45), 117 (21). Anal. Calcd for $C_{15}H_{19}NO_3 \cdot {}^1/_5H_2O$: C, 68.01; H, 7.38; N 5.28. Found: C, 68.06; H, 7.27; N, 5.17.

1-(*tert*-Butyloxycarbonyl)-3-(bromomethyl)-6-methoxyindole (18). A solution of 1-(*tert*-butyloxycarbonyl)-6-methoxy-3-methylindole **17** (4.0 g, 15.3 mmol) in CCl_4 (120 mL) was heated to reflux after which *N*-bromosuccinimide (2.87 g, 16.1 mmol) and AIBN (120 mg) were admixed carefully and added in three portions. The mixture was refluxed for 20 min. Another portion of AIBN (60 mg) was then added. The mixture was kept at reflux for 50 min and then allowed to cool. The succinimide which resulted as a precipitate was filtered off and washed with hexane (4 × 10 mL). The solvents were removed under reduced pressure to afford 3-(bromomethyl)indole **18** as a brown oil (4.79 g, 92%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.65 (s, 9 H), 3.86 (s, 3 H), 4.61 (s, 2 H), 6.90 (dd, 1 H, J = 2.0 and 8.1 Hz), 7.50 (d, 1 H, J = 8.2 Hz), 7.52 (s, 1 H), 7.70 (br, s, 1 H). The crude residue of 3-(bromomethyl)indole was flash evaporated under reduced pressure with dry THF three times and used directly in a later step without further purification. It is unstable on silica gel.

(3*S*,6*R*)-3-[[1-(*tert*-Butyloxycarbonyl)-6-methoxy-3-indolyl]methyl]-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (20). To a solution of (3*R*)-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (Schöllkopf chiral auxiliary) (**19**)[6] derived from D-valine (3.41 g, 16.1 mmol) in dry THF (60 mL) under nitrogen at −78 °C was added *n*-BuLi (2.5 M, 7.08 mL, 17.7 mmol) dropwise. The solution which resulted was stirred at −78 °C for 30 min and treated slowly with a solution of crude 3-(bromomethyl)indole **18** (4.79 g, about 14.1 mmol) in THF (30 mL). The mixture was stirred at −78 °C for 20 h and then allowed to slowly warm to rt. The solution was concentrated under reduced pressure and diluted with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried (K_2CO_3). After removal of solvent under reduced pressure, the residue was purified by flash chromatography (silica gel, hexane/ethyl acetate, 10/1) to afford **20** as an oil (6.04 g, 91%): $[\alpha]^{27}_D$ = +24.7 (c = 0.9, in $CHCl_3$); IR (NaCl) 2970, 1730, 1690 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.63 (d, 3 H, J = 6.8 Hz), 0.92 (d, 3 H, J = 6.9 Hz), 1.21 (t, 3 H, J = 7.1 Hz), 1.29 (t, 3 H, J = 7.1 Hz), 1.62 (s, 9 H), 2.15 (m, 1 H), 3.13 (d, 2 H, J = 4.8 Hz), 3.53 (t, 1 H, J = 3.4 Hz), 3.84 (s, 3 H), 3.94−4.16 (m, 4 H), 4.25 (q, 1 H, J = 3.8 Hz), 6.80 (dd, 1 H, J = 2.2 and 8.6 Hz), 7.21 (s, 1 H), 7.42 (d, 1 H, J = 8.6 Hz), 7.67 (br, s, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$)

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δ 14.4, 16.7, 19.0, 28.2, 29.4, 31.7, 55.6, 56.1, 60.4, 60.5, 60.7, 82.9, 99.0, 111.5, 116.7, 120.1, 122.8, 125.3, 136.1, 149.8, 157.7, 162.3, 163.5; MS (EI) *m/e* (relative intensity) 471 (M^+, 47), 261 (21), 212 (100), 169 (67), 141 (20), 57 (51). Anal. Calcd for $C_{26}H_{37}N_3O_5$: C, 66.22; H, 7.91; N 8.91. Found: C, 66.23; H, 7.90; N, 8.55.

L-6-Methoxytryptophan Ethyl Ester (21). To a solution of pyrazine **20** (100 mg, 0.21 mmol) in THF (2.5 mL) at 0 °C was added an aqueous solution of 2 N HCl (0.8 mL). The reaction mixture was allowed to warm to rt and stirred for 1.5 h. The solution was concentrated under vacuum. MeOH (0.5 mL) was added after which an aqueous solution of 4 N HCl (7 mL) was added at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 4 h. A cold aqueous solution of 15% NH_4OH was added. The solution was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (K_2CO_3) and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, EtOAc to EtOAc:MeOH = 95:5) to provide L-6-methoxytryptophan ethyl ester **21** (40 mg, 70%) as an oil. **21**: $[\alpha]^{27}_D = +5.1$ ($c = 0.92$, in $CHCl_3$); IR (NaCl) 3365, 2925, 1730, 1625 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (t, 3 H, $J = 7.1$ Hz), 1.79 (s, br, 2 H), 2.97 (dd, 1 H, $J = 7.8$ and 14.4 Hz), 3.21 (dd, 1 H, $J = 4.7$ and 14.3 Hz), 3.77 (s, 3 H), 3.73−3.80 (m, 1 H), 4.14 (q, 2 H, $J = 7.2$ Hz), 6.73−6.78 (m, 2 H), 6.84 (s, 1 H), 7.44 (d, 1 H, $J = 9.3$ Hz), 8.67 (s, br, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.0, 30.7, 54.9, 55.5, 60.8, 94.7, 109.2, 110.7, 119.1, 121.8, 121.9, 137.0, 156.4, 175.2; MS (EI) *m/e* (relative intensity) 262 (8), 160 (100), 145 (13), 117 (11); exact mass calcd for $C_{14}H_{18}N_2O_3$ 262.1317, found: 262.1346.

1-(*tert*-Butyloxycarbonyl)-2-bromo-6-methoxy-3-methylindole (22). To a solution of 1-(*tert*-butyloxycarbonyl)-6-methoxy-3-methylindole **17** (6.0 g, 23.0 mmol) in CCl_4 (90 mL) was added *N*-bromosuccinimide (4.30 g, 24.1 mmol). The mixture was heated to reflux for 60 min. The reaction solution was allowed to cool to rt. The succinimide which resulted was filtered off and washed with hexane (4 × 15 mL). The filtrates were combined, and the solvents were removed under reduced pressure to afford **22** (7.42 g, 95%) as a brownish residue: ^1H NMR (250 MHz, $CDCl_3$) δ 1.69 (s, 9 H), 2.22 (s, 3 H), 3.86 (s, 3 H), 6.86 (dd, 1 H, $J = 2.3$ and 8.7 Hz), 7.30 (d, 1 H, $J = 8.7$ Hz), 7.67 (d, 1 H, $J = 2.3$ Hz); The crude residue of 2-bromo-3-methylindole **22** was used directly in a later step without further purification.

1-(*tert*-Butyloxycarbonyl)-2-bromo-3-(bromomethyl)-6-methoxyindole (23). A solution of **22** (7.42 g, 21.8 mmol) in CCl_4 (90 mL) was heated to reflux after which an admixture of *N*-bromosuccinimide (NBS) (4.30 g, 24.1 mmol) and AIBN (200 mg) was carefully added in one portion under Ar. After completion of the addition, three portions of AIBN (3 × 50 mg) were added every 7 min. The mixture was heated at reflux for 60 min and cooled to rt. The succinimide which resulted was filtered off and washed with hexane (4 × 15 mL). The filtrates were combined, and the solvents were removed under reduced pressure to yield **23** (8.50 g, 93%) as a brown oil: ^1H NMR (250 MHz, $CDCl_3$) δ 1.69 (s, 9 H), 3.85 (s, 3 H), 4.61 (s, 2 H), 6.89 (dd, 1 H, $J = 2.2$ and 8.5 Hz), 7.44 (d, 1 H, $J = 8.5$ Hz), 7.66 (d, 1 H, $J = 2.2$ Hz); MS (EI) *m/e* (relative intensity) 419 (M^+, 19), 363 (15), 282 (12), 240 (99), 238 (100), 219 (11), 175 (9), 158 (38), 129 (14). The crude oil of 2-bromo-3-(bromomethyl)indole **23** was used in the next step without further purification.

(3*S*,6*R*)-3-[[1-(*tert*-Butyloxycarbonyl)-2-bromo-6-methoxy-3-indolyl]methyl]-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (24a) and (3*R*,6*R*)-3-[[1-(*tert*-Butyloxycarbonyl)-2-bromo-6-methoxy-3-indolyl]methyl]-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (24b). A solution of the Schöllkopf chiral auxiliary **19**[31] (5.11 g, 24.1 mmol) in THF (50 mL) was treated with *n*-butyllithium (2.5 M in hexane, 10.5 mL, 26.3 mmol) at −78 °C under nitrogen. The solution which resulted was stirred at −78 °C for 30 min after which a cold solution of dibromide **23** (8.50 g, 20.2 mmol) in THF (30 mL) under nitrogen was added dropwise. After the mixture was allowed to stir at −78 °C for 20 h, the reaction solution was slowly warmed to rt. Most of the solvent was removed under reduced pressure, and the residue which resulted was dissolved in CH_2Cl_2 (100 mL) and treated with a 10% aqueous solution of cold $NaHCO_3$ (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure to afford a mixture of **24a** and **24b** (80/20). The mixture was separated by flash chromatography (silica gel, hexane/ethyl acetate, 15/1) to afford **24a** (7.99 g, 72%) and **24b** (2.12 g, 19%). **24a**: an oil; IR (NaCl) 2970, 1735, 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.62 (d, 3 H, $J = 6.8$ Hz), 0.97 (d, 3 H, $J = 6.8$ Hz), 1.17 (t, 3 H, $J = 7.1$ Hz), 1.28 (t, 3 H, $J = 7.1$ Hz), 1.67 (s, 9 H), 2.20 (m, 1 H), 2.92 (dd, 1 H, $J = 8.1$ and 13.9 Hz), 3.28 (dd, 1 H, $J = 4.6$ and 13.9 Hz), 3.68 (t, 1 H, $J = 3.3$ Hz), 3.84 (s, 3 H), 3.95−4.25 (m, 5 H), 6.80 (dd, 1 H, $J = 2.2$ and 8.6 Hz), 7.38 (d, 1 H, $J = 8.6$ Hz), 7.63 (d, 1 H, $J = 2.1$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.3, 14.4, 16.6, 19.1, 28.2, 31.0, 31.5, 55.6, 55.8, 60.5, 60.7, 84.5, 99.6, 107.8, 111.6, 119.7, 120.6, 123.7, 137.3, 149.4, 157.7, 162.8, 163.4; MS (EI) *m/e* (relative intensity) 551 (M^+, 17), 549 (M^+, 17), 470 (64), 414 (61), 370 (58), 341 (32), 240 (49), 238 (49), 212 (72), 169 (100), 141 (39). Anal. Calcd for $C_{26}H_{36}N_3O_5$-Br: C, 56.73; H, 6.59; N 7.63. Found: C, 56.97; H, 6.47; N, 7.48. **24b**: an oil; IR (NaCl) 2970, 1730, 1690, 1360, 1310, 1235, 1155, 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.74 (d, 3 H, $J = 6.8$ Hz), 1.01 (d, 3 H, $J = 6.8$ Hz), 1.18 (t, 3 H, $J = 7.1$ Hz), 1.24 (t, 3 H, $J = 7.1$ Hz), 1.67 (s, 9 H), 2.05 (m, 1 H), 2.88 (dd, 1 H, $J = 8.6$ and 13.9 Hz), 3.27 (dd, 1 H, $J = 4.8$ and 13.9 Hz), 3.84 (s, 3 H), 3.82−4.28 (m, 6 H), 6.83 (dd, 1 H, $J = 2.3$ and 8.6 Hz), 7.38 (d, 1 H, $J = 8.6$ Hz), 7.64 (d, 1 H, $J = 2.3$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.2, 14.4, 17.7, 19.6, 28.2, 31.8, 31.9, 55.7, 55.9, 60.4, 60.6, 61.2, 84.4, 99.8, 107.7, 111.7, 119.5, 120.8, 123.6, 137.6, 137.5, 149.3, 157.7, 162.6, 163.2; MS (EI) *m/e* (relative intensity) 551 (M^+, 5), 549 (M^+, 5), 414 (10), 368 (17), 240 (33), 238 (35), 169 (100), 141 (25). Anal. Calcd for $C_{26}H_{36}N_3O_5Br$: C, 56.73; H, 6.59; N 7.63. Found: C, 57.10; H, 6.85; N, 7.48.

(3*S*,6*R*)-3-[[1-(*tert*-Butyloxycarbonyl)-2-bromo-6-methoxy-3-indolyl]methyl]-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (24a). To a solution of the pyrazine **20** (700 mg, 1.49 mmol) in dry CH_2Cl_2 (60 mL) was added NBS (0.292 g, 1.64 mmol) at rt. The reaction mixture was stirred at rt for 30 min after which the solvent was removed under reduced pressure. The residue was subjected to a short wash column (silica gel, ethyl acetate:hexane = 1:10) to provide **24a** (700 mg, 86%) as an oil. All spectroscopic data were identical with that for **24a** reported in the previous experiment.

(3*S*,6*R*)-3-[[1-(*tert*-Butyloxycarbonyl)-2-isoprenyl-6-methoxy-3-indolyl]methyl]-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (26). To a solution of 2-bromopyrazine **24a** (1.74 g, 3.09 mmol) in dry THF (25 mL) at −78 °C under nitrogen was added a solution of *n*-BuLi (2.5 M, 1.64 mL, 4.10 mmol) dropwise. The resultant mixture was stirred at −78 °C for 30 min and then warmed to 0 °C for 10 min. Then isoprenyl bromide (4-bromo-2-methylbutene) **25** (1.03 g, 6.91 mmol) was added quickly at 0 °C. The mixture was stirred at 0 °C for 1 h and warmed to rt overnight. The solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with a 5% aqueous solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (K_2CO_3). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 15/1) to provide **26** (1.44 g, 85%) as an oil: IR (NaCl) 2970, 1730, 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.61 (d, 3 H, $J = 6.8$ Hz), 0.94 (d, 3 H, $J = 6.8$ Hz), 1.18 (t, 3 H, $J = 7.1$ Hz), 1.31 (t, 3 H, $J = 7.1$ Hz), 1.61 (s, 3 H), 1.63 (s, 9 H), 1.70 (s, 3 H), 2.19 (m, 1 H), 2.88 (dd, 1 H, $J = 7.4$ and 14.2 Hz), 3.23 (dd, 1 H, $J = 3.9$ and 14.3 Hz), 3.56 (t, 1 H, $J = 3.4$ Hz), 3.69 (d, 2 H, $J = 6.0$ Hz), 3.83 (s, 3 H), 3.94−4.22 (m, 5 H), 5.16 (t, 1 H, $J = 5.8$ Hz), 6.78 (dd, 1 H, $J = 2.3$ and 8.5 Hz), 7.37 (d, 1 H, $J = 8.6$ Hz), 7.65 (d, 1 H, $J = 2.3$ Hz); MS (EI) *m/e* (relative intensity) 539 (M^+, 65), 439 (11), 328 (16), 272 (58), 228 (100), 212 (55), 169 (31), 141 (16), 57 (48). Anal. Calcd for $C_{31}H_{45}N_3O_5$: C, 68.99; H, 8.40; N 7.79. Found: C, 68.69; H, 8.66; N, 7.40.

(*S*)-1-(*tert*-Butyloxycarbonyl)-2-isoprenyl-6-methoxytryptophan Ethyl Ester (27). To a solution of 2-

prenylpyrazine **26** (1.27 g, 2.36 mmol) in THF (30 mL) at 0 °C was added an aqueous solution of 2 N HCl (10 mL). The reaction mixture was allowed to warm to rt. and stirred for 1.5 h. A cold aqueous solution of 15% NH_4OH was added. The solution was concentrated under vacuum and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (K_2CO_3) and the solvents were removed under vacuum. The residue was purified by flash chromatography (silica gel, ethyl acetate) to provide 1-BOC-2-isoprenyl-6-methoxytryptophan ethyl ester (**27**) (0.95 g, 94%) as an oil: IR (NaCl) 2975, 1730, 1615 cm^{-1}; $[\alpha]^{27}_D$ = +15.2 ° (*c* = 0.92, in $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (t, 3 H, *J* = 7.1 Hz), 1.46−1.55 (m, 2 H), 1.63 (s, 9 H), 1.66 (s, 3 H), 1.71 (s, 3 H), 2.82 (dd, 1 H, *J* = 8.8 and 14.2 Hz), 3.12 (dd, 1 H, *J* = 5.0 and 14.2 Hz), 3.68 (d, 2 H, *J* = 5.1 Hz), 3.70 (m, 1 H), 3.83 (s, 3 H), 4.13 (qd, 2 H, *J* = 2.1 and 7.1 Hz), 5.16 (t, 1 H, *J* = 5.1 Hz), 6.82 (dd, 1 H, *J* = 8.5 and 2.3 Hz), 7.33 (d, 1 H, *J* = 8.5 Hz), 7.69 (d, 1 H, *J* =2.3 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.0, 18.0, 25.5, 26.0, 28.1, 30.4, 55.6, 60.9, 83.5, 100.3, 111.3, 114.0, 118.5, 122.3, 123.7, 131.7, 136.6, 137.0, 150.4, 157.4, 175.0; MS (EI) *m/e* (relative intensity) 430 (M^+, 3), 272 (36), 228 (100); exact mass calcd for $C_{24}H_{34}N_2O_5$ 430.2468, found 430.2481. This material was employed directly in the next step.

The coupling of 2-isoprenyl-6-methoxytryptophan (27) with Troc-prolinyl Chloride To Provide 29. To a solution of 2-isoprenyl-6-methoxytryptophan **27** (300 mg, 0.69 mmol) in dry CH_2Cl_2 (15 mL) and triethylamine (200 mg, 2.00 mmol) was added a solution of [[(2,2,2-trichloroethyl)oxy]carbonyl]-L-prolinyl chloride **28**[43] (321 mg, 1.05 mmol) in CH_2Cl_2 (40 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 0.5 h and at rt for 2 h. The mixture was diluted with CH_2Cl_2 and washed with a 15% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (K_2CO_3). The solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 2/1) to provide **29** (412 mg, 84%) as an amorphous powder: IR (NaCl) 2980, 1728, 1365, 1325, 1165, 1130 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.11 (t, 3 H, *J* = 7.1 Hz), 1.63 (s, 9 H), 1.64 (s, 3 H), 1.70 (s, 3 H), 1.75−2.30 (m, 6 H), 3.08 (d, 2 H, *J* = 6.3 Hz), 3.45 (s, br, 2 H), 3.62 (d, 2 H, *J* = 5.3 Hz), 3.82 (s, 3 H), 4.05 (q, 2 H, *J* = 7.1 Hz), 4.25 (t, 1 H, *J* = 7.2 Hz), 4.69 (s, br, 2 H), 5.12 (s, br 1 H), 6.81 (dd, 1 H, *J* = 2.3 and 8.6 Hz), 7.31 (d, 1 H, *J* = 8.6 Hz), 7.65 (d, 1 H, *J* = 2.1 Hz); MS (CI, CH_4) *m/e* (relative intensity) 704 (M + 1, 5), 604 (32), 528 (63), 428 (100), 228 (55), 115 (86). Anal. Calcd for $C_{32}H_{42}N_3O_8Cl_3$: C, 54.67; H, 6.02; N 5.98. Found: C, 54.44; H, 6.16; N, 5.60.

Tryprostatin A (11). A solution of indoloproline **29** (100 mg, 0.14 mmol) and activated Zn dust (93 mg, 1.42 mmol) in dry MeOH (10 mL) was heated at reflux under nitrogen for 2 h. The solvent was removed under reduced pressure. The residue was passed through a wash column (silica gel, $CHCl_3$/MeOH 95/5) and used directly. The dipeptide **30** was heated (neat) at 160−180 °C for 45 min. The residue was purified by flash chromatography (silica gel, $CHCl_3$/MeOH 95/5) to afford tryprostatin A **11** (25 mg) as a solid in 50% yield. **11**: $[\alpha]^{27}_D$ = − 65.9 (*c* = 0.97, in $CHCl_3$) {lit.[38] $[\alpha]^{27}_D$ = −69.7 (*c* = 0.70, in $CHCl_3$)}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.73 (s, 3 H), 1.76 (s, 3 H), 1.85−2.07 (m, 3 H), 2.27−2.34 (m, 1 H), 2.89 (dd, 1 H, *J* = 11.4 and 15.0 Hz), 3.41 (d, 2 H, *J* = 7.2 Hz), 3.53−3.72 (m, 3 H), 3.81 (s, 3 H), 4.05 (dd, 1 H, *J* = 6.9 and 7.7 Hz), 4.32 (dd, 1 H, *J* = 2.7 and 11.1 Hz), 5.28 (dd, 1 H, *J* = 5.8 and 8.6 Hz), 5.61 (s, 1 H), 6.74 (dd, 1 H, *J* = 2.2 and 8.6 Hz), 6.81 (d, 1 H, *J* = 2.1 Hz), 7.32 (d, 1 H, *J* = 8.6 Hz), 7.80 (s, br, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 17.9, 22.6, 25.1, 25.8, 25.7, 28.3, 45.4, 54.6, 55.7, 59.2, 94.9, 104.4, 109.3, 118.3, 120.0, 122.3, 135.1, 136.3, 156.3, 165.8, 169.4; MS (EI) *m/e* (relative intensity) 381 (M^+, 4), 228 (100), 212 (14), 198 (9); MS (CI, CH_4) *m/e* (relative intensity) 382 (M + 1, 100), 228 (8); exact mass calcd for $C_{22}H_{27}N_3O_3$ 381.2052, found 381.2044. The spectral data for **11** were identical with that reported by Osada et al.[38]

(3*S*,6*R*)-3-[(6-Methoxy-2-bromo-3-indolyl)methyl]-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (31). To a solution of potassium *tert*-butoxide (0.65 g, 5.8 mmol) in dry diethyl ether (10 mL) at 0 °C was added water (26 mg, 1.44 mmol).[44] The mixture was kept at 0 °C for 5 min and treated with a solution of the pyrazine **24a** (300 mg, 0.55 mmol) in dry diethyl ether (8 mL). The solution which resulted was allowed to warm to rt and stirred for 1.5 h. Water (10 mL) was added to quench the reaction. The aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (20 mL) and dried (K_2CO_3). After removal of solvent under reduced pressure, the crude product **31** was obtained (208 mg, 85%) via a wash column (silica gel, EtOAc/hexane = 9:1) and used in the next step without further purification. **31**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.60 (d, 3 H, *J* = 6.8 Hz), 0.91 (d, 3 H, *J* = 6.9 Hz), 1.19 (t, 3 H, *J* = 7.1 Hz), 1.30 (t, 3 H, *J* = 7.1 Hz), 2.05−2.20 (m, 1 H), 3.04 (dd, 1 H, *J* = 6.5 and 14.1 Hz), 3.22 (dd, 1 H, *J* = 4.4 and 14.1 Hz), 3.37 (t, 1 H, *J* = 3.3 Hz), 3.79 (s, 3 H), 3.98−4.33 (m, 5 H), 6.60−6.70 (m, 2 H), 7.40 (d, 1 H, *J* = 8.7 Hz), 7.84 (s, br, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.4, 16.5, 19.1, 20.6, 30.2, 31.1, 55.6, 56.5, 60.2, 60.5, 60.7, 93.9, 107.0, 109.3, 112.2, 119.9, 122.8, 136.5, 156.3, 162.6, 163.5; MS (CI, CH_4) *m/e* (relative intensity) 450 (M + 1, 100), 452 (M + 1, 98).

L-6-Methoxy-2-bromotryptophan Ethyl Ester (32). To a solution of the pyrazine **31** (100 mg, 0.222 mmol) in THF (10 mL) was added an aqueous solution of 2 N HCl (10 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 2 h. The solution was concentrated under reduced pressure and then diluted with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was separated by flash chromatography to provide **32** (70 mg, 92%). **32**: IR (NaCl) 3360, 2930, 1730, 1625 cm^{-1}; $[\alpha]^{27}_D$ = +11.1 (*c* = 0.7, in $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.20 (t, 3 H, *J* = 7.2 Hz), 2.18 (s, br, 2 H), 2.94 (dd, 1 H, *J* = 8.2 and 14.3 Hz), 3.17 (dd, 1 H, *J* = 5.2 and 14.3 Hz), 3.77 (s, 3 H), 3.83 (dd, 1 H, *J* = 5.3 and 8.2 Hz), 4.13 (q, 2 H, *J* = 7.1 Hz), 6.68 (d, 1 H, *J* = 2.0 Hz), 6.73 (dd, 1 H, *J* = 2.1 and 8.7 Hz), 7.37 (d, 1 H, *J* = 8.7 Hz), 8.55 (s, br, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.1, 31.0, 54.9, 55.7, 61.1, 94.3, 107.0, 109.9, 111.2, 118.9, 122.2, 136.8, 156.7, 175.1; MS (CI, CH_4) *m/e* (relative intensity) 341 (M + 1, 24), 343 (M + 1, 22).

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