Regiospecific Bromination of 3-Methylindoles with NBS and Its Application to the Concise Synthesis of Optically Active Unusual Tryptophans Present in Marine Cyclic Peptides[1]

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A regiospecific bromination of substituted 3-methylindoles at either the C(3) alkyl moiety or the C(2) position was achieved *via* a free radical bromination or electrophilic process, respectively. The regiospecificity of the bromination could be controlled by variation of both the substituent and the N(1) protecting group on the indole ring. In addition, enantiospecific syntheses of 5-methoxytryptophan (**20**) and 5-hydroxy-6-chlorotryptophan (**21c**) as well as concise syntheses of optically active 2-bromotryptophan ethyl esters **26a**,**b** or their substituted derivatives in three steps from bifunctional dibromoindoles were achieved *via* the above regiospecific process.

Peptides comprise one of the five major groups of natural products and are classified as alkaloids.[2−9] Recently many cyclic peptides have been isolated from marine microorganisms such as the Okinawan marine sponge *Theonella* sp.[4] The 2-bromotryptophans were found to be constituents of a number of these cyclic peptides,[5−9] and representatives of this family are shown in Figure 1. Konbamide (**1**) has been shown to antagonize the effects of calmodulin in calmodulin-activated brain phosphodiesterase with an IC_{50} of 1×10^{-4} mol/dm^3.[7] It is well-known that calmodulin,[10] a Ca^{2+}-binding protein, regulates many cellular functions as a key mediator of signal transduction in mammalian cells. Furthermore, the related orbiculamide A (**2a**) was found to be cytotoxic against P388 murine leukemia cells (IC_{50} 4.7 μg/mL).[6] Keramamides B−D (**3**−**5**) have been shown to be potent inhibitors of the generation of the superoxide response of human neutrophiles elicited with fMLP,[8] while keramamide E (**6**) exhibited cytotoxic activity against L1210 murine leukemia cells (IC_{50} 1.60 μg/mL) and KB human epidermoid carcinoma cells (IC_{50} 1.55 μg/mL).[9] Keramamide H (**7**) exhibited weak cytotoxicity against the two types of cells mentioned in the preceding sentence (IC_{50} ∼10 μg/mL).[9] On the other hand, jaspamide (**8**),[5,11] a marine cyclodepsipeptide, has been found to possess antifungal, antihelminthic, insecticidal, and ichthyotoxic activity. All of these marine cyclic peptides contain a 2-bromotryptophan unit (see **8**) while most of them contain a 2-bromo-5-hydroxytryptophan. In contrast, the unusual 5-hydroxy-6-chlorotryptophan was found to be a constituent of keramamide A (**9**),[12] and this peptide exhibited inhibitory activity against sarcoplasmic reticulum Ca^{2+}-ATPase (IC_{50} 3×10^{-4} mol/dm^3). The presence of the unusual tryptophan amino acids in these cyclic peptides and their biological profiles[4−6,9,11,13] rendered these indoles attractive targets for synthesis capable of extension for SAR studies. The optically active substituted tryptophans or derivatives described below are important units for the synthesis of these cyclic peptides as well as serving as building blocks for the total synthesis of indole alkaloids such as 19,20-dehydro-10-methoxytalcarpine and sarpagine. The total syntheses of a number of *Alstonia* alkaloids (from D-tryptophan)[14−16] has been reported, consequently the enantiospecific synthesis of ring-A alkoxylated tryptophans would provide useful building blocks to prepare the sarpagine alkaloids.[17,18]

In 1995, Ashworth *et al.* reported the first total synthesis of jaspamide (**8**).[19] During the course of the preparation of this paper, Schmidt and Weinbrenner reported the syntheses of two isomers of konbamide (**1**).[20] Previous syntheses[20−24] of optically active 2-bromotryptophans relied on the bromination of multiprotected tryptophans using brominating agents such as NBS and pyridinium bromide perbromide. These methods gener-

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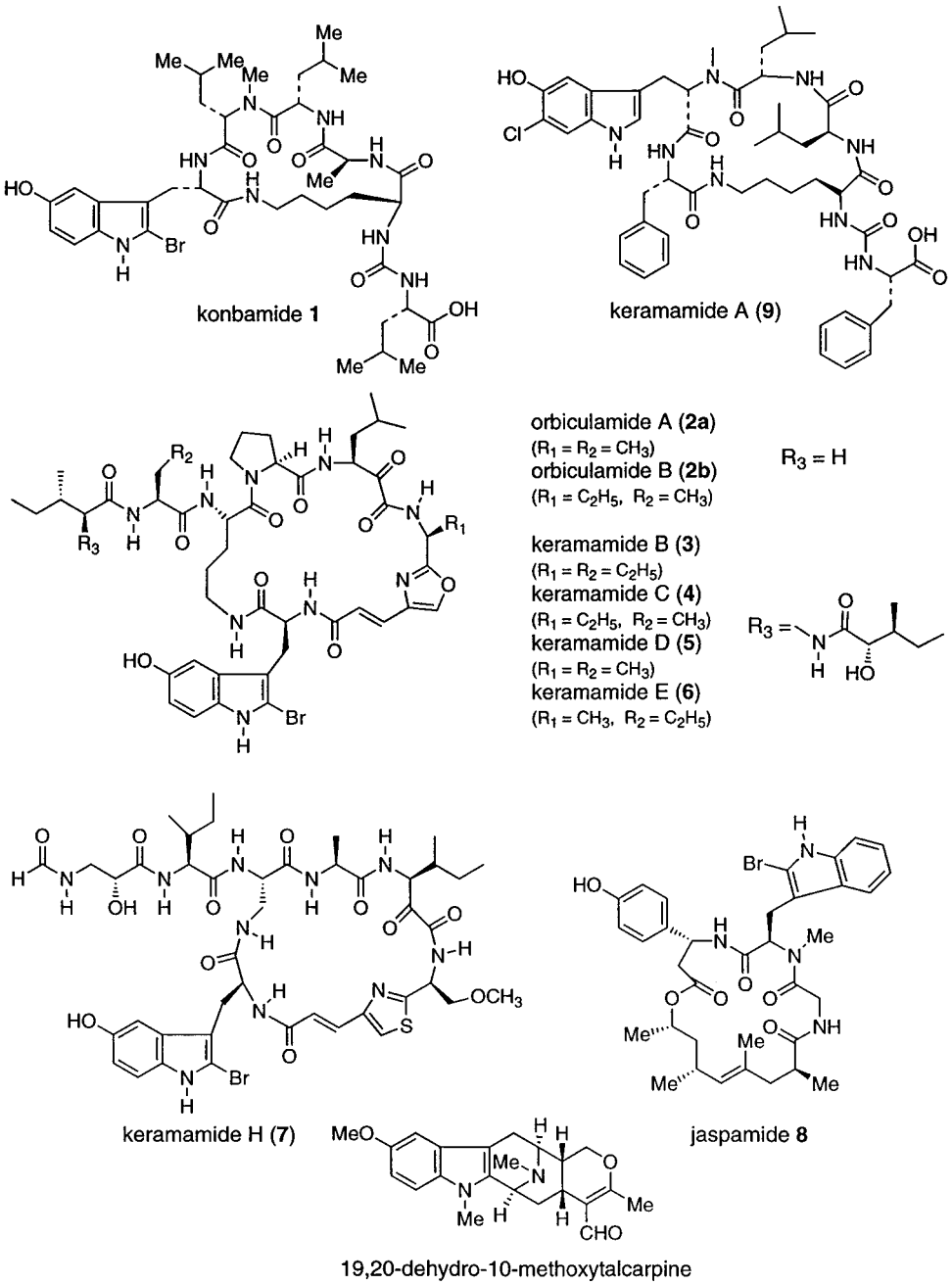

Figure 1.

ally suffer from the inability to provide the desired hydroxy-substituted tryptophans in yields high enough for further transformation or provide entry into only one enantiomer. During research directed toward the total synthesis of indole alkaloids,[17,18] a regiospecific bromination procedure for 3-methylindoles was developed and provided a route to various optically active substituted tryptophans. This approach employed the Schöllkopf chiral auxiliary, the synthesis of which can be scaled up to the 500 g level and provides entry into either enantiomer.[25,26] The regiospecific bromination of various substituted 3-methylindoles at either the C(3) alkyl moiety or the C(2) position as well as the synthesis of 2-bromotryptophans from bifunctional dibromoindoles **22a**,**b** prepared *via* this regiospecific bromination process is described below.

When N(1)-protected 5- or 6-methoxy-3-methylindoles were stirred with NBS under free radical conditions (benzoyl peroxide), electrophilic attack at the C(2) position and free radical bromination of the 3-methyl group were found to be competing processes which afforded the 3-(bromomethyl)indoles accompanied by some of the 2-bromo-3-methylindole regioisomer. The competition between electrophilic and free radical bromination is well recognized[27,28] in methyl-substituted anisoles when they are treated with NBS. To the best of our knowledge, the related competing bromination of (N_a-) protected 3-methylindoles has not been studied previously.

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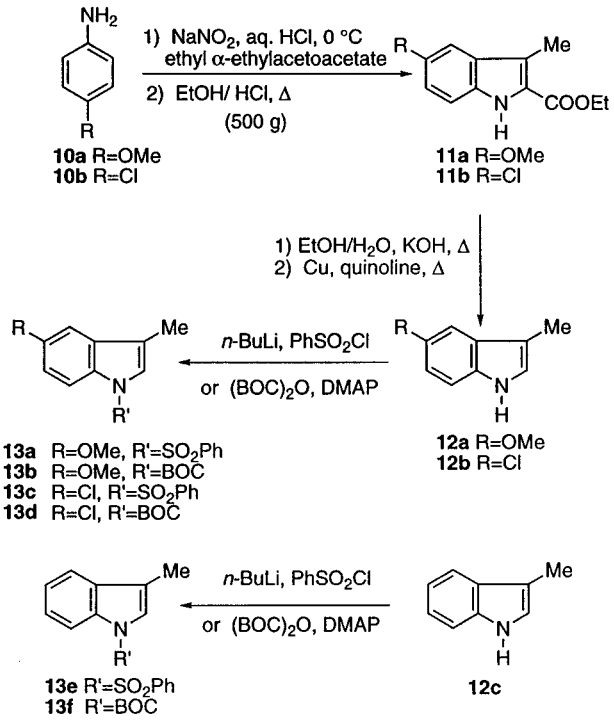
Scheme 1



The efficient synthesis of 3-methylindoles on multihundred-gram scale is illustrated in Schemes 1 and 2. Ethyl 3-methylindole-2-carboxylates **11a** and **11b** were prepared from the proper aniline **10** and ethyl α-ethylacetoacetate by the Fischer indole cyclization *via* a Japp−Klingmann azo−ester intermediate. This process has been fully explored by Abramovitch and Shapiro as well as reviewed.[29] Alkaline hydrolysis of the ester functions and subsequent copper/quinoline-mediated decarboxylation of the corresponding carboxylic acids which resulted afforded the 3-methylindoles **12a** and **12b**, respectively, in excellent yield. The protection of the 3-methylindoles with either di-*tert*-butyl dicarbonate or benzenesulfonyl chloride furnished the protected 3-methylindoles represented by **13a**−**d**.

With the N(1)-protected 3-methylindoles **13a**,**b** in hand, the bromination of 3-methylindoles with NBS was carried out under two sets of conditions (Scheme 3). In the electrophilic bromination process, 3-methylindoles **13a**,**b** were simply heated with NBS in refluxing carbon tetrachloride in the absence of the radical initiator AIBN to provide **14a**,**b**, respectively. In the radical bromination process, the 3-methylindoles were heated in refluxing CCl_4 and then treated with NBS and AIBN to afford **15a**,**b**, respectively (see Table 1). The AIBN was added in portions to the refluxing carbon tetrachloride solution over time.

On the other hand, as shown in Scheme 4, treatment of **13c**−**f** with NBS in the presence or absence of the radical initiator (AIBN) at reflux in CCl_4 afforded only the corresponding regioisomeric 3-(bromomethyl)indoles **14c**−**f** and in excellent yield (Table 2). The free radical reaction at the 3-methyl moiety of indoles **13c**−**f** was not surprising since the N(1) protecting group deactivated the indole core and permitted the radical bromination process as the principal pathway. A similar bromination has been previously observed in the formation of 1-(benzenesulfonyl)-5-bromo-3-(bromomethyl)indole.[30] In addition, Cugnon de Sevricourt *et al.* reported the bromination of 3-methylbenzofuran at either the 2-position or the 3-methyl position.[31]

However, when the parent (N_a-H) 3-methylindoles such as **12a** and **12c** were subjected to the above AIBN-mediated radical bromination process, bromination at the 3-methyl group was not observed (Scheme 5). Instead, electrophilic bromination took place at C(2) to provide only 2-bromo-3-methylindoles **15h** and **15i**, respectively (Table 3). These results illustrate that bromination of 3-methylindole at the 3-methyl group requires the deactivation of the indole core by an electron-withdrawing group (N_a) to prevent bromination at C(2). In the absence of deactivation at the N(1) position, the unprotected 3-methylindoles remain electron rich, promoting the electrophilic bromination at the C(2) position and dominating the bromination process to afford only attack at C(2).

Although the presence of an electron-withdrawing group at the N(1) position of **13a**,**b** retarded reaction at the C(2) position, the electrophilic bromination of indoles **13a**,**b** occurred readily at C(2) when they were stirred with NBS in the absence of a radical initiator (Scheme 3). In the case of **13a**,**b**, two contrasting factors were involved in the electrophilic *vs* free radical process. Even though indoles are reactive aromatic systems,[32] the presence of an electron-withdrawing group at the N(1) position would be expected to deactivate them to electrophilic attack. However, since the methoxyl group has been employed to promote the electrophilic bromination of methyl-substituted anisoles,[27] presumably it plays the same role in the bromination of indoles **13a**,**b** at the C(2) position. Consequently, deactivation of the indole 2,3-double bond by the N(1) protecting group and activation by the methoxyl group at the C(6) position of indoles **13a**,**b** are delicately balanced. A slight change in reaction conditions in the bromination process promotes the reaction in the direction of either the electrophilic or free radical bromination process. Moreover when indoles **13c**−**f**, which are devoid of a 5-methoxyl group, were treated with NBS in the absence of AIBN, only 3-(bromomethyl)indoles **14c**−**f** were observed (Scheme 4). The presence of the N(1) deactivating group and the absence of a methoxyl group promotes bromination of the 3-methylindole carbon rather than attack at C(2). Presumably, the radical bromination of **13c**−**f** to provide **14c**−**f** in the absence of AIBN was initiated by heat or light.

Clearly, the results demonstrated that the regiospecific bromination of 3-methyl-5-methoxyindoles can be controlled by judicious choice of the reaction conditions and the choice of the protecting group at the N(1) position. In the presence of an activating group on ring-A such as a methoxyl moiety, the protection of indoles at the N(1) position should be accomplished before the bromination is carried out. The 3-methylindoles protected in this fashion (e.g., **13a**,**b**) should lead to either 3-(bromomethyl)indoles or 2-bromo-3-methylindoles on the basis of the choice of the reaction conditions (free radical *vs* electrophilic). In the absence of ring-A oxygenated activating groups, free radical bromination at the 3-methyl group should be facilitated by the electron-withdrawing group

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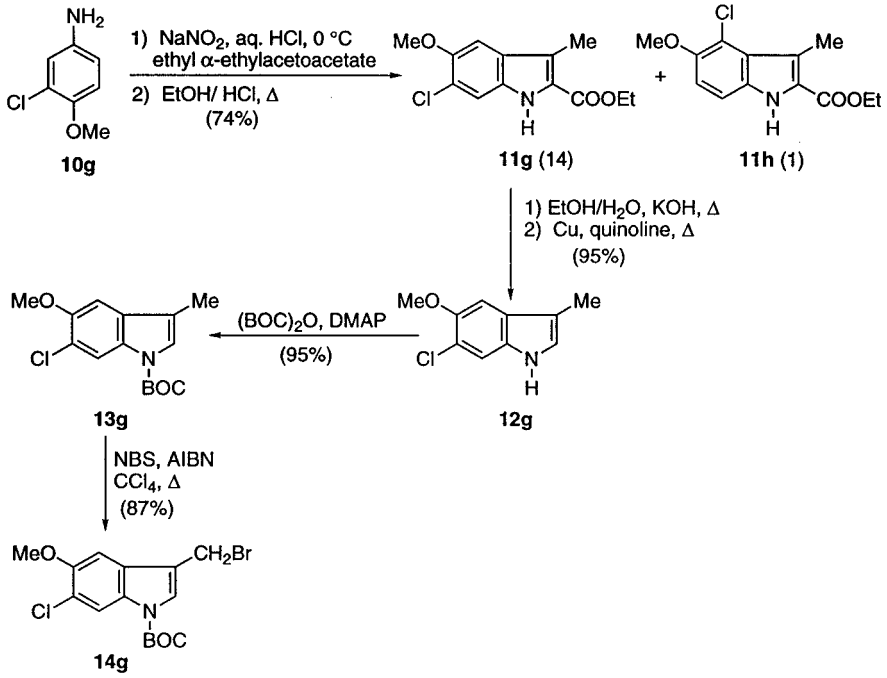
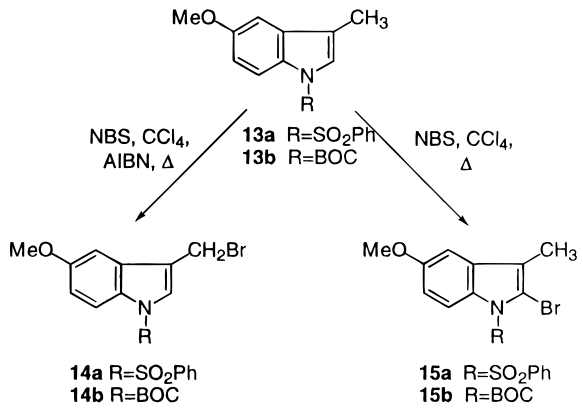
Scheme 2



Scheme 3



Scheme 4

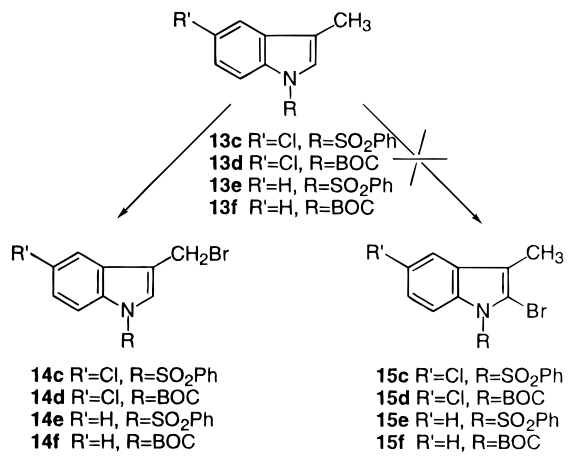


Table 1. Bromination of Deactivated 5-Methoxyindoles by NBS

compd	R	reaction conditions (initiator, time)	product (yield, %)	melting point (°C)
13a	$SO_2C_6H_5$	AIBN, 2 h	**14a** (83)	116−118
13a	$SO_2C_6H_5$	none, 3 h	**15a** (86)	148−150
13b	BOC	AIBN, 1 h	**14b** (92)	*a*
13b	BOC	none, 2 h	**15b** (95)	82−84

[a] **14b** was converted into 3-(hydroxymethyl)indole (mp 144−146 °C) and was thus characterized.

Table 2. Bromination of Deactivated Indoles by NBS

compd	R	R′	reaction conditions (initiator, time)	product (yield, %)	melting point (°C)
13c	$SO_2C_6H_5$	5-Cl	AIBN, 2 h	**14c** (93)	139−142
13c	$SO_2C_6H_5$	5-Cl	none, 10 h	**14c** (90)	139−142
13d	BOC	5-Cl	AIBN, 2 h	**14d** (91)	100−102
13d	BOC	5-Cl	none, 9 h	**14d** (89)	100−102
13e	$SO_2C_6H_5$	H	AIBN, 3 h	**14e** (94)	132−134
13e	$SO_2C_6H_5$	H	none, 10 h	**14e** (92)	132−134
13f	BOC	H	AIBN, 2 h	**14f** (95)	106−107
13f	BOC	H	none, 10 h	**14f** (92)	106−107

at the N(1) position of the 3-methylindole. On the other hand, in order to brominate 3-methylindoles at the C(2) position even when they lack the ring-A activating substituent, the bromination should proceed before the (N_a-) protection sequence is executed.

The 5-methoxytryptophan (**20**) and 5-hydroxy-6-chlorotryptophan (**21c**) were chosen as initial synthetic targets for the regiospecific bromination/Schöllkopf protocol (Schemes 6 and 7). When 3-(bromomethyl)indoles **14a** (Scheme 6) and **14g** (Scheme 7) were treated (individually) with the anion of the Schöllkopf chiral auxiliary, only the desired *trans* diastereomers **16** and **17**, respectively, were obtained. The acidic hydrolysis of the chiral auxiliary furnished the protected tryptophan ethyl esters **18** (Scheme 6) and **19** (Scheme 7), respectively. The careful hydrolysis of tryptophan ester **19** with varying amounts of boron tribromide afforded the various optically active 6-chloro-5-hydroxytryptophan derivatives **21a**−**c** regiospecifically, which can be used for the total synthesis of keramamide A (**9**). The optical purity of esters **21a** and **21b** was determined using Eu(hfbc)$_3$, an optically active NMR chiral shift reagent which imparts a different chemical shift pattern to each enantiomer; an approximate 3:1 molar ratio of ligand to shift reagent was optimal. This method was validated with racemic material as well as spiked (±)-material. In an NMR doping

Scheme 5

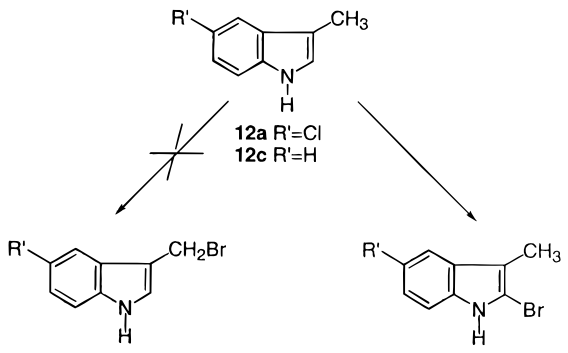
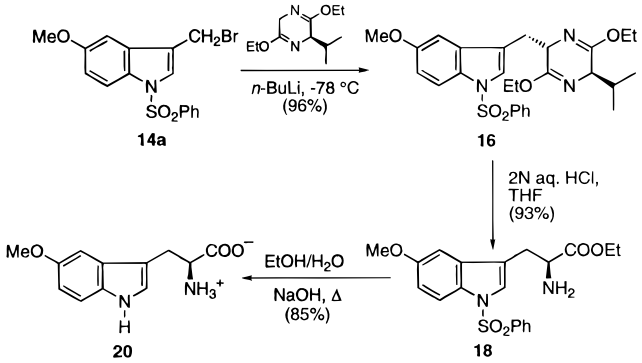


Table 3. Bromination of Indoles by NBS

compd	R′	reaction conditions (initiator, time)	product (yield, %)	melting point (°C)
12a	5-Cl	AIBN, 1 h	**15h** (87)	96−98
12a	5-Cl	none, 1 h	**15h** (98)	96−98
12c	H	AIBN, 1 h	**15i** (92)	91−93
12c	H	none, 3 h	**15i** (97)	91−93

Scheme 6



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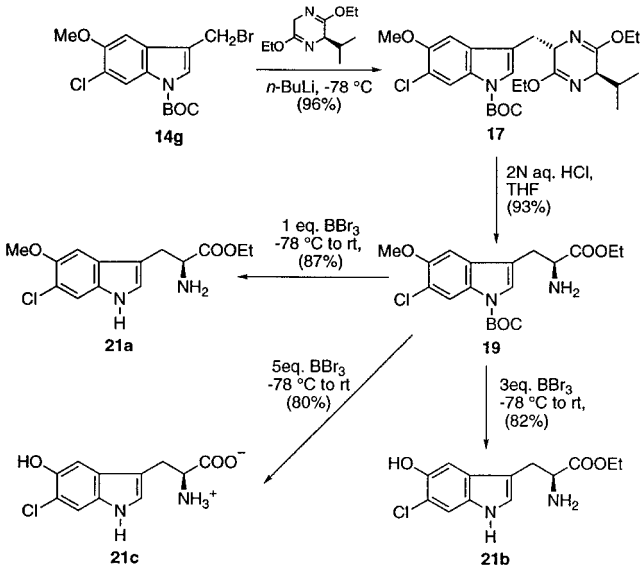
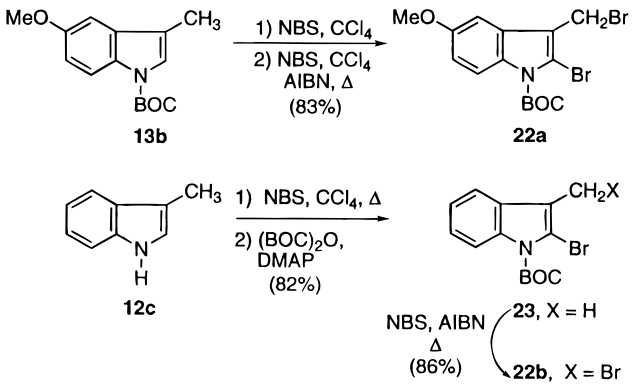


experiment addition of 2% of the enantiomer to **21a** or **21b** resulted now in observation of this minor isomer; consequently **21a** and **21b** were determined to be at least 98% ee. The removal of the benzenesulfonyl group from **18** (Scheme 6) was readily carried out under basic conditions to furnish the optically pure 5-methoxytryptophan (**20**). The optical rotation of compound **20** was virtually identical to the literature value.[33] Both the (+)- and (−)-enantiomers of these amino acids were prepared in optically pure form by varying the Schöllkopf chiral auxiliary.[25,26] The D-series can be prepared from L-valine while the L-series originates from D-valine. In addition, the Schöllkopf auxiliary can be prepared on 400−500 g scale with ease in either enantiomeric form.[34]

Scheme 8



The 2-bromo-3-(bromomethyl)indoles appeared to be reasonable starting materials for the synthesis of the unusual 2-bromotryptophans present in the marine natural products illustrated in Figure 1. The bromination of the BOC-protected 5-methoxy-3-methylindole **13b** was initially carried out with 2 equiv of NBS to facilitate bromination at the 2-position *via* electrophilic substitution. This was to be followed by reaction at the 3-methyl position *via* the free radical process by the addition of AIBN at a latter stage. Unfortunately, with **13b** it was found that bromination took place rapidly at the 2-position but was followed by bromination at the 4- and 6-positions. Two tribromoindoles, 1-BOC-2,4-dibromo-3-(bromomethyl)-5-methoxyindole and 1-BOC-2,6-dibromo-3-(bromomethyl)-5-methoxyindole were isolated and then identified by ^{1}H NMR and mass spectroscopy. Further experiments established that the desired dibromoindole **22a** was best prepared by heating the mixture of indole **13b** with 1 equiv of NBS followed by addition of another equivalent of NBS as an admixture with AIBN (Scheme 8). In this manner the regiocontrolled dibromination was achieved in good yield. On the other hand, for jaspamide (**8**), bromination of the unsubstituted 3-methylindole **12c** at the 2-position was required before BOC protection at the (N_a-) position, as noted previously. Consequently, the indole **12c** was converted into indole **23** by electrophilic bromination at the 2-position with NBS, followed by protection with the BOC group at the (N_a-) position. The free radical bromination of BOC-protected indole **23** at the 3-methyl moiety then furnished the desired dibromoindole **22b**, as shown in Scheme 8.

With the key dibromoindoles **22a**,**b** in hand, the synthesis of the 2-bromotryptophans **26a**−**c** was readily executed, as illustrated in Scheme 9. Briefly, dibromoindole **22a** or **22b** was treated with the anion of the Schöllkopf chiral auxiliary to provide a mixture of diastereomers **24a**:**24b** or **24c**:**24d** in a ratio of approximately 92:8, respectively. Interestingly, the alkylation of the Schöllkopf chiral auxiliary with a 3-(bromometh-

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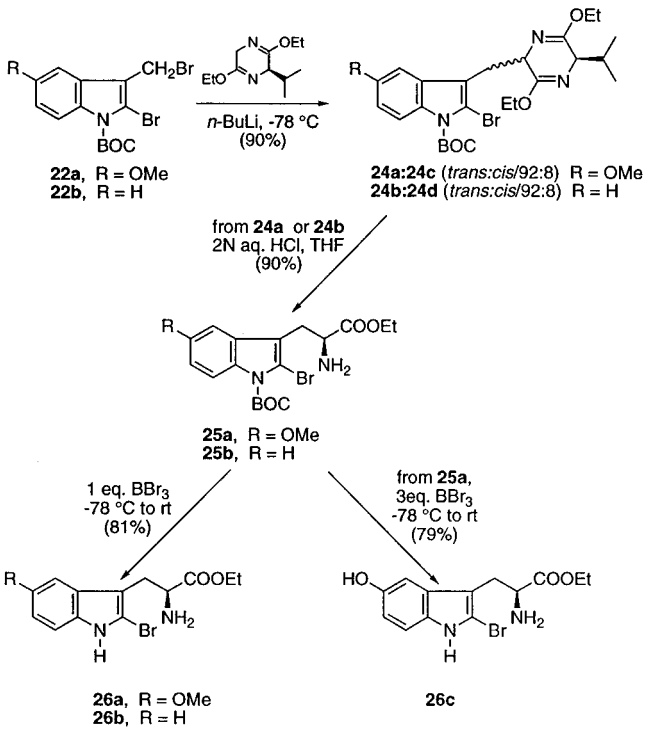
Scheme 9



yl)indole in the indole-2(H) series proceeded in enantiospecific fashion. No minor diastereomer was detected in contrast to the results with **22a**,**b** observed here. The desired *trans* diastereomer **24a** or **24b** was easily separated from **24c** or **24d** by flash chromatography (silica gel) and hydrolyzed under acidic conditions to furnish the L(+)-1-BOC-2-bromo-5-methoxytryptophan ethyl esters **25a** or **25b**, respectively, in high yield (Scheme 9). The D-valine ethyl ester which results from hydrolysis of the chiral auxiliary was readily recovered by Kugelrohr distillation. It was employed later to prepare more of the Schöllkopf chiral auxiliary. The BOC-protected tryptophan ethyl esters **25a** or **25b** were (individually) readily converted into the 2-bromotryptophans **26a**, **26b**, or **26c** when treated with varying amounts of boron tribromide as shown in Scheme 9 (see Experimental Section for details).

In summary, the regiospecific bromination of 3-methylindoles at either the C(2) position or the C(3) alkyl moiety has been developed. This process was employed for the enantiospecific syntheses of (+)- or (−)-5-methoxytryptophan **20** and 5-hydroxy-6-chlorotryptophan **21c** as well as for the facile synthesis of the optically active 2-bromotryptophans from the dibromoindole building blocks. These unusual tryptophan amino acids or amino esters can be used for the synthesis of the biologically active marine cyclic peptides represented in Figure 1. In addition, the bromoindoles should be useful in vinylation, acetylation, and arylation reactions *via* transition metal catalysts and provide versatile building blocks for the synthesis of ring-A alkoxylated indole alkaloids.[17,18]

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus or an Electrothermal Model IA8100 digital melting point apparatus and are reported uncorrected. The ^{1}H NMR spectra were recorded on a Bruker 250-MHz multiple-probe instrument or a GE 500-MHz spectrometer. Infrared spectra were recorded on a Nicolet Dx FTIR DX V5.07 spectrometer or a Mattson Polaris IR-10400 instrument. Low-resolution mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5985 B GC−mass spectrometer. High-resolution mass spectral data were taken on a VG auto spectrometer (double-focusing high-resolution GC/mass spectrometer, U.K.). Optical rotations were measured on a JASCO DIP-370 polarimeter. Microanalyses were performed on a Perkin-Elmer 240C carbon, hydrogen, and nitrogen analyzer. 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. All chemicals were purchased from Aldrich Chemical Co. unless otherwise indicated. Experiments with the Schöllkopf chiral auxillary on large scale have been reported elsewhere.[34]

Ethyl 5-Chloro-3-methylindole-2-carboxylate (11b).[25,29] To a mixture of 4-chloroaniline (50 g, 0.32 mol), concd aqueous HCl (80 mL), and water (140 mL) was added dropwise a solution of $NaNO_2$ (24.7 g, 0.35 mol) in 30 mL of water 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 (21 g, 0.27 mol). In a separate flask, a solution of ethyl α-ethylacetoacetate (57.4 g, 0.35 mol) in ethanol (250 mL) at 0 °C was treated with an aqueous solution of KOH (0.35 mol in 30 mL of H_2O), followed by addition of ice (400 g). The diazonium salt prepared above was immediately added to this alkaline solution. The mixture was then adjusted to pH 5−6 and stirred at 0 °C for 3 h. After the solution was kept for a further 12 h at 4 °C, the mixture was extracted with ethyl acetate (4 × 100 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 was added dropwise to a solution of 14.5% ethanolic HCl at 78 °C (or polyphosphoric acid at 120 °C). This reaction is exothermic, and the oil is added carefully to the solution of ethanolic hydrogen chloride. After addition, the mixture was held at 78 °C for 2 h. The solvent was removed under reduced pressure, and the residue was treated with water (100 mL) and CH_2Cl_2 (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with brine and dried (Na_2SO_4). Purification of the residue on a short wash column (silica gel, ethyl acetate/hexane, 1:3) gave the ester **11b** as a white solid (63 g, 74%): mp 162−163 °C; IR (KBr) 3337, 1669, 1452 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.42 (t, 3H, J = 7 Hz), 2.55 (s, 3H), 4.40 (q, 2H, J = 7 Hz), 7.23 (m, 2H), 7.61 (s, 1H), 8.67 (s, 1H); MS (EI) m/e (relative intensity) 239 (M^+, 39), 237 (M^+, 80), 191 (100), 163 (35), 128 (37), 101 (20). Anal. Calcd for $C_{12}H_{12}NO_2Cl$: C, 60.64; H, 5.09; N 5.89. Found: C, 60.77; H, 5.34; N, 5.67.

Ethyl 6-Chloro-5-methoxy-3-methylindole-2-carboxylate (11g). The indole **11g** was prepared in 72% yield from 3-chloro-*p*-anisidine (**10g**) following the procedure described above for the preparation of **11b**. The regioisomer ethyl 4-chloro-5-methoxy-3-methylindole-2-carboxylate (**11h**) was obtained as a minor product. The ratio of **11g** and **11h** was determined to be 14:1 by intergration of the ^{1}H NMR spectrum of the mixture. **11g**: mp 187.7−188.5 °C; IR (KBr) 3330, 2935, 1662, 1538 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.41 (t, 3H, J = 7.1 Hz), 2.55 (s, 3H), 3.94 (s, 3H), 4.40 (q, 2H, J = 7.1 Hz), 7.04 (s, 1H), 7.38 (s, 1H), 8.62 (s, 1H); MS (EI) m/e (relative intensity) 269 (M^+, 34), 267 (M^+, 65), 221 (100), 206 (35), 178 (20), 150 (20). Anal. Calcd for $C_{13}H_{14}NO_3Cl$: C, 58.32; H, 5.27; N 5.23. Found: C, 58.28; H, 5.30; N, 5.12. **11h**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.41 (t, 3H, J = 7.1 Hz), 2.87 (s, 3H), 3.91 (s, 3H), 4.40 (q, 2H, J = 7.1 Hz), 7.05 (d, 1H, J = 8.0 Hz), 7.19 (d, 1H, J = 8.0 Hz); MS (EI) m/e (relative intensity) 269 (M^+, 34), 267 (M^+, 65).

5-Chloro-3-methylindole (12b). A mixture of ethyl 5-chloro-3-methylindole-2-carboxylate **11b** (59.2 g, 0.25 mol), EtOH (150 mL), KOH pellets (85%, 49 g, 0.75 mol), and water (100 mL) was heated to reflux for 1 h. The volume was reduced to 30 mL under reduced pressure and brought to acidic pH 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 5-chloro-3-methylindole-2-carboxylic acid as a white solid (51 g, 99%). This acid (21 g, 0.1 mol) was then heated to reflux in a well-

stirred mixture of distilled quinoline (50 mL) and copper powder (0.8 g) under nitrogen for 2.5 h. The copper powder was removed by filtration, after which the filtrate was brought to pH 2−3 at 0 °C with an aqueous solution of 6 N HCl. 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 5-chloro-3-methylindole **12b** as a brown solid (15.1 g, 94%): mp 112−114 °C (lit.[35] mp 114−116 °C); IR (KBr) 2978, 1457 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.21 (s, 3H), 7.11 (d, 1H, J =2 Hz), 7.15 (d, 1H, J = 2 Hz), 7.20 (s, 1H), 7.45 (s, 1H), 8.05 (s, 1H); MS (EI) *m/e* (relative intensity) 167 (M^+, 57), 165 (M^+, 92), 154 (53), 129 (40), 102 (28), 65 (30); HRMS for C_9H_8NCl calcd 165.0345; found: 165.0357.

6-Chloro-5-methoxy-3-methylindole (12g) was prepared in 95% yield following the procedure described for the preparation of **12b**. **12g**: IR (KBr) 2935, 867, 717 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.95 (s, 3H), 6.94 (s, 1H), 7.01 (s, 1H), 7.36 (s, 1H), 7.75 (s, 1H); MS (EI) *m/e* (relative intensity) 197 (M^+, 32), 195 (M^+, 94), 182 (33), 180 (100), 152 (89), 117 (23), 89 (33). Anal. Calcd for $C_{10}H_{10}NOCl$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.54; H, 5.04; N, 6.98.

1-(Benzenesulfonyl)-3-methylindole (13e). To a solution of skatole (**12c**) (1.31 g, 10 mmol) in THF (50 mL) was added *n*-BuLi (2.5 M, 4.4 mL, 11 mmol in hexane) at −78 °C under nitrogen. The white suspension which resulted was kept at −78 °C for 15 min and slowly warmed to rt. After 2 h at rt, the mixture was cooled to −78 °C and treated with benzenesulfonyl chloride (1.40 mL, 11 mmol). After 20 min at −78 °C, the reaction solution was slowly warmed to rt, stirred overnight, and treated with a saturated aqueous solution of NH_4Cl (5 mL). The solvent was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 (30 mL). The organic layer was separated, washed with brine (20 mL), and dried (Na_2SO_4). After removal of solvent under reduced pressure, the residue was purified by flash chromatography (silica gel, hexane/ethyl acetate, 8/1) to afford **13e** as an off-white solid (2.54 g, 94%): mp 126−127 °C. ^1H NMR (250 MHz, $CDCl_3$) δ 2.24 (s, 3H), 7.2−7.55 (m, 7H), 7.86 (dd, 2H, J = 9.0 and 1.6 Hz), 8.01 (d, 1H, J = 8.0 Hz); MS (EI) *m/e* (relative intensity) 271 (M^+, 14.3), 130 (100.0). Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.42; H, 4.80; N 5.17. Found: C, 66.77; H, 4.87; N, 5.10.

1-(Benzenesulfonyl)-5-chloro-3-methylindole (13c) was prepared in 90% yield following the procedure for the preparation of **13e**. **13c**: mp 140.9−142.2 °C; IR (KBr) 3448, 3111, 2920, 1446 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.20 (s, 3H), 7.30 (m, 2H), 7.32 (s, 1H), 7.40−7.55 (m, 3H), 7.80−7.90 (m, 3H); MS (EI) *m/e* (relative intensity) 307 (M^+, 11), 305 (M^+, 33), 166 (31), 164 (100), 128 (43), 102 (45). Anal. Calcd for $C_{15}H_{12}NSO_2Cl$: C, 59.00; H, 3.90; N, 4.60. Found: C, 58.88; H, 3.89; N, 4.49.

1-(*tert*-Butyloxycarbonyl)-5-methoxy-3-methylindole (13b). A solution of 5-methoxy-3-methylindole[26] (12.8 g, 79 mmol) in CH_3CN (100 mL) under nitrogen was treated at rt with di-*tert*-butyl dicarbonate (18.6 g, 83 mmol) and DMAP (0.5 g, 4 mmol). The mixture was stirred at rt for 12 h and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), washed with an aqueous solution of 1 N HCl (2 × 30 mL) and brine (50 mL), and dried (Na_2SO_4). After removal of solvent under reduced pressure, the residue solidified to afford **13b** as a white solid in 95% yield: mp 58−60 °C; IR (KBr) 2974, 1721, 1452 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.67 (s, 9H), 2.23 (s, 3H), 3.87 (s, 3H), 6.92 (dd, 1H, J = 8.5, 2.6 Hz), 7.25 (s, 1H), 7.33 (br, 1H), 7.98 (d, 1H, J = 8.4 Hz); MS (EI) *m/e* (relative intensity) 261 (M^+, 21.2), 205 (100.0), 161 (63.6), 146 (63.3). Anal. Calcd for $C_{15}H_{19}NO_3 \cdot {}^1/_4H_2O$: C, 67.92; H, 7.35; N 5.28. Found: C, 68.12; H, 7.17; N, 5.26.

1-(*tert*-Butyloxycarbonyl)-5-chloro-3-methylindole (13d) was prepared in 95% yield following the procedure for the preparation of **13b**. **13d**: a white solid; mp 91−92 °C; IR (KBr) 3436, 2976, 1728 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.67 (s, 9H), 2.23 (s, 3H), 7.25 (dd, 1H, J = 2 and 9 Hz), 7.35 (s, 1H), 7.45 (d, 1H, J = 2 Hz), 8.04 (d, 1H, J = 9 Hz); MS (EI) *m/e* (relative intensity) 267 (M^+, 8), 265 (M^+, 24), 209 (54), 164 (100), 128 (34), 101 (50); HRMS for $C_{14}H_{16}NO_2Cl$ calcd 265.0869, found 265.0868. Anal. Calcd for $C_{14}H_{16}NO_2Cl$: C, 63.39; H, 6.06; N, 5.28. Found: C, 63.33; H, 6.20; N, 5.08.

1-(*tert*-Butyloxycarbonyl)-3-methylindole (13f) was prepared in 93% yield following the procedure for the preparation of **13b**. **13f**: mp 106−107 °C; IR (KBr) 2990, 1715, 1386 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.67 (s, 9H), 2.28 (s, 3H), 7.25−7.38 (m, 3H), 7.51 (dd, J = 6.8, 1.7 Hz, 1H), 8.12 (d, J = 7.7 Hz, 1H); MS (EI) *m/e* (relative intensity) 231 (M^+, 30), 175 (75), 131 (72), 130 (100), 103 (10). This material was used directly in a later step (see below).

1-(*tert*-Butyloxycarbonyl)-6-chloro-5-methoxy-3-methylindole (13g) was prepared in 95% yield using the same procedure as that described above for the preparation of **13b**. **13g**: mp 126.8−132.1 °C; IR (KBr) 3426, 2973, 1729, 1475 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.63 (s, 9H), 2.22 (s, 3H), 3.94 (s, 3H), 6.92 (s, 1H), 7.30 (s, 1H), 8.15 (s, 1H); MS (EI) *m/e* (relative intensity) 297 (M^+, 25), 295 (M^+, 71), 239 (93), 195 (100), 180 (92), 152 (24); HRMS for $C_{15}H_{18}NO_3Cl$ calcd 295.0975, found 295.0969. Anal. Calcd for $C_{15}H_{18}NO_3Cl$: C, 61.02; H, 6.15; N 4.75. Found: C, 61.15; H, 6.13; N, 4.63.

1-(Benzenesulfonyl)-3-(bromomethyl)-5-methoxyindole (14a). A solution of **13a**[26] (35.5 g, 0.118 mol) in CCl_4 (500 mL) was heated to reflux after which *N*-bromosuccinimide (22.2 g, 0.123 mol) and AIBN (500 mg) were carefully added in a portionwise manner over 5 min. After completion of the addition, three portions of AIBN (3 × 200 mg) were added, one each 30 min. After 3 h the mixture was cooled to rt and the succinimide which resulted was filtered off and washed with CCl_4 (3 × 50 mL). The solvent was removed under reduced pressure to yield a brown solid. A further purification by recrystallization from diethyl ether afforded **14a** as off-white colored crystals (37 g, 82.5%): mp 116−118 °C; IR (KBr) 3103, 2856, 1607 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.60 (s, 2H), 6.95 (dd, 1H, J = 8.7, 2.4 Hz), 7.05 (d, 1H, J = 2.3 Hz), 7.45 (t, 2H, J = 7.6 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.65 (s, 1H), 7.85 (m, 3H); MS (EI) *m/e* (relative intensity) 381 (M^+, 21.4), 379 (M^+, 18.3), 240 (51.1), 238 (53.4), 160 (39.1), 159 (100), 116 (77). Anal. Calcd for $C_{16}H_{14}BrNSO_3$: C, 50.54; H, 3.71; N, 3.68. Found: C, 50.36; H, 3.47; N, 4.01.

1-(*tert*-Butyloxycarbonyl)-3-(bromomethyl)-5-methoxyindole (14b) was prepared in 87% yield following the procedure for the preparation of **14a**. **14b**: a brown oil; ^1H NMR (250 MHz, $CDCl_3$) δ 1.66 (s, 9H), 3.89 (s, 3H), 4.66 (s, 2H), 6.97 (dd, 1H, J = 9.1, 2.6 Hz), 7.12 (d, 1H, J = 2.5 Hz), 7.13 (s, 1H), 8.04 (d, 1H, J = 8.9 Hz). MS (EI) *m/e* (relative intensity) 341 (M^+, 19), 339 (M^+, 21), 285 (27), 283 (29), 241 (92), 239 (100), 226 (38), 224 (43), 159 (33), 116 (71).

1-(Benzenesulfonyl)-3-(bromomethyl)-5-chloroindole (14c) was prepared in 93% yield following the procedure for the preparation of **14a**. **14c**: mp 139−142 °C; IR (KBr) 3449, 3141, 1579 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.51 (s, 2H), 7.31 (s, 1H), 7.47 (m, 2H), 7.62 (s, 1H), 7.86 (m, 4H); MS (EI) *m/e* (relative intensity) 386 (M^+, 3), 384 (M^+, 10), 304 (36), 163 (50), 141 (100), 128 (26), 101 (2); HRMS for $C_{15}H_{11}NO_2SClBr$ calcd 384.6748, found 384.6756.

1-(*tert*-Butyloxycarbonyl)-3-(bromomethyl)-5-chloroindole (14d) was prepared in 91% yield *via* the method described for the preparation of **14a**. **14d**: mp 100−102 °C; IR (KBr) 3017, 1510 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.60 (s, 9H), 4.6 (s, 2H), 7.35 (dd, 1H, J =2 and 8.7 Hz), 7.65 (d, 1H, J = 2 Hz), 7.70 (s, 1H), 8.11 (d, 1H, J = 8.7 Hz); MS (EI) *m/e* (relative intensity) 345 (M^+, 5), 344 (2), 343 (4), 164 (100), 163 (45), 101 (40). The material was employed directly in a later step.

1-(Benzenesulfonyl)-3-(bromomethyl)indole (14e) was prepared in 94% yield following the procedure for the preparation of **14a**. **14e**: mp 132−134 °C; IR (KBr) 3100, 2850, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.89 (s, 2H), 7.30−7.45 (m, 2H), 7.55−7.72 (m, 4H), 7.90−8.05 (m, 4H). MS (EI) *m/e* (relative intensity) 350 (M^+, 16.6), 348 (M^+, 17.2), 270 (73.0), 141 (97.6), 129 (100.0). Anal. Calcd for $C_{15}H_{12}BrNO_2S \cdot {}^1/_2H_2O$: C, 50.15; H, 3.62; N, 3.90. Found: C, 50.34; H, 3.40; N, 3.83.

(35) Fleming, I.; Woolias, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 829.

1-(*tert*-Butyloxycarbonyl)-3-(bromomethyl)indole (14f) was prepared in 95% yield following the procedure for the preparation of **14a**. **14f**: mp 106−107 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.68 (s, 9H), 4.69 (s, 2H), 7.81−7.95 (m, 2H), 7.70 (m, 2H), 8.18 (d, J = 7.8 Hz); MS (EI) m/e (relative intensity) 311 (M^+, 2.6), 309 (M^+, 3.1), 174 (32.0), 130 (100). Anal. Calcd for $C_{14}H_{16}BrNO_2$: C, 54.19; H, 5.16; N 4.52. Found: C, 54.15; H, 5.30; N, 4.73.

1-(*tert*-Butyloxycarbonyl)-3-(bromomethyl)-6-chloro-5-methoxyindole (14g) was prepared in 87% yield following the procedure for the preparation of **14a**. **14g**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.64 (s, 9H), 3.97 (s, 3H), 4.63 (s, 2H), 7.10 (s, 1H), 7.61 (s, 1H), 8.18 (s, 1H); IR (KBr) 2979, 1732, 1469, 1268, 1158, 744 cm^{-1}. This indole **14g** was employed directly in a later step without further purification.

1-(*tert*-Butyloxycarbonyl)-2-bromo-5-methoxy-3-methylindole (15b). A mixture of 3-methylindole **13b** (1.31 g, 5 mmol) and NBS (0.98 g, 5.5 mmol) in anhydrous CCl_4 (10 mL) was heated to reflux under nitrogen. When all the NBS was converted into succinimide, which floated on the surface of the CCl_4, the reaction solution was cooled to rt. The succinimide was removed by filtration and washed with CCl_4 (2 × 2 mL). The combined filtrates were concentrated under reduced pressure to afford **15b** as a brown solid (1.61 g, 95%). The residue was crystallized from a mixture of CCl_4 and hexane to afford 1-(*tert*-butyloxycarbonyl)-2-bromo-5-methoxy-3-methylindole (**15b**) as a white solid: mp 82−84 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.62 (s, 9H), 2.18 (s, 3H), 3.79 (s, 3H), 6.91 (dd, 1H, J = 9.0, 2.5 Hz), 7.07 (d, 1H, J = 2.4 Hz), 7.38 (d, 1H, J = 9.1 Hz). MS (EI) m/e (relative intensity) 341 (M^+, 18.9), 339 (M^+, 21.0), 285 (27.4), 283 (28.6), 241 (92.1), 239 (100.0), 226 (38.3), 224 (43.4). Anal. Calcd for $C_{15}H_{18}BrNO_3$: C, 52.94; H, 5.29; N, 4.12. Found: C, 52.72; H, 5.41; N, 3.87.

1-(Benzenesulfonyl)-2-bromo-5-methoxy-3-methylindole (15a) was prepared as described above for the preparation of **15b**. **15a**: mp 148−150 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.13 (s, 3H), 3.84 (s, 3H), 6.81 (d, 1H, J = 2.3 Hz), 6.93 (dd, 1H, J = 8.8, 2.4 Hz), 7.48−7.58 (m, 3H), 7.82 (d, 2H, J = 8.7 Hz), 8.18 (d, 1H, J = 8.9 Hz); MS (EI) m/e (relative intensity) 381 (M^+, 30.6), 379 (M^+, 26.4), 240 (74.0), 238 (71.9), 159 (100.0). Anal. Calcd for $C_{16}H_{14}BrNO_3S\cdot{}^1/_2H_2O$: C, 49.36; H, 3.86; N, 3.60. Found: C, 49.20; H, 3.49; N, 3.34.

2-Bromo-5-chloro-3-methylindole (15h) was prepared as described above for the preparation of **15b**. **15h**: mp 96−98 °C; IR (KBr) 3000, 1648 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.15 (s, 3H), 7.1 (dd, 1H, J = 2 and 8.7 Hz), 7.3 (s, 1H), 7.5 (d, 1H, J = 2 Hz), 11.8 (s, 1H, NH); MS (EI) m/e (relative intensity) 245 (M^+, 89), 244 (M^+, 48), 243 (M^+, 60), 242 (35), 164 (100). This material was employed directly in a later step.

2-Bromo-3-methylindole (15i) was prepared as described above for the preparation of **15b**. **15i**: mp 91−93 °C; IR (KBr) 2977, 1448 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.09 (s, 3H), 6.95−7.10 (m, 2H), 7.27 (d, 1H, J = 7.8 Hz), 7.46 (d, 1H, J = 7.8 Hz), 11.52 (br, 1H, D_2O exchangeable); MS (EI) m/e (relative intensity) 211 (M^+, 38.3), 209 (M^+, 38.3), 130 (100.0). This material was employed directly in a later step.

(3*S*,6*R*)-3-((1-(*tert*-Butyloxycarbonyl)-6-chloro-5-methoxy-3-indoyl)methyl)-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (17). To a solution of 3(*R*)-isopropyl-2,5-diethoxypyrazine[25,36] (6.8 g, 0.032 mol) in THF (200 mL) was added *n*-butyllithium (2.5 M in hexane, 12.83 mL, 0.032 mol) at −78 °C under nitrogen. The solution which resulted was stirred at −78 °C for 30 min after which a solution of **14g** (10 g, 0.026 mol) in THF (50 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 and treated with a saturated aqueous solution of $(NH_4)_2CO_3$ (10 mL). Most of the solvent was removed under reduced pressure, and the residue which resulted was treated with diethyl ether to give two layers. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford **17** as an oil (14 g, 96%): IR (KBr) 2974, 1729, 1691 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.69 (d, 3H, J = 6.9 Hz), 0.94 (d, 3H, J = 6.9 Hz), 1.21 (t, 3H, J = 7.1 Hz), 1.32 (t, 3H, J = 7.1 Hz), 1.63 (s, 9H), 2.20 (m, 1H), 3.12 (d, 2H, J = 4.8 Hz), 3.58 (t, 1H, J = 3.4 Hz), 3.92 (s, 3H), 4.00−4.28 (m, 4H), 4.30 (q, 1H, J = 4.6 Hz), 7.08 (s, 1H), 7.32 (s, 1H), 8.13 (s, 1H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.1, 14.3, 16.7, 19.3, 28.2, 29.3, 31.8, 56.1, 56.6, 60.5, 60.6, 60.8, 83.4, 102.5, 116.7, 117.3, 120.1, 125.0, 129.6, 130.8, 149.3, 151.2, 162.2, 163.7; MS (EI) m/e (relative intensity) 565 (M^+, 3), 237 (18), 212 (45), 194 (61), 169 (100), 141 (22), 113 (10). This material was employed directly in a later step without further purification.

(*S*)-1-(*tert*-Butyloxycarbonyl)-6-chloro-5-methoxytryptophan Ethyl Ester (19). To a solution of pyrazine **17** (5.05 g, 10 mmol) in THF (25 mL) at 0 °C was added an aqueous solution of 2 N HCl (25 mL). The mixture was allowed to warm to rt, stirred for 40 min, and poured into a cold aqueous solution of NH_4OH (final pH ∼9). The solution which resulted was concentrated, and CH_2Cl_2 (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of solvent under reduced pressure, the valine ethyl ester which resulted from the hydrolysis of the chiral auxiliary was removed by Kugelrohr distillation. This valine ethyl ester could be reused. The residue obtained was purified by flash chromatography (silica gel, ethyl acetate/hexane, 1/4, followed by ethyl acetate) to afford **19** (3.68 g, 93%) as a yellow solid: mp 118−120 °C; $[\alpha]^{30}_D$ = +6.5 (c = 1.9, in CH_2Cl_2); IR (KBr) 3361, 2978, 1732 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (t, 3H, J = 7.2 Hz), 1.65 (s, 9H), 3.18 (m, 2H), 3.91 (m, 1H), 3.98 (s, 3H), 4.18 (q, 2H, J = 7.1 Hz), 7.13 (s, 1H), 7.50 (s, 1H), 8.20 (br, 1H); MS (EI) m/e (relative intensity) 398 (M^+, 1.5), 396 (M^+, 3.9), 237 (16.2), 194 (100), 179 (14), 163 (22), 102 (30); HRMS for $C_{19}H_{25}N_2O_5Cl$ calcd 396.1452, found 396.1441. Anal. Calcd for $C_{19}H_{25}N_2O_5Cl$: C, 57.55; H, 6.36; N 7.07. Found: C, 57.64; H, 6.23; N, 6.96.

(*S*)-6-Chloro-5-methoxytryptophan Ethyl Ester (21a). To a solution of **19** (180 mg, 0.45 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added a solution of boron tribromide (145 mg, 0.54 mmol) in dry CH_2Cl_2 (2 mL) dropwise under nitrogen. The mixture was kept at −78 °C for 1 h and slowly warmed to rt. After being stirred for 5 h, the reaction solution was cooled to 0 °C and treated with ice−water (5 mL) and a concentrated aqueous solution of NH_4OH (1 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (3 mL) and brine (3 mL) and dried (Na_2SO_4). After removal of solvent, the residue was purified by flash chromatography on silica gel to afford **21a** in 87% yield. **21a** (HCl salt): mp 228−229 °C; $[\alpha]^{30}_D$ = +8.0 (c = 1, in CH_2Cl_2); IR (KBr) 3279, 2932, 1740 cm^{-1}; MS (EI) m/e (relative intensity) 298 (M^+, 14), 296 (M^+, 22), 223 (17), 194 (100), 179 (19), 151 (100); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (t, 3H, J = 7.2 Hz), 1.70 (br, 2H, NH_2), 3.00 (dd, 1H, J = 14.5 and 7.4 Hz), 3.20 (dd, 1H, J = 14.2 and 5.1 Hz), 3.78 (dd, 1H, J = 7.4 and 5.2 Hz), 3.90 (s, 3H), 4.15 (q, 2H, J = 7.2 Hz), 6.95 (d, 1H, J = 2.2 Hz), 7.07 (s, 1H), 7.32 (s, 1H), 8.05 (br, 1H); HRMS for $C_{14}H_{17}N_2O_3Cl$ calcd 296.0927, found 296.0923.

(*S*)-6-Chloro-5-hydroxytryptophan Ethyl Ester (21b). To a solution of **19** (180 mg, 0.45 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added boron tribromide (1.6 mL, 1.57 mmol, 1.0 M solution in CH_2Cl_2) dropwise under nitrogen. The mixture was kept at −78 °C for 1 h and slowly warmed to rt. After being stirred for 6 h, the reaction solution was cooled to 0 °C and treated with ice−water (5 mL) and a concentrated aqueous solution of NH_4OH (3 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL) and dried (Na_2SO_4). After removal of solvent, the residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH/aqueous NH_4OH = 25:10:1) to afford **21b** in 82% yield. **21b**: mp 80−81 °C; $[\alpha]^{30}_D$ = +18.6 (c = 1.4, in CH_2Cl_2); IR (KBr) 3350, 1725, 1432 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.1 Hz), 2.60−2.82 (br, 3H),

(36) Hamaker, L. K. Ph.D. Thesis, University of Wisconsin-Milwaukee, 1995.

3.01 (dd, 1H, J = 14.2 and 7.1 Hz), 3.18 (dd, 1H, J = 14.3 and 5.3 Hz), 3.79 (dd, 1H, J = 7.1 and 5.2 Hz), 4.13 (q, 2H, J = 7.1 Hz), 7.01 (s, 1H), 7.16 (s, 1H), 7.31 (s, 1H), 8.22 (br, 1H); MS (EI) m/e (relative intensity) 284 (M^+, 12), 282 (M^+, 22), 209 (20), 182 (40), 180 (100), 145 (15). Anal. Calcd for $C_{18}H_{15}N_2O_3Cl$: C, 63.14; H, 4.42; N 8.19. Found: C, 63.04; H, 4.91; N, 7.84.

6-Chloro-5-hydroxy-L-tryptophan (21c). To a solution of tryptophan ethyl ester **19** (0.52 g, 1.31 mmol) in dry CH_2Cl_2 (18 mL) was added a solution of boron tribromide (1.64 g, 6 mmol) in dry CH_2Cl_2 (5 mL) dropwise at −78 °C under nitrogen. The mixture was kept at −78 °C for 1 h and then slowly warmed to rt. After 24 h, the reaction solution was cooled to 0 °C and treated with ice water (5 mL). The aqueous layer was separated and washed with CH_2Cl_2 (2 × 5 mL), and its pH was adjusted with a dilute aqueous solution of NH_4OH to a final pH ∼4−5. The water was removed under reduced pressure. The residue which remained was purified by flash chromatography on silica gel ($CHCl_3$/MeOH/concentrated aqueous NH_4OH, 20/15/1.5) to afford **21c** (0.26 g, 80%) as a white solid: mp 275−280 °C dec; $[\alpha]^{30}_D$ = −3.0 (c = 1, in H_2O); IR (KBr) 3127, 3025, 1660 cm^{-1}; ^1H NMR (CD_3OD) δ 3.10 (dd, 1H, J = 15.4, 9.3 Hz), 3.42 (dd, 1H, J = 15.4, 3.9 Hz), 3.82 (dd, 1H, J = 9.2, 4.0 Hz), 4.61−5.12 (br, 5H), 7.18 (br, 2H), 7.33 (s, 1H); MS (EI) m/e (relative intensity) 256 (M^+, 5), 254 (M^+, 18), 208 (7), 180 (100), 145 (15), 116 (12); HRMS for $C_{11}H_{11}N_2O_3Cl$ calcd 254.0458, found 254.0458.

5-Methoxytryptophan (20). The experimental procedure for the preparation of **20** was reported in a previous paper.[26]

1-(*tert*-Butyloxycarbonyl)-2-bromo-3-(bromomethyl)-5-methoxyindole (22a). To a solution of 1-(*tert*-butyloxycarbonyl)-5-methoxy-3-methylindole **13b** (7.1 g, 27.2 mmol) in CCl_4 (100 mL) was added *N*-bromosuccinimide (5.4 g, 30 mmol). The reaction solution was heated to reflux for 3 h to afford 1-(*tert*-butyloxycarbonyl)-2-bromo-5-methoxy-3-methylindole (**15b**) as determined by the examination of the ^1H NMR spectrum. The 2-bromo-3-methylindole was gently heated at reflux after which *N*-bromosuccinimide (5.4 g, 30 mmol) and AIBN (50 mg) were added. After 2−5 min, another portion of AIBN (50 mg) was added and the reaction mixture was kept at reflux for 40 min. The reaction solution was allowed to cool to rt. The succinimide which resulted was removed by filtration and washed with CCl_4 (2 × 10 mL). The combined filtrates were concentrated under reduced pressure to afford **22a** as a brown solid (9.45 g, 83%): mp 91−92 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.71 (s, 9H), 3.88 (s, 3H), 4.67 (s, 2H), 6.93 (dd, 1H, J = 2.5 and 9.1 Hz), 7.02 (d, 1H, J = 2.5 Hz), 7.99 (d, 1H, J = 9.1 Hz); MS (EI) m/e (relative intensity) 421 (M^+, 5.1), 419 (M^+, 13.4), 417 (M^+, 5.7), 240 (100), 238 (94.0), 224 (24.5), 222 (24.7), 115 (65.3). This material was used in a later step without further purification.

1-(*tert*-Butyloxycarbonyl)-2-bromo-3-methylindole (23). To a solution of 3-methylindole **12c** (6.65 g, 50 mmol) in CCl_4 (100 mL) was added *N*-bromosuccinimide (9.29 g, 51 mmol). The mixture was heated to reflux for 30 min. The reaction solution was allowed to cool to rt. The succinimide obtained was filtered off and washed with cold CCl_4 (2 × 10 mL). The filtrates were combined, and the solvent was removed under reduced pressure to afford a brownish residue which was taken up in dry CH_3CN (150 mL). To the CH_3CN solution were added di-*tert*-butyl dicarbonate (11 g, 50 mmol) and DMAP (0.3 g, 2.5 mmol) at rt. After the mixture was stirred at rt for 30 min, ethyl acetate (200 mL) and an aqueous solution of 2 N HCl (50 mL) were added to the mixture. The organic layer was separated, washed with brine (30 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate, 6/1) to afford **23** as an oil: IR (KBr) 2975, 1734 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.67 (s, 9H), 2.25 (s, 3H), 7.24 (m, 2H), 7.42 (d, 1H, J =7.5 Hz), 8.05 (d, 1H, J = 7.5 Hz); MS (EI) m/e (relative intensity) 311 (M^+, 43), 309 (M^+, 43), 253 (34), 236 (22), 209 (100), 130 (57). The material was employed directly in a later step.

1-(*tert*-Butyloxycarbonyl)-2-bromo-3-(bromomethyl)indole (22b). A solution of **23** (5.1 g, 16.0 mmol) in CCl_4 (100 mL) was heated to reflux after which the *N*-bromosuccinimide (3.2 g, 17.6 mmol) and AIBN (100 mg) were added. The mixture was heated at reflux for 40 min and then cooled to rt. The succinimide produced as a byproduct was filtered off and washed with cold CCl_4 (2 × 10 mL). The filtrates were combined, and the solvent was removed under reduced pressure to afford **22b** as an oil which was directly used in the next step without further purification: IR (KBr) 2927, 1731, 1449 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.69 (s, 9H), 4.66 (s, 2H), 7.28 (t, 1H, J = 7.5 Hz), 7.51 (t, 1H, J =7.5 Hz), 7.58 (d, 1H, J = 7.5 Hz), 7.68 (d, 1H, J = 7.6 Hz); MS (EI) m/e (relative intensity) 377 (M^+, 2), 375 (M^+, 4), 373 (M^+, 2), 208 (50), 167 (30), 149 (100), 128 (32).

(3*S*,6*R*)-3-((1-(*tert*-Butyloxycarbonyl)-2-bromo-5-methoxy-3-indoyl)methyl)-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (24a) and (3*R*,6*R*)-3-((1-(*tert*-butyloxycarbonyl)-2-bromo-5-methoxy-3-indoyl)methyl)-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (24c). To a solution of 3(*R*)-isopropyl-2,5-diethoxypyrazine (3.0 g, 14 mmol) in THF (100 mL) was added *n*-butyllithium (2.5 M in hexane, 5.6 mL, 14 mmol) at −78 °C under nitrogen. The solution which resulted was stirred at −78 °C for 30 min after which a solution of 1-(*tert*-butyloxycarbonyl)-2-bromo-3-(bromomethyl)-5-methoxyindole (**22a**) (5 g, 12 mmol) in THF (20 mL) was added dropwise under nitrogen. After the mixture was allowed to stir at −78 °C for 20 h, the reaction solution was slowly warmed to rt and treated with a saturated aqueous solution of $NaHCO_3$ (30 mL). Most of the solvent was removed under reduced pressure, and the residue which resulted was treated with diethyl ether to give two layers. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a mixture of **24a** and **24c** (92/8) as an oil which was separated by flash chromatography on silica gel (hexane/ethyl acetate, 10/1). **24a**: IR (KBr) 2968, 1733, 1673 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.63 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz), 1.16 (t, 3H, J = 7.1 Hz), 1.26 (t, 3H, J = 7.1 Hz), 1.66 (s, 9H), 2.21 (m, 1H), 2.90 (dd, 1H, J = 8.2 and 14.0 Hz), 3.27 (dd, 1H, J = 4.7 and 14.0 Hz), 3.73 (t, 1H, J = 3.3 Hz), 3.81 (s, 3H), 3.83−4.25 (m, 5H), 6.83 (dd, 1H, J = 2.7 and 9.2 Hz), 6.98 (d, 1H, J = 2.3 Hz), 7.91 (d, 1H, J = 9.1 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.3, 16.6, 19.1, 28.2, 31.1, 31.4, 55.7, 60.5, 60.6, 60.8, 84.4, 102.3, 111.0, 112.5, 116.0, 120.4, 130.5, 131.2, 149.2, 155.8, 162.9, 163.7; MS (EI) m/e (relative intensity) 551 (M^+, 10), 549 (M^+, 10), 318 (20), 238 (70), 169 (72), 141 (100). This material was used in the next experiment without further purification. **24c**: IR (KBr) 2955, 1725, 1684, 1452 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.79 (d, 3H, J = 6.8 Hz), 1.03 (d, 3H, J = 6.8 Hz), 1.17 (t, 3H, J = 7.1 Hz), 1.22 (t, 3H, J = 7.1 Hz), 1.66 (s, 9H), 2.22 (m, 1H), 2.88 (dd, 1H, J = 8.2 and 14.0 Hz), 3.26 (dd, 1H, J = 5.0 and 14.0 Hz), 3.71 (t, 1H, J = 3.2 Hz), 3.82 (s, 3H), 3.83−4.28 (m, 5H), 6.84 (dd, 1H, J = 2.6 and 9.1 Hz), 6.99 (d, 1H, J = 2.4 Hz), 7.92 (d, 1H, J = 9.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.3, 17.8, 19.6, 28.2, 32.0, 55.7, 55.7, 60.6, 60.7, 61.2, 84.4, 102.0, 110.5, 112.6, 116.1, 120.6, 130.4, 131.4, 149.2, 155.8, 162.7, 163.3.

(*S*)-1-(*tert*-Butyloxycarbonyl)-2-bromo-5-methoxytryptophan Ethyl Ester (25a). To a solution of pyrazine **24a** (5 g, 9.1 mmol) in THF (50 mL) at 0 °C was added an aqueous solution of 2 N HCl (25 mL). The mixture was allowed to warm to rt, stirred for 40 min, and poured into a cold aqueous solution of NH_4OH (final pH ∼9). The solution which resulted was concentrated in vacuo, and CH_2Cl_2 (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of solvent under reduced pressure, the valine ethyl ester which resulted from hydrolysis of the chiral auxiliary was separated by high-vacuum distillation to be reused. The residue which remained was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1/4, followed by ethyl acetate) to afford **25a** (3.6g, 92%) as an oil (HCl salt): mp 116−120 °C dec; IR (KBr) 2984, 1728, 1616 cm^{-1}; $[\alpha]^{27}_D$ = +12.1 (c = 2.0, in CH_3OH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, 3H, J = 7.0 Hz), 1.31 (s, 9H), 3.42 (m, 1H), 3.61 (m, 1H), 3.80 (s, 3H), 3.99 (m, 2H), 4.39 (br, 1H), 6.81 (dd, 1H, J

= 9.3, 2.1 Hz), 7.25 (d, 1H, J = 1.7 Hz), 7.89 (d, 1H, J = 9.2 Hz), 9.05 (br, 3H); MS (EI) *m/e* (relative intensity) 442 (M^+, 4), 440 (M^+, 5), 361 (10), 305 (23), 238 (100), 187 (25), 149 (50). Anal. Calcd for $C_{19}H_{25}N_2O_5Br$: C, 51.81; H, 5.73; N 6.36. Found: C, 51.90; H, 6.01; N, 6.12.

2-Bromo-5-methoxy-L-tryptophan Ethyl Ester (26a). To a solution of tryptophan ethyl ester **25a** (0.4 g, 0.9 mmol) in dry CH_2Cl_2 (10 mL) was added a solution of boron tribromide (1 mL, 1.0 M solution in CH_2Cl_2) in dry CH_2Cl_2 (5 mL) dropwise at −78 °C under nitrogen. The mixture was kept at −78 °C for 1 h and then slowly warmed to rt. After 2 h, the reaction solution was cooled to 0 °C and treated with a dilute aqueous solution of NH_4OH to a final pH ∼8. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, washed with brine (30 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was purified by a wash column (silica gel, hexane/ethyl acetate, 1/1) to afford **26a** as an oil (81%). **26a** (HCl salt): mp 106−110 °C dec; IR (KBr) 2966, 1738, 1685 cm^{-1}; $[\alpha]^{27}_D$ = +10.00 (c = 1.0, in CH_3OH); ^1H NMR (250 MHz, DMSO-d_6) δ 0.99 (t, 3H, J = 7.1 Hz), 3.10 (m, 1H), 3.21 (m, 1H), 3.82 (m, 1H), 3.83 (s, 3H), 4.05 (m, 2H), 6.78 (dd, 1H, J = 8.5, 2.3 Hz), 7.08 (d, 1H, J = 1.6 Hz), 7.20 (d, 1H, J = 8.2 Hz), 8.60 (br, 3H, D_2O exchangeable), 11.7 (br, 1H, D_2O exchangeable).

2-Bromo-5-hydroxy-L-tryptophan Ethyl Ester (26c). Using a similar procedure to that described above for the preparation of **26a**, the removal of the *tert*-butyloxycarbonyl and methyl moieties of **25a** was accomplished with 3 equiv of boron tribromide to afford **26c** (79%) as a brown-yellow solid. **26c**: mp 164−170 °C dec; IR (KBr) 3295, 2986, 1724 cm^{-1}; $[\alpha]^{27}_D$ = +27.40 (c = 1.0, in CH_3OH); ^1H NMR (250 MHz, DMSO-d_6) δ 1.02 (t, 3H, J = 7.1 Hz), 2.10 (br, 2H, D_2O exchangeable), 2.75 (dd, 1H, J = 14.1, 7.4 Hz), 2.87 (dd, 1H, J = 14.1, 7.3 Hz), 3.54 (t, 1H, J = 7.0 Hz), 3.95 (q, 2H, J = 7.2 Hz), 6.58 (dd, 1H, J = 8.7, 2.2 Hz), 6.78 (d, 1H, J = 2.0 Hz), 7.04 (d, 1H, J = 8.5 Hz), 8.70 (s, 1H, D_2O exchangeable), 11.29 (s, 1H, D_2O exchangeable). MS (EI) *m/e* (relative intensity) 328 (M^+, 25), 326 (M^+, 31), 246 (50), 224 (100), 173 (20), 146 (35). Anal. Calcd for $C_{13}H_{15}N_2O_3Br$: C, 47.72; H, 4.62; N, 8.56. Found: C, 48.02; H, 4.56; N, 8.79.

(3*S*,6*R*)-3-((1-(*tert*-Butyloxycarbonyl)-2-bromo-3-indoyl)-methyl)-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (24b) and (3*R*,6*R*)-3-((1-(*tert*-butyloxycarbonyl)-2-bromo-3-indoyl)methyl)-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (24d) were prepared in a ratio of 90:10 using the same procedure employed earlier for the synthesis of **24a** and **24c**. **24b**: IR (KBr) 2989, 1730, 1671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.76 (d, 3H, J = 6.9 Hz), 1.03 (d, 3H, J = 6.6 Hz), 1.18 (t, 3H, J = 7.1 Hz), 1.23 (t, 3H, J = 6.9 Hz), 1.68 (s, 9H), 2.25 (m, 1H), 2.97 (dd, 1H, J = 8.6 and 14.0 Hz), 3.36 (dd, 1H, J = 4.8 and 14.0 Hz), 3.85 (t, 1H, J = 4.1 Hz), 3.90−4.29 (m, 5H), 7.19 (t, 1H, J = 7.5 Hz), 7.25 (t, 1H, J = 7.7 Hz), 7.53 (d, 1H, 7.7 Hz), 8.05 (d, 1H, J = 8.3 Hz); MS (EI) *m/e* (relative intensity) 521 (M^+, 8), 519 (M^+, 10), 440 (70), 338 (85), 208 (90), 169 (100), 141 (87). This material was employed directly in the next step without further purification. **24d**: IR (KBr) 2978, 1720, 1681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (d, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.6 Hz), 1.17 (t, 3H, J = 7.1 Hz), 1.22 (t, 3H, J = 6.9 Hz), 1.66 (s, 9H), 2.23 (m, 1H), 2.93 (dd, 1H, J = 8.6 and 14.0 Hz), 3.30 (dd, 1H, J = 4.8 and 14.0 Hz), 3.84 (t, 1H, J = 4.1 Hz), 3.90−4.29 (m, 5H), 7.18 (t, 1H, J = 7.5 Hz), 7.23 (t, 1H, J = 7.7 Hz), 7.51 (d, 1H, 7.7 Hz), 8.02 (d, 1H, J = 8.3 Hz).

(*S*)-1-(*tert*-Butyloxycarbonyl)-2-bromotryptophan Ethyl Ester (25b) was prepared from **24b** using the same procedure as described for the synthesis of **25a**. **25b** (HCl salt): mp 88−90 °C; $[\alpha]^{27}_D$ = +17.20 (c = 1.0, in CH_3OH); IR (KBr) 3396, 3191, 2979, 1738, 1450 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 0.91 (t, 3H, J = 7.0 Hz), 1.63 (s, 9H), 3.09 (m, 1H), 3.19 (m, 1H), 3.41 (m, 1H), 3.96 (q, 2H, J = 7.1 Hz), 7.28 (t, 1H, J = 7.6 Hz), 7.34 (t, 1H, J = 7.6 Hz), 7.76 (d, 1H, J = 7.6 Hz), 7.99 (d, 1H, J = 7.6 Hz), 8.87 (br, 3H, D_2O exchangeable); HRMS for $C_{18}H_{23}N_2O_4Br$ calcd 410.0841, found 410.0843.

(*S*)-2-Bromotryptophan ethyl ester (26b) was prepared following the procedure employed for the synthesis of **26a**. **26b** (HCl salt): mp 150−152 °C; $[\alpha]^{27}_D$ = +20.80 (c = 2.0, in CH_3OH); IR (KBr) 3392, 3193, 2980, 2919, 1736 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 0.93 (t, 3H, J = 7.2 Hz), 3.12 (m, 1H), 3.24 (m, 1H), 3.29 (m, 1H), 4.01 (m, 2H), 7.05 (t, 1H, J = 7.5 Hz), 7.11 (t, 1H, J = 7.4 Hz), 7.30 (d, 1H, J = 7.9 Hz), 7.53 (m, 1H), 8.60 (br, 3H, D_2O exchangeable), 11.85 (s, 1H, D_2O exchangeable); MS (EI) *m/e* (relative intensity) 312 (M^+, 21), 310 (M^+, 25), 157 (85), 130 (95), 129 (75), 108 (10); HRMS for $C_{13}H_{15}N_2O_2Br$ calcd 310.0317, found 310.0308. Anal. Calcd for $C_{13}H_{15}N_2O_2Br$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.46; H, 4.70; N, 8.79

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