Efficient Asymmetric Synthesis of Biologically Important Tryptophan Analogues via a Palladium-Mediated Heteroannulation Reaction

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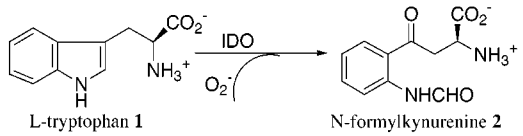
A novel and concise synthesis of optically active tryptophan derivatives was developed via a palladium-catalyzed heteroannulation reaction of substituted *o*-iodoanilines with an internal alkyne. The required internal alkyne **14a** or **25** was prepared in greater than 96% de via alkylation of the Schöllkopf chiral auxiliary **19** employing diphenyl phosphate as the leaving group. The Schöllkopf chiral auxiliary was chosen here for the preparation of L-tryptophans would be available from D-valine while the D-isomers required for natural product total synthesis would originate from the inexpensive L-valine (300-g scale). Applications of the palladium-catalyzed heteroannulation reaction were extended to the first asymmetric synthesis of L-isotryptophan **38** and L-benz[*f*]tryptophan **39**. More importantly, the optically pure 6-methoxy-D-tryptophan **62** was prepared by this protocol on a large scale (>300 g). This should permit entry into many ring-A oxygenated indole alkaloids when coupled with the asymmetric Pictet−Spengler reaction. In addition, an improved total synthesis of tryprostatin A (**9a**) was accomplished in 43% overall yield employing this palladium-mediated process.

Introduction

Indoleamine 2,3-dioxygenase (IDO) is a monomeric 42kd heme-containing enzyme that uses superoxide to cleave the indole 2,3-double bond.[1] One of the functions of IDO in cells is the oxidation of L-tryptophan to kynurenine, a principle metabolic pathway for L-tryptophan (Scheme 1).

Many intermediates in the kynurenine pathway, such as quinolinic acid and kynurenic acid, are known to be active in the CNS. Quinolinic acid has been shown to be present in the mammalian brain, to be an agonist for the excitatory amino acid receptors of the *N*-methyL-D-aspartate (NMDA) receptor-ion channel complex, and to cause excitotoxic brain lesions when present in high concentrations.[2−4] Moreover, the elevation of IDO activity, which results in the elevation of quinolinic acid concentrations as a consequence, is observed in HIV- and AIDS-associated dementia and wasting.[5,6] Other acute/chronic immunological and inflammatory diseases, which include parasitic, bacterial, viral, and fungal infections, have been associated with an increase in IDO activity.[7−9]

Scheme 1



L-tryptophan **1** N-formylkynurenine **2**

Other inflammatory diseases that are deleteriously affected by increased levels of IDO include meningitis, septicemia, and arthritis, etc.[8−13] Moreover, acute inflammatory events involving the induction of IDO are also associated with spinal cord injury and with brain ischemia. A host of both acute and chronic immunological and inflammatory disorders have been directly attributed to the increased activity of IDO principally initiated by the upregulation of the inflammatory cytokine interferon-γ. When interferon-γ levels are upregulated, IDO levels are upregulated![14] More recently, Mellor et al. [5] have shown that the IDO enzyme is involved in the survival of the concepti during pregnancy. Consequently, inhibitors of the IDO enzyme have important clinical implications. This has stimulated the search for inhibitors of this enzyme system that are required to study and to control the symptoms of diseases affected by this upregulation.

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(1) Botting, N. *Chem. Soc. Rev.* **1995**, *24*, 401.
(2) Perkins, M. N.; Stone, T. W. *Brain Res.* **1983**, *259*, 172.
(3) Stone, T. W.; Burton, N. R. *Prog. Neurobio.* **1988**, *30*, 333.
(4) Whetsell, W. O.; Shwarcz., R. *Neurosci. Lett.* **1989**, *97*, 271.
(5) Munn, D.; Zhou, M.; Attwood, J.; Bondarev, I.; Conway, S.; Marshall, B.; Brown, C.; Mellor, A. *Science* **1998**, *218*, 1191.
(6) Brown, R. R.; Ozaki, Y.; Datta, S. P.; Borden, E. C.; Sondel, P. M.; Malone, D. S. *Adv. Exp. Med. Biol.* **1991**, *294*, 425.
(7) Huengsberg, M.; Winer, J.; Compels, M.; Round, R.; Ross, J.; Shahmanesh, M. *Clin. Chem.* **1998**, *44*, 858.
(8) Malone, D. G.; Dolan, P. W.; Brown, R. R.; Kalayoglu, M. V.; Byrne, G. I.; Ozaki, Y. *Rheumatol.* **1994**, *21*, 1011.
(9) Blight, A. R.; Saito, K.; Heyes, M. P. *Brain Res.* **1993**, *632*, 314.
(10) Gupta, S. L.; Carlin, J. M.; Pyati, P.; Dai, W.; Pfefferkorn, E. R.; Murphy, M. J. *Infect. Immun.* **1994**, *62*, 2277.
(11) Beatty, W. L.; Belanger, T. A.; Desai, A. A.; Morrison, R. P.; Byrne, G. I. *Infect., Immun.* **1994**, *62*, 3705.
(12) Jacoby, D. B.; Choi., A. M. *Free. Rad. Biol. Med.* **1994**, *16*, 821.
(13) Dai, W.; Pan, H.; Kwok, O.; Dubney, J. P. *J. Interferon Res.* **1994**, *14*, 313.
(14) Werner-Flemayer, F.; Werner, E. R.; Fuchs, D.; Hausen, A.; Reibnegger, F.; Wachter, A. *Adv. Exp. Med. Biol.* **1991**, *294*, 505.

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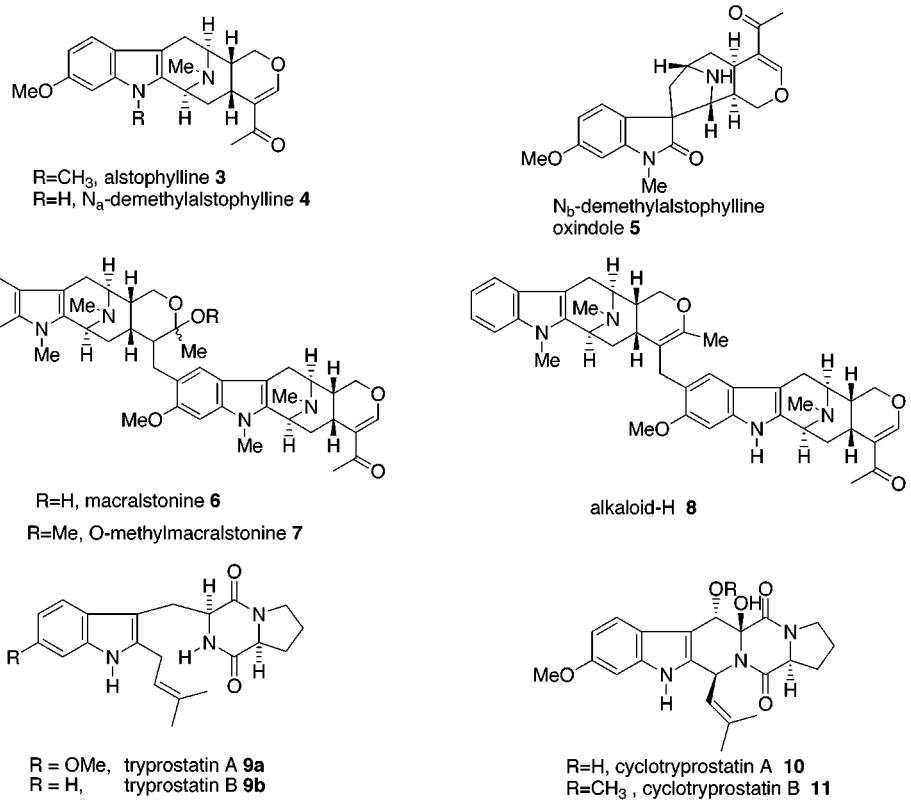


Figure 1. Alkaloids related to 6-methoxytryptophan.

The first competitive IDO inhibitor, 2,5-dihydro-L-phenylalanine ($K_i = 230\ \mu$M), was reported by Watanabe and co-workers in 1978.[15] Since then, Cady and Sono have also reported examples of competitive inhibitors of IDO.[16] Further research by Peterson et al.[17] and Southan et al.[18] has focused on the development of additional tryptophan analogues and related compounds to determine the SAR for interaction at the IDO active site. Although several compounds have exhibited inhibitory activity against IDO, none of these compounds inhibit IDO below micromolar levels. Therefore, highly potent inhibitors of human IDO (with low nanomolar affinity) are still required. On the basis of previous studies,[17,19] N_a-methyl-L-tryptophan was prepared and remains the most potent tryptophan-based competitive inhibitor reported to date.[17,19] This is important, for Mellor et al., using (±)-N_a-methyltryptophan, elegantly implicated the IDO enzyme in the arrest of T-cells important in survival of concepti during pregnancy (the "pregnancy paradox").[5] For these reasons, synthesis of optically active L-tryptophan derivatives are necessary in the search for more potent inhibitors of IDO. Due to the lack of efficient methods to synthesize optically active ring-A substituted tryptophans, a facile asymmetric synthesis of tryptophan derivatives was of interest. Moreover, a facile entry into ring-A methoxylated tryptophan alkyl esters would provide building blocks for the total synthesis of many ring-A alkoxylated indole alkaloids that possess antimalarial, antiamoebic, and antihypertensive activity.[20−22]

For example, a number of *Alstonia* alkaloids represent ring-A oxygenated natural products found in the macroline/sarpagine series including alstophylline **3**[23,24] and N_b-demethylalstophylline oxindole **5** (see Figure 1).[25] These bases could presumably be synthesized from 6-methoxy-D-tryptophan via the trans transfer of chirality in the asymmetric Pictet−Spengler reaction.[26,27] In addition to the macroline/sarpagine monomeric indole alkaloids, several bisindole alkaloids contain a 6-methoxytryptophan fragment: macralstonine **6**,[28,29] alkaloid H **8**,[30−32] and the newly isolated *O*-methylmacralstonine **7** (Figure 1).[33,34] *O*-Methylmacralstonine **7** is the 19-*O*-methyl

(15) Watanabe, Y.; Fujiwara, M.; Hayaishi, O.; Takeuchi, T.; Umezawa, H. *Biochem. Biophys. Res. Commun.* **1978**, *85*, 273.
(16) Cady, S. G.; Sono, M. *Arch. Biochem. Biophys.* **1991**, *292*, 326.
(17) Peterson, A. C.; Migawa, M. T.; Martin, M. J.; Hamaker, L. K.; Czerwinski, K. M.; Zhang, W.; Arend, R. A.; Fisette, P. L.; Ozaki, Y.; Will, J. A.; Brown, R. R.; Cook, J. M. *Med. Chem. Res.* **1994**, *3*, 531.
(18) Southan, M.; Truscott, R.; Jamie, J.; Pelosi, L.; Walker, M.; Maeda, H.; Iwamoto, Y.; Tone, S. *Med. Chem. Res.* **1996**, *5*, 343.
(19) Peterson, A. C.; Laloggia, A. J.; Hamaker, L. K.; Arend, R. A.; Fisette, P. L.; Ozaki, Y.; Will, J. A.; Brown, R. R.; Cook, J. M. *Med. Chem. Res.* **1993**, *3*, 473.
(20) Keawpradub, N.; Houghton, P. J.; Eno-Amooquaye, E.; Burke, P. J. *Planta Med.* **1997**, *63*, 97.
(21) Keawpradub, N.; Kirby, G. C.; Steele, J. C. P.; Houghton, P. J. *Planta Med.* **1999**, *65*, 690.
(22) Wright, C. W.; Allen, D.; Cai, Y.; Phillipson, J. D.; Said, I. M.; Kirby, G. C.; Warhurst, D. C. *Phytother. Res.* **1992**, *6*, 121.
(23) Garnick, R. L.; LeQuesne, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4213.
(24) Bi, Y.; Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Alkaloids. In *Studies in Natural Products Chemistry, Bioactive Natural Products, Part A*; Basha, F. Z., Rahman, A., Eds.; Elsevier Science: Amsterdam, 1993; Vol. 13, p 383.
(25) Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Sarpagine Alkaloids In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier Science: New York, 1995; Vol. 9, p 23.
(26) Zhang, L. H.; Cook, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 4088.
(27) Bi, Y.; Zhang, L. H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 9027.
(28) Cook, J. M.; LeQuesne, P. W. *Phytochemistry* **1971**, *10*, 437.
(29) Burke, D. E.; DeMarkey, C. A.; LeQuesne, P. W.; Cook, J. M. *J. Chem. Soc., Chem. Commun.* **1972**, 1346.
(30) Lazar, H. A. Ph.D. Thesis, University of Michigan, 1972.
(31) Burke, D. E.; Cook, G. A.; Cook, J. M.; Haller, K. G.; Lazar, H. A.; LeQuesne, P. W. *Phytochemistry* **1973**, *12*, 1467.
(32) Garnick, R. L., Ph.D. Thesis, Northeastern University, 1977.

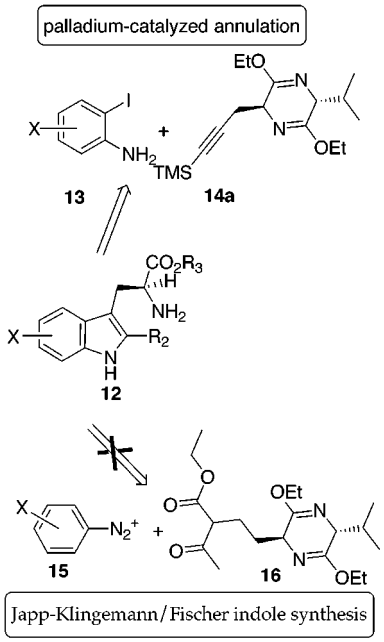
derivative of macralstonine **6**; however, this minor structural change has resulted in significantly enhanced antiplasmodial potency. Macralstonine **6** exhibited weak activity against the multidrug-resistant K1 strain of *Plasmodium falciparum* cultured in human erythrocytes with an IC_{50} value of 8.92 μM, while *O*-methylmacralstonine **7** was 10 times more active than **6** (IC_{50} = 0.85 μM).[21] The enhanced activity of **7** might result from increased lipophilicity, which would facilitate transport across cell membranes of the red blood cells or the parasites.[21] This is in agreement with the previously reported activity of 19-O-acetylmacralstonine.[22] In addition, there are at least 20 other sarpagine/macroline/ajmaline alkaloids that contain ring-A alkoxy groups.[35] For the total synthesis of the above indole alkaloids, optically pure 6-methoxytryptophan would serve as an important building block. Any route developed to provide optically active 6-methoxytryptophan for alkaloid synthesis must be capable of scale-up and be relatively easy to perform. This serves as one objective of the present research. In addition to the macroline/sarpagine alkaloids, tryprostatins A (**9a**) and B (**9b**) (Figure 1), which are closely related to tryptophan, have been isolated as secondary metabolites from the fermentation broth of a marine fungal strain of *Aspergillus fumigatus* BM939.[39−41] It was found that tryprostatins A (**9a**) and B (**9b**) completely inhibited cell cycle progression of tsFT210 cells in the G2/M phase at a final concentration of 50 μg/mL (**9a**) and 12.5 μg/mL (**9b**), respectively.[39−41] Tryprostatins A (**9a**) and B (**9b**) contain a 2-isoprenyltryptophan moiety and a proline residue, the latter of which is located in the diketopiperazine unit. These indole alkaloids differ from the representatives of the fumitremorgin series, for ring C has not been formed between positions designated C(18) and N(10).[42] The biological activity and unique 2-isoprenyltryptophan units of **9a** and **9b** prompted interest in such molecules. The first enantiospecific total synthesis of tryprostatin A was reported by Gan et al.[43,44] Described herein is a concise, enantiospecific route to the tryptophan moiety of these natural products that is improved over the previous route.[45]

Results and Discussion

a. Asymmetric Synthesis of Ring-A Substituted Tryptophans via a Palladium-Catalyzed Annulation Process.

A few of the current methods to synthesize optically active tryptophan derivatives include synthesis and subsequent resolution of the racemic compound,[46] transformation of a readily available optically active amino acid into tryptophan derivatives,[47−49] or synthesis of the indole precursor followed by reaction with the Schöllkopf chiral auxiliary.[44,50] However, these methods suffer either from length of steps or poor versatility in terms of the substitution pattern in ring A. It was decided to develop a convergent route to tryptophan derivatives that enjoys both efficiency and versatility (Scheme 2) and is capable of scale-up to the multihundred gram level.

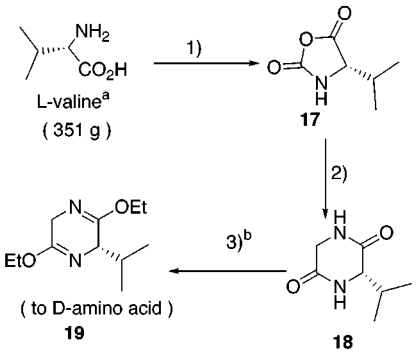
Scheme 2



Initially, a convergent synthetic route to substituted tryptophans was attempted via the Japp−Klingemann/Fischer indole strategy previously developed by Abramovitch and Shapiro.[51] The Schöllkopf chiral auxiliary was chosen in regard to asymmetry since this can be prepared in either enantiomeric form and on large scale.[52] The details of this approach are illustrated in Scheme 3 and in the Supporting Information. Model reactions were executed in an attempt to synthesize 5-methoxytryptophan. As shown in Scheme 4, the Schöllkopf chiral auxiliary **19** was deprotonated with 2 equiv of *n*-butyllithium at −78 °C followed by nucleophilic attack on 2-bromoethanol. The oxygen anion that resulted was trapped with *p*-toluenesulfonyl chloride, after which the reaction was warmed to facilitate the bromide replacement of the tosylate to provide **20**; the bromide ion had been generated in the previous step. This one-pot process provided the alkyl bromide **20** in 80% yield. The key α-alkylated ethyl acetoacetate intermediate **16** was prepared in 85% yield by alkylation of ethyl acetoacetate

(33) Yamazaki, M.; Suzuki, K.; Fujimoto, H.; Akiyama, T.; Sankawa, U.; Iitaka, Y. *Chem. Pharm. Bull.* **1980**, *28*, 861.
(34) Isidro, N.; Manalo, G. D. *J. Phillipine Pharm. Assoc.* **1967**, *53*, 8.
(35) Lounasmaa, M.; Hanhine., P.; Westersund, M. *The Sarpagine Group of Indole Alkaloids;* Cordell, G. A., Ed.; Academic Press: San Diego, 1999; Vol. 52.
(36) Cook, J. M. Ph.D. Thesis,. University of Michigan, 1971.
(37) Burke, D. E.; Cook, J. M.; LeQuesne, P. W. *J. Am. Chem. Soc.* **1973**, *95*, 546.
(38) Kishi, T.; Hesse, M.; Vetter, W.; Gemenden, C. W.; Taylor, W. I.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 946.
(39) Cui, C.; Kakeya, H.; Okada, G.; Onose, R.; Ubukata, M.; Takahashi, I.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 1382.
(40) Cui, C.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 534.
(41) Cui, C.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527.
(42) Steyn, P. S.; Vleggaar, R. Tremorgenic Mycotoxins In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Zachmiester, L., Eds.; Springer-Verlag, Vienna: 1985; Vol. 48, p 1.
(43) Gan, T.; Cook, J. M. *Tetrahedron Lett.* **1997**, *38*, 1301.
(44) Gan, T.; Liu, R.; Yu, P.; Zhao, S.; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 9298.
(45) Zhao, S.; Gan, T.; Yu, P.; Cook, J. M. *Tetrahedron Lett.* **1998**, *39*, 7009.
(46) Gerig, T. G.; Klinkenborg, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 4267.
(47) Masumi, F.; Takeuchi, H.; Kondo, S.; Suzuki, K.; Yamada, S. *Chem. Pharm. Bull.* **1982**, *30*, 3831.
(48) Hino, T.; Taniguchi, M.; Gonsho, A.; Nakagawa, M. *Heterocycles* **1979**, *12*, 1027.
(49) Irie, K.; Ishida, A.; Nakamura, T. *Chem. Pharm. Bull.* **1984**, *32*, 2126.
(50) Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 7411.
(51) Abramovitch, R. A.; Shapiro., D. S. *J. Chem. Soc.* **1956**, 4589.
(52) Hamaker, L. K. Ph.D. Thesis, University of Wisconsin−Milwaukee, 1995.

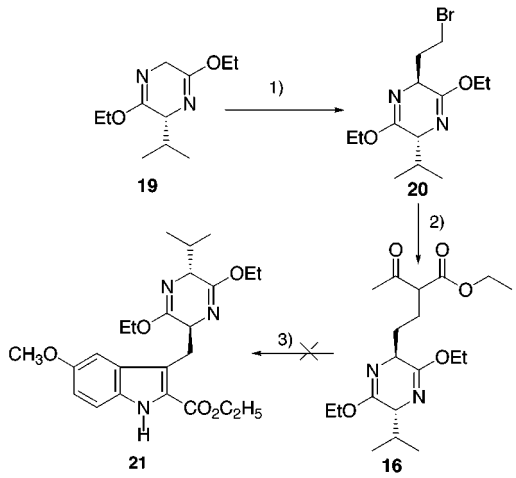
Scheme 3



1) phosgene, THF; or triphosgene, 99%. 2) $NH_2CH_2CO_2CH_2CH_3$, $CHCl_3$, Et_3N,THF, -70 °C; toluene, reflux,70%. 3) freshly prepared $Et_3O^+BF_4^-$, CH_2Cl_2, rt, 90%

a. The use of D-valine in this sequence will result in the Schöllkopf auxiliary for L-amino acids.
b. This material is also available from Aldrich Chemical Co.

Scheme 4



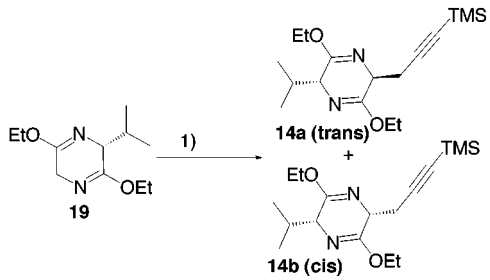
1) *n*-BuLi (2.1 eq), THF, -78°C, 0.5h; $BrCH_2CH_2OH$ (1.0 eq), -78°C-rt, 3h; TsCl (1.0 eq), rt, 2h, reflux, 18h, 80%,(1 pot)
2) $CH_3COCH_2CO_2C_2H_5$, $NaOC_2H_5$, C_2H_5OH,85%

3) KOH, ethanol;CH_3O–  –N_2^+; Δ
(Fischer-indole cyclization did not take place)

with bromide **20** (see Scheme 4). However, numerous attempts to synthesize 5-methoxyindole derivative **21** by the Fischer-indole cyclization of a Japp−Klingmann azo-ester intermediate failed. No indole product was obtained either by acid-mediated cyclization or thermal-effected cyclization. However, both intermediates, acetylester **16** and bromide **20**, could serve as templates for the synthesis of other unnatural α-amino acids.

In 1991, Larock et al.[53] reported an excellent method for the preparation of indoles that involved the palladium-catalyzed heteroannulation of internal alkynes with *o*-iodoanilines. Applications of this method have been extended in Larock's group[54−57] to the syntheses of indenones,[58] benzofurans,[59] etc. Importantly, Chen et al.

Scheme 5



1) n-BuLi, THF, -78 °C;
TMS–≡–X
22a-f

a. X=Br-
b. X=diethylphosphate
c. X=diphenylphospate
d. X=tosylate
e. X=p-methoxybenezenesulfonate
f. X=mesylate

prepared the 5-HT_{1D} receptor agonist MK-0462 on a very large scale employing this annulation strategy.[60] Consequently, this approach was chosen as the desired convergent route to synthesize optically active tryptophans (Scheme 2).

The synthetic strategy for the preparation of optically active ring-A substituted tryptophans **12** was envisaged to rely on the heteroannulation of *o*-iodoaniline derivatives **13** with the internal alkyne **14**. The alkyne **14** would be made available by diastereoselective alkylation of the Schöllkopf chiral auxiliary **19**. The Schöllkopf chiral auxiliary was chosen here for the preparation of L-tryptophans would be available from D-valine, while the D-isomers would originate from the inexpensive L-valine (Scheme 3).[52] The silyl group was introduced into the internal alkyne **14** to control the regioselectivity of the annulation process because of its size.[53] This versatile moiety could be readily removed or transformed into another functional group when necessary.

As indicated, the approach to the synthesis of chiral tryptophans began with the diastereoselective preparation of propargyl-substituted Schöllkopf chiral auxiliary **14** (Scheme 5). The popular Schöllkopf chiral auxiliary**,** bis-lactim ether **19,** derived from D-valine and glycine, was readily available on a large scale (see the Supporting Information for experimental details).[44,52] Metalation of the bis-lactim ether **19** with *n*-butyllithium in THF at low temperature was followed by alkylation with a variety of electrophiles and usually proceeded with a high degree of trans diastereoselectivity.[61−63] Initial attempts to prepare **14** rested on reaction of the Schöllkopf chiral auxiliary **19** with 3-bromo-1-(trimethylsilyl)-1-propyne (entry 1, Table 1). Unfortunately, the alkylation process furnished **16** with low diastereoselectivity (**14a**/**14b** = 2.5:1). Presumably, the selectivity was low because the

(53) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
(54) Larock, R. C.; Roesch, K. R. *Org. Lett.* **1999**, *1*, 1551.
(55) Larock, R. C.; Roesch, K. R. *Org. Lett.* **1999**, *1*, 553.
(56) Larock, R. C.; Gagnier, S. V. *J. Org. Chem.* **2000**, *65*, 1525.
(57) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.
(58) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.
(59) Larock, R. C.; Yum, E. K.; Doty, M. J. *J. Org. Chem.* **1995**, *60*, 3270.
(60) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Reamer, R. A.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 6981.
(61) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798.
(62) Schöllkopf, U. In *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer: Berlin, 1983; Vol. 109, p 65.
(63) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085.

Table 1. Diastereoselective Synthesis of Internal Alkyne 14

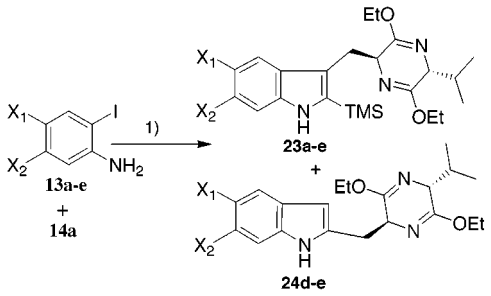
entry	X (leaving groups)	solvent	*T* (°C)	isolated yield (%)	**14a** (trans)/ **14b**(cis)[a]
1	−Br	THF	−78	80	2.5:1
2	−Br	THF	−100	78	1.6:1
3	−OTs	THF	−78	75	11:1
4	−OTs	DME	−58	74	5:1
5	$-OSO_2CH_3$	THF	−78	72	5:1
6	$-OSO_2(p\text{-}CH_3OPh)$	THF	−78	72	12:1
7	$-OPO(OEt)_2$	THF	−78	70	12:1
8	$-OPO(OPh)_2$	THF	−78	80	46:1

[a] The ratios were determined by the integration of the ^{1}H NMR spectrum of the crude reaction mixture.

rodlike propargyl system of the electrophile was not bulky enough to provide high diastereoselectivity at the site of reaction. Bis-lactim ethers derived from unnatural amino acids, have been reported to provide exceptionally high asymmetric induction,[64,65] but the relative cost and limited availability excluded them from this approach.

It was decided to study the alkylation conditions and modify the leaving group on **22** (Scheme 5) to provide substituted Schöllkopf chiral auxiliary **14** with high diastereoselectivity. The electrophiles represented by **22** (Table 1) were prepared either in situ by deprotonation of 3-trimethylsilyl-2-propyn-ol followed by trapping with various sulfonyl chlorides or chlorophosphates or by treatment of 3-trimethylsilyl-2-propynol with the corresponding sulfonyl chloride or chlorophosphate at 0 °C in the presence of KOH in diethyl ether.[66] As illustrated in Table 1, when the process was carried out at very low temperature, the selectivity was not improved (entry 2). Variation of the solvent (entry 4, Table 1) did not improve the diastereoselectivity. However, the leaving group does play an important role in formation of the desired trans diastereomer in preference to its cis counterpart. When the leaving group was bulkier and less prone to undergo SN_2 substitution, the diastereoselectivity increased (entries 6−8, Table 1). Alkylation of the Schöllkopf chiral auxiliary **19** with diphenyl (trimethylsilyl)propargyl phosphate provided the best trans diastereoselectivity (entry 8, Table 1, trans/cis = 46:1, >96% de). Only a trace of the undesired cis isomer was observed and was removed easily by chromatography. Presumably, the lesser reactivity of the phosphate and the bulkier size are the main factors for such an outcome. Further experiments are underway to obtain a fuller understanding of the effect of the leaving group (see section c). The substituted *o*-iodoanilines **13a**−**g** were prepared via direct iodination of the corresponding substituted anilines.[67,68] With the internal alkyne **14a** and substituted *o*-iodoanilines **13a**−**h** in hand, the palladium-catalyzed heteroannulation reaction was carried out (Scheme 6). The results of this process are summarized in Table 2. Lithium chloride was found to be a crucial component of this coupling process in agreement with the findings of Larock[53] and Yum.[69] Addition of PPh_3 retarded the reaction rate and resulted

Scheme 6



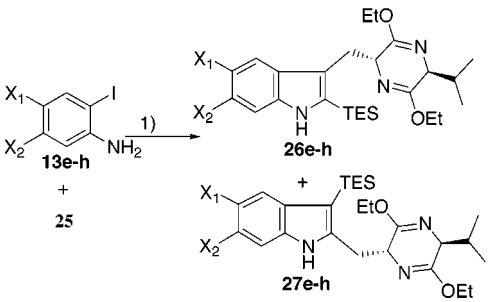
1) 5mol% $Pd(OAc)_2$, Na_2CO_3, LiCl, DMF,100°C.

Table 2. Results from the Palladium-Catalyzed Heteroannulation Process

entry	X_1	X_2	alkyne	$Pd(OAc)_2$ (%)	regioisomer	product yield (%)
1	H	H	**14a**	5	ND[a]	81 (**23a**)
2	CH_3	CH_3	**14a**	5	ND	70 (**23b**)
3	CH_3	H	**14a**	5	ND	63 (**23c**)
4	F	H	**14a**	5	15 (**24d**)	50 (**23d**)
5	NO_2	H	**14a**	5	22 (**24e**)	65 (**23e**)
6	NO_2	H	**25**[b]	5	4 (**27e**)	83 (**26e**)
7	NO_2	H	**25**	10	14 (**27e**)	72 (**26e**)
8	F	H	**25**	5	ND	62 (**26f**)
9	Cl	Cl	**25**	5	ND	80 (**26g**)
10	Cl	Cl	**25**	8	10 (**27g**)	67 (**26g**)
11[c]	OMe	H	**25**	5	<5	65 (**26h**)
12[d]	H	OMe	**25**	5	<5	77 (**26i**)

[a] The 2,3-regioisomer was not detected or isolated. The ratio was determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture. [b] The synthesis of this material will be discussed in section d. [c] This is based on unpublished data (Xuebin Liao and James M. Cook). [d] This case will be discussed in more detail in section d.

Scheme 7

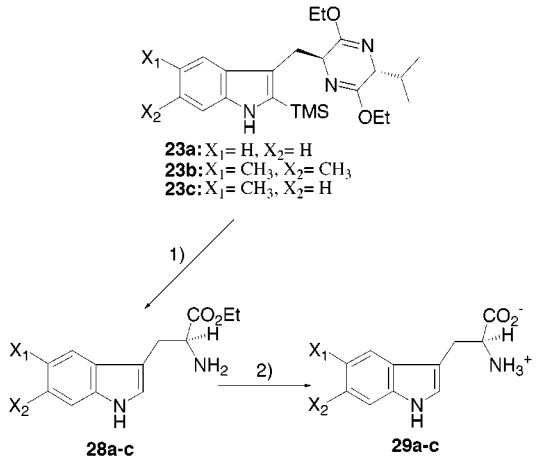


1) **25**, 5mol% $Pd(OAc)_2$, Na_2CO_3, LiCl, DMF,100 °C.

in the isolation of recovered starting material and diminished yields. Use of an excess of alkyne **14a** in this sequence was beneficial to the process. For the substrate listed in entry 2, the biaryl byproduct was isolated if only one equivalent of alkyne **14a** was employed. For electron-deficient iodoanilines (entries 4 and 5, Table 2), the heteroannulations were appreciably faster but with reduced regioselectivity. For these cases, the desired products **23d** and **23e** were obtained in 50% and 65% yield, respectively, along with the desilyated regioisomers **24d** and **24e**, isolated in 15% and 22% yield, respectively. For 4,5-dichloro-2-iodoaniline, 10% of the regioisomer **27g** was generated even though the bulkier triethylsilyl group **25** was employed (entry 10, Table 2; Scheme 7). In contrast to its trimethylsilyl counterpart, the triethylsilyl group in regioisomer **27g** was retained, presumably because the TES group is more stable than the TMS

(64) Schöllkopf, U.; Neubauer, H.-J. *Synthesis* **1982**, 861.
(65) Richter, L. S.; Gadek, T. R. *Tetrahedron*: *Asymmetry* **1996**, *7*, 427.
(66) Svatos, A.; Attygalle, A. B.; Meinwald, J. *Tetrahedron Lett.* **1994**, *35*, 9497.
(67) Sy, W.-W. *Synth. Commun.* **1992**, *22*, 3215.
(68) Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1941.
(69) Park, S. S.; Choi, J.-K.; Yum, E. K. *Tetrahedron Lett.* **1998**, *39*, 327.

Scheme 8



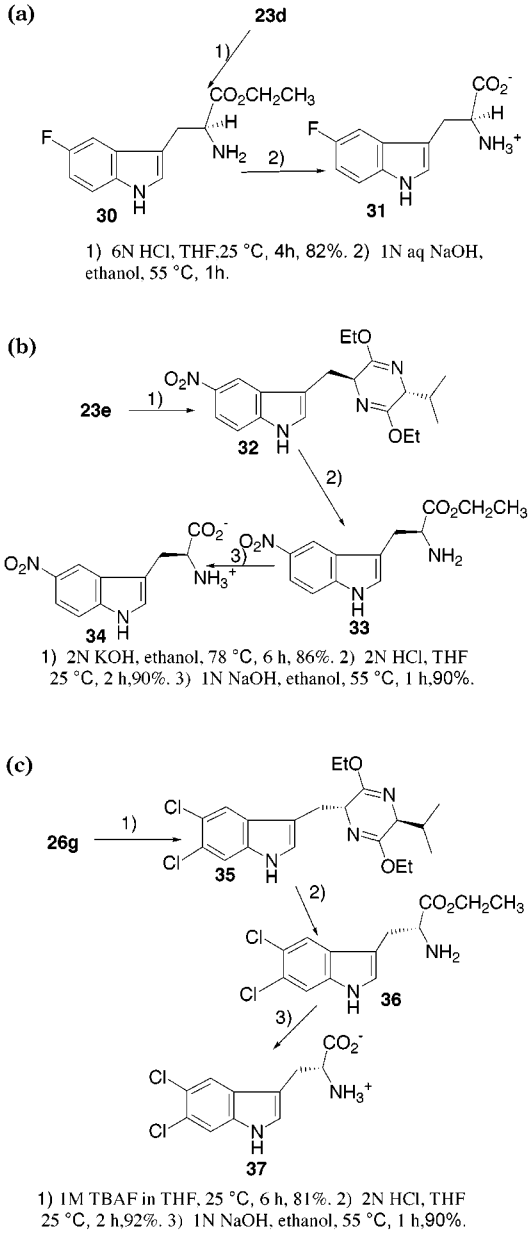
1) 2N HCl, THF, 25 °C, 6h. 2) 1N aq NaOH, ethanol,55 °C, 1h.

moiety. However, when 5% of the $Pd(OAc)_2$ catalyst was employed in place of 10%, no 2,3-regioisomer **27g** could be detected by integration of the ^1H NMR spectrum (entry 9, Table 2) of the crude product. In this manner, **26g** was prepared in regiospecific fashion, as desired. For electron-rich systems (entries 11 and 12, Table 2), the annulation process took place in 65% yield to provide the 5-methoxyindole derivative **26h**[70] and in 77% yield to furnish the 6-methoxyindole derivative **26i**. For both cases, less than 5% of the 2,3-regioisomer was detected by integration of the ^1H NMR spectrum of the crude material.

The catalytic cycle for the heteroannulation process is believed to follow that reported originally by Larock.[71,72] The regiochemical outcome is controlled by the insertion process.[70,71] It appears the controlling factor in the insertion process is the steric interactions present in the developing carbon−carbon bond or the orientation of the alkyne immediately prior to syn insertion of the alkyne into the arylpalladium bond. Alkyne insertion occurs so as to generate the least steric strain in the vicinity of the shorter, developing carbon−carbon bond rather than the longer carbon−palladium bond.[71] The arylpalladium bond and the alkyne must be parallel in order for the syn addition to occur; consequently, the alkyne may adopt an orientation in which the more sterically demanding silyl group (TES) is situated away from the sterically encumbered aryl group (see ref 70 for details). However, since the regioselectivity decreased significantly for the annulation with electron-deficient iodoanilines (Table 2), electronic factors must also play a role in the regiochemistry of the catalytic process. For the aryl iodides substituted with electron-withdrawing groups, the heteroannulations took place at a much faster rate, with a concomitant decrease in regioselectivity as mentioned.

To complete the synthesis of tryptophans, the pyrazine group in indoles **23a**−**e** and **26e**−**h** must be hydrolyzed and the silyl group required removal. When the indoles **23a**−**23c** were stirred with aqueous hydrochloric acid in THF (Scheme 8), the pyrazine moiety was hydrolyzed to the resulting amino acid ethyl ester with concomitant

Scheme 9



removal of the silyl group to provide the tryptophan ethyl esters **28a**−**c** directly. As shown in Scheme 8, electron-donating groups (X1 or X2) promoted the required protonation at C(2) or stabilized the β-silylcation or both to facilitate cleavage of the silyl moiety. The subsequent saponification furnished L-tryptophan derivatives **29a**−**c** in good yields. However, for indoles substituted with electron-withdrawing groups in ring A, the acid-mediated desilylation was troublesome, as expected (Scheme 9a). For the fluorine-substituted tryptophan **23d**, aqueous 6 N HCl instead of 2 N HCl was required to cleave the trimethylsilyl group. For the nitro-substituted tryptophan **23e**, desilylation failed under acidic conditions; however, when **23e** was treated with aqueous 2 N KOH in ethanol at 78 °C for 6 h, smooth removal of the silyl group occurred (Scheme 9b). Acid-mediated hydrolysis of the desilylated intermediate **32**, followed by saponification of the ester moiety, provided the desired 5-nitro-L-tryptophan **34** in good yield. For the dichloro-substituted indole **26g**, the triethylsilyl group was removed by treatment with tetrabutylammonium fluoride (Scheme

(70) Liao, X.; Cook, J. M. Unpublished data. See also: Ma, C. Ph.D. Thesis, University of Wisconsin−Milwaukee, 2000.

(71) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652−7662.

(72) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.

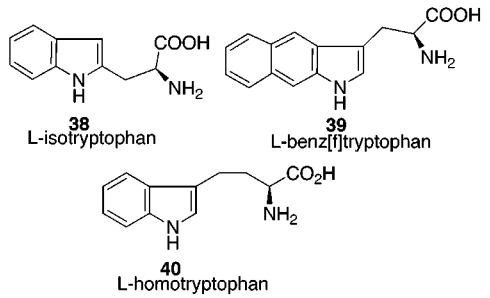


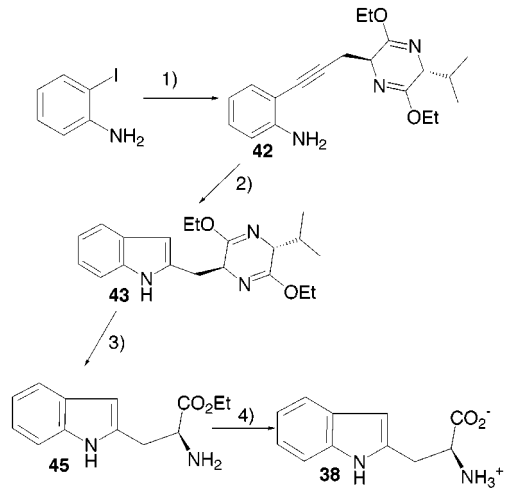
Figure 2. Structures of three important tryptophan analogues.

9c). Hydrolysis and saponification under similar conditions to **32** provided 5,6-dichloro-D-tryptophan **37**. The optical rotation of the optically active tryptophans obtained in this process were in good agreement with the literature values,[49,73] where available.

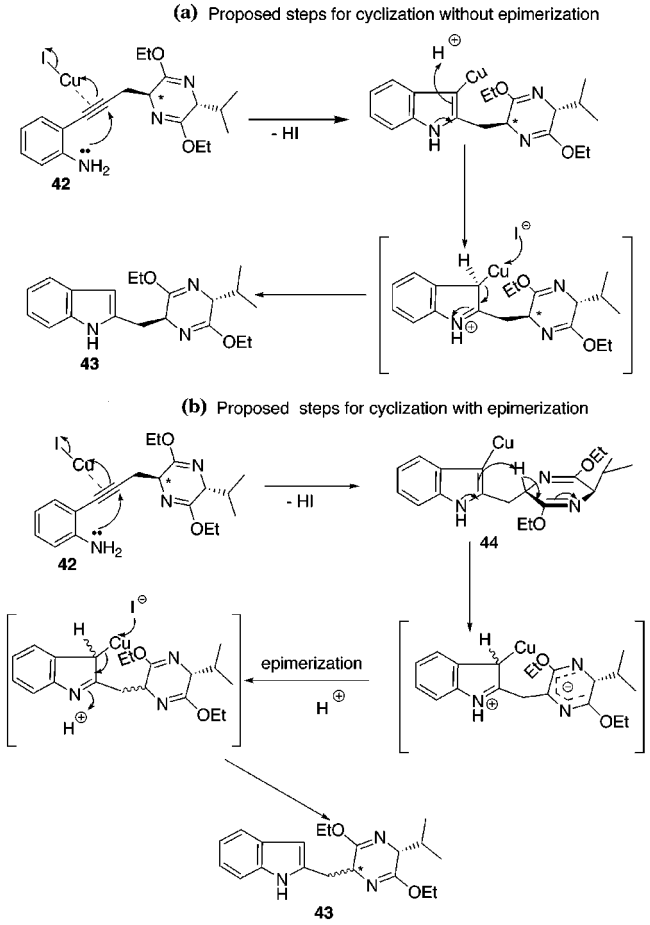
b. Asymmetric Synthesis of Important Tryptophan Analogues. In the continued effort to search for potent inhibitors of IDO, it was of interest to evaluate the IDO activity of the three structurally distinct and optically active tryptophan analogues: L-isotryptophan **38**, L-benzo[*f*]tryptophan **39**, and L-homotryptophan **40** (Figure 2). Multistep syntheses of the racemic form of these three tryptophan analogues have been reported previously;[74−76] however, none of them have been prepared enantioselectively. Described below is an efficient preparation of these three tryptophan analogues in optically active form (D or L) via the Schöllkopf chiral auxiliary.

Racemic isotryptophan was first synthesized by Kornfeld and was reported to exhibit some bacteriostatic activity.[74] The stereoselective synthesis of isotryptophan **38** developed here is depicted in Scheme 10. Palladium-catalyzed Heck coupling of *o*-iodoaniline with alkyne **41**[77] provided the aminoarylalkyne **42** in high yield. Intramolecular cyclization of **42** was successfully promoted by CuI while $PdCl_2$ and $NaAuCl_4$ both failed to effect the cyclization. Initially, the CuI-promoted reaction was carried out in pure DMF. Unfortunately, these conditions resulted in significant epimerization of the chiral center (*) in **43**. One possible pathway for the epimerization is shown in Scheme 11b. Organocopper compounds are considerably less basic than Grignard or organolithium reagents, but basicity increases when the temperature is raised. As indicated in Scheme 11, the indolylcopper intermediate could abstract a proton from the chiral center in the pyrazine group under the high reaction temperatures (80−90 °C). The reprotonation of the stabilized anion that results could occur from either face and effect epimerization of the cyclic pyrazine. However, additional experiments are required to determine if this is reasonable. This problem, however, was alleviated by addition of ethylene glycol to the medium as a proton source to suppress epimerization. In this fashion, indole **43** was obtained in 80% yield accompanied by only 6% of the epimerized (*) material, which was removed by flash chromatography. The desired L-isotryptophan **38** was obtained in 72% yield by acidic hydrolysis of **43**, followed by subsequent saponification(see the Experimental Section for details).

Scheme 10



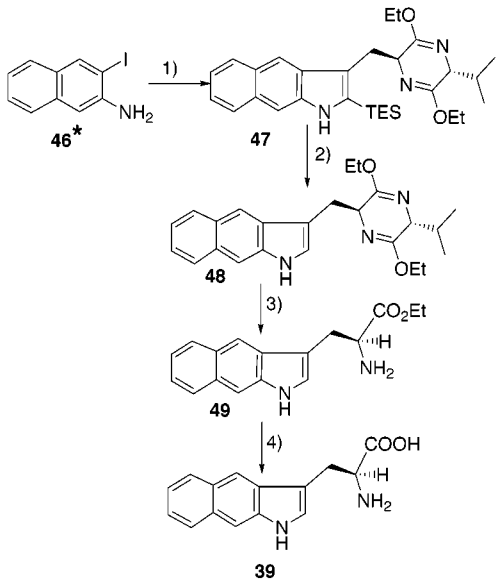
Scheme 11



The linear benzo[*f*]tryptophan was suggested as a potential fluorescent amino acid probe because of its red-shift from the natural amino acid.[75] In 1997, McLaughlin

(73) Fluka catalog **1999/2000**, 648.
(74) Kornfeld, E. C. *J. Org. Chem.* **1951**, *16*, 806.
(75) Yokum, T. S.; Tungaturthi, P. K.; McLaughlin, M. L. *Tetrahedron Lett.* **1997**, *38*, 5111.
(76) Snyder, H. R.; Pilgrim, F. J. *J. Am. Chem. Soc.* **1948**, *70*, 1962.
(77) Ma, C.; Yu., S.; He, X.; Liu, X.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 2781.

Scheme 12



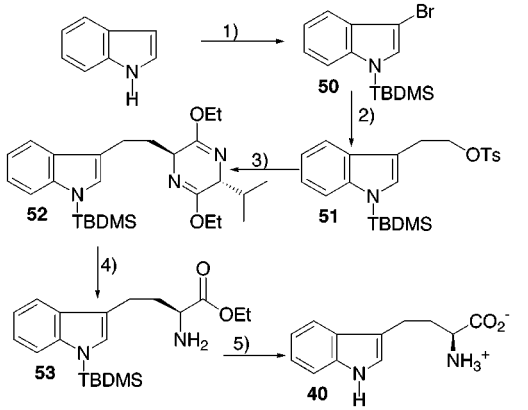
1) **25**, 4% $Pd(OAc)_2$, Na_2CO_3, LiCl, DMF, 100 °C, 16h, 65%. 2) 1 N TBAF in THF, rt, 2h,85%. 3) 1 N aqHCl, THF, rt, 2h, 85%. 4) 1 N aq NaOH, ethanol, 60 °C, 2h, 83%.

* The synthesis of this material is available in the Supporting Information.

first reported the synthesis of N_b-Boc-benzo[*f*]tryptophan in racemic form.[75] As described above, an efficient palladium-catalyzed heteroannulation sequence was developed for the synthesis of ring-A substituted optically active tryptophans. This approach was extended to L-benzo[*f*]tryptophan **39** (Scheme 12). The required 3-iodo-2-aminonaphthalene **46** was synthesized as previously reported (see the Supporting Information for details).[77,78] Heteroannulation of **46** and the internal alkyne **25** generated the key benzo-fused indole **47**, accompanied by 15% of the 2,3-substituted regioisomer, which was easily removed by flash chromatography. Desilylation of **47** was achieved with TBAF in THF to provide intermediate **48**; treatment of **48** with 1 N aqueous HCl/THF had failed to effect the desilylation. L-Benzo[*f*]tryptophan **39** was obtained in 75% yield by acidic hydrolysis of **48**, followed by saponification. As expected, analysis by spectroscopy indicated the UV absorption of L-benzo[*f*]-tryptophan **39** was red-shifted ~60 nm from the absorption of natural L-tryptophan. This analogue may provide an efficient probe to study biological processes (as well as peptides) that involve tryptophan (IDO, TDO, etc.).

Homotryptophan was prepared previously by Snyder as a racemate.[76] The strategy for the asymmetric synthesis of L-homotryptophan **40** was to effect a two-carbon homologation of an indole moiety to be followed by alkylation of the Schöllkopf chiral auxiliary, as depicted in Scheme 13. Initially, *N*-sulfonyl-3-bromoindole was chosen as the starting material to effect the lithium halogen exchange (*t*-BuLi) to generate a carbanion at position-3, as previously reported by Gribble.[79] However, in our hands, this carbanion at [C(3)] was readily converted into the thermodynamically more stable carbanion at position-2 (at −78 °C) due to the stabilizing effect of the *N*-sulfonyl group adjacent to the negative charge. Consequently, the *N*-TBDMS-substituted 3-bromoindole **50**[80] was employed as the starting bromide. Lithium halogen exchange of **50** with *tert*-butyllithium was followed by nucleophilic attack on the oxirane, the anion of which was trapped with *p*-toluenesulfonyl chloride to generate the tosylate **51** in one reaction vessel. Alkylation of the anion of the Schöllkopf chiral auxiliary with **51** furnished the intermediate **52** in high yield and diastereospecific fashion. Hydrolysis of **52** and subsequent desilylation followed by saponification provided L-homotryptophan **40** in high yield.

Scheme 13

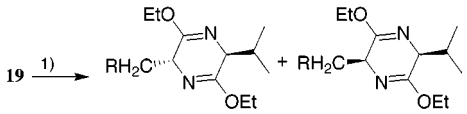


1) n-BuLi, THF, -78 °C; $(t\text{-}C_4H_9)(CH_3)_2SiCl$; NBS, -78 °C to rt, 84%.
2) *t*-BuLi, THF, -78°C, 10 min; , -78 °C to rt, 5h; TsCl (1.0 eq), rt, 18h, (one vessel, 84%). 3) **19**, n-BuLi, THF ,-78°C to rt,3h, 92%.
4) 1 N aq HCl/THF, rt, 99%. 5)TBAF/THF, rt; 1 N aq NaOH, ethanol,80 °C, 4h, 83%.

c. Diastereoselective Alkylation of the Schöllkopf Chiral Auxiliary.[81] In the early 1980s, Schöllkopf developed an excellent chiral auxiliary **19** to prepare a large variety of amino acids.[61] It can be readily prepared from L-valine and glycine on a large scale.[44,52] Numerous applications of this Schöllkopf chiral auxiliary in the synthesis of optically active unnatural amino acids have been reported, including the synthesis of the antitumor agent OF 4949-III/IV,[82] α-deuterated α-amino acids,[83] and tryptophan analogues.[50,84] In a few cases, however, alkylation of the Schöllkopf chiral auxiliary suffered from poor diastereoselectivity.[61,85] Attempts to overcome this drawback have been carried out by modification of the chiral auxiliary through replacement of the isopropyl group in **19** with bulkier groups such as *tert*-butyl to increase the diastereoselectivity.[64,65] Although the alkylation selectivity was increased, the relative cost and availability of those modified bis-lactim ethers have limited their utilization.[64,65] Because of the popularity of the Schöllkopf chiral auxiliary **19**, the focus here has shifted from the chiral auxiliary itself to the electrophiles employed for alkylation (Scheme 14). More specifically, a variety of leaving groups have been employed to provide a simple and practical solution to the problem mentioned above. Studies of the effect of the leaving group on alkylation diastereoselectivity were carried out by employing the

(78) Kelly, R. T.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072.
(79) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.
(80) Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 10.
(81) Ma, C.; He, X.; Liu, X.; Yu, S.; Zhao, S.; Cook, J. M. *Tetrahedron lett.* **1999**, *40*, 2917.
(82) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000.
(83) Rose, J. E.; Leeson, P. D.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1563.
(84) Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 9133.
(85) Gan, T. Ph.D. Thesis, University of Wisconsin—Milwaukee, 1997.

Scheme 14



1) n-BuLi, THF,-78 °C; RCH_2X (X = OTs or $OP(O)(OPh)_2$ or Br), **54a-e**

a, RCH_2= $H_2C{-}{\equiv}{-}TMS$

b, RCH_2= $H_2C{-}{\equiv}{-}TES$

c, RCH_2= 

d, RCH_2=

e, RCH_2= CH_2CH_3

Table 3. Effect of the Leaving Group on the Alkylation Selectivity of the Schöllkopf Chiral Auxiliary 19

Entry[a]	RCH_2	X=bromide		X=tosylate		X=diphenyl phosphate	
		Yield %	% de	Yield %	% de	Yield %	% de
1	$H_2C{-}{\equiv}{-}TMS$	81	43	82	83	80	95
2	$H_2C{-}{\equiv}{-}TES$	90	14	89	71	90	96
3		86	71	80	92	42	98
4	H_2C	88	97	82	67	40	97
5	CH_2CH_3	80	71	82	90	24	98

[a] The % de was determined by integration of the ^1H NMR spectrum of the crude reaction mixture.

bromide, tosylate, and diphenyl phosphate to effect alkylation of the Schöllkopf chiral auxiliary **19** at aliphatic, benzylic, propargylic, and allylic electrophilic centers.[81]

The diphenyl phosphates and tosylates were prepared either in situ by deprotonation of the corresponding alcohol with *n*-butyllithium followed by trapping of the resulting oxygen anion with a sulfonyl chloride or chlorophosphate or by treatment of the corresponding alcohol with benzene sulfonyl chloride or chlorophosphate at 0 °C in the presence of KOH in diethyl ether.[66,70] Alkylations of the Schöllkopf chiral auxiliary **19** were carried out in THF at −78 °C for 6 h. The diastereoselectivity was determined by integration of the ^1H NMR spectrum of the crude material. The results are depicted in Table 3.

As shown in Table 3, alkylation with the diphenyl phosphates furnished high diastereoselectivity (>95%) in all cases. The tosylate provided better diastereoselectivity than the bromide with the exception of one case (entry 4, Table 3). Bromide has been the leaving group most commonly employed;[61−63] unfortunately, it provided the poorest diastereoselectivity in most cases. In terms of both alkylation yield and selectivity, however, both tosylate and diphenyl phosphate exhibited specific advantages. At the propargylic position (entries 1 and 2, Table 3), diphenyl phosphate was the best group to effect efficient and selective alkylation. At the allylic position (entry 4, Table 3), the bromide was the leaving group of choice in agreement with the previous reports of Schöllkopf.[61] At the aliphatic and benzylic positions (entries 3 and 5, Table 3), tosylate provided the best results when the alkylation yield was balanced against stereoselectivity.

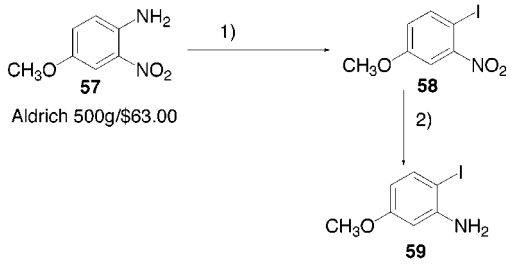
Although alkylation with the diphenyl phosphates provided very high diastereoselectivity, the lower yields in some cases compromised its utility. During the alkylation process, the electrophilic phosphorus could compete for the anion of the Schöllkopf chiral auxiliary with the electrophilic carbon atom, thus diminishing the yield of the desired carbon alkylation. In support of this hypothesis, decreased yields on carbon alkylation with diphenyl phosphate were found to be coupled with the production of phenol, a byproduct of alkylation at phosphorus.[70] An attempt to improve the yield of the alkylation was executed by modification of the character of the anion of the Schöllkopf chiral auxiliary **19**. When the lithium salt of **19** was transmetalated to provide a higher order (HO) organocuprate,[86,87] the alkylated products **55c** and **56c** were isolated in 81% yield in contrast to the 40% yield obtained with the lithium salt of **19** (entry 4, Table 3). However, the diastereoselectivity decreased from 97% de to 68% de. The alkylation mechanism may have changed when the lithium salt of **19** was converted into the higher order organocuprate resulting in lower de. Much work remains to be done on this system to understand this decrease.

Examination of the yields and diastereoselectivities in Table 3 provides a rational basis for the selection of the alkylating agent in the Schöllkopf approach to amino acids. In most cases, diphenyl phosphate and tosylate were found to be far superior to bromide, although the allylic system in entry 4 proves to be an exception. Further work is underway to understand the high % de achieved with the diphenyl phosphates.

d. Efficient Synthesis of 6-Methoxytryptophan as Well as an Improved Total Synthesis of Tryprostatin A. The enantiospecific synthesis of a number of *Alstonia* macroline/sarpagine alkaloids has been reported that employed the trans 1,3-transfer of asymmetry during the Pictet−Spengler reaction;[88−90] use of D-(+)-tryptophan provided the natural series via this approach.[26,27] Studies of the synthesis of ring-A oxygenated indole alkaloids (see Figure 1) has prompted the need for a preparative synthesis of 6-alkoxy-D-(+)-tryptophans via a route that would also provide the L-(−) enantiomers, if desired. D-(+)-Tryptophans via this chemistry (trans transfer of asymmetry) would provide the natural alkaloids in the *Alstonia* series, while the L-(−)-isomers would furnish the unnatural antipodes for biological screening.[24,25,88−90] Although both the Moody azide and regiospecific bromination methods can be employed to synthesize 6-methoxytryptophan,[44,91] it was felt the palladium-catalyzed heteroannulation process could provide 6-methoxytryptophan in a shorter and more efficient manner. More importantly, Chen et al. demonstrated this type of palladium-catalyzed reaction could be easily scaled up.[60]

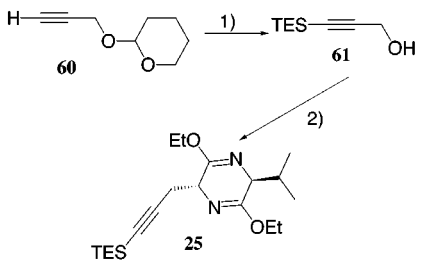
(86) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
(87) Beugelmans, R.; Bigot, A.; Bois-Choussy, M.; Zhu, J. *J. Org. Chem.* **1996**, *61*, 771.
(88) Bi, Y.; Cook, J. M. *Tetrahedron Lett.* **1993**, *34*, 4501.
(89) Czerwinski, K. M.; Deng, L.; Cook, J. M. *Tetrahedron Lett.* **1992**, *33*, 4721.
(90) Zhang, L. H. Ph.D. Thesis, University of Wisconsin−Milwaukee, 1990.
(91) Allen, M. S.; Hamaker, L. K.; LaLoggia, A. J.; Cook, J. M. *Synth. Commun.* **1992**, *22*, 2077.

Scheme 15[68]



1) $NaNO_2$/HCl, 0 °C; KI, 90% **(200 g)**. 2) NH_2NH_2, $FeCl_3 \cdot 6H_2O$/C, MeOH,reflux, 93%

Scheme 16



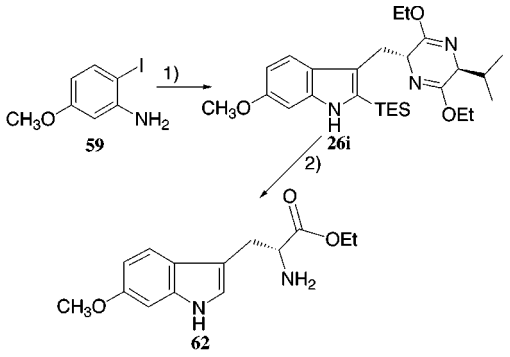
1) n-BuLi, THF; TESCl; PPTSA, MeOH, rt,91%. 2) $(PhO)_2POCl$, KOH, Et_2O, 0 °C; **19**, BuLi, THF, -78 °C, 90% (200g scale).

The synthesis began with a large-scale preparation of the 5-methoxy-2-iodoaniline **59**. Since the direct iodonation of *m*-anisidine lacked regioselectivity, attention turned to the classic Sandmeyer reaction.[68] As shown in Scheme 15, commercially available 2-nitro-3-methoxyaniline **57** ($63/500 g, Aldrich) was diazotized under standard conditions, followed by treatment of the diazonium ion that resulted with KI to give the iodo derivative **58** in 90% yield. Reduction of the nitro group was effected with hydrazine in the presence of a catalytic amount of $FeCl_3$ and active carbon in refluxing methanol to furnish the desired ortho iodoaniline **59** in 93% yield (100 g scale).

With *o*-iodoaniline **59** in hand, the diastereoselective preparation of the internal alkyne **25** (Scheme 16) was addressed. The THP-protected propargyl alcohol **60** was treated with *n*-BuLi, followed by quenching with TESCl to give the TES derivative in 95% yield. Hydrolysis of the THP group was effected with a catalytic amount of PPTS(pyridine *p*-toluenesulfonic acid) in methanol to afford the TES-protected propargyl alcohol **61** in 95% yield. Activation of the hydroxyl group by the diphenyl chlorophosphate moiety was realized in greater than 90% yield. The diphenyl phosphate that resulted was then stirred with the anion of the Schöllkopf chiral auxiliary **19** (derived from L-valine) at −78 °C to provide the alkyne **25** in 90% yield and greater than 96% de.

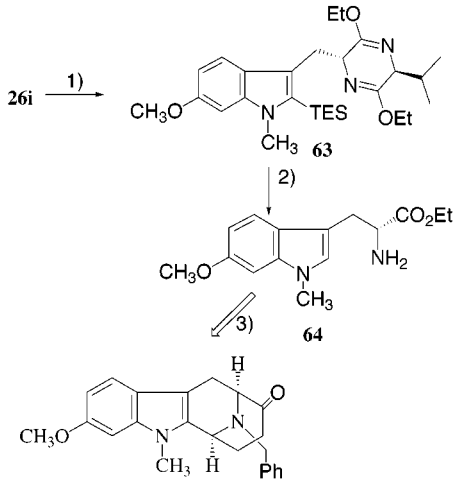
With both the TES-substituted alkyne **25** and the iodoaniline **59** readily available, the annulation was carried out in the presence of only 1% $Pd(OAc)_2$ to afford the desired indole **62** in 77% yield (Scheme 17) on a 300 g scale. No racemization of the chiral center was observed under these conditions. When this process was run on a >10 g scale, only a trace amount of the 2,3-regioisomer was isolated (less than 5%). Under similar conditions, the annulation of TMS-substituted alkyne **14a** with the iodoaniline **59** provided the corresponding indole in only 61% yield. This again illustrated that the TES-substituted alkyne **25** was preferred over the TMS-substituted counterpart for palladium-catalyzed annulations.[60] Treatment of the indole derivative **26i** with aqueous 2 N HCl in EtOH effected both hydrolysis of the Schöllkopf chiral auxiliary and removal of the indole-2-silyl group to provide optically active 6-methoxy-D-tryptophan ethyl ester **62**. Consequently, 6-methoxy-D-tryptophan ethyl ester **62** can be synthesized in optically active fashion and the route is amenable to scale-up to the multihundred gram level.

Scheme 17



1) **25**,1% $Pd(OAc)_2$, Na_2CO_3, LiCl, DMF,100 °C, 77% **(300g scale)**. 2) 2N aq HCl, EtOH, THF,-78 °C to 0 °C 86%

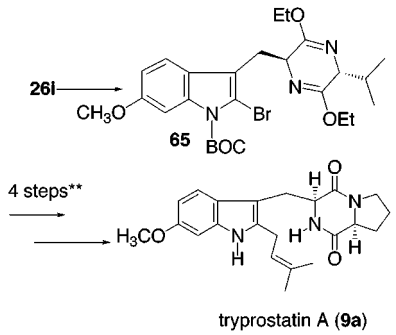
Scheme 18



1) NaH, DMF,MeI, 95%. 2) aq 2N HCl/THF, rt, 2h, 93%. 3) Pictet-Spengler reaction and Dieckmann reaction.

In addition, 6-methoxy-N_a-methyl-D-tryptophan **64** can be readily prepared from **26i** for the Schöllkopf chiral auxiliary is an excellent protecting group for the amino acid functionality of tryptophans. As shown in Scheme 18, treatment of indole **26i** with sodium hydride followed by addition of methyl iodide, resulted in the methylation of the indole N_a-H to provide **63** in 95% yield. The N_a-methyl indole **63** can be crystallized from hexanes to furnish white crystals. The absolute stereochemistry of **63** was determined by single-crystal X-ray analysis (see Figure S1 in the Supporting Information). The data obtained were accurate enough to provide the absolute configuration at C11 as *R* and at C14 as *S*. This X-ray structural analysis confirmed the stereochemical and regiochemical assignment of the entire series of tryptophans obtained from the palladium-catalyzed annulation. The desired 6-methoxy-N_a-methyl-D-tryptophan **64** was obtained in 93% yield by facile desilylation and hydrolysis of **63**. Currently, studies on the total synthesis of alstophylline **3** with this ester **64** are underway.

Scheme 19



1) NBS, CH_3CN,0 °C, 30 min; 2 eq $(BOC)_2O$,DMAP, 1h, 25 °C, 87%(1pot).

The first enantiospecific total synthesis of tryprostatin A was reported by Gan et al.,[43,44] with the bromide **65** as a synthetic intermediate. With the chemistry developed above, it was felt this intermediate could be synthesized from the readily available indole derivative **26i**. As depicted in Scheme 19, the 2-silylindole **26i**, which was synthesized in 77% yield via a palladium-catalyzed annulation, was treated with NBS in acetonitrile for 30 min, until analysis by TLC indicated complete reaction. Subsequent addition of 1 equiv of di-*tert*-butyl dicarbonate to the same reaction vessel, however, furnished the desired BOC-protected 2-bromoindole **65** in only 40% yield while about half of the N_a-H intermediate remained unreacted. Analysis of the reaction course suggested that the reaction byproduct (*N*-silylsuccinimide) might consume 1 equiv of di-*tert*-butyl dicarbonate, thus resulting in the insufficient supply of di-*tert*-butyl dicarbonate for the desired transformation. Indeed, *N*-BOC-succinimide was isolated from the reaction mixture. Consequently, 2 equiv of di-*tert*-butyl dicarbonate was needed to completely convert **26i** into **65**. As indicated in Scheme 19, N_a-BOC-2-bromoindole **65** was prepared in 87% yield in a one-pot fashion via treatment of **26i** with NBS and 2 equiv of di-*tert*-butyl dicarbonate. The spectral data of bromide **65** are identical to those reported by Gan.[44] Conversion of **65** into tryprostatin A (**9a**) can be executed following the route of Gan et al.[44] and Zhao. [45] Therefore, an improved total synthesis of tryprostatin A (**9a**) has been accomplished via a palladium-catalyzed heteroannulation process. The new synthesis is shorter (seven steps from commercial material **59**), easier to perform, and more efficient (43% overall yield from **59** when coupled with the improved procedure for removal of the BOC group in the final step[45]).

Conclusion

Internal alkyne **14a** was prepared in greater than 96% de via alkylation of the Schöllkopf chiral auxiliary **19** employing diphenyl phosphate as a leaving group. The palladium-catalyzed heteroannulation reaction of internal alkyne **14a** or **25** and substituted *o*-iodoanilines **13** was carried out to provide 2-silylindoles. Lithium chloride was found to be a crucial component of this Pd^0-mediated coupling process. Addition of the PPh_3 ligand retarded the reaction rate and resulted in the isolation of recovered starting material and diminished yields. For electron-deficient iodoanilines, the heteroannulations were appreciably faster but with reduced regioselectivity. More importantly, annulation with triethylsilyl (TES)-substituted internal alkyne **25** was found to provide better yields and regioselectivity[60] than the trimethylsilyl (TMS)-substituted agent **14a**. For electron-rich indoles that resulted from the annulation, both desilylation and hydrolysis of the pyrazine group took place simultaneously under acidic conditions. Subsequent saponification provided the desired optically active tryptophans. However, for electron-deficient indoles, desilylation would not take place under mildly acidic conditions. Alternatively, desilylation was achieved with TBAF or potassium hydroxide followed by subsequent hydrolysis and saponification to furnish the tryptophans. In addition, the efficient diastereoselective synthesis of three tryptophan analogues (L-isotryptophan **38,** L-benzo[*f*]tryptophan **39** and L-homotryptophan **40**) with potential activity toward IDO have been completed. These syntheses make available any of these tryptophans as D or L isomers in optically active form for the study of biological processes (IDO, TDO, etc.). The Schöllkopf/palladium-catalyzed heteroannulation protocol is short, practical, and versatile in operation because of the variety of iodoanilines and the availability of the Schöllkopf chiral auxiliary in both enantiomeric forms. Studies of the effect of the leaving group on the alkylation diastereoselectivity were carried out by employing the bromide, tosylate, and diphenyl phosphate to effect alkylations of the Schöllkopf chiral auxiliary **19** at aliphatic, benzylic, propargylic, and allylic electrophilic centers. Alkylation with the diphenyl phosphates furnished exceptionally high diastereoselectivity (>95%) in all cases. The tosylate provided better diastereoselectivity than the bromide with the exception of one case. Examination of the yields and diastereoselectivities in Table 3 provides a rational basis for the selection of alkylating agent in the Schöllkopf approach to amino acids. In most cases, diphenyl phosphate and tosylate were found to be far superior to bromide, although a few exceptions existed. With both the TES-substituted alkyne **25** and the iodoaniline **59** readily available, the Pd^0-mediated annulation was then carried out in the presence of only 1% $Pd(OAc)_2$ to afford the desired 6-methoxylindole **26i** in 77% yield. Treatment of the indole derivative **26i** with aqueous 2 N HCl in EtOH effected both the hydrolysis of the Schöllkopf chiral auxiliary and the removal of the indole-2-silyl group to provide optically active 6-methoxy-D-tryptophan ethyl ester **62** for natural product total synthesis. Consequently, 6-methoxy-D-tryptophan ethyl ester **62** was synthesized in optically active fashion and the route was amenable to scale-up to the multihundred gram level. The 2-silylindole **26i** was also reacted with NBS and 2 equiv of di-*tert*-butyl dicarbonate in a one-pot fashion to afford the key intermediate **26i**, which resulted in an improved synthesis of tryprostatin A (**9a**).

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 ^1H NMR spectra were recorded on a Bruker 250-MHz or 300-MHz multiple-probe instrument. Infrared spectra were recorded on a Nicolet Dx FTIR DX V5.07 spectrometer or a Perkin-Elmer 1600 Series FT-IR spectrometer. Low-resolution mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5985 B gas chromatograph−mass spectrometer. High-resolution mass spectral data were taken on a VG autospectrometer (double focusing high-resolution GC/mass spectrometer, UK). Optical rotations were measured on a JASCO DIP-370 pola-

rimeter. 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.

Indoles were visualized with Dragendorf's reagent or a saturated solution of ceric ammonium sulfate in 50% sulfuric acid. Ketones or aldehydes were visualized with an aqueous solution of 2,4-dinitrophenylhydrazine 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.

Diphenyl 3-(Trimethylsilyl)prop-2-ynyl Phosphate 22c. To a solution of 3-(trimethylsilyl)prop-2-yn-1-ol (1.4 g, 11.7 mmol) and diphenyl chlorophosphate (3.52 g, 13.1 mmol) in diethyl ether (30 mL) at −50 °C was added powdered potassium hydroxide (4.18 g, 74 mmol). The mixture that resulted was allowed to warm to 0 °C over 20 min and stirred at 0 °C for 12 h. The reaction mixture was poured into ice−water (100 mL), and the ether layer was separated. The aqeous layer was extracted with ether (2 × 50 mL). The combined ether layer was washed with water until the water washing was no longer alkaline to pH paper. The ether solution was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The colorless residue was chromatographed on silica gel (hexane/EtOAc 8:1) to provide pure **22c** (3.6 g) in 92% yield. **22c**: IR (NaCl) 3067, 2956, 2178, 1588 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.15 (s, 9H), 4.85 (d, 2H, J = 10.8 Hz), 7.28 (m, 10H); MS (EI) *m/e* (rel intensity) 360 (M^+, 49), 307 (16), 251 (16), 213 (43), 131 (100). This material was used in a later step without further characterization.

3-(Trimethylsilyl)prop-2-ynyl Tosylate 22d. *p*-Toluenesulfonyl chloride, 3-(trimethylsilyl)prop-2-yn-1-ol, and powdered potassium hydroxide were reacted under conditions analogous to those employed for the preparation of **22c** above to provide **22d** as a colorless oil in 90% yield. **22d**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 9H), 3.87 (s, 3H), 4.69 (s, 2H), 6.99 (d, 2H, J = 9 Hz), 7.88 (d, 2H, J = 8.9 Hz). This material was used in a later step without further characterization.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[3-(trimethylsilyl)-prop-2-ynyl]-2,5-dihydropyrazine 14a. To a solution of (2*R*)-3,6-diethoxy-2-isopropyl-2,5-dihydropyrazine **19** (0.827 g, 3.9 mmol) in dry THF (25 mL) under nitrogen was syringed *n*-BuLi (2.5 M, 1.72 mL, 4.3 mmol) dropwise at −78 °C. This solution was stirred at −78 °C for 30 min. To this solution was added slowly a solution of diphenyl 3-(trimethylsilyl)prop-2-ynyl phosphate **22c** (1.4 g, 39 mmol) in dry THF (20 mL) that was cooled to −78 °C. After the reaction mixture was allowed to stir for 6 h at −78 °C, it was allowed to slowly warm to room temperature. The solution was then quenched with the addition of water (2 mL). The THF was removed under reduced pressure, and the residue was partitioned between water (20 mL) and diethyl ether (60 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). After removal of solvent under reduced pressure, the residue was purified by chromatography (silica gel, hexane/EtOAc 98:2) to afford **14a** as a oil (1.0 g) in 80% yield. **14a**: IR (NaCl) 2950, 2167, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.61 (d, 3H, J = 6.8 Hz), 0.95 (d, 3H, J = 6.9 Hz), 1.19 (m, 6H), 2.2 (m, 1H), 2.63 (m, 2H), 3.87 (t, 1H, J = 3.3 Hz), 4.05 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 0.4, 14.4, 14.8, 16.7, 19.2, 26.6, 31.6, 54.6, 60.7, 60.8, 61.0, 86.6, 103.6, 161.2, 164.3; MS (EI) *m/e* (rel intensity) 322 (M^+, 12), 294 (8), 279 (13), 211 (76), 169 (100), 141 (8); exact mass calcd for $C_{17}H_{30}N_2O_2Si$ 322.2077, found 322.2078. This material was used directly in a later step.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[2-(trimethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine 23a. In a 100 mL round-bottom flask equipped with a stirring bar were placed 2-iodoaniline (200 mg, 0.91 mmol), (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[3-(trimethylsilyl)prop-2-ynyl]-2,5-dihydropyrazine **14a** (322 mg, 1 mmol), palladium(II) acetate (8 mg, 0.036 mmol), lithium chloride (39 mg, 0.91 mmol), sodium carbonate (193 mg, 1.8 mmol), and DMF (12 mL). The reaction mixture was degassed and then heated at 100 °C under argon until the starting iodoaniline was no longer detected on analysis by TLC (30 h). The DMF was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 (50 mL). The suspension that resulted was allowed to pass through a Celite pad to remove insoluble solids. The solution was concentrated in a vacuum, and the product was purified by flash chromatography (silica gel, hexane/EtOAc 98:2) to afford **23a** as an oil (301 mg) in 81% yield. **23a**: IR (NaCl) 3415, 2952, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.41 (s, 9H), 0.67 (d, 3H, J = 6.8 Hz), 1.03 (d, 3H, J = 6.8 Hz), 1.19 (t, 3H, J = 7.1 Hz), 1.30 (t, 3H, J = 7.1 Hz), 2.27 (m,1H), 2.88 (dd, 1H, J = 9.6, 14.2 Hz), 3.54 (dd, 1H, J = 3.6, 14.2 Hz), 3.87 (t, 1H), 4.14 (m, 5H), 7.05 (t, 1H, J = 7.9 Hz), 7.13 (t, 1H, J = 8.0 Hz), 7.32 (d, 1H, J = 8.1 Hz), 7.72 (d, 1H, J = 7.9 Hz), 7.93 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 0, 14.6, 14.8, 14.9, 17.1, 19.7, 32.4, 59.1, 61.0, 61.2, 111.1, 119.1, 121.0, 122.6, 123.4, 130.1, 134.4, 138.7, 163.3, 164.2; MS (EI) *m/e* (rel intensity) 413 (M^+, 4), 202 (100), 186 (18), 169 (36), 160 (11); exact mass calcd for $C_{23}H_{35}N_3O_2Si$ 413.2499, found 413.2473. This material was employed directly in a later step.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[5,6-dimethyl-2-(trimethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine 23b. The 4,5-dimethyl-2-iodoaniline, (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[3-(trimethylsilyl)prop-2-ynyl]-2,5-dihydropyrazine**14a**, palladium(II) acetate, lithium chloride, and sodium carbonate in DMF were heated under conditions analogous to those employed for the preparation of **23a** above to provide **23b** as a oil in 70% yield. **23b**: IR (NaCl) 3355, 2964, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.39 (s, 9H), 0.68 (d, 3H, J = 6.8 Hz), 1.03 (d, 3H, J = 6.9 Hz), 1.22 (t, 3H, J = 7.1 Hz), 1.32 (t, 3H, J = 7.1 Hz), 2.25 (m,1H), 2.33 (s, 3H), 2.36 (s, 3H), 2.95 (dd, 1H), 3.5 (dd, 1H), 3.86 (t, 1H), 4.13 (m, 5H), 7.1 (s, 1H), 7.49 (s, 1H), 7.72 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 0, 14.8, 14.9, 17.1, 19.6, 20.5, 20.9, 32.0, 32.5, 59.3, 60.9, 61.2, 107.8, 111.3, 121.0, 123.3, 127.6, 128.5, 131.6, 133.3, 137.7, 163.2, 164.2; MS (EI) *m/e* (rel intensity) 441 (M^+, 2.2), 230 (100), 214 (11), 169 (28); exact mass calcd for $C_{25}H_{39}N_3O_2Si$ 441.2812, found 441.2823. This material was employed in a later step.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[5-methyl-2-(trimethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine 23c. The 4-methyl-2-iodoaniline, (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[3-(trimethylsilyl)prop-2-ynyl]-2,5-dihydropyrazine**14a**, palladium(II) acetate, lithium chloride, and sodium carbonate in DMF were heated under conditions analogous to those employed for the preparation of **23a** above to provide **23c** as a oil in 70% yield. **23c**: IR (NaCl) 3427, 2964, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.39 (s, 9H), 0.67 (d, 3H, J = 6.8 Hz), 1.02 (d, 3H, J = 6.9 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.31 (t, 3H, J = 7.1 Hz), 2.30 (m,1H), 2.42 (s, 3H), 2.85 (dd, 1H, J = 9.6, 14.2 Hz), 3.51 (dd, 1H, J = 3.4, 14.1 Hz), 3.87 (t, 1H), 4.0−4.22 (m, 5H), 6.96 (dd, 1H, J = 1.3, 8.3 Hz), 7.20 (d, 1H, J = 8.3 Hz), 7.51 (s, 1H), 7.83 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 0.1, 14.9, 15.0, 17.2, 19.7, 21.9, 32.1, 32.4, 59.3, 61.0, 61.2, 110.7, 120.7, 123.0, 124.3, 128.2, 134.5, 137.1, 163.3, 164.2; MS (CI, CH_4) *m/e* (rel intensity) 428 (M + 1^+, 100); exact mass calcd for $C_{24}H_{37}N_3O_2Si$ 427.2655, found 427.2562. This material was employed in a later step.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[5-fluoro-2-(trimethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine 23d. The 4-fluoro-2-iodoaniline, (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[3-(trimethylsilyl)prop-2-ynyl]-2,5-dihydropyrazine **14a**, palladium(II) acetate, lithium chloride, and sodium carbonate in DMF were heated under conditions analogous to those employed for the preparation of **23a** above to provide **23d** as a oil in 50% yield as well as 15% of the 2,3-regioisomer **24d**. **23d**: IR (NaCl) 3462, 3391, 2952, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.41 (s, 9H), 0.67 (d, 3H, J = 6.8 Hz), 1.02 (d, 3H, J = 6.8 Hz), 1.22 (t, 3H, J = 7.1 Hz), 1.31 (t, 3H, J = 7.1

Hz), 2.28 (m,1H), 2.82 (dd, 1H), 3.52 (dd, 1H, J = 3.3, 14.3 Hz), 3.87 (t, 1H, J = 3.3 Hz), 4.10 (m, 5H), 6.89 (m, 1H), 7.23 (m, 1H), 7.4 (dd, 1H, J = 2.5, 10.1 Hz), 7.92 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 0, 14, 15, 17.3, 19.8, 32.3, 32.5, 59.3, 61.2, 61.4, 105.7, 106.1, 111.0, 111.3, 111.5, 111.7, 123.7, 130.6, 130.8, 135.3, 136.9, 156.5, 159.6, 163.6, 164.0; MS (EI) *m/e* (rel intensity) 431 (M^+, 3), 221 (18), 220 (100), 169 (59); exact mass calcd for $C_{23}H_{34}FN_3O_2Si$ 431.2404, found 431.2394. This material was employed directly in a later step. **24d**: IR (NaCl) 3368, 2966, 1689 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, 3H, J = 6.9 Hz), 1.0 (d, 3H, J = 6.9 Hz), 1.36 (m, 6H), 2.26 (m, 1H), 2.99 (dd, 1H), 3.41 (dd, 1H, J = 3.2, J = 14.8 Hz), 3.88 (t, 1H, J = 3.5 Hz), 4.15−4.24 (m, 5H), 6.22 (s, 1H), 6.8 (m, 1H), 7.16 (m, 2H), 9.26 (s, br, 1H); MS (CI, CH_4) *m/e* (rel intensity) 360 (M^+ + 1, 100), 340 (17), 211 (11).

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[5-nitro-2-(trimethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine 23e and the Regioisomer 24e. The 4-nitro-2-iodoaniline **13e**, (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[3-(trimethylsilyl)prop-2-ynyl]-2,5-dihydropyrazine **14a**, palladium(II) acetate, lithium chloride, and sodium carbonate in DMF were reacted under conditions analogous to those employed for the preparation of **23a** above to provide **23e** as a oil in 65% yield as well as 22% of the 2,3-regiosiomer **24e**. **23e**: IR (NaCl) 3379, 2952, 1687, 1515, 1461 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.46 (s, 9H), 0.68 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.9 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.34 (t, 3H, J = 7.1 Hz), 2.28 (m,1H), 2.89 (m, 1H), 3.62 (dd, 1H, J = 2.9, 14.3 Hz), 3.92 (m, 1H), 4.16 (m, 5H), 7.35 (d, 1H, J = 9 Hz), 8.07 (dd, 1H, J = 2.2, 9 Hz), 8.27 (s, br, 1H), 8.8 (d, 1H, J = 2.2 Hz); MS (EI) *m/e* (rel intensity) 458 (M^+, 2), 247 (87), 212 (72), 169 (100); exact mass calcd for $C_{23}H_{34}N_4O_4Si$ 458.2349, found 458.2355. **24e**: IR (NaCl) 3329, 1731, 1660, 1521 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, 3H, J = 6.9 Hz), 1.02 (d, 3H, J = 6.9 Hz), 1.36 (m, 6H), 2.28 (m, 1H), 2.99 (dd, 1H), 3.50 (dd, 1H), 3.94 (t, 1H, J = 3.3 Hz), 4.16−4.26 (m, 5H), 6.45 (s, 1H), 7.28 (d, 1H, J = 9.1 Hz), 8.04 (dd, 1H, J = 9.0 Hz and J = 2.0 Hz), 8.50 (d, 1H, J = 2.0 Hz), 9.88 (s, br, 1H); MS (CI, CH_4) *m/e* (rel intensity) 387 (M^+ + 1, 100).

(2*S*,5*R*)-3,6-Diethoxy-2-isopropyl-5-[5-nitro-2-(triethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine 26e. The 4-nitro-2-iodoaniline **13e**, TES-substituted alkyne **25**, 5 mol % palladium(II) acetate, lithium chloride, and sodium carbonate in DMF were heated under conditions analogous to those employed for the preparation of **23a** above to provide **26e** as an oil in 83% yield. **26e**: IR (NaCl) 3391, 2951, 1683, 1513, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61 (d, 3H, J = 6.8 Hz), 0.93 (m, 18H), 1.13 (t, 3H, J = 6.8 Hz), 1.24 (t, 3H, J = 6.3 Hz), 2.18 (m, 1H), 2.81 (dd, 1H), 3.51 (dd, 1H), 3.90 (m, 3H), 4.10 (m, 3H), 7.26 (d, 1H, J = 9.0 Hz), 7.99 (dd, 1H, J = 7.0, 2.0 Hz), 8.23 (s, br, 1H), 8.78 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.3, 7.3, 14.2, 16.7, 19.0, 31.7, 31.9, 58.7, 60.8, 110.3, 117.5, 118.7, 126.8, 129.2, 136.1, 141.0, 141.1, 162.9, 163.4; MS (EI) *m/e* (rel intensity) 500 (M^+, 8), 289 (88), 212 (100), 169 (37); exact mass calcd for $C_{26}H_{30}N_4O_4Si$ 500.2819, found 500.2837. This material was directly employed in a later step.

(2*S*,5*R*)-3,6-Diethoxy-2-isopropyl-5-[5,6-dichloro-2-(triethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine 26g and the Regioisomer 27g. The 4,5-dichloro-2-iodoaniline **13g**, TES-substituted alkyne **25**, 5 mol % palladium(II) acetate, lithium chloride, and sodium carbonate in DMF were heated under conditions analogous to those employed for the preparation of **23a** above to provide **26g** as an oil in 80% yield. **26g**: IR (NaCl) 3454, 2956, 1685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61 (d, 3H, J = 6.8 Hz), 0.92 (m, 18H), 1.19 (t, 3H, J = 7.1 Hz), 1.25 (t, 3H, J = 7.1 Hz), 2.2 (m,1H), 2.69 (dd, 1H), 3.44 (dd, 1H, J = 2.9, 14.3 Hz), 3.83−4.15 (m, 6H), 7.34 (s, 1H), 7.82 (s, 1H), 7.92 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.4, 7.2, 14.2, 14.3, 16.7, 19.0, 31.7, 31.8, 58.8, 60.7, 60.8, 60.9, 111.6, 122.1, 122.5, 123.7, 125.5, 129.5, 134.5, 137.0, 163.1; MS (EI) *m/e* (rel intensity) 523 (M^+, 7), 312 (67), 212 (100), 169 (32); exact mass calcd for $C_{26}H_{39}Cl_2N_3O_2Si$ 525.2159, found 525.2144; calcld 523.2189, found 523.2165. This material was employed directly in a later step. When 10mol % of palladium(II) acetate was employed, the yield for **26g** dropped to 67% while 10% of the 2,3-regioisomer **27g** was isolated. **27g**: IR (NaCl) 2942, 2355, 1684 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82−0.94 (m, 18H), 1.04 (d, 3H, J = 6.9 Hz), 1.19−1.24 (m, 6H), 2.15 (m, 1H), 2.71 (dd, 1H), 3.41 (dd, 1H, J = 2.8, 14.3 Hz), 3.86−4.13 (m, 6H), 7.35 (s, 1H), 7.75 (s, 1H), 7.83 (s, br, 1H).

5,6-Dimethyl-L-tryptophan Ethyl Ester 28b. To a solution of optically pure (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[5,6-dimethyl-2-(trimethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine **23b** (208 mg, 0.5 mmol) in THF (8 mL) at 0 °C was slowly added an aqueous solution of 2 N HCl (7 mL). The mixture was allowed to warm to room temperature and stirred for 2 h. Ice (5 g) was added to the solution, and the pH of the reaction mixture was adjusted to 8 with aqueous NH_4OH (concentrated) at 0 °C. The mixture was then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue that resulted was purified by flash chromatography (silica gel, EtOAc) to afford **28b** (117 mg) in 86% yield. **28b**: $[\alpha]^{27}_D$ = 1.92 (c = 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, H, J = 7.1 Hz), 1.83 (s, br, 2H), 2.33 (s, 6H), 2.99 (dd, 1H, J = 7.8 Hz and J = 14.3 Hz), 2.24 (dd, 1H, J = 4.6 Hz and J = 14.3 Hz), 3.79 (m, 1H), 4.14 (q, 2H, J = 7.1 Hz), 6.94 (s, 1H), 7.12 (s, 1H), 7.34 (s, 1H), 7.92 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 18.3, 18.6, 29.0, 53.0, 59.1, 108.0, 109.8, 117.0, 120.4, 124, 126.5, 129.5, 133.0, 176.1. This material was used in a later step without further characterization.

L-Tryptophan ethyl ester 28a was prepared in 90% yield following the procedure for preparation of **28b**. **28a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz), 1.82 (s, br, 2H), 3.05 (dd, 1H, J = 7.7 Hz and J = 14.4 Hz), 3.29 (dd, 1H, J = 4.8, 14.4 Hz), 3.81 (m, 1H), 4.17 (q, 2H, J = 7.1 Hz), 7.07 (d, 1H, J = 2.1 Hz), 7.10−7.20 (m, 2H), 7.35 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 7.8 Hz), 8.22 (s, br, 1H). This material was used in a later step without further characterization.

5-Methyl-L-tryptophan ethyl ester 28c was prepared in 91% yield following the procedure for preparation of **28b**. **28c**: $[\alpha]^{27}_D$ = 1.06° (c = 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz), 1.75 (s, br, 2H), 2.45 (s, 3H), 3.01 (dd, 1H, J = 7.8, 14.4 Hz), 3.25 (dd, 1H, J = 4.7, 14.4 Hz), 3.8 (dd, 1H, J = 4.7, 7.6 Hz), 4.17 (q, 2H, J = 7.0 Hz), 7.01 (m, 2H), 7.25 (d, 1H, J = 3.8 Hz), 7.39 (s, 1H), 8.23 (s, br, 1H). This material was used in a later step without further characterization.

5-Fluoro-L-tryptophan Ethyl Ester 30. To a solution of optically pure (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[5-fluoro-2-(trimethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine **23d** (216 mg, 0.5 mmol) in THF (8 mL) at 0 °C was slowly added an aqueous solution of 6 N HCl (7 mL). The mixture was allowed to warm to room temperature and stirred for 4 h. Ice (10 g) was added to the solution, and the pH of the reaction mixture was adjusted to 8 with aqueous NH_4OH (concentrated) at 0 °C. The mixture was then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue which resulted was purified by flash chromatography (silica gel, EtOAc) to afford **30** (102 mg) in 82% yield. **30**: $[\alpha]^{27}_D$ = 11.0° (c = 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.1 Hz), 1.64 (s, br, 2H), 3.02 (dd, 1H, J = 7.5, 14.5 Hz), 3.22 (dd, 1H, J = 5, 14.5 Hz), 3.78 (m, 1H), 4.15 (m, 2H), 6.93 (m, 1H), 7.1 (d, 1H, J = 2.4 Hz), 7.24 (m, 2H), 8.6 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 31.0, 55.3, 61.4, 104, 104.3, 110.8, 111.1, 111.9, 112.1, 112.3, 125.1, 128, 133.1, 158, 159.8, 175.0. This material was used in a later step without further characterization.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-(5-nitro-3-indolyl)-methyl-2,5-dihydropyrazine 32. To pyrazine **23e** (105 mg, 0.23 mmol) in 95% ethanol (10 mL) was added powdered KOH (300 mg, 5.4 mmol). The reaction mixture that resulted was heated to reflux for 8 h. Analysis by TLC (silica gel) indicated the absence of starting material; consequently, the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with water (2 × 15 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chroma-

tography (silica gel, EtOAc/hexanes 95:5) to afford **32** (76 mg) in 86% yield. **32**: IR (NaCl) 3368, 2961, 2347, 1692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.56 (d, 3H, J = 6.8 Hz), 0.83 (d, 3H, J = 6.9 Hz), 1.14 (t, 3H, J = 7.1 Hz), 1.29 (t, 3H, J = 7.1 Hz), 2.08 (m,1H), 3.22−3.29 (m, 3H), 3.93 (m, 1H), 4.11 (m, 3H), 4.27 (m, 1H), 7.01 (s, 1H), 7.23 (d, 1H, J = 9.0 Hz), 7.98 (dd, 1H, J = 2.2, 9.0 Hz), 8.47 (s, br, 1H), 8.80 (d, 1H, J = 2.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 14.3, 16.4, 18.9, 20.9, 29.2, 31.5, 56.3, 60.4, 60.6, 110.7, 114.6, 117.2, 117.3, 125.9, 127.8, 138.7, 141.4, 162.1, 163.6; MS (EI) *m/e* (rel intensity) 386 (M^+, 12), 289 (9), 212 (41), 169 (100), 141 (13); exact mass calcd for $C_{20}H_{26}N_4O_4$ 386.1954, found 386.1944. This material was employed directly in the next step.

5-Nitro-L-tryptophan Ethyl Ester 33. To a solution of (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-(5-nitro-3-indolyl)methyl-2,5-dihydropyrazine **32** (93 mg, 0.24 mmol) in THF (4 mL) at 0 °C was slowly added an aqueous solution of 2 N HCl (3 mL). The mixture was warmed to room temperature and stirred for 2 h. Ice (5 g) was added to the solution, and the pH of the reaction mixture was adjusted to 8 with an aqqueous solution of NH_4OH (concentrated) at 0 °C. The mixture was then extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc) to afford **33**(54 mg) in 91% yield. **33**: $[\alpha]^{27}_D$ = 18.8° (c = 1.14, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.1 Hz), 1.68 (s, br, 2H), 3.18 (m, 1H), 3.26 (m, 1H), 3.84 (m, 1H), 4.19 (m, 2H), 7.23 (s, 1H), 7.34 (d, 1H, J = 9.0 Hz), 8.07 (dd, 1H, J = 2.2, 9.0 Hz), 8.58 (d, 1H, J = 2.2 Hz), 8.8 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 30.5, 55.0, 61.7, 111.6, 113.0, 116.6, 118.2, 126.5, 127.5, 140.0, 142.5, 176.0. This material was used in a later step without further characterization.

5-Fluoro-L-tryptophan 31. Into a 25 mL round-bottom flask were added 5-fluoro-L-tryptophan ethyl ester **30** (85 mg, 0.33 mmol), aqueous 1 N NaOH (1.0 mL, 1 mmol), and ethanol (1.5 mL). The solution was heated to 50 °C for 2 h. Analysis by TLC (silica gel) indicated that all the starting material had disappeared (material now had R_f = 0). Most of the EtOH was removed under reduced pressure. A piece of ice was dropped into the flask and the mixture was brought to pH = 6−7 with an aqueous solution of 2 N HCl at 0 °C. The water in the solution that resulted was removed under reduced pressure until a white precipitate appeared. The total volume of solution was reduced to 0.5 mL. Cold water (1 mL) was then added, and the precipitate that formed was collected by vacuum filtration, washed with cold water (3 × 1 mL), and dried to provide 5-fluoro-L-tryptophan **31** (54 mg) in 70% yield. **31**: $[\alpha]^{27}_D$ = 5.6° (c = 0.98, 0.1 M aqueous HCl) [lit.[73] $[\alpha]^{27}_D$ = 5.5° (c = 1, in 0.1 M HCl]; mp 275−276 °C dec; IR (KBr) 3455, 1660, 1591, 1487 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 3.14 (dd, 1H, J = 7.7, 15.3 Hz), 3.28 (dd, 1H, J = 4.9, 15.3 Hz), 3.89 (dd, 1H, J = 4.9, 7.7 Hz), 6.92 (dt, 1H, J = 2.4, 9.2 Hz), 7.21 (s, 1H), 7.27 (dd, 1H, J = 2.5, 10.1 Hz), 7.33 (dd, 1H, J = 4.6, 8.9 Hz); ^{13}C NMR (75.5 MHz, D_2O) δ 26.8, 55.3, 103.3, 103.5, 108, 110.4, 110.8, 112.9, 113.1, 127, 127.2, 127.3, 131.2, 156.3, 159.4, 175.0; MS (EI) *m/e* (rel intensity) 222 (M^+, 3), 148 (100), 101 (19). Anal. Calcd for $C_{11}H_{11}FN_2O_2 \cdot {}^1/_8H_2O$: C, 58.86; H, 5.05; N, 12.48. Found: C, 59.11; H, 4.96; N, 12.21.

5,6-Dimethyl-L-tryptophan 29b. Into a 25 mL round-bottom flask were added 5,6-dimethyl-L-tryptophan ethyl ester **28b** (79 mg, 0.30 mmol), 1 N aqueous NaOH (1.0 mL, 1 mmol), and EtOH (1.5 mL). The solution that resulted was heated to 50 °C for 2 h. Analysis by TLC (silica gel) indicated that all the starting material had disappeared and the new material was on the baseline (R_f = 0). Most of the EtOH was removed under reduced pressure. A piece of ice was dropped into the flask, and the mixture was brought to pH = 6−7 with an aqueous solution of 2 N HCl at 0 °C. The water in the suspension that resulted was removed under reduced pressure until the volume of the mixture was reduced to about 0.5 mL. Cold water (1 mL) was added, and the precipitate that formed was collected by vacuum filtration, washed with cold water (3 × 1 mL), and dried to provide 5,6-dimethyl-L-tryptophan **29b** (60 mg) in 85% yield. **29b**: mp 277−279 °C dec; $[\alpha]^{27}_D$ = −6.57° (c = 0.67, 0.5 N aqueous NaOH), IR (KBr) 3389, 1667, 1583, 1467 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 9H), 2.85 (dd, 1H, J = 9.5, 15.1 Hz), 3.27 (dd, 1H, J = 3.5, 15.0 Hz), 3.38 (dd, 1H, J = 3.7, 9.3 Hz), 7.05 (s, 1H), 7.11 (s, 1H), 7.29 (s, 1H), 10.59 (s, br, 1H); MS (CI, CH_4) *m/e* (rel intensity) 233 (M^+ + 1, 100), 216 (100), 187 (20), 158 (19). Anal. Calcd. for $C_{13}H_{16}N_2O_2 \cdot {}^1/_7H_2O$: C, 66.48; H, 6.99; N, 11.93. Found: C, 66.72; H, 6.92; N, 11.70.

L-Tryptophan 29a was prepared in 88% yield from L-tryptophan ethyl ester **28a** following the procedure employed for preparation of **29b**. The optical rotation and spectral data for **29a** were identical to those obtained for an authentic sample from Aldrich Chemical Co. When the product **29a** was heated under the conditions of saponification employed in the previous experiments for 20 h, no racemization of **29a** was observed.

5-Methyl-L-tryptophan 29c was prepared in 87% yield from 5-methyl-L-tryptophan ethyl ester **28c** following the procedure employed for preparation of **29b**. **29c**: mp 272−273 °C dec; $[\alpha]^{27}_D$ = 10.82° (c = 0.61, 1 N aqueous HCl) [lit.[49] mp 275−277 °C, $[\alpha]^{20}_D$ = 11.2° (c = 1.0, 1 M aqueous HCl)]; IR (KBr) 3400, 1661, 1590, 1406 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.38 (s, 3H), 2.89 (dd, 1H, J = 9.3, 15.1 Hz), 3.29 (dd, 1H, J = 3.6, 15.1 Hz), 3.42 (dd, 1H, J = 3.6, 9.4 Hz), 6.89 (d, 1H, J = 8.3 Hz), 7.14 (s, 1H), 7.23 (d, 1H, J = 8.2 Hz), 7.33 (s, 1H), 10.75 (s, br, 1H); MS (EI) *m/e* (rel intensity) 218 (M^+, 3), 144 (100), 115 (14). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.45; H, 6.17; N, 12.55.

5-Nitro-L-tryptophan 34 was prepared in 84% yield from 5-nitro-L-tryptophan ethyl ester **33** following the procedure employed for preparation of **29b**. **34**: mp 264−266 °C dec; $[\alpha]^{27}_D$ = 49.9° (c = 0.9, 1 N aqueous HCl) [lit.[49] mp 266−268 °C, $[\alpha]^{20}_D$ = 49.1° (c = 1.0, 1 N aqueous HCl)]; IR (KBr) 3411, 1600, 1580 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.12 (dd, 1H, J = 7.5, 15.0 Hz), 3.29 (dd, 1H, J = 4.2, 15.1 Hz), 3.44 (dd, 1H, J = 4.5, 7.4 Hz), 7.44 (s, 1H), 7.51 (d, 1H, J = 9.0 Hz), 7.97 (dd, 1H, J = 2.2, 9.0 Hz), 8.63 (d, 1H, J = 2.2 Hz), 11.07 (s, br, 1H); MS (EI) *m/e* (rel intensity) 175 (64), 159 (24), 129 (100). MS (CI, CH_4) *m/e* (rel intensity) 250 (M^+ + 1, 19), 234 (22), 206 (54), 189 (100), 159 (33). Anal. Calcd. for $C_{11}H_{11}N_3O_4 \cdot {}^2/_5H_2O$: C, 51.52; H, 4.64; N, 16.39. Found: C, 51.78; H, 4.38; N, 16.09.

(2*S*,5*R*)-3,6-Diethoxy-2-isopropyl-5-(5,6-dichloro-3-indolyl)methyl-2,5-dihydropyrazine 35. The silyl compound **26g** (0.732 g, 1.4 mmol) was dissolved in 1 M tetrabutylammonium fluoride (TBAF) in THF (4 mL). The solution was stirred at room temperature for 30 min until analysis by TLC (silica gel) indicated the absence of starting material. Water (20 mL) was added, and the mixture was extracted with ether (3 × 40 mL). The combined ether layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes 4:96) to afford **35** (0.469 g) in 82% yield: IR (NaCl) 3443, 3176, 2969, 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.55 (d, 3H, J = 6.8 Hz), 0.83 (d, 3H, J = 6.9 Hz), 1.18 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.08 (m, 1H), 3.11−3.24 (m, 3H), 3.91 (m, 1H), 4.03−4.09 (m, 3H), 4.22 (m, 1H), 6.85 (d, 1H, J = 2.3 Hz), 7.30 (s, 1H), 7.66 (s, 1H), 7.98 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 14.3, 16.4, 18.9, 20.9, 29.3, 31.4, 56.5, 60.3, 60.4, 111.8, 112.1, 120.8, 123.0, 124.6, 125.2, 128.2, 134.4, 162.1, 163.5; MS (EI) *m/e* (rel intensity) 413 (M^+, 1.2), 411 (M^+, 7.5), 409 (M^+, 12), 212 (55), 198 (28), 169 (100); exact mass calcd for $C_{20}H_{25}Cl_2N_3O_2$ 409.1324, found 409.1282.

5,6-Dichloro-D-tryptophan ethyl ester 36 was prepared in 90% yield from **35** following the procedure for preparation of **30**. **36**: $[\alpha]^{27}_D$ = −29.09° (c = 1.1, C_2H_5OH); IR (NaCl) 3352, 3154, 1725, 1446 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 3H, J = 7.1 Hz), 1.55 (s, br, 2H), 2.95 (dd, 1H, J = 7.2, 14.5 Hz), 3.10 (dd, 1H, J = 5.0, 14.5 Hz), 3.71 (dd, 1H, J = 5.0, 7.2 Hz), 4.09 (m, 1H), 6.95 (d, 1H, J = 2.0 Hz), 7.29 (s, 1H), 7.61 (s, 1H), 8.53 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 30.2, 54.6, 61.1, 110.8, 112.6, 119.7, 123.5, 124.9, 125.8, 127.2, 134.9, 175.1. This material was used in the next step without further characterization.

5,6-Dichloro-D-tryptophan 37 was prepared in 86% yield from 5,6-dichloro-D-tryptophan ethyl ester **36** following the procedure employed for preparation of **29b**. **37**: mp 274−276 °C dec; IR (KBr) 3424, 1662 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 3.28 (dd, 1H, J = 8.1, 14.8 Hz), 3.43 (dd, 1H, J = 5.5, 14.8 Hz), 4.03 (dd, 1H, J = 5.3, 7.6 Hz), 7.35 (s, 1H), 7.69 (s, 1H), 7.88 (s, 1H); MS (EI) *m/e* (rel intensity) 202 (13), 200 (79), 198 (100), 164 (17), 128(33); MS (CI, CH_4) *m/e* (rel intensity) 275 ($M^+ + 1$, 51), 273 ($M^+ + 1$, 100), 258 (76), 239 (29), 222 (40), 200 (27). Anal. Calcd for $C_{11}H_{10}Cl_2N_2O_2$: C, 48.37; H, 3.69; N 10.26. Found: C, 48.47; H, 3.85; N, 9.99.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[3-(2-aminophenyl)-prop-2-ynyl]-2,5-dihydropyrazine 42. The (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-(prop-2-ynyl)-2,5-dihydropyrazine **41**(377 mg, 1.5 mmol) and 2-iodoaniline (300 mg, 1.4 mmol) were dissolved in dry triethylamine (20 mL) in a 100 mL round-bottom flask. The solution was degassed with argon for 10 min after which $(PPh_3)_2PdCl_2$ (19.2 mg, 0.027 mmol) and CuI (5.2 mg, 0.027 mmol) were added under Ar. The reaction mixture was degassed with argon for another 10 min. The yellow solution that resulted was stirred at room temperature for 18 h and a precipitate gradually appeared. Analysis by TLC (silica gel) indicated the absence of starting material. The reaction mixture was concentrated under vacuum to dryness, and the residue was taken up in ether. The solid was removed by vacuum filtration, and the ether was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes 5:95) to afford **42** (443 mg) in 95% yield. **42**: IR (NaCl) 2964, 1688, 1488 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.71 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.8 Hz), 1.28 (m, 6H), 2.28 (m, 1H), 2.96 (m, 2H), 4.01 (m, 1H), 4.16 (m, 7H), 6.62 (m, 2H), 7.06 (m, 1H), 7.17 (dd, 1H, J = 1, 8.8 Hz); MS (CI, CH_4) *m/e* (rel intensity) 342 ($M^+ + 1$, 100), 211 (3). This material was used in the next step without further characterization.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-(2-indolyl)methyl-2,5-dihydropyrazine 43. Into a 25 mL round-bottom flask equipped with a stirring bar were added (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[3-(2-aminophenyl)-prop-2-ynyl]-2,5-dihydropyrazine **42** (100 mg, 0.29 mmol), CuI (56 mg, 0.29 mmol), ethylene glycol (1.5 g), and anhydrous DMF (8 mL). The mixture was degassed and subsequently heated to 95 °C for 20 h until analysis by TLC (silica gel) indicated the absence of starting material. The DMF was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 mL). The organic solution was washed with water (5 × 30 mL), brine, and dried (Na_2SO_4). The CH_2Cl_2 was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes 2:98) to afford **43** (80 mg) as a white solid in 80% yield. **43**: $[\alpha]^{27}_D = -21.6°$ (c = 0.98, EtOAc); IR (NaCl) 3385, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (d, 3H, J = 6.8 Hz), 1.03 (d, 3H, J = 6.8 Hz), 1.34 (m, 6H), 2.24 (m, 1H), 3.10 (m,1H), 3.50 (m, 1H), 3.89 (t, 1H, J = 3.6 Hz), 4.26 (m, 5H), 6.28 (s, 1H), 7.12 (m, 2H), 7.29 (m, 1H), 7.55 (d, 1H, J = 7.6 Hz), 9.27 (s, br, 1H); MS (CI, CH_4) *m/e* (rel intensity) 342 (M^+ +1, 100), 211 (3); exact mass calcd for $C_{20}H_{27}N_3O_2$ 341.2103, found 341.2097. This material was employed in the next step without further characterization.

(2*S*)-2-Amino-3-(1*H*-indol-2-yl)-propionic acid ethyl ester 45 was prepared in 90% yield from (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-(2-indolyl)methyl-2,5-dihydropyrazine **43** following the procedure employed for the preparation of **28b**. **45**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 7.1 Hz), 1.88 (s, br, 2H), 3.03 (dd, 1H, J = 8.3, 14.9 Hz), 3.24 (dd, 1H, J = 4.0, 14.9 Hz), 3.76 (dd, 1H, J = 4.0 Hz and J = 8.3 Hz), 4.27 (q, 2H, J = 7.1 Hz), 6.33 (s, 1H), 7.15 (m, 2H), 7.35 (d, 1H, J = 8.1 Hz), 7.59 (d, 1H, J = 7.7 Hz), 9.48 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 32.6, 54.5, 61.3, 100.9, 110.7, 119.5, 119.8, 121.2, 128.2, 135.7, 136.0, 174.8; MS (EI) *m/e* (rel intensity) 232 (M^+, 18), 130 (100); exact mass calcd for $C_{13}H_{16}N_2O_2$ 232.1212, found 232.1212. This material was employed directly in the next step.

(2*S*)-2-Amino-3-(1*H*-indol-2-yl)-propionic acid (L-isotryptophan) 38 was prepared in 85% yield from (2*S*)-2-amino-3-(1*H*-indol-2-yl)-propionic acid ethyl ester **45** following the procedure employed for the preparation of **29b**. **38**: $[\alpha]^{27}_D = -17.9°$ (c = 1.26, in 0.2 N NaOH); mp 222−224 °C dec (lit.[74] mp 220−222 °C dec); IR (KBr) 3394, 1597, 1499 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.03 (dd, 1H, J = 8.0, 15.3 Hz), 3.33 (dd, 1H, J = 5.0, 15.3 Hz), 3.59 (dd, 1H, J = 8.0, 5.0 Hz), 6.25 (s, 1H), 6.98 (m, 2H), 7.31 (d, 1H, J = 8.0 Hz), 7.42 (d, 1H, J = 7.7 Hz), 11.4 (s, br, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 30.3, 54.0, 100.5, 111.3, 118.9, 119.6, 120.6, 128.6, 136.2, 136.6, 170.1; MS (EI) *m/e* (rel intensity) 204 (M^+, 9), 131 (21), 130 (100); exact mass calcd for $C_{11}H_{12}N_2O_2$ 204.0899, found 204.0894. Anal. Calcd for $C_{11}H_{12}N_2O_2 \cdot {}^1/_2H_2O$: C, 61.96; H, 6.15; N, 13.14. Found: C, 62.21; H, 5.98; N, 12.95.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[1*H*-2-(triethylsilyl)-benzo[*f*]indol-3-yl]methyl-2,5-dihydropyrazine 47. In a 100 mL round-bottom flask equipped with a stirring bar were placed 2-amino-3-iodonaphthalene **46** [77](194 mg, 0.72 mmol), (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[3-(triethylsilyl)-prop-2-ynyl]-2,5-dihydropyrazine **25** (289 mg, 0.79 mmol), palladium(II) acetate (7 mg, 0.031 mmol), lithium chloride (30 mg, 0.72 mmol), sodium carbonate (152 mg, 1.4 mmol), and dry DMF (10 mL). The reaction mixture was degassed at room temperature and then heated to 100 °C under argon until the starting material was no longer detected on analysis by TLC (30 h). The DMF was then removed under reduced pressure and the residue was taken up in CH_2Cl_2 (50 mL). The suspension which resulted was allowed to pass through a pad of Celite to remove insoluble solids. The filtrate was concentrated under reduced pressure and the pyrazine was purified by flash chromatography (silica gel, hexanes/EtOAc, 98:2) to afford **47** as an oil (236 mg) in 65% yield. **47**: IR (NaCl) 2956, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (d, 3H, J = 6.8 Hz), 1.02 (m, 18H), 1.16 (t, 3H, J = 7.1 Hz), 1.30 (t, 3H, J = 7.1 Hz), 2.28 (m,1H), 2.99 (dd, 1H, J = 9.6, 14.1 Hz), 3.60 (dd, 1H, J = 4.7, 14.2 Hz), 3.93 (m, 2H), 4.2 (m, 4H), 7.29 (m, 2H), 7.73 (s, 1H), 7.85 (m, 3H), 8.26 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.7, 7.5, 14.39, 14.44, 16.7, 19.2, 31.7, 32.2, 58.8, 60.6, 60.9, 80.2, 105.2, 118.1, 122.1, 123.1, 123.6, 127.2, 128.1, 128.3, 130.5, 131.6, 136.7, 139.0, 163.0, 163.8; MS (EI) *m/e* (rel intensity) 505 (M^+, 19), 362 (13), 337 (24), 310 (23), 294 (100), 212 (29), 169 (38); exact mass calcd for $C_{30}H_{43}N_3O_2Si$ 505.3124, found 505.3146. This material was employed in a later step without further characterization.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[1*H*-benzo[*f*]indol-3-yl]methyl-2,5-dihydropyrazine 48. The (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[1*H*-2-(triethylsilyl)benzo[*f*]indol-3-yl]methyl-2,5-dihydropyrazine **47**(150 mg, 0.3 mmol) was dissolved with 1 M tetrabutylammonium fluoride (TBAF) in THF (4 mL). The solution was stirred at room temperature for 2 h until analysis by TLC (silica gel) indicated the absence of starting material. Water (20 mL) was added to the solution, and the mixture was extracted with ether (3 × 40 mL). The combined ether layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes 3:97) to afford **48** (99 mg) in 85% yield. **48**: IR (NaCl) 2956, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (d, 3H, J = 6.8 Hz), 0.90 (d, 3H, J = 6.9 Hz), 1.22 (t, 3H, J = 7.1 Hz), 1.38 (t, 3H, J = 7.1 Hz), 2.17 (m, 1H), 3.3 (m, 1H), 3.91 (m, 1H), 4.02 (m, 1H), 4.16 (m, 4H), 4.41 (m, 1H), 7.14 (s, 1H), 7.36 (m, 2H), 7.74 (s, 1H), 7.90 (m, 3H), 8.14 (s, 1H); MS (CI, CH_4) *m/e* (rel intensity) 392(M^+ +1, 100); exact mass calcd for $C_{24}H_{29}N_3O_2$ 391.2260, found 391.2236. This material was employed in the next step.

(2*S*)-2-Amino-3-(1*H*-benzo[*f*]indol-3-yl)-propionic acid ethyl ester 49 was prepared in 85% yield from (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[1*H*-benzo[*f*]indol-3-yl]methyl-2,5-dihydropyrazine **48** under conditions analogous to those employed for preparation of **28b**. **49**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (dt, 3H, J = 2.3, 7.2 Hz), 1.65 (s, br, 2H), 3.17 (dd, 1H, J = 7.5, 14.4 Hz), 3.39 (dd, 1H, J = 4.9, 14.4 Hz), 3.91 (m, 1H), 4.16 (m, 2H), 7.27 (s, 1H), 7.35 (m, 2H), 7.77 (s, 1H), 7.87 (d, 1H, J = 7.4 Hz), 7.9 (dd, 1H, J = 2.0, 7.5 Hz), 8.01 (s, br, 1H), 8.1 (s, 1H). This material was used directly in the next step without further characterization.

(2*S*)-2-Amino-3-(1*H*-benzo[*f*]indol-3-yl)propionic acid (L-benzo[*f*]tryptophan) 39 was prepared in 83% yield from

(2*S*)-2-amino-3-(1*H*-benzo[*f*]indol-3-yl)-propionic acid ethyl ester **49** under conditions analogous to those employed for preparation of **29b**. **39**: $[\alpha]^{27}_D = 90.57°$ ($c = 0.53$, 1 N aqueous HCl); mp 283−285 °C dec; IR (KBr) 3400, 1706, 1661, 1594 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.12 (dd, 1H, $J = 8.9$, 15.2 Hz), 3.44 (dd, 1H, $J = 3.7$, 15.2 Hz), 3.60 (dd, 1H, $J = 3.8$, 8.7 Hz), 7.28 (m, 2H), 7.48 (s, 1H), 7.83 (s, 1H), 7.91 (m, 2H), 8.11 (s, 1H), 10.97 (s, br, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 27.6, 54.8, 106.5, 108.9, 115.7, 122.3, 123.4, 127.5, 127.9, 128.3, 129, 129.9, 137.6, 170.2; MS (EI) *m*/*e* (rel intensity) 254 (M^+, 23), 180 (100), 60 (14); exact mass calcd for $C_{15}H_{14}N_2O_2$ 254.1055, found 254.1051. Anal. Calcd for $C_{15}H_{14}N_2O_2 \cdot H_2O$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.38; H, 5.78; N, 9.99.

3-Bromo-1-(*tert*-butyldimethylsilyl)indole 50.[80] An oven-dried, 500 mL three-neck, round-bottom flask equipped with a magnetic stirring bar, 100 mL pressure-equalizing addition funnel, and an argon inlet and outlet tube was charged with indole (8.0 g, 0.068 mol) and THF (200 mL). The solution was stirred and cooled to −78 °C with a dry ice/EtOAc bath. A solution of butyllithium in hexanes (47 mL of a 1.6 M solution, 0.075 mol) was added dropwise via a cannula. The mixture was warmed to −10 °C, stirred for 15 min, and then cooled to −50 °C. A solution of *tert*-butyldimethylsilyl chloride (11.6 g, 0.077 mol) in THF (60 mL) was added dropwise to this mixture. The temperature was allowed to warm to 0 °C, and after 3 h the reaction mixture was cooled again to −78 °C. Freshly crystallized NBS (12.18 g, 0.068 mol) was added via a solid addition funnel, and the mixture that resulted was stirred in the dark at −78 °C for 2 h and then allowed to warm to room temperature. Hexanes (100 mL) and pyridine (1 mL) were added, and the suspension that resulted was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, hexanes) to provide **50** (17.8 g) as a colorless solid in 84% yield. **50**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.60 (s, 6H), 0.93 (s, 9H), 7.17 (s, 1H), 7.20 (m, 2H), 7.48 (m, 1H), 7.54 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −3.6, 19.8, 26.6, 94.1, 114.5, 119.6, 121, 122.9, 130.1, 130.3, 140.7. The spectral data for **50** were identical to that reported in the literature.[80]

2-(1-*tert*-Butyldimethylsilylindol-3-yl)ethyl Tosylate 51. To a solution of 3-bromo-1-(*tert*-butyldimethylsilyl)indole **50** (2.5 g, 8 mmol) in THF (40 mL) was added *t*-BuLi (1.7M, 10.0 mL, 2.2 equiv) slowly at −78 °C. The above solution was stirred for 10 min. Ethylene oxide (0.90 mL, 18 mmol) was collected in a graduated cylinder at −78 °C that had been covered with a septum, after which time cold THF (2 mL) was syringed into the cylinder. The solution that resulted was added dropwise to the indolyl anion solution through a cannula at −78 °C. The reaction mixture that resulted was allowed to warm to room temperature over a period of 2 h and stirred for another 2 h. Then *p*-toluenesulfonyl chloride (1.50 g, 8 mmol) was added to the above pale yellow solution, and this mixture was stirred at room temperature for 10 h. The reaction solution was then quenched with H_2O and the mixture which resulted was partitioned between H_2O and EtOAc. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, ether/hexanes 1:4) to afford **51** (1.70 g) in 84% yield. **51**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.71 (s, 6H), 1.03 (s, 9H), 2.50 (s, 3H), 3.24 (t, 2H, $J = 7.2$ Hz), 4.4 (t, 2H, $J = 7.2$ Hz), 7.1 (s, 1H), 7.24 (m, 2H), 7.34 (d, 2H, $J = 8.2$ Hz), 7.52 (d, 1H, $J = 7.3$ Hz), 7.58 (d, 1H, $J = 8.2$ Hz), 7.81 (d, 2H, $J = 8.3$ Hz). This material was used in a later step without further characterization.

(2*R*,5*S*)-3,6-Diethoxy-2-isopropyl-5-[2-(1-*tert*-butyldimethylsilylindol-3-yl)ethyl]-2,5-dihydropyrazine 52. To a solution of (2*R*)-3,6-diethoxy-2-isopropyl-2,5-dihydropyrazine **19** (0.89 g, 4.2 mmol) in dry THF (30 mL) under nitrogen was added *n*-BuLi (2.5 M, 1.7 mL, 4.3 mmol) dropwise at −78 °C via a syringe. This solution was stirred at −78 °C for 30 min. To this solution was added slowly a solution of tosylate **47** (1.52 g, 3.54 mmol) in THF (10 mL) at −78 °C. The reaction mixture that resulted was allowed warm to room temperature and stirred for 5 h. The reaction was quenched with H_2O, and the mixture that resulted was partitioned between water and ether. The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, ether/hexanes 1:6) to afford **52** (1.7 g) in 92% yield. **52**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.55 (s, 6H), 0.76 (d, 3H, $J = 6.8$ Hz), 0.89 (s, 9H), 1.03 (d, 3H, $J = 6.9$ Hz), 1.27 (m, 6H), 2.15 (m, 2H), 2.24 (m, 1H), 2.66 (m, 2H), 3.95 (t, 1H, $J = 3.4$ Hz), 4.16 (m, 5H), 6.9 (s, 1H), 7.1 (m, 2H), 7.44 (dd, 1H, $J = 1.5$, 7.1 Hz), 7.57 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −4.0, 14.36, 14.38, 16.6, 19.1, 19.5, 20.3, 26.3, 31.9, 34.4, 55.2, 60.5, 60.8, 106.8, 113.8, 118.1, 118.9, 119.1, 121.2, 127.7, 131.1, 141.5, 163.1, 163.4. This material was used in the next step without further characterization.

(2*S*)-2-Amino-4-(1-*tert*-butyldimethylsilylindol-3-yl)butyric Acid Ethyl Ester 53. To a solution of optically pure (2*R*,5*S*)-3,6-diethoxy-2-isopropyl-5-[2-(1-*tert*-butyldimethylsilyl-indol-3-yl)ethyl]-2,5-dihydropyrazine **52** (1.20 g, 2.64 mmol) in THF (6 mL) at 0 °C was slowly added an aqueous solution of 2 N HCl (3 mL). The mixture that resulted was allowed to warm to room temperature and then stirred for 1 h. Ice (10 g) was added to the solution, and the pH of the reaction mixture was adjusted to 8 with aqueous NH_4OH (concentrated) at 0 °C. The mixture was then extracted with ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexanes/ether 5:1) to afford **53** (940 mg) in 99% yield. **53**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.69 (s, 6H), 1.00 (s, 9H), 1.38 (dt, 3H, $J = 3.1$, 7.1 Hz), 1.74 (s, br, 2H), 2.09 (m, 1H), 2.25 (m, 1H), 2.98 (t, 2H, $J = 8$ Hz), 3.62 (m, 1H), 4.27 (q, 2H, $J = 7.1$ Hz), 7.09 (s, 1H), 7.24 (m, 2H), 7.59 (dd, 1H, $J = 1.5$, 7.1 Hz), 7.69 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.0, 16.0, 18.3, 20.2, 25.1, 34.0, 53.0, 59.5, 112.7, 116.1, 117.5, 118.1, 120.2, 126.8, 129.6, 140.3, 174.9. This material was used directly in the next step without further characterization.

(2*S*)-2-Amino-4-(1*H*-indol-3-yl)butyric Acid (L-Homotryptophan) 40. An oven-dried, 25 mL, round-bottom flask equipped with a magnetic stir bar, rubber septum, and a nitrogen inlet and outlet tube was charged with (2*S*)-2-amino-4-(1-*tert*-butyldimethylsilylindol-3-yl)butyric acid ethyl ester **53** (0.8 g, 2.2 mmol) and THF (10 mL). The mixture was stirred, and then a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (2.2 mL, 2.2 mmol) was added. After the solution was stirred for 10 min at room temperature, it was poured into a saturated aqueous solution of sodium carbonate (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (10 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexanes/ether 2:1) to afford an oil (518 mg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, 3H, $J = 7.3$ Hz), 1.88 (m, 1H), 2.08 (m, 1H), 2.79 (t, 2H, $J = 7.8$ Hz), 3.47 (m, 1H), 4.07 (m, 2H), 6.87 (s, 1H), 7.02 (m, 1H), 7.08 (m, 1H), 7,24 (d, 1H, $J = 7.9$ Hz), 7.52 (d, 1H, $J = 7.7$ Hz), 8.55 (s, br, 1H). To this oil was added ethanol (7.5 mL), water (5 mL), and aqueous 2 N NaOH (0.4 mL). The mixture that resulted was heated at 60 °C for 4 h until analysis by TLC (silica gel) indicated complete absence of starting material. Ethanol was removed under reduced pressure, and the mixture was then brought to pH 7 (pH paper) to give a white solid **40** (397 mg) in 83% yield. **40**: $[\alpha]^{27}_D = 37.5°$ ($c = 0.24$, in CH_3COOH); mp 268−270 °C dec; IR (KBr) 3397, 1660 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.96 (m, 1H), 2.09 (m, 1H), 2.77 (t, 2H, $J = 8.0$ Hz), 3.21 (m, 1H), 6.96 (m, 1H), 7.05 (m, 1H), 7.11 (s, 1H), 7.33 (d,1H, $J = 8$ Hz), 7.54 (d, 1H, $J = 7.8$ Hz), 10.8 (s, br, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 21.1, 31.9, 54.0, 111.3, 113.8, 118.0, 118.4, 120.8, 122.1, 127.1, 136.3, 169.8; MS (CI, CH_4) *m*/*e* (rel intensity) 219 ($M^+ + 1$, 100), 175 (12), 130 (20); exact mass calcd for $C_{12}H_{14}N_2O_2$ 218.1054, found 218.1055. Anal. Calcd for $C_{12}H_{14}N_2O_2 \cdot {}^1/_5H_2O$: C, 64.97; H, 6.54; N 12.63. Found: C, 64.51; H, 6.42; N, 12.21.

3-(Triethylsilyl)prop-2-yn-1-ol 61. To a solution of 2-prop-2-ynyloxytetrahydropyran **60** (103 g, 0.74 mol) in anhydrous

THF (800 mL) at −78 °C was slowly added *n*-BuLi (2.5 M, 293 mL). The solution that resulted was stirred at −78 °C for 1 h, after which time chlorotriethylsilane (100 g, 0.67 mol) was added quickly. The reaction solution that resulted was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with H_2O (10 mL), and the THF was removed under reduced pressure. The residue was partitioned between water (500 mL) and ethyl ether (250 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 150 mL). The combined ether layers were dried (Na_2SO_4). After the ether was removed under reduced pressure, the residue was dissolved in CH_3OH. To this solution was added PPTS (pyridinium *p*-toluenesulfonic acid, 17 g, 0.068 mol), and the solution that resulted was stirred for 24 h at room temperature. The CH_3OH was removed under reduced pressure, and the residue was dissolved in ether (200 mL). The ethereal solution was then washed with a saturated aqueous solution of sodium bicarbonate and dried (Na_2SO_4). After the ether was removed under reduced pressure, the residue was subjected to vacuum distillation at 80 °C (0.3 mmHg) to provide the title compound **61** (102 g, 90%). **61**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61 (q, 6H, J = 7.9 Hz), 0.99 (t, 9H, J = 7.7 Hz), 1.60 (t, 1H, J = 6.1 Hz), 4.29 (d, 2H, J = 6.1 Hz). The spectral data for **61** were identical to that reported in the literature.[93]

(2*S*,5*R*)-3,6-Diethoxy-2-isopropyl-5-[3-(triethylsilyl)-prop-2-ynyl]-2,5-dihydropyrazine 25. The triethylsilyl propargyl alcohol **61**(100 g) was dissolved in anhydrous ethyl ether (1 L), and then diphenyl chlorophosphate (1 equiv, 157.9 g) was added. The solution that resulted was cooled in a dry ice bath to below −10 °C, and solid 85% KOH (1.5 equiv, 50 g) was added. The mixture was then stirred vigorously with an overhead stir overnight (the temperature was kept below 5 °C). The suspension that resulted was filtered to remove inorganic solids, and the filtrate was concentrated under reduced pressure. The residue was flash evaporated several times with dry THF on a rotovapor under vacuum until examination of the NMR spectrum indicated the absence of the peak due to water: ^{1}H NMR (300 MHz, $CDCl_3$) for the residue δ 0.48 (q, 6H, J = 7.9 Hz), 0.86 (t, 9H, J = 7.8 Hz), 4.76 (d, 2H, J = 10.6 Hz), 7.15 (m, 10H). In a separate flask, 1 equiv (124.7 g) of the Schöllkopf chiral auxiliary **19** was dissolved in dry THF (1 L), to which *n*-BuLi (1.1 equiv, 2.5 N, 235 mL) was added. The solution that resulted was stirred at −78 °C for 1 h, after which time the previous residue (dissolved in 500 mL of dry THF, which had been cooled to −78 °C) was added dropwise to the anion of the Schöllkopf chiral auxiliary. After addition was complete, the solution was allowed to stir for 2 h at −78 °C and then allowed to warm to room temperature The reaction mixture was quenched by slow addition of H_2O. The solvent was removed under vacuum, and the residue was partitioned between water (200 mL) and ethyl ether (500 mL). After separation of the ether layer, the water layer was extracted with ethyl ether (3 × 500 mL). The combined ether layers were dried (Na_2SO_4). After the ether was removed under reduced pressure, the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 2:98) to provide **25** (192 g) in 90% yield. **25**: $[\alpha]^{27}_D = -36.09°$ (c = 0.92, $CHCl_3$); IR (NaCl) 2945, 2175, 1686 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.51 (q, 6H, J = 7.4 Hz), 0.70 (d, 3H, J = 6.8 Hz), 0.94 (t, 9H, J = 7.7 Hz), 1.02 (d, 3H, J = 6.9 Hz), 1.27 (t, 3H, J = 7.08 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.30 (m,1H), 2.69 (dd, 1H, J = 16.6, 4.3 Hz), 2.84 (dd, 1H, J = 16.5, 4.4 Hz), 3.97 (t, 1H, J = 3.3 Hz), 4.06−4.20 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 4.5, 7.3, 14.3, 16.7, 19.1, 26.5, 31.7, 54.6, 60.6, 60.7, 61, 83.5, 104.5, 161.2, 164.2; MS (EI) *m/e* (rel intensity) 364 (M^+, 17), 307 (27), 211 (60), 169 (100), 141 (14); exact mass calcd for $C_{20}H_{36}N_2O_2Si$ 364.2546, found 364.2588. Anal. Calcd for $C_{20}H_{36}N_2O_2Si\cdot{}^1/_5H_2O$: C, 65.24; H, 9.96; N, 7.61. Found: C, 65.01; H, 9.82; N, 7.57.

(92) Meerwein, H. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 1080.

(93) Ostwald, R.; Chavant, P.; Stadtmueller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143.

(5*R*,2*S*)-3,6-Diethoxy-2-isopropyl-5-[6-methoxy-2-(triethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine 26i. To a three-neck flask (3 L) equipped with an overhead stir were charged 2-iodo-5-methoxyaniline **59** (150 g) and the Schöllkopf derivative **25** (265 g), as well as lithium chloride (2.55 g), sodium carbonate (159 g), palladium(II) acetate (1.75 g), and dry DMF (2L). The mixture was then degassed with a vacuum pump at room temperature. The suspension that resulted was heated for 36 h at 100 °C under an atmosphere of Ar. Examination of the mixture by TLC (silica gel) indicated the iodoaniline **59** had been consumed, and then the reaction mixture was cooled to room temperature and the DMF was removed under vacuum (aspirator). Methylene chloride (2L) was added to the residue, and the suspension that resulted was filtered to remove unwanted salts. After removal of the CH_2Cl_2, the crude product was purified by flash chromatography (silica gel, 2% EtOAc/hexanes) to give 77% of the desired 6-methoxy substituted indole **26i**. **26i**: $[\alpha]^{27}_D = -21.39°$ (c = 1.58, in $CHCl_3$); IR (NaCl) 3388, 2944, 1683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (d, 3H, J = 6.8 Hz), 0.85−1.05 (m, 18H), 1.20 (t, 3H, J = 7.1 Hz), 1.30 (t, 3H, J = 7.1 Hz), 2.25 (m,1H), 2.80 (dd, 1H, J = 13.5, 10.6 Hz), 3.46 (dd, 1H, J = 14.1, 3.1 Hz), 3.84 (s, 3H), 3.88 (t, 1H, J = 3.9), 4.01−4.21 (m, 5H), 6.70 (dd, 1H, J = 8.7, 2.2 Hz), 6.82 (d, 1H, J = 2.1 Hz), 7.60 (d, 1H, J = 8.7 Hz), 7.77 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 4.1, 7.9, 14.7, 14.8, 17.1, 19.5, 32.1, 32.5, 56.0, 59.3, 60.9, 61.0, 61.1, 93.9, 109.3, 121.8, 124.4, 124.7, 130.5, 139.5, 157.0, 163.1, 164.2; MS (CI, CH_4) *m/e* (rel intensity) 486 (M^+ + 1, 100), 456 (13), 372 (51), 274 (27); exact mass calcd for $C_{27}H_{43}N_3O_3Si$ 485.3074, found 485.3055. This material was employed directly in the next step.

6-Methoxy-D-tryptophan Ethyl Ester 62. To a solution of optically pure (2*S*,5*R*)-3,6-diethoxy-2-isopropyl-5-[6-methoxy-2-(triethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine **26i** (15 g, 31 mmol) in THF (200 mL) at −78 °C was slowly added the solution of aqueous HCl in ethanol (50 mL, concentrated aqueous HCl/ethanol, 1:5). The mixture was allowed to warm to 0 °C and stirred for 30 min. An aqueous solution of 2 N HCl (150 mL) was added to this solution, and the mixture was stirred at room temperature for another 2 h. Ice (100 g) was added to the solution, and the pH of the reaction mixture was adjusted to 8 (pH paper) with aqueous NH_4OH (concentrated) at 0 °C. The mixture was then extracted with EtOAc (3 × 250 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue which resulted was purified by flash chromatography (silica gel, gradient elution: EtOAc/hexanes 3:7, to remove L-valine ethyl ester, then EtOAc) to afford **62** (6.98 g) in 86% yield. **62**: $[\alpha]^{27}_D = -5.07°$ (c = 0.71, in $CHCl_3$); IR (NaCl) 3365, 1730, 1625 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, J = 7.1 Hz), 1.60 (s, br, 2H), 3.0 (dd, 1H, J = 7.7, 14.3 Hz), 3.22 (dd, 1H, J = 14.4, 4.8 Hz), 3.78 (m, 1H), 3.81 (s, 3H), 4.15 (q, 2H, J = 7.2 Hz), 6.80 (m, 2H), 6.90 (d, 1H, J = 2.0 Hz), 7.45 (d, 1H, J = 8.5 Hz), 8.15 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 30.7, 54.5, 54.9, 60.8, 94.7, 109.2, 111.0, 119.1, 121.8, 121.9, 136.5, 156.1, 175.2; MS (CI) *m/e* 263 (M^+ + 1, 100). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.12; H, 6.87; N, 10.69. Found: C, 63.96; H, 6.98; N, 10.54.

(5*R*,2*S*)-3,6-Diethoxy-2-isopropyl-5-[6-methoxy-1-methyl-2-(triethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine 63. To a mixture of **26i** (100 g, 0.21 mol), methyl iodide (44 g, 0.31 mol), and anhydrous DMF (1000 mL) at 0 °C was added sodium hydride (60% in mineral oil, 12.4 g) in several portions. After this mixture was stirred for 2 h, analysis by TLC (silica gel) indicated the absence of starting material. The reaction solution was quenched with water (8 mL), and the mixture that resulted was subsequently poured into hexanes (5000 mL) to precipitate out sodium hydroxide that was removed by filtration. The solvent was then removed under reduced pressure, and the residue was crystallized from hexanes at 0 °C to afford **63** as white needlelike crystals in several crops. The product in the mother liquor was purified by flash chromatography (silica gel, EtOAc/hexanes, 3:97). The combined material **63** (94 g) was obtained in 90% yield. **63**: $[\alpha]^{27}_D = -17.53°$ (c = 0.81, in $CHCl_3$); mp 91−92 °C; IR (NaCl)

2945, 1688, 1613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (d, 3H, $J = 6.8$ Hz), 0.95 (m, 15H), 0.98 (d, 3H, $J = 6.9$ Hz), 1.14 (t, 3H, $J = 7.1$ Hz), 1.23 (t, 3H, $J = 7.1$ Hz), 2.23 (m, 1H), 2.80 (dd, 1H, $J = 14$, 4.5 Hz), 3.45 (dd, 1H, $J = 14$, 3.5 Hz), 3.73 (s, 3H), 3.84 (s, 3H), 3.85 (m, 1H), 3.90−4.15 (m, 5H), 6.65 (m, 2H), 7.50 (d, 1H, $J = 9.2$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 4.8, 7.6, 14.3, 14.4, 16.7, 19.1, 31.6, 31.9, 33.1, 55.7, 59.2, 60.4, 60.5, 60.7, 91.9, 108.2, 121.2, 124.2, 124.6, 132.3, 140.6, 156.7, 162.7, 163.9; MS (CI, CH_4) *m/e* (rel intensity) 500 ($M^+ + 1$, 100), 470 (16), 386 (14), 288 (21). Anal. Calcd for $C_{28}H_{45}N_3O_3Si$: C, 67.29; H, 9.08; N, 8.41. Found: C, 67.49; H, 9.16; N, 8.34.

X-ray experimental data for 63: $C_{28}H_{45}N_3O_3Si$, (0.43 × 0.26 × 0.18 mm), monoclinic, space group $P2_1$, $a = 7.710(1)$ Å, $b = 19.596(1)$ Å, $c = 19.730(1)$ Å, $\beta = 90.31(1)°$, $V = 2980.8(3)$ Å^3, $Z = 4$, $\rho_{calc} = 1.11$ mg mm^{-3}, $\mu = 0.93$ mm^{-1}, $F(000) = 1088$, 4269 unique data, R1 = 0.038 for 4014 observed data. Further data are available in the Supporting Information.

Data were collected on a Bruker P4 automated serial diffractometer with a graphite monochromator in the incident beam. Face corrected. The structure, with two molecules per asymmetric unit, was solved by routine application of direct methods and refined by full-matrix least-squares on F^2 values using programs in the SHELXTL*PLUS* package.[94] The absolute configuration was clearly indicated by the experimental data (Flack parameter = 0.005 (30)). Other parameters refined included the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were included using a riding model. Additional experimental details, ORTEP illustration (Figure S1), and structural analysis are available as Supporting Information, and coordinates are also available from the Cambridge Crystallographic Database.[95]

6-Methoxy-N_a-methyl-D-tryptophan Ethyl Ester 64. To a solution of optically pure (5*R*,2*S*)-3,6-diethoxy-2-isopropyl-5-[6-methoxy-1-methyl-2-(triethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine **63** (50 g, 0.1 mol) in THF (1000 mL) at 0 °C was slowly added a cold aqueous solution of 2 N HCl (875 mL). The mixture was allowed to warm to room temperature and stirred for 2 h. Ice (800 g) was added to the solution, and the pH of the reaction mixture was adjusted to 8 (pH paper) with aqueous NH_4OH (concentrated) at 0 °C. The mixture was then extracted with CH_2Cl_2 (4 × 1000 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. After all of the solvent appeared to be removed, the residue was subjected to Kugelrohr distillation at 80 °C (0.3 mmHg) to remove L-valine ethyl ester while pure 1-methyl-6-methoxy-D-tryptophan ethyl ester **64** (25.7 g, 93%) remained. An analytical sample was obtained by flash chromatography (silica gel, EtOAc) to afford **64** as a light yellow oil. **64**: $[\alpha]^{27}_D = -7.21°$ ($c = 2.01$, $CHCl_3$) [lit.[52] $[\alpha]^{27}_D = -7.09°$ ($c = 2.06$, in $CHCl_3$)]; IR (NaCl) 3374, 3311, 2980, 2938, 1736, 1623, 1560, 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, $J = 7.1$ Hz), 1.62 (s, br, 2H), 2.99 (dd, 1H, $J = 7.7$, 14.4 Hz), 3.24 (dd, 1H, $J = 14.3$, 4.7 Hz), 3.65 (s, 3H), 3.79 (dt, 1H, $J = 7.4$, 2.6 Hz), 3.89 (s, 3H), 4.18 (q, 2H, $J = 7.1$ Hz), 6.75−6.83 (m, 3H), 7.48 (d, 1H, $J = 8.6$ Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.1, 30.6, 32.5, 55.2, 55.8, 60.6, 93.1, 108.9, 109.8, 119.6, 122.6, 126.5, 137.8, 156.6, 175.0; MS (EI) *m/e* (rel intensity) 276 (M^+, 4), 174 (100), 159 (11). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.18; H, 7.30; N 10.14. Found: C, 64.96; H, 7.36; N, 10.24. The spectral data for **67** were identical to that reported by Hamaker.[52]

(5*S*,2*R*)-3,6-Diethoxy-2-isopropyl-5-[1-*tert*-butyloxycarbonyl-2-bromo-6-methoxy-3-indolyl]methyl-2,5-dihydropyrazine 65. To a solution of (5*S*,2*R*)-3,6-diethoxy-2-isopropyl-5-[6-methoxy-2-(triethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine **26i** (500 mg, 1.03 mmol) in acetonitrile (40 mL) at 0 °C was syringed a solution of NBS (183 mg, 1.03 mmol) that had been dissolved in acetonitrile (10 mL). The reaction mixture was stirred at 0 °C for 30 min, at which time analysis by TLC (silica gel) indicated the absence of starting material. To this solution were then added 4-(dimethylamino)-pyridine (DMAP, 7 mg, 0.057 mmol) and di-*tert*-butyl dicarbonate (450 mg, 2.06 mmol) at room temperature. After the reaction solution was stirred for another 1 h, analysis by TLC (silica gel) indicated the disappearance of the intermediate. The solvent was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes 4:96) to afford **65** (492 mg) as an oil in 87% yield. The spectral data for **65** were identical to that reported by Gan et al. in the literature.[44] This material was converted into tryprostatin A employing the procedure of Gan[43] and Zhao.[45]

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Supporting Information Available: The experimental procedure for the synthesis of compounds **13b**−**g**, **17**−**19** (large scale), **41**, **46** and **58**, **59** (large scale). The ORTEP illustration and data for X-ray structure **63**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001679S

(94) Sheldrick, G. **1995**. *SHELXTL-PLUS* Version 5.03, Bruker Analytical X-ray Systems, Madison, WI.

(95) Cambridge Crystallographic Database, 12 Union Road, Cambridge CB2 1EZ, U.K.