Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8569–8573
Tetrahedron Letters

Synthesis of optically active ring-A substituted tryptophans as IDO inhibitors

Xiaoyan Li, Wenyuan Yin, P. V. V. Srirama Sarma, Hao Zhou, Jun Ma and James M. Cook*

Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, WI 53201, USA

Received 7 July 2004; revised 14 September 2004; accepted 15 September 2004
Available online 1 October 2004

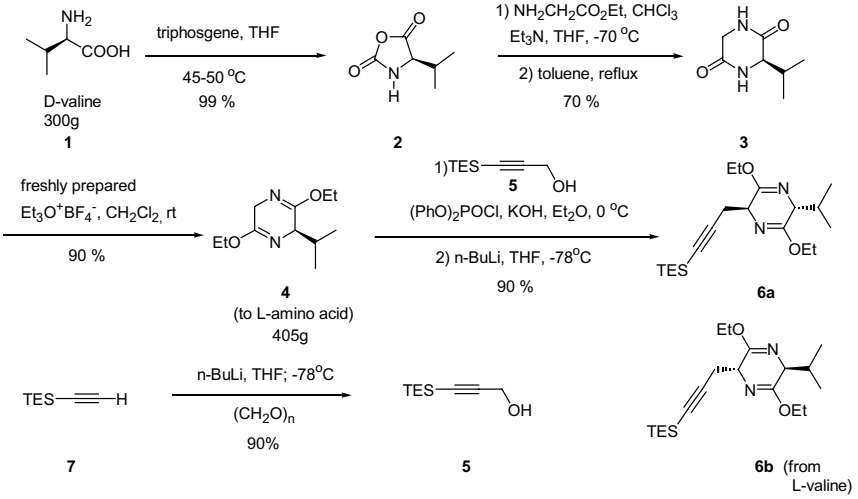
Abstract—The first synthesis of optically active 7-methoxy-D-tryptophan as well as other ring-A substituted tryptophans is described.

Indoleamine 2,3-dioxygenase (IDO) is a monomeric cytosolic enzyme that is distributed in many human tissues including the lens, brain, lung, kidney, spleen, and in macrophages.[1] It is a heme-containing enzyme that uses superoxide or oxygen to cleave the 2,3-double bond of the pyrrole ring of L-tryptophan to yield *N*-formylkynurenine. This is the first and rate-determining step of the kynurenine pathway (KP), which is the major metabolic path for the breakdown of tryptophan (catabolism).[2–4] *N*-Formylkynurenine is then readily hydrolyzed to kynurenine, and subsequently converted to a range of metabolites including quinolinic acid. Many diseases including HIV- and AIDS-associated dementia and wasting as well as acute/chronic immunological and inflammatory diseases have been found to be associated with the elevation of IDO activity[5] and quinolinic acid. More recently, investigations by Kerr et al. have shown[6] that quinolinic acid (QA) production was inhibited in a concentration dependant manner by 6-chloro-D-tryptophan in HIV-1 infected macrophages. In addition, Mellor et al. have demonstrated that N_a-methyl-D-tryptophan may have clinical potential for protection of the mammalian fetus from maternal T-cell attack and this mechanism might have wider implications for the control of T-cell responses.[7–10] This IDO inhibitor, first prepared in this laboratory,[11,12] has been employed to study the 'pregnancy paradox' by Mellor et al.[7–10] and suggests IDO/tryptophan catabolism plays an important role in this process. For these reasons, synthesis of optically active tryptophan derivatives is necessary in the search for more potent inhibitors of IDO.[11–13] Syntheses of some tryptophan analogs have been previously reported.[14–17] We wish to report the preparation of 6-chloro-L-tryptophan **28**, 5,6-dichloro-L-tryptophan **29**, 5-nitro-D-tryptophan **36**, 6-nitro-D-tryptophan **37**, and 6-aza-D-tryptophan **45** as well as the first synthesis of 7-methoxy-D-tryptophan **41** via the Schöllkopf chiral auxiliary.

The approach to the synthesis of these tryptophans began with the preparation of the propargyl substituted bislactim ethyl ether on 400 g scale. Schöllkopf had earlier discovered a method to prepare a variety of amino acids based on the metallation and subsequent alkylation of bislactim ethers (Schöllkopf chiral auxiliary).[18] The popular Schöllkopf chiral auxiliary, bislactim ether **4** derived from D-valine and glycine, was readily available (Scheme 1) on large scale.[17] The TES protected propargyl alcohol **5** required for preparation of the alkylating agent can be obtained in 90% yield in one step by treating triethylsilyl acetylene **7** with *n*-BuLi, followed by the addition of paraformaldehyde[19] instead of the previous three step route[17] from propargyl alcohol. 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 **4** (derived from D-valine) at −78 °C to provide the alkyne **6a** in 90% yield with 100% diastereoselectivity. The D-isomer **6b** would originate from L-valine in the

Keywords: Optically active tryptophans; IDO; 7-Methoxy-D-tryptophan.
* Corresponding author. Tel.: +1 414 229 5856; fax: +1 414 229 5530; e-mail: capncook@uwm.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.113



Scheme 1.

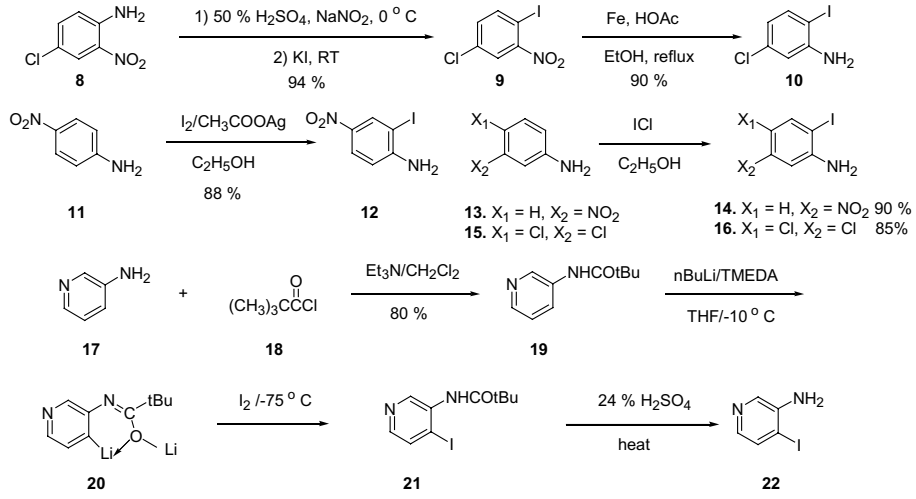
same fashion, as that illustrated in Scheme 1, to provide alkyne **6b** also in 90% yield.

Commercially available 2-nitro-4-chloroaniline **8** was diazotized under standard conditions,[20] followed by treatment of the diazonium ion that resulted with KI to give iodo derivative **9** in 94% yield. Reduction of the nitro group was effected with acetic acid and iron powder in refluxing ethanol to furnish the desired ortho iodoaniline **10** in 90% yield.

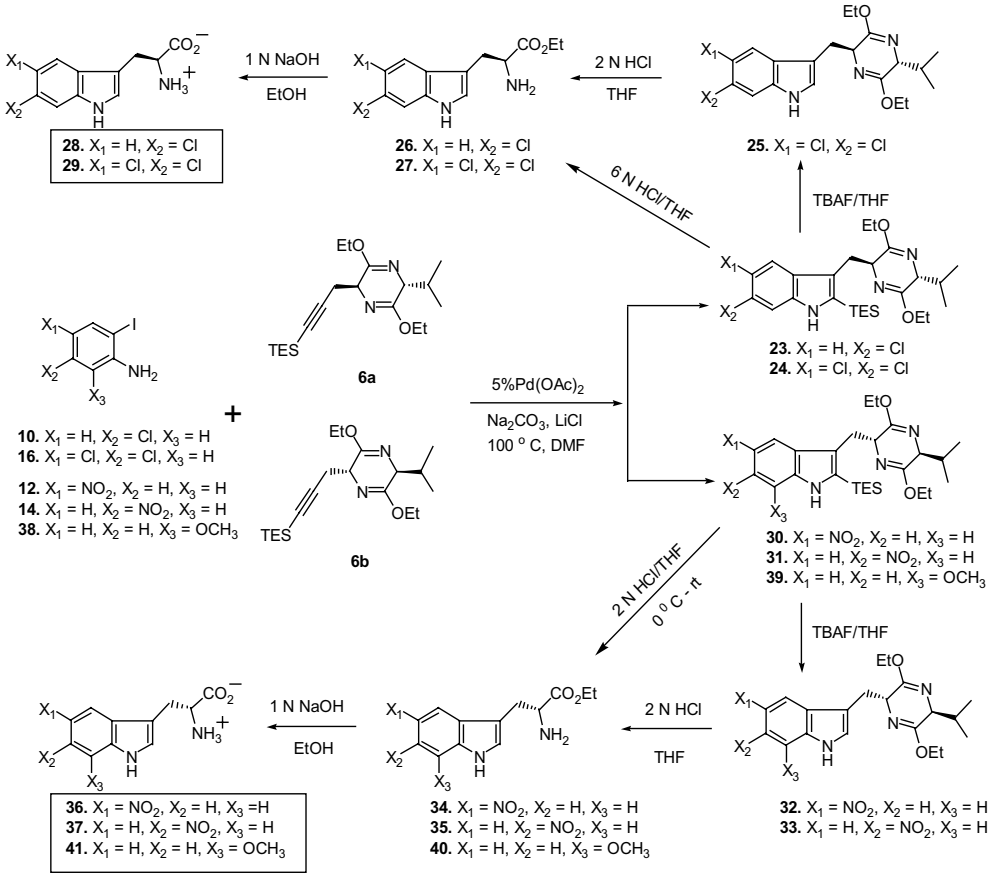
With both the TES-substituted alkyne **6a** and the iodoaniline **10** in hand, the Larock heteroannulation was carried out in the presence of 5% $Pd(OAc)_2$ to afford the desired indole **23** in 68% yield (Scheme 3), accompanied by 10% of the 2,3-regioisomer. This byproduct may have originated from a Heck-type coupling process. Treatment of the indole derivative **23** with 6 N aqueous HCl in THF effected both hydrolysis of the Schöllkopf chiral auxiliary and removal of the indole-2-silyl group to provide the optically active 6-chloro-L-tryptophan ethyl ester **26**. Hydrolysis of the ester **26** at 50 °C with 1 N aq NaOH in ethanol provided 6-chloro-L-tryptophan **28** in 72% yield.

For the synthesis of 5-nitro-D-tryptophan **36** and 5,6-dichloro-L-tryptophan **29**, respectively, the required 2-iodo-4-nitroaniline **12** and 2-iodo-4,5-dichloroaniline **16** were synthesized via standard conditions from commercially available 4-nitroaniline **11** and 4,5-dichloroaniline **15**, respectively (Scheme 2). These conditions were similar to those employed to provide 5-nitro-substituted indole **36**. The triethylsilyl group was later removed by treatment with tetrabutylammonium fluoride. Acid-mediated hydrolysis of the desilylated intermediate **32**, followed by saponification of the ester moiety, provided 5-nitro-D-tryptophan **36** and 5,6-dichloro-L-tryptophan **29** (Scheme 3) in good yield.

In the same manner employed to provide 5-nitro-D-tryptophan **36**, 6-nitro-D-tryptophan **37** was synthesized in good yield. The chemistry required for the synthesis of



Scheme 2.



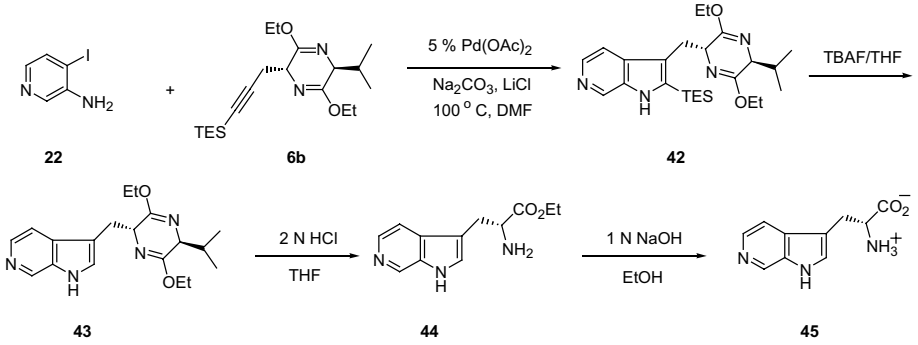
Scheme 3.

the enantiomers (5-nitro-L-tryptophan and of 5,6-dichloro-D-tryptophan) have been previously reported.[17]

The 7-methoxy-D-tryptophan ethyl ester[21] **41** was prepared (Scheme 3) via the Larock heteroannulation[22] process from 2-iodo-6-methoxy-aniline[23] **38** and the propargyl-substituted Schöllkopf chiral auxiliary **6b**[17] in the presence of $Pd(OAc)_2$, K_2CO_3, LiCl in DMF at 100 °C (75% yield). This material was accompanied by 5% of a byproduct, which could be removed by chromatography. The annulation could be carried out both on small scale (100 mg) and large scale (100 g) in comparable yields. Hydrolysis of the Schöllkopf chiral auxiliary accompanied by concomitant loss of the indole-2-silyl group with 2 N aqueous HCl in THF provided optically active 7-methoxy-D-tryptophan ethyl ester **40** in a single step in 92% yield. Finally, the ethyl ester **40** was hydrolyzed to the carboxylic acid **41** with 1 N aq NaOH in ethanol, as illustrated in Scheme 3.

For the preparation of 6-aza-L-tryptophan, the 3-amino-4-iodopyridine **22** (see Scheme 1) was prepared from commercially available 2-amino-pyridine **17**. This amine was stirred with pivaloyl chloride in methylene chloride/triethylamine to give pivaloylpyridine **19** in 80% yield.[25] This aminopyridine, protected as a pivaloylamide **19**, was then subjected to *ortho*-directed lithiation by addition of an excess of butyllithium/TMEDA to give the lithio derivative **20** (Et_2O, −10 °C),[26] which was then stirred with iodine at −75 °C to furnish the corresponding *o*-iodo-(pivaloylamino) pyridine **21**. This amide **21** was hydrolyzed in aqueous sulfuric acid (24%) to give 3-amino-4-iodopyridine **22** in 85% yield.[24,27] The 6-aza-L-tryptophan ethyl ester **44** was prepared via the Larock heteroannulation process from 3-amino-4-iodopyridine **22** and the propargyl substituted Schöllkopf chiral auxiliary **6b** in the presence of $Pd(OAc)_2$, Na_2CO_3, LiCl in DMF at 100 °C (42% isolated yield). Again, a small amount (15%) of the 2,3-regioisomer was obtained. Removal of the TES group from the indole 2-position was achieved by reaction with TBAF in THF to furnish indole **43** in 91% yield. Hydrolysis of the Schöllkopf chiral auxiliary with 2 N aqueous HCl in THF provided optically active 6-aza-D-tryptophan ethyl ester **44** in 76% yield. Finally, the ethyl ester **44** was hydrolyzed to the corresponding carboxylic acid **45** with 1 N aq NaOH in ethanol in 50% yield (see Scheme 4).

In summary, the efficient stereoselective synthesis of optically active 6-chloro-L-tryptophan, 5-nitro-D-tryptophan, 6-nitro-D-tryptophan, 5,6-dichloro-L-tryptophan, 6-aza-D-tryptophan as well as the first synthesis of optically active 7-methoxy-D-tryptophan with potential activity at IDO has been completed.[28] These syntheses render these tryptophans (D- or L-isomers) available in optically active form for the study of biological processes (IDO, TDO, etc.).



Scheme 4.

Acknowledgements

The authors wish to thank the NIMH (MH-46851) for generous financial support.

References and notes

1. Yamazaki, F.; Kuroiwa, T.; Takikawa, O.; Kido, R. *Biochem. J.* **1985**, *230*, 635.
2. Stone, T.; Darlington, L. *Nat. Rev. Drug Disc.* **2002**, *1*, 609.
3. Stone, T. *Prog. Neurobiol.* **2001**, *64*, 185.
4. Botting, N. *Chem. Soc. Rev.* **1995**, *24*, 401.
5. Lestage, J.; Verrier, D.; Palin, K.; Dantzer, R. *Brain Behav. Immunity* **2002**, *16*, 596.
6. Kerr, S. J.; Armati, P. J.; Pemberton, L. A.; Smythe, G.; Tattam, B.; Brew, B. J. *J. Neurol.* **1997**, *49*, 1671.
7. Munn, D.; Zhou, M.; Attwood, J.; Bondarev, I.; Conway, S.; Marshall, B.; Brown, C.; Mellor, A. *Science* **1998**, *218*, 1191.
8. Mellor, A. L.; Munn, D. H. *Immunol. Today* **1999**, *10*, 469.
9. Munn, D. H.; Shafizadeh, E.; Attwood, J. T.; Bondarev, I.; Pashine, A.; Mellor, A. L. *J. Exp. Med.* **1999**, *189*, 1363.
10. Mellor, A. L.; Keskin, D. B.; Johnson, T.; Chandler, P.; Munn, D. H. *J. Immunol.* **2002**, *168*, 3771.
11. 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.
12. 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**, *4*, 531.
13. Southan, M.; Truscott, R.; Jamie, J.; Pelosi, L.; Walker, M.; Maeda, H.; Iwamoto, Y.; Tone, S. *Med. Chem. Res.* **1996**, *5*, 343.
14. Ma, C.; He, X.; Liu, X.; Yu, S.; Zhao, S.; Cook, J. M. *Tetrahedron Lett.* **1999**, *40*, 2917.
15. Ma, C.; Liu, X.; Yu, S.; Zhao, S.; Cook, J. M. *Tetrahedron Lett.* **1999**, *40*, 657.
16. Ma, C.; Yu, S.; He, X.; Liu, X.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 2781.
17. Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525.
18. Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798.
19. Jones, G. B.; Wright, J. M.; Ploudre, G. W.; Hynd, G.; Huber, R. S.; Mathews, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 1937.
20. Salituro, F. G.; Tomlinson, R. C.; Baron, B. M.; Palfreyman, M. G.; McDonald, I. A. *J. Med. Chem.* **1994**, *37*, 334.
21. Zhou, H.; Liao, X.; Cook, J. M. *Org. Lett.* **2004**, *6*(2), 249.
22. Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
23. Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507.
24. Perry, C. W.; Teitel, S. US Patent 3965129 19760622, **1976**.
25. Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401.
26. Estel, L.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 2740.
27. Malm, J.; Rehn, B.; Hornfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1994**, *31*, 11.
28. Compound (**28**): 6-Chloro-L-tryptophan: mp 248–253 °C, $[\alpha]_D^{25}$ −16.0 (*c* 0.15, 1 M HCl) {lit. [24] $[\alpha]_D^{22}$ −15.4 (*c* 1, HOAc)}, IR (KBr) 3638, 2353, 1718, 1525, 1301 cm^{-1}, ^1H NMR (300 MHz, D_2O) δ 3.13–3.21 (dd, 1H, *J* = 7.8 and 15.4 Hz), 3.27–3.36 (m, 1H), 3.91 (dd, 1H, *J* = 4.9 and 7.8 Hz), 7.06 (dd, *J* = 1.8 and 8.5 Hz), 7.19 (s, 1H), 7.44 (d, 1H, *J* = 1.7 Hz), 7.56 (d, 1H, *J* = 8.5 Hz), ^{13}C NMR (300 MHz, D_2O) δ 26.7, 54.9, 91.2, 107.7, 111.4, 119.4, 119.6, 125.3, 125.5, 127.2, 136.5; MS (EI) *m/e* (relative intensity) 238 (M^+, 7), 166 (42), 164 (100), 128 (15), 101 (12), HRMS calcd 238.05 found, 238.050544. Anal. Calcd for $C_{11}H_{11}ClN_2O_2 \cdot 1/3\ H_2O$: C, 54.13; H, 4.81; N, 11.47. Found: C, 54.68; H, 4.62; N, 11.26.
Compound (**29**): 5,6-Dichloro-L-tryptophan: mp 249–251 °C, $[\alpha]_D^{26}$ −37 (*c* 0.15, 1 M aq HCl). IR (KBr) 3424, 1662 cm^{-1}. ^1H NMR (DMSO): δ 1.03 (d, 1H, *J* = 6.09 Hz), 4.14 (s, 2H), 7.12 (s, 1H), 7.37 (s, 1H), 7.63 (s, 1H), 8.36 (s, 2H), 11.44 (s, 1H). MS (EI) *m/e* (relative 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, 48.86; H, 4.21; N, 9.66.
Compound (**36**): 5-Nitro-D-tryptophan: mp 250–255 °C, $[\alpha]_D^{25}$ 21.4 (*c* 0.14, 1 M aq HCl), IR (KBr) 3411, 2363, 1635, 1587, 1330 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6) δ 3.12 (dd, 1H, *J* = 7.5 and 15 Hz), 3.29 (dd, 1H, *J* = 4.2 and 15.1 Hz), 3.44 (dd, 1H, *J* = 4.5 and 7.4 Hz) 7.44 (s, 1H), 7.51 (d, 1H, *J* = 9.0 Hz), 7.97 (dd, 1H, *J* = 2.2 and 9.0 Hz), 8.63 (d, 1h, *J* = 2.2 Hz), 11.07 (s, br s, 1H); MS (EI) *m/e* (relative intensity) 249 (M^+, 4), 175 (100), 129 (100), 102 (30), 74 (25), Anal. Calcd for $C_{11}H_{11}N_3O_4 \cdot 1/3\ H_2O$: C, 51.76; H, 4.60; N, 16.46. Found: C, 51.48; H, 4.43; N, 15.06.
Compound (**37**): 6-Nitro-D-tryptophan: mp 260–264 °C, $[\alpha]_D^{25}$ 52.0 (*c* 0.15, 1 M HCl), IR (KBr) 3449, 3182, 2366, 1623, 1334 cm^{-1}, ^1H NMR (300 MHz, D_2O) δ 3.23–3.31 (m, 2H), 3.92 (m, 1H), 7.47 (s, 1H), 7.63 (d, 1H, *J* = 9.0 Hz), 7.86 (dd, 1H, *J* = 1.8 Hz and 9.0 Hz), 8.28 (d, 1H, *J* = 1.9 Hz), MS (EI) *m/e* (relative intensity) 249 (M^+, 4), 175 (100), 129 (100), 102 (32), 74 (22), Anal. Calcd for $C_{11}H_{11}N_3O_4 \cdot 1/4\ H_2O$: C, 52.07; H, 4.56; N, 16.56. Found: C, 52.21; H, 4.42; N, 16.51.

Compound (**41**): 7-Methoxy-D-tryptophan: mp 234–235 °C (dec), $[\alpha]_D^{26}$ 28.4 (*c* 0.43, H_2O); IR (neat): 3393, 1625, 1579, 1255, 1024 cm^{-1}, ^1H NMR (300 MHz, D_2O) δ 2.99 (dd, 1H, $J = 14.6$, 7.5 Hz), 3.16 (dd, 1H, $J = 14.6$, 5.1 Hz), 3.61 (t, 1H, $J = 6.3$ Hz), 3.91 (s, 3H), 6.75 (d, 1H, $J = 7.7$ Hz), 7.05 (t, 1H, $J = 7.9$ Hz), 7.15 (s, 1H), 7.28 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (300 MHz, D_2O) δ 29.2, 55.6, 56.0, 102.6, 110.4, 111.7, 119.8, 124.1, 126.3, 128.7, 145.9, 180.5. Anal. Calcd for $C_{12}H_{14}N_2O_3 \cdot 2/3\ H_2O$: C, 58.53; H, 6.25; N, 11.38. Found: C, 58.52; H, 6.33; N, 11.02.

Compound (**45**): 6-Aza-D-tryptophan: mp > 300 °C (dec) $[\alpha]_D^{25}$ 27.8 (*c* 0.15, 1 M aq HCl); IR, 2922, 1725, 1609, 1260, 1026, 795 ^1H NMR (D_2O): δ 1.25 (d, 1H, $J = 6.79$ Hz), 2.89–3.05 (m, 2H), 6.11(s, 1H), 7.16 (d, 1H, $J = 2.6$ Hz), 7.62 (s, 1H), 7.71 (d, 1H, $J = 4.0$ Hz), MS (EI) *m/e* (relative intensity) 205 (M^+, 8), 157 (12) 145 (45), 131 (69), 69 (55), 55 (100). Anal. Calcd for $C_{10}H_{11}N_3O_2 \cdot 2/3\ H_2O$: C, 55.29; H, 5.72; N, 19.35. Found: C, 55.06; H, 5.89; N, 18.97.