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Enantioselective Synthesis of Ethyl 6-Substituted-2,3,3a,4,5,6-hexahydro-1*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylates from Tryptophan†

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Abstract: Optically pure ethyl 6-substituted-2,3,3a,4,5,6-hexahydro-1*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylates (**6-9**) have been prepared from ethyl 6-benzotriazolyl-2,3,3a,4,5,6-hexahydro-1*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (**5**), itself obtained from the reaction of the ethyl ester of *L*-tryptophan with benzotriazole and 2,5-dimethoxytetrahydrofuran.

The development of methods for enantioselective or diastereoselective synthesis of optically active indolo[3,2,1-*de*][1,5]naphthyridines is an important synthetic goal. Such indole alkaloids exhibit antimicrobial, cytotoxic and antibacterial activities.[1] Pictet-Spengler condensation is a general synthetic method for indolo[3,2,1-de][1,5]naphthyridines.[2] Many such reports[1b-d, 2a,c-e] refer to 6-oxoindolo[3,2,1-*de*][1,5]naphthyridines of type **1**, while those dealing with 6-substituted indolo[3,2,1-de][1,5]naphthyridines (**2**) are limited [2b,f] [R=H, OH, COOMe].

Recently, we used intermediates (4*S*,5*R*)-5-(benzotriazol-1-yl)-4-phenyl-[1,2-*a*]oxazolopyrrolidine (**3**) and (3*S*)-5-benzotriazolyl-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole (**4**) to prepare 2-substituted and 2,5-disubstituted pyrrolidines,[3] and 2-substituted and 2,6-disubstituted piperidines,[4] Continuing our research on asymmetric syntheses of biologically significant polycycles *via* benzotriazole methodology, we now report the utility of ethyl 6-benzotriazolyl-2,3,3a,4,5,6-hexahydro-1*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (**5**) in the preparation of optically pure ethyl 6-substituted-2,3,3a,4,5,6-hexahydro-1*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylates (**6-9**) (Scheme).

Intermediate **5** was prepared in 60% yield from the reaction of the ethyl ester of *L*-tryptophan with benzotriazole and 2,5-dimethoxytetrahydrofuran in acetic acid at room temperature. The ^{1}H and ^{13}C NMR spectra show that product **5** is obtained as a diastereoisomeric mixture of Bt[1] derivatives. The stereochemistry of **5** was demonstrated by the ^{1}H, ^{13}C NMR and NOE spectra of its elimination product (**10**), which is optically pure. Upon irradiation of H-2 at 3.95-4.02 ppm in **10**, enhancement was observed for H-3a at 4.27-4.34 ppm,

†Submitted to honor the memory of Derek Barton, inspirational chemist and valued friend.

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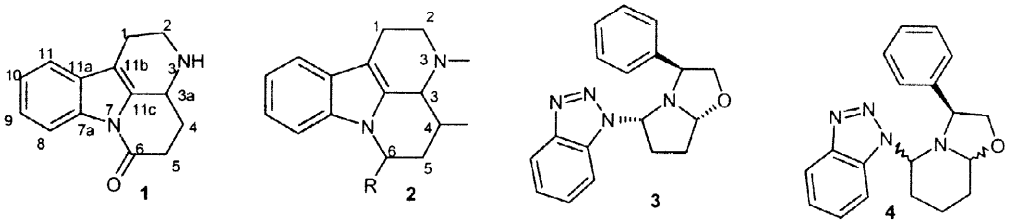
indicating H-3a is *cis* to H-2. Our previous work[4,5] demonstrated that the mechanism of Bt substitution involves a planar iminium salt intermediate and indicated that both diastereoisomers form the same intermediate when Bt is substituted by nucleophiles. Thus, we used intermediate **5** directly as a diastereomeric mixture of Bt[1] isomers in subsequent reactions.



The addition of boron trifluoride-diethyl etherate to a mixture of **5** and 1-phenyl-1-(trimethylsilyloxy)-ethylene in acetonitrile gave a diastereoisomeric mixture (97:3 by GC analysis) of the indolo[3,2,1-*de*][1,5]naphthyridine esters (**6a,b**) from which **6a** and **6b** were isolated in 81% and 1.6% yields, respectively. Addition of boron trifluoride-diethyl etherate prior to the addition of 1-phenyl-1-(trimethylsilyloxy)ethylene to **5** gave a mixture of the elimination product **10** along with **6a** and **6b** (the ratio of **10:6a:6b** was about 5:92:3). The structure of **10** was demonstrated by ^{1}H, ^{13}C NMR and NOE (described above). The detailed structure of **6a** was determined by X-ray crystallography as shown in Figure. The silane nucleophiles underwent dominant attack on the same face of the molecule as the 4-axial hydrogen, possibly because in the iminium cation benzotriazole anion shielded the other face. This is consist with a literature report.[6] Treatment of **5** with (2,2-dimethyl-1-methylenepropoxy)trimethylsilane using the above conditions yielded **7a** and **7b**. Protons NMR signals in **7a** were assigned by a 2D-cosy experiment. The similar chemical shifts and coupling constants of H-2, H-3a and H-6 of **7a** as compared with the corresponding protons in **6a** indicated that both compounds **6a** and **7a** had the same configuration as shown in Figure. Compound **7b** was detected in small quantity by GC-MS analysis and from the crude NMR spectra, but was not isolated.

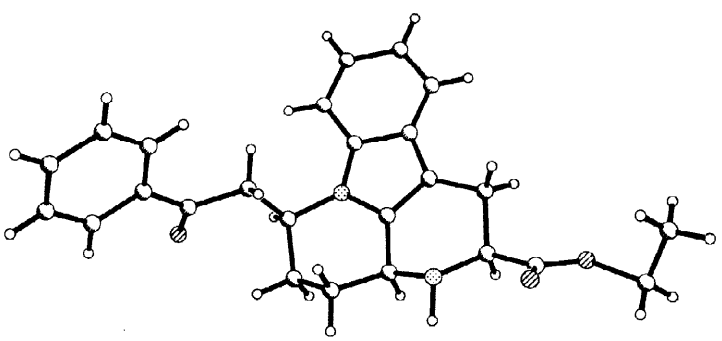
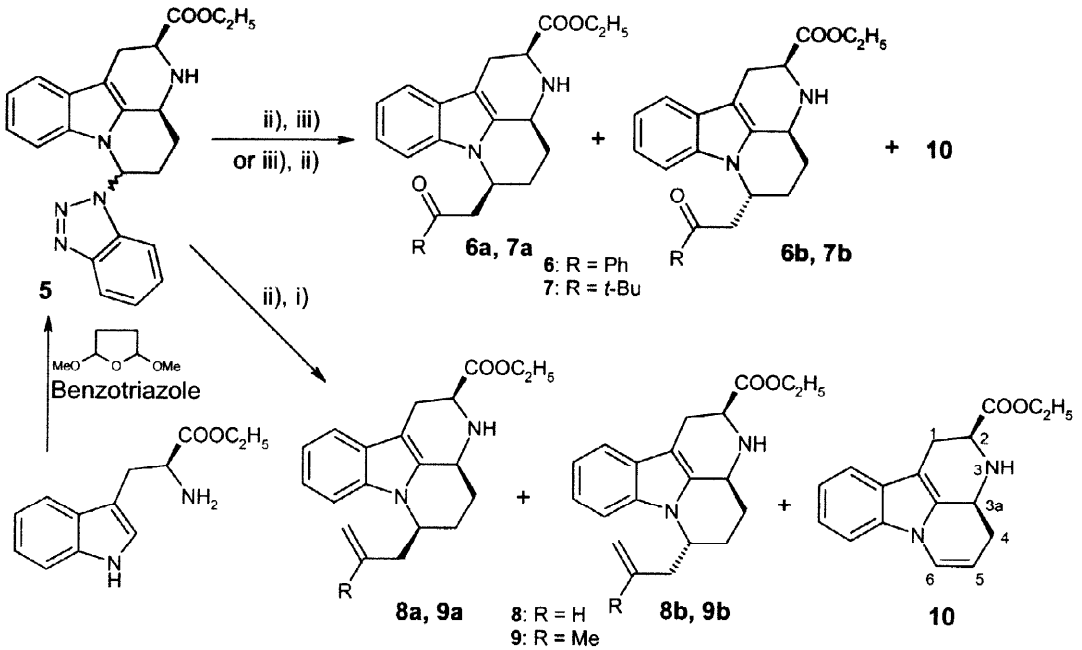


Figure. Perspective view of the X-ray crystal structure of **6a**.



i) allyl trimethylsilane, 0 °C; ii) $BF_3 \cdot OEt_2$, 0 °C; iii) trimethyl (2-substituted-vinyloxy)silane

Scheme

Similarly, the reaction of **5** with allyltrimethylsilane or (2-methylallyl)-trimethylsilane produced, respectively, **8a** and **8b** in a 92:8 ratio from which **8a** was isolated in 80% yield, and **9a** and **9b** in a 93:7 ratio from which **9a** was isolated in 81% yield. The elimination product (**10**) was also obtained when boron trifluoride-diethyl etherate was added prior to the silane reagent. The structures of **8a** and **9a** were identified by 2D-cosy and comparison of both ^1H and ^{13}C NMR data with those of **6a**.

In conclusion, several optically pure indolo[3,2,1-*de*][1,5]naphthyridines **6-10** have been obtained from the reaction of organosilane reagents with intermediate **5**, which was in turn prepared from *L*-tryptophan, 2,5-dimethoxytetrahydrofuran and benzotriazole. This provides a simple and highly diastereoselective method for synthesizing indolo[3,2,1-*de*][1,5]naphthyridines.

EXPERIMENTAL

General. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ with TMS or $CDCl_3$ as the internal reference. Elemental analyses were performed on a Carlo Erba-1106 instrument. High resolution mass spectra were measured on a Kratos/AE1-MS 30 mass spectrometer. $[\alpha]_D$ were recorded on a Perkin Elmer 341 polarimeter at 20 °C. Gas chromatographic analyses were performed on a Hewlett Packard 5890 Gas Chromatograph.

Synthesis of Ethyl 6-benzotriazolyl-2,3,3a,4,5,6-hexahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (5).

A solution of the ethyl ester of *L*-tryptophan (2.69g, 10 mmol), benzotriazole (2.40 g, 20 mmol) and 2,5-dimethoxy-tetrahydrofuran (2.8 mL, 20 mmol) in acetic acid (40 mL) was stirred at room temperature for 48 h. The reaction mixture was washed with 2N NaOH and water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried with anhydrous sodium sulfate. After removing the solvent, the residue was applied to a silica gel column to give compound **5** (thick oil, 2.40 g, yield 60%). ^{1}H NMR δ 8.08-8.12 (m, 1H) [7.87-7.83 (m, 1H)], 6.75-7.50 (m, 7H), 6.42 (d, 1H, J = 8.0 Hz) [6.16 (d, 1H, J = 8.0 Hz)], 4.00-4.40 (m, 4H), 2.06-3.50 (m, 6H), 1.65-1.85 (m, 1H), 1.30-1.46 (m, 3H); ^{13}C NMR δ 172.7 [173.7], 146.8 [145.8], 137.3 [135.8], 136.3 [135.2], 131.6 [130.6], 128.5 [128.0], 127.8 [127.9], 124.3 [123.8], 122.4 [122.3], 120.9 [120.8], 120.4 [119.6], 118.3 [118.6], 110.4 [109.6], 110.1 [109.3], 109.5 [107.7], 69.7 [66.8], 61.2 [60.2], 56.6 [57.2], 51.4 [51.5], 29.6 [31.0], 27.9 [30.8], 25.5 [25.1], 14.2 [14.1]. HRMS Calcd for $C_{23}H_{23}N_5O_2$: 401.1852 (M^+). Found 401.1856.

*General procedure for the synthesis of **6,7,8,9** and **10**.*

To a mixture of **5** (0.40 g, 1 mmol) and organosilane reagent (3 mmol) in solvent, acetonitrile (10 mL) for **6** and **7** or methylene chloride (10 mL) for **8** and **9**, boron trifluoride-diethyl etherate (0.4 mL, 3 mmol) was added at 0°C. The resulting mixture was stirred at this temperature for 12-20 h, washed with aqueous NaOH (2N, 2 x 5 mL) and water (2 x 5 mL) and then extracted with $CHCl_3$ (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate. After removal of solvent, the residue was separated on a silica gel column to yield products **6a-9a** and **6b** (the minor products **7b-9b** were not isolated). A by-product (**10**) was obtained when boron trifluoride-diethyl etherate was added before the organosilane reagent.

*Ethyl (2S,3aS,6S)-6-(2-oxo-2-phenylethyl)-2,3,3a,4,5,6-hexahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate **(6a)**.*

White solid, yield 81%, $[\alpha]_D^{20}$ = -159.3 (c = 1.3, $CHCl_3$); m.p. 167-168°C; ^{1}H NMR δ 7.85 (d, 2H, J = 7.2 Hz), 7.46-7.58 (m, 2H), 7.41 (t, 1H, J = 7.9 Hz), 7.24 (d, 1H, J = 7.4 Hz), 7.08-7.20 (m, 2H), 5.21-5.32 (m, 1H), 4.30 (q, 2H, J = 7.1 Hz), 4.00-4.10 (m, 1H), 3.96 (dd, 1H, J = 11.2, 5.3 Hz), 3.12-3.32 (m, 3H), 2.86-2.98 (m, 1H), 2.08-2.42 (m, 4H), 1.68 (q, 1H, J = 9.6 Hz), 1.36 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 198.0, 173.1, 136.5, 135.6, 135.4, 133.5, 121.3, 119.8, 118.5, 110.4, 105.3, 61.2, 57.3, 52.0, 48.1, 40.1, 26.7, 25.6, 23.8, 14.2. Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.59; H, 6.52; N, 6.96. Found: C, 74.30; H, 6.59; N, 6.91.

*Ethyl (2S,3aS,6R)-6-(2-oxo-2-phenylethyl)-2,3,3a,4,5,6-hexahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate **(6b)**.*

Oil, yield 1.6%, $[\alpha]_D^{20}$ = +25.7 (c = 1.3, $CHCl_3$); ^{1}H NMR δ 7.97 (d, 2H, J = 7.2 Hz), 7.46-7.58 (m, 2H), 7.31 (t, 1H, J = 7.9 Hz), 7.10-7.20 (m, 2H), 4.87-5.00 (m, 1H), 4.29 (q, 2H, J = 7.1 Hz), 3.95-4.10 (m, 2H), 3.30-3.45 (m, 1H), 3.10-3.25 (m, 1H), 2.68-2.92 (m, 2H), 2.00-2.30 (m, 4H), 1.6-1.83 (m, 1H), 1.35 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ 197.4, 173.2, 137.2, 136.8, 135.9, 133.6, 128.8, 128.7, 128.0, 121.2, 119.5, 118.4,

109.9, 104.7, 61.1, 56.8, 51.8, 49.3, 45.9, 29.9, 27.5, 26.0, 14.3. Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.59; H, 6.52; N, 6.96. Found: C, 74.13; H, 6.13; N, 6.73.

Ethyl (2S,3aS,6S)-6-(3,3-dimethyl-2-oxobutyl)-2,3,3a,4,5,6-hexahydro-1H-indolo[3,2,1-de][1,5] naphthyridine-2-carboxylate ***(7a)***.

Oil, yield 83%, $[\alpha]_D^{20}$ = -129.4 ° (*c* = 0.80, $CHCl_3$); ^{1}H NMR δ 7.49 (d, 1H, *J* = 7.2 Hz), 7.08-7.22 (m, 3H), 5.05-5.13 (m, 1H), 4.30 (q, 2H, *J* = 7.1 Hz), 4.04-4.09 (m, 1H), 3.95 (dd, 1H, *J* = 11.4, 5.4 Hz), 3.13-3.23 (m, 1H), 2.84-2.94 (m, 1H), 2.74-2.80 (m, 2H), 2.22-2.36 (m, 1H), 1.96-2.38 (m, 3H), 1.56-1.72 (m, 1H), 1.35 (t, 3H, *J* = 7.1 Hz), 1.06 (s, 9H); ^{13}C NMR δ 214.0, 173.1, 135.6, 135.3, 128.4, 121.2, 119.8, 118.5, 110.4, 105.2, 61.2, 57.4, 52.0, 48.0, 44.5, 38.7, 26.8, 26.1, 25.6, 23.8, 14.3. HRMS Calcd for $C_{23}H_{30}N_2O_3$: 382.2256 (M^+). Found 382.2214.

Ethyl (2S,3aS,6S)-6-allyl-2,3,3a,4,5,6-hexahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate ***(8a)***.

Oil, yield 79 %, $[\alpha]_D^{20}$ = -139.8 ° (*c* = 0.86, $CHCl_3$); ^{1}H NMR δ 7.48 (d, 1H, *J* = 7.8 Hz), 7.28 (d, 1H, *J* = 8.1 Hz), 7.17 (t, 1H, *J* = 6.9 Hz), 7.10 (t, 1H, *J* = 7.2 Hz), 5.68-5.84 (m, 1H), 5.05-5.15 (m, 2H), 4.44-4.52 (m, 1H), 4.29 (q, 2H, *J* = 7.2 Hz), 3.96-4.06 (m, 1H), 3.95 (dd, 1H, *J* = 11.4, 5.1 Hz), 3.12-3.22 (m, 1H), 2.80-2.94 (m, 1H), 2.62-2.74 (m, 1H), 2.00-2.28 (m, 5H), 1.63-1.80 (m, 1H), 1.35 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR δ 173.2, 135.7, 135.3, 134.5, 128.3, 120.9, 119.5, 118.4, 118.0, 110.7, 104.6, 61.1, 57.4, 52.0, 51.8, 36.1, 25.7, 25.0, 23.4, 14.3. HRMS Calcd for $C_{20}H_{24}N_2O_2$: 324.1838 (M^+). Found 324.1830.

Ethyl (2S,3aS,6S)-6-(2-methyl-2-propenyl)-2,3,3a,4,5,6-hexahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate ***(9a)***.

Oil, yield 81 %, $[\alpha]_D^{20}$ = -120.5 ° (*c* = 1.3, $CHCl_3$); ^{1}H NMR δ 7.45 (d, 1H, *J* = 7.8 Hz), 7.28 (d, 1H, *J* = 8.1 Hz), 7.17 (t, 1H, *J* = 6.9 Hz), 7.10 (t, 1H, *J* = 6.9 Hz), 4.87 (s, 1H), 4.74 (s, 1H), 4.59 (m, 1H), 4.29 (q, 2H, *J* = 7.2 Hz), 3.90-4.04 (m, 2H), 3.16 (ddd, 1H, *J* = 15.3, 5.4, 1.8 Hz), 2.82-2.94 (m, 1H), 2.56-2.65 (m, 1H), 2.00-2.28 (m, 5H), 1.84 (s, 3H), 1.62-1.78 (m,1H), 1.35 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 173.2, 142.1, 135.7, 135.3, 128.3, 120.9, 119.5, 118.4, 113.6, 110.5, 104.7, 61.1, 57.4, 52.0, 50.2, 39.6, 25.7, 24.6, 23.3, 22.3, 14.2. HRMS Calcd for $C_{21}H_{26}N_2O_2$: 338.1994 (M^+). Found 338.2026.

Ethyl (2S,3aS)-2,3,3a,4-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate ***10.***

Oil, yield 4 %, $[\alpha]_D^{20}$ = -307.9 ° (*c* = 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 1H, *J* = 7.8 Hz), 7.35 (d, 1H, *J* = 8.1 Hz), 7.21 (t, 1H, *J* = 7.2 Hz), 7.12 (d, 1H, *J* = 7.2 Hz), 7.05 (dd, 1H, *J* = 7.5, 3.3 Hz), 5.22-5.29 (m, 1H), 4.30 (q, 2H, *J* = 7.2 Hz), 4.27-4.34 (m, 1H), 3.98 (dd, 1H, *J* = 10.8, 4.8 Hz), 3.12-3.22 (m, 1H), 2.82-2.94 (m, 1H), 2.58-2.70 (m, 1H), 2.12-2.25 (m, 1H), 1.36 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 172.9, 148.5, 134.7, 134.6, 128.4, 122.6, 122.1, 120.3, 118.6, 108.8, 106.9, 106.0, 61.3, 57.3, 48.7, 27.8, 25.6, 14.3. HRMS Calcd for $C_{17}H_{18}N_2O_2$: 282.1368 (M^+). Found 282.1368.

X-Ray Crystallography: Data were collected with a Siemens SMART CCD area detector, using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined on F^2 using all data by full-matrix least-squares procedures. Hydrogen atoms were included in calculated positions with isotropic displacement parameters 1.2 times the isotropic equivalent of their carrier atoms. The function minimised was $\Sigma w(F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2) + (0.1123P)^2 + 1.15P]^{-1}$, where $P = [\max(F_o)^2 + 2F_c^2]/3$.

Crystal Data for ***6a*** *at -120°C:* $C_{25}H_{25}N_2O_3$, M = 402.48, orthorhombic, space group $P2_12_12_1$, a = 8.179(5), b = 9.671(4), c = 25.833(12) Å, V = 2043(2), Z = 4, F(000) = 856, D_X = 1.308 $g.cm^{-3}$, colorless block, 0.58 x 0.46 x 0.19 mm, μ = 0.086 mm^{-1}, $2\theta_{max}$ 48 °, 3338 unique reflections, 291 parameters, R = 0.0757 for 2668 data with $I > 2\sigma(I)$.

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