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SYNTHESIS OF TETRAHYDRO- β -CARBOLINES VIA RADICAL CYCLIZATION OF 2-ALKENYLTHIOANILIDES[†]

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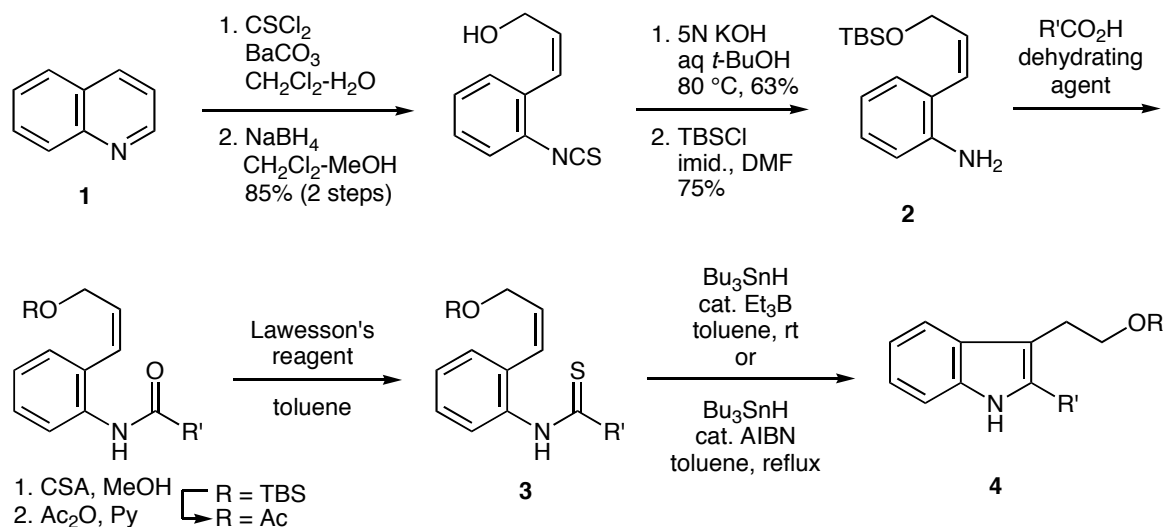
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Abstract – A synthetic protocol of 1,2,3,4-tetrahydro- β -carbolines from *o*-alkenylaniline and α -amino acid was developed. Condensation of α -amino acids with 2-alkenylaniline derived from quinoline gave *o*-alkenylanilides. Conversion of the anilides to thioanilides was effected with Lawesson's reagent in the presence of pyridine, which was crucial to suppress epimerization of the chiral center. After formation of an indole skeleton by radical cyclization, 1,2,3,4-tetrahydro- β -carbolines were obtained *via* intramolecular *N*-alkylation.

INTRODUCTION

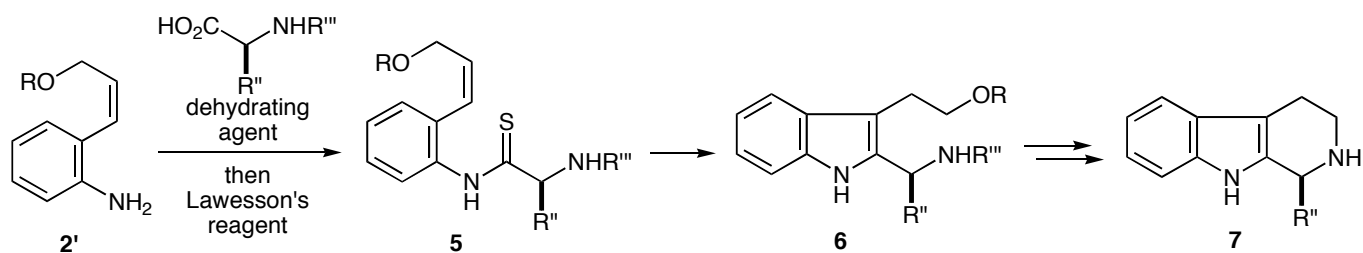
Since a number of biologically important 1,2,3,4-tetrahydro- β -carboline derivatives have been found in nature,¹ stereoselective synthesis of this class of compounds has attracted a great deal of attention from synthetic chemists. To date, a variety of methods have already been reported including a diastereoselective Pictet-Spengler reaction,² diastereoselective alkylation at the C(1) position,³ and conversion of 3,4-dihydro- β -carbolines by enantioselective reduction⁴ or addition of organometallic reagents on C(1)-N(2) double bond.⁵ None of these, however, is sufficient for generality and functional group compatibility. Thus, development of a mild and versatile method has been a continuing research topic. We have recently developed a synthesis of 2,3-disubstituted indoles by radical cyclization of *o*-alkenylthioanilides (**3**) (Scheme 1).⁶ Due to the high functional group compatibility as well as chemo- and regioselectivities, this reaction has played a key role in constructing a number of structurally complex indole alkaloids.⁷⁻⁹ The notable features of this method are versatility and generality for the preparation of

[†]This paper is dedicated to the memory of Professor Kenji Koga (1938–2004).



Scheme 1. Indole Synthesis by Radical Cyclization of 2-Alkenylthioanilides.⁶

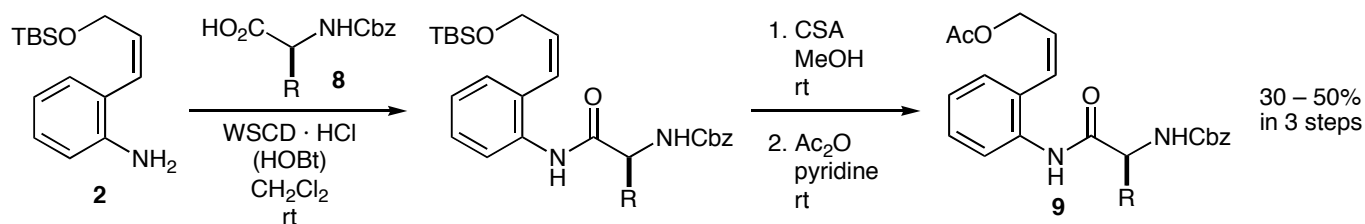
the indole precursors (**3**). Thus, substituents at the indole 2-position were incorporated in a modular fashion by condensation of carboxylic acids and 2-alkenylaniline (**2**), which is readily prepared from quinoline (**1**)¹⁰ by a several-step sequence (Scheme 1).⁶ As an extension of this methodology, the indole formation reaction of the precursors (**5**) prepared from optically active α -amino acids is expected to give the indole derivatives (**6**) bearing chiral alkylamino groups at the 2-position. These compounds, in turn, could easily be converted to optically active tetrahydro- β -carboline (**7**) by formation of the piperidine ring.¹¹ Herein, we report synthesis of tetrahydro- β -carboline *via* radical cyclization of 2-alkenylthioanilide derived from α -amino acids (Scheme 2).



Scheme 2. Synthesis of Tetrahydro- β -carboline from 2-Alkenylthioanilides derived from α -Amino Acids.

RESULTS AND DISCUSSION

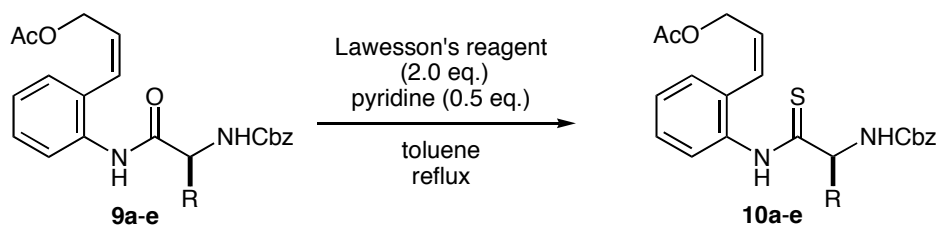
The requisite 2-alkenylanilides (**9a-e**) were readily prepared without appreciable racemization¹² by condensation of *N*-Cbz protected amino acids (**8**) with 2-alkenylaniline (**2**) under standard conditions followed by desilylation and acetylation of the allylic alcohol (Scheme 3). Then, the 2-alkenylanilides (**9**) were subjected to a thionation reaction. Upon treatment of thioanilide (**9a**) with two equivalents of Lawesson's reagent in toluene at reflux, the desired reaction proceeded smoothly to give the



Scheme 3. Preparation of 2-Alkenylanilides derived from α -Amino Acids and 2-Alkenylaniline.

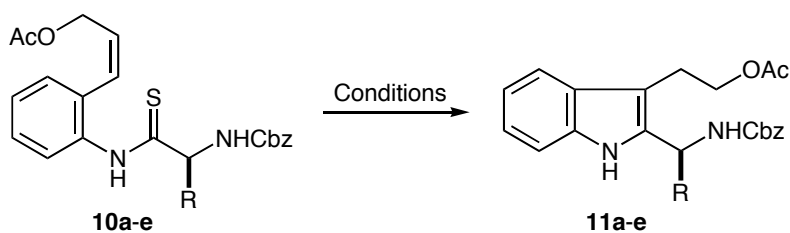
corresponding thioanilide. However, HPLC analysis of the thioanilide product (**10a**) using the corresponding racemic compound as a reference revealed that considerable racemization occurred during thionation, with an ee of 33%.¹³ After extensive efforts at optimization, we have found that the epimerization was best suppressed by addition of a half equivalent of pyridine. This modification was also effective for the substrates derived from other amino acids (Table 1).

Table 1. Conversion of Anilides to Thioanilides.



Entry	Substrate	Time (min)	Yield (%)	%ee
1	9a (R = Me)	20	68	93
2	9b (R = Pr- <i>i</i>)	10	43	81
3	9c (R = CH ₂ Ph)	5	49	71
4	9d (R = CH ₂ OTBS)	10	75	73
5	9e (R = -(CH ₂) ₃ -)	10	65	93

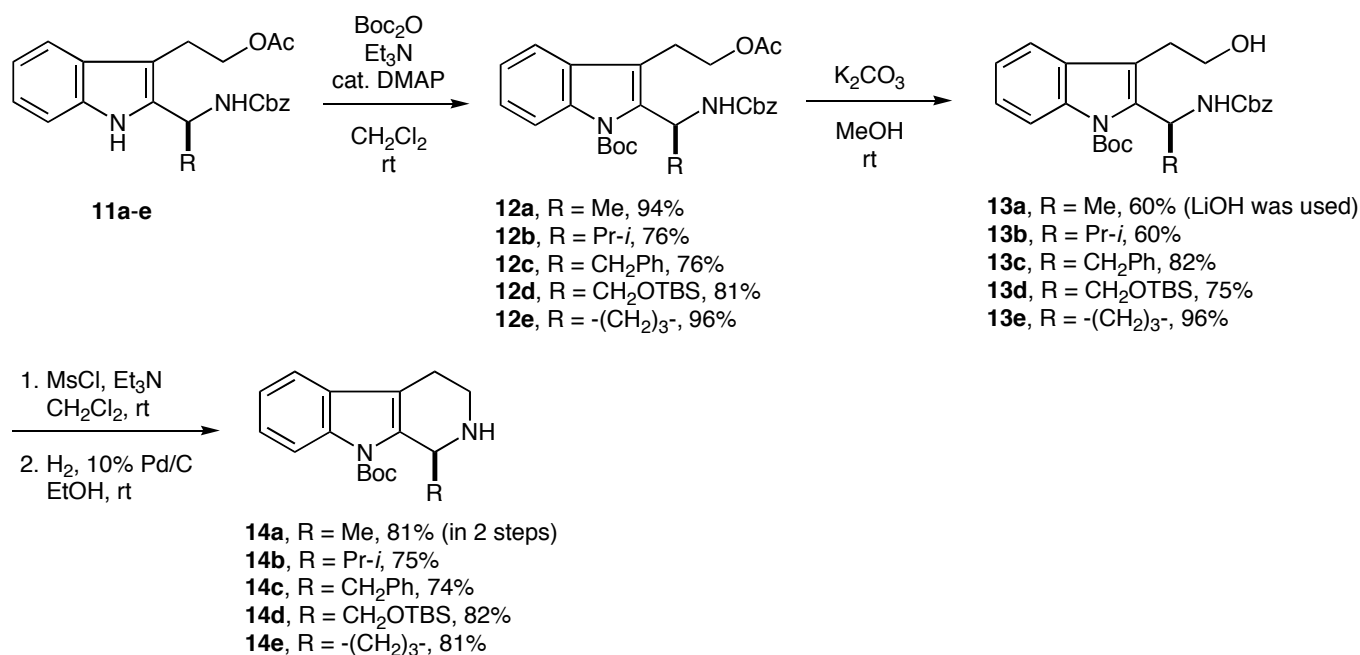
We next examined the crucial indole formation reaction. Upon subjection of the thioanilides to the radical reaction conditions using Et₃B as a radical initiator,¹⁴ the desired reaction took place at ambient temperature in a short period of time and the corresponding indoles were obtained with modest to good yields (Table 2, Entries 1 and 4-7). The substrate bearing TBS ether and that derived from proline were compatible to the reaction conditions (Entries 6 and 7). In addition, the indole formation was carried out by the conventional radical conditions, namely using AIBN and tributyltin hydride in refluxing toluene (Entry 2). Furthermore, while the yield remained modest, tin-free conditions with a combination of H₃PO₂ and AIBN^{15,7b} were employed (Entry 3), in which tedious removal of tin byproduct is unnecessary during work-up. During the indole formation, no detectable racemization was observed.¹⁶

Table 2. Indole Formation Reaction of 2-Alkenylthioanilides.

Entry	Substrate	Conditions	Time(min)	Yield (%)
1	10c (R = CH ₂ Ph)	A	5	86
2	10c (R = CH ₂ Ph)	B	60	74
3	10c (R = CH ₂ Ph)	C	10	54
4	10a (R = Me)	A	5	82
5	10b (R = Pr- <i>i</i>)	A	10	63
6	10d (R = CH ₂ OTBS)	A	30	84
7	10e (R = -(CH ₂) ₃ -)	A	5	70

Condition A: Bu₃SnH (3.0 eq.), Et₃B (0.1 eq.), toluene, rt; Condition B: Bu₃SnH (3.0 eq.), AIBN (0.1 eq.), toluene, reflux; Condition C: H₃PO₂ (15 eq.), AIBN (1.5 eq.), Et₃N (1.5 eq.), *n*-PrOH, reflux.

Transformation of the indole products to the corresponding tetrahydro- β -carboline derivatives was executed in a straightforward manner (Scheme 4). After installation of a Boc group at the indole nitrogen, the acetate was converted to the corresponding mesylate. Finally, deprotection of the Cbz group under hydrogenation conditions and concomitant intramolecular *N*-alkylation furnished the tetrahydro- β -carboline derivatives.

**Scheme 4.** Transformation of Indole Derivatives into Tetrahydro- β -carbolines.

In summary, we have developed a synthesis of tetrahydro- β -carboline derivatives *via* an improved thionation of 2-alkenylanilides with Lawesson's reagent in the presence of pyridine and a subsequent radical cyclization to form the indole skeleton. Since indole precursors, thioanilides, are readily prepared from various α -amino acids and quinolines, this methodology would be useful for the synthesis of structurally complex tetrahydro- β -carboline derivatives.

EXPERIMENTAL

General. All non-aqueous reactions were carried out in oven-dried glass tubes under a slight positive pressure of argon unless otherwise noted. Toluene and benzene were distilled from calcium hydride. Dehydrated tetrahydrofuran, ether, acetonitrile, *N,N*-dimethylformamide, methanol, and ethanol were purchased from Kanto Chemical Co., Inc. and stored over molecular sieves 3Å or 4Å. Dehydrated dichloromethane was purchased from Wako Pure Chemical Industries, Ltd. and stored under argon atmosphere. All other reagents were commercially available and used without further purification. Flash column chromatography separations were performed on Silica Gel 60 (spherical, 40-100 μ m) purchased from Kanto Chemical Co., Inc. unless otherwise noted. Analytical thin layer chromatography (TLC) separations were performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F₂₅₄. Preparative TLC separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F₂₅₄. ¹H and ¹³C NMR spectra were recorded on a JEOL ECX-400 MHz spectrometer. Chemical shifts for ¹H NMR spectrum were reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are indicated in Hertz (Hz). Chemical shifts for ¹³C NMR spectrum were reported in ppm, relative to the central line of the triplet at 77.0 ppm for deuteriochloroform. IR spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer and are reported in wavenumbers (cm⁻¹). HRMS spectra were obtained on a JEOL JMS-700 in positive FAB ionization method. Optical rotations were measured on a JASCO DIP-1000 Digital Polarimeter at room temperature, using the sodium D line.

Acetic acid 3-[2-((2*S*)-2-benzyloxycarbonylamino-3-methylbutyrylamino)phenyl]allyl ester (**9b**).

White powder; $[\alpha]_D^{24} = -7.46^\circ$ (*c* 0.55, CHCl₃); IR (film, cm⁻¹) 752, 1041, 1240, 1533, 1577, 1655, 1689, 1740, 2959, 3284; ¹H NMR (400 MHz, CDCl₃) δ 0.98 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 2.02 (s, 3H), 2.23-2.45 (m, 1H), 4.10-4.25 (m, 1H), 4.50-4.65 (m, 2H), 5.05-5.19 (m, 2H), 5.57 (br s, 1H), 5.65-5.73 (m, 1H), 6.46-6.64 (m, 1H), 7.03-7.18 (m, 2H), 7.25-7.43 (m, 5H), 7.88-8.09 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 17.6, 19.4, 20.9, 30.9, 61.1, 61.6, 67.2, 122.2, 124.7, 127.4, 128.2, 128.3, 128.3, 128.6, 128.6, 129.4, 129.4, 130.0, 130.0, 134.4, 136.2, 156.5, 169.5, 171.1; HRMS (FAB⁺) calcd for C₂₄H₂₈N₂O₅ 424.1998, found 424.1998; Anal. Calcd for C₂₄H₂₈N₂O₅: C, 67.91; H, 6.60; N, 6.65. Found: C, 67.71; H, 6.70; N, 6.45.

General Procedure for the Conversion of 2-Alkenylanilides to 2-Alkenylthioanilides.

The solution of 2-alkenylanilide, pyridine (0.5 equiv.), and Lawesson's reagent (2.0 equiv.) in toluene (*ca.* 0.1 M based on the concentration of the substrate) is heated for 5-20 min at reflux. The mixture is purified by PTLC or directly subjected to column chromatography on silica gel (25% ethyl acetate in *n*-hexane) to afford the corresponding thioanilides.

Acetic acid 3-[2-((2*S*)-2-benzyloxycarbonylamino-3-methylthiobutyrylamino)phenyl]allyl ester (10b).

Slightly yellow oil; $[\alpha]_D^{25} -11.6^\circ$ (*c* 0.09, CHCl₃); IR (film, cm⁻¹) 755, 1029, 1231, 1371, 1506, 1699, 2964, 3244; ¹H NMR (400 MHz, CDCl₃) δ 0.93-1.12 (m, 6 H), 2.02 (s, 3H), 2.40 (br, 1H), 4.34-4.71 (m, 2H), 4.99-5.17 (m, 2H), 5.67-6.25 (m, 2H), 6.48-6.75 (m, 1H), 7.15-7.59 (m, 9H), 7.75-8.03 (m, 1H), 9.50-9.68 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 19.8, 20.0, 20.8, 33.7, 37.5, 62.0, 67.1, 76.7, 126.3, 126.5, 127.4, 127.9, 128.0, 128.2, 128.5, 128.6, 129.1, 129.2, 129.8, 129.9, 131.8, 135.6, 156.2, 164.9, 171.4; HRMS (FAB⁺) calcd for C₂₄H₂₈N₂O₄S 440.1770, found 440.1827.

General Procedure for the Indole Formation Reaction.

To a solution of a 2-alkenylthioanilide of toluene (0.25 M) are added *n*-Bu₃SnH (3 equiv.) and THF solution of Et₃B (0.1 equiv.). After stirring for 10-30 min at rt, the reaction mixture is concentrated under reduced pressure. Then the residue is purified by flash column chromatography on silica gel (50% ether in *n*-hexane) to afford the indole product.

Acetic acid 2-[2-((1*S*)-1-benzyloxycarbonylamino-2-methylpropyl)-1*H*-indol-3-yl]ethyl ester (11b).

Colorless oil; $[\alpha]_D^{27} -11.0^\circ$ (*c* 0.23, CHCl₃); IR (film, cm⁻¹) 743, 1027, 1238, 1388, 1459, 1523, 1704, 2961, 3370; ¹H NMR (400 MHz, CDCl₃) δ 0.82 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 2.03 (s, 3H), 2.38 (br s, 1H), 3.08 (br s, 2H), 4.25 (br s, 2H), 4.40 (br s, 1H), 5.06 (s, 2H), 5.49-5.62 (m, 1H), 7.06-7.40 (m, 8H), 7.58 (d, *J* = 8.0 Hz, 1H), 8.75 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 20.0, 21.3, 23.8, 23.8, 29.6, 55.2, 65.1, 67.4, 108.4, 111.1, 118.6, 119.9, 122.3, 127.8, 127.8, 128.2, 128.2, 128.5, 128.5, 128.5, 135.4, 136.1, 156.4, 171.0; HRMS (FAB⁺) calcd for C₂₄H₂₈N₂O₄ 408.2049, found 408.2255.

General Procedure for Protection of Indole Nitrogen with Boc group.

To a solution of an indole derivative, Et₃N (1.5 equiv.), and DMAP (0.1 equiv.) in CH₂Cl₂ (0.25 M based on the substrate) is added Boc₂O (1.2 equiv.). The mixture is stirred overnight at rt before quenching the reaction with sat. NH₄Cl, and diluting with AcOEt. The organic layer is separated, washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (15-25% ethyl acetate in *n*-hexane) to afford the corresponding *N*-Boc indole product.

3-(2-Acetoxyethyl)-2-((1*S*)-1-benzyloxycarbonylamino-2-methylpropyl)indole-1-carboxylic acid *tert*-butyl ester (12b).

Colorless oil; $[\alpha]_D^{25} -16.9^\circ$ (c 0.29, CHCl_3); IR (film, cm^{-1}) 747, 1025, 1123, 1242, 1322, 1367, 1456, 1491, 1717, 2966, 3430; ^1H NMR (400 MHz, CDCl_3) δ 0.69 (d, $J = 6.6$ Hz, 3H), 1.11 (d, $J = 6.6$ Hz, 3H), 1.70 (s, 9H), 2.02 (s, 3 H), 2.25-2.38 (m, 1H), 3.04-3.34 (m, 2H), 4.20-4.40 (m, 2H), 4.91 (dd, $J = 10.4$, 10.4 Hz, 1H), 5.01 (d, $J = 12.4$ Hz, 2H), 5.16 (d, $J = 12.4$ Hz, 1H), 6.75 (d, $J = 10.4$ Hz, 1 H), 7.21-7.40 (m, 7H), 7.56-7.63 (m, 1H), 7.87-7.96 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.4, 20.5, 21.1, 24.1, 28.2, 31.1, 54.2, 63.9, 66.6, 84.8, 115.5, 115.7, 117.9, 119.3, 122.9, 122.9, 124.7, 127.9, 128.1, 128.5, 129.6, 135.4, 135.6, 136.2, 151.4, 156.3, 171.0; HRMS (FAB^+) calcd for $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6$ 508.2573, found 508.1251.

General Procedure for the Methanolysis of Acetate.

A suspension of an acetate and K_2CO_3 (1 equiv.) in MeOH (0.03 M) is stirred for 20-40 min at rt before quenching with 1N HCl, and diluting with CHCl_3 . The organic layer was separated, washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue is purified by preparative TLC (25% ethyl acetate in *n*-hexane) to afford the corresponding indolethanol derivative.

2-((1*S*)-1-Benzoyloxycarbonylamino-2-methyl-propyl)-3-(2-hydroxyethyl)indole-1-carboxylic acid *tert*-butyl ester (13b).

Colorless oil; $[\alpha]_D^{25} -43.2^\circ$ (c 0.2, CHCl_3); IR (film, cm^{-1}) 746, 1025, 1123, 1257, 1323, 1370, 1456, 1497, 1717, 2968, 3423; ^1H NMR (400 MHz, CDCl_3) δ 0.67 (d, $J = 6.6$ Hz, 3H), 1.10 (d, $J = 6.6$ Hz, 3H), 1.60 (s, 9H), 2.25-2.76 (br s, 1H), 3.12 (dd, $J = 5.6$, 6.8 Hz, 6H), 3.80-4.07 (m, 2H), 4.86 (t, $J = 12.2$ Hz, 1H), 4.98 (d, $J = 12.2$ Hz, 1H), 5.16 (d, $J = 12.4$ Hz, 2H), 6.84 (d, $J = 10.4$ Hz, 1H), 7.20-7.42 (m, 7H), 7.52 (d, $J = 7.2$ Hz, 1H), 7.94 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.7, 20.7, 26.2, 28.5, 28.5, 28.5, 31.4, 54.9, 61.9, 67.2, 84.9, 116.1, 116.1, 119.4, 119.4, 123.1, 123.1, 124.9, 128.4, 128.4, 128.8, 128.8, 130.1, 135.8, 137.0, 152.0, 157.7; HRMS (FAB^+) calcd for $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_5$ 466.2468, found 466.2463.

General Procedure for the Formation of 1,2,3,4-Tetrahydro- β -carboline.

To a solution of an indolethanol derivative and Et_3N (1.3 equiv.) in CH_2Cl_2 (*ca.* 0.1 M) is added MsCl (1.3 equiv.). After stirring for 1 h at rt, the reaction is quenched with sat. NaHCO_3 , and diluted with CHCl_3 . The organic layer is separated, washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue is purified by preparative TLC to afford the corresponding mesylate. The suspension of the mesylate and Pd/C (10 mol%) in EtOH is stirred under H_2 (1 atm) for 1 h at rt. Then Pd/C is removed by filtration through a pad of Celite and the filtrate is concentrated under reduced pressure. The residue is purified by preparative TLC (5% *i*-PrNH₂ in *n*-hexane) to afford the corresponding 1,2,3,4-tetrahydro- β -carboline.

(1*S*)-1-Isopropyl-1,2,3,4-tetrahydro- β -carboline-9-carboxylic acid *tert*-butyl ester (14b).

Colorless oil; $[\alpha]_D^{24} -63.4^\circ$ (c 0.29, CHCl_3); IR (film, cm^{-1}) 745, 1142, 1324, 1369, 1456, 1728, 2968; ^1H

NMR (400 MHz, CDCl₃) δ 0.72 (d, J = 7.2 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H), 1.66 (s, 9H), 2.25-2.39 (m, 1H), 2.58-2.75 (m, 2H), 3.00 (ddd, J = 4.8, 7.6, 13.2 Hz, 1H), 3.31 (ddd, J = 5.2, 5.2, 13.2 Hz, 1H), 4.45-4.55 (m, 1H), 7.25-7.36 (m, 2H), 7.42 (d, J = 6.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 16.8, 19.8, 23.1, 28.2, 31.7, 40.8, 57.3, 83.6, 115.3, 117.6, 117.7, 122.5, 123.9, 129.3, 136.6, 137.3, 150.5; HRMS (FAB⁺) calcd for C₁₉H₂₆N₂O₂ 314.1994, found 314.1830.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. Reviews, see: (a) B. J. Baker, *Alkaloids: Chemical and Biological Perspectives*, 1996, **10**, 357. (b) R. F. James and B. R. Holmstedt, *Phytochemistry*, 1980, **19**, 1573.
2. (a) I. W. J. Still and J. McNulty, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1329. (b) H. Waldmann, G. Schmidt, H. Henke, and M. Burkard, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2402. (c) M. Nakagawa, T. Hino, N. Fukui, T. Kawate, and T. Soe, *Heterocycles*, 1996, **42**, 347. (d) C. Gremmen, B. Willemse, M. J. Wanner, and G.-J. Koomen, *Org. Lett.*, 2000, **2**, 1955.
3. A. I. Meyers and M. F. Loewe, *Tetrahedron Lett.*, 1985, **26**, 3291.
4. R. Noyori, T. Ikariya, S. Hashiguchi, A. Fujii, and N. Uematsu, *J. Am. Chem. Soc.*, 1996, **118**, 4916.
5. M. Nakamura, A. Hirai, and E. Nakamura, *J. Am. Chem. Soc.*, 1996, **118**, 8489.
6. H. Tokuyama, T. Yamashita, M. T. Reding, Y. Kaburagi, and T. Fukuyama, *J. Am. Chem. Soc.*, 1999, **121**, 3791.
7. (a) M. T. Reding and T. Fukuyama, *Org. Lett.*, 1999, **1**, 9730. (b) M. T. Reding, Y. Kaburagi, H. Tokuyama, and T. Fukuyama, *Heterocycles*, 2002, **56**, 313.
8. (a) S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, and T. Fukuyama, *J. Am. Chem. Soc.*, 2002, **124**, 2137. (b) T. Kuboyama, S. Yokoshima, H. Tokuyama, and T. Fukuyama, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 11966. (c) S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, and T. Fukuyama, *Pure Appl. Chem.*, 2003, **75**, 29.
9. Y. Kaburagi, H. Tokuyama, and T. Fukuyama, *J. Am. Chem. Soc.*, 2004, **126**, 10246.
10. For the ring-opening reaction of quinolines with thiophosgene, see: (a) R. Hull, *J. Chem. Soc. (C)*, 1968, 1778. (b) R. Hull, P. J. van den Brook, and M. L. Swain, *J. Chem. Soc., Perkin Trans. 1*, 1975, 922.
11. For a total synthesis of (±)-catharanthine based on the similar strategy, see ref. 6.
12. The enantiomeric excess was determined by chiral HPLC column (DAICEL CHIRALCEL OD 4.6

- I.D. x 250 mm, *n*-hexane/*i*-PrOH, 95/5, flow rate 0.5 mL/min) using the racemic compounds as reference (ee of **9a**, **9b**, **9c**, **9d**, and **9e** were >99%, >99%, 97%, 96%, and >99%, respectively).
13. The enantiomeric excess was determined by chiral HPLC column (DAICEL CHIRALCEL OD 4.6 I.D. x 250 mm, *n*-hexane/*i*-PrOH, 90/10-95/5, flow rate 1.0 mL/min) using the racemic compounds as a reference.
 14. K. Nozaki, K. Oshima, and K. Utimoto, *Tetrahedron*, 1989, **45**, 923.
 15. (a) D. H. R. Barton, D. O. Jang, and J. C. Jaszberenyi, *J. Org. Chem.*, 1993, **58**, 6838. (b) C. G. Martin, C. R. Murphy, and C. R. Smith, *Tetrahedron Lett.*, 2000, **41**, 1833. (c) A. E. Graham, A. V. Thomas, and R. Yang, *J. Org. Chem.*, 2000, **65**, 2583. (d) H. Yorimitsu, H. Shinokubo, and K. Oshima, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 225.
 16. The indole products were converted to the corresponding (+)-MTPA amides by deprotection of the Cbz group and treatment with (+)-MTPA. ¹H NMR spectral analysis of these (+)-MTPA amides using the corresponding (+)-MTPA amides derived from racemic compounds proved that there was no loss of optical purity during the indole formation reaction.