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STEREOSPECIFIC RING-EXPANDING SKELETAL REARRANGEMENT OF ISOINDOLINE TO TETRAHYDROISOQUINOLINE VIA A SEQUENTIAL AZIRIDINE RING FORMATION/OPENING

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This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

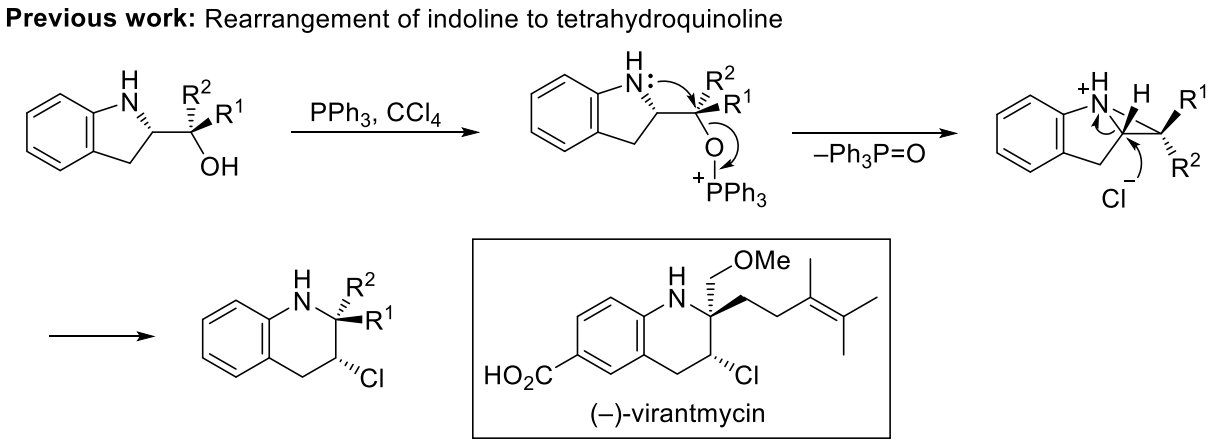
Abstract – A stereospecific skeletal rearrangement of isoindoline to tetrahydroisoquinoline was developed under Appel reaction conditions using a combination of PPh_3 and CCl_4. This reaction involves a sequential ring formation/opening of a labile aziridine and enables the construction of a quaternary carbon center, offering a highly useful method for accessing 3,3,4-trisubstituted tetrahydroisoquinolines.

INTRODUCTION

Nitrogen-containing heterocycles have long attracted the attention of chemists and biologists due to the particular importance of these compounds in medicinal chemistry.[1] Tetrahydroisoquinolines are a major class of alkaloids abundant in bioactive natural products and pharmaceuticals, as represented by ecteinascidin 743.[2] To date, extensive efforts have been devoted to constructing this key framework, establishing some robust synthetic methods, such as the Pictet-Spengler reaction.[3]

In our research on the synthesis of bioactive heterocycles, we developed a PPh_3/CCl_4-mediated stereospecific skeletal rearrangement of indoline-2-methanol to 2,2,3-trisubstituted tetrahydroquinoline, which was applied to the total synthesis of the natural product virantmycin (Scheme 1).[4] During the reaction, an aziridine ring formation and subsequent ring opening via nucleophilic attack of a chloride ion formed a 2,2,3-trisubstituted tetrahydroquinoline with adjacent quaternary and tertiary stereocenters.

Inspired by this unique rearrangement reaction, we envisioned a similar transformation from isoindolines to tetrahydroisoquinolines.

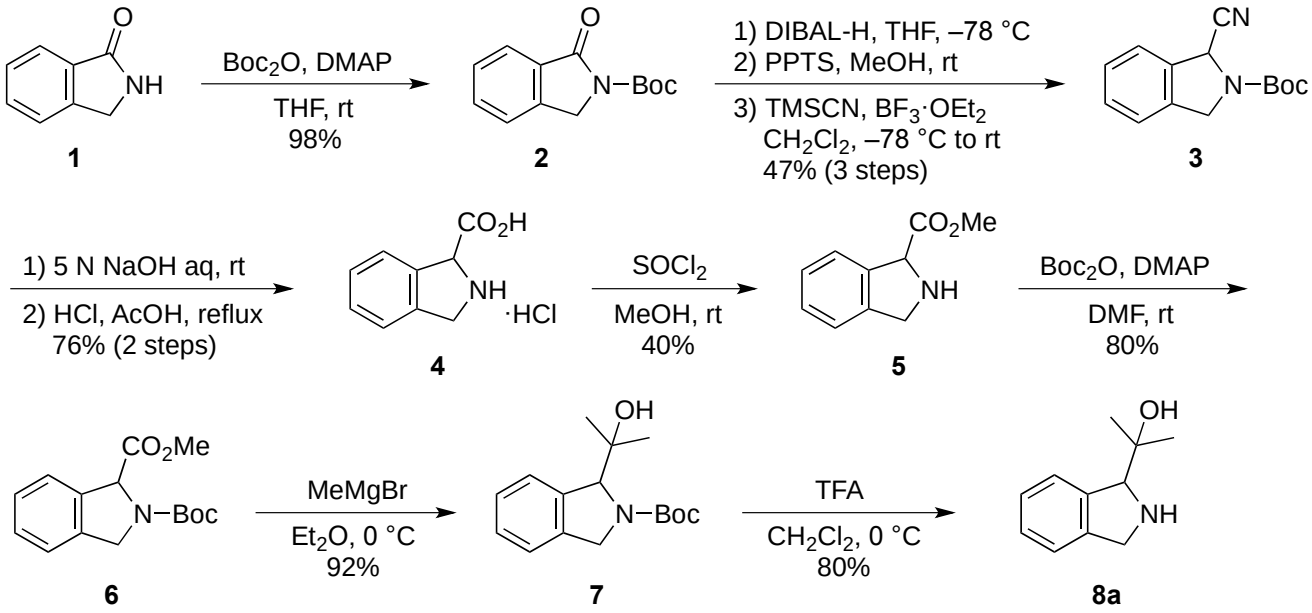


Scheme 1. Skeletal rearrangements of indoline and isoindoline

In this paper, we report the stereospecific ring-expanding skeletal rearrangement of isoindoline to 4-chloro-3,3-dialkyltetrahydroisoquinoline and discuss the reaction mechanism featuring an aziridine ring formation/opening sequence.

RESULTS AND DISCUSSION

To examine the envisaged rearrangement reaction, the simple isoindoline substrate **8** with dimethyl groups was initially prepared (Scheme 2). Commercially available isoindolin-1-one (**1**) was first protected with a Boc group to give **2** in 98% yield.[5] Following the literature, **2** was converted to known methyl ester **5** in six steps, including DIBAL reduction, aminal formation, cyanation, hydrolysis, and methyl esterification.[6] The Boc group was re-introduced to give **6** in 80% yield. Ester **6** was then reacted with methylmagnesium bromide (MeMgBr) to produce tertiary alcohol **7** in 92% yield, from which the Boc group was finally removed with trifluoroacetic acid (TFA) to furnish desired dimethyl derivative **8a** in 80% yield. However, difficulties in handling some intermediates in the lengthy 10-step sequence prompted us to develop an improved method for preparing **8a**.



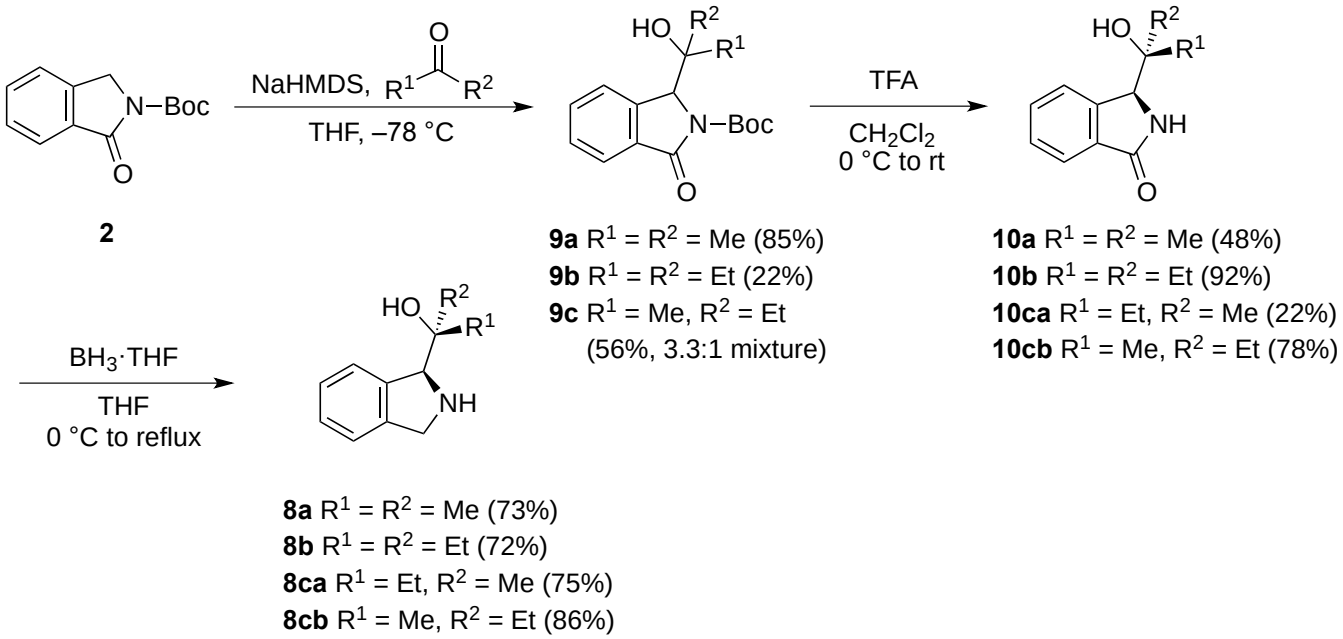
Scheme 2. Synthesis of dimethyl derivative **8a**

After a literature search, the efficient three-step preparation of **8a** from **2** was achieved (Scheme 3). For functionalization at the benzylic position, substrate **2** was deprotonated by sodium bis(trimethylsilyl)amide (NaHMDS), and the resulting metalated species was reacted with acetone to afford the desired tertiary alcohol **9a** in 85% yield.[7] Removal of the Boc group in **9a** with TFA (**10a**, 48%) was followed by reduction of the amide group with BH_3·THF to produce substrate **8a** for the rearrangement reaction in 73% yield.[8]

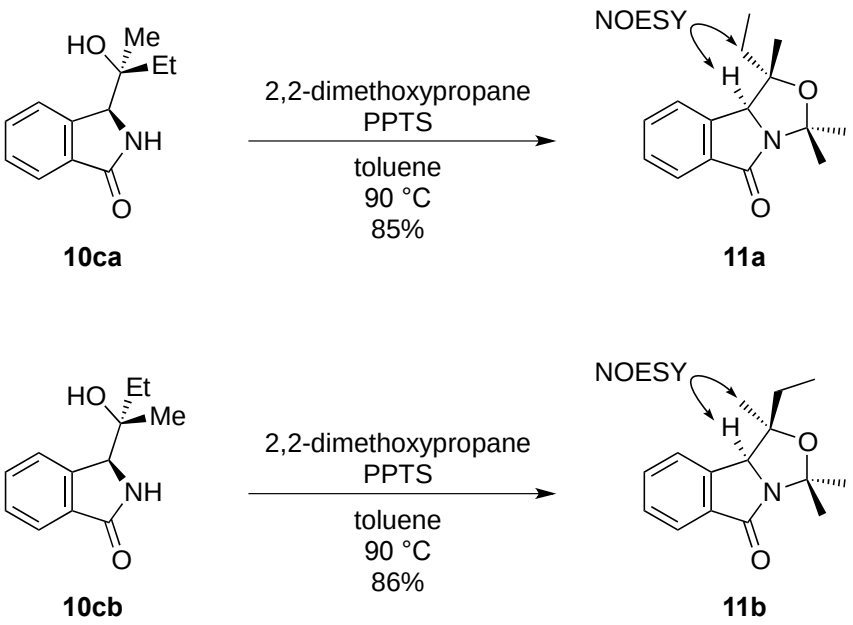
By following the synthetic scheme for **8a**, substrate **8b** bearing two ethyl groups was similarly prepared by using 3-pentanone instead of acetone in the first step. For the substrate with a methyl and an ethyl group, two diastereomers were separated after Boc deprotection by repeated flash chromatography to give **10ca** and **10cb**, which were reduced to isoindolines **8ca** and **8cb**, respectively.

The relative stereochemistries of **10ca** and **10cb** were deduced after conversion to acetonides **11a** and **11b**, respectively, based on the NOESY spectra, in which strong correlations between the methine and methylene protons in **11a**, and between the methine and methyl protons in **11b**, were observed (Scheme 4).

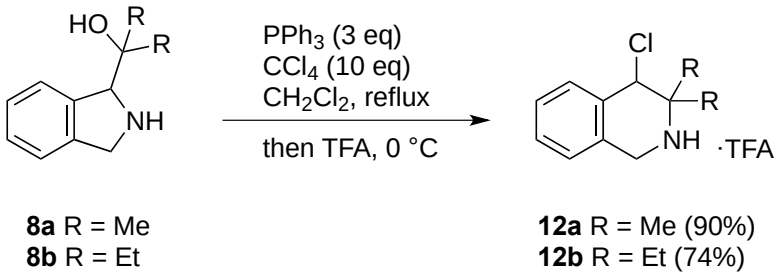
The key reaction was performed and the results are summarized in Schemes 5 and 6. According to the literature,[4] dimethyl derivative **8a** was treated with PPh_3 (3 equiv) and CCl_4 (10 equiv) in refluxing CH_2Cl_2, and the rearrangement reaction proceeded smoothly to afford the desired 4-chloro-3,3-dimethyltetrahydroisoquinoline in 90% yield, which was isolated as TFA salt **12a** because the free amine was unstable, probably due to the nucleophilicity of the nitrogen atom.[9] Diethyl derivative **8b** similarly gave rearranged product **12b** in 74% yield.



Scheme 3. Synthesis of the precursor isoindolines for the skeletal rearrangement

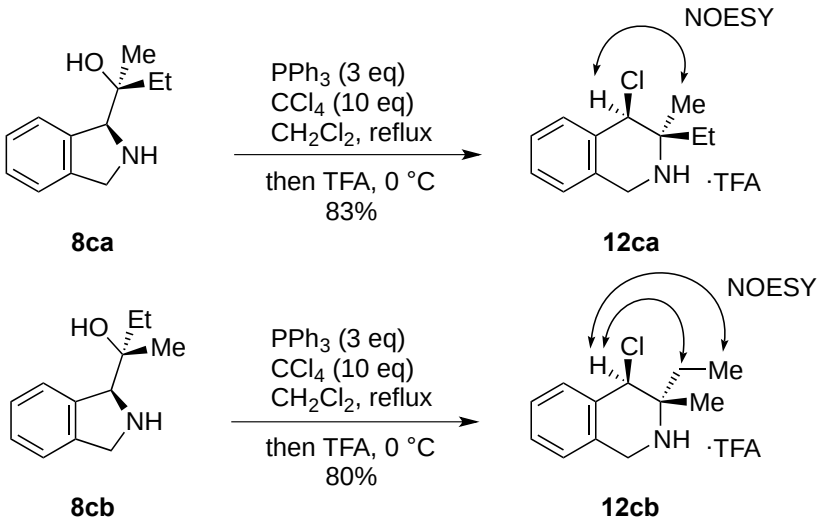


Scheme 4. Determination of the relative stereochemistries of **10ca** and **10cb**



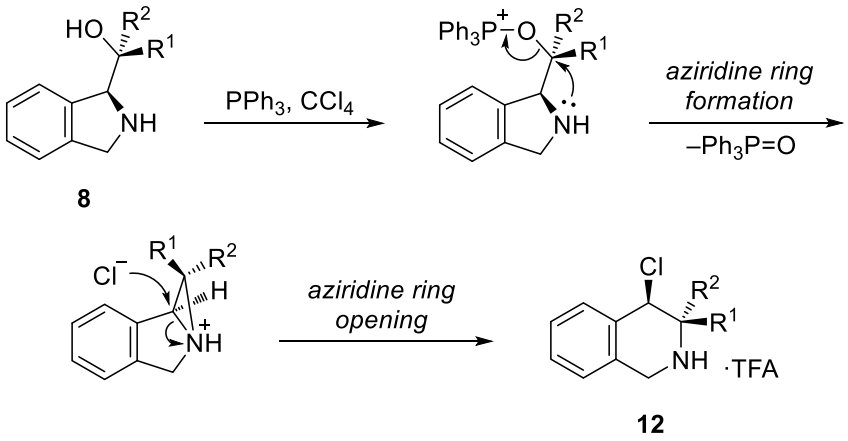
Scheme 5. Rearrangement reaction of isoindolines **8a** and **8b** to tetrahydroisoquinolines **12a** and **12b**

To obtain stereochemical information about the reaction pathway, each isomer of the methyl/ethyl derivatives **8ca** and **8cb** was used in the rearrangement reaction (Scheme 6). As expected, each isomer underwent stereospecific rearrangement: **8ca** and **8cb** gave **12ca** and **12cb** in 83% and 80% yield, respectively. The relative configurations of products **12ca** and **12cb** were confirmed by NOESY experiments, which showed strong correlations between H4 and singlet methyl protons for **12ca**, and between H4 and ethyl protons for **12cb**.



Scheme 6. Comparison of the rearrangement reaction in diastereomeric substrates **8ca** and **8cb**

Based on these results and previous reports,[4] we proposed a putative reaction mechanism. As depicted in Scheme 7, the tertiary alcohol in substrate **8** is initially activated by the chlorophosphonium salt derived from PPh_3 and CCl_4, and triphenylphosphine oxide is eliminated by S_N2 attack of the proximal nitrogen atom to form a labile aziridine ring. The ring undergoes ring opening triggered by S_N2 attack of a chloride ion,[10] furnishing 4-chloro-3,3-dialkyltetrahydroisoquinoline **12**.



Scheme 7. Putative reaction mechanism of the rearrangement reaction

In conclusion, we developed a ring-expanding skeletal rearrangement of isoindoline to tetrahydroisoquinoline, in which sequential aziridine ring formation and opening enables a stereospecific transformation. This rearrangement reaction offers a novel synthetic methodology for preparing highly functionalized tetrahydroisoquinolines. We are currently applying this method to the preparation of bioactive molecules containing the tetrahydroisoquinoline framework, and the results will be disclosed in future publications.

EXPERIMENTAL

General: ^{1}H NMR spectra were recorded on 300 MHz (JNM-AL300, JEOL) or 400 MHz (JNM-AL400, JEOL) instruments. The chemical shifts are expressed in ppm relative to tetramethylsilane ($\delta = 0$) as an internal standard ($CDCl_3$ or DMSO-d_6 solution). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. ^{13}C NMR spectra were measured at 100 MHz (JNM-AL400, JEOL). The chemical shifts are reported in ppm relative to the central line of the triplet at 77.0 ppm for $CDCl_3$. Infrared (IR) spectra were measured on a Fourier transform-IR spectrometer (VALOR-III, JASCO) and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were obtained using a mass spectrometer (JMS 700, JEOL) with a direct inlet system. Optical rotations were measured on a polarimeter (P-2200, JASCO) using a cell with an optical path length of 100 mm. Melting points (mp) were measured on a Yanaco micro melting point apparatus. Column chromatography was performed on silica gel (40-100 mesh). Analytical thin-layer chromatography was conducted using 0.25 mm silica gel 60-F plates.

tert-Butyl 1-(2-hydroxypropan-2-yl)isoindoline-2-carboxylate (7)

MeMgBr (3.0 M solution in Et_2O, 0.61 mL, 1.8 mmol) was added to a stirred solution of **6** (169 mg, 0.61 mmol) in Et_2O (6.0 mL) at 0 °C, and the reaction mixture was stirred for 3 h. The reaction was quenched with water (10 mL), and the mixture was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5:1 cyclohexane/EtOAc) to afford alcohol **7** (155 mg, 98% yield) as a yellow oil. IR ($CHCl_3$) 3619, 3421, 3013, 1663, 1116, 887, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.37 (s, 3H), 1.52 (s, 9H), 4.56 (d, J = 14.8 Hz, 1H), 4.79 (d, J = 14.8 Hz, 1H), 5.00 (s, 1H), 5.17 (s, 1H), 7.25-7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9 (2C), 28.4 (3C), 52.9, 72.3, 75.9, 81.0, 122.3, 124.2, 126.8, 127.8, 137.8, 137.9, 157.3; HRMS (FAB+) *m*/*z* calcd for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1756 found 278.1758.

2-(Isoindolin-1-yl)propan-2-ol (8a)

TFA (0.080 mL, 1.1 mmol) was added to a stirred solution of **7** (14 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C, and the reaction mixture was stirred for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5:1 $CHCl_3$/MeOH) to afford isoindoline **8a** (7.0 mg, 80% yield) as a red-purple amorphous solid. IR ($CHCl_3$) 3337, 2972, 2849, 1508, 1163, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.34 (s, 3H), 2.58 (br s, 2H), 4.22 (d, *J* = 14.7 Hz, 1H), 4.28 (d, *J* = 14.7 Hz, 1H), 4.34 (br s, 1H), 7.18-7.27 (m, 3H), 7.30-7.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 25.9, 52.5, 73.1, 73.2, 122.4, 123.7, 126.6, 127.3, 141.0, 142.3; HRMS (FAB+) *m*/*z* calcd for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1232 found 178.1238.

***tert*-Butyl 1-(2-hydroxypropan-2-yl)-3-oxoisoindoline-2-carboxylate (9a)**

NaHMDS (1.0 M solution in THF, 11 mL, 11 mmol) was slowly added to a stirred solution of **2** (1.30 g, 5.57 mmol) in THF (50 mL) over 20 min at –78 °C. After stirring for 40 min, acetone (4.2 mL, 57 mmol) was added dropwise to the reaction mixture over 15 min, and the stirring was continued for 1 h. The reaction was quenched with AcOH. The resultant solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with Et_2O three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (3:2 hexane/EtOAc) to afford alcohol **9a** (1.38 g, 85% yield) as a pale yellow solid. mp 168-171 °C; IR ($CHCl_3$) 3208, 2981, 1739, 1702, 1614, 1470, 1370, 1281, 1127, 842, 793 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (br s, 3H), 1.52 (s, 9H), 1.56 (br s, 3H), 5.06 (s, 1H), 6.45 (br s, 1H), 7.47-7.62 (m, 3H), 7.88 (dt, *J* = 7.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 21.6, 27.8 (3C), 62.8, 82.2, 83.9, 123.9, 124.0, 128.6, 131.9, 132.8, 143.5, 151.7, 171.0; HRMS (FAB+) *m*/*z* calcd for $C_{16}H_{22}NO_4$ $[M+H]^+$: 292.1549 found 292.1545.

***tert*-Butyl 1-(3-hydroxypentan-3-yl)-3-oxoisoindoline-2-carboxylate (9b)**

Compound **9b** (197 mg, 22% yield, colorless oil) was obtained from **2** (640 mg, 2.74 mmol) and 3-pentanone (2.9 mL, 27 mmol) by a procedure similar to the one used to synthesize **9a**. IR ($CHCl_3$) 3206, 2978, 1699, 1614, 1469, 1368, 1275, 1254, 1132, 871, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.71 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H), 1.52 (s, 9H), 1.72 (dq, *J* = 14.7, 7.5 Hz, 1H), 1.92 (dq, *J* = 14.7, 7.5 Hz, 1H), 2.00 (dq, *J* = 14.7, 7.5 Hz, 1H), 2.08 (dq, *J* = 14.7, 7.5 Hz, 1H), 5.24 (s, 1H), 6.43 (br s, 1H), 7.46-7.60 (m, 3H), 7.87 (dt, *J* = 7.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 8.3, 26.4, 26.5, 27.8

(3C), 60.5, 82.1, 88.0, 124.1, 124.3, 128.6, 131.8, 132.7, 143.6, 151.7, 170.5; HRMS (FAB+) *m*/*z* calcd for $C_{18}H_{26}NO_4$ $[M+H]^+$: 320.1862 found 320.1859.

***tert*-Butyl 1-(2-hydroxybutan-2-yl)-3-oxoisoindoline-2-carboxylate (9c)**

Compound **9c** (886 mg, 3.3:1 diastereomeric mixture, 56% yield, yellow amorphous solid) was obtained from **2** (1.20 g, 5.14 mmol) and 2-butanone (3.5 mL, 51 mmol) by a procedure similar to the one used to synthesize **9a**. IR ($CHCl_3$) 3207, 2979, 1737, 1701, 1616, 1469, 1369, 1276, 1255, 1124, 850, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for major isomer: δ 1.04 (t, *J* = 7.2 Hz, 3H), 1.12 (s, 3H), 1.52 (s, 9H), 2.10 (dq, *J* = 14.7, 7.2 Hz, 1H), 2.16 (dq, *J* = 14.7, 7.2 Hz, 1H), 5.26 (br s, 1H), 6.41 (br s, 1H), 7.42-7.62 (m, 3H), 7.87 (dt, *J* = 6.3, 0.9 Hz, 1H), for minor isomer: δ 0.95 (t, *J* = 7.5 Hz, 3H), 1.24 (s, 3H), 1.53 (s, 9H), 1.78 (dq, *J* = 14.7, 7.5 Hz, 1H), 1.97 (dq, *J* = 14.7, 7.5 Hz, 1H), 5.26 (br s, 1H), 6.41 (br s, 1H), 7.42-7.62 (m, 3H), 7.85 (dt, *J* = 7.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) for major isomer: δ 7.3, 18.8, 27.8 (3C), 28.0, 60.5, 82.0, 85.6, 123.8, 124.3, 128.4, 131.9, 132.6, 144.4, 151.8, 171.4, for minor isomer: δ 7.4, 18.7, 27.5, 27.8 (3C), 61.0, 82.1, 86.3, 123.6, 124.1, 128.6, 131.8, 133.0, 143.1, 151.7, 170.8; HRMS (FAB+) *m*/*z* calcd for $C_{17}H_{24}NO_4$ $[M + H]^+$: 306.1705 found 306.1706.

3-(2-Hydroxypropan-2-yl)isoindolin-1-one (10a)

TFA (2.5 mL, 33 mmol) was added dropwise to a stirred solution of Boc derivative **9a** (478 mg, 1.64 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 1 h, and then quenched with saturated aqueous $NaHCO_3$ (28 mL). The resulting mixture was extracted with CH_2Cl_2 20 times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10:1 $CHCl_3$/MeOH) to afford isoindolinone **10a** (152 mg, 48% yield) as a yellow amorphous solid. IR ($CHCl_3$) 3281, 2977, 1682, 1470, 1145, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.36 (s, 3H), 2.04 (br s, 1H), 4.56 (s, 1H), 6.91 (br s, 1H), 7.43-7.63 (m, 3H), 7.86 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 26.3, 66.1, 73.1, 123.8, 123.9, 128.4, 131.8, 132.7, 144.3, 171.4; HRMS (FAB+) *m*/*z* calcd for $C_{11}H_{14}NO_2$ $[M+H]^+$: 192.1025 found 192.1020.

3-(3-Hydroxypentan-3-yl)isoindolin-1-one (10b)

Compound **10b** (125 mg, 92% yield, yellow oil) was obtained from **9b** (197 mg, 615 μmol) by a procedure similar to the one used to synthesize **10a**. IR ($CHCl_3$) 3281, 2969, 1686, 1469, 1215, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H), 1.37 (dq, *J* = 14.8, 7.2 Hz, 1H), 1.45-1.64 (m, 2H), 1.68 (dq, *J* = 15.2, 7.2 Hz, 1H), 1.78 (br s, 1H), 4.75 (s, 1H), 6.57 (br s, 1H), 7.45-7.60 (m, 3H), 7.86 (br d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4, 7.5, 27.7, 28.3, 62.9,

76.3, 123.9, 124.0, 128.2, 131.7, 132.9, 144.4, 171.4; HRMS (FAB+) *m*/*z* calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1338 found 220.1346.

(*S)-3-((*S**)-2-Hydroxybutan-2-yl)isoindolin-1-one (10ca) and (*S**)-3-((*R**)-2-hydroxybutan-2-yl)-isoindolin-1-one (10cb)**

Compounds **10ca** (61.8 mg, 22% yield, yellow solid) and **10cb** (219 mg, 78% yield, yellow solid) were obtained from **9c** (415 mg, 1.36 mmol) by a procedure similar to the one used to synthesize **10a**.

10ca: mp 115-119 °C; IR ($CHCl_3$) 3281, 2974, 1684, 1470, 1141, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.5 Hz, 3H), 1.15 (s, 3H), 1.64 (br s, 1H), 1.23-1.40 (m, 2H), 4.59 (s, 1H), 6.28 (br s, 1H), 7.45-7.66 (m, 3H), 7.82-7.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2, 22.6, 30.2, 65.3, 74.8, 123.8, 124.1, 128.3, 1317, 132.7, 144.6, 171.5; HRMS (FAB+) *m*/*z* calcd for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181 found 206.1183.

10cb: mp 99-103 °C; IR ($CHCl_3$) 3274, 2974, 1683, 1471, 1214, 1141, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.07 (t, *J* = 7.5 Hz, 3H), 1.27 (br s, 1H), 1.69 (dq, *J* = 14.4, 7.5 Hz, 3H), 1.76 (dq, *J* = 14.4, 7.5 Hz, 3H), 4.61 (s, 1H), 6.59 (br s, 1H), 7.45-7.59 (m, 3H), 7.86 (dt, *J* = 7.2, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4, 21.2, 31.6, 65.1, 75.0, 123.7, 123.9, 128.3, 131.7, 132.9, 144.2, 171.6; HRMS (FAB+) *m*/*z* calcd for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181 found 206.1181.

2-(Isoindolin-1-yl)propan-2-ol (8a)

BH_3·THF (1.0 M solution in THF, 2.6 mL, 2.6 mmol) was slowly added to a stirred solution of isoindolinone **10a** (125 mg, 0.651 mmol) over 15 min at 0 °C, and the resultant mixture was refluxed for 17 h. After cooling to room temperature, THF (4 mL), ice-cold water (3 mL), and 1 M NaOH (3 mL) were successively added to the reaction mixture, which was then extracted with Et_2O three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10:1→1:1 $CHCl_3$/MeOH) to afford isoindoline **8a** (115 mg, 73% yield) as a red-purple amorphous solid.

3-(Isoindolin-1-yl)pentan-3-ol (8b)

Compound **8b** (84 mg, 72% yield, red-purple oil) was obtained from **10b** (125 mg, 569 μmol) by a procedure similar to the one used to synthesize **8a**. IR ($CHCl_3$) 3336, 2966, 2938, 2880, 1458, 1396, 956, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.2 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H), 1.16 (dq, *J* = 14.8, 7.2 Hz, 1H), 1.44 (dq, *J* = 14.8, 7.2 Hz, 1H), 1.58 (dq, *J* = 14.8, 7.2 Hz, 1H), 1.78 (dq, *J* = 14.8, 7.2 Hz, 1H), 2.65 (br s, 2H), 4.22 (d, *J* = 14.8 Hz, 1H), 4.27 (d, *J* = 14.8 Hz, 1H), 4.59 (br s, 1H), 7.15-7.35

(m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5, 7.8, 27.0, 27.7, 52.5, 69.2, 76.3, 122.4, 123.9, 126.6, 127.2, 140.6, 142.4; HRMS (FAB+) *m*/*z* calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1545 found 206.1553.

(*S)-2-((*S**)-Isoindolin-1-yl)butan-2-ol (8ca)**

Compound **8ca** (66.4 mg, 75% yield, red-purple amorphous solid) was obtained from **10ca** (95.0 mg, 0.463 mmol) by a procedure similar to the one used to synthesize **8a**. IR ($CHCl_3$) 3336, 2972, 2936, 2879, 1683, 1508, 1457, 1215, 1160, 921, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.5 Hz, 3H), 1.01-1.16 (m, 1H), 1.24 (s, 3H), 1.39 (dq, *J* = 13.8, 7.5 Hz, 1H), 2.00 (br s, 2H), 4.19 (dd, *J* = 14.4, 1.5 Hz, 1H), 4.27 (d, *J* = 14.4 Hz, 1H), 4.41 (d, *J* = 1.5 Hz, 1H), 7.16-7.28 (m, 3H), 7.30-7.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5, 22.3, 29.1, 52.4, 73.2, 75.0, 122.4, 123.9, 126.7, 127.3, 140.5, 142.1; HRMS (FAB+) *m*/*z* calcd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1388 found 192.1394.

(*R)-2-((*S**)-Isoindolin-1-yl)butan-2-ol (8cb)**

Compound **8cb** (141 mg, 86% yield, red-purple oil) was obtained from **10cb** (175 mg, 0.854 mmol) by a procedure similar to the one used to synthesize **8a**. IR ($CHCl_3$) 3345, 2972, 2936, 2880, 1459, 1375, 1163, 931, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.05 (t, *J* = 7.5 Hz, 3H), 1.64 (dq, *J* = 14.1, 7.5 Hz, 1H), 1.68 (br s, 2H), 1.73 (dq, *J* = 14.1, 7.5 Hz, 1H), 4.21 (d, *J* = 14.7 Hz, 1H), 4.27 (d, *J* = 14.7 Hz, 1H), 4.39 (br s, 1H), 7.16-7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 21.9, 31.0, 52.5, 71.4, 74.8, 122.4, 123.7, 126.6, 127.3, 140.7, 142.2; HRMS (FAB+) *m*/*z* calcd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1388 found 192.1389.

4-Chloro-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate (12a)

CCl_4 (0.10 mL, 1.0 mmol) and PPh_3 (78.6 mg, 300 μmol) were added successively to a stirred solution of alcohol **8a** (17.4 mg, 98.2 μmol) in CH_2Cl_2 (2.0 mL) at room temperature, and the resulting solution was refluxed for 1 h. After cooling to 0 °C, TFA (0.20 mL, 2.6 mmol) was added to the reaction mixture, which was stirred for 30 min, diluted with toluene, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (30:2:1 $CHCl_3$/MeOH/TFA) to afford **12a** (27.3 mg, 90% yield) as a yellow oil. IR ($CHCl_3$) 3421, 3019, 1674, 1202, 1135, 754 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (s, 3H), 1.54 (s, 3H), 4.40 (d, *J* = 16.8 Hz, 1H), 4.45 (d, *J* = 16.8 Hz, 1H), 5.53 (s, 1H), 7.29-7.36 (m, 1H), 7.37-7.46 (m, 2H), 7.45-7.53 (m, 1H), 9.32 (br s, 1H), 10.18 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.5, 23.4, 56.0, 61.6, 69.4, 117.2*, 126.6, 127.2, 128.2, 129.1, 129.9, 131.8, 158.1* (*These signals are split into a quartet by three fluorine atoms.); HRMS (FAB+) *m*/*z* calcd for $C_{11}H_{15}ClN$ $[M+H]^+$: 196.0893 found 196.0894.

4-Chloro-3,3-diethyl-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate (12b)

Compound **12b** (17.3 mg, 74% yield, brown amorphous solid) was obtained from **8b** (14.2 mg, 69.2 μmol) by a procedure similar to the one used to synthesize **12a**. IR ($CHCl_3$) 3420, 2978, 1682, 1670, 1619, 1434, 1203, 1130, 760 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H), 1.45-1.61 (m, 2H), 1.84-2.04 (m, 2H), 4.33 (d, J = 17.2 Hz, 1H), 4.42 (d, J = 17.2 Hz, 1H), 5.64 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.49 (d, J = 7.6 Hz, 1H), 9.17 (br s, 1H), 9.78 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 6.6, 7.5, 22.1, 25.7, 59.7, 61.6, 79.3, 116.8*, 126.7, 127.4, 128.2, 129.2, 130.2, 132.0, 158.1* (*These signals are split into a quartet by three fluorine atoms.); HRMS (FAB+) m/z calcd for $C_{13}H_{19}ClN$ $[M+H]^+$: 224.1206 found 224.1211.

(3*R,4*R**)-4-Chloro-3-ethyl-3-methyl-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate (12ca)**

Compound **12ca** (24.1 mg, 83% yield, yellow amorphous solid) was obtained from **8ca** (17.2 mg, 89.9 μmol) by a procedure similar to the one used to synthesize **12a**. IR ($CHCl_3$) 3393, 2985, 1672, 1616, 1456, 1201, 1136, 722 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.94 (t, J = 7.2 Hz, 3H), 1.50 (s, 3H), 1.64 (dq, J = 14.8, 7.2 Hz, 1H), 1.74 (dq, J = 14.8, 7.2 Hz, 1H), 4.38 (d, J = 17.2 Hz, 1H), 4.45 (d, J = 17.2 Hz, 1H), 5.62 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.37-7.45 (m, 2H), 7.47-7.54 (m, 1H), 9.34 (br s, 1H), 10.12 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 7.4, 20.5, 26.8, 58.8, 60.3, 79.2, 117.0*, 126.6, 127.3, 128.1, 129.1, 129.9, 131.8, 158.2* (*These signals are split into a quartet by three fluorine atoms.); HRMS (FAB+) m/z calcd for $C_{12}H_{17}ClN$ $[M+H]^+$: 210.1050 found 210.1046.

(3*S,4*R**)-4-Chloro-3-ethyl-3-methyl-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate (12cb)**

Compound **12cb** (47.0 mg, 80% yield, yellow amorphous solid) was obtained from **8cb** (34.7 mg, 181 μmol) by a procedure similar to the one used to synthesize **12a**. IR ($CHCl_3$) 3394, 3019, 2982, 1673, 1456, 1437, 1394, 1202, 1135, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.06 (t, J = 7.2 Hz, 3H), 1.25 (s, 3H), 1.85 (dq, J = 14.4, 7.2 Hz, 1H), 1.99 (dq, J = 14.4, 7.2 Hz, 1H), 4.44 (br s, 2H), 5.59 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 1H), 9.08 (br s, 1H), 10.18 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 6.9, 17.2, 29.9, 58.9, 59.6, 79.2, 116.2*, 126.7, 127.3, 128.1, 129.3, 130.3, 131.9, 158.6* (*These signals are split into a quartet by three fluorine atoms.); HRMS (FAB+) m/z calcd for $C_{12}H_{17}ClN$ $[M+H]^+$: 210.1050 found 210.1052.

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