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STEREOSELECTIVE SYNTHESIS OF A 4a,9-DISUBSTITUTED OCTAHYDROACRIDINE FROM ISATIN

Hideki Abe,[1] Yoshimi Sato,[2] Kazuhiro Watanabe,[1] Sakae Aoyagi,[2]* Chihiro Kibayashi,[2] and Tadashi Katoh[1]*

[1]Department of Chemical Pharmaceutical Science, Tohoku Pharmacuetical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan (e-mail: katoh@tohoku-pharm.ac.jp), [2]School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Dedicated to Professor EmeritusKeiichiro Fukumoto on the occasion of his 75th birthday

Abstract – An efficient method for stereoselective synthesis of a 4a,9-disubstituted octahydroacridine derivative from isatin (2,3-indolinedione) was developed; the method is based on an intramolecular reaction of an *N*-acyliminium ion with a conjugated diene system.

INTRODUCTION

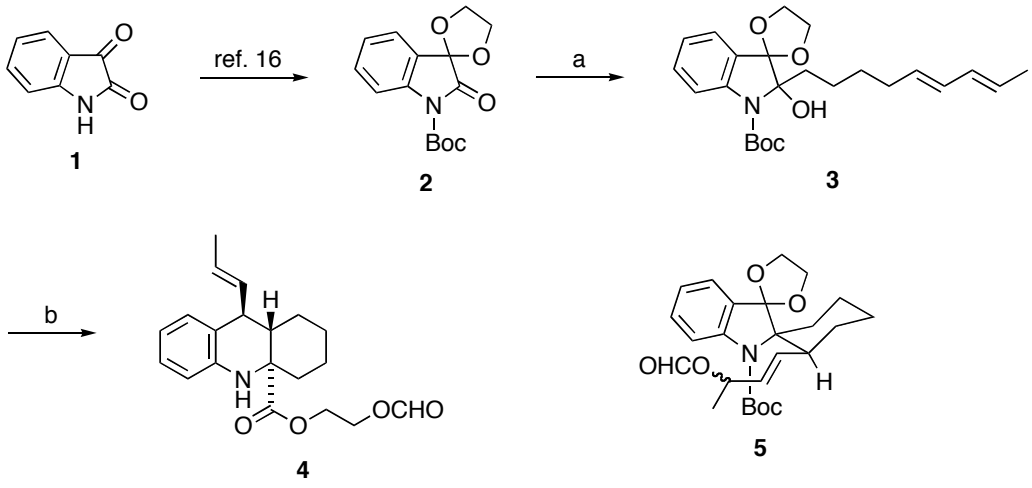
Acridine derivatives, particularly octahydroacridines, form an important class of bioactive molecules in the field of pharmaceuticals and are inhibitors of gastric acid secretion.[1] Although many different methods have thus far been reported for construction of the octahydroacridine skeleton,[2–7] almost of these reactions lack stereoselectivity.

The *N*-acyliminium ion is an extremely important species in the synthesis of nitrogen-containing natural products. A large number of reactions between *N*-acyliminium ions and nucleophiles have been developed to date, and these have found widespread use in total syntheses of bioactive natural products,[8] in which species such as olefins, allylsilanes, and aromatic rings act as π-nucleophiles in inter- or intramolecular reactions involving spirocyclization.[9–14] We recently reported that a total synthesis of tricyclic marine alkaloids based on *N*-acyliminium ion–conjugated diene spirocyclization strategy.[15] Herein, we report the stereoselective and efficient synthesis of a 4a,9-disubstituted octahydroacridine

derivative **4** from isatin, which was discovered during an investigation of formic acid–induced spirocyclization of *N*-acylindolium ions with conjugated dienes.

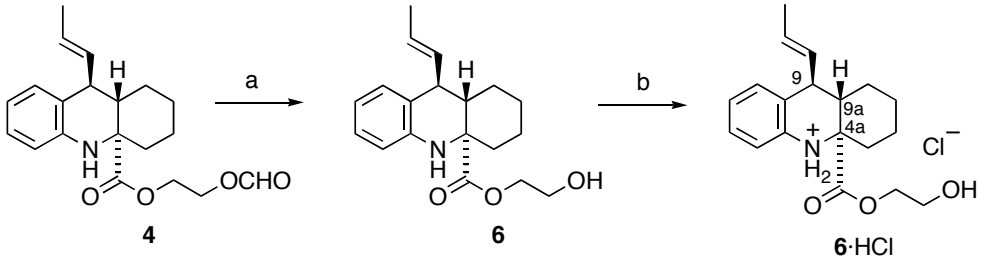
RESULTS AND DISCUSSION

We began our investigation by preparing hemiaminal **3**, an *N*-acylindolium ion precursor, from isatin (2,3-indolinedione, **1**) as shown in Scheme 1. The *N*-Boc-oxyindole derivative **2** was obtained in two steps by protection of the benzylic carbonyl group in **1** as an ethylene acetal, and of the anilinic nitrogen atom with a Boc group.[16] Addition of a Grignard reagent derived from (2*E*,4*E*)-9-bromonona-2,4-diene to **2** provided hemiaminal **3** in 56% yield. Treatment of **3** with formic acid in CH_2Cl_2 at 0 °C resulted in stereoselective formation of octahydroacridine derivative **4** in 54% yield as a single isomer, rather than spirocyclic compound **5**, which is a reaction product expected from formic acid–induced spirocyclization based on our previous investigations.[15]



Scheme 1. Synthesis of octahydroacridine 4. a) (2*E*,4*E*)-9-bromonona-2,4-diene, Mg, THF, 0 °C, 1 h, 56%; b) HCO_2H, CH_2Cl_2, 0 °C, 48 h, 54%.

Although it was not possible to confirm the stereochemistry of the resulting acridine derivative **4** itself, the relative configuration of the octahydroacridine structure was determined as 4a*R**,9*S**,9a*S** (Figure 1) by X-ray crystallographic analysis of the hydrochloride salt **6**·HCl, which was derived from **4** via



Scheme 2. Synthesis of octahydroacridine hydrochloride salt 6·HCl. a) $NaBH_4$, MeOH, 0 °C, 0.5 h, 98%; b) 1 M HCl, MeOH.

deformylation followed by treatment with 1 M HCl, as shown in Scheme 2.

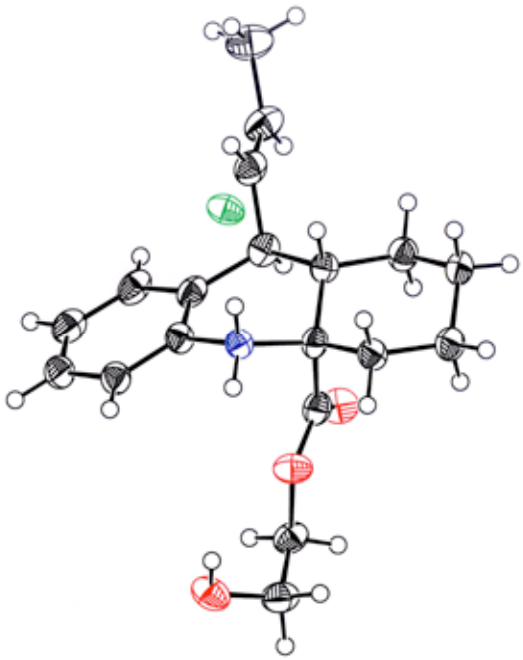
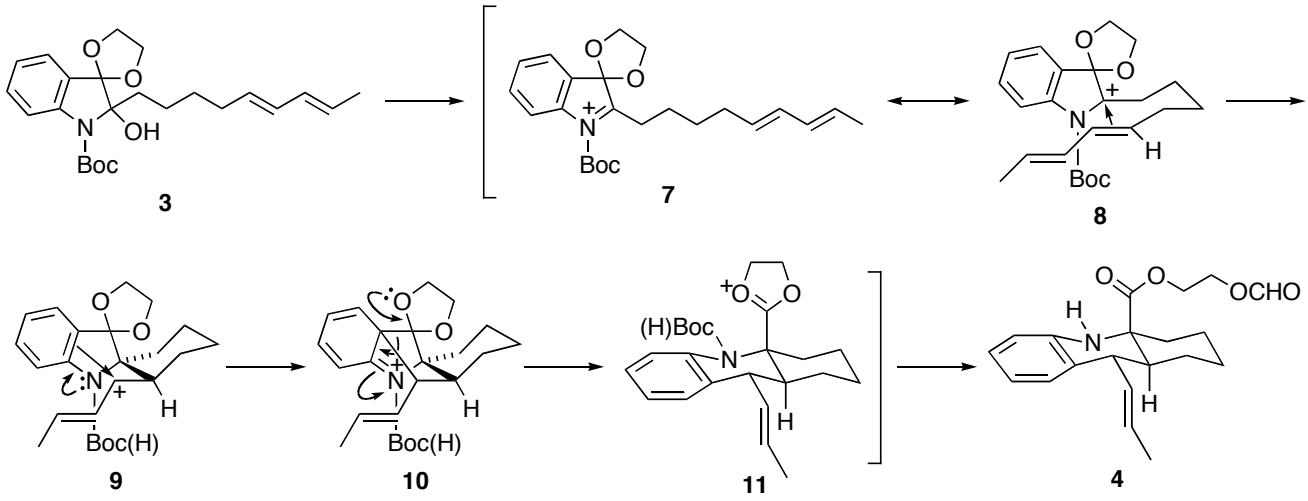


Figure 1. ORTEP drawing of the X-ray structure of 6·HCl.

A reasonable mechanism for the formation of the octahydroacridine skeleton from the hemiaminal **3** is assumed as shown in Scheme 3 by a π-complex theory.[17] Thus, an *N*-acylindolium ion **7** generated in situ from **3** forms a π-complex **8** with a nitrogen stabilized carbocation. Nucleophilic attack of the olefin moiety through a chairlike six-membered transition structure forms an intermediate π-complex **9** with a stable allyl cation in the side chain. Subsequent nucleophilic attack of the aromatic ring to an allyl cation, giving rise to an iminium intermediate **10**, followed by aromatization then delivers a octahydroacridine skeleton **11**, which is finally solvolyzed by formic acid to produce the octahydroacridine **4**.



Scheme 3. Proposed mechanism for the formation of octahydroacridine derivative **4**.

In summary, we have demonstrated the stereoselective and efficient construction of an octahydroacridine skeleton from 2,3-indolinedione. This methodology offers a new route for the synthesis of 4a,9-disubstituted octahydroacridine derivatives, the new acridine analogues. Investigation of the detailed reaction mechanism is currently in progress in our laboratories.

EXPERIMENTAL

***tert*-Butyl 2-hydroxy-3,3-ethylenedioxy-2-[(5*E*,7*E*)-nona-5,7-dienyl]indoline-1-carboxylate (3).** To a cooled (0 °C) solution of **2** (1.28 g, 4.40 mmol) in THF (44 mL) was added dropwise a solution of Grignard reagent (13 mL), freshly prepared from (2*E*,4*E*)-9-bromonona-2,4-diene (2.68 g, 13.2 mmol) and magnesium (321 mg, 13.2 mmol) in THF solution, and the reaction mixture was stirred for 40 min at 0 °C. Saturated aqueous NH_4Cl was added and the mixture was extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–AcOEt, 5:1) to give **3** (1.02 g, 56%) as a yellow oil. IR (neat) 3393, 2977, 2929, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19–1.33 (4H, m), 1.43–1.51 (11H, m, including 9H, s, at δ 1.51), 1.70 (3H, d, *J* = 6.7 Hz), 1.90–2.02 (2H, m), 2.39 (1H, t, *J* = 7.3 Hz), 4.03–4.32 (4H, m), 5.41–5.60 (2H, m), 5.88–6.00 (2H, m), 7.08 (1H, m), 7.33 (1H, m), 7.62 (1H, m), 7.99 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.0, 22.9, 28.3 (3C), 29.7, 32.1, 36.2, 65.5 (2C), 80.3, 95.4, 108.0, 121.7, 122.9, 123.5, 125.2, 126.7, 130.3, 130.6, 131.3, 131.6, 136.8, 153.1; HRMS (ESI–TOF) calcd for $C_{24}H_{34}NO_5$ ($[M+H]^+$) 416.2437, found 416.2445. Anal. Calcd for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.49; H, 8.09; N, 3.17.

2-(Formyloxy)ethyl (4a*R,9*S**,9a*S**)-9-[(1*E*)-prop-1-enyl]-1,3,4,9,9a,10-hexahydroacridine-4a(2*H*)-carboxylate (4).** To a cooled (0 °C) solution of **3** (146 mg, 0.350 mmol) in CH_2Cl_2 (3.5 mL) was added dropwise formic acid (3.5 mL). After stirring for 48 h at 0 °C, the organic solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexane–AcOEt, 5:1) to give **4** (65.2 mg, 54%) as a yellow oil. IR (neat) 3373, 2936, 2859, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26–1.41 (2H, m), 1.61–1.84 (9H, m, including 3H, dd, *J* = 6.4, 1.6 Hz, at δ 1.76), 2.08 (1H, dd, *J* = 11.2, 1.3 Hz), 3.40 (1H, t, *J* = 9.8 Hz), 4.16–4.32 (5H, m), 5.14 (1H, ddd, *J* = 15.0, 9.3, 1.6 Hz), 5.63 (1H, dq, *J* = 15.0, 6.5 Hz), 6.51 (1H, dd, *J* = 7.9, 1.0 Hz), 6.69 (1H, td, *J* = 7.5, 1.1 Hz), 6.96 (1H, t, *J* = 7.6 Hz), 7.05 (1H, dd, *J* = 7.7, 1.0 Hz), 7.87 (1H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.9, 22.4, 25.8, 26.1, 37.1, 44.3, 44.8, 60.4, 61.4, 61.5, 114.7, 118.6, 124.7, 126.8, 128.2, 129.9, 133.8, 142.6, 160.4, 173.6; HRMS (ESI–TOF) calcd for $C_{20}H_{26}NO_4$ ($[M+H]^+$) 344.1826, found 344.1852.

2-Hydroxyethyl (4a*R,9*S**,9a*S**)-9-[(1*E*)-prop-1-enyl]-1,3,4,9,9a,10-hexahydroacridine-4a(2*H*)-carboxylate (6) and its hydrochloride salt (6·HCl).** To a solution of **4** (15.8 mg, 46.1 μmol) in MeOH

(0.5 mL) was added $NaBH_4$ (2.75 mg, 69.1 μmol) at 0 °C. After stirring for 30 min at 0 °C, H_2O (1 mL) was added to the reaction mixture. The mixture was extracted with Et_2O (2 × 10 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–AcOEt, 3:1) to afford **6** (14.3 mg, 90%) as a colorless oil. IR (neat) 3522, 3367, 2958, 2936, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28–1.78 (10H, m, including 3H, d, *J* = 6.4 Hz, at δ 1.76), 1.83–1.86 (2H, m), 2.14 (1H, d, *J* = 12.3 Hz), 3.34 (1H, t, *J* = 9.8 Hz), 3.48–3.59 (2H, m), 4.04 (1H, m), 4.18–4.26 (2H, m), 5.15 (1H, ddd, *J* = 14.9, 9.5, 1.0 Hz), 5.63 (1H, m), 6.54 (1H, d, *J* = 7.9 Hz), 6.72 (1H, t, *J* = 7.4 Hz), 7.00 (1H, t, *J* = 7.4 Hz), 7.09 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.4, 17.9, 25.8, 26.2, 36.7, 44.6, 45.2, 60.6, 61.1, 65.8, 114.5, 118.8, 125.0, 127.0, 128.3, 130.1, 133.7, 143.2, 174.1; HRMS (ESI–TOF) calcd for $C_{19}H_{26}NO_3$ ($[M+H]^+$) 316.1913, found 316.1923.

To a solution of **6** in MeOH was added 1M aqueous HCl, and the mixture was concentrated in vacuo. The resulting white crystals were recrystallized from THF–hexane to give **6**·HCl as colorless prisms. Mp 144–145 °C; IR (KBr) 3441, 2946, 1749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (1H, br s), 1.59 (1H, m), 1.72–1.91 (10H, m, including 3H, dd, *J* = 6.5, 1.6 Hz, at δ 1.73), 2.35 (1H, m), 3.35 (1H, t, *J* = 4.7 Hz), 3.50–3.58 (2H, m), 4.00–4.15 (2H, m), 5.11 (1H, ddd, *J* = 15.1, 9.2, 1.6 Hz), 5.72 (1H, dq, *J* = 14.9, 6.5 Hz), 7.17 (1H, m), 7.22–7.29 (3H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.6, 22.8, 26.0, 27.1, 35.2, 44.6, 45.6, 60.5, 65.9, 68.3, 122.4, 129.1, 129.2, 131.9, 132.3, 132.4, 133.2, 133.3, 170.1; HRMS (ESI–TOF) calcd for $C_{19}H_{26}NO_3$ ($[M·HCl–Cl]^+$) 316.1913, found 316.1910.

Crystal data for hydrochloride salt (6·HCl). Crystal size: 0.45 × 0.45 × 0.25 mm; Cell dimension: *a* = 8.5990 (13) Å, *b* = 10.015 (3) Å, *c* = 11.427 (3) Å; Cell volume: 936.2 (3) $Å^3$; *Z* = 2.

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