SYNTHETIC STUDIES TOWARD ISOSCHIZOGAMINE:
CONSTRUCTION OF PENTACYCLIC CORE STRUCTURE

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Abstract – Development of a concise construction of the pentacyclic core skeleton of isoschizogamine was described. Tetracyclic A,B,D,F-rings structure was assembled by intramolecular aza-Diels−Alder reaction via an ortho-iminoquinone methide intermediate. The C-ring was formed by oxidation of the benzylic position with a combination of Cr(CO) 6 and t-BuOOH, followed by the introduction of an aminoethyl side chain, C−H oxidation of the lactam ring with CrO 3 and n-Bu 4 NI, and final cyclization to construct the cyclic aminal moiety.

INTRODUCTION
Isoschizogamine (1) was first isolated from the shrub Schizozygia caffaeoides by Renner and co-workers, 1 and its structure was initially reported as the ethano-bridged perhydro- β-carboline 1’ (Figure 1). This was later revised to the etheno-bridged tetrahydroquinoline by Hajicek and co-workers 1, which contains an aminal moiety, on the basis of extensive NMR studies. 2 Although no biological activity of isoschizogamine has been reported, its intriguing structure has attracted great attention as a synthetic target. In 1999, Heathcock accomplished the first total synthesis of (±)-isoschizogamine via a biomimetic route that involved the intramolecular formation of aminal via a diamino ketone intermediate. 3a Then, Fukuyama’s, 3b Li’s, 3c and Zhu’s groups 3d reported the enantioselective total synthesis of 1. Recently, our group also achieved the asymmetric total synthesis of 1, in which the assembly of the tetracyclic quinolone skeleton took place through a cascade cyclization and the construction of the aminal moiety via late-stage C−H functionalization. 4 In addition to these total syntheses, a number of synthetic studies on
have been reported. Considering these backgrounds and as a continuation of our work, we have conducted an investigation aiming to further explore the concise construction of the highly fused structure of 1. Herein, we report a facile assembly of a model compound (2) that possesses the core structure of isoschizogamine.

Figure 1. Isoschizogamine and related compounds

RESULTS AND DISCUSSION
The retrosynthetic analysis of model compound 2 is shown in Scheme 1. We selected tetracyclic 3 as the key intermediate, since we anticipated that it would be easily assembled by the intramolecular aza-Diels–Alder (IMADA) reaction of ortho-iminoquinone methide 7 following a modification of an analogous reaction reported by Corey and co-workers that involves the corresponding carbamate. Thus, ortho-iminoquinone methide 7 should be generated by the elimination of HX from ortho-halomethyl anilide 8. Anilide 8 should be, in turn, readily obtained by the condensation of aniline 9 with carboxylic acid 10. After construction of the key tetracyclic intermediate 3, a cascade of reactions including oxidation of the benzylic position, introduction of an aminoethyl side chain, and aminal

Scheme 1. Retrosynthetic analysis of a partial structure of isoschizogamine (1)
formation after the chemoselective C–H oxidation at the α-position of the nitrogen atom would eventually afford the C-ring. In this plan, the crucial synthetic challenges to be addressed are as follows: the establishment of chemoselective oxidation of the benzylic position of 3 and the methine C–H of lactam 5, as well as the feasibility of the IMADA reaction.

We examined utility of the synthetic strategy including the IMADA and two oxidations for construction the core skeleton of isoschizogamine with a model compound. First, we synthesized anilide 11 to investigate the IMADA reaction for the construction of the quinoline structure (Scheme 2). After reducing 2-nitrobenzyl alcohol (12) and protecting benzyl alcohol, the resultant aniline 14 was condensed with carboxylic acid 15 via the corresponding acid chloride. Deprotection of the TBS group with TBAF and chlorination of the hydroxy group afforded the desired ortho-chloromethyl anilide 11. With anilide 11 in hand, the IMADA reaction was examined under Corey’s conditions using cesium carbonate. The IMADA reaction proceeded to give the desired tricyclic lactam 16 in a modest yield. To the best of our knowledge, this constitutes the first example of the IMADA reaction of an ortho-iminoquinone methide generated from an amide precursor.

Next, we studied the crucial C–H oxidations on quinoline skeleton. To find suitable conditions for the oxidation of both the benzylic position and C–H group on the lactam ring of 3, a variety of conditions examined. For the study of the oxidation at the benzylic position, compound 16 was treated with a combination of Cr(CO)₆ and tert-butyl hydroperoxide at reflux. The oxidation proceeded to afford a mixture of the expected ketone 17 and enone 18 in 12% and 29%, respectively (Scheme 3, Eq. 1). Enone is most likely generated by the C–H oxidation of ketone 17 to hemiaminal 19, followed by dehydration. This over-oxidation could be suppressed to some extent by performing the reaction at lower temperature, which afforded the desired ketone 17 in 35% yield as the major product. On the other hand, the C–H oxidation of 17 at the α-position of the nitrogen could be smoothly conducted using a combination of
and tetrabutylammonium (meta)periodate, which we previously established in the total synthesis of (−)-isoschizogamine\(^4\) following the seminal report by Fuchs and co-workers, to give enone 18 in 50\% yield (Scheme 3, Eq. 2).\(^8\)

\[
\begin{align*}
\text{Eq. 1: Oxidation at benzylic position} \\
\text{MeCN (0.15 M)} & \quad 0.5 \text{ eq } \text{Cr(CO)}_6 \quad t-\text{BuOOH} \quad \text{temp. time} \\
\begin{array}{c}
16 \\
17 \\
18
\end{array} \\
\end{align*}
\]

<table>
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<th>entry</th>
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<th>time (h)</th>
<th>yield (%)</th>
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<tr>
<td>1</td>
<td>reflux</td>
<td>24</td>
<td>17 29</td>
</tr>
<tr>
<td>2</td>
<td>60 °C</td>
<td>11</td>
<td>35 13</td>
</tr>
</tbody>
</table>

\[
\text{Eq. 2: Oxidation at } \alpha\text{-position of nitrogen} \\
\begin{align*}
\text{MeCN-CH}_2\text{Cl}_2 & \quad -40 \text{ to } -20 \text{ °C} \\
\begin{array}{c}
17 \\
19 \\
18
\end{array} \\
\end{align*}
\]

**Scheme 3.** Examination of two Cr-mediated oxidations

Having established synthetic method using the IMADA and following the two oxidative transformations, we applied these transformations to the key intermediate 23. Initially, aniline 14 was condensed with carboxylic acid 21 via the corresponding acid chloride, which was readily prepared from cyclopentene in four steps following a reported procedure (Scheme 4).\(^9\) The substrate 23 was obtained through desilylation and chlorination. With the substrate 23 for the IMADA in hand, treatment of 23 with cesium carbonate at reflux in dichloromethane solvent. Although the desired tetracyclic compound was obtained, the yield of 3 was low. We then conducted extensive optimizations of the reaction conditions using bases, such as metal carbonates and triethylamine. However, no improvement in the yield was achieved. Careful inspection of the byproducts revealed the generation a substantial amount of ester 25, which be formed by an electrocyclic reaction of the Z-form of ortho-iminoquinone methide 7 and subsequent hydrolysis of imidate 24 (Scheme 5). We considered the low yield of product 3 would be attributed to the generated ring strain. Therefore, the electrocyclic reaction should proceed preferentially. Further investigation of reaction conditions, such as solvents, reaction temperature, addition of dehydrating agents, and Lewis acid additives was not effective to prevent this undesired reaction.
Scheme 4. Base-mediated IMADA with various bases

<table>
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<tr>
<td>1</td>
<td>Cs₂CO₃</td>
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<tr>
<td>2</td>
<td>K₂CO₃</td>
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<tr>
<td>3</td>
<td>Na₂CO₃</td>
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<tr>
<td>4</td>
<td>Li₂CO₃</td>
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<tr>
<td>5</td>
<td>CaCO₃</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ag₂CO₃</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>Et₃N</td>
<td>0</td>
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</table>

Scheme 5. Plausible reaction mechanism of side product

In spite of the low yields of the IMADA reaction product 3, we tackled the crucial two Cr-mediated oxidations and constructed the pentacyclic core skeleton of isoschizogamine (Scheme 6). Oxidation using combination of Cr(CO)₆ and tert-butyl hydroperoxide was successfully applied to tetracyclic lactam 3, affording ketone 6 in 72% yield. In this case, the over-oxidation was completely suppressed by the steric hindrance around the α-position of nitrogen. Then, the aminoethyl group was constructed at the benzylic position by a four-step sequence. Thus, 1,2-addition of allylmagnesium chloride occurred from the less hindered convex face with complete diastereoselectivity, and subsequent protection of the homoallylic alcohol led to silyl ether 26 as a sole product. Ozonolysis of the terminal olefin, followed by reduction
NaBH₄ gave primary alcohol 27, which was then subjected to Mitsunobu reaction with N-alloc-o-nitrobenzenesulfonamide to give imide 28. The key C–H oxidation of 28 proceeded smoothly using a combination of CrO₃ and tetrabutylammonium (meta)periodate to furnish the desired hemiaminal 29 in 81% yield. After removal of allyl group, we then examined cyclization for construction of the pentacyclic aminal structure. Although a treatment of 30 with PPTS as a Brønsted acid was not effective, CSA gave pentacyclic product 31 in 31% yield. Next, we studied activating reagents of hydroxy group. desired compound 31 was obtained in moderate yield by using MsCl. After further investigations, we that BF₃·OEt₂ was effective to give the desired product 31 in high yield. The formation of the aminal structure was unambiguously confirmed by the HMBC correlations observed between H₂ and aminal carbon.

**Scheme 6.** Construction of a partial structure of isoschizogamine (1)
Finally, construction of the pentacyclic core structure of isoschizogamine (1) was completed by deoxygenation at the benzylc position using Barton-McCombie protocol (Scheme 7). After removal of TES group, the resultant tertiary alcohol 32 was converted to methyl xanthate. Radical deoxygenation AIBN and n-Bu3SnH furnished the target compound 33.

Scheme 7. Removal of hydroxy group at benzylic position

In conclusion, we accomplished the synthesis of the partial structure of isoschizogamine. The established synthesis features a concise construction of the tetracyclic quinoline ring through the IMADA reaction of ortho-iminoquinone methide, and formation of the C-ring via two Cr-mediated oxidations followed by cyclization of nosyl amide.

EXPERIMENTAL

Materials were obtained from commercial suppliers and used without further purification unless mentioned. All reactions were carried out in oven-dried glassware under a slight positive pressure of unless otherwise noted. Anhydrous THF, CHCI3, and MeCN were purchased from Kanto Chemical Co. Anhydrous toluene and DMF were purchased from Wako Pure Chemical Industries. Anhydrous MeOH, EtOH, Et3N, i-Pr2NEt, EtOAc, and CHCl3 were dried and distilled according to the standard protocols. Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50 µm) using the indicated eluent. Preparative TLC and analytical TLC were performed on Merck 60 F254 glass plates pre-coated with a 0.25 mm thickness of silica gel. All melting points were determined on a Yanaco micro melting point apparatus and uncorrected. IR spectra were measured on a SHIMADZU FTIR–8300 spectrometer. NMR spectra were recorded on a JNM-LA400 spectrometer, a GX500 spectrometer, and a JEOL ECA600 spectrometer with tetramethylsilane (0 ppm) and chloroform (7.26 ppm) as internal standards. Chemical shifts were expressed in δ (ppm) values, and coupling constants were expressed in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, and br = broad. Mass spectra were recorded on a JEOL JMS-DX-303 or a JMS-700 or a JMS-T100GC spectrometers or a Brucker microOTOF II (ESI).

2-[[1,1-Dimethylethyl]dimethylsiloxy]methyl]benzenamine (13)

A 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a
rubber septum was charged with 2-nitrobenzyl alcohol (12) (51.0 g, 333 mmol), 10% palladium on activated carbon (14.2 g, 6.66 mmol), and EtOAc/EtOH (666 mL, 1/1). The mixture was stirred under hydrogen atmosphere (balloon pressure) at room temperature for 18 h. The resulting mixture was filtered through a pad of Celite and concentrated under reduced pressure. Recrystallization from CH₂Cl₂-hexanes gave 2-aminobenzyl alcohol (13) (35.3 g, 86%) as a white solid. Its spectral data were identical with those reported.¹²

2-Aminobenzyl t-butyldimethylsilyl ether (14)

A flame-dried 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with 60% dispersion of sodium hydride in mineral oil (12.4 g, 311 mmol) and THF (300 mL). The mixture was cooled in an ice-water bath, and to the solution was added 2-aminobenzyl alcohol (13) (36.4 g, 296 mmol) in THF (290 mL) dropwise. After stirring for 10 min, TBSCI (53.5 g, 355 mmol) was added to the solution. After stirring for 7 h, the ice-water bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 10.5 h, the reaction was quenched with H₂O and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes only to 5/95 EtOAc/hexanes) to give silyl ether 14 (74.1 g, quant.) as a colorless oil. Its spectral data were identical with those reported.¹²

N-[2-(2-Chloromethyl)phenyl]pent-4-enamide (11)

According to the same procedure described for 22 and 23, benzyl chloride 11 was prepared from aniline 15 on a 11.4 mmol scale (1.65 g, 65% for 4 steps) as a white solid; Rᵣ = 0.43 (Silica gel, 50/50 EtOAc/hexanes); mp 105 °C (EtOAc/hexanes); IR (KBr, cm⁻¹) 1699, 1425, 1101, 762; ¹H NMR (500 MHz, CDCl₃) δ 7.86 (d, 1H, J = 8.0 Hz), 7.54 (br s, 1H), 7.37 (dd, 1H, J = 8.0, 7.5 Hz), 7.31 (d, 1H, J = 7.5 Hz), 7.15 (dd, 1H, J = 7.5, 7.5 Hz), 5.95-5.89 (m, 1H), 5.16 (d, 1H, J = 15.0 Hz), 5.08 (d, 1H, J = 10.0 Hz), 4.60 (s, 2H), 2.54 (br s, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 170.7, 136.5, 136.2, 129.90, 129.86, 128.3, 125.3, 124.6, 116.0, 44.2, 36.7, 29.5; HRMS (EI) m/z: calcd. for C₁₂H₁₄ClNO [M⁺] 223.0764, found 223.0768.

3,3a,4,5-Tetrahydropyrrolo[1,2-a]quinolin-1(2H)-one (16)

According to the same procedure described for 3, tricyclic amide 16 was prepared from benzyl chloride 11 on a 5.31 mmol scale (451 mg, 45%) as a white solid; Rᵣ = 0.38 (Silica gel, 50/50 EtOAc/hexanes); mp 110 °C (EtOAc/hexanes); IR (KBr, cm⁻¹) 2939, 1684, 1491, 1369, 1323, 764; ¹H NMR (400 MHz, CDCl₃) δ 8.69 (d, 1H, J = 8.0 Hz), 7.19 (dd, 1H, J = 8.0, 7.6 Hz), 7.12 (d, 1H, J = 7.6 Hz), 7.01 (dd, 1H, J = 7.6, 7.6 Hz), 3.92-3.85 (m, 1H), 2.95 (ddd, 1H, J = 18.0, 12.8, 5.6 Hz), 2.84 (dd, 1H, J = 16.8, 4.8 Hz),
2.61 (ddd, 1H, \( J = 16.8, 10.8, 9.6 \) Hz), 2.51-2.45 (ddd, 1H, \( J = 13.2, 10.0, 1.2 \) Hz), 2.32-2.25 (m, 1H),
2.16 (ddd, 1H, \( J = 13.2, 2.8, 2.8 \) Hz), 1.79-1.65 (m, 2H);
13\(^C\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 173.5, 136.7, 129.0, 126.7, 125.7, 123.5, 119.0, 58.0, 32.2, 29.4, 27.7, 25.4; HRMS (EI) \( m/z \): calcd. for C\(_{12}\)H\(_{13}\)NO [M\(^+\)] 187.0997, found 187.0996.

**2,3,3a,4-Tetrahydropyrrolo[1,2-\( a \)]quinoline-1,5-dione (17)**

A screw top test tube equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with tricyclic amide 16 (114 mg, 535 µmol), chromium(0) hexacarbonyl (58.8 mg, 267 µmol), and MeCN (3.6 mL). To the mixture was added \( t \)-butyl hydroperoxide in H\(_2\)O (760 µL, 70% wt/v) dropwise and the tube was sealed with a teflon-coated screw cap. The reaction mixture was stirred and heated at 60 °C for 3 days. The reaction mixture was allowed to cool to room temperature and the reaction was quenched with sat. aqueous Na\(_2\)SO\(_3\). After the resulting mixture was filtered through a pad of Celite, the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (80/20, EtOAc/hexanes) to give ketone 17 (43.0 mg, 35%) as a white solid and enone 18 (15.9 mg, 13%) as a white solid; \( R_f = 0.55 \) (Silica gel, 80/20, EtOAc/hexanes); mp 165 °C (EtOAc/hexanes); IR (KBr, cm\(^{-1}\)) 2984, 1674, 1593, 1475, 1304, 1207, 789; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.67 (dd, 1H, \( J = 8.8, 0.8 \) Hz), 8.01 (dd, 1H, \( J = 8.0, 2.0 \) Hz), 7.59 (ddd, 1H, \( J = 8.8, 7.6, 2.0 \) Hz), 7.19 (ddd, 1H, \( J = 8.0, 7.6, 0.8 \) Hz), 4.36 (ddd, 1H, \( J = 15.0, 8.8, 6.8, 3.6 \) Hz), 2.92 (dd, 1H, \( J = 16.8, 3.6 \) Hz),
2.74-2.65 (m, 3H), 2.44 (ddd, 1H, \( J = 15.0, 8.4, 6.8, 4.0 \) Hz), 1.97-1.86 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 192.3, 173.5, 141.2, 135.4, 127.5, 124.1, 122.2, 119.1, 57.0, 45.2, 31.8, 25.2; HRMS (EI) \( m/z \): calcd. for C\(_{12}\)H\(_{11}\)NO\(_2\) [M\(^+\)] 201.0790, found 201.0791.

**\( \alpha \),\( \beta \)-Unsaturated ketone (18)**

A flame-dried 20-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with chromium(VI) oxide (16.7 mg, 167 µmol) and MeCN/CH\(_2\)Cl\(_2\) (0.19 mL, 3/1). The reaction mixture was cooled in a dry ice-MeCN bath, and to the solution was added ketone 17 (11.2 mg, 55.7 µmol) in CH\(_2\)Cl\(_2\) (0.09 mL). After stirring for 5 min, to the solution was added tetrabutylammonium periodate (72.4 mg, 167 µmol) in MeCN (0.28 mL) dropwise. After stirring for 1 h, the reaction was quenched with sat. aqueous Na\(_2\)SO\(_3\), and then the reaction mixture was allowed to warm to room temperature. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (50/50 to 80/20 EtOAc/hexanes) to give hemiaminal 18 (5.6 mg, 50%) as a white solid; \( R_f = 0.09 \) (Silica gel, 50/50, EtOAc/hexanes); mp 193 °C (EtOAc:hexanes); IR (KBr, cm\(^{-1}\)) 1759, 1639, 1597, 1481, 1150, 783; \(^1\)H
NMR (400 MHz, CDCl$_3$) $\delta$ 9.07 (d, 1H, $J = 8.8$ Hz), 8.32 (dd, 1H, $J = 8.0, 1.2$ Hz), 7.72-7.67 (m, 1H), 7.49 (ddd, 1H, $J = 8.0, 7.6, 1.2$ Hz), 6.24 (d, 1H, $J = 0.8$ Hz), 3.22-3.18 (m, 2H), 2.94-2.89 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.7, 175.2, 154.7, 136.5, 132.9, 126.4, 126.2, 125.2, 117.8, 109.0, 29.2, 22.9; HRMS (EI) $m/z$: calcd. for C$_{12}$H$_9$NO$_2$ [M$^+$] 199.0633, found 199.0636.

Cyclopent-2-enylacetic acid (21)

A flame-dried 3-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with palladium acetate (6.35 g, 28.3 mmol), manganese dioxide (59.0 g, 679 mmol), $p$-benzoquinone (12.2 g, 113 mmol), and acetic acid (1.13 L). The reaction mixture was stirred and heated at 50 °C for 2.5 h. Then, cyclopentene (20) (850 mL, 566 mmol) was added to the reaction mixture. After stirring for 10 h, the reaction mixture was allowed to cool to room temperature. The resulting mixture was filtered through a pad of Celite, and to the filtrate was added H$_2$O. The aqueous layer was extracted with Et$_2$O. The combined organic extracts were washed with H$_2$O, 1 M aqueous NaOH, and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was distilled under reduced pressure to give cyclopent-2-enyl acetate (32.8 g, 46%) as a yellow oil. Its spectral data were identical with those reported.

A flame-dried 1000-mL, three-necked, round-bottomed flask equipped with a reflux condenser, a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with 60% dispersion of sodium hydride in mineral oil (5.70 g, 142 mmol) and THF (138 mL). The mixture was cooled in an ice-water bath, and dimethyl malonate (16.2 g, 296 mmol) was added dropwise to the mixture. After stirring for 10 min, to the reaction mixture were added palladium acetate (802 mg, 3.57 mmol), triphenylphosphine (3.12 g, 11.9 mmol), and acetate (15.0 g, 119 mmol) in THF (100 mL). The reaction mixture was heated at reflux for 16.5 h. The reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite. To the filtrate was added H$_2$O and then the aqueous layer was extracted with Et$_2$O. The combined organic extracts were washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes only to 10/90, EtOAc/hexanes) to give dimethyl 2-(cyclopent-2-enyl)malonate (31.1 g, 60%) as a yellow oil. Its spectral data were identical with those reported.

A 1-L, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with malonate (9.00 g, 45.4 mmol), H$_2$O (1.60 mL, 90.8 mmol), and DMSO (114 mL). To the reaction mixture was added sodium cyanide (2.90 g, 59.2 mmol) and the reaction mixture was stirred and heated at 130 °C. After stirring for 8.5 h, the reaction mixture was allowed to cool to room temperature. The reaction was quenched with H$_2$O and then the aqueous layer was extracted with Et$_2$O. The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica.
gel (10/90 to 30/70, EtOAc/hexanes) to give methyl 2-(cyclopent-2-enyl)acetate (5.37 g, 84%) as a yellow oil. Its spectral data were identical with those reported.\(^2\)

A 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with ester (20.7 g, 148 mmol) and MeOH (370 mL). The reaction mixture was stirred and cooled in an ice-water bath while 1 M aqueous NaOH (370 mL) was added. After the addition, the ice-water bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 1.5 h, the reaction mixture was concentrated under reduced pressure. The resulting solution was washed with Et\(_2\)O, and then neutralized with 1 M aqueous HCl. The solution was extracted with CH\(_2\)Cl\(_2\). The combined organic extracts were washed with brine, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure to give carboxylic acid 21 (17.5 g, 94%) as a pale yellow oil. The product was subjected to the next reaction without further purification.

### 2-(Cyclopent-2-enyl)-N-(2-hydroxymethylphenyl)acetamide (22)

A flame-dried 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with carboxylic acid 21 (18.9 g, 150 mmol), DMF (1.20 mL, 15.0 mmol), and CH\(_2\)Cl\(_2\) (300 mL). The mixture was cooled in an ice-water bath while oxalyl chloride (15.6 mL, 180 mmol) was added dropwise. After the addition, the ice-water bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 3.5 h, the reaction mixture was concentrated under reduced pressure. To the residue was added CH\(_2\)Cl\(_2\) (300 mL) to give acid chloride solution in CH\(_2\)Cl\(_2\).

A flame-dried 2-L, three-necked, round-bottomed flask equipped with a dropping funnel, a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with aniline 14 (35.6 g, 150 mmol), triethylamine (63.0 mL, 450 mmol) and CH\(_2\)Cl\(_2\) (200 mL). The mixture was cooled in an ice-water bath while the solution of the acid chloride obtained above (300 mL) was added dropwise over a period of 2 h through dropping funnel. After stirring for an hour, the reaction was quenched with H\(_2\)O and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The residual crude product was subjected to the next reaction without further purification.

A flame-dried 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with the silyl ether obtained above and THF (300 mL). The mixture was cooled in an ice-water bath, and to the solution was added TBAF in THF (170 mL, 170 mmol, 1.0 M). After stirring for 1.5 h, the reaction was quenched with H\(_2\)O and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. Recrystallization from EtOAc gave benzyl alcohol 22 (25.6 g, 74% for 3 steps) as a white solid. The mother liquid was concentrated under reduced pressure,
and then purified by flash column chromatography on silica gel (hexanes only to 30/70 EtOAc/hexanes) to give benzyl alcohol 22 (2.63 g, 7% for 3 steps) as a white solid; Rf = 0.19 (Silica gel, 30/70 EtOAc/hexanes); mp 141 °C (EtOAc); IR (KBr, cm⁻¹) 3263, 1651, 1529, 1456, 1040; ¹H NMR (400 MHz, CDCl₃) δ 8.56 (br s, 1H), 7.99 (d, 1H, J = 7.6 Hz), 7.31 (dd, 1H, J = 7.2, 7.2 Hz), 7.17 (d, 1H, J = 7.2 Hz), 7.07 (dd, 1H, J = 7.6, 7.2 Hz), 5.79 (dd, 1H, J = 3.2, 2.0 Hz), 5.72 (dd, 1H, J = 3.2, 2.0 Hz), 4.66 (s, 2H), 3.18 (br s, 1H), 2.74 (br s, 1H), 2.47-2.29 (m, 4H), 2.21 -2.13 (m, 1H), 1.53 (ddt, 1H, J = 12.8, 8.8, 6.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 137.2, 133.5, 131.6, 129.8, 129.0, 128.8, 124.3, 122.6, 64.4, 44.1, 42.7, 32.0, 29.7; HRMS (EI) m/z: calcd. for C₁₄H₁₇NO₂ [M⁺] 231.1259, found 231.1261.

N-(2-Chloromethylphenyl)-2-(cyclopent-2-enyl)acetamide (23)
A flame-dried 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with benzyl alcohol 22 (34.1 g, 148 mmol) and CH₂Cl₂ (493 mL). The mixture was cooled in an ice-water bath, and to the solution was added thionyl chloride (12.9 mL, 177 mmol). After stirring for 30 min, the reaction was quenched with H₂O and sat. aqueous NaHCO₃. The aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. Recrystallization from EtOAc gave benzyl chloride 23 (30.9 g, 84%) as a white solid. The mother liquid was concentrated under reduced pressure, and then purified by flash column chromatography on silica gel (hexanes only to 20/80, EtOAc/hexanes) to give benzyl chloride 23 (2.10 g, 5%) as a white solid; Rf = 0.44 (Silica gel, 30/70, EtOAc/hexanes); mp 135 °C (EtOAc); IR (KBr, cm⁻¹) 3171.0, 137.2, 133.5, 131.6, 129.8, 129.0, 128.8, 124.3, 122.6, 64.4, 44.1, 42.7, 32.0, 29.7; HRMS (EI) m/z: calcd. for C₁₄H₁₇NO₂ [M⁺] 249.0920, found 249.0905.

2a,3,4,4a,5,9c-Hexahydro-2H-9b-azapentaleno[1,6-ab]naphthalen-1-one (3)
A flame-dried 2-L, three-necked, round-bottomed flask equipped with a reflux condenser, a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with cesium carbonate (39.1 g, 123 mmol). The reagent was stirred and heated at 100 °C under reduced pressure for 9 h. After the reagent was allowed to cool to room temperature, to the flask was added benzyl chloride 23 (10.2 g, 40.8 mmol) in CH₂Cl₂ (816 mL). The reaction mixture was stirred and heated at reflux for 4.5 days. The reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes only to 30/70, EtOAc/hexanes) to give tetracyclic amide 3 (1.81 g, 21%) and ester 25 (6.80 g,
Tetracyclic amide 3; a white solid, R<sub>f</sub> = 0.18 (Silica gel, 30/70, EtOAc/hexanes); mp 98 °C (EtOAc/hexanes); IR (KBr, cm<sup>-1</sup>) 2966, 1693, 1381, 1331, 764; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.10 (d, 1H, J = 8.0 Hz), 7.23 (dd, 1H, J = 8.0, 7.6 Hz), 7.16 (d, 1H, J = 7.6 Hz), 7.07 (dd, 1H, J = 7.6, 7.6 Hz), 4.07 (dd, 1H, J = 5.6, 5.6 Hz), 3.08 (dd, 1H, J = 17.2, 7.6 Hz), 2.90 (dd, 1H, J = 17.2, 8.8 Hz), 2.76-2.69 (m, 1H), 2.69 (dd, 1H, J = 17.2, 4.0 Hz), 2.52-2.44 (m, 1H), 1.85-1.79 (m, 1H), 1.57-1.48 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.1, 135.7, 128.8, 127.6, 126.4, 124.5, 121.4, 64.4, 39.7, 39.5, 35.5, 32.5, 30.3, 29.2; HRMS (EI) m/z: calcd. for C<sub>14</sub>H<sub>15</sub>NO [M<sup>+</sup>] 213.1154, found 213.1163.

Compound 25; IR (neat, cm<sup>-1</sup>) 3464, 3377, 2941, 1719, 1628, 1169, 1142; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.18 (d, 1H, J = 7.5 Hz), 7.15 (dd, 1H, J = 7.5, 7.5 Hz), 6.74 (dd, 1H, J = 7.5, 7.5 Hz), 6.68 (d, 1H, J = 7.5 Hz), 5.74 (br s, 1H), 5.63 (br s, 1H), 5.11 (s, 2H), 4.06 (br s, 2H), 3.07 (br s, 1H), 2.40 (dd, 1H, J = 15.0, 7.0 Hz), 2.34-2.25 (m, 3H), 2.13-2.06 (m, 1H), 1.44 (dddd, 1H, J = 18.5, 9.0, 9.0, 6.5 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.1, 145.8, 133.5, 131.6, 131.3, 130.0, 120.3, 118.3, 116.1, 64.0, 42.0, 40.3, 31.8, 29.5; HRMS (EI) m/z: calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub> [M<sup>+</sup>] 231.1259, found 231.1249.

2.2a,3,4,4a,9c-Hexahydro-9b-azapentaleno[1,6-ab]naphthalene-1,5-dione (6)
A 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with tetracyclic amide 3 (1.10 g, 5.16 mmol), chromium(0) hexacarbonyl (567 mg, 2.58 mmol), and MeCN (34 mL). To the mixture was added t-butyl hydroperoxide in H<sub>2</sub>O (7.40 mL, 70% wt/v) dropwise and the reaction mixture was stirred and heated at 60 °C for 15.5 h. The reaction mixture was allowed to cool to room temperature and the reaction was quenched with sat. aqueous Na<sub>2</sub>SO<sub>3</sub>. After the resulting mixture was filtered through a pad of Celite, the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (40/60, EtOAc/hexanes) to give tetracyclic ketone 6 (847 mg, 72%) as a white solid; R<sub>f</sub> = 0.25 (Silica gel, 50/50, EtOAc/hexanes); mp 144 °C (EtOAc/hexanes); IR (KBr, cm<sup>-1</sup>) 2972, 1699, 1678, 1595, 1477, 1375, 1294, 789; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.25 (d, 1H, J = 8.5 Hz), 8.01 (dd, 1H, J = 8.5, 2.0 Hz), 7.60 (ddd, 1H, J = 8.5, 7.5, 2.0 Hz), 7.23 (dd, 1H, J = 8.5, 7.5 Hz), 4.73 (dd, 1H, J = 5.5, 5.0 Hz), 3.00 (dd, 1H, J = 16.5, 8.5 Hz), 2.91 (m, 2H), 2.43 (d, 1H, J = 16.5 Hz), 2.24-2.11 (m, 2H), 1.97-1.88 (m, 1H), 1.77-1.73 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 194.3, 173.2, 139.4, 135.1, 127.6, 124.7, 122.2, 121.0, 66.7, 52.9, 40.0, 34.9, 33.6, 27.4; HRMS (EI) m/z: calcd. for C<sub>14</sub>H<sub>13</sub>NO<sub>2</sub> [M<sup>+</sup>] 227.0946, found 227.0927.

5-Allyl-5-triethylsiloxy-2a,3,4,4a,5,9c-hexahydro-2H-9b-azapentaleno[1,6-ab]naphthalen-1-one (26)
A flame-dried 30-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with tetracyclic ketone 6 (592 mg, 2.64 mmol) and THF (8.80 mL). The mixture was cooled in a dry ice-acetone bath, and to the solution was added allylmagnesium chloride in toluene (2.6 mL, 5.3 mmol, 2.0 M) dropwise. After stirring for 30 min, the reaction was quenched with sat. aqueous NH₄Cl and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residual crude product was subjected to the next reaction without further purification.

A flame-dried 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with the allyl alcohol obtained above and CH₂Cl₂ (26.4 mL). The mixture was cooled in a dry ice-acetone bath, and to the solution were added 2,6-lutidine (1.23 mL, 10.5 mmol) and TESOTf (1.79 mL, 8.92 mmol) dropwise. After stirring for 2 h, the reaction mixture was cooled in a dry ice-MeCN bath. After stirring for an hour, the reaction mixture was cooled in a dry ice-CCl₄ bath. After stirring for 3 h, the reaction was quenched with H₂O and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes only to 20/80, EtOAc/hexanes) to give silyl ether 26 (725 mg, 72% for 2 steps) as a white solid; Rf = 0.34 (Silica gel, 30/70, EtOAc/hexanes); mp 122 °C (EtOAc/hexanes, decomp.); IR (KBr, cm⁻¹) 2955, 1690, 1489, 1371, 1088, 739; ¹H NMR (500 MHz, CDCl₃) δ 8.27 (dd, 1H, J = 8.0, 1.5 Hz), 7.51 (dd, 1H, J = 7.5, 1.5 Hz), 7.27 (ddd, 1H, J = 7.5, 7.0, 1.5 Hz), 7.13 (ddd, 1H, J = 8.0, 7.0, 1.5 Hz), 5.63-5.54 (m, 1H), 5.04-5.01 (m, 2H), 4.36 (dd, 1H, J = 5.0, 4.5 Hz), 2.85 (dd, 1H, J = 17.0, 8.0 Hz), 2.75-2.62 (m, 3H), 2.34 (ddd, 1H, J = 11.0, 6.5, 4.5 Hz), 2.29 (d, 1H, J = 17.0 Hz), 2.04 (ddddd, 1H, J = 15.5, 10.5, 10.5, 8.0 Hz), 1.88-1.82 (m, 1H), 1.72-1.63 (m, 1H), 1.57-1.51 (m, 1H), 0.93 (t, 9H, J = 7.5 Hz), 0.65-0.56 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 173.2, 134.6, 134.5, 132.0, 127.8, 127.2, 124.1, 120.2, 118.0, 75.8, 65.0, 52.1, 49.9, 40.3, 35.7, 31.7, 27.2, 7.3, 7.1; HRMS (FAB) m/z: calcd. for C₂₁H₂₈NO₂Si [M⁺–29 (C₂H₅)] 354.1889, found 354.1887.

5-(2-Hydroxyethyl)-5-triethylsiloxy-2a,3,4,4a,5,9c-hexahydro-2H-9b-azapentaleno[1,6-ab]naphthalene-1-one (27)

A 30-mL, two-necked, round-bottomed flask equipped with a fitted gas dispersion tube, a magnetic stirring bar and a rubber septum was charged with silyl ether 26 (498 mg, 1.30 mmol) and CH₂Cl₂/MeOH (14.3 mL, 10/1). After the reaction mixture was stirred and cooled in a dry ice-acetone bath, ozone was passed through the solution for 30 min. The reaction mixture was flushed with oxygen for 20 min. To the mixture were added MeOH (13 mL) and sodium borohydride (291 mg, 7.79 mmol). The dry ice-acetone bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 1.5 h, to the reaction mixture was added sodium borohydride (400 mg, 21.4 mmol) portionwise over a
period of 1.5 h. The reaction mixture heated at 45 °C for 30 min. The reaction mixture was allowed to cool to room temperature and the reaction was quenched with sat. aqueous NH₄Cl and 1 M aqueous HCl. After the resulting mixture was concentrated under reduced pressure, the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (50/50, EtOAc/hexanes) to give alcohol 27 (396 mg, 79%) as a white solid; Rf = 0.31 (Silica gel, 50/50, EtOAc/hexanes); mp 122 °C (EtOAc/hexanes, decomp.); IR (KBr, cm⁻¹) 3439 (br), 2959, 1695, 1666, 1483, 1394, 1142, 737; ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, 1H, J = 7.6 Hz), 7.51 (dd, 1H, J = 7.6, 1.2 Hz), 7.28 (ddd, 1H, J = 7.6, 7.2, 1.2 Hz), 7.14 (dd, 1H, J = 7.6, 7.2 Hz), 4.33 (dd, 1H, J = 5.2, 4.4 Hz), 3.82-3.67 (m, 2H), 2.87 (dd, 1H, J = 17.2, 8.0 Hz), 2.77-2.70 (m, 1H), 2.49 (ddd, 1H, J = 11.2, 6.4, 4.4 Hz), 2.31 (d, 1H, J = 17.2 Hz), 2.24 (dd, 1H, J = 14.4, 7.2 Hz), 2.15-2.05 (m, 2H), 1.91-1.85 (m, 2H), 1.71-1.56 (m, 2H), 0.92 (t, 9H, J = 8.0 Hz), 0.65-0.49 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 134.2, 131.5, 128.1, 127.1, 124.1, 120.3, 76.3, 65.3, 59.1, 49.6, 49.0, 40.3, 35.5, 32.0, 26.9, 7.2, 7.0; HRMS (EI) m/z: calcd. for C₂₂H₃₃NO₃Si [M⁺] 387.2230, found 387.2215.

5-[2-(N-2-Nitrobenzenesulfonyl-N-allylcarbonylimide)ethyl]-5-triethylsiloxy-2a,3,4,4a,5,9c-hexahydro-2H-9b-azapentaleno[1,6-ab]naphthalen-1-one (28)

A flame-dried 20-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with alcohol 27 (227 mg, 586 µmol), o-NsAlloc-imide (184 mg, 644 µmol), triphenylphosphine (384 mg, 1.47 mmol), and toluene/THF (6.00 mL, 1/1). The reaction mixture was stirred and cooled in an ice-water bath while toluene solution of DEAD (668 µL, 1.47 mmol, 2.2 M) was added dropwise. The ice-water bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 10.5 h, the reaction mixture was filtered with a sintered glass funnel. To the resulting solution was added H₂O and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (15/85 EtOAc/toluene) to give o-NsAlloc-imide 28 (220 mg, 64%) as a white solid; Rf = 0.35 (silica gel, 50/50 EtOAc/hexanes); mp 150 °C (EtOAc/hexanes, decomp.); IR (KBr, cm⁻¹) 2957, 1734, 1695, 1545, 1371, 1175, 739; ¹H NMR (400 MHz, CDCl₃) δ 8.33-8.29 (m, 2H), 7.77-7.70 (m, 3H), 7.56 (d, 1H, J = 8.0 Hz), 7.29 (ddd, 1H, J = 8.0, 7.6, 1.2 Hz), 7.15 (dd, 1H, J = 7.6, 7.6 Hz), 5.74 (ddt, 1H, J = 16.4, 10.4, 6.0 Hz), 5.24-5.19 (m, 2H), 4.54 (d, 2H, J = 6.4 Hz), 4.36 (dd, 1H, J = 4.8, 4.8 Hz), 4.08-4.00 (m, 1H), 3.92-3.84 (m, 1H), 2.90 (dd, 1H, J = 12.8, 8.0 Hz), 2.80-2.74 (m, 1H), 2.53 (ddd, 1H, J = 11.2, 6.8, 4.8 Hz), 2.41-2.30 (m, 3H), 2.13 (ddd, 1H, J = 16.8, 11.2, 9.6 Hz), 1.89 (ddd, 1H, J = 6.8, 6.4, 6.0 Hz), 1.75-1.60 (m, 2H), 0.93 (t, 9H, J = 8.0 Hz), 0.65-0.50 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 151.5, 147.9, 134.5, 134.4, 134.2, 132.8, 131.8, 131.3, 130.6, 128.2, 127.2, 124.5, 124.1, 120.4, 119.9, 75.2, 68.0, 65.4,
5-[2-(2-Nitrobenzensulfonylamide)ethyl]-5-triethylsiloxy-9c-hydroxy-2a,3,4a,5,9c-hexahydro-2H-9b-azapentaleno[1,6-ab]naphthalen-1-one (29)

A flame-dried 20-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with chromium(VI) oxide (88.3 mg, 883 µmol) and MeCN/CH₂Cl₂ (5.00 mL, 9/1). The reaction mixture was cooled in a dry ice-MeCN bath, and to the solution was added tetrabutylammonium periodate (383 mg, 883 µmol). After stirring for 5 min, to the solution was added imide 28 (193 mg, 294 µmol) in CH₂Cl₂ (1.00 mL) dropwise. After stirring for 30 min, the reaction was quenched with sat. aqueous Na₂SO₃, and then the reaction mixture was allowed to warm to room temperature. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (50/50, EtOAc/hexanes) to give hemiaminal 29 (161 mg, 81%) as a white solid; Rf = 0.23 (Silica gel, 50/50, EtOAc/hexanes); mp 75 °C (EtOAc/hexanes); IR (KBr, cm⁻¹) 3369 (br), 2957, 1736, 1683, 1545, 1371, 1175, 739; ¹H NMR (400 MHz, CDCl₃) δ 8.34 (d, 1H, J = 7.2 Hz), 7.92 (d, 1H, J = 8.0 Hz), 7.77-7.72 (m, 3H), 7.63 (d, 1H, J = 7.6 Hz), 7.36 (dd, 1H, J = 8.0, 7.6 Hz), 7.22 (dd, 1H, J = 7.6, 7.2 Hz), 5.88-5.78 (m, 1H), 5.31-5.26 (m, 2H), 4.63 (d, 2H, J = 6.0 Hz), 4.08-3.98 (m, 2H), 3.08 (br s, 1H), 2.98 (dd, 1H, J = 18.0, 8.0 Hz), 2.69-2.42 (m, 4H), 2.26-2.15 (m, 2H), 2.12-1.94 (m, 2H), 1.68 (ddd, 1H, J = 12.4, 7.6, 7.6 Hz), 0.79 (t, 9H, J = 8.0 Hz), 0.36 (q, 6H, J = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 172.6, 151.7, 147.9, 134.6, 134.3, 134.2, 132.8, 132.7, 131.8, 130.6, 128.8, 126.3, 125.2, 124.5, 123.5, 120.2, 100.0, 74.3, 68.3, 54.5, 44.9, 43.9, 40.9, 37.1, 32.7, 27.6, 7.0, 6.4; HRMS (FAB) m/z: calcd. for C₃₂H₄₀N₅O₈Si [M⁺–17 (HO)] 654.2305, found 654.2286.

5-[2-(2-Nitrobenzenesulfonylamide)ethyl]-5-triethylsiloxy-9c-hydroxy-2a,3,4a,5,9c-hexahydro-2H-9b-azapentaleno[1,6-ab]naphthalen-1-one (30)

A 10-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with imide 29 (238 mg, 354 µmol) and CHCl₃ (3.50 mL). The reaction mixture was stirred and cooled in an ice-water bath while acetic acid (1.20 mL), N-methylmorpholine (2.40 mL), and Pd(PPh₃)₄ (2.0 mg, 3.54 µmol) were added. After stirring for 20 min, the ice-water bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 8 h, the reaction was quenched with H₂O and then the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (60/40,
EtOAc/hexanes) to give amide 30 (209 mg, quant.) as a white solid; \( R_f = 0.55 \) (Silica gel, 50/50 EtOAc/hexanes); mp 80 °C (EtOAc/hexanes); IR (KBr, cm\(^{-1}\)) 3342, 2957, 1684, 1541, 1348, 1165, 1067, 741; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.13-8.09 (m, 1H), 8.01 (d, 1H, \( J = 8.0 \) Hz), 7.84 -7.82 (m, 1 H), 7.74-7.70 (m, 2H), 7.39 (d, 1H, \( J = 8.0 \) Hz), 7.29 (dd, 1H, \( J = 8.0, 7.6 \) Hz), 7.16 (dd, 1H, \( J = 8.0, 7.6 \) Hz), 5.83 (t, 1H, \( J = 5.6 \) Hz), 4.11 (br s, 1H), 3.35-3.17 (m, 2H), 3.01 (dd, 1H, \( J = 17.6, 8.0 \) Hz), 2.59-2.52 (m, 2H), 2.35 (ddd, 1H, \( J = 14.0, 8.0, 6.4 \) Hz), 2.23-2.08 (m, 3H), 1.89 (ddd, 1H, \( J = 12.8, 12.8, 7.2 \) Hz), 1.68 (m, 1H), 1.52 (dddd, 1H, \( J = 6.8, 6.8, 6.4, 6.4 \) Hz), 0.76 (t, 9 H, \( J = 8.0 \) Hz), 0.41-0.30 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 173.2, 148.0, 133.52, 133.48, 133.42, 133.42, 132.1, 131.2, 128.6, 126.3, 125.3, 125.0, 122.5, 99.6, 74.9, 52.5, 43.1, 42.2, 39.8, 37.6, 31.7, 27.5, 7.0, 6.6; HRMS (FAB) \( m/z \): calcd. for C\(_{28}\)H\(_{36}\)N\(_3\)O\(_6\)Si \([M^+–17(\text{HO})]\) 570.2094, found 570.2073.

**Siloxypentacyclic aminal (31)**

A flame-dried 20-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with hemiaminal 30 (172 mg, 293 µmol) and CH\(_2\)Cl\(_2\) (5.90 mL). The reaction mixture was cooled in an ice-water bath, and to the solution was added boron trifluoride diethyl etherate (36.0 µL, 293 µmol) dropwise. After stirring for 20 min, the reaction was quenched with H\(_2\)O and then the aqueous layer was extracted with CH\(_2\)Cl\(_2\). The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30/70, EtOAc/hexanes) to give aminal 31 (146 mg, 87%) as a white solid; \( R_f = 0.46 \) (Silica gel, 50/50, EtOAc/hexanes); mp 168 °C (EtOAc/hexanes); IR (KBr, cm\(^{-1}\)) 2957, 1709, 1541, 1354, 1159, 995, 746; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.44 (d, 1H, \( J = 8.8 \) Hz), 8.11 (dd, 1H, \( J = 8.0, 1.6 \) Hz), 7.77-7.68 (m, 3H), 7.56 (dd, 1H, \( J = 8.0, 1.6 \) Hz), 7.29 (dd, 1H, \( J = 8.0, 7.6 \) Hz), 7.17 (dd, 1H, \( J = 8.0, 7.6 \) Hz), 3.57 (ddd, 1H, \( J = 13.2, 3.2, 0.4 \) Hz), 3.27-3.15 (m, 2H), 2.87 (dd, 1H, \( J = 13.2, 13.2, 3.6 \) Hz), 2.35 (dd, 1H, \( J = 12.4, 6.0 \) Hz), 2.25-2.08 (m, 3H), 1.91-1.84 (m, 1H), 1.70-1.67 (m, 1H), 1.48 (dd, 1H, \( J = 12.0, 8.4 \) Hz), 1.22 (ddddd, 1H, \( J = 12.4, 12.4, 12.4, 8.0 \) Hz), 1.03 (t, 9H, \( J = 8.0 \) Hz), 0.82-0.71 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 174.4, 147.8, 135.0, 134.3, 133.0, 132.1, 130.4, 128.7, 128.1, 125.5, 124.9, 124.5, 118.5, 89.5, 74.1, 53.2, 45.5, 42.2, 40.5, 38.4, 32.6, 24.0, 7.1, 6.9; HRMS (EI) \( m/z \): calcd. for C\(_{28}\)H\(_{35}\)N\(_3\)O\(_6\)Si \([M^+]\) 569.2016, found 569.2028.

**Hydroxypentacyclic aminal (32)**

A flame-dried 20-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with silyl ether 31 (145 mg, 255 µmol) and THF (2.60 mL). The mixture was cooled in an ice-water bath, and to the solution was added TBAF in THF (280 µL, 280 µmol, 1.0 M). After stirring for an hour, the reaction was quenched with H\(_2\)O and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\),
filtered, and concentrated under reduced pressure. Recrystallization from EtOAc gave alcohol 32 (87.4 mg, 76%) as a white solid. The mother liquid was concentrated under reduced pressure, and then purified by preparative TLC (3/97, MeOH/CH2Cl2) to give alcohol 32 (26.8 mg, 22%) as a white solid; Rf = 0.12 (Silica gel, 50/50, EtOAc/hexanes); mp 249 °C (EtOAc); IR (KBr, cm⁻¹) 3497, 1717, 1690, 1533, 1364, 980, 613; ¹H NMR (400 MHz, CDCl3) δ 8.44 (d, 1H, J = 8.8 Hz), 8.08 (dd, 1H, J = 8.0, 1.6 Hz), 7.79-7.71 (m, 2H), 7.68 (dd, 1H, J = 7.6, 1.6 Hz), 7.31 (ddd, 1H, J = 8.8, 7.2, 1.6 Hz), 7.19 (dd, 1H, J = 7.6, 7.2 Hz), 3.56 (ddd, 1H, J = 13.2, 5.2, 1.6 Hz), 3.31 (dd, 1H, J = 18.0, 8.0 Hz), 2.87 (ddd, 1H, J = 13.2, 13.2, 5.2 Hz), 2.39 (dd, 1H, J = 12.4, 6.0 Hz), 2.23 (br s, 1H), 2.14 (d, 1H, J = 18.0 Hz), 2.05 (ddd, 1H, J = 13.2, 13.2, 5.2 Hz), 1.88 (ddd, 1H, J = 12.4, 7.6, 6.0 Hz), 1.71 (ddd, 1H, J = 13.2, 3.6, 1.6 Hz), 1.52 (ddd, 1H, J = 13.6, 8.0, 1.6 Hz), 1.16 (ddd, 1H, J = 12.4, 12.4, 12.4, 8.0 Hz); ¹³C NMR (100 MHz, CDCl3) δ 174.5, 147.8, 135.2, 134.3, 132.8, 132.0, 130.5, 128.7, 127.7, 125.2, 124.7, 124.6, 119.0, 89.4, 71.6, 53.0, 45.3, 41.0, 40.5, 38.5, 32.9, 23.2; HRMS (EI) m/z: calcd. for C22H21N3O6S [M⁺] 455.1151, found 455.1147.

Xanthate (36)
A flame-dried screw top test tube equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with alcohol 32 (50.0 mg, 110 µmol) and THF (1.10 mL). The reaction mixture was cooled in an ice-water bath, and to the solution was added 60% dispersion of sodium hydride in mineral oil (5.3 mg, 132 µmol). After stirring for 10 min, to the reaction mixture was added carbon disulfide (66.0 µL, 1.10 mmol). After stirring for 10 min, to the reaction mixture was added methyl iodide (68.0 µL, 1.10 mmol) and the ice-water bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for additional 1.5 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (50/50, EtOAc/hexanes, twice) to give xanthate 36 (43.7 mg, 73%) as a white solid; Rf = 0.37 (Silica gel, 50/50, EtOAc/hexanes); mp 225 °C (EtOAc/hexanes, decomp.); IR (KBr, cm⁻¹) 1717, 1541, 1356, 1047; ¹H NMR (500 MHz, CDCl3) δ 8.44 (d, 1H, J = 8.0 Hz), 8.06 (d, 1H, J = 7.5 Hz), 7.78-7.72 (m, 2H), 7.69 (d, 1H, J = 7.0 Hz), 7.55 (d, 1H, J = 7.0 Hz), 7.36 (dd, 1H, J = 8.0, 7.0 Hz), 7.23 (dd, 1H, J = 7.5, 7.0 Hz), 4.03 (dd, 1H, J = 12.5, 5.5 Hz), 3.76-3.70 (m, 2H), 3.35 (dd, 1H, J = 17.0, 8.0 Hz), 3.22 (dd, 1H, J = 12.5, 5.5 Hz), 3.03-2.97 (m, 1H), 2.55 (s, 3H), 2.28-2.18 (m, 2H), 1.85-1.78 (m, 2H), 1.52 (dd, 1H, J = 12.5, 8.0 Hz), 1.30 (dddd, 1H, J = 12.5, 12.5, 12.5, 8.0 Hz); ¹³C NMR (102 MHz, CDCl3) δ 174.5, 147.8, 135.2, 134.3, 132.8, 132.0, 130.5, 128.7, 127.7, 125.2, 124.7, 124.6, 119.0, 89.4, 71.6, 53.0, 45.3, 41.0, 40.5, 38.5, 32.9, 23.2; HRMS (EI) m/z: calcd. for C24H23N3O6S3 [M⁺] 545.0749, found 545.0738.

Pentacyclic aminal (33)
A flame-dried screw top test tube equipped with a magnetic stirring bar, argon gas inlet, and a rubber
Septum was charged with xanthate 36 (11.7 mg, 21.4 µmol), tributyltin hydride (17.3 µL, 64.3 µmol), and degassed toluene (420 µL). To the reaction mixture was added AIBN (3.5 mg, 21.4 µmol) and the tube was sealed with a teflon-coated screw cap. The reaction mixture was heated at 80 ºC for 18 h. To the reaction mixture was added additional AIBN (3.5 mg, 21.4 µmol). After stirring for 5 h, the reaction mixture was diluted with MeCN and washed with hexanes. The resulting solution was concentrated under reduced pressure. The residue was purified by preparative TLC (CH$_2$Cl$_2$ only to 1/99, MeOH/CH$_2$Cl$_2$) to give alkane 33 (3.5 mg, 37%) as a white solid; R$_f$ = 0.39 (Silica gel, 50/50, EtOAc/hexanes); mp 180 ºC (MeOH/CH$_2$Cl$_2$, decomp.); IR (KBr, cm$^{-1}$) 1707, 1543, 1356, 1167, 1069, 762; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.48 (d, 1H, J = 8.0 Hz), 8.09 (dd, 1H, J = 6.8, 2.4 Hz), 7.77-7.65 (m, 3H), 7.29 -7.25 (m, 1H), 7.12-7.08 (m, 2H), 3.40-3.34 (m, 2H), 3.27 (d, 1H, J = 2.0 Hz), 3.16 (dd, 1H, J = 8.8, 8.4 Hz), 2.89 (ddd, 1H, J = 13.2, 13.2, 3.6 Hz), 2.31 (ddd, 1H, J = 12.8, 6.0, 2.0 Hz), 2.26-2.03 (m, 3H), 1.72-1.64 (m, 2H), 1.45 (ddd, 1H, J = 13.6, 8.0, 1.6 Hz), 1.12 (ddddd, 1H, J = 12.8, 12.8, 8.0 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.9, 147.8, 136.3, 134.1, 133.1, 132.0, 130.5, 128.7, 127.6, 125.2, 124.7, 124.4, 119.4, 86.0, 46.7, 42.3, 40.5, 37.9, 35.5, 34.0, 33.0, 26.0; HRMS (EI) m/z: calcd. for C$_{22}$H$_{21}$N$_3$O$_5$S [M$^+$] 439.1202, found 439.1180.

**Hydroxypentacyclic aminal with Boc group (37)**

A screw top test tube equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with Ns amide 31 (57.9 mg, 102 µmol), Cs$_2$CO$_3$ (99.3 mg, 305 µmol) and MeCN (1.0 mL). To the mixture was added PhSH (21 µl, 200 µmol) at room temperature. After stirring for 11 h, the reaction mixture was diluted with CH$_2$Cl$_2$ and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residual crude product was subjected to the next reaction without further purification.

A flame-dried 10-mL round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with the crude amine 31, Et$_3$N (64 µl, 457 µmol) and 1,2-dichloroethane (1.0 mL). To the mixture was added Boc$_2$O (69.4 mg, 305 µmol) at room temperature. After stirring for 3.5 h, the reaction was heated to 60 ºC and stirred for 10 h. Then, additional Boc$_2$O (34.5 mg, 150 µmol) was added to the mixture and the resulting mixture was stirred for 2 h. H$_2$O was added to the mixture and the aqueous layer was extracted with CH$_2$Cl$_2$ three times. The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residual crude product was subjected to the next reaction without further purification.

A flame-dried screw top test tube equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with the crude silyl ether and THF (1.0 mL). The mixture was cooled in an ice-water bath, and to the solution was added TBAF in THF (110 µL, 110 µmol, 1.0 M). After stirring for 1.5 h, the reaction was quenched with H$_2$O and then the aqueous layer was extracted with CH$_2$Cl$_2$ three times. The
combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (35/65, EtOAc/hexanes) to give hydroxypentacyclic aminal with Boc group 37 (27.4 mg, 77% for 3 steps) as a colorless oil; R$_f$ = 0.18 (Silica gel, 30/70, EtOAc/hexanes); IR (neat, cm$^{-1}$) 3420, 2976, 2949, 17170, 1684, 1368, 1168, 759; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.45 (d, 1H, $J$ = 8.4 Hz), 7.61 (dd, 1H, $J$ = 7.6, 1.2 Hz), 7.30 (ddd, 1H, $J$ = 8.4, 7.2, 1.2 Hz), 7.17 (dd, 1H, $J$ = 7.6, 7.2 Hz), 3.99 (ddd, 1H, $J$ = 13.6, 4.4, 1.6 Hz), 3.69 (dd, 1H, $J$ = 13.2, 8.0 Hz), 3.53-3.46 (m, 1H), 2.65 (ddd, 1H, $J$ = 13.6, 13.6, 4.4 Hz), 2.33-2.14 (m, 3H), 2.06-2.02 (m, 1H), 1.90-1.82 (m, 1H), 1.75-1.71 (m, 1H), 1.60-1.53 (m, 1H), 1.43 (s, 9H), 1.25-1.19 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 213.6, 175.0, 154.1, 134.7, 128.9, 125.5, 124.7, 119.3, 90.1, 87.6, 81.1, 47.4, 43.3, 41.8, 39.9, 36.7, 32.5, 28.3, 24.2, 19.6; HRMS (ESI) $m/z$: calcd. for C$_{21}$H$_{26}$N$_2$NaO$_4$ $[M+Na]^+$ 393.1805, found 393.1785.

**Xanthate with Boc group (34)**

A flame-dried screw top test tube equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with 60% dispersion of sodium hydride in mineral oil (11.4 mg, 285 µmol) and THF (0.70 mL). The reaction mixture was cooled in an ice-water bath, and to the solution was added a solution of alcohol (21.1 mg, 57.0 µmol) in THF (0.70 mL). After stirring for 40 min, to the reaction mixture was added carbon disulfide (69 µL, 1.1 mmol) at 0 °C. After stirring for 15 min at room temperature, to the reaction mixture was added methyl iodide (71 µL, 1.1 mmol) at 0 °C and the ice-water bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for additional an hour, the reaction was quenched with sat. aqueous NaHCO$_3$ and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (20/80, EtOAc/hexanes, twice) to give xanthate 34 (10.2 mg, 39%) as a colorless oil; R$_f$ = 0.50 (Silica gel, 30/70, EtOAc/hexanes); IR (neat, cm$^{-1}$) 2975, 1710, 1335, 1043, 757; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.49 (dd, 1H, $J$ = 8.4, 1.2 Hz), 7.55 (dd, 1H, $J$ = 8.4, 1.2 Hz), 7.35 (ddd, 1H, $J$ = 8.4, 7.6, 1.6 Hz), 7.21 (ddd, 1H, $J$ = 8.4, 7.6, 1.2 Hz), 4.03 (ddd, 1H, $J$ = 13.6, 6.0, 2.4 Hz), 3.96 (dd, 1H, $J$ = 13.2, 5.6 Hz), 3.75-3.66 (m, 2H), 3.46-3.40 (m, 1H), 2.80 (ddd, 1H, $J$ = 13.6, 11.6, 4.4 Hz), 2.55 (s, 3H), 2.23-2.18 (m, 2H), 1.82-1.75 (m, 2H), 1.58-1.54 (m, 1H), 1.43 (s, 9H), 1.41-1.30 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 213.6, 175.0, 154.1, 134.7, 128.9, 125.5, 124.7, 119.3, 90.1, 87.6, 81.1, 47.4, 43.3, 41.8, 39.9, 36.7, 32.5, 28.3, 24.2, 19.6; HRMS (ESI) $m/z$: calcd. for C$_{23}$H$_{29}$N$_2$O$_4$S$_2$ [M+H]$^+$ 461.1575, found 461.1563.

**Pentacyclic aminal with Boc group (35)**

A flame-dried screw top test tube equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with xanthate 34 (5.5 mg, 12 µmol), tributhyltin hydride (10 µL, 36 µmol), and degassed benzene (2.4 mL). To the reaction mixture was added AIBN (2.5 mg, 24 µmol) and the tube was
sealed with a teflon-coated screw cap. The reaction mixture was heated at 80 °C for 20 min. The residue was purified by preparative TLC (20/80, EtOAc/hexanes,) to give alkane 35 (5.3 mg, quant) as a white solid; Rf = 0.38 (Silica gel, 25/75, EtOAc/hexanes); IR (neat, cm⁻¹) 2943, 1708, 1488, 1366, 1153, 757; ¹H NMR (600 MHz, CDCl₃) δ 8.50 (d, 1H, J = 8.4 Hz), 7.27-7.24 (m, 1H), 7.13 (dd, 1H, J = 8.4, 1.8 Hz), 7.08 (ddd, 1H, J = 8.4, 7.8, 1.8 Hz), 3.78 (ddd, 1H, J = 13.2, 6.0, 1.8 Hz), 3.71 (dd, 1H, J = 16.8, 7.8 Hz), 3.42-3.37 (m, 1H), 3.24 (br s, 1H), 2.67 (ddd, 1H, J = 13.2, 12.6, 4.2 Hz), 2.21 (ddd, 1H, J = 13.2, 5.4, 1.8 Hz), 2.16-2.13 (m, 2H), 2.06-2.02 (m, 1H), 1.74-1.68 (m, 2H), 1.50-1.46 (m, 1H), 1.43 (s, 9H), 1.20-1.14 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 175.8, 154.9, 128.8, 127.2, 126.1, 124.2, 119.4, 119.1, 83.9, 80.6, 68.2, 46.6, 41.8, 40.1, 39.4, 35.4, 34.4, 32.8, 28.3, 25.2; HRMS (ESI) m/z: calcd. for C₂₂H₂₁N₃O₅S [M+H⁺] 355.2002, found 355.2016.

ACKNOWLEDGEMENTS
This work was supported by JSPS KAKENHI Grant Numbers JP16H01127 in Middle Molecular Strategy and JP16H00999 in Precisely Designed Catalysts with Customized Scaffolding, a Grant-in aid for Scientific Research (A) (26253001) and (C) (17K08204).

REFERENCES AND NOTES


11. The HMBC correlations of compound of 31 were shown below.

![ HMBC correlations of compound of 31 ](image)


13. The low yield in radical condition would be attributed to existence of nosyl group. According to our further investigations, we found the Barton-McCombie deoxygenation of a xanthate bearing Boc group afforded the desired deoxygenated product in quantitative yield.

![ Reaction Scheme ](image)