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SYNTHETIC STUDIES TOWARD ISOSCHIZOGAMINE: CONSTRUCTION OF PENTACYCLIC CORE STRUCTURE

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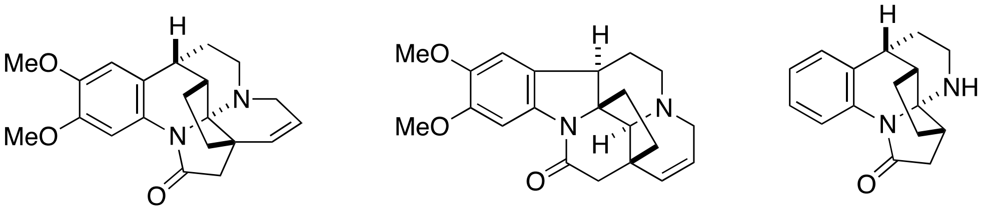
Abstract – Development of a concise construction of the pentacyclic core skeleton of isoschizogamine was described. Tetracyclic A,B,D,F-rings structure was assembled by intramolecular aza-Diels–Alder reaction via an *ortho*-iminoquinone methide intermediate. The C-ring was formed by oxidation of the 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_4NI, 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 diaminoketone 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

1[5a-d] 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.

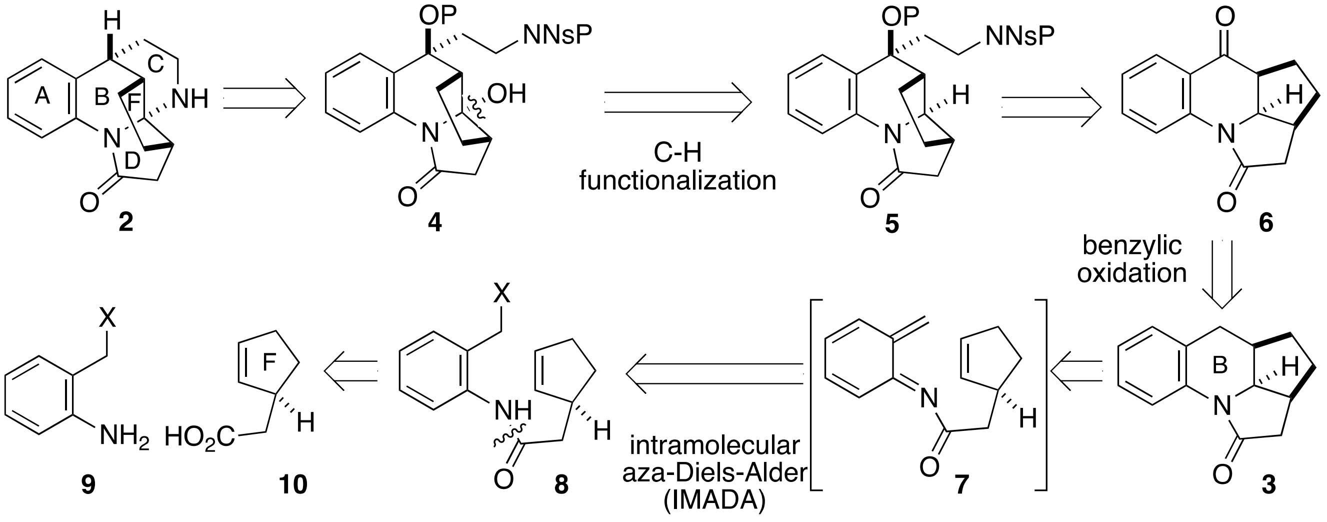


(–)-isoschizogamine (**1**) **1'** **2**

Figure 1. Isoschizogamine and related compounds

RESULTS AND DISCUSSION

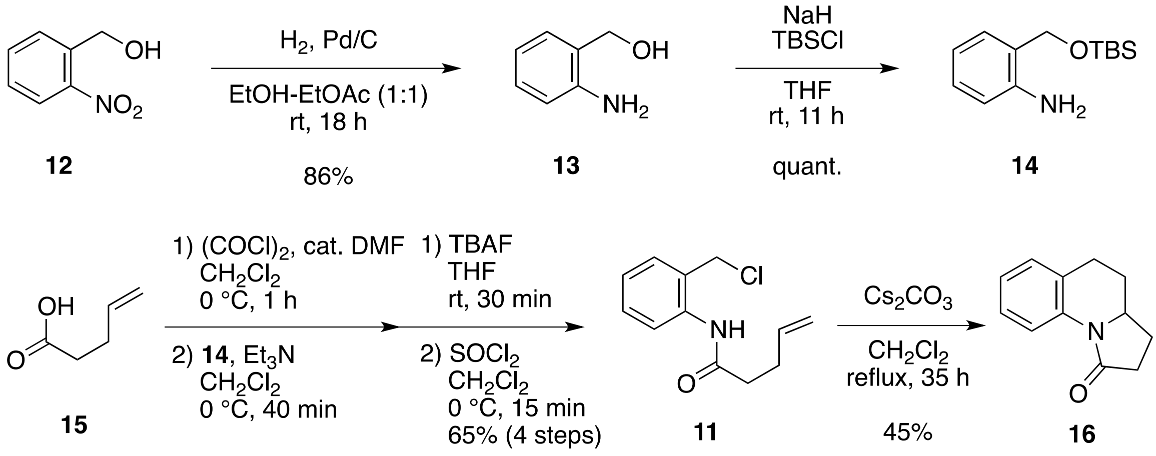
The retrosynthetic analysis of model compound **2** is shown in Scheme 1. We selected tetracyclic **3** as the key intermediate, since we anticipated that it would be easily assembled by the intramolecular aza-Diels–Alder (IMADA) reaction of *ortho*-iminoquinone methide **7** following a modification of an analogous reaction reported by Corey and co-workers that involves the corresponding carbamate.[6] To the best of our knowledge, there is no example of such reaction using an amide derivative.[6] 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**)

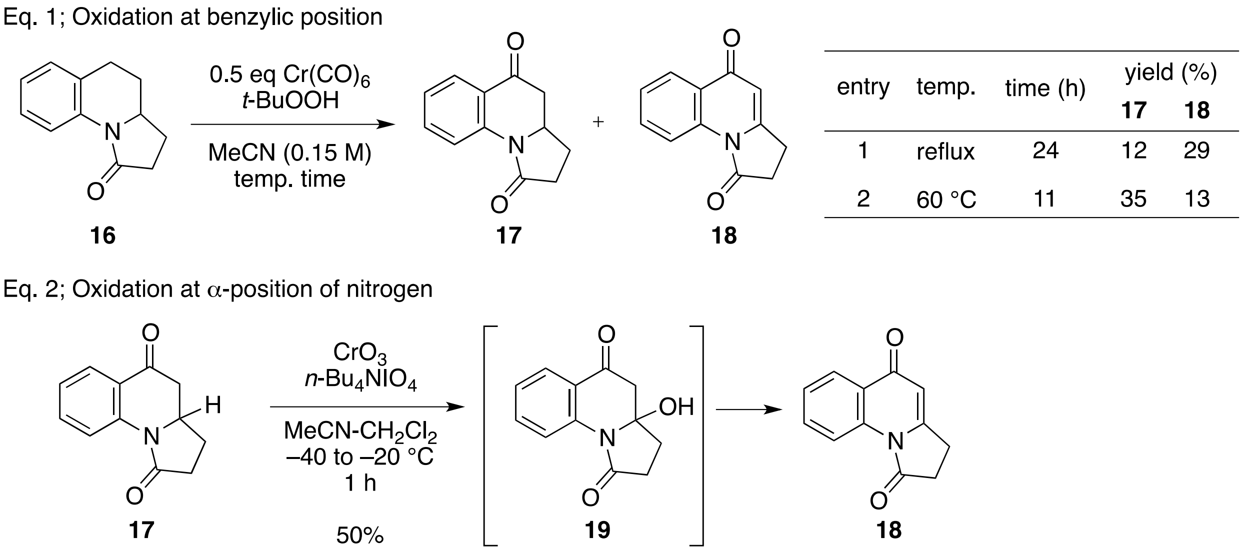
formation after the chemoselective C–H oxidation at the α-position of the nitrogen atom would eventually afford the C-ring. In this plan, the crucial synthetic challenges to be addressed are as follows: the establishment of chemoselective oxidation of the benzylic position of **3** and the methine C–H 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[6] 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.



Scheme 2. Construction of quinoline skeleton by IMADA

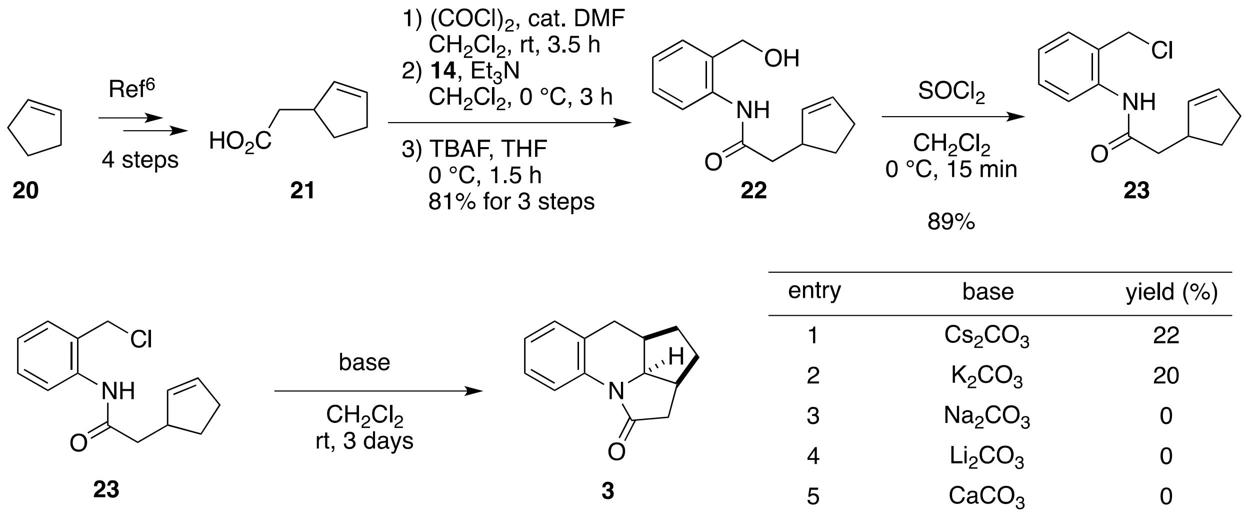
Next, we studied the crucial C–H oxidations on quinoline skeleton. To find suitable conditions for the oxidation of both the benzylic position and C–H group on the lactam ring of **3**, a variety of conditions examined. For the study of the oxidation at the benzylic position, compound **16** was treated with a combination of $Cr(CO)_6$ and *tert*-butyl hydroperoxide at reflux.[7] 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]



entry	temp.	time (h)	yield (%) 17	yield (%) 18
1	reflux	24	12	29
2	60 °C	11	35	13

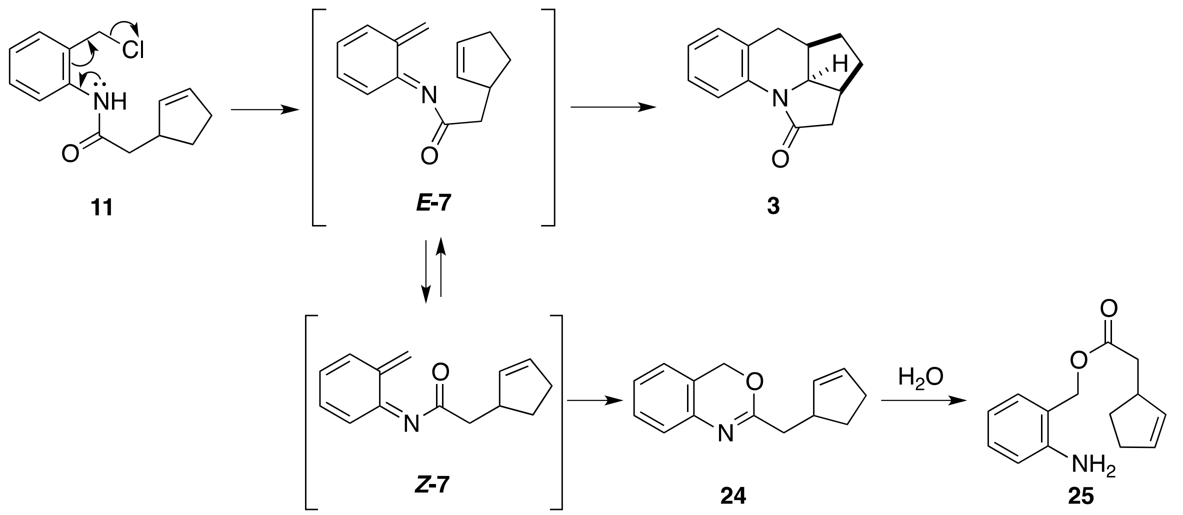
Scheme 3. Examination of two Cr-mediated oxidations

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.



entry	base	yield (%)
1	Cs_2CO_3	22
2	K_2CO_3	20
3	Na_2CO_3	0
4	Li_2CO_3	0
5	$CaCO_3$	0
6	Ag_2CO_3	18
7	Et_3N	0

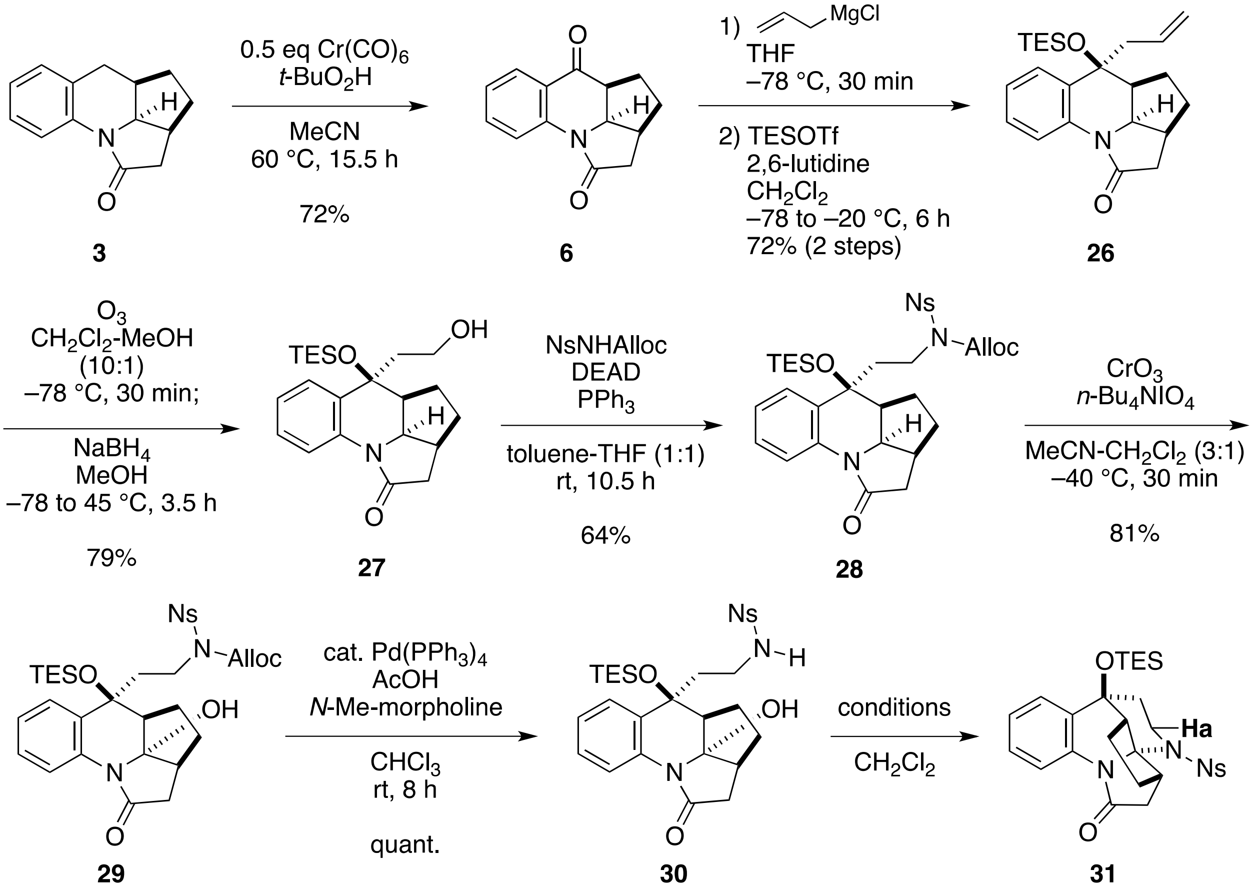
Scheme 4. Base-mediated IMADA with various bases



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

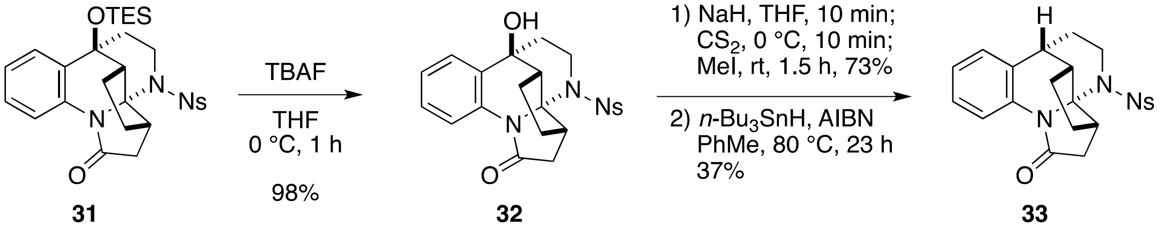
$NaBH_4$ gave primary alcohol **27**, which was then subjected to Mitsunobu reaction with *N*-alloc-*o*-nitrobenzenesulfonamide to give imide **28**. The key C–H oxidation of **28** proceeded smoothly using a combination of CrO_3 and tetrabutylammonium (meta)periodate to furnish the desired hemiaminal **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 $BF_3\cdot OEt_2$ was effective to give the desired product **31** in high yield.[10] The formation of the aminal structure was unambiguously confirmed by the HMBC correlations observed between H_a and aminal carbon.[11]



entry	reagents	temp.	time	yield (%)
1	PPTS	rt	2 days	trace
2	CSA	rt	4 h	31
3	Ac_2O, DMAP	rt	2 days	0
4	$SOCl_2$	0 °C to rt	110 min	39
5	MsCl	0 to 80 °C	24 h	47
6	$BF_3\cdot OEt_2$	0 °C	20 min	87

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 benzylic position using Barton-McCombie protocol (Scheme 7).[12] After removal of TES group, the resultant tertiary alcohol **32** was converted to methyl xanthate. Radical deoxygenation AIBN and n-Bu_3SnH furnished the target compound **33**.[13]



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, CH_2Cl_2, and MeCN were purchased from Kanto Chemical Co. Anhydrous toluene and DMF were purchased from Wako Pure Chemical Industries. Anhydrous MeOH, EtOH, Et_3N, i-Pr_2NEt, EtOAc, and $CHCl_3$ 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 F_{254} 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-AL400 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 micrOTOF 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 CH_2Cl_2-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, TBSCl (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 H_2O 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. 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; R_f = 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, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{12}H_{14}ClNO$ [M^+] 223.0764, found 223.0768.

3,3a,4,5-Tetrahydropyrrolo[1,2-*a*]quinolin-1(2*H*)-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; R_f = 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, $CDCl_3$) 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, $CDCl_3$) δ 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_2O (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_2SO_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, $CDCl_3$) δ 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 (dddd, 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 (dddd, 1H, *J* = 15.0, 8.4, 6.8, 4.0 Hz), 1.97-1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

α,β-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_2Cl_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_2Cl_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_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{12}H_9NO_2$ [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_2O. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with H_2O, 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.[7]

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_2O and then the aqueous layer was extracted with Et_2O. 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.[7]

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_2O (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_2O and then the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_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.[7]

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_2O, and then neutralized with 1 M aqueous HCl. The solution was extracted with CH_2Cl_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_2Cl_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_2Cl_2 (300 mL) to give acid chloride solution in CH_2Cl_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_2Cl_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_2O and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_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_2O 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; R_f = 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{17}NO_2$ [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 CH_2Cl_2 (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 H_2O and sat. aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, 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; R_f = 0.44 (Silica gel, 30/70, EtOAc/hexanes); mp 135 °C (EtOAc); IR (KBr, cm^{-1}) 3269, 1651, 1531, 1458, 1298, 729; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, 1H, *J* = 7.6 Hz), 7.56 (br s, 1H), 7.36 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.31 (d, 1H, *J* = 7.2 Hz), 7.14 (dd, 1H, *J* = 7.6, 7.2 Hz), 5.83 (br s, 1 H), 5.76 (br s, 1H), 4.60 (s, 2H), 3.23 (br s, 1H), 2.54-2.37 (m, 4H), 2.25-2.17 (m, 1H), 1.57 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 136.4, 133.5, 132.0, 130.0, 129.5, 128.2, 125.3, 124.6, 44.2, 43.7, 42.6, 31.9, 29.6; HRMS (EI) *m/z*: calcd. for $C_{14}H_{16}ClNO$ [M^+] 249.0920, found 249.0905.

2a,3,4,4a,5,9c-Hexahydro-2*H*-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 CH_2Cl_2 (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, 72%).

Tetracyclic amide **3**; a white solid, R*f* = 0.18 (Silica gel, 30/70, EtOAc/hexanes); mp 98 °C (EtOAc/hexanes); IR (KBr, cm^{-1}) 2966, 1693, 1491, 1381, 1331, 764; ^{1}H NMR (400 MHz, $CDCl_3$) 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), 2.30 (d, 1H, *J* = 17.2 Hz), 2.12-2.02 (m, 1H), 1.85-1.79 (m, 1H), 1.57-1.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{15}NO$ [M$^+$] 213.1154, found 213.1163.

Compound **25**; IR (neat, cm^{-1}) 3464, 3377, 2941, 1719, 1628, 1169, 1142; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{17}NO_2$ [M$^+$] 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_2O (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_2SO_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 flash column chromatography on silica gel (40/60, EtOAc/hexanes) to give tetracyclic ketone **6** (847 mg, 72%) as a white solid; R*f* = 0.25 (Silica gel, 50/50, EtOAc/hexanes); mp 144 °C (EtOAc/hexanes); IR (KBr, cm^{-1}) 2972, 1699, 1678, 1595, 1477, 1375, 1294, 789; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{13}NO_2$ [M$^+$] 227.0946, found 227.0927.

5-Allyl-5-triethylsiloxy-2a,3,4,4a,5,9c-hexahydro-2*H*-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 NH_4Cl and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, 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 CH_2Cl_2 (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-CCl_4 bath. After stirring for 3 h, the reaction was quenched with H_2O and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, 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; R_f = 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, $CDCl_3$) 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 (dddd, 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{21}H_{28}NO_2Si$ [M^+–29 (C_2H_5)] 354.1889, found 354.1887.

5-(2-Hydroxyethyl)-5-triethylsiloxy-2a,3,4,4a,5,9c-hexahydro-2*H*-9b-azapentaleno[1,6-*ab*]naphthalen-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 CH_2Cl_2/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 flashed 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 NH_4Cl 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 $MgSO_4$, 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; R_f = 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{33}NO_3Si$ [M^+] 387.2230, found 387.2215.

5-[2-(*N*-2-Nitrobenzenesulfonyl-*N*-allylcarbonylimide)ethyl]-5-triethylsiloxy-2a,3,4,4a,5,9c-hexahydro-2*H*-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 H_2O 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. 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; R_f = 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, 49.4, 46.4, 44.6, 40.2, 35.6, 32.0, 27.0, 7.2, 7.0; HRMS (FAB) *m/z*: calcd. for $C_{30}H_{36}N_3O_8SSi$ [M^+–29 (C_2H_5)] 626.1992, found 626.2010.

5-[2-(*N*-2-Nitrobenzenesulfonyl-*N*-allylcarbonylimide)ethyl]-5-triethylsiloxy-9c-hydroxy-2a,3,4,4a,5,9c-hexahydro-2*H*-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/CH_2Cl_2 (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 CH_2Cl_2 (1.00 mL) dropwise. After stirring for 30 min, the reaction was quenched with sat. aqueous Na_2SO_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, EtOAc/hexanes) to give hemiaminal **29** (161 mg, 81%) as a white solid; R_f = 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{32}H_{40}N_3O_8SSi$ [M^+–17 (HO)] 654.2305, found 654.2286.

5-[2-(2-Nitrobenzenesulfonylamide)ethyl]-5-triethylsiloxy-9c-hydroxy-2a,3,4,4a,5,9c-hexahydro-2*H*-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 $CHCl_3$ (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 $Pd(PPh_3)_4$ (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 H_2O and then the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, 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; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13-8.09 (m, 1H), 8.01 (d, 1H, *J* = 8.0 Hz), 7.84-7.82 (m, 1H), 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, 9H, *J* = 8.0 Hz), 0.41-0.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 148.0, 133.52, 133.48, 133.42, 132.7, 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 $C_{28}H_{36}N_3O_6SSi$ [M^+ −17 (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_2Cl_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_2O and then the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_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; ^1H NMR (400 MHz, $CDCl_3$) δ 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 (dddd, 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, $CDCl_3$) δ 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 $C_{28}H_{35}N_3O_6SSi$ [M^+] 569.2016, found 569.2028.

Hydroxypentacyclic aminal (32)

A flame-dried 10-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_2O and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_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/CH_2Cl_2) to give alcohol **32** (26.8 mg, 22%) as a white solid; R_f = 0.12 (Silica gel, 50/50, EtOAc/hexanes); mp 249 °C (EtOAc); IR (KBr, cm^{-1}) 3497, 1717, 1690, 1533, 1364, 980, 613; ^{1}H NMR (400 MHz, $CDCl_3$) 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, 2.0 Hz), 7.61 (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), 3.21 (ddd, 1H, *J* = 9.6, 8.0, 1.6 Hz), 2.87 (ddd, 1H, *J* = 13.2, 5.2, 1.6 Hz), 2.39 (dd, 1H, *J* = 12.4, 6.0 Hz), 2.32 (br s, 1H), 2.29-2.20 (m, 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 (dddd, 1H, *J* = 12.4, 12.4, 12.4, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{21}N_3O_6S$ [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; R_f = 0.37 (Silica gel, 50/50, EtOAc/hexanes); mp 225 °C (EtOAc/hexanes, decomp.); IR (KBr, cm^{-1}) 1717, 1541, 1356, 1047; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 174.0, 147.9, 134.5, 134.3, 132.8, 132.0, 130.4, 129.1, 125.5, 125.2, 124.69, 124.66, 119.2, 89.5, 89.0, 47.8, 45.3, 40.5, 38.6, 36.6, 32.7, 23.9, 19.6; HRMS (EI) *m/z*: calcd. for $C_{24}H_{23}N_3O_6S_3$ [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), tributhyltin 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 °C 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_2Cl_2 only to 1/99, MeOH/CH_2Cl_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 °C (MeOH/CH_2Cl_2, decomp.); IR (KBr, cm^{-1}) 1707, 1543, 1356, 1167, 1069, 762; ^1H NMR (400 MHz, $CDCl_3$) δ 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 (dddd, 1H, *J* =12.8, 12.8, 12.8, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{22}H_{21}N_3O_5S$ [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_2CO_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_2Cl_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_3N (64 μl, 457 μmol) and 1,2-dichloroethane (1.0 mL). To the mixture was added Boc_2O (69.4 mg, 305 μmol) at room temperature. After stirring for 3.5 h, the reaction was heated to 60 °C and stirred for 10 h. Then, additional Boc_2O (34.5 mg, 150 μmol) was added to the mixture and the resulting mixture was stirred for 2 h. H_2O was added to the mixture and and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_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_2O and then the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_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; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 175.4, 154.3, 135.3, 128.4, 124.9, 124.6, 119.0, 87.4, 80.9, 71.6, 52.9, 43.4, 41.8, 41.3, 40.0, 32.7, 28.3, 23.6; HRMS (ESI) *m/z*: calcd. for $C_{21}H_{26}N_2NaO_4$ $[M+Na]^+$ 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; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 213.6, 175.0, 154.1, 134.7, 128.9, 125.5, 125.4, 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 $C_{23}H_{29}N_2O_4S_2$ $[M+H]^+$ 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; $R_f = 0.38$ (Silica gel, 25/75, EtOAc/hexanes); IR (neat, cm^{-1}) 2943, 1708, 1488, 1366, 1153, 757; ^1H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{22}H_{21}N_3O_5S$ $[M+H]^+$ 355.2002, found 355.2016.

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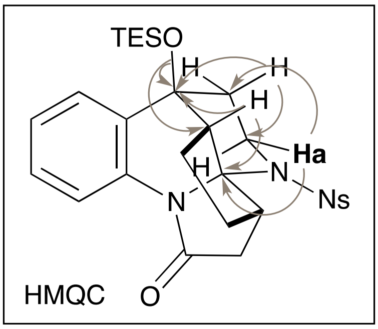

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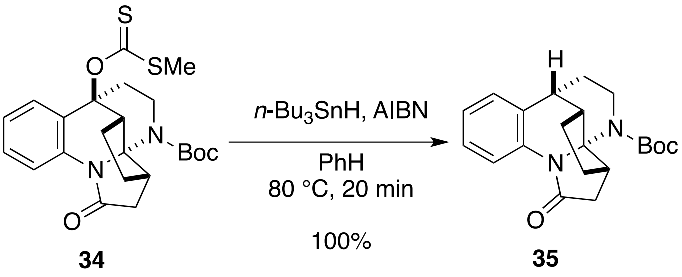

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