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Synthetic studies about strychnopivotine: synthesis of the bridged azatricyclic fragment

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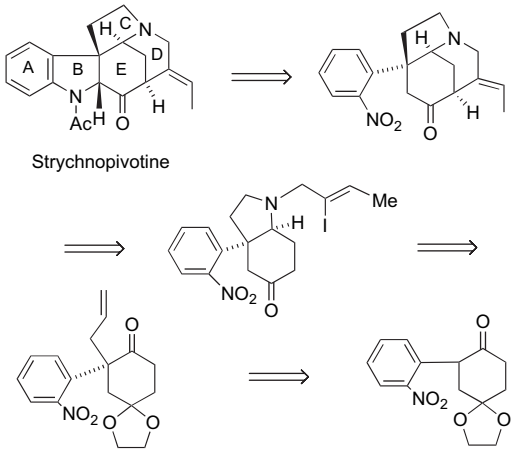
Abstract—Pd(0)-promoted coupling of an amino-tethered vinyl iodide and ketone enolate is the key step to synthesize the CDE ring system of the indole alkaloid strychnopivotine. Attempts to induce the same process in a compound bearing an *o*-nitrophenyl group as a latent indole moiety failed.

1. Introduction

Strychnopivotine, isolated in 1980 from the root bark of *Strychnos variabilis*,[1] is the only *Strychnos* alkaloid[2] bearing a 2-acylindoline moiety in its pentacyclic framework. No total synthesis of this natural product has been published to date.[3,4] We wish to explain here our results[5] in developing a Pd-catalyzed intramolecular cyclization approach toward the CDE azatricyclic fragment of strychnopivotine as the key step in the search for a synthetic entry to this alkaloid.

We envisioned a synthetic approach to strychnopivotine implying the use of a non-indolic advanced intermediate, with the crucial quaternary center already constructed, and the B ring present in a latent form (Scheme 1). After the incorporation of the nitrophenyl group and formation of the quaternary center, the crucial steps would be: (i) closure of the pyrrolidine ring through a one-pot procedure involving ozonolysis of the allyl group and a double (inter- and intramolecular) reductive amination;[6] (ii) closure of the piperidine D ring by an α-alkenation of the remaining ketone group, using the Pd-mediated intramolecular coupling of vinyl halides and ketone enolates;[7,8] and (iii) formation of the indoline ring either by reductive cyclization of α-(2-nitrophenyl)ketones[9] or through the Smalley reaction.[10]



Scheme 1. Synthetic strategy toward strychnopivotine.

2. Results and discussion

Beginning with a model compound without the aryl group, such as the amino-tethered vinyl iodide ketone **1**, we initially studied the Pd-catalyzed coupling of this ketone to check the constitutional stability of the resulting bridged azatricyclic compound **2**, since we have previously observed the tendency of some related 4-alkylidene-2-azabicyclo[3.3.1]-nonan-6-ones (DE strychnopivotine ring) to undergo isomerization to the corresponding enamines.[7b]

Taking the known α-allylcyclohexanedione **4**[11] as a starting material, the required azabicyclic compound **5** was prepared by the tandem process of ozonolysis and double reductive amination, using (*Z*)-2-iodo-2-butenylamine,[12–14] to elaborate the octahydroindole ring (31%). Hydrolysis of **5** provided the amino-tethered vinyl halide **1**, which was subjected to Pd-promoted cyclization in the presence of KOPh. This ring formation led to the azatricyclic compound **2** in 52% yield (Scheme 2).

Having successfully achieved the strychnopivotine azatricyclic ring core formation, we decided to extend the synthetic pathway using as starting material a cyclohexanedione

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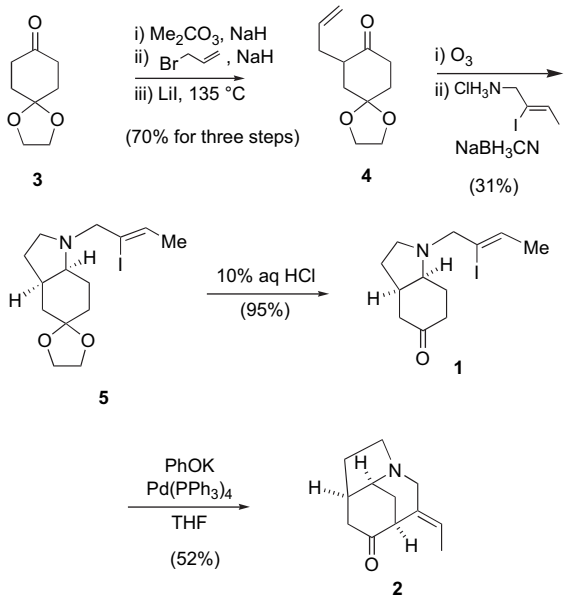


Scheme 2. Synthesis of the CDE ring system of strychnopivotine.

incorporating the *o*-nitrophenyl group as a latent form of the indole nucleus.

Our approach to the synthesis of strychnopivotine commenced with *o*-nitroarylation of the 1,4-cyclohexanedione monoethylene acetal (**3**). Among the three procedures reported in the literature for the synthesis of 2-(*o*-nitrophenyl)cyclohexanone,[15] we decided to use the Rawal's protocol[15b,16] to prepare the undescribed aryl ketone **6**. The starting ketone **3** was transformed into its silyl enol ether (not shown) and then treated with *o*-nitrophenylphenyliodonium fluoride (NPIF) to furnish **6** in 82% overall yield (Scheme 3). The elaboration of the quaternary center was accomplished by O-allylation and a subsequent Claisen rearrangement. Thus, treatment of nitrophenyl ketone **6** with allyl bromide and Cs_2CO_3 provided allyl vinyl ether **7**, which, on heating at 185 °C, was converted to the α,α-disubstituted cyclohexanedione **8** in 95% yield (70% overall yield for the three initial steps). The next step involved the elaboration of the pyrrolidine ring by introducing the amino moiety in a double reductive amination process: firstly in an intermolecular way upon the aldehyde obtained by ozonolysis, and then in an intramolecular manner way upon the ketone carbonyl group. Thus, ozonolysis of the allyl group of **8**, followed by reaction of the ozonide intermediate with (*Z*)-2-iodo-2-butenylamine hydrochloride[12–14] and sodium cyanoborohydride gave *cis*-octahydroindole **9** in 36% overall yield. In addition, *trans*-**9** was isolated as a minor product (9%). The amino-tethered ketone vinyl iodide **11** required for the Pd-catalyzed cyclization was obtained by acid hydrolysis of **9**. In an alternative path, when methylamine hydrochloride was used as the aminocyclization agent, octahydroindole **10** was isolated in 59% yield together with small amounts (12%) of *trans*-**10**. Unfortunately, treatment of **10** with α-(chloroethyl) chloroformate and subsequent heating in a methanol solution of the carbamate intermediate furnished the corresponding secondary amine in poor yield. Finally, when the latter was alkylated with (*Z*)-1-bromo-2-iodo-2-butene[14] the required **9** was rendered in only 20% overall yield. Because of these disappointing yields, the protocol (**8**→**10**→**9**) was discarded and we decided to use the original route for the preparation of **9**.

The stereochemistry of the synthesized azabicyclic compounds was elucidated by 2D NMR spectra (COSY, HSQC). The key evidence for the relative configuration, cis or trans, was the ^{1}H NMR chemical shift of the most deshielded aromatic proton, which appears as a doublet at δ >8.60 in *trans*-3a-(*o*-nitrophenyl)octahydroindol-5-one derivatives, but at δ <7.60 in the cis series. The cis stereochemistry and its preferred conformation were apparent from the 7a-methine proton multiplicity, since it appeared as a broad singlet, which is consistent only with an equatorial disposition of H-7a with respect to the cyclohexane ring (Fig. 1). The ^{13}C NMR chemical shifts of C-4, C-6, and

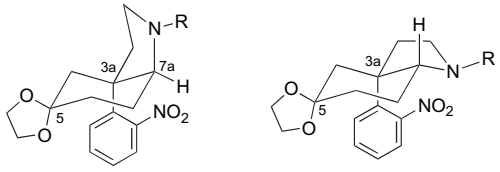
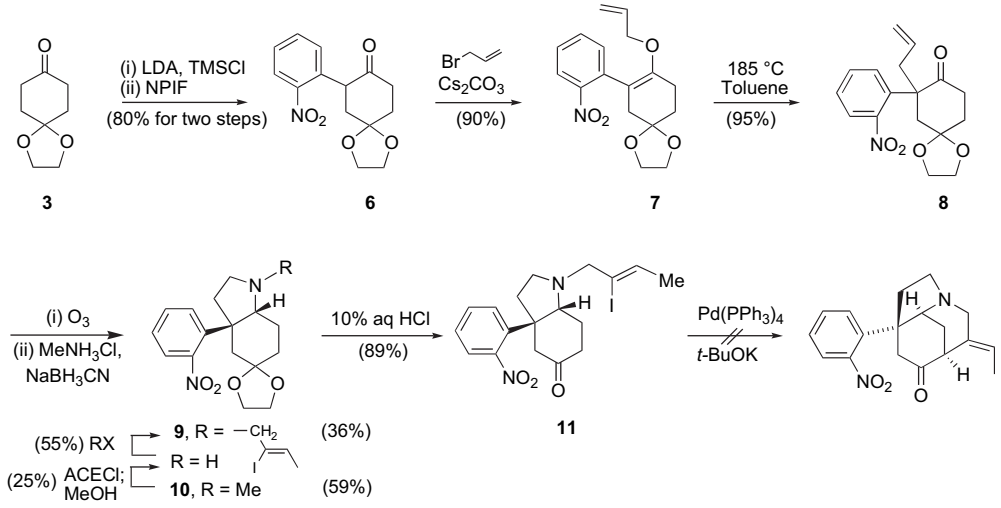


Figure 1. *cis*- and *trans*-Octahydroindoles **9** and **10**.



Scheme 3. Synthesis of *cis*-3a-(*o*-nitrophenyl)octahydroindol-5-ones.

Table 1. ^{13}C NMR data for octahydroindol-5-ones

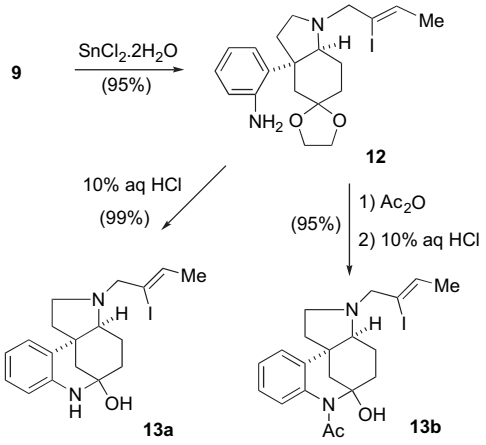
	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	NCH_2	CHI	=CH	CH_3
1[b]	51.7	31.1	36.6	43.4	213.6	35.7	24.6	59.7	65.7	109.9	130.9	21.7
5[b]	51.1	31.1	37.6	29.1	109.5	28.6	23.6	60.5	65.4	111.1	129.8	21.6
9[c]	50.1	38.6	48.8	39.8	108.3	29.4	21.7	63.1	65.1	110.0	131.0	21.8
trans-**9**[c]	50.9	39.0	48.6	44.2	108.5	35.0	20.7	74.3	66.8	110.0	132.1	21.8
10[a]	54.1	39.2	48.5	40.9	108.2	29.1	21.4	66.5	40.0			
trans-**10**[b]	54.1	39.0	48.4	44.3	108.3	35.0	20.4	77.3	41.6			
11[b]	51.2	37.1	51.6	50.2	210.5	34.7	23.1	64.5	64.7	108.3	131.6	21.6
12[b]	50.4	29.4	48.0	38.1	108.9	37.4	22.1	64.7	64.7	109.4	131.1	21.7
14[c]	50.1	29.3	48.9	40.7	109.6	38.5	22.4	63.1	65.7	110.7	130.1	21.7
15[c]	50.6	34.9	50.9	50.4	212.7	37.9	23.1	65.6	65.5	109.6	130.8	21.8
16[c]	51.1	34.6	50.8	49.7	212.4	38.4	33.8	62.9	40.5	73.9	80.3	3.3
17[a]	50.6	34-0	51.1	50.9	212.2	38.4	23.1	65.6	55.3	143.9	128.0	17.8

The assignments were aided by HSQC experiments for compounds **10** and **17**, and DEPT in all cases.
[a] All spectra were recorded in $CDCl_3$ at 100 MHz.
[b] All spectra were recorded in $CDCl_3$ at 75 MHz.
[c] All spectra were recorded in $CDCl_3$ at 50 MHz.

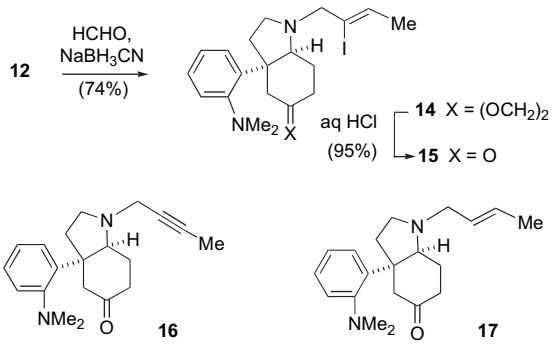
C-7a are strongly shielded in cis compounds in comparison with those of trans derivatives (see Table 1 in Section 3).

Attempts to induce the cyclization of vinyl iodide **11** failed. Decomposition of the starting material was always observed when using *t*-BuOK as the base and $Pd(PPh_3)_4$ as the catalyst in a THF solution at reflux temperature, the root of the problem probably being the known instability of nitrophenyl derivatives in a basic medium.[17]

Since we were concerned that the nitro group might be interfering with the coupling step, a simpler compound with a reduced group was prepared. Reduction of the nitro compound **9** with $SnCl_2\cdot 2H_2O$ gave aniline **12** (95%), which was hydrolyzed to give hemiaminal **13a**. When the aniline **12** was acetylated, a hemiaminal **13b** was again formed after acetal hydrolysis (Scheme 4). To avoid this undesired reactivity and to obtain a 3a-aryloctahydroindole with which to attempt the Pd-catalyzed cyclization, the amino group was blocked. The resulting dimethylamino derivative **14**[18] was of course inadequate for the total synthesis but it was useful for evaluating the scope of the synthetic methodology (Scheme 5). Efforts to synthesize other diprotected amino derivatives were unsuccessful. After hydrolysis of **14**, ketone **15** was isolated, but disappointingly, a cyclized product was



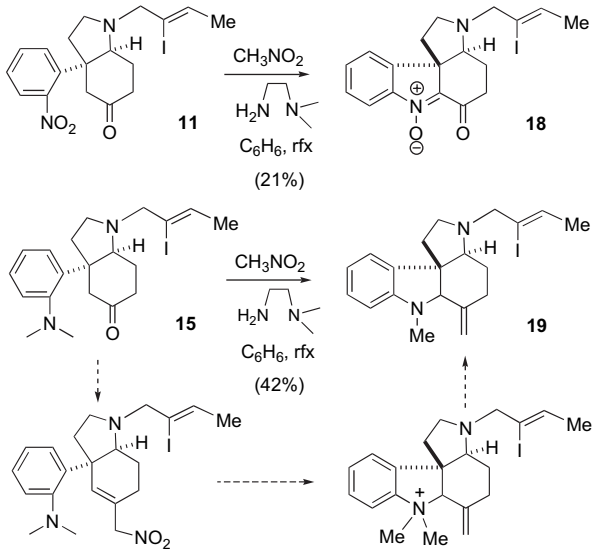
Scheme 4. Hemiaminal derivatives.



Scheme 5.

never observed from this substrate. Using *t*-BuOK as the base, alkyne **16** was isolated from an elimination process, while using KPhO led to the reduced alkene **17**.

As a result of our inability to obtain the desired cyclization, we turned our attention to the formation of the corresponding allylic nitro derivatives of ketones **11** and **15**. In 2004, we described that vinyl halides undergo intramolecular coupling with amino-tethered allylic nitro moieties in the presence of a palladium catalyst and base.[19] Interestingly, neither ketone **11** nor ketone **15** on treatment with nitromethane using a catalytic amount of *N*,*N*-dimethylethylenediamine as a base in benzene solution[20] gave the corresponding allylic nitro compound, but cyclized compounds **18** and **19** were isolated, respectively (Scheme 6). In these reaction conditions, ketone **11** was transformed into an α-activated species, which evolved through an addition to the nitrophenyl group to give the corresponding nitrone **18**. On the other hand, tetracyclic pyrrolocarbazole **19** was formed through an initial allylic nitro compound, which experimented an allylic substitution,[21] the aniline being the nucleophilic species. In this way, the strychnopivotine B ring was achieved. Finally, the generated ammonium salt underwent a dealkylation process to give **19** in 42% overall yield. Although compounds **18** and **19** embodied the tetracyclic pyrrolocarbazole fragment of strychnopivotine, the low yield in which the compounds were isolated as well as their functionalization induced us to close this synthetic approach using 3a-nitrophenyl octahydroindol-5-ones as intermediates.



Scheme 6. Pyrrolo[2,3-*d*]carbazoles **18** and **19**.

In summary, although it was not possible to carry out the intramolecular coupling using 3a-(*o*-nitro or dimethylamino)phenyl substituted octahydroindolone derivatives, a synthetic entry to the functionalized CDE ring of strychnopivotine was achieved when the octahydroindolone was unsubstituted at C-3a. Further studies of this methodology are needed to determine if another *o*-substituted phenyl derivative in the Pd-catalyzed α-alkenation of ketone enolates could allow the key bond formation. It would also be useful to explore the potential of azatricyclic ketone **2** to achieve the pentacyclic strychnopivotine with a Japp–Klingemann indolization.[22]

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) and the spots were located with iodoplatinate reagent or 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–240 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or 300, or a Varian Mercury 400 instrument. Chemical shifts are reported in parts per million downfield (δ) from Me_4Si. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy.

3.2. *cis*-1-[(*Z*)-2-Iodo-2-butenyl]octahydroindol-5-one ethylene acetal (5)

A stirred solution of 2-allyl-1,4-cyclohexanedione monoethylene acetal[11] (**4**, 1.50 g, 7.64 mmol) in CH_2Cl_2 (120 mL) at −78 °C was charged with a constant stream of ozone. After 25 min, the solution turned characteristic pale blue and was purged with oxygen. The solvent was evaporated without warming, and the residue was dissolved in MeOH (26 mL). To this solution were added first 2-iodobut-2-enylamine hydrochloride[12] (3.77 g, 16.16 mmol) and then $NaBH_3CN$ (350 mg, 5.29 mmol). After being stirred for 30 min, an additional portion of $NaBH_3CN$ (370 mg, 5.59 mmol) was added and stirring was continued for 1 h. At this time, an additional portion of $NaBH_3CN$ (960 mg, 14.51 mmol) was added. The reaction mixture was stirred overnight, and then the MeOH was evaporated. The crude was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. Concentration of the dried organic extracts give a residue, which was purified by chromatography (CH_2Cl_2) to give **5** (862 mg, 31%): ^1H NMR (200 MHz, $CDCl_3$) 1.32–1.75 (m, 5H), 1.77 (dd, J=6.6, 1.5 Hz, CH_3), 1.80–2.30 (m, 5H), 2.54 (q, J=3 Hz, H-7a), 2.88 (d, J=14 Hz, 1H, NCH_2), 3.12 (td, J=9.2, 6 Hz, 1H, H-2), 3.58 (dt, J=14, 1.8 Hz, 1H, NCH_2), 3.94 (s, 4H, OCH_2), 5.82 (q, J=7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

3.3. *cis*-1-[(*Z*)-2-Iodo-2-butenyl]octahydroindol-5-one (1)

To a solution of compound **5** (0.55 g, 1.51 mmol) in THF (60 mL) was added 10% aqueous HCl (60 mL). After stirring at room temperature overnight, the mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give **1** (468 mg, 95%), which was used without purification in the next step: ^1H NMR (300 MHz, $CDCl_3$) 1.40 (m, 1H), 1.78 (dd, J=6.6, 1.5 Hz, CH_3), 1.80–2.0 (m, 3H), 2.1–2.2 (m, 2H), 2.32 (dd, J=15, 6.6 Hz, H-4), 2.42 (dd, J=15, 6.6 Hz, H-4), 2.60 (m, 1H), 2.72 (m, 1H), 2.78 (ddd, J=8.5, 8.1, 3.6 Hz, H-2), 3.03 (td, J=8.5, 2.1 Hz, H-2), 3.06 (d, J=13.8 Hz, 1H, NCH_2), 3.58 (dt, J=13.8, 1.8 Hz, 1H, NCH_2), 5.84 (q, J=6.4 Hz, =CH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

3.4. (1*RS*,7*RS*,8*RS*)-2-(*E*)-Ethylidene-4-azatricyclo-[5.2.2.0^{4,8}]undecan-10-one (2)

To a stirred solution of ketone **1** (75 mg, 0.232 mmol) and phenol (69 mg, 0.729 mmol) in THF (30 mL) were added under argon *t*-BuOK (0.58 mL of a 1 M solution in *tert*-butyl alcohol) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol). The solution was heated at reflux overnight. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and 1 M aqueous NaOH. The organic layer was dried and concentrated. The residue was purified by chromatography (CH_2Cl_2/MeOH 98:2 to CH_2Cl_2/DEA 90:10) to give ketone **2** (23 mg, 52%): ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 1.63 (d, J=7 Hz, 3H, CH_3), 1.65 (m, 2H, H-6), 2.00 (br d, J=14 Hz, H-9), 2.14 (m, 1H, H-11), 2.42 (m, 1H, H-9), 2.55 (m, H-7), 2.60 (m, 1H, H-11), 2.79 (td, J=11.2, 6 Hz, 1H, H-5), 2.95 (d, J=15.5 Hz, 1H, H-3), 3.15 (m, 1H, H-5), 3.38 (m, 1H, H-1), 3.63 (br s, 1H, H-8), 3.78 (d, J=15.5 Hz, 1H, H-3), 5.49 (q, J=7 Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, gHSQC) 13.1 (CH_3), 25.9 (C-9), 32.4 (C-6), 38.8 (C-7), 41.4 (C-11), 45.5 (C-1), 51.2 (C-5), 52.6 (C-3), 55.8 (C-8), 125.0 (=CH), 211.2 (C-10). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.98; N, 7.32. Found: C, 74.98; H, 9.28; N, 7.05.

3.5. 2-(2-Nitrophenyl)-1,4-cyclohexanedione monoethylene acetal (6)

A solution of 1,4-cyclohexanedione monoethylene acetal (**3**, 5.06 g, 31.4 mmol) in THF (20 mL) was added to a cooled solution (−78 °C) of LDA (26 mL, 1.5 M in cyclohexane) in THF (80 mL) over 10 min. After stirring for 1 h, TMSCl (7.2 mL, 55.60 mmol) was slowly added over 5 min. The solution was allowed to warm-up to room temperature and, after stirring for 1 h, the solvent was evaporated. Dry pentane (100 mL) was added and the LiCl removed by filtration. Concentration of the filtrate gave the corresponding silyl enol ether (6.82 g, 95%), which was used without purification in the next step.

To a stirred solution of NPIF[15b] (6.06 g, 17.56 mmol) in dry DMSO/CH_2Cl_2 (25/37 mL) was added the above silyl enol ether (4.15 g, 18.17 mmol) dropwise at −40 °C. The mixture was stirred for 2 h at this temperature and allowed to warm to room temperature gradually over 2–3 h. The reaction mixture was poured into H_2O (50 mL), and the whole was extracted with ether. The extracts were washed with brine, dried, and concentrated. The residue was purified by chromatography (hexane to hexane/EtOAc 1:1) to give **6** (4.03 g, 83%): IR (NaCl) 1716, 1523, 1339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 2.12 (dm, J=13.2 Hz, 1H), 2.22 (td, J=13.8, 5.1 Hz, 1H), 2.30 (ddd, J=13, 6, 3.6 Hz, 1H), 2.48 (t, J=13 Hz, 1H), 2.53 (ddd, J=15, 4.8, 2.7 Hz, 1H), 2.85 (tdd, J=14.5, 7.2, 0.8 Hz, 1H), 4.02–4.13 (m, 4H), 4.54 (dd, J=10.5, 6 Hz, 1H), 7.29 (dd, J=7.8, 1.2 Hz, 1H), 7.44 (td, J=8, 1.5 Hz, 1H), 7.60 (td, J=8, 1.2 Hz, 1H), 8.03 (dd, J=8.1, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) 33.9 (CH_2), 38.1 (CH_2), 40.3 (CH_2), 50.3 (CH), 64.7 (CH_2), 64.8 (CH_2), 107.1 (C), 125.1 (CH), 128.0 (CH), 130.6 (CH), 133.0 (C), 133.3 (CH), 148.9 (C), 206.3 (CO). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.22; H, 5.50; N 4.92.

3.6. 4-Allyloxy-3-(2-nitrophenyl)-3-cyclohexenone ethylene acetal (7)

A mixture of ketone **6** (6.3 g, 22.8 mmol), allyl bromide (5.2 mL, 60.2 mmol), and anhydrous Cs_2CO_3 (23.5 g, 70.6 mmol) in acetone (125 mL) was stirred at reflux temperature overnight. The solvent was removed, and the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated to give enol ether **7** (6.50 g, 90%) as an oil, which was used in the next step without further purification: ^1H NMR (200 MHz, $CDCl_3$) 1.95 (m, 2H), 2.40 (m, 2H), 2.65 (m, 2H), 2.59 (s, 2H), 4.03 (s, 2H), 4.06 (m, 4H), 5.00 (ddt, J=10.5, 2.5, 1.5 Hz, 1H), 5.05 (ddt, J=17.2, 2.5, 1.5 Hz, 1H), 5.65 (ddt, J=17.2, 10.5, 5.4 Hz, 1H), 7.35 (ddd, J=8.2, 7.3, 1.5 Hz, 1H, H-4′), 7.40 (dd, J=7.8, 1.5 Hz, 1H, H-6′), 7.55 (ddd, J=7.8, 7.3, 1.2 Hz, 1H, H-5′), 7.85 (dd, J=8.2, 1.2 Hz, 1H, H-3′); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) 24.1 (CH_2), 31.1 (CH_2), 39.0 (CH_2), 64.5 (OCH_2), 68.6 (CH_2), 107.2 (C), 116.5 (CH_2), 123.8 (CH), 127.1 (CH), 128.0 (C), 131.0 (CH), 132.4 (CH), 133.8 (CH), 148.0 (C).

3.7. 2-Allyl-2-(2-nitrophenyl)-1,4-cyclohexanedione monoethylene acetal (8)

A solution of enol ether **7** (6.50 g, 20.5 mmol) in toluene (60 mL) was stirred at 180–190 °C in a sealed tube for 12 h. After the solvent was evaporated, the residue was crystallized (1% EtOAc in hexane) affording **8** (6.17 g, 95%) as pale brown crystals: IR (KBr) 1701, 1519, 1359 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 2.03 (d, J=13 Hz, 1H), 2.41–2.60 (m, 3H), 2.79 (m, 1H), 2.84 (d, J=13.5 Hz, 1H), 2.97 (dd, J=16.5, 6 Hz, 1H), 3.39 (dd, J=16.5, 7.2 Hz, 1H), 3.95 and 4.12 (AA′BB′ system, 4H), 4.93 (dd, J=10, 1.5 Hz, 1H), 5.06 (dd, J=17, 1.5 Hz, 1H), 5.36 (dddd, J=17, 10, 7, 6 Hz, 1H), 7.39 (td, J=8, 1.5 Hz, 1H), 7.44–7.62 (m, 2H), 7.87 (dd, J=8, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) 32.4 (CH_2), 36.1 (CH_2), 40.3 (CH_2), 47.4 (CH_2), 56.1 (C), 64.1 (CH_2), 64.8 (CH_2), 107.1 (C), 117.9 (CH_2), 125.7 (CH), 127.6 (CH), 129.3 (CH), 132.6 (C), 132.8 (CH), 136.4 (C), 149.0 (C), 206.2 (CO). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.28. Found: C, 64.19; H, 6.09; N, 4.31.

3.8. *cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-(2-nitrophenyl)-octahydroindol-5-one ethylene acetal (9)

Following the above procedure for the aminocyclization of **4** to **5**, from ketone **8** (940 mg, 2.97 mmol) and 2-iodobut-2-enamine hydrochloride (1.18 g, 5.04 mmol), **9** (517 mg, 36%) and *trans*-**9** (129 mg, 9%) were obtained after chromatography (hexane to hexane/EtOAc 1:1).

Data for **9**: ^1H NMR (200 MHz, $CDCl_3$) 1.38 (dm, J=11.4 Hz, 1H), 1.79 (dd, J=6.4, 1.8 Hz, CH_3), 1.90–2.29 (m, 7H), 2.90 (d, J=14 Hz, 1H), 3.13 (m, 1H), 3.56–3.70 (m, 3H), 3.76–3.89 (m, 4H), 5.88 (q, J=6.6 Hz, 1H), 7.26–7.48 (m, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

Compound *trans*-**9**: ^1H NMR (300 MHz, $CDCl_3$) 0.95 (m, 1H), 1.58 (m, 2H), 1.80 (dd, J=6.5, 1.5 Hz, CH_3), 1.88 (m, 1H), 2.05 (qd, J=12.6, 4.5 Hz, H-7ax), 2.17 (m, 1H), 2.28–2.41 (m, 2H), 2.57 (ddd, J=12.5, 8, 2.1 Hz, H-7a), 2.71 (dd, J=13.5, 1.5 Hz, 1H, NCH_2), 3.01 (q, J=8.5 Hz, H-2), 3.05 (d, J=13.5 Hz, 1H, NCH_2), 3.58 (m, 1H), 3.77 (m, 4H, OCH_2), 5.86 (q, J=6.5 Hz, =CH), 7.26 (td, J=8, 1.5 Hz, 1H, ArH), 7.47 (m, 2H, ArH), 8.91 (d, J=8 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

3.9. 2-Methyl-3a-(2-nitrophenyl)octahydroindol-5-one ethylene acetal (10)

A stirred solution of ketone **8** (520 mg, 1.64 mmol) in CH_2Cl_2 (30 mL) at −78 °C was treated with a constant stream of ozone. After 15 min, the solution turned characteristic pale blue and was purged with oxygen. The solvent was removed with a rotatory evaporator without warming, and the residue was dissolved in MeOH (15 mL). To this solution were added first methylamine hydrochloride (1.72 g, 25.0 mmol) and then sodium cyanoborohydride (74 mg, 1.12 mmol). After being stirred for 30 min, an additional portion of sodium cyanoborohydride (88 mg, 1.33 mmol) was added and stirring was continued for 1 h. At this time, a third portion of sodium cyanoborohydride (203 mg, 3.1 mmol) was added, and stirring was continued overnight. After removal of the methanol under reduced pressure, CH_2Cl_2 was added and the resulting organic solution was washed with saturated aqueous $NaHCO_3$ solution, dried, and concentrated. The resulting oil was purified by

chromatography (CH_2Cl_2) to give 356 mg (59%) of **10** and 72 mg (12%) of *trans*-**10**.

Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.38 (ddd, J=12, 6, 3.2 Hz, H-6eq), 1.89 (td, J=12, 6 Hz, H-6ax), 1.97 (m, 1H, H-3), 1.99–2.05 (m, 2H, H-7), 2.02 (d, J=14.4 Hz, H-4), 2.10 (dd, J=14, 4, 1.6 Hz, H-4), 2.24 (m, 2H, H-2 and H-3), 2.30 (s, NCH_3), 2.69 (br s, H-7a), 3.18 (ddd, J=10.5, 7, 7 Hz, H-2), 3.57 and 3.82 (2 m, 2H each, OCH_2), 7.30 (ddd, J=7, 6.8, 2 Hz, 1H, ArH), 7.42–7.50 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, gHSQC), see Table 1. Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.02; H, 7.22; N, 8.51.

Compound *trans*-**10**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.56–1.67 (m, 4H), 1.80–2.05 (m, 3H), 2.27–2.42 (m, 2H), 2.38 (s, NCH_3), 2.52 (ddd, J=12.5, 8.1, 3 Hz, 1H), 3.16 (dt, J=10, 8 Hz, H-2), 3.56 (m, 1H), 3.77 (m, 4H, OCH_2), 7.25 (td, J=8, 1.5 Hz, 1H, ArH), 7.43 (td, J=8, 1.5 Hz, 1H, ArH), 7.49 (dd, J=8, 1.5 Hz, 1H, ArH), 8.58 (dd, J=8, 1.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

3.10. *cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-(2-nitrophenyl)-octahydroindol-5-one (11)

To a solution of **9** (531 mg, 1.10 mmol) in THF (10 mL) was added 10% aqueous HCl (15 mL). After being stirred overnight, the mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give ketone **11** (444 mg, 92%), which was used without purification in the next step. An analytical sample was obtained by chromatography (CH_2Cl_2): ^{1}H NMR (300 MHz, $CDCl_3$) 1.79 (dd, J=6.3, 1.2 Hz, CH_3), 1.91–2.06 (m, 2H), 2.11–2.31 (m, 4H), 2.79 (d, J=15 Hz, 1H, H-4ax), 2.82 (ddd, J=17, 12, 6 Hz, 1H, H-6ax), 2.96 (dd, J=15, 0.6 Hz, 1H, H-4eq), 3.02 (d, J=13.5 Hz, 1H, NCH_2), 3.11 (m, 1H), 3.27 (t, J=3 Hz, 1H, H-7a), 3.65 (dt, J=13.5, 1.8 Hz, 1H, NCH_2), 5.85 (qd, J=6.3, 1.8 Hz, =CH), 7.37 (m, 1H, ArH), 7.49–7.52 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1. Anal. Calcd for $C_{18}H_{21}IN_2O_3$: C, 49.10; H, 4.81; N, 6.36. Found: C, 49.19; H, 4.79; N, 6.32.

3.11. Attempts of cyclization of 11

To a stirred solution of ketone **11** (77 mg, 0.175 mmol) in freshly distilled THF (5 mL) were added under argon *t*-BuOK (0.180 mL of 1 M solution in *tert*-butyl alcohol) and $Pd(PPh_3)_4$ (47 mg, 0.041 mmol). The solution was heated at reflux for 45 min. After being cooled to room temperature, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was dried and concentrated to give a residue resulting in decomposition of the starting material.

3.12. *cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-(2-aminophenyl)-octahydroindol-5-one ethylene acetal (12)

To a solution of **11** (877 mg, 1.81 mmol) in DMF (20 mL) was added $SnCl_2\cdot 2H_2O$ (4.30 g, 18.68 mmol). After stirring at room temperature for 24 h, the reaction mixture was basified with 50% aqueous NaOH, extracted with CH_2Cl_2, and washed with brine. The organic layers were dried and concentrated to give **12** (782 mg, 95%), which was used without purification in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (dm, J=9 Hz, 1H), 1.80 (dd, J=6.3, 1.2 Hz, CH_3), 1.95 (m, 3H), 2.07–2.27 (m, 4H), 2.72 (dd, J=13.8, 1.5 Hz, 1H), 2.92 (d, J=13.5 Hz, 1H), 3.08–3.16 (m, 2H), 3.57 (q, J=8 Hz, 1H), 3.68–3.90 (m, 5H), 5.88 (q, J=6.6 Hz, =CH), 6.64 (dd, J=7.5, 1.5 Hz, 1H, ArH), 6.73 (td, J=7.5, 1.5 Hz, 1H, ArH), 7.02 (td, J=7.5, 1.5 Hz, 1H, ArH), 7.18 (dd, J=7.5, 1.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

3.13. Hydrolysis of acetal 12

To a solution of compound **12** (47 mg, 0.103 mmol) in THF (2 mL) was added 10% aqueous HCl (2 mL). After stirring at room temperature overnight, the reaction mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give quantitatively **13a**: ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) 21.6 (CH_3), 21.7 (CH_2), 30.8 (CH_2), 35.1 (CH_2), 40.3 (CH_2), 47.0 (C), 50.3 (CH_2), 65.4 (CH_2), 68.5 (CH), 81.5 (C), 110.9 (C), 113.4 (CH), 117.1 (CH), 123.9 (CH), 124.6 (C), 127.6 (CH), 130.2 (CH), 144.5 (C).

Acetylation of aniline **12** (Ac_2O) followed by acid treatment of the resulting amido acetal gave tetracyclic hemiaminal **13b**: ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) 21.7 (CH_3), 23.9 (CH_2), 25.6 (NAc), 30.7 (CH_2), 32.2 (CH_2), 41.4 (CH_2), 46.1 (C), 49.6 (CH_2), 65.3 (CH_2), 66.2 (CH), 89.7 (C), 110.3 (C), 123.6 (CH), 124.1 (CH), 124.3 (CH), 126.3 (CH), 130.4 (CH), 135.1 (C), 138.7 (C), 175.6 (C).

3.14. *cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-[2-(*N*,*N*-dimethylamino)phenyl]octahydroindol-5-one ethylene acetal (14)

To a stirred solution of **12** (782 mg, 1.72 mmol) and 37% aqueous formaldehyde (1.6 mL) in acetonitrile (7 mL) was added $NaBH_3CN$ (0.41 g, 6.20 mmol). Glacial acetic acid (0.180 mL) was added over 10 min, and the reaction mixture was stirred at room temperature for 2 h. An additional amount of glacial acetic acid (0.180 mL) was added, and stirring was continued for further 30 min. The reaction mixture was poured into CH_2Cl_2, basified with 1 N NaOH, and washed with brine. The organic layers were dried and concentrated. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) to give **14** (613 mg, 74%): ^{1}H NMR (200 MHz, $CDCl_3$) 1.44 (dm, J=8 Hz, 1H), 1.68 (m, 1H), 1.79 (dd, J=6.3, 1.2 Hz, CH_3), 1.97–2.27 (m, 5H), 2.56 and 2.58 (2s, 6H, NMe), 2.77 (dd, J=14, 2 Hz, 1H), 2.94 (d, J=14 Hz, 1H), 3.07 (br, 1H), 3.15 (ddd, J=9.2, 9.2, 6.4 Hz, 1H), 3.50 (m, 1H), 3.60 (m, 1H), 3.75–3.90 (m, 4H), 5.88 (q, J=6.2 Hz, =CH), 7.07–7.35 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

3.15. *cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-[2-(*N*,*N*-dimethylamino)phenyl]octahydroindol-5-one (15)

To a solution of compound **14** (1.16 g, 2.41 mmol) in THF (10 mL) was added 10% aqueous HCl (30 mL). After stirring at room temperature for 23 h, the reaction mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2. The

organic extracts were dried and concentrated to give **15** (1.00 g, 95%), which was used without purification in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) 1.58 (m, 1H), 1.79 (dd, J=6.3, 1.8 Hz, CH_3), 1.95–2.06 (m, 2H), 2.10–2.19 (m, 2H), 2.28–2.39 (m, 2H), 2.55 and 2.58 (2s, 3H each, NMe), 2.72–2.82 (m, 2H), 3.02–3.18 (m, 3H), 3.64 (d, J=13.5 Hz, 1H, NCH_2), 5.84 (q, J=6.3 Hz, =CH), 7.24 (td, J=8, 1.5 Hz, 1H, ArH), 7.23–7.30 (m, 2H, ArH), 7.39 (dd, J=8, 1.5 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1. Anal. Calcd for $C_{20}H_{27}IN_2O$: C, 54.80; H, 6.21; N, 6.39. Found: C, 54.46; H, 6.50; N, 6.12.

3.16. Attempts of cyclization of 15

(a) To a stirred solution of ketone **15** (65 mg, 0.148 mmol) in freshly distilled THF (5 mL) were added under argon *t*-BuOK (0.230 mL of 1 M solution in *tert*-butyl alcohol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol). The solution was heated at reflux for 45 min. After being cooled to room temperature, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was dried and concentrated. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 92:8) to give alkyne **16** (40 mg, 87%): ^{1}H NMR (200 MHz, $CDCl_3$) 1.71 (s, CH_3), 2.0–2.5 (m, 6H), 2.58 (s, 6H, NMe), 2.65–3.15 (m, 4H), 3.30–3.55 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

(b) To a stirred solution of ketone **15** (300 mg, 0.685 mmol) and phenol (194 mg, 2.05 mmol) in freshly distilled THF (5 mL) were added under argon *t*-BuOK (1.70 mL of 1 M solution in *tert*-butyl alcohol) and $Pd(PPh_3)_4$ (81 mg, 0.069 mmol). The solution was heated at reflux for 2 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and 1 N aqueous NaOH. The organic layer was dried and concentrated. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 84:16) to give **17** (41 mg, 19%): ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.68 (d, J=6 Hz, CH_3), 2.05 (m, 2H, H-6 and H-7), 2.10 (m, 2H, H-3 and H-7), 2.20 (m, 1H, H-6), 2.30 (m, 1H, H-2), 2.45 (masked, 1H, H-3), 2.50 (br s, 6H, NMe), 2.82 (d, J=15 Hz, H-4), 2.83 (masked, 1H, NCH_2), 2.99 (d, J=15 Hz, H-4), 3.15 (br, 1H, H-7a), 3.20 (m, 1H, H-2), 3.39 (dd, J=13.2, 4.8 Hz, 1H, NCH_2), 5.55 (m, =CH), 5.60 (m, =CH), 7.14 (td, J=8, 1.5 Hz, 1H, ArH), 7.25 (m, 2H, ArH), 7.38 (dd, J=8, 1.5 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, gHSQC), see Table 1.

3.17. Treatment of ketone 11 with nitromethane in basic medium

In a round-bottomed flask fitted with a Dean–Stark trap were placed **11** (444 mg, 1.01 mmol), nitromethane (1.0 mL, 17.54 mmol), *N*,*N*-dimethylethylenediamine (40 μL, 0.346 mmol), and benzene (10 mL), and the solution was refluxed for 8 h. The benzene solution was cooled, washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) to give tetracyclic keto nitrone 3-[(*Z*)-2-iodo-2-butenyl]-7-oxide-1,2,3,3a,4,5-hexahydropyrrolo[2,3-*d*]carbazol-6-one (**18**, 89 mg, 21%): ^{1}H NMR (300 MHz, $CDCl_3$) 1.56 (tt, J=14.1, 3.5 Hz, H-5), 1.81 (dd, J=6.3, 1.2 Hz, CH_3), 1.82 (masked, 1H), 2.05 (dm, J=14.5 Hz, 1H), 2.41 (td, J=12.3, 3.6 Hz, H-4), 2.51 (dm, J=16 Hz, 1H), 2.79 (ddd, J=12, 9.3, 5.1 Hz, 1H), 3.11 (ddd, J=16, 14.5, 3.6 Hz, 1H), 3.26 (dd, J=9, 6.6 Hz, 1H), 3.37 (br s, 1H, H-3a), 3.40 (d, J=12 Hz, 1H, NCH_2), 3.66 (dt, J=12, 1.5 Hz, 1H, NCH_2), 5.95 (q, J=6.3 Hz, 1H, =CH), 7.47–7.59 (m, 3H, ArH), 7.86 (d, J=8 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) 21.8 (CH_3), 27.0 (CH_2), 36.9 (CH_2), 37.0 (CH_2), 51.7 (CH_2), 55.9 (C), 65.2 (CH), 65.5 (CH_2), 109.0 (C), 116.9 (CH), 122.2 (CH), 128.8 (CH), 132.1 (CH), 131.6 (CH), 141.6 (C), 142.4 (C), 145.9 (C), 190.3 (C).

3.18. Treatment of ketone 15 with nitromethane in basic medium

In a round-bottomed flask fitted with a Dean–Stark trap were placed **15** (444 mg, 1.01 mmol), nitromethane (1.3 mL, 22.80 mmol), *N*,*N*-dimethylethylenediamine (54 μL, 0.467 mmol), and benzene (5 mL), and the solution was refluxed for 8 h. The benzene solution was cooled, washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated. The residue was purified by chromatography (CH_2Cl_2) to give 3-[(*Z*)-2-iodo-2-butenyl]-7-methyl-6-methylene-1,2,3,3a,4,5,6a,7-octahydropyrrolo-[2,3-*d*]carbazole (**19**, 180 mg, 42%): ^{1}H NMR (200 MHz, $CDCl_3$) 1.37 (m, 1H), 1.71 (m, 1H), 1.75 (d, J=6.6 Hz, CH_3), 1.85 (m, 1H), 2.11–2.30 (m, 2H), 2.37 (m, 1H), 2.52 (m, 1H), 2.60 (s, 3H, NMe), 2.70 (m, 1H), 2.80 (m, 1H), 3.17 and 3.39 (2d, J=14 Hz, 1H each, NCH_2), 3.23 (s, H-6a), 4.99 and 5.08 (2s, 1H each, =CH_2), 5.82 (q, J=6.6 Hz, =CH), 6.49 (d, J=8 Hz, 1H, ArH), 6.74 (t, J=8 Hz, 1H, ArH), 7.12 (t, J=8 Hz, 1H, ArH), 7.24 (d, J=8 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) 21.7 (CH_3), 26.1 (CH_2), 30.3 (CH_3), 33.5 (CH), 34.8 (CH_2), 50.4 (CH_2), 54.4 (C), 63.6 (CH_2), 67.3 (CH), 79.1 (CH), 107.5 (CH), 109.9 (C),114.6 (CH_2), 118.3 (CH), 123.5 (CH), 127.6 (CH), 130.3 (CH), 137.7 (C), 143.8 (C), 151.7 (C). Anal. Calcd for $C_{20}H_{25}IN_2$: C, 57.15; H, 5.99; N, 6.66. Found: C, 56.79; H, 6.29; N, 6.44.

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