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Total Syntheses of Aporphine Alkaloids via Benzyne Chemistry: An Approach to the Formation of Aporphine Cores

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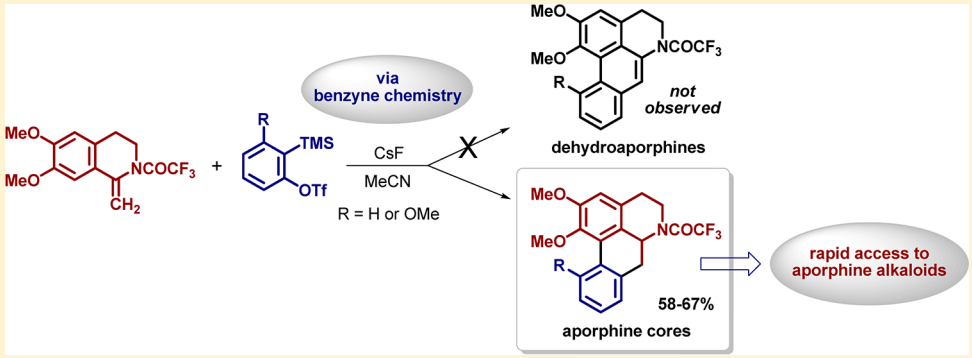
Supporting Information



ABSTRACT: Total syntheses of lysicamine, (±)-nuciferine, (±)-nornuciferine, (±)-zanthoxyphylline iodide, (±)-*O*-methylisothebaine, and (±)-trimethoxynoraporphine were accomplished by an approach that involves the formation of aporphine cores through reactions between an isoquinoline derivative and silylaryl triflates promoted by CsF. Unprecedented formations of aporphine cores proceeded in good yields presumably through [4 + 2] cycloaddition reactions followed by hydrogen migrations.

INTRODUCTION

Aporphine alkaloids are biosynthetic derivatives of isoquinoline alkaloids and can be found in several families of plants.[1] In terms of structural features, aporphine skeletons are constituted by four rings (A–D) with a nitrogen atom present in the B ring (Figure 1). Aporphinoids compose a class of compounds with important pharmacological properties, including, for example, anti-HIV activity,[2] anticancer activity,[3] and dopaminergic activities.[4] In this sense, (*R*)-(−)-apomorphine hydrochloride, an example of an aporphine prototype, has currently been employed in Parkinson's disease therapy[5] and erectile dysfunction treatment[6] (Figure 1).

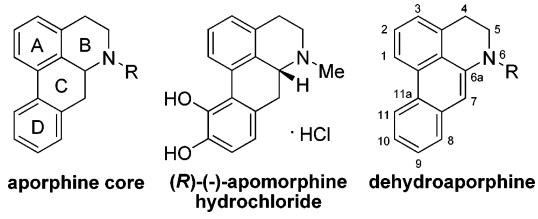


Figure 1. Examples of aporphine structures.

Because of the enormous pharmacological potential of aporphinoids, several synthetic approaches for the production of aporphine cores have been reported in the literature.[7−10] Among all the approaches for the production of aporphine alkaloids, those based on biosynthetic routes have in common the construction of the C ring employing 1-benzyltetrahydroisoquinoline intermediates.[7−9] The classical method for representing this strategy is the Pschorr reaction.[7] In the same direction, still considering well-established approaches, those based on benzyne chemistry, which involve reactions between 1-methyleneisoquinolines and arenediazonium-2-carboxylates, provide aporphine skeletons through [4 + 2] cycloaddition reactions followed by spontaneous dehydrogenations.[10] In general, Pschorr reaction,[7] and other closely related transformations,[8,9] lead to aporphinoids in relatively low yields, require high temperatures, or employ transition metals. Conversely, employing 1-methyleneisoquinolines and arenediazonium-2-carboxylates, dehydroaporphines are exclusively produced in moderate yields[10] (Figure 1). However, some researchers have discouraged the use of anthranilic acid-derived aryne precursors for safety reasons.[10a] In addition, reduction of dehydroaporphines to aporphines is not a well-documented transformation, and the procedures of choice disclosed in the literature involve expensive metal[8d] or harsh conditions.[8e] Nevertheless, syntheses of aporphine alkaloids via benzyne chemistry, from a synthetic point of view, emerge as convergent

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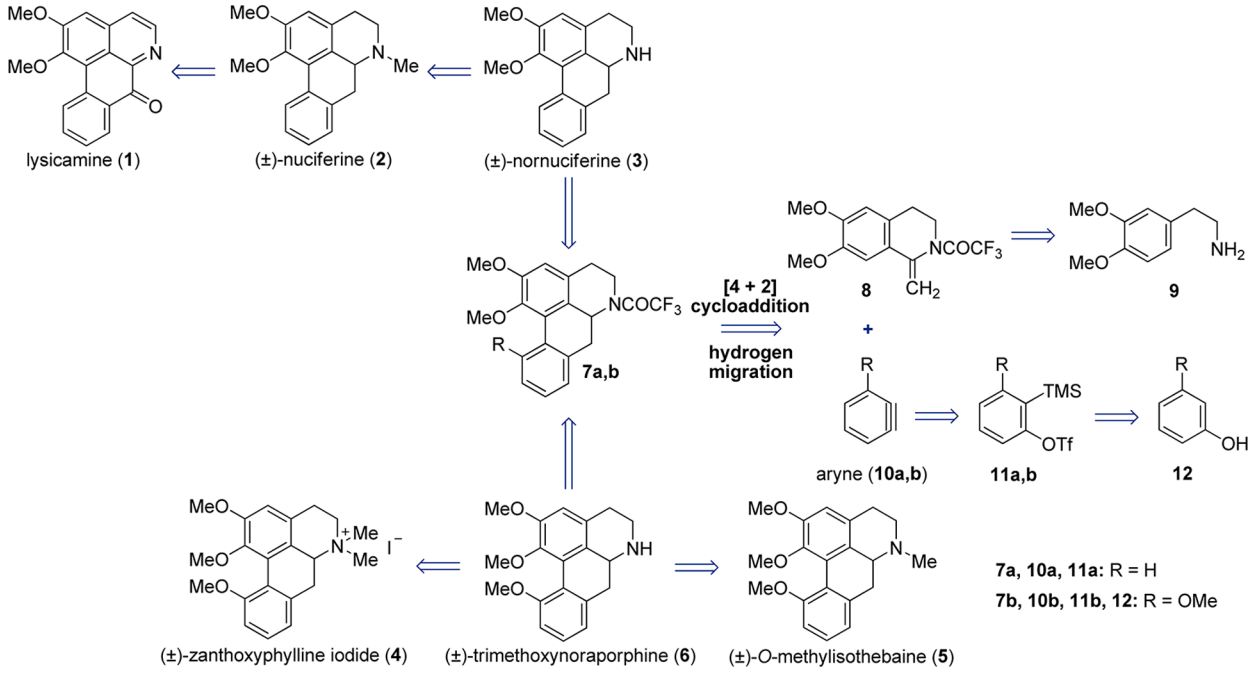
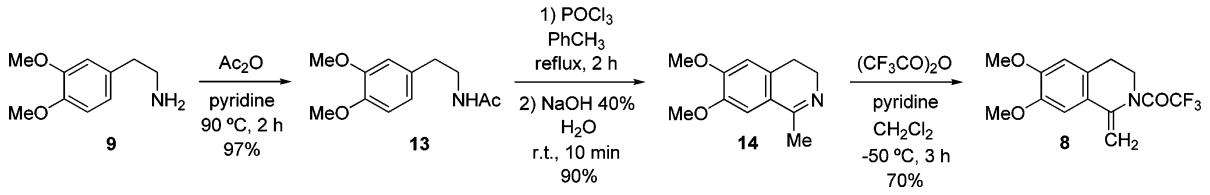
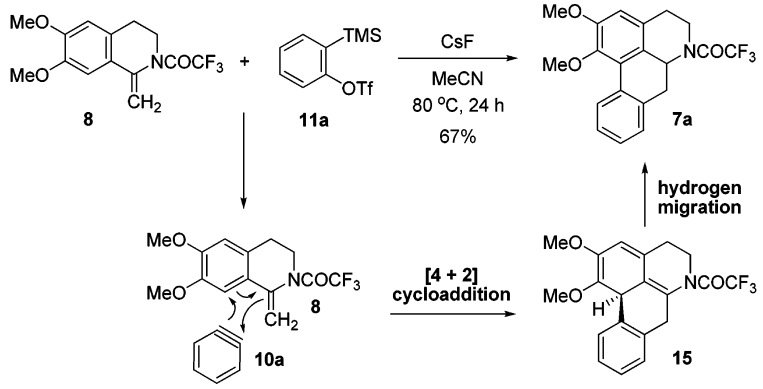
Scheme 1. Retrosynthetic Analysis for Aporphine Compounds



Scheme 2. Synthesis of Intermediate 8



Scheme 3. Synthesis and Proposed Mechanisms for the Aporphine Core 7a



approaches.[10] In this context, we conceived that reactions between an isoquinoline derivative (**8**) and arynes (**10**), formed from their silylaryl triflates (**11**) under almost neutral conditions, could directly provide aporphine cores (**7**) instead of dehydroaporphine skeletons, which have been accessed by arenediazonium-2-carboxylates under acidic conditions.[10]

RESULTS AND DISCUSSION

We disclose herein advances toward the direct formation of aporphine cores (**7**) with applications in concise syntheses of aporphine alkaloids. In this sense, our retrosynthetic analysis for lysicamine (**1**), (±)-nuciferine (**2**), (±)-nornuciferine (**3**), (±)-zanthoxyphylline iodide (**4**), (±)-*O*-methylisothebaine (**5**), and (±)-trimethoxynoraporphine (**6**) is outlined in Scheme 1.

Lysicamine (**1**), (±)-nuciferine (**2**), (±)-nornuciferine (**3**), (±)-zanthoxyphylline iodide (**4**), (±)-*O*-methylisothebaine (**5**), and (±)-trimethoxynoraporphine (**6**) are reached by reactions between an isoquinoline derivative (**8**) and silylaryl triflates (**11**), which promote the formation of aporphine cores (**7**) through [4 + 2] cycloadditions followed by hydrogen migrations (Scheme 1).

Intermediate **8** was prepared by minor modifications of well-established reactions.[10b,c,11−13] Commercially available amine **9** was treated with acetic anhydride in pyridine to produce corresponding amide **13** in 97% yield.[11] Amide **13** was

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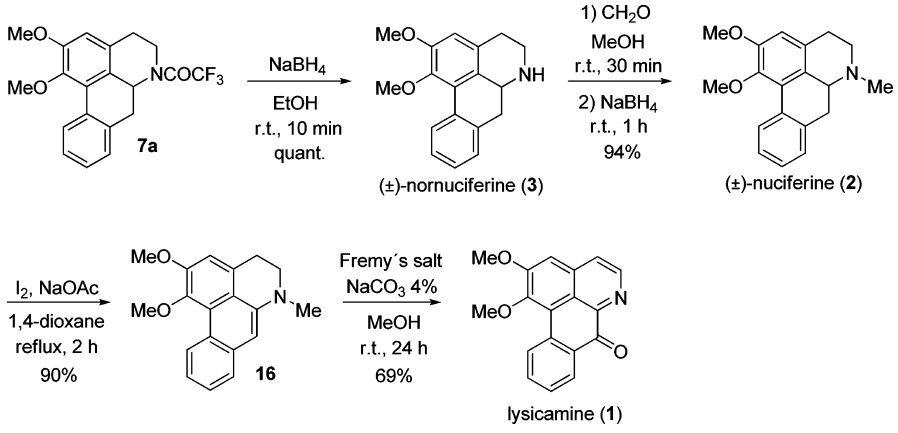
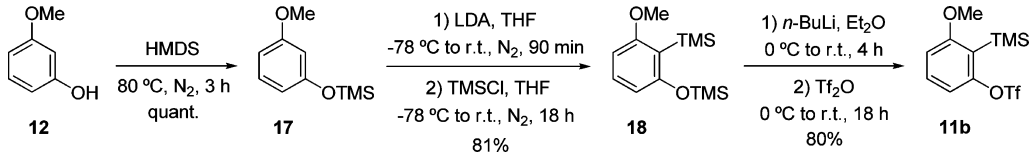
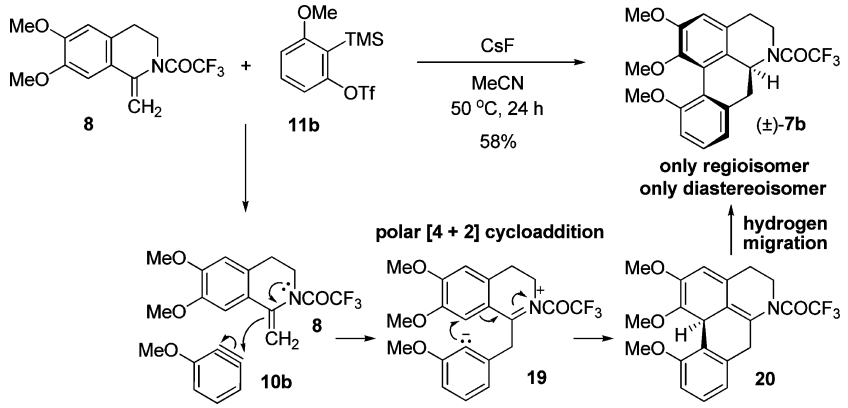
Scheme 4. Transformations for the Production of Aporphine Alkaloids 1−3



Scheme 5. Synthesis of Intermediate 11b



Scheme 6. Synthesis and Proposed Mechanisms for the Aporphine Core 7b



converted by Bischler−Napieralski reaction to heterocyclic intermediate **14** in 90% yield.[12] Compound **14** was allowed to react with trifluoroacetic anhydride in pyridine, leading to the formation of intermediate **8** in an isolated yield of 70%[10b,c,13] (Scheme 2).

Allowing the reaction between isoquinoline derivative **8** and 1.5 equiv of benzyne precursor **11a** in the presence of 3 equiv of CsF at room temperature for 24 h, intermediate **7a** was obtained in 43% yield. Performing the same reaction at 50 °C, compound **7a** was produced in an isolated yield of 50%. When the reaction was carried out at 80 °C, intermediate **7a** was obtained in a 67% yield. In these transformations, compounds **8** and **11a** were partially recovered. The corresponding dehydroaporphine, however, was not observed (Scheme 3).

Reaction between isoquinoline derivative **8** and 2-(trimethysilyl)phenyl triflate **11a** resulted in compound **7a** presumably by a sequence of transformations involving a [4 + 2] cycloaddition reaction followed by a hydrogen migration (Scheme 3).

Afterwards, intermediate **7a** was deprotected in the presence of $NaBH_4$[10b] to produce (±)-nornuciferine (**3**)[14] in a quantitative yield. Aporphine alkaloid **3** was *N*-alkylated employing formaldehyde and $NaBH_4$,[9a] leading to (±)-nuciferine (**2**)[15] in 94% yield. To demonstrate that oxoaporphine alkaloids can be achieved from intermediate **7a**, we subjected compound **2** to a reaction with I_2 and NaOAc,[16] leading to compound **16** in 90% yield, which was oxidized in the presence of Fremy's salt,[10b] affording lysicamine (**1**)[17] in 69% yield (Scheme 4).

(±)-Nornuciferine (**3**) was obtained after 6 steps with an overall yield of 41%; (±)-nuciferine (**2**) was synthesized in 7 steps with overall yield of 38%, and lysicamine (**1**) was achieved in 9 steps with an overall yield of 24%.

Intermediate **11b** was obtained employing the route outlined in Scheme 5.[18] 3-Methoxyphenol (**12**) was allowed to react with hexamethyldisilazane (HMDS) to give protected phenol **17** in quantitative yield. Compound **17** was treated with lithium diisopropylamide (LDA) and trimethylsilyl chloride (TMSCl) to produce disilylated intermediate **18** in an isolated yield of 81%. Intermediate **18** had its hydroxyl group deprotected in the presence of *n*-BuLi, and the resulting phenolate ion was trapped

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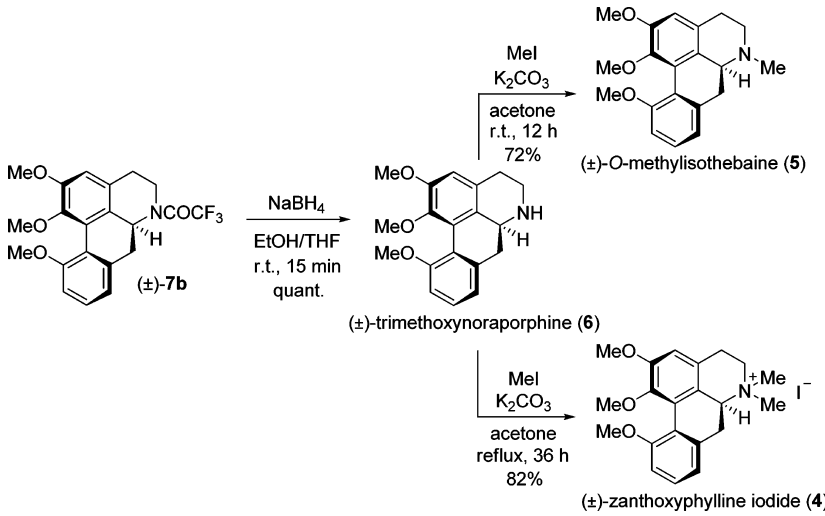
Scheme 7. Transformations for the Production of Aporphinoids 4−6



with triflic anhydride (Tf_2O), leading to intermediate **11b** in 80% yield (Scheme 5).[18]

Allowing the reaction between isoquinoline derivative **8** and 1.5 equiv of silylaryl triflate **11b** in the presence of 3 equiv of CsF at room temperature for 24 h, intermediate **7b** was obtained in 40% yield. Performing the same reaction at 50 °C, compound **7b** was produced in an isolated yield of 58%. When the reaction was carried out at 80 °C, no improvement in yield was observed, and intermediate **7b** was obtained in 55% yield. In these experiments, compounds **8** and **11b** were partially recovered, and the corresponding dehydroaporphine was not observed (Scheme 6).

Reaction between isoquinoline derivative **8** and silylaryl triflate **11b** produced compound **7b** as a single regio- and diastereoisomer[19] constituted by *P,S* and *M,R* enantiomers, presumably by a sequence of transformations involving a polar [4 + 2] cycloaddition reaction followed by a hydrogen migration (Scheme 6).

Afterwards, intermediate **7b** was deprotected in the presence of $NaBH_4$[10b] to produce (±)-trimethoxynoraporphine (**6**)[20] in quantitative yield. In this case, aporphine alkaloid **6** was *N*-alkylated and *N,N*-dialkyated employing MeI and K_2CO_3[21] to produce (±)-*O*-methylisothebaine (**5**)[22] and (±)-zanthoxyphylline iodide (**4**)[23] in yields of 72 and 82%, respectively (Scheme 7).

(±)-Trimethoxynoraporphine (**6**) was obtained after 6 steps with an overall yield of 35%. (±)-*O*-Methylisothebaine (**5**) and (±)-zanthoxyphylline iodide (**4**) were both synthesized in 7 steps with overall yields of 26 and 29%, respectively.

The structures of compounds **2**−**6**, **8**, **11b**, **13**, **14**, and **16**−**18** were assigned according to their LRMS, IR, ^1H, and ^{13}C NMR spectra. The structure of compound **1** was assigned according to its IR, ^1H, and ^{13}C NMR spectra. DEPT, COSY, and HSQC NMR spectra were obtained to confirm the structure of compound **4**. HRMS were obtained for compounds **1**, **4**, and **6**. The structure of compound **7a** was assigned according to its LRMS, HRMS, IR, ^1H, ^{13}C, DEPT, COSY, and HSQC NMR spectra. The structure of compound **7b** was assigned according to its LRMS, HRMS, IR, ^1H, ^{13}C, DEPT, COSY, HSQC, and HMBC NMR spectra and unambiguously confirmed by single-crystal X-ray diffraction (Supporting Information).

In summary, we have developed concise routes toward the syntheses of lysicamine (**1**), (±)-nuciferine (**2**), (±)-nornuciferine (**3**), (±)-zanthoxyphylline iodide (**4**), (±)-*O*-methylisothebaine (**5**), and (±)-trimethoxynoraporphine (**6**). Our approach involves the formation of aporphine cores (**7**) by reactions between isoquinoline derivative **8** and silylaryl triflates (**11**) promoted by CsF. The formation of aporphine cores (**7**) proceeded in good yields, presumably through [4 + 2] cycloaddition reactions followed by hydrogen migrations. The chemistry disclosed represents an advance for the synthesis of aporphine alkaloids, providing aporphine cores under mild reaction conditions, and should find an application in the preparation of other aporphinoids.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on spectrometers operating at 500 or 300 MHz. ^{13}C NMR spectra were recorded on spectrometers operating at 125 or 75 MHz. ^1H NMR spectra were taken in deuterated solvents, and the chemical shifts were given in ppm with respect to tetramethylsilane (TMS) used as an internal standard. ^{13}C NMR spectra were taken in deuterated solvents, and the chemical shifts were given in ppm with respect to deuterated solvents used as references. Infrared spectra were obtained using attenuated total reflectance (ATR) or KBr pellets in the 4000−400 cm^{-1} region. Mass spectra were carried out employing a gas chromatograph connected to a mass spectrometer using electron impact ionization at 70 eV or employing a liquid chromatograph connected to a mass spectrometer using an electrospray ionization source. High resolution mass spectra were obtained using a time-of-flight mass spectrometer. Melting point values are uncorrected. Column chromatography separations were carried out using 70−230 mesh silica gel. Preparative thin layer chromatography separations were carried out using silica gel matrix with inorganic binder and a fluorescent indicator. Commercially obtained reagents were employed without further purification. High purity cesium fluoride (99.99%) was used in the experiments. THF and diethyl ether were distilled from sodium/benzophenone under a nitrogen atmosphere before use.[24] *n*-Butyllithium (*n*-BuLi) was titrated against *sec*-butanol using 1,10-phenanthroline as an indicator under a nitrogen atmosphere.[25] Lithium diisopropylamide (LDA) was generated following a typical procedure before use.[26] Acetonitrile was distilled from calcium hydride under a nitrogen atmosphere prior to use.[24] Solvents were treated when necessary according to the literature.[24]

***N*-(3,4-Dimethoxyphenethyl)acetamide (13).**[11] To a round-bottomed flask were added 2-(3,4-dimethoxyphenyl)ethanamine (**9**) (10 mmol, 1.81 g, 1.70 mL), dry pyridine (11 mmol, 870 mg, 0.90

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mL), and acetic anhydride (11.5 mmol, 1.17 g, 1.10 mL). The round-bottomed flask was capped with a rubber septum, and the reaction mixture was maintained under stirring at 90 °C for 2 h. After that, the reaction was poured into a beaker containing crushed ice (50 g), and concentrated HCl (15 mL) was added. The resulting mixture was stirred with a glass rod for 5 min. Afterwards, a saturated aqueous solution of $NaHCO_3$ (50 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with a saturated aqueous solution of $CuSO_4$ (50 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording desired product **13**. R_f = 0.81 (eluent, methanol); yield: 2.16 g (97%); off-white solid; mp 99−100 °C (lit.[27] mp 99−100 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (dd, J = 5.6, 3.0 Hz 1H), 6.73 (dd, J = 5.8, 2.0 Hz, 2H), 5.96 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.48 (q, J = 6.7 Hz, 2H), 2.76 (t, J = 7.1 Hz, 2H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 148.8, 147.4, 131.2, 120.4, 111.7, 111.2, 55.7, 55.6, 40.6, 35.0, 23.0; IR (KBr, cm^{-1}) 3251.9, 3080.3, 2972.3, 2927.9, 1633.7, 1608.6, 1566.2, 1516.0, 1417.6, 1377.1, 1261.4, 1035.7; GC/MS (m/z, %): 223 (7.3), 180 (0.3), 164 (100.0), 151 (41.6), 121 (4.1), 108 (3.4), 107 (7.9).

Procedure for preparation of intermediate salt and compound 14.[12] To a round-bottomed flask were added *N*-(3,4-dimethoxyphenethyl)acetamide (**13**) (4 mmol, 892 mg) and toluene (4.5 mL). The round-bottomed flask was equipped with a reflux condenser and capped with a rubber septum. The mixture was heated at 40 °C under stirring and anhydrous conditions. After that, $POCl_3$ (9.6 mmol, 1.47 g, 0.88 mL) was added dropwise using syringe and needle. The rubber septum was substituted by a glass cap and the reaction mixture was refluxed for 2 h. Then, the mixture was cooled with an ice bath for 4 h. The solvent was evaporated under reduced pressure, affording an intermediate salt. Afterwards, the intermediate salt was dissolved in water (10 mL) and a 40% (w/v) aqueous solution of NaOH (10 mL) was added to the mixture, which was maintained under stirring for 10 min. The mixture was extracted with $CHCl_3$ (3 × 20 mL). The organic phase was washed with distilled water (10 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording the desired product **14**.

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinolinium phosphorodichloridate (intermediate salt). R_f = 0.13 (eluent, methanol); yield, 1.36 g (quantitative); yellowish solid; mp 146−149 °C (lit.[12] mp 148−152 °C); ^{1}H NMR (300 MHz, D_2O) δ 7.14 (s, 1H), 6.87 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.71 (t, J = 7.5 Hz, 2H), 2.94 (t, J = 8.1 Hz, 2H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, D_2O) δ 175.3, 155.5, 147.4, 134.0, 117.6, 111.7, 110.8, 56.2, 55.9, 40.8, 24.3, 19.6; IR (KBr, cm^{-1}) 3431.3, 3205.6, 3089.6, 3055.2, 2972.3, 2927.9, 2891.3, 1664.5, 1602.8, 1566.2, 1516.0, 1427.3, 1346.3, 1217.0, 1165.0, 1068.5, 1012.6; LC/MS (m/z, %) ESI-(+) 206.3 (100.0), 190.2 (60.2), 174.4 (16.2), 162.2 (8.1), 144.1 (16.2), 132.3 (32.4), and ESI-(−) 137.1 (18.1), 135.0 (63.3), 133.0 (100.0).

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (14). R_f = 0.38 (eluent, methanol); yield, 738 mg (90%); brownish solid; mp 102−103 °C (lit.[28] mp 100−102 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.69 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.63 (tq, J = 7.6, 1.4 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 2.37 (t, J = 1.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 150.8, 147.3, 131.0, 122.4, 110.1, 108.9, 56.1, 55.9, 46.9, 25.6, 23.3; IR (KBr, cm^{-1}) 2993.5, 2962.6, 2922.1, 1602.8, 1514.1, 1408.4, 1350.1, 1213.2, 1060.8; GC/MS (m/z, %) 205 (100.0), 190 (57.9) 174 (21.5), 160 (21.4), 147 (12.8), 132 (4.3).

1-(6,7-Dimethoxy-1-methylene-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethanone (8).[10b,c,13] To a round-bottomed flask capped with a rubber septum were added 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**14**) (1 mmol, 205 mg) and a solution of dry pyridine (1.25 mmol, 98.9 mg) in CH_2Cl_2 (3.1 mL). The mixture was cooled to −50 °C under stirring and a nitrogen atmosphere. A solution of trifluoroacetic anhydride (1.25 mmol, 263 mg) in CH_2Cl_2 (0.75 mL) was added dropwise using a syringe and needle. The reaction mixture was maintained at −50 °C under stirring and a nitrogen atmosphere for 3 h. Afterwards, the reaction was diluted with CH_2Cl_2 (10 mL) and washed with distilled water (10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent, affording desired product **8**. R_f = 0.60 (eluent, dichloromethane); yield, 211 mg (70%); off-white solid; mp 83−85 °C (lit.[13] mp 80 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.59 (s, 1H), 5.62 (s, 1H), 5.24 (s, 1H), 4.04 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 2.94 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (q, J = 35.8 Hz), 150.1, 148.1, 126.3, 123.4, 116.5 (q, J = 286.5 Hz), 111.1, 106.8, 106.6, 106.5, 56.0, 55.9, 44.6, 28.4; IR (KBr, cm^{-1}) 3014.7, 2962.6, 2931.8, 1697.3, 1608.6, 1512.1, 1438.9, 1338.6, 1273.0, 1132.2, 1033.8; GC/MS (m/z, %): 301 (82.0), 286 (5.7), 270 (3.5), 232 (100.0), 204 (59.1).

2,2,2-Trifluoro-1-(1,2-dimethoxy-6a,7-dihydro-4*H*-dibenzo[*de*,*g*]quinolin-6(5*H*)-yl)ethanone (7a). To a vial (20 mL) were added heterocyclic compound **8** (0.3 mmol, 90.3 mg), silylaryl triflate **11a** (0.45 mmol, 134 mg), acetonitrile (5 mL), and CsF (0.9 mmol, 137 mg). The vial was sealed using a cap, and the mixture was stirred at 80 °C for 24 h. Afterwards, brine (10 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using CH_2Cl_2 as eluent, affording desired product **7a**. R_f = 0.68 (eluent, dichlorometane); yield, 75.8 mg (67%); off-white solid; mp 156−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 7.8 Hz, 1H), 7.37−7.26 (m, 3H), 6.68 (s, 1H), 5.03 (dd, J = 13.7, 4.0 Hz, 1H), 4.25−4.20 (m, 1H), 3.90 (s, 3H), 3.68 (s, 3H), 3.36 (td, J = 12.9, 2.3 Hz, 1H), 2.74−3.09 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8 (q, J = 35.3 Hz), 152.4, 146.1, 135.7, 131.3, 128.6, 128.5, 128.3, 128.0, 127.7, 127.3, 124.5, 116.3 (q, J = 285.0 Hz), 111.2, 60.0, 55.9, 52.2, 41.1, 33.5, 30.3; IR (KBr, cm^{-1}) 2933.7, 2617.4, 1678.1, 1608.6, 1593.2, 1423.5, 1373.3, 1259.5, 1197.8, 1141.9, 927.8, 655.8; GC/MS (m/z, %) 377 (49.0), 308 (5.5), 281 (4.3), 251 (100.0), 165 (28.6); HRMS calcd for $[C_{20}H_{18}F_3NO_3 + H]^+$ 378.1312, found 378.1311.

1,2-Dimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]-quinoline (3).[10b] To a round-bottomed flask capped with a rubber septum were added compound **7a** (0.18 mmol, 67.9 mg) and ethanol (10 mL). The resulting suspension was maintained under stirring until complete solubilization of compound **7a**. Then, $NaBH_4$ (1.8 mmol, 68.1 mg) was added, and the reaction mixture was maintained at room temperature under stirring and a nitrogen atmosphere for 10 min. Afterwards, the ethanol was evaporated under reduced pressure, and brine (10 mL) was added to the residue, which was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording alkaloid **3**.[14] R_f = 0.26 (eluent, methanol); yield, 50.4 mg (quantitative); off-white solid; mp 124−125 °C (lit.[14] mp 128−129 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 7.8 Hz, 1H), 7.19−7.11 (m, 3H), 6.54 (s, 1H), 3.77 (s, 3H), 3.70 (dd, J = 13.4, 4.5 Hz, 1H), 3.57 (s, 3H), 3.23−3.26 (m, 1H), 2.95−2.83 (m, 2H), 2.76−2.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 145.2, 136.2, 132.2, 128.9, 128.9, 128.4, 127.8, 127.4, 127.0, 126.6, 111.9, 60.3, 55.9, 53.6, 43.2, 37.5, 29.2; IR (KBr, cm^{-1}) 3324.5, 2928.1, 2835.5, 2316.6, 1593.3, 1451.5, 1423.5, 1251.9, 1248.0, 1034.8, 754.2; GC/MS (m/z, %) 281 (49.3), 280 (100.0), 264 (17.7), 250 (22.2), 236 (18.0), 221 (16.2), 165 (16.0).

1,2-Dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo-[*de*,*g*]quinolone (2).[9a] To a round-bottomed flask were added nornuciferine (**3**) (0.14 mmol, 39.3 mg), methanol (3.8 mL), and a 37% (w/v) aqueous solution of CH_2O (1.1 mL). The reaction mixture was stirred at room temperature for 30 min. Then, $NaBH_4$ (2.8 mmol, 106 mg) was added, and the mixture was stirred at room temperature for 1 h. Afterwards, brine (10 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using methanol as eluent, affording alkaloid **2**.[15] R_f = 0.60 (eluent, methanol); yield, 38.7 mg (94%); yellowish solid; mp 168−169 °C (lit.[15] mp 165.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 7.8 Hz, 1H), 7.25−7.16 (m, 3H), 6.56 (s,

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1H), 3.81 (s, 3H), 3.57 (s, 3H), 3.12−2.98 (m, 4H), 2.50 (s, 1H), 2.42−2.66 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 144.9, 136.1, 131.9, 128.4, 128.2, 127.8, 127.3, 127.2, 127.0, 126.7, 110.9, 62.1, 60.2, 55.7, 53.0, 43.7, 34.7, 28.8; IR (KBr, cm^{-1}) 2950.1, 2930.8, 2834.4, 1594.2, 1451.4, 1321.2, 1301.0, 1249.9, 1035.8; GC/MS (*m*/*z*, %) 295 (32.0), 293 (100.0), 278 (45.6), 264 (16.9), 250 (18.3), 235 (34.9).

1,2-Dimethoxy-6-methyl-5,6-dihydro-4*H*-dibenzo[*de*,*g*]-quinolone (16).[16] A solution of iodine (0.12 mmol, 30.5 mg) in dioxane (2.9 mL) was added dropwise to a refluxing suspension of nuciferine (**2**) (0.12 mmol, 36.3 mg) and anhydrous NaOAc (0.48 mmol, 38.7 mg) in dioxane (2.1 mL). The reaction mixture was refluxed under stirring and anhydrous conditions for 2 h. Afterwards, the solvent was evaporated under reduced pressure. To the residue was added a saturated aqueous solution of $Na_2S_2O_3$ (10 mL), and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using methanol/ethyl acetate (1:1) as eluent, affording desired product **16**. R_f = 0.68 (eluent, methanol); yield, 31.7 mg (90%); brownish solid; mp 128−130 °C (lit.[16] mp 130−131 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (d, J = 8.4 Hz, 1H), 7.56 (dd, J = 8.0, 1.1 Hz, 1H), 7.37 (td_{ap}, J = 7.4, 1.0 Hz, 1H), 7.25 (td_{ap}, J = 7.7, 1.5 Hz, 1H), 6.93 (s, 1H), 6.55 (s, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.28 (t_{ap}, J = 6.0 Hz, 2H), 3.18 (t_{ap}, J = 6.0 Hz, 2H), 3.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 145.8, 134.6, 129.0, 127.7, 126.9, 126.5, 125.8, 124.8, 123.0, 119.0, 111.5, 59.7, 56.4, 50.3, 40.7, 30.7; IR (KBr, cm^{-1}) 2926.0, 2880.7, 1559.5, 1448.5, 1423.5, 1332.8, 1199.7, 1117.8, 1003.0, 826.5; GC/MS (*m*/*z*, %) 293 (100.0), 278 (43.8), 263 (15.5), 250 (21.8), 235 (47.0).

1,2-Dimethoxy-7*H*-dibenzo[*de*,*g*]quinolin-7-one (1).[10b] To a solution of dehydronuciferine (**16**) (0.072 mmol, 21.2 mg) in methanol (10 mL) was added Fremy's salt ($(KSO_3)_2NO$, 0.72 mmol, 193 mg) in a 4% (w/v) aqueous solution of Na_2CO_3 (5 mL). The reaction mixture was maintained under stirring at room temperature for 24 h. Afterwards, brine (10 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using methanol as eluent to afford alkaloid **1**.[17] R_f = 0.68 (eluent, methanol); yield, 14.4 mg (69%); yellowish solid; mp 204−206 °C (dec) (lit.[17] mp 210−211 °C (dec)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (d, J = 8.3 Hz, 1H), 8.91 (d, J = 5.2 Hz, 1H), 8.60 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 5.1 Hz, 1H), 7.76 (d, J = 7.32 Hz, 1H), 7.58 (t_{ap}, J = 6.0 Hz, 1H), 7.23 (s, 1H), 4.11 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7, 156.9, 152.1, 145.3, 144.9, 135.5, 134.4, 134.3, 132.1, 128.9, 128.8, 128.5, 123.6, 122.2, 119.80, 106.5, 56.2, 50.8; IR (KBr, cm^{-1}) 3309.9, 2922.2, 2848.9, 1670.4, 1483.3, 1305.8, 1261.5, 1043.5, 869.9, 746.5; HRMS calcd for $[C_{18}H_{13}NO_3 + H]^+$ 292.0968, found 292.0973.

(3-Methoxyphenoxy)trimethylsilane (17).[18] To a round-bottomed flask capped with a rubber septum were added 3-methoxyphenol (**12**) (10 mmol, 1.24 g, 1.4 mL) and hexamethyldisilazane (HMDS) (15 mmol, 2.42 g, 3.2 mL). The reaction mixture was maintained at 80 °C under stirring and a nitrogen atmosphere for 3 h. The volatile substances were removed under reduced pressure, affording desired product **17**. R_f = 0.39 (eluent, hexane/dichlorometane (3:1)); yield, 1.96 g (quantitative); yellowish oil;[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (t, J = 8.1 Hz, 1H), 6.53 (ddd, J = 8.3, 2.4, 0.8 Hz, 1H), 6.45 (ddd, J = 8.0, 2.2, 0.8 Hz, 1H), 6.41 (t, J = 2.3 Hz, 1H), 3.76 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 156.3, 129.7, 112.5, 107.0, 106.2, 55.2, 0.2; IR (ATR, cm^{-1}) 3066.8, 3001.2, 2958.8, 2900.9, 2835.3, 1597.0, 1489.0, 1450.4, 1253.7, 1041.5, 840.9; GC/MS (*m*/*z*, %) 196 (54.6), 181 (100.0), 151 (15.5), 135 (2.1), 121 (4.7), 107 (2.4), 89 (12.2).

(3-Methoxy-2-(trimethylsilyl)phenoxy)trimethylsilane (18).[18] To a round-bottomed flask capped with a rubber septum were added (3-methoxyphenoxy)trimethylsilane (**17**) (5 mmol, 981 mg) and THF (7.5 mL). The mixture was cooled to −78 °C under stirring and a nitrogen atmosphere. Then, LDA (5.5 mmol, 10 mL of a 0.55 mol L^{-1} solution in THF) was added dropwise using a syringe and needle. The reaction mixture was heated to and maintained at room temperature for 90 min. After that, the mixture was cooled to −78 °C under stirring and a nitrogen atmosphere. Then, trimethylsilyl chloride (TMSCl, 6 mmol, 648 mg, 0.76 mL) was added. The reaction mixture was heated to and maintained at room temperature for 18 h. Afterwards, a saturated aqueous solution of NH_4Cl (50 mL) was added to the reaction, which was extracted with ethyl acetate (3 × 50 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/CH_2Cl_2 (3:1) as eluent, affording desired product **18**. R_f = 0.69 (eluent, hexane/dichlorometane (3:1)); yield, 1.09 g (81%); colorless oil;[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, J = 8.2 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 6.41 (d, J = 8.1 Hz, 1H), 3.73 (s, 3H), 0.30 (s, 9H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 161.2, 130.8, 116.7, 110.8, 103.2, 55.1, 1.5, 0.7; IR (ATR, cm^{-1}) 3082.2, 3051.3, 2954.9, 2897.0, 2831.5, 1570.1, 1431.1, 1234.4, 1087.8, 833.2; GC/MS (*m*/*z*, %) 268 (40.9), 253 (100.0), 238 (7.8), 237 (16.5), 163 (6.2), 133 (11.7), 105 (16.9), 89 (7.0), 73 (38.8).

3-Methoxy-2-(trimethylsilyl)phenyl Trifluoromethanesulfonate (11b).[18] To a round-bottomed flask capped with a rubber septum were added (3-methoxy-2-(trimethylsilyl)phenoxy)-trimethylsilane (**18**) (1 mmol, 268 mg) and diethyl ether (10 mL). The mixture was cooled to 0 °C under stirring and a nitrogen atmosphere. Then, *n*-BuLi (1.1 mmol, 0.75 mL of a 1.47 mol L^{-1} solution in hexane) was added dropwise using a syringe and needle. The reaction mixture was heated to and maintained at room temperature for 4 h. After that, the mixture was cooled to 0 °C under stirring and anhydrous conditions. Then, triflic anhydride (2 mmol, 564 mg, 0.37 mL) was added. The reaction mixture was heated to and maintained at room temperature for 18 h. Afterwards, a 10% (w/v) aqueous solution of $NaHCO_3$ (10 mL) was added to the reaction, which was extracted with diethyl ether (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/CH_2Cl_2 (2:1) as eluent, affording desired product **11b**. R_f = 0.59 (eluent, hexane/dichlorometane (2:1)); yield, 262 mg (80%); colorless oil;[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (t, J = 8.3 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 3.82 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 154.7, 131.6, 120.8, 118.6 (q, J = 320.7 Hz), 112.7 (q, J = 1.5 Hz), 109.5, 55.6, 0.75; IR (ATR, cm^{-1}) 2956.8, 2900.9, 2839.2, 1597.0, 1458.1, 1415.7, 1284.5, 1247.9, 1161.1, 1138.0, 1047.3, 932.9, 825.5; GC/MS (*m*/*z*, %) 328 (1.1), 313 (91.7), 180 (100.0), 165 (17.2), 105 (21.2).

2,2,2-Trifluoro-1-(1,2,11-trimethoxy-6a,7-dihydro-4*H*-dibenzo[*de*,*g*]quinolin-6(5*H*)-yl)ethanone (7b). To a vial (20 mL) were added heterocyclic compound **8** (0.3 mmol, 90.3 mg), silylaryl triflate **11b** (0.45 mmol, 148 mg), acetonitrile (5 mL), and CsF (0.9 mmol, 137 mg). The vial was sealed using a cap, and the mixture was stirred at 50 °C for 24 h. Afterwards, brine (10 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using CH_2Cl_2 as eluent. The solid obtained after chromatography was washed with cold methanol, affording compound **7b**. R_f = 0.55 (eluent, dichloromethane); yield, 70.8 mg (58%); off-white solid; mp 218−219 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 7.9 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 7.4 Hz, 1H), 6.67 (s, 1H), 4.89 (dd, J = 13.0, 3.3 Hz, 1H), 4.22 (d, J = 13.3 Hz, 1H), 3.90 (s, 3H), 3.90 (s, 3H), 3.64 (s, 3H), 3.30 (td, J = 13.0, 2.3 Hz, 1H), 2.97−2.91 (m, 2H), 2.77−2.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 156.0 (q, J = 35.6 Hz), 152.2, 146.3, 138.3, 128.9, 126.7, 125.5, 125.2, 120.3, 116.3 (q, J = 288.3 Hz), 111.1, 110.4, 77.2, 60.7, 55.9, 55.7, 52.4, 41.4, 34.6, 29.9; IR (KBr, cm^{-1}) 2995.5, 2956.9, 2835.4, 1691.6, 1606.7, 1465.9, 1433.1, 1365.6, 1271.1, 1227.0, 1172.7, 1141.9, 1045.4, 929.7, 817.8, 841.0; GC/MS (*m*/*z*, %) 407 (91.8), 392 (2.4), 361 (1.6), 338 (4.9), 307

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(3.7), 281 (100.0), 279 (5.3), 191 (8.3), 126 (4.6); HRMS calcd for $[C_{21}H_{20}F_3NO_4 + H]^+$ 408.1417, found 408.1415.

1,2,11-Trimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]-quinoline (6).[10b] To a round-bottomed flask capped with a rubber septum were added compound **7b** (0.1 mmol, 40.8 mg) and THF (5 mL). The resulting suspension was maintained under stirring until complete solubilization of compound **7b**. Then, ethanol (5 mL) and $NaBH_4$ (0.3 mmol, 11.4 mg) were added, and the reaction mixture was maintained at room temperature under stirring and a nitrogen atmosphere for 15 min. Afterwards, the mixture of solvents was evaporated under reduced pressure, and brine (10 mL) was added to the residue, which was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording alkaloid **6**.[20] R_f = 0.25 (eluent, metanol); yield, 31.1 mg (quantitative); off-white solid; mp 162−163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, J = 7.9 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 6.66 (s, 1H), 4.01 (s, 1H), 3.87 (s, 6H), 3.74 (dd, J = 12.4, 1.7 Hz, 1H), 3.61 (s, 3H), 3.45−3.37 (m, 1H), 3.10−2.97 (m, 2H), 2.86 (dd, J = 13.7, 3.7 Hz, 1H), 2.79−2.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 152.0, 145.7, 138.2, 129.0, 128.3, 127.0, 124.1, 121.1, 119.7, 111.5, 110.1, 60.8, 55.9, 55.6, 53.9, 42.6, 37.7, 28.0; IR (KBr, cm^{-1}) 3431.4, 2991.6, 2935.7, 2831.5, 1591.3, 1462.0, 1423.5, 1269.2, 1248.0, 1037.7; GC/MS (m/z, %) 311 (51.9), 310 (36.3), 296 (73.7), 280 (100.0), 265 (32.6); HRMS calcd for $[C_{19}H_{21}NO_3 + H]^+$ 312.1594, found 312.1610.

1,2,11-Trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (5).[21] To a round-bottomed flask capped with a rubber septum were added trimethoxynoraporphine (**6**) (0.1 mmol, 31.1 mg), K_2CO_3 (0.2 mmol, 27.6 mg), acetone (4 mL), and methyl iodide (0.15 mmol, 21.3 mg, 9.4 μL). The reaction mixture was maintained at room temperature under stirring and nitrogen atmosphere for 6 h. Afterwards, brine (10 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using methanol as eluent to afford alkaloid **5**.[22] R_f = 0.54 (eluent, methanol); yield, 23.4 mg (72%); yellowish solid; mp 147−149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, J = 7.7 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 7.0 Hz, 1H), 6.67 (s, 1H), 3.88 (s, 6H), 3.76 (dd, J = 13.5, 3.0 Hz, 1H), 3.61 (s, 3H), 3.50−3.40 (m, 1H), 3.10−2.95 (m, 2H), 2.89 (dd, J = 13.6, 3.5 Hz, 1H), 2.80−2.60 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 152.1, 145.7, 138.1, 128.8, 128.4, 127.0, 124.1, 121.1, 119.7, 111.5, 110.2, 60.8, 55.9, 55.7, 54.0, 42.7, 37.7, 29.7, 28.0; IR (KBr, cm^{-1}) 2935.7, 2831.5, 1591.3, 1458.2, 1423.5, 1269.2, 1247.9, 1037.7; GC/MS (m/z, %) 325 (43.3), 324 (20.8), 310 (77.7), 294 (100.0), 279 (36.3).

1,2,11-Trimethoxy-6,6-dimethyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinolin-6-ium Iodide (4).[21] To a round-bottomed flask were added trimethoxynoraporphine (**6**) (0.1 mmol, 31.1 mg), K_2CO_3 (200 mg), acetone (8 mL), and methyl iodide (2 mL). The round-bottomed flask was equipped with a reflux condenser and capped with a glass cap. The mixture was maintained under reflux, stirring, and a nitrogen atmosphere for 36 h. Afterwards, the mixture was evaporated under reduced pressure. The material obtained was washed with distilled water (3 × 3 mL) and separated by centrifugation (4000 rpm for 10 min), affording desired product **4**.[23] Yield, 38.2 mg (82%); off-white solid; mp 248−250 °C (lit.[23] mp 256 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.33 (t, J = 7.9 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.96 (s, 1H), 4.48 (dd, J = 13.3, 1.9 Hz, 1H), 3.85 (s, 3H), 3.83−3.77 (m, 4H), 3.72−3.64 (m, 4H), 3.39−3.36 (m, 4H), 3.23 (ddd, J = 17.1, 12.2, 5.2 Hz, 1H), 3.00 (dd, J = 18.3, 4.0 Hz, 1H), 2.90 (s, 3H), 2.73 (t, J = 13.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 156.8, 153.1, 146.4, 135.4, 129.6, 124.1, 123.4, 121.8, 120.2, 120.1, 111.5, 68.4, 60.9, 60.6, 56.3, 56.0, 53.6, 43.4, 30.5, 23.4; IR (KBr, cm^{-1}) 2999.3, 2926.0, 2833.4, 1593.2, 1454.3, 1425.4, 1273.0, 1248.0, 1035.8; LC/MS (m/z, %) ESI-(+) 341.3 (100.0) and ESI-(−) 127.1 (100.0); HRMS calcd for $[C_{21}H_{26}NO_3]^+$ 340.1913, found 340.1924.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01634.

Copies of NMR spectra and single-crystal X-ray diffraction data (PDF)

CIF file for **7b** (CIF)

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Notes

The authors declare no competing financial interest.

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