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

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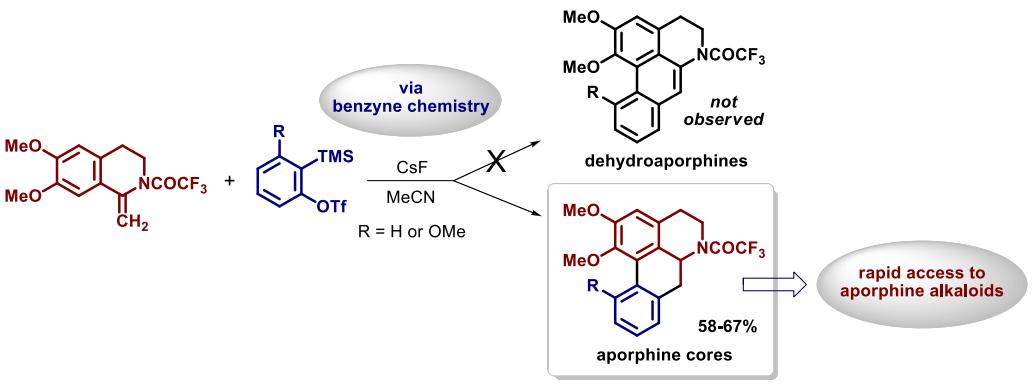


ABSTRACT: Total syntheses of lysicamine, (±)-nuciferine, (±)-nornuciferine, (±)-zanthoxyphylline iodide, (±)-*O*-methylisothebaine and (±)-trimethoxynoraporphine were accomplished by approach which involves the formation of aporphine cores by reactions between isoquinoline derivative and silylaryl triflates 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 plants of several families.[1] In terms of structural features, aporphine skeletons are constituted by four rings (A-D), with 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 aporphine prototype, has currently been employed in Parkinson's disease therapy[5] and erectile dysfunction treatment[6] (**Figure 1**).

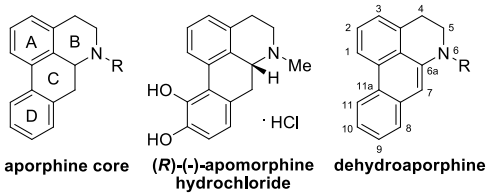


Figure 1. Examples of aporphine structures.

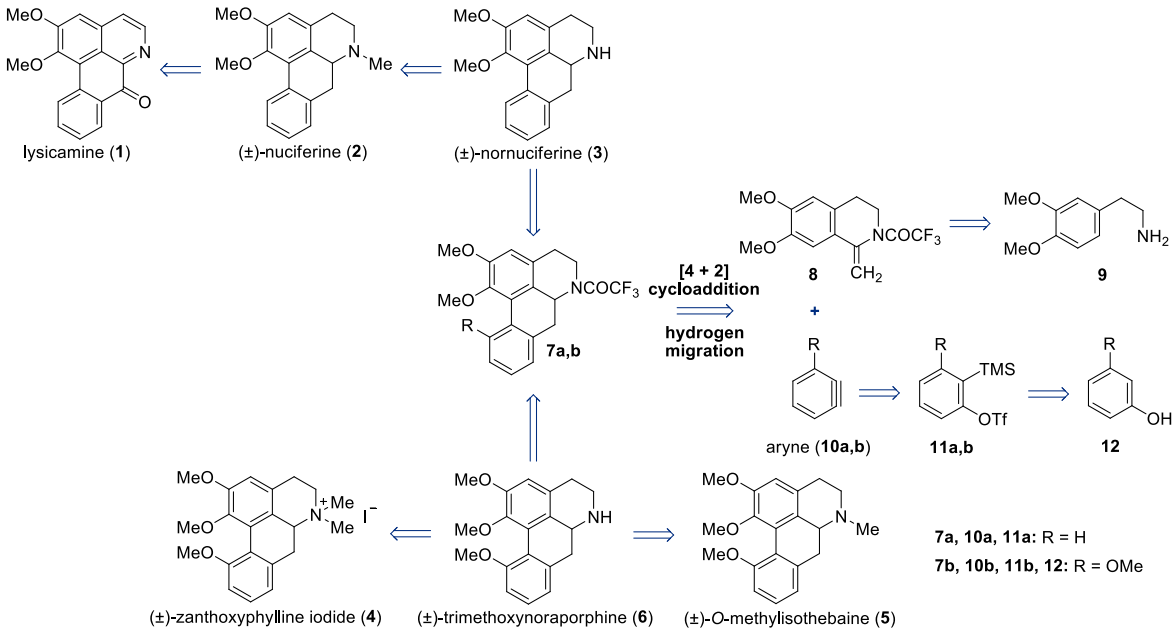
Due to the enormous pharmacological potential of aporphinoids, several synthetic approaches for production of aporphine cores have been reported in the literature.[7-10] Among all approaches for the production of aporphine alkaloids, those based on biosynthetic routes have in common the construction 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 by [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. On the other hand, 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 arynes 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 approaches.[10] In this context, we conceived that reactions between 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 direct formation of aporphine cores (**7**) with application 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**.

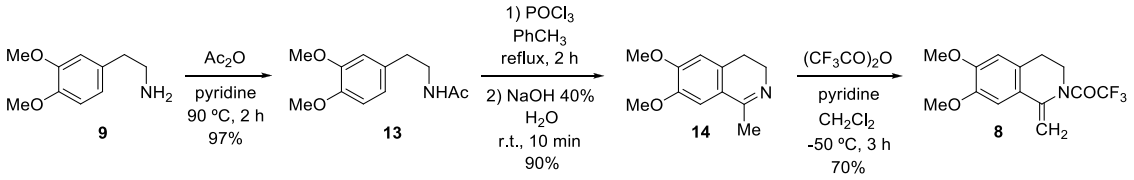
Scheme 1. Retrosynthetic analysis for aporphine compounds.



Lysicamine (**1**), (±)-nuciferine (**2**), (±)-nornuciferine (**3**), (±)-zanthoxyphylline iodide (**4**), (±)-*O*-methylisothebaine (**5**) and (±)-trimethoxynoraporphine (**6**) are reached by reactions between 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**).

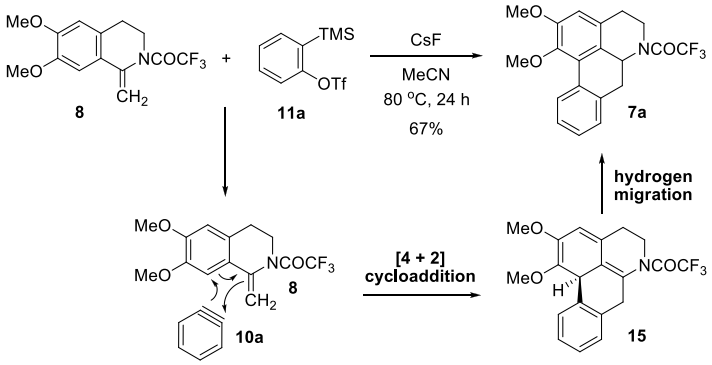
Intermediate **8** was prepared by minor modifications of well-established reactions.[10b,c,11-13] Commercially available amine (**9**) was treated with acetic anhydride in pyridine to produce the corresponding amide **13** in a 97% yield.[11] Amide **13** was converted by Bischler-Napieralski reaction to the heterocyclic intermediate **14** in a 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**).

Scheme 2. Synthesis of intermediate **8**.



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 hours, intermediate **7a** was obtained in a 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. Besides, the corresponding dehydroaporphine was not observed (**Scheme 3**).

Scheme 3. Synthesis and proposed mechanisms for the aporphine core **7a**.

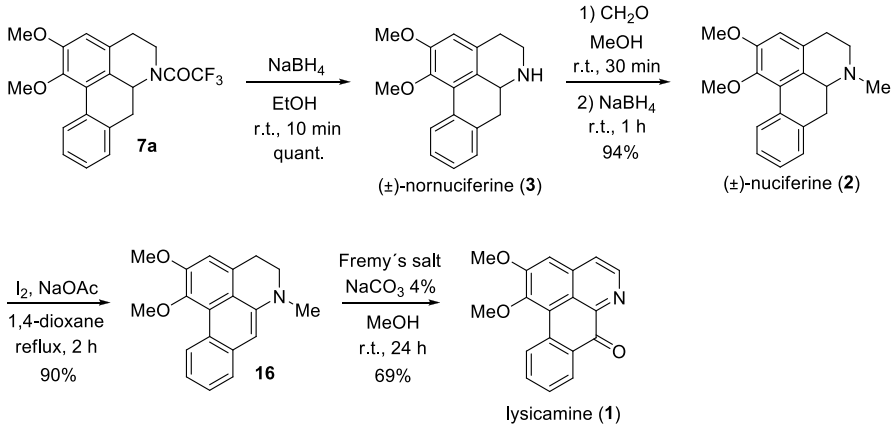


Reaction between isoquinoline derivative (**8**) and 2-(trimethysilyl)phenyl triflate (**11a**) resulted in compound **7a** presumably by sequence of transformations involving a [4 + 2] cycloaddition reaction followed by a hydrogen migration (**Scheme 3**).

Afterwards, intermediate **7a** was deprotected in the presence of $NaBH_4$[10b] to produce (±)-nornuciferine (**3**)[14] in quantitative yield. Aporphine alkaloid **3** was *N*-

alkylated employing formaldehyde and $NaBH_4$[9a] leading to (±)-nuciferine (**2**)[15] in a 94% yield. In order to demonstrate that oxoaporphine alkaloids can be achieved from the intermediate **7a**, compound **2** was subjected to reaction with I_2 and NaOAc[16] leading to the compound **16** in a 90% yield, which was oxidized in the presence of Fremy´s sat[10b] affording lysicamine (**1**)[17] in a 69% yield (**Scheme 4**).

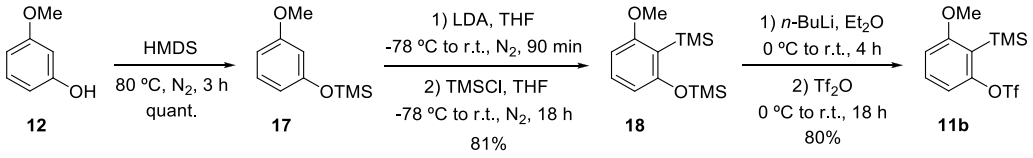
Scheme 4. Transformations for production of aporphine alkaloids **1**, **2** and **3**.



(±)-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 overall yield of 24%.

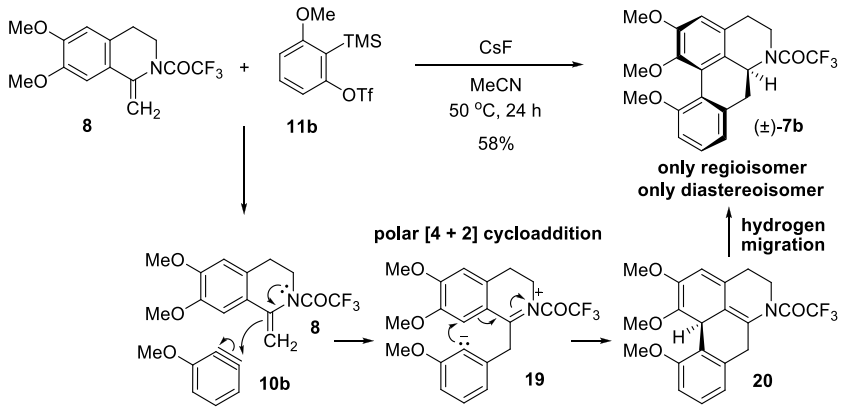
Intermediate **11b** was obtained employing route outlined in **Scheme 5**.[18] 3-Methoxyphenol (**12**) was allowed to react with hexamethyldisilazane (HMDS) to give the protected phenol **17** in quantitative yield. Compound **17** was treated with lithium diisopropylamide (LDA) and trimethylsilyl chloride (TMSCl) to produce the 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 with triflic anhydride (Tf_2O), leading to the intermediate **11b** in an 80% yield (**Scheme 5**).[18]

Scheme 5. Synthesis of intermediate **11b**.



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 hours, intermediate **7b** was obtained in a 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 the intermediate **7b** was obtained in a 55% yield. In these experiments, compounds **8** and **11b** were partially recovered and the corresponding dehydroaporphine was not observed (**Scheme 6**).

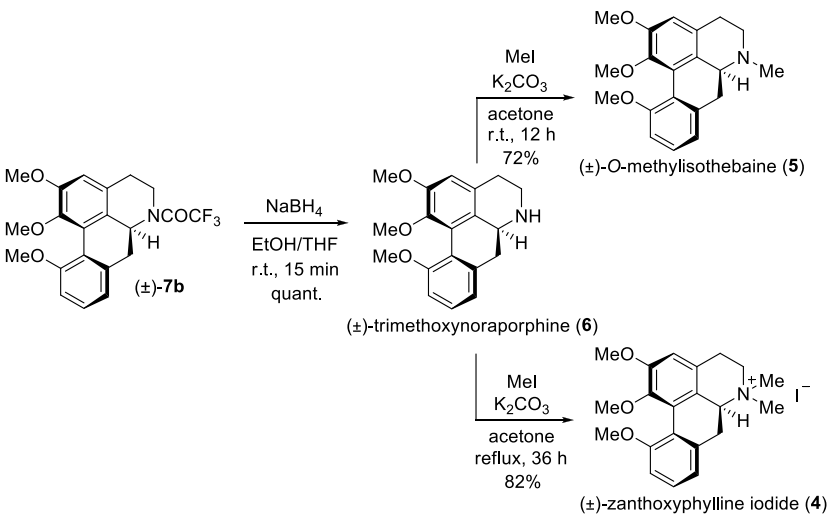
Scheme 6. Synthesis and proposed mechanisms for the aporphine core **7b**.



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 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**).

Scheme 7. Transformations for production of aporphinoids **4**, **5** and **6**.



(±)-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, ^{1}H, and ^{13}C NMR spectra. The structure of compound **1** was assigned according to its IR, ^{1}H, 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, ^{1}H, ^{13}C, DEPT, COSY, and HSQC NMR spectra. The structure of compound **7b** was assigned according to its LRMS, HRMS, IR, ^{1}H, ^{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 application in the preparation of other aporphinoids.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on spectrometers operating at 500 MHz or 300 MHz. ^{13}C NMR spectra were recorded on spectrometers operating at 125 MHz or 75 MHz. ^{1}H NMR spectra were taken in deuterated solvents and the chemical shifts were given in ppm with respect to tetramethylsilane (TMS) used as 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 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 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 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 nitrogen atmosphere before use.[24] *n*-Butyllithium (*n*-BuLi) was titrated against *sec*-butanol using 1,10-phenanthroline as indicator under nitrogen atmosphere.[25] Lithium diisopropylamide (LDA) was generated following typical procedure before use.[26] Acetonitrile was distilled from calcium hydride under 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 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 ºC 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 x 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 the desired product **13**. Rf = 0.81 (eluent: methanol); yield: 2.16 g (97%); off-white solid; m.p. 99-100 ºC (lit.[27] m.p. 99-100 ºC); ^{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 ºC 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 x 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)**.* Rf = 0.13 (eluent: methanol); yield: 1.36 g (quantitative); yellowish solid; m.p. 146-149 ºC (lit.[12] m.p. 148-152 ºC); ^{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**).* Rf = 0.38 (eluent: methanol); yield: 738 mg (90%); brownish solid; m.p. 102-103 °C (lit.[28] m.p. 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 nitrogen atmosphere. A solution of trifluoroacetic anhydride (1.25 mmol, 263 mg) in CH_2Cl_2 (0.75 mL) was added dropwise using syringe and needle. The reaction mixture was maintained at -50 °C under stirring and 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 the desired product **8**. Rf = 0.60 (eluent: dichloromethane); yield: 211 mg (70%); off-white solid; m.p. 83-85 °C (lit.[13] m.p. 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 the heterocyclic compound **8** (0.3 mmol, 90.3 mg), the 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 ºC for 24 h. Afterwards, brine (10 mL) was added to the mixture, which was extracted with ethyl acetate (3 x 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 the desired product **7a**. Rf = 0.68 (eluent: dichlorometane); yield: 75.8 mg (67%); off-white solid; m.p. 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 the compound **7a** (0.18 mmol, 67.9 mg) and ethanol (10 mL). The resulting suspension was maintained under stirring until complete solubilization of the compound **7a**. After that, $NaBH_4$ (1.8 mmol, 68.1 mg) was added and the reaction mixture was maintained at room temperature under stirring and 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 x 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording the alkaloid **3**.[14] Rf = 0.26 (eluent: metanol); yield: 50.4 mg (quantitative); off-white solid; m.p. 124-125 °C (lit.[14] m.p. 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-Trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinolone (2).[9a] To a round-bottomed flask was 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 x 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 the alkaloid **2**.[15] Rf = 0.60 (eluent: methanol); yield: 38.7 mg (94%); yellowish solid; m.p. 168-169 °C (lit.[15] m.p. 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, 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).

1,2,11-Trimethoxy-6-methyl-5,6,6a,7-tetrahydro-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 x 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 the desired product **16**. Rf = 0.68 (eluent: methanol); yield: 31.7 mg (90%); brownish solid; m.p. 128-130 °C (lit.[16] m.p. 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 the 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 x 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 the alkaloid **1**.[17] Rf = 0.68 (eluent: methanol); yield: 14.4 mg (69%); yellowish solid; m.p. 204-206 °C (decomp.) ((lit.[17] m.p. 210-211 °C (decomp.)); ^{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 ºC under stirring and nitrogen atmosphere for 3 h. The volatile substances were removed under reduced pressure, affording the desired product **17**. Rf = 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 ºC under stirring and nitrogen atmosphere. After that, LDA (5.5 mmol, 10 mL of a 0.55 mol.L^{-1} solution in THF) was added dropwise using syringe and needle. The reaction mixture was heated to room temperature and maintained at room temperature for 90 min. Then, the mixture was cooled to -78 ºC under stirring and nitrogen atmosphere. After that, trimethylsilyl chloride (TMSCl) (6 mmol, 648 mg, 0.76 mL) was added. The reaction mixture was heated to room temperature 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 x 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 the desired product **18**. Rf = 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 ºC under stirring and nitrogen atmosphere. After that, *n*-BuLi (1.1 mmol, 0.75 mL of a 1.47 mol.L^{-1} solution in hexane) was added dropwise using syringe and needle. The reaction mixture was heated to room temperature and maintained at room temperature for 4 h. Then, the mixture was cooled to 0 ºC under stirring and

anhydrous conditions. After that, triflic anhydride (2 mmol, 564 mg, 0.37 mL) was added. The reaction mixture was heated to room temperature 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 x 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 the desired product **11b**. Rf = 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 the heterocyclic compound **8** (0.3 mmol, 90.3 mg), the 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 ºC for 24 h. Afterwards, brine (10 mL) was added to the mixture, which was extracted with ethyl acetate (3 x 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**. Rf = 0.55 (eluent: dichloromethane); yield: 70.8 mg (58%); off-white solid; m.p. 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 (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 the compound **7b** (0.1 mmol, 40.8 mg) and THF (5 mL). The resulting suspension was maintained under stirring until complete solubilization of the compound **7b**. After that, 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 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 x 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording the alkaloid **6**.[20] Rf = 0.25 (eluent: metanol); yield: 31.1 mg (quantitative); off-white solid; m.p. 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 x 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 the alkaloid **5**.[22] Rf = 0.54 (eluent: methanol); yield: 23.4 mg (72%); yellowish solid; m.p. 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 nitrogen atmosphere for 36 h. Afterwards, the mixture was evaporated under reduced pressure. The material obtained

was washed with distilled water (3 x 3 mL) and separated by centrifugation (4000 rpm for 10 min), affording the desired product **4**.[23] Yield: 38.2 mg (82%); off-white solid; m.p. 248-250 ºC (lit.[23] m.p. 256 ºC); ^{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

Copies of NMR spectra, single-crystal X-ray diffraction data and crystallographic information file (CIF) are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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