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A One-Pot Cascade to Protoberberine Alkaloids via Stevens Rearrangement of Nitrile-Stabilized Ammonium Ylides

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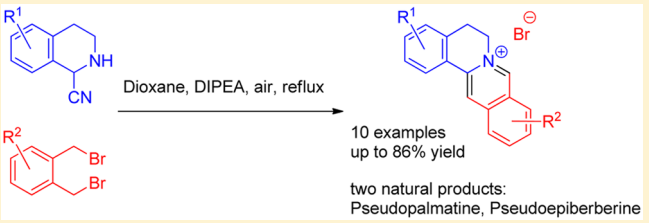
Supporting Information

ABSTRACT: A facile one-pot synthesis of protoberberines from readily accessible 1,2,3,4-tetrahydroisoquinoline-1-carbonitriles and 1,2-bis(bromomethyl)arenes is described. The reaction cascade comprises four consecutive transformations, all of which can be effected under a single set of conditions. Ten protoberberines, including the alkaloids pseudopalmatine and pseudoepiberberine, were prepared in yields up to 86% according to this strategy. No chromatographic purification of the products is required, and the route is devoid of any protecting group manipulations.



A major goal of preparative organic chemistry is the development of straightforward synthetic methods allowing the reduction of waste and the use of resources. The generation of product structural diversity by combination of simple building blocks is another important aspect that is particularly attractive for the optimization of desired product properties. Modular one-pot syntheses may fulfill both criteria and reduce not only the number of linear synthetic steps but also the operations required to obtain a desired product or a series of related compounds. Here, we report a simple one-pot procedure for the synthesis of quaternary protoberberines from 1,2,3,4-tetrahydroisoquinoline-1-carbonitriles and 1,2-bis-(bromomethyl)arenes.

The protoberberines represent a large class of alkaloids characterized by the 5,6-dihydroisoquinolino[3,2-*a*]-isoquinolinium skeleton.[1] The quaternary protoberberines together with their partially reduced analogues, the dihydro- and the tetrahydroprotoberberines, are widely distributed in plants and more than a hundred representatives are known to date.[1,2] In particular, the permanently charged quaternary protoberberines possess pronounced biological activities, such as antimicrobial,[3−5] anti-inflammatory,[6] antimalarial,[7,8] and antitumor.[9,10] These activities have partly been attributed to their DNA intercalating capability[11] as well as to their general electrophilic reactivity.[12] In spite of their biological activity, surprisingly few methods[13] for the synthesis of the quaternary protoberberines have been developed.[14−21] These include Donohoe's palladium-catalyzed enolate arylation constructing the complete carbon backbone before introduction of the nitrogen[22] and Kametani's thermolysis of benzocyclobutene-substituted 3,4-dihydroisoquinolines, which undergo ring enlargement via *o*-quinodimethane intermediates.[23] Other methods are Lenz's photocyclization of *N*-formyl enamides derived from 1-benzyl-3,4,-dihydroisoquinolines[24] already containing the entire skeleton of the products and MacLean's mercaptal cyclization,[25] which introduces the carbon atom in position 13 of the protoberberine ring system to a 2-benzyl-3,4-dihydroisoquinolinium salt via a formyl anion equivalent.

In the course of our work on Stevens rearrangements[26,27] of nitrile-stabilized ammonium ylides,[28−31] quaternary protoberberine **6** was detected as a side product of the synthesis of spiro salt **3** from *α*-aminonitrile **1** with 1,2-bis(bromomethyl)-benzene (**2**) in the presence of 1.2 equiv of DIPEA in THF. This observation encouraged us to vary the reaction conditions in order to maximize the yield of **6** in a fast access to quaternary protoberberines. We found that at least 2 equiv of DIPEA and the presence of aerial oxygen are required for the reaction to proceed. To shorten the reaction time, THF was replaced by the higher boiling solvent 1,4-dioxane. The best results in terms of reaction time and conversion were observed when 10 equiv of DIPEA in refluxing 1,4-dioxane were employed. Under these optimized conditions, *α*-aminonitrile **1** and dibromide **2** furnished protoberberine **6** in 56% yield. This cascade reaction most likely begins with the formation of the spirocyclic ammonium bromide **3**, which is then deprotonated by DIPEA to yield a nitrile stabilized ammonium ylide. After Stevens rearrangement to the *α*-aminonitrile **4**, a spontaneous dehydrocyanation[32] produces enamine **5**, which is ultimately oxidized by aerial oxygen under aromatization to quaternary protoberberine **6** (Scheme 1).

To verify this sequence, the course of the reaction was monitored by HPLC-MS. With the exception of **4**, all intermediates could be observed as discrete species. Furthermore, spiro salt **3** was isolated in 57% yield by using only 1 equiv of DIPEA in THF. When subjected to the reaction conditions for the one-pot procedure, it furnished protoberberine **6** in 76% yield (Scheme 2).

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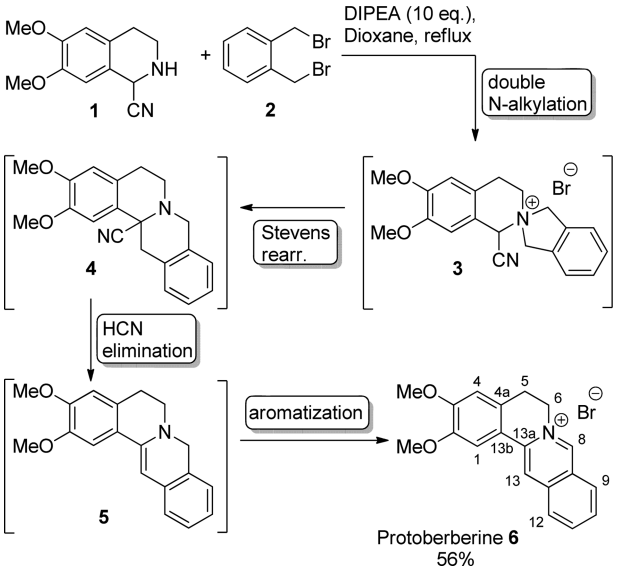
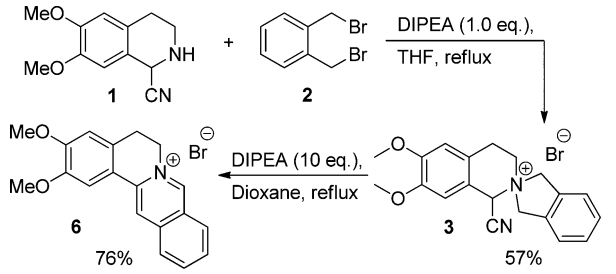
Scheme 1. Proposed Reaction Sequence for the Formation of Model Compound 6



Scheme 2. Stepwise Preparation of Protoberberine 6 via Spirocyclic Ammonium Salt 3



To explore the scope of the reaction, a series of dibromides and α-aminonitriles were prepared along known routes and were subjected to the optimized conditions; the results are summarized in Table 1.

Thus, the naturally occurring quaternary protoberberines pseudoepiberberine[33] (**8**) and pseudopalmatine[34,35] (**7**) were obtained in 44% and 54% yield, respectively. Phenanthrene- and naphthalene-based dibromides permit the preparation of extended ring systems that exhibit longer absorption wavelengths and were obtained as intensely yellow to dark orange crystalline solids. The variation of the isolated yields is likely due to the different solubility of the individual compounds **6**–**15**, which were separated from the reaction medium by crystallization after removal of dioxane in vacuo and trituration of the residue with acetone or Et_2O/MeOH (1:1). For the three arbitrarily chosen compounds **6**, **8**, and **12**, the desired protoberberine clearly was the major constituent of the crude concentrated reaction mixture besides DIPEA hydrobromide, as judged by ^{1}H NMR spectroscopy (see the Supporting Information). Thus, an optimization of the isolation procedure should permit an improvement of the overall efficiency of the protocol. For unsymmetrical dibromides, the formation of regioisomeric products is to be expected unless the migratory aptitude of the two benzylic methylene groups differs significantly. Experiments on 2′-cyano-5-methoxyspiro[isoindoline-2,1′-piperidin]-1′-ium bromide carrying a single methoxy group but being devoid of the additional benzylic stabilization of the intermediate ammonium ylide, however, indicated a low selectivity.

In summary, a simple and straightforward modular one-pot synthesis of quaternary protoberberines via a cascade reaction including a Stevens rearrangement[36−43] of a nitrile-stabilized ammonium ylide[44−46] has been developed. It allows a fast and modular access to this compound class and permitted the syntheses of the natural products pseudoepiberberine and pseudopalmatine.

EXPERIMENTAL SECTION

General Methods. Reactions requiring a temperature of 0 °C were performed using a water/ice bath. All reagents and solvents were obtained from commercial suppliers without further purification. Melting points were determined in open capillary tubes and are uncorrected. NMR spectra were recorded with a 300 MHz spectrometer (300 MHz ^{1}H and 75.5 MHz ^{13}C), a 400 MHz (400 MHz ^{1}H and 100.6 MHz ^{13}C), or with a 600 MHz spectrometer (600 MHz ^{1}H and 151 MHz ^{13}C) equipped with direct (300/400 MHz) or inverse (600 MHz) 5 mm probes. Deuterated solvents were used as internal standard. The δ values are reported in parts per million (ppm) downfield from TMS and were referenced to the residual solvent signal ($CDCl_3$, D_2O, DMSO-d_6).[47] Coupling constants J are given in hertz (Hz). IR spectra were recorded using a diamond ATR unit and are reported in terms of frequency of absorption (ν, cm^{-1}). ESI-HRMS spectra were recorded on a Q-TOF instrument with a dual source and a suitable external calibrant. Thin-layer chromatography was carried out on 0.2 mm silica gel plates with fluorescence indicator. Substance bands were detected by illumination with UV light (254 and 360 nm).

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (1). A solution of homoveratrylamine (43.0 g, 40.0 mL, 0.24 mol) and ethyl formate (58.5 g, 63.8 mL, 0.79 mol, 3.3 equiv) was heated under reflux for 16 h. Excess ethyl formate was removed under reduced pressure to afford crude formamide, which was dissolved in DCM (100 mL) and added dropwise to a vigorously stirred solution of PCl_5 (60.0 g, 0.29 mol, 1.2 equiv) in DCM (55 mL) at room temperature. After the addition was complete, the reaction mixture was stirred for 30 min and then carefully hydrolyzed with a mixture of ice (110 g) and *n*-hexane (60 mL). The organic layer was separated and washed with water (60 mL). The combined aqueous layers where alkalized with solid potassium hydroxide to pH 12 and extracted with DCM (4 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford 6,7-dimethoxy-3,4-dihydroisoquinoline (46.5 g, quant.) as a brown oil. R_f = 0.31 ($CHCl_3$/Methanol = 98/2). IR (ATR): 3004 (w), 2939 (m), 2836 (w), 1464 (s), 1278 (s), 1264 (s), 1117 (s), 1015 (m), 988 (m), 730 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.23 (t, J = 2.1 Hz, 1H, H-1), 6.81 (s, 1H, H-8), 6.67 (s, 1H, H-5), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.79−3.66 (m, 2H, H-3), 2.75−2.60 (m, 2H, H-4). The spectroscopic data are in accordance with the literature.[48]

To a solution of 6,7-dimethoxy-3,4-dihydroisoquinoline (8.40 g, 44 mmol) in methanol (20 mL) was added solid KCN (12.3 g, 189 mmol, 4.3 equiv). The stirred reaction mixture was cooled to 0 °C, and AcOH (23 mL) was added over a period of 30 min. After the addition was complete, the reaction mixture was stirred for 30 min at room temperature. The reaction vessel was purged with argon to remove remaining HCN, before the mixture was diluted with water (20 mL), carefully alkalized with 2 N NaOH to pH 8, and quickly extracted with DCM (7 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (8.9 g, 41 mmol, 92%) as an orange solid, mp 105−106 °C, lit. mp 106−107 °C.[32]

R_f = 0.27 ($CHCl_3$/methanol = 98/2). IR (ATR): 3336 (w), 2936 (m), 1610 (m), 1517 (s), 1464 (s), 1261 (s), 1223 (s), 1107 (s), 732 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.63 (s, 1H, H-8), 6.57 (s, 1H, H-5), 4.91 (s, 1H, H-1), 3.82 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.23−3.13 (m, 2H, H-3), 2.88−2.73 (m, 1H, H_a-4), 2.63 (dt, J = 16.3, 3.6, 1H, H_b-4), 2.16 (bs, 1H, NH).

The spectroscopic data are in accordance with the literature.[32,48]

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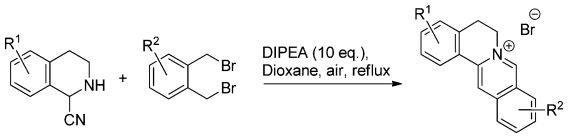
Table 1. Protoberberines Prepared via the One-Pot Procedure



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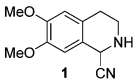
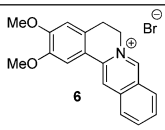
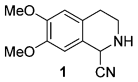
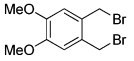
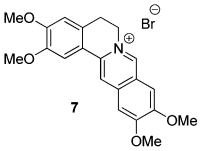
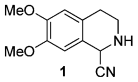
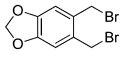
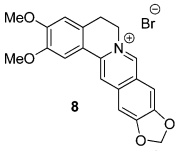
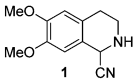
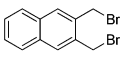
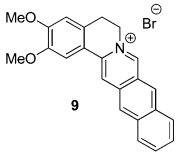
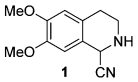
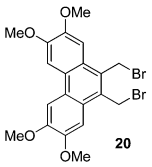
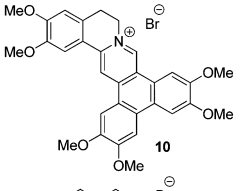
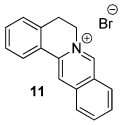
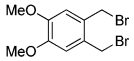
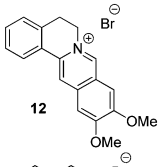
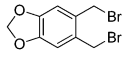
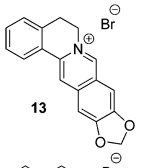
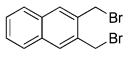
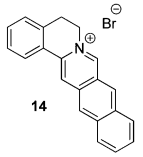
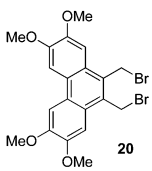
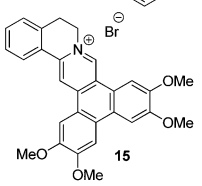
1				56%
2				54%
3				44%
4				74%
5				86%
6				65%
7				15%
8				36%
9				30%
10				76%

1′-Cyano-6′,7′-dimethoxy-3′,4′-dihydro-1′*H*-spiro[isoindoline-2,2′-isoquinolin]-2-ium Bromide (3). A solution of 1,2-bis(bromomethyl)benzene (**2**, 1.20 g, 4.55 mmol) and DIPEA (590 mg, 0.78 mL, 4.58 mmol, 1.0 equiv) in THF 40 mL was heated to

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reflux. To the refluxing mixture, a solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**, 1.00 g, 4.58 mmol. 1.0 equiv) in THF (10 mL) was added dropwise, and heating was continued for 24 h. The volatiles were removed under reduced pressure, and the residue was partially dissolved in a mixture of diethyl ether/methanol (1/1). The remaining solid was filtered to afford the title compound (1.05 g, 2.62 mmol, 57%) as a colorless solid, mp 170−172 °C.

IR (ATR): 3412 (m, br), 2963 (m), 2938 (m), 1613 (m), 1522 (s), 1464 (m), 1266 (s), 1230 (s), 1124 (s), 764 (m). ^{1}H NMR, COSY (300 MHz, DMSO-d_6): δ = 7.60−7.37 (m, 4H, H-4, H-5, H-6, H-7), 7.06 (s, 1H, H-5′), 7.02 (s, 1H, H-8′), 6.62 (s, 1H, H-1′), 5.35 (s, 2H, H-1), 5.18 (d, J = 14.9 Hz, 1H, H-2), 4.95 (d, J = 14.9 Hz, 1H, H-2), 4.09 (t, J = 6.0 Hz, 2H, H-3′), 3.82 (s, 3H, C$^{6'}$−OCH$_3$), 3.77 (s, 3H, C$^{7'}$−OCH$_3$), 3.34 (t, J = 6.0 Hz, 2H, C-4′). ^{13}C NMR, HMBC, HSQC (75 MHz, DMSO-d_6): δ = 150.6 (C6′), 148.3 (C7′), 132.3 (C7a), 131.9 (C3a), 129.2, 129.2, 123.6, 123.5 (4 × Ar-C), 122.7 (C4a′), 114.5 (C8a′), 113.9 (CN), 112.1 (C5′), 110.1 (C8′), 68.4 (C1), 65.5 (C3), 59.7 (C1′), 56.3 (C3′), 55.9 (C$^{6'}$−OCH$_3$), 55.8, (C$^{7'}$−OCH$_3$) 23.5 (C4′). ESI-MS: m/z (%) = 321.1 (100) [M]$^+$. ESI-HRMS: calculated for [$C_{20}H_{21}N_2O_2$]$^+$: m/z = 321.1603, found: 321.1605

1,2,3,4-Tetrahydroisoquinoline-1-carbonitrile (16). 3,4-Dihydroisoquinoline was prepared according to the method of Shi et al.[49] To a solution of tetrahydroisoquinoline (10.5 g, 10.0 mL, 78.8 mmol) in DCM (150 mL) was added NBS (15.7 g, 88.2 mmol, 1.1 equiv), and the mixture was stirred for 1 h at room temperature. To the mixture, an aqueous 30% NaOH solution (50 mL) was added dropwise over a period of 30 min, and the mixture was stirred for 2.5 h at ambient temperature. The organic layer was separated and washed with water (2 × 100 mL) and 2 N HCl (2 × 100 mL). The acid extracts were made alkaline with 2 N NaOH to pH 11 and extracted with DCM (2 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford 3,4-dihydroisoquinoline (9.38 g, 71.5 mmol, 91%) as a brown oil. R_f = 0.52 ($CHCl_3$/methanol = 98/2). IR (ATR): 3021 (w), 2944 (m), 2897 (w, sh), 2848 (w), 1626 (s), 1576 (m), 1209 (s), 1005 (m), 879 (s), 752 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.31 (bs, 1H), 7.38−7.20 (m, 3H), 7.11 (d, J = 7.1 Hz, 1H), 3.85−3.68 (m, 2H), 2.76−2.65 (m, 2H). The spectroscopic data are in accordance with the literature.[50]

To a solution of 3,4-dihydroisoquinoline (5.00 g, 38.1 mmol) in methanol (10 mL) was added solid KCN (10.67 g, 164 mmol, 4.3 equiv). The stirred reaction mixture was cooled to 0 °C, and AcOH (19.6 mL) was added over a period of 30 min. After the addition was complete, the reaction mixture was stirred for 15 h at room temperature. The reaction vessel was purged with argon to remove remaining HCN, before the mixture was carefully alkalized with 2 N NaOH to pH 8 and quickly extracted with DCM (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (5.82 g, 36.7 mmol, 96%) as an orange amorphous solid.

R_f = 0.43 ($CHCl_3$/methanol = 98/2). IR (ATR): 3339 (w), 2836 (w), 2807 (w), 1494 (m), 1454 (m), 1428 (m, sh), 1126 (m), 944 (m), 732 (s), 658 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34−7.08 (m, 4H, Ar-H), 5.05 (s, 1H, H-1), 3.37−3.20 (m, 2H), 3.03−2.86 (m, 1H), 2.85−2.72 (m, 1H), 2.04 (br s, 1H, NH).

The spectroscopic data are in accordance with the literature.[51]

1,2-Bis(bromomethyl)-4,5-dimethoxybenzene (17). The title compound was prepared according to a modified method of Diederich et al.[52] To a solution of 1,2-dimethoxybenzene (10.0 g, 72.0 mmol) and paraformaldehyde (4.3 g, 143 mmol, 2.0 equiv) was slowly added 33% HBr in AcOH (31 mL) at 0 °C. Then, the reaction mixture was stirred for 20 h at room temperature and for 1 h at 65 °C. After cooling to room temperature, the mixture was poured on ice. The resulting precipitate was filtered and washed extensively with water to afford the title compound (16.33 g, 50.4 mmol, 70%) as a colorless solid, mp 106−108.°C, lit. mp 108−110 °C.[52]

R_f = 0.53 (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.84 (s, 2H, Ar-H), 4.63 (s, 4H, 2 × CH_2Br), 3.89 (s, 6H, OCH_3).

The spectroscopic data are in accordance with the literature.[52]

5,6-Bis(bromomethyl)-1,3-benzodioxole (18). The title compound was prepared according to a modification of a protocol by Dallacker et al.[53] Piperonyl alcohol (2.96 g, 19.5 mmol), 48% HBr (18 mL), and paraformaldehyde (1.80 g, 59.9 mmol, 3.0 equiv) were mixed at 0 °C. Then, the reaction mixture was heated up to 45 °C over a period of 90 min and kept at this temperature for 18 h. The resulting precipitate was filtered off, washed extensively with water, and recrystallized from petroleum ether to afford the title compound (5.28 g, 17.1 mmol, 88%) as a colorless solid, mp 94−96 °C, lit. mp 97.5.[53]

R_f = 0.48 (petroleum ether/AcOEt = 8/2). IR (ATR): 2900 (m), 1502 (s, sh), 1485 (s), 1375 (s), 1035 (s), 928 (s), 867 (s), 735 (s), 610 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.82 (s, 2H, Ar-H), 5.98 (s, 2H, O-CH_2-O), 4.59 (s, 4H, 2 × CH_2-Br).

General Procedure for the Cascade Reaction. A solution of dibromide (1 equiv) and DIPEA (10 equiv) in 1,4-dioxane (0.2 M) was heated to reflux. To the refluxing solution, a solution of α-aminonitrile in 1,4-dioxane (0.2 M) was added dropwise, and the mixture was kept under these conditions for 2−48 h. The volatiles were removed under reduced pressure, and the residue was triturated with a mixture of diethyl ether/methanol (1/1) or with acetone. The remaining solid was filtered off to afford the corresponding protoberberines **6**−**15** unless stated otherwise.

2,3-Dimethoxy-5,6-dihydroisoquinolino[3,2-*a*]isoquinolinium Bromide (6). *Method A.* According to the general procedure, 1,2-bis(bromomethyl)benzene (**2**, 242.8 mg, 0.92 mmol) was reacted with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**, 200.0 mg, 0.92 mmol. 1.0 equiv). After 48 h, trituration with diethyl ether/methanol (1/1) afforded the title compound (191.9 mg, 0.52 mmol, 56%) as a yellow solid, mp 291−292 °C, lit. mp. > 250 °C.[54]

IR (ATR): 2934 (w), 1641 (m), 1603 (m), 1515 (s), 1366 (s), 1262 (s), 1233 (s), 1216 (s), 874 (s), 756 (s). ^{1}H NMR, COSY (600 MHz, DMSO-d_6): δ = 10.04 (s, 1H, H-8), 9.12 (s, 1H, H-13), 8.42 (d, J = 8.4, 1H, H-9), 8.27 (d, J = 8.1, 1H, H-12), 8.20 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H, H-11), 7.97 (ddd, J = 8.4, 6.8, 1.1 Hz, 1H, H-10), 7.77 (s, 1H, H-1), 7.13 (s, 1H, H-4), 4.88 (t, J = 6.4 Hz, 2H, H-6), 3.95 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.26 (t, J = 6.4 Hz, 2H, H-5). ^{13}C NMR, HMBC, HSQC (151 MHz, DMSO-d_6): δ = 151.9 (C_qOMe), 150.4 (C8), 148.8 (C_qOMe), 139.9 (C13a), 138.5 (C12a), 136.8 (C11), 130.4 (C10), 130.0 (C9), 129.1 (C4a), 127.1 (C12), 125.4 (C8a), 120.1 (C13), 118.8 (C13b), 111.3 (C4), 109.0 (C1), 56.2 (OCH_3), 55.9 (OCH_3), 55.4 (C6), 25.9 (C5). ESI-MS: m/z (%) = 292.1 (100) [M]$^+$. ESI-HRMS: calculated for [$C_{19}H_{18}NO_2$]$^+$: m/z = 292.1338, found: 292.1344

Method B. A solution of 1′-cyano-6′,7′-dimethoxy-3′,4′-dihydro-1′*H*-spiro[isoindoline-2,2′-isoquinolin]-2-ium bromide (**3**, 200 mg, 0.50 mmol) and DIPEA (640 mg, 0.84 mL, 5.0 mmol, 10 equiv) in 1,4-dioxane (10 mL) was heated to reflux for 48 h. The volatiles were removed under reduced pressure, and the residue was partially dissolved in a mixture of diethyl ether/methanol (1/1). The remaining solid was filtered to afford the title compound (142 mg, 0.38 mmol, 76%) as a yellow solid, mp 292.5−293.3 °C, lit. mp. > 250 °C.[54] The spectroscopic data were identical to those of the sample prepared by method A.

2,3,10,11-Tetramethoxy-5,6-dihydroisoquinolino[3,2-*a*]isoquinolinium Bromide (7). According to the general procedure, 1,2-bis(bromomethyl)-4,5-dimethoxybenzene (**17**, 295.2 mg, 0.92 mmol) was reacted with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**, 200.0 mg, 0.92 mmol. 1.0 equiv). After 48 h, trituration with diethyl ether/methanol (1/1) afforded the title compound (215.4 mg, 0.49 mmol, 54%) as a yellow solid, mp 254−255 °C, lit. mp 250 °C.

IR (ATR): 3412 (m, br), 2943 (m, br), 1606 (s), 1512 (s), 1461 (s), 1425 (s), 1359 (s), 1213 (s), 1127 (s). ^{1}H NMR, COSY (600 MHz, DMSO-d_6): δ = 9.55 (s, 1H, H-8), 8.88 (s, 1H, H-13), 7.71 (s, 1H, H-9), 7.66 (s, 1H, H-1), 7.62 (s, 1H, H-12), 7.10 (s, 1H, H-4), 4.79 (t, J = 6.4 Hz, 2H, H-6), 4.07 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.22 (t, J = 6.4 Hz, 2H, H-5). ^{13}C NMR, HMBC, HSQC (151 MHz, DMSO-d_6): δ = 157.4 (C_qOMe), 152.2 (C_qOMe), 151.5 (C_qOMe), 148.7 (C_qOMe), 145.6 (C8), 138.4 (C13a), 136.7 (C12a), 128.6 (C4a), 122.0 (C8a), 118.9 (C13b), 118.0 (C13), 111.3 (C4), 108.5 (C1), 106.5 (C9),

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105.3 (C12), 56.7 (OCH_3), 56.4 (OCH_3), 56.1 (OCH_3), 55.9 (OCH_3), 54.7 (C6), 26.1 (C5). ESI-MS: m/z (%) = 352.2 (100) $[M]^+$. ESI-HRMS: calculated for $[C_{21}H_{22}NO_4]^+$: m/z = 352.1549, found: 352.1544.

2,3-Dimethoxy-5,6-dihydro[1,3]dioxolo[4,5-*g*]isoquinolino-[2,1-*b*]isoquinolin-7-ium Bromide (8). According to the general procedure, 5,6-bis(bromomethyl)-1,3-benzodioxole (**18**, 281.4 mg, 0.92 mmol) was reacted with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**, 200.0 mg, 0.92 mmol. 1.0 equiv). After 48 h, trituration with diethyl ether/methanol (1/1) afforded the title compound (168.4 mg, 0.40 mmol, 44%) as a yellow solid, mp 292−293 °C.

IR (ATR): 3400 (w, br), 2980 (w), 1606 (m), 1515 (s), 1460 (s), 1356 (s), 1271 (s), 1247 (s), 1187 (s), 1029 (s). ^{1}H NMR, COSY (300 MHz, DMSO-d_6): δ = 9.50 (s, 1H, H-8), 8.82 (s, 1H, H-14), 7.71 (s, 1H, H-9), 7.67 (s, 1H, H-1), 7.55 (s, 1H, H-13), 7.11 (s, 1H, H-4), 6.42 (s, 2H, H-11), 4.76 (t, J = 6.3 Hz, 2H, H-6), 3.93 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.21 (t, J = 6.3 Hz, 2H, H-5). ^{13}C NMR, HMBC, HSQC (75 MHz, DMSO-d_6): δ = 156.0 (C_qOCH_2O), 151.7 (C_qOMe), 150.8 (C_qOCH_2O), 148.7(C_qOMe), 145.9 (C8), 138.9 (C14a), 138.9 (C_q), 128.8 (C4a), 123.5 (C_q), 118.7 (C14), 118.7 (C14b), 111.4 (C4), 108.8 (C1), 103.9 (C9), 103.7 (C11), 102.5 (C13), 56.2 (OCH_3), 55.9 (OCH_3), 54.7 (C6), 26.0 (C5). ESI-MS: m/z (%) = 336.2 (100) $[M]^+$. ESI-HRMS: calculated for $[C_{20}H_{18}NO_4]^+$: m/z = 336.1236, found: 363.1242.

2,3-Dimethoxy-5,6-dihydrobenzo[*g*]isoquinolino[2,1-*b*]-isoquinolinium Bromide (9). According to the general procedure, 2,3-bis(bromomethyl)naphthalene (**19**, 125.0 mg, 0.40 mmol) was reacted with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**, 87.3 mg, 0.40 mmol. 1.0 equiv). After 48 h, trituration with acetone afforded the title compound (125.5 mg, 0.30 mmol, 74%) as a dark orange solid, mp 274−275 °C.

IR (ATR): 3443 (m, br), 3360 (m, br), 3011 (m), 1635 (m), 1606 (m), 1517 (m), 1501 (s), 1352 (m), 1279 (m), 748 (s). ^{1}H NMR, COSY (400 MHz, DMSO-d_6): δ = 10.37 (s, 1H, H-8), 9.27 (s, 1H, H-9), 9.19 (s, 1H, H-15), 8.87 (s, 1H, H-14), 8.41 (d, J = 8.4 Hz, 1H, H-10), 8.34 (d, J = 8.4 Hz, 1H, H-13), 7.88 (ddd, J = 8.4, 6.7, 1.0 Hz, 1H, H-12), 7.79 (s, 1H, H-1), 7.79 (ddd, J = 8.4, 6.7, 1.0 Hz, 1H, H-11), 7.12 (s, 1H, H-4), 4.95 (t, J = 6.1 Hz, 2H, H-6), 3.97 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.29 (t, J = 6.1 Hz, 2H, H-5). ^{13}C NMR, HMBC, HSQC (151 MHz, DMSO-d_6): δ = 153.9 (C8), 151.4 (C_qOMe), 148.8 (C_qOMe), 137.1 (C_q), 136.7 (C15a), 132.8 (C9), 132.7 (C_q), 132.3 (C_q), 131.0 (C12), 129.7 (C10), 128.6 (C13), 128.6 (C_q), 128.2 (C11), 126.0 (C14), 122.5 (C_q), 119.5 (C15), 119.2 (C_q),111.3 (C4), 108.7 (C1), 56.2 (OCH_3), 55.9 (OCH_3), 55.7 (C6), 26.2 (C5). ESI-MS: m/z (%) = 342.2 (100) $[M]^+$. ESI-HRMS: calculated for $[C_{23}H_{20}NO_2]^+$: m/z = 342.1494, found: 342.1503.

2,3,6,7,14,15-Hexamethoxy-11,12-dihydrodibenzo[*f*,*h*]-isoquinolino[2,1-*b*]isoquinolinium Bromide (10). According to the general procedure, 9,10-bis(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene[28] (**20**, 250.0 mg, 0.52 mmol) was reacted with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**, 112.6 mg, 0.52 mmol. 1.0 equiv). After 48 h, trituration with acetone afforded the title compound (26.0 mg, 0.45 mmol, 86%) as a yellow solid, mp 261−262 °C.

IR (ATR): 3558 (m, br), 2928 (m, br), 2853 (w), 1606 (m), 1606 (m), 1514 (s), 1467 (m), 1429 (m), 1287 (m), 1245 (m). ^{1}H NMR, COSY (300 MHz, DMSO-d_6): δ = 10.23 (s, 1H, H-9), 9.16 (s, 1H, H-17), 8.37 (s, 1H), 8.10 (s, 1H, H-1), 8.03 (s, 1H), 7.75 (s, 2H), 7.18 (s, 1H), 4.99 (t, J = 5.9 Hz, 2H, H-11), 4.13 (s, 3H, OCH_3), 4.09−4.03 (m, 9H, 3 × OCH_3), 4.02 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.34 (t, J = 5.9 Hz, 2H, H-12). ^{13}C NMR, HMBC, HSQC (151 MHz, DMSO-d_6): δ = 153.5, 152.3, 151.3, 150.0, 149.5, 148.6 (6 × C_qOMe), 142.6 (C9), 141.4, 138.4, 129.7, 128.4, 124.7, 122.3, 119.7, 119.0, 118.9 (9 × C_q), 115.8 (C17), 111.4 (C13), 110.8, 107.8, 105.3, 105.0, 104.8 (5 × Ar-C), 56.6, 56.5, 56.4, 56.3, 56.2, 56.0 (6 × OCH_3), 54.4 (C11), 26.0 (C12). ESI-MS: m/z (%) = 512.3 (100) $[M]^+$. ESI-HRMS: calculated for $[C_{31}H_{30}NO_6]^+$: m/z = 512.2073, found: 512.2083.

5,6-Dihydroisoquinolino[3,2-*a*]isoquinolinium Bromide (11). According to the general procedure, 1,2-bis(bromomethyl)benzene (**2**, 339.7 mg, 1.29 mmol) was reacted with 1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**16**, 203.1 mg, 1.28 mmol. 1.0 equiv). After 2 h, the reaction mixture was cooled to room temperature, aq $NaHCO_3$ (100 mL) was added, and the mixture was stirred for 30 min and extracted with cyclohexane (4 × 100 mL), and the aqueous layer was concentrated *in vacuo*. The remaining residue was extensively washed with chloroform and the filtrate was concentrated *in vacuo* to afford the title compound (260.1 mg, 0.83 mmol, 65%) as a beige solid, mp 238−242 °C.

IR (ATR): 3420 (s, br), 3033 (m, br), 3002 (m), 1640 (s), 1518 (m), 1347 (m), 1213 (w), 1153 (w), 771 (s), 761 (s). ^{1}H NMR, COSY (400 MHz, DMSO-d_6): δ = 10.16 (s, 1H, H-8), 9.21 (s, 1H, H-13), 8.48 (d, J = 8.2 Hz, 1H, H-9), 8.35 (d, J = 8.3 Hz, 1H, H-12), 8.3−8.27 (m, 1H, Ar-H), 8.24 (pseudo-t, J = 7.4 Hz, 1H, H-11), 8.03 (pseudo-t, J = 7.4 Hz, 1H, H-10), 7.64−7.49 (m, 3H, Ar-H), 4.95 (t, J = 6.2 Hz, 2H, H-6), 3.36 (t, J = 6.2 Hz, 2H, H-5). ^{13}C NMR, HMBC, HSQC (101 MHz, DMSO-d_6): δ = 150.8 (C8), 139.5 (C13a), 138.3 (C12a), 136.8 (C11), 135.3 (C4a), 131.7 (Ar-C), 130.9 (C10), 130.0 (C9), 128.6 (Ar-C), 128.3 (Ar-C), 127.5 (C12), 127.0 (C13b), 126.2 (Ar-C), 125.9 (C8a), 121.4 (C13), 55.2 (C6), 26.3 (C5). ESI-MS: m/z (%) = 232.1 (100) $[M]^+$. ESI-HRMS: calculated for $[C_{17}H_{14}N]^+$: m/z = 232.1126, found: 232.1125

10,11-Dimethoxy-5,6-dihydroisoquinolino[3,2-*a*]isoquinolinium Bromide (12). According to the general procedure, 1,2-bis(bromomethyl)-4,5-dimethoxybenzene (**17**, 405.6 mg, 1.25 mmol) was reacted with 1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**16**, 200.0 mg, 1.26 mmol. 1.0 equiv). After 4 h, trituration with diethyl ether/methanol (1/1) afforded the title compound (70.0 mg, 0.19 mmol, 15%) as a yellow solid, mp 240−241 °C.

IR (ATR): 3394 (m, br), 2986 (w), 2837 (w), 1608 (m), 1491 (s), 1429 (s), 1250 (s), 1213 (s), 1159 (s), 929 (s). ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ = 10.79 (s, 1H), 8.41 (s, 1H), 8.01−9.94 (m, 1H), 7.95 (s, 1H), 7.5 3−7.48 (m, 2H), 7.47 (s, 1H), 7.39−7.33 (m, 1H), 5.12 (t, J = 6.3 Hz, 2H), 4.16 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 3.27 (t, J = 6.3 Hz, 2H). ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ = 158.5 (C_qOMe), 153.2 (C_qOMe), 146.9 (C8), 138.2 (C13a), 136.8 (C12a), 134.6 (C4a), 131.9, 128.9 128.8 (3 × Ar-C), 126.9 (C13b), 125.6 (Ar-C), 123.5 (8a), 118.6 (C13), 107.8 (C9), 105.3 (C12), 57.3, 57.3 (2 × OCH_3), 54.6 (C6), 27.7. ESI-MS: m/z (%) = 292.2 (100) $[M]^+$. ESI-HRMS: calculated for $[C_{19}H_{18}NO_2]^+$: m/z = 292.1338, found: 292.1346

5,6-Dihydro[1,3]dioxolo[4,5-*g*]isoquinolino[2,1-*b*]isoquinolin-7-ium Bromide (13). According to the general procedure, 5,6-bis(bromomethyl)-1,3-benzodioxole (**18**, 385.4 mg, 1.25 mmol) was reacted with 1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**16**, 200.0 mg, 1.26 mmol. 1.0 equiv). After 4 h, trituration with diethyl ether/methanol (1/1) afforded the title compound (160.2 mg, 0.45 mmol, 36%) as a colorless solid, mp 250−252 °C.

IR (ATR): 3458 (m), 2972 (w), 1616 (m), 1503 (s), 1437 (s), 1220 (s), 1030 (s), 933 (s), 918 (m, sh), 782 (s). ^{1}H NMR, COSY (300 MHz, DMSO-d_6): δ = 9.63 (s, 1H, H-8), 8.92 (s, 1H, H-14), 8.34−8.00 (m, 1H, Ar-H), 7.76 (s, 1H, H-9), 7.67 (s, 1H, H-13), 7.60−7.54 (m, 2H, Ar-H), 7.54−7.47 (m, 1H, Ar-H), 6.44 (s, 2H, H-11), 4.82 (t, J = 6.3 Hz, 2H, H-6), 3.31 (d, J = 6.3 Hz, 2H, H-5). ^{13}C NMR, HMBC, HSQC (75 MHz, DMSO-d_6): δ = 156.0 (C_qOCH_2O), 151.2 (C_qOCH_2O), 146.2 (C8), 138.7 (C13a), 138.5 (C14a), 135.1 (C4a), 131.5, 128.6, 128.2 (3 × Ar-C), 126.9 (C14b), 125.7 (Ar-C), 124.1 (C8a), 119.7 (C14), 104.0 (C9), 103.9 (C11), 103.0 (C13), 54.5 (C6), 26.4 (C5). ESI-MS: m/z (%) = 276.1 (100) $[M]^+$. ESI-HRMS: calculated for $[C_{18}H_{14}NO_2]^+$: m/z = 276.1025, found: 276.1034

5,6-Dihydrobenzo[*g*]isoquinolino[2,1-*b*]isoquinolinium Bromide (14). According to the general procedure, 2,3-bis(bromomethyl)naphthalene (**19**, 125.0 mg, 0.40 mmol) was reacted with 1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**16**, 63.3 mg, 0.40 mmol. 1.0 equiv). After 48 h, trituration with acetone afforded the title compound (43.6 mg, 0.12 mmol, 30%) as an orange solid, mp 232−233 °C.

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IR (ATR): 3421 (s, br), 3041 (m, br), 2928 (m), 1638 (s, sh), 1603 (w), 1420 (w), 931 (w), 767 (m). ^{1}H NMR, COSY (400 MHz, DMSO-d_6): δ = 10.47 (s, 1H, H-8), 9.32 (s, 1H, H-9), 9.25 (s, 1H, H-15), 8.95 (s, 1H, H-14), 8.44 (d, J = 8.1 Hz, 1H, H-10), 8.35 (d, J = 8.4 Hz, 1H, H-13), 8.34−8.28 (m, 1H, Ar-H), 7.90 (ddd, J = 8.4, 6.7, 1.1 Hz, 1H, H-12), 7.81 (ddd, J = 8.1, 6.7, 1.0 Hz, 1H, H-11), 7.60−7.56 (m, 2H, Ar-H), 7.54−7.50 (m, 1H, Ar-H), 5.01 (t, J = 6.1 Hz, 2H, H-6), 3.38 (t, J = 6.1 Hz, 2H, H-6). ^{13}C NMR, HMBC, HSQC (101 MHz, DMSO-d_6): δ = 154.6 (C8), 137.4 (C13a), 136.9 (C15a), 135.5 (C_q), 133.3 (C9), 133.3 (C9a), 132.3 (C14a), 131.6 (C12), 131.6 (Ar-C), 130.2 (C10), 129.1 (C11), 129.1 (C13), 128.9 (Ar-C), 128.7 (Ar-C), 127.7 (C_q), 127.0 (C14), 126.3 (Ar-C), 123.2 (C8a), 121.5 (C15), 55.9 (C6), 27.1 (C5). ESI-MS: m/z (%) = 282.1 (100) $[M]^+$. ESI-HRMS: calculated for $[C_{21}H_{16}N]^+$: m/z = 282.1283, found: 282.1288

2,3,6,7-Tetramethoxy-11,12-dihydrodibenzo[*f*,*h*]isoquinolino[2,1-*b*]isoquinolinium Bromide (15). According to the general procedure, 9,10-bis(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene[28] (**20**, 250.0 mg, 0.52 mmol) was reacted with 1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**16**, 81,6 mg, 0.52 mmol. 1.0 equiv). After 48 h, trituration with acetone afforded the title compound (211.3 mg, 0.40 mmol, 76%) as a yellow solid, mp 247−248 °C. IR (ATR): 3443 (m, br), 3003 (m, br), 1610 (m, sh), 1523 (s), 1467 (m, sh), 1428 (s), 1275 (s), 1231 (m), 1049 (m, sh). ^{1}H NMR, COSY (600 MHz, DMSO-d_6): δ = 10.39 (s, 1H, H-9), 9.43 (s, 1H, H-17), 8.71−8.62 (m, 1H, H-14), 8.46 (s, 1H, H-1), 8.28 (s, 1H, H-8), 8.03 (s, 1H, H-4), 8.02 (s, 1H, H-5), 7.69−7.64 (m, 2H, H15, H16), 7.60−7.57 (m, 1H, H-13), 5.03 (t, J = 6.4 Hz, 2H, H-11), 4.14 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 4.09 (s, 6H, OCH_3), 3.43 (t, J = 6.4 Hz, 2H, H-12). ^{13}C NMR, HMBC, HSQC (151 MHz, DMSO-d_6): δ = 153.5, 151.4, 149.6, 149.6 (4 × C_qOMe), 142.9 (C9), 141.1 (C16b), 138.3 (C17a), 135.7 (12a), 132.0 (Ar-C), 128.5 (C13), 128.4 (C4a), 128.1 (Ar-C), 127.3 (C14), 126.9 (C16a), 124.8 (C4b), 122.9 (C8b), 119.5 (C8a), 118.9 (C17b), 116.4 (C17), 107.2 (C1), 105.2 (C4), 104.9 (C5), 104.7 (C8), 56.5, 56.4, 56.2, 56.1, (4 × OCH_3) 54.3 (C11), 26.3 (C12). ESI-MS: m/z (%) = 452.3 (100) $[M]^+$. ESI-HRMS: calculated for $[C_{29}H_{26}NO_4]^+$: m/z = 452.1862, found: 452.1860.

■ ASSOCIATED CONTENT

Supporting Information

General methods and spectra for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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