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Syntheses of Aporphine and Homoaporphine Alkaloids by Intramolecular *ortho*-Arylation of Phenols with Aryl Halides via $S_{RN}1$ Reactions in Liquid Ammonia

Silvia M. Barolo,[†] Xin Teng,[‡] Gregory D. Cuny,*[,‡] and Roberto A. Rossi*[,†]

INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, 5000 Córdoba, Argentina, and Laboratory for Drug Discovery in Neurodegeneration, Brigham & Women's Hospital and Harvard Medical School, 65 Landsdowne Street, Cambridge, Massachusetts 02139

gcuny@rics.bwh.harvard.edu

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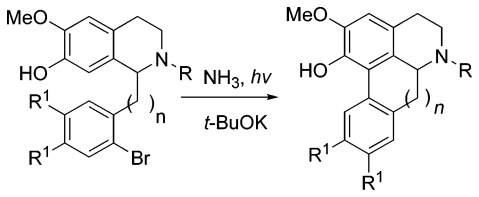
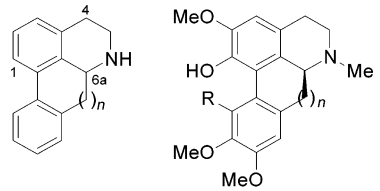


The photostimulated intramolecular *ortho*-arylation reactions of bromoarenes linked with pendant phenoxy containing N-substituted tetrahydroisoquinolines in liquid ammonia afforded aporphine (54−82% yield) alkaloid derivatives via $S_{RN}1$ reactions. This strategy was extended for the first time to the synthesis of a homoaporphine derivative (40% yield). Tetrahydroisoquinoline precursors that contained electron-withdrawing groups on nitrogen (i.e., amides, sulfonamides, and carbamates) gave cyclized products, whereas precursors with basic nitrogens (i.e., NH or NMe) either failed to yield cyclized products or gave aporphines in only low yield.

Introduction

Aporphines (**1**)[1] and homoaporphines (**2**)[2] are structurally diverse classes of natural products. Many aporphines have demonstrated interesting and assorted biological activities, while homoaporphines have been less studied.[3] A common structural feature among both alkaloid classes is the presence of a hydroxy at the 1-positions of the 5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]-quinoline and 4,5,6,6a,7,8-hexahydro-6-azabenzo[4,5]cyclohepta-[1,2,3-de]naphthalene ring systems. For example, (+)-thalicmidine, **3**,[4] and (+)-kreysigine, **4**,[5] both contain this structural element.



1 *n* = 1
2 *n* = 2

3 R = H; *n* = 1
4 R = OMe; *n* = 2

Several strategies have been utilized for the synthesis of 1-hydroxyaporphines and 1-hydroxyhomoaporphines. For example, substrates containing an additional hydroxy on the pendent aryl ring (i.e., **5**) have been cyclized to **7** utilizing oxidative coupling with Ph_2SeO,[6] $PhI(OAc)_2$,[7] $FeCl_3$,[8] or by biotransformation.[9] Another general strategy employed is to cyclize substrates containing a bromine-substituted pendent aryl

[†] Universidad Nacional de Córdoba.
[‡] Brigham & Women's Hospital and Harvard Medical School.

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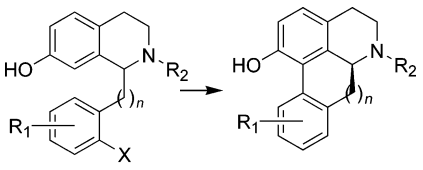
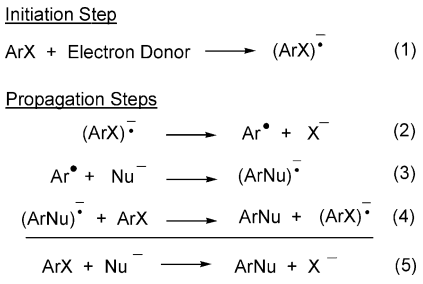
ring (i.e., **6**) using either a Pd-catalyzed *ortho*-arylation reaction[10] or a photostimulated coupling.[10d,11] In the present study, we further explore the syntheses of both aporphine and homoaporphine derivatives utilizing photostimulated coupling of suitable precursors.

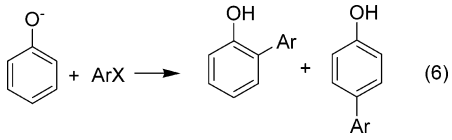


The radical nucleophilic substitution, or $S_{RN}1$, reaction is a process through which an aromatic nucleophilic substitution is achieved. The scope of this process has increased considerably and nowadays serves as an important synthetic strategy.[12] The $S_{RN}1$ mechanism is presented in Scheme 1. The initiation step (eq 1) is an electron transfer (ET) from the nucleophile to the substrate to afford a radical anion. In some systems, the ET step is spontaneous, but in others, light is required to induce the reaction. Electrons from dissolved alkali metals in liquid ammonia, from a cathode or inorganic salts (i.e., Fe^{2+} or SmI_2), can initiate the reaction. The propagation steps consist of fragmentation of the radical anion to afford a radical and the leaving group (eq 2), coupling of the radical with the nucleophile to afford a radical anion (eq 3), followed by ET to the substrate (eq 4) forming the intermediate necessary to continue the propagation cycle. Summation of eqs 2−4 gives an overall nucleophilic substitution (eq 5) in which radicals and radical anions serve as intermediates.

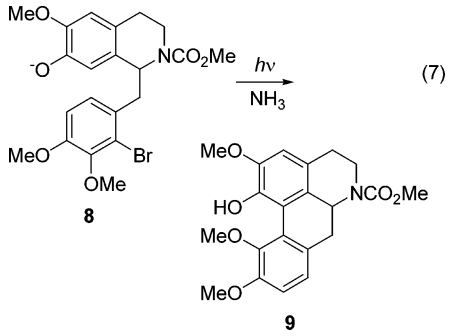
SCHEME 1



Several nucleophiles can be used for $S_{RN}1$ reactions, such as carbanions and heteroatom anions, resulting in the formation of new C−C or C−heteroatom bonds in good yields. An exception to this is the reaction of aromatic alkoxides with aromatic substrates. In these cases, C−O bond formation is not observed, but C−C bond formation is achieved instead. This is primarily due to the unfavorable thermodynamic driving force (∼5 kcal/mol) for C−O bond formation between the anion and the radical (eq 3) compared to C−C bond formation for an enolate (∼ −19 kcal/mol).[13] The unsubstituted PhO^- ions have been reported to react with *p*-$C_6H_5COC_6H_4Br$ upon electrolysis in liquid ammonia,[14] and with *p*-$NCC_6H_4N_2SR$ in DMSO under thermal or light initiation,[15] to afford the *ortho*- (ca. 40%) and *para*- (ca. 20%) coupled products (eq 6).



When a substrate has both the leaving group and the nucleophilic center, the *intramolecular* reaction will afford a cyclic product.[16] Intramolecular $S_{RN}1$ reactions have been used to prepare *N*-alkyl-1,3-dihydroxyindol-2-ones and 1,4-dihydro-2*H*-isoquinolin-3-ones in fair to good yields.[17] 2-Methyl and 2-phenyl-1,3-benzothiazoles,[18] tetrahydronaphthalene 1,3-carboxyamide,[19] a precursor of the alkaloids eupoulauramine,[20] (±)-tortuosamine,[21] and an Ergot-type alkaloid[22] were also obtained utilizing this approach. Recently, this method has been applied to the synthesis of 1-phenyl-1-oxazolinoindane derivatives containing quaternary C atoms.[23] Finally, this approach has been used for the synthesis of the aporphine skeleton **9**, although in low yield (19%) as shown in eq 7.[10d] Presumably, the methoxy group *ortho* to the leaving group bromine retards the coupling reaction. This is the only reported example of the synthesis of this structure by the $S_{RN}1$ mechanism.



Results and Discussion

The photostimulated reaction of **10a** with *t*-BuOK in liquid ammonia under a nitrogen atmosphere afforded 75% of **11a**.

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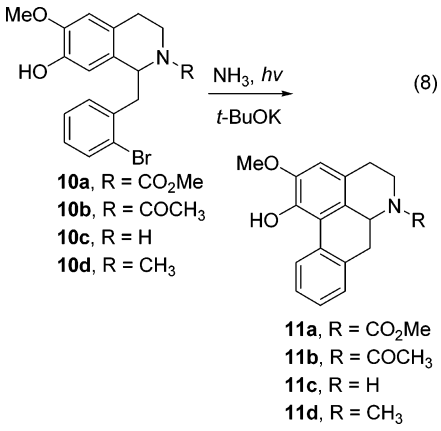
TABLE 1. Ring Closure Reactions[a]

expt.	substrate (mmol)	*t*-BuOK (mmol)	Br^- (%)[b]	product (%)[c]
1[d]	**10a** (0.10)	0.20	<2	
2	**10a** (0.50)	1.00	93	**11a** (75)
3[e]	**10a** (0.10)	0.20	90	**11a** (54)
4[f]	**10a** (0.10)	0.20	74	**11a** (53)
5	**10b** (0.18)	0.22	92	**11b** (82)
6	**10c** (0.25)	0.30	88	**15** (51), **16** (18)
7	**10d** (0.15)	0.18	84	**11d** (28)
8	**19a** (0.20)	0.40	87	**20a** (50), **21** (7)
9	**19c** (0.20)	0.40	88	**20c** (75)[g]
10	**22** (0.50)	1.00	70	**23** (54)[h]
11	**24** (0.20)	0.40	100	**25** (40)[g]

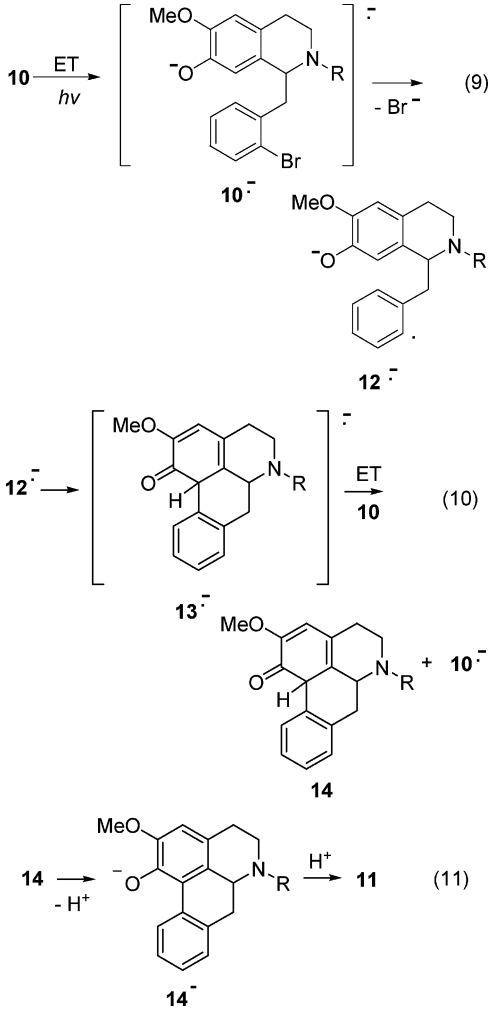
[a] The photostimulated reactions were carried out in 150 mL of dry liquid ammonia under nitrogen for 180 min. [b] The bromides were determined potentiometrically. [c] The products were determined by GLC, unless otherwise indicated. [d] Dark conditions. [e] *p*-DNB (20 mol %) was added. [f] The photostimulated reactions were carried out in 5 mL of dry DMSO under nitrogen. [g] The products were determined by ^{1}H NMR. [h] The products were determined by HPLC.

There is no reaction in the dark, and the photostimulated reaction was partially inhibited by *p*-dinitrobenzene (*p*-DNB), a well-known inhibitor of $S_{RN}1$ reactions (Table 1, experiments 1−3).



Together these results indicated that the reaction occurs by the $S_{RN}1$ mechanism, as depicted in Scheme 2. The initiation step is the photoinduced ET to the substrate, yielding the radical dianion $\mathbf{10}^{-\bullet}$.[24] Fragmentation of the C−Br bond of $\mathbf{10}^{-\bullet}$ gives the distonic radical anion $\mathbf{12}^{-\bullet}$ and Br^- ion (eq 9). The intermediate radical anion $\mathbf{12}^{-\bullet}$, via a intramolecular reaction, affords the radical anion $\mathbf{13}^{-\bullet}$.[25] An additional ET from **10** affords the intermediates **14** and the radical anion $\mathbf{10}^{-\bullet}$, which propagates the reaction (eq 10). The intermediate **14** gives the anion $\mathbf{14}^-$ under the basic reaction conditions. Upon acidification of the reaction media, product **11** is isolated (eq 11).

SCHEME 2



A reaction that competes with the cyclization is the reduction of the radical anion $\mathbf{12}^{-\bullet}$ by hydrogen abstraction from the solvent. Due to the mass balance being lower than 100%, we studied the photochemical stability of product **11a**. Irradiation of **11a** in liquid ammonia with *t*-BuOK for 180 min resulted in a 78% recovery of **11a**. This result indicates that **11a** suffers some decomposition under the irradiation conditions. The photostimulated reaction of **10a** in DMSO as solvent also afforded **11a**, but the yield was only 53% (Table 1, experiment 4). Likewise, the photostimulated reaction of **10b** with *t*-BuOK in liquid ammonia afforded 82% of **11b** (Table 1, experiment 5).

Quite different results were obtained in the photostimulated reaction of **10c** (R = H). In this case, the photostimulated reaction of **10c** with *t*-BuOK in liquid ammonia under nitrogen afforded only **15** and **16**. No ring closure product was observed (Table 1, experiment 6).

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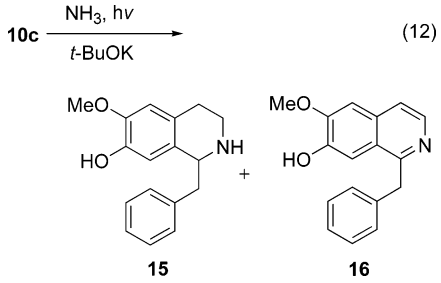
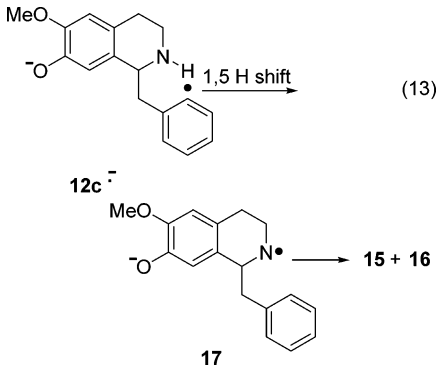
(23) Roydhouse, M. D.; Walton, J. C. *Chem. Commun.* **2005**, 4453−4455.
(24) The possibility of an intramolecular ET from the phenoxy moiety to the bromoarene can be ruled out since without excess *t*-BuO^- ions the reaction is quite slow. Furthermore, the fact that the reaction is inhibited by *p*-DNB is indicative of radical anion intermediates. Moreover, *t*-BuO^- ion (pK_a of *t*-BuOH is 32.2 in DMSO) is a better electron donor than phenoxide anions (pK_a of PhOH is 18.0 in DMSO). See: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463 and references therein.
(25) The driving force of the coupling reaction is that the conjugated radical anion $\mathbf{13}^{-\bullet}$ is ca. 40 kcal/mol more stable than the distonic radical anion $\mathbf{12}^{-\bullet}$ (AM1/UHF method).



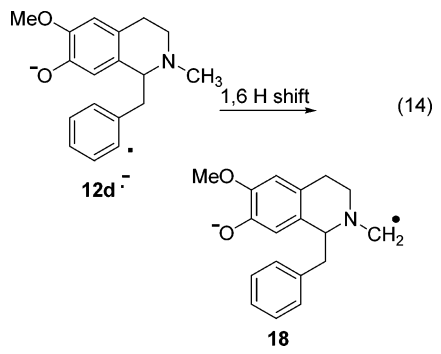
(12)

These results suggest that, when the aryl radical **12c**$^{-\bullet}$ is formed, an 1,5-hydrogen shift affords the aminyl radical **17** that leads to **15** and isoquinoline **16**. One potential pathway to account for the formation of **15** and **16** is disproportionation of **17** to give the products. The intermediate dihydroquinoline presumably could undergo oxidation upon workup to afford the isolated isoquinoline **16** (eq 13).[26]



(13)

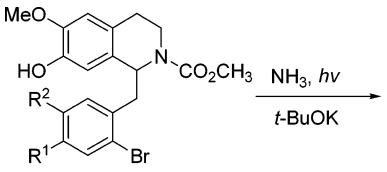
The photostimulated reaction of **10d** with *t*-BuOK in liquid ammonia under a nitrogen atmosphere afforded 28% of **11d** (Table 1, experiment 7). The low yield suggests that the radical intermediate **12d**$^{-\bullet}$ may also undergo a 1,6-hydrogen shift to give the radical **18**;[27] however, no products from this radical could be isolated (eq 14). Although the translocation of hydrogens is known in radicals,[28] there is only one previous report of translocation in $S_{RN}1$ reactions.[29]



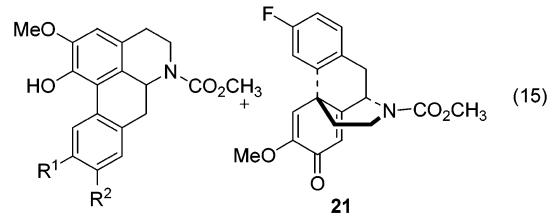
(14)

The $S_{RN}1$ reactions of substrates containing two leaving groups with nucleophiles afford either monosubstituted or disubstituted products depending on the structure of the substrate, the nature of the leaving group, or the nucleophile.[12] Fluorobenzene[30] and 2-fluoropyridine[31] react with acetone enolate ion under irradiation in liquid ammonia to afford the substitution products with displacement of fluorine. However, 3-fluoroiodobenzene[32] or 4-bromo-2-fluorobiphenyl[33] chemoselectively reacts under irradiation in liquid ammonia with acetone enolate ion to give the monosubstitution product with retention of fluorine and displacement of iodine and bromine, respectively.

In the photostimulated reaction of **19a** with *t*-BuOK in liquid ammonia under nitrogen, products **20a** (arylation in the *ortho*-position of the phenoxy group, 50% yield) and the 5,6,8,14-tetradehydromorphinan-7-one derivative **21** (arylation in the *para*-position of the phenoxy group, 7%) were isolated (eq 15; Table 1, experiment 8). Both products resulted from displacement of the bromine and retention of the fluorine.[34]



19a, R^1 = F, R^2 = H
19b, R^1 = H, R^2 = Cl
19c, R^1 = R^2 = OMe



(15)

20a, R^1 = F, R^2 = H
20b, R^1 = H, R^2 = Cl
20c, R^1 = R^2 = OMe

Several other substitution patterns were also investigated, for example, **19b**. However, in this case, the photostimulated reaction with an excess of *t*-BuOK in liquid ammonia, the product **20b** was not found. A complex mixture of products was obtained instead. In the case of the dimethoxy derivative **19c**, the photostimulated reaction affords product **20c**, a precursor to the natural product (±)-thalicmidine, in good yield (Table 1, experiment 9).

The photostimulated reaction of sulfonamide **22** with *t*-BuOK afforded aporphine product **23** in 54% yield (eq 16; Table 1, experiment 10).

(26) The driving force of the 1,5-hydrogen shift is that secondary aminyl radicals are ca. 15−20 kcal/mol more stable than phenyl radicals (AM1/UHF method). For the bond dissociation energy (BDE) of dimethylamine, see: (a) Feng, Y.; Liu, L.; Wang, J. T.; Zhao, S. W.; Guo, Q. X. *J. Org. Chem.* **2004**, *69*, 3129−3138. For the BDE of benzene see: (b) Ervin, K. M.; DeTuri, V. F. *J. Phys. Chem. A* **2002**, *106*, 9947−9956.

(27) The driving force of the 1,6-hydrogen shift is that radical **18** is ca. 20 kcal/mol more stable than radical **12d**$^{-\bullet}$ (AM1/UHF method). The BDE of CH_3 is 110.4 kcal/mol, whereas for benzene, it is 112.9 kcal/mol. For a review of BDE for organic molecules, see: Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255−263 and references therein.

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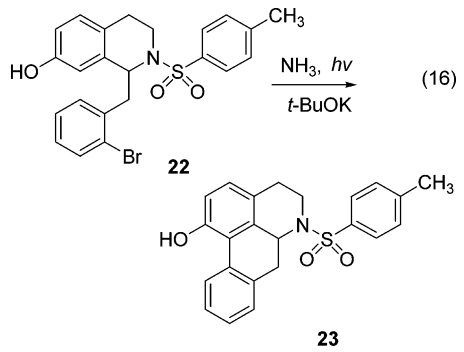
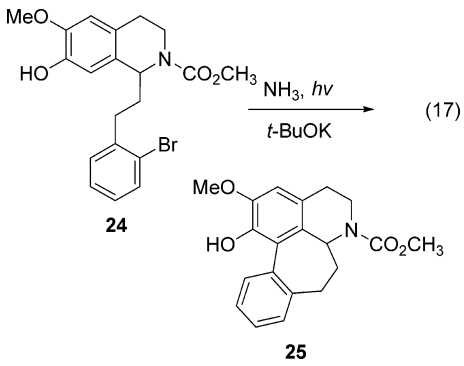
(34) The fact that this is the only example of ring closure at the *para*-position of the phenoxy group may be due to the more electrophilic character of the 3-fluoro-substituted phenyl radical compared to that of the phenyl radical.



To further explore the scope and limitations of these reactions, a substrate (i.e., **24**) containing a longer carbon tether between the tetrahydroisoquinoline and the aryl bromide was subjected to photostimulation in the presence of *t*-BuOK in liquid ammonia. The reaction afforded the 4,5,6,6a,7,8-hexahydro-6-azabenzo[4,5]cyclohepta[1,2,3-de]naphthalene derivative **25** in 40% yield (eq 17; Table 1, experiment 11). This reaction also produced several other unidentified products. Overall, this reaction demonstrates for the first time the potential for utilizing this methodology in the synthesis of homoaporphine alkaloids.



Conclusions

The photostimulated reaction of 1-(2-bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-7-ol derivatives, with N-substituents, such as SO_2Ar, C(═O)Me, and CO_2Me, afforded aporphine products in 54−82% yield. Tetrahydroisoquinoline precursors that contained basic nitrogens (i.e., NH or NMe) failed to give cyclized products or gave aporphines in low yield. Most likely this was due to a hydrogen shift from the N−H or the N−Me groups to the aryl radical intermediates. Pendent phenyl ring substituents, such as OMe and F, did not interfere with the cyclization reactions. However, in some cases, the formation of aporphines was accompanied by ring closure at the *para*-position to give small amounts of 5,6,8,14-tetradehydromorphinan-7-one derivatives. In substrates that contained two reactive halogens (i.e., Br and Cl) on the pendent phenyl rings, a complex mixture of products was obtained. Finally, the photostimulated reaction was extended to the synthesis of homoaporphine derivatives for the first time by utilizing a substrate containing a two-carbon tether between the tetrahydroisoquinoline ring and the aryl bromide.

Experimental Section

Synthesis of Substrates. The substrates **10a**−**d**, **19a**−**c**, **22**, and **24** were prepared according to literature procedures.[10a,b]

1-[1-(2-Bromobenzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]ethanone (10b). The ratio of major to minor rotamers was 74:26. Major: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 1.5, 7.5 Hz, 1H), 7.26−7.21 (m, 1H), 7.16−7.11 (m, 1H), 7.07−7.02 (m, 1H), 6.96 (s, 1H), 6.61 (s, 1H), 5.62 (s, 1H), 5.02 (dd, J = 3.0, 4.5 Hz, 1H), 3.89 (s, 3H), 3.38 (dd, J = 3.5, 13.0 Hz, 1H), 3.20−3.09 (m, 1H), 3.08 (dd, J = 11.5, 14.5 Hz, 1H), 2.89 (ddd, J = 5.5, 12.0, 16.0 Hz, 1H), 2.73−2.64 (m, 1H), 1.40 (s, 3H). Minor: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.40 (m, 1H), 7.19−7.15 (m, 1H), 7.16−7.11 (m, 1H), 7.07−7.02 (m, 1H), 6.64 (s, 1H), 6.56 (s, 1H), 5.83 (dd, J = 5.5, 8.5 Hz, 1H), 5.53 (s, 1H), 4.06 (t, J = 6.5 Hz, 1H), 3.87 (s, 3H), 3.73 (dt, J = 5.0, 12.5 Hz, 1H), 3.60 (ddd, J = 5.0, 9.0, 12.0 Hz, 1H), 3.32 (dd, J = 5.5, 14.0 Hz, 1H), 2.81 (ddd, J = 5.0, 10.0, 16.0 Hz, 1H), 2.73−2.64 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 170.1, 169.4, 146.0, 145.7, 144.3, 137.9, 137.4, 133.0, 132.8, 132.2, 131.6, 129.4, 129.1, 129.0, 128.4, 128.1, 127.2, 126.1, 125.5, 125.3, 124.9, 113.5, 112.7, 111.0, 110.5, 56.6, 56.2, 52.5, 43.0, 41.7, 41.5, 35.1, 28.9, 28.2, 22.0, 20.6; mp 178−179 °C; FT-IR (KBr pellet, ν_{max}, cm^{-1}) 3123brs, 3058s, 2922s, 2840m, 1629s, 1600s, 1536s, 1469s, 1283m, 1238m, 1221m, 1029m, 878m, 762m, 590m; HRMS [M + H]$^+$ 390.0710 (calcd for $C_{19}H_{20}BrNO_3$ + H]$^+$, 390.0705).

1-(2-Bromobenzyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (10d): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 1.0, 8.0 Hz, 1H), 7.20 (dt, J = 1.5, 8.0 Hz, 1H), 7.12−7.04 (m, 2H), 6.57 (s, 1H), 6.36 (s, 1H), 5.40 (brs, 1H), 3.86 (s, 3H), 3.85 (t, J = 7.5 Hz, 1H), 3.31 (ddd, J = 5.0, 10.0, 15.0 Hz, 1H), 3.17 (dd, J = 8.0, 14.0 Hz, 1H), 2.99 (dd, J = 5.5, 13.5 Hz, 1H), 2.94−2.87 (m, 1H), 2.83 (ddd, J = 3.0, 6.0, 12.5 Hz, 1H), 2.56 (ddd, J = 2.5, 5.5, 16.5 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 145.6, 143.5, 138.8, 132.9, 132.5, 129.1, 128.2, 127.3, 125.2, 125.0, 114.2, 110.8, 62.44, 56.0, 45.8, 42.2, 41.7, 24.2; mp 95−96 °C; FT-IR (KBr pellet, ν_{max}, cm^{-1}) 3415brs, 3006s, 2933s, 2840m, 1504s, 1441m, 1271s, 1259s, 1107m, 1027m, 864m, 788m, 751m, 661m, 569m; HRMS [M + H]$^+$ 362.0766 (calcd for $C_{18}H_{20}BrNO_2$ + H]$^+$, 362.0755).

1-(2-Bromo-4-fluorobenzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester (19a). The ratio of major to minor rotamers was 55:45. Major: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 1H), 7.09−6.98 (m, 1H), 6.97−6.88 (m, 1H), 6.85 (s, 1H), 6.60 (s, 1H), 5.53 (s, 1H), 5.32 (dd, J = 4.0, 11.0 Hz, 1H), 4.31 (ddd, J = 2.5, 6.0, 13.5 Hz, 1H), 3.88 (s, 3H), 3.44−3.24 (m, 2H), 3.25 (s, 3H), 2.97 (dd, J = 11.0, 14.5 Hz, 1H), 2.89 (ddd, J = 6.0, 11.0, 17.0 Hz, 1H), 2.70−2.58 (m, 1H). Minor: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 1H), 7.09−6.98 (m, 1H), 6.97−6.88 (m, 1H), 6.68 (s, 1H), 6.57 (s, 1H), 5.47 (s, 1H), 5.41 (dd, J = 5.0, 9.5 Hz, 1H), 3.96 (dt, J = 6.0, 13.5 Hz, 1H), 3.87 (s, 3H), 3.58 (s, 3H), 3.44−3.24 (m, 2H), 3.05 (dd, J = 9.5, 13.5 Hz), 2.81 (ddd, J = 6.0, 11.0, 17.0 Hz, 1H), 2.70−2.58 (m, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 162.5, 160.1, 156.0, 145.8, 145.7, 144.2, 144.1, 134.0, 133.9, 133.9, 133.8, 132.4, 132.3, 132.2, 132.1, 129.2, 129.1, 125.8, 125.3, 125.2, 125.1, 125.0, 119.8, 119.6, 114.6, 114.4, 114.3, 114.2, 113.1, 112.7, 110.9, 110.7, 56.1, 54.5, 53.8, 52.8, 52.3, 42.0, 41.4, 38.8, 37.5, 28.5, 28.4; mp 164−165 °C; FT-IR (KBr pellet, ν_{max}, cm^{-1}) 3366brs, 3004s, 2950s, 2850m, 1690s, 1597m, 1510m, 1485m, 1465m, 1265m, 1200m, 1103, 1025m, 988m, 866m, 764m, 574m; HRMS [M + H]$^+$ 424.0570 (calcd for $C_{19}H_{19}BrFNO_4$ + H]$^+$, 424.0559).

1-(2-Bromo-5-chlorobenzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester (19b). The ratio of major to minor rotamers was 65:35. Major: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.44 (m, 1H), 7.10−7.04 (m, 2H), 6.83 (s, 1H), 6.61 (s, 1H), 5.52 (s, 1H), 5.36 (dd, J = 3.5, 10.0 Hz, 1H), 4.30 (ddd, J = 2.5, 5.5, 12.5 Hz, 1H), 3.88 (s, 3H), 3.45−3.22 (m, 2H), 3.28 (s, 3H), 3.05−2.60 (m, 3H). Minor: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.44 (m, 1H), 7.10−7.04 (m, 2H), 6.71 (s, 1H), 6.58 (s, 1H), 5.48 (s, 1H), 5.41 (dd, J = 5.0, 9.0 Hz, 1H), 4.05−3.97 (m, 1H), 3.87 (s, 3H), 3.59 (s, 3H), 3.45−3.22 (m, 2H), 3.05−2.60 (m, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 156.1, 156.0, 145.8, 145.7, 144.3, 144.2, 139.9, 139.7, 133.8, 133.6, 133.2, 133.0, 131.5, 131.3, 129.1, 128.9, 128.4, 125.9, 125.8, 123.4, 123.1, 113.1, 112.7,

111.0, 110.7, 56.1, 54.2, 53.8, 52.8, 52.4, 42.8, 42.2, 38.7, 37.7, 28.5, 28.3; mp 129−130 °C; FT-IR (KBr pellet, ν_{max}, cm^{-1}) 3392brs, 2949s, 2931s, 2844m, 1686s, 1511m, 1460m, 1274m, 1199m, 1102m, 1032m, 883m, 794m, 504m; HRMS [M + H]$^+$ 440.0270 (calcd for $C_{19}H_{19}BrClNO_4$ + H]$^+$, 440.0264).

1-(2-Bromo-4,5-dimethoxybenzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester (19c). The ratio of major to minor rotamers was 63:37. Major: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.82 (s, 1H), 6.59 (s, 1H), 6.49 (s, 1H), 5.51 (s, 1H), 5.28 (dd, J = 4.0, 9.5 Hz, 1H), 4.26 (ddd, J = 2.0, 5.5, 12.5 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 3.40−3.20 (m, 2H), 3.32 (s, 3H), 2.95 (dd, J = 10.0, 14.0 Hz, 1H), 2.86 (ddd, J = 6.0, 11.0, 16.5 Hz, 1H), 2.61 (dt, J = 5.0, 15.5 Hz, 1H). Minor: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.66 (s, 1H), 6.56 (s, 1H), 6.55 (s, 1H), 5.46 (s, 1H), 5.40 (dd, J = 5.5, 7.5 Hz, 1H), 3.92−3.82 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 3.63 (s, 3H), 3.40−3.20 (m, 2H), 3.02 (dd, J = 8.0, 14.0 Hz, 1H), 2.76 (ddd, J = 5.5, 10.5, 15.5 Hz, 1H), 2.54 (dt, J = 7.0, 16.0 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 156.2, 148.4, 148.3, 148.2, 148.0, 145.7, 145.6, 144.2, 144.1, 130.0, 129.7, 129.3, 129.2, 126.0, 115.4, 115.3, 115.2, 115.1, 114.2, 113.9, 113.3, 112.9, 110.9, 110.6, 56.4, 56.3, 56.1, 54.7, 54.4, 52.8, 52.4, 42.3, 41.4, 39.0, 37.8, 28.4; mp 158−160 °C; FT-IR (KBr pellet, ν_{max}, cm^{-1}) 3366brs, 3000s, 2936s, 2843m, 1684s, 1510s, 1460s, 1261s, 1162m, 1104m, 1029m, 993m, 870m, 764m, 571m; HRMS [M + H]$^+$ 466.0851 (calcd for $C_{12}H_{24}BrNO_6$ + H]$^+$, 466.0865).

1-[2-(2-Bromophenyl)ethyl]-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester (24). The ratio of major to minor rotamers was 55:45. Major: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.46 (m, 1H), 7.30−7.18 (m, 2H), 7.07−7.00 (m, 1H), 6.67 (s, 1H), 6.57 (s, 1H), 5.47 (s, 1H), 5.10−5.03 (m, 1H), 4.33−4.24 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.42−3.25 (m, 1H), 3.00−2.75 (m, 3H), 2.65 (t, J = 4.0 Hz, 1H), 2.16−1.90 (m, 2H). Minor: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.46 (m, 1H), 7.30−7.18 (m, 2H), 7.07−7.00 (m, 1H), 6.67 (s, 1H), 6.55 (s, 1H), 5.45 (s, 1H), 5.26−5.19 (m, 1H), 4.12−4.03 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.42−3.25 (m, 1H), 3.00−2.75 (m, 3H), 2.62 (t, J = 3.0 Hz, 1H), 2.16−1.90 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 156.6, 145.6, 144.1, 141.5, 141.2, 133.1, 133.0, 132.9, 130.7, 130.5, 130.3, 130.1, 127.8, 127.7, 125.6, 125.3, 124.5, 124.0, 113.1, 112.8, 111.1, 110.9, 56.1, 54.5, 52.9, 38.3, 37.8, 37.0, 33.6, 28.3, 28.0; mp 58−59 °C; FT-IR (KBr pellet, ν_{max}, cm^{-1}) 3369brs, 3007s, 2953s, 2841m, 1693s, 1514s, 1471s, 1448s, 1266s, 1204s, 1099m, 1022m, 752m, 657m, 554m; HRMS [M + H]$^+$ 420.0810 (calcd for $C_{20}H_{22}BrNO_4$ + H]$^+$, 420.0811).

Photostimulated Reaction of 1-(2-Bromobenzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester (10a) with *t*-BuOK in Liquid Ammonia. The following procedure is representative. Into a three-necked, 250 mL, round-bottomed flask equipped with a cold-finger condenser charged with dry ice−ethanol, a nitrogen inlet, and a magnetic stirrer was condensed 150 mL of ammonia previously dried with Na metal under nitrogen. The *t*-BuOK (1.00 mmol) and **10a** (0.50 mmol) were added, and the mixture was irradiated for 180 min. The reaction was quenched by addition of NH_4NO_3 in excess, and the ammonia was allowed to evaporate. The residue was dissolved with water (60 mL) and then extracted with methylene chloride (3 × 20 mL), and the organic extract was washed twice with water (2 × 20 mL) and dried over anhydrous Na_2SO_4. The bromide ions in the aqueous solution were determined potentiometrically. The product **11a** was purified by column chromatography and quantified by GLC using the internal standard method.

Reaction of 10a with *t*-BuOK in Liquid Ammonia in the Dark. The procedure was similar to that for the previous reaction, except that the reaction flask was wrapped with aluminum foil.

Inhibited Photostimulated Reaction of 10a with *t*-BuOK in Liquid Ammonia. The procedure was similar to that for the previous reaction, except that *p*-DNB (20 mol %) was added to the solution.

Isolation and Identification of Products. 1-Hydroxy-2-methoxy-4,5,6*a*,7-tetrahydro-dibenzo[*de*,*g*]quinoline-6-carboxylic acid methyl ester (11a): The product was identical to an authentic sample.[10b]

1-(1-Hydroxy-2-methoxy-4,5,6*a*,7-tetrahydro-dibenzo[*de*,*g*]-quinolin-6-yl)ethanone (11b): Compound **11b** was purified by column chromatography (eluent: dichloromethane/ether gradient elution). It was recrystallized from chloroform:hexane to give white crystals; mp 260−262 °C (dec). ^{1}H NMR (CD_3SOCD_3): δ 8.77 (brs, 1H), 8.40 (d, J = 7.7 Hz, 1H), 7.29−7.20 (cplx m, 3H), 6.80 (s, 1H), 4.85−4.49 (m, 1H), 4.06−4.00 (m, 1H), 3.84 (s, 3H), 3.19−3.13 (m, 1H), 2.87−2.63 (cplx m, 4H), 2.12 (s, 3H). ^{13}C NMR (CD_3SOCD_3): δ 168.4, 146.7, 142.4, 136.3, 132.1, 128.6, 128.0, 126.7, 126.2, 125.7, 123.9, 119.8, 110.8, 56.0, 49.6, 41.4, 33.8, 29.7, 22.2. EM, *m*/*z* (%): 310 (10), 309 (44), 251 (6), 250 (18), 238 (26), 237 (100), 235 (6), 223 (8), 194 (9), 152 (6). HRMS (EI) calcd for $C_{19}H_{19}NO_3$: 309.1365. Found: 309.1369.

2-Methoxy-6-methyl-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]-quinolin-1-ol (11d): Compound **11d** was purified by column chromatography (eluent: dichloromethane/ether gradient elution). It was recrystallized from benzene to give white crystals; mp 163−165 °C dec (lit[35] 167−169 °C). ^{1}H NMR (CD_3COCD_3): δ 8.44−8.39 (cplx m, 1H), 7.57 (brs, 1H), 7.35−7.12 (cplx m, 3H), 6.69 (s, 1H), 3.87 (s, 3H), 3.18−2.87 (cplx m, 4H), 2.65−2.33 (cplx m, 3H), 2.48 (s, 3H). ^{13}C NMR (CD_3COCD_3): δ 147.5, 143.1, 137.3, 133.9, 129.6, 129.2, 128.7, 127.6, 127.3, 124.9, 120.4, 111.2, 63.8, 56.7, 54.5, 44.5, 36.1. EM, *m*/*z* (%): 282 (16), 281(84), 280 (100); 279 (58); 266 (20); 265 (21); 264 (36); 238 (36); 237 (10); 234 (11); 220 (18), 207 (10), 206 (19), 165 (16), 139 (10), 124 (16), 109 (22).

1-Benzyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol (15):[36] Compound **15** was purified by column chromatography (eluent: petroleum ether (60−80 °C)/acetone gradient elution). It was recrystallized from benzene to give pale yellow crystals. ^{1}H NMR (CD_3SOCD_3): δ 8.52 (brs, 1H), 7.33−7.13 (m, 5H), 6.63 (s, 1H), 6.55 (s, 1H), 3.92−3.89 (m, 1H), 3.69 (s, 3H), 3.25 (brs, 1H), 3.04−2.96 (m, 2H), 2.76−2.64 (m, 2H), 2.54−2.52 (m, overlapped, 2H). ^{13}C NMR (CD_3SOCD_3): δ 145.9, 144.2, 139.8, 131.3, 129.3, 128.0, 125.8, 125.6, 113.3, 112.3, 56.1, 55.6, 42.1, 40.0, 29.0. EM, *m*/*z* (%): 266 (8), 179 (12), 178 (100), 163 (19), 134 (6), 91 (8), 65 (5). Compound **15** exhibited spectral and analytical data in agreement with ref 36.

1-Benzyl-6-methoxyisoquinolin-7-ol (16): Compound **16** was purified by column chromatography (eluent: petroleum ether (60−80 °C)/acetone gradient elution). It was recrystallized from benzene to give white crystals; mp 205−207 °C (lit[37] 210−212 °C). ^{1}H NMR (CD_3SOCD_3): δ 9.81 (brs, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.50 (d, J = 5.5 Hz, 1H), 7.43 (s, 1H), 7.29−7.09 (cplx m, 6H), 4.43 (s, 2H), 3.91 (s, 3H).^{13}C NMR (CD_3SOCD_3): δ 156.7, 152.0, 147.7, 139.7, 139.7, 132.1, 128.4, 128.3, 125.9, 122.7, 118.5, 107.3, 105.7, 55.6, 41.1. EM, *m*/*z* (%): 266 (5), 265 (36), 264 (100), 249 (13), 248 (8), 221 (6), 220 (5), 204 (7), 102 (8), 96 (6), 51(5).

10-Fluoro-1-hydroxy-2-methoxy-4,5,6*a*,7-tetrahydrodibenzo-[*de*,*g*]quinoline-6-carboxylic acid methyl ester (20a): Compound **20a** was purified by chromatography on silica gel (eluted: petroleum ether (60−80 °C)/dichloromethane gradient elution). It was recrystallized from dichloromethane/petroleum ether as white crystals; mp 183−184 °C. ^{1}H NMR ($CDCl_3$): δ 8.20 (dd, J = 11.5, 2.8 Hz, 1H), 7.21 (dd, J = 8.2, 6.0 Hz, overlapped, 1H), 6.92 (ddd, J = 8.4, 8.2, 2.8 Hz, 1H), 6.64 (s, 1H), 6.22 (s, 1H), 4.76 (dd, J = 13.5, 4.0 Hz, 1H), 4.43 (m, 1H), 3.93 (s, 3H), 3.77 (s, 3H), 3.05−2.56 (cplx m, 5H). ^{13}C NMR ($CDCl_3$): δ 164.1, 159.3, 155.9, 145.7, 142.1, 133.4 (d, J_{C-F} = 8.1 Hz, 1C), 131.9 (d, J_{C-F} = 2.7 Hz, 1C),

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129.2 (d, J_{C-F} = 8.1 Hz, 1C), 126.1, 125.0, 115.6 (d, J_{C-F} = 24.4 Hz, 1C), 113.8 (d, J_{C-F} = 20.3 Hz, 1C), 110.1, 56.3, 52.7, 51.7, 39.1, 34.3, 30.0. GC/MS EI, *m*/*z* (%): 344 (15), 343 (70), 257 (8), 256 (46), 255 (100), 241 (24), 212 (11), 183 (10), 88 (8), 59 (15). HRMS (EI) calcd for $C_{19}H_{18}FNO_4$: 343.1220. Found: 343.1221.

1-Hydroxy-2,9,10-trimethoxy-4,5,6*a*,7-tetrahydrodibenzo[*d*,*e*,*g*]quinoline-6-carboxylic acid methyl ester (20c): Compound **20c** was purified by column chromatography (eluent: petroleum ether (60−80 °C)/ether gradient elution). It was recrystallized from ether/petroleum ether (60−80 °C) to give white crystals; mp 123−125 °C. ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H), 6.78 (s, 1H), 6.58 (s, 1H), 6.18 (s, 1H), 4.82−4.73 (m. 1H), 4.45−4.39 (m, 1H), 3.93 (s, 3H), 3.91 (s, 6H), 3.77 (s, 3H), 3.06−2.56 (cplx m, 5H). ^{13}C NMR ($CDCl_3$): δ 156.0, 148.0, 147.2, 145.8, 141.2, 129.4, 125.6, 125.0, 124.5, 120.2, 112.6, 111.3, 108.9, 56.3, 56.0, 55.8, 52.6, 52.0, 39.2, 34.6, 30.1. GC/MS EI, *m*/*z* (%): 386 (9), 385 (36), 298 (22), 297 (100), 283 (7), 282 (5), 267 (6), 207 (15). HRMS (EI) calcd for $C_{21}H_{23}NO_6$: 385.1525. Found: 385.1537.

3-Fluoro-6-hydroxy-5,6,8,14-tetrahydromorphin-7-one-15-carboxylic acid methyl ester (21): Compound **21** was purified by chromatography on silica gel (eluent: petroleum ether (60−80 °C)/ether gradient elution). Recrystallization from petroleum ether (60−80 °C)/dichloromethane produced white crystals; mp 195−196 °C. ^{1}H NMR ($CDCl_3$): δ 7.15−7.08 (cplx m, 2H), 6.95 (ddd, J = 8.2, 8.2, 2.6 Hz, 1H), 6.39 (brs, 1H), 6.31 (s, 1H), 5.28−5.15 (m, 1H), 4.09−3.91 (m, 1H), 3.81 (s, 3H), 3.73 (brs, 3H), 3.31 (dd, J = 17.5, 5.1 Hz, 1H), 3.17 (d, J = 17.5 Hz, 1H), 2.82 (td, J = 12.8, 3.3 Hz, 1H), 2.00 (brd, 1H), 1.71 (td, J = 12.8, 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 180.4, 164.5, 159.6, 158.0, 151.9, 139.6 (d, J_{C-F} = 5.4 Hz, 1C), 130.5, 130.0 (d, J_{C-F} = 8.1 Hz, 1C), 122.5, 117.4, 114.8 (d, J_{C-F} = 21.7 Hz), 112.3 (d, J_{C-F} = 21.7 Hz), 55.2, 53.0, 52.6, 42.6, 42.0, 38.3, 37.9. GC/MS EI, *m*/*z* (%): 344 (16), 343 (74), 328 (31), 326 (17), 325 (19), 315 (25), 312 (11), 311 (25), 300 (19), 284 (34), 283 (21), 282 (17), 269 (12), 268 (43), 256 (41), 255 (71), 252 (15), 242 (22), 241 (23), 240 (40), 237 (15), 236 (41), 227 (34), 226 (15), 225 (24), 224 (38), 223 (22), 214 (30), 213 (36), 212 (37), 199 (23), 198 (19), 197 (27), 196 (27), 195 (14), 185 (15), 184 (19), 183 (49), 171 (25), 170 (50), 157 (14), 133 (22), 88 (16), 59 (100), 56 (14), 55 (20), 53 (16), 51 (20). HRMS (EI) calcd for $C_{19}H_{18}FNO_4$: 343.1220. Found: 343.1221.

6-Benzenesulfonyl-2-methoxy-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinolin-1-ol (23): The product was identical to an authentic sample.[10a]

1-Hydroxy-2-methoxy-4,5,7,8-tetrahydro-6*aH*-6-azabenzo-[4,5]cyclohepta[1,2,3-*de*]naphthalene-6-carboxylic acid methyl ester (25): Compound **25** was purified by column chromatography (eluent: petroleum ether (60−80 °C)/ether gradient elution) to give a mixture with two isomers that have a relation of 60:40 and different NMR spectra. Recrystallization from ether/petroleum ether (60−80 °C) produced white crystals; mp 190−192 °C. ^{1}H NMR ($CDCl_3$): δ 7.57−7.49 (m, 2H), 7.30−7.27 (cplx m, 6H), 6.64 (s, 2H), 5.68 (brs, 1H), 4.82−4.74 (m, 1H), 4.67−4.58 (m, 1H), 4.38−4.28 (m, 1H), 4.17−4.09 (m, 1H), 3.91 (s, 6H), 3.64 (s, 3H), 3.57 (s, 3H), 3.35−3.17 (cplx m, 2H), 3.04−2.87 (cplx m, 2H), 2.73 (brs, 1H), 2.66 (brs, 1H), 2.57−2.49 (cplx m, 4H), 2.36−2.08 (cplx m, 4H). GC/MS EI, *m*/*z* (%): 340 (10), 339 (45), 324 (12), 323 (23), 322 (100), 308 (12), 251 (21), 237 (8), 165 (7). HRMS (EI) calcd for $C_{20}H_{21}NO_4$: 339.1471. Found: 339.1482.

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Supporting Information Available: General methods and ^{1}H and ^{13}C NMR of **10b**, **10d**, **11b**, **11d**, **15**, **16**, **19a**−**c**, **20a**, **20c**, **21**, and **24**; ^{1}H, ^{13}C NMR, DEPT, HETCOR, and ^{1}H−^{1}H COSY of **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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