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Lewis Acid Catalyzed Three-Component Hetero-Diels−Alder (Povarov) Reaction of *N*-Arylimines with Strained Norbornene-Derived Dienophiles

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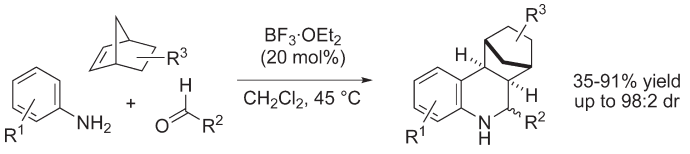

Generally, the hetero-Diels−Alder reaction (Povarov reaction) of *N*-arylimine dienes are limited to reaction with activated, electron-rich alkenes. However, introduction of ring strain in the dienophile, as with moderately strained bicyclo[2.2.1]heptenes (norbornene), enables three-component Povarov reaction with in situ formed *N*-arylimines under Lewis acid catalyzed conditions ($BF_3 \cdot OEt_2$). The reactions proceed efficiently with a diverse set of commercially available anilines and benzaldehydes, as well as a variety of substituted norbornenes. The corresponding tetrahydroquinolines are formed with high complexity in a multicomponent fashion and are obtained in good yield and high diastereoselectivity. In addition, more reactive ethyl glyoxylate derived imines were utilized to achieve faster, room temperature reactions with norbornene. In all cases, attack of the *N*-arylimine dienes occurred exclusively from the *exo*-face of the norbornene ring, but the relative stereochemistry of the substituent α to the tetrahydroquinoline nitrogen, as well as the regioselectivity of reaction, was shown to depend upon subtle substituent effects on the aniline precursors. In most cases, a preference for the formation of *exo*-*exo* diastereomeric adducts was observed, but for reactions of *ortho*- or *meta*-substituted anilines, the formation of *exo*-*endo* adducts was also observed. These observations may be rationalized by two competing mechanistic models, involving either a concerted asynchronous [4 + 2]-like mechanism or a stepwise mechanism.

Introduction

Hetero-Diels−Alder reactions of azadienes constitute one of the most convenient approaches to the synthesis of nitrogen heterocycles.[1] One variant of these reactions is the Povarov reaction, in which tetrahydroquinolines[2] are formed by the coupling of electron-deficient *N*-arylimines (2-azadienes) and electron-rich alkenes (Scheme 1).[3] The Povarov reaction is usually promoted by either protic or Lewis acidic catalysis and can be performed in a multicomponent fashion by the coupling of alkenes, aldehydes, and anilines via in situ imine formation and subsequent formal [4 + 2]-cycloaddition. The formal [4 + 2]-cycloaddition can be viewed as occurring either through a concerted inverse-electron demand Diels−Alder reaction mechanism or via a stepwise Mannich-like reaction/intramolecular electrophilic aromatic substitution sequence. While a wide variety of anilines and aldehydes are known to participate in the Povarov reaction, the dienophile component is usually limited to activated, electron-rich alkenes, such as cyclic and acyclic enamines, enamides and enol ethers, and cyclic conjugated dienes.

Generally, the use of simple alkenes as dienophiles has met with limited success in the Povarov reaction. However, the limitation of requiring activated, electron-rich dienophiles for the Povarov reaction can be overcome through the

(1) For a review on the hetero-Diels−Alder reaction, see: (a) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Permagon Press: Oxford, 1991; Vol. 5; pp 401−449. (b) Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Permagon Press: Oxford, 1991; Vol. 5; pp 451−512. (c) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138. (d) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558–3588. (e) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; pp 151−209.

(2) For recent reviews of tetrahydroquinoline synthesis, see: (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070. (b) Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141–161.

(3) For reviews on the Povarov reaction, see: (a) Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2008**, *77*, 137–159. (b) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656−670 and references cited therein.

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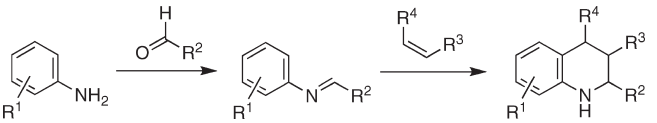
SCHEME 1. Formation of Tetrahydroquinolines from the Povarov Reaction

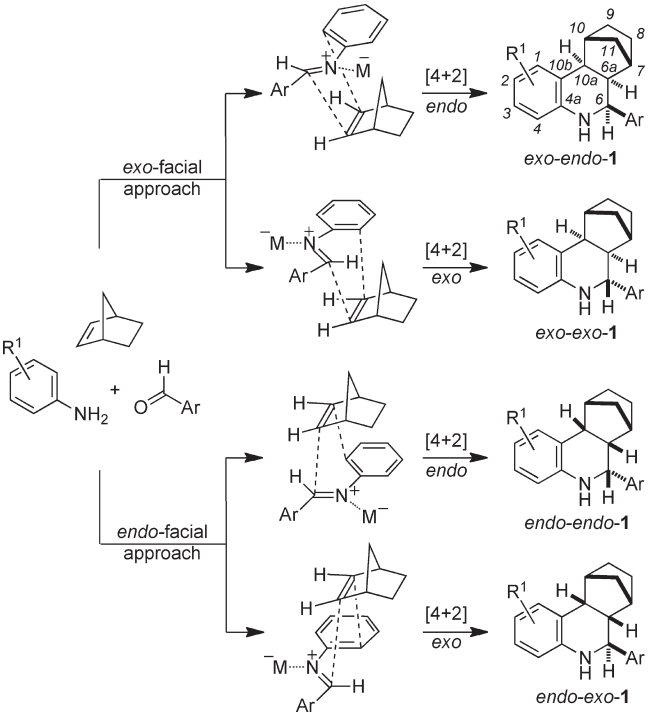


introduction of ring strain in the dienophile.[4−7] Examples of strained dienophiles used in the Povarov reaction include methylenecyclopropanes and azetidines.[4] The use of ring-strained bicyclic alkenes provides another general strategy for dienophile activation. Increasing the reactivity of alkenes through the introduction of ring strain is known for many reactions. Perhaps one of the most well-used classes of moderately strained alkenes is bicyclo[2.2.1]heptenes (norbornenes). For example, norbornene has recently been used as an activated dienophile in 1,3-dipolar cycloadditions of nitrile oxides[8] and has been shown to be more reactive toward allylic hydroxylamines in a thermal tandem Cope-type hydroamination/[2,3]-rearrangement sequence.[9] Norbornene is also required as an additive in the palladium-catalyzed Catellani reaction.[10] There are few examples on the use of norbornene as a dienophile in the Povarov reaction, and selectivity effects in these reactions have not been studied.[5,6] We now report the use of moderately strained bicyclo[2.2.1]heptenes[11] as dienophile components in the three-component Povarov reaction using Lewis acid catalysis, including investigations on the regio- and diastereoselectivity of these reactions, and the use of substituted norbornenes. The resultant products have complex natural product-like[12] tetracyclic architectures that could have interesting biological properties.

Results and Discussion

The Povarov reaction of the parent bicyclo[2.2.1]heptene, norbornene, can potentially lead to four possible diastereomers of **1**,[13] arising from the facial selectivity of addition to either face of norbornene and the relative stereochemistry of the initial bond-forming event between C-6 and C-6a (Scheme 2). However, the strong inherent preference of norbornene to react via the *exo*-face would be expected to limit the observed diastereomers to *exo-endo*-**1** and *exo-exo*-**1**.[14,15]

SCHEME 2. Three-Component Povarov Reaction of *N*-Arylimines with Norbornene



Initial screening studies using a three-component coupling approach revealed that a range of Lewis acids were capable of promoting the reaction between methyl 4-aminobenzoate **2** (1.0 equiv), 4-bromobenzaldehyde **3** (1.1 equiv), and excess norbornene (Table 1). Using $BF_3 \cdot OEt_2$, *exo-exo*-**1a** was obtained in 38% yield along with 3% of the corresponding quinoline **5** and 11% of **6**, presumably resulting from reduction of the in situ formed imine (Table 1, entry 1).[16] Raising the temperature to 45 °C increased the yield of **1a** to 85% (Table 1, entry 2). Metal and lanthanide triflates

(4) For examples using activated strained alkenes, see: (a) Trifonov, L. S.; Orahovats, A. S. *Heterocycles* **1984**, *22*, 355–364. (b) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *Chem. Commun.* **2002**, 444–445. (c) Shao, L.-X.; Shi, M. *Adv. Synth. Catal.* **2003**, *345*, 963–966. (d) Shao, L.-X.; Xu, B.; Shi, M. *Org. Lett.* **2003**, *5*, 579–582. (e) Lu, J.-M.; Shi, M. *Org. Lett.* **2007**, *9*, 1805–1808.

(5) Single examples on the use of norbornadiene and norbornene have been reported, both of which are reported to occur via unusual *endo*-facial attack on the alkene. See: (a) Destro, F.; Prato, M.; Lucchini, V. *Tetrahedron Lett.* **1984**, *25*, 5573–5576. (b) Campos, P. J.; Lamaza, I.; Rodriguez, M. A.; Canal, G. *Tetrahedron Lett.* **1997**, *38*, 6741–6744.

(6) A trifluoroacetic acid (1.0 equiv) promoted coupling of anilines, aldehydes, and norbornene has been applied to the synthesis of bridged phenanthridines; however, the diastereoselectivity of the reaction and relative stereochemistry of the adducts were not reported. See: Ralbovsky, J. L.; Beckett, R. P. U.S. Patent 20080214537, September 4, **2008**.

(7) (a) For a related reaction of *N*-arylnitrilium salts with norbornene, see: Moustafa, A. H.; Hitzler, M. G.; Lutz, M.; Jochims, J. C. *Tetrahedron* **1997**, *53*, 625–640. (b) For a related reaction using an azomethine ylide with norbornene, see: Pohlhaus, P. D.; Bowman, R. K.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2294–2295. (c) For a related metalloporphyrin-catalyzed radical reaction of *para*-cyano-*N*,*N*-dimethylaniline with norbornene, see: Dicken, C. M.; Lu, F.-L.; Bruice, T. C. *Tetrahedron Lett.* **1986**, *27*, 5967–5970.

(8) Mayo, P.; Hecnar, T.; Tam, W. *Tetrahedron* **2001**, *57*, 5931–5941.

(9) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874–875.

(10) (a) Catellani, M.; Fagnola, M. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2421–2422. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119–122.

(11) (a) An indication of the strain release on going from a norbornene system to a norbornane is apparent from the heat of hydrogenation, which was determined to be −33.1 kcal mol^{-1}. This strain release is 6 kcal mol^{-1} higher than the conversion of cyclohexene to cyclohexane: Turner, R. B.; Meador, W. R.; Winkler, R. E. *J. Am. Chem. Soc.* **1957**, *79*, 4116–4121. (b) The strain energy of norbornene has been recently calculated as 21.6 kcal mol^{-1} (B3LYP/6-31G*): Khoury, P. R.; Goddard, J. D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103–8112.

(12) For recent reviews on reactions suitable for diversity and target-oriented synthesis, see: (a) Shaw, J. T. *Nat. Prod. Rep.* **2009**, *26*, 11–26. (b) Nandy, J. P.; Prakesch, M.; Khadem, S.; Reddy, P. T.; Sharma, U.; Arya, P. *Chem. Rev.* **2009**, *109*, 1999–2060.

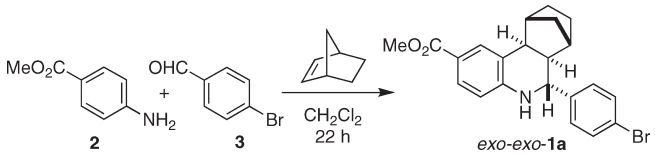
(13) This assumes that *syn*-addition of the imine diene occurs across the alkene of the norbornene.

(14) The following notation is used to differentiate between the possible diastereomers. The first term results from the mode of facial selectivity for addition to the norbornene system (*exo* or *endo*), while the second term (*exo* or *endo*) is defined on the basis of the Diels−Alder reaction, where H-6 and H-6a have a *trans* and *cis* relationship, respectively.

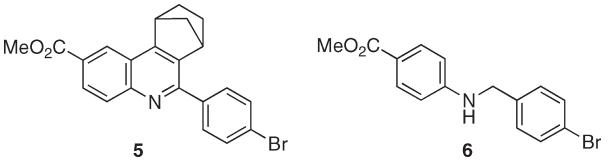
(15) Campos has suggested that a highly unusual *endo*-facial attack on the norbornene occurs in reaction of *N*-(methoxymethyl)arylamines; see ref 5b. We did not observe any formation of *endo-endo*-**1** or *endo-exo*-**1** diastereomers in our study.

(16) This diastereomer was assigned based on comparison to other related tetrahydroquinolines and their H-6−H-6a and H-6a−H-10a coupling constants (typically J = 10−11 Hz and J = 8−9 Hz, respectively).

TABLE 1. Optimization of Three-Component Povarov Reaction of 2, 3 and Norbornene



entry	catalyst (mol %)	temp (°C)	yield (%)[a] (**1a**/**5**/**6**)[b]
1	$BF_3 \cdot OEt_2$ (20)	rt	38 (38:4:11)
2	$BF_3 \cdot OEt_2$ (20)	45	85 (85:6:9)
3	$Yb(OTf)_3$ (10)	45	42 (42:2:5)[c]
4	$Sc(OTf)_3$ (10)	45	81 (81:6:13)
5	$Cu(OTf)_2$ (10)	45	71 (71:6:10)
6	TfOH (10)	45	32 (32:4:9)
7	CAN (10)[e]	45	NR[d]
8	$BF_3 \cdot OEt_2$ (20) + DDQ (2 equiv)	45	36[f]



[a]Yields determined by ^{1}H NMR integration relative to 1,3,5-trimethoxybenzene as an internal standard. [b]Determined by relative ^{1}H NMR integrations (H-6 or H-10a). [c]40% of the in situ formed imine present. [d]In situ formed imine **4** (not shown) was isolated. [e]Performed in CH_3CN. [f]Isolated yield of quinoline **5**.

were also competent catalysts (Table 1, entries 3−5), with $Sc(OTf)_3$ giving the highest yield. On the other hand, protic acids such as triflic acid were less effective as catalysts (Table 1, entry 6), perhaps due to competing oligomerization reactions.[6] For each of these reactions (Table 1, entries 1−6), small amounts of quinoline **5** and amine **6** were also formed in an approximately 1:2 ratio. The formation of these side products is most likely the result of a hydrogen transfer mechanism.[17] Variation of the reaction stoichiometry, solvent, and the temperature did not significantly affect the formation of these side products. The use of cerium ammonium nitrate (CAN),[18] which can act as both a Lewis acid and an oxidant, was unsuccessful (Table 1, entry 7). However, a combination of $BF_3 \cdot OEt_2$ and DDQ led to the exclusive formation of quinoline **5** (Table 1, entry 8). Attempts to apply the optimized $BF_3 \cdot OEt_2$-based conditions to less reactive dienophiles such as cyclohexene and cyclopentene were unsuccessful.

Application of the optimized conditions of $BF_3 \cdot OEt_2$ (20 mol %) in CH_2Cl_2 at 45 °C for 22 h to a variety of commercially available aromatic aldehydes and anilines with norbornene led to the formation of tetrahydroquinolines **1a**−**t** in good to excellent yields (Table 2). The electronic nature of the aniline and aromatic aldehyde had little effect upon product formation. However, the position of the substituents on the aniline did affect the diastereoselectivity of the reaction. In all cases, exclusive *exo*-facial selectivity on the norbornene ring was observed;[16] however, the relative stereochemistry of the C-6 substituent with respect to C-6a/C-10a was not always selective. Sole formation of the *exo-exo* diastereomer of **1a**−**i** was observed with all anilines containing *para* substituents. X-ray crystallography of **1d** revealed an *exo-exo* relative stereochemistry[19] and validated the stereochemical assignment for all of the other *exo-exo* diastereomers. Next, a survey of differentially substituted chloroanilines was conducted. *ortho*-Chloroanilines gave a mixture of diastereomers (Table 2, entries 10−12), with a modest preference for the formation of the *exo-exo*-**1** diastereomer. Following separation of the diastereomers of **1l** by column chromatography, the stereochemistry of the *exo-endo* diastereomer was confirmed by X-ray crystallography.[19] Unexpectedly, a complete reversal in diastereoselectivity was observed for the reaction of the di-*meta*-substituted 3,5-dichloroaniline, which exclusively afforded *exo-endo*-**1m** (Table 2, entry 13). The use of 2,5-dichloroaniline, which has both *ortho*- and *meta*-chloro substituents, resulted in the preferential formation of the *exo-exo* diastereomer **1n** in a 76:24 dr (Table 2, entry 14). In this case, the *exo-exo* directing effect of the *ortho*-chloro substituent appears to override the *exo-endo* directing effect of the *meta*-chloro substituent. Modest regioselectivity was observed[20] for the Povarov reaction with *meta*-substituted anilines (Table 2, entries 15−17), although each regioisomer was formed with remarkably high diastereoselectivity. The 3-substituted regioisomers were formed as the *exo-exo*-**1** diastereoisomers (≥98:2), whereas the 1-substituted regioisomers were formed as the *exo-endo*-**1** diastereoisomers

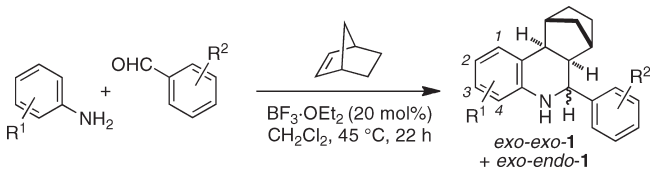
(17) For similar hydrogen transfer mechanisms, see: (a) Shindoh, N.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *J. Org. Chem.* **2008**, *73*, 7451–7456. (b) Itoh, T.; Nagata, K.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **2002**, *43*, 3105–3108.

(18) For recent examples of CAN-catalyzed Povarov reactions, see: (a) Sridharan, V.; Avendano, C.; Menéndez, J. C. *Synlett* **2007**, 1079–1082. (b) Savitha, G.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 3589–3593.

(19) For details of single-crystal X-ray analysis, see the Supporting Information.

(20) Hayashi, R.; Cook, G. R. *Org. Lett.* **2007**, *9*, 1311–1314.

TABLE 2. Formation of Tetrahydroquinolines 1 from the $BF_3 \cdot OEt_2$-Catalyzed Three-Component Coupling Reaction of Anilines, Aromatic Aldehydes, and Norbornene[a]



entry	aniline (R^1)	aldehyde (R^2)	product	yield[b] (%)	dr[c] (*exo-exo*:*exo-endo*)
1	4-CO_2Me	4-Br	**1a**	60(85)[d]	≥98:2
2	4-CO_2Me	H	**1b**	74	≥98:2
3	H	H	**1c**	76	≥98:2
4	4-CO_2Me	3,4-Cl	**1d**	74(87)[d]	≥98:2
5	4-CO_2Me	4-NO_2	**1e**	81	≥98:2
6	4-OMe	4-Br	**1f**	69	≥98:2
7	4-Cl	2-OMe	**1g**	58	≥98:2
8	4-Cl	4-Br	**1h**	78[e]	≥98:2
9	4-Cl	3,4-Cl	**1i**	82	≥98:2
10	2-Cl	4-Br	**1j**	70[e]	72:28
11	2-Cl	3,4-Cl	**1k**	59	59:41
12	2,4-Cl	3,4-Cl	**1l**	65	55:45
13	3,5-Cl	3,4-Cl	**1m**	91	2:98
14	2,5-Cl	3,4-Cl	**1n**	55	76:24
15	3,4-Me	4-Br	**1o/1p**	82	≥98:2/≤2:98[f]
16	3-Cl	4-Br	**1q/1r**	82	≥98:2/≤2:98[g]
17	3-F	4-Br	**1s/1t**	76	≥98:2 /≥ 98:2[h]

[a]Aniline (1.0 equiv), aldehyde (1.1 equiv), norbornene (2.0 equiv). [b]Isolated yields based on the aniline. [c]Determined by the relative integrations of H-6 in the ^{1}H NMR of the crude reaction mixture. [d]Estimated yield (by ^{1}H NMR) in parentheses. [e]10% of the corresponding quinoline was isolated. [f]Isolated as a 60:40 mixture of 2,3-Me (**1o**)/1,2-Me (**1p**). [g]Isolated as a 36:64 mixture of 3-Cl (**1q**)/1-Cl (**1r**) regioisomers. [h]Isolated as a 56:44 mixture of 3-F (**1s**)/1-F (**1t**) regioisomers.

(≥98:2). However, in the case of the reactions of *meta*-fluoroaniline, only *exo-exo*-**1** diastereomers were observed for both regioisomers (Table 2, entry 17).

^{1}H NMR analysis of the Povarov adducts **1** was generally sufficient to distinguish between the *exo-exo*-**1** and *exo-endo*-**1** diastereomers. The most diagnostic observations for the determination of the relative stereochemistry were the chemical shift of the H-6 proton and the coupling constant between protons H-6 and H-6a. The chemical shift of the H-6 proton was consistently more downfield in the *exo-endo* series by approximately 0.6 ppm (e.g., H-6; *exo-endo* = 4.16 ppm, *exo-exo* = 3.50 ppm for **1l**). The coupling constant values for $^3J_{H6-6a}$ were in the range of 4−5 Hz for the *exo-endo* series and 10−11 Hz in the *exo-exo* series (e.g., $^3J_{H6-6a}$ = 4.5 Hz for *exo-endo*-**1l** and $^3J_{H6-6a}$ = 10.0 Hz for *exo-exo*-**1l**). For a rigid cyclohexane, these coupling constant values are indicative of a pseudo-axial−equatorial coupling and pseudo-axial−axial coupling, respectively.

In addition to confirming the relative stereochemical assignments, a comparison of the X-ray crystallographic structures of compounds *exo-exo*-**1d** and *exo-endo*-**1l** revealed that in both cases the tetrahydroquinoline ring adopts a half-chair conformation, with the C-6 aryl substituent in a pseudo-equatorial position.[19] The torsional angle (H-6−C-6−C-6a−H-6a) for the solid state structure of *exo-exo*-**1d** was determined to be 165.5°, which is consistent with the observed $^3J_{H6-6a}$ coupling constants of 10−11 Hz for the *exo-exo* series, with H-6 and H-6a adopting pseudo-axial positions with an *anti* relationship. In contrast, the measured (H-6−C-6−C-6a−H-6a) torsional angle for *exo-endo*-**1l** was determined to be 43.8°, which is consistent with the observed $^3J_{H6-6a}$ coupling constants of 4−5 Hz for the *exo-endo* series, characteristic of the *syn* relationship of these protons in a pseudo-axial−equatorial relationship. These observations are in agreement with the observed ^{1}H NMR coupling constants of the *exo* and *endo* products in the furo[3,2-*c*]quinolines and pyrrolo[3,2-*c*]quinolines previously studied in our group.[21]

In several cases, additional ^{1}H 2D ROESY experiments were also used to confirm the relative stereochemical assignments. For example, a comparison of the ROESY spectra for both diastereomers of **1j** revealed ROE enhancements for both H-6a and H-10a with the proximal protons on the ethano bridge of the norbornene ring (blue arrows) and strong ROE enhancements between the H-6a and H-10a protons (pink arrows), thus confirming that the tetrahydroquinoline core was attached to the *exo*-face of norbornene (Figure 1). A strong ROE correlation between H-6 and the proximal hydrogen of the methano bridge (red arrow) was diagnostic for the *exo-exo* diastereoisomer. For the *exo-endo* diastereoisomer, diagnostic strong ROE correlations were observed between both H-6 and H-6a (red arrow) and a weak ROE correlation between H-6 and H-10a (black arrow).

Substituted norbornenes were also investigated as partners in the Povarov reaction (Table 3). Reaction with norbornadiene **7a** produced the corresponding *exo-exo* adduct **8a** in 35% yield (Table 3, entry 1). The formation of a

(21) (a) Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J.; Batey, R. A. *Chem. Commun.* **1999**, 651–652. (b) Powell, D. A.; Batey, R. A. *Chem. Commun.* **2001**, 2362–2363. (c) Powell, D. A.; Batey, R. A. *Tetrahedron Lett.* **2001**, *42*, 7935–7939. (d) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916. (e) Powell, D. A. Multi-component Hetero Diels−Alder Reaction of N-Arylimines: Synthesis of Functionalized Tetrahydroquinolines and Total Synthesis of the Martinelline Alkaloids. Ph.D. Thesis, University of Toronto, **2003**, pp 38−42.

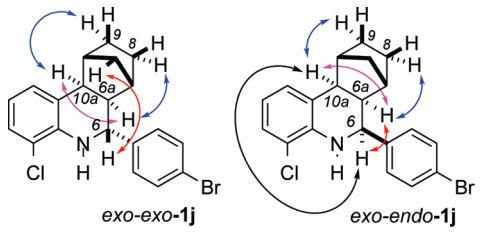


FIGURE 1. Relevant ROE enhancements for *exo-exo*-**1j** and *exo-endo*-**1j**.

significant amount of amine **6** (25%) and quinoline **9** (10%) was responsible for the low yield of **8a** obtained. The unusual formation of **9** most likely arises from an oxidation to the 3,4-dihydroquinoline followed by a retro-[4 + 2]-cycloaddition. Both *endo*- and *exo*-dicyclopentadiene afforded the corresponding tetrahydroquinolines **8b** and **8c** in 63 and 75% yield (Table 3, entries 2 and 3), respectively. In both cases, an inseparable mixture of regioisomers (2:1) was isolated. Of particular note is the high chemoselectivity observed, as only reaction with the norbornene alkene bond occurs, thus demonstrating the activating effect of increased strain on the bicyclic skeleton. In order to simplify characterization, the regioisomers of both **8b** and **8c** were subjected to diimide reduction using potassium azodicarboxylate (PADA) to give the reduced adducts **10** and **11**, respectively (Scheme 3).[22] Reaction of *endo*-norbornene methanol **7d** gave **8d** as a mixture of regioisomers (1.1:1) in a combined yield of 50% (Table 3, entry 4).[23] Interestingly, only one regioisomer of **8e** was isolated when the corresponding *p*-nitrobenzoyl-protected substrate **7e** was used (Table 3, entry 5). Both the *endo*- and *exo*-isomers of cyclic anhydride-substituted norbornene **7f** were found to be completely unreactive (entry 6), presumably due to the deactivating effect of the electron-withdrawing carbonyl groups. However, the bis(methoxymethyl)-substituted norbornene **7g** proved to be more reactive, resulting in a 68% yield of **8g** (Table 3, entry 7).

An approach to complement the generally lower reactivity of norbornenes (compared to electron-rich dienophiles) is to utilize more reactive imines. The use of ethyl glyoxylate derived imines led to faster reactions even at room temperature (Scheme 4). However, isolation of the ethyl ester substituted tetrahydroquinolines **12a** and **12b** (not shown) proved to be difficult because of their instability in air and in solution, resulting in lower yields.[24] Instead, immediate reduction of the crude Povarov reaction mixture using $LiAlH_4$ in THF led to adducts **13a** and **13b**, which were isolated in 60 and 55% yield as a 5:1 and 4.5:1 mixture of diastereoisomers, respectively. X-ray crystallography of the major stereoisomer of **13a** confirmed the *exo-exo* relative stereochemical assignment.[19]

(22) For the preparation of potassium azodicarboxylate (PADA), see: (a) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083–1090. For PADA reduction procedure, see: (b) Patterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3016–3020.

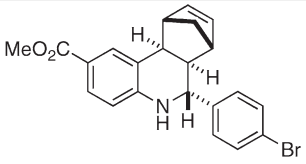
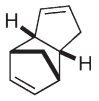
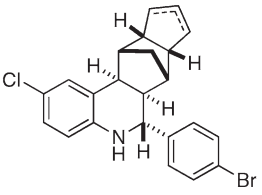
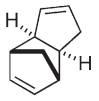
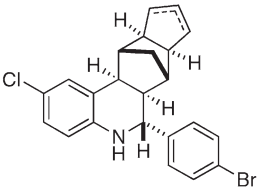
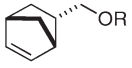
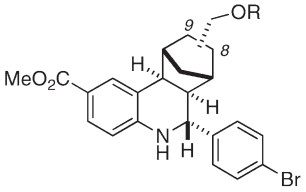
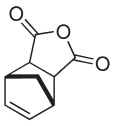
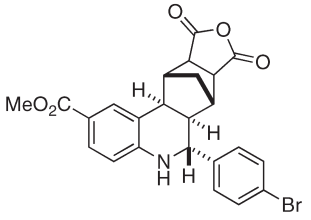
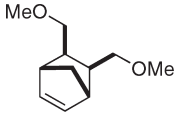
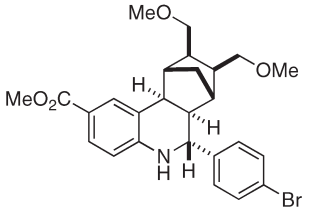
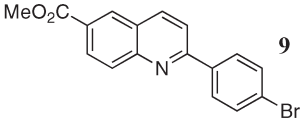
(23) In addition, no other side products were isolated as might have been envisaged had an intramolecular trapping by the hydroxyl group occurred in the case of a stepwise Povarov mechanism.

(24) The ethyl ester substituted tetrahydroquinolines **12a** and **12b** were isolated with acceptable purity and in 44 and 40% yield, respectively. See the Experimental Section for characterization data and the Supporting Information for copies of ^1H and ^{13}C NMR spectra.

Substituent effects on the aniline-derived ring appear to play a remarkable role upon the diastereoselectivity achieved in these reactions. As for other Povarov reactions, there are two general mechanisms that can be envisaged for the formation of the adducts: (i) a concerted [4 + 2]-like mechanism or (ii) a stepwise Mannich-like process. For the [4 + 2]-like process, asynchronous C-6−C-6a and C-10a−C-10b bond formation can be envisaged. For the [4 + 2]-like mechanism orienting the Lewis acid coordinated imine C=N and imine C−Ar groups away from the bridging methylene (C-11) of norbornene would be expected to minimize steric interactions in the *exo-exo*-**TS** transition state (Figure 2a). Reaction via *exo-exo*-**TS** would lead initially to intermediate **14**, which after loss of a proton would lead to *exo-exo*-**1**. An analogous [4 + 2]-like transition state leading to *exo-endo*-**1** is unlikely on steric grounds. For the stepwise Mannich-like mechanism, orienting the Lewis acid coordinated imine C=N and imine C−Ar groups away from the bridging methylene of norbornene, such that the C=N bond is antiperiplanar to the norbornene C=C bond in the *exo-endo*-**TS**, would minimize steric interactions (Figure 2b). Reaction via *exo-endo*-**TS** would lead initially to intermediate **15** via C-6−C-6a bond formation. Bond rotation of **15** to **16**, followed by C-10a−C-10b bond formation to **17** and proton loss would then lead to *exo-endo*-**1**.

The diastereoselectivity observed in most cases suggests an inherent preference for reaction via a concerted [4 + 2]-like transition state *exo-exo*-**TS** over the stepwise *exo-endo*-**TS** transition state. This preference may be accounted for by destabilization of the *exo-endo*-**TS** transition state due to the greater charge separation and potentially increased steric interaction between the *N*-Ar group and the norbornene, relative to the *exo-exo*-**TS** transition state. Introduction of a single *meta*-*N*-aryl substituent as for methyl and chlorine (Table 2, entries 15 and 16) leads to the formation of regioisomeric 1- and 3-substituted products, both formed with very high, yet opposite, diastereoselectivities. Thus, for formation of the 3-substituted regioisomers **1o**, **1q**, and **1s**, reaction occurs to give exclusive formation of the *exo-exo*-isomers. In these cases, the presence of a *meta* substituent at position R^3 would not exert any significant additional steric destabilization of the *exo-exo*-**TS**. On the other hand, formation of the 1-substituted regioisomers **1p** and **1r** occurs preferentially to give exclusive formation of the *exo-endo*-isomers. In these cases, unfavorable steric interactions between the R^1 substituent and the norbornene ring system in *exo-exo*-**TS** would result in preferential reaction via *exo-endo*-**TS**. This notion is further supported by the result obtained with the di-*meta*-*N*-aryl-substituted case (R^1/R^3 = Cl) for which exclusive formation of the diastereomer *exo-endo*-**1m** occurs. In the case of the 1-fluoro-substituted regioisomer **1t**, exclusive formation of the *exo-exo* diastereomer was nevertheless observed, which is not unexpected based on steric arguments since fluorine is isosteric with hydrogen. Introduction of an *ortho*-*N*-aryl substituent R^4 = Cl leads to an erosion in stereoselectivity, as exemplified by the formation of diastereomeric mixtures for **1j**, **1k**, **1l**, and **1n**. In these cases, the presence of the R^4 = Cl substituent presumably results in the *N*-Ar ring tilting out of the plane of the C=N system to avoid any destabilizing *syn*-pentane-like interaction between the C−Cl and N−BF_3 bonds in *exo-exo*-**TS** (and *exo-endo*-**TS**). As a result, a concerted [4 + 2]-like mechanism is disfavored, and the differentiation

TABLE 3. Povarov Reactions of Substituted Norbornenes[a]

entry	dienophile	product		yield (%)[b]
1	 **7a**		**8a**	35[c]
2	 **7b**		**8b**	63
3	 **7c**		**8c**	75
4	 **7d** R = H		**8d**	50[d]
5	**7e** R = *p*-NO_2Bz	R = 8-CH_2O*p*-NO_2Bz	**8e**	52
6	 *endo*- and *exo*-**7f**		**8f**	NR
7	 **7g**		**8g**	68
			**9**	

[a]Conditions: aniline (1.0 equiv), aldehyde (1.1 equiv), norbornene (2.0 equiv), $BF_3 \cdot OEt_2$ (20 mol %), 45−75 °C, CH_2Cl_2, 22−72 h. [b]Isolated yields based on the aniline. [c]10% of quinoline **9** and 25% of amine **6** were isolated. [d]Formed as a separable 1.1:1 mixture of 8- and 9-substituted regioisomers.

between the skewed *exo-exo* and *exo-endo* transition states is low, leading to low intrinsic diastereoselectivity.

The regioselectivity of Povarov reactions with *meta*-substituted anilines is little studied.[3] In the current study, the regioselectivity of formation of the 1-substituted to 3-substituted adducts was roughly 2:1 for Cl (Table 2, entry 16), 4:5 for F (Table 2, entry 17), and 2:3 for Me (Table 2, entry 15). Interestingly, a comparable trend in regioselectivities with intramolecular Friedel−Crafts reaction has been reported.[20] In this study, an In(III)-promoted cyclization of

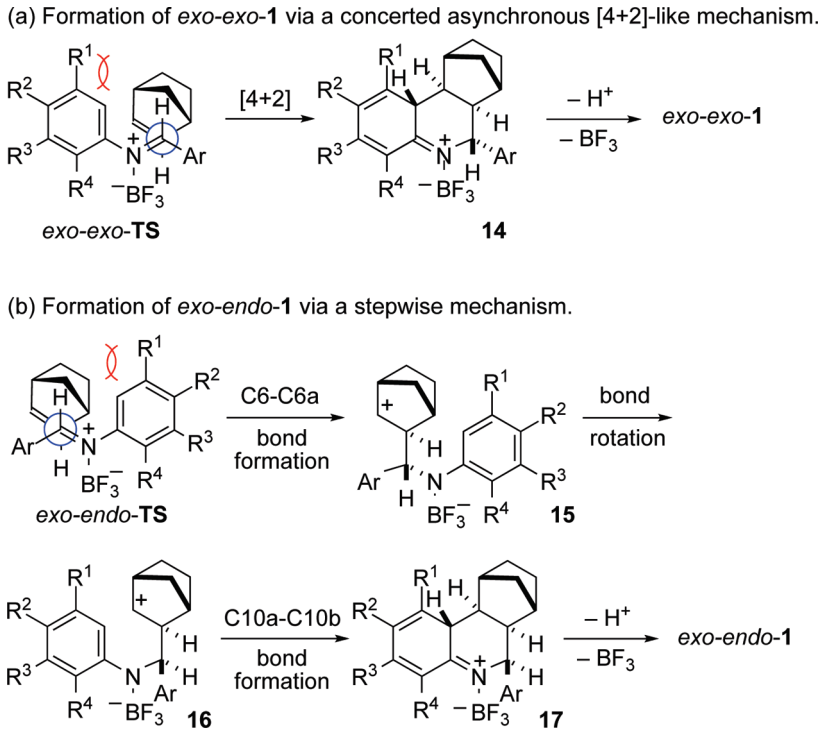
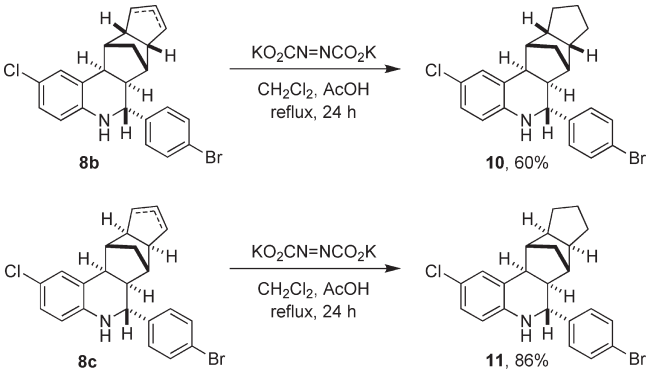
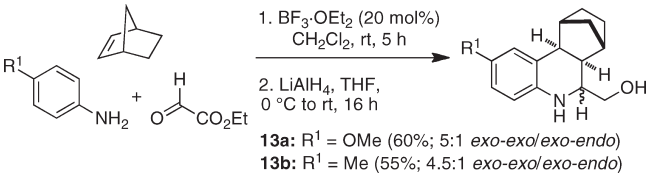


FIGURE 2. Transition state models and mechanistic rationale for the formation of *exo-exo*-**1** and *exo-endo*-**1**.

SCHEME 3. Reduction of Dicyclopentadiene Adducts 8b and 8c



SCHEME 4. Three-Component Povarov Reaction with Ethyl Glyoxylate Derived Imines



meta-substituted aromatic rings onto a tethered allylic bromide functionality led to the formation of a new six-membered ring. The regioselectivities of the corresponding 1-substituted and 3-substituted products were 2:1 from the *meta*-Cl, 1:4 from the *meta*-F, and 1:2 from the *meta*-Me-substituted precursors.

The results obtained in the present study are different than those found for many known Povarov reactions, where Lewis acidic catalysis leads preferentially to the formation of *endo* adducts.[25] In general, the formation of *endo* adducts is often believed to occur via an asynchronous concerted pathway, whereas the corresponding formation of the more thermodynamically stable *exo* adducts is believed to occur via a stepwise pathway. However, for the reactions of norbornenes, preferential formation of *exo-exo* adducts occurs via an asynchronous concerted [4 + 2] pathway. This difference in selectivity can be attributed to the additional steric constraints, in the respective transition states, imposed by the bicyclic nature of the norbornene ring, particularly the bridging methylene (C-11). Povarov reaction of norbornene via the *exo-endo* transition state is operative only in cases where *meta* and *ortho* substituents are present on the aniline ring. To the best of our knowledge, this effect has not been observed with other Povarov reactions.

Conclusion

In summary, bicyclo[2.2.1]hepta-5-ene systems are demonstrated to behave as activated dienophiles in the three-component Povarov reaction. They have greater reactivity than simple alkenes but lower reactivity than the dienophiles typically used in the Povarov reaction. The products are highly functionalized natural product-like tetracyclic systems, which may be useful as biologically relevant targets. For example, they have been demonstrated as cannabinoid receptor ligands with potential therapeutic implications for inflammatory conditions, including pain, arthritis, and asthma.[6] The diastereoselectivity and regioselectivity of the Povarov reactions of norbornenes are influenced by subtle steric/electronic effects on the substitution pattern of the

(25) The mechanistic pathway and diastereoselectivity for Povarov reactions can also be dependent on other factors, such as the choice of Lewis acid, the polarity of the solvent, and the nature of the diene and dienophile used.

precursor anilines. Furthermore, the diastereoselectivity obtained is shown to differ from that typically observed in Lewis acid catalyzed Povarov reactions, a factor which is attributed to additional steric interactions that occur in the transition states for the norbornene-based reactions and the competing concerted and stepwise pathways. Further investigations are ongoing to establish whether these selectivity differences occur in a more general sense or whether other strained alkenes, such as cyclobutenes and cyclopropenes, can be used.

Experimental Section

General Procedure for the Three-Component Povarov Reaction. An oven-dried 2−5 mL microwave vial was charged with the aniline (0.26 mmol, 1 equiv), aldehyde (0.29 mmol, 1.1 equiv), and norbornene-based dienophile (0.39 or 0.52 mmol, 1.5 or 2.0 equiv), and freshly distilled CH_2Cl_2 (1.3 mL, 0.2 M) was added followed by $BF_3{\cdot}OEt_2$ (0.056 mmol, 0.2 equiv). The microwave vial was purged with nitrogen before it was tightly sealed, and the reaction mixture was heated to 45 °C for 22 h. The reaction mixture was cooled to room temperature, treated with a few drops of MeOH, and finally concentrated in vacuo. The crude residue was dry loaded onto silica and purified by silica gel flash chromatography.

Methyl 6-(4-bromophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine-2-carboxylate (*exo-exo*-1a). Purification by flash column chromatography on silica gel using a gradient elution of 5 to 10% ethyl acetate in hexanes afforded the title compound (65 mg, 60%) as a white solid: mp 215−216 °C; R_f = 0.26 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3339, 2958, 1700, 1607, 1510, 1436, 1322, 1291, 1260, 1009, 831, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (1H, s), 7.70 (1H, ddd, J = 8.5, 2.0, 1.0 Hz), 7.51 (2H, d, J = 8.5 Hz), 7.30 (2H, d, J = 8.5 Hz), 6.56 (1H, d, J = 8.5 Hz), 4.00 (1H, br s), 3.90 (3H, s), 3.60 (1H, d, J = 10.0 Hz), 2.77 (1H, d, J = 4.0 Hz), 2.69 (1H, d, J = 9.0 Hz), 2.13 (1H, dd, J = 9.5, 9.5 Hz), 2.06 (1H, d, J = 4.0 Hz), 1.39−1.71 (4H, m), 1.14−1.22 (1H, m), 1.13 (1H, d, J = 10.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 151.0, 142.9, 132.0, 130.8, 129.7, 128.5, 126.3, 121.9, 120.8, 115.0, 60.4, 53.6, 51.9, 43.9, 43.0, 39.7, 34.0, 29.9, 29.1; MS (EI^+) m/e (rel intensity) 413 (24), 412 (100), 411 (36), 410 (99), 343 (59), 342 (55), 263 (16), 257 (15), 256 (85), 248 (16), 246 (16), 214 (20), 188 (48); HRMS (EI) m/e (M^+) calcd for $C_{22}H_{22}{}^{79}BrNO_2$ 411.0833, found 411.0841.

Methyl 6-phenyl-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine-2-carboxylate (*exo-exo*-1b). Purification by flash column chromatography on silica gel using a gradient elution of 5 to 10% ethyl acetate in hexanes afforded the title compound (65 mg, 74%) as a white solid: mp 171−172 °C; R_f = 0.33 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3395, 2950, 2871, 1717, 1699, 1606, 1455, 1301, 1259, 1230, 1175, 1104, 1003, 849, 775, 737, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (1H, s), 7.70 (1H, ddd, J = 8.5, 2.0, 1.0 Hz), 7.32−7.45 (5H, m), 6.55 (1H, d, J = 8.5 Hz), 4.08 (1H, br s), 3.87 (3H, s), 3.62 (1H, d, J = 10.0 Hz), 2.77 (1H, d, J = 4.0 Hz), 2.70 (1H, d, J = 9.0 Hz), 2.20 (1H, dd, J = 9.5, 9.0 Hz), 2.10 (1H, d, J = 4.0 Hz), 1.35−1.72 (4H, m), 1.11−1.34 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 151.3, 143.9, 130.8, 128.8, 128.4, 128.0, 126.3, 120.5, 114.9, 61.0, 53.5, 51.8, 43.9, 43.0, 39.7, 34.0, 30.0, 29.1; MS (EI^+) m/e (rel intensity) 334 (25), 333 (100), 332 (17), 265 (14), 264 (73), 256 (58), 188 (25), 169 (20), 91 (31); HRMS (EI) m/e calcd for $C_{22}H_{23}NO_2$ [M^+] 333.1729, found 333.1729.

6-Phenyl-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1c). Purification by flash column chromatography on silica gel using a gradient elution of 3 to 5% ethyl acetate in hexanes afforded the title compound (65 mg, 60%) as a colorless oil (53 mg, 76%): R_f = 0.61 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3346, 3026, 2951, 2868, 1604, 1587, 1493, 1468, 1451, 1346, 1296, 1255, 1103, 751, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (2H, dd, J = 8.5, 1.5 Hz), 7.24−7.39 (4H, m), 6.99 (1H, dd, J = 7.5, 1.0 Hz), 6.80 (1H, ddd, J = 7.5, 1.5, 1.0 Hz), 6.56 (1H, dd, J = 8.0, 1.0 Hz), 3.68 (1H, br s), 3.57 (1H, d, J = 10.5 Hz), 2.67−2.71 (2H, m), 2.19 (1H, dd, J = 9.5, 9.5 Hz), 2.07 (1H, d, J = 4.5 Hz), 1.62−1.71 (2H, m), 1.38−1.56 (2H, m), 1.14−1.22 (1H, m), 1.10 (1H, tt, J = 10.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 144.5, 128.7, 128.6, 128.1, 127.8, 127.3, 126.3, 119.5, 115.4, 61.8, 53.9, 44.2, 42.6, 39.4, 34.1, 30.0, 29.3; MS (EI^+) m/e (rel intensity) 276 (24), 275 (100), 274 (20), 206 (74), 198 (60), 130 (24), 91 (31); HRMS (EI) m/e calcd for $C_{20}H_{21}N$ [M^+] 275.1674, found 275.1673.

Methyl 6-(3,4-dichlorophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine-2-carboxylate (*exo-exo*-1d). Purification by flash column chromatography on silica gel using a gradient elution of 5 to 20% ethyl acetate in hexanes afforded the title compound (79 mg, 74%) as a white solid: mp 223−224 °C; R_f = 0.26 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3356, 2950, 2864, 1713, 1605, 1435, 1256, 1010, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, s), 7.70 (1H, ddd, J = 8.0, 2.0, 1.0 Hz), 7.54 (1H, d, J = 2.0 Hz), 7.45 (1H, d, J = 8.0 Hz), 7.25 (1H, dd, J = 8.0, 2.0 Hz), 6.58 (1H, d, J = 8.5 Hz), 4.00 (1H, br s), 3.88 (3H, s), 3.60 (1H, d, J = 10.0 Hz), 2.77 (1H, d, J = 3.5 Hz), 2.70 (1H, d, J = 8.5 Hz), 2.12 (1H, dd, J = 9.5, 9.5 Hz), 2.06 (1H, d, J = 4.0 Hz), 1.40−1.72 (4H, m), 1.15−1.24 (1H, m), 1.14 (1H, d, J = 10.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 150.7, 144.2, 132.9, 132.0, 131.1, 130.8, 129.9, 128.5, 127.4, 126.2, 121.1, 115.0, 60.1, 53.5, 51.9, 43.8, 43.1, 39.7, 34.0, 29.9, 29.1; MS (EI^+) m/e (rel intensity) 403 (66), 402 (31), 401 (100), 398 (20), 396 (28), 371 (38), 369 (24), 368 (56), 333 (46), 331 (60), 308 (25), 306 (31), 275 (31), 256 (72), 238 (19), 236 (24), 188 (46), 164 (21), 91 (29); HRMS (EI) m/e (M^+) calcd (for $C_{22}H_{21}{}^{35}Cl_2NO_2$) 401.0956, found 401.0949.

Methyl 6-(4-nitrophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine-2-carboxylate (*exo-exo*-1e). Purification by flash column chromatography on silica gel using a gradient elution of 5 to 20% ethyl acetate in hexanes afforded the title compound (79 mg, 81%) as a yellow solid: mp 227−229 °C; R_f = 0.08 (95:5 hexanes/EtOAc); IR (thin film) ν_{max} 3355, 2951, 2870, 1709, 1606, 1520, 1435, 1347, 1302, 1257, 1197, 1104, 849, 773, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (2H, d, J = 8.5 Hz), 7.98 (1H, s), 7.70 (1H, dd, J = 8.5, 1.0 Hz), 7.59 (2H, dd, J = 8.5 Hz), 6.61 (1H, d, J = 8.5 Hz), 4.13 (1H, br s), 3.87 (3H, s), 3.77 (1H, d, J = 9.5 Hz), 2.76 (1H, d, J = 3.5 Hz), 2.72 (1H, d, J = 9.0 Hz), 2.13 (1H, d, J = 9.5, 9.0 Hz), 2.08 (1H, d, J = 3.5 Hz), 1.36−1.81 (4H, m), 1.09−1.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 151.2, 150.2, 147.6, 130.6, 128.6, 128.4, 126.0, 123.9, 121.1, 114.9, 60.3, 53.2, 51.7, 43.6, 43.1, 39.6, 33.8, 29.6, 28.9; MS (EI^+) m/e (rel intensity) 379 (17), 378 (100), 309 (26), 256 (16), 149 (18), 84 (16); HRMS (EI) m/e calcd for $C_{22}H_{22}N_2O_4$ [M^+] 378.1580, found 378.1563.

6-(4-Bromophenyl)-2-methoxy-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1f). Purification by flash column chromatography on silica gel using a gradient elution of 2 to 5% ethyl acetate in hexanes afforded the title compound (66 mg, 69%) as a yellow solid: mp 128−130 °C; R_f = 0.40 (95:5 hexanes/EtOAc); IR (thin film) ν_{max} 3341, 2951, 2868, 1700, 1612, 1502, 1465, 1281, 1245, 1161, 1098, 1071, 1043, 1009, 875, 823, 736, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (2H, d, J = 8.5 Hz), 7.31 (2H, d, J = 8.5 Hz), 6.87 (1H, d, J = 2.0 Hz), 6.61 (1H, dd, J = 8.5, 2.5 Hz), 6.52 (1H, d, J = 8.5 Hz), 3.77 (3H, s), 3.49 (2H, d, J = 10.5 Hz, H-2 + NH), 2.65−2.70 (2H, m), 2.09 (1H, dd, J = 9.5, 9.5 Hz), 2.01 (1H, d, J = 3.5 Hz), 1.35−1.72 (4H, m), 1.14−1.21 (1H, m), 1.10 (1H, d, J = 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 143.3, 140.8, 131.5, 129.6, 128.2, 121.3, 115.8, 114.0, 111.8, 61.6, 55.7, 53.5, 44.4, 42.3, 39.1,

33.9, 29.6, 29.1; MS (ESI^+) *m*/*e* (rel intensity) 387 (21), 386 (94), 385 (25), 384 (100); HRMS (ESI) *m*/*e* calcd for $C_{21}H_{22}NO^{79}Br$ $[M + H]^+$ 384.0957, found 384.0948.

2-Chloro-6-(2-methoxyphenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1g). Purification by flash column chromatography on silica gel using a gradient elution of 3 to 5% ethyl acetate in hexanes afforded the title compound (58 mg, 58%) as a colorless oil: R_f = 0.31 (95:5 hexanes/EtOAc); IR (thin film) ν_{max} 3357, 2954, 2870, 1688, 1599, 1494, 1455, 1287, 1244, 1028, 908, 816, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dd, J = 7.5, 2.0 Hz), 7.21−7.28 (2H, m), 6.97 (1H, ddd, J = 7.5, 1.5, 1.0 Hz), 6.87−6.94 (2H, m), 6.45 (1H, d, J = 8.5 Hz), 4.21 (1H, d, J = 9.5 Hz), 3.82 (3H, s), 3.71 (1H, br s), 2.69 (1H, d, J = 9.0 Hz), 2.60 (1H, d, J = 4.0 Hz), 2.24 (1H, dd, J = 9.5, 9.0 Hz), 2.07 (1H, d, J = 4.0 Hz), 1.62−1.72 (2H, m), 1.47−1.56 (1H, m), 1.37−1.44 (1H, m), 1.19−1.26 (1H, m), 1.09 (1H, ddd, J = 10.0, 2.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 146.1, 132.0, 129.1, 128.33, 128.32, 127.8, 125.8, 123.4, 120.9, 116.3, 110.4, 55.4, 52.6, 51.9, 44.3, 43.2, 40.0, 34.2, 29.7, 29.3; MS (EI^+) *m*/*e* (rel intensity) 341 (45), 340 (42), 339 (100), 338 (26), 270 (35), 232 (37), 164 (25), 127 (25), 121 (22), 119 (27), 91 (32); HRMS (EI) *m*/*e* calcd for $C_{21}H_{22}{}^{35}ClNO$ $[M^+]$ 339.1382, found 339.1380.

6-(4-Bromophenyl)-2-chloro-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1h). Purification by flash column chromatography on silica gel using a gradient elution of 2 to 4% ethyl acetate in hexanes afforded the title compound (78 mg, 78%) as a white solid: mp 140−142 °C; R_f = 0.31 (95:5 hexanes/EtOAc); IR (thin film) ν_{max} 3356, 2952, 2870, 1487, 1457, 1406, 1340, 1294, 1256, 1071, 1010, 860, 820, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, d, J = 8.5 Hz), 7.29 (2H, d, J = 8.5 Hz), 7.24 (1H, m), 6.94 (1H, ddd, J = 8.5, 2.5, 1.0 Hz), 6.49 (1H, d, J = 8.5 Hz), 3.66 (1H, br s), 3.49 (1H, d, J = 10.5 Hz), 2.65 (2H, d, J = 7.0 Hz), 2.09 (1H, dd, J = 10.5, 10.0 Hz), 2.02 (1H, d, J = 4.0 Hz), 1.33−1.72 (4H, m), 1.08−1.20 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 143.1, 131.9, 129.8, 128.9, 128.5, 126.2, 124.2, 121.8, 116.6, 61.1, 53.6, 44.2, 42.7, 39.4, 34.1, 29.8, 29.2; MS (EI^+) *m*/*e* (rel intensity) 391 (24), 390 (25), 389 (100), 388 (32), 387 (82), 319 (57), 317 (43), 234 (28), 232 (85), 190 (20), 166 (23), 164 (56), 91 (36); HRMS (EI) *m*/*e* calcd for $C_{20}H_{19}{}^{79}Br^{35}ClN$ $[M^+]$ 387.0389, found 387.0381.

2-Chloro-6-(3,4-dichlorophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1i). Purification by flash column chromatography on silica gel using a gradient elution of 5 to 10% ethyl acetate in hexanes afforded the title compound (84 mg, 82%) as an off-white solid: mp 177−178 °C; R_f = 0.53 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3359, 2953, 2870, 1599, 1489, 1457, 1401, 1332, 1290, 1256, 1126, 1030, 907, 812, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 2.0 Hz), 7.43 (1H, d, J = 8.0 Hz), 7.24−7.27 (2H, m), 6.95 (1H, dd, J = 8.0, 1.5 Hz), 6.50 (1H, d, J = 8.5 Hz), 3.65 (1H, s), 3.49 (1H, d, J = 10.0 Hz), 2.64−2.66 (2H, m), 2.07 (1H, dd, J = 9.5, 9.5 Hz), 2.03 (1H, d, J = 4.0 Hz), 1.37−1.72 (4H, m), 1.13−1.22 (1H, m), 1.13 (1H, d, J = 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 144.4, 132.8, 131.9, 130.7, 129.9, 128.8, 128.5, 127.4, 126.3, 124.4, 116.6, 60.7, 53.5, 44.1, 42.7, 39.4, 34.1, 29.8, 29.1; MS (ESI^+) *m*/*e* (rel intensity) 382 (34), 380 (95), 378 (100); HRMS (ESI) *m*/*e* calcd for $C_{20}H_{18}N^{35}Cl_3$ $[M + H]^+$ 378.0577, found 378.0577.

6-(4-Bromophenyl)-4-chloro-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-endo*-1j). Purification by flash column chromatography on silica gel using a gradient elution of 2 to 4% ethyl acetate in hexanes afforded the title compound (16 mg, 16%) as a white solid: mp 205−207 °C; R_f = 0.71 (98:2 hexanes/EtOAc); IR (thin film) ν_{max} 3367, 2956, 2873, 1599, 1478, 1417, 1364, 1298, 1281, 1127, 1070, 1007, 971, 842, 823, 797, 781, 739, 725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (2H, d, J = 8.5 Hz), 7.35 (2H, d, J = 8.5 Hz), 7.05−7.13 (2H, m), 6.72 (1H, dd, J = 8.0, 8.0 Hz), 4.31 (1H, s), 4.20 (1H, d, J = 4.5 Hz), 3.04 (1H, d, J = 8.5 Hz), 2.23 (1H, d, J = 4.0 Hz), 2.12 (1H, dd, J = 8.5, 4.5 Hz), 1.95 (1H, d, J = 2.0 Hz), 1.52−1.64 (2H, m), 1.25−1.45 (2H, m), 0.98−1.09 (1H, m), 0.87 (1H, d, J = 10 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4 (C), 141.7 (C), 131.6 (CH), 130.1 (C), 128.6 (CH), 128.2 (CH), 126.1 (CH), 120.9 (C), 119.8 (C), 119.1 (CH), 58.8 (CH), 50.8 (CH), 49.6 (CH), 47.0 (CH), 36.7 (CH), 34.8 (CH_2), 31.3 (CH_2), 28.4 (CH_2); MS (EI^+) *m*/*e* (rel intensity) 391 (20), 390 (22), 389 (100), 388 (39), 387 (86), 386 (27), 385 (21), 320 (61), 318 (41), 232 (45); HRMS (EI) *m*/*e* calcd for $C_{20}H_{19}{}^{79}Br^{35}ClN$ $[M^+]$ 387.0389, found 387.0371.

6-(4-Bromophenyl)-4-chloro-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1j). Purification by flash column chromatography on silica gel using a gradient elution of 2 to 4% ethyl acetate in hexanes afforded the title compound (54 mg, 54%) as a white solid: mp 147−148 °C; R_f = 0.47 (98:2 hexanes/EtOAc); IR (thin film) ν_{max} 3362, 3026, 2952, 2869, 1700, 1597, 1473, 1420, 1400, 1340, 1300, 1262, 1246, 1136, 1106, 1073, 1010, 974, 927, 818, 753, 733, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (2H, d, J = 8.5 Hz), 7.32 (2H, d, J = 8.5 Hz), 7.18 (1H, d, J = 7.5 Hz), 7.10 (1H, d, J = 8.0 Hz), 6.71 (1H, dd, J = 8.0, 8.0 Hz), 4.32−4.40 (1H, s), 3.53 (1H, d, J = 10.5 Hz), 2.67−2.73 (2H, m), 2.13 (1H, dd, J = 9.5, 9.5 Hz), 2.05 (1H, d, J = 4.0 Hz), 1.36−1.73 (4H, m), 1.11−1.22 (1H, m), 1.12 (1H, d, J = 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 143.0, 131.9, 129.8, 128.8, 127.0, 126.4, 121.8, 119.9, 119.1, 60.6, 53.8, 44.5, 43.0, 39.6, 34.0, 29.9, 29.1; HRMS (EI) *m*/*e* calcd for $C_{20}H_{19}{}^{79}Br^{35}ClN$ $[M^+]$ 387.0389, found 387.0389.

4-Chloro-6-(3,4-dichlorophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-endo*-1k). Purification by flash column chromatography on silica gel using a gradient elution of 1 to 5% ethyl acetate in hexanes afforded the title compound (26 mg, 26%) as a white solid: mp 163−164 °C; R_f = 0.46 (99:1 hexanes/EtOAc); IR (thin film) ν_{max} 3358, 3065, 2954, 2924, 2870, 1598, 1576, 1470, 1417, 1395, 1361, 1279, 1130, 1030, 975, 907, 783, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 2.0 Hz), 7.48 (1H, d, J = 11.0 Hz), 7.30 (1H, dd, J = 8.5, 2.0 Hz), 7.11 (1H, dd, J = 8.0, 1.0 Hz), 7.08 (1H, dd, J = 7.5, 0.5 Hz), 6.73 (1H, dd, J = 7.5, 7.5 Hz), 4.28 (1H, s), 4.20 (1H, d, J = 4.5 Hz), 3.04 (1H, d, J = 8.5 Hz), 2.23 (1H, d, J = 4.5 Hz), 2.12 (1H, dd, J = 8.5, 4.5 Hz), 1.95 (1H, d, J = 2.0 Hz), 1.54−1.60 (2H, m), 1.32−1.42 (2H, m), 1.03−1.09 (1H, m), 0.88 (1H, d, J = 10 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 143.0, 132.7, 131.1, 130.5, 130.0, 128.8, 128.2, 126.2, 126.1, 119.9, 119.3, 58.5, 50.6, 49.6, 47.0, 36.7, 34.8, 31.3, 28.3; MS (EI^+) *m*/*e* (rel intensity) 379 (84), 378 (39), 377 (100), 376 (27), 312 (25), 310 (64), 308 (64), 232 (55); HRMS (EI) *m*/*e* calcd for $C_{20}H_{18}N^{35}Cl_3$ $[M^+]$ 377.0505, found 377.0510.

4-Chloro-6-(3,4-dichlorophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1k). Purification by flash column chromatography on silica gel using a gradient elution of 1 to 5% ethyl acetate in hexanes afforded the title compound (33 mg, 33%) as a crystalline white solid: mp 148−150 °C; R_f = 0.51 (99:1 hexanes/EtOAc); IR (thin film) ν_{max} 3359, 3059, 3023, 2956, 2922, 2871, 1596, 1572, 1466, 1416, 1399, 1336, 1302, 1289, 1253, 1105, 1029, 977, 819, 761, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 2.0 Hz), 7.25 (1H, d, J = 8.0 Hz), 7.28 (1H, dd, J = 8.0, 2.0 Hz), 7.19 (1H, d, J = 7.5 Hz), 7.12 (1H, dd, J = 8.0, 1.0 Hz), 6.73 (1H, dd, J = 8.0, 8.0 Hz), 4.36 (1H, s), 3.54 (1H, d, J = 10.0 Hz), 2.68−2.72 (2H, m), 2.12 (1H, dd, J = 9.5, 9.5 Hz), 2.06 (1H, d, J = 4.0 Hz), 1.64−1.72 (1H, m), 1.51−1.62 (2H, m), 1.38−1.46 (1H, m), 1.17−1.24 (1H, m), 1.13 (1H, ddd, J = 10.0, 2.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 142.6, 132.7, 131.7, 130.5, 129.8, 128.5, 127.2, 126.8, 126.2, 119.8, 119.1, 60.0, 53.5, 44.2, 42.8, 39.4, 33.8, 29.6, 28.9; MS (EI^+) *m*/*e* (rel intensity) 379 (97), 378 (29), 377 (100), 310 (64), 308 (64), 232 (62), 164 (25); HRMS (EI) *m*/*e* calcd for $C_{20}H_{18}N^{35}Cl_3$ $[M^+]$ 377.0505, found 377.0500.

2,4-Dichloro-6-(3,4-dichlorophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-endo*-1l). Purification by flash column chromatography on silica gel using a gradient elution of 100% hexanes to 5% ethyl acetate in hexanes afforded the title compound (41 mg, 19%) as a white solid: mp 159−160 °C; R_f = 0.40 (100% hexanes); IR (thin film) ν_{max} 3358, 2955, 2924, 2872, 1573, 1475, 1396, 1278, 1130, 1030, 906, 858, 817, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, J = 2.0 Hz), 7.48 (1H, d, J = 8.0 Hz), 7.28 (1H, dd, J = 8.5, 2.0 Hz), 7.12 (1H, d, J = 2.5 Hz), 7.07 (1H, d, J = 2.5 Hz), 4.25 (1H, s), 4.16 (1H, d, J = 4.5 Hz), 3.00 (1H, d, J = 8.5 Hz), 2.25 (1H, d, J = 4.5 Hz), 2.11 (1H, dd, J = 8.5, 4.5 Hz), 1.94 (1H, d, J = 2.5 Hz), 1.52−1.64 (2H, m), 1.31−1.42 (2H, m), 1.02−1.09 (1H, m), 0.90 (1H, d, J = 10 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5 (C), 141.8 (C), 132.8 (C), 131.3 (C), 131.1 (C), 130.6 (CH), 128.7 (CH), 128.1 (CH), 126.2 (CH), 125.8 (CH), 123.4 (C), 120.1 (C), 58.4 (CH), 50.4 (CH), 49.6 (CH), 46.9 (CH), 36.7 (CH), 34.8 (CH_2), 31.2 (CH_2), 28.2 (CH_2); MS (EI^+) m/e (rel intensity) 415 (15), 413 (60), 411 (80), 409 (70), 407 (50), 380 (100), 378 (75), 343 (38), 266 (22), 198 (20); HRMS (EI) m/e calcd for $C_{20}H_{17}N^{35}Cl_4$ [M^+] 411.0115, found 411.0106.

2,4-Dichloro-6-(3,4-dichlorophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1l). Purification by flash column chromatography on silica gel using a gradient elution of 100% hexanes to 5% ethyl acetate in hexanes followed by an additional flash column using a gradient elution of 1 to 3% ethyl acetate in hexanes afforded the title compound (101 mg, 46%) as a white solid: mp 198−199 °C; R_f = 0.22 (100% hexanes); IR (thin film) ν_{max} 3348, 2956, 2909, 2868, 1589, 1471, 1328, 1300, 1126, 1028, 871, 853, 816, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, J = 2.0 Hz), 7.45 (1H, d, J = 8.5 Hz), 7.26 (1H, dd, J = 8.0, 2.0 Hz), 7.18 (1H, s), 7.12 (1H, d, J = 2.0 Hz), 4.32 (1H, s), 3.50 (1H, d, J = 10.0 Hz), 2.64−2.69 (2H, m), 2.11 (1H, dd, J = 9.5, 9.5 Hz), 2.06 (1H, d, J = 4.0 Hz), 1.65−1.74 (1H, m), 1.51−1.60 (2H, m), 1.37−1.45 (1H, m), 1.15−1.23 (1H, m), 1.15 (1H, d, J = 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7 (C), 141.3 (C), 132.7 (C), 131.9 (C), 130.6 (CH), 129.7 (CH), 129.6 (C), 127.1 (CH), 126.9 (CH), 125.9 (CH), 123.3 (C), 120.0 (C), 59.9 (CH), 53.3 (CH), 44.3 (CH), 42.8 (CH), 39.4 (CH), 33.8 (CH_2), 29.5 (CH_2), 28.8 (CH_2); MS (EI^+) m/e (rel intensity) 415 (35), 413 (100), 412 (25), 411 (77), 345 (26), 343 (53), 341 (38), 268 (32), 266 (55), 200 (25), 198 (35), 86 (38), 84 (56); HRMS (EI) m/e calcd for $C_{20}H_{17}N^{35}Cl_4$ [M^+] 411.0115, found 411.0105.

1,3-Dichloro-6-(3,4-dichlorophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-endo*-1m). Purification by flash column chromatography on silica gel using a gradient elution of 5 to 10% ethyl acetate in hexanes afforded the title compound (101 mg, 91%) as a white foam: mp 48−49 °C; R_f = 0.52 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3381, 2953, 2871, 1589, 1570, 1468, 1390, 1332, 1294, 1256, 1175, 1131, 1104, 1029, 947, 906, 882, 835, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.36 (2H, m), 7.02 (1H, dd, J = 8.5, 2.0 Hz), 6.81 (1H, d, J = 2.0 Hz), 6.42 (1H, d, J = 2.0 Hz), 4.09 (1H, d, J = 4.5 Hz), 3.97 (1H, s), 2.88 (1H, d, J = 9.0 Hz), 2.64 (1H, s), 2.20 (1H, s), 2.12 (1H, dd, J = 8.5, 4.5 Hz), 1.46−2.05 (4H, m), 1.26−1.33 (1H, m), 1.08 (1H, d, J = 10 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1 (C), 145.1 (C), 135.6 (C), 132.5 (C), 132.1 (C), 131.3 (C), 130.6 (CH), 129.1 (CH), 126.0 (CH), 122.7 (C), 119.7 (CH), 113.3 (CH), 58.0 (CH), 49.5 (CH), 44.3 (CH), 43.0 (CH), 41.9 (CH), 34.3 (CH_2), 29.4 (2 × CH_2); MS (EI^+) m/e (rel intensity) 415 (28), 413 (79), 411 (61), 345 (47), 343 (100), 239 (27), 237 (43), 198 (25); HRMS (EI) m/e calcd for $C_{20}H_{17}N^{35}Cl_4$ [M^+] 411.0115, found 411.0104.

1,4-Dichloro-6-(3,4-dichlorophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-endo*-1n). Purification by flash column chromatography on silica gel using a gradient elution of 2 to 4% ethyl acetate in hexanes afforded the title compound (19 mg, 18%) as a colorless oil: R_f = 0.67 (95:5 hexanes/EtOAc); IR (thin film) ν_{max} 3358, 2956, 2926, 2870, 1587, 1449, 1415, 1265, 1157, 1130, 1031, 979, 906, 790, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, d, J = 2.0 Hz), 7.49 (1H, d, J = 8.5 Hz), 7.28 (1H, dd, J = 8.5, 2.0 Hz), 7.07 (1H, d, J = 8.5 Hz), 6.81 (1H, d, J = 8.5 Hz), 4.36 (1H, s), 4.17 (1H, d, J = 4.5 Hz), 3.23 (1H, d, J = 9.0 Hz), 2.43 (1H, d, J = 4.0 Hz), 2.15−2.20 (1H, m), 1.96 (1H, d, J = 2.0 Hz), 1.04−1.62 (5H, m), 0.93 (1H, d, J = 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (C), 142.3 (C), 133.2 (C), 132.8 (C), 131.3 (C), 130.6 (CH), 128.7 (CH), 127.5 (C), 126.7 (CH), 126.2 (CH), 120.2 (CH), 118.4 (C), 58.4 (CH), 50.7 (CH), 46.8 (CH), 45.2 (CH), 37.2 (CH), 35.4 (CH_2), 31.0 (CH_2), 28.5 (CH_2); MS (EI^+) m/e (rel intensity) 413 (95), 412 (36), 411 (82), 345 (49), 344 (33), 343 (100), 342 (40), 341 (78), 266 (35), 239 (30), 237 (45), 200 (74), 198 (96), 187 (25), 161 (30), 67 (72); HRMS (EI) m/e calcd for $C_{20}H_{17}NCl_4$ [M^+] 411.0115, found 411.0124.

1,4-Dichloro-6-(3,4-dichlorophenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1n). Purification by flash column chromatography on silica gel using a gradient elution of 2 to 4% ethyl acetate in hexanes afforded the title compound (38 mg, 36%) as a white foam: R_f = 0.57 (95:5 hexanes/EtOAc); IR (thin film) ν_{max} 3379, 3049, 2955, 2926, 2872, 1587, 1564, 1471, 1394, 1276, 1166, 1130, 1030, 979, 906, 821, 788, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (1H, d, J = 8.0 Hz), 7.31 (1H, d, J = 2.0 Hz), 7.05 (1H, d, J = 8.5 Hz), 6.99 (1H, dd, J = 8.0, 2.0 Hz), 6.74 (1H, d, J = 8.5 Hz), 4.67 (1H, s), 4.22 (1H, dd, J = 4.5, 2.0 Hz), 2.92 (1H, d, J = 9.0 Hz), 2.63 (1H, s), 2.25 (1H, s), 2.18 (1H, dd, J = 8.5, 4.5 Hz), 1.47−1.72 (4H, m), 1.25−1.36 (1H, m), 1.08 (1H, dd, J = 10.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (C), 141.6 (C), 133.3 (C), 132.6 (C), 131.2 (C), 130.6 (CH), 129.0 (CH), 127.1 (CH), 125.9 (CH), 125.6 (C), 119.4 (CH), 117.6 (C), 57.7 (CH), 49.6 (CH), 44.6 (CH), 43.2 (CH), 42.6 (CH), 34.4 (CH_2), 29.6 (CH_2), 29.4 (CH_2); MS (EI+) m/e (rel intensity) 413 (84), 411 (89), 409 (37), 407 (26), 382 (33), 380 (69), 378 (47), 345 (42), 343 (100), 341 (55), 268 (25), 266 (49), 239 (23), 237 (38), 200 (38), 198 (52); HRMS (EI) m/e calcd for $C_{20}H_{17}N_{35}Cl_4$ [M^+] 411.0115, found 411.0112.

6-(4-Bromophenyl)-2,3-dimethyl-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1o) and 6-(4-Bromophenyl)-1,2-dimethyl-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-endo*-1p). Purification of the crude material (60:40 **1o**/**1p**) by flash column chromatography on silica gel using a gradient elution of 2 to 4% ethyl acetate in hexanes afforded two fractions containing an 89:11 mixture of **1o** and **1p** (19 mg, 16%) followed by three fractions containing a 27:73 mixture of **1o** and **1p** (58 mg, 49%) in the form of off-white foams: R_f = 0.75 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3355, 3000, 2920, 2867, 1588, 1485, 1295, 1263, 1203, 1072, 1009, 831, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (**1o**) δ 7.48 (2H, d, J = 8.5 Hz), 7.30 (2H, d, J = 8.5 Hz), 7.04 (1H, s), 6.38 (1H, s), 3.45−3.55 (1H, br s), 3.50 (1H, d, J = 10.0 Hz), 2.68 (1H, d, J = 3.5 Hz), 2.63 (1H, d, J = 9.0 Hz), 2.18 (3H, s), 2.15 (3H, s), 2.07 (1H, dd, J = 9.5, 9.5 Hz), 2.00 (1H, d, J = 4.0 Hz), 1.05−1.74 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) (**1o/1p**) δ 145.0 (**1p**), 144.7 (**1o**), 143.5 (**1o**), 142.5 (**1p**), 135.6 (**1p**), 134.3 (**1o**), 131.5 (**1o**), 131.4 (**1p**), 129.6 (**1o**), 129.4 (**1o**), 128.9 (**1p**), 127.8 (**1p**), 127.4 (**1p**), 127.3 (**1o**), 125.2 (**1p**), 124.2 (**1o**), 121.3 (**1o**), 120.7 (**1p**), 116.5 (**1o**), 112.6 (**1p**), 61.3 (**1o**), 58.7 (**1p**), 53.6 (**1o**), 50.6 (**1p**), 44.6 (**1p**), 43.6 (**1o**), 42.6 (**1p**), 42.5 (**1p**), 42.3 (**1o**), 39.2 (**1o**), 34.2 (**1p**), 33.8 (**1o**), 29.8 (**1p**), 29.7 (**1o**), 29.5 (**1p**), 29.0 (**1o**), 20.1 (**1p**), 19.4 (**1o**), 19.0 (**1o**), 16.5 (**1p**); MS (EI^+) m/e (rel intensity) 384 (13), 383 (90), 382 (24), 381 (100), 314 (47), 312 (49), 226 (26), 158 (12), 86 (10), 84 (14); HRMS (EI) m/e calcd for $C_{22}H_{24}N^{79}Br$ [M^+] 381.1092, found 381.1102.

6-(4-Bromophenyl)-3-chloro-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1q) and 6-(4-Bromophenyl)-1-chloro-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-endo*-1r). Purification of the crude material (36:64 **1q**/

1r) by flash column chromatography on silica gel using a gradient elution of 2 to 4% ethyl acetate in hexanes afforded one fraction containing **1q** (13 mg, 13%), one fraction containing an 84:16 mixture of **1q** and **1r** (29 mg, 29%), two fractions containing a 5:95 mixture of **1q** and **1r** (28 mg, 28%), and one fraction containing **1r** (14 mg, 13%). *exo-exo*-**1q**: Isolated as a colorless oil; R_f = 0.57 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3358, 2953, 2870, 1597, 1487, 1460, 1294, 1087, 1072, 1010, 922, 906, 823, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, dd, J = 8.5, 2.0 Hz), 7.29 (2H, dd, J = 8.5, 2.0 Hz), 7.18 (1H, d, J = 8.0 Hz), 6.76 (1H, dd, J = 8.0, 2.0 Hz), 6.56 (1H, d, J = 2.0 Hz), 3.67 (1H, s), 3.53 (1H, d, J = 10.0 Hz), 2.61−2.65 (2H, m), 2.10 (1H, dd, J = 9.5, 9.5 Hz), 2.03 (1H, d, J = 3.5 Hz), 1.09−1.71 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 142.8, 131.7, 131.4, 129.6, 129.5, 125.4, 121.6, 119.3, 114.9, 60.7, 53.4, 43.5, 42.6, 39.3, 33.8, 29.6, 29.0; MS (EI^+) m/e (rel intensity) 389 (85), 387 (65), 320 (88), 318 (72), 232 (35), 166 (27), 164 (60), 68 (31), 67 (100); HRMS (EI) m/e calcd for $C_{20}H_{19}{}^{79}Br^{35}ClN$ [M^+] 387.0389, found 387.0388. *exo-endo*-**1r**: Isolated as a colorless oil; R_f = 0.45 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3377, 3061, 2953, 2924, 2870, 1593, 1577, 1485, 1292, 1072, 1010, 986, 910, 835, 754, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (2H, dd, J = 8.5, 2.0 Hz), 7.11 (2H, d, J = 8.5 Hz), 6.89 (1H, dd, J = 8.0, 8.0 Hz), 6.79 (1H, dd, J = 8.0, 1.0 Hz), 6.39 (1H, dd, J = 8.0, 1.0 Hz), 4.09 (1H, d, J = 5.0 Hz), 3.90 (1H, s), 2.91 (1H, d, J = 9.0 Hz), 2.70 (1H, s), 2.20 (1H, s), 2.13 (1H, dd, J = 8.5, 5.0 Hz), 1.74 (1H, d, J = 10.0 Hz), 1.47−1.65 (3H, m), 1.25−1.31 (1H, m), 1.07 (1H, ddd, J = 10.0, 1.5, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 144.4, 135.1, 131.6, 128.7, 127.1, 124.3, 120.9, 119.9, 113.5, 58.6, 49.9, 44.2, 43.0, 42.3, 34.3, 29.6, 29.5; MS (EI^+) m/e (rel intensity) 389 (100), 388 (28), 387 (87), 322 (25), 320 (92), 318 (66), 232 (46), 164 (34); HRMS (EI) m/e calcd for $C_{20}H_{19}{}^{79}Br^{35}ClN$ [M^+] 387.0389, found 387.0371.

6-(4-Bromophenyl)-3-fluoro-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1s) and 6-(4-Bromophenyl)-1-fluoro-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine (*exo-exo*-1t). Purification of the crude material (56:44 **1s**/**1t**) by flash column chromatography on silica gel using a gradient elution of 2 to 3% ethyl acetate in hexanes afforded one fraction containing **1s** (4.4 mg, 4.5%) followed by five fractions containing a 59:41 mixture of **1s** and **1t** (68 mg, 70%) and finally one fraction containing **1t** (2.2 mg, 2.2%). *exo-exo*-**1s**: Isolated as a colorless oil; R_f = 0.52 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3362, 3028, 2953, 2870, 1616, 1510, 1487, 1298, 1157, 1107, 1072, 1010, 908, 839, 783, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, dd, J = 8.5, 2.0 Hz), 7.30 (2H, dd, J = 8.5, 2.0 Hz), 7.17−7.24 (1H, m, H1), 6.50 (1H, ddd, J = 8.5, 8.0, 2.5 Hz, H2), 6.28 (1H, dd, J = 10.0, 2.5 Hz, H4), 3.70 (1H, s), 3.54 (1H, d, J = 10.5 Hz), 2.61−2.65 (2H, m), 2.06 (1H, dd, J = 9.5, 9.5 Hz), 2.03 (1H, d, J = 4.0 Hz), 1.37−1.71 (4H, m), 1.09−1.26 (2H, m); ^{19}F (376 MHz, $CDCl_3$) δ −117.6; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (C, $^1J_{C-F}$ = 241 Hz), 147.3 (C, $^3J_{C-F}$ = 8.0 Hz), 142.9 (C), 131.7 (CH), 129.6 (CH, $^3J_{C-F}$ = 9.5 Hz), 129.5 (CH), 122.5 (C, $^4J_{C-F}$ = 3.0 Hz), 121.5 (C), 106.0 (CH, $^2J_{C-F}$ = 21 Hz), 101.8 (CH, ^2J = 24 Hz), 60.7 (CH), 53.4 (CH), 43.4 (CH), 42.7 (CH), 39.2 (CH), 33.7 (CH_2), 29.6 (CH_2), 29.0 (CH_2); MS (EI^+) m/e (rel intensity) 373 (10), 371 (15), 304 (17), 302 (16), 216 (12), 148 (38), 68 (18), 67 (100); HRMS (EI) m/e calcd for $C_{20}H_{19}{}^{79}BrFN$ [M^+] 371.0685, found 371.0675. *exo-exo*-**1t**: Isolated as a colorless oil; R_f = 0.47 (90:10 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (2H, d, J = 8.5 Hz), 7.17−7.33 (2H, m), 6.90−6.98 (1H, m), 6.44−6.51 (1H, m), 6.32 (1H, d, J = 8.0 Hz), 3.85 (1H, s), 3.80 (1H, d, J = 8.5 Hz), 2.76−2.80 (2H, m), 2.03−2.07 (2H, m), 1.45−1.71 (3H, m), 1.18−1.26 (2H, m), 1.09 (1H, d, J = 10.0 Hz); ^{19}F (376 MHz, $CDCl_3$) δ −113.6; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (C, $^1J_{C-F}$ = 242 Hz), 147.9 (C, $^3J_{C-F}$ = 9.5 Hz), 143.5 (C), 131.6 (CH), 129.3 (CH), 127.1 (CH, $^3J_{C-F}$ = 10.5 Hz), 121.3 (C), 113.7 (C, $^2J_{C-F}$ = 18 Hz), 110.5 (CH, $^4J_{C-F}$ = 2.5 Hz), 105.7 (CH, $^2J_{C-F}$ = 23 Hz), 59.4 (CH), 51.1 (CH), 42.5 (CH), 42.4 (CH), 40.1 (CH), 39.6 (CH), 33.8 (CH_2), 30.2 (CH_2), 28.7 (CH_2).

Methyl 6-(4-bromophenyl)-5,6,6a,7,10,10a-hexahydro-7,10-methanophenanthridine-2-carboxylate (*exo-exo*-8a) and Methyl 2-(4-bromophenyl)quinoline-6-carboxylate (9). Synthesized according to the general procedure. Purification by flash column chromatography on silica gel using a gradient elution of 10 to 30% ethyl acetate in hexanes afforded *exo-exo*-**8a** followed by **9**. *exo-exo*-**8a**: Isolated (38 mg, 34%) as a yellow foam; R_f = 0.25 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3340, 2958, 1698, 1624, 1500, 1328, 1288, 1278, 1017, 883, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, s), 7.72 (1H, dd, J = 8.0, 1.0 Hz), 7.52 (2H, d, J = 8.5 Hz), 7.31 (2H, d, J = 8.5 Hz), 6.64 (1H, d, J = 8.0 Hz), 6.31 (1H, dd, J = 5.5, 3.0 Hz), 6.05 (1H, dd, J = 5.5, 3.0 Hz), 4.12 (1H, s), 3.88 (3H, s), 3.63 (1H, d, J = 10.0 Hz), 3.34 (1H, s), 2.65 (1H, s), 2.56 (1H, d, J = 8.5 Hz), 1.98 (1H, dd, J = 9.5, 9.0 Hz), 1.62 (1H, d, J = 9.0 Hz), 1.36 (1H, ddd, J = 9.0, 2.0, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 150.6, 142.6, 137.4, 136.4, 131.8, 130.4, 129.4, 128.4, 126.1, 121.8, 120.8, 114.6, 62.4, 51.7, 48.0, 47.9, 44.8, 43.4, 39.2; MS (EI^+) m/e (rel intensity) 411 (4), 409 (4), 345 (51), 344 (85), 343 (88), 342 (79), 341 (24), 312 (22), 310 (20), 203 (12), 189 (10), 188 (100); HRMS (EI) m/e calcd for $C_{22}H_{20}{}^{79}BrNO_2$ [M^+] 409.0677, found 409.0679. Compound **9**: Isolated (10 mg, 10%) as a white foam; R_f = 0.08 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 2957, 2946, 2871, 1694, 1565, 1480, 1341, 1073, 1009, 985, 839, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (1H, d, J = 2.0 Hz), 8.33 (1H, d, J = 2.0 Hz), 8.31 (1H, d, J = 2.0 Hz), 8.17 (1H, d, J = 9.0 Hz), 8.09 (2H, d, J = 8.5 Hz), 7.91 (1H, d, J = 8.5 Hz), 7.67 (2H, d, J = 9.0 Hz), 4.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 158.0, 150.1, 138.2, 137.9, 132.1, 130.6, 129.9, 129.3, 129.2, 127.9, 126.3, 124.6, 119.1, 52.4; MS (EI^+) m/e (rel intensity) 343 (90), 341 (93), 312 (78), 310 (83), 284 (24), 282 (23), 203 (62), 202 (29), 86 (65), 84 (100), 51 (24), 49 (75), 44 (66), 32 (39); HRMS (EI) m/e calcd for $C_{17}H_{12}{}^{79}BrNO_2$ [M^+] 341.0051, found 341.0049.

***exo-exo*-8b and 6-(4-Bromophenyl)-2-chloro-6,6a,7,7a,8,9,10,10a,11,11a-octahydro-5*H*-7,11-methanocyclopenta[*j*]phenanthridine (10).** Synthesized according to the general procedure with the exception that the reaction was heated to 50 °C for 60 h. Purification of the crude material (~2:1 mixture of regioisomers) by flash column chromatography on silica gel using an elution of 5% ethyl acetate in hexanes afforded *exo-exo*-**8b** as a 2.7:1 mixture of regioisomers (145 mg, 63%) in the form of a yellow foam: R_f = 0.51 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3357, 3041, 2947, 2885, 2849, 1590, 1487, 1453, 1340, 1295, 1254, 1071, 1010, 907, 862, 818, 732, 702, 641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (4H, d, J = 8.5 Hz), 7.27 (4H, d, J = 8.5 Hz), 7.14−7.19 (2H, m), 6.93 (2H, dd, J = 8.5, 1.0 Hz), 6.47 (2H, d, J = 8.5 Hz), 5.60−5.70 (3H, m), 5.36−5.39 (1H, m), 3.62 (1H, s), 3.58 (1H, d, J = 10.5 Hz), 3.47 (1H, d, J = 10.0 Hz), 3.20−3.26 (1H, m), 3.03−3.08 (1H, m), 2.76 (2H, m), 2.65−2.73 (2H, m), 2.50−2.57 (2H, m), 2.34−2.45 (2H, m), 2.10−2.20 (4H, m), 1.79−1.94 (3H, m), 1.73 (1H, d, J = 10.0 Hz), 1.34−1.39 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 145.6, 142.7, 142.6, 131.96, 131.90, 131.7, 131.67, 131.66, 131.4, 129.7, 129.6, 129.5, 129.0, 128.1, 127.2, 125.9, 125.8, 124.1, 123.9, 121.5, 116.3, 116.2, 61.6, 60.3, 53.0, 52.5, 48.6, 47.5, 45.7, 45.3, 44.1, 42.5, 42.3, 41.7, 38.9, 37.2, 36.8, 36.0, 32.5, 32.3 (only 41 of 42 expected carbon signals are resolved at 100 MHz). The mixture of regioisomers was subjected to diimide reduction following a literature procedure.[22] To a colorless solution of *exo-exo*-**8b** (77 mg, 0.18 mmol) in dry CH_2Cl_2 (4.0 mL) was added in three portions potassium azodicarboxylate (283 mg, 0.460 mmol) at reflux. The yellow suspension was treated with glacial AcOH (220 μL, 4.1 mmol) over 2 h, after which the reaction mixture was heated at reflux for 22 h. The white suspension was filtered by gravity, and the filtrate was

concentrated in vacuo. Purification by flash column chromatography on silica gel using 5% ethyl acetate in hexanes afforded *exo-exo*-**10**: isolated (56 mg, 60%) as a white solid; mp 156−158 °C; R_f = 0.50 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3362, 2948, 2879, 1590, 1488, 1455, 1407, 1339, 1295, 1257, 1118, 1087, 1071, 1010, 907, 862, 818, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, d, J = 8.5 Hz), 7.29 (2H, d, J = 8.5 Hz), 7.19 (1H, d, J = 1.0 Hz), 6.94 (1H, dd, J = 8.5, 1.5 Hz), 6.50 (1H, d, J = 8.5 Hz), 3.66 (1H, s), 3.55 (1H, d, J = 10.0 Hz), 2.91 (1H, d, J = 9.0 Hz), 2.52−2.64 (2H, m), 2.34−2.43 (1H, m), 2.35 (1H, dd, J = 10.0, 9.5 Hz), 1.92 (1H, d, J = 4.5 Hz), 1.78 (1H, d, J = 10.0 Hz), 1.54−1.71 (5H, m), 1.40 (1H, d, J = 10.0 Hz), 1.25−1.43 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 142.7, 131.7, 129.6, 129.5, 127.6, 125.8, 124.0, 121.6, 116.3, 61.2, 47.5, 46.7, 45.8, 45.2, 44.3, 38.9, 36.9, 29.0, 26.9, 26.6; MS (EI^+) m/e (rel intensity) 429 (100), 428 (27), 427 (84), 320 (25), 272 (47); HRMS (EI) m/e calcd for $C_{23}H_{23}N^{79}Br^{35}Cl$ [M^+] 427.0702, found 427.0707.

***exo-exo*-8c and 6-(4-Bromophenyl)-2-chloro-6,6a,7,7a,8,9,10,10a,11,11a-octahydro-5*H*-7,11-methanocyclopenta[*j*]phenanthridine (11).** Synthesized according to the general procedure with the exception that the reaction was heated to 50 °C for 41 h. Purification of the crude material (∼2:1 mixture of regioisomers) by flash column chromatography on silica gel using a gradient elution of 50 to 80% dichloromethane in hexanes afforded *exo-exo*-**8c** as a 2:1 mixture of regioisomers (173 mg, 75%) in the form of an off-white foam: R_f = 0.42 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3363, 3040, 2940, 2844, 1598, 1486, 1454, 1284, 1251, 1113, 1071, 1011, 907, 857, 821, 808, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (4H, d, J = 8.5 Hz), 7.30 (4H, d, J = 8.5 Hz), 7.25−7.27 (2H, m overlaps with residual chloroform peak), 6.93−6.97 (2H, m), 6.51 (2H, d, J = 8.5 Hz), 5.53−5.71 (3H, m), 5.36−5.38 (1H, m), 3.66 (1H, s, NH), 3.65 (1H, s, NH), 3.52 (1H, d, J = 10.5 Hz), 3.49 (1H, d, J = 10.5 Hz), 2.80−2.83 (1H, m), 2.49−2.74 (5H, m), 2.45 (1H, s), 2.36−2.46 (2H, m), 2.09−2.18 (3H, m), 1.97−2.02 (1H, m), 1.80−1.86 (2H, m), 1.74 (1H, s), 1.25−1.29 (4H, m). The mixture of regioisomers was subjected to diimide reduction following a literature procedure.[22] To a colorless solution of *exo-exo*-**8c** (46 mg, 0.11 mmol) in dry CH_2Cl_2 (2.5 mL) was added in three portions potassium azodicarboxylate (169 mg, 0.873 mmol) at reflux. The yellow suspension was treated with glacial AcOH (140 μL, 2.4 mmol) over 2 h, after which the reaction mixture was heated at reflux for 22 h. The white suspension was filtered by gravity, and the filtrate was concentrated in vacuo to afford *exo-exo*-**11**: isolated (40 mg, 86%) as an off-white solid; mp 176−179 °C; R_f = 0.40 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3353, 3058, 2942, 2861, 1590, 1487, 1455, 1406, 1340, 1296, 1259, 1249, 1193, 1111, 1085, 1072, 1010, 906, 860, 816, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (2H, d, J = 8.5 Hz), 7.30 (2H, d, J = 8.5 Hz), 7.25 (1H, s), 6.95 (1H, dd, J = 8.5, 1.5 Hz), 6.51 (1H, d, J = 8.5 Hz), 3.66 (1H, s), 3.50 (1H, d, J = 10.5 Hz), 2.57 (1H, d, J = 9.0 Hz), 2.41 (1H, s), 1.82−2.05 (3H, m), 1.72−1.80 (3H, m), 1.60−1.69 (1H, m), 0.82−1.35 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 143.0, 131.7, 129.6, 128.7, 128.3, 126.0, 124.0, 121.5, 116.2, 60.9, 52.5, 48.2, 47.7, 46.8, 43.6, 43.2, 32.2, 32.1, 28.1, 27.3; MS (EI^+) m/e (rel intensity) 429 (100), 428 (25), 427 (81), 320 (76), 318 (55), 272 (45); HRMS (EI) m/e calcd for $C_{23}H_{23}N^{79}Br^{35}Cl$ [M^+] 427.0702, found 427.0683.

Methyl 6-(4-bromophenyl)-8-(hydroxymethyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine-2-carboxylate (*exo-exo*-8d) and Methyl 6-(4-bromophenyl)-9-(hydroxymethyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine-2-carboxylate (*exo-exo*-8d′). Synthesized according to the general procedure. Purification of the crude material (1:1.1 mixture of regioisomers **8d**/**8d′**) by flash column chromatography on silica gel using a gradient elution of 35 to 50% ethyl acetate in hexanes afforded *exo-exo*-**8d** followed by *exo-exo*-**8d′**. *exoexo*-**8d**: Isolated (22 mg, 26%) as a yellow solid; mp >225 °C; R_f = 0.28 (65:35 hexanes/EtOAc); IR (thin film) ν_{max} 3452 (br O−H), 3338 (N−H), 2950, 2872, 1703, 1605, 1505, 1486, 1435, 1300, 1259, 1196, 1130, 1105, 1071, 1010, 909, 825, 771, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, s), 7.70 (1H, d, J = 8.5 Hz), 7.49 (2H, d, J = 8.5 Hz), 7.30 (2H, d, J = 8.5 Hz), 6.57 (1H, d, J = 8.5 Hz), 4.03 (1H, s), 3.87 (3H, s), 3.68 (1H, d, J = 10.0 Hz), 3.55−3.67 (1H, m), 3.40−3.49 (1H, m), 2.77 (1H, d, J = 4.0 Hz), 2.64 (1H, d, J = 9.0 Hz), 2.43 (1H, dd, J = 9.5, 9.0 Hz), 2.03−2.29 (2H, m), 1.94 (1H, ddd, J = 12.5, 5.0, 4.5 Hz), 1.75 (1H, d, J = 10.0 Hz), 1.27 (1H, d, J = 11.0 Hz), 0.89−0.97 (1H, m), 0.88 (1H, t, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C), 150.7 (C), 142.2 (C), 131.9 (CH), 130.5 (CH), 129.3 (CH), 128.4 (CH), 125.7 (C), 121.9 (C), 120.8 (C), 114.8 (CH), 64.1 (CH_2), 59.9 (CH), 51.7 (CH_3), 45.7 (CH), 44.1 (CH), 43.2 (CH), 41.8 (CH), 41.2 (CH), 35.3 (CH_2), 33.6 (CH_2); MS (EI^+) m/e (rel intensity) 443 (37), 441 (59), 425 (46), 424 (19), 423 (62), 345 (24), 344 (100), 343 (26), 342 (87), 188 (37); HRMS (EI) m/e calcd for $C_{23}H_{24}{}^{79}BrNO_3$ [M^+] 441.0940, found 441.0939. *exo-exo*-**8d′**: Isolated (20 mg, 24%) as a white solid; mp 196−200 °C; R_f = 0.18 (65:35 hexanes/EtOAc); IR (thin film) ν_{max} 3488 (O−H), 3317 (N−H), 2945, 2909, 2878, 1684, 1601, 1511, 1486, 1434, 1301, 1256, 1246, 1126, 1105, 1051, 1009, 902, 832, 773, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.70 (1H, d, J = 8.5 Hz), 7.49 (2H, d, J = 8.5 Hz), 7.28 (2H, d, J = 8.5 Hz), 6.57 (1H, d, J = 8.5 Hz), 4.02 (1H, s), 3.86 (3H, s), 3.70−3.77 (2H, m), 3.61 (1H, d, J = 9.5 Hz), 3.00 (1H, d, J = 9.0 Hz), 2.85 (1H, d, J = 2.0 Hz), 2.25−2.30 (1H, m), 2.03−2.11 (1H, m), 1.79 (1H, dd, J = 12.0, 5.0 Hz), 1.72 (1H, d, J = 9.0 Hz), 1.45 (1H, dd, J = 5.0, 4.5 Hz), 1.27 (1H, d, J = 8.0 Hz), 0.65−0.73 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C), 151.1 (C), 142.6 (C), 131.8 (CH), 130.1 (CH), 129.4 (CH), 128.3 (CH), 126.1 (C), 121.7 (C), 120.9 (C), 114.8 (CH), 64.0 (CH_2), 60.4 (CH), 53.9 (CH), 51.6 (CH_3), 44.4 (CH), 42.3 (CH), 40.0 (CH), 35.9 (CH), 35.4 (CH_2), 32.8 (CH_2); MS (EI^+) m/e (rel intensity) 443 (41), 442 (22), 441 (57), 344 (100), 343 (20), 342 (89), 188 (22); HRMS (EI) m/e calcd for $C_{23}H_{24}{}^{79}BrNO_3$ [M^+] 441.0940, found 441.0941.

Methyl 6-(4-bromophenyl)-8-{[(4-nitrobenzoyl)oxy]methyl}-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine-2-carboxylate (*exo-exo*-8e). Synthesized according to the general procedure with the exception that 1.05 equiv of norbornene **7e** was used and the reaction was first stirred at 60 °C for 22 h and then after addition of 0.7 mL of CH_3CN was stirred at 75 °C for 16 h. Purification by flash column chromatography on silica gel using a gradient elution of 10 to 25% ethyl acetate in hexanes afforded the title compound (82 mg, 52%) as a yellow solid: mp 212−213 °C; R_f = 0.29 (80:20 hexanes/EtOAc); IR (thin film) ν_{max} 3346, 2953, 2870, 1716, 1606, 1527, 1435, 1274, 1103, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (2H, d, J = 9.0 Hz), 7.98 (1H, s), 7.71 (2H, d, J = 9.0 Hz), 7.70 (1H, d, J = 8.5 Hz), 7.23−7.30 (4H, m), 6.57 (1H, d, J = 8.5 Hz), 4.42 (1H, dd, J = 11.5, 6.0 Hz), 4.10−4.18 (1H, m), 3.99 (1H, s), 3.87 (3H, s), 3.65 (1H, d, J = 10.5 Hz), 2.85 (1H, d, J = 4.0 Hz), 2.68 (1H, d, J = 9.0 Hz), 2.47 (1H, dd, J = 9.5, 9.0 Hz), 2.40−2.47 (1H, m), 2.23 (1H, d, J = 3.0 Hz), 2.02 (1H, ddd, J = 12.0, 5.0, 4.5 Hz), 1.81 (1H, d, J = 10.0 Hz), 1.34 (1H, d, J = 10.5 Hz), 1.01 (1H, ddd, J = 12.0, 5.0, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (C), 164.1 (C), 150.7 (C), 150.5 (C), 142.1 (C), 134.9 (C), 131.6 (CH), 130.4 (CH), 130.2 (CH), 129.5 (CH), 128.5 (CH), 125.2 (C), 123.6 (CH), 121.8 (C), 120.9 (C), 114.9 (CH), 65.7 (CH_2), 60.0 (CH), 51.7 (CH_3), 45.9 (CH), 44.0 (CH), 42.8 (CH), 41.1 (CH), 37.8 (CH), 35.0 (CH_2), 32.9 (CH_2); MS (ESI^+) m/e (rel intensity) 594 (17), 593 (53), 592 (19), 591 (55); HRMS (ESI) m/e calcd for $C_{30}H_{27}N_2O_6{}^{79}Br$ [M + H]$^+$ 591.1125, found 591.1101.

Methyl 8,9-bis(methoxymethyl)-6-(4-methylphenyl)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine-2-carboxylate (*exo-exo*-8g). Synthesized according to the general procedure. Purification by flash column chromatography on silica gel

using a gradient elution of 10 to 30% ethyl acetate in hexanes afforded the title compound (95 mg, 68%) as a white solid: mp 176−178 °C; R_f = 0.05 (80:20 hexanes/EtOAc); IR (thin film) ν_{max} 3336, 3061, 3024, 2949, 2922, 2891, 2833, 2810, 1705, 1606, 1487, 1435, 1298, 1251, 1197, 1126, 1103, 1010, 910, 823, 771, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (1H, s), 7.69 (1H, dd, J = 8.0, 1.0 Hz), 7.48 (2H, d, J = 8.5 Hz), 7.26 (2H, d, 8.5 Hz), 6.55 (1H, d, J = 8.5 Hz), 4.02 (1H, br s), 3.87 (3H, s), 3.62 (1H, d, J = 9.5 Hz), 3.47 (1H, dd, J = 9.0, 6.0 Hz), 3.36 (3H, s), 3.29−3.35 (2H, m), 3.23 (3H, s), 3.16−3.21 (1H, m), 2.76 (1H, d, J = 9.0 Hz), 2.70 (1H, s), 2.04−2.23 (2H, m), 2.02 (1H, s), 1.87−1.95 (1H, m), 1.46 (1H, d, J = 11.0 Hz), 1.38 (1H, d, J = 11.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 150.6, 142.6, 131.8, 130.6, 129.3, 128.4, 125.7, 121.7, 120.7, 114.7, 72.6, 72.4, 60.1, 58.7, 58.5, 52.9, 51.6, 46.4, 45.3, 44.8, 43.5, 43.3, 29.6; MS (ESI^+) m/e (rel intensity) 502 (100), 500 (97), 470 (23), 468 (18); HRMS (ESI) m/e calcd for $C_{26}H_{30}{}^{79}BrNO_4$ $[M + H]^+$ 500.1430, found 500.1411.

Ethyl 2-methoxy-5,6,6a,7,8,9,10,10a-octahydro-7,10-ethanophenanthridine-6-carboxylate (*exo-exo*-12a). To a solution of *p*-anisidine (31 mg, 0.25 mmol) in dry CH_2Cl_2 (1.3 mL) was added ethyl glyoxylate (45 wt % solution in toluene, 55 μL, 0.25 mmol). After stirring at room temperature for 2.5 h, norbornene (49 mg, 0.51 mmol) was added in one portion followed by dropwise addition of $BF_3 \cdot OEt_2$ (7.0 μL, 0.056 mmol). The reaction was stirred at room temperature for 5 h and then treated with saturated aqueous $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL), and then the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude material by flash column chromatography on silica gel using a gradient elution of 10 to 30% ethyl acetate in hexanes afforded the title compound (34 mg, 44%) as a brown foam: R_f = 0.37 (80:20 hexanes/EtOAc); IR (thin film) ν_{max} 3366, 2949, 2868, 2829, 1734, 1623, 1570, 1501, 1465, 1205, 1118, 1035, 847, 813, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (1H, d, J = 8.5 Hz), 6.60 (1H, dd, J = 8.5, 2.5 Hz), 6.56 (1H, d, J = 8.5 Hz), 4.15 (2H, q, J = 7.0 Hz), 3.88 (1H, br s), 3.74 (3H, s), 3.50 (1H, d, J = 6.5 Hz), 2.70 (1H, d, J = 9.0 Hz), 2.46 (1H, d, J = 4.0 Hz), 2.37−2.43 (1H, m), 1.34 (1H, d, J = 3.0 Hz), 1.53−1.69 (3H, m), 1.40−1.44 (2H, m), 1.22 (3H, dd, J = 7.0, 7.0 Hz), 1.05 (1H, ddd, J = 10.0, 2.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (C), 153.3 (C), 138.7 (C), 128.6 (C), 116.3 (CH), 114.0 (CH), 112.2 (CH), 61.0 (CH_2), 58.7 (CH_3), 55.5 (CH), 45.9 (CH), 45.1 (CH), 44.1 (CH), 42.1 (CH), 34.1 (CH_2), 30.1 (CH_2), 28.9 (CH_2), 14.2 (CH_3); MS (ESI^+) m/e (rel intensity) 301 (100), 228 (34); HRMS (ESI) m/e calcd for $C_{18}H_{23}NO_3$ $[M + H]^+$ 302.1750, found 302.1748.

(2-Methoxy-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridin-6-yl)methanol (13a). To a solution of *p*-anisidine (201 mg, 1.63 mmol) in dry CH_2Cl_2 (8 mL) was added ethyl glyoxylate (45 wt % solution in toluene, 450 μL, 2.04 mmol). After stirring at room temperature for 20 min, norbornene (306 mg, 3.25 mmol) was added in one portion followed by dropwise addition of $BF_3 \cdot OEt_2$ (41 μL, 0.32 mmol). The reaction was stirred at room temperature for 4 h and then concentrated in vacuo. The crude residue was dissolved in dry THF (4 mL) and then transferred by cannula to a cooled (0 °C) suspension of $LiAlH_4$ (195 mg, 4.88 mmol) in dry THF (8 mL). The reaction mixture was warmed to room temperature and stirred overnight, after which the mixture was cooled in an ice bath and subjected to a Fieser workup (successive dropwise addition of 200 μL of H_2O, 200 μL of 15% NaOH solution, and 600 μL of H_2O). The resultant granular suspension was stirred at room temperature for 2 h, filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Purification of the crude material by flash column chromatography on silica gel using a gradient elution of 25 to 50% ethyl acetate in hexanes afforded *exo-endo*-**13a** followed by *exo-exo*-**13a**. *exo-endo*-**13a**: Isolated (48 mg, 11%) as a brown foam; R_f = 0.37 (50:50 hexanes/EtOAc); IR (thin film) ν_{max} 3380 (br O−H), 3359 (N−H), 2950, 2869, 2830, 1605, 1504, 1463, 1256, 1159, 1129, 1040, 998, 908, 850, 809, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, d, J = 3.0 Hz), 6.59 (1H, dd, J = 8.5, 3.0 Hz), 6.53 (1H, d, J = 8.5 Hz), 3.76−3.87 (2H, m), 3.75 (3H, s), 3.05−3.10 (1H, m), 2.88 (1H, d, J = 8.5 Hz), 2.55−2.85 (1H, br s), 2.22 (1H, d, J = 4.5 Hz), 2.14 (1H, d, J = 2.0 Hz), 1.90 (1H, dd, J = 8.5, 4.0 Hz), 1.36−1.66 (4H, m), 1.19−1.28 (1H, m), 0.92 (1H, d, J = 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0 (C), 140.6 (C), 129.7 (C), 116.2 (CH), 114.7 (CH), 112.2 (CH), 65.7 (CH_2), 56.8 (CH), 55.6 (CH_3), 48.1 (CH), 46.9 (CH), 45.3 (CH), 36.6 (CH), 35.0 (CH_2), 31.5 (CH_2), 28.5 (CH_2); MS (ESI^+) m/e (rel intensity) 261 (23), 260 (100); HRMS (ESI) m/e calcd for $C_{16}H_{21}NO_2$ $[M + H]^+$ 260.1645, found 260.1639. *exo-exo*-**13a**: Isolated (206 mg, 49%) as colorless needles; mp 92−94 °C; R_f = 0.28 (50:50 hexanes/EtOAc); IR (thin film) ν_{max} 3242 (N−H), 3201 (br O−H), 2951, 2868, 2827, 1611, 1501, 1458, 1340, 1238, 1202, 1164, 1119, 1082, 1039, 986, 904, 848, 826, 787, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (1H, d, J = 2.0 Hz), 6.54−6.63 (2H, m), 3.84 (1H, dd, J = 10.5, 3.0 Hz), 3.75 (3H, s), 3.54 (1H, dd, J = 10.5, 10.0 Hz), 2.79 (1H, dd, J = 8.5, 3.0 Hz), 2.58−2.62 (2H, m), 2.12 (1H, s), 1.77 (1H, dd, J = 9.0, 9.0 Hz), 1.27−1.74 (7H, m), 1.07 (1H, d, J = 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0 (C), 139.3 (C), 128.6 (C), 116.2 (CH), 113.9 (CH), 112.0 (CH), 65.9 (CH_2), 57.4 (CH), 55.6 (CH_3), 45.5 (CH), 43.5 (CH), 43.2 (CH), 40.7 (CH), 34.3 (CH_2), 29.5 (CH_2), 29.3 (CH_2); MS (EI^+) m/e (rel intensity) 259 (14), 241 (15), 240 (35), 229 (16), 228 (100), 160 (37); HRMS (EI) m/e calcd for $C_{16}H_{21}NO_2$ $[M^+]$ 259.1572, found 259.1566.

Ethyl 2-methyl-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridine-6-carboxylate (*exo-exo*-12b). To a solution of *p*-toluidine (81 mg, 0.76 mmol) in dry CH_2Cl_2 (3.5 mL) was added ethyl glyoxylate (45 wt % solution in toluene, 200 μL, 0.91 mmol). After stirring at room temperature for 15 min, norbornene (143 mg, 1.51 mmol) was added in one portion followed by dropwise addition of $BF_3 \cdot OEt_2$ (19 μL, 0.15 mmol). The reaction was stirred at room temperature for 5 h and then concentrated in vacuo. Purification of the crude material by flash column chromatography on silica gel using a gradient elution of 4 to 12% ethyl acetate in hexanes afforded the title compound (85 mg, 40%) as a colorless oil: R_f = 0.35 (90:10 hexanes/EtOAc); IR (thin film) ν_{max} 3368, 2950, 2869, 1734, 1616, 1507, 1473, 1369, 1297, 1253, 1196, 1027, 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (1H, s), 6.80 (1H, d, J = 8.0 Hz), 6.54 (1H, d, J = 8.0 Hz), 4.16 (2H, q, J = 7.0 Hz), 3.90−4.05 (1H, br s), 3.55 (1H, d, J = 6.5 Hz), 2.68 (1H, d, J = 9.0 Hz), 2.46 (1H, d, J = 3.0 Hz), 2.36−2.44 (1H, m), 2.35 (1H, d, J = 2.5 Hz), 2.23 (3H, s), 1.26−1.71 (5H, m), 1.23 (3H, t, J = 7.0 Hz), 1.07 (1H, ddd, J = 10.0, 2.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (C), 142.4 (C), 129.3 (CH), 128.6 (C), 127.2 (C), 126.9 (CH), 115.5 (CH), 61.0 (CH_2), 58.5 (CH), 46.1 (CH), 45.2 (CH), 43.7 (CH), 42.2 (CH), 34.1 (CH_2), 30.1 (CH_2), 28.9 (CH_2), 20.7 (CH), 14.2 (CH_3); MS (ESI^+) m/e (rel intensity) 286 (100), 212 (24); HRMS (ESI) m/e calcd for $C_{18}H_{23}NO_2$ $[M + H]^+$ 286.1801, found 286.1802.

(2-Methyl-5,6,6a,7,8,9,10,10a-octahydro-7,10-methanophenanthridin-6-yl)methanol (13b). To a solution of *p*-toluidine (93 mg, 0.87 mmol) in dry CH_2Cl_2 (3.5 mL) was added ethyl glyoxylate (45 wt % solution in toluene, 210 μL, 0.95 mmol). After stirring at room temperature for 10 min, norbornene (163 mg, 3.25 mmol) was added in one portion followed by dropwise addition of $BF_3 \cdot OEt_2$ (22 μL, 0.17 mmol). The reaction was stirred at room temperature for 4 h and then concentrated in vacuo. The crude residue was dissolved in dry THF (4 mL) and then transferred by cannula to a cooled (0 °C) suspension of $LiAlH_4$ (104 mg, 2.60 mmol) in dry THF (4 mL). The reaction mixture was slowly warmed to room temperature and stirred overnight, after which the mixture was cooled in an ice bath and subjected

to a Fieser workup (successive dropwise addition of 105 μL of H_2O, 105 μL of 15% NaOH solution, and 315 μL of H_2O). The resultant granular suspension was stirred at room temperature for 2 h, filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Purification of the crude material by flash column chromatography on silica gel using a gradient elution of 20 to 35% ethyl acetate in hexanes afforded *exo-endo*-**13b** followed by *exo-exo*-**13b**. *exo-endo*-**13b**: Isolated (22 mg, 10%) as a brown foam; R_f = 0.47 (65:35 hexanes/EtOAc); IR (thin film) ν_{max} 3380 (br O−H), 3366 (N−H), 2952, 2921, 2869, 1615, 1508, 1455, 1372, 1297, 1278, 1039, 908, 812, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (1H, s), 6.80 (1H, dd, J = 8.0, 2.0 Hz), 6.52 (1H, d, J = 8.0 Hz), 3.77−3.89 (2H, m), 3.07−3.14 (1H, m), 2.87 (1H, d, J = 8.5 Hz), 2.24 (3H, s), 2.21 (1H, d, J = 4.5 Hz), 2.15 (1H, d, J = 2.0 Hz), 1.92 (1H, dd, J = 8.5, 4.0 Hz), 1.34−1.66 (6H, m), 1.18−1.27 (1H, m), 0.92 (1H, d, J = 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2 (C), 130.2 (CH), 128.6 (C), 128.3 (C), 126.7 (CH), 115.5 (CH), 65.8 (CH_2), 56.7 (CH), 48.2 (CH), 46.5 (CH), 45.4 (CH), 36.7 (CH), 35.0 (CH_2), 31.6 (CH_2), 28.5 (CH_2), 20.6 (CH_3); MS (ESI^+) m/e (rel intensity) 245 (19), 244 (100); HRMS (ESI) m/e calcd for $C_{16}H_{21}NO$ $[M + H]^+$ 244.1695, found 244.1696. *exo-exo*-**13b**: Isolated (94 mg, 45%) as an off-white solid; mp 112−114 °C; R_f = 0.34 (65:35 hexanes/EtOAc); IR (thin film) ν_{max} 3350 (br O−H), 3325 (N−H), 3017, 2946, 2869, 1615, 1508, 1455, 1359, 1294, 1256, 1082, 1040, 1025, 909, 813, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, s), 6.80 (1H, d, J = 8.0 Hz), 6.52 (1H, d, J = 8.0 Hz), 3.81 (1H, dd, J = 10.5, 3.0 Hz), 3.52 (1H, dd, J = 10.5, 8.5 Hz), 2.79 (1H, dd, J = 8.5, 3.0 Hz), 2.55−2.59 (2H, m), 2.24 (3H, s), 2.11 (1H, d, J = 3.5 Hz), 1.76 (1H, dd, J = 9.0, 9.0 Hz), 1.54−1.71 (2H, m), 1.52 (1H, dt, J = 10.0, 1.5 Hz), 1.27−1.42 (2H, m), 1.05 (1H, dt, J = 10.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 129.0, 128.3, 127.3, 126.8, 115.5, 65.9, 57.1, 45.6, 43.3, 43.1, 40.8, 34.3, 29.5, 29.3, 20.7; MS (ESI^+) m/e (rel intensity) 245 (27), 244 (100); HRMS (EI) m/e calcd for $C_{16}H_{21}NO$ $[M + H]^+$ 244.1695, found 244.1702.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for all new compounds. Experimental procedures and characterization data for all precursors and isolated side products. Crystallographic data for compounds *exo-exo*-**1d**, *exo-endo*-**1l**, and *exo-exo*-**13a**. This material is available free of charge via the Internet at http://pubs.acs.org.