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Synthesis of Functionally Diverse and Conformationally Constrained Polycyclic Analogues of Proline and Prolinol

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Alkylation of the monoenolate of *N*-Boc-L-pyroglutamic acid methyl ester with a variety of benzylic halides and their homologues gave the corresponding *anti*-C-4-alkylated products as major products. Formation of the *N*-Boc-iminium ion and Friedel−Crafts intramolecular cationic ring closure afforded a series of fused 1-azacyclodihydroindene derivatives with interesting topologies. Functional diversity was introduced via further manipulation of pendant groups on the original proline motif as well as on the aromatic moiety.

Polycyclic compounds that incorporate a pyrrolidine ring are an interesting class of heterocycles, some of which exhibit pharmacological activity. For example, *N*-alkylindanopyrrolidines (**1**) have been reported to have hypoglycemic activity[1] (Figure 1). Conformationally restricted analogues of nicotine such as **2** have been studied as analgesics.[2] Bicyclic and polycyclic analogues of proline and pipecolic acids are potent inhibitors of angiotensin converting enzyme (ACE).[3] Azasteroids patterned after a homoequinelin structure such as **3** are reported to have antibacterial activity.[4] The pyrrolidine motif is also found in the structures of alkaloidal natural products such as martinellic acid[5] **4** and sceletium alkaloid A_4,[6] **5** (Figure 1). Recently, Carroll and co-workers[7] have reported the synthesis of hexahydro-2-substituted-1-methylindeno[1,2-*b*]pyrroles and demonstrated high affinity and selectivity for the PCP binding site in conjunction with the NMDA receptor complex.

In the context of a program concerned with the design and synthesis of topologically interesting and functionally versatile scaffolds derived from readily available amino acids,[8] we report herein on the facile synthesis of enantiopure tricyclic amino acids represented by the general structure **7** (Figure 2). To the best of our knowledge, such aryl-functionalized tricyclic analogues of proline have very few precedents.[6,7] They can be considered as conformationally constrained analogues of ACE inhibitors.[3a,9] The incorporation of an amino acid functionality at one extremity, and an aromatic moiety at the other side of

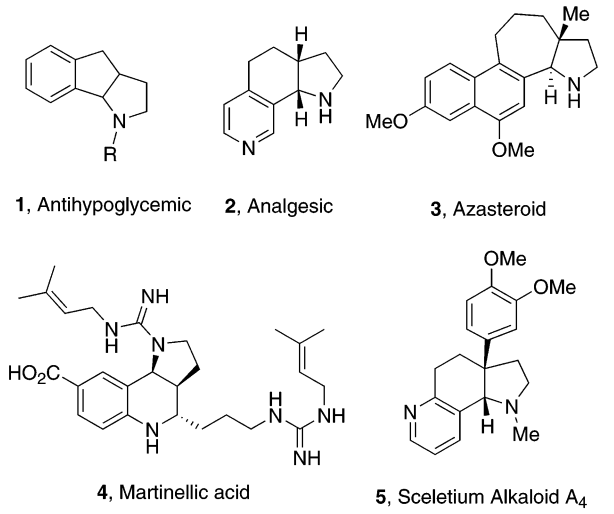

FIGURE 1. Structures of biologically relevant tricyclic pyrrolidines.

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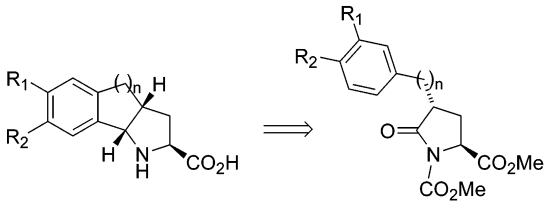

FIGURE 2. Alkylated precursors to tricyclic pyrrolidines.

the tricyclic motif, coupled with their molecular shapes depending on the size of the middle ring, offer unique opportunities for their utilization as scaffolds for diversity.

The tricyclic structures are easily assembled via an intramolecular Friedel−Crafts-type cationic cyclization[10] of an appropriately functionalized iminium ion precursor[11] derived from 4-substituted D- or L-pyroglutamic acids **6** (Figure 2).[12] The synthesis of the indanopyrrolidinecarboxylic acids is shown in Scheme 1. Alkylation of the enolate derived from methyl *N*-methoxycarbonyl L-pyroglutamate[13] **8** with various benzyl bromides under standard conditions led to the *trans*-4-arylmethyl-substituted analogues **9**−**11** as major products.[14] Reduction of the lactam carbonyl with Super-Hydride,[15] followed by acetylation, gave the corresponding acetylated hemiaminals. Treatment with $AlCl_3$ in dichloromethane effected smooth ring closure via the intermediacy of the corresponding iminium ions to afford the enantiopure tricyclic products **12**−**14**. As expected, only a cis-fused ring system was formed. A survey of *N*-protecting groups (Cbz, Boc, methoxycarbonyl), hemiaminal substituents (OAc, OMe, OH), and Lewis acids (BF_3·Et_2O, $SnCl_4$, $TiCl_4$, $AlMe_3$, $AlCl_3$) led us to the *N*-methoxycarbonyl group and $AlCl_3$ as the most efficacious combinations for the cationic cyclization reaction of 5-acetoxy proline methyl esters.

In all the tricyclic structures bearing a carbamate-type protecting group, a cis/trans isomerism with regard to the orientation of the methoxycarbonyl group was observed by proton and carbon NMR, with the ratio of the isomers changing slightly depending on the compound. The energetic barriers to rotation in carbamates are usually lower than those in the corresponding amides and insensitive to solvents effects.[16] Since cis and trans isomers of carbamate bonds are usually of very similar energy, it may be argued that the conformational features and the stereoelectronic properties[16] of the methyl ester group α to the nitrogen could play a role in determining the observed cis/trans ratio in each compound. Cleavage of the ester of the unsubstituted analogue afforded X-ray quality crystals for **16** (Scheme 1). Although hydrolysis with methanolic KOH could be accomplished in small scale to afford the amino acid **17**, the reaction proved to be capricious at times, requiring prolonged refluxing periods with recovery of starting material. Reduction of the acid **15** with borane dimethyl sulfide complex afforded the alcohol **18**, which could be smoothly deprotected under basic conditions, most likely via intramolecular assistance of the primary hydroxyl group to give the amino alcohol **19**. Protection as the *N*-Boc **20** derivative and oxidation[17] to **21** followed by acid hydrolysis afforded the free amino acid **17** in excellent overall yield. As seen in the ORTEP diagram (Scheme 1) and the stick representation in Figure 3 (left panel), the carbamate **16** exists as a cis-oriented rotamer. The molecule has an L-shaped structure in which the ester group adopts a pseudoaxial orientation.[18] The availability of the bromoaryl intermediate **13** led us to explore its suitability in a Suzuki biaryl coupling.[19] In the event, treatment of **13** with phenylboronic acid in the presence of triphenylphosphine and Pd(OAc)$_2$ led to the expected adduct **22** in 77% yield.

The synthesis of the tetrahydronaphthalenopyrrolidine carboxylic acid analogue (Figure 2, $n = 2$) is shown in Scheme 2. To circumvent the lower reactivity of phenylethyl bromide as an electrophile, and its propensity for elimination, we chose instead to treat the Li enolate of **8** with phenylacetaldehyde to afford a 3:1 mixture of the aldol products.[9,14b,20] Mesylation and in situ elimination afforded the expected conjugated olefin **23** and a small amount of the styryl adduct. Catalytic hydrogenation of the mixture with 10% Pd/C gave the cis-oriented phenylethyl adduct **24**. Conventional manipulation of the lactam carbonyl group gave the corresponding hemiaminal acetate, which was subjected to intramolecular cationic ring closure as previously described for the lower homologue (Scheme 1). Thus, treatment with $AlCl_3$ in dichloromethane gave a 10:1 mixture of the cis- and trans-fused tricyclic compounds **25** and **26**, respectively. A *Si* face pseudoaxial approach may be favored in the case of **25** due to a better overlap of the aromatic ring with the iminium ion, despite the steric bias of an $AlCl_3$-

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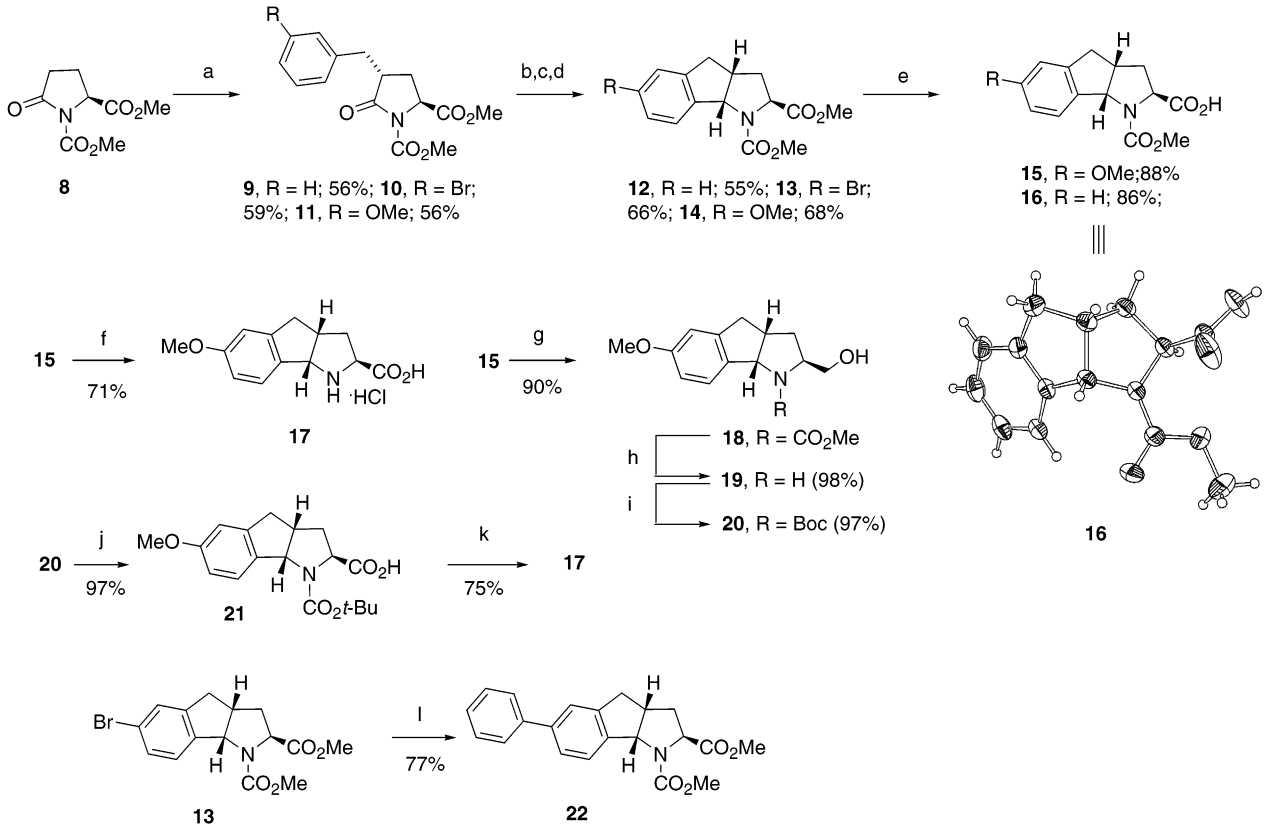
SCHEME 1[a]



[a] Reagents and conditions: (a) (i) LiHMDS, THF, −78 °C, (ii) 3-RBnBr; (b) $LiEt_3BH$, THF, −78 °C; (c) Et_3N, DMAP, Ac_2O, CH_2Cl_2, 0 °C to rt; (d) $AlCl_3$, CH_2Cl_2, 0 °C; (e) LiOH, THF/H_2O, rt; (f) KOH, MeOH, reflux, then aqueous HCl; (g) $BH_3{\cdot}Me_2S$, THF, rt; (h) KOH, MeOH, reflux; (i) $(Boc)_2O$, CH_2Cl_2, rt; (j) TEMPO, NaClO, $NaClO_2$, MeCN, phosphate buffer, 35 °C; (k) TFA, CH_2Cl_2, then aqueous HCl; (l) $Pd(OAc)_2$, PPh_3, phenylboronic acid, *n*-PrOH/H_2O, 60 °C.

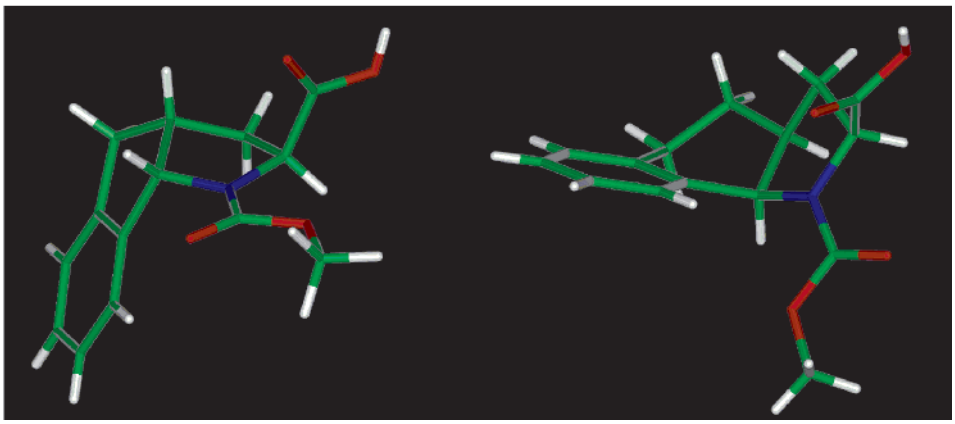


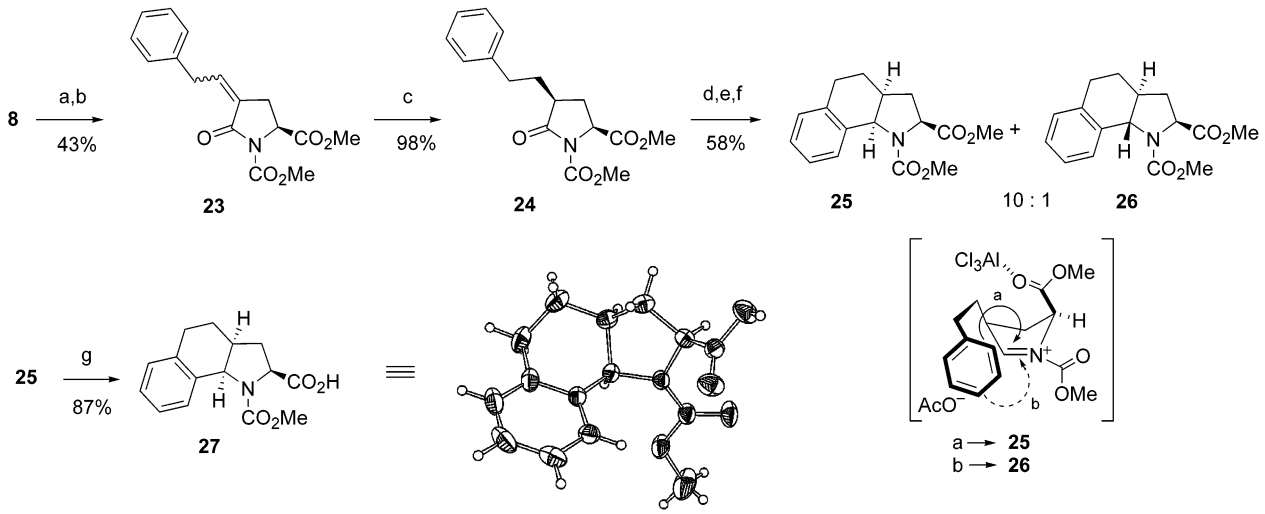
FIGURE 3. Left: *cis*-methoxycarbonyl rotamer in compound **16**. Right: *trans*-methoxycarbonyl in rotamer compound **27** (see ORTEP diagrams, Schemes 1 and 2).

coordinated ester group[21] as illustrated in Scheme 2. Hydrolysis of **25** afforded the corresponding acid **27** which was suitable for single-crystal X-ray analysis. Perspective viewing of the ORTEP diagram in Scheme 2 and the stick representation in Figure 3 (right panel) shows the ester group in a pseudoaxial orientation, as observed in **16**, and in other *N*-substituted prolines due mainly to A-strain.[18] The central ring exists as a boat form, and the *N*-methoxycarbonyl group adopts a trans-rotameric orientation contrary to **16** (Figure 3, left panel). The molecule has an L-shape, although the bend is not as pronounced as in **16**.

The 5,7-fused tricyclic proline analogue (Figure 2, $n = 3$) was synthesized according to the same protocol for the lower homologues. Thus, alkylation of the Li enolate of **8** with cinnamyl and *p*-methoxycinnamyl bromide afforded the trans-adducts **28** and **29**, respectively (Scheme

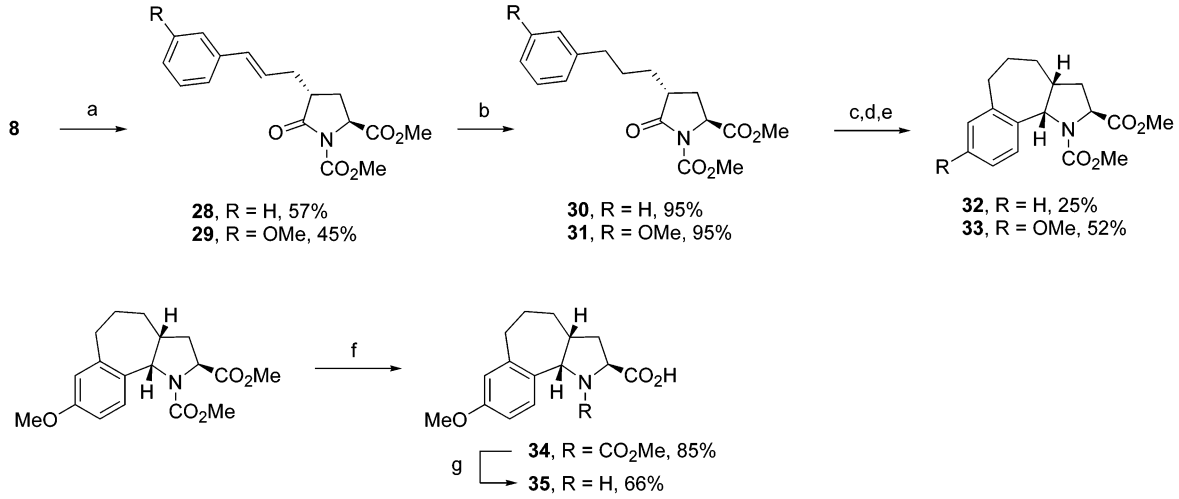
(21) For a related example of cuprate coordination, see: Ludwig, C.; Wistrand, L.-G. *Acta Chim. Scand.* **1994**, *48*, 367; see also the preceding papers.

SCHEME 2[a]



[a] Reagents and conditions: (a) (i) LiHMDS, THF, −78 °C, (ii) phenylacetaldehyde; (b) Et_3N, MsCl, CH_2Cl_2, rt; (c) 10% palladium-on-carbon, MeOH, rt; (d) $LiEt_3BH$, THF, −78 °C; (e) Et_3N, DMAP, Ac_2O, CH_2Cl_2, 0 °C to rt; (f) $AlCl_3$, CH_2Cl_2, 0 °C; (g) LiOH, THF/H_2O, rt.

SCHEME 3[a]



[a] Reagents and conditions: (a) (i) LiHMDS, THF, −78 °C, (ii) 3-R-cinnamyl bromide; (b) 10% palladium-on-carbon, MeOH, rt; (c) $LiEt_3BH$, THF, −78 °C; (d) Et_3N, DMAP, Ac_2O, CH_2Cl_2, 0 °C to rt; (e) $AlCl_3$, CH_2Cl_2, 0 °C; (f) LiOH, THF/H_2O, rt; (g) KOH, MeOH, reflux.

3). The modest yield of the *m*-methoxy analogue was due to competing dialkylation. Catalytic hydrogenation afforded compounds **30** and **31**, respectively. Activation of the lactam through the corresponding hemiaminal acetate and subsequent Friedel−Crafts cyclization in the presence of $AlCl_3$ afforded the expected tricyclic compounds **32** and **33,** respectively. The cyclization of the unsubstituted analogue **30** was accompanied by substantial quantities of ene-carbamate[22] formation by *β*-elimination of the 5-acetoxy group. The lower nucleophilicity of the phenyl ring compared to the *p*-methoxy analogue as well as a less favorable trajectory of approach could account for these results. Also, the yield was much lower than in the case of the phenethyl analogue (Scheme 2), which may be due to entropic effects. Apparently, the activating effect of the *p*-methoxy group in **31** is able to overcome the presumed interactions in the unsubstituted core **30**. The cis stereochemistry at the ring junction was secured from detailed NOE studies. Hydrolysis of the ester group in the *p*-methoxyphenyl derivative **33** afforded the corresponding acid **34**, which was further treated with alcoholic potassium hydroxide to afford the corresponding free amino acid **35**.

To increase the options for functional diversity in the tricyclic indanopyrrolidine carboxylic acids, we explored methodology to introduce aldehyde and carboxylic acid groups in the aryl portion. The required aromatic intermediate **37** was prepared as shown in Scheme 4. Alkylation of the Li enolate of **8** with the bromide **37** gave **38** as the major product (Scheme 5). Conventional manipulation of the lactam function, followed by Friedel−Crafts cyclization, gave the tricyclic analogue **39**. Attempts to transform this bromo derivative into the corresponding methoxycarbonyl analogue via halogen−lithium exchange, and subsequent treatment with CO_2 or methyl

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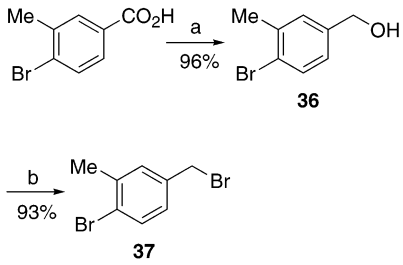
SCHEME 4[a]



[a] Reagents and conditions: (a) $LiAlH_4$,Et_2O, rt; (b) PBr_3, Et_2O, rt to reflux.

chloroformate, proved to be problematic. We therefore opted to introduce a carboxyl group via a three-step procedure.

Reduction of the ester to the alcohol **41** followed by Stille[23] coupling with vinyltributylstannane in the presence of tetrakis-triphenylphosphinepalladium gave the corresponding vinyl adduct with concomitant formation of a cyclic carbamate **42**. The structure and stereochemistry of this product were confirmed by single-crystal X-ray analysis. After cleavage of the carbamate and *N*-protection, the product **45** was oxidatively cleaved to the aldehyde **46** and further manipulated to give the orthogonally protected amino acid **48.** Each protective group was then selectively removed to afford the corresponding derivatives **49**, **50**, and **47**, in good to excellent yields, with three potential sites for diversification.

We extended the cationic cyclizations to include tetra- and pentacyclic systems as shown in Schemes 6 and 7. Thus, alkylation of the lithium enolate of **8** with 2-bromomethyl naphthalene gave the expected 4-substituted lactam **51** in 69% yield. Cationic cyclization as described above led to a 1:3 mixture of the tetracyclic compounds **52** and **53** which could be separated after reduction of the ester group to give **56** and **57**. Hydrolysis of **57** afforded the prolinol analogue **58**, which was easily converted to the corresponding *N*-Boc derivative **59**.

Alkylation of **8** with 1-bromomethyl phenanthrene gave **60** in 52% yield which upon cationic cyclization led to a 1:1 mixture of regioisomers **61** and **62** in low yield. Further manipulation gave **65** and **66** as a mixture of rotamers. Finally, the 4-phenylbenzyl analogue **67** was subjected to cationic cyclization and deprotection to give the 2-hydroxymethyl pyrrolidine analogue **71**.

We have reported on methods for the synthesis of enantiopure tricyclic constrained analogues of L-proline and L-prolinol with up to three sites of diversity that can be orthogonally manipulated.[24] The overall molecular shapes of these compounds can be varied to provide degrees of "curvature" depending on the size of the middle ring. The extended polycyclic aromatic analogues offer interesting topologies that can be useful in the study of constrained aromatic amino acids,[25] as DNA intercalators,[26] and as templates for helical peptides.[27]

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Experimental Procedures

General Procedure for Alkylation Reactions of Methyl *N*-Methoxycarbonyl-L-pyroglutamate (8). To a solution of pyroglutamate **8 (**10 mmol) in THF (50 mL) stirred at −78 °C was added a 1 M solution of lithium hexamethyldisilazide in THF (12 mL, 1.2 equiv) dropwise. After the reaction mixture was stirred at −78 °C for 1 h, the suitable benzyl- or cinnamyl bromide (12 mmol, 1.2 equiv) in THF (6 mL) was added via syringe, and stirring was continued for 2 h at −78 °C. The reaction mixture was then quenched with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (20 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The resulting crude was purified by flash column chromatography to afford the desired compound.

(2*S*,4*R*)-4-Benzyl-5-oxopyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (9). By using the general procedure described above, compound **9** was obtained, after column chromatography (hexanes/ethyl acetate, 7/3), as a white solid (56%): mp 79−81 °C; $[\alpha]_D$ −49.2 (1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.01−2.14 (m, 2H), 2.70 (dd, 1H, J = 13.9, 9.2 Hz,), 2.91−2.97 (m, 1H), 3.26 (dd, 1H, J = 14, 4.3 Hz), 3.74 (s, 3H), 3.88 (s, 3H), 4.57 (dd, 2H, J = 8.9, 2.2 Hz), 7.17−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 28, 35.9, 43.3, 52.6, 53.8, 56.6, 126.6, 128.6, 128.9, 137.9, 151.8, 171.2, 173.6; HRMS (FAB) calcd for $C_{15}H_{18}NO_5$ $[M + H]^+$ 292.11850, found 292.11930. Anal. Calcd for $C_{15}H_{18}NO_5$: C, 61.63; H, 6.21; N, 4.79. Found: C, 61.67; H, 5.96; N, 4.79.

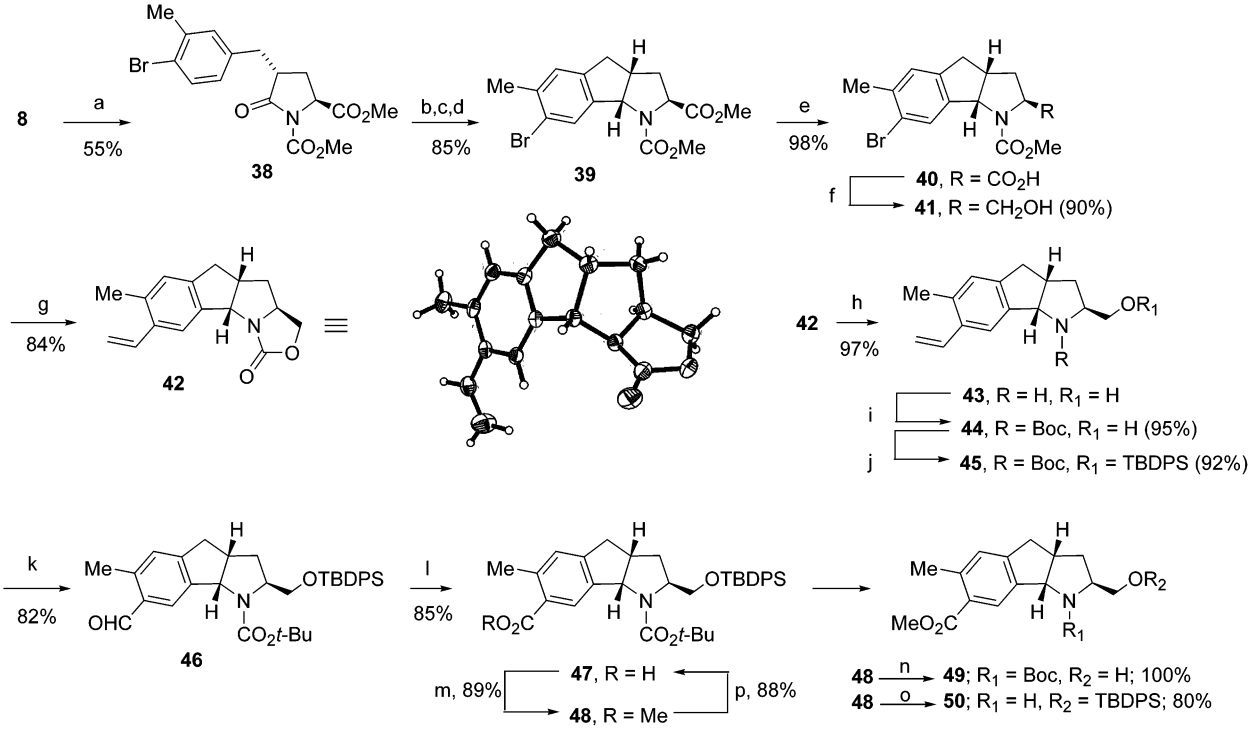
(2*S*,4*R*)-4-(3-Bromobenzyl)-5-oxopyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (10). By using the general procedure described above, compound **10** was obtained, after column chromatography (hexanes/ethyl acetate, 6/4), as a white solid (59%): mp 83−84 °C; $[\alpha]_D$ −30.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2−2.16 (m, 2H), 2.65 (dd, 1H, J = 13.9, 9.1 Hz), 2.88−2.94 (m, 1H), 3.24 (dd, 1H, J = 14, 4.4 Hz), 3.76 (s, 3H), 3.88 (s, 3H), 4.59 (dd, 1H, J = 9.3, 1.5 Hz), 7.1−7.19 (m, 2H), 7.32−7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 14.5, 21, 27.2, 35.3, 42.7, 53.8, 56.6, 60.4, 122.6, 130.1, 132, 140.3, 151.5, 170.7, 173.6; HRMS (FAB) calcd for $C_{15}H_{17}{}^{79}BrNO_5$ $[M + H]^+$ 370.02918, found 370.03008. Anal. Calcd for $C_{15}H_{16}BrNO_5$: C, 48.67; H, 4.36; N, 3.78. Found: C, 48.50; H, 4.41; N, 3.68.

(2*S*,4*R*)-4-(3-Methoxybenzyl)-5-oxopyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (11). By using the general procedure described above, compound **11** was obtained, after column chromatography (hexanes/ethyl acetate, 65/35), as a white solid (56%): mp 73−74 °C; $[\alpha]_D$ −24.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2−2.15 (m, 2H), 2.62−2.67 (dd, 1H, J = 9.4, 13.9 Hz), 2.88−3 (d, 1H, J = 15.7 Hz), 3.22−3.26 (dd, 1H, J = 13.8, 4.2 Hz), 3.74 (s, 3H), 3.79 (s, 3H), 3.88 (s, 3H), 4.57 (dd, 1H, J = 9.1, 1.7 Hz), 6.71−6.78 (m, 3H), 7.25−7.16 (d, 1H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 28.1, 36, 43.2, 52.6, 53.8, 55, 56.6, 111.8, 114.6, 121.2, 129.6, 151.8, 159.7, 139.5, 171.2, 173.6; HRMS (FAB) calcd for $C_{16}H_{20}NO_6$ $[M + H]^+$ 322.12906, found 322.12990. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.74; H, 6.30; N, 4.33.

2*S*,4*R*)-5-Oxo-4-(3-phenylallyl)pyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (28). By using the general procedure described above, compound **28** was obtained, after column chromatography (hexanes/ethyl acetate, 6/4), as a white solid (57%): mp 89−90 °C; $[\alpha]_D$ −25.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.50 (s, 9H), 2.03−2.12 (ddd, 1H, J = 13.3, 11.5, 9.7), 2.18−2.24 (ddd, 1H, J = 13.3, 8.6, 1.7 Hz), 2.35−2.43 (m, 1H), 2.72−2.84 (m, 2H), 3.77 (s, 3H), 4.56 (dd, 1H, J = 9.7, 1.7 Hz), 6.12 (dt, 1H, J = 15.9, 7.3 Hz), 6.45 (d, 1H, J = 15.9 Hz), 7.20−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 27.9, 33.3, 41.5, 52.6, 53.8, 56.7, 125.3, 126, 127.3, 128.4, 133.1, 136.7, 151.8, 171.3, 173.7;

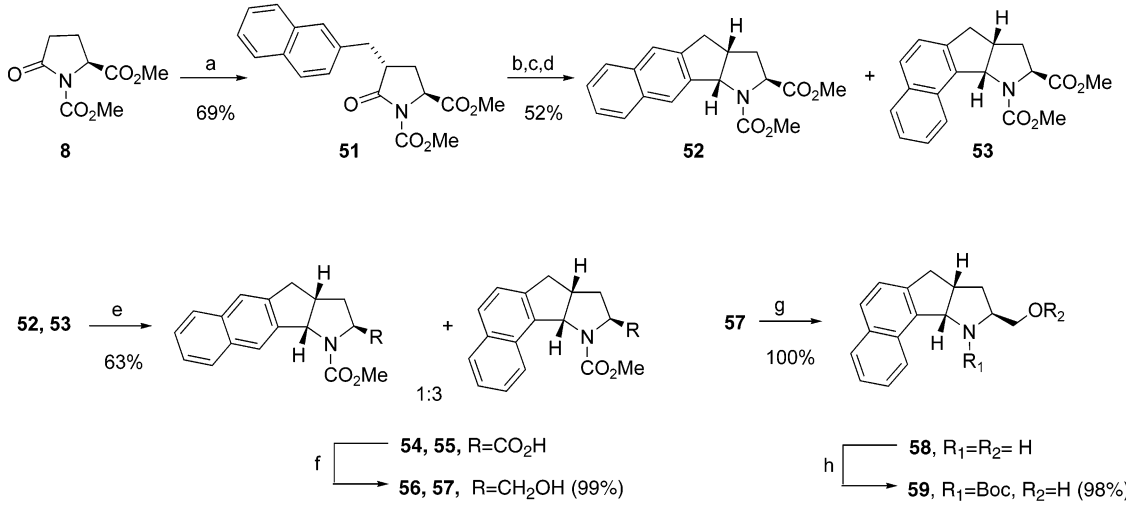
(27) Andrews, M. J. I.; Tabor, A. B. *Tetrahedron* **1999**, *55*, 11711.

SCHEME 5[a]



[a] Reagents and conditions: (a) (i) LiHMDS, THF, −78 °C, (ii) **37**; (b) $LiEt_3BH$, THF, −78 °C; (c) Et_3N, DMAP, Ac_2O, CH_2Cl_2, 0 °C to rt; (d) $AlCl_3$, CH_2Cl_2, 0 °C; (e) LiOH, THF/H_2O, rt; (f) $BH_3{\cdot}Me_2S$, THF, rt; (g) $(Ph_3P)_4Pd$, $Bu_3SnCH{=}CH_2$, toluene, reflux; (h) KOH, MeOH, reflux; (i) $(Boc)_2O$, CH_2Cl_2, rt; (j) TBDPSCl, imidazole,THF, rt; (k) $NaIO_4$, OsO_4(cat.), THF/H_2O, rt; (l) 2-methyl-2-butene, $NaClO_2$, *t*-BuOH/THF, phosphate buffer, 0 °C; (m) K_2CO_3, MeI, acetone, rt; (n) TBAF, THF, rt; (o) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt; (p) KOH, dioxane/H_2O, 100 °C.

SCHEME 6[a]



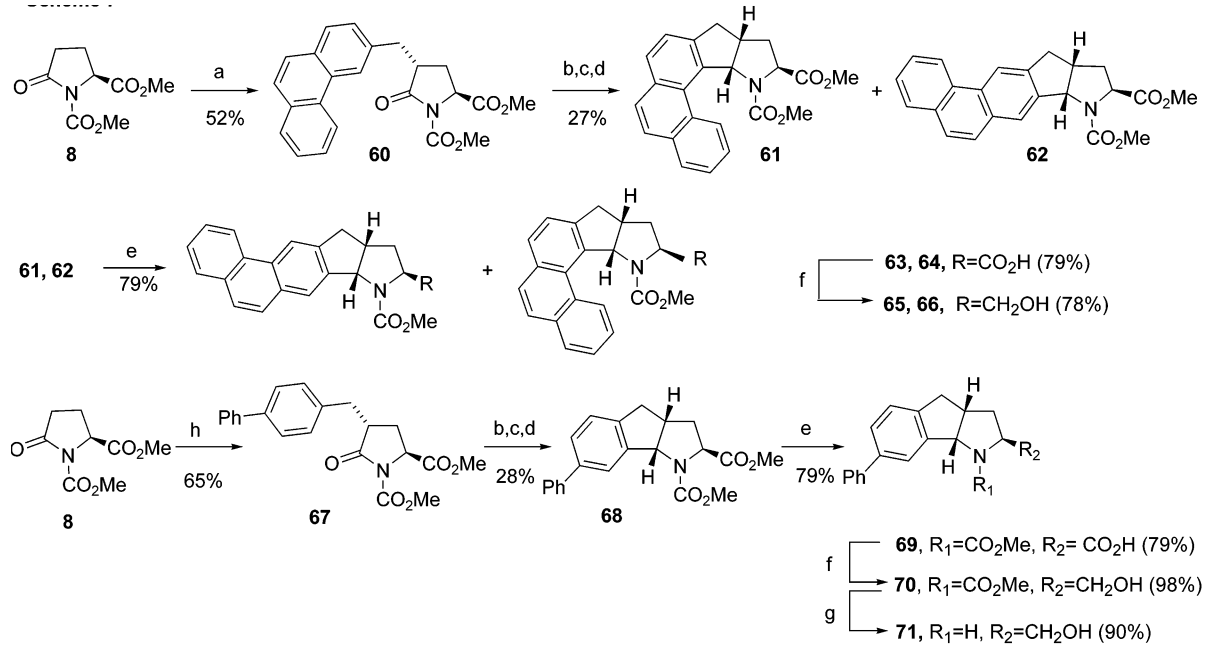
[a] Reagents and conditions: (a) (i) LiHMDS, THF, −78 °C, (ii) 2-bromomethylnaphthalene; (b) $LiEt_3BH$, THF, −78 °C; (c) Et_3N, DMAP, Ac_2O, CH_2Cl_2, 0 °C to rt; (d) $AlCl_3$, CH_2Cl_2, 0 °C; (e) LiOH, THF/H_2O, rt; (f) $BH_3.Me_2S$, THF, rt; (g) KOH, MeOH, reflux; (h) $(Boc)_2O$, CH_2Cl_2, rt.

HRMS (FAB) calcd for $C_{17}H_{20}NO_5$ $[M + H]^+$ 318.13432, found 318.13420. Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 63.93; H, 6.25; N, 4.36.

(2*S*,4*R*)-4-[3-(3-Methoxyphenyl)allyl]-5-oxopyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (29). By using the general procedure described above, compound **29** was obtained, after column chromatography (hexanes/ethyl acetate, 1/1), as a light yellow oil (45%): $[\alpha]_D$ −27.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.1−2.17 (m, 1H), 2.24−2.3 (m, 1H), 2.37−2.45 (m, 1H), 2.72−2.78 (m, 1H), 2.81−2.87 (m, 1H), 3.78 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 4.65 (dd, 1H, J = 9.5, 1.4 Hz), 6.11 (dt, 1H, J = 15.7, 7.3 Hz), 6.43 (d, 1H, J = 15.7 Hz), 6.77−6.8 (m, 1H), 6.86−6.87 (m, 1H), 6.92 (d, 1H, J = 7.6 Hz), 7.2−7.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 27.9, 33.2, 41.4, 52.7, 53.8, 55.1, 56.7, 111.3, 113, 118.7, 125.7, 129.4, 133, 138.2, 151.7, 159.7, 171.3, 173.7; HRMS (FAB) calcd for $C_{18}H_{22}NO_6$ $[M + H]^+$ 348.14489, found 348.14418.

(2*S*,4*R*)-4-(4-Bromo-3-methylbenzyl)-5-oxopyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (38). By using the general procedure described above, compound **38** was obtained,

SCHEME 7[a]



[a] Reagents and conditions: (a) (i) LiHMDS, THF, −78 °C, (ii) 3-bromomethylphenanthrene; (b) $LiEt_3BH$, THF, −78 °C; (c) Et_3N, DMAP, Ac_2O, CH_2Cl_2, 0 °C to rt; (d) $AlCl_3$, CH_2Cl_2, 0 °C; (e) LiOH, THF/H_2O, rt; (f) $BH_3{\cdot}Me_2S$, THF, rt; (g) KOH, MeOH, reflux; (h) (i) LiHMDS, THF, −78 °C, (ii) 4-bromomethylbiphenyl.

after column chromatography (hexanes/ethyl acetate, 65/35), as a white solid (55%): mp 102−103 °C; $[\alpha]_D$ −27.9 (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.02−2.15 (m, 2H), 2.37 (s, 3H), 2.62−2.67 (dd, 1H, J = 14, 9 Hz), 2.89−2.94 (m, 1H), 3.15−3.19 (dd, 1H, J = 14, 4.2 Hz), 3.76 (s, 3H), 3.89 (s, 3H), 4.57−4.60 (d, 1H, J = 9.2 Hz), 6.85−6.87 (d, 1H, J = 8.1 Hz), 7.05 (s, 1H), 7.43−7.45 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.3, 28.6, 35.7, 43.6, 53.2, 54.4, 57, 123.5, 128.4, 131.9, 132.9, 137.6, 138.6, 152.3, 171.7, 173.9; HRMS (TOF EI) calcd for $C_{16}H_{18}BrNO_5$ [M] 383.03683, found 383.03687. Anal. Calcd for $C_{16}H_{18}BrNO_5$: C, 50.02; H, 4.72; N, 3.65. Found: C, 49.85; H, 4.92; N, 3.66.

General Procedure for the Intramolecular Friedel−Crafts-Type Cationic Cyclization. To a stirred solution of the suitable 4-substituted methyl *N*-methoxycarbonyl L-pyroglutamate (5 mmol) in THF (40 mL) was added a 1 M solution of lithium triethylborohydride (Super-Hydride) (6 mL, 1.2 equiv) dropwise at −78 °C. The mixture was stirred at this temperature for 30 min, quenched with saturated aqueous sodium hydrogen carbonate solution (13 mL), and allowed to stand until the temperature reached 0 °C. Then, 35 drops of H_2O_2 (30% w/w) were added, and the mixture was stirred at 0 °C for 30 min. The aqueous layer was extracted with ether (3 × 30 mL), and the combined organic phases were washed with brine (10 mL), dried over sodium sulfate, filtered, and evaporated to dryness.

The crude hemiaminal was dissolved in CH_2Cl_2 (30 mL), the stirred solution was chilled to 0 °C, and triethylamine (2.1 mL, 15 mmol, 3 equiv), 4-(dimethylamino)pyridine (0.12 g, 1 mmol, 0.2 equiv), and acetic anhydride (1.4 mL, 15 mmol, 3 equiv) were subsequently added. After 30 min at 0 °C, the reaction mixture was warmed to room temperature and stirred overnight and then quenched with saturated aqueous sodium hydrogen carbonate solution (30 mL). The mixture was then extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic phases were washed with brine (10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The resulting crude was quickly purified by filtering through a pad of silica gel, washed with ethyl acetate/hexanes (1/1).

After evaporation to dryness, the acetylated hemiaminal was immediately dissolved in CH_2Cl_2 (90 mL), and the resulting solution was stirred and cooled to 0 °C before adding aluminum trichloride (3.33 g, 25 mmol, 5 equiv) in one portion. The resulting mixture was stirred at 0 °C for 1 h and then quenched with saturated aqueous sodium hydrogen carbonate solution (35 mL). The mixture was then extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were washed with brine (20 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The resulting crude was purified by flash column chromatography to afford the desired compound.

(2*S*,3a*S*,8a*R*)-1,3a,8,8a-Tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid Dimethyl Ester (12). By using the general procedure described above, compound **12** was obtained, after column chromatography (hexanes/ethyl acetate, 8/2), as a white solid (55%): mp 65−67 °C; $[\alpha]_D$ −143.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.8−1.97 (m, 1H), 2.14−2.27 (m, 1H), 2.71 (d, 1H, J = 15.7 Hz), 3.03−3.21 (m, 2H), 3.73 (s, 3H), 3.79 (s, 1.5H), 3.81 (s, 1.5H), 4.32 (t, 1H, J = 8.8 Hz), 5.48 (d, 0.5H, J = 7.6 Hz), 5.52 (d, 0.5H, J = 7.6 Hz), 7.13−7.26 (m, 3H), 7.52 (d, 0.5H, J = 5.4 Hz), 7.70 (d, 0.5H, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) (34.3), 34.5, (34.7), 35.7, (39.2), 40.5, (52.3), 52.6, (60.4), 60.5, (66.9), 67.6, 125.4, (125.9), 126.4, (126.8), 127, (127.1), 128, (140.5), 140.7, (142.7), 143.1, (155.8), 156, (172.9), 173; HRMS (FAB) calcd for $C_{15}H_{18}NO_4$ $[M + H]^+$ 276.12360, found 276.12320.

(2*S*,3a*S*,8a*R*)-6-Bromo-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid Dimethyl Ester (13). By using the general procedure described above, compound **13** was obtained, after column chromatography (hexanes/ethyl acetate, 6/4), as light yellow oil (66%): $[\alpha]_D$ −180 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.82−1.94 (m, 1H), 2.14−2.28 (m, 1H), 2.70 (d, 1H, J = 15.8 Hz), 3.02−3.25 (m, 2H), 3.68 (s, 1.5H), 3.73 (s, 1.5 H), 3.74 (s, 1.5H), 3.85 (s, 1.5H), 4.33 (t, 1H, J = 8.6 Hz), 5.37 (d, 0.5H, J = 7.7 Hz), 5.43 (d, 0.5H, J = 7.7 Hz), 7.37−7.30 (m, 2.5H), 7.66 (d, 0.5H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) (34.1), 34.2, (34.5), 34.8, (39.4), 40.7, (51.9), 52.2, (60.1), 60.2, (65.7), 67.1, 122, 127.4, 128.2, 128.4, 128.5, 130.3, (141.8), 142.2, (142.6), 142.8,

(155. 7), 156, (172.8), 172.9; HRMS (FAB) calcd for $C_{15}H_{17}BrNO_4$ $[M + H]^+$ 354.03409, found 354.03310.

(2*S*,3a*S*,8a*R*)-6-Methoxy-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid Dimethyl Ester (14). By using the general procedure for the intramolecular Friedel−Crafts cyclization, compound **14** was obtained, after column chromatography (hexanes/ethyl acetate, 7/3), as a white solid (68%): mp 76−77 °C; $[\alpha]_D$ −194.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.83−1.96 (m, 1H), 2.14−2.25 (m, 1H), 2.69 (d, 1H, J = 19.5 Hz), 2.98−3.18 (m, 2H), 3.74 (s, 1.5H), 3.75 (s, 1.5H), 3.77 (s, 1.5H), 3.78 (s, 1.5H), 3.88 (s, 1.5H), 4.32 (d, 0.5H, J = 8.9 Hz), 4.34 (d, 0.5H, J = 8.9 Hz), 5.39 (d, 0.5H, J = 7.5 Hz), 5.50 (d, 0.5H, J = 7.5 Hz), 6.66−6.77 (m, 2H), 7.40 (d, 0.5H, J = 8.4 Hz), 7.68 (d, 0.5H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) (35), 35.5, 35.8, (36.3), 40.3, (41.53), 52.7, 53.1, (53.2), 55.8, 60.8, (61), (66.8), 67.6, 110.6, (110.7), 113.7, (113.8), (127.2), 128, (135.4), 136, 142.7, (143), (156.3), 156.5, (160.4), 160.4, (173.5), 173.6; HRMS (FAB) calcd for $C_{16}H_{20}NO_5$ $[M + H]^+$ 306.13432, found 306.13452.

(2*S*,3a*S*,9b*R*)-2,3,3a,4,5,9b-Hexahydrobenzo[*g*]indole-1,2-dicarboxylic Acid Dimethyl Ester (25). By using the general procedure described above, compound **25** was obtained, after column chromatography (hexanes/ethyl acetate, 8/2), as a white solid (58%): mp 72−74 °C; $[\alpha]_D$ +47.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.37−1.68 (m, 2H), 2.08−2.19 (m, 1H), 2.3−2.41 (m, 1H), 2.55−2.78 (m, 3H), 3.60 (s, 3H), 3.77 (s, 3H), 4.44 (s, 1H), 4.91 (s, 0.5H), 5.15 (s, 0.5H), 7.05−7.29 (m, 3H), 7.59 (s, 0.5H), 7.69 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) (23.5), 24, (25.5), 26.1, 34.1, (36.4), 36.9, (51.9), 52.7, 58.4, (58.9), 59.6, (126.2), 126.6, (127.2), 127.6, 128.6, 135.8, 156.4, 172.5; HRMS (FAB) calcd for $C_{16}H_{20}NO_4$ $[M + H]^+$ 290.13941, found 290.13925.

(2*S*,3a*R*,10b*S*)-3,3a,4,5,6,10b-Hexahydro-2*H*-1-azabenzo[*e*]azulene-1,2-dicarboxylic Acid Dimethyl Ester (32). By using the general procedure described above, compound **32** was obtained, after column chromatography (hexanes/ethyl acetate, 8/2), as colorless oil (25%): $[\alpha]_D$ −111.0 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 0.48−0.62 (m, 1H), 1.46−1.57 (m, 1H), 1.54−1.8 (m, 3H), 1.91−1.99 (m, 1H), 2.42−2.63 (m, 1H), 2.64−2.75 (m, 1H), 2.88−3.01 (m, 1H), 3.58 (d, 1.5H, J = 43.4 Hz), 3.62 (d, 1.5H, J = 43.4 Hz), 3.76 (d, 1.5H, J = 6.1 Hz), 3.78 (d, 1.5H, J = 6.1 Hz), 5.30 (d, 0.5H, J = 8.9 Hz), 5.36 (d, 0.5H, J = 8.9 Hz), 7.03−7.1 (m, 1H), 7.12−7.2 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) (22.2), 22.3, (26.2), 29.9, (34.8), 35.3, (38.1), 39.1, 52, (52.3), 52.6, (59.2), 59.3, (60.3), 60.7, (124), 124.1, 126.2, 126.6, 127.8, 135.8, (136.1), 136.2, (155), 155.2, (173), 173.1; HRMS (FAB) calcd for $C_{17}H_{22}O_4N$ $[M + H]^+$ 304.15506, found 304.15522.

(2*S*,3a*R*,10b*S*)-8-Methoxy-3,3a,4,5,6,10b-hexahydro-2*H*-1-azabenzo[*e*]azulene-1,2-dicarboxylic Acid Dimethyl Ester (33). By using the general procedure described above, compound **33** was obtained, after column chromatography (hexanes/ethyl acetate, 75/25), as a white solid (70%): mp 87−89 °C; $[\alpha]_D$ −122.7 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 0.53−0.6 (m, 1H), 1.48−1.52 (m, 1H), 1.58−1.74 (m, 3H), 1.9−2.04 (m, 1H), 2.39−2.6 (m, 1H), 2.6−2.71 (m, 1H), 2.85−2.97 (m, 1H), 3.63 (s, 1.5H), 3.75 (s, 1.5H), 3.76 (s, 1.5H), 3.77 (s, 1.5H), 3.78 (s, 1.5H), 3.80 (s, 1.5H), 4.52 (d, 0.5H, J = 8.8 Hz), 4.58 (d, 0.5H, J = 8.8 Hz), 5.22 (d, 0.5H, J = 8.8 Hz), 5.27 (d, 0.5H, J = 8.8 Hz), 6.66−6.74 (m, 2H), 6.88, (d, 1H, J = 8.3 MHz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) (22.3), 22.4, (27.1), 30, (34.7), 35.2, (37.8), 38.8, (52.1), 52.3, (55), 59.6, (60.1), 60.8, (110.1), 110.2, (115), 115.1, (124.5), 124.7, (128), 129.1, (137.6), 137.7, (155.2), 155.8, 159, 174; HRMS (FAB) calcd for $C_{18}H_{24}O_5N$ $[M + H]^+$ 334.16544, found 334.16680.

(2*S*,3a*S*,8a*R*)-5-Bromo-6-methyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid Dimethyl Ester (39). By using the general procedure described above, compound **39** was obtained, after column chromatography (hexanes/ethyl acetate, 75/25), as a white foamy solid (85%): $[\alpha]_D$ −179 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1.2/1 of rotamers δ (ppm) 1.85−1.91 (m, 1H), 2.15−2.25 (m, 1H), 2.36 (s, 1.6H, major), 2.37 (s, 1.4H, minor), 2.6−2.64 (d, 1H, J = 16.2 Hz), 2.95−3.07 (m, 1H), 3.07−3.20 (m, 1H), 3.73 (s, 1.6H, major), 3.75 (s, 1.6H, major), 3.76 (s, 1.4H, minor), 3.89 (s, 1.4H, minor), 4.3−4.32 (d, 0.55H, J = 8.7 Hz, major), 4.34−4.36 (d, 0.45H, J = 8.7 Hz, minor), 5.39−5.41 (d, 0.45H, J = 7.5 Hz, minor), 5.49−5.51 (d, 0.55H, J = 7.5 Hz, major), 7.06 (s, 0.55H, major), 7.07 (s, 0.45H, minor), 7.64 (s, 0.45H, minor), 7.94 (s, 0.55H, major); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 23.3, (23.4), 34.8, (34.9), 35, (36.2), 40.2, (41.5), 52.7, (52.8), 53.2, (53.3), 60.8, (61), 67, (67.7), 123.7, (123.8), 127.8, (128), 130.2, (130.8), 137.9, (138), 140.4, (140.7), 142.8, (143.3), 156, (156.4), 173.3, (173.4); HRMS (TOF EI) calcd for $C_{16}H_{18}BrNO_4$ [M] 367.04191, found 367.04236.

General Procedure for Deprotection of Methyl Ester from Tricyclic Analogues. To a stirred solution of the corresponding methyl ester (5 mmol) in THF (45 mL) at room temperature was added 0.2 N aqueous lithium hydroxide (45 mL, 1.8 equiv), and the resulting light-yellow solution was stirred at room temperature for 8 h. The reaction mixture was then neutralized with 3 N aqueous HCl (3 mL), the THF was removed by evaporation, and the remaining aqueous suspension was acidified with 3 N aqueous HCl (1.5 mL) and then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness. The resulting crude white foamy solid was used in the next step without any further purification.

(2*S*,3a*S*,8a*R*)-6-Methoxy-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid 3-Methyl Ester (15). By using the general procedure described above, compound **15** was obtained from methyl ester **14** as a white foamy solid (88%): mp 48−50 °C; $[\alpha]_D$ −160.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.88−1.98 (m, 1H), 2.27−2.33 (m, 1H), 2.67 (dd, 1H, J = 16.3, 3.4 Hz), 3.01−3.22 (m, 2H), 3.74 (s, 1.5H), 3.77 (s, 1.5H), 3.78 (s, 1.5H), 3.88 (s, 1.5H), 4.33 (d, 0.5H, J = 8.7 Hz), 4.38 (d, 0.5H, J = 8.7 Hz), 5.36 (d, 0.5H, J = 7.5 Hz), 5.48 (d, 0.5H, J = 7.5 Hz), 6.7−6.78 (2H, m), 7.39 (d, 0.5H, J = 8.4 Hz), 7.68 (d, 0.5H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) (34.7), 34.9, (35.2), 35.7, (39.5), 41, (52.8), 52.9, 55.2, (60.4), 60.5, (66), 67, (110.1), 110.2, (113.3), 113.4, (126), 127.5, (134.8), 135.3, (142.3), 142.5, 156.2, 160, (177.1), 177.4; HRMS (FAB) calcd for $C_{15}H_{18}NO_5$ $[M + H]^+$ 292.11867, found 292.11898.

(2*S*,3a*S*,8a*R*)-1,3a,8,8a-Tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid 3-Methyl Ester (16). By using the general procedure described above, compound **16** was obtained from methyl ester **12** as a white solid (86%): mp 177−179 °C dec; $[\alpha]_D$ −131.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1.5 of rotamers: δ (ppm) 1.81−1.90 (m, 0.6H), 1.94−1.99 (m, 0.4H), 2.31−2.42 (m, 1H), 2.73−2.78 (dd, 1H, J = 16.1, 5.5 Hz), 3.06−3.24 (m, 2H), 3.77 (s, 1.2H), 3.93 (s, 1.8H), 4.36 (d, 0.4H, J = 8.9 Hz), 4.41 (d, 0.6H, J = 8.9 Hz), 5.43 (d, 0.6H, J = 6.9 Hz), 5.57 (d, 0.4H, J = 7.4 Hz), 7.21−7.31 (m, 3H), 7.53 (d, 0.6H, J = 7.6 Hz), 7.79 (d, 0.4H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) (34.5), 35.1, 35.5, (36.1), (39.7), 41.3, (53.2), 53.5, 60.6, (61.0), 67.6, (68.2), (125.7), 126.1, 126.4, (127.3), 127.6, (127.7), (128.6), 128.7, (140.8), 141.3, 142.8, (143.6), (156.5), 157.0, 176.5, (177.9); HRMS (FAB) calcd for $C_{14}H_{16}NO_4$ $[M + H]^+$ 262.10794, found 262.10930.

(2*S*,3a*S*,9b*R*)-2,3,3a,4,5,9b-Hexahydrobenzo[*g*]indole-1,2-dicarboxylic Acid 1-Methyl Ester (27). By using the general procedure described above, compound **27** was obtained from methyl ester **25** as an oil (87%): $[\alpha]_D$ +41.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.42−1.78 (m, 2H), 2.09−2.21 (m, 1H),

2.33−2.41 (m, 1H), 2.55−2.78 (m, 3H), 3.77 (s, 3H), 4.38−4.52 (m, 1H), 4.94 (s, 0.5H), 5.10 (s, 0.5H), 7.27−7.05 (m, 3H), 7.50 (s, 0.5H), 7.65 (s, 0.5H), 10.51 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) (24.2), 24.4, (25.3), 26, 34.3, (36.1), 36.5, (51.9), 52.1, (58.3), 58.6, (127.1), 127.8, (128.2), 128.8, 130, 136, 157, 171.5; HRMS (FAB) calcd for $C_{15}H_{18}NO_4$ $[M + H]^+$ 276.12376, found 276.12398.

(2*S*,3a*R*,10b*S*)-8-Methoxy-3,3a,4,5,6,10b-hexahydro-2*H*-1-azabenzo[*e*]azulene-1,2-dicarboxylic Acid 1-Methyl Ester (34). By using the general procedure described above, compound **34** was obtained from methyl ester **33** as a white solid (85%): mp 178−181 °C; $[\alpha]_D$ −119.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1.5/1 of rotamers δ (ppm) 0.55−0.62 (m, 1H), 1.52−1.59 (m, 1H), 1.6−1.78 (m, 3H), 2.04−2.11 (m, 1H), 2.51−2.7 (m, 2H), 2.87−2.95 (m, 1H), 3.64 (s, 2H, major), 3.74 (s, 1H, minor), 3.78 (s, 1H, minor), 3.80 (s, 2H, major), 4.53 (d, 0.4H, J = 9.2 Hz, minor), 4.62 (d, 0.6H, J = 9.2 Hz, major), 5.26 (d, 0.6H, J = 8.9 Hz, major), 5.31 (d, 0.4H, J = 8.9 Hz, minor), 6.67−6.75 (m, 2H), 6.87−6.9 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) (19.7), 19.8, (24.5), 27.6, (31.5), 33.2, (35.1), 36.1, (50.4), 50.5, 52.6, (56.5), 56.7, (58.5), 58.7, 108, (112.7), 112.8, (121.9), 122, (125.5), 126.1, (135.5), 135.6, (152.5), 154, 156.3, (175), 176; HRMS (FAB) calcd for $C_{17}H_{22}O_5N$ $[M + H]^+$ 320.14997, found 320.14937.

(2*S*,3a*S*,8a*R*)-5-Bromo-6-methyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid 3-Methyl Ester (40). By using the general procedure described above, compound **40** was obtained from methyl ester **39** as a white solid (98%): mp 82−84 °C; $[\alpha]_D$ −170 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.83−1.98 (m, 1H), 2.32−2.37 (m, 1H), 2.36 (s, 1.5H), 2.37 (s, 1.5H), 2.62−2.67 (dd, 1H, J = 16.5, 5 Hz), 2.96−3.04 (m, 1H), 3.11−3.2 (m, 1H), 3.77 (s, 1.5H), 3.92 (s, 1.5H), 4.33−4.35 (d, 0.5H, J = 8.8 Hz), 4.38−4.4 (d, 0.5H, J = 8.8 Hz), 5.37−5.39 (d, 0.5H, J = 7.5 Hz), 5.49−5.51 (d, 0.5H, J = 7.5 Hz), 7.07 (s, 0.5H), 7.09 (s, 0.5H), 7.64 (s, 0.5H), 7.93 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 23.4, (23.5), 34.7, (34.8), 35, (36.1), 40.1, (41.6), 53.4, (53.6), 60.9, (61), 67, (67.7), 123.7, (123.9), 127.8, (128.1), 130.2, (130.9), 138, (138.2), 140.3, (140.7), 142.4, (143.1), 156.4, (156.6), 177.5, (178.4); HRMS (TOF EI) calcd for $C_{15}H_{16}BrNO_4$ [M] 353.02626, found 353.02573. Anal. Calcd for $C_{15}H_{16}BrNO_4 \cdot H_2O$: C, 48.40; H, 4.87; N, 3.76. Found: C, 49.66; H, 4.75; N, 3.70.

(2*S*,3a*S*,8a*R*)-6-Methoxy-1,2,3,3a,8,8a-hexahydro-3-azacyclopenta[*a*]indene-2-carboxylic Acid Hydrochloride Salt (17). To a solution of **15** (25 mg, 0.086 mmol) in MeOH (5 mL) was added KOH (964 mg, 17.2 mmol). The mixture was refluxed at 90 °C under argon for 24 h, and then the contents were cooled and acidified to pH 7 with aqueous 12 N HCl. The solvent was then removed by evaporation and the residue purified by Dowex 50WX8-100 ion-exchange resin to yield the free amino acid as a white solid: yield 71%; mp 187−189 °C. The product was then dissolved in water (1.5 mL), and under stirring, the pH was adjusted to pH 2 with aqueous 1 N HCl; the solution was then evaporated to dryness to afford compound **17** as a white solid. The amino acid hydrochloride salt obtained by this route showed identical spectroscopic properties compared to the compound prepared starting from the Boc-protected acid **21** (vide infra).

(2*S*,3a*S*,8a*R*)-2-Hydroxymethyl-6-methoxy-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-3-carboxylic Acid Methyl Ester (18). To a stirred solution of **15** (2 g, 6.87 mmol) in 35 mL of THF at room temperature was added dropwise a 2 M solution of borane−methyl sulfide complex in THF (27.5 mL, 8 equiv), and the mixture was then stirred at room temperature for 5 h. The reaction mixture was then quenched by adding 35 mL of methanol dropwise (**CAUTION:** hydrogen evolution), and stirring was continued for an additional 1 h. The solvent was removed by rotary evaporator to yield a residue that was dissolved in CH_2Cl_2 (80 mL), washed with water (20 mL) and then brine (20 mL), dried over sodium sulfate, filtered, and evaporated to dryness to afford a crude oil that was purified by flash chromatography (ethyl acetate/hexanes, 1/1) to give the title compound (1.71 g, 90%) as a white solid: mp 130−131 °C; $[\alpha]_D$ −142 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 3/1 of rotamers δ (ppm) 1.72−1.79 (m, 1H), 1.86−1.92 (m, 0.75H, major), 2.16−2.21 (m, 0.25H, minor), 2.67−2.71 (d, 1H, J = 14.7 Hz), 3.02−3.15 (m, 2H), 3.68−3.74 (m, 1H), 3.77 (s, 0.75H, minor), 3.78 (s, 0.75H, minor), 3.79 (s, 2.25H, major), 3.86 (s, 2.25H, major), 3.97−4.04 (m, 1H), 4.1−4.13 (dd, 1H, J = 7.7, 2.9 Hz), 5.26−5.28 (d, 0.75H, J = 7 Hz, major), 5.36−5.38 (d, 0.25H, J = 7 Hz, minor), 6.73−6.76 (m, 2H), 7.38−7.40 (d, 0.75H, J = 8.35 Hz, major), 7.75−7.77 (d, 0.25H, J = 8.35 Hz, minor); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 34.6, (34.8), (36), 36.3, (40.1), 41.4, (52.9), 53, 55.8, (60.2), 61.6, (64.5), 67.3, 67.4, 110.6, (113.5), 113.6, 127.3, (128.4), 135.2, (136.4), (143.3), 144, (156.4), 157.6, (160.3), 160.4; HRMS (TOF EI) calcd for $C_{15}H_{19}NO_4$ [M] 277.13140, found 277.13085. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.31; H, 7.12; N, 4.86.

(2*S*,3a*S*,8a*R*)-(6-Methoxy-1,2,3,3a,8,8a-hexahydro-3-azacyclopenta[*a*]inden-2-yl)methanol (19). A mixture of **18** (400 mg, 1.44 mmol) and potassium hydroxide (5 g, 62 equiv) in methanol (40 mL) was stirred and refluxed for 3 h, cooled to 0 °C, and neutralized with 6 N aqueous HCl. Most of the methanol was then evaporated, and the pH was adjusted to 8−9 with saturated aqueous sodium hydrogen carbonate solution. The aqueous phase was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over sodium sulfate, filtered, and evaporated to dryness to give a light yellow solid (310 mg, 98%): mp 89−90 °C; $[\alpha]_D$ +20.8 (*c* 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.55−1.60 (m, 1H), 1.84−1.91 (m, 1H), 2.67−2.72 (dd, 1H, J = 16.48, 3 Hz), 2.96 (broad s, 2H), 3.06−3.13 (m, 1H), 3.14−3.22 (m, 2H), 3.41−3.45 (dd, 1H, J = 10.9, 6.43 Hz), 3.58−3.62 (dd, 1H, J = 10.9, 3.95 Hz), 3.78 (s, 3H), 4.70−4.72 (d, 1H, J = 7 Hz), 6.70 (s, 1H), 6.75−6.78 (dd, 1H, J = 8.3, 2.4 Hz), 7.17−7.19 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 37, 39.6, 42.5, 55.8, 59.4, 64.2, 67.9, 109.9, 113.7, 125.6, 137.4, 145.3, 160.2; HRMS (TOF EI) calcd for $C_{13}H_{17}NO_2$ [M] 219.12592, found 219.12550. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 69.71; H, 7.88; N, 6.14.

(2*S*,3a*S*,8a*R*)-2-Hydroxymethyl-6-methoxy-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-3-carboxylic Acid *tert*-Butyl Ester (20). To a stirred solution of **19** (310 mg, 1.42 mmol) in CH_2Cl_2 (20 mL), at room temperature, was added di-*tert*-butyl dicarbonate (930 mg, 3 equiv) in one portion, the mixture was stirred for 4 h, the solvent was removed in vacuo, and the resulting crude yellow oil was purified by flash chromatography (hexanes/ethyl acetate, 6/4) to afford a white foamy solid (440 mg, 97%): $[\alpha]_D$ −231 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) for a mixture approximately 2.6/1 of rotamers δ (ppm) 1.51 (s, 2.5H, minor), 1.58 (s, 6.5H, major), 1.64−1.75 (m, 1H), 1.81−1.88 (m, 0.72H, major), 2.10−2.16 (m, 0.28H, minor), 2.63−2.78 (d, 1H, J = 14.7 Hz), 2.98−3.09 (m, 2H), 3.63−3.73 (m, 1H), 3.75−3.82 (m, 1H), 3.78 (s, 0.84H, minor), 3.79 (s, 2.16H, major), 3.95−4 (m, 1H), 4.52 (broad s, 1H), 5.24−5.26 (d, 0.72H, J = 6.8 Hz, major), 5.32−5.34 (d, 0.28H, J = 7 Hz, minor), 6.73−6.78 (m, 2H), 7.53−7.56 (d, 0.72H, J = 8.3 Hz, major), 7.34−7.76 (d, 0.28H, J = 8.3 Hz, minor); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) (28.9), 29, 34.7, (34.8), 36, (40), 41.2, 55.8, (60.2), 61.3, (65), (66.74), 67.3, 68.2, (80.4), 81.3, (110.6), 110.8, (113.4), 113.5, 127.2, (128.4), 135.8, (137), (143.2), 143.7, (155.2), 156.9, (160.2), 160.28; HRMS (TOF EI) calcd for $C_{18}H_{25}NO_4$ [M] 319.17835, found 319.17897.

(2*S*,3a*S*,8a*R*)-6-Methoxy-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid *tert*-Butyl Ester (21). To a stirred solution of the alcohol **20** (64 mg, 0.2 mmol) in acetonitrile (1 mL) was added a sodium phosphate buffer (0.74 mL of a 0.67 M aqueous solution of $NaH_2PO_4 \cdot H_2O$ buffered at pH 6.8 with 2 N aqueous sodium hydroxide), the

mixture was vigorously stirred at room temperature for 5 min, and then TEMPO (2.2 mg, 0.07 equiv), a solution of sodium chlorite in water (36 mg dissolved in 0.37 mL of water, 2 equiv), and a commercial bleach solution, previously diluted with water (0.091 mL of a 5.25% solution diluted in 0.66 mL of water, 0.32 equiv), were subsequently added. The resulting red-brown solution was stirred and heated at 35 °C for 15 h, cooled to room temperature, and diluted with water (1.6 mL), and the pH was adjusted to pH 8 by adding few drops of 2 N aqueous sodium hydroxide. The solution was then cooled to 0 °C, quenched with aqueous sodium sulfite solution (53 mg dissolved in 1 mL of water), stirred for 30 min at 0 °C, and then extracted with ether (2 × 10 mL). The organic phases were discarded, while the aqueous one was acidified (pH 3−4) with 1 N HCl and then extracted with ether (2 × 10 mL) and then with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered, and evaporated to dryness. The resulting white foamy solid (65 mg, 97%) was used in the next step without any further purification: $[\alpha]_D$ −215 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.47 (s, 4.5H), 1.61 (s, 4.5H), 1.74−1.85 (m, 0.5H), 1.91−2.02 (m, 0.5H), 2.26−2.33 (dd, 0.5H, *J* = 13, 7.4 Hz), 2.38−2.44 (dd, 0.5H, *J* = 13, 7.4 Hz), 2.65−2.72 (dd, 1H, *J* = 15.7, 4.2 Hz), 3−3.23 (m, 2H), 3.79 (s, 1.5H), 3.80 (s, 1.5H), 4.27−4.30 (d, 0.5H, *J* = 8.6 Hz), 4.34−4.37 (d, 0.5H, *J* = 8.6 Hz), 5.30−5.33 (d, 0.5H, *J* = 7.4 Hz), 5.47−5.49 (d, 0.5H, *J* = 7.4 Hz), 6.71−6.81 (m, 2H), 7.52−7.55 (d, 0.5H, *J* = 8.4 Hz), 7.65−7.68 (d, 0.5H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.7, (29), 34.5, (35.3), 35.9, (36), 40.2, (41.6), 55.8, (55.9), 60.8, (60.9), 67, (67.1), 80.8, (81.8), 110.5, (110.7), 113.7, (113.8), 127.1, (128), 135.7, (136.3), 142.6, (143), 155.1, (156), 160.3, (160.4), 177.6, (179.5); HRMS (TOF EI) calcd for $C_{18}H_{23}NO_5$ [M] 333.15762, found 333.15678.

(2*S*,3a*S*,8a*R*)-6-Methoxy-1,2,3,3a,8,8a-hexahydro-3-aza-cyclopenta[*a*]indene-2-carboxylic Acid Hydrochloride Salt (17). To a solution of the acid **21** (26 mg, 0.078 mmol) in CH_2Cl_2 (1.5 mL) at room temperature was added trifluoroacetic acid (0.06 mL, 10 equiv), and the resulting mixture was stirred overnight at room temperature. The solvent and the excess of acid were then removed in vacuo, and the resulting crude TFA salt of **17** was taken with ether, filtered, and dried. The product was then suspended in water (2 mL), and under stirring, the pH was adjusted to pH 2 with aqueous 1 N HCl; the resulting solution was then evaporated to dryness to afford a white solid (16 mg, 75%): mp 211−212 °C dec; $[\alpha]_D$ −14.1 (*c* 0.7, MeOH); ^{1}H NMR (D_2O, 400 MHz) δ (ppm) 2.18−2.3 (m, 1H), 2.41−2.56 (m, 1H), 2.87−2.92 (d, 1H, *J* = 17 Hz), 3.22−3.46 (m, 2H), 3.80 (s, 3H), 4.22−4.26 (t, 1H, *J* = 7.5 Hz), 5.33−5.34 (d, 1H, *J* = 7.4 Hz), 6.87−7 (m, 2H), 7.38−7.4 (d, 1H, *J* = 8.9 Hz); ^{13}C NMR (D_2O, 75 MHz) δ (ppm) 35.7, 37.9, 40.85, 55.8, 60.2, 68.1, 110.2, 114.6, 127, 128.3, 146.8, 161.1, 172.1; HRMS (TOF EI) calcd for $C_{13}H_{15}NO_3$ [M] 233.10519, found 233.10466.

(2*S*,3a*S*,8a*R*)-6-Phenyl-1,3a,8,8a-tetrahydro-2*H*-3-aza-cyclopenta[*a*]indene-2,3-dicarboxylic Acid Dimethyl Ester (22). To a solution of **13** (109 mg, 0.31 mmol) in *n*-PrOH (5.0 mL) and water (0.5 mL) were added $Pd(OAc)_2$ (0.3 mg, 5 mol %), triphenylphosphine (0.8 mg, 10 mol %), Na_2CO_3 (39 mg, 0.37 mmol), and phenylboronic acid (41 mg, 0.33 mmol). The mixture was stirred at 60 °C for 4 h and then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3 × 5 mL), and the organics were combined and washed with brine (1 × 5 mL). The organic phase was then dried with Na_2SO_4 and concentrated by rotary evaporator to yield a residue that was purified by column chromatography (hexanes/ethyl acetate, 3/7) to yield the title compound (**22**) (82 mg, 77% yield) as pale yellow oil: $[\alpha]_D$ −213.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.89−2.06 (m, 1H), 2.21−2.31 (m, 1H), 2.78 (d, 1H, *J* = 19.8 Hz), 3.1−3.28 (m, 2H), 3.75 (1.5H), 3.76 (s, 1.5H), 3.79 (s, 2H), 3.9 (s, 1H), 4.37 (d, 0.5H, *J* = 8.3 Hz), 4.4 (d, 0.5H, *J* = 8.3 Hz), 5.52 (d, 0.5H, *J* = 7.6 Hz), 5.62 (d, 0.5H, *J* = 7.6 Hz), 7.26−7.36 (m, 2H), 7.38−7.48 (m, 3.5H), 7.55−7.61 (m, 2H), 7.88 (d, 0.5H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 34.8, 35.3, 40.4, 52.3, 52.5, 60.2, 67.5, 124.6, 125.8, 125.9, 126.6, 128.1, 128.2, 135.1, 140.6, 141.2, 142.4, 155.5, 173.4; HRMS (FAB) calcd for $C_{21}H_{22}NO_4$ $[M + H]^+$ 352.15706, found 352.15734.

5-Oxo-4-phenethylidenepyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (23). LiHMDS (1.0 M, 17.8 mmol) in THF was stirred in dry THF (25 mL) at −78 °C under argon. A solution of **8** (2.98 g, 14.8 mmol) in dry THF (20 mL) was stirred at −78 °C under argon and transferred via cannula to the solution of LiHMDS in THF. The resulting mixture was stirred for 2 h before phenylacetaldehyde (2.08 mL, 17.8 mmol) was added via syringe. After 1 h, the contents were quenched with saturated aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (3 × 75 mL). The organic extracts were combined, dried with sodium sulfate, and filtered. The solvent was removed by rotary evaporator to yield a residue that was dissolved in CH_2Cl_2 (40 mL) and stirred under argon as methanesulfonyl chloride (2.29 mL, 29.6 mmol) and TEA (4.13 mL, 29.6 mmol) were added. The contents were stirred for 16 h, then quenched with saturated aqueous $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The solids were filtered off, and the solvent was removed by rotary evaporator to yield a residue which was purified by column chromatography (hexanes/ethyl acetate, 2/8) to give the title compound (**23**): yellow oil (1.93 g, 43% yield); $[\alpha]_D$ −23.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.62−2.71 (m, 1H), 2.95−3.06 (m, 1H), 3.44−3.54 (m, 2H), 3.77 (s, 3H), 3.83 (s, 3H), 4.64 (dd, 1H, *J* = 10.3, 3.5 Hz), 6.88−6.93 (m, 1H), 7.14−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 25.5, 35.2, 52.1, 52.5, 55.6, 126.3, 126.6, 128.2, 128.6, 129.2, 136.1, 150, 165.3, 170.1; HRMS (FAB) calcd for $C_{16}H_{18}NO_5$ $[M + H]^+$ 304.12067, found 304.12011.

(2*S*,4*S*)-5-Oxo-4-phenethylpyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (24). To a solution of **23** (1.35 g, 4.45 mmol) in MeOH (15 mL) was added a catalytic quantity of 10% palladium-on-carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a period of 14 h. The mixture was filtered over Celite and the Celite rinsed with MeOH (3 × 10 mL). The solvent was removed by rotary evaporator to yield the title compound (**24**) (1.33 g, 98% yield), as a pale yellow oil: $[\alpha]_D$ +14.6 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.22−1.45 (m, 1H), 1.61−1.71 (m, 1H), 1.88−2.01 (m, 2H), 2.23 (dd, 1H, *J* = 13.2, 1.3 Hz), 2.56−2.66 (m, 2H), 3.76 (s, 3H), 3.84 (s, 3H), 4.58 (dd, 1H, *J* = 9.6, 1.3 Hz), 7.21−7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 27.8, 32.5, 32.8, 41.5, 52.6, 53.8, 57, 126.1, 128.3, 128.4, 140.5, 151.9, 171.5, 174.3; HRMS (FAB) calcd for $C_{16}H_{20}NO_5$ $[M + H]^+$ 306.13232, found 306.13297.

(2*S*,4*R*)-5-Oxo-4-(3-phenylpropyl)pyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (30). To a solution of **28** (1.17 g, 3.64 mmol) in MeOH (12 mL) was added a catalytic quantity of 10% palladium-on-carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a period of 14 h. The mixture was filtered over Celite and the Celite rinsed with MeOH (3 × 10 mL). The solvent was removed by rotary evaporator to yield the title compound (**30**) (1.10 g, 95% yield) as a white solid: mp 59−64 °C; $[\alpha]_D$ −23.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.35−1.45 (m, 1H), 1.61−1.71 (m, 2H), 1.89−2.02 (m, 3H), 2.23 (ddd, 1H, *J* = 13.2, 8.6, 1.3 Hz), 2.56−2.67 (m, 3H), 3.76 (s, 3H), 3.83 (s, 3H), 4.6 (dd, 1H, *J* = 9.6, 1.3 Hz), 7.13−7.17 (m, 3H), 7.23−7.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 14, 20.9, 28.5, 28.6, 29.8, 35.6, 41.3, 52.6, 53.7, 56.7, 60.2, 125.7, 128.1, 128.2, 141.6, 151.8, 171.3, 174.3; HRMS (FAB) calcd for $C_{17}H_{22}NO_5$ $[M + H]^+$ 320.14981, found 320.15050.

(2*S*,4*R*)-4-[3-(3-Methoxyphenyl)propyl]-5-oxopyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (31). To a solution of **29** (1.18 g, 3.64 mmol) in MeOH (12 mL) was added a catalytic amount of 10% palladium-on-carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a period of 14 h. The mixture was filtered over

Celite and the Celite rinsed with MeOH (3 × 10 mL). The solvent was then removed by rotary evaporator to yield the title compound (**31**) (1.11 g, 95% yield): colorless oil; $[\alpha]_D$ −20.3 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.32−1.39 (m, 1H), 1.56−1.65 (m, 2H), 1.82−1.95 (m, 2H), 2.17 (dd, 1H, J = 13, 8.9 Hz), 2.5−2.61 (m, 3H), 3.7 (s, 3H), 3.71 (s, 3H), 3.78 (s, 3H), 4.55 (d, 1H, J = 9.4 Hz), 6.64−6.7 (m, 3H), 7.1−7.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 28.3, 28.5, 29.8, 35.6, 41.3, 52.6, 53.6, 54.9, 56.7, 111, 113.9, 120.6, 129.2, 143.3, 151.7, 159.5, 171.3, 174.4; HRMS (FAB) calcd for $C_{18}H_{24}NO_6$ $[M + H]^+$ 350.15854, found 350.15850.

(2*S*,3a*R*,10b*S*)-8-Methoxy-1,2,3,3a,4,5,6,10b-octahydro-1-azabenzo[*e*]azulene-2-carboxylic Acid (35). To a solution of **34** (25 mg, 0.078 mmol) in MeOH (5 mL) was added KOH (893 mg, 15.6 mmol). The mixture was refluxed at 90 °C under argon for 24 h, and then the contents were cooled and acidified to pH 7 with aqueous 12 N HCl. The solvent was then removed by rotary evaporator and the residue purified by ion-exchange chromatography to yield the title compound (66%): $[\alpha]_D$ −15.5 (*c* 1.1, $CHCl_3$); ^1H NMR (CD_3OD, 400 MHz) δ (ppm) 0.97−1.02 (m, 1H), 1.46−1.49 (m, 1H), 1.61−1.75 (m, 3H), 2.15−2.23 (m, 1H), 2.65−2.75 (m, 2H), 2.77−2.85 (m, 1H), 3.68 (s, 3H), 4.27 (d, 1H, J = 7.1 Hz), 5.15 (d, 1H, J = 7.6 Hz), 6.58−6.63 (m, 2H), 6.88−6.95 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ (ppm) 18.3, 23.8, 27.2, 32.2, 34.1, 48.5, 49.7, 106.1, 112.4, 121, 127.1, 131.5, 151, 152.1; HRMS (FAB) calcd for $C_{15}H_{20}O_3N$ $[M + H]^+$ 262.14449, found 262.14403.

(4-Bromo-3-methylphenyl)methanol (36). To a stirred suspension of 4-bromo-3-methylbenzoic acid (4.5 g, 20.92 mmol) in ether (110 mL), at room temperature, was added portionwise lithium aluminum hydride (1.59 g, 2 equiv) during 90 min. The reaction mixture was stirred at room temperature for an additional 2 h, cooled to 0 °C, and quenched with saturated aqueous ammonium chloride (16 mL), added dropwise (**CAUTION:** hydrogen evolution). Stirring was continued for 20 min, and then the mixture was filtered through a pad of Celite that was subsequently washed with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered, and evaporated to dryness. The crude red oil was then purified by flash chromatography (hexanes/ethyl acetate, 8/2) to afford the alcohol as a white solid (4 g, 96%): mp 31−32 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.58−1.68 (broad s, 1H), 2.4 (s, 3H), 4.62 (s, 2H), 7.02−7.06 (dd, 1H, J = 8, 1.85 Hz), 7.23 (d, 1H, J = 1.85 Hz), 7.49−7.52 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.3, 65.1, 124.3, 126.3, 129.8, 132.9, 138.5, 140.5; HRMS (TOF EI) calcd for C_8H_9BrO [M] 199.98367, found 199.98400. Anal. Calcd for C_8H_9BrO: C, 47.79; H, 4.51. Found: C, 47.95; H, 4.79.

1-Bromo-4-bromomethyl-2-methylbenzene (37). To a stirred solution of alcohol **36** (8 g, 39.8 mmol) in ether (220 mL) was added dropwise a solution of phosphorus tribromide (2.65 mL, 0.7 equiv) in ether (15 mL) during 30 min. Once the addition was completed, the mixture was stirred for 30 min at room temperature and then 1 h at reflux. The reaction mixture was then poured into a water/ice mixture (200 mL), the organic phase was separated, and the aqueous phase was washed with additional ether (2 × 100 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate solution (50 mL) and brine (50 mL) and then dried over sodium sulfate. The resulting clear solution was filtered through a pad of silica gel that was subsequently washed with additional ether. The organic phases were then evaporated at ambient pressure to afford a low melting point solid (9.8 g, 93%) that was immediately used in the next step without any further purification: mp 26−27 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.41 (s, 3H), 4.43 (s, 2H), 7.07−7.1 (dd, 1H, J = 8.1, 1.85 Hz), 7.27 (d, 1H, J = 1.85 Hz), 7.49−7.52 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.3, 33, 125.4, 128.3, 131.8, 133.2, 137.4, 138.9; HRMS (TOF EI) calcd for $C_8H_8Br_2$ [M] 261.89927, found 261.89902.

(2*S*,3a*S*,8a*R*)-5-Bromo-2-hydroxymethyl-6-methyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-3-carboxylic Acid Methyl Ester (41). To a stirred solution of **40** (1.9 g, 5.37 mmol) in 30 mL of THF at room temperature was added dropwise a 2 M solution of borane−methyl sulfide complex in THF (21.5 mL, 8 equiv), and the mixture was then stirred at room temperature for 5 h. The reaction mixture was then quenched by adding 45 mL of methanol dropwise (**CAUTION:** hydrogen evolution), and stirring was continued for an additional 1 h. The solvent was removed by rotary evaporator to yield a residue that was dissolved in CH_2Cl_2 (70 mL), washed with water (15 mL) and then brine (15 mL), dried over sodium sulfate, filtered, and evaporated to dryness to afford a crude oil that was purified by flash chromatography (hexanes/ethyl acetate, 6/4) to give the title compound (1.65 g, 90%) as a white solid: mp 138−140 °C; $[\alpha]_D$ −149 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 2.5/1 of rotamers δ (ppm) 1.64−1.76 (m, 1H), 1.86−1.95 (m, 0.7H, major), 2.15−2.22 (m, 0.3H, minor), 2.35 (s, 0.9H, minor), 2.36 (s, 2.1H, major), 2.61−2.65 (d, 1H, J = 16.3 Hz), 2.95−3 (dd, 1H, J = 16.3, 7.2 Hz), 3.07−3.13 (m, 1H), 3.6−3.9 (m, 2H), 3.78 (s, 0.9H, minor), 3.88 (s, 2.1H, major), 3.92−4.01 (m, 1H), 5.26−5.28 (d, 0.7H, J = 7.4 Hz, major), 5.36−5.38 (d, 0.3H, J = 7.4 Hz, minor), 7.06 (s, 0.3H, minor), 7.07 (s, 0.7H, major), 7.62 (s, 0.7H, major), 8 (s, 0.3H, minor); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 23.4, 34.5, (34.8), 35.3, (35.6), 40.1, (41.4), 53, (53.1), 60.1, (61.6), 64.4, (67), 67.3, (67.4), 123.5, (123.6), 127.8, (127.95), 130.4, (131.2), 137.8, (138.1), 141, (141.6), 142.6, (143.7), 156.3, (157.3); HRMS (TOF EI) calcd for $C_{15}H_{18}BrNO_3$ [M] 339.04700, found 339.04732. Anal. Calcd for $C_{15}H_{18}BrNO_3$: C, 52.96; H, 5.33; N, 4.12. Found: C, 53.08; H, 5.67; N, 4.16.

(3a*S*,4a*R*,9b*S*)-7-Methyl-8-vinyl-3,3a,4,4a,5,9b-hexahydroindeno[2′,1′:4,5]pyrrolo[1,2-*c*][1,3]oxazol-1-one (42). To a stirred suspension of **41** (500 mg, 1.47 mmol) in toluene (20 mL) were added tetrakis(triphenylphosphine)palladium (150 mg, 0.09 equiv) and then tributyl(vinyl)tin (0.5 mL, 1.15 equiv), and the mixture was stirred and refluxed for 24 h. The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2 (20 mL), filtered through a pad of Celite, and evaporated to dryness. The resulting crude was taken with CH_2Cl_2 (100 mL) and aqueous potassium fluoride saturated solution (150 mL) and stirred vigorously at room temperature overnight. The organic phase was then separated, the aqueous phase was washed with ethyl acetate (2 × 30 mL), and the combined organic phases were dried over sodium sulfate, filtered, and evaporated to dryness. The crude was dissolved in chloroform and purified by flash chromatography (hexanes/ethyl acetate, 7/3) to afford a white solid (314 mg, 84%). Slow evaporation of a sample from methanol yielded X-ray-quality crystals: mp 137−139 °C; $[\alpha]_D$ −78.3 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.81−1.89 (m, 1H), 1.96−2 (m, 1H), 2.34 (s, 3H), 2.73−2.77 (dd, 1H, J = 15, 2.2 Hz), 3.23−3.38 (m, 2H), 3.76−3.87 (m, 1H), 4.16−4.18 (dd, 1H, J = 8.1, 1.2 Hz), 4.42−4.46 (dd, 1H, J = 8.1, 7.7 Hz), 5.27−5.3 (d, 1H, J = 11 Hz), 5.43−5.45 (d, 1H, J = 6.3 Hz), 5.66−5.70 (d, 1H, J = 17 Hz), 6.87−6.94 (dd, 1H, J = 17, 11 Hz), 6.98 (s, 1H), 7.6 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 20.3, 38.5, 39.2, 42.3, 57.9, 67.7, 68.4, 115.7, 123.1, 126.6, 134.7, 136.7, 136.9, 139.2, 142.7, 161.4; HRMS (TOF EI) calcd for $C_{16}H_{17}NO_2$ [M]: 255.12592, found 255.12686. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.92; H, 6.91; N, 5.39.

(2*S*,3a*S*,8a*R*)-(6-Methyl-5-vinyl-1,2,3,3a,8,8a-hexahydro-3-azacyclopenta[*a*]inden-2-yl)methanol (43). A mixture of **42** (200 mg, 0.78 mmol) and potassium hydroxide (2.71 g, 62 equiv) in methanol (22 mL) was stirred and refluxed for 4 h, cooled to 0 °C, and then neutralized with 3 N aqueous HCl. Most of the methanol was then evaporated, and the pH was adjusted to 8−9 with saturated aqueous sodium hydrogen carbonate solution. The aqueous phase was then extracted with CH_2Cl_2 (5 × 20 mL). The combined organic phases were dried over sodium sulfate, filtered, and evaporated to dryness to give an off-white solid (173 mg, 97%): mp 132−133 °C; $[\alpha]_D$ +136.6 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm)

1.57−1.59 (m, 1H), 1.88−1.92 (m, 1H), 2.33 (s, 3H), 2.66−2.71 (dd, 1H, J = 16.5, 2.4 Hz), 2.75−2.84 (broad s, 2H), 3.03−3.13 (m, 1H), 3.15−3.21 (m, 2H), 3.41−3.45 (dd, 1H, J = 10.7, 6.4 Hz), 3.57−3.61 (dd, 1H, J = 10.7, 3.9 Hz), 4.74−4.76 (d, 1H, J = 7 Hz), 5.25−5.28 (d, 1H, J = 11 Hz), 5.63−5.67 (d, 1H, J = 17.4 Hz), 6.88−6.96 (dd, 1H, J = 17.4, 11 Hz), 6.98 (s, 1H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 20.3, 36.7, 39.1, 42.2, 59.5, 64.1, 68.3, 115, 121.6, 126.9, 135.1, 135.8, 136.3, 142.9, 143.3; HRMS (TOF EI) calcd for $C_{15}H_{19}NO$ [M] 229.14666, found 229.14644. Anal. Calcd for $C_{15}H_{19}NO \cdot {}^1/_2H_2O$: C, 75.59; H, 8.46; N, 5.88. Found: C, 75.49; H, 8.62; N, 5.82.

(2*S*,3a*S*,8a*R*)-2-Hydroxymethyl-6-methyl-5-vinyl-1,3a,-8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-3-carboxylic Acid *tert*-Butyl Ester (44). To a stirred solution of **43** (31 mg, 0.135 mmol) in CH_2Cl_2 (2 mL), at room temperature, was added di-*tert*-butyl dicarbonate (88 mg, 3 equiv) in one portion, the mixture was stirred for 4 h,the solvent was removed in vacuo, and the resulting crude oil was purified by flash chromatography (hexanes/ethyl acetate, 6/4) to afford a white foamy solid (42 mg, 95%): $[\alpha]_D$ −184.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 3/1 of rotamers δ (ppm) 1.54 (s, 2.25H, minor), 1.62 (s, 6.75H, major), 1.69−1.74 (m, 1H), 1.82−1.87 (m, 0.75H, major), 2.06−2.09 (m, 0.25H, minor), 2.33 (s, 3H), 2.63−2.67 (d, 1H, J = 15 Hz), 2.98−3.08 (m, 2H), 3.66−3.69 (m, 1H), 3.78−3.83 (dd, 1H, J = 11, 8 Hz), 4−4.04 (m, 1H), 4.43−4.49 (broad s, 1H), 5.21−5.24 (d, 0.25H, J = 11 Hz, minor), 5.26−5.29 (d, 0.75H, J = 11 Hz, major), 5.29−5.31 (d, 0.75H, J = 6 Hz, major), 5.39−5.4 (d, 0.25H, J = 6 Hz, minor), 5.59−5.63 (d, 0.75H, J = 17 Hz, major), 5.61−5.65 (d, 0.25H, J = 17 Hz, minor), 6.91−7 (m, 1H), 6.98 (s, 0.25H), 7 (s, 0.75H), 7.83 (s, 0.75H, major), 8.03 (s, 0.25H, minor); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.6, (28.3), 28.5, 34.1, (34.2), 34.9, (35.1), (39.1), 40.5, (59.7), 60.7, (64.4), (66.6), 67, 67.5, (79.78), 80.7, 114.2, (114.3), 122.9, (123.6), (126.7), 126.9, (134.5), 135.1, 135.5, 135.7, 141, 141.1, (142.3), 156.3; HRMS (TOF EI) calcd for $C_{20}H_{28}NO_3$ $[M + H]^+$ 330.20691, found 330.20578.

(2*S*,3a*S*,8a*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-6-methyl-5-vinyl-1,3a,8,8atetrahydro-2*H*-3-azacyclopenta[*a*]indene-3-carboxylic Acid *tert*-Butyl Ester (45). To a stirred solution of **44** (50 mg, 0.152 mmol) and imidazole (26 mg, 2.5 equiv) in THF (3 mL) was added dropwise, at room temperature, *tert*-butyldiphenylsilyl chloride (0.08 mL, 2 equiv), and the resulting milky suspension was stirred at room temperature overnight. The reaction mixture was then diluted with water and extracted with ethyl acetate (2 × 10 mL); the combined organic phases were washed with brine (10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The oily crude was purified by flash column chromatography (hexanes/acetone, 9/1) to afford a white foamy solid (79 mg, 92%): $[\alpha]_D$ −65 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.11 (s, 4.5H), 1.12 (s, 4.5H), 1.39 (s, 4.5H), 1.64 (s, 4.5H), 1.62−1.74 (m, 1H), 2.18−2.23 (dd, 0.5H, J = 12.5, 7.6 Hz), 2.34−2.46 (m, 0.5H), 2.35 (s, 3H), 2.63−2.71 (t, 1H, J = 15.2 Hz), 2.97−3.16 (m, 1.5H), 3.23−3.24 (m, 0.5H), 3.61−3.66 (m, 0.5H), 3.75−3.81 (m, 1H), 3.86−3.89 (m, 0.5H), 3.95−3.97 (m, 0.5H), 4.07−4.11 (dd, 0.5H, J = 9.8, 4.9 Hz), 5.23−5.26 (d, 0.5H, J = 11 Hz), 5.28−5.3 (d, 0.5H, J = 11 Hz), 5.32−5.34 (d, 0.5H, J = 7.3 Hz), 5.38−5.4 (d, 0.5H, J = 7.3 Hz), 5.64−5.68 (d, 1H, J = 17 Hz), 6.89−7.01 (m, 1H), 7.01 (s, 0.5H), 7.02 (s, 0.5H), 7.42−7.47 (m, 6H), 7.71−7.72 (m, 4H), 7.91 (s, 0.5H), 8.07 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 19.7, (19.8), (20.2), 20.3, 27.3, (27.4), 28.8, (29.2), 34.6, (35.4), 35.8, 39.6, (41.4), 59.9, (60.1), (64.1), 64.6, 67.1, (67.4), 79.8, (80), (114.6), 114.9, (123.5), 124.2, 127.3, (127.6), 128.1, (128.2), 128.2, 130, (130.1), 130.2, 133.8, (133.9), 134, (134.3), (135.1), 135.6, 135.7, (135.8), 135.9, (136), 136.1, (136.2), (136.3), 136.4, 141.3, (141.7), (142.5), 143.2, (154.4), 155.2; HRMS (FAB) calcd for $C_{36}H_{46}NO_3Si$ $[M + H]^+$ 568.32471, found 568.32360.

(2*S*,3a*S*,8a*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-5-formyl-6-methyl-1,3a,8,8a-tetrahydro-2*H*-3-aza-cyclopenta[*a*]indene-3-carboxylic Acid *tert*-Butyl Ester (46). To a stirred solution of **45** (80 mg, 0.14 mmol) in a mixture of THF (10.5 mL) and water (7 mL), at room temperature, were subsequently added sodium periodate (105 mg, 3.5 equiv) and catalytic osmium tetraoxide. The mixture became brown and then light yellow, was stirred for 90 min, then was quenched with few crystals of sodium thiosulfate pentahydrate and stirred for 15 min. The reaction mixture was then extracted with ethyl acetate (4 × 15 mL); the combined organic phases were washed with brine (15 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The oily crude was purified by flash chromatography (hexanes/acetone, 9/1) to afford the desired aldehyde as a white foamy solid (40 mg). Subsequent elution of the column (hexanes/ethyl acetate 1/1) afforded the corresponding diol intermediate (30 mg) that was immediately dissolved at room temperature in a mixture of THF (1.5 mL) and water (1 mL) and treated, under stirring, with sodium periodate (16 mg, 1.5 equiv). The reaction mixture was stirred at room temperature for 2 h, diluted with water, and extracted with ether (3 × 10 mL). The combined organic phases were then washed with brine (10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The crude was purified by flash chromatography (hexanes/acetone, 9/1) to afford a second batch of the aldehyde **46** that was combined with the first batch (66 mg, total yield 82%): $[\alpha]_D$ −148.5 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1.3/1 of rotamers δ (ppm) 1.08 (s, 9H), 1.37 (s, 5H, major), 1.48−1.62 (m, 1H), 1.64 (s, 4H, minor), 2.18−2.23 (dd, 0.44H, J = 12.5, 7.3 Hz, minor), 2.35−2.4 (dd, 0.56H, J = 12.5, 7.3 Hz, major), 2.63 (s, 1.68H, major), 2.65 (s, 1.32H, minor), 2.69−2.77 (t, 1H, J = 16.3 Hz), 2.99−3.24 (m, 1.56H), 3.26−3.3 (dd, 0.44H, J = 10.6, 7 Hz, minor), 3.6−3.64 (dd, 0.56H, J = 9.5, 7 Hz, major), 3.68−3.81 (m, 1H), 3.84−3.87 (m, 0.56H, major), 3.9−3.96 (m, 0.44H, minor), 4.04−4.08 (dd, 0.44H, J = 9.5, 4.8 Hz, minor), 5.32−5.33 (d, 0.44H, J = 7.5 Hz, minor), 5.38−5.40 (d, 0.56H, J = 7.5 Hz, major), 7.1 (s, 1H), 7.4−7.46 (m, 6H), 7.67−7.73 (m, 4H), 8.23 (s, 0.44H, minor), 8.27 (s, 0.56H, major), 10.1 (s, 0.56H, major), 10.25 (s, 0.44H, minor); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 19.6, (19.7), (20), 21, 27.3, (27.3), 28.8, (29.1), (34.6), 34.7, (36), 36.3, 39.6, (41.4), 59.9, (60.1), (64.1), 64.5, 66.8, (66.9), 80.2, (80.6), 128.1, (128.2), 128.3, 129, (129.1), (130.1), 130.2, 130.3, (130.4), 133.7, (133.8), 133.8, 133.9, (134), (134.2), 134.4, 135.9, (135.9), 136, 140.8, (141.1), (142.9), 143.3, 148, (148.7), (154.3), 155.2, (192.5), 194; HRMS (FAB) calcd for $C_{35}H_{44}NO_4Si$ $[M + H]^+$ 570.30396, found 570.30180.

(2*S*,3a*S*,8a*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-6-methyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-3,5-dicarboxylic Acid 3-*tert*-Butyl Ester (47). A stirred solution of the aldehyde **46** (50 mg, 0.088 mmol) in *tert*-butyl alcohol (1.75 mL) at room temperature was treated with a 2 M solution of 2-methyl-2-butene in THF (0.66 mL, 15 equiv) and then cooled to 0 °C. To this mixture was added dropwise a previously prepared solution of $NaH_2PO_4 \cdot H_2O$ (100 mg, 8.25 equiv) and sodium chlorite (60 mg, 7.5 equiv) in water (1.75 mL), and the resulting suspension was stirred at 0 °C for 2 h and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The resulting crude (44 mg, 85%) white foamy solid was used in the next step without any further purification: $[\alpha]_D$ −117.2 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1.6/1 of rotamers δ (ppm) 1.1 (s, 9H), 1.20−1.28 (m, 1H), 1.38 (s, 3.6H, minor), 1.65 (s, 5.4H, major), 2.18−2.23 (dd, 0.6H, J = 12.5, 7.3 Hz, major), 2.35−2.4 (dd, 0.4H, J = 12.5, 7.3 Hz, minor), 2.62 (s, 1.2H, minor), 2.66 (s, 1.8H, major), 2.68−2.75 (t, 1H, J = 16.3 Hz), 2.99−3.18 (m, 1.4H), 3.26−3.28 (dd, 0.6H, J = 10.6, 7 Hz, major), 3.6−3.63 (dd, 0.4H, J = 9.5, 7 Hz, minor), 3.7−3.82 (m, 1H), 3.84−3.88 (m, 0.4H, minor), 3.92−3.98 (m, 0.6H, major), 4.04−4.08 (dd, 0.6H,

J = 9.5, 4.8 Hz, major), 5.32−5.34 (d, 0.6H, J = 7 Hz, major), 5.38−5.40 (d, 0.4H, J = 7 Hz, minor), 7.1 (s, 0.4H, minor), 7.12 (s, 0.6H, major), 7.4−7.46 (m, 6H), 7.67−7.73 (m, 4H), 8.51 (s, 0.4H, minor), 8.56 (s, 0.6H, major); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) (19.6), 19.7, (22.5), 22.8, (26.9), 27.3, (28.8), 28.9, 34.6, 35.9, (36), (39.6), 41.4, (59.9), 60.1, 64.1, (64.5), (66.8), 66.9, (80.2), 80.6, 127.4, (128.1), 128.2, 128.3, 129.4, 130.1, 130.2, (130.3), 133.8, (133.9), 134, 134.2, 135.9, (136), 136.1, (141.3), 141.9, 142.3, (142.8), 147, (147.8), 154.3, (155.1), (173.1), 173.4; HRMS (FAB) calcd for $C_{35}H_{44}NO_5Si$ [M + H]$^+$ 586.29889, found 586.29790.

(2*S*,3a*S*,8a*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-6-methyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-3,5-dicarboxylic Acid 3-*tert*-Butyl Ester 5-Methyl Ester (48). To a stirred solution of the acid **47** (35 mg, 0.06 mmol) in acetone (1.5 mL) at room temperature, kept in the dark, were added potassium carbonate (41.5 mg, 5 equiv) and then iodomethane (0.037 mL, 10 equiv), and the resulting suspension was stirred at room temperature for 7 h. The reaction mixture was then filtered and diluted with ethyl acetate and water, the organic phase was separated, and the aqueous phase was washed with ethyl acetate (2 × 10 mL); the combined organic phases were washed with brine (15 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The crude methyl ester was then purified by flash column chromatography (hexanes/ethyl acetate, 9/1) to afford a white foamy solid (32 mg, 89%): $[\alpha]_D$ −126 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1.3/1 of rotamers δ (ppm) 1.08 (s, 4H, minor), 1.09 (s, 5H, major), 1.21−1.27 (m, 1H), 1.37 (s, 4H, minor), 1.64 (s, 5H, major), 2.17−2.22 (dd, 0.56H, J = 12.5, 7.6 Hz, major), 2.33−2.38 (dd, 0.44H, J = 12.5, 7.6 Hz, minor), 2.57 (s, 1.3H, minor), 2.61 (s, 1.7H, major), 2.66−2.73 (dd, 1H, J = 16.5, 11.5 Hz), 2.98−3.16 (m, 1.44H), 3.24−3.28 (dd, 0.56H, J = 11, 7.5 Hz, major), 3.58−3.62 (dd, 0.44H, J = 9.5, 7.5 Hz, minor), 3.69−3.77 (m, 1H), 3.84−3.88 (m, 0.44H, minor), 3.84 (s, 1.3H, minor), 3.89 (s, 1.7H, major), 3.93−3.95 (m, 0.56H, major), 4.02−4.06 (dd, 0.56H, J = 10, 4.8 Hz, major), 5.29−5.31 (d, 0.56H, J = 7.4 Hz, major), 5.35−5.37 (d, 0.44H, J = 7.4 Hz, minor), 7.08 (s, 0.44H, minor), 7.09 (s, 0.56H, major), 7.4−7.46 (m, 6H), 7.67−7.69 (m, 4H), 8.37 (s, 0.44H, minor), 8.44 (s, 0.56H, major); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) (19.1), 19.2, (21.5), 21.8, (26.7), 26.8, (28.2), 28.4, 33.9, 35.2, (35.4), (39.1), 40.9, 51.4, (51.5), (59.3), 59.5, 63.6, (64), (66.3), 66.4, (79.4), 79.8, (127.4), 127.5, 127.6, (127.7), 127.8, 127.9, (128), (128.1), 128.5, 128.8, (129.1), 129.4, (129.5), (129.6), 129.7, (133.2), 133.3, (133.4), 133.6, (135.3), 135.4, (135.5), 135.6, (139.8), 140.5, 141.6, (142.2), (145.5), 146.1, 153.7, (154.6), 167.6, (168.1); HRMS (FAB) calcd for $C_{36}H_{46}NO_5Si$ [M + H]$^+$ 600.31451, found 600.31260.

(2*S*,3a*S*,8a*R*)-2-Hydroxymethyl-6-methyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-3,5-dicarboxylic Acid 3-*tert*-Butyl Ester 5-Methyl Ester (49). To a stirred solution of **48** (42 mg, 0.07 mmol) in THF (3 mL) at room temperature was added a 1 M solution of tetrabutylammonium fluoride in THF (0.098 mL, 1.4 equiv), and the resulting light yellow solution was stirred overnight. The reaction mixture was then quenched with saturated aqueous ammonium chloride (2 mL), diluted with water, and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were then washed with brine (10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The crude was then purified by flash column chromatography (hexanes/ethyl acetate, 1/1) to afford a white foamy solid (25 mg, 100%): $[\alpha]_D$ −159 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 5/1 of rotamers δ (ppm) 1.54 (s, 1.35H, minor), 1.63 (s, 7.65H, major), 1.67−1.72 (m, 1H), 1.86−1.9 (m 0.85H, major), 2.17−2.22 (m, 0.15H, minor), 2.56 (s, 0.45H, minor), 2.6 (s, 2.55H, major), 2.67−2.71 (d, 1H, J = 16 Hz), 3.02−3.14 (m, 2H), 3.66−3.69 (m, 1H), 3.76−3.81 (dd, 1H, J = 11, 7.5 Hz), 3.84 (s, 0.45H, minor), 3.88 (s, 2.55H, major), 3.98−4.02 (m, 1H), 4.23−4.27 (broad s, 1H), 5.27−5.29 (d, 0.85H, J = 7 Hz, major), 5.38−5.4 (d, 0.15H, J = 7 Hz, minor), 7.06 (s, 0.15H, minor), 7.09 (s, 0.85H, major), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) (22.1), 22.3, 28.8, (30.1), (32.3), 34.4, (34.7), 35.9, (39.9), 41.1, 52, (60.2), 61.23, (64.9), (66.9), 67.1, 67.9, (80.6), 81.6, 128.3, (128.7), 129.1, 129.4, (129.6), (140.5), 141.3, 141.4, (142.4), (145.9), 146.7, 156.7, 168.1, (168.62); HRMS (TOF EI) calcd for $C_{20}H_{27}NO_5$ [M + H]$^+$ 361.18892, found 361.18857.

(2*S*,3a*S*,8a*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-6-methyl-1,2,3,3a,8,8a-hexahydro-3-azacyclopenta[*a*]indene-5-carboxylic Acid Methyl Ester (50). To a stirred solution of **48** (21 mg, 0.035 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C were subsequently added 2,6-lutidine (0.017 mL, 4.25 equiv) and trimethylsilyl triflate (0.0155 mL, 2.4 equiv). The reaction mixture was stirred at 0 °C for 3 h, and then warmed to room temperature and stirred at this temperature for 3 h. The mixture was quenched with saturated aqueous sodium hydrogen carbonate solution (1.5 mL), diluted with water, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were then washed with brine (10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The crude was then purified by flash column chromatography (CH_2Cl_2/MeOH, 95/5) to afford the amine **50**: colorless oil (14 mg, 80%); $[\alpha]_D$ +54 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.06 (s, 9H), 1.53−1.58 (m, 1H), 1.93−2 (m, 1H), 2.28−2.32 (broad s, 1H), 2.58 (s, 3H), 2.71−2.76 (dd, 1H, J = 17, 2 Hz), 3.04−3.12 (m, 2H), 3.16−3.22 (dd, 1H, J = 17, 9 Hz), 3.61−3.65 (dd, 1H, J = 10, 4.9 Hz), 3.72−3.75 (dd, 1H, J = 10, 4.4 Hz), 3.87 (s, 3H), 4.8−4.82 (d, 1H, J = 7 Hz), 7.05 (s, 1H), 7.36−7.45 (m, 6H), 7.64−7.66 (m, 4H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.2, 21.7, 26.7, 36.8, 38.7, 41.4, 51.5, 59.1, 65.4, 67.8, 127.5, 127.6, 127.7, 128.3, 129.5, 133.3, 133.4, 135.4, 139.8, 147.7, 167.9; HRMS (TOF EI) calcd for $C_{31}H_{37}NO_3Si$ [M + H]$^+$ 499.25427, found 499.25315.

(2*S*,3a*S*,8a*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-6-methyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-3,5-dicarboxylic Acid 3-*tert*-Butyl Ester (47). To a stirred solution of **48** (20 mg, 0.033 equiv) in 1,4-dioxane (2 mL) was added 1 N aqueous potassium hydroxide (0.33 mL, 10 equiv), and the mixture was stirred at 100 °C for 1 h. The mixture was then cooled to room temperature, acidified with 1 N aqueous HCl (pH 4), diluted with water, and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were then washed with brine (20 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The crude was then purified by flash column chromatography (hexanes/ethyl acetate, 6/4) to afford the acid **47** as a white foamy solid (17 mg, 88%). The acid obtained by this route showed spectroscopic properties identical to those for the compound prepared by oxidation of the corresponding aldehyde **46** (vide supra).

(2*S*,4*R*)-4-Naphthalen-2-ylmethyl-5-oxopyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (51). By using the general procedure described above, target compound was obtained, after column chromatography (dichloromethane/methanol, 99/1), as a white foam (69%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.1−2.2 (m, 2H), 2.9 (dd, 1H, J = 13.3, 8.9 Hz,), 3.0−3.1 (m, 1H), 3.4 (dd, 1H, J = 13.6, 4.7 Hz), 3.7 (s, 3H), 3.9 (s, 3H), 4.6 (dd, 2H, J = 5.9, 4.7 Hz), 7.3 (dd, 1H, J = 8.4, 1.7 Hz), 7.4−7.5 (m, 2H), 7.6 (s, 1H), 7.8 (m, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm) 28.1, 36.0, 43.3, 52.6, 53.8, 56.6, 125.6, 126.1, 127.1, 127.3, 127.4, 127.5, 128.3, 132.1, 133.3, 135.4, 151.8, 171.1, 173.6; HRMS (FAB) calcd for $C_{19}H_{19}NO_5$ [M + H]$^+$ 342.134148, found 342.133200.

(2*S*,3a*S*,10a*R*)-1,3a,10,10a-Tetrahydro-2*H*-3-azapentaleno[1,2-*b*]naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (52) and (7a*R*,9*S*,10a*S*)-7,8,9,10a-Tetrahydro-7a*H*-10-azapentaleno[1,2-*a*]naphthalene-9,10-dicarboxylic Acid Dimethyl Ester (53). By using the general procedure described above, compounds **52** and **53** were obtained, after filtration through silica pad (dichloromethane), as a white solid (48%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/3 of regioisomers and rotamers

(approximately 1/1 for the minor product and 1/3 for the major one) δ (ppm) 2.0−2.3 (m, 2H), 2.8−3.0 (m, 1H), 3.15−3.3 (m, 2H), 3.8 (s, 6H), 4.2−4.4 (m, 1H), 5.6 (d, 0.09H, J = 8.6 Hz), 5.7 (d, 0.13H, J = 8.6 Hz), 5.9 (bs, 0.20H), 6.1 (d, 0.56H, J = 6.2 Hz), 7.3−8.5 (m, 6H); HRMS (TOF EI) calcd for $C_{19}H_{19}NO_4$ $[M + H]^+$:325.131408, found 325.132138.

(2*S*,3a*S*,10a*R*)-1,3a,10,10a-Tetrahydro-2*H*-3-azapentaleno[1,2-*b*]naphthalene-2,3-dicarboxylic Acid 3-Methyl Ester (54) and (7a*R*,9*S*,10a*S*)-7,8,9,10a-Tetrahydro-7a*H*-10-azapentaleno[1,2-*a*]naphthalene-9,10-dicarboxylic Acid 10-Methyl Ester (55). By using the general deprotection of methyl esters procedure described above, a mixture of the target compounds was obtained from corresponding methyl ester as a white solid (63%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/3 of regioisomers and rotamers (approximately 1/1 for the minor product and 1/3 for the major one) δ (ppm) 2.1−2.2 (m, 1H), 2.3−2.4 (m, 1H), 2.9 (m, 1H), 3.2 (m, 2H), 3.8 (bs, 2.5H), 4.0 (s, 0.5H), 4.2−4.4 (m, 1H), 5.5 (d, 0.12H, J = 9.4 Hz) 5.7 (d, 0.12H, J = 9.4 Hz), 5.9 (bs, 0.18H), 6.1 (bs, 0.5H), 7.3−7.9 (m, 5H), 8.5 (d, 0.6H, J = 7.5 Hz); HRMS (TOF EI) calcd for $C_{18}H_{17}NO_4$ $[M + H]^+$ 311.115758, found 311.115967.

(2*S*,3a*S*,10a*R*)-2-Hydroxymethyl-1,3a,10,10a-tetrahydro-2*H*-3-azapentaleno[1,2-*b*]naphthalene-3-carboxylic Acid Methyl Ester (56) and (7a*R*,9*S*,10a*S*)-9-Hydroxymethyl-7,8,9,10a-tetrahydro-7a*H*-10-azapentaleno[1,2-*a*]naphthalene-10-carboxylic Acid Methyl Ester (57). By using the general procedure described for compound **18**, the target compounds were obtained and separated, after column chromatography (hexanes/ethyl acetate, 50/50), from the corresponding acid (total yield 99%). Isomer **56** (152 mg, 25%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 3/1 of rotamers δ (ppm) 1.7−1.8 (m, 1H), 1.9−2.0 (m, 1H), 2.9 (d, 1H, J = 12.3), 3.1−3.2 (m, 2H), 3.6−3.8 (m, 1.7H), 3.8−3.9 (m, 2.3H), 3.95 (s, 2.4H), 4.05 (m, 1H), 5.5 (d, 0.75H, J = 6.2 Hz), 5.6 (d, 0.25H, J = 6.2 Hz), 7.4 (m, 2H), 7.7 (s, 1H), 7.8 (m, 2H), 7.9 (s, 0.75H), 8.3 (s, 0.25H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 34.2, 35.3, 36.3, 38.2, 40.2, 41.6, 53.0, 61.8, 67.3, 67.4, 124.1, 125.5, 125.7, 126.3, 127.8, 128,6, 133.4, 134.1, 140.5, 142.0, 157.7; HRMS (TOF EI) calcd for $C_{18}H_{19}NO_3$ $[M]^+$ 297.136494, found 297. 135363. Isomer **57** (385 mg, 75%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a single rotamer δ (ppm) 1.9−2.0 (m, 1H), 2.9−3.0 (m, 1H), 3.1−3.2 (m, 2H), 3.65 (bs, 3.1H), 3.85 (bs, 3.4H), 5.9 (bs, 1H), 7.3−7.5 (m, 3H), 7.8 (dd, 2H, J = 11.0, 30.6 Hz), 8.2 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 35.2, 38.3, 42.4, 52.6, 62.5, 65.7, 68.5, 123.7, 125.2, 126.4, 128.9, 130.0, 131.6, 133.4, 157.7; HRMS (TOF EI) calcd for $C_{18}H_{19}NO_3$ $[M + H]^+$ 297.136494, found 297.136076.

(7a*R*,9*S*,10a*S*)-(7,7a,8,9,10,10a-Hexahydro-10-azapentaleno[1,2-*a*]naphthalen-9-yl)methanol (58). By using the general procedure described for compound **19**, the target compound was obtained and processed without further purification (total yield 100%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.6−1.7 (m, 1H), 1.9−2.1 (m, 1H), 2.9 (dd, 1H, J = 15,2 Hz, 2.8 Hz), 3.1−3.3 (m, 2H), 3.3−3.5 (m, 2H), 3.5−3.6 (m, 1H), 5.1 (d, 1H, J = 10.3 Hz), 7.3 (d, 1H, J = 10.5 Hz), 7.4−7.5 (m, 1H), 7.5−7.6 (m, 1H), 7.7 (d, 1H, J = 8.5 Hz), 7.9 (d, 1H, J = 8.5 Hz), 8.05 (d, 1H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 37.1, 40.8, 42.0, 59.7, 63.9, 67.6, 123.7, 124.3, 125.5, 127.0, 129.0, 129.1.

(7a*R*,9*S*,10a*S*)-9-Hydroxymethyl-7,8,9,10a-tetrahydro-7a*H*-10-azapentaleno[1,2-*a*]naphthalene-10-carboxylic Acid *tert*-Butyl Ester (59). To a stirred solution of **58** (240 mg, 0.99 mmol) in CH_2Cl_2 (15 mL), at room temperature, was added di-*tert*-butyl dicarbonate (655 mg, 3 equiv) in one portion, the mixture was stirred overnight, the solvent was removed in vacuo, and the resulting crude yellow oil was purified by flash chromatography (hexanes/ethyl acetate, 60/40) to afford a white foamy solid (331 mg, 98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.6 (s, 6H), 1.9 (m, 1H), 2.9 (d, 1H, J = 16.0 Hz), 3.1−3.3 (m, 2H), 3.5−3.6 (m, 1H), 3.8 (d, 1H, J = 3.7 Hz), 6.05 (d, 1H, J = 9.2 Hz), 7.35 (d, 1H, J = 9.8 Hz), 7.4−7.55 (m, 2H), 7.8 (d, 1H, J = 9.8 Hz), 7.9 (d, 1H, J = 9.8 Hz).

(2*S*,4*R*)-5-Oxo-4-phenanthren-3-ylmethylpyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (60). By using the general procedure described above, compound **60** was obtained, after column chromatography (hexanes/ethyl acetate, 50/50), as a white foam (52%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.1−2.2 (m, 2H), 3.0 (dd, 1H, J = 12.9 Hz, 10.3 Hz), 3.05−3.15 (m, 1H), 3.55 (dd, 1H, J = 12.9 Hz, 2.6 Hz), 3.75 (s, 3H), 3.9 (s, 3H), 4.6 (m, 1H), 7.45 (d, 1H, J = 9.0 Hz), 7.6−7.8 (m, 4.5H), 7.85 (d, 1H, J = 9.7 Hz), 7.9 (d, 1H, J = 9.7 Hz), 8.5 (s, 1H), 8.7 (d, 1H, J = 11.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 28, 37, 43, 52.5, 54.5, 57, 114, 122.5, 123.5, 127, 127.2, 128, 129, 129.5, 130, 131, 131.5, 133, 138.5, 152, 172, 174; HRMS (FAB) calcd for $C_{23}H_{21}NO_5$ $[M + H]^+$ 391.141973, found 391.142614.

Phenanthrene Derivatives 61 and 62. By using the general procedure described above, target compound was obtained, after column chromatography (hexanes/ethyl acetate, 70/30), as white foam (27%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of regioisomers and rotamers (approximately 1/1 and 1/2, respectively) δ (ppm) 1.9−2.4 (m, 2.7H), 2.4−2.9 (m, 2.8H), 3.0−3.4 (m, 3.8H), 3.7−3.9 (m, 5.25H), 4.0 (s, 0.72H), 4.4 (t, 0.7H, J = 11.5 Hz), 4.5 (t, 0.2H, J = 7.7 Hz), 4.8 (t, 0.3H, J = 7.7 Hz), 5.7 (d, 0.25H, J = 6.2 Hz), 5.8 (d, 0.25H, J = 6.2 Hz), 5.9 (bs, 0.12H), 6.2 (bs, 0.25H), 7−8 (m, 7.8H), 8.29 (s, 0.3H), 8.5−8.7 (m, 1.4H), 9.1 (d, 0.2H, J = 9.2 Hz); LRMS (FAB) 376 $[(M + H)^+]$.

Phenanthrene Derivatives 63 and 64. By using the general procedure described above, a mixture approximately 1/1 of regioisomers of the target compound was obtained from the corresponding methyl ester as a colorless oil (79%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of regioisomers and rotamers (approximately 1/1 and 1/2, respectively) δ (ppm) 2.2 (m, 1H), 2.3−3.2 (m, 4.6H), 3.4 (m, 2H), 3.8 (s, 1.3H), 4.1 (s, 0.8H), 4.4 (dd, 0.7H, J = 17.1 Hz, 8.9 Hz), 4.6 (t, 0.2H, J = 8.5 Hz), 4.9 (t, 0.2H, J = 8.5 Hz), 5.6 (d, 0.25H, J = 6.9 Hz), 5.7 (d, 0.25H, J = 7.4 Hz), 5.9 (bs, 0.25H), 6.1 (bs, 0.25H), 7.0−7.4 (m, 1.7H), 7.4 (d, 0.6H, J = 7.8 Hz), 7.6−7.9 (m, 5.5H), 8 (s, 0.3H), 8.3 (s, 0.3H), 8.5 (d, 0.6H, J = 7.6 Hz), 8.65 (d, 0.6H, J = 5.86 Hz), 9 (d, 0.3H, J = 8.7 Hz); HRMS (FAB) calcd for $C_{22}H_{19}NO_4$ $[M + H]^+$ 362.137891, found 362.138000.

Phenanthrene Derivatives 65 and 66. By using the general procedure described for compound **18**, the target compounds were obtained and separated, after column chromatography (hexanes/ethyl acetate, 30/70), from the corresponding acid (total yield 78%). Isomer **65** (35 mg, 60%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 2/1 of rotamers δ (ppm) 1.7−1.8 (m, 1H), 1.9−2.0 (m, 1H), 3.0 (d, 1H, J = 15,7), 3.1−3.2 (m, 2H), 3.7−3.9 (m, 3.6H), 3.99 (s, 1.8H), 4.1 (m, 1H), 5.5 (d, 0.6H, J = 6.9 Hz), 5.6 (d, 0.3H, J = 6.9 Hz), 7.6−7.8 (m, 4H), 7.9 (d, 0.8H, J = 6.6 Hz), 8.0 (s, 0.6H), 8.4 (s, 0.25H), 8.5 (s, 0.8H), 8.6 (d, 0.8H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 34.3, 34.6, 35.8, 35.9, 40.3, 41.6, 53.0, 53.2, 60.3, 60.9, 61.8, 64.3, 67.1, 67.5, 125.2, 119.3, 119.5, 123.1, 126.3, 126.5, 126.7, 127.0, 127.6, 127.9, 129.0, 130.4, 131.0, 132.0, 132.5, 141.2, 142.3, 157.6; HRMS (FAB) calcd for $C_{22}H_{21}NO_3$ $[M + H]^+$ 348.159969, found 348.160400. Isomer **66** (22 mg, 40%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a single rotamer δ (ppm) 1.9−2.0 (m, 1H), 2.2−2.3 (m, 1H), 3.0−3.2 (m, 2H), 3.2−3.3 (m, 1H), 3.9 (m, 2.3H), 4.5 (m, 1H), 6.0 (d, 1H, J = 4.9 Hz), 7.45 (d, 1H, J = 8.0 Hz), 7.5−7.8 (m, 5H), 7.9 (m, 1H), 8.9 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 31.2, 36.9, 36.3, 47.4, 51.6, 63.2, 68.3, 70.7, 123.9, 125.8, 126.6, 126.7, 128.1, 128.3, 128.8, 130.7, 132.2, 133.7, 138.1, 145.4; HRMS (FAB) calcd for $C_{22}H_{21}NO_3$ $[M + H]^+$ 348.159969, found 348.159300.

(2*S*,4*R*)-4-Biphenyl-4-ylmethyl-5-oxo-pyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (67). By using the general procedure described above, compound **67** was obtained,

after column chromatography (hexanes/ethyl acetate, 60/40), as a white solid (65%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.05−2.2 (m, 2H), 2.75 (dd, 1H, J = 9.6, 14.5 Hz), 2.95−3.05 (m, 1H), 3.3 (dd, 1H, J = 14.5, 4.8 Hz), 3.75 (s, 3H), 3.9 (s, 3H), 4.6 (d, 1H, J = 9.6), 7.25 (d, 2H, J = 9.6), 7.3−7.4 (m, 1H), 7.45 (dd, 2H, J = 5.3 Hz, 7.2 Hz), 7.55 (dd, 4H, J = 8.4 Hz, 16.9 Hz); HRMS (TOF EI) calcd for $C_{21}H_{21}NO_5$ [M] 367.141973, found 367.141169.

(2*S*,3a*S*,8a*R*)-5-Phenyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid Dimethyl Ester (68). By using the general procedure described above, target compound was obtained, after column chromatography (hexanes/ethyl acetate, 70/30), as white foam (35%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers δ (ppm) 1.9−2.0 (m, 1H), 2.1−2.15 (m, 1H), 2.9 (d, 1H, J = 13.8 Hz), 3.1−3.2 (m, 2H), 3.7−3.8 (m, 4.5H), 3.9 (s, 1.5 H), 4.2 (dd, 1H, J = 10.3 Hz, 22.1 Hz), 5.5 (d, 0.5H, J = 10.3 Hz), 5.6 (d, 0.5H, J = 10.3 Hz), 7.3−7.6 (m, 8H), 7.7 (s, 0.5H), 8.0 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 35, 35.3, 36.3, 40.1, 41.4, 52.8, 53.2, 60.9, 61.1, 64.9, 67.4, 68.1, 125.2, 126, 126.3, 127.47, 125,52, 127.7, 127.8, 129.1, 129.2; HRMS (FAB) calcd for $C_{21}H_{21}NO_4$ $[M + H]^+$ 352.153541, found 352.1542.

(2*S*,3a*S*,8a*R*)-5-Phenyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-2,3-dicarboxylic Acid 3-Methyl Ester (69). By using the general procedure described above, the target compound was obtained from the corresponding methyl ester as a yellow oil (79%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 1/1 of rotamers: δ (ppm) 1.87−2.0 (m, 1H), 2.35−2.4 (m, 1H), 2.75 (dd, 1H, J = 2,3 Hz, 14.6 Hz), 3.11−3.24 (m, 2H), 3.75 (s, 1.5H), 3.9 (s, 1.5H), 4.40 (dd, 1H, J = 8.9 Hz, 20.0 Hz), 5.5 (d, 0.5H, J = 7.6 Hz) 5.61 (d, 0.5H, J = 7.6 Hz), 7.3−7.6 (m, 8H), 7.7 (s, 0.5H), 8.0 (s, 0.5H).

(2*S*,3a*S*,8a*R*)-2-Hydroxymethyl-5-phenyl-1,3a,8,8a-tetrahydro-2*H*-3-azacyclopenta[*a*]indene-3-carboxylic Acid Methyl Ester (70). By using the general procedure described for compound **18**, the target compound was obtained, after filtration through silica pad (hexanes/ethyl acetate, 30/70) (total yield 98%): ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture approximately 3/1 of rotamers δ (ppm) 1.7−1.8 (m, 1H), 1.9−2.0 (m, 1H), 2.8 (d, 1H, J = 11.5 Hz), 3.1−3.2 (m, 2H), 3.7−3.9 (m, 5.8H), 4.0−4.2 (m, 1H), 5.4 (d, 0.75H, J = 6.9 Hz), 5.5 (d, 0.25H, J = 6.9 Hz), 7.2−7.6 (m, 7H), 7.7 (s, 0.75H), 8.2 (s, 0.25H); HRMS (FAB) calcd for $C_{20}H_{219}NO_3$ $[M + H]^+$ 324.158626, found 324.158700.

(2*S*,3a*S*,8a*R*)-(5-Phenyl-1,2,3,3a,8,8a-hexahydro-3-azacyclopenta[*a*]inden-2-yl)methanol (71). By using the general procedure described for compound **19**, the target compound was obtained, after column chromatography (dichloromethane/methanol/ammonium hydroxide, 85/15/0.7) (total yield 90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.55−1.65 (m, 1H), 1.95−2.0 (m, 1H), 2.75−2.8 (dd, 1H, J = 16,7 Hz, 2.9 Hz), 3.1−3.3 (m, 3H), 3.45 (dd, 1H, J = 10.8 Hz, 6.5 Hz), 3.6 (dd, 1H, J = 10,8 Hz, 3.9 Hz), 4.8 (d, 1H, J = 7.3 Hz), 7.3 (d, 1H, J = 10.5 Hz), 7.2−7.6 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 36.8, 39.1, 42.2, 59.5, 64.2, 68.5, 123.7, 125.5, 127.4, 127.5, 129.2, 140.8, 141.6, 142.7, 145.7.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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