Synthesis of Methoxy and Hydroxy Analogues of 1,2,3,4,4a,9a-Hexahydro-4a-fluorenamine: Rigid Phencyclidine Analogues as Probes of Phencyclidine Binding Site Topography

Yuan-Ping Pang and Alan P. Kozikowski*

Neurochemistry Research, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, Florida 32224

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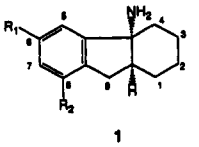
(+)-1,2,3,4,4a,9a-Hexahydro-4a-fluorenamine (HFA) was found to be a potent and selective ligand for the phencyclidine (PCP) binding site of the *N*-methyl-D-aspartate (NMDA) receptor. This conformationally rigid PCP analogue has provided information about the binding conformation of PCP and the topography of its binding site. To further probe the topography of the PCP binding site, methods were developed for the synthesis of six oxygenated analogues of HFA that serve as probes of the putative hydrogen bonding interaction between the ligands and this binding site. This chemistry involves the Diels–Alder reaction of an appropriately substituted methyl indene-3-carboxylate with butadiene. Synthetic routes to all possible monomethoxylated derivatives of indene-3-carboxylate were thus devised and are detailed herein. An alternative method was developed to generate the homoenolate equivalent of 1-indanone, and a *tert*-butyl ester was demonstrated to act as a masked acid equivalent in the Friedel–Crafts acylation reaction.

We reported previously the discovery of a rigid phencyclidine (PCP) analogue of high binding affinity for the PCP binding site of the *N*-methyl-D-aspartate (NMDA) receptor.[1] This rigid PCP analogue, (+)-1,2,3,4,4a,9a-hexahydro-4a-fluorenamine (HFA), was found to be a potent noncompetitive NMDA antagonist.[2] Further structural manipulations of this analogue may lead to useful probes of receptor topography that can provide further information about the nature of hydrogen bonding interaction between the ligand and the receptor. Accordingly, we have designed six new analogues of 1,2,3,4,4a,9a-hexahydro-4a-fluorenamine, compounds **1a–1f**. These compounds contain hydroxy or methoxy groups situated at one or both "meta" positions (relative to the cyclohexyl substituent) of the aromatic ring. Selection of the meta position as the site of substitution was governed by the observation that *m*-OH-PCP (*m*-hydroxyphencyclidine) as well as *m*-MeO-PCP bind with higher affinity to the PCP site than PCP itself while other hydroxylated derivatives bind with lower affinity.[3,4] Such observations indicate the presence of a possible hydrogen bond donor group in the neighborhood of the meta substituent within the PCP recognition site (Figure 1). In this article, we report synthetic routes for the preparation of six new oxygenated analogues of HFA. Since both enantiomers of these compounds were required for our biological studies, the syntheses disclosed herein are of the racemic materials. Classical methods of chemical resolution would be resorted to in the event that one or more of the racemates exhibited high binding affinity.



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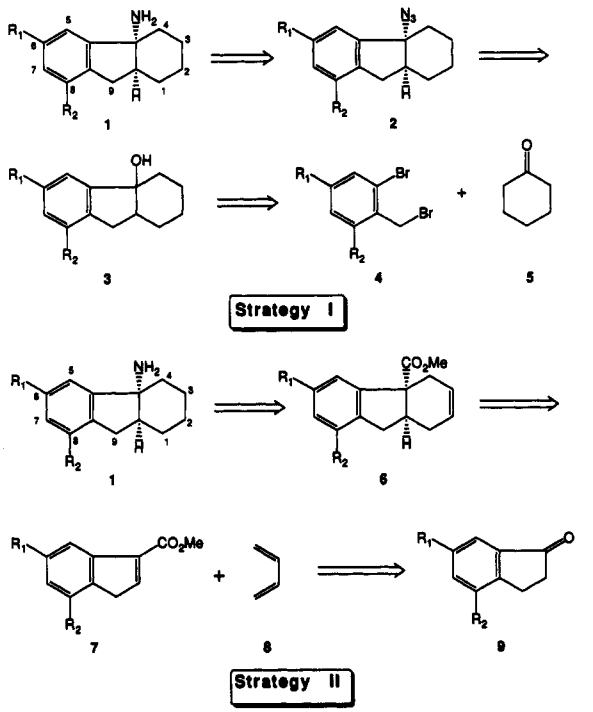
a: R_1 = OMe, R_2 = H;
b: R_1 = H, R_2 = OMe;
c: R_1 = OMe, R_2 = OMe;
d: R_1 = OH, R_2 = H;
e: R_1 = H, R_2 = OH;
f: R_1 = OH, R_2 = OH.

Scheme I. Retrosynthetic Analysis of 1a–1f



Synthetic Studies. To synthesize compounds **1a–1f**, our attention focused on methods for accomplishing the regioselective introduction of oxygen functionality into the aromatic ring of the hexahydrofluorenamine in addition to creation of its cis ring fusion stereochemistry. Two basic synthetic strategies were selected that are designated as strategy I and strategy II in Scheme I. The first of these strategies involved the possibility of alkylating cyclohexanone with an *o*-bromobenzyl bromide **4** followed by intramolecular carbon–carbon bond formation to deliver the hydroxyfluorene **3**. Replacement of the hydroxyl group of **3** by an amino group might in turn be accomplished through trapping of the derived carbocation by azide anion followed by a reduction step. Strategy II would proceed from the indanone **9** via the indenecarboxylic acid methyl ester **7** to the fluorene derivative **6** by use of Diels–Alder cycloaddition chemistry. As in our earlier synthetic work,[5]

(1) Kozikowski, A. P.; Pang, Y.-P. *Mol. Pharmacol.* **1990**, *37*, 352.
(2) Pang, Y.-P.; Wroblewski, J. T.; Kozikowski, A. P. *Soc. Neurosci. Abstr.* **1990**, *20*, 356.16.
(3) Manallack, D. T.; Wong, M. G.; Costa, M.; Andrews, P. R.; Bert, P. M. *Mol. Pharmacol.* **1988**, *34*, 863.
(4) Kamenka, M. M.; Chiche, B.; Goudal, R.; Geneste, P.; Vignon, J.; Vincent, J. P.; Lazdunski, M. *J. Med. Chem.* **1982**, *25*, 431.
(5) (a) Kozikowski, A. P.; Pang, Y.-P. *Synlett* **1990**, *1*, 58. (b) Godefroi, E. K.; Simanyi, L. H. *J. Org. Chem.* **1963**, *28*, 1112.

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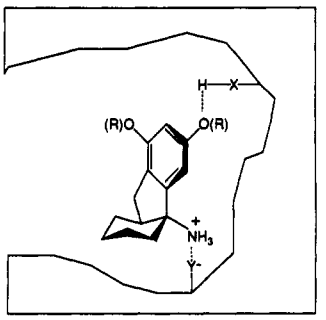
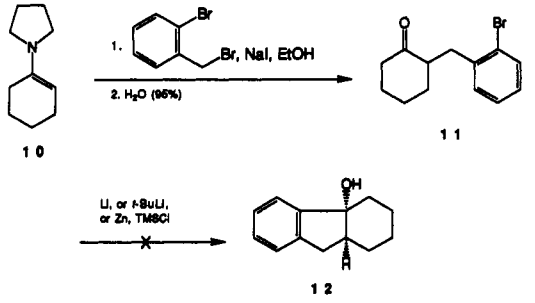
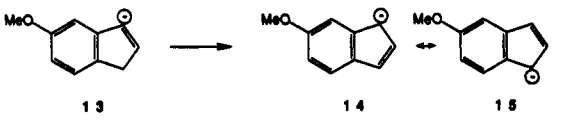


Figure 1. Illustration of possible hydrogen bonding interactions between the PCP binding site and oxygenated HFA.

Scheme II



Scheme III



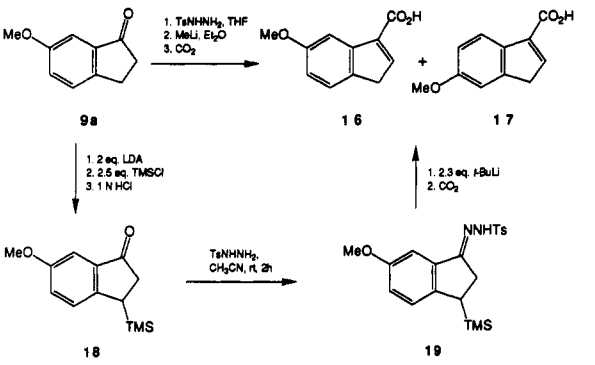
the ester group of 6 would be transformed to amine by Hofmann rearrangement.

In the onset of our work, model studies were conducted to test the feasibility of strategy I. 2-(*o*-Bromobenzyl)-cyclohexanone (11) was thus prepared in order to examine the formation of 12 by way of an anion- or radical-induced ring closure. Reaction of the pyrrolidine enamine of cyclohexanone with *o*-bromobenzyl bromide in the presence of sodium iodide gave compound 11 in 95% yield upon hydrolysis (Scheme II).[6] Unfortunately, although 11 was subjected to the Barbier reaction,[7a] to halogen–metal exchange conditions, and to Zn/TMSCl/2,6-lutidine treatment,[7b] none of these procedures led to formation of the desired hydroxyfluorene derivative 12.

Consequently, our attention turned to strategy II. This strategy hinged upon our ability to procure the appropriately substituted indanone derivative 9 as well as to transform such derivatives to the corresponding indene-3-carboxylic acid methyl esters 7.

In a preliminary study, we investigated the consequences of transforming 6-methoxy-1-indanone to the desired product 16 via the Shapiro reaction (Scheme IV). While the vinyl carbanion intermediate 13 (Scheme III) was expected to result upon treating the tosylhydrazone of 9a with methyllithium, several mechanistic possibilities exist for the transformation of 13 to the aromatic system 14. Trapping of this resonance-stabilized anion would lead in turn to the desired 5-methoxy isomer 16 or the undesired 6-methoxy isomer 17 via resonance structure 15. Although formation of 14/15 was anticipated, we envisioned that the

Scheme IV



methoxy group might direct the regiochemical course of electrophile introduction by its electronic effects. Unfortunately, the desired 5-methoxy isomer 16 was found to be contaminated with an equal part of the 6-methoxy isomer 17. This mixture of acids could not be separated by conventional means. By running the Shapiro reaction at −78 °C and trapping with CO_2 at the same temperature, we hoped to enhance the directing effect of the methoxy substituent. In this case, a 1.4:1 mixture of 16 and 17 was produced. The result, while better, was still unsatisfactory.

With an eye toward blocking carboxylation of the undesired benzylic position, we conceived of the idea of introducing one or two bulky trimethylsilyl (TMS) groups at this site. The monosilylated product 18 was formed in 88% yield by treating 6-methoxy-1-indanone (9a) first with 2 equiv of LDA and then with 2.5 equiv of TMSCl in THF followed by quenching with 1 N HCl. The disilylated product could be prepared in a similar fashion by use of 3 equiv of LDA and 3.5 equiv of TMSCl; however, the yield was quite low.

Interestingly, when we examined the conversion of 18 to its corresponding hydrazone 19, we observed that use of identical reaction conditions as employed in the preparation of the hydrazone of 9a led to the production of only a small amount of 19 (Scheme III). Apparently, the TMS group is capable of attenuating the electrophilic character of the ketone carbonyl. The partial positive charge character of the carbonyl carbon is stabilized by the β-effect of silicon ($(p\text{-}\sigma)_\pi$ conjugation) operating through the aromatic nucleus.[8] Use of the more polar solvent acetonitrile in place of THF allowed us, however, to obtain the desired hydrazone 19 in 90% yield (Scheme IV). With the desired hydrazone in hand, the Shapiro reaction was carried out using *t*-BuLi as base in order to avoid nucleophilic attack at the silicon center. Unfortunately, a 1.0:1.4 mixture of 16 and 17, respectively, was isolated. This result indicates that $(p\text{-}d)_\pi$ back-bonding to silicon, which consequently stabilizes the isomer with an anion located at the undesired benzylic position, may override the steric hindrance exerted by the TMS group.

While several other approaches to 16 were examined including carboxylation of an enol triflate intermediate,[9,10] as well as cyanohydrin formation and subsequent dehydration,[11] we eventually turned to an *umpolung* method using 2-lithio-1,3-dithiane (Scheme V). In early efforts, difficulties were encountered during attempts to dethioacetalize the dithiane addition product 20.[12] Despite

(6) This represents a significant improvement in yield over the literature procedure[5b] and avoids a difficult separation of dialkylated product.

(7) (a) Pearce, P. J.; Richards, D. H.; Scilly, N. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1655. (b) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.

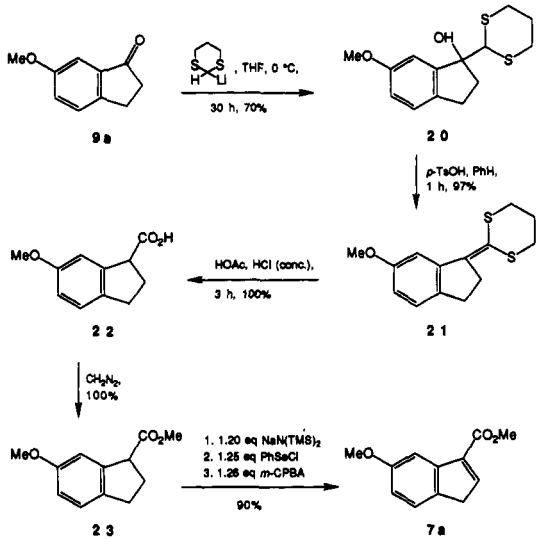
(8) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley: London, 1977; p 81.

(9) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

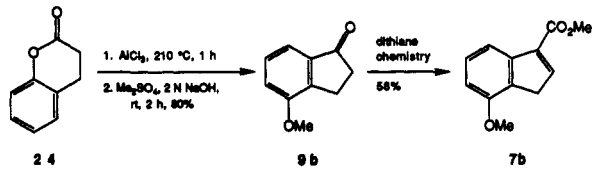
(10) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.

(11) Oda, M.; Yamamuro, A.; Watabe, T. *Chem. Lett.* **1979**, 1427.

Scheme V



Scheme VI



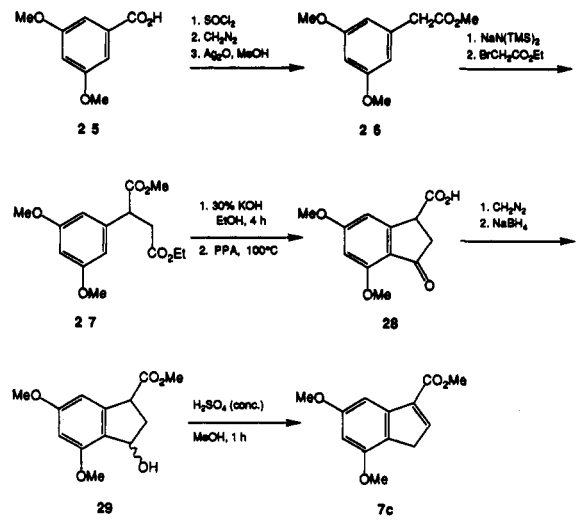
extensive efforts, this reaction could be accomplished in only a low yield. Accordingly, we first dehydrated the dithiane addition product to obtain the ketene dithioacetal **21**. Next, this intermediate was hydrolyzed by HOAc/HCl treatment to generate the desired indan-1-carboxylic acid **22**. After esterification by diazomethane, a selenylation/selenoxide elimination sequence provided the desired methyl indene-3-carboxylate **7a**. The best conditions for conducting this latter reaction consisted of deprotonating **23** with 1.2 equiv of sodium hexamethyldisilazide, then treating the anion with 1.25 equiv of PhSeCl followed by oxidation of the selenide using 1.26 equiv of *m*-CPBA. The overall yield for introduction of the unsaturation was 90% (Scheme V).

While this route to **7a** may appear lengthy, the sequence is in fact operationally simple to execute. The entire sequence from **9a** to **7a** can be carried out without rigorously purifying any of the reaction intermediates until the last step. At the carboxylic acid stage any accumulated impurities can be removed easily by filtration over a short silica gel column by elution first with methylene chloride and then with ethyl acetate. The overall yield from **9a** to **7a** is 61%.

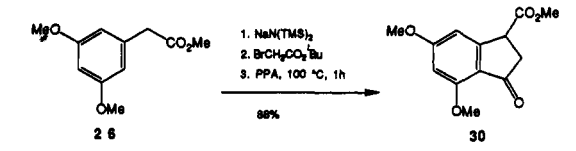
To employ a similar strategy for the preparation of compounds **1b**, **1c**, **1e**, and **1f**, access to the appropriately functionalized indanones was required. In the case of 4-methoxy-1-indanone, slight modification of a literature procedure involving the Lewis acid catalyzed rearrangement of dihydrocoumarin **24** provided **9b** in 80% yield.[13] Application of the foregoing dithiane chemistry to **9b** provided the indene ester **7b** in a satisfactory yield (Scheme VI).

Unexpectedly, attempts to obtain 4,6-dimethoxy-1-indanone (**9c**) through chemistry involving the dinitration of indanone[14] or by cyclization of 7-methoxycoumarin, 7-methoxy-3,4-dihydrocoumarin, 3-(2,4-dimethoxyphenyl)propionic acid, or 2,4-dimethoxycinnamic acid proved fruitless.

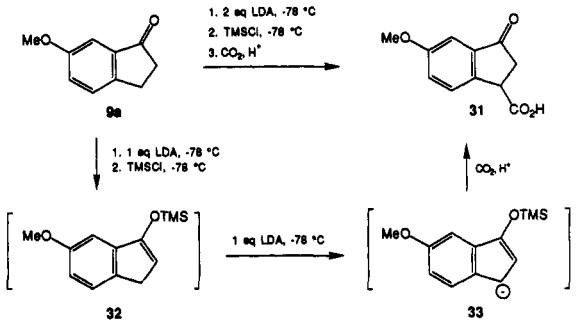
Scheme VII



Scheme VIII



Scheme IX



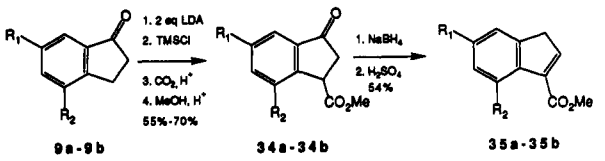
Alternatively, a somewhat lengthier route (Scheme VII) starting from 3,5-dimethoxybenzoic acid was found successful. An intramolecular Friedel–Crafts reaction served to create the indanone ring system with the ketone carbonyl group serving for introduction of the required degree of unsaturation.

To further abbreviate the synthesis of **7c**, methyl 3,5-dimethoxyphenylacetate (**26**) was alkylated with *tert*-butyl bromoacetate and the resulting crude diester was cyclized directly with PPA in an excellent yield as shown in Scheme VIII. The success of this cyclization protocol demonstrates the use of the *tert*-butyl ester as a masked acid equivalent in the Friedel–Crafts acylation reaction. Reduction of the ketone carbonyl of **30** and dehydration by sulfuric acid led to **7c** in a satisfactory overall yield.

In order to devise a synthetic route to all possible monomethoxylated derivatives of indene-3-carboxylic acid ester, we investigated the possibility of transforming 6-methoxy-1-indanone to methyl 6-methoxyindene-3-carboxylate (**35a**) via β-carboxylation of the homoenolate equivalent of **9a**. It is known from the literature that 2 equiv of LDA fail to generate the dianion of 6-methoxy-

(12) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.
(13) Kelly, T. R.; Bell, S. H.; Ohashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 6471.
(14) Olah, G. A.; Kuhn, S. J. *Org. Synth.* **1967**, *47*, 56.

Scheme X



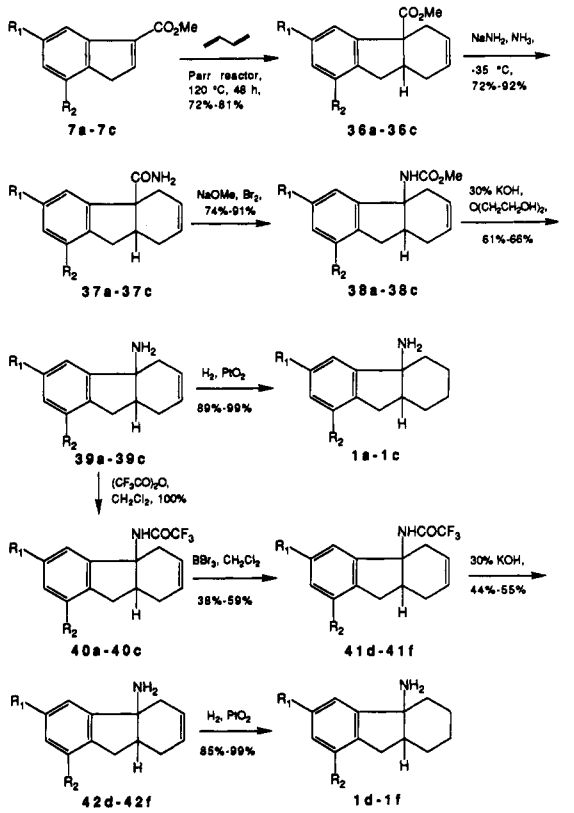
1-indanone at −78 °C because the benzylic proton is not acidic enough. To generate the dianion as a homoenolate equivalent, a solution of the ketone and 2.5 equiv of LDA must be warmed slowly to 0 °C and then stirred at that temperature for another 4 h.[15] Since we found the literature procedure to be somewhat inconvenient, an alternative method to generate the homoenolate equivalent was developed that is based upon an observation made during the synthesis of silylated compound **18**. Quite simply, the pK_a of the benzylic proton can be reduced by converting the indanone **9a** to the indene **32** (Scheme IX). After the addition of 2 equiv of LDA to **9a**, only 1 equiv of LDA is consumed to generate the enolate anion, the other equivalent of LDA remains unreacted. At this stage the color of the solution is green-yellow. Upon addition of TMSCl in the second step, the enolate anion is converted to the enol silyl ether **32**. At this stage, the benzylic proton is acidic enough to be deprotonated by the remaining equivalent of LDA to generate the homoenolate equivalent **33**. The color of the solution consequently changes to deep red, indicating the formation of the indene anion. Trapping the homoenolate equivalent with carbon dioxide affords the β-carboxylation product **31**. In this reaction, several carboxylating reagents ($BrCO_2Et$, $(MeO)_2CO$, and CO_2) were examined in order to optimize the yield. Maximum yields were obtained by use of CO_2.

The chemistry developed in the context of this work can be used to access any of the monomethoxylated indenecarboxylic acids. While application of the dithiane chemistry to **9a** and **9b** provides access to **7a** and **7b** (Schemes V and VI), the homoenolate equivalent chemistry described previously involving deprotonation of the enol silyl ether of **9a** and **9b** followed by carboxylation, esterification, reduction, and dehydration leads to **35a** and **35b** (Scheme X).

With all required indene-3-carboxylic acid methyl esters in hand, we could now examine their conversion to fluorenamines. The Diels–Alder cycloaddition with butadiene was carried out as described previously[5] to provide solely the cis-fused tetrahydrofluorenes **36** (Scheme XI). Attempts at the conversion of the ester group to amide by reaction with NH_4OH in diethylene glycol at high temperatures were complicated by the incursion of the retro-Diels–Alder reaction. While one may consider reducing the double bond prior to amide formation, we believed this choice to be inappropriate. It may well prove advantageous to retain the double bond until the very end of the synthesis where it could be used either for purposes of incorporating a radiolabel (e.g., catalytic tritiation) for binding studies or, perhaps, electrophilic alkylating groups capable of irreversible labeling of the recognition sites. Fortunately, we found that reaction of **36** with sodium amide in liquid ammonia led to the desired amides **37** in ~80% yield. The conversion of the amides to amines **39** proceeded along lines reported previously.[5]

To effect cleavage of the methoxy group to the free alcohol, BBr_3 was found to be the reagent of choice. The use of dilute reaction concentrations and low temperatures

Scheme XI



(−20 to −10 °C) were required, for higher concentrations and temperatures led to considerable product decomposition. To adequately isolate the water-soluble demethylation products, trifluoroacetylation of the amine nitrogen prior to O-demethylation proved advantageous. The final hexahydrofluorenamines were generated by catalytic hydrogenation over platinum oxide. A representative reaction sequence is illustrated in Scheme XI.

In summary, the Diels–Alder reaction of 1,3-butadiene with a functionalized indene-3-carboxylic acid methyl ester provides a useful route to hydroxy- and methoxy-substituted 1,2,3,4,4a,9a-hexahydro-4a-fluorenamines. The biological testing of these newly synthesized oxygenated fluorenamines reveals that (±)-6-MeO-HFA (**1a**) and (±)-6-OH-HFA (**1d**) exhibit binding affinities for the PCP site of the NMDA receptor complex that are comparable to that of (±)-HFA. The (±)-8-substituted and (±)-6,8-disubstituted HFA's (**1b**, **1c**, **1e**, and **1f**) exhibit poorer binding affinities than (±)-HFA. These results provide important information as to the possibility of a hydrogen bonding interaction between the ligands and the PCP binding site. A detailed description of these binding experiments together with the results of molecular modeling studies will be reported separately.[16]

Experimental Section

THF and Et_2O were distilled from sodium benzophenone ketyl prior to use. Benzene and toluene were distilled from CaH_2 prior to use. CH_2Cl_2 was dried by passage through a column of activity I neutral alumina and stored over 4-Å molecular sieves. Solvents used for chromatography were purchased in 5-gal drums, redistilled in an all-glass apparatus, and stored in glass bottles. Silica gel 60 (Merck, 70–230 mesh ASTM, or 230–400 mesh ASTM for flash chromatography) was used for column chromatography. TLC was performed on Merck silica gel 60F-254 (0.25 mm, precoated on glass). Other reagents were used as supplied by the

(15) Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1977**, *42*, 3212.

(16) Kozikowski, A. P.; Pang, Y.-P. *Mol. Pharmacol.*, submitted for publication.

Aldrich Chemical Co. or the Sigma Chemical Co. or purified as noted. Melting points were determined in open capillary tubes and are uncorrected.

6-Methoxyindan-1-carboxylic Acid Methyl Ester (23). To a solution of 11.73 g (97.6 mmol) of 1,3-dithiane in 138 mL of THF under N_2 was added dropwise 74.4 mL (91.5 mmol) of *n*-BuLi (1.2 M in hexane) at −30 °C. The solution was allowed to warm to −15 °C and stirred at this temperature for 2 h. A solution of 9.9 g (61.0 mmol) of 6-methoxy-1-indanone in 336 mL of THF was added dropwise at −15 °C. The resulting solution was allowed to warm to 0 °C and stirred at this temperature for 30 h. The solvent was removed under reduced pressure, and the residue was diluted with 5% HCl and extracted with Et_2O. The ethereal extracts were washed successively with 5% aqueous HCl, H_2O, and saturated aqueous NaCl. Concentration of the extract under reduced pressure gave rise to the crude dithiane **20** as a yellow solid: R_f = 0.21 (30% EtOAc in hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, J = 8.3 Hz, 1 H), 7.01 (d, J = 2.3 Hz, 1 H), 6.86 (dd, J = 2.6, 8.3 Hz, 1 H), 4.58 (s, 1 H), 3.81 (s, 3 H), 3.00–2.70 (m, 8 H), 2.21–2.00 (m, 2 H), 1.95–1.75 (m, 1 H). A solution of crude **20** (24.2 g) and 2.4 g of $TsOH·H_2O$ in 15 mL of benzene under N_2 was refluxed in a flask equipped with a Dean-Stark apparatus for 1 h. The solution was washed successively with H_2O, saturated aqueous Na_2CO_3, and saturated aqueous NaCl and dried over $MgSO_4$. Concentration under reduced pressure afforded 23.8 g of crude **21** as a yellow oil: R_f = 0.57 (30% EtOAc in hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, J = 2.5 Hz, 1 H), 7.12 (d, J = 8.2 Hz, 1 H), 6.74 (dd, J = 2.6 Hz, 8.3 Hz, 1 H), 3.82 (s, 3 H), 3.08–2.80 (m, 8 H), 2.27–2.15 (m, 2 H). A mixture of crude **21** (23.8 g), 320 mL of glacial HOAc, and 107 mL of concentrated HCl was refluxed for 3 h. The mixture was concentrated under reduced pressure. Several portions of toluene were added to the residue, and the mixture was concentrated after each addition. The residue was then taken up in H_2O and extracted with CH_2Cl_2. The extract was washed successively with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. The concentrated extract was partially purified by passage through a short column of silica gel, first eluting with CH_2Cl_2 to remove the nonpolar impurities and then with EtOAc to give the partially purified acid **22** as brown crystals together with a small amount of highly polar impurities: R_f = 0.32 (50% EtOAc in hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14 (d, J = 8.3 Hz, 1 H), 6.98 (d, J = 2.0 Hz, 1 H), 6.79 (dd, J = 2.4, 8.3 Hz, 1 H), 4.05 (t, J = 6.7 Hz, 1 H), 3.79 (s, 3 H), 3.09–2.96 (m, 1 H), 2.91–2.80 (m, 1 H), 2.51–2.28 (m, 2 H). To an ice-cooled solution of 7.7 g (40.06 mmol) of the previous acid **22** in 400 mL of EtOAc in an Erlenmeyer flask covered with an empty balloon was added dropwise 160 mL of an ethereal solution of CH_2N_2 prepared from 16.5 g of *N*-nitroso-*N*-methylurea and 48 mL of 40% aqueous KOH. (*Caution! CH_2N_2 is toxic and explosive. The operation must be carried out in a good hood with an adequate shield. Ground glass joints and sharp surfaces should be avoided.*) After the addition was complete, the resulting solution was stirred gently at rt for 0.5 h, and N_2 gas was bubbled through the reaction mixture to remove the excess CH_2N_2. Concentration under reduced pressure and column chromatography on silica gel, eluting with 10% EtOAc in hexane, afforded 8.16 g (65% based on 6-methoxy-1-indanone) of the ester **23** as a yellow oil: R_f = 0.39 (20% EtOAc in hexane); IR (neat) ν 3447, 2988, 2949, 2905, 2826, 1724, 1595, 1576, 1480, 1429, 1321, 1271, 1227, 1182, 1165, 1132, 1086, 1020, 806, 727 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, J = 8.3 Hz, 1 H), 6.92 (d, J = 2.3 Hz, 1 H), 6.77 (dd, J = 2.6, 8.3 Hz, 1 H), 4.03 (t, J = 6.8 Hz, 1 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 3.08–2.98 (m, 1 H), 2.89–2.79 (m, 1 H), 2.48–2.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 174.3, 158.8, 142.1, 136.1, 125.1, 113.7, 110.2, 55.5, 52.0, 50.3, 30.9, 29.3; MS (70 eV) m/z 206 (M^+), 147, 131, 115, 103, 91; HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0943.

5-Methoxyindene-3-carboxylic Acid Methyl Ester (7a). To a solution of 11.6 mL (11.6 mmol) of $NaN(TMS)_2$ (1.0 M in THF) in 67 mL of THF under N_2 was added dropwise at −78 °C a solution of 2.0 g (9.7 mmol) of the ester **23** in 12.5 mL of THF. After the addition was completed, the solution was stirred at −78 °C for 1 h. A solution of 2.3 g (12.1 mmol) of PhSeCl in 6.2 mL of THF was then added. The resulting solution was stirred at −78 °C for 10 min and was then allowed to warm to rt over a period of 2 h. It was poured into saturated aqueous NH_4Cl and extracted with EtOAc. (The emulsion was broken up by adding a small amount of H_2O.) The extract was washed successively with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl and dried over $MgSO_4$. Evaporation under reduced pressure gave 4.1 g of the crude selenylated product. To a solution of 4.1 g of this product in 32 mL of THF under Ar was added a solution of 2.5 g (12.2 mmol) of *m*-CPBA (83%) in 7.8 mL of THF at −78 °C. The resulting solution was stirred at −78 °C for 1 h and then warmed to rt. The solution was then taken up in H_2O and extracted with EtOAc. The extracts were washed successively with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. Flash column chromatography on silica gel (the solid extract was dissolved in a minimum amount of CH_2Cl_2, which was applied onto the silica gel column), eluting with 10% EtOAc in hexane afforded 1.48 g (75%) of **7a** as an orange-red oil: R_f = 0.43 (20% EtOAc in hexane); IR (neat) ν 3069, 2992, 2949, 2901, 2830, 1713, 1603, 1557, 1464, 1427, 1377, 1356, 1314, 1279, 1242, 1219, 1186, 1136, 1092, 1036, 961, 883, 802, 739, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.64 (d, J = 2.5 Hz, 1 H), 7.48 (t, J = 1.9 Hz, 1 H), 7.35 (d, J = 8.2 Hz, 1 H), 6.84 (dd, J = 2.5, 8.3 Hz, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.47 (d, J = 1.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 164.1, 158.8, 145.7, 141.9, 135.5, 135.2, 123.9, 112.0, 107.2, 55.2, 51.2, 37.5; MS (70 eV) m/z 204 (M^+), 189, 172, 145, 130, 115, 102, 76, 63, 51; HRMS calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0786.

6-Methoxy-1,4,4a,9a-tetrahydro-4a-fluorenecarboxylic Acid Methyl Ester (36a). A solution of 1.5 g (7.3 mmol) of the dienophile **7a** and 8 mL (63.8 mmol) of liquified 1,3-butadiene in 4 mL of toluene containing 80 mg of 4-*tert*-butylcatechol was stirred in a 125-mL Parr pressure reactor at 120 °C for 48 h. After being cooled, the solution was taken up in H_2O and extracted with EtOAc. The extracts were washed successively with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. Flash column chromatography on silica gel using 10% EtOAc in hexane as eluent gave rise to 1.5 g (80%) of the adduct **36a** as a yellowish oil: R_f = 0.32 (20% EtOAc in hexane); IR ($CHCl_3$) ν 3434, 3019, 2986, 2947, 2897, 2828, 1723, 1605, 1574, 1480, 1420, 1321, 1275, 1215, 1196, 1144, 1045, 1024, 855, 804, 675, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, J = 8.2 Hz, 1 H), 6.83 (d, J = 2.1 Hz, 1 H), 6.73 (dd, J = 2.1, 8.2 Hz, 1 H), 5.83–5.70 (m, 2 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.18–3.08 (m, 1 H), 3.00 (dd, J = 7.6, 14.8 Hz, 1 H), 2.85–2.78 (m, 1 H), 2.59 (dd, J = 9.5, 14.7 Hz, 1 H), 2.49–2.41 (m, 1 H), 2.09–2.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 175.2, 158.7, 148.8, 134.0, 126.0, 125.5, 125.3, 112.6, 108.7, 55.5, 55.3, 52.1, 41.0, 36.8, 31.2, 26.6; MS (70 eV) m/z 258 (M^+), 226, 204, 184, 171, 145, 115, 102, 77, 51; HRMS calcd for $C_{16}H_{18}O_3$ 258.1256, found 258.1255.

6-Methoxy-1,4,4a,9a-tetrahydro-4a-fluorenecarboxylic Acid Amide (37a). To a stirred solution of $NaNH_2$, prepared *in situ from* 500 mg (21.7 mmol) of Na metal and 30 mL of liquid NH_3 in the presence of 50 mg of anhydrous $FeCl_3$, was added a solution of 1.0 g of the ester **36a** (3.9 mmol) in 40 mL of THF at −40 to −35 °C under Ar. After being stirred for 40 min, the reaction was quenched with powdered NH_4Cl and the NH_3 was allowed to evaporate. H_2O was added to the residue, and the mixture was extracted with EtOAc. The extract was washed with saturated aqueous NH_4Cl, dried with $MgSO_4$, and concentrated under reduced pressure to afford the crude amide. Column chromatography on silica gel using 80% EtOAc in hexane as eluent gave rise to 870 mg (92%) of the amide **37a** as a yellowish oil: R_f = 0.48 (EtOAc); IR (neat) ν 3466, 3337, 3179, 3023, 2930, 2901, 2832, 1659, 1597, 1568, 1480, 1269, 1221, 1142, 1020, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15 (d, J = 8.2 Hz, 1 H), 6.81 (d, J = 2.4 Hz, 1 H), 6.76 (dd, J = 2.4, 8.2 Hz, 1 H), 5.88–5.72 (m, 2 H), 5.70–5.45 (m, 2 H), 3.79 (s, 3 H), 3.01 (dd, J = 6.9, 14.7 Hz, 1 H), 2.90–2.74 (m, 2 H), 2.58 (dd, J = 6.7, 14.8 Hz, 1 H), 2.45–2.30 (m, 1 H), 2.24–2.10 (m, 1 H), 2.04–1.85 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 179.0, 158.8, 148.5, 134.5, 125.8, 125.6, 125.5, 113.0, 108.8, 56.3, 55.2, 43.0, 36.8, 30.4, 26.8; MS (70 eV) m/z 243 (M^+), 199, 184, 158, 128, 121, 115, 102, 91, 77, 65; HRMS calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1259.

6-Methoxy-1,4,4a,9a-tetrahydro-4a-fluorenylcarbamic Acid Methyl Ester (38a). To a sodium methoxide solution, freshly prepared from 44 mg (1.9 mmol) of Na in 1.6 mL of dry MeOH, was added a solution of 100 mg (0.41 mmol) of the amide **37a** in 0.40 mL of MeOH at rt under Ar. The mixture was then cooled to −20 °C, at which stage 12 μL (2.9 mmol) of Br_2 was added

dropwise at that temperature. Upon completion, the solution was allowed to warm to rt and then refluxed for 1.5 h at which time HOAc (74 μL) was added at 0 °C. The solution was concentrated under reduced pressure, and the residue was extracted with ethyl ether. The organic phase was washed successively with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. Immediate column chromatography on silica gel using 30% EtOAc in hexane as eluent afforded 100 mg (89%) of the carbamate **35a** as white crystals: mp 132–133 °C; R_f = 0.64 (50% EtOAc in hexane); IR ($CHCl_3$) ν 3333, 3017, 2936, 2901, 2820, 1719, 1707, 1603, 1510, 1483, 1445, 1418, 1319, 1278, 1244, 1221, 1184, 1040, 1020, 855, 797, 766, 654 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, J = 8.2 Hz, 1 H), 6.82 (s, 1 H), 6.73 (dd, J = 2.3, 8.2 Hz, 1 H), 5.81–5.67 (m, 2 H), 4.91 (s, 1 H), 3.78 (s, 3 H), 3.60 (s, 3 H), 3.20–3.05 (m, 1 H), 2.99 (dd, J = 7.4, 14.6 Hz, 1 H), 2.52–2.32 (m, 3 H), 2.31–2.22 (m, 1 H), 2.10–2.01 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 158.7, 155.1, 149.7, 132.8, 126.4, 125.7, 123.8, 112.7, 107.4, 62.8, 55.2, 51.4, 41.4, 35.7, 33.3, 26.3; MS (70 eV) m/z 273 (M^+), 219, 198, 187, 160, 145; HRMS calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1365.

6-Methoxy-1,4,4a,9a-tetrahydro-4a-fluorenamine (39a). A suspension of 100 mg (0.37 mmol) of the carbamate **38a** and 5.2 mL of 30% aqueous KOH in 1.1 mL of diethylene glycol under N_2 was stirred at 100 °C for 48 h. After being cooled, the reaction mixture was extracted with ethyl ether. The extracts were concentrated under reduced pressure, and the residue was added to 100 mL of 5% HCl. The aqueous solution was washed with CH_2Cl_2, and the pH of the aqueous solution was adjusted to 12 with 5 N NaOH. This solution was extracted with CH_2Cl_2, and the extracts were concentrated to afford 50 mg (63%) of the amine **39a** as a colorless oil: R_f = 0.52 (5% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR (neat) ν 3360, 3295, 3017, 2922, 2897, 2828, 1607, 1476, 1420, 1321, 1267, 1221, 1208, 1152, 1067, 1017, 853, 806, 644 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, J = 8.1 Hz, 1 H), 6.88 (d, J = 2.3 Hz, 1 H), 6.72 (dd, J = 2.4, 8.2 Hz, 1 H), 5.85–5.70 (m, 2 H), 3.81 (s, 3 H), 2.87 (dd, J = 7.2, 14.7 Hz, 1 H), 2.55–2.44 (m, 2 H), 2.31–2.10 (m, 4 H), 1.56 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 158.9, 154.2, 132.8, 125.7, 125.2, 125.0, 112.6, 106.8, 60.3, 55.5, 48.1, 35.8, 35.4, 25.5; MS (70 eV) m/z 215 (M^+), 199, 186, 174, 161, 146, 130, 118, 103, 91, 77, 65, 61, 51, 43; HRMS calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1310.

6-Methoxy-1,2,3,4,4a,9a-hexahydro-4a-fluorenamine (1a). A solution of 13 mg (0.06 mmol) of the amine **39a** in 500 μL of dry EtOH was stirred with 0.3 mg of PtO_2 under H_2 (1 atm) at rt for 2.5 h. Filtration and flash column chromatography on silica gel half-saturated with NH_3 using 5% MeOH in $CHCl_3$ as eluent gave rise to 13 mg (99%) of the amine **1a** as white crystals:[17] R_f = 0.32 (5% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR ($CHCl_3$) ν 3360, 3291, 3292, 2918, 2843, 1603, 1572, 1472, 1451, 1443, 1316, 1263, 1215, 1194, 1024, 839, 787 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, J = 8.0 Hz, 1 H), 6.79 (d, J = 2.3 Hz, 1 H), 6.72 (dd, J = 2.4, 8.1 Hz, 1 H), 3.80 (s, 3 H), 2.86 (dd, J = 7.1, 15.1 Hz, 1 H), 2.58 (dd, J = 7.7, 15.1 Hz, 1 H), 2.17–2.10 (m, 1 H), 1.85–1.30 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 158.9, 153.1, 133.4, 126.0, 112.6, 107.1, 61.9, 55.5, 49.4, 35.7, 33.9, 26.4, 22.5, 22.0; MS (70 eV) m/z 217 (M^+), 174, 160, 146, 130, 119, 99, 84, 69, 55; HRMS calcd for $C_{14}H_{19}NO$ 217.1467, found 217.1467.

6-Methoxy-*N*-(trifluoroacetyl)-1,4,4a,9a-tetrahydro-4a-fluorenamine (40a). To a solution of 30 mg (0.14 mmol) of methoxyfluorenamine **39a** in 160 μL of dry CH_2Cl_2 in the presence of 23 μL of Et_3N under Ar was added dropwise 29 μL of $(CF_3C(O))_2O$ at 0 °C. The resulting solution was warmed to rt and stirred at this temperature for 3 h. The solution was then taken up in H_2O and extracted with EtOAc. The extracts were washed with 5% HCl and dried over $MgSO_4$. Column chromatography on silica gel employing 10% EtOAc in hexane as eluent afforded 43 mg (100%) of the amide **40a** as white crystals: mp 82–83 °C; R_f = 0.59 (30% EtOAc in hexane); IR ($CHCl_3$) ν 3420, 3310, 3023, 2936, 2903, 2832, 1711, 1701, 1609, 1539, 1483, 1316, 1273, 1192, 1175, 1146, 1018, 804, 646 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.15 (d, J = 8.9 Hz, 1 H), 6.82–6.72 (m, 2 H), 6.31 (s, 1 H), 5.90–5.65 (m, 2 H), 3.79 (s, 3 H), 3.20–3.14 (m, 1 H), 3.07 (dd, J = 7.4, 15.0 Hz, 1 H), 2.75–2.65 (m, 1 H), 2.52 (dd, J = 7.5, 15.0 Hz, 1 H), 2.45–2.30 (m, 2 H), 2.10–2.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 159.1, 156.2 (q, J = 36 Hz), 147.2, 133.4, 127.3, 126.3, 123,4, 115.6 (q, J = 289 Hz), 113.8, 107.6, 65.2, 55.5, 41.3, 36.3, 32.4, 27.0; MS (70 eV) m/z 311 (M^+), 278, 270, 257, 242, 198, 183, 160, 59; HRMS calcd for $C_{16}H_{16}NO_2F_3$ 311.1133, found 311.1133.

6-Hydroxy-*N*-(trifluoroacetyl)-1,4,4a,9a-tetrahydro-4a-fluorenamine (41d). A solution of 47 mg of the previous trifluoroacetamide **40a** in 1.7 mL of dry CH_2Cl_2 under Ar was slowly added to a precooled solution of 0.33 mL of BBr_3 (99.99%) in 5.3 mL of dry CH_2Cl_2 at −30 °C. The resulting solution was slowly warmed to −12 °C and stirred at this temperature in the dark for 6 h. The reaction was quenched by adding ice, and the product was extracted with EtOAc. The extracts were washed successively with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. Flash column chromatography on silica gel with 20% EtOAc in hexane as eluent afforded 21 mg (47%) of **41d** as white crystals: R_f = 0.36 (30% EtOAc in hexane); IR ($CHCl_3$) ν 3391, 3293, 3098, 3029, 2932, 2841, 1688, 1642, 1613, 1545, 1480, 1441, 1333, 1200, 1180, 1146, 841, 812, 739 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 6.94 (d, J = 8.0 Hz, 1 H), 6.58 (d, J = 2.1 Hz, 1 H), 6.54 (dd, J = 2.2, 7.9 Hz, 1 H), 5.75–5.60 (m, 2 H), 3.16–3.05 (m, 1 H), 2.90 (dd, J = 7.5, 14.8 Hz, 1 H), 2.65–2.55 (m, 1 H), 2.45–2.25 (m, 2 H), 2.24–2.14 (m, 1 H), 2.05–1.95 (m, 1 H); ^{13}C NMR (CD_3OD, 125.76 MHz) δ 158.2 (q, J = 36 Hz), 157.4, 149.6, 133.1, 127.0, 126.9, 125.2, 117.2 (q, J = 288 Hz), 115.6, 109.8, 65.9, 42.2, 36.8, 33.4, 27.2, 21.6; MS (70 eV) m/z 297 (M^+), 266, 256, 243, 184, 165, 146, 131, 115, 91, 77, 58; HRMS calcd for $C_{15}H_{14}NO_2F_3$ 297.0977, found 297.0977.

6-Hydroxy-1,4,4a,9a-tetrahydro-4a-fluorenamine (42d). To a solution of 56 mg (0.19 mmol) of the previous trifluoroacetamide **41d** in 5.0 mL of MeOH under Ar was added dropwise 7.0 mL of aqueous 30% KOH at 0 °C. The resulting solution was stirred at rt for 2 h. The reaction mixture was quenched by adding 390 mL of saturated aqueous $NaHCO_3$. The product was extracted with one 250-mL portion and five 50-mL portions of EtOAc. Evaporation of the combined organic extracts and flash column chromatography on silica gel half-saturated with NH_3 using 15% MeOH in $CHCl_3$ as eluent gave rise to 36 mg (44%) of the unsaturated amine **42d** as white crystals: R_f = 0.25 (10% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR (CH_3OH) ν 3318, 3302, 3258, 3017, 2920, 2895, 2834, 1601, 1570, 1445, 1368, 1343, 1281, 1250, 1209, 1173, 1020, 858, 800 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 6.90 (d, J = 8.0 Hz, 1 H), 6.68 (d, J = 2.3 Hz, 1 H), 6.50 (dd, J = 2.3, 8.0 Hz, 1 H), 5.7–5.6 (m, 2 H), 2.81 (dd, J = 7.0, 14.5 Hz, 1 H), 2.44–2.20 (m, 3 H), 2.10–1.90 (m, 3 H); ^{13}C NMR (CD_3OD, 125.76 MHz, 35 °C) δ 157.5, 154.0, 133.0, 126.8, 126.6, 125.8, 115.1, 109.6, 61.7, 47.9, 37.1, 36.2, 27.1; MS (70 eV) m/z 201 (M^+), 184, 172, 165, 159, 147, 130, 55; HRMS calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1540.

6-Hydroxy-1,2,3,4,4a,9a-hexahydro-4a-fluorenamine (1d). A solution of 12 mg (0.06 mmol) of the unsaturated amine **42d** in 4.0 mL of dry EtOH was stirred with 1.0 mg of PtO_2 under H_2 (1 atm) at rt for 2 h. Filtration and flash column chromatography on silica gel half-saturated with NH_3 using 15% MeOH in $CHCl_3$ as eluent afforded 12 mg (99%) of the hydroxy amine **1d** as white crystals:[17] R_f = 0.20 (10% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR (KBr) ν 3420, 3306, 3260, 3160, 2924, 2843, 2483, 1593, 1466, 1302, 1267, 1250, 1208, 1107, 1036, 853, 806 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 6.95 (d, J = 8.1 Hz, 1 H), 6.63 (d, J = 2.3 Hz, 1 H), 6.54 (dd, J = 2.3, 7.9 Hz, 1 H), 2.86 (dd, J = 6.7, 15.0 Hz, 1 H), 2.40 (dd, J = 5.9, 15.1 Hz, 1 H), 2.16–2.02 (m, 1 H), 1.88–1.65 (m, 2 H), 1.65–1.05 (m, 6 H); ^{13}C NMR (CD_3OD, 125.76 MHz) δ 157.5, 152.4, 133.7, 127.1, 115.3, 109.9, 63.1, 49.7, 36.2, 35.3, 28.3, 23.9, 23.1; MS (70 eV) m/z 203 (M^+), 186, 160, 146, 108, 95, 83, 68, 55; HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1310.

4-Methoxy-1-indanone (9b). A mixture of 58 g of $AlCl_3$, 12 g of NaCl, and 10 mL (78.9 mmol) of dihydrocoumarin was heated with mechanical stirring at 200–210 °C for 1 h. After the mixture was cooled, ice (100 g) and 50 mL of concentrated HCl were added simultaneously, and the resulting suspension was stirred for 20 min at rt. The black precipitate was collected by filtration through Celite and washed with 200 mL of H_2O. To 15 g of this black precipitate in 136 mL of 2 N NaOH was added dropwise 14 mL of Me_2SO_4. The suspension was stirred at rt for 4 h. The pre-

(17) Compounds **1a–1e** began to decompose before reaching their melting points.

cipitate was collected by filtration through Celite. Column chromatography on silica gel using 20% EtOAc in hexane as eluent gave 10.2 g (80%) of the indanone **9b** as yellow needles: mp 104–105 °C; R_f = 0.55 (50% EtOAc in hexane); IR (KBr) ν 3000, 2961, 2924, 2839, 1699, 1597, 1478, 1427, 1391, 1287, 1254, 1231, 1069, 1024, 899, 779, 677, 640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.34 (m, 2 H), 7.06–7.01 (m, 1 H), 3.91 (s, 3 H), 3.06–3.03 (m, 2 H), 2.71–2.67 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 207.1, 157.0, 144.0, 138.5, 128.8, 115.2, 114.7, 55.4, 36.1, 22.4; MS (70 eV) m/z 162 (M^+), 134, 119, 104, 91, 77, 65, 51; HRMS calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0682.

4-Methoxyindan-1-carboxylic Acid Methyl Ester (23′). The same procedure as employed in the preparation of **23** was followed to afford 7.6 g (60%) of the title ester **23′** as a yellowish oil: R_f = 0.30 (10% EtOAc in hexane); IR (neat) ν 3447, 2998, 2940, 2899, 2828, 1724, 1580, 1470, 1425, 1321, 1263, 1244, 1194, 1161, 1065, 1017, 972, 758, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17 (t, J = 7.7 Hz, 1 H), 6.98 (d, J = 7.6 Hz, 1 H), 6.73 (d, J = 8.1 Hz, 1 H), 4.07 (t, J = 7.5 Hz, 1 H), 3.83 (s, 3 H), 3.72 (s, 3 H), 3.10–3.00 (m, 1 H), 2.91–2.80 (m, 1 H), 2.48–2.31 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 174.4, 156.1, 142.6, 132.0, 128.0, 117.0, 109.0, 55.2, 52.0, 50.6, 28.5; MS (70 eV), m/z 206 (M^+), 147, 115, 103, 91; HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0943.

7-Methoxyindene-3-carboxylic Acid Methyl Ester (7b). The same procedure as employed in the preparation of **7a** was followed to afford 1.90 g (96%) of the ester **7b** as white crystals: mp 65–66 °C; R_f = 0.43 (20% EtOAc in hexane); IR ($CHCl_3$) ν 3011, 2969, 2947, 2903, 2828, 1709, 1603, 1586, 1559, 1468, 1451, 1431, 1368, 1258, 1202, 1146, 1026, 930, 810, 768, 727, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, J = 7.7 Hz, 1 H), 7.46 (t, J = 1.9 Hz, 1 H), 7.35 (t, J = 8.0 Hz, 1 H), 6.80 (d, J = 8.2 Hz, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.47 (d, J = 1.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 164.5, 155.1, 144.8, 142.3, 136.0, 130.4, 128.4, 115.4, 107.7, 55.1, 51.5, 35.9; MS (70 eV) m/z 204 (M^+), 189, 172, 157, 145, 129, 115, 102, 76, 63, 59, 51, 43; HRMS calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0757.

8-Methoxy-1,4,4a,9a-tetrahydro-4a-fluorenecarboxylic Acid Methyl Ester (36b). The same procedure as employed in the preparation of **36a** was followed to afford 1.66 g (72%) of the ester **36b** as white crystals: mp 49–51 °C; R_f = 0.45 (20% EtOAc in hexane); IR (KBr) ν 3023, 2990, 2945, 2926, 2895, 2832, 1723, 1595, 1580, 1476, 1451, 1424, 1260, 1184, 1047, 775, 735, 656 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16 (t, J = 7.8 Hz, 1 H), 6.88 (d, J = 7.6 Hz, 1 H), 6.72 (d, J = 8.1 Hz, 1 H), 5.85–5.70 (m, 2 H), 3.82 (s, 3 H), 3.71 (s, 3 H), 3.19–3.06 (m, 2 H), 2.90–2.80 (m, 1 H), 2.64–2.40 (m, 2 H), 2.20–2.00 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 175.3, 156.1, 149.1, 129.7, 128.0, 126.2, 125.6, 115.1, 108.9, 56.1, 55.0, 52.1, 40.6, 34.3, 31.3, 26.9. MS (70 eV) m/z 258 (M^+), 217, 199, 184, 172, 158, 145, 115, 102, 91, 77, 59, 51; HRMS calcd for $C_{16}H_{18}O_3$ 258.1256, found 258.1246.

8-Methoxy-1,4,4a,9a-tetrahydro-4a-fluorenecarboxylic Acid Amide (37b). The same procedure as employed in the preparation of **37a** was followed to afford 120 mg (72%) of the amide **37b**: R_f = 0.70 (EtOAc); IR ($CHCl_3$) ν 3464, 3330, 3181, 3023, 2925, 2896, 2824, 1665, 1576, 1466, 1426, 1360, 1260, 1098, 1063, 1044, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (t, J = 7.9 Hz, 1 H), 6.86 (d, J = 7.5 Hz, 1 H), 6.73 (d, J = 8.1 Hz, 1 H), 6.09 (s, 1 H), 5.87–5.74 (m, 2 H), 5.51 (s, 1 H), 3.82 (s, 3 H), 3.05 (dd, J = 7.2, 15.7 Hz, 1 H), 2.90–2.70 (m, 2 H), 2.57 (dd, J = 6.3, 15.7 Hz, 1 H), 2.42–2.30 (m, 1 H), 2.25–2.16 (m, 1 H), 2.00–1.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 179.1, 156.5, 148.9, 130.8, 128.7, 126.1, 126.0, 115.7, 109.3, 57.3, 55.3, 43.0, 34.7, 30.8, 27.5; MS (70 eV) m/z 243 (M^+), 199, 184, 171, 158, 146, 115, 84, 69, 49; HRMS calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1259.

8-Methoxy-1,4,4a,9a-tetrahydro-4a-fluorenylcarbamic Acid Methyl Ester (38b). The same procedure as employed in the preparation of **38a** was followed to afford 100 mg (74%) of compound **38b** as a colorless oil: R_f = 0.63 (30% EtOAc in hexane); IR ($CHCl_3$) ν 3339, 3021, 2942, 2901, 2834, 1703, 1584, 1508, 1470, 1267, 1246, 1179, 1042, 766 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (t, J = 7.7 Hz, 1 H), 6.89 (d, J = 7.5 Hz, 1 H), 6.72 (d, J = 8.1 Hz, 1 H), 5.82–5.68 (m, 2 H), 4.98 (s, 1 H), 3.82 (s, 3 H), 3.59 (s, 3 H), 3.15–3.05 (m, 2 H), 2.50–2.38 (m, 3 H), 2.34–2.27 (m, 1 H), 2.12–2.05 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 156.2, 155.3, 150.0, 128.8, 128.1, 127.0, 124.2, 114.1, 109.1, 63.6, 55.2, 51.6, 41.2, 33.8, 33.5, 26.8; MS (70 eV) m/z 273 (M^+), 258, 241, 232, 219, 198, 187, 160, 115, 91; HRMS calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1365.

8-Methoxy-1,4,4a,9a-tetrahydro-4a-fluorenamine (39b). The same procedure as employed in preparation of **39a** was followed to afford 52 mg (66%) of the amine **39b** as a colorless oil: R_f = 0.50 (10% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR ($CHCl_3$) ν 3355, 3272, 3019, 2929, 2892, 2830, 1580, 1468, 1430, 1299, 1248, 1057, 1044, 866, 776, 712, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (t, J = 7.8 Hz, 1 H), 6.94 (d, J = 7.5 Hz, 1 H), 6.71 (d, J = 8.1 Hz, 1 H), 5.85–5.70 (m, 2 H), 3.82 (s, 3 H), 3.02 (dd, J = 7.2, 15.3 Hz, 1 H), 2.60–2.35 (m, 2 H), 2.32–2.10 (m, 4 H), 1.84 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 156.1, 154.4, 128.3, 128.1, 125.4, 125.2, 113.8, 108.8, 60.9, 55.2, 47.1, 35.6, 33.1, 25.8; MS (70 eV) m/z 215 (M^+), 161, 146, 130, 117, 103, 91, 84, 77, 69, 58; HRMS calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1310.

8-Methoxy-1,2,3,4,4a,9a-hexahydro-4a-fluorenamine (1b). A solution of 13 mg (0.06 mmol) of the tetrahydrofluorenamine **39b** in 500 μL of dry ethanol was stirred with 0.3 mg of PtO_2 under H_2 (1 atm) at rt for 40 min. Filtration and evaporation gave the fluorenamine **1b** in quantitative yield as white crystals:[17] R_f = 0.66 (10% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR ($CHCl_3$) ν 3361, 3280, 2988, 2919, 2846, 1596, 1582, 1470, 1434, 1254, 1069, 1054, 764, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (t, J = 7.8 Hz, 1 H), 6.86 (d, J = 7.4 Hz, 1 H), 6.72 (d, J = 8.1 Hz, 1 H), 3.83 (s, 3 H), 2.93 (dd, J = 7.1, 15.7 Hz, 1 H), 2.56 (dd, J = 7.4, 15.7 Hz, 1 H), 2.18–2.10 (m, 1 H), 1.89–1.20 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 156.6, 153.6, 128.8, 128.1, 113.9, 108.8, 62.2, 55.3, 48.5, 35.9, 31.3, 26.6, 22.6, 22.0; MS (70 eV) m/z 217 (M^+), 174, 160, 146, 84, 69; HRMS calcd for $C_{14}H_{19}NO$ 217.1467, found 217.1467.

8-Methoxy-*N*-(trifluoroacetyl)-1,4,4a,9a-tetrahydro-4a-fluorenamine (40b). The same procedure as employed in the preparation of **40a** was followed to afford 194 mg (100%) of the amide **40b** as a yellowish oil: R_f = 0.41 (20% EtOAc in hexane); IR ($CHCl_3$) ν 3424, 3312, 3073, 3025, 2934, 2898, 2834, 1704, 1592, 1542, 1472, 1432, 1293, 1264, 1252, 1198, 1173, 1148, 1046, 884, 766, 708, 658 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (t, J = 7.7 Hz, 1 H), 6.86 (d, J = 7.5 Hz, 1 H), 6.77 (d, J = 8.1 Hz, 1 H), 6.31 (s, 1 H), 5.90–5.65 (m, 2 H), 3.83 (s, 3 H), 3.19–3.11 (m, 2 H), 2.75–2.65 (m, 1 H), 2.55–2.40 (m, 3 H), 2.11–2.04 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 156.5, 156.2 (q, J = 37 Hz), 147.5, 129.5, 128.7, 127.7, 123.8, 115.6 (q, J = 289 Hz), 114.0, 109.9, 66.0, 55.3, 41.0, 34.1, 32.7, 27.3; MS (70 eV) m/z 311 (M^+), 278, 257, 242, 198, 183, 160, 115, 59; HRMS calcd for $C_{16}H_{16}NO_2F_3$ 311.1133, found 311.1133.

8-Hydroxy-*N*-(trifluoroacetyl)-1,4,4a,9a-tetrahydro-4a-fluorenamine (41e). The same procedure as employed in the preparation of **41d** was followed to afford 18 mg (38%) of the hydroxy amide **41e** as white crystals: R_f = 0.30 (30% EtOAc in hexane); IR ($CHCl_3$) ν 3391, 3310, 3094, 3032, 2926, 2903, 2839, 1701, 1584, 1549, 1458, 1290, 1265, 1206, 1175, 1152, 909, 772, 708 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 6.92 (t, J = 7.7 Hz, 1 H), 6.61 (d, J = 7.4 Hz, 1 H), 6.54 (d, J = 7.7 Hz, 1 H), 5.75–5.58 (m, 2 H), 3.15–3.05 (m, 1 H), 2.99 (dd, J = 7.7, 15.1 Hz, 1 H), 2.62–2.50 (m, 1 H), 2.40–2.29 (m, 2 H), 2.25–2.15 (m, 1 H), 2.03–1.95 (m, 1 H); ^{13}C NMR (CD_3OD, 75.46 MHz) δ 158.2 (q, J = 37 Hz), 155.0, 150.2, 129.0, 128.3, 127.2, 125.5, 117.2 (q, J = 288 Hz) 115.1, 114.1, 66.4, 41.7, 34.3, 33.7, 27.5; MS (70 eV) m/z 297 (M^+), 264, 256, 243, 184, 165, 146, 130, 115, 102, 91, 77, 69, 55; HRMS calcd for $C_{15}H_{14}NO_2F_3$ 297.0977, found 297.0977.

8-Hydroxy-1,4,4a,9a-tetrahydro-4a-fluorenamine (42e). The same procedure as employed in the preparation of **42d** was followed to afford 7 mg (55%) of the unsaturated amine **42e** as white crystals: R_f = 0.29 (10% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR ($CHCl_3$) ν 3324, 3266, 3179, 3025, 2925, 2915, 2848, 1717, 1582, 1457, 1364, 1301, 1260, 1200, 1148, 778 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 6.91 (t, J = 7.7 Hz, 1 H), 6.72 (d, J = 7.4 Hz, 1 H), 6.49 (d, J = 7.9 Hz, 1 H), 5.75–5.58 (m, 2 H), 2.90 (dd, J = 6.1, 14.0 Hz, 1 H), 2.45–2.15 (m, 3 H), 2.10–1.95 (m, 3 H); ^{13}C NMR (CD_3OD, 125.76 MHz) δ 154.9, 154.5, 129.0, 127.8, 126.9, 126.1, 114.9, 113.8, 62.0, 47.1, 36.3, 34.3, 27.2; MS (70 eV) m/z 201 (M^+), 184, 172, 167, 160, 147, 130, 69, 57; HRMS calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1154.

8-Hydroxy-1,2,3,4,4a,9a-hexahydro-4a-fluorenamine (1e). A solution of 7 mg (0.035 mmol) of the unsaturated amine **42e** in 500 μL of dry ethanol was stirred with 0.2 mg of Pt_2O under

H_2 (1 atm) at rt for 40 min. Filtration and flash chromatography on a short column of silica gel saturated with NH_3 using 15% MeOH in $CHCl_3$ as eluent afforded 6 mg (85%) of **1e** as white crystals:[17] R_f = 0.18 (10% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR ($CHCl_3$) ν 3337, 3270, 3042, 3013, 2921, 2844, 2657, 2589, 1578, 1465, 1374, 1270, 1067, 990, 926, 888, 770, 703 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 6.93 (t, J = 7.6 Hz, 1 H), 6.67 (d, J = 7.4 Hz, 1 H), 6.52 (d, J = 7.9 Hz, 1 H), 2.85 (dd, J = 6.9, 15.6 Hz, 1 H), 2.42 (dd, J = 6.1, 15.5 Hz, 1 H), 2.15–1.98 (m, 1 H), 1.86–1.64 (m, 2 H), 1.64–1.08 (m, 6 H); ^{13}C NMR (CD_3OD, 125.76 MHz) δ 155.6, 152.3, 129.0, 128.6, 115.1, 114.1, 63.5, 36.0, 32.5, 28.5, 23.9, 23.0; MS (70 eV) m/z 203 (M^+), 187, 160, 146; HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1310.

Methyl 3,5-Dimethoxyphenylacetate (26). To a suspension of 12.2 g (67.2 mmol) of 3,5-dimethoxybenzoic acid and one drop of pyridine in 108 mL of benzene under N_2 was added 9.7 mL (133.0 mmol) of freshly distilled $SOCl_2$. After the mixture was refluxed for 1 h, the clear yellow solution was concentrated under reduced pressure. The resulting acid chloride in 200 mL of ethyl ether was added dropwise with gentle stirring to a solution of CH_2N_2 (403.6 mmol) in 1 L of ethyl ether, prepared from 41.6 g of *N*-nitroso-*N*-methylurea and 75 mL of 40% aqueous KOH in an Erlenmeyer flask covered with an empty balloon. After addition was completed, the solution was stirred gently at rt for 1 h. N_2 gas was then bubbled through the reaction mixture to remove the excess CH_2N_2. Evaporation under reduced pressure gave 16 g of the diazo ketone as yellow crystals. A mixture of 72 mL of dry MeOH and 1.08 g of Ag_2O was refluxed under Ar for 5 min, after which time 16 g of the crude diazo ketone was added with evolution of N_2. The mixture was refluxed for 30 min, and an additional 0.54 g of Ag_2O was added. After a further 15 min at reflux, 0.27 g more of Ag_2O was added. After a total time of 1 h at reflux, the solution was filtered through Celite and concentrated under reduced pressure. Flash column chromatography on silica gel eluting with 30% EtOAc in hexane afforded 14.0 g (99%) of the ester **26** as a yellowish oil: R_f = 0.43 (30% EtOAc in hexane); IR (neat) ν 3455, 3001, 2951, 2837, 1734, 1591, 1449, 1420, 1323, 1306, 1279, 1247, 1190, 1146, 1053, 1003, 937, 824, 723, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.44 (d, J = 2.0 Hz, 2 H), 6.37 (t, J = 2.1 Hz, 1 H), 3.78 (s, 6 H), 3.70 (s, 3 H), 3.56 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 171.6, 160.7, 135.9, 107.1, 98.93, 55.0, 51.8, 41.1; MS (70 eV) m/z 210 (M^+), 165, 151, 121, 91, 77, 65; HRMS calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0892.

4,6-Dimethoxy-3-oxoindan-1-carboxylic Acid Methyl Ester (30). To a solution of 35.7 mL (35.7 mmol) of $NaN(TMS)_2$ (1.0 M in THF) in 25 mL of THF under N_2 was added dropwise 5.0 g (23.8 mmol) of **26** in 50 mL of THF at −78 °C. After the addition was complete, the solution was stirred at −78 °C for 20 min, and 6.55 mL (40.6 mmol) of *tert*-butyl bromoacetate was added. The resulting solution was stirred at −78 °C for 10 min and was then allowed to warm to rt over a period of 3 h. It was poured into saturated aqueous NH_4Cl and extracted with EtOAc (the emulsion was broken up by adding a small amount of water). The extracts were washed successively with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl and dried over $MgSO_4$. Evaporation under reduced pressure gave 11.4 g of the crude diester as a deep orange oil: R_f = 0.50 (30% EtOAc in hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.42 (d, J = 2.3 Hz, 2 H), 6.36 (m, 1 H), 3.95 (dd, J = 5.1, 10.4 Hz, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.68 (s, 3 H), 3.08 (dd, J = 10.4, 16.5 Hz, 1 H), 2.57 (dd, J = 5.0, 16.5 Hz, 1 H), 1.42 (s, 9 H). A mixture of 11.4 g of the crude diester and 100 g of PPA were heated with mechanical stirring at 100 °C for 1 h, during which time the color of the mixture changed to dark red. The reaction mixture was quenched with ice and extracted with EtOAc. The extracts were washed successively with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. Column chromatography on silica gel using 80% EtOAc in hexane as eluent afforded 5.24 g (88%) of the keto ester **30** as yellowish crystals: mp 124–125 °C; R_f = 0.50 (EtOAc); IR (KBr) ν 3013, 2984, 2951, 2928, 2836, 1726, 1688, 1589, 1516, 1464, 1427, 1346, 1321, 1232, 1200, 1175, 1150, 1071, 1040, 1013, 978, 947, 862, 833, 804, 735, 696, 646 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.67 (m, 1 H), 6.38 (d, J = 1.9 Hz, 1 H), 4.15 (dd, J = 3.7, 8.2 Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.77 (s, 3 H), 3.06 (dd, J = 3.8, 18.6 Hz, 1 H), 2.83 (dd, J = 8.2, 18.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 199.9, 172.0, 166.9, 159.1, 155.6, 118.2, 101.6, 98.3, 55.7 (2 C), 52.4, 43.1, 39.9; MS (70 eV) m/z 250 (M^+), 235, 221, 191, 161, 148, 133, 118, 105, 89, 77, 69, 61, 51; HRMS calcd for $C_{13}H_{14}O_5$ 250.0841, found 250.0841.

5,7-Dimethoxyindene-3-carboxylic Acid Methyl Ester (7c). To a stirred solution of 1.0 g (4.0 mmol) of the keto ester **30** in 6.6 mL of THF and 6.6 mL of MeOH was added 230 mg (6.0 mmol) of $NaBH_4$ (98%) portionwise over 5.5 h at rt. The mixture was stirred at rt for 0.5 h, diluted with H_2O, and extracted with $CHCl_3$ (3×). The combined extracts were washed with H_2O and dried over $MgSO_4$. Column chromatography on silica gel eluting with 60% EtOAc in hexane afforded 0.72 g (71%) of the hydroxy ester: R_f = 0.45 (60% EtOAc in hexane); ^1H NMR ($CDCl_3$, 300 MHz) of the major diastereomer: δ 6.46 (d, J = 1.4 Hz, 1 H), 6.36 (d, J = 1.7 Hz, 1 H), 5.30–5.22 (m, 1 H), 3.92 (dd, J = 2.7, 5.5 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 3.20 (d, J = 8.5 Hz, 1 H), 2.60–2.48 (m, 1 H), 2.35–2.25 (m, 1 H). To a solution of 1.6 g of the hydroxy ester in 260 mL of MeOH under Ar was added dropwise 0.4 mL of concentrated H_2SO_4. The resulting solution was refluxed for 40 min. The reaction was quenched with H_2O, and the product was extracted with CH_2Cl_2 (3×). The combined extracts were washed with H_2O and dried over $MgSO_4$. Flash chromatography on silica gel eluting with 20% EtOAc in hexane afforded 0.82 g (55%) of **7c** as white crystals: mp 117–118 °C; R_f = 0.50 (30% EtOAc in hexane); IR (KBr) ν 3088, 2988, 2940, 2834, 1707, 1595, 1561, 1462, 1447, 1427, 1344, 1275, 1236, 1196, 1138, 1094, 1026, 961, 924, 847, 826, 760, 729, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47 (t, J = 1.8 Hz, 1 H), 7.28 (d, J = 2.0 Hz, 1 H), 6.42 (d, J = 1.9 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.42 (d, J = 2.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 164.4, 160.7, 155.3, 145.6, 142.6, 135.5, 122.9, 98.9, 96.6, 55.5, 55.0, 51.4, 35.3; MS (70 eV) m/z 234 (M^+), 219, 202, 175, 145, 132, 117, 102, 89; HRMS calcd for $C_{13}H_{14}O_4$ 234.0892, found 234.0892.

6,8-Dimethoxy-1,4,4a,9a-tetrahydro-4a-fluorenecarboxylic Acid Methyl Ester (36c). A solution of 2.0 g (8.5 mmol) of **7c** and 9 mL (71.8 mmol) of liquified 1,3-butadiene in 8.6 mL of toluene containing 100 mg of *tert*-butylcatechol was stirred in a 125-mL Parr pressure reactor at 120 °C for 48 h. The solution was then taken up in H_2O and saturated aqueous NaCl and dried over $MgSO_4$. Column chromatography on silica gel using 10% EtOAc in hexane as eluent gave 2.0 g (81%) of the adduct **36c** as a yellowish oil: R_f = 0.39 (20% EtOAc in hexane); IR (neat) ν 3021, 2996, 2947, 2897, 2832, 1717, 1591, 1483, 1447, 1427, 1327, 1298, 1267, 1196, 1134, 1024, 926, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.44 (d, J = 1.7 Hz, 1 H), 6.32 (d, J = 1.8 Hz, 1 H), 5.85–5.70 (m, 2 H), 3.79 (s, 6 H), 3.72 (s, 3 H), 3.18–2.96 (m, 2 H), 2.90–2.76 (m, 1 H), 2.52–2.40 (m, 2 H), 2.15–2.00 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 175.4, 160.4, 156.6, 149.6, 126.4, 125.5, 121.9, 99.4, 97.2, 56.3, 55.5, 55.2, 52.2, 40.8, 33.8, 31.3, 26.9; MS (70 eV) m/z 288 (M^+) 247, 234, 229, 214, 202, 188, 175, 165, 151, 141, 128, 115, 102, 91, 77, 69, 59; HRMS calcd for $C_{17}H_{20}O_4$ 288.1362, found 288.1353.

6,8-Dimethoxy-1,4,4a,9a-tetrahydro-4a-fluorenecarboxylic Acid Amide (37c). The same procedure as employed in the preparation of **37a** was followed to afford crude amide. Crystallization from EtOAc gave 600 mg of pure amide **37c**. The mother liquor was chromatographed on silica gel using 80% EtOAc in hexane as eluent to furnish an additional 160 mg of the amide **37c** as a yellowish oil (total: 760 mg, 80%): R_f = 0.46 (EtOAc); IR ($CHCl_3$) ν 3457, 3333, 3183, 3017, 2990, 2932, 2909, 2830, 1663, 1589, 1478, 1447, 1443, 1323, 1300, 1190, 1136, 1038, 924, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.40 (d, J = 1.9 Hz, 1 H), 6.33 (d, J = 2.0 Hz, 1 H), 5.88–5.77 (m, 2 H), 5.64 (s, 1 H), 5.54 (s, 1 H), 3.80 (s, 6 H), 2.99 (dd, J = 7.4, 15.2 Hz, 1 H), 2.88–2.78 (m, 2 H), 2.51 (dd, J = 6.1, 15.1 Hz, 1 H), 2.43–2.34 (m, 1 H), 2.21–2.15 (m, 1 H), 2.00–1.93 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 179.1, 160.7, 156.9, 149.3, 126.0, 125.9, 122.7, 99.6, 97.5, 57.3, 55.5, 55.1, 43.0, 34.0, 30.6, 27.4; MS (70 eV) m/z 273 (M^+), 229, 214, 188, 175, 151, 128, 115, 102, 91, 77, 69; HRMS calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1353.

6,8-Dimethoxy-1,4,4a,9a-tetrahydro-4a-fluorenylcarbamic Acid Methyl Ester (38c). To a sodium methoxide solution freshly prepared from 717 mg (31.2 mmol) of Na in 45 mL of dry MeOH was added 916 mg (3.35 mmol) of the previous amide **37c** at rt. An additional 30 mL of MeOH was then added at the same temperature. The mixture was warmed to 35 °C and stirred at that temperature until all of the amide was dissolved. The clear solution was then cooled to −20 °C, at which stage 240 μL (4.7

mmol) of Br_2 was added dropwise at −20 °C. The solution was allowed to warm to rt and was then refluxed for 1.5 h. HOAc (1.0 mL) was added to the ice-cooled solution. The mixture was concentrated under reduced pressure, and the residue was extracted with ethyl ether. The organic phase was washed successively with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. Immediate column chromatography on silica gel using 40% EtOAc in hexane as eluent afforded 925 mg (91%) of the carbamate **38c** as white crystals: R_f = 0.27 (30% EtOAc in hexane); IR ($CHCl_3$) ν 3341, 3019, 2992, 2938, 2907, 2832, 1721, 1703, 1593, 1499, 1483, 1451, 1424, 1325, 1306, 1250, 1219, 1194, 1134, 1038, 924, 920, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.43 (d, J = 1.4 Hz, 1 H), 6.30 (d, J = 2.0 Hz, 1 H), 5.85–5.65 (m, 2 H), 4.90 (s, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.60 (s, 3 H), 3.15–2.95 (m, 2 H), 2.55–2.20 (m, 4 H), 2.15–2.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 160.5, 156.7, 155.2, 150.6, 127.0, 124.0, 120.9, 98.2, 97.4, 63.7, 55.5, 55.2, 51.6, 41.3, 33.8, 32.9, 26.8; MS (70 eV) m/z 303 (M^+), 249, 234, 217, 202, 190, 175, 165, 153, 128, 115, 103, 91, 77, 69, 55; HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1473.

6,8-Dimethoxy-1,4,4a,9a-tetrahydro-4a-fluorenamine (39c). The same procedure as employed in preparation of **39a** was followed to afford 35 mg (61%) of the title amine **39c**: R_f = 0.54 (10% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR ($CHCl_3$) ν 3356, 3281, 3019, 2994, 2926, 2897, 2832, 1589, 1481, 1451, 1443, 1424, 1323, 1308, 1204, 1190, 1136, 1055, 1038, 922, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.51 (d, J = 2.0 Hz, 1 H), 6.29 (d, J = 2.0 Hz, 1 H), 5.85–5.65 (m, 2 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 2.92 (dd, J = 6.8, 14.5 Hz, 1 H), 2.55–2.40 (m, 1 H), 2.40–2.10 (m, 5 H), 1.81 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 160.6, 156.7, 154.8, 125.5, 125.0, 120.3, 97.8, 97.2, 61.0, 55.6, 55.3, 47.5, 35.5, 32.6, 25.8; MS (70 eV) m/z 245 (M^+), 228, 224, 216, 212, 204, 191, 176, 160, 105, 77, 69, 55; HRMS calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1397.

6,8-Dimethoxy-1,2,3,4,4a,9a-hexahydro-4a-fluorenamine (1c). A solution of 20 mg (0.08 mmol) of **39c** in 680 μL of dry EtOH was stirred with 0.4 mg of PtO_2 under H_2 (1 atm) at rt for 2 h. Filtration and flash column chromatography on silica gel half-saturated with NH_3 using 5% MeOH in $CHCl_3$ as eluent gave 18 mg (89%) of the saturated amine **1c** as white crystals:[17] R_f = 0.46 (10% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR ($CHCl_3$) ν 3360, 3289, 2988, 2920, 2847, 1591, 1481, 1451, 1443, 1427, 1343, 1327, 1296, 1194, 1134, 1072, 1038, 1007, 924, 818 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.42 (d, J = 1.7 Hz, 1 H), 6.31 (d, J = 1.7 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 2.84 (dd, J = 7.1, 15.3 Hz, 1 H), 2.49 (dd, J = 7.5, 15.3 Hz, 1 H), 2.16–2.05 (m, 1 H), 1.90–1.30 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 160.6, 157.1, 154.1, 120.8, 97.9, 97.1, 62.2, 55.6, 55.3, 48.9, 35.7, 30.6, 26.5, 22.5, 21.9; MS (70 eV) m/z 247 (M^+), 230, 204, 190, 176, 160, 146, 133, 115, 102, 91, 84, 77, 69, 55; HRMS calcd for $C_{15}H_{21}NO_2$ 247.1522, found 247.1522.

6,8-Dimethoxy-*N*-(trifluoroacetyl)-1,4,4a,9a-tetrahydro-4a-fluorenamine (40c). The same procedure as employed in the preparation of **40a** was followed to afford 52 mg (100%) of the trifluoroacetamide **40c** as white crystals: mp 149–150 °C; R_f = 0.46 (30% EtOAc in hexane); IR (KBr) ν 3324, 3038, 2945, 2915, 2841, 1713, 1615, 1591, 1543, 1483, 1425, 1308, 1188, 1171, 1154, 1011, 930, 818, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.39 (d, J = 1.8 Hz, 1 H), 6.35 (d, J = 1.9 Hz, 1 H), 6.26 (s, 1 H), 5.90–5.65 (m, 2 H), 3.80 (s, 6 H), 3.15–3.00 (m, 2 H), 2.75–2.65 (m, 1 H), 2.55–2.36 (m, 3 H), 2.12–2.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 160.9, 157.0, 156.1 (q, J = 36 Hz), 148.0, 127.6, 123.6, 121.6, 115.6 (q, J = 289 Hz), 98.1, 66.0, 55.6, 55.3, 41.1, 33.5, 32.5, 27.3; MS (70 eV) m/z 341 (M^+), 287, 228, 190, 115, 74; HRMS calcd for $C_{17}H_{18}NO_3F_3$ 341.1239, found 341.1253.

6,8-Dihydroxy-*N*-(trifluoroacetyl)-1,4,4a,9a-tetrahydro-4a-fluorenamine (41f). The same procedure as employed in preparation of **41d** was followed to afford 26 mg (59%) of the amide **41f** as white crystals: R_f = 0.34 (50% EtOAc in hexane); IR ($CHCl_3$) ν 3393, 3316, 3092, 3030, 2917, 2839, 1697, 1601, 1535, 1456, 1329, 1198, 1181, 1150, 986, 831, 750, 652 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 6.12 (s, 1 H), 6.07 (s, 1 H), 5.72–5.60 (m, 2 H), 3.14–3.05 (m, 1 H), 2.88 (dd, J = 7.7, 14.8 Hz, 1 H), 2.60–2.52 (m, 1 H), 2.38–2.20 (m, 2 H), 2.19–2.13 (m, 1 H), 2.03–1.95 (m, 1 H); ^{13}C NMR (CD_3OD, 125.76 MHz) δ 158.7, 158.2 (q, J = 36 Hz), 155.4, 151.0, 127.0, 125.3, 119.0, 117.2 (q, J = 288 Hz), 102.6, 101.4, 66.2, 41.8, 33.5 (2 C), 27.3; MS (70 eV) m/z 313 (M^+), 259, 200, 185, 162, 147, 128, 115, 91, 77, 69, 58; HRMS calcd for $C_{15}H_{14}NO_3F_3$ 313.0926, found 313.0926.

6,8-Dihydroxy-1,4,4a,9a-tetrahydro-4a-fluorenamine (42f). The same procedure as employed in the preparation of **42d** was followed to afford 32 mg (50%) of the unsaturated amine **42f** as white crystals: R_f = 0.29 (20% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR (CH_3OH) ν 3331, 3264, 3028, 2905, 2834, 2670, 2621, 1591, 1456, 1445, 1341, 1323, 1167, 1127, 1017, 986, 829 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 6.21 (s, 1 H), 6.02 (t, J = 1.1 Hz, 1 H), 5.70–5.55 (m, 2 H), 2.82 (dd, J = 11.0, 18.5 Hz, 1 H), 2.42–2.25 (m, 1 H), 2.25–2.12 (m, 2 H), 2.12–1.90 (m, 3 H); ^{13}C NMR (CD_3OD, 125.76 MHz) δ 159.0, 155.5, 153.5, 127.3, 125.6, 118.9, 102.6, 101.2, 62.6, 46.6, 35.6, 33.9, 27.4; MS (70 eV) m/z 217 (M^+), 200, 163, 146, 128, 115, 106, 99, 91, 84, 77, 69, 58, 51; HRMS calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1717.

6,8-Dihydroxy-1,2,3,4,4a,9a-hexahydro-4a-fluorenamine (1f). A solution of 7.0 mg (0.03 mmol) of the unsaturated amine **42f** in 400 μL of dry ethanol was stirred with 0.6 mg of Pt_2O under hydrogen (1 atm) at rt for 2 h. Filtration and flash column chromatography on silica gel saturated with NH_3 using 25% MeOH in $CHCl_3$ as eluent afforded 6.1 mg (86%) of the dihydroxy amine **1f** as a brownish oil: R_f = 0.23 (20% MeOH in $CHCl_3$, silica TLC saturated with NH_3); IR (25% MeOH in $CHCl_3$) ν 3328, 3258, 3158, 2926, 2849, 2594, 1591, 1452, 1344, 1166, 1120, 1004, 834, 749 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 6.18 (d, J = 1.8 Hz, 1 H), 6.09 (d, J = 1.8 Hz, 1 H), 2.80 (dd, J = 6.6, 15.2 Hz, 1 H), 2.33 (dd, J = 4.8, 15.3 Hz, 1 H), 2.16–2.04 (m, 1 H), 1.94–1.81 (m, 1 H), 1.80–1.66 (m, 1 H), 1.61–1.06 (m, 6 H); ^{13}C NMR (CD_3OD, 125.76 MHz) δ 159.0, 156.1, 152.5, 119.5, 102.8, 101.5, 63.6, 49.9, 35.7, 32.0, 28.7, 24.1, 23.1; MS (70 eV) m/z 219 (M^+), 202, 176, 162, 131, 123, 115, 105, 99, 95, 91, 84, 69, 65, 58, 53, 49; HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1259.

5-Methoxy-3-oxoindan-1-carboxylic Acid Methyl Ester (34a). To a solution of 254 μL of diisopropylamine (1.8 mmol) in 4.0 mL of THF under Ar was added 1.2 mL (1.7 mmol) of *n*-BuLi (1.47 M in hexane) at 0 °C. The resulting solution was stirred at 0 °C for 20 min and then cooled to −78 °C. A solution of 122 mg (0.76 mmol) of 6-methoxy-1-indanone in 1.5 mL of THF was added dropwise at −78 °C. After the addition was complete, the solution was stirred at −78 °C for 1 h, after which time 134 μL of TMSCl was added dropwise at −78 °C. The resulting solution was stirred at −78 °C for 1 h, whereupon it became deep red in color. The solution was then transferred onto 10 g of dry ice (CO_2) contained in an Erlenmeyer flask covered with an empty balloon. The mixture was shaken occasionally at rt for 2 h, after which time 5% HCl was added and the resulting keto acid was extracted with EtOAc. A solution of 200 mg of the crude keto acid in 30 mL of MeOH containing 5 drops of concentrated H_2SO_4 was refluxed under Ar for 2.5 h, after which time the solution was concentrated under reduced pressure. The keto ester was then extracted with EtOAc and washed with H_2O. Column chromatography on silica gel with 30% EtOAc in hexane as eluent afforded 160 mg (70% based on 6-methoxy-1-indanone) of the keto ester **34a** as white crystals: mp 72.5–73.0 °C; R_f = 0.30 (30% EtOAc in hexane); IR (KBr) ν 3000, 2949, 2834, 1730, 1707, 1605, 1487, 1456, 1429, 1398, 1319, 1275, 1240, 1213, 1192, 1163, 1038, 1017, 976, 843, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (d, J = 8.4 Hz, 1 H), 7.20–7.10 (m, 2 H), 4.18 (dd, J = 3.3, 7.8 Hz, 1 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.10 (dd, J = 3.3, 19.1 Hz, 1 H), 2.84 (dd, J = 7.9, 19.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 204.0, 172.4, 160.4, 143.7, 137.6, 127.2, 124.0, 105.1, 55.6, 52.6, 42.8, 40.1; MS (70 eV) m/z 220 (M^+), 161, 133, 118, 90, 58; HRMS calcd for $C_{12}H_{12}O_4$ 220.0736, found 220.0736.

6-Methoxyindene-3-carboxylic Acid Methyl Ester (35a). To a stirred solution of 30 mg (0.1 mmol) of the keto ester **34a** in 240 μL of THF and 240 μL of MeOH was added 3 mg (0.08 mmol) of $NaBH_4$ portionwise over 15 min at rt. The mixture was stirred at rt for 1 h, diluted with H_2O, and extracted with $CHCl_3$ (3×). The combined extracts were washed with H_2O and dried over $MgSO_4$. Evaporation under reduced pressure gave 29 mg of the crude hydroxy ester as white crystals: R_f = 0.62 (60% EtOAc in hexane); ^1H NMR ($CDCl_3$, 300 MHz) of the major diastereomer δ 7.25 (d, J = 8.3 Hz, 1 H), 7.02 (d, J = 2.5 Hz, 1 H), 6.85 (dd, J = 2.6, 8.4 Hz, 1 H), 5.09 (dd, J = 2.2, 6.8 Hz, 1 H), 3.95 (dd, J = 2.7, 7.9 Hz, 1 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 2.64–2.52 (m, 1 H), 2.49 (br, s, 1 H), 2.36–2.25 (m, 1 H). To a

solution of 29 mg of the crude hydroxy ester in 5 mL of MeOH was added dropwise 10 μL of concentrated H_2SO_4. The resulting solution was refluxed for 40 min under Ar. The reaction was quenched with H_2O, and the product was extracted with CH_2Cl_2 (3×). The combined extracts were dried over $MgSO_4$. Flash column chromatography on silica gel using 15% EtOAc in hexane as eluent afforded 15 mg (54% based on the keto ester) of the indenecarboxylate **35a** as yellowish needles: mp 91-92 °C; R_f = 0.54 (30% EtOAc in hexane); IR (KBr) ν 3090, 2982, 2940, 2911, 2836, 1701, 1599, 1559, 1480, 1427, 1285, 1248, 1209, 1132, 1090, 1018, 930, 851, 822, 737, 548 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.92 (d, J = 8.5 Hz, 1 H), 7.32 (t, J = 2.0 Hz, 1 H), 7.05 (d, J = 2.1 Hz, 1 H), 6.91 (dd, J = 2.3, 8.4 Hz, 1 H), 3.90 (s, 3 H), 3.84 (s, 3 H), 3.49 (d, J = 1.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 164.7, 158.4, 145.3, 142.3, 135.7, 133.8, 122.9, 112.4, 110.1, 55.5, 51.6, 38.4; MS (70 eV) m/z 204 (M^+), 189, 173, 161, 145, 130, 115, 102, 76, 59, 51; HRMS calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0786.

7-Methoxy-3-oxoindan-1-carboxylic Acid Methyl Ester (34b). The same procedure as employed in the preparation of **34a** afforded 160 mg (70% based on 6-methoxy-1-indanone) of the keto ester **34b** as a yellowish oil: R_f = 0.68 (50% EtOAc in hexane); IR (neat) ν 3004, 2943, 2835, 1733, 1708, 1592, 1475, 1430, 1392, 1324, 1272, 1261, 1191, 1151, 1074, 1025, 888, 784, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46-7.36 (m, 2 H), 7.08 (d, J = 7.7 Hz, 1 H), 4.22 (dd, J = 3.5, 8.2 Hz, 1 H), 3.89 (s, 3 H), 3.72 (s, 3 H), 2.99 (dd, J = 8.3, 18.9 Hz, 1 H), 2.77 (dd, J = 3.5, 18.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 203.9, 173.3, 156.9, 140.4, 138.2, 130.5, 115.6, 115.3, 55.7, 52.3, 41.0, 40.9; MS (70 eV) m/z 220 (M^+), 161, 131, 118, 99, 95, 89, 84; HRMS calcd for $C_{12}H_{12}O_4$ 220.0736, found 220.0736.

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Supplementary Material Available: ^1H spectral data for all new compounds (38 pages). Ordering information is given on any current masthead page.

Synthesis of 2(*E*),4(*E*)-Dienamides and 2(*E*),4(*E*)-Dienoates from 1,3-Dienes via 2-Phenylsulfonyl 1,3-Dienes

Niklas A. Plobeck and Jan-E. Bäckvall*

Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala, Sweden

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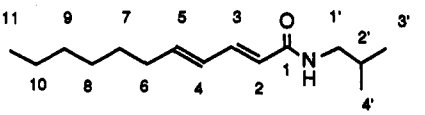
A procedure for the preparation of 2*E*,4*E* unsaturated carboxylic acid derivatives from dienes was developed. Transformation of terminal 1,3-dienes to (*E*)-2-phenylsulfonyl 1,3-dienes and subsequent addition of a carboxy anion equivalent and elimination of benzenesulfinic acid led to 2,4-dienoic amides and esters. In this way the natural products *N*-isobutyl-2(*E*),4(*E*)-undecadienamide (**1a**), *N*-isobutyl-2(*E*),4(*E*)-decadienamide (pellitorine, **1b**), and methyl 2(*E*),4(*E*)-decadienoate (**1c**) were obtained in high isomeric purity.

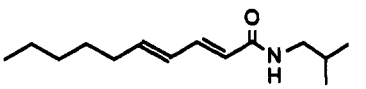
Introduction

2,4-Diunsaturated carboxylic acid derivatives belong to a group of naturally occurring compounds that show some interesting biological activity.[1] *N*-Isobutyl-2(*E*),4(*E*)-undecadienamide (**1a**) has been identified in extracts from the plant *Leucocyclus formosus*.[2] The analogous *N*-isobutyl-2(*E*),4(*E*)-decadienamide, pellitorine (**1b**), was isolated from roots of the plant *Anacyclus pyrethrum*[3] and has insecticidal activity.[1a] Methyl 2(*E*),4(*E*)-decadienoate (**1c**) is a flavor substance in pears.[4]

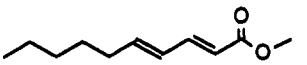
The essential synthetic problem has been to prepare the functionalized diene system in a highly stereoselective manner, and a wide variety of synthetic approaches has been used.[5-15] We have recently developed procedures for the preparation of 2-phenylsulfonyl 1,3-dienes and demonstrated the use of these compounds in organic synthe-



1a



1b



1c

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