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Diastereoselective Syntheses of New Analogues of the Farnesyltransferase Inhibitor RPR 130401

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The access to several benzo[*f*]perhydroisoindolic analogues of farnesyltransferase inhibitors from a single dienic precursor is reported. An initial [4 + 2] cycloaddition between diphenylisobenzofuran **6** and pyrrolines **11**, **14**, and **15** led to either the syn or the anti isomers, depending on the mode of activation of the cycloaddition. The syn diastereomers were isolated in 90% de under 12 kbar at room temperature, while their anti counterparts were obtained with the same selectivity by warming the reaction mixture to 110 °C in toluene at atmospheric pressure. Both syn and anti adducts were separately N-deprotected, and the resulting amines reacted with an activated ester derived from the acid (**20**) to afford the final targets (**5**). Two new analogues (**5a** and **5b**) of the FT inhibitor RPR 130401 were thus synthesized in a mere three-step synthetic scheme with overall yields from 30 to 60%.

Introduction

Ras proteins are small GTP[1a] binding proteins that participate in many cellular functions, such as cell growth and cellular differentiation. The regular cell division process[2] first involves a farnesylation and the binding of the Ras-GDP[1b] protein to the inner surface of the cell membrane. After phosphorylation into Ras-GTP, a signal cascade is triggered, leading to the translocation into the nucleus and to the activation of gene transcription. The reversibility of the transformation of Ras-GDP into Ras-GTP ensures a normal and regular cell growth. The mutation of the Ras protein prevents the hydrolysis of the Ras-GTP into Ras-GDP, and a continuous cell proliferation signal is then issued. Mutant Ras genes are found in a wide range of human tumors, in particular, in colon and pancreas cancers.[3] Various biochemical approaches have been used for understanding the consequences of the presence of mutated Ras proteins,[4−6] among which the inhibition of the farnesyltransferase (FT), which prevents Ras-GDP from fixing on the cell wall, is the subject of numerous investigations[7−10] and has shown to be one of the most successful approaches to date.

A major obstacle related to this strategy is the lack of selectivity of inhibitors for FT over geranylgeranyltransferase (GGT). Among the numerous series of compounds optimized toward an acceptable selectivity, the benzo[*f*]-perhydroisoindole (BPHI) class (studied by Aventis) is one of the most efficient in vitro.[11] Compounds such as RPR 115135 (**1**; Figure 1) show acceptable cellular potency with moderate in vivo activity. The optimization

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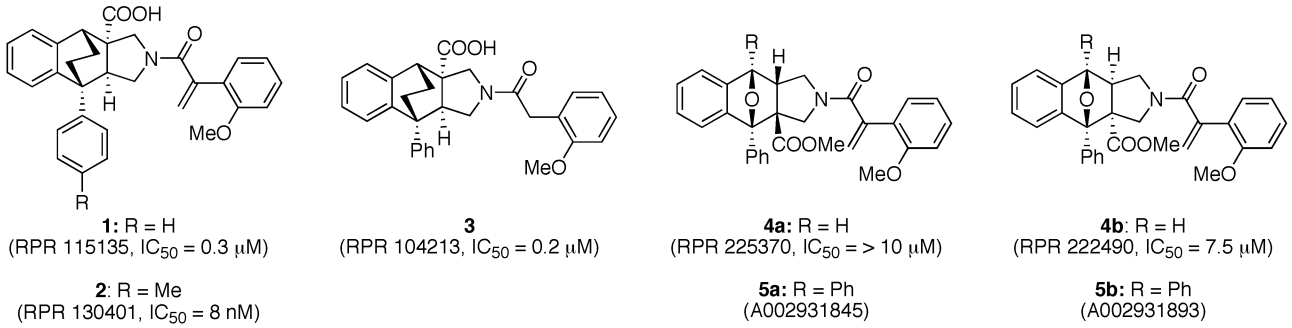
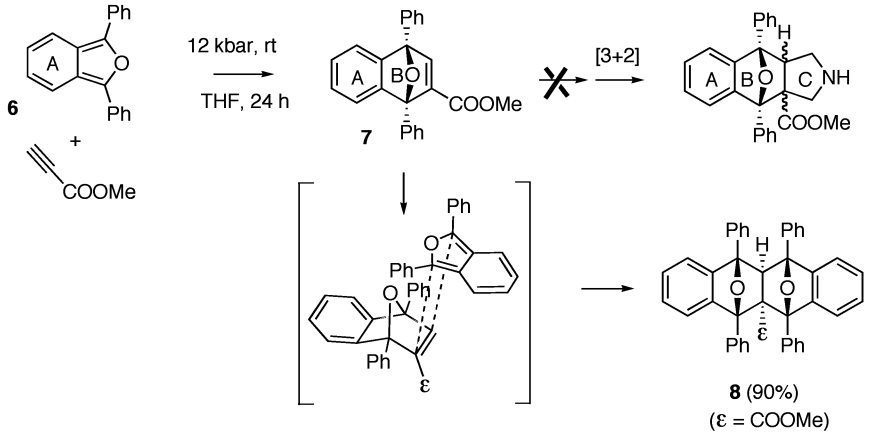


FIGURE 1. Farnesyltransferase inhibitors RPR 130401 and analogues (IC_{50} for Ki-Ras).

SCHEME 1



of this series afforded RPR 104213 and RPR 130401 (**3** and **2**, respectively; Figure 1), with the latter exhibiting potent in vivo activity.

Our laboratory has been interested in the synthesis of new BPHI analogues in which the ethylene bridge of **1**, **2**, and **3** was replaced by an oxo bridge, and the relative position of the angular acid group was altered (Figure 1).[12] Thus, compounds **4a** (syn isomer, RPR 225370) and **4b** (anti isomer, RPR 222490) have been synthesized following either a [3 + 2]/[4 + 2] or a [4 + 2]/[3 + 2] sequence of reactions. Biological activities are disappointing with these two substrates as **4a** did not exhibit any inhibition of farnesylation and **4b** only retained moderate potency (IC_{50} = 7.5 μM). We considered that a trans relationship between the acid group at position 11 and an aromatic ring adjacent to the oxo bridge could be necessary for preserving significant biological results. Thus, access to the new BPHI derivatives **5a** (syn isomer) and **5b** (anti isomer) featured in Figure 1 has been studied. We present in this paper selective access to either diastereomer through a single synthetic pathway.

Results and Discussion

Our original synthetic approach to **5** (syn/anti) relied on a step-by-step [4 + 2]/[3 + 2] sequence starting with diphenylisobenzofuran **6** (DPIB, at the origin of rings A and B) and methyl propiolate (Scheme 1).

The Diels−Alder reaction between benzofuran **6** and methyl propiolate was conducted under 12 kbar for 24 h at room temperature. Biscycloadduct **8** was the sole product isolated in a 90% yield. It results from a double [4 + 2] cycloaddition of the diene on the acetylenic dienophiles and was obtained even when less than 1 equiv of benzofuran was used. The stereoselectivity of this process is assumed to be related to the concave topology of tricyclic intermediate **7**, which forces the second equivalent of benzofuran **6** to approach along an exo-type trajectory (Scheme 1) previously described by Lautens *et al.* in a comparable reaction conducted under thermal conditions.[13] Rather than trying to stop the reaction after the first cycloaddition by changing the solvent[14] or using a different dienophile,[15] we chose to explore the alternative route described below.

This new strategy relied on pyrrolines **11**, **14**, and **15** containing the desired carboxyl group (Scheme 2). Pyrroline **11** was obtained following a [3 + 2] cycloaddition described by Sakurai and Achiwa.[12,16] Thus, in the presence of a catalytic amount of trifluoroacetic acid in dichloromethane, amine **9** generates dipole **10**, which

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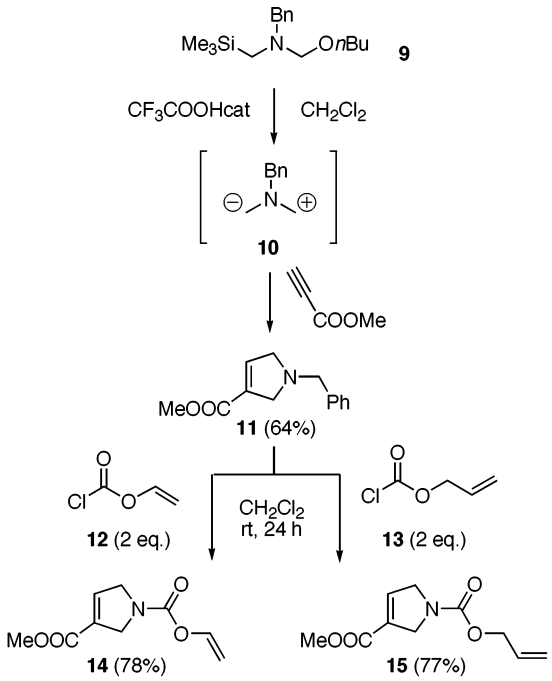
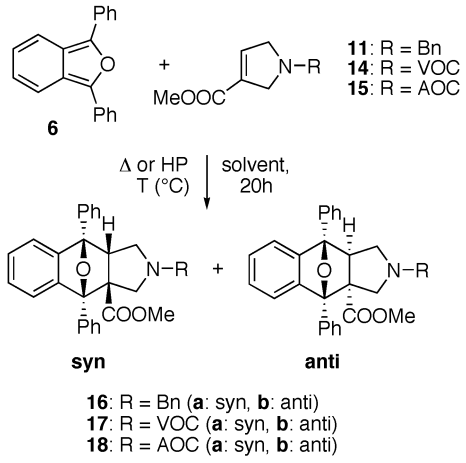
SCHEME 2



immediately reacts at room temperature with methyl propiolate, yielding pyrroline **11** in 64% yield. Pyrroline **11** was then used as the precursor for pyrrolines **14** and **15**. When a debenzylation procedure reported by Olofson was adapted,[17] treatment of **11** with 2 equiv of vinyloxycarbonyl chloride **12** and allyloxycarbonyl chloride **13** in dichloromethane at room temperature for 24 h gave pyrrolines **14** and **15** in 78 and 77% isolated yields, respectively.

Diels−Alder cycloadditions have been conducted between DPIB **6** and pyrrolines **11**, **14**, and **15** in various solvents with a thermal or hyperbaric activation (Scheme 3).

SCHEME 3



The syn and anti labels designate the relative positions between the oxo bridge and the ester group in cycloadducts **16**−**18**. Considering that the main secondary interactions are likely to be due to the ester moiety, the endo and exo transition states are associated to the anti and syn isomers, respectively. The results summarized in Table 1 show that this diastereoselectivity is highly dependent upon the method of activation.

TABLE 1. Cycloaddition Reactions between DPIB 6 and Pyrrolines 11, 14, and 15 in 20 h under Thermal or Hyperbaric Activation

entry	pyrroline	solvent	*T* (°C)	*P* (kbar)	adduct	syn/anti	conv %
1	**11**	CH_2Cl_2	40	$\times10^{-3}$	**16**	95/5	<5
2		THF	70			60/40	93
3		toluene	110			5/95	80
4		THF	rt	12		95/5	92
5	**14**	THF	70	$\times10^{-3}$	**17**	62/38	72
6		THF	rt	12		95/5	77
7	**15**	CH_2Cl_2	40	$\times10^{-3}$	**18**	93/7	95
8		THF	70			86/14	97
9		toluene	70			80/20	80
10		toluene	110			*a*	*a*
11		CH_2Cl_2	rt	12		100/0	94

[a] Decomposition.

The syn diastereomers are the sole (entry 11 of Table 1, **18a**) or main (entry 4, **16a**, and entry 6, **17a**) products isolated under high pressure at room temperature, whatever the solvent. Thermal activation at atmospheric pressure seems to privilege the syn isomers as the major products when the temperature does not exceed 70−80 °C (entries 1 and 2 for adduct **16**, entries 7−9 for adduct **18**). However, the proportion of the anti isomer increases when going from 40 °C (entries 1 and 7) to 70 °C (entries 2, 8, and 9). It is also worth noting that the diastereomeric excess is hardly dependent on the solvent as both toluene and tetrahydrofuran give a similar syn/anti ratio at 70 °C (entries 8 and 9). By contrast, at a higher temperature (110 °C), either a degradation of the starting material (entry 10) or the almost exclusive formation of the anti isomer (entry 3) is observed. The differences of reactivity and selectivity observed among pyrrolines **11**, **14**, and **15** also call for comment. *N*-benzylpyrroline **11** seems more sluggish than carbamates **14** and **15** (compare entries 1 and 7). Also, the weaker preference for the anti isomer under thermal conditions when using allyloxy carbamate **18** (compare entries 2 and 8) can probably be assigned to a competition between the latter function and the ester appendage when it interacts with the π system of DPIB.

Overall, this part of the study provides evidence that the diastereoselectivity of the cycloaddition may be controlled by simply changing the mode of activation (thermal *vs* high pressure). This observation is particularly convincing for pyrroline **11**, which leads to adduct **16a** (12 kbar; entry 4) or **16b** (110 °C; entry 3) in 90% de and yields up to 76%. Each diastereomer has been isolated separately by column chromatography.

As shown in Figure 2 for adduct **16**, the hyperbaric preference for the syn derivative, of which stereochemistry could be firmly established by a single-crystal X-ray analysis, would be the consequence of the compactness (despite its "exo" character) of the corresponding transition state with respect to that leading to the anti isomer. This observation is in complete accordance with the well-known preference of high pressure for compact transition

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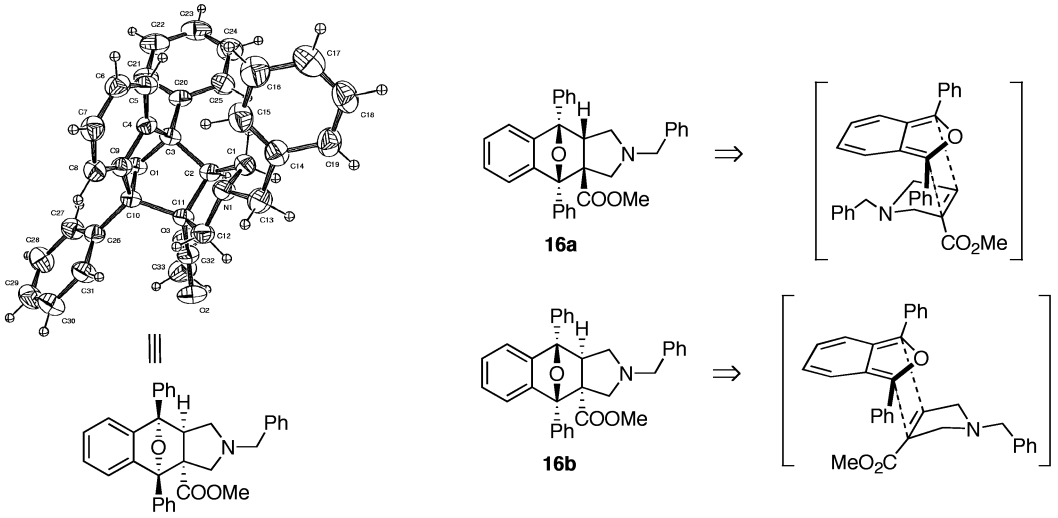
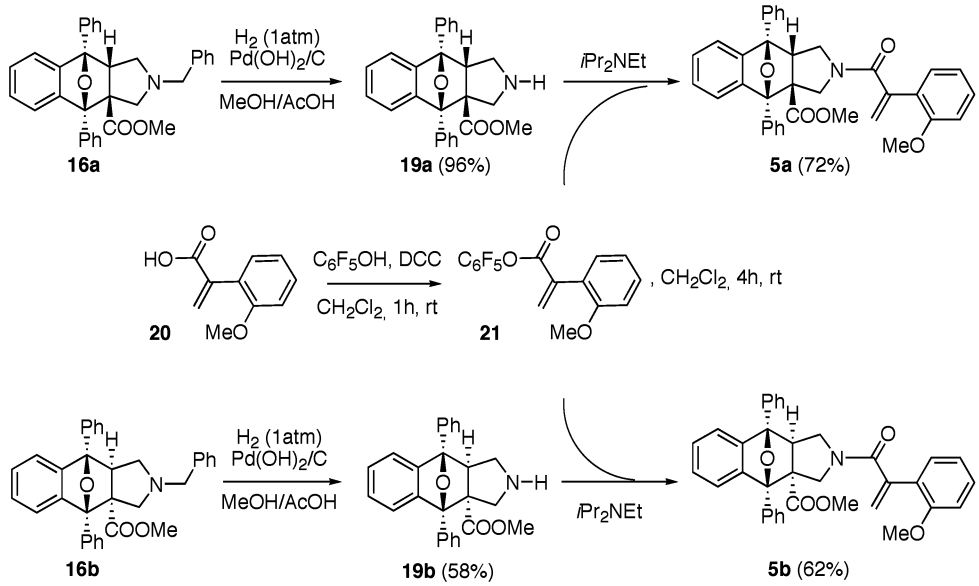


FIGURE 2. DPIB **6** by pyrroline **11** exo (top, compact) and endo (bottom, loose) approaches.

SCHEME 4



states,[18] and **16a**, **17a**, and **18a**[19] are certainly the main compounds isolated in these conditions of activation.

Finally, to determine the kinetic and thermodynamic nature of the product of the reaction, **16a** was warmed in toluene at 110 °C for 24 h. Conversion (80%) into **16b** has been observed, a result which indicates that the syn diastereomer corresponds to the kinetic product while its anti counterpart is the thermodynamic one.

The functionalization steps necessary for converting each adduct (**16**−**18a**,**b**) into their respective BPHI analogues **5** proceed initially through an N-deprotection (Scheme 4). The first attempts to hydrogenolyze **16a** and **16b** in the presence of palladium hydroxide in methanol (Pearlman's conditions[20]) proved to be unsuccessful. In contrast, the same catalyst used in a methanol/acetic acid mixture leads to the expected free amines **19a** and **19b** in 96 and 58% yields, respectively. The good results observed in the presence of acetic acid may be explained by the fact that this cosolvent is known to allow for a better recovery of amines.[21]

The N-deprotection of carbamates **17** and **18** has also been studied. Unfortunately, the treatment of **17a** and **17b** by a hydrochloric acid solution in methanol[12,15] did not give the desired amine **19**. On the other hand, *N*-carbamate **18a** has been submitted to the action of a catalytic amount of palladium acetate (10%) and triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt (TPPTS, 20%) in the presence of 10 equiv of diethylamine in an acetonitrile/H_2O mixture, following Genêt's procedure.[22] Thus, **19a** was recovered in 92% yield after 30 min at room temperature. This route was not explored further since amine **16** gave satisfactory results with the simple debenzylation mentioned above.

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(19) On the basis of strong analogies between ^{1}H NMR spectra (see experimental details).
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The final coupling step between each isomer of **19** was carried out with pentafluorophenol ester **21**, prepared from α-(methoxyphenyl)acrylic acid **20**[23] and pentafluorophenol in the presence of dicyclohexylcarbodiimide (DCC). The crude ester was immediately allowed to react with amines **19a** and **19b** for 4 h in dichloromethane and in the presence of diisopropylethylamine, giving target compounds **5a** and **5b** in 72 and 62% isolated yields, respectively, for this last step.

Conclusions

Two synthetic routes to new oxygen-bridged analogues of BPHI FT inhibitors have been studied in this work. Both approaches rely on a single, commercially available, dienic precursor **6** and an initial [4 + 2] cycloaddition. The first synthetic path, based on methylpropiolate as the dienophile, led to the double addition of **6** in hyperbaric conditions (12 kbar). The second strategy involved a [4 + 2] cycloaddition between three different pyrrolines and **6**. Syn compounds **16**−**18a** were obtained in diastereomeric excesses up to 90% under high pressure (12 kbar) at room temperature, while anti isomer **16b** was recovered as the major product (de > 90%) at 110 °C in toluene at atmospheric pressure. All of these cycloadducts were separately deprotected and coupled with an activated ester to provide the final target of **5**. Thus, **5a** and **5b** were obtained from **6** in about 60 and 30% overall yields, respectively, following two similar three-step pathways that differ only by the mode of activation for the [4 + 2] cycloaddition key step.

Biological Activities. Both new analogues **5a** and **5b** of FT inhibitors, as well as the syn and anti isomers of intermediates **16** and **18**, have been evaluated but did not exhibit any inhibition of a Kirsten-Ras4B related peptide by FT (Table 2). A very small activity has only been noticed for **5b** (32% inhibition at 50 μM, entry 2). These disappointing results are difficult to analyze in the prospect of our original hypothesis on the respective "trans" orientations of the ester and phenyl groups unless the supplementary phenyl group on **5** and its precursors jeopardize the expected fit between the receptor and the ligand. Further works taking this hypothesis into account are currently under way.

TABLE 2. Inhibition of Kirsten-Ras4B Farnesylation Activity by Compounds 5, 16, and 18

entry	compound	IC_{50}, μM (% at 50 μM)
1	**5a**	>50 (0)
2	**5b**	>50 (32)
3	**16a**	>50 (0)
4	**16b**	>50 (12)
5	**18a**	>50 (2)
6	**18b**	>50 (0)

Experimental Section

General Aspects. NMR spectra were recorded at room temperature on spectrometers operating at 300 or 200 MHz(^{1}H) and 75 or 50 MHz (^{13}C). Chemical shifts (δ) are given in parts per million (ppm) and the coupling constants (*J*) in hertz. The solvent was deuteriochloroform. IR spectra were obtained by transmission on an FTIR spectrometer. The mass spectra were obtained either under electron impact conditions (EI) at 70 eV ionizing potential or under fast atom bombardment (FAB) by a Xe beam accelerated under 4 kV (current threshold = 10 mA) on a glycerol or 3-nitrobenzyl alcohol matrix. Melting points were determined using a microscope apparatus. Thin-layer chromatography (TLC) was carried out on fluorescent plates. The silica gel used for flash chromatography[24] was 0.040−0.063 mm. All reagents were of reagent grade and were used as such or distilled prior to use. Due to the presence of rotamers being noticed for compounds **16**, **17**, **9**, **10**, and **5**, some NMR signals (^{1}H and ^{13}C) may be doubled. In this case, both chemical shifts have been indicated.

5,12-6,11-Diepoxy-5,5a,6,11,11a,12-hexahydro-5,6,11,12-tetraphenylnaphthacene-5a-carboxylic Acid Methyl Ester 8. A solution of diphenylisobenzofuran **6** (302 mg, 1.12 mmol, 1 equiv) and methyl propiolate (93 μL, 1.12 mmol, 1 equiv) in tetrahydrofuran (5 mL) was transferred via a syringe into a glass cell. After 24 h under 12 kbar at room temperature, the solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel (eluent, heptane/ethyl acetate 70:30) gave **8** as a white solid (315 mg, 90%): mp 105 °C (heptane/ethyl acetate); IR (film, NaCl) ν 3059, 2947, 1727, 1263, 1211 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.23 (3H, s), 4.72 (1H, s), 6.74−8.00 (28H, m); ^{13}C NMR (75 MHz) δ 51.6, 67.0, 78.7, 86.6, 88.2, 88.5, 90.8, 118.9, 121.2, 122.5, 122.9, 125.6, 126.3, 126.4, 126.5, 126.8, 127.1, 127.2, 127.3, 127.5, 127.6, 127.7, 128.0, 128.2, 128.3, 129.5, 134.3, 134.4, 136.0, 137.6, 144.6, 144.7, 146.9, 149.6, 171.2. Anal. Calcd for $C_{44}H_{32}O_4$: C, 84.59; H, 5.16. Found: C, 84.66; H, 4.87.

1-Benzyl-2,5-dihydropyrrole-3-carboxylic Acid Methyl Ester 11.[12,16] A solution of *N*-benzyl-*N*-(butyloxymethyl)-trimethylsilylmethylamine **9** (10 g, 35.8 mmol, 1.2 equiv) in dichloromethane (20 mL) was added under argon to a solution of methyl propiolate (2.66 mL, 29.8 mmol, 1 equiv) in dichloromethane (10 mL). A solution of trifluoroacetic acid (230 μL, 2.98 mmol, 0.1 equiv) in dichloromethane (5 mL) was transferred via a syringe dropwise at 0 °C over a period of 5 min. The resulting mixture was allowed to warm to room temperature and then stirred for 3 h before being neutralized by addition of a saturated solution of $NaHCO_3$ (20 mL). The organic layer was washed with a saturated solution of NaCl (15 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent, heptane/ethyl acetate 60:40) gave **11** as a yellow oil (4.15 g, 64%): IR (film) ν 1724, 1671, 1242 cm^{-1}; EIMS (70 eV) *m*/*z* 217 (M^+, 46), 202 (M^+ − Me, 16), 140 (M^+ − C_6H_5, 15), 126 (M^+ − $C_6H_5CH_2$, 100); ^{1}H NMR (200 MHz) δ 3.65 (2H, s), 3.72 (4H, s), 3.79 (3H, s), 6.73 (1H, s), 7.30 (5H, m). The NMR spectrum is identical to the one described in the literature.[16b]

2,5-Dihydropyrrole-1,3-dicarboxylic Acid 3-Methyl Ester 1-Vinyl Ester 14.[17] Pyridine (47 μL, 0.583 mmol, 1.5 equiv) and vinyl chloroformate **12** (50 μL, 0.583 mmol, 1.5 equiv) were successively added at room temperature to a solution of 1-benzyl-2,5-dihydropyrrole-3-carboxylic acid methyl ester **11** (85 mg, 0.389 mmol, 1 equiv) in dichloromethane (5 mL). The resulting mixture was stirred for 24 h before being quenched by the addition of a saturated solution of $NaHCO_3$ (3 mL). The organic layer was washed with a saturated solution of NaCl (3 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent, heptane/ethyl acetate 70:30) gave **16** as a white solid (60 mg, 78%): mp 81 °C (heptane/ethyl acetate 70:30); IR (neat) ν 1732, 1654, 1424, 1300 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.64 (3H, s), 4.24 (2H, m), 4.26 (2H, m), 4.35 (1H, dd, *J* = 1.4 and 6.2), 4.66 and 4.68

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(1H, dd, J = 1.5 and 14.0), 6.61 (1H, dd, J = 1.6 and 5.7), 7.09 (1H, dd, J = 6.3 and 14.0); ^{13}C NMR (50 MHz) δ 51.7, 51.8 and 52.1, 53.6 and 54.0, 95.5, 131.5, 136.2, 142.0, 151.2 and 151.4, 162.6. Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.82; H, 5.58; N, 6.78.

2,5-Dihydropyrrole-1,3-dicarboxylic Acid 3-Methyl Ester 1-Allyl Ester 15. Allyl chloroformate **13** (2.94 mL, 27.6 mmol, 3 equiv) was added at room temperature to a solution of 1-benzyl-2,5-dihydropyrrole-3-carboxylic acid methyl ester **11** (2 g, 9.2 mmol, 1 equiv) in dichloromethane (5 mL). The resulting mixture was stirred for 24 h before being quenched by addition of a saturated solution of $NaHCO_3$ (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent, heptane/ethyl acetate 70:30) gave **15** as a yellow solid (1.5 g, 77%): mp 34 °C (heptane/ethyl acetate 70:30); IR (neat) ν 1715, 1645, 1436, 1408, 1328, 1288 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.73 (3H, s), 4.33 (4H, s), 4.57 (2H, d, J = 5.64), 5.15−5.31 (2H, m), 5.83−5.96 (1H, m), 6.68−6.72 (1H, m); ^{13}C NMR (75 MHz) δ 51.7 and 52.2, 51.8, 53.5 and 54.0, 65.9, 117.4, 131.7 and 131.8, 132.7 and 132.8, 136.5 and 136.6, 154.2, 162.9.

4,9-Epoxy-4,9-diphenyl-2-phenylmethyl-1,3,3a,4,9,9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic Acid Methyl Ester 16. Thermal Activation. A solution of diphenylisobenzofuran **6** (500 mg, 1.85 mmol, 1 equiv) and 1-benzyl-2,5-dihydropyrrole-3-carboxylic acid methyl ester **11** (441 mg, 2.03 mmol, 1.1 equiv) in toluene (15 mL) was heated at 110 °C for 24 h. After the solution was cooled to room temperature, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent, heptane/ethyl acetate 70:30) gave **16a** (36 mg, 4%) and **16b** (684 mg, 76%) as pale yellow solids. The syn/anti ratio corresponds to 5:95.

Hyperbaric Activation. A solution of diphenylisobenzofuran **6** (100 mg, 0.369 mmol, 1 equiv) and 1-benzyl-2,5-dihydropyrrole-3-carboxylic acid methyl ester **11** (127 mg, 0.585 mmol, 1.6 equiv) in tetrahydrofuran (5 mL) was transferred via a syringe into a glass cell. After 24 h under 12 kbar at room temperature, the solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel (eluent, heptane/ethyl acetate 70:30) gave **16a** (159 mg, 88%) and **16b** (7 mg, 4%) as pale yellow solids. The syn/anti ratio corresponds to 96:4. Data for **16a** follow: mp 124 °C (heptane/ethyl acetate 70:30, retro-Diels−Alder); IR (neat) ν 2784, 1726, 1454 cm^{-1}; FAB (Xe, glycerol) m/z 488 (MH^+, 20), 270 ($MH^+ - C_6H_5CH_2$, 42); ^{1}H NMR (300 MHz) δ 2.55 (1H, dd, J = 2.9 and 9.5), 2.60−2.75 (1H, m), 2.69 (1H, d, J = 10.5), 2.99 (1H, d, J = 10.2), 3.25 (2H, s), 3.26 (3H, s), 3.99 (1H, dd, J = 2.9 and 7.3), 6.68−7.60 (19H, m); ^{13}C NMR (75 MHz) δ 51.8, 54.3, 56.3, 57.5, 59.6, 68.5, 90.3, 92.7, 120.2, 120.7, 125.4, 126.6, 126.7, 127.0, 127.6, 127.8, 127.9, 128.2, 128.3, 128.4, 128.8, 136.2, 138.0, 138.4, 145.8, 147.9, 173.8. Anal. Calcd for $C_{33}H_{29}NO_3$: C, 81.29; H, 5.99; N, 2.87. Found: C, 81.12; H, 5.97; N, 2.84. Data for **16b** follow: mp 94 °C (heptane/ethyl acetate 70:30); IR (neat) ν 2812, 1732, 1448 cm^{-1}; FAB (Xe, glycerol) m/z 488 (MH^+, 21), 270 ($MH^+ - C_6H_5CH_2$, 40); ^{1}H NMR (300 MHz) δ 1.92 (1H, t, J = 8.7), 2.25 (1H, d, J = 9.4), 3.00 (1H, t, J = 8.8), 3.37 (3H, s), 3.40 (2H, s), 3.44 (1H, d, J = 9.5), 3.63 (1H, t, J = 8.8), 6.90−7.82 (19H, m); ^{13}C NMR (75 MHz) δ 52.1, 56.8, 57.6, 59.6, 60.4, 68.5, 90.1, 92.0, 119.3, 120.1, 126.0, 126.6, 126.7, 126.8, 127.3, 127.6, 127.9, 128.1, 128.2, 128.3, 128.5, 136.1, 137.0, 138.8, 145.7, 147.9, 173.9. Anal. Calcd for $C_{33}H_{29}NO_3$: C, 81.29; H, 5.99; N, 2.87. Found: C, 81.12; H, 6.06; N, 2.97.

4,9-Epoxy-4,9-diphenyl-2-vinyloxycarbonyl-1,3,3a,4,9,-9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic Acid Methyl Ester 17. Thermal Activation. A solution of diphenylisobenzofuran **6** (137 mg, 0.51 mmol, 1 equiv) and 2,5-dihydropyrrole-1,3-dicarboxylic acid 3-methyl ester 1-vinyl ester **14** (100 mg, 0.51 mmol, 1 equiv) in tetrahydrofuran (10 mL) was heated at 70 °C for 24 h. After the solution was cooled to room temperature, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent, heptane/ethyl acetate 70;30) gave **17a** (107 mg, 45%) and **17b** (65 mg, 27%) as yellow oils. The syn/anti ratio corresponds to 62:38.

Hyperbaric Activation. A solution of diphenylisobenzofuran **6** (275 mg, 1.02 mmol, 1.02 equiv) and 2,5-dihydropyrrole-1,3-dicarboxylic acid 3-methyl ester 1-vinyl ester **14** (200 mg, 1.02 mmol, 1 equiv) in THF (5 mL) was transferred via a syringe into a glass cell. After 24 h under 12 kbar at room temperature, the solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel (eluent, heptane/ethyl acetate 70:30) gave **17a** (348 mg, 73%) and **17b** (19 mg, 4%) as yellow oils. The syn/anti ratio corresponds to 95:5. Data for **17a** follow: IR (film, NaCl) ν 1724, 1646, 1424, 1225, 1151 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.24 and 3.25 (3H, s), 3.38 and 3.43 (1H, t, J = 7.5), 3.50 and 3.77 (1H, dd, J = 1.9 and 12.1), 3.71 and 3.81 (1H, t, J = 12.6), 3.92 and 3.97 (1H, dd, J = 2.3 and 7.5), 4.29−4.35 (1H, m), 4.57−4.68 (1H, m), 6.73−6.81 (1H, m), 6.93−7.00 (1H, m), 7.13−7.62 (14H, m); ^{13}C NMR (75 MHz) δ 46.0 and 46.2, 49.2 and 49.4, 52.2 and 52.25, 55.3 and 55.5, 67.2 and 67.9, 90.6 and 90.7, 93.4 and 93.45, 95.2 and 95.3, 120.2 and 120.7, 120.8 and 121.1, 125.3, 127.0 and 127.2, 127.3, 127.6, 127.8, 128.0 and 128.1, 128.15 and 128.2, 128.6 and 128.65, 135.2 and 135.3, 136.7 and 136.75, 142.0 and 142.05, 143.5 and 143.7, 145.2 and 145.25, 150.0 and 150.2, 172.5 and 172.6. Anal. Calcd for $C_{29}H_{25}NO_5$: C, 74.50; H, 5.39; N, 3.00. Data for **17b** follow: IR (film, NaCl) ν 1727, 1646, 1428, 1149 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.24 (1H, dd, J = 5.8 and 11.3), 3.50−3.55 (1H, m), 3.59 (3H, s), 3.73−3.83 (1H, m), 3.93 (1H, dd, J = 9.5 and 11.3), 4.22 (1H, d, J = 12.1), 4.45 (1H, dd, J = 1.5 and 6.2), 4.72 and 4.80 (1H, s), 7.18−8.00 (15H, m); ^{13}C NMR (75 MHz) δ 48.4 and 48.8, 51.9 and 52.3, 52.5, 56.7 and 57.8, 67.5 and 68.5, 90.4 and 90.7, 92.3 and 92.4, 95.4, 119.3, 121.0 and 121.2, 125.8, 127.0, 127.5, 128.0, 128.3 and 128.4, 128.8, 129.8, 133.0, 135.3 and 135.4, 136.1 and 136.2, 142.2, 144.8 and 145.0, 147.1 and 147.2, 151.2, 172.9 and 173.0.

2-Allyloxycarbonyl-4,9-epoxy-4,9-diphenyl-1,3,3a,4,9,-9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic Acid Methyl Ester 18. A solution of diphenylisobenzofuran **6** (192 mg, 0.71 mmol, 1 equiv) and 2,5-dihydropyrrole-1,3-dicarboxylic acid 3-methyl ester 1-allyl ester **15** (150 mg, 0.71 mmol, 1 equiv) in dichloromethane (10 mL) was refluxed for 24 h. After the solution was cooled to room temperature, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent, heptane/ethyl acetate 70:30) gave **18a** (303 mg, 88%) and **18b** (23 mg, 7%) as yellow solids. The syn/anti ratio corresponds to 93:7. Data for **18a** follow: mp 69 °C (heptane/ethyl acetate 70:30, retro-Diels−Alder); IR (neat) ν 1698, 1434 cm^{-1}; FAB (Xe, 3-nitrobenzyl alcohol) m/z 482 (MH^+, 5), 270 ($MH^+ - C_{10}H_{13}NO_4$, 100); ^{1}H NMR (300 MHz) δ 3.19 and 3.21 (3H, s), 3.25−3.80 (4H, m), 3.87 and 3.92 (1H, dd, J = 2.1 and 7.5), 4.10−4.25 (2H, m), 5.05−5.20 (2H, m), 5.60−5.80 (1H, m), 6.85−7.60 (14H, m); ^{13}C NMR (75 MHz) δ 45.9 and 46.2, 49.1 and 49.5, 52.1 and 52.2, 55.5 and 55.9, 65.6, 67.3 and 68.1, 90.7, 93.5, 117.2, 120.2, 120.6 and 120.8, 121.1, 125.4, 126.9 and 127.0, 127.2, 127.5 and 127.7, 128.0 and 128.2, 128.6, 132.9, 135.4, 135.5, 136.9, 143.8 and 144.0, 145.4 and 145.5, 152.7 and 152.9, 172.7 and 172.8. Anal. Calcd for $C_{30}H_{27}NO_5$: C, 74.83; H, 5.65; N, 2.91. Found: C, 74.62; H, 5.72; N, 2.73. Data for **18b** follow: mp 60 °C (heptane/ethyl acetate 70:30); IR (neat) ν 1724, 1448 cm^{-1}; FAB (Xe, 3-nitrobenzyl alcohol) m/z 482 (MH^+, 4), 270 ($MH^+ - C_{10}H_{13}NO_4$, 100); ^{1}H NMR (200 MHz) δ 3.09 (1H, dd, J = 5.8 and 10.9), 3.41 (1H, d, J = 12.4), 3.49 (3H, s), 3.62−3.71 (1H, m), 3.77−3.85 (1H, m), 4.09 (1H, d, J = 12.1), 4.46 (2H, d, J = 5.5), 5.08−5.22 (2H, m), 5.70−5.92 (1H, m), 6.90−7.92 (14H, m); ^{13}C NMR (75 MHz) δ 48.3 and 48.7, 51.8 and 52.1, 52.3, 56.6 and 57.8, 65.7, 67.5 and 68.6, 90.4, 92.3, 117.1, 119.1, 120.9, 126.0, 126.2, 126.8 and 127.0, 127.3, 127.8 and 128.0, 128.1 and 128.2, 128.3, 128.5 and 128.7,

132.9, 135.6, 136.2, 145.0, 147.3, 153.9, 173.1. Anal. Calcd for $C_{30}H_{27}NO_5$: C, 74.83; H, 5.65; N, 2.91. Found: C, 74.96; H, 5.71; N, 2.94.

4,9-Epoxy-4,9-diphenyl-1,3,3a,4,9,9a-hexahydrobenzo-[*f*]isoindole-3a-carboxylic Acid Methyl Ester 19a. Method A[20] with $Pd(OH)_2$/C. Palladium hydroxide on carbon (20 wt % Pd/C) (33 mg, 0.031 mmol, 0.1 equiv) was added to a solution of 4,9-epoxy-4,9-diphenyl-2-phenylmethyl-1,3,3a,4,9,9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic acid methyl ester **16a** (150 mg, 0.307 mmol, 1 equiv) in a 1:1 (v/v) methanol/acetic acid mixture (5 mL). The reaction mixture was placed under a saturated atmosphere of hydrogen for 24 h and vigorously stirred. After filtration, the palladium salts were washed with a 1:1 (v/v) methanol/acetic acid mixture (10 mL) and the filtrate was neutralized with $NaHCO_3$ powder until a pH of 8 was obtained. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the resulting organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (eluent, dichloromethane/methanol 95:5) gave amine **19a** as a white solid (118 mg, 96%).

Method B[23] with $Pd(OAc)_2$/TPPTS/Diethylamine. 2-Allyloxycarbonyl-4,9-epoxy-4,9-diphenyl-1,3,3a,4,9,9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic acid methyl ester **18a** (1.04 g, 2.15 mmol, 1 equiv), palladium acetate (47.5% Pd, 100 mg, 0.215 mmol, 0.1 equiv), and triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt (244 mg, 0.43 mmol, 0.2 equiv) were successively introduced into a 1:1 (v/v) water/acetonitrile mixture (10 mL). After all of the solids were dissolved, diethylamine (3 mL, 21.5 mmol, 10 equiv) was added and the resulting reaction mixture was stirred at room temperature for 2 h before being quenched with the addition of a saturated solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with dichloromethane (2 × 5 mL), and then the resulting organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (eluent, dichloromethane/methanol 95:5) gave amine **19a** as a white solid (792 mg, 92%): mp 72 °C (dichloromethane/methanol 95:5); IR (neat) ν 3341, 1723, 1452 cm^{-1}; FAB (Xe, glycerol) *m*/*z* 398 (MH^+, 5); ^1H NMR (300 MHz) δ 2.71 (1H, d, J = 12.8), 2.84 (1H, dd, J = 7.2 and 13.2), 2.93 (1H, d, J = 13.6), 3.14 (1H, d, J = 13.9), 3.19 (3H, s), 3.84 (1H, dd, J = 1.1 and 6.8), 6.90−7.60 (14H, m); ^{13}C NMR (75 MHz) δ 48.6, 51.8, 52.1, 59.1, 71.0, 90.2, 92.6, 120.3, 120.4, 125.3, 127.1, 127.5, 127.8, 128.1, 128.4, 128.5, 135.9, 137.3, 144.3, 146.6, 173.8. Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.58; H, 6.09; N, 3.41.

4,9-Epoxy-4,9-diphenyl-1,3,3a,4,9,9a-hexahydrobenzo-[*f*]isoindole-3a-carboxylic Acid Methyl Ester 19b.[20] Palladium hydroxide on carbon (20 wt % Pd/C) (65 mg, 0.061 mmol, 0.08 equiv) was added to a solution of 4,9-epoxy-4,9-diphenyl-2-phenylmethyl-1,3,3a,4,9,9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic acid methyl ester **16b** (360 mg, 0.740 mmol, 1 equiv) in a 1:1 (v/v) methanol/acetic acid mixture (10 mL). The reaction mixture was placed under a saturated atmosphere of hydrogen for 24 h and vigorously stirred. After filtration, the palladium salts were washed with a 1:1 (v/v) methanol/acetic acid mixture (10 mL) and the filtrate was neutralized with $NaHCO_3$ powder until a pH of 8 was obtained. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the resulting organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (eluent, dichloromethane/methanol 95:5) gave amine **19b** as a white solid (170 mg, 58%): mp 70 °C (dichloromethane/methanol 95:5); IR (neat) ν 3318, 1725, 1453 cm^{-1}; FAB (Xe, glycerol) *m*/*z* 398 (MH^+, 5); CI (NH_3) 398 (MH^+, 100); ^1H NMR (300 MHz) δ 2.65 (1H, dd, J = 5.6 and 12.4), 2.96 (1H, d, J = 12.4), 3.01 (1H, dd, J = 7.5 and 12.4), 3.16 (1H, d, J = 12.4), 3.38 (1H, dd, J = 5.6 and 7.5), 3.44 (3H, s), 6.85−7.44 (14H, m); ^{13}C NMR (75 MHz) δ 51.1, 52.0, 55.2, 60.6, 70.4, 90.5, 92.1, 118.9, 121.1, 125.9, 126.5, 127.0, 127.1, 127.7, 128.0, 128.2, 128.6, 136.0, 136.7, 146.2, 148.3, 173.9. Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.73; H, 5.87; N, 3.44.

2-(2-Methoxyphenyl)acrylic Acid Pentafluorophenyl Ester 21. A solution of 1,3-dicyclohexylcarbodiimide (DCC) in tetrahydrofuran (5 mL) was added under argon and at room temperature to a solution of 2-(2-methoxyphenyl)propen-2-oic acid **20** (120 mg, 0.6226 mmol, 1 equiv) and pentafluorophenol (128 mg, 0.6792 mmol, 1.2 equiv) in tetrahydrofuran (5 mL). After 1 h at room temperature, the solution was filtered to eliminate the dicyclohexylurea (DCU). The filtrate was diluted four times with ether, filtered to remove the last traces of DCU, and then concentrated. The crude ester (**21**) was used immediately without any further purification.

4,9-Epoxy-2-[2,2-(methoxyphenyl)propen-2-oyl]-4,9-diphenyl-1,3,3a,4,9,9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic Acid Methyl Ester 5a. A solution of 4,9-epoxy-4,9-diphenyl-1,3,3a,4,9,9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic acid methyl ester **19a** (225 mg, 0.566 mmol, 1 equiv) and diisopropylethylamine (295 μL, 1.698 mmol, 3 equiv) in tetrahydrofuran (5 mL) was added to a solution of 2-(2-methoxyphenyl)acrylic acid pentafluorophenyl ester **21** (0.6226 mmol, 1 equiv) in tetrahydrofuran (5 mL). The reaction mixture was stirred at room temperature for 4 h before being quenched by the addition of a 0.5 M solution of NaOH (5 mL). The organic layer was washed with a new 0.5 M solution of NaOH (5 mL) and followed by a saturated solution of NaCl (2 × 5 mL) and then, after recovering, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (eluent, heptane/ethyl acetate 50:50) gave **5a** as a white solid (229 mg, 72%): mp 125 °C (heptane/ethyl acetate 50:50, retro-Diels−Alder); IR (neat) ν 1723, 1639, 1431, 1278, 1236 cm^{-1}; FAB (Xe, 3-nitrobenzyl alcohol) *m*/*z* 558 (MH^+, 50), 270 ($MH^+ - C_{16}H_{17}NO_4$, 100); HRMS−FAB (*m*/*z*) [MH^+] found, M = 558.2281, $C_{36}H_{32}NO_5$ requires 558.2280; ^1H NMR (300 MHz) δ 3.30 (3H, s), 3.25−3.55 (2H, m), 3.68−3.75 (1H, m), 3.78 (3H, s), 3.94−4.10 (2H, m), 5.05 and 5.13 (1H, dd, J = 1.1 and 26.7), 5.55 (1H, s), 6.88−7.70 (18H, m); ^{13}C NMR (75 MHz) δ 46.5 and 49.0, 49.8 and 52.6, 52.7 and 52.75, 55.8 and 56.0, 56.1 and 56.9, 67.4 and 69.1, 91.1 and 91.4, 93.9, 111.4 and 111.5, 119.8 and 120.2, 120.7 and 121.0, 121.4 and 121.5, 121.7 and 122.1, 125.6 and 125.9, 126.5 and 126.7, 127.3 and 127.4, 127.7 and 128.0, 128.1 and 128.2, 128.4, 128.6 and 128.65, 129.0 and 129.1, 129.6 and 129.8, 130.1 and 130.2, 135.9 and 136.0, 137.4, 142.6, 144.8 and 145.2, 146.0 and 146.3, 156.6 and 156.7, 169.1 and 169.7, 173.3 and 173.5. Anal. Calcd for $C_{36}H_{31}NO_5$: C, 77.54; H, 5.60; N, 2.51. Found: C, 77.48; H, 5.92; N, 2.46.

4,9-Epoxy-2-[2,2-(methoxyphenyl)propen-2-oyl]-4,9-diphenyl-1,3,3a,4,9,9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic Acid Methyl Ester 5b. The procedure reported above for **5a** was applied to synthesize **5b** as a white solid (104 mg, 62%). A solution of 4,9-epoxy-4,9-diphenyl-1,3,3a,4,9,9a-hexahydrobenzo[*f*]isoindole-3a-carboxylic acid methyl ester **19b** (119 mg, 0.33 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added to a solution of 2-(2-methoxyphenyl)acrylic acid pentafluorophenyl ester **21** (0.33 mmol, 1 equiv) in tetrahydrofuran (5 mL): mp 100 °C (heptane/ethyl acetate 50:50, retro-Diels−Alder); IR (neat) ν 1723, 1639, 1431 cm^{-1}; FAB (Xe, 3-nitrobenzyl alcohol) *m*/*z* 558 (MH^+, 55), 270 ($MH^+ - C_{16}H_{17}NO_4$, 80); ^1H NMR (300 MHz) δ 2.99−3.10 (1H, m), 3.30−3.37 and 3.42 (1H, m), 3.36 and 3.48 (3H, s), 3.56 and 3.59 (3H, 1s), 3.59−3.70 (1H, m), 4.05−4.15 (1H, m), 4.44 (1H, d, J = 13.6), 5.23 and 5.25 (1H, 1s), 5.47 and 5.52 (1H, 1s), 6.60−7.90 (18H, m); ^{13}C NMR (75 MHz) δ 47.7 and 51.0, 51.1 and 54.3, 52.3 and 52.4, 55.4 and 55.5, 56.3 and 57.8, 67.4 and 68.7, 90.3 and 90.8, 92.4 and 92.7, 110.8 and 111.1, 118.6, 119.2 and 119.3, 120.7, 120.9 and 121.0, 125.8 and 125.9, 126.4 and 126.5, 126.9 and 127.0, 127.3, 127.4 and 127.5, 127.9 and 128.0, 128.2, 128.3 and 128.4, 128.7 and 128.8, 129.4 and 129.5, 129.7, 135.4 and 135.5, 136.2 and 136.3, 142.3 and 142.6, 144.8 and 145.2, 147.2 and 147.4, 156.3 and 156.4, 169.2 and 169.3, 173.0.

Anal. Calcd for $C_{36}H_{31}NO_5$: C, 77.54; H, 5.60; N, 2.51. Found: C, 77.48; H, 5.69; N, 2.43.

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Supporting Information Available: Copies of the IR, ^{1}H NMR, and/or ^{13}C NMR spectra for compounds **5a**, **8**, **15**, **17a**, **17b**, and **19a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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