Synthesis of Oxa-Bridged Analogues of Farnesyltransferase Inhibitor RPR 115135

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Two synthetic routes to new oxygen-bridged analogues of farnesyltransferase inhibitors are described that follow either a [3 + 2]/[4 + 2] or a [4 + 2]/[3 + 2] sequence of reactions. The first approach has been achieved by reacting the in situ generated phenylisobenzofuran (PIBF) **4** with pyrroline **5a** and has led stereoselectively to racemic **18**, which was transformed in a few steps into the target molecule **2**. The second pathway relies on a key intermediate **6**, obtained either by condensation of PIBF with methyl acrylate, followed by a deprotonation/selenation and an oxidation/elimination sequence, or by cycloaddition between PIBF and α-phenylselenoacrylate **11**, followed by the same oxidation/elimination sequence. The reaction of **6** with amino dipole **7** gives diastereoselective access to pyrrolidine **25**, a precursor of the second target **3**, an epimer of **2**.

Introduction

The central role played by mutations of the Ras protein in human cancerogenesis, especially in colon and pancreas tumors, has been well documented lately.[1] Three different mutation types, the so-called Harvey-Ras, Neuroblastoma-Ras, and Kirsten-Ras 4B, have been identified and are characterized by their C-terminal variations. The early steps of the regular cell division process involve the farnesylation and binding of the Ras-GDP protein to the inner wall of the cell. This event, followed by a phosphorylation into Ras-GTP, induces a signal cascade ending with the translocation into the nucleus and the gene transcription activation. Because it is unable to switch back from the Ras-GTP to the Ras-GDP form, the mutated protein keeps on firing a continuous cell proliferation signal. Among the various biochemical strategies studied to reverse this phenomenon, the inhibition of farnesyl transferase (FT), which prevents the Ras-GDP fixation on the cell wall, has turned out to be the most efficient one and has opened promising new directions in cancer therapy. There is, however, one major difficulty associated with this approach, and that is the selective inhibition of FT with respect to related enzymes such as geranylgeranyltransferase (GGT), of which Ras is also a substrate. Several classes of compounds have been developed to reach an acceptable level of selectivity, among which is the benzo[*f*]perhydroisoindole (BPHI) class.

Compounds such as RPR 115135 (**1**, Figure 1), which combines a remarkably low GGT inhibition profile with an elevated cellular potency and moderate in vivo activities,[2] constitutes a particularly effective lead molecule in this series. A large investigation on the structure−activity relationship has already been achieved around this skeleton and has revealed key features such as the presence of two aromatic rings, one on the lateral amide chain and the other one at the 9 position.[2] However, several other important structural characteristics such as the nature of the bridging element, or the position of the angular acid group, have not been taken into account yet. The possible role played by these fragments in the drug−enzyme interaction led us to prepare the two new analogues displayed in Figure 1, i.e., **2** (RPR 225,370) and **3** (RPR 222,490). We present in this paper the different synthetic pathways we have studied to access these compounds.

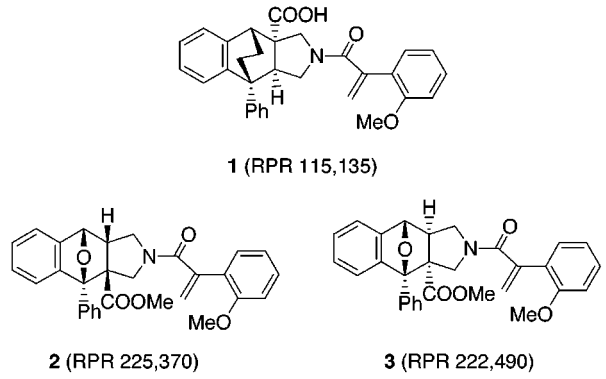

Figure 1. Farnesyl transferase inhibitor RPR 115135 and its analogues.

Results and Discussion

The synthesis of the skeleton of **2** and **3** has been tackled through the routes summarized in Figure 2,

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(1) Bos, J. L. *Cancer Res.* **1989**, *49*, 4682.

(2) Mailliet, P.; Laoui, A.; Bourzat, J. D.; Capet, M.; Chevé, M.; Commerçon, A.; Dereu, N.; Le Brun, A.; Martin, J. P.; Peyronel, J. F.; Salagnad, C.; Thompson, F.; Zucco, M.; Guitton, J. D.; Pantel, G.; Bissery, M. C.; Brealey, C.; Lavayre, J.; Lelièvre, Y.; Riou, J. F.; Vrignaud, P.; Duchesne, M.; Lavelle, F. In *Farnesyltransferase and Geranylgeranyltransferase Inhibitors in Cancer and Cardiovascular Therapy*; Sebti, S., Ed.; Humana Press: Totowas, NJ, in press.

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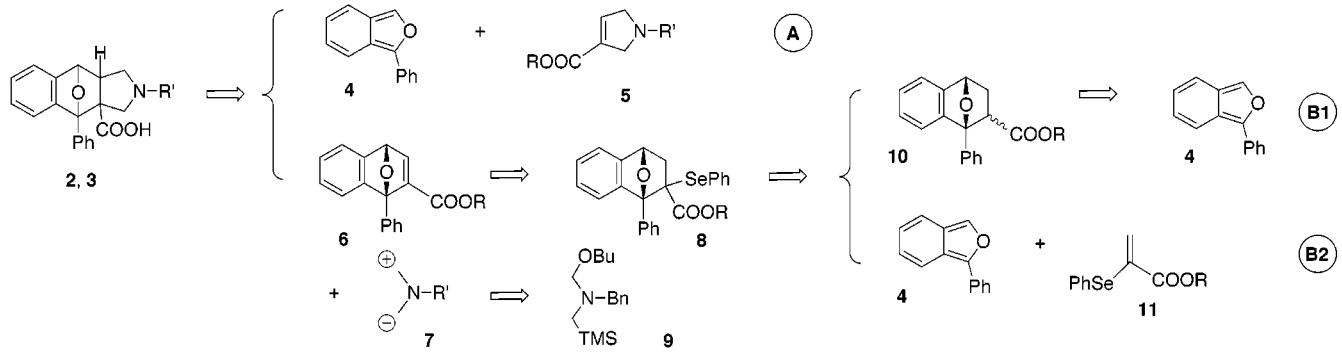
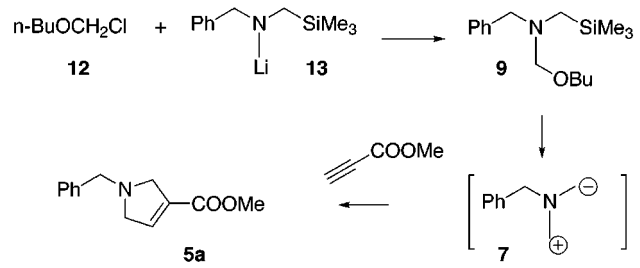
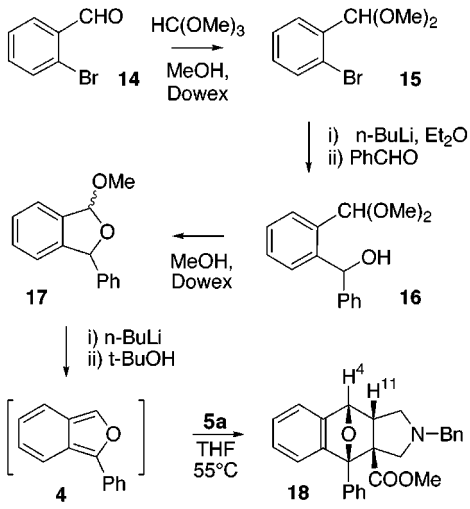


Figure 2. Three retrosynthetic routes to analogue **2** and **3** skeleton.

Scheme 1



Scheme 2



corresponding to disconnections based on either a [3 + 2]/[4 + 2] or a [4 + 2]/[3 + 2] cycloaddition sequence. The key step in route A relies on the reaction between phenylisobenzofuran **4** and the pyroline **5**. In route B, the tetracyclic skeleton is obtained by addition of dipole **7** (derived from amine **9**) on the double bond of **6**. This latter compound can be obtained from the corresponding α-selenoester **8**. Two possibilities open at that stage, the first one (B1) relying on ester **10**, obtained by reacting PIBF **4** and an acrylate. The second path of the fork (B2) is based on the direct reaction between **4** and the α-selenoacrylate **11**. We will see in the following that each of these pathways A and B leads stereoselectively to precursors of **2** and **3**, respectively.

Route A: Access to Analogue 2

Let us first discuss the case of route A. The two partners needed for this approach are relatively easy to prepare. The pyroline skeleton of **5** is indeed accessible through the [3 + 2] scheme proposed by Sakurai and Achiwa (Scheme 1).[3] The reaction of chloromethylbutyl ether **12** with lithium amide **13** provides the tertiary amine **9**. The action of a catalytic amount of trifluoroacetic acid on the latter in methylene chloride generates the dipole **7**, which reacts in situ with methyl propiolate at room temperature to yield pyroline **5a** in 59% yield.

On the other hand, phenylisobenzofuran **4** is a well-known compound of which synthesis have been described under both acidic and basic conditions.[4] An acidic medium was anticipated to be hardly compatible with the strained oxygen bridge in the expected adducts. We have thus preferred to prepare the diene through a basic process and resorted to the method described by Tobia and Rickborn,[4c] which relies on phthalane **17** (Scheme 2). This compound has been obtained following Rodrigo and co-workers' convenient procedure.[5] Thus, acetalization of *o*-bromobenzaldehyde **14** followed by bromine−lithium exchange and benzaldehyde condensation provides alcohol **16**, which cyclizes in methanol in the presence of acidic Dowex 50W-X2. The phthalane **17** obtained presents a syn/anti ratio of 43:57. Addition of *n*-butyllithium to **17** triggers a *δ*-elimination and affords, after *tert*-butyl alcohol quenching,[6] the 1-phenylisobenzofuran (PIBF) **4**. This diene has not been isolated or purified and has been trapped in situ by pyrroline **5a** under mild thermal conditions (3 h 20 min at 55 °C in THF). A single adduct **18** was recovered after flash chromatography on silica gel in a mediocre 22% yield for the two steps (Scheme 2).

The NMR analysis indicates that the ring junction proton H^{11} appears as a doublet, indicative of both the regioselectivity and "exo" (with respect to the ester group) selectivity of this reaction. The coupling between H^{11} and H^4 is indeed characteristic of the *β*-orientation of H^{11}. The

(3) (a) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117. (b) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 2762.

(4) (a) Keay, B. A.; Plaumann, H. P.; Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1983**, *61*, 1987. (b) Hayakawa, K.; Yamaguchi, Y.; Kanematsu, K. *Tetrahedron Lett.* **1985**, *26*, 2689. (c) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3849. (d) Porsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. *J. Org. Chem.* **1989**, *54*, 4280.

(5) (a) Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc. Chem. Commun.* **1980**, 354. (b) Kuroda, T.; Takahashi, M.; Kondo, K.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 9560.

(6) Using methanol to quench this reaction leads to a double conjugated addition of lithium methylate on methyl propiolate, providing to the known 2,2-dimethoxy methyl propionate. See, for instance: (a) Walia, J. S.; Walia, A. S. *J. Org. Chem.* **1976**, *41*, 3765. (b) Bertz, S. H.; Dabbagh, G.; Cotte, P. *J. Org. Chem.* **1982**, *47*, 2216. (c) Tietze, L. F.; Meier, H.; Voss, E. *Synthesis* **1988**, 274. (d) Hosokawa, T.; Aoki, S.; Murahashi, S. I. *Synthesis* **1992**, 558.

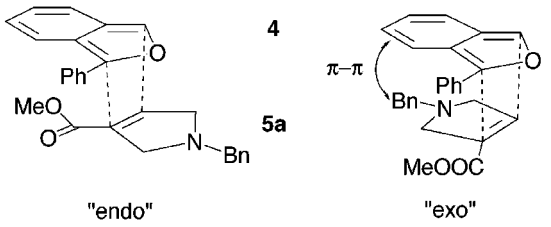
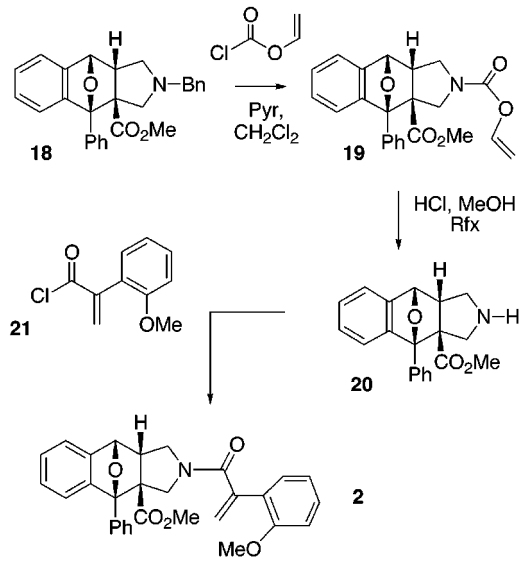


Figure 3. Endo and exo approaches of phenylisobenzofuran **21** by pyroline **3a**.

Scheme 3

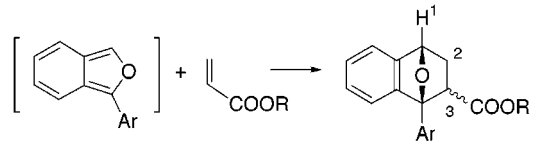


latter, in the α-position, would correspond to a singlet, due to the 90° dihedral angle between H^{11} and H^{4}, as evidenced below. This exo selectivity can be rationalized by a putative $\pi-\pi$ interaction taking place between the benzylic part of **5a** and the cyclohexadienic moiety of **4** (Figure 3).

The following functionalization steps to convert adduct **18** into analogue **2** first go through a debenzylation. All attempts made to hydrogenolyze **18** in the presence of palladium hydroxide (Pearlman's catalyst) have remained unsuccessful, despite several attempts to vary the pressure, the solvent, and the temperature. The N-dealkylation of tertiary amines is known to be possible by the action of vinyl chloroformate (Voc-Cl).[7] The addition of 2 equiv of vinylchloroformate to **18** in dichloromethane in the presence of 2 equiv of pyridine provides carbamate **19** in 49% yield (Scheme 3). The unprotected pyrrolidine **20** is then obtained in 41% yield by refluxing **19** in a methanol solution of hydrochloric acid for 4 h. The final coupling between **20** and the known[8] α-(2-methoxyphenyl)acrylic acid has been accomplished through its chloride **21** in standard conditions.[9] The low 26% yield in the target amide **2** corresponds to an nonoptimized reaction.

In conclusion, this study of route A indicates that the [4 + 2] cycloaddition between PIBF **4** and pyrroline **5a** provides the expected tetracyclic adducts in modest yields but in a fully diastereoselective way. The following functionalization steps have been achieved to connect the resulting adduct to the lateral chain determined from a preliminary structure−activity relationship study.[2] The samples thus obtained have been evaluated for their in vitro activities as farnesyltransferase inhibitors (see below).[10]

Scheme 4



4: Ar = Ph
22: Ar = o-Tol

23a: Ar = Ph, R = Me (endo/exo = 38:62)
23b: Ar = Ph, R = *t*-Bu (endo/exo = 57:43)
24: Ar = o-Tol, R = Me (endo/exo = 44:56)

Route B: Synthesis of Analogue 3

The most convergent B-type approach to the key-synthon **6** requires methylpropiolate and PIBF **4** (Figure 4). Unfortunately, no reaction was observed between these compounds (or propiolic acid and PIBF) at room temperature, while a complex mixture of products, from which no cycloadduct could be identified, was recovered after 4 h 30 min at 100 °C in toluene. We have therefore tried to prepare **6** through the oxidation of the corresponding α-selenoesters **8**, accessible through routes B1 or B2 (Figure 2).

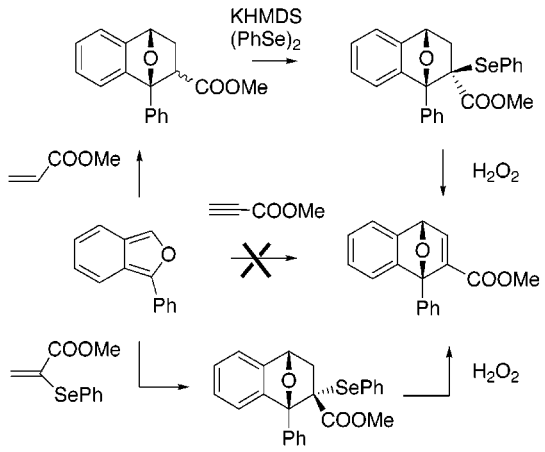


Figure 4. Routes between phenylisobenzofuran **21** and ester **22**.

We first considered the B1 approach by reacting freshly prepared **4** with methyl acrylate at room temperature for 3 h (Scheme 4). The adduct **23a** is obtained as a mixture of isomers in an overall 48% yield. Examples taken from the literature suggest that a mixture of regioisomers was to be expected, even if mainly the "ortho" substitution pattern could be anticipated.[11] A careful NMR analysis led us to the conclusion that only the "ortho" regioisomer **23a** represented had been obtained as a 38:62 mixture of endo and exo isomers.

(7) (a) Olofson, R. A.; Yamamoto, Y. S.; Wancowicz, D. J. *Tetrahedron Lett.* **1977**, 1563. (b) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.

(8) Giraud, E.; Luttmann, C.; Lavelle, F.; Riou, J. F.; Mailliet, P.; Laoui, A. *J. Med. Chem.* **2000**, *43*, 1807.

(9) Only a slight excess of thionyl chloride is to be used to convert the acid **25** into its chloride **26**, since a conjugated addition of chloride onto the acrylate double bond can occur.

(10) Martin, C.; Pichon, N.; Harrison-Marchand, A.; Maddaluno, J.; Mailliet, P., to be published.

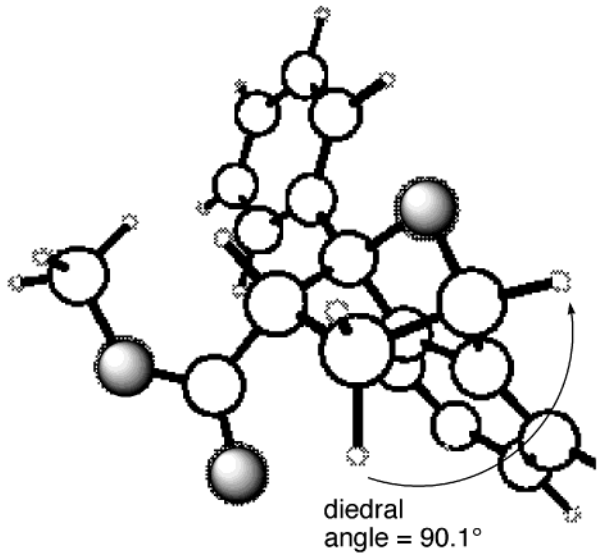
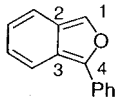


Figure 5. AM1-optimized conformation of cycloadduct **24a**.

Table 1. AM1 Coefficients for the HOMO and Atomic Charges of Phenylisobenzofuran 4



4

HOMO coeff	atomic charges
C1: +0.40	C1: −0.09
C2: +0.03	C2: −0.11
C3: +0.20	C3: −0.01
C4: −0.39	C4: 0.00

A peculiar coupling pattern between their protons H^2 and proton H^1 is worth underlining. Molecular models (as well as the AM1 optimization of **23a** endo, Figure 5) indeed show that the bridgehead proton H^1 lies in a plane more or less perpendicular to the H^2 syn to the bridging oxygen (H^2_β), leading to their almost null coupling constant.[12] This topological peculiarity can be confusing since a superficial analysis of the NMR spectrum could erroneously suggest that the "meta" regioisomer is obtained selectively. The preferred "ortho" regioselectivity can be qualitatively rationalized on the basis of the AM1 analysis of the HOMO coefficients of **4** (Table 1), albeit only very small differences are obtained at this level of calculation for the reagent alone and in its steady state. Regarding the tendency to an exo-favored addition, it is often reported for isobenzofurans[13] but remains difficult to explain. The attribution of the endo and exo structures to the isomers is based on the analysis of the NMR coupling constants. H^2_β is indeed identified through its coupling with H^1, while the amplitude of its coupling constant with H^3 determines the syn or anti character between H^3 and H^2_β, thus the exo or endo character of **23a**.

The possible influence of steric factors on both the regio- and endo/exo selectivities of this reaction has been considered. The access to other regioisomers of **3** was indeed attractive to extend the structure/activity relationship study in this series, and reversing the regioselectivity of the above cycloaddition seemed possible considering the low differences between orbitalar coefficients in the HOMO of **4** (Table 1). To increase the dienophile bulkiness, we resorted to *tert*-butyl acrylate. Its cycloaddition with PIBF takes place at reflux of THF in 2 h and provides adduct **23b** in 73% yield.[14] The regioselectivity remains unaltered while the endo selectivity is slightly enhanced (endo/exo = 57:43, Scheme 4). Mellor and Webb have reported a comparable improvement of the endo preference with the increase of the steric hindrance of the acrylates.[15] The ease of approach of the isobenzofuran nucleus has been also modified replacing the phenyl group of **4** by an *o*-tolyl appendage. The *o*-tolylisobenzofuran **22** has been prepared following the procedure described above (Scheme 2). Its reaction with methyl acrylate takes place at room temperature and provides adduct **24** in 49% yield after 3 h. The regioselectivity is once more unchanged and the endo/exo ratio is 44:56 (Scheme 4). This set of experiments tends to indicate that the regio- and the endoselectivity can hardly be influenced by the choice of the partners.

The oxidation step needed to set the double bond in **6** has been achieved through deprotonation and selenation of **23**. As reported previously,[16] KHMDS is well suited to this task, provided diphenyl diselenide is added to the medium before the deprotonation.[17] The stereoconvergence observed in this reaction converts the two epimeric esters **23** into a single ("endo") α-phenylselenoester **8a** (Figure 4 and Scheme 5). The occurrence of a common intermediate potassium enolate (except for the *E*(O)/*Z*(O) ratio), of which only the convex face is accessible to the electrophile, can explain this selectivity.[16]

Interestingly, the route B2, viz. the thermal cycloaddition between methyl α-phenylselenoacrylate **11** (easily prepared from methyl acrylate and phenylselenium chloride)[18] and in situ generated PIBF **4**, yields selectively the opposite ("exo")[19] epimer **8b**. Because they both feature a proton syn to the selenium atom, the two isomers can be smoothly oxidized by H_2O_2, separately or together, in the same bridged unsaturated ester **6** (Scheme 5).

The crude reaction medium can then undergo a [3 + 2] dipolar cycloaddition with the ylid **7** prepared from amine **9** according to Achiwa's conditions as above. The

(11) (a) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 336. (b) Contreras, L.; McLean, D. *Can. J. Chem.* **1980**, *58*, 2573. (c) Smith, J. G.; Welankiwar, S. S.; Chu, N. G.; Lai, E, H.; Sondheimer, S. J. *J. Org. Chem.* **1981**, *46*, 4658. (d) Rodrigo, R.; Knabe, S. M.; Taylor, N. J.; Rajapaksa, D.; Chernishenko, M. J. *J. Org. Chem.* **1986**, *51*, 3973. (e) Sugahara, M.; Moritani, Y.; Terakawa, Y.; Ogiku, T.; Ukita, T.; Iwasaki, T. *Tetrahedron Lett.* **1998**, *39*, 1377.

(12) For a comparable observation, see: Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267.

(13) (a) Nozaki, H.; Yamaguti, T.; Ueda, S.; Kondo, K. *Tetrahedron* **1968**, *24*, 1445. (b) Hickmott, P. W.; Simpson, R. *J. Chem. Soc. C* **1972**, 302. (c) Smith, J. G.; Welankiwar, S. S.; Shantz, B. S.; Lai, E. H.; Chu, N. G. *J. Org. Chem.* **1980**, *45*, 1817. (d) Rodrigo, R.; Knabe, S. M. *J. Org. Chem.* **1986**, *51*, 3973.

(14) Adduct **23** and **24** cannot be chromatographed on silica gel on which they decompose. See the Experimental Section for details.

(15) Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 17.

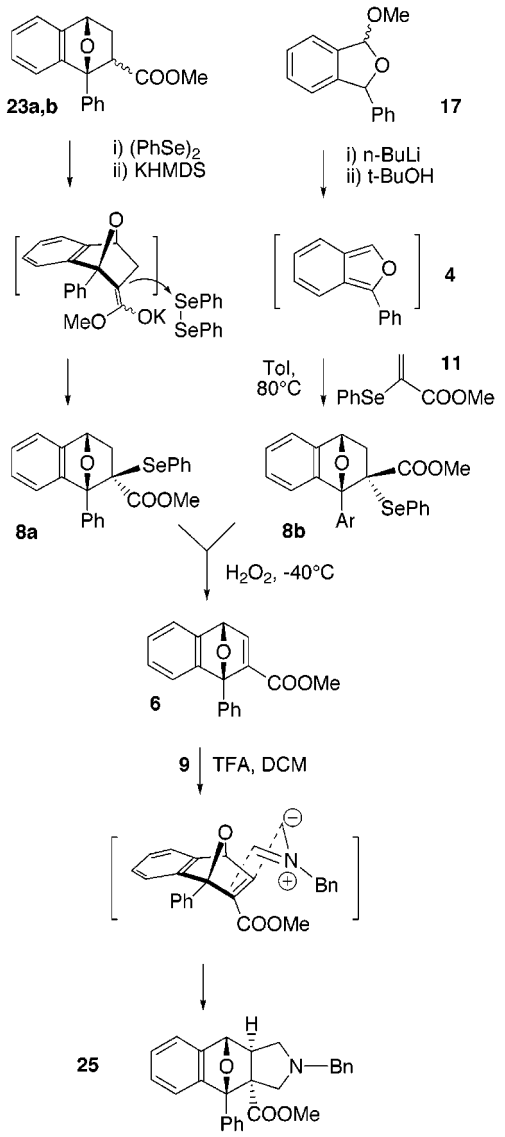
(16) Martin, C.; Maillet, P.; Maddaluno, J. *Org. Lett.* **2000**, *2*, 923.

(17) Rodrigo and colleagues have shown that the electrophile is to be added to PIBF adducts before the base to prevent the oxygen-bridge opening: Keay, B.; Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 1093.

(18) Piettre, S.; Janousek, Z.; Merenyi, R.; Viehe, H. G. *Tetrahedron* **1985**, *41*, 2527.

(19) By contrast, α-phenylthioacrylate reacts with cyclopentadiene under catalytic conditions to yield a major *endo* isomer: Aggarwal, V. K.; Jones. D. E.; Martin-Castro, A. M. *Eur. J. Org. Chem.* **2000**, 2939.

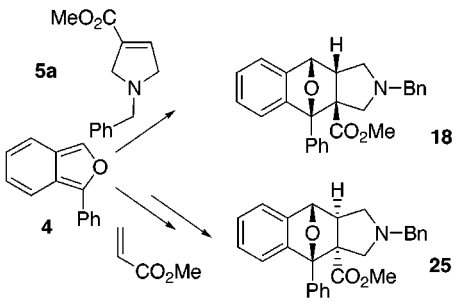
Scheme 5



strong concavity of the bridged skeleton in **6** (Scheme 5) explains why the addition takes place only on the "exo" face,[20] giving pyrrolidine **25** as a single isomer in 7−14% yield from **17** (three to four steps).

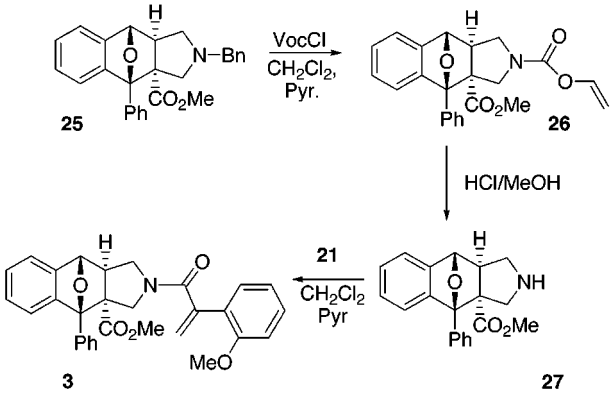
The most important feature of this reaction is definitely its total diastereoselectivity in favor of epimer **25**, indicating that the two B-type strategies (Figure 2) are complementary to route A that provides only **18** (Scheme 6).

Scheme 6



(20) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1.

Scheme 7



The late functionalization steps to convert **25** into **3** are identical to those presented above to transform **18** into **2**. The reaction of **25** with Voc-Cl under the same conditions as in Scheme 3 gives access to carbamate **26** in 53% yield. This compound is deprotected by the same acidic treatment to afford pyrrolidine **27** (Scheme 7) in 70% yield after chromatography. The final coupling with acid chloride **21** takes place in methylene chloride at room temperature and affords the target-amide **3** in 47% purified yield.

In conclusion to this part of the work, the [4 + 2]/[3 + 2] strategy offers a diastereoselective access to **3**, another analogue of farnesyltransferase inhibitor **1**. The bending of the tricyclic intermediate skeleton, due to the presence of the bridging oxygen, is probably responsible for the differentiation of the concave and convex faces toward incoming dipole during the [3 + 2] step.

Conclusion and Biological Activities

Several synthetic routes to new oxygen-bridged analogues of farnesyltransferase inhibitors have been evaluated in this work. The construction of their tetracyclic core has been considered following either a [3 + 2]/[4 + 2] or a [4 + 2]/[3 + 2] sequence of reactions. The first one (route A, Figure 2) has been studied by reacting in situ generated PIBF with pyrroline **5a** and has led stereoselectively to **18**, which has been converted in three steps into **2**. The second approach relies on a key intermediate **6** that could not be prepared by direct reaction between methyl propiolate and PIBF. Its synthesis has been achieved through either: (1) the condensation of PIBF with methyl acrylate, followed by a deprotonation/selenation and an oxidation/elimination sequence (route B1); or (2) the stereoselective cycloaddition between PIBF and α-phenylselenoacrylate **11**, followed by the same oxidation/elimination sequence (route B2).

The reaction between **6** and amino dipole **7** gives a diastereoselective access to **25**, epimer of **18**. The former can be converted into analogue **3** through the same three-step procedure used with **18**.

Finally, these two independent routes have provided two (racemic) stereoselective accesses to the two epimers **2** and **3**, which have been evaluated in farnesyltransferase inhibition tests. New extensions are currently brought to these strategies[10] in an attempt to prepare a larger set of compounds that could help to the detailed mapping of the drug−enzyme active site interaction.

Table 2. Farnesyltransferase Inhibitory Activity of 1−3[a]

compd	FT inhibition (IC_{50},[b] μM)
RPR 115135	0.3
(rac) RPR 115135-methyl ester	1.7
2	$\gg 10$[c]
3	7.5

[a] Purified human Ftase was incubated at 37 °C for 1 h with 50 nM of a Ki-Ras related peptide, Biot-(bA)3-S-K-D-G-(K)6-S-K-T-K-C-V-I-M, 120 nM of FPP and various concentrations of inhibitor in 100 μL final volume. Then 150 μL of a suspension of streptavidin PVT beads was added at pH = 4, thus blocking the farnesylation reaction and giving, thanks to biotin/streptavidin interaction, a scintillation that was measured on a scintillator. [b] IC50 values as means of two or more determinations. [c] 3 and 5% inhibition were found at 10 μM in two separate determinations.

Using X-ray data of a truncated form of human FT cocrystallized with benzo[*f*]perhydroisoindole (BPHI) derivatives,[21] docking experiments suggested that moving the phenyl ring from position 9 to position 4, while keeping the relative stereochemistry of the bridging element and the carboxylate function at position 3a such as in compound **3**, could be easily accommodated in the FPP-binding pocket of FT. On the other hand, similar moving of the phenyl ring from position 9 to position 4, without keeping the relative stereochemistry of the bridge and the carboxylate, such as in compound **2**, should be prohibited. As expected, **2** does not exhibit any inhibition of farnesylation of a Kirsten-Ras 4B related peptide by FT (Table 2). More surprisingly, compound **3** only retains moderate potency (IC50 = 7.5 μM). The FPP-binding pocket of FT is highly hydrophobic and mainly composed of aromatic residues in its deepest part.[22] Since the molecular shape of methyl ester **3** is likely to be accommodated by FT *(docking experiments not shown)*, the drop in activity (4−5-fold) observed with **3**, when compared to methyl ester derivative of RPR 115135 **1** is suspectedly related to the less hydrophobic nature of oxa bridge when compared to the ethano bridge.

Experimental Section

General Aspects. ^{1}H NMR spectra were recorded at 200 or 300 MHz and ^{13}C NMR spectra at 50 MHz; chemical shifts (δ) are given in parts per million (ppm) and the coupling constants (J) in hertz. The solvent was deuteriochloroform or deuteriobenzene. IR spectra were realized by transmission. Gas chromatography analyses were performed on a high-resolution DB-1 type column (30 m, 0.25 mm DB-1). GC/MS analyses were performed on an instrument equipped with the same column. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; methane (CH_4), isobutane (*t*-BuH), or ammonia (NH_3) were used for chemical ionization (CI). The silica gel used for flash chromatography was 0.040−0.063 mm. All reagents were of reagent grade and were used as such or distilled prior to use.

***N*-Benzyl-3-(methylformate)-2,5-dihydropyrrole 5a.**[3b] Under argon was diluted *N*-benzyl-*N*-(butyloxymethyl)trimethylsilylmethylamine **9** (16.74 g, 59.4 mmol, 1.2 equiv) in 100 mL of dry dichloromethane. Methyl propiolate (4.46 mL, 49.6 mmol, 1 equiv) was then added at 0 °C, followed, dropwise, by a solution of trifluoroacetic acid (0.38 mL, 1.7 mmol, 0.03 equiv) in 5 mL of dichloromethane. The reaction was exothermic. The medium was stirred at room temperature for 4 h before being neutralized by adding a saturated solution of $NaHCO_3$. The organic phase was washed with 20 mL of a saturated solution of NaCl and then dried ($MgSO_4$) and evaporated under reduced pressure. Thus, 13.3 g of a crude oil was recovered and purified by silica gel chromatography eluting with petroleum ether/ethyl acetate 60/40 mixture (yield = 59%): IR (neat) 2950, 1724, 1671, 1242, 732 cm^{-1}; EIMS (70 eV) *m*/*z* 217 (M^+, 46), 202 ($M^+ - CH_3$, 16), 184 ($M^+ -$ MeOH − H, 14), 140 ($M^+ -$ Ph, 15), 126 ($M - CH_2Ph$, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 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.[3b]

2-Bromobenzaldehydemethyl Ketal 15. In 8 mL of dry methanol containing Dowex acidic resin (50W-8.50, 100 mesh) was diluted 2-bromobenzaldehyde (1 g, 5.4 mmol, 1 equiv). Trimethylorthoformate (1.80 mL, 3 equiv) was then added and the medium warmed to reflux for 22 h. After filtration, the organic phase was evaporated under reduced pressure. Thus, 1.13 g of a yellow oil was recovered, which did not need purification (yield = 91%): IR (neat) 2934, 1934, 1434, 1102, 754 cm^{-1}; EIMS (70 eV) *m*/*z* 232−230 (M^+, 17), 201−199 ($M^+ - OCH_3$, 100), 185−183 ($M^+ - OCH_3 - CH_3$, 30), 157−155 ($M^+ - CH(OCH_3)_2$, 18), 119 ($M^+ - Br - OCH_3$, 13); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.36 (6H, s), 5.54 (1H, s), 7.16 (1H, dt, J = 1.8, 7.6 Hz), 7.31 (1H, dt, J = 1.2, 7.4 Hz), 7.56 (2H, dd, J = 1.2, 7.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 53.79, 102.86, 122.87, 128.08, 128.23, 129.98, 132.79, 136.74.

Hydroxybenzyl-2-benzaldehyde Methyl Ketal 16. Under argon was diluted 2-bromobenzaldehyde methyl ketal **15** (2.42 g, 10.47 mmol, 1 equiv) in 24 mL of dry ether. At −60 °C was added a solution of *n*-butyllithium 2.4 M (4.8 mL, 1.1 equiv). After 1 h of stirring at the same temperature, a solution of benzaldehyde (1.2 mL, 1.1 equiv) in 4 mL of dry ether that had been previously sonicated for 10 min was added. The medium was stirred at −60 °C for 1 h 30 min before being quenched by addition of 7 mL of water at rt. The aqueous phase was extracted twice with 20 mL of dichloromethane. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Thus, 2.92 g of a colorless oil which did not need any purification was recovered (yield = 95%): IR (neat) 3427, 2902, 1963, 1700, 1456, 1203, 1065 cm^{-1}; GC/EIMS (70 eV) *m*/*z* 256 (13), 241 ($M^+ -$ OH, 24), 225 (73), 209 ($M^+ -$ OMe − H_2O, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.25 (3H, s), 3.30 (3H, s), 3.49 (1H, d, J = 4.7 Hz), 5.40 (1H, s), 6.21 (1H, d, 4.7 Hz), 7.23−7.56 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 53.31, 53.55, 72.41, 102.35, 126.44, 127.03, 128.11, 128.97, 135.18, 141.80−142.60.

1,3-Dihydro-1-methoxy-3-phenylisobenzofuran 17.[5a] A solution of hydroxybenzyl-2-benzaldehyde methyl ketal **28** (2.64 g, 10.23 mmol, 1 equiv) in 30 mL of dry methanol containing Dowex acidic resin (50W-8.50, 100 mesh) was warmed to reflux for 20 h. After filtration, the medium was evaporated under reduced pressure. Thus, an orange oil that did not need any purification was recovered. The product was obtained as a cis/trans (43/57) mixture (yield = 85%): IR (neat) 3040, 2893, 1677, 1475, 1272, 1000, 752 cm^{-1}; EIMS (70 eV) *m*/*z* 225 ($M^+ -$ H, 16), 194 ($M^+ -$ MeOH, 84), 165 ($M^+ -$ OMe − OCH, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) cis product 3.58 (3H, s), 6.11 (1H, s), 6.22 (1H, s), 7.02 (1H, m), 7.23−7.41 (8H, m), trans product 3.53 (3H, s), 6.27 (1H, d, J = 2.0 Hz), 6.35 (1H, d, J = 2.0 Hz), 7.02 (1H, m), 7.23−7.41 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ(ppm) (cis/trans mixture) 55,10, 55.41, 85.06, 85.86, 107.16, 107.53, 122.14, 122.71, 122.83, 127.28, 127.58, 127.97, 128.27, 128.45, 128.57, 128.91, 129.67, 137.15, 137.52, 140.67, 141.61, 142.79, 143.17.

4,9-Epoxy-9-phenyl-2-phenylmethyl-1,3,4,9,1,11-hexahydrobenzo[*f*]isoindole-10β-methylcarboxylate 18. Under argon, to a solution of 1,3-dihydro-1-methoxy-3-(2-phenyl)-isobenzofuran **17** (1.04 g, 4.60 mmol, 1 equiv) in 10 mL of dry ether, was added, at rt, a solution of *n*-butyllithium (2.85 mL, 2.1 M, 5.6 mmol, 1.3 equiv). The medium became dark. After 15 min, a solution of *tert*-butyl alcohol (0.44 g, 5.6 mmol, 1.3 equiv) in 3 mL of dry THF was added, and the medium became red. After 5 min, pyrroline **5a** (1.02 g, 1 equiv) was added, the reaction mixture was warmed to 55 °C for 3 h 20 min, and

(21) Laoui, A. *Structure-aided approach for lead optimisation: Application to farnesyltransferase inhibitors*; oral communication #227 at the 221st ACS National Meeting, San Diego, April 1−5, 2001.

(22) Park, H.-W.; Bodoluri, S. R.; Moomaw, J. F.; Casey, P. J.; Beese, L. S. *Science* **1997**, *275*, 1800.

then the reaction was quenched with 8 mL of water. The aqueous phase was extracted three times with 10 mL of ether. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Thus, 2.33 g of an oil was recovered, which was purified by silica gel chromatography eluting with heptane/ethyl acetate 90/10 then 80/20 mixture (yield = 22%). The product **18** could be recrystallized in ethyl acetate (F = 116 °C): IR (neat) 2782, 1723, 1456, 1267, 1207, 899, 733 cm^{-1}; CIMS (*t*-BuH) *m/z* 412 (M + 1, 100); HRMS/CI (*t*-BuH) calcd for $C_{27}H_{26}O_3N$ *m/z* 412.1913, found 412.1924; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.31 (1H, dd, J = 6.9, 7.5 Hz), 2.62 (1H, d, J = 10.5 Hz), 2.75 (1H, d, J = 10.5 Hz), 3.14 (2H, s), 3.22 (3H, s), 3.69 (2H, m), 5.45 (1H, d, J = 5.5 Hz), 6.77 (2H, m), 7.12−7.50 (12H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 51.77, 52.53, 52.96, 56.91, 59.53, 66.05, 80.24, 94.22, 120.25, 120.31, 125.21, 126.48, 126.68, 126.93, 127.02, 127.59, 127.69, 127.90, 128.13, 128.40, 128.81, 136.03, 138.40, 144.85, 145.34, 173.90.

Methyl 4,9-Epoxy-2-vinylformate-9-phenyl-1,3,4,9,1,11-hexahydrobenzo[*f*]isoindole-10β-carboxylate 19. Procedure A. To a solution of pyrrolidine **18** (145 mg, 0.36 mmol, 1 equiv) in 1.5 mL of dichloromethane were added, at rt, pyridine (0.058 mL, 0.72 mmol, 2 equiv) and vinyl chloroformate (0.066 mL, 0.72 mmol, 2 equiv). After 5 h 20 min, the medium was quenched with 1 mL of a saturated solution of $NaHCO_3$. The organic phase was washed with 1 mL of a saturated solution of sodium chloride, dried ($MgSO_4$), and evaporated under reduced pressure. Thus, 151 mg of an oil was recovered, which was purified by silica gel chromatography eluting with dichloromethane/methanol 98/2. After purification, 70 mg of solid **19** was obtained (yield = 49.5%).

Procedure B. Under argon, to a solution of 1,3-dihydro-1-methoxy-3-phenylisobenzofuran **17** (1.72 g, 7.61 mmol, 1 equiv) in 17 mL of dry ether was added, at rt, a solution of *n*-butyllithium (4.20 mL, 2.35 M, 9.9 mmol, 1.3 equiv). The medium became dark. After 15 min, 0.13 mL of water was added, and the medium became red. After 2 min, a solution of pyrroline **5b** (1.5 g, 1 equiv) in 17 mL of THF was added. The medium was warmed at 55 °C for 3 h 30 min, and then the reaction was quenched with 5 mL of water. The aqueous phase was extracted twice with 20 mL of ether. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Thus, 4 g of an oil was recovered, which was purified by silica gel chromatography eluting with a dichloromethane/methanol (98/2) mixture (yield = 27%): F = 118 °C; IR (neat) 2957, 1728, 1428, 1272, 1226, 1152, 733 cm^{-1}; CIMS (*n*-BuH) *m/z* 392 (M + 1, 56), 263 (26), 195 (M + 1 − **3b**, 100); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) (two rotamers) 3.12 (1H, m), 3.15 (1H, m), 3.21 (3H, s), 3.23 (3H, s), 3.27 (1H, d, J = 8.8 Hz), 3.31 (1H, d, J = 7.4 Hz), 3.55 (1H, d, J = 12.7 Hz), 3.62 (1H, d, J = 12.8 Hz), 3.64 (1H, m), 3.70 (1H, d, J = 10.7 Hz), 3.71 (1H, d, J = 12.7 Hz), 4.31 (1H, dd, J = 1.4, 6.2 Hz), 4.60 (1H, dd, J = 1.2, 14.0 Hz), 5.54 (1H, d, J = 4.7 Hz), 6.71 (1H, dd, J = 6.5, 14.0 Hz), 6.78 (1H, dd, J = 6.4, 13.0 Hz), 7.14−7.54 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) (two rotamers) 44.83, 44.92, 48.96, 49.04, 51.78, 52.14, 64.92, 65.52, 80.28, 94.98, 95.21, 120.22, 120.41, 120.72, 121.02, 125.10, 126.97, 127.22, 127.58, 127.68, 128.02, 128.17, 135.06, 141.95, 142.02, 143.13, 143.27, 149.87, 150.04, 172.65.

Methyl 4,9-Epoxy-9-phenyl-1,3,4,9,1,11-hexahydrobenzo[*f*]isoindole-10β-carboxylate 20. Carbamate **19** (389 mg, 0.99 mmol, 1 equiv) was diluted in 5 mL of a solution of hydrochoric acid 1.5 M in methanol. The medium was warmed at reflux for 3h45 then evaporated under reduced pressure. The residue was diluted in 5 mL of dichloromethane and neutralized with saturated $NaHCO_3$. The organic phase was washed with 1 mL of brine, dried ($MgSO_4$), and evaporated under reduced pressure. Thus, 239 mg of an oily compound was recovered that was purified by silica gel chromatography eluting with a dichloromethane/methanol (95/5) mixture (yield = 41%): F = 167 °C; IR (neat) 2948, 1728, 1461, 1323, 1267, 908, 738 cm^{-1}; CIMS (*n*-BuH) *m/z* 322 (M + 1, 100); HRMS/CI (*n*-BuH) calculated for $C_{20}H_{20}O_3N$ *m/z* 322.1443, found 322.1445; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.46 (1H, d, J = 13.0 Hz), 2.58 (1H, dd, J = 6.6, 13.0 Hz), 2.81 (1H, d, J = 13.6 Hz), 3.07 (1H, d, J = 13.6 Hz), 3.19 (3H, s), 3.61 (1H, dd, J = 5.8, 6.0 Hz), 5.43 (1H, d, J = 5.5 Hz), 7.17−7.51 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 47.29, 51.73, 55.54, 68.65, 80.05, 94.25, 120.01, 120.54, 125.09, 127.42, 127.74, 128.05, 135.69, 143.46, 143.88, 173.84.

Methyl-4,9-epoxy-2-[2-(2-methoxyphenyl)propen-2-oyl]-9-phenyl-1,3,4,9,1,11-hexahydrobenzo[*f*]isoindole-10β-carboxylate 2. Under argon, to a solution of 2-(2-methoxyphenyl)propen-2-oic acid (144 mg, 0.72 mmol, 1.9 equiv) in 1.5 mL of dichloromethane was added thionyl chloride (0.06 mL, 0.76 mL, 2 equiv). After 15 h at rt, the excess of thionyl chloride was evaporated under reduced pressure. The 2-(2-methoxyphenyl)propen-2-oyl chloride **21** left over was then diluted directly in 1 mL of dichloromethane and added to a solution of amine **20** (124 mg, 0.38 mmol, 1 equiv) in 4 mL of dichloromethane and pyridine (0.064 mL, 0.79 mmol, 2.1 equiv) at 0 °C and under argon. The medium was stirred at rt for 1 h 15 min before being quenched by 1 mL of a saturated solution of $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. After purification by silica gel chromatography eluting with dichloromethane/methanol 95/5 mixture, 42 mg of **33** was recovered (two rotamers: 55/45) (yield = 26%): IR (neat) 2957, 1728, 1640, 1452, 1296, 1221, 927, 758 cm^{-1}; CIMS (*n*-BuH) *m/z* 482 (M + 1, 24), 288 (**33**, 94), 251 (42), 195 (**4** + 1, 100); HRMS/CI (*n*-BuH) calcd for $C_{30}H_{28}O_5N$ *m/z* 482.1968, found 482.1985; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) (two rotamers) 2.90 (2H, m), 3.24 (3H, s), 3.30 (1H, d, J = 12.7 Hz), 3.40 (2H, m), 3.68 (3H, s), 3.70 (3H, s), 3.77 (1H, m), 3.84 (1H, m), 3.86 (1H, d, J = 11.6 Hz), 4.88 (1H, s), 5.10 (1H, s), 5.43 (1H, s), 5.45 (1H, d, J = 6.3 Hz), 5.48 (1H, s), 5.55 (1H, d, J = 5.5 Hz), 6.77−7.54 (13H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) (2 rotamers) 44.70, 47.28, 48.95, 51.75, 51.66, 52.13, 52.49, 52.78, 55.50, 55.65, 64.48, 66.19, 80.28, 80.55, 95.12, 110.84, 110.96, 116.31, 120.11, 120.19, 120.39, 120.99, 121.30, 121.43, 124.94, 125.14, 127.24, 127.49, 127.67, 127.93, 128.14, 129.00, 129.22, 129.61, 135.16, 142.06, 142.31, 142.51, 143.18, 144.37, 156.07, 156.26, 168.14, 168.09, 172.94.

3-Methylcarboxylate-1,4-epoxy-4-phenyl-1,2,3,4-tetrahydronaphthalene 23a. Under argon, to a solution of 1,3-dihydro-1-methoxy-3-(2-phenyl)isobenzofuran **17** (111 mg, 0.48 mmol, 1 equiv) in 2 mL of dry ether was added, at rt, a solution of *n*-butyllithium (0.52 mL, 2.3 M, 2.5 equiv). The medium became dark. After 15 min, *tert*-butyl alcohol (0.11 mL, 20.5 equiv) was added, and the medium became red. After 5 min, methyl acrylate (0.086 mL, 2 equiv) was added. The medium was stirred at rt for 1 h 30 min and quenched with 1 mL of water. The aqueous phase was extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Thus, the crude product was recovered as an endo/exo mixture (endo/exo 38/62) that was purified by silica gel chromatography eluting with petroleum ether/ethyl acetate 95/5 then 90/10 mixture (yield = 48%). The two epimers could be separated by flash chromatography on silica gel: IR (neat) 2950, 1732, 1460, 1170, 910, 732 cm^{-1}; CIMS (*n*-BuH) *m/z* 281 (M + 1, 100); HRMS/CI (*n*-BuH) calculated for $C_{18}H_{17}O_3$ *m/z* 281.1178, found: 281.1169; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) endo product 1.97 (1H, dd, J = 3.9, 11.6 Hz), 2.65 (1H, m), 3.45 (3H, s), 3.64 (1H, dd, J = 4.0, 10.4 Hz), 5.49 (1H, d, J = 5.0 Hz), 7.00−7.74 (9H, m), exo product 1.94 (1H, dd, J = 8.4, 11.4 Hz), 2.63 (1H, ddd, J = 4.6, 5.2, 11.4 Hz), 3.05 (1H, dd, J = 4.6, 8.4 Hz), 3.30 (3H, s), 5.66 (1H, d, J = 5.2 Hz), 7.10−7.59 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) endo product 34.78, 47.24, 51.67, 78.28, 91.70, 118.68, 121.32, 126.46, 127.24, 127.77, 128.19, 128.43, 135.61, 144.37, 145.98, 173.43, exo product 35.15, 49.17, 51.49, 78.06, 91.70, 118.54, 119.11, 125.64, 126.73, 127.10, 127.58, 128.09, 135.61, 145.60, 146.79, 173.48.

3-Butylcarboxylate-1,4-epoxy-4-phenyl-1,2,3,4-tetrahydronaphthalene 23b. Under argon, to a solution of 1,3-dihydro-1-methoxy-3-phenylisobenzofuran **17** (0.29 g, 1.28 mmol, 1 equiv) in 7 mL of dry ether was added, at rt, a solution of *n*-butyllithium (1.15 mL, 2.25 M, 2 equiv). The medium became dark. After 15 min, a solution of *tert*-butyl alcohol (0.19 g, 2.58 mmol, 2 equiv) in 2 mL of ether was added, and the

medium became red. After 5 min, a solution of *tert*-butyl acrylate (0.37 mL, 2.58 mmol, 2 equiv) in 10 mL of dry THF was added. The medium was warmed at reflux for 2 h 20 min and then was quenched with 5 mL of water. The aqueous phase was extracted twice with 10 mL of ethyl acetate. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Thus, 0.46 g of an oil was recovered that could not be purified by silica gel chromatography. The product was obtained under an endo/exo (57/43) mixture. A gummy precipitate appeared upon dilution into a petroleum ether/ethyl acetate (90/10) mixture, that was discarded by centrifugation. The remaining solution was then evaporated under reduced pressure and compound **34** recovered as an orange oil (yield = 73%): CIMS (CH_4) *m*/*z* 323 (M + 1, 47), 195 (M + 1 − CH_2CHCO_2-*t*-Bu, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) endo product 0.99 (9H, s), 1.96 (1H, dd, J = 4.0, 10.9 Hz), 2.56 (1H, ddd, J = 5.5, 9.8, 10.9 Hz), 3.57 (1H, m), 5.46 (1H, d, J = 5.0 Hz), 7.20−7.80 (9H, m), exo product: 1.03 (9H, s), 1.86 (1H, dd, J = 8.2, 11.7 Hz), 2.63 (1H, ddd, J = 4.7, 4.0, 11.7 Hz), 2.88 (1H, dd, J = 4.0, 8.4 Hz), 5.62 (1H, d, J = 4.7 Hz), 7.20−7.80 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) endo/exo mixture 27.70, 28.00, 34.42, 34.88, 48.07, 49.55, 77.59, 78.00, 80.45, 80.84, 118.60, 118.99, 121.45, 126.18, 126.51, 126.93, 127.18, 127.46, 127.96, 128.17, 128.35, 135.85, 136.70, 144.49, 145.95, 146.13, 170.57, 171.97.

3-Methylcarboxylate-1,4-epoxy-4-(*o*-tolyl)-1,2,3,4-tetrahydronaphthalene 24. Under argon, to a solution of 2-bromobenzaldehyde methyl ketal **15** (2.03 g, 8.78 mmol, 1 equiv) in 10 mL of dry ether was added, at −55 °C, *n*-butyllithium (3.85 mL, 2.5 M, 9.65 mmol, 1.1 equiv). After 1 h of stirring at −60 °C, a solution of *o*-tolualdehyde (1.10 mL, 9.65 mmol, 1.1 equiv) in 4 mL of dry ether was added, which had been previously sonicated for 10 min. The medium was stirred at −60 °C for 1 h 30 min before being quenched by adding 10 mL of water at rt. The aqueous phase was extracted twice with 15 mL of dichloromethane. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Thus, 2.17 g of a colorless oil corresponding to hydroxybenzyl-2-*o*-tolualdehyde methyl ketal was recovered, that cristallized later on (yield = 91%): mp = 63 °C; IR (neat) 3434, 2970, 1467, 1377, 1203 cm^{-1}; CIMS (CH_4) *m*/*z* 255 (M − OH, 38), 209 (M + 1 − $(OMe)_2$, 100);^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.06 (3H, s), 3.32 (3H, s), 3.39 (3H, s), 5.54 (1H, s), 6.42 (1H, s), 6.87−7.46 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 19.11, 53.10, 53.99, 68.48, 103.23, 125.75, 126.37, 127.09, 127.15, 127.38, 127.69, 128.94, 130.11, 135.15, 135.55, 140.59, 141.41.

A solution of hydroxybenzyl-2-*o*-tolualdehyde methyl ketal prepared above (1.61 g, 5.91 mmol, 1 equiv) in 20 mL of dry methanol containing Dowex acid resin (50W-8.50, 100 mesh) was warmed for 13 h at reflux. After filtration, the medium was evaporated under reduced pressure. Thus, 1.04 g of an orange oil was recovered, which did not need any purification, and the 1,3-dihydro-1-methoxy-3-(2-tolyl)isobenzofuran, precursor of **22**, was obtained as a cis/trans (36/64) mixture (yield = 73%): IR (neat) 2939, 1668, 1608, 1465, 1373, 1000, 756 cm^{-1}; EIMS (70 eV) *m*/*z* 240 (M^+, 6), 239 (M^+ − H, 17), 208 (M^+ − MeOH, 100), 194 (M^+ − OMe − Me, 30); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) cis product 2.57 (3H, s), 3.54 (3H, s), 6.28 (1H, s), 6.49 (1H, s), 7.06−7.47 (8H, m), trans product: 2.43 (3H, s), 3.59 (3H, s), 6.36 (1H, d, J = 1.8 Hz), 6.61 (1H, bs), 7.06−7.47 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) (cis/trans mixture) 19.27, 19.48, 55.18, 55.45, 82.18, 82.45, 107.05, 107.33, 122.11, 122.17, 122.85, 123.03, 126.24, 127.73, 127.88, 127.97, 128.24, 129.45, 130.34, 130.84, 135.58, 136.36, 137.76, 138.12, 139.34, 142.61, 142.89.

Under argon, to a solution of 1,3-dihydro-1-methoxy-3-(2-tolyl)isobenzofuran prepared above (0.31 g, 1.29 mmol, 1 equiv) in 8 mL of dry ether was added a solution of *n*-butyllithium (1.15 mL, 2.25 M, 2 equiv) at rt. The medium became dark. After 15 min, a solution of *tert*-butyl alcohol (0.19 g, 2.58 mmol, 2 equiv) in 2 mL of ether was added, and the medium became red. After 10 min was added methyl acrylate (0.20 mL, 2.58 mmol, 2 equiv). The medium was stirred at rt for 3 h and then was quenched by adding 3 mL of water. The aqueous phase was extracted twice with 10 mL of ethyl acetate. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Thus, 0.45 g of crude product was recovered as an endo/exo (44/56) mixture, which was purified by silica gel chromatography eluting with petroleum ether/ethyl acetate 90/10 mixture (yield = 49%). During the flash chromatography, the two epimers could be separated: IR (neat) 2948, 1732, 1461, 1267, 1166, 908, 756 cm^{-1}; CIMS (*t*-BuH) *m*/*z* 295 (M + 1, 100); HRMS/CI (*t*-BuH) calcd for $C_{19}H_{19}O_3$ *m*/*z* = 295.1334, found 295.1353; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) endo product 1.92 (1H, dd, J = 3.6, 11.5 Hz), 2.02 (3H, s), 2.58 (1H, ddd, J = 5.0, 11.5, 10.2 Hz), 3.44 (3H, s), 3.85 (1H, dd, J = 3.6, 10.2 Hz), 5.51 (1H, d, J = 5.0 Hz), 6.84 (1H, d, J = 7.1 Hz), 7.08−7.34 (6H, m), 7.93 (1H, m), exo product 1.02 (1H, dd, J = 8.6, 11.3 Hz), 2.57 (4H, m), 3.30 (1H, m), 3.37 (3H, s), 5.62 (1H, d, J = 5.2 Hz), 7.06−7.60 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ(ppm) endo product 21.63, 34.43, 47.05, 51.68, 78.18, 92.22, 118.91, 121.09, 125.22, 126.39, 127.09, 128.73, 129.16, 131.82, 133.65, 139.67, 144.23, 144.55, 172.36, exo product 21.83, 35.35, 48.59, 51.59, 77.40, 92.55, 119.17, 120.07, 125.64, 126.4, 126.87, 127.07, 127.71, 131.74, 134.60, 146.04, 146.49, 173.82.

3α-Methylcarboxylate-3*β*-phenylselenyl-1,4-epoxy-4-phenyl-1,2,3,4-tetrahydronaphthalene 8a. To a solution of the endo isomer of 3-methylcarboxylate-1,4-epoxy-4-phenyl-1,2,3,4-tetrahydronaphthalene **23a** (59 mg, 0.21 mmol, 1 equiv) in 1 mL of THF were added, under argon at rt, a solution of diphenyldiselenide (0.13 g, 0.42 mL, 2 equiv) in 1.3 mL of THF and a solution of KHMDS in THF (0.9 M, 0.46 mL, 0.42 mmol, 2 equiv). After 30 min, the solvent was evaporated under reduced pressure before the addition of dichoromethane. The medium was filtered. The liquid phase was evaporated under reduced pressure. Thus, 0.19 g of an oil was recovered that could be purified by silica gel chromatography eluting with a petroleum ether/ethyl acetate (95/5) mixture (yield = 34%). This compound is difficult to purify and was thus generally used as a crude mixture in the next step. When the mixture of the two isomers of **23** was used as starting material, the reaction time had to be increased from 30 min to 3 h: IR (neat) 3056, 2950, 1724, 1460, 1262 cm^{-1}; CIMS (*t*-BuH) *m*/*z* 437 (M + 1, 45), 281 (M + 1-SePh, 100); HRMS/CI (*t*-BuH) calcd for $C_{24}H_{21}O_3Se$ *m*/*z* 437.0656, found 437.0662 for ^{80}Se, 435.0613 for ^{78}Se; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.51 (1H, d, J = 12.8 Hz), 2.73 (H, dd, J = 5.1, 12.8 Hz), 3.41 (3H, s), 5.50 (1H, d, J = 5.1 Hz), 7.10−8.15 (14H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 43.62, 51.91, 59.90, 77.73, 119.07, 121.58, 125.77, 126.63, 127.34, 127.82, 128.15, 128.59, 128.93, 135.67, 137.12, 143.82, 145.63, 172.02.

3-Methylcarboxylate-1,4-epoxy-4-phenyl-1,4-dihydronaphthalene 6. To a solution of crude 3α-methylcarboxylate-3*β*-phenylselenyl-1,4-epoxy-4-phenyl-1,2,3,4-tetrahydronaphthalene **8a** (1.01 g) in 8 mL of dichloromethane was added a 35% solution of H_2O_2 (0.42 mL) at −40 °C. The medium was stirred for 1 h at −40 °C. The organic phase was washed with a saturated solution of sodium sulfite until negative peroxide test. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Thus, 0.46 g of a yellow oil was recovered. Compound **22** could not be purified by flash chromatography and was therefore used as such in the next step. The procedure was the same when using 3*β*-methylcarboxylate-3α-phenylselenyl-1,4-epoxy-4-phenyl-1,2,3,4-tetrahydronaphthalene **8b** as starting material: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.62 (3H, s), 5.86 (1H, d, J = 1.8 Hz), 7.00−7.75 (H, m), 7.80 (1H, d, J = 1.8 Hz).

Methyl α-Phenylselenoacrylate 11.[17] A solution of phenylselenium chloride (0.46 g, 2.40 mmol, 1 equiv) in 5 mL of dichloromethane was added on dry $ZnCl_2$ (0.32 g, 1 equiv) under argon. The medium was stirred for 45 min at rt and then was added dropwise methyl acrylate (0.21 mL, 1 equiv); the solution became colorless. After addition of triethylamine (0.50 mL, 1,5 equiv) and 10 mL of toluene, the reaction was brought to reflux for 13 h. Water (8 mL) was then added after the mixture returned to rt. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried

($MgSO_4$) and evaporated under reduced pressure. Thus, 0.47 g of a dark oil was recovered (yield = 82%): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.80 (3H, s), 5.31 (1H, s), 6.64 (1H, s), 7.10−7.60 (5H, m). This NMR spectrum is identical to that described in the literature.[17]

3*β*-Methylcarboxylate-3α-phenylselenyl-1,4-epoxy-4-phenyl-1,2,3,4-tetrahydronaphthalene 8b. Under argon, to a solution of 1,3-dihydro-1-methoxy-3-phenylisobenzofuran **17** (2.57 g, 11.39 mmol, 1 equiv) in 35 mL of dry ether was added, at rt, a solution of *n*-butyllithium (7.70 mL, 2.22 M, 1.5 equiv). The medium became dark. After 15 min, *tert*-butyl alcohol (1.60 mL, 1.5 equiv) was added, and the medium became red. After 5 min, a solution of methyl α-phenylselenoacrylate **11** (3.31 g, 1.2 equiv) in 30 mL of dry toluene was added. The medium was warmed at 80 °C for 2 h and then was quenched with 20 mL of water. The aqueous phase was extracted twice with 40 mL of ethyl acetate. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Thus, 5.82 g of a dark oil was recovered. The purification by silica gel chromatography (petroleum ether/ethyl acetate 95/5 mixture) was inefficient, and **23b** was obtained in less than 25% yield. Therefore, compound **23b** was generally used in the next step as a crude mixture: IR (neat) 2995, 2858, 1726, 1444, 1385, 1237, 1120 cm^{-1}; CIMS (CH_4) *m*/*z* 437 (M + 1, 15), 279 (M + 1 − SePh − H_2, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.83 (1H, d, J = 12.4 Hz), 3.08 (3H, s), 3.52 (H, dd, J = 5.4, 12.4 Hz), 5.53 (1H, d, J = 5.4 Hz), 7.03−7.95 (14H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 41.76, 52.16, 59.21, 77.67, 94.38, 119.08, 125.79, 126.64, 127.39, 127,74, 127.82, 128.17, 128.35, 128.63, 128.95, 135.70, 136.40, 137.13, 144.22, 143.92, 146.15, 171.54.

Methyl 4,9-Epoxy-9-phenyl-2-phenylmethyl-1,3,4,9,1,-11-hexahydrobenzo[*f*]isoindole-10α-carboxylate 25. To crude 3-methylcarboxylate-1,4-epoxy-4-phenylnaphthalene **6** in 20 mL of dichloromethane and under argon was added amine **9** (4.29 g, 1 equiv with respect to starting 1,3-dihydro-1-methoxy-3-phenylisobenzofuran **17**) in 5 mL of dichloromethane. At rt, trifluoroacetic acid (0.10 mL, 0.1 equiv) was added dropwise. After 3 h 15 min, the medium was neutralized by a saturated solution of sodium bicarbonate. The organic phase was washed with 5 mL of saturated solution of sodium chloride, dried ($MgSO_4$), and evaporated under reduced pressure. An oily compound (4.79 g) was thus recovered, which was purified by silica gel chromatography eluting with a petroleum ether/ethyl acetate (90/10) mixture (yield = 3−14% for three steps): IR (neat) 2951, 2783, 1713, 1456, 1258, 1212, 901 cm^{-1}; CIMS (*t*-BuH) *m*/*z* 412 (M + 1, 100); HRMS/CI (*t*-BuH) calcd for $C_{27}H_{26}O_3N$ *m*/*z* 412.1913, found 412.1913; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.27 (1H, d, J = 9.6 Hz), 2.35 (1H, t, J = 8.1 Hz), 3.20 (1H, t, J = 7.9 Hz), 3.34 (1H, d, J = 7.9 Hz), 3.40 (3H, s), 3.48 (1H, d, J = 9.5 Hz), 3.56 (2H, s), 5.22 (1H, s), 6.94−7.77 (14H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 52.02, 54.82, 58.28, 59.71, 59.91, 66.27, 81.06, 92.94, 119.29, 120.43, 126.57, 126.84, 127.06, 127.22, 127.87, 128.15, 128.38, 136.00, 138.63, 144.87, 145.83, 173.83.

Methyl 4,9-Epoxy-2-vinylformate-9-phenyl-1,3,4,9,1,11-hexahydrobenzo[*f*]isoindole-10α-carboxylate 26. To a solution of compound **25** (195 mg, 0.47 mmol, 1 equiv) in 2 mL of dichloromethane were added, at rt, pyridine (0.08 mL, 2 equiv) and vinyl chloroformate (0.09 mL, 2 equiv). After 4 h, the medium was quenched with 1 mL of a saturated solution of $NaHCO_3$. The organic phase was washed with 1 mL of a saturated solution of sodium chloride, dried ($MgSO_4$), and evaporated under reduced pressure. Thus, 195 mg of an oil was recovered, which was purified by silica gel chromatography, eluting with a dichloromethane/methanol (99.5/0.5) mixture (yield = 53%): IR (neat) 2948, 1719, 1410, 1221, 1152, 908, 756 cm^{-1}; CIMS (*t*-BuH) *m*/*z* 392 (M + 1, 38), 374 (M + 1 − H_2O, 7), 263 (100); HRMS/CI (*t*-BuH) calculated for $C_{23}H_{22}O_5N$ *m*/*z* 392.1498, found 392.1496; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) (two rotamers) 3.15 (1H, m), 3.45 (3H, s), 3.47 (1H, d, J = 12.2 Hz), 3.60 (1H, dd, J = 5.2, 13.6 Hz), 4.02 (2H, m), 4.39 (2H, m), 4.67 (1H, d, J = 14.0 Hz), 4.77 (1H, d, J = 14.0 Hz), 5.28 (1H, s), 7.11−7.73 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) (two rotamers) 50.29, 50.61, 51.49, 52.07, 52.31, 54.23, 65.12, 66.17, 82.66, 93.49, 95.32, 95.46, 119.15, 121.35, 121.57, 126.80, 127.43, 128.20, 128.37, 135.33, 142.10, 144.53, 144.82, 151.04, 151.30, 172.84.

Methyl 4,9-Epoxy-9-phenyl-1,3,4,9,1,11-hexahydrobenzo[*f*]isoindole-10α-carboxylate 27. Carbamate **26** (97.5 mg, 0.25 mmol, 1 equiv) was diluted in 1.5 mL of a solution of hydrochloric acid 1.5 M in methanol. The medium was warmed at reflux temperature for 6 h 30 min, and then methanol was evaporated under reduced pressure. The residue was diluted in dichloromethane and neutralized with saturated $NaHCO_3$. The organic phase was washed with brine (1 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Thus, 56.2 mg of an oily compound was recovered, that was purified by silica gel chromatography eluting with a dichloromethane/methanol (92/8) mixture (yield = 57%): IR (neat) 2930, 1728, 1461, 1277, 1207, 908, 738 cm^{-1}; CIMS (*t*-BuH) *m*/*z* 322 (M + 1, 100); HRMS/CI (*t*-BuH) calcd for $C_{20}H_{20}O_3N$ *m*/*z* 322.1443, found 322.1438; ^{1}H NMR (200 MHz, C_6D_6) δ (ppm) 2.80 (2H, m), 3.02 (3H, s), 3.10 (1H, m), 3.15 (1H, d, J = 12.5 Hz), 3.32 (1H, d, J = 12.5 Hz), 4.75 (1H, s), 6.80−7.30 (7H, m), 8.11 (2H, d, J = 7.5 Hz); ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 51.01, 53.00, 55.26, 58.51, 66.67, 82.04, 93.10, 118.66, 121.68, 126.21, 126.58, 127.20, 127.68, 136.73, 146.07, 146.99, 173.71.

Methyl 4,9-Epoxy-2-[2-(2-methoxyphenyl)propen-2-oyl]-9-phenyl-1,3,4,9,1,11-hexahydrobenzo[*f*]isoindole-10α-carboxylate 3. To a solution of amine **27** (87 mg, 0.27 mmol, 1 equiv) in 3 mL of dichloromethane was added pyridine (0.021 mL, 0.27 mmol, 1 equiv), under argon and at 0 °C, and the solution of the acyl chloride **21** previously prepared. The medium was stirred at rt for 1 h 30 min before being quenched with 2 mL of saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. After silica gel chromatography eluting with a dichloromethane/methanol (92/8) mixture, 61 mg of **3** (two rotamers 50/50) was recovered as a white solid (yield = 47%): F = 170 °C; IR (neat) 2957, 1742, 1627, 1433, 1295, 1320, 908, 738 cm^{-1}; CIMS (*t*-BuH) *m*/*z* 482 (M + 1, 10), 288 (M + 1 − **21**, 100); HRMS/CI (*t*-BuH) calcd for $C_{30}H_{28}O_5N$ *m*/*z* 482.1968, found 482.1981; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) (two rotamers) 3.15 (2H, dd, J = 5.7 Hz, J = 9.2 Hz), 3.38 (3H, s), 3.38 (1H, d, J = 12.1 Hz), 3.41 (1H, m), 3.50 (3H, s), 3.50 (1H, m), 3.60 (1H, m), 3.64 (3H, s), 3.73 (3H, s), 4.00 (1H, d, J = 12.3 Hz), 4.07 (1H, dd, J = 7.1, 10.8 Hz), 4.32 (1H, dd, J = 9.4, 12.1 Hz), 4.35 (1H, d, J = 12.2 Hz), 5.14 (1H, s), 5.31 (1H, s), 5.36 (1H, s), 5.48 (1H, s), 5.56 (1H, s), 5.69 (1H, s), 6.72−7.75 (13H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) (two rotamers) 49.39, 50.92, 52.16, 52.27, 52.67, 53.37, 53.93, 55.46, 55.66, 64.95, 66.36, 82.10, 82.66, 93.69, 110.96, 118.79, 118.92, 119.01, 119.21, 120.87, 120.94, 121.10, 121.53, 126.69, 127.06, 127.42, 128.06, 128.25, 129.39, 129.60, 129.75, 135.32, 142.44, 143.11, 144.39, 144.61, 144.89, 145.23, 156.34, 168.97, 169.34, 172.95.

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Supporting Information Available: Copies of the ^{1}H NMR and ^{13}C spectra for compounds **2**, **3**, **6**, **8**, **15**−**20**, and **22**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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