Open Analogues of Arcyriaflavin A. Synthesis through Diels−Alder Reaction between Maleimides and 1-Aryl-3-*tert*-butyldimethylsiloxy-1,3-butadienes

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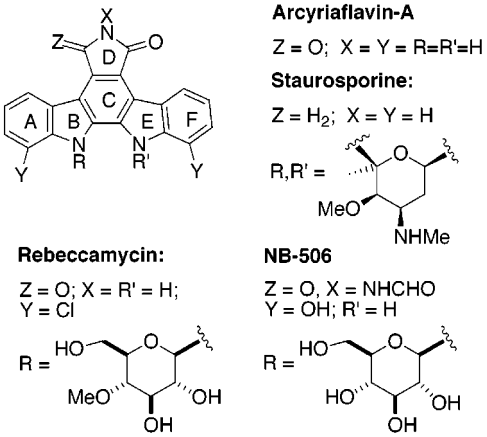
The preparation of a range of open analogues of arcyriaflavin A is described. The synthetic approach is based on the use of perhydroisoindole-1,3,5-triones as key intermediates, which were obtained via Diels−Alder methodology using 1-aryl-3-siloxy-1,3-butadienes as starting materials. Fischer indolization and aromatization processes afforded different methoxy-substituted arylpyrrolocarbazoles. The stereochemistry and conformation of the Diels−Alder products and the regiochemistry of the indolization reactions are supported by NMR and molecular modeling studies.

Introduction

There is a growing interest in the preparation of analogues of indolocarbazole alkaloids, aimed at modulating the biological properties of these natural products. Staurosporine and rebeccamycin, isolated from *Streptomyces staurosporeus*[1] and *Saccharotrix aerocolonigenes*, respectively,[2] are representative members of this family and display noteworthy cytotoxicity due to the inhibition of protein kinase C (PKC)[3] or mammalian topoisomerase I.[4] A broad variety of related compounds has been obtained from broth cultures and either by semisynthesis or total synthesis,[5] taking the natural products arcyriaflavin A[6] and staurosporine aglycon as the simplest models. At first sight, slight structural variations change the molecular mechanism of their biological activities[7] (mainly PKC or topoisomerase I inhibition and DNA intercalation). Among them, NB-506, a topoisomerase I inhibitor, is currently undergoing clinical trials as an antitumor agent.[8]



With a view to synthesizing new analogues of the aforementioned molecules, we recently began a research line aimed at the preparation of open analogues of rebeccamycin or staurosporine aglycons, leading to the final compound shown in Scheme 1, which exhibits promising cytotoxicity against nonsmall cell lung and breast cancer cell lines.[9] Our approach to the synthesis of that compound was based on the retrosynthetic analysis depicted below (Scheme 1), through the preparation of 7-phenylperhydroisoindole-1,3,5-triones as key intermediates en route to pyrrolocarbazoles,[10] which were subsequently obtained by Fischer indolization. Considerable efforts have been devoted to synthesizing arcyriaflavin A,[11] staurosporine,[12] rebeccamycin,[13] and other indolocarbazoles,[14] but there are few references concerning the synthesis of analogues with structures similar

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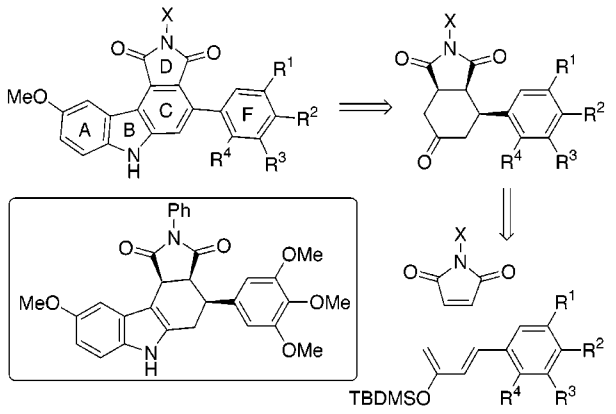
Scheme 1



to these described in this paper. Three of these approaches also use Diels−Alder methodology. In Moody's synthesis of the staurosporine aglycon,[15] an intramolecular cycloaddition between an alkyne and a pyranoindolone yielded an open 4-phenylpyrrolo[3,4-*c*]carbazole analogue, a synthetic precursor of the target substance finally obtained via nitrene insertion. Starting from a C-4 ester of a pyridazino[4,5-*b*]indole, a similar approach to the same target has recently been reported.[16] Finally, the Hoffman−La Roche group has developed a strategy based on the use of maleimides as dienophiles and 2-vinyl-*N*-alkyl-substituted indoles as dienes, for the final Diels−Alder step in its synthesis, leading to 4-heteroarylpyrrolo-[3,4-*c*]carbazoles[17] (which show cytotoxicity through PKC inhibition). Further examples of the design and synthesis of this kind of analogues is a series of pyrrolo[3,4-*c*]-carbazoles (some of them with thrombopoietic activity)[18] and the formation of 4-(1-aminophenyl)pyrrolo[3,4-*c*]-carbazoles by heating bisindolyl maleimides in toluene.[19]

Here we report the results obtained by application of our synthetic methodology for the preparation of new analogues of arcyriaflavin A and the rebeccamycin aglycon. Different substitution patterns on the **F** ring, the imide N-atom, and the **A** ring are readily introduced by the use of different starting benzaldehydes, N-substituted maleimides, or hydrazine derivatives, respectively.

Results and Discussion

We followed the general sequence depicted in Scheme 1 to prepare a broad variety of pyrrolocarbazoles. Trimethoxy- and dimethoxyphenyldienes were chosen as reagents for the Diels−Alder reaction because these residues confer a lipophilic character to several antitumor compounds, which act through different mechanisms: topoisomerase inhibitors,[20] antitubulin agents,[21] and antimetabolites.[22] Thus, starting from dimethoxy- or trimethoxybenzaldehydes, the unsaturated ketones **1** were prepared by Claisen−Schmidt condensation with acetone (which also yields minor amounts, ≤10%, of double condensation products **2**), followed by treatment with *tert*-butyldimethylsilyltriflate to produce, in good yield (≥80%, two steps), *tert*-butyldimethylsiloxydienes **3**,[23] bearing 3,4,5-trimethoxy-, 2,5-dimethoxy-, and 3,4-dimethoxyphenyl moieties (Scheme 2).

The Diels−Alder reactions between dienes **3** and maleimides (R = Ph, Me, or H) were carried out at rt in benzene, yielding reaction products **4a**−**i**, which were hydrolyzed by acidic treatment (HCl−CH_2Cl_2) to cyclohexanones **5a**−**i** and then purified by ether insolubilization. As we reported in our preliminary communication about the synthesis of our lead compound in Scheme 1,[9] the Diels−Alder reaction mainly yields the endo products **4a**−**i**. In some cases, a minor reaction product was observed in the ^{1}H NMR spectra of the crude of reaction, which was then assumed to be the exo product, although it was never isolated as the silyl enol ether **4** or as the cyclohexanone **5**.

Due to the conformational flexibility of the cis-fused systems, the ^{1}H NMR spectra were difficult to interpret, and further evidence of the stereochemical outcome of the reaction was needed. Consequently, a theoretical study and extensive NMR experiments were performed. For this purpose, the transition states leading to the diastereomeric endo and exo Diels Alder adducts were modeled by means of a systematic Monte Carlo conformational search, followed by energy minimization using the MM2 force field with the parameter set for the Diels−Alder reaction derived by Houk et al.[24] The differences in the heats of formation for the diastereomeric transition state pairs (typically 2−9 kJ/mol in favor of the endo transition state; e.g., 5.4 kJ/mol for the reaction leading to **4d**) suggested that the proposed endo products are the major kinetic reaction products, in good qualitative agreement with the interpretation of the experimental results. The stereochemical course of the reaction was also confirmed by comparing the NMR data derived from the minimal energy conformations of the hydrolysis products with those observed experimentally (see below).

Initially, each hydrogen atom of these molecules was assigned by two-dimensional NMR correlations and 1D

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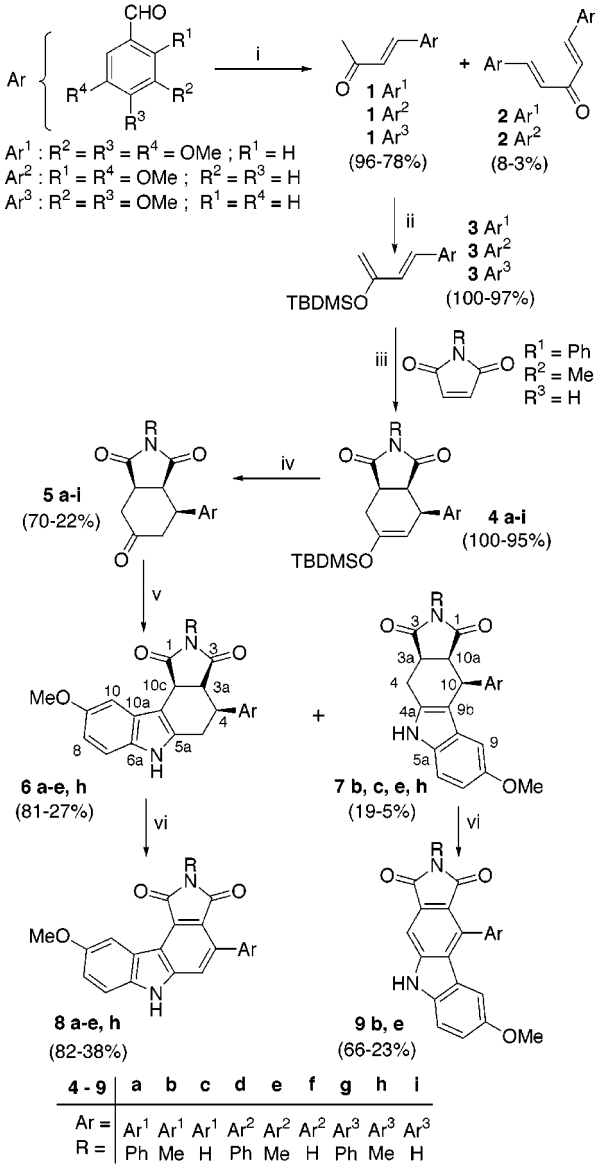
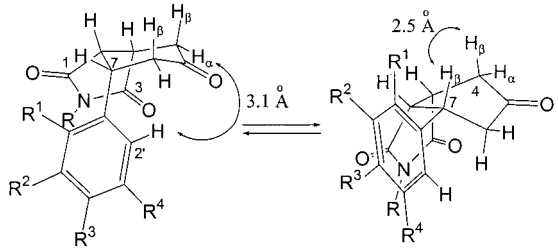
Scheme 2[a]



[a] Key: (i) acetone, NaOH, rt; (ii) TBDMSTf, Et_3N, CH_2Cl_2, rt; (iii) C_6H_6, rt; (iv) H^+, CH_2Cl_2; (v) *p*-MeO-C_6H_4-NH-NH_2·HCl, HOAc/EtOH 1:1, reflux; (vi) DDQ, C_6H_6, rt.

NOE experiments, which unequivocally indicated their stereochemistries. The NOE experiments for the ketone **5a**, carrying a phenyl substituent on the imide nitrogen, revealed a noticeable effect between $H_{4\alpha}/H_{2'}$, which requires a chair conformation A (Figure 1). The chair was also found to be the most stable conformation of **5a**, the difference being 3.5 kJ/mol, in the molecular mechanics calculations. Compound **5g** also showed NOEs between $H_{4\alpha}/H_{2'}$ although an additional NOE between $H_{7\beta}/H_{4\beta}$, which requires a boat conformation as depicted in B (Figure 1) to bring these hydrogens together, was also observed. These NOEs can be explained in terms of an equilibrium between the chair (A) and boat (B) conformations, in agreement with the similar stability calculated for both conformations of **5g**.

For imides without an *N*-phenyl substituent (**5b**,**e**,**h**, R = Me; **5c**,**f**,**i**, R = H) and for the 2,5-dimethoxyphenyl derivative (**5d**, R = Ph, Ar^2), the aforementioned NOE between the $H_{4\alpha}$ and $H_{2'}$ was not observed in agreement with the greater stability (≥7 kJ/mol) calculated for the



Conformation	Chair **A**	Boat **B**
Representative nOe's	$H_{4\alpha}$-$H_{2'}$	$H_{4\beta}$-$H_{7\beta}$
Preferred conformation	**5a** **5g** (equilibrium)	**5g** (equilibrium) **5b**, **5c**, **5d**, **5e**, **5f**, **5h**, **5i**

Figure 1. Most stable conformations of ketones **5** as deduced from NMR and MM.

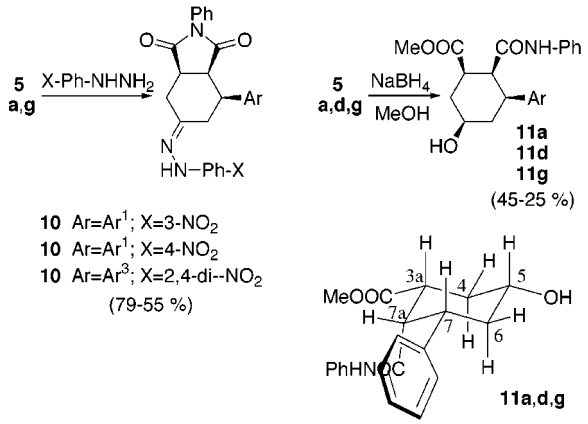


Figure 2. Hydrazones **10** and hydroxy derivatives **11** obtained from ketones **5**. Most stable conformation of compounds **11a**,**d**,**g**.

boat conformation (B) as compared to the chair conformation (A), for this series of compounds. The stabilization due to the interaction between the aromatic moieties in compounds **5a** and **5g** is counterbalanced by the higher steric hindrance of the methoxy group in position 2′ of compound **5d** ($R^1 = OCH_3$), accounting for the shift in the stability from the chair conformation, A, to the boat conformation, B. The absence of stabilization due to the presence of the phenyl group on the imide nitrogen is in agreement with the lower stability of the chair conformation A in compounds **5b**,**c**,**e**,**f**,**h**,**i.**

Despite all the NMR and modeling evidence, definitive confirmation of the endo geometry was still needed for the ketones obtained by hydrolysis of the Diels−Alder products. Hydrazones **10** were prepared in order to obtain crystalline products, but it was not possible to isolate crystals of sufficient quality for X-ray diffraction studies, and their NMR spectra were also inconclusive. Fortunately, alcohols **11** obtained by $NaBH_4$/MeOH treatment of **5** showed fully resolved multiplets in the ^1H NMR spectra, with larger vicinal coupling constants characteristic of a chair conformation (**11a**,**d**,**g**: $J_{3a,4\alpha} = 12.8$ Hz; $J_{3a,4\beta} = 4.4$ Hz; $J_{3a,7a} = 4.4$ Hz; $J_{4\alpha,4\beta} = 12.4$ Hz; $J_{4\alpha,5} = 12.4$ Hz; $J_{4\beta,5} = 4.4$ Hz; $J_{5,6\alpha} = 12.0$ Hz; $J_{5,6\beta} = 2.1$ Hz; $J_{6\alpha,6\beta} = 12.0$ Hz; $J_{6\alpha,7} = 12.5$ Hz; $J_{6\beta,7} = 4.4$ Hz; $J_{7,7a} = 4.2$ Hz). The NOE studies also supported the structure and conformation depicted in Figure 2 for alcohols **11** ({H_{3a}}: H_{7a}, $H_{4\beta}$; {$H_{4\beta}$}: H_{3a}, $H_{5\beta}$; {$H_{5\beta}$}: H_7, H_{3a}, $H_{4\beta}$, $H_{6\beta}$; {$H_{6\alpha}$}: $H_{2'}$, $H_{4\alpha}$; {$H_{6\beta}$}: $H_{2'}$, $H_{5\beta}$, H_7, $H_{6\alpha}$; {H_7}: $H_{2'}$, H_{3a},

Table 1. Results of the Diels−Alder Reaction under Different Conditions

entry	solvent	T[a]	reagents[a] R = Ph (time)	products (yield,[b] %)	reagents[a] R = Me (time)	products (yield,[b] %)
1	CH_2Cl_2	−10 °C	Ar^1 (20 d)	**4a** (>90)	Ar^1 (40 d)	**4b** (>70)
2			Ar^3 (20 d)	**4g** (>90)	Ar^3 (20 d)	**4g** (>90)
3	benzene	rt	Ar^1 (3 d)	**4a** (>95)	Ar^1 (4 d)	**4b** (>95)
4			Ar^2 (3 d)	**4d** (>95)	Ar^2 (3 d)	**4e** (>95)
5			Ar^3 (3 d)	**4g** (>95)	Ar^3 (3 d)	**4h** (>95)
6	xylene	rt	Ar^1 (2 d)	**4a** (>95)	Ar^1 (2 d)	**4b** (>95)
7			Ar^3 (2 d)	**4g** (>95)		
8	CH_2Cl_2	rt	Ar^3 (3 d)	**4g** (>95)		
9	DMF	rt	Ar^1 (2 d)	**4a** (>95)	Ar^1 (2 d)	**4b** (>95)
10			Ar^3 (2 d)	**4g** (>95)		
11	benzene	reflux	Ar^1 (5 h)	**4a** (>85)	Ar^1 (5 h)	**4b** (>85)
12	xylene	reflux	Ar^1 (2 h)	**4a** → **12a** (>85)	Ar^1 (2 h)	**4b** (>85)
13			Ar^3 (2 h)	**4g** → **12g** (>65)		
14	CH_2Cl_2	reflux	Ar^1 (5 h)	**4a** + **12a**	Ar^1 (5 h)	**4b** (>90)
15				(30+70)		
			Ar^3 (5 h)	**4 g** (>90)	Ar^3 (5 h)	**4h** (>90)
16	DMF	reflux	Ar^1 (2 h)	**4a** → **12a** (>85)	Ar^1 (2 h)	**4b** → **12b** (>65)
17			Ar^3 (2 h)	**12g** (>65)		

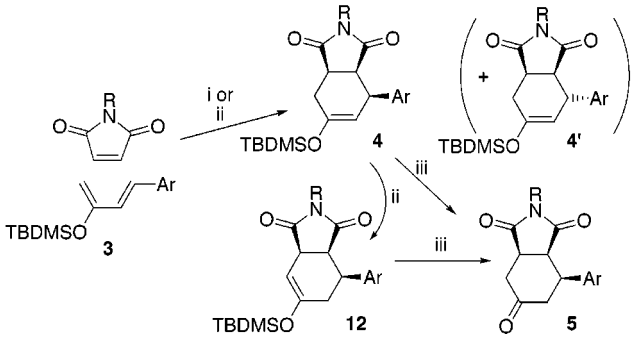
[a] Maleimide (R = Ph or Me) and diene **3** (Ar). [b] Yields are deduced from ^{1}H NMR of crude reaction products.

$H_{5\beta}$, $H_{6\beta}$; {H_{7a}}: $H_{2'}$, H_{3a}; {$H_{2'}$}: 3′-OCH_3, $H_{6\alpha}$, H_7, H_{7a}), and the calculated minimal energy conformations are also in good agreement with the NMR data.

The imide ring opening, leading to compounds **11**, might result from the attack of the methanol used as solvent. The cis-fused imide ring of compounds **5a**,**d**,**g** was no longer present, which explains the observed change in the conformational preferences between the starting **5a**,**d**,**g** (a chair with an axial Ar group, boat-chair equilibrium, or boat) and **11a**,**d**,**g** (a chair with an equatorial Ar group).

To further confirm these studies, the Diels−Alder reactions were carried out between maleimides (R = Ph, Me) and dienes **3**, in different solvents, at −10 °C, room temperature, and under reflux (Table 1). These reactions were checked by NMR of the crude reaction products or the hydrolyzed material. In all cases, the initial reaction product was the endo product **4**, although a low percentage of a compound presumed to be the exo isomer can be observed in some cases (Ar = Ar^1, R = Me). To investigate whether this minor product is formed under thermodynamic control, the reactions were carried out at increasing temperature in solvents of different boiling point or polarity, namely CH_2Cl_2, benzene, xylene, and DMF. As can be observed in Table 1, entries 12−17, conversion of the initially produced **4** into a new product **12** was observed when refluxing in CH_2Cl_2, xylene, or DMF. Surprisingly, these new products are different from the minor products assigned as *exo* cycloadducts **4′**, and their structures **12** were established as a result of their hydrolysis to the same ketones **5** as those obtained from cycloadducts **4** (Figure 3). An exhaustive NMR study of **12a** confirmed the proposed structure, with an endo stereochemistry and a boat conformation. Indeed, a similar isomerization has been described in structurally related cycloadducts.[25]

Following the synthetic strategy depicted in Scheme 1, the perhydroindole-2,3,5-triones were subjected to Fischer indolization with *p*-methoxyphenylhydrazine, to afford tetrahydrocarbazoles in good to moderate yields (Scheme 2) (owing to the cytotoxic properties of our



Key: (i) C_6H_6 or Xylene or CH_2Cl_2 or DMF at -10°C or r.t.;
(ii) Xylene or CH_2Cl_2 or DMF at reflux; (iii) HCl, CH_2Cl_2.

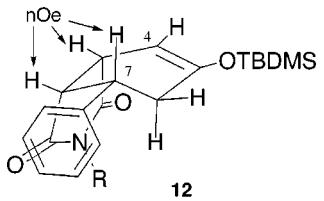


Figure 3. Products of the reaction between maleimides and dienes **3**. (for Ar and R, see Table 1).

previous compound **6a**, our first group of synthetic targets was a series of methoxy-substituted analogues). The two possible regioisomers **6** and **7** were detected in the crude product mixture of the reaction in all cases, and in some cases could be isolated. The most characteristic differences in the ^{1}H NMR of both regioisomers lie in the signals shown in Figure 4 for compounds **6** and **7**, specifically in the narrow aromatic doublet of the proton ortho to the methoxy group (**6b**: H-10: 7.47 ppm, deshielded by the C=O group, and **7b**: H-9: 6.79 ppm, shielded by the aromatic ring, Ar). The outcome of these reactions, yielding compounds **6** and **7** is shown in Table 2. The regioisomeric ratios are in agreement with the regioselectivity observed in the Fischer reaction with cyclohexanones,[10] thus, in all cases pyrrolo[3,4-*c*]carbazoles are the major products and pyrrolo[2,3-*c*]carbazoles the minor ones.

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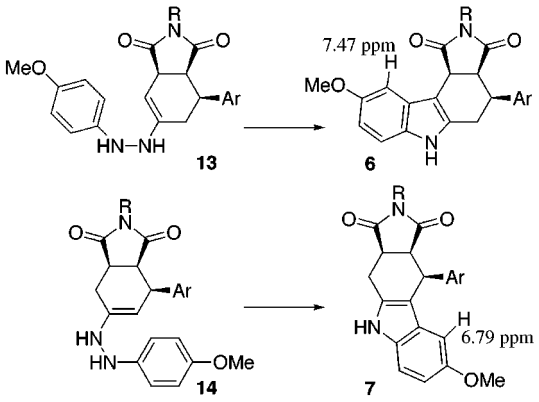

Figure 4. Indolization intermediates to regioisomeric products **6** and **7**.

Table 2. Regioisomeric Ratios 6:7 of the Indolization Reaction of 5a–e,h by ^{1}H NMR (Isolated Yields of 6 and 7)

	R		
Ar	Ph (**6**:**7**, %)	Me (**6**:**7**, %)	H (**6**:**7**, %)
Ar^1	**a**, 5:1 (81, –)	**b**, 2:1 (35, 15)	**c**, 3:1 (42, 5)
Ar^2	**d**, 3:1 (33, –)	**e**, 7:3 (32, 19)	
Ar^3		**h**, 7:2 (27, 4)	

The regiochemistry of the Fischer indolization reaction under less than extremely acidic conditions can be explained by the relative stabilities of the intermediate enehydrazines **13** and **14** (Figure 4), which lead to the indolization products.[26] In an attempt to confirm this hypothesis, we carried out molecular modeling studies on the enehydrazines (**13** or **14**), and the results were compared with the experimental outcome of the indolization reaction. Overall, the major product formed was that coming from the most stable intermediate enehydrazine **13** (>5 kJ/mol more stable than isomer **14**), thus supporting former studies on this kind of reaction.[27]

The aromatization of **6** and **7** with DDQ afforded the carbazole derivatives **8** and **9** (Scheme 2), with a planar aromatic system. The NMR data agree with the reported structures and the high deshielding of H-10 upon transformation of **6** (7.46–7.50 ppm) into **8** (8.51–9.16 ppm), and the shielding of H-9 when **7** (6.79–7.26 ppm) was converted into **9** (6.54–6.57 ppm). The conformational change induced by the aromatization can also be followed by the ^{1}H NMR deshielding of the N(2)-Me in planar compounds **8b**,**h** (**6**: 2.74, 2.79, **8**: 3.22, 3.18 ppm) and **9b** (**7**: 2.45, **9**: 3.12 ppm).

In summary, we have extended the synthetic utility, already reported by us,[9,23,28] of different 1-aryl-3-*tert*-butyldimethylsiloxy-1,3-butadienes by preparing a range of open analogues of arcyriaflavin A lacking the *E* ring. NMR and molecular modeling studies for both the Diels–Alder and Fischer indolization processes on arylsiloxydienes and isoindole-1,3,5-triones, respectively, offer a rationale to support the regio- and stereochemical outcome of those reactions. Further transformations of these analogues are currently under way, and the biological activities of the present and forthcoming compounds, similar and more elaborated, will be communicated in due course.

Experimental Section

General Methods. Melting points are uncorrected. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded at 200.13 and at 50.3 MHz, respectively, in deuteriochloroform solutions and with tetramethylsilane as internal standard. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI or FAB methods. Normal and flash chromatographies were performed on Merck 60 silica gel (0.063–0.2 mm or 0.040–0.063 mm). TLC was developed on precoated silica gel polyester plates with the UV 254 fluorescent indicator. Microanalyses were carried out in a CHN elemental analyzer at the Inorganic Chemistry Laboratory of the Faculty of Pharmacy (Salamanca). Solvents of analytical grade were used as purchased and, when necessary, dried using standard procedures.

General Procedure for the Preparation of (*E*)-4-(*n*-Methoxyphenyl)-3-buten-2-ones (1a–c). To the corresponding benzaldehyde (10.2 mmol) dissolved in aqueous ethanol (136 mL, 50% v/v) were slowly added from a dropping funnel acetone (3.6 mL, 51.0 mmol) and then a 10% solution of NaOH (12.0 mL, 30.0 mmol). After 45, 30, or 75 min, respectively, a precipitate was filtered from the solution, corresponding to the double-condensation products **2a**,**b**. The filtrate was neutralized with 2 N HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. Crystallization gave compounds **1a–c** as yellow crystals.

1 (Ar = Ar^1) (crystallization from CH_2Cl_2/hexane 1:1, 78%): mp 84 °C; IR (KBr): 1670, 1625, 1580, 1500 cm^{-1}; ^{1}H NMR δ 2.36 (s, 3H), 3.88 (s, 9H), 6.62 (d, J = 16.2 Hz, 1H), 6.78 (s, 2H),7.63 (d, J = 16.2 Hz, 1H); ^{13}C NMR δ 27.2 (q), 56.0 (q, 2C), 60.7 (q), 105.7 (d, 2C), 126.4 (d), 129.8 (s), 140.5 (s), 143.1 (d), 153.8 (s, 2C), 197.7 (s); MS (FAB) *m*/*z* 236 (M$^+$, 100). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.29; H, 6.95.

1 (Ar = Ar^2) (crystallization from CH_2Cl_2/hexane 1:1, 88%): yellow crystals; mp 64 °C; MS (EI) *m*/*z* 206 (M$^+$, 19), 175 (100). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.75; H, 6.75.

1 (Ar = Ar^3) (crystallization from diethyl ether/hexane 1:1, 96%): yellow crystals; mp 85 °C; MS (FAB) *m*/*z* 206 (M$^+$, 64), 191 (100). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.68; H, 6.80.

(1*E*,4*E*)-1,5-Bis(3,4,5-trimethoxyphenyl)-1,4-pentadien-3-one (2, Ar = Ar^1**)** (crystallization from ethanol, 8%): yellow crystals; mp 128 °C; IR (KBr) 1650, 1620, 1580, 1500 cm^{-1}; ^{1}H NMR δ 3.90 (s, 6H), 3.91 (s, 12H), 6.85 (s, 4H), 6.99 (d, J = 15.8 Hz, 2H), 7.67 (d, J = 15.8 Hz, 2H); ^{13}C NMR δ 56.2 (q, 4C), 60.9 (q, 2C), 105.9 (d, 4C), 124.8 (d, 2C), 130.3 (s, 2C), 140.5 (s, 2C), 143.2 (d, 2C) 153.5 (s, 4C), 188.4(s); MS (FAB) *m*/*z* 461 (M$^+$+ 2Na, 10), 185 (100).

General Procedure for the Preparation of (*E*)-3-*tert*-Butyldimethylsiloxy-1-(*n*-methoxyphenyl)-1,3-Butadienes (3 Ar$^{1-3}$). To a solution of the given compound (**1 Ar$^{1-3}$**) (0.85 mmol) in CH_2Cl_2 (20 mL) under Ar were added dropwise triethylamine (0.66 mL, 4.61 mmol) and *tert*-butyldimethylsilyltriflate (0.49 mL, 2.12 mmol). The reaction mixture was allowed to react for 1 h and then Et_3N (0.19 mL) added, diluted in CH_2Cl_2, washed diluted with aqueous saturated $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave the corresponding dienes.

3 (Ar = Ar^1) (100%): yellow oil; ^{1}H NMR δ 0.15 (s, 6H), 0.94 (s, 9H), 3.77 (s, 3H), 3.81 (s, 6H), 4.33 (s, 1H), 4.37 (s, 1H), 6.41 (d, J = 15.5 Hz, 1H), 6.54 (s, 2H), 6.68 (d, J = 15.5 Hz, 1H).

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3 (Ar = Ar^2**)** (100%): yellow oil. **3 (**Ar = Ar^3**)** (100%): yellow oil.

General Procedure for the Preparation of (±)-(3a*R*,7*S*,-7a*S*)-2-Substituted-7-(*n*-methoxyphenyl)perhydroisoindole-1,3,5-triones (5). Diels−Alder Reaction. The corresponding diene and maleimide (7.8 mmol each) were dissolved in 25 mL of dry benzene. They were allowed to react at room temperature in the dark. The reaction was monitored by ^{1}H NMR and TLC (reaction time: 2−4 days). For the preparation of cycloadduct **4h**, the reaction was carried out under reflux for 2−4 h. Benzene was evaporated to give cycloadducts **4** (95−100% yield) as deduced by NMR.

(±)-(3a*S*,4*S*,7a*R*)-2-Phenyl-6-*tert*-butyldimethylsiloxy-4-(3,4,5-trimethoxyphenyl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione (4a) (crystallization from ethyl acetate/hexane, 84%): yellow crystals; mp 125 °C; IR (KBr) 2954, 1715, 1590, 1502 cm^{-1}; ^{1}H NMR δ 0.21 (s, 6H), 0.97 (s, 9H), 2.54 (dd, J = 18.3, 10.24 Hz, 1H), 3.04 (dt, J = 18.3, 2.2 Hz, 1H), 3.40 (m, 2H), 3.74 (s, 6H), 3.80 (s, 3H), 4.02 (bt, J = 6.6 Hz, H), 5.20 (dd, J = 6.6, 2.2 Hz), 6.36 (s, 2H), 6.55 (m, 2H), 7.32 (m, 3H); ^{13}C NMR δ −4.2 (q), −4.5 (q), 17.8 (s), 23.8 (t), 25.0 (q), 38.7 (d), 41.4 (d), 44.0 (d), 55.9 (q, 2C), 60.5 (q), 104.4 (d), 106.1 (d, 2C), 125.9 (d, 2C), 128.2 (d), 128.7 (d, 2C), 131.4 (s), 134.8 (s), 137.2 (s), 150.4 (s), 152.9 (s, 2C), 176.2 (s), 178.2 (s). Anal. Calcd for $C_{29}H_{37}NO_6Si$: C, 66.51; H, 7.12; N, 2.67. Found: C, 66.39; H, 7.02; N, 2.60.

Hydrolysis of Silyl Enol Ethers. The cycloadduct (6.8 mmol) in 75 mL of CH_2Cl_2 was treated with 5 mL of concentrated HCl and then stirred for 2 h. After workup (dilution with CH_2Cl_2, aqueous $NaHCO_3$, brine, and Na_2SO_4 and evaporation) by precipitation in diethyl ether or by column chromatography and crystallization (in CH_2Cl_2/diethyl ether) triones **5** were obtained. Yields after precipitation obtained for the two steps cycloaddition−hydrolysis process.

(±)-(3a*R*,7*S*,7a*S*)-2-Phenyl-7-(3,4,5-trimethoxyphenyl)-perhydroisoindole-1,3,5-trione (5a) (precipitation in diethyl ether, 62%): white solid; mp 118 °C; IR (KBr) 1700, 1595, 1515 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.69 (dd, J = 17.9, 9.3 Hz, 1H), 2.78 (dd, J = 17.9, 5.2 Hz, 1H), 2.89 (dd, J = 17.9, 9.3 Hz, 1H), 3.18 (dd, J = 17.9, 2.0 Hz, 1H), 3.58 (td, J = 9.3, 2.0 Hz, 1H), 3.65 (dd, J = 9.3, 5.6 Hz, 1H), 3.77 (s, 6H), 3.81 (s, 3H), 3.83 (m, 1H), 6.36 (s, 2H), 6.97 (dd, J = 6.9, 1.4 Hz, 2H), 7.2 (m, 3H); ^{13}C NMR (100 MHz) δ 36.4 (t), 38.3 (d), 39.9 (d), 42.1 (t), 44.7 (d), 56.0 (q, 2C), 60.8 (q), 105.1 (d, 2C), 126.1 (d, 2C), 128.8 (d), 129.1 (d, 2C), 131.3 (s), 133.6 (s), 137.4 (s), 153.2 (s, 2C), 174.8 (s), 176.8 (s), 206.7 (s); MS (FAB) m/z 409 (M$^+$, 8), 185 (100). Anal. Calcd for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.21; H, 5.52; N, 3.15.

(±)-(3a*R*,7*S*,7a*S*)-2-Methyl-7-(3,4,5-trimethoxyphenyl)-perhydroisoindole-1,3,5-trione (5b) (precipitation in diethyl ether, 65%): white solid; mp 188 °C; IR (KBr) 1698, 1591, 1511 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.55 (dd, J = 18.3, 12.1 Hz, 1H), 2.78 (dd, J = 18.3, 4.5 Hz, 1H), 2.84 (dd, J = 17.7, 9.5 Hz, 1H), 2.95 (s, 3H), 3.11 (dd, J = 17.7, 3.8 Hz, 1H), 3.48 (td, J = 9.5, 3.8 Hz, 1H), 3.57 (dd, J = 9.5, 4.9 Hz, 1H), 3.73 (ddd, J = 12.1, 4.9, 4.5 Hz, 1H), 3.88 (s, 9H), 6.42 (s, 2H); ^{13}C NMR δ 25.0 (q), 37.0 (t), 38.2 (d), 39.2 (d), 41.5 (t), 44.3 (d), 56.1 (q, 2C), 60.8 (q), 105.1 (d, 2C), 133.8 (s), 137.3 (s), 153.1 (s, 2C), 175.7 (s), 177.7 (s), 206.8 (s); MS (EI) m/z 347 (M$^+$, 100). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.1; H, 6.01; N, 3.98.

(±)-(3a*R*,7*S*,7a*S*)-7-(3,4,5-Trimethoxyphenyl)perhydroisoindole-1,3,5-trione (5c) (precipitation in diethyl ether, 68%): white solid; mp 94 °C; IR (KBr) 3219, 1715, 1509 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.61 (dd, J = 18.4, 12.4 Hz, 1H), 2.74 (dd, J = 18.4, 3.8 Hz, 1H), 2.81 (dd, J = 17.4, 8.0 Hz, 1H), 3.01 (dd, J = 17.4, 1.6 Hz, 1H), 3.45 (m, 1H), 3.52 (dd, J = 9.4, 5.3 Hz, 1H), 3.64 (ddd, J = 12.4, 5.3 Hz, J = 3.8 Hz, 1H), 3.80 (s, 9H), 6.38 (s, 2H), 8.50 (bs, 1H); ^{13}C NMR (100 MHz) δ 36.9 (t), 39.1 (d), 39.4 (d), 41.6 (t), 45.4 (d), 56.2 (q, 2C), 60.9 (q), 105.2 (d, 2C), 133.6 (s), 153.2 (s, 2C), 153.6 (s), 175.7 (s), 177.8 (s), 206.8 (s); MS (EI) m/z 333 (M$^+$, 100). Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.74; N, 4.20. Found: C, 61.15; H, 5.67; N, 3.11.

(±)-(3a*R*,7*S*,7a*S*)-2-Phenyl-7-(2,5-dimethoxyphenyl)-perhydroisoindole-1,3,5-trione (5d) (precipitation in diethyl ether, 66%): white solid; mp 79 °C; HRMS (FAB) calcd for $C_{22}H_{21}NO_5$ 380.1497, found m/z 380.1450.

(±)-(3a*R*,7*S*,7a*S*)-2-Methyl-7-(2,5-dimethoxyphenyl)-perhydroisoindole-1,3,5-trione (5e) (precipitation in diethyl ether, 41%): brown solid; mp 163 °C.

(±)-(3a*R*,7*S*,7a*S*)-7-(2,5-Dimethoxyphenyl)perhydroisoindole-1,3,5-trione (5f) (precipitation in diethyl ether, 21%): white solid; mp 98 °C; MS (EI) m/z 303 (M$^+$ 100).

(±)-(3a*R*,7*S*,7a*S*)-2-Phenyl-7-(3,4-dimethoxyphenyl)-perhydroisoindole-1,3,5-trione (5g) (hexane/AcOEt 1:9, 41%): white solid; mp 218 °C; IR (KBr) 1713, 1594, 1501 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.69 (dd, J = 18.2, 10.6 Hz, 1H), 2.78 (dd, J = 18.2, 4.6 Hz, 1H), 2.90 (dd, J = 17.5, 9.0 Hz, 1H), 3.17 (dd, J = 17.5, 2.5 Hz, 1H), 3.57 (td, J = 9.0, 2.5 Hz, 1H), 3.64 (dd, J = 9.0, 5.8 Hz, 1H), 3.79 (s, 3H), 3.78 (m, 1H), 3.84 (s, 3H), 6.67 (dd, J = 8.0, 2.0 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 8.0, 1.2 Hz, 2H), 7.36 (m, 3H); ^{13}C NMR (100 MHz) δ 36.6 (t), 38.2 (d), 39.0 (d), 41.8 (t), 44.5 (d), 55.8 (q, 2C), 111.0 (d), 111.3 (d), 119.7 (d), 126.1 (d, 2C), 128.7 (d), 129.0 (d, 2C), 130.4 (s), 131.3 (s), 148.3 (s), 148.8 (s), 174.9 (s), 176.9 (s), 207.0 (s); MS (FAB) m/z 379 (M$^+$, 100). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.57; N, 3.69. Found: C, 69.43; H, 5.45; N, 3.52.

(±)-(3a*R*,7*S*,7a*S*)-2-Methyl-7-(3,4-dimethoxyphenyl)-perhydroisoindole-1,3,5-trione (5h) (precipitation in diethyl ether, 70%): violet solid; mp 83 °C; MS (EI) m/z 317 (M$^+$, 100). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.19; H, 5.93; N, 4.33.

(±)-(3a*R*,7*S*,7a*S*)-7-(3,4-Dimethoxyphenyl)perhydroisoindole-1,3,5-trione (5i) (precipitation in diethyl ether, 22%): white solid; mp 94 °C; MS (EI) m/z 303 (M$^+$, 100).

Fischer Indolization Reactions. Hydropyrrolo[3,4-*c*]-carbazoles (6) and Hydropyrrolo[3,4-*b*]carbazoles (7). A 0.86 mmol portion of trione was dissolved in 100 mL of AcOH/EtOH (1:1 vol/vol). After addition of 1.72 mmol of *p*-methoxyphenylhydrazine, the reaction mixture was refluxed for 1.5−4 h and then basified with caution (solid $NaHCO_3$), extracted with AcOEt, washed with brine, and dried (Na_2SO_4). Evaporation of the solvent, followed by precipitation in diethyl ether, crystallization (diethyl ether/CH_2Cl_2), or column chromatography (SiO_2 or Al_2O_3) gave the corresponding pyrrolocarbazoles. Depending on the case, a single regioisomer or both regioisomers were isolated.

(±)-(3a*S*,4*S*,10c*S*)-2-Phenyl-9-methoxy-4-(3,4,5-trimethoxyphenyl)-3a,4,5,10c-tetrahydro-6*H*-pyrrolo[3,4-*c*]-carbazole-1,3-dione (6a) (diethyl ether precipitation, 81%): white solid; mp 188 °C; IR (KBr) 3340, 1715, 1600 cm^{-1}; ^{1}H NMR (DMSO) δ 3.07 (dd, J = 16.2, 7.2 Hz, 1H), 3.22 (dd, J = 16.2, 4.5 Hz, 1H), 3.39 (s, 6H), 3.62 (s, 3H), 3.65 (m, 1H), 3.75 (s, 3H), 4.03 (dd, J = 7.6, 4.8 Hz, 1H), 4.57 (d, J = 8.0 Hz, 1H), 6.58 (s, 2H), 6.72 (dd, J = 8.0, 2.4 Hz, 1H), 6.78 (m, 2H), 7.23 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.35 (m, 3H), 11.00 (bs, 1H); ^{13}C NMR (DMSO) δ 26.2 (t), 39.2 (d), 40.4 (d), 45.4 (d), 55.4 (q), 55.8 (q, 2C), 59.9 (q),102.2 (d), 102.6 (s), 106.4 (d, 2C), 110.4 (d), 111.4 (d), 126.6 (d, 2C), 127.0 (s), 128.0 (d), 128.6 (d, 2C), 131.2 (s), 132.3 (s), 135.7 (s), 136.6 (s), 136.8 (s), 152.3 (s, 2C), 153.3 (s), 175.7 (s), 176.1 (s); MS (EI) m/z 512 (M$^+$, 15), 105 (100). Anal. Calcd for $C_{30}H_{28}N_2O_6$: C, 70.30; H, 5.51; N, 5.47. Found: C, 70.15; H, 5.40; N, 3.40.

(±)-(3a*S*,4*S*,10c*S*)-2-Methyl-9-methoxy-4-(3,4,5-trimethoxyphenyl)-3a,4,5,10c-tetrahydro-6*H*-pyrrolo[3,4-*c*]-carbazole-1,3-dione (6b) (hexane/AcOEt 3:7 and diethy ether precipitation, 35%): white solid; mp 240 °C; MS (EI) m/z 450 (M$^+$ 100). Anal. Calcd for $C_{25}H_{26}N_2O_6$: C, 66.65; H, 6.21; N, 5.82. Found: C, 66.40; H, 6.11; N, 5.76.

(±)-(3a*S*,4*S*,10c*S*)-9-Methoxy-4-(3,4,5-trimethoxyphenyl)-3a,4,5,10c-tetrahydro-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (6c) (hexane/AcOEt 3:7 and precipitation in diethyl ether, 42%): white solid; mp 245 °C; HRMS (FAB) calcd for $C_{24}H_{24}N_2O_6$ 437.1712, found m/z 437.1726.

(±)-(3a*S*,4*S*,10c*S*)-2-Phenyl-9-methoxy-4-(2,5-dimethoxyphenyl)-3a,4,5,10c-tetrahydro-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (6d) (hexane/AcOEt 1:1 and precipitation in diethyl ether, 33%): white solid; mp 279 °C.

(±)-(3a*S*,4*S*,10c*S*)-2-Methyl-9-methoxy-4-(2,5-dimethoxyphenyl)-3a,4,5,10c-tetrahydro-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (6e) (hexane/AcOEt 1:1 and precipitation in diethyl ether, 32%): red solid; mp 286 °C; MS (EI) *m*/*z* 420 (M^+, 100).

(±)-(3a*S*,4*S*,10c*S*)-2-Methyl-9-methoxy-4-(3,4-dimethoxyphenyl)-3a,4,5,10c-tetrahydro-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (6h) (hexane/AcOEt 3:7 and precipitation in diethyl ether, 27%): white solid; mp 150 °C; HRMS (FAB) calcd for $C_{24}H_{24}N_2O_5$ 421.1763, found *m*/*z* 421.1712.

(±)-(3a*R*,10*S*,10a*S*)-2-Methyl-8-methoxy-10-(3,4,5-trimethoxyphenyl)-3a,4,10,10a-tetrahydro-5*H*-pyrrolo[3,4-*b*]carbazole-1,3-dione (7b) (hexane/AcOEt 2:8 and diethyl ether precipitation, 15%): brown solid; mp 255 °C; IR (KBr) 3333, 1700, 1591, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.45 (s, 3H), 3.20 (dd, J = 17.0, 10.8 Hz, 1H), 3.40 (ddd, J = 10.8, 8.2 Hz, J = 2.3 Hz, 1H), 3.49 (dd, J = 8.2, 6.8 Hz, 1H), 3.63 (dd, J = 17.0, 2.3 Hz, 1H), 3.73 (s, 9H), 3.78 (s, 3H), 4.73 (d, J = 6.8 Hz, 1H), 6.19 (s, 2H), 6.78 (dd, J = 9.4, 2.4 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 7.20 (d, J = 9.4 Hz, 1H), 8.24 (bs, 1H); ^{13}C NMR δ 18.7 (t), 24.0 (q), 38.4 (d), 39.1 (d), 46.9 (d), 56.0 (q, 3C), 60.7 (q), 100.6 (d), 105.7 (d, 2C), 110.5 (s), 111.5 (d, 2C), 126.6 (s), 131.5 (s), 132.6 (s), 135.2 (s), 136.9 (s), 152.7 (s, 2C), 154.2 (s), 177.5 (s), 179.3 (s); MS (EI) *m*/*z* 450 (M^+, 100). Anal. Calcd for $C_{25}H_{26}N_2O_6$: C, 66.65; H, 6.21; N, 5.82. Found: C, 66.36; H, 6.05; N, 5.72.

(±)-(3a*R*,10*S*,10a*S*)-8-Methoxy-10-(3,4,5-trimethoxyphenyl)-3a,4,10,10a-tetrahydro-5*H*-pyrrolo[3,4-*b*]carbazole-1,3-dione (7c) (hexane/AcOEt 2:8 and precipitation in diethyl ether, 5%): brown solid; mp 185 °C. Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 65.88; H, 5.29; N, 6.21.

(±)-(3a*R*,10*S*,10a*S*)-2-Methyl-8-methoxy-10-(2,5-dimethoxyphenyl)-3a,4,10,10a-tetrahydro-5*H*-pyrrolo-[3,4-*b*]carbazole-1,3-dione (7e) (hexane/AcOEt 2:8 and diethyl ether precipitation, 19%): brown solid; mp 185 °C; MS (EI) *m*/*z* 420 (M^+, 100).

(±)-(3a*R*,10*S*,10a*S*)-2-Methyl-8-methoxy-10-(3,4-trimethoxyphenyl)-3a,4,10,10a-tetrahydro-5*H*-pyrrolo[3,4-*b*]carbazole-1,3-dione (7h) (hexane/AcOEt 3:7 and precipitation in diethyl ether, 5%): brown solid; mp 112 °C; MS (EI) *m*/*z* 420 (M^+, 88), 278 (100). Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.55; H, 6.66; N, 5.75. Found: C, 68.30; H, 6.49; N, 5.66.

General Procedure for the Aromatization of Hydropyrrolocarbazoles. A 0.12 mmol portion of the corresponding hydropyrrolocarbazole dissolved in 5 mL of benzene was reacted with 0.30 mmol of 2,3-chloro-5,6-dicyano-*p*-benzoquinone (DDQ) for 3 h at rt. The crude reaction mixture was diluted in AcOEt, washed with $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Precipitation in diethyl ether or chromatography (SiO_2) gave the corresponding aromatized products.

2-Phenyl-9-methoxy-4-(3,4,5-trimethoxyphenyl)-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (8a) (76%): brown solid; mp 282 °C; IR (KBr) 3309, 1695, 1618, 1514 cm-^{1}; ^1H NMR (py-d_5) δ 3.83 (s, 6H), 3.95 (s, 3H), 3.99 (s, 3H), 5.13 (bs, 1H), 7.26 (s, 2H), 7.34 (m, 1H), 7.46 (dd, J = 8.9, 2.5 Hz, 1H), 7.54 (m, 2H), 7.67 (d, J = 8.9 Hz, 1H), 7.83 (m, 2H), 8.00 (s, 1H), 9.16 (d, J = 2.5 Hz, 1H); ^{13}C NMR (py-d_5) δ 55.8 (q), 56.4 (q, 2C), 60.7 (q), 108.0 (d), 108.5 (d, 2C), 112.8 (d), 117.5 (d), 118.9 (d), 119.6 (s), 122.1 (s), 122.2 (s), 127.8 (d, 2C), 127.9 (d), 129.2 (d, 2C), 133.5 (s), 134.1 (s), 136.0 (s), 138.2 (s, 2C), 139.1 (s), 145.8 (s), 153.5 (s, 2C), 155.2 (s), 168.0 (s), 168.5 (s); HRMS (FAB) calcd for $C_{30}H_{24}N_2O_6$ 509.1712, found *m*/*z* 509.1712.

2-Methyl-9-methoxy-4-(3,4,5-trimethoxyphenyl)-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (8b) (59%): yellow crystaline solid; mp 286 °C; HRMS (FAB) calcd for $C_{25}H_{22}N_2O_6$ 447.1556, found *m*/*z* 447.1533.

9-Methoxy-4-(3,4,5-trimethoxyphenyl)-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (8c) (66%); red crystalline solid; mp >300 °C; HRMS (FAB) calcd for $C_{24}H_{20}N_2O_6$ 433.1399, found *m*/*z* 433.1380.

2-Phenyl-9-methoxy-4-(2,5-dimethoxyphenyl)-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (8d) (38%): orange crystaline solid; mp 132 °C.

2-Methyl-9-methoxy-4-(2,5-dimethoxyphenyl)-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (8e) (54%): yellow crystaline solid; mp 266 °C; HRMS (FAB) calcd for $C_{24}H_{20}N_2O_5$ 417.1450, found *m*/*z* 417.1452.

2-Methyl-9-methoxy-4-(3,4-dimethoxyphenyl)-6*H*-pyrrolo[3,4-*c*]carbazole-1,3-dione (8h) (82%): brown crystalline solid; mp 238 °C; HRMS (FAB) calcd for $C_{24}H_{20}N_2O_5$ 417.1450, found *m*/*z* 417.1404.

2-Methyl-8-methoxy-10-(3,4,5-trimethoxyphenyl)-5*H*-pyrrolo[3,4-*b*]carbazole-1,3-dione (9b) (66%): brown crystalline solid; mp 252 °C; IR (KBr) 3284, 1695, 1589, 1503 cm^{-1}; ^1H NMR δ 3.12 (s, 3H), 3.55 (s, 3H), 3.85 (s, 6H), 3.96 (s, 3H), 6.57 (d, J = 2.4 Hz, 1H), 6.77 (s, 2H), 7.07 (dd, J = 8.8, 2.4 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.88 (s, 1H), 9.01 (bs, 1H); ^{13}C NMR δ 23.9 (q), 55.4 (q), 56.3 (q, 2C), 61.1 (q), 104.4 (d), 106.1 (d), 106.3 (d, 2C), 112.2 (d), 117.8 (d), 118.8 (s), 123.2 (s), 125.5 (s), 130.1 (s), 131.0 (s), 135.6 (s), 136.3 (s), 138.1 (s), 142.3 (s), 153.5 (s, 2C), 154.4 (s), 168.4 (s), 168.9 (s); HRMS (FAB) calcd for $C_{25}H_{22}N_2O_6$ 447.1556, found *m*/*z* 447.1541.

2-Methyl-8-methoxy-10-(2,5-dimethoxyphenyl)-5*H*-pyrrolo[3,4-*b*]carbazole-1,3-dione (9e) (23%): green crystalline solid; mp 248 °C; HRMS (FAB) calcd for $C_{24}H_{20}N_2O_5$ 417.1450, found *m*/*z* 417.1439.

General Procedure for the Preparation of (±)-(3a*R*,7*S*,7a*S*)-2-Phenyl-7-(*n*-methoxyphenyl)-5-(*n*-nitrophenylhydrazono)perhydroisoindol-1,3,5-trione (10). A 60 mg (0.16 mmol) portion of **5c** was dissolved in 6 mL of MeOH with 4 drops of AcOH, and 2,4-dinitrohydrazine (38.0 mg, 0.16 mmol) was added. The reaction was stirred at reflux for 75 min and precipitation in cold ethanol and crystallization gave the product **10**.

(±)-(3a*R*,7*S*,7a*S*)-2-Phenyl-7-(3,4-dimethoxyphenyl)-5-(2,4-dinitrophenylhydrazono)perhydroisoindol-1,3,5-trione (10, Ar = Ar^3**)** (crystallization in CH_2Cl_2/diethyl ether 10:1, 55%): orange solid; mp 214 °C; IR (KBr) 3317, 1713, 1594, 1517 cm^{-1}; ^1H NMR δ 2.86 (dd, J = 17.4, 11.0 Hz, 1H), 2.97 (dd, J = 17.4, 2.5 Hz, 1H), 3.16 (dd, J = 15.3, 6.2 Hz, 1H), 3.31 (dd, J = 15.3, 2.6 Hz, 1H), 3.63 (m, 1H), 3.83 (m, 2H), 3.90 (s, 6H), 6.92 (m, 3H), 7.09 (m, 2H), 7.35 (m, 3H), 8.04 (d, J = 9.5 Hz, 1H), 8.37 (dd, J = 9.5, 2.5 Hz, 1H), 9.14 (d, J = 2.5 Hz, 1H), 11.14 (bs, 1H); ^{13}C NMR δ 28.9(t), 31.5 (t), 37.7 (d), 39.9 (d), 44.9 (d), 56.0 (q, 2C), 111.2 (d), 111.4 (d), 116.6 (d), 119.8 (d), 123.5 (d), 126.2 (d, 2C), 129.0 (d), 129.3 (d, 2C), 129.7 (s), 130.4 (d), 131.5 (s), 138.7 (s), 144.8 (s), 148.7 (s), 149.1 (s), 153.1 (s, 2C), 175.1 (s), 177.1 (s). Anal. Calcd for $C_{28}H_{25}N_5O_8$: C, 60.11; H, 4.50; N, 12.52. Found: C, 59.96; H, 4.41; N, 12.37.

General Procedure for the Reduction of 5 to (±)-(1*R*,2*S*,3*R*,5*R*)-Methyl-2-phenylcarbamoyl-5-hydroxy-3-(*n*-methoxyphenyl)cyclohexanecarboxylate (11). To a solution of the compounds **5a**,**d**,**g** (100.0 mg, 0.24 mmol) in anhydrous MeOH (1.3 mL) at 0 °C was added $NaBH_4$ (18.1 mg, 0,08 mmol) dissolved in anhydrous MeOH (2.13 mL). Once the addition was finished, the ice bath was removed, and the reaction was stirred at room temperature for 15−20 min. The reaction mixture was extracted with AcOEt, washed with brine, and dried (Na_2SO_4). Column chromatography and precipitation in diethyl ether gave the pure compounds **11**.

(±)-(1*R*,2*S*,3*S*,5*R*)-Methyl-2-phenylcarbamoyl-5-hydroxy-3-(3,4,5-trimethoxyphenyl)cyclohexanecarboxylate (11a) (32%): light brown solid; mp 65 °C; IR (KBr) 3359, 1596, 1505 cm^{-1}; ^1H NMR (400 MHz) δ 2.07 (dt, J = 12.0, 4.0 Hz, 1H), 2.19 (c, J = 12.0 Hz, 1H), 2.42 (dt, J = 12.4, 4.4 Hz, 1H), 2.52 (c, J = 12.4 Hz, 1H), 2.79 (dt, J = 12.4, 4.4 Hz, 1H), 3.02 (dt, J = 12.0, 4.2 Hz, 1H), 3.10 (dd, J = 4.4, 4.2 Hz, 1H), 3.69 (s, 9H), 3.83 (s, 3H), 3.85 (m, 1H),6.35 (bs, H), 6.46 (s, 2H), 7.02 (m, 1H), 7.22 (m, 2H), 7.43 (bd, 2.8, 2H); ^{13}C NMR (100 MHz) δ 32.8 (t), 34.9 (t), 44.1 (d), 44.2 (d), 49.1 (d), 52.1

(q), 56.2 (q, 2C), 60.7 (s), 70.2 (d), 104.5 (d, 2C), 119.8 (d, 2C), 124,2 (d), 128.7 (d, 2C), 137.1 (s), 137.2 (s), 137.8 (s), 153.5 (s, 2C), 169.7 (s), 173.2 (s); MS (EI) *m*/*z* 444 (M^+, 100). Anal. Calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.83; H, 6.51; N, 3.09.

(±)-(1*R*,2*S*,3*S*,5*R*)-Methyl-2-phenylcarbamoyl-5-hydroxy-3-(2,5-dimethoxyphenyl)cyclohexanecarboxylate (11d) (25%): light brown solid; mp 90 °C; HRMS (FAB) calcd for $C_{23}H_{27}NO_6$ 414.1916, found *m*/*z* 414.1889.

(±)-(1*R*,2*S*,3*S*,5*R*)-Methyl-2-phenylcarbamoyl-5-hydroxy-3-(3,4-dimethoxyphenyl)cyclohexanecarboxylate (11g) (45%): light brown solid; MS (FAB) *m*/*z* 414 (M^+, 100).

General Procedure for the Isomerization of Diels−Alder Adducts to (±) (3a*S*,4*S*,7a*R*)-2-Phenyl-6-*tert*-butyldimethylsiloxy-4-(*n*-methoxyphenyl)-3a,4,5,7a-tetrahydroisoindole-1,3-dione (12). The compounds **4a**,**b**,**g** in DMF or xylene were stirred at reflux for 4 h. Evaporation of the solvent gave the compounds **12** (100%).

(±)-(3a*S*,4*S*,7a*R*)-2-Phenyl-6-*tert*-butyldimethylsiloxy-4-(3,4,5-trimethoxyphenyl)-3a,4,5,7a-tetrahydroisoindole-1,3-dione (12a): ^{1}H NMR δ 2.52 (m, 2H), 3.50 (m, 2H), 3.77 (s, 6H), 3.80 (m, 1H), 3.82 (s, 3H), 5.24 (d, J = 4.00 Hz, 1H) 6.65 (s, 2H), 6.77 (m, 2H), 7.33 (m, 3H); ^{13}C NMR δ −4.3 (q), 18.1 (s), 25.6 (q), 33.5 (t), 39.7 (d), 42.0 (d), 44.3 (d), 56.1 (q), 60.9 (q), 97.1 (d), 105.8 (d), 126.4 (d), 128.6 (d), 129.1 (d), 131.6 (s), 136.1 (s), 137.2 (s), 153.1 (s), 153.7 (s), 176.2 (s), 176.5 (s).

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Supporting Information Available: Tables of ^{1}H and ^{13}C data of all the synthesized compounds and copies of ^{1}H and ^{13}C NMR spectra of one representative compound of each class (**4a**, **5a**,**b**, **6b**, **7b**, **8b**, **9b**, **10**, **11a**, and **12a**). This material is available free of charge via the Internet at http://pubs.acs.org.

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